Exploring the efficacy and advancements of medical pleurodesis: a comprehensive review of current research

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Shareable abstract (@ERSpublications)
This review provides an overview of medical pleurodesis techniques, their indications and potential adverse effects. It examines various nonsurgical techniques for managing pleural effusions and pneumothorax. https://bit.ly/3zuHPgk

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Abstract

This narrative review aims to provide an overview of medical pleurodesis techniques, and their indications and potential adverse effects. Pleurodesis is a procedure performed with the aim of obliterating the pleural space. It has indications in the management of both malignant and benign pleural effusions and pneumothorax. Various nonsurgical techniques exist to perform pleurodesis. The scope of this work is to review the different nonsurgical techniques and their indications. This narrative review was performed checking scientific databases for medical literature, focusing especially on the data derived from randomised controlled trials. Pleurodesis is an effective method to manage pleural effusions and pneumothorax, and minimally invasive techniques are now frequently used with good results. Further research is needed to assess the efficacy of new treatments and the possibility of using different techniques in association.

Introduction

Malignant pleural effusions (MPEs), recurrent or refractory nonmalignant pleural effusions (NMPEs) and recurrent pneumothorax significantly affect patient morbidity and quality of life. Various therapeutic interventions are available for these conditions, including simple pleural aspiration, talc pleurodesis, indwelling pleural catheter (IPC) placement and surgical management.

Currently, apart from for MPE, there is limited evidence guiding physicians in selecting the optimal pleurodesis procedure, particularly in the case of NMPE. For instance, while talc pleurodesis is commonly used as a first-line intervention for MPE, its use in NMPE is less consistent, reflecting the varied nature of nonmalignant conditions and the corresponding need for individualised treatment approaches.

Moreover, the choice between IPC and talc pleurodesis often depends on the patient's clinical status, underlying condition and expected prognosis, with some studies suggesting a preference for IPC in patients with limited life expectancy. Consequently, managing these conditions relies heavily on the physician's expertise and the patient's preferences.

This narrative review aims to serve as a valuable resource for clinicians navigating the complexities of pleural effusion management, ultimately contributing to more standardised and effective care practices. We will explore the efficacy and safety profiles of the different methods and highlight the main issues involved in their application to various clinical scenarios. In addition, we will delve into the commonly employed

agents for chemical pleurodesis, such as talc, doxycycline and bleomycin, discussing their mechanisms of action, effectiveness and potential side-effects. Furthermore, we will address potential future directions in managing specific indications, considering emerging therapies and novel approaches that may offer improved outcomes for patients with MPE, NMPE and recurrent pneumothorax. Through this detailed examination, we aim to equip healthcare providers with a deeper understanding and updated knowledge to enhance patient care in these challenging conditions.

Methods

This manuscript is written as per SANRA (Scale for the Assessment of Narrative Review Articles) [1]. A comprehensive online literature search *via* Medline/PubMed and the Cochrane database for the period January 2010 to December 2023 was performed for articles published using the keywords "pleurodesis", "poudrage", "slurry", "talc" or "indwelling pleural catheter". Relevant references were additionally considered when deemed appropriate by the authors. A particular focus was placed on the available randomised controlled trials (RCTs). The search strategy is summarised in table 1.

Medical pleurodesis: techniques

Medical pleurodesis used to be achieved mainly through the intrapleural instillation of inflammation-inducing substances, resulting in sclerosis, and in the development of adhesions between the parietal and visceral pleura. The ideal sclerosing agent should be economical, readily available, easily administrable, demonstrate a high rate of pleurodesis success and pose a low risk of adverse reactions. Up to now, the ideal agent has not been identified. However, a variety of agents have been used over the centuries, including autologous blood, doxycycline, iodopovidone, OK 432 and silver nitrate [2]. According to the current literature, talc stands out as the safest and most effective pleurodesis agent [3]. Talc pleurodesis demonstrates an overall success rate ranging from 80% to 95%, depending on the dose, the number of administrations, the pathological entity being treated and the patient's condition [4–6]. Although all the aforementioned agents are generally effective, no evident superiority exists for any of them over talc [7, 8].

A meta-analysis by Xia *et al.* [9] revealed a significant superiority for talc pleurodesis in terms of overall success rate when compared to other sclerosants (relative risk (RR) 1.21, 95% CI 1.01–1.45; p = 0.035; random-effects model). More recently, a large Cochrane meta-analysis by Dipper *et al.* [10] confirmed that talc slurry (ranked 6, 95% credible interval (Cr-I) 3–10) results in fewer pleurodesis failures when compared to bleomycin (OR 2.24, 95% Cr-I 1.10–4.68; low certainty; ranked 11, 95% Cr-I 7–15 for bleomycin *versus* talc slurry) and doxycycline (OR 2.51, 95% Cr-I 0.81–8.40; low certainty; ranked 12, 95% Cr-I 5–18 for doxycycline *versus* talc slurry).

Besides the choice of the agent for pleurodesis, another significant matter of controversy is the choice of the optimal size of chest tube. The BTS guideline advocates the use of smaller tubes (<16 French (F)) over large tubes for drainage and to achieve pleurodesis [4]. The rational for this recommendation stays in the fact that small-bore tubes are associated to smaller incision and less pain both during and after insertion.

