

# Expert Review on Spontaneous Pneumothorax: Advances, Controversies, and New Directions

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## Abstract

### Keywords

- ▶ pneumothorax
- ▶ pleural porosity
- ▶ conservative management
- ▶ ambulatory management
- ▶ persistent air leak

For decades, there has been scanty evidence, most of which is of poor quality, to guide clinicians in the assessment and management of pneumothorax. A recent surge in pneumothorax research has begun to address controversies surrounding the topic and change the face of pneumothorax management. In this article, we review controversies concerning the etiology, pathogenesis, and classification of pneumothorax, and discuss recent advances in its management, including conservative and ambulatory management. We review the evidence base for the challenges of managing pneumothorax, including persistent air leak, and suggest new directions for future research that can help provide patient-centered, evidence-based management for this challenging cohort of patients.

Until recently, spontaneous pneumothorax (SP) was an underrepresented topic in the literature. Over the last 10 years, there has been an increase in research into SP, its assessment and management, and with the publication of the two largest ever randomized controlled trials (RCTs) in the field, there is now a growing evidence base that is beginning to challenge long-held practices and beliefs. There remain, however, many unanswered questions and emerging technologies that have yet to be evaluated, which are likely to form the basis of future research.

## Controversies of Etiology and Pathogenesis

### Cause of Air Leak: Bleb Rupture or Pleural Porosity?

Fundamental to improving management and patient care is understanding the basic etiology and pathogenesis of pneumothorax formation. Traditionally, it was felt the underlying pathological cause of SP was the rupture of small bullae or blebs on the pleural surface, which allowed egress of air from the lung into the pleural space.<sup>1</sup> These blebs are much more common in patients with primary SP (PSPs) than the general population. A study by Bense et al described the computed tomography (CT) finding of localized areas of low attenua-

tion with thin or imperceptible walls in the pulmonary tissues as emphysema-like changes (ELCs) and identified them in CT studies in over 80% of nonsmokers with PSP compared with 0% of healthy volunteers.<sup>2</sup> The role of ELC is debated in part because of the potential treatment implications, particularly in recurrence prevention.<sup>3</sup> If ELCs are solely responsible, then only the excision of the ELC is vital for recurrence prevention. If there are other causative mechanisms which extend beyond the boundaries of the blebs, then a pleurodesis procedure, to achieve pleural symphysis, is also required.

There are reasons to challenge the unique role of blebs and ELC in pneumothorax formation. Not all patients have macroscopic blebs on thoracoscopy<sup>4</sup> and there is an unclear correlation between number of blebs on CT evaluation and risk of future recurrence.<sup>5</sup> An alternative causative mechanism to bleb rupture is leakage of air via pores in the pleura. This is not a new proposal; a study in 1980 using electron microscopy on histological samples of blebs and bullae taken during thoracoscopy noted the presence of microscopic pores on the surface of blebs.<sup>6</sup> They postulated that these pores could cause air leakage into the pleura, without bleb rupture.<sup>6</sup> Noppen and colleagues went further than this and

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suggested that pleural porosity may extend to the macroscopically normal pleura.<sup>7</sup> Using inhaled aerosolized 10% fluorescein solution during thoracoscopy, they were able to determine that areas of extensive subpleural fluorescein accumulation and fluorescein leakage were not necessarily associated with blebs or bullae or other abnormalities visible at white light inspection.<sup>8</sup> It was postulated that the visceral pleural mesothelial cells are replaced by an inflammatory cell layer with increased porosity. Noppen termed this “pleural porosity.” This suggests that patients with PSP may suffer from a more extensive disease process of parenchymal inflammation and destruction than previously believed and challenges the idea that bleb or bulla rupture is involved in the pathogenesis of every case of PSP. There are however several recognized limitations, which prevent universal adoption, with Noppen’s study. The assessment at thoracoscopy was unblinded, they used a semiquantitative assessment, and it is unclear what the pathological correlation was. No one has attempted to replicate the results in a follow-up study.

Two recent surgical studies have examined whether bleb resection alone or pleurodesis alone is sufficient. Min et al randomized 289 PSP patients in two centers to either thoracoscopic wedge resection only ( $n = 144$ ) or thoracoscopic wedge resection and mechanical pleurodesis ( $n = 145$ ).<sup>9</sup> It found that thoracoscopic mechanical pleurodesis did not significantly decrease PSP recurrence compared with simple wedge resection alone, suggesting that bleb resection was the most vital component to surgery. A RCT looking at whether parietal pleurectomy alone versus pulmonary wedge resection plus parietal pleurectomy has just finished recruiting 360 patients and will be published in 2024 after follow-up has been completed.<sup>10</sup> These results will help determine whether a bullectomy is necessary, and therefore the role of diffuse pleural porosity in pneumothorax formation.

### Pathogenesis of Persistent Air Leak

The natural history of the resultant air leak, regardless of its underlying pathogenesis, is unclear. Observational studies suggest the air leaks are not quick to resolve, with a retrospective study assessing air leak in 104 patients with SP requiring chest tube drainage recording a mean duration of air leak of 5.19 days (standard deviation [SD]: 3.50) in PSP patients and 9.90 days (SD: 11.54) in secondary SP (SSP) patients.<sup>11</sup> This long duration conflicts with physiological and clinical studies. A study using inhaled chlorofluorocarbons (CFCs) to assess the presence of persistent air leak (PAL) found that in 35% of PSP and 20% of SSP, no CFC was detected at needle aspiration (NA) performed at presentation suggesting that there was no ongoing air leak.<sup>12,13</sup> An additional 35% of PSP and 29% of SSP had CFC detected at NA, but showed sustained improvement radiographically following NA, a phenomenon the authors suggest is due to the negative pressure of aspiration causing an ongoing leak through the defect, which then resolved on completion of aspiration. In fact, only 21% of PSP and 23% of SSP had both detectable CFC at NA and showed reaccumulation of their pneumothorax on

postaspiration imaging, suggesting that in the majority of both PSP and SSP, the air leaks are self-limiting and may not require intervention.

Clinical studies support the self-limiting nature of air leak. An RCT of 316 patients randomized between conservative management group and intercostal drain (ICD) insertion found that only 15% of patients in the conservative arm required intervention,<sup>14</sup> suggesting that an equilibrium is eventually reached and that, without intervention, many of these air leaks would be self-limiting or have already resolved by the time of presentation. This discrepancy has led that to the hypothesis that placement of an ICD, by virtue of creating a more negative pressure gradient, increases the flow of air through a visceral pleural defect, preventing healing and prolonging the air leak.<sup>15</sup> Studies in surgical patients have also raised the question of whether we are contributing to the problem of PAL. In 2017, Chopra et al described the concept of a pressure-dependent air leak after using pleural manometry to assess intra-pleural pressure during cough in a patient with PAL postlung resection.<sup>16</sup> Chopra et al found that even following spikes in intrapleural pressure with cough when the drain is clamped, the intrapleural pressure rapidly returned to baseline, suggesting the leak exists purely to equalize pleural and alveolar pressure. A subsequent observational study of 22 patients with PAL postlung resection found that 80% of these patients had a drainage-dependent air leak and all but one were able to have their drains removed with resolution of their pneumothorax and without the need for further intervention.<sup>17</sup>

Without intervening, the question of whether a patient has PAL is a challenging one to evaluate. Currently, we find ourselves in a paradoxical situation; we can only evaluate PAL by insertion of a chest drain, or at the very least a NA kit, by which point we have intervened, running the risk of potentiating an air leak that may have healed spontaneously on its own. Evaluating the presence or absence of PAL and understanding the role our interventions play in its development still requires significant research effort.

