Pneumonia

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# Chest tube drainage *versus* repeated therapeutic thoracentesis for the management of pleural infections: a retrospective multicentre propensity-matched study

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## Abstract

**Background** Drainage of infected pleural fluid is pivotal in the management of pleural infections, either by chest tube drainage (CTD) or repeated therapeutic thoracocentesis (RTT), in association with the use of intrapleural fibrinolytic therapy (IPFT) and DNase.

**Methods** The aim of this study was to compare the efficacy and the safety of these two methods of pleural drainage. We conducted a multicenter retrospective study, which included all the patients who was hospitalized for suspected pleural infection in three university hospitals between 2012 and 2021 drained by CTD or RTT. A propensity-score matching was performed to compare patients drained by RTT (RTT group) and by chest tube (CTD group) with adjunctive IPFT and DNase.

**Results** Two hundred and twenty-nine patients with suspected pleural infection were included. After a propensity-score matching, 78 patients were included in the final analysis, divided in two groups of 39 patients each. Patients in RTT group had a reduced length of drainage (6 days [4.3–8] *vs* 9 [6.5–13], OR = 1.41, 95%CI [1.05–1.89]) and a reduced length of hospital stay (15 days [11.5–21.5] *vs* 21 [14–30.5], OR = 1.28, 95%CI [1.01–1.61]). There was no significant difference in mortality rates, surgical referral, relapse, and drainage-related complications between the two groups.

**Conclusions** The management of pleural infections through RTT with IPFT and DNase appears to be as effective and as safe as CTD. Randomized controlled trials comparing RTT and CTD would be required to confirm these results.

**Keywords** Pleural infection, Pleural empyema, Chest tube, Repeated thoracic thoracentesis, Intrapleural fibrinolytic therapy, DNase

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## Background

Pleural infections are severe and hard-to-treat infections, associated with poor outcomes, especially in at-risk patients with intermediate or high RAPID score [1, 2]. Over the past decades, incidence of pleural infections has increased, reaching 6 to 10 per 100 000 per year in the most recent estimates [3–6].

Based on current guidelines, the backbone of the treatment of pleural infections relies on effective antibiotic therapy and drainage of the infected pleural fluid [7, 8]. The most common method of drainage is, by far, chest tube drainage (CTD), but recent studies have suggested that repeated therapeutic thoracocentesis (RTT) could be an alternative [9–11]. A French survey revealed heterogeneous practices in the management of complicated parapneumonic effusions (CPPE): 58% of physicians used CTD, but 33% of them reported giving preference to RTT [12]. To date, only one observational study published in 1992 has compared these two methods of pleural drainage including 94 patients [13]. In this study, patients treated by RTT had a reduced length of hospital stay (2.3 *vs* 5 weeks), lower occurrence of bronchopleural fistulas, and no significant difference on mortality rates was observed.

Administration of an intrapleural fibrinolytic alone, such as streptokinase or alteplase, failed to demonstrate any substantial benefit in randomized controlled studies [14–16]. In addition, only the combination of intrapleural fibrinolytics and desoxyribonuclease (DNase) has proven to be effective in the MIST-2 trial, by reducing hospital length of stay and surgical referral in comparison with placebo, alteplase or DNase alone [17]. A recent retrospective study found that the administration of urokinase and DNase with RTT significantly reduced the time to apyrexia and the length of hospital stay, and increased the volume of fluid drained in comparison with urokinase alone [11]. To our knowledge, no study has compared CTD and RTT as methods of pleural drainage, in the era of intrapleural fibrinolytics and DNase administration.

The aim of this multicenter retrospective study was to compare the efficacy of the pleural drainage between CTD and RTT for patients hospitalized with pleural infections receiving intrapleural fibrinolytic therapy (IPFT) and DNase.

## Methods

### Study population

In this multicenter retrospective study, all adult patients (> 18 years) hospitalized for pleural infection in the University Hospitals of Rennes, Brest and Poitiers between January 1th, 2012 and December 31th, 2021 were included. Suspected pleural infection was defined by the association of clinical criterion (cough, dyspnea, fever, and/or chest pain) and at least one of the following characteristics of pleural fluid: large (*i.e.* suprafhilar) parapneumonic effusion, intrapleural loculations, frank pus, microorganisms observed after Gram staining or positive pleural fluid culture. Patients with macroscopic purulent pleural fluid were considered as having pleural empyema. In the absence of frank pus, pleural infection was classified as CPPE. Of note, the pH was not used for the diagnosis of pleural infection because the measurement method employed was the pH stick indicator, which has been demonstrated to substantially overestimate pH values [18]. Low pleural fluid glucose < 3.3 mmol/L or high pleural fluid lactate dehydrogenase > 900 UI/L were used as diagnostic criteria in case of suspected pleural infection without microbiological identification.

