
ORIGINAL ARTICLE

# Ambulatory treatment in the management of pneumothorax: a systematic review of the literature

Fraser John H Brims,[1,2] Nick A Maskell[3]

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[1]Respiratory Department, Sir Charles Gairdner Hospital, Perth, Western Australia, Australia
[2]Division of Surgery and Interventional Sciences, University College London, London, UK
[3]Academic Respiratory Unit, School of Clinical Sciences, University of Bristol, Bristol, UK

**Correspondence to**
Dr Fraser John H Brims, Respiratory Department, B block, Sir Charles Gairdner Hospital, Hospital Avenue, Nedlands, Perth, WA 6009, Australia;
Fraser.Brims@health.wa.gov.au

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## ABSTRACT

**Introduction** Spontaneous pneumothorax (SP) is broken down into primary (PSP: no known underlying lung disease), secondary (SSP: known lung disease) and from trauma or iatrogenic pneumothorax (IP). Current treatments include a conservative approach, needle aspiration, chest drain, suction and surgery. A Heimlich valve (HV) is a lightweight one-way valve designed for the ambulatory treatment of pneumothorax (with an intercostal catheter).

**Methods** We performed a systematic review across nine electronic databases for studies reporting the use of HV for adults with pneumothorax. Randomised controlled trials (RCT), case control studies and case series were included, unrestricted by year of publication. Measures of interest included the use only of a HV to manage SP or IP, (ie, avoidance of further procedures), successful treatment as outpatient (OP) and complications.

**Results** Eighteen studies were included reporting on the use of HV in 1235 patients, 992 cases of SP (of which 413 were reported as PSP) and 243 IP. The overall quality of the reports was moderate to poor with high risk of bias. Success with HV alone was 1060/1235 (85.8%) and treatment as OP successful in 761/977 (77.9%). Serious complications are rare. Long-term outcomes are comparable with current treatments.

**Conclusions** High-quality data to support the use of HV for ambulatory treatment of pneumothorax is sparse. The use of HV in such circumstances may have benefits for patient comfort, mobility and avoidance of hospital admission, with comparable outcomes to current practice. There is urgent need for a carefully designed RCT to answer his question.

## Key messages

**What is the key question?**

- Controversy exists with the optimal management of pneumothorax, and Heimlich valves (HV) with an intercostal catheter may offer an alternative to current conventional therapy. We performed a systematic review to examine the existing data for effectiveness and safety for the use of HV in spontaneous and iatrogenic pneumothorax.

**What is the bottom line?**

- Quality reliable data is sparse, but there is enough to suggest that HV for pneumothorax may be effective and safe in the ambulatory treatment of pneumothorax with avoidance of further procedures in the majority of cases.

**Why read on?**

- The ambulatory management of pneumothorax is attractive as it is likely to improve comfort and mobility, and reduce or avoid hospital admission, with comparable outcomes to current treatments.

## INTRODUCTION

Pneumothorax is defined as the presence of air in the pleural space.[1] It was first described by Itard in 1803, and treatment with needle aspiration (NA) then described by Bell in 1804.[2] Spontaneous pneumothorax (SP) is broken down into primary (PSP: no known underlying lung disease), secondary (SSP: known lung disease) and non-spontaneous from trauma or iatrogenic pneumothorax (IP: most commonly from subclavian vein catheterisation and transthoracic biopsy[3]). In the USA, the incidence of PSP presenting to hospital is 7.4/100 000 for men and 1.2/100 000 for women per year, and for SSP 6.3/100 000 (men) and 2.0/100 000 (women) per year.[4] In the UK, between 1950 and 1997, the incidence of SP (PSP and SSP combined) in those presenting to hospital was 16.7/100 000 for men and 5.8/100 000 for women per year.[5] When combined with new presentations to primary care, the rates rise to 40.7 (men) and 15.6 (women) per 100 000 per year.[5] SP classically affects men more than women (ratio 2.5:1)[5 6] and those with 'ectomorphic' body habitus.[1] PSP carries a very low mortality with most cases of death from SP occurring above the age of 55 years,[5] suggesting that the majority of these cases are likely to have SSP with underlying lung disease. The underlying pathological cause of SP is likely to be the rupture of small bullae or blebs (so-called 'emphysema-like changes') on the pleural surface, which allows egress of air from the lung into the pleural space.[7]

Despite recognition of pneumothorax for more than 200 years, there still remains significant controversy and a wide variation in treatment both nationally and internationally.[8–11] The poor consensus in recommended management of SP is highlighted by three international guidelines (the American College of Chest Physicians Delphi consensus statement from 2001,[12] the British Thoracic Society guidelines 2010[8] and the Belgian Society of Pulmonology guidelines 2005[13]) contrasting sharply in many aspects of proposed treatment, and these international bodies do not even agree on a definition of

size of pneumothorax. Many experts increasingly argue that treatment options for PSP should concentrate more on patient-orientated aspects, such as symptoms, rather than chest x-ray (CXR) appearances.[9] The approach of managing PSP based on clinical and symptomatic criteria as compared with CXR appearance, is currently being examined in a large Australasian randomised controlled trial.[14] The lack of clear consensus in treatment likely contributes to both the poor adherence to guidelines and wide variations in practice that are observed worldwide.

Conventionally, the recognised treatment options for SP include a conservative approach (ie, observation alone) for small SP, NA of air from the pleural cavity, or placement of an intercostal chest tube (ICT) connected to an underwater seal.[8 12] Persistent air leak can be managed with the use of an ICT with underwater seal connected to suction (a practice with little evidence base) and, after prolonged air leak, surgery to repair or resect the damaged lung followed often by pleurodesis (the iatrogenic induction of pleural fibrosis) is advocated.[8 12] NA alone has been demonstrated to carry a highly variable success rate of 30–80%[8]; after NA failure, with current accepted approaches, admission for inpatient treatment is required for persistent pneumothorax.

Ambulatory treatments for some diseases are desirable for healthcare institutions not least for the potential financial implications of inpatient bed-days saved. The treatment of SP, and in particular PSP would lend itself well to outpatient (OP)-orientated management; patients are generally young, with few or no comorbidities, and the condition itself caries a low morbidity and mortality.[5] This is not a new concept, with reports in the literature dating back to 1973[15] advocating the use of a Heimlich flutter valve (HV: a lightweight one-way valve specifically designed for the ambulatory treatment of pneumothorax[16]) attached to an intercostal catheter with patients managed out of hospital. This approach is very attractive to patients as it does not involve connection to a drain bottle, and thus, encourages mobility and ability to more comfortably perform common activities of daily living.[17 18]

This systematic review was designed to concisely assess the published literature to examine the evidence for the use of Heimlich valves (HVs) in the management of adults with pneumothorax as compared with conventional approaches and, furthermore, to establish if such management can be safely and effectively performed in an OP environment.

## METHODS

We used a systematic review methodology based on the PRISMA[19] approach and principles. As the authors were aware that high-quality trials data is lacking in this subject field, we specifically allowed consideration of case series within the summation of the literature.

### Eligibility criteria

Studies were considered eligible for inclusion with the following criteria: adult patients with spontaneous (primary and secondary) and IP; interventions consisting of conservative approach, NA, ICT, catheter and HV; comparator with any one of the above; outcome: an assessment of the efficacy or reported success of the treatment modality; randomised controlled trials (RCTs), case control study, case series. Exclusions consisted of the following: letters, editorials and studies examining pneumothorax post-thoracic surgery or traumatic pneumothorax. Studies involving postsurgery cases with a clear delineation of outcomes between SP and surgery cases were permitted.

### Sources of information

The search strategy included several data sources unrestricted by years of publication although the full text of the study must have been in English. The literature search included the following electronic (online) databases: Cochrane Library (including the Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Databases of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE), Heath Technology Assessment (HTA) database, National Health Service (NHS) Economic Evaluation database (EED)), Medline (through Pubmed interface), Embase, and Web of Science.

Searches were conducted between 5 April and 15 May 2012. We used the following search terms, adapted for each database as appropriate

- (Drainage OR thoracic drainage OR ambulatory care OR catheters OR catheterisation OR aspiration OR needles OR needle OR manual OR simple OR spontaneous (MeSH terms), with HV (all fields)) AND
- (pneumothorax (MeSH term) OR pneumothoraces (all fields)) AND
- (clinical trial OR randomised controlled trial OR comparative study OR evaluation OR case report (publication type)).

In addition to electronic database scrutiny, we hand-searched textbooks and reference lists of included studies and articles. Lead authors and subject experts were contacted to establish any unpublished grey literature. We included any studies fulfilling the above criteria, and then independently screened and assessed each article identifying those potentially relevant. Studies were reviewed in three stages based on the title, abstract, and then full text with consensus sought at each stage of review. Two authors (FJB and NAM) independently performed the literature search and assimilation of suitable reports. The protocol utilised for the study is available in the supplementary material online.

### Data collection process

For selected studies, data were extracted onto an electronic form (Microsoft Excel 2010, Microsoft Corp, USA). Extracted information included: authors, year, geographical area, sample size, nature of pneumothorax (primary, secondary, iatrogenic, mix), intervention type(s), any control/comparator measures, outcomes reported—for each intervention, timescale of assessment, reported complications, study type, assumptions/simplifications.

### Quality—risk of bias in individual studies

The overall quality of each study was judged independently by the two authors (FJB and NAM) including assessment of study type, internal validity, generalisability, heterogeneity and precision.

For comparative experimental studies we assessed the adequacy of sequence generation, allocation concealment, blinding, completeness of data, outcome reporting and baseline comparability.

### Measures of interest

The primary measure of interest was use only of a HV (with intercostal catheter) to manage the pneumothorax, that is, avoidance of larger ICT and/or surgery; this outcome forms the definition of 'overall success' within the presentation of results.

Additional measures of interest were as follows: where applicable—use of a HV to facilitate only *outpatient-based* treatment; use of HV for different types of pneumothorax (PSP/SSP/IP)

need for surgery; recurrence rate (more than 1 week after treatment); financial assessment/implications; reported complications with 'serious' complication defined by the following: death, life threatening or serious injury, need for hospital admission, or prolonged admission, persistent or significant disability or incapacity. For financial considerations, due to variance in currency and wide difference in dates of studies, a cost ratio was calculated, rather than using original costs reported.

### Synthesis of results

Where possible, estimates of effect were collated across the selected studies. Due to the wide heterogeneity and non-comparative nature of the studies, a simple proportion of each outcome of interest was calculated.

## RESULTS

Eighteen studies from nine countries over a period of four decades reporting on the use of a HV in 1235 patients were eligible for review. Figure 1 presents a flow chart for full breakdown in the identification of suitable studies. This included two RCTs[20 21] and three prospective series,[17 18 22] the rest were retrospective case series.[15 23–34] There were 992 cases of SP (of which 413 were reported as PSP) and 243 IP. Two studies included reports on postsurgical patients, from which the results were clearly separated from SP and IP, allowing inclusion.[18 24] Table 1 provides a summary of included reports.

### Risk of bias assessment

As all but two of the studies available were case series, the overall quality assessment of the assimilated data was assessed as moderate to poor, with a high risk of bias.

### Primary and secondary outcomes

Data synthesis on outcomes was not possible. The two randomised controlled studies included had different comparators with use of HV against NA,[20] and HV against ICT,[21] prohibiting further evaluation. Therefore, we provide a narrative synthesis. Table 2 provides a summary of key outcomes. Reported overall success (use of HV with no further intervention) was 85.8% (95% CI 83.7 to 87.7). Thirteen studies describe the use of a HV in an OP setting with a reported success rate of 77.9% (95% CI 75.2 to 80.4).[18 20 22–30 33 34]

### Variance in management and approach

There was a wide variance on methodological approach within the reports. Seven studies clearly stated a conservative approach

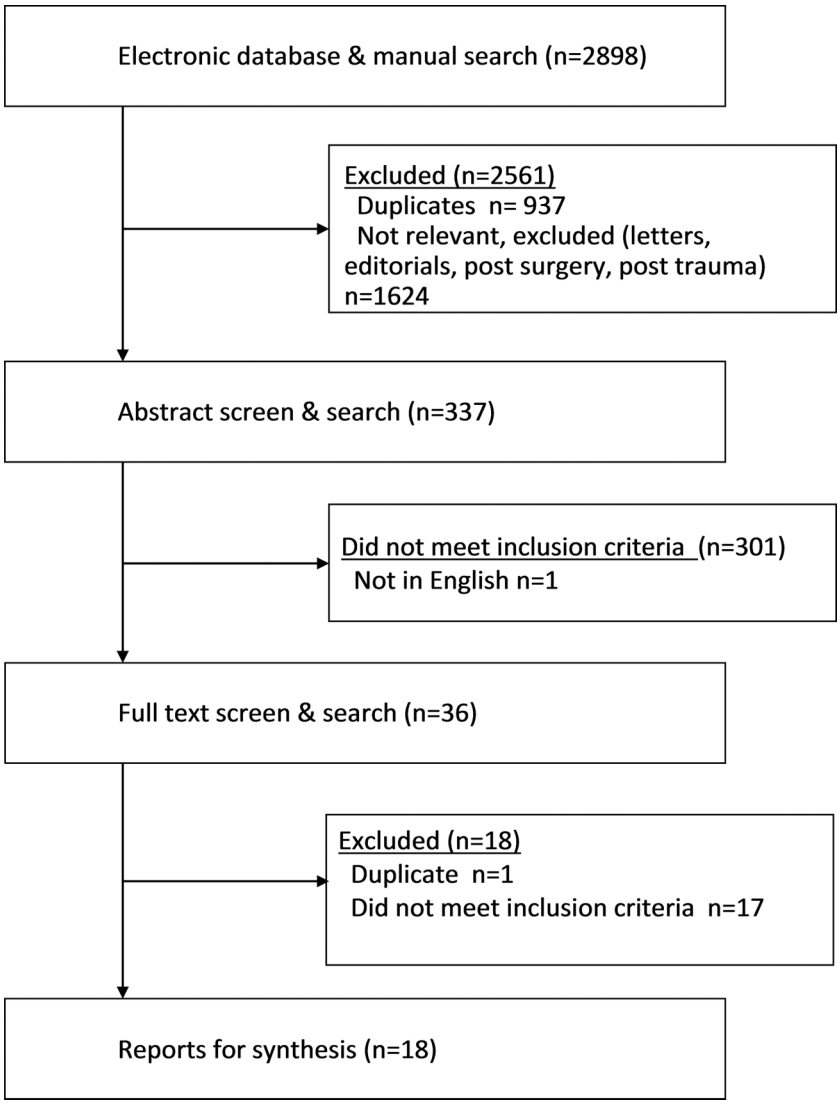


**Figure 1** PRISMA flow diagram of evidence synthesis.

**Table 1** Summary and characteristics of studies included

| Authors | Year | Study design | Outcome | Intervention n= | Pneumothorax type | Exclusions | Setting | Quality |
|---|---|---|---|---|---|---|---|---|
| Ho *et al* | 2011 | RCT | Need for second procedure | 25 (23 controls) | PSP | Tension pneumothorax, trauma, pleural effusions, SSP, bleeding disorders | Single centre. Singapore | Very good |
| Roeggla *et al* | 1996 | RCT | Need for second procedure | 19 (13 controls) | SP—not defined | None stated | Single centre. Austria | Moderate |
| Vallee *et al* | 1988 | Prospective series | Re-expansion | 37 | PSP (19), SSP (18) | Need for mechanical ventilation, hydrothorax, tension pneumothorax | Single centre. USA | Good |
| Marquette *et al* | 2006 | Prospective consecutive cases | Re-expansion | 41 | PSP | Previous pneumothorax | Single centre. France | Good |
| Dernevik *et al* | 2003 | Prospective series | Treatment as outpatient | 55 | PSP (35), SSP (20) | None stated | Single centre. Sweden | Moderate |
| Lai *et al* | 2012 | Retrospective case-note review | Need for second procedure | 55 | PSP | Tension pneumothorax | Single centre. Singapore | Poor |
| Ponn *et al* | 1997 | Retrospective series | Treatment as outpatient | 240 | PSP (96), SSP (80) | Pleural effusion, pleural infection | Single centre. USA | Poor |
| Hassani *et al* | 2009 | Retrospective case series | Re-expansion | 62 | PSP | SSP, IP, postsurgery, traumatic, tension pneumothorax, effusion | Single centre. Canada | Moderate |
| Campisi *et al* | 1997 | Retrospective case series | Treatment as outpatient | 14 | PSP (13), SSP (1) | None stated | Single centre. USA | Poor |
| Cannon *et al* | 1981 | Retrospective series | Treatment as outpatient | 41 | PSP (34), IP (7) | None stated | Single centre. USA | Poor |
| Mercier *et al* | 1976 | Case series | Treatment as outpatient | 226 | PSP (174), SSP (52) | None stated | Single centre. Canada | Poor |
| Page *et al* | 1975 | Retrospective case series | Treatment as outpatient | 104 | PSP | None stated | Single centre. Canada | Poor |
| Conces *et al* | 1988 | Retrospective case series | Re-expansion | 84 | PSP (14), IP (66) | None stated | Single centre. USA | Poor |
| Bernstein *et al* | 1973 | Retrospective case series | Re-expansion | 18 | SP—not defined | None stated | Single centre. UK | Poor |
| Minami *et al* | 1992 | Prospective case series | Re-expansion | 71 | SP—not defined | IP | Single centre. Japan | Moderate |
| Martin *et al* | 1996 | Retrospective case series | Re-expansion | 84 | PSP (11), SSP (21), IP (52) | hydropneumothorax, tension pneumothorax, need for mechanical ventilation | Single centre. USA | Moderate |
| Choi *et al* | 2007 | Retrospective case series | Treatment as outpatient | 47 | PSP (43), SSP (4) | Trauma, hydropneumothorax, pleural infection | Single centre. Korea | Moderate |
| Gupta *et al* | 2008 | Retrospective case series | Treatment as outpatient | 191 | IP | None stated | Single centre. USA | Moderate |