### Controversies in Phenotyping Spontaneous Pneumothorax

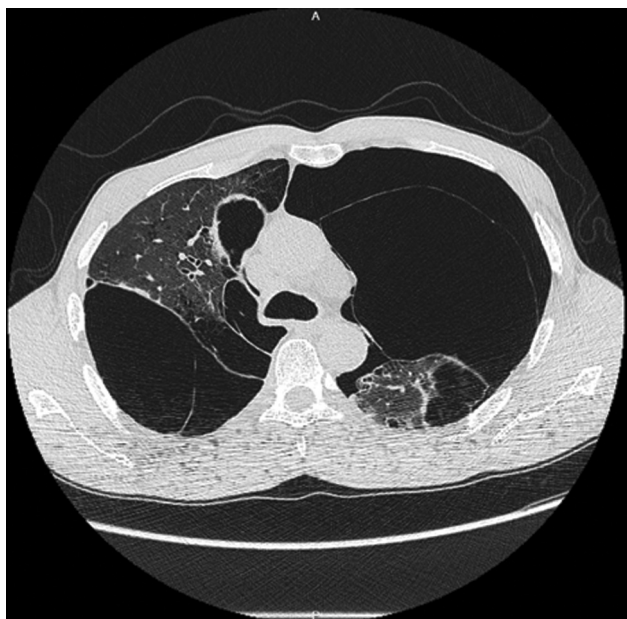
A distinction between PSP, occurring in patients with no known underlying lung disease, and SSP, occurring in patients with a known underlying lung disease, has been recognized for almost a century<sup>18</sup> and the management of these as two separate clinical conditions is advised in clinical guidelines worldwide.<sup>19,20</sup> The bimodal age distribution of SP, with a first peak in those aged 15 to 34, and a second peak occurring over the age of 60<sup>21</sup> supports the belief that there are two distinct clinical entities within SP. However, the overlaps in pathology, management, and outcome may limit this binary distinction.

### Pathology

It is recognized that patients with PSP have abnormal lungs, with our understanding of the mechanism underlying PSP evolving over the last 30 years since the advent of

widespread CT use. Studies have found pathological changes (blebs, bullae, ELC) in 80 to 90% of patients presenting with PSP,<sup>2,22</sup> challenging the paradigm that PSP is a condition that occurs in those with normal underlying lung parenchyma. Bense et al also identified ELC more commonly in the affected lung in those diagnosed with PSP than on the contralateral side,<sup>2</sup> suggesting that these changes may have predisposed the patient to developing PSP. Equally, the strong correlation between smoking both tobacco and cannabis and the development and recurrence of PSP supports the theory that parenchymal abnormalities occurring as a result of smoking contribute to a patient's risk of developing PSP. A study analyzing histological samples obtained from video-assisted thoracoscopic surgery (VATS) for PSP found evidence of more extensive respiratory bronchiolitis and higher rates of pneumothorax recurrence, even after surgical intervention, in tobacco smokers than non-smokers.<sup>23</sup> A retrospective analysis of patients who underwent VATS for pneumothorax found that cannabis smokers presented with larger pneumothoraces, a higher incidence of tension pneumothorax, more severe bullous disease, and a higher rate of recurrence than nonsmokers (→Fig. 1).<sup>24</sup> However, in clinical trials, cannabis smokers are typically classified as PSP. In the Randomized Ambulatory Management of Primary Pneumothorax (RAMPP) trial of 236 patients with PSP, only 112 (48%) of patients had never smoked cannabis, with 30% ( $n = 66$ ) of the cohort active cannabis smokers.<sup>25</sup>

Also incorporated in the PSP cohort are women who may have sex-specific cause for their pneumothorax, such as catamenial pneumothorax and endometriosis-related pneumothorax.<sup>26</sup> This may be an under recognized phenomenon, with pathological studies suggesting that these gender-specific pneumothorax account for up to 40% of pneumothorax in women referred for surgery.<sup>27,28</sup>



**Fig. 1** CT image of secondary spontaneous pneumothorax in a young patient with severe bullous disease secondary to cannabis and tobacco use. CT, computed tomography.

## Management

Clinical guidelines advise different management strategies for patients with PSP and SSP based on evidence that suggests different responses to interventions. A Singaporean study in 1994 showed higher failure rates following NA in patients aged >50 years (39%, 5/13) compared to those <50 years (19%, 4/17) and in those with underlying lung disease (33.3%, 5/15) compared to those with no lung disease (21%, 4/19).<sup>29</sup> These data support an earlier U.K. study, which found that NA was successful in only 33% (4/12) of patients with underlying lung disease, compared to 83% (15/18) of patients without.<sup>30</sup> In recent years, a RCT conducted in Norway allocated all patients presenting with a SP to either NA or ICD and found that 59% of patients with SSP had immediate success with NA, suggesting that there may be an argument for attempting NA in this cohort.<sup>31</sup> A recently started U.K.-based study will further examine NA versus ICD in SSP (PRINCE-SSP, NIHR204137).

## Outcomes

In addition to the varying pathology and management guidelines between these two cohorts of patients, there is also evidence to suggest that the clinical course of their disease differs. As described earlier, SSPs are more likely to have longer air leaks, with the rate of PAL lasting >7 days more common in patients diagnosed with SSP than PSP (61 vs. 75%). Hallifax et al also noted that the presence of underlying lung disease was associated with an increased risk of recurrence in all age groups at all stages of follow-up over a 5-year period<sup>21</sup>; an important point of consideration when counselling patients about management options for their pneumothorax. However, the recurrence rates varied widely, based on other factors, including sex and age. The overall recurrence rate for a male patient defined as PSP was 20.6% at 5 years, representative across all age groups. The overall recurrence rate at 5 years for female patients defined as PSP was similar at 21.6%, but there was an increased rate at age 35 to 49 of 27%.<sup>21</sup> This finding was replicated by a study by Bobbio et al which found that in the 30 to 49 age group rehospitalization was more frequent in women than in men.<sup>32</sup> Nevertheless, the presence of underlying lung disease was the largest determinant of recurrence risk, with recurrence rates of 33% in men and 31% in women defined as SSP.<sup>21</sup>

There are also differences in other outcomes between PSP and SSP, with patients with SSP more likely to die in hospital and have longer hospital length of stays (LoS).<sup>33</sup> It is clear, however, that SSP represents a very heterogeneous population, that can range under current criteria from a 50-year-old smoker to an elderly patient with advanced interstitial lung disease (ILD).<sup>19</sup> Whilst it is difficult to determine different outcomes within this group, as they are typically classified together in studies, there are demonstrable within-group differences. For example, patients with ILD have been shown to have significantly worse outcomes after surgery for SSP than patients with chronic obstructive pulmonary disease or other causes of SSP.<sup>34</sup>

## Controversies in Management

Whilst the management of many other respiratory diseases continues to advance rapidly, the management of pneumothorax remains broadly similar to practice 40 to 50 years ago, and the heterogeneity between clinical guidelines<sup>19,20</sup> reflects the lack of high-quality evidence on which these are based. For PSP, the current British Thoracic Society (BTS) guidelines advise NA, followed by ICD insertion if unsuccessful,<sup>19</sup> but evidence from multiple RCTs comparing NA to ICD demonstrates high rates of radiological failure with NA (37–40%)<sup>35,36</sup> and that over half of patients initially managed with NA ultimately require hospital admission.<sup>35</sup> Meanwhile for patients with SSP, guidelines support ICD insertion if amenable; a procedure which often commits patients to an inpatient stay until resolution of their pneumothorax. Over the last 10 years, there has been increasing interest in less invasive methods of managing pneumothorax and reducing the number of procedures to which patients are subjected. Additionally, in the current climate of unprecedented bed pressures, management strategies that avoid lengthy inpatient stays are favored. Emerging evidence evaluating both conservative and ambulatory management of patients with SP is now challenging our current practices and offering new strategies in pneumothorax management.

