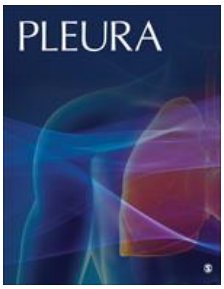

Review
Talc Pleurodesis in Pleural Disease

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Abstract: Since its first medical use in 1935, talc has become the most frequently used sclerosing agent for chemical pleurodesis. This review article encompasses all topics related to talc pleurodesis, from basic science to indications, contraindications, techniques of administration and potential complications.

Key words: talc, chemical pleurodesis, malignant pleural effusion, talc poudrage

Raw Talc

Broughton Mine
St-Pierre-de-Broughton, Quebec, Canada

Courtesy of The Arkenstone
www.irockscom

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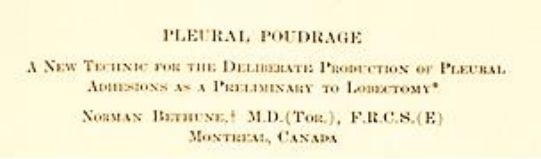
Introduction

In his 1935 landmark article in the Journal of Thoracic Surgery[1], Norman Bethune reported the first successful use of talc to establish pleural adhesions in humans and described his novel thoracoscopic approach using a return-air powder blower for talc insufflation.



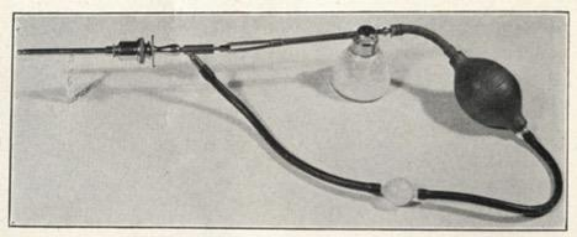
PLEURAL POUDRAGE

A New Technic for the Deliberate Production of Pleural Adhesions as a Preliminary to Lobectomy*

Norman Bethune,† M.D.(Tor.), F.R.C.S.(E)
Montreal, Canada

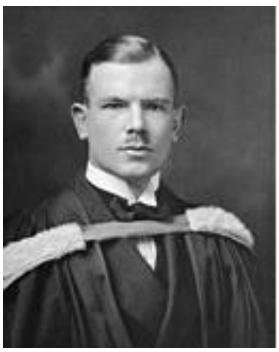
Norman Bethune's original 1935 article[1].

His goal was to achieve selective pleural symphysis prior to pulmonary resection, as it was thought that anchoring a non-resected lobe would remove the main obstacles to successful lobectomy, an approach described by Samuel Robinson in 1917[1, 2]. In 1958, twenty-three years after Bethune's original article, J.S. Chambers reported his first successful use of talc for the palliative treatment of malignant pleural effusion (MPE)[3].



Bethune's return-air pleural powder blower, inserted through the air-tight cannula of a Jacobeus-Unverricht thoracoscope[1].

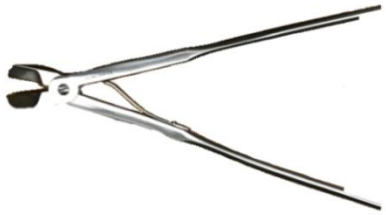
In this review dedicated to talc pleurodesis we first pay homage to Norman Bethune, whose breakthrough procedure established the foundation of modern chemical pleurodesis in the management of pleural disease. His legacy is one of a pioneer in thoracic surgery and military medicine, as well as a humanitarian.



Norman Bethune
1890-1939 *

His accomplishments may however have been overshadowed by his unconventional personality, iconoclastic thinking, and public affiliation with Communism. Born in 1890, in Ontario, Canada, Henry Norman Bethune was to become, as Dr. Alexander J. Walt wrote in his 1983 tribute, the "best-known physician in the world"[4]. During his childhood, Bethune was deeply inspired by the accomplishments of his own grandfather and namesake, Norman Bethune (1822-1892), who served as a military surgeon and worked alongside social activist Henry Dunant, founder of the International Red Cross[5, 6].

Bethune, a World War I veteran, began his career in Michigan before settling in Montreal where he led a prolific career as a thoracic surgeon[4, 7, 8]. He authored numerous scientific publications and developed many surgical procedures and instruments[9], including talc insufflation for pleurodesis and the Bethune Rib Shears which are still used today.



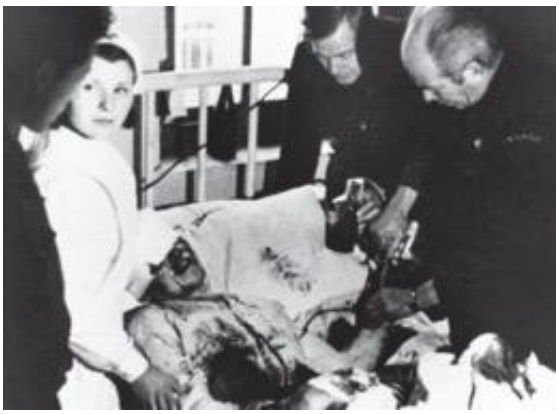
Bethune Rib Shears
Image by
Mathieu Marcoux, MD

Norman Bethune contracted tuberculosis in 1926. An artificial pneumothorax, the only therapeutic option available prior to the discovery of streptomycin in 1943, was induced to treat his tuberculosis infection[7]. Bethune himself would later become an advocate of this therapeutic approach and perform collapse therapy on patients afflicted with tuberculosis[10]. His personal experience with tuberculosis also led him to reconsider the impact of lower socioeconomic status on diseases. As economic and public health conditions deteriorated during the Great Depression, Bethune grew critical of the deficiencies in the Canadian health care system and became an advocate for more accessible and free healthcare for all.

Edward Archibald, Surgeon-in-Chief at the Royal Victoria Hospital (Montreal, Canada), assisted by Norman Bethune, performing the first pneumonectomy using individual ligation of hilar vessels and bronchus (1933). The patient, a 31-year-old man with left upper lobe sarcoma, was the fourth patient to undergo successful pneumonectomy[11, 12]. *

* Norman Bethune Images Courtesy of Library & Archives of Canada

Bethune later became a member of the Canadian Communist Party and joined the leftist Republic Loyalists in the Spanish Civil War against Franco's Nationalists. There, Bethune created the first known mobile blood transfusion service, the "*Servicio Canadiense de Transfusion de Sangre Al Fiente*", to transport blood supplies to the battlefront[6].



Bethune (*right*) with medical team assisting a soldier and transfusing blood during the Spanish Civil War[7].*

In 1938, following the outbreak of the Second Sino-Japanese war, Bethune left for China where he met Mao Zedong and volunteered in the Chinese Communist 8th Route Army. Bethune performed surgery on wounded soldiers and civilians, trained doctors and nurses, and actively contributed to the renovation of hospital facilities. Bethune died in 1939, at age 49, of infectious complications from a finger injury which he sustained while he was operating. Following his death, Norman Bethune was made a national hero in China. Mao Zedong wrote a eulogy for Bethune, the only one to have been written by him for a foreigner.

Talc Properties, Commercial Preparations and Mechanisms of Pleurodesis

Chemical and Physical Properties of Talc

Talc is a natural mineral composed primarily of hydrated magnesium silicate ($Mg_3Si_4O_{10}(OH)_2$). When extracted from mining sites, talc also contains calcium, magnesium, iron and variable amounts of mineral contaminants, such as chlorite, dolomite, calcite and quartz.

Talc particles by scanning electron microscopy (magnification 1,500).

Comparative Mean Sizes:

U.S. talc preparation 10 μm.

French talc preparation 30 μm.

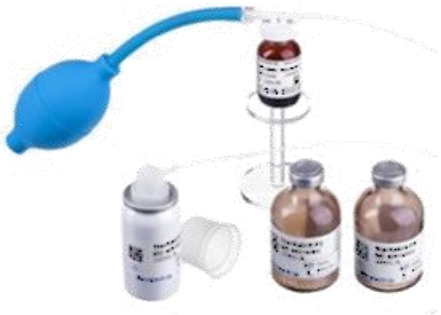
FDA-approved industrial talc is carefully selected to remain asbestos-free. Sterilization is performed by gamma irradiation. When processed, pulverized talc is graded according to the size of its particles. Smaller-size particles (< 5-10 μm) are removed to reduce systemic absorption and dissemination through the pleural lymphatic system. European medical talc particles have been found to have larger mean size than American talc (10 vs 30 μm). [20]

Courtesy Johnson Historical Society
Johnson, Vermont

Animal and human studies have shown that the lymphatic channels drain pleural fluid via stomas with a median diameter of 8-10 μm located on the mesothelial layer of the parietal pleura[13, 14, 15]. Smaller talc particles have been shown to increase pleural and systemic inflammatory responses and may raise the risk of related respiratory complications[16, 17, 18, 19]. Properties of talc preparations differ by source location, with variation in the mineral contaminant quantity and particle size distribution[20]. Pleural fluid content also appears to influence the distribution of talc particle size. Using dynamic light scattering, *Gilbert et al.* found that exposure to a protein rich environment, either in bovine serum albumin or human pleural fluid, led to larger aggregated talc particles (> 100 μm)[21].

