BTS guidelines for the management of pleural infection

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There is great variation worldwide in the management of patients with pleural infection, and approaches differ between physicians.[1–14] In the UK up to 40% of empyema patients come to surgery due to failed catheter drainage[4] and, overall, 20% of patients with empyema die.[4] The process of rapid evaluation and therapeutic intervention appears to reduce morbidity and mortality, as well as health care costs.

This paper presents the results of a peer reviewed systematic literature review, combined with expert opinion, of the preferred management of pleural infection. The clinical guidelines generated from this process are shown in fig 1. The guidelines are aimed predominantly at physicians involved in general and respiratory medicine, and specifically do not cover in detail the complex areas of surgical management or the management of post pneumonectomy empyema.

1 HISTORICAL PERSPECTIVE, PATHOPHYSIOLOGY AND BACTERIOLOGY OF PLEURAL INFECTION

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

1.1 Historical perspective

Pleural infection was first described by Hippocrates in 500BC. Open thoracic drainage was the only treatment for this disorder until the 19th century when closed chest tube drainage was first described but not adopted.[15] This technique became widely practised during an influenza epidemic in 1917–19 when open surgical drainage was associated with a mortality rate of up to 70%.[16] This high mortality was probably due to respiratory failure produced by the large open pneumothorax left by open drainage.[16] This was particularly true of *Streptococcus haemolyticus* infections which produce streptokinase and probably reduce adhesion formation.[16] A military commission investigated this high mortality rate and produced recommendations that remain the basis for treatment today. They advocated adequate pus drainage with a closed chest tube, avoidance of early open drainage, obliteration of the pleural space, and proper nutritional support. These changes reduced the mortality rate to 3.4% during the later stages of the epidemic.

The introduction of antibiotics both reduced the incidence of empyema and changed its bacteriology. Before antibiotics 60–70% of cases were caused by *Streptococcus pneumoniae*, which now accounts for about 10% of culture positive cases.[17] The prevalence of *Staphylococcus aureus* rose and the development of staphylococcal resistance in the 1950s increased complications and mortality.[18 19] More recently, the reported prevalence of anaerobic infections[14 18 20] and Gram negative organisms[14 20] has risen. Intrapleural fibrinolytic therapy was first introduced in 1949,[21] but the impure agents used caused adverse reactions. Most recently, thoracoscopic surgery has introduced the early use of video assisted thoracoscopic (VATS) pleural debridement.[9]

1.2 Pathophysiology of pleural infection

Pneumonia leads to about 50 000 hospital admissions each year in the UK.[22] Up to 57% of patients with pneumonia develop pleural fluid[23 24] and there are about 60 000 cases of pleural infection in the USA per year.[3] A significant proportion of cases are related to community and hospital acquired pneumonia, or are secondary to iatrogenic causes. Pleural infection may also develop without evidence of pneumonia—so called primary empyema. Most forms of pleural infection represent a progressive process that transforms a fluid self-resolving parapneumonic pleural effusion into a complicated multiloculated fibrotic and purulent collection which significantly impairs respiratory reserve and is only amenable to surgical drainage.

1.3 Normal pleural fluid physiology

In health, the volume of pleural fluid in humans is small (<1 ml), forming a film about 10 μl thick between the visceral and parietal pleural surfaces.[25] 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 higher levels of bicarbonate, lower levels of sodium, and similar levels of glucose.[26] 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 the pleurolymphatic communication. The pleurolymphatic communication is poorly documented but probably consists of a series of stomas in selected areas of pleura overlying connective tissue and a series of dilated lymphatic channels with regulatory valves.[25]

1.4 Pleural effusion development with pneumonia

The development of empyema in association with pneumonia is a progressive process that moves from a simple exudate to a fibrinopurulent stage and later to an organising stage with scar tissue formation.[27] The stage when the pleural fluid is a straightforward exudate is often called a "simple parapneumonic effusion". The early fibrinopurulent stage when the pleural fluid has developed

