



# Intrapleural Fibrinolytic and Enzyme Therapy:

Is the benefit worth the bleed?

CHEST / June 15th 2022

## THE CLINICAL QUESTION



What is the risk of bleeding associated with IET use in pleural infection?

## TAKE HOME MESSAGE

- In patients being treated with intrapleural fibrinolytics and enzyme therapy, the incidence of pleural bleeding is about 4%. Concomitant systemic anticoagulation use and a high RAPID score are independent predictors of pleural bleeding. Thus, if clinically feasible, systemic anticoagulation should be held during the IET
- In patients who are high risk for temporary withholding of anticoagulation, alternative therapy options such as surgical options should be entertained. If these high-risk patients are also deemed to be non-surgical candidates, lesser effective modalities such as instillation of saline into the pleural cavity can be considered.
- In end stage renal disease patients, lowering dose of tPA should be considered to decrease incidence of bleeding.
- Patients should also be made aware of the risk of pain associated with IET prior to initiation of the treatment and appropriate analgesia should be utilized during this therapy.



# BACKGROUND



- The Landmark MIST 2 Trial has established combination intrapleural fibrinolytic and enzyme therapy (IET) as a therapeutic option in pleural infection.
- Despite the widespread use of this treatment, present data is mixed regarding the incidence of adverse effects such as intrapleural bleeding and the factors that can affect this.
- The aim of this study was to assess the overall bleeding risk and safety profile associated with IET use, including the effects of concurrent therapeutic anticoagulation, and the nature and extent of nonbleeding complications.
- The study also explores a variety of factors to identify predictors of bleeding from IET use.

# STUDY DESIGN



**Type of trial:** This was an international multicenter retrospective observational cohort study conducted in 24 centers across the United Kingdom and United States of America.

**N:** 1833

**Study groups:** Adults with a diagnosis of pleural infection based on standard internationally agreed criteria

**Settings:** 24 Participating Centers in United Kingdom and United States of America

## **Statistical Analysis:**

- Comparisons of proportions were conducted using the Fisher exact test (two-sided) and the  $\chi^2$  test for variables with more than two levels.
- Data were analyzed using descriptive statistics, and binary outcomes were analyzed using logistic regression models. Multivariate regression models were used to identify independent predictors.
- Data analysis was carried out using SPSS version 27 software (IBM).

## Enrollment:

Treatment period: Data collected for cases between January of 2012 to May of 2019.

## Primary outcome

- Overall Incidence of pleural bleeding.
- Pleural bleeding was defined as a change in pleural fluid hematocrit during therapy to  $\geq 50\%$  serum hematocrit or pleural fluid hematocrit of 25% to 50% with clinical suspicion prompting intervention was required.

## Secondary outcome(s)

- The incidence of pleural bleeding and its association with
  - varying dosing and administration regimens of IET
  - use of therapeutic systemic anticoagulation
  - platelets level
  - antiplatelet use
- Analysis on potential associations and predictors of bleeding events, including the RAPID score
- Management of pleural bleeding complications
- Non bleeding adverse events

## Intervention(s)

Use of at least one dose of combination IET (both tPA and deoxyribonuclease) after standard medical treatment failure (as determined by the local investigator) as per local site IET protocol.

# POPULATION



## Inclusion criteria:

- Adult patients ( $\geq 18$  years)
- Evidence of pleural infection
- Clinical history compatible with pleural infection
  - pleural collection that met one of the below criteria: (a) purulent, (b) gram-stain or culture positive, (c) acidic with a low pH of  $< 7.2$ , (d) low pleural fluid glucose (in the absence of an accurate pH measurement), or (e) septated pleural fluid on ultrasound (or CT scan) that is likely secondary to pleural infection.

- at least one dose of combination IET (both tPA and deoxyribonuclease) after standard medical treatment failure (as determined by the local investigator) as per local site IET protocol.

### **Exclusion criteria:**

- Patients to whom IET was administered for recurrence of pleural infection after surgical treatment were excluded.
- **Baseline Characteristics of study population: N=1833**
  - Median age was 58 years
  - Male:1,173(64%), Female:660(26%)
  - Hospital-acquired infection:372(20.3%)
  - Small (<15F) chest tube:1,334(72.8%)
  - Median BMI: 27.2
  - Pleural fluid findings
    - Culture positive: 819 (44.7%)
    - Pus: 829 (45.3%)
    - Median pH: 7.12
    - Median Pleural fluid lactate dehydrogenase, IU: 1,985
    - Radiologic loculation: 1,501 (81.9%)
  - Comorbidities
    - Respiratory: 472 (25.8%)
    - Cardiac: 361 (19.7%)
    - Liver cirrhosis: 89 (4.9%)
    - Diabetes: 370 (20%)
    - End-stage kidney disease: 107 (5.9%)
    - Chemotherapy or immunosuppression: 297 (16.2%)
    - Active cancer: 323 (17.7%)

## **OUTCOMES**

### **Primary outcome:**

The incidence of pleural bleeding during IET for pleural infections was 4.1 % (76 of 1,833 patients)

### **Secondary outcomes:**

#### **1.) Impact of Systemic Anticoagulation**

- anticoagulation status during treatment was known in 1,825 of 1,833 patients (99.6%).
- 1510 patients were not on anticoagulation and the incidence of bleeding was noted in 54 of 1510 (3.6%).

