# Intrapleural Thrombolytics as First Line Therapy for Complicated Parapneumonic Effusions and Empyema in Patients with Prohibitive Surgical Risk: A Cases Series

Sulimar Morales-Colón, MD; Mariela M. Rivera-Agosto, MD; Mariana Mercader-Pérez, MD; Onix Cantres-Fonseca, MD; William Rodríguez-Cintrón, MD, MACP

**Objective: In complicated parapneumonic effusion or Empyema, approximately 25% of patients require surgical intervention which can be associated with a mortality risk of almost 20%. However, the use combination of rt-tPA and DNase in elderly patients with prohibitive surgical risk has improved outcomes. The main goal of our study is to highlight the utility of intrapleural thrombolysis in patients with prohibitive risk for surgery.**

**Methods: A retrospective record review study of patients (n=23) with complicated parapneumonic pleural effusion or empyema treated with tPA and DNase from January 1st of 2015 to March 18th, 2019 at VACHCS. Data collected to describe the outcome of intrapleural thrombolytics included demographic, pleural fluid analysis, surgical risk assessment, diagnosis and initiation treatment day, doses, chest imaging, drainage rate, chest tube size and average days in place, inflammatory markers, microbiology, antibiotics, and complications.**

**Results: Only 21.7% of patients were considered surgical candidates. Seventy-four percent had a 30-day post-surgical mortality risk of > 2.5% using the National Surgery Office (NSO) risk calculator. Post-operative inpatient stay was 99.7% and estimated post-operative ICU stay average was >80%. Primary outcome (pleural drainage improvement) obtained in 73.9%. Most common serious complications included sepsis (52.2%) and nonserious was residual hydropneumothorax (47.8%).**

**Conclusion: This study demonstrates that administration of intrapleural thrombolytics through a percutaneous pleural catheter achieved successful drainage safely and without the need for surgical interventions in a selected group of advanced age, elderly patients with pleural infections who were deemed to be high surgical risk. [*P R Health Sci J 2023;42(3):241-245*]**

*Key words: Complicated parapneumonic pleural effusion, Empyema, Recombinant tissue plasminogen activator, Deoxyribonuclease*

A pleural effusion is the abnormal accumulation of fluid in the pleural space (the area between the two layers of the membrane that covers the lungs) (1). They are caused by conditions including heart failure, cirrhosis, malignancies, infections, amongst other (2). Pleural infection can be broken into complex parapneumonic effusion (CPPE) and empyema. A parapneumonic pleural effusion occurs secondary to a lung parenchymal infection or pneumonia. The standard treatment of a pleural infection is the administration of systemic antibiotics and pleural drainage. When complicated, invasive procedures such as thoracentesis, insertion of an intra-pleural catheter, and video-assisted or open surgery are required to avoid progression to pleural fibrosis, trapped lung, or persistent infection (3). Some of the morbidity associated to complicated parapneumonic effusions are secondary to the need of invasive procedures for resolution, and the complications of those interventions. Those procedures, especially surgical interventions, have significant risk of complications such as pneumothoraxes, bronchopleural fistulas, life threatening bleeding, respiratory failure, and prolonged hospital stay, especially in the elderly population (4).

An empyema occurs when the infected pleural effusion develops frank pus in the pleura space. The pus accumulates secondary to infection, causing severe inflammation, and loculations with septa. These processes can culminate in

Division of Pulmonary and Critical Care Medicine, Department of Medicine VA Caribbean Health Care System, San Juan, Puerto Rico

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Address correspondence to: William Rodríguez-Cintron, MD, MACP, Chief PCCM Training program, VA Caribbean Health Care System, Pulmonary and Critical Care Medicine (111-E), 10 Casia Street, San Juan, PR 00921-3201. Email: William.Rodriguez@va.gov

intrapleural adherences, neovascularization of the pleural surface, fibrosis and trapping of the lung tissue when not treated adequately. When the parapneumonic effusion evolves to an empyema, the probability of resolution with simple drainage decreases significantly, with even almost 30% of patients requiring surgery. In some patients, those surgical interventions can be associated with a mortality risk of almost 20% (5).

