Enzymatic therapy versus video-assisted thoracoscopic surgery for pleural infections: a systematic review and meta-analysis

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Shareable abstract (@ERSpublications)
From the results of this systematic review, it remains unclear whether video-assisted thoracoscopic surgery or intrapleural enzymatic therapy is superior in the treatment of pleural infections. High-quality studies are needed to define optimal treatment. https://bit.ly/4gvtTUj

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Abstract

Aims Parapneumonic pleural infections are frequently encountered, but the optimal treatment regimen remains controversial. The aim of this systematic review was to investigate whether immediate video-assisted thoracoscopic surgery (VATS) has advantages over intrapleural enzymatic therapy (IET).

Methods We searched MEDLINE, Embase and Web of Science Core Collection till November 2023 and included studies comparing IET and VATS in adult patients with parapneumonic pleural infections. Primary outcome was length of hospital stay (LOS); secondary outcomes included mortality and morbidity. Study quality was assessed using ROBINS-I and RoB 2. Inverse variance random-effects meta-analysis was performed.

Results We screened 2263 articles; eight were included in the final analysis, covering 1023 patients (n=465 IET (mostly single agent IET); n=558 VATS). Six were non-randomised studies (n=5 with serious risk of bias) comprising 964 patients, and two were small, randomised feasibility studies (n=1 with high risk of bias), comprising 59 patients. In the meta-analysis, LOS in non-randomised studies was shorter for patients treated by VATS (mean difference 4.2 days; 95% CI 1.5–7.0). However, no significant difference was reported in the randomised feasibility studies. Mortality and morbidity rates showed no significant difference.

Interpretation In this meta-analysis of non-randomised studies with a high risk of selection bias, VATS appears superior to IET regarding LOS in the treatment of parapneumonic pleural infections, without increased mortality and morbidity rate. Two recently published randomised feasibility studies failed to confirm this finding, but were not designed to detect a difference in LOS. This meta-analysis highlights the need for high-quality studies.

Introduction

Pneumonia is a frequently encountered clinical problem, with ~50% of patients developing a pleural effusion ("parapneumonic pleural effusion"), that will be contaminated with bacteria in 15% of patients ("pleural infection") [1]. Parapneumonic pleural effusions can be classified into uncomplicated parapneumonic effusions (UPPE), complicated parapneumonic effusions (CPPE) and empyemas. UPPE is defined as parapneumonic pleural fluid without signs of infection of the pleural fluid itself that will resolve by treating the underlying pneumonia with antibiotics and medical therapy. On the other hand, CPPE is defined as parapneumonic fluid with signs of infection, and empyema as the presence of pus in the thoracic cavity. Both CPPE and empyema require drainage for evacuation of the infected pleural fluid. Parapneumonic pleural infections (CPPE and empyemas) are associated with high morbidity and mortality rates [2].

A recently published guideline from the British Thoracic Society (BTS) and a statement from the European Respiratory Society (ERS) and European Society of Thoracic Surgeons (ESTS) advise administering intrapleural enzymatic therapy (IET) in the form of tissue plasminogen activator (t-PA) and DNase once intrapleural fluid resolution is not sufficiently achieved by a chest tube alone [1, 3]. This combination therapy is suggested because monotherapy with IET has not been shown to be effective in improving the drainage of pleural fluid [4]. The Second Multicenter Intrapleural Sepsis Trial (MIST2) showed significantly improved fluid drainage and reduced additional surgical interventions when IET was used for 3 days compared to the use of only one of these agents [5]. Studies show success rates of 70–95% after treatment with IET, *i.e.* no need for referral for surgery [6–9]. However, surgery is a well-established alternative for evacuation of pleural fluid and treatment of parapneumonic pleural infections. Video-assisted thoracoscopic surgery (VATS) is a minimally invasive approach which is associated with decreased length of hospital stay (LOS) and morbidity rate compared to open surgery [10–12]. Even in the organising phase of empyema, VATS with decortication can still be feasible [13]. Therefore, the European Association for Cardio-Thoracic Surgeons (EACTS) recommends the use of VATS in all cases of parapneumonic pleural infections, except for patients who are unsuitable for surgical intervention [14].

It is currently unclear whether early use of VATS in the treatment of parapneumonic pleural infections improves patient outcome. Therefore, we conducted a systematic review and meta-analysis of available studies comparing VATS *versus* IET (both single agent and dual agent) in adults with parapneumonic pleural infections. Outcomes of interest were LOS, mortality, morbidity, patient-reported outcomes and costs.

Methods

Protocol

This systematic review was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [15] and registered in PROSPERO on 23 May 2023 (CRD42023389753).

Eligibility criteria

We included studies reporting on clinical outcomes of IET *versus* VATS for the treatment of parapneumonic pleural infection. Studies were included when IET was used as the initial treatment in one group, and VATS was used as the initial treatment in a second group, and at least our primary outcome (LOS, days from intervention till discharge) was reported for both groups. Both randomised and (prospective or retrospective) non-randomised studies were eligible. Only studies published after the year 2000, human studies and studies with patients of 18 years and older were eligible. Studies reporting on other treatment options besides IET and VATS were only included when separate data on both IET and VATS could be extracted. When no separate data could be extracted in the IET and/or VATS group, we only included a study when the proportion of patients that received another treatment option was less than a third. Studies on malignant pleural effusions, empyema after (thoracic) surgery, tuberculosis, post-traumatic empyema, iatrogenic empyema or chronic empyema were excluded. Case reports or case series including less than five patients were also excluded, as well as conference abstracts.

Search strategy

A comprehensive search was performed in Ovid MEDLINE, Embase and Clarivate Analytics/Web of Science Core Collection from inception till November 2023 in collaboration with a medical information specialist (J.C.F. Ket). The search consisted of search blocks of "empyema" combined with search blocks of "fibrinolytics", restricted to adult patients. The search was performed without restrictions for methodology, date or language. The full search strategies can be found in supplementary material A. Duplicate articles were excluded using Endnote X20.0.1 (Clarivate), following the Amsterdam Efficient Deduplication (AED) method [16] and the Bramer method [17]. We also informally searched Google Scholar on 8 May 2023 for additional references.

Selection process

Two reviewers (W.R. de Jonge and B. Smits) independently screened all relevant titles and abstracts for eligibility using Covidence (www.covidence.org). Conflicts between the two reviewers were resolved by a third reviewer (D.J. Heineman). After this, full-texts of the remaining articles were collected, and two reviewers (W.R. de Jonge and B. Smits) independently assessed all, with conflicts being resolved by a third reviewer (D.J. Heineman).

