TREATMENT OF COMPLICATED PARAPNEUMONIC EFFUSIONS AND PLEURAL EMPYEMA : A FOUR-YEAR PROSPECTIVE STUDY

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ABSTRACT

We studied prospectively the microbiologic findings, management, including the use of intrapleural streptokinase to improve pleural drainage, and outcome of 33 patients with complicated parapneumonic effusions (6) frank empyema (27) treated by our unit over a 4-year period. The mean age was 61 years, with more male (26) than female (7) patients. Seventy-nine percent of the patients had some form of underlying illness, especially chronic lung disease (46%), followed by diabetes mellitus (23%). Fifteen percent of the pleural collections were loculated. Pleural fluid cultures were positive in 58%, Staph aureus and Kleb pneumoniae being the most prevalent aerobic isolates. The incidence of anaerobic isolates was 32%. Besides empirical antibiotics, all patients had drainage of the pleural collections at diagnosis. Four patients were treated with needle aspiration; 28 (85%) required thoracostomy tube drainage for a mean of 8 days, 5 of these went on to surgical decortication. Thirteen patients received intrapleural streptokinase (SK) to facilitate drainage, with significant increase in the volume drained. The mean duration of stay for the whole group was 22 days. The administration of intrapleural SK did not significantly shorten the duration of hospital stay. There were six deaths (18%), none as a direct result of the empyema. We describe a therapeutic approach to parapneumonic effusions and empyema which tailors the interventional modality to the clinical stage of disease.

Keywords: pleural effusion, empyema, streptokinase

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INTRODUCTION

Pleural empyema is a serious suppurative condition of the chest which often complicates the treatment of pneumonias. Even with the application of conventional diagnostic techniques, treatment with appropriate antimicrobial agents and interventional procedures, pleural empyema is associated with substantial morbidity and mortality[1-4]. Accurate assessment and expeditious treatment of infection in the pleural cavity is a challenging problem for the physician[1-15] and involves the co-ordination of multiple disciplines which may include biochemical laboratory, microbiology, diagnostic and therapeutic radiology and thoracic surgery.

Opinion varies widely however, even among chest physicians, on the mode and timing of drainage procedures and choice of empiric antibiotics. The views on timing and mode of surgical intervention differ even more[1,5-7]. The roles of newer treatment modalities such as intra-pleural fibrinolytic agents and thoracoscopic drainage remain undefined.

This paper describes a four-year prospective study of the bacteriology, treatment modalities and outcomes of a series of patients with complicated or high-risk parapneumonic effusions and frank empyema. We also recommend appropriate interventional steps for the treatment of pleural empyema at different stages of its natural history, based on personal experience of managing such patients and review of recent literature.

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METHODS AND PATIENTS

Thirty-three consecutive patients with complicated parapneumonic effusions or frank empyema (27) were studied prospectively over a 4-year period. Patients who acquired pleural infection in hospital following thoracic surgery were not included. Empyema was defined as pleural effusion that fulfilled one or more of the following criteria: (1) grossly purulent fluid, (2) fluid culture positive, or (3) positive pleural fluid gram stain. Complicated parapneumonic effusion was defined biochemically as pleural fluid with pH < 7.00, glucose < 2.2 mmol/L or LDH level > 1000 u/L[1,2,8-10].

The clinical suspicion of pleural effusion was confirmed with postero-anterior and lateral chest X-rays, for all patients. If the quantity of fluid was suspected to be small or loculated, a lateral decubitus chest film was also taken[5,10]. Loculated pleural fluid collections were evacuated under direct imaging, viz ultrasound, fluoroscopy or computed tomographic scanning (CT-scan)[11].

All patients had diagnostic thoracocenteses under sterile conditions with a 14G venula. Pleural fluid samples were sent for biochemical analysis (sugar, protein, LDH), pH, cytospin for cell types, gram-smear, aerobic and anaerobic cultures, smear and culture for acid-fast bacillus (AFB), and histopathology. Fungal smear and culture was requested when indicated. Patients with tuberculous pleural effusion were not included in this paper.

