Online Appendix C4 BTS Guideline for Pleural Disease

Section C Pleural infection

Question C4 Evidence Review and Protocol

C4 For adults with pleural infection, does intrapleural therapy improve outcomes compared to other treatment options (e.g. drainage alone or surgical intervention)?

Contents

Question Evidence Review

C4 For adults with pleural infection, does intrapleural therapy improve outcomes compared to other treatment options (e.g. drainage alone or surgical intervention)?

Background

Patients with pleural infection generally have a poor outcome and some may require surgery to resolve their illness. Intra-pleural therapies have been used to improve drainage and avoid the need for surgery in patients with complicated parapneumonic effusions (CPPE) or empyema and these include fibrinolytics, saline irrigation and intra-pleural antibiotics. This review will investigate if intrapleural therapies improve clinical outcomes in adults with pleural infection (including tuberculous empyema) when compared with other treatment options such as drainage alone or surgical intervention.

Outcomes

Mortality, need for repeat intervention, surgery, quality of life, patients' symptoms, length of hospital stay, complications, radiological outcomes

Evidence review

Sixty-four studies were identified, of which 16 met the criteria for inclusion. Nine were randomised controlled trials (RCTs) in patients with bacterial empyema or CPPE[1-9] and three were RCTs in patients with tuberculous empyema[10-12]. Three single arm observational studies in bacterial pleural infection[13-15] and a prospective observational study in patients with bacterial empyema or CPPE are also discussed[16]. Finally, a single RCT investigated pleural irrigation[4] and no eligible studies investigated intra-pleural antibiotics.

Intrapleural therapies included intrapleural fibrinolytics (streptokinase[3,5,6] or urokinase[1,9,11]), alteplase (tissue plasminogen activator (TPA)) and dornase alfa (DNAse), with TPA and DNAse given separately or in combination[7,13-16], and saline irrigation[4]. Comparators included chest drainage alone[6,10,11] or chest drainage with intra-pleural placebo (usually 100 ml of normal saline)[1-5,7-9,12].

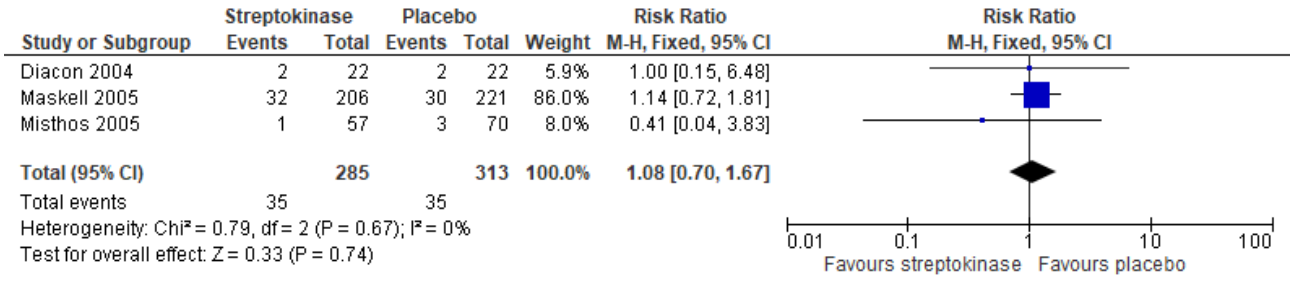
Mortality

Seven studies (five RCTs[3-7] and two observational studies[15,17]) reported mortality following treatment with intrapleural therapy versus placebo or standard care, but the time points at which survival was assessed were varied. Where studies reported mortality at more than one time point (two studies[5,7]), the first time point was used in the meta-analyses to ensure consistency (i.e. where studies only reported one time point, this was regarded as the "first" time point).

Streptokinase versus placebo or standard care

Three studies compared streptokinase versus placebo or standard care.[3,5,6] Meta-analysis of the RCTs revealed no difference in mortality rate in patients treated with streptokinase compared with placebo 121 per 1000 (78 to 187) and 112 per 1000 respectively (Figure C4a).

Figure C4a: Mortality rate (streptokinase versus placebo or standard care)



Saline irrigation versus standard care

A further study compared saline irrigation (250 ml saline TDS) with standard care (30ml saline TDS) and showed no meaningful difference in mortality in the saline irrigation group (2 deaths from 18 patients) compared with the standard care group (0 deaths in 17 patients).[4]

TPA plus DNAse, TPA or DNAse versus placebo

A single study compared survival in patients treated with placebo, TPA, DNAse or TPA plus DNASe and showed similar mortality at three months in all four treatment arms (p = 0.46).[7] Two observational studies also reported mortality in single-arm cohorts of people with bacterial pleural infection treated with TPA+DNAse at three months[13] and during hospitalisation[15]. A final study comparing concurrent with sequential instillation TPA plus DNAse also reported on mortality[16] and a summary of the results is shown in Table C4a.