### Is Conservative Management Safe and Effective in Managing Spontaneous Pneumothorax?

The debate about the role of conservative management of PSP dates back to the 1960s. Whilst some were lauding the success of interventional management,<sup>37–40</sup> several single-center retrospective analyses from the 1960s found that 74 to 91% of all SPs presenting to their center during the study period had been successfully managed conservatively.<sup>41–43</sup> Time to resolution was similar across these studies at 3 to 4 weeks. Stradling and Poole found that few required NA (10/119, 8%), ICD insertion (8/119, 7%), or surgical intervention (13/119, 11%) and only 3/119 patients (3.4%) failed conservative management and did not show full re-expansion at 6 weeks.<sup>43</sup> Perhaps more remarkably, most patients managed conservatively remained at work. A common finding was that patients' symptoms resolved more rapidly than their radiographic findings, and that adverse events were higher in interventional than conservative groups.<sup>41–43</sup> Recurrence rates ranged from 9 to 21% for conservative management and 14 to 17% for ICD insertion, although these data were limited by small sample sizes, variable follow-up periods, and high rates of loss to follow-up.<sup>39,40,42,43</sup>

All told, these studies provide compelling evidence that outpatient (OP) conservative management of SP can be both safe and effective, albeit providing less rapid resolution. However, since then, guidelines have taken a more interventional approach, despite a lack of robust evidence to suggest that this is safer or reduces recurrence risk. It is unclear whether this has been driven by the widespread availability of more user-friendly plastic ICD insertion equipment, a desire from patients, clinicians and health care systems for rapid resolution of such an apparently solvable problem, the temptation to

treat an X-ray, rather than the patient in front of us, or a sense that because we can intervene, we should. Perhaps it is the threat of the much feared but seldom witnessed tension pneumothorax that has led practice to become more interventional. More recently, it has been proposed that this is a much less common phenomenon in a self-ventilating patient than previously thought, particularly in the context of PSP. It is argued that it is factors other than supra-atmospheric pleural pressures, such as poor physiological reserve in patients with SSP, that cause the clinical deterioration in pneumothorax patients.<sup>44</sup> It remains likely that concerns regarding the development of tension pneumothorax have contributed to the eschewing of conservative management, despite decades-old evidence in its favor.

Regardless of the drivers, research into SP management since the 1960s has focused on comparing different interventions for SP,<sup>35,36,45</sup> rather than intervention of any sort with conservative care. Recently, there has been renewed interest in the concept of conservative management of SP. The results of the first multicenter RCT comparing conservative management with intervention were published in 2020; 316 patients were randomized to either conservative care or insertion of a 12Fr ICD and completed 12 months follow-up, with a primary outcome of radiographic resolution at 8 weeks.<sup>14</sup> In total, 84.6% of those randomized to conservative care were successfully managed conservatively, with only 15.4% requiring intervention, most commonly due to abnormal physiological observations or intolerable symptoms. Radiographic resolution was demonstrated in 98.5% of those managed with ICD and 94.4% of those managed conservatively ( $p = 0.02$  for noninferiority). As with earlier studies, time to resolution was longer with conservative management (30 vs. 16 days), although patients managed conservatively spent less time in hospital, returned to work more quickly, were referred for surgery less frequently, and reported higher patient satisfaction than those in the intervention arm. The recurrence rates were lower (8.8 vs. 16.8%, relative risk: 1.90, 95% confidence interval: 1.03–3.52) and the time to recurrence longer in patients managed conservatively. Additionally, adverse events were less common with conservative management.

The findings from Brown's study are supported by a systematic review published the same year<sup>46</sup>; analysis of 10 papers, including Brown's, comparing conservative management with intervention found no difference between resolution rates, and noted lower risk of adverse events with patients managed conservatively. Interestingly this analysis found no difference in recurrence rates between conservative management and ICD insertion. It is important to note that most of these studies, except for Brown's, were retrospective, with no element of randomization; therefore, clinicians will likely have made clinical judgements based on existing guidelines about which patients required intervention and which could be managed conservatively. Were patients with smaller pneumothoraces, which were more likely to resolve spontaneously, managed conservatively, whilst those with larger, more symptomatic pneumothoraces were interventionally managed?

The strength of Brown's study is its prospective, randomized design, the likes of which have, until now, been conspicuous by their absence when it comes to the question of conservative management. However, there are still questions that remain unanswered; for one, the high number of patients screened out of the study, including those with previous pneumothorax, raises the question of how generalizable these results are.<sup>14</sup> The high screen failure rate may explain why the median scores for pain and breathlessness at enrolment in Brown et al study were lower (interventional group: pain 2/10 and breathlessness 1/10; conservative group: pain 2/10 and breathlessness 1/10)<sup>14</sup> than a recent interventional study on PSP (interventional group: pain 41/100 and breathlessness 43/100; standard care group: pain 37/100 and breathlessness 41/100).<sup>25,47</sup> In addition, the primary outcome from this study—lung re-expansion at 8 weeks—was never really in question; studies dating back 50 years demonstrate this.<sup>41–43</sup> Perhaps a primary outcome of more importance to the patients, such as rates of re-intervention or recurrence rates, which were both measured, or patient-reported outcome measures (PROMs) would have been of more value. What these studies do highlight is the need to consider conservative management in patients with a low symptom burden, reducing their risk of adverse events associated with intervention and the need for hospital admission. A new U.K. study is currently recruiting patients with PSP to either conservative care or U.K. standard of care, with re-intervention as the primary outcome (CONCEPT study, NIHR133653).

