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## Treatment of complicated parapneumonic pleural effusion and pleural parapneumonic empyema

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### Summary

**Background:**

We performed this observational prospective study to evaluate the results of the application of a diagnostic and therapeutic algorithm for complicated parapneumonic pleural effusion (CPPE) and pleural parapneumonic empyema (PPE).

**Material/Methods:**

From 2001 to 2007, 210 patients with CPPE and PPE were confirmed through thoracocentesis and treated with pleural drainage tubes (PD), fibrinolytic treatment or surgical intervention (videothoracoscopy and posterolateral thoracotomy). Patients were divided into 3 groups: I (PD); II (PD and fibrinolytic treatment); IIIa (surgery after PD and fibrinolysis), and IIIb (direct surgery). The statistical study was done by variance analysis (ANOVA),  $\chi^2$  and Fisher exact test.

**Results:**

The presence of alcohol or drug consumption, smoking and chronic obstructive pulmonary disease (COPD) were strongly associated with a great necessity for surgical treatment. The IIIa group was associated with increased drainage time, length of stay and complications. No mortality was observed. The selective use of PD and intrapleural fibrinolysis makes surgery unnecessary in more than 75% of cases.

**Conclusions:**

The selective use of PD and fibrinolysis avoids surgery in more than 75% of cases. However, patients who require surgery have more complications, longer hospital stay, and more days on PD and they are more likely to require admittance to the Intensive Care Unit.

**key words:**

**empyema • intrapleural fibrinolysis • surgery**

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## BACKGROUND

Pleural empyema, in spite of continuous advances in antimicrobial therapeutics, continues to be a serious medical problem, as much for its frequency as for its associated morbidity and mortality. Epidemiological studies describe an increasing incidence of this problem. The presence of multi-resistant and nosocomial infections, as well as a rise in the elderly population and those affected with immune deficiencies contribute to this rise [1,2]. Complicated parapneumonic pleural effusion (CPPE) is defined as the presence of biochemical criteria of complication, and requires a pleural drainage (PD) for its treatment. Pleural parapneumonic empyema (PPE) is defined as the presence of pus after pulmonary pneumonia [3]. Its phases and clinical, therapeutic and prognostic implications have been well established by Light [4]. Pleural empyema is considered secondary if it was produced after surgical intervention, thoracic trauma, or for contiguity after an adjacent infection. The modern treatment principles of pleural infections management are based on early diagnosis, correct use of antibiotic treatment and prompt PD [1,5]. Pleural fibrinolysis and surgical treatment are used in cases of clinical or radiological lack of resolution using PD. There is ongoing debate as to the optimal management of patients with CPPE and PPE [1].

With the aims of establishing better therapeutic options and discovering the optimal management of CPPE and PPE, we present a study that analyzes our results in the diagnosis and treatment of CPPE and PPE in our unit over the last several years.

## MATERIAL AND METHODS

### Study participants

This study was carried out on all patients admitted with CPPE and PPE at our hospital between 2001 and 2007. Patients excluded were those with non-complicated pleural effusion, patients with tuberculous infection, terminal stage of a neoplastic disease and those with pleural empyemas secondary to mediastinitis, trauma, diagnostic techniques or surgical interventions. We excluded 54 cases using these criteria. The study included 210 patients (168 males, 80%), with an average age of  $51 \pm 16.1$  years. The location was on the right in 121 cases (57.6%), left in 88 cases (41.9%), and bilateral in 1 case (0.5%). On 27 occasions (12.8%) admittance to the Intensive Care Unit (ICU) was required for respiratory infection alone. During this period of time 2700 patients with pneumonia were admitted at our hospital.

### Study design

This was a prospective observational analysis, consecutively collecting dates of all patients with the aforementioned inclusion criteria and diagnoses of CPPE or PPE. The study was approved by the local Institutional Review Board, and all patients gave their consent to use their data set for clinical research.