Table C4a: Mortality rates of intrapleural TPA and DNAse versus placebo for the treatment of pleural infection

		Mortality rate (no. patients)	
Intervention	**Comparator**	**Intervention**	**Comparator**
TPA	Placebo	13% (6/46)	4% (2/50)
DNAse	Placebo	8% (4/48)	4% (2/50)
TPA plus DNAse	Placebo	8% (4/48)	4% (2/50)
TPA plus DNAse	-	8% (9/107)	-
TPA plus DNAse	-	11% (12/109)	-
TPA plus DNAse (concurrent)*	-	10% (2/20)	-
TPA plus DNAse (sequential)*	-	11% (2/18)	-

* TPA and DNAse administered concurrently or sequentially

TPA – tissue plasminogen activator

No studies reported on mortality following urokinase treatment.

Need for repeat intervention

Streptokinase versus placebo or standard care

The need for repeat drain insertion or further pleural intervention following streptokinase or placebo was reported in one study and demonstrated comparable re-intervention rates with either treatment (2/22 patients in the streptokinase group versus 3/22 in the placebo group.[3]

TPA plus DNAse

A single-arm observational study of patients treated with TPA plus DNAse reported that 62% (67/109) required a second drain to be inserted, most commonly to drain a separate pocket of fluid or to increase drain size (over half of patients had a small initial drain of <12 Fr).[15]

No studies reported on the need for repeat intervention following intrapleural urokinase, single agent TPA or DNAse, or saline irrigation.

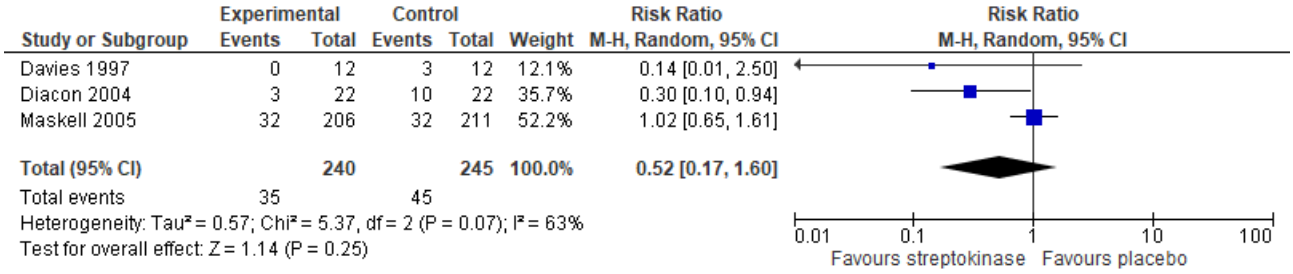
Surgery

Nine studies compared the proportion of patients who required thoracic surgery following intrapleural therapy versus placebo or standard care.[1-5,7,9,13,15]

Streptokinase versus placebo or standard care

Three studies compared the need for thoracic surgery following streptokinase or placebo/standard care and meta-analysis showed no overall difference between the two treatments (96 per 1000 patients (31 to 294) versus and 184 per 1000 respectively) (Figure C4b).[2,3,5]

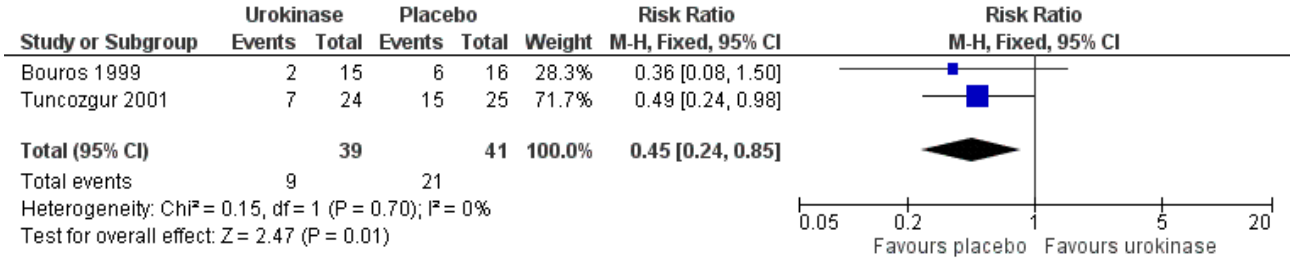
Figure C4b: Need for thoracic surgery (following streptokinase or placebo/standard care)



Urokinase versus placebo

Two studies also compared urokinase versus placebo, with meta-analysis showing a decreased need for thoracic surgery following urokinase treatment (230 per 1000 patients (123 to 435)) compared with 512 per 1000 following placebo (Figure C4c).[1,9]

Figure C4c: Need for thoracic surgery (following urokinase or placebo)



Saline irrigation

One study compared the need for surgery following saline irrigation versus saline flushes and demonstrated a significant reduction in the number of patients referred for thoracic surgery after saline irrigation compared with standard care (2/18 patients (11%) versus 8/17 patients (47%) respectively, $p = 0.03$).[4]

TPA plus DNAse, TPA or DNAse versus placebo

One study compared TPA plus DNAse, TPA or DNAse versus placebo.[7] Two further single arm observational studies reported on the need for surgery following TPA and DNAse.[13,15] A summary of the results is shown in Table C4b and generally showed a reduction in the need for surgery with intrapleural therapy, when compared to placebo/standard care, except when single-agent DNAse was used.