A meta-analysis of four prospective RCTs found similar rate of success and complication for small-bore chest tubes and large-bore chest tubes when used to insufflate a sclerosing agent [11]. However, the TIME1 trial found that large-bore tubes are superior to small-bore tubes (<12 F) in achieving pleurodesis (failure rate: 24 F tubes, 48 out of 244 (19.7%); 12F tubes, 15 out of 50 (30.0%); difference −10%, 95%

TABLE 1 Search strategy summary

Items	Specification
Databases and other sources searched	Medline (PubMed, OVID) Cochrane Database of Systematic Reviews
Search terms used	Pleurodesis, poudrage, slurry, talc, indwelling pleural catheter
Timeframe	January 2010 to December 2023
Inclusion criteria	Original article, research article, full paper, English language
Exclusion criteria	Editorial, comments, letters, proceedings, books, abstracts, non-English papers
Selection process	A. Fantin and N. Castaldo conducted the selection process and literature review, and selected the studies based on the eligibility criteria All authors reviewed the final list of studies included in the review and proposed additional references to be considered

CI −21%–∞) [12]. An important limitation of this trial was the inclusion of both talc slurry pleurodesis and thoracoscopy cases, for which only large-bore tubes are used. Therefore, the direct comparison of small-bore and large-bore tubes for the same procedure was limited to few cases.

Talc slurry versus *talc poudrage*

Talc slurry involves introducing a talc suspension into the pleural space through a liquid medium, typically saline or sterile water, using a chest tube or an IPC [13]. This technique is predominantly used in treating MPE and NMPE [8]. In some selected cases, it may also be considered for the treatment of pneumothorax [14].

Talc poudrage involves access to the pleural space and dry-insufflating fine-powdered talc directly into the pleural cavity (figure 1). This method enables broader coverage of the pleura, facilitating increased contact between talc particles and pleural surfaces [15].

While talc slurry pleurodesis can be performed on an outpatient basis, talc poudrage generally necessitates an inpatient hospital stay [16]. Talc poudrage has traditionally been regarded as the most effective technique in recent decades. However, this belief has been challenged by several RCTs.

Dresler *et al*. [17] demonstrated a comparable success rate in fluid control at 30 days between thoracoscopic talc poudrage and talc slurry pleurodesis (78% *versus* 71%, respectively). Notably, talc poudrage pleurodesis was associated with a higher incidence of complications, including infections, respiratory failure, bronchopleural fistula and arrhythmia [17]. A RCT including 30 cases of MPE similarly reported findings indicating no significant difference between talc slurry and talc poudrage pleurodesis regarding both pleurodesis success and hospitalisation rates [18].

More recently, the TAPPS trial affirmed the absence of any significant difference in pleurodesis failure rates between the poudrage and slurry arms [13]. The failure rates were 22% and 24%, respectively, with an odds ratio of 0.91 (95% CI 0.54–1.55, p=0.74). Adverse events were comparable between the poudrage and slurry arms (29% *versus* 28%; OR 1.05, 95% CI 0.63–1.73; p=0.86), as well as the all-cause mortality at 180 days (40% in the poudrage group and 42% in the slurry group, p=0.70) [13]. In contrast to the findings of the TAPPS trial, a subgroup analysis of the meta-analysis by Xia *et al*. [9] revealed that talc poudrage was superior to control therapies in managing MPE (RR 1.74, 95% CI 1.11–2.73; p = 0.015). Conversely, no significant difference in efficacy was observed when comparing the subgroup receiving talc slurry and controls (RR 1.05, 95% CI 0.87–1.27; p = 0.588) [9].

Indwelling pleural catheters

IPCs are tunnelled catheters that can be left in place for an extended period, enabling the intermittent drainage of pleural fluid without the need for hospitalisation or repeated pleural punctures [19]. In managing pleural effusions, especially MPE, IPCs have become an increasingly appealing option [20, 21]. The primary goals of IPCs include symptom relief, evacuation of the pleural space and the promotion of spontaneous pleurodesis without the use of sclerosing agents (figure 2). One of the critical advantages of IPCs is the ability to perform the procedure in an outpatient setting [19]. Despite IPCs being comparable to chemical pleurodesis in alleviating dyspnoea, IPCs exhibit variable pleurodesis rates, ranging from 16% to 65%, depending on the underlying pleural disease [22, 23].

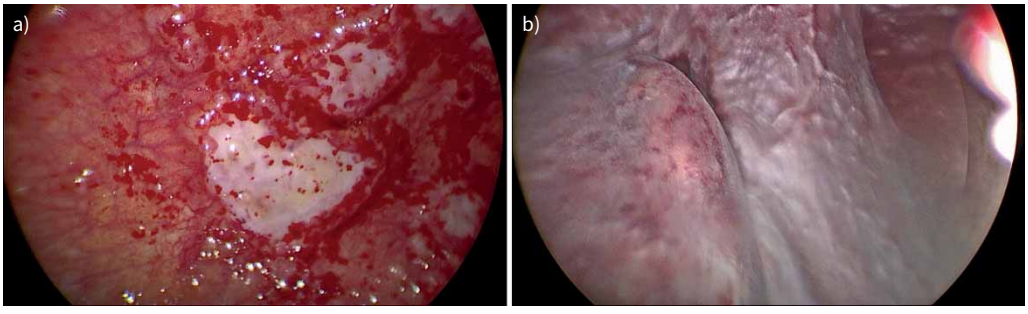

FIGURE 1 Thoracoscopic view of the pleural cavity. a) Pleural nodule in a patient with lung adenocarcinoma with pleural metastases and malignant pleural effusion. b) View of the pleural cavity after insufflation of sterile talc.