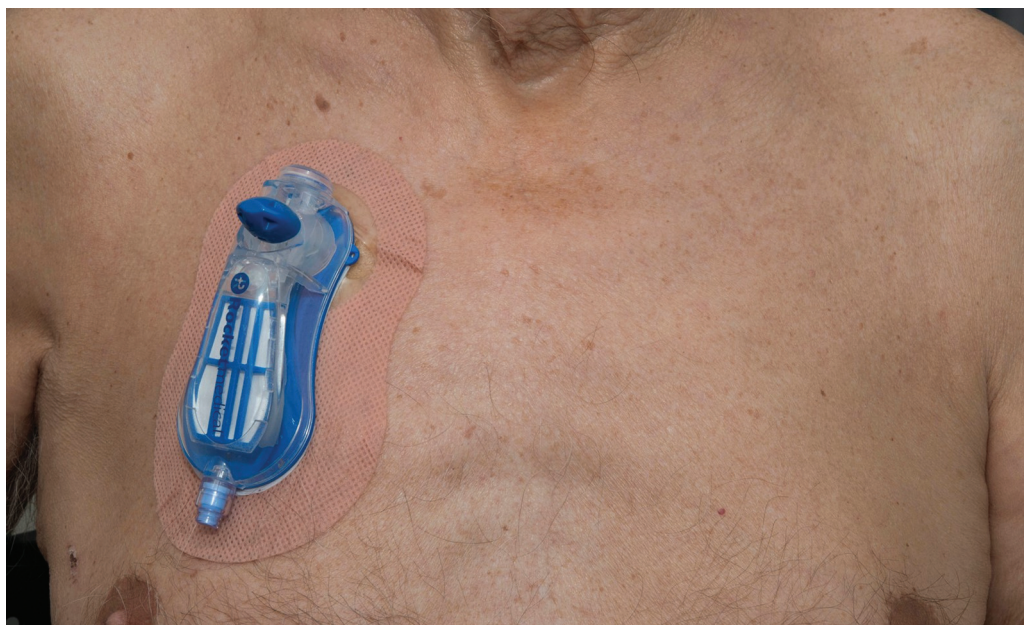
And what of SSP? The data on this topic remain even more sparse. One retrospective study reviewing the management of 82 patients presenting with SSP over a 7-year period found that 39% of patients were managed conservatively, and that none of these patients required further intervention, allowing for marginally, although statistically significant, shorter

hospital stays (7.9 vs. 9 days,  $p=0.004$ ).<sup>48</sup> Again, we must interpret these results in their context; patients were not randomized to one treatment arm or another, but rather clinicians made their own judgements on how to manage each patient based on existing clinical guidelines and their own experience. The conservative treatment group on average had smaller pneumothoraces, and more patients with a pneumothorax measuring  $<1$  cm at the hilum were managed conservatively than those measuring  $>1$  cm. That said, these data did demonstrate that nearly half of the patients with a pneumothorax measuring  $>1$  cm at the hilum were successfully managed conservatively. Whilst there remains doubt about the safety and success rates of managing SSP conservatively, this study and the paucity of high-quality research on the topic highlight that this concept warrants further investigation.

### Is the One-Way Valve Device Safe and Effective for Spontaneous Pneumothorax?

Whilst Brown's recent study demonstrated that a select cohort of patients with PSP with minimal symptom burden can be safely managed conservatively, the exclusion of patients with a history of pneumothorax, which some estimate to represent 25% of patients,<sup>25</sup> and those with abnormal physiological parameters, which are common findings in those presenting with a PSP, suggests that there may be a cohort of patients in which intervention is required. The question really is whether our current practice is necessarily the right intervention for these patients.

In the last decade there has been a renewed interest in evaluating methods by which patients who do require intervention for SP could be managed as an OP, often using one-way valves connected to ICDs or self-contained devices (→ Fig. 2), which allow egress of air from the pleural space without the need for patients to be attached to an



**Fig. 2** Image of a Rocket Pleural Vent in use in a patient with a spontaneous pneumothorax.

underwater seal. This method of managing pneumothorax has the added benefits of not restricting patients' mobility and providing the opportunity for them to be managed in the OP setting, but what evidence is available to support their use?

The body of evidence available to support ambulatory management of SP is limited and often of poor quality. A systematic review of 1,235 patients across 18 studies using Heimlich valves (HVs) in spontaneous or iatrogenic pneumothoraces suggested that ambulatory management can be both safe and effective in selected patients; OP management was successful in 77.9% of SP patients and management with HV alone was successful in 83.3% of PSP and 88.7% of SSP.<sup>49</sup> No deaths associated with OP or HV management were reported, and serious complications were rare. Perhaps even more compelling was the suggestion that, based on these success rates, ambulatory management could save approximately 12,000 bed days/year in England alone. These data ought to be interpreted with caution; the two RCTs included in this review were small and underpowered<sup>50,51</sup> and the remaining studies were prospective or retrospective case series; therefore, although the results seem compelling in favor of ambulatory management, these studies were limited by small numbers, the lack of a comparator arm and selection bias, particularly in the case of SSP, where more unstable and complex patients would be less likely to be offered ambulatory management.

This paucity of high-quality evidence has begun to be addressed more recently. A multicenter open label RCT published in 2020 randomized 236 patients with PSP to ambulatory care with the Rocket Pleural Vent or standard care (NA ± ICD) and found that patients in the ambulatory care arm had a significantly shorter LoS than those randomized to standard care (0 vs. 4 days), with nearly twice as many patients in the ambulatory arm discharged on the same day, even after excluding patients in the standard care arm who proceeded directly to ICD without an attempted NA.<sup>25</sup> Patients in the ambulatory arm also required fewer pleural procedures than the standard care arm; 47% of patients managed with NA required a further procedure, consistent with findings from previous studies.<sup>35,36</sup> Surgical referral rates and recurrence rates at 1 to 12 months were similar across both arms. Patients in the ambulatory care arm did have a longer time to successful completion of treatment (3 vs. 2 days), but authors speculate that this may reflect clinician concern about removing the device too early, or that OP management, in which the patients are only reviewed every 24 to 48 hours, reduces the opportunities at which resolution can be assessed and the device can be removed. Rates of adverse events were higher in the ambulatory care arm (55 vs. 39%) and all serious adverse events occurred within the ambulatory care group. Although higher than in the standard care arm, the absolute numbers of serious adverse events related to the device were small; 8/117 patients (6.8%) required readmission to hospital and chest tube insertion for device-related issues, including enlarging pneumothorax or device blockage, dislodgment, or leaking. Other serious adverse events were not device-

related, such as three unrecognized hemopneumothoraces and one episode of pleurisy. It is also worth noting that the adverse events were recorded in such a way that patients could have more than one adverse event, which may lead to overrepresentation of the total number of patients affected.<sup>25</sup> This study provides compelling evidence that ambulatory management of PSP is both safe and effective, but before this becomes common practice, clear and responsive pathways need to be in place to ensure that patients with ambulatory devices can be followed up regularly by clinicians familiar with device and pneumothorax management to ensure that this can be done safely.

There remains uncertainty about whether ambulatory management could or should be offered to patients with SSP. By virtue of their age, comorbidities and poorer physiological reserve, these patients are often more unwell at presentation and therefore less suitable for OP management. There is evidence that patients with SSP spend longer in hospital,<sup>32</sup> are at higher risk of PAL, and have higher inpatient mortality<sup>11</sup> than their PSP counterparts. In some settings, once a period of stability has been reached, ambulatory management may allow patients to be managed in their own homes and maintain their mobility and independence.

A single-center prospective study of patients with both PSP and SSP managed with HV found that 62/64 (96.8%) of PSP were felt to be suitable for OP management, compared to 49/99 (49.5%) of SSP.<sup>52</sup> Their primary outcome was complete radiographic resolution at day 5, which was achieved in 79% of PSP and 65% of SSP. Drainage times were similar across both groups and complications were rare, occurring in 2/62 PSP and 6/49 SSP. The authors estimated cost savings of £1188.80/patient using this management algorithm. Whilst the results from the study strongly support the need for further research into this management strategy, the study is limited by its lack of a true comparator arm; it would understandably have been futile for the authors to compare their OP SSP cohort with SSP patients receiving standard care in this nonrandomized study as, by virtue of the fact that they required inpatient treatment, those receiving standard care are likely to be more unwell and at higher risk of poorer outcomes.

