EUROPEAN CLINICAL RESPIRATORY JOURNAL
2023, VOL. 10, 2174645
https://doi.org/10.1080/20018525.2023.2174645

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REVIEW ARTICLE

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Does the time to diagnosis and treatment influence outcome in adults with pleural infections

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ABSTRACT

Objective: To investigate the effect of early diagnosis and intervention in adult patients with complicated parapneumonic pleural effusion or pleural empyema and the impact on outcomes.
Methods: A systematic review based on a literature search of the PubMed database was performed.
Results: Eleven eligible studies were included; nine observational studies and two randomised controlled trials totalling a study population of 10,717 patients. The studies were conducted from 1992 to 2018, all in Europe and Northern America except one. Results varied between studies, but a trend towards better outcome in patients with shorter duration of symptoms and quicker initiation of treatment was found. We found that duration of symptoms before treatment may affect length of hospital stay, rate of conversion to open surgery, and frequency of complications.
Conclusion: We found that an earlier intervention in adults suffering from complicated parapneumonic pleural effusion and pleural empyema may potentially improve the outcome of patients in terms of length of stay, conversion to open surgery, and general complications following treatment, but not regarding mortality. Further studies are required to specify the timing of each intervention, and direct comparison in early management of interventions.

ARTICLE HISTORY
Received 24 February 2022
Accepted 26 January 2023

KEYWORDS
Pleural empyema; diagnosis; treatment; adult

Introduction

Pleural infection in association with pneumonia has traditionally been classified into three stages: simple exudative stage, fibrinopurulent stage, and a third organizing stage with scar tissue formation [1]. More recent clinical guidelines use the result of pleural fluid aspiration to categorise patients with pleural infection due to pneumonia into simple parapneumonic effusion, complicated parapneumonic effusion, and pleural empyema [2]. Pleural infections evolve through these stages through time, often over the course of three to six weeks, although the timeline varies from each individual patient, implicating that not all patients reach the empyema stage [3].

While a simple parapneumonic effusion has an overall good prognosis when treated with antibiotics, invasive treatment is generally required in complicated parapneumonic effusion and pleural empyema with median hospital stays of 13 days [4]. Despite improvement regarding diagnostics and treatment, the 1-year mortality remains unchanged at an estimated 15–20% [3,5]. Additionally, the incidence of pleural infection has seen a rise over the past decades [6–8].

It is generally assumed that diagnosis and management of pleural infection requires urgent intervention [9]. Evidence regarding this assumption is sparse as only a few studies have specifically addressed the aspect of the timing of an intervention [6]. Current guidelines [2,5,10] encourage antibiotics as initial treatment in suspected infected pleural effusion, and intervention in terms of drainage of complicated parapneumonic effusion and pleural empyema. Early diagnosis and intervention are likely to be critical factors in improving outcomes. Thus, timely use of diagnostic thoracentesis, imaging, and treatment including invasive intervention is of importance. Initial invasive treatment is typically in the form of ultrasound guided drainage or surgical pleural drain, whereas surgery either by open surgery or by video-assisted thoracoscopic surgery (VATS) is most often used as secondary treatment options [2,5,10].

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The optimal timing of treatment and invasive intervention in patients with ongoing pleural infection is unclear but may be important to the prognosis; thus, an overview of existing data regarding importance of early diagnosis and timing of intervention is needed. To answer the above, we present the study question as follows: Does the time to diagnosis and treatment influence outcome in adults with pleural infections?

Material and methods

Study type

For this systematic review a literature search of the PubMed database was conducted. The search strategy can be found in the supplementary data, Appendix 1. The concluding search was conducted mid-July 2022 with no restrictions on the date of publication. Only articles in English were included.

Screening and assessment of study eligibility

All papers identified by the search were screened for study inclusion using titles and abstracts. Eligibility used for the relevant original articles is described in detail below. The references of included key publications were reviewed for additional articles. Screening and assessment of eligibility was performed by Klausen, as well as data extraction and analysis. A total of 904 abstracts were screened, of which 274 full articles were retrieved. In addition, two articles were identified from lists of references, retrieved, and included in the study.

Eligibility criteria

Observational studies or randomised controlled trials (RCTs) examining the relation between symptom duration in patients diagnosed with pleural infection (complicated parapneumonic effusion or pleural empyema) and specific outcomes after treatment were included in this paper. Staging of pleural infection was in accordance with the staging used by both the British Thoracic Society (BTS) and the American Association for Thoracic Surgery (AATS). Only studies reporting data on duration of symptoms (DOS) and time of treatment initiation were included. The term 'duration of symptoms' is defined as from the first time the patients were registered in the study or from when they recall their first symptoms and until the time of first treatment/intervention specific to the study. Outcomes were mortality, length of hospital stay (LOS), and morbidity including post-operative/post-intervention complications. Treatment modalities were antibiotics, drainage, intrapleural fibrinolytic (± DNase), and surgery either as VATS or open surgery. The exclusion criteria were editorial commentaries, reviews, or other language than English. Studies were also excluded if they lacked data on DOS, included pediatric patients, or lacked primary data. Two hundred and sixty-five articles were excluded based on the lack of relevant outcome parameters or no data on duration of symptoms.

