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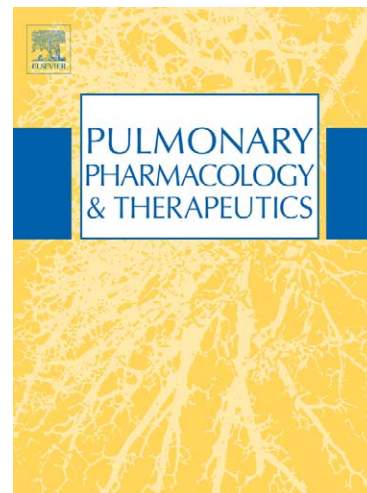
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Intrapleural fibrinolytic therapy for pleural infection

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ABSTRACT

Pneumonia with secondary pleural infection causes considerable morbidity and mortality. Intrapleural instillation of fibrinolytic agents to dissolve fibrinous adhesions is intended to improve pleural fluid drainage and prevent pleural loculations. The last 20 years their application in the every day clinical practice has drugged much of attention and several studies have supported their use in the management of parapneumonic pleural effusions (PPE) and pleural empyema (PE). However, recent published data cast doubt on the effectiveness of intrapleural fibrinolytic agents in promoting drainage of infected pleural effusions. Pending future clinical trials, fibrinolytic therapy may be used selectively in patients who fail drainage with appropriately sized, image-guided chest tubes if reasons exist to delay or avoid definitive surgical drainage. The scope of this article is to systematically review evidence for the efficacy of intrapleural fibrinolytic therapy in the treatment of PPE and PE with emphasis on controlled trials and present some of the future perspectives.

Introduction

Parapneumonic effusions and empyemas present difficult diagnostic and therapeutic challenges because of their highly variable clinical presentation and response to therapy [1] [2]. It is estimated that at least 40% of hospitalized patients with pneumonia develop a parapneumonic effusion, which is associated with an increased morbidity and a mortality of 15% [1-3]. There is considerable variation in the clinical course of patients with parapneumonic effusions. Appropriate therapy varies depending on clinical circumstances and includes antibiotic therapy alone for uncomplicated effusions, chest tube or surgical drainage for complicated effusions, and surgical drainage for established, organized empyemas.

Recommendations exist to instill the fibrinolytic drugs, streptokinase or urokinase, into the pleural space of patients undergoing chest tube drainage to lyse fibrinous adhesions, enhance pleural fluid drainage and reduce the need for surgical drainage and mechanical debridement [3]. Existing studies, however, conflict in demonstrated efficacy of these approaches. More recent reports have increased interest in the intrapleural use of novel drugs, singly or in combination with fibrinolytic drugs, that decrease the viscosity of empyema pus to promote drainage¹ or interfere with the formation of intrapleural fibrous bands [1] [2]. Limited data exist regarding the utility of these agents.

This review will discuss the use of fibrinolytic agents based on existing data and describe the potential utility of more novel approaches to the non-surgical management of PPE and PE.

Methods

A MEDLINE, EMBASE, and Cochrane database search for all English-language randomized controlled trials (RCT), controlled clinical trials, and meta-analyses published from 1966 to 2005 that report the effectiveness of intrapleural fibrinolytic drugs for the treatment of adults with PPE and PE. The terms “fibrinolytic” or “streptokinase” or “urokinase” and “pleural effusion” or “parapneumonic” or “empyema” were used. Abstracts of identified articles were reviewed and articles possibly fulfilling inclusion criteria were retrieved in full. The most recent search was conducted in 15th of December 2005.

Definitions

Parapneumonic pleural effusions (PPE) are pleural effusions that develop as a consequence of bacterial pneumonia, lung abscess or bronchiectasis [4] [5]. An uncomplicated PPE are 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 pleural empyema (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 nonpurulent pleural fluid [4] [5].

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.

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 [4] [5]. 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 [6]. 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 a battery of chemokines (C-X-C group), cytokines (IL-1, IL-6, IL-8, TNF- α , MCP-1), oxidants and proteases. Activated mesothelial cells also regulate the recruitment of neutrophils and mononuclear phagocytes to the pleural space [7-10]. 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 [9].

