



# Management of empyema: a comprehensive review

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**Abstract:** Empyema is a state of purulent pleural effusion in the thoracic cavity. The principle of treatment is the administration of appropriate antibiotics and thoracic drainage. If thoracic drainage is insufficient, thoracic surgeons may perform surgical intervention. It is important that our readers, thoracic surgeons, understand the pathogenesis of empyema and know how to treat it. Medline was used to search for English literature related to “empyema” and “pleural infection”. Searches were limited to the years 2010–2020 and limited to human studies. There have been numerous reports on empyema over the last decade. Regarding guidelines, the British Thoracic Society issued guidelines for pleural disease in 2010. Regarding intrapleural fibrinolytic therapy, the results of Multicenter Intrapleural Sepsis Trial (MIST)—two were reported in 2011 following MIST-1 in 2005, demonstrating the usefulness of intrapleural fibrinolytic therapy. Subsequently, a RAPID (renal, age, purulence, infection source, and dietary factors) risk category was proposed in 2014 as a prognostic factor for pleural infection using MIST-1 and MIST-2 data. Regarding surgery, prospective comparative studies are scarce, but as retrospective reports, the frequency and prognosis of postoperative empyema following lung cancer surgery were reported in 2018. In open window thoracostomy, attention has been paid to using a vacuum-associated closure device to accelerate recovery. There have been numerous reports on empyema and significant progress has been made in the last decade. Further large-scale clinical studies need to be performed to improve the prognosis for empyema.

**Keywords:** Empyema; pleural infection; RAPID

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## Introduction

Empyema is the state in which purulent fluid is present in the thoracic cavity. If pleural effusion is purulent, a diagnosis of empyema is given even if a microbial test is not positive. Empyema is associated with high morbidity and mortality (1–3). Most causes of empyema are from pneumonia, which often begins with parapneumonic pleural effusion, but the physiology is variable. The number of patients with empyema is increasing in both children and adults (4–8). Empyema has a 10–20% mortality rate, long hospital stays, and a heavy financial burden (7,9,10). One third of patients being treated require surgical

treatment (7,9). Recently, evidence-based medicine has been advocated, and randomized controlled trials have been conducted and guidelines have been set. The British Thoracic Society Pleural Disease Guideline 2010 details the history, frequency, pathophysiology and treatment of pyothorax, and it is textbook content (1). For the sake of an explanation, the content may overlap with the British Thoracic Society (BTS) guidelines. The purpose of this review is to update for the reader, the thoracic surgeon, current diagnosis and necessary treatment.

Medline was used to search for English literature related to “empyema” and “pleural infection”. The search was limited to the years 2010–2020 and limited to human

studies. Regarding the frequency, prognosis, and treatment of empyema, we focused on guidelines, randomized controlled trials, and articles with a large number of cases.

### Classification and guideline of empyema

In the 1960s, from the viewpoint of pathophysiology, the degree of empyema progression was divided into three stages: (I) simple exudate, (II) fibrinopurulent stage, and (III) later organizing stage with scar tissue formation (11). This classification was used as a guide for later research, and as the elucidation of the fibrinopurulent stage progressed, the theory of intrapleural fibrinolytic therapy was established. Various surgical treatments (open thoracotomy with decortication, rib resection, and open drainage) are performed during the organizing phase of the chronic phase (1,12).

About 20 years ago, the American College of Chest Physicians (ACCP), BTS and Light *et al.* classified empyema based on the pleural effusion volume, properties, biochemical data (pH, LDH, glucose), and bacterial culture, and suggested treatment strategies (12-14). As pyothorax progresses, pleural effusion increases, bacteria increase, pleural effusion becomes purulent, pH decreases (pH <7.2), LDH increases (LDH >1,000 IU), and glucose is depleted (glucose <40 mg/dL). The initial stage of treatment is only antibiotics, and thoracic drainage is performed according to progression. Intrapleural fibrinolytic therapy or surgical treatment is performed when these treatments do not show improvement or there is further progression. Empyema is a variety of conditions, but classification itself can be a guide. However, these classifications are expert opinions and are not based on evidence.

