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Task Force Report

ERS Statement on Benign Pleural Effusions in Adults

Anand Sundaralingam, Elzbieta M Grabczak, Patrizia Burra, M.Inês Costa, Vineeth George, Eli Harriss, Ewa Jankowska, Julius P Janssen, Georgia Karpathiou, Christian B Laursen, Kornelija Maceviciute, Nick Maskell, Federico Mei, Blin Nagavci, Vasiliki Panou, Valentina Pinelli, José M Porcel, Sara Ricciardi, Samira Shojaee, Hugh Welch, Alberto Zanetto, Udaya Prabhakar Udayaraj, Giuseppe Cardillo, Najib M Rahman

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ERS Statement on Benign Pleural Effusions in Adults

Authors

Anand Sundaralingam[1,2,3] MRCP
Elzbieta M Grabczak[4] MD
Patrizia Burra[5] MD, PhD
M.Inês Costa[6] MD
Vineeth George[7,8] BMed
Eli Harriss[9] MSc
Ewa A Jankowska[10] PhD
Julius P Janssen[11] MD, PhD
Georgia Karpathiou[12] BSc, MD, PhD
Christian B Laursen[13,14] MD, PhD
Kornelija Maceviciute[15] MD
Nick Maskell[16] DM
Federico Mei[17,18] MD
Blin Nagavci[19] MD MSc
Vasiliki Panou[13,14,20] MD, PhD
Valentina Pinelli[21] MD
José M Porcel[22] MD, PhD
Sara Ricciardi[23,24] MD
Samira Shojaee[25] MD, MPH
Hugh Welch[16] MRCP
Alberto Zanetto[5] MD, PhD
Udaya Prabhakar Udayaraj[26,27] MD, FRCP
Giuseppe Cardillo[28,29] FRCS, FETCS
Najib M Rahman[1,2,30,31] DPhil

1. Oxford Respiratory Trials Unit, Churchill Hospital, Headington, UK
2. Oxford Pleural Unit, Oxford Centre for Respiratory Medicine, Oxford University Hospitals NHS Trust, Oxford, UK
3. School of Pharmacy and Biomedical sciences, University of Portsmouth
4. Department of Internal Medicine, Pulmonary Diseases and Allergy, Medical University of Warsaw
5. Gastroenterology and Multivisceral Transplant Unit, Department of Surgery, Oncology, and Gastroenterology, Padua University Hospital, Padua, Italy.
6. Pulmonology Department, Centro Hospitalar Universitário de Santo António, Porto, Portugal
7. Department of Respiratory and Sleep Medicine, John Hunter Hospital, Newcastle, Australia
8. Hunter Medical Research Institute, Newcastle, Australia

9. Bodleian Health Care Libraries, University of Oxford, Oxford, United Kingdom
10. Division of Translational Cardiology and Clinical Registries, Institute of Heart Diseases, Wroclaw Medical University, Poland
11. Dept of Pulmonary Diseases, Canisius Wilhelmina Hospital, Nijmegen, The Netherlands
12. Pathology Department, University Hospital of Saint Etienne, France
13. Department of Respiratory Medicine, Odense University Hospital, Odense, Denmark.
14. Odense Respiratory Research Unit (ODIN), Department of Clinical Research, University of Southern Denmark, Odense, Denmark
15. St Bartholomew's Hospital, London, UK
16. Academic Respiratory Unit, University of Bristol, Bristol, UK
17. Department of Biomedical Sciences and Public Health, Polytechnic University of Marche, Italy
18. Respiratory Disease Unit, University Hospital, Ancona, Italy
19. Institute for Evidence in Medicine, Faculty of Medicine and Medical Center, University of Freiburg, Germany.
20. Department of Respiratory Diseases, Aalborg University Hospital, Aalborg, Denmark
21. Division of Pulmonology Pulmonology, ASL5 Spezzino, Italy
22. Pleural Medicine Unit, Arnau de Vilanova University Hospital, Lleida, Spain
23. Division of Thoracic Surgery, San Camillo Forlanini Hospital, Rome, Italy
24. PhD program Alma Mater Studiorum, University of Bologna, Bologna, Italy
25. Division of Allergy, Pulmonary and Critical Care Medicine, Vanderbilt University Medical Center
26. Oxford kidney Unit, Churchill hospital, Oxford, UK
27. Nuffield Department of Medicine, Henry Wellcome Building for Molecular Physiology, Old Road Campus, University of Oxford, Oxford, UK
28. Unit of Thoracic Surgery, Azienda Ospedaliera San Camillo Forlanini, Rome, Italy
29. Unicamillus, International University of Health Sciences, Rome, Italy
30. NIHR Oxford Biomedical Research Centre, University of Oxford, Oxford, UK
31. Chinese Academy of Medical Health Sciences, University of Oxford, Oxford, UK

Corresponding author
Dr Anand Sundaralingam MRCP
Oxford Respiratory Trials Unit (ORTU), CCVTM, Churchill Hospital, Headington, Oxford, OX3 7LE, United Kingdom
Email: Anand.Sundaralingam@ndm.ox.ac.uk

Conflicts of interest
AS, MG, PB, IC, VG, EH, EJ, JJ, GK, CL, KM, NM, FM, VP, VP, JMP, SR, SS, HW, AZ, UU, GC, NMR have no conflicts of interest to declare

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List of Acronyms

MPE = Malignant pleural effusion
NMPE = Non-malignant pleural effusion
TF = Taskforce
PF = Pleural fluid
HF = Heart failure
CVC = Central venous catheter
OHS = Ovarian hyperstimulation syndrome
LDH = Lactate dehydrogenase
AUC = Area under the curve
sROC = summary receive operating characteristics
LR = Likelihood ratio
CT = Computed Tomography
HU = Hounsfield units
MRI = Magnetic resonance imaging
ADC = Apparent diffusion coefficient
TxAsp = Therapeutic aspiration
IPC = Indwelling pleural catheter
ICD = Intercostal drain
VATS = Video-assisted thoracoscopic surgery
CRTD = Cardiac resynchronisation therapy device
PROMS = Patient reported outcome measures
QoL = Quality of life
VAS = Visual analogue score
RCT = Randomised controlled trial
TT = Therapeutic thoracocentesis
BNP = Brain natriuretic peptide
TUS = Thoracic ultrasound
TIPS = Transjugular intrahepatic portosystemic shunt
LoS = Length of stay
HH = Hepatic hydrothorax
ePTFE = expanded polytetrafluoroethylene
ICU = Intensive care unit
ESRF = End stage renal failure
PD = peritoneal dialysis
HD = haemodialysis
BAPE = Benign asbestos related pleural effusion
DPT = Diffuse pleural thickening
SUVmax = Maximum standardised uptake value

CXR = Chest x-ray
CPA = Costophrenic angle
MPM = Malignant pleural mesothelioma
TLC = Total lung capacity
DLCO = Diffusing capacity for carbon monoxide
FEV1 = Forced expiratory volume in 1 second
FVC = Forced vital capacity
MRC = Medical research council
PET-CT = Positron emission tomography–computed tomography
CABG = Coronary artery bypass graft
PPS = Post-pericardiotomy syndrome
NSAIDs = Non-steroidal anti-inflammatories
IMA = Internal mammary artery
OHT = Post-orthotopic heart transplant
NSP = Non-specific pleuritis
MT = Medical thoracoscopy
RFB = Rigid forcep biopsy
SRFB = Semi-rigid forcep biopsy
CB = Cryobiopsy
BAP1 = BRCA1-associated protein 1
IHC = Immunohistochemistry
FISH = Fluorescence in-situ hybridization
MTAP = 50-methylthioadenosine phosphorylase
DWI = Diffusion weighted MRI
NNF = Number needed to follow-up

Abstract

The incidence of non-malignant pleural effusions (NMPE) far outweighs that of malignant pleural effusions (MPE) and is estimated to be at least 3-fold higher. These so called "benign" effusions do not follow a "benign course" in many cases, with mortality rates matching and sometimes exceeding that of MPEs. In addition to the impact on patients, healthcare systems are significantly affected, with recent US epidemiological data demonstrating that 75% of resource allocation for pleural effusion management is spent on NMPEs (excluding empyema). Despite this significant burden of disease, and by existing at the junction of multiple medical specialties, reflecting a heterogenous constellation of medical conditions, NMPEs are rarely the focus of research or the subject of management guidelines. With this ERS Taskforce, we assembled a multi-specialty collaborative across eleven countries and three continents to provide a Statement based on systematic searches of the medical literature to highlight evidence in the management of the following clinical areas: a diagnostic approach to transudative effusions, heart failure, hepatic hydrothorax, end stage renal failure, benign asbestos related pleural effusion, post-surgical effusion and non-specific pleuritis.

Introduction

Pleural effusions are a common medical presentation, with an estimated incidence of 337 per 100,000 of the population.[1] Of this, the majority of cases are due to non-malignant (NMPE), or "benign" pleural effusions (252 per 100,000).[2] Despite their prevalence, there is an absence of established guidelines to support clinicians in diagnosis and management. In part, this may be explained by a lack of high-quality evidence; however, the heterogeneity of conditions that lead to NMPE, poor definitions and classification systems and patient care spread across different speciality groups has almost certainly contributed to this paucity of guidance.[3] Nonetheless, such patients carry a high symptom burden, and significant morbidity and mortality. Observational series have estimated high 1-year mortality rates in heart (50%), renal (46%) and liver (25%) failure, rendering the term "benign" something of a misnomer.[4] The impact is felt by healthcare systems across the world. Recent epidemiological data from the USA suggests 75% of the total resource allocation for pleural effusions was spent on the management of NMPE (excluding empyema) alone.[5] With an aging population and medical advances, the proportion of patients living with chronic disease is rising. Thus, the incidence of NMPE is expected to increase.[1] There is therefore an imperative to support clinicians who routinely manage the care of such patients.

This statement aims to produce a narrative review of the current evidence with regards to the management of NMPE in adults. The statement specifically excludes the management of pleural infection, which in contrast to the other forms of "benign" pleural effusion, is supported by high-quality evidence and a number of international guidelines and consensus statements.[6] The taskforce considered other topics that may be considered part of the spectrum of "benign" pleural effusions (chronic lymphocytic exudates, connective tissue related effusions and chylothorax) but ultimately settled on the groups presented below in view of their respective clinical burden of disease, paucity of existing guidance and suitability for future standalone guidance in the topics specifically excluded.

The current statement does not make clinical practice recommendations. However, in specific areas where the evidence is scarce or mixed, such limitations are described and a description of the Taskforce (TF) members own experience and practice is provided for information, but not with the aim of guiding clinical practice.

Methods

A TF was formed, with the goal of producing a Statement: a comprehensive, scientific review of the literature, identified by systematic searches, with conclusions supported by accompanying references. Membership comprised of nine respiratory physicians (with subspecialist expertise in pleural disease and interventional pulmonology), one thoracic surgeon, two hepatologists, one nephrologist and one cardiologist, with the support of five early-career members. There was representation from nine European countries, the United States (USA) and Australia.

The scope of the statement was agreed at the initial meeting in January 2022, specifically outlining the topics: an approach to transudative effusions, heart failure, hepatic hydrothorax, end stage renal failure, benign asbestos related pleural effusion, post-surgical pleural effusion and non-specific pleuritis. Working groups produced key questions in a PICO style format for each topic, assisted by an ERS methodologist (BN) and following TF debate a number were selected for each group. The literature search was undertaken for each PICO question, by each working group with the assistance of a medical librarian (EKH). Medline (National Library of Medicine, USA), Ovid EMBASE (Elsevier, the Netherlands) and the Cochrane Central Register of Controlled Trials were searched using a combination of appropriate MeSH headings and keywords. The searches were run between August to October 2022. All studies published to date within the medical literature were included, with no limits on date of publication for the majority of searches.

The full search strategy for each clinical question is shown in the online supplement. Once the search had been run, further potentially eligible articles were identified by reviewing the reference lists of identified papers. The search was repeated in June 2023 to identify recently published papers and the statement was updated accordingly.

Title, abstract and full-texts were screened independently for inclusion by subgroup members and were included based on pre-specified eligibility criteria (online supplement). Any queries or disagreements were resolved through discussion at taskforce virtual meetings, with final decisions made by the taskforce chairs (GC and NMR). Subgroups prepared drafts summarising the relevant literature for their clinical question and in some cases algorithms that described the practice of TF members based on extracted data from the evidence presented, which then underwent review by the full taskforce before being revised and submitted to the chairs.

The taskforce chairs collated the drafts into a complete statement and the final draft was approved by all members prior to submission to the ERS and hence represents a statement of the entire taskforce.

Results

An overall diagnostic approach:

What tests are used to categorise a pleural effusion as a transudate?

P: - Patients with pleural effusions of any cause
I: - Pleural fluid tests and imaging features
C: - NOT required for literature search (but can use the *Actual Final Diagnosis* as the benchmark against which the investigations are compared against)
O: - Diagnostic accuracy, sensitivity, specificity, false negative, false positive rates

Summary

- *Light's Criteria has been shown to be effective at not missing exudates, but due to moderate specificity (70%), misclassification of transudates as exudates was found to commonly occur (∽25% misclassification rate).*

- *To overcome this gap, alternative tests have been suggested over the last few decades, but none has been shown to be superior to Light's criteria in detecting exudates correctly.*

- *When heart failure is highly suspected, but Light's criteria suggest an exudate, a serum-effusion albumin gradient was found to be useful. A result >1.2 g/dl, was shown to indicate the pleural effusion can be accurately reclassified as a transudate due to cardiac failure.*

- *NT-proBNP serum or PF levels >1500 µg/mL were reported to be accurate at diagnosing HF as the cause of pleural effusion.*

- *In the presence of a high pre-test probability for liver failure, a pleural fluid to serum albumin ratio < 0.6 was shown to confirm hepatic hydrothorax, when Light's criteria is ambiguous.*

- *If a serum sample is not available, a pleural fluid LDH greater than 67% the upper limit of normal serum LDH or pleural fluid cholesterol >55 mg/dL was reported to have a high discriminative capacity in diagnosing exudates, equivalent to that of Light's criteria.*

In total 1534 studies were screened to identify 43 studies of relevance in producing this section. These consisted of 2 editorials, 1 guideline, 27 retrospective observational studies, 11 prospective observational studies and 2 systematic reviews and meta-analyses (see supplementary material).

Why distinguish transudates from exudates?

Even though there are multiple causes of pleural effusion, only a few are responsible for the majority of cases in clinical practice.[7, 8] The most frequent causes of pleural effusion include heart failure (HF) (29%), malignancy (26%), pneumonia (16%), tuberculosis (6%), post-surgery (4%), pericardial diseases (4%), and cirrhosis (3%).[9, 10] Aetiologies will vary according to whether the effusion is unilateral or bilateral. In a large series by Porcel et al, the most common cause of bilateral effusions were: HF (53.5%), followed by malignancy (18%) and then pericardial disease (7%).[9] The series by Walker et al demonstrated similar findings, with HF and renal failure more likely to present with bilateral effusions (19.8% and 23.1% respectively) compared to pleural infection (9%).[4]

Given the causes of pleural effusion are varied and broad, establishing the characteristics of pleural fluid (PF) is considered the first key step in the diagnostic approach. Classification of pleural effusion as transudate or exudate reflects the pathophysiologic mechanisms explaining fluid formation. More than 80% of transudates are due to HF, followed by liver cirrhosis (10%), hypoalbuminemia, nephrotic syndrome and atelectasis (table 1).[10] Most transudates can be successfully treated with diuretics, making further investigations unnecessary. By contrast, patients with exudates warrant additional diagnostic procedures to rule out specific important causes (eg. malignancy) or conditions requiring urgent specific treatment (eg. pleural infection).[11]

It should be noted, however, that categorisation of a pleural effusion as transudate or exudate is not always indicative of a particular aetiology or group of aetiologies. Thus, while some pleural effusions are always exudative (eg. tuberculosis) [12, 13], misclassification of cardiac and liver transudates as exudates is relatively common ($\backsim$25-30 % misclassification rate).[8] Some conditions may cause either transudate or exudate (eg. non-expansile lung, chylothorax, superior vena cava syndrome) [5] and, finally, other pleural effusions that are typically exudative may, rarely, fulfil the criteria for a transudate (eg. 3-4% of malignant pleural effusions).[14–16] The complexity is compounded further when we consider that multiple aetiologies may account for up to 30% of pleural effusions.[17] Therefore, there is no substitute for thorough assessment, integration of clinical features and findings from investigations and in certain circumstances trials of therapy before determining aetiology.

Table 1
Causes for pleural effusions according to laterality (unilateral vs bilateral) and incidence.

Transudates	Exudates
Common causes	***Common causes***
Heart failure Liver cirrhosis	Malignancy Pneumonia Tuberculosis Post-surgery (cardiothoracic, abdominal) Pericardial diseases
Less common causes	***Less common causes***
Hypoalbuminemia Nephrotic syndrome Pulmonary arterial hypertension Atelectasis Volume overload (eg. in ESRF) Non-expandible lung * Peritoneal dialysis	Trauma Idiopathic Pulmonary embolism # Abdominal diseases Autoimmune diseases Uremic pleural effusion
Rare causes	***Rare causes***
Superior vena cava syndrome* Constrictive pericarditis * Urinothorax * Cerebrospinal fluid Non-cirrhotic portal hypertension Extravascular migration of CVC	Oesophageal perforation Chylothorax # Gynaecologic conditions (e.g: Meigs syndrome, Endometriosis, OHS) Drugs Benign asbestos pleural effusion Viral Sarcoidosis Amyloidosis # Thoracic radiotherapy

* They may be also exudates
# They may be also transudates (when non-Light's criteria have been used)
Abbreviations: CVC= central venous catheter; OHS= ovarian hyperstimulation syndrome.
From Porcel et al (with permission) [10]

Pleural fluid tests for differentiating transudates from exudates

Since the landmark study by Light et al. [18], measurement of PF protein and lactate dehydrogenase (LDH), which are associated with pleural microvascular permeability and inflammation, respectively, has been adopted in routine clinical practice to distinguish between transudates and exudates.[19]

The most recent data indicate that Light's criteria (table 2) yield the following operating characteristics for identifying exudates [10]: sensitivity 98%, specificity 72%, positive likelihood ratio (LR) 3.5, and negative LR 0.03. One of the likely reasons explaining the specificity of Light's criteria when applied to real world clinical practice is that the criteria were originally conceived to maximize the detection of exudates, in order to reduce the risk of failing to diagnose potentially serious conditions (eg. malignancy, infection). To overcome some of the limitations of Light's criteria (i.e. low specificity, need of serum samples for ratio calculations, application of dichotomous cut-off values to continuous variables), alternative tests have been suggested over the last few decades, but none have been shown to be superior. If a serum sample is not available, using an "or" rule, of LDH greater than 67% the upper limit of normal serum LDH and cholesterol >55 mg/dL in PF has been shown to have a discriminative capacity equivalent to that of Light's criteria.[10, 20–22] On the other hand, a Bayesian approach, considering the pre-test probability of a transudate or exudate, followed by the application of continuous LR for the elements of Light's criteria to calculate post-test probabilities, although elegant, is cumbersome and adds little to the interpretation of test results compared to clinical judgment.[23, 24]

When Light's criteria provide results close to the cut-off points for an exudate, in the presence of a high pre-test probability for HF or cirrhosis, an albumin gradient (serum albumin minus PF albumin) >1.2 g/dl or an albumin ratio (PF albumin divided by serum albumin) <0.6, respectively, has been shown to correctly reclassify about 80% of these "false" exudates [25]. An alternative to identify HF-related effusions is the measurement of the natriuretic peptide NT-proBNP in PF (or serum, if thoracentesis is not planned). Several diagnostic accuracy studies dedicated to assessing the role of natriuretic peptides in the blood (especially NT-proBNP) for diagnosing pleural effusion of cardiac origin have been performed.[26–34] Generally, the studies have demonstrated high sensitivity and specificity, and a meta-analysis in 2015 reported a pooled sensitivity and specificity of an elevated blood NT-proBNP for diagnosis of cardiac failure as the cause of pleural effusion of 0.92 (95% CI: 0.86-0.95) and 0.88 (95% CI: 0.77-0.94), and PF NT-proBNP sensitivity and specificity of 0.94 (95% CI: 0.90-0.96) and 0.91 (95% CI:0.86-0.95), respectively. The AUC on the sROC curves for blood NT-proBNP and PF NT-proBNP (accounting for differing thresholds of 'normal' range) were 0.94 and 0.96, respectively [31] Levels greater than 1500 μg/mL are the most accepted threshold with a positive LR of 7.8 (95% CI: 3.7-16.3) and negative LR of 0.10 (95% CI: 0.06-0.16) in blood NT-proBNP and a positive LR of 10.9 (95% CI 6.4-18.6) and negative LR of 0.07 (95% CI: 0.04-0.12) in PF NT-proBNP, respectively (see figure 1).[33]

Table 2
Light's criteria to classify a pleural effusion as an exudate [35]

Parameter	**Thresholds***
PF to S protein ratio	> 0.5
PF to S LDH ratio	> 0.6
PF LDH	> 2/3 upper limit of normal serum value

(*meeting any one of the criteria constitutes an exudative effusion
PF = Pleural Fluid
S = Serum
LDH = Lactate dehydrogenase)

What are the scoring systems for categorizing a pleural effusion as a transudate?

P: - Patients with pleural effusions of any cause
I: - Composite scoring systems/ Risk prediction tools
C: - NOT required for literature search (but can use the *Actual Final Diagnosis* as the benchmark against which the investigations are compared against)
O: - Diagnostic accuracy, Sensitivity/ Specificity, False Negative

Summary

- *When faced with pleural effusions categorised as an exudate by Light's criteria, studies have shown a combined clinical-radiological scoring model (table 3) can correctly identify cardiac failure as the cause.*

- *Mean attenuation values on CT or patterns of echogenicity on thoracic US have been shown to be unreliable for transudate-exudate discrimination.*

- *Studies have demonstrated that radiological findings alone cannot replace biochemical analysis of PF in combination with clinical data, when attempting to categorize a pleural effusion as a transudate or exudate.*

Transudate-exudate differentiation: scoring systems and imaging studies

There is scarce literature that has focused on the creation of a scoring system based on simple and available clinical data which allows distinction between transudate and exudate, or identification of falsely categorized transudates. Porcel et al. conducted a study in which a clinical scoring model for identifying pleural effusions due to HF was designed and validated, intended to be applied when effusions meet Light's criteria for exudates (table 3).[36] A score of 7 or more greatly increased the probability of a cardiac aetiology (diagnostic accuracy 92%, LR positive 12.7, LR negative 0.39) and proved to exceed the discriminative capabilities of protein and albumin gradients in isolation.[36]

Table 3
Scoring system for diagnosing pleural effusions secondary to cardiac failure in exudates (from Porcel et al [36])

Parameters	Score
Age ≥ 75 years	3
Albumin gradient > 1.2 g/dL[a]	3
PF LDH < 250 U/L[b]	2
Bilateral pleural effusion on chest X-ray	2
Protein gradient > 2.5 g/dL[c]	1

([a] = serum albumin minus PF albumin,
[b] = this figure represents two-thirds of the upper limit of normal for serum LDH in the laboratory the score was derived in,
[c] = serum protein minus PF protein)

The role of imaging as a non-invasive method for differentiating transudative and exudative pleural effusions has been addressed in several studies.