Data extraction

A structured data extraction sheet to review the included studies was designed in Covidence. One reviewer (W.R. de Jonge) extracted the data, and one reviewer (B. Smits) checked the extracted data. Disagreements

were resolved by a discussion between the reviewers. We extracted the first author, year of publication, country of origin, study design, the total number of patients in the study, interventions and the number of patients in each intervention group. Data regarding demographics were also extracted, including age, sex, comorbidities, stage of empyema and details about the hospital admission. Finally, we extracted outcome data, including LOS (primary outcome), mortality rate (at day 30 and day 90), complications (including bleeding after administration of IET) and morbidity rate, duration of chest tubes, additional treatments (in addition to IET or VATS), readmission rate at 30 days, patient-related outcomes such as pain and quality of life (QoL) and costs of treatment. We used the Clavien–Dindo Classification to define and grade post-operative complications [18].

Quality assessment

Study quality for non-randomised studies was assessed using the Risk of Bias in Non-randomised Studies of Interventions (ROBINS-I) tool [19]. This addresses potential bias in seven domains: confounding, selection of participants, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes and selection of the reported result. For each domain, an overall risk of bias is classified as low, moderate, serious or critical risk. Study quality for randomised data was assessed using the Cochrane risk of bias tool for randomised trials [20]. This addresses potential bias with regard to random sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome and other. Judgement can be low, high or unclear risk of bias. One reviewer (W.R. de Jonge) assessed the risk of bias of all included studies, and an author specialised in epidemiology (D.A. Korevaar) was consulted to check the risk of bias assessment; conflicts were resolved by discussion between them.

Statistical analysis

Data for non-randomised studies and randomised studies were analysed separately, as the latter are at lower risk of selection bias. For our primary outcome, we aimed to perform inverse variance random-effects meta-analysis to obtain a summary estimate of the mean difference (and corresponding 95% confidence interval (95% CI)) in LOS in patients treated with IET *versus* VATS. Meta-analysis was only performed if at least two studies were identified that reported LOS as a mean±SD. Statistical heterogeneity was explored using the I^2 test. In case a subset of studies only reported medians and interquartile ranges (IQRs) for LOS in both groups, SDs were recalculated by dividing the width of the IQR by 1.35, as previously reported [21]. A z-test was performed to calculate p-values, which were two-sided and considered statistically significant when $p<0.05$. Meta-analysis was performed using Review Manager (RevMan) (revman.cochrane.org). Secondary outcomes were summarised narratively. For continuous outcome variables we reported mean±SD or median (IQR). For dichotomous data, we reported proportions.

Results

Search results

After removing duplicates, a total of 2263 studies were identified in the literature searches (figure 1). After screening titles and abstracts, 36 studies were selected for full-text review of which eight studies were included for final analyses [22–29]. Searches in Google Scholar did not identify any additional relevant studies.

Study and patient characteristics and quality assessment

Characteristics of the included studies and patients are presented in tables 1 and 2, respectively. All included studies were published between 2010 and 2023; six were non-randomised [22–27] and two were randomised feasibility studies [28, 29]. One of the non-randomised studies was prospective [23], and the other five were retrospective [22, 24–27]. Three included studies were multicentre studies [25, 27, 28]. A total of 1023 patients with parapneumonic pleural infections were included in this systematic review: 465 were treated by IET and 558 by VATS (non-randomised studies: 436 IET and 528 VATS; randomised feasibility studies: 29 IET and 30 VATS). Besides patients receiving these treatments, the study from Metin *et al.* [22] also included a group of patients treated with a chest tube only (without IET; 47 patients), but these were not considered in the current review. The same study included 17 patients who were treated with a chest tube prior to surgery to improve their septic condition. Muhammad *et al.* [23] included both patients treated with VATS and open surgery (24 patients); however, the results of both subgroups were reported separately, allowing for inclusion of this article in our analysis. In the study of Kermenli *et al.* [26], four patients with non-intubated VATS were included. We included this study in our analysis since the majority of patients (86%) were treated by an intubated VATS. In the study of Wilshire *et al.* 2022 [27], the surgical group consisted of VATS patients, patients converted to open surgery and patients who were treated with open surgery primarily. Since the vast majority (68%) of patients were treated by VATS only, we chose to include this study in our analysis. The randomised trials were both feasibility studies and included patients in an observational group, but these were reported separately, making it possible to include these studies [28, 29].

