WHITE PAPER

STERITALC® and indwelling pleural catheter (IPC)

A perfect match?

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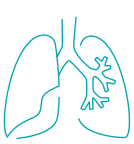


Malignant pleural effusions – treatment priorities

Malignant pleural effusion (MPE) is a common complication in patients with a range of advanced malignancies. Although the worldwide incidence of MPE is unknown, it has an estimated annual incidence of between 150,000 and 250,000 cases in the United States, resulting in close to 125,000 hospitalizations.[1–3] People with lung and/or breast cancer account for 50-65% of all malignant effusions, followed by people with lymphomas, genitourinary and gastrointestinal tract cancers, which make up further 25%.[4–6] Up to fifteen percent of people with cancer will develop pleural effusion during the course of their disease. Given the global surge in cancer diagnoses, the disease and healthcare burden associated with MPE will continue to rise.[7,8]

A diagnosis of MPE usually portends a poor prognosis and limited life expectancy. The estimated median survival has been reported as 3-24 months, but is frequently no more than 4-6 months after diagnosis.[2,9–11]

All existing treatments, from thoracentesis to pleurodesis and home-based drainage via an indwelling pleural catheter (IPC), are aimed at draining pleural fluids and, wherever possible, preventing their reaccumulation. Unsurprisingly, management remains palliative in nature, with a distinct focus on relieving the primary (and often most distressing) symptom: dyspnea.

Given the short life expectancy of patients with MPE, treatment should aim to improve and/or maintain quality of life for as long as possible, while minimizing invasive procedures and time spent in hospital.[7,10,12,13]

State of the art

A brief look at the MPE research milestones of the past decade (Figure 4, page 10) reveals a steep increase in the number of high-quality research studies and clinical trials. Figure 4 also shows clearly how developments in the research field have gone hand in hand with changes to professional guidance.

Over the past decade, effusion drainage and pleurodesis remained the cornerstones of MPE treatment strategies, with talc considered the most effective sclerosant available.[2,4,6,14] As the world's most commonly used pleurodesis agent today, talc boasts the largest body of evidence on efficacy and the most comprehensively evaluated and evidenced adverse events profile.[2,4–6,15,16] Historic reports of an association with acute respiratory distress syndrome (ARDS)[17] have been thoroughly discounted as linked to small-particle, non-calibrated talc and/or excessively high doses.[15,16,18–21]

Although ambulatory drainage options are becoming common in some regions,[22,23] these are not available to most patients worldwide and do not reliably lead to cessation of fluid accumulation.[22,24–26] Pleurodesis therefore remains the default treatment for the majority of individuals with MPE hoping for definitive treatment.[2,5,6] However, subgroups of patients in whom pleurodesis (whether on an inpatient or outpatient basis) is simply not feasible require more tailor-made treatment options.[13]

Concerted efforts to optimize symptom management in specific subgroups of patients have resulted in a distinct trend towards less invasive treatment options and a move away from inpatient to ambulatory management.[13,27–29]

Motivated (at least in part) by cost considerations[30–32] and a lack of robust randomized evidence for surgical interventions,[4,33,34] this paradigm shift also reflects a more patient-centered approach to symptom palliation. This weighs available treatment options against patient-specific factors such as: a low performance status (which may make the patient an unsuitable candidate for surgery and/or sedation); cancer type (life expectancy may increase the potential benefits of seeking a definitive procedure); and of course the degree of lung re-expansion following

pleural fluid evacuation.[2,4,6,35–37] Treating physicians also need to take into account the patient's estimated remaining lifespan, which may rule out more invasive procedures or even restrict options to repeat thoracenteses. Similarly, the availability or non-availability of at-home support may determine the feasibility of outpatient management via an indwelling pleural catheter.[2,6,13,36,38]

Indwelling pleural catheters (IPC)

The first indwelling pleural catheter received FDA approval in 1997, a whole 39 years after John Chambers first described the use of talc for palliative treatment of patients with MPE.[39] Initially intended to provide effective, long-term pleural fluid drainage on an outpatient basis,[40] the devices soon started to be used in a subset of MPE patients in whom pleurodesis is contraindicated (due to previous pleurodesis failure and/or non-expandable lung).[38]