Intervention, use of a HV for treatment of a pneumothorax; IP, iatrogenic pneumothorax; PSP, primary spontaneous pneumothorax; RCT, randomised controlled trial; SP, spontaneous pneumothorax; SSP, secondary spontaneous pneumothorax.

to small PSP.[17 20 27–31] Algorithms for active treatment varied from placement of a catheter with HV followed by NA,[22 30] HV plus underwater seal,[28 29] HV plus suction,[25] or HV with no further action.[17 20 21 27 31] Several series did not discharge patients from hospital unless there had been objective improvements in CXR appearances of the pneumothorax by whatever means.[23 25 28 29 33 34]

The size of intercostal catheter used varied at 5.5–20 F tubes, with the older reports favouring larger tubes; all the reports in the last 10 years used catheters less than 12F. Anatomical placement of the tubes varied between the second intercostal space, midclavicular line and fifth intercostal space, anterior midaxillary line.

**Table 2** Overall outcomes from all studies

| Outcome measure: | n/N= | % | 95% CI |
|---|---|---|---|
| Success with HV alone: | | | |
| All cases | 1060/1235 | 85.8 | 83.7 to 87.7 |
| As outpatient | 761/977 | 77.9 | 75.2 to 80.4 |
| PSP | 344/413 | 83.3 | 79.4 to 86.6 |
| SSP | 110 124 | 88.7 | 81.9 to 93.4 |
| Iatrogenic pneumothorax | 237/243 | 97.5 | 94.7 to 98.9 |
| Need for surgery (all HV cases) | 119/1181 | 10.1 | 8.5 to 11.9 |
| Reoccurrence (all HV cases: 6–31 months follow up) | 40/266 | 15.0 | 11.2 to 19.8 |

'Success' is defined as the 'use only of a HV (with intercostal catheter) to manage the pneumothorax, that is, avoidance of larger ICT and/or surgery' with all studies having variable designs and management algorithms.
HV, Heimlich valve; PSP, primary spontaneous pneumothorax; SSP, secondary spontaneous pneumothorax.

## Need for surgery

All but two studies[18 21] presented outcome data for patients requiring surgery for persistent pneumothorax. For all patients treated with HV, 119/1181 (10.1%) required surgical intervention, usually for persistent air leak. Protocol and methodological approach as to the appropriate timing and indication for surgery varied widely. One study from Korea reported a remarkably high requirement for surgery of 26/47 (55.3%)[33] with little explanation, although the use of suction was not commented upon.

### Financial

Four studies reported healthcare economic utilisation, with data for three usable. One study[22] compared the use of HV in inpatients as compared with standard inpatient ICT and reported a cost ratio of 1:3. The same study examined the cost of NA versus inpatient ICT, and reported a cost ratio of 1:7. Two studies[27 33] compared the use of OP HV with inpatient ICT reporting cost ratios of 1:3.5 and 1:5.

### Recurrence

Data on long-term recurrence of pneumothorax after HV treatment was presented in five studies. Reported recurrence rates varied between 11% and 24% with follow-up periods between 6 months and 31 months.[15 17 25 33] One study reported a recurrence rate after HV use of 7% with no follow-up period stated.[32]

### Complications

Serious complications were rare, and no deaths were reported as a consequence of HV treatment. Table 3 presents a summary of data on complications.

## DISCUSSION

This is the first systematic review to examine the evidence for the use of HV in the treatment of pneumothorax. Despite nearly 40 years of reports in the literature, quality evidence to support the use of HV for pneumothorax remains sparse with just one good-quality randomised controlled trial to accompany more than a thousand other reported cases. Despite mixed methodology and a high risk of reporting bias, there is enough data to support the notion that HV might be useful in the treatment of non-traumatic pneumothorax with reasonable treatment success on varied parameters in the studies assessed. This treatment has the potential for significant improvements in the treatment of pneumothorax, pending the results of well designed and conducted comparative studies.

The use of a HV attached to a secure intercostal catheter would potentially facilitate ambulatory treatment of pneumothorax and plausibly, in selected individuals' OP-based care. Indeed this management option has been attempted in the vast majority of cases we have identified, with reported success in 761/977 (77.9%; 95% CI 75.2 to 80.4). Strategy varied widely as to when a patient was discharged after initial placement of the ICT and HV. Nevertheless, given the young age group, minimal comorbidity and low mortality associated with PSP,[5] there is now persuasive evidence to support further research as to the usability and safety of this approach.

**Table 3** Reported complications from all studies (n=1235)

| Complication | n= |
|---|---|
| Death | 0 |
| Visceral puncture/injury | 0 |
| Haemothorax (all managed conservatively) | 4 |
| Incorrect connection—tension pneumothorax | 1 |
| Local cellulitis | 1 |
| Tube blockage with exudate | 2 |
| HV/catheter dislodged | 8 |
| Pain after insertion | 1 |
| Surgical emphysema | 4 |

HV, Heimlich valve.

In cases where there was clear delineation between PSP and SSP, there appears to be similar success rates with the use of HV (PSP 344/413 (83.3%; 95% CI 79.4 to 86.6) and SSP (110/124 (88.7%; 95% CI 81.9 to 93.4)), although the likelihood of selection bias in SSP cases in particular is high, with more severe or sick cases likely not to be selected for this innovative treatment. IP appears to have a good success rate with a HV (reported as 97.5%; 95% CI 94.7 to 98.9), which again may be biased by selection, or that these patients usually improve well, anyway, as there is frequently no ongoing air leak.

### Complications

In considering the case for the use of HV in the management of pneumothorax, it is important to consider the complications associated with their use; table 3 lists the significant complications reported from the studies. With consideration for likely marked limitations with bias and under-reporting, there are no deaths and no visceral punctures reported, with the most common problem appearing to be tube blockage or dislodgement. Despite the frequent use of larger drains in the older reports there were few reports of significant pain. These data should be compared with known complications with insertion of chest drains where more serious harm and pain is well recognised,[8] with a recent British Thoracic Society pleural procedures audit from the UK stating 25% of patients reported significant pain after insertion of a chest drain for pneumothorax.[35]

### Recurrence and need for surgery

The indications for, and timing of, surgery in the management of SP remains controversial with little evidence base to support practice, and there was a wide spectrum of timing and indications in the studies examined for this review. The rates of those deemed to require surgery in this report (10.1%) are comparable with reports from randomised trials examining NA versus tube drainage for SP.[36–39] Similarly, long-term recurrence rates reported in the HV studies (15.0%, range 7–24%) are also similar to those reported elsewhere in the literature (22–29%).[36–39] It is important to note that the use and timing of surgery for management of SP is controversial, with Chee *et al* reporting on 115 patients with SP where 97% of PSP and 79% of SSP with persistent air leak resolved spontaneously with tube drainage alone, with no mortality in the groups.[40] Current guidelines suggest consideration of surgical referral with persistent air leak, or failure of lung re-expansion, at 3–5 days after presentation.[8]

### Implications for healthcare resources

There is little reliable data from this review to confidently state a possible healthcare economic benefit from the use of HV to avoid hospital admission, although two studies suggest a benefit in favour of HV use compared with ICT as an inpatient.[27 33] In 2005/2006, hospital episode statistics report 5954 finished consultant episodes for PSP in England.[41] If half the attempts at treatment with NA are successful[8] this suggests that upwards of 3000 patients with PSP will be admitted for ICT each year, with a mean length of hospital stay of 5 days.[36 39] Assuming HV is successful in the treatment of pneumothorax in approximately 80% of cases, the adoption of this treatment could save nearly 12 000 bed days per year in England alone. A detailed economic analysis of healthcare utilisation of possible benefits should be integral to future prospective studies.

### Limitations

Overall, the data quality for this systematic review is fairly poor, with a high risk of reporting bias and, therefore, interpretation of these results in this study should be guarded. After direct communication with the author seeking clarity with RCT design, just one report may be regarded as very good quality[20] although a prospective consecutive case series of 42 patients also provides useful data, albeit with no control group.[17] Both these reports present comparable outcome and safety data to the rest of the reports in this review.

## SUMMARY

After 40 years of reports using HVs in the ambulatory care of SP, reliable, quality data are sparse. The use of HV in such circumstances may have benefits for patient comfort, mobility and avoidance of hospital admission, with comparable outcomes to current practice, although the current published literature cannot reliably inform this. There is an unmet need to examine the potential for ambulatory treatment of SP with high-quality RCTs required to provide reliable data on outcomes, health-related quality of life, total days hospitalised and pain scores to inform future management.

**Contributors** FJHB conceived the project, performed data collection, analysis, synthesis and manuscript preparation. NAM performed data collection, analysis and manuscript preparation.

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**Competing interests** FJHB has received reimbursement for travel expenses to medical conferences from Rocket Medical, and has worked on the advisory board for CareFusion. NAM has received research funding from Novartis and CareFusion, and has worked on the advisory board for CareFusion.

**Provenance and peer review** Not commissioned; externally peer reviewed.

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THORAX

# Ambulatory treatment in the management of pneumothorax: a systematic review of the literature

Fraser John H Brims and Nick A Maskell

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## Pleural disease 1

# Pleural infection: past, present, and future directions

*John P Corcoran, John M Wrightson, Elizabeth Belcher, Malcolm M DeCamp, David Feller-Kopman, Najib M Rahman*

**Pleural space infections are increasing in incidence and continue to have high associated morbidity, mortality, and need for invasive treatments such as thoracic surgery. The mechanisms of progression from a non-infected, pneumonia-related effusion to a confirmed pleural infection have been well described in the scientific literature, but the route by which pathogenic organisms access the pleural space is poorly understood. Data suggests that not all pleural infections can be related to lung parenchymal infection. Studies examining the microbiological profile of pleural infection inform antibiotic choice and can help to delineate the source and pathogenesis of infection. The development of radiological methods and use of clinical indices to predict which patients with pleural infection will have a poor outcome, as well as inform patient selection for more invasive treatments, is particularly important. Randomised clinical trial and case series data have shown that the combination of an intrapleural tissue plasminogen activator and deoxyribonuclease therapy can potentially improve outcomes, but the use of this treatment as compared with surgical options has not been precisely defined, particularly in terms of when and in which patients it should be used.**

*Lancet Respir Med* 2015; 3: 563–77

This is the first in a **Series** of two papers about pleural disease

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See **Online** for a discussion with Nick Maskell and Najib Rahman

**Oxford Centre for Respiratory Medicine** (J P Corcoran MRCP, J M Wrightson DPhil, N M Rahman DPhil) **and Department of Cardiothoracic Surgery** (E Belcher PhD)**, Oxford University Hospitals NHS Trust, Oxford, UK; University of Oxford Respiratory Trials Unit, Churchill Hospital, Oxford, UK** (J P Corcoran, J M Wrightson, N M Rahman)**; NIHR Oxford Biomedical Research Centre, University of Oxford, Oxford, UK** (J M Wrightson, N M Rahman)**; Division of Thoracic Surgery, Northwestern Memorial Hospital, Northwestern University Feinberg School of Medicine, Chicago, IL, USA** (Prof M M DeCamp MD)**; and Division of Pulmonary and Critical Care Medicine, Johns**

## Introduction

Despite advances in medical diagnostic and therapeutic strategies, pleural infection (empyema or complex parapneumonic effusion) is an important problem worldwide that continues to be associated with substantial morbidity and mortality. This disorder was reliably described by Hippocrates more than two millennia ago and has claimed many lives since that time, including those of medical luminaries such as Guillaume Dupuytren (1777–1835) and William Osler (1849–1919). The basic principles of treating pleural infection, which include adequate drainage of the infected fluid collection, nutritional support, and an appropriate antibiotic therapy, have remained constant since the mid 20th century.

The incidence of pleural infection in both adult and paediatric populations continues to rise inexorably.[1–5] Postulated reasons for this rise include an improvement in clinical awareness and diagnostics, a replacement phenomenon associated with widening use of multivalent pneumococcal vaccines,[3,6,7] and a vulnerable ageing population living with chronic disease. One in five patients will need surgical intervention to adequately treat their pleural infection,[8,9] whereas the 1-year mortality from the disorder has remained steady at about 20% for more than two decades.[5,8–10] Of particular concern is that the greatest increase in caseload is in patients aged older than 65 years[1] and immunocompromised patients, whose mortality from pleural infection is above 30%,[1,8,9,11] related to frail health and comorbidity. There are any number of potential reasons for the failure of treatments to have a substantial and lasting effect on key clinical outcomes. These reasons might include variability in clinical practice and disagreement about how these patients are best managed,[12–17] despite the availability of consensus guidelines.[5,18]

This Series paper addresses our understanding of pleural infection, specifically its pathophysiology, diagnosis, and treatment, together with developments in clinical and laboratory research, and future areas of investigation for management of this disorder.