Data extraction

Data extracted from the included studies were authors, publication year, study period, country of origin, study design, number of patients included, mean/median age of patients, intervention/treatment, LOS, DOS, and data on specific outcomes mentioned above. Conversions to open surgery were included as an outcome.

Quality assessment

A quality assessment was made of included studies applying the assessment tools suggested by the National Heart, Lung and Blood Institute [11].

RCT-studies were assessed based on quality of randomisation, calculation of statistical power, blinding, intention-to-treat principle, balancing of patient characteristics at baseline, and termination.

Observational studies were evaluated according to the relevance of the study question including clearly defined, valid, reliable, and consistently executed exposures as well as outcomes [11].

Patients and public involvement

No patients were involved due to the nature of the paper.

Results

Included studies

Eleven studies were included in this analysis with a total of 10,717 patients. The process of selection for inclusion and exclusion of studies in this paper is depicted in Figure 1. Table 1 contains an overview of the included studies. The median age of patients in the included studies spanned from 50 ± 17 years to 61 ± 18 years. Data analyzed in the included studies were collected in the period from 1992 to 2018. Seven studies were retrospective. In several studies, patients suffering complicated parapneumonic pleural effusion and

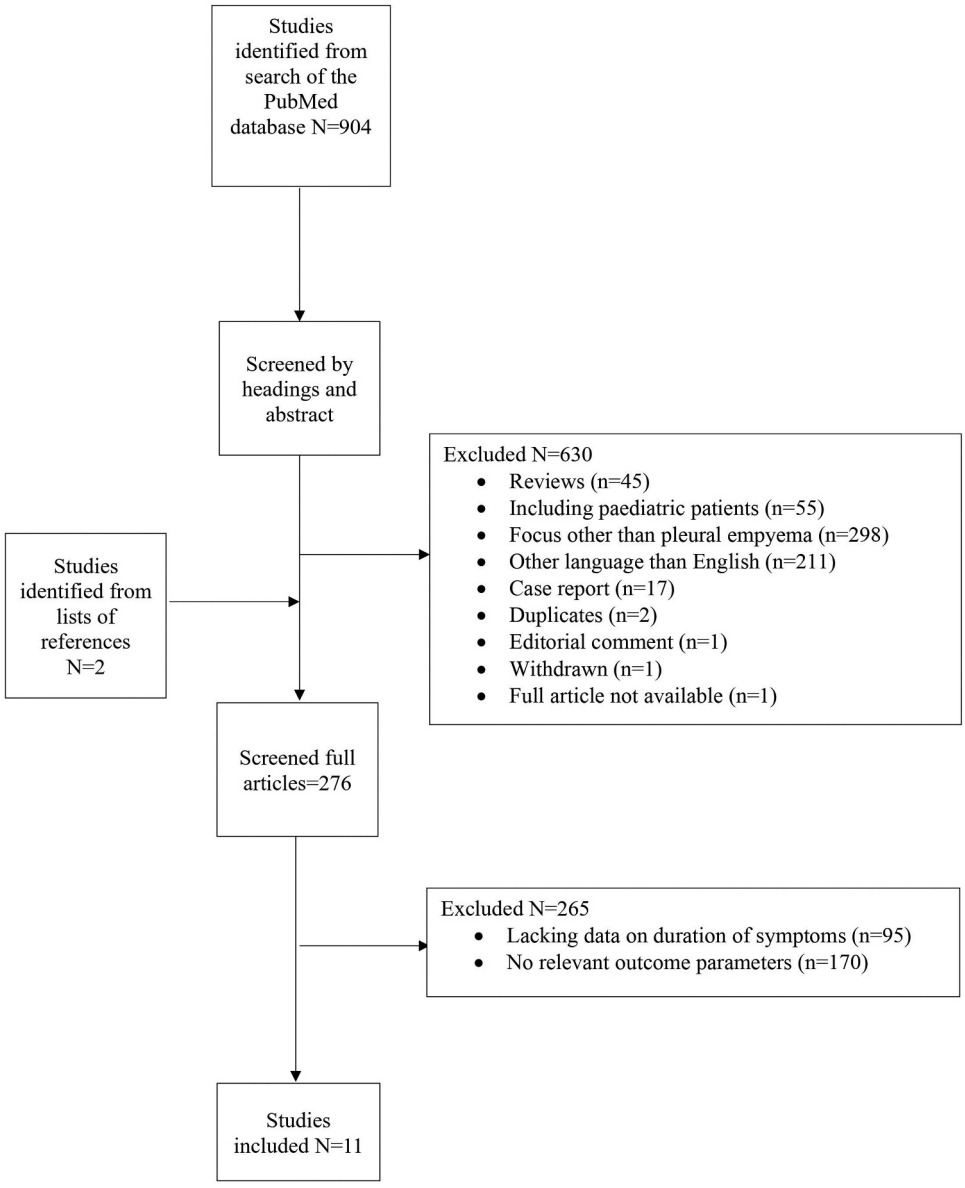

Figure 1. Process of study inclusion/exclusion.

pleural empyema could not be separated. Lacking separation of disease stages in the results made it hard to define the most common stage of disease. Majority of studies were conducted in Europe and Northern America [12–22].

Two different study types were included in this analysis: RCT- and observational studies; however, merely two RCTs were included. One observational study included a large cohort of 9,014 patients; the remaining ten studies included between 64 and 454 patients. All studies presented data on stage of disease prior to intervention except for one [12]. Antibiotics were used as primary treatment in all included studies along with tube drainage. Further intervention included VATS and open surgery as well as intrapleural fibrinolytic instillation. All included studies, except one [19], had LOS as an outcome of treatment. Two studies [15,22] defined LOS as days from intervention with tube thoracostomy and not from primary admission to hospital. Three other studies specified LOS as days after surgery [12,16,18]. One study reported both LOS from admission to hospital as well as postoperatively [14]. Three studies had conversion to open surgery as outcome of VATS [14,16,19] while one study focused on the need for additional procedures after failure of first intervention [17]. The comparators for the interventions are displayed in Table 1 as outcome parameters. Time periods for the included studies and the country of origin can be found in Table 1 as well. Four studies were performed in multiple centers with