Commercial Talc Preparations

Commercial talc preparations for pleurodesis come in the form of sterile powder in a glass vial or as an aerosol spray canister. Steritalc® and Steritalc® Spray are produced by Novatech SA in France. FDA approved Steritalc® vials are offered in 3 doses (2, 3 & 4 g), while the aerosol formulation Steritalc® Spray is currently available only in Europe. In comparing their physical characteristics, one study[20] showed that talc particles in the preparations from France (talc supplied by Luzenac Europe SAS, used in the Steritalc®) had a mean median diameter of 31.3 µm (10^{th} and 90^{th} percentile of 10.5 µm and 90 µm, respectively).

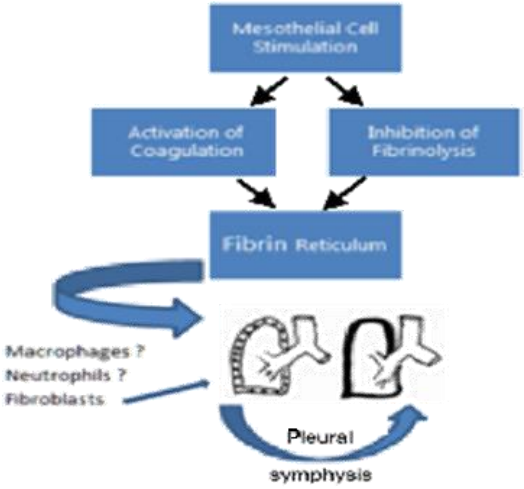


Commercial talc preparations for pleurodesis are provided in an aerosol spray canister (*bottom left*; available only in Europe) and sterile talc powder in a glass vial. Steritalc® is offered in doses of 2, 3 & 4 g. The Talcair™ blower *(top)* is compatible with the talc vial of 3 g.

Image courtesy of Novatech SA, France.

Mechanism of pleurodesis

The goal of talc administration is to provoke an adequate pleural inflammatory response through the release of pro-inflammatory cytokines that leads to pleural adhesions and ultimately complete pleural symphysis with obliteration of the pleural space. The underlying mechanisms are incompletely understood[22, 23]. Pleural mesothelial cells are thought to act as precursors to the process of pleurodesis through the release of inflammatory mediators and the shifting of the pleural coagulation-fibrinolytic balance. Stimulation of mesothelial cells leads to the activation of the coagulation cascade and the inhibition of the pleural fibrinolytic activity, a key factor in the formation of fibrin adhesions, recruitment of fibroblasts and collagen synthesis[22, 23, 24].



Activation of the coagulation cascade with inhibition of fibrinolysis by activated mesothelial cells is thought to be a key mechanism leading to pleurodesis with the use of sclerosing agents. Plasminogen Activator Inhibitor inhibits fibrinolysis[23].

Fibroblast growth factors, such as basic fibroblast growth factor (bFGF), transforming growth factor-β (TGF-β) and platelet-derived growth factor (PDGF), have been found in the pleural fluid of patients who received sclerosing agents[22, 25]. *Antony et al*[25] found higher levels of bFGF in the pleural fluid of patients with successful pleurodesis than in those who did not respond to treatment. Results also showed an inverse correlation between bFGF levels and tumor involvement of the pleura. Thus, talc will most likely be more efficient when applied on a pleural surface with a preserved mesothelial layer and limited neoplastic involvement. This hypothesis has also been proposed to explain why lower talc doses are required to achieve pleurodesis in recurrent pneumothorax than in MPE[2].

Indications for Chemical Pleurodesis

Table 1. Indications for Chemical Pleurodesis
Recurrent symptomatic malignant effusion
Recurrent symptomatic non-malignant pleural effusion
Recurrent primary and secondary spontaneous pneumothorax
Persistent air-leak (alveolo-pleural fistula)

Recurrent Symptomatic Malignant Pleural Effusion (MPE)

Recurrent symptomatic MPE despite repeated thoracentesis remains the most frequent indication for chemical pleurodesis[26]. Successful pleurodesis rates with talc in MPE has been reported in up to 93 % of cases[27].

Clive et al. developed a prognostic scoring system, the LENT score, to predict survival at 1, 3 and 6 months among patients with MPE[28]. The LENT score incorporates the ***L***DH level, ***E***astern Cooperative Oncology Group (ECOG) performance score, blood ***N***eutrophil to lymphocyte ratio, and ***T***umor type (**Appendix Table 1**). Patient prognosis can influence the decision whether to perform talc pleurodesis for MPE. The application of this scoring system in guiding the management of recurrent MPE remains to be further defined.

Surgical options, such as pleurectomy and mechanical pleurodesis through pleural abrasion, will not be covered. They remain more invasive and are now rarely performed given the well-established efficacy of chemical pleurodesis and IPCs in palliating symptoms. As the presence of MPE comes with a poorer prognosis, goals of care should be personalized and centered on symptom palliation, quality of life improvement, reducing MPE-related hospitalization time and re-interventions.

Talc versus Other Sclerosing Agents

Although talc remains the most used and studied agent for chemical pleurodesis, other agents with variable efficacy can also be employed to achieve chemical pleurodesis. These include tetracycline derivatives (doxycycline being the most studied), silver nitrate, povidone iodine, bleomycin, mepacrine and *Corynebacterium parvum*[27, 29, 30, 31]. However, few trials have compared these agents directly to talc. One randomized trial of 60 patients with MPE compared the efficacy and safety of silver nitrate 0.5% with talc slurry (5 g) [32]. At 30 days, effective pleurodesis was shown in 96% of subjects in the silver nitrate group and 84% in the talc group. However, the difference between both study arms was not found to be significant. As the authors reported, results must be interpreted in light of the small sample size and significant loss to follow-up. In a review by Bucknor et al.[33] which addressed specifically the efficacy of silver nitrate, this agent was shown in three studies to provide satisfactory results in MPE by achieving pleurodesis in 89-96% at 30 days. Two meta-analyses compared the efficacy of talc to the other sclerosing agents. *Tan et al.*[30] showed that talc led to fewer recurrences of MPE when compared to bleomycin and tetracycline. In a 2016 network meta-analysis[31], talc poudrage was found to be more effective in achieving pleurodesis than other sclerosing agents, including doxycycline, bleomycin, mepacrine and iodine. However, interpretation of those results remains limited by the significant level of heterogeneity and high risk of bias present in the included studies. More evidence on other sclerosing agents is required to compare their efficacy and safety to talc. The ideal sclerosing agent should provide efficacy superior or at least similar to talc, without carrying risks of serious complica-

tions , including acute respiratory failure and ARDS. Although rare, those complications have been described with talc pleurodesis and will be later reviewed.

Talc Pleurodesis versus Indwelling Pleural Catheter (IPC)

Insertion of an IPC can be considered as an alternative or even used in combination with talc pleurodesis. The main advantage of the IPC is that it is performed as an outpatient procedure and remains the procedure of choice in the absence of lung re-expansion following complete fluid drainage. In our experience, when lung re-expansion is less than 90%, chemical pleurodesis will most likely be unsuccessful and is not attempted. However, when lung re-expansion over this threshold is present, both options can be considered[34, 35]. Rates of spontaneous pleurodesis with IPC (cessation of pleural fluid drainage) in clinical trials ranged from 24% to 51%[36, 37, 38, 39, 40]. Four randomized-controlled trials (TIME2, AMPLE, NVALT-14 and CALGB 30102[38, 39, 41, 42]) compared IPC insertion with talc pleurodesis in MPE (**Table 2**). Talc slurry was used in all studies. Hospitalization days (all-cause and effusion-related) and need for further ipsilateral pleural interventions were reduced in the IPC group. The two approaches provided similar improvement in quality of life and dyspnea, with the exception of the TIME2 trial which showed a small, but statistically significant improvement in the Visual Analog Scale for dyspnea at 6 months in favor of IPC (mean difference -14.0 mm, 95% CI, -25.2 to -2.8; p=0.01)[38]. In contrast, adverse events occurred more frequently in the IPC group. Reported IPC-related adverse events included bleeding, blockage, displacement, infection (skin or pleural space) and chest pain. A pooled analysis from the four trials showed a fivefold increase in the risk of cellulitis with the use of IPCs (RR=5.83, 95% CI = 1.56-21.87) and a trend for an increased risk of pleural infections (RR = 3.32, 95% CI = 0.82-13.44)[34]. From a cost analysis perspective, several studies have shown IPCs to be more cost-effective than talc pleurodesis in patients with MPE and limited survival – defined as less than 6 weeks (*Olden et al.*)[43], 14 weeks (*Penz et al.* and *Olfert JA et al.*, who also found increased costs when nursing time for drainage was greater than 2 hours per week)[44, 45], 3 months (*Puri V et al.*)[46] and 6 months (*Shafiq et al.*)[47].

The accumulating evidence now provides a better understanding of the respective advantages and disadvantages of IPC and talc pleurodesis on patient-centered outcomes. This allows a more personalized approach in the management of MPE, based on each patient's preferences, and with the goal of improving quality of life. Furthermore, the silver nitrate coated IPC has shown promise in preliminary animal and human studies[48, 49, 50]. As the first drug-eluting IPC, it could have the potential to replace standard pleural catheters by adding a chemical pleurodesis effect with its slow-release silver nitrate coating. Results from the multicenter, randomized controlled trial SWIFT should provide further evidence of its efficacy and safety profile when compared to the conventional approved IPC.