Many elderly patients are not candidates for surgical interventions due to risk of complications and comorbidities. For such interventions, a 30-day mortality estimated risk of more than 2.5% has been noted. As well as more than 8% high risk for complications and prolonged hospitalization, has been documented, the latter also a prohibitive risk of mortality (6). Considering the high comorbidities predominant in an elderly predominant population as the one of the VACHS, other strategies have been tried out to avoid progression to empyema and speed infection resolution (7). Some of those patients even have prohibitive surgical risks of mortality, prolonged hospitalization, and intensive care unit use, even without surgical intervention, due to age and comorbidities.

Since 2011, randomized studies including the Multicenter Intrapleural Sepsis Trial 2 (MIST 2), have shown the effectiveness of combined intrapleural direct-acting fibrinolytic agent (recombinant tissue plasminogen activator or rt-PA) and hydrolytic enzyme of Deoxyribonuclease (DNAase) for patients with surgical contraindications. This combination of therapy when given intrapleurally and when early utilized during the disease process, has proven to increase pleural drainage, improve radiographic imaging, decrease duration of hospitalization, avoid adverse events and surgical referral (8). Also, literature recommends early use of intrapleural therapy for better outcomes (9-10). In addition, early administration of thrombolytics (< 14 days from symptoms onset) is thought to be a limiting factor for adequate response to intrapleural therapy (11). It is considered that late therapy has less yield in empyema resolution. Other studies define early use of thrombolytics as intrapleural drug instillation in less than 24 hours from diagnosis. Instead, late use is defined as more than 24 hours after diagnosis (12). At this time published studies have not presented clear recommendations for dosing interval, frequency, total number of doses, efficacy of sequential vs concurrent administration of therapy (13).

In our case, we are presenting a cases series where the instillation of rt-PA and DNase occurs in a group of patients with prohibitive risk for surgery. The main goal of our study is to show the outcome of a patient cases series highlighting the utility of intrapleural thrombolysis in relation to its temporal utilization and the timing of clinical diagnosis and/or a variable regimen dosing, in patients with prohibitive risk for surgery.

## Study design and Methods

A retrospective record review study of patients (n=23) with complicated parapneumonic pleural effusion or empyema treated with tPA and DNase from January 1st of 2015 to March 18th, 2019 at the VA Caribbean Healthcare System (VACHS). Inclusion criteria included veterans from age 21-95 years of age with the diagnosis of pleural infection who received intrapleural thrombolytic from January 1st of 2015 to March 18th of 2019. The exclusion criteria included veterans without pleural infection and veterans with pleural effusion who did not receive intrapleural thrombolytic. Upon completion of regulatory documents and evaluation by the IRB (Institutional Review Board) program, we received the ACOS (Associate Chief for Research and Development Service) notification letter of approval to start our retrospective record review. A list of the names and Social Security numbers of the patients that received the above therapy was requested to evaluate the outcome. Patients' information was obtained through Vista, CPRS. The VACHS Pharmacy service provided the list of the total number of patients that received combined intrapleural therapy of a direct-acting fibrinolytic agent and hydrolytic enzyme of DNA for complicated parapneumonic pleural effusions. Subjects were identified by a numerical code. After the above information was obtained, patients' demographic information (age, gender) was collected. Additional data obtained included pleural fluid analysis, diagnosis date, days between diagnosis and initiation of treatment, doses, chest imaging results, drainage rate, chest tube size and average days in place, inflammatory markers, microbiology results, antibiotics and complications (serious, nonserious). Surgical candidacy was evaluated using the Veterans Health Administration National Surgery Office (NSO) Surgical Risk Calculator. Information was evaluated to describe the outcome of intrapleural thrombolytic therapy.