The formation of a mature PE can be divided into three stages: (i) the exudative stage, (ii) the fibropurulent stage and (iii) the organization stage. The exudative phase is characterized by a sterile exudate secondary to increased permeability of the visceral pleura. The fibropurulent phase 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 increases 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 defenses, and the timing and effectiveness of antibiotic therapy. Various classifications have been proposed to clinically stage the extent of pleural inflammation and PPE formation [11] [12].

TREATMENT OF PPE and PE

Early, appropriate antibiotic therapy represents the cornerstone of therapy for pneumonia and PPE. When PPE advances beyond the exudative stage and becomes complicated, early drainage of pleural fluid becomes necessary for a good clinical outcome. Multiple techniques exist for draining the pleural space and include repeated thoracentesis, tube thoracostomy (standard chest tube), insertion of image-guided percutaneous catheters, surgical incision with debridement, and thoracoscopy either by medical thoracoscopy or video-assisted thoracoscopic surgery (VATS) (Table 1). The choice of drainage technique depends on multiple factors that include the viscosity, location, volume, and extent of loculations in combination with the general condition of the patient.

Selection of any specific algorithmic approach to complicated PPE, however, remains controversial. Only a few prospective randomized trials exist to inform treatment strategies [6] [13]. Even greater controversy exists regarding the use of fibrinolytic agents for enhancing the drainage of PPE and PE for patients with chest tubes or percutaneous catheters in place. The use of fibrinolytic agents is appealing because the most common reason for failure of pleural drainage among patients with an appropriately positioned catheter is occlusion of the catheter by viscous, fibrin-rich fluid and cellular debris or the existence of fibrin strands that form pleural loculations that prevent sequestered fluid from reaching the chest tube [14-18]. Fibrinolytic agents have the potential to lyse fibrin clots and adhesions to promote pleural fluid drainage.

The intrapleural instillation of fibrinolytic enzymes (partially purified streptococcal concentrates) in the treatment of hemothorax and postpneumonic empyema was first described in 1949, by Tillett and Sherry [19]. Side effects from impurities dampened enthusiasm, but more purified streptokinase and the availability of urokinase led to reappraisal of this fibrinolytic therapy [16] [17] [20] [21].

Pharmacology of Fibrinolytics

Streptokinase is a non-enzymatic protein produced by the Lancefield group C strain of β -hemolytic streptococci (exotoxin), which activates the fibrinolytic system indirectly [20]. Streptokinase forms a 1:1 stoichiometric complex with plasminogen, which then undergoes a transition and exposes an active site in the modified plasminogen moiety, whereby the complex becomes a potent plasminogen activator. This complex has protease activity and cleaves a second plasminogen molecule, resulting in plasmin. Plasmin, a trypsin-like enzyme, active at neutral pH, hydrolyses fibrin, fibrinogen and other coagulant factors, leading to lysis of fibrin coagula [16] [20] [22].

Urokinase is a direct plasminogen activator, initially isolated from human urine. It is manufactured from cultured human embryonic kidney cells. For each molecule of urokinase, one molecule of plasmin is produced, thus making more efficient use of the pre-existent plasminogen. In contrast to streptokinase, urokinase is not antigenic and its efficacy is not reduced by antibody production. The rare reactions observed with it are probably related to contaminants (pyrogens) in the solution [16] [17] [23] [24].

Fibrinolytic regimens: The usual regimens for streptokinase are 250,000 IU daily, or 12 hourly, and 100,000 IU daily for urokinase instilled into and retained with the pleural space for 2-4 hours [1]. Fibrinolytic drugs are usually diluted in 30-100 mL of normal saline, with the chest tube clamped for 2-4 h after instillation before water-seal or suction drainage [16] [17] [24]. The effective half-life of streptokinase and urokinase is less than 30 min, which suggests that fibrin deposition may occur between drug doses given once or twice a day [25] [26]. A rationale exists, therefore, to dose fibrinolytic agents several times daily.

Contraindications: Other than an allergic history to these agents, contraindications for intrapleural administration of fibrinolytics are not clearly established and derive largely from anecdotal clinical experience (Table 2) [16].

