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BRITISH THORACIC SOCIETY GUIDELINE FOR PLEURAL DISEASE

British Thoracic Society Pleural disease Guideline Development Group

and

BRITISH THORACIC SOCIETY CLINICAL STATEMENT ON PLEURAL PROCEDURES

British Thoracic Society Pleural procedures Clinical Statement Group

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BTS Guideline for pleural disease Guideline Development Group

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On behalf of the British Thoracic Society

The BTS Guideline for pleural disease has been endorsed by:

Association of Respiratory Nurse Specialists
Association for Palliative Medicine of Great Britain & Ireland
British Thoracic Oncology Group
Royal College of Pathologists
Royal College of Radiologists
Society for Cardiothoracic Surgery in Great Britain & Ireland

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Healthcare providers need to use clinical judgement, knowledge and expertise when deciding whether it is appropriate to apply recommendations for the management of patients. The recommendations cited here are a guide and may not be appropriate for use in all situations. The guidance provided does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of each patient, in consultation with the patient and/or their guardian or carer.

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Glossary and Abbreviations

AAFB	Acid alcohol fast bacilli
ADA	Adenosine deaminase
ANA	Antinuclear antibody
bd	bis die (to be taken twice times daily)
CA15-3	Cancer antigen 15-3
CA19-9	Carbohydrate antigen 19-9
CA72-4	Cancer antigen 72-4
CEA	Carcinoembryonic antigen
CDSR	Cochrane database of systematic reviews
CENTRAL	Cochrane central register of controlled trials
CI	Confidence intervals
COPD	Chronic obstructive pulmonary disease
CPPE	Complicated/complex parapneumonic effusion
CRP	C-reactive protein
CT	Computed tomography
CXR	Chest x-ray
CYFRA 21-1	Fragment of cytokeratin 19
DVT	Deep vein thrombosis
GDG	Guideline development group
GPP	Good practice point
GRADE	Grading of recommendations, assessment, development and evaluation
ICD	Intercostal chest drain/drainage
IFN-gamma	Interferon gamma
IPC	Indwelling pleural catheter
IgG4	Immunogobulin G4
LDH	Lactate dehydrogenase
LOS	Length of hospital stay
LVEF	Left ventricular ejection fraction
MPE	Malignant pleural effusion
MPM	Malignant pleural mesothelioma
MRI	Magnetic resonance imaging
MRSA	Methicillin-resistant Staphylococcus aureus
NA	Needle aspiration
NEL	Non-expandable lung
NSCLC	Non-small-cell lung carcinoma
NT-proBNP	N-terminal pro hormone pro-brain natriuretic peptide
PET-CT	Positron emission tomography-computed tomography

PICO	Population, intervention, comparator and outcome
PPE	Parapneumonic effusions (PPE)
PSP	Primary spontaneous pneumothorax
QoL	Quality of life
RPO	Re-expansion pulmonary oedema
SACT	systemic anti-cancer therapy
SP	Spontaneous pneumothorax
SSP	Secondary spontaneous pneumothorax
TB	Tuberculosis
TDS	Ter die sumendum (to be taken three times daily)
TPA	Tissue plasminogen activator
TPE	Tuberculous pleural effusion
TUS	Thoracic ultrasound
UPPE	Uncomplicated parapneumonic effusion
VATS	Video-assisted thoracoscopy surgery
VEGF	Vascular endothelial growth factor

British Thoracic Society Guideline for pleural disease

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SUMMARY OF RECOMMENDATIONS AND GOOD PRACTICE POINTS

Spontaneous pneumothorax

Acute management for spontaneous pneumothorax

Recommendations

- ► Conservative management can be considered for the treatment of minimally symptomatic (ie, no significant pain or breathlessness and no physiological compromise) or asymptomatic primary spontaneous pneumothorax in adults regardless of size. (Conditional—by consensus)
- ► Ambulatory management should be considered for the initial treatment of primary spontaneous pneumothorax in adults with good support, and in centres with available expertise and follow-up facilities. (Conditional)
- ► In patients not deemed suitable for conservative or ambulatory management, needle aspiration or tube drainage should be considered for the initial treatment of primary spontaneous pneumothorax in adults. (Conditional)
- ► Chemical pleurodesis can be considered for the prevention of recurrent of secondary spontaneous pneumothorax in adults (eg, patients with severe chronic obstructive pulmonary disease who significantly decompensated in the presence of a pneumothorax, even during/after the first episode). (Conditional)
- ► Thoracic surgery can be considered for the treatment of pneumothorax in adults at initial presentation if recurrence prevention is deemed important (eg, patients presenting with tension pneumothorax, or those in high-risk occupations). (Conditional)

Good practice points

- ✓ When establishing local ambulatory treatment pathways, planning and coordination between with the emergency department, general medicine and respiratory medicine is vital.
- ✓ When performing chemical pleurodesis for the treatment of pneumothorax in adults, adequate analgesia should be provided before and after treatment.
- ✓ All treatment options should be discussed with the patient to determine their main priority, with consideration for the least invasive option.

Optimal management after the resolution of a first episode of pneumothorax

Good practice points

- ✓ Elective surgery may be considered for patients in whom recurrence prevention is deemed important (eg, at-risk professionals (divers, airline pilots, military personnel), or those who developed a tension pneumothorax at first episode).
- ✓ Elective surgery should be considered for patients with a second ipsilateral or first contralateral pneumothorax.
- ✓ Discharge and activity advice should be given to all patients post pneumothorax.

Optimal management for spontaneous pneumothorax and ongoing air leak

Good practice point

- ✓ If a patient is not considered fit for surgery, autologous blood pleurodesis or endobronchial therapies should be considered for the treatment of pneumothorax with persistent air leak in adults.

Optimal surgical approach and surgical operation for pneumothorax management

Recommendations

- ► Video-assisted thoracoscopy access can be considered for surgical pleurodesis in the general management of pneumothorax in adults. (Conditional)
- ► Thoracotomy access and surgical pleurodesis should be considered for the lowest level of recurrence risk required for specific (eg, high-risk) occupations. (Conditional)
- ► Surgical pleurodesis and/or bullectomy should be considered for the treatment of spontaneous pneumothorax in adults. (Conditional)

Investigation of the undiagnosed unilateral pleural effusion

Radiology for diagnosing unilateral pleural effusions of benign aetiology

Good practice points

- ✓ Imaging findings of a unilateral pleural effusion should be interpreted in the context of clinical history and knowledge of pleural fluid characteristics.

✓ CT follow-up should be considered for patients presenting with pleural infection to exclude occult malignancy if there are ongoing symptoms, or other clinically concerning features.
✓ Positron emission tomography-CT (PET-CT) should not be used in the assessment of pleural infection.

Image-guided versus non-image-guided intervention for suspected unilateral pleural effusion

Recommendation

► Image-guided thoracentesis should always be used to reduce the risk of complications. (Strong—by consensus)

Optimal volume and container for pleural aspiration samples

Recommendations

► 25–50 mL of pleural fluid should be submitted for cytological analysis in patients with suspected malignant pleural effusion (MPE). (Strong—by consensus)
► Pleural fluid should be sent in both plain and blood culture bottle tubes in patients with suspected pleural infection. (Strong—by consensus)

Good practice points

✓ At least 25 mL, and where possible 50 mL, of pleural fluid should be sent for initial cytological examination.
✓ If volumes of ≥25 mL cannot be achieved, smaller volumes should be sent, but clinicians should be aware of the reduced sensitivity.
✓ If small volume aspirate (<25 mL) has been non-diagnostic, a larger volume should be sent, if achievable, except when there is high suspicion of a tumour type associated with low pleural fluid cytology sensitivity (especially mesothelioma).
✓ Pleural fluid samples should be processed by direct smear and cell block preparation.
✓ In patients with an undiagnosed pleural effusion where pleural infection is possible and volume of fluid sample available allows, microbiological samples should be sent in both white top containers and volumes of 5–10 mL inoculated into (aerobic and anaerobic) blood culture bottles.
✓ In cases where volume available does not allow 5–10 mL inoculation, volumes of 2–5 mL should be prioritised to blood culture bottles rather than a plain, sterile container.

Pleural fluid tests (biomarkers) for diagnosing unilateral pleural effusion

Recommendations

► Pleural fluid cytology should be used as an initial diagnostic test in patients with suspected secondary pleural malignancy, accepting that a negative cytology should lead to consideration of further investigation. (Conditional)
► Pleural fluid biomarkers should not be used for diagnosing secondary pleural malignancy. (Conditional)
► In high prevalence populations, pleural fluid adenosine deaminase (ADA) and/or interferon gamma (IFN-gamma) test(s) can be considered for diagnosing tuberculous pleural effusion. (Conditional)
► In low prevalence populations, pleural fluid ADA can be considered as an exclusion test for tuberculous pleural effusion. (Conditional)
► Tissue sampling for culture and sensitivity should be the preferred option for all patients with suspected tuberculous pleural effusion. (Strong—by consensus)
► Pleural fluid antinuclear antibody (ANA) should be considered to support a diagnosis of lupus pleuritis. (Conditional)

Good practice points

✓ The clinical utility of pleural fluid cytology varies by tumour subtype, including diagnostic sensitivity and predictive value for response to subsequent cancer therapies. This should be taken into consideration when planning the most suitable diagnostic strategy (eg, direct biopsies in those with a likely low cytological yield can be considered).
✓ Pleural fluid N-terminal prohormone brain natriuretic peptide (NT-proBNP) is useful when considering heart failure as a cause in unilateral pleural effusions but not superior to serum NT-proBNP and therefore should not be ordered routinely.

Serum biomarkers for diagnosing unilateral pleural effusion

Recommendation

► Serum NT-proBNP should be considered to support a diagnosis of heart failure in patients with unilateral pleural effusion suspected of having heart failure. (Conditional)

Good practice points

✓ Serum biomarkers should not currently be used to diagnose secondary pleural malignancy, pleural infection or autoimmune pleuritis.
✓ Serum biomarkers should not routinely be used to diagnose tuberculous pleural effusion, but may be considered in high prevalence areas.
✓ Serum biomarkers, including NT-proBNP, should not be used in isolation for diagnosing unilateral pleural effusion, as multiple conditions may co-exist.

Pleural biopsy for diagnosing unilateral pleural effusion

Recommendations

► Thoracoscopic or image-guided pleural biopsy may be used depending on the clinical indication and local availability of techniques (including need for control of pleural fluid). (Strong)
► Blind (non-image-guided) pleural biopsies should not be conducted. (Strong—by consensus)

Pleural infection

Predicting clinical outcomes of pleural infection

Recommendation

► Renal, age, purulence, infection source, dietary factors (RAPID) scoring should be considered for risk stratifying adults with pleural infection and can be used to inform discussions with patients regarding potential outcome from infection. (Conditional)

Pleural fluid, or radiology parameters for determining which patients can be treated with intercostal drainage

Recommendations

► For patients with parapneumonic effusion (PPE) or suspected pleural infection, where diagnostic aspiration does not yield frank pus, immediate pH analysis should be performed. (Strong—by consensus)
► For patients with suspected complex parapneumonic effusion (CPPE):
  – If pleural fluid pH is ≤7.2, this implies a high risk of CPPE or pleural infection and an intercostal drain (ICD) should be inserted if the volume of accessible pleural fluid on ultrasound makes it safe to do so. (Strong—by consensus)
  – If pleural fluid pH is >7.2 and <7.4, this implies an intermediate risk of CPPE or pleural infection. Pleural

fluid lactate dehydrogenase should be measured and if >900 IU/L ICD should be considered, especially if other clinical parameters support CPPE (specifically ongoing temperature, high pleural fluid volume, low pleural fluid glucose (72 mg/dL ≤4.0 mmol/L), pleural contrast enhancement on CT or septation on ultrasound. (Strong—by consensus)
  - If pleural fluid pH is ≥7.4, this implies a low risk of CPPE or pleural infection and there is no indication for immediate drainage. (Strong—by consensus)
- ► In the absence of readily available immediate pleural fluid pH measurement, an initial pleural fluid glucose <3.3 mmol/L may be used as an indicator of high probability of CPPE/pleural infection and can be used to inform decision to insert ICD in the appropriate clinical context. (Strong—by consensus)

Good practice points

- ✓ Clinicians should be mindful of alternative diagnoses that can mimic PPE with a low pH and potential for loculations (eg, rheumatoid effusion, effusions due to advanced malignancy/mesothelioma).
- ✓ Pleural fluid samples taken for pH measurement should not be contaminated with local anaesthetic or heparin (eg, by extruding all heparin from an arterial blood gas syringe) as this lowers pleural fluid pH. Delays in obtaining a pleural fluid pH or residual air in the sampling syringe will also increase pleural fluid pH.
- ✓ In patients where a clinical decision is made not to insert an ICD at initial diagnostic aspiration, regular clinical reviews should be performed and repeat thoracocentesis considered to ensure that CPPE is not missed.

Optimal initial drainage strategy for established pleural infection

Recommendation

- ► Initial drainage of pleural infection should be undertaken using a small bore chest tube (14F or smaller). (Conditional—by consensus)

Good practice points

- ✓ Due to the lack of supporting evidence, early surgical drainage under video-assisted thoracoscopy surgery (VATS) or thoracotomy should not be considered over chest tube ('medical') drainage for the initial treatment of pleural infection.
- ✓ Due to lack of supporting evidence, medical thoracoscopy should not be considered as initial treatment for pleural infection.

Intrapleural therapy for managing pleural infection

Recommendations

- ► Combination tissue plasminogen activator (TPA) and DNAse should be considered for the treatment of pleural infection, where initial chest tube drainage has ceased and leaves a residual pleural collection. (Conditional—by consensus)
- ► Saline irrigation can be considered for the treatment of pleural infection when intrapleural TPA and DNase therapy or surgery is not suitable. (Conditional—by consensus)
- ► Single agent TPA or DNAse should not be considered for treatment of pleural infection. (Conditional—by consensus)
- ► Streptokinase should not be considered for treatment of pleural infection. (Conditional)

Good practice points

- ✓ Patient consent should be taken when using TPA and DNase as there is a potential risk of bleeding.
- ✓ When administering TPA plus DNase the regime should be 10 mg TPA twice daily (10 mg two times per day)+5 mg DNase two times per day for 3 days, based on randomised controlled trial data. Based on retrospective case series data, lower dose 5 mg TPA two times per day+5 mg DNase two times per day for 3 days may be as effective, and can be used if considered necessary.
- ✓ Reduced doses of TPA may be considered in those with a potentially higher bleeding risk (eg, those on therapeutic anticoagulation which cannot be temporarily ceased).
- ✓ For details on administration of intrapleural treatments, please refer to the British Thoracic Society (BTS) Clinical Statement on Pleural Procedures.[1]

Optimal surgical approach and surgical method for managing pleural infection

Recommendation

- ► VATS access should be considered over thoracotomy for adults in the surgical management of pleural infection. (Conditional)

Good practice points

- ✓ When selecting a surgical access for the treatment of pleural infection in adults, it is important to ensure the technique can facilitate optimal clearance of infected material and achieve lung re-expansion where appropriate.
- ✓ Extent of surgery should be tailored according to patient and empyema stage when the lung is not completely trapped (drainage vs debridement).
- ✓ Decortication should be a decision that is individualised to the patient with a trapped lung based on assessment of patient fitness and empyema stage.

Pleural malignancy

Optimal imaging modality for diagnosing pleural malignancy

Recommendations

- ► Ultrasound may be a useful tool at presentation to support a diagnosis of pleural malignancy, particularly in the context of a pleural effusion, where appropriate sonographic skills are present. (Conditional)
- ► CT allows assessment of the entire thorax, and positive findings may support a clinical diagnosis of pleural malignancy when biopsy is not an option (Conditional); however, a negative CT does not exclude malignancy. (Strong—by consensus)
- ► PET-CT can be considered to support a diagnosis of pleural malignancy in adults when there are suspicious CT or clinical features and negative histological results, or when invasive sampling is not an option. (Conditional)

Good practice points

- ✓ Imaging can play an important role in the assessment of pleural malignancy, but results should be interpreted in the context of clinical, histological and biochemical markers.
- ✓ Features of malignancy may not be present on imaging at presentation. Unless a clear diagnosis is reached by other means (eg, biopsy), monitoring with follow-up imaging of patients presenting with pleural thickening and unexplained unilateral pleural effusion should be considered to exclude occult malignancy.

✓ MRI has potential as a diagnostic tool in pleural malignancy. Its clinical value has yet to be determined and its use should be limited to highly selected cases and research studies at the present time.

Systemic therapy for reducing the need for definitive pleural intervention for malignant pleural effusion

Recommendation

► Definitive pleural intervention should not be deferred until after systemic anticancer therapy (SACT). (Conditional—by consensus)

Managing malignant pleural effusion

Pleural aspiration with no pleurodesis agent versus talc slurry pleurodesis

Recommendation

► Management of MPE using talc pleurodesis (or another method) is recommended in preference to repeated aspiration especially in those with a better prognosis, but the relative risks and benefits should be discussed with the patient. (Conditional—by consensus)

Good practice points

✓ Decisions on the best treatment modality should be based on patient choice.

✓ Informed decision-making should include the role of inpatient versus ambulatory management and the potential risk of requiring further pleural interventions.

Indwelling pleural catheter versus talc slurry pleurodesis

Recommendation

► Patients without known non-expandable lung should be offered a choice of indwelling pleural catheter (IPC) or pleurodesis as first-line intervention in the management of MPE. The relative risks and benefits should be discussed with patients to individualise treatment choice. (Conditional)

Good practice points

✓ The psychological implications and potential altered body image aspects of having a semi-permanent tube drain in situ should not be underestimated and must be considered prior to insertion.

✓ All patients who have had an IPC inserted should be referred to the community nursing team on discharge for an early assessment of the wound site, symptom control, support with IPC drainage and removal of sutures.

✓ Patients and their relatives should be supported to perform community drainage and complete a drainage diary if they feel able to do so, to promote independence and self-management.

✓ Complications such as infection refractory to community management, suspected drain fracture, loculations or blockage with persistent breathlessness should be referred back to the primary pleural team for further assessment.

Thoracoscopy and talc poudrage pleurodesis versus chest drain and talc slurry pleurodesis

Recommendation

► Talc slurry or talc poudrage may be offered to patients with MPE to control fluid and reduce the need for repeated procedures. (Conditional)

Good practice point

✓ Where a diagnostic procedure is being conducted at thoracoscopy (pleural biopsies), if talc pleurodesis is reasonable, this should be conducted during the same procedure via poudrage.

Surgical pleurodesis, or surgical decortication versus talc slurry pleurodesis

Recommendation

► In selected patients considered fit enough for surgery, either surgical talc pleurodesis or medical talc slurry can be considered for the management of patients with MPE. The relative risks, benefits and availability of both techniques should be discussed with patients to individualise treatment choice. (Conditional—by consensus)

Good practice points

✓ Informed decision-making should include the role of surgery versus ambulatory management with an IPC for the management of MPE in selected patients.

✓ Decortication surgery may improve pleurodesis success in patients wih MPE with non-expandable lung, but the risks and benefits of IPC and surgical treatment should be discussed with patients, and treatment individualised according to circumstances (eg, fitness to undergo thoracic surgery).

Managing malignant pleural effusion and non-expandable lung

Pleural aspiration, talc slurry pleurodesis, talc poudrage pleurodesis, decortication surgery or indwelling pleural catheter

Good practice points

✓ Decisions on treatment modality for MPE and non-expanded lung should be based on patient choice, with the relative risks and benefits of each modality discussed with the patient, but patients should be made aware of the limited evidence base regarding treatment options for non-expandable lung.

✓ IPCs are effective at controlling symptoms in non-expandable lung and should be considered, but it may be appropriate to undertake pleural aspiration first to assess symptomatic response.

✓ Pleural aspiration may result in a need for multiple procedures so alternatives should be discussed with the patient.

✓ In patients with radiologically significant (>25%) non-expandable lung requiring intervention for a symptomatic MPE, current evidence suggests the use of an IPC rather than talc pleurodesis.

✓ In patients with MPE and <25% non-expandable lung, talc slurry pleurodesis may improve quality of life, chest pain, breathlessness and pleurodesis rates.

✓ Decortication surgery may improve pleurodesis success in selected patients with MPE and non-expandable lung, but the risks and benefits of IPC and surgical treatment should be discussed with patients, and treatment individualised according to circumstances (eg, fitness to undergo thoracic surgery).

Managing malignant pleural effusion and septated effusion (on radiology)

Intrapleural enzymes versus surgery, or no treatment

Good practice points

✓ Intrapleural fibrinolytics can be considered in highly selected symptomatic patients with MPE and septated effusion to try to improve breathlessness.

✓ Intrapleural fibrinolytics may be used in patients with MPE and septated effusion and an IPC to improve drainage if flushing the IPC with normal saline or heparin saline does not improve drainage.
✓ Surgery can be considered for palliation of symptoms in a minority of patients with significantly septated MPE and associated symptoms and otherwise good prognosis and performance status.

Managing malignant pleural effusion treated with an indwelling pleural catheter

Symptom-based/conservative drainage versus daily drainage

Recommendations

► Where IPC removal is a priority, daily IPC drainages are recommended to offer increased rates of pleurodesis when compared with less frequent drainages of symptom-guided or alternate drainage regimes. (Conditional)
► Patients should be advised that they do not require daily drainage to control symptoms of breathlessness and chest pain if they wish to opt for a less intensive regime. (Strong—by consensus)

Good practice points

✓ Decisions on the optimal drainage frequency should be based on patient choice.
✓ Informed decision-making should include the explanation of the effect of drainage regimes on the patient-centre outcomes such as breathlessness and the possibility of autopleurodesis during the disease course.
✓ Although daily drainage may result in earlier removal of IPC, there may be an associated cost associated with the increased number of drainage events (both to the healthcare system and to the patient). This has been addressed in a modelling study[2] and should be considered.

Intrapleural agents (talc or other pleurodesis agents)

Recommendation

► Instillation of talc via an IPC should be offered to patients with expandable lung where the clinician or patient deems achieving pleurodesis and IPC removal to be important. (Conditional—by consensus)

Intrapleural chemotherapy versus systemic treatment for treating pleural malignancy

Recommendation

► Intrapleural chemotherapy should not be routinely used for the treatment of MPE. (Conditional—by consensus)

Good practice point

✓ All patients of good performance status with metastatic malignancy should be considered for SACT as standard of care as per national guidelines.

Using prognostic or predictive scores to provide prognostic information for patients with malignant pleural effusion

Good practice points

✓ Clinicians may consider using a validated risk score for MPE, if the information is of use in planning treatments or in discussion with patients.
✓ Patients with pleural malignancy should be managed in a multidisciplinary way, including referral to specialist palliative care services where appropriate.

INTRODUCTION

Aim of the guideline

This guideline aims to provide evidence-based guidance on the investigation and management of:

a. Spontaneous pneumothorax (SP)
b. Undiagnosed unilateral pleural effusion
c. Pleural infection
d. Pleural malignancy

Pleural disease is common and represents a major and rapidly developing subspecialty that presents to many different hospital services. Since the last British Thoracic Society (BTS) Guideline for pleural disease published in 2010,[3–9] many high-quality and practice changing studies, using patient-centred outcomes, have been published. The paradigms for the investigation and management of pleural disease have therefore shifted. For example, ambulatory treatments have become much more prominent in the management of pleural disease. This guideline aims to capture this evidence and use it to answer the most important questions relevant to today's practice.

Intended users of the guideline and target patient populations

The guideline will be of interest to UK-based clinicians caring for adults with pleural disease, including chest physicians, respiratory trainees, specialist respiratory nurses, specialist lung cancer nurses, specialist pleural disease nurses, pathologists, thoracic surgeons, thoracic surgeon trainees, acute physicians, oncologists, emergency physicians, hospital practitioners, intensive care physicians, palliative care physicians, radiologists, other allied health professional and patients and carers. Guideline group members were selected to offer a broad geographical coverage of the UK and to include specialists with backgrounds in respiratory medicine, thoracic surgery, oncology, palliative care, nursing and pathology. The group included specialists from tertiary centres as well as district general hospitals.

Scope of the guideline

The guideline is specifically designed to answer important questions in the investigation and management of pleural disease in adults. Questions have been agreed by the whole guideline group. While as many important questions as possible have been included, there are areas that have not been covered. As this guideline covers four broad areas of pleural disease, the number of questions is limited by the practicalities of writing a guideline with a large scope that remains relevant and up to date at the point of publication and a workload manageable by the guideline group.

This guideline covers adult patients in both inpatient and ambulatory settings, and questions from investigation to management in the inpatient and outpatient settings and by specialists of all disciplines involved in the care of patients with pleural disease.

Areas not covered by the guideline

Mesothelioma has been excluded from this guideline as this is already covered in the BTS Guideline for the investigation and management of pleural mesothelioma.[10] Benign (non-infectious, non-pneumothorax) pleural disease and rare pleural diseases are also excluded. Guidance on pleural interventions are covered in the BTS Clinical Statement on Pleural Procedures.[1]

Limitations of the guideline

Healthcare providers need to use clinical judgement, knowledge and expertise when deciding whether it is appropriate to apply recommendations for the management of patients. The recommendations cited here are a guide and may not be appropriate for use in all situations. The guidance provided does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of each patient, in consultation with the patient and/or their guardian or carer.

Members of the Guideline Development Group

The Guideline Development Group (GDG) was chaired by three respiratory consultants—Professor Nick Maskell, Professor Najib Rahman and Dr Mark Roberts. The GDG had a wide membership and included colleagues from respiratory medicine, oncology, radiology, pathology and palliative medicine. Two patient representatives were recruited to the group, but due to personal circumstances both had to withdraw before completion of the guideline (August 2019 and July 2021). However, two further patient representatives were recruited at the end of the guideline process to review the final guideline and provide the patients' perspective. Those on the group were not required to be BTS members and a full list of members can be seen in Appendix 2.

Acknowledgements

The co-chairs would like to acknowledge the huge contributions of all guideline group members both to robust discussions during the meetings and sourcing, critically reviewing papers and formulating judgements. They would also like to specifically thank Dr Kirstie Opstad at BTS Head Office who has coordinated the whole process, performed searches and initial abstract filtering, supported the evidence review process and ensured consistency of presentation of the whole guideline.

The GDG would like to thank Mr Richard Bremner, Mr Yannick Mouchilli, Mr Chris Smith and Dr Tim Wallington (patient representatives) for their helpful contributions during development of this guideline.

METHODOLOGY OF GUIDELINE PRODUCTION

Establishment of Guideline Development Group

The GDG was convened in July 2018, with the first meeting taking place in November 2018. The full GDG met 10 times during the development of the guideline and kept in close contact by teleconference and email throughout the process.

Methodology

This BTS Guideline uses Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methodology in the guideline development process. Full details are provided in the BTS Guideline production manual (https://www.brit-thoracic.org.uk/quality-improvement/guidelines/).

Summary of key questions, outcomes and literature search

Clinical questions were defined from the scope of the guideline and formulated into systematic review type questions (diagnostic accuracy, intervention or prognostic) according to the nature of the question. A full list of clinical questions for each section of the guideline is provided in Appendix 3.

Patient-centred outcomes were agreed by the group for each question.

The Population, Intervention, Comparator and Outcome (PICO) framework, or equivalent for the diagnostic accuracy and prognostic review questions, formed the basis of the literature search. The initial searches were completed by the University of York (and latterly by BTS Head Office). Systematic electronic database searches were conducted to identify all papers that may be relevant to the guideline. For each question, the following databases were searched: Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, MEDLINE and EMBASE. The search strategy is available for review in online supplemental appendix 1.

Literature review

Two literature searches were conducted for the guideline, with the number of resulting abstracts from each search shown in table 1.

Letters, conference papers and news articles were removed and criteria for initial screening of the abstracts were:

- Does the study type match the study type criteria in the clinical question protocols?
- Does the population match the clinical question population(s)?
- Is the abstract in English?

The remaining abstracts were screened by Professor Maskell, Professor Rahman and Dr Roberts and potentially relevant abstracts allocated to the relevant clinical questions. Abstracts were not rejected on the basis of the journal of publication, authorship or country of origin.

GDG members were allocated to work on individual questions in small groups. Each abstract was read and at least two members agreed whether the abstract was 'potentially relevant' or 'not relevant' to the clinical question of interest. Abstracts were excluded if they were deemed 'not relevant' to the clinical question.

Full papers were obtained for all abstracts assigned as 'potentially relevant'. Each full paper was reviewed to assess if it addressed:

i. The clinical question population;
ii. The index test and reference standard (for diagnostic accuracy questions), the intervention and comparator (for intervention questions) or the exposure and referent (for prognostic questions);
iii. The study type(s) defined in the clinical question protocol;
iv. The clinical question outcome(s).

Table 1 Literature searches were conducted for each section of the guideline as follows

Section	Search 1 date	Number of abstracts	Search 2 date	Number of abstracts
Spontaneous pneumothorax	20 March 2020	6325	18 May 2021	1260
Investigation of the undiagnosed unilateral pleural effusion	18 March 2019	6773	13 May 2021	2199
Pleural infection	17 December 2019	4138	20 May 2021	822
Pleural malignancy	03 April 2019	14 276	11 May 2021	3641

Table 2 Evidence statement (GRADE) score definitions

GRADE		Definition
High	⊕⊕⊕⊕	High confidence that the true effect is close to the estimated effect.
Moderate	⊕⊕⊕◯	Moderate confidence that the true effect is close to the estimated effect.
Low	⊕⊕◯◯	Low confidence that the true effect is close to the estimated effect.
Very low	⊕◯◯◯	Very low confidence that the true effect is close to the estimated effect.
Ungraded		GRADE analysis not possible, but evidence deemed important by the GDG.

GDG, Guideline Development Group; GRADE, Grading of Recommendations, Assessment, Development and Evaluation.

Each full paper fulfilling the above criteria, and agreed by at least two members of the GDG, was 'accepted' for meta-analysis and subsequent critical appraisal.

In circumstances where there was little, or no supporting evidence that fulfilled the above criteria, the full paper inclusion strategy was widened to include evidence that partially addressed the clinical question.

The second literature search (Search 2, table 1) was undertaken in May 2021 to capture additional published evidence while the guideline was in development prior to finalising the draft document. The additional abstracts were reviewed and allocated to the clinical questions as above.

The full list of abstracts has been retained and is kept in an archive.

Systematic review of the evidence

Each 'accepted' full paper underwent a systematic review. Data were extracted and meta-analyses were performed for each clinical question on an outcome-by-outcome basis for intervention reviews, or an index test basis for diagnostic accuracy reviews. If meta-analysis was not possible, for example, if there was insufficient evidence to perform a meta-analysis, if data could not be extracted to input into a meta-analysis, or data across studies had been published in different formats, all relevant supporting data were tabulated where possible.

All full papers contributing towards a meta-analysis underwent critical appraisal. For all non-meta-analysed data included in an evidence review, contributing papers also underwent critical appraisal where possible.

Meta-analyses and risk of bias assessments (critical appraisal) were performed in Review Manager V.5.3 and agreed by at least two members of the GDG. Diagnostic accuracy meta-analyses involved an additional step which was performed by BTS Head Office using the MetaDTA app.[11] Papers no longer deemed relevant were removed from the systematic review, with the decision to 'exclude' a paper solely based on it not fulfilling the clinical question criteria.

GRADE analysis of the evidence

Having generated evidence profiles for each of the clinical question, GDG question groups assessed the quality of the evidence using the GRADE methodology.[12] Where meta-analysis was not possible, but studies had used comparable methodologies and data reporting methods to allow an assessment of the quality of the data, a prognostic review GRADE analysis approach was used.[13 14]

Where GRADE analysis was not possible, but GDG members felt the evidence was important to be included in the evidence statements, these have been listed as (Ungraded). Definitions of the evidence statement (GRADE) scores are shown in table 2.

Each clinical question review was reviewed by the full GDG during the regular meetings and consensus was reached in relation to the evidence summary.

Development of recommendations

The GDG proceeded to decide on the direction and strength of recommendations considering the quality of the evidence, the balance of desirable and undesirable outcomes and the values and preferences of patients and others. GRADE specifies two categories of strength for a recommendation, as shown in table 3.

From the outset, it was acknowledged that there would be little high-quality evidence for some of the clinical questions identified. In this instance, low-grade evidence was considered, along with the expert opinion of the GDG via informal consensus at the meetings.

Good practice points (GPPs) were developed by informal consensus in areas where there was no quality evidence, but the GDG felt that some guidance, based on the clinical experience of the GDG, might be helpful to the reader. These are indicated as shown below.

✓ Advised best practice based on the clinical experience of the GDG.

In some instances where evidence was limited, but GDG members felt that it was important to include a recommendation rather than a GPP, recommendations were agreed by informal consensus and categorised as (Strong—by consensus) or (Conditional—by consensus), based on the same criteria detailed in table 3.

Cost-effectiveness was not considered in detail as in-depth economic analysis of recommendations falls outside of the scope of the BTS Guideline production process. However, the GDG were asked to be mindful of any potential economic barriers to the implementation of recommendations and GPPs.

Research recommendations were also identified and are detailed in online supplemental appendix 2.

Drafting the guideline

The guideline group corresponded regularly by email and meetings of the full group were also held in the period between November 2018 and late 2020. A revised draft guideline document was circulated to all the relevant stakeholders for consultation in May 2022 followed by a period of online consultation.

Table 3 Explanation of the terminology used in BTS recommendations

Strength	Benefits and risks	Implications
Strong Recommended, so 'offer'	Benefits appear to outweigh the risks (or vice versa) for the majority of the target group.	Most service users would want to, or should receive this intervention.
Conditional Suggested, so 'consider'	Risks and benefits are more closely balanced, or there is more uncertainty in likely service users' values and preferences.	Service users should be supported to arrive at a decision based on their values and preferences.

The BTS Standards of Care Committee reviewed the 'Investigation of the undiagnosed unilateral pleural effusion' and 'Pleural malignancy' sections of the draft guideline in March 2020 and the full guideline in March 2022.

Review of the guideline

The guideline will be reviewed 5 years after the date of publication.

Declarations of interests

BTS declarations of interest forms have been completed by all members for each year they were part of the GDG. Details of these forms can be obtained from BTS Head Office. 'Declarations of interests' was a standing item at each GDG meeting.

Stakeholders

Stakeholders were identified at the start of the process. All stakeholder organisations were notified when the guideline was available for public consultation and a list is published in Appendix 4.

SPONTANEOUS PNEUMOTHORAX

Introduction

The term pneumothorax describes air in the pleural space and is characterised as spontaneous in the absence of trauma or causative medical intervention. It is an increasing problem, with annual hospital admission rates rising from 9.1 to 14.1 per 100 000 population in the last 50 years, leading to substantial symptom burden and healthcare utilisation.[15 16] Since the last version of the BTS pneumothorax guideline, published in 2010,[5] there have been several large high-quality clinical trials examining the management of SP.[17–20]

This guideline seeks to consolidate and update the pneumothorax guidelines in the light of this subsequent research using GRADE methodology and addresses the following clinical questions addressing adults with pneumothorax:

- What is the best acute management for SP? (Question A1)
- What is the optimal management of patients after resolution of first episode of pneumothorax? (Question A2)
- What is the optimal management of patients with ongoing air leak? (Question A3)
- What is the optimal surgical approach when performing surgery? (Question A4)
- What is the optimal operation when performing surgery? (Question A5)

Other areas of clinical importance that are not covered by the guideline questions are discussed in the 'Other areas of clinical importance not covered by the clinical questions' section, including traumatic and iatrogenic pneumothorax which are not specifically covered in the evidence review.