Table 1. Overview of included studies.

First Author, Year, Reference	Country of origin and time period	Study design	No. of Patients (n)	Mean age of Patients (years)	Stage of pleural infections	Intervention	Outcome parameters
Nayak et al. 2019 [12]	Canada, January 1996 to December 2015	Retrospective cohort study	9,014	60.6 ± 16.4	Complicated parapneumonic pleural effusion and pleural empyema	OS, CTF, or VATS	LOS, mortality and complications
Bongiolatti et al. 2017 [13]	Italy, 2012 to 2015	Retrospective cohort study	64	57.8 ± 16.4	Complicated parapneumonic pleural effusion and pleural empyema	Uniportal-VATS or OS	LOS, mortality, complications and in-hospital mortality
Jagelavicius et al. 2017 [14]	Lithuania, January 2011 to June 2014	Prospective cohort study	71	52 ± 16	Complicated parapneumonic pleural effusion and pleural empyema	VATS	LOS, mortality, conversion to OS and complications
Metin et al. 2010 [15]	Turkey, January 1995 to December 2007	Retrospective cohort study	114	50 ± 17	Light's criteria: stage 5 (complicated parapneumonic pleural effusion)	Tube thoracostomy, streptokinase or VATS	LOS and complications
Stefani et al. 2013 [16]	Italy, 2005 to 2012	Retrospective cohort study	97	Median: 54 (IQR: 21–83)	Complicated parapneumonic pleural effusion and pleural empyema	VATS	LOS, mortality, conversion to OS and complications
Wozniak et al. 2009 [17]	USA, 2000 to 2006	Retrospective cohort study	104	55.7 ± 1.4	Simple parapneumonic pleural effusion and complicated parapneumonic pleural effusion	Tube drainage, VATS or OS	LOS, additional procedures, mortality and complications
Chung et al. 2014 [18]	South Korea, April 2004 to March 2012	Retrospective cohort study	128	Group 1: 52.93 ± 14.8 Group 2: 50.06 ± 12.8 Group 3: 51.07 ± 19.5	Simple parapneumonic pleural effusion, complicated parapneumonic pleural effusion and pleural empyema	VATS or open decortication	LOS, mortality and complications
Lardinois et al. 2005 [19]	Switzerland, 1992 to 2002	Prospective cohort study	328	Median: 55 (IQR: 18–90)	Complicated parapneumonic pleural effusion and pleural empyema	VATS or open decortication	Mortality, conversion to OS and complications
Paz et al. 2021 [20]	France, 2001 to 2018	Retrospective cohort study	133	59.0 ± 17.2	Complicated parapneumonic pleural effusion and pleural empyema	RTT with urokinase or RTT with Urokinase and DNase	LOS, mortality, RTT failure, ICU admission, time to apyrexia, and volume of pleural fluid drained
Maskell et al. 2005 [21]	United Kingdom, June 1999 to December 2002	Randomised controlled trial	454	Streptokinase: 60 ± 18 Placebo: 61 ± 18	Complicated parapneumonic pleural effusion and pleural empyema	Intrapleural streptokinase or placebo along with routine antibiotics, chest-tube drainage and surgery if needed	LOS, mortality, need for surgery, and radiographic outcome
Rahman et al. 2011 [22]	United Kingdom, December 2005 to November 2008	Randomised controlled trial	210	Placebo: 58 ± 19 t-PA+DNase: 60 ± 19 DNase: 57 ± 18 t-PA: 60 ± 17	Complicated parapneumonic pleural effusion and pleural empyema	Double placebo, intrapleural t-PA+DNase, t-PA, or DNase	LOS, mortality, need for surgery, radiographic outcome, and adverse events