Table 2. Randomized-controlled trials comparing IPC insertion with talc pleurodesis for the management of MPE.
LOS = length of stay; IQR = interquartile range; IPC = indwelling pleural catheter; TP = talc pleurodesis; QOL = quality of life.

	Sample size	Months Follow-up	Talc Form	All-cause hospital LOS *days, median IQR]*	Effusion-related hospital LOS *days, median [IQR]*	Pleural Re-intervention	Adverse Events	Improve-ment in dyspnea & QOL
AMPLE (2017)	146	12	Slurry	*IPC < TP* 10 (3-17) vs 12 (7-21)	*IPC < TP* 1 (1-3) vs 4 (3-6)	*IPC < TP* 4 vs 22%	*IPC > TP* 30 vs 18%	*IPC = TP*
NVALT-14 (2017)	94	6	Slurry	*IPC < TP* 2 vs 7	*Not reported*	*IPC = TP** 16 vs 33%	*IPC = TP***	*IPC = TP*
TIME2 (2012)	106	12	Slurry	*Not reported*	*IPC < TP* 1 (0-3) vs 4.5 (2.5-7.5)	*IPC < TP* 6 vs 22%	*IPC > TP* 40 vs 13%	*IPC > TP* (dyspnea) at 6 months
CALGB 30102 (2012)	67	1	Slurry	*Not reported*	*Not reported*	*Not reported*	*IPC > TP****	*IPC > TP* (dyspnea) in subjects with poor lung expansion

* Mean number of interventions lower in the IPC group in the intention-to treat analysis (0.5 vs 0.2, p=0.05).
** Comparisons made for each complication type.
*** Overall complication rate not reported

Combination of Talc Pleurodesis and IPC

A combination of IPC insertion and talc pleurodesis is an approach showing increasing interest. In patients without significant lung entrapment, IPC insertion followed by talc slurry administration via the catheter was shown to be more effective in achieving successful pleurodesis than IPC alone[40]. Such results were shown in the IPC-Plus trial, which had a successful pleurodesis rate at 35 days of 43% in the IPC plus talc group compared to 23% in the IPC with placebo group. This difference was maintained at 70 days (51% vs 27%). Although comparative trials are currently lacking to address the benefits of combining talc poudrage with IPC insertion during medical thoracoscopy, results obtained from two small prospective studies did show satisfactory pleurodesis rates with a shorter hospital length-of-stay compared to historical controls of talc insufflation alone[51, 52]. No cases of catheter blockage were reported. In a retrospective study of 36 patients with refractory symptomatic pleural effusions due to congestive heart failure, *Majid et al.*[53] also found a higher pleurodesis success rate and shorter duration of catheter placement when talc slurry was combined to IPC insertion, as compared to IPC alone. Those promising results should prompt future research to delineate the impact of combining chemical pleurodesis with IPC insertion on patient-centered outcomes and health-care resource utilization, including the need for pleural re-interventions and hospital length-of-stay.

Impact of Pleurodesis in Patients Receiving Mutation-Targeted Therapy or Immunotherapy

The role of chemical pleurodesis in MPE warrants reassessment in the era of mutation-targeted therapies and immunotherapy. These treatments provide longer progression-free survival (PFS) than conventional chemotherapy alone in stage IV lung cancer, as well as prolonged disease control in a subset of patients[54, 55, 56]. However, in the setting of MPE, there is limited evidence comparing their efficacy to pleurodesis or IPC insertion in reducing recurrences. In one observational cohort study of 34 patients positive for epidermal growth factor receptor (EGFR) mutation receiving tyrosine-kinase inhibitors (TKI), no significant difference was found in the recurrence-free period of MPE with or without talc pleurodesis[57]. Although such results must be interpreted in light of the study design and limited sample size, further data will be required to address pleurodesis in patients receiving TKIs or immunotherapy.

Recurrent Symptomatic Non-Malignant Pleural Effusion

Successful use of talc has been described for symptomatic and refractory non-malignant pleural effusions (NMPE), but with less robust evidence than for MPE. Three case series reported 75 and 80% success rates in chemical pleurodesis for NMPE[58, 59, 60]. Non-malignant conditions in which talc has been used include heart failure, hepatic hydrothorax, nephrotic syndrome, chronic ambulatory peritoneal dialysis, chylothorax, systemic lupus erythematosus, and yellow nail syndrome[60]. *Sudduth et al.*[60] caution that talc use in recurrent NMPE should only be considered when the following criteria are met:

- *Symptomatic pleural effusion;*
- *Pleural fluid recurrence despite maximal treatment of the underlying condition;*
- *Lung re-expansion following drainage.*

The potential adverse effects of talc, including respiratory failure, must be considered. Reported complications related to talc administration will be reviewed later. Although uncommon, these have undesirable consequences in already frail patients with a significant underlying comorbidity. Alternative methods include insertion of a tunneled pleural catheter, mechanical pleurodesis, or other sclerosing agents for chemical pleurodesis. However, the effectiveness of non-talc agents in the setting of NMPE is not well-defined in the literature.

Recurrent Primary and Secondary Spontaneous Pneumothorax

Chemical pleurodesis can be considered for recurrent primary spontaneous pneumothorax (PSP; pneumothorax without underlying lung disease) and secondary spontaneous pneumothorax (SSP; pneumothorax in the setting of an underlying lung disease). In this population, careful consideration should be given to the appropriate approach for pleurodesis. A surgical approach with VATS is safe and effective. During a single procedure, the diagnosis and resection of bullae can be accomplished along with mechanical pleurodesis by abrasion of the parietal pleura or with partial parietal pleurectomy[61, 62, 63]. Agents such as talc can also be used during the procedure. VATS has been shown to be highly effective in preventing pneumothorax recurrence. In *Cardillo et al.'s* retrospective study of 432 patients with PSP who underwent VATS, recurrence rate was 4.4%[62]. In a retrospective study by *Shaikhrezai et al.*, 569 patients who underwent VATS for pneumothorax, freedom from further surgery at 10 years was 97.8% for PSP and 96.1% for SSP[63].

Chemical pleurodesis can be achieved with a sclerosing agent administered alone via a chest tube or by insufflation during medical thoracoscopy. Both routes have been applied in the prevention of pneumothorax, although talc poudrage via medical thoracoscopy is more frequently utilized and reported[64]. Both methods

present advantages over VATS. First, they avoid the need for general anesthesia, an important consideration in a frail patient. Second, they offer satisfactory results. Some studies on reducing pneumothorax recurrence have demonstrated similar results to VATS[65, 66, 67, 68]. There is also controversy over the impact of bullectomy on reducing pneumothorax recurrence rates[69, 70, 71, 72]. However, safety concerns arise from serious, although infrequent, talc-related toxicities and adverse events, which will be reviewed later. For these reasons, some experts favor the use of alternative agents such as tetracycline derivatives[73, 74, 75, 76].

We share the recommendations provided by the ACCP and BTS guidelines and expert consensus for prevention of recurrent pneumothorax, which favor a surgical approach by VATS[77, 78]. Chemical pleurodesis alone is an acceptable alternative when based on surgical risk or patient preference[74, 75]. Based on the available evidence, the decision between these approaches should be based on factors including surgical risk, patient preference, high-risk professions and activities, e.g., airplane pilots and deep-sea divers, need for bullectomy (although its impact on recurrence remains controversial), as well as center expertise.

Persistent Air-Leak (PAL)

Persistent air-leak (PAL), defined as an air-leak lasting more than five days, is associated with prolonged chest tube duration, longer hospital length-of-stay, and increased morbidity[79]. This phenomenon occurs when there is communication between the pleural space and alveoli (alveolo-pleural fistula [APF]) or bronchus (broncho-pleural fistula [BPF]). PAL may be encountered in settings such as lung surgery, spontaneous pneumothorax (most commonly in the presence of an underlying lung disease), chest trauma, barotrauma from mechanical ventilation, pleural procedures, pulmonary infections (especially necrotizing pneumonia) and lung malignancy[79, 80]. Management is based upon the location of the fistula (APF or BPF), its cause, as well as the patient's preferences and surgical risk. In our opinion, chemical pleurodesis should only be considered for PAL in the setting of APF, when the following criteria are met:

- *Lung re-expansion is present (≥ 90%);*
- *No suction is required (water seal);*
- *Patient is not a candidate for VATS;*
- *Patient is not a candidate for intrabronchial valves (if resource and expertise available).*

In a case-control study by *Liberman et al.*[81], 78 PALs were identified among 1,393 patients (5.6%) who underwent lobectomy or bilobectomy by thoracotomy. Forty-one patients with PAL and APF received a sclerosing agent, mostly talc. Forty cases (98%) were successfully managed. Although such results are encouraging, the indication and effectiveness of talc pleurodesis in this setting will need to be further confirmed by trials comparing this approach to alternative non-surgical interventions. Among those, autologous blood patch pleurodesis and intrabronchial valves (Spiration® Valve System) are the best studied and have shown promising results[82, 83, 84].