Exclusion criteria were as follows: i) patients with non-complicated parapneumonic effusion; ii) absence of pleural drainage; iii) patients with early surgical referral (before any other drainage method), iv) critically ill patients receiving vasopressors or meeting criteria for septic shock. After an initial screening, patients who did not receive the combination of IPFT plus DNase were secondarily excluded from analyses.

Patients included were divided in two groups according to the type of drainage used during pleural infection management. Patients from Rennes were drained by repeated therapeutic thoracentesis, while patients from Brest and Poitiers had chest tube insertion.

### Data collection

We used a previously published cohort of patients managed by RTT and who received intrapleural urokinase and DNase between 2012 and 2018 at Rennes University Hospital [11]. We then screened and included patients who were drained by RTT and received intrapleural urokinase and DNase from 2019 to 2021. For patients managed by CTD, data were collected in two centers (Brest and Poitiers University Hospitals) between 2012 and 2021. For all patients, data were collected from medical files through the same standardized questionnaire which included demographic, clinical, biological data and imaging features. The clinical outcomes analysed were: in-hospital mortality, one-year mortality, drainage failure, length of hospital stay and drainage-related complications.

### Drainage protocol

The RTT group had repeated therapeutic thoracentesis performed under local anaesthesia, at the patient's bedside, after ultrasound control in most cases, and aiming to evacuate a maximum volume of pleural fluid using an 8-French laparoscopic trocar ('Boutin Trocart' -Novatech®, La Ciotat, France) (Supplementary appendix). Intrapleural urokinase 100 000 IU and adjunctive DNase (Pulmozyme®) 5000 IU diluted in 50 ml of saline

serum were instilled at the end of the procedure, no more than once a day. The criteria selected by the clinician for repeating thoracocentesis were uncontrolled sepsis or the persistence of a moderate or large pleural effusion in a patient still accepting to have thoracentesis. The duration of drainage for the RTT group was equivalent to the time interval between the first and the last thoracentesis.

The CTD group was drained by a 12 to 16-French chest tube. Intrapleural therapy consisted of the instillation of a fibrinolytic associated with DNase through the chest tube once or twice a day (depending on the clinician and centre). Saline serum lavage could also be performed.

Procedures in CTD and RTT groups were performed by senior pulmonologist or fellow under the supervision of senior pulmonologist. We considered drainage to be a failure in the following situations: when a switch in the pleural drainage technique was necessary, after a second chest tube insertion, or in cases of secondary surgical referral or in-hospital death.

### Statistical analysis

Characteristics of patients included in the two groups were described. Median and interquartile range (IQR) were used for quantitative variables; relative frequencies were reported for qualitative variables. We excluded missing data from the denominator for each variable. The Mann–Whitney test, and Fisher's exact test were used, as appropriate.

We built a matched propensity-score for treatment allocation for confounding factors: age, underlying comorbidities (diabetes mellitus, malignancy, chronic heart failure, alcoholism), pleural empyema, large (*i.e.* suprahilar) pleural effusion, lung abscess, infection source (community-acquired or nosocomial), pleural loculations, urea blood level, infection due to *Staphylococcus aureus* or enterobacteria. Exact RAPID-score was not used because of missing data for albumin blood level. Then, the 'nearest neighbor' matching method based on propensity score was applied to a logistic regression for the following outcomes: in-hospital mortality, one-year mortality, drainage failure, ICU admission, relapse, secondary surgical referral, complications of drainage; and linear regression (after logarithmic transformation for non-normally distributed variables) for the following outcomes: length of pleural drainage, length of hospital stay. Covariate balance after matching was evaluated by checking standardized differences (Supplementary Fig. 1). Two-tailed p-values were reported, with $p < 0.05$ considered as statistically significant. Statistical analysis was performed with R-Studio 2015 software, Integrated Development for R (R-Studio, Boston, MA, USA), using the ''MatchIt" package.

### Ethics

The local Ethics Committee of University Hospital of Rennes approved the design of this study (approval number 22.49). Patients were informed about the study and could refuse to be enrolled.

### Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

## Results

### Baseline characteristics

From January 1st, 2012, through December 31, 2021, a total of 1355 patients were screened. Two hundred and twenty-nine of them presented a suspected pleural infection and were included, including 91 patients treated by RTT and 138 by CTD, respectively. Characteristics of all patients included are summarized in Supplementary Table 1.