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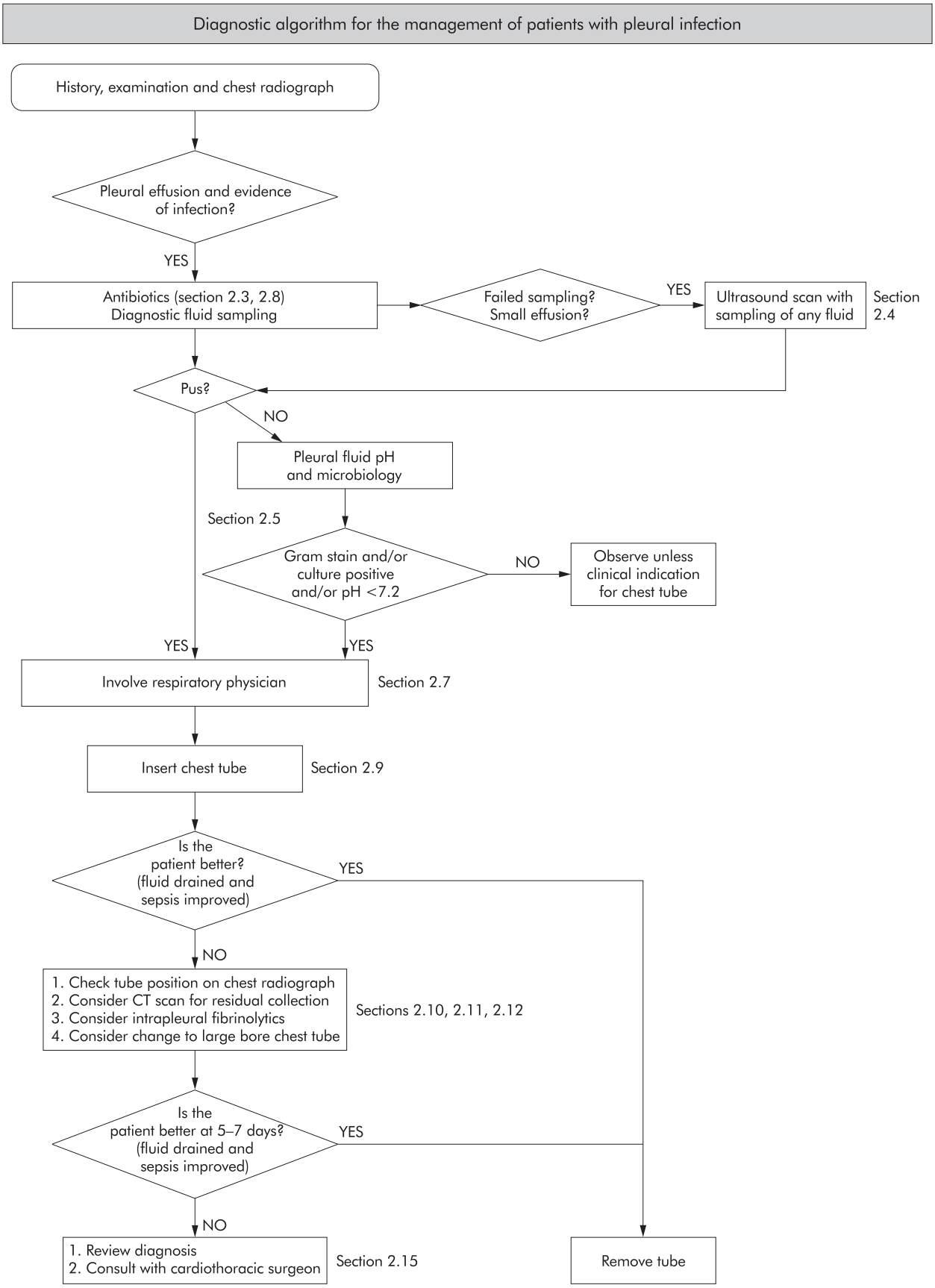

Figure 1 Flow diagram describing the management of pleural infection.

Table 1 Characteristics of parapneumonic pleural effusions

Stages	Macroscopic appearance	Pleural fluid characteristics	Comments
Simple parapneumonic	Clear fluid	pH >7.2 LDH <1000 IU/l Glucose >2.2 mmol/l No organisms on culture or Gram stain	Will usually resolve with antibiotics alone. Perform chest tube drainage for symptom relief if required
Complicated parapneumonic	Clear fluid or cloudy/turbid	pH <7.2 LDH >1000 IU/l Glucose >2.2 mmol/l May be positive Gram stain/culture	Requires chest tube drainage
Empyema	Frank pus	May be positive Gram stain/culture	Requires chest tube drainage No additional biochemical tests necessary on pleural fluid (do not measure pH)

LDH=lactate dehydrogenase.

features of infection but is not yet overtly purulent is termed a "complicated parapneumonic effusion". Frank pus is termed "empyema". The features of these three stages are summarised in table 1.

In the early exudative stage there is fluid movement into the pleural space due to increased capillary vascular permeability, accompanied by the production of proinflammatory cytokines.[28] 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, a lactate dehydrogenase (LDH) level less than half that in the serum, normal pH and glucose levels, and does not contain bacterial organisms.[6 24 29–32] Treatment with antibiotics at this stage is likely to be adequate and most effusions of this type do not require chest tube drainage.[6 24 32]

1.5 Development of complicated parapneumonic effusion and empyema

Parapneumonic effusions in the exudative stage progress to the fibrinopurulent stage with increasing fluid accumulation and bacterial invasion across the damaged endothelium. Bacterial invasion accelerates the immune reaction, promoting further migration of neutrophils and also activation of the coagulation cascade leading to increased procoagulant and depressed fibrinolytic activity.[28 33] This favours fibrin deposition and allows septations to form within the fluid. Neutrophil phagocytosis and bacterial death fuel the inflammatory process by the release of more bacteria cell wall derived fragments and proteases.[28] This combination of events leads to increased lactic acid production, associated with a fall in pleural fluid pH,[34] accompanied by increased glucose metabolism and a rise in LDH levels due to leucocyte death leading to the characteristic biochemical features of a fibrinopurulent collection (pH <7.20, glucose <2.2 mmol/l, LDH >1000 IU/l).

The organising stage follows with the proliferation of fibroblasts.[28] As a solid fibrous pleural peel replaces the soft fibrin, the re-expansion of lung is prevented, impairing lung function and creating a persistent pleural space with continuing potential for infection.

1.6 Bacteriology of pleural infection

Currently, aerobic organisms are those most frequently identified from empyemas. Gram positive organisms from the streptococcal species, including the *S milleri* group of organisms, and *Staphylococcus aureus* are most commonly found.[10 11 13 20 35–47] Most patients with *S aureus* have postoperative or nosocomial empyemas or are immunocompromised.[42] *S aureus* is seen frequently in patients following trauma and surgery.[38 45] Gram negative organisms are also the most commonly found aerobic bacteria in pleural infection, including *Escherichia coli*, *Pseudomonas* spp, *Haemophilus influenzae*, and *Klebsiella* spp.[11 13 20 36 37 40 42–44 46–48] These organisms are commonly part of mixed growths with other Gram negative organisms or with anaerobes[11 20 38 39 41–45] and rarely occur in isolation.

