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

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INTRODUCTION

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

This article presents the results of a peer-reviewed systematic literature review combined with expert opinion of the preferred management of pleural infection in adults for clinicians in the UK. The clinical guidelines generated from this process are presented in figure 1. The guidelines are aimed predominantly at physicians involved in adult general and respiratory medicine and specifically do not cover in detail the complex areas of pleural interventions and thoracic or oesophageal surgery, trauma or oesophageal perforation account for the majority of remaining cases. Many patients have no apparent risk factors.

The Egyptian physician Imhotep initially described pleural infection around 3000 BC, although Hippocrates has been more famously credited with its recognition in 500 BC. Until the 19th century open thoracic drainage was the recommended treatment for this disorder but carried an associated mortality of up to 70%.4 5 This high mortality was probably due to respiratory failure produced by the large open pneumothorax left by drainage.5 This was particularly true of Streptococcus pneumoniae infections which now only accounts for approximately 10% of culture-positive cases.6 The prevalence of Staphylococcus aureus rose and the development of staphylococcal resistance in the 1950s increased complications and mortality.7 8 More recently, the reported prevalence of anaerobic infections2 9 10 and Gram-negative organisms9 10 has risen. Use of intrapleural fibrinolytic therapy was first suggested in 194911 but the impure agents available caused adverse reactions. Most recently, early use of video-assisted thoracoscopic surgical (VATS) techniques has been introduced.12

Epidemiology of pleural infection

The overall incidence of pleural infection is increasing.3 13 It is well recognised that pleural infection occurs most commonly in the paediatric and elderly populations and recent large-scale cohort studies concur with this finding. Farjah et al13 studied 4424 patients with pleural infection and observed an increase in incidence of 2.8% per year (95% CI 2.2% to 3.4%). Similarly, in a study population of 11 294, between 1995 and 2005 Finley et al14 found an increase in the pleural infection incidence rate ratio (IRR) of 2.2 (95% CI 1.56 to 3.10) in patients aged <19 years and 1.25 (1.14–1.34) in those aged >19 years. Age-adjusted incidence rates also increased in their cohort by almost 15% during the 8-year period.5

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

Normal pleural fluid physiology

In health, the volume of pleural fluid in humans is small (<1 ml), forming a film about 10 μm thick between the visceral and parietal pleural surfaces.14 Pleural fluid contains protein at concentrations similar to the interstitial fluid, a small number of cells (predominantly mesothelial cells, macrophages and lymphocytes) and some large molecular weight proteins such as lactate dehydrogenase (LDH). Compared with serum, pleural fluid in health also contains greater levels of bicarbonate, lower levels of sodium and similar
levels of glucose. The pH of normal pleural fluid is around 7.6. These parameters change when disease processes affecting the adjacent lung or vascular tissue activate an immune response.

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

**Pathophysiology of pleural infection**

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

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

In the early exudative stage there is fluid movement into the pleural space due to increased capillary vascular permeability. This is accompanied by the production of proinflammatory cytokines such as interleukin 8 (IL-8) and tumour necrosis factor-α (TNF-α). These produce active changes in the pleural...
mesothelial cells to facilitate fluid entry into the pleural cavity. Initially, the fluid is a free-flowing exudate characterised by a low white cell count, an LDH level less than half that in the serum, normal pH and glucose levels and does not contain bacterial organisms.\textsuperscript{17} \textsuperscript{22} \textsuperscript{28} This stage, when the pleural fluid is a straight-forward sterile exudate, is often called a ‘simple parapneumonic effusion’. Treatment with antibiotics at this stage is likely to be adequate and most effusions of this type do not require chest tube drainage.\textsuperscript{17} \textsuperscript{23} \textsuperscript{24}

If appropriate treatment is not commenced, a simple parapneumonic effusion may progress to the fibrinopurulent stage with increasing fluid accumulation and bacterial invasion across the damaged endothelium. Bacterial invasion accelerates the immune response, promoting further migration of neutrophils and activation of the coagulation cascade leading to increased procoagulant and depressed fibrinolytic activity.\textsuperscript{20} \textsuperscript{21} \textsuperscript{27} Increased levels of plasminogen activator inhibitors and decreased tissue-type plasminogen activator (tPA) are seen which favour levels of plasminogen activator inhibitors and decreased tissue-deposition and promote formation of septations within the pathogen in about 14% of culture-positive cases.\textsuperscript{7} \textsuperscript{9} \textsuperscript{29} \textsuperscript{36} \textsuperscript{38}

