ORIGINAL ARTICLE

Intrapleural Use of Tissue Plasminogen Activator and DNase in Pleural Infection

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ABSTRACT

BACKGROUND

More than 30% of patients with pleural infection either die or require surgery. Drainage of infected fluid is key to successful treatment, but intrapleural fibrinolytic therapy did not improve outcomes in an earlier, large, randomized trial.

METHODS

We conducted a blinded, 2-by-2 factorial trial in which 210 patients with pleural infection were randomly assigned to receive one of four study treatments for 3 days: double placebo, intrapleural tissue plasminogen activator (t-PA) and DNase, t-PA and placebo, or DNase and placebo. The primary outcome was the change in pleural opacity, measured as the percentage of the hemithorax occupied by effusion, on chest radiography on day 7 as compared with day 1. Secondary outcomes included referral for surgery, duration of hospital stay, and adverse events.

RESULTS

The mean (±SD) change in pleural opacity was greater in the t-PA–DNase group than in the placebo group (–29.5±23.3% vs. –17.2±19.6%; difference, –7.9%; 95% confidence interval [CI], –13.4 to –2.4; P=0.005); the change observed with t-PA alone and with DNase alone (–17.2±24.3 and –14.7±16.4%, respectively) was not significantly different from that observed with placebo. The frequency of surgical referral at 3 months was lower in the t-PA–DNase group than in the placebo group (2 of 48 patients [4%] vs. 8 of 51 patients [16%]; odds ratio for surgical referral, 0.17; 95% CI, 0.03 to 0.87; P=0.03) but was greater in the DNase group (18 of 46 patients [39%]) than in the placebo group (odds ratio, 3.56; 95% CI, 1.30 to 9.75; P=0.01). Combined t-PA–DNase therapy was associated with a reduction in the hospital stay, as compared with placebo (difference, –6.7 days; 95% CI, –12.0 to –1.9; P=0.006); the hospital stay with either agent alone was not significantly different from that with placebo. The frequency of adverse events did not differ significantly among the groups.

CONCLUSIONS

Intrapleural t-PA–DNase therapy improved fluid drainage in patients with pleural infection and reduced the frequency of surgical referral and the duration of the hospital stay. Treatment with DNase alone or t-PA alone was ineffective. (Funded by an unrestricted educational grant to the University of Oxford from Roche UK and by others; Current Controlled Trials number, ISRCTN57454527.)

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Pleural infection affects more than 65,000 patients each year in the United States and the United Kingdom,[1] and the incidence is increasing in both countries — in both children[2-4] and adults.[5,6] The mortality rate from pleural infection is between 10% and 20%,[5,7-9] and drainage through a chest tube and administration of antibiotics fail in approximately one third of patients, who then require surgical drainage.[5,9] The median duration of the hospital stay for these patients is 12 to 15 days,[5,6,8,9] with 25% hospitalized for more than a month. Care of each patient costs approximately $5,000,[10,11] totaling more than $320 million per year in the United Kingdom and United States combined.

Standard therapy consists of antibiotics and tube drainage of the infected pleural fluid; surgery is required when sepsis and infected fluid are not effectively controlled. Observational data suggest that intrapleural administration of fibrinolytic drugs reduces the frequency of failed drainage and subsequent surgery by cleaving intrapleural fibrinous septations and improving chest-tube drainage,[12-17] but the large First Multicenter Intrapleural Sepsis Trial (MIST1)[9] showed no benefit of intrapleural streptokinase; this finding was subsequently supported by a meta-analysis.[18]

The hypothesis that the division of pleural septations with the use of fibrinolytic agents would result in improved pleural drainage has strong clinical and scientific support[19]; thus, this trial used a different direct-acting fibrinolytic agent, recombinant tissue plasminogen activator (t-PA). Data from case series support this approach in adults[20,21] and children.[22-27] Because the presence of extracellular DNA and other bacterial components in the pleural space may increase viscosity and permit biofilm formation,[28-32] we also tested the use of recombinant human DNase.[33,34] Intrapleural DNase (5 mg twice daily) has been shown in an animal model[35] and in a small case series[36,37] to be a potential treatment for pleural infection.