A subsequent RCT recruited 41 patients with SSP and randomized them to either standard care or ambulatory management with a self-contained device (Rocket Pleural Vent) or a one-way valve (Atrium Pneumostat, Atrium Medical, Merrimack, NH), depending on whether an ICD had already been inserted.<sup>53</sup> The study found that although the mean initial LoS was shorter in the ambulatory care arm, (1 vs. 3.5 days), there was no difference in mean LoS in the first 30 days (11.5 vs. 8.7 days). In total, 33/59 (56%) of adverse events occurred in the ambulatory care arm; high rates of treatment failure were observed in those managed with a pleural vent, with 6/13 patients requiring a further ICD insertion within the first week of treatment and the pleural vent was subsequently removed from the study. Authors speculate that the smaller gauge (8Fr) of the pleural vent may have been insufficient to contend with the larger air leak often seen in SSP, compared to the 12Fr catheters used with

the Atrium Pneumostat. On comparing the outcomes of patients with each one-way valve, there was a trend toward shorter LoS with the Atrium Pneumostat and no early treatment failures, suggesting that the failure rate observed in the study may be device-specific.<sup>53</sup>

The question of whether patients with SSP can be managed in the ambulatory setting is somewhat more nuanced than in PSP, with suitability for OP management and patient outcomes likely to be device-, patient- and disease-specific, depending on their care needs, social support network, and their physiological reserve.

### Management of Persistent Air Leak

One of the greatest challenges in managing patients with PAL is the lack of clinical guidance on how they ought to be managed. The reasons for this are manifold; there is very limited evidence available and the heterogenous nature of the cohort means that one size certainly does not fit all. The new BTS pleural disease guidelines, due to be published in early 2023, openly acknowledge that “there is insufficient evidence to make any recommendations on the best treatment method for pneumothorax and PAL in adults.”<sup>54</sup> We know surgery to be effective, but what of those patients who do not want or, more commonly, are not fit enough to withstand a surgical procedure?

Suction is frequently implemented in an attempt to achieve pleural apposition and thus seal the causative defect,<sup>19,55</sup> but evidence to support this practice is limited and some believe that this could even perpetuate the leak, especially in the presence of larger defects. Studies in surgical patients have found suction to be either detrimental<sup>56</sup> or to be no better than underwater seal<sup>57</sup> in managing PAL.

The use of autologous blood patch pleurodesis (ABP) has perhaps the best, although still limited, evidence base for managing such patients; the use of ABP for PAL was first described in the early 1990s by Dumire et al<sup>58</sup> and subsequent case series and prospective nonrandomized studies supported its success. Resolution of air leak was achieved after between one and three administrations of intrapleural autologous blood in 59 to 84% of patients across these studies, whilst duration of chest tube drainage and hospital stays were consistently shorter.<sup>58–60</sup> However, these studies were all limited by small numbers, and the absence of randomization and a control arm for comparison.

These shortfalls have been addressed more recently in two RCTs exploring ABP in patients with PAL secondary to SP. Cao et al randomized 44 patients with SSP and PAL at 7 days, who were unfit for surgery, 1 of 3 escalating doses of autologous blood or normal saline via their ICD, with a maximum of 2 repeated doses at 48-hour intervals.<sup>61</sup> PAL resolved within 7 days of ABP in 82% of patients who received 1 to 2 mL/kg, compared to just 8% of those who received normal saline, suggesting that ABP is safe, effective, and superior to standard care in this cohort of patients. This was supported by a further RCT comparing early ABP after just 3 days with conservative care in 47 patients with SSP and PAL who were unfit or unwilling to undergo surgery; air leak was demonstrated to resolve in

78% of those in the early ABP arm, compared to 8% in the conservative care arm.<sup>62</sup>

So why is ABP not used more widely in PAL? Some clinicians remain concerned about the risk of pleural infection with ABP, but data from multiple studies suggest infection rates of just 8.7 to 10%,<sup>59,62,63</sup> whilst higher rates were observed with conservative care (16.7%)<sup>62</sup> perhaps related to longer duration of chest tube drainage. Others fear the chest tube blocking following ABP, putting patients at risk of tension pneumothorax; this is understandable given that many of these studies were carried out in patients with larger bore (20–28Fr) chest tubes, rather than the narrower 12–18Fr tube frequently inserted by chest physicians. This highlights the need for further investigation; with only a handful of RCTs evaluating ABP in PAL secondary to SP, there remain many unanswered questions, including whether narrower bore drains can be safely used, what the optimal mode of delivery of an ABP is, and what the best time is at which to perform an ABP.<sup>61–63</sup>

Endobronchial valves (EBVs) have also shown promise in management of PAL; in a study published in 2009, 40 patients with PAL secondary to SP of mixed etiologies were managed with EBV.<sup>64</sup> Balloon catheters were used to occlude the airways suspected of supplying the leak and the effect on air leak assessed qualitatively to identify the target airways for EBV. EBV successfully resolved the air leak in 47.5% of patients and reduced or resolved the leak in 92.5% of patients. Only 6/40 patients experienced adverse events. Markedly better success rates were reported with the use of either endobronchial ABP or silicone spigots to occlude airways supplying a PAL, with cessation of air leak reported in 82% (41/50) of patients managed with endobronchial ABP and 84% (42/50) of patients managed with bronchial occlusion spigots at 14 days, compared to only 60% (30/50) of patients managed with chest tube drainage alone.<sup>65</sup>

Although there are multiple management options available, the heterogeneity of the patient cohort, the variations in size of air leak, the patients' suitability for surgical management, and limited availability of more specialist procedures make the development of a management algorithm or even evaluation of the most effective management techniques of this complex cohort challenging and controversial.

## New Directions

### Enhanced Phenotyping of Spontaneous Pneumothorax

In this age of patient-centered and precision medicine can we better phenotype patients with pneumothorax, to identify factors that may influence their outcomes and alter care accordingly?

### Genetic Phenotyping in Spontaneous Pneumothorax

An estimated 10% of individuals presenting with SP have a positive family history of pneumothorax.<sup>66</sup> Some of these are attributable to identifiable genetic disorders, caused by mutations in tumor suppressor genes, such as Birt-Hogg-Dubé syndrome (BHGS) and lymphangiomyomatosis

(LAM), fibrillin and collagen genes, causing connective tissue disorders such as Marfan's and vascular Ehlers–Danlos, and conditions affecting the lung architecture, such as alpha-1 antitrypsin deficiency and cystic fibrosis.<sup>67</sup>

But what difference does knowing that a pneumothorax is just one part of a larger picture actually make? In truth, this knowledge can drastically change the way in which these patients are managed, both in relation to their pneumothorax and their management more holistically. First, recurrence rates are estimated to be higher in familial pneumothorax than sporadic (70 vs. 25%),<sup>21,68</sup> therefore some would argue we ought to focus our management on reducing their risk of recurrence, whether that be with early surgical intervention or medical pleurodesis.<sup>69</sup>

Second, these inherited syndromes come hand in hand with other systemic manifestations that may warrant additional investigations to allow early identification and treatment or ongoing surveillance, for example, of renal tumors in BHGS or aortic root dilatation in Marfan's. It is also recognized that there is a more equal sex preponderance in familial pneumothorax (male to female ratio 1.7:1)<sup>66</sup>; LAM, although rare, is a condition that almost exclusively affects women and can lead to progressive deterioration in lung function, so monitoring of lung function and radiographic progression could be beneficial to enable early intervention. The increased risk to women with these syndromes during pregnancy and childbirth should also be noted; LAM cells are sensitive to female sex hormones, so rapid progression in disease may be observed during pregnancy, in addition to the patient being at higher risk of pneumothorax at this time. This knowledge impacts the counselling clinicians give women prior to and during pregnancy and may alter their management pathway during the peripartum period to reduce their risk of complications.<sup>67,69</sup>