The median age was 63 years old (IQR [50–75]) and most patients were men ($n = 166/229$, 72%). Alcoholism and swallowing disorders were more frequent in the RTT group. However, there was no significant difference regarding the other comorbidities. Seventy-five percent of pleural infections were community-acquired ($n = 171/229$). In the RTT group, patients had more symptoms at initial presentation such as fever, cough, chest pain and dyspnea. There were 60% of empyema in the RTT group compared to 64% in the CTD group. The use of CT scan ($n = 208/229$, 91%) and thoracic ultrasound ($n = 194/229$, 85%) revealed presence of loculations in 66% of cases ($n = 150/229$). Pleural fluid culture was positive in 58% of patients, most commonly for Streptococci of *anginosus* group ($n = 60/229$, 26%) or anaerobes ($n = 47/229$, 21%). In the RTT group, *Streptococcus pneumoniae* was more frequently identified than in the CT group (22% *vs* 4%).

### Propensity-score matched population

One hundred and thirty patients fulfilled criteria of pleural infection managed by pleural drainage and receiving IPFT plus intrapleural DNase in the three participating centers. After matching, 78 patients were included in the final analysis, divided in two groups of 39 patients each (Fig. 1). One group received IPFT plus DNase through CT (CTD group), and the other group was managed using RTT with at least one instillation of urokinase plus DNase (RTT group).

Characteristics of each group are described in Table 1. In the population, 71% were men ($n = 55/78$) and the median age was 60 years (IQR [51–71]). Most of pleural infections were community-acquired ($n = 55/78$, 71%). The two groups were comparable for the following

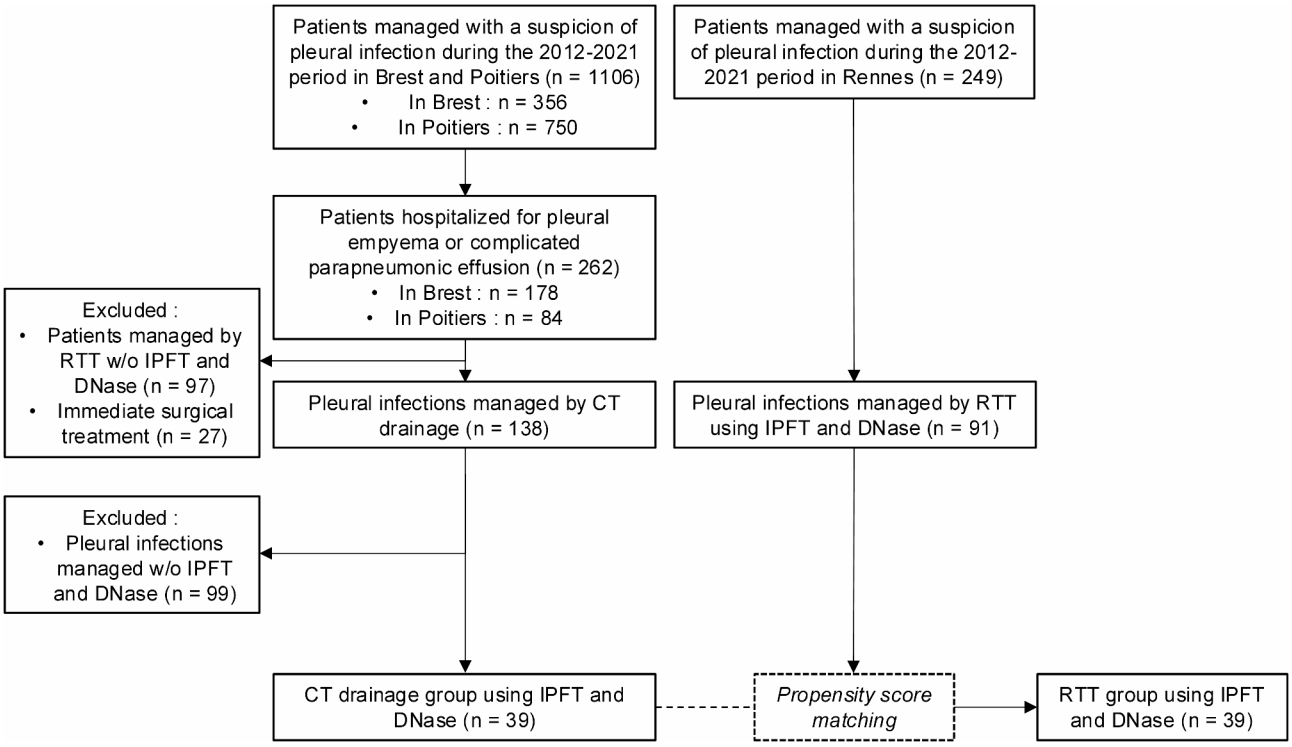


**Fig. 1** Flowchart of the study
CT= Chest Tube; IPFT = Intrapleural Fibrinolytic Therapy; RTT = Repeated Therapeutic Thoracocentesis

variables: age, sex-ratio, medical history of smoking, alcoholism, previous pleural infection, immunodepression, diabetes mellitus, malignancy and use of immunosuppressive treatments. Swallowing disorders were more frequent in the RTT group (18% *vs* 5%).