Table C4b: Comparison of treatment with intrapleural TPA and/or DNAse on the need for thoracic surgery in patients with pleural infection

		% patients requiring surgery (no. patients)		
Intervention	**Comparator**	**Intervention**	**Comparator**	***p***
TPA and DNAse[7]	Saline	4% (2/48)	16% (8/51)	0.03
TPA and DNAse[17]	-	8% (8/107)	-	-
TPA and DNAse[15]	-	14% (15/109)	-	-
TPA[7]	Saline	6% (3/48)	16% (8/51)	0.10
DNAse[7]	Saline	39% (18/46)	16% (8/51)	0.01

A further study using reduced dose TPA (5 mg) and standard dose DNAse (5 mg) reported that the majority of patients (57/61, 93.4%) did not require thoracic surgery. The authors concluded that 5mg TPA could be a cheaper, effective dose in the combination TPA/DNAse regimen.[14]

Quality of life

No studies reported on patient quality of life.

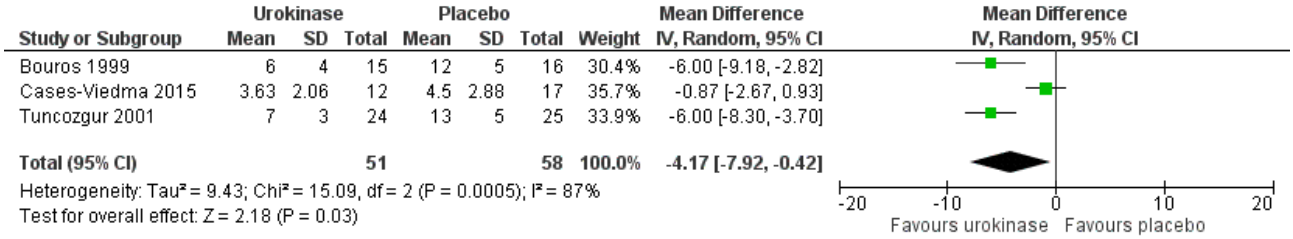
Patient symptoms

Seven studies reported on patient symptoms, which included persistent chest pain, cough, fever and breathlessness and debilitation.[1,4,6,7,9-11]

Urokinase versus placebo

Time to resolution of fever following urokinase or placebo was reported in three studies and meta-analysis showed that patients treated with urokinase achieved defervesence 4.2 days (0.4 to 7.9) faster than those treated with placebo.[1,9,11] One of these studies also reported lower rates of patients with one or more symptom at day three following urokinase treatment (3/15 patients (20%)) compared with placebo (13/16 patients (81%))[1] and a fourth study noted a lower incidence of chest pain on inspiration at 6 months post treatment for tuberculous empyema with urokinase (7/78 patients (9%)) compared with drainage alone (22/78 patients (29%), p <0.01) (Figure C4d).[10]

Figure C4d: Time to resolution of fever (urokinase versus placebo)



TPA plus DNAse, TPA or DNAse versus placebo

Rahman et al reported the number of patients who experienced a persistent fever following TPA plus DNAse, TPA alone, DNAse alone or placebo and a summary of the results is shown in Table C4c.[7]

Table C4c: Comparison of number of patients experiencing fevers following treatment with TPA plus DNAse, TPA, DNAse or saline

		% patients experiencing one or more symptoms (no. patients)	
Intervention	**Comparator**	**Intervention**	**Comparator**
TPA and DNAse	Saline	7% (3/44)	14% (6/42)
TPA	Saline	12% (5/41)	14% (6/42)
DNAse	Saline	20% (9/44)	14% (6/42)

Streptokinase vs standard care

Only one study compared streptokinase versus standard care for the treatment of pleural infection and showed a greater proportion of patients reporting complete resolution of symptoms following streptokinase treatment (49/57 patients (86%)) compared with drainage alone (33/70 patients (47%), p <0.001).[6]

Saline irrigation vs standard care

A single study also showed no difference in median time to resolution of fevers following saline irrigation or standard care (5 days (range 0 to 6) versus 4.5 days, (range 0 to 6) respectively).[4]

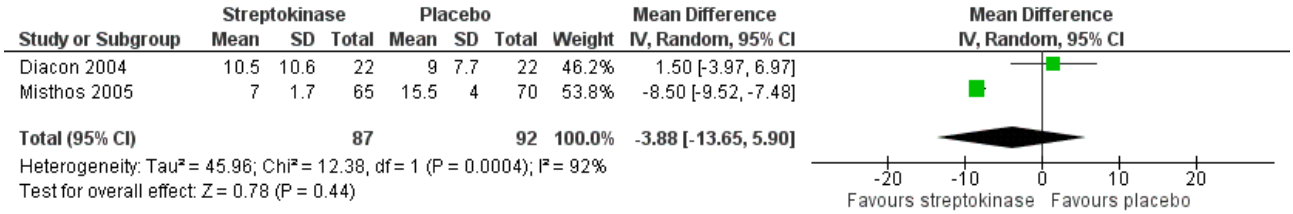
Length of hospital stay

Length of hospital stay was reported in ten studies.[1,3-7,9,11,15,17]