Empirical antibiotic therapy was commenced immediately after the diagnostic tap. Closed thoracostomy drainage were instituted if pleural fluid was grossly purulent or when the effusion was large. This was usually carried out with a size #24 chest tube connected to an underwater seal system at the bedside. Loculated collections in non-dependent areas or deep in the fissures were drained by ultrasound-guided insertion of 7-12 Fr pigtail catheters[1,2,5,7,12].

Repeat imaging for adjustment or replacement of tubes, and sometimes insertion of more chest tubes were done as required on a case-by-case basis.

Intrapleural streptokinase (SK) was instilled if there was persistent fluid collection (< 100 mL drained during the previous 24 hours) despite proper placement of tube and adequate antibiotic therapy, or where multiloculation was confirmed on

CT-scan. A dose of 250 000 U of SK diluted in 100 mL of normal saline per day was instilled via the chest-tube. The tube was subsequently clamped for 4 hours before being reopened to passive drainage or, where a pigtail catheter was used, manual aspiration was done at the end of the 4-hour period and again just before the next instillation[6,10,12-14]. The total number of doses given depends on patient's response and tolerability. Contraindications to the use of SK were known allergy to streptokinase and a history of bleeding peptic ulcer disease[15]. The chest tube was removed only when the daily drainage dropped to below 50 mL and when there was clinical and radiological resolution.

Patients were referred for open surgical drainage and decortication when there was no clinical response to all the above measures and the empyema became organised with a pleural peel evident on thoracic CT-scan[3,6,7,11]. Those patients with persistent pleural empyema who were unfit for general anaesthesia and open surgical drainage were left on chronic chest-tube drainage and when a fistula was well formed, the tube was removed and a stoma bag applied over the fistula site for collection of fluid. Daily care of the "stoma" site was done by the patient himself.

Antibiotic therapy was continued or altered depending on clinical response and bacterial culture results. If the fluid drained was extremely foul-smelling, antibiotic cover for anaerobic organism was added. Total treatment duration was at least 2 weeks[10,16,17].

All results are expressed as mean values ± SEM. Paired/unpaired t-test were used to calculate statistical significance.

RESULTS

There were 33 patients (26 men, 7 women) over a 4-year period (March 1991 to Jan 1995). The ages ranged between 16-88 years (mean, 61 ± 3 years). Sixty-four percent of the patients were older than 55 years.

Clinical characteristics of patients

Twenty-six (79%) patients had some form of underlying illness, 10 (38%) had more than one disease (Table I). The incidence of diabetes mellitus in this group was high at 23%. There were 12 (46%) patients with underlying lung diseases. In 29 (88%) patients, the empyema were parapneumonic, the accompanying pneumonia suggested by cough with purulent sputum and/or alveolar consolidation were documented on radiographs.

Radiology

Chest radiographs were done before and after tube placement as stated above. Those who required SK had repeat films prior to instillation to recheck the position of tubes placed.

Nineteen (58%) of the empyema were right-sided. Five (15%) patients had loculated collections as confirmed by either ultrasound or CT-thorax, or whom 4 had 2 or more locules that required repeated ultrasound-guided placement of drainage tubes (7-12 Fr). One patient had a total of 5 tubes being inserted into 3 separate locules over a period of 17 days, with complete recovery.

Pleural fluid biochemistry

The biochemistry of the initial pleural exudates is described in Table II.

The protein levels were elevated (> 30 g/L) consistent with "exudates" except in 6 patients who were nutritionally deficient and had underlying chronic illnesses. The sugar levels were generally low, consistent with pleural infection, except in two patients with poorly controlled diabetes mellitus, whose blood sugar levels were also high during the period of acute illness.

The LDH levels were elevated in all specimens (> 1000 u/L) except for one patient (368 u/L), a post-renal transplant patient with cryptococcal infection of the pleura[7].

The pH levels were measured in 18 patients, 7 (39%) were < 7.00. Those with higher levels despite the effusion being frankly purulent may be due to technical errors made during transportation of specimen, when it was not placed in anaerobic container nor transported in ice.