The most obvious feature that may help differentiate a transudative cause from an exudative one, is size of effusion. Massive pleural effusions tend to be seen in malignancy (ie. exudative effusion), however hepatic hydrothoraces can also present with sizeable effusions, and therefore this is not an absolute rule, and does not replace the need for further assessment.[37, 38]

Chest CT is commonly used in the evaluation of patients with pleural effusion of undetermined aetiology. [7, 11] Under the rationale that exudative effusions have a greater content of protein, LDH, and cholesterol, studies have addressed whether these biochemical characteristics translate to greater radiodensity, and higher attenuation values of pleural fluid measured in Hounsfield units (HU). Although most studies show that exudates have higher mean attenuation values than transudates, this parameter is not useful for discriminating purposes because of significant overlapping of HU values between transudates and exudates.[39–44] For example, in the largest study (n=127 exudates and 100 transudates based on underlying disease) at the best threshold value of ≥4 HU, CT identified exudates with a sensitivity of 69%, a specificity of 66%, a LR positive of 2, and a LR negative of 0.47.[44]

Chest CT can identify thickening and pleural nodules and provide information about the degree of organization and loculation of a pleural effusion. However, although these alterations are more frequently seen in exudative effusions, they are not exclusive to exudates, and are therefore not reliable parameters to confidently discriminate between transudate and exudate.[45, 46]

The echogenicity of PF on thoracic ultrasound has been explored to discern transudate from exudate. Pleural effusions can be categorized as simple (or anechoic) or complex (hyperechoic), and categories within complex include: complex non-septated, complex septated and homogenously echogenic. Combining data from 5 series, comprising 560 transudates and 672 exudates [47–51], demonstrates anechoic sonographic pattern has a sensitivity of 80%, specificity of 63%, LR positive of 2.16 and LR negative of 0.32 for transudates. When transudates fall into the complex sonographic category, they are mostly complex non-septated.[49, 50] The overlapping patterns of echogenicity make this feature unreliable for transudate-exudate discrimination. Therefore, echogenicity of PF alone influencing the decision whether to aspirate a pleural effusion is questionable, based on the literature to date. Conversely, other ultrasound characteristics (such as pleural nodularity) strongly support the diagnosis of malignant pleural effusion (sensitivity 42.5% and specificity 96.9% in a recent meta-analysis of seven studies).[52] Figure 2 illustrates some of these features.

Magnetic resonance imaging (MRI) allows morphological and functional imaging of the pleura and can be of value in detecting pleural malignancy and local tumour invasion in mesothelioma cases.[53] However, MRI has no practical applicability in determining the transudative or exudative nature of a pleural effusion. Transudates are more often T2-weighted hyperintense and return low signal intensity on T1-weighted images.[54]

Moreover, on diffusion-weighted imaging protocols, the apparent diffusion coefficient (ADC) is generally slightly lower in exudates than in transudates.[55] In short, no imaging replaces the biochemical analysis of PF in combination with clinical data to categorize a pleural effusion as transudate or exudate.

Areas of future research	Question
Diagnostic accuracy	What features might suggest an effusion has been falsely labelled as an exudate and what features might help reclassify them?
Diagnostic overlap and integration	How can we integrate clinical information, radiography, pleural fluid biochemistry and bedside ultrasound to produce scoring systems to better diagnose the aetiology of pleural effusions?

Heart failure

What are the management options for refractory heart failure related effusions?

P - Patients with refractory heart failure related effusions
I - Pleural interventions (TxAsp/ IPC/ ICD + Slurry/ Poudrage/ VATS), Cardiological interventions (Diuresis, Fluid restriction, CRTD, Valvular surgery, Dialysis)
C - Not required
O - PROMs on QoL, VAS dyspnoea scores, hospital attendance rates, complications from pleural interventions (eg. bleeding, infection), complications to planned surgery as a result of pleural interventions (i.e. due to pleurodesis)

TxAsp = therapeutic aspiration, IPC = indwelling pleural catheter, ICD = intercostal drain, VATS = video-assisted thoracoscopic surgery, CRTD = Cardiac resynchronisation therapy device, PROMS = Patient reported outcome measures, QoL = Quality of life, VAS = Visual analogue score

Summary

- *In cases of recurrent heart failure-related pleural effusions, refractory to medical treatment, evidence has demonstrated effective palliation of symptoms with pleural interventions.*

- *Ultrasound-guided thoracocentesis, indwelling pleural catheters (IPCs), pleurodesis, and more rarely surgical procedures and pleuro-peritoneal or pleuro-venous shunting have been described in the literature as pleural procedures for symptomatic relief of patients with recurrent pleural effusions secondary to heart failure.*

- *The results of the only randomised controlled trial that compared the use of IPCs with repeated thoracocenteses for refractory transudative effusions showed no advantage in dyspnoea relief with the use of IPCs and a greater adverse event rate. However, several retrospective studies suggest that IPCs provide palliation of symptoms and reduced length of hospital stay and may be beneficial in patients that require frequent thoracocenteses (>3 events).*

- *The authors practice is to perform repeat pleural aspiration for recurrent, symptomatic cardiac effusions, refractory to medical therapies, with consideration of other treatments only if this strategy does not work or frequent re-intervention is required.*

- *The literature suggests IPC compared to talc poudrage for the palliation of patients with recurrent pleural effusions due to cardiac failure results in fewer adverse events.*

Review of the evidence

In total 1034 studies were screened to identify 34 studies relevant to producing this section. These consisted of 2 editorials or narrative reviews, 2 guidelines, 12 retrospective observational studies, 6 prospective observational studies, 4 non-randomised interventional (comparator) studies, 3 RCTs, 2 case series, and 3 systematic reviews and meta-analyses (see supplementary material).

There are no studies comparing cardiological and pleural interventions for patients that present with recurrent pleural effusions due to heart failure. However, there is consensus in the literature that pleural interventions should only be considered in patients with symptomatic heart failure-related pleural effusions refractory to medical treatment. [56–69] The definition of "refractory" is poorly described in the literature. The authors would consider patients with persistent effusions despite maximal tolerated doses of diuresis as "refractory." With the advent of novel pharmacological agents (eg. SGLT2 inhibitors), the incidence of HF related pleural effusions is expected to decrease, nonetheless pleural intervention is expected to play an ongoing role in management.

Ultrasound-guided thoracocentesis and chest tube drainage are feasible and low-risk procedures which relieve symptoms in patients with heart failure.[70, 71] There are no studies investigating complications of these procedures specifically for patients with heart failure-related pleural effusions. A comprehensive review of general pleural procedural related complications can be found elsewhere.[72]

12 studies reporting the use of indwelling pleural catheters (IPC) for recurrent pleural effusions secondary to heart failure were identified(see table A, supplementary material).[56–69] Most studies report symptomatic palliation, reduced hospital admissions and a low to moderate rate of serious adverse events. There are no studies investigating the optimal drainage frequency and volume for non-malignant pleural effusions (NMPE). In practice, common drainage frequency to begin with is three times per week and around 500-1000 ml pleural fluid per session. However, two randomized trials found daily drainage for patients with malignant pleural effusion [73, 74] which in MPE appear to drive "auto-pleurodesis". The most common IPC complications include pneumothorax, IPC malfunction, IPC-related pain and infections, with empyema and drain site infection being the most prevalent.[3, 58, 59, 61, 62, 64, 65, 67] A systematic review and meta-analysis reports spontaneous pleurodesis in 42% of cardiac failure-related pleural effusions.[60]

The only randomised controlled trial (RCT) to date which evaluates the outcomes of therapeutic thoracocentesis (TT) was the randomised trial of indwelling pleural catheters for refractory transudative pleural effusions (REDUCE) by Walker et al.[56] This was an open label study from 13 British centres which randomised patients with symptomatic pleural effusions secondary to cardiac, renal or hepatic failure to undergo either indwelling pleural catheter insertion or sequential TT, where TT was defined as "standard care". No significant difference in breathlessness for the two procedures was reported, which was the primary outcome, despite greater pleural fluid drainage for the IPC group (17.4 L versus 2.9 L over 12 weeks). Furthermore, a higher rate of adverse events was observed in the IPC arm (59%

versus 37%) and IPC use was associated with a higher loss of serum albumin during treatment. Patients that received IPC underwent fewer additional invasive pleural procedures but they did require lifelong drainage several times per week.

Pleurodesis using external chemical agents has been mostly investigated in the context of malignant pleural effusions. Nonetheless, different pleurodesis agents have been used for the palliation of recurrent non-malignant pleural effusion as well, with talc being the best described. Pleurodesis with ungraded talc with small particles (<10 μM) has been shown to be less safe in a randomized trial due to significantly greater levels of systemic inflammation and poorer gas exchange [75]. Talc may be delivered as a slurry through a chest drain or via thoracoscopy as poudrage. Retrospective studies report a success rate of 75%-80% for the use of talc pleurodesis in recurrent NMPE, including patients with heart failure.[76, 77]

There are two retrospective studies comparing the management of cardiac-related pleural effusions with talc poudrage with or without IPC placement versus IPC alone.[64, 66] There was no significant difference in symptom relief between the two techniques. Talc poudrage was associated with longer hospital stay, and higher readmission rate, mortality and morbidity. Pleurodesis was achieved at a higher rate in patients who received talc poudrage, thus patients with IPC alone had a longer time to catheter removal.

Pleuro-peritoneal or pleuro-venous shunting of pleural fluid from the pleural space for non-malignant pleural effusions is described in case series.' [3, 78, 79] In only two cases, the pleuro-peritoneal devices achieved effective symptomatic relief and required short hospitalization, while no serious complications were reported.[3, 79] However, this technique is contraindicated in patients with ascites.

Surgical approaches are rarely attempted for patients with heart failure related recurrent pleural effusions due to frailty and comorbidity. The authors have on occasion considered surgical pleurectomy in a carefully selected subgroup of patients where non-invasive techniques have failed or are contraindicated, especially where there is trapped lung.[3]

Areas of future research	Question
Treatment options	What is the optimal pleural intervention for patients with heart failure related pleural effusions: IPC (+/- talc slurry pleurodesis), repeat thoracocentesis, talc pleurodesis?
Optimising existing treatment paradigms	What is the optimal drainage frequency and volume for patients with heart failure related pleural effusions and an IPC in situ? What is the safe maximum drainage volume during thoracocentesis in a patient with heart failure related pleural effusion?

What investigations are used for a unilateral effusion in a patient with known cardiac failure?

P - Patients with known (decompensated) heart failure and presenting with a unilateral effusion

I - Stratification to conservative management or invasive diagnostics according to clinical algorithms (using non-invasive tests: serum BNP, TUS)

C - Not required

O - Complications arising from invasive investigations (bleeding, infection, pneumothorax), Outcomes (mortality, risk of circulatory or respiratory failure), delayed diagnosis of clinically relevant differential diagnosis (eg. malignant pleural effusion, pleural infection)

BNP = Brain natriuretic peptide, TUS = thoracic ultrasound

Summary

- *Several studies have assessed diagnostic accuracy of non-invasive tests such as serum natriuretic peptides or bedside ultrasound in patients with unilateral pleural effusion of unknown origin.*
- *However, no study to date has addressed a patient population with known heart failure and unilateral pleural effusion stratified or randomized to conservative management or invasive diagnostics based on clinical algorithms using serum natriuretic peptides or bedside ultrasound.*
- *Several studies have demonstrated acceptable diagnostic accuracy for identifying patients with a cardiac pleural effusion in unselected patients with unilateral pleural effusion.*
- *The authors adopt a pragmatic approach using a combination of serum tests and ultrasound to guide management in patients with unilateral pleural effusion and known heart failure, to ensure a reasonable balance between the risk of missing a non-cardiac cause of pleural effusion, and the risks of performing an invasive diagnostic procedure (i.e. thoracentesis) (Figure 3 & Table 4).*

Table 4
Non-invasive bedside test findings in patients with cardiac failure and unilateral pleural effusion

Modality	Findings supporting pleural effusion of cardiac origin	Findings suggesting pleural effusion of non-cardiac origin
Echocardiography		
Cardiac findings	• Findings consistent with systolic or diastolic cardiac failure • Other findings consistent with pleural effusion of cardiac origin (eg. severe valve abnormality)	• No apparent findings consistent with cardiac failure or other cause for cardiac decompensation • Findings suggesting malignancy, inflammation or infection (eg. large pericardial effusion, complex pericardial effusion, visible tumour) • Findings suggesting possible thromboembolic disease (eg. visible thrombus, D-sign, McConnell's sign)
Assessment of inferior vena cava	• Signs indicating grossly elevated central venous pressure	• No obvious signs of elevated central venous pressure
Thoracic Ultrasound		
Thoracic ultrasound	• Presence of interstitial syndrome • Simple pleural effusion • Sono-morphology consistent with simple compression atelectasis (in case of visible lung consolidation)	• Absence of interstitial syndrome • Complex pleural effusion • Findings suggesting possible malignant pleural effusion (eg. parietal pleural or diaphragmatic thickening / nodularity, lung parenchymal pathology not typical for simple compression atelectasis) • Findings suggesting possible thromboembolic disease (eg. hypoechoic pleural-based lesion)
Serum Tests		
NT-proBNP	• ≥ 1500 µg/mL	• < 1500 µg/mL

Review of the evidence

Patients with known cardiac failure presenting with a unilateral pleural effusion is a clinical dilemma for the treating physician and the patient. Whilst not considered typical for cardiac failure, in one large series of patient presenting with acute decompensated heart failure and pleural effusion (n=1504), pleural effusions were unilateral in 41% of cases.[80] Potential benefits of performing additional diagnostic and invasive procedures will be a more accurate determination of whether the pleural effusion is caused by decompensated heart failure and more importantly help to minimise the risk of potentially delayed diagnosis of clinically relevant differential diagnosis such as malignant pleural effusion and bacterial pleural infection. There is often also a belief that a hypoxaemic patient with a pleural effusion, albeit transudative may benefit from drainage. However, there is now consistent evidence to the contrary that a pleural effusion tends not to cause hypoxaemia and drainage rarely leads to correction, outside of specific settings (eg. large bilateral effusions).[81]

The potential drawback of additional diagnostic and invasive procedures is the increased risk of complications to invasive procedures (eg. bleeding, infection, pneumothorax), increased costs and time use, and a delay in goal directed therapy in known cardiac disease.

Of special interest is whether an approach based on non-invasive tests can be used to accurately identify a subgroup of patients in which diagnostic and therapeutic invasive procedures (eg. thoracocentesis) can safely be avoided. The multi-organ impairment often seen in patients with cardiac failure as well as concomitant comorbidities and overlapping risk factors (eg. smoking) makes it a clinical challenge to isolate a single most likely aetiology for unilateral pleural effusion.

Several blood biomarkers have been assessed to diagnose cardiac failure and pleural effusion of cardiac origin (see “An approach to transudative effusions”). Measurement of natriuretic peptides in the blood such as B-type natriuretic peptide (BNP) or N-terminal pro-B-type natriuretic peptide (NT-proBNP) are considered standard in the initial assessment of patients with suspected heart failure, especially as a rule-out tool [82]. Different cut-off points to define a positive test result have however been used and some studies were performed in selected patient populations (eg. patients with pleural transudates). The systematic literature search did not reveal any studies in which the role of natriuretic peptides had been specifically assessed in a population comprised of unselected patients with known cardiac failure and in which the cause of a unilateral pleural effusion had to be determined. Based on the currently published literature, natriuretic peptides are most likely of clinical utility in patients with known cardiac failure and a unilateral pleural effusion. Low values usually raise suspicion of an alternate cause of pleural effusion, whereas high values support a cardiac origin, provided features of an alternative diagnosis are not present (refer to figure 3).

Imaging

As a non-invasive technique for determining causes of pleural effusion, several imaging modalities have been studied in the context of patients with possible heart failure.[83, 84] The most commonly studied modality has been ultrasound, with the systematic search identifying a single study assessing the role of more advanced imaging.[85]

Echocardiography remains the standard initial diagnostic imaging modality in patients with suspected cardiac failure.[82] For patients with cardiac failure, echocardiographic assessed parameters such as systolic pulmonary artery pressure and E/A ratio (early to late ventricular filling ratio) have been shown to be risk factors for the formation of pleural effusion.[86] Focused cardiac ultrasound performed by non-cardiologists have been shown to have an acceptable diagnostic accuracy for diagnosing systolic left sided heart failure.[87] Sonographic features suggestive of decompensated heart failure with cardiogenic pulmonary oedema are presented in table4.[88–94] Whilst interstitial syndrome per se is not specific for cardiogenic pulmonary oedema, when integrated with the clinical assessment and other findings, it outperformed NT-proBNP, chest X-ray and clinical assessment alone in differentiating acute decompensated heart failure from non-heart failure related causes for dyspnoea. The additional benefit of ultrasound is the ability to detect alternative causes for pleural effusion (eg. malignant pleural effusion, pulmonary embolism, pneumonia) in the presence of specific findings.[95–98]

Despite the many studies assessing the role of bedside ultrasound for diagnosing cardiac failure, decompensated cardiac failure with cardiogenic pulmonary oedema, and non-cardiogenic causes of pleural effusions, the systematic literature review did not identify any studies in which bedside ultrasound had been used in a setting of patients with known cardiac failure and with the diagnostic dilemma of a unilateral pleural effusion.

Although studies assessing the use of ultrasound to determine the cause of unilateral pleural effusion in patients with cardiac failure are lacking, studies assessing the use of thoracic ultrasound to monitor patients with cardiac failure have been demonstrated to have potential clinical impact on clinically relevant outcomes.[93, 99, 100] Two randomised clinical trials in which patients with heart failure have been randomised to therapeutic strategies according to a usual care approach vs a lung ultrasound guided approach. The primary endpoints assessed cardiac adverse events (cardiovascular death, readmission, or emergency department or day hospital visit due to worsening heart failure at 6 months). Both studies differ in their findings, with one showing no differences between the interventions and one favouring a lung ultrasound guided approach.[99, 100] Despite these differences, the study findings may show promise for further trials assessing non-invasive ultrasound guided diagnostic and therapeutic strategies versus usual standard of care.

In summary, currently published literature shows that bedside clinical ultrasound is able to detect features of decompensation in patients with known cardiac failure (eg. interstitial syndrome) whilst demonstrating an absence of features to suggest an alternative cause for a unilateral effusion (eg. parietal or diaphragmatic nodularity) which sometimes aids clinician decision making on diagnostic and therapeutic approaches (Figure 2). Where this

does not apply, additional diagnostic tests including invasive procedures are sometimes necessary.

Areas of future research	Question
Diagnostic accuracy	What is the diagnostic accuracy of non-invasive bedside testing (eg. ultrasound, NT-proBNP) when used in a selected population of patients with cardiac failure and unilateral pleural effusion?
Diagnostic overlap and integration	What is the optimal integrated use of multiple non-invasive bedside testing (eg. ultrasound, NT-proBNP) when used in a selected population of patients with cardiac failure and unilateral pleural effusion?
Clinical impact	Can use of non-invasive bedside testing (eg. ultrasound, NT-proBNP) when used in a selected population of patients with cardiac failure and unilateral pleural effusion have a positive impact on clinically relevant outcomes (eg. adverse events, length of hospitalization, PROMs)?

Hepatic Hydrothorax:

What are the therapeutic options in patients with symptomatic refractory hepatic hydrothorax (HH)?

P - Patients with decompensated chronic liver disease, who are eligible for liver transplant and have refractory hepatic hydrothorax

I - Pleural interventions (TxAsp/ IPC/ ICD + Slurry/ Poudrage/ VATS), Hepatological interventions (TIPS, Albumin infusion, Abdominal paracentesis, Diuresis)

C - Not required

O - Dyspnoea, Quality of life, Need for re-intervention, Hospital LoS, Survival Complications

HH = Hepatic hydrothorax, TIPS = Transjugular intrahepatic portosystemic shunt, LoS = Length of stay

Summary

- *The management of refractory hepatic hydrothorax (HH) can be challenging and multidisciplinary team involvement comprising of hepatology, pleural and transplant services is key.*

- *Hepatic transplantation is considered to be the only curative treatment for HH – the authors own practice is to refer all patients, who are eligible, for liver transplantation.*

- *Therapeutic thoracentesis has been shown to be effective at providing temporary control of dyspnoea and was observed to have a low rate of procedural complications.*

- *TIPS has been demonstrated to result in improvement of HH in approximately 50% of cases, although mortality in patients who undergo TIPS for HH remains high.*

- *Both therapeutic thoracentesis and TIPS have been used by the authors to control effusions while awaiting transplantation.*

- *Data to support chest tube pleurodesis and surgical approaches is limited to small case series with evidence of high complication rates and associated mortality.*

- *IPCs have been show to offer similar control of dyspnoea when compared to repeat thoracentesis but with a greater rate of complications - if a prolonged transplant waiting list time is expected, provided the risk is acceptable to the patient and clinician, an IPC may be offered.*

- *In non-transplant candidates, for those requiring more than three thoracenteses, or where repeated thoracentesis is considered high risk, in the authors practice, an IPC is an acceptable palliative option.*

In total 3260 studies were screened to identify 27 studies relevant to producing this section. These consisted of 3 editorials or narrative reviews, 19 retrospective observational studies, 1 prospective observational study, 1 non-randomised interventional (comparator) studies, 1 RCT and 2 case series (see supplementary material).

Definition of refractory HH

Hepatic hydrothorax (HH) is defined as a pleural effusion that occurs in the context of advanced liver disease without an underlying cardiorespiratory cause. It is common, occurring in up to 15% of patients with cirrhosis and portal hypertension and is associated with disabling dyspnoea and poor prognosis.[101, 102]

Most patients with hepatic hydrothorax can be managed with medical therapies alone, which focuses on salt restriction and diuretic therapy. However, approximately 25% are considered to have refractory disease: disease that does not respond to medical management.[101, 103] This frequently requires procedural intervention.

Therapeutic thoracentesis in hepatic hydrothorax

Therapeutic thoracentesis (TT) is widely used to provide temporising control of breathlessness in refractory HH and has even been considered "standard care" in research settings.[56] Despite this, there is little high-quality data to guide its use. In the aforementioned REDUCE trial, only 16/68 (24%) patients had HH. Nonetheless, no difference in breathlessness was seen in subgroup analysis of those with HH [56].

Six non-randomised studies which evaluated TT were identified, involving >1500 patients. There were significant variations in study design but the majority were retrospective and no definition of refractory HH was provided. Three did not compare TT against another intervention but used controls who did not have HH to assess outcomes.
Mortality ranged from 18.6% at 30 days[104] to 30% at 180 days.[105] It is likely that these reflect the prognosis associated with HH rather than TT associated complications as procedure-related complication rates were low (4.9%-7.7%).[106, 107]

The largest study evaluating TT for HH was conducted by Hung et al [104] who examined Taiwanese insurance registry data to evaluate survival outcomes in patients who had undergone thoracentesis for HH, compared to those who underwent "catheter drainage". No precise definition of catheter drainage was given but the authors note that most of these patients underwent "pigtail drainage". There were 1278 patients in each group with propensity matching used to control for known confounders. The 30-day mortality was significantly higher in the group treated with catheter drainage compared to those who underwent thoracentesis (23.5 vs 18.6%, p=0.001). However, the study lacked granular detail, particularly regarding pre-intervention decision making and it is possible that patients who underwent catheter insertion were more severe or refractory, independent of known confounders.

The role of TIPS in patients with hepatic hydrothorax.

Six retrospective studies evaluating the role of Transjugular intrahepatic portosystemic shunt (TIPS) in the management of HH were included (see Table B in supplementary material).[108–113]

Notably, definition of "refractory" was lacking in 5/6 studies and there were significant differences in study design, timing and indication for TIPS. The outcomes included in the analyses were also heterogenous and included the need for post-TIPS thoracentesis, risk of hospital readmission, and TIPS-related adverse events. Some of these outcome metrics were subjective or poorly defined (eg. generic "clinical improvement"). In total, 304 patients underwent TIPS; these patients were mostly male (~60%), with alcohol and/or viral-related cirrhosis (~50%); the median Model for end stage liver disease score (MELD) was 17; Child-Pugh stage was not available in most series. Duration of post-TIPS follow-up for outcome assessment ranged between 1-6 months. Rates of complete resolution of HH at 6 months were reported in 3 studies and ranged between 20%-55%.[111–113] Importantly, only Jindal et al evaluated the association between porto-systemic pressure gradient reduction and resolution of HH, finding no optimal threshold for HH reduction.[112] Three studies evaluated the risk of TIPS-related adverse events; the most common complication was hepatic encephalopathy in 15% of TIPS recipients;[111, 112] patients older than 70 years old were at higher risk of early re-hospitalization due to hepatic encephalopathy.[108]

Notably, only the study by Young et al [113] included patients who received expanded polytetrafluoroethylene (ePTFE) covered stents; most of these studies included patients who received uncovered TIPS with no data on TIPS diameter. Uncovered stents are associated with a higher risk of stent thrombosis and/or dysfunction; therefore, results from studies of uncovered stents should not be extrapolated to the currently used ePTFE covered stents, which are likely to achieve better results than uncovered stents; further studies assessing the efficacy and safety of covered TIPS in patients with HH are expected. Additionally, no clear information on patient selection such as exclusion of patients with diastolic dysfunction and/or chronic kidney disease is available due to the retrospective design.[114]

Mortality after TIPS was between 40%-50% at 6-12 months [111, 112] and was predicted by severity of liver dysfunction (MELD score), indicating that these patients should be promptly evaluated for liver transplantation, which remains the only curative option for HH.