In the RTT group, patients had more symptoms at initial presentation, especially more fever (77% *vs* 59%), cough (74% *vs* 33%), sputum (41% *vs* 21%) and dyspnea (85% *vs* 72%). Signs of respiratory distress were numerically higher at the admission in the RTT group (33% *vs* 15%).

Biological data and imaging features were similar in both groups. Hilar or suprahilar effusion was reported in 73% of patient ($n = 57/78$). Intrapleural loculations were present in 73% of cases ($n = 57/78$). Pleural fluid culture was positive in half of cases ($n = 40/78$, 51%). The *anginosus* group streptococci were the most common bacteria ($n = 20/78$, 26%), followed by strict anaerobes ($n = 11/78$, 14%) and *Streptococcus pneumoniae* ($n = 8/78$, 10%).

In the RTT group, a median of 4 thoracocenteses [3–6] were performed, with a median interval of 6 days between the first and last thoracocentesis (Table 2). In the CTD group, median drainage duration was 9 days [6.5–13]. The total number of administrations of IPFT plus DNase in the two groups were similar ($n = 3$, [2–5]). Urokinase was the only fibrinolytic agent used in the RTT group, whereas alteplase was mostly used in the CTD group (alteplase use = 89%, urokinase use = 11%). Saline lavages occurred only in the CTD group ($n = 35/39$, 90%). The most common complication was chest pain which required the use of morphine in 42% of cases. Iatrogenic pneumothorax ($n = 6/78$, 8%), iatrogenic hemothorax ($n = 6/78$, 8%) and thromboembolic disease ($n = 5/78$, 6%) were less frequent.

Median duration of intravenous antibiotics (13 days, [7–24]) and median total duration of antibiotic therapy (42 days, [28–43]) were comparable in the two groups. Amoxicillin/clavulanic acid ($n = 36/78$, 46%) and ceftriaxone/metronidazole ($n = 18/78$, 23%) were the two most common empirical regimen used. Then, half of patients pursued orally amoxicillin/clavulanic acid ($n = 38$, 49%) or amoxicillin only ($n = 18$, 23%). Most of patients received chest physiotherapy ($n = 69$, 88%) during hospitalization.

## Outcomes

After propensity-score matching (Table 3), there was no significant difference in in-hospital (OR = 0.95, 95%CI [0.84–1.07]) or one-year mortality (OR = 0.79, 95%CI [0.85–1.24]) between the two groups. Eight percent of patients died during hospitalization and 17 patients died within the first year (22%). Drainage failure occurred in 26% of patients and secondary surgical referral was needed for 12% of them, but no difference was found between RTT and CTD groups (OR = 1.03, 95%CI [0.83–1.27] and OR = 0.97, 95%CI [0.84–1.13] respectively). More precisely, causes of RTT failures were as follows:

