# Treatment options for malignant pleural effusion

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**Purpose of review**

Thirty percent of lung cancers eventually result in malignant pleural effusion (MPE). Devastating consequences of MPE, such as dyspnea and cough, severely deteriorate the quality of life of these patients. Malignant pleural effusion portends a dismal prognosis of less than 6-month longevity, with the exception of breast and ovarian cancer. Given the poor prognosis of the majority of these patients, palliation, rather than cure, should be the goal of therapy.

**Recent findings**

Chest tube insertion and sclerotherapy remain the standard of care. Emerging therapeutic options such as medical pleuroscopy and indwelling pleural catheters offer cost-effective and outpatient treatments for MPE.

**Summary**

In the following review, the medical, economic, and social aspects of different current options for the management of MPE are discussed.

**Keywords**

malignant pleural effusion, pleural catheter, pleurodesis, pleuroscopy, poudrage, thoracoscopy, trapped lung

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## Introduction

Pleural effusions are a common and devastating complication of advanced malignancies. The annual incidence of malignant pleural effusion (MPE) in the United States is estimated to be around 150 000–175 000 cases per year [1–3]. In vast majority of cases, MPE signifies as incurable disease with high morbidity and mortality. For the same reason, several studies have argued in favor of a palliative approach, rather than a conventional curative approach for the treatment of MPE. Long hospitalizations and immobility imposed by chest tube insertion, as well as pain and discomfort associated with talc slurry, doxycycline, or similar agents may not be the most compassionate way of treating this terminal complication of advanced malignancies. New modalities, such as pleuroscopy and long-term indwelling pleural catheters, offer cost-effective [4], outpatient [5] or minimal hospital stay, less discomfort, and a chance to spend time with loved ones in the comfort of the home or hospice care.

## Etiology and pathogenesis

Lung and breast cancers cause approximately 75% of all MPEs. Other major causes include lymphoma, ovarian cancer, and gastric cancer, in order of decreasing frequency [6,7]. In approximately 7% of patients with MPE, the primary site of malignancy is unknown at the time of initial diagnosis.

In the setting of underlying malignancy, the presence of malignant cells in the pleural fluid establishes the diagnosis of MPE. An effusion found in the setting of a known malignancy, but without any cytological evidence of malignancy in the pleural fluid, is termed a paramalignant effusion. The lack of malignant cells in the pleural fluid is related to the fact that the tumor has not directly extended or metastasized to the pleura or pleural space [8]. Paramalignant effusions are most commonly caused by lymphatic obstruction [8,9] but can also be related to central airway obstruction, pneumonia, atelectasis, or trapped lung. These effusions may also result from the systemic effects of the tumor or the adverse effects of chemotherapy or radiation.

Several mechanisms have been proposed to explain the development of MPE. The inability of the parietal pleura to reabsorb pleural fluid because of involvement of mediastinal lymph nodes by tumor is likely the most common cause of MPE. Therefore, tumors that involve the mediastinal lymph nodes, such as lung cancer, breast cancer and lymphoma, are responsible for the vast majority of MPEs. Other possible mechanisms for

MPE formation include direct tumor invasion, as is sometimes seen in lung cancer, chest wall neoplasms, and breast cancer, as well as hematogenous spread to the parietal pleura.

## Signs and symptoms of malignant pleural effusion

Malignant pleural effusion portends a poor prognosis, with a mean length of survival of 6 months from the time of diagnosis, with the exception of breast and ovarian cancer [3]. Malignant pleural effusions may cause significant dyspnea, cough, and chest pain. Given the terminal nature of the underlying disease and debilitating recurrent symptoms, a palliative rather than a curative approach should be considered at an early stage.

## Current therapeutic options

The patient's symptoms, functional status, life expectancy, and the type of tumor responsible for MPE should be kept in mind when considering therapeutic options (Fig. 1) [10••]. In MPE associated with breast cancer and small cell lung cancer, chemotherapy may be all that is required. Similarly, radiation may suffice for the MPE associated with lymphoma, precluding any further intervention (Table 1).