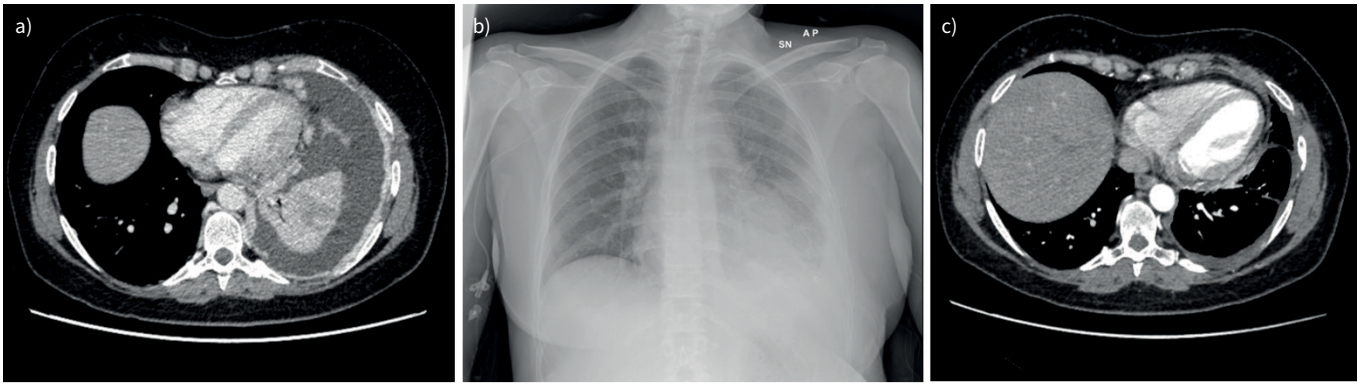

FIGURE 2 Patient with recurrent malignant pleural effusion secondary to breast cancer, already subjected to talc slurry, with consequent recurrence of symptomatic effusion successfully treated with an indwelling pleural catheter. a) Left pleural effusion with pleural thickening. b) Chest radiograph immediately following placement of an indwelling pleural catheter. c) Achievement of complete pleurodesis after catheter placement and modification of molecular targeted oncological therapy.

In general, IPCs are considered a suitable option for patients with a history of pleurodesis failure and those with limited life expectancy [21, 24]. A definitive pleurodesis procedure would be recommended for patients with a life expectancy >1 month [20]. Moreover, IPCs can be employed in cases of talc pleurodesis failure or for patients who underwent previous ipsilateral talc pleurodesis [25].

The use of IPCs is also increasingly prevalent worldwide in patients with NMPE. Despite the potential therapeutic effects of IPCs in NMPE, currently, no strong evidence exist on their routinely use in this subset of patients. Indeed, our understanding of IPCs for NMPE is predominantly derived from retrospective cohort studies, case series and case reports [26].

To the best of our knowledge, a single small trial investigated on IPCs for NMPE. Recently, Walker *et al*. [27] randomly assigned 68 patients with NMPE to receive IPCs (33 patients) or standard care with repeated aspirations (35 patients). Overall, no difference in breathlessness score over the 12-week study period was found (39.7±29.4 mm in the IPC group *versus* 45.0±26.1 mm in the standard care group, p=0.67). In addition, a more significant proportion of patients in the IPC group had adverse events (p=0.04).

In our opinion, IPCs could be considered as an alternative option only in heart failure patients, when thoracentesis fails or becomes more frequent.

Autologous blood patch pleurodesis

Autologous blood patch pleurodesis (ABPP) requires the collection of fresh venous blood from the patient, which is instilled into the pleural cavity to achieve pleurodesis. It is employed explicitly in treating primary and secondary spontaneous pneumothorax, persistent postoperative air leak (PAL), and hydrothorax secondary to peritoneal dialysis [28]. In a recent meta-analysis, this technique appeared to be more effective in achieving pleurodesis in patients with PAL than using the drainage system alone [29].

Although there are variations in the protocols used, ABPP typically requires a regular chest tube connected to a drainage system with a water seal. In patients in whom it is impossible to clamp the drain after instilling the aliquots of autologous blood, the drainage tube can be positioned in a loop to allow air recovery from the pleural cavity and leave the blood instilled inside the pleural cavity. The loop should be maintained for ⩾2 h [30].

There is an ongoing debate regarding the optimal amount of blood to be used in ABPP, with some studies suggesting that larger volumes may be associated with greater effectiveness [31]. A meta-analysis found no significant difference in effectiveness when comparing a lower dose of ABPP *versus* higher dose (50 *versus* 100 mL; mean difference in time to seal air leak of 1.48 days (95% CI −0.07–3.02 days), p=0.06) and considerable heterogeneity (I^2=80%, p=0.03) [32]. Furthermore, there is no relevant difference in adverse event rates, including the occurrence of empyema, between ABPP and conservative treatment with chest drainage alone [29–32]. A RCT is needed to establish definitive benefits and identify the optimal protocol.