Serial levels of LDH and pH were measured in some patients to monitor the progress of the empyema and to aid in timing of SK administration; increasing levels of LDH and/or decreasing pH suggest that the effusion is becoming "complicated", and tubes should be inserted for proper drainage or if tubes are in-situ, intrapleural SK be administered[8,9].

Table I – Underlying illness(es) of 26 patients

		total N°	(%)
Respiratory illnesses		11	42
COAD	8		
Bronchiectasis	1		
Carcinoma of the lung	1		
Pulmonary tuberculosis	1		
Diabetes mellitus (DM)		6	23
DM alone	1		
DM + IHD + CRF	3		
DM + CA lung	1		
DM + duodenal ulcer	1		
Chronic renal failure (CRF)		3	12
Hypertension (± stroke)		3	12
Alcoholic liver cirrhosis		2	7
Rheumatoid arthritis and duodenal ulcer		1	4

COAD = Chronic Obstructive Airway Disease
IHD = Ischaemic Heart Disease
DM = Diabetes Mellitus
CRF = Chronic Renal Failure

Table II – Biochemistry of pleural fluid

	Range	Mean ± SE
Protein (g/L)	13 – 67	40 ± 2
Sugar (mmol/L)	1 – 11.5	2.4 ± 0.4
LDH (u/L)	368 – 61050	17975 ± 2973
pH	5.77 – 7.58	6.95 ± 0.12

Bacteriology and antimicrobial drugs

Pleural fluid culture was positive in 19 (58%) patients; of which 4 (21%) were polymicrobial (Table III). *Staph aureus* and *Klebsiella pneumoniae* were the most prevalent aerobic isolates. The incidence of anaerobic isolates (32%) was high with *Bacteroides fragilis* being the most prevalent. All three pathogens - *Staph aureus, Klebsiella pneumoniae* and *Bacteroides fragilis* are β-lactamase producing organisms and did not show in vitro sensitivity to penicillin. In 3 patients with sterile pleural fluid, one had positive sputum culture for *Pseudomonas aeruginosa* and 2 had positive blood cultures (one *Strept pneumoniae*, one α-streptococcus).

Ten patients with frank empyema had negative fluid culture. These culture-negative empyema may be contributed to by pre-admission antibiotic therapy given by general practitioners.

In view of the high incidence of underlying systemic illness, especially diabetes mellitus, the initial antibiotic therapy usually consisted of intravenous anti-staphylococcal penicillin plus a third generation cephalosporin; erythromycin or clindamycin was

Table III – Bacteriologic data of 19 patients with positive isolates (number of single isolate cultures enclosed in parentheses)

Aerobic gram + cocci		total 9 (7)
Staph aureus	4 (3)	
Strept pneumoniae	2 (2)	
Strept (other sp)	2 (1)	
Enterococcus faecalis	1	
Aerobic gram - bacilli		total 8 (5)
Pseud. aeruginosa	1 (1)	
Kleb. pneumoniae	5 (4)	
Enterobacter sp	1	
E coli	1	
Anaerobes		total 6 (2)
Strept milleri	2 (1)	
Bacteroides fragilis	3	
Peptostreptococcus	1 (1)	
Fungal		total 1(1)
Cryptococcus neoformans	1 (1)	

substituted if there was known allergy to penicillin. Where anaerobic infection was strongly suspected, usually on the basis of grossly purulent and foul smelling exudate, clindamycin was added. One patient with a renal transplant developed cryptococcal empyema and was treated with intravenous fluconazole.

Outcome of treatment

Treatment modalities used varied according to the different stages of effusion and general status of the patients. The outcome of treatment is discussed (Fig 1).

Exudative stage - simple aspiration

Four patients (12%) were cured by simple aspiration of pleural fluid. Thoracostomy drainage was not attempted in these patients due to the small amount of fluid. Repeat aspirations were needed in 3 of these patients to fully evacuate the pleural cavity. One elderly diabetic patient died of fulminant streptococcal septicaemia on day 4, despite adequate clearance of the empyema (2200 mL in one aspiration) and appropriate antibiotic therapy; the death was probably related to the advanced age, underlying diabetes and late presentation (third day of illness) to hospital.