Therapeutic thoracentesis should be performed in each case, not only to establish a cytological diagnosis, but also to document symptomatic improvement and the presence or absence of trapped lung. Lack of symptomatic improvement after thoracentesis may dissuade one from further interventions. A diagnosis of trapped lung should prompt one to consider strategies other than chest tube insertion and talc pleurodesis, such as indwelling pleural catheters [11], which are discussed in detail below. Symptomatic, recurrent, and recalcitrant (to chemotherapy or radiation therapy) MPEs should be addressed with a definitive, palliative care plan.

## Therapeutic thoracentesis

The first step in the management of MPE is to determine whether the patient achieves symptomatic benefit from removal of the pleural fluid. A considerable number (up to 50%) of patients with MPE may not achieve significant improvement in breathlessness or exercise tolerance after thoracentesis, because of comorbid conditions (e.g. emphysema), general debility from the tumor, or the

**Figure 1 Treatment algorithm for malignant pleural effusion**

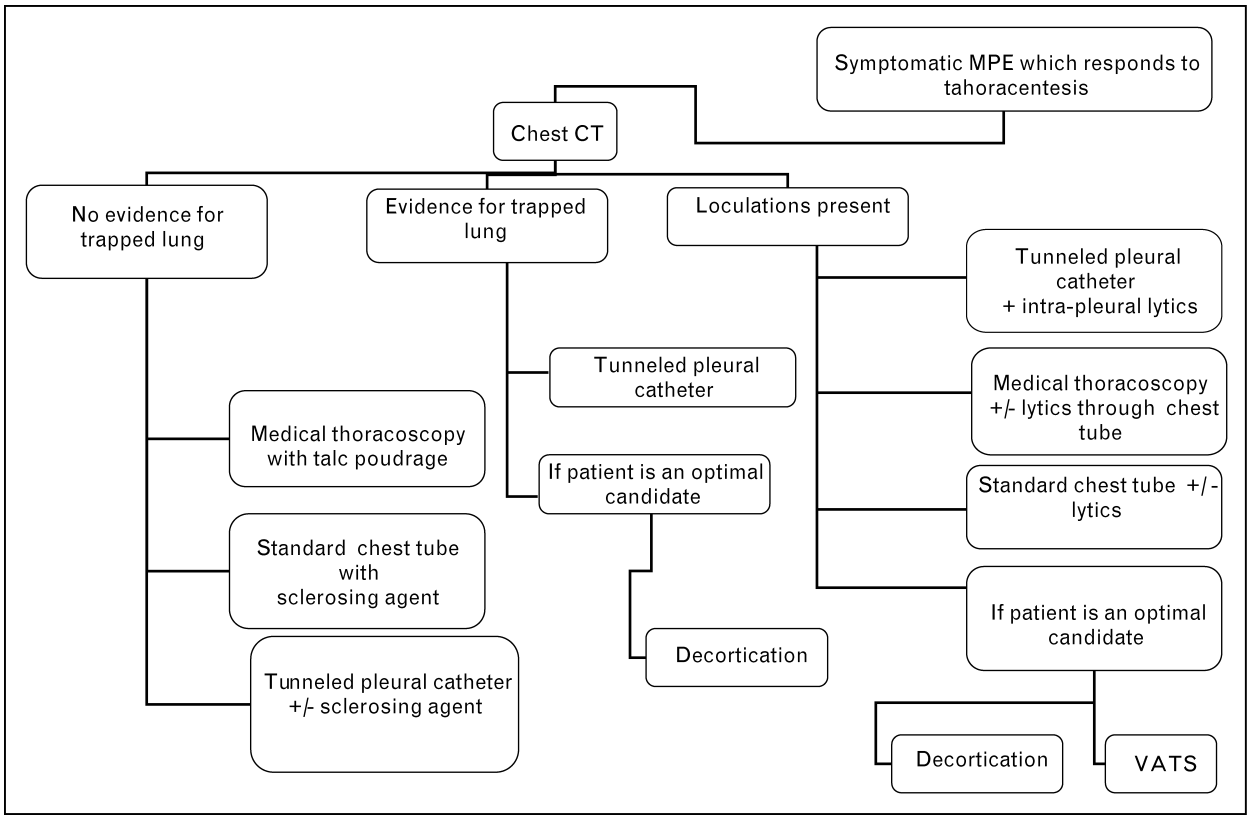


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**Table 1 Management options for malignant pleural effusions**