**Table 1** Baseline characteristics of the study population with use of intrapleural fibrinolytic and DNase

| | Total, *n* = 78 (%) | RTT group, *n* = 39 (%) | CTD group, *n* = 39 (%) | *P*-value |
|---|---|---|---|---|
| ***Baseline characteristics*** | | | | |
| Median age (years), [IQR] | 60 [51–71] | 63 [51.5–70.5] | 58 [51–71.5] | 0.70 |
| Male gender | 55 (71) | 27 (69) | 28 (72) | 1 |
| Median BMI (kg/m$^2$), [IQR] | 23 [20.55–27.9] | 22 [19.75–25.6] | 26 [22.1–29.4] | 0.03 |
| Active smoking | 30 (38) | 13 (33) | 17 (44) | 0.35 |
| Previous pleural effusion | 4 (5) | 2 (5) | 2 (5) | 1 |
| Previous pneumonia | 8 (10) | 5 (13) | 3 (8) | 0.71 |
| ***Comorbidities*** | | | | |
| Chronic heart disease | 14 (18) | 8 (21) | 6 (15) | 0.77 |
| Diabetes mellitus | 16 (21) | 7 (18) | 9 (23) | 0.78 |
| Immunosuppression | 7 (9) | 3 (8) | 4 (10) | 1 |
| Alcoholism | 22 (28) | 12 (31) | 10 (26) | 0.80 |
| Malignancy | 22 (28) | 11 (28) | 11 (28) | 1 |
| Chronic kidney disease | 4 (5) | 3 (8) | 1 (3) | 0.62 |
| Chronic liver disease | 8 (10) | 5 (13) | 3 (8) | 0.48 |
| Swallowing disorders | 9 (12) | 7 (18) | 2 (5) | 0.15 |
| ***Immunosuppressive treatments*** | | | | |
| Non-steroid anti-inflammatory drugs | 16 (21) | 9 (23) | 7 (18) | 0.78 |
| Oral corticosteroids | 7 (9) | 4 (10) | 3 (8) | 0.71 |
| Other immunosuppressive treatment | 4 (5) | 2 (5) | 2 (5) | 1 |
| ***Clinical presentation*** | | | | |
| Community-acquired infection | 55 (71) | 27 (69) | 28 (72) | 0.80 |
| Fever (T° > 38°C) | 53 (68) | 30 (77) | 23 (59) | 0.22 |
| Cough | 42 (54) | 29 (74) | 13 (33) | 0.001 |
| Sputum | 24 (31) | 16 (41) | 8 (21) | 0.14 |
| Chest pain | 47 (60) | 24 (62) | 23 (59) | 1 |
| Dyspnea | 61 (78) | 33 (85) | 28 (72) | 0.40 |
| Signs of respiratory distress | 19 (24) | 13 (33) | 6 (15) | 0.18 |
| ***Biological data*** | | | | |
| Leucocytes (G/l), [IQR] | 16 [13–20.3] | 16 [11.85–18.65] | 17 [13.1–21.2] | 0.49 |
| CRP (mg/l), [IQR] | 196 [115.25–260.75] | 192 [109.75–251.48] | 215 [137.5–263.2] | 0.55 |
| Creatinine (µmol/l), [IQR] | 62 [52–83] | 70 [52–90.5] | 58 [52–68] | 0.24 |
| Urea (mmol/l), [IQR] | 5 [3.63–7.2] | 5 [3.6–7.55] | 5 [4.3–6.6] | 0.92 |
| Albumin (g/l)$^*$, [IQR] | 27 [24.2–31.6] | 29 [24.63–31.9] | 27 [24–30.8] | 0.36 |
| ***Radiological data*** | | | | |
| CT scan | 75 (96) | 38 (97) | 37 (95) | 1 |
| Pleural ultrasonography | 66 (85) | 33 (85) | 33 (85) | 1 |
| Right side location | 49 (63) | 24 (62) | 25 (64) | 1 |
| Hilar or suprahilar effusion | 57 (73) | 28 (72) | 29 (74) | 1 |
| Bilateral effusion | 9 (12) | 4 (10) | 5 (13) | 1 |
| Mediastinal shift | 8 (10) | 5 (13) | 3 (8) | 0.73 |
| Pleural loculations | 57 (73) | 29 (74) | 28 (72) | 1 |
| Associated pneumonia | 41 (53) | 22 (56) | 19 (49) | 0.71 |
| Pulmonary abscess | 10 (13) | 4 (10) | 6 (15) | 0.73 |
| Associated pneumothorax | 7 (9) | 4 (10) | 3 (8) | 1 |
| ***Pleural fluid analysis*** | | | | |
| Frank pus | 42 (54) | 22 (56) | 20 (51) | 0.82 |
| Protein (g/l), [IQR] | 46 [39.8–49] | 46 [41.88–49.03] | 44 [36.4–49] | 0.59 |
| LDH (IU/l), [IQR] | 1402 [694–3566.5] | 1231 [589–3803] | 1955 [977–3012] | 0.39 |
| pH$^\#$, [IQR] | 8 [7.63–8] | 8 [7.75–8] | 8.5 [7.75–8.5] | 0.05 |
| Neutrophils (%), [IQR] | 84 [72.5–96] | 85 [75–96] | 80 [71–93] | 0.41 |
| Micro-organisms observed on Gram staining | 29 (37) | 13 (33) | 16 (41) | 0.64 |

