

Streptokinase did not reduce mortality or need for surgical drainage in pleural infection

Maskell NA, Davies CW, Nunn AJ, et al. U.K. Controlled trial of intrapleural streptokinase for pleural infection. *N Engl J Med.* 2005;352:865-74.

Clinical impact ratings: Hospitalists ★★★★★☆☆ Infectious Disease ★★★★★☆☆ Pulmonology ★★★★★☆☆

QUESTION

In patients with pleural infection, does streptokinase reduce mortality and the need for surgical drainage more than placebo?

METHODS

Design: Randomized placebo-controlled trial (First Multicenter Intrapleural Sepsis Trial [MIST1]).

Allocation: Concealed.*

Blinding: Blinded (clinicians, patients, and outcome assessors).*

Follow-up period: 12 months.

Setting: 52 centers in the United Kingdom.

Patients: 454 patients with macroscopically purulent pleural fluid or fluid that had a positive culture for bacterial infection, was positive for bacteria on Gram staining, or had pH < 7.2 and clinical evidence of infection. Exclusion criteria included age < 18 years; concomitant serious illness; previous intrapleural fibrinolytic therapy for this empyema; previous video-assisted thoracic drainage, thoracotomy, pleural decortication, or open surgical drainage for this empyema; major surgery in the past 5 days; and pregnancy or lactation.

Intervention: Streptokinase, 250 000 IU (Streptase, Aventis, UK) (*n* = 208), or placebo (*n* = 222) in 30 mL of normal saline delivered through the chest tube into the pleural

space every 12 hours for 6 doses. All patients received chest-tube drainage and antibiotics.

Outcomes: A composite endpoint of death or need for surgical drainage of the infected pleural fluid at 3 months. Secondary outcomes included the composite endpoint at 12 months, the individual components of the composite endpoint, and hospital length of stay. The study had 80% power to detect a 40% reduction in the primary outcome with streptokinase.

Patient follow-up: 430 patients (95%) (mean age 61 y, 70% men). Primary outcome data were available for 427 patients (94%).

MAIN RESULTS

The streptokinase and placebo groups did not differ for the primary outcome of death or need for surgical drainage at 3 months

(Table). The lack of difference remained at 12 months (Table). Groups did not differ for death or need for surgical drainage analyzed separately at 3 or 12 months (Table). Streptokinase and placebo groups did not differ for hospital length of stay (median 13 vs 12 d, *P* = 0.16).

CONCLUSION

In patients with pleural infection, streptokinase did not reduce mortality, the need for surgical drainage, or hospital length of stay more than placebo.

Source of funding: UK Medical Research Council.

For correspondence: Dr. C.W. Davies, Oxford Radcliffe Hospital, Oxford, England, UK. E-mail Robert.davies@ndm.ox.ac.uk. ■

*See Glossary.

Streptokinase vs placebo for pleural infection†

Outcomes	Follow-up	Streptokinase	Placebo	RRI (95% CI)	NNH
Death or surgical drainage	3 mo	31%	27%	14% (-15 to 54)	Not significant
	12 mo	40%	34%	18% (-8.3 to 52)	Not significant
Death	3 mo	16%	14%	14% (-28 to 81)	Not significant
	12 mo	23%	20%	12% (-23 to 61)	Not significant
Surgical drainage	3 mo	16%	14%	7.3% (-31 to 68)	Not significant
	12 mo	18%	16%	16% (-24 to 77)	Not significant

†Abbreviations defined in Glossary; RRI, NNH, and CI calculated from data in article.

COMMENTARY

Pleural space infection comprises a spectrum of diseases, from the early, relatively free-flowing effusion to the organized empyema. Despite the adoption of routine use of thrombolytics, the trial by Maskell and colleagues is the first that is sufficiently powered to adequately assess the potential benefit of this practice. This important trial suggests that routine use of streptokinase with a chest tube placed without imaging in all patients with pleural infections does not decrease mortality or the need for surgery compared with saline flushes. However, while the study answers the question it asks, those of us who treat complicated pleural effusion take issue with the conclusions. An accompanying editorial outlines several important caveats, including the broad inclusion criteria and the advanced age and comorbid conditions of many of the patients (1).

It is important to place the trial in the proper context. First, it is possible that routine flushing of chest tubes with saline every 12 hours for the first 3 days provides the same benefit as streptokinase without its associated side effects. Second, simply placing a chest tube and observing without flushing the tube is probably not sufficient. However, this trial does not inform us of alternative approaches to complicated pleu-

ral infections that incorporate thrombolytics. Many centers adopt a systemic approach to complicated pleural infections, including computed tomography, radiographic placement of chest tubes, and administration of streptokinase to promote drainage in an iterative process until the pleural space is cleared. Anecdotal evidence suggests that this approach rarely leads to the need for surgical intervention. However, it has not been studied in randomized controlled trials of sufficient size to support this assertion and it remains unclear whether saline flushes alone, rather than streptokinase, would provide similar outcomes. Despite the results of this excellent trial, many of us would find it premature to suggest that streptokinase does not have a role in the treatment of pleural infections. However, the onus is now on advocates of streptokinase for empyema to test its use in well-designed trials.

*Sean P. Keenan, MD
University of British Columbia
Vancouver, British Columbia, Canada*

Reference

1. Heffner JE. Multicenter trials of treatment for empyema—after all these years. *N Engl J Med.* 2005;352:926-8.