| Options | Advantages | Disadvantages |
|---|---|---|
| Observation | Noninvasive | Most will progress and require therapy |
| Repeated therapeutic thoracentesis | Good option for patients with limited life expectancy<br>Prompt relief of dyspnea | Rapid reaccumulation<br>Repeated procedures<br>Multiple hospital visits<br>Procedure related complications<br>Re-expansion pulmonary edema<br>Reduced quality of life |
| Chemical pleurodesis with chest tubes | Highly effective (pleurodesis 81–93%) | Hospitalization 5–7 days<br>Expensive<br>Invasive<br>Associated morbidity |
| Medical thoracoscopy and VATS | Highly effective (pleurodesis in greater than 90% of patients)<br>Diagnosis and pleurodesis can be performed at the same time | Inpatient<br>Invasive<br>Associated morbidity<br>Contraindicated if patient cannot tolerate single-lung ventilation (VATS) |
| Pleuroperitoneal shunts | Could be an option in patients with failed chemical pleurodesis | Shunt malfunction<br>Infection<br>Requires frequent pumping by the patient |
| Chronic indwelling pleural catheters | Good option for motivated patients<br>Inpatient or outpatient placement of catheter and mostly outpatient management of catheter and drainage<br>Minimally invasive<br>Cost-effective<br>Control of dyspnea<br>Outpatient pleurodesis (42–58%) without chemicals<br>Can be used in patients with trapped lung for palliation of symptoms<br>Catheter can be used to administer intrapleural anticancer agents | Family member or a visiting nurse required for home drainage<br>Catheter site infection<br>Low pleurodesis rate compared with chemical pleurodesis with chest tube or VATS/medical pleuroscopy |

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presence of a trapped lung. In such cases, the utility of removing pleural fluid or performing pleurodesis is limited.

For patients who carry a poor prognosis, with only weeks or months to live, and who are unable to undergo invasive procedures or hospitalization, repeated thoracentesis may be an option. This approach is purely palliative and should not be used on long-term basis. The physician should, however, have a candid discussion with the patient regarding the increased risk of potential complications, such as infection, bleeding, and pneumothorax, associated with repeated thoracentesis.

The volume of pleural fluid that can be safely removed during a therapeutic thoracentesis is unknown. However, removal of only 1.0–1.5 l of fluid per thoracentesis is recommended [2]. Therapeutic thoracentesis is not reliably effective for long-term control of MPE, as pleural fluid may reaccumulate and become symptomatic rapidly. In one study, symptomatic MPE was noted to recur within an average of 4.2 days after thoracentesis [12]. Reexpansion pulmonary edema, though rare, may occur after rapid removal of pleural fluid. There are no absolute contraindications to performing thoracentesis. Relative contraindications include a minimal effusion (less than 1 cm in thickness on a lateral decubitus chest film), bleeding diathesis, anticoagulation, and mechanical ventilation.

## Chest tube thoracostomy and chemical pleurodesis

Chest tube thoracostomy and chemical pleurodesis with talc is the most commonly used modality for managing MPE in the United States and worldwide. It is an inpatient procedure that requires an average of 5–7 days in the hospital. It may produce significant discomfort related to pain and fever following the instillation of talc. Generally, a 28–32-Fr plastic tube is inserted in the pleural space with the patient under local anesthesia or conscious sedation. This procedure can be done at the bedside, in the minimally invasive procedure unit, or in the operating room. General anesthesia is not required for this procedure, however.

There are emerging data on the use of small-bore tubes for chemical pleurodesis. In a recent prospective study by Spiegler *et al.* [13], small 14-Fr catheters resulted in successful chemical pleurodesis in 79% of patients (complete pleurodesis in 48%, partial pleurodesis in 31%). Agents other than talc have also been used to achieve pleurodesis more quickly and in a higher percentage of patients. In an animal model, transforming growth factor was shown to produce pleurodesis more quickly than talc [14].

Pleurodesis is attempted only after complete reexpansion of the lung occurs after pleural fluid evacuation, with no

evidence of trapped lung. A chest radiograph is obtained to document complete reexpansion of the lung after evacuation of the fluid. Intravenous (i.v.) narcotic analgesics or conscious sedation or both are often administered to reduce the pain associated with many sclerosing agents. The sclerosing agent of choice is instilled into the pleural space via the chest tube, typically in a solution of 50–100 ml of sterile saline. The chest tube is then clamped for 1–2 h, with or without rotation of the patient. The chest tube is then reconnected to $-20$ cm $H_2O$ suction until the 24-h output from the chest tube is less than 150 ml.

