Review Article

Management of empyema: a comprehensive review

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Contributions: (I) Conception and design: All authors; (II) Administrative support: All authors; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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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

Received: 15 February 2020; Accepted: 02 March 2020; Published: 25 November 2020.

doi: 10.21037/ccts.2020.03.02

View this article at: http://dx.doi.org/10.21037/ccts.2020.03.02

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 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), British thoracic society (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

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.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editor (Satoshi Shiono) for the series "Empyema" published in *Current Challenges in Thoracic Surgery*. The article has undergone external peer review.

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/ccts.2020.03.02). The series "Empyema" was commissioned by the editorial office without any funding or sponsorship. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/ccts.2020.03.02
Cite this article as: Kanai E, Matsutani N. Management of empyema: a comprehensive review. Curr Chall Thorac Surg 2020;2:38.

