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Intrapleural Fibrinolytics and Deoxyribonuclease for Treatment of Indwelling Pleural Catheter-Related Pleural Infection: A Multi-Center Observational Study

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Keywords

Catheter-related infections · Empyema · Fibrinolytic agents · Pleural diseases · Thoracic surgery · Video-assisted

Abstract

Background: Indwelling pleural catheters (IPC) are increasingly used for management of recurrent (especially malignant) effusions. Pleural infection associated with IPC use remains a concern. Intrapleural therapy with tissue plasminogen activator (tPA) and deoxyribonuclease (DNase) significantly reduces surgical referrals in non-IPC pleural infection, but data on its use in IPC-related pleural infection are scarce. ***Objective:*** To assess the safety and efficacy of intrapleural tPA and DNase in IPC-related pleural infection. ***Methods:*** Patients with IPC-related pleural infection who received intrapleural tPA/DNase in five Australian and UK centers were identified from prospective databases. Outcomes on *feasibility* of intrapleural tPA/DNase delivery, its *efficacy* and *safety* were recorded. ***Results:*** Thirty-nine IPC-related pleural infections (predominantly *Staphylococcus aureus* and gram-negative organisms) were treated in 38 patients; 87% had malignant effusions. In total, 195 doses (median 6 [IQR = 3–6]/patient) of tPA (2.5 mg–10 mg) and DNase (5 mg) were instilled. Most (94%) doses were delivered via IPCs using local protocols for non-IPC pleural infections. The mean volume of pleural fluid drained during the first 72 h of treatment was 3,073 (SD = 1,685) mL. Most (82%) patients were successfully treated and survived to hospital discharge without surgery; 7 required additional chest tubes or therapeutic aspiration. Three patients required thoracoscopic surgery. Pleurodesis developed post-infection in 23/32 of successfully treated patients. No major morbidity/mortality was associated with tPA/DNase. Four patients received blood

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transfusions; none had systemic or significant pleural bleeding. ***Conclusion:*** Treatment of IPC-related pleural infection with intrapleural tPA/DNase instillations via the IPC appears feasible and safe, usually without additional drainage procedures or surgery. Pleurodesis post-infection is common.

Introduction

Pleural effusion can cause breathlessness that is debilitating and impairs quality of life. Indwelling pleural catheter (IPC) has been proven to be a useful option for management of malignant pleural effusion (MPE) and a suitable first-line intervention in recent MPE guidelines [1]. IPC has also been used for management of refractory benign effusions [2] and selected cases of chronic empyema [3]. Despite the increasing use of IPC, concerns regarding IPC-related pleural infection remain and limit its uptake.

Pleural infection is associated with high morbidity and mortality [4–8]. When infected, the pleural tissue and fluid act as a reservoir for bacteria to multiply and fuel ongoing sepsis. Drainage of the infected pleural fluid is usually required. This approach alone routinely fails in approximately 15% and up to 50% of patients are referred for surgery [4–6, 9, 10]. Combined intrapleural therapy with tissue-plasminogen activator (tPA) and deoxyribonuclease represents a major advance in pleural infection management and significantly reduces surgical referrals [6, 11]. Ongoing research focuses on optimizing the dosing regimen (e.g., de-escalation studies of tPA) of the intrapleural therapy, to increase safety and ease of administration [12, 13].

IPC-related pleural infection is a new entity and is a recognized complication in 2–12% of patients fitted with an IPC [14–17]. Typically, the effusion becomes loculated and fails to drain. Evacuation of the infected fluid is pertinent to avoid ongoing sepsis and, rarely, death. Most patients managed with IPC have advanced malignancies, are frail from multiple comorbidities and are not ideal candidates for surgery. An effective non-invasive treatment option, such as intrapleural tPA/DNase therapy, would be of particular benefit to this cohort.

Published series to date on the use of tPA/DNase included mainly patients with community-acquired pleural infection without underlying pleural diseases. IPC-related pleural infection presents a very different setting. First, patients with non-IPC pleural infection require insertion of a conventional chest drain through which tPA and DNase are delivered. IPC has been classically considered a one-way drainage device but has potential to be utilized for intrapleural drug (e.g., tPA/DNase) delivery in IPC-related pleural infection although this has not been formally evaluated. Second, patients treated with IPC typically have underlying pleural cancers with a complex pleural environment (including tissue thickening and tumor adhesion/septations) and non-expandable lung is common. Whether tPA/DNase is effective in this setting remains to be tested. Third, interaction between tPA/DNase and the pathological (especially malignant) pleural tissues may pose a different adverse event profile.

Administration of tPA/DNase via IPC to treat IPC-related infection, if effective, could present a new management for this cohort and alleviate the need for surgery. This multicenter retrospective observational review is the first to interrogate the outcomes of tPA/DNase therapy in IPC-related pleural infection focusing particularly on its *feasibility*, *efficacy*, and *safety*.

Materials and Methods

An invitation to submit data was sent to 12 centers with known expertise in pleural disease and IPC management. Five centers in Australia (Sir Charles Gairdner Hospital) and the UK (Guys and St Thomas', Southmead, Oxford Radcliffe and Queen Elizabeth University Hospitals) agreed to take part, all with local ethical approval (online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/0005514643). Individual centers identified cases from prospective databases over available periods (online suppl. Table 1).