An algorithm for assessing patients with a potential familial syndrome has been suggested, in which any patient presenting with a first pneumothorax who has any of the following should have a CT scan of the chest and a referral for genetic testing should be considered:

- Female gender.
- Family history of pneumothorax, lung blebs, cysts, or bullae.
- Family/personal history and/or examination suggestive of a pneumothorax-associated syndrome.<sup>69</sup>

Implementation of this algorithm is dependent on clinicians having a high enough index of suspicion to ask the pertinent questions and elicit the history or clinical signs that may indicate the presence of a pneumothorax-associated syndrome. Given the potential ramifications of not making a diagnosis of a familial pneumothorax-associated syndrome, we need to ensure that this is an integral part of any consultation regarding pneumothorax.

### Radiographic Phenotyping

The decision to undergo a thoracic surgical procedure to reduce a patients' risk of recurrence is a significant one, and over recent years there has been a drive to find ways in which

clinicians can risk stratify patients, to better understand who is most likely to benefit from a surgical procedure. Of interest is whether high-resolution CT can be used to phenotype patients, and predict recurrence risk, but the utility of this remains unclear. The concept of a "bleb score" was first introduced by Warner et al in 1991 in a prospective case series of 26 patients presenting with PSP.<sup>70</sup> This study noted a higher bleb score in the ipsilateral lung in patients with a history of prior pneumothorax, those who developed a recurrence during the follow-up period, and those who required chest tube drainage. Subsequent studies utilizing this or similar bleb scores have had mixed success.

A single-center retrospective analysis of 176 patients with PSP found ipsilateral and contralateral recurrence rates of 44.8 and 12%, respectively.<sup>71</sup> The risk of recurrence in the presence of blebs and/or bullae was 68.1%, compared to just 6.1% in those without and a direct relationship between the dystrophic severity score was noted, with the presence of multiple lesions and therefore a higher score being associated with increased ipsilateral recurrence risk of up to 82%. A smaller study of just 23 patients with PSP found a higher 5-year recurrence rate (86.7 vs. 50%) in patients with any dystrophic lesions, and that recurrence risk increased with the number of dystrophic lesions seen.<sup>72</sup> By contrast, two smaller, prospective studies found no correlation between bleb score and recurrence risk,<sup>73,74</sup> although it should be noted that 15% of patients in one study received pleurodesis, and recurrence rates in that study were particularly low (19%).<sup>73</sup>

Although the question of how useful bleb scores are in predicting recurrence and which patients may benefit from surgery remains open to debate, these studies have helped us understand who is *unlikely* to benefit from surgical intervention; contralateral recurrence rates even in the presence of blebs or bulla remain low (19–27%)<sup>71,75</sup>; therefore, early surgical intervention on the contralateral side should not be advised. In addition, although the positive predictive value of CT bleb scores in ipsilateral recurrence is relatively low (68.1%), the negative predictive value remains high (93.9%), which could help identify those who are at lower risk of recurrence.<sup>71</sup> Ultimately, larger prospectively collected observational studies are needed to assess the utility of bleb scores and other markers in predicting recurrence.

### Better Clinical Outcome Predictors

One of the challenges of radiological evaluation of pneumothorax is the dynamic nature of the condition, particularly in cases of PAL. Innovative techniques are required to identify, either prior to pleural intervention or at initial pleural procedure, the presence and predicted duration of visceral air leak to better characterize patients.

### Digital Air Leak Monitoring

Digital chest drainage systems, which provide continuous air leak monitoring, are a promising technology to better characterize air leak and may predict clinical outcomes. A study by Hallifax et al used daily digital airflow measurements for 10-minute periods in patients with PSP, either via a chest drain or a



small bore (8Fr) ambulatory pleural vent, to determine if early (day 1 or 2) measurement predicted future incidence of PAL.<sup>76</sup> They demonstrated high early digital air-leak measurements were predictive of persistent bubbling via standard chest drain or unexpanded lung at day 4. If these results are verified in a larger prospective study, these patients could be triaged to early thoracic surgery for air-leak management rather than waiting with daily reviews until day 4.

### Novel Computed Tomography Imaging

Plain CT imaging captures just one moment in time, usually whilst the patient is breath-holding and is generally not useful in assessing for either the presence or the site of an air leak. Recent advances in dynamic chest imaging could help tackle this problem; a study in Japan used intrapleural normal saline and sustained vocalization to demonstrate air leaks on CT imaging in 11 patients with a chest tube in situ for SP and who subsequently required thoracic surgery for PAL.<sup>77</sup> They were able to identify air bubbles on CT following instillation of intrapleural normal saline in 9/11 patients, and identified other radiological signs thought to be consistent with air leak that were not present on plain CT images, in a process they termed “saline-filled CT thoracography.” This technique could be used to assess both the presence of air leak and to localize the leak to guide endobronchial or surgical management.

### Conclusion

For decades, pneumothorax has been vastly under-researched and the evidence available to clinicians was often poor quality, which was reflected in the disparity between clinical guidelines worldwide. The recent burgeoning evidence base is now challenging decades-old practice and highlighting the fact that ICD insertion is not a panacea for all our patients. This understanding opens the door for more patient-centered medicine that reserves intervention for those who truly need it and reduces unnecessary admissions to hospital. Larger scale randomized studies are required to evaluate whether, with the implementation of novel technologies, there are ways in which we can better phenotype the pneumothorax cohort to assess who is most likely to benefit from intervention, improve our understanding of who is at highest risk of recurrence, and offer treatment that provides the best outcomes for our patients.

#### Conflict of Interest

None declared.