Adverse effects: The obscuring effects of systemic responses to the underlying pneumonia prevent a reliable estimate of the frequency of adverse effects from these agents [16] [17] [24]. Immunologic reactions to streptokinase, however, represent the most commonly reported adverse effects. The initial use of nonpurified solutions of streptokinase resulted in frequent febrile reactions, general malaise, and leukocytosis. Current preparations cause far fewer allergic reactions with fever occurring in 0 to 20% of patients. A prospective study by Maskell and coworkers [27] observed only a trend toward more commonly occurring serious adverse events (chest pain, fever, or allergy) with streptokinase as compared with placebo (7 %, vs. 3 %; relative risk, 2.49 [95 percent confidence interval, 0.98 to 6.36]; $p=0.08$).

Rare reports exist of local and systemic hemorrhage with intrapleural fibrinolytic therapy [15] [16]. One case study reported that 500,000 units of intrapleural streptokinase caused systemic hemorrhage with a mild-moderate disturbance of clotting indices [16]. Additionally, Temes et al. reported in a case series a patient of significant local bleeding that required thoracotomy [28].

Intravenous administration of streptokinase generates a systemic antibody response that can neutralize a later dose of streptokinase [29-35]. No clear evidence exists that the intrapleural instillation of streptokinase produces a similar antibody response. In a recent report, however, Laisaar and coworkers observed in a single patient that intrapleural administration of streptokinase increased serum levels of antistreptokinase antibody, as occurs with intravenous infusions [36].

Urokinase is non-antigenic but may still cause acute reactions with fever as a result of immediate a hypersensitivity reaction with histamine release [37] and cardiac arrhythmias [38]. A case of acute hypoxemic respiratory failure following intrapleural instillation of both streptokinase and urokinase for empyema drainage has also been reported [39].

CLINICAL TRIALS OF INTRAPLEURAL FIBRINOLYTICS

UNCONTROLLED CASE SERIES

Twenty five small, uncontrolled clinical trials [20] [28] [40-62] report the safety and efficacy of intrapleural streptokinase or urokinase for decreasing the need for surgical drainage of PPE and PE. The aggregate mean success rate in these reports for avoiding surgery was 82% (range, 44-100%) for streptokinase [20] [28] [40-53] (Table 3) and 84% (range, 55-100%) for urokinase [54-62] (Table 4). These studies are limited by small numbers of enrolled patients, heterogeneous case mix that included patients with PPE and PE, and the retrospective design of most of the reports.

RANDOMIZED CONTROLLED CLINICAL STUDIES

Seven randomized controlled trials (RCT) of intrapleural fibrinolytics have been reported of which one trial compared streptokinase to urokinase [63] (Table 5), four trials had placebo controls (Table 5) [27] [64-67], and one compared streptokinase with thoracoscopy [68].

Comparison of streptokinase versus urokinase

Bouros and coworkers examined in 50 patients, who presented with complicated parapneumonic effusions that failed chest tube drainage, the relative efficacy, safety, and cost of streptokinase 250,000 IU versus urokinase 100,000 IU in a double-blind RCT that did not include a placebo-controlled arm [63]. Both drugs similarly increased pleural fluid

drainage and appeared to decrease the need for surgical drainage, which was required in only 2 patients in each group. The cost of urokinase was higher but the side-effect profile more acceptable with 2 patients developing high fever in the streptokinase group. The authors recommended the use of either agent as safe adjuncts to chest tube drainage although they favored urokinase because its lower incidence of allergic reactions justified its higher cost.

Comparison of streptokinase or urokinase versus placebo

Davies and colleagues [64] conducted a RCT of streptokinase versus saline placebo administered from the second to fifth hospital days and enrolled 24 patients with parapneumonic effusions that appeared frankly purulent or fulfilled biochemical criteria for infected pleural fluid. Primary endpoints included the 1) total volume of pleural fluid drainage; 2) volume of fluid drainage during the interval of streptokinase administration; and 3) improvement of chest radiographs from baseline to hospital discharge. Streptokinase caused an increased rate of fluid drainage and greater improvement of chest radiographs. Systemic fibrinolysis or hemorrhagic complications did not occur. Although surgical drainage was required in three placebo-treated patients and none in the streptokinase group, differences in this and other clinical endpoints did not reach statistical differences.

Bouros and colleagues compared urokinase and saline placebo in 31 patients with multiloculated parapneumonic effusions in a double-blind study [65]. Urokinase resulted in a larger volume of pleural fluid drainage and higher rate of initial success of chest tube drainage (87% versus 25%, $p < 0.001$). Two patients treated with urokinase required VATS drainage and 12 patients treated with placebo required cross over to urokinase therapy with 6 of these 12 patients eventually requiring VATS drainage ($p < 0.05$). Chest radiographs, duration of hospitalization, duration of chest tube drainage, and time before

defervescence favored the urokinase group, but the study was not sufficiently powered to demonstrate a mortality effect.

