Classification of parapneumonic pleural effusions

From the pathophysiology to classification and modern treatment

Stavros Anevlavis, MD, PhD[1]
Demosthenes Bouros MD, PhD, FCCP[2]

[1]Pneumonologist, University Hospital of Alexandroupolis
[2]Professor of Pneumonology, Medical School, Democritus University of Thrace, and ERS visiting professor, Medical University of Vienna, Editor-in –chief PNEUMON

Key words:
- classification
- empyema
- parapneumonic pleural effusions
- pleural effusions
- treatment

Correspondence to:
Demosthenes Bouros MD, PhD, FCCP
Professor of Pneumonology
Head, Dept of Pneumonology,
and Chairman, Dept of Internal Medicine,
Democritus University of Thrace
and University Hospital of Alexandroupolis
Alexandroupolis, Greece, 68100
Tel/Fax: +30-25510-76106,
Email: bouros@med.duth.gr

Parapneumonic pleural effusions (PPE) and pleural empyema (PE) are pleural effusions that develop as a consequence of bacterial pneumonia, lung abscess or bronchiectasis[1,2].

It is estimated that every year 4 million cases of pneumonia occur in USA, 20% require hospitalization, 20% of them have effusions, 20% progress to empyema and 20% is the mortality of empyemas**.**

PPE and PE are clinically challenging conditions, both therapeutically and diagnostically, because of their heterogeneity[3]. They range from small, uncomplicated, pleural effusions that do not require specific treatment to multiloculated effusions and empyema with pleural fibrosis, trapped lung, systemic sepsis, respiratory failure, and metastatic infection[3,4].

DEFINITIONS

An **uncomplicated PPE** is usually small in volume, free-flowing without loculations, and inflammatory in nature without the presence of detectable pathogens. Most often, uncomplicated PPE resolve with antibiotic therapy of the underlying pneumonia. A **complicated PPE** usually results from pleural infection and requires at least catheter drainage of pleural fluid and possibly surgical intervention. A PPE progresses to a PE when the concentration of leukocytes becomes sufficient to form pus, as characterized by viscous, whitish-yellow, and turbid to opaque fluid. **Empyema** fluid consists of fibrin, cellular debris, and viable or dead bacteria. Empyemas are not defined by results of chemical pleural fluid analysis (e.g., low pH) or the presence of detectable intrapleural pathogens in the setting of non-purulent pleural fluid[1,2].

A **loculated PPE** develops from the intrapleural formation of fibrinous and fibrous adhesions that prevent the free-flow of pleural fluid. Loculated effusions may be unilocular or multilocular.

Table 1 shows the biochemical characteristics of a parapneumonic effusion.

TABLE 1. Biochemical Characteristics of the Stages of Parapneumonic Pleural Effusions and Empyema (ref. 3).

Parameter	*Uncomplicated*	*Undetermined*	*Complicated*
pH	>7.3	7.3-7.1	<7.1
Glucose (mg/dL)	>60	60-40	<40
LDH (IU/L)	>500	<1000	>1000

PATHOPHYSIOLOGY AND CLASSIFICATION

The progression of an uncomplicated PPE to an organized PE represents an inflammatory continuum from a small, free-flowing, non-infected pleural effusion to a large volume of frank pus, which may be multi-loculated with thick visceral pleural peels that prevent the underlying lung from expanding to the chest wall after pleural fluid drainage ("trapped lung").

During the early stages of pneumonia, pleural membranes respond to pulmonary pathogens with a vigorous inflammatory response that promotes the formation of pleural fluid, which is exudative in nature with increased concentrations of leukocytes and proteins. Initially, the pleural fluid has a normal glucose (>60 mg/dL) and pH (>7.30) and the lactic acid dehydrogenase (LDH) concentration and the white blood cell count are low[1,2]. The increased rate of pleural fluid formation results from increased lung interstitial fluid in regions of the pneumonia and increased permeability of pleural capillaries and the pleural mesothelial monolayer barrier[5]. When the amount of pleural fluid entering the pleural space exceeds the capacity of the pleural lymphatics to reabsorb the fluid, a pleural effusion develops. Eventual deposition of fibrin along pleural membranes may occlude lymphatic stomata decreasing the reabsorption capacity of the pleural space for fluid.

Mesothelial cells play a pivotal regulatory role in the development of the intrapleural inflammatory cascade. Mesothelial cells act as phagocytes and trigger an inflammatory response when activated by bacteria, with the release of chemokines (C–X–C group), cytokines (IL-1, IL-6, IL-8, TNF-a, MCP-1), oxidants and proteases. Activated mesothelial cells also regulate the recruitment of neutrophils and mononuclear phagocytes to the pleural space[6, 7]. It is probable that the milieu of the pleural space is modulated by the temporal presence of selective chemotactic cytokines for these inflammatory cells, which stimulates their movement from the vascular compartment along a chemotactic gradient to the pleural space.