**Table 1** (continued)

| | Total, *n* = 78 (%) | RTT group, *n* = 39 (%) | CTD group, *n* = 39 (%) | *P*-value |
|---|---|---|---|---|
| ***Microbiological identification*** | | | | |
| Positive pleural fluid culture | 40 (51) | 17 (44) | 23 (59) | 0.26 |
| Positive blood culture | 10 (13) | 6 (15) | 4 (10) | 0.73 |
| Positive pneumococcal urine antigen | 3 (4) | 2 (5) | 1 (3) | 1 |
| Positive sputum examination | 7 (9) | 4 (10) | 3 (8) | 1 |
| ***Identified bacteria*** | | | | |
| Anginosus group streptococci | 20 (26) | 9 (23) | 11 (28) | 0.80 |
| Anaerobes | 11 (14) | 3 (8) | 8 (21) | 0.14 |
| *Streptococcus pneumoniae* | 8 (10) | 6 (15) | 2 (5) | 0.26 |
| Other *Streptococcus spp.* | 6 (8) | 4 (10) | 2 (5) | 0.67 |
| *Staphylococcus aureus* | 6 (8) | 2 (5) | 4 (10) | 0.67 |
| Other Gram-negative bacilli | 4 (5) | 2 (5) | 2 (5) | 1 |
| *Pseudomonas aeruginosa* | 1 (1) | 0 (0) | 1 (3) | 1 |
| *Enterobacterales* | 7 (9) | 4 (10) | 3 (8) | 1 |
| Polymicrobial infection | 15 (19) | 6 (15) | 9 (23) | 0.34 |

*BMI* Body Mass Index, *CRP* C-Reactive Protein, *CTD* Chest Tube Drainage, *IQR* Interquartile range, *LDH* Lactate Deshydrogenase, *RTT* Repeated Therapeutic Thoracocentesis

*Due to missing data, measures were available in 61 of the 78 patients

#The pH level was determined using a pH indicator stick

**Table 2** Clinical management in the matched population

| | Total, *n* = 78 (%) | RTT group, *n* = 39 (%) | CTD group, *n* = 39 (%) | *P*-value |
|---|---|---|---|---|
| ***Thoracic drainage*** | | | | |
| Drainage duration (days), [IQR] | 7 [5–11] | 6 [4.5–8.5] | 9 [6.5–6] | 0.003 |
| Number of IPFT + DNase administered, [IQR] | 3 [2–5] | 3 [2–4] | 3 [1–6] | 0.75 |
| Intrapleural saline lavage | 35 (45) | 0 (0) | 35 (90) | < 0.001 |
| Volume of pleural fluid retrieved at first 24h (ml), [IQR] | 300 [100–552.5] | 250 [100–500] | 305 [127.5–592.5] | 0.73 |
| ***Drainage complications*** | 46 (59) | 21 (54) | 25 (64) | |
| At least one blank thoracocentesis | 11 (14) | 11 (28) | 0 (0) | 0.001 |
| Morphine use due to chest pain | 33 (42) | 15 (38) | 18 (46) | 0.65 |
| Iatrogenic pneumothorax | 6 (8) | 2 (5) | 4 (10) | 0.67 |
| Iatrogenic hemothorax | 6 (8) | 1 (3) | 5 (13) | 0.20 |
| Thromboembolic disease | 5 (6) | 3 (8) | 2 (5) | 1 |
| Excluded, angled or blocked chest tube | 2 (3) | 0 (0) | 2 (5) | 0.67 |
| ***Other treatments*** | | | | |
| Duration of IV antibiotics (days) | 13 [7–24] | 13 [8.3–18.5] | 14 [5.5–27] | 0.87 |
| Intravenous amoxicillin/clavulanic acid | 36 (46) | 21 (54) | 15 (38) | 0.26 |
| Intravenous ceftriaxone plus metronidazole | 18 (23) | 9 (23) | 9 (23) | 1 |
| Other antibiotics | 24 (31) | 9 (23) | 15 (38) | 0.17 |
| Total duration of antibiotic (days) | 42 [28–42.75] | 42 [38–46.5] | 36 [28–42] | 0.004 |
| Amoxicillin | 18 (23) | 11 (28) | 7 (18) | 0.58 |
| Amoxicillin/clavulanic acid | 38 (49) | 22 (56) | 16 (41) | 0.61 |
| Chest physiotherapy | 69 (88) | 37 (95) | 32 (82) | 0.11 |

*CTD* Chest Tube Drainage, *IPFT* Intrapleural fibrinolytic therapy, *IQR* Interquartile range, *IV* Intravenous, *RTT* Repeated Therapeutic Thoracocentesis

three patients were referred to surgery, one patient had only blank thoracenteses (< 50 mL retrieved, but IPFT plus DNase could have been administered), one patient was transferred to ICU due to increased oxygen flow (but no need for CTD insertion), one patient died of sepsis, and one patient required chest tube drain insertion after RTT failure. Patients in RTT group had a reduced length of drainage (6 days [4.3–8] *vs* 9 [6.5–13], OR = 1.41, 95%CI [1.05–1.89]) and a reduced length of hospital stay (15 days [11.5–21.5] *vs* 21 [14–30.5], OR = 1.41, 95%CI [1.05–1.89]). No significant difference was found for rehospitalization for relapse.

