

Key Points

- Pleural effusions are a common clinical problem.
- Transudative effusions should be distinguished from exudative effusions because of differences in etiology and treatment.
- Definitive diagnosis may require thoracoscopy and pleural biopsy.
- Transudative effusions respond to management of underlying etiology.
- Exudative effusions, especially if cancer-related, are usually managed by pleurodesis.

Pleural effusions are a common and significant clinical problem. During the past 2 decades, several advances have made possible a more systematic approach to their management, and research, based primarily on animal models, has provided a better understanding of their pathophysiology.¹⁻³ Characterization of the biochemical characteristics of pleural fluid has improved our ability to diagnose the cause of an effusion by using the relatively noninvasive approach of thoracentesis (Light, 1983).^{4,5} The advent of computed tomography (CT) in the late 1970s also dramatically improved the noninvasive evaluation of pleural disease. Thoracoscopy, which was always a popular procedure in Europe (Deslauriers and Lacquet, 1990),^{6,7} is now widely practiced in North America for the diagnosis and treatment of pleural disease because of the development of video-assisted technology in the early 1990s. Patients who previously were subjected to multiple thoracenteses and percutaneous pleural biopsies are now offered thoracoscopy if the initial noninvasive evaluation is not diagnostic. Finally, pleurodesis for malignant pleural effusions, which was often performed in a highly individualized manner, has been evaluated in well-designed prospective trials.

A better understanding of pathophysiology, better imaging, faster and more accurate methods of diagnosis, and the careful assessment of therapy have improved the diagnosis and treatment of pleural effusions. This chapter covers the current approach to the management of pleural effusions, focusing on malignant pleural effusions, which are the most common problem seen by surgeons.

PATHOPHYSIOLOGY

The anatomy and physiology of the pleural space were described in detail in Chapter 82. Pleural effusions develop because of a disturbance in the mechanisms that normally

move 5 to 10 L of fluid across the pleural space every 24 hours and resorb it, leaving only 5 to 20 mL present at any time.^{3,8} Increased capillary permeability (inflammation or tumor implants), increased hydrostatic pressure (congestive heart failure), decreased oncotic pressure (hypoalbuminemia), increased negative intrapleural pressure (atelectasis), and decreased lymphatic drainage (lymphatic obstruction by a tumor or radiation-induced fibrosis) can all cause a pleural effusion. In patients with cancer, several different mechanisms often contribute to the formation of an effusion (Table 85-1). These mechanisms may relate directly to the presence of the tumor (e.g., obstruction of lymphatic channels), may reflect underlying medical problems (e.g., congestive heart failure, hypoalbuminemia), or may be a combination of both.

CLINICAL PRESENTATION AND DIAGNOSIS

Small pleural effusions are asymptomatic. Larger pleural effusions cause dyspnea, cough, and chest discomfort. Dullness to percussion and diminished breath sounds are present on the physical examination. The clinical diagnosis is confirmed by chest radiography. Small pleural effusions cause blunting of the costophrenic angle. If the pleural space is free, larger effusions produce the classic picture of a fluid level with a meniscus sign (Fig. 85-1). A lateral decubitus radiograph confirms freely flowing fluid (Fig. 85-2). Massive effusions cause a complete opacification of the hemithorax. Rarely, they manifest as a tension hydrothorax, with a mediastinal shift, respiratory distress, and hemodynamic instability. Loculated pleural effusions are harder to diagnose on a standard chest radiograph. They manifest as opacities of varying size and shape that can be hard to distinguish from a pulmonary parenchymal process such as atelectasis or dense consolidation (Fig. 85-3). Lateral decubitus radiographs do not show layering of the fluid. Ultrasonography detects a loculated fluid collection and can help determine the proper site for thoracentesis, but the most useful examination under these circumstances is a CT scan. This helps direct therapy by outlining the size and location of fluid collections and by distinguishing underlying parenchymal disease from pleural fluid and thickening (Fig. 85-4). Thin-section CT, with images at intervals of 2 to 5 mm, is more accurate in identifying pleural metastases than standard CT because it detects very small pleural nodules.⁹

The clinical setting in which an effusion occurs influences the approach to diagnosis and therapy. A patient who develops a small effusion in conjunction with pneumonia but is improving while receiving antibiotics is likely to have a para-

TABLE 85-1 Interaction Among Pathogenetic Mechanisms and Contributing Factors Favoring the Accumulation of Pleural Fluid

Pathogenetic Mechanisms	Impaired Lymphatic Drainage	Increased Pleural Permeability Pressure	Increased Capillary Pressure	Increased Venous Pressure
Pleural implants	+	+	+	–
Lymphatic metastases				
Mediastinal nodes	+	+	–	–
Lymphangitis	+	+	–	–
Tumor cell suspension	+	+	+	–
Contributing syndromes				
Superior vena cava syndrome	+	+	–	+
Congestive heart failure	+	+	–	+
Pericarditis or effusion	+	+	–	–
Infection	+	+	+	–
Mediastinal irradiation	+	+	–	–
Ascites	+	+	–	+
Hypoalbuminemia	–	+	–	–

+, contributes; –, does not contribute.

Data from Roth JA, Ruckdeschel JC, Weisenburger TH (eds): *Thoracic Oncology*. Philadelphia, WB Saunders, 1989, p 596; and Harper GR: *Pleural effusions in cancer*. *Clin Cancer Briefs* 1:1, 1979.

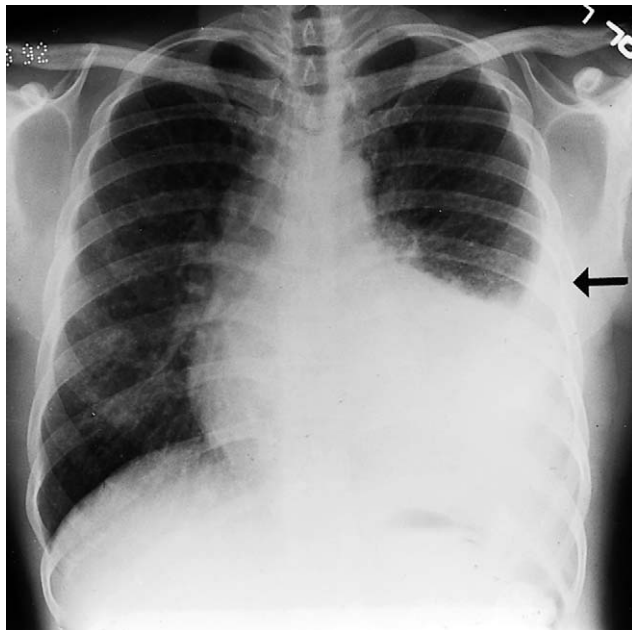


FIGURE 85-1 Posteroanterior chest radiograph of a patient with widely disseminated lung cancer and a left pleural effusion. The retrocardiac region is opacified, and there is a fluid level with a typical meniscus sign (arrow).

