Current Geriatrics Reports (2020) 9:47–53
https://doi.org/10.1007/s13670-020-00320-y

PULMONOLOGY AND RESPIRATORY CARE (D BREEN, SECTION EDITOR)

Pleural Infection—a Growing Problem in the Elderly

Maged Hassan[1] · Cyrus Daneshvar[1] · John P. Corcoran[1]

Published online: 9 March 2020

Abstract

Purpose of Review Pleural infection is a common cause of hospitalisation and associated with high morbidity and mortality. This review summarises our current knowledge and practice in cases of pleural infection, with a particular focus on the evidence relevant to the management of this condition in older adults.

Recent Findings The incidence of pleural infection is rising in older adults, who often present with less specific symptoms and commonly suffer from one or more comorbidities that can both confound diagnosis and impact on longer-term outcomes. Aspiration of oropharyngeal contents plays an important role in the pathogenesis of pleural infection in older adults which needs to be taken into consideration when deciding on management strategies including antibiotic selection. Treatment focuses on improving the patient's general condition, appropriate antibiotic therapy and adequate drainage of the infected pleural collection. In cases of failure of initial medical treatment, intrapleural fibrinolytics and surgical debridement of the pleural space are the two main options. Despite the fact that advanced age is a risk factor for poor outcome from pleural infection, older patients are less likely to be referred for definitive surgical treatment in these circumstances. However, the current evidence base does not necessarily show a significantly worse post-operative course in older patients undergoing surgical treatment for pleural infection in comparison to younger adults.

Summary Pleural infection is an increasingly common and frequently under-recognised pathology. Timely diagnosis and treatment can have a positive impact on morbidity and mortality, but further research is needed to allow a better understanding of how different or more aggressive treatment strategies might influence the outcome in an elderly and more vulnerable population.

Keywords Pleural infection · Empyema · Parapneumonic effusion · Pleural effusion

Introduction

Up to 50% of patients with pneumonia develop pleural effusion [1]. The majority of these effusions are only reactionary and are termed 'simple'. Pleural infection occurs when offending pathogens access the pleural space, either in the setting of contiguous pneumonia (described as complicated parapneumonic effusion) or primarily pleural space infection without lung affection [2]. Pleural infection is a serious medical problem associated with considerable morbidity and mortality and consequently imposes a substantial burden on healthcare resources. It is relatively common with a reported incidence of 9 per 100,000 population [3]. A recent systematic review reported that pleural infection is associated with long hospital admissions, ranging between 13 and 27 days with an estimated 30-day mortality of 4–11% [4•]. With the advent of minimally invasive surgery for the management of pleural infection and the growing use of medical adjuncts such as intrapleural fibrinolytics, the average healthcare cost per hospitalisation now exceeds 4000 USD [3].

Several studies have demonstrated a shift in the demographics of patients with pleural infection over time, with higher incidence rates seen in older adults in the past two decades [3, 5, 6, 7•]. This is compounded in recent years by the rising mortality rates due to pleural infection, which has been observed in adult but not paediatric patients [2]. The reasons for this changing clinical picture are incompletely understood with a range of theories including an evolving microbiome with more invasive Pneumococcal serotypes as

This article is part of the Topical Collection on *Pulmonology and Respiratory Care*

✉ Maged Hassan
maged.fayed@nhs.net

[1] Interventional Pulmonology Service, Department of Respiratory Medicine, University Hospitals Plymouth NHS Trust, Plymouth PL6 8DH, UK

a result of multivalent vaccination, the increasing use of immunosuppressive medication for autoimmune conditions and cancer and perhaps a greater awareness of the condition resulting in diagnostic suspicion bias [8]. Whilst these are all likely to be true to a greater or lesser extent, there is also little doubt that a growing population of older adults, with a complex range of comorbidities, as seen in more than 70% of this cohort of patients [4•], is also a contributory factor. For the same reasons, the management of pleural infection in older adults requires careful thought and consideration.

This review summarises our current knowledge of and best practice in managing pleural infection, with a particular focus on the evidence that exists regarding the treatment of this common and frequently life-threatening condition in older adults.