- 315 of 1,825 patients (17.3%) were receiving therapeutic anticoagulation at baseline, and the incidence of bleeding was noted in 22 of 315 (6.9%)
- Anticoagulation was withheld in 118 of 315 patients, and the incidence of bleeding was 3 in 118 patients (2.5%).
- Anticoagulation was continued in 197 of 315 patients and 19 of 197 (9.6%) had incidence of bleeding.

## 2.) Dose regimen

- Complete dosing details of IET were available in 1792 patients, out of which 1620 patients received MIST2 trial dosing of IET and 172 patients had reduced dosing. There was no statistical significance on the incidence of bleeding in these two varied dosing groups ( $p=0.47$ ).

## 3.) Antiplatelets

- 29 patients were on antiplatelet therapy, of which 19 patients continued antiplatelet therapy and 10 patients held antiplatelet therapy during the TEP. There was no incidence of bleeding events in these 29 patients.

## 4.) Platelet Levels

- Median platelet count was  $275 \times 10^9/L$
- Platelet level 50 to  $100 \times 10^9/L$ : Incidence of bleeding was 11 of 84 patients (13.1%)
- Platelet level greater than  $100 \times 10^9/L$ : Incidence of bleeding was 52 of 1390 patients (3.7%)
- Patients with platelets less than  $50 \times 10^9/L$  were excluded from analysis

## 5.) RAPID score

Complete RAPID score data were available for 1,494 of 1,833 patients (81.5%).

- There were 12 bleeding events in 447 patients (2.6%) with low RAPID score (0-2)
- There were 25 bleeding events in 692 patients (3.5%) with medium RAPID score (3-4)
- There were 31 bleeding events in 355 patients (8%) with high RAPID score (5-7)

Urea was the only significant independent predictor of bleeding within the RAPID score variables.

6.) Other independent predictors of bleeding

- Active anticoagulation: OR of 1.8, P value=0.48
- RAPID category: OR of 1.72, P value=0.005

7.) Management of Bleeding complications in the 76 patients

- 12(15.8%): conservative management with observation alone (level 1)
- 40(52.6%) required blood product transfusion including correction of coagulopathy. (level 2)
- 5(6.6%) required additional chest tube for drainage or upsizing of existing chest tube. (level 3)
- 19(25%) required surgical interventions or transfer to higher level of care or both (level 4)

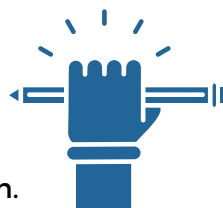
8.) Non pleural bleeding adverse events occurred in 561 of 1833 patients (30.6%)

- Pain requiring escalating doses of analgesics was reported in 224 of 1833 patients (12.2%).
- Increased oxygen requirement was reported in 71 of 1833(3.9%) patients
- Tachycardia occurred in 12 (0.7%)
- Red/ bloody discoloration of pleural fluid not meeting pleural bleeding criteria in 11(0.6%)
- Chest wall hematoma in 8 (0.4%) patients
- Unexplained drop hemoglobin without pleural bleeding in 5(0.3%) patients.
- Air leak or bronchopleural fistula in 5 (0.3%) patients
- Fever in 4 (0.2%) patients
- GI bleeding in 4 (0.2%) patients.
- Hypotension in 3 (0.2%) patients.
- Allergic or Hypersensitivity reaction in 3 (0.2%) patients.
- Death before hospital discharge 16 of 1833(0.9%) patients

## COMMENTARY

**Study Strengths:**

- Large study cohort
- Multicenter setting
- High rates of data completion.
- This study had a referable definition of pleural bleeding which improved the uniformity of the reported primary outcome.



### Study Limitations:

- This is a retrospective study which could lead to selection bias.
- The low number of patients on antiplatelet therapy precludes drawing conclusions based on this study.
- Also effect of concurrent prophylactic anticoagulation on IET associated adverse effects was not analyzed in this study



## FUNDING



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## SUGGESTED READING



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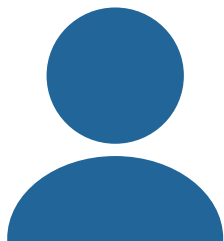
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