IPCs inserted for both malignant and benign indications were included. IPC-related infection was defined as present if:

- the patient had clinical evidence compatible with infection (e.g., systemic inflammatory response, elevated inflammatory markers) *and*
- was treated by the attending team with antibiotics *and*
- at least one of the following features in their pleural fluid: fluid became purulent *or* was positive on bacterial culture *or* became loculated and failed to drain.

Patients with symptomatic loculated effusions (without the above evidence of infection) requiring fibrinolytics therapy were not included.

Data were collected regarding baseline patient demographics, clinical presentation at the time of infection, treatment details including starting dose of tPA/DNase (defined as the dose administered at the first instillation) and number of instillations, protocol utilized (e.g., timing of administration of each dose), antibiotics and therapeutic procedures, and outcomes including surgical referrals, duration of hospital stay and mortality. Laboratory investigations including markers of inflammation (white cell count and C-reactive protein), pleural fluid biochemistry and microbiological cultures were recorded where available. Chest x-ray (CXR) was graded for opacification as per Light et al. [18] as 0 (none), 1 (blunting of costophrenic angle), 2 (<25% of the hemithorax), 3 (25–50%), 4 (50–75%) and 5 (>75% of hemithorax).

Outcome Measures

Successful treatment was defined as survival to hospital discharge without the need for surgery as per our previous tPA/DNase studies [11]. The proportion of patients requiring a further intervention defined as therapeutic aspirate (>200 mL) or intercostal catheter insertion was recorded. IPC removal was documented as removed due to 1) persistent infection; 2) pleurodesis post-clearance of the infected pleural space; or 3) other reasons. Clinically relevant re-accumulation of pleural effusion, after removal of IPC, was defined by presence of pleural fluid on imaging *and* the need for pleural procedural intervention. CXR grade, blood leukocyte count and C-reactive protein were collected post-intervention where available.

Statistical analyses were performed using SPSS v.26 (IBM, Armonk, NY, USA). Descriptive statistics are presented as mean (SD), median [IQR] and percentages where appropriate. Paired samples were compared using a paired *t*-test or Wilcoxan signed-rank test and between groups comparisons were performed using two-tailed independent *t*-test or the Mann Whitney test depending on the normality of the distribution. Multiple group comparisons were performed using one-way ANOVA with Tukey's post hoc test or ANOVA on ranks followed by Dunn's post-hoc test. Correlations were assessed using the Pearson or Spearman method as appropriate. Survival analysis was performed by the Kaplan-Meier method. Significance was defined as $p < 0.05$.

Table 1. Baseline demographics of 39 IPC-related infection cases from 38 patients with a mean (SD) age of 67.2 (11.7) years

Demographics and characteristics	*n*	%
Gender, male	24	63.2
Side, right	24	63.2
ECOG		
0–1	28	73.6
2–3	8	21.1
Unknown	2	5.3
Medical comorbidities	38	100
Noncancer	30	78.9
Cancer	34	89.5
Diabetes	3	7.9
Chemotherapy at time of infection	5	12.8
Indication for IPC		
Malignant effusion (*n* = 34)	34	89.5
Mesothelioma	24	
Lung cancer	6	
Breast cancer	2	
Ovarian	2	
Nonmalignant effusion (*n* = 4)	4	10.5
Cardiac	3	
Chronic empyema	1	
Trapped lung	16	42.1

IPC, Indwelling pleural catheter.

Results

Baseline Characteristics

Thirty-nine IPC-related pleural infections in 38 patients (24 were male, mean age 67.2 (SD = 11.7) years) treated with intrapleural tPA/DNase were included (Table 1). Most IPCs (*n* = 33, 86.8%) were inserted for management of symptomatic malignant pleural effusion, at a median of 44 [IQR = 13-138] days following the diagnosis of MPE. Three IPCs were inserted for recurrent benign effusions (congestive heart failure) and two for chronic pleural infection (one with underlying mesothelioma associated with hydro-pneumothorax, which became infected while a short-term intercostal catheter was in situ). Non-expandable (trapped) lung was identified in 42.1% (*n* = 16) of patients at time of IPC insertion.

Presentation of IPC-Pleural Infection

IPC-related infection occurred at a median of 66 [IQR = 31–130] days post-insertion. Symptoms at admission with infection included fever (61.5%), dyspnea (56.4%), chest pain (38.5%) and lethargy (15.4%). Five (12.8%) patients were on chemotherapy at the time of presentation.

Appearance of the fluid had changed to purulent in 20 cases (51.3%) and 26 (66.7%) patients reported a decrease in IPC output. Most (28/39) cases presented with moderate-to-large effusion (>25% opacification of the hemi thorax on CXR) and represented an increase from their baseline post-IPC insertion.

The mean peripheral blood total leukocyte count was 12.5 (SD = 5.1) × 10^9/L and median C-reactive protein was 192 [IQR = 137–302] mg/L which represented a 54 and 640% increase from baseline respectively ($p < 0.0001$). Where matched pleural fluid biochemistry results at insertion and infection were available, changes were consistent with significant pleural inflammatory response (shown in Fig. 1).