Epidemiology

The incidence of pleural infection is on the rise and this is most pronounced in the elderly. A study in Denmark looking at incidence rates at the turn of the twenty-first century found that pleural infection diagnosis rates witnessed an absolute increase of 27% in adults between 40 and 64 years of age, in comparison to an increase of 87% in people aged 80 years or more [6]. Data from Canada estimate the incidence of pleural infection among adults between 75 and 79 years of age to be 19 per 100,000 population in comparison to an incidence rate of 2–6 per 100,000 in adults between 20 and 40 years old [5]. It is noteworthy that this pattern is not uniform across the world, as it has been shown that the average age of patients diagnosed with pleural infection from high-income economies was 57 years in comparison to an average age of 43 years in patients from lower income economies [4•].

Comorbid illness is very common in elderly adults with pleural infection which is an important factor to consider when constructing a management plan for these patients. In general, more than 50% of patients with pleural infection suffer from one or more comorbidities [2, 4•]. In a comparative study of patients with pleural infection coming from independent living in the community and those coming from nursing homes, the prevalence of comorbidity was 47% in the former in comparison to 89% in the latter group [9]. Not surprisingly, cardiovascular and neurological comorbidities are more common in older patients with pleural infection [10].

Pathogenesis

The means by which pleural infection develops are incompletely understood [8]. Up to a half of patients who suffer from pneumonia develop a parapneumonic effusion, but only a small proportion of these patients go on to develop actual pleural infection [11]. Moreover, pleural infection can develop without contiguous lung parenchymal infection [12].

In the elderly, aspiration pneumonia, whether in community-acquired or hospital-acquired infections, is very common and comprises up to 70% of hospitalised cases with pneumonia [13]. This is relevant since the general pattern of the microbiology of pleural infection differs significantly from that of pneumonia, with a predominance of oropharyngeal pathogens as common causes of pleural infection as opposed to the bacteria that are typically associated with pneumonia [14•]. This suggests differing patho-biologic mechanisms for the two conditions [8, 12]. The higher prevalence of aspiration as a common mechanism may explain, at least in part, the higher incidence of pleural infection among older adults. In a study of patients with community-acquired pleural infection, a history of aspiration was present in 20% of patients older than 65 years as opposed to only 6% in those younger than 65 years [15].

Diagnosis

Clinical Presentation

The typical symptoms of pleural infection include chest pain (usually of a pleuritic nature) and fever of an acute onset. This may also be associated with cough and purulent sputum in patients with pleural infection complicating pneumonia [1]. In the elderly, the clinical presentation is often sub-acute with less pronounced fever, chest pain, or cough [9]. Patients instead usually present with less specific systemic complaints such as dyspnoea, anorexia, loss of weight, or general malaise; they are commonly anaemic and hypoalbuminaemic [9, 10, 15]. Similar to pneumonia in the elderly, many of these patients suffer from other debilitating long-term conditions such as ischemic heart disease, cerebrovascular or other neurological diseases and chronic obstructive pulmonary disease [16]. Therefore, a thorough clinical examination and a high index of suspicion are necessary for timely diagnosis of this potentially fatal condition. This is particularly pertinent in the vulnerable elderly population since any delay in the institution of appropriate therapy is associated with worse outcomes [17, 18].

Radiology

Clinical suspicion of a pleural effusion should be confirmed by imaging, the most basic of which is a standard postero-anterior chest X-ray [19]. There are no X-ray features pathognomonic of pleural infection, but the presence of either pleural fluid encystment, as suggested by a steep rise of the upper margin of the pleural fluid towards the axilla (Fig. 1), and/or pleural fluid loculation as suggested by the D sign (a bulging opacity originating from the chest wall Fig. 1) should