Fibrino-purulent stage - closed tube drainage with fibrinolysis

Twenty-eight (85%) patients required pleural drainage via chest-tube in-situ for a mean of 8 ± 5 days (range 2 - 20 days). The number of tubes inserted varied from 1-5 (median one tube) (Fig 2). Nine (32%) of these patients had 3 chest tubes inserted under direct-imaging. Of the fifteen patients who responded with tube drainage, 9 (60%) received SK. The 13 (47%) non-respondents had varied outcomes: 5 went for thoracotomy (see below); 5 patients died (3 of sepsis, 2 of acute myocardial infarct [AMI]); one patient with underlying bronchogenic carcinoma had persistent malignant effusion after successful treatment of the pleural infection and was sent home with an indwelling chest-tube (for more than 5 months since discharge from hospital); two patients had persistent fistula with "colostomy" bag attached for collection of pus after removal of chest-tube. One fistula closed after 2 months, the other closed after $1^1/_2$ years.

A total of 13 (39%) patients received SK, varying from 1-10 doses (mean 4 doses), during their hospital stay. The average total volume of fluid drained per patient for the whole group was 1447 mL (40-5500 mL). For the SK group, there was significant increase in the drainage volume post-SK (Fig 3). No

Fig 1 - Outcome of treatment for all 33 patients

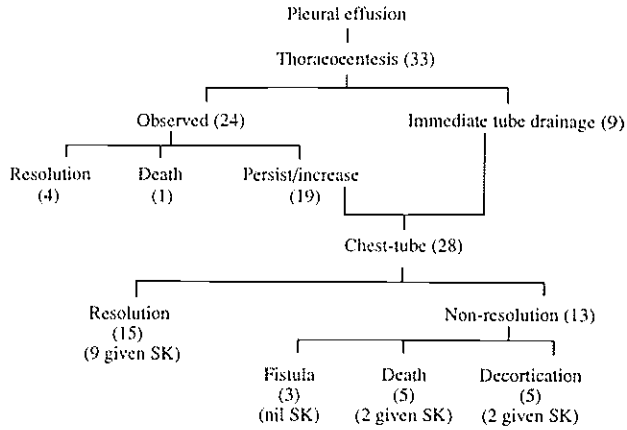
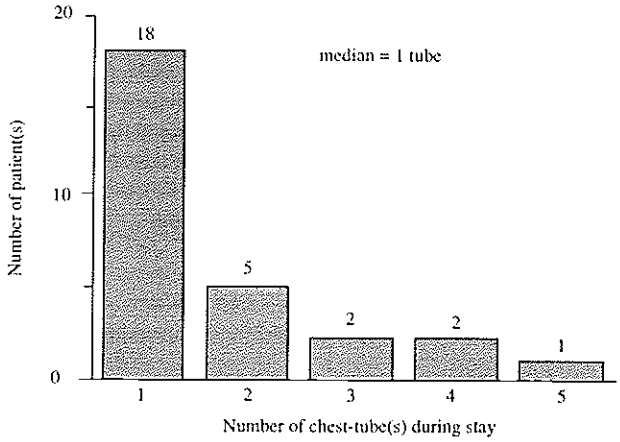


Fig 2 – Number of chest-tube(s) inserted per patient



adverse reactions were noted with administration of SK in any patient. The two deaths in this group were unrelated to its use, one of AMI and the other, sepsis. The cumulative volume of pleural fluid drained in the group of patients who received SK was significantly higher (mean 2100±515 mL) when compared to those who did not receive SK (mean 1022 ± 195 mL, $p<0.05$).