Definitions and treatment principles

Spontaneous pneumothoraces can be subclassified into primary spontaneous pneumothorax (PSP) in the absence of suspected lung disease or SSP in patients with established underlying lung disease. This distinction does not imply that patients with PSP have normal underlying lung parenchyma, with the majority demonstrating emphysema-like pulmonary changes on CT imaging, but instead reflects that current management and outcomes differ between the two patient groups. Patients can also be characterised as SSP if they are older than 50 years of age and have a smoking history. This categorisation reflects case series data that this cohort may respond differently to needle aspiration (NA) than younger patients or non-smokers.

There have been substantial changes in recommendation in this BTS guideline compared with the 2010 guidelines. Size of pneumothorax is no longer an indication for invasive management (although does dictate the safety of conducting an intervention) and the use of chest drains is mainly centred around patients with high-risk characteristics (Appendix 1, Pneumothorax pathway). The expanded evidence base now allows for a more personalised approach and greater patient choice. For details of interventions and how these are best conducted, please refer to the BTS Clinical Statement on Pleural Procedures for further details.[1]

What is the best acute management for spontaneous pneumothorax?

Drainage of symptomatic pneumothorax, either with NA or intercostal chest drain (ICD) attached to an underwater seal is the current standard of care for PSP. There is ongoing debate over the respective benefits of NA over ICD, with multiple recent randomised trials comparing NA with ICD. Conservative management (ie, no active intervention) is often undertaken in patients with small or incidental PSP, but could be an alternative to NA or chest drain in patients with larger pneumothoraces.

Ambulatory treatment using a purpose-made device containing a one-way valve, or Heimlich valve attached to chest drain has the potential to allow outpatient management of pneumothorax. A proportion of pneumothoraces will recur and both chemical pleurodesis via chest tube and thoracic surgery have the potential to reduce this risk. Thoracic surgery is often the treatment of choice for ongoing air leak, or for those with recurrent pneumothorax. However due to the risk of recurrence, trials have been performed to establish whether thoracic surgery could be offered as first presentation of pneumothorax. Conservative management, in which no intervention is undertaken and the patient is observed or reviewed repeatedly, is also a further alternate initial potential treatment strategy. Hence, the first clinical question is:

> A1 For adults with spontaneous pneumothorax, is conservative management, needle aspiration, ambulatory management, chemical pleurodesis or thoracic surgery better than intercostal drainage at improving clinical outcomes?

A summary of the evidence review is shown in table 4 and the evidence statements (conclusions from the evidence review), recommendations and GPPs are presented below. The full evidence review is available in online supplemental appendix A1.

Evidence statements

Conservative management

- Length of hospital stay appears to be shorter following conservative management for the treatment of PSP in adults when compared with ICD. (Ungraded)
- Risk of pneumothorax recurrence appears to be greater following ICD when compared with conservative management for the treatment of PSP in adults. (Very low)
- There may be more complications experienced following ICD when compared with conservative management for the treatment of PSP in adults. (Ungraded)

Needle aspiration

- Length of hospital stay appears to be shorter following NA for the treatment of PSP in adults when compared with ICD. (Low)

Table 4 Evidence review summary for 'What is the best acute management for spontaneous pneumothorax?'

Clinical outcomes	Summary of evidence review (treatment vs ICD) (95% CI)				
(Treatment)	Conservative management	NA	Ambulatory management	Chemical pleurodesis	Thoracic surgery
LOS	Shortened LOS with conservative management*	2.55 days shorter (2.24 to 2.87) with NA (PSP)†	3.47 days shorter (2.20 to 4.73) with ambulatory management†	No difference	No difference
Pneumothorax recurrence	Lesser risk with conservative management (111/1000 (80 to 155)) compared with (179/1000)†	No difference	No difference	Lesser risk with chemical pleurodesis (179/1000 (138 to 227)) compared with 320/100 (PSP and SSP)†	Lesser risk with thoracic surgery (54/1000 (36 to 80)) compared with 298/1000 (PSP and SSP)†
Re-admission	Not enough evidence	Not reported	No difference	Not reported	Not reported
Need for further pleural procedures	Not enough evidence	Greater need with NA (626/1000 (544 to 719) compared with 240/1000	No difference	Not reported	Not reported
Complications	Reduced post-treatment complications with conservative management*	No overall difference in complications, but may be an reduction in subcutaneous emphysema following NA (9/1000 (1 to 70) compared with 92/1000)	No difference	Not enough evidence	No difference
Pain and breathlessness	Not enough evidence	Not enough evidence	Not enough evidence	Greater need for opioids with chemical pleurodesis*	Not reported
Quality of life	Not enough evidence	Not reported	Not reported	Not reported	Not reported
Mortality	Not reported	Not reported	Not reported	Not reported	No difference

*Meta-analysis not possible, data reported in different formats.
†Meta-analysis results reported as per 1000 patients.
ICD, intercostal drainage; LOS, length of stay; NA, needle aspiration; PSP, primary spontaneous pneumothorax; SSP, secondary spontaneous pneumothorax.

- There appears to be no difference in the rate of recurrence between NA or ICD for the treatment of PSP in adults. (Very low)
- There appears to be a greater need for further pleural procedures following NA when compared with ICD for the treatment of PSP in adults. (Very low)
- The risk of overall complications following NA or ICD appear to be the same for the treatment of PSP in adults (Very low), but there may an increased risk of subcutaneous emphysema following ICD. (Low)

Ambulatory management

- There appears to be a reduction in the length of hospital stay following ambulatory management when compared with standard care for the treatment of PSP in adults. (Moderate)
- There appears to be no difference in the rate of pneumothorax recurrence, the rate of hospital re-admission, the need for pleural procedures or complications following ambulatory management or standard care for the treatment of PSP in adults. (Very low)

Chemical pleurodesis

- There appears to be no difference in the length of hospital stay following chemical pleurodesis or ICD alone for the treatment of PSP in adults. (Low)
- The risk of pneumothorax recurrence appears to be lower following chemical pleurodesis when compared with ICD alone for the treatment of PSP or SSP in adults. (Very low)
- There appears to be a greater need for opioid pain relief following chemical pleurodesis when compared with ICD alone for the treatment of PSP in adults. (Moderate)
- Although there appears to be no difference in mortality rate at time of treatment (Very low), tetracycline chemical pleurodesis may cause greater post-treatment mortality when compared with ICD alone for the treatment of pneumothorax in adults. (Very low)

Thoracic surgery

- Length of hospital stay appears to be shorter following thoracic surgery, when compared with ICD, for the treatment of PSP in adults. (Very low)
- The rate of pneumothorax recurrence appears to be reduced following thoracic surgery, when compared with ICD, for the treatment of PSP in adults. (Very low)
- Pneumonia and persistent air leak complications appear to be greater following video-assisted thoracic surgery (VATS), when compared with ICD, for the treatment of PSP in adults. (Very low)
- There appears to be no difference in the rate of mortality following thoracic surgery or ICD, for the treatment of pneumothorax in adults, with the mortality rate being very low for both treatments. (Very low)

Recommendations

- ► Conservative management can be considered for the treatment of minimally symptomatic (ie, no significant pain or breathlessness and no physiological compromise) or asymptomatic PSP in adults regardless of size. (Conditional—by consensus)
- ► Ambulatory management should be considered for the initial treatment of PSP in adults with good support, and in centres with available expertise and follow-up facilities. (Conditional)
- ► In patients not deemed suitable for conservative or ambulatory management, NA or tube drainage should be considered for the initial treatment of PSP in adults. (Conditional)

- ► Chemical pleurodesis can be considered for the prevention of recurrent SSP in adults (eg, patients with severe chronic obstructive pulmonary disease who significantly decompensated in the presence of a pneumothorax, even during/after the first episode). (Conditional)
- ► Thoracic surgery can be considered for the treatment of pneumothorax in adults at initial presentation if recurrence prevention is deemed important (eg, patients presenting with tension pneumothorax, or those in high-risk occupations). (Conditional)

Good practice points

- ✓ When establishing local ambulatory treatment pathways, planning and coordination between with the emergency department, general medicine and respiratory medicine is vital.
- ✓ When performing chemical pleurodesis for the treatment of pneumothorax in adults, adequate analgesia should be provided before and after treatment.
- ✓ All treatment options should be discussed with the patient to determine their main priority, with consideration for the least invasive option.

What is the optimal management of patients after resolution of a first episode of pneumothorax?

Recurrence following SP is a frequent concern and overall occurs in 32% of patients after a single episode of PSP[21] and 13%–39% after a first episode of SSP.[16] Current usual practice in the UK is to consider surgical intervention after the second episode of an SP to reduce subsequent further recurrences. The aim of the next question was to assess if there was evidence to support the use of surgical intervention (surgical pleurodesis or bullectomy) at an earlier stage in an elective context, prior to the first recurrence, comparing against non-surgical techniques (non-surgical talc or conservative management):

> A2 What is the optimal management of patients after resolution of a first episode of pneumothorax?

The evidence statement and GPPs are presented below; and the full evidence review is presented in online supplemental appendix A2.

Evidence statement

There was no evidence relevant to the review.

Recommendations

Due to the lack of supporting evidence, no recommendations can be made on the role of elective surgery at an earlier stage to prevent recurrence.

Good practice points

- ✓ Elective surgery may be considered for patients in whom recurrence prevention is deemed important (eg, at-risk professionals (divers, airline pilots, military personnel), or those who developed a tension pneumothorax at first episode).
- ✓ Elective surgery should be considered for patients with a second ipsilateral or first contralateral pneumothorax.
- ✓ Discharge and activity advice should be given to all patients post pneumothorax.

Discharge advice, flying and activity

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 (CXR) after 2–4 weeks to monitor resolution. Patients managed with an ambulatory device may need to be seen more frequently to monitor for complications and prompt removal at resolution.

Patients with a persistent closed pneumothorax (ie, no pleural breach or communication across the chest wall, and incompletely resolved on CXR) should not travel on commercial flights until complete radiological resolution. An exception to this is the very rare case of a loculated or chronic localised air collection which has been very carefully evaluated. In those with resolved pneumothorax confirmed radiologically (ie, at least CXR), patients can fly 7 days after the X-ray demonstrates full resolution (the rationale for waiting 7 days is to exclude early recurrence). The BTS Clinical Statement on air travel for passengers with respiratory disease (2022) addresses this with greater detail.[22] After a pneumothorax, scuba diving (ie, with pressurised gas tanks) should be discouraged permanently unless a very secure definitive prevention strategy has been performed such as surgical pleurectomy. The BTS Guidelines on respiratory aspects of fitness for diving deal with this in greater detail.[23] Smoking influences the risk of recurrence so cessation should be advised.

What is the optimal management of patients with ongoing air leak?

Most spontaneous pneumothoraces will resolve once the air leak has ceased. However, some patients will have persistent/prolonged air leak and/or failure of the lung to re-expand on CXR. There are several treatment options available including application of thoracic suction, converting to larger-bore chest drain, blood patch or chemical pleurodesis, endobronchial valves or thoracic surgery and the next clinical question asked if any of these treatment options give better clinical outcomes than ongoing chest tube drainage alone:

> A3 In adults with spontaneous pneumothorax and ongoing air leak (excluding postsurgical patients), which treatments are better than ongoing chest tube drainage alone at improving clinical outcomes?

Due to a lack of evidence, not all treatment strategies were reviewed, but the evidence statements and GPPs are presented below and the full evidence review is available in online supplemental appendix A3.

Evidence statements

- – Length of hospital stay appears to be shorter following autologous blood pleurodesis treatment, regardless of delivery method, for pneumothorax and persistent air leak in adults when compared with chest drainage alone. (Ungraded)
- – There was no evidence to suggest that the application of suction is beneficial to treat pneumothorax and persistent air leak in adults.
- – Limited evidence suggests that endobronchial therapies may have the potential to treat pneumothorax and persistent air leak. (Ungraded)

Table 5 Evidence review summary for 'What is the optimal surgical approach when performing surgery?'

Clinical outcome	Summary of evidence review (VATS vs thoracotomy) (95% CI)
Length of hospital stay	3.66 days shorter (3.40 to 3.91) with VATS*
Pneumothorax recurrence	Slightly higher with VATS (31/1000 (23 to 41) compared with 15/1000) but low with both surgical techniques*
Need for further treatment	Slightly higher with VATS (59/1000 (37 to 94) compared with 31/1000)*
Complications	Reduced with VATS (99/1000 (88 to 112) compared with 138/1000)*
Pain and breathlessness	Reduced need for postoperative analgesia with VATS†
Duration of air leak	Not reported in any study
Quality of life	Not reported in any study
Mortality	No difference

*Meta-analysis results reported as per 1000 patients.
†Meta-analysis not possible, data reported in different formats.
VATS, video-assisted thoracoscopy surgery.

Recommendations

There is insufficient evidence to make any recommendations on the best treatment method for pneumothorax and persistent air leak in adults.

Good practice point

✓ If a patient is not considered fit for surgery, autologous blood pleurodesis or endobronchial therapies should be considered for the treatment of pneumothorax with persistent air leak in adults (please refer to the BTS Clinical Statement on Pleural Procedures).[1]

What is the optimal surgical approach when performing surgery?

Pneumothorax can be treated surgically, either acutely to treat a persistent air leak or prevent recurrence in patients whose initial pneumothorax has resolved. Surgery can be via thoracotomy, that is, an open incision into the pleural cavity, or via VATS, whereby instruments are introduced into the pleural cavity via ports in the chest wall. Within these two categories, there is significant variation, particularly in the size of incision and number of ports. Both approaches allow access to the pleural space to perform bullectomy, pleurodesis or pleurectomy as required, but there may be significant differences in key outcomes. Hence, the aim of this review was to compare these two main surgical approaches for the treatment of adults with pneumothorax:

> A4 For adults with pneumothorax, what is the optimal surgical approach when performing surgery?

A summary of the evidence review is shown in table 5 and the evidence statements and recommendations are presented below. The full evidence review is presented in online supplemental appendix A4.

Evidence statements

– The rate of pneumothorax recurrence after surgical intervention appears to be very low. However, pneumothorax recurrence rate and the need for further procedures appear to be slightly increased following VATS when compared with thoracotomy. (Very low)
– Length of hospital stay, postoperative pain and complications appear to be reduced following VATS when compared with thoracotomy. (Very low)

Recommendations

► Video-assisted thoracoscopy access can be considered for surgical pleurodesis in the general management of pneumothorax in adults. (Conditional)
► Thoracotomy access and surgical pleurodesis should be considered for the lowest level of recurrence risk required for specific (eg, high-risk) occupations. (Conditional)

There is no evidence on which to base the ideal timing for thoracic surgical intervention in cases of persistent air leak. The BTS 2010 pleural guidelines advised thoracic surgical opinion at 3–5 days to balance the risks of ongoing air leak and potentially unnecessary surgical procedures.[5] 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. Patient choice should inform the decision, weighing the benefits of a reduced recurrence risk against that of chronic pain and paraesthesia. Accepted indications for surgical advice are as follows:

- First pneumothorax presentation associated with tension and first secondary pneumothorax associated with significant physiological compromise;
- Second ipsilateral pneumothorax;
- First contralateral pneumothorax;
- Synchronous bilateral SP;
- Persistent air leak (despite 5–7 days of chest tube drainage) or failure of lung re-expansion;
- Spontaneous haemothorax;
- Professions at risk (eg, pilots, divers), even after a single episode of pneumothorax;
- Pregnancy.

What is the optimal operation when performing surgery?

Thoracic surgery for pneumothorax can be broadly divided into two different types:

i. Resection of lung parenchyma (often visible blebs which are usually <1–2 cm and subpleural, or bullae which are usually >1–2 cm, although the terms are used interchangeably) to remove the suspected source of the current air leak and prevent future potential sources of air leaks; and
ii. Surgical pleurodesis to obliterate the pleural space via an inflammatory symphysis of the visceral and parietal pleura to prevent the accumulation of air within that space and prevent any future episodes of pneumothorax.

The former requires a 'bullectomy', a form of wedge resection using stapler equipment, and can also include the use of a 'sealant' (such as glue and a mesh) to further fortify the site of lung resection. The latter can be achieved through a number of different methods intra-operatively including pleural abrasion, partial pleurectomy and talc poudrage. The next question compares these two main types of pneumothorax surgery for the treatment of SP in adults:

> A5 In adults with spontaneous pneumothorax what is the optimal operation for improving clinical outcomes?

A summary of the evidence review is shown in table 6 and the evidence statements and recommendation are presented below. The full evidence review is presented in online supplemental appendix A5.

Table 6 Evidence review summary for 'What is the optimal operation when performing surgery?'

Clinical outcome	Summary of evidence review (bullectomy vs surgical pleurodesis)
Length of hospital stay	No overall difference, but inconsistency between studies
Pneumothorax recurrence	No difference
Need for further treatment	No difference
Complications	No difference
Pain and breathlessness	Not enough evidence
Duration of air leak	No difference
Quality of life	Not reported
Mortality	No difference

Evidence statements

- There appears to be no difference in pneumothorax recurrence (Very low), length of hospital stay (Very low), the need for further treatment (surgery, chest drain or conservative management) (Very low), duration of air leak (Very low), complications (Very low) or mortality (Very low) following bullectomy or surgical pleurodesis for the treatment of SP in adults.
- There is insufficient evidence to comment on pain and breathlessness and quality of life following bullectomy or surgical pleurodesis for the treatment of SP in adults.

Recommendation

► Surgical pleurodesis and/or bullectomy should be considered for the treatment of SP in adults. (Conditional)

Other areas of clinical importance not covered by the clinical questions

Some areas of clinical importance which have not been covered by the guideline clinical questions are included below as a guide for clinicians.

Pregnancy

Pneumothorax in pregnancy can pose risks to the mother and fetus. Physiological changes during pregnancy increase the maternal oxygen consumption and the accelerated pattern of breathing in pregnant subjects may heighten the risk of further bleb rupture.[24] 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 or chest tube drainage can be used.

Oxygen consumption can increase by 50% during labour and repeated Valsalva manoeuvres during spontaneous delivery may increase the intrathoracic pressures, increasing the size of the pneumothorax.[24] 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, close liaison with the obstetric team is required on the safest approach for both mother and baby and may take the form of elective assisted delivery at or near term, with regional (epidural) anaesthesia. If caesarean section is unavoidable because of obstetric considerations, then a spinal anaesthetic is preferable to a general anaesthetic.

Catamenial pneumothorax

The typical combination of chest pain, dyspnoea and haemoptysis occurring within 72 hours before or after menstruation in young women should prompt consideration of catamenial pneumothorax. The true incidence is unknown among women undergoing routine surgical treatment for recurrent pneumothorax, catamenial pneumothorax has been diagnosed in as many as 25%.[25] Thus, it may be relatively underdiagnosed, and should be suspected in female patients who have recurrent pneumothoraces.

The associated pneumothorax is usually right-sided and there is a heightened tendency to recurrence coinciding with the menstrual cycle. Patients have a history of pelvic endometriosis.[26] 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, which may be present on the visceral pleural surface. 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.

Management of catamenial pneumothorax should be multidisciplinary and include hormonal treatment or surgery by VATS. Medical therapy to achieve ovarian rest is often advocated in the postoperative period.[27]

Pneumothorax and cystic fibrosis

SSP remains a common complication of cystic fibrosis, occurring in 0.64% of patients per annum and 3.4% of patients overall.[28] 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.[29] Contralateral pneumothoraces occur in up to 40%.[29 30] An increased morbidity also results, with increased hospitalisation and a measurable decline in lung function.[28] 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 reduce recurrence.[31–33] Partial pleurectomy is generally regarded as the treatment of choice in patients with recurrent unilateral pneumothoraces or evidence of bilateral pneumothorax, with chemical pleurodesis an alternative strategy in those not deemed fit for surgery.[29]

Surgical emphysema

Please refer to the 'Intercostal drain insertion, troubleshooting' section in the BTS Clinical Statement on Pleural Procedures for information on surgical emphysema.[1]

Iatrogenic and traumatic pneumothorax

Traumatic pneumothorax is a distinct entity from SP, with its own considerations including diagnosis (often made on trauma CTs) and treatment requirements (patients may require positive pressure ventilation), and hence not specifically addressed in this guideline. The GDG are however aware of ongoing randomised trials which are addressing conservative management in this population. Iatrogenic pneumothorax (eg, post-CT-guided lung biopsy or pacemaker insertion) is also a different entity to SP.

Good quality data on iatrogenic pneumothorax optimal management is required, but in general, these pneumothoraces tend to resolve more easily and intervention may not be required.

Familial pneumothorax

Around 10% of pneumothorax cases in some series have a family history of pneumothorax, and in such cases, clinicians should seek potential familial causes. These include Birt-Hogg-Dubé syndrome, tuberous sclerosis complex, lymphangioleiomyomatosis and connective tissue disorders such as Marfan syndrome and Ehlers-Danlos syndrome. If a familial pneumothorax is suspected, CT imaging would always be part of the standard workup and advice from specialists in this area, or specialist pneumothorax clinics, should be considered.

INVESTIGATION OF THE UNDIAGNOSED UNILATERAL PLEURAL EFFUSION

Introduction

Pleural effusions are a common medical problem with >60 recognised causes including disease local to the pleura or underlying lung, systemic conditions, organ dysfunction and drugs.

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, in order to facilitate treatment (for common causes of pleural effusion please refer to Tables 2, 4 and 6 of Appendix 1, Unilateral pleural effusion diagnostic pathway).

A careful history and physical examination of the patient remains the most important first step when evaluating someone with an undiagnosed pleural effusion. The likely cause can often be elucidated by careful history taking, which will then allow directed further investigations. The patient's drug history should always be recorded, as a number of medications have been reported to cause exudative pleural effusions. A useful resource can be found by downloading the Pneumotox app, which contains comprehensive data in this regard (available from the Apple App Store and Google Play). Interestingly, since the management of a malignant pleural effusion (MPE): British Thoracic Society Pleural Disease Guideline 2010,[6] the frequency of causative drugs has changed with the most common drug implicated as causing exudative pleural effusions being tyrosine kinase inhibitors. A detailed occupational history, including any previous asbestos exposure is also vital information when investigating all pleural effusions.

Thoracic ultrasound (TUS) is now an extension of the physician's arm and has never been as important, both as a diagnostic tool and to improve the safety of invasive procedures. TUS should be performed on every patient at their initial presentation and again whenever a pleural procedure is being performed. The initial TUS evaluation will help to answer the question 'Is it safe to perform a diagnostic aspiration?' However, it will also provide information on the size and character of the effusion. Signs of malignancy with nodularity of the diaphragm and parietal pleural are highly suggestive of malignancy and assist in optimising the patient pathway and streamlining investigations.

If it is not safe to proceed with a pleural aspiration, a CT scan should be obtained as the next step. If malignancy is suspected, the CT scan should include the chest, abdomen and pelvis; if malignancy is not likely, then a CT of the thorax with pleural contrast (venous phase) should be performed.

When a firm diagnosis cannot be made, it is sensible to reconsider diagnoses with a specific treatment (eg, tuberculosis (TB), pulmonary embolism, lymphoma, IgG4 disease and chronic heart failure) (refer to box 1 in Appendix 1, Unilateral pleural effusion diagnostic pathway). Watchful waiting with interval CT scans is often an appropriate management strategy in this setting and also in those with a persistent pleural effusion that is too small to sample.

Diagnosing pleural effusion

Pleural effusion can be diagnosed using radiology, pleural aspiration or pleural biopsy, so the clinical questions in this section were focused on determining the optimal method(s) for diagnosing unilateral pleural effusion in adults:

- What is the diagnostic accuracy of radiology? (Question B1)
- Is image-guided intervention better than non-image-guided intervention? (Question B2)
- What is the optimal volume and container for a pleural aspiration sample? (Question B3)
- What is the diagnostic accuracy of pleural fluid tests (biomarkers)? (Question B4)
- What is the diagnostic accuracy of serum biomarkers? (Question B5)
- What is the diagnostic accuracy of pleural biopsy? (Question B6)

What is the diagnostic accuracy of radiology?

Radiological tests form a key role in the detection and diagnostic pathway of a unilateral pleural effusion in adults and may include CXR, CT, TUS, positron emission tomography-CT (PET-CT) and MRI. The first clinical question in the 'Investigation of the undiagnosed unilateral pleural effusion' section reviews the diagnostic accuracy of radiology when investigating unilateral pleural effusions of benign aetiology:

> B1 What is the diagnostic accuracy of radiology when diagnosing benign pleural disease as a cause of unilateral pleural effusion in adults?

Please note that the diagnostic accuracy of radiological tests for distinguishing benign from malignant disease is addressed in the 'Pleural malignancy' subsection 'Which imaging modality is best for diagnosing adults with suspected pleural malignancy?'.

An overview of the evidence review is shown in the 'Pleural infection' and 'Non-infective causes of unilateral pleural effusions' subsections below, followed by the evidence statements and GPPs. The full evidence review is available in online supplemental appendix B1.

Pleural infection

The absence of malignant radiological features (circumferential pleural thickening with nodularity involving the mediastinal surface) is suggestive of a benign pleural effusion, but there is overlap in the imaging features of malignancy and infection. On CT, features that are more common in pleural infection (parapneumonic, empyema and TB) than malignancy are[34 35]:

i. Lentiform configuration of pleural fluid;
ii. Visceral pleural thickening ('split pleura sign');
iii. Hypertrophy of extrapleural fat (>2 mm);
iv. Increased density of the extrapleural fat;
v. Presence of pulmonary consolidation.

Table 7 Ancillary imaging observations potentially linked to the aetiology of a unilateral pleural effusion

Aetiology	Examples of ancillary findings
Benign asbestos pleural effusion	Calcified pleural plaques may be present
Cardiac dysfunction	Usually bilateral; cardiomegaly; pericardial effusion
Postcardiac surgery	Temporal relationship with surgery; usually left sided
Traumatic	Rib fractures; signs of active bleeding on CT; high density on CT in the acute phase
Abdominopelvic pathology	Signs of cirrhosis; adnexal mass

However, poor sensitivity of these features (0.20–0.48) highlights the need for diagnostic thoracentesis in unexplained pleural effusions to allow pleural fluid characterisation.

Malignancy can also co-exist with pleural infection, with synchronous disease processes found in approximately 5% of cases.[36 37] In this context, the presence of a mass involving the extrapleural fat and mediastinal pleural thickening may be markers of co-existent malignancy,[37] but common clinical practice is to perform follow-up imaging for up to 2 years to exclude occult disease if there are ongoing symptoms or other clinically concerning features.

TB pleuritis may mimic malignancy with circumferential pleural thickening >1 cm, involvement of the mediastinal surface and nodularity,[35] but, unlike malignancy, is not associated with chest wall invasion.[38] On ultrasound, tuberculous effusions tend to be highly complex with internal septations, unlike malignancy, and in lymphocyte-rich pleural effusions, the presence of complex internal septation is reported as predictive of TB.[39]

Non-infective causes of unilateral pleural effusions

Pleural effusions due to non-infective inflammatory causes, including rheumatoid arthritis, Dressler syndrome, organising pneumonia, pulmonary emboli and benign asbestos-related pleural effusion, are typically bland in appearance on CT, showing mild smooth thickening of the parietal pleura not involving the mediastinum.[34] Chronic inflammatory effusions are commonly associated with the development of pleuroparenchymal bands and subsequently folded lung. In many cases, aetiology of pleural effusion may be inferred based on circumstantial findings (table 7).

Evidence statements

- CT features such as lentiform pleural collection, enhancement of the visceral pleura, adjacent hypertrophied extrapleural fat of increased density and an absence of malignant features may suggest pleural infection over malignancy. (Ungraded)
- TB may mimic malignancy on imaging. (Ungraded)
- Malignancy may co-exist with pleural infection. (Ungraded)
- In the context of pleural infection, PET-CT is not a useful test to identify pleural malignancy. (Ungraded)
- Assessment of extrathoracic structures on imaging may provide clues to underlying aetiology. (Ungraded)

Recommendations

There is not enough evidence to make any recommendations.

Good practice points

- ✓ Imaging findings of a unilateral pleural effusion should be interpreted in the context of clinical history and knowledge of pleural fluid characteristics.
- ✓ CT follow-up should be considered for patients presenting with pleural infection to exclude occult malignancy if there are ongoing symptoms, or other clinically concerning features.
- ✓ PET-CT should not be used in the assessment of pleural infection.

Is image-guided intervention better than non-image-guided intervention?

Thoracentesis (pleural aspiration) is a key intervention for both diagnostic and therapeutic purposes in the investigation and management of the patient with a unilateral pleural effusion. The use of TUS immediately prior to pleural intervention for suspected fluid has been strongly advocated as a means of improving patient safety by reducing the frequency of iatrogenic complications and improving diagnostic yield. This is different to the temporally and geographically remote use of TUS prior to pleural intervention, also known as the 'X marks the spot' technique. The next clinical question therefore assesses whether image-guided (ie, ultrasound-assisted techniques where the anatomy is confirmed on ultrasound and an intervention is immediately conducted and 'real time' or ultrasound guided where needles are watched under ultrasound into the pleural space) intervention has better clinical outcomes when compared with non-image-guided intervention in adult patients with suspected unilateral pleural effusion:

> B2 For adults with suspected unilateral pleural effusion, is image-guided intervention better than non-image-guided intervention at improving clinical outcomes?

A summary of the evidence is shown in table 8 and the evidence statements and recommendation are presented below. The full evidence review is available in online supplemental appendix B2.

Evidence statements

- The use of ultrasound guidance immediately prior to thoracentesis appears to reduce the risk of pneumothorax when compared with non-image-guided thoracentesis. (Very low)
- Image-guided thoracentesis appears to reduce the risk of pneumothorax when compared with non-image-guided thoracentesis. (Very low)
- Image-guided thoracentesis appears to improve the rate of successful fluid sampling when compared with non-image-guided thoracentesis. (Very low)
- Length of hospital stay does not appear to be reduced if choosing image-guided thoracentesis over non-image-guided thoracentesis. (Ungraded)

Box 1 Diagnostic test definitions

- Definitive diagnosis: A final diagnosis made after getting the results of tests, such as blood tests or biopsies.[66]
- Diagnostic yield: The likelihood that a test or procedure will provide the information needed to establish a diagnosis.[67]
- Sensitivity: The conditional probability that a person having a disease will be correctly identified by a clinical test.[67]
- Specificity: The probability that a person not having a disease will be correctly identified by a clinical test.[67]

Table 8 Evidence review summary for 'Is image-guided intervention better than non-image-guided intervention?'

Clinical outcome	Summary of evidence review (image-guided intervention vs non-image-guided intervention) (95% CI)
Length of hospital stay	No difference
Success of obtaining pleural fluid	Increased success with image-guided intervention (1000/1000 (923 to 1000) compared with 782/1000)*
Need for another procedure	Not reported
Complications—bleeding	No difference and very small risk of bleeding with both techniques (≈3/1000)†
Complications—pneumothorax	Less risk with image-guided intervention (38/1000 (33 to 43) compared with 50/1000)*
Mortality	Not reported

*Meta-analysis results reported as per 1000 patients.
†Data reported as per 1000 patients.

Recommendation

► Image-guided thoracentesis should always be used to reduce the risk of complications. (Strong—by consensus)

What is the optimal volume and container for a pleural aspiration sample?

Increasing the volume of pleural fluid in a pleural aspiration sample may aid in the cytological diagnosis of malignancy and understanding the optimal volume and container should allow optimisation of clinical pathways for the diagnosis of pleural malignancy and infection. Hence, the next clinical question is:

> B3 What is the optimal volume and container for a pleural aspiration sample when diagnosing unilateral pleural effusion in adults?

The evidence statements, recommendations and GPPs are presented below, and the full evidence review is available in online supplemental appendix B3.

Evidence statements

Based on a narrative review:

– The evidence does not support an optimal pleural fluid volume for initial cytological diagnosis but suggests that increasing pleural fluid volume above 50 mL provides no diagnostic benefit. (Ungraded)
– The evidence supports the use of aerobic blood culture bottles, anaerobic blood culture bottles and plain ('white top') containers when investigating suspected pleural infection. (Ungraded)

Recommendations

► 25–50 mL of pleural fluid should be submitted for cytological analysis in patients with suspected MPE. (Strong—by consensus)
► Pleural fluid should be sent in both plain and blood culture bottle tubes in patients with suspected pleural infection. (Strong—by consensus)

Good practice points

✓ At least 25 mL, and where possible 50 mL, of pleural fluid should be sent for initial cytological examination.
✓ If volumes of ≥25 mL cannot be achieved, smaller volumes should be sent, but clinicians should be aware of the reduced sensitivity.
✓ If small volume aspirate (<25 mL) has been non-diagnostic, a larger volume should be sent, if achievable, except when there is high suspicion of a tumour type associated with low pleural fluid cytology sensitivity (especially mesothelioma).
✓ Pleural fluid samples should be processed by direct smear and cell block preparation.
✓ In patients with an undiagnosed pleural effusion where pleural infection is possible and volume of fluid sample available allows, microbiological samples should be sent in both white top containers and volumes of 5–10 mL inoculated into (aerobic and anaerobic) blood culture bottles.
✓ In cases where volume available does not allow 5–10 mL inoculation, volumes of 2–5 mL should be prioritised to blood culture bottles rather than a plain, sterile container.

What is the diagnostic accuracy of pleural fluid tests (biomarkers)?

Unilateral pleural effusion may result from a variety of diseases, including malignant, inflammatory, infectious and cardiovascular illnesses. Pleural fluid aspiration facilitates measurement of various disease biomarkers. If accurate, pleural fluid tests may obviate the need for pleural biopsy or other investigations and facilitate early treatment initiation, including early ICD in patients with complex PPE or empyema, so the next question asked:

> B4 What is the diagnostic accuracy of pleural fluid tests when diagnosing adult patients with unilateral pleural effusion?

To address this question, it was first necessary to define the disease states that are of clinical interest in adults presenting with unilateral effusion, and to define a relevant gold standard

Table 9 Reviewed disease state subgroups and associated gold standards

Disease state	Gold standard
Secondary pleural malignancy	Malignant fluid cytology or pleural biopsy, or malignant pleural nodules/thickening on imaging and confirmed extrapleural primary cancer.
Tuberculous pleural effusion (TPE)	Clinical composite, including definite TPE (AAFB in pleural tissue or fluid culture, or sputum AAFB plus effusion) and probable TB (granulomatous histology or lymphocytic fluid, effusion resolved after TB therapy and other causes excluded).
Heart failure	Clinical composite including reduced LVEF on echo±MRI.
Complex parapneumonic effusion or empyema	Clinical composite including evidence of infection plus purulent fluid, positive culture or Gram's stain, fluid pH <7.2.
Autoimmune pleuritis	Clinical compositive based on all available data.