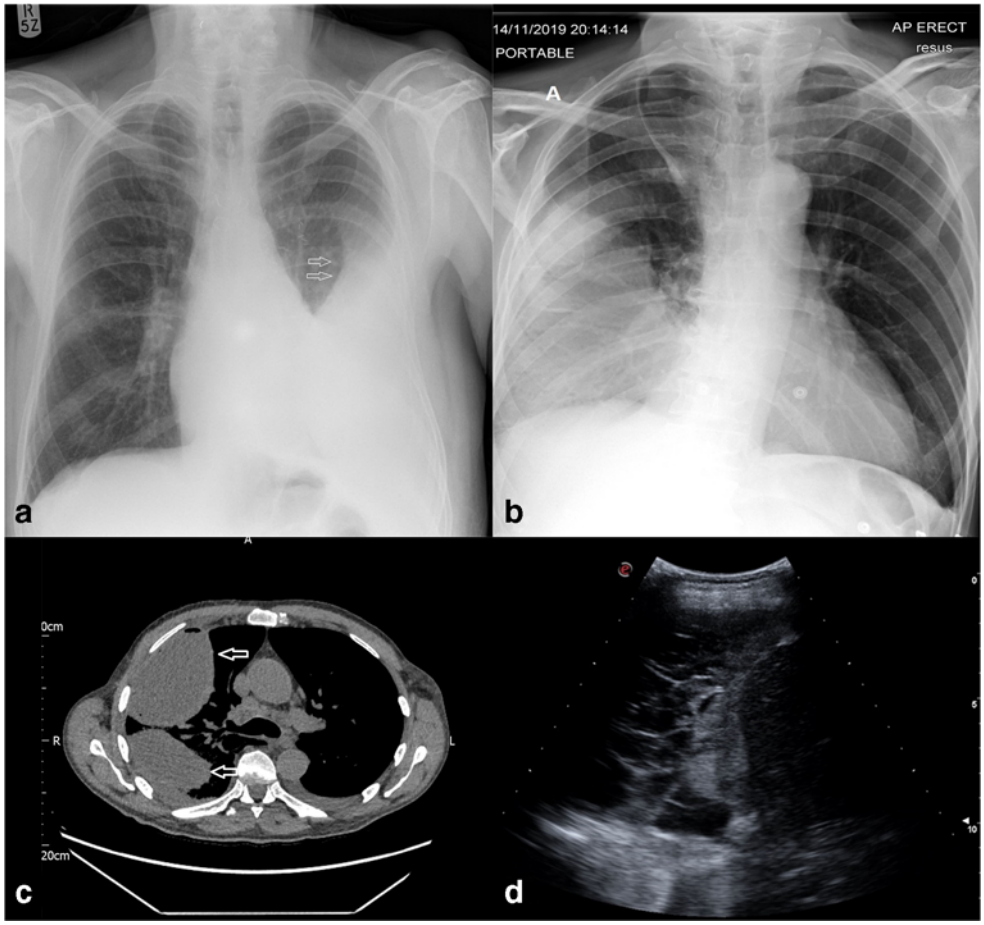

Fig. 1 **a** Chest X-ray with partially encysted left-sided pleural effusion with steep upper border of the opacity (arrows). **b** Chest X-ray with right-sided opacification exhibiting a "D" shape suggestive of a loculated pleural collection. **c** Axial computed tomography image following on from chest X-ray in **b**, confirming the presence of two distinct pleural collections (arrows). **d** Ultrasound images following on from chest X-ray in **b** and CT in **c**, showing a heavily septated pleural collection; subsequent pleural aspiration confirmed the presence of frank pus

immediately raise the suspicion of pleural infection in the correct clinical circumstances [2]. Thoracic ultrasound (TUS) is, given the overwhelming evidence base [20, 21], mandatory in modern clinical practice immediately prior to any intervention into the pleural space for suspected fluid in order to ensure safe entry and minimise the risk of iatrogenic complications. In addition, certain sonographic features can again raise suspicion for pleural infection including the presence of increased echogenicity or septations within the pleural collection (Fig. 1) [22].

Contrast-enhanced computed tomography (CT) may also be helpful in characterising the pleural anatomy further. It is not usually required for the initial diagnosis of pleural infection unless the X-ray, and TUS appearances are difficult to interpret, which is occasionally seen with multi-loculated infections (Fig. 1). CT features that may be suggestive of pleural infection include smooth pleural enhancement which appears as the 'split pleura' sign when both visceral and parietal layers are involved [23]. CT is often utilised in those cases where sub-optimal drainage of the infected pleural space has occurred, and further intervention (e.g. surgery) is being contemplated. It is noteworthy however that CT is inferior to TUS in delineating the presence and extent of pleural fluid septations [22], a feature that has been thought to herald failure of medical treatment but for which prospective data are still lacking [24, 25].