Administration of autologous blood into the pleural space, also known as 'blood patch' or 'blood pleurodesis,' to treat prolonged air-leak was first been described in 1992 by *Dumire et al.*[85]. The underlying mechanisms remain questioned. However, it is believed that the instillation of blood into the pleural space may patch the air-leak through coagulation and may also lead to pleurodesis[86]. Optimal blood quantity to achieve satisfying results appears to be 100 cc and may be repeated as needed in the following days if the PAL persists[86, 87]. In a review of 10 publications by *Chambers et al.*[82], overall success in treating PAL following lung resection surgery and pneumothorax has been reported to be 92.7% and 91.7%, respectively. Although its efficacy has not been directly compared to talc,

autologous blood patch offers advantages, including its accessibility and lower cost. In contrast with talc and other agents used for chemical pleurodesis, lung re-expansion is not required; however, suction must be weaned and water seal well tolerated. Adverse events also remain a concern and will need to be further addressed. *Chambers et al.* reported complication rates from 0 to 18% among studies, including fever, pleural effusion and empyema[82]. In a systematic review by *Rinaldi et al.*[86], empyema was the complication most frequently reported.

The Spiration® intrabronchial valve, initially designed for endoscopic lung volume reduction in emphysema, has been approved by the FDA with a humanitarian device exemption in the setting of APF with PAL. In a retrospective multicenter study of 26 patients, *Majid et al.*[84] showed an increased success rate of PAL resolution with intrabronchial valves in the absence of collateral ventilation – defined as a fissure at least 90% complete on computed tomography (CT). Thus, intrabronchial valves should only be considered in the presence of intact fissure integrity between the target lobe and its adjacent lobe.

In the absence of proper comparative trials, the selection of a specific intervention versus conservative management (observation with chest drainage device or Heimlich valve) relies on various factors as summarized in **Tables 3 & 4.** A summary of the management options for APF with PAL can also be found in the Appendix (**Figure 1**).

Table 3. Persistent Alveolo-Pleural Fistula Management Considerations	
Air-leak etiology	Lung re-expansion
Comorbidities, surgical risk	Collateral ventilation (fissure integrity on CT)
Air-leak severity, ability to tolerate off suction	Local resources & experience

Conservative management		Chest Drainage Device — Heimlich Valve
Video-Assisted Thoracoscopy		Privileged approach in PSP and SSP based on surgical risk
Non-surgical options	Chemical Pleurodesis	Passive drainage (water seal) — Lung re-expansion 90%
	Autologous Blood Patch	Pleurodesis with passive drainage (water seal) Concern for adverse events, e.g., empyema
	Intrabronchial Valves	Fissure integrity 90% on CT

Table 4 Therapeutic options are available for APF with PAL. This figure summarizes the principal factors in the selection of personalized and optimal management, therapeutic or conservative. Talc is the most commonly used and studied sclerosing agent for APF with PAL .

The presence of incomplete lung re-expansion (< 90%) should also favor an alternative approach over chemical pleurodesis since the absence of apposition of the parietal and visceral pleura may lead to failure of leak closure.

Finally, the severity of the air leak should be considered in management decisions. The Cerfolio classification provides a grading system for air leak severity[88]. The impact of this classification of air-leak severity on treatment outcomes needs to be further explored.

Table 5 Cerfolio Qualitative Air Leak Classification	
Grade 1 → Forced expiratory	Leak during forced expiration (coughing) only
Grade 2 → Expiration	Leak during expiration only
Grade 3 → Inspiration	Leak during inspiration only
Grade 4 → Continuous	Continuous air leak throughout the respiratory cycle. Usually seen in the presence of broncho-pleural fistula or with mechanical ventilation.

Table 5. Cerfolio classification of air leaks[88]. Qualitative assessment of air leaks is made based on the timing of bubbling visualization in the water seal chamber or air leak meter.

Contraindications

Contraindications to Thoracoscopy

The contraindications for thoracoscopy, including medical thoracoscopy and VATS, are summarized in **Table 6**. They may vary according to local practice and experience in thoracoscopy[89, 90, 91, 92, 93, 94, 95]. Pleural adhesions, prior history of pleurodesis and advanced empyema (organizing phase), although not contraindications, represent additional technical challenges for thoracoscopy.

Under those circumstances, VATS is preferred over medical thoracoscopy. Moreover, persistent cough or inability to tolerate lateral decubitus position should also be considered as contra-indications to medical thoracoscopy when performed under moderate sedation. Proper preoperative cardiovascular assessment should always be performed prior to any thoracoscopic procedure (medical thoracoscopy or VATS) and should follow the ACC/AHA Guidelines[96].

Contraindications to Talc Pleurodesis

Table 6. Contraindications to Thoracoscopy
Lack of pleural space with fusion of the parietal and visceral pleura (adhesions)
Acute respiratory failure
Hemodynamic instability
Recent cardiovascular event (< 3 months)
ASA* Physical Status Classification > III * American Society of Anesthesiologists
Uncorrectable coagulopathy, thrombocytopenia (platelet count < 40,000 – 60,000/L)
Under moderate sedation (medical thoracoscopy): • Persistent cough • Inability to tolerate lateral decubitus position

The main contraindications for chemical pleurodesis include incomplete lung expansion

following pleural fluid drainage (< 90%), unresolved pleural space infection, and pregnancy. Pleural fluid characteristics and concomitant use of medications with anti-inflammatory effects may also have an association with pleurodesis failure. However, their impact is less clear based on the available evidence, which will be reviewed here. Contraindications to talc pleurodesis are summarized in **Table 7.**

Table 7. Contraindications to Talc Pleurodesis
Factors increasing the risk of pleurodesis failure: • Lung entrapment or trapped lung with incomplete lung expansion (< 90%) • Pleural fluid pH < 7.15 • Corticosteroid (animal studies)
Pleural space infection
Pregnancy

Incomplete Lung Expansion

Lung expansion with apposition of the visceral and parietal pleura is required for talc to achieve pleural symphysis through inflammation and adhesion formation. The inability of the lung to re-expand following drainage significantly increases the risk of pleurodesis failure with the use of sclerosing agents. Although complete lung re-expansion is ideal, a residual pneumothorax, if present, should remain minimal.

No specific threshold of lung re-expansion has been validated to predict pleurodesis success or failure. In our experience, lung re-expansion of at least 90%, as visually assessed on the chest x-ray, should be present to consider chemical pleurodesis. Incomplete lung re-expansion may occur in the context of lung entrapment (active infectious, inflammatory or malignant process leading to an immobile visceral pleura) or trapped lung (remote and resolved inflammation leading to a thickened, fibrotic visceral pleura).

Certain radiographical signs suggest such entrapment. In the setting of a large pleural effusion, the absence of an expected contralateral mediastinal shift, and, more significantly, the presence of an ipsilateral deviation should raise suspicion of a non-expandable lung or endobronchial obstruction and should prompt an endoscopic evaluation.

Pleural fluid pressure during thoracentesis may signal a non-expandable lung. Early chest discomfort during thoracentesis, manometry showing a rapid decline in intra-pleural pressure with high pleural elastance ($\Delta P/\Delta V$; variation of pleural pressure in relation to the volume of removed fluid) and the presence of a *pneumothorax ex vacuo* following fluid drainage (**Figure 12**) are also suggestive of an underlying non-expandable lung.

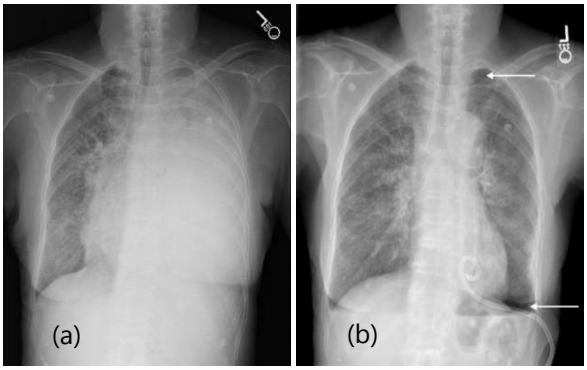


Figure 12. (a) 85-year-old female with prior history of breast adenocarcinoma presenting with a massive left pleural effusion with slight contralateral shift of the mediastinum. **(b)** A 14 Fr pigtail catheter was inserted for fluid drainage. Lung entrapment was confirmed by the presence of a persistent pneumothorax (white arrows) without an air-leak into the chest drainage device. These findings are also found in *pneumothorax ex vacuo* which may occur in the setting of abnormal lung re-expansion, and in the context of lobar atelectasis through a decrease in negative intra-pleural pressure. Pleural fluid cytology confirmed the presence of malignant cells consistent with adenocarcinoma of breast origin.

Images Courtesy of Van Holden, MD
Beth Israel Deaconess Medical Center

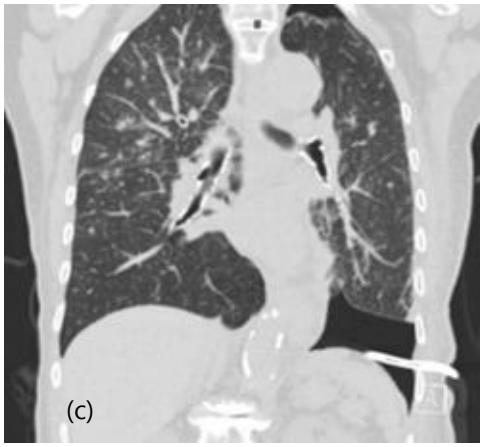


Figure 12(c). An IPC was later inserted when the patient presented pleural effusion recurrence. Chest CT showing lung entrapment with the pigtail catheter inserted in the pleural space. Signs of lymphangitic carcinomatosis and multiple metastatic nodules were also present.

