

# Intrapleural streptokinase in the management of empyema

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## Abstract

**Background** – Significant morbidity and mortality result from the ineffective evacuation of empyema. Failure of conventional first line treatment with closed intercostal tube drainage and antibiotic therapy may result in fibrin deposition and loculated empyema. Enzymatic debridement using intrapleural instillation of streptokinase is a non-invasive therapeutic option which may obviate the need for surgical intervention.

**Methods** – Eleven adults with multiloculated post-pneumonic empyemas who had failed to respond satisfactorily to intercostal tube drainage and antibiotic therapy were treated with intrapleural streptokinase between November 1992 and January 1994. A small catheter was inserted under ultrasound guidance into a loculation within the pleural space. Aliquots of 250 000 units of streptokinase in 100 ml normal saline were instilled into the pleural cavity and the tube clamped for four hours. Response was assessed by clinical outcome, measurement of drain output after unclamping, and subsequent pleural ultrasound, chest radiography, or both.

**Results** – Streptokinase enhanced drainage in all patients. Complete resolution of the empyema with re-expansion of the underlying lung was effected in eight patients, all of whom remain well. Further resolution of minimal pleural thickening was shown on subsequent chest radio-

graphs. Two patients with considerably thickened visceral pleura following empyema drainage underwent successful decortication. The other, with myocarditis and a pyopneumothorax, underwent surgery for non-resolution of the pneumothorax but died perioperatively from cardiac failure. The number of streptokinase instillations per patient ranged from two to six (median three), and the volume of empyema fluid drained per patient ranged from 100 ml to 4870 ml (median 900 ml). Streptokinase was well tolerated in all patients.

**Conclusions** – Intrapleural streptokinase is an effective adjunct in the management of complicated empyema and may reduce the need for surgery.

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Thoracic empyemas continue to cause substantial morbidity and mortality<sup>1</sup> despite the advent of antimicrobial therapy in the 1940s. Failure of conventional first line therapy – namely, intercostal tube drainage and antibiotics – occurs when pleural fluid is no longer free flowing. Inadequate drainage is usually associated with the fibrinopurulent stage of the empyema process, in which empyema fluid becomes multiloculated by the formation of fibrin strands. Fibrin deposition within the pleural cavity may take only a few days.<sup>2</sup> Thus patients may present with multiloculated effusions which are not amenable to tube drainage

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## Clinical data of 11 patients in study

Patient no.	Sex	Age (years)	Predisposing factor	Pleural culture	Days from first drainage to streptokinase instillation	Number of streptokinase instillations	Volume of fluid drained (ml)	Duration of stay after streptokinase (days)	Factors complicating recovery after streptokinase	Outcome
1	F	25	Smoker	—	7	3 over 4 days	1180	5	—	Well at 56 weeks
2	M	26	Myocarditis	<i>Clostridium perfringens</i> , <i>Pneumocystis carinii</i>	43	3 over 3 days	1160	—	Severe cardiac failure	Surgery, died postoperatively
3	M	26	Smoker	—	28	3 over 4 days	360	—	—	Surgery, successful decortication
4	M	39	Drug abuser	—	63	2 over 3 days	100	4	—	Well at 8 weeks (lost to follow up)
5	M	40	Smoker	—	42	3 over 4 days	900	6	—	Well at 30 weeks
6	M	48	Infected pulmonary infarction	<i>Escherichia coli</i> , <i>Bacterioides</i>	5	3 over 5 days	280	21	Malnourished, fractured tibia and fibula	Well at 6 weeks
7	M	55	Cardiac failure	<i>Staphylococcus aureus</i>	10	6 over 20 days	4870	42	Cardiac, renal failure and surgery for strangulated inguinal hernia	Well at 18 weeks
8	M	59	—	<i>Mycobacterium tuberculosis</i>	90	5 over 35 days	1980	—	—	Surgery, successful decortication
9	F	63	Rheumatoid arthritis, methotrexate	—	2	2 over 2 days	100	7	—	Well at 5 weeks
10	M	66	—	—	49	4 over 7 days	1160	12	—	Well at 24 weeks
11	F	74	Asthma	<i>Streptococcus milleri</i>	4	2 over 2 days	580	40	Malnourished, fractured wrist	Well at 22 weeks