## Pathophysiology

Parapneumonic effusions occur in up to half of all cases of community-acquired pneumonia, with about 10% of these effusions becoming complex due to co-infection of the pleural space.[19,20] The initial formation of a parapneumonic effusion is thought to be caused by increased permeability of the visceral pleural membranes and leakage of interstitial fluid in response to inflammation of the underlying lung parenchyma. The promotion of neutrophil migration together with the release of pro-inflammatory cytokines, including interleukin-6, interleukin-8, and tumour necrosis

### Key messages

- The incidence of pleural infection continues to rise and this disease remains associated with a poor clinical outcome, with up to 20% of patients requiring surgery or dying
- The process by which bacteria translocate the infected lung and multiply in the pleural space is incompletely understood, but there is an increasing understanding of the inflammatory pathways associated with progression from simple to complex, fibrinous infected effusion
- A score to predict clinical outcome at baseline in pleural infection has been derived and might be helpful in the future to plan treatment escalation and invasive interventions
- The microbiological profile of pleural infection suggests a different set of organisms to those seen in pneumonia, with oropharyngeal and microaspiration potential sources
- Conventional microbiological analysis is only slightly sensitive for the identification of causative organism, and this can be improved by the inoculation of pleural fluid into culture media bottles, and potentially in the future by the use of molecular microbiological techniques
- Intrapleural tPA and DNase has been shown to significantly improve drainage and can have important effects on reducing surgical requirement and hospital stay
- Surgery remains a key treatment modality in selected cases, but the precise surgical method of choice, patient selection, and timing are not well defined

**Hopkins Hospital, Baltimore, MD, USA** (D Feller-Kopman MD)

Correspondence to:
Dr Najib M Rahman,
Oxford Centre for Respiratory Medicine, Churchill Hospital, Oxford OX3 7LE, UK
**najib.rahman@ndm.ox.ac.uk**

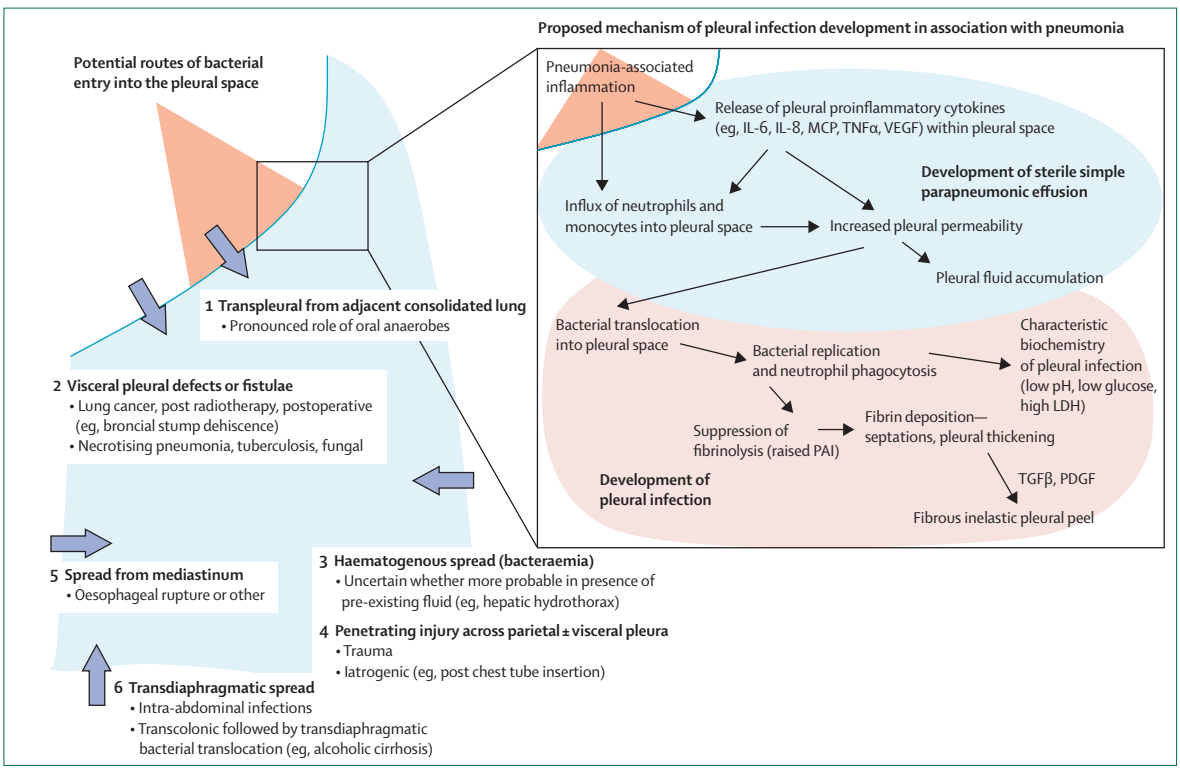


***Figure 1:*** **Development of pleural infection—possible routes and mechanisms**
IL-6=interleukin-6. IL-8=interleukin-8. MCP=monocyte chemoattractant protein. TNFα=tumour necrosis factor-α. VEGF=vascular endothelial growth factor. TGFβ=tumour growth factor-β. PDGF=platelet-derived growth factor. LDG=lactate dehydrogenase. PAI=plasminogen activator inhibitor.

factor-α (TNFα), result in the development of intercellular gaps between pleural mesothelial cells[21,22] that facilitate the accumulation of excess pleural fluid. During this early exudative stage, the fluid is uncomplicated and shows no microbiological or biochemical features of pleural infection. In most cases, the parapneumonic effusion will simply resolve with appropriate antibiotic therapy for the underlying pneumonia.

The reasons why and means by which secondary bacterial invasion of the pleural space occurs are incompletely understood, a knowledge gap that is likely to be one of the barriers to therapeutic progress. Although studies in animals frequently rely on artificial infection of the pleural space via a percutaneous route (rather than due to co-infected lung parenchyma), practical and ethical limitations exist in clinical research, notably the need for repeated invasive sampling to study the evolution of pleural infection.[23] An additional complication is that pleural infection can arise spontaneously without underlying lung consolidation,[24–26] implying contamination of the pleural space by another route (eg, haematogenous seeding of bacteria). Nonetheless, a study using a murine in-vivo model together with in-vitro cell line studies[27] has shown that *Streptococcus pneumonia* (*S pneumonia*), a common cause of pleural infection in both adults and children, is capable of translocating through visceral mesothelial cells from the parenchyma to pleural space, thereby instigating the inflammatory cell and cytokine responses associated with pleural infection.

As bacteria multiply, various changes occur within the pleural space (figure 1), resulting in the characteristic clinical and biochemical features associated with a complicated parapneumonic effusion, so-called because of the adverse clinical outcomes seen unless the collection is drained. Bacterial metabolism and neutrophil phagocytic activity result in the production of lactic acid and carbon dioxide production, causing in turn a decrease in pleural fluid pH and glucose concentration,[28,29] both of which are clinically used as laboratory markers of pleural infection.[5,30] The continued release of inflammatory cytokines such as interleukin-6, interleukin-8, TNFα, vascular endothelial growth factor (VEGF), and monocyte chemotactic protein (MCP), which are all linked to ongoing excess fluid production, occurs together with rising levels of fibrinolysis inhibitors such as tissue plasminogen activator inhibitor (PAI).[31] This depression of fibrinolytic activity is unique to infected effusions,[31] resulting in fibrin deposition that both coats the visceral and parietal pleural surfaces and divides the space into separate pockets. Finally, purulent fluid (empyema) develops in the context of bacterial and leucocytic cell death and lysis.

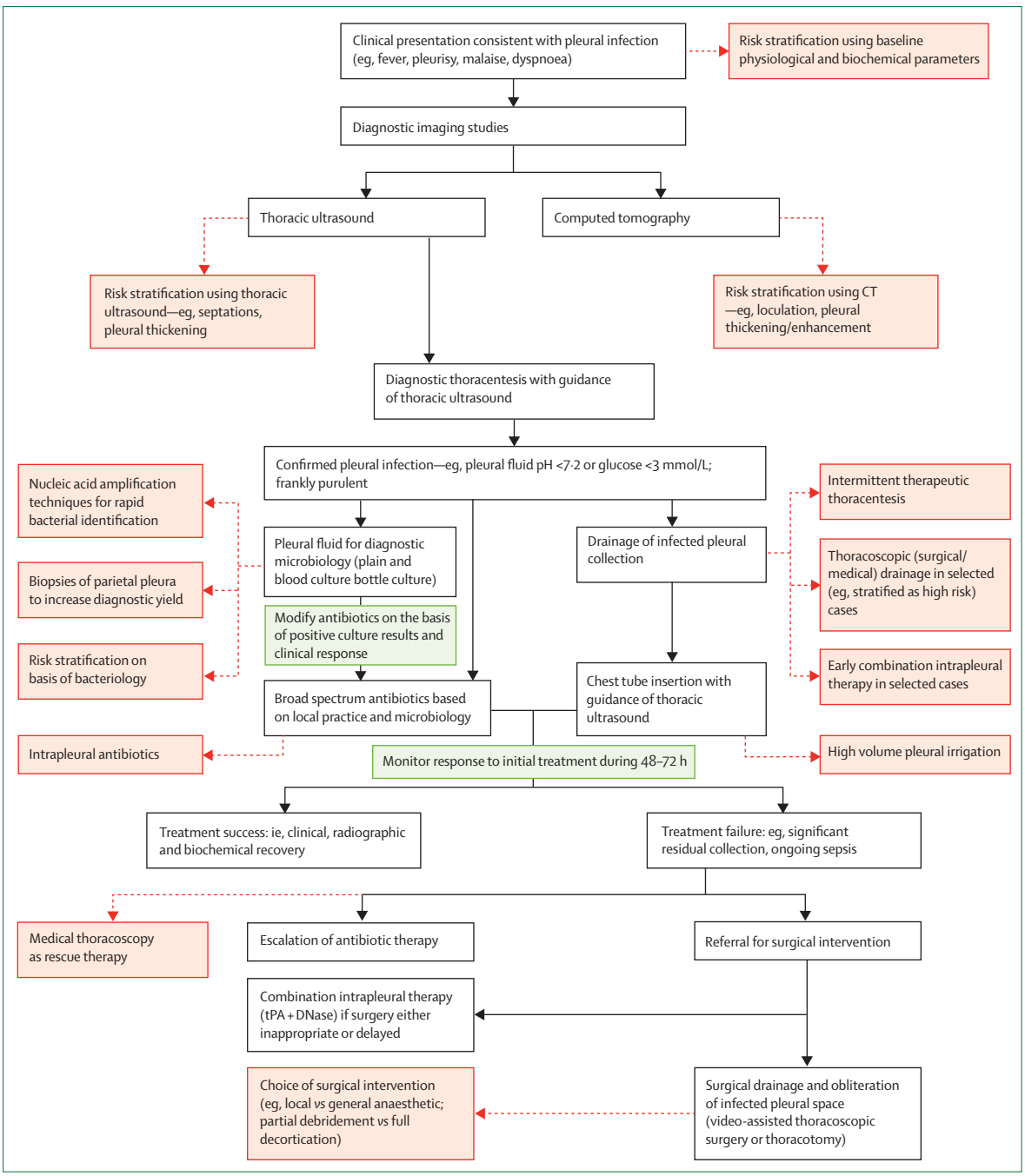


***Figure 2:*** **Diagnostic and therapeutic pathway for the patient with pleural infection**
Black boxes, text & arrows represent established treatment pathway; red boxes, text & arrows represent potential future directions for clinical care and research. tPA=tissue plasminogen activator.

As the infection progresses from an acute to a chronic state, fibroblast proliferation occurs along the established fibrin matrix. This proliferation creates dense inelastic septations and collagenous thickening within and around the pleural cavity, walling off residual infection but also restricting lung expansion and compliance. The rate at which this change occurs varies greatly between individuals, with data from rabbit and mouse models of pleural infection or fibrosis suggesting a role for signalling proteins such as platelet-derived growth factor (PDGF) and transforming growth factor-β (TGFβ),[32] which offers the prospect of a novel therapeutic target for future investigation.[33] Although surgical intervention is

almost certainly needed by this point to ensure adequate clearance of infected material from the pleural space, clinical outcomes are unpredictable, with some patients having no long-term sequelae and others showing permanent impairment of lung function.

## Diagnosis and outcome prediction

The diagnosis and treatment of pleural infection depends on the awareness of the clinician assessing the patient (figure 2). An absence of improvement despite adequate antibiotic therapy for apparently uncomplicated (assumed by the clinician) pneumonia or presentation with a pleural effusion alongside symptoms that vary from those specific for infection (fever, rigours) to those non-specific for infection (malaise, anorexia) should all prompt suspicion for a potential diagnosis of pleural infection. This situation is especially true in elderly and nursing-home patients who often present with an indolent course characterised by a so-called failure to thrive, anaemia, and weight loss.[34] The delayed recognition and subsequent treatment of pleural infection inevitably negatively affects morbidity and mortality,[10,12] inspiring the often repeated maxim that the sun should never set on a parapneumonic effusion. In the absence of any reliable alternative means to determine which parapneumonic effusions are either already infected or will probably become infected, pleural fluid sampling is always indicated. Current guidelines[5] strongly recommend the use of thoracic ultrasound to guide any intervention for pleural fluid (figure 2). With evidence showing how thoracic ultrasound reduces the risk of iatrogenic complications,[35,36] blind thoracentesis in this clinical scenario is almost impossible to justify. Ultrasound guidance is additionally useful in the context of suspected infection when collections might be septated, in small volume, or multi-loculated.

The diagnosis of pleural infection can be confirmed if appropriate laboratory investigations are requested and correctly interpreted. If pus or microbiologically positive fluid (by Gram staining or culture) is clearly noted, diagnosis confirmation is straightforward. However, almost half of infected pleural effusions turn out to be microbiologically negative.[37] The potential delay in waiting for a positive culture result when infection is already suspected is clinically unacceptable. Therefore, in most cases, clinicians use pleural fluid pH and glucose concentration as biochemical surrogates of bacterial infection to make a diagnosis.[5,30] Pleural fluid pH is most sensitive in isolation, but is also prone to instability and contamination depending on how and when it is analysed;[38] if concerns regarding the accuracy of a pH result exist, then pleural fluid glucose can be used as a more stable and reliable measure. Ultimately, any test should be interpreted by taking into account the clinical presentation.

Once the diagnosis of pleural infection has been confirmed, standard treatment consists of drainage of the infected collection, usually via a percutaneous chest drain, and broad-spectrum antibiotics.[5] A small but substantial proportion of patients will either not improve with this conservative approach and need surgical intervention, or will die within a year of their initial diagnosis.[8,9] The identification of individuals who are at increased risk of morbidity and mortality early in their treatment is of crucial importance so that appropriate resources can be used to improve clinical outcome. However, clinicians have no reliable means by which to risk stratify patients with pleural infection. Studies on this topic have implicated features including fluid purulence, loculation of or septations within a collection, low pleural fluid white cell count, pathogenic organism, and delayed presentation and drainage, as all having a potential effect on outcome.[12,37,39–41] However, none of the studies were prospectively validated or provided an easily accessible, specific, and systematic approach to patient assessment.

In view of the increasingly widespread use of bedside thoracic ultrasound by respiratory clinicians, particular interest in sonographic surrogates of poor response to medical therapy in pleural infection exists.[42,43] Two studies[40,41] have directly addressed such surrogates and have suggested that the presence of septations is predictive of poor outcome in pleural infection. This probably supports the suggestion that the septations in pro-fibrotic infected pleural collections lead to difficulty in percutaneous tube drainage, and therefore ineffectiveness of medical therapy. However, results from these two studies are weak due to their unblinded design. Consequently, more prospective studies are needed to elucidate the clinical meaning and relevance of septations within the infected pleural space as identified by thoracic ultrasound. Furthermore, ultrasound is operator-dependent, and the expertise of the individual clinician at the bedside is probably an additional confounding factor when applying this technique on a wide basis to guide clinical care.

A prediction model,[44] reported in 2014, derived from two large prospective randomised trials[8,9] of patients with pleural infection, offers promise in potentially allowing the risk stratification of patients with pleural infection, and is being studied by a large multicentre observational study (ISRCTN 50236700) to ascertain its validity. Whether this or another outcome prediction model will have any influence on either morbidity or mortality from pleural infection is unclear. However, the availability of a validated risk stratification score will certainly have an effect on the way patients with a pleural infection are managed as has been the case in other respiratory diseases.

## Microbiological overview

### Development of pleural infection

The means by which bacteria enter the pleural space is being investigated.[27] In view of the association between

pleural infection and pneumonia, bacterial spread across the visceral pleura from consolidated lung probably has a substantial role in pleural infection. Such a concept, however, might be a considerable oversimplification since the two diseases have substantially different bacteriological patterns.

Animal models of pleural infection provide useful insight into the development of infection. Experimental inoculation of bacteria directly into the pleural space of rabbits creates biochemically and histocytologically similar patterns of pleural infection to human disease, although substantial challenges remain in closely modelling human pleural infection. One challenge is that bacterial inoculation alone often results in either bacterial clearance or animal death from sepsis unless additional experimental steps are taken to allow a localised empyema to develop. For example, nutrient broth has been injected together with the bacterial inoculant (to encourage bacterial replication within the pleural space), parenteral antibiotics have been given (to prevent animal death from sepsis),[45] and other techniques have been used to cause pleural inflammation (thereby creating an initial exudative pleural effusion, proposed to sustain initial bacterial replication).[29,46] The second challenge is that these models of disease failed to reproduce the initial pneumonia often associated with pleural infection. However, one mouse model of pleural infection has successfully used intranasal inoculation with *S pneumoniae* to cause consolidation and pleural infection, with a pattern similar to human disease.[27] Early fibrinous adhesions were noted, as were characteristic visceral pleural mesothelial cell changes (and eventual cell necrosis) and bacteria in close proximity to the submesothelial cell layer. Importantly, in-vitro studies using mesothelial cells and confocal microscopy suggested that *S pneumoniae* crosses the mesothelial cell layer using an intracellular route, rather than a paracellular route. These findings, taken together, are highly suggestive of a transpleural spread of infection, at least for *S pneumoniae* in this mouse model of disease.

