

Intrapleural fibrinolytic therapy for pleural infections: Outcomes from a cohort study

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ABSTRACT

Introduction: Pleural infections are a significant cause of mortality. Intrapleural fibrinolytic therapy (IPFT) utilising alteplase and dornase is a treatment option for patients unsuitable for surgery. The optimal dose of alteplase is unknown, and factors affecting treatment success in an Asian population are unclear. We sought to determine the factors affecting treatment success in Tan Tock Seng Hospital, Singapore and evaluate the efficacy of lower doses of IPFT.

Method: A retrospective analysis of patients with pleural infections treated with IPFT between July 2016 and November 2023 was performed. Treatment success was defined as survival without surgery at 3 months. Data, including patient demographics; comorbidities; RAPID (renal, age, purulence, infection source and dietary factor) scores; and radiological characteristics, were extracted from medical records and analysed. Linear mixed effects model and logistic regression were performed to determine factors affecting treatment success.

Results: A total of 131 cases were analysed. Of these, 51 (38.9%) reported positive pleural fluid culture, and the most common organism was *Streptococcus anginosus*. Mean age was 65 years (standard deviation [SD] 15.5). Mean time from chest tube insertion to first dose of IPFT was 10.2 days (SD 11.5). Median starting dose of alteplase was 5 mg. Treatment success was reported in 112 cases (85.5%). There were no significant differences between the alteplase dose and radiological clearance. Patient age (odds ratio [OR] 0.94, confidence interval [CI] 0.89–0.98) and interval between chest tube insertion to first dose (OR 0.95, CI 0.91–0.99) were statistically significant variables for the treatment success.

Conclusion: Lower starting doses of alteplase remain effective in the treatment of pleural infection. Early IPFT may result in better outcomes.

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Keywords: biostatistics, infectious diseases, pneumonia, pulmonary, respiratory medicine

CLINICAL IMPACT

What is New

- This study examined the use of intrapleural fibrinolytic therapy (IPFT) in an Asian cohort with a mean age that is older than that investigated in prior studies.
- IPFT remains effective for pleural infections even with lower alteplase doses.

Clinical Implications

- Early initiation of IPFT is associated with better outcomes, and efforts should be taken to minimise any delay.
- Lower doses of alteplase may be preferred for patients with higher bleeding risk.

INTRODUCTION

Pleural infection, defined as bacterial infection and replication in the pleural space,¹ remains a significant cause of mortality.² Over 80,000 cases of pleural infection are diagnosed each year in the US and the UK.^{3,4} Data from East Asia suggest that the annual incidence of pleural infections is 8.4 to 9.6 per 100,000.⁵

Intrapleural fibrinolytic therapy (IPFT) is one of the treatment options for patients in whom surgery is contraindicated. The combination of alteplase (tPA) and dornase (DNase) was first studied in the Multicenter Intrapleural Sepsis Trial (MIST2), showing good treatment success in terms of clearance of pleural opacity on chest X-ray (CXR) and an overall reduction in hospital stay (10 mg tPA/5 mg DNase, twice a day).⁶ Subsequent open-label series of intrapleural tPA/DNase demonstrated

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treatment success rates of 84–93%, with the Alteplase Dose Assessment for Pleural Infection Therapy (ADAPT) project (5 mg tPA/5 mg DNase, BD) and ADAPT-2 (2.5 mg tPA/5 mg DNase, BD) trials demonstrating noninferiority in terms of treatment success with lower doses of alteplase.^{7–9}

However, the MIST2 is the only dosing regimen evaluated in a comparative randomised controlled trial, with drug doses selected empirically rather than through traditional dose-escalation studies. Information is limited on the pharmacokinetics when delivered into the pleural space and hence, the optimum dosing remains unknown. This has resulted in variations in dosing and regimes in real-world clinical practice. Furthermore, emerging evidence in anti-thrombotic therapies suggests that East Asians have a higher risk of bleeding compared with Caucasian counterparts. While the underlying mechanisms of this “East Asian paradox” are postulated to be complex and multifactorial, this has called for ethnicity-tailored strategies.¹⁰

In Tan Tock Seng Hospital (TTSH), Singapore, IPFT has been used with lower starting doses since the publication of both ADAPT and ADAPT-2 trials. These studies mostly involved a Caucasian population, with very little Asian representation. As such, we sought to perform a retrospective analysis of IPFT performed in TTSH to compare our cohort of patients to those from prior studies and determine if applying a similar dosing regimen in an Asian population yielded similar treatment outcomes. We also aimed to identify any potential factors affecting treatment success in our cohort of patients.

