REVIEW

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Pleural Infection and Empyema

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Increasing incidence of pleural infection has been reported worldwide in recent decades. The pathogens responsible for pleural infection are changing and differ from those in community acquired pneumonia. The main treatments for pleural infection are antibiotics and drainage of infected pleural fluid. The efficacy of intrapleural fibrinolytics remains unclear, although a recent randomized control study showed that the novel combination of tissue plasminogen activator and deoxyribonuclease had improved clinical outcomes. Surgical drainage is a critical treatment in patient with progression of sepsis and failure in tube drainage.

Keywords: Empyema; Etiology; Drainage; Fibrinolytic Agents

Introduction

Pleural infection is an ancient disease that remains an important clinical problem. The incidence of this disease decreased rapidly after antibiotic use, representing 5% of pneumonias in the pre-antibiotic era, and 2% in the post-antibiotic era beginning in the 1940s[1]. However, the incidence of pleural infection has increased in recent years[1]. In a study about pleural infection in hospitalized adults conducted in the United States, the frequency was 3.96 cases per 100000 in 1996 and 8.10 cases per 100000 in 2008[2]. Causes for the increase in incidence remain uncertain, but the use of a wide range of pneumococcal vaccines in children and an increasingly aging global society, with an increase of elderly with chronic diseases have been suggested[1].

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This review of pleural infection focuses on pathogens and medical managements of this disease.

Pathophysiology of Pleural Infection

Depending on the degree of progression of this disease, pleural infection has been divided into three stages[3]. The first step is a simple exudate (early exudative stage). There is an increased permeability of the capillary in this stage, and movement of fluid into pleural space occurs without a bacterial infection in pleural fluid. Pleural effusion moves freely in pleural cavity and is characterized by a low white blood cell count, lactate dehydrogenase levels less than half in the serum, and normal pH and glucose levels. Antibiotics are sufficient for the treatment in this stage, and a chest tube is not required.

If proper care is not provided at this stage, it progresses to the fibrinopurulent stage, in which the bacteria invade and multiply in the pleural cavity, accelerating migration of neutrophils and activation of coagulation cascades leading to increased procoagulation and decreasing fibrinolysis[4-6]. Fibrin deposition and septation formation occurs in the pleural fluid[4]. In addition, the pH and sugar in pleural fluid are reduced and lactate dehydrogenase activity is increased in this stage[3].

The last step is the organizing step, in which the proliferation of fibroblasts occurs and thickened fibrous pleural peel encases the lung preventing expansion of the lung[5].

Pathogens and Selection of Antibiotics

The proper use of antibiotics is the most important predictor for death in this disease. Understanding of the bacteriology is critical in treatment of pleural infection. However, bacterial pathogens in this disease are different from those in community acquired pneumonia (CAP). The First Multicenter Intrapleural Sepsis Trial (MIST1) was a bacteriologic evaluation for the usefulness of streptokinase in pleural infection. Common pathogens of community-acquired pleural infection were streptococcal species, such as *Streptococcus intermedius* (24%), *Streptococcus pneumoniae* (21%), and other streptococcus (7%), followed by anaerobic bacteria (20%) and staphylococci (10%)[7]. The most common pathogens in hospital acquired infections were staphylococci (35%) and Gram-negative bacteria (23%)[7]. However, since isolation of the causative pathogen is difficult in about 40% of pleural infections, the selection of antibiotics is based on pathogens in communities and on clinical judgment[7,8]. Unfortunately, few studies have evaluated pathogens of pleural infection in Korea. In a study for adult patients with pleural infection, pathogens were isolated in 31 of 115 cases of pleural infections; alpha-hemolytic streptococci was the most common pathogen in nine cases (26%) followed by *Klebsiella pneumoniae* in eight cases (26%), and *Staphylococcus aureus* in five cases (16%)[9].

Blood cultures of pleural fluid using the BACTEC blood culture system increased isolation of bacteria in pleural infections from 38% in conventional culture to 59%[10].

Medical Treatment in Pleural Infection

The use of proper antibiotics and prompt drainage of pleural fluid are also critical to the medical treatment of pleural infections. Ultrasound or computed tomography-guided insertion of a chest tube and drainage of pleural fluid are recommended due to its safety and efficacy[3]. Traditionally, a large tube more than 24 French is appropriate for draining thick pleural fluid, but a small-bore chest tube (10-14F) may be equally effective and less painful, according to a subanalysis of a large study investigating the utility of intraplueural fibrinolytic therapy[11]. However, no direct comparative randomized trial has yet been done.