In 2010, the British Thoracic Society proposed guidelines for empyema and indicated evidence levels from A to D (1). The commentary also described the circumstances up to that point and is textbook-like content. The guidelines include items of historical perspective, epidemiology, physiology, pathophysiology, bacteriology, diagnosis, and treatment. Here are some of the more interesting points.

- ❖ The importance of whole body management such as nutrition management and thrombosis prophylaxis is described (15-17);
- ❖ although no previous classification (ACCP, 2003 BTS, Light) was mentioned, the usefulness of C reactive protein (CRP) was suggested (18,19);
- ❖ in diagnostic imaging, the usefulness of ultrasound

is common, but “split pleural sigh”, which enhances parietal and visceral pleural surfaces by contrast-enhanced CT scanning, was introduced (20);

- ❖ empyema is diagnosed if the pleural effusion is purulent, even if it is not positive by microbiological testing, but about 40% are negative in conventional pleural fluid cultures. Attempts have been made to increase the rate of bacterial identification using PCR or pleural biopsy (21,22).

### Intrapleural fibrinolytic therapy for empyema

When simple parapneumonic effusion progresses to the fibrinopurulent stage, bacteria invade, accelerate the immune response, promote the migration of neutrophils, and activate the coagulation cascade (1,23-25). The increase in fibrin and the density of the septations were thought to inhibit drainage and make treatment difficult. Various intrapleural fibrinolytic therapies were performed, and an improvement of pleural fluid drainage was obtained (26-31).

#### MIST1

The first Multicenter Intrapleural Sepsis Trial (MIST1) was held in the United Kingdom from 2002 to 2004 (9). The trial was a placebo-controlled randomized trial assessing the use of intrapleural streptokinase that recruited 454 patients. Short-term drainage benefits were not associated with reduced mortality, the frequency of surgery, or the length of hospital stay.

#### MIST2

MIST2 was performed on 210 patients between 2005 and 2008 (32). A randomized-controlled trial assessing the use of intrapleural DNase and tissue plasminogen activator (tPA), demonstrated a significant improvement in the primary outcome measure (radiographic improvement) for the combination treatment compared with placebo. Combination therapy of DNase and tPA had a statistically significant benefit in duration of hospital stay, referral to surgery, and death, and confirmed that neither fibrinolytic alone or DNase in isolation were better than placebo. However, there were only 52 cases of the combination therapy, which has not yet been strongly recommended. Further large-scale clinical research is ongoing, including verification of costs and adverse events.

**Table 1** Predicting mortality of the RAPID score (data taken from reference 2 after modification) (2)

Variable	Died 3 months (%)	P value	Score
Age, years			
<50	0.8	<0.001	0
50–70	4.9		1
≥70	29.1		2
Albumin, g/L			
≥27	7.2	0.008	0
<27	16.8		1
Urea, mM			
<5	3.3	<0.001	0
5–8	4.8		1
≥8	33.3		2
Infection			
Community	10.1	0.03	0
Hospital	26.1		1
Purulence			
Purulent	10.9	0.04	0
Nonpurulent	17.1		1
RAPID risk categories			
Low-risk, score 0–2	1.4		
Medium-risk, score 3–4	10.8		
High-risk, score 5–7	43.8		

RAPID, renal, age, purulence, infection source, and dietary factors.

## RAPID

MIST1 and MIST2 collected patient background, treatment, and prognostic data for empyema. These are prospective and accurate data which was utilized in various analyses as highly reliable information. Using these, a clinical risk score of empyema was calculated (2). First, using the data of MIST1 as a predictive model, five factors (renal, age, purulence, infection source, and dietary factors) related to prognosis were extracted and a scoring system was constructed. Then, the data of MIST2 was verified as a validation model. In the RAPID score, high risk (score 5–7) had a 3-month mortality rate of 43.8%, medium risk (score 3–4) was 10.8%, and low risk (score 0–2) was 1.4% [modified reference (2), *Table 1*] (2). The RAPID score is very useful as a prognostic score for empyema and is expected to be used

in future clinical studies.