Pleural Fluid Analysis

Pleural fluid aspiration (thoracentesis) should be carried out as soon as possible in the setting of suspected pleural infection, immediately following the identification of a safe site for intervention by TUS. For smaller or loculated collections, real-time TUS guidance may be required in order to ensure safe and adequate sampling.

Macroscopic examination of the aspirated fluid may yield the diagnosis if frank pus is noted. Otherwise, bedside pH measurement of the pleural fluid using a blood gas analyser is the recommended next step, remembering that the sample needs to be processed promptly to ensure accurate results [19, 26]. A pleural fluid pH $\leq$ 7.20 is highly suggestive of pleural infection and, in the correct clinical context, should trigger further management steps for pleural infection including the insertion of a chest tube. It is important to be aware that other causes of pleural effusion such as malignancy (which is not uncommon in the elderly) and rheumatoid pleurisy can also have very low pH values [27] and clinical judgement is therefore important to avoid unnecessary interventions.

Conversely, a pleural fluid pH that is not lower than 7.20 cannot sufficiently rule out pleural infection, particularly in the presence of TUS features suggesting a complex pleural space (i.e. septations). It is known that the pleural pH is not uniform in multiloculated effusions, and even in the presence of pleural infection, a sampled locule may have a normal pH [28]. It is a standard practice to send pleural fluid samples for biochemical analysis (LDH, protein and glucose), microbiological tests (gram stain, culture and sensitivity, smear for acid-fast bacilli and culture for *Mycobacterium tuberculosis*) and cytology. In the absence of low pleural fluid pH, other findings to support a diagnosis of pleural infection are a positive gram stain and/or culture, and pleural fluid glucose < 60 mg/dL (< 3.3 mmol/L).

In order to maximise the chances of identifying the offending pathogen, it is a good practice to send pleural fluid samples in aerobic and anaerobic blood culture bottles in addition to the standard sample sent in a plain container [29]. In the aforementioned study of patients with pleural infection coming from the community and nursing homes, aerobic gram-positive bacteria were more commonly isolated from community dwellers in comparison to a higher prevalence of anaerobic infection in nursing home dwellers [9]. However, another study found the *Streptococcus milleri* group was the most commonly isolated pathogen in pleural infection in adult patients of all ages [15]. The main difference reported from this study was that fungi were three times more commonly isolated from patients with pleural infection > 65 years old [15], although this remained an unusual pathogenic organism overall. Molecular tests to detect bacterial genetic material are more sensitive than standard cultures [12, 30] and can sometimes be resorted to in the management of pleural infection if standard cultures are negative and a patient is failing empirical treatment.

Treatment

General Measures

A comprehensive assessment of a patients' nutritional status, potentially with the early involvement of a dietician, is an integral part of the management of elderly patients with pleural infection. Patients are at increased risk of venous thromboembolism as a result of reduced mobility and an inflammatory state and appropriate prophylaxis should be instituted accordingly.

Antibiotics

The cornerstones of managing pleural infection are the early commencement of appropriate antibiotics and adequate drainage of the infected material. Almost always, the initial choice of antibiotic regimen for pleural infection is empirical. Pleural fluid cultures are negative in up to 60% of cases, and in these situations, the antibiotic choice remains entirely empirical [19]. As a result, clinicians should be aware of local patterns of disease in their population given the geographic variations seen in pleural infection across the world [14•]. Given the higher risk of aspiration among the elderly, anaerobic cover should always be ensured. An important factor to take into consideration is whether the infection is community-acquired or hospital-acquired, as the usual culprits in either settings are different with an abundance of gram-positive aerobes and anaerobic bacteria in community-acquired infections, as opposed to gram-negative bacteria in hospital-acquired infection [14•]. Intravenous co-amoxiclav with or without metronidazole is a recommended regime that provides reasonable coverage for community-acquired pleural infection. In penicillin-allergic subjects, a fluoroquinolone combined with metronidazole is usually sufficient. Pleural infection by atypical bacteria is uncommon [31, 32], and therefore, the addition of macrolides and tetracyclines has a limited role in its management. In hospital-acquired pleural infections, an anti-pseudomonal antibiotic is strongly recommended such as piperacillin-tazobactam or meropenem, either of which will additionally cover anaerobic infection. Infection by *Staphylococcus aureus* and, in particular, the methicillin-resistant isolates, are common in hospital-acquired pleural infection, and coverage should be considered at an early stage in subjects either not responding to initial treatment or known to be colonised by this organism [2].