## Results

A total of 23 patients with pleural infection received concurrent rt-PA and DNase treatment. Their mean age was 74.9 years, and 100% were men. Sixteen (69.9%) underwent right-sided chest tube insertion. Small-bore chest tubes (≤ 14 French) were inserted in 91.3% (21 of 23) of patients. Large chest tubes (>15 French) were used in 8.7% (2 of 21) of patients. The baseline demographic and clinical characteristics, treatment, and outcomes of the patients are shown in (Table 1-2). Fifteen (65.2%) of patients were smokers, including active and former smokers; most common medical comorbidities were uncontrolled diabetes mellitus and uncontrolled hypertension with 65.2% (15 of 23) of patients (Table 1). Only 21.7% (5 of 23) of patient were considered surgical candidate, with the use of NSO surgical risk calculator. Seventy-four (17 of 23) percent of patients had a 30-day post-surgical mortality risk of > 2.5% using the NSO risk calculator. Estimated post-operative inpatient stay was almost 100% (99.7%) and estimated post-operative ICU stay average >80%.

**Table 1**. Baseline demographic characteristics

| | n | % |
|---|---|---|
| *Sex* | | |
| Male | 23 | 100.0 |
| Female | 0 | 0.0 |
| *Smoker* | | |
| Yes | 6 | 26.1 |
| No | 8 | 34.8 |
| Former | 9 | 39.1 |
| *Comorbidities* | | |
| COPD (class B – D) | 2 | 8.7 |
| HFrEF (< 50%) | 3 | 13.0 |
| ESRD on HD | 3 | 13.0 |
| CLD/Active Hepatitis | 2 | 8.7 |
| U-DM/U-HTN | 15 | 65.2 |
| BMI >30 but <40 | 5 | 21.7 |
| CVA/MI < 3 months | 0 | 0.0 |
| *Surgical candidate* | 5 | 21.7 |
| *Diagnosis** | | |
| Right | 16 | 69.6 |
| Left | 8 | 34.8 |

*One subject was diagnosed with bilateral pneumonia. He was included in both categories

The median pleural fluid pH and lactate dehydrogenase levels were 7.6 IU/L and 1,162 IU/L, respectively (Table 2). 94.9% of patients had a positive gram stain or culture, including pleural and blood organisms. Pleural fluid microbiology culture yielded Escherichia coli (n=2), extended-spectrum beta lactamase (ESBL)-producing Escherichia coli (n=2), Streptococcus anginosus (n=2), Klebsiella (n=1), Klebsiella pneumoniae (n=1), Enterococcus faecium (n=1), Enterococcus faecalis (n=1), Enterococcus avium (n=1), Methicillin-resistant Staphylococcus aureus (MRSA) (n=1), Methicillin-susceptible Staphylococcus aureus (MSSA) (n=1), Pseudomonas aeruginosa (n=1), Streptococcus milleri (n=1). Blood microbiology culture also yield K. pneumoniae but carbapenem-resistant

**Table 2**. Clinical characteristics, treatment and outcomes

| | Mean | SD | Median | Range |
|---|---|---|---|---|
| Age | 74.9 | 10.5 | 75 | 56 – 91 |
| Pack years | 22.8 | 4.9 | 20.5 | 20 – 30 |
| *Treatment* | | | | |
| Dx to Tx days | 6.0 | 7.3 | 4 | 1 – 32 |
| TPA | 10.0 | 0.0 | 10 | 10 – 10 |
| DNase | 5.0 | 0.0 | 5 | 5 – 5 |
| Number of doses | 5.2 | 1.7 | 6 | 1 – 6 |
| Pleural pH | 7.1 | 0.5 | 7.6 | 6 – 8 |
| Pleural protein | 4.1 | 1.3 | 4.4 | 0.9 – 5.5 |
| Pleural LDH | 1,300.3 | 781.4 | 1,162 | 148 – 2,500 |
| Pleural glucose | 45.9 | 41.2 | 47 | 2 – 125 |
| Pleural WBCs | 65,108.2 | 162,891.8 | 5,885 | 39 – 644,100 |
| Antibiotic days | 25.5 | 13.0 | 23 | 8 – 46 |
| Sed rate | 90.8 | 30.2 | 103 | 38 – 120 |
| CRP | 183.1 | 101.3 | 147.9 | 9 – 300 |
| Average tube days | 13.4 | 8.6 | 10 | 4 – 30 |
| Rate of daily draining | 2,925.1 | 1,506.9 | 3,190 | 110 – 5,668 |