The most common complications of chemical pleurodesis are fever and pain [15]. Other rare complications include local site infection, empyema, arrhythmias, cardiac arrest, myocardial infarction, and hypotension. Acute respiratory distress syndrome (ARDS), acute pneumonitis, and respiratory failure have also been reported after both talc poudrage and slurry [15]. In a recent multicentre, prospective study of 558 patients with MPE, none of the patients developed ARDS who received large-particle talc pleurodesis [16]. In a recent review by Tan *et al.* [17], 46 randomized control trials with a total of 2053 patients with MPE were reviewed to assess the efficacy of pleurodesis. Talc was associated with fewer recurrences of MPE when compared with bleomycin [relative risk (RR) 0.64; 95% confidence interval (CI) 0.34–1.20]. Tetracycline (or doxycycline) was not superior to bleomycin (RR 0.92; 95% CI 0.61–1.38). When compared with bedside talc slurry, thoracoscopic talc insufflation, also known as talc poudrage, was associated with a reduction in recurrence (RR 0.21; 95% CI 0.05–0.93). Techniques such as rolling the patient after instillation of the sclerosing agent, protracted drainage of the effusion, and use of larger bore chest tubes were not found to be associated with any substantial advantages. Talc, therefore, appears to be effective and should be the agent of choice for pleurodesis. Thoracoscopic talc insufflation is associated with fewer recurrences of MPE compared with bedside talc slurry, but this conclusion is based on two small studies. When thoracoscopy is unavailable, bedside talc slurry via chest tube has a high success rate and is the next best option.

When initial pleurodesis for MPE fails, several alternatives may be considered. Repeat pleurodesis may be performed, either with instillation of sclerosant through a chest tube or by thoracoscopy and talc poudrage. Repeated thoracentesis would be the reasonable choice for the terminal patient with short life expectancy, as discussed above. Pleuroperitoneal shunting has fallen out of favor because of its increased risk of infection and high failure rate. Pleurectomy is an option for only a small fraction of patients because of its operative demands. The majority of MPE patients are not healthy enough to withstand an extensive surgical procedure and recovery. Replacement of the chest tube with a small-bore indwelling pleural catheter for an indefinite period of time is another option for terminally ill patients.

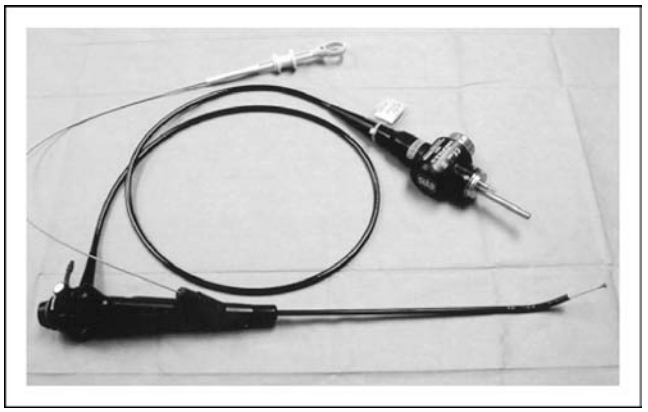
## Medical thoracoscopy (pleuroscopy)

Medical thoracoscopy, also known as pleuroscopy, is slowly becoming another tool in the armamentarium of pulmonologists and thoracic surgeons for the rapid diagnosis and treatment of malignant and nonmalignant pleural effusions. Medical thoracoscopy has a very high diagnostic and therapeutic yield. These qualities, along with minimal ancillary requirements, make medical thoracoscopy a preferred procedure for a relatively sick patient population [17,18].