Tuncozgun and coworkers compared urokinase versus saline placebo in 49 patients with empyema and observed a lower incidence of need for decortication (60% vs. 29%, $p < 0.001$), shorter duration of fever (7 vs. 13 days, $p < 0.01$), greater volume of drained fluid (1.8 vs. 0.8 L, $p < 0.001$), and shorter duration of hospitalization (14 vs. 21 days, $p < 0.001$) in the urokinase treated group [66]. No differences in mortality were noted in this small study.

After publication of the above four, small RCTs with and without placebo control, [63-66] a Cochrane Collaboration systematic review assessed the evidence for efficacy of fibrinolytic therapy [23]. The reviewers concluded that the aggregate data demonstrated that fibrinolytic therapy provided significant benefits in terms of hospital stay, duration of fever, radiographic improvement, and need for surgical drainage without serious side effects of therapy, but study results were not consistent across the investigations. Because of the small sample sizes and heterogeneous study designs, the reviewers could not recommend routine use of fibrinolytic therapy.

Subsequently, Diacon and coworkers reported a single-center, placebo-controlled RCT to determine whether streptokinase instillations adjunctive to chest tube drainage reduce the need for surgery and improve outcome in 53 patients who had frank pleural pus (81%), positive pleural fluid cultures (62%), or low pleural fluid pH values (mean pH 6.60) [67]. The study is important because it is the first RCT of intrapleural streptokinase that evaluated the clinical outcomes of a need for surgery and clinical success as primary endpoints [67] [69]. After seven days, streptokinase treated patients had a higher clinical success rate (82% vs. 48%, $p = 0.01$) and fewer referrals for surgery (43% vs. 9%, $p = 0.02$). Furthermore, no significant radiological or functional differences were observed between groups during follow-up over six months.

Recently, the Multicenter Intrapleural Sepsis Trial (MIST1) reported data from the first large (n=454), multicenter, double-blind RCT of streptokinase (250,000 IU twice daily for three days) versus placebo in patients with PPE as defined by the presence of purulent pleural fluid (>80% of patients), pleural fluid pH <7.2 with signs of infection, or proven bacterial invasion of the pleural space [27]. Primary endpoints were the number of patients who had died or needed surgical drainage at three months and the secondary end points were the rates of death and of surgery at 3 and 12 months, radiographic outcome, and duration of hospital stay. The proportion of patients who died or needed surgery at 3 months after randomization was similar between streptokinase and placebo (31% vs. 27%, $p=0.43$). No differences were noted in terms of mortality, rate of surgery, radiographic outcomes, or length of hospital stay.

Comparisons of the MIST1 and Diacon studies to understand their opposing results demonstrate differences in investigational design and study population [70] [71]. Patients in MIST1 were older with more comorbidities suggesting that their outcomes may have been determined by their underlying conditions. Also, patients enrolled in MIST1 in contrast to the Diacon study underwent drainage with small catheters that were placed without image guidance and were not confirmed by subsequent CT imaging to be in an appropriate position. And finally, all management decisions for MIST1 patients were made by bedside clinicians as opposed to the Diacon study wherein a protocol guided interventions and determined primary endpoints.

Nevertheless, results of the MIST1 trial have decreased interest in the routine instillation of fibrinolytic therapy immediately after chest tube insertion regardless of stage of the PPE or the adequacy of drainage. The Diacon study [67] supports the utility of fibrinolytic therapy for patients who fail chest tube drainage although the indications for use are not clearly defined by this small study.

Comparison of streptokinase versus VATS

In the only prospective RCT of fibrinolytic therapy versus VATS for patients with PPE, Wait and coworkers randomly assigned 20 patients with complicated, multiloculated PE to receive either streptokinase (250,000 IU in 100 ml normal saline) administered daily for three days through a chest tube or immediate VATS [68]. The authors found that the VATS group had a significantly higher treatment success rate (91% vs. 44%, $p < 0.05$), lower duration of drainage (5.8 vs. 9.8 days, $p = 0.03$), and shorter hospital stay (8.7 vs. 12.8 days, $p = 0.0009$) as compared with the streptokinase group. All patients who failed streptokinase therapy could be managed by VATS without the need for open thoracotomy drainage.