Manometry has been shown to be helpful in the diagnosis and characterization of non-expandable lung, and may therefore predict failure to achieve pleurodesis[97, 98]. *Lan et al*[98], using bleomycin, found that the incidence of trapped lung was significantly higher in patients with a pleural elastance above 19 cm/L (79% vs 6% when below this threshold). No successful pleurodesis was achieved when the pleural elastance was above 19 cm/L.

Pleural Fluid pH

Pleural fluid pH may play a role in predicting chemical pleurodesis failure. In MPE, low pH values have been associated with poorer survival, greater neoplastic involvement of the pleural space, and may be found in the presence of trapped lung or lung entrapment[22, 23]. The presence of a low pleural fluid pH could also have a negative impact on the biological effects of talc to achieve pleurodesis[22, 23]. *Rodriguez-Panadero et al*[23] showed a decline in pleurodesis success rates with pleural fluid pH < 7.20, with no successful cases reported with pH < 7.15. In a meta-analysis assessing the predictive and discriminative role of pH, *Heffner et al*[99] found that a pH value below a decision threshold of 7.28 provided a modest predictive value and discriminative property. Through a multivariate analysis, pleural pH was found to be the only independent predictor for pleurodesis failure. Lower pH values, especially below a threshold of 7.15, increased the probability of unsuccessful pleurodesis. However, studies in the multivariate analysis presented design and methodological weaknesses, so caution should be taken in the interpretation of the results. Thus, based on the quality of evidence, pleural fluid characteristics, including pH, currently have a limited value in predicting pleurodesis failure.

Anti-Inflammatory Medications

There is a concern that anti-inflammatory medications may reduce the efficacy of sclerosis agents. Only assessed in two animal studies, corticosteroids have been shown to reduce adhesion formation with talc[100, 101]. NSAIDs, however, have shown conflicting results. In animal studies, diclofenac was associated with reduced adhesion formation when talc was used for pleurodesis[101], while Ketoprofen did not affect its efficacy[102]. The impact of NSAIDs on pleurodesis success was addressed in one human study, the TIME1 randomized-controlled trial[103] (not to be confused with the TIME2 trial, which compared IPC with talc pleurodesis in MPE). In this trial which used a 2 x 2 factorial design, subjects with MPE either received Ibuprofen or opiates for analgesia, and a small versus large-bore chest tube (12 or 24 Fr). In terms of the pleurodesis failure rate at 3 months, Ibuprofen was found to be non-inferior to opiates. Thus, based on the limited evidence on medications with anti-inflammatory properties, discontinuation of corticosteroids should be considered, notwithstanding the absence of human studies. However, results from the TIME1 trial provide stronger evidence that NSAIDs, and particularly Ibuprofen, may be used in the setting of chemical pleurodesis. Additional evidence from trials will be needed to further address the impact of anti-inflammatory medications on successful pleurodesis.

Talc Administration

Pleurodesis can be achieved with talc poudrage (insufflation) performed by medical thoracoscopy or VATS, or with a talc slurry administered bedside through a chest tube. In the following section, technical aspects of talc poudrage and slurry administration, including talc preparation for each method, will be reviewed. The techniques described are based on local experience. Some elements may change from one center to another. However, the usual and essential steps remain similar.

Talc Poudrage Versus Slurry

Comparing both methods in MPE, talc poudrage has been shown to be at least as effective[104, 105, 106, 107, 108, 109] or even superior to talc slurry[33, 34, 110, 111, 112, 113]. Comparative trials are lacking in the setting of NMPE, spontaneous pneumothorax and PAL. Three meta-analyses, including one network meta-analysis, compared the efficacy of both methods in MPE[33, 34, 109]. A 2006 meta-analysis by *Tan et al.*[33] showed a significant reduction in MPE recurrences in favor of talc poudrage (RR 0.21; 95% CI = 0.05-0.93). In a 2016 network meta-analysis by *Clive et al.*[34], talc poudrage was shown to be the most effective method. It resulted in less pleurodesis failures than the other methods, including talc slurry. However, as the authors noted, interpretation of those findings should consider the presence of significant heterogeneity and high risk of bias among the included studies. *Mummadi et al.*[109], in their 2014 meta-analysis, did not report a significant difference in pleurodesis success rates between talc poudrage and talc slurry. However, respiratory complications were found to be significantly more common in talc poudrage (RR 1.91; 95% CI = 1.24-2.93), findings that could have been driven by the largest trial comparing both methods. In this latter 2005 trial, *Dresler et al*[112] examined both methods in MPE with 501 randomized subjects. Superiority of talc poudrage in achieving successful pleurodesis at 30 days was only shown in a post-hoc subgroup analysis of subjects with lung and breast cancer. Respiratory complications were found to be more common with talc poudrage (13.5%) than with slurry (5.6%).

Based upon the available evidence, talc poudrage in MPE to achieve pleurodesis may be superior to talc slurry. However, no clear superiority has been documented. Therefore, the choice of the talc administration method should be made based on the medical context: patient performance status and preference, local expertise, and the need for thoracoscopy for diagnostic purposes. The TAPPS trial[114], a multicenter, open-label, randomized-controlled trial currently ongoing in the United Kingdom aims to compare pleurodesis success rates between talc slurry and talc poudrage in 330 patients with MPE. Results from this trial will add further evidence to the pleurodesis efficacy of both methods.

Pre-Procedural Precautions

Although the optimal dosage is not known, 5 g of talc is often recommended for MPE and NMPE pleurodesis[115]. Two grams may be sufficient for the treatment of spontaneous pneumothorax[116]. Before proceeding to the description of talc pleurodesis procedures, reducing the risk of systemic talc absorption and related complications warrants mention. Such precautions include the following[17, 18, 20, 22, 117, 118, 119, 120]:

- Not exceeding a dose of 5 g;
- Using a size-calibrated talc preparation containing larger particles (< 5-10 μm constituting < 10% of the preparation);
- Avoiding bilateral talc pleurodesis or talc administration following significant pleural injury or numerous pleural biopsies.

Technique

Talc Slurry

Talc slurry offers the main advantage of being administered at the patient's bedside. If not already done, a chest tube must be placed first. Once pleural drainage is complete and full lung expansion is confirmed on imaging, talc slurry can be administered bedside via the chest tube. The tubing can be hung on an IV pole or drip stand to use gravity to help maximize the amount of talc slurry delivered into the pleural space. Extra-length tubing is often required.

Small versus Large-Bore Chest Tubes

The impact of chest tube size on pleurodesis efficacy is less clear and will need to be further explored in additional comparative studies. Two retrospective studies[121, 122] and three randomized-controlled trials[103, 123, 124] compared the use of small and large-bore chest tubes for chemical pleurodesis in MPE. No significant differences were found in pleurodesis efficacy with the exception of the TIME1 trial[123, 124], the largest trial to address this question[103]. This 2x2 factorial design trial was aimed to assess the impact of chest tube size and analgesia (NSAIDs versus opiates) on pain scores and pleurodesis efficacy. Subjects could receive thoracoscopy or talc slurry based on clinical judgment. If thoracoscopy was performed, a 24 Fr chest tube was placed, and those subjects were not considered for the primary analysis of the chest tube size outcomes.

If talc slurry was considered, subjects were then randomized to receive either a small-bore (12 Fr) or larger (24 Fr) chest tube. Although a total of 320 subjects were recruited for TIME1, only 114 received talc slurry. Small-bore chest tubes led to lower pain scores than larger chest tubes. However, the 12 Fr group failed to reach the criteria of non-inferiority for pleurodesis efficacy (set at -15%), and showed higher failure rates (30 vs 24%, respectively). As the study might have been underpowered for reaching the 15% non-inferiority margin for this outcome, more complications also occurred during the insertion of 12 Fr chest tubes. Thus, until further evidence confirms an impact of chest tube size on pleurodesis efficacy, we recommend the use of small-bore chest tubes as it provides more comfort to the patients. Moreover, talc administration through an indwelling pleural catheter in MPE has also been described with successful results[40, 125]

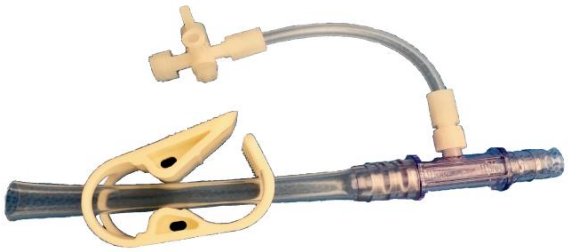


Figure 13 (a). Chest tube adapter for talc slurry administration.

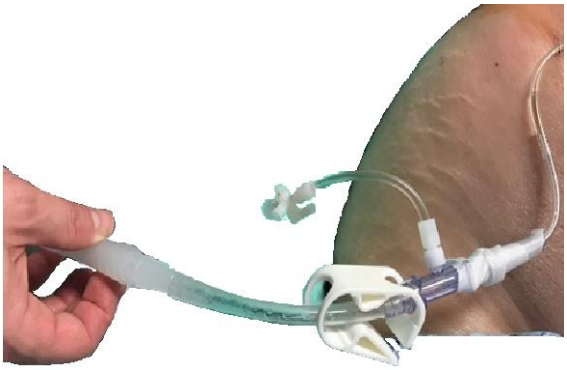


Figure 13 (b). Chest tube adapter in place.