Streptokinase versus placebo or standard care

Three studies compared the length of hospital stay following pleural infection treatment with streptokinase or placebo/standard care[3,5,6], but Maskell et al reported median length of stay (13 days (range 1 to 271) in the streptokinase group and 12 days (range 2 to 152) in the placebo group, no significant difference) and hence was not included in the meta-analysis[5]. Meta-analysis of the remaining two studies showed that the length of stay was 3.9 days (5.9 to 13.7) shorter following streptokinase, but there was inconsistency across the studies (Figure C4e).[3,6]

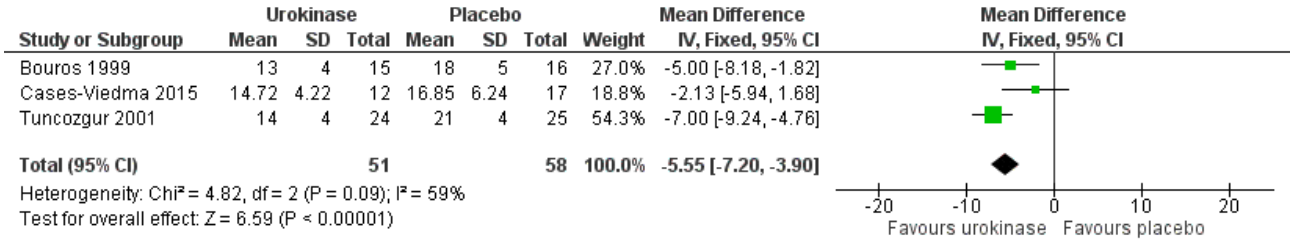
Figure C4e: Length of hospital stay (streptokinase versus placebo/standard care)



Urokinase versus placebo or standard care

Three studies also compared urokinase versus placebo for the treatment of pleural infection (two in bacterial infection[1,9] and one in tuberculous empyema[11]). Meta-analysis showed that length of hospital stay was 5.6 days (3.9 to 7.2) shorter in the urokinase group (Figure C4f).

Figure C4f: Length of hospital stay (urokinase versus placebo)



TPA plus DNAse, TPA or DNAse versus placebo

In one study a shorter length of stay was reported in patients randomised to receive TPA plus DNAse compared with placebo, but not with single agent TPA or DNAse (Table C4d).[7] Median lengths of stay of 10 days (interquartile range (IQR) 6 to 17) and 10.5 days (IQR 6.5 to 19) were reported in two "real-world" observational studies of patients treated with TPA and DNAse.[15,17] Similarly, a study comparing TPA plus DNAse administration strategy (concurrent versus sequential instillation) reported median lengths of hospital stay of 12 days (IQR 5 to 16) and 13 days (IQR 10 to 15) respectively.[16]

Table C4d: Comparison of length of stay following treatment with intrapleural TPA and/or DNAse or placebo

		Length of hospital stay (days, mean ± SD) [no. patients]		
Intervention	**Comparator**	**Intervention**	**Comparator**	***p***
TPA and DNAse	Saline	11.8 ± 9.4 [46]	24.8 ± 56.1 [55]	<0.001
TPA	Saline	16.5 ± 22.8 [52]	24.8 ± 56.1 [55]	0.21
DNAse	Saline	28.2 ± 61.4 [51]	24.8 ± 56.1 [55]	0.73

Finally, Popowicz et al who investigated reduced dose TPA (5 mg) and standard dose DNAse (5 mg) reported a median length of stay of 7 days (IQR 5 to 10).[14]

Saline irrigation versus usual care

Finally, one study reported a median length of stay of 8 days (range 4 to 36) in patients treated with pleural irrigation, compared with 14 days (range 3 to 42) in the standard care group (p = 0.22).[4]

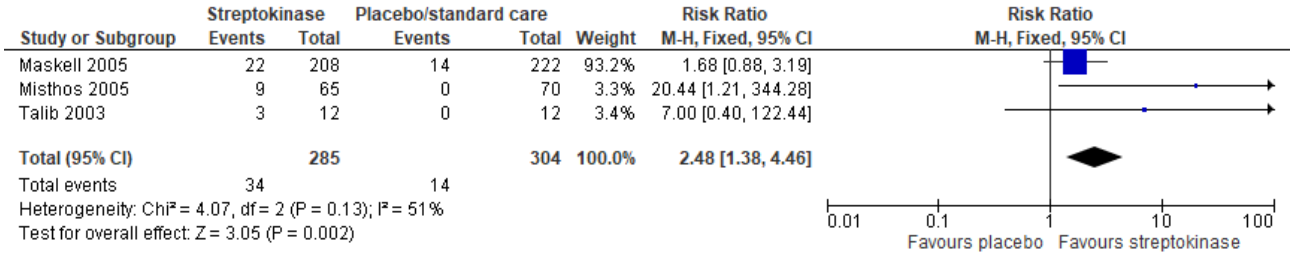
Complications

Post-treatment complications following treatment for pleural infection were reported in seven studies and included chest pain, bleeding, fever and tube blockage/dislodgement.[5-8,12,15,17]