The prevention of progression in pleural infection from simple pleural infection to the fibropurulent and organizing step consists mainly of drainage of the infected pleural fluid. Until recently, the use of intrapleural fibrinolytic agents was widely applied in clinical practice. However, the MIST1 large, double-blind, randomized trial failed to achieve beneficial effects of intrapleural streptokinase administration in mortality, surgical referral rate, and the length of the hospital stay[12]. Contentious issues in this study include recruitment of patients late in the disease process and failure to stratify for the presence of septations[13].

The subsequent study (MIST2) for pleural infection to facilitate infected pleural fluid using recombinant tissue plasminogen activator (t-PA) and DNase targeting both fibrinolysis and reducing fluid viscosity and possible biofilm formation was performed in the United Kingdom[14]. The primary outcome was the change of pleural opacity measured with chest radiographic findings between day 0 and day 7. Secondary outcomes were surgical referral rate, duration of hospital stay, and mortality. Combined t-PA and DNase therapy were significantly improved in both primary and secondary outcomes compared to those in placebo group, but t-PA alone or DNase alone did not produce any significant difference in primary and secondary outcomes compared to those in the placebo group. However, the absolute difference in number of surgical referrals was only one between t-PA group (3/48) and t-PA-DNase group (2/48), although only the t-PA-DNase group had a statistical significant difference compared to the placebo group. The number of enrolled patients may not have been enough to provide robust evidence for the routine use of these agents for pleural infection.

The role of intrapleural fibrinolytic treatment in pleural infection remained debatable mainly due to the results of the MIST1 and 2 large randomized studies. However, a recent systematic review analyzed seven randomized controlled studies including MIST1 and MIST2 showed that fibrinolytic treatment was beneficial for surgical intervention or death (risk ratio [RR], 0.50; 95% confidence interval [CI], 0.28–0.87) and surgical intervention alone (RR, 0.61; 95% CI, 0.45–0.82) in pleural infection[15]. The authors concluded that fibrinolytic treatment may be considered in loculated pleural infection although studies analyzed in this meta-analysis were significant heterogeneous, and a systematic review may have publication bias.

Medical thoracoscopy is a video-assisted thoracoscopy performed under local anesthesia. The usefulness of this procedure in pleural infection has not been well evaluated. Several retrospective studies reported high success rates with low complication rates in multiloculated empyema[16,17]. However, since there was no randomized study for the utility and safety of this procedure in pleural infection, further prospective comparative studies are needed.

Surgical Treatment in Pleural Infection

Early surgical treatment may improve the outcome and duration of hospitalization[8,18-20]. In a study conducted in Korea, surgical decortications as the first treatment also showed better success rate compared to that in chest tube drainage in advanced empyema[20]. However, since medical treatment produced high success rates in the majority of patients with empyema, surgical treatment was recommended only in

patients with a persistent sepsis and a residual pleural collection despite chest tube drainage and antibiotics[3]. Video-assisted thoracoscopic surgery is widely performed in pleural infection because it decreases the length of hospital stay and postoperative pain, and complications including atelectasis, prolonged air-leak, sepsis, and 30-day mortality[18]. No objective criteria exist to identify when and which patients require surgical treatment. In one study addressing the optimal timing of surgical treatment in pleural infection, patients with symptom duration of less than 4 weeks showed better outcome compared to those with a duration greater than 4 weeks[19].

Conclusions

Pleural infections are increasing and remain an important clinical problem. Early diagnosis and appropriate antibiotic treatment are critical to reduce mortality. The pathogens in pleural infection are different from those in CAP, but there are scant data in Korea. Combined treatment with t-PA and DNase improves treatment outcomes in pleural infection. However, larger studies are needed to provide more conclusive evidence about the efficacy and safety of this treatment. Intrapleural fibrinolytic treatment may be an alternative treatment to facilitate the drainage of infected pleural fluid. Surgical treatment of pleural infection should be done if chest tube drainage and antibiotics fail to improve sepsis and radiologic findings.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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