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Review Article

Empyema Thoracis: An Insight into the Current Standard of Care

Amit Srivastava[1*], Vivek Srivastava[2], Sanjay Kumar[3], Arvind Kumar Pandey[4], Afreen Ali[5], Pratik K Jha[5], Awgesh Kumar Verma[5]

[1*]**Senior Cardio Thoracic & Vascular Surgeon, Apex Super Speciality Hospital, Varanasi, UP, India.**
[2]**Associate Professor & General Surgeon, SSH & IMS, BHU, Varanasi, UP, India.**
[3]**Associate Professor & Senior Consultant Cardiothoracic Surgeon, SSH & IMS, BHU, Varanasi, UP, India.**
[4]**Assistant Professor & Cardiothoracic Surgeon, SSH & IMS, BHU, Varanasi, UP, India.**
[5]**Junior Resident, SSH & IMS, BHU, Varanasi, UP, India.**

ABSTRACT

Empyema is the infection of space around the lungs and has been a disease since time immemorial. With time, various forms of surgical and non-surgical treatment methods have evolved.

In spite of current medical advances, thoracic empyema continues to be a challenging problem, associated with significant morbidity and mortality. This review gives an insight into the global burden of this disease and the evolution of treatment modalities over time.

Keywords: Empyema; Morbidity; Mortality; Global Burden.

***Correspondence to:**

Dr. Amit Srivastava,
Senior Cardio Thoracic & Vascular Surgeon,
Apex Super Speciality Hospital,
Varanasi, Uttar Pradesh, India.

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INTRODUCTION

Empyema is used to describe collections of pus in the pleural cavity around the lungs. It is derived from the Greek word *empyein,* which means "pus producing." The serious nature of thoracic empyema was first described by Hippocrates more than 2400 years ago.[1]

Even during those times, the need for surgical intervention was well established and the only treatment available until the late 19th century was open drainage. In 1891, Gotthard Bülau reported the first closed method of drainage of infected pleural fluid. This was often done early in the acute phase before the development of adhesions resulting in lung collapse and respiratory compromise. However, the early mortality rate was 30.2% in this group of otherwise healthy, young men. The better understanding of the pathology and evolution of empyema was obtained later as a result of the Empyema Commission. Thus, with the use of closed drainage, the mortality rate dropped drastically to 4.3%. Graham's principles consisting of avoidance of open drainage during the acute phase along with sterilization and obliteration of the infected space, constitute the fundamentals of modern therapy for empyema.[2]

Presently, approximately 50% of empyemas result from pneumonia. They may also result from lung surgery, trauma, oesophageal perforation or transdiaphragmatic spread of an intra-abdominal infection. At least 40% of all patients hospitalized with pneumonia have an ipsilateral pleural effusion.[3] The fatality rate in hospitalised patients is around 7.2% which is lower for children (0.4%) than for adults aged above 65 years (16.1%).[4]

Antibiotics introduction, however, led to the appearance of resistant infections, polymicrobial infection, and partially treated empyemas. The incidence of streptococcal empyema decreased markedly and *Staphylococcus aureus* emerged as the predominant pathogen with the rapid use of antibiotics. In the present time, gram-negative and anaerobic bacteria also have become important pathogens. Despite of the current advances in the field of medicine, thoracic empyema continues to be a challenging problem, resulting in significant morbidity and mortality.[5,6]

BACTERIOLOGY

The commonly associated bacteria with parapneumonic empyema are *Streptococcus pneumonia, Streptococcus pyogenes, Staphylococcus aureus.* More recently, *Streptococcus anginosus* (formerly *Streptococcus milleri*) has been added to the list. The anaerobes have been identified solely or coexisting with another pathogen in approximately 25% to 76% of cases. The most of the increased incidence of empyema are associated with