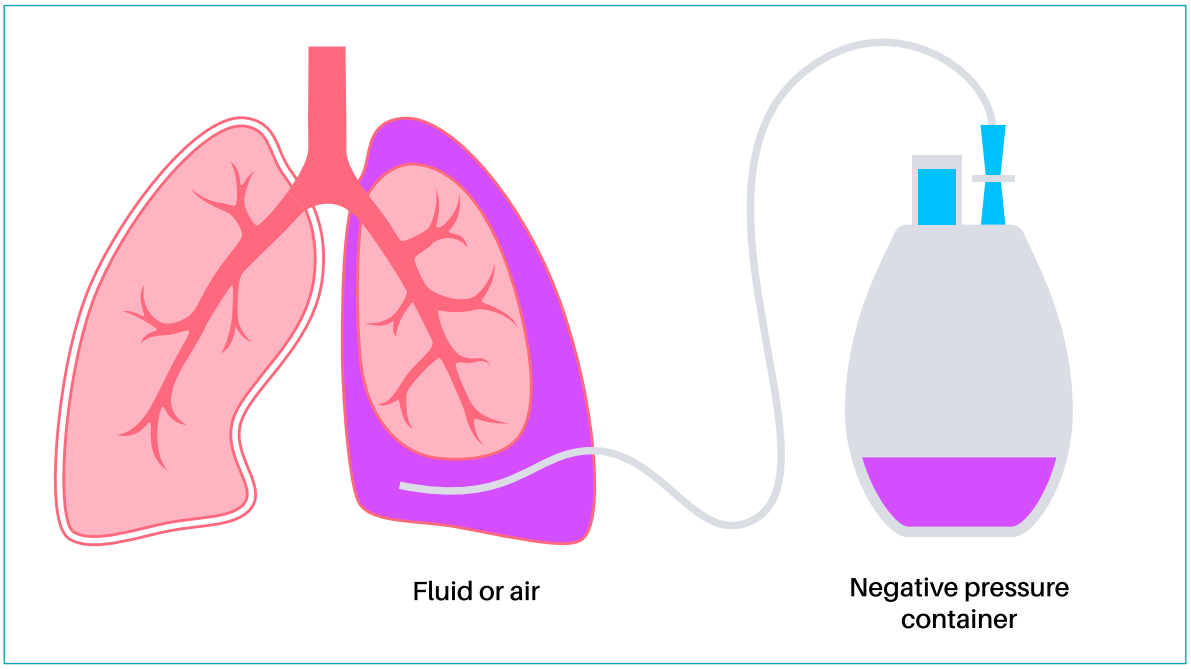
Multiple retrospective and prospective studies, including the first two RCTs comparing talc pleurodesis with IPC, have since confirmed IPC to be equally as effective as talc pleurodesis.[4,41–44] Although associated with a higher rate of side effects, IPC also appears to reduce the risk of repeat pleural interventions and, hence, overall time in hospital.[45–47]

One particularly interesting and beneficial side effect of this treatment modality is spontaneous pleurodesis, which has been reported to occur in approximately 45% of patients.[48] Lower rates of between 23% and 24% have been reported with less aggressive IPC drainage protocols, and likely reflect a more realistic, real-world picture.[22,49,50]

IPC plus talc

At a time when professional guidance recommended pleurodesis as the first-line treatment for patients with MPE (Figure 4),[6,14,51] Reddy et al. (2011)[41] developed a rapid pleurodesis protocol combining medical thoracoscopy with talc insufflation and the simultaneous placement of a tunneled pleural catheter (Table 1). Their pleurodesis rate of 92% was soon replicated by Krochmal et al. (2016),[52] who achieved 93% using the same protocol, although the recurrence of

Figure 1



Pleural drainage: The indwelling catheter is connected to a negative pressure container. Fluids and/or air are drained from the pleural space, improving lung expansion and relieving respiratory distress.