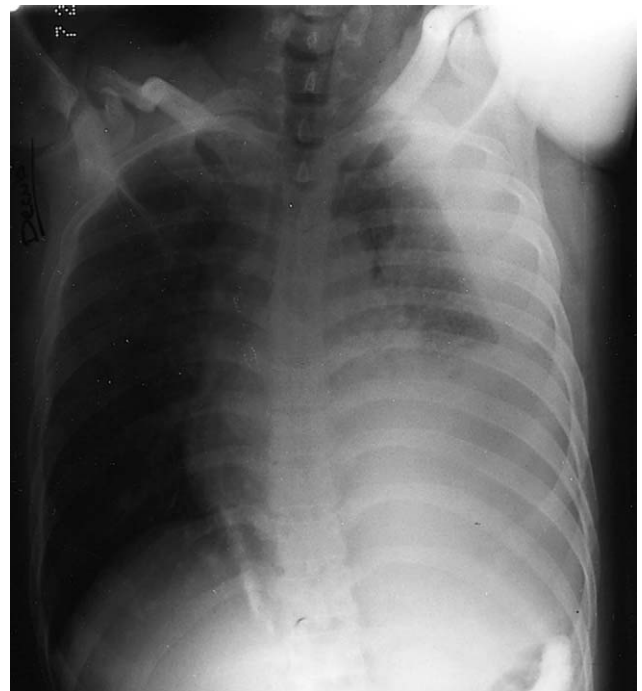


FIGURE 85-2 The lateral decubitus chest radiograph of the patient shown in Figure 85-1 shows that the pleural effusion layers easily and is, therefore, free flowing.

pneumonic effusion and could be treated expectantly. The same would be true of a patient with known cirrhosis and ascites who has a small pleural effusion. These effusions are known to occur in the absence of primary intrathoracic disease and are related to the presence of peritoneopleural communication.¹⁰ In contrast, a woman who develops a new pleural effusion several years after treatment for a node-positive breast cancer merits intensive investigation. Before

any invasive workup is initiated, the patient with a pleural effusion needs to have a careful history and physical examination so that all subsequent evaluation is directed toward the clinically likely causes (Box 85-1).

Knowledge of the most common causes of pleural effusions is also helpful in defining etiology. The four most common causes of pleural effusions in North America are congestive

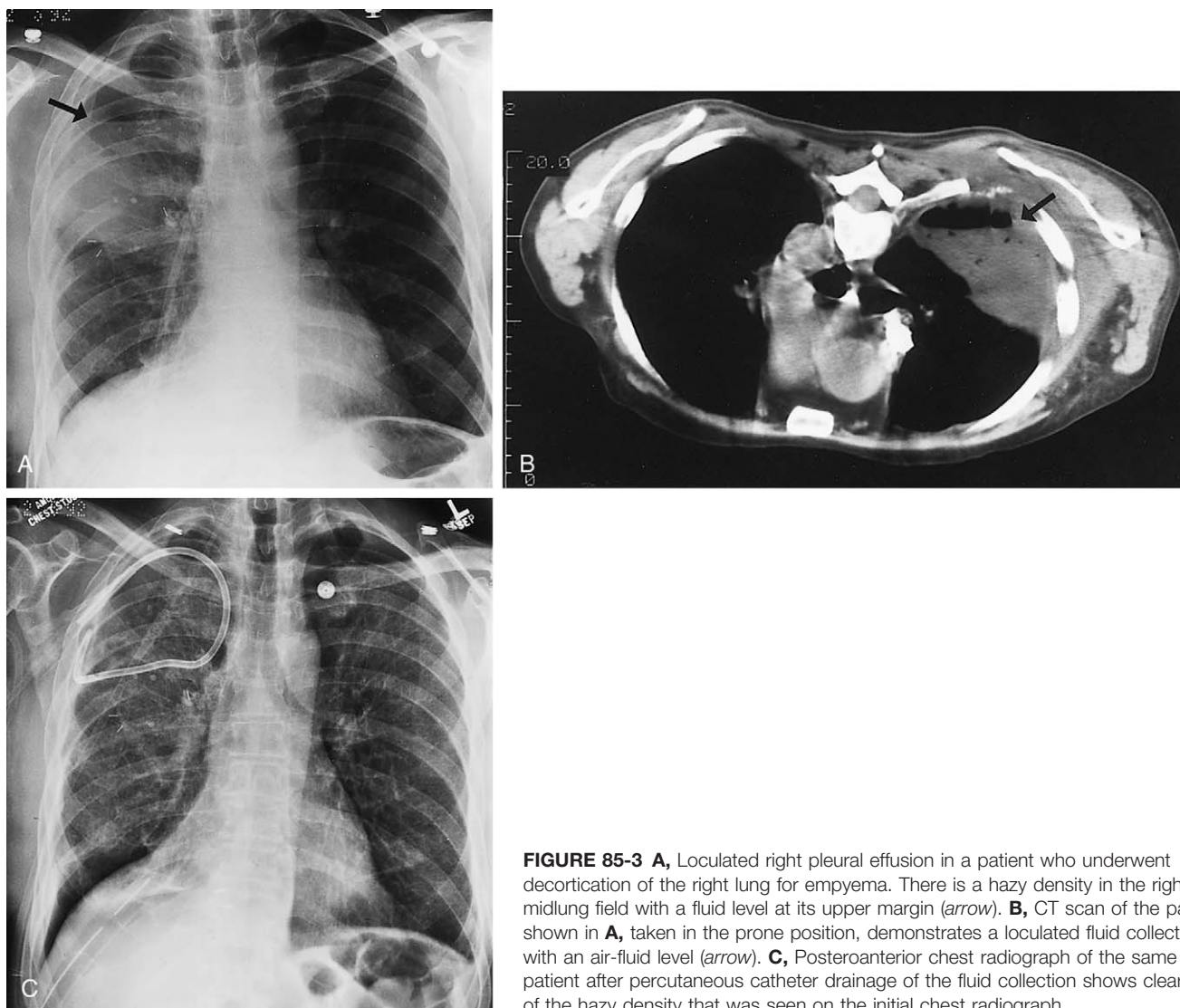


FIGURE 85-3 **A**, Loculated right pleural effusion in a patient who underwent decortication of the right lung for empyema. There is a hazy density in the right midlung field with a fluid level at its upper margin (*arrow*). **B**, CT scan of the patient shown in **A**, taken in the prone position, demonstrates a loculated fluid collection with an air-fluid level (*arrow*). **C**, Posteroanterior chest radiograph of the same patient after percutaneous catheter drainage of the fluid collection shows clearing of the hazy density that was seen on the initial chest radiograph.

heart failure, bacterial pneumonia, malignancy, and pulmonary emboli. Viral pneumonia, cirrhosis with ascites, gastrointestinal disease, collagen-vascular disease, and tuberculosis are less common causes.⁴ The most common causes of malignant pleural effusion are lung cancer, breast cancer, and lymphoma. However, the frequency of the type of cancer responsible for a pleural effusion depends on the patient's gender. Lung cancer, lymphoma, and gastrointestinal cancer are the three most common causes in men; breast cancer, gynecologic cancer, and lung cancer are the most common ones in women (Tables 85-2, 85-3, and 85-4).

If the diagnosis is not clinically obvious, a thoracentesis needs to be performed and the character of the fluid noted. Bloody fluid occurs with pulmonary emboli, malignancy, or trauma. Clear milky fluid is strongly suggestive of a chylothorax; turbid or purulent fluid is indicative of an empyema.

Send the pleural fluid for cytologic examination, culture, and cell count. Obtain simultaneous determinations of pleural fluid and serum glucose, protein, and lactic dehydrogenase

levels. Effusions are classified as exudative or transudative based on the levels of protein and lactic dehydrogenase (LDH). An effusion is considered an exudate if the pleural fluid-to-serum ratio of protein is greater than 0.5, the LDH ratio is greater than 0.6, or the absolute pleural LDH level is greater than two thirds of the normal upper limit for serum.⁵ The most common cause of transudative effusions is congestive heart failure. There are many causes of exudative effusions, but the most common ones are malignancy, infection, and pulmonary emboli. The pleural fluid concentration of glucose is also helpful because a level less than 60 mg/dL is seen only in four conditions: malignancy, tuberculous pleuritis, parapneumonic effusions, and rheumatoid pleural effusion.¹¹⁻¹³ Therefore, a patient who has a bloody exudative effusion with a low glucose level is likely to have a malignancy.