Staphylococci and these patients have the longest lengths of hospital stay and highest mortality rate.[7,8] However, various studies have documented significant reductions in the incidence of pneumonia hospitalizations after the introduction of seven-valent pneumococcal conjugate vaccine (PCV7) vaccine.[9,10] Also, the incidence of parapneumonic empyemas classified as being caused by unknown pathogens has increased significantly. Establishing the etiology of empyema is not an easy task, and it is unclear whether this increase is related to truly unknown pathogens, to imperfect laboratory testing, or to the increased use of antibiotics before hospitalization. Many studies using molecular techniques have shown that a significant percentage of culture-negative empyema may be caused by pneumococci, mainly serotype 1.[11-15] Some parapneumonic empyemas have mixed bacterial infections.[16] The exact cause of the observed increase in the incidence is not clear and part of the increase may be related to the increased incidence of antibiotic-resistant.

DISEASE PATHOGENESIS

The development of empyema has traditionally been described to occur in three clinical stages: *the exudative stage, the fibrinopurulent stage, and the organizing stage*. Initially with an infection, the pleura reacts with edema formation, and exudation of proteins and neutrophils into the pleural cavity. The pleural mesothelial and capillary cells permeability is increased due to cytokine release resulting in fluid accumulation. The mesothelial cells are activated by bacteria and act as phagocytes triggering an inflammatory cascade with the release of chemokines, cytokines, oxidants, and proteases and recruitment of polymorphonuclear cells.[3] In the early exudative stage, bacterial growth may be minimal with a sterile exudate. However, it may progress rapidly depending on the type and virulence of the organism, host defences and antibiotic treatment initiation. The Staphylococcal pneumonias are commonly associated with pleural effusions. In uncomplicated parapneumonic effusions, the pleural fluid has a pH > 7.20, comparatively normal glucose levels, and elevated lactate dehydrogenase (LDH) levels that are typically less than 3 times the upper limit of normal. Most of these patients respond to antibiotics alone. Nevertheless, the untreated exudative effusions may turn into fibrinopurulent or complex parapneumonic effusions. In fibrinopurulent stage, there is deposition of fibrin on the visceral and parietal pleural membranes with formation of loculations. The phagocytosis and cell lysis result in a pleural fluid pH < 7.20, low glucose and LDH levels, more than 3 times normal. When the concentration of leukocytes becomes sufficient to form frank pus, a complex parapneumonic effusion develops into a pleural empyema which consists of fibrin, cellular debris, and viable or dead bacteria. Deposition of fibrin into the pleural space occludes the lymphatic channels, further increasing the amount of pleural fluid. The fibrin strands lead to loculations of the pleural space and prevent drainage using a single needle or tube.[17] It is more likely to get a positive Gram stain and/or positive bacterial cultures in this stage. The third phase is the organizing phase. It is characterized by the fibroblasts recruitment with formation of a thick, fibrous pleural peel along with the ongoing maturation of dense septations. Both the layers of pleura may become severely thickened with significant fluid remaining in the pleural space.

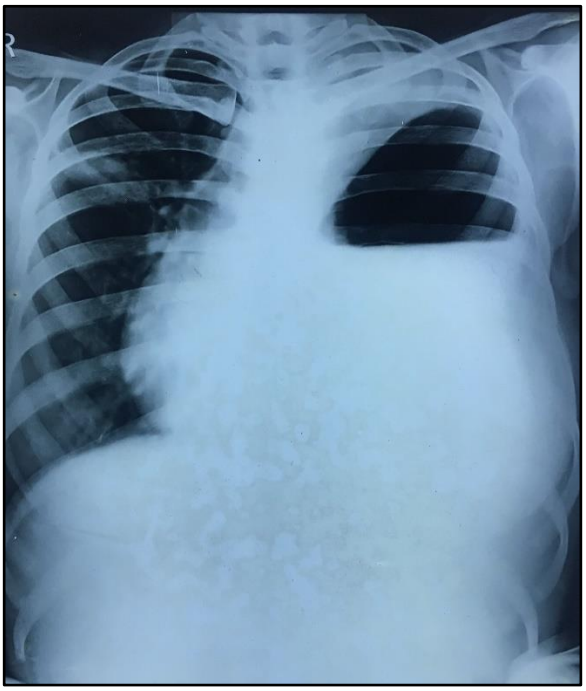

Figure 1: X-Ray chest (posteroanterior view) showing massive effusion in left hemithorax with mediastinal shift to the right.