Pleural Fluid Microbiology

Culture of pleural fluid was positive for microbes in most (*n* = 36, 92.3%) cases. Of the 42 cultured organisms, the most common were a variety of gram-negative bacilli (*n* = 21, 54%) and *Staphylococcus aureus* (*n* = 12, 31%) (Table 2). Three cases had polymicrobial infections. Both of the chronic empyema cases grew gram-negative organisms, though one was culture-negative by the time of treatment with tPA/DNase. The majority (32 of 39) of samples were aspirated from the IPC itself only. In 6 cases, a separate "clean" sample was taken via aspiration or a second chest drain, 4 of which were also culture-posi-

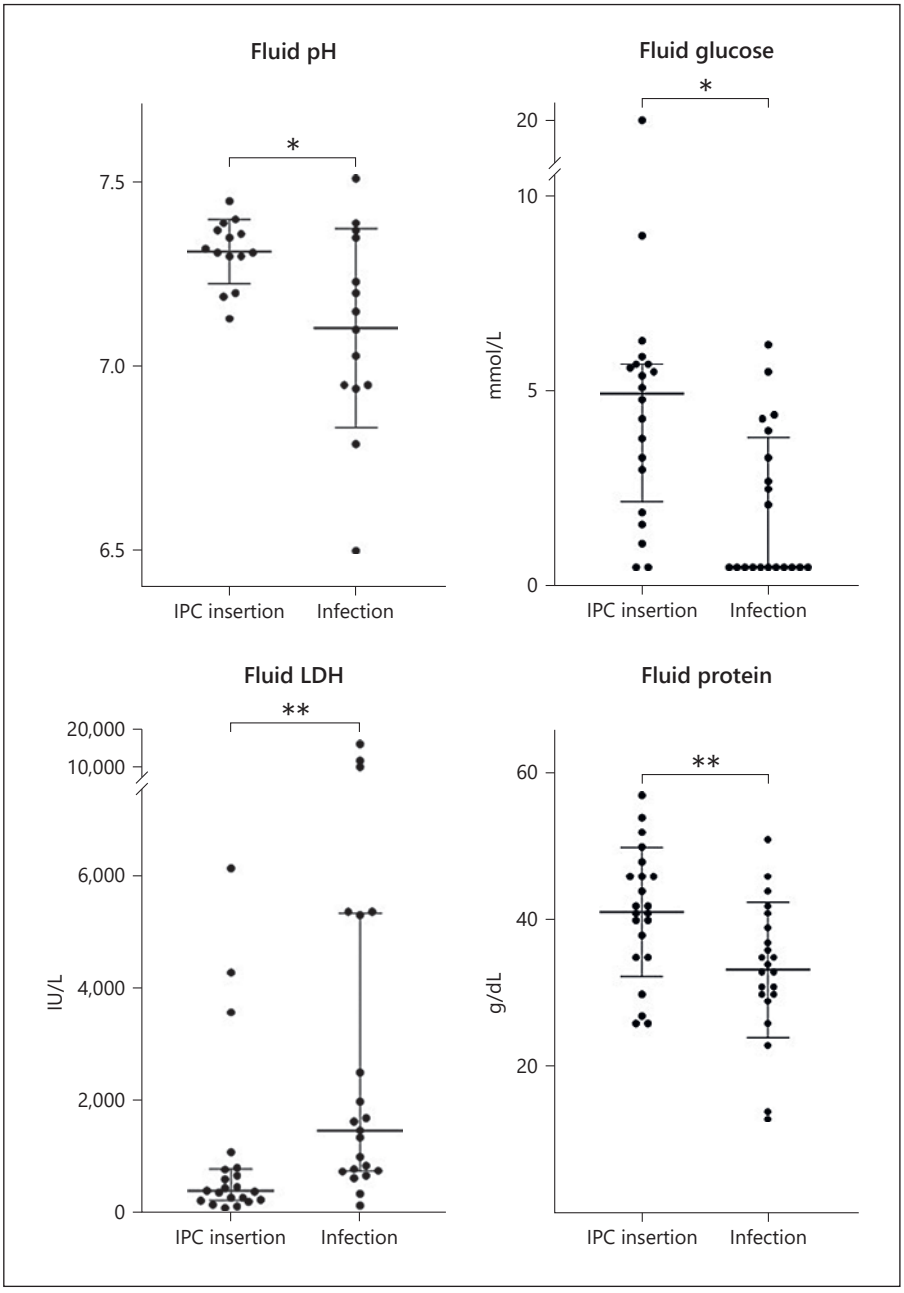

Fig. 1. Change in pleural fluid biochemistry from insertion of the IPC to time of presentation with IPC-related pleural infection. There was a significant decrease in pH (n = 14, mean 7.31 (SD = 0.1) vs. 7.1 (SD = 0.3), p = 0.015) and glucose (n = 20, median 4.95 [IQR = 3.53] vs. 0.5 [IQR = 3.33] mmol/L, p = 0.03) and rise in LDH (n = 21, median 395 [IQR = 559] vs. 1,470 [IQR = 4,585] IU/L, p = 0.005). Pleural fluid protein was decreased at the time of the infection (n = 22, mean 41.2 (SD 8.8) g/dL vs. 33.3 (SD = 9.2) g/dL, p = 0.003). (Paired t-test for parametric data and Wilcoxan signed-rank test for non-parametric data). These results are consistent with the presence of infection but can also be a consequence of progressive malignancy as seen in longitudinal IPC studies [24] *$p < 0.05$; **$p < 0.01$. IPC, indwelling pleural catheter.

tive. The two that were culture-negative were sampled after at least 72 h of intravenous antibiotics and had previously grown either abundant staphylococcus aureus or acinetobacter from the IPC.