Organizing stage - open drainage and decortication

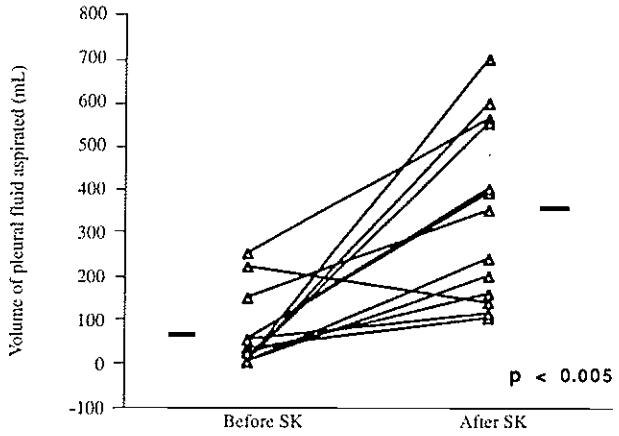
Five patients who failed to respond to tube-drainage required surgical drainage and decortication. Two of these had a trial of SK-instillation prior to thoracotomy. Repeat thoracotomy was necessary in two patients due to incomplete clearance of the empyema and break-down of the sutures resulting in a bronchopleural fistula draining infected material from the proximal airways.

The mean duration of hospital stay for the whole study group was 22 ± 2 days (range 4 - 58 days). The administration of SK though significantly improved the drainage volume, did not shorten the duration of in-patient stay. There were 6 (18%) deaths, 2 died of acute myocardial infarct, 4 died of severe sepsis, 2 of whom had streptococcal septicaemia.

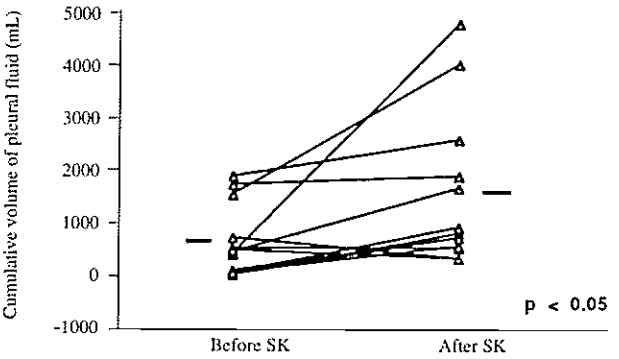
DISCUSSION

The evolution of parapneumonic effusion can be divided into three stages, which influence the choice of treatment modality. These stages gradually merge one into the other, depending on the virulence of the infecting organism[1,5,6,12] and pace of therapeutic interventions. The first is the **exudative** stage, characterised by the exudation of fluid into the pleural space in response to the inflammatory process involving the pleura. The

Fig 3 – (a) Amount of fluid drained immediately before and after the first dose of SK



(b) Cumulative amount of fluid drained before and after SK



fluid has a low cellular content, normal LDH, glucose and pH levels; the underlying lung is readily re-.expandable. Progression into the **fibrinopurulent** stage, often occurs within 24 to 48 hours. There is now accumulation of large quantities of frank pus and fibrin. The fluid tend to accumulate laterally and posteriorly, the fibrin is deposited in a continuous sheet, covering both the visceral and parietal pleura. Fibrin deposition gradually forms a thick pleural peel, restricting the lung movement. The formation of limiting membranes within the pleural space results in loculation, making drainage more difficult. The last stage is the **organising** stage, which probably occurs 2 to 3 weeks after initial pleural fluid formation, fibroblasts grow into the exudate from both the visceral and parietal pleural surfaces, resulting in a thick, inelastic membrane, easily visualised on CT-thorax. There is generalised contraction of the affected hemithorax, the lung movement and expansion become extremely restricted. If untreated, the empyema may drain spontaneously through the chest wall (empyema necessitatis) or into the lung (bronchopleural fistula)[1,12]. The natural progress of disease may be interrupted at any stage by appropriate therapy.