Several other biochemical tests are helpful in specific clinical situations. The amylase level is elevated in three conditions: esophageal perforation, pancreatitis, and malignant effusions. Obtain a triglyceride level if a chylothorax is sus-

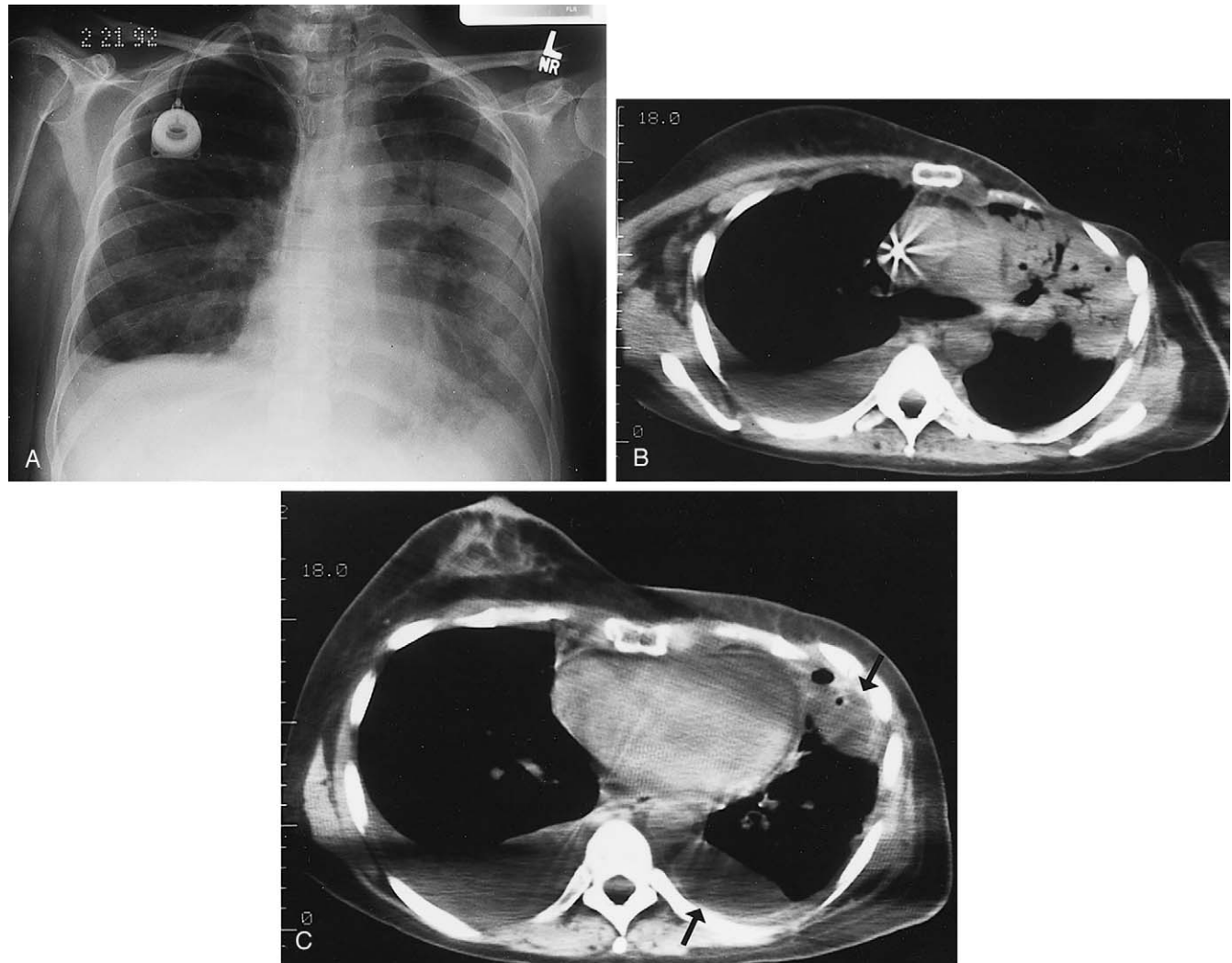


FIGURE 85-4 **A**, Another example of a loculated pleural effusion that is extremely difficult to distinguish from underlying parenchymal disease in a patient who had severe radiation-induced fibrosis. The posteroanterior chest radiograph shows a hazy density in the midlateral aspect of the left lung with an underlying air bronchogram. **B**, CT scan of the same patient at the level of the carina shows dense consolidation of the left upper lobe with an air bronchogram. There is no pleural fluid at this level. **C**, CT scan of the same patient at the level of the midheart shows a large free-flowing right pleural effusion and a multiloculated left pleural effusion (arrows). This combination of parenchymal disease and multiloculated pleural effusion accounts for the abnormalities seen on the plain chest radiograph in **A**. It would be hard to interpret the chest radiograph and make a determination of whether drainage of the pleural effusion would be appropriate without the aid of the CT scan.

pected. A level greater than 110 mg/dL is considered diagnostic. Pleural fluid pH and glucose levels have been used in the evaluation of parapneumonic effusions. Light reported that a pH less than 7.00 in conjunction with a glucose level less than 60 mg/dL indicates that a parapneumonic effusion will progress to a frank empyema.⁴ However, other authors have not found the pH and glucose levels to be as reliable in the management of parapneumonic effusions. Complement, rheumatoid factor, and antinuclear antibody levels are often elevated in collagen-vascular disease and need to be obtained if this is being considered in the differential diagnosis.⁴

Other tests have been used to determine the cause of pleural effusions and particularly to ascertain whether an effusion is malignant. The level of carcinoembryonic antigen (CEA) has been the most widely used pleural fluid marker.

Levels of this antigen higher than 5.0 ng/mL are a specific but relatively insensitive marker of malignancy.¹⁴⁻¹⁷ Creatine kinase isoenzyme BB, adenosine deaminase, and galactosyl-transferase have been reported to distinguish benign from malignant effusions in small series of patients.¹⁸⁻²⁰ Various immunohistochemical stains have been used to identify malignant cells and to distinguish them from reactive mesothelial cells.²¹ Flow cytometry is relatively inaccurate in diagnosing malignancy because cytologically positive pleural effusions do not always contain aneuploid cells.²² Cytogenetic techniques can diagnose malignant pleural effusions, but they are labor intensive and do not consistently add to the standard cytologic examination.²³⁻²⁶ Uptake of technetium 99m phosphate in malignant pleural effusions has been anecdotally reported in patients undergoing bone scans to search for

Box 85-1 Differential Diagnosis of Pleural Effusions

- I. Transudative pleural effusions
 - A. Congestive heart failure
 - B. Cirrhosis
 - C. Nephrotic syndrome
 - D. Peritoneal dialysis
 - E. Glomerulonephritis
 - F. Myxedema
 - G. Pulmonary emboli
 - H. Sarcoidosis
- II. Exudative pleural effusions
 - A. Neoplastic diseases
 - 1. Metastatic disease
 - 2. Mesothelioma
 - B. Infectious diseases
 - 1. Bacterial infections
 - 2. Tuberculosis
 - 3. Fungal infections
 - 4. Parasitic infections
 - 5. Viral infections
 - C. Pulmonary embolization
 - D. Gastrointestinal disease
 - 1. Pancreatitis
 - 2. Subphrenic abscess
 - 3. Intrahepatic abscess
 - 4. Esophageal perforation
 - 5. Diaphragmatic hernia
 - E. Collagen-vascular diseases
 - 1. Rheumatoid pleuritis
 - 2. Systemic lupus erythematosus
 - 3. Drug-induced lupus
 - 4. Immunoblastic lymphadenopathy
 - 5. Sjögren's syndrome
 - 6. Familial Mediterranean fever
 - 7. Wegener's granulomatosis
 - F. Drug-induced pleural disease
 - 1. Nitrofurantoin
 - 2. Dantrolene
 - 3. Methysergide
 - 4. Bromocriptine
 - 5. Procarbazine
 - 6. Methotrexate
 - 7. Practolol
 - G. Miscellaneous diseases and conditions
 - 1. Asbestos exposure
 - 2. Postpericardiectomy or postmyocardial infarction syndrome
 - 3. Meigs' syndrome
 - 4. Yellow nail syndrome
 - 5. Sarcoidosis
 - 6. Uremia
 - 7. Trapped lung
 - 8. Radiation therapy
 - 9. Electrical burns
 - 10. Urinary tract obstruction
 - 11. Iatrogenic injury
 - H. Hemothorax
 - I. Chylothorax

From Light RW: *Pleural Diseases*. Philadelphia, Lea & Febiger, 1983, p 62, with permission.