effusions in four patients after catheter removal (at a median of 10 (IQR 7–14) days) reduced the overall success rate to 79%. Both studies compared well with pleurodesis rates of between 48 % and 82 % reported for pleurodesis with tube thoracostomy alone.[52,53] Boujaoude et al. (2015) compared patients undergoing talc poudrage combined with IPC with historical controls undergoing conventional pleuroscopic pleurodesis.[53] Their successful pleurodesis rate of 92% matched those of the other two studies and exceeded that of the control group (82%), although the difference was not statistically significant. Majid et al. (2016) compared a treatment protocol involving thoracoscopic talc poudrage and a tunneled pleural catheter with tunneled catheter drainage alone in patients with pleural effusions secondary to heart failure.[54] A pleurodesis rate of 80% achieved using the combination protocol compared favorably with a significantly lower rate of 25% in patients treated with IPC alone.

The aptly named IPC-PLUS trial was the first attempt to investigate the potential benefits of an IPC-plus-talc combination regimen in a randomized, controlled manner.[50] All patients underwent identical protocols for IPC insertion and initial drainage prior to randomization on day ten and instillation of either 4 g of talc slurry or placebo through the indwelling pleural catheter on an outpatient basis. Talc and placebo were administered on a single blind basis. The two groups differed significantly in terms of the primary endpoint, pleurodesis at day 35, with the IPC-plus-talc arm achieving almost double the pleurodesis rate of the IPC-plus-placebo arm (43 % vs 23%). At day 70, the rates were 51% v 27 %, respectively. Participants who received IPC-plus-talc also had better quality of life scores and better symptom scores at all assessment points. This included significantly better VAS scores for pain on day 14 and day 28, in addition to significantly better VAS scores for dyspnea at day 54. One important aspect of the trial protocol was the exclusion of a relatively large number of patients (≤ 2 months life expectancy, moderate to poor health performance status after fluid removal, lung entrapment of ≥ 25% at randomization), meaning results may only apply to a selected group of patients with MPE.

Other relevant non-RCT-based studies have been conducted and have confirmed the principal findings regarding excellent pleurodesis rates combined with a significant reduction in days spent in hospital.[26,55,56]

One of these, the EPIToME (Early Pleurodesis via IPC with Talc for Malignant Effusion) study, published in 2019,[56] assessed the feasibility of a clinical algorithm incorporating results from the IPC-PLUS trial and four others (AMPLE, AMPLE2, TIME2, ASAP)[22–24,43,50]. Designed as an observational, real-world study, EPIToME addressed some of the limitations of clinical trials with highly selective inclusion criteria. Wishing to test the feasibility of a real-world treatment protocol, the study had no specific exclusion criteria. All patients underwent IPC insertion and lung evaluation; patients with expandable lung underwent talc instillation, following which they were discharged and underwent a regimen of daily drainages for 14 days (or until pleurodesis). Patients unable to undergo pleurodesis (e.g., due to trapped lung; prior failed pleurodesis; patient/oncologist preference) were discharged with a regimen of symptom-guided drainage. Using this protocol, 74% of patients achieved pleurodesis after a median of 20 days. However, a high percentage of this unselected patient population were unable to undergo talc pleurodesis. For these patients, first-line IPC offered optimal care.[56]

An interesting prospective study from the UK, testing the safety and efficacy of thoracoscopic talc poudrage plus IPC as a single day case procedure, was published in 2021.[57] Designed in response to limited hospital bed capacity, the study showed a median length of stay of 0 (IQR 0–0) days, with successful pleurodesis attained in 77.8% of patients at 6 months. The study reported no procedure-related deaths or IPC-related infections, suggesting that ambulatory

thoracoscopic talc poudrage with IPC insertion is a safe and effective option in patients with MPE.[57]