METHOD

We performed a retrospective analysis of all patients with pleural infections who underwent IPFT in TTSH between July 2016 and November 2023. Pleural infection was diagnosed based on clinical presentation, with supportive features on pleural fluid sampling—either one of (1) purulence macroscopically, (2) presence of bacteria by Gram staining or microbial culture or (3) pleural fluid pH ≤ 7.20 and/or glucose ≤ 3.0 mmol/L. Based on our institution protocol, IPFT may be considered if patients have no clinical improvement despite 12–24 hours of pleural drainage.

All patients were managed with tube thoracostomy and systemic antibiotics in accordance with guidelines and local practice. Referrals for surgical intervention were left to the discretion of the treating physician. The decision to administer, timing to initiate IPFT and initial dose of alteplase, was left to the treating physician. Dose escalation of alteplase was permitted at any time at the discretion of the attending physician.

The IPFT protocol of TTSH involves the sequential intrapleural administration of variable doses of alteplase (diluted in 30 mL normal saline) and 5 mg dornase alpha (diluted in 30 mL sterile water), twice a day over 72 hours (6 doses in total). Following the instillation of alteplase, the chest tube is flushed with normal saline and kept clamped for 45 minutes, before being left on free drainage for 45 minutes before instillation of the second drug. Blood tests, including full blood count and inflammatory markers as well as CXR, are monitored throughout the treatment duration.

Treatment success was defined as survival without the need for surgical intervention at the 3-month mark. Data extracted retrospectively from the medical records included patient demographics; comorbidities; Charlson comorbidity index (CCI); renal, age, purulence, infection source and dietary factors (RAPID) score; and pleural fluid studies and radiological characteristics. Two experienced respiratory physicians (GY and JW), measured radiographic variables including the presence of loculation on CXR, computed tomography (CT), pleural thickening >2 mm (measured in axial cut of the thickest pleural lining) and CXR scores as described in previous publications.⁶ Data on treatment details and outcomes as well as adverse events, including pleural bleeding and death during admission, were also recorded.

Statistical analysis was performed using STATA version 16 or higher (StataCorp, College Station, TX, US). For continuous or discrete variables, summary statistics (i.e. arithmetic mean, standard deviation [SD], median, minimum and maximum values) were presented, with counts and percentages presented for categorical variables.

The chi-square test was performed to determine the association between categorical variables. Fisher’s Exact test was applied in the case of small cell counts. Analysis of variance (ANOVA) was used to compare the continuous variables among alteplase dose groups.

For CXR scoring, we used an ANCOVA model to investigate the effect of alteplase dose on the change from baseline in CXR scoring at day 3, or day 6 or 7, and a linear mixed effects model to investigate the effect of alteplase dose on the change from baseline in CXR over time. This model included age, baseline CXR score as covariates, with alteplase dose group and day of CXR as factors. An unstructured covariance structure was used to model the covariance structure among visits.

For the primary outcome of treatment success and 3-month survival without requiring surgery, logistic regression was fitted with age and time to the insertion of chest tube to first dose of IPFT as

covariates, with the starting dose of alteplase as a factor. Odds ratio and the corresponding 95% confidence interval were presented. All the tests were based on a 2-sided 5% significance level.

The study was approved by the Domain Specific Review Board of the National Healthcare Group (2023/00830) and was conducted in accordance with the amended Declaration of Helsinki.

RESULTS

There were a total of 129 subjects, with 131 records due to 2 subjects having 2 admissions. Baseline characteristics, stratified across 4 groups according to first dose of alteplase, are provided in Table 1. The mean age was 65 years (SD 15.5), with 99 (76.7%) subjects being male. The median CCI was 2 (3 for males, 2 for females). Top comorbidities included hypertension (75/129, 58%), hyperlipidaemia (51/129, 39.7%) and diabetes mellitus (DM) (47/129, 36.6%).

Pleural infection characteristics

Pus was present in 16 cases (12.2%), while pleural fluid culture was positive in 51 cases (38.9%).

The most common organism was *Streptococcus anginosus*. Among those that had CT (129 cases), 89 (69%) had loculations, while only 39 of 131 cases (29.8%) demonstrated loculations on CXR. Pleural thickening >2 mm on CT was present in 96 cases (75.0%).