With increasing use of cross-sectional imaging, pleural infection without adjacent consolidation has become a recognised event, although it only occurs in a few cases (about 30% in an unreported analysis of the MIST2 cohort[9]). This pattern of disease suggests that other mechanisms are also responsible for bacterial entry into the pleural space, including haematogeneous spread, transdiaphragmatic spread, or spread from oesophageal or mediastinal disease (figure 1).

Animal models of pleural infection show that sustained pleural space bacterial replication is more likely in the presence of fluid. Patients with pre-existing pleural effusions might therefore be at higher risk of pleural infection than those patients without pre-existing pleural effusions. Indeed, spontaneous bacterial empyema is increasingly recognised as a complication of hepatic hydrothorax in patients with cirrhosis, analogous to spontaneous bacterial peritonitis.[24,26] Transient bacteraemia, together with the impaired reticuloendothelial phagocytic activity associated with cirrhosis, are proposed to cause bacterial seeding of the hepatic hydrothorax.Transcolonic translocation followed by transdiaphragmatic translocation of bacteria to the pleural space is another possible mechanism for pleural space entry.

More studies are needed to clarify the ability of different bacteria to enter and cause disease within the pleural space, particularly in view of the different bacteriological features of pleural infection and pneumonia. Whereas *S pneumoniae* and atypical organisms (ie, *Mycoplasma* and *Legionella* spp) account for most community-acquired pneumonia, the *Streptococcus milleri* (*S milleri*) group, *Staphylococcus aureus* (*S aureus*), and aerobic Gram-negative organisms have a much larger role in patients with pleural infection, especially in pleural infection acquired in hospital (see section on overall bacteriology). Vaccine studies in humans suggest that pneumococcal serotypes vary in their propensity to cause pleural infection.[47] Additionally, experimental evidence suggests that host responses (including cytokine release profile and mesothelial cell death) vary depending on bacterial species, after these have gained access to the pleural space.[48,49]

## Overall bacteriology

Large multicentre studies have characterised the bacteriological features of pleural infection and show key differences between community-acquired and hospital-acquired infections. Bacterial isolate data from the MIST1 study,[8,37] the largest multicentre randomised trial of pleural infection in adults with 454 participants, showed that community-acquired infection in adults is most commonly streptococcal (52%), with 24% from the *S milleri* group (*Streptococcus anginosus-constellatus-intermedius*) and 21% from *S pneumonia*, 20% from anaerobic microbes, 10% from *S aureus,* and 8% from Enterobacteriaceae (including *Escherichia coli* and *Proteus* spp). Hospital-acquired infection in adults is most commonly caused by *S aureus* (35%), particularly methicillin-resistant *S aureus*, 18% from Enterobacteriaceae, 18% from *Streptococcus* spp (7% from the *S milleri* group, 5% from *S pneumoniae*), 12% from *Enterococcus* spp, and 8% from anaerobes. Similar patterns have been observed in other studies[9,50] and highlight the importance of including methicillin-resistant *S aureus* and resistant Gram-negative coverage in empirical antibiotic choice for hospital-acquired infection. Pleural tuberculosis causes a type 4 hypersensitivity reaction within the pleural space, and is a common cause of pleural effusion in high-prevalence settings, but is beyond the scope of this Series paper.

Age-dependent variation in the type of bacterial infection has also been shown, with a strikingly higher rate of *S pneumoniae* (up to 85%) and *Streptococcus pyogenes* in children.[51,52] Although patterns of pleural infection in adults are similar in the UK,[9,37] Scandinavia,[53]

| | Brims et al (2014)[50] | Meyer et al (2011)[53] | Meyer et al (2011)[53] | Lin et al (2010)[55] | Maskell et al (2006)[37] | Rahman et al (2011)[9] | Marks et al (2012)[12] |
|---|---|---|---|---|---|---|---|
| Country | Australia | Denmark | Taiwan | Taiwan | UK | UK | UK |
| Total number of patients or isolates | 713 patients | 291 isolates | 139 isolates | 169 isolates | 396 isolates | 97 isolates | 406 patients |
| Staphylococcus aureus | 12 | 18 | 6 | .. | 14 | 16 | 16 |
| Viridans streptococci | 9 | 25 | 27 | 18 | .. | .. | .. |
| *Streptococcus milleri* group | 7 | .. | 19 | .. | 21 | 21 | 4 |
| Streptococcus pneumoniae | .. | 7 | 4 | .. | 19 | 25 | 10 |
| Anaerobes | .. | 17 | 27 | .. | 18 | 7 | 6 |
| Haemophilus influenzae | .. | 1 | 4 | .. | .. | .. | .. |
| Enterobacteriaceae | .. | 12 | 34 | .. | 9 | 9 | 6 |
| Klebsiella pneumoniae | 3 | .. | 24 | 24 | .. | .. | .. |
| *Enterococcus spp* | .. | 4 | 1 | .. | 3 | .. | 3 |
| *Pseudomonas spp* | 5 | 2 | 2 | .. | .. | .. | 4 |
| Yeasts | .. | 2 | .. | .. | .. | .. | 2 |
| *Mycobacterium spp* | .. | .. | .. | .. | 1 | 3 | 9 |

Values shown are expressed as % of isolates (or patients). ..=not reported.

***Table:*** **Representative bacteriological analysis from large international studies of pleural infection**

and Australia,[50] substantial geographical variation occurs in Asia, where *Klebsiella pneumoniae* is often the most common pathogen, causing up to 25% of cases (table).[54,55] Patient risk stratification might be achieved by knowledge of bacterial causes, since specific mortality profiles are associated with each bacterial pattern. One study showed that one-year mortality values varied depending on bacterial subtype: 17% with *Streptococcal spp*, 20% with anaerobes, 45% with Gram-negative bacteria, 44% with *S aureus*, and 46% with mixed aerobic bacteria.[37] These findings appear to hold true beyond the confounding effects of whether infection was community or hospital acquired; however, they do not provide definitive evidence that the organisms are the cause of the variation in mortality.

## Pneumococcal disease

Most studies suggest that the incidence of pneumococcal infections have increased in the past 10–15 years.[56,57] An emergence of virulent serotypes, including serotypes 1, 7F, and 19A, associated with pleural infection has also taken place.[58,59] One study suggested a four-fold increase in serotype 19A,[59] which is particularly associated with prolonged duration of fever, need for intensive care admission, and surgical treatment for pleural infection.[60] The original seven-valent pneumococcal conjugate vaccine introduced in the USA in 2000 covered serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F. Studies have suggested that widespread vaccination programmes might have caused a replacement phenomenon with non-vaccine serotypes becoming increasingly responsible for disease—in Utah, non-vaccine serotypes accounted for 62% of cases of paediatric pneumococcal empyema before introduction of the seven-valent pneumococcal conjugate vaccine, rising to 98% in 2007.[61] The updated conjugate vaccine (13-valent pneumococcal conjugate vaccine) has added six further serotypes (1, 3, 5, 6A, 7F, and 19A), and the consequent effects on pleural infection will be of interest for the health-care community, although preliminary data have not shown an effect on rates of pleural infection.[62]

## Oropharyngeal commensals

The role of oropharyngeal bacteria in pleural infection has long been recognised, particularly those bacteria reported in the gingival crevices. Studies from the 1920s investigated the polymicrobial anaerobic and facultatively anaerobic bacteria seen in lung abscesses and empyema. Noting these bacteria to be very similar to gingival crevice bacteria, Smith[63] inoculated the trachea of animals with human periodontal material, successfully causing lung abscess and empyema. This suggested that aspiration of these bacteria probably has a role in disease development.

The *S milleri* group of bacteria are the most frequent cause of community-acquired pleural infection and are facultatively anaerobic commensals of the oropharynx. They are infrequent causes of pneumonia and their overrepresentation in pleural infection is therefore of interest. Nucleic acid amplification techniques (NAAT) have reported co-localisation of *S milleri* and anaerobes in pleural infection,[64] and experimental evidence suggests that they are synergistic.[65] Routine laboratory culturing of pleural fluid samples probably underestimates anaerobes, given their fastidious nature and possible prior antibiotic use in the patient. In NAAT and enhanced culture studies, anaerobes were noted in 33–74% of cases.[64,66] NAAT studies have also identified substantial polymicrobiality associated with anaerobic infection, identifying many species previously not reported in the pleural space but almost all recognised as oropharyngeal commensals.[64] Other oropharyngeal

bacteria previously isolated include *Eikenella corrodens* (a facultatively anaerobic Gram-negative bacillus), *Gemella morbillorum* (a microaerophilic Gram-positive coccus), *Capnocytophaga spp* (a carbon dioxide-dependent Gram-negative bacillus), and *Mycoplasma salivarium*.[64,67–70] The frequent role and polymicrobiality of oropharyngeal bacteria in pleural infection adds to the evidence that aspiration plays a key part in the development of pleural infection. The defective mucociliary clearance and low oxygen tension associated with an atelectatic or consolidated lung could create the ideal conditions to allow oropharyngeal anaerobes to flourish in the lung and potentially spread into the pleural space.

### Atypical pneumonia pathogens and other unusual pleural space pathogens

Despite the high frequency with which atypical organisms cause pneumonia, these organisms are rarely identified in pleural infection, suggesting an absence of tropism for the pleural space and also that routine atypical antibiotic coverage is not necessary for pleural infection.[5,37,53] Other bacteria reported to rarely cause pleural infection (usually in immunosuppressed patients), include *Pasteurella multocida* (usually associated with animal bites or scratches), non-typhoidal salmonella, *Nocardia* spp, and non-tuberculous mycobacteria such as *Mycobacterium abscessus, chelonae,* and *kansasii*.

### Cirrhosis-associated spontaneous bacterial empyema

Data for pathogens noted with cirrhosis-associated spontaneous bacterial empyema are restricted to case series. However, the patterns of infection are clearly not typical of either community-acquired or hospital-acquired pleural infection. Bacteria reported in these cases are mostly associated with the gastrointestinal tract, including *Enterococcus* spp, *Salmonella enteritidis*, *Clostridium perfringens*, *Pasteurella multocida*, and *Aeromonas* spp.[24,26]

### Non-bacterial causes

Fungal pleural infection is associated with substantial mortality and is usually iatrogenic or associated with comorbidities or immunosuppression.[71] Candidal pleural infection is particularly suggestive of oesophageal rupture (either spontaneous or malignant) with *Candida albicans* seen most frequently and with *Candida glabrata* or *Candida tropicalis* seen less frequently. Other fungi, mostly *Aspergillus* spp, are also occasionally isolated particularly in patients who have received lung transplants.[71,72] Despite the ubiquity of *Pneumocystis jirovecii* in the upper and lower respiratory tract, one study[73] reported no evidence of this fungus in pleural infection using highly sensitive quantitative NAAT.

Although bacterial pleural infection is associated with epidemics of influenza (eg, the 2009 H1N1 influenza A epidemic was associated with increased rates of pneumococcal and *S pyogenes* pleural infection),[74] only a few small studies have addressed the direct role of common respiratory viruses in community-acquired pleural infection. One study[75] used NAAT to search for nine groups of viruses in forty-eight pleural fluid samples (only twelve of which were parapneumonic), but showed no evidence of viral infection. Another study[76] reported evidence of a novel torque teno mini virus in pleural infection, the relevance of which is unclear given the ubiquity of such viruses in human beings and the absence of a clear association with disease. Pleural effusions are associated with adenovirus, hantavirus, cytomegalovirus, and herpes viruses.

Although outside the scope of this Series paper, many protozoa can cause pleural infection including *Entamoeba histolytica*, *Toxoplasma gondii* (particularly in immunosuppressed individuals), and *Trichomonas spp*. *Trichomonas tenax* is of particular interest, being an oropharyngeal commensal; it is unlikely to be seen as a lone pathogen since its reproduction is reliant on bacteria to provide nutrients.[77] Other parasites, including hydatid disease (*Echinococcus spp*), filariasis (*Wuchereria bancrofti*), *Paragonimus westermani*, and *Strongyloides stercoralis*, have also been reported to cause pleural disease.

### Microbiological diagnostic yield in pleural infection

In view of positive culture tests in only 30–40% of cases of pleural infection,[9,37] studies have addressed methods to improve bacterial aetiological diagnosis. One study showed that bedside inoculation of pleural fluid into blood culture bottles (besides conventional aerobic and anaerobic culture) might increase sensitivity by about 20%.[78] Diagnosis of pneumococcal disease can be improved by testing pleural fluid using commercially-available immunochromatographic pneumococcal antigen tests. Studies have shown these tests to have sensitivity greater than 84% and specificity greater than 94%.[79,80]

NAAT, which can amplify and detect DNA (or RNA) present in clinical samples, has been studied in aetiological diagnosis. NAAT has significant theoretical advantages. Unlike culture tests, organism detection is less susceptible to prior antibiotic use. Furthermore, these techniques will not suffer from the methodological difficulties associated with culture of fastidious organisms. Particular success has been achieved using NAAT in paediatric pleural infection to amplify pneumococcal gene targets, such as the *autolysin* and *pneumolysin* genes.[51,81,82] Besides techniques targeting single pathogens, multiplex polymerase chain reaction assays can test for many pathogens in a single NAAT experiment.[83] Quantification of bacterial load can likewise be achieved with quantitative NAAT assays. Polymerase chain reaction-based estimates of bacterial load are associated with conventional pleural fluid parameters such as pH, glucose, lactate dehydrogenase, purulence, and culture status. Such estimates might be associated with key clinical outcomes such as length of hospital stay or duration of pleural drainage.[84]

Technological advances and decreasing costs of nucleic acid sequencing have led to interest in the role of sequencing-based strategies for the diagnosis of infection. Nucleic acid sequencing, unlike other NAAT, provides a relatively assumption-free strategy for the identification of pathogens, including the recognition of unknown or unsuspected pathogens. A common sequencing target used for bacterial identification is the 16S ribosomal RNA gene, present in all bacteria. In the past, capillary-based sequencing of the 16S ribosomal RNA gene was methodologically restricted in being able to identify only one pathogen per clinical sample unless expensive cloning techniques were used.[37,85] These limitations have been overcome with next-generation sequencing capable of identifying thousands of species in one sample.[64]

## Intrapleural therapies

Besides appropriate antibiotic coverage based on local microbiological prevalence and resistance patterns, the treatment of pleural infection necessitates adequate drainage of the infected collection. Since most patients are initially managed with a percutaneous chest tube, great importance is placed on maximising the success of this approach and limiting treatment failure. Clinicians have been interested in the potential value of intrapleural fibrinolytic drugs for over half a century and how these drugs might prevent the progression of pleural infection to its more chronic fibrotic state.[86] This interest has focused on the physiological changes that occur in the infected pleural space, notably the depression of intrinsic fibrinolytic activity and consequent increase in fibrin load.[31] Reversal of this process has been assumed to facilitate both drainage of the collection by disrupting septations (further assumed to correlate with relevant clinical outcomes) and reduce the burden of fibrous thickening that might otherwise restrict the underlying lung.

Streptokinase and urokinase were the first fibrinolytic drugs to be widely available and used in both adult and paediatric pleural infection, with several case series and trials showing promise but without being able to provide definitive proof of effect on patient morbidity or mortality.[87] An exception to this was a single, small, but well-designed trial demonstrating reduced need for surgery and reduced mortality with intrapleural streptokinase.[88] However, subsequent reporting of a large multi-centre randomised controlled trial[8] of intrapleural streptokinase versus placebo (MIST1) with 454 participants showed no evidence of a significant improvement in key outcomes including death, rate of surgical referral, length of hospital stay, or lung function. Postulated reasons for this include recruitment of patients who have already progressed to the late stages of their infection, and failure to stratify for the presence or absence of septations on ultrasound. Heterogeneity within the study population regarding the intrapleural activity of endogenous PAI-1 might be of relevance; this mediator not only directly inhibits streptokinase but has also been shown in an animal model of pleural injury to contribute to the severity of loculation and poor outcomes with intrapleural fibrinolytic therapy.[89,90] This principle is reaffirmed in a follow-up study by the same group in rabbits, which has shown that direct inhibition of PAI-1 significantly increases the duration and efficacy (as measured by breakdown of intrapleural septations) of streptokinase.[91] Although this pathway merits further investigation as a potential future therapeutic target, this investigation is presently hindered by the absence of any widely available means of monitoring or understanding the baseline PAI-1 activity in human participants with pleural infection. Since streptokinase is dependent on the physiological availability of plasminogen to form its active complex, clinicians should consider whether it might be the wrong choice of fibrinolytic agent when used in isolation. Additionally, because streptokinase has no effect on fluid viscosity, this disadvantage together with the development of intrapleural septations represents another barrier to successful drainage.