TABLE 85-2 Primary Organ Site or Neoplasm Type in Male Patients With Malignant Pleural Effusions

Primary Site or Tumor Type	No. Patients	%
Lung	140	49.1
Lymphoma/leukemia	60	21.1
Gastrointestinal tract	20	7.0
Genitourinary tract	17	6.0
Melanoma	4	1.4
Miscellaneous less common tumors	10	3.5
Primary site unknown	31	10.9
Total	285	100.0

From Johnson WW: *The malignant pleural effusion: A review of cytopathologic diagnoses of 584 specimens from 472 consecutive patients*. *Cancer* 56:905, 1985.

TABLE 85-3 Primary Organ Site or Neoplasm Type in Female Patients With Malignant Pleural Effusions

Primary Site or Tumor Type	No. Patients	%
Breast	70	37.4
Female genital tract	38	20.3
Lung	28	15.0
Lymphoma/leukemia	14	8.0
Gastrointestinal tract	8	4.3
Melanoma	6	3.2
Urinary tract	2	1.1
Miscellaneous less common tumors	3	1.6
Primary site unknown	17	9.1
Total	187	100.0

From Johnson WW: *The malignant pleural effusion: A review of cytopathologic diagnoses of 584 specimens from 472 consecutive patients*. *Cancer* 56:905, 1985.

TABLE 85-4 Primary Tumor Site in Patients With Malignant Pleural Effusion

Primary Tumor Site	Salyer ¹⁴¹ (n=95)	Chernow ¹⁴² (n=96)	Johnston ¹⁴³ (n=472)	Sears ¹⁴⁴ (n=592)	Hsu ¹⁴⁵ (n=785)	Total (%)
Lung	42	32	168	112	410	764 (37.5)
Breast	11	20	70	141	101	343 (16.8)
Lymphoma	11	–	75	92	56	234 (11.5)
Gastrointestinal tract	–	13	28	32	68	141 (6.9)
Genitourinary tract	–	13	57	51	70	191 (9.4)
Other	14	5	26	88	15	148 (7.3)
Unknown primary	17	13	48	76	65	219 (10.7)

From Antunes G, et al: BTS Guidelines for the management of malignant pleural effusions. Thorax 58(Suppl II):ii29-ii38, 2003. Reproduced with permission from the BMJ Publishing Group.

osseous metastases.^{27,28} Although this is not likely to be useful as a routine diagnostic test, remember its clinical significance as an incidental finding.

More recently, molecular biologic techniques have been applied to the diagnosis of pleural effusions. These include the development of a sensitive and specific assay, based on the reverse transcriptase–polymerase chain reaction (RT-PCR), to detect epithelial tumor cells that potentially increase the diagnosis of malignancy in cytologically negative effusions.²⁹ The detection of specific molecular alterations, such as *KRAS* mutations, may also enhance the diagnosis of malignancy in pleural effusions.³⁰ Telomerase activity is frequently observed in malignant effusions but also is occasionally seen in some inflammatory conditions such as tuberculosis.^{31,32} The precise benefit of molecular techniques in the diagnosis of pleural effusion requires further investigation.

The long list of tests that can be performed on pleural effusions to pinpoint a cause are of academic rather than practical interest. The character of the fluid (e.g., bloody versus serous), a determination of whether it is an exudate or a transudate, measurement of the glucose level, and culture and cytologic examination are the most important initial tests.³³⁻³⁵ Additional biochemical or molecular analyses are used selectively, based on the clinical setting. If the examination of the pleural fluid is nondiagnostic, consider a percutaneous or thoracoscopic pleural biopsy. A percutaneous pleural biopsy alone yields a diagnosis of malignancy in 40% to 69% of cases. When pleural fluid cytologic findings and pleural biopsy results are combined, the yield increases to 80% to 90%.³⁶⁻³⁹ Pleural biopsy can also diagnose some benign diseases, such as tuberculous effusion or amyloidosis, in situations in which the pleural fluid analysis is uninformative.⁴⁰⁻⁴²

Patients whose effusions remain undiagnosed after a thoracentesis with or without percutaneous pleural biopsy undergo a CT scan of the chest and abdomen, a bronchoscopy, and a thoracoscopy. If the effusion is large, do the CT scan after the fluid has been evacuated so that the lung can be imaged when it is fully expanded. The CT detects underlying pulmonary parenchymal and abdominal disease that may not be evident otherwise. Bronchoscopy diagnoses endo-

bronchial tumors (primary or metastatic) that may be responsible for an effusion due to postobstructive atelectasis. Thoracoscopy is performed to obtain a tissue diagnosis by directed pleural biopsy and to do a pleurodesis, usually by talc poudrage. Several large series have reported a diagnostic accuracy of 80% to 100% for thoracoscopy, depending on the reasons for which thoracoscopy was performed. In almost all patients, it is the definitive way of diagnosing a malignancy involving the pleura.⁴³⁻⁵¹ The exceptions are patients in whom thoracoscopy cannot be performed because of a fused pleural space. The development of video-assisted thoracoscopy (VATS) significantly expanded the diagnostic potential of this technique by making lung and lymph node biopsies possible.^{52,53} In the past, patients often underwent multiple thoracenteses and percutaneous pleural biopsies in an effort to avoid a thorotomy for diagnosis. Thoracoscopy, widely used in Europe for a long time, was a largely forgotten procedure in North America for the diagnosis of pleural disease.⁵⁴ With the popularization of VATS, patients with undiagnosed pleural effusions are now referred sooner for this minimally invasive and highly diagnostic procedure.

MANAGEMENT

General Principles

Transudative pleural effusions are managed by treatment of the underlying disease and usually resolve after it has been controlled.^{4,55} Occasionally, additive intervention is required, either because the effusion is symptomatic or because the underlying medical problem is refractory to maximal medical treatment. For example, tube thoracostomy might be necessary to drain a large effusion secondary to a pulmonary embolus, or a pleurodesis or pleuroperitoneal shunt might be required to control a symptomatic effusion in a patient with medically refractory ascites.

Some exudative effusions also resolve after treatment of the underlying disease. This is true of effusions caused by gastrointestinal disease, drugs, collagen vascular disease, and nonbacterial infections.^{4,6,42} Some exudative effusions caused by malignancy are also best managed in this manner if the

tumor is highly responsive to chemotherapy or irradiation. The classic example is an effusion or chylothorax caused by a lymphoma, which usually resolves quickly after chemotherapy or irradiation alleviates the lymphatic obstruction.³⁵ Effusions caused by solid tumors, such as breast cancer and ovarian cancer metastases, for which effective chemotherapy is available, also may resolve spontaneously after chemotherapy is instituted.^{6,55,56}

The most difficult management problem is the malignant pleural effusion caused by a tumor that is refractory to chemotherapy. Traditionally, these have been treated by some form of pleurodesis. Before proceeding with pleurodesis, however, it is important to make certain that the patient does not have “trapped” lung with a fixed pleural space. The lung is often encased by a peel of visceral pleural tumor that causes chronic collapse of the lung and prevents the parietal and visceral pleural surfaces from coming into apposition with each other. Effective pleurodesis under these circumstances is obviously impossible. Partial entrapment of the lung with smaller loculated effusions is also common in patients with cancer. Sometimes this is not caused by a pleural tumor but is the result of a chronic effusion that contains a lot of protein and fibrinous debris, which create a limited fibrothorax. A trapped lung is readily recognized by lack of expansion of the lung after therapeutic thoracentesis or chest tube insertion (Fig. 85-5). Complete or near-complete expansion of the lung and evacuation of the pleural space is documented on a chest radiograph before proceeding with pleurodesis.