Management of pleural infections

The mean time from chest tube insertion to first dose of IPFT was 10.2 days (11.5 days). Table 2A summarises the pleural infection characteristics among our cases and management prior to IPFT.

The median starting dose of alteplase was 5 mg (0.5–10). Sixty-two cases (48.4%) received a starting dose of 5 mg, while 37 cases (28.6%) started with 2.5 mg and only 12 cases (9.5%) started with 10 mg. Doses less than 2.5 mg were initiated in 17 cases (13.5%). Dose escalation occurred in 23 cases (17.6%). The 6-dose regime was terminated in 37 cases (28.2%). Common reasons for this included chest tube dislodgement, concerns of broncho/alveolopleural fistula or bleeding and physician decision. Patients who had received higher starting doses of alteplase tended to have lower CCI

Table 1A. Baseline characteristics.

Variables	Alteplase dose (mg) ^a				P value ^b	Total ^c n=129
	<2.5 n=17	2.5 n=36	5 n=61	10 n=12		
Age					0.29	
Mean (SD)	69.5 (13.4)	67.1 (17.3)	62.8 (14.9)	62.6 (16.1)		65.1 (15.5)
Median (minimum, maximum)	69 (47, 95)	66.5 (19, 97)	62 (22, 89)	66 (30, 80)		66 (19, 97)
Sex, no. (%)					0.35	
Female	3 (17.7)	12 (33.3)	13 (21.3)	1 (8.3)		30 (23.3)
Male	14 (82.3)	24 (66.7)	48 (78.7)	11 (91.7)		99 (76.7)
BMI					0.18	
No.	17	32	51	9		112
Mean (SD)	23.2 (4.8)	20.3 (4.7)	22.2 (4.7)	20.6 (3.6)		21.6 (4.7)
Median (minimum, maximum)	22.6 (17.6, 36.2)	20.3 (13.2, 35.7)	21.4 (13.8, 36.2)	20.7 (16.1, 27.9)		21.1 (13.2, 36.2)
RAPID score					0.1	
Mean (SD)	4.2 (1.3)	3.5 (1.1)	3.4 (1.1)	3.5 (0.7)		3.5 (1.1)
Median (minimum, maximum)	4 (2, 6)	3 (2, 6)	3 (2, 6)	3 (3, 5)		3 (2, 6)

BMI: body mass index; RAPID score: renal, age, purulence, infection source and dietary factor; SD: standard deviation

^a Three subjects had no record of alteplase dose.

^b P value was obtained using one-way analysis of variance or Fisher’s Exact test (sex).

^c All 129 subjects were included.

Table 1B. Comorbidities.

Variables	Alteplase dose (mg) ^a				P value	Total ^b
	<2.5	2.5	5	10		
Hypertension, no. (%)					0.07	
Yes	14 (82.3)	22 (61.1)	30 (49.2)	6 (50)		75 (58.1)
No	3 (17.6)	14 (38.9)	31 (50.8)	6 (50)		54 (41.9)
Hyperlipidaemia, no. (%)					0.002	
Yes	14 (82.3)	13 (36.1)	20 (32.8)	4 (33.3)		51 (39.5)
No	3 (17.6)	23 (63.9)	41 (67.2)	8 (66.6)		78 (60.5)
DM, no. (%)					0.03	
Yes	12 (70.6)	10 (27.8)	21 (34.4)	4 (33.3)		47 (36.4)
No	5 (29.4)	26 (72.2)	40 (65.6)	8 (66.7)		82 (63.6)
CKD, no. (%)					0.003	
Yes	7 (41.2)	5 (13.9)	4 (6.6)	3 (25)		19 (14.7)
No	10 (58.8)	31 (86.1)	57 (93.4)	9 (75)		110 (85.3)
ESRF; patients on dialysis, no. (%)					0.03	
Yes	3 (17.6)	4 (11.1)	1 (1.6)	0		8 (6.2)
No	14 (82.4)	32 (88.9)	61 (98.4)	12		121 (93.8)
Anaemia, no. (%)					0.02	
Yes	8 (47.1)	9 (25.0)	8 (13.1)	3 (25.0)		29 (22.5)
No	9 (52.9)	27 (75.0)	53 (86.9)	9 (75.0)		100 (77.5)
CCI score, no. (%)					0.0001	
Mean (SD)	6.4 (3.7)	3.3 (3.2)	2.6 (2.4)	3 (3.1)		3.3 (3.1)
Median (minimum, maximum)	7 (0, 13)	2.5 (0, 12)	2 (0, 8)	1.5 (0, 10)		2 (0, 13)

CCI: Charlson comorbidity index; CKD: chronic kidney disease; DM: diabetes mellitus; ESRF: end-stage renal failure; SD: standard deviation

^a Three subjects had no record of alteplase dose.