Medical thoracoscopy is performed by a trained pulmonologist or a thoracic surgeon with a nondisposable, flexible pleuroscope (model XLTF-240; Olympus, Tokyo, Japan). It can be performed under local anesthesia, with or without conscious sedation, or in an endoscopy suite or sterile procedure room. General anesthesia, intubation, and single-lung ventilation are not required. The pleuroscope is a semirigid instrument with a handle similar to that of a standard flexible bronchoscope. The outer diameter of the shaft is 7.0 mm. The length of the insertion portion is 27 cm, which consists of a proximal rigid portion (22 cm) and a bendable distal end (5 cm). The tip is movable in one plane, much like a flexible bronchoscope. A 2.8-mm single working channel accommodates biopsy forceps and other instruments. The pleuroscope connects to a standard video processor and light source (models CLV-U40 and CV-240, respectively; Olympus) identical to that of a standard flexible bronchoscope. The video processors and the light sources for the flexible pleuroscope and the flexible bronchoscope are interchangeable (Fig. 2) [17].

Medical thoracoscopy is performed using a single-puncture technique. Patients are placed in the lateral decubitus position, with the affected side up. Most patients receive i.v. conscious sedation, with appropriate monitoring. After local anesthesia is achieved, a small incision is made in the mid-axillary line, and an 11-mm trocar is inserted into the pleural space. After some pleural fluid is suctioned away, the pleuroscope is then introduced into the pleural cavity, and the lung, diaphragm, and pleural surfaces are inspected. More fluid can be evacuated through the pleuroscope as needed to clear the field for visual inspection or biopsy. Parietal pleural biopsy specimens are obtained when indicated, and the procedure is followed by talc poudrage with 5 g of sterilized talc. After the procedure, a 24-Fr standard chest tube is inserted through the trocar. A chest radiograph is

**Figure 2 Flexible pleuroscope (model XLTF-240; Olympus)**



obtained to verify chest tube position and evaluate for pneumothorax.

Talc poudrage performed during pleuroscopy has a mean pleurodesis success rate of greater than 90% [19–22]. Various major and minor complications may occur with thoracoscopy, but most are infrequent. The most common complication is pneumothorax, occurring in 8.3% of patients in one series [19]. Other complications in the same study included subcutaneous emphysema (5.3%), fever (3.6%), and pain (1.2%). Major complications such as death, severe sepsis, pulmonary embolism, or hypercapnic coma occurred in 0.6% of patients [19]. One of the larger studies of medical thoracoscopy for MPE was published from that of Steffen *et al.* [23]. They reported their experience with 102 patients (45 women, 57 men; 20–83 years of age) who underwent medical thoracoscopy and talc pleurodesis for recurrent MPE. The success rate of pleurodesis at 180 days was 82.6% (38 out of 46) among surviving patients. The type of primary neoplasm had no significant influence on the success rate. Adverse events included empyema in one case and malignant invasion of the trocar-site scar in another patient. No episodes of talc-induced ARDS were observed.

## Video-assisted thoracic surgery

Video-assisted thoracic surgery (VATS) is quite different from medical thoracoscopy. It demands a higher level of surgical expertise, as well as significantly more ancillary and logistical support. However, it provides better access to the pleural space and a greater number of diagnostic and therapeutic options. VATS requires general anesthesia and single-lung mechanical ventilation. It is contraindicated for patients who cannot tolerate single-lung ventilation, including those with prior contralateral pneumonectomy, airway abnormalities which preclude placement of a double-lumen endotracheal tube, and complex pleural adhesions.

After induction of general anesthesia and intubation, VATS is performed in the lateral decubitus position with a 10-mm port in the sixth intercostal space at the midaxillary line and a 5-mm inframammary port. Most of the effusion is suctioned away, followed by deflation of the lung. A thorough inspection of the pleural cavity is then performed. Adhesiolysis is performed to ensure maximal expansion of the underlying lung in cases necessary [24], followed by biopsy of the pleura or lung, if indicated. VATS, as opposed to medical thoracoscopy, offers safer access to the visceral pleura and lung parenchyma for diagnostic and therapeutic procedures. Once expansion of the lung has been achieved, and any remaining fluid drained, 4–5 g of sterile talc is insufflated into the pleural cavity. A 20-Fr intercostal drain is inserted and directed toward the lung apex, and a 28-Fr drain is directed toward the lung base; both are connected to underwater seal drain bottles [24,25].

