Intra pleural agents for pleural infection

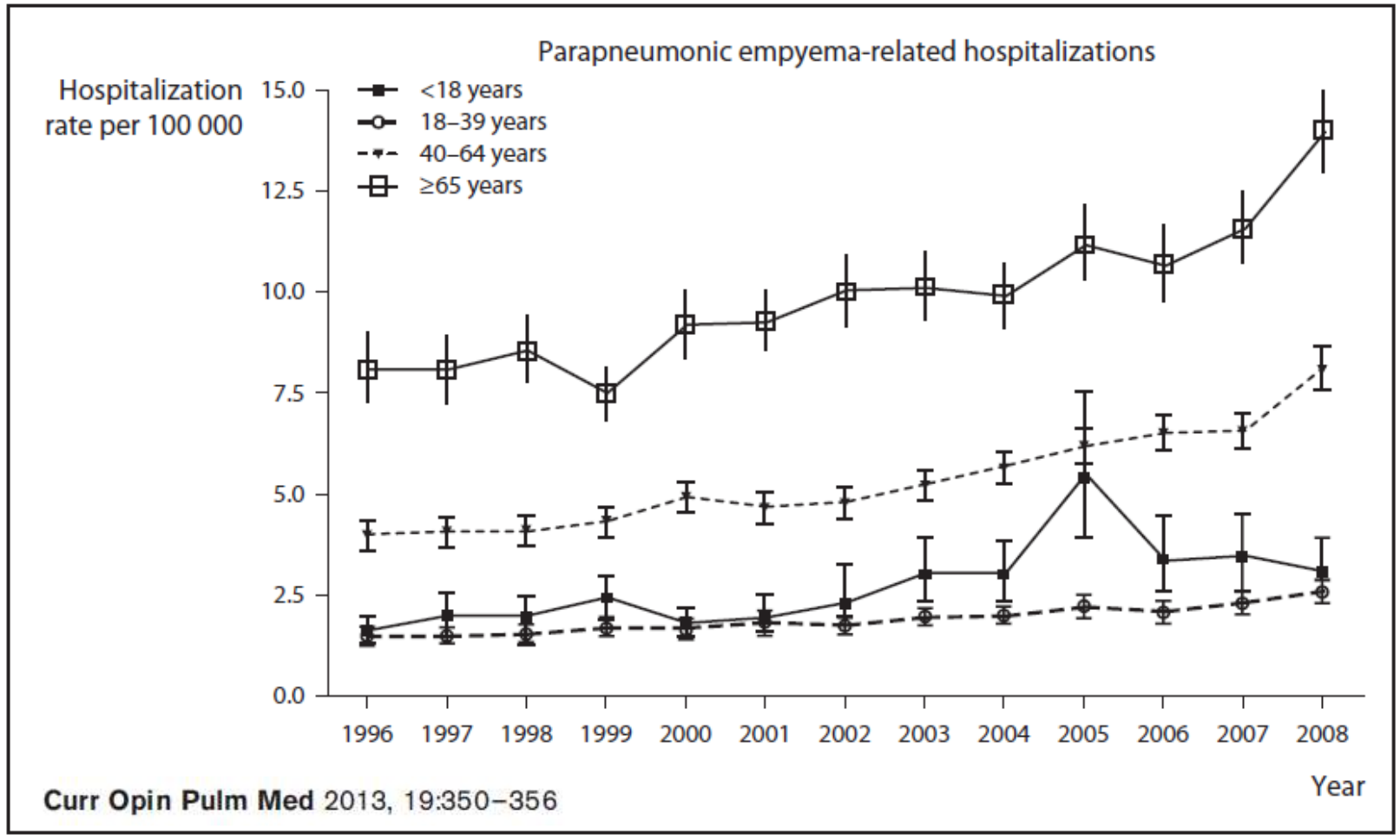
D.M. Seminar

Dr.M.V.Nagarjuna

Epidemiology of Pleural infection

CURRENT OPINION

The increasing incidence of empyema



Curr Opin Pulm Med 2013, 19:350–356

Intra pleural agents for pleural infections.

1. Intra pleural Fibrinolytics
2. Intra pleural antimicrobial agents

Fibrinolytic agents

	Fibrin Selectivity	Systemic lytic state	Needs Plasminogen for activation	Allergic reactions	Half life (plasma)	Intrapleural administration
Streptokinase	No	Yes	Yes (Indirect)	Yes	30 minutes	Yes
Antistreplase	No	Yes	No (Direct)	Yes	88-112 minutes	No
Urokinase	No	Yes	No (Direct)	No	20 minutes	Yes
Alteplase	Yes (+)	No	No (Direct)	No	3-5 minutes	Yes
Tenecteplase	Yes(++)	No	No (Direct)	No	20-24 minutes	No
Reteplase	Yes(+)	No	No (Direct)	No	13-16 minutes	No

Do we have evidence to support the use of intrapleural fibrinolytics/DNAase ??

1. Streptokinase
2. Urokinase
3. Alteplase (rtPA)

THE ACTION OF STREPTOCOCCAL DESOXYRIBOSE NUCLEASE (STREPTODORNASE),[1] *IN VITRO* AND ON PURULENT PLEURAL EXUDATIONS OF PATIENTS[2]

By SOL SHERRY, ALAN JOHNSON, and WILLIAM S. TILLETT
(*From the Department of Medicine of the New York University College of Medicine and the Third Medical Division of Bellevue Hospital, New York City*)

(Received for publication April 11, 1949)

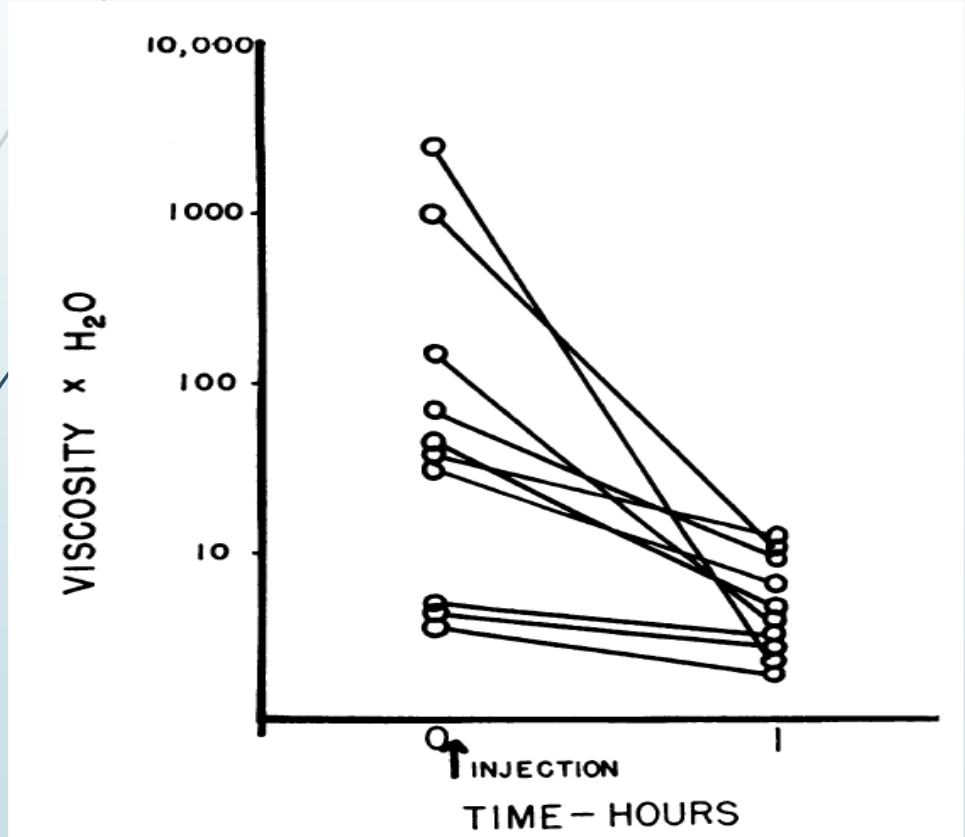


FIG. 7. THE EFFECT OF STREPTODORNASE, INTRAPLEURALLY INJECTED, ON THE VISCOSITY OF THE PLEURAL EXUDATES IN NINE CASES OF EMPYEMA

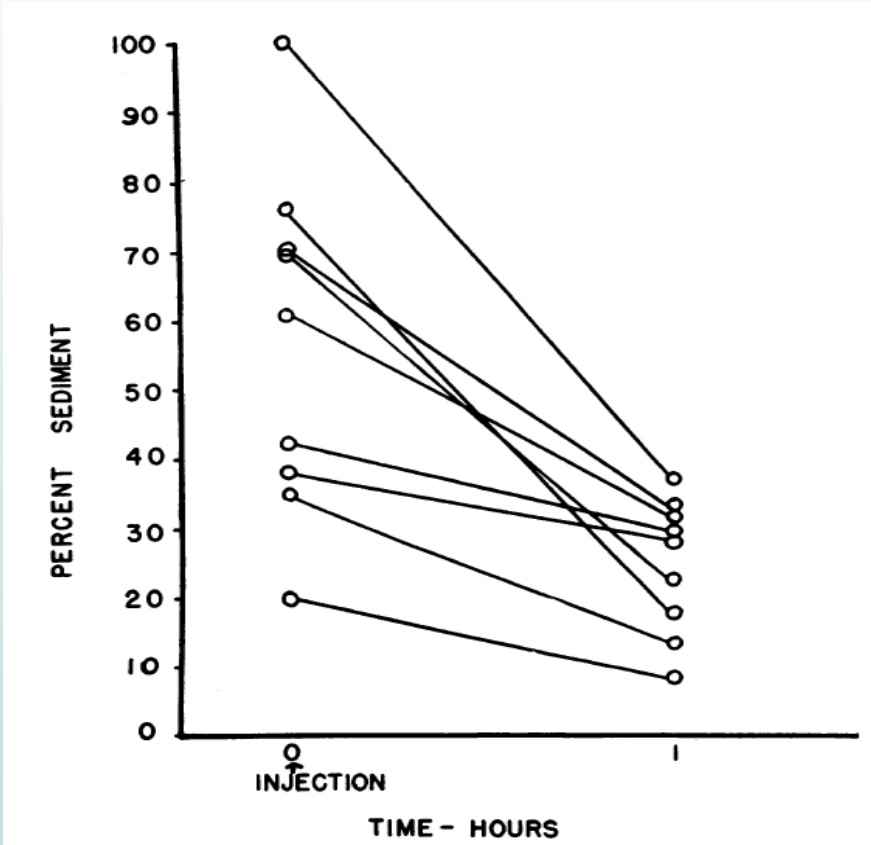


FIG. 8. THE EFFECT OF STREPTODORNASE, INTRAPLEURALLY INJECTED, ON THE PERCENTAGE SEDIMENT OF PLEURAL EXUDATES IN NINE CASES OF EMPYEMA

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

- In 1951, they published the first case series of 25 patients treated with Streptokinase-streptodornase combination (extracts from streptococci).
- All had Loculated empyema.