^b All 129 subjects were included.

($P=0.0001$). Using Fisher's Exact test, patients with comorbidities of anaemia ($P=0.02$), chronic kidney disease (CKD) ($P=0.003$), end-stage renal failure (ESRF) ($P=0.03$), hyperlipidaemia ($P=0.002$) and DM ($P=0.03$) tended to receive lower doses of alteplase. Table 2B summarises the use of IPFT in our cohort of patients, and Fig. 1 depicts the distribution of alteplase starting doses.

Outcomes

Treatment success was achieved in 112 cases (85.5%). The CXR score at baseline, day 3 and day 6 or 7, stratified according to alteplase dose, is presented in Fig. 2. The median area of hemithorax

occupied by pleural opacity reduced from 27% (2–100%) to 10% (0.2–100%). A linear mixed effects model did not suggest any significant differences between the alteplase dose and change in CXR score (Fig. 2).

One subject had a length of stay (LoS) of 438 days and was excluded from analysis. The remaining cases are represented in Fig. 3. A one-way ANOVA model was used to compare LoS based on different alteplase doses. There was a statistically significant difference among alteplase dose levels in LoS ($P=0.003$). LoS in the group with alteplase dose less than 2.5 mg (mean 58.7 days, SD 35.8) was significantly longer than in the 5 mg (mean

Table 2A. Pleural infection characteristics and management prior to IPFT.

Variables	Alteplase dose (mg)				Total
	<2.5 n=17	2.5 n=37	5 n=62	10 n=12	
Baseline CXR loculation, no. (%)					
Yes	4 (23.5)	14 (37.8)	16 (25.8)	4 (33.3)	39 (29.8)
No	13 (76.5)	23 (62.2)	46 (74.2)	8 (66.7)	92 (70.2)
Loculations on CT, no. (%)					
Yes	9 (52.9)	23 (65.7)	48 (77.4)	7 (58.3)	89 (69)
No	8 (47.1)	12 (34.3)	14 (22.6)	5 (41.7)	40 (31)
Pleural thickening >2 mm, no. (%)					
Yes	13 (76.5)	24 (68.6)	46 (75.4)	12 (100)	96 (75)
No	4 (23.5)	11 (31.4)	15 (24.6)	0	32 (25)
Time from chest tube insertion to first dose (days)					
Mean (SD)	13 (8.3)	12.6 (13.8)	8.5 (11.5)	8.3 (7.4)	10.2 (11.5)
Median (minimum, maximum)	10.5 (2, 27)	7 (1, 60)	5 (1, 67)	6 (1, 21)	6.5 (1, 67)

CXR: chest X-ray; CT: computed tomography; SD: standard deviation

Table 2B. Description of IPFT use.

Variables	Alteplase dose (mg)				Total
	<2.5	2.5	5	10	
No. of doses					
Mean (SD)	5.5 (2.0)	5.6 (1.4)	5.4 (1.9)	4.8 (1.9)	5.4 (1.8)
Median (minimum, maximum)	6 (1, 9)	6 (1, 8)	6 (1, 13)	6 (1, 6)	6 (1, 13)
Dose escalation, no. (%)					
Yes	7 (41.2)	6 (16.2)	10 (16.1)	0	23 (17.6)
No	10 (58.8)	31 (83.8)	52 (83.9)	12 (100)	108 (82.4)
Cessation of regime, no. (%)					
Yes	7 (41.2)	6 (16.2)	19 (30.6)	5 (41.7)	37 (28.2)
No	10 (58.8)	31 (83.8)	43 (69.4)	7 (58.3)	94 (71.8)

IPFT: intrapleural fibrinolytic therapy;
SD: standard deviation

29.9 days, SD 25.4) or 10 mg group (mean 26.6 days, SD 1.5).

Logistic regression showed that age and interval between chest tube insertion to first dose were statistically significant variables for the primary outcome of treatment success. With 1 unit increase in time of insertion to first dose, the odds of 3-month survival decrease by 5% ($P=0.014$). With 1

year increase in age, the odds of 3-month survival decrease by 6% ($P=0.01$). Alteplase dosing was not significant in predicting treatment success in this model (Table 3).