The frequency of anaerobic isolates is rising and anaerobes may be present in up to 76% of cases.[18 36 37 49] However, most series report anaerobes in 12–34% of positive pleural fluid cultures.[4 10 11 13 20 39 41 43 44 47] Anaerobes may cause empyema without other aerobic co-pathogens in about 14% of culture positive cases.[10 18 20 41 44] Infections with anaerobes are more likely to have an insidious clinical onset,[36] with less fever, greater weight loss, and are more common following possible aspiration pneumonia and with poor dental hygiene.[36]

2 IDENTIFICATION AND RADIOLOGICAL ASSESSMENT OF PNEUMONIA ASSOCIATED PLEURAL EFFUSION

This section presents the detail of the literature evidence and expert opinion behind the guideline presented in fig 1.

2.1 Identification

A pleural effusion may be obvious on the chest radiograph[50] and the co-existence of pulmonary infiltrates and fluid should alert the clinician to the possibility of a parapneumonic collection. Empyema should be suspected in patients who are failing to respond to appropriate antibiotic therapy. Lateral chest radiographs may confirm pleural fluid not suspected on the posteroanterior chest radiograph.[24] Ultrasound scanning, which is now readily available, is the preferred investigation and enables exact location of any fluid collection and allows guided diagnostic aspiration if required.[50 51]

Occasionally, pleural sepsis is caused by oesophageal rupture and this diagnosis should be suspected in patients who develop a pleural effusion soon after significant retching or vomiting. Oesophageal imaging and the detection of an oesophageal leak should prompt immediate referral to a surgeon with expertise in the management of oesophageal rupture.[43]

2.2 Radiological assessment

Ultrasound may help to identify exudative pleural effusions; in a study of 320 cases of pleural effusion[52] all echogenic effusions were caused by exudates and homogeneous echogenic effusions were due to either empyema or haemorrhage. In a review of both ultrasound and computed tomographic (CT) appearances in a group of patients with parapneumonic effusion requiring drainage, the appearances at ultrasound (septations, echogenicity, fig 2) did not correlate with the length of history, presence or absence of purulence, or the biochemical staging of pleural infection, but pleural thickness on contrast enhanced CT scanning was greater in those with frankly purulent effusions.[53]

In cases of diagnostic difficulty, contrast enhanced CT scanning may help to differentiate pleural empyema from a parenchymal lung abscess. 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.[54 55] The "split pleura" sign, caused

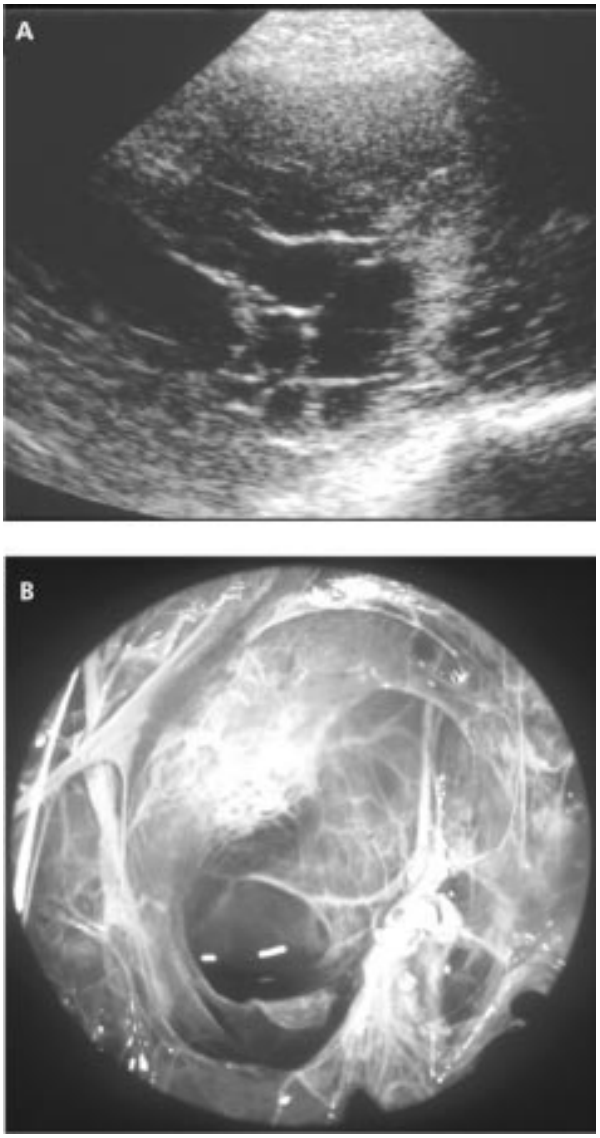

Figure 2 (A) Typical pleural ultrasound appearance of pleural infection and (B) the macroscopic appearances of pleural fibrinous septation. The pleural ultrasound image (A) shows the pleural space divided into a multi-septated collection with varying echogenic appearances within the divided fluid indicating varying degrees of fluid purulence. The pleural photograph (B) is taken at thoracoscopy and shows the macroscopic appearance of fibrinous pleural septation, in this case an infected malignant pleural effusion.