AAFB, acid alcohol fast bacilli; LVEF, left ventricular ejection fraction.

Table 10 Summary of the diagnostic accuracies of secondary pleural malignancy pleural biomarkers

Biomarker	Contributing studies (n)	Sensitivity (95% CI)	Specificity (95% CI)
Cytology	7	0.46 (0.40 to 0.52)	1.00 (0.00 to 1.00)
CEA	8	0.54 (0.40 to 0.68)	1.00 (0.96 to 1.00)
CYFRA21-1	3	0.58 (0.48 to 0.67)	0.88 (0.78 to 0.94)
CA19-9	3	0.22 (0.18 0.27)	1.00 (0.00 to 1.00)
CA15-3	6	0.44 (0.39 to 0.50)	0.99 (0.97 to 1.00)
CA72-4	3	0.38 (0.30 to 0.46)	0.99 (0.97 to 1.00)

CA15-3, cancer antigen 15-3; CA19-9, carbohydrate antigen 19-9; CA72-4, cancer antigen 72-4; CEA, carcinoembryonic antigen; CYFRA21-1, fragment of cytokeratin 19.

for each (table 9). The index tests reviewed vary with the target disease resulting in five subquestions, each containing relevant index test gold standard pairs.

A summary of the evidence review for each disease state (table 9) is shown in subsections below, followed by the evidence statements, recommendation and GPPs. The full evidence review is available in online supplemental appendix B4.

Secondary pleural malignancy

A summary of the diagnostic accuracies of cytology and pleural biomarkers carcinoembryonic antigen (CEA), fragment of cytokeratin 19 (CYFRA21-1), carbohydrate antigen 19-9 (CA19-9), cancer antigen 15-3 (CA15-3) and cancer antigen 72-4 (CA72-4) for diagnosing secondary pleural malignancy are shown in table 10.

Tuberculous pleural effusion

The point estimate diagnostic accuracies of pleural biomarkers adenosine deaminase (ADA) and interferon gamma (IFN-gamma) for diagnosing tuberculous pleural effusion are shown in table 11.

Heart failure

The point estimate diagnostic accuracy of pleural fluid N-terminal prohormone brain natriuretic peptide (NT-proBNP) for diagnosing heart failure pleural effusion is shown in table 12.

Pleural infection (complex parapneumonic effusion or empyema)

No studies directly investigated the diagnostic accuracy of pleural fluid tests for diagnosing pleural infection (complex parapneumonic effusion (CPPE) or empyema). This was primarily due to the use of inappropriate reference standards, failure to adequately describe reference standards used, discovery biomarker analyses without validation and the use of biomarkers for prognostic, not diagnostic, analyses.

Table 11 Summary of the diagnostic accuracies of tuberculous pleural effusion pleural biomarkers

Biomarker	Contributing studies (n)	Sensitivity (95% CI)	Specificity (95% CI)
ADA	24	0.91 (0.87 to 0.93)	0.88 (0.86 to 0.93)
IFN-gamma	6	0.95 (0.85 to 0.98)	0.96 (0.90 to 0.98)

ADA, adenosine deaminase; IFN-gamma, interferon gamma.

Table 12 Summary of the diagnostic accuracy of heart failure pleural effusion pleural biomarkers

Biomarker	Contributing studies (n)	Sensitivity (95% CI)	Specificity (95% CI)
NT-proBNP	5	0.93 (0.88 to 0.96)	0.93 (0.86 to 0.97)

NT-proBNP, N-terminal pro hormone BNP.

Autoimmune pleuritis (lupus pleuritis)

The point estimate sensitivity and specificity of pleural fluid antinuclear antibody (ANA) for diagnosing lupus pleuritis is shown in table 13.

Evidence statements

- Pleural fluid biomarkers do not provide improved sensitivity, when compared with cytology, for diagnosing secondary pleural malignancy. (Low)
- Pleural fluid ADA and IFN-gamma provide high sensitivity and specificity for diagnosing tuberculous pleural effusion. (Very low)
- Pleural fluid NT-proBNP provides high sensitivity and specificity for diagnosing heart failure in patients with unilateral pleural effusion. (Very low)
- Pleural fluid ANA provides high sensitivity and specificity for diagnosing lupus pleural effusion. (Low)

Recommendations

- ► Pleural fluid cytology should be used as an initial diagnostic test in patients with suspected secondary pleural malignancy, accepting that a negative cytology should lead to consideration of further investigation. (Conditional)
- ► Pleural fluid biomarkers should not be used for diagnosing secondary pleural malignancy. (Conditional)
- ► In high prevalence populations, pleural fluid ADA and/or IFN-gamma test(s) can be considered for diagnosing tuberculous pleural effusion. (Conditional)
- ► In low prevalence populations, pleural fluid ADA can be considered as an exclusion test for tuberculous pleural effusion. (Conditional)
- ► Tissue sampling for culture and sensitivity should be the preferred option for all patients with suspected tuberculous pleural effusion. (Strong—by consensus)
- ► Pleural fluid ANA should be considered to support a diagnosis of lupus pleuritis. (Conditional)

Good practice points

- ✓ The clinical utility of pleural fluid cytology varies by tumour subtype, including diagnostic sensitivity and predictive value for response to subsequent cancer therapies. This should be taken into consideration when planning the most suitable diagnostic strategy (eg, direct biopsies in those with a likely low cytological yield can be considered).

Table 13 Summary of the diagnostic accuracy of lupus pleuritis pleural biomarkers

Biomarker	Contributing studies (n)	Sensitivity (95% CI)	Specificity (95% CI)
ANA	4	0.94 (0.72 to 0.99)	0.87 (0.77 to 0.93)

ANA, antinuclear antibody.

Table 14 Summary of the diagnostic accuracies of secondary pleural malignancy serum biomarkers

Biomarker	Studies (n)	Cut-point	Sensitivity	Specificity
CRP	1	35.5 mg/L	0.71	0.56
CYFRA21-1	1	3.12 ng/mL	0.71	0.93
CEA	1	3.35 mg/L	0.57	0.93
CA15-3	1	30.86 ng/mL	0.49	0.93

CA15-3, cancer antigen 15-3; CEA, carcinoembryonic antigen; CRP, C reactive protein; CYFRA21-1, fragment of cytokeratin 19.

✓ Pleural fluid NT-proBNP is useful when considering heart failure as a cause in unilateral pleural effusions but not superior to serum NT-proBNP and therefore should not be ordered routinely.

What is the diagnostic accuracy of serum biomarkers?

Unilateral pleural effusion may result from a variety of conditions, including malignant, inflammatory, infectious and cardiovascular illnesses. Serum biomarkers that directly reflect underlying pathophysiology have the potential to shorten diagnostic pathways, either by obviating the need for invasive pleural investigations or by directing interventions such as tissue biopsy or fluid drainage. As for the review on pleural fluid tests ('What is the diagnostic accuracy of pleural fluid tests (biomarkers)?' section above), it was again necessary to define the disease states that are of clinical interest in adults presenting with unilateral effusion and to define a relevant gold standard for each (please see table 9 for details), as the index tests reviewed varied with target disease. The next clinical question was:

> B5 What is the diagnostic accuracy of serum biomarkers when diagnosing adult patients with unilateral pleural effusion?

A summary of the evidence review for each disease state (table 9) is shown in the 'Secondary pleural malignancy', 'Tuberculous pleural effusion', 'Heart failure' and 'Pleural infection (CPPE or empyema) and autoimmune pleuritis' subsections below. This is followed by evidence statements, recommendation and GPPs and the full evidence review is available in online supplemental appendix B5.

Secondary pleural malignancy

The sensitivity and specificity of serum CA15-3, CEA, C reactive protein (CRP) and CYFRA21-1 for diagnosing secondary pleural malignancy is shown in table 14. Please note that all presented data are based on data from single studies.

Tuberculous pleural effusion

The diagnostic accuracies of serum biomarkers T-spot and TB antibody for diagnosing tuberculous pleural effusion are shown in table 15. Please note again that the presented data come from single studies.

Table 15 Summary of the diagnostic accuracies of tuberculous pleural effusion serum biomarkers

Biomarker	Studies (n)	TPE prevalence	Sensitivity (95% CI)	Specificity (95% CI)
T-spot	1	41%	0.93 (0.83 to 0.97)	0.69 (0.58 to 0.78)
TB antibody	1	68%	0.48 (0.35 to 0.61)	0.76 (0.55 to 0.89)

TB, tuberculosis; TPE, tuberculous pleural effusion.

Table 16 Summary of the diagnostic accuracy of heart failure pleural effusion serum biomarkers

Biomarker	Contributing studies (n)	Sensitivity (95% CI)	Specificity (95% CI)
NT-proBNP	4	0.90 (0.84 to 0.94)	0.88 (0.71 to 0.96)

NT-proBNP, N-terminal prohormone brain natriuretic peptide.

Heart failure

The diagnostic accuracy of NT-proBNP as a diagnostic serum biomarker for diagnosing heart failure in patients with unilateral pleural effusion is shown in table 16.

Pleural infection (CPPE or empyema) and autoimmune pleuritis

No studies directly reported on the diagnostic accuracy of serum biomarkers to diagnose CPPE, empyema or autoimmune pleuritis in patients with unilateral pleural effusion.

Evidence statements

- Serum NT-proBNP provides high sensitivity and specificity for diagnosing heart failure in patients with unilateral pleural effusion. (Low)
- There is insufficient evidence to support the use of serum biomarkers to diagnose secondary pleural malignancy, pleural infection, tuberculous pleural effusion or autoimmune pleuritis in patients with unilateral pleural effusion.

Recommendation

► Serum NT-proBNP should be considered to support a diagnosis of heart failure in patients with unilateral pleural effusion suspected of having heart failure. (Conditional)

Good practice points

✓ Serum biomarkers should not currently be used to diagnose secondary pleural malignancy, pleural infection or autoimmune pleuritis.

✓ Serum biomarkers should not routinely be used to diagnose tuberculous pleural effusion, but may be considered in high prevalence areas.

✓ Serum biomarkers, including NT-proBNP, should not be used in isolation for diagnosing unilateral pleural effusion as multiple conditions may co-exist.

What is the diagnostic accuracy of pleural biopsy?

Obtaining pleural tissue is often necessary to achieve definitive diagnosis in patients presenting with pleural effusion and/or thickening. There are a variety of pleural biopsy techniques (see the BTS Clinical Statement on Pleural Procedures for further details[1]) and the aim of the final clinical question in this section was to assess which biopsy method(s) is/are best for achieving accurate histological diagnosis:

> B6 What is the diagnostic accuracy of pleural biopsy in adults with suspected pleural disease?

Large heterogeneity in study methodology and result reporting made meta-analysis impossible, so a pragmatic approach was adopted to achieve a structured stepwise narrative approach, focusing on studies where direct comparative data were available. Confirming a diagnosis of malignant pleural disease or pleural infection, specifically tuberculous pleuritis, were both considered. Making a histological diagnosis of non-specific pleuritis (also referred to as other terms such as fibrinous pleurisy

Table 17 Evidence review summary of 'What is the diagnostic accuracy of pleural biopsy?'

Comparison	Summary of evidence review
Medical versus surgical thoracoscopic pleural biopsy	No difference in diagnostic yield, sensitivity or specificity*
Medical rigid versus medical semi-rigid thoracoscopic pleural biopsy	No difference in 'intention to treat' or 'biopsy successfully obtained' diagnostic yield
Thoracoscopic pleural biopsy versus image-guided closed pleural biopsy	Definitive diagnosis and diagnostic yield higher with thoracoscopic pleural biopsy (p=0.04 for both)
Thoracoscopic pleural biopsy versus blind closed pleural biopsy	Definitive diagnosis and diagnostic yield higher with thoracoscopic pleural biopsy (p=0.01 and 0.03, respectively)
CT-guided closed pleural biopsy versus ultrasound-guided closed pleural biopsy	No difference in definitive diagnosis
Closed pleural biopsy using core needle versus Abrams needle	Higher diagnostic yield with Abrams needle (p=0.02)*
Image-guided closed pleural biopsy versus blind closed pleural biopsy	Higher diagnostic yield with image-guided closed pleural biopsy (p=0.01)
Medical—awake thoracoscopic pleural biopsy, surgical—video-assisted thoracoscopy surgery pleural biopsy under general anaesthesia. *Based on a single study.	

and pleural fibrosis) was also considered a genuine and clinically relevant finding when followed-up for at least 12 months.

A summary of the evidence review is shown in table 17 using the definitions shown in box 1.

The evidence statements and recommendations are shown below and the full evidence review is available in online supplemental appendix B6.

Evidence statements

- There is insufficient evidence to determine the diagnostic test performance comparing awake thoracoscopic pleural biopsy and video-assisted thoracoscopic pleural biopsy under general anaesthesia. (Ungraded)
- There is no difference in diagnostic yield when using rigid thoracoscopy or semi-rigid thoracoscopy to obtain a pleural biopsy. (Low)
- Definitive diagnosis is more likely with thoracoscopic pleural biopsy when compared with image-guided closed pleural biopsy. (Low)
- Diagnostic accuracy appears to be higher with thoracoscopic pleural biopsy when compared with image-guided closed pleural biopsy. (Ungraded)
- Definitive diagnosis is more likely with thoracoscopic pleural biopsy when compared with blind closed pleural biopsy. (Ungraded)
- Diagnostic yield appears to be higher with thoracoscopic pleural biopsy when compared with blind closed pleural biopsy. (Very low)
- There is no difference in diagnostic accuracy between CT-guided closed pleural biopsy and ultrasound-guided closed pleural biopsy. (Very low)
- Image-guided closed pleural biopsy may increase definitive diagnosis and diagnostic accuracy when compared with blind closed pleural biopsy (for malignant disease and tuberculous pleuritis). (Ungraded)

Recommendations

- ► Thoracoscopic or image-guided pleural biopsy may be used depending on the clinical indication and local availability of techniques (including need for control of pleural fluid). (Strong)
- ► Blind (non-image-guided) pleural biopsies should not be conducted. (Strong—by consensus)

PLEURAL INFECTION

Introduction

Pleural infection remains a common medical problem with significant mortality and morbidity despite a better understanding of the aetiology, pathophysiology and recent advances in management approaches. With a combined incidence of over 80 000 cases per annum in the USA and the UK, and an incidence of 11.2 cases per 100 000 population per year in the UK, pleural infection continues to cause a considerable burden to health systems.[40]

A number of studies have been published demonstrating that the incidence of pleural infection is increasing across the Western world,[41–43] including recent data from the UK,[44] and the precise cause of the increase in infection rate, especially in the elderly population, is as yet unclear.

This guideline is intended to address key areas of new evidence since publication of the last BTS Guideline in 2010,[7] which included the specific following questions addressing adults with pleural infection:

- What is the best predictor of clinical outcomes? (Question C1)
- Do pleural fluid or radiology parameters accurately determine which patients should be treated with ICD? (Question C2)
- What initial drainage strategy provides the best clinical outcomes? (Question C3)
- Does intrapleural therapy improve outcomes compared with other treatment options (eg, drainage alone or surgical intervention)? (Question C4)
- Which surgical approach provides the best clinical outcomes? (Question C5)
- Which method of surgery provides the best clinical outcomes? (Question C6)

Areas of clinical importance not covered by the guideline questions are discussed in the 'Pleural infection, Other areas of clinical importance not covered by the clinical questions' section.

Other specific areas that have not been covered in this guideline can be referenced from the Management of pleural infection in adults: British Thoracic Society Pleural Disease Guideline 2010, including pathophysiology and the developmental stages of pleural infection.[7]

Definitions and treatment principles

Pleural infection is defined as bacterial entry and replication in the pleural space[45]—the terms 'complicated' and 'uncomplicated' PPE have been used, but these terms suggest that an associated pneumonia is always a requirement to establish pleural infection which is not the case. The term 'empyema' refers to the macroscopic detection of purulent pleural fluid and represents one end of a spectrum of pleural infection.[46] Here,

Table 18 RAPID score*

Parameter	Measure		Score
Renal	Urea (mmol/L)	<5.0	0
		5.0–8.0	1
		>8.0	2
Age	<50 years		0
	50–70 years		1
	>70 years		2
Purulence of pleural fluid	Purulent		0
	Non-purulent		1
Infection source	Community acquired		0
	Hospital acquired		1
Dietary factor	Albumin (g/L)	>27.0	0
		<27.0	1
Risk category	Score 0–2		Low risk
	Score 3–4		Medium risk
	Score 5–7		High risk

*The RAPID score takes into account serum urea level, age, pleural fluid purulence, infection source and serum albumin levels to risk stratify patients into low-risk, medium-risk or high-risk groups.[68]

the term 'pleural infection' is used to include both empyema and CPPE.

The cornerstones of management of pleural infection are unchanged since the last guideline. These include early identification of cases and accurate diagnosis (covered in the section on approach to the undiagnosed effusion), prompt and suitable antibiotic therapy, nutrition management and deep vein thrombosis prophylaxis and efficient drainage of infected collections (covered in this guideline) via chest tube and adjunctive therapies including intrapleural agents and ultimately surgical management.[7]

What is the best predictor of clinical outcomes?

Clinical outcomes in pleural infection remain poor, with up to 20% of patients dying after an episode of pleural infection over 12 months, and the requirement for surgery in around 15%.[47 48] Understanding which patients are at greater risk of adverse outcomes may allow clinicians to identify means by which their care can be improved to reduce mortality and morbidity, and potentially target invasive treatment to those at highest risk. Hence, the first clinical question in this section asked whether there are baseline clinicoradiological markers that predict clinically important outcomes from pleural infection:

C1 For adults with pleural infection, what is the best predictor of clinical outcomes?

The evidence statements and recommendation are presented below; and the full evidence review is presented in online supplemental appendix C1.

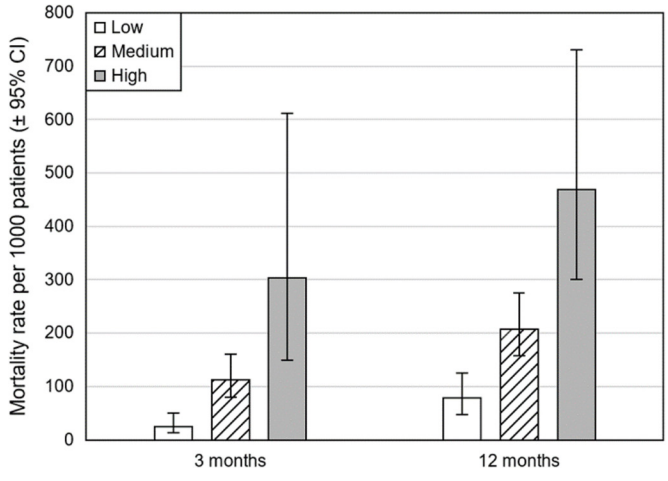

Figure 1 Comparison of the risk of mortality with low, medium and high RAPID scores (based on the meta-analysis results from online supplemental appendix C1, table C1d and figures C1a–C1f).

Evidence statements

Microbiology parameters

Based on limited evidence:

- Pleural infection causative organism does not appear to have an effect on predicting mortality rate, hospital length of stay or the need for thoracic surgery in adults with pleural infection. (Ungraded)
- Healthcare-acquired pleural infection may increase mortality rate and increase hospital length of stay when compared with community-acquired pleural infection in adults. (Ungraded)

Radiological parameters

- The presence of septation features on ultrasound in adults with pleural infection may be associated with an increased length of hospital stay and increased need for thoracic surgery when compared with non-septated ultrasound features. (Ungraded)
- The presence of complex septated ultrasound features may be associated with an increased mortality rate, an increased treatment failure rate and an increased length of hospital stay when compared with complex non-septated ultrasound features. (Ungraded)
- A PPE CT scoring system* may show acceptable discrimination for predicting mortality and/or the need for surgery. (Ungraded)

*Scoring system based on CT radiological features (pleural contrast enhancement, pleural microbubbles, increased attenuation of extrapleural fat and pleural fluid volume >400 mL) for identifying CPPE and defined as a CT score ≥4.[49]

Clinical parameters

- Higher RAPID scores (table 18) appear to indicate an increased risk of mortality (Low) (figure 1) and may indicate an increased length of hospital stay. (Ungraded)
- The Charlson Comorbidity Index Score (CCIS) is associated with an increased risk of mortality with increased CCIS score. (Ungraded)

Recommendation

► RAPID scoring should be considered for risk stratifying adults with pleural infection and can be used to inform discussions with patients regarding potential outcome from infection. (Conditional)

Do pleural fluid or radiology parameters accurately determine which patients should be treated with intercostal drainage?

Where bacteria have translocated into the pleural space, ICD is likely to be required to resolve infection, and here this is termed 'pleural infection'. The presence of macroscopically purulent pleural fluid is termed empyema and diagnostic of pleural infection, and such cases require ICD. In the absence of purulent pleural fluid, there are challenges in determining

Table 19 Evidence review summary for 'For adults with established pleural infection, what initial drainage strategy provides the best clinical outcomes?'

Clinical outcome	Summary of evidence review (surgical drainage* vs chest tube drainage)
Length of hospital stay	Shorter following surgical drainage†
Need for repeat intervention	Increased with chest tube drainage†
Need for thoracic surgery	Not enough evidence
Patient symptoms	Not reported
Complications	Not enough evidence
Quality of life	Not reported
Mortality	Not enough evidence

*Via video-assisted thoracoscopy surgery or open thoracotomy.
†Meta-analysis not possible, data reported in different formats.

when best to treat patients with PPE by ICD. Various parameters are available at the point of considering a diagnosis of pleural infection to inform initial decision-making regarding ICD and classification as CPPE which requires drainage, or uncomplicated parapneumonic effusion which will resolve without recourse to drainage. Such parameters include pleural fluid biochemistry (pH, lactate dehydrogenase (LDH), glucose) and radiological features (TUS and CT). Prompt identification of patients with pleural infection who require drainage is necessary to improve patient outcomes by potentially preventing progression to more advanced stages of empyema, so the next clinical question asked:

> C2 For adults with pleural infection, do pleural fluid or radiology parameters accurately determine which patients should be treated with intercostal drainage?

The evidence statements, recommendations and GPPs are presented below; and the full evidence review is presented in online supplemental appendix C2.

Evidence statements

- Pleural fluid pH appears to have a high specificity and high sensitivity for identifying patients who will undergo a complicated clinical course (complicated parapneumonic effusion (CPPE)) and thus require intercostal drainage. (Ungraded)
- In the context of clinically suspected pleural infection:
  - Pleural fluid pH >7.38 appears to indicate a very low risk of CPPE. (Ungraded)
  - Pleural fluid pH ≤7.15 appears to indicate a high risk of CPPE. (Ungraded)
  - Pleural fluid pH between 7.16 and 7.38 appears to indicate a decreasing risk of CPPE/pleural infection with increasing pH, especially with pH >7.22. (Ungraded)
  - Pleural fluid LDH or glucose measurements appear to be less accurate than pH in initial, independent prediction of which patients should be treated with intercostal drainage. (Ungraded)
  - Pleural fluid pH and glucose are highly correlated, and thus where immediate or accurate pH measurement is not possible, an initial glucose of 4.0 mmol/L (in the non-diabetic patient) indicates a moderate-to-high likelihood of CPPE. (Ungraded)
- CT pleural fluid contrast enhancement may improve detection of CPPE. (Ungraded)

Recommendations

- For patients with PPE or suspected pleural infection, where diagnostic aspiration does not yield frank pus, immediate pH analysis should be performed. (Strong—by consensus)
- For patients with suspected CPPE:
  - If pleural fluid pH is ≤7.2, this implies a high risk of CPPE or pleural infection and an ICD should be inserted if the volume of accessible pleural fluid on ultrasound makes it safe to do so. (Strong—by consensus)
  - If pleural fluid pH is >7.2 and <7.4, this implies an intermediate risk of CPPE or pleural infection. Pleural fluid LDH should be measured and if >900 IU/L ICD should be considered, especially if other clinical parameters support CPPE (specifically ongoing temperature, high pleural fluid volume, low pleural fluid glucose (72 mg/dL ≤4.0 mmol/L), pleural contrast enhancement on CT or septation on ultrasound. (Strong—by consensus)
  - If pleural fluid pH is ≥7.4, this implies a low risk of CPPE or pleural infection and there is no indication for immediate drainage. (Strong—by consensus)
- In the absence of readily available immediate pleural fluid pH measurement, an initial pleural fluid glucose <3.3 mmol/L may be used as an indicator of high probability of CPPE/pleural infection and can be used to inform decision to insert ICD in the appropriate clinical context. (Strong—by consensus)

Good practice points

- ✓ Clinicians should be mindful of alternative diagnoses that can mimic PPE with a low pH and potential for loculations (eg, rheumatoid effusion, effusions due to advanced malignancy/mesothelioma).
- ✓ Pleural fluid samples taken for pH measurement should not be contaminated with local anaesthetic or heparin (eg, by extruding all heparin from an arterial blood gas syringe) as this lowers pleural fluid pH. Delays in obtaining a pleural fluid pH will also increase pleural fluid pH.
- ✓ In patients where a clinical decision is made not to insert an ICD at initial diagnostic aspiration, regular clinical reviews should be performed and repeat thoracocentesis considered to ensure that CPPE is not missed.

The data derived from this question review have been integrated into an updated decision-making algorithm for the diagnosis of patients with pleural infection which includes both pleural fluid and radiological parameters—see Appendix 1, Suspected pleural infection, non-purulent fluid—initial decision tree.

What initial drainage strategy provides the best clinical outcomes?

Adequate drainage of infected fluid from the pleural space in order to achieve source control is a cornerstone of pleural infection management. There are a number of means by which the infected pleural fluid may be removed, ranging from simple percutaneous aspiration or drainage via chest tube to more invasive thoracoscopic and surgical measures. The next clinical question is:

> C3 For adults with established pleural infection, what initial drainage strategy provides the best clinical outcomes and includes discussion on initial size of chest tube to be used for the treatment of pleural infection and whether initial surgical management should be considered?

Table 20 Evidence review summary for 'For adults with pleural infection, does intrapleural therapy improve outcomes compared with other treatment options (eg, drainage alone or surgical intervention)?'

Clinical outcomes	Summary of evidence review (fibrinolytic treatment vs standard care*) (95% CI)					
(Fibrinolytic treatment)	Streptokinase	Urokinase	TPA plus DNAse	TPA	DNAse	Saline irrigation
Length of hospital stay	No difference	3.9 days shorter (5.9 to 13.7) with urokinase	Shorter with TPA plus DNAse	No difference†	No difference†	No difference†
Need for repeat intervention	No difference†	Not reported	Not enough evidence	Not reported	Not reported	Not reported
Need for thoracic surgery	No difference	Reduced need with urokinase (230/1000 (123 to 435) compared with 512/1000)¶	Reduced need with TPA plus DNAse†	Reduced need with TPA†	No difference†	Reduced need with saline irrigation†
Patient symptoms‡	Reduced symptoms with streptokinase†	Defervesence achieved 4.2 days faster (0.4 to 7.9) with urokinase	Reduced symptoms with TPA plus DNAse†	No difference†	No difference†	No difference†
Complications§	Increased with streptokinase (114/1000 (64 to 205) compared with 46/1000)¶	Not reported	Inconclusive results	Inconclusive results	Inconclusive results	No difference†
Quality of life	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Mortality	No difference	Not reported	No difference†	No difference†	No difference†	No difference†
Radiological opacification	Inconclusive results	Increased resolution with urokinase†	Increased resolution with TPA plus DNAse†	No difference†	No difference†	Increased resolution with saline irrigation†
Radiographic resolution of effusion	No difference	Greater resolution with urokinase†	Greater resolution with TPA plus DNAse†	Greater resolution with TPA†	Not reported	Not reported
Pleural thickening	No difference†	Potential reduced pleural thickening with urokinase†	Not reported	Not reported	Not reported	Not reported

*Standard care—chest drainage alone or chest drainage with intrapleural placebo.
†Reported in a single study.
‡Including persistent chest pain, cough, fever, breathlessness and debilitation.
§Including chest pain, bleeding, fever and tube blockage/dislodgement.
¶Meta-analysis results reported as per 1000 patients.
TPA, tissue plasminogen activator.

A summary of the evidence review is shown in table 19 and the evidence statements, recommendation and GPPs are presented below. The full evidence review is presented in online supplemental appendix C3.

Evidence statements

- Chest tube bore size appears to have no effect on mortality rate, the need for post-treatment thoracic surgery or the length of hospital stay following chest tube drainage to treat pleural infection in adults, but bore size >14F may increase post-treatment pain. (Ungraded)
- Drainage under VATS or open thoracotomy appears to reduce the need for repeat intervention and the length of hospital stay when compared with standard chest tube drainage for the treatment of pleural infection in adults. (Ungraded)

Recommendation

► Initial drainage of pleural infection should be undertaken using a small bore chest tube (14F or smaller). (Conditional—by consensus)

Good practice points

✓ Due to the lack of supporting evidence, early surgical drainage under VATS or thoracotomy should not be considered over chest tube ('medical') drainage for the initial treatment of pleural infection.

► Due to lack of supporting evidence, medical thoracoscopy should not be considered as initial treatment for pleural infection.

Conclusions from the evidence review (please see above and online supplemental appendix B3) have been integrated into the pleural infection treatment algorithm (see Appendix 1, Pleural infection treatment pathway).

Does intrapleural therapy improve outcomes compared with other treatment options (eg, drainage alone or surgical intervention)?

Pleural infection results in the arrangement to the usual fibrinolytic characteristics of the pleural space and it is well established that fibrin deposition and septations occur during the development of pleural infection. On this basis, intrapleural treatments have been used for many years in an attempt to reduce septations and improve drainage, thereby attempting to avoid the need for more invasive surgical management in patients with pleural infection. Intrapleural therapies include fibrinolytics, combined intrapleural enzyme therapy, saline irrigation and intrapleural antibiotics.

The next question investigates if intrapleural therapies improve clinical outcomes in adults with pleural infection (including tuberculous empyema) compared with other treatment options such as drainage alone or surgical intervention:

> C4 For adults with pleural infection, does intrapleural therapy improve outcomes compared with other treatment options (eg, drainage alone or surgical intervention)?

Table 21 Evidence review summary for 'Which surgical approach provides the best clinical outcomes?'

Clinical outcome	Summary of evidence review (VATS vs thoracotomy) **(95% CI)**
Length of hospital stay	2.3 days shorter (1.2 to 3.4) with VATS
Need for repeat intervention	No difference and very low for both (≈35/1000)*
Patient symptoms	Less postoperative pain with VATS†
Complications	Less with VATS (152/1000 patients (138 to 167) compared with 197/1000*
Quality of life	Not reported in any study
Mortality	Slightly lower with VATS (35/1000 (29 to 42) compared with 47/1000)*

*Meta-analysis results reported as per 1000 patients.
†Meta-analysis not possible, data reported in different formats.
VATS, video-assisted thoracoscopy surgery .

A summary of the evidence review is shown in table 20 and the evidence statements, recommendations and GPPs are presented below. The full evidence review is presented in online supplemental appendix C4.

Evidence statements

- Streptokinase appears to have no effect on mortality (Very low), length of hospital stay (Very low), the need for thoracic surgery (Very low) or radiographic resolution of effusion (Very low) for the treatment of pleural infection.
- Streptokinase increases post-treatment complications (Very low) when compared with chest drainage alone or placebo for the treatment of pleural infection.
- Urokinase appears to reduce the need for thoracic surgery (Low), hasten the time to resolution of fever (Very low) and reduce the length of hospital stay (Low) compared with placebo or standard care in adults with pleural infection.
- TPA plus DNAse appears to reduce the length of hospital stay (Ungraded), reduce the likelihood of persistent fevers (Ungraded) and increase improvements in CXR opacification (Ungraded), when compared with placebo in the treatment pleural infection, but TPA plus DNAse may increase the risk of post-treatment complications (serious and non-serious). (Ungraded)
- Single agent TPA or single agent DNAse do not appear to improve clinical outcomes when compared with placebo for treating pleural infection. (Ungraded)
- Saline irrigation (250 mL saline three times a day) may reduce the need for thoracic surgery (Ungraded) but appears to have no impact on mortality (Ungraded), length of hospital stay (Ungraded) or time to resolution of fever (Ungraded) when compared with saline flushes.

Recommendations

- ► Combination tissue plasminogen activator (TPA) and DNAse should be considered for the treatment of pleural infection, where initial chest tube drainage has ceased and leaves a residual pleural collection. (Conditional—by consensus)
- ► Saline irrigation can be considered for the treatment of pleural infection when intrapleural TPA and DNase therapy or surgery is not suitable. (Conditional—by consensus)
- ► Single agent TPA or DNAse should not be considered for treatment of pleural infection. (Conditional—by consensus)
- ► Streptokinase should not be considered for treatment of pleural infection. (Conditional)

Good practice points

- ✓ Patient consent should be taken when using TPA and DNase as there is a potential risk of bleeding.
- ✓ When administering TPA plus DNase, the regime of should be 10 mg TPA twice daily (10 mg two times per day)+5 mg DNase two times per day for 3 days, based on randomised controlled trial data. Based on retrospective case series data, 5 mg TPA two times per day+5 mg DNase two times per day for 3 days may be as effective, and can be used if considered necessary.
- ✓ Reduced doses of TPA may be considered in those with a potentially higher bleeding risk (eg, those on therapeutic anticoagulation which cannot be temporarily ceased).
- ✓ For details on administration of intrapleural treatments, please refer to the BTS Clinical Statement on Pleural Procedures.[1]

Conclusions from the evidence review (please see above and online supplemental appendix C4) have been integrated into the pleural infection treatment algorithm (see Appendix 1, Pleural infection treatment pathway).

Which surgical approach provides the best clinical outcomes?

A significant proportion of patients with pleural infection fail to improve following optimal medical therapy, and surgical intervention is then required, accepting that not all patients are suitable to undergo surgical treatment. Precise criteria of when to refer for surgery, or what parameters constitute 'failed medical therapy' remain unclear.

Different surgical approaches can be used to access the infected space in pleural infection; and these are broadly classified as endoscopic techniques, termed VATS, or open techniques, termed thoracotomy. The next clinical question assessed what the optimal surgical approach is for treating patients with pleural infection:

> C5 For adults with pleural infection, which surgical approach provides the best clinical outcomes?

A summary of the evidence review is shown in table 21 and the evidence statements, recommendation and GPP are presented below. The full evidence review is presented in online supplemental appendix C5.

Evidence statements

- Postoperative mortality and the need for repeat intervention are similar following VATS or thoracotomy for pleural infection. (Very low)
- Immediate postoperative pain appears to be less following VATS than thoracotomy for pleural infection. (Ungraded)
- Length of hospital stay appears to be shorter following VATS than thoracotomy for pleural infection. (Very low)
- VATS access appears to cause fewer postoperative complications than thoracotomy for pleural infection. (Very low)

Recommendation

- ► VATS access should be considered over thoracotomy for adults in the surgical management of pleural infection. (Conditional)

Good practice point

- ✓ When selecting a surgical access for the treatment of pleural infection in adults, it is important to ensure the technique can facilitate optimal clearance of infected material and achieve lung re-expansion where appropriate.

Which method of surgery provides the best clinical outcomes?