Images by Mathieu Marcoux, MD and Alichia Paton, NP
Beth Israel Deaconess Medical Center

3-Step Procedure

1. Talc Preparation

50 mL of isotonic sodium chloride (NaCl 0.9%) is injected slowly into a talc powder bottle (5 g Sterile Talc Powder™ or Steritalc®) using a 60 mL LuerLok syringe equipped with a 16-gauge needle. The bottle is then swirled continuously to disperse the talc powder and to avoid settling. Its contents are aspirated back into the 60 mL syringe or equally divided (25 mL) into two separate syringes, each containing 25 mL of saline. Talc slurry should be used immediately after preparation. If not, the preparation should be stored in a refrigerator and discarded if not used within 12 hours.

2. Talc Injection

Slurry administration is performed using sterile gloves. Up to 25 mL (250 mg) of 1% lidocaine is usually instilled into the pleural space prior to talc administration. The syringe(s) containing the talc preparation should be continuously agitated to disperse the talc evenly and avoid its settlement. The talc slurry is then injected via a chest tube adapter or 3-way stopcock for pig-tail catheters and IPCs (**Figures 13 and 14**). Once the administration is completed, the two following approaches are available:

- Clamped drain method: Chest tube (or IPC) is immediately clamped for a period of one to two hours. This approach should be considered in the absence of an air leak. If a minimal air-leak is present (only during expiration or coughing; Cerfolio grade 1-2), and the patient has previously shown a capacity to tolerate a prolonged clamping period (of at least one hour), then this approach may be used.
- Unclamped drain method: This approach is performed in patients with air leaks and who are not meeting the aforementioned criteria.

Patient rotation (supine, left and right lateral) every 15 minutes during the one to two-hour period can be considered to obtain a more homogeneous distribution of talc. However, two randomized controlled trials showed that rotation did not affect the incidence of recurrence[126, 127]. *Mager et al.*[127] used 99mTc-sestamibi-labeled talc suspension for pleurodesis. Scintigraphic imaging did not show an impact of rotation on talc distribution at one minute and one hour. Finally, after completion of this period, low-grade suction is then applied. If necessary, depending on the patient's condition, suction may be increased up to -20 cm H_2O.

Figure 14. Setup example of the PleurX™ IPC lockable drainage line for talc slurry administration. The access tip (left) is inserted into the pleural catheter valve which attaches to the suction bottle. The T-plunger (right) is connected to the indwelling chest drainage device. A 3-way stopcock is added before the T-plunger for lidocaine and talc slurry administration.

Image by Mathieu Marcoux, MD

3. Chest Tube Removal

Removal may be done after 24 hours if there is absence of fluid drainage or < 150 cc/24h. If fluid drainage persists, talc administration may be repeated similarly. In one randomized controlled trial, no significant differences were seen in pleural effusion recurrences when chest drains were removed at 24 versus 72 hours following talc slurry administration[128]. As expected, length of stay was significantly reduced when the chest

tube was removed at 24 hours (4 versus 8 days). Thus, early removal of the chest tube at 24 hours, in the absence of significant fluid drainage, can be safe and without reduced efficacy.

Talc Poudrage

Talc poudrage is performed during medical thoracoscopy or VATS. The technical approach for medical thoracoscopy will be briefly reviewed here. This method of pleurodesis can be performed in the operating room or in an adequately equipped and monitored procedural suite. It can usually be executed under moderate sedation, but general anesthesia can also be considered for more complex cases. Usual surgical sterile methods are used for the procedure.

4-Step Procedure

1. Talc Preparation

Sterile talc powder for insufflation comes commercially prepared as a pressurized spray canister (Steritalc® Spray), or a in a vial (Steritalc®). Talc powder preparations are joined to a powder blower (also termed a pneumatic atomizer or manual insufflator; **Figure 15**).

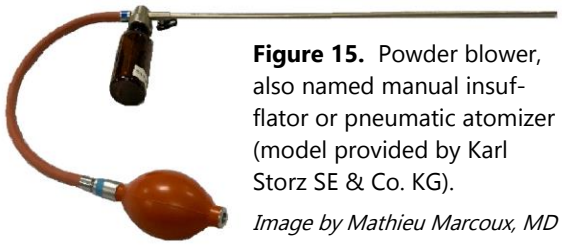


Figure 15. Powder blower, also named manual insufflator or pneumatic atomizer (model provided by Karl Storz SE & Co. KG).

Image by Mathieu Marcoux, MD

These preparations have not been compared in their efficacy. Selection is usually based on local resources, costs, and availability. Talc powder also offers the advantage of being suitable for both talc insufflation and talc slurry preparation.

2. Medical Thoracoscopy

The patient is initially placed in a lateral decubitus position with the affected side facing up. Disinfection of the surgical site is performed with the application of an antiseptic solution and the patient is draped in the usual sterile fashion. One or two entry sites are then created with the insertion of a trocar into each (**Figure 16**).

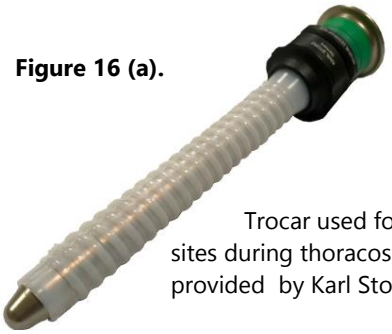
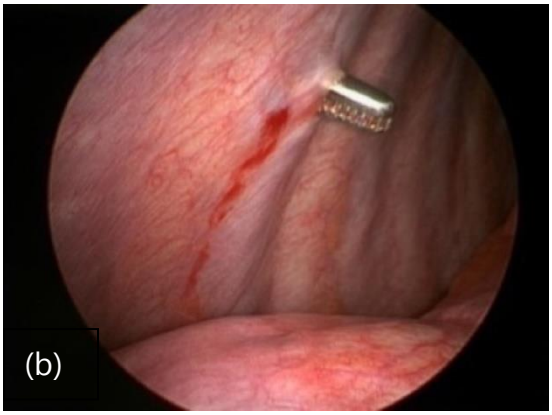


Figure 16 (a). Trocar used for port entry sites during thoracoscopy (model provided by Karl Storz SE & Co.

Figure 16 (b). Under direct thoracoscopic visualization, creation a second entry site.



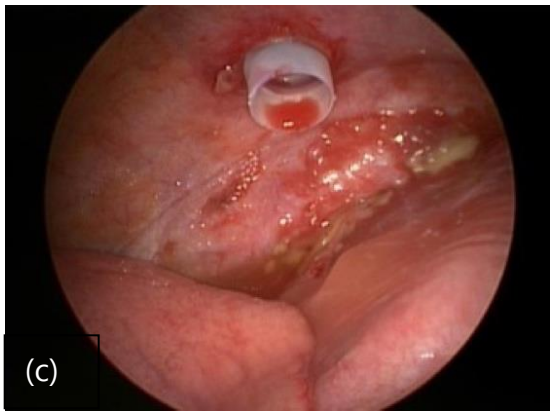


Figure 16 (c). Thoracoscopic visualization of the trocar sheath. *Images by Mathieu Marcoux & Adnan Majid,MD*

The site of entry is usually recommended to be at the level of the 4th or 5th intercostal space, in the midaxillary line. When a second port is considered, the location should be in line with the first entry site and with a distance of approximatively two intercostal spaces. Prior ultrasound assessment for each site is recommended. Rigid or semi-rigid thoracoscopes can be used for the procedure (**Figures 17 and 18**).

Figures 17 (a) & (b) Rigid thoracoscope with an angled eyepiece, 10 mm diameter and 6 mm working channel (model provided by Karl Storz SE & Co. KG). Other models have a straight (0 degree) angle of vision.

Thoracoscope Images by Mathieu Marcoux, MD and Adnan Majid, MD

The type of thoracoscope is not expected to have an impact on pleurodesis success rate, although it may influence the quality of pleural biopsy and diagnostic yield. Biopsy specimens obtained with the flexible forceps are usually smaller and more superficial than those from the forceps used in rigid thoracoscopy[129, 130, 131]. This aspect has raised questions about its impact on diagnostic accuracy. One randomized controlled trial did demonstrate a superior diagnostic yield, as well as larger biopsy samples, for rigid thoracoscopy when compared to semi-rigid thoracoscopy[129]. However, the diagnostic yield was not shown to be superior when pleural biopsy was successfully performed in both groups. Two other studies, one a randomized pilot study[130] and one retrospective[131], did not find a difference in the diagnostic accuracy between rigid and semi-rigid thoracoscopy.