by enhancement of both parietal and visceral pleural surfaces (fig 3), and their separation in empyema is characteristic of a pleural collection. Pleural thickening is seen in 86–100% of empyemas[56–58] and 56% of exudative parapneumonic effusions.[56] The absence of pleural thickening indicates a likely simple parapneumonic effusion.[56] In pleural infection there is pleural enhancement with CT contrast studies,[57] and the extrapleural subcostal fat is of increased attenuation.[55–58]

2.3 Which patients with a parapneumonic effusion need diagnostic pleural fluid sampling?

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

It is currently impossible to clinically differentiate patients with a complicated parapneumonic effusion requiring chest tube drainage from those with a simple effusion that may resolve with antibiotics alone, and there are no specific data relating to which patients with a parapneumonic effusion can be managed without diagnostic pleural fluid sampling. There are no differences in age, white cell count, peak temperature, incidence of pleural pain, or the degree of radiological infiltrate between those requiring chest tube drainage for resolution of symptoms and those who may resolve with antibiotics alone.[24] In patients with pneumococcal pneumonia the development of parapneumonic effusions may be associated with a longer duration of symptoms and the presence of bacteraemia,[23] but the majority of these patients will have a "simple parapneumonic effusion" and will not require chest tube drainage. Similarly, there are no reliable clinical[59 60] or radiological[59] characteristics that will predict which patients with pleural infection will come to surgery.

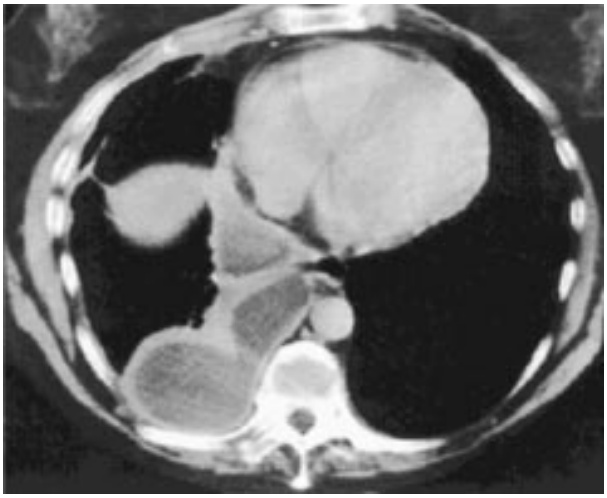

Figure 3 Typical contrast enhanced CT appearances of pleural empyema. The image shows a multiloculated pleural collection forming separate lenticular pleural opacities. The "split pleura sign" with enhancing pleural tissue visible on both the visceral and parietal pleural surfaces is shown. Note that the septation within individual locules that is seen on ultrasound (fig 2A) is not seen on CT scanning.

Pleural fluid characteristics remain the most reliable diagnostic test to guide management[6 24 29 32 60–63] and diagnostic pleural fluid sampling is therefore recommended in all patients with a pleural effusion in association with a pneumonic illness or recent chest trauma or surgery. Patients in an intensive care (ICU) setting frequently develop pleural effusions that are not caused by pleural infection.[64] 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.[64] Pleural fluid should be sampled if there are features of sepsis, possibly under ultrasound guidance if patients are receiving positive pressure ventilation.

2.4 Patients with a small pleural effusion or who have failed diagnostic pleural fluid sampling

- **In the event of a small effusion or a failed previous attempt at pleural fluid sampling, an ultrasound scan and image guided fluid sampling is recommended. [C]**
- **Pleural effusions with maximal thickness <10 mm on ultrasound scanning can be observed, with pleural fluid sampling if the effusion enlarges. [C]**

In the event of a small effusion, failure of an attempt to gather a pleural fluid sample, or an inexperienced operator, an ultrasound scan and image guided pleural fluid sampling is simple and will reduce patient discomfort.[50] Small effusions of

<10 mm thickness on a decubitus chest radiograph will usually resolve with antibiotics alone.[24 32] As ultrasound is used in preference to decubitus chest radiography in the UK, it seems reasonable to observe any effusion where maximal thickness is <10 mm on ultrasound scanning. An increase in the size of the effusion should warrant re-evaluation and a diagnostic pleural fluid sample if clinically indicated.

2.5 When to use chest tube 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.[24 32 62 63] Purulent fluid is more frequent in patients who fail chest tube drainage and require surgery or in those who die.[59]

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

The presence of organisms identified by positive Gram staining indicates bacterial invasion and implies progression from a simple effusion into empyema and hence the need for chest tube drainage.[24 32 62 63] Some frankly purulent or culture positive parapneumonic effusions due to pneumococcus may resolve without chest tube drainage,[23 60] but clinicians should be aware of the common co-existence of anaerobes not readily cultured in the laboratory before making a therapeutic decision not to drain a frank empyema.

- **Pleural fluid pH should be assessed in all non-purulent, possibly infected effusions. [B]**
- **pH <7.2 indicates chest tube drainage is required. [B]**
- **Parapneumonic effusions that do not fulfil these criteria for chest tube drainage should 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 and probably chest tube drainage. [B]**

Parapneumonic pleural effusions are inflammatory exudates dominated by polymorphonuclear leucocytes. The absolute protein values are of no value in determining the likelihood of spontaneous resolution of the effusion or chest tube drainage requirements.[6 24 31 60] The pleural fluid leucocyte count shows a wide variation in values between simple effusions and frankly purulent empyemas,[32] and a predominance of lymphocytes in an exudate should raise the possibility of malignancy or tuberculosis. Some non-purulent collections will show biochemical evidence of infection and are likely to need chest tube drainage for resolution of sepsis.[24 29–32 34 61–63] The development of a pleural fluid acidosis associated with a rising pleural level of LDH and a falling glucose level are characteristic and constitute the biochemical criteria for pleural infection.[24 32 63]