Treatment Administered

Intrapleural tPA/DNase therapy was started at a median of 1 [IQR = 1–3] day after hospital admission for IPC-related pleural infection. All patients received DNase 5 mg in combination with tPA. The median number of doses of tPA was 6 [IQR = 3–6]. In total, 195 doses of tPA and DNase were instilled (184 via patients' IPCs) using local protocols for non-IPC pleural infections without need for modifications. The starting dose of tPA varied and was 10 mg in 12 (30.8%), 5 mg in 12 (30.8%) and 2.5 mg in 15 cases (38.5%). Higher subsequent doses of tPA were given to 6 patients (3 in each of those who started with 2.5 and 5 mg) due to inadequate response.

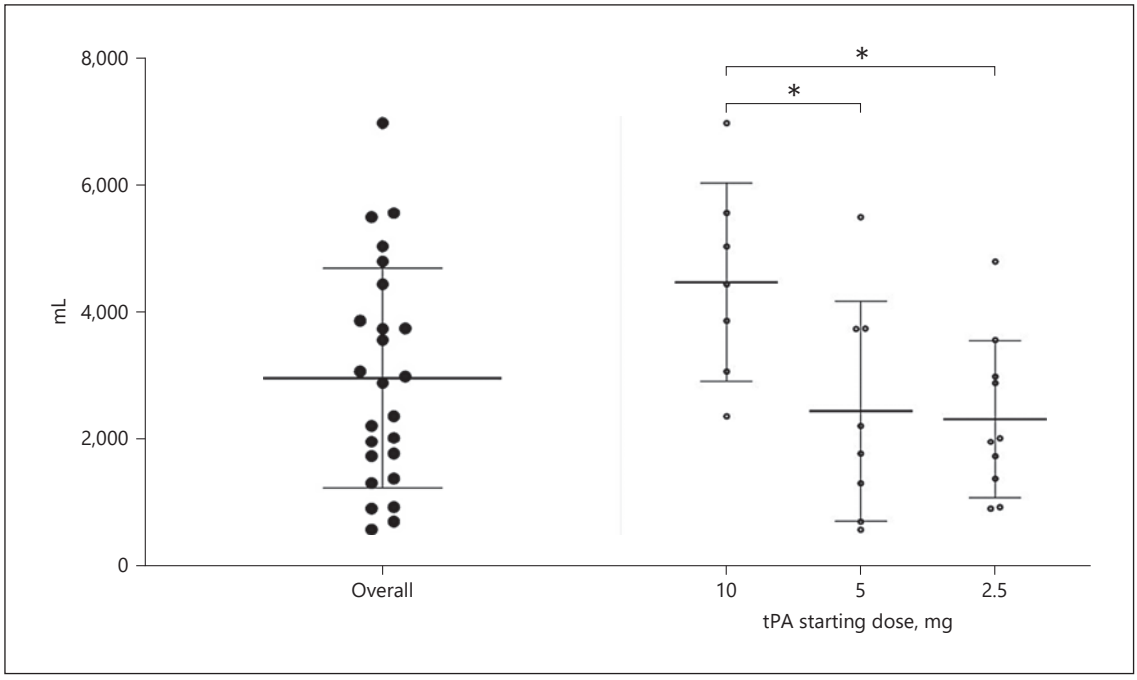

Fig. 2. Cumulative pleural fluid output over the 72 h post-initiation of tPA/DNase. The volume of fluid drained in the first 72 h was available in 25 patients (mean 3073 mL, SD = 1,685) and was significantly higher in those receiving a starting tPA dose of 10 mg. The total amount of tPA instilled was 60 mg [median, IQR = 60.0–60.0] in patients who received a starting dose of 10 mg (n = 7). This was significantly higher than the total amount of tPA of 30 mg [16.3–37.5] and 10 mg [5.0–18.8] given to the groups who received a starting tPA dose of 5 mg (n = 8) and 2.5 mg (n = 10), respectively ($p < 0.05$ for both).

The median total amount of tPA administered was 30 mg [IQR = 12.5–52.5] for the entire cohort. Patients who received a higher starting dose were more likely to receive a larger total amount of tPA. The median total amount of tPA instilled was 60 mg [IQR = 37.5–60.0], 30 mg [IQR = 22.5–30] and 12.5 mg [IQR = 5–15] in those started on 10, 5, and 2.5 mg of tPA respectively ($p < 0.001$, ANOVA on rank). There were no differences in leukocyte count or C-reactive protein levels at the time of infection among the 3 groups.

Apart from the variation in dosing, most participating units administered tPA/DNase therapy as per the protocol of the Multicentre Intrapleural Sepsis Trial (MIST)-2 and twice daily [6]. In brief, tPA was diluted in 30–50 mL of saline and instilled, after which the IPC was closed for 45–60 min. The catheter was then opened for drainage. DNase (diluted in 30–50 mL of saline) was then instilled followed by closing of the IPC for 45–60 min before allowing free drainage. Minor protocol alterations were adopted in some centers, such as simultaneous drug instillation.