### Diagnosis of pleural effusion/empyema

The suspected diagnosis of PPE was made in all cases through clinical manifestations, analysis and a chest radiograph

**Table 1.** Porcel and Light classification of CPPE and PPE.

<b>Light and porcel classification of complicated metapneumonic pleural effusion and pleural empyema (3)</b>	
CLASS 1 (not significant pleural effusion)	Little. <10 mm gross in decubitous chest radiogram. Thoracocentesis not indicated
CLASS 2 (typical pleural effusion)	>10 mm gross in decubitous chest radiogram glucose >40; pH >7.2, Gram and cultures negatives
CLASS 3 (borderline pleural effusion)	pH 7.0–7.2 and/or LDH > 1400 and/or loculation glucose > 40, Gram and cultures negatives
CLASS 4 (simple complicated effusion)	pH <7.0 and/or glucose <40 and/or Gram or cultures positives. Not loculation nor pus
CLASS 5 (complex complicated effusion)	pH <7.0 and/or glucose <40 and/or Gram or cultures positives. Multiloculation. Not pus
CLASS 6 (simple empyema)	Pus. Unique loculation or free effusion
CLASS 7 (complex empyema)	Pus. Multiple loculations

Glucose in mg/dl.

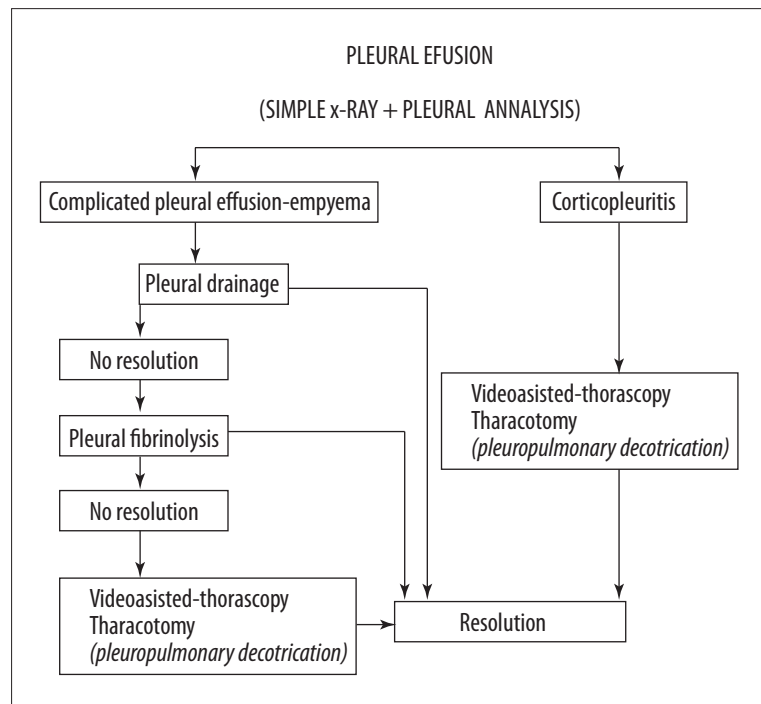
(postero-anterior and lateral, showing pleural-based opacity obscuring the diaphragm). The diagnosis was confirmed through thoracocentesis with biochemical and/or microbiological analysis of the pleural fluid. It was considered CPPE/ PPE in cases where pneumonia and pleural effusion were involved and further complicated by some of the following parameters (corresponding to classes 3, 4, 5, 6 and 7 of Light's classification) (Table 1):

1. Presence of purulent fluid (PPE).
2. Presence of bacteria in the pleural fluid, manifested in the culture and/or Gram stain (PPE).
3. Biochemical criteria of pleural effusion: pH lower than 7.2; lactodeshydrogenase (LDH) over 1400 UI and glucose lower than 40 mg/dl [3] (CPPE).