These biochemical criteria have been reviewed in a systematic meta-analysis of the data justifying their use.[63] This report showed that pleural fluid pH is the most useful index predicting the need for chest tube drainage and that the pleural LDH and glucose levels did not further improve diagnostic clarity. A pleural pH of about 7.2 was identified as best indicating the need for pleural drainage while previous studies had favoured a lower action threshold (~7.00).[65] The increased mortality associated with older age and co-morbid disease should be an indication for more aggressive management and earlier chest tube drainage.[63]

Pleural fluid for pH should be collected anaerobically with heparin and then measured in a blood gas analyser. It is not advisable, and should not be necessary, to put frank pus through a blood gas analyser as this already indicates a need for chest tube drainage of the effusion. However, where there is uncertainty whether a turbid/cloudy fluid is infected, pH can be measured safely using a blood gas analyser. Extensive clinical experience of this technique, particularly in the US, has shown that it does not damage the blood gas analyser. Measurement of pleural fluid pH is unreliable when analysed by pH litmus paper or a pH meter, and these should not be considered as acceptable alternatives to a blood gas analyser.[66 67] Physicians should be aware that lignocaine is acidic and can depress measured pH if given in large volumes or left in the same syringe used for local anaesthetic administration.[68]

Parapneumonic pleural effusions that do not fulfil these criteria for chest tube drainage may be observed and are likely to resolve with antibiotics alone. However, some patients with an initial pleural pH of >7.2 will fail to resolve their sepsis syndrome and will require surgery despite chest tube drainage.[59] These occasional cases confirm that, while pleural pH is specific in predicting the need for pleural drainage, it is less than 100% sensitive[59] and does not accurately predict eventual need for surgery.[59 62] Unsatisfactory clinical progress therefore indicates the need for repeated pleural fluid sampling and possible chest tube drainage. When needle aspiration is straightforward, it may occasionally be possible to remove all the fluid at initial thoracocentesis. In some cases the fluid will not then return and no further intervention will be required.

2.6 Other indications for chest tube drainage

- **Patients with a loculated pleural collection should receive earlier chest tube drainage. [C]**
- **Large non-purulent effusions should be drained by chest tube for symptomatic benefit. [C]**

The presence of loculation on the chest radiograph or ultrascan is associated with a poorer outcome and may be an additional indication for early chest tube drainage.[32 61 69] Larger pleural collections (>40% of the hemithorax) may be more likely to require surgery,[4 69] and non-purulent effusions without acidosis can be drained with a chest tube if indicated for symptomatic benefit.

2.7 Respiratory specialist

- **A respiratory physician or thoracic surgeon should be involved in the care of all patients requiring chest tube drainage for a 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 treatment, it is appropriate to focus the care of this disorder in specialist hands. Delay to chest tube drainage of the pleural space is probably associated with increased morbidity and duration of hospital stay,[5 10 13 38 59 70 71] and may lead to increased mortality.[38] Misdiagnosis, inappropriate antibiotics, and inappropriate chest tube placement have been cited as important factors contributing to the progression of pleural infection.[70]

An appropriate physician requires the skills to identify patients for surgery and experience in assessing thoracic surgical risk as well as expertise in managing the substantial co-morbidity in these patients. A respiratory physician best combines these skills as well as having the advantage of an established liaison with a thoracic surgeon. In centres with thoracic surgery immediately available, care may be under a surgeon and a surgical opinion is appropriate after approximately 7 days in any patient not settling with drainage and antibiotics.

Table 2 Illustrative antibiotic regimens for the initial treatment of culture negative pleural infection

Origin of infection	Intravenous antibiotic treatment	Oral antibiotic treatment
Community acquired culture negative pleural infection	Cefuroxime 1.5 g tds iv + metronidazole 400 mg tds orally or 500 mg tds iv Benzyl penicillin 1.2 g qds iv + ciprofloxacin 400 mg bd iv Meropenem 1 g tds iv + metronidazole 400 mg tds orally or 500 mg tds iv	Amoxycillin 1 g tds + clavulanic acid 125 mg tds Amoxycillin 1 g tds + metronidazole 400 mg tds Clindamycin 300 mg qds
Hospital acquired culture negative pleural infection	Piperacillin + tazobactam 4.5 g qds iv Ceftazidime 2 g tds iv Meropenem 1 g tds iv ± metronidazole 400 mg tds orally or 500 mg tds iv	Not applicable

No particular regimen is the single "ideal" choice. Drug doses should be appropriately adjusted in the presence of renal or hepatic failure.

2.8 Antibiotics

- **All patients should receive antibiotics. [B]**
- **Where possible, antibiotics should be guided by bacterial culture results. [B]**
- **Where cultures are negative, antibiotics should cover community acquired bacterial pathogens and anaerobic organisms. [B]**
- **Hospital acquired empyema requires broader spectrum antibiotic cover. [B]**

All patients should receive antibiotic therapy as soon as pleural infection is identified, and where possible, antibiotics should be chosen based on the results of pleural fluid culture and sensitivities. A significant proportion of both aerobes and anaerobes isolated from pleuropulmonary infections may be resistant to penicillin,[18 72 73] but beta-lactams remain the drugs of choice for pneumococcal[74] and the *S milleri* group infections.[75 76] Both penicillins and cephalosporins show good penetration of the pleural space,[35 77 78] and there is no need to administer antibiotics directly into the pleural space. Aminoglycosides should be avoided as they have poor penetration into the pleural space and may be inactive in the presence of pleural fluid acidosis.[35 79]

In the absence of positive culture results, antibiotics should be chosen to cover the likely organisms that may cause pleural infection. There are a considerable number of reasonable drug combinations and the chosen regimen should reflect whether the infection was contracted in the community or in hospital. The actual regimen choice should reflect local hospital policy.