Twenty-one cases (53.8%) received 6 doses of tPA/DNase. Fewer doses were administered in 16 cases, most

Table 2. Microbiology of organisms cultured from pleural fluid of IPC-related pleural infections

Category	Cultured organism	*n*
Gram-positive bacteria	*Staphylococcus aureus*	12
	Coagulase-negative staphylococci*	6
	Enterococcus	1
	Corynebacterium	1
	Propionobacterium	1
Gram-negative bacteria	*Pseudomonas* spp.*	8
	*Klebsiella**	3
	Escherichia coli	1
	*Enterobacter**	3
	Serratia	2
	Stenotrophomonas	1
	Acinetobacter	1
	*Citrobacter**	1
	Other (unspecified)	1
Total		42

IPC, Indwelling pleural catheter. * Organisms involved in polymicrobial infections.

commonly due to complete clearance of pleural fluid (n = 12). Additional doses were given in 2 cases. Seven (18.0%) patients required a second drainage procedure during the admission (6 small-bore chest tubes and 1 therapeutic aspiration), despite administration of tPA/DNase, due to loculated fluid distant from the IPC. Three of these received additional doses of tPA/DNase via the chest tube. There was no association between complications, length of hospitalization or duration of antibiotics and starting dose of tPA. Fluid output within the first 72 h was documented in 25 cases (mean 3073 mL, SD = 1,685) and was significantly higher in those receiving a starting tPA dose of 10 mg (shown in Fig. 2). The volume drained correlated with the total amount of tPA (mg) administered (r_s = 0.561, p = 0.004).

All but one patient received intravenous antibiotics, with piperacillin/tazobactam as the most common choice (51.3%); one patient received oral antibiotics only. Patients received a median of 31 [IQR = 22–41] days of antibiotics therapy including intravenous therapy for median 14 [IQR = 9–25] days.

Outcomes

Successful treatment, defined as survival to hospital discharge without surgery, was achieved in 32 (82.1%) cases (95%CI = 66.5–92.5%). Three patients underwent video-assisted thoracoscopic surgery (VATS) for ongoing infection; all of whom made a full recovery and were discharged. There were no differences in Outcomes between those with and without trapped lung. Median length of stay was 8 [IQR = 6–12] days.

Four (10.5%) patients died during the admission with pleural infection, including two for whom IPC was inserted for management of known chronic empyema. Those two patients (one with mesothelioma) received 3 doses of tPA/DNase but deteriorated despite appropriate treatment and were palliated. Another patient who died had advanced metastatic breast cancer and malignant effusion. During treatment for the IPC-infection, they developed malignant ascites causing obstructive nephropathy. Only one dose of tPA/DNase had been administered when active treatment was withdrawn on the basis of progressive and extensive malignancy. A 95-year-old patient with multiple comorbidities and a transudative cardiac failure effusion was treated with tPA/DNase (6 doses) but was ultimately palliated.

At the time of censoring, 89.7% had died. This included a further patient who, following successful treatment of the IPC-infection, died from cancer progression 25 days after initial presentation of infection. Overall median survival from the date of admission with IPC-infection was 247 (95%CI = 96–398) days. At follow up, white cell count, CRP and chest x-ray grading where available, were all reduced compared to presentation (shown in Fig. 3).

IPC was removed in 29 (74.4%) cases, most (n = 23) because of development of pleurodesis following resolution of the infection. Four were removed due to ongoing infection (persistent fever or elevated inflammatory markers), 2 of whom underwent VATS, and 2 catheters were removed due to blockage not alleviated by flushing, one of whom underwent VATS and the other had a new intercostal catheter via which tPA/DNase was administered. Seven patients had radiological evidence of re-accumulation during follow-up, of whom 4 underwent a repeat procedure: 1 had an attempted aspiration, 1 had an intercostal catheter insertion followed by talc pleurodesis and another had a chest tube for a recurrent/persistent pleural infection post-IPC removal. One patient had a new IPC inserted into the same pleural cavity upon fluid re-accumulation 118 days post-first admission with infection. The effusion was culture-negative at the time of IPC insertion but subsequently (10 weeks later) also became infected (and is included in this cohort).

Complications of tPA/DNase were uncommon and no systemic bleeding was documented. Four patients, one post-VATS, received a blood transfusion because of a decrease in hemoglobin (median drop 39 [IQR = 31–49] g/L) at a median of 1.5 [IQR = 0.8–2.3] days following the last dose of tPA, without hemodynamic compromise; all were successfully managed conservatively.

Discussion/Conclusion

This multi-center report, within the confines of its retrospective nature, provides the largest cohort data to date suggesting that intrapleural tPA/DNase therapy may be used successfully and safely for management of IPC-related pleural infection. Delivering tPA/DNase via the IPC was possible in most cases, negating the need for additional drain insertion for instillation of the drugs. All centers employ similar tPA/DNase regimens as for non-IPC pleural infection cases. The majority of patients showed clinical, biochemical and radiological improvement with tPA/DNase treatment, in conjunction with antibiotics, and did not require surgery. Complications associated with tPA/DNase use via IPC were few and readily manageable. Pleurodesis was common following an IPC-related pleural infection treated with tPA/DNase therapy and often allowed removal of the catheter.