Current evidence suggests that TIPS may lead to resolution (or at least improvement) of HH in up to 50% of patients within 6 months. Further prospective studies evaluating the use of new ePTFE-covered, controlled-expansion TIPS in the management of HH are eagerly expected.

Chest tube pleurodesis

Two trials evaluating chest tube pleurodesis were identified, including 51 patients in total. Both studies were prospective but there were differences in the definition of refractory HH, sclerosant used, delivery method and outcome measures.

In the largest of these, Mahmud and colleagues randomised 40 patients following a second presentation of HH 1:1 to either tigecycline or bleomycin via a pigtail catheter.[115] The primary outcome was pleurodesis failure, assessed radiologically at 3 months. This was significantly higher in the tigecycline group 10/20 compared to 5/20 in the bleomycin group (50% vs 25% respectively p=0.031). Tigecycline was also shown to have fewer side effects.

The other study by Lee et al prospectively assessed 11 patients who had not responded to medical treatment.[116] The majority of patients (9/11) underwent chest tube pleurodesis with 2 patients undergoing VATs pleurodesis. Patients underwent a median of 3 pleurodesis "sessions." Viscum album was used in 6, talc in 3 and taurolidine in 2. Successful pleurodesis, defined as the absence of dyspnoea with no radiological evidence of effusion was seen in 8/11 (72.2%) patients at one month although 3 of these individuals had recurrence within one year. Concerningly, 5 (45.5%) patients were suspected to have procedure-related mortality secondary to acute renal failure.

The inferences that can be drawn from these trials are limited by their scale, single centre nature, lack of blinding and only a radiological outcome measure.

Indwelling tunnelled pleural catheters

Ten studies of IPC as the intervention of choice for HH management met inclusion criteria (see Table C in supplementary material).[56, 59, 61, 65, 69, 117–122] With the exception of one RCT by Walker et al evaluating the role of IPC vs TT,[56] and one prospective study of 24 participants,[117] all other studies were retrospective. A cumulative total of 269 patients with HH were included in these studies. The definition of refractory HH was lacking in some of the studies and most studies did not have a comparator arm.

Walker et al included 16 patients (8 in each arm) with HH. Although the study sample size of HH subgroup was small, this is the first study to examine a patient-centric primary outcome in comparison to another intervention in the HH population [56].

The largest three studies were remarkable for higher risk of complications and lower pleurodesis rate in the HH population compared to historical non-HH effusion data, although no head-to-head comparisons are available to date. Catheter dwell time was not reported in all studies but median time to spontaneous pleurodesis ranged between 55-222 days and pleurodesis success was noted in 11-51%. [117, 118, 123]

Detailed data regarding the IPC placement indication was lacking in most studies. The two largest studies with sample sizes of 62 and 79, reported that 9/9 IPC removals and 11/22 IPC removals occurred after transplant, respectively.[118, 119] Patients who undergo liver transplant with their IPCs still in place, may experience resolution of their portal hypertension followed by cessation of excess pleural fluid accumulation. In such a scenario, patients may not have undergone pleurodesis per-se, but simply returned to physiological volumes of pleural fluid production, hence meeting the pleurodesis definition criteria utilized in these studies. This, as well as selection bias, retrospective design, and lack of long-term follow-up data, may explain the overestimated pleurodesis rate within the selected studies.

The most common complication in all studies was infection (5–16%), primarily of the pleural space and often in conjunction with catheter site cellulitis. This is slightly higher than that noted amongst the general IPC population (5.8%, 95% CI 5.1-6.7%).[72] Other complications such as fluid leakage and catheter dislodgement were reported less frequently. A mortality rate of 2.5-5% was reported in the two largest cohorts. One study reported a case of catheter related sepsis and death, in a patient with an IPC as a bridge to transplant.[107]

Another study reported a small but statistically significant decrease in BMI (1.13 kg/m^2, p=0.008) and serum albumin levels (0.3 g/dl, p=0.005) following IPC placement.[118] The optimal drainage volume and frequency, and the role of albumin replacement in pleural fluid drainage of HH are yet to be determined, however, most studies used a symptom guided or alternate day drainage strategy.

In view of the reported significant adverse event rates, including empyema and death from sepsis following IPC placement in patients with HH, the authors practice is to avoid this intervention in patients who are considered eligible for a transplant, especially if they are likely to receive a transplant within 3 months. The role of IPC in reducing breathlessness during the first 3 months of IPC placement may be similar to TT but it's longer-term benefit in alleviating patient symptoms in unknown. It is the TF member's practice to individualise IPC use in HH following careful evaluation in a multidisciplinary fashion, which may well include palliative care teams whilst also accounting for patient preference. Figure 4 outlines an approach practised by TF members in managing patients with HH.

Surgical management:

Thoracoscopy and pleurodesis, diaphragmatic defect repair

Four retrospective series examining surgical management were included, involving a total of 69 patients. Only one out of four did not have a definition for refractory HH.[124] A variety of sclerosants were used, of which talc was most common, and three out of four trials did not have a comparator arm. Reported success rates varied from 47.6%- 66.6%[125, 126] although there was inconsistency in follow up periods and efficacy were assessed on the basis of CXR findings rather than PROMs.

Two studies, which involved 7 patients in total also combined diaphragmatic repair with chemical pleurodesis.[125, 126]. De Campos et al reported a 60% success rate in 3/5 patients who underwent diaphragmatic closure compared to 43.7% in those who did not.[126] However, it should be noted that 2/5 who did not report success had major complications including empyema and death at day 18 post procedure.

Liver Transplant

in the one retrospective single-centre study specifically evaluating the outcome of 28 patients with HH undergoing transplantation (12/18 with refractory HH), post-transplant survival was excellent and comparable to that of matched controls transplanted for other indications. Secondary outcomes such as length of surgery, ICU stay, days of mechanical ventilation, and transfusion requirements were also comparable.[127]

Areas of future research	Question
Diagnostic accuracy	What are the features that predict an alternate diagnosis in patients with presumed HH?
Prognostication	What are the clinical and radiographic predictors of complications (specifically including IPC related infections) in patients undergoing pleural intervention for HH?
Risk prediction	Define bleeding risk in the HH population, identify risk factors for bleeding, are there subpopulations which require evaluation of coagulopathy and platelet function/quantity
Treatments	What is the efficacy of talc pleurodesis for HH in prospective comparative trials? What is the optimal drainage regimen for patients with HH and an IPC in-situ? What is the role of ambulatory aggressive drainage and talc pleurodesis in HH symptom palliation and mortality? How should spontaneous bacterial empyema be managed? How should ascites be managed in the context of HH? What are the relative benefits of TIPS revision vs IPC in the subpopulation of patients with delayed TIPS failure? What is the efficacy of contemporary covered, small-diameter TIPS? What are the indications for TIPS revision?

End stage renal failure (ESRF)

Within the dialysis population what are the management strategies for effusion control in the event of recurrent effusions?

P - ESRF receiving dialysis

I - Pleural procedures (TxAsp/ IPC/ ICD + Talc/ MT/ VATS), Renal Interventions (high dose diuretics, aggressive fluid removal at dialysis, salt + fluid restriction, use of hypertonic exchanges, use of icodextrin fluid on PD, switch from PD to HD)

C - Not required

O - Patient reported symptom measures, QoL, Frequency and duration of dialysis sessions, Volume of fluid removed during dialysis (+complications), pleural procedural complications, total number of pleural interventions required, number of breakthrough pleural interventions required

MT = Medical thoracoscopy, PD = peritoneal dialysis, HD = haemodialysis

Summary

- *Evidence on treating pleural effusions in ESRF are limited, with a single RCT, with only 6 patients from this population represented.*

- *This population are frail, have a poor prognosis and carry a high symptom burden, thus usually proposed treatments are for palliative intent.*

- *The commonest aetiology for effusions described in the literature, in this population is fluid overload, but not all patients will present with bilateral effusions or even transudates.*

- *In this population, there is a significant risk of pleural infection or malignancy. Where there is clinical suspicion and further investigation is deemed appropriate, it is the authors practice to conduct cross-sectional imaging early in the diagnostic pathway.*

- *If the aetiology is fluid overload, aggressive medical management or RRT has been shown to adequately treat pleural effusions. However, in many cases the adverse event rates of aggressive RRT can limit this approach. In contrast, pleural interventions have been shown to be relatively safe across several observational studies.*

- *The choice of pleural intervention is guided by patient choice and available treatment methods, but similar symptomatic relief has been achieved by repeat thoracocentesis alone when compared with IPCs in observational studies.*

- *Given the high adverse event and increased drainage volume with IPCs seen in RCTs of benign pleural effusions, the authors practice is to offer serial thoracentesis as the first treatment option, with IPCs or attempted talc pleurodesis reserved for refractory cases.*

In total 1763 studies were screened, and 21 studies were found to be of relevance in producing this section. These consisted of 16 retrospective observational studies, 3 prospective observational studies and 2 case series (see supplementary material).

Pleural Effusions in end-stage renal failure

Pleural effusions in the end stage renal failure (ESRF) population are common and secondary to varying pathophysiological processes. In the series by Jarrat and Sahn, the overall incidence of pleural effusion amongst a hospitalised population receiving haemodialysis was 21%, but only a fraction were attributed to uraemic pleuritis (16%), with the majority ascribed to cardiac impairment (46%). It is noteworthy that this series predated the modern use of echocardiography and the authors did not appear to differentiate cardiac failure from hypervolaemia.[128] Recent studies have tended to differentiate between cardiac failure and fluid overload and suggest the latter is the leading cause of pleural effusions amongst hospitalised patients: 9.6% vs 61.5% respectively.[129] A summary of the prevalence of pleural effusions and aetiologies described in the medical literature are presented in table D (in supplementary material). Estimates on the prevalence of pleural effusions amongst patients with ESRF vary (6.7-51%), heavily influenced by imaging modality, degree of renal impairment and form of renal replacement therapy (RRT). With this in mind, the estimated prevalence of pleural effusions amongst the studies reviewed is 1190/4826 (24.7% 95% CI 23-26%).[128–139]

Patients with ESRF may present with effusions due to many causes:

- Hydrostatic and oncotic imbalances
- Cardiac failure
- Fluid overload
- Hypoalbuminaemia (secondary to nephrotic syndrome, for example)
- Inflammation of the parietal pleura (secondary to autoimmune disease, for example)
- Infection or malignancy as a result of immunosuppression (secondary to ESRF, or following transplant, for example)

More unusual causes are recognised and are presented in table 5.

Table 5
Unusual causes of pleural effusion in ESRF, with proposed management options from the medical literature

Cause of pleural effusion	Proposed mechanisms	Diagnostic features	Management
Uraemic pleuritis [140, 141]	Mechanism unknown - suggested that toxins produced as a result of uraemia lead to effusion formation or this represents a fibrotic process following bleeding into pleural cavity as a result of circulating heparin (administered as part of RRT) or due to coagulopathy due to uraemia	- Usually a diagnosis of exclusion - Pleural fluid is exudative, often haemorrhagic - Chronic fibrinous pleuritis in pleural biopsy histology	- Increase intensity of RRT - Tube thoracostomy +/- pleurodesis - Pleural decortication - Consider systemic corticosteroids
Urinothorax [142]	Urine diverted into pleural cavity through diaphragmatic defects or lymphatic channels as a result of obstructive uropathy or trauma of urinary system	- Pleural fluid may be transudative or exudative (if high LDL), and of low pH, PF creatinine/ Serum creatinine >1 -Renal scintigraphy with ^{99m}Tc ethylene dicysteine (detection of extravasation of the tracer dye and its collection in the pleural cavity)	- Surgical or radiological intervention for anatomical defect
Nephrotic syndrome [142]	Low oncotic pressure (due to proteinuria) and increased hydrostatic pressure (due to salt retention) result in increased PF production Hypercoagulability leading to pulmonary embolism may also lead to pleural effusion, as may pleural infection secondary to immunoparesis due to loss of immunoglobulins	-Pleural fluid usually transudative but may be exudative in view of the alternative mechanisms highlighted	- Treatment of fluid overload and hypoproteinaemia and direct management of Nephrotic syndrome
Vascular abnormalities secondary to complications from haemodialysis [143]	Increase in hydrostatic pressure due to vascular obstruction leads to increased pleural fluid formation and decreased lymphatic clearance	- Often a unilateral transudative pleural effusion -Venogram diagnostic	-Ligation of fistula or venoplasty

Peritoneal dialysis associated pleuro-peritoneal leak [144] (see following PICO)	Increase intra-abdominal pressures following peritoneal dialysis and porosities in the diaphragm lead to pleural effusion formation	- Often an extreme transudate with very low protein values (<1g/dL) and very elevated glucose values (PF glucose: Serum glucose ratio >1) - CT Peritoneography or Scintigraphy - Trial of peritoneal dialysis cessation	- Alternative mode of renal replacement therapy - Pleurodesis - Surgical repair

Diagnostic implications for pleural effusions in ESRF

Whilst the usual pathways for investigating pleural effusions apply,[19] there are specific areas in regards to the ESRF population which need considering in the diagnostic approach (figure 5).

Management strategies for end-stage renal failure patients who present with effusions

Many of the studies in this review included patients with a myriad of different aetiologies driving pleural effusion, and therefore caution should be exercised in applying the evidence to all patients. It may not always be apparent that an effusion is secondary to fluid overload given some of the dual mechanisms involved, and therefore a pragmatic approach is often applied, with trials of therapies.

However, it is clear that patients with ESRF who manifest a pleural effusion tend to have a poorer prognosis, and a greater degree of cardiac comorbidity and death from cardiovascular disease, when compared to those without pleural effusion.[133, 145] This is supported by observational data from Walker et al, who found a 6-month and 1-year mortality of 31% and 46% respectively, thrice that observed in the general ESRF population (1-year mortality 15.6%) and others.[146–148] In addition to poor outcomes, there is a significant symptom burden, with many patients reporting dyspnoea.[135, 137]

In one of the few trials of pleural intervention in ESRF patients with recurrent effusions, Potechin et al describe a case series of 9 indwelling pleural catheters (IPC) inserted in 8 patients, who had recurrent effusion (at least two thoracocenteses in the preceding 2 weeks) and were already on maximal medical therapy (furosemide 160 mg/day, spironolactone 400 mg/day) and intolerant of dialysis. The study's primary outcome measure was patient reported dyspnoea scores: using a baseline dyspnoea index (BDI) and transitional dyspnoea index (TDI) two weeks after IPC insertion. They observed a significant improvement in dyspnoea (median TDI 6) and no significant fall in serum albumin after a median of 34 days post-IPC insertion. Auto pleurodesis was observed in 3 patients, after a median of 77 days. There were no major complications, including pleural infection. The baseline characteristics indicated a somewhat frail and elderly population. [149] In a thoracoscopy study amongst 10 ESRF patients with unexplained pleural effusion, Colella et al demonstrated safety and successful resolution of recurrent effusion in 4 patients who received a poudrage.[150]

Only 6/68 patients in the REDUCE trial and 13/350 patients in the meta-analysis of IPCs in NMPEs had had ESRF. Therefore interpretation and applicability of the observed findings are difficult in this population.[56, 60]

Surgical options are limited, particularly given the overall frailty of this population. Data from early literature showed invasive surgical interventions such as decortication and lung release in treating fibrothorax due to uraemic pleuritis, and more aggressive drainage strategies to prevent rounded atelectasis resulted in an improvement in lung function and

clinical course.[151–153] Presentations of fibrothorax are less commonly encountered since the advent of RRT and most pleural physicians are in agreement that rounded atelectasis itself requires no aggressive therapy.

The data on medical management of effusions in ESRF is also elusive; observational data on 1038 peritoneal dialysis (PD) patients, in whom 82 had a pleural effusion found that 10 (12.2%) resolved with intensive hypertonic PD alone, whilst the remainder required thoracocentesis for both diagnostic and therapeutic purposes. In the series by Jabbar, 236/280 (84%) were “medically” managed, though specific details of therapy are lacking. [135] A summary of studies of intervention in pleural effusions secondary to ESRF are shown in table E (in supplementary material).

Areas of future research	Question
Diagnostic accuracy	Can we improve the specificity of Light's criteria for the ESRF population in order to avoid mislabelling a transudate (due to fluid overload) as a false exudate? Can we produce through expert consensus (eg. Delphi) precise criteria for defining the aetiology for pleural effusions in ESRF patients?
Treatments	What are the most effective therapeutic interventions in addressing recurrent effusions in the ESRF population, with a focus on PROMs, QoL metrics and health economic analyses?

What is the usual investigation and management of a PD associated pleuro-peritoneal leak (PPL)

P - Patients receiving PD

I - Ix: Pleural fluid analysis according to defined cut-off values, peritoneal injected contrast agents, trial of cessation from PD
Mx: Pleural interventions (Pleurodesis via slurry, poudrage, surgical), Renal interventions (permanently cease PD, temporary pause of PD)

C - Not required

O - Diagnostic accuracy, time to diagnosis, efficacy (resolution of pleural effusion), complications

Summary

- *Evidence on options for investigating and treating PD associated PPLs are limited to observational series.*

- *The ability to pause and resume PD whilst observing for recurrence has been used as a diagnostic tool in many of the observational series and several proposed investigative pathways in the literature adopt this approach.*

- *The literature describes many patients successfully treated with conservative measures, however a significant few went on to require pleural interventions.*

- *There is little evidence to draw firm conclusions for the different forms of pleural intervention, and the choice usually depends on both patient suitability and access to surgical services.*

In total 411 studies were screened, and 14 studies were of relevance in producing this section. These consisted of 1 editorial, 11 retrospective observational studies, 2 case series (see supplementary material).

Pleuroperitoneal leaks in patients receiving peritoneal dialysis

Hydrothorax due to a pleuroperitoneal leak (PPL) in patients receiving peritoneal dialysis (PD) has a reported incidence of 1.0%-5.1%. [154–157] They are mostly unilateral with the majority (88%) occurring on the right side.[155] In one series, 50% of cases occurred within the first 30 days of initiation of PD and a further 18% beyond the first year. Some cases occurred as late as up to 8 years following initiation of PD.[155] In this same series, 26 % of the cases were asymptomatic (see table F in supplementary material).

Diagnosis of PPL

The pleural fluid (PF) is clear or straw coloured and has traditionally been described as having the characteristics of an extreme transudate with very low protein values of <1g/dL and very elevated glucose values of 350-450 mg/dL (19.4-25 mmol/L), and often reflects a value between the serum glucose and dialysate glucose levels.[158]. Several studies have assessed diagnostic cut off values for PF glucose, and optimal imaging but there are no studies directly comparing the sensitivity or specificity of each test.[159–163] Figure 6 describes the usual diagnostic and therapeutic approach of TF members in PD patients with a suspected PPL.

Treatment of PPL

Immediate management of a PPL is to usually discontinue PD and consider thoracocentesis for symptom relief in those presenting with dyspnoea. Long term management strategies for PPL include a retrial of PD after temporary PD cessation (during which alternative RRT may be needed), followed by chemical pleurodesis via tube thoracostomy or medical thoracoscopy, VATS assisted mechanical or chemical pleurodesis with or without surgical repair, or finally open surgical repair of any anatomical defects. There are no studies directly comparing the outcomes of these different management approaches.

In one series, hydrothorax resolved completely in 27 (54%) of the 50 patients of whom 19 (38 %) had only brief cessation of PD and a further eight patients with low volume exchanges in semi erect position or pleurodesis with tetracycline or other agents.[155] In a systematic review by Chow et al, temporary discontinuation of PD for a period of 2-6 weeks was successful in 53% of patients without recurrence.[154] Alternatively, low volume PD exchanges in reclining position have also been used successfully as the reduced intraabdominal pressure and gravitational factors allow spontaneous closure of the defects. As there is no reliable way of predicting response to a temporary suspension of PD, one sometimes considers instituting other treatment strategies in addition to this, depending on patient and clinician preference. Conventional tube thoracostomy directed pleurodesis has been used successfully in 48% of cases.[154]

Recurrence following a temporary discontinuation of PD or following pleurodesis has been attributed to large diaphragmatic defects that requires surgical repair either by thoracotomy or VATS, with success rates of 100% and 88% reported respectively.[154, 162, 164] Due to the perioperative risk associated with thoracotomy, VATS with chemical or mechanical pleurodesis with Marlex or prolene mesh have been increasingly used.[154, 165] In addition to pleurodesis, additional procedures at thoracoscopy such as endoscopic suturing and repair using a Teflon patch have been described to prevent recurrences. The timing of when to resume PD is arbitrary, but a rest period of 3-4 weeks after surgical repair or pleurodesis has been recommended before reinitiating.[154] In one study of 27 patients, by 26 months, withdrawal from PD due to recurrence was seen in 88% of those managed non-surgically compared to a failure rate of zero in the surgical group (VATS diaphragmatic repair).[162]

Chen et al report outcomes on 35 patients with PPL who underwent VATS assisted surgical interventions using a variety of techniques such as mechanical pleurodesis with prolene mesh, chemical pleurodesis with talc or tetracycline, direct surgical closure or a combination of the above.[166] The lowest recurrence rates were seen when combination mechanical and talc pleurodesis were performed (10%) compared to 33% for other techniques. Using data from historical cohorts from other studies they report in comparison to discontinuation of PD alone, combined pleurodesis has an odds ratio (OR) for recurrence of 0.12 whilst other techniques had an OR 0.54.[166] Selecting mode of delivery of pleurodesis depends upon patient suitability, access to thoracic surgery and the suspicion of sizeable diaphragmatic defect such that more invasive surgical interventions may be warranted.[154] There are no prognostic markers to predict response to treatment with any of the above interventions. However, treatment failure was more common amongst females, patients

with polycystic kidney disease, and hydrothorax secondary to early leaks (<30 days of commencing PD).[154] Table G in the supplementary material summarises the success rates of various treatments to address a PPL.

Areas of future research	Question
Predicters of treatment failure	Can we predict which patients with a PD-associated PPL will respond to PD interruption, and offer upfront definitive interventions for this cohort?
Diagnostics	Can we define a standardised method for obtaining a Pleural Fluid to Serum (PF/S) glucose gradient and/or ratio? What form of imaging is most sensitive/ specific at diagnosing a PPL?
Treatments	What are the most effective interventions to treat a PPL?

Benign Asbestos Related Pleural Effusions (BAPE)

In patients with suspected BAPE/DPT, what are the clinical features that can identify risk factors, diagnose the condition, and identify prognostic features?

P - Patients with suspected BAPE/ DPT
I - Clinical features (pleural fluid, histopathology, radiology), Risk factors, Prognostic factors
C - Not required
O - Diagnosis of BAPE/DPT/Exclusion of mesothelioma, Diagnostic accuracy rates of BAPE, Rates of evolution of BAPE, Rates of lung function decline, Rates of radiological progression

BAPE = Benign asbestos related pleural effusion, DPT = Diffuse pleural thickening

Summary

- *BAPE & DPT are manifestations of inflammatory-driven responses to exposure to asbestos fibres and in observational series, present following a mean latency period from exposure to onset of 30-38 years.*

- *The cardinal symptoms reported in these studies are cough, breathlessness, chest pain and flu-like symptoms.*

- *Diagnostic workup includes plain film and cross-sectional imaging, with histo- or cytological analysis via thoracentesis or biopsy.*

- *PET-CT has been shown to be a useful adjunct in differentiating BAPE/DPT from malignant processes.*

- *DPT is defined as shouldered pleural thickening measuring >5cm axially by >8cm craniocaudally with a minimum thickness of 3mm.*

- *Pleural fluid has been found to be predominantly a lymphocytic or eosinophilic exudate and may be haemorrhagic.*

- *Bilateral disease confers a worse symptomatic prognosis in observational series.*

In total 2048 studies were screened to identify 29 studies relevant to producing this section. These consisted of 1 editorial or narrative review, 17 retrospective observational studies, 4 prospective observational study, 5 case series or single case reports, 1 systematic review and meta-analysis and 1 trial protocol (see supplementary material).

Risk Factors

Both benign asbestos pleural effusion (BAPE) and diffuse pleural thickening (DPT) are known to develop following asbestos exposure.[167] However, there are a number of other causes of DPT that need to be excluded before a firm diagnosis of asbestos related DPT can be made. This statement will focus on DPT related to asbestos exposure.