**Table 2**. Clinical characteristics, treatment and outcomes (Cont.)

| | n | % |
|---|---|---|
| *Improvement of image* | 17 | 73.9 |
| *Pleural organism* | | |
| E. coli | 2 | 8.7 |
| E. coli ESBL | 2 | 8.7 |
| Klebsiella | 1 | 4.3 |
| E. faecium | 1 | 4.3 |
| E. faecalis | 1 | 4.3 |
| E. avium | 1 | 4.3 |
| K. pneumoniae | 1 | 4.3 |
| MRSA | 1 | 4.3 |
| MSSA | 1 | 4.3 |
| P. aeruginosa | 1 | 4.3 |
| S. anginosus | 2 | 8.7 |
| S. milleri group | 1 | 4.3 |
| *Blood culture organism* | | |
| S. hominis | 1 | 4.3 |
| B. fragilis | 1 | 4.3 |
| C. parapsilosis | 1 | 4.3 |
| K. pneumoniae CRE | 1 | 4.3 |
| S. epidermis | 1 | 4.3 |
| MSSA | 1 | 4.3 |
| S. auricularis | 1 | 4.3 |
| *Antibiotics* | | |
| Vancomycin | 16 | 69.6 |
| Piperacillin/Tazobactam | 13 | 56.5 |
| Meropenem | 4 | 17.4 |
| Levofloxacin | 3 | 13.0 |
| Azithromycin | 6 | 26.1 |
| Cefepime | 5 | 21.7 |
| *Tube size* | | |
| Small | 21 | 91.3 |
| Large | 2 | 8.7 |
| *Serious complications* | | |
| Bleeding with blood transfusion | 1 | 4.3 |
| Sepsis | 12 | 52.2 |
| New infection (Chest tube/Blood) | 0 | 0.0 |
| *Non-serious complications* | | |
| Chest pain | 6 | 26.1 |
| Erythema/Rash | 0 | 0.0 |
| Residual Hydropneumothorax | 11 | 47.8 |

Enterobacteriaceae (CRE) (n=1), MSSA (n=1), other microorganisms are shown in (Table 2 Cont).

The median average tube and antibiotic days were 23 and 10 respectively. Most patients were treated with Vancomycin in 69.6% (16 of 23) and Zosyn in 56.5% (13 of 23) of patients. Chest images showed improvement of pleural effusion in 73.9% (17 of 23) of patients. Most common residual imaging finding was hydropneumothorax in 47.8% (11 of 23) of patients. The rest showed almost complete resolution of effusion. Zero percent the patients (0 of 23) required surgical intervention for resolution of infectious symptoms, or secondary to progression of effusion.

## Discussion

More than half of patients followed in these cases series showed almost complete resolution of the pleural effusion.

Although 5 of the 23 patients were considered surgical candidates, the pleural infection resolved with intrapleural therapy, without the need for surgical intervention. Most of the patients had a high estimated risk of 30-day mortality, and postoperative inpatient prolonged hospitalization and intensive care unit stay. Residual hydropneumothorax was the most common residual finding.

Complicated parapneumonic pleural effusion and empyema are associated with an intense inflammatory response which cause cytokine release and stimulation of plasminogen activator inhibitor. This inflammatory response leads to a profibrotic state, fibrin deposition, and loculations. Leukocyte degradation has as a consequence high levels of deoxyribonucleoprotein with DNA which increases the viscosity of pleural fluid (9-10). The tPA/DNase mechanism of action has not yet been well established. The possible mechanisms include that DNase diminishes fluid viscosity, whereas tPA breaks down loculations within the pleural space which induces large volumes of pleural fluid. MIST1 and MIST2 demonstrated that combination of intrapleural rt-PA and DNase therapy improved fluid drainage in patients with pleural infection. They also concluded the combination therapy reduced the frequency of surgical referral and the hospital stay duration (8, 14-15).