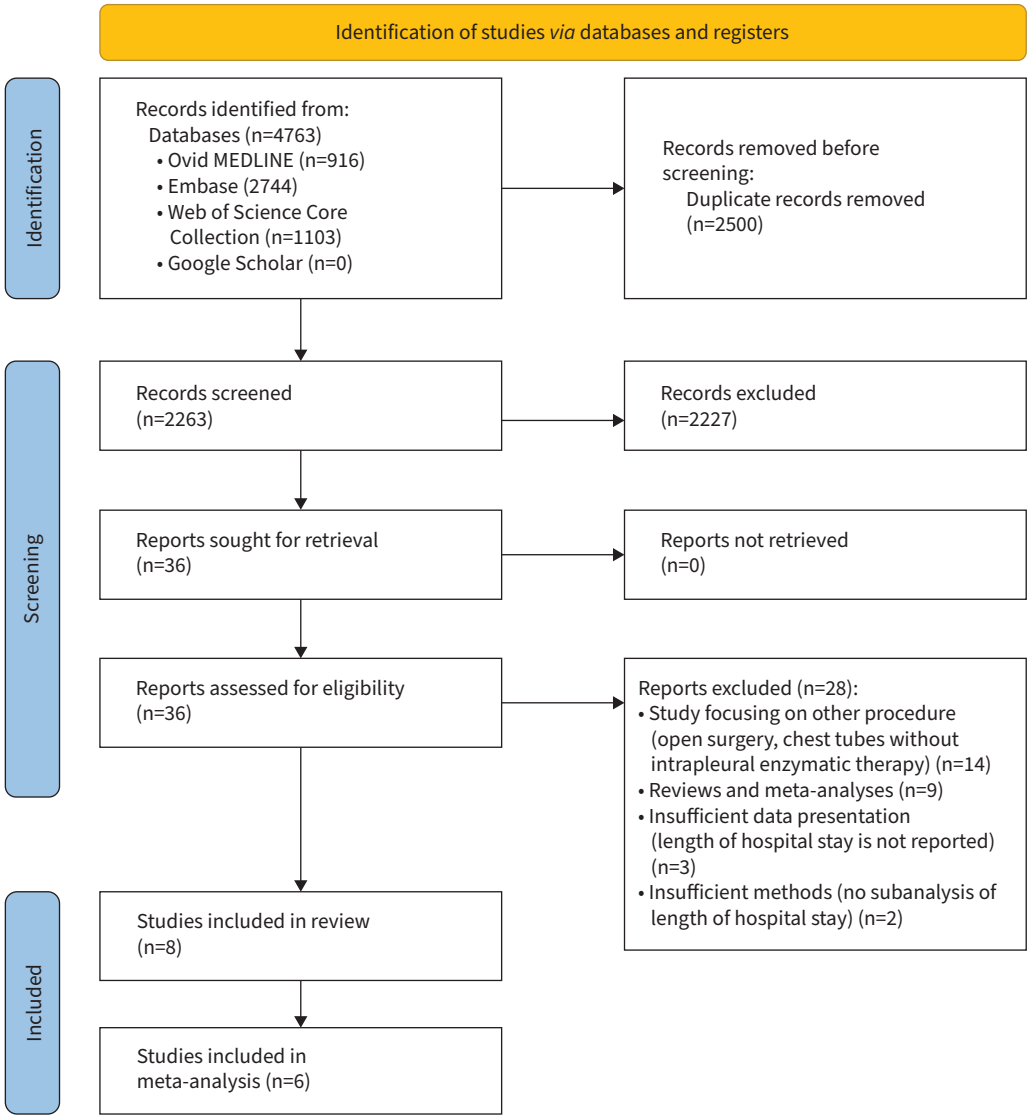

FIGURE 1 Flow chart of study selection.

In both randomised feasibility studies patients were treated by chest tube for drainage of the pleural cavity before randomisation to either IET or VATS [28, 29].

One study used single agent alteplase [26], and three studies used single agent streptokinase [22–24] as the enzymatic agent. Two studies changed their IET management during inclusion, using IET according to the dual agent regimen used in the MIST2 trial [25, 27]. Two studies used dual agent IET for the whole study period [28, 29]. There were no differences in patient characteristics except for age in one study (table 2) [25].

The risk of bias assessment is summarised in supplementary material B. In the non-randomised studies, overall risk of bias was serious in five studies [22, 24–27] and moderate in one study [23]. Especially in the domain of selection of patients some serious risk was observed. In the randomised feasibility studies, the risk of bias was high in one study [28], and another showed some concerns [29]. This was mostly due to deviations from the intended interventions and measurement of the outcomes.

Primary outcome

Outcome data are summarised in table 3. In line with our inclusion criteria, the primary outcome (LOS in days) was reported in all included studies. In the non-randomised studies, the mean or median LOS in the IET group varied between 6 and 14 days. For VATS, this varied between 3 and 10 days. Five out of six

TABLE 1 Basic characteristics of included studies

Author	Publication year	Country	Design	Time period	Population		Participants (IET/VATS)	Type of IET and frequency
					Inclusion criteria	Exclusion criteria		
Metin *et al.* [22]	2010	Turkey	Retrospective cohort study	1995–2007	Patients who were⩾18 years of age and had Class 5 empyema (according to Light's criteria)	<18 years, unloculated and chronic empyema	67 (23/44)[#]	Streptokinase (250 000 units in a 250 mL saline solution) Repeated until the drainage dropped below 100 mL and became serous in nature With a mean streptokinase application of 5.4±2.4 (range 2–11) days
Muhammad *et al.* [23]	2012	Saudi Arabia	Prospective cohort study	2008–2010	Adults with a complicated parapneumonic effusion (category 4 or 5, according to Light's classification). And adults with a single or multiple loculated empyema that had frank pus on thoracocentesis (Light's category 6 or 7)	Post-traumatic pleural infection, tuberculous pleural infection, malignancy-related empyema, HIV, previous thoracic surgery, destroyed lung, diagnosed bronchopleural fistulas, a shrunken haemothorax on CT, contraindication to streptokinase or administration of streptokinase in the previous 2 years	45 (20/25)[¶]	Streptokinase (250 000 units in 100 mL of saline solution) once daily for up to 7 days, or until net drainage was <100 mL per day
Samancilar *et al.* [24]	2018	Turkey	Retrospective cohort study	2005–2014	Patients with parapneumonic empyema with multiloculation and septation in the pleural cavity	NR	78 (24/54)	Daily administration of 250 000 units of streptokinase for 5 days
Federici *et al.* [25]	2021	Switzerland	Retrospective multicentre cohort study	2014–2018	Patients that were considered operable (Karnofsky performance status score of 60 to 80), diagnosed with ATS-2/3 PPE. PPE was diagnosed based on chest CT, inflammation parameters in the bloodwork, pleural fluid contents and pleural fluid cultures	Pleural effusions originating from neoplasia, following surgery or related to chronic infection. No major cardiovascular comorbidities	159 (93/66)	Urokinase (250 000 units in 30 mL of 0.9% NaCl, twice a day for 5 days) From December 2016: t-PA/DNase (10 mg t-PA, 5 mg DNase in 30 mL of 0.9% NaCl, twice a day for 3 days)

Continued

TABLE 1 Continued

Author	Publication year	Country	Design	Time period	Population		Participants (IET/VATS)	Type of IET and frequency
					Inclusion criteria	Exclusion criteria		
Kermenli *et al.* [26]	2021	Turkey	Retrospective cohort study	2015–2020	Patients that were treated for empyema and were treated with chest tubes+intrapleural alteplase or underwent VATS deloculation	Patients with known bleeding diathesis, cerebrovascular bleeding, bronchopleural fistula and coagulopathy were excluded in alteplase treatment	49 (21/28)[+]	Alteplase: in 5 (23.8%) patients 10 mg (10 times) twice a day for 5 days in 16 patients (76.2%) 10 mg (5 times) twice a day for 3 days
Wilshire *et al.* 2022 [27]	2022	United States	Retrospective multicentre cohort study	2015–2018	Patients with complicated pleural infections defined as having a clinical suspicion of a pleural space infection as well as pleural fluid analysis of positive Gram stain/ culture, purulence, LDH >1000·units L^{-1}, glucose <60 mg·dL^{-1} or pH <7.2 who were treated with surgery or dual-agent IET	Loculations alone, without other positive pleural fluid analysis. Prior chest surgery, malignant/ paramalignant pleural effusion, haemothorax, incomplete medical records, oesophageal perforation and indwelling pleural catheter *in situ*	566 (255/311)	Any dose/schedule of dual-agent IET MIST2 dosing was described as 10 mg alteplase and 5 mg dornase for 5–6 doses administered in a twice daily fashion
Bedawi *et al.* [28]	2023	United Kingdom	Multicentre randomised trial	2019–2021	Clinical presentation compatible with pleural infection and a pleural collection with a chest tube *in situ*. Pleural fluid on sampling that was macroscopically purulent, positive on Gram staining or culture for bacterial infection, or pleural fluid pH <7.2 Evidence of residual collection/ongoing sepsis, including the presence of fever and elevated serum levels of inflammatory markers. And willing to give written informed consent	<18 years; previous treatment with IET for empyema; known sensitivity to DNase or t-PA; coincidental stroke; major haemorrhage or major trauma; major surgery in the previous 5 days; previous pneumonectomy on the infected side; pregnancy or lactation; patients with an expected survival of <3 months	39 (19/20)[§]	Intrapleural tPA (10 mg) and DNase (5 mg) through the chest tube (maximum six doses over 72 h) The mean±SD number of given doses was 4.8±1.4