- Results :
  - 21 of the 25 patients improved clinically with resolution of the effusion.
  - Only 4 patients needed closed thoracotomy

. J Thorac Surg 1951; 21: 275–97.

Intrapleural Streptokinase - Observational studies

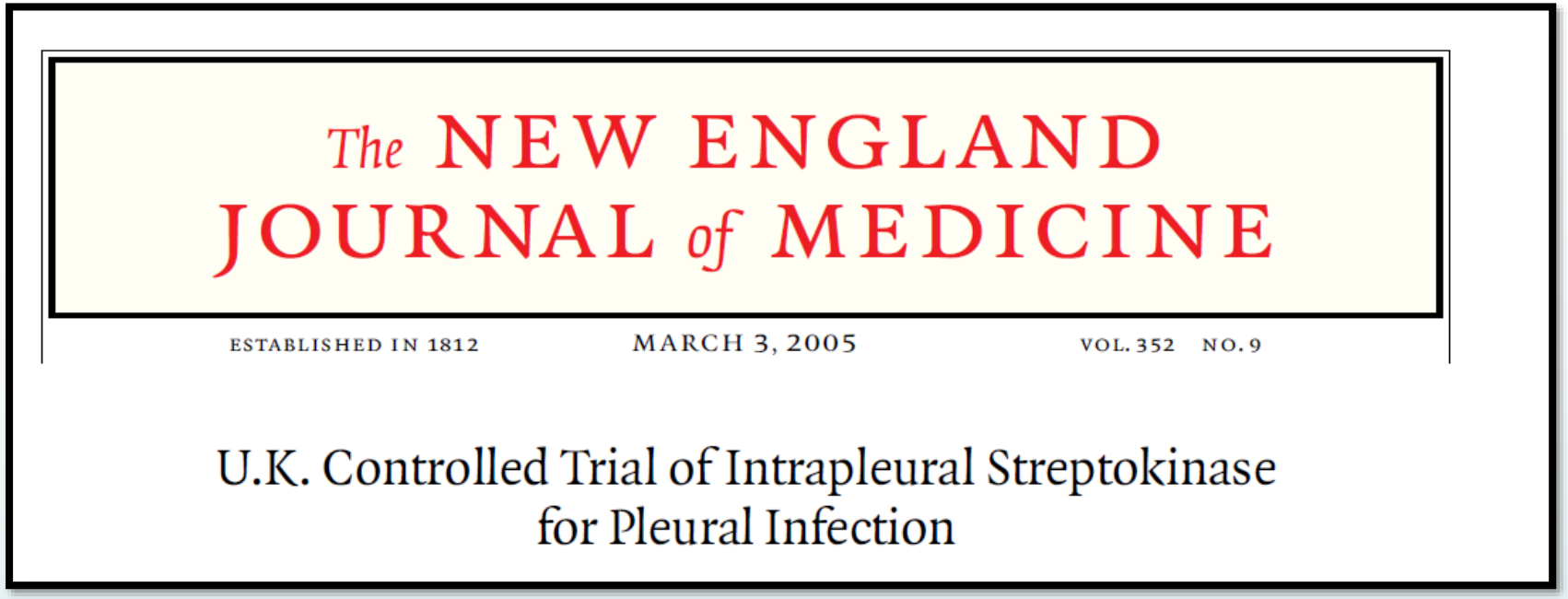
Author	Year	No.of patients	Dose used	Outcome
Bergh et al	1977	38	NA	Lung re expansion in 79% patients
Fraedrich et al	1982	27	5,00,000 u/day x 5 days	Cure in 44 % patients
Mitchell et al	1989	9	NA	Cure in 44% patients
Willsie Ediger	1990	3	NA	Cure in all
Aye et al	1991	14	NA	Increased output in 93%
Henke et al	1992	12	2,50,000 U once	Radiologic improvement in 75%.Clinical in 67%
Bouros et al	1994	20	2,50,000 U OD(3-10days)	Radiologic improvement in 85%
Taylor et al	1994	11	2,50,000 U OD(2-6 days)	Lung re expansion in 73%
Laisaar et al	1996	23	2,50,000 U OD x 4 days	Clinical response in 72 %
Temes et al	1996	26	3,00,000 U OD x 6 days	Clinical response in 69%
Jerjes et al	1996	30	2,50,000 U OD(2-10days)	92% clinical improvement
Roupie et al	1996	16	2,50,000 U OD(1-2 days)	Clinical improvement in 87.5%

Controlled trials - Streptokinase

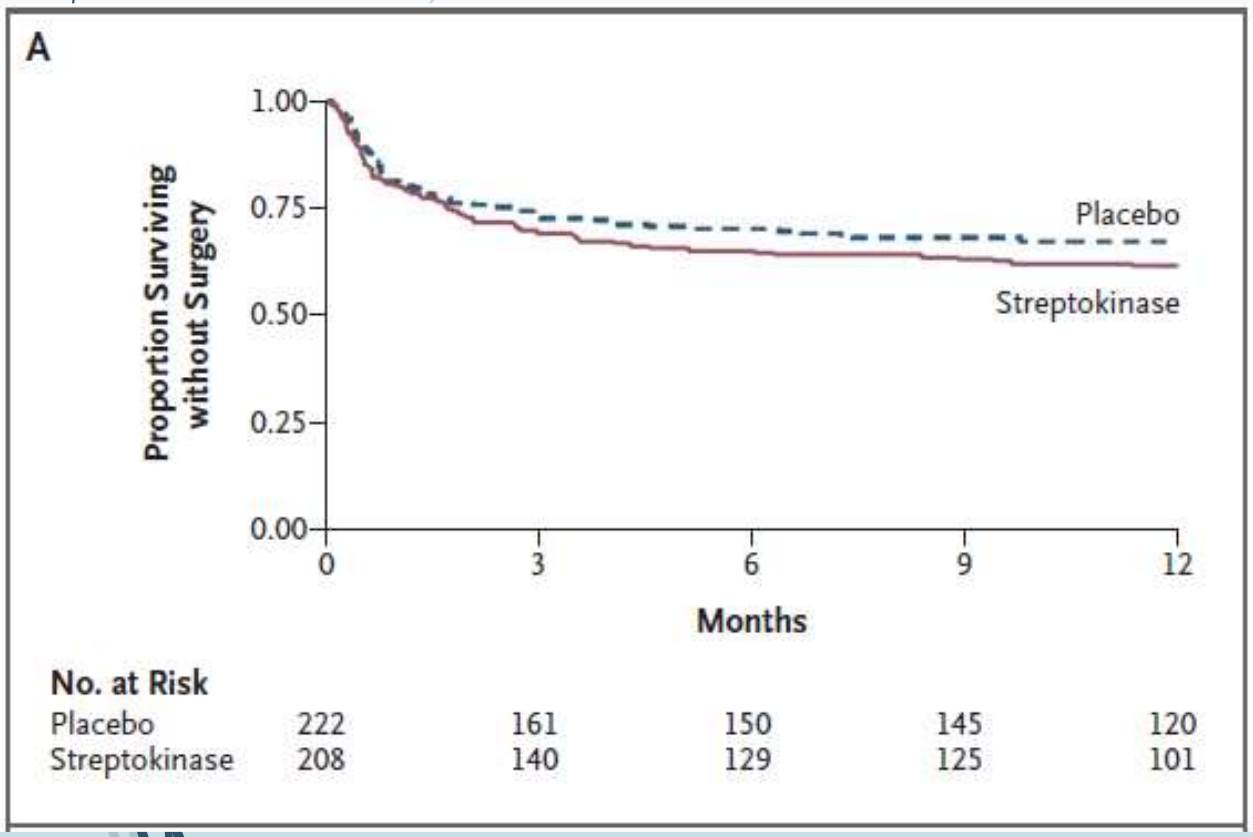
Author	Disease	Type of trial	Drug	Number	Dose used	ICTD size	Results
Chin et al (Chest 1997)	E/CPE	Controlled trial (Non randomized)	STK vs Placebo	52	2,50,000 U OD (1-10 days)	24 Fr	Drain output increased but no change in clinical outcomes
Davies et al (Thorax 1997)	E/CPE	RCT	STK vs Placebo	24	2,50,000 U OD (1-5 days	14 Fr	Drain output, radiologic clearance and surgical referral rates better with STK
Diacon et al (AJRCCM 2004)	E/CPE	RCT	STK vs Placebo	44	2,50,000 U OD (1-7 days)	24-28Fr	Better clinical success and fewer patients referred to surgery in the STK arm
Misthos et al (2005)	E/CPE	RCT	STK vs Placebo	127	2,50,000 U OD x 3days	28-32 Fr	Better clinical success and lesser surgical referrals in the STK arm

Streptokinase vs Surgery

Author	DIse ase	Type of trial	Drug	Nu mb er	Dose used	ICTD size	Results
Wait etal (CHEST 1997)	E/CP E	RCT	STK vs VATS	20	2,50,000 U OD x 3 days	36 Fr	Treatment success better in the VATS group. Shorter hospital stay
Lim et al (ERJ 1999)	E/CP E	Controlle d trial	Drain alone vs STK vs STK+Early Op	82	2,50,000 U OD	7-24Fr	Lesser mortality and lesser hospital stay in th early surgery arm



- MIST 1 trial (Multicentric Intra pleural Sepsis trial)
- 454 patients randomized to receive either streptokinase (2,50,000U) or placebo BD for 3 days.
- Inclusion criteria : Empyema, Positive pleural fluid gram stain or culture, Pleural fluid pH <7.2
- Chest tube size used – 12 French
- Median duration of symptoms before randomization– 14 days
- Empyema – 83%


A
Proportion Surviving without Surgery
1.00
0.75
0.50
0.25
0.00
0
3
6
9
12
Months
Placebo
Streptokinase
No. at Risk
Placebo 222 161 150 145 120
Streptokinase 208 140 129 125 101