Chest Drainage

Except with very small collections, inserting a chest tube is always indicated to ensure adequate drainage of the infected pleural fluid. Evidence suggests that small-bore drains (12–18 F) are as effective as larger bore drains (≥ 24 F) in the management of pleural infection, with the latter causing considerably more chest discomfort [33, 34]. Regular flushing with 20–30 mL of normal saline four times daily of smaller-bore drains is necessary to avoid blockage by tissue debris. It has also been shown in a recently published pilot study that more regular irrigation of the pleural space with larger volumes of saline may enhance fluid drainage and reduce the need for referral to surgery, although this needs to be replicated in a larger multicentre study before entering mainstream practice [35].

Intrapleural Fibrinolytics

For patients with suboptimal drainage and/or features of ongoing sepsis such as fever and persistently raised inflammatory markers from pleural infection, further measures need to be considered to adequately clear infected material from the

pleural space. Conventionally, this was achieved through surgical thoracotomy and decortication but this approach has changed considerably in the last two decades. The MIST-2 trial has shown that the combination of tissue plasminogen activator, and DNase instilled into the infected pleural cavity improved drainage of pleural fluid and reduced the need for referral to surgery [36•]. Further real-life data attested to the efficacy and safety of this regime in managing pleural infection [37]. This option is particularly relevant in elderly patients with multiple comorbidities who are traditionally regarded as poor candidates for surgery. However, since this is an off-label use of these medications, it should only be utilised after appropriate discussion with a specialist.

Surgery

Surgery is indicated if there are persistent sepsis and suboptimal drainage of the infected pleural collection [19]. It remains the preferred pathway for patients with non-draining pleural infection who can tolerate a procedure under general anaesthesia. Video-assisted thoracoscopic surgery (VATS) is now the preferred approach to debride the infected pleural space [38] due to equivalent efficacy to conventional open thoracotomy, the latter of which is associated with higher procedural morbidity and longer hospital stays [39].

In a retrospective study of 33 patients older than 65 years of age with pleural infection, VATS had a 30-day mortality of 3%. Eighty-four percent of these patients were stable on discharge with a mean hospital stay of 27.5 days [40]. By comparison, in another report of patients > 80 years of age with pleural infection who underwent surgery, the in-hospital mortality was 3%, most commonly as a result of severe sepsis. This study showed that post-operative mortality in those > 80 years of age (1 in 37 patients with pleural infection) was not significantly worse than that of younger patients (14 in 185 patients) [10]. In a study comparing the outcomes from surgery for pleural infection, early surgical intervention in patients younger than 65 years was associated with faster recovery, but this faster recovery was also noticed in those older than 65 years who had early surgical intervention [15]. Despite this, there remains an element of nihilism when considering whether or not to surgically manage older adults with pleural infection who have failed to respond to initial medical treatment, with surgical case series consistently reporting outcomes in a population that is on average 10 years younger than that seen in unselected studies of all-comers with pleural infection.

Outcomes

Mortality from pneumonia remains strongly associated with older age [41], and this is also true for pleural infection. In a study looking at predictors of poor outcome that combined data from two large randomised trials in pleural infection, an age > 70 years was an independent risk factor for death at 3 months with an odds ratio of 25.6 [42•]. The same study also found that hypoalbuminaemia and raised serum urea (as a marker of renal impairment), both commonly found in elderly patients with pleural infection, were also independent predictors of poor outcome [42•]. Age, serum urea and serum albumin, together with other clinical parameters, are used to calculate the RAPID score which assigns patients with pleural infection to a certain 3-tier risk level (low, medium and high) which correlates with the risk of death at 3 months (Table 1) [42•].