To achieve successful drainage, in-vitro studies effectively show the need to not only break down the physical barrier created by fibrinous septations, but also to modify the viscosity of pleural fluid, which is frequently increased in infection as a consequence of cell degradation products. Results from a study of human-derived samples of purulent fluid incubated with streptokinase, urokinase, combination streptokinase and strepdornase (streptococcal deoxyribonuclease, DNase), or saline showed that only the fluid incubated with the combination streptokinase and strepdornase achieved liquefaction.[92] Similar results were seen in a larger study[93] of purulent pleural fluid derived from an experimental rabbit model of empyema proving the importance of DNase specifically in reducing fluid viscosity. The combination of intrapleural direct tissue plasminogen activator (tPA)—a fibrinolytic agent that avoids the plasminogen complex step needed by streptokinase—and DNase in another study[23] that used the same animal model suggests additional promise in reducing the anatomical sequelae of pleural infection.

For the translation of in-vitro results to a human adult population, the MIST2 study[9] was designed as a double-placebo randomised controlled trial in pleural infection, using tPA as a directly-acting fibrinolytic drug to disrupt septations and DNase with the aim of reducing fluid viscosity within the pleural space and enhancing drainage. This four group study with 210 participants showed that combination tPA and DNase intrapleural therapy significantly reduced chest radiographic opacification (the primary outcome), whereas tPA or DNase alone had no effect compared with placebo. In the combination therapy group, secondary outcome measures including surgical referral rate and length of hospital stay showed trends for a reduction but these were not statistically

significant.[9] Intrapleural drugs given alone showed no benefit and DNase alone was actually associated with an increased surgical referral rate. No significant increases in mortality or adverse event rate in any experimental study group were shown when compared with placebo,[9] implying a good safety profile for the combination intrapleural treatment. This finding was further re-affirmed in a later retrospective case series.[94]

The results of the MIST2 study[9] were consistent with those of MIST1[8] in ruling out a role for single agent fibrinolytics in pleural infection. Therefore, the combination of DNase to reduce fluid viscosity together with a fibrinolytic such as tPA to lyse septations is probably most efficacious at maximising drainage. Randomisation of participants in the MIST2 study[9] was minimised (to prevent imbalances between the treatments received by patients in specified sub-groups) by purulence of pleural fluid in view of a previous study that suggested that this characteristic might be associated with variation in key clinical outcomes from pleural infection.[39] However, the presence of purulence was not reported to be directly associated with the efficacy of combination intrapleural therapy in the MIST2 study. This finding implies that the mechanism of action of DNase is not associated with a crude macroscopic measure of the likely DNA load within the pleural space, assuming that purulent fluid will contain more DNA than non-purulent fluid. Therefore, small amounts of DNA within infected pleural fluid are possibly of some clinical relevance, either by causing a degree of increased fluid viscosity, or perhaps supporting the yet unproven hypothesis that biofilm formation by bacteria within the pleural space affects outcome. This theory might also explain the increased surgical referral rate seen in those study participants who were randomised to intrapleural DNase alone. DNase might have lysed biofilms and released bacteria that could not be drained in the absence of tPA, increasing local and systemic inflammation and thereby prompting surgical referral.

Nonetheless, the means by which fibrinolytics improve clearance of infected material from the pleural space is almost certainly more complex than mere mechanical disruption. Data from animal[23] and human[94] studies show that the administration of intrapleural tPA is associated with up to a ten-fold increase in pleural fluid output. A study using an in-vivo mouse model of pleural infection[95] has shown this to be a class effect with streptokinase, urokinase, and tPA all stimulating excess pleural fluid formation. Contemporaneous studies by the same group using cell lines in vitro and the same murine model suggest that this is mediated via MCP-1 expression and protein release by mesothelial cells, with pleural fluid levels of this cytokine directly correlating with volume of fluid produced. Furthermore, blockade of MCP-1 activity results in loss of the fluid stimulating effect of tPA in mice.[95] This potent stimulation of fluid production might have additional benefits by causing a therapeutic lavage of the pleural space and aiding the clearance of infected material—this would be consistent with a pilot study that has shown a potential benefit from saline irrigation via the intercostal chest drains of people with pleural infection.[96] MCP-1 is already known to have a potential role in mechanisms of repair following pleural injury, as well as inducing endothelial permeability and the co-activation of other inflammatory pathways.[22,97] Scientific research is needed to better define the mechanisms of this pathway and identify potential translational uses for clinical benefit.

## Surgical management

Current guidelines[5,18] advocate the use of surgery as a rescue therapy in cases of pleural infection that have either failed to respond to standard medical treatment (ie, percutaneous drainage and antibiotics) or if progression to an advanced fibrotic state is suspected with extensive pleural thickening requiring decortication. The timing of surgical intervention to ensure adequate clearance of infected material from the pleural space is crucial and has been shown to be potentially life-saving in this selected population of patients. Although randomised trial data[8,9] have shown that most patients (around 80%) can be successfully managed medically, surgery is a first-line treatment for pleural infection and empyema, particularly in the USA. This approach of early surgical intervention has been justified on the basis of improved clinical outcome and shorter hospital stays for patients managed in this way.[12,15,98–100]

Although surgical treatment for pleural infection used to necessitate open thoracotomy, most cases are now managed using video-assisted thoracoscopic surgery (VATS). This less invasive approach potentially widens the population who might be suitable for surgical therapy,[100] although large case series[2,12] from both the USA and UK show a continued preference to operate on younger and less comorbid individuals than seen in an unselected population of patients with pleural infection.[8,9] Nonetheless, a meta-analysis[101] has suggested that VATS is superior to thoracotomy with respect to length of hospital stay, postoperative morbidity and complication rate, and similar from the perspective of disease resolution. Surgical clearance of potentially infected material from the pleural space need not be perfect, but rather sufficient to allow the patient to recover. A more conservative debridement without full decortication might be adequate in selected cases to avoid compromising key long-term outcomes.[102] For patients who are not fit for general anaesthesia, thoracoscopic drainage can still be used with sedation and local anaesthesia. This approach has been applied successfully by thoracic surgeons[103] and also physicians with expertise in medical thoracoscopy but only in small studies.[104,105]

Compared with larger studies that have assessed the efficacy of intrapleural fibrinolytics with or without DNase, few data are available on the use of surgery and

specifically VATS as a first-line intervention. In a small randomised trial[106] of 20 participants, which compared VATS with intercostal drainage plus intrapleural streptokinase, VATS was successful as a first-line therapy in 91% of participants as compared with 44% in the streptokinase group, with patients not needing any additional invasive therapeutic intervention. VATS was also associated with a significant reduction in the duration that a chest tube remained in situ, decreased lengths of intensive care unit and hospital stays, and a reduction in overall costs.[106] Other small studies[107,108] of early surgery (ie, on or very soon after admission to hospital) in adults with pleural infection have also suggested that this is associated with reduced hospital lengths of stay and cost. However, these studies and other reported studies relating to this approach recruited small participant numbers and were underpowered as a result. Nevertheless, delayed referral for surgical treatment does clearly result in more difficult procedures including a higher rate of conversion of VATS to thoracotomy.[109]

The surgical data in adults seem to contradict data from children with pleural infection, for whom a series of larger randomised studies[110–112] have shown no clinical benefit and increased cost of VATS compared with chest tube drainage in fibrinolytic therapy. A smaller study[113] that randomised 18 paediatric patients to VATS or tube thoracostomy (with or without fibrinolytics as indicated) did find that surgery was associated with a shorter hospital admission. This difference might be the result of differing microbiological organisms,[109] with most paediatric pleural infection being caused by *S pneumoniae* as opposed to the many different organisms seen in adult pleural infection. This difference raises the question of whether microbiological analysis might be one means by which patients could be stratified as low risk or high risk for morbidity or mortality. The high-risk group, which potentially includes patients with Gram-negative organisms or hospital-acquired infections, is suitable for early aggressive therapy including surgery with the aim of improving relevant clinical outcomes. However, this paradigm of using less invasive treatment options for patients deemed to be of low risk according to their microbiological profile might be changing with the increasing prevalence of empyema complicating pneumococcal pneumonia in both children and adults.[114,115] This alarming trend has been seen despite an increasing uptake of the multivalent pneumococcal conjugate vaccine,[3,57] with the rate of pneumococcal pneumonia admissions falling at the same time as empyema increases, potentially as a result of selection of more invasive serotypes.

For patients in whom decortication fails, empyema recurs, or who have a bronchopleural fistula, thoracoplasty might be a good surgical option in a highly selected group of patients. Modern techniques using muscle flaps to eliminate residual pleural space issues have reduced the need for radical chest wall mobilisation and mutilation.[116] Open window thoracotomy remains a potentially life-saving option for patients with persistent pleural space infection after thoracic surgical procedures—for example, pneumonectomy or lobectomy. Techniques centre on resection of two or more ribs with marsupialisation to facilitate open drainage and are associated with acceptable long-term outcomes in high-risk population.[117] The use of vacuum-associated closure devices might enhance the care of these patients by accelerating recovery[118] and this approach merits further assessment. The chronically infected pleural space unsuitable for additional surgical intervention—for example, in the setting of severe comorbidity or poor performance status—can also be managed using long-term thoracostomy. This can take the form of a wide-bore drain with one-way (Heimlich) valve or tunnelled catheter.[119,120] In all these circumstances, long-term antibiotic suppression therapy is probably needed as an adjunct to achieve adequate sepsis control.

From a practical perspective, clinicians should consider both the available data as well as local resources (ie, the presence of a thoracic surgeon skilled in minimally invasive surgery) when devising a cogent treatment plan for patients with pleural infection. A short illness of less than 10 days without gross purulence together with the absence of septations on ultrasound examination or many locules detected by CT favours a conservative approach using chest tube drainage with or without intrapleural fibrinolytics. However, a combination of features including symptom duration of more than 2 weeks, gross purulence on thoracentesis, pleural loculation, or a sign of split pleura with pleural enhancement on CT examination might suggest the presence of a visceral cortex and the need for surgical debridement to re-expand the affected lung and obliterate the infected pleural space. Regardless of this, although surgery remains a key intervention in the management of pleural infection, more large-scale randomised trials are needed to define when and how it should be used in this population.

## Future directions

Although avoidance of thoracotomy is clearly a desired outcome, avoidance of surgery might not be the outcome measure that should be examined in future studies of treatment in pleural infection. If VATS can be the definitive therapeutic procedure for empyema and permit discharge from hospital in less than a week (whereas the average hospital length of stay for patients receiving combination tPA and DNase in the MIST2 trial was 12 days),[9] VATS might become the procedure of choice as a first-line treatment advised immediately on admission to hospital. Additionally, since the drug cost alone of tPA and DNase intrapleural therapy is roughly £1000, early VATS might achieve substantial cost savings in the UK and also other countries where VAT is easily available. A cost analysis of the MIST2 trial is underway, although a multicentre trial comparing early VATS with combination tPA and DNase

intrapleural therapy assessing key clinical outcomes in pleural infection is needed, and being planned by the authors to answer these questions.

In view of the therapeutic primacy of achieving successful drainage of infected material from the pleural space, most studies have focused on how this might be best achieved, for example, through chest tube drainage (with or without intrapleural fibrinolytics) or by surgical intervention. A subset of patients might exist, however, in whom outpatient management using therapeutic thoracentesis only whenever needed or for whom drainage is not even necessary, is an acceptable strategy.[121] The development of a method for the identification of these patients using a combination of clinical, radiological, biochemical, and microbiological data might help reduce treatment costs through avoidance of hospital admission. However, this will only be possible once our understanding of the pathogenesis and progression of pleural infection is improved.

The primary outcome in the MIST2 study[9] was improvement in the chest radiograph (a surrogate marker for successful clearance of the infected collection) and the study was underpowered to assess for significant improvements in mortality and morbidity from pleural infection. Future large multicentre trials should address this key question and other patient-centred endpoints. Since about 70% of patients can avoid surgery, future trials should try to identify patients in whom medical therapy is likely to fail to enable them to be sent for surgery early during their admission. Likewise, the identification of patients who might do well with medical therapy would be useful so that surgery can be avoided in these individuals (regardless of the outcome of any cost-benefit analysis comparing medical and surgical treatment pathways).

The development and validation of a risk stratification model for patients with pleural infection based on biochemical and physiological parameters at initial presentation to hospital is already in progress.[44] However, other easily accessible biomarkers could provide additional prognostic information. These biomarkers might include radiological features such as septation density on ultrasound, pleural thickening or loculation on CT, or microbiological cause. These biomarkers have all been shown to have potential value in retrospective studies[10,37,122] and merit prospective assessment on a wider scale. Newer biomarkers including MCP-1[95] and PAI-1[91] are still being investigated in the laboratory setting and are unlikely to reach the bedside for several years—however, they offer promise as both therapeutic targets and a means of monitoring response to treatment. Future laboratory studies involving these and other biomarkers should also investigate the precise mechanisms by which intrapleural fibrinolytics act. An increased understanding of these pathways might help us stratify patients into those who are likely to respond to intrapleural fibrinolytics and those who might be better served by surgery in the event that initial medical treatment fails.

### Search strategy and selection criteria

We searched Embase and Medline for peer-reviewed articles published in English from Jan 1, 2000 to Dec 31, 2014, using the search terms "pleural empyema", "pleural effusion", "empyema", "parapneumonic effusion", "pleural infection", "pleural collection", and "parapneumonic infection". Reference lists of identified articles deemed to be of relevance were searched. Other studies including conference abstracts that were known to the authors to be relevant but not identified by this search strategy were also screened.

Another aspect of the MIST2 protocol that is under investigation is the dosing regimen. In the MIST2 study,[9] tPA was given and the chest drain clamped for one hour, followed by administration of DNase and further clamping of the chest drain for another hour, with this pattern being repeated twice daily for three days. This labour-intensive practice has led some treatment centres to combine the drugs as part of an abridged administration protocol;[94] however, we do not recommend this approach on the basis of evidence available. More studies are needed to ascertain the optimum doses of tPA and DNase. If a lower dosing regimen than that used in the MIST2 study can be shown to be equally efficacious, the cost-benefit analysis would substantially change and might make combination intrapleural therapy a more attractive and widely available option.

As with tuberculous effusions, the pleural fluid might not be the best type of sample to undertake culture tests. Parietal pleural biopsies used in culture tests might substantially increase the diagnostic microbiological yield in pleural infection (thereby reducing the number of culture negative cases that have to be treated with empirical or blind use of antibiotics), and a specific study to assess this possibility is planned. Different antibiotics have the ability to penetrate the pleural space at widely different rates, with some of them not achieving therapeutic levels as shown in rabbits,[123–125] particularly for spaces that are multiloculated with pus and fibrin. Continued investigation in both the laboratory setting and with human participants addressing the precise pharmacokinetics of intravenous antibiotics and how this translates across to the infected pleural space is necessary to inform clinicians. These data might affect antibiotic choice, dosing regimens, and duration of therapy. Data are also scarce regarding the intra-pleural administration of antibiotics and whether this direct approach (as opposed to waiting for antibiotics administered intravenously to gradually diffuse into the pleural space) might accelerate sterilisation of the pleural space; further investigation is necessary focusing on experimental models together with translational studies at the bedside. Another potential therapeutic adjunct that has been reported and needs additional study is the use of pleural irrigation, either with saline[96] or povidone-iodine.[126]

Fundamental for the improvement of management of patients with pleural infection is an understanding of the progression from pneumonia to an infected pleural space, where parenchymal infection is present. Little robust data exists describing how this process might occur. We propose that the factors associated with the development of pleural infection are probably related to host inflammatory and immune status or variation, and bacterial characteristics. Translational studies addressing bacterial translocation, fluid formation, and the establishment of infectious niches within the pleural space in parallel to host assessments are necessary. The changing aspects of pneumococcal infection,[3,6,7,57,115] as a result of serotype selection after the introduction of multivalent vaccines, might be one way to increase our understanding of how and why pleural infection develops in different settings.