Abbreviations CTF, chest tube drainage with/without fibrinolytics; ICU, intensive care unit; IQR, interquartile range; LOS, length of hospital stay; NS, not specified; OS, open surgery; RTT, repeated therapeutic thoracentesis; t-PA, intrapleural tissue plasminogen activator; VATS, video-assisted thoracic surgery.

participation of both medical and surgical departments [12,20–22] while the remaining seven studies were performed primarily in thoracic surgical departments.

Quality assessment of included studies

Nine observational studies were included in this paper, of which seven were retrospective [12,13,15–18,20] and two were prospective [14,19]. A quality assessment of the observational studies is presented in Table 2. Four studies were rated as 'good' [12,16,18,20]. Based on short insufficient time of follow-up the quality of two studies were assessed to be 'fair' [14,19]. Additionally, three studies were also rated as fair, since one study had no information on time of follow-up [17], while two studies omitted adjustment for potential confounders [13,15].

The two RCTs included in this paper were analysed according to the assessment tool described earlier [11]. Both RCTs used adequate means of randomisation according to the play of chance and were both double-blinded [21,22]. Generally, the quality of both RCTs was considered 'good'.

Stages of pleural infections

Patient groups differed in the aspect of pleural infection stages. Ten studies staged pleural infection according to the classification described by the American Thoracic Society [13,14,16–22]. Patients with complicated parapneumonic effusion or pleural empyema were included in eight studies [12–14,16,19–22]. Wozniak et al. [17] and Chung et al. [18] both included patients suffering from simple parapneumonic effusions, and unfortunately those patients could not be separated in the above two studies, and the studies could thus not be included in the data analysis. One study [15] staged pleural empyema based on Light's Criteria including only patients with class 5 pleural infection, which would be equivalent to a complicated parapneumonic effusion [23]. Generally, the studies did not group patients regarding the stage of pleural infection; thus, it was not possible to analyse the disease stages separately, though it would be more clarifying to do so. Even less so did they perform analysis on the correlation between stage disease, DOS, and outcomes.

Duration of symptoms (DOS)

Studies defined DOS as the time from onset of symptoms or diagnosis of respiratory disease until the time of first intervention, being one of the study-specific interventions presented in Table 1. Patients were grouped based on intervention. Data on DOS was then calculated for each intervention with the potential of clarifying the role of DOS as a possible confounder for successful treatment. Mean DOS varied vastly from 4 to 29.5 days [15,16]. An overview of DOS for all included studies is presented in Table 3.

Table 2. Quality assessment of included observational studies.

First Author, Year, Reference	Clear and relevant study question	Specified and clearly defined population	Clearly defined, valid, reliable, and consistently executed exposures	Clearly defined, valid, reliable, and consistently executed outcome	Statistically adjusting for potential confounders	Sufficient follow-up rate and timeline of outcomes	Quality assessment
Nayak et al. 2019 [12]	Yes.	Yes.	Yes.	Yes.	Yes.	Yes. One-year mortality.	Good.
Bongiolatti et al. 2017 [13]	Yes.	Yes.	Yes.	Yes.	No.	Yes. 2 weeks of monitoring with chest x-ray. Monitored regularly clinically radiogically for 12–24 months.	Fair.
Jagelavicius et al. 2017 [14]	Yes.	Yes.	Yes.	Yes.	Yes.	Yes. 30-days mortality.	Fair.
Metin et al. 2010 [15]	Yes.	Yes.	Yes.	Yes.	No.	Yes. Out of the 114 patients, 100 were followed up after 26.1 (mean, range 2–86) months.	Fair.
Stefani et al. 2013 [16]	Yes.	Yes.	Yes.	Yes.	Yes.	Yes. Follow-up 6 months.	Good.
Wozniak et al. 2009 [17]	Yes.	Yes.	Yes.	No.	Yes.	No.	Fair.
Chung et al. 2014 [18]	Yes.	Yes.	Yes.	Yes.	Yes.	Yes. The mean follow-up time after surgery was 488.76 days (range, 9 days to 2,709 days).	Good.
Lardinois et al. 2005 [19]	Yes.	Yes.	Yes.	Yes.	Yes.	Yes. 30-day mortality.	Fair.
Paz et al. 2021 [20]	Yes.	Yes.	Yes.	Yes.	Yes.	Yes. One-year mortality.	Good.