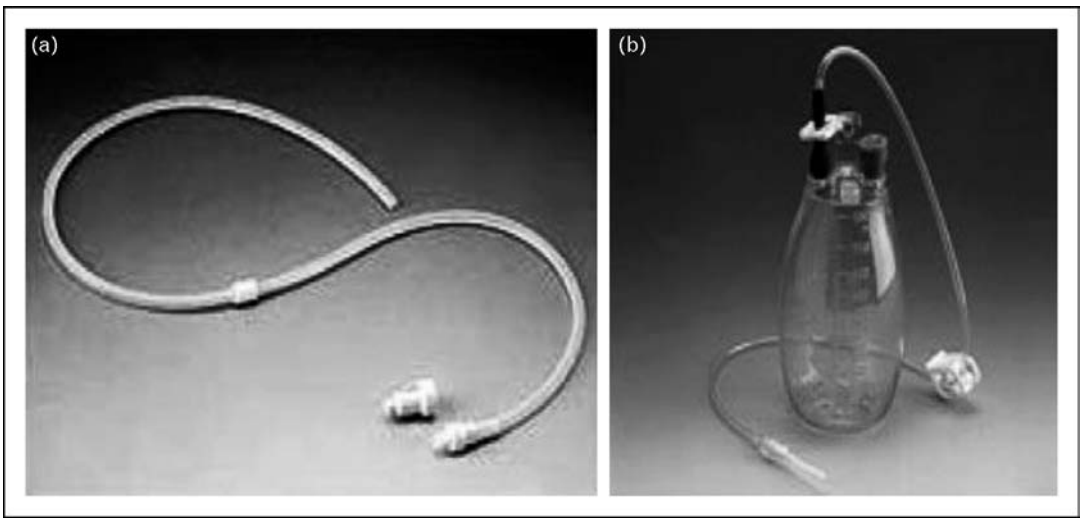
In summary, VATS with talc poudrage is an effective and safe procedure that yields a high rate of success on the first attempt and achieves long-term control of MPE [26,27]. Concomitant biopsies of the pleura or lung parenchyma can be performed during the procedure and may enhance subsequent decision-making. In spite of these advantages, VATS requires general anesthesia with selective endobronchial intubation and multiple ports of entry. In comparison, medical thoracoscopy can be performed in the endoscopy suite, under conscious sedation with only one port of entry and no intubation.

## Pleuroperitoneal shunts

The pleuroperitoneal shunt for managing MPE has gradually fallen out of favor. Pleuroperitoneal shunts transfer pleural fluid from the pleural space into the peritoneal cavity when manually pumped. The shunts are indicated for refractory pleural effusions, either malignant or chylous. This approach can also be used for patients who cannot achieve successful pleurodesis because of trapped lung. Pleuroperitoneal shunting is also a viable option for symptomatic MPEs that have failed chemical pleurodesis or for patients who cannot undergo surgery. The procedure is safe and effective in the hands of experienced operators, with palliation achieved in 80–90% of properly selected patients. The pleuroperitoneal shunt may be particularly beneficial in refractory chylothorax, as it allows the recirculation of chyle.

The major problem with pleuroperitoneal shunt has been shunt failure, which is most commonly due to clotting of the catheter. Infections and manual operation are other

**Figure 3 Pleural catheter with one-way valve**




Pleural catheter with one-way valve at the end (a) and disposable vacuum bottle with drainage tubing (b). Reproduced by courtesy of Cardinal Health, Inc. All rights reserved.

factors that have limited their popularity. Reich *et al.* [28] used 17 Denver pleuroperitoneal shunt in 13 patients between 1991 and 1992. Dyspnea was relieved in all patients. The average length of shunt patency was 2.5 months and fewer than 25% of the shunts clotted. Lee *et al.* [29] published their experience with 20 pleuroperitoneal shunt in 19 patients between 1991 and 1993. All but one patient achieved relief of dyspnea. The mean duration of patency was 26 months and fewer than 25% of the shunts clotted in this study.

## Indwelling, tunneled pleural catheters

Over the last decade, indwelling pleural catheter drainage has established itself as a less expensive, minimally invasive, and palliative modality for the management of MPE. Dozens of recent publications on its utility and efficacy for the long-term management of MPE have increased its popularity as an alternative to conventional modalities [30–33]. The commercially available indwelling, tunneled pleural catheter was approved by the US Food and Drug Administration in 1997 (Fig. 3).