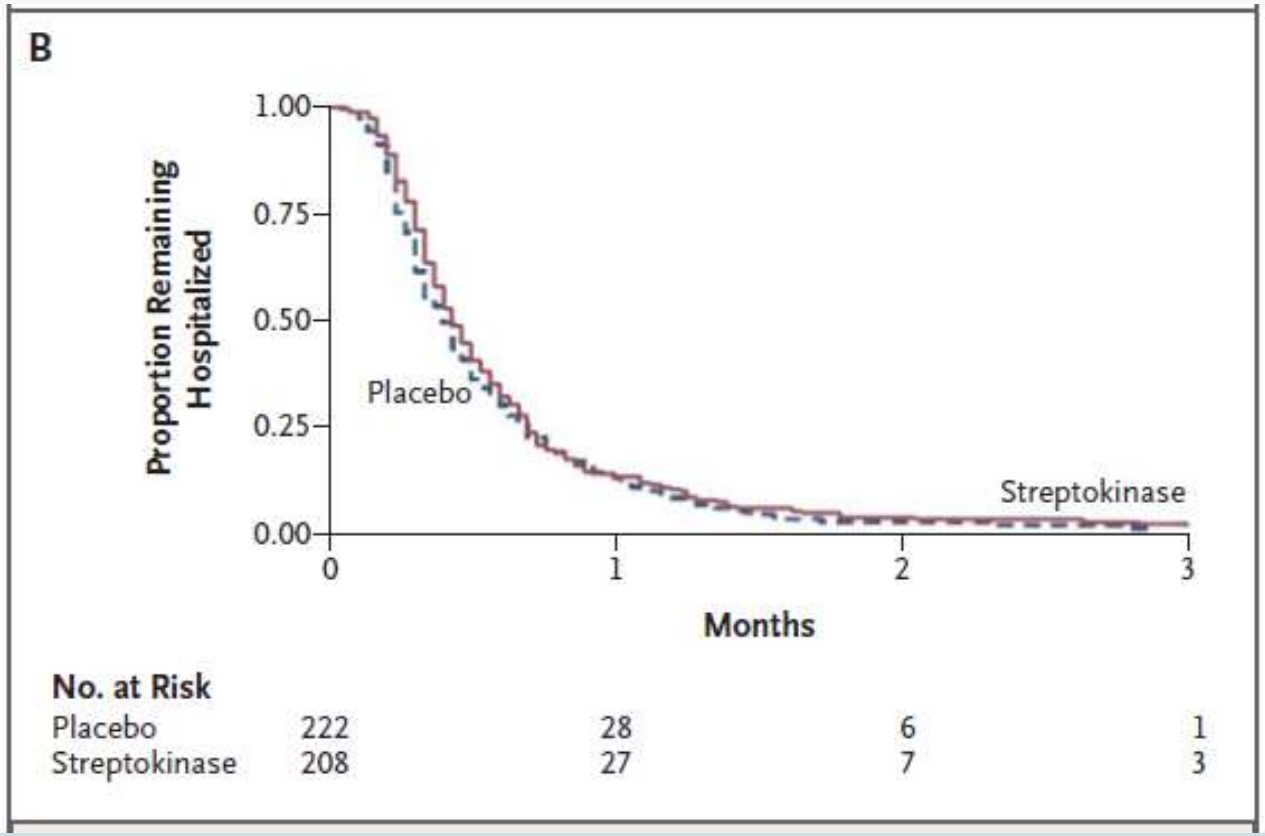

B
Proportion Remaining Hospitalized
1.00
0.75
0.50
0.25
0.00
0
1
2
3
Months
Placebo
Streptokinase
No. at Risk
Placebo 222 28 6 1
Streptokinase 208 27 7 3

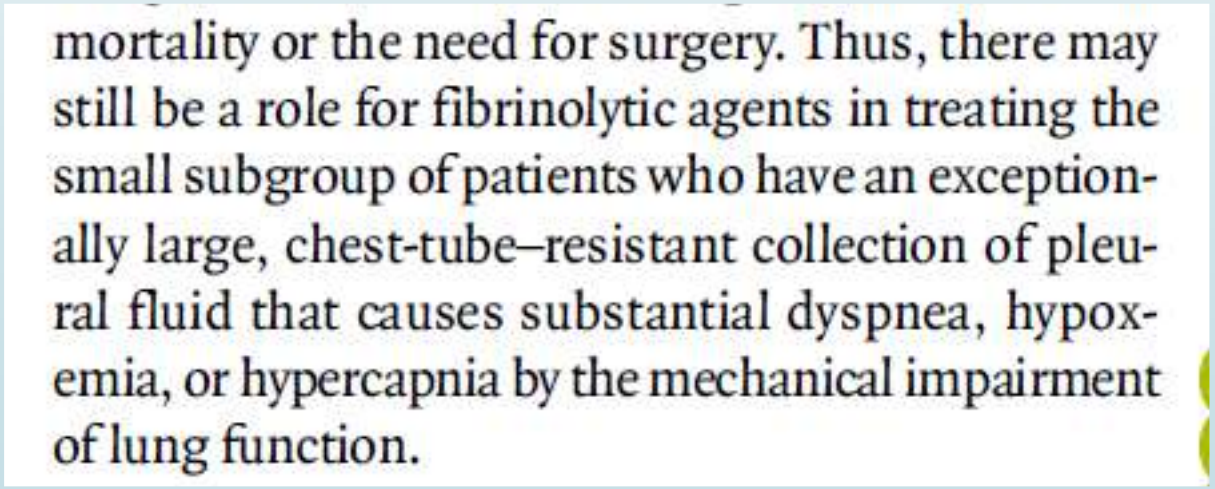
Table 3. Outcomes on Chest Radiography at Three Months.*

Outcome	Streptokinase	Placebo	Difference between Groups (95% CI)	P Value
Residual pleural thickening at lateral chest wall — mm†	12±14	15±19	3 (−1 to 7)	0.20
Vertical height of thorax on affected side — mm†	209±30	221±33	12 (4 to 19)	0.003
Improvement in the area of pleural-fluid opacity in patients not requiring surgery — no. (%)‡				0.30§
No. of patients	102	133		
0–25%	7 (7)	12 (9)		
26–75%	6 (6)	12 (9)		
76–90%	12 (12)	24 (18)		
>90%	77 (75)	85 (64)		

Postulated reasons

1. Streptokinase only breaks the fibrin strands but does not reduce the viscosity of the pus thereby hindering drainage through the small bore chest tube.

2. Streptokinase needs plasminogen for its initial activation. As the amount of plasminogen in the pleural fluid is low, the actual amount available for conversion to plasmin is decreased.


mortality or the need for surgery. Thus, there may still be a role for fibrinolytic agents in treating the small subgroup of patients who have an exceptionally large, chest-tube–resistant collection of pleural fluid that causes substantial dyspnea, hypoxemia, or hypercapnia by the mechanical impairment of lung function.

Draw backs of this trial

1. Included patients without loculated collections also
2. Duration of symptoms prior to randomization is 14 days
3. Use of small bore chest tubes (12 fr) in patients even with frank empyema
4. Only CXR used for assessing response.
5. Treatment protocols (antibiotics) were not uniform.

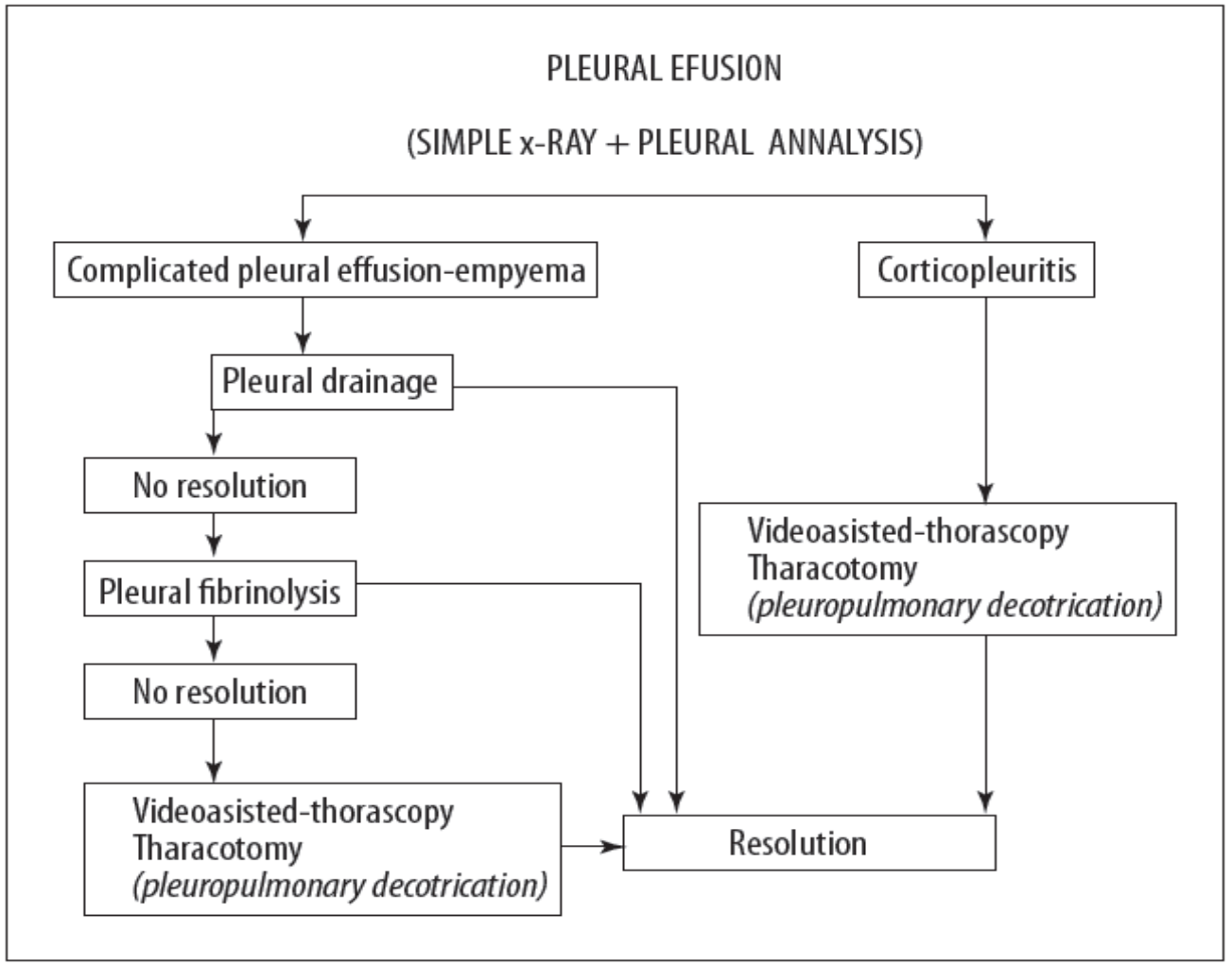
Intra pleural Urokinase

- Observational Trials
- RCTs

Intrapleural Urokinase- Observational studies

Author	Year	No. of patients	Dose used	Outcome
Moulton et al	1989	13	80,000 -1,5000 U OD	92% success rate
Lee et al	1991	10	1,00,000 U OD (1-8 days)	90% success rate
Pollak et al	1994	9	NA	89% success rate
Robinson et al	1994	13	1,00,000 U OD x 7 days	77% success rate
Bouros et al	1996	20	50,000 U OD x 5 days	65% success rate
Suarez et al	2012	210	1,00,000 U OD x 3 days	75% success rate