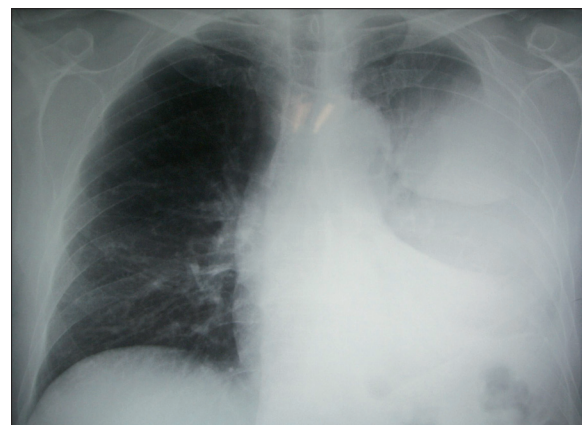
### Treatment

Once the diagnosis of CPPE/ PPE was confirmed, empirical or specific antibiotic treatment was continued, changed or established in cases in which there was a known organism. The treatment was maintained for 3 weeks (in cases of discharge from hospital, the patient continued the treatment at home). The CPPE/PPE treatment schedule is shown in Figure 1. For pleural effusion, a 28 French PD tube was placed. In the case of a clinical and radiological suspicion of multiloculations (Figure 2), a thoracic ultrasonography was done. When this revealed the presence of other sensitive areas for drainage, a corresponding PD was placed.

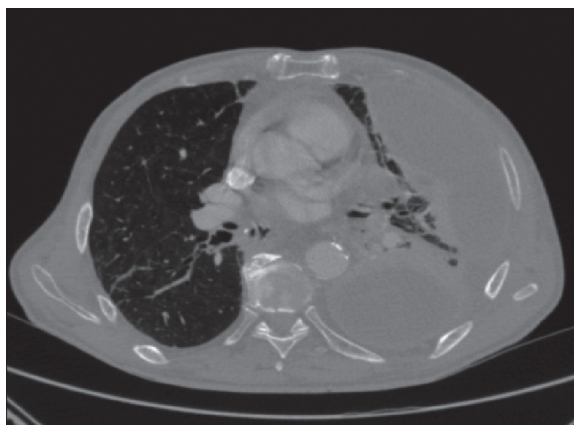
Failure to resolve the CPPE/ PPE with PD was suspected in the presence of clinical manifestations (fever, leucocytosis



**Figure 1.** Empyema treatment protocol used in this study.



**Figure 2.** Multiloculations in chest radiograph.



**Figure 3.** CT imaging: severe pleural and parietal encasement and impossibility of lung expansion.

and general malaise) and chest radiograph. These findings indicated an ultrasonography to test the correct positioning of the PD and detect the presence of multiloculated pleural collections. Once confirmed, endopleural urokinase (100.000 UI/3 dose/day for 48 hours) was established in an attempt to lyse the loculations. The quantity of effusion and the presence and quantity of loculations were classified by the pleural effusion evaluation scale described by Wait [6].

Surgical indication was immediately established in patients who failed to improve with antibiotics, PD and fibrinolysis, and who had persisting clinical and radiological signs of pleural fibrosis and the impossibility of lung expansion. A CT was used to test this (Figure 3). Surgery was indicated without previous fibrinolysis in cases of severe pleural encasement detected by CT. A thoracotomy was performed in cases of severe pulmonary encasement. If the intervention was indicated by the presence of pleural cavities with multiloculations

that were unresponsive to fibrinolytic treatment, VATS was started and, when necessary, switched to thoracotomy.

According to the stratification detailed above, the patients were divided into the following groups:

- I. PD.
- II. PD and fibrinolysis.
- III. Surgical treatment.
  - A. Indicated directly, after thoracocentesis and PD.
  - B. Indicated due to failure of PD and fibrinolysis.

The comorbidity of each group was evaluated along with its relation to the treatment performed, as well as the morbidity of the techniques, the hospital stay attributable to each technique, days on drainage and length of ICU stay.

The follow-up was done in the outpatient clinic every 3 months for 1 year. The patient was discharged definitively after 1 year.

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**Table 2.** Treatment groups and comorbidity including statistical analysis.