Streptokinase versus placebo or standard care

Three RCTs compared the number of patients who experienced complications following streptokinase or placebo and meta-analysis showed a greater number of complications following streptokinase (114 per 1000 patients (64 to 205)) compared with 46 per 1000 following placebo or standard care (Figure C4g).[5,6,12]

Figure C4g: Complications (streptokinase versus placebo)



TPA plus DNAse, TPA or DNAse versus placebo

Rahman et al reported adverse events following TPA plus DNAse, TPA alone, DNAse alone or placebo[7], whilst Thommi et al reported complications following TPA alone or placebo[8]. In general, more complications were reported following treatment with fibrinolytics (Table C4e).

Table C4e: Comparison of adverse events following pleural infection treatment with TPA plus DNAse, TPA, DNAse or saline

		Adverse events per treatment group (no. patients per group)	
Intervention	**Comparator**	**Intervention**	**Comparator**
TPA and DNAse[7]	Saline	12 (52)	7 (55)
TPA[7]	Saline	7 (52)	7 (55)
DNAse[7]	Saline	10 (51)	7 (55)
TPA[8]	Saline	7 (35)	4 (32)

Saline irrigation versus usual care

Hooper et al reported one complication in each treatment arm in people treated with saline irrigation (18 patients) and standard care (17 patients).[4]

Complications were not recorded for any of the urokinase trials.

Radiological outcomes

Eleven studies reported on radiological outcomes, which included improvement in hemithoracic opacification[1-4,7,12,17], radiographic resolution of effusion[1,2,5,8] and pleural thickening on chest X-ray (CXR) or computed tomography (CT)[5,10,11].

Radiological opacification

Saline irrigation, streptokinase, urokinase, TPA plus DNAse, TPA or DNAse versus placebo or standard care

Six RCTs compared improvement in radiological opacification following intrapleural therapy or placebo/standard care.[1-4,7,12] The studies used different methods to measure changes in radiological opacification between baseline and post-treatment, with the data summarised in Table C4f.

Table C4f: Radiological opacification improvement following intrapleural therapy or placebo/standard care

		Radiological opacification changes (no. patients)		
Study	**Intrapleural therapy**	**Intrapleural therapy**	**Placebo/standard care**	***p***
Bouros 1999[1]	Urokinase	2.7 ± 0.6* (15)	1.2 ± 0.9* (16)	<0.001
Davies 1997[2]	Streptokinase	6.0 ± 2.7† (12)	3.4 ± 2.7† (12)	<0.05
Diacon 2004[3]	Streptokinase	17.5 ± 11.8§ (22)	25.3 ± 25.2§ (22)	NS
Diacon 2004[3]	Streptokinase	24.5 ± 15.0# (22)	22.8 ± 19.7# (22)	NS
Hooper 2015[4]	Saline irrigation	32.3 [19.6-43.7]¶ (18)	15.3, [-5.5-28]¶ (16)	0.03
Rahman 2011[7]	TPA/DNAse	29.5 ± 23.3‡ (52)	17.2 ± 19.6‡ (55)	0.005
Rahman 2011[7]	TPA	17.2 ± 24.3‡ (52)	17.2 ± 19.6‡ (55)	NS
Rahman 2011[7]	DNAse	14.7 ± 16.3‡ (51)	17.2 ± 19.6‡ (55)	NS
Talib 2003[12]	Streptokinase	0.17 (12)	2.67 (12)	<0.001

* Chest radiographic improvement score (0-3), mean ± SD

† Reduction in the largest linear dimension (cm), mean ± SD

§ Lateral pleural shadowing on chest X-ray (CXR) at discharge (mm), mean ± SD

Percentage of hemithorax opacified at discharge, mean ± SD

¶ Percentage change from baseline in hemithorax area occupied by effusion, median [IQR]

‡ Percentage change from baseline in hemithorax area occupied by effusion, mean ± SD

IQR – interquartile range; NS – not significant; SD – standard deviation; TPA – tissue plasminogen activator