With regard to adverse events, there was a low incidence of pleural bleeding (8/131, 6.1%). Incidence of pain post-IPFT was not accurately recorded and hence not reported. There were no allergic reactions

Fig. 1. Distribution of alteplase starting doses.

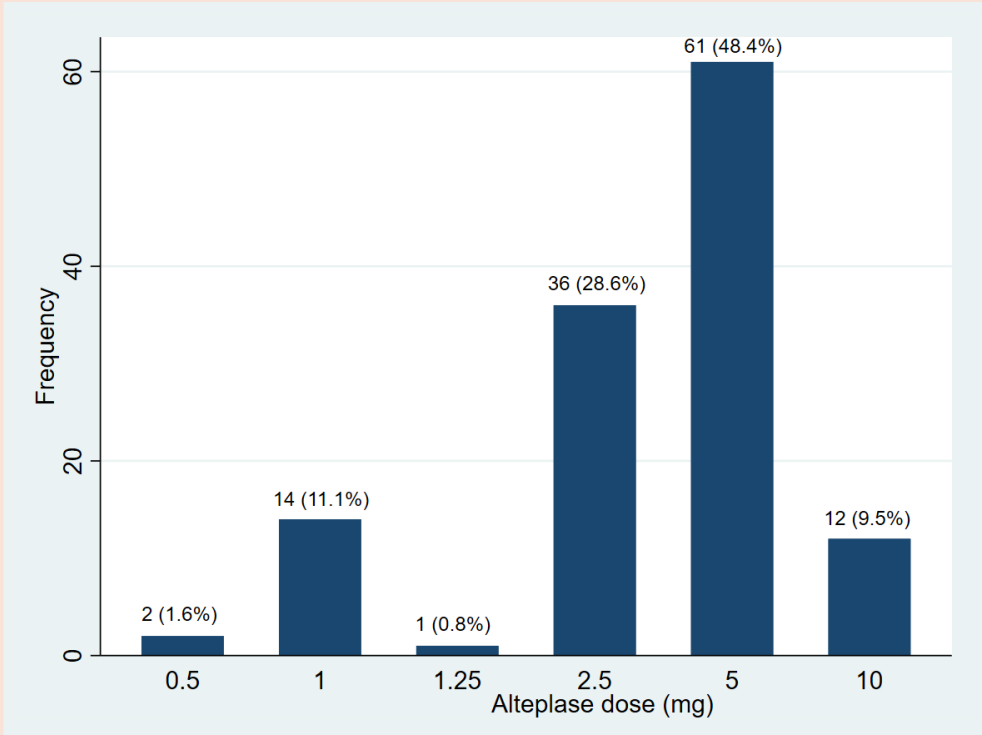
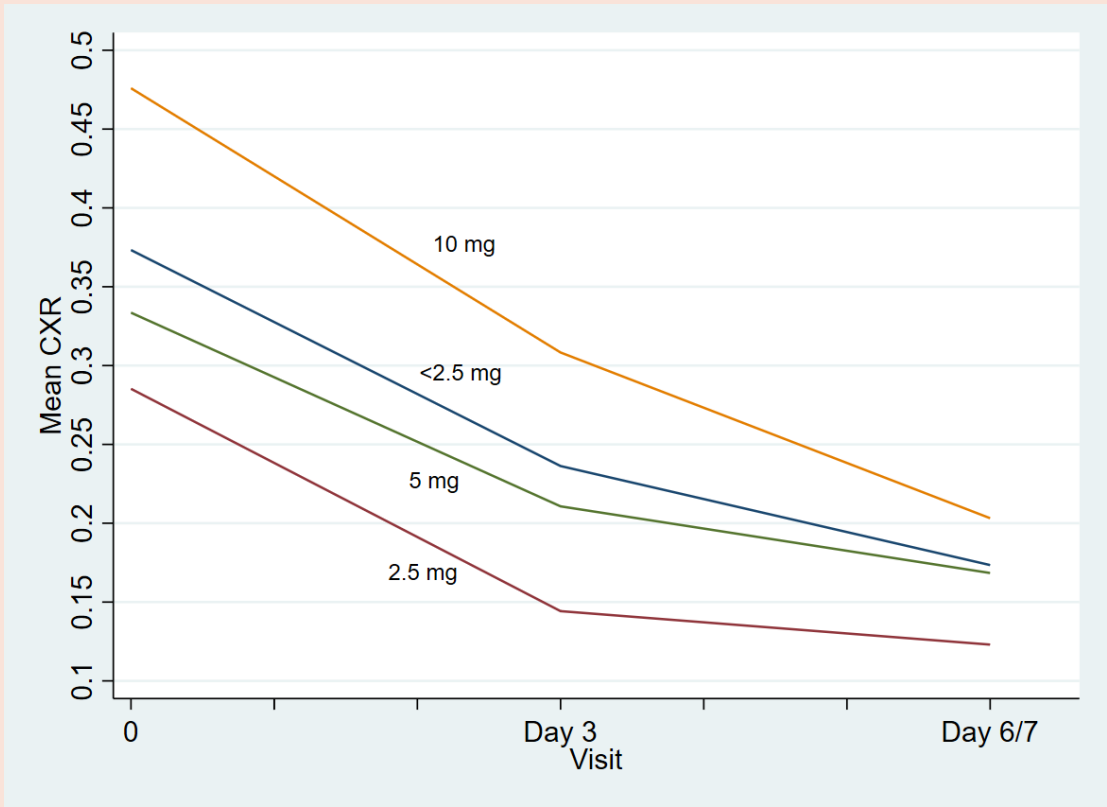
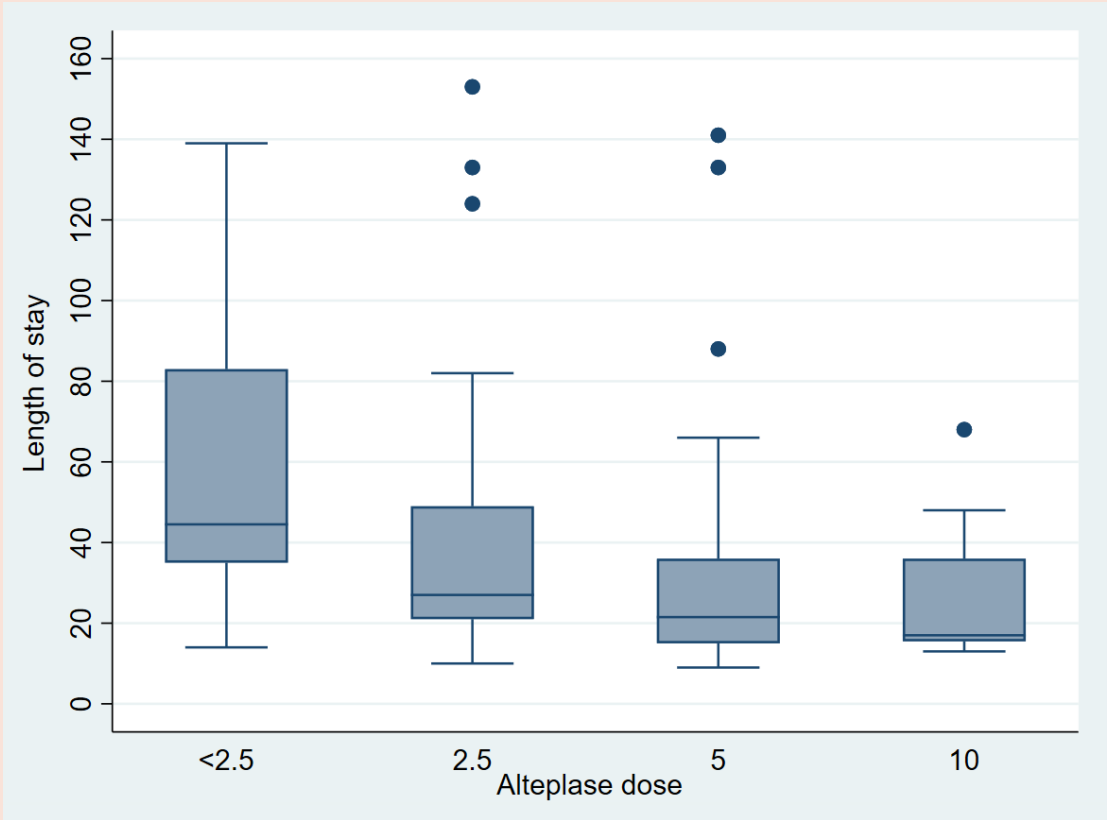


Fig. 2. Improvement in chest X-ray score across alteplase doses.