Cost considerations

One real-word consideration that has a significant impact on both treatment availability and patient choice is cost. Over the past 10 to 15 years, clinical research has focused on minimizing time spent in hospital by shifting MPE management to the outpatient setting.[41,50,52,57,58] While some of this development was driven by quality of life considerations in a patient population with limited life expectancy, it would be naïve to ignore the cost implications of different treatment modalities and how these are likely to determine which treatments are offered in the future. Based purely on reduced time in hospital, IPC would appear to be the most cost-effective method.[11,32,43,59–62] Other analyses, however, have found talc to be less costly than IPC,[11,30] although IPC became more cost-effective when life expectancy was 6 weeks or less.[11]

Cost comparisons are not made easier by differences in healthcare systems, which in turn may influence treatment availability, rates of recurrence, and frequency and duration of hospitalizations.[25,26,63,64] While results from the ASAP and AMPLE2 trials (Figure 4) support aggressive drainage regimens,[22,24] overall costs can become prohibitive. Overall costs are determined not only by the duration and intensity of any in-hospital or community-based nursing required for catheter drainage,[59,61,62] but also by the frequency and severity of complications requiring after-care.[61,65] A cost-effectiveness analysis by Shafiq et al. in 2020 suggested that IPC plus talc may be a cost-effective alternative to symptom-guided drainage, but that symptom-guided drainage was cost-effective for pleurodesis rates > 20% and life expectancy < 4 months. Daily drainage was not cost-effective under any circumstance.[31]

Figure 2

In the USA, Novatech's STERITALC® is approved as a pharmaceutical product.

There are other types of costs which will feed into treatment availability and/or feasibility and, ultimately, patient choice – some of them healthcare system-dependent. A questionnaire-based study by Aboudara et al.[66], evaluating the socioeconomic costs of IPC, revealed significant copay levels for private insurers, as well as additional costs related to the IPC in 55% of cases. 85 % of patients reported receiving assistance from non-paid caregivers, of whom 12% had to take time off work to assist with IPC management. 20% of patients reported significant life changes after IPC (such as having to move in with a carer or downsize in order to cut costs).[66]

A more patient-centered approach also needs to focus on the potential psychological impact of different treatment modalities (surgery, inpatient treatment vs outpatient treatment, body image considerations with IPC).[4,13,67]

The number of studies now focusing on health-related quality of life, rather than merely symptom control, is promising in this regard.[45,66,68–71]

An observational study from the UK (MY-IPC)[72] aims to explore and understand the impact that IPCs have on patients with MPE from a psychological point of view, while a multicenter, prospective survey-based study from Ireland[73] will evaluate a newly developed mobile app intended to support patients with MPE treated with an IPC.

What the future holds

Most of the research to date has focused on IPC-plus-talc protocols involving thoracoscopic talc pleurodesis (also commonly referred to as talc poudrage or insufflation) and relatively intensive home drainage regimens (Figure 4 and Table 1).[41,52–54,56] Only the IPC-PLUS trial[50] and the day-case study by Foo et al. (2021)[57] combined talc-based pleurodesis with less intensive drainage regimens which are more likely to be manageable for patients and their carers – and justifiable in terms of costs.

The IPC-PLUS trial remains the only RCT to date to have published results on a combination regimen involving talc slurry and IPC-based drainage. In this context, findings from the OPTIMUM study,[74] a randomized clinical trial to evaluate the outpatient management of patients with MPE using a combination regimen of IPC plus talc slurry pleurodesis, will be particularly interesting.

Despite a respectable number of retrospective and observational studies that have delivered comparatively positive results on the combination of talc poudrage and IPC,[23,50,53,56,57] the TACTIC trial is the first randomized controlled trial to examine the benefits of combining thoracoscopic talc poudrage with IPC.[75] Just as the Foo et al. day-case study[57], the TACTIC protocol combines IPC use and talc poudrage into a single ambulatory procedure, comparing it to current UK standard care (as per the 2010 BTS guidelines[6]). In addition to using patient-centered outcomes such as dyspnea management and quality of life, the TACTIC team will evaluate time spent in hospital and cost-effectiveness.[75]