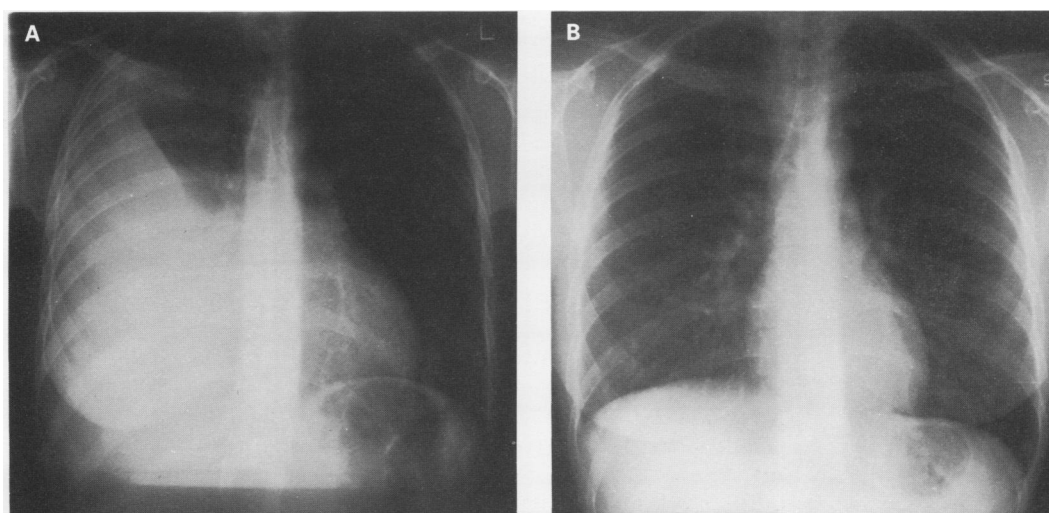


Figure 1 Chest radiographs of patient 1 (A) at presentation and (B) 40 weeks after treatment with streptokinase.

alone. In an attempt to facilitate drainage and obviate surgery, enzymatic debridement of the pleural cavity with streptokinase is a non-invasive therapeutic option. Intrapleural instillation of streptokinase was first described in 1949 by Tillet and Sherry.<sup>3</sup> Its use did not gain acceptance, however, because of the rare occurrence of intrapleural haemorrhage and systemic fibrinolysis.<sup>4,5</sup> With the availability of purer fibrinolytic formulations there has been a resurgence in the use of intrapleural fibrinolytic therapy<sup>6-8</sup> in countries outside the UK. We have reviewed our experience of enzymatic lysis of adhesions in the pleural cavity with streptokinase in 11 patients with complicated empyemas.

## Methods

### PATIENTS

Eleven adults (eight men) of mean age 47 years (median 48, range 25–74) with multiloculated empyemas were treated with intrapleural streptokinase. All patients had post-pneumonic empyemas and had failed to respond satisfactorily to antibiotics and intercostal tube drainage. Pleural ultrasound examinations confirmed the presence of multiple loculations in all patients. In order to maximise fluid drainage prior to the instillation of streptokinase, all catheters (either 8 FG pigtail nephrostomy tube with 10 side holes or 14 FG double-lumen: Merck, Hampshire, UK) were inserted under ultrasound or fluoroscopic control into the largest loculation of fluid and were regularly flushed once or twice daily with 20 ml normal saline to maintain patency. Suction had been applied to the drains of six patients before streptokinase was given. Two patients (nos 2 and 11) had more than one drain in situ at the time of streptokinase instillation; the second catheter was inserted under ultrasound guidance into the largest loculation which was separate from the area already drained. The underlying predisposing factors and pleural pathogens are listed in the table. Despite ultrasound guided placement of catheters, the use of suction, and

the maintenance of tube patency, drainage was considered to be inadequate and so streptokinase was instilled into the pleural cavity.

### ADMINISTRATION OF STREPTOKINASE

Aliquots of 250 000 units streptokinase in 100 ml normal saline were instilled into the pleural cavity via the small catheter and the tube(s) clamped. Patients were then rotated in various positions to improve the dispersal of streptokinase and the clamp(s) were released after four hours. Maximum drainage was achieved by assiduously maintaining the patency of the catheters by flushing. Maximum expansion was achieved by placing the drains on to negative pressure (10–20 cm H<sub>2</sub>O) suction before drain removal. The response to streptokinase was assessed by (a) clinical outcome (reduction in pain, dyspnoea, cough, and fever, and improvement in general wellbeing); (b) quantity of output from drain after unclamping; and (c) subsequent pleural ultrasound and serial chest radiography. Repeat instillation of streptokinase was performed if residual fluid was present 24 hours after the previous instillation.