Continued

TABLE 1 Continued

Author	Publication year	Country	Design	Time period	Population		Participants (IET/VATS)	Type of IET and frequency
					Inclusion criteria	Exclusion criteria		
Wilshire *et al.* 2023 [29]	2023	United States	Randomised trial	2019–2021	Patients were eligible if they were 18 years or older, had a clinical pleural infection and had positive results of pleural fluid analysis	<18 years; unable/refused to give consent; not proficient in English; history of prior ipsilateral complicated pleural infection; known sensitivity to DNase or alteplase; history of acute intracranial haemorrhage, stroke, haemorrhage or trauma within the last 3 months; prior ipsilateral surgery; pregnant or lactating; expected survival <6 months; tunnelled pleural catheter in place; on anticoagulation that cannot be interrupted for surgical intervention; known or suspected malignant pleural effusion; renal failure; prior history of or concern for chylothorax or pseudochylothorax; vulnerable populations (prisoners); haemothorax; not having standard health insurance; evidence of clinically significant bilateral effusions at time of evaluation; IET given prior to study screening	20 (10/10)[f]	5 to 6 doses of IET with 10 mg of tissue plasminogen activator and 5 mg of deoxyribonuclease delivered twice a day through the chest tube 6 (60%) had 6 doses, 2 (20%) had 5 doses, and 2 (20%) had 4 doses

IET: intrapleural enzymatic therapy; VATS: video-assisted thoracoscopic surgery; HIV: human immunodeficiency virus; CT: computed tomography; NR: not reported: ATS: American Thoracic Society; PPE: parapneumonic effusion; t-PA: tissue plasminogen activator; LDH: lactate dehydrogenase; MIST2: Second Multicenter Intrapleural Sepsis Trial. [#]: subgroup with 47 patients that had only chest tubes; [¶]: subgroup of 24 patients that had open surgery subgroup; [+]: in four patients in the VATS group the surgical procedure was performed non-intubated because general anaesthesia was found to be a high risk; [§]: subgroup with 21 patients that received standard care following the BTS guidelines; [f]: subgroup of six patients in an observation group.

TABLE 2 Patient characteristics of included studies

Study	Participants (IET/VATS)	Sex, male, n (%)				Age years, mean±SD (range)/median (IQR)				Comorbidities, n (%)				Mean time from onset of symptoms to procedure (days), mean±SD (range)/ median (IQR)			Stage of empyema, n (%)	
		All	IET	VATS	p-value	All	IET	VATS	p-value	All	IET	VATS	p-value	IET	VATS	p-value	IET	VATS
Metin *et al.* [22]	67 (23/44)[#]	77 (67.5)[¶]	17 (73.9)	26 (59.1)	0.494[¶]	Mean 50±16 (18–89)[¶]	Mean 55±16 (26–89)	Mean 49±15 (18–89)	0.407[¶]	Cardiac diseases: 2 (1.8)[¶] DM: 6 (5.3)[¶] Oncological history: 1 (0.9)[¶] Respiratory diseases: 8 (7.0)[¶]	NR	NR	NR	Mean 5 ±1 (2–8)	Mean 4 ±1 (2–8)	0.625	Light's stage 5	Light's stage 5
Muhammad *et al.* [23]	45 (20/25)[+]	52 (75.4)[¶]	15 (75.0)	19 (76.0)	0.758[¶]	Mean 32 (18–50)[¶]	Mean 32.3 ±9.62	Mean 31.1 ±8.99	NR	NR	NR	NR	NR	NR	NR	NR	Light's stage 4 or 5: 13 (65) Light's stage 6 or 7: 7 (35)	Light's stage 4 or 5: 19 (76) Light's stage 6 or 7: 6 (24)
Samancilar *et al.* [24]	78 (24/54)	60 (76.9)	19 (79.2)	41 (75.9)	0.754	Mean 46.05 ±15.9 (16–75)	Mean 45.75 ±13.17 (21–66)	Mean 44.48 ±16.77 (16–72)	0.744	Cardiac diseases: 1 (1.28) DM: 5 (6.41) Respiratory diseases: 15 (19.23)	Cardiac diseases: 0 (0) DM: 5 (20.8) Respiratory diseases: 5 (20.8)	Cardiac diseases: 1 (1.85) DM: 0 (0) Respiratory diseases: 10 (18.5)	0.055	NR	NR	NR	Light's stage 5, 6 or 7	Light's stage 5, 6 or 7
Federici *et al.* [25]	159 (93/66)	110 (69.2)	64 (68.8)	46 (69.7)	0.906	NR	Mean 62 ±17 (23–94)	Mean 56 ±16 (17–84)	0.048	Cardiac diseases: 34 (21.4) DM: 20 (12.6) Oncological history: 22 (13.8) Respiratory diseases: 15 (9.4)	Cardiac diseases: 15 (22.4) DM: 14 (20.9) Oncological history: 12 (17.9) Respiratory diseases: 7 (10.5)	Cardiac diseases: 19 (28.8) DM: 6 (9.1) Oncological history: 10 (15.1) Respiratory diseases: 8 (12.1)	Cardiac diseases: NR DM: 0.057 Oncological history: 0.669 Respiratory diseases: 0.705	NR	NR	NR	ATS- 2/3	42 (63.6) ATS-2 24 (36.4) ATS-3
Kermenli *et al.* [26]	49 (21/28)	35 (71.5)	NR	NR	0.785[§]	Mean 50.6 ±17.8 (23–82)	NR	NR	0.294[f]	Cardiac diseases: 2 (4.1) DM: 8 (16.3) Oncological history: 7 (14.9) Respiratory diseases: 6 (12.2)	Cardiac diseases: 0 (0) DM: 4 (19.0) Oncological history: 3 (14.3) Respiratory diseases: 1 (4.8)	Cardiac diseases: 2 (7.1) DM: 4 (14.3) Oncological history: 4 (14.3) Respiratory diseases: 5 (17.9)	0.292	Mean 5.2 ±2.2	Mean 6.57 ±3.46	NR	NR	NR