Pleurodesis for Malignant Effusions

At one time, it was believed that malignant pleural effusions could be controlled by serial thoracentesis or tube thoracostomy alone without pleurodesis. Although Lambert and colleagues reported a recurrence rate of only 17% for effusions managed by tube thoracostomy alone, subsequent experience

with this approach demonstrated that virtually all patients experienced a rapid reaccumulation of their effusion.^{57,58} Today, drainage of the effusion without pleurodesis (usually by serial thoracentesis) is considered appropriate only for terminally ill patients who are unwilling or unable to tolerate other therapies.

A large number of agents have been used intrapleurally to try to control malignant pleural effusions. These agents can be classified in two broad categories, according to their modes of action:

1. *Cytostatic agents*: Presumably control the effusion by reducing the tumor volume
2. *Sclerosants*: Produce a chemical pleuritis that leads to the formation of adhesions and subsequent obliteration of the pleural space⁵⁹

Radioactive colloids and some chemotherapeutic agents (nitrogen mustard, doxorubicin, and bleomycin) may combine both modes of action when administered intrapleurally. However, with the exception of cisplatin and perhaps thiotepa and 5-fluorouracil, most chemotherapeutic drugs act predominantly as sclerosants.

The early experience with pleurodesis for malignant pleural effusions was comprehensively reviewed.^{60,61} Nitrogen mustard controlled the effusions in approximately one third of cases but caused significant pleuritic pain and fever and was associated with bone marrow depression.^{58,62} Thiotepa and 5-fluorouracil have fewer side effects but are no better at controlling effusions.⁵⁵ Response rates as high as 80% have been reported for intrapleural doxorubicin, but the associated problems of pain, fever, and nausea and vomiting preclude its routine use.⁶³⁻⁶⁵ Quinacrine was an effective sclerosant that controlled effusions in up to 80% of patients but caused severe pleuritic pain, fever, nausea, and occasionally, hypotension, hallucinations, and seizures.^{66,67} These agents were abandoned, either because of their ineffectiveness or because of

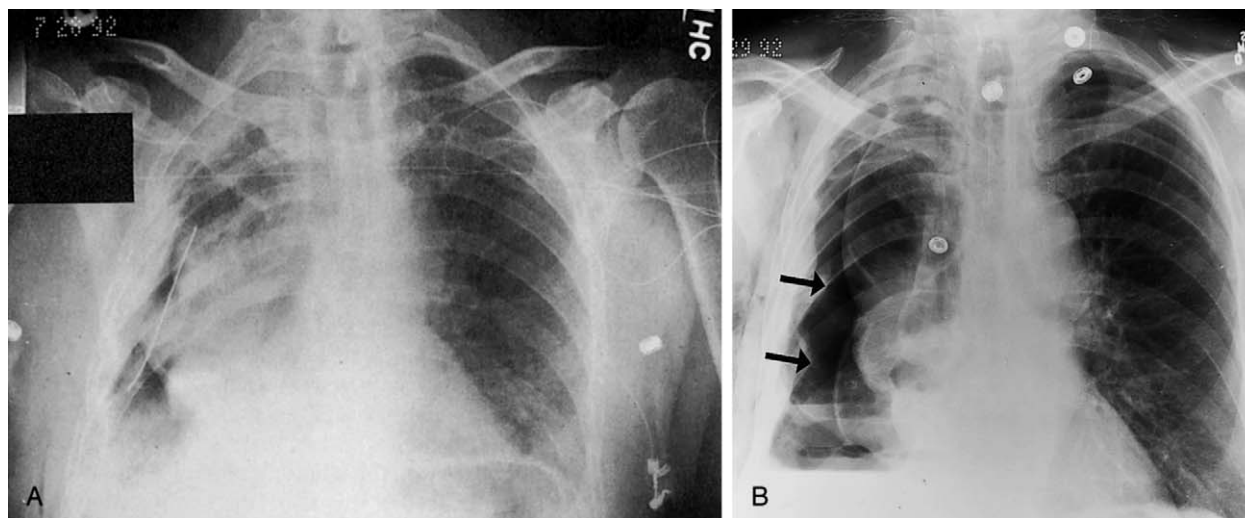


FIGURE 85-5 **A**, Posteroanterior chest radiograph on a patient with malignant mesothelioma who underwent a thoracoscopy for diagnosis. The lung was clearly trapped at thoracoscopy. The initial postoperative portable chest radiograph shows evacuation of the pleural space with an unexpanded lung. **B**, The chest radiograph obtained on the following day, after removal of chest tube, shows this more clearly. There is a fixed pleural space (arrows) and lack of re-expansion of the underlying lung. This patient would not be an appropriate candidate for pleurodesis.

significant toxicity. Radioactive colloids including radioactive zinc (^{63}Zn), gold (^{198}Au), and chromium phosphate ($\text{Cr}_{32}\text{PO}_4$) were associated with little toxicity but were successful in only 50% to 60% of patients.^{61,68} They were also expensive and inconvenient because of the need to shield hospital personnel from radioactivity and therefore are no longer routinely used. Experience with these agents, however, established that pleurodesis was more likely to be successful if the pleural space was fully evacuated by tube thoracostomy before instillation of the sclerosant and the chest tube was left in place after the pleurodesis until the drainage was minimal. This remains an important principle in performing a pleurodesis.

Tetracycline pleurodesis was introduced in 1972. It had the advantage of being inexpensive, easily available, and relatively nontoxic. Its major side effect was severe pleuritic pain, which was often difficult to control even with appropriate systemic premedication and the use of intrapleural lidocaine.⁶⁹⁻⁷¹ Success rates ranging from 39% to 83% were reported with tetracycline in several prospective studies comparing it with other agents (Table 85-5). The effectiveness of tetracycline depended on the dose and technique. Tetracycline had so many advantages over other sclerosants that it rapidly became the agent of choice, even though it did not always result in a successful pleurodesis.

Bleomycin also became a popular sclerosant.⁷²⁻⁷⁴ Its success rate was at least as good and perhaps better than that of tetracycline, and it caused less pain.⁷⁵ A prospective randomized trial that compared pleurodesis with 1 g of tetracycline versus 60 units of bleomycin found that the median time to recurrence or progression of the effusion was 32 days for tetracycline and 46 days for bleomycin. The recurrence rate within 90 days after instillation was 30% with bleomycin and 53% with tetracycline. Toxicity was similar for the two agents.⁷⁵ Although bleomycin usually is well tolerated, it can occasionally cause nephrotoxicity in patients with underlying renal insufficiency. Bleomycin is also expensive.

In the early 1990s, the manufacture of tetracycline was discontinued, and in North America this led to a resurgence in the use of talc, a sclerosant first used by Bethune in 1935 that was always popular in Europe.⁷⁶ Because talc is insoluble, it is administered either as a powder, by insufflation at thoracoscopy or thoracotomy ("talc poudrage"), or as a suspen-

sion, via tube thoracostomy ("talc slurry").⁷⁷⁻⁷⁹ This approach has become increasingly popular, and the success rates with talc slurry approximate those achieved by VATS and talc poudrage.^{80,81} Experimentally, talc was shown to cause an intense chemical pleuritis that exceeds that caused by other agents.^{59,77} Table 85-6 summarizes some of the published experience with talc. Its reported success rate has consistently been 90% or better.⁸²⁻⁹⁸ Several randomized trials showed that talc is superior to tetracycline or bleomycin.^{7,87,99-101} Iodine was sometimes added to the talc to keep the talc sterile and to intensify the pleuritis,^{79,102} but this is clearly not necessary in light of the high success rate of noniodized talc.