The prevalence of pleural infection continues to increase with substantial long-term mortality, rising as high as 30% in the most elderly patients with pronounced frailty or comorbidity. This high mortality is probably due not only to the effect of medical comorbidity but also to a chronic inflammatory effect and alteration in immune response similar to that seen in other respiratory infections, which include exacerbations of chronic obstructive pulmonary disease and community-acquired pneumonia.[127–131] The identification of strategies by which this legacy effect can be modified, for example, by optimising the management of comorbidities such as diabetes, ischaemic heart disease, and airways disease, is probably crucial in altering the long-term outlook after pleural infection.

## Conclusion

Despite pronounced advances in medical and surgical treatment, pleural infection remains an important and morbid clinical challenge. Our understanding of the pathophysiological process whereby organisms gain access to the pleural space and establish infection is incomplete. Future studies that address the progression of pleural infection might shed light on how interventions can reduce the substantial morbidity and mortality associated with this disease. Study on the microbiological profile of pleural infection suggests a broad range of causative organisms that are distinct from the causes of lung parenchymal infection. Clinical scoring systems to predict poor outcome in patients with pleural infection are being assessed and might provide not only a method of risk stratification at baseline, but also the potential to select patients early that need more invasive and expensive treatments. Although promising data exist regarding the use of intrapleural tPA and DNase treatment for pleural infection, the exact role of these treatments is uncertain, especially compared with early VATS. More studies are necessary to define the role of these treatments more clearly.

**Contributors**

JPC and NMR conceived and designed the Series paper. JPC and JMW did the scientific literature search and contributed equally to the collection and analysis of the results. JPC wrote the sections on introduction, pathophysiology, diagnosis and outcome prediction, and intrapleural therapies. JMW wrote the section on microbiology. EB and MMDC wrote the section on surgical management. DF-K and NMR wrote the sections on future directions, conclusion, and revised the article. All authors approved the final version of the article.

**Declaration of interests**

JPC is study coordinator for PILOT (ISRCTN 50236700), an observational study of pleural infection funded by the Medical Research Council, UK. DF-K has provided consultancy services to Spiration, Inc. NMR has provided consultancy services for Rocket Medical UK and was corresponding author for the MIST2 study, which was supported by an unrestricted educational grant from Roche UK to the University of Oxford. NMR is also chief investigator for the PILOT study and is director of the University of Oxford Respiratory Trials Unit that published the MIST1 and MIST2 studies. JMW, EB, and MMDC declare no competing interests.

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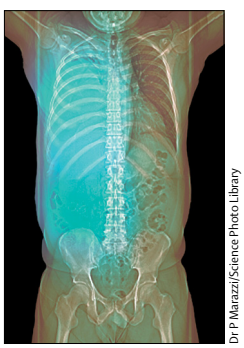
# Individualised management of malignant pleural effusion



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Malignant pleural effusion (MPE) is a potentially debilitating disorder in which cancer (commonly of the breast or lung) causes accumulation of fluid in the pleural cavity. MPE often results in severe breathlessness, which can be improved by pleural drainage procedures. As a result of the increasing global cancer prevalence and more effective, better tolerated, systemic therapies, the burden of MPE is rising. An increasing number of high-quality, suitably powered randomised trials in MPE have begun to provide a robust evidence base for some of the treatment approaches available.[1,2] Therefore, dedicated pleural services, providing a wider range of management strategies, including indwelling pleural catheters (IPC) and local anaesthetic thoracoscopy, are becoming widespread. Because of the expansion of these alternative treatment options, the traditional approach of admitting all patients with MPE for a chest drain and pleurodesis is now outdated. Ambulatory management can be a realistic and appealing treatment strategy for many patients.

Inflammation seems to have a crucial role in MPE by contributing to both morbidity and mortality. Markers of both systemic inflammation (eg, blood neutrophil-lymphocyte ratio)[3-5] and localised pleural inflammation (eg, pleural fluid lactate dehydrogenase)[4,6] are associated with a worse prognosis. These findings have led to a need for more accurate prognostic methods to assist clinicians and patients in selecting the most appropriate treatment. Several prognostic scores exist for patients with MPE associated with pleural mesothelioma, which although complex to calculate, can help to predict an individual's survival.[5,7,8]

International collaboration has led to the development of the LENT prognostic score for all cell types of malignant effusions. This score combines markers of local and systemic inflammation along with tumour type and Eastern Cooperative Oncology Group (ECOG) performance score and can help predict survival more accurately than performance status alone.[4] In those patients with the highest scores, treatment could be best focused on symptom control and end-of-life care in the community rather than attempting to achieve a definitive pleurodesis. The LENT score requires more widespread validation and impact analysis before its routine clinical use. However, it has the potential to improve the information available to clinicians during the early assessment of patients with MPE and assist appropriate recruitment to clinical trials.

Localised pleural inflammation is also essential for successful pleurodesis through the formation of adhesions and fibrosis that obliterate the pleural cavity; however, pleural inflammation could also contribute to side-effects such as pain and fever after administration of intrapleural sclerosants. Even within the context of large randomised trials, pleurodesis success rates remain lower than 80%,[1,2] which has led to the search for more effective treatments and modes of delivery. The potential of harnessing the host immune response to induce pleural inflammation has led to the study of intrapleural bacterial moieties including *Corynebacterium parvum*, Lipoteichoic Acid-T, and *Streptococcus pyogenes* (OK-432), with varying degrees of success.[9-11]

IPCs are increasing in popularity and offer a cost-effective long-term outpatient management strategy for patients with MPE. Findings from the Therapeutic Interventions in the Malignant Effusions-2 trial[1] showed IPCs conferred similar control of breathlessness and quality of life but significantly shorter length of hospital stay than did inpatient talc pleurodesis. IPCs also allow long-term, outpatient access to the pleural cavity, making them an ideal potential portal for local drug delivery. Instillation of sclerosants through an IPC in those patients with complete lung re-expansion is an attractive proposition, which could harness the benefits of both techniques. Trial data regarding the efficacy of this approach is awaited with interest.

There is also a role for IPCs in the context of a so-called trapped lung, whereby the lung fails to completely re-expand after drainage of an effusion. This complication affects 10–20% of patients with MPE, and those with a high pleural tumour burden (resulting in a visceral pleural rind) or a heavily loculated effusion are likely to be at highest risk. The absence of parietal and visceral pleural apposition greatly reduces the chances of pleurodesis success and potentiates the production of pleural fluid to fill the space between the pleural layers (effusion ex-vacuo), which can result in pain during pleural aspirations, rapid recurrence of breathlessness after drainages, and more limited long-term treatment options.

There is a common misconception that active effusion management in trapped lung is futile. However, pleural effusion drainage might relieve pressure on surrounding

structures and improve diagphragmatic motion, thereby enhancing respiratory mechanics and improving symptoms of breathlessness. However, trapped lung often goes under-recognised in clinical practice. The diagnosis might be suspected if a patient shows marked symptoms (chest discomfort and pain) during fluid drainage or if a post-aspiration chest radiograph shows a hydropneumothorax. Alternatively, pleural manometry, which measures the change in pleural pressure during a pleural aspiration, could be used to identify those with trapped lung and establish the extent of residual visceral pleural elasticity, although its routine clinical role is debated.[12,13] Early work evaluating M-mode ultrasound to detect trapped lung has also shown some promise.[14]

In theory, the early identification and management of malignant effusions might help limit the formation of trapped lung by promoting complete lung re-expansion, maintaining visceral pleural elasticity, and minimising the formation of septations and loculations due to repeated invasive procedures. Specific studies assessing this concept, as well as examining improved identification techniques and management options for patients with trapped lung, are much needed to provide robust data regarding this under-researched subgroup.

A proactive approach to MPE treatment in general has several potential benefits in terms of streamlining the patient pathway and avoiding recurrent and prolonged hospital admissions. Early observational data in those with known MPE suggests that the combination of thoracoscopic talc poudrage with an IPC might be an effective management strategy, although randomised data are needed to evaluate this approach in more detail.[15] Taking this idea a step further, in those with suspected MPE, a diagnostic thoracoscopy in conjunction with talc poudrage or insertion of an IPC, or both, might be an attractive one-stop approach to diagnosis and management in the future.

As the treatment options for MPE become more complex, the outcome measures used by future clinical trials need to be carefully considered. Rigorously recorded, patient reported outcome measures, such as breathlessness scales, quality-of-life scores, and patient satisfaction, are essential to ensure clinically relevant conclusions are drawn regarding the relative efficacy of the various management strategies.

Several questions remain unanswered regarding the management of MPE. In the future, more creative management strategies that combine the benefits of a few established treatments might help improve care of patients with MPE and facilitate ambulatory management. Provision of a variety of treatment approaches according to an individual's prognosis, clinical features, and personal preferences is necessary to ensure an individualised, patient-centred approach to care.

*Amelia O Clive, Rahul Bhatnagar, Ioannis Psallidas, *Nick A Maskell*

Academic Respiratory Unit, School of Clinical Sciences, University of Bristol, Southmead Hospital, Bristol BS10 5NB UK (AOC, RB, NAM); Oxford Respiratory Trials Unit, Oxford Centre for Respiratory Medicine, Oxford University Hospitals, Churchill site, Oxford, UK (IP)
nick.maskell@bristol.ac.uk

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# Pleural disease 2

# Spontaneous pneumothorax: time to rethink management?

*Oliver J Bintcliffe*, Rob J Hallifax*, Anthony Edey, David Feller-Kopman, Y C Gary Lee, Charles H Marquette, Jean-Marie Tschopp, Douglas West, Najib M Rahman, Nick A Maskell*

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This is the second in a **Series** of two papers about pleural disease

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*These authors contributed equally

**Academic Respiratory Unit, School of Clinical Sciences, University of Bristol, Bristol, UK** (O J Bintcliffe MBChB, N A Maskell DM); **Oxford Centre for Respiratory Medicine and Oxford NIHR Biomedical Research Centre, Churchill Hospital, Oxford, UK** (R J Hallifax BMBCh, N M Rahman DPhil); **Department of Radiology, North Bristol NHS Trust, Bristol, UK** (A Edey MBBS); **Johns Hopkins Hospital, Baltimore, MD, USA** (Prof D Feller-Kopman MD); **Centre for Asthma, Allergy and Respiratory Research, School of Medicine and Pharmacology, University of Western Australia, Perth, Australia** (Prof Y C G Lee PhD); **Service de Pneumologie, Centre Hospitalier Universitaire de Nice, France** (Prof C H Marquette PhD); **Centre Valaisan de Pneumologie, Montana, Switzerland** (Prof J-M Tschopp MD); **and University Hospitals Bristol, Bristol, UK** (D West MBChB)

Correspondence to: Dr Nick A Maskell, Academic Respiratory Unit, School of Clinical Sciences, University of Bristol, Learning and Research, Southmead Hospital, Bristol BS10 5NB, UK
**nick.maskell@bristol.ac.uk**

**There are substantial differences in international guidelines for the management of pneumothorax and much geographical variation in clinical practice. These discrepancies have, in part, been driven by a paucity of high-quality evidence. Advances in diagnostic techniques have increasingly allowed the identification of lung abnormalities in patients previously labelled as having primary spontaneous pneumothorax, a group in whom recommended management differs from those with clinically apparent lung disease. Pathophysiological mechanisms underlying pneumothorax are now better understood and this may have implications for clinical management. Risk stratification of patients at baseline could help to identify subgroups at higher risk of recurrent pneumothorax who would benefit from early intervention to prevent recurrence. Further research into the roles of conservative management, Heimlich valves, digital air-leak monitoring, and pleurodesis at first presentation might lead to an increase in their use in the future.**

## Introduction

Spontaneous pneumothorax is a common clinical problem. However, the best management strategy is controversial, with substantial variation in practice, largely driven by a paucity of evidence. In this Series paper, we provide an overview of existing data and suggest that new approaches to definition, risk stratification, and treatment of pneumothorax might be necessary. We challenge the traditional view of primary spontaneous pneumothorax occurring in patients with no underlying lung disease; it may be that such patients should be considered on a continuum with secondary spontaneous pneumothorax. We explore the evidence behind current management guidelines, with emphasis on newer and controversial strategies such as conservative or ambulatory management, methods of risk stratification in primary spontaneous pneumothorax (including lung density assessment and air-leak measurement), as well as medical and surgical approaches to treating prolonged air leak and preventing recurrence.

### Key messages

- There is increasing evidence of underlying lung abnormalities in patients traditionally labelled as having primary spontaneous pneumothorax
- Advances in our understanding could allow a reclassification of pneumothorax that more clearly addresses the underlying cause
- Careful consideration of specific disorders associated with causes of pneumothorax might lead to improvements in management tailored to the individual patient
- If radiological, clinical, and demographic information can be shown to stratify patients according to risk of recurrence after an initial pneumothorax, this would allow the early targeted use of recurrence-prevention strategies
- Research into the use of Heimlich valves might lead to an increase in their use in the future, allowing ambulatory management in the patient's home
- The safety and efficacy of conservative management in patients with large primary spontaneous pneumothoraces is being assessed in a large randomised controlled trial that is currently recruiting participants
- Smoking cessation is associated with a reduction in the risk of recurrent pneumothorax and is strongly advised in all patients

## (Re)classification of pneumothorax

The classification of pneumothorax as either primary or secondary dates back to the early 20th century; the first description of pneumothorax in patients with no known underlying respiratory disease was published by Kjærgaard in 1932.[1] This report acknowledged the distinction between "pneumothorax simple" (in patients with no underlying lung disease) and pneumothorax secondary to tuberculous disease. It was important to distinguish between tuberculosis and other causes of pneumothorax to avoid unnecessary confinement of a patient in a sanatorium for a year.[2] The classification of pneumothorax as primary and secondary was, therefore, proposed when the relevant causes, spectrum of disease, and treatment options were markedly different from those seen now. Our understanding of pneumothorax has advanced such that even in patients labelled with primary pneumothorax without known previous respiratory disease, detectable lung abnormalities are seen, including emphysema-like changes,[3] subpleural blebs, and bullae.[4] Additionally, smoking is the main risk factor for primary spontaneous pneumothorax; it increases the risk of pneumothorax because of damage to lung parenchyma. This association exposes the misconception that primary spontaneous pneumothorax occurs in normal lungs. The distinction between primary and secondary pneumothorax has become artificial because of the frequent presence of lung abnormalities in all categories of patients with pneumothorax, although the nature and degree of underlying lung abnormality

remains an important determinant of prognosis and recommended management.

The bimodal age distribution seen in pneumothorax, with one peak occurring in patients aged 15–34 years and another in those aged over 55 years,[5] in addition to the difference in recurrence rates between primary and secondary spontaneous pneumothorax,[6] supports the argument that these disorders have different causal mechanisms. However, the differences in recommended management between groups have never been prospectively validated. There is probably a continuum between primary spontaneous pneumothorax (eg, in a tall, otherwise healthy 18-year-old man who has never smoked) and secondary spontaneous pneumothorax (eg, in a 65-year-old man with chronic obstructive pulmonary disease [COPD]), and the reality is a spectrum between these two extremes, somewhat similar to the distinction between chronic bronchitis and emphysema, which are now regarded under the umbrella term of COPD.

In view of our improved understanding of the pathological processes and causes of pneumothorax, are patients well served by the traditional distinctions between primary and secondary spontaneous pneumothorax? Does the high prevalence of respiratory bronchiolitis in patients with primary spontaneous pneumothorax point towards a poorly understood parenchymal process implicated in the development of pneumothorax?[7,8] Should a more robust assessment of idiopathic pneumothorax be recommended to exclude the presence of underlying parenchymal disease? A more comprehensive categorisation, taking into account the degree of lung abnormality, might allow more effective tailoring of treatment and management priorities and allow a distinction to be made between individuals with genuinely idiopathic pneumothorax and those with detectable lung abnormalities. This approach could potentially provide a more accurate assessment of risk of pneumothorax recurrence (table) and hence improve management.

