Original Article

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# Role of Medical Interventions in Complicated Parapneumonic Pleural Effusion and Empyema

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## ABSTRACT

**Background:** Complicated parapneumonic effusion (PPE) and empyema require intercostal drainage (ICD), failure of which usually leads to surgery. Intrapleural instillation of fibrinolytic agents (IFT) enhance pleural drainage and reduce the need for surgery. This study aimed to evaluate the role of medical interventions (ICD and IFT) in complicated PPE and empyema.

**Methods:** In a prospective, cohort study conducted at National Academy of Medical Sciences, Bir Hospital. Patients aged >18 years with complicated PPE and empyema were included. ICD was placed in all. In those with significant residual effusion and loculations after ICD, intrapleural Streptokinase was instilled and daily drain output recorded. Outcomes were measured as complete, partial response and treatment failure. The duration of ICD tube in situ, length of hospital stay and need for surgical interventions was evaluated at three-month follow up.

**Results:** A total of 51 patients were enrolled into the study. Commonest symptoms were dyspnea, cough, chest pain and fever with a median duration of 14 days (IQR = 7–28). The etiologies of effusions were presumed or proven bacterial infection in 36 (70.5%), tuberculosis in 8 (15.7%) and parasitic infection in 2 (3.9%). ICD was successful in achieving a complete drainage in 22 (43.1%) patients. In the remaining 29 (56.9%), intrapleural Streptokinase was instilled which led to increase in drain output by 760.34 ± 283.90 ml. Post Streptokinase instillation; 18 (62.1%), 4 (15.8%) and 7 (24.2%) patients met the predefined criteria of "complete" response, "partial" response and treatment failure respectively. The mean duration of ICD tube in situ and hospital stay was 10.98 ± 3.56 and 13.51 ± 3.92 days respectively.

**Conclusions:** In patients with complicated parapneumonic effusion and empyema, intercostal drainage and intrapleural fibrinolytic have high success rates and a potential to significantly reduce the need for surgical interventions. These results are relevant to us as thoracic surgery and VATS services are limited and only available at few centers in Nepal.

**Keywords:** Complicated parapneumonic effusion; empyema; intercostal tube drainage; intrapleural fibrinolysis; streptokinase.

## INTRODUCTION

Parapneumonic effusion and empyema are common complications of pneumonia and cause significant morbidity and mortality.[1,2] Effusions complicated by pus formation, bacterial infection, low glucose (<60 mg/dl) and pH (<7.2) require intercostal drainage (ICD) in addition to broad spectrum antibiotics.[3] ICDs are ideally placed under ultrasound (USG) or computed tomography (CT) guidance and left in place until the drainage rate is less than 50 ml per day and the empyema cavity has closed.[3] Conservative measures fail in up to a third of the patients, eventually leading to surgical interventions which are more costly and associated with more complications. The use of intrapleural fibrinolytic therapy (IFT) to cleave the fibrinous septations and enhance pleural drainage has been shown to decreases the frequency of failed drainage and need of surgical interventions.[3-6] Intrapleural Enzymatic therapy (IET) in the form of DNAse has also been combined with IFT

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in recent studies to facilitate drainage.[5] No prior study has evaluated the role of ICD and IFT in our population. This study was conducted to assess the role of these medical interventions in complicated PPE and empyema in resource limited settings like ours.

## METHODS

This was a prospective, cross-sectional, observational study conducted in the Department of Pulmonary, critical care at National Academy of Medical Sciences, Bir Hospital between October 2024 to April 2025. Patients aged >18 years with complicated parapneumonic pleural effusion were included into the study. Complicated effusion was defined by any of the following characteristics: (1) macroscopically purulent, (2) pleural fluid positive for bacteria on gram stain or culture, (3) pleural fluid glucose < 60 mg/dl, (4) loculated pleural effusion.[7] Ultrasonography was performed in all patients to localize and characterize the effusion in terms of echogenicity, septations and volume of fluid. Patients with highly organized effusions and significant amount of thick pleura in CT chest were directly referred for surgery and excluded from the study. Effusions with underlying lung mass and/or cytology positive for malignant cells were also excluded. Bacterial PPE and empyema were labeled 'proven' if culture positive and 'presumed' if culture negative.