Various **classification** schemes have been described,

TABLE 2. Classification and Treatment Scheme for Parapneumonic Effusions and Empyema (Light 1995).

Class 1 Nonsignificant parapneumonic effusion	Small <10 mm thick on decubitus X-ray No thoracentesis indicated
Class 2 Typical parapneumonic effusion	>10 mm thick Glucose >40 mg/dL, pH >7.20 Gram stain and culture negative Antibiotics alone
Class 3 Borderline complicated parapneumonic effusion	7.00 < pH < 7.20 and/or LDH >1000 and glucose >40 mg/dL Gram stain and culture negative Antibiotics plus serial thoracentesis
Class 4 Simple complicated parapneumonic effusion	pH<7.00 and/or glucose <40 mg/dL and/or Gram stain or culture positive Not loculated not frank pus Tube thoracostomy plus antibiotics
Class 5 Complex complicated parapneumonic effusion	pH <7.00 and/or glucose <40 mg/dL and/or Gram stain or culture positive Multiloculated Tube thoracostomy plus thrombolytics (Rarely require thoracoscopy or decortication)
Class 6 Simple empyema	Frank pus present Single locule or free flowing Tube thoracostomy± decortication
Class 7 Complex empyema	Frank pus present Multiple locules Tube thoracostomy+thrombolytics Often require thoracoscopy or decortication

Adapted from (9)

adding to confusion regarding the right management of PPE/PE.

The first classification has been described by Andrews et al (1962)[8]. The formation of a PPE can be divided into four stages: (i) the dry "sicca" pleuritis stage, (ii) the exudative stage, (iii) the fibropurulent stage and (iv) the organization stage. In the **dry "sicca" pleuritis** stage, the inflammatory process of the pulmonary parenchyma extends to the visceral pleura, causing a local pleuritic reaction. This leads to a pleural rub and a characteristic pleuritic chest pain which originates from the sensitive innervations of the adjacent parietal pleura. A significant number of patients with pneumonia report pleuritic chest pain without developing a pleural effusion, suggesting that the involvement of the pleura may be limited to this stage in many cases of pneumonia. The **exudative** stage is characterized by a sterile exudate secondary to increased permeability of the visceral pleura. The **fibropurulent** stage represents pleural infection with the deposition of fibrin on visceral and parietal pleural membranes and the formation of loculations. Pleural fluid glucose and pH decrease and LDH increase in pleural fluid. The **organization stage** occurs with the influx of fibroblasts into the pleural space and formation of inelastic pleural peels and dense fibrous septations. The rapidity and extent of progression to a mature PE depend on the type and virulence of the pathogen, the patient's host defences, and the timing and effectiveness of antibiotic therapy. Various classifications have been proposed to clinically stage the extent of pleural inflammation and PPE formation[9,10].

In 1995 Light[9] proposed a classification which was designed to assist the physician in determining how aggressive to be with the initial therapy (table 2). This classification is based on the quantity of fluid present, the results of Gram stains and cultures of the pleural fluid, the biochemical characteristics of the pleural fluid, the presence or absence of loculations, and the gross characteristics of the pleural fluid. Patients with class 4 (simple complicated PPE) usually require tube thoracostomy plus antibiotics while patients with class 5 (complex complicated PPE) require tube thoracostomy plus thrombolytics or thoracoscopy if the thrombolytics are ineffective. Patients with class 6 (simple empyema) is suggested to be treated with tube thoracostomy plus thrombolytics ± decortication while patients with complex empyema (class 7) usually require thoracoscopy or decortications.

The American College of Chest Physicians (ACCP) has developed a new classification system for PPE/PE[1], which is based on radiological characteristics of the effusion, the pleural fluid bacteriology, and the pleural fluid chemistry (table 3). The key aspects are the characteristics that indicate that the patient has a moderate to high risk of poor outcome without drainage. An effusion that occupies >50% of the hemithorax, is loculated, or is associated

TABLE 3. American College of Chest Physicians classification of Parapneumonic Effusions

Pleural space anatomy		*Pleural fluid bacteriology*		*Pleural fluid chemistry*	*Category*	*Risk of poor outcome*	*Drainage*	*Additional fibrinolytic, VATS or surgery required*
A0: minimal, free-flowing effusion (<10 mm on lateral decubitus)	AND	BX: culture and Gram stain results unknown	AND	CX: pH unknown	1	Very low	No	No
A1: small to moderate free-flowing effusion (<10 mm and <1/2 hemithorax)	AND	B0: negative culture and Gram stain	AND	C0: pH >7.20	2	Low	No	No
A2: large, free-flowing effusion (≥1/2 hemithorax), loculated effusion, or effusion with thickened parietal pleura	OR	B1: positive culture or Gram stain	OR	C1: pH <7.20	3	Moderate	Yes	Yes
		B2: pus			4	High	Yes	Yes

Adapted from (1)

TABLE 4. British Thoracic Society classification scheme for parapneumonic pleural effusions.