## Specific causes of pneumothorax

Although height and male sex are risk factors for primary spontaneous pneumothorax,[9] smoking is the most important risk factor contributing to development of the disease. Large observational studies of primary spontaneous pneumothorax have shown that most patients are smokers and detected a dose-response relation between number of cigarettes smoked and risk of pneumothorax.[10] Smoking cessation is associated with a substantial reduction in the risk of recurrence.[11]

Cannabis smoking is associated with severe emphysema, mimicking the process seen with tobacco smoke, but can produce marked lung destruction and extensive bullous disease.[12,13] The pattern of lung injury and development of pneumothorax might be attributed to the deeper inhalation often seen in cannabis smokers and valsalva-like manoeuvres associated with it.[14] The accelerated lung damage seen in some cannabis smokers would suggest that this disease process might be more akin to secondary spontaneous pneumothorax, even in the absence of previous clinically apparent lung disease.

Several important inherited disorders predispose to pneumothorax, such as Marfan's syndrome,[15] Birt-Hogg-Dubé syndrome,[16] other mutations of the folliculin gene (FLCN),[17] α1-antitrypsin deficiency,[18] and homocysteinuria.[19] Although most of the individual inherited disorders are rare, taken together they make up a substantial minority. The identification of these inherited disorders may have implications for management of the initial pneumothorax or other multisystem aspects of patient management; it could also indicate the need for screening of relatives. The identification of Birt-Hogg-Dubé syndrome, for instance, which may be present in 5–10% of patients with primary spontaneous pneumothorax,[20] could be important to ensure targeted screening for renal tumours.

The association between anorexia nervosa and pneumothorax, a process likely explained by the effects of malnutrition on pulmonary parenchyma, may call for an individualised management plan in view of the apparent tendency towards prolonged air leak and an increased incidence of contralateral recurrence in patients with a body-mass index (BMI) less than 18·5 kg/m².[21,22] A French study reported that thoracic endometriosis was present on histopathological examination in seven of 32 women referred for surgery for pneumothorax.[23] Although it is unclear whether these rates are representative of the total population of women with apparent primary spontaneous pneumothorax, or indeed if the abnormalities are causally related to their pneumothoraces, the recognition of this process could allow tailored treatment, including hormone therapy, for

| | Management issues |
|---|---|
| Iatrogenic pneumothorax | Likely benign course in which conservative management may be appropriate |
| Traumatic pneumothorax | Management of coincident trauma or parenchymal injury |
| Pneumothorax associated with endometriosis | Potential role for hormone treatment; high risk of recurrence |
| Pneumothorax with a genetic predisposition (eg, Marfan's syndrome, Birt-Hogg-Dubé syndrome) | Related multisystem pathology; familial screening |
| Idiopathic pneumothorax | Likely low risk of recurrence; conservative or ambulatory management may be appropriate |
| Pneumothorax with previously unrecognised abnormal parenchyma (eg, respiratory bronchiolitis or bullous disease) | Smoking cessation; consideration of early surgical intervention in selected cases |
| Pneumothorax associated with infection or immunocompromise | Identification of underlying immunocompromise; targeted antimicrobial treatment |
| Pneumothorax with abnormal parenchyma in context of known lung disease (eg, COPD, cystic fibrosis, lung cancer, interstitial lung disease) | High risk of ongoing air leak and recurrence; suitability for surgical intervention; optimising management of existing lung disease |

COPD=chronic obstructive pulmonary disease.

***Table:*** **A possible alternative classification system to categorise pneumothorax**

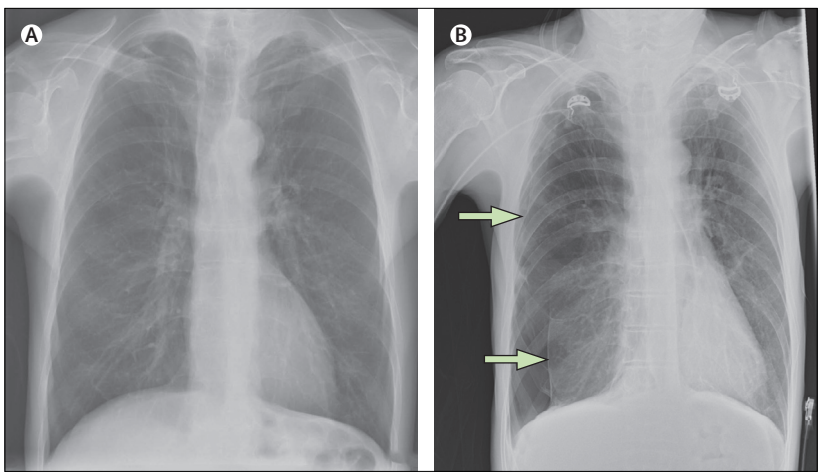


***Figure 1:*** **Chest radiographs of a patient with chronic obstructive pulmonary disease before (A) and after (B) pneumothorax**
Radiographs show lung hyperexpansion (A) and a right-sided pneumothorax (B) particularly marked in the right lower zone, with a more shallow rim of pneumothorax in the upper zone (see arrows).

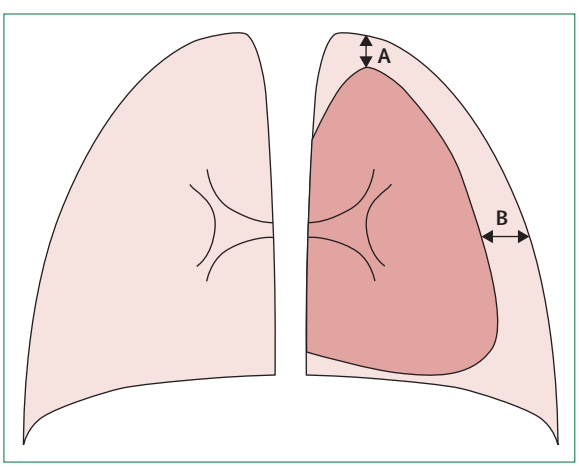


***Figure 2:*** **Size classification of pneumothorax**
(A) The American College of Chest Physicians (2001) defines the size of a pneumothorax by the apex to cupola distance (≥3 cm large; <3 cm small).[30] (B) The British Thoracic Society (2010) defines the size of a pneumothorax by the interpleural distance measured at the hilum (≥2 cm large; <2 cm small).[31]

this patient group in whom surgical intervention is commonly required to prevent recurrence.[24] The role of cancer antigen 125 (CA125) in the diagnosis of thoracic endometriosis has been prospectively assessed in patients requiring surgery for complicated or recurrent spontaneous pneumothorax.[25] CA125 concentration was substantially higher in women with evidence of thoracic endometriosis at video-assisted thoracoscopic surgery (VATS) than those without, and showed impressive diagnostic characteristics in this one study (area under the curve 0·994).[25]

In the developed world, the disease most commonly associated with secondary spontaneous pneumothorax is COPD (figure 1).[26] In endemic areas, pulmonary tuberculosis might be the most common cause.[27] Other causes of parenchymal lung disease predisposing to the development of pneumothorax are cystic fibrosis, lung cancer, and interstitial lung disease (eg, histiocytosis X and lymphangioleiomyomatosis).

## Current guidelines

As early as 1966, differing approaches to pneumothorax management were postulated. In the same issue of one journal, one article suggested active surgical management,[28] whereas another recommended a policy of non-intervention and outpatient management.[29] Nearly 50 years later, questions remain about the respective roles of conservative and more invasive treatment. International guidelines stratify patients to treatment options depending on the combination of symptoms and an assessment of the size of the pneumothorax.[30,31]

The British Thoracic Society (BTS) defines the size of a pneumothorax by the interpleural distance measured at the hilum—ie, distance from chest wall (parietal pleura) to the lung edge (visceral pleura)—with large pneumothoraces having an intrapleural distance of 2 cm or greater.[31] This distance corresponds with a pneumothorax occupying approximately 50% of the hemithorax.[31,32] The choice of a 2 cm depth intrapleural distance was chosen to provide a balance between the risks of parenchymal needle trauma during intervention for pneumothorax smaller than 2 cm and the prolonged period expected before the spontaneous resolution of a pneumothorax larger than 2 cm. One study estimated that conservatively treated (non-drained) pneumothoraces re-expand at a rate of 2% per day,[33] although the use of supplemental oxygen may hasten resolution.[34]

There is, however, substantial discrepancy between classifications of large pneumothoraces between international guidelines.[30,31,35] By contrast with the BTS, the American College of Chest Physicians (ACCP)[30] defines the size of a pneumothorax by the distance measured from the apex of the lung to the ipsilateral thoracic cupola at the parietal surface, with a small pneumothorax defined as less than 3 cm and a large pneumothorax as 3 cm or greater (figure 2).[30] A study comparing the definitions and management recommendations in three international guidelines (BTS, ACCP, and Belgian Society of Pulmonology)[30,31,35] reported that they agreed on classification of pneumothoraces into size groups in only 47% of cases, and their suggested subsequent treatment options also varied.[36]

An initial attempt at simple needle aspiration for primary spontaneous pneumothorax is justified in view of the results of randomised studies that have shown equivalent immediate and long-term success rates between aspiration and chest drain insertion for patients with the disease.[31,37,38] Success rates of initial aspiration in these studies were 50–70%, and in the event of failure to re-expand the lung, insertion of a small-bore (<14 F) chest drain is recommended and

admission of the patient to hospital. International guidelines suggest the use of smaller bore drains (with a Seldinger technique) rather than large-bore surgical drains in uncomplicated pneumothorax.[30,31] Smaller drains have a similar success rate to larger drains and lower levels of discomfort associated with their use.[30,31,39,40]

Patients with secondary spontaneous pneumothorax tend to have more severe symptoms, greater co-morbidity, and higher mortality rates than do those with primary spontaneous pneumothorax;[41,42] treatment recommendations therefore differ. The BTS and ACCP guidelines suggest that all patients with secondary spontaneous pneumothoraces are admitted to hospital, with most patients requiring chest drain insertion,[30,31] due in part to the reduced likelihood of spontaneously resolving an air leak.[43,44] BTS guidelines suggest that an air leak in secondary spontaneous pneumothorax beyond 48 h is an indication for surgical referral.[31] Most of the ACCP consensus panel recommended surgical intervention after an initial secondary spontaneous pneumothorax,[30] and both guidelines comment on medical pleurodesis as an option in patients unfit for surgery and the use of Heimlich valves in selected patients.[30,31]

Evidently, guidelines cannot be wholly prescriptive in managing all patients with pneumothorax, and as a result there is extensive variation in practice, both between individual clinicians and geographically. In some countries there is a lower threshold for offering surgical intervention at the first episode of pneumothorax, and in other countries a much more conservative approach is favoured. This variation is shown by the recommendation in some countries that all patients are admitted to hospital, global variability in the uptake of needle aspiration versus intercostal drain insertion, and the relative willingness in some countries to observe patients with pneumothoraces that have few or no symptoms.[45–47]

## Lung apposition and pneumothorax resolution

Fundamental to the lack of progress in management of primary spontaneous pneumothorax is a poor understanding of its precise causal mechanisms. For decades, clinicians believed that primary spontaneous pneumothorax resulted from the leakage of air from the lung into the pleural cavity via a single breach site (eg, bleb) in the visceral pleura. A major revelation the past decade is that the "one-airway-one-bleb-one-leak" concept is over-simplistic and likely to be incorrect. Although blebs can be a source of air leak, many patients do not have detectable blebs.[48,49] Noppen and colleagues[50,51] have described diffuse areas of weakness in the visceral pleura, which may be responsible for air leak, reiterating an old suggestion that the visceral pleura is lined with pores that permit air passage into the pleural cavity.

The importance of collateral ventilation within, and even between, lobes of the lung (from incomplete fissures) is now well established, in part from lessons learned from endobronchial lung volume reduction strategies. This mechanism also applies in pneumothorax; on average three endobronchial valves are needed to stop an air leak, suggesting the existence of multiple feeding pathways.[52] Unravelling the mechanism of how air moves from the lung to the pleural cavity will have major effects on how primary spontaneous pneumothorax should be managed.

Two crucial questions arise when presented with a patient with primary spontaneous pneumothorax: has the air leak stopped and what is the risk of recurrence? Conventional maxims on the approach to both questions have recently been challenged, making the management of primary spontaneous pneumothorax an exciting area of research.

Removal of the pleural air in an attempt to re-expand the lung has been the standard approach passed on from one generation to the next. Stradling and Poole[29] first proposed that visceral leak sites are more likely to heal if the lung is collapsed, allowing apposition of the visceral wound. This concept has been downplayed as clinicians became more concerned about improving the appearances of radiographs. Large drains, apical placement of tubes, and application of suction were all tried and are still routinely used to restore full lung expansion during ongoing air leaks. Although striving for lung re-expansion may, in some cases, be needed to improve patient symptoms, it might not be necessary in patients with primary spontaneous pneumothorax, in whom symptoms usually subside after 24 h.[53] Clinicians have rarely questioned how expansion of the lung aids healing of the leak. Bringing normal visceral and parietal pleura surfaces together would not usually facilitate a spontaneous pleurodesis. Half a century since the report by Stradling and Poole,[29] the non-intervention approach is finally being tested in a randomised trial in Australasia that is recruiting clinically stable patients with large primary spontaneous pneumothoraces (ACTRN12611000184976).

If the Stradling and Poole hypothesis is true, and that healing of the visceral wound is the key to management, then recent data on the resurgence of the role of blood patch in persistent air leak (especially in secondary spontaneous pneumothorax) should be further explored.[54] Blood instillation could promote clotting over the wound as a mechanism of healing the air leak rather than a means of achieving symphysis of the pleural surfaces.

## Lung density and risk stratification

An accurate assessment of the risk of recurrence is crucial to improving care in spontaneous pneumothorax. Most centres (and international guidelines) recommend reserving definitive recurrence prevention

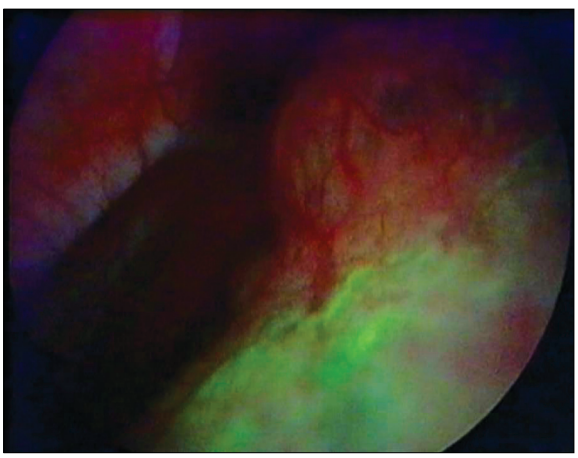

*Figure 3:* **Fluorescein-enhanced autofluorescence thoracoscopy after pneumothorax**
The lung (on the right of the image) has a green-yellow hue, indicating subpleural fluorescein, which suggests the presence of a region of parenchymal abnormality. Image courtesy of Marc Noppen.

approaches until the second or third presentation of primary spontaneous pneumothorax. This recommendation is based on the commonly quoted figure of a 20–30% risk of recurrence after an initial primary spontaneous pneumothorax; however, high-quality studies have quoted recurrence rates in excess of this.[55,56] Two of the largest randomised controlled trials (RCTs) to date have shown high recurrence rates of 49% (in 214 patients with primary spontaneous pneumothorax)[55] and 41% (in 229 patients with primary or secondary spontaneous pneumothorax)[56] in control groups who received simple drainage only. The discrepancy between the recurrence rates recorded in these trials and those from smaller cohort studies could have two explanations. First, most of the smaller studies were retrospective and thus vulnerable to selection bias. Second, the two large RCTs had an intervention group and required, as an entry criterion, a pneumothorax of adequate size for drainage. If the recurrence rate for patients with a pneumothorax of an adequate size for drainage is in fact in excess of 40%, this would favour the selected early use of strategies to prevent recurrence.

All international guidelines have so far treated all primary spontaneous pneumothoraces in the same way with regards to recurrence prevention, irrespective of established risk factors such as height, family history, smoking status, and the size of the initial pneumothorax. It is possible that a patient with Marfan's syndrome with multiple blebs on CT, presenting with a complete lung collapse, will have a higher risk of recurrence than a patient with a small rim of primary spontaneous pneumothorax and no other risk factors. Thus, there is a need for stratification of primary spontaneous pneumothoraces based on phenotype, demographic and radiological features, or biomarkers, which will require a longitudinal observational database on a multinational scale.