All included patients underwent either a chest tube or USG guided pigtail drainage. The choice of intercostal drain type and size was left to the discretion of the treating clinician. After placement of intercostal drain, the volume and characteristics of pleural fluid was recorded daily. Once the drainage became clear and less than 50 ml per day, a repeat chest X-ray and USG chest was done. In patients with significant lung expansion and residual effusion less than 50 ml on USG, ICD was removed. In those with residual effusion more than 50 ml and significant loculations, IFT was performed. IFT was attempted by instillation of 6 or 8 doses of 250000 U Streptokinase mixed with 50 ml of normal saline 12 hours apart.[6] The ICD tube was clamped for one hour post instillation and then released. Patients were monitored for adverse effects like fever, chest pain and allergic reactions for at least 24 hours post-procedure. The character and volume of fluid drained was recorded daily. In case of grossly hemorrhagic drainage, Streptokinase instillation was stopped.

The response to streptokinase instillation was documented by serial chest X-ray and USG chest as follows: (1) Complete response: Complete or near complete lung expansion on chest X-ray without residual collection or minimal fluid (depth of < 1cm) in supine position without residual septations or loculations on USG. (2) Partial response: Incomplete expansion on chest X-ray with more than 50% reduction in maximal depth or residual fluid depth of 1-3 cm in USG. (3) Treatment failure: Trapped lung on chest X-ray or less than 50% reduction in maximal depth or presence of loculated effusion on USG. Those with treatment failure were referred for surgery either VATS or open thoracotomy. The duration of chest drain in situ and hospital stay was recorded. Patients were then followed up at 3 months for assessment of symptoms, chest X-ray for recurrence and need of surgical drainage.

Data were analyzed using SPSS statistics version 26. Continuous variables were tested for normality using the Shapiro-wilk test. Normally distributed variables were presented as mean ± standard deviation (SD), whereas non-normally distributed variables were presented as median and interquartile range (IQR). Categorical variables were expressed as frequencies and percentage.

Ethical clearance was obtained from the Institutional Review Board of NAMS. An informed written consent was obtained from all participants prior to inclusion into the study. The relevant data was extracted from patient records and entered in Microsoft Excel maintaining anonymity. Patients were followed up during the entire course of hospital stay and three months after discharge.

## RESULTS

A total of 51 patients with a mean age of 44.84 ± 16.8 years were enrolled into study. Most effusions were present on the right side. Common symptoms were dyspnea, cough, chest pain and fever with a median duration of 14 days (IQR = 7–28) at presentation. The commonest pleural fluid abnormalities were low glucose in 41 (78.8%), loculated fluid on USG in 29 (56.9%), presence of turbid fluid in 6 (11.8%), presence of frank pus in 5 (9.8%) and isolation of organism in pleural fluid culture in 4 (7.7%) patients. The etiology of effusion was either presumed or proven bacterial infection in 36 (70.5%) patients. In 8 (15.7%) patients pleural fluid Xpert MTB/Rif assay was positive and 2 (3.9%) had parasitic infection. The baseline characteristics of the study population is presented in table 1.

**Table 1. Baseline characteristics of study population. (n=51)**

| Characteristics | Frequency |
|---|---|

| | | |
|---|---|---|
| **Age in years** | | |
| Less than 30 | 9 | 17.6 |
| 30 - 60 | 31 | 60.8 |
| More than 60 | 11 | 21.6 |
| **Gender** | | |
| Male | 40 | 78.4 |
| Female | 11 | 21.6 |
| **Presenting symptoms** | | |
| Dyspnea | 43 | 84.3 |
| Cough | 39 | 76.5 |
| Chest pain | 33 | 64.7 |
| Fever | 31 | 60.8 |
| **Side of effusion** | | |
| Right | 28 | 54.9 |
| Left | 23 | 45.1 |
| **Pleural fluid characteristics** | | |
| Straw colored | 36 | 70.6 |
| Turbid | 6 | 11.8 |
| Frank pus | 5 | 9.8 |
| Hemorrhagic | 4 | 7.8 |
| Pleural fluid glucose < 60mg/dl | 41 | 78.8 |
| Pleural fluid culture positive | 4 | 7.7 |
| Xpert MTB/Rif assay positive | 8 | 15.7 |
| **Radiology** | | |
| Chest X-ray | | |
| Non loculated effusion | 41 | 80.4 |
| Loculated effusion | 10 | 19.6 |
| Ultrasonography (USG) | | |
| Non loculated effusion | 22 | 43.1 |
| Loculated effusion | 29 | 56.9 |
| **Etiology** | | |
| Parapneumonic | 28 | 54.9 |
| Tubercular | 13 | 25.5 |
| Bacterial empyema | 8 | 15.7 |
| Parasitic | 2 | 3.9 |

