



## Pleural disease 2

# Spontaneous pneumothorax: time to rethink management?

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

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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.

## (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.<sup>1</sup> 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.<sup>2</sup> 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,<sup>3</sup> subpleural blebs, and bullae.<sup>4</sup> 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

## 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

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,<sup>5</sup> in addition to the difference in recurrence rates between primary and secondary spontaneous pneumothorax,<sup>6</sup> 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?<sup>27,8</sup> 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,<sup>9</sup> 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.<sup>10</sup> Smoking cessation is associated with a substantial reduction in the risk of recurrence.<sup>11</sup>

Cannabis smoking is associated with severe emphysema, mimicking the process seen with tobacco smoke, but can produce marked lung destruction and extensive bullous disease.<sup>12,13</sup> 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.<sup>14</sup> 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.

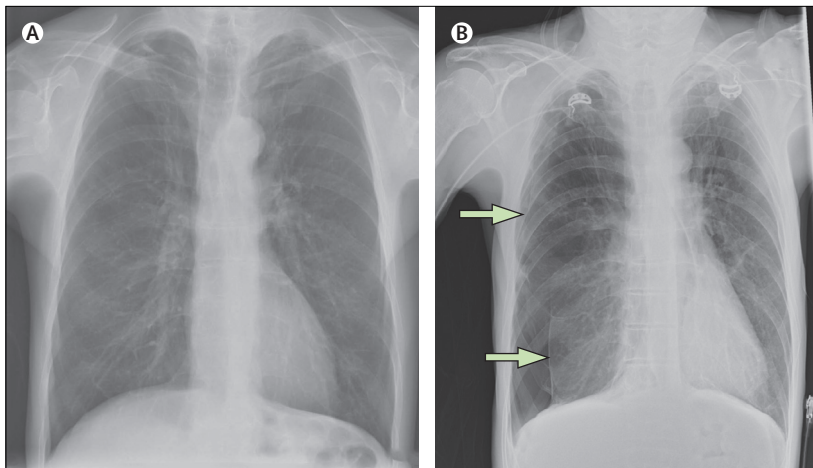
Several important inherited disorders predispose to pneumothorax, such as Marfan's syndrome,<sup>15</sup> Birt-Hogg-Dubé syndrome,<sup>16</sup> other mutations of the folliculin gene (FLCN),<sup>17</sup>  $\alpha$ 1-antitrypsin deficiency,<sup>18</sup> and homocysteinuria.<sup>19</sup> Although most 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,<sup>20</sup> 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/m<sup>2</sup>.<sup>21,22</sup> A French study reported that thoracic endometriosis was present on histopathological examination in seven of 32 women referred for surgery for pneumothorax.<sup>23</sup> 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

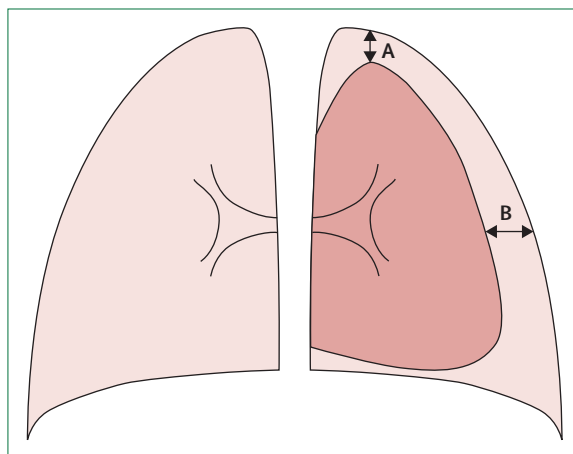
COPD=chronic obstructive pulmonary disease.

**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 ( $\geq 3$  cm large;  $< 3$  cm small).<sup>30</sup> (B) The British Thoracic Society (2010) defines the size of a pneumothorax by the interpleural distance measured at the hilum ( $\geq 2$  cm large;  $< 2$  cm small).<sup>31</sup>

this patient group in whom surgical intervention is commonly required to prevent recurrence.<sup>24</sup> 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.<sup>25</sup> 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).<sup>25</sup>

In the developed world, the disease most commonly associated with secondary spontaneous pneumothorax is COPD (figure 1).<sup>26</sup> In endemic areas, pulmonary tuberculosis might be the most common cause.<sup>27</sup> 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,<sup>28</sup> whereas another recommended a policy of non-intervention and outpatient management.<sup>29</sup> 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.<sup>30,31</sup>

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.<sup>31</sup> This distance corresponds with a pneumothorax occupying approximately 50% of the hemithorax.<sup>31,32</sup> 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,<sup>33</sup> although the use of supplemental oxygen may hasten resolution.<sup>34</sup>

There is, however, substantial discrepancy between classifications of large pneumothoraces between international guidelines.<sup>30,31,35</sup> By contrast with the BTS, the American College of Chest Physicians (ACCP)<sup>30</sup> 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).<sup>30</sup> A study comparing the definitions and management recommendations in three international guidelines (BTS, ACCP, and Belgian Society of Pulmonology)<sup>30,31,35</sup> reported that they agreed on classification of pneumothoraces into size groups in only 47% of cases, and their suggested subsequent treatment options also varied.<sup>36</sup>