CXR: chest X-ray

Fig. 3. Hospital length of stay across alteplase doses.



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Table 3. Logistic regression.

Parameter	OR	95% CI	P value
Age	0.94	(0.89, 0.98)	0.01
Time of chest tube insertion to first IPFT dose	0.95	(0.91, 0.99)	0.014
Alteplase dose (mg)			
2.5 vs <2.5	4.44	(0.79, 24.91)	0.09
5 vs <2.5	1.53	(0.37, 6.30)	0.56
10 vs <2.5	2.94	(0.26, 32.93)	0.38

CI: confidence interval; IPFT: intrapleural fibrinolytic therapy; OR: odds ratio

to IPFT. Mortality rate during admission was 12.2%, with 3-month and 6-month mortality rates being 13.0% and 16.8%, respectively.

DISCUSSION

IPFT has gained acceptance as an alternative treatment to surgery for pleural infection, following the seminal MIST2 trial.⁶ While there have been multiple subsequent studies demonstrating similar efficacy with lower doses of alteplase, the current dosing regimen suggested in guidelines (10 mg

tPA/5 mg DNase) are weak recommendations or good practice points based on the MIST2 trial.¹¹ This retrospective study evaluated the real-life application of IPFT in patients with pleural infections in an Asian cohort, with selection of alteplase doses adjusted according to the patient’s profile. Our treatment success rate of 85.5% remains comparable to prior studies published despite a trend towards lower doses of alteplase. This continues to add to the body of evidence that IPFT remains effective in the treatment of pleural infection, and

that treatment success can be achieved with lower doses than originally used in the MIST2 trial.

The median starting dose of alteplase was 5 mg in our cohort, and majority (48.8%) of our patients had received this starting dose. Patients who had received lower doses tended to have more comorbidities, such as anaemia, CKD and ESRF. This could reflect the conscious effort by clinicians to balance the perceived increased bleeding risks against efficacy. Interestingly, Akulian et al. found that a dose-reduction strategy (10 mg vs 5 mg alteplase) was not associated with a significant reduction in bleeding risks. However, serum urea level was found to be a significant independent predictor of bleeding, and patients with ESRF who had received a full dose regime tended to have an increased incidence of bleeding.¹²

When assessing the degree of CXR clearance, our study demonstrated similar rates of improvement in CXR opacity from baseline to the end of IPFT regardless of starting doses. While significant radiological improvements have been consistently demonstrated with IPFT use, prior studies have not compared the differences in CXR clearance stratified to alteplase doses. In addition, studies have consistently used a similar composite endpoint to define treatment success, which has not included the degree of radiological improvement on CXR. Studies have also demonstrated continued improvement in CXR clearance at day 30 from IPFT initiation.⁷ Whether there is correlation between radiological improvement following IPFT and treatment outcomes or extent of CXR clearance to predict treatment success is unclear. It is possible that the degree of CXR clearance in isolation during the IPFT regimen itself has limited sensitivity in determining treatment success. Managing physicians should exercise caution not to administer IPFT for the purpose of achieving radiological resolution in isolation.

Notably, our study showed a lack of association between the starting dose of alteplase and treatment outcomes. Being a retrospective study, definitive conclusions cannot be drawn in the absence of head-to-head comparisons across the various doses while controlling for confounding variables. Nonetheless, the consistent signal of high treatment success rates across the MIST2 trial, subsequent dose de-escalation series (ADAPT, ADAPT-2) and as reflected in our current study strengthens the evidence of its use in pleural infections, though it also reinforces the need for further studies to evaluate the optimal dosing of alteplase.

The LoS for patients with lower starting doses of alteplase was longer compared to higher starting doses. Despite this, our results showed that there

was no difference in treatment success across various alteplase starting doses. We postulate that the longer LoS may have been confounded by other factors, such as patient comorbidities (higher CCI, $P=0.0001$) (Table 1B).

Age remains a key factor when discussing pleural infections. Although our cohort was generally older compared to that investigated in prior studies, with a mean age of 65.1 years (MIST2 59 years,⁶ Piccolo et al. 55.7 years,⁹ Mehta et al. 54.6 years,¹³ ADAPT 57 years,⁸ ADAPT2 61 years⁷), treatment success was similar. However, an increasing age was also shown to reduce the odds of survival in our cohort of patients. Scoring systems, such as the RAPID score,¹⁴ reflect the significance of age.