Stages	*Macroscopic appearance*	*Pleural fluid characteristics*	*Comments*
Simple parapneumonic	Clear fluid	pH >7.2 LDH <1000 IU/l Glucose >2.2 mmol/l No organisms on culture or Gram stain	Will usually resolve with antibiotics alone. Perform chest tube drainage for symptom relief if required
Complicated parapneumonic	Clear fluid or cloudy/ turbid	pH <7.2 LDH >1000 IU/l Glucose >2.2 mmol/l May be positive Gram stain/culture	Requires chest tube drainage
Empyema	Frank pus	May be positive Gram stain/culture	Requires chest tube drainage No additional biochemical tests necessary on pleural fluid (do not measure pH)

Adapted from (5).

with thickened pleura, is associated with poor prognosis. A positive culture and/or Gram stain or the presence of pus is associated with poor prognosis. The pleural fluid chemistry criterion associated with a poor prognosis is a pleural fluid pH of <7.20. Alternative pleural chemistry criteria are a pleura fluid glucose of <60 mg/dL or a pleural fluid LDH more than three times the upper limit of normal serum levels. The ACCP recommends that patients classified in categories 3 and 4 with moderate to high risk of poor outcome to be treated with drainage.

In 2003, British Thoracic Society[5] proposed a simple classification scheme for parapneumonic pleural effusions. It contains 3 stages (table 4), with stages 2 and 3 (complicated parapneumonic and empyema, respectively)

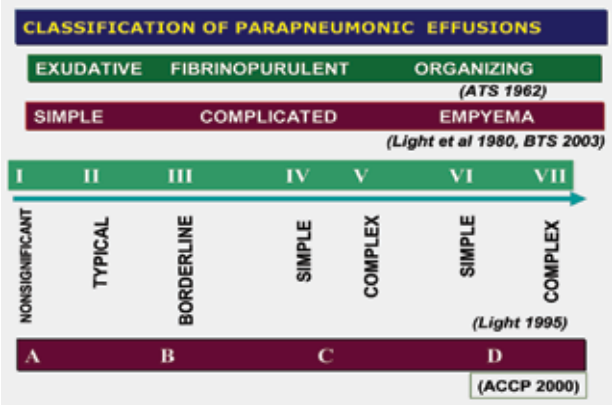

FIGURE 1. Schematic presentation of the classifications of parapneumonic pleural effusions. Adapted from (3).

requiring chest tube drainage.

A schematic presentation of the classifications of parapneumonic pleural effusions is shown on Fig. 1.

REFERENCE

1. Colice GL, Curtis A, Deslauriers J, et al. Medical and surgical treatment of parapneumonic effusions : an evidence-based guideline. Chest 2000;118:1158-71
2. Bouros D, Hamm H. Infectious pleural effusions. Eur Respir Monogr 2002;7:204-218.
3. Bouros D. Parapneumonic Pleural Effusions and Empyema. In: Bouros D (ed). Pleural Disease. Informa, New York, 2009;pp.308-38
4. Light R. Pleural Diseases. Philadelphia, PA:Lippincott and Williams and Wilkins 2001
5. Davies CW, Gleeson FV, Davies RJ. BTS guidelines for the management of pleural infection. Thorax 2003;58 Suppl 2: ii18-ii28
6. Antony VB, Godbey SW, Kunkel SL, et al. Recruitment of inflammatory cells to the pleural space. Chemotactic cytokines, IL-8, and monocyte chemotactic peptide-1 in human pleural fluids. J Immunol 1993;151:7216-23
7. Sahn SA. Use of fibrinolytic agents in the management of complicated parapneumonic effusions and empyemas. Thorax 1998;53 Suppl 2:S65-S72
8. Andrews NC, Parker EF, Shaw RR. Management of nontuberculous empyema. Am Rev Respir Dis 1962;85:935-6
9. Light RW. A new classification of parapneumonic effusions and empyema. Chest 1995;108:299-301
10. Light RW, Girard WM, Jenkinson SG, George RB. Parapneumonic effusions. Am J Med 1980;69:507-12: published online, doi:0002-9343(80)90460-X [pii]