Fever and pleuritic pain occur after the administration of talc, although pain seems to be far less common and less severe than with tetracycline. There have been rare reports of adult respiratory distress syndrome developing after talc pleurodesis,^{103,104} but given the thousands of patients treated with talc over several decades, the risk of this complication appears to be low.¹⁰⁵ It has been hypothesized that the development of adult respiratory distress syndrome may be related to the amount of talc used or to contaminants within the talc preparation.¹⁰⁶ However, published series report using widely varying amounts of talc (usually at least 5 to 10 g), and some do not specify the amount of talc used at all. Moreover, when a talc poudrage is performed, it is hard to estimate the amount of talc remaining in the pleural space because some of it is dissipated into the air during the procedure. There was some concern in the past that talc pleurodesis might lead to a significant decrease in pulmonary function and predispose to the development of malignancy. A mild restrictive defect was seen as a late sequela in patients who underwent talc pleurodesis for spontaneous pneumothorax.¹⁰⁷ Long-term follow-up (14-40 years) by the British Thoracic Association of 210 patients who underwent pleurodesis disclosed no increased incidence of lung cancer or mesothelioma.¹⁰⁸ The risk of carcinogenesis from talc may have been related to contamination of the talc preparations with asbestos. Talc prepared for medical use today is asbestos free. Neither one of these issues is important for patients with malignant pleural effusions, who usually have a life expectancy of less than 1 year and who need pleurodesis to palliate their dyspnea.

Several early collective reviews^{55,60,61} attempted to assess the relative merits of the various agents used as sclerosants (Table 85-7). This was difficult because many of the published series were retrospective and uncontrolled. Prospective trials have often been poorly designed because they are based on small numbers of patients and loosely defined eligibility and response criteria. Follow-up is usually short, and a central review of chest radiographs to verify the response data is rare.¹⁰⁹ In addition, patients with malignant pleural effusions represent a difficult patient population in which to carry out clinical trials. They have a limited life expectancy, with about half of the patients dying within 3 months of therapy. Therefore, large numbers of patients must be entered into a study to have statistically adequate numbers available to analyze response rates and toxicity. Many patients require ongoing radiation therapy or chemotherapy, which can make it hard to evaluate the effect and morbidity of pleurodesis.

TABLE 85-5 Results of Tetracycline Pleurodesis in Pleural Effusions

No. Successful/Total Patients	Success Rate (%)
10/12	83
7/7	100
10/12	83
53/60	80
15/25	60
101/108	94

Adapted from Boutin C, Viallat JR, Aelony Y: Practical Thoracoscopy. Berlin, Springer-Verlag, 1991, p 68.

TABLE 85-6 Results of Studies of Talc Pleurodesis for Malignant Pleural Effusions

Author (Year)	Method of Administration	No. Controlled/No. Treated (%)
Chambers (1958)	Suspension, chest tube	17/20 (85)
Camishion et al (1962)	Poudrage, thoracotomy	30/31 (97)
Roche (1963)	Poudrage, thoracoscopy	6/6 (100)
Pearson and MacGregor (1966)	Poudrage, thoracotomy or trocar	17/19 (89)
Adler and Rappole (1967)	Poudrage, thoracoscopy	4/4 (100)
Jones (1969)	Poudrage, thoracoscopy	22/23 (96)
Shedbalkar et al (1971)	Not stated	22/28 (96)
Adler and Sayek (1976)	Suspension, chest tube	41/44 (93)
Harley (1979)	Poudrage, thoracoscopy	41/44 (93)
Austin and Flye (1979)	Suspension, chest tube	38/41 (91)
Todd et al (1980)	Poudrage, thoracotomy or trocar	158/163 (97)
Scarbonchi et al (1981)	Poudrage, thoracoscopy	70/77 (91)
Migueres et al (1981)	Poudrage, thoracoscopy	15/26 (58)
Sorensen et al (1984)	Suspension, chest tube	9/9 (100)
Ladjimi et al (1985)	Poudrage, thoracoscopy	66/78 (85)
Viallat et al (1986)	Poudrage, thoracoscopy	23/25 (92)
Fentiman et al (1986)	Poudrage, thoracoscopy	11/12 (92)
Boniface and Guerin (1989)	Poudrage, thoracoscopy	233/254 (92)
Ladjimi et al (1989)	Poudrage, thoracoscopy	192/218 (88)
Hamed et al (1989)	Poudrage, thoracoscopy	10/10 (100)
Daniel et al (1990)	Poudrage, thoracoscopy	18/20 (90)
Ladjimi et al (1991)	Poudrage, thoracoscopy	18/21 (84)
Aelony et al (1991)	Poudrage, thoracoscopy	23/28 (82)
Engeler (1992)	Poudrage, thoracoscopy	19/20 (95)
Ohri et al (1992)	Poudrage, thoracoscopy	35/37 (95)
Webb et al (1992)	Suspension, chest tube	37/37 (100)
Hartman et al (1993)	Poudrage, thoracoscopy	22/25 (88)

Underlying pleural or pulmonary disease and minor degrees of entrapment of the lung confuse the interpretation of the response on chest radiographs. Assessment of symptoms is rarely meaningful because patients often have multiple reasons to feel dyspneic (e.g., pleural effusion plus lymphangitic spread of the tumor). Only recently has there been an attempt to develop well-designed clinical trials that include an adequate number of patients. A recent Cochrane review¹¹⁰ critically examined a total of 36 randomized clinical trials with 1499 subjects available for meta-analysis and concluded that the available evidence supported the use of chemical sclerosants for successful pleurodesis.

Intrapleural Cytotoxic Agents

Several different agents have been used in attempts to control pleural effusions by cytotoxicity rather than sclerosis. Some of these are thought to act indirectly by immunomodulation; others exert direct cytotoxicity. *Corynebacterium parvum*

enjoyed a period of popularity as an intrapleural agent after it was found to have antitumoral activity in an animal model.¹¹¹⁻¹¹³ Success rates ranging from 56% to 100% were reported, but at least one study found the incidence of pain and fever to be greater than with tetracycline.¹¹⁴ Tetracycline is not used routinely because the same or better results can be achieved with sclerosants that are more easily available. Intrapleural interleukin-2 was found to control effusions in a small number of patients in whom it induced lymphokine-activated killer cells.^{115,116} The expense and systemic toxicity of interleukin-2 limit its routine use, and its role outside the research setting remains to be shown.

Cisplatin is the drug that has been the most widely used for intracavitary chemotherapy. Multiple studies of intraperitoneal cisplatin, primarily for the treatment of ovarian cancer, showed that it acts through cytotoxicity rather than sclerosis and that the local pharmacologic advantage achieved by intracavitary administration can lead to tumor regression when systemic treatment has failed.^{117,118} The depth of pen-

TABLE 85-7 Results of the Principal Randomized, Controlled Studies of Pleurodesis in the Treatment of Pleurisy

No. Patients	Agents Used	Success Rates (%)
25	Quinacrine/Thiot	64/27
22	TCN/quinacrine	83/90
25	TCN/bleomycin	58/54
21	Cory/mustine	56/42
24	TCN/drainage	72/36
37	Mustard/talc	56/90
24	TCN/drainage	77/22
21	Talc/drainage	100/60
40	Talc/TCN	90/50
32	Cory/TCN	88/79
41	Talc/TCN	92/48
32	Cory/bleomycin	65/13
34	TCN/bleomycin	39/31
30	Talc/doxycycline	90/63

Cory, Corynebacterium parvum; TCN, tetracycline; Thiot, thiotepa. Adapted from Boutin C, Viallat JR, Aelony Y: Practical Thoracoscopy. Berlin, Springer-Verlag, 1991.