In addition, for chest drains, a thick bore did not necessarily have a high therapeutic effect, and a thin bore showed less disability and was more comfortable. MIST2 used tubes of 15 French or less (9,32).

## Surgical treatment for empyema

First of all, regarding surgical treatment for empyema, the BTS guidelines state that “Further properly powered and blind trials are needed” (1). Although the usefulness of video assisted thoracic surgery (VATS) has been shown in various scenarios, there are only two clinical studies comparing initial treatment with medical treatment, and the number of cases is very small and problems with credibility have been pointed out (33–38). The usefulness of Intrapleural

fibrinolytic therapy has been demonstrated in the MIST2 trial, and a large-scale comparative study of VATS and Intrapleural fibrinolytic therapy is needed in the future (3,32,39). For high risk (score 5–7) using the RAPID score, surgery at an early stage where surgery can be tolerated is expected to improve prognosis, and future clinical studies are expected (2).

Surgical treatment for empyema is indicated when there is no improvement by medical treatment (1,3). The usefulness of VATS has been shown in comparison with conventional thoracotomy (40). Open window thoracotomy has been used as a life-saving measure in postoperative empyema and empyema with bronchial fistula (1). At that time, a vacuum-associated closure device has been attracting attention as a treatment for promoting recovery (39,41).

### Postoperative empyema

Detailed data on postoperative empyema in 4,772 patients who had surgery for lung cancer were reported (42). The incidence of empyema after lung cancer surgery was 0.9% and mortality was 11.6% (42). The frequency of empyema was around 10% before 2000, but around 1% after 2000 (43–49). Mortality was 14.8% or 22.2% around 1980, but it has been decreasing due to medical progress (42,44,50).

### Discussion

**Dr. Satoshi Shiono: What is the timing of surgery for acute empyema?**

The BTS guidelines indicate that although VATS is useful, it does not address indications or timing of surgery. Surgery is generally indicated to be performed when drainage is ineffective. Originally, it seems that VATS should be performed at an acute stage, but there are few evidences for randomized controlled trial.

**Dr. Satoshi Shiono: Elderly patients with empyema tend to have some comorbidities. What is the management of those with empyema?**

Empyema in the elderly patient has a poor prognosis, and the surgery intervention is recommended at an early stage with physical strength based on the RAPID score. However, there is no randomized controlled trial, and the

evidence is low.

**Dr. Satoshi Shiono: Is there any limitation of VATS for empyema?**

In simple exudate stage, VATS is overly invasive because this stage can be cured with conservative treatment. Other than that, there seems to be no particular limitation for VATS.

### Conclusions

Clinical studies on empyema, such as intrapleural fibrinolytic therapy, have yielded various results. On the other hand, large-scale randomized controlled trials for surgical treatment of empyema have not been conducted, and future research is expected.