S milleri’ proliferate.\textsuperscript{21} A solid inflammatory process by the release of more bacteria cell wall-derived fragments and proteases.\textsuperscript{21} This combination of events leads to increased lactic acid and carbon dioxide production resulting in a fall in pleural fluid pH,\textsuperscript{20} accompanied by increased glucose metabolism and a rise in LDH levels due to leucocyte death. This leads to the characteristic biochemical features of a fibrinopurulent but not overtly purulent collection that is pH <7.20, glucose <2.2 mmol/l and LDH >1000 IU/l consistent with a ‘complicated parapneumonic effusion’.\textsuperscript{17} \textsuperscript{17} Frank pus is termed ‘empyema’.

The final stage is the organising phase in which fibroblasts proliferate.\textsuperscript{23} A solid fibrous pleural peel begins to form which occasionally encases the lung preventing re-expansion, impairing lung function and creating a persistent pleural space with continuing potential for infection.

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

**Bacteriology of pleural infection**

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

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

**Community-acquired pleural infection**

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

The frequency of anaerobic isolates is rising and positive pleural fluid cultures in most series report anaerobes in 12–34%,\textsuperscript{1} \textsuperscript{9} \textsuperscript{29} \textsuperscript{33} \textsuperscript{35} \textsuperscript{38} \textsuperscript{40} \textsuperscript{42} However, when identified using different methods such as DNA amplification, anaerobes may be present in up to 76% of cases.\textsuperscript{7} \textsuperscript{31} \textsuperscript{52} \textsuperscript{46} and may be the only pathogen in about 14% of culture-positive cases.\textsuperscript{7} \textsuperscript{9} \textsuperscript{29} \textsuperscript{36} \textsuperscript{53}

<table>
<thead>
<tr>
<th><strong>Community-acquired</strong></th>
<th><strong>Common organisms</strong></th>
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<tbody>
<tr>
<td>Streptococcus spp. (~52%)</td>
<td><em>S milleri</em></td>
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<tr>
<td><em>S pneumoniae</em></td>
<td><em>S intermedius</em></td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em> (11%)</td>
<td>Gram-negative aerobes (9%)</td>
</tr>
<tr>
<td><em>Enterobacteriaceae</em></td>
<td><em>Escherichia coli</em></td>
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<tr>
<td>Anaerobes (20%)</td>
<td><em>Fusobacterium</em> spp.</td>
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<tr>
<td><em>Bacteroides</em> spp.</td>
<td><em>Peptostreptococcus</em> spp.</td>
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<tr>
<td>Mixed</td>
<td><em>Klebsiella</em> spp.</td>
</tr>
<tr>
<td>Anaerobes (8%)</td>
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Infections with anaerobes are more likely to have an insidious clinical onset,\textsuperscript{31} with less fever, greater weight loss and are more common following possible aspiration pneumonia and with poor dental hygiene.\textsuperscript{51}

**Hospital-acquired pleural infection**

In patients with hospital-acquired infection, up to 50% of patients with positive pleural fluid cultures isolate *S aureus*.\textsuperscript{4} Meticillin-resistant *S aureus* (MRSA) may account for up to two-thirds of cases,\textsuperscript{2} although the prevalence of these infections may reduce as greater measures to reduce MRSA infection have been introduced in the last few years. Gram-negative organisms, most commonly *E coli*, *Enterobacter* spp. and *Pseudomonas* spp., are responsible for the majority of the remainder and significantly higher rates of Gram-negative aerobes have been reported in patients who need admission to the intensive care unit.\textsuperscript{47} \textsuperscript{48}

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

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

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

Despite a clinical picture of pleural infection with biochemical confirmation, pleural fluid culture is negative in approximately 40% of aspirates\textsuperscript{2} \textsuperscript{54} and, although use of PCR may identify causative organisms more sensitively than conventional culturing methods, PCR is not yet a part of routine clinical practice in most UK centres.\textsuperscript{7} \textsuperscript{55}
LITERATURE EVIDENCE AND EXPERT OPINION BEHIND THE GUIDELINE