In parallel to the surgical approaches described in the 'Which surgical approach provides the best clinical outcomes?' section above (and corresponding online supplemental appendix C5), at the referral point for surgery, different surgical methods can be deployed, broadly classified into drainage, debridement and visceral decortication. The final clinical question in this section therefore aimed to investigate what the best surgical method is for treating pleural infection:

> C6 For adults with pleural infection, which method of surgery provides the best clinical outcomes?

The evidence statement and GPPs are presented below; and the full evidence review is presented in online supplemental appendix C6.

Evidence statement

– Based on very limited evidence, decortication surgery for pleural infection may be associated with a longer postoperative stay and higher mortality than surgery that does not involve decortication, but is associated with less breathlessness. (Ungraded)

Recommendations

No recommendations can be made based on the available evidence.

Good practice points

✓ Extent of surgery should be tailored according to patient and empyema stage when the lung is not completely trapped (drainage vs debridement).

✓ Decortication should be a decision that is individualised to the patient with a trapped lung based on assessment of patient fitness and empyema stage.

Other areas of clinical importance not covered by the clinical questions

Microbiology

The microbiology of pleural infection is a large topic in itself, and not specifically covered by this guideline. However, knowledge of likely microbiological cause will influence the required antibiotic therapy which in a significant proportion of patients will be empirical throughout the treatment course. Large-scale studies have demonstrated that conventional microbiological tests (culture of pleural fluid in plain tubes) results in a sensitivity of 50%–60% at best, with blood cultures having a yield of <10%. There is now good evidence that microbiological yield can be increased by inoculating pleural fluid into blood culture bottle media, and by the use of image-guided parietal pleural biopsy for microbiological assessment (covered in the 'Investigation of the undiagnosed unilateral pleural effusion, What is the optimal volume and container for a pleural aspiration sample?' section of this guideline).

Data on likely microbiological cause in pleural infection are little changed compared with the 2010 guideline,[7] and it remains the case that the majority of community-acquired pleural infection is caused by Gram-positive aerobic organisms, especially streptococcal species including the anginosus group and *Staphylococcus aureus*. Gram-negative bacteria are less commonly cultured in community-acquired disease, but anaerobic bacteria are commonly seen both in isolation and as co-infection with aerobic organisms. In contrast, hospital-acquired pleural infection is dominated by resistant Gram-positive organisms (including methicillin-resistant *Staphylococcus aureus* (MRSA)) and Gram-negative organisms such as *Escherichia coli*, *Enterobacter* and *Pseudomonas*, with significant anaerobic involvement. Polymicrobial infection is commonly seen in both community-acquired and hospital-acquired disease, especially when molecular diagnostic techniques are used.

Fungal pleural infection is rare (<1% of cases overall),[50] and usually seen in immunosuppressed individuals, associated with a very high mortality.[51] The diagnosis of fungal pleural infection (especially in those without known immunocompromise) should prompt investigation for other sources of potential infection including oesophageal leak.

Antibiotics

Initial antibiotic treatment for suspected or confirmed pleural infection should commence before results of culture tests are available and will be dictated by the likely source of infection (community-acquired or hospital-acquired disease) as per the likely microbiological cause. Local audit and assessment of likely bacteria is encouraged, as there are geographic differences in microbiological pattern. Initial treatment should include cover of likely organisms including anaerobes, and discussion with local microbiological services should occur. An example of empirical initial antibiotic choice in community-acquired pleural infection is a combination of a second-generation cephalosprin with anaerobic cover (cefuroxime+metronidazole) which covers all likely organisms, whereas empirical treatment for hospital-acquired pleural infection should cover resistant Gram-negative organisms and potentially MRSA (eg, vancomycin+meropenem). A positive culture test from pleural fluid or blood culture may allow narrowing of empirical antibiotics, specifically if pneumococcus is detected, as this is usually a monomicrobial disease.

In general, between 2 and 6 weeks of antibiotic therapy is used according to clinical response, as shorter courses may result in earlier clinical relapse. However, there has not, to date, been an adequately powered study addressing shorter antibiotic duration for pleural infection, and the optimal length of treatment therefore remains unknown. Similarly, direct comparative studies of the use of intravenous or oral antibiotics for pleural infection are lacking, and it is therefore usual practise to treat with intravenous antibiotics initially while patients are in hospital, transitioning to suitable oral therapy according to clinical response and on discharge from hospital. Where oral therapy is not possible (due to bacterial sensitivities or drug allergies), consideration should be given to ambulatory services providing home intravenous treatment.

PLEURAL MALIGNANCY

Introduction

MPE are of increasing incidence with around a global incidence of around 70 per 100 000 per year.[52] The most common causes of secondary pleural malignancy are lung cancer and breast cancer. Other common primary sites for pleural metastasis include lymphoma, gastrointestinal malignancy and genitourinary malignancy. Malignant pleural mesothelioma (MPM) is a common cause of MPE but is not specifically addressed as part of this guideline, although principles of fluid management and pleurodesis remain similar. MPM is specifically addressed in the British Thoracic Society Guideline for the investigation and management of pleural mesothelioma 2018.[10] The management of MPE has developed hugely since the publication of the management of an MPE: British Thoracic Society Pleural Disease Guideline 2010.[6] Where previously pleural fluid

cytology and chest tubes with talc pleurodesis were the mainstay of diagnosis and treatment, there are now many evidence-based options available to clinicians. Medical thoracoscopy is now more widely available and allows the combination of diagnosis and treatment (please see the 'Medical thoracoscopy' section in the BTS Clinical Statement on Pleural Procedures for further details[1]). Ambulatory pathways are now a realistic option for patients, and there is evidence for the relative effectiveness of each option.

Diagnosis, treatment and prognosis

Diagnosis

When a patient presents with MPE breathlessness is a common symptom,[53] although up to a quarter of those presenting may not be breathless.[54] Constitutional symptoms, such as fever, chills, fatigue, weakness and weight loss, may be prominent and other symptoms, such as chest pain, are usually because of malignant infiltration of structures in the chest wall.

MPE can be diagnosed by radiology, pleural aspiration under ultrasound guidance or image-guided pleural biopsy. The diagnostic accuracy of various imaging modalities used for diagnosing MPE are explored in the first clinical question and provide an understanding of the relative merits of each technique (see the 'Which imaging modality is best for diagnosing adults with suspected pleural malignancy?' section below).

Diagnostic pleural aspiration under ultrasound guidance also remains an important first intervention and may lead to a diagnosis in many cases. Since the widespread adoption of medical thoracoscopy, diagnosis and management of MPE may be combined. This provides a 'one-stop' intervention for patients and may significantly shorten the patient pathway. Image-guided pleural biopsy may also be useful where there is significant volume of disease, but little pleural fluid or limited availability of medical thoracoscopy (please see the 'Ultasound-guided pleural biopsy' section in the BTS Clinical Statement on Pleural Procedures for further details[1]). Both of these techniques are discussed in the 'Investigation of the undiagnosed unilateral pleural effusion, Is image guided intervention better than non-image guided intervention?' section.

Treatment

For patients with a known MPE, management options now include ambulatory intermittent intervention with recurrent aspiration, home-based management with indwelling pleural catheters (IPCs) (also combined with pleurodesis) and traditional inpatient admission with a chest tube and talc slurry pleurodesis. In this guideline, the relative merits of each approach are explored, but it is important to stress that in most cases there is not a 'right' answer as to the best approach. Patient preference is always important and various online tools and documents have been developed to help patients navigate the various options. The presented evidence will allow clinicians and patients to make the right decision, including the relative value of pleurodesis and optimum drainage strategies (see 'Is pleural aspiration with no pleurodesis agent better than talc slurry?', 'Is an indwelling pleural catheter better than talc slurry pleurodesis?', 'Is thoracoscopy and talc poudrage pleurodesis better than chest drain and talc slurry pleurodesis?', 'Is surgical pleurodesis or surgical decortication better than talc slurry pleurodesis?', 'Is symptom-based/conservative drainage better than daily drainage?' and 'Do intrapleural agents (talc or other pleurodesis agents) improve clinical outcomes in patients with MPE treated with an indwelling pleural catheter?' sections below). Please note that all procedural techniques are covered separately in the BTS Clinical Statement on Pleural Procedures.[1]

For patients with complex malignant pleural disease, the management of trapped lung is an important question, and the guideline has addressed this in the 'Is pleural aspiration, talc slurry pleurodesis, talc poudrage pleurodesis or decortication surgery better than using an indwelling pleural catheter to treat malignant pleural effusion and non-expandable lung?' section below. The use of fibrinolytics for complex pleural effusions has also been explored in the 'Is intrapleural chemotherapy better than systemic treatment for treating pleural malignancy?' section.

Finally, the value of systemic anticancer treatment (SACT) or intrapleural chemotherapy for the treatment of MPE are investigated in the 'Does systemic therapy avoid the need for definitive pleural intervention?' and 'Is intrapleural chemotherapy better than systemic treatment for treating pleural malignancy?' sections, respectively.

Prognosis

Prognosis is a question that is frequently asked, but one which can be difficult to answer. The final clinical question aimed to address if prognostic or predictive scores could provide patients wih MPE with important information about their prognosis ('Does the use of prognostic or predictive scores provide important prognostic information for the patient?', Question D12).

The full list of clinical questions in relation to the management of malignant pleural disease in adults were:

- Which imaging modality is best for diagnosing adults with suspected pleural malignancy? (Question D1)
- Does systemic therapy avoid the need for definitive pleural intervention? (Question D2)
- Is pleural aspiration with no pleurodesis agent better than talc slurry? (Question D3)
- Is an indwelling pleural catheter better than talc slurry pleurodesis? (Question D4)
- Is thoracoscopy and talc poudrage pleurodesis better than chest drain and talc slurry pleurodesis? (Question D5)
- Is surgical pleurodesis or surgical decortication better than talc slurry pleurodesis? (Question D6)
- Is pleural aspiration, talc slurry pleurodesis, talc poudrage pleurodesis or decortication surgery better than using an indwelling pleural catheter to treat malignant pleural effusion and non-expandable lung? (Question D7)
- Are intrapleural enzymes better than surgery, or no treatment, for treating malignant pleural effusion and septated effusion (on radiology)? (Question D8)
- Is symptom-based/conservative drainage better than daily drainage? (Question D9)
- Do intrapleural agents (talc or other pleurodesis agents) improve clinical outcomes in patients with MPE treated with an indwelling pleural catheter? (Question 10)
- Is intrapleural chemotherapy better than systemic treatment for treating pleural malignancy? (Question D11)
- Does the use of prognostic or predictive scores provide important prognostic information for the patient? (Question D12)

Topics not covered in the 'Pleural malignancy' section

The following topics have not been covered in the 'Pleural malignancy' section:

Table 22 Summary of the diagnostic accuracy of thoracic ultrasound (TUS), CT and PET-CT

	Diagnostic accuracy		
Modality	**Pooled sensitivity (95% CI)**	**Pooled specificity (95% CI)**	**No. studies**
TUS*	0.80 (0.70 to 0.87)	0.90 (0.81 to 0.94)	2
CT	0.80 (0.62 to 0.90)	0.81 (0.72 to 0.88)	6
PET-CT	0.89 (0.80 to 0.95)	0.92 (0.88 to 0.95)	2

*Studies performed in patients with pleural effusion suspected of pleural malignancy.

1. The management of malignant mesothelioma as this is covered in the BTS Guideline for the investigation and management of pleural mesothelioma.[10]
2. The size of chest tube for optimum drainage, as recent data adequately address this.[55]
3. The importance of maintaining tube patency and securing the drain to prevent dislodgement cannot be overemphasised but have not been specifically covered in this guideline.
4. Patient rotation is no longer common practice and hence has not been specifically addressed.
5. Tube clamping and removal, while important, are addressed indirectly by studies addressing pleurodesis agents (see 'Is pleural aspiration with no pleurodesis agent better than talc slurry?', 'Is an indwelling pleural catheter better than talc slurry pleurodesis?, 'Is thoracoscopy and talc poudrage pleurodesis better than chest drain and talc slurry pleurodesis?' and 'Is surgical pleurodesis or surgical decortication better than talc slurry pleurodesis?' sections).
6. Malignant tract seeding is a problem that frequently arises in the management of malignant mesothelioma, but less often in other pleural malignancies, therefore has not been covered within this guideline.

Topics of important consideration

Although there are clinical questions that have not been addressed, patient safety is an important issue that must be considered. While this has not been the subject of rigorous investigative methodology, rate of drainage of an MPE should be addressed. In the UK, various alerts from the National Patient Safety Agency have appeared over recent years (https://www.england.nhs.uk/patient-safety/national-patient-safety-alerting-committee/). Consensus would suggest that the maximum rate of drainage for an MPE in a closed system would be 1.5 L in the first hour, with an hourly rate of 1 L thereafter until drainage is complete. More rapid drainage can be associated with lung re-expansion that is too rapid and the phenomenon of re-expansion pulmonary oedema, which carries significant morbidity and mortality (see the 'Pleural aspiration (diagnostic and therapeutic), Complications' section in the BTS Clinical Statement on Pleural Procedures for further details[1]).

Which imaging modality is best for diagnosing adults with suspected pleural malignancy?

Detailed radiological evaluation is commonly performed as part of the assessment for patients with clinical or X-ray findings raising the possibility of pleural malignancy. A range of imaging tools are available including TUS, CT, PET-CT and MRI. Histological confirmation is the gold standard for diagnosis of pleural malignancy, but where tissue sampling is not possible a clinical diagnosis may be made on the basis of disease behaviour over time. Hence, the first clinical question in this section evaluated the diagnostic accuracy of radiological tests to distinguish malignant from benign pleural pathology:

> D1 What is the diagnostic accuracy of radiology in adults with suspected pleural malignancy?

A summary of the diagnostic accuracies of TUS, CT and PET-CT is shown in table 22 (taken from online supplemental appendix D1, table D1e).

The use of MRI for evaluation of the pleura is relatively uncommon, but three studies, each assessing different techniques, met the criteria for inclusion. One study assessed the morphological assessment of the pleura, using criteria by Leung *et al*[56] with MRI, and found it comparable to CT assessment (sensitivity 0.98, specificity 0.92).[57] However, MRI was better able to detect subtle chest wall and/or diaphragmatic infiltration than CT. Malignant pleural disease also tended to be hyperintense on T_2-weighted images and gadolinium-enhanced T_1-weighted images, unlike benign disease. A second study identified the presence of multiple hyperintense foci on the pleura on high b-value diffusion-weighted images ('pointillism') as a marker of malignancy (sensitivity 0.93, specificity 0.79).[58] The final study described a novel marker of pleural malignancy defined by early contrast enhancement on dynamic contrast-enhanced images which, when combined with recognised morphological features, resulted in a sensitivity and specificity of 0.92 and 0.78, respectively. However, comparison with CT evaluation in the same cohort (sensitivity 0.56, specificity 0.77) did not show a statistically significant difference.[59]

The evidence statements, recommendations and GPPs are presented below, and the full evidence review is available in online supplemental appendix D1.

Please also note that the presented data should be supplemented by reference to Section 5 of the BTS Guideline for the investigation and management of pleural mesothelioma.[10]

Evidence statements

- Ultrasound allows detailed evaluation of the peripheral pleura in the presence of a pleural effusion and has a moderate sensitivity and high specificity for diagnosing pleural malignancy. (Moderate)
- CT has a moderate sensitivity and specificity for the diagnosis of pleural malignancy. (Low)
- PET-CT has a high sensitivity and specificity for the diagnosis of pleural malignancy. (Low)
- MRI, using different techniques, appears to show high sensitivity and specificity for the diagnosis of pleural malignancy. (Ungraded)

Recommendations

- ► Ultrasound may be a useful tool at presentation to support a diagnosis of pleural malignancy, particularly in the context of a pleural effusion, where appropriate sonographic skills are present. (Conditional)
- ► CT allows assessment of the entire thorax, and positive findings may support a clinical diagnosis of pleural malignancy when biopsy is not an option (Conditional), however a negative CT does not exclude malignancy. (Strong—by consensus)
- ► PET-CT can be considered to support a diagnosis of pleural malignancy in adults when there are suspicious CT or clinical

Table 23 Evidence review summary for 'Is an indwelling pleural catheter better than talc slurry pleurodesis?'

Clinical outcome	Summary of evidence review (talc slurry pleurodesis vs IPC) (95% CI)
Length of hospital stay	Longer for initial procedure and total inpatient stay with talc slurry*
Pleurodesis rates	Not enough evidence
Need for re-intervention	Increased need with talc slurry (251/1000 compared with 77/1000 (42 to 138))†
Complications	No difference, but approximately 20%–25% of patients are likely to experience complications when treated with either technique
Symptoms‡	No difference in dyspnoea, but both treatments show significant improvements
Quality of life (QoL)	Improved QoL with talc slurry pleurodesis and IPC, but no significant difference between the two treatments

*Meta-analysis not possible, data reported in different formats.
†Meta-analysis results reported as per 1000 patients.
‡Breathlessness, chest pain.
IPC, indwelling pleural catheter.

features and negative histological results, or when invasive sampling is not an option. (Conditional)

Good practice points

- ✓ Imaging can play an important role in the assessment of pleural malignancy, but results should be interpreted in the context of clinical, histological and biochemical markers.
- ✓ Features of malignancy may not be present on imaging at presentation. Unless a clear diagnosis is reached by other means (eg, biopsy), monitoring with follow-up imaging of patients presenting with pleural thickening and unexplained unilateral pleural effusion should be considered to exclude occult malignancy.
- ✓ MRI has potential as a diagnostic tool in pleural malignancy. Its clinical value has yet to be determined and its use should be limited to highly selected cases and research studies at the present time.

Does systemic therapy avoid the need for definitive pleural intervention?

MPE often recur after initial aspiration.[6] Since MPE is a marker of advanced disease and is associated with a poor prognosis, treatment focuses on palliation of symptoms and maintenance of quality of life. Anecdotal reports suggest that MPEs often resolve rapidly after initiation of chemotherapy, avoiding the need for a definitive procedure, so the next clinical question aimed to determine whether SACT reduces the requirement for pleural drainage and pleurodesis, with specific focus on treatment-sensitive tumours:

> D2 For adults with malignant pleural effusion, does systemic therapy avoid the need for definitive pleural intervention?

The evidence statements, recommendation and GPPs are presented below and the full evidence review is available in online supplemental appendix D2.

Evidence statements

- There was no evidence to support the use of SACT to reduce the need for definitive pleural procedures in adults with MPE.
- Systemic anti-angiogenesis agents may improve pleural effusion control in non-small-cell lung carcinoma, but methodological constraints limit the interpretation of the results.

Recommendation

- ► Definitive pleural intervention should not be deferred until after SACT. (Conditional—by consensus)

Is pleural aspiration with no pleurodesis agent better than talc slurry?

Chest drain insertion with talc pleurodesis provides definitive management of MPE by creating permanent fusion of the pleural layers. This requires hospitalisation with a chest drain in situ for a number of days. Pleural aspiration with no attempt at pleurodesis is an alternative approach and has the advantage of not requiring hospital admission but fluid may recur. Understanding which of these interventions has the most benefit for important clinical outcomes would permit rational treatment choices, so the next clinical question was:

> D3 For adults with malignant pleural effusion, is pleural aspiration with no pleurodesis agent better than talc slurry at improving clinical outcomes?

The evidence statements, recommendation and GPPs are presented below, and the full evidence review is available in online supplemental appendix D3.

Evidence statements

Based on very limited evidence:

- Talc slurry pleurodesis may be associated with a longer hospital stay than pleural aspiration. (Ungraded)
- Talc slurry pleurodesis appears to reduce the need for re-intervention and reduces the overall number of complications compared with pleural aspiration alone. (Ungraded)
- Patients undergoing pleural aspiration as the first intervention will often require a second procedure, with approximately one-third requiring this within 2 weeks. (Ungraded)
- Pleural aspiration appears to improve breathlessness. (Ungraded)

Recommendation

- ► Management of MPE using talc pleurodesis (or another method) is recommended in preference to repeated aspiration especially in those with a better prognosis, but the relative risks and benefits should be discussed with the patient. (Conditional—by consensus)

Good practice points

- ✓ Decisions on the best treatment modality should be based on patient choice.
- ✓ Informed decision-making should include the role of inpatient versus ambulatory management and the potential risk of requiring further pleural interventions.

Is an indwelling pleural catheter better than talc slurry pleurodesis?

Chest drain insertion with talc pleurodesis and IPCs provide definitive treatment options in the management of MPE. Talc

Table 24 Evidence review summary for 'Is thoracoscopy and talc poudrage pleurodesis better than chest drain and talc slurry pleurodesis?'

Clinical outcome	Summary of evidence review (thoracoscopy and talc poudrage pleurodesis vs chest drain and talc slurry pleurodesis) **(95% CI)**
Length of hospital stay	No difference
Need for re-intervention	Reduced with thoracoscopy and talc poudrage pleurodesis (138/1000 (103 to 189) compared with 206/1000)*
Complications	No difference in the occurrence of one, or more complications, but thoracoscopy and talc poudrage may cause an increased number of complications per patient
Symptoms†	No difference in chest pain or breathlessness
Quality of life	No difference

*Meta-analysis results reported as per 1000 patients.
†Breathlessness, chest pain.

pleurodesis has long been considered the standard of care, however, understanding the role of IPCs in comparison is key to provide optimal options to patients with MPE. This led to the next clinical question:

> D4 For adults with malignant pleural effusion, is an indwelling pleural catheter better than talc slurry pleurodesis at improving clinical outcomes?

A summary of the evidence is shown in table 23 and the evidence statements, recommendation and GPPs are presented below. The full evidence review is available in online supplemental appendix D4.

Evidence statements

- Talc slurry pleurodesis and IPCs appear to improve dyspnoea and quality of life scores, but there are no observable differences between the two treatments. (Ungraded)
- IPC insertion appears to be associated with a shorter length of initial hospital stay at the time of intervention and fewer subsequent inpatient days. (Ungraded)
- IPCs appear to be associated with a reduced need for further pleural intervention (defined as requirement for a further pleural procedure) when compared with talc slurry pleurodesis. (Moderate)
- There appears to be no difference in adverse events for patients treated with talc slurry pleurodesis or IPC. (Very low)

Recommendation

► Patients without known non-expandable lung (for a definition of non-expandable lung please see the 'Is pleural aspiration, talc slurry pleurodesis, talc poudrage pleurodesis or decortication surgery better than using an indwelling pleural catheter to treat malignant pleural effusion and non-expandable lung?' section) should be offered a choice of IPC or pleurodesis as first-line intervention in the management of MPE. The relative risks and benefits should be discussed with patients to individualise treatment choice. (Conditional)

Good practice points

✓ The psychological implications and potential altered body image aspects of having a semi-permanent tube drain in situ should not be underestimated and must be considered prior to insertion.

✓ All patients who have had an IPC inserted should be referred to the community nursing team on discharge for an early assessment of the wound site, symptom control, support with IPC drainage and removal of sutures.

✓ Patients and their relatives should be supported to perform community drainage and complete a drainage diary if they feel able to do so, to promote independence and self-management.

✓ Complications such as infection refractory to community management, suspected drain fracture, loculations or blockage with persistent breathlessness should be referred back to the primary pleural team for further assessment.

Is thoracoscopy and talc poudrage pleurodesis better than chest drain and talc slurry pleurodesis?

In adults with MPE, talc pleurodesis is commonly used to provide long-term control of fluid. However, there is debate as to the best way to administer talc. This can either be talc slurry (emulsification of talc in normal saline which is then administered via a chest drain) or poudrage (administration of talc powder as an aerosol during thoracoscopy). Both techniques enable effective delivery of talc to the pleural space, but it has been theorised that talc poudrage may allow better coverage of the pleural space as the talc is directly visualised and may be associated with shorter length of stay as talc is delivered at the same procedure as fluid drainage. However, thoracoscopy is a more invasive procedure. The next clinical question assesses if thoracoscopy and talc poudrage is better than chest drain and talc slurry pleurodesis:

> D5 For adults with MPE is thoracoscopy and talc poudrage pleurodesis better than chest drain and talc slurry pleurodesis at improving clinical outcomes?

A summary of the evidence is shown in table 24 and the evidence statements, recommendation and GPPs are presented below. The full evidence review is available in online supplemental appendix D5.

Evidence statements

- There appears to be no difference in health-related quality of life, length of hospital stay, chest pain or breathlessness in adults with MPE treated with chest drain and talc slurry, or thoracoscopy and talc poudrage. (Ungraded)
- Pleurodesis failure rate may be lower in adults who have thoracoscopy and talc poudrage for the treatment of MPE when compared with chest drain and talc slurry. (Low)
- There appears to be no difference in the occurrence of one or more complications following treatment with chest drain and talc slurry or thoracoscopy and talc poudrage in adults with MPE (Very low), but thoracoscopy and talc poudrage may cause an increased number of complications per patient. (Ungraded)

Recommendation

► Talc slurry or talc poudrage may be offered to patients with MPE to control fluid and reduce the need for repeated procedures. (Conditional)

Good practice point

✓ Where a diagnostic procedure is being conducted at thoracoscopy (pleural biopsies), if talc pleurodesis is reasonable, this should be conducted during the same procedure via poudrage.

Is surgical pleurodesis or surgical decortication better than talc slurry pleurodesis?

In adults with MPE, talc pleurodesis via slurry or poudrage, IPCs and aspiration are common treatment options and widely

available. However, surgical intervention is a treatment option in those able to tolerate surgery, so the next clinical question reviewed if there are relative benefits of using a surgical approach in MPE compared with the above 'physician' approach:

D6 For adults with malignant pleural effusion, is surgical pleurodesis or surgical decortication better than talc slurry pleurodesis at improving clinical outcomes?

The evidence statements, recommendation and GPPs are presented below, and the full evidence review is available in online supplemental appendix D6.

Evidence statements

There was insufficient evidence to accurately address the question and published evidence was in highly selected, non-randomised patients.

- Surgical and non-surgical treatments for MPE may improve quality of life and reduce breathlessness. (Ungraded)
- Surgical MPE treatments may require a longer stay in hospital compared with talc slurry pleurodesis. (Ungraded)
- VATS with talc pleurodesis may reduce the need for early postsurgery re-intervention. (Ungraded)
- Pleurodesis failure rates may increase in patients wih MPE with non-expandable lung if thoracoscopic decortication is not performed. (Ungraded)

Recommendation

► In selected patients considered fit enough for surgery, either surgical talc pleurodesis or medical talc slurry can be considered for the management of patients with MPE. The relative risks, benefits and availability of both techniques should be discussed with patients to individualise treatment choice. (Conditional—by consensus)

Good practice points

✓ Informed decision-making should include the role of surgery versus ambulatory management with an IPC for the management of MPE in selected patients.

✓ Decortication surgery may improve pleurodesis success in patients with MPE with non-expandable lung, but the risks and benefits of IPC and surgical treatment should be discussed with patients, and treatment individualised according to circumstances (eg, fitness to undergo thoracic surgery).

Is pleural aspiration, talc slurry pleurodesis, talc poudrage pleurodesis or decortication surgery better than using an indwelling pleural catheter to treat malignant pleural effusion and non-expandable lung?

Management of patients with non-expandable lung can be challenging. IPCs have become the preferred management technique for these patients, so the next question reviewed the usefulness of using alternative techniques (pleural aspiration, talc slurry pleurodesis, talc poudrage pleurodesis and decortication surgery) to manage non-expandable lung in malignant pleural disease:

D7 For adults with malignant pleural effusion and non-expandable lung, is pleural aspiration, talc slurry pleurodesis, talc poudrage pleurodesis or decortication surgery better than using an indwelling pleural catheter at improving clinical outcomes?

There is no well-defined objective definition of what constitutes 'non-expandable lung', but for the purposes of this guideline, non-expandable lung has been defined on expert group consensus as radiologically significant (with >25% of the lung not apposed to the chest wall) based on CXR appearances. It should be noted that there is significant interobserver variation in chest radiograph interpretation of the presence of non-expandable lung. Non-expandable lung may be associated with worse prognosis in MPE.[60] Non-expandable lung is preferred as a term to trapped or entrapped lung as it includes both visceral pleural thickening limiting re-expansion and endobronchial obstruction preventing re-expansion.

The evidence statements and GPPs are presented below, and the full evidence review is available in online supplemental appendix D7.

Evidence statements

- IPCs may improve quality of life and breathlessness in patients with MPE and non-expandable lung but may result in the IPC remaining in situ for a prolonged period (>100 days). IPC carries a small risk of pleural infection in patients with MPE and non-expandable lung. (Ungraded)
- There is no direct evidence to support the use of talc slurry pleurodesis over IPC, but talc slurry pleurodesis may improve quality of life, symptoms and pleurodesis rate in patients with MPE and <25% lung non-expandable lung. (Ungraded)
- There is no direct evidence to support the use of talc poudrage pleurodesis over IPC in patients with MPE and non-expandable lung. (Ungraded)
- Pleurodesis failure rates may increase in patients with MPE and non-expandable lung if thoracoscopic decortication is not performed. (Ungraded)

Recommendations

No recommendations can be made on the use of pleural aspiration, talc slurry pleurodesis, talc poudrage pleurodesis or decortication surgery versus an IPC to control symptoms in patients with MPE and non-expandable lung.

Good practice points

✓ Decisions on treatment modality for MPE and non-expandable lung should be based on patient choice, with the relative risks and benefits of each modality discussed with the patient, but patients should be made aware of the limited evidence base regarding treatment options for non-expandable lung.

✓ IPCs are effective at controlling symptoms in non-expandable lung and should be considered, but it may be appropriate to undertake pleural aspiration first to assess symptomatic response.

✓ Pleural aspiration may result in a need for multiple procedures so alternatives should be discussed with the patient.

✓ In patients with radiologically significant (>25%) non-expandable lung requiring intervention for a symptomatic MPE, current evidence suggests the use of an IPC rather than talc pleurodesis.

✓ In patients with MPE and <25% non-expandable lung, talc slurry pleurodesis may improve quality of life, chest pain, breathlessness and pleurodesis rates.

✓ Decortication surgery may improve pleurodesis success in selected patients with MPE and non-expandable lung, but the risks and benefits of IPC and surgical treatment should be discussed with patients, and treatment individualised according to circumstances (eg, fitness to undergo thoracic surgery).

Table 25 Evidence review summary for 'Are intrapleural enzymes better than surgery, or no treatment, for treating malignant pleural effusion and septated effusion (on radiology)?'

Clinical outcome	Summary of evidence review (intrapleural enzymes vs no treatment) (95% CI)
Length of hospital stay	Shorter with intrapleural enzymes*
Pleurodesis rates/Need for re-intervention	Lower with intrapleural enzymes (287/1000 (177 to 464) compared with 377/1000)†
Complications	Not reported
Symptoms‡	Reduced breathlessness with intrapleural enzymes (278/1000 (168 to 470) compared with 480/1000)
Quality of life	No difference*

*Based on a single study.
†Meta-analysis results reported as per 1000 patients.
‡Breathlessness, chest pain.

Are intrapleural enzymes better than surgery, or no treatment, for treating malignant pleural effusion and septated effusion (on radiology)?

Patients with MPE and septated effusion are less likely to benefit from pleural fluid drainage because percutaneous drainage alone cannot effectively drain the effusion. This group of patients has been reported as having a worse prognosis than other patients with MPE.[61] Septated effusions can occur both in inpatients with chest drains and ambulant patients with IPCs. Effective drainage of the pleural space, either by decortication or by intrapleural enzymes, may improve symptoms. However, surgical intervention is invasive, and carries a significant risk of morbidity and mortality, and may not be appropriate in these patients. The next question compares the use intrapleural agents to achieve clearance of septated malignant effusion against surgical intervention or placebo.

> D8 For adults with malignant pleural effusion and septated effusion (on radiology), are intrapleural enzymes better than surgery, or no treatment at improving clinical outcomes?

No studies compared intrapleural enzymes against surgery; and furthermore, no studies were identified that looked at the role of surgery in patients with septated MPE. One reason for this may be that septated effusion is identified on ultrasound and surgeons have not historically performed ultrasound in their patients. Hence, the lack of literature supports the view that surgery is rarely used for these patients.

A summary of the intrapleural enzymes versus no treatment evidence review is shown in table 25 and the evidence statements and GPPs are presented below. The full evidence review is available in online supplemental appendix D8.

Evidence statements

There was insufficient evidence to determine if intrapleural enzymes are better than surgery at improving clinical outcomes in adults with MPE and septated effusion (on radiology).

For inpatients with a chest drain

- Intrapleural fibrinolytic treatment may shorten hospital stay in patients with MPE and septated effusion when compared with no treatment. (Ungraded)
- Intrapleural fibrinolytic treatment appears to decrease pleurodesis failure rate, when compared with no treatment, in patients with MPE and septated effusion. (Very low)
- Intrapleural fibrinolytic treatment appears to decrease breathlessness, when compared with no treatment, in patients with MPE and septated effusion. (Very low)

For ambulant patients with indwelling pleural catheters

- Intrapleural fibrinolytics, when compared with no treatment, may improve breathlessness in patients with MPE and septated effusion, but there is a high rate of recurrent symptomatic loculation. (Ungraded)

Recommendations

Due to the lack of supporting evidence, no recommendations can be made on the use of intrapleural enzymes or surgery for treating adults with MPE and septated effusion (on radiology).

Good practice points

- ✓ Intrapleural fibrinolytics can be considered in highly selected symptomatic patients with MPE and septated effusion to try to improve breathlessness.
- ✓ Intrapleural fibrinolytics may be used in patients with MPE and septated effusion and an IPC to improve drainage if flushing the IPC with normal saline or heparinised saline does not improve drainage.
- ✓ Surgery can be considered for palliation of symptoms in a minority of patients with significantly septated MPE and associated symptoms and otherwise good prognosis and performance status.

Is symptom-based/conservative drainage better than daily drainage?

IPCs offer an ambulatory management pathway in patients with refractory MPE. The original studies (TIME2, the second Therapeutic Intervention in Malignant Effusion Trial and AMPLE, the Australasian Malignant Pleural Effusion trial)[62 63] used regimes of alternate day drainages and this has been incorporated in routine practice. There has been interest on the optimal drainage regime, whether a once-daily drainage regime would offer better clinical outcomes than the less frequent standard alternate days or whether it would be better to offer drainage when patients are symptomatic (symptom-based/conservative drainage regimes). Hence, the next question was:

> D9 For adults with malignant pleural effusion treated with indwelling pleural catheters, does symptom-based/conservative drainage have better clinical outcomes than daily drainage?

A summary of the evidence review is shown in table 26 and the evidence statements, recommendations and GPPs are presented below. The full evidence review is available in online supplemental appendix D9.

Table 26 Evidence review summary for 'Is symptom-based/conservative drainage better than daily drainage?'

Clinical outcome	Summary of evidence review (symptom-based/conservative drainage vs daily drainage) (95% CI)
Length of hospital stay	No difference*
Pleurodesis rates	Lower with symptom-based/conservative drainage (190/1000 (125 to 293) compared with 431/1000)†
Need for re-intervention	Not reported
Complications	No difference
Symptoms‡	No difference
Quality of life	Reduced with symptom-based/conservative drainage

*Meta-analysis not possible, data reported in different formats.
†Meta-analysis results reported as per 1000 patients.
‡Breathlessness, chest pain.