Combination of techniques for pleurodesis

An intriguing opportunity presented by IPCs is the possibility of using the tunnelled catheter for talc administration in an outpatient setting. The IPC-PLUS trial randomised a total of 154 patients to undergo IPC placement followed by either talc slurry pleurodesis or a placebo, on an outpatient basis. Overall, talc pleurodesis was associated with a significantly higher likelihood of achieving pleurodesis than IPC alone (success rates of 43% in the talc group *versus* 23% in the placebo group; hazard ratio 2.20 (95% CI 1.23–3.92), p=0.008) [33].

Recently, the combination of thoracoscopic talc poudrage and the insertion of an IPC as a single-day case procedure is gaining prominence as an alternative for treating MPE. In 2011, Reddy *et al.* [34] described 30 cases of MPE treated through medical thoracoscopy with talc poudrage and IPC insertion in a unified procedure. The average hospitalisation duration was <2 days, with all patients reporting improvements in dyspnoea and quality of life. The pleurodesis success rate was 92%. Boujaoude *et al.* [35] reported comparable success rates of pleurodesis, with a mean hospitalisation duration of 3 days, and symptoms improved in 100% of cases (30 patients). In 2016, a case series including 29 patients undergoing the rapid pleurodesis protocol was documented. The median hospitalisation duration was similar to the aforementioned case series, while the pleurodesis success rate was slightly lower (79%) [36].

More recently, Foo *et al.* [37] published a case series encompassing 45 patients with MPE who underwent a combination of thoracoscopic poudrage and IPC insertion in an ambulatory setting. The most prevalent cancers were mesothelioma, lung and breast cancer. Overall, pleurodesis was achieved in 71.1% and 78.8% of cases at 3 and 6 months, respectively. Unlike other reported studies, this case series did not routinely admit patients following the procedure. Therefore, ∼87% of patients were discharged on the same day as the procedure [37]. To the best of our knowledge, only case series have documented this strategy to date.

The randomised thoracoscopic talc poudrage plus IPCs *versus* thoracoscopic talc poudrage only in malignant pleural effusion trial (TACTIC) is the RCT currently ongoing to examine the benefit of a combined thoracoscopy and IPC procedure. The results are awaited and are expected to provide valuable insight into the utility of this approach [38].

Indications for pleurodesis

Malignant pleural effusions

Given that the occurrence of MPE is typically associated with advanced stages of oncological disease [6, 39], the focus of MPE management should be on improving symptoms and enhancing the quality of life, thereby reducing the frequency of thoracentesis and the need for recurrent medical interventions [40].

According to the BTS guidelines for pleural disease, patients with MPE and expected expandable lung should be considered for IPC or definitive pleurodesis procedures [21]. The selection of the appropriate technique is influenced by several factors, such as the severity of symptoms, the type of tumour identified, its response to systemic therapy and the patient's performance status [21].

In general, medical pleurodesis proves effective in 68–78% of patients with MPE. Failure is primarily attributed to the presence of trapped lung and incomplete drainage of the pleural fluid [16, 41–43]. Numerous trials support the efficacy and safety of medical pleurodesis in managing MPE.

In the TIME2 trial, patients with MPE were randomly assigned to receive either talc slurry pleurodesis or an IPC [16]. Overall, dyspnoea improved in both groups without a significant difference in the first 42 days (mean visual analogue scale (VAS) dyspnoea score of 24.7 mm in the IPC group (95% CI 19.3–30.1 mm) *versus* 24.4 mm (95% CI 19.4–29.4 mm) in the talc group; difference of 0.16 mm (95% CI −6.82–7.15), p=0.96). However, a statistically significant improvement in dyspnoea for patients with IPC was observed at 6 months (mean VAS score difference between the IPC and talc groups of −14.0 mm, 95% CI −25.2– −2.8 mm; p=0.01). As expected, hospitalisation duration was significantly shorter in the IPC group (difference of −3.5 days, 95% CI −4.8– −1.5 days; p<0.001) [16].

The AMPLE trial demonstrated that patients with MPE receiving an IPC had a significantly shorter hospital stay than those undergoing talc pleurodesis (median (interquartile range) 10.0 (3–17) days in IPC group *versus* 12.0 (7–21) days in talc group, p=0.03; difference 2.92 days, 95% CI 0.43–5.84 days). However, no significant differences in breathlessness or quality of life were demonstrated [44].

In a recent open-label RCT (OPTIMUM), talc pleurodesis following IPC and chest drain were compared [45]. Overall, there was no significant difference at day 30 between IPC and chest drain regarding the improvement

of health-related quality of life and symptoms (mean intergroup difference in the baseline-adjusted global health status of 2.06, 95% CI −5.86–9.99; p=0.61) [45]. Furthermore, pleurodesis failure was significantly higher in the IPC arm than in the chest drain arm (69% *versus* 26.5% at 90 days, respectively). However, the authors acknowledged some limitations of this result. First, pleurodesis was defined as a failure in all patients in whom the IPC remained *in situ*, including those who chose not to have their IPCs removed despite successful pleurodesis. Additionally, patients in the IPC arm had larger effusions and many were under systemic therapy [45].