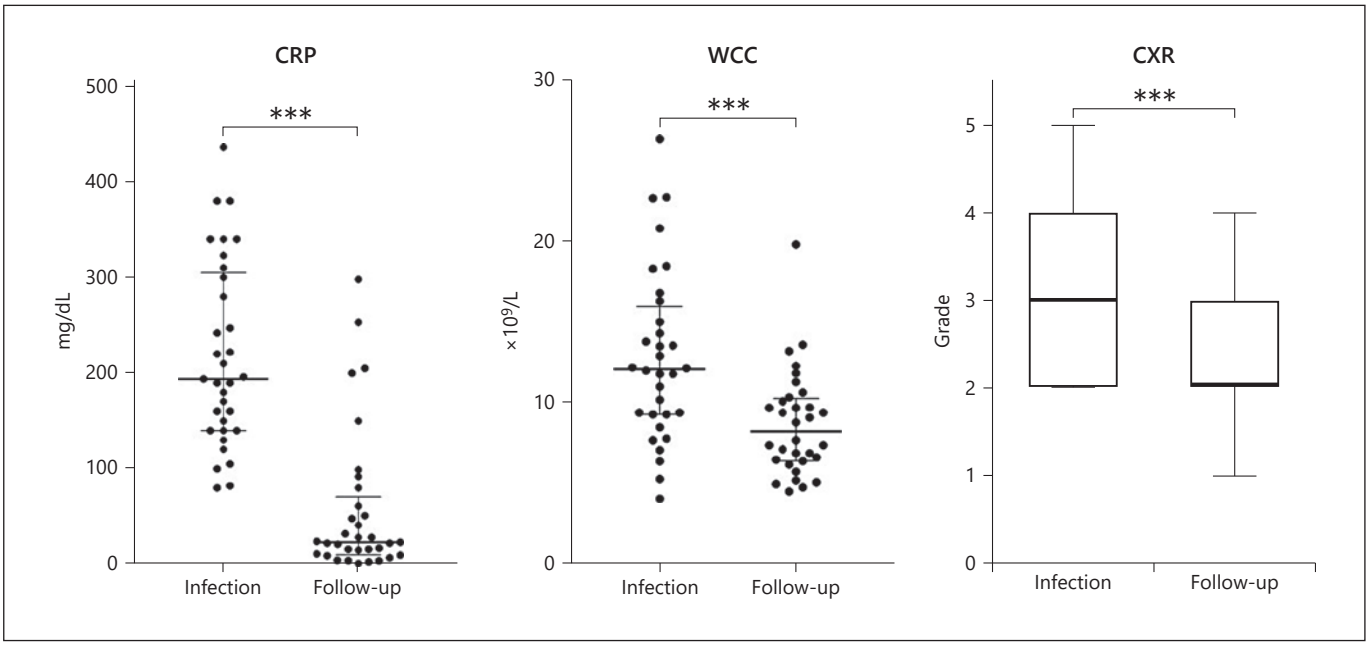

Fig. 3. Change in white cell count (WCC, $\times 10^9$), C-reactive protein (CRP, mg/L) and chest x-ray (CXR) grading (graded from 0 to 5 as per Light et al. [18]) from time of admission with IPC-related pleural infection to follow up. There was a significant decrease in WCC ($n = 34$) from median 12.2 [IQR = 9.3–15.3] $\times 10^9$/L to median 9.0 [IQR = 6.5–104] $\times 10^9$/L and in CRP ($n = 33$) from median 194 [IQR = 140–305] mg/L to median 23 [IQR = 10–70] mg/L. CXR grade ($n = 33$) decreased from median 3 [IQR = 2–4] to median 2 [IQR = 2–3] (Wilcoxan signed-rank test). ***$p < 0.001$. IPC, indwelling pleural catheter.

The use of IPC for recurrent, especially malignant, pleural effusion is growing rapidly worldwide. Pleural infection is a recognized complication of IPC use and its rate varies from 2 to 12% in the literature [14–17]. Anecdotally concerns regarding IPC-related infection remain among clinicians, as the majority require admission to hospital and a proportion may be difficult to manage [14]. The cornerstones of management of pleural infection are evacuation of the infected pleural fluid and systemic antimicrobial therapy [19]. In non-IPC pleural infection, surgery is needed in a third of patients who fail chest tube drainage and antibiotic treatment [4, 5, 9]. Surgery is invasive, costly and requires recovery time, making it unsuitable for typical IPC-treated patients who usually have significant comorbidities (e.g., advanced cancer) and limited prognoses. The latest clinical guidelines recommend "treating through" IPC-related pleural infection with antibiotics and removal of the catheter only in refractory sepsis [1]. A non-invasive and safe way to enhance fluid drainage during IPC-related pleural infection can potentially hasten recovery and will be particularly beneficial for this patient cohort.

Intrapleural tPA/DNase therapy has been shown in randomized and cohort studies to successfully cure pleural infection in the majority of patients, without needing surgery, and shorten hospitalization (when compared with placebo) [6]. These series predominantly included patients with community- (±hospital-) acquired pleural infections. No published report has focused on use of tPA/DNase (especially its feasibility, efficacy and safety) in IPC-related pleural infection which has key differences from community-acquired ones.

