

A breakthrough in the treatment of empyema: what we have learnt 50 years on from Tillett and Sherry's original case report

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Date accepted for publication 22 December 2003

Abstract

The scientists William S. Tillett and Sol Sherry were responsible for the introduction of intrapleural fibrinolytics as therapeutic agents, thus supplementing antimicrobial therapy in the treatment of empyema. They were the first to suggest the possibility that the use of these drugs in empyema might obviate the need for radical surgical procedures. This article highlights their original work and contributions in this field.

[Abstract](#)

[Keywords](#)

[Introduction](#)

[A novel concept](#)

[Conclusion](#)

[References](#)

[Home Page](#)

[Title Page](#)



[Go Back](#)

[Full Screen](#)

[Close](#)

[Quit](#)

GR

Keywords

Empyema; intrapleural fibrinolytics.

Introduction

'Empyema thoracis' refers to the collection of pus within the pleural cavity. Empyema often results from progression of a parapneumonic effusion caused by a community-acquired pneumonia. Over the years, various measures have been employed to treat empyema comprising antibiotics, pleural drainage, open surgical drainage and ultimately, thoracotomy and rib resection. Although surgical drainage has until recently been widely used, the risks of morbidity and mortality are high. These are also invasive, major surgical interventions associated with additional complications from using general anaesthesia and requiring surgical expertise not available in all centres.

The discovery of fibrinolytic agents in the late 1940s led to the first use of intrapleural fibrinolytics. However, it was nearly 50 years later that advances in drugs and radiological techniques allowed them to be widely used. The scientists William S. Tillett and Sol Sherry were responsible for the introduction of these drugs as therapeutic agents, thus supplementing antimicrobial therapy in the treatment of empyema. They were the first to suggest the possibility that the use of these drugs in empyema might obviate the need for radical surgical procedures. This article highlights their original work and contributions in this field.

A novel concept

In 1933, W. S. Tillett and R. L. Garner^[1] conducted experiments to study the fibrinolytic activity of haemolytic streptococci. Human plasma or fibrinogen was mixed with both cultures of haemolytic streptococci obtained from patients with acute streptococcal infections. It was observed that lysis of human plasma clot occurred within 10 min while

Abstract

Keywords

Introduction

A novel concept

Conclusion

References

[Home Page](#)

[Title Page](#)



[Go Back](#)

[Full Screen](#)

[Close](#)

[Quit](#)

fibrinolysis was rapid, taking 2 min. The lytic action was attributed to an 'active fibrinolytic factor' elaborated by the bacterial cultures. Streptokinase was thus discovered and given its name by Christensen and MacCleod who, in 1945, stated that it activated plasminogen present in the human blood converting it into an 'active fibrin lysing system', which they termed plasmin. Plasmin is responsible for the breakdown of fibrinogen, the parent protein, into soluble fibrin fragments.

Study of the physical qualities, and chemical analysis of empyemal pus due to *Klebsiella* infection led to the observation by Tillet, Sherry and Christensen in 1948 that a nucleoprotein in addition to the fibrin accounted for the gelatinous, fibrinous nature characteristic of purulent pleural exudates^[2]. They reported that the desoxyribose nucleoprotein thus isolated constituted nearly 30–70% of solid sediments and contained 26–50% of nitrogen. Experiments conducted later that year demonstrated the lytic action of the desoxyribonuclease or streptodornase produced by the group A haemolytic streptococci on the nucleoprotein present in the exudates^[3].

These earlier experiments provided the basis for the clinical study undertaken by Tillet and Sherry in 1949 in which 'the effect of intrapleural instillations of streptococcal fibrinolysin (streptokinase) and streptococcal desoxyribonuclease on fibrinous, purulent and sanguinous pleural exudations' was investigated^[4]. Patients were categorised into three groups:

1. Acute fibrinous pleurisy;
2. Bacterial empyema;
3. Haemothorax.

Overall, 8 patients with bacterial empyema due to varying causes like tuberculosis, *Klebsiella*, pneumococcus, post-pneumonic and anaerobic streptococci were chosen. It was noted, on aspiration of the pus prior to the injection, that large amounts of desoxyribonucleoprotein were present when compared to fibrinogen. The strain used was haemolytic *Streptococcus* (H46A) of Lancefeld group C. This is potent in its production of both streptokinase and desoxyribonuclease. The pleural cavities of all the patients were then injected with concentrated and partially purified haemolytic streptococcal cultures

[Abstract](#)[Keywords](#)[Introduction](#)[A novel concept](#)[Conclusion](#)[References](#)[Home Page](#)[Title Page](#)[Go Back](#)[Full Screen](#)[Close](#)[Quit](#)

containing about 160 000 U of desoxyribonuclease and 400 000 U of streptokinase in 10 cc saline.

Parameters observed were viscosity of pus, quantity of sediment, free streptokinase, pH and drainage of pus from the pleural cavity. A substantial decrease in viscosity, measurable sediment and free streptokinase over the space of an hour were noted after the injection. These factors registered a falling trend over the next 24 h. This was in stark contrast to increased pleural drainage and formol titratable material. The study also revealed that streptococcal concentrates were inactivated at an acidic pH.

The patients improved symptomatically, their temperature soon normalised and leukocytosis disappeared after a few days. X-ray of the chest showed resolution of the empyema and absence of previous loculation.

On analysing the results, the researchers concluded that both fibrinolysis due to streptokinase and nucleoprotein depolymerisation by nuclease had occurred. Enzymatic action by nuclease explained the fall in viscosity and nucleoprotein sediment while streptokinase accounted for changes in the fibrin lysing system and formol titration.