Table 3. Duration of symptoms and complications.

First Author, Year, Reference	Duration of symptoms (DOS)	Length of hospital stay (mean, days)	Conversion to open surgery	Complications (readmission, resurgery, additional procedures, pneumonia, etc.)
Nayak et al. 2019 [12]	Mean DOS: OS: 11.5 days. CTF: 6.6 days. VATS: 9.9 days.	*Post operation stay* OS: 20 CTF: 20 VATS: 20 (1996–2000) ➔ 16 (2011–15)	NS	*Readmission 90 days*: • All cause: OS: 479 patients (18,8%). CTF: 1323 patients (21.1%). VATS: 188 patients (17.6%) • Empyema specific: OS: 81 patients (3.2%). CTF: 281 patients (5.4%). VATS: 40 patients (3.7%).
Bongiolatti et al. 2017 [13]	Uniportal-VATS: 13 ± 4 days. OS: 25 ± 14 days.	Uniportal-VATS: 6.7 ± 1.9. OS: 12.2 ± 4.7.	3/30 (10%) from Uniportal-VATS to VATS. None to OS.	*Reintervention, blood transfusion, late recurrence, etc.*: Uniportal-VATS: 3(10%). OS: 16 (47%).
Jagelavicius et al. 2017 [14]	19 days (IQR: 10–25).	*Median*: VATS: 11 (IQR: 9–17) Conversion to OS: 11 (IQR: 8–17).	VATS: 53 patients. Conversion to OS: 18 patients.	*Reintervention or readmission*: VATS: 10 (18.9%). Conversion: 4 (22.2%).
Metin et al. 2010 [15]	TT: 7 ± 3 days SK: 5 ± 1 days VATS: 4 ± 1 days	*Postoperative stay* TT: 13 ± 4 SK: 11 ± 3 VATS: 3 ± 1	No conversions.	*Remaining pleural space, recurrence, etc.*: TT: 23 patients SK: 9 patients VATS: 3 patients
Stefani et al. 2013 [16]	VATS: 19.5 (5–75) days. OS: 29.5 (7–92) days.	*Postoperative stay, median*: VATS (post surgery): 8.3 (IQR: 3–30). OS (post surgery): 8.4 (IQR: 3–44).	57 patients (59%) were converted from VATS to OS.	*Air leak, bleeding, etc.*: VATS: 5 patients (12.5%). OS: 18 patients (32%).
Wozniak et al. 2009 [17]	Success of first intervention: 15.1 ± 2.0 days. Failure of first intervention: 11.8 ± 2.6 days.	Success of first intervention: 17.3 ± 1.5 Failure of first intervention: 22.6 ± 3.1	Success of first intervention: 72 patients. Failure of first intervention: 32 patients.	*Major complications, not specified*: Success of first intervention: 25 patients (78%) Failure of first intervention: 13 patients (18%)
Chung et al. 2014 [18]	VATS: <2 week: 73 patients. 2–4 weeks: 33 patients. >4 weeks: 14 patients. Directly to OS: >4 weeks: 8 patients.	*Postoperative stay* Symptom duration: <2 weeks: 9.49 ± 4.3. 2–4 weeks: 9.73 ± 4.2. >4 weeks: 13.5 ± 6.4. >4 weeks and directly to OS: 19 ± 12.8.	1 (1,4%) conversion in group<2 weeks.	*Postoperative bleeding, resurgery, additional drainage, or prolonged air leakage*: <2 weeks: 7 patients (9.5%). 2–4 weeks: 1 patient (3%). >4 weeks: 5 patients (35.6%).
Lardinois et al. 2005 [19]	VATS: 9.8 ± 3.2 days OS: 17.3 ± 3.8 days	Raw data not presented in article.	79 of 178 (44%) VATS patients were converted to OS.	*Prolonged air leak, renal insufficiency, resurgery due to bleeding, etc.*: 30 patients (9%). *Recurrence of empyema*: 8 patients (24%).
Paz et al. 2021 [20]	Urokinase: 12 days (IQR: 7.5–20.5) Urokinase and DNase: 11 days (IQR: 6–17)	Urokinase: 23 (IQR: 18–41) Urokinase and DNase: 16 (IQR: 12–24)	NS	*Urokinase*: RTT failure: 19%, ICU admission: 15%, re-hospitalization rate: 12% *Urokinase and DNase*: RTT failure: 17%, ICU admission: 15%, re-hospitalization: 10%
Maskell et al. 2005 [21]	Streptokinase: 14 days (IQR: 8–28) Placebo: 15 days (IQR: 8–28)	Streptokinase: 13 (range: 1–271) Placebo: 12 (range: 2–152)	NS	*Need for surgery*: Streptokinase: 32 patients (16%) Placebo: 30 patients (14%)
Rahman et al. 2011 [22]	Placebo: 13 days (IQR: 7–21) t-PA+DNase: 13 days (IQR: 7–22) DNase: 14 days (IQR: 7–30) t-PA: 14 days (IQR: 7–30)	Placebo: 24.8 ± 56.1 t-PA+DNase: 11.8 ± 9.4 DNase: 28.2 ± 61.4 t-PA: 16.5 ± 22.8	NS	*Referral for surgery*: Placebo: 8 patients (16%) t-PA+DNase: 2 patients (4%) DNase: 18 patients (39%) t-PA: 3 patients (6%)