Treatment of complicated parapneumonic pleural effusion and pleural parapneumonic empyema



Med Sci Monit, 2012; 18(7): CR443-449

Intrapleural Urokinase- RCTs

Author	Disease	Type of trial	Drug	Number	Dose used	ICTD size	Results
Bouros et al (1999)	E/CPE	RCT	Urokinase vs placebo	31	1,00,000 U OD x 3 days	28-32 Fr	Lesser surgical referral. No effect on mortality
Tuncozgur et al (2001)	E	RCT	Urokinase vs Placebo	49	1,00,000 U OD x 3 days	24-36 Fr	Lesser surgical referral. No effect on mortality

Intra pleural DNAase

- Case reports

Intra pleural DNAase

- Invitro studies demonstrated the efficacy of DNA ase in liquefying empyema pus.

Chest 2000;117:1728-33.

Lung 2000;178:13-8.

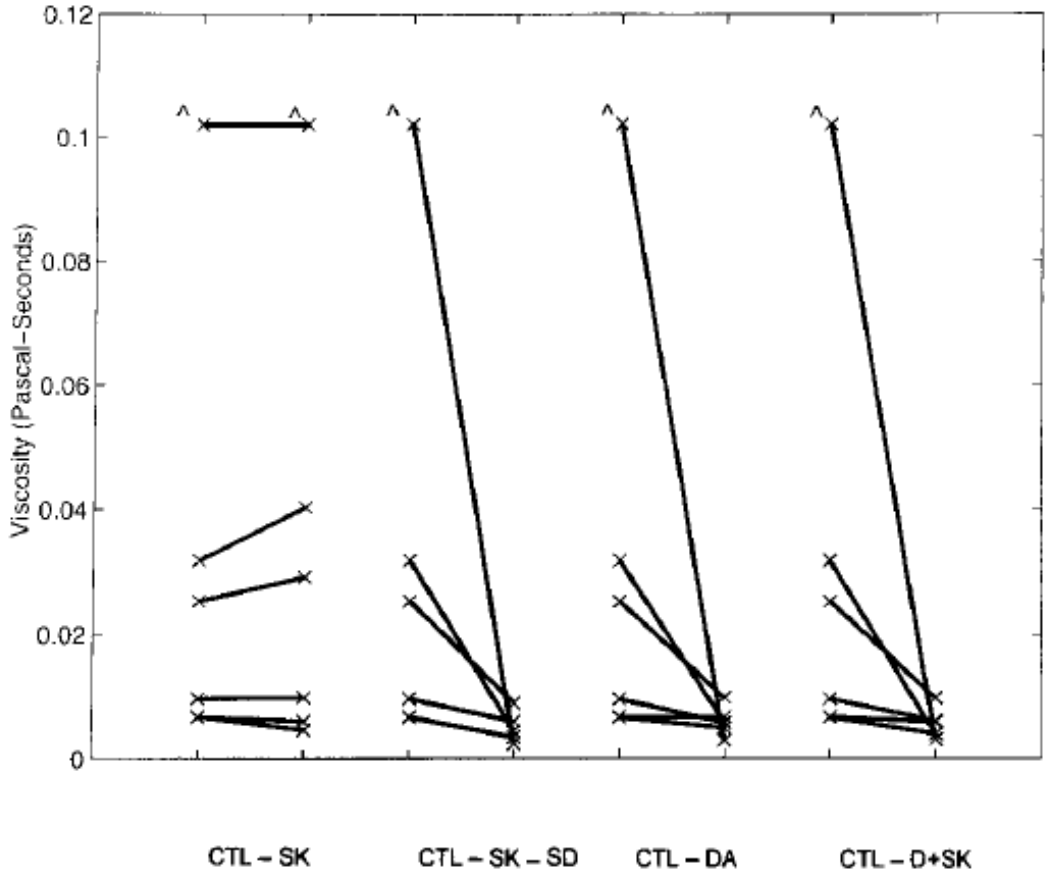


FIGURE 5. Viscosity assays for empyema cases. Each panel shows the changes from the control to each enzyme treatment. In one

Thorax 2003;58:365–366

CASE REPORT

Successful treatment of empyema thoracis with human recombinant deoxyribonuclease

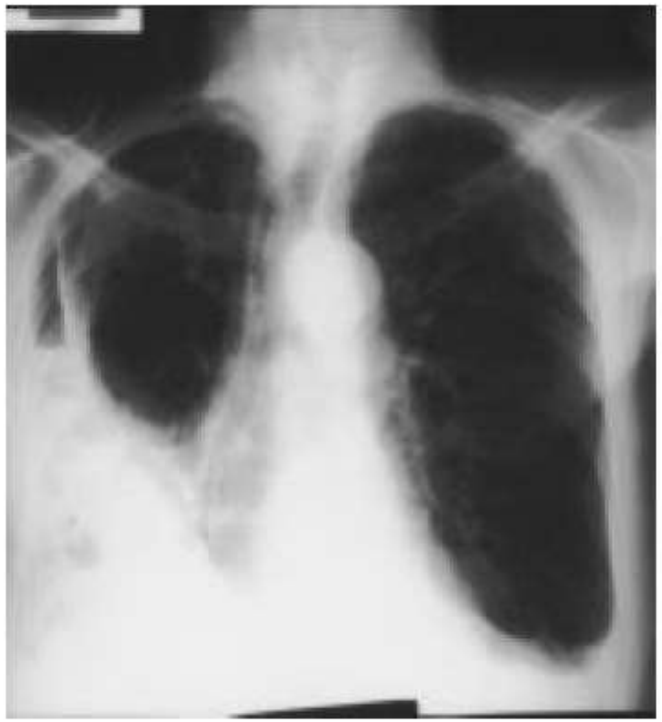


Figure 1 Posteroanterior radiograph of patient following 3 days of treatment with intrapleural streptokinase.

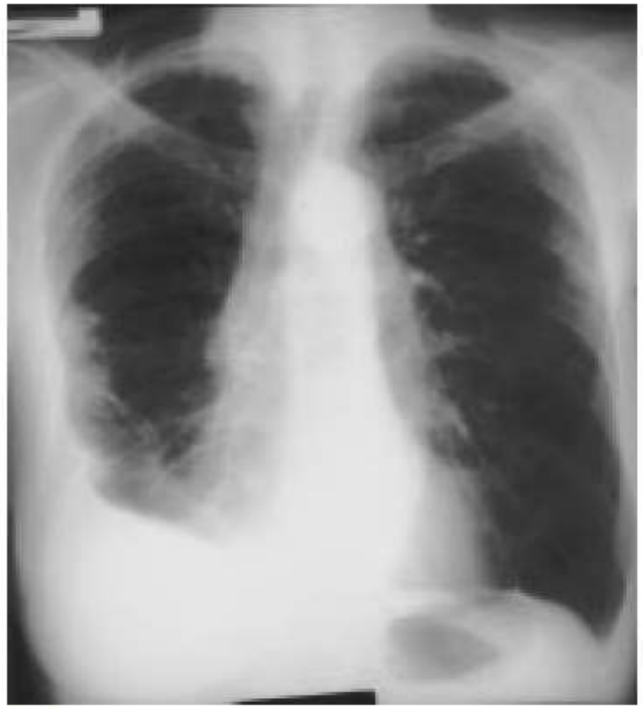


Figure 2 Posteroanterior radiograph of patient after 3 days of treatment with intrapleural DNase showing marked reduction in the size of the right sided empyema.

BRAZ J INFECT DIS. 2013;17(1):90–93

Case report

New therapy of pleural empyema by deoxyribonuclease

- Two patients of loculated empyema treated with intra pleural DNAase alone
- 2.5 mg given for 2 consecutive days.
- Both the patients clinically improved

Intra pleural Alteplase (rtPA)

- Observational studies
- RCTs

Intrapleural tPA – Observational studies

Author	Institute	Year	No.of patients	Dose used	Outcome
Saleh et al	University of Ottawa, Canada	2013	186	16 mg OD x 3days	85% success rate
Sharn et al	University of North Carolina	2011	62	25 mg OD (1-8 days)	86.4% success rate
Zuckerman et al	University hospital, Cincinnatti	2009	25	6 mg (every 8-12 hrs) 1-4 doses	72% success rate
Marios et al	University of Alexandropoulis, greece	2008	20	25 mg OD (1-5 days)	95% success rate
Debra t al	Massachussetts general hospital	2008	66	4-6 mg BD X 3days (1-2 cycles)	86% success rate
Thommi et al	New York general Hospital	2007	83	10-100 mg OD x 3-8 days	85% success rate
Gray M et al	Mayo clinic	2007	30	2 mg every 8 hrs (upto 9 doses)	100% success rate
Dionne etal	University of North Carolina	2004	42	2-50 mg OD x 1-4 days	78% success rate

N Engl J Med 2011;365:518-26.