	Pleural empyema comorbidity				Total 210
	Groups				
	I (n=74)	II (n=84)	IIIa (n=29)	IIIb (n=23)	
Age	50.3±14.2	51.7±12.5	53.2±13.4	52.5±11.6	51±16.1
Sex	13 (17.6%)	17 (20.2%)	7 (24.1%)	5 (21.7%)	42 (20%)
Smoking	39 (52.7%)	45 (53.5%)	16 (55.2%)	17 (73.9%)*	117 (55.7%)
Diabetes	13 (17.6%)	14 (16.6%)	3 (10.3%)	3 (13%)	33 (15.7%)
Drugs	10 (13.5%)	12 (14.3%)	2 (6.8%)	8 (34.7%)*	32 (15.2%)
Alcohol	12 (16.2%)	9 (10.7%)	5 (17.2%)	5 (21.7%)*	31 (14.7%)
COPD	7 (9.5%)	12 (14.3%)	7 (24.1%)*	5 (21.7%)*	31 (14.7%)
Neoplasm	8 (10.8%)	8 (9.5%)	6 (20.6%)	4 (17.4%)	26 (12.3%)
Cardiopathy	6 (8.1%)	5 (6%)	3 (10.3%)	2 (8.7%)	16 (7.6%)
AIDS	4 (5.4%)	3 (3.5%)	2 (6.9%)	1 (4.3%)	9 (4.3%)
Corticotherapy	–	1 (1.2%)	1 (3.4%)	1 (4.3%)	3 (1.4%)
Chemotherapy	–	1 (1.2%)	–	–	1 (0.5%)

\* p&lt;0.05.

### Statistical analysis

The various relationships of patient morbidity, radiological data and pleural fluid characteristics among the different groups were compared. The values of continuous variables are presented as means ± standard deviation (SD) and were compared by variance analysis (ANOVA). Categorical variables were compared by  $\chi^2$  test and, when necessary, Fisher exact test, with a p<0.05 significance factor. Values of p<0.05 were considered as significant. Data analysis was performed using SPSS software, version 17 (SPSS, Chicago, IL, USA).

### RESULTS

The group of patients in this study presented a significant comorbidity (Table 2). Chronic obstructive pulmonary disease (COPD) was present in 14.7% of patients, 55.7% were smokers and 15.7% were current drug abusers. The presence of these factors along with alcohol consumption has been strongly associated with a great necessity for surgical treatment (Table 2).

The clinical presentation was largely in the form of febrile syndrome (n=151; 71.9%), 148 (70.5%) presented chest pain, 95 patients (45.2%) had cough and purulent expectoration, 93 patients (44.3%) had respiratory difficulty, and 56 (26.6%) had a clinical picture of general malaise. On 12 occasions (5.7%) empyema was a finding in the face of unspecified and not particularly noticeable clinical manifestations.

Blood analysis revealed that 121 patients (57.6%) had anemia and 171 (81.4%) had leukocytosis. A simple chest radiograph, as the only diagnostic test, indicated PD on 104 occasions (49.5%). An ultrasonography was necessary in 83 (39.5%). In the remaining 23 cases (11%) a thoracic CT was done after the radiograph, and direct surgical treatment was considered after the failure of PD. The characteristic

pleural fluid loculation and its amount found in the imaging media showed no significant differences between groups II and III (Table 3).

Regarding the biochemical characteristics of the pleural fluid, the average pH was 6.69±0.56, glucose 31.2±8.1 mg/dl, LDH 1526±342 UI and proteins 4.37±1.29. A diagnosis of CPPE/PPE was arrived at through biochemical data in 101 cases (48%), by microscopic confirmation when pus was present in 89 (42.3%), and by microbiological examination in 20 (9.5%). There were no significant differences among the studied groups. The definitive confirmation of the microorganism occurred in 154 cases (blood, pleural fluid and sputum cultures) (73.3%), and in 56 (26.6%) there was a polymicrobial infection. The infectious agents most frequently isolated were *Streptococcus pneumoniae*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Staphylococcus aureus* and *Hemophilus influenzae*.

PD was the initial treatment in 187 cases (89%), and on 42 occasions (20%) it was necessary to place more than 1 tube. Endopleural urokinase was administered on 113 occasions (53.8%), and in 52 patients (24.7%) surgery was performed (VATS in 21 cases and thoracotomy in 31). Of those, in 23 (11%) thoracotomy was directly indicated due to radiological findings of severe pleural fibrosis coating visceral and parietal pleura. In the remaining 29 cases requiring intervention, surgery was indicated due to failure of PD and fibrinolytic treatment.