BAPE/DPT can occur after low dose asbestos exposure [168] but is more commonly seen following moderate to high exposures. Its incidence increases with higher exposures in keeping with a dose-response effect.[167–170] DPT has been postulated to occur both as a sequela to an inflammatory BAPE effusion and independently as a result of parenchymal fibrotic inflammation extending into the visceral pleura in line with asbestos fibre migration patterns.[171–174] BAPE/DPT have a mean reported latency period of 30-38 years.[169, 175, 176] High rates of smoking have been observed in patients with BAPE/DPT however, it is unlikely there is a causative relationship.[169] BAPE/DPT have been most frequently reported in patients exposed to crocidolite and chrysotile fibres however no statistically significant data exists to define risk conferred by fibre type.[177, 178] Similarly, BAPE/DPT patients tend to be male, which correlates to occupation and exposure patterns rather than being an independent risk factor.[168, 169]

Clinical Features

Patients with BAPE/DPT present to medical services at varying points in their natural disease course. At the point of presentation there is wide variation in symptomatology, and some are asymptomatic - however the cardinal symptoms are cough, breathlessness, chest pain and flu-like symptoms.[167, 169, 176, 179, 180] It is expected that there is evidence of asbestos exposure which may be evident in the clinical history and/or the presence of pleural plaques on chest imaging.[181]

Diagnostic Investigations

Pertinent diagnostic investigations undertaken in the first instance include CT imaging, thoracentesis and/or biopsy. Diagnosis remains based on exclusion of other pathologies, with some authors advocating MDT discussion and a period of monitoring of at least 24 months without development of radiological features of malignancy.

Radiology

BAPE effusions occur most frequently on the right (69-76%) but may be left sided or bilateral at presentation.[169, 176, 180, 182, 183] There are often concomitant signs of

asbestos exposure, such as pleural plaques, pleural thickening, asbestosis and folded lung/rounded atelectasis.[169, 184]
CT appearances of BAPE may be indistinguishable from early-stage malignant pleural mesothelioma (MPM), hence it is a diagnosis of exclusion. However, pleural thickening > 1cm, pleural nodularity, chest wall invasion, involvement of the mediastinal pleura and high grade "pleural irregularities" are strong indicators of malignant pleural effusion or MPM.[184–186] In cases of diagnostic uncertainty, despite tissue biopsy, PET-CT may have a limited role, with MPM often exhibiting higher SUVmax levels, prompting consideration of a repeat biopsy.[187–189] DPT is classically defined as thickening of the visceral pleura of at least 3mm thickness seen on chest x-ray (CXR) that obliterates the costophrenic angle (CPA).[190] However, Lynch et al define DPT as pleural thickening of at least 3mm thickness, and measuring >5cm axially and >8cm craniocaudally, with or without CPA involvement (see figure 7).[170, 191]
CT may show a constellation of pleural thickening, pleuro-parenchymal bands/"crow's feet" and folded lung.[192] Ultra low dose CT has been shown to be effective in identification of DPT (sensitivity 90.9%, specificity 100%, PPV 100% and NPV 97.8%). However, intravenous contrast may be of use when excluding malignancy.[193] As with BAPE, PET-CT may be used to identify malignant features.[187–189, 194]

Laboratory Investigations

Pleural fluid is usually exudative and often haemorrhagic. It has variable cytological predominance but most commonly is lymphocytic or eosinophilic.[3, 9, 11, 30] By definition, there must be no malignant cells present. Pleural fluid hyaluronic acid and secretory leukocyte peptidase inhibitor levels have been found to be lower in BAPE than malignant processes thus may be of use in differentiating BAPE from MPM.[31, 32]

Investigations for other pathologies such as infection or multisystem inflammatory disease are frequently undertaken to exclude these conditions.[3, 33]

Histopathological samples may show a variety of features, including signs of chronic inflammation, the fusion of parietal and visceral pleura, and the loss of submesothelial elastic tissue. Honeycombing and basket weave fibrous focal lymphocytic collections may be seen in lung adjacent to fibrotic pleura. Evidence of chronic asbestos exposure may also be seen in histopathological samples with high asbestos fibre counts.[178] Again, malignant cells must be absent, on full thickness biopsies (i.e. to fat) as must histopathological markers of mesothelioma such as BAP1 loss and p16.[195] Recent advances in microRNA analysis have shown promise in differentiating between BAPE and MPM but are yet to be developed into validated clinical markers.[196]

Clinical Course and Prognosis

The disease course of BAPE is varied, however the majority experience a transient pleural effusion which resolves within 3-12 months. Patients may develop contralateral effusions and recurrence on either side.[167, 168, 196] Effusions that do not resolve may become organised over time. BAPE may progress to DPT in as 30-40% of cases.[176, 181] The

majority of patients with DPT have unilateral disease at presentation, however 24-39% progress to bilateral disease within 2 years.[176, 196] In those that do not progress, DPT exhibits radiological stability. No risk factors or prognostic indicators for progression of BAPE or DPT have been established. Bilateral DPT at presentation and the presence of concomitant asbestosis have been shown to be markers of greater respiratory compromise.[196]

Development of MPM

BAPE/DPT have been increasingly recognised to have the potential to evolve to MPM, with a recent meta-analysis finding an evolution rate of 6%, and retrospective study demonstrating 14.5% evolution.[197, 198] The results of a prospective study of BAPE-MPM evolution rates are awaited.[199]

Lung function

Both BAPE and DPT are thought to exert a restrictive defect on lung function. In patients who experienced regression or resolution of effusions, once vital capacity dropped to <60% expected, it did not recover in one retrospective series.[181] This may not directly be due to the presence of effusion, as other studies have shown only modest impact on lung function due to pleural effusion, and may speak to other mechanisms implicated in BAPE and DPT.[81] DPT has been shown in multiple studies to decrease TLC and DLCO with FEV_1/FVC ratio preservation.[171, 200, 201] DPT CT findings are known to correlate with lung function deficit, with bilateral DPT and DPT obliterating the CPA shown to exert the most potent effect on FVC and TLCO.[17, 43] No correlation has been found between MRC breathlessness scoring and FVC/TLCO or radiological findings, perhaps reflecting the complexity of breathless is this cohort.[200]

Unfortunately, data on progression of lung function is lacking.

Areas of future research	Question
Diagnostics	Can reliable serological or histological biomarkers for BAPE/DPT be identified? In the case of negative or unachievable biopsy, can PET-CT be used to reliably differentiate between malignant and non-malignant DPT? Can a diagnostic classification system be developed to improve upon current diagnosis of exclusion approach?
Prognostication	What is the impact of BAPE or DPT on Lung Function over time?

In patients with established BAPE/DPT, what are the options for follow up?

P - Patients with established BAPE/DPT
I - Duration of CT follow up period, use of PET-CT, use of biopsy and/or re-biopsy
C - Not required
O - Reduction in length of follow up and number of interval CT scans, rates of malignancy

Summary

- *In the authors practice, diagnosis is made following biopsy proven exclusion of a malignant process, and serial follow up imaging +/- repeat sampling suggested, over a 2-year period.*

- *In observational series, the majority of BAPE was seen to resolve over 1 year, although up to 40% developed DPT following effusion resolution.*

- *BAPE/DPT has been shown to progress to mesothelioma in 6-14% of cases – no prognostic indicators of progression to mesothelioma have yet been identified. In the event of suspected progression re-biopsy may be indicated.*

Published evidence for this question is limited. This statement sets is based upon a synopsis of available literature and the authors' clinical expertise. It is hoped that identifying this area as lacking in evidence will drive future research and investigation.

Biopsy and re-biopsy

As BAPE/DPT is a diagnosis of exclusion, biopsy is an essential part of workup and, where possible, is usually undertaken at presentation.[169, 178, 180] Biopsy site is guided by imaging and may be undertaken percutaneously, thoracoscopically or surgically (please refer to non-specific pleuritis chapter).

In some cases biopsy will not be possible due to lack of accessible target or poor performance status. There is a dearth of literature to guide management in cases such as these, however the authors would undertake serial imaging and clinical review to monitor progress – this strategy allows for identification of biopsy targets if they evolve, or the demonstration of clinical stability.

In patients with initial investigations that are suggestive of benign asbestos related pleural disease, the development of new or evolving pleural lesions with malignant appearing features would prompt the TF members to always investigate with (re-)biopsy to exclude malignancy, when clinically appropriate.[182]

CT follow-up

Patients with BAPE/DPT undergo a period of follow up, with or without initial biopsy, to ensure resolution or stability of their disease and allow for diagnosis of evolution of malignancy.[202] However, the follow up period reported in literature varies from months to 30 years.[169, 176, 177, 196] The median time of DPT progression is reported as 2-3 years, which is reflected in the 2 year follow up period adopted by multiple authorities.[176, 180, 182] Similarly, the follow up period for malignant evolution currently under investigation in the Meso-ORIGINS study is two years.[199]

Within the two year follow up, serial CT imaging can demonstrate progression or highlight new changes suggestive of malignancy and may be performed at 6, 12 and 24 month intervals. [176, 180, 182]

PET-CT has been used to effectively differentiate between malignant and non-malignant pleural disease.[187, 189, 194] Kramer et al demonstrated PET-CT at the point of diagnosis has a negative predictive value for malignant pleural thickening of 0.92 (95% CI 0.78-1.00). Although this study is small, three years of follow up data were included, in which time only one false negative case (a slow growing solitary fibrous tumour) was identified. Yildirim et al demonstrated that PET-CT may achieve a sensitivity of 88.2% and specificity of 92.9% for malignant pleural disease, albeit in a smaller sample without a long term follow up period. Both studies suggest that PET-CT may be effective in differentiating between malignant and non-malignant pleural disease, however further prospective data is required before this approach is widely adopted.

Further prospective work is required to delineate the optimum follow up imaging strategy for BAPE/DPT. Although PET-CT at the point of presentation shows promising diagnostic potential, the reported evolution rates of MPM from larger scale studies indicate serial CT imaging over an extended period might be needed. Therefore, the role of PET-CT currently appears to be in differentiating between malignant and non-malignant disease in equivocal cases and cases where no cytological or histological samples may be obtained, and for identification of areas of high avidity that may represent that most diagnostic biopsy targets.

Areas of future research	Question
Diagnostics	Can PET-CT obviate/reduce the requirement for serial CT imaging?
Prognostication	Can prognostic biomarkers of progression from BAPE to DPT, and BAPE/DPT to MPM be identified?

Post-surgical pleural effusions

Usual treatment of post-surgical pleural effusions: thoracentesis/chest drain vs. conservative treatment.

P – Adults (>18 years of age) with post-surgical pleural effusions after cardiac or thoracic surgery
I – Effusion drainage by thoracentesis or chest drain insertion
C – Medical management or observation
O – Re-admission, length of stay, symptom scores, recurrence of effusion, radiological improvement, complications, quality of life, mortality

Summary

- *Post-operative pleural effusions are common but there is no evidence to suggest they have an impact on morbidity or mortality.*

- *Aetiology and presentation vary according to primary diagnosis and surgery type and management varies accordingly.*

- *Studies have shown most effusions do not require intervention and radiological features alone should not dictate the need for intervention. Where studies exist, a protocolised pathway for intervention resulted in small improvements in walking distance with no impact on quality of life or self-reported symptoms and reduced lengths of hospital stay.*

- *Most studies on pleural effusion management post-thoracic surgery have focused on timing of post-operative drain removal; earlier drain removal following thoracic surgery, at higher than traditionally accepted drain outputs (450 mls/24 hours) has been shown to be safe and efficacious.*

- *US guided thoracocentesis has largely replaced the need for more invasive surgical tube thoracostomy and is both effective and well tolerated by patients in observational series.*

- *The literature on 'Late' post-operative pleural effusions is sparse, and in most instances, comprehensive investigation is carried out before attributing it to a post-operative cause.*

Pleural effusions are a non-specific and well-known complication following cardiothoracic and heart/ lung transplant procedures and often follow a benign course. Currently, there is little consensus on the optimal treatment of a post-operative pleural effusion. In total 900 studies were screened to identify 20 studies relevant to producing this section. These consisted of 3 editorials or narrative review, 8 retrospective observational studies, 5 prospective observational studies, 1 non-randomised comparative study, 3 RCTs (see supplementary material)

Prevalence of post-operative pleural effusions

Pulmonary complications after cardiothoracic surgery lead to higher mortality rates.[203, 204] Whilst pleural effusions are included amongst the spectrum of pulmonary complications, to date no evidence has demonstrated an isolated effect of post-operative pleural effusion on mortality.

Post-operative pleural effusions are divided into "Early" and "Late" categories depending on the time of onset following surgery. Early effusions are those occurring within 30 days of surgery and late beyond 30 days.

Analysis of early pleural effusions show they have higher erythrocyte, LDH and eosinophil counts, whereas late pleural effusions are predominantly lymphocytic, with lower LDH levels. Whilst both are exudative, the differences are likely due to changing biochemical processes occurring at different stages of the post-operative period. Early effusions are more often related to the trauma and bleeding of surgery itself, while the biochemical characteristics of late effusions suggests an immune mediated response.[205] Pleural effusions may also arise as a result of operative damage to the thoracic duct (chylothorax) or represent a post-operative infection.

Several authors classify pleural effusions into "clinically significant" and "non-significant," based on symptoms: increased respiratory support, shortness of breath, cough, tachypnoea and pain. Whilst a large proportion of patients (42%-89%), have radiographic findings of pleural effusion in the early post-operative period, not all of them are considered "clinically significant" requiring intervention.[203, 205–207] Diagnosis of, and intervention in late pleural effusions can be somewhat mixed, as this varies according to the usual follow-up pathways amongst different surgical units and there is a paucity of literature on their characteristics or management.

Prevalence of pleural effusions requiring intervention following coronary artery bypass grafting (CABG) or valve surgery are approximately 6.6%.[205] Large or symptomatic pleural effusions usually prompt intervention (thoracentesis or chest drain), with the definition of a large effusion differing: >25%, > 30%, >1/3 of the hemithorax on a frontal chest radiograph in various studies.[208–210] Decisions to intervene are usually based on a combination of clinical and radiological features rather than individual parameters.[211] Xing et al report 1.2% patients require thoracocentesis due to recurrent pleural effusions, but do not necessarily specify what criteria prompted intervention in some and not others.[212] Moreover, recurrence despite intervention is documented in around 21%.[205]

In an observational series Usta et al suggested a protocolised pathway for intervention in post-operative pleural effusion (if symptomatic and estimated pleural effusion volume >480mls) reduced length of stay by 3 +/- 1.5 days, compared to patients managed with diuresis alone.[211] Hansen et all investigated whether dedicated follow-up and intervention on pleural effusions enhanced recovery rates or improved quality of life and symptoms. They compared a standard follow-up protocol with physicians' decision on when to intervene on pleural effusions, to more frequent follow-up with a dedicated protocol for intervention (effusions of estimated volume >400 mls, or <400 mls and symptomatic). They found no significant difference in self-reported symptoms or quality of life, but an improvement in walking distance when the pleural effusions were drained according to a standardised protocol. They conclude that recovery rates can be enhanced by up to 15% with dedicated follow-up and drainage regimes.[213] Ultrasound guided thoracentesis has now replaced the more invasive surgical tube thoracostomy as the initial intervention of choice, and is well tolerated by patients.[211–213]

Effusion after Cardiac surgery

There are differences in the presentation and management of post-operative effusions according to surgery type: cardiac vs thoracic. This can in part be explained by the differences in co-morbidity which have led to surgical intervention in the first instance, and differences in surgical technique and approach. There is more evidence in the medical literature on pleural effusion management following cardiac surgery, such as Coronary artery bypass graft (CABG), valve replacements, aortic interventions, as opposed to following thoracic surgery (eg. lung resection). A further distinct entity, post-pericardiotomy syndrome (PPS), characterised by fever, pleuritic pain, pleural and/or pericardial effusion, thought to represent an auto-inflammatory process, is recognised.[214, 215] In symptomatic patients, anti-inflammatories (NSAIDs, aspirin, colchicine and glucocorticoids) may be beneficial.[215] However, only post-operative colchicine has been shown to be of benefit, as a preventative measure in reducing the incidence of PPS.[216]

Differences between techniques within the same procedure have been studied. CABG with internal mammary artery (IMA) harvesting and preserving the integrity of the pleura had a lower rate of pleural effusion development compared to IMA harvesting and breaching of the pleura.[217] One study addressed pulmonary compromise after a Maze procedure, which entails creating scar tissue in the atria with a scalpel or an energy delivering device, to stop abnormal electrical conduction and thus treating atrial fibrillation. Ad et al compared prophylactic continuous furosemide infusion versus boluses after the Maze procedure and demonstrated this to have a significantly lower incidence of pulmonary complications and necessity for effusion drainage.[218] However, the Maze procedure is thought to reduce the production of atrial natriuretic peptide, which may underpin a different mechanism in the development of effusion, compared to more routine cardiac surgical procedures.

Effusion after Thoracic surgery

Literature on post-operative effusion management following Thoracic surgery has concentrated more on the optimal timing of chest drain removal, and the impact on important outcome measures such as readmission rates and need for further pleural intervention. Cut-offs of the ideal amount of drainage per day before removal of the chest

drain is based on expert opinion rather than evidence, hence several studies have attempted to assess greater than normally accepted practice limits (250mls/24h).[219] Higher thresholds (450mls/24h vs 250mls/24h) for chest tube removal post-lung resection improved respiratory function, reduced infection rate and pain symptoms, and enabled chest tubes to be taken out earlier. Relatively low effusion recurrence and reintervention rates were observed. Earlier chest tube removal enabled a reduction in the length of stay in hospital.[212, 219] Readmission rates due to symptomatic pleural effusion were low and did not differ between higher and lower threshold groups.[219] Interventions following readmission due to symptomatic effusions ranged between repeated VATS/thoracotomy, thoracentesis and observation.[219] A Danish study by Bjerregaard et al noted that only 2.8% of patients developed pleural effusions requiring reintervention, despite allowing high volume output before removing the chest tube and most patients with recurrence could be managed without invasive intervention.[220]

Overall, these studies show that higher thresholds of up to 450mls/day drainage used for chest drain removal is safe, with low reintervention rates and improved patient experience.[212, 219, 220]

Effusion post-transplantation

Pleural effusions are a common occurrence in lung transplant recipients, involving 25-100% of patients in the early period.[221, 222] These effusions are usually exudative, tend to be bloody, with a predominant neutrophilia and are usually small to moderate in size.[222] Several causes of effusions during the early postoperative period have been suggested, including pleural inflammation, increased alveolar permeability, atelectasis, impaired lymphatic drainage and host immune response.[222] Late effusions (>15 days post-transplant) are common and are usually exudative and lymphocyte-predominant and tend not to recur following thoracentesis.

Although post-orthotopic heart transplant (OHT) pleural effusions have been described in several studies, little data exists describing the characteristics of these effusions.[204, 223] Early post OHT effusions are usually bilateral, exudative, moderate to large, and are usually more neutrophilic and less haemorrhagic compared to post-CABG effusions.[207]

Limitations

No randomized controlled trials comparing interventions against conservative measures for recurrent post-operative pleural effusions exist. Alternative options for patients that did not receive thoracentesis for recurrent pleural effusions are described in the literature but the specific details of therapies are vague, and these were not head to head comparisons.

Due to the different nature of cardiac and thoracic surgery, it is difficult to compare the reintervention rates between the two. Management of post-operative drains (and timing of removal) differs between these two groups; this may also impact the rates of recurrence and decisions for subsequent reintervention, between groups.

Areas of future research	Question
Diagnosis	Can we establish diagnostic criteria for late post-operative pleural effusion?
Management	Is thoracocentesis more effective than medical management (i.e. diuresis) in post-cardiac surgery related pleural effusions?

Non-specific pleuritis

What are the options for investigating a patient with an initial NSP finding on histology?

P - Patients with NSP on Histology from image guided pleural biopsies AND/OR thoracoscopic pleural biopsies

I - Further biopsy procedures: medical thoracoscopy, image guided biopsies +/- VATs, Conservative management/ Observation, further ancillary tests (biomarkers/ histological techniques)

C - Not required

O - Detection of underlying malignant process (i.e. false negative), identification of additional pathologies

Summary

- *A histological diagnosis of NSP following thoracoscopy has been found in up to 40% of cases in various series and the most difficult question is whether this is truly a benign diagnosis or a false negative. A possible malignant aetiology has been found in 8% of patients, with mesothelioma being most common malignancy diagnosed.*

  Histological patterns of inflammation and fibrosis vary greatly in individual cases of NSP, and likely represent different stages in the process of tissue injury and remodelling. Ancillary techniques, such as FISH for CDKN2A deletion and/or BAP1 or MTAP immunohistochemical loss have been shown to be essential in differentiating between NSP and mesothelioma in situ. Clinical features that may suggest a false negative NSP result mirror those that make one suspicious for malignancy (particularly MPM)
- *Although there is evidence for both thoracic ultrasound and diffusion weighted MRI in distinguishing benign from malignant pleural disease, most of the evidence for differentiating malignant from benign pleural disease comes from CT studies.*

- *Biomarkers for identification of non-specific pleuritis are not well established and their role remains unclear.*

- *Parietal pleural biopsy with rigid forceps is shown to have a better diagnostic yield compared to biopsy with flexible forceps or cryobiopsy. Adipose tissue was more likely to be present using rigid forceps. Given invasion of adipose layers is a crucial diagnostic feature for mesothelioma, this is a significant advantage of rigid forceps biopsy.*
- *In the authors experience, false-negative diagnoses of NSP, which eventually turn out to be mesothelioma, may be related to difficulties visualising the pleural cavity at thoracoscopy due to adhesions, excessive fibrinous thickening or early-stage malignant disease with no obvious target for biopsy, rather than type of thoracoscopy performed.*

In total 1949 studies were screened to identify 40 studies relevant to producing this section. These consisted of 5 editorials or narrative review, 22 retrospective observational studies, 3 prospective observational studies, 3 RCTs, 2 laboratory studies, 4 systematic reviews and meta-analyses and 1 guideline (see supplementary material).

Definition and incidence of NSP

Histological analysis of a thoracoscopic pleural biopsy is considered the "gold standard" for diagnosis in pleural disease and is recommended as the final diagnostic step for an unexplained exudative effusion.[224] However, in up to 40% of pleural biopsies, a histologic pattern of "non-specific pleuritis" (NSP) is found.[225–239] In contrast to malignant and TB pleuritis which have distinct histological features, most other causes of pleural disease are associated with non-specific biopsy findings (inflammation and fibrosis).[240] There are currently no recommendations regarding the optimal diagnostic “work-up” in patients with a histological diagnosis of NSP. The TF members include in their baseline evaluation a detailed history including history of asbestos exposure, and a panel of blood tests and imaging modalities according to pre-test suspicion of aetiology. Following work up, a probable cause is identified in most cases, but in up to 48%, a clear cause cannot be identified and a clinical diagnosis of “idiopathic pleuritis” is made.[225–232, 234, 235, 237, 238, 240–242]

While most pleural effusions associated with biopsy findings of NSP resolve spontaneously, in 8% (range: 3-38%) a malignant aetiology is eventually recognized, and malignant pleural mesothelioma (MPM) is the most frequent cause .[225, 227–229, 231, 232, 234, 235, 237–244] The substantial range in the eventual development of pleural malignancy following a finding of NSP may be due to several factors; inter and intra-centre differences in thoracoscopy operator experience and technique, pathology technique and expertise, geographical variation in prevalence of asbestos exposure and follow-periods between studies. When a diagnosis of NSP is made, the first concern is whether it represents a truly benign condition, or a false-negative biopsy due to sampling or other diagnostic error. To date, there is no consensus on what constitutes a false-negative result due to error, as opposed to late progression to malignancy.[225]

Histopathological features of NSP

Microscopic examination of these cases reveals varying degrees of inflammation and fibrosis. These are demonstrated in Figure 9.