Studies have previously explored whether the risk of recurrence of pneumothorax depends on the presence of blebs, bullae, or parenchymal abnormalities. The difference in recurrence rates for pneumothorax between primary and secondary disease types suggests that the presence of diffuse lung disease predisposes to recurrent episodes.[6] Patients with primary spontaneous pneumothorax who have emphysema-like changes might represent a group at a higher risk of recurrence than patients with no such lung abnormalities because the natural history of their pneumothorax may more closely resemble secondary spontaneous pneumothorax than it does in those with genuinely idiopathic pneumothorax. However, advanced techniques such as fluorescein-enhanced autofluorescence thoracoscopy, which is mainly a research tool at present, might be needed to identify these emphysema-like changes (figure 3).[50]

Low-radiation dose CT may, in the future, allow a risk stratification of patients at baseline through identification of lung abnormalities, either ipsilaterally or in the contralateral lung. Previous studies with different designs have investigated the presence of bullae on CT scans, with contradictory results. Early small studies had suggested that presence of bullae might be predictive of high recurrence rate and hence justify early surgical intervention.[57,58]

Sihoe and colleagues[58] reported that contralateral recurrence was substantially more common in patients with blebs and bullae on the contralateral lung at the time of initial surgery for unilateral primary spontaneous pneumothorax than it was in patients without contralateral blebs and bullae. However, the statistical significance calculations in this study were later called into question.[59] Other studies have shown no difference in recurrence rates, irrespective of presence or absence of blebs or bullae.[4,60,61] There were no differences in the thoracoscopic features of blebs and bullae between patients with first and recurrent pneumothoraces in a study of 82 patients, suggesting that recurrence of pneumothorax cannot be predicted by thoracoscopic features.[62] Ouanes-Besbes and colleagues[63] assessed a bullae scoring system in a prospective cohort of 80 patients and recorded no difference in recurrence rates between patients with and without dystrophic lesions seen on CT. However, a subsequent study of 176 patients, which used the same dystrophic severity score as Ounes-Besbes and colleagues, did suggest that blebs and bullae were predictive of recurrence.[64] Therefore, the usefulness of CT in predicting recurrence of pneumothorax has not been firmly established and needs prospective validation.

An alternative radiological predictor could incorporate the objective quantification of low-density areas within the lung (rather than bullae), which correspond to emphysema-like change and may predispose to recurrent episodes. Smit and colleagues[65] reported that

lung density measurements on CT done during expiration were lower in patients with primary spontaneous pneumothorax (21 with, 20 without bullae) in both the affected lung and the contralateral lung, compared with 41 healthy volunteers, suggesting the presence of air trapping in patients with pneumothorax. These changes seemed to be independent of smoking behaviour and presence or absence of bullae.[65] Unpublished pilot work from the Bristol pleural research group lends support to these findings by showing that volumetric apical low lung density on CT (less than –950 Hounsfield units is substantially greater in patients with primary pneumothorax than in controls who are smokers or non-smokers (Maskell NA, unpublished). Whether lung density in patients with primary spontaneous pneumothorax is correlated with risk of recurrence is yet to be established, but if so, this association could allow a more accurate estimate of the risk of recurrence.

If physiological, demographic, or radiological information is shown to act as a predictor for risk of recurrence, this will allow more informed discussions with patients about their individual risk. If this approach proves possible, the early identification of patients at the highest risk of recurrence could be of great value in establishing a subgroup of patients who would benefit from being offered definitive intervention after an initial pneumothorax.

## Ambulatory care: the role of Heimlich valves

The clinical value of observing stable patients, especially those with primary spontaneous pneumothorax, for days in hospital can be questioned. Patients requiring chest drain insertion have historically been admitted to hospital and the drain connected to a bulky underwater seal or suction device. This approach has remained unchanged despite decades of documented use of Heimlich valves (one-way valves connected to the end of the chest drain), which allow greater mobility and potentially allow patients to be discharged home, thus letting the lung re-expand over time at home.

As early as 1976, small studies have shown the feasibility of this outpatient management of primary spontaneous pneumothorax. A case series of 226 patients with primary spontaneous pneumothorax managed by observation or flutter valve concluded that outpatient management was "safe, efficient, and economical".[66] A randomised trial of 30 patients with primary spontaneous pneumothorax (17 assigned to thoracic vent, 13 to standard chest drain) showed no significant difference between groups in complications or re-expansion rates, but 70% of patients assigned to thoracic vent were managed as outpatients and needed fewer analgesics, with patients in the control group staying in hospital for a mean of 8 days.[67] A systematic review of 18 studies of ambulatory management with Heimlich valves reported an overall success rate of 86% and successful outpatient management in 78% of cases, with few complications.[68] However, the evidence was of poor quality with a high risk of bias, consisting mainly of two small randomised trials with the remainder being case series. Despite further observational studies reporting effectiveness and a cost saving,[69,70] the paucity of robust data is probably the reason for low levels of uptake of Heimlich valves into standard clinical practice.

The BTS guidelines mention Heimlich valves briefly with respect to "facilitating mobilisation and outpatient care", but the guidance is not more prescriptive in its recommendation.[31] The ACCP consensus statement, however, provides the physician with the option to discharge "reliable" patients home with a small-bore catheter attached to a Heimlich valve if the lung has re-expanded after the removal of pleural air.[30] Appropriately powered and robust RCTs will help to identify whether there are advantages associated with the use of Heimlich valves and to ascertain the patient population in whom their use is beneficial. A grant to undertake such a trial has recently been supported in the UK (National Institute of Health Research grant: PB-PG-0213–30098).

## Digital air-leak measurement

When standard management does not sufficiently resolve the air leak, surgical referral is recommended.[31] However, the optimum timing of definitive intervention is unknown. Current guidelines suggest that in patients with a persistent air leak or failure of lung re-expansion, an early (3–5 days) thoracic surgical opinion should be sought, but there are no published data on prediction of persistent air leak or requirement for inpatient surgical intervention.

If persistent air leak could be predicted early (ie, within 48 h), this would allow triage of patients to new management pathways with informed patient-physician discussions. Stable patients predicted to have low probability of long-term leak could be discharged home with an ambulatory drain to allow resolution at home; those likely to have significant persistent air leak could be triaged early for assessment for more definitive intervention, rather than waiting for daily assessment and referral after four or five nights in hospital.

Digital measurement of air leak is possible with commercially available systems capable of providing regulated suction (via rotary pump and diaphragm) and validated measurements of air leak (through a revolutions per minute counter or thermodilution principles).[71] There are, so far, no published studies assessing air leak in medical patients with either primary or secondary spontaneous pneumothoraces; however, postoperative data from patients who have undergone thoracic surgery suggest that digital measurement of air leak might be a useful strategy.[72]

A case series of 142 patients who had undergone thoracic surgery reported postoperative air leak of more

than 180 mL/min on day 2 after surgery to be predictive of prolonged air leak (>5 days).[73] Five RCTs, a case-control study, and one large observational study (total of 956 postsurgical patients) showed that digital suction devices measured air leak more accurately than the traditional "bubbles in a chamber" method (currently used in medical management of pneumothorax), and reduced length of drainage and hospital stay after surgery.[74–76]

Although digital air-leak measurement has not been robustly assessed in the medical management of pneumothorax, and is not considered standard management, these studies of surgical patients suggest that it may well be a surrogate marker for persistent air leak, and hence non-resolving pneumothorax, and therefore allow early identification of patients who require more definitive management. However, caution is required in the application of postsurgical data to patients with medical spontaneous pneumothorax.

## Conservative management

International guidelines suggest a role for conservative management (observation alone) of clinically stable patients with primary spontaneous pneumothorax with close radiological follow-up to ensure resolution.[30,31] The previously mentioned study in Australasia (ACTRN12611000184976) is randomly assigning clinically stable patients with large primary spontaneous pneumothoraces to either observation without pleural intervention or standard care with needle aspiration and intercostal drain insertion. If leaving primary spontaneous pneumothorax undrained is shown to support healing of air leaks, it will profoundly alter management approaches worldwide.

Historically, studies of pneumothorax have focused on radiological evidence of lung re-expansion, rather than patient-centred outcomes such as degree of breathlessness and the need for further intervention. This approach has extended into international guidelines, in which achieving lung re-expansion has often been seen as the primary objective, rather than a means to reduce patient symptoms and ensure haemodynamic stability.

## Prevention of pneumothorax recurrence

Medical or surgical pleurodesis is advised for second ipsilateral primary spontaneous pneumothorax.[30,31,35] However, because of the high rates of recurrence reported in the first year, the argument could be made to offer pleurodesis at the first episode.

Chen and colleagues[55] provide an important insight into the feasibility of pleurodesis after simple aspiration for primary spontaneous pneumothorax and attempt to redefine a treatment algorithm for the first episode of the disease. There are, however, important limitations to consider. The difference between the typically quoted recurrence rates for primary spontaneous pneumothorax (around 30%),[37] and the rate recorded in their control group (49%) calls into question the relevance of the statistically significant difference between the minocycline and control groups (29% *vs* 49%). Tetracycline and its derivatives are no longer recommended sclerosing agents in the UK;[31] however, ACCP guidelines suggest use of either doxycycline or talc slurry. Although there are no directly comparative controlled trials for pneumothorax, graded talc seems more effective than tetracyclines and has been shown to be safe.[77–80] The high success rate of talc poudrage during thoracoscopy might be explained by a diffuse distribution of talc particles within the pleural cavity under direct vision or the brief interval between talc application and lung re-expansion within the same procedure.[78]

When invasive procedures are inappropriate (either patient suitability or preference), medical pleurodesis is a suitable alternative. However, the case for instillation of minocycline as first-line treatment for a first episode of pneumothorax to achieve a recurrence rate similar to that provided by simple aspiration or drainage in other studies is not sufficiently convincing to prompt a decisive change in standard patient management.

## Targeted surgical management

Elective surgery is commonly undertaken to reduce the risk of recurrent pneumothorax after a second episode, but surgical intervention is also recommended when simple medical management does not resolve an acute air leak.[31] However, the best possible timing for surgery has not been established. UK guidelines suggest 5–7 days from the onset of air leak but evidence is limited.[31] Indeed, one study including patients with both primary and secondary spontaneous pneumothoraces reported that after 14 days of drainage, air leaks had stopped in all cases of primary spontaneous pneumothorax and in 79% of those with secondary spontaneous pneumothorax, although many of these patients also received chemical pleurodesis.[44] Another study suggests that most primary spontaneous pneumothoraces resolve by 9 days, thereby advocating referral at 7–9 days.[81] By contrast, a UK series reported inferior outcomes when surgery was delayed beyond 21 days from acute presentation.[82] The chosen timescales might reflect the degree of acceptability to patients, the clinician's patience, and available health-care resources, rather than high-quality evidence.

Current indications for more invasive treatment to prevent recurrence are second (ie, recurrent) ipsilateral pneumothorax, bilateral pneumothorax, and professions at risk (eg, pilots and divers).[31] Surgical bullectomy alone is associated with a high rate of pneumothorax recurrence (6–14%),[83–85] suggesting that resection of bullae alone is not sufficient, unless there is a proven air leak at this site. Surgical series showing poorer rates of recurrence prevention with simple bullectomy compared

with bullectomy and pleurectomy or pleurodesis confirm that it is necessary to also undertake diffuse treatment of the visceral pleura.[83–85]

There are two approaches for pneumothorax surgery: thoracotomy or VATS. Irrespective of the approach, visible blebs and bullae are usually resected and then partial pleurectomy, pleural abrasion, or instillation of a sclerosing agent (ie, talc) is undertaken. VATS is better tolerated than open thoracotomy.[86] VATS has grown in popularity, and accounted for over 80% of pneumothorax surgery in the UK in 2010.[87] However, some studies have reported higher rates of pneumothorax recurrence in patients assigned to VATS than in those assigned to open thoracotomy, with respective recurrence rates of 5% versus 1% in a meta-analysis[88] and 3·8% versus 1·8% in a study that used propensity score analysis.[89] Another study of minithoracotomy compared with VATS showed similar rates of recurrence (2·7% and 3%, respectively) and postoperative pain.[90] Patients assigned to VATS had higher patient satisfaction level (assessed by use of the ipsilateral arm postoperatively) and return to activity than patients assigned to minithoracotomy.[90] After bullectomy at VATS for primary spontaneous pneumothorax, coverage of the staple line with a cellulose mesh and fibrin glue has been shown to be no worse than mechanical pleurodesis in terms of recurrence of pneumothorax in a large RCT.[91] New approaches including single port or awake VATS have also been described.[92,93] Reductions in morbidity may lead to a re-evaluation of the role and timing of surgery for primary spontaneous pneumothorax.

An earlier RCT assessing the efficacy of talc pleurodesis by medical thoracoscopy under local anaesthesia compared with chest tube drainage in cases of recurrent or complicated primary spontaneous pneumothorax, showed a very low long-term recurrence rate (around 5%) after talc poudrage with no difference in costs or complication rates between these two approaches.[78] There has been a trend towards the use of less invasive surgical approaches, such as VATS, driven by strong evidence of their efficacy in treating patients with recurrent pneumothorax.[90] However, the case could be made for referral of higher risk patients on first presentation.

## Important questions for future research

The identification of factors predicting both persistent air leak and recurrence of pneumothorax would be of great value in early stratification of patients to the appropriate management strategy. Digital measurement of air leak and radiological features, respectively, could hold promise in this area. Modern resources potentially allow a more detailed work-up of patients with primary spontaneous pneumothorax than was possible historically; however, the extent to which this will alter management and the role, for instance, of measuring CA125 concentration in female patients with primary spontaneous pneumothorax warrants further exploration.

The role of conservative management in pneumothorax is being assessed in a large RCT that is currently recruiting participants (ACTRN12611000184976), and funding has been made available from the National Institute of Health Research—Research for Patient Benefit Grant (RfPB) for a randomised, controlled trial assessing length of stay for ambulatory management (using valve device) against standard BTS guidelines for primary spontaneous pneumothorax, to begin recruiting in UK in 2015. These two trials will help to map out the roles of conservative and ambulatory management.

There is evidence from an RCT suggesting a role for bedside (chemical) pleurodesis in reducing the risk of recurrence in primary spontaneous pneumothorax.[55] However, for this strategy to be taken up more widely, further work will be necessary because of the high rates of pneumothorax recurrence seen in this study.

### Search strategy and selection criteria

We identified relevant studies for inclusion in this Series paper by searches of Medline, between Jan 1, 1980 to Jan 13, 2015, without language restrictions, with the search term "pneumothorax" appearing within the title and abstract of relevant study types (all clinical trials, guidelines, reviews, systematic reviews, and meta-analyses). Studies were restricted to those on adult patients and recent studies were prioritised. Additionally, the most up-to-date guidelines from international societies (American College of Chest Physicians, British Thoracic Society, and the Belgian Society of Pneumonology) were reviewed. Titles and abstracts were screened for relevance. We excluded studies related to traumatic pneumothorax or management of complications after thoracic surgery. Where relevant, further studies were identified through reference lists of reviewed papers. For foreign language studies, translations were used.

## Conclusions

Pneumothorax has been an under-researched area, and available evidence has been of fairly low quality, giving rise to international guidelines largely based on consensus and observational evidence, with few areas of agreement between them. Future high-quality studies may allow development of tailored management strategies, increasingly personalised care, a move towards outpatient-based treatment, and more conservative management. A risk stratification system at first presentation could identify patients who will benefit from intervention to prevent recurrence at the first presentation, rather than, as has historically been the case, simply waiting for a recurrence to occur. Further studies are needed to redefine the treatment

framework that would provide early triage to patients who can be treated conservatively, those who are suitable for ambulatory management as outpatients, and those who require early intervention. Such a framework would allow availability of a tailored spectrum of options and ensure that invasive treatments are offered promptly to those at high risk of recurrence.

#### Contributors

OJB and RJH contributed equally to the search and appraisal of relevant studies for inclusion and the initial drafting of the manuscript. AE, DF-K, YCGL, CHM, J-MT, DW, NMR, and NAM reviewed the manuscript and proposed amendments, corrections, and clarifications. All authors approved the final version for submission.

#### Declaration of interests

DF-K reports personal fees from Spiration, outside of the submitted work. DW reports grants from Covidien, outside of the submitted work. NAM reports grants from CareFusion to run the IPC plus study and personal fees to attend a CareFusion advisory board meeting, outside of the submitted work. NMR reports grants and personal fees from Rocket Medical UK, outside of the submitted work. All other authors declare no competing interests.

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