In community acquired infection, empirical treatment with a second generation cephalosporin (e.g. cefuroxime) or an aminopenicillin (e.g. amoxycillin) will cover expected organisms such as *Pneumococcus, Staphylococcus aureus*, and *Haemophilus influenzae*.[80] A beta-lactamase inhibitor or metronidazole should also be given because of the frequent co-existence of penicillin resistant aerobes and anaerobes.[18 72 81] Clindamycin can combine this spectrum into a single agent. Intravenous benzyl penicillin combined with a quinolone also has an appropriate spectrum and may be associated with a reduced incidence of *Clostridium difficile* diarrhoea.

There is evidence for a probable synergistic role of anaerobes with the *S milleri* group of organisms[82 83] and patients with these mixed infections have a higher mortality from empyema.[76] Patients with an allergy to penicillin can be treated by clindamycin alone[18 80] or in combination with a cephalosporin.[3] 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.[73 84]

Pleural effusions may occur in patients with *Legionella* pneumonia and are usually self-resolving.[85] *Legionella* has rarely been reported as a cause of empyema[86] and a macrolide should only be added in suspected cases. Similarly, pleural effusions may occur in 5–20% of patients with pneumonia due to *Mycoplasma pneumoniae*,[87 88] but these are usually small reactive effusions. Most will resolve with suitable antibiotics such as a macrolide, but diagnostic pleural fluid sampling should be performed to ensure that a complicated parapneumonic effusion is not present. In all cases antibiotic regimens should be adjusted according to the results of subsequent culture results (while remembering that anaerobic pathogens are difficult to grow).

In hospital acquired empyema, usually secondary to nosocomial pneumonia, trauma or surgery, the antibiotics should be chosen to treat both Gram positive and Gram negative aerobes and also anaerobes. Postoperative and trauma related empyema requires antistaphylococcal cover. Recommended antibiotics include antipseudomonal penicillins (piperacillin-tazobactam and ticarcillin-clavulinic acid), carbapenems (meropenem), or third generation cephalosporins.[35]

The duration of treatment for pleural infection has not been assessed in detailed clinical trials and remains controversial. Antibiotics are often continued for several weeks, based on the experience of clinicians managing this and other purulent pulmonary diseases such as lung abscess[3 18 72] but, providing there is adequate pleural drainage, long term treatment may not be necessary. Treatment for about 3 weeks is probably appropriate. When prolonged treatment is used, the antibiotic regimen is usually changed to an oral combination after the fever and sepsis syndrome has settled.

Suggested antibiotic regimens for the initial treatment of culture negative community and hospital acquired pleural infections are shown in table 2.

2.9 Chest tube drainage

- **There is no consensus on the size of the optimal chest tube for drainage.**
- **If a small bore flexible catheter is used, regular flushing and suction is recommended to avoid catheter blockage. [C]**

Chest tube drainage is usually performed in one of three ways: tube insertion under radiological guidance, tube insertion without radiological guidance, and tube insertion at time of surgical debridement. Traditionally, the closed chest tube drainage of pus from the pleural cavity has been via the insertion of a large bore chest tube, inserted without radiological guidance. More recently, flexible small bore catheters which seem less traumatic to insert and more comfortable for the patient have been employed. These smaller catheters are usually inserted under ultrasound or CT guidance.

There are no controlled trials comparing the use of traditional large bore chest tubes with smaller catheters and no clinical consensus on the optimal choice. Most of the published data relate to the use of image guided small bore catheters and suggest these can have a good outcome as a primary drainage procedure[50 89 93–95] or as a rescue treatment when larger tubes have failed.[50 89–95] 10–14 Fr catheters are popular in these series and have a low complication rate.[50 89 91–93 96] There is

also a substantial body of opinion that considers large bore tubes to be more effective for draining thick pus, based on clinical experience. Sound clinical trials are needed to clarify the optimal size of chest tube.

There is no controlled evidence about optimal drain management regarding issues such as drain flushing and drain suction. In most of the studies with small bore catheters, both catheter flushing and suction were used[50 89–95 97] and regular flushing (30 ml saline every 6 hours via three-way tap) is therefore recommended for small catheters. To ensure reliability, trained nurses should ideally perform this task. Flushing larger bore drains is technically more difficult as these do not have three-way taps and disconnection for irrigation might introduce secondary infection. There are no studies to suggest any advantage from the regular flushing of large drains and it is therefore not recommended routinely. Suction (20 cm H_2O) is employed in the belief it improves drainage but there is no sound evidence or clinical consensus on which to base specific guidelines in this area.[98 99]

2.10 Management of cessation of chest tube drainage in the presence of a residual pleural fluid collection

- **If the chest tube becomes blocked or pus is unable to drain, it should be flushed with saline to ensure its patency. If poor drainage persists, a chest radiograph or CT scan should be performed to check drain position. [C]**

In the event that the chest tube should become blocked or pus is unable to drain, it may be flushed with 20–50 ml normal saline to ensure its patency. If poor drainage persists, imaging should be performed to check chest tube position and tube distortion and to look for undrained locules. Kinks may occur at the skin with smaller drains which can be repositioned and redressed. A number of commercial dressings are now available to secure small drains to reduce kinking and which have a low fall out rate. If the chest tube is permanently blocked, it should be removed and a further chest tube inserted if indicated.