First, IPCs are designed with a one-way valve that permits drainage of pleural fluid but prohibits intrapleural migration of external air or fluid. Recently, retrograde instillation of a single dose of talc slurry via IPC has been shown feasible [16]. Our report is the largest to confirm the feasibility of repeated dosing of tPA and DNase via IPC, by using an adaptor that bridges the catheter's one-way valve. Delivery of tPA/DNase therapy via IPC followed the same local protocols without modification as their instillation through standard chest drains in our participating centers. Although the optimal size tube for pleural infection remains controversial [20], IPCs (15.6Fr silicon tubes) appear adequate in size to drain infected fluid, associated debris and the (potentially large) volume of fibrinolytic-induced pleural fluid [11].

Second, existing data on efficacy of tPA/DNase mainly centers on pleural infection patients without underlying pleural disease. The pleural environment in IPC-related pleural infection is often more complex. Most IPC patients have advanced malignant pleural involvement including pleural thickening (from tumor and/or prior pleurodesis) and loculation/septations, the latter often further aggravated by long-term in situ placement of the catheter. Additionally, the bacteriology of IPC-related infections differs considerably from de novo pleural infections [14, 21, 22].

Our data provide confidence that tPA/DNase therapy remains effective in the setting of an infected, IPC-containing pleural cavity. Most patients were treated with up to 6 doses and made a good recovery without resorting to surgery. The mortality from IPC-related pleural infection was low in our report, as seen previously, despite the significant comorbidity profile [14, 22]. It is possible that regular pleural drainage via the catheter allows early recognition of signs of infected fluid and minimizes residual fluid in situ. When admitted, the IPC provides a pre-existing conduit for drainage and tPA/DNase instillation, avoiding delay in waiting for insertion of a new chest tube. IPC is much longer in length than usual chest tube and with many more fenestrations presenting a theoretical advantage in better distributing treatment drugs around the pleural cavity. Post-infection pleurodesis, previously observed in other IPC-related pleural infection series, remained common in our cohort and was not seemingly affected by the use of tPA/DNase [14].

Third, our data provide safety information on tPA/DNase use via IPC, particularly in malignant pleural disease. Cancer tissues are often prone to vascular hyperpermeability and bleeding. Prior studies in non-IPC infection suggest that intrapleural tPA/DNase therapy was not associated with systemic bleeding. Local (pleural) "bleed," as defined by a decline in blood hematocrit/hemoglobin, occurs in a small number of patients and is generally a result of oozing of blood from vascular leakage, without any hemodynamic compromise [11]. Our results from this IPC-related pleural infection cohort were similar to reported literature of patients with no underlying pleural diseases/cancers [8]. In particular, there were no cases of major bleeding.

It should be noted that the dose of tPA used varied in our series. Although 10 mg was the dose of tPA used in the original clinical studies [6], ongoing dose de-escalation studies have shown that 5 mg of tPA can be as efficacious [12]. Further studies of lower doses are in progress and case reports of doses as low as 1 mg have been published [23]. In this small cohort, outcomes were not different among various doses. Pleural bleeding was rare at all doses of tPA and was managed conservatively in all cases.

Our study has limitations including those recognized for a retrospective study. The delivery of the tPA/DNase therapy was not protocolized. Despite this, all cases were treated with similar regimens with variations among centers that reflected the real-life pragmatic nature of the data. The absence of a control group raises caution in the interpretation of the findings on efficacy and safety, especially in a population of high comorbidity. As a retrospective audit only of the IPC-related pleural infection cases, we did not have data on the number of infection cases not treated with tPA/DNase. Nonetheless, the high incidence of success without needing surgery, and low rate of complications, provide reassurance that tPA/DNase can be trialed in IPC-related pleural infection. Our study provides a platform upon which prospective comparison trials can build to confirm the benefits.

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Statement of Ethics

Prospective ethical approval for the reporting of outcomes of tPA/DNase therapy was obtained at Sir Charles Gairdner Hospital (No. 2012-214). This study qualified for a waiver of ethical approval at all UK sites (online suppl. Table 1).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Y.C.G.L.: guarantor; Y.C.G.L., D.B.F., and S.M.: conceptualization, methodology; D.B.F., S.M., S.T., H.I., R.A., S.W., J.U., A.M., L.A., N.M.R., N.A.M., K.G.B., and Y.C.G.L.: investigation and data curation D.B.F. and Y.C.G.L.: statistical analysis; D.B.F., S.M., and Y.C.G.L.: writing – original draft; D.B.F., S.M., S.T., H.I., R.A., S.W., J.U., A.M., L.A., N.M.R., N.A.M., K.G.B., and Y.C.G.L.: writing – review and editing, final approval.