The ASAP trial, published in 2017, demonstrated that aggressive (daily) drainage from an IPC was superior to standard (alternate day) drainage in achieving autopleurodesis (47% *versus* 24%, respectively, p=0.003) [23].

As of now, two RCTs comparing thoracoscopic talc poudrage plus IPC *versus* thoracoscopic talc poudrage, as well as IPC (with or without talc pleurodesis) *versus* video-assisted thoracoscopic surgery in MPE, are currently ongoing [38, 41]. The results of these trials are eagerly awaited. Table 2 provides an overview of the included RCTs focusing on pleurodesis for MPE.

Nonmalignant pleural effusions

NMPEs are commonly encountered in clinical practice. Congestive heart failure (CHF), hepatic hydrothorax, renal failure and pleural infection are the leading causes of NMPE [46, 47]. Other possible causes are benign asbestos-related pleural effusion, pulmonary embolism, post-coronary artery bypass graft, drug reaction, rheumatoid effusion, trapped lung and pancreatitis [46, 47]. The aetiology is unknown in 12.5% of cases [44]. Most of these effusions are subclinical and resolve spontaneously or with treatment of the underlying condition. However, some patients require dedicated treatment.

While the management of MPE has been extensively investigated through numerous RCTs and is addressed explicitly by BTS guidelines [21], there is a notable scarcity of evidence for NMPE. Thoracentesis is the first therapeutic option to relieve symptoms and establish the diagnosis through fluid analysis. Pleural fluid evacuation generally rapidly improves patient symptoms [46]. As for MPE, depending on the degree of symptom relief and the speed of fluid reaccumulation, multiple and repeated thoracentesis may be required in NMPE. However, many reasons exist to avoid multiple thoracenteses: to reduce hospital access and minimise the risk of procedural complications [48].

Talc pleurodesis ca not be considered a definite treatment option in NMPE due to low yield and high complication rate (especially in renal and liver failure). However, in real life, this procedure is attempted in multiple cases of NMPE.

The choice of whether to perform pleurodesis in this setting is controversial and should be cautiously pondered, considering patients' preferences, and ensuring comprehension of both the short and long-term possible adverse events. Overall success rates of talc pleurodesis for NMPEs range from 75% up to 80% [49–51]. The success rate largely depends on the underlying aetiology.

In a case series of 25 NMPE from Sudduth *et al.* [50], pleurodesis *via* chest tube was achieved in 80% of the cases. Success rates were 66% among patients undergoing chronic peritoneal dialysis (four out of six), and 100% in patients with yellow nail syndrome (YNS) (n=2), chylothorax (n=6) and nephrosis (n=1).

In another retrospective and partially prospective study, the use of talc slurry was successful in 12 out of 16 patients with NMPE [49]. The population included six patients with CHF, four with liver cirrhosis, one with systemic lupus erythematosus, one with YNS, one with chylothorax and three patients with effusion of unknown origin. Pleurodesis failed in one case of CHF, one case of liver cirrhosis, the YNS case and the chylothorax [49].

Although thoracoscopic talc poudrage pleurodesis is frequently used to manage NMPE, it should be pointed out that this procedure carries significant risks and variable success rates in these cases. Steger *et al.* [51] conducted a retrospective study including 611 patients who underwent thoracoscopic talc pleurodesis between 1994 and 2003. A total of 68 cases of MPE were included; the overall success rate was 77% and the 1-year survival rate was 78.5%. However, no information regarding either the aetiology of the NMPE and the complications related to procedure is available.

Milanez de Campos *et al.* [52] described a case series of 21 NMPEs in patients receiving thoracoscopy for management of hepatic hydrothorax. The overall rate of success was of 47.6% and mortality was 38.9% at 3 months.

TABLE 2 Main randomised controlled trials focusing on pleurodesis for the management of malignant pleural effusions