The median total leukocyte count in pleural fluid was 1600 cells/μL (IQR = 3000-389,000 cells/ μL). The median protein level was 4.6 g/dL (IQR = 1.0 to 6.5 g/dL), glucose was 37 mg/dL (IQR = 2 to 190 mg/dL), LDH was 980 U/L (IQR = 81 to 9890 U/L) and ADA level was 50 U/L (IQR = 6.8 to 274 U/L).

Of the 51 patients included into the study, 30 (58.8 %) underwent USG guided pigtail drainage and 21 (41.2%) underwent chest tube insertion. The mean volume of fluid drained was 888.24 ± 446.83 ml. Complete drainage of pleural infection was achieved in 22 (43.1%) after ICD insertion. In the remaining 29 (56.9%), with persistent effusion and/or loculation, intrapleural Streptokinase was instilled. The flow of the patients in the study and the outcomes are depicted in Figure 1. The mean drain output post Streptokinase instillation was 760.34 ± 283.90 ml. Fever and chest pain were the commonest adverse symptoms reported after Streptokinase infusion. Hemorrhage leading to termination of the IPFT occurred in three (10%) patients. In all three cases, hemorrhage stopped within 24 hours once Streptokinase was stopped.

Post Streptokinase instillation, 18 (62.1%) and 4 (15.8%) patients had “complete” or “partial” response respectively. Seven (24.1%) had “treatment failure”. Procedure related details of the study interventions is depicted in figure 1 and table 2.