Conclusion

MPE is a diverse condition. Given the heterogeneity of underlying conditions and variable prognoses, it is not surprising that no one treatment option represents the best approach for all patients.[13,75] The new BTS Guideline (published in July 2023)[13] heralds a new age of patient-centered practice, recommending that clinical decision-making take patient views and preferences into account in order to improve symptoms and enhance quality of life in a way that ensures maximum patient autonomy and satisfaction.[5,13,76]

Treatment options are as diverse as the condition itself, and include repeated thoracenteses, chemical pleurodesis (e.g., with talc), and the placement of an indwelling pleural catheter (IPC).[2,6,13] Each treatment option has its advantages and disadvantages. Repeated thoracentesis is not recommended in patients with longer life expectancy, as the procedure has to be repeated every four weeks.[63] Pleurodesis, which is both safe and effective, offers the highest chance of definitive treatment, but usually necessitates an inpatient stay of approximately 5-7 days.[31,77]

While IPC alone has been shown to cause spontaneous pleurodesis in a proportion of patients,[22,24,44,48] this effect can be significantly enhanced through combination with talc.[50,56,57]

This combination of treatments holds enormous potential and is at the center of a number of high-quality trials currently underway, the results of which are being eagerly awaited by practitioners from across the globe.[71,74,75,78]

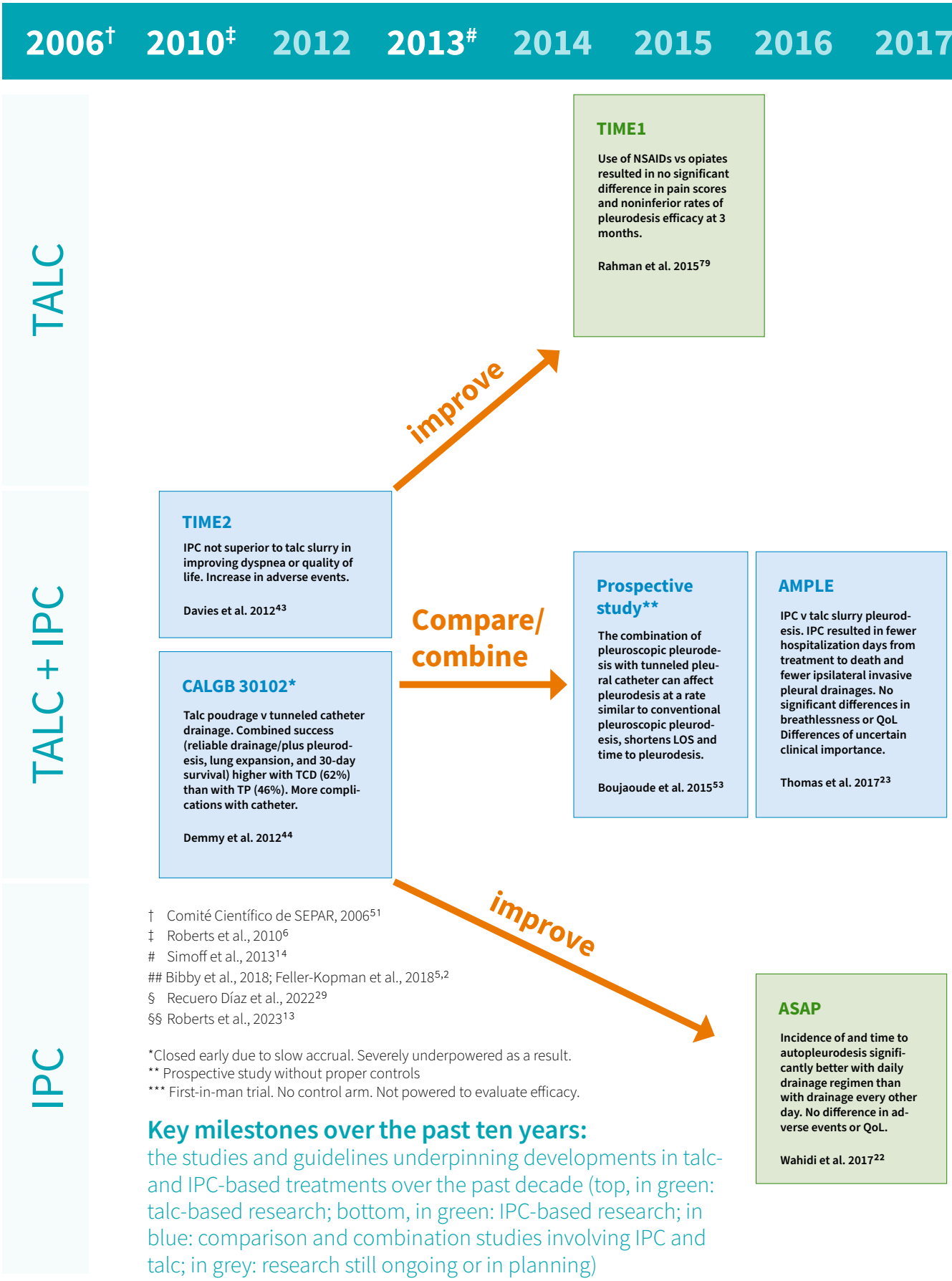
Table 1 Published studies evaluating IPC + talc