METHODS

STUDY DESIGN

This double-blind, double-dummy, factorial randomized trial (the Second MIST trial [MIST2]) was conducted at 11 centers in the United Kingdom from December 2005 to November 2008. The sponsor was the University of Oxford, which received an unrestricted educational grant from Roche UK. The study drugs and placebos were provided by Roche UK and Boehringer Ingelheim UK. The authors designed the study, analyzed and held the data, wrote the manuscript, made the decision to submit the manuscript for publication, and vouch for the accuracy and completeness of the data and analyses.

The study was conducted in accordance with the trial protocol; the protocol and the statistical analysis plan are available with the full text of this article at NEJM.org. Ethical and regulatory approval for the study was obtained before recruitment began. Further details than those presented here concerning chest tubes, antibiotic management, and statistical methods are provided in the Supplementary Appendix (available at NEJM.org).

PATIENTS

Eligibility criteria were clinical evidence of infection and pleural fluid that was macroscopically purulent, positive on culture for bacterial infection, or positive for bacteria on Gram's staining, or pleural fluid that had a pH of less than 7.2 (measured by means of a blood-gas analyzer). Evidence of infection, which was assessed by the recruiting physician, included the presence of fever and elevated serum levels of inflammatory markers such as C-reactive protein or an elevated white-cell count.

Exclusion criteria were an age of less than 18 years; previous treatment with intrapleural fibrinolytic agents, DNase, or both for empyema; known sensitivity to DNase or t-PA; coincidental stroke; major hemorrhage or major trauma; major surgery in the previous 5 days; previous pneumonectomy on the infected side; pregnancy or lactation; and expected survival of less than 3 months, owing to a pathologic condition other than that responsible for the pleural abnormalities.

RANDOMIZATION

After each patient provided written informed consent, he or she was assigned to a study group by means of minimization[38] with a random component, with the group assignments carried out by a central telephone service. Minimization criteria were the presence of purulent pleural fluid, the presence of a hospital- or community-acquired infection, and a pleural collection that occupied 30% or less of the total hemithorax on the initial chest radiograph. The four possible study treatments were t-PA plus DNase, DNase plus placebo, t-PA plus placebo, and double placebo. Placebos were identical in appearance and packaging to the corresponding active drugs.

The dose of DNase (Pulmozyme, Roche) was 5 mg, and the dose of t-PA (Actilyse, Boehringer Ingelheim) was 10 mg. Intrapleural medications were each given twice daily for 3 days, and each administration was followed by clamping of the drain to permit the study drug to remain in the pleural space for 1 hour.

OUTCOMES

Primary End Point

The primary end point was the change in the area of pleural opacity, measured as the percentage of the ipsilateral hemithorax occupied by effusion on chest radiography, from day 1 (randomization) to day 7. The area of pleural opacity and the area of the ipsilateral hemithorax were measured digitally (Fig. 1) by two separate assessors (see the Supplementary Appendix). Validation studies showed that this measurement strategy predicted 71% of the exact change in the volume of pleural-fluid collection, quantified by means of multislice thoracic computed tomography.

Secondary End Points

The secondary end points were the relative change in the area of pleural opacity on chest radiography, expressed as the percent reduction from the baseline area; the proportions of patients referred for thoracic surgery by 3 months and by 12 months; the duration of the hospital stay between randomization and discharge to home or to a convalescent care facility; the volume of pleural fluid drained between randomization and day 7; the change in inflammatory markers (i.e., white-cell count, C-reactive protein level, and presence of fever [temperature >37.5°C]) between randomization and day 7; death from any cause by 3 months and by 12 months; and the frequency of serious and nonserious adverse events during the study period.

Local investigators recorded the reasons for referring patients for surgical treatment, which were subject to an independent, blinded review to identify reasons for surgery before data analysis.