Evidence statements

- Symptoms (breathlessness and chest pain), complications and length of hospital stay appear to be the same for daily drainage, symptom-guided drainage or alternate daily drainage. (Ungraded)
- There appear to be no differences in the occurrence of complications between daily drainage and symptom-based/conservative drainage regimes. (Low)
- Daily drainage increases pleurodesis rates when compared with alternate drainage or symptom-based drainage regimes. (Low)
- Daily drainage may improve quality of life when compared with a symptom-based/conservative drainage approach, but there is no current evidence that daily drainage improves quality of life when compared with alternate daily drainages. (Ungraded)

Recommendations

- ► Where IPC removal is a priority, daily IPC drainages are recommended to offer increased rates of pleurodesis when compared with less frequent drainages of symptom-guided or alternate drainage regimes. (Conditional)
- ► Patients should be advised that they do not require daily drainage to control symptoms of breathlessness and chest pain if they wish to opt for a less intensive regime. (Strong—by consensus)

Good practice points

- ✓ Decisions on the optimal drainage frequency should be based on patient choice.
- ✓ Informed decision-making should include the explanation of the effect of drainage regimes on the patient-centred outcomes such as breathlessness and the possibility of autopleurodesis during the disease course.
- ✓ Although daily drainage may result in earlier removal of IPC, there may be an associated cost associated with the increased number of drainage events (both to the healthcare system, and to the patient). This has been addressed in a modelling study[2] and should be considered.

Do intrapleural agents (talc or other pleurodesis agents) improve clinical outcomes in patients wih MPE treated with an indwelling pleural catheter?

With the increasing use of IPCs to control breathlessness in patients with MPE, there has been interest in 'combination' procedures, where a pleurodesis agent is inserted via a functioning IPC after a period of drainage. The next clinical question assessed the evidence for the clinical benefits of using this strategy:

> D10 For adults with malignant pleural effusion treated with indwelling pleural catheters, do intrapleural agents (talc or other pleurodesis agents) improve clinical outcomes?

The evidence statements and recommendation are presented below and the full evidence review is available in online supplemental appendix D10.

Evidence statements

Based on one paper:

- Pleurodesis rates and quality of life may be improved in patients with MPE and expandable lung (defined as >75% of hemithorax) who have talc instilled via an IPC. (Ungraded)
- Chest pain and breathlessness may be reduced in patients with MPE and expandable lung (defined as >75% of hemithorax) who have talc instilled via an IPC. (Ungraded)
- Complication rates do not appear to differ between patients with MPE treated with an IPC and talc or placebo. (Ungraded)

Recommendation

- ► Instillation of talc via an IPC should be offered to patients with expandable lung where the clinician or patient deems achieving pleurodesis and IPC removal to be important. (Conditional—by consensus)

Is intrapleural chemotherapy better than systemic treatment for treating pleural malignancy?

SACT provides the mainstay of active treatment for all patients with metastatic cancer, including those with disease spread to the pleura. Symptomatic malignant effusions can affect quality of life, breathing and performance status of these patients and hinder their ability to tolerate SACT, with drainage often needed prior to SACT commencing. Historically, some chemotherapy agents were delivered intrapleurally to act as sclerosants to aid pleurodesis. Recently, with the advent of medical thoracoscopy, regular insertion of IPCs and a growing number of novel anticancer treatments including immunological and biological agents, the intent of delivering intrapleural anticancer treatments has expanded beyond obtaining pleurodesis. Hence, the next question investigated if intrapleural anticancer therapies improve clinical outcomes over systemic treatments:

> D11 For adults with pleural malignancy, is intrapleural chemotherapy better than systemic treatment at improving clinical outcomes?

No studies directly compared intrapleural anticancer therapy with SACT alone, but the five studies included in the review compared:

i. Intrapleural chemotherapy versus intrapleural combination therapy (chemotherapy plus vascular endothelial growth factor (VEGF) inhibitor);
ii. Intrapleural chemotherapy versus intrapleural sodium chloride;
iii. Intrapleural chemotherapy versus intrapleural combination therapy (chemotherapy plus angiogenesis inhibitor);
iv. Intrapleural chemotherapy;
v. Intracavitary (mixed intrapleural and intra-abdominal) chemotherapy versus intracavitary combination therapy (chemotherapy plus angiogenesis inhibitor).

The evidence statements, recommendation and GPP are presented below. The full evidence review is available in online supplemental appendix D11.

Evidence statements

There was no direct evidence to support this question; and based on very limited evidence:

- Intrapleural combination therapies (chemotherapy plus VEGF inhibitor or angiogenesis inhibitor) may improve effusion control and increase quality of life, progression-free survival and survival time when compared with chemotherapy alone.

Recommendation

- ► Intrapleural chemotherapy should not be routinely used for the treatment of MPE. (Conditional—by consensus)

Good practice point

- ✓ All patients of good performance status with metastatic malignancy should be considered for SACT as standard of care as per national guidelines.

Does the use of prognostic or predictive scores provide important prognostic information for the patient?

MPE are associated with short survival as, with the exception of MPM, they signify advanced or metastatic disease. Numerous other factors, including patient characteristics, pleural fluid parameters and biochemical and haematological values have been shown to be related to clinical outcomes in MPE, however these findings have often lacked validation in independent cohorts. Relating separate findings to each other, and interpreting them in the context of patients, is also often difficult. By combining prognostic factors into validated scoring systems, these may be more clinically useful, so final clinical question in this section aimed to determine if validated prognostic scores exist for MPE and, if so, their use improves clinical outcomes for adults with MPE (excluding mesothelioma):

> D12 For adults with pleural malignancy, does the use of prognostic and predictive scores improve clinical outcomes?

No studies compared clinical outcomes in patients who had treatment directed by a prognostic score at baseline compared with those who had treatment directed using standard measures. Two externally validated prognostic scoring systems have been reported for MPE, the LENT (pleural fluid LDH, Eastern Cooperative Oncology Group (ECOG) performance score, neutrophil-to-lymphocyte ratio, tumour type) and PROMISE (pleurodesis response markers in malignant pleural effusion) scores, however the impact of these scores on clinical decision-making and outcomes other than survival has not been evaluated.[64 65]

The LENT score combines pleural fluid LDH levels, ECOG performance status, serum neutrophil-to-lymphocyte ratio (NLR) and underlying tumour type to predict patients at low risk, moderate risk or high risk of mortality.[64] The PROMISE score evaluates seven clinical biomarkers and one pleural fluid biomarker (haemoglobin, CRP, white blood cell count, ECOG performance status, cancer type, pleural fluid tissue inhibitor of metalloproteinases 1 (TIMP1) concentrations and previous chemotherapy or radiotherapy) to predict absolute risk of death at 3 months.[65]

The evidence statements, recommendation and GPPs are presented below. The full evidence review is available in online supplemental appendix D12.

Evidence statements

- LENT and PROMISE provide estimates of survival for patients with MPE, but neither have been assessed in their ability to improve outcomes. (Ungraded)

Recommendations

No recommendation can be made from the presented evidence.

Good practice points

- ✓ Clinicians may consider using a validated risk score for MPE, if the information is of use in planning treatments or in discussion with patients.
- ✓ Patients with pleural malignancy should be managed in a multidisciplinary way, including referral to specialist palliative care services where appropriate.

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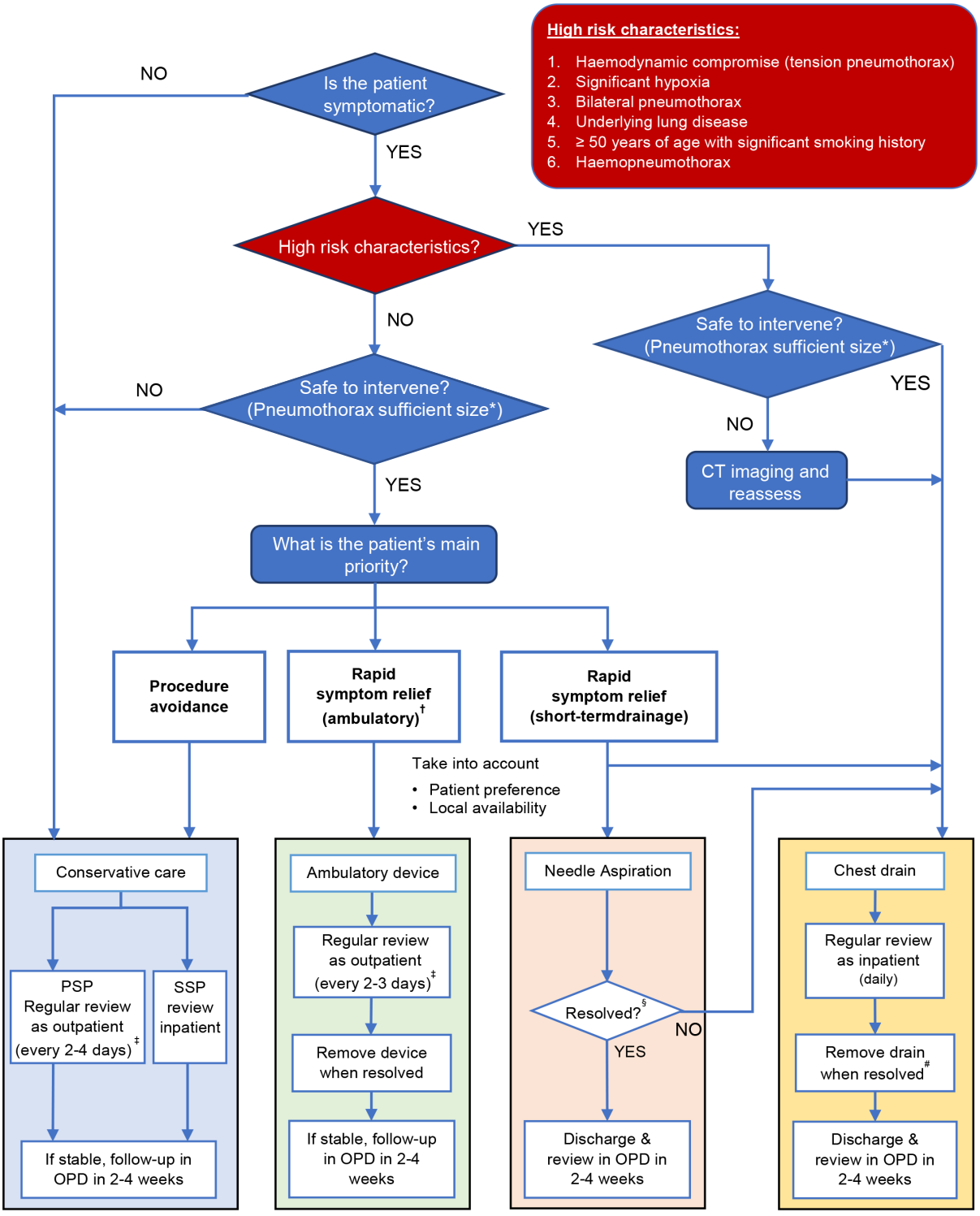
APPENDIX 1 - CLINICAL PATHWAYS/DECISION TREES

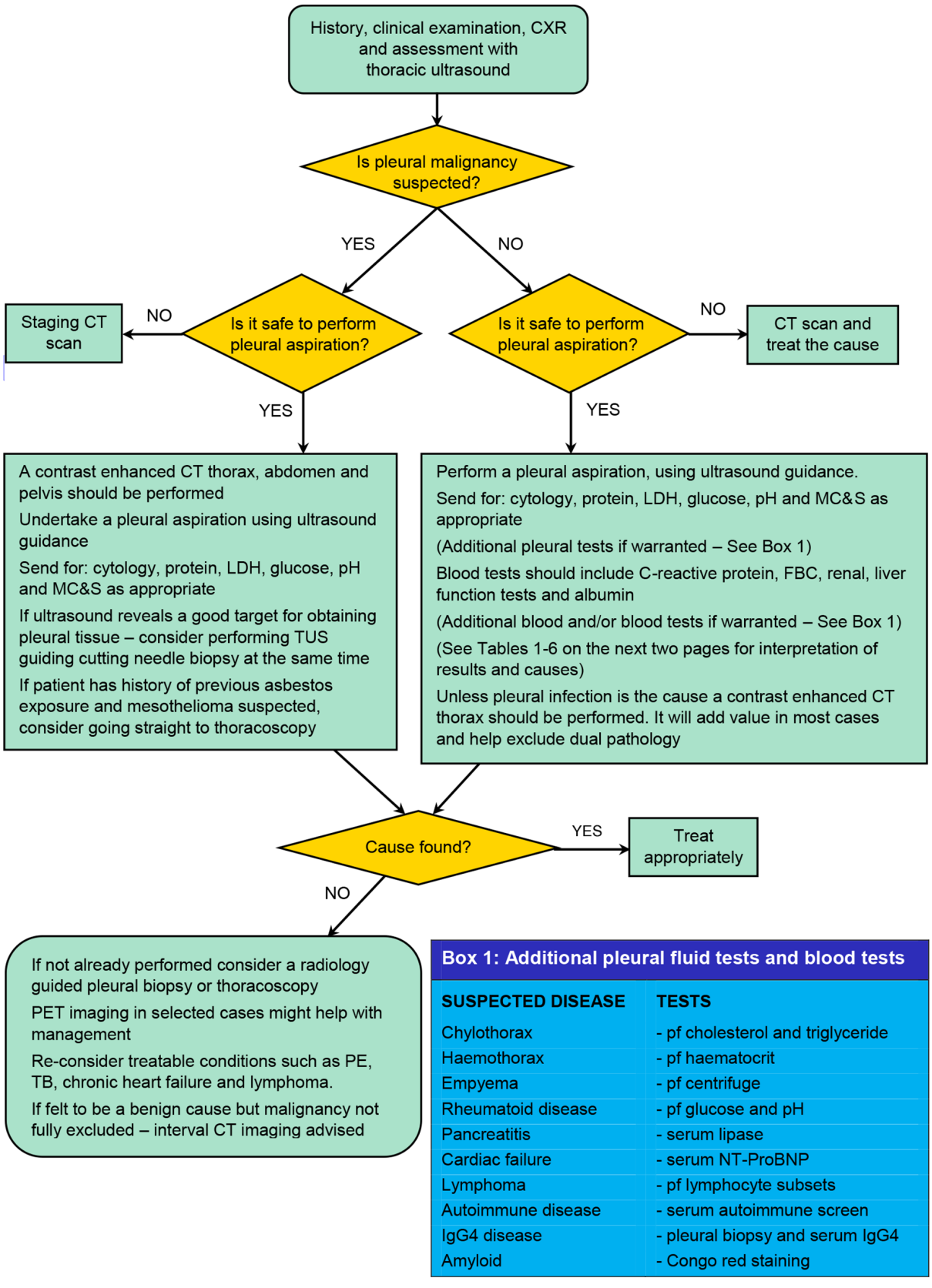
Pneumothorax Pathway



* Pneumothorax of sufficient size to intervene depends on clinical context but, in general, usually ≥ 2cm laterally or apically on CXR, or any size on CT scan which can be safely accessed with radiological support.
† If ambulatory pathway available locally.
‡ At review, if enlarging pneumothorax or symptoms consider chest drain insertion and admission.
§ Success: improvement in symptoms and sustained improvement on CXR.
# Talc pleurodesis can be considered on the first episode of pneumothorax in high risk patients in whom repeat pneumothorax would be hazardous (eg, severe COPD).

CXR, chest X-ray; COPD, chronic obstructive pulmonary disease; OPD, outpatient department; PSP, primary spontaneous pneumothorax; SSP, secondary spontaneous pneumothorax.

Unilateral pleural effusion diagnostic pathway



Box 1: Additional pleural fluid tests and blood tests

SUSPECTED DISEASE	TESTS
Chylothorax	- pf cholesterol and triglyceride
Haemothorax	- pf haematocrit
Empyema	- pf centrifuge
Rheumatoid disease	- pf glucose and pH
Pancreatitis	- serum lipase
Cardiac failure	- serum NT-ProBNP
Lymphoma	- pf lymphocyte subsets
Autoimmune disease	- serum autoimmune screen
IgG4 disease	- pleural biopsy and serum IgG4
Amyloid	- Congo red staining

CXR, chest X-ray; FBC, full blood count; LDH, lactate dehydrogenase; NT-proBNP, N-terminal prohormone brain natriuretic peptide; PE, pulmonary embolism; TB, tuberculosis; TUS, thoracic ultrasound.

Table 1

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

Table 2

Transudates	Exudates
Common	Common
• Congestive cardiac failure	• Malignancy
• Liver cirrhosis	• Pleural infection
• Hypoalbuminaemia	• Pulmonary embolism
• Nephrotic syndrome	• Autoimmune pleuritis
Less common	**Less common**
• Nephrotic syndrome	• Drugs
• Mitral stenosis	• Lymphatic disorders
• Peritoneal dialysis	• Meigs syndrome
• Chronic hypothyroidism	• Post-coronary artery bypass graft
• Constrictive pericarditis	• Benign asbestos related pleural effusion

Table 3

Causes of lymphocytic pleural effusion
Malignancy
Tuberculosis
Lymphoma
Congestive cardiac failure
Post-coronary bypass graft
Rheumatoid arthritis
Chylothorax
Yellow nail syndrome

Table 4

Causes of bilateral pleural effusions
Congestive cardiac failure
Hypoalbuminaemia
Renal failure
Liver failure
SLE and other autoimmune diseases
Widespread malignancy including abdominal/pelvic malignancy
Bilateral pulmonary embolus

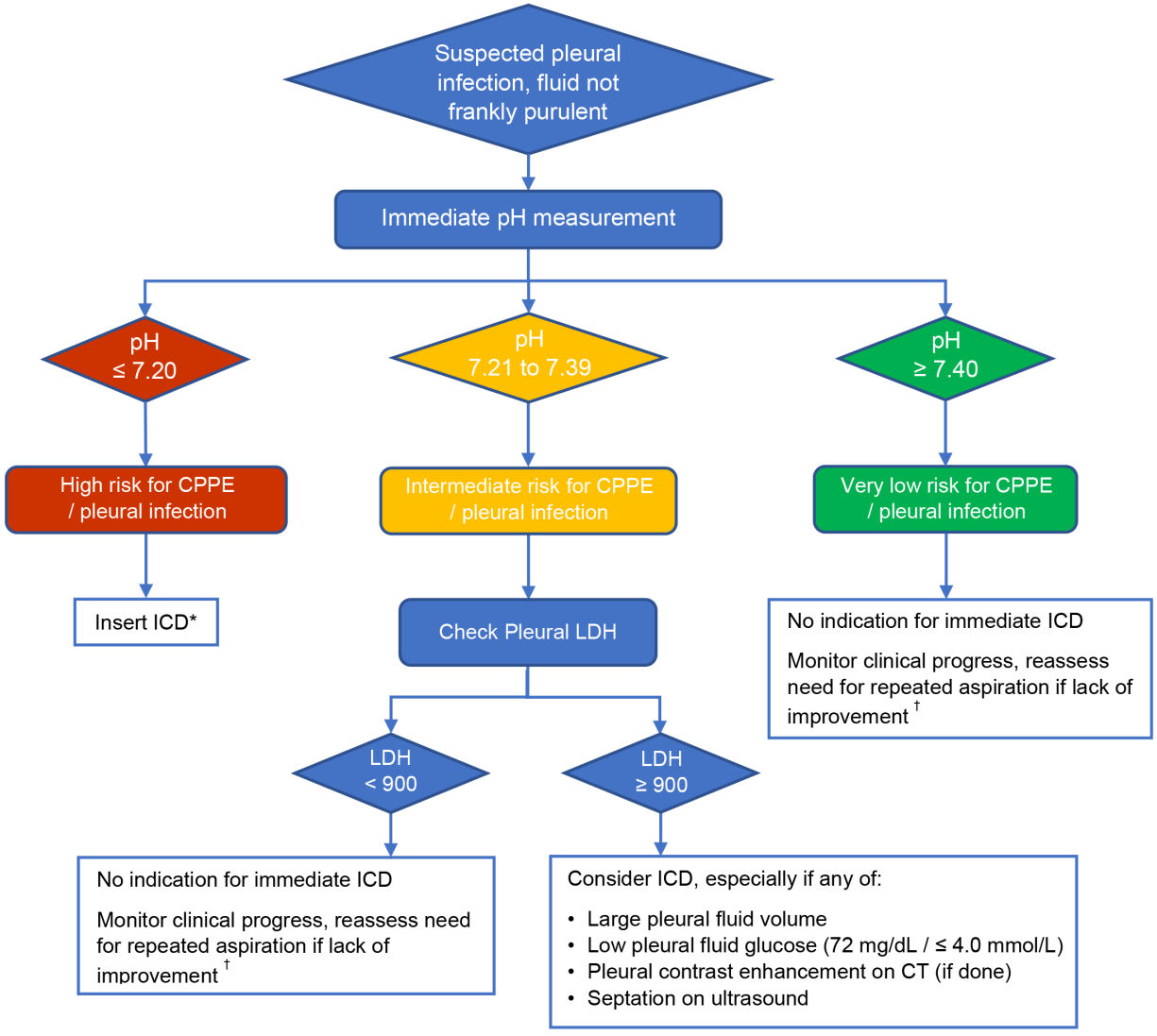
Table 5

Pleural fluid lipid values in chylothorax and pseudochylothorax	
Chylothorax:	
• Triglycerides	– high>1.24 mmol/L (110 mg/dL)
• Cholesterol	– low
• Cholesterol crystals	– absent
• Chylomicrons	– usually present
Pseudochylothorax:	
• Triglycerides	– low
• Cholesterol	– high>5.18 mmol/L (200 mg/dL)
• Cholesterol crystals	– often present
• Chylomicrons	– absent

Table 6

Causes of chylothorax and pseudochylothorax	
Chylothorax:	
• Trauma:	thoracic surgery (especially if involving posterior mediastinum, for example, oesophagectomy), thoracic injuries
• Neoplasm:	lymphoma or metastatic carcinoma
• Miscellaneous:	disorders of lymphatics (including lymphangioleiomyomatosis), tuberculosis, cirrhosis, obstruction of the central veins, chyloascites
• Idiopathic (about 10%)	
Pseudochylothorax:	
• Tuberculosis	
• Rheumatoid arthritis	

Suspected pleural infection, non-purulent fluid – initial decision tree

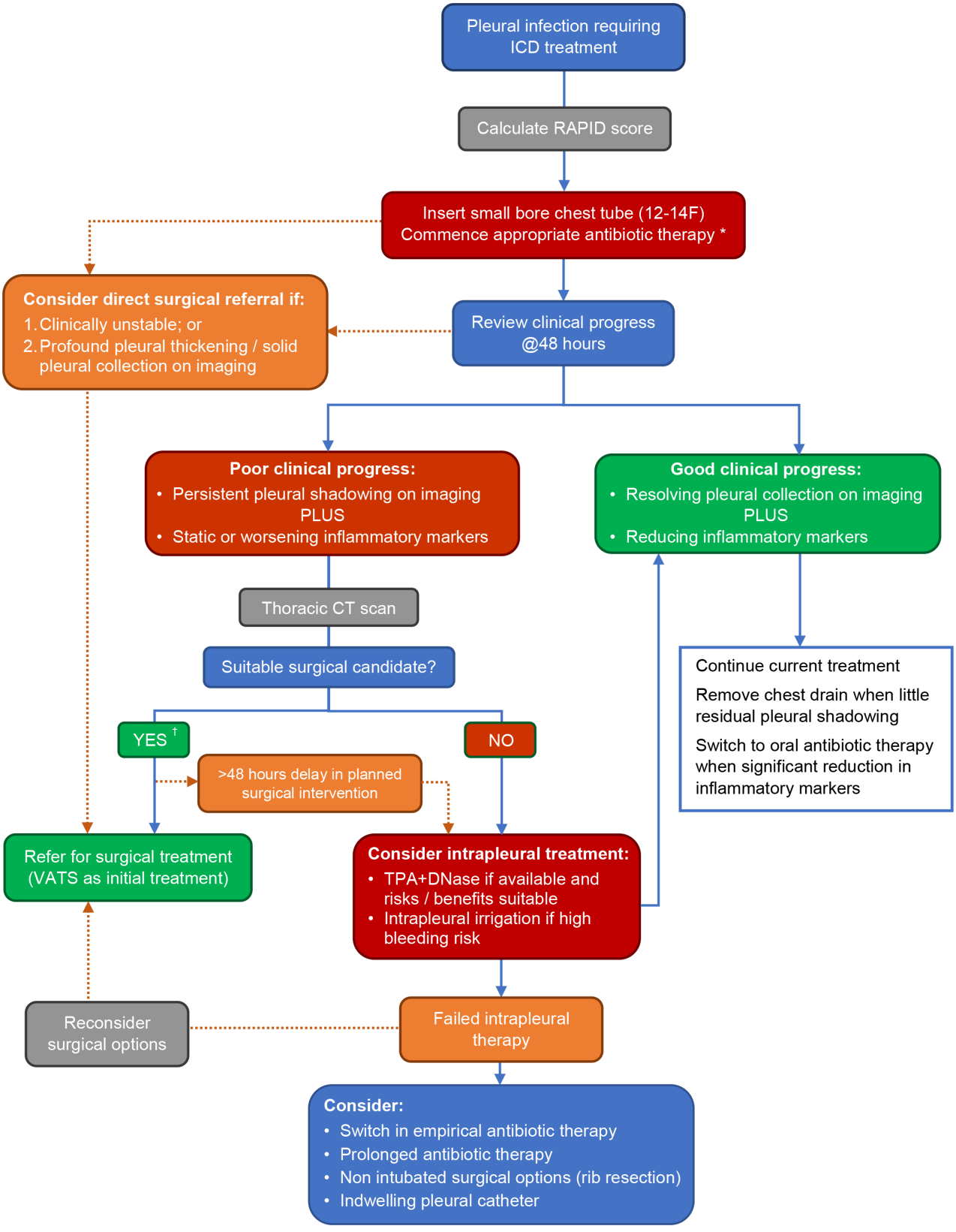


* Assuming ultrasound demonstrates safe volume of accessible pleural fluid.
† As evidenced by ongoing temperature, persisting elevation of inflammatory markers. Those with septations and pleural pH >7.4 should also be considered for drainage.

Initial pH	Level of risk for CPPE / pleural infection	Initial action regarding drainage
≤ 7.2	High risk	Insert ICD, assuming ultrasound demonstrates safe volume of accessible pleural fluid
> 7.2 to < 7.4	Intermediate risk	Check LDH and review other parameters which may support CPPE / pleural infection. Consider ICD insertion if LDH > 900, especially if any of the following: • Large pleural fluid volume • Low pleural fluid glucose (72 mg/dL / ≤ 4.0 mmol/L) • Pleural contrast enhancement on CT • Septation on ultrasound
≥ 7.4	Very low risk	No indication for immediate ICD

CPPE, complex parapneumonic effusion; LDH, lactate dehydrogenase; ICD, intercostal drain.

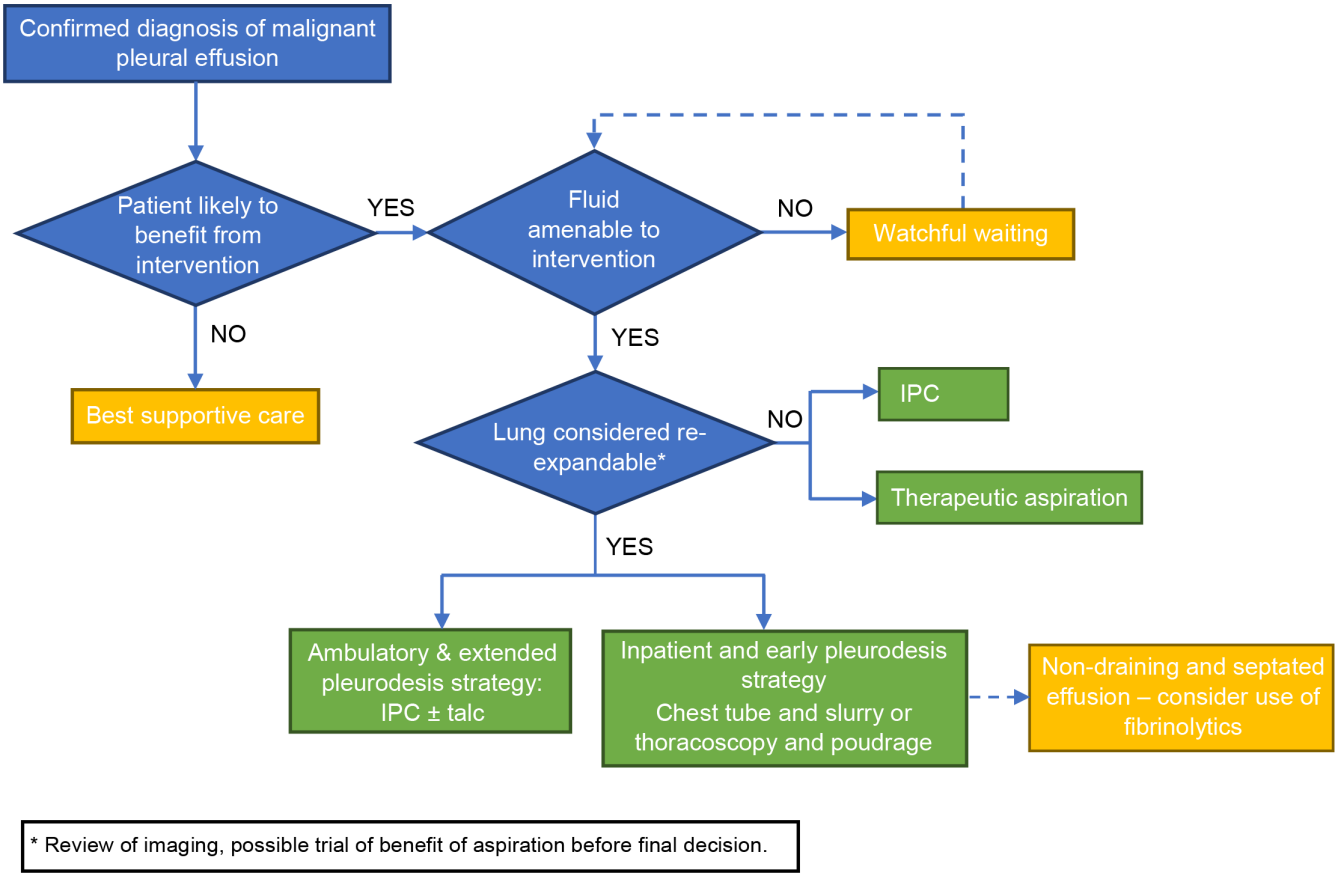
Pleural infection treatment pathway



* Antibiotic therapy should be based on likely organisms initially and adapted according to positive culture results, with consideration of anaerobic cover throughout.
† Intrapleural treatment may be considered prior to surgical treatment in liaison with surgical expertise.

ICD, intercostal drain; TPA, tissue plasminogen activator; VATS, video-assisted thoracoscopy surgery.

Malignant pleural effusion pathway



IPC, indwelling pleural catheter.

APPENDIX 2 – GUIDELINE DEVELOPMENT GROUP MEMBERS

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Mr Richard Bremner	Patient representative (November 2018 – August 2019)
Mr Yannick Mouchilli	Patient representative (November 2018 – August 2020)

APPENDIX 3 – CLINICAL QUESTIONS

Pneumothorax

A1 Are conservative, aspiration, ambulatory, chemical pleurodesis or surgical interventions better than, or as good as, intercostal drainage at improving clinical outcomes in adult pneumothorax patients?

A2 In adults who have resolved their first episode of pneumothorax, is surgery a better elective management strategy than non-surgery at improving clinical outcomes?

A3 In adults with spontaneous pneumothorax and ongoing air leak (excluding post-surgical patients), which treatments are better than ongoing chest tube drainage alone at improving clinical outcomes?

A4 In adults with spontaneous pneumothorax undergoing surgery, what is the optimal operation for improving clinical outcomes?

A5 What is the optimal surgical approach when performing pneumothorax surgery?

Investigation of the undiagnosed pleural effusion

B1 What is the diagnostic accuracy of radiology when diagnosing benign pleural disease as a cause of unilateral pleural effusion in adults?

B2 For adults with suspected unilateral pleural effusion, is image-guided intervention better than non-image-guided intervention at improving clinical outcomes?

B3 What is the optimal volume and container for a pleural aspiration sample when diagnosing unilateral pleural effusion in adults?

B4 What is the diagnostic accuracy of pleural fluid tests when diagnosing adult patients with unilateral pleural effusion?

B5 What is the diagnostic accuracy of serum biomarkers when diagnosing adult patients with unilateral pleural effusion?

B6 What is the diagnostic accuracy of pleural biopsy in adults with suspected pleural disease?

Pleural infection

C1 For adults with pleural infection, what is the best predictor of clinical outcomes?

C2 For adults with pleural infection, do pleural fluid or radiology parameters accurately determine which patients should be treated with intercostal drainage?

C3 For adults with established pleural infection, what initial drainage strategy provides the best clinical outcomes?

C4 For adults with pleural infection, does intrapleural therapy, in comparison to other options (drainage or surgical drainage), improve outcomes?

C5 For adults with pleural infection, which method of surgery provides the best clinical outcomes?

C6 For adults with pleural infection, which surgical approach provides the best clinical outcomes?

Pleural Malignancy

D1 What is the diagnostic accuracy of radiology in adults with suspected pleural malignancy?

D2 For adults with malignant pleural effusion, does systemic therapy avoid the need for definitive pleural intervention?

D3 For adults with malignant pleural effusion, is pleural aspiration with no pleurodesis agent better than talc slurry at improving clinical outcomes?

D4 For adults with malignant pleural effusion, is an indwelling pleural catheter better than talc slurry pleurodesis at improving clinical outcomes?

D5 For adults with malignant pleural effusion, is thoracoscopy (local anaesthetic or VATS) and talc poudrage pleurodesis better than chest drain and talc slurry pleurodesis at improving clinical outcomes?

D6 For adults with malignant pleural effusion, is surgery better than talc slurry pleurodesis at improving clinical outcomes?

D7 For adults with malignant pleural effusion and non-expandable lung, is pleural aspiration, talc slurry pleurodesis, talc poudrage pleurodesis or decortication surgery better than using an indwelling pleural catheter at improving clinical outcomes?

D8 For adults with malignant pleural effusion and septated effusion (on ultrasound or CT), are intrapleural enzymes better than surgery or no treatment at improving clinical outcomes?

D9 For adults with malignant pleural effusion treated with indwelling pleural catheters, does symptom-based drainage have better clinical outcomes than daily drainage?

D10 For adults with malignant pleural effusion treated with indwelling pleural catheters, do intrapleural agents (talc or other pleurodesis agents) improve clinical outcomes?

D11 For adults with pleural malignancy, is intrapleural chemotherapy better than systemic treatment at improving clinical outcomes?

D12 For adults with pleural malignancy, does the use of prognostic and predictive scores improve clinical outcomes?