Abbreviations CD, cannot determine; CTF, chest tube drainage with/without fibrinolytics; DOS, duration of symptoms; IQR, interquartile range; NA, not applicable; NR, not reported; NS, not specified; OS, open surgery; SK, streptokinase; t-PA, intrapleural tissue plasminogen activator; TT, tube thoracostomy; VATS, video-assisted thoracic surgery.

Length of hospital stay (LOS)

Ten studies reported data on LOS as an outcome (see Table 3). Two studies found shorter LOS in patients with shorter DOS [17,18]. None of the remaining eight studies calculated an effect of DOS on LOS.

Complications

All studies reported data on complications related to prognosis and treatment of pleural infection, although the complications identified differed. Complications included e.g. reintervention, readmission, bleeding, prolonged air leak, need for surgery, and recurrence. In the study by Nayak et al. [12] readmission was the only complication included, generally showing a trend of lower rate of readmission in patients treated surgically. Paz et al. [20] collected data on failure of repeated thoracentesis (RTT), ICU admission, and re-hospitalization. Two studies primarily reported data on the need for surgery as a complication along with radiological findings over time [21,22]. In the seven remaining studies data on complications was reported as a total rate of all types of complications. The studies had complication rates spanning from 3% in a group of patients from the study by Chung et al. [18] to 78% in the study of Wozniak et al. [17]. Chung et al. [18] found that 9.5% of patients with DOS of <2 weeks had complications, whilst 35% of patients with DOS>4 weeks had complications. An overview of complications reported in each study can be found in Table 3.

Intraoperative conversions from VATS to open surgery

Seven studies reported data on conversions from VATS to open surgery (Table 3), although in one study conversions were defined as going from uniportal-VATS to conventional three-port VATS [13]. Stefani et al. [16] performed a multivariate analysis of independent predictors and found an OR (odds-ratio) for conversion to open surgery of 1.97 (1.12–3.48, $p = 0.018$) in patients with DOS of more than 20 days. Likewise, Jagelavicius et al. [14] performed a multivariate analysis and found an OR of 1.1 (1.0–1.2, $p = 0.004$) for conversion to open surgery following each day of illness prior to surgery. Lardinois et al. [19] also found a significant correlation between DOS and risk of conversion ($p < 0001$). Three studies did not calculate the relation between DOS and the rate of conversion [13,15,17].

Referral and need for surgery

The two clinical trials, MIST1 and MIST2 [21,22], used 'need for surgery' and 'referral for surgery', respectively, as end points for disease complications. Maskell et al. [21] found no statistically significant difference in the need for surgical drainage between the two different groups of intervention and no difference in DOS, although the effect of DOS on need for surgery was not calculated. Rahman et al. [22] found significant difference in surgical referral between the t-PA-DNase group compared to the placebo group (p-value = 0.03). They also found showed shorter LOS in the t-PA-DNase group (p-value<0.001). Unfortunately, the effects of DOS on LOS and surgical referral were not calculated.

Mortality

Mortality differed vastly from 1.4% 30-day mortality in the study by Jagelavicius et al. [14] to 32.3% one-year mortality in one subgroup in the study by Nayak et al. [12]. None of the included studies calculated mortality related to DOS.