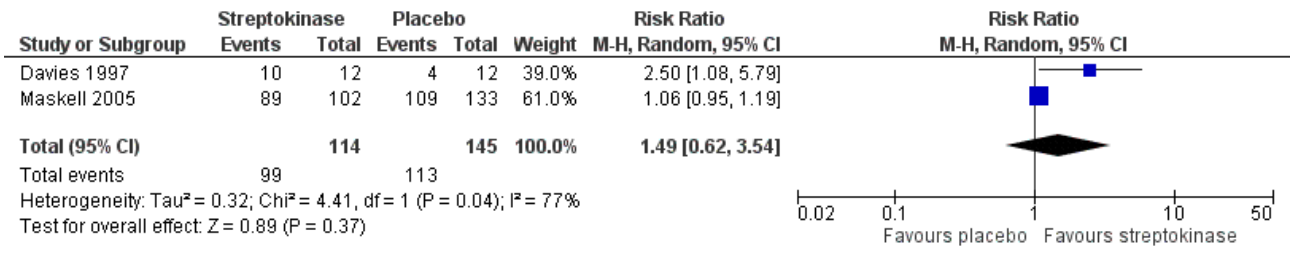
The observational study using reduced dose TPA (5 mg) and standard dose DNAse (5 mg) also reported a reduction in median radiological opacity from 42% [IQR, 22 to 58] to 16% [IQR, 8 to 31] after at least 72 hours (p = 0.001). This was further reduced to 5% [IQR, 0.5 to 14.4] at Day 30.[14]

Radiographic resolution of effusion

Streptokinase versus placebo

Two studies compared radiographic resolution of effusion (defined as >75% improvement in pleural effusion size from baseline) following streptokinase or placebo and meta-analysis confirmed no significant difference in resolution rates between the two treatments (1000 per 1000 patients (483 to 1000) and 779 per 1000 respectively) (Figure C4h).[2,5]

Figure C4h: Radiographic resolution of effusion (streptokinase versus placebo)



Urokinase versus placebo

One study reported on radiographic resolution of effusion after administration of urokinase or placebo to people with non-resolving empyema. 87% of participants in the urokinase group (13/15) demonstrated effusion resolution compared with 25% in the placebo group (4/16) (p <0.001).[1]

TPA versus placebo and TPA plus DNAse

One study also compared TPA with placebo in infected effusions that had failed to respond to initial drainage. 91% (32/35 patients) effusions resolved following TPA compared with 12% after placebo (4/33 patients).[8]

A second observational study comparing concurrent versus sequential instillation of TPA and DNAse in 38 patients with pleural infection also noted improvements in pleural effusion size on CXR and CT reporting median reductions of 12.2% [2, 27] and 13.8% [1, 25] respectively with CXR and median effusion volume reductions of 46% [IQR, 38 to 79] and 39.5% [IQR, 24 to 68] respectively with CT.[16]

Pleural thickening

Finally, pleural thickening following intrapleural fibrinolytic therapy or placebo/standard care was reported in three RCTs.[5,10,11] Outcomes were reported as continuous data (pleural thickness measured on CXR or CT) in two studies[5,11] and dichotomous data (presence of ≥10 mm pleural thickening) in one[10].

Streptokinase versus placebo

One study compared streptokinase versus placebo for the treatment of pleural infection and reported mean residual pleural thickening of 12 ± 14 mm and 15 ± 19 mm for each arm respectively, three months after treatment (mean ± SD, p = 0.20).[5]

Urokinase versus placebo or standard care

Mean residual pleural thickening at six months post-treatment was reported in a study comparing urokinase or simple drainage for the treatment of tuberculous pleural infection. Urokinase patients had mean residual pleural thickening of 1.45 ± 0.89 mm compared with 7.47 ± 10.95 mm in controls (mean ± SD, p <0.05), although control patients had more initial pleural thickening than the urokinase group (14.78 versus 8.09 mm respectively) and follow-up results were not adjusted for baseline values.[11] A second study compared urokinase with simple drainage in the treatment of tuberculous empyema and reported the presence of pleural thickening ≥10mm at 6 months post-treatment. In the control group, 7/77 (9.1%) patients had ≥10 mm residual pleural thickening, compared with 0/78 people treated with urokinase (p <0.05).[10]

Evidence statements

Streptokinase appears to have no effect on mortality rate (**Very low**), length of hospital stay (**Very low**), the need for thoracic surgery (**Very low**) or radiographic resolution of effusion (**Very low**), but it may increase post-treatment complications (**Very low**) when compared with chest drainage alone, or placebo for the treatment of pleural infection in adults

Urokinase appears to reduce the need for thoracic surgery (**Low**), hasten the time to resolution of fever (**Very low**) and reduce the length of hospital stay (**Low**) compared with placebo or standard care in adults with pleural infection

Based on very limited evidence, TPA plus DNAse may reduce the length of hospital stay (**Ungraded**), reduce the likelihood of persistent fevers (**Ungraded**), and increase improvements in chest X-ray opacification (**Ungraded**), when compared with placebo or standard care in the treatment of adults with pleural infection, but TPA plus DNAse may increase the risk of post-treatment complications (serious and non-serious) (**Ungraded**)

Single agent TPA or DNAse do not appear to improve clinical outcomes when compared with placebo or standard care for treating pleural infection in adults (**Ungraded**)

Saline irrigation (250 ml saline TDS) may reduce the need for thoracic surgery **(Ungraded)** but appears to have no impact on mortality (**Ungraded**), length of hospital stay (**Ungraded**) or time to resolution of fever (**Ungraded**) when compared with standard care (30 ml saline TDS)