### Results

Complete resolution with re-expansion of the underlying lung was effected in eight patients. The mean follow up period was 20 weeks (range 5–56 weeks, median 20 weeks). All eight remain well and further resolution of minimal pleural thickening was shown in subsequent chest radiographs (figs 1–3). One patient, a 59 year old man with thickened visceral pleura in whom complete re-expansion did not occur following drainage of a chronic tuberculous empyema of 10 weeks duration, underwent successful decortication. A 26 year old man with a 10 week history of unresolved empyema drained 360 ml fluid after streptokinase. In view of persisting thickened visceral pleura identified on ultrasound examination, however, decortication was performed. A 26 year old man

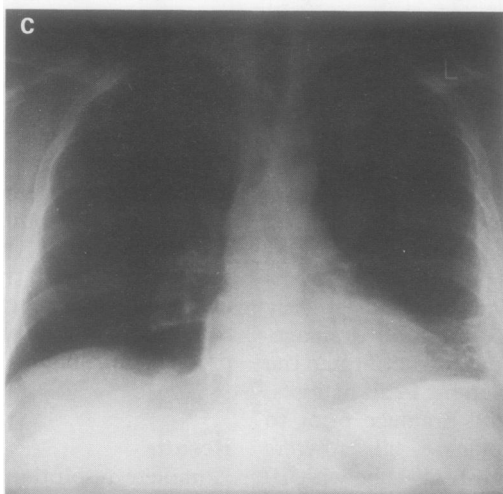
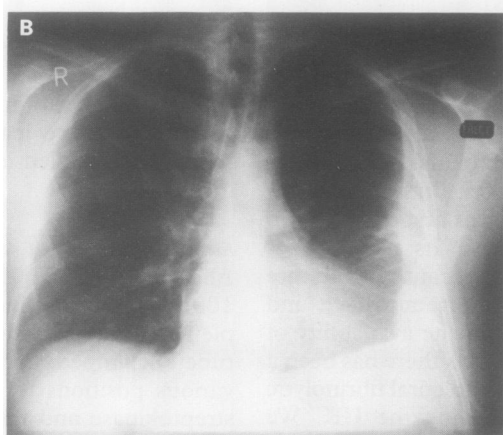
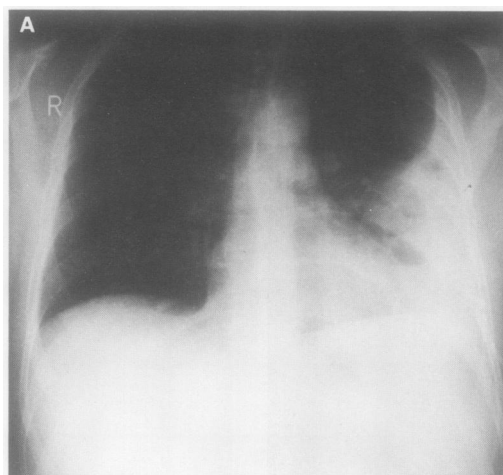


Figure 2 Chest radiographs of patient 5 (A) with catheter in situ revealing multiple fluid levels before treatment with streptokinase, (B) after two instillations of streptokinase, and (C) 13 weeks after administration of streptokinase.

with myocarditis who was on the waiting list for cardiac transplantation had a pyopneumothorax. Following streptokinase instillation, the empyema drained but the pneumothorax persisted. He therefore underwent surgery for non-resolution of the pneumothorax but died perioperatively from cardiac failure.

The number of streptokinase instillations per patient ranged from two to six with a median