STATISTICAL ANALYSIS

Patients who did not receive any assigned study medication or who had pleural fluid occupying less than 5% of the hemithorax area on chest radiography on day 1 were excluded from the primary analysis (on the basis of a modified intention-to-treat protocol). All analyses were planned before any data analysis was performed, except as otherwise specified. For patients who died or underwent surgery before day 7, the last chest radiograph obtained after baseline but before surgery or death

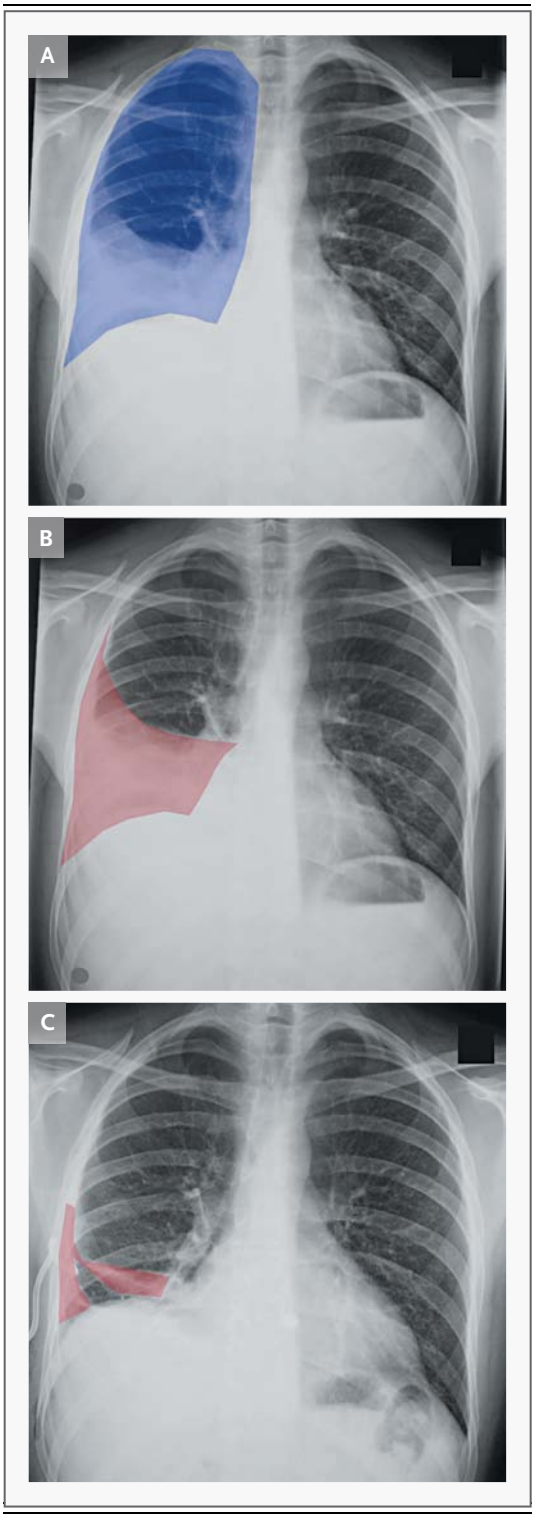

Figure 1 (facing page). Study Measurements on a Digital Chest Radiograph.

The hemithorax area is delineated in Panel A. (The hemithorax area was measured on day 1 and day 7 but is shown only once here.) The area of pleural opacity is shown at baseline (day 1) in Panel B and at day 7 in Panel C. The percentage of the hemithorax area occupied by pleural opacity on day 1 was calculated as the colored area in Panel B divided by that in Panel A and then multiplied by 100. The corresponding percentage on day 7 was calculated by dividing the colored area in Panel C by that in Panel A and multiplying by 100. The change in the percentage of hemithorax area occupied by pleural opacity (the primary outcome) between day 7 and day 1 (which was –31% in the example given here) was calculated, as was the relative change: a secondary outcome, measured as the negative of (the colored area in Panel B minus that in Panel C), multiplied by (100 divided by the area in Panel B) (here, –79%).

was used as the day 7 radiograph for purposes of analysis.