Successful management of complicated pleural effusions and empyema requires prompt treatment with appropriate antibiotics and adequate drainage. All patients with bacterial pneumonia should be monitored closely for the first signs of para-pneumonic effusions. Once the diagnosis is confirmed radiologically, needle aspiration must be done promptly to identify the group of patients with pleural fluid biochemical characteristics which indicate a high risk for subsequent development of frank empyema. These high risk or complicated para-pneumonic effusions should be identified and drained on the same day, "the sun must never set" on them[18].

The common organisms responsible for the formation of empyema are *Staph aureus, Strept pneumoniae, Kleb pneumoniae* and anaerobic bacteria (especially Bacteroides species)[1,16,17]. The resistance of Staphylococcus and Bacteroides group of bacteria to penicillins is well recognised. Antibiotics chosen thus have to cover β-lactamase-producing gram-positive cocci and common anaerobes. Clindamycin, cefoxitin, the combination of penicillin and β-lactamase inhibitor are generally acceptable. A gram-negative cover (third generation cephalosporins or aminoglycosides) may be added as guided by the gram-smear and culture findings. We would like to emphasise that evacuation of the pleural cavity is the most important treatment modality for suppurative pleural infections. Administration of antibiotic without pleural drainage is not adequate treatment and has been associated with higher mortality rates[1,6,19].

Intermittent closed drainage by repeated needle thoracocentesis may be adequate treatment in the early exudative phase (12% of our patients). If the fluid reaccumulates rapidly, or the patient continues to be toxic, a continuous tube-drainage may be needed. There may be a role for the use of SK even at this early stage of the disease in preventing further progression to frank fibrino-purulent empyema[7,20].

Frankly purulent effusions should be drained immediately with a closed intercostal tube of adequate size. If the effusion has not yet loculated, full lung expansion will usually be achieved. Repeated needle thoracocentesis for drainage of effusion in this fibrinopurulent stage is inadequate and should be discouraged. Adequate drainage is characterised by resolution of fever and general clinical improvement together with radiologic improvement. If there is loculation, more than one drainage tube may be necessary. If drainage is unsatisfactory despite appropriate antibiotics and well-positioned thoracostomy tube, we advocate the early use of fibrinolytic agents in this stage. The potential use of streptokinase as a means of effecting intrapleural fibrinolysis was recognised as early as 1949. The haemorrhagic complications reported initially were associated with the use of higher doses of SK, and the indwelling period was longer (more than 4 hours). The better enzyme preparations nowadays and shorter indwelling period have been associated with fewer unwanted side effects[13,14,20]. Our experience with the use of SK in 13 patients clearly showed that it is both well tolerated and effective in improving pleural drainage.

If the lungs do not re-expand and pus continued to be drained after 14 days of closed drainage and antibiotic therapy, surgical intervention should be considered (25% of our patients - including those not fit for surgery). In this stage where the empyema is well organised, the choice of surgical therapy depends on the condition of the patient and the extent of the disease process[2-4,7,12]. The options are rib resection, decortication and thoracoplasty. Rib resection, first described in 1935, allows the surgeon to mechanically remove the exudates and free the loculations; however, long-term drainage is required and hospital stay is prolonged. Decortication is the treatment of choice for patients with established empyema with thickened pleura and significant loss of volume. The inflamed pleural peel is removed allowing the underlying lung to re-expand and obliterate the pleural space. This procedure should not be performed on seriously ill or debilitated patients as the surgery takes a long time, and it may precipitate a bacteraemia. The mortality reported in the last decade varied between 0% to 33%. Thoracoplasty was widely indicated in the pre-chemotherapeutic era of pulmonary tuberculosis. It is now less popular as it is labour intensive, disfiguring, and there is availability of other modes of therapy.

The key to successful outcome with minimal morbidity for patients with empyema thus lies in early diagnosis, prompt and

meticulous tube placement under direct imaging, and repeated real-time-guided tube adjustment or replacement where necessary[7].

The aims of the aggressive approach are to save life, to re-expand the trapped lung, preserve normal respiratory function and to eliminate the morbidity and mortality associated with chronicity. Intrapleural streptokinase seems an effective adjunct in the management of complicated effusions but the timing and duration of its use will require further studies.

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