Respiratory specialist care

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

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

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

Nutrition

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

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

Thrombosis prophylaxis in pleural infection

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

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

Identification: clinical

- Features of ongoing sepsis and raised C reactive protein in patients with pneumonia after ≥3 days may indicate progression to pleural infection. (C)

- All patients with suspected pleural infection should have blood cultures for aerobic and anaerobic bacteria performed. (C)

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

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

A recent study used a number of pneumonia severity scores and clinical variables to predict the likelihood of development of complicated parapneumonic effusion and empyema in patients with community-acquired pneumonia. None of the severity scores had any predictive value but seven clinical variables were identified predicting development of pleural infection. The presence of chronic obstructive pulmonary disease was associated with reduced risk of progression to pleural infection, but the following variables were positively predictive: (1) albumin <50 g/l; (2) CRP >100 mg/l; (3) platelet count >400 x 10^9/l; (4) sodium <130 mmol/l; (5) intravenous drug abuse; and (6) chronic alcohol abuse. Using two or more points as the cut-off, the sensitivity was 57%, specificity 82.5%, positive predictive value 17.7% and negative predictive value 98.5%. The scoring system requires independent prospective validation.

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

Identification: imaging

Initial imaging

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

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

Further radiological assessment

Ultrasound

Pleural ultrasonography may help to identify pleural infection. In a study of 520 cases of pleural effusion, all echogenic
effusions were caused by exudates and homogeneous echogenic effusions were due to either empyema or haemorrhage.

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

**CT scanning**

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

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

**MRI**

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

**Identification: pleural fluid aspiration**

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

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

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

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

Imaging guidance should be used since this minimises risks of organ perforation and improves the recovery rate of pleural fluid. Sampling using thoracic ultrasound is simple, safer and will reduce patient discomfort (see guideline on pleural intervention). Sampling can be performed by sterile procedure using a needle and syringe with local anaesthetic if necessary. Small effusions (ie, <10 mm thickness) will usually resolve with antibiotics alone. Observation may be appropriate for these patients, but an increase in the size of the effusion or ongoing sepsis should warrant re-evaluation and diagnostic pleural fluid sampling.

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

> Pleural fluid pH should be assessed in all non-purulent effusions when pleural infection is suspected. (B)

> If pleural fluid pH measurement is not available, pleural fluid glucose assessment should be performed where pleural infection is possible. (B)

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

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**Figure 2** Typical contrast-enhanced CT appearances of pleural empyema. The image shows a multiloculated pleural collection forming separate lenticular pleural opacities. The ‘split pleura’ sign with enhancing pleural tissue visible on both the visceral and parietal pleural surfaces is shown.
Indications for pleural fluid drainage in pleural infection

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

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

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

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

- Pleural fluid pH <7.2 in patients with suspected pleural infection indicates a need for chest tube drainage. (B)

- Parapneumonic effusions that do not fulfil any of these criteria for chest tube drainage could be treated with antibiotics alone provided clinical progress is good. (B)

- Poor clinical progress during treatment with antibiotics alone should lead to prompt patient review, repeat pleural fluid sampling and probably chest tube drainage. (B)

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

- Patients with a loculated pleural collection should receive early chest tube drainage. (C)

- Large non-purulent effusions could be drained by aspiration and/or chest tube if required for symptomatic benefit. (C)

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

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

Chest tube drainage

- A small-bore catheter 10–14 F will be adequate for most cases of pleural infection. However, there is no consensus on the size of the optimal chest tube for drainage. (C)

- If a small-bore flexible catheter is used, regular flushing is recommended to avoid catheter blockage. (C)
Antibiotics to cover anaerobic infection should be used. (D) All patients should receive antibiotics targeted to treat pathogens and anaerobic organisms. (B)

When bacterial cultures are negative, antibiotics should cover both common community-acquired bacterial pathogens and anaerobic organisms. (B)

Empirical antibiotic treatment for hospital-acquired empyema should include treatment for MRSA and anaerobic bacteria. (B)