An explanation for the wide range of eventual malignant diagnoses, following an NSP finding across different datasets may be due to pathology expertise. Use of ancillary histological techniques may minimise “false-negatives”; the best evidence tests to distinguish MPM from reactive mesothelial conditions are homozygous deletion of *CDKN2A* detected by Fluorescence in-situ hybridization (FISH) (100% specificity, sensitivity ranging from 14% to 85%) and loss of BAP1 (BRCA1-associated protein 1) expression on immunohistochemistry (IHC) (high specificity, lower sensitivity).[245] Loss of MTAP (50-

methylthioadenosine phosphorylase) on IHC has recently been shown to be useful; in a study of 125 MPMs diagnosed at the National MESOPATH Reference Centre, loss of MTAP cytoplasmic staining showed 96% specificity and 86% sensitivity to detect homozygous deletion of *CDKN2A.* [246, 247]

Time to progression from mesothelioma in-situ to invasive MPM has been shown to range from 1-15 years.[248] Therefore, the latest WHO classification system for MPM acknowledges "mesothelioma in-situ" as a stage of disease and defines it as: non-resolving pleural effusion, no thoracoscopic or imaging evidence of tumour, single layer (but papillary proliferations are accepted) of mesothelial cells on the pleural surface without invasion, and loss of BAP1 or MTAP by IHC, or *CDKN2A* homozygous deletion by FISH, followed by multidisciplinary discussion.[249] It therefore remains unclear which cases should undergo further histological analysis with these techniques,[249, 250]. The authors practice is to use them in all cases of suspected MPM.

Factors associated with a false-negative finding of non-specific pleuritis on biopsy:

Clinical features:

Davies et al found a strong association between the referring physicians' level of clinical suspicion of pleural malignancy prior to thoracoscopy and eventual malignant diagnosis following an NSP result, but found the operator's impression at time of thoracoscopy to be a poor predictor.[235] They also found recurrence of pleural effusion associated with eventual malignant diagnosis.[235] This was also noted by Yu et al: a greater likelihood of diagnosing pleural malignancies in patients with an initial false-negative NSP result when faced with recurrent pleural effusion, pleural nodules, or pleural plaques.[238]

Clinical risk factors for a false negative NSP result mirror that for suspicion of malignancy (particularly MPM). Those which may sometimes warrant heightened surveillance and further biopsy, include:

- Recurrence of pleural effusion
- Ipsilateral chest pain
- History of asbestos exposure

Imaging features:

When NSP is identified in pleural biopsies after thoracoscopy, imaging findings, may lead the clinician to suspect malignancy (ie false-negative NSP) and pursue further work-up.

CT

Across two studies, CT findings suggestive of malignant involvement (parietal pleural thickening (> 1 cm), nodular pleural thickening, mediastinal pleural thickening, circumferential pleural thickening and a mass lesion) were associated with a false negative NSP result.[225, 236] In a recent study, 102 cases of NSP or atypical mesothelial proliferation diagnosed at VATS, progression of CT findings determined whether re-biopsy was attempted.[251]

Thoracic ultrasound

Several studies have explored the utility of morphological findings of transthoracic ultrasound (TUS) as a tool for detecting MPE. Certain TUS findings were shown to have a high sensitivity and specificity for malignant pleural effusion.[96] These findings were disputed in a recent meta-analysis, which suggested pleural thickening, has low sensitivity and variable specificity, and only visceral or parietal nodularity is specific for malignant pleural disease with a high positive predictive value.[52]

MRI

There is growing interest in the role of diffusion weighted magnetic resonance imaging (DWI), which can distinguish tumoral from non-tumoral tissue. In a recent study, the sensitivity of DWI MRI in detecting pleural malignancy exceeded CT (94.2% vs 67.3%), with similar specificity.[252] Revelli et al. demonstrated DWI MRI was able to distinguish benign pleural disease from MPM even in small lesions and in the sarcomatoid subtype in patients undergoing thoracoscopic biopsy (n=56).[253]

Although both TUS findings and DWI evaluation play a role in distinguishing benign from malignant pleural disease, given the abundance of evidence and minimal inter-operator variability, the most frequently used imaging modality remains CT.

Biomarkers

MPM is the main malignant diagnosis of concern following an NSP histological finding. Biomarkers for early detection of MPM in a high-risk population have been widely studied, and promising biomarkers include mesothelin, osteopontin and fibulin-3. Only mesothelin has received US Food and Drug Administration approval for clinical use.[254] In early mesothelioma diagnosis, mesothelin has a higher sensitivity for MPM in pleural effusion vs serum (79% vs 61%, with estimates of specificity of 85% and 87%, respectively).[255] While numerous studies have demonstrated that PE-SMRP levels are higher in patients with MPM than in subjects with benign mesothelial lesions [256], no data are available regarding the role of PE-SMRP as a blanket tool in subjects following a histological finding of NSP.

For the clinician, a biomarker able to identify patients more likely to develop pleural malignancy after an NSP diagnosis is an important tool that might improve management (eg. enhanced surveillance and follow-up). Not all guidelines recommend the use of mesothelin as an diagnostic tool in MPM [257], and further work is required to determine whether it can be used to increase the pre-test probability of an eventual malignant diagnosis, following a biopsy finding of NSP.[257]

Biopsy technique:

The options for obtaining a pleural biopsy in undiagnosed exudative pleural effusions include image guided pleural biopsies (ultrasound or CT-guided), and thoracoscopic pleural biopsies (MT or VATS).[224]

Image guided pleural biopsies

Image-guided pleural biopsies have a high sensitivity for the diagnosis of malignancy using both CT and ultrasound guidance.[258] A recent systematic review and meta-analysis including 30 studies showed pooled yield with both procedures of 84% for TUS and 93% for CT guided biopsy without meaningful differences in safety.[259] However, diagnostic yield with these techniques can depend on radiological features (eg. identifying pleural thickening) in contrast to direct visualisation of the parietal pleura through thoracoscopy.[260] The authors therefore, generally reserve image guided biopsies, for those patients in whom thoracoscopy is not possible.[224]

Rigid and semi-rigid thoracoscopic biopsies

Medical thoracoscopy (MT) allows direct visualization of the pleura and allows targeted biopsies, providing a specificity of close to 100% for malignancy, and sensitivity of between 85% and 94%.[224]

In 14 studies of 4189 patients with undiagnosed pleural effusion undergoing MT, 1665 received a histological diagnosis of NSP (40%, 95% CI 38%-41%). Of cases where outcomes were reported, 182/2249 cases of malignant pleural pathology were eventually established (8%, 95% CI 7-9%), mainly MPM.[225] Most false negative cases were attributed to sampling errors; multiple factors bear consideration with regards to biopsy technique and are covered below.

Number of biopsies

Whilst early studies on thoracoscopic technique recommended a greater number of biopsies (eg. 15-20), with advancements in procedural and pathological techniques this has reduced to just 5-10.[226, 237, 261]

Depth of biopsies

A crucial histological feature to make a diagnosis of MPM is to adipose tissue invasion. In the presence of thickened pleura or when difficult to obtain deeper biopsies, a "biopsy into biopsy" technique with repeated sampling at the same site has been proposed to achieve "full thickness" biopsies and reduce false negative sampling errors.[262]

Size of biopsy specimens and type of scope

MT can be performed using either rigid forcep (RFB) or semi-rigid (SRFB) thoracoscopes; this directly determines the size of biopsy specimens obtained .[263]

Table H (supplementary material) summarises studies comparing different thoracoscopic biopsy techniques.

Biopsy specimens were found to be larger in RFB vs SRFB techniques (24±12.9 versus 11.2±7.6 mm^2) [264] and in patients with extensive adhesions, superior diagnostic yields were attained from RFB compared to SRFB (97.8% vs 73.3, respectively).[265] Different strategies have been explored to overcome the limitations of small biopsies acquired with the semi-rigid thoracoscope, including the use of cryobiopsy (CB). A recent systematic

review and meta-analysis (22 studies, 1647 biopsies) demonstrated CB did not increase diagnostic yield over SRFB in semirigid thoracoscopy.[266, 267] The only intra-patient comparison of parietal pleural biopsies acquired using RFB, SRFB and CB during MT confirms superior yield of RFBs over CBs (difference: 12.7%). RFB specimens were larger than CB and SRFB, and deep biopsies containing fat were collected in 63% of RFBs vs 49.5% and 39.5% in CBs and SRFBs respectively.[268] There are no studies on the prevalence of NSP histology and eventual malignant diagnoses comparing these techniques.

Video-assisted thoracoscopic surgical biopsies (VATS)

No RCTs have compared MT and VATS, and only few retrospective studies have evaluated the diagnostic accuracy of both MT and VATS in excluding malignancy.

A retrospective study in 177 patients comparing MT (n=78) and VATS (n=99) showed similar diagnostic yield (93.6% and 96%, respectively). Whilst the incidence of NSP in MT was greater compared to VATS (43.8% vs 24.2%, respectively), this did not result in differences in rates of eventual malignant diagnosis during follow-up (12.5% MT vs 17.4% VATS).[269]

A more recent retrospective study evaluated the eventual malignancy rates in 295 patients initially diagnosed with NSP after MT (1.7%) or VATS (0.55%) and demonstrated good negative predictive values for both (0.982 and 0.994, respectively).[244]

In a further large VATS series (n=400), patients suspected to have MPM underwent biopsy, of whom 102 (25.5%) were deemed to have either NSP or atypical mesothelial proliferation (AMP). Over a median follow up of 5 months, a further 11 (10.7%) underwent repeat biopsy and were subsequently found to have malignancy, giving an overall sensitivity for VATS of 96%. Reasons for misdiagnosis included: lack of macroscopic pleural abnormalities, extensive adhesions and dense fibrosis making adequate tissue acquisition challenging.[251]

To summarise, pleural biopsies through MT or VATS appear to have similar incidence for NSP histology and a similar negative predictive value in excluding pleural malignancy. An NSP diagnosis made by MT does not therefore suggest the need to repeat the biopsy through VATS. The authors would usually consider a repeat biopsy after MT or VATS in patients found to have diffuse pleural thickening with no target area for biopsy, or dense adhesions impeding complete inspection (Figure 8), in the latter scenario the authors sometimes consider a more invasive technique (eg. thoracotomy) to allow complete inspection and biopsy.

Areas of future research	Question
Diagnosis	What is the role of ancillary pathology techniques in differentiating NSP from pre-invasive mesothelial lesions? How reliable is the thoracoscopist's impression when faced with a finding of NSP?
Prognostication	Can we establish a risk stratification model for patients following an NSP result that incorporates clinical data points, imaging, thoracoscopic and histological findings and makes use of relevant biomarkers?

What are the options for follow up in patients with an NSP diagnosis?

P - Patients with a histologically confirmed diagnosis of NSP
I - Follow up duration, PET-CT as part of interval imaging
C - Not required
O - Rates and timing of evolving malignancy

Summary

- *In the literature, when faced with a false negative NSP result, an eventual malignant diagnosis is established within a median period of 6 months but may take longer in MPM. It is the usual practice of the TF members, to follow-up patients for 1-year, which may be extended if there are risks factors for MPM.*

In total 105 studies were screened to identify 9 studies relevant to producing this section. These consisted of 9 retrospective observational studies (see supplementary material).

Follow up duration of patients with an NSP diagnosis, evidence in the literature.

Table I (in supplementary material) summarises studies of NSP with rates of eventual malignancy and follow-up durations.

In the majority of cases, malignancy was detected within 12 months of initial NSP biopsy.[231, 234, 235, 238–244] Janssen et al found eventual malignancy diagnosed following NSP after a mean follow-up of 4.4 months, though when studying MPM diagnoses specifically, the mean interval was 8.7 months, indicating longer latency.[234] Of note, the studies by DePew and Metintas found patients eventually diagnosed with malignancy reported persistent pleural pain.[236, 241] Reuter et al developed the concept of "number-needed-to-follow-up" (NNF) in NSP to diagnose a single case of malignancy, and found an NNF of 18 in year 1, increasing to 260 by year 3.[239]

The TF members usually follow-up patients for a period of 1 year in-order to pick up most eventual malignancies, although in the presence of red-flag symptoms (eg. chest pain) or risk factors for MPM, this might be further extended.

PET-CT scan as part of interval imaging

No studies have addressed the use of PET-CT scan in the follow-up of NSP.

Areas of future research	Question
Diagnosis	When faced with eventual malignant diagnosis, what time cut-off should be used to declare an NSP result as a false negative versus a de novo malignant process?
Follow up	Is PET-CT more sensitive at detection of evolution of malignant pleural disease following an NSP result during surveillance follow-up, compared to standard of care (eg. CT)? What is the role of thoracic US in NSP follow-up?

Conclusion

This statement has summarised the evidence base on the management of the most pressing causes of NMPEs. A cross-cutting theme across the statement was the need for a multidisciplinary approach. Several of the conditions outlined in the statement require input from single-organ specialty groups, but equally the benefit of a more generalist and holistic perspective cannot be overstated. In particular, the involvement of the palliative care team earlier into the pathway, when deemed appropriate would serve many of these patients well and provide them with the support needed in the face of a life limiting condition. NMPEs represent a significant burden of disease and as this statement has demonstrated, there remains a paucity of evidence to guide best practice. However, this should be viewed as an opportunity and the areas for future research highlighted in this statement represent a starting point to begin addressing these gaps in the evidence-base.

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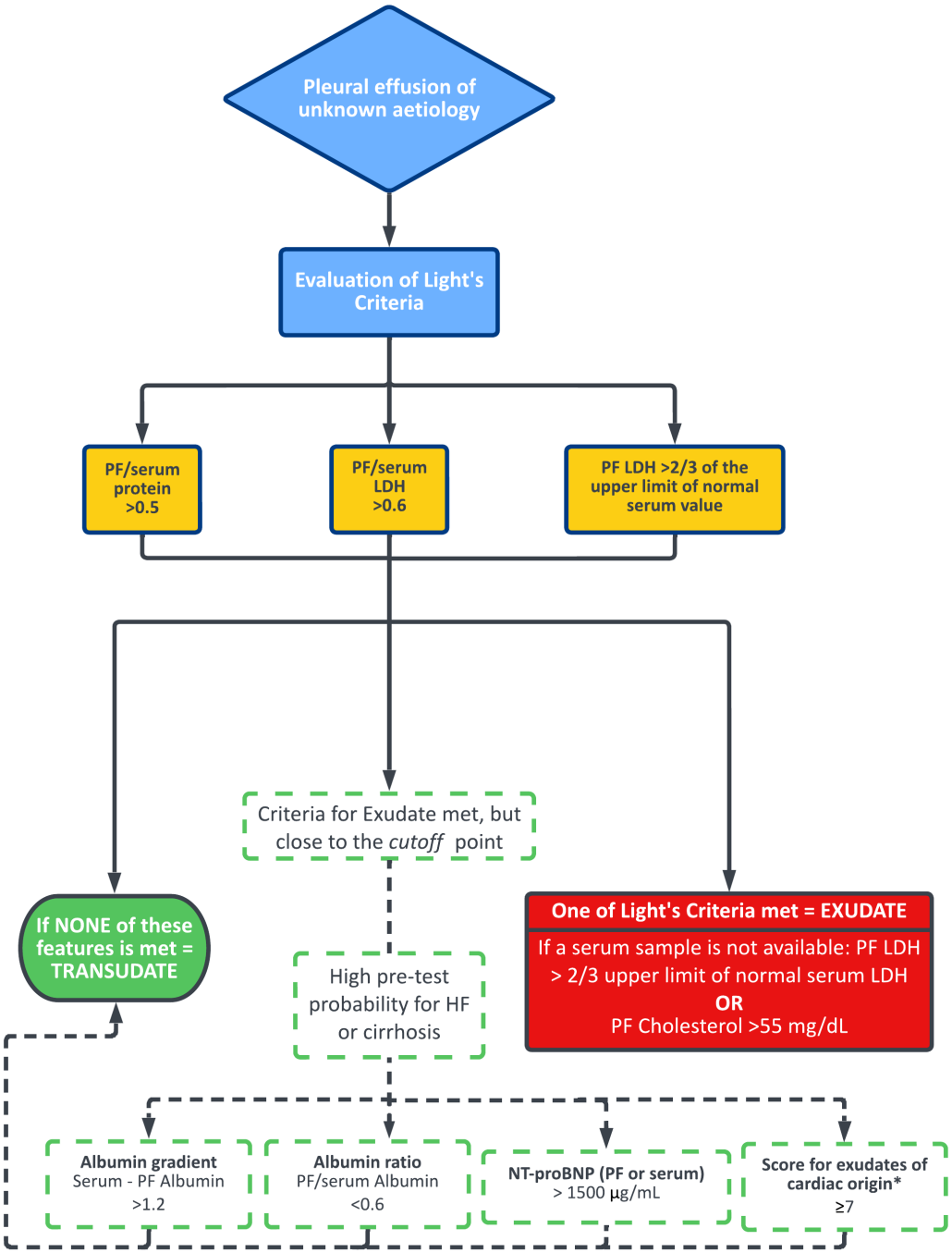
Figure 1
A visual depiction of the TF members practice for evaluating a pleural effusion of unknown aetiology

(This describes current practice of the TF members, and is not intended as a recommendation for clinical practice)



*From Porcel et al 2018

Figure 2
Imaging features seen in transudates and exudates (suggestive but NOT diagnostic)

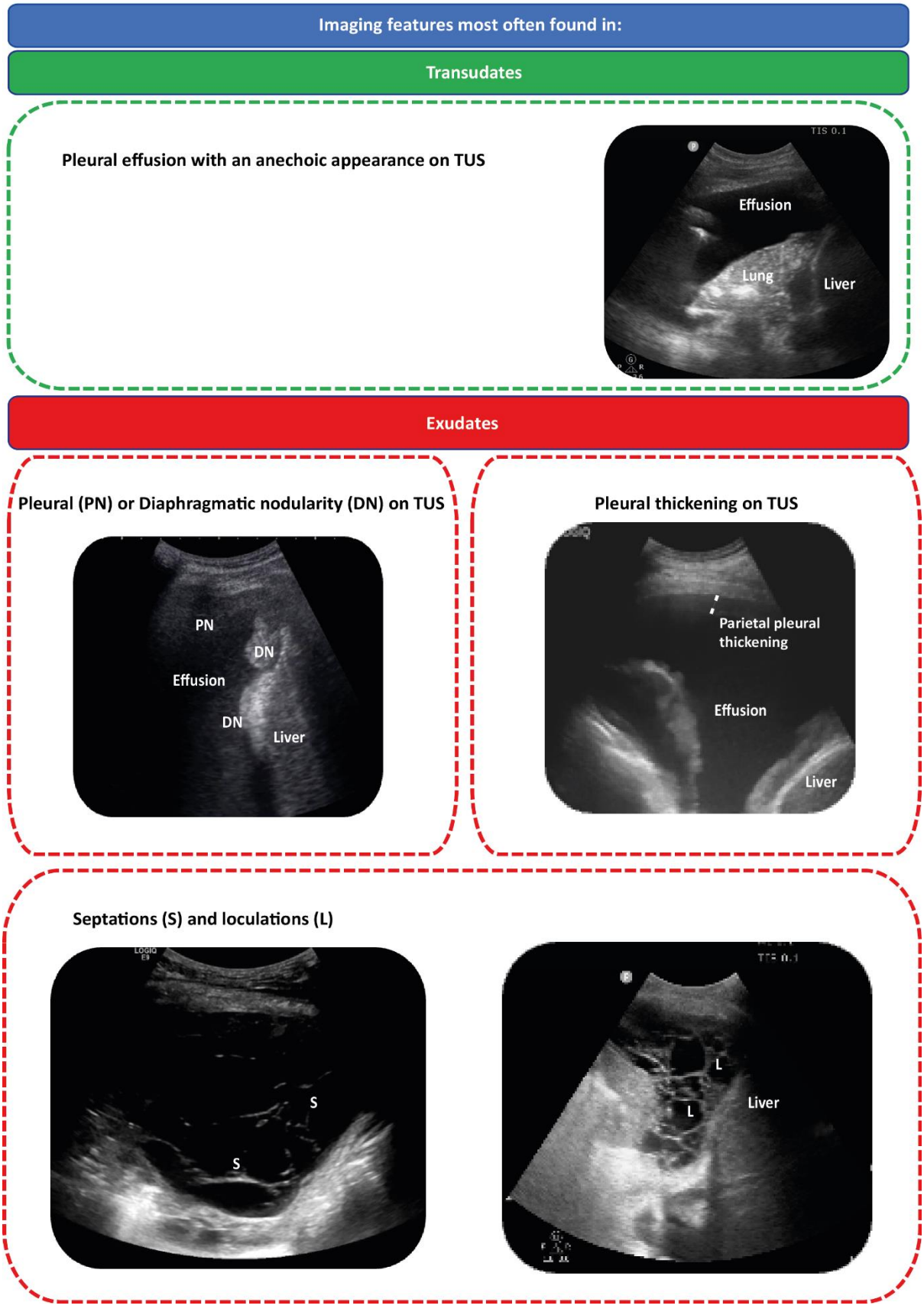
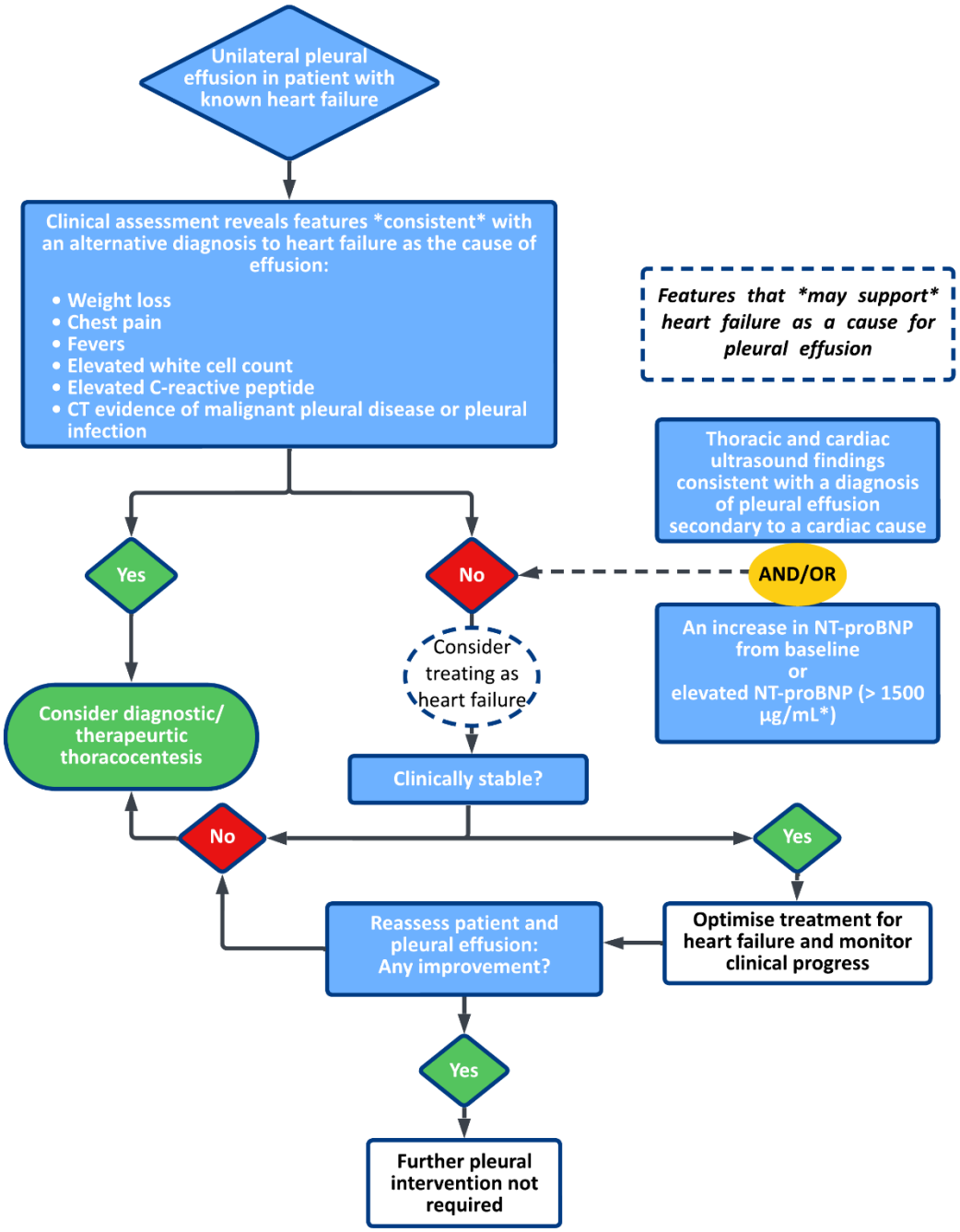


Figure 3
A visual depiction of the TF members practice when assessing a unilateral pleural effusion in a patient with know heart failure

(This describes current practice of the TF members, and is not intended as a recommendation for clinical practice)