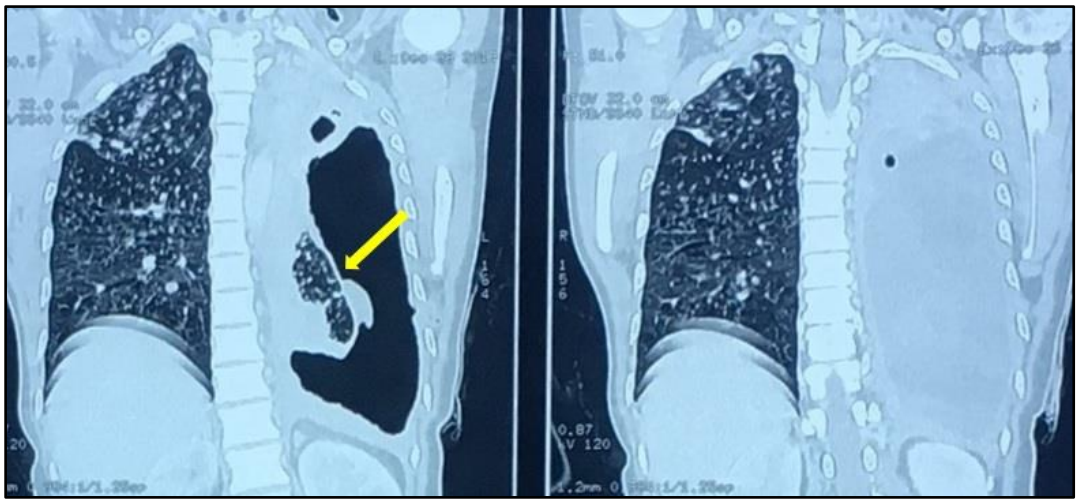

Figure 2: Computed Axial Tomography of chest showing non layering of effusion in the right hemithorax with thickened visceral pleura peel (arrow).

DIAGNOSIS

Empyemas have a varied clinical presentation depending on the underlying bacterial etiology. The patient infected with aerobes tend to be more acutely ill with an initial presentation akin to pneumonia. It may be followed by a non-resolving scenario with pleuritic chest pain, fever spikes, and failure to improve despite appropriate antibiotic therapy. Older adults, immunocompromised patients and those with anaerobic infections may have a more indolent course and may experience constitutional symptoms.[18] Upright chest radiographs generally help in identifying most pleural effusions (Figure 1). Lateral decubitus films are useful in determining whether the fluid is free flowing and amenable to complete percutaneous drainage. Leukocytosis, radiographic evidence of a pleural effusion, and the presence of purulent fluid on thoracentesis are classic findings of empyema. The presenting signs or symptoms of infection, history related to malignancy, or associated medical diseases such as cardiac failure or liver or kidney disease can be helpful in determining the cause. Ultrasonography can help in detection of loculations and in determination of an appropriate site for thoracentesis. Computed axial tomographic (CAT) scan can establish the size and the location of the effusion and provides clue regarding associated underlying parenchymal and pleural pathologies. A CAT scan with intravenous contrast can further characterize the empyema, suggesting loculations or a thickened pleura or rind (Figure 2). The lung-fluid interface on inspection may suggest entrapped lung and may reveal an underlying parenchymal process such as an abscess or tumor. The presence of effusion and fluid-lung interface can give indications as to the need for operative intervention. The cause of an effusion can be established with the help of thoracocentesis. The pleural fluid evaluation should include a cytologic evaluation, pH level, gram stain and culture, cell count, and total protein, glucose, and LDH levels. Based on protein and LDH levels, effusions are classified as exudate or transudate. A pleural fluid protein/serum protein level higher than 0.5 and a pleural fluid LDH/serum LDH level higher than 0.6 signifies exudate effusion. Increased white blood cell count in the pleural fluid, particularly with a preponderance of neutrophils, low pleural fluid glucose and a pH less than 7.20 are indicators of active pleural infection and the need for pleural drainage.