The results of hospital stay, PD days, ICU stay and complications are shown in Table 4. The hospital stay showed statistically significant differences in groups that had required surgical treatment after PD and/or fibrinolytic therapy (Table 4). Surgery or VATS post fibrinolysis is associated with increase drainage time and length of stay in healthcare facilities.



**Table 3.** Parameters in CPPE and PPE in the groups.

	Features of pleural effusion			
	Groups			
	I (n=74)	II (n=84)	IIIa (n=29)	IIIb (n=23)
Albumin/serum	2.6±0.3	2.7±0.2	2.7±0.1	2.8±0.3
WBC*	14.2	15.3	13.4	16.3
pH	6.7±0.5	6.9±0.2	6.6±0.3	6.8±0.4
Size	2.7±0.3	2.8±0.5	3.2±0.4	3.3±0.3
Cultures**	52 (70.3%)	66 (78.6%)	19 (65.5%)	17 (73.9%)
Loculations (CT/ultrasound)	–	79 (94.0%)	29 (100.0%)	23 (100.0%)
Single	–	43	–	–
Multiple	–	36	29 (100.0%)	23 (100.0%)

\* White blood cells; \*\* blood, sputum and pleural cultures.

**Table 4.** Outcome according the groups.

	Outcome of the patients			
	Groups			
	I (n=74)	II (n=84)	IIIa (n=29)	IIIb (n=23)
Stay(days)	5.6±2.1	8.7±2.3	13.1±3.4	10.2±2.7*
Days ICU	0.2±0.2	0.4±0.2	1.6±1.3	2.1±1.1*
Drainage days	3.7±1.5	6.1±1.3	9.6±1.2	7.8±1.1*
Mortality	0	0	0	0
Complications	2	5	4	5*

\* p < 0.05.

There were no complications with PD, although in 5 patients (2.7%) there was persistent air leakage controlled with the same PD. As to fibrinolysis, there was 1 case of hemoptysis that stopped spontaneously and 2 residual pleural cavities that needed another PD. In those patients on whom surgery was performed, there were 7 patients who had complications (17.3%). There were 3 cases of postoperative hemothorax (2 in thoracotomy and 1 in VATS), all of which required surgical re-intervention. Two infections of the surgical scar developed, which were treated with localized cures. On 2 occasions, persistent air leakage of more than 5 days occurred but was controlled with the same PD, and the presence of a residual post-VATS pneumothorax was detected and it was drained. Statistically significant differences were found in complications between the patients treated surgically and those treated with PD and/or fibrinolytics. No mortality was observed and there were no deaths recorded during the follow-up period.

**DISCUSSION**

The management of CPPE and PPE implies the treatment of the pulmonary infection at the same time, and also the

comorbidity that this type of patient might present, which could delay the evolution of the clinical picture. In fact, in our series, surgical treatment was significantly more frequent in COPD patients and in people addicted to alcohol or drugs; this has also been recognized in other studies [7].

Establishment of the evolutionary phase of CPPE and PPE should be done prior to stratifying the treatment [8]. This is well defined in the work of Light and Porcel [5]. In our experience, it was determined with radiological studies (chest radiograph, ultrasonography and CT).

The treatment of the evolutionary phases 5 and 6 of CPPE and PPE is controversial. The previous phases and the most evolved (complex empyema or class 7) seem to have a consensus as to their treatment. Although having described its successful conservative treatment [9], PD is the treatment considered as the “gold standard” in stage 3 (complicated adjacent pleural effusion) and stage 4 (simple complicated pleural effusion). In class 7, surgical treatment is almost always necessary. This is the basis of our diagnostic-therapeutic protocol. In this situation, found in 11% of the cases, we always confirmed multiple pleural loculations and pulmonary encasement identified by thoracic CT (Figure 1).

There are various possibilities for managing pleural infections; however, there are many limitations because of the shortcomings of the scientific evidence. Repeating multiple aspiration thoracocentesis is included among these, but is avoided by most experts. PD has been used as the traditional first approach, but VATS and thoracotomy are used currently [1]. We used large-bore tubes according to the recommendations of most authors [10].