Trial	Year	Country	First author [ref.]	Treatment arms	Summary of findings
TAPPS	2020	UK	Bhatnagar [13]	Talc poudrage *versus* talc slurry pleurodesis	No significant difference in pleurodesis failure at 90 days between talc poudrage and talc slurry pleurodesis (22% and 24%, respectively; OR 0.91 (95% CI 0.54–1.55), p=0.74) No differences in pleurodesis failure at 180 days (29% *versus* 29% in poudrage and slurry, respectively; OR 1.05 (95% CI 0.63–1.73), p=0.86) No differences in mean number of nights in hospital (12 *versus* 11 nights in poudrage and slurry, respectively; p=0.35) No differences in all-cause mortality at 180 days (40% and 42% for poudrage and slurry, respectively; p=0.70) Adverse events were comparable between the two arms (29% *versus* 28% in poudrage and slurry arms, respectively (OR 1.05 (95% CI 0.63–1.73), p=0.86)
IPC-PLUS	2018	UK	Bhatnagar [33]	Talc slurry pleurodesis or placebo instilled *via* IPC on an outpatient basis	Talc pleurodesis was associated with a significantly higher probability of pleurodesis (success rates of 43% in the talc group *versus* 23% in the placebo group; HR 2.20 (95% CI 1.23–3.92), p=0.008) No significant differences in effusion size and complexity, number of inpatient days, mortality or number of adverse events were found No significant excess of obstructions of the IPCs was found in the talc group
TIME2	2012	UK	Davies [16]	Talc slurry pleurodesis *versus* IPC placement alone	Dyspnoea improved in both groups without a significant difference in the first 42 days (mean VAS dyspnoea score of 24.7 mm in the IPC group (95% CI 19.3–30.1 mm) *versus* 24.4 mm (95% CI 19.4–29.4 mm) in the talc group; difference of 0.16 mm (95% CI −6.82–7.15), p=0.96) A statistically significant improvement in dyspnoea for patients with IPCs was observed at 6 months (mean VAS score difference between the IPC and talc groups of −14.0 mm (95% CI −25.2– −2.8 mm), p=0.01) Hospitalisation duration was significantly shorter in the IPC group (difference of −3.5 days (95% CI −4.8– −1.5 days), p<0.001)
AMPLE	2017	Australia New Zealand Singapore Hong Kong	Thomas [44]	Talc slurry pleurodesis *versus* IPC placement alone	Lower hospitalisation length in the IPC group (median 10.0 days (IQR 3–17 days) in IPC group *versus* 12.0 days (IQR, 7–21 days) in pleurodesis group, p=0.03; Hodges–Lehmann estimate of difference 2.92 days (95% CI 0.43–5.84 days) Fewer patients in IPC group required further pleural drainages (4.1% *versus* 22.5%; difference 18.4% (95% CI 7.7–29.2%)) No significant differences in improvements in breathlessness, quality of life or adverse events
OPTIMUM	2023	UK	Sivakumar [45]	Talc pleurodesis following IPC placement of classical chest drain	No significant difference at day 30 (mean intergroup difference in baseline-adjusted global health status of 2.06 (95% CI −5.86–9.99), p=0.61), day 60 or day 90 No significant differences in breathlessness and chest pain scores Pleurodesis failure was significantly higher in the IPC arm than in the chest drain arm (69% *versus* 26.5% at 90 days, respectively)
ASAP	2017	UK USA	Wahidi [23]	Daily drainage *versus* every other day drainage of pleural fluid *via* an IPC	Rate of autopleurodesis was higher in the aggressive drainage arm than the standard drainage arm (47% *versus* 24%, respectively; p=0.003) Median time to autopleurodesis was shorter in the aggressive arm (54 days (95% CI 34–83 days) *versus* 90 days (95% CI 70–nonestimable) Rate of adverse events, quality of life and patient satisfaction were not significantly different

IPC: indwelling pleural catheter; HR: hazard ratio; VAS: visual analogue scale; IQR: interquartile range.

As an alternative to attempting to perform a definitive pleurodesis treatment, IPC for the management of NMPE is supported by several observational studies, especially as regards congestive cardiac failure, hepatic hydrothorax or idiopathic pleuritis-related NMPE [53–56]. Overall, the rates of occurrence of spontaneous pleurodesis through IPC for NMPE range from 33% to 60% [57]. Likewise, for pleurodesis induced by sclerosing agents, the success rates of spontaneous pleurodesis depend on the underlying condition and the average daily fluid production [57].

The REDUCE trial recently demonstrated that IPCs and standard care with repeated aspiration for NMPE were comparable in terms of difference in breathlessness over 12 weeks. Furthermore, repeated aspiration was associated with fewer complication [27].

Majid *et al.* [58] analysed a cohort of 36 patients with CHF-related NMPE and reported a pleurodesis rate of 80% through talc poudrage thoracoscopy, compared to 25% in the group receiving with IPC alone.

As regards hepatic hydrothorax, pleurodesis rates after IPC placement range from 15% to 28% across studies [56, 59, 60]. Notably, the main concern related to IPC in these patients is the risk of infection and the high mortality related to this complication [56, 59, 60].

Pneumothorax

The treatment goals of both primary spontaneous pneumothorax (PSP) and secondary spontaneous pneumothorax (SSP) consist of evacuation of air from the pleural space, closure of the pulmonary breach, relief of symptoms and preventing recurrence [61] (figure 3).