The aforementioned epidemiological study from Denmark reported the 30-day mortality from pleural infection for patients aged 80 years or more was 20.2%, compared to only 1.2% in patients aged 15–39 years [6]. Another study which strictly included patients with community-acquired pleural infection only did not show a mortality difference according to age, but reported a longer hospital stay for older adults with a median duration of 20 days for younger patients in comparison to a median of 29 days in patients older than 65 years of age [15]. Longer hospital stay was also noted in those with nursing home-acquired pleural infection in comparison to those with community-acquired infection with median hospital stays of 21 vs. 13 days, respectively [9]. It is not clear whether higher mortality in the elderly is purely due to their

Table 1 The components of the RAPID score for prediction of outcome for patients with pleural infection

Parameter	Designated score
Renal function (serum urea)	
< 5 mmol/L	0
5–8 mmol/L	1
> 8 mmol/L	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 factors (serum albumin)	
> 27 g/L	0
< 27 g/L	1

Risk categories: scores 0–2, low risk (3-month mortality of 3% approx.); scores 3–4, medium risk (3-month mortality of 9%); and scores 5–7, high risk (3-month mortality of 31%)

frailty and comorbidity, or whether a tendency to be less interventional in older patients including an aversion to definitive surgical treatment is also contributory.

Conclusion and Future Directions

The available data show that pleural infection in the elderly is associated with considerable morbidity and mortality. Diagnosis of the condition can be more challenging in this population who often present with atypical symptoms. Prompt institution of antibiotic treatment and drainage is vital to successful management. In patients not draining sufficiently, current practice favours intrapleural fibrinolytic therapy over surgery due to a fear of complications from the latter. However, in carefully selected patients, current evidence does not show worse surgical outcomes in the elderly population. Future studies are needed to compare treatment outcomes of pleural infection with different modalities, including surgery, in elderly patients not responding to initial medical treatment to see if it is possible to reduce the substantial morbidity and mortality associated with this condition. In particular, the use of a clinical risk score to identify those patients at greatest risk from their pleural infection as part of these studies may allow clinicians to identify those in whom more aggressive intervention should be considered with the aim of improving an otherwise bleak prognosis.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflicts of interest.

Human and Animal Rights This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
• Of importance