*note the cut-off value of 1500 µg/mL was derived from observational studies differentiating heart failure as the cause of effusion compared to alternative diagnoses, rather than unilateral effusions presenting in patients with known heart failure

Figure 4
A visual depiction of the TF members practice in managing a refractory symptomatic Hepatic hydrothorax

(This describes current practice of the TF members, and is not intended as a recommendation for clinical practice)

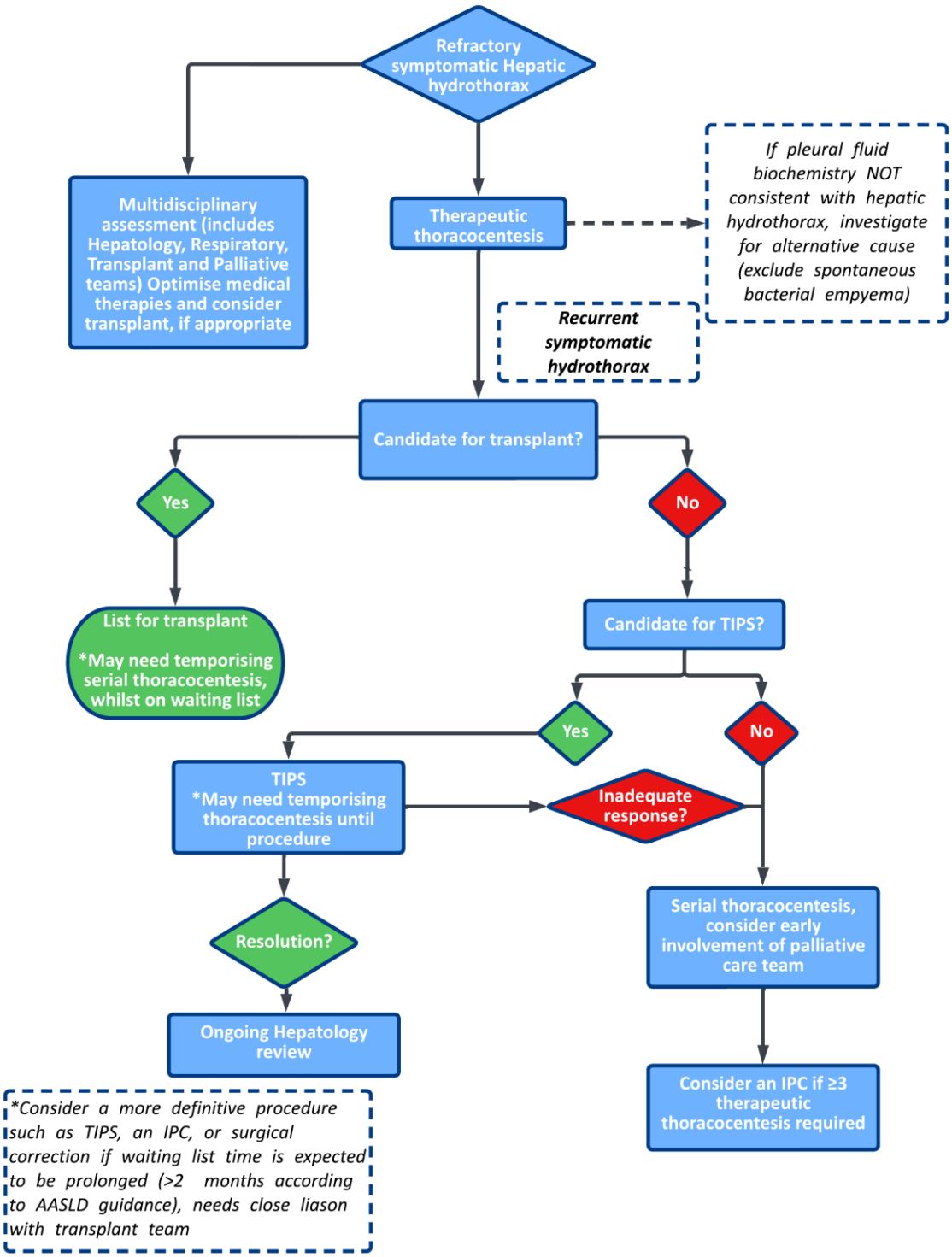
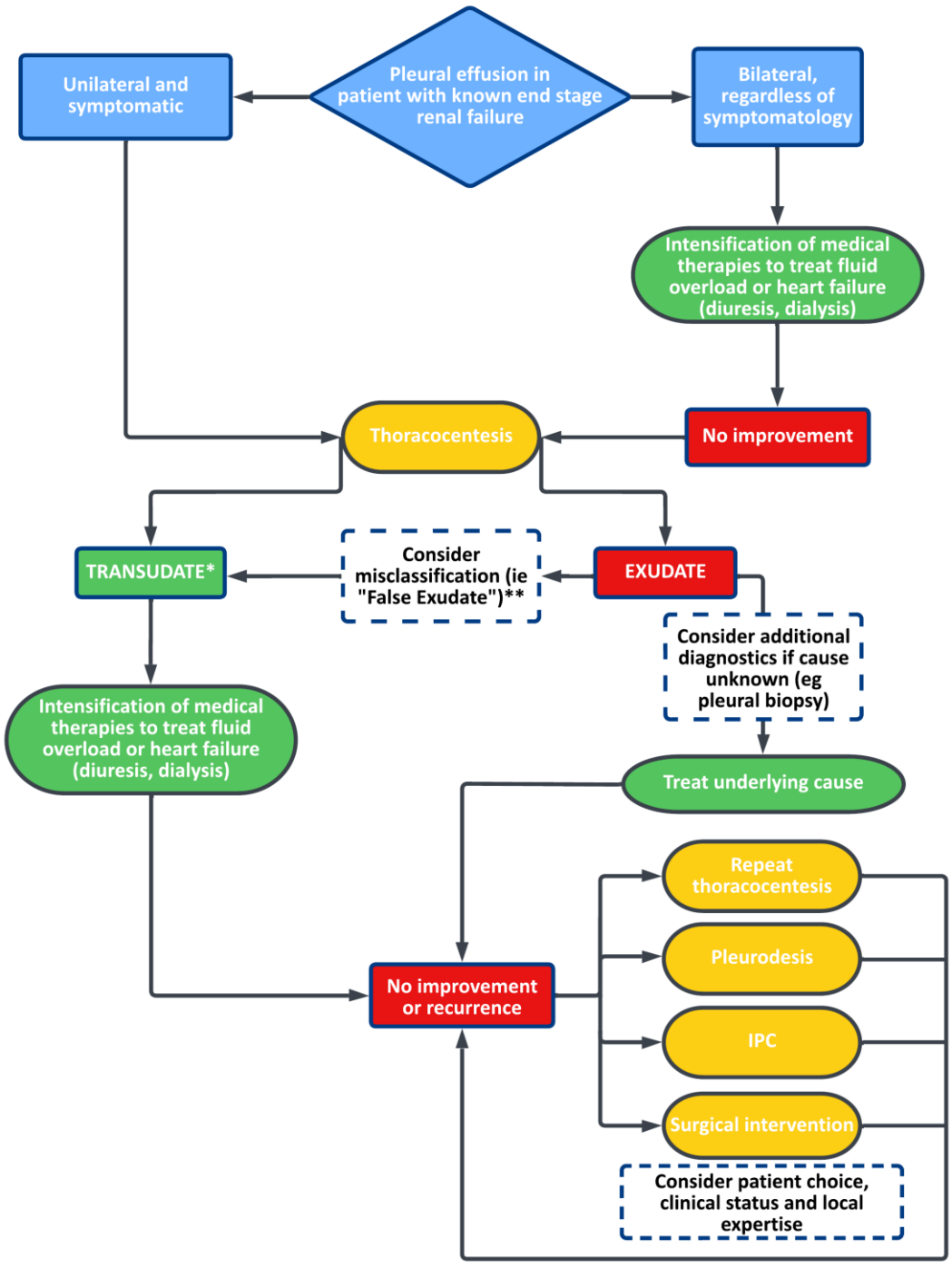


Figure 5
A visual depiction of the TF members practice in managing a patient with ESRF and pleural effusion

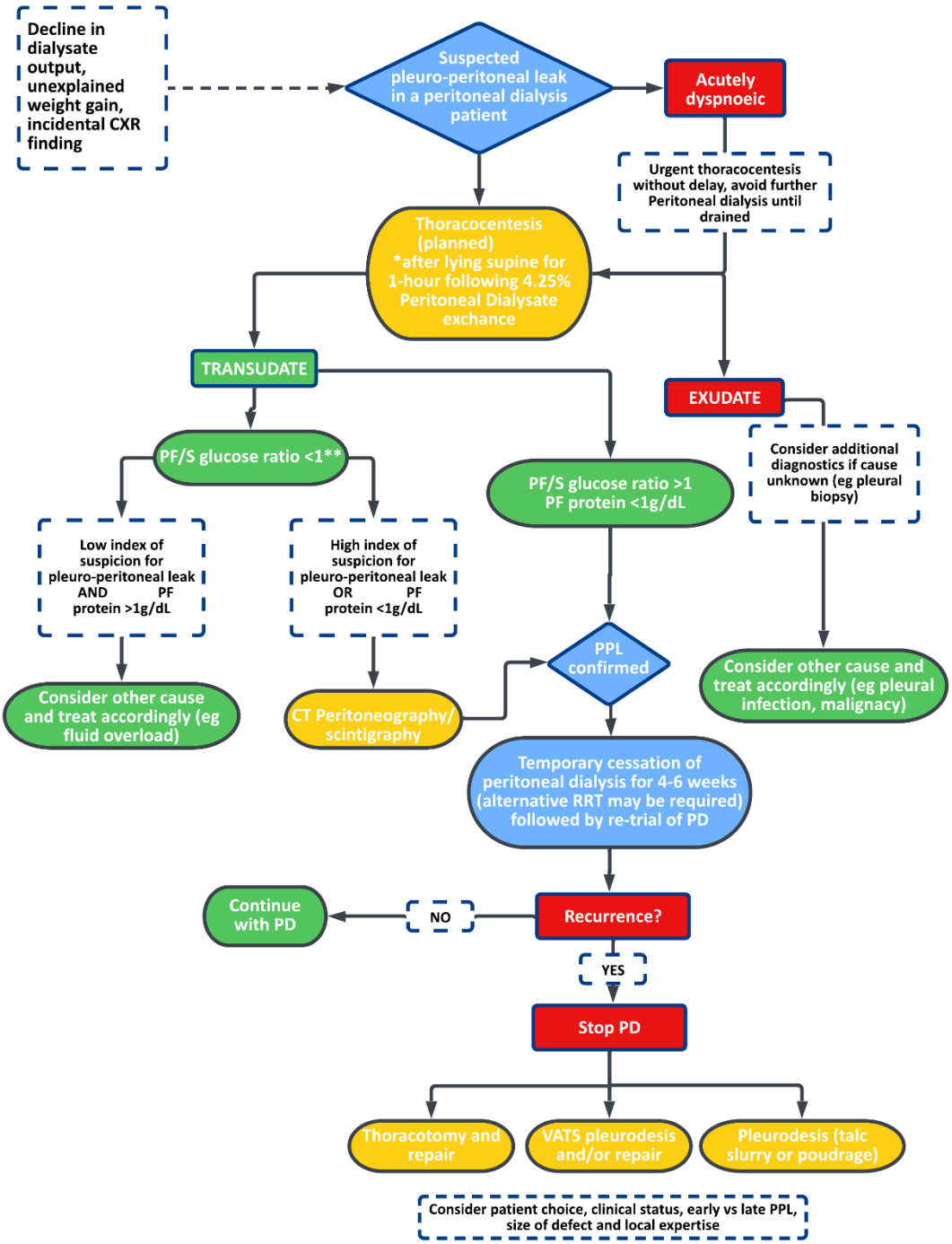
(This describes current practice of the TF members, and is not intended as a recommendation for clinical practice)



* Doelken et al demonstrated that PF protein content was greater in patients with pleural effusions secondary to ESRF compared to heart failure (23 grams/L vs 18 grams/L)
** Corbett et al demonstrated Light's criteria to be poorly specific (spec 44%) in the dialysis population,with a greater false positive rate (i.e. false exudate) then seen in an undifferentiated population

Figure 6
A visual depiction of the TF members practice in managing a suspected pleuro-peritoneal leak in a peritoneal dialysis patient

(This describes current practice of the TF members, and is not intended as a recommendation for clinical practice)



* In the study by Momenin et al, a standardised approach to performing thoracocentesis was proposed, in order to minimise confounders in the results observed in the PF/S glucose gradient (the size of the diaphragmatic defect and patient posture affecting rate of fluid movement into the pleural cavity, fluctuating blood sugar levels in patients with diabetes and reabsorption of glucose from the pleural cavity due to delays in obtaining the PF sample)
** In this same study across 48 patients with a PPL, 20% of patients had PF/S glucose gradients of < 50 mg/dL (2.8 mmol/L), 13% had values between 51–100 mg/dL (2.8-5.6 mmol/L) and 67% had values >100 mg/dL (5.6 mmol/L) whilst the PF/S glucose ratio was always >1

Figure 7
Axial CT scan showing typical features of diffuse pleural thickening (solid arrows) with associated folded lung (dashed arrows).

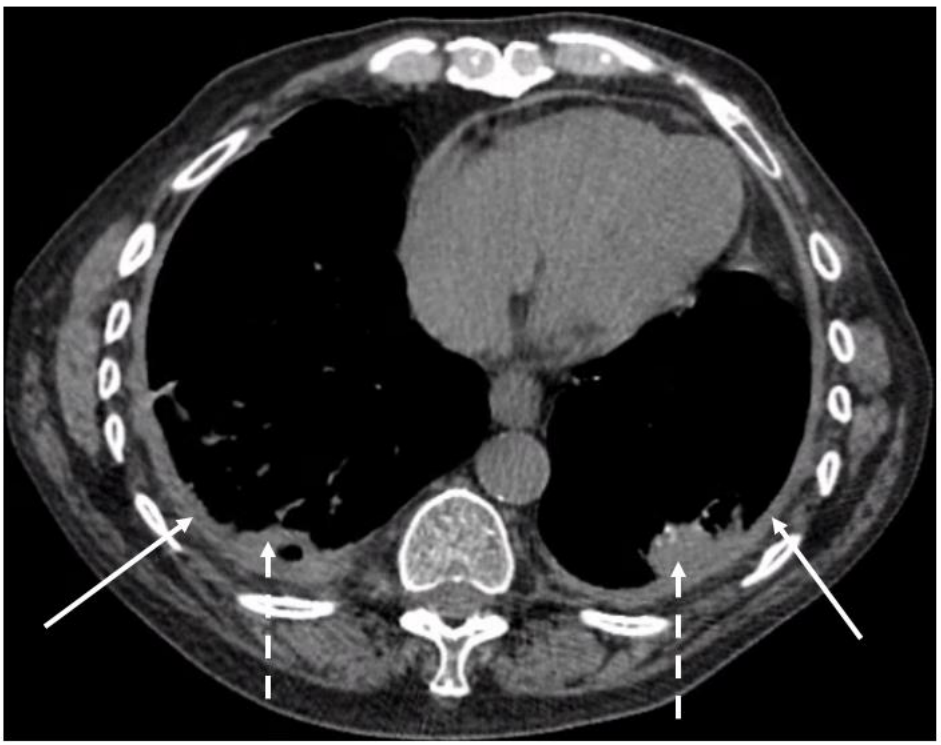


Figure 8

Endoscopic appearance of pleural cavity with adhesions (bold arrow) and fibrinous layer on the parietal pleura (thin arrows)

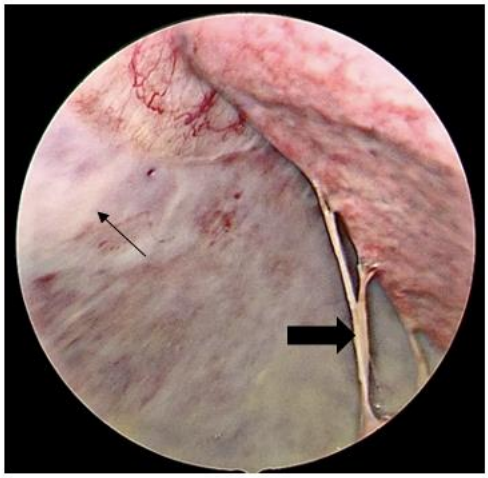
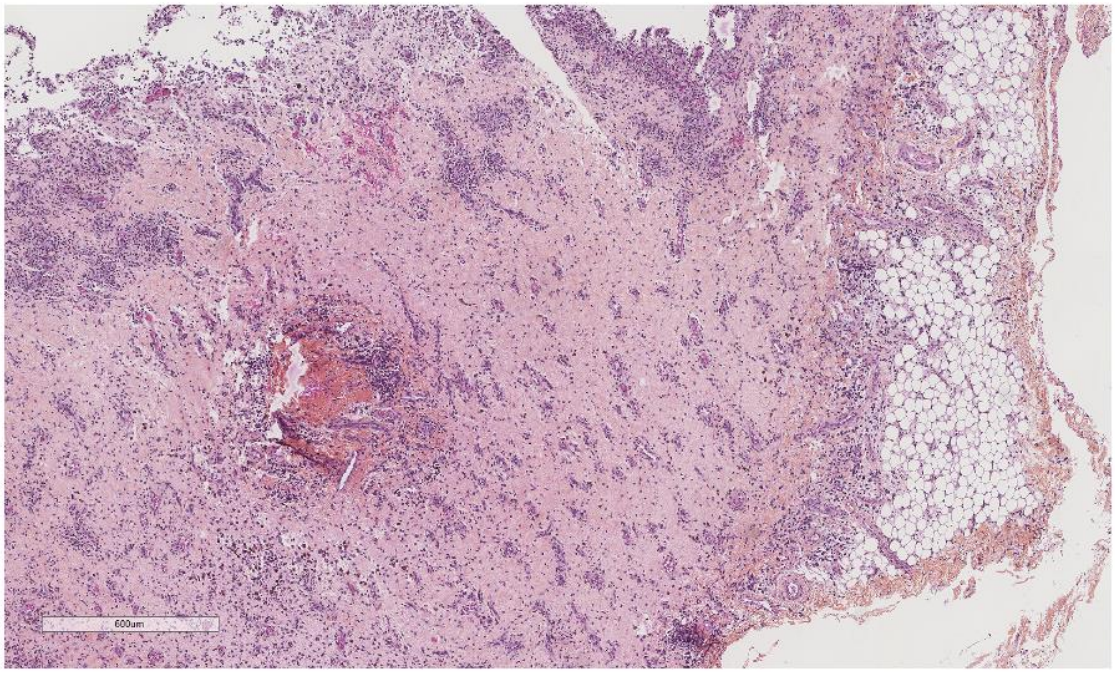


Figure 9

A severely thickened parietal pleura consisting of fibrosis, inflammatory elements, and numerous blood vessels without any granulomatous or malignant process (haematoxylin, eosin, safran coloration x 40).



Supplementary Material

First author, year	Study characteristics	Intervention	Sample size	Age, years	Gender	Rate of spontaneous pleurodesis	Rate of IPC[a]-related adverse events	Reported IPC-related adverse events
Walker, 2021 [1]	Multicenter randomised control trial	IPC versus TT[b]	68 patients with transudative pleural effusion 66% CHF[c] IPC: 33 65% CHF TT: 35 71% CHF	IPC: Mean=73.2 (SD 12) TT: Mean=73.6 (SD 12.1)	IPC: 82% men TT: 74% men	Not reported	IPC: 59% TT: 37%	- Fluid leakage 6% -Device malfunction 3% -Nondrainage 3% -Localised swelling (noninfected) 3% -Chest pain 12% -Pleural infection 3% -Localised peri-device cellulitis 3% -Chest infection 9% -Cellulitis (nonthoracic) 6% -Infection (other, nonrelated) 6% -Admission secondary to decompensation of underlying disease 27% -Acute kidney injury 6% -Other, nonrelated 30%
Frost, 2020 [2]	Retrospective study	IPC	54 patients with NMPE[d] 48% CHF	Median=68.5 (Range 32-95)	Overall 59% men	CHF: 24.1%	CHF: 17%	-Infections 7.4% -Local infection 1.9% -Empyema 5.6% -IPC malfunction 18.5% -IPC occlusion 3.7% -IPC dislodgement 9% -Leakage 5.6% -Bleeding 1.9%
Li , 2019 [3]	Retrospective study	IPC	252 patients with NMPE 32% CHF	Mean=70 (SD 14)	Overall 62% men	CHF: 65%	Overall 11%	-Loculations 4% -Dislodgement 2% -Pleural infection 2% -Leakage 1% -Symptomatic re-expansion pulmonary edema 1% -Pain requiring removal 0.3% -Mechanical failure 0.3%
Patil, 2017 [4]	Systematic review & Meta-analysis	IPC	325 patients with NMPE 50% CHF	Range 27-95	Overall 54% men	CHF: 42%	CHF: 16%	-Empyema 2.3% -Fluid loculation 2% -IPC dislodgement 1.3% -Pleural fluid leakage 1.3% -Pneumothorax 1.2% -Skin infection 2.7% -Blockage and drainage failure 1.1% -Subcutaneous emphysema 1.1% -Other 2.5%
Krishnan, 2015 [5]	Retrospective study	IPC	37 patients with NMPE, 67% CHF	Mean= 74 (SD 13.4)	54% men	Overall 84%	0	None

Majid, 2015 [6]	Retrospective study	IPC versus IPC+TP [e]	36 patients with CHF - IPC: 23 - IPC+TP: 13	Mean=82.5 (Range 61-97)	47% men	Overall 44% IPC: 25% IPC+TP: 80%	Overall 16% IPC: 13% IPC+TP: 23%	IPC: -Hypotension 4% -Empyema 4% -Parapneumonic effusion 1% IPC+TP: -Hypotension 8% -Cellulitis 15%
Bhatnagar, 2014 [7]	Retrospective study	IPC	57 patients with NMPE 16% CHF	Mean=67 (27-93)	Overall 65% men	44% for CHF	Overall 16%	Overall -Infection 7% -Fluid loculation 7% -Drain site leakage 2% -Pain 4% -Blockage 2% -Acute renal failure 4% -Mechanical failure of IPC 2%
Freeman, 2014 [8]	Retrospective study	IPC versus TP	80 patients with CHF IPC: 40 TP: 40	IPC: Mean=69 (SD 11) TP: Mean=66 (SD 13)	IPC: 43% men TP: 43% men	Not reported	IPC: 2.5% TP: 20%	Respiratory insufficiency 2.5%
Srour, 2013 [9]	Prospective study	IPC	38 patients with CHF	Mean=78.7	58% men	29%	34%	-Loculation 4.7% -Pneumothorax 11.6% -Subcutaneous emphysema 11.6% -Leak 2.3%
Chalhoub, 2011 [10]	Retrospective study	IPC	64 patients, 23 with NMPE, 13 with CHF	For CHF: Mean=77.8 (SD 10)	CHF: 62% men	Overall 87%	0	None
Herlihy, 2009 [11]	Case series	IPC	5 patients with CHF	Range 20-92	60% men	Not reported	60%	-Empyema 40% -Loculation 20%
Murthy, 2006 [12]	Retrospective study	IPC	58 patients, 17% with NMPE, 3 with CHF	Median=60.7	Overall 47% men	Not reported	Overall 7%	-Pneumothorax 1.8% -Seroma 1.8% -Empyema 1.8% -Catheter-related pain 1.8%

[a] Indwelling pleural catheters
[b] Repeated therapeutic thoracocentesis
[c] Refractory heart failure
[d] Non-malignant pleural effusion
[e] Thoracoscopic pleurodesis

Table A

A summary of studies on the use of indwelling pleural catheters in congestive cardiac failure patients

First author, year	Study type	Sample size	Intervention and indication	Complications (%)	Patient-centric outcomes	Clinical outcomes
Dhanasekaran, 2010	Single-center, Retrospective	73	TIPS	HE (15.1%) Infections (8.2%) Procedure-related bleeding (6.8%) Acute renal failure (2.7%, 2/73) Acute respiratory distress syndrome (2.7 %, 2/73)	Not reported	Clinical response at 1 month: complete response — 58.9% (43/73); partial response — 20.5% (15/73) and absent response — 20.5% (15/73) MELD score prior to TIPS and resolution of HH after TIPS were independent predictors of survival;
Badillo, 2013	Bicentric, retrospective,	77	Diuretics and TT alone (83%), TIPS (10%), liver transplant (5%)	Not reported	Not reported	Not reported
Jindal, 2018	Single-center, retrospective,	51	667 medical treatment; 122 thoracentesis, of whom 51 TIPS and 109 catheter (14/109 pleurodesis)	HE (15.1%) Liver failure (8%)	Not reported	50% patients had improvements in HH; complete resolution in 19.6% of patients No optimal PPG threshold for HH reduction.
Young, 2019	Single-center, retrospective,	33	TIPS	Not reported	Not reported	50% complete resolution of pleural fluid at 6 months, 14% partially resolved, no response in 36%
Adlakha, 2020	Single-center, retrospective	100	TIPS	Not reported	Not reported	Risk of readmission after TIPS was higher in patients > than 70 years old (34% vs. 12%)
Bisht, 2020	Single-center, retrospective	40	TIPS	Not reported	Not reported	Resolution of portal hypertension in 40% of the patients

Table B
Studies of Trans-jugular intrahepatic portosystemic shunt (TIPS) in hepatic hydrothorax

First author, year	Study type	Sample size	Intervention and indication	Complications (%)	Patient-centric outcomes	Pleurodesis (%) / time to pleurodesis (days)
Chalhoub, 2011	Single-center, retrospective	8	IPC, palliative	Exit site infection (12.5%)	3.8 + 0.4/ 4 procedure satisfaction score	-Not reported/ 73.6 ± 9 (mean, SD)
Bhatnagar, 2014	Multicenter, retrospective	19	IPC, palliative	Pleural infection (5.3%) Renal failure (5.3%) Loculation (5.3%) IPC dislodgement (5.3%)	Not reported	11% / median of 222
Chen, 2016	Single-center prospective	24	IPC, palliative (80%), bridge to transplant (20%)	Pleural infection (16.7%)	Not reported	33% / 131.8 (range 14–287)
Kniese, 2018	Single-center , retrospective	62	IPC, palliative (47%), bridge to transplant (53%)	Overall (35%) Empyema (16%) Death due to infection (5%) Cellulitis (2%) IPC dislodgement (10%)	Not reported	14.5% / 118 ±139.6(mean, SD)
Shojaee, 2018	Multicenter, retrospective	79	IPC, palliative (73%) bridge to transplant (27%)	Pleural infection (10%) Death due to infection (2.5%) Renal failure (2.5%) Pleural fluid leakage (5%) Seroma (6%)	Not reported	28% / median of 55 (range 10-370)
Li,2019	Single-center, retrospective	42	IPC, palliative	Pleural infection (7.1%)	Not reported	51% / median of 115 (IQR 57-191)
Frost, 2020	Single-center, retrospective	27	IPC, palliative	Cellulitis, IPC malfunction (37.3%)	No additional intervention needed in 93% of total population	21% / etiology-specific time not available No additional intervention needed in 93% of total population
Walker, 2022	RCT prospective	16 (therapeutic thoracentesis: 8, IPC: 8)	IPC, palliative	No complication reported	Mean daily breathlessness score over 12 weeks from randomization	Visual Analogue Scale (VAS) score was not significantly different between IPC vs therapeutic thoracentesis arm - Hospital length of stay, pleurodesis rate and EQ-5D index were not significantly different.