We conducted a standard factorial-study analysis, with an initial test for interaction between DNase, t-PA,[39] and the outcome. If the result of the interaction test was nonsignificant, we conducted a factorial analysis, but if the result was significant (at the 5% level), we instead compared each intervention group with placebo. All analyses were adjusted on the basis of the area of effusion on chest radiography at baseline[40] and for minimization factors.[41-43]

Continuous outcomes were analyzed by means of linear regression models, and binary outcomes were analyzed with the use of logistic-regression models. The white-cell count, C-reactive protein level, and temperature were analyzed longitudinally with the use of mixed-effects models. Stata software, version 11, was used for data analyses.

On the basis of the MIST1 trial,[9] we assumed that the area of pleural opacity 1 week after randomization would be halved in 50% of patients receiving double placebo. Therefore, our study was powered to determine whether intrapleural DNase or t-PA therapy could increase the proportion of patients who had a 50% reduction in the area of opacity, from 50% of patients to 70%. To detect this difference using a factorial design (and assuming no interaction), we calculated that we would need to enroll a total of 210 patients, randomly assigned in equal numbers to the four groups (for 80% power, with an alpha level of 0.05 and a 5% rate of noncompliance).

RESULTS

PATIENTS

A total of 210 participants were enrolled (see the Supplementary Appendix): 55 receiving double placebo, 52 receiving t-PA only, 51 receiving DNase only, and 52 receiving both t-PA and DNase. Six did not receive study medication, and 11 had pleural opacity at baseline that was less than 5% of the hemithorax area on chest radiography. The primary analysis therefore included 193 patients: 51 receiving double placebo, 48 receiving t-PA only, 46 receiving DNase only, and 48 receiving both t-PA and DNase. The baseline demographic, clinical, and microbiologic characteristics of the patients were similar across all four groups (Table 1, and the Supplementary Appendix).

Data on the primary outcome were available for all 210 participants; although 7 patients (3%) died before day 7, radiographs were available from the day of death for all these patients. Data regarding survival were available for 209 of the 210 patients (99.5%) at 3 months and for 203 patients (97%) at 12 months. Data on referral for surgery were available for 209 of the 210 patients (99.5%) at 3 months and for 203 patients (97%) at 12 months.

PRIMARY END POINT

Because of a highly significant interaction (P=0.002) between t-PA and DNase with regard to the primary outcome, the modified intention-to-treat analysis of 193 patients was performed as a comparison of the t-PA, DNase, and t-PA–DNase groups with the placebo group (i.e., the patients who received double placebo). The difference in the mean change in pleural opacity from day 1 to day 7 between the t-PA–DNase group (–29.5%) and the placebo group (–17.2%) was clinically and statistically significant (–7.9%; 95% confidence interval [CI], –13.4 to –2.4; P=0.005) (Table 2). There was no significant improvement in the primary outcome with either t-PA or DNase alone as compared with double placebo (Table 2).

Neither an unadjusted analysis nor an intention-to-treat sensitivity analysis that included data from all 210 participants materially altered the results (see the Supplementary Appendix).

SUBGROUP ANALYSES

There was no evidence of a differential treatment effect in any of the preplanned subgroup analyses: purulent versus nonpurulent pleural fluid, use of

Table 1. Baseline Characteristics of the Patients, According to Study Group.*

Characteristic	t-PA (N=52)	DNase (N=51)	t-PA–DNase (N=52)	Placebo (N=55)
Age — yr	60±17	57±18	60±19	58±19
Male sex — no. (%)	39 (75)	42 (82)	31 (60)	39 (71)
Percent of hemithorax occupied with pleural fluid	39.8±22.6	41.9±22.9	44.2±24.9	36.3±23.3
Duration of symptoms before randomization — days				
Median	14	14	13	13
Interquartile range	7–30	7–30	7–22	7–21
Small-bore tube, <15 French — no. (%)†	41 (80)	44 (88)	48 (94)	49 (91)
Community-acquired infection — no. (%)	44 (85)	44 (86)	45 (87)	49 (89)
Radiographic evidence of loculation — no. (%)‡	49 (94)	47 (92)	49 (94)	47 (85)
Purulent pleural fluid — no. (%)	24 (46)	25 (49)	27 (52)	26 (47)
Positive Gram's stain or culture of pleural fluid — no. (%)	5 (10)	5 (10)	4 (8)	7 (13)
Pleural-fluid pH				
Median	6.9	7.0	6.9	6.9
Interquartile range	6.8–7.1	6.8–7.1	6.8–7.1	6.8–7.1
Lactate dehydrogenase in pleural fluid — IU/liter				
Median	2935	3077	3418	3337
Interquartile range	871–9908	365–7903	1321–7328	1034–8943