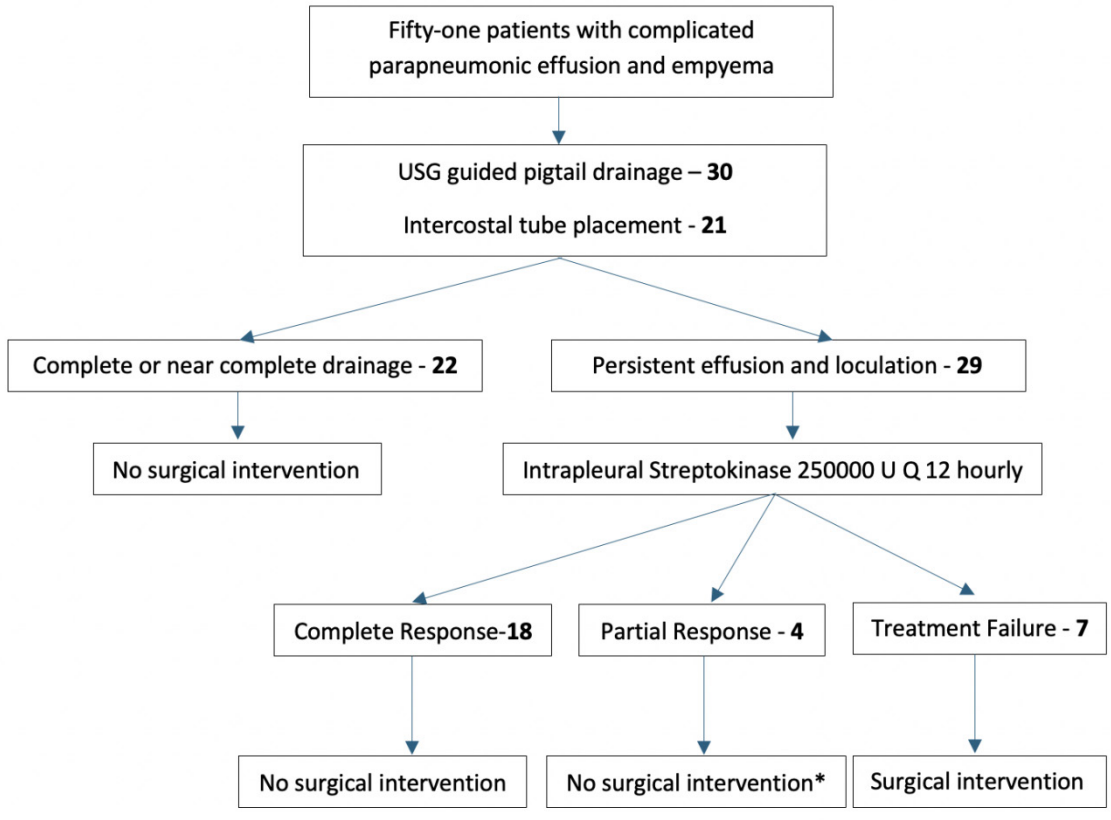


**Figure 1. Flow of patients enrolled into the study.**

**Table 2. Procedure related details of IFT with Streptokinase. (n = 29)**

| Parameters | Number of patients | Percentage (%) |
|---|---|---|
| **Number of doses** | | |
| 6 doses | 29 | 100 |
| 8 doses | 26 | 89.6 |
| | 3 | 10.4 |
| **Outcomes after streptokinase instillation** | | |
| Complete response | 18 | 62.1 |
| Partial response | 4 | 13.8 |
| Treatment failure | 7 | 24.1 |
| **Side effects** | | |
| Fever | 5 | 17.2 |
| Chest pain | 4 | 13.8 |
| Bleeding | 3 | 10.3 |
| Allergic reaction | 1 | 3.4 |
| **Volume of fluid drained post Streptokinase** | | |
| Mean | 760.34 ± 283.90 ml | |
| Range | 300 - 1300 ml | |
| **Volume of pleural fluid in day 7** | | |
| Mean | 946.07 ± 358.72 ml | |
| Range | 350 - 1800 ml | |

The mean duration of ICD tube in situ was 10.98 ± 3.56 days. The mean duration of hospital stay was 13.51 ± 3.92 days. On follow up at three months, a total of 8 of the 51 (15.6%) patients required surgical intervention; seven with "treatment failure" and one additional patient had recurrent empyema post drainage. The overall success rate of closed pleural drainage and intrapleural Streptokinase in our study was 84% (43 of the 51 patients).

## DISCUSSION

Parapneumonic effusion is the collection of exudative fluid in the pleural space and occurs in 20 – 40% of in-patients with pneumonia. Uncomplicated PPEs are treated with systemic antibiotics and do not warrant a drainage procedure.[7] Complicated effusions and empyema occur due to invasion of pleura by causative organisms and account for 5 – 25 % cases.[7,8] Complicated PPEs and empyema usually require closed pleural drainage, failure of which usually leads to surgical interventions like decortication. The success of non-surgical management of complicated effusions and empyema is variable.[8]

In our study, conservative management with ICD and intrapleural Streptokinase led to successful drainage in 43 of the 51 patients (84%). The first successful use of IFT for drainage of empyema was reported 75 years ago by Tillet et al.[9] In a subsequent study by Wait et al, the success rate of intrapleural Streptokinase was low compared to that of Video Assisted Thoracoscopic Surgery (44% vs 91%).[10] This study had a very small sample size, i.e. only 9 patients received IFT, to draw any definite conclusions. Buros et al demonstrated the utility of another fibrinolytic agent Urokinase with a success rate of 87%, in a small, randomized control trial[3]. Although the First Multicenter Intrapleural Sepsis Trial (MIST1) failed to establish the superiority of Streptokinase over placebo, the overall success rate of Streptokinase in this study was 69%.[6] The second Multicenter Intrapleural Sepsis Trial (MIST 2) showed that a combination of a fibrinolytic (tissue Plasminogen Activator - tPA) and intrapleural enzymatic therapy (DNAse) improved drainage and reduced frequency of surgical referrals.[5] In this study, only 3 of the 48 (6%) patients randomized to tPA arm needed surgical referral.