1. Bhatnagar R, Maskell NA. Treatment of complicated pleural effusions in 2013. Clin Chest Med. 2013;34:47–62.
2. Bedawi EO, Hassan M, Rahman NM. Recent developments in the management of pleural infection: a comprehensive review. Clin Respir J. 2018;12:2309–20.
3. Shen H-N, Lu C-L, Li C-Y. Epidemiology of pleural infections in Taiwan from 1997 through 2008: pleural infections in Taiwan. Respirology. 2012;17:1086–93.
4.• Cargill TN, Hassan M, Corcoran JP, Harriss E, Asciak R, Mercer RM, et al. A systematic review of comorbidities and outcomes of adult patients with pleural infection. Eur Respir J. 2019;54:1900541 **A recently published systematic review detailing the extent of comorbidity in adults with pleural infection and the impact on outcomes.**
5. Finley C, Clifton J, Fitzgerald JM, Yee J. Empyema: an increasing concern in Canada. Can Respir J. 2008;15:85–9.
6. Søgaard M, Nielsen RB, Nørgaard M, Kornum JB, Schønheyder HC, Thomsen RW. Incidence, length of stay, and prognosis of hospitalized patients with pleural empyema. Chest. 2014;145:189–92.
7.• Grijalva CG, Zhu Y, Nuorti JP, Griffin MR. Emergence of parapneumonic empyema in the USA. Thorax. 2011;66:663–8 **A detailed epideliological paper outlining the changing face of pleural infection over time**.
8. Corcoran JP, Wrightson JM, Belcher E, DeCamp MM, Feller-Kopman D, Rahman NM. Pleural infection: past, present, and future directions. Lancet Respir Med. 2015;3:563–77.
9. El Solh AA, Alhajjhasan A, Ramadan FH, Pineda LA. A comparative study of community- and nursing home-acquired empyema thoracis. J Am Geriatr Soc. 2007;55:1847–52.
10. Schweigert M, Solymosi N, Dubecz A, Fernández MJ, Stadlhuber RJ, Ofner D, et al. Surgery for parapneumonic pleural empyema–what influence does the rising prevalence of multimorbidity and advanced age has on the current outcome? Surgeon. 2016;14:69–75.
11. Lisboa T, Waterer GW, Lee YCG. Pleural infection: changing bacteriology and its implications: pleural infection: changing bacteriology. Respirology. 2011;16:598–603.
12. Dyrhovden R, Nygaard RM, Patel R, Ulvestad E, Kommedal Ø. The bacterial aetiology of pleural empyema. A descriptive and comparative metagenomic study. Clin Microbiol Infect. 2018;25:981–6.
13. Teramoto S, Yoshida K, Hizawa N. Update on the pathogenesis and management of pneumonia in the elderly-roles of aspiration pneumonia. Respir Investig. 2015;53:178–84.
14.• Hassan M, Cargill T, Harriss E, Asciak R, Mercer RM, Bedawi EO, et al. The microbiology of pleural infection in adults: a systematic review. Eur Respir J. 2019;54:1900542 **A recently published systematic review detailing the microbiology of pleural infection and variation according to global geography.**
15. Tsai T-H, Jerng J-S, Chen K-Y, Yu C-J, Yang P-C. Community-acquired thoracic empyema in older people: thoracic empyema in older people. J Am Geriatr Soc. 2005;53:1203–9.
16. Marrie TJ. Community-acquired pneumonia in the elderly. Clin Infect Dis. 2000;31:1066–78.
17. Tsang KY, Leung WS, Chan VL, Lin AWL, Chu CM. Complicated parapneumonic effusion and empyema thoracis: microbiology and predictors of adverse outcomes. Hong Kong Med J Xianggang Yi Xue Za Zhi. 2007;13:178–86.
18. Nielsen J, Meyer CN, Rosenlund S. Outcome and clinical characteristics in pleural empyema: a retrospective study. Scand J Infect Dis. 2011;43:430–5.
19. Davies HE, Davies RJO, Davies CWH, on behalf of the BTS Pleural Disease Guideline Group. Management of pleural infection in adults: British Thoracic Society pleural disease guideline 2010. Thorax. 2010;65:ii41–53.
20. Mercaldi CJ, Lanes SF. Ultrasound guidance decreases complications and improves the cost of care among patients undergoing thoracentesis and paracentesis. Chest. 2013;143:532–8.
21. Patel PP, Singh S, Atwell TD, Kashyap R, Kern RM, Mullon JJ, et al. The safety of ultrasound-guided thoracentesis in patients on novel oral anticoagulants and clopidogrel: a single-center experience. Mayo Clin Proc. 2019;94:1535–41.
22. Kearney SE, Davies CW, Davies RJ, Gleeson FV. Computed tomography and ultrasound in parapneumonic effusions and empyema. Clin Radiol. 2000;55:542–7.
23. Leung AN, Müller NL, Miller RR. CT in differential diagnosis of diffuse pleural disease. AJR Am J Roentgenol. 1990;154:487–92.