The value of medical thoracoscopy as compared with fibrinolytic therapy or VATS-initiated drainage for the management of PPE has not been evaluated in clinical trials. Medical thoracoscopy has potential benefits as compared with VATS in that medical thoracoscopy can be performed under local anesthesia or conscious sedation in an endoscopy suite at a lower expense [72].

Future investigation

Streptokinase and urokinase represent less than ideal drugs for managing PPE because they have short half-lives and require repeated instillations, lack specificity for fibrin, present a potential for systemic absorption, and do not decrease the viscosity of intrapleural pus to enhance chest tube drainage. Other drugs are undergoing evaluation to identify a more effective drug or combination of drugs for patients with PPE and PE [73]. Combination therapy is especially appealing if the fibrinolytic effects of existing agents can be complemented with drugs that lower the viscosity of pleural fluid to promote drainage and prevent the formation of intrapleural fibrosis to prevent loculations.

Streptodornase

The increased viscosity of pleural pus in patients with PE is attributable to high concentrations of DNA resulting from the breakdown of phagocytes, bacteria, and other intrapleural cells. Streptodornase is a mixture of four DNAase enzymes released by streptococci that reduces the viscosity of pus through the digestion of DNA. In combination with fibrinolytic drugs or used as a single agent, streptodornase liquefies pleural pus *in vitro* from patients and animal models with PE more effectively than urokinase or streptokinase alone [74, 75]. Although streptodornase was the first intrapleural drug used to promote chest tube drainage in the management of PE [41], no RCTs exist to evaluate its *in vivo* efficacy. Clinical trials are needed to evaluate the efficacy of streptodornase in combination with fibrinolytic drugs for patients with highly viscous, multiloculated PE that fail chest tube drainage.

Deoxyribonuclease (human recombinant [hr]DNAase)

Commercially available hrDNAase digests DNA and may potentially decrease the viscosity of PE pus without the risk of allergic reactions as occur with streptococcal extracts. Simpson and coworkers used an *in vitro* assay to determine the relative effects of streptokinase versus hrDNAase on the viscosity of pus from soft tissue abscesses and from six patients with PE of varying etiology [75]. Streptokinase had little or no effect, but hrDNAase significantly reduced pus viscosity. No clinical trials have been performed, however, with hrDNAase in the management of PE. Only one case study reports the successful use of hrDNAase in an elderly patient with PE after failure of chest tube drainage with fibrinolytic therapy [76].

Tissue plasminogen activator (Alteplase®, t-PA)

Tissue plasminogen activator provides fibrinolytic activity without the antigenicity of streptokinase. Only two case reports and a single retrospective study in pediatric age groups exist to support the utility of t-PA for managing PPE [77-79]. The retrospective

study treated 71 children with chest tube drainage supplemented with either urokinase or t-PA [78]. Patients treated with t-PA had a greater volume of chest tube drainage but no other significant benefits in clinical outcome.

Single-chain urokinase plasminogen activator

Single-chain urokinase lyses fibrin by preferentially activating plasminogen bound to the fibrin polymer. This target specificity decreases the risk of systemic fibrinolysis and suggests that this agent would have greater efficacy with a longer duration of effect as compared with streptokinase or urokinase. Recently, Idell and coworkers demonstrated in a rabbit model of pleural fibrosis that a single dose of single-chain urokinase plasminogen activator decreased the extent and severity of intrapleural adhesions [80]. No studies of single-chain urokinase have been conducted in humans.

Anti-growth factor antibodies

Transforming growth factor (TGF) and vascular endothelial growth factor (VEGF) are naturally occurring growth factors that play crucial roles in tissue development, cell differentiation, embryonic development as well as numerous other signaling pathways. In the setting of pleural space infections, intrapleural generation of these agents promotes the formation of fibrotic bands leading to pleural loculations [81]. It has been proposed that intrapleural instillation of anti-TGF and anti-VEGF antibodies may prevent the formation of loculations in patients undergoing chest tube drainage [81-83]. No clinical trials or animal studies have been performed to date.