Discussion

We investigated the relation between early diagnosis and treatment in patients with pleural infection in the form of complicated parapneumonic effusion or pleural empyema. The included studies explored different interventions and outcomes. We found a trend towards better outcome in patients treated early in the process of disease, suggesting that treatment should be initiated as quickly as possible. Focus was on complicated parapneumonic effusion or pleural empyema as these pose a more complex clinical problem, whereas treatment of simple parapneumonic effusions is well documented, simpler, and less debated [2,5,10]. The fact that patients with simple parapneumonic effusions could not be separated in the studies by Wozniak et al. and Chung et al. must be considered when discussing the data [17,18], especially since Chung et al. found a lower rate of complications in patients with shorter DOS. It is important to underline that we are looking at the time of disease debut and intervention, not specifically the type of intervention.

Overall, a correlation between DOS and outcome was found in six studies. Three studies [14,16,19] found DOS to be a significant predictive factor for intraoperative conversion to open surgery from VATS. These results suggest that earlier intervention may decrease the rate of conversions to open surgery

and in turn potentially improve the prognosis of pleural infection patients, as intervention with VATS seems to have fewer complications [3]. Metin et al. [15] found DOS to be significantly longer in the group treated with tube thoracostomy compared to patients treated with more invasive methods, although selection-biased allocation of treatment based on patient characteristics cannot be excluded. Chung et al. [18] found patients with DOS<4 weeks had significantly shorter chest tube duration, shorter LOS, and reduced duration of surgical procedure, all indicating a benefit of early intervention. Since we believe that mortality is an important outcome to investigate, it was included as an outcome when we designed the study. Unfortunately, none of the included studies analyzed the effect of DOS on mortality. Thus, we were not able to draw conclusions on the mortality as an outcome, but in the future it will be a very important outcome nonetheless.

All studies included in this paper reported DOS as time from onset of symptoms or diagnosis of respiratory infection until intervention based on either retrospective processing of databases or recollection of memory in prospective studies. Since some studies report beginning of symptoms as the recollection from patients while other studies report from the diagnosis of disease it may have resulted in varying DOS because of difference in starting point. It also entails uncertainty in the accuracy of reporting with inherent recall bias. However, this is the only feasible way of including data on DOS, as monitoring of patients before they are diagnosed would probably require screening of the primary care population for pleural infection. There is no reason to assume that patients' recall of DOS is affected by choice of treatment when asked prior to intervention, which reduces risk of bias. Nonetheless, intervention may be chosen on basis of DOS, which would cause confounding by indication, as patients may be treated more/less aggressively depending on DOS. Whether or not the duration of symptoms has an influence on outcome depends highly on patient characteristics, perception of pain, healthcare system, etc.; thus, DOS has inherited bias. In addition, using DOS as a marker of timely diagnosis may not be representative since it complies major risk of confounding. Patients at risk for more serious illness, such as elderly patients or patients with respiratory disease, may be more likely to have longer DOS and worse outcome. Drawing conclusions based on timely diagnosis and treatment using DOS as a marker will therefore be subject to great uncertainty. Unfortunately, it is the only marker included in studies on pleural infections. Future studies aiming to determine the effects of timely diagnosis and treatment of pleural infections should aim to find more comparable metrics to do so. One option might be to measure the time from admission to intervention in all studies as this information would typically be more easily accessible and less affected by the memory of the patient. However, this outcome parameter is also highly dependent on the setting, resources, etc. of the given hospital/healthcare system.

The definition of LOS varied between included studies making comparison of patient outcomes difficult. Some studies reported postoperative LOS while other reported LOS from admission to hospital discharge making comparison between different studies less accurate, making it very difficult to objectively convert LOS to a universal and comparable unit of measure.

Data on outcomes differed between studies since complications were reported as a wide variety of conditions connected to pleural infections and intervention. The diversity made comparison of the morbidity after treatment difficult as the rate of complications were often referred as a total rate of all complications rather than exact data on rate of each complication. Studies included were conducted in several different countries though most of them European, two were conducted in Northern America [12,17] and one in South Korea [18]. Differences in cultures should be considered when analysing studies from different continents. In addition, the studies were performed in a period from 1992 to 2015, spanning over more than 20 years. In this period a lot has changed in the organization of healthcare and a lot of new methods of treatment have emerged. The department at which the study was conducted may also have affected the use of surgical interventions. Most studies were conducted primarily at surgical departments, though some of the bigger studies were performed on larger populations from multiple centers including medical departments.

Almost half of the included studies had a relatively short period of follow-up, thus potentially underestimating both mortality and morbidity, as outcomes such as death, readmission, and re-do surgery may occur several months after intervention [4]. Six studies [12,13,16,20–22] had persistent follow-up of six months or more. In most of the included studies follow-up differed greatly from 9 days to 2.709 days, making it difficult to estimate long-term outcome.