Alhabeeb, 2022	Single center, retrospective	40	IPC, palliative in all but 3 patients (bridge to transplant in 2, bridge to TIPS in 1)	Pleural infection (17.5%)	Baseline and transition dyspnoea index	Not reported – 48.8% of catheters were removed (149+/-50.2 days) but the proportion that were removed due to pleurodesis not reported
Romero, 2022	Multi-center, retrospective	84	Thoracocentesis in 62 (73.8%), 10 (12%) TIPS, 28 (33%) transplant	Pneumothorax in 17 (15%) of thoracocentesis	Not reported	Not reported
Han, 2022	Multi-center retrospective	164	Pigtail catheter 115, thoracocentesis 49	4 cases of bleeding and 1 empyema (3% overall)	Mortality, readmission rates	51.3% in pigtail group

Table C

Studies of indwelling pleural catheters (IPC) in hepatic hydrothorax

First author, year	Patients and study characteristics	Sample size	Prevalence of pleural effusion n/N (%)	Aetiology of pleural effusions n/N (%)	Age (mean + SD) years	Gender, ratio	Effusion laterality (%)	Effusion biochemical properties, n or %
Jarratt, 1995 [13]	HD patients Inpatient population Age >16 Dialysis duration > 3 months	311 admissions of 100 HD patients	64/311 (21%)	HF (46/100, 46%) Uraemic pleuritis (16/100, 16%) Parapneumonic effusion (15/100, 15%) Atelectasis (11/100, 11%) MPE (3/100, 3%) Unknown (2/100, 2%)	55 +/- 1.4[a]	M:F 3:2	57% Bilateral - 83% in cardiac failure - 50% in uraemic pleuritis	Transudative in HF (n = 7) Exudative in uraemic pleuritis (n = 8)
Coşkun, 1999 [14]	HD patients Symptomatic (cough, dyspnoea, fever, malaise, weight loss) Undergoing CT scans	117	60/117 (51%)	Not reported	Not reported	Not reported	63% Bilateral	Not reported
Bakirci, 2007 [15]	HD patients Inpatient population Age >16 Dialysis duration > 3 months	257	52/257 (20.2%)	Overhydration (32/52, 61.5%) HF (5/52, 9.6%) Parapneumonic effusion (5/52, 9.6%) Uraemic pleuritis (2/52, 3.8%) Atelectasis (1/52, 1.9%) TB (1/52, 1.9%) Unknown (6/52, 11.5%)	55 +/- 16.5[a]	Not reported	50% Bilateral - 68.8% of all fluid overload cases - 40% of all HF cases - 50% of all uraemic pleuritis cases 50% Unilateral - 31.2% of all fluid overload cases - 60% of all HF cases - 100% of all parapneumonic cases -50% of all uraemic pleuritis cases	64.3% Transudate 35.7% Exudate
Lakadamyali, 2008 [16]	HD patients Symptomatic (cough, dyspnoea, fever, malaise, weight loss)	64	29/64 (43.5%)	Not reported	Not reported	Not reported	- 59% Bilateral	Not reported

	Undergoing CT scans							
Ray, 2013 [17]	Patients with CKD 3-5 (RRT status not stated) or post-renal transplant	464 - 430 CKD patients - 34 post renal transplant patients	31/464 (6.7%) - 29/430 CKD (6.7%) - 2/34 (5.9%)	HF (13/31, 42%) TB (8/31, 26%) Uraemic (6/31, 19%) Empyema (2/31, 6.5%) Nephrotic syndrome (2/31, 6.5%)	37.2 +/- 1.8[a]	M:F 2:1	39% Bilateral	48% Transudate 52% Exudate
Rashid-Farokhi, 2013 [18]	HD patients Symptomatic (with respiratory complaints) Inpatient population	76	Not reported	Fluid overload (5/76, 6.6%) HF (15/76, 19.7%) Parapneumonic effusion (18/76, 23.7%) TB (5/76, 6.6%) Uraemic pleuritis (18/76, 23.7%) MPE (4/76, 5.3%) Pulmonary emboli (1/76, 1.3%) Atelectasis (1/76, 1.3%) Post cardiac bypass (1/76, 1.3%) Eosinophilic pneumonia (1/76, 1.3%) Iatrogenic haemothorax (1/76, 1.3%) Unknown (6/76, 7.9%)	53.48 +/- 13.08	M:F 2.2:1	32.3% Bilateral	25.8% Transudate 74.2% Exudate
Potechin, 2015 [19]	Patients with ESRF requiring IPC insertion for effusion control	8 : - 1 PD - 7 HD	Not reported	HF (3/8, 37.5%) Uraemic pleuritis (2/8, 25%) PD related pleuro-peritoneal leak (1/8, 12.5%) Unknown (2/8, 25%)	82.2 (72.1- 87.7)[b]	M:F 1.6:1	Not reported	50% Transudate 50% Exudate
Kumar, 2015 [b] [20]	Patients with CKD (stage 4-5) presenting with exudative effusions suspicious for pleural TB	107 : - 91 on HD - 3 on PD	Not reported	TB (6/107, 5.6%) Nonspecific pleuritis (20/107, 19.2%)	45.3 +/- 12.4	M:F 4.1:1	11.2% Bilateral 88.8% Unilateral - 62% right sided	42.1% Transudate 57.9% Exudate
Qureshi, 2016 [21]	Patients with ESRF Dialysis duration > 6 months	1250	250/1250 (20%)	Fluid overload (101/250, 40%) HF (32/250, 13%) TB (77/250, 31%) Parapneumonic (39/250, 15%) Uraemic pleuritis (1/250, 0.4%)	40.75 +/- 13	M:F 1.5:1	Not reported	53.2% Transudate 46.8% Exudate
Colella, 2017 [22]	Patients with CKD (RRT status not stated) undergoing medical thoracoscopy for unexplained pleural effusion	10	Not reported	Uraemic pleuritis (6/10, 60%) Hydrothorax (2/10, 20%) Chronic lymphocytic pleurisy (2/10, 20%)	72.4 +/- 6.5	M:F 9:1	Not reported	10% Transudate 90% Exudate
Hamada, 2018 [23]	HD patients Duration of dialysis >3 months	82	40/82 (49%)	Not reported	74.7 +/- 9.5	M:F 3:1	52.5% Bilateral	Not reported
Uzan, 2019 [24]	HD patients with persistent pleural effusions	43	Not reported	Infection (24/43, 56%): TB (20/43, 46%) Parapneumonic (3/43, 7%) Empyema (1/43, 2%) MPE (4/43, 9%) Lung cancer (3/43, 7%) Renal cancer (1/43, 2%) SLE (1/43, 2%) Liver abscess (1/43, 2%) Pulmonary embolism (2/43, 4%) Idiopathic (11/43, 25%)	48.16+/- 14.5	M:F 1.4:1	51% Bilateral 30% Right sided 18% Left sided	7% Transudate 93% Exudate
Pant, 2019 [25]	Patients with CKD 3-5 (RRT status not disclosed) Age > 16 Inpatient population	165	18/165 (10.8%)	Not reported	Not reported	Not reported	Not reported	Not reported
Jabbar, 2021 [26]	Patients with CKD (of all stages) Inpatient population	789 patients - 121 HD patients	280/789 (35%)	Fluid overload (148/280, 53%) HF (39/280, 14%) Nephrotic syndrome (25/280, 9%) TB (37/280, 13%) Uraemic pleuritis (21/280, 7.5%) Empyema (10/280, 3.5%)	55.5 +/- 14.8	M:F 1.3:1	83.6% Bilateral	75.7% Transudate 24.3% Exudate
Shaik, 2021 [27]	HD patients Duration of HD > 12 months Age > 18	250	23/250 (33.8%)	Not stated	Not reported	Not reported	Not reported	Not reported

Wu, 2022 [28]	HD patients Inpatient population Age > 18	1077	343/1077 (31.9%)	HF (267/343, 77.8%) Parapneumonic (38/343, 11%) Low Albumin (11/343, 3.2%) Uraemic pleuritis (9/343, 2.6%) Malignancy (6/343, 1.8%) TB (6/343, 1.8%) Hepatic hydrothorax (2/343, 0.6%) Unknown (4/343, 1.2%)	58.43 +/- 15.08	M:F 1.56:1	76.4% Bilateral 23.6% Unilateral	Not reported
Summary	NA	NA	1190/4826 (24.7%, 95% CI 23-26%) [13–17, 21, 23–28]	Fluid overload: 286/1692 (16.9%, 95% CI 15.1-18.8%) HF: 420/1692 (24.8%, 95% CI 22.8-27%) Nephrotic syndrome: 38/1692 (2.2%, 95% CI 1.6-3.1%) Uraemic pleuritis: 81/1692 (4.8%, 95% CI 3.8-5.9%) Parapneumonic effusion/ Empyema: 131/1692 (7.7%, 95% CI 6.5-9.1%) TB: 154/1692 (9.1%, 95% CI 7.8-10.6%) MPE: 17/1692 (1%, 95% CI 0.6-1.6%) [13, 15, 17–19, 21, 22, 24, 26, 28]	NA	M:F 1.7:1 (810:478)	Bilateral-713/1138 (62.7%, 95% CI 60-65.5%) Unilateral -425/1138 (37.3%, 95% CI 34.5-40.2%)	Transudate – 448/821 (54.6%, 95% CI 25.4-63.2%) Exudate 373/821 (45,4%, 95% CI 36.8-74.6%)

Abbreviations: HD -haemodialysis, CKD -chronic kidney disease, ESRF end stage renal failure, HF – heart failure, MPE – malignant pleural effusion, TB – tuberculous pleural effusion, M-male, F-female, PD = peritoneal dialysis, NA not applicable

[a] = standard error of mean

[b] = interquartile range

Table D

Pleural effusion prevalence, aetiology and clinical characteristics in end stage renal failure

First author, year	Study type	Indication	Intervention	Sample size, n	Outcome measured	Results in context of studied procedure
Only ESRF patients with PF						
Potechin, 2015 [19]	Retrospective Cohort study	Pleural effusion unresponsive to maximal medical therapy	IPC	8 patients -1 x PD -6 x HD	Dyspnea index Complications	Significant improve in dyspnoea index Limited number of complications Autopleurodesis in 3 patients

Colella, 2017 [22]	Retrospective	Unexplained pleural effusion in CKD	Medical thoracoscopy + pleurodesis in 4 pts	10 patients	Pleural effusion recurrence Complications	4 x successful pleurodesis 1 x autoplerodesis 1 x empyema
ESRF patients with PF as a small part of study population						
Patil, 2017 [29]	Systematic review and meta-analysis	Symptomatic benign pleural effusion	IPC	325 patients -13 patients with ESRF)	Autopleurodesis rates Complications	No ESRF specific patient outcomes
Walker, 2022 [30]	Multicentre RCT	Symptomatic benign pleural effusion	IPC vs repeated thoracocentesis	68 patients - 1. Liver failure (21 vs 25) - 2. HF (8 vs 8) - renal failure (4 vs 2)	Daily VAS dyspnoea scores over 12 weeks Hospitalisations QoL Autopleurodesis rate Treatment failure Serum albumin concentration	No significant difference between treatments in VAS More AE (59% vs 37%) in IPC group Lower albumin concentration in IPC group Fewer invasive additional procedures in IPC group but greater drainage volumes No ESRF specific patient outcomes

Abbreviations: CKD chronic kidney disease, IPC – indwelling pleura catheter, VAS visual analogue scale, ESFR end stage renal failure; AE adverse events, QoL -quality of life, HF - heart failure

Table E

Interventions in the management of pleural effusions in ESRF

First author, year	Sample size, n	Gender (M:F), age (years)	Onset time after PD	Laterality of PF %, n/N	Symptoms % (n/N)	Method of diagnosis performed
Benz, 1985 [30]	5	100% F, Mean 60	1.4-32 weeks (10d – 8 months)	Not reported	Not reported	Racemic lactate buffor for dialyses and assessment of isomers of lactate in PF
Nomoto, 1989 [31, 32]	50*	1.17, Mean 49	0.1-416 weeks (1d - 8 years 50% of pts in <30 days; 18% after 1 year)	96% Unilateral 48/50, -R-88%, 44/50 -L- 8%, 4/50	Dyspnoea – 74% (37/50) None – 26% (13/50)	-Glu_f/glu_s >2 -Injection of methylene blue, indigo carmine, -99mTc MAA
Ramon, 1998 [33]	4	1, Mean 53	5-20 weeks (mean 12 weeks)	100% Unilateral -R-100%	Dyspnoea and decrease in dialysate volume-100% (4/4)	-Elevated glucose -99mTc MAA
Chow, 2002 [34]	9	0.12, Mean 46	Not reported	100% Unilateral R-100%	100% (9/9)	-99mTc MAA

Mak, 2002 [35]	8	1, Mean 46	4-312 weeks (1 moth-6 years)	100% Unilateral -R-100%	Not reported	-Pleural fluid exam
Tang, 2003 [36]	9	0.5, Mean 53	0.3-46.4 weeks (2 days- 11.6 months)	100% Unilateral -R- 89%,8/9	Drastic reduction in ultrafiltration volume 100% - shortness of breath -44.4% (4/9)	-Fluid biochemistry, (Protein content <4g/l; pleural fluid-to-serum glucose concentration difference of>50 mg/dl – 9/9, -radionuclide scan (Tc99m tin-colloid) -6/9 -contrast CT peritoneography 3/9; -direct visualization by methylene blue injection -4/9
Momenin, 2012 [37]	47 (based on review of case reports-includes 9 pts from Tang paper), data here presented for 38	0.65, Mean 52.4	0.4-432 weeks (0.1-108 months <3 months – 50% 3-6 months - 27%, > 6 months – 23%	95% Unilateral 36/38 -R- 87%, 33/38	Dyspnoea -96% (36/38) Chest pain 80%	-scintigraphy in 18/38, 47% (99mTc MAA -8, Tc-99m sulfur colloid–5, Tc-99m – 3, Tc-99m DTPA – 1, Tc-99m Sn, niobium-tin - 1), -VATS+thoracoscopy – 7, 18%, - high PF-S glucose gradients – 4, 10.5% (PF-S glucose gradient <50 mg/dL in 20%; 51–100 mg/dL- 13%, >100 mg/dL- 67%); -Glu$_{f}$/glu$_{S}$ ratio>1 - 100% -Resolution of PF 6, 16% -Contrast -3, 8%
Matsuoka, 2020 [38]	25	2.1, Mean 59	Not reported	At least 96%Unilateral -R- 96%, 24/25 Other data not reported	Dyspnoea -72% (18/25) Inadequate ultrafiltration 16% Asymptomatic – 12%	-Glucose concentration -CT peritoneography
Prasad, 2021 [39]	12	3, Mean 53.3	7-50 weeks	92% Unilateral 11/12 -R 83.3%,	Dyspnoea 83.3% (10/12) Chest pain/discomfort 66.6% inadequate ultrafiltration 33.3% Asymptomatic 16.6%.	-peritoneal scintigraphy 10/12 -CT peritoneography 5/12 -Both exams in 2 cases
Chen, 2021 [40]	35	1.2, Mean 60.8	3-81 weeks (21–570 days)	100% Unilateral 35/35 -R-94.3%	Not reported	-peritoneal fistulogram 14/35 , -corroborating clinical findings 11/35 -CT peritoneogram 10/35
Summary	195	0.99 97M:98F	0.1-432 weeks	Unilateral PF 96.8%, 184/190 (95%, CI 95.4-99.97%) R-.91%; 173/190 (95% CI 88.1-99.9%)	Dyspnoea 80.3% (118/147) (95% CI 62.8-99.9%)	

*Pts with other causes of PE were excluded, 99mTc MAA- technetium -99-labeled macroaggregated albumins; Tc-99m DTPA -, diethylene triamine pentaacetic acid

Table F

Characteristics of pleural effusions in pleuro-peritoneal leak in patients receiving peritoneal dialysis

First author, year	Study period/ Country	Prevalence of PF due to PPL n/N, (%)	Resolution n/N, (%)	Success rate of various treatment methods				
				Brief interruption of PD, n/N, (%)	Change in PD regimen n/N, (%)	Pleurodesis via drain n/N, (%)	Thoracoscopy n/N, (%)	Surgical approach n/N, (%)
Benz, 1985 [32]	5 years USA	5/99, (5%)	1/5 (20%)	NA	NA	1/2 (50%) -tetracycline	NA	NA
Nomoto, 1989 [31]	1980-1988 Japan (161 centres)	50/3195 children 1/111, (1.6%*)	27/50 (54%)	19/50 (38%)	8/15 (53%) small exchange volume in semi sitting position + **pleurodesis (via drain)**	**+ change in PD regiment** in 8/15 (53%) -Tetracycline 3/6 -Autoblood- 3/5 -N-CWS 1/2, -OK-432-1/2	NA	NA
Shemin, 1989 [41]	1987 USA	86/3000, (About 2.9%#)	49/86 (57%)	Not reported	Not reported	Not reported	Not reported	Not reported
Ramon, 1998 [33]	1986 -1997S, Spain	4/128, (3%)	0/2 (2 pts were directed straight for HD)	NA	NA	0/2 (blood via drain), procedure was repeated, in 1 patient results unknown, due to other complications HD was ordered	NA	NA
Chow, 2002 [34]	1986- 2001 China	9/874, (1%)	6/9 (67%)	1/1	NA	4/5 (80%) Talc	1/2 (50%)	NA
Mak, 2002 [35]	1994 – 1998 Hong Kong, China	8/397, (2%)	6/8 (75%)	NA	1/4 (25%) Intermittent peritoneal dialysis using 1-L exchange cycles.	0/2 pleurodesis (talc, tetracycline)	5/6 (83.3%) thoracoscopic pleurodesis (2/2– talc, 3/4 – mechanical rub)	NA
Tang, 2003 [36]	1998 -2002 (2 hospitals) Hong Kong, China	9/475, (1.9%)	8/9 (89%)	NA	NA	NA	8/9 (88.9%) -talc pleurodesis (in one case the procedure has to be repeated after 7.5 months – finally 9/9)	NA
Matsuoka, 2020 [38]	2007-2019 Japan (6 centres)	27/982, (2 pts excluded from analyses) (2.7%)	17/25& (68%)	NA	6/14 (43%) Stopping overnight PD	NA	NA	11/11 (100%) VATS with suture of diaphragmatic lesions or stapler (In no case PD withdrawal due to PF, other causes)
Prasad, 2021 [39]	1998 – 2018 India	12/1876, (0.64%)	8/12 (66.6%)	0/3	NA	4/5 (80%) (tetracycline 3/4; betadine 1/1)	NA	4/4 (100%) VATS suture+talc pleurodesis in 1 case
Chen, 2021 [40]	2009 to January 2019 Hong Kong China	Not reported	23/31 (74%) (excluded 4 pts directed for HD after surgery without a try of PD) Recurrence of PE (in 0–181 days)	NA	NA	NA	Notreported	Data for 31 pts: Mechanical+ talc pleurodesis 9/10 (10 mechanical pleurodesis+ talc,); Other than concomitant mechanical and talc 14/21 (15 mechanical pleurodesis, 3 repair + mechanical+ talc pleurodesis, 2 repair + talc, 1 talc, 1 mechanical pleurodesis + tetracycline, 1 decortication)

Nemeth, 2022 [42]	2011-2020 Germany	Not reported	12/12 (100%)	NA	NA	NA	NA	12/12 (100%) VATS + polypropylene mesh insertion
Summary		210/11 026, 1.9% (95% CI 1.3-3.3%)	157/249 63% (95% CI 56.7-69.1%)	20/54 37% (95% CI -79,4 -171,4	7/18 39% (95% CI 17-64%)	17/31 54.8% (95% CI 5.2 - 88%)	14/17 82.3% (95%CI 21.8 – 126.3)	50/58 86% nonhomogeneous group, various technics used

Pts with other causes of PE were excluded, # survey study, &efficacy assessed as PD withdrawal was 56% (14/25 pts), in table presented as number of pts without PF recurrence; N-CWS-*Norcardia rubra* cell wall skeleton, PD – peritoneal dialyses, PF- pleural fluid, PPL – pleuro-peritoneal leak, NA- non applicable

Table G

Interventions in the management pleuro-peritoneal leak in patients receiving peritoneal dialysis

First author, year	Subjects, *n*	Study design	Study groups	Biopsy size	Diagnostic yield n/N (%)
Rozman, 2013 **[43]**	79	Prospective	RFB (n= 38) and FFB (n= 41) in different subjects	Mean area RFB: 24.7 mm^2, FFB: 11.7 mm^2	RFB: 38/38 (100%) FFB: 40/41 (97.8%)
Dhooria, 2014 **[44]**	90	Prospective randomized	RFB and FFB in the same subjects	Median size RFB: 13.9 mm, FFB: 4.4 mm	RFB: 44/45 (97.8%) FFB: 33/45 (73.3%)
Wurps, 2016 **[45]**	80	Prospective	RFB, FFB and CB in the same subject	Mean area RFB: 22.6 mm^2, CB: 14.4 mm^2, FFB: 7.1 mm^2	RFB: 79/80 (98.7%) CB: 73/80 (91.3%) FFB: 74/80 (92.5%)
Dhooria, 2019 **[46]**	50	Randomized controlled	CB and FFB in the same subject	Median size CB: 7.0 mm, FFB: 4.0 mm	CB: 39/50 (78%), FFB: 38/50 (76%)