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https://doi.org/10.1183/23120541.00619-2024

TABLE 2 Continued

Study	Participants (IET/VATS)	Sex, male, n (%)				Age years, mean±SD (range)/median (IQR)				Comorbidities, n (%)				Mean time from onset of symptoms to procedure (days), mean±SD (range)/ median (IQR)			Stage of empyema, n (%)	
		All	IET	VATS	p-value	All	IET	VATS	p-value	All	IET	VATS	p-value	IET	VATS	p-value	IET	VATS
Wilshire *et al.* 2022 [27]	566 (255/311)	374 (66)	210 (68)	164 (64)	NR	Median 58 (IQR 46–68)	Median 58 (IQR 46–68)	Median 57 (IQR 46–67)	NR	DM: 123 (22) Respiratory diseases: 132 (23.2)	DM: 57 (22) Respiratory diseases: 73 (28.6)	DM: 66 (21) Respiratory diseases: 59 (19)	NR	Median 2 (IQR 1–5)	Median 3 (IQR 1–6)	0.002	CPPE: 163 (64) Empyema: 92 (36)	CPPE: 159 (51) Empyema: 142 (49)
Bedawi *et al.* [28]	39 (19/20)[##]	25 (64.1)	14 (73.7)	11 (55.0)	NR	NR	Median 66 (IQR 56–71)	Median 66 (IQR 59–74)	NR	Cardiac diseases: 20 (51.3) Respiratory diseases: 10 (25.6)	Cardiac diseases: 10 (52.6) Respiratory diseases: 4 (21.1)	Cardiac diseases: 10 (50) Respiratory diseases: 6 (30)	NR	NR	NR	NR	NR	NR
Wilshire *et al.* 2023 [29]	20 (10/10)[¶¶]	15 (75)	7 (70)	8 (80)	NR	Median 57 (IQR 46–65)	Median 55 (IQR 41–62)	Median 57 (50–70)	NR	DM: 2 (10) Oncological history: 1 (5) Respiratory diseases: 2 (10)	DM: 1 (10) Oncological history: 1 (10) Respiratory diseases: 1 (10)	DM: 1 (10) Oncological history: 0 (0) Respiratory diseases: 1 (10)	NR	NR	NR	NR	CPPE: 6 (60) Empyema: 4 (40)	CPPE: 6 (60) Empyema: 4 (40)

IET: intrapleural enzymatic therapy; IQR: interquartile range; NR: not reported; VATS: video-assisted thoracoscopic surgery; DM: diabetes mellitus; ATS: American Thoracic Society; CPPE: complicated parapneumonic effusion; BTS: British Thoracic Society. [#]: subgroup with 47 patients that had only chest tubes; [¶]: numbers and values include other subgroups with other treatment arms; [+]: subgroup of 24 patients that had open surgery; [§]: no statistically significant difference between the patient groups in terms of sex; [f]: no statistically significant difference between the patient groups in terms of age; [##]: subgroup with 21 patients that received standard care following the BTS guidelines; [¶¶]: subgroup with six patients in an observation group.

non-randomised studies reported a statistically significant lower LOS for VATS. Meta-analysis of the non-randomised studies showed a statistically significant shorter LOS for patients treated by VATS compared to patients treated by IET (mean difference 4.2 days; 95% CI 1.5–7.0; p=0.003) (figure 2).

The randomised feasibility studies were not powered sufficiently for this outcome; however, with their small, included patient cohorts, they both showed no significant difference regarding LOS. In one study, the median LOS was 7 days in the IET group and 7 days in the VATS group (p=0.62) [28]. The other study showed a median LOS of 11 days in the IET group and 5 days in the VATS group (p=0.08) [29].

Secondary outcomes

30-day mortality was reported in six studies, but in four of these studies no mortality at 30 days occurred in any of the included patients [22, 23, 25, 29]. Wilshire *et al.* 2022 [29] found no significant differences in 30-day and 90-day mortality (p=0.719 and p=0.933 respectively). Bedawi *et al.* [28] reported a difference in 30-day mortality between the IET group (n=0; 0%) and VATS group (n=2; 10%; p-value not reported).

Grade III/IV complications were reported in six studies [22, 25–27]. In three studies no complications were observed [22, 26, 28], and the other three showed no significant differences between the IET and VATS groups: for Federici *et al.* [25] this was 0% (n=0) *versus* 3% (n=2; p=0.17), for Wilshire *et al.* 2022 [27] this was 12% (n=31) *versus* 12% (n=38; p=1.000), and for Wilshire *et al.* 2023 [29] this was 50% (n=5) *versus* 20% (n=2; p=0.35).

The need for additional treatments was reported differently between studies. Federici *et al.* [25] looked at additional chest tube insertions, and at surgery (either referral for surgery in case of IET, or redo surgery in case of VATS). Both outcomes were significantly higher in the IET group compared to VATS (21.5% (n=20) *versus* 4.6% (n=3; p=0.003) and 12.9% (n=12) *versus* 3% (n=2; p=0.03), respectively). Wilshire *et al.* 2022 [27] found that significantly more additional treatments were needed in the IET group (p<0.001): 39% (n=100) of the patients in this group needed additional treatments (additional chest tube or surgery), whereas in the VATS group additional treatments (reoperation or an additional chest tube) were needed in only 10% (n=32) of patients. The other included studies did not report significant differences between additional treatments comparing patients treated by IET *versus* patients treated by VATS.

Grade I/II complications were reported in five studies, ranging from 0% to 40% for the IET group and from 7% to 40% for the VATS group. The study from Federici *et al.* [25] reported rates of arrhythmia (grade II) which were significantly higher in the VATS group: 6.1% (n=4) *versus* 0% (n=0; p=0.027) in the IET group. In addition, 6.1% (n=4) of patients had persistent air leak in the VATS group (Clavien–Dindo grade I). The other included studies did not report significant differences between grade I/II complications comparing both groups.

The rate of bleeding complications after the administration of IET (Clavien–Dindo grade I) was reported in five studies. Federici *et al.* [25] noted that pleural haemorrhage occurred in 9.6% (n=9) of patients in the IET group. These patients were managed by treatment interruption without the need for additional treatment. In Kermenli *et al.* [26], 4.7% (n=1) of the IET group had a non-massive bleed after the last dose of alteplase. In Metin *et al.* [22], 4.3% (n=1) of the IET group had pleural haemorrhage after the second IET instillation, after which IET was stopped. Samancilar *et al.* [24] reported that IET could not be completed in 25% (n=6) of the IET group because of haemorrhagic chest tube production after the third or fourth dose of streptokinase. Finally, in Wilshire *et al.* 2023 [29], 10% (n=1) reported a haemothorax after four doses of IET, which prompted abortion.