ORIGINAL ARTICLE

Intrapleural Use of Tissue Plasminogen Activator and DNase in Pleural Infection

- MIST 2 trial (Multicentric intrapleural sepsis trial 2)
- 210 patients randomized to four arms
  - Double placebo
  - tPA (10 mg BD x 3 days) plus DNAase (5 mg BD x 3 days)
  - tPA (10 mg BD x 3 days) plus placebo
  - DNAase (5 mg BD x 3 days) plus placebo
- Loculated effusion in 90% of the patients
- Mean duration of symptoms prior to randomization – 14 days
- Chest tube size used <15 Fr

Table 2. Primary and Major Secondary Outcomes, According to Study Group.*

Outcome	t-PA	DNase	t-PA–DNase	Placebo
Change from baseline in hemithorax area occupied by effusion (primary outcome) — %	−17.2±24.3	−14.7±16.3	−29.5±23.3	−17.2±19.6
Percent difference vs. placebo (95% CI)	2.0 (−4.6 to 8.6)	4.5 (−1.5 to 10.5)	−7.9 (−13.4 to −2.4)	NA
P value	0.55	0.14	0.005	NA
Surgical referral — no. referred/total no. (%)	3/48 (6)	18/46 (39)	2/48 (4)	8/51 (16)
Odds ratio vs. placebo (95% CI)	0.29 (0.07 to 1.25)	3.56 (1.30 to 9.75)	0.17 (0.03 to 0.87)	NA
P value	0.10	0.01	0.03	NA
Hospital stay — no. of days	16.5±22.8	28.2±61.4	11.8±9.4	24.8±56.1
Percent difference vs. placebo (95% CI)	−8.6 (−40.8 to 3.3)	3.6 (−19.0 to 30.8)	−14.8 (−53.7 to −4.6)	NA
P value	0.21	0.73	<0.001	NA

- Conclusions ;
  - Intrapleural tPA plus DNAase combination improved radiologic resolution, Decreased surgical referrals and also reduced the hospital stay.
  - tPA alone or DNAase alone did not lead to any improved outcomes

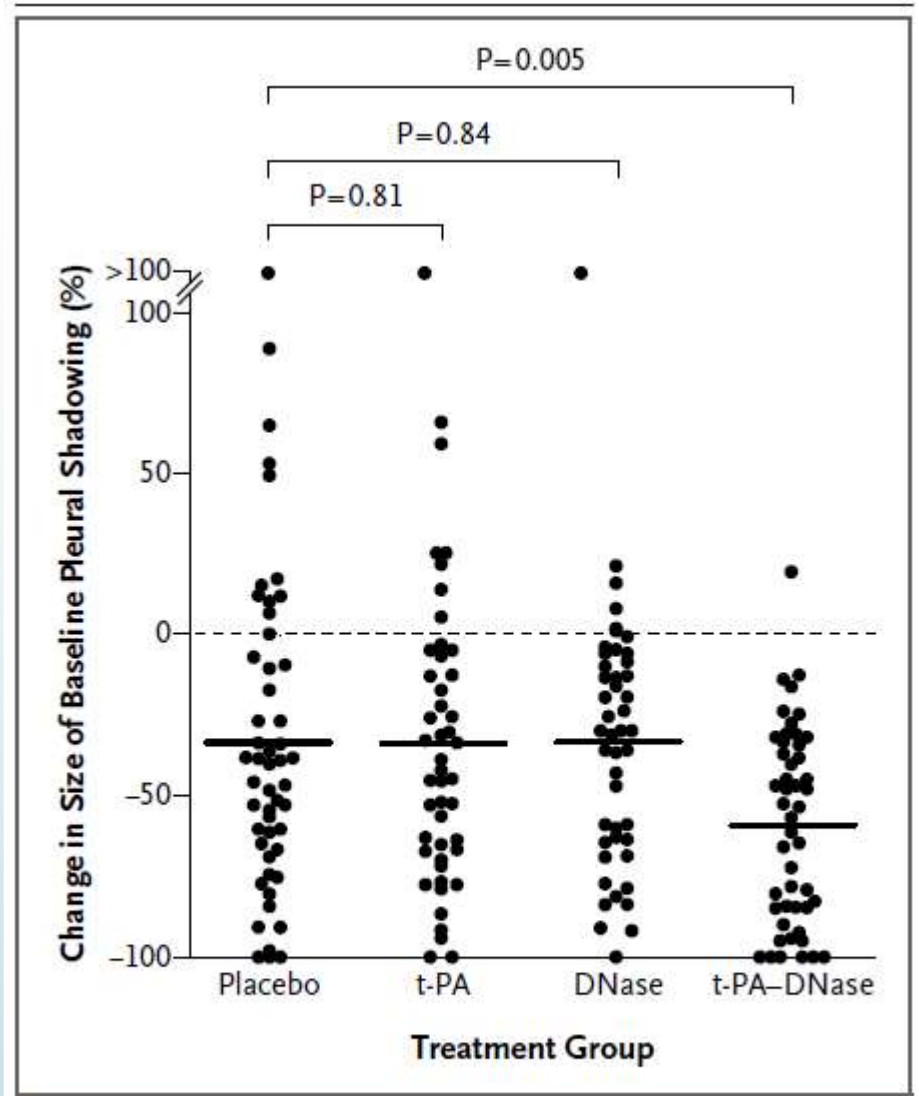


Figure 2. Change in Area of Pleural Fluid on Chest Radiography on Day 7 versus Day 1, According to Study Group.

DNAase monotherapy may be harmful (Increases surgical referrals and hospital stay)

Postulation :

- Systemic absorption of bacterial or inflammatory components after DNAase mediated biofilm disruption.
- Compounded by poor drainage due to undisrupted fibrinous septations.

A double blind randomized cross over trial comparing rate of decortication and efficacy of intrapleural instillation of alteplase vs placebo in patients with empyemas and complicated parapneumonic effusions

Respiratory Medicine (2012) 106, 716–723

- 108 patients were included in the RCT
- Patients with empyema, complicated parapneumonic effusion who failed standard medical management (antibiotic plus chest tube drainage) and who were being considered for surgical drainage were included.
- A cross over trial
- Dose of alteplase : 25 mg OD x 3 days
- Results
  - 58 of 61 patients who received alteplase improved (95%)
  - 4 of 32 patients who received placebo improved (12%)

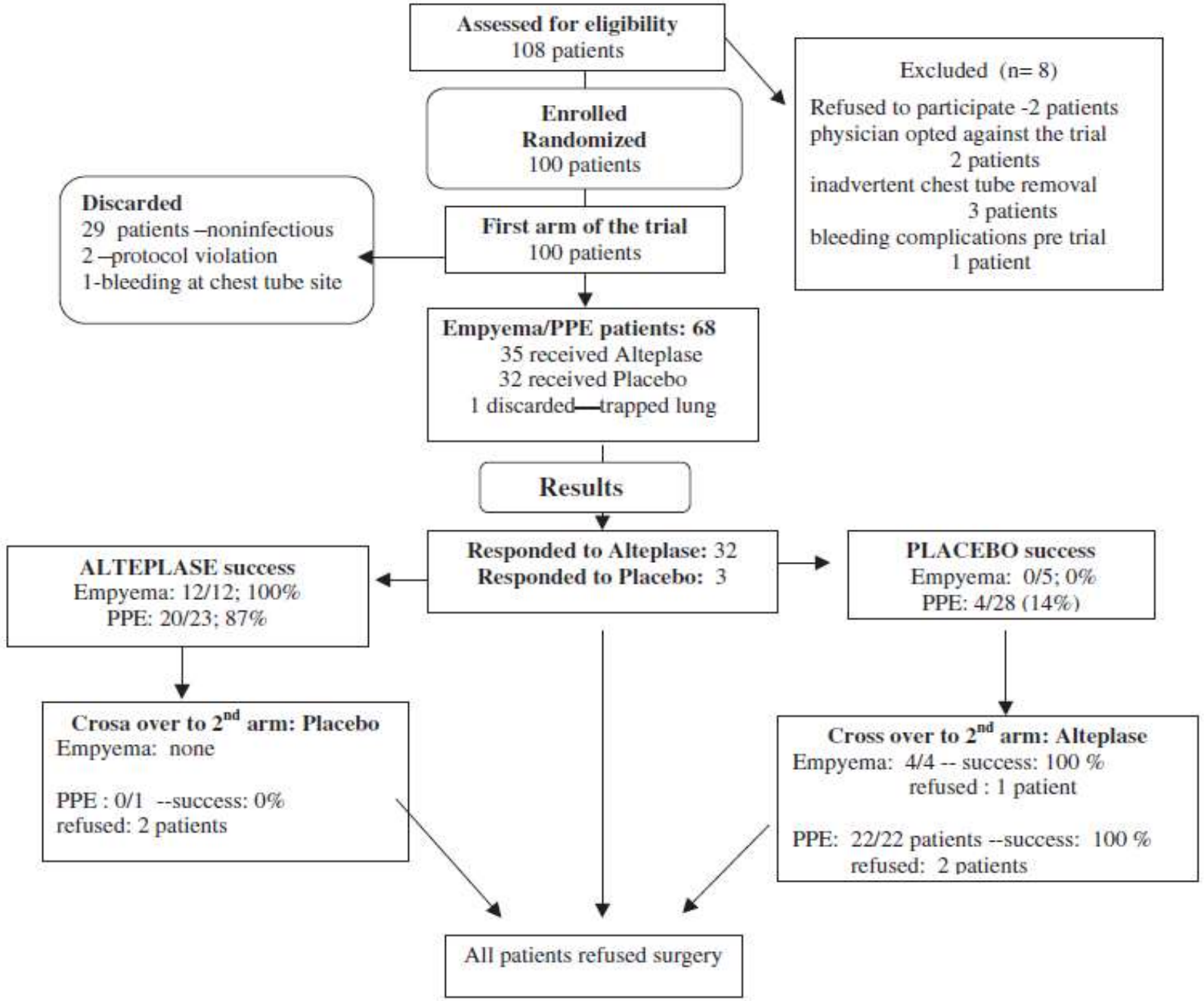
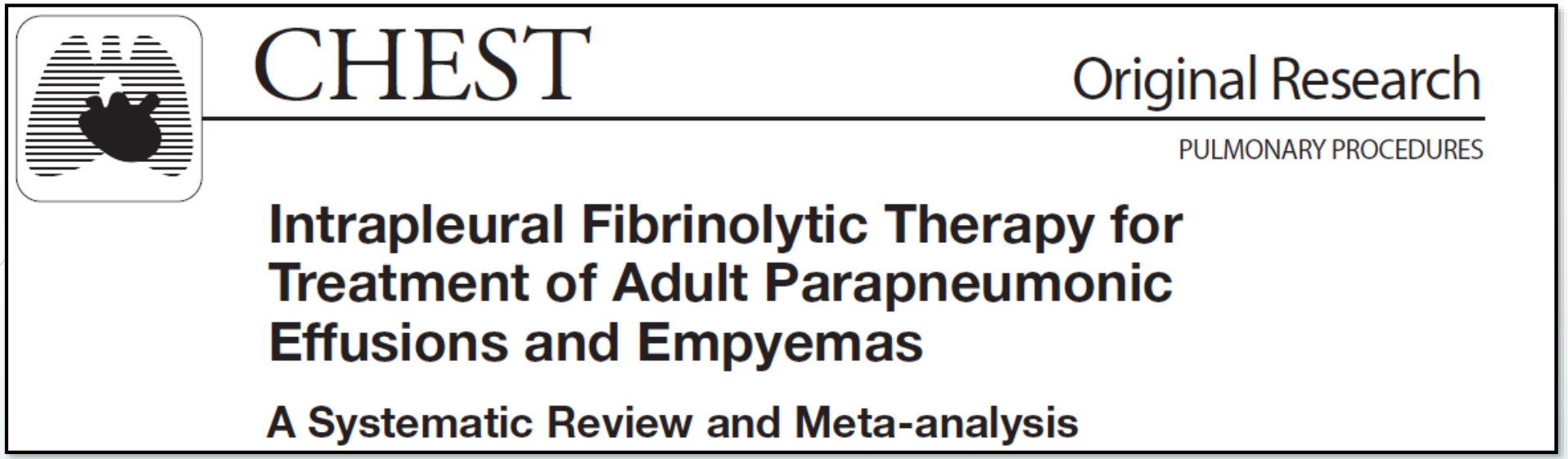