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.<sup>31,37,38</sup> 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.<sup>30,31</sup> Smaller drains have a similar success rate to larger drains and lower levels of discomfort associated with their use.<sup>30,31,39,40</sup>

Patients with secondary spontaneous pneumothorax tend to have more severe symptoms, greater comorbidity, and higher mortality rates than do those with primary spontaneous pneumothorax;<sup>41,42</sup> 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,<sup>30,31</sup> due in part to the reduced likelihood of spontaneously resolving an air leak.<sup>43,44</sup> BTS guidelines suggest that an air leak in secondary spontaneous pneumothorax beyond 48 h is an indication for surgical referral.<sup>31</sup> Most of the ACCP consensus panel recommended surgical intervention after an initial secondary spontaneous pneumothorax,<sup>30</sup> and both guidelines comment on medical pleurodesis as an option in patients unfit for surgery and the use of Heimlich valves in selected patients.<sup>30,31</sup>

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.<sup>45–47</sup>

### 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.<sup>48,49</sup> Noppen and colleagues<sup>50,51</sup> 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.<sup>52</sup> 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.

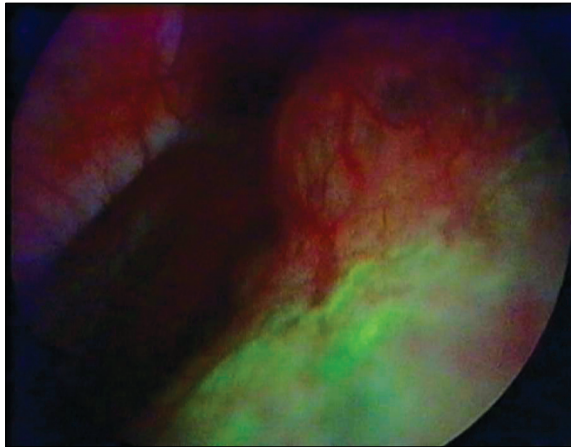
Removal of the pleural air in an attempt to re-expand the lung has been the standard approach passed on from one generation to the next. Stradling and Poole<sup>29</sup> first proposed that visceral leak sites are more likely to heal if the lung is collapsed, allowing apposition of the visceral wound. 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.<sup>53</sup> 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,<sup>29</sup> 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.<sup>54</sup> 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.<sup>55,56</sup> Two of the largest randomised controlled trials (RCTs) to date have shown high recurrence rates of 49% (in 214 patients with primary spontaneous pneumothorax)<sup>55</sup> and 41% (in 229 patients with primary or secondary spontaneous pneumothorax)<sup>56</sup> 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.<sup>6</sup> 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).<sup>50</sup>

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.<sup>57,58</sup>

Sihoe and colleagues<sup>58</sup> 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.<sup>59</sup> Other studies have shown no difference in recurrence rates, irrespective of presence or absence of blebs or bullae.<sup>4,60,61</sup> 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.<sup>62</sup> Ouanes-Besbes and colleagues<sup>63</sup> 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 Ouanes-Besbes and colleagues, did suggest that blebs and bullae were predictive of recurrence.<sup>64</sup> 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<sup>65</sup> 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.<sup>65</sup> 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”.<sup>66</sup> 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.<sup>67</sup> 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.<sup>68</sup> 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,<sup>69,70</sup> 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.<sup>31</sup> 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.<sup>30</sup> 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.<sup>31</sup> 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).<sup>71</sup> 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.<sup>72</sup>

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).<sup>73</sup> 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.<sup>74–76</sup>

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.<sup>30,31</sup> 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.<sup>30,31,35</sup> 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<sup>55</sup> 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%),<sup>37</sup> 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;<sup>31</sup> 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.<sup>77–80</sup> 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.<sup>78</sup>

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.<sup>31</sup> 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.<sup>31</sup> 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.<sup>44</sup> Another study suggests that most primary spontaneous pneumothoraces resolve by 9 days, thereby advocating referral at 7–9 days.<sup>81</sup> By contrast, a UK series reported inferior outcomes when surgery was delayed beyond 21 days from acute presentation.<sup>82</sup> 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).<sup>31</sup> Surgical bullectomy alone is associated with a high rate of pneumothorax recurrence (6–14%),<sup>83–85</sup> 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.<sup>83–85</sup>

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.<sup>86</sup> VATS has grown in popularity, and accounted for over 80% of pneumothorax surgery in the UK in 2010.<sup>87</sup> 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<sup>88</sup> and 3.8% versus 1.8% in a study that used propensity score analysis.<sup>89</sup> Another study of minithoracotomy compared with VATS showed similar rates of recurrence (2.7% and 3%, respectively) and postoperative pain.<sup>90</sup> 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.<sup>90</sup> 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.<sup>91</sup> New approaches including single port or awake VATS have also been described.<sup>92,93</sup> 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.<sup>78</sup> 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.<sup>90</sup> 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

### 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 Pneumology) 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.

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 a RCT suggesting a role for bedside (chemical) pleurodesis in reducing the risk of recurrence in primary spontaneous pneumothorax.<sup>55</sup> 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.

### 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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