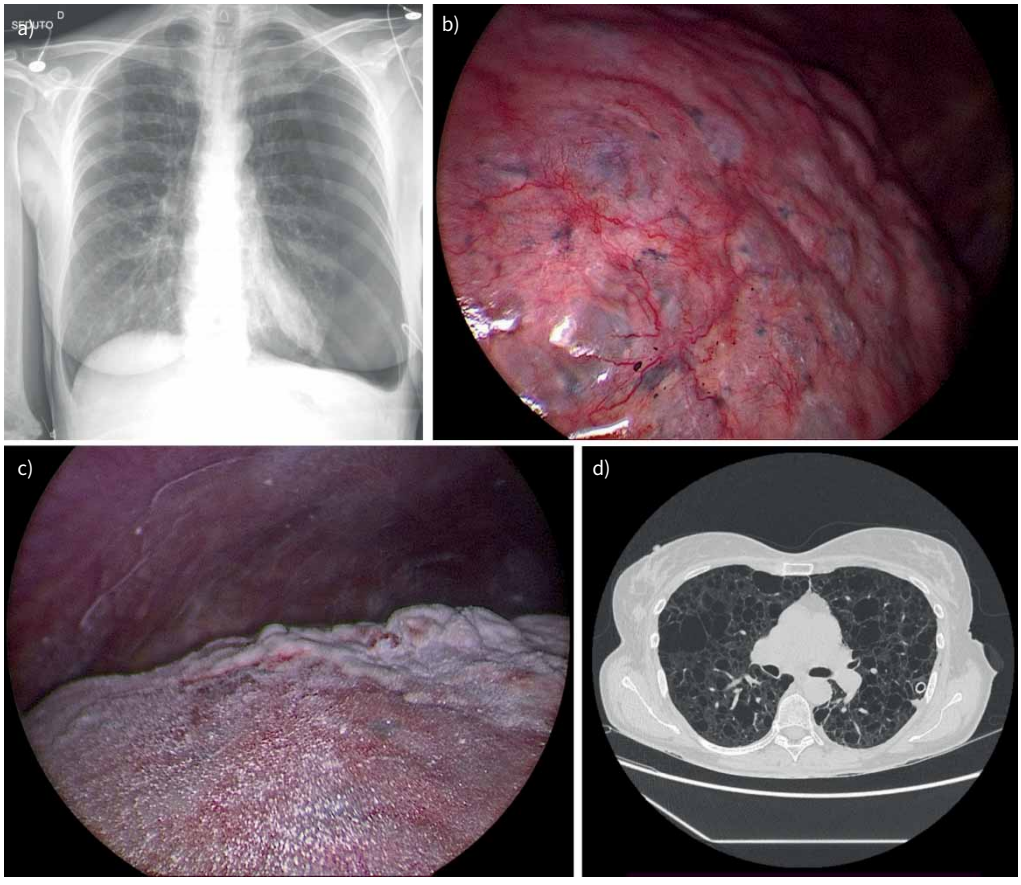

FIGURE 3 Case of secondary spontaneous pneumothorax in a patient suffering from lymphangioleiomyomatosis managed by medical thoracoscopy and talc poudrage. a) Chest radiograph at diagnosis showing a massive left pneumothorax. b) Direct endoscopic view of the pleural cavity and visceral pleura with subpleural cystic lesions. c) Deposition of sterile talc at the end of the insufflation. d) Final computed tomography result with chest drain clamped in place showing complete lung expansion and achievement of pleurodesis.

Conservative management is recommended for the treatment of asymptomatic or minimally symptomatic PSP [20]. When treatment is required, the choice of the optimal technique depends on the patient's symptoms, the size of the pneumothorax and the persistence of air leakage [62–65]. In general, simple needle aspiration or chest tube drainage are the first-line procedures [20].

According to the European Respiratory Society (ERS) statement on PSP, a definitive procedure aimed at preventing the recurrence of PSP should be proposed in some specific cases, including recurrent PSP, air leak for >35 days, bilateral pneumothorax, hemopneumothorax and professions at risk [61]. In addition, tension pneumothorax and SSP need definitive treatment since they are associated with a higher risk of complications [61].

Regarding the choice of the pleurodesis technique, according to the Société de Pneumologie de Langue Française/Société Française de Médecine d'Urgence/Société de Réanimation de Langue Française/Société Française d'Anesthésie et de Réanimation/Société Française de Chirurgie Thoracique et Cardio-Vasculaire guidelines for managing patients with PSP, a minimally invasive procedure should be preferred [66].

Pleurodesis, either chemical or mechanical, is also recommended to prevent the recurrence of SSP. In particular, the BTS guidelines suggest the surgery as a first-line approach for the treatment of those patients with SSP at risk of dying in the case of recurrence (*e.g.* those presenting with tension pneumothorax or those in high-risk occupations) [20].

However, the ERS statement affirms that both chemical pleurodesis and a surgical approach may be efficiently proposed without significant differences in terms of recurrence risk [61]. However, there is a lack of conclusive data comparing the efficacy and safety of medical and surgical pleurodesis in managing recurrent SSP [67].

When persistent air leakage is present, the vast majority of studies agree that surgical intervention should always be preferred to reduce the length of hospitalisation and the chances of recurrence [20]. When surgery is not feasible, ABPP or endobronchial therapies are generally preferred [20].

The majority of RCTs on pneumothorax focus on talc poudrage pleurodesis. A RCT comparing talc poudrage to drainage alone for PSP reported recurrence rates at 5 years of 5.1% in the talc poudrage arm *versus* 34% in the drainage group [68].

Talc slurry pleurodesis *via* chest drainage may be attempted in patients who are unable or unwilling to undergo thoracoscopy. However, the consensus among experts is that talc slurry is less effective than talc poudrage for pneumothorax, primarily due to the low probability of reaching the apical lung area [69]. Interestingly, no RCT specifically investigated talc slurry *versus* poudrage for this indication.

Complications of medical pleurodesis

Although medical pleurodesis is generally considered a safe procedure, it can be associated with certain complications, the likelihood of which depends on the chosen technique. A meta-analysis of the largest prospective studies found that, although the probability of experiencing complications following talc slurry or talc poudrage is very similar, the absolute number of complications is higher in the talc poudrage group [20].

In the case of talc slurry pleurodesis, the most common adverse events are pain and fever, which typically follow the treatment as signs of ongoing inflammation [13]. Empyema might also occur in some cases. A retrospective study demonstrated that the risk of empyema is higher in patients with prolonged drainage time and those who used antibiotics prior to talc slurry pleurodesis [70].