* All baseline characteristics were well matched among the four groups (P>0.05). Plus–minus values are means ±SD.
† Data on tube size were missing for one patient in each study group.
‡ Radiographic loculation was assessed by means of combined blind scoring of chest radiographs and thoracic computed tomographic scans, where available (see the Supplementary Appendix).

a large-bore versus small-bore chest tube, and radiographic evidence of loculation versus no evidence of loculation.

SECONDARY END POINTS

Pleural Effusion

Figure 2 shows the change in the area of pleural opacity on day 7 as compared with day 1. A clinically and statistically significant reduction was found with t-PA–DNase as compared with double placebo; no benefit was found with t-PA or DNase alone.

Referral for Surgery

The frequency of surgical referral at 3 months was lower in the t-PA–DNase group than in the placebo group (2 of 48 patients [4%] vs. 8 of 51 patients [16%]; odds ratio for surgical referral, 0.17; 95% CI, 0.03 to 0.87; P=0.03) (Table 2). As compared with referrals for surgery in the placebo group at 3 months, referrals were increased in the DNase-only group (18 of 46 patients [39%]; odds ratio, 3.56, 95% CI, 1.30 to 9.75; P=0.01) and were nonsignificantly reduced in the t-PA group (3 of 48 patients [6%]; odds ratio, 0.29; 95% CI, 0.07 to 1.25; P=0.10).

Seven patients (2 receiving placebo and 5 receiving DNase) who were referred for surgery did not undergo surgical débridement during the 90-day outcome period. Two of these patients died before surgical intervention, and 1 underwent surgery after the 90-day period. A post hoc analysis of surgical-intervention data showed that as compared with the placebo group (in which 6 of 51 patients [12%] underwent surgery), the t-PA–DNase group had a nonsignificant decrease in the rate of surgery (2 of 48 patients [4%]); odds ratio, 0.23; 95% CI, 0.04 to 1.29; P=0.10), as did the t-PA group (3 of 48 patients [6%]; odds ratio, 0.42; 95% CI, 0.09 to 1.87; P=0.25), whereas the DNase group had an increased rate of surgery (13 of 46 patients [28%]; odds ratio, 2.72; 95% CI, 0.88 to 8.42; P=0.08).

An independent review of the reasons for re-

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

* Plus–minus values are means ±SD. The mean values for the primary analysis are unadjusted, whereas the treatment effects have been adjusted for minimization criteria and opacification of the chest radiograph at baseline, according to the statistical analysis plan. Data on hospital stay are for all patients in the primary analysis (i.e., including two patients with outlying results). NA denotes not applicable.

ferral for surgery showed that all referrals for surgery were due to clinical evidence of worsening infection.

Duration of Hospital Stay

Hospital stays were shorter on average in the t-PA–DNase group than in the placebo group, whereas in the DNase-only group and the t-PA-only group, stays were similar in length to the hospital stay in the placebo group (Table 2). The hospital-stay data included two outlying results: one patient in the DNase group had a hospital stay of 386 days, and one in the placebo group had a stay of 391 days. A post hoc analysis excluding these observations showed that the mean hospital stay was significantly reduced in the t-PA–DNase group (11.8 days, vs. 17.0 days in the placebo group; difference, −6.7 days; 95% CI, −12.0 to −1.9; P=0.006). The mean hospital stay in the other two treatment groups remained similar to the value in the placebo group (19.3 days in the DNase group; difference, 1.9 days; 95% CI, −5.1 to 10.8; P=0.61; and 16.5 days in the t-PA group; difference, −0.6 days; 95% CI, −6.9 to 10.5; P=0.93).