The two clinical trials, MIST1 [21] and MIST2 [22], assessed different types of intrapleural therapy as a treatment for clinically proven complex parapneumonic effusions and pleural empyemas. MIST2 [22] reported that combination of intrapleural fibrinolytic

(t-PA) and enzyme (DNase) therapy is likely to improve drainage of pleural fluid and reduce LOS and the likelihood of surgery. MIST1 [21] found no significant effect of fibrinolytic monotherapy on outcomes. Compared to data on DOS from other studies included in this paper, patients included in the MIST-studies reported very similar DOS, except for the study by Metin et al. [15]. These similarities in DOS may be an indicator that patients generally suffer from symptoms of pleural infection for up to several weeks before being diagnosed. A trend towards better outcomes is found in patients diagnosed earlier in the disease course and treated in accordance with the actual stage of disease, although differences in recollection and definitions of symptoms across studies may affect these results. This may justify a more aggressive primary approach at admission. This is also the case in regard to surgery, as Stefani et al. [16] found the chance of conversion to open surgery from VATS to be significantly increased when performed more than 20 days after symptom onset.

Another important perspective on DOS and the outcome of patients is that patients who present earlier may have better outcomes compared to those that present at a later stage of disease. Whether the effect is due to early contact to healthcare providers or early diagnosis and treatment may be difficult to separate. In the current study it is likely that both factors play an important role. It would be of great interest to investigate whether DOS can predict the rate of success for specific interventions and why.

Based on the results in this paper the outcome of patients may be improved if supplementary interventions such as surgical drainage or intrapleural fibrinolytic and enzyme therapies are implemented as early in the progress of disease as possible. A trend of better outcome for patients managed more aggressively in the choice of intervention during the first two weeks of symptoms supports this [16,18]. However, it should be noted that confounding by indication may apply to patients in non-randomised studies in which potentially more aggressive interventions are triaged to those with the best likely outcome and no comorbidities.

Future studies should aim to determine the importance of optimal timing of all available interventions, using predefined criteria for initial chest tube and antibiotic failure, to arbitrate a consensus on the treatment regimen for escalating therapy. Comparison of studies on pleural infection is complicated by different classifications as well as different definitions of outcomes. Thus, international consensus on classification and outcome parameters would improve the quality of studies using different treatment modalities. Another limitation is the uncertainty whether the study populations are representative of the intended population given that many of the included studies are of relatively low methodological quality with a high risk of selection bias.

An important limitation of the study is that the several studies highlighting new aspects of the pathogenesis leading to pleural infection as well as a new prognostic scoring system for pleural infection has been published following the publication of most of the included studies in this review [24]. The classical description of the different stages in development of pleural empyema, as well the terms simple and complicated parapneumonic effusions, are based on a pathogenesis involving bacterial spread to the pleural cavity from the lung tissue. Recent studies have, however, demonstrated the need to consider more complex pathogeneses since a significant proportion of the patients with culture positive pleural empyema seem to have primary pleural infection rather than spread of the infection from the lung [25]. Furthermore, several studies have described and subsequently, prospectively validated clinical risk prediction scoring systems in adult patients with pleural infection [4]. The studies indicate the need for a revision of the classical dogma within the field of pleural infection, including studies assessing the integrated use of validated outcome scoring systems to guide treatment decisions. Since previously published studies primarily use the classical descriptions and stratification of pleural infection, it is not yet possible to conduct a systematic review based on the more recent studies.

Conclusion

We found that an earlier intervention in adults suffering from complicated parapneumonic pleural effusion and pleural empyema may potentially improve the outcome of patients in terms of LOS, conversion to open surgery, and general complications following treatment, but not regarding mortality. Further studies are required to specify the timing of each intervention, and direct comparison in early management of interventions.

Disclosure statement

Thomas Decker Christensen has been on the speaker bureaus for AstraZeneca, Boehringer-Ingelheim, Pfizer, Roche Diagnostics, Takeda, Merck Sharp & Dohme (MSD) and Bristol-Myers Squibb and has been in an Advisory Board for Bayer, Merck Sharp & Dohme (MSD), Sanofi and AstraZeneca.

Christian B. Laursen has received a speaker's fee from AstraZeneca.

Morten Bendixen has received a teaching fee from Pulmonx Corporation.

Najib M Rahman is a consultant for Rocket Medical and Lung Therapeutics, USA.

Other authors: None declared.

Funding

This work received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Data sharing statement

Data sharing not applicable as no datasets generated and/or analysed for this study.

Ethic statement

Given the nature of the study as a systematic review, no experiments were conducted on either humans or animals in the process of conducting this paper.

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