Intravenous antibiotics should be changed to oral therapy once there is clinical and objective evidence of improvement in sepsis. (D)

Intrapleural antibiotics are not recommended. (D)

Prolonged courses of antibiotics may be necessary and can often be administered as an outpatient after discharge. (D)

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

A significant proportion of both aerobic and anaerobic organisms from pleuropulmonary infection may demonstrate resistance to penicillin, but β-lactam antibiotics remain the agents of choice for S pneumonie and S milleri infections. Aminopenicillins, penicillins combined with β-lactamase inhibitors (eg, co-amoxiclav, piperacillin-tazobactam) and cephalosporins show good penetration of the pleural space. There is no evidence that administering antibiotics directly into the pleural space offers any advantage.

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

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

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

Pleural effusions may occur in patients with Legionella pneumonia but are usually self-resolving. Although Legionella was not identified in a large recent series of UK adult pleural
There is no indication for the routine use of intrapleural fibrinolitics and fluid viscosity and biofilm-disrupting agents such as streptodornase and deoxyribonuclease (DNase). In experimental/translational studies, this combination reduced infected pus viscosity when compared with fibrinolitics (streptokinase) alone and can disrupt infected biofilms. Such therapeutic combinations are currently in human clinical trials. Preliminary results from one of these trials suggests that a combination of intrapleural tPA and DNase may provide superior drainage to a fibrinolytic alone, but full publication of these results is awaited.

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

Persistent sepsis and pleural collection

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

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

Patients with persistent sepsis

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

No objective criteria exist to define the point at which surgical intervention for control of pleural infection is required and the decision to operate on a patient remains subjective. Although previous observational studies have indicated that patients with purulent fluid and/or loculations at presentation are more likely to require surgery, many of these patients will settle without an operation and recent data indicate these features are not predictive. Patients should be considered for surgery if they have ongoing signs of sepsis in association with a persistent...
pleural collection despite drainage and antibiotics. Failure of sepsis to resolve within 5–7 days is suggested as an appropriate period following which a surgical opinion should be sought. Discussion with a thoracic surgeon should be considered in all cases failing to respond.

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

Two small unblinded randomised trials have directly compared surgical and medical therapy. Wait et al studied 20 patients with pleural infection who were suitable for general anaesthesia and randomised them to receive either immediate VATS or chest tube insertion (by junior resident medical staff) with additional instillation of intrapleural streptokinase for 5 days. The surgical group had higher primary treatment success (10/11 patients) and all streptokinase medical failures (5/9 patients) were salvaged by surgery without requiring thoracotomy. Surgical patients also had a shorter drainage period (3.8 vs 9.8 days) and hospital stay (8.7 vs 12.8 days). The results of this study are of doubtful robustness as the trial was very small, had an unusually high clinical failure rate in the control arm (55%) which explains the positive result, and was not blinded and so open to bias.

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

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

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

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

### Bronchoscopy

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

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

### Follow-up

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

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

### Prognosis in pleural infection

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

No reliable clinical, radiological or pleural fluid characteristics accurately determine patients’ prognosis at initial presentation. Hypoalbuminaemia, the presence of loculated fluid and anaerobic infections have been related to adverse outcome in previous studies although not in recent reports. Long-term sequelae of pleural empyema may include residual pleural thickening (up to 15% of patients). This is not usually associated with functional impairment although, rarely, extensive incapacitating pleural fibrosis may develop. Surgical decortication may occasionally provide symptomatic benefit for patients with a fibrothorax. Pleural calcification, bronchopleural fistula formation and development of empyema necessitans (disruption of the parietal pleura with spontaneous discharge of pleural contents evident under the chest wall) are other rare complications.
Pyothorax-associated lymphoma

Lymphoma is rare. It may arise in approximately 2% of patients with a long-standing pyothorax (>20 years), usually following induction of an artificial pneumothorax for tuberculosis.²²¹⁻²²² It predominantly occurs in Japanese populations, with few reports of cases from the Western world.²²³⁻²²⁴ Histologically, it is a non-Hodgkin's lymphoma with a distinctive B cell phenotype. The exact pathogenesis remains unclear, however there is a recognised association with Epstein–Barr virus infection.²²³⁻²²⁴

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

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

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