Intrapleural therapy was given in our study in a variable regimen, with variable timing and dosing. In our retrospective analysis, most of patients received 6 doses of rt-TPA and DNase, nevertheless, some patients received only 1 dose of each medication with adequate response. There was variability of doses regimen, with some patients receiving sequential/subsequent therapy administration (rt-TPA first, then DNase), versus concurrent therapy administration (rt-TPA first and DNase drugs at the same). Finally, timing to start therapy was variable in this patient group, with some patients starting on intrapleural thrombolytics in the first 24 hours from diagnosis (early), and other started therapy after 14 days and even after 30 days of presentation (late).

Our study had several characteristics similar to the MIST2 trial including male gender prevalence (100%) of patients, positive gram stain or culture (94.9%) of patients, small bore chest tube use (≤ 14 French in 91.3% of patients) and primary outcome obtained (chest images showed improvement of pleural effusion in 73.9% of patients without the need for surgical interventions).

In contrast to MIST2 trial, our study showed improvement in images and infection resolution without surgical intervention in empyema treated with late rt-TPA & DNase, even in patients with > 14 days of diagnosis. Also, the proposed intrapleural drug regime of 6 doses was altered, showing resolution of pleural infection with less than 6 doses, even in patients with a single dose of each agent. Some patients received concurrent intrapleural infusion, without increase in complications, including bleeding, instead of receiving the medications in sequential/subsequent infusion similar MIST2 trial.

In this limited retrospective record review study of 23 patients with complex pleural infections at high-surgical risk, successful drainage of the pleural space was achieved with intrapleural thrombolytic therapy with both sequential and concurrent rt-TPA and DNase administration.

### Interpretation

This study demonstrates that administration of intrapleural thrombolytics through a percutaneous pleural catheter achieved successful drainage safely and without the need for surgical interventions in a selected group of advanced age, elderly patients with pleural infections who were deemed to be high surgical risk.

### Take-Home Points

Intrapleural thrombolytics should be considered in patients with pleural infections and prohibitive surgical risk. Our study showed primary outcome (pleural drainage improvement) was obtained in 73.9%. It also showed that administration of therapy is safe in the very elderly patients without need of surgery.

## Resumen

En el derrame paraneumónico complicado o empiema, aproximadamente el 25% de los pacientes requieren intervención quirúrgica que puede asociarse con un riesgo de mortalidad de casi el 20%. Sin embargo, el uso de la combinación de rt-tPA y DNasa en pacientes ancianos con riesgo quirúrgico prohibitivo ha mejorado los resultados. Objetivo El propósito principal de nuestro estudio es resaltar la utilidad de trombolíticos intrapleural en pacientes con contraindicaciones para cirugía. Métodos Se registro retrospectivamente pacientes con efusiones para-pneumonicas complicadas o empiema (n=23) tratados con tPA y DNase desde 2015-2019 en VACHS. Data recogida para uso de trombolíticos intrapleural incluyo información demográfica, análisis de líquido pleural, riesgo de cirugía, diagnóstico, día de inicio de tratamiento, dosis, imágenes radiográficas, cantidad de drenaje, tamaño de tubo de pecho y promedio de días utilizado, marcadores de inflamación, microbiología, antibióticos, y complicaciones. Resultados Solo 21.7% de los pacientes fueron considerados candidatos quiricos y 74% tenían riesgo de mortalidad a los 30 días de >2.5%, utilizando la calculadora de riesgo del National Surgery Office. La taza de estadía en el hospital fue de 99.7% y la estadía posoperativa en ICU fue un promedio de >80%. Resultado principal (mejoría en drenaje pleural) fue 73.9%. La complicación sería más común fue sepsis (52.2%) y la más común no-seria fue hidroneumotórax (47.8%). Conclusión Este estudio demuestra que la administración de trombolíticos intrapleurales a través de un catéter pleural percutáneo logró un drenaje exitoso de manera segura y sin necesidad de intervenciones quirúrgicas en un grupo seleccionado de pacientes ancianos de edad avanzada con infecciones pleurales que fueron considerados de alto riesgo quirúrgico.

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