Contrast enhanced CT scanning is the most useful imaging modality in patients failing chest tube drainage to provide anatomical detail such as locules and to ensure accurate chest tube placement. Pleural thickening seen on contrast enhanced CT scanning represents a "fibrinous" peel, which may prevent lung re-expansion despite adequate drainage of the pleural space.[100] Contrast enhanced CT scanning cannot accurately differentiate early and late fibrinopurulent stage disease,[57] and pleural thickness on the CT scan does not appear to predict the outcome from tube drainage.[59] Pleural peel may resolve over several weeks in patients spared surgery.[101] Residual calcification,[57] thickening of extrapleural tissues,[57] and pleural scarring[101] may persist long after empyema treatment. Both ultrasound and chest radiography may also be useful in patients failing to drain.

2.11 Intrapleural fibrinolytic drugs

- **Intrapleural fibrinolytic drugs (streptokinase 250 000 IU twice daily for 3 days or urokinase 100 000 IU once a day for 3 days) improve radiological outcome and current best evidence recommends their use. [B] It is not known if they reduce mortality and/or the need for surgery and clinical trials are underway to address this question.**
- **Patients who receive intrapleural streptokinase should be given a streptokinase exposure card and should receive urokinase or tissue plasminogen activator (TPA) for subsequent indications. [C]**

Intrapleural fibrinolytic therapy was first used in 1949.[21] The agents used initially were impure and produced side effects due to immunological events such as fever, leucocytosis and general malaise,[21] and these agents fell out of use. More recently, intrapleural fibrinolytic drugs have been reassessed. Several observational series suggest improved pleural drainage with these agents,[21 102–128] and these reports have been supplemented by small controlled trials.[110 129–132]

There are four small randomised trials of intrapleural fibrinolytic agents. The first[129] reported 24 patients randomised to streptokinase or saline placebo. Pleural drainage was improved on radiographic criteria. The study was not large enough to address surgery rates, mortality or safety. The second study[131] compared urokinase and a saline placebo in 31 patients with pleural infection. Patients were randomised after failed chest tube drainage alone. Successful pleural drainage was significantly more frequent in those receiving urokinase, but again the study was not powered for mortality, surgery rates or safety. The third study[103] is currently only reported in abstract form and included 128 patients with loculated parapneumonic pleural effusion randomised to receive either intrapleural urokinase, streptokinase, or control flushes. As with the other studies,[129 131] groups who received fibrinolytic therapy drained more fluid and had improved radiology. The fourth study is in children and shows that urokinase reduces hospital stay compared with placebo. Again it was not powered to assess the main clinical end points of mortality and surgery frequency.[132]

In these studies, drained pleural fluid volume is uninterpretable since intrapleural streptokinase increases pleural fluid production.[133] The current literature is therefore encouraging but does not establish benefit for the primary end points of clinical interest: patient mortality, surgery rates, and residual lung function. The Medical Research Council and British Thoracic Society are currently recruiting to a multicentre study to assess definitively the efficacy of intrapleural streptokinase.

Most reported adverse events due to intrapleural fibrinolytic agents are immunological and occur with intrapleural streptokinase. Fever has been noted,[103 115–117 134] but only in subjects receiving fibrinolytics for pneumonia associated pleural infection where the varying fever of the primary illness makes it difficult to quantify this effect reliably. Systemically administered streptokinase generates a systemic antibody response that can neutralise later administration of streptokinase.[135–142] It is not yet known whether intrapleurally administered fibrinolytic agents produce a similar response. In the absence of such data it is advisable to manage patients as if they had received their initial fibrinolytic systemically, with urokinase or tissue plasminogen activator (TPA) being used for later myocardial infarction or pulmonary embolism.

Two studies of small patient groups suggest that intrapleural streptokinase does not produce systemic fibrinolysis up to a total cumulative dose of 1.5 million IU.[119] There are isolated reports of local pleural haemorrhage[106 112 116] and systemic bleeding[118] associated with intrapleural fibrinolytic use. There have also been reports of nose bleeds,[116] pleural pain,[109 116 121] and transient disorientation (without evidence of intracerebral bleeding on CT brain scan).[109] Urokinase is non-antigenic but may still cause acute reactions (due to immediate hypersensitivity and histamine release) with fever[124] and cardiac arrhythmia.[143] There is a report of adult respiratory distress syndrome (ARDS) in a patient who received both streptokinase and urokinase for empyema drainage.[144] The true incidence of these occasional but major side effects is not known and will be clarified by the currently recruiting MRC/BTS trial.

Streptokinase 250 000 IU daily,[21 103–119 121 129] or 250 000 IU 12 hourly,[119] or urokinase 100 000 U daily[131 134] retained for 2–4 hours in the pleural space are the usual regimens. Their use may be most beneficial in high risk patients of an older age or with co-morbidity where surgery has a greater risk.

Recently, there has been interest in other intrapleural agents including combination drugs consisting of streptokinase and streptodornase-α, DNase.[145 146] In an experimental

setting in which fluid viscosity was assessed, this combination reduced the amount of non-liquefied material and therefore viscosity compared with streptokinase alone.[145 146] These in vitro studies suggest that it is the DNA content of pus that determines the viscosity and that, if it is effective, streptokinase may work predominantly by breaking down loculations and not by changing pus viscosity. Clinical trials will be required to assess whether DNase compounds are effective adjuncts in pleural drainage, and their use in patients cannot yet be recommended.