Conclusions and Recommendations

No high-grade evidence from large-scale, RCT support the utility of fibrinolytic therapy in the management of patients with PPE or PE. Consequently, fibrinolytic therapy should not be used routinely for all patients with PPE who require chest tube drainage.

Antibiotics alone remain indicated for uncomplicated parapneumonic effusions. Traditional therapy with chest tube or percutaneous catheter drainage for free-flowing complicated PPE and unilocular PE in the absence of a trapped lung remains the standard of care. Patients who fail chest tube drainage and patients with multilocular PPE, organized PE with a trapped lung, or highly viscous pleural fluid should be referred promptly for surgical drainage.

Intrapleural fibrinolytic therapy remains an option for poor surgical candidates who fail chest tube drainage or who require a period of medical stabilization before surgery is performed. Fibrinolytic drugs are most likely to be successful in patients with early PPE. Additional investigations are needed to confirm these recommendations and to evaluate the role of anti-fibrotic, DNAase, and other fibrinolytic drugs both as primary and adjunctive therapy.

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Table 1 Methods for treatment of complicated parapneumonic effusions and pleural empyema.

1. Antibiotics
2. Daily thoracentesis
3. Tube thoracostomy (standard chest tube)
4. Image-guided percutaneous catheter
5. Intrapleural fibrinolytic debridement
6. Medical thoracoscopy
7. Video-assisted thoracoscopic surgery (VATS)
8. Standard or limited ("muscle sparing") thoracotomy
9. Chronic open drainage

Table 2 Contraindications for fibrinolytic therapy.

Absolute contraindications

Previous allergic reaction

Bronchopleural fistula

Trauma or surgery within 48 hrs

Relative contraindications

Major thoracic or abdominal surgery within two weeks

History of hemorrhagic stroke

Cranial surgery or trauma within two weeks

Coagulation defects

Previous streptokinase thrombolysis (for streptokinase only)

Previous streptococcal infection (for streptokinase only)

Table 3. Series of streptokinase instillation in parapneumonic effusions and pleural empyema in adults.

First Author (Year)	Study design	Number of patients Disease	Success criteria	Success Rate (%)	Complications	Comments
Bergh et al. ⁴⁰ (1977)	RCS	12 empyemas	Volume of fluid drainage CXR improvement	100	Fever Decreased Hgb	Small chest tubes Failed conventional drainage
Fraedrich et al. ⁴¹ (1982)	RCS	27 empyemas	Volume of fluid drainage CXR improvement	44	Fever	Limited success rate 15 patients needed decortication
Henke et al. ⁴⁴ (1992)	RCS	12 CPE	CXR, clinical improvement Increased drainage	67	None	Small sample size Failed chest tube drainage
Bouros et al. ⁴⁶ (1994)	PCS	15 CPE, 5 empyemas	Clinical and radiological improvement	95	fever	Small number of patients Failure of chest tube drainage
Taylor et al. ⁴⁷ (1994)	RCS	11 empyemas	Clinical and CXR improvement, Pleural drainage	75	None	Heterogeneity of patients Failed chest tube drainage Small catheters
Chin et al. ⁴⁸ (1996)	PCS	13 CPE and empyemas	Clinical and CXR improvement	69	None	Older patients Failed chest tube drainage
Roupie et al. ⁴⁹ (1996)	RCS	16 empyemas	Increased pleural drainage CT improvement	88	Chills and fever	Failed chest tube drainage
Jerjes-Sanchez et al. ⁵⁰ (1996)	PCS	30 empyemas	CXR and PFT improvement	92	Pleuritic pain, fever, rash	Heterogeneity of population Open uncontrolled trial with other thrombolytic drugs Failed chest tube drainage
Laisaar et al. ⁵¹ (1996)	RCS	21 empyemas, 1 CPE	Increased pleural drainage Clinical and radiological improvement	68	Chest pain, fever bleeding	Failed chest tube drainage
Temes et al. ²⁸ (1996)	PCS	19 empyemas	Clinical and radiological improvement	69	Fever, bleeding	Small number of patients Heterogeneity of patients Limited success rate
Chin et al. ⁵² (1997)	PCS	17 empyemas, 6 CPE	Pleural drainage Clinical and radiological improvement	78	None	No difference with the drainage group in mortality, morbidity rates
Lim et al. ⁵³ (1999)	PCS	23 CPE and empyemas	Clinical and radiological improvement, fluid drainage	91	None	Lack of randomization Unblinded study Heterogeneity of studied groups/ Small sample size

Abbreviations: CPE: Complicated Parapneumonic Effusions, CT: Computed Tomography, CXR: Chest X-ray Hgb: Haemoglobin, PCS: Prospective Case Series, PFT: Pulmonary Function Test, RCS: Retrospective Case Series

Table 4. Case series of urokinase instillation in parapneumonic effusions and pleural empyema in adults.