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## References

- Davies HE, Davies RJ, Davies CW, et al. Management of pleural infection in adults: British Thoracic Society Pleural Disease Guideline 2010. *Thorax* 2010;65 Suppl 2:ii41-53.
- Rahman NM, Kahan BC, Miller RF, et al. A clinical score (RAPID) to identify those at risk for poor outcome at presentation in patients with pleural infection. *Chest* 2014;145:848-55.
- Bedawi EO, Hassan M, Rahman NM. Recent developments in the management of pleural infection: A comprehensive review. *Clin Respir J* 2018;12:2309-20.
- Roxburgh CS, Youngson GG. Childhood empyema in North-East Scotland over the past 15 years. *Scott Med J* 2007;52:25-7.
- Munoz-Almagro C, Jordan I, Gene A, et al. Emergence of invasive pneumococcal disease caused by nonvaccine serotypes in the era of 7-valent conjugate vaccine. *Clin Infect Dis* 2008;46:174-82.
- Finley C, Clifton J, Fitzgerald JM, et al. Empyema: an increasing concern in Canada. *Can Respir J* 2008;15:85-9.
- Farjah F, Symons RG, Krishnadasan B, et al. Management of pleural space infections: a population-based analysis. *J Thorac Cardiovasc Surg* 2007;133:346-51.
- Grijalva CG, Zhu Y, Nuorti JP, et al. Emergence of parapneumonic empyema in the USA. *Thorax* 2011;66:663-8.
- Maskell NA, Davies CW, Nunn AJ, et al. U.K. Controlled trial of intrapleural streptokinase for pleural infection. *N Engl J Med* 2005;352:865-74.
- Davies CW, Kearney SE, Gleeson FV, et al. Predictors of outcome and long-term survival in patients with pleural infection. *Am J Respir Crit Care Med* 1999;160:1682-7.
- Watkins E, Jr., Fielder CR. Management of nontuberculous empyema. *Surg Clin North Am* 1961;41:681-93.
- Colice GL, Curtis A, Deslauriers J, et al. Medical and surgical treatment of parapneumonic effusions : an evidence-based guideline. *Chest* 2000;118:1158-71.
- Light RW. A new classification of parapneumonic effusions and empyema. *Chest* 1995;108:299-301.
- Davies CW, Gleeson FV, Davies RJ, et al. BTS guidelines for the management of pleural infection. *Thorax* 2003;58 Suppl 2:ii18-28.
- Ferguson AD, Prescott RJ, Selkon JB, et al. The clinical course and management of thoracic empyema. *QJM* 1996;89:285-9.
- Dentali F, Douketis JD, Gianni M, et al. Meta-analysis: anticoagulant prophylaxis to prevent symptomatic venous thromboembolism in hospitalized medical patients. *Ann Intern Med* 2007;146:278-88.
- Geerts W, Selby R. Prevention of venous thromboembolism in the ICU. *Chest* 2003;124:357S-63S.
- Chalmers JD, Singanayagam A, Hill AT. C-reactive protein is an independent predictor of severity in community-acquired pneumonia. *Am J Med* 2008;121:219-25.
- Hansson LO, Hedlund JU, Ortvist AB. Sequential changes of inflammatory and nutritional markers in patients with community-acquired pneumonia. *Scand J Clin Lab Invest* 1997;57:111-8.
- Kearney SE, Davies CW, Davies RJ, et al. Computed tomography and ultrasound in parapneumonic effusions and empyema. *Clin Radiol* 2000;55:542-7.
- Maskell NA, Batt S, Hedley EL, et al. The bacteriology of pleural infection by genetic and standard methods and its mortality significance. *Am J Respir Crit Care Med* 2006;174:817-23.
- Saglani S, Harris KA, Wallis C, et al. Empyema: the use of broad range 16S rDNA PCR for pathogen detection. *Arch Dis Child* 2005;90:70-3.
- Idell S, Girard W, Koenig KB, et al. Abnormalities of pathways of fibrin turnover in the human pleural space. *Am Rev Respir Dis* 1991;144:187-94.
- Kroegel C, Antony VB. Immunobiology of pleural inflammation: potential implications for pathogenesis, diagnosis and therapy. *Eur Respir J* 1997;10:2411-8.
- Aleman C, Alegre J, Monasterio J, et al. Association between inflammatory mediators and the fibrinolysis system in infectious pleural effusions. *Clin Sci (Lond)* 2003;105:601-7.
- Chin NK, Lim TK. Controlled trial of intrapleural streptokinase in the treatment of pleural empyema and complicated parapneumonic effusions. *Chest* 1997;111:275-9.
- Ryan JM, Boland GW, Lee MJ, et al. Intracavitary urokinase therapy as an adjunct to percutaneous drainage in a patient with a multiloculated empyema. *AJR Am J Roentgenol* 1996;167:643-7.
- Temes RT, Follis F, Kessler RM, et al. Intrapleural fibrinolytics in management of empyema thoracis. *Chest* 1996;110:102-6.
- Cameron R, Davies HR. Intra-pleural fibrinolytic therapy versus conservative management in the treatment of