Year/ref.	IPC + Talc protocol
Reddy et al. 2011[41]	Rapid pleurodesis protocol combining medical thoracoscopy with talc poudrage and simultaneous placement of a tunneled pleural catheter (TPC) **Drainage > poudrage > daily drainage** TPC drained until output < 150 ml on two consecutive attempts, then removed.
Boujaoude et al. 2015[53]	Talc poudrage combined with IPC **Drainage > poudrage > daily home drainage** If catheter output consistently < 150 mL per day, TPC removed.
Majid et al. 2016[54]	Thoracoscopy with talc poudrage and IPC v IPC alone in patients with pleural effusions secondary to heart failure. **Drainage > talc poudrage > daily drainage for 2 weeks** (then three times per week if necessary, until output > 50 mL for three consecutive drainages). Catheter removed if output 200 ml or less
Krochmal et al. 2016[52]	Same protocol as Reddy et al. 2011 **Drainage > poudrage > daily drainage**
Bhatnagar et al. 2018[50] **IPC-PLUS**	RCT comparing IPC plus talc slurry pleurodesis with IPC plus placebo **IPC insertion and drainage > talc slurry pleurodesis > discharge > at least twice per week drainage for duration of trial**
Fitzgerald et al. 2019[71]	**IPC insertion & drainage > (if lungs expanded) talc instillation > daily home drainage for 14 days or until pleurodesed** (if unsuitable for pleurodesis: discharged with symptom-guided drainage)
Frost et al. 2019[55]	N=14 patients treated with IPC received additional talc slurry via IPC. No protocol specified.
Foo et al. 2021[57]	TTP and insertion of IPC as a single day case procedure. **Thoracoscopy and fluid evacuation > IPC insertion via new incision> talc poudrage> IPC daily drainage started after discharge (daily first two days, then thrice weekly or as determined by physician)**
Mohs et al. 2022[26]	Retrospective review of Veterans Affairs' Corporate Data Warehouse data. Comparing IPC, Talc pleurodesis and IPC + talc pleurodesis. No protocol specified
Not yet published	
OPTIMUM[74]	**Randomized controlled trial comparing outpatient management of malignant pleural effusion via an IPC and talc slurry pleurodesis v standard inpatient management (chest drain + talc pleurodesis) in improving health-related QoL** Secondary outcomes: breathlessness and pain
ASAPII[78]	**Randomized Controlled Trial of Talc Instillation In Addition To Daily Drainage Through a Tunneled Pleural Catheter to Improve Rates of Outpatient Pleurodesis in Patients With Malignant Pleural Effusion - The ASAP II Trial** (suspended)
TACTIC[75]	**First randomized controlled trial (RCT) to examine the benefit of a combined TTP and IPC procedure, evaluating cost-effectiveness and patient-centered outcomes such as symptoms and QoL.**