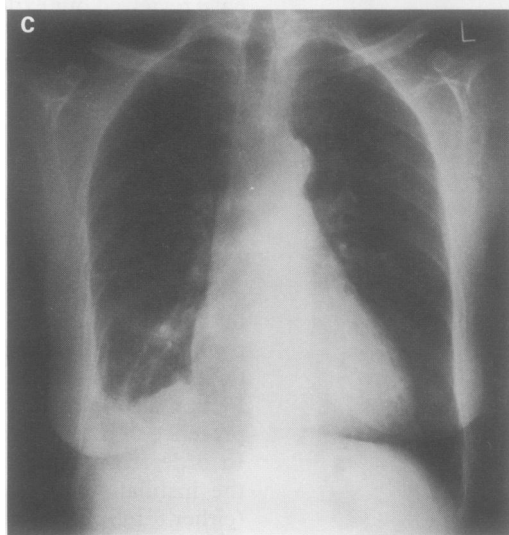
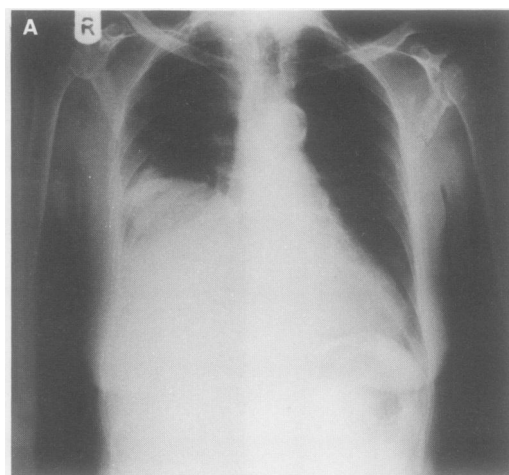


Figure 3 Chest radiographs of patient 11 (A) at presentation, (B) with catheter in situ before streptokinase administration, and (C) 11 weeks after treatment with streptokinase.

of three. The volume of empyema fluid drained per patient following streptokinase (after subtraction of the injected volumes) ranged from 100 ml to 4870 ml with a median of 900 ml (table). Streptokinase was well tolerated by all patients. One patient, a 74 year old woman, complained of mild ipsilateral chest pain after both instillations of streptokinase. There was no evidence of intrapleural haemorrhage or clinical manifestation of systemic coagulopathy.



## Discussion

We have given intrapleural streptokinase to 11 patients with empyemas which have not resolved with intercostal tube drainage and antibiotic therapy. The next therapeutic manoeuvre would usually have been surgery. In our experience streptokinase promoted drainage of loculated empyemas, permitting clinical resolution and obviating thoracic surgery. In view of the considerable morbidity and mortality associated with decortication,<sup>9</sup> the application of this non-invasive therapeutic option appears to be beneficial. Streptokinase effected complete resolution of the empyema in two patients (nos 7 and 11) who were at high risk of serious morbidity and mortality if they had undergone thoracotomy and decortication. In two patients, failure of streptokinase to achieve complete clinical resolution may be attributed to considerable pleural thickening which had developed before streptokinase therapy. It seems likely that, if enzymatic therapy is initiated early in the evolution of an empyema – that is, before fibrinopurulence is established and organisation occurs – more extensive surgical procedures could be avoided.

All patients tolerated intrapleural streptokinase well; only one complained of mild chest discomfort shortly after each streptokinase instillation. Other authors<sup>10</sup> have described the successful use of lignocaine given intrapleurally 15 minutes before streptokinase administration. It is of note that previous reports of anaphylaxis and febrile reactions developed in patients in whom streptokinase had been left in the pleural cavity for longer time periods (up to 24 hours).<sup>6,11</sup> It is likely that the shorter instillation time of four hours, combined with the use of only highly purified preparations, contributed to the lack of adverse reactions in this series. As in more recent studies,<sup>7,11</sup> intrapleural haemorrhage did not occur. It is of note that steroid cover was not given in anticipation of possible systemic reactions to repeated streptokinase instillations which were given at intervals during a period of 20 and 35 days to two patients (nos 7 and 8 respectively); all such instillations were well tolerated. Radiological intervention with placement of small catheters under ultrasound or fluoroscopic control into specific loculations has optimised the

outcome of this technique. Subsequent assessment with serial pleural ultrasound examinations has provided information on the presence or absence of fluid or pleural thickening. Indeed, the success of this technique may be attributed partly to the use of ultrasound guided drainage of large loculations, although it is noteworthy that, in this study, adequate drainage was not achieved by ultrasound guided placement of drains alone.

In summary, intrapleural purified streptokinase may be used as an adjunct to initial chest tube drainage when there is a residual collection of pleural fluid. Streptokinase enhances the drainage of fluid which is loculated or is too viscous to be drained by tube thoracostomy alone. Subsequent surgical intervention is not jeopardised by the prior use of streptokinase. The optimum time for the introduction of intrapleural streptokinase in the medical management of complicated empyema remains controversial. Multicentre controlled trials will be necessary to clarify the role of this technique and such a trial is underway.

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