First Author (Year)	Study design	Number of patients/ Disease	Success criteria	Success Rate (%)	Complications	Comments
Moulton et al. ⁵⁴ (1989)	RCS	11 CPE	Clinical outcome Absence of residual fluid	100	None	Small catheters Failure of chest tube drainage
Lee et al. ⁵⁵ (1991)	PCS	10 empyemas	Complete drainage	90	None	Small catheters No CT guided
Robinson et al. ⁵⁷ (1994)	RCS	10 CPE / empyemas	Clinical and radiological improvement	77	None	Heterogeneity of patients Two patients initially improved but subsequently required decortication
Moulton et al. ⁵⁹ (1995)	RCS	27 CPE 79 empyemas	Clinical and radiological Improvement, pleural drainage <20 mL	94	None	Small catheters
Bouros et al. ⁶⁰ (1996)	PCS	13 CPE 7 empyemas	Volume of drained fluid, radiological improvement	95	None	Lack of comparison among several dose regimens
Park et al. ⁶¹ (1996)	RCS	31 CPE	Lung expansion on CXR	81	None	Small catheters US with linear septations and honeycombing associated with failure
Souza et al. ⁶² (2000)	RCS	26 empyemas	Clinical and radiological improvement, fluid drainage, lung expansion	55	None	Older patients Failure of chest tube drainage

Abbreviations: CPE: Complicated Parapneumonic Effusion, CT: Computed Tomography, CXR: Chest radiograph, PCS: Prospective Case Series, RCS: Retrospective Case Series ,
US: Ultrasound

Table 5. Summary of six randomized, controlled trials of fibrinolytics in adult patients with parapneumonic effusions and pleural empyema without a surgery study arm.

First author (Year)	Mean \pm SD /Median age-yrs (age range-yrs)	Streptokinase n (%)	Urokinase n (%)	Chest Tube + Normal Saline n (%)	PRIMARY OUTCOME
Bouros et al. ⁶³ (1997)	(15-92)	25 (92)	25 (92) +		<ol style="list-style-type: none"> 1. Improvement in imaging (CXR, CT and/or chest ultrasound) 2. Duration and total volume of pleural drainage 3. Time to apyrexia 4. Cost of treatment 5. Hospital stay
Davies et al. ⁶⁴ (1997)	(18-90)	12 (100)		12 (25)	<ol style="list-style-type: none"> 1. Total volume of pleural drainage. 2. Volume of fluid drainage between days 2-5. 3. Improvement of chest radiograph from baseline to discharge
Bouros et al. ⁶⁵ (1999)	56 (21-78)		15 (87)	16 (25)	<ol style="list-style-type: none"> 1. Improvement in imaging (CXR, CT and/or chest ultrasound) 2. Duration and total volume of pleural drainage 3. Subjective clinical improvement 4. Time to apyrexia
Tuncozgun et al. ⁶⁶ (2001)	(15-85)		25 (60)	24 (29)	<ol style="list-style-type: none"> 1. Time to apyrexia 2. Duration and total volume of drainage 3. Duration of hospital stay 4. Improvement in chest radiography and CT
Diacon et al. ⁶⁷ (2004)	39 \pm 13	22 (82)		22 (48)	<ol style="list-style-type: none"> 1. Clinical treatment success 2. Need for referral to surgery
Maskell et al. ²⁷ (2005)	Streptokinase: 60 \pm 18 PLACEBO: 61 \pm 18	208 (69)		222 (73) +	<ol style="list-style-type: none"> 1. Death or need for surgery 2. Rates of death and of surgery 3. Radiographic outcome 4. Length of hospital stay.

Abbreviations: n= number of patients, (%) = success rate, CT = Computed Tomography, VATS = Video-Assisted Thoracoscopic Surgery, + = not significantly different.