Deaths

Mortality rates were similar among all four study groups both at 3 months and at 12 months. At 3 months, 2 of 50 patients (4%), 4 of 48 patients (8%), 4 of 48 patients (8%), and 6 of 46 patients (13%) had died in the placebo group, t-PA–DNase group, t-PA group, and DNase group, respectively (P=0.46 by Fisher's exact test). At 12 months, 4 of 48 patients (8%), 5 of 47 patients (11%), 5 of 46 patients (11%), and 9 of 45 patients (20%) had died (P=0.37 by Fisher's exact test).

Inflammatory Measures

By day 7, average C-reactive protein levels were nonsignificantly lower in the t-PA–DNase group than in the placebo group (difference, −0.8 mg per liter; 95% CI, −27.3 to 25.8; P=0.95). In contrast, by day 7 and in comparison with the placebo group, average C-reactive protein levels were nonsignificantly greater in the t-PA group (difference, 4.1 mg per liter; 95% CI, −22.1 to 30.4; P=0.76) and in the DNase group (difference, 12.7 mg per liter; 95% CI, −14.1 to 39.6; P=0.35).

By day 7, the average white-cell count in the systemic circulation was nonsignificantly higher with t-PA and nonsignificantly lower with DNase than with placebo. The average count was significantly lower in the t-PA–DNase group than in the placebo group (difference, -3.4×10^9 per liter; 95% CI, −6.4 to −0.3; P=0.03).

The odds of fever on day 6 or 7 was nonsignificantly lower in the t-PA group than in the placebo group (5 of 41 patients [12%] had fever, vs. 6 of 42 patients [14%]; odds ratio, 0.38; 95% CI, 0.11 to 1.33; P=0.13) and was nonsignificantly higher in the DNase group (9 of 44 patients [20%]; odds ratio, 1.75; 95% CI, 0.46 to 6.64; P=0.41). The t-PA–DNase group had a significantly reduced odds of fever on day 7 as compared with placebo (3 of

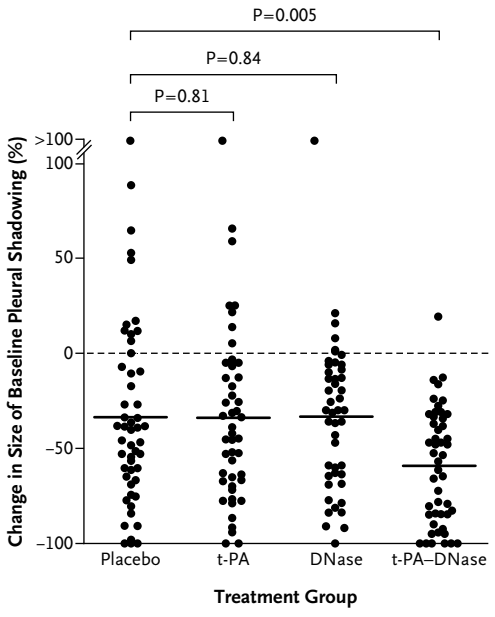

Figure 2. Change in Area of Pleural Fluid on Chest Radiography on Day 7 versus Day 1, According to Study Group.

Each circle represents an individual patient, and mean changes are indicated by the horizontal bars.

44 patients [7%] had fever; odds ratio, 0.09; 95% CI, 0.03 to 0.34; P<0.001). The Supplementary Appendix shows graphically the changes in the C-reactive protein level, white-cell count, and incidence of fever over time in the three treatment groups as compared with the placebo group, as well as the results of other secondary analyses.

Adverse Events

Thoracic surgery and deaths due to pleural infection were analyzed as secondary outcomes. Other serious and nonserious adverse events were evenly distributed across the trial groups (Table 3).

COMPLIANCE WITH STUDY DRUGS

A total of 137 of 193 patient (71%) received all assigned doses of study drugs. The within-group proportion of patients with 100% compliance was similar across all four study groups (see the Supplementary Appendix).

DISCUSSION

Our trial shows that as compared with placebo, combined treatment with t-PA and DNase improved the drainage of infected fluid in patients with pleural infection. Each of the agents alone was ineffective. The reduction in the infected pleural fluid collection was approximately doubled with the use of the combination therapy (with clearing of approximately 30% of the ipsilateral hemithorax volume and approximately a 60% reduction in the baseline pleural collection). This new treatment effect was not associated with an excess of adverse events.