No. of participants/ subgroups	Main findings	Talc/IPC used
N=30	PR 92% LoS 1.79 days MTT IPC 7.56 days	"Five grams of sterile talc was then insufflated or aerosolized" PleurX (CareFusion; McGaw Park, Illinois)
N=29 in TPC group, N=33 in CPP group (historical controls)	PR 92% (v 82% in historical controls undergoing conventional pleuroscopic pleurodesis) PR at 6 months 96% of surviving patients MTT IPC 6 days (v 9 days in controls) Median LoS 3 days	"FDA-approved sterile talc with controlled particle size" (Sterile Talc Powder; Bryan Corporation, Woburn, MA) PleurX (CareFusion, McGaw Park, IL)
N=36	PR 80% in talc+ IPC group v 25% in IPC alone MTT IPC 11.5 days v 66 days in IPC alone.	"4 to 8 g of talc poudrage (mean, 5 g)" (Sclerosol Intrapleural Aerosol; Bryan Corporation, Woburn, MA) PleurX (CareFusion Corporation, San Diego, CA)
N=29	Initial PR 93%, later 79% MTT IPC 8 days no chemo v 10 with chemo; 12 days in patients with lung cancer v 9 days in non-lung cancer Median LoS: 2 days	"4 to 5 grams of commercially available sterile talc" PleurX (Care Fusion; McGaw Park, Illinois or Rocket; Rocket Medical; Hingham, MA)
N=154 (n= 76 placebo, n=78 talc slurry)	PR at day 35 : 43% talc group v 23% placebo group; at day 70: 51% v 27%	"4 g of sterile, graded talc (Steritalc, Novatech)" as slurry, as per BTS guideline
N=102 consecutive (unselected) patients	PR 74% after median 20 days. High percentage (54%) of real-world, unselected MPE patient population not suitable for talc pleurodesis	Not specified (conference abstract, no full-text version available)
N=395 (IPC+talc n=14)	PR 44.5%, more common in patients < 60 years. Use of talc slurry highly predictive for pleurodesis (HR 7.8, p = 0.009)	Talc not specified. PleurX®, CareFusion, San Diego (CA), USA)
N=45	PR 71.1 and 77.8% at 3 and 6-months Median LoS 0 days 86.7% discharged on day of procedure.	3 g of Steritalc® (Novatech SA, France) Rocket® IPC™
N=414 (IPC + talc n= 38)	IPC+ talc LoS 2 days (compared with 3 days for IPC alone and 7 days for talc alone) IPC alone: higher failure rates than either talc alone or IPC+talc	Talc not specified IPC not specified
Recruitment target N=142		
Target N=152		
Target N=124		

IPC – indwelling tunneled pleural catheter
LoS – length of stay
MTT IPC – median time to IPC removal
PR – pleurodesis rate
TTP – thoracoscopic talc poudrage

Figure 4



† Comité Científico de SEPAR, 2006[51]
‡ Roberts et al., 2010[6]
# Simoff et al., 2013[14]
Bibby et al., 2018; Feller-Kopman et al., 2018[5,2]
§ Recuero Díaz et al., 2022[29]
§§ Roberts et al., 2023[13]

*Closed early due to slow accrual. Severely underpowered as a result.
** Prospective study without proper controls
*** First-in-man trial. No control arm. Not powered to evaluate efficacy.

Key milestones over the past ten years:
the studies and guidelines underpinning developments in talc- and IPC-based treatments over the past decade (top, in green: talc-based research; bottom, in green: IPC-based research; in blue: comparison and combination studies involving IPC and talc; in grey: research still ongoing or in planning)

2018## 2019 2020 2021 2022§ 2023§§ 2024 ...

TIME3

Urokinase (fibrinolytic) + talc pleurodesis vs placebo + talc pleurodesis. No significant difference in time to pleurodesis failure, which occurred in 37% of patients on urikinase and 32% of patients on placebo.

Mishra et al. 2018[80]

TAPPS

Talc poudrage v talc slurry. No significant difference in pleurodesis failure at 90 days, nights spent in hospital, pain and dyspnea, health-related QoL, all-cause mortality.

Bhatnagar et al. 2020[69]

SIMPLE

RCT comparing ultrasound-guided care with standard care in patients undergoing talc pleurodesis (by either poudrage or slurry).