### References

- Noppen M, Baumann MH. Pathogenesis and treatment of primary spontaneous pneumothorax: an overview. *Respiration* 2003;70(04):431–438
- Bense L, Lewander R, Eklund G, Hedenstierna G, Wiman LG. Nonsmoking, non-alpha 1-antitrypsin deficiency-induced emphysema in nonsmokers with healed spontaneous pneumothorax, identified by computed tomography of the lungs. *Chest* 1993; 103(02):433–438
- Haynes D, Baumann MH. Pleural controversy: aetiology of pneumothorax. *Respirology* 2011;16(04):604–610
- Cardillo G, Carleo F, Giunti R, et al. Videothoracoscopic talc poudrage in primary spontaneous pneumothorax: a single-institution experience in 861 cases. *J Thorac Cardiovasc Surg* 2006;131(02):322–328
- Walker SP, Bibby AC, Halford P, Staddon L, White P, Maskell NA. Recurrence rates in primary spontaneous pneumothorax: a systematic review and meta-analysis. *Eur Respir J* 2018;52(03): 1800864
- Ohata M, Suzuki H. Pathogenesis of spontaneous pneumothorax. With special reference to the ultrastructure of emphysematous bullae. *Chest* 1980;77(06):771–776
- Noppen M, Stratakos G, Verbanck S, D’Haese J, Meysman M, Vincken W. Fluorescein-enhanced autofluorescence thoracoscopy in primary spontaneous pneumothorax. *Am J Respir Crit Care Med* 2004;170(06):680–682
- Noppen M, Dekeukeleire T, Hanon S, et al. Fluorescein-enhanced autofluorescence thoracoscopy in patients with primary spontaneous pneumothorax and normal subjects. *Am J Respir Crit Care Med* 2006;174(01):26–30
- Min X, Huang Y, Yang Y, et al. Mechanical pleurodesis does not reduce recurrence of spontaneous pneumothorax: a randomized trial. *Ann Thorac Surg* 2014;98(05):1790–1796, discussion 1796
- Neudecker J, Malzahn U, Heuschmann P, Behrens U, Walles T. Pulmonary wedge resection plus parietal pleurectomy (WRPP) versus parietal pleurectomy (PP) for the treatment of recurrent primary pneumothorax (WOPP trial): study protocol for a randomized controlled trial. *Trials* 2015;16(01):540
- Chee CBE, Abisheganaden J, Yeo JKS, et al. Persistent air-leak in spontaneous pneumothorax—clinical course and outcome. *Respir Med* 1998;92(05):757–761
- Seaton D, Yoganathan K, Coady T, Barker R. Spontaneous pneumothorax: marker gas technique for predicting outcome of manual aspiration. *BMJ* 1991;302(6771):262–265
- Kiely DG, Ansari S, Davey WA, Mahadevan V, Taylor GJ, Seaton D. Bedside tracer gas technique accurately predicts outcome in aspiration of spontaneous pneumothorax. *Thorax* 2001;56(08): 617–621
- Brown SGA, Ball EL, Perrin K, et al; PSP Investigators. Conservative versus interventional treatment for spontaneous pneumothorax. *N Engl J Med* 2020;382(05):405–415
- Walker SP, Hallifax R, Rahman NM, Maskell NA. Challenging the paradigm of persistent air leak: are we prolonging the problem? *Am J Respir Crit Care Med* 2022;206(02):145–149
- Chopra A, Doelken P, Judson MA, Huggins T. The pressure-dependent air leak after partial lung resection. *Thorax* 2017;72(03): 290–291
- Chopra A, Hu K, Judson MA, et al. Association between drainage-dependent prolonged air leak after partial lung resection and clinical outcomes: a prospective cohort study. *Ann Am Thorac Soc* 2022;19(03):389–398
- Kjaergaard H. Spontaneous pneumothorax in the apparently healthy. *Lancet* 1938;232(6002):632–633
- MacDuff A, Arnold A, Harvey JBTS Pleural Disease Guideline Group. Management of spontaneous pneumothorax: British Thoracic Society pleural disease guideline 2010. *Thorax* 2010;65 (Suppl 2):ii18–ii31
- Baumann MH, Strange C, Heffner JE, et al; AACP Pneumothorax Consensus Group. Management of spontaneous pneumothorax: an American College of Chest Physicians Delphi consensus statement. *Chest* 2001;119(02):590–602
- Hallifax RJ, Goldacre R, Landray MJ, Rahman NM, Goldacre MJ. Trends in the incidence and recurrence of inpatient-treated spontaneous pneumothorax, 1968–2016. *JAMA* 2018;320(14): 1471–1480