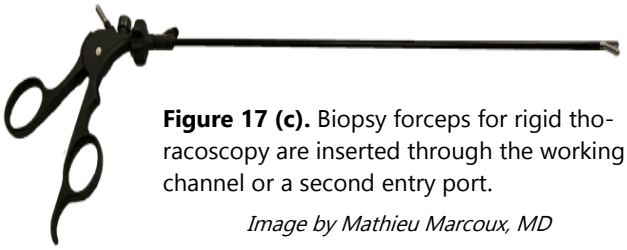


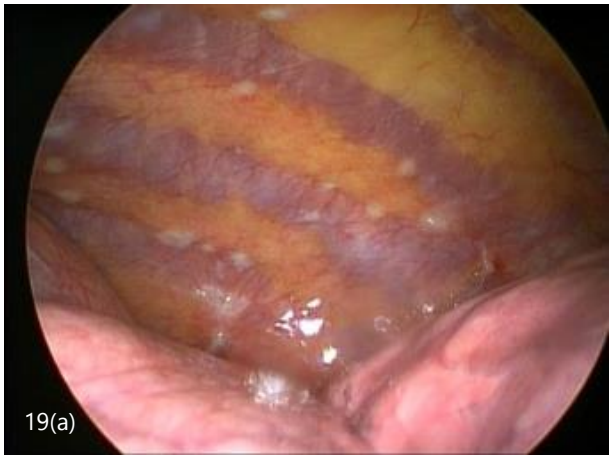
Figure 17 (c). Biopsy forceps for rigid thoracoscopy are inserted through the working channel or a second entry port.

Image by Mathieu Marcoux, MD

Figure 18 (a) Semi-rigid (semi-flexible) thoracoscope with a 7 mm distal end outer diameter and 2.8 mm working channel (model LTF-160 provided by Olympus). Dedicated instruments can be inserted through the working channel, such as biopsy forceps, a spray catheter for the administration of a sclerosing agent, an electrosurgical knife and a coagulation electrode.

Figure 18 (b) The flexible distal tip allows an upward angle of 160◦ and 130◦ downward.

Images by Mathieu Marcoux, MD



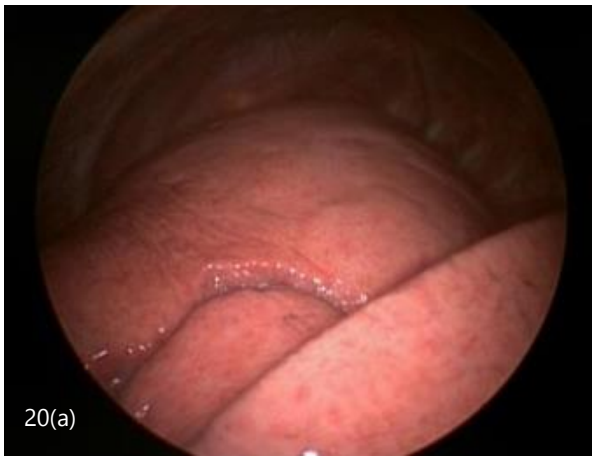


Figure 19. (a) Inspection showing pleural nodularity.

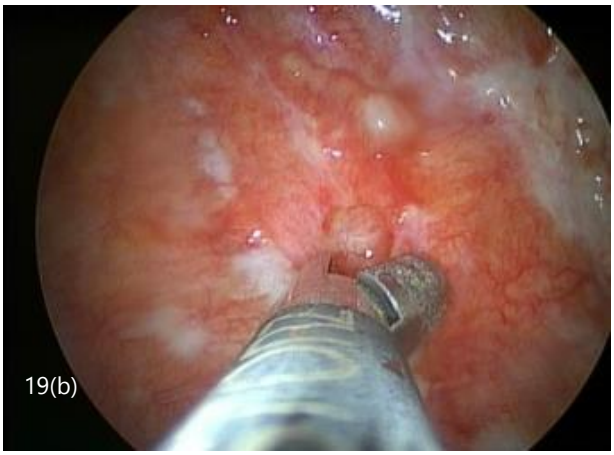
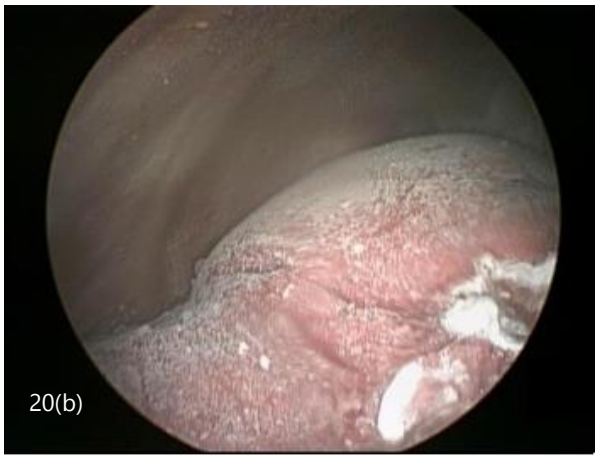


Figure 19 (b). Pleural biopsy. Biopsy results confirmed pleural involvement by an adenocarcinoma of lung origin.

Images by Adnan Majid, MD



Figures 20 (a) and (b). The pleural space is shown prior to and following talc insufflation.

Images by Adnan Majid, MD

Talc Administration

Talc can be insufflated homogeneously by using the aerosol spray canister or powder blower with short bursts under direct visualization. Patients should be made aware that discomfort and pain might be felt during talc insufflation. Appropriate measures should be taken for analgesia. After talc has been administered, complete visualization of the pleura is recommended to confirm homogeneous talc spread over the pleural surfaces (**Figure 20**).

Chest Tube Insertion and Management

Once talc administration has been completed, a chest tube (16-24 Fr) is placed. The tube is oriented towards the apex in the setting of a spontaneous pneumothorax, or to the posterior costophrenic recess for a pleural effusion. In MPE, an IPC can also be inserted for a "rapid pleurodesis protocol", as described by *Reddy et al.*[48] (**Figure 21**). Finally, chest tube management for drainage, suction and removal is similar to the approach previously described following talc slurry administration.

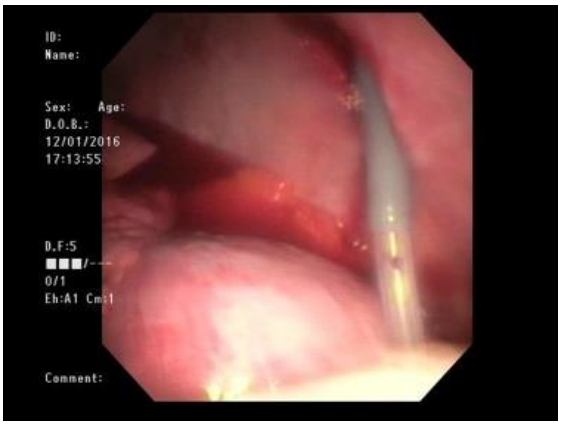


Figure 21 IPC insertion during medical thoracoscopy.

Image by Adnan Majid, MD

Complications

The most commonly reported adverse effects of talc pleurodesis include post-procedural fever and chest pain[64, 111, 112]. Post-procedural fever has been reported in up to 69% of cases. It typically arises 4 to 12 hours following talc administration and may last up to 72 hours[64].

Although infrequently described, the most dreaded respiratory complications include acute respiratory failure, acute pneumonitis and Acute Respiratory Distress Syndrome (ARDS). It has been suggested that variability in the reported respiratory complications may be partly attributable to differing talc doses and particle size calibration[22]. As previously mentioned, graded talc preparations should contain larger-size particles (> 5-10 μm) and be used at lower doses (5 g or less) to reduce the risk of systemic absorption and to reduce the risk of respiratory complications[132]. Systemic absorption and dissemination of talc has been demonstrated in both animal and human studies. Talc has been documented to be present in the bronchoalveolar lavage of patients who developed ARDS following talc administration, as well as in numerous organs of a patient who died from this complication[133, 134].

Appendix Table 2 (a) & (b) summarizes the talc-related respiratory failure events in several observational studies, including the largest retrospective and prospective cohort studies of talc pleurodesis. A shown in this table, acute respiratory failure event, including ARDS, occurred mainly in studies that reported the use of a talc dose greater than 5 g, but were also reported in studies using lower talc doses. Among those, *Bouchama et al.*[135] reported a case of acute pneumonitis with bilateral effusions following talc pleurodesis with a dose of 2 g. *Rehse et al*[136], in a retrospective review of 78 patients, reported the highest rate of ARDS, which was 9%. Although the authors reported the use of 10 g of talc for two procedures, all ARDS events only occurred in patients who received 5 g of talc. One patient received simultaneous insufflation of talc for bilateral pneumothoraces, therefore the cumulative dose of talc could have been higher. Three of those patients also had a prior mechanical abrasion of the pleura. In a retrospective study of 550 patients who received talc poudrage (dose 2 g) for both MPE and NMPE, *de Campos et al.*[133] also reported 7 cases (1.3%) of respiratory failure with ARDS.

Other large cohorts did not report respiratory failure or ARDS following talc pleurodesis with lower doses of graded talc. In a prospective European cohort study of 418 patients assessing the short-term safety of thoracoscopic talc pleurodesis for recurrent PSP (dose of 2 g), *Bridevaux et al.*[137] did not report any case of ARDS or VATS (dose of 2 g), *Cardillo et al*[138] did not report any postoperative ARDS or mortality event. Absence of talc-related respiratory failure or

ARDS was also reported by *Viallat JR et al.*[139] (360 patients, average dose of 3 to 4.5 g), *Janssen et al.*[119] (558 patients, dose of 4 g) and *Weissberg et al.*[140] (360 patients, dose of 2 g).