2.12 Persistent sepsis and pleural collection

- **Patients with persistent sepsis and a residual pleural collection should undergo further radiological imaging. [C]**

In patients who do not respond to medical treatment and who have sepsis in association with a persistent pleural collection, the diagnosis should be reviewed and a further chest radiograph performed. Thoracic CT scanning will identify chest tube position, pleural thickening, and anatomy of the effusion, and may also identify endobronchial obstruction of the bronchi by malignancy[147–150] or foreign body, and pathology in the mediastinum when there is inadequate resolution of pleural sepsis following drainage.

2.13 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, but it is clear from the BTS empyema series[4] that British chest physicians consider bronchoscopy an important investigation in patients with pleural infection. In this series,[4] 43 of 119 patients (40%) underwent bronchoscopy, usually to exclude a tumour predisposing to empyema; tumour was only found in five patients, less than 4% of the total sample. Bronchoscopy is usually performed at the time of surgery by most thoracic surgeons, but only a small number of these patients have obstructing tumour predisposing to empyema.[43] In view of the small number of patients in whom bronchoscopy is helpful, it is only recommended where there is a high index of suspicion for bronchial obstruction. Features that should raise this suspicion include a mass or loss of volume on radiographic imaging or a history of possible aspiration/inhalation.

2.14 Nutrition

- **Clinicians should ensure adequate nutritional support commencing as soon as possible after pleural infection is identified. [C]**

Poor nutrition was identified during the First World War as one of the important determinants of outcome from pleural empyema,[16] but is still sometimes overlooked. Patients with empyema suffer the catabolic consequences of chronic infection which may lead to further immunodeficiency and slow recovery. Clinicians should provide adequate nutritional support from the time the diagnosis is made. Hypoalbuminaemia is associated with a poor outcome from pleural infection.[4]

2.15 Referral for surgical treatment

- **Failure of chest tube drainage, antibiotics and fibrinolytic drugs should prompt early discussion with a thoracic surgeon. [C]**
- **Patients should be considered for surgical treatment if they have persisting sepsis in association with a persistent pleural collection, despite chest tube drainage and antibiotics. [C]**

Audit points

- Pleural fluid should be sampled for diagnostic purposes within 24 hours in over 95% of cases of suspected pleural infection.
- Pleural fluid pH should be measured with a blood gas analyser at the first diagnostic pleural fluid tap in all cases unless the pleural fluid sample is visibly purulent.
- All pleural fluid samples assessed in a blood gas analyser must be heparinised.
- All patients treated for pleural infection should receive appropriate antibiotic treatment.
- Unless there is a clear contraindication to chest drainage, all pleural effusions being treated as infected should be drained by a chest tube.
- All patients should have had an assessment of the effectiveness of the drainage of the pleural fluid collection and the resolution of their fever and sepsis 5–8 days after starting chest tube drainage and antibiotics for pleural infection. The result of this assessment should be recorded in the clinical notes.
- All patients who have not achieved effective pleural drainage at the outcome assessment described above should be discussed with a thoracic surgeon to consider surgical drainage of the infected collection.

The decision to operate to achieve empyema drainage is subjective, and there are no established objective criteria to define the point at which a patient should proceed to surgery. Patients with purulent fluid[59] and/or loculations[69] at presentation are more likely to require surgical drainage, although many patients settle without surgery. Patients should be considered for surgery if they have a residual sepsis syndrome in association with a persistent pleural collection, despite drainage and antibiotics. Failure of sepsis to begin resolution within 7 days[45 151] is suggested as an appropriate period after which a surgical opinion should be sought.

A number of surgical approaches are available including video assisted thoracoscopic surgery (VATS), open thoracic drainage, or thoracotomy and decortication. The type of procedure performed will depend on many factors including patient age and co-morbidity, and surgical preference including the local availability of video assisted surgical techniques. The choice of surgical procedure is beyond the remit of these guidelines and is not considered further.

One small trial has directly compared surgical and medical treatment. Wait *et al*[9] randomised 20 patients with pleural infection who were suitable for general anaesthesia to receive immediate VATS or intrapleural streptokinase for 3 days instilled into a chest tube. Chest tubes were not inserted under radiological guidance in the medical group and were inserted by junior resident medical staff. The surgical group had higher primary treatment success (10/11 patients) and all medical failures (5/9 patients) were salvaged by surgery without requiring thoracotomy. Surgical patients required shorter drainage time (5.8 *v* 9.8 days) and had a shorter stay in hospital (8.7 *v* 12.8 days). The results of this study need to be interpreted in the light of the small sample size and the unusually high failure rate in the control limb (55%). Further appropriately powered studies are needed.

2.16 Patients not considered fit for surgery and not improving with chest tube drainage and antibiotics

- **In cases of ineffective chest tube drainage and persistent sepsis in patients unable to tolerate general anaesthesia, re-imaging the thorax and placement of further image guided small bore catheters, large bore chest tubes, or intrapleural fibrinolytic therapy should be considered. [C]**

- **Local anaesthetic surgical rib resection should be considered in patients unsuitable for general anaesthesia. [C]**

Ineffective chest tube drainage and persistent sepsis in patients unfit for general anaesthesia 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[50 89–91 93 94] and large bore chest tubes can be tried for "thick" pus.[96] Alternatively, patients may proceed to surgical rib resection and open drainage under local anaesthesia.

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