- 22 Mittlehner W, Friedrich M, Dissmann W. Value of computer tomography in the detection of bullae and blebs in patients with primary spontaneous pneumothorax. *Respiration* 1992;59(04):221–227
- 23 Cheng Y-L, Huang T-W, Lin C-K, et al. The impact of smoking in primary spontaneous pneumothorax. *J Thorac Cardiovasc Surg* 2009;138(01):192–195
- 24 Stefani A, Aramini B, Baraldi C, et al. Secondary spontaneous pneumothorax and bullous lung disease in cannabis and tobacco smokers: a case-control study. *PLoS One* 2020;15(03):e0230419
- 25 Hallifax RJ, McKeown E, Sivakumar P, et al. Ambulatory management of primary spontaneous pneumothorax: an open-label, randomised controlled trial. *Lancet* 2020;396(10243):39–49
- 26 Alifano M. Catamenial pneumothorax. *Curr Opin Pulm Med* 2010;16(04):381–386
- 27 Alifano M, Legras A, Rousset-Jablonski C, et al. Pneumothorax recurrence after surgery in women: clinicopathologic characteristics and management. *Ann Thorac Surg* 2011;92(01):322–326
- 28 Legras A, Mansuet-Lupo A, Rousset-Jablonski C, et al. Pneumothorax in women of child-bearing age: an update classification based on clinical and pathologic findings. *Chest* 2014;145(02):354–360
- 29 Ng AW, Chan KW, Lee SK. Simple aspiration of pneumothorax. *Singapore Med J* 1994;35(01):50–52
- 30 Archer GJ, Hamilton AA, Upadhyay R, Finlay M, Grace PM. Results of simple aspiration of pneumothoraces. *Br J Dis Chest* 1985;79(02):177–182
- 31 Thelle A, Gjerdevik M, SueChu M, Hagen OM, Bakke P. Randomised comparison of needle aspiration and chest tube drainage in spontaneous pneumothorax. *Eur Respir J* 2017;49(04):1601296
- 32 Bobbio A, Dechartres A, Bouam S, et al. Epidemiology of spontaneous pneumothorax: gender-related differences. *Thorax* 2015;70(07):653–658
- 33 Onuki T, Ueda S, Yamaoka M, et al. Primary and secondary spontaneous pneumothorax: prevalence, clinical features, and in-hospital mortality. *Can Respir J* 2017;2017:6014967
- 34 Ichinose J, Nagayama K, Hino H, et al. Results of surgical treatment for secondary spontaneous pneumothorax according to underlying diseases. *Eur J Cardiothorac Surg* 2016;49(04):1132–1136
- 35 Noppen M, Alexander P, Driesen P, Slabbynck H, Verstraeten A. Manual aspiration versus chest tube drainage in first episodes of primary spontaneous pneumothorax: a multicenter, prospective, randomized pilot study. *Am J Respir Crit Care Med* 2002;165(09):1240–1244
- 36 Harvey J, Prescott RJ British Thoracic Society Research Committee. Simple aspiration versus intercostal tube drainage for spontaneous pneumothorax in patients with normal lungs. *BMJ* 1994;309(6965):1338–1339
- 37 Klassen KP, Meckstroth CV. Treatment of spontaneous pneumothorax: prompt expansion with controlled thoracotomy tube suction. *JAMA* 1962;182(01):1–5
- 38 Baronofsky ID, Warden HG, Kaufman JL, Whatley J, Hanner JM. Bilateral therapy for unilateral spontaneous pneumothorax. *J Thorac Surg* 1957;34(03):310–319, discussion 319–322
- 39 Smith WG, Rothwell PPG. Treatment of spontaneous pneumothorax. *Thorax* 1962;17(04):342–349
- 40 Ruckley CV, McCormack RJ. The management of spontaneous pneumothorax. *Thorax* 1966;21(02):139–144
- 41 Hyde L. Spontaneous pneumothorax. *Dis Chest* 1963;43(05):476–480
- 42 Beumer HMA. Ten-year review of spontaneous pneumothorax in an armed forces hospital. *Am Rev Respir Dis* 1964;90:261
- 43 Stradling P, Poole G. Conservative management of spontaneous pneumothorax. *Thorax* 1966;21(02):145–149
- 44 Simpson G, Vincent S, Ferns J. Spontaneous tension pneumothorax: what is it and does it exist? *Intern Med J* 2012;42(10):1157–1160
- 45 Carson-Chahhoud KV, Wakai A, van Agteren JE, et al. Simple aspiration versus intercostal tube drainage for primary spontaneous pneumothorax in adults. *Cochrane Database Syst Rev* 2017;9(09):CD004479
- 46 Lee JH, Kim R, Park CM. Chest tube drainage versus conservative management as the initial treatment of primary spontaneous pneumothorax: a systematic review and meta-analysis. *J Clin Med* 2020;9(11):3456
- 47 Hallifax RJ, Walker S, Walters J, Maskell N, Rahman NM. Management of primary spontaneous pneumothorax: less is more – Authors’ reply. *Lancet* 2021;396(10267):1973–1974
- 48 Gerhardy BC, Simpson G. Conservative versus invasive management of secondary spontaneous pneumothorax: a retrospective cohort study. *Acute Med Surg* 2021;8(01):e663
- 49 Brims FJH, Maskell NA. Ambulatory treatment in the management of pneumothorax: a systematic review of the literature. *Thorax* 2013;68(07):664–669
- 50 Ho KK, Ong MEH, Koh MS, Wong E, Raghuram J. A randomized controlled trial comparing minichest tube and needle aspiration in outpatient management of primary spontaneous pneumothorax. *Am J Emerg Med* 2011;29(09):1152–1157
- 51 Röggl M, Wagner A, Brunner C, Röggl G. The management of pneumothorax with the thoracic vent versus conventional intercostal tube drainage. *Wien Klin Wochenschr* 1996;108(11):330–333
- 52 Khan F, Vali Y, Naeem M, Reddy R. Safety and efficacy of ambulatory management of secondary spontaneous pneumothorax: a case series. *BMJ Open Respir Res* 2019;6(01):e000373
- 53 Walker SP, Keenan E, Bintcliffe O, et al. Ambulatory management of secondary spontaneous pneumothorax: a randomised controlled trial. *Eur Respir J* 2021;57(06):2003375
- 54 Maskell N, Rahman N, Roberts M, et al. British Thoracic Society Pleural Disease Guidelines [Internet]. 2022 Accessed December 22 at: <https://www.brit-thoracic.org.uk/quality-improvement/guidelines/pleural-disease/>
- 55 Pompili C, Salati M, Brunelli A. Chest tube management after surgery for pneumothorax. *Thorac Surg Clin* 2017;27(01):25–28
- 56 Cerfolio RJ, Bass C, Katholi CR. Prospective randomized trial compares suction versus water seal for air leaks. *Ann Thorac Surg* 2001;71(05):1613–1617
- 57 Alphonso N, Tan C, Utley M, et al. A prospective randomized controlled trial of suction versus non-suction to the under-water seal drains following lung resection. *Eur J Cardiothorac Surg* 2005;27(03):391–394
- 58 Dumire R, Crabbe MM, Mappin FG, Fontenelle LJ. Autologous “blood patch” pleurodesis for persistent pulmonary air leak. *Chest* 1992;101(01):64–66
- 59 Cagirici U, Sahin B, Cakan A, Kayabas H, Buduneli T. Autologous blood patch pleurodesis in spontaneous pneumothorax with persistent air leak. *Scand Cardiovasc J* 1998;32(02):75–78
- 60 Ando M, Yamamoto M, Kitagawa C, et al. Autologous blood-patch pleurodesis for secondary spontaneous pneumothorax with persistent air leak. *Respir Med* 1999;93(06):432–434
- 61 Cao Gq, Kang J, Wang F, Wang H. Intrapleural instillation of autologous blood for persistent air leak in spontaneous pneumothorax in patients with advanced chronic obstructive pulmonary disease. *Ann Thorac Surg* 2012;93(05):1652–1657
- 62 Ibrahim IM, Elaziz MEA, El-Hag-Aly MA. Early autologous blood-patch pleurodesis versus conservative management for treatment of secondary spontaneous pneumothorax. *Thorac Cardiovasc Surg* 2019;67(03):222–226
- 63 Shackcloth MJ, Poullis M, Jackson M, Soorae A, Page RD. Intrapleural instillation of autologous blood in the treatment of prolonged air leak after lobectomy: a prospective randomized controlled trial. *Ann Thorac Surg* 2006;82(03):1052–1056
- 64 Travaline JM, McKenna RJ Jr., De Giacomo T, et al; Endobronchial Valve for Persistent Air Leak Group. Treatment of persistent pulmonary air leaks using endobronchial valves. *Chest* 2009;136(02):355–360

- 65 Zhang HT, Xie YH, Gu X, et al. Management of persistent air leaks using endobronchial autologous blood patch and spigot occlusion: a multicentre randomized controlled trial in China. *Respiration* 2019;97(05):436–443
- 66 Abolnik IZ, Lossos IS, Zlotogora J, Brauer R. On the inheritance of primary spontaneous pneumothorax. *Am J Med Genet* 1991;40(02):155–158
- 67 Scott RM, Henske EP, Raby B, Boone PM, Rusk RA, Marciniak SJ. Familial pneumothorax: towards precision medicine. *Thorax* 2018;73(03):270–276
- 68 Lenler-Petersen P, Grunnet N, Jespersen TW, Jaeger P. Familial spontaneous pneumothorax. *Eur Respir J* 1990;3(03):342–345
- 69 Boone PM, Scott RM, Marciniak SJ, Henske EP, Raby BA. The genetics of pneumothorax. *Am J Respir Crit Care Med* 2019;199(11):1344–1357
- 70 Warner BW, Bailey WW, Shipley RT. Value of computed tomography of the lung in the management of primary spontaneous pneumothorax. *Am J Surg* 1991;162(01):39–42
- 71 Casali C, Stefani A, Ligabue G, et al. Role of blebs and bullae detected by high-resolution computed tomography and recurrent spontaneous pneumothorax. *Ann Thorac Surg* 2013;95(01):249–255
- 72 Primavesi F, Jäger T, Meissnitzer T, et al. First episode of spontaneous pneumothorax: CT-based scoring to select patients for early surgery. *World J Surg* 2016;40(05):1112–1120
- 73 Ouanes-Besbes L, Golli M, Knani J, et al. Prediction of recurrent spontaneous pneumothorax: CT scan findings versus management features. *Respir Med* 2007;101(02):230–236
- 74 Martínez-Ramos D, Ángel-Yepes V, Escrig-Sos J, Miralles-Tena JM, Salvador-Sanchís JL. Usefulness of computed tomography in determining risk of recurrence after a first episode of primary spontaneous pneumothorax: therapeutic implications [in Spanish]. *Arch Bronconeumol* 2007;43(06):304–308
- 75 Sihoe ADL, Yim APC, Lee TW, et al. Can CT scanning be used to select patients with unilateral primary spontaneous pneumothorax for bilateral surgery? *Chest* 2000;118(02):380–383
- 76 Hallifax RJ, Laskawiec-Szkonter M, Rahman NMRAMPP Trial collaborators. Predicting outcomes in primary spontaneous pneumothorax using air leak measurements. *Thorax* 2019;74(04):410–412
- 77 Nakanishi K, Shimotakahara A, Asato Y, Ishihara T. A new method to detect air leakage in a patient with pneumothorax using saline solution and multidetector-row spiral CT scan. *Chest* 2013;144(03):940–946