CURRENT TREATMENT STRATEGIES

The treatment of empyema is governed by its stage. The initiation of antibiotic coverage of patients with parapneumonic effusions is generally dictated by treatment guidelines for pneumonia and may be modified according to blood and pleural fluid microbial cultures and sensitivities. The empiric anaerobic antibiotic coverage may be initiated although they are less likely to be cultured. Nosocomial empyema needs adequate gram-negative coverage. Appropriate antibiotic therapy in early stages represents the cornerstone of therapy for pneumonia and parapneumonic effusion.

The minimal size free-flowing effusion may be observed because the risk of a complication is remote. However, all other free flowing effusions should be aspirated to establish the diagnosis. Uncomplicated exudative effusions that are of small volume, free flowing without loculations, with a negative Gram stain, pH > 7.20, and negative cultures are usually inflammatory. They generally resolve with antibiotic treatment and can be observed without the need of a formal drainage.[3] However, early drainage becomes necessary when a parapneumonic effusion advances to the fibrinopurulent stage and becomes a complicated parapneumonic effusion. Indications for immediate drainage include large effusions (larger than half the hemithorax), effusions with loculations, pH < 7.20, low glucose levels and positive Gram stain or culture. Frank pus on aspiration also requires immediate and complete drainage.[3] The various options for drainage include serial thoracenteses, tube thoracostomy (with or without intrapleural fibrinolytics), thoracoscopic drainage, thoracotomy and drainage (decortication), and chronic open drainage. The choice of drainage is established on the basis of the viscosity of the pleural fluid; location, extent, and volume of loculations; and patient's general condition. A 24 to 32 Fr chest tube is generally placed in a dependent area (usually the posterior costophrenic recess) for tube thoracostomy. If all fluid is drained and a pleural infection is established, then the tube is generally left in place until drainage typically less than 30 to 40 mL/day. On the other hand, complicated parapneumonic effusions and empyema are characterized by a procoagulant state within the pleural space, which results in the progressive development of dense layers of fibrin and loculation and are unlikely to be adequately drained with simple tube thoracostomy. In order to aid drainage of loculated areas of empyema, instillation of fibrinolytic agents via the chest tube has been proposed as a means of avoiding operation. Intrapleural instillation of fibrinolytic agents can theoretically dissolve fibrinous clots and adhesions and prevent pleural loculations. The side effects with fibrinolytics are minimal with rare reports of fever and bleeding.[19] Streptokinase, urokinase, and tissue plasminogen activator have all been used Streptokinase is administered as 250,000 IU in 100 to 200 mL saline daily for up to 7 days. The dose of Urokinase is 100,000 to 200,000 IU in 100 mL saline daily up to 3 days. Tissue plasminogen activator is given in the dose of 10 to 25 mg twice daily up to 3 days. It requires clamping of drain for several hours following the administration of the fibrinolytic. Tissue plasminogen activator, a recombinant agent doesn't have the risk of antigenic-based reactions seen with repeated administration of streptokinase.[20] Tuncozgur and colleagues[21] compared fibrinolytic versus saline instillation via chest tube in 49 patients. They found a significantly lower decortication rate (60% vs. 29%) and shorter duration of hospitalization (14 vs. 21 days) with instillation of intrapleural fibrinolysis as well as a greater volume of chest tube drainage (1.8 liters vs. 0.8 liters). However, even a 14-day hospital stay is considerably longer than what is expected following an expeditious video-assisted thoracic surgery (VATS) decortication. Tokuda and co-workers[22] performed a meta-analysis of all the major placebo-controlled studies involving intrapleural fibrinolysis. The meta-analysis showed a trend towards improved survival and a decreased need for surgical interventions. The differences, however, failed to be statistically significant.