etration of drugs given by the intracavitary route appears to be 5 mm or less; therefore, they are not effective in the setting of bulky tumor.¹¹⁹ Cisplatin-based chemotherapy has also been administered intrapleurally,^{120,121} and the pharmacokinetic properties were found to be analogous to those obtained with the intraperitoneal route of administration.¹²² One study of cisplatin-based intrapleural chemotherapy for malignant pleural effusions reported a 49% response rate.¹²³ Intrapleural cisplatin carries the potential of significant toxicity because a significant amount is absorbed systemically¹²²; therefore, it is unlikely to be used routinely for the management of malignant pleural effusions. Rather, it may be useful in clinical trials designed to maximize the local intrathoracic effects of chemotherapy.¹²⁴

TECHNIQUES OF ADMINISTRATION

Administration of Sclerosing Agents by Tube Thoracostomy

Good and Sahn believed strongly that the technique of administration of tetracycline affected the success of pleurodesis.¹²⁵ They recommended insertion of a chest tube in the eighth or ninth intercostal space in the posterior axillary line and drainage of the effusion for 24 hours. Complete drainage of the pleural effusion and full expansion of the lung was documented by chest radiography. A dose of 15 to 20 mg/kg of tetracycline mixed in 75 mL of sterile water was then instilled through the chest tube into the pleural space. This was followed by 200 mL of air to facilitate contact of the tetracycline with both visceral and parietal pleural surfaces. The chest tube was clamped, and the patient was

rotated to the left and right lateral decubitus, prone, and supine positions every 30 minutes to disperse the tetracycline solution throughout the pleural cavity. At the end of 2 hours, the chest tube was unclamped and placed back on suction. It was removed when the drainage was less than 150 mL per 24 hours.

The methods proposed by Good and Sahn became widely accepted guidelines for the administration of any sclerosing agent by tube thoracostomy.¹²⁵ However, in practice there are some variations in the precise technique used with respect to drug dose and the amount of fluid in which it is mixed. The length of time that the chest tube is left to drainage before instillation of the intrapleural agent also varies. There is not clear evidence that the amount of chest tube drainage should be allowed to decrease to 100 to 150 mL per 24 hours before instillation of the intrapleural agent (Antunes et al, 2003).¹²⁶ Instillation can occur as soon as the pleural space is completely evacuated, usually within 48 hours after insertion of the chest tube. Some physicians remove the chest tube 24 hours after pleurodesis; others leave it in place until the drainage is less than 150 mL per 24 hours. However, the principles to be considered in performing a pleurodesis by tube thoracostomy remain as follows: First, for a pleurodesis to be effective, the lung must be fully expanded so that the parietal and visceral pleural surfaces are in apposition. Second, there must be good dispersion of the agent throughout the pleural space. This is less likely to occur if the chest tube has been in place for several days and loculations have begun to form around the tube. Third, the pleural surfaces must be kept in close apposition after instillation of the agent for the chemical pleuritis to progress to pleural symphysis. This is most likely to happen if the chest tube is left in place and on suction until drainage is minimal.

Talc Poudrage

Talc is often insufflated by poudrage. Traditionally, asbestos-free talc was dry heat sterilized by hospital pharmacies and stored in sterile glass containers (test tubes or Petri dishes) in 5- to 10-g aliquots. It was then transferred to a bulb syringe or powder blower and insufflated at thoracoscopy or thoracotomy. Attaching the bulb syringe to a red rubber catheter facilitates insufflation at thoracoscopy. Insufflation by a powder blower can also be done by attaching it to a source of pressurized air or oxygen, just as with an atomizer. This produces a finer and more uniform coverage of the pleura than does hand insufflation with a bulb syringe, but either method seems to produce a satisfactory pleurodesis. A spray can containing 4 g of sterile asbestos-free talc is now commercially available. This eliminates many of the logistic problems previously faced by hospitals in the preparation of sterile talc. Talc produces a rapid pleural symphysis, and it is helpful to insert two chest tubes (28 Fr anterior and posterior tubes or 28 Fr anterior and 32 Fr right-angle diaphragmatic tubes) to prevent loculated fluid collections. If these develop during the immediate postoperative period, they usually are resorbed over the subsequent 1 to 2 months.

A recent multicenter randomized clinical trial compared the use of talc slurry via tube thoracostomy with VATS talc

poudrage. In 482 eligible randomized patients, efficacy and risk for these two approaches were similar, but better results were obtained after VATS poudrage in patients with a lung or breast primary (Dresler et al, 2005).¹²⁷

Administration of Cytotoxic Agents

A technique similar to that described by Good and Sahn for tetracycline is used for the administration of cytotoxic agents intrapleurally, but different considerations apply for cytotoxic than for sclerosing agents. Cytotoxic agents are left in the pleural space longer to maximize contact with the pleural tumor. The length of instillation time is dictated by the pharmacokinetic properties of the individual drug. Cisplatin is left in the peritoneal or pleural space for 4 hours because by that time it has been almost totally absorbed into the systemic circulation.^{122,128} The chest tube can be immediately removed after instillation of a cytotoxic drug because there is no need to produce pleural symphysis. However, full expansion of the lung before instillation of the drug needs to be documented because an effusion caused by a trapped lung is no more effectively treated by cytotoxic than by sclerosing agents.

MANAGEMENT OF AN EFFUSION IN PATIENTS WITH A TRAPPED LUNG

Patients who have a trapped lung are not candidates for therapy with sclerosants and are unlikely to benefit from intrapleural cytotoxic agents because they have bulky tumor. Even though they have a collapsed, unexpandable lung, some of these patients experience a relief of dyspnea and chest discomfort when the effusion is evacuated, perhaps because this alleviates mediastinal compression. Some patients have a lung that can re-expand partially and experience a definite improvement in pulmonary function with drainage of the effusion. The insertion of a pleuroperitoneal shunt is one way to palliate such patients.¹²⁹⁻¹³² The device used for this procedure, the Denver pleuroperitoneal shunt (Codman and Shurtleff, Randolph, MA) is a single-unit silicone rubber conduit consisting of a unidirectional valved pumping chamber located between fenestrated pleural and peritoneal catheters. One catheter is introduced into the pleural space with the use of a Seldinger technique and directed toward the posterior costophrenic sulcus. The other catheter is placed into the peritoneal cavity via a small upper quadrant muscle-splitting incision. The pumping chamber is positioned in a subcutaneous pocket created over the anterolateral costal margin that provides a stable base for shunt compression.¹³³ Pleuroperitoneal shunting is also a therapeutic option for patients with pleural effusions secondary to intractable ascites, and it has sometimes been combined with peritoneovenous shunting for such patients. However, active participation by the patient or family is required for the shunt to function because the pumping chamber must be actively compressed approximately 25 times every 4 hours. Patients who are unable to cooperate with this routine should not have a shunt implanted. In properly selected patients, pleuroperitoneal shunting provides good palliation with minimal morbidity. The risk of infection is minimal, but shunt occlusion as a result of fibrin deposition over the ends of the catheter

occurs occasionally and may require replacement of the shunt.

Another alternative for patients who have a symptomatic pleural effusion and a trapped lung is intermittent drainage via an indwelling catheter (Pleurx; Denver Biomaterials, Golden, CO). The catheter is inserted under local anesthesia and can be used by the patient and family at home as needed to drain pleural fluid whenever the effusion becomes symptomatic. The efficacy and safety of this approach were shown in both a retrospective study and a prospective multi-institutional trial (Putnam et al, 1999; Putnam et al, 2000).^{134,135} Intermittent drainage via an indwelling pleural catheter is now the easiest and most accepted management option for patients with a symptomatic effusion in the presence of a trapped lung.