When cost of treatment is compared, tPA is more expensive than Streptokinase. Intrapleural Enzymatic Therapy (DNAse) is currently not available in our country. Hence, Streptokinase continues to be used as a cheaper alternative fibrinolytic agent in Nepal. The success rates of intrapleural Streptokinase is variably reported in studies from our part of the world.[11-13] The adverse effects are fever, bleeding and allergic reactions.[14]

The commonest cause of empyema is bacterial pneumonia and the resulting parapneumonic effusion.[7,15] Other causes include penetrating chest trauma, thoracic surgery, esophageal rupture, pulmonary tuberculosis, lung abscess, bronchiectasis, subphrenic abscess, and osteomyelitis of ribs.. TB was seen in a fourth of patients in our study which is like other Indian studies.[11,12,16] Barthwal et al reported that nearly a third of their patients with PPE and empyema had a tubercular etiology. Shukla et al., in their study of 102 patients reported Tubercular etiology in more than two-third of their patients. Tubercular empyema is generally reported in higher proportions in studies from the Indian subcontinent owing to its higher prevalence here.

The diagnostic evaluation of PPE usually begins with a chest X-ray, which can also suggest loculated effusions but lacks sensitivity in small effusions. Contrast CT chest provide a detailed anatomical information and help assess loculations, parenchymal involvement and pleural thickening but is expensive and exposes the patient to radiation.[17] Ultrasonography is cheap and can be performed at the bedside. It can detect smaller effusions, loculations and septations and guide drainage procedures.[18] One of the strengths of this study is that we used USG as the primary imaging modality in all our patients. Pigtail insertions were also guided by USG. We strongly recommend the use of bedside USG for diagnosis and management of pleural effusions and empyema.

Pleural effusions are often drained by either a chest tube or pigtail catheter. Chest tube insertion is performed under local anesthesia with a small incision in the intercostal space. Pigtail catheters are placed in the pleural space under sonographic guidance using the Seldinger technique. Previous studies have shown that the diameter of the drainage tube does not affect the effectiveness of the procedure.[19] Smaller size tubes are prone to obstruction and if thick pus is present, frequent flushing is required. We left choice of tube type and size to the discretion of the treating clinician. We also did not compare the volume of drainage by various tube sizes. However, the overall drained volume increased in all patients after instillation of fibrinolytic. The average duration of ICD in situ and hospital stay in this study was short compared to the study by Nandeesh et al.[20] This is likely due to the use of IFT with Streptokinase in patients with failed ICD in our study.

Indications of surgery in complicated PPE and empyema are failure of medical therapy, inadequate drainage despite ICD and fibrinolytics, persistent or recurrent loculations, trapped or entrapped lung and chronic organized empyema.[20,21] Video assisted thoracoscopy surgery (VATS) and open thoracotomy with decortication is the preferred surgical treatment. The advantages of VATS over open thoracotomy are less post operative pain, faster recovery and shorter hospital stay.[21]

This study has a small sample size and was conducted at a single center which limits the generalizability of the results. This study was uncontrolled as all patients who had loculation or persistent collection post ICD received fibrinolytics. Lack of control group prevented direct comparison of fibrinolytic therapy. Exclusion of highly organized effusion might have biased the study results towards better responders. However, this study does show a high rate of successful treatment of complicated PPE and empyema by conservative management i.e. ICD and IFT. These findings are relevant in the context of Nepal as thoracic surgery and VATS services are limited and only available at a few centers and provide options of noninvasive treatment to the patient.

## CONCLUSIONS

In patients with complicated parapneumonic effusion and empyema, medical management with early imaging, intercostal drainage and intrapleural fibrinolytics has high success rate. These interventions have a potential to significantly reduce the need for surgical interventions. The results of this study are relevant to us as thoracic surgery and VATS services are limited and only available at a few centers in Nepal.

## CONFLICT OF INTERESTS

The authors declare no conflict of interests.

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