Chart 1 Alteplase/Placebo-Flowchart.

- Conclusions :
  - Intrapleural instillation of alteplase is significantly superior to placebo in treating Loculated effusions.
  - Safe and no major ADR noted.



- Published in 2012
- Included 7 RCTs

- Conclusions :
  - Fibrinolytic therapy is potentially beneficial in managing parapneumonic effusions in adults.
  - May be considered in patients with Loculated pleural effusions
  - Further RCTs with adequate power are needed.

Table 1—*Characteristics of the Studies Included in the Meta-analysis*

Study/Year	Country	Study Size (N)	Study Population	Imaging	Chest Tube Size (F)	Intervention
Davies et al[10]/1997	UK	24	CPE or E	CXR, CT scan, U/S	14	Streptokinase, 250,000 International Units OD × 3 d
Bouros et al[9]/1999	Greece	31	CPE or E	CT scan, U/S	28-32	Urokinase, 100,000 International Units OD × 3 d
Tuncozgur et al[27]/2001	Turkey	49	E stage II[a]	CXR, CT scan, U/S	24-36	Urokinase, 100,000 International Units OD × 3 d
Diacon et al[11]/2004	South Africa	53	CPE or E	CXR, U/S	24 or 28	Streptokinase, 250,000 International Units OD × 7 d[b]
Misthos et al[28]/2005	Greece	127	E	CXR, U/S	28-32	Streptokinase, 250,000 International Units OD × 3 d
MIST1[7]/2005	UK	454	CPE or E	CXR	12 (12-20)[c]	Streptokinase, 250,000 International Units bid × 3 d
MIST2[29]/2011	UK	210	CPE or E	CXR	< 15[d]	Alteplase, 10 mg bid × 3 d; DNase, 5 mg bid × 3 d; combination of alteplase and DNase

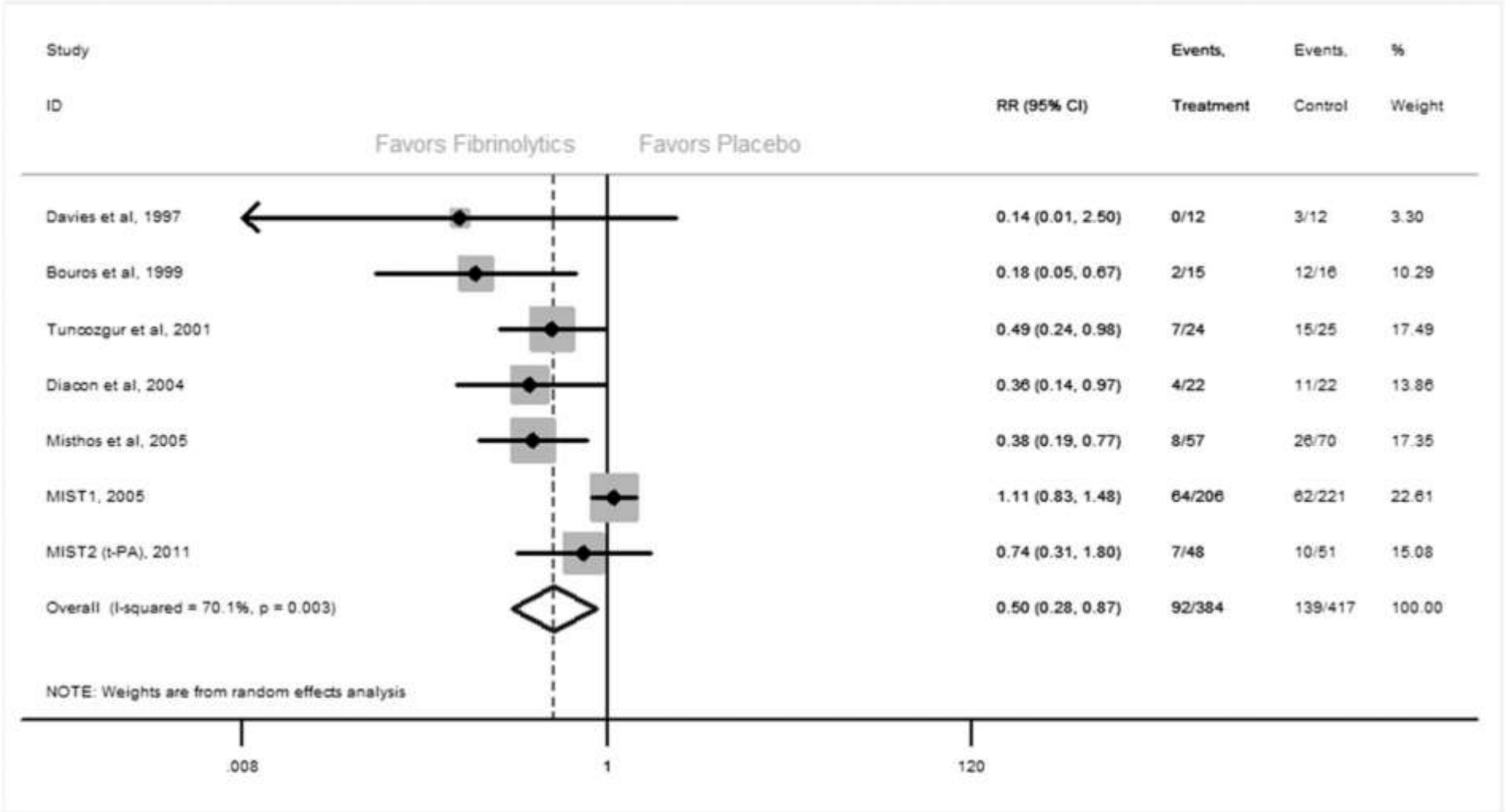


FIGURE 2. Forest plot for outcome of treatment failure (surgical intervention or death) for fibrinolytic therapy vs placebo.[7,9-11,27-29] MIST = Multicenter Intrapleural Sepsis Trial; RR = risk ratio; t-PA = alteplase.

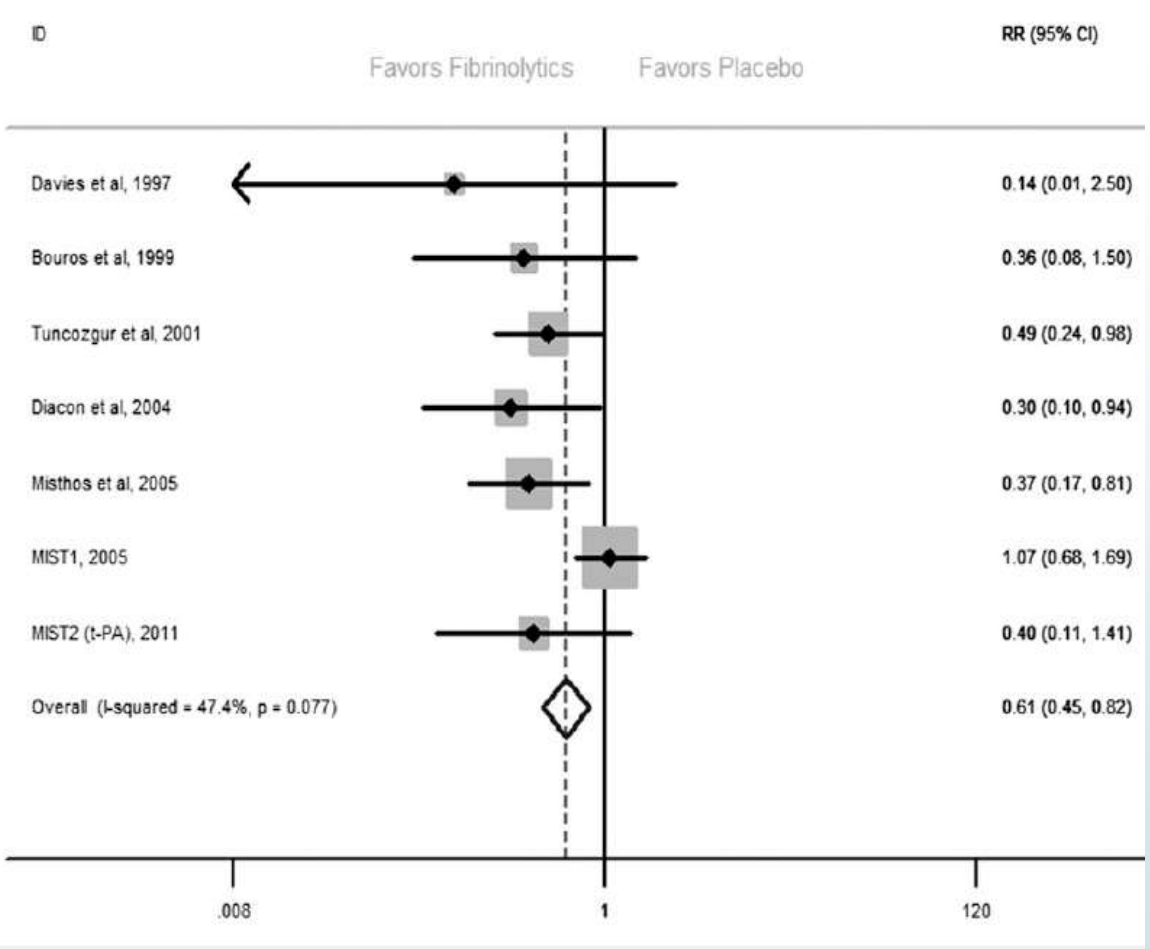


FIGURE 3. Forest plot for outcome of surgical intervention for fibrinolytic therapy vs placebo.[7,9-11,27-29] See abbreviations.