Readmissions at 30 days were reported in four studies [25, 27–29]. Wilshire *et al.* 2022 [27] reported a readmission in 12% (n=31) of the IET group patients *versus* 5% (n=17) in the VATS group (p=0.004), Bedawi *et al.* [28] found an equal rate of readmissions for the IET group (26.3%; n=5) and VATS group (30%; n=6; p-value not reported). No readmissions occurred in the studies by Federici *et al.* [25] and Wilshire *et al.* 2023 [29].

All non-randomised studies provided data regarding the duration of chest tube insertion. This was shorter in the VATS group in all six studies; in four studies the difference was significant (p<0.001 in all four studies) [24, 26, 27, 29]. The size of the chest tubes was similar in these studies and varied between 28 and 32 French for both IET and VATS. For the two randomised studies, the duration of the chest tube was only reported in Wilshire *et al.* 2023 [29] and showed no significant difference (p=0.21). In these studies, the minimal size of the chest tube was 12 French.

TABLE 3 Outcomes of included studies

Study	Length of hospital stay (days), mean±SD (range)/median (IQR)			30-day mortality, n (%)			Complications/morbidity (Clavien–Dindo III/IV), n (%)			Additional treatments, n (%)			Readmissions in 30 days, n (%)			Duration of chest tubes (days), mean±SD (range)/median (IQR)			Pain score, mean±SD		
	IET	VATS	p-value	IET	VATS	p-value	IET	VATS	p-value	IET	VATS	p-value	IET	VATS	p-value	IET	VATS	p-value	IET	VATS	p-value
Metin *et al.* [22]	Mean 11±3 (6–23)	Mean 3±1 (1–5)	<0.001	0 (0)	0 (0)	NR	0 (0)	0 (0)	NR	Open decortication needed: 0 (0)	Open decortication needed: 0 (0)	NR	NR	NR	NR	Mean 9±3 (5–20)	Mean 2±1 (1–3)	<0.001	NR	NR	NR
Muhammad *et al.* [23]	Mean 11.65±3.68	Mean 7.76±4.63	0.003[#]	0 (0)	0 (0)	NR	NR	NR	NR	Referral to surgery: 10 (50)	NR	NR	NR	NR	NR	Mean 6.65±2.08	Mean 5.72±3.27	0.133[a]	NR	NR	NR
Samancilar *et al.* [24]	Mean 14.25±6.44 (3–28)	Mean 6.91±2.63 (4–15)	<0.001	NR	NR	NR	NR	NR	NR	Decortication *via* thoracotomy: 1 (4.1)	Decortication *via* thoracotomy: 4 (7.4)	0.577	NR	NR	NR	Mean 17.33±9.006[¶]	Mean 7.24±4.047[¶]	<0.001	NR	NR	NR
Federici *et al.* [25]	Median 11 (IQR 7–19)	Median 7 (IQR 5–10)	<0.001	0 (0)	0 (0)	NR	0 (0)	2 (3)	0.17	Additional chest tube: 20 (21.5) Referral to surgery or redo: 12 (12.9)	Additional chest tube: 3 (4.6) Referral to surgery or redo: 2 (3)	Additional chest tube: 0.003 Referral to surgery or redo: 0.03	0 (0)	0 (0)	NR	Median 5 (IQR 4–7)	Median 3 (IQR 2–4)[¶]	<0.001	NR	NR	NR
Kermenli *et al.* [26]	Mean 6.73±1.94 (5–10)	Mean 6.35±1.32	0.181	NR	NR	NR	0 (0)	0 (0)	NR	Referral to surgery: 4 (19)	Required thoracotomy: 3 (10.7)	NR	NR	NR	NR	Mean 7.1±2[¶]	Mean 6.96±2.7[¶]	0.853	Mean VAS pain score 24 h after the intervention 2.1±0.7	Mean VAS pain score 24 h after the intervention 2.86±0.9	0.002
Wilshire *et al.* 2022 [27]	Median 12 (IQR9–19)	Median 10 (IQR 7–14)	<0.001	13 (5)	18 (6)	0.719	31 (12)[+]	38 (12)[+]	1.000	100 (39)[§]	32 (10)[§]	<0.001	31 (12)	17 (5)	0.004	Median 7 (IQR 5–10)[¶]	Median 5 (IQR 3–7)[¶]	<0.001	NR	NR	NR
Bedawi *et al.* [28]	Median 7 (IQR 5.5–10)	Median 7 (IQR 5.5–10.5)	0.62	0 (0)	2 (10)	NR	0 (0)	0 (0)	NR	Additional chest tube: 1 (5.3) Other: 1 (5.3)	Additional chest tube: 1 (5) Referral to surgery or redo: 1 (5)	NR	5 (26.3)	6 (30.0)	NR	NR	NR	NR	Mean pain score post tube insertion: 36.4 (19.0)	Mean pain score post tube insertion: 29.2 (14.5)	0.89[#]
Wilshire *et al.* 2023 [29]	Median 11 (IQR 4–18)	Median 5 (IQR 4–6)	0.08	0 (0)	0 (0)	>0.99	5 (50)	2 (20)	0.35	Open decortication: 1 (10) Empyema tube: 1 (10)	Open decortication: 0 (0) Empyema tube: 0 (0)	0.46	0 (0)	0 (0)	>0.99	Median 5 (IQR 4–8)[¶]	Median 4 (IQR 3–5)[¶]	0.21	NR	NR	NR

IET: intrapleural enzymatic therapy; VATS: video-assisted thoracoscopic surgery; IQR: interquartile range; NR: not reported; VAS: visual analogue scale. [#]: numbers included subgroup; [¶]: patients were managed/discharged with a Heimlich valve or discharged with a chest tube; [+]: complications were categorised according to the Ottawa Classification of Thoracic Morbidity and Mortality into minor (grade I–II) and major (grade III–V) complications (in the table only major grades are mentioned); [§]: this includes additional pigtail/chest tube, reoperation, thoracentesis/aspiration of collection, IET >6 doses, IET following surgery, or surgery following IET.