Thoracoscopic talc poudrage has been associated with pain, fever, residual pneumothorax and infections. Subcutaneous emphysema, prolonged drainage needs, prolonged air leakage and thromboembolism have also been described [71].

Rarer complications of talc poudrage pleurodesis include acute respiratory distress syndrome, lung injury, re-expansion pulmonary oedema, pulmonary embolism, cardiac arrhythmia, arterial hypotension and renal dysfunction [71].

The use of IPCs is associated with complications in approximately 10–20% of cases [72–74]. Some complications are not unique to IPCs and may occur in any procedure involving the placement of a small-

bore catheter in the pleural space, such as skin infection, bleeding, lung injury and pneumothorax [53, 75]. Certain complications, however, are specific to IPC use. Among these, pleural infection incidence varies from 4.9% to 12% [53, 73, 76]. Generally, when the infection is promptly recognised, it can be effectively managed with antibiotics and removal of the IPC is typically unnecessary [53, 73, 76, 77]. A comprehensive, real-life study involving >1000 patients with MPE treated with IPCs has been published [77]. Overall, nearly 5% of the patients developed an IPC-related pleural infection and 95% of them were successfully treated solely with antibiotic therapy. Notably, 74% of the infected patients were hospitalised, with 62% receiving at least one dose of intravenous antibiotic therapy. However, no difference in the healing success rate was observed between those treated with only oral therapy and those receiving intravenous antibiotics [77].

Catheter tract metastasis is another potential complication, particularly prevalent in patients with mesothelioma [76]. Reported incidences of catheter tract metastasis range from 5% to 10% [75, 78], with the highest rates observed in patients with mesothelioma.

IPC-related spontaneous pleurodesis can also induce septations and loculations within the pleural space, impeding effective fluid drainage and contributing to pleurodesis failure. This complication occurs in up to 14% of IPC insertions [79], especially with mesothelioma [77, 80]. Recently, a case series showed that prior talc pleurodesis does not increase the risk of loculations in subsequent IPC use [25].

Some complications can also be associated with the talc type used during the pleurodesis attempt. It is well known that graded talc with medium or large particles is associated with lower systemic side effects rates [78], as small particle-size talc can be systemically absorbed through parietal lymphatics and subsequently induce systemic inflammation [81]. *In vivo* studies have shown that pleurodesis with nongraded talc (talc including particles <10 μm) is associated with worsened gas exchange (mean±SD oxygen gradient change with nongraded talc 2.17±1.74 kPa (16.3±13.1 mmHg) *versus* graded talc 0.72±2.46 kPa (5.4±18.5 mmHg); difference 1.45 kPa (95% CI 0.2–2.7 kPa), p=0.03) and significantly higher rates of post-procedure fever (41% of patients receiving mixed talc *versus* 4% of those receiving graded talc; difference 37% (95% CI 15–59%), p<0.001) [81]. Notably, marked heterogeneity exists in the physical characteristics of the talc preparations used worldwide [82].

Conclusions

Symptomatic and recurrent MPE, NMPE and pneumothorax continue to pose challenges for both patients and physicians in clinical practice. Among the available management options, definitive pleurodesis techniques allow the patient not to have to keep permanent or long-term devices in place. However, IPCs alone or as part of a combination of techniques provide an increased likelihood of pleurodesis, and appear to be a safe and cost-effective strategy. Despite the knowledge gained from available studies, additional data are needed to comprehend the efficacy of these treatments in order to maximise patient morbidity reduction and symptom control while achieving the best therapeutic outcome.

Key points

- Medical pleurodesis involves inducing inflammation to create adhesions between the parietal and visceral pleura. The ideal sclerosing agent remains elusive, but talc, according to current evidence and guidelines, stands out as the safest and most effective option. Talc pleurodesis demonstrates success rates ranging around 80%, surpassing alternative agents in meta-analyses.
- Talc slurry and talc poudrage are techniques for talc administration in pleurodesis. Recent trials challenge the superiority of talc poudrage, revealing its comparable success rates with talc slurry but higher complication rates.
- IPCs offer outpatient management with intermittent drainage, especially in MPEs. IPCs exhibit variable pleurodesis rates (16–65%), making them especially suitable for patients with pleurodesis failure with other techniques or limited life expectancy. IPCs look promising in NMPEs, although success rates depend on the underlying condition.
- ABPP, employing the patient's blood for pleurodesis, is effective in persistent postoperative air leak. Debate exists over the optimal blood volume but current evidence does not favour larger volumes. ABPP efficacy and adverse event rates require validation through future RCTs.
- Combining IPCs with talc pleurodesis enhances success rates in MPE, as seen in the IPC-PLUS trial. Single-day procedures involving thoracoscopic talc poudrage and IPC insertion offer potential for effective pleurodesis.
- Complications, though generally rare, vary by technique. Talc poudrage may have higher absolute complication rates than talc slurry. IPCs are associated with 10–20% complication rates, with infections being the most common. Talc characteristics influence complications, with nongraded talc associated with higher systemic side-effects.

Data availability: Materials are available upon reasonable request.

Consent for publication: Informed consent was obtained from all patients regarding the publication of data in anonymised form.

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