24. Chen KY, Liaw YS, Wang HC, Luh KT, Yang PC. Sonographic septation: a useful prognostic indicator of acute thoracic empyema. J Ultrasound Med. 2000;19:837–43.
25. Chen C-H, Chen W, Chen H-J, Yu Y-H, Lin Y-C, Tu C-Y, et al. Transthoracic ultrasonography in predicting the outcome of small-bore catheter drainage in empyemas or complicated parapneumonic effusions. Ultrasound Med Biol. 2009;35:1468–74.
26. Bowling M, Lenz P, Chatterjee A, Conforti JF, Haponik EF, Chin R. Perception versus reality: the measuring of pleural fluid pH in the United States. Respir Int Rev Thorac Dis. 2012;83:316–22.
27. Mercer RM, Corcoran JP, Porcel JM, Rahman NM, Psallidas I. Interpreting pleural fluid results. Clin Med (Lond). 2019;19:213–7.
28. Maskell NA, Gleeson FV, Darby M, Davies RJO. Diagnostically significant variations in pleural fluid pH in loculated parapneumonic effusions. Chest. 2004;126:2022–4.
29. Menzies SM, Rahman NM, Wrightson JM, Davies HE, Shorten R, Gillespie SH, et al. Blood culture bottle culture of pleural fluid in pleural infection. Thorax. 2011;66:658–62.
30. Maskell NA, Batt S, Hedley EL, Davies CWH, Gillespie SH, Davies RJO. The bacteriology of pleural infection by genetic and standard methods and its mortality significance. Am J Respir Crit Care Med. 2006;174:817–23.
31. Porcel JM, Esquerda A, Vives M, Bielsa S. Etiology of pleural effusions: analysis of more than 3,000 consecutive thoracenteses. Arch Bronconeumol. 2014;50:161–5.
32. Wrightson JM, Wray JA, Street TL, Chapman SJ, Gleeson FV, Maskell NA, et al. Absence of atypical pathogens in pleural infection. Chest. 2015;148:102–3.
33. Maskell NA, Davies CWH, Nunn AJ, Hedley EL, Gleeson FV, Miller R, et al. U.K. controlled trial of intrapleural streptokinase for pleural infection. N Engl J Med. 2005;352:865–74.
34. Rahman NM, Maskell NA, Davies CWH, Hedley EL, Nunn AJ, Gleeson FV, et al. The relationship between chest tube size and clinical outcome in pleural infection. Chest. 2010;137:536–43.
35. Hooper CE, Edey AJ, Wallis A, Clive AO, Morley A, White P, et al. Pleural irrigation trial (PIT): a randomised controlled trial of pleural irrigation with normal saline versus standard care in patients with pleural infection. Eur Respir J. 2015;46:456–63.
36.• Rahman NM, Maskell NA, West A, Teoh R, Arnold A, Mackinlay C, et al. Intrapleural use of tissue plasminogen activator and DNase in pleural infection. N Engl J Med. 2011;365:518–26 **Landmark practice-changing RCT demonstrating improved outcomes from combination intrapleural fibrinolytic therapy in pleural infection, after a previous randomised study of an alternative fibrinolytic (see reference33) had reported negative results.**
37. Piccolo F, Pitman N, Bhatnagar R, Popowicz N, Smith NA, Brockway B, et al. Intrapleural tissue plasminogen activator and deoxyribonuclease for pleural infection. An effective and safe alternative to surgery. Ann Am Thorac Soc. 2014;11:1419–25.
38. Scarci M, Abah U, Solli P, Page A, Waller D, van Schil P, et al. EACTS expert consensus statement for surgical management of pleural empyema. Eur J Cardiothorac Surg. 2015;48:642–53.
39. Luh S-P, Chou M-C, Wang L-S, Chen J-Y, Tsai T-P. Video-assisted thoracoscopic surgery in the treatment of complicated parapneumonic effusions or empyemas: outcome of 234 patients. Chest. 2005;127:1427–32.
40. Tsai C-H, Lai Y-C, Chang S-C, Chang C-Y, Wang W-S, Yuan M-K. Video-assisted thoracoscopic surgical decortication in the elderly with thoracic empyema: five years' experience. J Chin Med Assoc. 2016;79:25–8.
41. American Thoracic Society, Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am J Respir Crit Care Med. 2005;171:388–416.
42.• Rahman NM, Kahan BC, Miller RF, Gleeson FV, Nunn AJ, Maskell NA. A clinical score (RAPID) to identify those at risk for poor outcome at presentation in patients with pleural infection. Chest. 2014;145:848–55 **Recently validated clinical risk score for adults with pleural infection, allowing clinicians to predict outcome at baseline presentation. Understanding how or whether this should change management approaches remains unclear.**