PLEURECTOMY

Pleurectomy with or without decortication was one of the early approaches used for malignant pleural effusions. Jensik and associates reported a series of 52 pleurectomies, 15 of which were associated with decortication.¹³⁶ The immediate mortality rate was 6%, and the 30-day mortality rate was 18%. Two patients developed recurrent effusions, and the average survival time was only 10.4 months. Subsequently, Martini and colleagues reported on a series of 106 patients whose malignant pleural effusion was treated by pleurectomy.¹³⁷ Most patients required two to three units of blood transfusion intraoperatively, and the overall 30-day mortality rate was 10%. In both of these series, which antedate modern chemotherapeutic regimens, patients with breast cancer had the longest survival.

More recently, Fry and Khandekar reported the results of pleurectomy and decortication performed via axillary thoracotomy in 24 patients who did not respond to standard treatment for malignant pleural effusion. Three patients died postoperatively, for an overall mortality rate of 12.5%, and the other 21 patients all experienced control of their recurrent effusions.¹³⁸ The high operative mortality rates undoubtedly reflect the poor performance status and limited reserve of patients who have malignant pleural effusions. With less morbid therapeutic options now available, thoracotomy and pleurectomy for the palliation of malignant pleural effusions has largely been abandoned. However, VATS pleurectomy is associated with a much lower risk. Waller and colleagues reported 19 patients who underwent VATS parietal pleurectomy.¹³⁹ The procedure required less than 1 hour to perform, and there were no postoperative deaths or episodes of respiratory failure. Therefore, VATS pleurectomy can be considered an option in patients who are not candidates for simpler approaches such as talc pleurodesis.

SUMMARY

Patients who present with a pleural effusion first undergo a thorough clinical evaluation to try to identify the likely cause. The size and location of the effusion and the determination of whether it is free flowing is made on posteroanterior, lateral, and lateral decubitus chest radiographs. CT is helpful in characterizing effusions that appear loculated and in detect-

ing underlying pulmonary or intra-abdominal disease that may be responsible for the effusion. Thoracentesis with biochemical analysis of the pleural fluid, culture, and cytologic examination is then performed to determine whether the effusion is a transudate or an exudate, to establish whether it is malignant, and to direct further evaluation. Ultrasonography and CT can localize loculated effusions for thoracentesis. If the cytologic findings are negative and malignancy is suspected, percutaneous pleural biopsy, or repeat thoracentesis, or especially thoracoscopy is indicated to establish a definitive tissue diagnosis.

Transudative effusions are managed by treatment of the underlying medical condition. Exudative effusions are also treated in this manner if they are not malignant. Patients with malignant effusions must have a determination made as to whether the lung will fully re-expand after evacuation of the effusion. If the lung expands completely, the effusion can be managed by sclerosis. Talc is probably the most effective sclerosant currently available, although tetracycline, doxycycline, and bleomycin have also been popular. Intrapleural cytotoxic agents are still considered investigational. If the lung is trapped and the patient is symptomatic, intermittent drainage via an indwelling pleural catheter is the simplest and most effective option. However, the recent reviews from the American and British Thoracic Societies and from the Cochrane Collaboration now support the systematic approach to management of pleural effusion, as outlined in this chapter, and provide guidelines for pleurodesis (Fig. 85-6) (Antony et al, 2000; Antunes et al, 2003).^{110,126,140}

COMMENTS AND CONTROVERSIES

A pleural effusion arises when there is a disruption between the formation and reabsorption of pleural fluid. Its presence can be diagnosed by conventional imaging, and its cause can be documented by means of thoracentesis with biochemical analysis, culture and cytologic examination of the pleural fluid, percutaneous pleural biopsy, or thoracoscopic examination with biopsy. As discussed by Doctor Rusch, initial thoracentesis is useful to determine whether the effusion is a transudate or an exudate, whether the effusion is hemorrhagic, and whether the effusion is purulent. Patients whose effusions remain undiagnosed after one or more thoracenteses may have a percutaneous needle biopsy. Unfortunately, this procedure has a low diagnostic yield in malignant neoplasms because of the patchy distribution of disease.

Thoracoscopic examination of the pleural space is the most definitive diagnostic technique, with an accuracy greater than 95%. The procedure allows direct access to 90% to 100% of both the visceral and parietal surfaces and, for most patients, clarifies whether the effusion is caused by a malignant process. At the time of thoracoscopy, a pleurodesis can also be achieved, should it be necessary. Because of such techniques, the cause of most pleural effusions can be established accurately and in a timely fashion, and few circumstances occur in which open thoracotomy is necessary.

Finally, it is important to remember that, in a patient with a current malignant disease or a history of a previously treated neoplastic disorder, the likely cause of the effusion might be obvious. It will also be obvious in patients with bacterial pneumonia who have an asso-

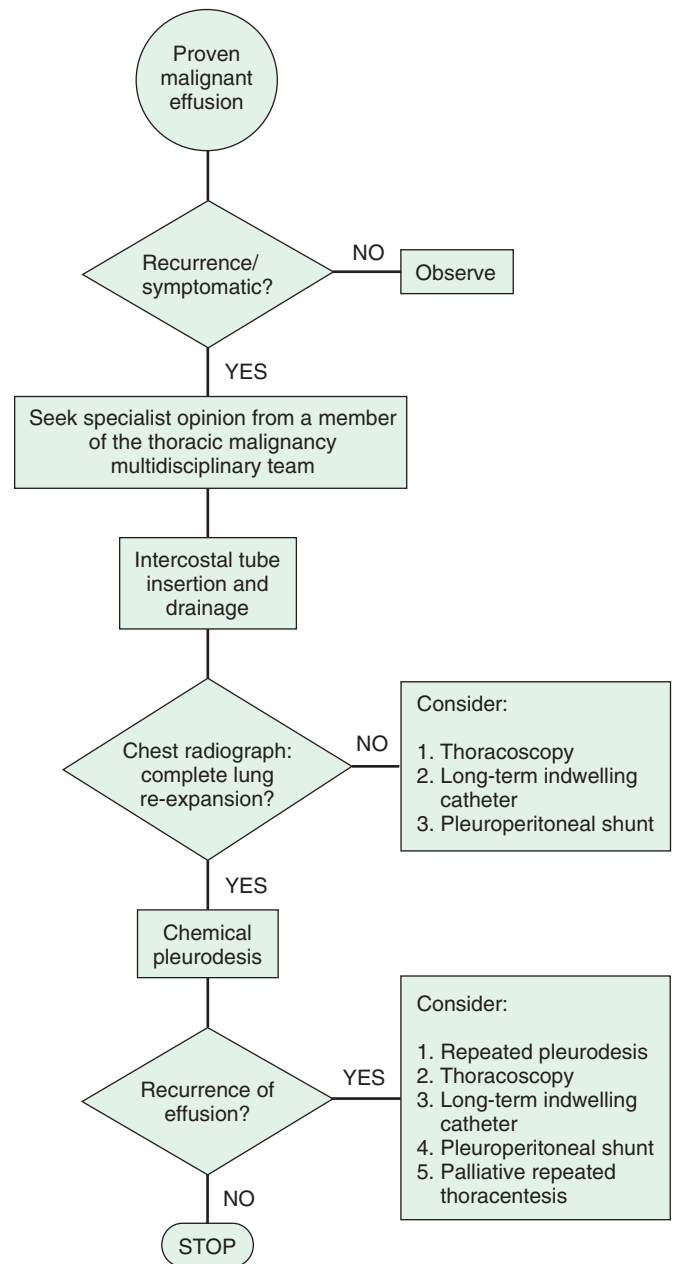


FIGURE 85-6 Algorithm for the management of pleural effusions. (ADAPTED FROM ANTUNES VB, ET AL: BTS GUIDELINES FOR THE MANAGEMENT OF MALIGNANT PLEURAL EFFUSIONS. THORAX 58[SUPPL II]: I129-I138, 2003; REPRODUCED WITH PERMISSION FROM BMJ PUBLISHING GROUP.)

ciated effusion and in patients with known congestive heart failure who develop a right-sided effusion. The clinical setting in which a pleural effusion occurs is therefore important in trying to identify its cause.

J. D.

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