Recommendations

- Combination tissue plasminogen activator (TPA) and DNASe should be considered for the early treatment of pleural infection in adults, following discussion of the risks and benefits with the patient (**Conditional** – by consensus)
- Saline irrigation can be considered for the treatment of pleural infection in adults when intrapleural fibrinolytic therapy or surgery is not suitable (**Conditional** – by consensus)
- Single agent tissue plasminogen activator (TPA) or DNASe should not be considered for treatment of pleural infection in adults (**Conditional** – by consensus)
- Streptokinase should not be considered for treatment of pleural infection in adults (**Conditional**)

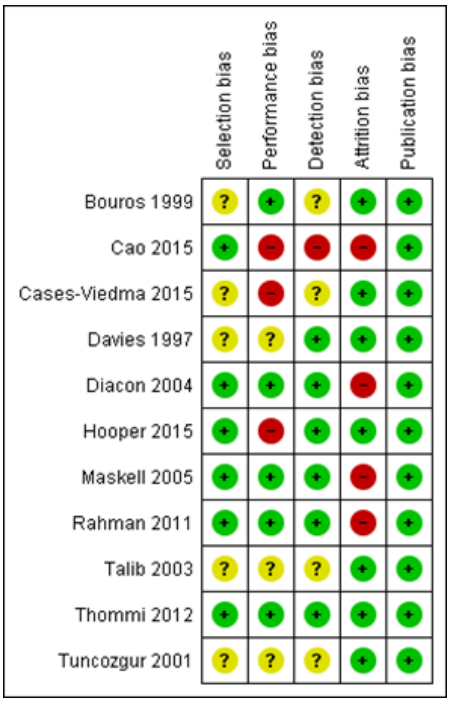
Good Practice Points

- ✓ Patient consent should be taken when using TPA and DNase as there is a potential risk of bleeding
- ✓ When administering TPA plus DNase the regime of should be 10 mg TPA twice daily (10 mg bd) + 5 mg bd DNase for 3 days, based on RCT data. Based on retrospective case series data, TPA twice daily (5 mg bd) + 5 mg bd DNase for 3 days may be as effective, and can be used if considered necessary
- ✓ Reduced doses of TPA may be considered in those with a potentially higher bleeding risk (for example those on therapeutic anticoagulation which cannot be temporarily ceased)

Research Recommendations

- Further research is needed into the role of combination tissue plasminogen activator (TPA) and DNASe and saline irrigation for treating pleural infection in adults, specifically relating to reduced dose regimens and concurrent administration.
- Further research is needed to determine the role of intra-pleural irrigation compared with medical or surgical thoracoscopy in the management of CPPE and empyema

Risk of bias summary



GRADE analyses

For adults with pleural infection, does intrapleural therapy improve outcomes compared to other treatment options (e.g. drainage alone or surgical intervention)?

Population: Adults aged 18+ with pleural infection

Intervention: Streptokinase

Comparator: Chest drainage alone or placebo (standard care)

Outcome	Number of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects		Quality of the Evidence (GRADE)
			Standard care	Streptokinase	
Mortality	598 (3 studies)	RR 1.08 (0.70 to 1.67)	**112 per 1000**	**121 per 1000** (78 to 187)	⨁◯◯◯ **VERY LOW** [a,b,c]
Surgery	485 (3 studies)	RR 0.52 (0.17 to 1.60)	**184 per 1000**	**96 per 1000** (31 to 294)	⨁◯◯◯ **VERY LOW** [a,b,c]
Complications	589 (3 studies)	RR 2.48 (1.38 to 4.46)	**46 per 1000**	**114 per 1000** (64 to 205)	⨁◯◯◯ **VERY LOW** [a,b,c]
Resolution of effusion	259 (2 studies)	RR 1.49 (0.62 to 3.54)	**779 per 1000**	**1000 per 1000** (483 to 1000)	⨁◯◯◯ **VERY LOW** [a,b,c]

CI: Confidence interval

Explanations

a. High risk of bias across the studies
b. Some inconsistency across the studies
c. Serious imprecision, CIs cross both MIDs

For adults with pleural infection, does intrapleural therapy improve outcomes compared to other treatment options (e.g. drainage alone or surgical intervention)?

Population: Adults aged 18+ with pleural infection

Intervention: Urokinase

Comparator: Chest drainage alone or placebo (standard care)

Outcome	Number of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects		Quality of the Evidence (GRADE)
			Standard care	Urokinase	
Surgery	80 (2 studies)	RR 0.45 (0.24 to 0.85)	**512 per 1000**	**230 per 1000** (123 to 435)	⨁⨁◯◯ **LOW** [a,b]

CI: Confidence interval

Explanations

a. High risk of bias across the studies
b. Some imprecision, CIs cross one MID

For adults with pleural infection, does intrapleural therapy improve outcomes compared to other treatment options (e.g. drainage alone or surgical intervention)?