In the largest prospective, multicenter, double-blind controlled trial to date, the Multicenter Intrapleural Sepsis Trial (MIST) studied the use of intrapleural streptokinase for the treatment of empyema.[23] A total of 454 patients with pleural pus, pH less than 7.20, or positive bacterial culture from the pleural space were randomized to chest tube drainage with streptokinase (250,000 IU twice daily for 3 days) versus chest tube drainage with placebo as saline. The primary endpoints of the study were death and need

for surgical intervention. The proportion of patients who died or needed surgery at 3 months (primary endpoints) was similar between streptokinase and control (31% vs. 27%). No differences in mortality, rate of surgery, radiographic outcomes, or length of hospital stay were shown. The study showed that intrapleural streptokinase offered no additional benefit in the treatment of empyema over chest tube drainage alone. Hence, for free-flowing uncomplicated parapneumonic effusions or empyema, tube thoracostomy or percutaneous catheter drainage remains the gold standard. Fibrinolytic therapy may be contemplated in poor surgical candidates who fail chest tube drainage, in patients who require a period of medical stabilization before surgery is performed, and in centers with limited surgical facilities. Thoracoscopic drainage is indicated in patients who fail chest tube drainage, in patients whose lung does not re-expand following either thoracentesis or tube thoracostomy, or as the initial treatment in patients who, based on chest computed tomography (CT) appearance, are unlikely to be effectively treated with a chest tube drainage. These include loculated effusions, thick pus, or a thick pleural rind on CT scan. The loculations can be broken down, thick pleural fluid and debris completely evacuated, the pleural space can be extensively lavaged with careful placement of chest tubes. Several small retrospective and nonblinded prospective studies suggest that thoracoscopy is superior to tube thoracostomy with fibrinolytics, with the need for thoracotomy halved.[24-26]

In chronic organizing phase of empyema, often a thick fibrous peel builds up on the visceral pleura that restricts lung mechanics and prevents lung re-expansion, even after adequate fluid drainage. It requires excision of all the fibrous tissue from the pleura to permit lung re-expansion.[27]

Decortication relies on lung elasticity and failure of re-expansion of the lung in the acute phase may result when there is densely consolidated lung that does not fully re-expand after drainage of fluid, even with decortication. Empyema can reduce lung perfusion by 20% to 25% on the involved side. Decortication can improve lung perfusion and improve vital capacity from 62% up to 80% and the forced expiratory volume after 1 second (FEV1) from 50% to 69%. Nonetheless, it has significant morbidity and the mortality rate may reach up to 10%.[27]

In overwhelming sepsis, pleural drainage by tube thoracostomy or expeditious VATS is required immediately with decortication performed at a later date when the patient is stable. Delayed decortication is advised if there remains significant restriction of the affected lung and if the patient is a high risk for surgery. If sepsis cannot be controlled acutely with thoracoscopic drainage and in whom decortication is not appropriate, window thoracostomy may be considered. It may be the procedure of choice if there is a permanent supply of causative organisms as a result of a bronchopleural fistula or if there is a space issue such as in a postpneumonectomy empyema.

CONCLUSION

The patients who present with pneumonia and associated pleural effusion should undergo thoracentesis for evaluation. Indications for drainage include pleural fluid analysis showing bacteria on Gram stain or culture, presence of loculations, low glucose or low pH, and frank pus. Empyema and non loculated parapneumonic effusion may be adequately treated with tube thoracoscopy, but in loculated effusions, or in those inadequately drained with a chest tube, thoracoscopic drainage should be contemplated. The elementary goals of therapy are to remove infection and allow for lung re-expansion.

When visceral pleural scarring results in lung entrapment, then decortication is needed. With recent advances in VATS technology and skills, most decortications can be performed using minimally invasive techniques. Open decortication is usually reserved for patients with severe scarring after remote pleural empyema. If decortication is not possible and significant pleural space exist, then the options are open window drainage, thoracoplasty, or muscle flap transposition.

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