Controversy focuses especially on when to apply one or the other of these treatments in persistent CPPE and PPE and in the real value of endopleural fibrinolytics. Some studies have reported important benefits of using endopleural streptokinase and urokinase, avoiding surgery in most cases [1,11], although its benefits in treatment of pleural infections have

lately been cast into doubt by results of a large randomized controlled trial [12]. Other controlled studies concluded, as in our study, that subgroups of patients with CPPE/PPE may benefit from fibrinolytic therapy, although its routine use is not advised. One of the most important findings of our study is the increased drainage time and length of stay in health facilities in the patients surgically treated after fibrinolysis. Recognizing patients who are not responding to fibrinolysis could be very important and should be included in future studies. Another unclear matter about fibrinolytic treatment is the possible advantage of streptokinase over urokinase, the majority opinion being that both are equally successful. Data on dosage and treatment period is variable in each work [13–17]. It would be advantageous to reach a consensus on this matter, perhaps in a multicenter study.

In this work, stratified treatment of CPPE/PPE is described based on data from diagnostic image media, especially ultrasonography and CT. In our experience, in an average time period of 6 days, CPPE/PPE is cured with PD and/or fibrinolytic treatment, or the establishment of a surgical indication is made. With that, a statistically significant decrease of the average stay, drainage days and stay in the ICU can be obtained, which can be higher in cases treated surgically. Also, good results can be obtained in respect to morbidity. There was no mortality in our study. This kind of strategy is in line with findings of other articles on CPPE/PPE [8].

To indicate PD in CPPE/PPE in the majority of cases, a chest radiograph is sufficient, and when there are doubts about location or the presence of loculations and septations, thoracic ultrasonography [18–20] can be done. In our study, PD was indicated after a chest radiograph in 104 cases (49.5%) and through ultrasonography in 83 cases (39.5%). In a period of 2-3 days, after failure to resolve the case and once there is ultrasonographic proof of the absence of resolution, endopleural fibrinolysis can be indicated [8,20,21], which in our experience was carried out 113 times (53.8%). Failure to resolve after another 2 days of treatment indicates the necessity for surgical treatment, which was done in 29 patients (7.2%). As in other works, therefore, most of our patients did not require surgery [1,17,21].

Medical thoracoscopy has been used successfully by some authors [22,23]. Nevertheless, we, as well as other authors, performed VATS [8,24–27] when CPPE/PPE classes 5 or 6 were suspected and were not resolved with fibrinolysis. VATS provides minimally invasive access to promote drainage of multiloculated pleural infections. In most cases, however, thoracotomy may be necessary. Decortication through thoracotomy is directly indicated when PD fails, or when persistent infection symptoms and radiological signs of septation, loculation and pulmonary encasement are detected. Both interventions are considered to be equally effective [27].

In this work we used all current therapeutic methods available to treat CPPE/PPE, obtaining good results with regard to average stay, morbidity and mortality. There have been studies that tried to compare the use of each existing method [28–30], even comparing PD and endopleural fibrinolysis with VATS [5,29]. A comparison of a surgical intervention (VATS or thoracotomy) with fibrinolytic treatment by PD can obviate some risks and complications of surgical techniques [31]. We consider that a selective use

of PD, fibrinolysis and surgical techniques can be more effective and less aggressive for the patients. In our experience we have been able to avoid surgery in more than 75% of the cases. Unlike other authors [26,31–33], we consider that good results in the treatment of CPPE/PPE can be obtained without resorting to surgery in the majority of cases.

## CONCLUSIONS

We conclude that CPPE/PPE in COPD patients, smokers and alcohol and drug abusers requires surgical intervention more frequently than in other CPPE/PPE patients. Patients needing surgical treatment have more complications, longer hospital stay, higher number of days on PD and longer ICU stay. Surgical management after fibrinolysis increases drainage time and length of stay in healthcare facilities. In most cases, the selective use of PD and fibrinolysis avoids surgical treatment.

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