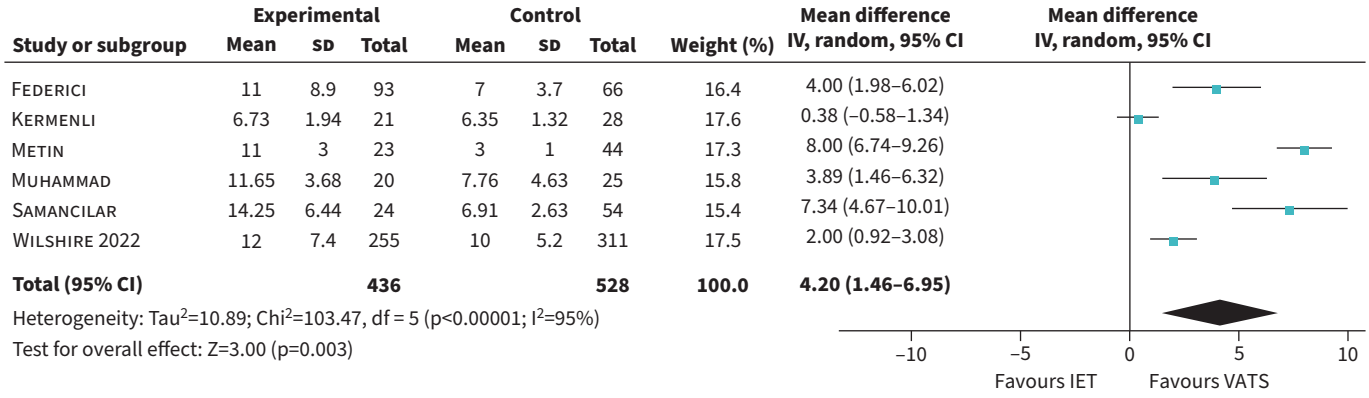

FIGURE 2 Forest plot of mean difference of length of hospital stay (LOS) in patients with parapneumonic pleural infections who were treated with intrapleural enzymatic therapy (IET) or video-assisted thoracoscopic surgery (VATS). The mean LOS (days) of each study are shown as the middle of the square, the size of the square stands for the weight, and the horizontal lines show the 95% confidence interval (CI). The summarised mean difference is presented as a diamond; the heterogeneity test result is also presented below. IV: inverse variance.

Pain scores were analysed in two studies. In the study of Kermenli *et al.* [26] the Visual Analogue Scale pain score was used (scale 1–10) 24 h after the insertion of a chest tube (mean pain score 2.1) or after surgery (mean pain score 2.86), and they reported that the score was significantly higher in the VATS group (p=0.002). The study of Bedawi *et al.* [28] reported a mean pain score post tube insertion of 36.4 in the IET group and 29.2 in the VATS group (scale 1–100; p=0.89). They also investigated QoL using the EQ-5D utility index scores, comparing baseline with 2 months after the intervention. The IET group (0.35–0.83) showed a significantly greater improvement in QoL compared to VATS (0.38–0.59; p=0.0023). Other patient-related outcome measures, such as dyspnoea, fear or return to work, and cost of treatment were not reported in any of the included studies.

Discussion

In this systematic review, we compared the use of IET administered through a chest tube with VATS as the initial treatment in patients with a parapneumonic pleural infection. Eight studies were included comprising 1023 patients. Regarding our primary outcome, we showed VATS resulted in shorter LOS compared to IET in a meta-analysis of the non-randomised studies (comprising 964 patients, both single agent and dual agent IET). However, data from two small randomised feasibility studies showed no difference in LOS (comprising 59 patients). Both treatments show no statistical differences in morbidity and mortality rates. Quality assessment showed a high risk of bias in most studies, with selection bias being the most frequent in the non-randomised studies. The randomised feasibility studies also showed concerns regarding the risk of bias, especially due to deviations from the intended interventions and measurement of the outcomes. This study highlights the lack of robust data and the need for high-quality studies to answer this relevant research question.

Determining the optimal treatment strategy of parapneumonic pleural infections remains challenging, especially in the current era of minimally invasive surgery, and the widespread use of IET since the publication of the encouraging results of the MIST2 trial [5]. Previous comparative studies such as those included in our review combine highly heterogeneous treatment approaches, both for surgical management (open surgery and minimally invasive surgery) and for non-surgical management (chest tube with/without IET, different types or combinations of IET). This heterogeneity is increased by a lack of definitions for medical treatment failure and chest tube failure, and due to this heterogeneity, solid recommendations for optimal treatment are difficult. Therefore, most guidelines advise treatment with dual agent IET, followed by surgical consultation when this approach fails to resolve the pleural collections [1, 3].

Regarding our primary outcome, the meta-analysis of the non-randomised studies showed that LOS is significantly reduced with initial treatment with VATS compared to IET. The study of Kermenli *et al.* [26] is the only study in the meta-analysis with no favour to VATS. This might be explained by the fact that this was the only study that used alteplase as IET or the fact that the VATS group consisted of patients with high risk for general anaesthesia (ASA-4 patients), resulting in a non-intubated VATS, with a possibility of a worse prognosis. The study of Metin *et al.* [22] shows the most favour towards treatment

with VATS, which could be explained by the fact that there was a percentage of patients who were treated priorly with a chest tube to improve their septic condition before VATS. A wide range of the mean LOS with the use of IET was noticed, varying between 6 and 14 days across studies. For VATS, this varied between 3 and 10 days. This variation may be explained by differences in the definition of LOS between the studies or a difference in IET regimes (single agent or dual agent according to the MIST2 protocol). Our definition of LOS was the number of days from intervention to discharge. Some studies used the day of intervention (first dose of IET or VATS) as a starting point [22–24, 29], whereas others used the day of randomisation as a starting point [28] or the day of hospitalisation [27]. Also, some studies measured the LOS till discharge and others till the day that chest tubes were removed [25]. And in some studies, it is not clear how they measured the LOS [26].

Contrarily, the two included randomised feasibility studies failed to show a significant difference in LOS between IET and VATS. This difference in results might be due to selection bias in the non-randomised studies, or due to the fact that both randomised studies were designed as small feasibility studies for a definitive, appropriately powered trial, and might have been underpowered for this outcome. The latter may be illustrated by the fact that in one of these randomised studies, LOS was 11 *versus* 5 days in favour of VATS, which is in line with our meta-analysis result [29]. However, only 20 patients were included in this study, resulting in a statistically non-significant result (p=0.08). Contrarily, the other randomised study (comprising 39 patients) showed a median LOS of 7 days in both groups (p=0.70) [28].