Interestingly, in all randomized trials comparing talc pleurodesis with IPC insertion for MPE (NVALT-14[41], CALGB 30102[42], AMPLE[39], TIME2[38]), no cases of acute respiratory failure or ARDS were reported in subjects who received talc. In the IPC-Plus trial[40] which compared IPC with slurry administration versus IPC alone in MPE, no subjects in the talc pleurodesis arm presented acute respiratory failure events. However, in the largest trial comparing talc poudrage with slurry by *Dresler et al.*[112] (419 randomized subjects received talc pleurodesis, dose range 4 to 5 g), respiratory failure was reported in 26 cases (6%). Eight cases occurred in the talc slurry group (4%) with five related deaths, while 18 were reported in the poudrage group (8.1%) with six related deaths.

Thus, based on the evidence from observational studies and randomized trials, calibrated talc appears to be safer when used at lower doses (5 g or less). Nevertheless, occasional cases of acute respiratory failure and ARDS have been reported with the use of lower doses, so this risk should be considered. Beside respiratory failure, other reported post-procedural complications include wound infection, empyema, pneumonia, arrhythmia, re-expansion edema, bleeding and myocardial infarction. Talc pleurodesis has shown long-term safety on lung function among younger patients treated for PSP without an increase in the incidence of lung cancer or mesothelioma[141,142].

Future Considerations

Since its first use in 1934 by Norman Bethune, significant progress has been made in our understanding of talc in the management of pleural disease. Still, further evidence will be required to help compare the efficacy and safety of talc to alternative methods or sclerosing agents in the setting of MPE, NMPE, pneumothorax, and PAL. Upcoming results from randomized-controlled trials should provide a better insight into the management of MPE, such as the efficacy of talc poudrage over talc slurry with the TAPPS trial. Moreover, results from the SWIFT trial should help define the role of the novel silver nitrate coated IPC as opposed to the conventional approved pleural catheter. Thus, with an evolving spectrum of therapeutic interventions, future randomized controlled trials with standardized outcome measures, as well as patient-centered outcomes, will be required with a collaboration between specialized centers in pleural disease. The validated LENT prognostic score should also be integrated in trials involving therapeutic methods for patients with MPE, and could be of interest in the assessment of quality-adjusted life years. Finally, our understanding of the biological mechanisms behind chemical pleurodesis should help us to find new therapeutic avenues. For example, the use of intra-pleural TGF-β2 in animal studies, by stimulating mesothelial cell production of collagen, has shown promising results in achieving successful pleurodesis, along with the potential of a better safety profile[143, 144, 145]. Through a collaborative effort, such promising and innovative research avenues will contribute to the refinement of our state-of-the-art approach to the management of pleural disease.

Appendix

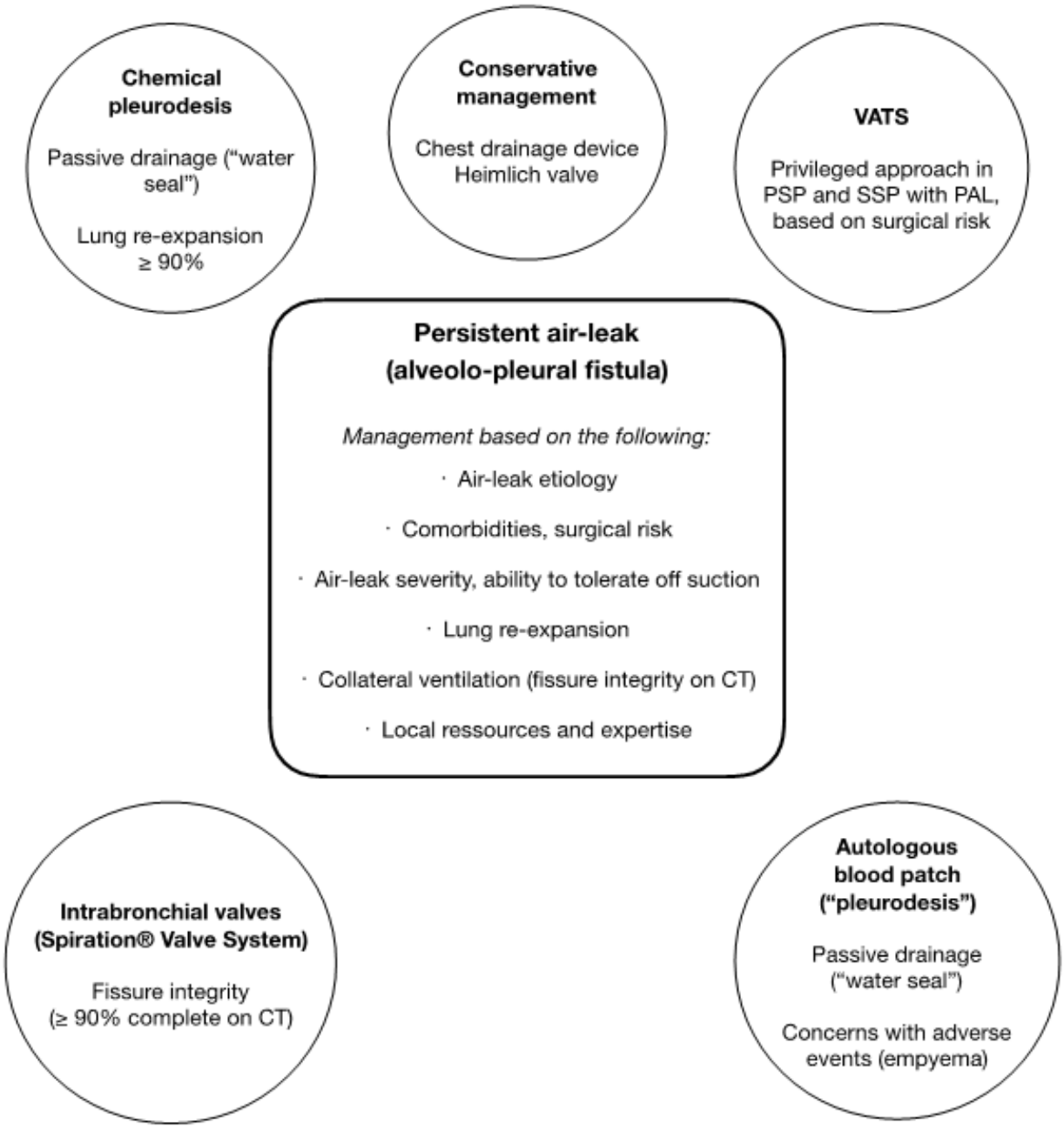
The **LENT** prognostic score for survival in MPE[28].

***Score**: low risk 0-1, moderate risk 2-4, high risk 5-7.*

Table 1	Variable	Value	Score
L	***L*** DH (pleural fluid; IU/L)	< 1500 ≥ 1500	0 1
E	***E*** COG Prognostic Score	0 1 2 3-4	0 1 2 3
N	***N*** eutrophil to Lymphocyte Ratio (blood count)	< 9 ≥ 9	0 1
T	***T*** umor type	Mesothelioma Hematologic malignancy Breast Gynecologic cancer Renal cell carcinoma Lung Other cancer	0 1 2

Appendix Figure 1

Management of Alveolo-Pleural Fistula



Appendix Table 2 (a)

Studies reporting use of talc > 5 g				
Study	**Patients**	**Talc dose**	**Form**	**Talc-related respiratory failure**
Rinaldo et al.[134]	4	5 g (1 pt) 10 g (3 pts)	Slurry	3 ARDS (talc dose of 10 g)
Alder et al.[146]	41	10 g	Slurry	None
Kennedy et al.[147]	56	10 g	Slurry	5 cases of acute respiratory failure 3 cases required mechanical ventilation ≤ 72h (One considered procedure-related, received bilateral talc instillation)
Gonzales et al.[117]	138	2-8 g (median 6 g)	Poudrage	8 cases of lung injury (did not meet ARDS criteria; 4 cases considered talc-related, association not excluded for the other patients)
Rehse et al.[136]	78	5 g 2.5 & 10 g in 4 procedures	Poudrage or slurry	7 ARDS (talc dose of 5 g) 1 death following ARDS (patient received simultaneous talc insufflation for bilateral pneumothoraces)
Rodriguez-Panadero et al.[148]	330	5-8 g	Poudrage	3 cases of acute respiratory failure (not specified if talc-related)

Appendix Table 2 (b)

Studies using talc ≤ 5 g or dose non-specified				
Study	**Patients**	**Talc dose**	**Administration method**	**Talc-related respiratory failure**
Bouchama et al.[135]	1	2 g	Poudrage	Acute respiratory failure with pneumonitis and bilateral pleural effusions
de Campos et al.[133]	550	2 g	Poudrage	7 ARDS (3 deaths)
Brideveaux et al.[149]	418	2 g	Poudrage	None
Cardillo et al.[150]	861	2 g	Poudrage	None
Viallat JR et al.[151]	360	3-4.5 g	Poudrage	None
Janssen et al.[119]	558	4 g	Poudrage	None
Weissberg et al.[140]	360	2 g	Poudrage or slurry	None
Györik et al.[152]	112	Not specified	Poudrage	None

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