No substantial difference was found in drainage complications rates (OR = 1.17, 95%CI [0.94–1.45]) between

**Table 3** Outcome comparison between CTD and RTT groups after overlap propensity-score matched analysis

| Outcomes | RTT group, *n* = 39 (%) | CTD group, *n* = 39 (%) | *P-value* | Matched OR (95%CI) |
|---|---|---|---|---|
| Length of drainage (days) | 6 [4.3–8] | 9 [6.5–13] | 0.02 | 1.41 (1.05–1.89) |
| Length of hospital stay (days) | 15 [11.5–21.5] | 21 [14–30.5] | 0.04 | 1.28 (1.01–1.61) |
| Drainage failure | 9 (23) | 11 (28) | 0.81 | 1.03 (0.83–1.27) |
| Secondary surgical referral | 5 (13) | 4 (10) | 0.73 | 0.97 (0.84–1.13) |
| Relapse | 3 (8) | 4 (10) | 0.76 | 1.02 (0.91–1.14) |
| Drainage complications | 21 (54) | 25 (64) | 0.17 | 1.17 (0.94–1.45) |
| ICU admission | 6 (15) | 9 (23) | 0.56 | 1.05 (0.87–1.25) |
| In-hospital mortality | 4 (10) | 2 (5) | 0.40 | 0.95 (0.84–1.07) |
| One-year mortality | 8 (21) | 9 (23) | 0.79 | 1.03 (0.85–1.24) |

*CTD* Chest Tube Drainage, *ICU* Intensive Care Unit, *OR* Odds-Ratio, *RTT* Repeated Therapeutic Thoracocentesis

RTT and CTD procedures. Just under half of patients (*n* = 33/78, 42%) used morphine due to chest pain, which constituted the primary complication associated with pleural drainage. Iatrogenic pneumothorax and hemothorax were low in both groups but more frequent in the CTD group than in the RTT group, with rates of 10% (*vs* 5%) and 13% (*vs* 3%).

## Discussion

Based on MIST-2 results, IPFT with adjunctive DNase achieved consensus for the management of pleural infections [19, 20]. Nevertheless, to our knowledge, this study is the first to compare CTD and RTT in patients who received IPFT plus DNase. The primary finding of this propensity-matched cohort study is that RTT was associated with a reduced length of drainage and hospitalization in comparison with CTD. No significant difference was found for the mortality rates or the need for secondary surgical referral. The tolerability of the two procedures appears to be similar.

In 1992, Storm et al. found that the treatment of pleural infections with RTT may reduce the length of hospitalization compared to surgical chest tube management, with comparable mortality rates for each group of treatment [13]. In this study, no IPFT nor intrapleural DNase was used. More recently, Arnold et al. conducted a study to investigate the feasibility of a randomized trial comparing RTT and CTD [21]. Unfortunately, due to the COVID-19 pandemic, recruitment was limited to 10 patients, of whom only 4 underwent IPFT. Preliminary results suggested a potential reduction in length of hospitalization using RTT compared to CTD (5.4 *vs* 13 days). Our study offers a complementary analysis by investigating a medical management with RTT or CTD systematically associated with IPFT plus DNase. Our findings are in line with these results, highlighting a reduction in hospital stay associated with RTT as pleural drainage method. CT insertion allows a continuous drainage, which is required for severe pleural infections. However, when a CT is inserted, it is left in place for several days before being removed, which confines the patient to bed. On the other hand, complicated parapneumonic effusion (*i.e.* without macroscopic pus) can be managed with few thoracenteses, and with patients able to ambulate and to receive early pleural physiotherapy during hospitalization. Ultrasound-guided RTT may also allow intrapleural enzymatic therapy to be injected at a different site during each procedure, which may improve fibrinolytic activity in multiloculated effusions. These differences in mild to moderate infections may explain the shorter durations of drainage and hospitalization found in the RTT group.

Furthermore, several prognostic factors in pleural infections have been identified in the literature so far. Advanced age, malignancy, alcoholism, diabetes mellitus or heart failure are associated with a higher risk of mortality in case of pleural infection [22, 23]. A recent study by Shirosita et al. involving 711 patients demonstrated a 13% increase in mortality at 3 months among patients with pleural infection complicated by bronchopleural fistula [24]. In the TORPIDS study, analyzing 263 pleural fluids using a 16S rRNA sequencing technique, the presence of *Staphylococcus aureus* or the predominance of enterobacteria were associated with a decreased survival [25]. The presence of intrapleural loculations is also associated with an extension of length of drainage and of hospital stay [26, 27]. In our study, the propensity-score matching included these criteria and were balanced in order to properly assess the intrinsic efficacy of the method of pleural drainage. In addition, 4 out of 5 items of the RAPID-score criteria were included in the propensity score analysis, although the exact RAPID score could not be used due to a significant amount of missing data regarding albumin values.