- parapneumonic effusions and empyema. *Cochrane Database Syst Rev* 2004;(2):CD002312.
30. Diacon AH, Theron J, Schuurmans MM, et al. Intrapleural streptokinase for empyema and complicated parapneumonic effusions. *Am J Respir Crit Care Med* 2004;170:49-53.
  31. Misthos P, Sepsas E, Konstantinou M, et al. Early use of intrapleural fibrinolytics in the management of postpneumonic empyema. A prospective study. *Eur J Cardiothorac Surg* 2005;28:599-603.
  32. Rahman NM, Maskell NA, West A, et al. Intrapleural use of tissue plasminogen activator and DNase in pleural infection. *N Engl J Med* 2011;365:518-26.
  33. Brutsche MH, Tassi GF, Gyorik S, et al. Treatment of sonographically stratified multiloculated thoracic empyema by medical thoracoscopy. *Chest* 2005;128:3303-9.
  34. Ravaglia C, Gurioli C, Tomassetti S, et al. Is medical thoracoscopy efficient in the management of multiloculated and organized thoracic empyema? *Respiration* 2012;84:219-24.
  35. Hajjar WM, Ahmed I, Al-Nassar SA, et al. Video-assisted thoroscopic decortication for the management of late stage pleural empyema, is it feasible? *Ann Thorac Med* 2016;11:71-8.
  36. Scarci M, Abah U, Solli P, et al. EACTS expert consensus statement for surgical management of pleural empyema. *Eur J Cardiothorac Surg* 2015;48:642-53.
  37. Wait MA, Sharma S, Hohn J, et al. A randomized trial of empyema therapy. *Chest* 1997;111:1548-51.
  38. Bilgin M, Akcali Y, Oguzkaya F. Benefits of early aggressive management of empyema thoracis. *ANZ J Surg* 2006;76:120-2.
  39. Corcoran JP, Wrightson JM, Belcher E, et al. Pleural infection: past, present, and future directions. *Lancet Respir Med* 2015;3:563-77.
  40. Chambers A, Routledge T, Dunning J, et al. Is video-assisted thoroscopic surgical decortication superior to open surgery in the management of adults with primary empyema? *Interact Cardiovasc Thorac Surg* 2010;11:171-7.
  41. Palmen M, van Breugel HN, Geskes GG, et al. Open window thoracostomy treatment of empyema is accelerated by vacuum-assisted closure. *Ann Thorac Surg* 2009;88:1131-6.
  42. Matsutani N, Yoshiya K, Chida M, et al. Postoperative empyema following lung cancer surgery. *Oncotarget* 2018;9:29810-9.
  43. Brohee D, Vanderhoeft P, Smets P. Lung cancer and postoperative empyema. *Eur J Cancer* 1977;13:1429-36.
  44. Pastorino U, Valente M, Piva L, et al. Empyema following lung cancer resection: risk factors and prognostic value on survival. *Ann Thorac Surg* 1982;33:320-3.
  45. Deslauriers J, Ginsberg RJ, Piantadosi S, et al. Prospective assessment of 30-day operative morbidity for surgical resections in lung cancer. *Chest* 1994;106:329S-30S.
  46. Di Giorgio A, Sammartino P, Arnone P, et al. Prognostic significance of postoperative empyema in lung cancer. *Int Surg* 1996;81:407-11.
  47. Duque JL, Ramos G, Castrodeza J, et al. Early complications in surgical treatment of lung cancer: a prospective, multicenter study. Grupo Cooperativo de Carcinoma Broncogenico de la Sociedad Espanola de Neumologia y Cirugia Toracica. *Ann Thorac Surg* 1997;63:944-50.
  48. Shiono S, Yoshida J, Nishimura M, et al. Risk factors of postoperative respiratory infections in lung cancer surgery. *J Thorac Oncol* 2007;2:34-8.
  49. Yamauchi Y, Isaka M, Maniwa T, et al. Chest tube tip culture as a predictor of postoperative infection in lung cancer operations. *Ann Thorac Surg* 2013;96:1796-802.
  50. Nagasaki F, Flehinger BJ, Martini N. Complications of surgery in the treatment of carcinoma of the lung. *Chest* 1982;82:25-9.

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