APPENDIX 4 – STAKEHOLDER ORGANISATIONS

Association for Palliative Medicine of Great Britain & Ireland
Association of Respiratory Nurse Specialists
British Society of Thoracic Imaging
British Thoracic Oncology Group
Royal College of Pathologists
Royal College of Radiologists
Society for Cardiothoracic Surgery in Great Britain & Ireland

BTS Clinical Statement for pleural procedures Clinical Statement Group

Prof Naj Rahman (chair), Dr Rachelle Asciak, Dr Eihab Badawi, Dr Rahul Bhatnagar, Dr Amelia Clive, Dr Maged Hassan, Mrs Heather Lloyd, Dr Raja Reddy, Dr Helen Roberts

On behalf of the British Thoracic Society

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British Thoracic Society Clinical Statement on pleural procedures

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British Thoracic Society Clinical Statement on pleural procedures

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► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/thorax-2022-219371).

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INTRODUCTION

A total of 21 659 pleural aspirations or drain insertions were conducted in England in 2019/2020 with a combined cost of £13.4 million.[1] There are now a variety of different pleural procedures, which have different invasiveness, risks and benefits, and an abundance of data driving high-quality practice in interventional pleural practice. In the context of a number of national safety alerts related to pleural procedures in the last 10 years, it is therefore important that clinicians are as up to date as possible in interventional practice.

This statement is intended to sit in parallel with the BTS Guideline for Pleural Disease 2023,[2] and with a particular focus on pleural interventions in adults. The statement provides a narrative review of areas not covered in the main guideline.

The main statement focuses on important areas of safe clinical practice, patient selection, evidence for complication rates, the consent process and troubleshooting guidance in the following areas:

- Safety and preparation for pleural procedures.
- Pleural aspiration (diagnostic and therapeutic).
- Intercostal drain insertion.
- Indwelling pleural catheter (IPC) insertion, management and removal.
- Image-guided pleural biopsy.
- Medical thoracoscopy.

Online supplemental appendices cover brief "how to" guides on areas that will be of use to clinicians:

1. Local anaesthetic for pleural procedures (online supplemental appendix 1).
2. Sample consent form for pleural procedures (online supplemental appendix 2).
3. Pleural aspiration (online supplemental appendix 3).
4. Intercostal drain insertion (online supplemental appendix 4).
5. IPC insertion technique (online supplemental appendix 5).
6. Image-guided pleural biopsy (online supplemental appendix 6).
7. Medical thoracoscopy (online supplemental appendix 7).
8. How to set up a chest drain bottle and underwater seal drain (online supplemental appendix 8).
9. How to drain an IPC with vacuum bottle (online supplemental appendix 9).
10. Suction and digital chest drain devices (online supplemental appendix 10).
11. Ambulatory devices (online supplemental appendix 11).
12. Intrapleural treatment guides (online supplemental appendix 12).
13. Sample patient information leaflet—IPC (online supplemental appendix 13).

SCOPE

The purpose of this document is to provide concise and pragmatic guidance to help clinicians in secondary care settings to safely undertake pleural interventions in adults.

The statement addresses adults undergoing the following procedures:

1. Pleural aspiration—diagnostic and therapeutic.
2. Intercostal drain insertion—guidewire and blunt dissection (including suture and securing).
3. IPC—insertion and removal.
4. Image-guided pleural biopsy.
5. Medical thoracoscopy—rigid and semi-rigid.
6. Setting up a chest drain bottle/underwater seal/vacuum bottle for IPC.
7. Digital suction.
8. Ambulatory devices.
9. Intrapleural treatment—talc/autologous blood patch/combined intrapleural tissue plasminogen activator (t-PA) and recombinant human DNase/irrigation.

Areas for future research focus are highlighted at the end of each section.

METHODOLOGY

The clinical statement group (CSG) was chaired by NMR, with membership drawn from experts in respiratory medicine and respiratory nursing. The CSG identified key areas requiring clinical practice points and the overall content was developed to reflect the scope approved by the BTS Standards of Care Committee (SOCC). While BTS guidelines follow the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methodology for guideline development,[3 4] which includes a full systematic review of the literature, BTS clinical statements focus on a narrative review of the literature to give a 'snapshot in time' of current knowledge and best practice.[5] Following discussions of broad statement content, individual sections were drafted by group members. A final edited draft was reviewed by the BTS SOCC before posting for public consultation and peer review on the BTS website in

June 2022. The revised document was re-approved by the BTS SOCC in October 2022 before final publication.

SUMMARY OF CLINICAL PRACTICE POINTS

Safety and preparation for pleural procedures

- Before carrying out a pleural procedure, safety and preparation should be taken into consideration.

Pleural aspiration (diagnostic and therapeutic)

- Thoracentesis should be performed above a rib to minimise risk of damage to the neurovascular bundle.
- Thoracic ultrasound (TUS) must be used for aspiration of pleural effusion.
- Small bore needles are preferred to minimise the risk of complications from a thoracentesis.
- For therapeutic pleural aspiration >60 mL, a catheter should be used rather than a needle alone.
- Use of the Veress needle may reduce the risk of damaging underlying structures.
- Routine use of pleural fluid manometry does not help to reduce the risk associated with large volume pleural aspiration.
- Therapeutic pleural aspiration should be performed slowly using either manual syringe aspiration or gravity drainage. Vacuum bottles or wall suction should not be used.
- In general, a maximum of 1.5 L should be drained in one attempt.
- The procedure should be stopped if symptoms of chest tightness, pain, persistent cough or worsening breathlessness develop.

Intercostal drain insertion

- Small-bore drains (<14F) are suitable for most indications including draining empyema.
- Larger bore drains should be considered in unstable trauma patients and pneumothorax complicating mechanical ventilation.
- Consider a larger bore drain (>14F) if pleurodesis is intended.
- Before drain insertion, aspiration of air or fluid with the needle applying the anaesthetic is necessary, and failure to do so should prompt further assessment.
- Where possible, using guards over the plastic dilators for Seldinger drains is advised to reduce the risk of insertion of unnecessary excessive lengths of the sharp-tipped dilators.
- All chest drains should be fixed with a holding suture to prevent fall out.
- A chest drain inserted for managing pleural effusion should be clamped promptly in patients with repetitive coughing or chest pain to avoid re-expansion pulmonary oedema (RPO) which is a potentially fatal complication.
- A follow-up chest radiograph should be conducted within a few hours of insertion to ensure appropriate drain position inside the thorax.
- For pleural fluid, the volume to be drained over specific time periods should be specified in the procedure report and in handover (eg, 500 mL/hour).
- In cases of a non-functioning intercostal drain where another drain is required, the old track must be avoided when inserting the new drain.

IPC insertion, management and removal

- IPCs have a well-defined role in malignant pleural effusion (MPE) management.
- The role of IPCs in transudative non-MPE remains controversial and there is currently insufficient evidence to advocate routine use in transudative non-MPE, although they may have a role in selected patients with very frequent therapeutic aspiration requirements despite optimisation of treatment of the underlying pathology.
- An IPC should not be a contraindication to chemotherapy, although judicious IPC insertion timing, and meticulous aseptic catheter care is advisable.
- After both sutures are removed, patients can have a bath and swim, although care should be taken to keep the IPC site clean and dry, such as with a waterproof dressing and prompt changing of the dressing should it get wet.
- There is a lack of robust data on treatment of non-draining septated IPC-related effusions, however, a trial of intrapleural fibrinolytics may be considered in selected patients.
- Consider removal of IPCs when <50 mL are drained on three consecutive occasions and there is an absence of symptoms of fluid reaccumulation and no substantial residual pleural effusion on imaging.
- Drainage frequency should be guided by patient symptoms, unless aiming for pleurodesis in those with expansile lungs, in which case IPC drainage should be as frequent as possible (daily) as tolerated by the patient.

Ultrasound-guided pleural biopsy

- The preferred patient position is lateral decubitus and biopsies should be targeted along the mid-axillary line to minimise complications.[6]
- A real-time, freehand technique is advocated whereby a suitable site is identified using a low frequency probe (2–5 MHz) and the biopsy performed while the patient remains in the same position. Doppler ultrasound screening of the intercostal vessels using the same probe can be conducted to avoid vessels.[7]
- Inferior biopsy sites closer to the diaphragm have shown to be more likely to elicit positive biopsy samples due to the anatomical predilection of secondary metastases to this area.[8]
- A biopsy site with underlying pleural effusion to act as a buffer is preferable to reduce the risk of lung perforation and subsequent pneumothorax. If pleural fluid is not present it is preferable for the procedure to be performed under CT guidance.
- When preparing the cutting biopsy needle, it is helpful to demonstrate the ‘firing’ mechanism of the needle to the patient outside their chest so as not to cause alarm when they first hear the sound.
- The cutting needle should be angled in a way to ensure that the core of tissue obtained will contain the full thickness of the pleura and the needle tip ends in the pleural fluid creating an oblique biopsy tract.
- While an assistant releases the tissue cores into a cytolyte container (with saline for samples for microbiology) and rinses the needle in a small pre-prepared tray of saline between biopsies, it is useful for the operator to intermittently check for any evidence of bleeding by looking for echogenic material gathering in the pleural space, or use of Doppler.[9]
- Usually at least six cores are obtained (extrapolated from TB practice[10]). If the pleura is not very thickened, it may be judicious to perform more (as the number of passes increases, be aware that the introduction of air with each biopsy may negatively impact the quality of the real-time ultrasound image).

How to set up a chest drain bottle and underwater seal drain

(The clinical practice points below are taken from online supplemental appendix 8)

- Aseptic non-touch technique (ANTT) should be employed when changing a chest drain bottle/underwater seal drain or drain tubing.
- The drain bottle must be kept below the insertion site at all times.
- The drain must be kept upright at all times.
- The drain must have adequate water in the system to cover the end of the tube.
- For patients with pneumothorax and suspected/confirmed COVID-19, a viral filter should be considered to minimise the risk of droplet exposure via the chest drain circuit.
- Drains should be checked daily for wound infection, fluid drainage volumes and the presence of respiratory swinging and/or bubbling should be documented on a dedicated chest drain observation chart.
- Clamping a bubbling chest tube should be avoided unless under specialist pleural supervision and in specific circumstances only.
- Instructions related to chest drain clamping/rate of fluid drainage must be given and recorded.[11 12]
- Drainage of a large pleural effusion should be controlled to prevent the potential complication of RPO.

How to drain an IPC with vacuum bottle

(The clinical practice points below are taken from online supplemental appendix 9)

- All manufacturers' drainage packs contain comprehensive procedure guidelines which should be adhered to.
- The rate of fluid drainage should be slowed or stopped if pain is experienced during drainage.
- Antibiotic therapy should be commenced if IPC-related infection is suspected.
- Prompt referral to the respiratory team is required if pleural infection/empyema is suspected.
- Secondary care advice should be sought in the event drainage stops in the presence of worsening breathlessness.
- If the catheter drains less than 50 mL on three consecutive occasions the respiratory team should be contacted for consideration of catheter removal.

Suction and digital chest drain devices

(The clinical practice points below are taken from online supplemental appendix 10)

- Suction should be avoided soon after drain insertion to minimise the risk of RPO.
- Suction pressures should be prescribed or documented by the medical team before it is commenced and institutions should be consistent about the units of suction they use (KPa/mm Hg/cmH_20).
- Routine use of thoracic suction should be avoided given a lack of data demonstrating clinical benefit.
- If suction is used, low pressure, high volume thoracic suction should be used to minimise complications.
- Digital suction devices are an alternative technology that can be used to deliver thoracic suction and measure air leak. This may have a role in patients with pneumothorax.
- Patients receiving suction should have a viral filter or a digital device should be used to minimise the risk of aerosol generation.

Ambulatory devices

(The clinical practice points below are taken from online supplemental appendix 11)

- Build expertise by using the devices for early ambulation on the ward before establishing an ambulatory pneumothorax service.
- A pleural nurse is an essential component of an ambulatory pneumothorax service.

GLOSSARY

ANTT, Aseptic non-touch technique
BMI, Body mass index.
CPAP, continuous positive airway pressure.
CrCl, creatinine clearance.
CSG, clinical statement group.
CT.
CXR, chest X-ray.
DOAC, direct oral anticoagulant medication.
FBC, full blood count.
GMC, General Medical Council.
HCT, haematocrit.
HFFM, high fraction-inspired oxygen facial mask.
HFNO, high-flow nasal oxygen.
ICU, intensive care unit.
INR, international normalised ratio.
IPC, indwelling pleural catheter.
LAM, lipoaribomannan assay.
LAT, local anaesthetic thoracoscopy.
LDH, lactate dehydrogenase.
LFT, liver function test.
LMWH, low-molecular-weight heparin.
LocSSIPs, local safety standards for invasive procedures.
MC and S microscopy, culture and sensitivity.
MPE, malignant pleural effusion.
NEL, non-expandable lung.
NPSA, National Patient Safety Agency.
PTX, pneumothorax.
RCT, randomised controlled trial.
RPO, re-expansion pulmonary oedema.
SOCC, BTS Standards of Care Committee.
TB, tuberculosis.
t-PA, tissue plasminogen activator.
TUS, thoracic ultrasound.
U&E, urea and electrolytes.
US, ultrasound.
UGBx, ultrasound-guided pleural biopsy.

SAFETY AND PREPARATION FOR PLEURAL PROCEDURES

Pleural procedures are commonly undertaken but are associated with significant risks, and thus, consideration of safety and appropriate preparation are key to good practice.

The following were the views of the committee:

Operator training and competence

- The operator for any pleural procedure should have been adequately trained.
- Operators learning to undertake a pleural procedure must be adequately supervised and should record anonymised details of the procedure in their training portfolio.
- Procedures must be appropriately documented in the medical notes (please refer to 'BTS Guidance to support the implementation of Local Safety Standards for Invasive Procedures

(LocSSIPs)-Bronchoscopy and Pleural Procedures'[13]). In line with the BTS guidance,[13] this should include at least:
  - The intervention conducted.
  - All medication given.
  - The recovery plan and observations required postprocedure.
  - Any immediate complications.
- It is advised that all operators monitor procedure outcomes and complications (see relevant sections for major and common complications).

Consent and preprocedure patient written information

- Informed patient consent must be taken and clearly documented before any pleural procedure, in line with General Medical Council (GMC) recommendations.[14] The discussion should include recognised risks and any risk of serious harm, however unlikely it is to occur. For those without capacity, those close to them, or advocating for them, should be involved.
- The decision to proceed should be reviewed immediately before the procedure, especially in cases of delay between consent being taken and the procedure, or if the operator did not take initial consent. It should be made clear to the patient, or their advocate, that they can withdraw their consent at any time.
- In accordance with GMC guidance, an accurate record of the exchange of information leading to a decision must be kept in the medical notes.[14] Consent forms are a standard way to record decisions which can make regular review easier.
- It is advised that written information for the patient is provided, particularly for more invasive procedures. For elective procedures, where possible, written information should be given to the patient to read in their own time.

Timing of pleural procedures

- It is strongly endorsed that pleural procedures are undertaken in normal working hours wherever possible. Procedures should only be undertaken out of hours in an emergency.

Medication check including antiplatelets and anticoagulation

There are no large prospective studies to accurately define bleeding risk associated with pleural procedures in patients who are taking antiplatelet agents, anticoagulant therapy, or those with coagulopathy.

Several small studies have found no increased bleeding risk of thoracentesis or small-bore chest drain insertion in patients on clopidogrel, or with an uncorrected bleeding risk.[8 15–19]

Elective pleural procedures

The risks and benefits of interrupting medication and/or the need for bridging therapy before the procedure should be discussed with the patient. For those with a high thrombotic risk (eg, cardiac stents), the discussion may need to include other relevant specialty teams.[20]

In line with anticoagulation and antiplatelet therapy guidelines, published in the British Journal of Haematology,[21] when a decision has been made to interrupt medication for an elective procedure:

- It is advised that warfarin is stopped 5 days before the procedure with an international normalised ratio (INR) check preprocedure to confirm INR is ≤1.5.
- Direct oral anticoagulant medication (DOAC) should be stopped 24–48 hours before the procedure. The guidance is based on the drug half-life, the bleeding risk of the procedure, a clinical evaluation of individual risk factors for thrombosis and bleeding, and in the case of dabigatran, the creatinine clearance (CrCl). DOAC should be resumed 1 day after a low risk procedure and 2–3 days after a high risk procedure. Daily prophylactic heparin should be considered for patients at high risk of venous thrombosis prior to DOAC recommencement (figure 1). Clopidogrel and prasugrel should be stopped 5 days pre-elective procedure and ticagrelor 7 days preprocedure. Aspirin therapy and prophylactic dose heparin can be continued.
- No specific guidance is given regarding phosphodiesterase inhibitors, such as dipyridamole, but most local guidelines recommend they should be stopped at least 24 hours before a procedure with a high risk of bleeding.

Emergency pleural procedures

If an emergency procedure is required, it may not be possible to fully treat factors associated with increased bleeding risk, particularly in patients who are taking antiplatelet or anticoagulation agents. The operator should consider the risks and benefits of the proposed procedure and the timing of the procedure. Any bleeding risk should be corrected where practical and in complex situations, input from haematology specialist teams may be required.

Environment, procedure room and aseptic precautions

- All required equipment should be available and prepared before commencing any procedure. Procedures should be undertaken in a clean, dedicated procedure room. Procedures undertaken 'at the bedside' should be avoided.

DOAC	Procedural bleeding risk	Perioperative DOAC management									
		Day -5	Day -4	Day -3	Day -2	Day -1	Day 0	Day +1	Day +2	Day +3	Day +4
Direct Xa inhibitors and Dabigatran (CrCl ≥ 50 mL/min)	Low	✓	✓	✓	✓	OMIT	Day of procedure DO NOT administer any DOAC	✓	✓	✓	✓
	High	✓	✓	✓	OMIT	OMIT		OMIT	Resume day +2 or day +3		✓
Dabigatran (CrCl < 50 mL/min)	Low	✓	✓	✓	OMIT	OMIT		✓	✓	✓	✓
	High	✓	OMIT	OMIT	OMIT	OMIT		OMIT	Resume day +2 or day +3		✓

✓ - DOAC may be taken or administered

Figure 1 Usual time to discontinue DOAC before surgery or invasive procedures for which anticoagulation needs to be stopped. (Reproduced with permission of the British Society for Haematology and John Wiley & Sons 2022 British Society for haematology and John Wiley & Son).[149] DOAC, direct oral anticoagulant medication.

- Equipment/stock lists for specific procedures may help with efficiency and ensure supply of equipment.
- In line with BTS Guidance to implement LocSSIPs for bronchoscopy and pleural procedures,[13] the following should be considered:
  - Sufficient floor space.
  - Scrubbing facilities/sink which should be in the room.
  - The presence of an ultrasound machine.
  - Sterile trollies and space for initial sample processing.
  - Oxygen supply and suction.
  - Patient monitoring equipment.
  - Access to the crash trolley with availability of an advanced life support trained individual.
  - Consideration of safe equipment storage both during and after procedures.

Preprocedure physiological parameters

- Physiological measurements should be measured before, and after pleural procedures (and during for longer procedures as required) to ensure complications are recognised and safety is maintained. In the case of abnormal baseline physiological parameters, operators should be aware that these may influence risk and this information should inform discussions as to the risks/benefits.

Safety checklists

A safety checklist should be completed before, and after, all pleural procedures to reduce harm and risk of complications. A local document should be produced for pleural interventions and detailed guidance is available in 'the BTS Guidance to support the implementation of LocSSIPs-Bronchoscopy and Pleural Procedures'.[13]

Important preprocedure checks include:

- Checking site and side of procedure (particularly important in pleural procedures).
- Verification of patient details.
- Review of consent.
- Review of radiology.
- Allergy review.
- Review of bleeding and other patient-specific risks.
- Marking of procedure site if appropriate.
- Review of monitoring equipment.

Important postprocedure checks include:

- Confirmation of the procedure site and side.
- Specimen count and correct label check.
- Recovery management plan.
- Documentation of any equipment issues.
- Completion of the procedure report.
- Medication check and signature.
- Disposal of equipment confirmation.

Preprocedural investigations

A set of routine blood tests (full blood count, urea and electrolytes, liver function test) prior to the procedure are normally conducted to identify potential causes of breathlessness or pleural pathology. There is no agreement on timing of preprocedure blood tests.

Coagulation profile check is not required if there is no past history of coagulopathy and the patient is not on anticoagulants.[22]

In patients with cirrhosis, the EASL (European Association for the study of the liver) guidelines state that traditional haemostasis tests cannot generally predict procedural bleeding risk although they may guide management in the case of postprocedure bleeding. Specific recommendations can be found at EASL Clinical Practice Guidelines on prevention and management of bleeding and thrombosis in patients with cirrhosis.[23]

Preprocedural imaging in the operative position and marking of position

A recent radiological image (chest X-ray (CXR), CT or ultrasound) should be available to confirm the indication for the procedure and side of the pathology.[24] The only exception of note is tension pneumothorax. This is diagnosed using clinical signs and should be treated urgently without imaging if required.

Ultrasound guidance is mandatory prior to pleural fluid procedures (except in emergency situations) and in the position the procedure is done. This allows marking of the appropriate site for the procedure (with the procedure conducted immediately after and without moving the patient) and reduces risk of inadvertently operating on the wrong side. Overall, use of ultrasound guidance in pleural aspiration increases yield and reduces risk of complications; in particular the risk of pneumothoraces and inadvertent organ puncture.[25] Ultrasound guidance will reveal underlying abnormalities not apparent on plain chest radiograph such as cardiac enlargement/displacement, a raised hemidiaphragm or adherent lung.

In patients with pneumothorax, ultrasound is generally not required (as the CXR provides sufficient information and ultrasound does not permit assessment of lung position) but can be useful in locating a site for chest drain insertion in cases of loculated pneumothorax/tethered lung.[26] The use of ultrasound requires training and expertise as described in the British Thoracic Society Training Standards for TUS.[25]

CT guidance may be required in some situations, including loculated pneumothorax with tethered lung, the presence of bullae, or posteriorly loculated pleural fluid collections, where sonographic views are not optimal.

Local anaesthesia

Lidocaine 1% (10 mg/mL) is the most common preparation used for local anaesthesia at a dose of up to 3 mg/kg (max. 250 mg=25 mL). However, there is no consensus on the maximum dose and many use doses of up to 4.5 mg/kg (max. 300 mg or 30 mL) without significant increase in side effects.[27] Combination of lidocaine with 1:200 000 adrenaline allows larger dose of up to 7 mg/kg (max 500 mg or 50 mL of 1% lidocaine) to be infiltrated.[28] Larger volumes (rather than doses) aid spread of the effective anaesthetic area and therefore a dilute preparation (1% rather than 2%) is preferable. Smaller volumes are sufficient for simple procedures such as diagnostic pleural aspiration and larger volumes for more invasive procedures such as medical thoracoscopy.

Please see online supplemental appendix 1 (Local anaesthetic for pleural procedures) for a guide on how to target local anaesthesia for pleural procedures.

General aftercare applicable to all pleural procedures

Patients should be carefully observed after the procedure, with the duration dependent on the specific procedure. For simple procedures (such as pleural aspiration) a set of observations soon after the procedure is sufficient provided that observations remain stable. However, for major procedures, such as thoracoscopy, there is no consensus as to the frequency of observations, but more frequent observations are advisable during and immediately after the procedure (table 1).[12]

Table 1 Advised postprocedure monitoring for pleural procedures

Procedure	Postprocedure observations	Monitoring
Pleural aspiration	Immediately after completion of procedure	None unless admitted
Chest drain or IPC* insertion	Immediately after completion of procedure and at 15 min	Every 30 min for 1 hour followed by four hourly observations (if admitted)
Thoracoscopy	Continuous until completion of procedure and at 15 min	Every 30 min for 1 hour followed by four hourly observations

*IPC insertions should be observed for a minimum of 30 min before discharge.
IPC, indwelling pleural catheter.

Clinical practice point

- Before carrying out a pleural procedure, safety and preparation should be taken into consideration

Research questions

- Do drugs such as clopidogrel need to be withheld in patients undergoing pleural procedures including thoracoscopy?
- Can pleural procedures be undertaken safely within a 20–24 hour window in patients taking low-molecular-weight heparin with normal renal function?

PLEURAL ASPIRATION (DIAGNOSTIC AND THERAPEUTIC)

Indications and relative contraindications

Pleural aspiration (thoracocentesis/thoracentesis) may be performed for diagnostic purposes when a sample of around 50 mL of fluid is removed, or for therapeutic purposes where between 500 mL and 1500 mL is removed to relieve symptoms. Indications[29] and contraindications are summarised in box 1 and box 2. Box 2 identifies relative contraindications to pleural aspiration whereby risks of adverse outcome may be increased, and caution may be required.

Complications

Pleural aspiration is a low-risk intervention; however, the most serious complications such as pneumothorax, haemothorax and RPO can lead to increased morbidity, mortality and healthcare cost.[26 30] Other complications which should be included in the consent process include pain, infection, vasovagal syncope, other organ puncture and procedure failure, including failure to make a diagnosis or improve breathlessness. The frequency of these complications is discussed below.

Pneumothorax

Pneumothorax is the most common complication associated with pleural aspiration, although the incidence varies widely between series. The identification of a pneumothorax on a post aspiration CXR can result from a number of mechanisms:

- Iatrogenic pneumothorax due to an alveolar/bronchopleural fistula caused by either inadvertent puncture of the visceral pleura or shearing of the visceral pleura during lung re-expansion.
- Non-expandable lung (NEL or pneumothorax ex vacuo) where a thickened visceral pleural rind reduces elasticity of the visceral pleura, preventing lung re-expansion when effusion is aspirated.
- Entrainment of air into the pleural cavity through the aspiration device during the procedure.

Therefore, the true incidence of clinically significant postprocedural pneumothorax is difficult to establish, as many small pneumothoraces identified on CXR are a result of entrainment of air or NEL which are of no clinical consequence.

Several studies have demonstrated ultrasound guidance reduces pneumothorax incidence.[31–36] Risk of iatrogenic pneumothorax may be increased when larger volumes of fluid are removed[37–40] in underweight patients[37] and may be related to operator experience and smaller depth of fluid marking.[40] A summary of the risk data is presented in Appendix 1 which can be used as a guide to inform consent discussions.

Bleeding

Bleeding complications following pleural aspiration are uncommon although iatrogenic intrapleural haemorrhage is potentially life-threatening (see Appendix 1).

Appropriate site selection is important to reduce risk of haemorrhage. The aspiration site should always be directly above a rib

Box 1 Indications for pleural aspiration[29]

Pneumothorax
⇒ Spontaneous primary pneumothorax (any size).
⇒ Small secondary spontaneous pneumothorax.

Pleural effusions
⇒ Small volume aspiration for diagnosis.
⇒ Larger volume aspiration to relieve symptoms of dyspnoea.
⇒ Evaluate whether non-expandable lung is present to help guide future management (particularly in MPE).
⇒ In the context of sepsis (suspected empyema), a diagnostic aspiration may help guide management (eg, need for chest drain).

MPE, malignant pleural effusion.

Box 2 Relative contraindications to pleural aspiration

⇒ Uncooperative patient.
⇒ Coagulopathy or concurrent anticoagulation treatment (see safety and preparation section).
⇒ Local infection/cutaneous disease at proposed puncture site.

Pneumothorax
⇒ No safe site for aspiration of pneumothorax (eg, lung tethering, suspicion of bullous disease mimicking pneumothorax, small volume pneumothorax).
⇒ Mechanical ventilation which may increase the likelihood of tension pneumothorax or bronchopleural fistula (chest drain preferred).

Pleural effusions
⇒ No availability of thoracic ultrasound to identify procedure site.
⇒ No safe site for aspiration of fluid identified on thoracic ultrasound (very small or posterior fluid collections (given risk to neurovascular bundle)).

to avoid the neurovascular bundle. A posterior approach should be avoided as the neurovascular bundle may not be covered by the lower flange of the rib in this position.[41 42] The preferred site of insertion of the needle should be the triangle of safety, directly above a rib to avoid accidental puncture of the intercostal vessels.[43]

There are some early data to show it may be feasible to use doppler ultrasound to identify intercostal vessels to minimise the risk of puncture, although there is, as yet, no comparative evidence to suggest this reduces bleeding complications.[7 41]

Re-expansion pulmonary oedema

RPO is a rare but potentially life-threatening complication, characterised by development of hypoxaemia and new diffuse alveolar infiltrates as a result of rapid lung re-expansion, usually occurring within the first hour after thoracentesis.[44 45]

The true incidence of RPO is not well established, particularly as some patients may display radiographic changes on CXR without substantial symptoms and for most, symptoms resolve spontaneously.[46] The largest case series report symptomatic RPO in <1% of patients undergoing thoracentesis.[37 46] The National Patient Safety Agency (2020) recorded 16 UK incidents of RPO over 3 years (including two deaths and one cardiac arrest).[12] As a result, an alert was issued to highlight the risk and ensure close monitoring of patients after chest drain insertion and controlled drainage of large effusions.

RPO has been reported following drain insertion for pneumothorax. Limiting the rate of lung re-expansion in this setting is more challenging given the rare but serious risk of tension by clamping a bubbling drain.

Management of RPO is summarised in box 3.

Minor complications

There is a scarcity of published data regarding incidence of minor complications associated with thoracentesis, particularly related to iatrogenic infection. Symptoms of chest discomfort, cough or low oxygen saturations should prompt early termination of the procedure, but these usually settle shortly afterwards. The consent process should include the risk of failure to make a diagnosis from the diagnostic samples (see online supplemental appendix 2 (Sample consent form for pleural procedures)). Pleural fluid cytology has a diagnostic sensitivity of around 60% for all malignancies,[29 47] however, with the development of personalised oncological treatments, 47% of cytology positive effusions may contain insufficient material to permit molecular testing and guide oncological treatment.[48] The initial pleural aspiration therefore may not achieve either definitive diagnosis or treatment given the recent advances in oncological treatments. The 2015 BTS national pleural procedures and patient safety audit[49] recorded some minor complications in 1162 patients undergoing either diagnostic or therapeutic aspiration (included in Appendix 1).

A brief guide on how to perform a pleural aspiration and the equipment required is shown in online supplemental appendix 3 (Pleural aspiration).

Box 3 Management of re-expansion pulmonary oedema

1. Rapid A–E assessment, including full set of observations.
2. If chest drain in situ for pleural effusion, clamp the drain or stop therapeutic aspiration.
3. Commence oxygen according to target prescribed oxygen saturations.
4. Request urgent CXR to confirm drain position and assess for complications.
5. Consider:
   - ICU referral if appropriate
   - CPAP/HFNO/HFFM (if the patient has a pneumothorax as the indication of drain insertion, a functional, open chest drain must be in situ if CPAP is considered, given risk of worsening pneumothorax and risk of tension by the positive pressure).
   - Opiates and diuretics are suggested by some practitioners (not evidence based).

CPAP, continuous positive airway pressure; CXR, chest X-ray; HFFM, high fraction-inspired oxygen facial mask; HFNO, high-flow nasal oxygen; ICU, intensive care unit.

Size and type of needle

Small bore needles should be used to minimise the risks associated with diagnostic pleural aspiration (often a 21G/40 mm (green) needle is used). Although a number of observational studies have suggested, using univariate analysis, that smaller needles reduce the risk of postprocedure pneumothorax, this association was not maintained when considering other factors in multivariable analysis (thoracentesis method, effusion amount and tap type).[50 51] Other observational case series did not find an association between needle diameter and pneumothorax risk.[52]

If inadvertent puncture of an intercostal vessel or visceral injury occurs during the procedure, smaller needles are theoretically likely to result in less damage than larger needles, although there are no comparative studies.

The depth of the pleural cavity from the skin surface varies between patients and can exceed that of a 21G/40 mm (green) needle often used for diagnostic aspiration.[53] The distance from the skin to the parietal pleura can be measured using ultrasound to select optimal needle length, and measurement of effusion depth can ensure the needle is not advanced too far, risking damage to distal structures.

Commercially available therapeutic pleural aspiration kits generally have a larger needle diameter than would routinely be used for a diagnostic aspiration (6F (2 mm outer diameter) or 8F (2.7 mm outer diameter) vs 0.9 mm outer diameter for a 21G needle).

Speed and method of drainage

Given the rare but potentially serious complication of RPO, the use of pleural fluid manometry to monitor pleural pressure and elastance change has been evaluated, but has not been shown to predict development of RPO.[38] A recent randomised controlled trial (RCT) of 191 patients comparing manometry-guided to symptom-guided large volume therapeutic thoracentesis found no difference in patient symptoms, suggesting that use of manometry does not prevent pain or procedure-related complications.[54]

The speed of pleural fluid drainage may be of importance in preventing complications. Theoretically, slower, more controlled drainage may allow the lung to re-expand more gradually and symptoms/signs that might suggest the onset of RPO (such as worsening breathlessness, hypoxia or chest tightness) to be identified earlier, allowing the procedure to be stopped before more serious symptoms develop. The aspiration kit should include a three-way tap (or equivalent) to allow drainage to be terminated quickly if needed (NPSA 2020).[12]

A recent RCT of 100 patients undergoing therapeutic pleural aspiration compared syringe manual evacuation (n=49) with continuous suction (vacuum bottle or wall system (n=51)) and found that vacuum use was associate with more complications, including pneumothorax (0 in the manual group vs 3 in the vacuum group), haemothorax (0 vs 1, respectively) and RPO (0 vs 1, respectively). Patients in the vacuum group were more likely to have the procedure terminated early (1 vs 8) and suffered more pain, although the procedures were faster. Therefore, manual aspiration appears safer and better tolerated than vacuum drainage.[55]

The GRAVITAS Trial randomised 142 patients undergoing therapeutic pleural aspiration to either active aspiration using a syringe or drainage by gravity. This demonstrated no difference in chest discomfort 5 min after the procedure or discomfort/breathlessness within 48 hours. Gravity drainage took substantially longer, although the amount of time gained was modest (7.4 min (10.2–4.6), mean difference (CIs), p<0.001).[56]

The use of aspiration via syringe or gravity for therapeutic aspiration is therefore advised. Vacuum drainage bottles or wall suction should be avoided in therapeutic thoracentesis.

Volume of drainage for a single procedure

For a diagnostic pleural aspiration, the use of a 60 mL syringe should provide ample fluid for diagnostic sampling. An overview of fluid to be sent routinely and in specific scenarios is summarised in table 2.