References

1 Feller-Kopman DJ, Reddy CB, DeCamp MM, Diekemper RL, Gould MK, Henry T, et al. Management of malignant pleural effusions. An official ATS/STS/STR clinical practice guideline. Am J Respir Crit Care Med. 2018; 198(7):839–49.
2 Bhatnagar R, Reid ED, Corcoran JP, Bagenal JD, Pope S, Clive AO, et al. Indwelling pleural catheters for non-malignant effusions: a multicentre review of practice. Thorax. 2014; 69(10):959–61.
3 Davies HE, Rahman NM, Parker RJ, Davies RJ. Use of indwelling pleural catheters for chronic pleural infection. Chest. 2008;133(2): 546–9.
4 Davies CW, Kearney SE, Gleeson FV, Davies RJ. Predictors of outcome and long-term survival in patients with pleural infection. Am J Respir Crit Care Med. 1999;160(5 Pt 1):1682–7.
5 Maskell NA, Davies CW, Nunn AJ, Hedley EL, Gleeson FV, Miller R, et al. U.K. Controlled trial of intrapleural streptokinase for pleural infection. N Engl J Med. 2005;352(9): 865–74.
6 Rahman NM, Maskell NA, West A, Teoh R, Arnold A, Mackinlay C, et al. Intrapleural use of tissue plasminogen activator and DNase in pleural infection. N Engl J Med. 2011;365(6): 518–26.
7 Rahman NM, Kahan BC, Miller RF, Gleeson FV, Nunn AJ, Maskell NA. A clinical score (RAPID) to identify those at risk for poor outcome at presentation in patients with pleural infection. Chest. 2014;145(4):848–55.
8 Brims F, Popowicz N, Rosenstengel A, Hart J, Yogendran A, Read CA, et al. Bacteriology and clinical outcomes of patients with culture-positive pleural infection in Western Australia: A 6-year analysis. Respirology. 2019;24(2):171–8.
9 Farjah F, Symons RG, Krishnadasan B, Wood DE, Flum DR. Management of pleural space infections: a population-based analysis. J Thorac Cardiovasc Surg. 2007;133(2):346–51.
10 Corcoran JP, Psallidas I, Gerry S, Piccolo F, Koegelenberg CF, Saba T, et al. Prospective validation of the RAPID clinical risk prediction score in adult patients with pleural infection: the PILOT study. Eur Respir J. 2020; 56(5):2000130.
11 Piccolo F, Pitman N, Bhatnagar R, Popowicz N, Smith NA, Brockway B, et al. Intrapleural tissue plasminogen activator and deoxyribonuclease for pleural infection. An effective and safe alternative to surgery. Ann Am Thorac Soc. 2014;11(9):1419–25.
12 Popowicz N, Bintcliffe O, De Fonseka D, Blyth KG, Smith NA, Piccolo F, et al. Dose De-escalation of intrapleural tissue plasminogen activator therapy for pleural infection: the ADAPT project. Ann Am Thorac Soc.. 2017; 14(6):929–36.
13 Mehta HJ, Biswas A, Penley AM, Cope J, Barnes M, Jantz MA. Management of intrapleural sepsis with once daily use of tissue plasminogen activator and deoxyribonuclease. Respiration. 2016;91(2):101–6.
14 Fysh ETH, Tremblay A, Feller-Kopman D, Mishra EK, Slade M, Garske L, et al. Clinical outcomes of indwelling pleural catheter-related pleural infections: an international multicenter study. Chest. 2013;144(5):1597–602.
15 Muruganandan S, Azzopardi M, Fitzgerald DB, Shrestha R, Kwan BCH, Lam DCL, et al. Aggressive versus symptom-guided drainage of malignant pleural effusion via indwelling pleural catheters (AMPLE-2): an open-label randomised trial. Lancet Respir Med. 2018; 6(9):671–80.
16 Bhatnagar R, Keenan EK, Morley AJ, Kahan BC, Stanton AE, Haris M, et al. Outpatient talc administration by indwelling pleural catheter for malignant effusion. N Engl J Med. 2018;378(14):1313–22.
17 Thomas R, Fysh ETH, Smith NA, Lee P, Kwan BCH, Yap E, et al. Effect of an indwelling pleural catheter vs talc pleurodesis on hospitalization days in patients with malignant pleural effusion: the AMPLE randomized clinical trial. JAMA. 2017;318(19):1903–12.
18 Light RW, Rogers JT, Cheng D, Rodriguez RM. Large pleural effusions occurring after coronary artery bypass grafting. Cardiovascular Surgery Associates, PC. Ann Intern Med. 1999;130(11):891–6.
19 Group BTSPDG; Davies HE, Davies RJ, Davies CW. Management of pleural infection in adults: British Thoracic Society Pleural Disease Guideline 2010. Thorax. 2010;65(Suppl 2):ii41–53.
20 Rahman NM, Maskell NA, Davies CW, Hedley EL, Nunn AJ, Gleeson FV, et al. The relationship between chest tube size and clinical outcome in pleural infection. Chest. 2010; 137(3):536–43.
21 Maskell NA, Batt S, Hedley EL, Davies CW, Gillespie SH, Davies RJ. The bacteriology of pleural infection by genetic and standard methods and its mortality significance. Am J Respir Crit Care Med. 2006;174(7):817–23.
22 Bibby AC, Clive AO, Slade GC, Morley AJ, Fallon J, Psallidas I, et al. Survival in patients with malignant pleural effusions who developed pleural infection: a retrospective case review from six UK centers. Chest. 2015;148(1): 235–41.
23 Hart JA, Badiei A, Lee YCG. Successful management of pleural infection with very low dose intrapleural tissue plasminogen activator/deoxyribonuclease regime. Respirol Case Rep. 2019;7(3):e00408.
24 Thomas R, Cheah HM, Creaney J, Turlach BA, Lee YC. Longitudinal measurement of pleural fluid biochemistry and cytokines in malignant pleural effusions. Chest. 2016; 149(6):1494–500.