Wen et al. demonstrated in their audit a complication rate (excluding pain induced by the procedure) of 16.9% for chest drains and 4.1% for thoracocentesis [28]. Even though chest tube drainage is a commonly performed procedure, complications such as bronchopleural fistula, thoracic or abdominal injury, insertion site infection and drain-related chest pain may occur [29]. Ultrasonography

became pivotal to guide pleural procedures to enable a safer procedure [30, 31]. Indeed, in the three participating centers, ultrasonography was used in 85% of cases, which probably contributes to the low complication rate. However, RTT require more procedures than a single CT insertion. This may increase the risk of procedure-related complications, although drainage-related complications were not significantly different between the RTT and CTD groups. In addition, RTT require more medical staff than for a single CT insertion. Consequently, RTT should be considered in respirology departments with teams experienced in the practice of thoracentesis, and where there are sufficient medical staff available to perform repeated thoracenteses.

For antibiotic therapy, experts recommend a minimum of 3 weeks of treatment, including 5 to 7 days of intravenous antibiotics [32]. However, the 2023 BTS guidelines indicate that between 2 and 6 weeks of antibiotic therapy is generally used in clinical practice to prevent relapse [33]. In our study, the duration of antibiotic therapy was between 4 and 6 weeks in most cases. The total duration of antibiotic therapy was significantly longer in the RTT group, which can be attributed to a centre bias. Indeed, one centre (Rennes) exclusively employed the RTT technique, where the local antibiotic protocol for pleural infections systematically recommended 6 weeks of treatment. However, the antibiotic regimens were homogeneous between centres, with a common use of amoxicillin with clavulanic acid or metronidazole.

This study has limitations. First, as a retrospective study, this work suffers from inherent biases due to the study design. However, missing data were low and the data collection was standardized across the centers. In order to reduce the selection bias, a propensity score method was applied. Second, the definition of suspected pleural infection was based on the French National College of Pulmonology, which slightly differs from the British Thoracic Society or the American Association for Thoracic Surgery guidelines [7, 33]. Third, our results were based on a small sample size that can reduce the power of detecting significant differences. Fourth, the heterogeneity in clinical practice could have led a center bias. For example, fibrinolytics used were not the same in all centers: pulmonologists from Rennes used urokinase while those from Brest preferred alteplase. Other discrepancies in clinical practice between the centres, such as the duration of intravenous antibiotic therapy or the experience of clinicians performing the procedures, may have influenced the outcomes. Fifth, patients had more symptoms and more severe presentation at the admission in the RTT group than in the CTD group. Surprisingly, this difference does not appear to negatively influence the results of the RTT group.

In conclusion, our study showed that the management of pleural infection by RTT with intrapleural fibrinolytic plus DNase is associated with a reduction of the length of drainage and hospital stay in comparison with CTD. Further prospective and larger studies are required to confirm that RTT is a safe and effective alternative strategy to CTD for the management of pleural infections.

**Abbreviations**

| | |
|---|---|
| BMI | Body Mass Index |
| CI | Confidence Interval |
| CPPE | Complicated Parapneumonic Effusion |
| CRP | C-reactive protein |
| CTD | Chest Tube Drainage |
| ICU | Intensive Care Unit |
| IPFT | Intrapleural Fibrinolytic Therapy |
| IQR | Interquartile Range |
| LDH | Lactate Deshydrogenase |
| OR | Odds Ratio |
| RTT | Repeated Therapeutic Thoracocentesis |
| SD | Standard Deviation |

## Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s41479-025-00167-x.

Supplementary Material 1: Supplementary Figure 1. Covariate balance of absolute standardized differences before and after.

Supplementary Material 2: Supplementary Appendix.

Supplementary Material 3: Supplementary Table 1. Baseline characteristics of the study population before matching.

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**Authors' contributions**
Contributorship: MC and DLP had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. DLP did the analysis. DLP, MC and SJ co-wrote the original draft. VR, CGG, EMJ, LL, BH and JCM contributed substantially to the investigation data collection and reviewed the manuscript. DLP acted as guarantor.

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**Data availability**
No datasets were generated or analysed during the current study.

## Declarations

**Ethics approval and consent to participate**
The study was approved by the Ethics Committee of Rennes University Hospital (approval number 22.49). Patients were informed about the study and could refuse to be enrolled.

**Consent for publication**
Not applicable.

**Competing interests**
The authors declare no competing interests.

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