The maximum volume that should be safely drained during a single procedure has been subject to debate, given concerns regarding RPO and postprocedure pneumothorax. There are reports of large volumes being aspirated at one time without complication,[46] however, guidance is conservative due to the potentially high mortality of RPO if it does occur. As discussed in the previous section on complications, large volume aspiration may also increase the risk of postprocedure pneumothorax.[37 40]

Table 2 Pleural fluid diagnostics tests and sample collection guidance

Test	Notes		
Fluid appearance			
Advised 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. Light's criteria: The fluid is an exudate if one or more of the following criteria are met: ► Pleural fluid protein is more than half the serum protein ► Pleural fluid LDH is more than 0.6 times the serum LDH ► Pleural fluid LDH is more than 2/3 the upper limit of normal of the serum LDH		
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	At least 25 mL in a plain universal container. Refrigerate if delay in processing anticipated (eg, out of hours).		
Glucose	Useful in establishing degree of pleural inflammation and the diagnosis of pleural infection where pH measurement is not reliable, and useful in diagnosis of rheumatoid effusion. 1–2 mL in fluoride oxalate tube sent to biochemistry.		
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 and consider use of a fine bore needle to prevent machine damage.		
Acid-fast bacilli and TB culture	When there is clinical suspicion of TB pleuritis, or in areas of high TB prevalence. Request with MC and S. 5 mL sample in plain container.		
Triglycerides and cholesterol	To distinguish chylothorax from pseudochylothorax in milky effusions.		
		Pseudochylothorax	Chylothorax
	Common causes	► TB ► Rheumatoid arthritis	► Trauma (including thoracic surgery) ► Neoplasia ► Other lymphatic disorders (eg, LAM); TB; cirrhosis; chyloascites ► Idiopathic (10%)
	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
Amylase	Pleural fluid amylase/serum amylase >1 may suggest pancreatitis-related effusion. Can usually be requested with routine biochemistry.		
Haematocrit	>50% of serum HCT supports diagnosis of haemothorax. 1–2 mL sample in EDTA container sent to haematology.		
Flow cytometry and cytogenetics	Useful for the diagnosis of haematological malignancy, particularly in undiagnosed lymphocytic effusions (discuss with local haematology lab for guidance on sample container and volume required).		
Pleural fluid ADA	Useful in diagnosis of TB pleuritis in areas of high TB prevalence as a rule out test.		

ADA, adenosine deaminase; HCT, haematocrit; LAM, lipoaribomannan assay; LDH, lactate dehydrogenase; MC and S, microscopy, culture and sensitivity; TB, tuberculosis.

Symptoms of chest tightness, pain or breathlessness during an aspiration may be a marker of impending RPO or non-expandable lung and the procedure should be stopped if these occur.

In light of this, 1.5 L is advised as a maximum drainage volume in one attempt; however, should the patient develop symptoms at a lower volume the aspiration should be stopped. Larger volumes may be aspirated under certain circumstances with monitoring by expert teams.

Postprocedure imaging

Whether to perform a CXR after a pleural aspiration depends on the clinical context.

For immediate safety reasons, if a patient develops symptoms which do not resolve promptly after aspiration, if the procedure is complicated or if multiple aspiration attempts are required, a CXR should be considered to evaluate for possible complications. However, if the procedure is straightforward and the patient is asymptomatic, a routine CXR is not required.

A CXR may, however, be useful in other circumstances; in those with MPE, a postprocedure CXR is useful to identify substantial non-expandable lung, which may alter future decisions regarding appropriateness of talc pleurodesis.[57] CXRs should be considered as a record of the post aspiration appearance, if ultrasound images are not available on PACS.

Clinical practice points

- Thoracentesis should be performed above a rib to minimise risk of damage to the neurovascular bundle.
- TUS must be used for aspiration of pleural effusion.
- Small bore needles are preferred to minimise the risk of complications from a thoracentesis.
- For therapeutic pleural aspiration >60 mL, a catheter should be used rather than a needle alone.
- Use of the Veress needle may reduce the risk of damaging underlying structures.
- Routine use of pleural fluid manometry does not help to reduce the risk associated with large volume pleural aspiration.
- Therapeutic pleural aspiration should be performed slowly using either manual syringe aspiration or gravity drainage. Vacuum bottles or wall suction should not be used.
- In general, a maximum of 1.5 L should be drained in one attempt
- The procedure should be stopped if symptoms of chest tightness, pain, persistent cough or worsening breathlessness develop

Research question

- Does the use of doppler ultrasound to identify intercostal vessels reduce the risk of puncture and reduce bleeding complications?

INTERCOSTAL DRAIN INSERTION

The size of intercostal (chest) drains is measured in 'French' units which equal one third of a mm[58] and thus a 12F drain has an outer diameter of 4 mm. Chest drains are traditionally described as small-bore if their calibre is 14F or less and large bore for larger sizes.[59]

The usual method for inserting small-bore drains is the Seldinger technique (ie, using a guidewire).[60] Large-bore drains (particularly >20F) are mainly inserted by means of blunt dissection. Some chest drains come equipped with a sharp-tipped metal trocar. This can be used as a scaffold to 'thrust' the drain into the pleural cavity without dissection, but this technique should be avoided as it can result in potentially fatal complications.[58 61 62]

The choice of type of chest drain should depend on indication, training/and expertise of the operator. Small-bore drains seem to be associated with less pain during insertion[63 64] while in situ,[63–65] requiring a smaller incision, and leaving a smaller scar which usually does not need a closing suture.[66] On the other hand, large-bore drains have less tendency to kink or block.[66] In a BTS audit of chest drain practices in more than 100 hospitals in the UK in 2011, 88% of chest drains inserted were Seldinger drains (6–16F).[49]

Indications

In general, there are no absolute contraindications for chest drain insertion especially in emergencies.[58] The indications for inserting a chest drain are listed in box 4.

Drain size

Seldinger drains of up to 12F bore are suitable for most indications. In certain situations such as post thoracic surgery, haemothorax in an unstable patient, or pneumothorax with substantial air leak (in trauma, secondary pneumothorax or ventilated patients) a large-bore drain is required.[59 67] In an ex vivo experiment using a model simulating drainage of a massive haemothorax, 28F drains offered the best balance between efficiency of flow rate, less tendency to block and smaller size.[68] Thus, in situations where a larger bore drain is required, sizes larger than 32F are unlikely to be necessary.[69] A consensus statement of four international societies of thoracic surgeons recommended the use of chest drains of 28–32F post thoracotomy.[70]

Spontaneous or iatrogenic pneumothorax[59 67] and pleural infection (including frank empyema[64]) can be managed with chest drains <14F. However, larger-bore drains are the preferred first choice by some operators for cases with secondary spontaneous pneumothorax who may have large air leaks. Patients with pneumothorax that occurs as a complication of barotrauma from mechanical ventilation may be better managed with larger bore drains, as smaller drains appear to have lower success rates.[71] The BTS Guideline for Pleural Disease 2023 can be consulted for specific guidance on the management of pneumothorax due to different aetiologies.[2]

Meta-analyses of studies on different chest drain sizes for pleurodesis show similar risks of procedure failure with large- and small-bore drains.[72 73] However, these meta-analyses combined results from observational and interventional studies. The only RCT with adequate sample size found small-bore drains to be non-inferior to large-bore drains in terms of pleurodesis efficacy.[65] Chest drains inserted with a view to talc slurry pleurodesis should be at least 12F (and probably of larger size to ensure

Box 4 Indications for chest drain insertion

⇒ Pneumothorax failing other treatments.
⇒ Simple drainage of large benign or malignant pleural effusions.
⇒ Symptomatic pleural effusions in patients on mechanical ventilation.
⇒ Talc pleurodesis.
⇒ Pleural infection.
⇒ Traumatic haemothorax and/or pneumothorax.
⇒ Post thoracic cavity procedures (ie, medical thoracoscopy, thoracic, oesophageal or cardiac surgery).

good quality pleurodesis, eg, 18F) as smaller drains may easily block with talc particles.

In trauma patients with haemothorax or pneumothorax, it is customary to insert large-bore drains which are less susceptible to blockage with blood clots and are better able to handle large air leaks.[59 74] While this is the case for unstable trauma patients, several studies have challenged this tradition for more stable patients. In cases of traumatic pneumothorax 14F drains were as effective as 28F drains with no increased complications.[63 75] Similarly, small-bore drains have been used to drain traumatic haemothorax in stable patients with no excess failure or complication rate.[74 75]

Procedure planning

Patient positioning, choice of insertion site and a brief procedure guide are covered in online supplemental appendix 4 (Intercostal drain insertion).

Complications

Despite being considered a generally safe procedure, chest drain insertion is associated with complications in 8%–20%.[76–79]

Mortality directly related to chest drain insertion is related to either the occurrence of RPO or organ puncture.[80] Fortunately, mortality is rare and has not been encountered in large series by Jackson *et al*[76] and Kong *et al*,[81] but a mortality rate of 0.1% was reported in the 2015 BTS Pleural procedures and patient safety audit.[49] Many of the serious complications involving organ damage have been reported in procedures where the 'trocar technique' was used.[58 61 62] Reported rates of organ puncture vary from 0% to 0.6%.[49 76 77 81] Complications are grouped as immediate, insertional or delayed and a table summarising the rates of different complications is shown in Appendix 2.

Post insertion care

The rate of fluid drainage after insertion should follow the advice above to avoid RPO. Regardless of volume, chest drains should be promptly clamped in any patient with repetitive coughing or chest pain to avoid complications.[62] Pneumothorax drainage, particularly when pneumothorax size is large, carries a risk of RPO which is evident radiologically in up to one third of cases, although a minority are symptomatic.[82] Therefore routine application of suction at the initial drainage of pneumothorax is not advised.[61] Management of RPO is detailed above.

An intercostal drain insertion report should mention details of sutures used, distance at which the drain was fixed, colour of fluid drained, instructions for when to clamp/unclamp the drain, follow-up imaging needed and who to contact in case of complications with the drain. In locked drains, instruction on how to release the lock prior to removal must be clearly documented. A follow-up chest radiograph should be conducted within a few hours of insertion to ensure appropriate drain position. It is good practice for the operator inserting the chest drain to prescribe appropriate analgesia, prophylactic anticoagulation, and 6–8 hourly 30 mL saline flushes (for small bore drains) to ensure this is not missed in handover.

Removal

The decision to remove a chest drain depends on the clinical situation. In pneumothorax, when there is full lung re-expansion and cessation of air leak, performing a 'clamping trial' (to unmask a less visible air leak) is not uniformly performed. In a 2001 American College of Chest Physicians panel on pneumothorax management, only half of panel members would conduct a clamping test before removing a chest drain for a patient with a primary (47% of the respondents) or secondary (59% of the respondents) pneumothorax.[83] Retrospective data from traumatic pneumothorax series show conflicting results on whether clamping trials reduce need for further ipsilateral invasive pleural procedures.[84 85] Notably, in one of the studies, a clamping trial unveiled a small air leak in two of 214 cases (<1%). Prospective studies are needed to inform practice and to explore the potential utility of digital suction devices in measuring extent of air leak prior to chest drain removal.

The task of drain removal should be conducted by suitably trained individuals depending on setting. In some settings, nurses are trained in removal of Seldinger and large bore drains. The timing of removal (whether at the end of inspiration or expiration) does not seem to have a bearing on risks of a large residual pneumothorax[86 87] as long as a Valsalva manoeuvre has been performed.[88] The removal should occur using a steady continuous pull followed quickly by occlusion of the wound with a swab.[61] With large-bore drains, it may be useful to have an assistant to tie the closing suture,[89] however, this can be done by the person removing the drain after a few seconds of occluding the wound.

A post removal chest radiograph should be considered to check for complications, particularly re-accumulation or appearance of pneumothorax.

Troubleshooting

Surgical emphysema

The development of surgical (subcutaneous) emphysema following chest drain insertion for pneumothorax and thoracoscopic procedures[90] is common and is often of minimal clinical consequence. However, in certain instances, substantial amounts of air can progressively accumulate subcutaneously. Risk factors include drain blockage and poor drain placement or fixation (leading to migration of the side-holes subcutaneously) in the context of large air leak.[61 90] Figure 2 summarises the management of problematic surgical emphysema.

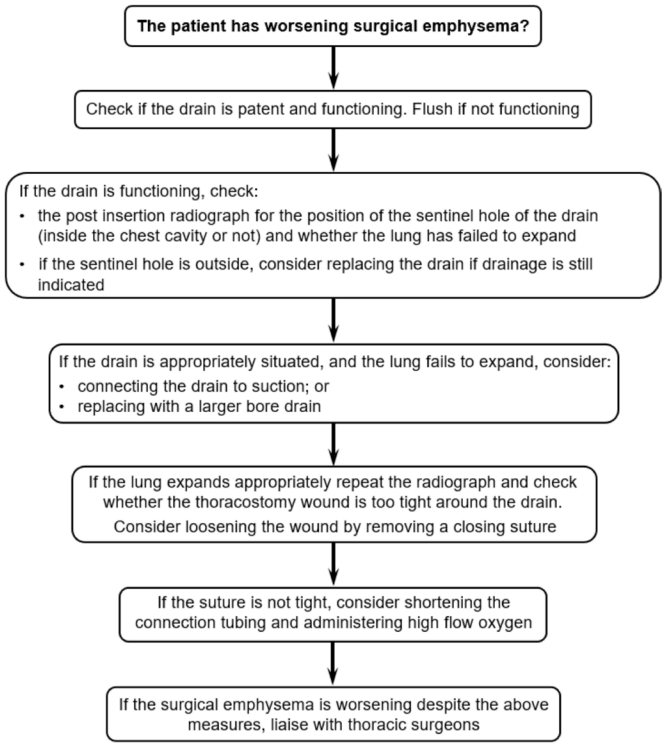

Figure 2 Management of problematic surgical emphysema.

Non-functioning drain

The cessation of swinging of liquid in the drain tubing is usually a manifestation of drain blockage which is often resolved with simple saline flushing. The full length of the drain and the tubing should be inspected to rule out any kinking as a cause of drain non-function.

The assessment of a non-functioning chest drain is summarised in figure 3. Where high flow oxygen is used, caution should be employed in those with chronic lung disease and an arterial blood gas considered after 30 min to ensure hypercapnia is not developing.

Malposition on follow-up radiology

As long as a chest drain is functioning and all side-holes are within the thoracic cavity, regardless of where the tip of the drain lies, changing the position of the drain or replacement should not be attempted. The exception is when the drain is too far in with symptoms suggesting irritation of the pleura, where withdrawing the drain to some degree is advised to relieve symptoms. For misplaced or poorly placed drains that are too far out, pushing the drain in is contraindicated as this carries a risk of introducing infection. In such a situation, or if a drain is completely dislodged, the need for further drainage should be considered carefully, and if deemed necessary, another site chosen[61] since the original wound will be challenging to appropriately anaesthetise or clean.

Thoracostomy wound leakage

Leakage of fluid from around the drain is seen with large volumes of pleural effusion with wide thoracostomy wounds and is usually exacerbated when the drain is clamped or blocked. In most instances the leakage ceases with thorough drainage of the effusion, but to avoid consistently wet dressings which may predispose to chest wall cellulitis, a simple interrupted suture may be required to narrow the aperture around the drain.

Clinical practice points

- Small-bore drains (<14F) are suitable for most indications including draining empyema.
- Larger bore drains should be considered in unstable trauma patients and pneumothorax complicating mechanical ventilation.
- Consider a larger bore drain (>14F) if pleurodesis is intended.
- Before drain insertion, aspiration of air or fluid with the needle applying the anaesthetic is necessary, and failure to do so should prompt further assessment.
- Where possible, using guards over the plastic dilators for Seldinger drains is advised to reduce the risk of insertion of unnecessary excessive lengths of the sharp-tipped dilators.

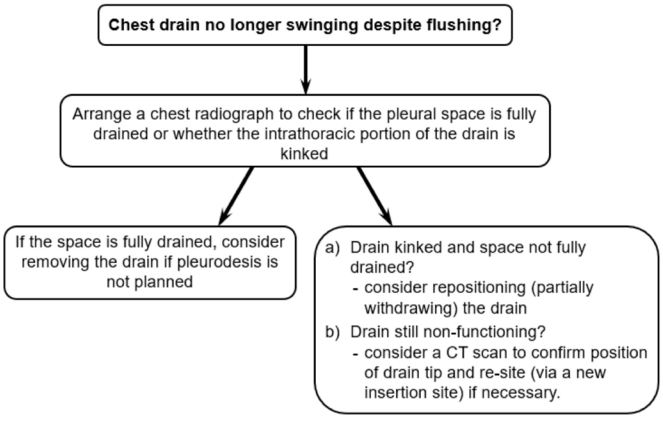

Figure 3 Assessment of a non-functioning chest drain.

- All chest drains should be fixed with a holding suture to prevent fall out.
- A chest drain inserted for managing pleural effusion should be clamped promptly in patients with repetitive coughing or chest pain to avoid RPO, which is a potentially fatal complication.
- A follow-up chest radiograph should be conducted within a few hours of insertion to ensure appropriate drain position inside the thorax.
- For pleural fluid, the volume to be drained over specific time periods should be specified in the procedure report and in handover (eg, 500 mL/hour).
- In cases of a non-functioning intercostal drain where another drain is required, the old track must be avoided when inserting the new drain.

Research questions

- What is the clinical utility of routine suction use in managing pleural infection, pneumothorax and pleurodesis?
- What is the utility of 'clamping trials' prior to removal of chest drains inserted for pneumothorax?

IPC INSERTION, MANAGEMENT AND REMOVAL

IPC insertion and removal

The procedures for IPC insertion and removal are detailed in online supplemental appendix 5 (IPC insertion technique).

Indications for IPC insertion

IPC insertion is indicated as first line for recurrent MPE according to patient choice (on the basis of two randomised trials), and in the setting of non-expandable lung (on the basis of small case series) or as second line after failed chemical pleurodesis (on the basis of clinical practice). IPCs may be considered in selected patients with recurrent non-MPEs.[91 92]

IPCs in patients undergoing systemic chemotherapy with possible neutropenic side effects

There is no robust evidence to suggest IPCs increase the risk of infection in those receiving chemotherapy. In a study of 262 IPCs for MPE and an overall IPC-related infection rate of 6%, there was no statistically significant difference in IPC-related complications comparing patients receiving chemotherapy and those not receiving chemotherapy (9/173 (5.2%) vs 7/89 (7.9%), respectively (p=0.4)) and no difference in pleural infection rates.[93] These findings have been replicated elsewhere.[94 95] An IPC should therefore not be a contraindication to chemotherapy; however, careful consideration of IPC insertion timing, and meticulous aseptic catheter care are advisable.

IPC duration in situ

IPCs are designed to be a permanent solution to recurrent pleural effusions and therefore have no defined limit on how long they can be kept in situ. The risk of IPC-related pleural infection increases with duration of IPC (4.9% of 1021 patients with IPC, after a median of 62 days after IPC insertion), highlighting the importance of patient and carer education regarding fastidious care of the IPC.[96] The polyester cuff stimulates granulation tissue formation and fibrosis which anchors the drain in place decreasing the chance of catheter fall out, and provides a barrier to infection.

Indications for IPC removal

Successful IPC-related pleurodesis is defined in several clinical trials as <50 mL drainage from the IPC on three

consecutive occasions, absence of symptoms of fluid re-accumulation, and absence of substantial residual pleural effusion on imaging.[97–99] It would be reasonable to use these same criteria in clinical practice when planning IPC removal. IPC-related spontaneous pleurodesis has previously been reported in around 45% of IPC insertions according to a systematic review published in 2011.[100] However, lower rates of 23%–24% have been reported with standard IPC drainage protocols in more recent and robust RCT studies, and this likely reflects the 'real' pleurodesis rate.[97 99]

Other reasons for IPC removal include intractable pain, IPC-related skin/pleural infection which do not resolve with antibiotics and fluid drainage alone, irreparable device damage, and irreversible IPC blockage with ongoing fluid formation.

Talc can be instilled via IPC, allowing the option of chemical pleurodesis in an outpatient setting, and was associated with a 43% rate of pleurodesis vs 23% without talc at 35 days after IPC insertion.[97]

IPC care after insertion and advice to give patients

Baths, swimming

A waterproof dressing is usually applied after IPC insertion, and patients are advised to avoid swimming and having baths until the suture(s) are removed (usually after 7–10 for the closing suture, and 21 days for the holding suture (see figure 4), with the latter used in some centres to provide added security to the IPC while the cuff is granulating). Provided the IPC site is kept clean and dry, patients should be able to shower normally. After both sutures are removed, patients are usually advised that they can have a bath or swim, although ideally these activities would be undertaken in a way that allows the IPC site to be kept clean and dry such as with a waterproof dressing and prompt changing of the dressing should it get wet. Ideally, these activities should be timed with drainage so that a clean and dry dressing can be applied after the activity and IPC drainage.

Drainage frequency

The usual starting drainage frequency is three times per week, however, recent evidence suggests that daily drainage increases pleurodesis rates and shortens time to pleurodesis compared with alternate day drainage or symptom-guided drainage.[98 99] Daily drainage should be considered in patients with expandable lung and where pleurodesis is a priority, and where drainage does not cause undue patient discomfort. However, daily drainage frequency has cost and patient impact implications. Drainage can be performed by community nurses at the patients' home, or by the patient or relatives. If daily drainage is not possible, such as in the case where access to community healthcare staff may be limited, or if the patient does not tolerate this, drainage should be as frequent as possible as tolerated by the patient.

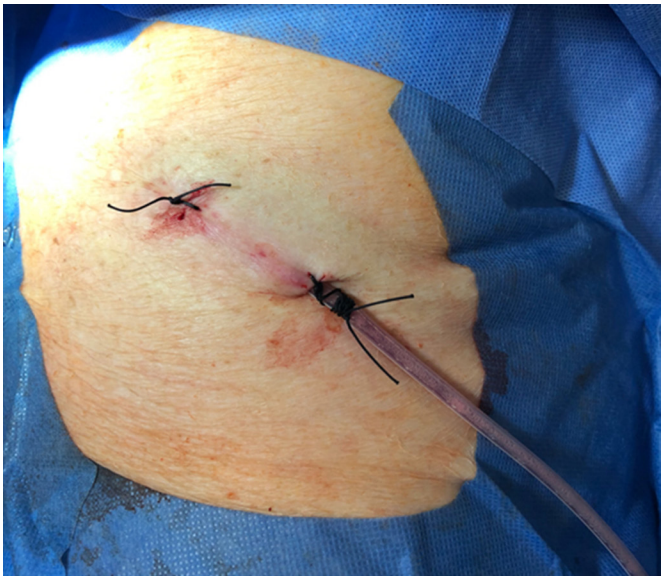

Figure 4 Image showing an IPC immediately after insertion, with a closing suture (left) and a holding suture (right) anchoring the IPC. IPC, indwelling pleural catheter.

Drainage volume

Usually around 500 mL are drained, but up to 1500 mL pleural fluid may be drained—the maximum recommended by guidelines (Grade C recommendation) although this is arbitrary and based on the fact that complications rarely arise when draining this volume at one go.[43] However, in practice, smaller volumes tend to be drained, as tolerated by patients, and drainage stopped if the patient develops chest discomfort or persistent cough.

IPC-related complications

IPC-related complications can be divided into:

1. Procedure-related complications
   These are similar to other pleural procedures (see above). Unsuccessful insertion occurs in 4%.[101] It is common for air to become entrained in the pleural cavity during the procedure, and appear as a small pneumothorax on the post procedure CXR. This usually resolves spontaneously or is drained from the pleural cavity during the first IPC fluid drainage. Larger collections of air, especially if associated with pain, should raise concern about underlying visceral injury, although may be indicative of underlying non-expandable lung. Subcutaneous emphysema has been reported after IPC insertion, although usually in the setting of IPC insertion post video-assisted thoracoscopic surgery (VATS).[102]
2. Complications associated with the IPC being in situ
   Pain or discomfort at the IPC insertion site for a few days after the procedure can be managed by simple analgesia. Other IPC-related complications are summarised in Appendix 3. IPC mechanical issues including failure or detachment of the one-way valve or detachment occur rarely. Makeshift solutions have been reported with valves from new IPC kits fitted onto the original IPC[103 104]; however, our advice is to replace the IPC to minimise the risk of infection or air entrainment through an open IPC end.
3. Complications associated with IPC removal.
   Inability to remove the IPC can occur if the intrapleural portion of the IPC has become enveloped and trapped by pleural tumour anchoring the intrapleural part of the catheter, or if the cuff is unable to be freed of extensive fibrous tissue, particularly if the IPC has been in situ for several months. The external portion of the IPC can be severed under tension, allowing the proximal intrapleural and subcutaneous portion of the IPC to retract into the pleural space, and the remaining portion cut flush with the skin. This results in a retained IPC fragment within the pleural space and subcutaneous tissue but does not seem to be associated with long-term complications such as pain or infection.[105]

Catheter fracture has been reported to occur on attempted IPC removal, although rare (n=1 of 202 (0.5%) IPC insertions) also leading to a retained IPC fragment.[106] In the presence of an IPC retained fragment, early review of the patient is advised to ensure no complications develop.

A table showing IPC-related complications, rates of occurrence and management is shown in Appendix 3.

IPC use in transudative non-MPE

IPCs were originally licensed for use in MPE in 1997, but were only approved for use in non-MPE in 2016.[107] Medical management is usually sufficient for non-MPE, however IPC may be considered in selected cases.

Using IPC in non-MPE has shown patient satisfaction and symptom benefit,[108–111] however, is less likely to lead to pleurodesis when compared with MPE.[108] IPC-related complication rates appear similar between MPE and non-MPE, with 5% empyema rate reported in most studies,[91 109] although reported in 16.1% (n=10) in a study of 62 IPC insertions in patients with hepatic hydrothorax.[112]

Since publication of the above case series (which suffer with inherent bias), the first RCT of IPC treatment vs standard care (pleural aspiration) has been published. The REDUCE trial randomised 33 patients to IPC treatment, and 35 to as needed pleural aspiration. There was no difference in overall breathlessness between the two groups, despite far greater fluid drainage in the IPC group (17.4 L vs 2.9 L over 12 weeks) with the aspiration group undergoing three aspirations on average in the trial period. There was, in addition, a statistically significant excess of adverse events in the IPC group compared with aspiration.[113]

On this basis, we do not in general endorse IPCs in the treatment of transudative effusion. Their use may be considered where repeated aspiration (>3 events) is required despite full optimisation of the cause of the effusion (eg, cardiac/liver/renal dysfunction), and where risks of complications of pleural interventions (eg, clotting abnormalities) are high, with full discussion of potential risks and benefits.

Successful IPC use in empyema has been reported in cases of failed surgical management or where surgical management was not possible due to patient frailty or comorbidities,[91 114]; however, there are no large studies or case series available in the literature. Routine use of IPC in acute empyema is not advised but there is a possible role in selected cases.

Fitness for technique

General contraindications to IPC insertion include those common to any pleural procedure (see above). Contraindications specific to IPC insertion include inability for the patient to tolerate the catheter, inability for the patient, relatives or healthcare services to manage and support the outpatient management of the IPC, cellulitis or significant malignant infiltration of the skin at the proposed IPC insertion site, and pleural infection with evidence of ongoing sepsis.

In general, IPC is considered in patients whose life expectancy is likely to be longer than a few weeks, during which time the pleural effusion is likely to reaccumulate. However, during the COVID-19 pandemic, IPC was often a preferred option to chest drain insertion and talc pleurodesis across many centres because of an attempt to keep patients, especially those with cancer and immunosuppression, out of hospital as much as possible. This is likely to have lowered the threshold for IPC insertion in preference to therapeutic aspiration in frail patients with a short life expectancy.

IPC removal

Indications

For indications of IPC removal, please see the 'IPC insertion, management and removal, Indications for IPC removal' section above

Catheter tract metastases

Pleural tumours, especially mesothelioma, can spread along instrumentation sites, leading to catheter tract metastases. This has been noted to occur in association with IPCs in 6.7% of cases, but usually does not necessitate IPC removal.[115] Two RCTs, one of which included IPCs, have not shown any patient benefit from prophylactic irradiation of pleural procedure sites.[116 117] Should pain develop from the chest wall metastases and is resistant to analgesia, localised radiotherapy may be considered.

Clinical practice points

- IPCs have a well-defined role in MPE management.
- The role of IPCs in transudative non-MPE remains controversial and there is currently insufficient evidence to advocate routine use in transudative non-MPE, although they may have a role in selected patients with very frequent therapeutic aspiration requirements despite optimisation of treatment of the underlying pathology.
- An IPC should not be a contraindication to chemotherapy, although judicious IPC insertion timing, and meticulous aseptic catheter care is advisable.
- After both sutures are removed, patients can have a bath and swim, although care should be taken to keep the IPC site clean and dry, such as with a waterproof dressing and prompt changing of the dressing should it get wet.
- There is a lack of robust data on treatment of non-draining septated IPC-related effusions (see Appendix 3), however, a trial of intrapleural fibrinolytics may be considered in selected patients.
- Consider removal of IPCs when <50 mL are drained on three consecutive occasions and there is absence of symptoms of fluid reaccumulation and no substantial residual pleural effusion on imaging.
- Drainage frequency should be guided by patient symptoms, unless aiming for pleurodesis in those with expansile lungs, in which case IPC drainage should be as frequent as possible (daily) as tolerated by the patient.

Research questions

- Studies to investigate the role of fibrinolytic treatment in septated effusion related to IPC use in MPE patients.
- Studies addressing the use of single or dual stiches after IPC insertion.

ULTRASOUND-GUIDED PLEURAL BIOPSY

Introduction

In circumstances where local anaesthetic thoracoscopy (LAT) is not feasible, physician-based ultrasound-guided cutting needle pleural biopsy provides a less invasive modality of pleural tissue sampling (please refer to the BTS Guideline for Pleural Disease 2023, 'What is the diagnostic accuracy of pleural biopsy?' section[2]).

Traditionally, ultrasound-guided pleural biopsy (UGBx) has been the domain of specialised radiologists. However, in 2004, Diacon *et al* reported one of the first experiences of a pleural biopsy service led by respiratory physicians where lesions >20 mm in diameter were biopsied under US guidance with

a 14G cutting needle in 91 patients. They reported an overall sensitivity for malignancy of 85.5% with a low complication (4%).[118] Since then, with the increasing use of TUS, the practice has extended to more centres, although is still far from commonplace. More recently, a retrospective review of physician-led UGBx in a UK pleural service obtained sufficient sample for a histological diagnosis in 47 of 50 pleural biopsy procedures (overall sensitivity 94%). Both studies demonstrate yields and complication rates comparable to those reported by radiologists for image-guided pleural biopsies using ultrasound and CT guidance,[119 120] and similar to LAT.

In a study by Hallifax *et al*, 13 UGBx were conducted in patients after failed LAT attempt as an 'on table' conversion (prior consent was obtained for both procedures) with high diagnostic yield, meaning there was no delay to their diagnostic pathway and preventing the need for a further admission and intervention. There were no immediate or delayed complications.[121]

Comparative diagnostic yields between USGBx, LAT and CT-guided biopsies are addressed in the BTS Guideline for Pleural Disease 2023, 'What is the diagnostic accuracy of pleural biopsy?' section[2].

Pleural USGBx consent considerations

When consenting a patient for pleural USGBx, potential risks and complications (box 5) should be considered.

Indicative radiology: is parietal pleural thickening a prerequisite to USGBx?

Although it seems logical that pleural thickening would increase the diagnostic yield in USGBx, the literature suggests the presence of pleural thickening is not mandatory for a diagnostic pleural biopsy. In an observational study from Koegelenberg *et al*, 100 consecutive patients undergoing USGBx of the pleura had an overall diagnostic yield of 88%. Of the 100 patients, 65 had no demonstrable pleural thickening on ultrasound and this group specifically had an overall sensitivity of 58/65 (89.2%). Specifically for malignancy, the sensitivity was 24/27 (88.9%) in the absence of pleural thickening comparable to the 18/20 (90%) sensitivity when pleural thickening was present.[122] In the study from Hallifax *et al,* despite the high overall sensitivity of 47/50 (94%), 12 patients had no significant pleural thickening on CT scan in the mid-axillary line.[121] In the AUDIO study, evidence of pleural thickening was not a prerequisite to pleural biopsy for microbiology.[123]

Overview of cutting needles

Blind or 'closed' pleural biopsy with an Abrams or Cope needle has been in use since it was proposed as a less invasive option to 'open' pleural biopsy (via thoracoscopy) in 1958.[124] Since the use of ultrasound has become standard practice, blind techniques such as this are diminishing, except in the context of TB in areas with high prevalence where closed pleural biopsy may still have a role.

Cutting needle biopsy devices (eg, Temno or Tru-cut) have been a relatively more recent addition.[125] They are designed for manual capture of high-quality tissue samples, including a core biopsy device and sometimes a removable stylet to enable multiple sampling. An ultrasound example is shown in figure 5.

Cutting needles can usually be obtained in a range of sizes from 14G to 21G. There is no high-quality evidence as to whether size affects diagnostic yield. In one small study, the use of a larger cutting needle (18G vs 14G) was not shown to be of any diagnostic benefit.[126] Most radiological studies tend to favour mid-range 16–18G needle sizes.[120]

Advantages of UGBx

- Image-guided biopsy using US guidance is safe with a lower overall rate of adverse events (3%) in comparison to CT (7%).
- In contrast to LAT, patient sedation is not usually required.
- US-guided biopsy facilitates real time visualisation of the needle with no radiation risk to the patient.
- Patient movement due to heavy breathing in a dyspneic patient can be compensated for in real time.
- US-guided biopsy is cheap, relatively accessible and requires minimal consumables (see figure 6).
- While it is helpful to have an assistant to process samples in between biopsies and provide sterile supplies as required, there is minimal additional need for support staff.

Limitations of the US-guided approach

1. Areas inaccessible to ultrasound (eg, behind ribs) cannot be biopsied.
2. Pleural lesions/areas of pleural thickening smaller than 1 cm result in lower diagnostic yields.

In both these circumstances, CT-guided biopsy may be preferred as studies have shown lesions as small as 5 mm can be effectively biopsied.[126]

Contraindications

See the 'Safety and preparation for pleural procedures' section.

Box 5 Pleural ultrasound-guided pleural biopsy consent considerations

⇒ Failure to make a diagnosis.
⇒ Pain.
⇒ Wound infection (3%).
⇒ Pleural infection (empyema) (<1%).
⇒ Pneumothorax (4%).
⇒ Organ puncture; mainly lung but liver/spleen also possible when targeting basal lesions.
⇒ Bleeding requiring treatment.
⇒ Low blood pressure/vasovagal syncope.

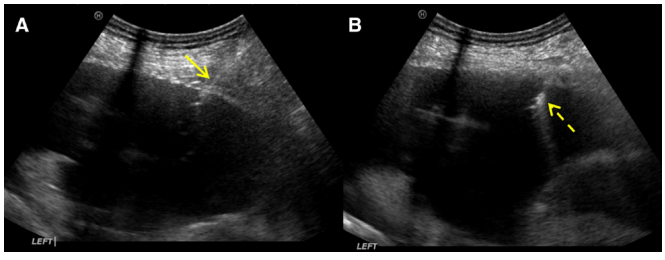

Figure 5 Cutting needle traversing skin to pleura during an US-guided pleural biopsy. The cutting needle (solid arrow) (A) is an example of a semiautomated biopsy device that requires manual advancement of the trocar to expose the side notch (dashed arrow) (B). With pressure on its plunger, an automated biopsy action rapidly advances the cutting cannula over the specimen-containing side notch of the trocar. US, ultrasound.