In this systematic review we did not find a statistical difference in mortality and Clavien–Dindo grade III/IV complications between IET and VATS, which is mainly due to the fact that both outcomes were rare in both treatment arms. Some studies also used the Ottawa Classification for grading complications [27, 29]; however, since this is similar to the Clavien–Dindo classification, we converted this to one classification. Our mortality rates are in line with the results from a Cochrane review comparing surgical and non-surgical management of pleural empyema, in which no significant difference in mortality was found [30]. However, this Cochrane review included studies of all age groups, included patients treated with chest tube only (without IET) and included different types of surgery (not only VATS).

The need for additional treatments varied between the included studies. Two studies showed significantly higher numbers of additional treatment in the IET group [25, 27]. This can be explained through the more invasive technique of a VATS, making it easier to remove all loculated pleural fluid and perform a decortication if necessary to acquire pleural apposition. While the MIST2 trial showed a remarkably high success rate with dual agent IET with t-PA and DNase through the chest tube [5], up to 50% of patients in the IET group in this review were referred for additional surgery [23]. This may be explained by the fact that not all included studies used the MIST2 treatment regimen (table 1). Wilshire *et al.* 2022 [27] confirm this, showing that applying a non-MIST2 dosing was associated with higher odds of crossover compared to MIST2 dosing. The number of additional treatments may be lower in the VATS group, but it must be considered that in multiple studies a conversion from VATS to thoracotomy was done: 15% (n=10) in Federici *et al.* [25], and in the study of Muhammad *et al.* [23], the conversion rate was 8% (n=2). However, because conversion is decided intra-operatively, this is not recorded as additional treatment.

Bleeding after IET, requiring a change in treatment regimen, was found in five studies, and ranged from 4.3% to 25%. However, it should be noted that the majority of included studies were non-randomised and retrospective, with possible underreporting of bleeding complications. A Cochrane review on the effectiveness of IET showed low certainty evidence that there may be a risk of more side-effects, such as bleeding, after the use of IET [31]. The varying bleeding prevalence may, at least in part, be explained by the different types and doses of IET used, as well as different inclusion criteria. For example, Kermenli *et al.* [26] found a low number of bleeding complications (4.7%, n=1), but they excluded patients with known bleeding diathesis, recent cerebrovascular bleeding and coagulopathy in alteplase treatment. Previous studies including the MIST2 trial and a study from 2022 with over 1800 patients reported low numbers of pleural bleeding (around 4%) [5, 32, 33]. A complication that was more often seen in the VATS group and that is not uncommon after pulmonary surgery was the rate of arrhythmia. In the study by Federici *et al.* [25] the rate of arrhythmia was significantly higher in the VATS group (p=0.027) when compared with the IET group. In other studies, supraventricular arrhythmias after pulmonary surgery are reported with rates of up to 5% for both VATS and open surgery [34, 35].

Four of the included studies showed a significantly decreased duration of chest tube insertion when a patient was treated by VATS. However, a considerable number of patients in all included studies were discharged with a chest tube or Heimlich valve (range 2.5–22.4%: IET and VATS groups combined). This explains that in some studies, patients had a shorter LOS than their actual duration of chest tube insertion [24, 26].

The total cost of treatment was not described in any of the included studies, but a previously published cost-effectiveness analysis of IET *versus* VATS for early empyema showed that costs are nearly equivalent [36]. However, an older study from 1997 reports that VATS has less costs compared to IET [37]. Also, studies measuring patient-reported outcome measures in parapneumonic pleural infections are limited. One of the included studies compared QoL at baseline and 2 months after intervention and found better improvement of QoL in the IET group compared to VATS (p=0.0023) [28]. Two studies reported on pain, with one study reporting significantly lower pain scores in the IET group (p=0.002) [26].

This review has several limitations. We were only able to include non-randomised studies in the meta-analysis, mostly with a retrospective design. In addition, one study in the meta-analysis compromised half of the included patients, which is not ideal for a meta-analysis and could have influenced the results. The only two available randomised studies were feasibility studies with a limited number of patients and could not be included in the meta-analysis. The lack of sufficiently powered randomised evidence introduces a higher risk of bias which affects the validity and reliability of the data. For example, patients who were not suitable (for example because of comorbidities) for VATS were automatically treated in the IET group in some of the included studies, resulting in differences between the treatment groups. In addition, there was considerable heterogeneity between studies with regard to the included population and treatment procedures. For example, different regimens of IET were used. Current guidelines recommend IET according to MIST2 (a combination of t-PA and DNase) [1, 3]. In the meta-analysis of non-randomised studies different IET regimens were compared to VATS. Of the six studies, two changed their regimen during the study to the MIST2 regimen (before changing to this regimen they either used single agent IET or any other dose/schedule of dual agent IET than the MIST2 regimen) [25, 27], and the other four studies used single agent IET with streptokinase or alteplase [22–24, 26]. In the studies where the regimen was changed to the MIST2 regimen, numbers of LOS from patients that received the MIST2 regimen were not available in all studies, and therefore it was not possible to perform an analysis on dual agent IET *versus* VATS for this outcome. This may have led to the conclusion that patients treated by a VATS had a shorter LOS. However, this might be an overestimation considering that most patients in the IET group did not receive optimal dual agent IET. This might have resulted in a longer LOS and more additional treatments. This would also explain the discrepancy with the results from the randomised feasibility studies that show no significant difference in LOS while they are using the IET regimen of MIST2. Next to this, we included studies where no separate data were available when a small proportion of patients received a different treatment from IET or VATS. Although these numbers were small (defined upfront as always less than a third of the included patients), it might have influenced the analyses. Also, in the study from Bedawi *et al.* [28] 50% of the patients in the VATS group received an alternative intervention because the risk/benefit balance of VATS was no longer in favour of proceeding with surgery by the time an operation was feasible. Lastly, for this review, we did not focus on the use of antibiotics. Only the study from Federici *et al.* [25] described the type of antibiotics prescribed to their patients. Other studies reported that antibiotics were used, but not the specific regimens. However, the choice and length of course of antibiotics may have a significant impact on the course of the disease.

This systematic review identifies important knowledge gaps in the treatment of parapneumonic pleural infections. In everyday medical practice, patients with parapneumonic pleural infections frequently receive IET first and are only considered for VATS if this initial treatment fails. The current review looks at initial treatment of parapneumonic pleural infections by IET or VATS and therefore differs from everyday practice. However, currently there are ongoing randomised controlled trials, the DICE and FIVERVATS studies [38, 39], which compare early VATS with early dual agent IET. Further randomised studies are needed to investigate the right order and ideal timing and patient selection for the different treatment modalities. Therefore, clear definitions of what a parapneumonic pleural infection and treatment failure is are needed before starting a study. Furthermore, secondary topics such as chest tube duration after IET or VATS, the role and duration of antibiotics and patient-related outcomes should be incorporated as outcome parameters in future studies.

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