Population: Adults aged 18+ with pleural infection

Intervention: Streptokinase

Comparator: Chest drainage alone or placebo

Outcome	Number of participants (studies)	Estimate of effect	Quality of the Evidence (GRADE)
Length of hospital stay	179 (2 studies)	3.88 days lower (13.65 to 5.90 higher) in the intervention group	⨁◯◯◯ **VERY LOW** [a,b]

Explanations

a. High risk of bias across the studies
b. Serious inconsistency across the studies

For adults with pleural infection, does intrapleural therapy improve outcomes compared to other treatment options (e.g. drainage alone or surgical intervention)?

Population: Adults aged 18+ with pleural infection

Intervention: Urokinase

Comparator: Chest drainage alone or placebo

Outcome	Number of participants (studies)	Estimate of effect	Quality of the Evidence (GRADE)
Length of hospital stay	109 (3 studies)	5.55 days lower (7.20 to 3.90 lower) in the intervention group	⨁⨁◯◯ **LOW** [a]
Patient symptoms	109 (3 studies)	Mean fever 4.17 lower (7.92 to 0.42 lower) in the intervention group	⨁◯◯◯ **VERY LOW** [a,b]

Explanations

a. High risk of bias across the studies
b. Some inconsistency across the studies

Recommendation Table

Question Details

POPULATION:	Adults aged 18+ with pleural infection
INTERVENTION:	Streptokinase
COMPARISON:	Chest drainage alone or placebo
OUTCOMES:	Mortality, need for repeat intervention, surgery, quality of life, patients' symptoms, length of hospital stay, complications, radiological outcomes

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	**Probably yes**	Yes		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
BALANCE OF EFFECTS	Favours the comparison	Probably favours the comparison	**Does not favour the intervention or the comparison**	Probably favours the intervention	Favours the intervention	Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	**Conditional recommendation against the intervention**	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
☐	☒	☐	☐	☐

CONCLUSIONS

Recommendation

Streptokinase should not be considered for treatment of pleural infection in adults

Justification

Streptokinase appears to have no effect on mortality rate (Very low), length of hospital stay (Very low), the need for thoracic surgery (Very low) or radiographic resolution of effusion (Very low), but it may increase post-treatment complications (Very low) when compared with chest drainage alone, or placebo for the treatment of pleural infection in adults

Subgroup considerations

Streptokinase was a subgroup analysis

Research priorities

Further research into the use of streptokinase should not be considered

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Question Protocol

Field	Content
Review Question	For adults with pleural infection, does intrapleural therapy, in comparison to other options (drainage or surgical drainage), improve outcomes?
Type of review question	Intervention review
Objective of the review	To determine whether intrapleural agents (fibrinolytics, irrigation or antibiotics) alter the outcome in patients with known pleural infection.
Eligibility criteria – population / disease / condition / issue / domain	Adults (18+) with pleural infection
Eligibility criteria – intervention(s)	Intrapleural therapy (fibrinolytics, irrigation or antibiotics)
Eligibility criteria – comparators(s)	Chest tube drainage Surgery (VATS / thoracotomy)
Outcomes and prioritisation	Mortality Need for repeat intervention Surgery Quality of life Patient symptoms Length of hospital stay Complications Radiological outcome
Eligibility criteria – study design	RCTs Prospective comparative studies Case series of >100 patients
Other inclusion /exclusion criteria	Non-English language excluded unless full English translation Conference abstracts, Cochrane reviews, systematic reviews, reviews Cochrane reviews and systematic reviews can be referenced in the text, but **DO NOT** use in a meta-analysis
Proposed sensitivity / subgroup analysis, or meta-regression	Intrapleural therapy – fibrinolytics alone Intrapleural therapy – fibrinolytics + DNase Intrapleural therapy – pleural irrigation

	Intrapleural therapy – antibiotics
Selection process – duplicate screening / selection / analysis	Agreement should be reached between Guideline members who are working on the question. If no agreement can be reached, a decision should be made by the Guideline co-chairs. If there is still no decision, the matter should be brought to the Guideline group and a decision will be made by consensus
Data management (software)	RevMan5 — Pairwise meta-analyses Evidence review/considered judgement. Storing Guideline text, tables, figures, etc. Gradeprofiler — Quality of evidence assessment Gradepro — Recommendations
Information sources – databases and dates	MEDLINE, Embase, PubMED, Central Register of Controlled Trials and Cochrane Database of Systematic Reviews 1966 - present
Methods for assessing bias at outcome / study level	RevMan5 intervention review template and NICE risk of bias checklist (follow instructions in '*BTS Guideline Process Handbook – Intervention Review'*)
Methods for quantitative analysis – combining studies and exploring (in)consistency	If 3 or more relevant studies: RevMan5 for meta-analysis, heterogeneity testing and forest plots (follow instructions in '*BTS Guideline Process Handbook – Intervention Review'*)
Meta-bias assessment – publication bias, selective reporting bias	GRADEprofiler — Intervention review quality of evidence assessment for each outcome (follow instructions in '*BTS Guideline Process Handbook – Intervention Review'*)
Rationale / context – what is known	Patients with pleural infection have a poor outcome, and some require surgery to resolve their illness. Fibrinolytics are used in some patients. What is the evidence to support their use?