Psallidas et al. 2022[82]

AMPLE3[71]

RCT (Australia) comparing IPC + talc v VATS-based pleurodesis (mechanical/talc poudrage/other).

Recruiting.

OPTIMUM[74]

Outpatient regimen using IPC + talc slurry pleurodesis v standard inpatient treatment with chest drain and talc slurry pleurodesis.

Not yet published.

TACTIC[75]

TTP + ICP vs standard care (TTP) to test if combined TTP + ICP offers effective pleurodesis at the time of diagnostic biopsy. Focus on outcomes that are highly important to patients as symptoms and quality of life.

Recruiting.

IPC-PLUS

IPC + talc v IPC + placebo. In patients without lung entrapment, the outpatient administration of talc through an IPC resulted in a significantly higher chance of pleurodesis at 35 days than IPC alone, with no deleterious effects.

Bhatnagar et al. 2018[50]

Prospective study**

Poudrage plus IPC as a single day case procedure (prompted by restricted bed capacity during pandemic) - 77.8% had pleurodesis success at 6-month follow-up
Randomized trial needed to confirm.

Foo et al. 2021[57]

NVALT-14

IPC as first-line treatment not superior to talc pleurodesis. No difference in patient-reported dyspnea scores but hospitalization significantly shorter and fewer reinterventions. Trial has major weaknesses.

Boshuizen et al. 2018[59]

ASAP II[78]

Randomized controlled trial of talc instillation in addition to daily IPC drainage v daily drainage.

Suspended. Protocol amendment pending.

Prospective study (EPIToME)

IPC + talc and daily drainage v IPC and symptom-guided drainage in a real-world patient population. 74% achieved pleurodesis within median 20 days. Many unsuitable for talc instillation.

Fitzgerald et al. 2019[56]

Prospective study** NCT05372055[73]

Observational study (Ireland) of patient experience regarding the use of a mobile app for IPC patients.

Recruiting.

SWIFT

Silver nitrate-coated IPC v standard IPC. No improvement in pleurodesis efficacy. No significant difference in pain, patient-reported dyspnea, QoL, and treatment-related adverse event rates.

Shrager et al. 2022[83]

Prospective study (MY-IPC)**[72]

Prospective survey-based study (UK) to evaluate the psychosocial impact of IPCs on patients.

Not yet recruiting.

AMPLE 2

Higher rate of spontaneous pleurodesis with daily drainage.
No difference in breathlessness control or days spent in hospital.

Muruganandam et al. 2018[24]

SEAL-MPE***

First-in-man silver nitrate-coated IPC. Needs RCT to confirm potential. (See SWIFT).

Bhatnagar et al. 2018[81]

MesoTRAP[84]

Pilot RCT (UK) comparing VATS-based partial pleurectomy v IPC in mesothelioma patients with trapped lung.

Not yet published.

STERITALC®

The only FDA-approved talc indicated to decrease recurrence of malignant pleural effusions and to decrease recurrence of pneumothorax in adults.

- Granulometrically controlled talc.
- Three dosage forms: 2, 3 or 4 grams, allowing application as a slurry or via poudrage.

- Contraindicated in pregnant women.
- Safety and effectiveness have not been established in pediatric patients.
- Acute Pneumonitis and ARDS (Acute Respiratory Distress Syndrome) have been reported with intrapleural use of various talc products.
- Sclerosis of the pleural space may preclude or complicate subsequent ipsilateral surgery and diagnostic procedures.
- Lead is present in STERITALC® as an impurity.
- Common adverse reactions observed with intrapleural use of various talc products are fever and pain.
- You are encouraged to report negative side effects of prescription drugs to the FDA. Visit MedWatch or call 1-800-FDA-1088.

Prescribing Information

https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/205555s000lbl.pdf

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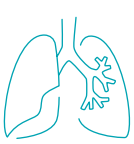

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Dr. Karen Schafheutle has a Master's degree in Environmental Analysis and Health and completed her PhD in Epidemiology.
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