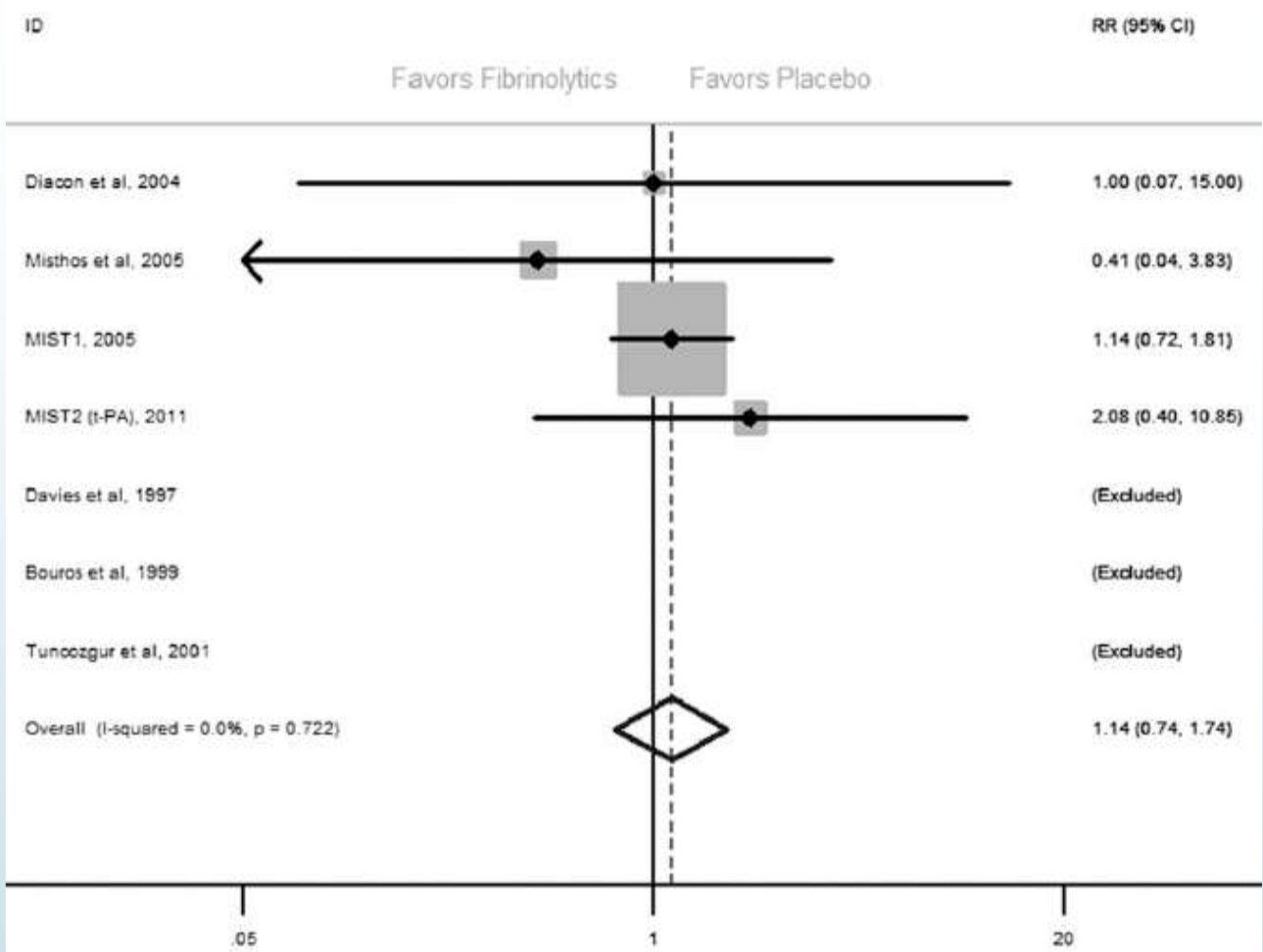


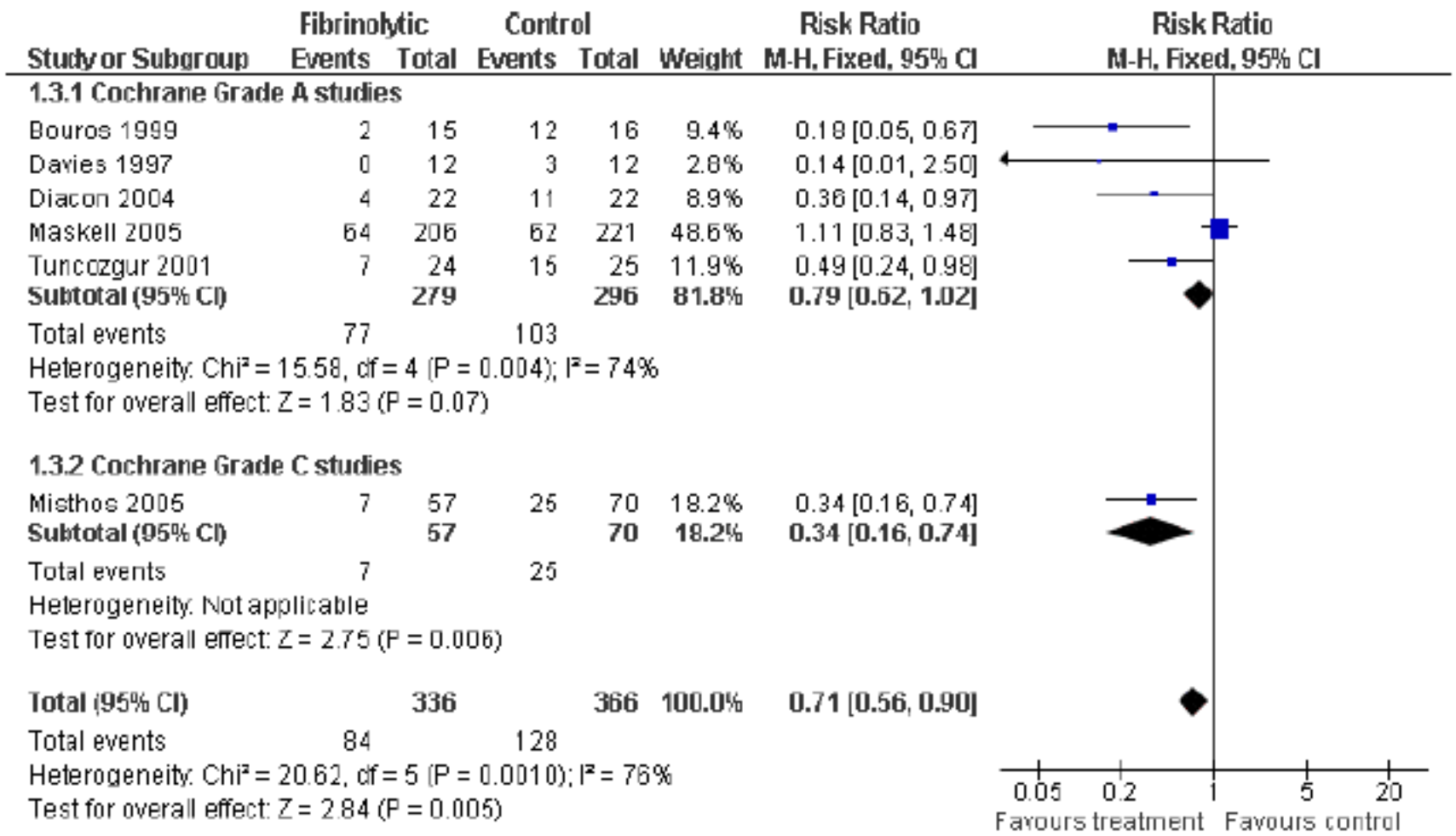
FIGURE 4. Forest plot for outcome of death for fibrinolytic therapy vs placebo.[7,9-11,27-29] See Figure 2 legend

THE COCHRANE COLLABORATION®

Intra-pleural fibrinolytic therapy versus conservative management in the treatment of adult parapneumonic effusions and empyema (Review)

- Cochrane review published in the year 2009
- Prior to MIST2 trial
- Included 6 RCTs

- Conclusions :
  - Intrapleural fibrinolytic therapy confers benefit in reducing the need for surgical intervention.
  - Subgroup analysis (only loculated effusions) also shows similar results
  - No mortality benefit.


Fibrinolytic
Control
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
1.3.1 Cochrane Grade A studies
Bouros 1999 2 15 12 16 9.4% 0.18 [0.05, 0.67]
Davies 1997 0 12 3 12 2.8% 0.14 [0.01, 2.50]
Diacon 2004 4 22 11 22 8.9% 0.36 [0.14, 0.97]
Maskell 2005 64 206 62 221 48.6% 1.11 [0.83, 1.48]
Tuncozgur 2001 7 24 15 25 11.9% 0.49 [0.24, 0.98]
Subtotal (95% CI) 279 296 81.8% 0.79 [0.62, 1.02]
Total events 77 103
Heterogeneity: Chi² = 15.58, df = 4 (P = 0.004); I² = 74%
Test for overall effect: Z = 1.83 (P = 0.07)
1.3.2 Cochrane Grade C studies
Misthos 2005 7 57 25 70 18.2% 0.34 [0.16, 0.74]
Subtotal (95% CI) 57 70 18.2% 0.34 [0.16, 0.74]
Total events 7 25
Heterogeneity: Not applicable
Test for overall effect: Z = 2.75 (P = 0.006)
Total (95% CI) 336 366 100.0% 0.71 [0.56, 0.90]
Total events 84 128
Heterogeneity: Chi² = 20.62, df = 5 (P = 0.0010); I² = 76%
Test for overall effect: Z = 2.84 (P = 0.005)
0.05
0.2
1
5
20
Favours treatment
Favours control

Which fibrinolytic to choose??