Our study also showed that there were fewer patients with positive pleural cultures (38.9%). This was similar to another Singapore study, which showed a 40% positive pleural culture rate in patients with complicated pleural infections.¹⁵ The lower culture positivity in our study compared to other international cohorts deserves further investigation.

Significantly, our study revealed that our cohort of patients had a relatively long interval between chest tube insertion and first dose of IPFT. This delay may have been contributed by physician preference, waiting times for CT imaging, delays while awaiting surgical assessments and in certain cases, interventions to adjust chest drain positions or obtain additional drains. These may have been further confounded by disease complexity. The 2023 British Thoracic Society Guideline for pleural disease recommends a review of patients' clinical progress at 48 hours before considering IPFT for those with poor clinical progress. Delays in obtaining source control and evacuating the pleural space may worsen the underlying pleural sepsis, and lead to progression to a more organised stage, portending worse outcomes. With logistic regression demonstrating reduced odds of survival with every delay in initiating IPFT, our mean time of 10.2 days between chest tube insertion and first dose of IPFT, earlier recognition of inadequate pleural drainage following tube thoracostomy alone should alert the clinician to expedite the administration of IPFT when treating pleural infections.

The bleeding risk of 6.1% in our study is low and comparable to larger international studies (e.g. Akulian et al. 4.1%). Another retrospective study conducted in Singapore by Goh et al. also reported a similar 6.7% incidence of pleural bleeding.¹⁴ The suggestion that lower dosages may lead to fewer adverse events seems plausible, but it is noteworthy that a dose-response relationship between alteplase dose and bleeding risk has not been demonstrated

in large multicentre retrospective studies.¹¹ On the contrary, our findings suggest that dose selection is influenced by patient comorbidities, and further work to refine this approach could provide more insights into dosing alteplase.

This study has its limitations. First, it is a retrospective study, with no direct head-to-head comparison between doses of alteplase. The confines of an observational study, including the lack of randomisation, blinding or inability to control for confounding variables in clinical practice or adherence to protocol, may have inadvertently affected clinical outcomes. Significantly, the publication of dose de-escalation studies may have inadvertently influenced physicians' decisions on the starting dose of alteplase. It is noteworthy that the tPA-DNase arm in the MIST2 trial had a compliance rate of 66.7%, while 36% of patients in the ADAPT study had early treatment discontinuation due to clinical improvement, and the median number of doses in the ADAPT-2 trial was 5. Additionally, 11.5% and 24.6% of patients in the ADAPT and ADAPT-2 studies respectively received dose escalations during the entire course of their treatment. These underscore the challenges and complexities of managing pleural infections, which may be even more unpredictable in a real-world setting such as in this study. A more nuanced management strategy over a protocolised treatment regimen may be preferred when managing pleural infections.

Second, in this real-world application of IPFT, patient outcomes may have been affected by factors separate to the IPFT regime received. These include the factors demonstrated to be significant predictors for treatment success such as age, time interval to receiving IPFT, as well as other potential confounders due to heterogeneity in the management of pleural infections, such as comorbidities, severity of illness and decisions involving end-of-life discussions (especially relevant given the older population compared to other studies). The cause of death was not recorded, limiting any interpretation of the mortality data. Therefore, it may be challenging to ascribe any success or failure of treatment to the IPFT regime itself.

CONCLUSION

IPFT regimes utilising lower starting doses of alteplase remain effective in the treatment of pleural infection. Early initiation of IPFT should be considered for all suitable patients, as this affects survival. The usage of IPFT remains relevant in an ageing population where surgical management may be contraindicated. In patients with comorbidities that increase bleeding risks, starting with lower

doses of alteplase should be considered, with the option of increasing doses subsequently. While the optimal dose has not been determined in prospective studies, there appears to be increasing evidence for lower starting doses of alteplase and a trend towards personalised dosing. Considering the mechanism of action of IPFT within the infected pleural space, additional studies on the physiological effects of IPFT on lung function post-recovery may further validate its potential as an alternative to surgical intervention.

Ethics statement

This study was approved by the Domain Specific Review Board of the National Healthcare Group (2023/00830) and was conducted in accordance with the amended Declaration of Helsinki.

Declaration

The authors declare there are no affiliations with or involvement in any organisation or entity with any financial interest in the subject matter or materials discussed in this manuscript. No generative artificial intelligence (AI) or AI-assisted technologies were used.

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