Complications

A recent systematic review and meta-analysis addressing safety of image-guided pleural biopsy contained data on complications from 18 studies included 1342 patients who had undergone USGBx. The overall probability of developing major complications was 1% (95% CI 0.00% to 0.01%) and minor complications 2% (95% CI 0.01% to 0.03%).[127] Complication rates as high as 10% have been reported in individual studies.[126 128]

Clinical practice points

- The preferred patient position is lateral decubitus and biopsies should be targeted along the mid-axillary line to minimise complications.[6]
- A real-time, freehand technique (figure 6) is advocated whereby a suitable site is identified using a low frequency probe (2–5 MHz) and the biopsy performed while the patient remains in the same position. Doppler ultrasound screening of the intercostal vessels using the same probe can be conducted to avoid vessels.[7]
- Inferior biopsy sites closer to the diaphragm have shown to be more likely to elicit positive biopsy samples due to the anatomical predilection of secondary metastases to this area.[8]
- A biopsy site with underlying pleural effusion to act as a buffer is preferable to reduce the risk of lung perforation and subsequent pneumothorax. If pleural fluid is not present it is preferable for the procedure to be performed under CT guidance.
- When preparing the cutting biopsy needle, it is helpful to demonstrate the 'firing' mechanism of the needle to the patient outside their chest so as not to cause alarm when they first hear the sound.
- The cutting needle should be angled in a way to ensure that the core of tissue obtained will contain the full thickness of the pleura and the needle tip ends in the pleural fluid creating an oblique biopsy tract (figure 7).
- While an assistant releases the tissue cores into a cytolyte container (with saline for samples for microbiology) and rinses the needle in a small pre-prepared tray of saline between biopsies, it is useful for the operator to intermittently check for any evidence of bleeding by looking for echogenic material gathering in the pleural space, or use of Doppler.[9]
- Usually at least six cores are obtained (extrapolated from TB practice[10]). If the pleura is not very thickened, it may be judicious to perform more (as the number of passes increases, be aware that the introduction of air with each biopsy may negatively impact the quality of the real-time ultrasound image).

Postprocedural care

- Ensure no oozing from biopsy site or no chest wall haematoma and apply mepore dressing.
- See 'General aftercare applicable to all pleural procedures' section.
- At the end of the routine observation period and prior to discharge, a chest radiograph is advised to document absence of a pneumothorax and haemothorax.

Research questions

- Can contrast-enhanced US improve diagnostic yield from USGBx through differentiating benign and malignant pleural disease?
- Can US elastography reliably allow non-invasive differentiation between benign (soft) and malignant (hard) tissue to guide USGBx?

MEDICAL THORACOSCOPY

For the purposes of this statement, the term LAT is intended to describe the thoracoscopic procedure undertaken by respiratory physicians, which is commonly also referred to in the literature as medical thoracoscopy or pleuroscopy. The practice of VATS or any other forms of surgeon-led thoracoscopy are beyond the scope of this document, even when using a single port and/or local anaesthetic instead of general anaesthetic.

Current UK LAT service provision

The number of UK sites offering LAT increased dramatically in the early 2000s, from a handful of specialist sites to approximately 17.[97 129] By 2018, a survey of UK practice suggested that approximately 50 centres were offering LAT.[130] At present, most regions of the UK have access to LAT services or are able to offer these themselves.

Indications for LAT

Although LAT has been used to access the pleural cavity for a wide variety of reasons, in the majority of cases LAT is undertaken with

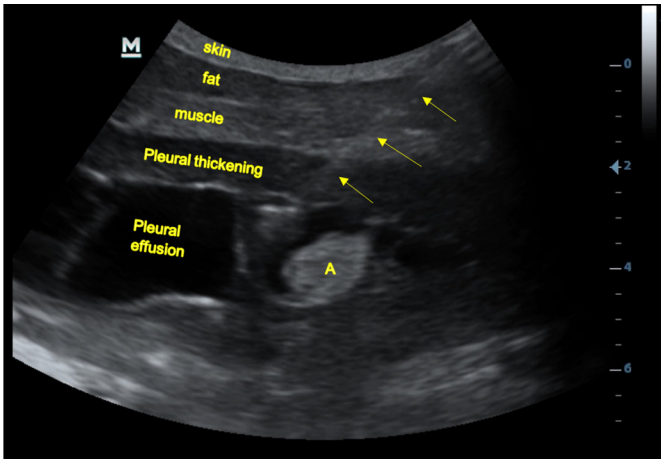

Figure 6 Ultrasound anatomy during cutting needle biopsy. Yellow arrows=biopsy needle track; A=meshwork of closely interlaced septations.

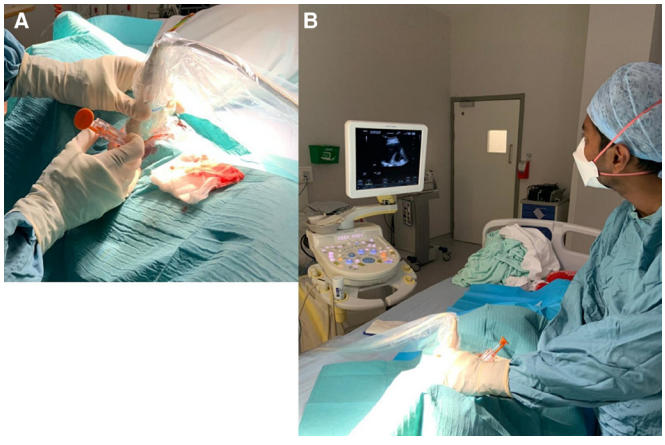

Figure 7 Real-time free-hand technique demonstrated with dominant hand controlling the cutting needle (A). Operator should be positioned facing the ultrasound machine with patient in lateral decubitus position in between (B).

a view to obtaining parietal pleural biopsies in order to confirm or refute a diagnosis of pleural malignancy (figure 8).[131] This is almost always undertaken in the context of a pleural effusion. For patients with confirmed MPE, a LAT may be performed specifically with a view to rapid maximal drainage (± septation breakdown), followed by some form of definitive MPE intervention (usually talc poudrage with or without IPC insertion) to achieve pleurodesis. A rare, but previously described indication for LAT, also includes drainage (± adhesiolysis, ± irrigation) of pleural infection.[132–135] In cases where pleural tuberculosis is suspected, pleural biopsies obtained at LAT have been shown to have an extremely high sensitivity for diagnosis.[136]

Patient selection

Patients should be able to lie in the proposed procedure position (usually on their side) for up to 1 hour and be able to tolerate moderate sedation. It is advised that patients have a WHO performance status of 3, or better when the LAT is undertaken. Box 6 lists absolute contraindications to LAT. Although the presence of heavy fluid septation/loculation is not an absolute contraindication, this finding may mean some operators choose to pursue an alternative procedure.

Complications and consent

Overall, LAT is a safe procedure. In data obtained from 47 studies, death occurred in 0.3% of cases, although, in the 28 of these studies reporting on diagnostic LAT without talc, no deaths occurred. Other major reported complications, occurring in 1.8% of patients, included pleural infection, significant haemorrhage, port site or tract metastasis, bronchopleural fistula, pneumothorax or air leak, and pneumonia. Thirty-one of these studies reported minor complications in 7.3%, including non-significant bleeding, hypotension, fever, atrial fibrillation, wound infection and subcutaneous emphysema.[137] When taking consent for LAT, it is prudent to mention the possibility of intra and postprocedural pain and cough.

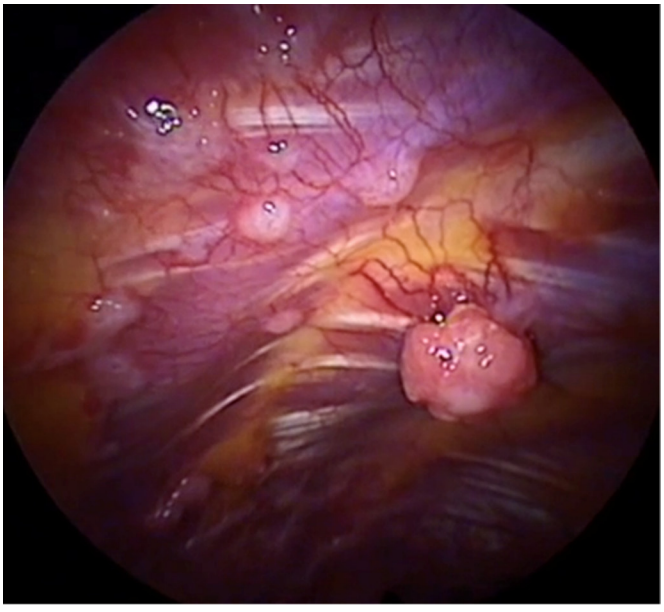

Figure 8 Thoracoscopic view of the parietal pleura, demonstrating multiple small nodules and single larger nodule, which when biopsied demonstrated lung adenocarcinoma.

Peri-procedural analgesia, local anaesthesia and sedation

Patients should be encouraged to take simple analgesia prior to their attendance at the hospital. Preparation of a prescription chart containing simple analgesia and basic opiates (eg, oral liquid morphine) before the procedure is advised to avoid unnecessary discomfort in the recovery period/area.

In the UK, management of sedation is usually the responsibility of the thoracoscopist, although in select centres a dedicated anaesthetist may be available, which may in turn allow for a more complex sedation regimen.[138]

During the procedure, 20 mL of 1% lidocaine (± adrenaline) is advised for skin and tract anaesthesia. In the UK, LAT is usually undertaken under light to moderate sedation using incremental doses of an intravenous benzodiazepine (eg, midazolam 0.5–5 mg). This may be combined with an intravenous opiate (eg, fentanyl 25–100 μg) for control of pain and cough. Additional doses should be available during the procedure in case of pain or agitation.

Rigid versus semi-rigid LAT

The majority of UK LAT operators use a rigid system, with fewer than 10% opting solely for a semi-rigid system (currently only manufactured by Olympus).[130] Previous comparative data have shown biopsy samples obtained using the semi-rigid system to be consistently smaller than those obtained with rigid scopes, however, this does not appear to translate into meaningfully lower diagnostic rates.[139–142] Benefits of the semi-rigid system may include: a more natural learning curve for respiratory physicians who are already trained in bronchoscopy, as the devices are similar in design; ability to access and visualise a greater proportion of the thoracic cavity; and the scope being autoclavable. Disadvantages of the semi-rigid system include considerably greater scope cost compared with rigid systems, smaller volume biopsies[142] and less lateral stability when taking biopsies, which may lead to difficulty obtaining samples, especially in cases where the visceral pleura is firmer. A comparison of rigid and semi-rigid scopes is shown in figure 9.

Additional techniques during LAT

The scope of activity for physicians in the UK is usually limited to parietal pleural biopsies (as above), talc poudrage, and limited manual (ie, without electrocautery) adhesiolysis. Although more advanced procedures are technically possible, these are usually only undertaken as part of research studies or in a very small number of individual centres with particular expertise and are thus beyond the scope of this document.

Identifying non-expandable lung

For patients undergoing surgical thoracoscopy with the assistance of mechanical ventilation, it may be feasible to selectively inflate the

Box 6 Absolute contraindications to local anaesthetic thoracoscopy

- ⇒ Uncorrectable bleeding tendency.
- ⇒ Significant (associated with symptoms or heart failure) pulmonary hypertension.
- ⇒ Cutaneous infection, metastasis or rib fracture around port insertion site.
- ⇒ Uncorrectable type 1 respiratory failure.
- ⇒ Ongoing type 2 respiratory failure.
- ⇒ Cardiovascular instability.
- ⇒ Complete absence of a pleural space due to adhesions.

collapsed lung at the end of the procedure to make an informed estimate as to likelihood of re-expansion.[102] However, although certain visual features may be suggestive (eg, visceral pleural rind, limited diaphragmatic movement), recent data have shown that NEL (or its extent) cannot be reliably or consistently identified during LAT using visual appearances alone.[143]

Talc as part of a LAT

Talc in the context of LAT is almost exclusively used to treat known or suspected MPE. In the UK, a standard dose is 3–4 g, given in graded form as this is proven to be significantly safer than the ungraded form.[144] Talc may be delivered during LAT as poudrage (a dry powder sprayed directly onto the pleural surfaces), or shortly after LAT in the form of slurry via the chest drain which is placed postprocedure (once lung expansion is confirmed). Robust RCT data has confirmed that there is no significant difference in pleurodesis or health economic outcomes when comparing the use of poudrage with slurry (in patients with known MPE), with both leading to approximately 75% 'success' rates at 3 months postprocedure.[145]

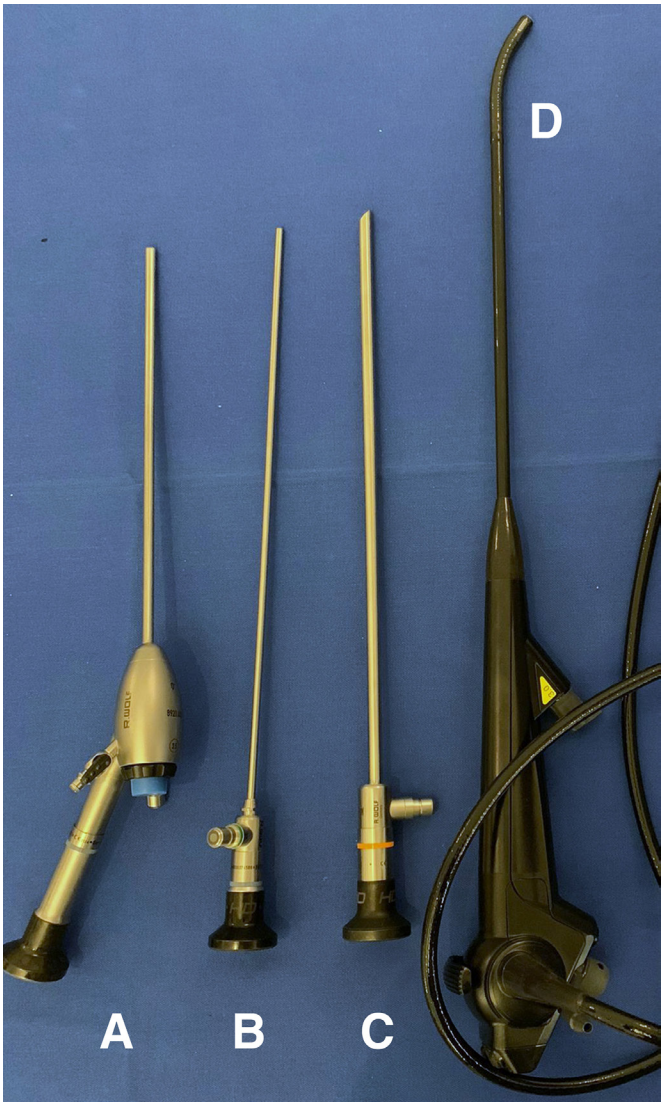

Figure 9 Comparison of medical thoracoscopes (left-to-right, (A)). 0° rigid scope with working channel and in-line suction port; (B) standard 0° rigid scope; (C) standard 50° rigid scope; and (D) semi-rigid thoracoscope with working channel and in-line suction port.

Common perceived benefits of poudrage at LAT include the ability to apply talc under direct vision, ensuring even pleural spread; and, where applicable, the added convenience of combining diagnostic and therapeutic procedures. Conversely, compared with a solely diagnostic LAT, poudrage usually extends the duration of a patient's procedure and their hospital stay; introduces the risk of talc-related side effects and complications; and often has to be given before non-expandable lung can be excluded.[137]

Post LAT chest tube

The size of chest tube to be inserted at the end of a LAT should be determined by taking into consideration:

1. The size of port used to access the pleural space, ensuring that the tube chosen is slightly larger than the diameter of the access tract.
2. The width of the patient's rib space.

The typical range of tube size for UK operators is 16F–24F. Any tube should be secured in line with the guidance detailed in online supplemental appendix 4 (Intercostal drain insertion). If a tube is expected to remain in place (eg, so that talc slurry can be given once lung expansion is confirmed), then a three-way tap should be added into the drainage circuit. This may require an additional connector (figure 10).

IPC in combination with LAT

There is currently no consensus regarding when placement of an IPC should be combined with LAT. Accordingly, patient selection should be made based on individualised discussions, taking into consideration factors such as rapidity of prior fluid accumulation; previous failed pleurodesis attempts; knowledge of pre-existing non-expandable lung and symptomatic improvement with thoracentesis; and geographical location, which may influence the ability for patients to return for additional procedures. If being undertaken, procedural consent should be extended to include potential complications relating to the IPC insertion specifically. Limited evidence suggests that the combination of LAT, poudrage and IPC may confer benefits in terms of duration of post procedure stay and pleurodesis success.[146]

Should an IPC be placed as part of a LAT procedure, it is advised that the IPC normally be inserted into the pleural cavity at least one rib space either above or below the LAT port site. However, if a small introducer is used for the LAT, then it may also be feasible to use the existing tract to place the IPC.

Post LAT drainage and imaging

As the thoracic cavity will be largely empty immediately post LAT, it is advised that the chest tube circuit be left 'open' to allow free

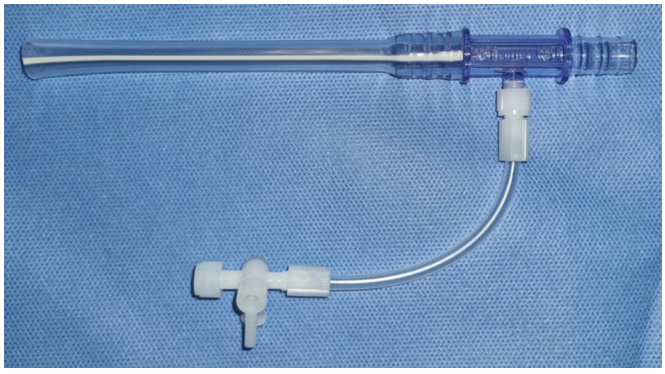

Figure 10 Example of a connector which allows the easy installation of pleural agents (eg, talc slurry or saline flush) into a large chest drain.

drainage of air and any remaining fluid. It is common for patients to experience coughing and some transient chest discomfort as the lung re-expands initially. Pilot data have suggested that the use of 'digital' suction devices, which are able to quantify air leak, may predict the presence of non-expandable lung which may not have been diagnosed pre LAT.[147]

A chest radiograph performed approximately 1-hour post-procedure will usually be sufficient to identify the degree of initial lung expansion. For most, complete expansion would be expected to happen almost immediately. However, for those with a degree of underlying NEL, or who had a significant degree of atelectasis, a more prolonged period of chest drainage and observation may be required. For those not attached to digital suction, a CXR should be obtained every 24–48 hours to assess for degree of lung expansion. For those who continue to exhibit incomplete expansion or ongoing air leak, on a case-by-case basis, thoracic suction may be considered, although there are no robust data to support or oppose its use at present. It is advised that a maximum pressure of −20 cm H_2O be applied, as tolerated.

For those patients in whom talc has been administered, it is advised that the chest drain be left in situ until drain output has reduced to 200–250 mL in the preceding 24-hour period, although evidence for this target volume is weak. As an alternative, a recent RCT demonstrated that the use of serial, 9-point, TUS scans (using lack of visible lung sliding as a surrogate for pleurodesis) post talc reduced the duration of hospital stay by 1 day when compared with standard monitoring.[148]

For those with persistent high fluid output, regardless of prior talc use, consideration should be given to removing the tube and discharging the patient, with a view to later placement of an IPC as an outpatient. For those with persistent air leak or poor lung expansion despite the above strategies, consideration should be given to ambulatory management/discharge with a Heimlich device.

LAT as a day-case

Previous data have suggested that between 24% and 46% of UK LATs are performed as day case procedures (ie, no in patient overnight stay), although this is now likely to be inaccurate in light of pressures placed on diagnostic services during the COVID-19 pandemic.[130] The majority of practitioners will limit day-case LAT to diagnostic biopsies±IPC insertion, omitting talc pleurodesis. However, there are a limited number of UK centres who choose to undertake LAT, talc poudrage, and IPC insertion as a single day-case procedure.

LAT service emergency support

Recent data suggest only 27% of UK LAT centres have access to on-site thoracic surgical support.[130] It is strongly endorsed that all LAT practitioners develop lines of communication with local thoracic surgical colleagues/centre for advice and/or assistance in the event of rare LAT complications such as diaphragmatic, visceral or major vessel injury. Intercostal artery injury and subsequent haemothorax may require assistance from thoracic surgical colleagues, however, this complication may also be managed by interventional radiology colleagues, who may be available locally.

In addition to the above, it is strongly advised that sites undertaking LAT develop pathways for common emergency scenarios both during and post LAT. These will likely involve protocols for urgent liaison with back-up services as above. Scenarios may include major haemorrhage due to intercostal injury; cardiovascular instability due to sedation and/or biopsies; or suspected RPO.

LAT troubleshooting

A guide to LAT troubleshooting is shown in Appendix 4.

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APPENDIX 1: SUMMARY OF STUDIES EVALUATING THORACENTESIS-RELATED COMPLICATIONS IN THE LAST 6 YEARS

(please note that Appendix references are listed as a separate list at the end of the appendices)

Author	Study type	Main finding	Overall risk estimate for consent
Pneumothorax			<5%
Cavanna 2014[1]	Retrospective cohort	Decreased risk of PTX with ultrasound guidance used for 445 cancer patients. 3.37% incidence of PTX, 0.97% with ultrasound guidance, 8.89% without.	
Perazzo 2014[2]	Prospective study	Decreased risk of PTX with ultrasound guidance (1.25% vs 12.5%)	
Ault 2015[3]	Prospective cohort	9230 thoracenteses. 0.61% PTX rate; PTX associated with>1500 mL removed, unilateral procedure, more than one pass through skin and low BMI (<18). 0.18% bleeding episodes, 0.01% RPO.	
Cho 2017[4]	Retrospective cohort	0.62% PTX rate. PTX associated with low BMI (<18.5)	
Shechtman 2020[5]	Retrospective cohort	12% PTX rate. PTX associated with higher rate of congestive heart failure, smaller depth of pleural fluid, larger volume of fluid drained and bilateral procedures.	
Touray 2017[6]	Retrospective cohort	Iatrogenic PTX rate 1.38% with use of ultrasound.	
Hooper 2015[7]	National Audit (BTS)	15/1162 (1.3%) patients developed an iatrogenic pneumothorax.	
Bleeding complications			<1%
Ault 2015[3]	Prospective study	0.18% bleeding complications, 0.01% haemothorax, 0.05% rate of haemothorax without correction of bleeding risk; no association of bleeding risk with patient or laboratory parameters.	
Touray 2017[6]	Retrospective cohort	Bleeding complication rate 0.4%	
Perl 2020[8]	Retrospective case control	No increased bleeding risk in clopidogrel treated patients. 2.2% vs 1.2%	
Hooper 2015[7]	National Audit (BTS)	13/1162 (1.1%) patients developed a haemothorax and 12/1162 (1%) developed a chest wall haematoma.	
Re-expansion pulmonary oedema (RPO)			<1%
Ault 2015[3]	Prospective cohort	10/9320 (0.01%) incidence of RPO; association with volume of fluid removed and non-inflammatory conditions.	
Senitko 2019[9]	Prospective randomised study	Vacuum aspiration associated with increased risk of complications (5/51 vs 0/49 p=0.03), PTX n=3, surgically treated haemothorax and death (n=1), RPO causing respiratory failure (n=1)	
Failed procedure / dry tap			4%
Hooper 2015[7]	National Audit (BTS)	43/1162 (3.7%) had a failed procedure or dry tap.	
Pain			5%
Hooper 2015[7]	National Audit (BTS)	112/1162 (5%) developed pain.	
Symptomatic hypotension			<1%
Hooper 2015[7]	National Audit (BTS)	7/1162 (0.6%) developed symptomatic hypotension.	
Ault 2015[3]	Prospective cohort	6/9320 (0.1%) had a vasovagal reaction.	
Organ puncture			<1%
Hooper 2015[7]	National Audit (BTS)	3/1162 (0.3%) had an organ puncture.	
Ault 2015[3]	Prospective cohort	1/9320 (0.01%) splenic rupture.	

BMI, body mass index; PTX, pneumothorax; RPO, re-expansion pulmonary oedema

APPENDIX 2: SUMMARY OF THE RATES OF DIFFERENT COMPLICATIONS RELATED TO INTERCOSTAL DRAINS

(please note that Appendix references are listed as a separate list at the end of the appendices)

Complication	Study type	Study details	Risk of complication per study	Overall risk estimate for consent
Immediate complications				
Pain				8%
Hooper 2015[7]	UK National Audit (BTS)	1394 procedures, 88% 6–16F intercostal drains.	8%	
Inappropriate placement				1% (small-bore drains) 6% (large-bore drains)
Vilkki 2020[10]	Retrospective cohort	1169 procedures, more than half were small-bore drain insertions.	0.43%	
Hooper 2015[7]	UK National Audit (BTS)	See above	2%	
Kong 2014[11]	Retrospective cohort	1050 drain insertions for trauma patients, 32F or larger.	6%	
Maritz 2009[12]	Local audit at a tertiary hospital	273 drain insertions for trauma patients, no information on drain sizes.	6.9%	
Symptomatic hypotension				2%
Hooper 2015[7]	UK National Audit (BTS)	See above	1.9%	
Iatrogenic haemothorax				<1%
Jackson 2021[13]	Retrospective cohort	879 small-bore drain insertions.	0.1%	
Kong 2014[11]	Retrospective cohort	See above	0.2%	
Hooper 2015[7]	UK National Audit (BTS)	See above	1.3%	
Organ Puncture				<1%
Vilkki 2020[10]	Retrospective cohort	See above	0%	
Jackson 2021[13]	Retrospective cohort	See above	0%	
Kong 2014[11]	Retrospective cohort	See above	0.4%	
Hooper 2015[7]	UK National Audit (BTS)	See above	0.6%	
Delayed complications				
Pain				16%
Hooper 2015[7]	UK National Audit (BTS)	See above	15.6%	
Drain blockage				8%
Hooper 2015[7]	UK National Audit (BTS)	See above	8.2%	
Drain displacement				5%
Kong 2014[11]	Retrospective cohort	See above	1.3%	
Jackson 2021[13]	Retrospective cohort	See above	3.9%	
Hooper 2015[7]	UK National Audit (BTS)	See above	9.2%	
Surgical emphysema				5%
Hooper 2015[7]	UK National Audit (BTS)	See above	4.2%	
Jackson 2021[13]	Retrospective cohort	See above	4.6%	
Skin infection				1%
Hooper 2015[7]	UK National Audit (BTS)	See above	1%	
Re-expansion pulmonary oedema				<1%
Jackson 2021[13]	Retrospective cohort	See above	0%	
Hooper 2015[7]	UK National Audit (BTS)	See above	0.6%	
Pleural space infection				<1%
Jackson 2021[13]	Retrospective cohort	See above	0.4%	
Hooper 2015[7]	UK National Audit (BTS)	See above	0.4%	
Death				<1%
Kong 2014[11]	Retrospective cohort	See above	0%	
Jackson 2021[13]	Retrospective cohort	See above	0%	
Hooper 2015[7]	UK National Audit (BTS)	See above	0.1%	

APPENDIX 3: IPC-RELATED COMPLICATIONS, RATES OF OCCURRENCE AND MANAGEMENT

(please note that Appendix references are listed as a separate list at the end of the appendices)

Complication	Outcomes	Risk of complication per study	Overall risk estimate for consent
Pain necessitating IPC removal			<1%
Asciak 2019[14] Tremblay 2006[15]	Severe or persistent pain should raise concern for intercostal nerve irritation, and IPC removal should be considered.	0.4%–0.5%	
Pain towards the end of the drainage procedure			Not quantified in literature, but commonly encountered in clinical practice
	May indicate the presence of underlying non-expandable lung. Routine pre-drainage analgesia may help reduce discomfort, or a revised drainage protocol may be required, with less frequent or smaller volumes of fluid drainage.	Fairly common	
IPC-related infection			5%
Asciak 2019[14] Fysh 2013[16] Tremblay 2006[15]	IPC related pleural infections carry a 0.29% mortality rate, but the majority (94%) respond to antibiotics treatment. Some may require intravenous antibiotics and continuous IPC drainage (by attaching the IPC to an underwater seal).[16] The majority do not require the IPC to be removed.[17]	Superficial (cellulitis): 1.6%–2.5% Pleural infection: 3.2%–5%	
Non-draining septated IPC-related pleural effusion			<15%
Asciak 2019[18] Thomas 2015[19]	Treatment with intrapleural fibrinolytics. A small study showed a single dose of fibrinolytic agent (majority given 4–10 mg tissue plasminogen activator (TPA)) was associated with an increased volume of drainage and decreased symptoms but was also associated with a 3% risk of non-fatal pleural bleed.[19] There is a lack of robust data on the right treatment but often there is a lack of alternatives in patients who are not suitable candidates for surgery, thus intrapleural fibrinolytics can be considered in select patients.	4%–14%	
IPC blockage			4%
Van Metre 2011[20]	Usually due to fibrinous debris. A catheter flush with sterile saline often clears any catheter obstruction, however, fibrinolytic therapy (eg, 4 mg alteplase in 20 mL sterile saline instilled through the IPC (similar to the method used for central line unblocking), repeated a second time if inadequate drainage (<150 mL)), may be considered for more resistant occlusion, although this carries considerable cost and re-obstruction may occur.[21 22 23]	4%	
IPC fall out or dislodgement			1%
Tremblay 2006[15]	May require new IPC insertion if ongoing pleural effusion re-accumulation.	1%	

IPC-related complications, rates of occurrence and management

APPENDIX 4: LAT TROUBLESHOOTING GUIDANCE

(please note that Appendix references are listed as a separate list at the end of the appendices)

Situation	Potential approach
No fluid / small fluid volume in lateral decubitus position	It is common for fluid to "fall" away anteriorly and posteriorly with the patient lying on their side, thus it is advised that patients be scanned in clinic prior to listing for LAT to avoid this situation. However, if encountered, a per-patient decision needs to be made as to whether to: 1. Abandon the procedure (perhaps with a view to re-listing after further fluid accumulation), 2. Attempt an on-table induced pneumothorax (usually with direct US guidance of a needle into fluid), or 3. Proceed with a 'dry' LAT, whereby a careful surgical dissection method is used to access the pleural space and allow air to entrain. Recent data suggest 78% of UK LAT sites would induce a pneumothorax for LAT if needed.[24] As above, the procedure can be undertaken whilst on the table (with thoracic US to check for absence of sliding and seashore sign) or shortly prior to LAT (with a lateral decubitus CXR to check for sufficient lung collapse).
Inability to aspirate fluid during anaesthesia or collapse lung following blunt dissection	This situation is likely to occur when fluid is heavily loculated or septated, perhaps due to chronicity or infection, and may not be appreciable until pleural access is attempted on table. As above, a per-patient decision needs to be made to either: 1. Abandon the procedure with a view to considering alternative pleural biopsy techniques at a later date (eg, VATS or image-guided), or 2. Proceed to on-table US-guided parietal pleural biopsy.
Unable to advance trochar through rib space	This may occur in patients who have intrinsically narrow rib spaces or in those who have been positioned on the table in such a way as to promote 'rib crowding'. For the former, an alternative rib space/location may be required, although due consideration should be given to whether the likely risk of pain and/or injury to sub-costal structures may be excessive. In all cases, it may be possible to widen the chosen rib space by placing a folded pillow or blanket between the patient and the bed, creating a gentle convex arch in their spine.
Difficulty penetrating pleural layer (especially with trochar)	It is common for the dissection tract to collapse due to pressure from surrounding tissues, impeding passage of instruments. This is more likely to occur in larger or obese patients, in whom there may be a significant distance from the skin to the parietal pleural layer. This can be accurately measured using US prior to beginning dissection. However, this situation can usually be overcome by slow, methodical, repeated dissection along the same tract. However, this may increase the risk of pain, subsequent local surgical emphysema post procedure, and delayed tract healing.
Unable to visualise ribs on inspection	This is common in patients with significant or chronic pleural inflammation, fibrosis, or malignant infiltration. Using a rigid instrument (usually a 0 degree scope with closed biopsy forceps attached), it may be possible to press against the posterior thoracic wall and slide from side to side, thus allowing the operator to 'feel' where the rib spaces are. In rare circumstances, external transillumination may also be an option.
Unable to visualise posterior thoracic wall due to adhesions or loculations	In some instances of severe septation, it may be necessary to abandon the LAT±convert to an on-table US-guided biopsy. However, if free-flowing fluid is present, it is usually possible to undertake careful, methodical dissection of adhesions and septations to create a tract to the posterior thoracic wall. This is typically done using a blunt instrument, such as closed biopsy forceps. Where feasible, electrocautery may also be considered but should only be used by those with adequate experience and training.
Pain during biopsies	The parietal pleural layer is highly innervated and thus a degree of discomfort during pleural biopsies is to be expected, with these occasionally being extremely painful. Direct application of local anaesthesia is usually impractical. If biopsies are limited by pain, then additional boluses of opiate (eg, fentanyl 25 µg) should be considered. Accordingly, care should be taken to ensure sufficient intravenous analgesia is available and that it can be administered by a non-sterile member of the team during LAT.
Vasovagal syncope during talc poudrage	This complication can arise due to severe pain, acute local inflammatory effects of talc or, with some aerosol talc preparations, cold gas hitting the pleural surface. Treatment is supportive and, although symptoms are usually transient, they may be extreme enough to require early termination of LAT to allow rapid drain insertion and for the patient to be nursed on their back. Occasionally, bolus intravenous fluids are required.
Suspected intercostal artery damage	This usually occurs because of biopsies and should prompt planned diagnostic and therapeutic treatments to be immediately abandoned in favour of emergency procedures. Intercostal artery laceration is usually visually distinct from the expected post-biopsy pleural ooze, which is typically self-limiting. As above, it is strongly endorsed that all LAT centres adopt a site-specific standardised protocol for management of this scenario and that this be prepared in line with local major haemorrhage pathways. Intercostal artery bleeds may also present post-LAT if laceration occurred during initial dissection but was concealed by the trochar causing tamponade during the procedure. As well as abandoning diagnostic procedures, actions should include: 1. Application of external pressure over the suspected bleeding site. 2. Insertion of at least two large-bore venous cannulas. 3. Urgent venous sampling for full blood count, renal function, clotting screen, group and screen, and crossmatch (four units). Venous blood gas analysis should also be performed to obtain immediate values for haemoglobin and lactate. 4. Intravenous fluid resuscitation. 5. Frequent, regular measurement of observations (pulse, blood pressure, respiratory rate, peripheral saturations) 6. Insertion of large bore chest tube via LAT tract. 7. Portable chest x-ray and arranging contrast-enhanced CT thorax to identify bleeding vessel. 8. As per local policy, contacting either thoracic surgical colleagues or interventional radiology colleagues. 9. Moving the patient to a high-care area with continuous monitoring.
Complications during post procedure lung expansion	Rapid lung expansion following insertion of the chest drain post LAT can lead to severe pain, coughing, and/or vasovagal syncope. Although such symptoms usually settle rapidly once complete expansion is achieved, they may require the chest tube to be opened to atmosphere to allow the lung to partially collapse once more, particularly if the patient has a degree of non-expandable lung. It is strongly advised that the chest drain be sutured and secured prior to connecting to the drainage circuit, to avoid symptoms while interventions are still taking place.

CXR, chest X-ray; LAT, local anaesthetic thoracoscopy; US, ultrasound; VATS, video-assisted thoracic surgery

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