The pleural catheter is a 66 cm long, 15.5 Fr, silicone rubber catheter with fenestrations along the distal 24 cm. A valve at the proximal end of the catheter prevents fluid or air from traveling through the catheter until the matched drainage line is properly attached. A polyester cuff helps prevent infection and secures the catheter in place by inciting granulation in the subcutaneous tunnel. Catheter placement is usually performed under conscious sedation, on an outpatient basis, in the day surgery or ambulatory procedure unit. The insertion technique is essentially a combination of thoracentesis and a modified Seldinger technique. A recent publication by Tremblay and Michaud [34] describes the technique in a step-by-step manner. After pleural catheter placement, pleural fluid may be drained periodically from the chest into vacuum bottles by connecting the drainage line access tip to the valve. Subsequent drainage is performed using a special vacuum bottle system. The bottle has a preconnected tube containing a catheter to be inserted into the valve of the pleural catheter. Drainage is usually performed every other day but can be done more frequently. Recent case reports [35] suggest that daily drainage of all the fluid in the pleural space may result in earlier and more frequent pleurodesis. Drainage takes approximately 10–15 min and is readily accomplished by a visiting nurse, family member, or the patient himself. When the pleural fluid output drops to less than 50 ml on three consecutive drainages, pleurodesis is assumed and, after the absence of fluid in the pleural space is confirmed with a chest radiograph, the pleural catheter is removed [36].

In 1999, Putnam *et al.* [37] published a study comparing long-term pleural drainage catheters with doxycycline sclerotherapy. Equivalent safety and efficacy were shown, and there was no difference in median survival. The pleural catheter group had a trend toward greater improvement in dyspnea after exercise at 1–3 months, but similar improvements were seen in quality of life. The median hospitalization time was 1 day for pleural catheter patients, compared with 6.5 days for sclerotherapy patients. Spontaneous pleurodesis developed in 46% of pleural catheter patients (median 29 days, range 8–223 days), whereas pleurodesis occurred in 54% of sclerotherapy patients.

A cost analysis by Putnam *et al.* [4] looked at 100 pleural catheter patients (60 outpatients, 40 inpatients) treated between 1994 and 1998 and compared them with 68 consecutive inpatients treated with tube thoracostomy and pleurodesis between 1994 and 1997 at their institution. Hospital charges were obtained from date of insertion (day 0) through day 7. They found significantly ($P = 0.001$) lower hospital charges for outpatients who received pleural catheter (mean charge: $\$3339 \pm 1753$), compared with inpatients who received pleural catheter ($\$11\,188 \pm 7964$) and inpatients treated with tube thoracostomy and pleurodesis ($\$7830 \pm 4497$).

In 2004, Musani *et al.* [5] in a retrospective analysis of 24 outpatients and 27 pleural catheters reported control of MPE with 100% relief of dyspnea and spontaneous pleurodesis in 58% of patients, without any added intervention, over a mean period of 39 days (range 7–85 days).

Complication rates related to pleural catheters are low and compare favorably with those seen with other treatment options. In a series of 250 patients [34], the most common complications of pleural catheters were symptomatic pleural fluid loculation occurring in 8% of patients, followed by unsuccessful insertion and asymptomatic pleural fluid loculation in 4%, empyema in 3%, and pneumothorax in 2%. Rare complications included cellulitis, bleeding, catheter dislodgment, tumor seeding the catheter site, and pain requiring removal of catheter.

The experience with pleural catheters continues to grow and appears promising. Advantages of pleural catheters include cost-effectiveness, outpatient control of the effusion, a minimally invasive approach, and user-friendly technology. Pleurodesis may occur spontaneously in 42–58% [5] of patients within 4–6 weeks. Chemical pleurodesis remains an option with pleural catheters. In addition, pleural catheters could potentially be used in the future to administer anticancer agents and novel therapies, such as gene therapy vectors, for intrapleural malignancies.

## Conclusion

Indwelling pleural catheters and medical thoracoscopy offer cost-effective and minimally invasive options for the management of MPE. These options should be considered in the algorithm for treating MPE in all MPE patients [10••].

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A.I.M., MD, serves as member speaker panel, Cardinal Health (previously, Denver Biomedical, Inc).

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- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 395).

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