In addition to the drainage benefit, t-PA–DNase therapy may improve the natural history of pleural infection. The group of patients receiving the combination treatment had 77% fewer referrals for thoracic surgery and a 6.7-day reduction in the hospital stay, as compared with the patients receiving placebo. Larger studies are needed to assess this benefit more precisely.

No drainage benefit was seen with either t-PA alone or DNase alone (Fig. 2). This result supports data from the MIST1 trial,[9] which remain a source of clinical debate.[44-48] It is unclear why fibrinolytic agents do not appear to be helpful in patients with extensive deposition of fibrin in the pleural space.[49-51] This lack of efficacy suggests that free DNA cleavage is necessary to reduce fluid viscosity and permit pleural clearance by fibrinolytic drugs. A similar treatment combination has been shown to be helpful in other diseases.[52-54] The current trial somewhat clarifies this debate by showing that the use of a different fibrinolytic agent (i.e., t-PA rather than streptokinase) and the additional cleavage of uncoiled DNA by DNase may have allowed fibrinolytic treatment to work. This observation is consistent with in vitro studies[33,34] and an animal model[35] of pleural infection, which show that free DNA cleavage is necessary to reduce fluid viscosity and permit pleural clearance by fibrinolytic drugs. Thus, our results are consistent with the MIST1 results and suggest a new therapeutic strategy for this disease.

DNase monotherapy was ineffective in improving pleural drainage and was associated with an increase in surgical referrals by a factor of 3. Independent review of the indications for surgery indicated that this was due to clinical evidence of worsening infection. We hypothesize that this deterioration may be due to systemic absorption of bacterial or inflammatory components after DNase-mediated biofilm disruption in a pleural space with ineffective drainage due to undisrupted fibrinous septations. Whatever the mechanism, our study shows that DNase monotherapy pro-

Table 3. Serious and Nonserious Adverse Events at the Time of Hospital Discharge.*

Type of Adverse Event	t-PA (N=52)	DNase (N=51)	t-PA–DNase (N=52)	Placebo (N=55)	P Value
			no. of patients (%)		
Serious	0	2 (4)	3 (6)	1 (2)	0.22 by Fisher's exact test
Nonserious	7 (13)	8 (16)	9 (17)	6 (11)	0.80 by chi-square test (χ^2 [3 df]=1.0)

* The 6 serious adverse events included 2 intrapleural hemorrhages (both in the t-PA–DNase group), 1 episode of hemoptysis (in the t-PA–DNase group), 2 episodes of gastrointestinal bleeding (both in the DNase group), and 1 clinical deterioration (in the placebo group). The 30 nonserious adverse events included chest pain at the drainage site during study-drug administration (14 cases: 2 with placebo, 3 with t-PA, 3 with DNase, and 6 with t-PA–DNase; P=0.54 by Fisher's exact test), nausea (5 cases: 3 with placebo, 1 with DNase, and 1 with t-PA), transient confusion (4 cases: 2 with placebo, 1 with t-PA–DNase, and 1 with DNase), and erythema or rash (3 cases: 2 with t-PA–DNase and 1 with DNase).

vides no fluid-drainage benefit and significantly increases the need for surgery, and it should therefore be avoided.

The area of the pleural effusion was reduced by 17% from baseline in the placebo group in this study. This finding underscores the need for placebo-controlled trials to establish the efficacy of intrapleural adjuvant therapies in patients with pleural infection, since in the absence of a robust trial design, we cannot assume that radiographic improvements from baseline are true treatment effects.

Our trial shows that combination intrapleural t-PA and DNase therapy improves the drainage of pleural fluid in patients with pleural infection and that such treatment is associated with reductions in the hospital stay and the need for thoracic surgery that are likely to be clinically significant. This combined treatment may therefore be useful in patients in whom standard medical management has failed and thoracic surgery is not a treatment option. However, appropriate trials are needed to accurately define the treatment effects. If confirmed in further studies, our results will inform the choice of intrapleural adjuvant therapy for pleural infection and improve the management of this disorder.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

This article is dedicated to the memory of Prof. Robert J.O. Davies, M.D.

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