Adverse reactions to the streptococcal concentrates were also reported. The most common was a transient febrile reaction beginning 6–8 h after the injection, peaking at 24 h and then gradually waning over the next few days. Other side effects were general malaise, nausea, gastrointestinal discomfort and local pain in some cases. Of particular interest was the increase in leukocytes, which was shown to have no correlation either to dosage or number of injections administered.

In 1951, Tillett, Sherry and Read published their article on ‘the use of streptokinase–streptodornase (DNase) in the treatment of postpneumonic empyema’^[5]. This study stated that the lytic enzymatic therapy resulted in extensive evacuation of the loculated empyemal cavities followed by significant re-expansion of the underlying lung within 24 h. In addition, it was pointed out that in patients with positive bacterial cultures, the enzymatic debridement achieved rapid sterilisation of the cavities. This was probably because of more effective contact between antibiotics and bacteria. Out of the 25 patients assigned to this study, 21 were treated effectively with intrapleural fibrinolytics, but the remaining 4 required in addition closed thoracotomy.

[Abstract](#)[Keywords](#)[Introduction](#)[A novel concept](#)[Conclusion](#)[References](#)[Home Page](#)[Title Page](#)[◀◀](#) [▶▶](#)[◀](#) [▶](#)[Go Back](#)[Full Screen](#)[Close](#)[Quit](#)

However, the clinical use of fibrinolytic drugs fell into disrepute owing to the allergic reactions including rare instances of intrapleural haemorrhage and systemic fibrinolysis. The impure nature of the extracts was to blame and thus they were disregarded for use in the UK.

The past 20 years has seen a renewed interest in the therapeutic use of intrapleural fibrinolytics with the availability of newer highly purified concentrates^[6]. Randomised controlled studies have now provided evidence confirming better clinical outcome, improved pleural drainage and chest radiology after the use of intrapleural streptokinase.

The first^[7] randomised controlled trial used intrapleural streptokinase in community-acquired parapneumonic effusions. 24 patients randomly received either streptokinase or saline flushes for 3 days. Results were in favour of streptokinase with improved pleural drainage and radiological appearance in the streptokinase group. Early introduction of streptokinase was also suggested in the treatment plan. None of the streptokinase group required further surgery.

A second study^[8] conducted in Turkey involved random allocation of 128 patients with loculated parapneumonic effusions who received either intrapleural urokinase or streptokinase or control saline flushes. Increased pleural drainage and radiological improvement were noted among the urokinase group compared to the streptokinase and saline groups. They concluded that urokinase was safe, cost-effective and might avert surgery.

Another study was a prospective, double-blinded, randomised controlled trial from Greece^[9]. In this study, 31 patients with multiloculated pleural effusions were randomised to receive either intrapleural urokinase or normal saline for 3 days after failure of chest drainage. Conclusions drawn from the trial corroborated the previous study that urokinase improved chest tube drainage, chest X-ray and also decreased the duration of hospitalisation. It was suggested that its use might decrease the need for further surgery. Earlier use of urokinase was also recommended.

The last^[10] study was a double-blinded, randomised controlled trial of intrapleural fibrinolytics in childhood empyema. 60 children were randomly assigned urokinase or normal saline for 3 days. The primary outcome measured was the duration of hospital

[Abstract](#)[Keywords](#)[Introduction](#)[A novel concept](#)[Conclusion](#)[References](#)[Home Page](#)[Title Page](#)[Go Back](#)[Full Screen](#)[Close](#)[Quit](#)

stay. The findings revealed a 28% longer hospital stay in the placebo group. Use of smaller drains was also associated with shorter duration of hospitalisation.

All the trials conducted so far show a positive outlook regarding the apparent benefits of using intrapleural fibrinolytics in parapneumonic effusions and empyema. None of the trials documented any severe adverse effects of these drugs. The current British Thoracic Society (BTS) guidelines recommend the use of intrapleural fibrinolytic drugs in the management of loculated parapneumonic effusions and empyema^[11]. Further studies should be undertaken to estimate key outcomes such as mortality rates, frequency of surgery and residual lung function. A large multicentre study is at the moment being conducted by the Medical Research Council (MRC) and BTS to assess in large numbers the use of intrapleural streptokinase. New methods such as video-assisted thoracoscopic surgery (VATS) have been reported to have faster resolution and shorter hospital stays. However, larger trials need to corroborate this and the fact that VATS is an invasive procedure using general anaesthesia seems to be a drawback.

Conclusion

The work of Tillett and Sherry serves to demonstrate the milestones they achieved in relation to the management of empyema. A clear understanding of the mode of action of fibrinolytic agents and the application of those principles clinically, reveal a carefully thought out scientific methodology. Tillett and Sherry were pioneers in this regard with a concept that still has far-reaching consequences. As a result of their work, almost 50 years later, increasing numbers of empyema cases are being managed medically without resorting to surgery.

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[Abstract](#)[Keywords](#)[Introduction](#)[A novel concept](#)[Conclusion](#)[References](#)[Home Page](#)[Title Page](#)[Go Back](#)[Full Screen](#)[Close](#)[Quit](#)

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[Abstract](#)[Keywords](#)[Introduction](#)[A novel concept](#)[Conclusion](#)[References](#)[Home Page](#)[Title Page](#)[Go Back](#)[Full Screen](#)[Close](#)[Quit](#)