An ideal fibrinolytic agent….

Pharmacokinetics/Dynamics :

- Fibrin Specific
- Direct plasminogen activator
- Short half life

Clinical :

- Good efficacy
- Less side effects

Practical :

- Easily available
- Affordable

Comparision between agents

- Only one trial compared streptokinase with urokinase (head to head)
- Included 50 patients (25 in each group)
- Doses used : (5 days mean)
  - STK : 2,50,000 U OD
  - Urokinase : 1,00,000 U OD

- Good treatment response in 23 patients of each group
- 2 patients on STK developed high fever

- Conclusion : Urokinase is as efficacious as but safer than Streptokinase

Am J Respir Crit Care Med. 1997 Jan;155(1):291-5.

Side effects ….

- Unique to Streptokinase
  - Fever
  - Anaphylactic reactions
- Common to all
  - Chest pain
  - Local bleeding (Hemothorax, ICTD site bleed)
  - Systemic bleed

U.K. Controlled Trial of Intrapleural Streptokinase for Pleural Infection

Table 2. Adverse Events Possibly Attributable to Study Treatment, According to Severity and Type.

Variable	Streptokinase (N=208)	Placebo (N=222)	Relative Risk (95% CI)*	P Value
	no. (%)			
Severity				
Serious	14 (7)	6 (3)	2.49 (0.98–6.36)	0.08
Other	8 (4)	8 (4)	1.07 (0.41–2.81)	0.91
Total	22 (11)	14 (6)	1.68 (0.88–3.19)	0.15
Type				
Hemorrhage (local pleural or systemic)	7 (3)	6 (3)		
Chest pain	4 (2)	1 (<1)		
Fever, rash, and allergy	5 (2)	1 (<1)		
Other	6 (3)	6 (3)		

Risk of bleeding….

- MIST 2 trial : 5 patients had serious bleeding
  - 2 intra pleural hemorrhage (rtPA + DNAase group)
  - 1 hemoptysis (rtPA + DNAase group)
  - 2 GI hemorrhage (DNAase alone group)
- 2012 RCT (Alteplase)
  - 1 patient had severe ICTD site bleed
  - 1 patient had intra pleural hemorrhage

Intrapleural fibrinolytic therapy (IPFT) in loculated pleural effusions—analysis of predictors for failure of therapy and bleeding: a cohort study

BMJ Open 2013;**3**:e001887.

Serious bleed occurred in 15 patients (6.6%).
Three patients needed emergency thoracotomy
One patient died because of massive hemorrhage

Table 5 Univariate analysis (bleeding)

Variable	p Value
INR>1.4	0.46
PTT>40 s	0.43
Platelets <80	0.5
Prophylactic anticoagulation	0.4
Complete anticoagulation	0.54
Antiplatelet therapy	0.02
Clopidogrel (Plavix)	0.35
Streptokinase	0.05

INR, international normalised ratio; PTT, pro-thrombin time.

Table 6 Multivariate analysis (bleeding)

Variable	p Value
Antiplatelet therapy	0.08
Streptokinase	0.9

Adjunctive Intrapleural Tissue Plasminogen Activator Administered via Chest Tubes Placed with Imaging Guidance: Effectiveness and Risk for Hemorrhage[1]

Radiology: Volume 246: Number 3—March 2008

- 4 patients of the 66 patients treated with fibrinolytics developed major intra pleural hemorrhage (5 events). Dose received was 4- 6mg
- All survived. One patient needed VATS

Risk based on systemic anticoagulation : ($p<0.0001$)

- Hemorrhages occurred only in patients on therapeutic anticoagulation . 5 out of 12 (33.3 %)
- No hemorrhage occurred in 38 patients on prophylactic anticoagulation
- 16 patients were not on any anticoagulation

Conclusion :

- Caution to be used in patients who are on systemic anticoagulation.

Pleural thickness-
Does it predict failure ??

- Conflicting results from 3 studies which reported this outcome

1. Park et al in their study on 31 patients found that pleural thickness >5 mm predicts failure with Urokinase.

2. Saleh et al in their study on 237 patients showed that pleural thickness > 2mm predicts treatment failure (using a multivariate analysis)

3. Debra et al however showed that fibrinolytics can cause radiologic clearance even with pleura upto 13 mm thick.

Radiology: Volume 246: Number 3—March 2008

AJR Am J Roentgenol 1996;167:649–652.

BMJ Open 2013;3:e001887

Unanswered questions…..

1. Optimal dose to be used
2. Optimal Frequency
3. Optimal duration
4. Optimal indwelling time

Intra pleural antimicrobial agents. Do they have a role??

Intrapleural antimicrobials

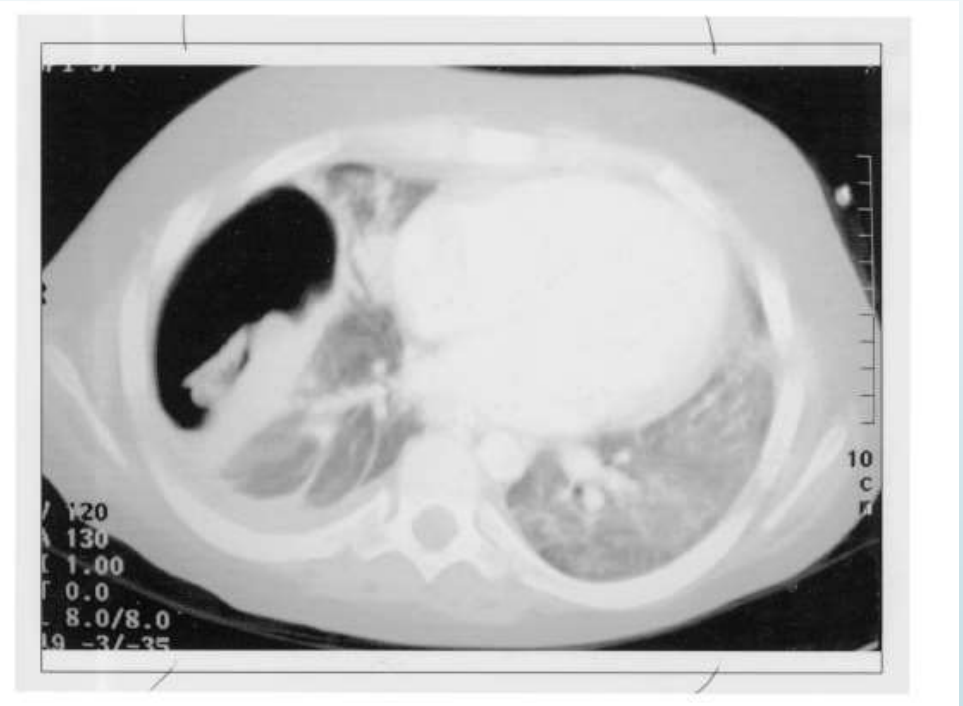
- Only described in case reports.
- Most of these are old studies
- No large study describing the role of intra pleural antimicrobial agents

- So far, used only as an experimental method of treatment

THE PEDIATRIC INFECTIOUS DISEASE JOURNAL Vol. 22, No. 5, May 2003

COMBINED SYSTEMIC AND INTRAPLEURAL TREATMENT OF *ASPERGILLUS* PULMONARY EMPYEMA AFTER INVASIVE ASPERGILLOSIS

- 12 year old immunocompromised boy with invasive aspergillosis,
- Developed bronchopleural fistula and pleural extension of infection
- Received 45 days of intra pleural 50 mg amphotericin B in addition to systemic antifungals
- Improved



SOME PERSONAL OBSERVATIONS ON THE EFFECT OF INTRA-PLEURAL INJECTION OF NITROGEN GAS IN TUBERCULOSIS.[1]

BY DR. H. P. LOOMIS.

NEW YORK.

- Much before the anti tubercular drugs were discovered
- The treatment was intrapleural injection of Nitrogen.
- Causes lung collapse and was supposed to give rest to the affected lung, thereby resulting in cure.

Can Respir J Vol 15 No 5 July/August 2008

Treatment of a tuberculous empyema with simultaneous oral and intrapleural antituberculosis drugs

Richard Long MD FCCP[1], James Barrie MD[2], Kenneth Stewart MD[3], Charles A Peloquin PharmD[4]

- 71 year old man with tubercular empyema and oropharyngeal cancer treated with intra pleural therapy.

- Drugs used intrapleurally: Twice a week
  - INH 3 mg (20 Ug/ml)
  - Amikacin 12 mg (80 Ug/ml)
  - Levofloxacin 1.5 mg (10 Ug /ml)

- Other drugs tried intrapleurally in tubercular empyema include
  - Streptomycin
  - Oxytetracycline
  - Para amino salicylic acid
  - Hydrocortisone

- Intrapleural penicillin has also been tried in bacterial empyemas

- *Tubercle. 1960 Oct;41:358-62.*
- *Minerva Med. 1956 Jun 6;47(45):1788-90.*
- *Schweiz Z Tuberc Pneumonol. 1956;13(1):67-74.*
- *Athena. 1950 Nov;16(11):257-61.*
- *G Ital Della Tuberc. 1950 Nov-Dec;4(6):456-79.*
- *Rev Esp Tuberc. 1951 Oct;20(199):599-641.*

Intrapleural Injection of Transforming Growth Factor-β Antibody Inhibits Pleural Fibrosis in Empyema*

(CHEST 2004; 126:1636–1644)

Design: Prospective, randomized, blinded study.
Setting: Animal research laboratory.
Subjects: Nineteen rabbits.

- 10 rabbits injected with drug. 9 served as controls.
- Injection of intra pleural anti TGF beta after an induced empyema significantly reduces pleural fibrosis.

Summarizing the evidence…

- Intra pleural fibrinolytics definitely have a role in the management of complicated para pneumonic effusions.
- When used in the subset of patients with non resolving collections (despite placement of chest drain), they decrease the surgical referral rates
- No effect on mortality
- Though less common, patients need to be monitored for evidence of bleeding (especially if on therapeutic anticoagulation)