RFB- rigid forceps biopsy; FFB- flexible forceps biopsy; CB - cryobiopsy

Table H

Studies evaluating the diagnostic yield of rigid forceps biopsy, flexible forceps biopsy, and cryobiopsy

First author, year	Procedure	Sample size (all biopsies)	Total number of NSP diagnoses (% of all biopsies)	Total number of eventual malignancies (% of NSPs)	Type of malignancies	Time to eventual malignant diagnosis	Duration of follow-up	Mode of diagnosis	Other aetiologies
Boutin, 1981 [47]	LAT	215	65 (20%)	0 (not reported)	N/A	N/A	12 months	N/A	CCF (9, 14%) BAPE (8, 12%) Parapneumonic (3, 5%) Hepatic Hydrothorax (2, 3%) Haemothorax (1, 2%) Traumatic (1, 2%) PE (1, 2%) Idiopathic (40, 62%)
Page, 1989 [48]	VATS	121	31 (26%)	1 (3%)	MPM	Not reported	Not reported	Not reported	Idiopathic (15, 48%) Parapneumonic (6, 19%) Rheumatoid (2, 6%) Pleural fibroma (2, 6%) Haemothorax (1, 3%) Meig's syndrome (1, 3%) CCF (1, 3%) TB (1, 3%) Aneurysm (1, 3%)
Hucker, 1991 [49]	VATS	102	41 (40%) (reported as 21x Inflammatory 20 x Non-diagnostic	15 (37%)	7 x Squamous cell carcinoma 4 x Adenocarcinoma 1 x CLL 1 x Lymphoma 2 x MPM	Not reported	Not reported	7 x Thoracotomy 1 x Bronchoscopy 1 x Laparotomy 1 x Skin nodule biopsy	PE (1, 2%) CCF (1, 2%) Meig's syndrome (1, 2%) Ankylosing Spondylitis (1, 2%) Alport's (1, 2%) Idiopathic (21, 52%)
Menzies, 1991 [50]	LAT	102	57 (56%)	4 (7%)	MPM	Not reported	24 months	Thoracotomy	Idiopathic (22, 39%) BAPE (8, 14%) Chylothorax (3, 5%) Dressler (3, 5%) Rheumatoid/SLE (3, 5%) PE (3, 5%) Trauma or Haemothorax (3, 5%) TB (3, 5%) CCF (2, 4%) Post-obstructive pneumonia (2, 4%) Rounded atelectasis (1, 2%)
Ohri, 1992 [51]	VATS	56	18 (32%)	Not reported	N/A	N/A	Not reported (for NSP group)	N/A	TB (2, 11%) Parapneumonic (2. 11%) Eosinophilic pleuritis (3, 17%) CCF (1, 6%) Hepatic hydrothorax (1, 6%) PBC (1, 6%) Pulmonary Fibrosis (1, 6%) Idiopathic (7, 39%)
Kendall, 1992 [52]	VATS	48	16 (33%)	6 (38%)	3 x MPM 2 x Lung adenocarcinoma 1 x Renal metastases	MPM at 2, 7, 9 months Lung adenocarcinoma at 1, 2 months Renal metastases at 3 months	Not reported	2 x Blind pleural biopsy 2 x Thoracotomy 2 x Thoracocentesis	Parapneumonic (7, 44%) Rheumatoid (4, 25%) CCF (3, 19%) Pulmonary fibrosis (2, 13%) Idiopathic (2, 13%)
Ferrer, 1996 [53]	Various	Not reported	40	2 (5%)	1 x MPM	6 months 24 months	Median 60 months (range 36-108 months)	Cutting needle pleural biopsy	BAPE (3, 8%) Hepatic hydrothorax (1, 3%)

					1 x Lung adenocarcinoma			Lung nodule biopsy	CCF (1, 3%) Rheumatoid (1, 3%)
Hansen, 1998 [54]	LAT	147	53 (36%)	12 (23%)	Not reported	Not reported	Not reported	Not reported	Idiopathic (45, 85%) SLE (2, 4%) IPF (2, 4%) Rheumatoid (1, 2%) Sarcoidosis (1, 2%) EGPA (2, 4%)
Blanc, 2002 [55]	LAT	149	57 (38%)	Not reported	N/A	N/A	Range 12 - 70 months	N/A	SLE (1, 2%) Radiotherapy induced (1, 2%) PE (1, 2%)
Janssen, 2004 [56]	LAT	709	391 (55%)	31 (8%)	10 x MPM 21 x Metastases	MPM (mean 8.3 months)	24 months	2 x Diagnostic errors in initial biopsy 1 x Tru-cut biopsy 1 x Pericardial aspiration 2 x Laparoscopy 4 x Thoracoscopy 6 x Thoracocentesis 12 x Thoracotomy 2 x Autopsy	Parapneumonic (59, 15%) Reactive secondary to abdominal/ thoracic inflammation (38, 10%) CCF/ CABG (36, 9.2%) TB (17, 4%) Post-radiation (10, 3%) Rheumatoid (5, 1%) BAPE (5, 1%) PE (4, 1%) Hepatic hydrothorax (3, 1%) Trauma (2, 1%) Amyloidosis (2, 1%) Chylothorax (1, 0.3%) Schwannoma (1, 0.3%) Idiopathic (177, 45%)
Venekamp, 2005 [57]	LAT VATS	Not reported	75	11 (15%) - 5 counted as False Negative Bx due to immediate Dx of Ca from another site	3 x MPM, 3 x Lung 5 x Not reported in the study.	10 days 14 days for 2 x MPM	36 months	Thoracotomy, LAT	BAPE (9, 12%) Parapneumonic (9, 12%) Post CABG (6, 8%) Radiotherapy (3, 4%) Empyema (4, 5%) TB (0) Trauma (2, 3%) SLE/MCTD (2, 3%) CCF (1, 1%) PE (1, 1%) Amyloidosis (1, 1%) Drugs (1, 1%) Whipples (1, 1%) Idiopathic (15, 20%)
Davies, 2010 [58]	LAT	142	44 (31%)	5 (11%)	MPM	3, 5, 7, 13, 39 months	21 months	1 x LAT 1 x Umbilical biopsy 3 x Autopsy	Idiopathic (26, 59%) BAPE (4, 9%) Drug related (2, 5%) Systemic Amyloidosis (1, 2%) Rheumatoid (1, 2%) Post CABG (1, 2%) Pre-operative screening (2, 5%)
Metintas, 2011 [59]	LAT	287	101 (35%)	18 (18%)	16 MPMs, 2 Metastases	Not reported	24 months	Not reported	Not reported
De Pew, 2014 [60]	VATS Thoracotomy Sternotomy	Not reported	86	3 (4%)	MPM	2, 8, 10 months	60 months	1 x Transthoracic needle aspiration, 1 x Thoracotomy, 1 x Pneumonectomy	Idiopathic (64, 71%) Prev thoracic surgery (11, 13%) Autoimmune disease (6, 7%) Parapneumonic (5, 6%)
Gunluoglu, 2015 [61]	VATS	Not reported	53	2 (3.7%)	MPM	11 and 24 months	Median 24 months (range 6-60 months)	Thoracocentesis VATS	Parapneumonic (12, 23%) CCF (8, 15%) TB (1, 2%)

									PE (1, 2%) EGPA (1, 2%) Drug induced (1, 2%) Idiopathic (27, 51%)
Vakil*, 2017 [62]	MT	199 - Patients were largely selected if they had active malignancy (172/199)	90 (45%)	3 (3%)	Not reported	Not reported	23 months	Not reported	Chemotherapy related (18, 20%) Radiation induced (27, 30%) Paramalignant (11, 12%) Idiopathic (31, 34%)
Reuter, 2018 [63]	VATS	658	547 (83%)	29 (5%)	13 x MPM 5 x Lung 3 x Haematological 5 x Urogynaecological 1 x Gastrointestinal 2 x Other	< 2 months x 15 2-6 months x 9 6-12 months x 3 16 months x 1 (MPM) 34 months x 1 (Diffuse large B-cell lymphoma)	36 months	Not reported	Not reported
Karpathiou, 2020 [64]	VATS LAT	Not reported	295	10 (3%)	3 x MPM 5 x Lung 1 x Lymphoma 1 x Bowel	60, 62, 64 months for MPM 1 month x 4 and 60 months for Lung 18 months for lymphoma 36 months for Bowel	Mean 47.3 months (range 12-144 months)	Bronchoscopy LN biopsy	Not reported
Yu, 2021 [65]	LAT	1254	154 (12%)	19 (12%)	7 x Lung cancer 6 x MPM 2 x Urogynaecological 1 x Breast 1 x Prostate 1 x Plasmacytoma 1 x Thymoma	9 x 1 month 2 x 2 months 1 x 3 months 1 x 4 months 3 x 5 months 1 x 4 months 3 x 5 months 1 x 8 months 1 x 9 months 1 x 10 months	61 months	2 x LAT 6 x Image guided pleural biopsy 1 x Open lung biopsy 2 x Thoracocentesis 1 x Liver biopsy 1 x Prostate biopsy 1 x Ovarian biopsy 1 x Bronchoscopy 1 x Bone marrow aspirate	Idiopathic (67, 44%) TB (24, 16%) CCF (16, 10%) Parapneumonic (13, 8%) CTD (5, 3%) PE (4, 3%) Pneumosilicosis (4, 3%) Post splenic embolization (1, 1%) Post CABG (1, 1%)
Sundaralingam, 2023 [66]	VATS LAT	Not reported	175	11 (6%)	4 x Lung cancer 6 x MPM 1 x unknown	Mean 13.9 months (maximum 32 months)	Not reported	Not reported	Idiopathic (80, 44%) Pleural infection (27, 15%) BAPE (22, 12%) CCF (11, 6%) Malignancy (11, 6%) Autoimmune (7, 4%) Other (5, 3%) Rheumatoid arthritis (4, 2%) Drug related (4, 2%) Post traumatic (3, 2%) Renal failure (2, 1%) Occupational exposure (non-asbestos) (2, 1%) Haemothorax (2, 1%) Post-operative (1, 0.6%)
Summary			Incidence of NSP following Pleural Bx: 1665/4189	Rate of evolution/ False Negative Bx:		Time to evolution: Median: 6 months (IQR 2-8)			

			(0.40, 95% CI 0.38-0.41)	182/2249 (0.08, 95% CI 0.07 - 0.09)					

(* selective group of patients, with known active malignancy)

Table I

Studies of non-specific pleuritis diagnoses following thoracoscopy and associated outcomes

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ERS Benign Pleural Effusions Taskforce - An approach to transudative effusions:

PICO Questions

What are the tests for categorizing a pleural effusion as a transudate?

P: - Patients with pleural effusions of any cause
I: - Pleural fluid tests and imaging features
C: - NOT required for literature search (but can use the *Actual Final Diagnosis* as the benchmark against which the investigations are compared against)
O: - Diagnostic accuracy, Sensitivity/ Specificity, False Negative

What are the scoring systems for categorizing a pleural effusion as a transudate?

P:- Patients with pleural effusions of any cause
I:- Composite scoring systems/ Risk prediction tools
C:- NOT required for literature search (but can use the *Actual Final Diagnosis* as the benchmark against which the investigations are compared against)
O:- Diagnostic accuracy, Sensitivity/ Specificity, False Negative

Literature search methodology

Search strategies run on 05/08/2022 by Eli Harriss, a librarian at the Bodleian Health Care Libraries, University of Oxford, and updated on 06/06/2023.

Methodology

> Medline, Ovid Embase, and the Cochrane Central Register of Controlled Trials were searched by an information specialist (EH) on 05/08/2022 and updated on 06/06/2023. The search strategies used text words and relevant indexing to capture relevant literature by combining terms and phrases for pleural effusion, transudate, and diagnostic studies. This search strategy uses the Scottish International Guidelines' Network search filter for Diagnostic Studies, available from: https://www.sign.ac.uk/what-we-do/methodology/search-filters/. The full strategies are available below. All references were exported to Endnote 20 (Thomson Reuters, New York, NY), and duplicates were removed using the Deduklick programme developed by Risklick (https://www.risklick.ch/deduklick/) and manually for the updates. The reference lists of included papers were assessed for additional relevant studies, forwards citation searching was conducted via Google Scholar.

SIGN. Diagnostic Studies search filter [Available from: https://www.sign.ac.uk/assets/search-filters-diagnostic-studies.docx.

Search Strategies

05/08/2022

Medline

((("Pleural Effusion"[Mesh]) OR ("pleural effusion*"[Title/Abstract] or "pleura effusion*"[Title/Abstract])) AND (("Exudates and Transudates"[Mesh]) OR (transudate*[Title/Abstract]))) AND (("Sensitivity and Specificity"[Mesh]) OR ((sensitivity[Text Word] OR specificity[Text Word]) OR (((pre-test[Text Word] OR pretest[Text Word]) AND probability[Text Word])) OR ("post-test probability"[Text Word] OR "predictive value*"[Text Word] OR "likelihood ratio*"[Text Word])))

Database: Embase 1974 to present
Search Strategy:
---
1 exp *pleura effusion/ (15575)
2 "pleura* effusion*".ti,ab,kw. (43997)
3 1 or 2 (46620)
4 *pleura fluid/ (1743)
5 ("pleura* fluid*" or transudate*).ti,ab,kw. (12492)
6 4 or 5 (12859)
7 exp "SENSITIVITY AND SPECIFICITY"/ (439575)
8 sensitivity.tw. (1185447)
9 specificity.tw. (677579)
10 ((pre-test or pretest) adj probability).tw. (4728)
11 post-test probability.tw. (979)
12 predictive value$.tw. (189966)
13 likelihood ratio$.tw. (24886)
14 *Diagnostic Accuracy/ (16756)
15 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 (1758286)
16 3 and 6 and 15 (1406)

Cochrane Central Register of Controlled Trials
Issue 7 of 12, July 2022

#1	("pleura effusion*" OR "pleural effusion*"):ti,ab,kw	2139
#2	("pleura* fluid*" or transudate*):ti,ab,kw	371
#3	MeSH descriptor: [Sensitivity and Specificity] explode all trees	16186
#4	(sensitivity OR specificity):ti,ab,kw	67565
#5	((pre-test or pretest) near/1 probability):ti,ab,kw	182
#6	"post-test probability":ti,ab,kw	48
#7	"predictive value*":ti,ab,kw	14444
#8	"likelihood ratio*":ti,ab,kw	635
#9	#3 or #4 or #5 or #6 or #7 or #8	78415
#10	#1 and #2 and #9	7

06/06/2023 (2022-present only)

Medline

((("Pleural Effusion"[Mesh]) OR ("pleural effusion*"[Title/Abstract] or "pleura effusion*"[Title/Abstract])) AND (("Exudates and Transudates"[Mesh]) OR (transudate*[Title/Abstract]))) AND (("Sensitivity and Specificity"[Mesh]) OR ((sensitivity[Text Word]

OR specificity[Text Word]) OR (((pre-test[Text Word] OR pretest[Text Word]) AND probability[Text Word])) OR ("post-test probability"[Text Word] OR "predictive value*"[Text Word] OR "likelihood ratio*"[Text Word]))) Filters: **from 2022 - 2023**

Database: Embase 1974 to present

Link to search history:

https://ovidsp.ovid.com/ovidweb.cgi?T=JS&NEWS=N&PAGE=main&SHAREDSEARCHID=2mZpfTG35fHyVHzpin0fYLbOlXOQUnJQxy431GKqWLR7oIqhv1l5AYdcotvQWqkWd

Search Strategy:

1 exp *pleura effusion/ (18823)

2 "pleura* effusion*".ti,ab,kw. (46786)

3 1 or 2 (51592)

4 *pleura fluid/ (1837)

5 ("pleura* fluid*" or transudate*).ti,ab,kw. (13191)

6 4 or 5 (13562)

7 exp "SENSITIVITY AND SPECIFICITY"/ (484480)

8 sensitivity.tw. (1277089)

9 specificity.tw. (727981)

10 ((pre-test or pretest) adj probability).tw. (5111)

11 post-test probability.tw. (1059)

12 predictive value$.tw. (206077)

13 likelihood ratio$.tw. (26981)

14 *Diagnostic Accuracy/ (19411)

15 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 (1889155)

16 3 and 6 and 15 (1497)

17 limit 16 to yr="2022 -Current" (107)

Cochrane Central Register of Controlled Trials
Issue 6 of 12, June 2023

#1	("pleura effusion*" OR "pleural effusion*"):ti,ab,kw	2300
#2	("pleura* fluid*" or transudate*):ti,ab,kw	401
#3	MeSH descriptor: [Sensitivity and Specificity] explode all trees	19917
#4	(sensitivity OR specificity):ti,ab,kw	72692
#5	((pre-test or pretest) near/1 probability):ti,ab,kw	199
#6	"post-test probability":ti,ab,kw	52
#7	"predictive value*":ti,ab,kw	16155
#8	"likelihood ratio*":ti,ab,kw	689
#9	#3 or #4 or #5 or #6 or #7 or #8	85160
#10	#1 and #2 and #9	9

Limited: 2022-2023

Search Results

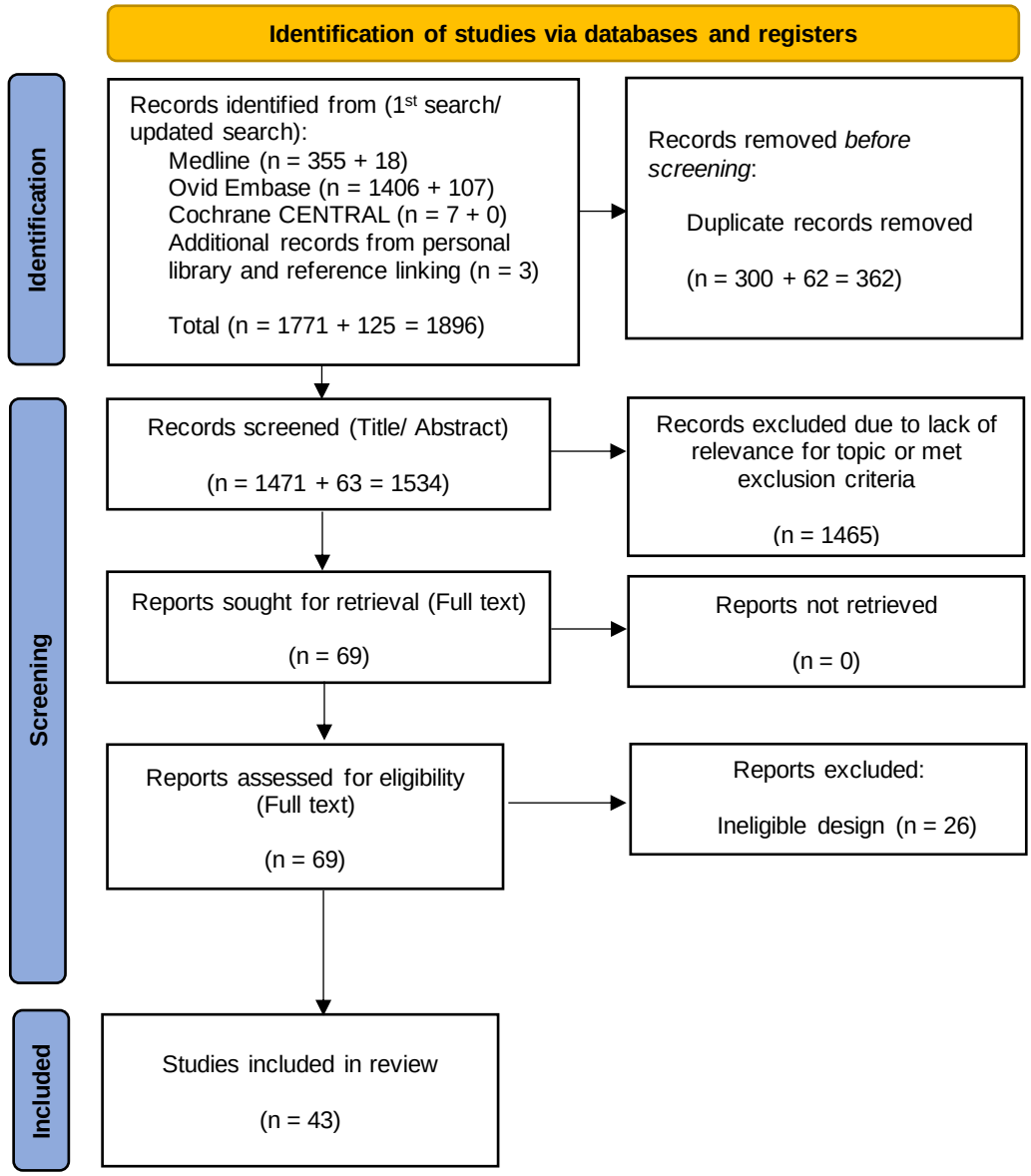
	Search results 05/08/2022	Search results 06/06/2023 (2022-present only)
Medline	355	18
Ovid Embase	1406	107
Cochrane CENTRAL	7	0
Total	1768	125
Total after deduplication	1468	
Unique since 05/08/2022		63

Inclusion/Exclusion criteria

Inclusion criteria	**Exclusion criteria**
Systematic reviews	Informal reviews
Meta-analysis	Case reports (n = 1)
RCTs	Conference abstracts
Interventional studies (non-randomised)	Paediatric studies
Observational studies (retrospective or prospective)	Animal studies
Case series	
Editorials	
Guidelines	

PRISMA Flowchart

What are the tests for categorizing a pleural effusion as a transudate? What are the scoring systems for categorizing a pleural effusion as a transudate?



From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

Summary of findings (included in manuscript)

In total 1534 studies were screened to identify 43 studies of relevance in producing this section. These consisted of 2 editorials, 1 guideline, 27 retrospective observational studies, 11 prospective observational studies and 2 systematic reviews and meta-analyses (see below).

Full list of included studies with categorisation

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23. Heffner JE, Highland K, Brown LK. A meta-analysis derivation of continuous likelihood ratios for diagnosing pleural fluid exudates. *Am J Respir Crit Care Med* 2003; 167: 1591–1599.

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ERS Benign pleural effusions Taskforce: BAPE

PICO Questions

In patients with suspected BAPE/DPT, what are the clinical features that can identify risk factors, diagnose the condition, and identify prognostic features?

P- Patients with suspected BAPE/ DPT
I- Clinical features (pleural fluid, histopathology, radiology), Risk factors, Prognostic factors
C- Not required
O- Diagnosis of BAPE/DPT/Exclusion of mesothelioma, Diagnostic accuracy rates of BAPE, Rates of evolution of BAPE, Rates of lung function decline, Rates of radiological progression

In patients with established BAPE/DPT, what are the options for follow up?

P- Patients with established BAPE/DPT
I- Duration of CT follow up period, use of PET-CT, use of biopsy and/or re-biopsy
C- Not required
O- Reduction in length of follow up and number of interval CT scans, rates of malignancy

Literature search methodology

Search strategies run on 05/08/2022 by Eli Harriss, a librarian at the Bodleian Health Care Libraries, University of Oxford, and updated on 06/06/2023.

Methodology

Medline, Ovid Embase, and the Cochrane Central Register of Controlled Trials were searched by an information specialist (EH) on 05/08/2022 and updated on 06/06/2023. The search strategies used text words and relevant indexing to capture relevant literature about BAPE, diffuse pleural thickening, pleural fluid, radiology and risk factor excluding records with the terms child*, paediatr*, or pediatr* in the title or abstract fields. The full strategies are available below. All references were exported to Endnote 20 (Thomson Reuters, New York, NY), and duplicates were removed using the Deduklick programme developed by Risklick (https://www.risklick.ch/deduklick/) and then manually for the updates. The reference lists of included papers were assessed for additional relevant studies, forwards citation searching was conducted via Google Scholar.

Search Strategies

05/08/2022

Medline

((BAPE[Text Word] OR "benign asbestos pleural effusion*"[Text Word] OR DPT[Text Word] OR "diffuse pleural thickening"[Text Word]) AND (((((("pathology" [Subheading] OR "Pathology"[Mesh]) OR "Radiology"[Mesh]) OR "Risk Factors"[Mesh]) OR "Prognosis"[Mesh]) OR ("Diagnosis"[Mesh] OR "diagnosis" [Subheading])) OR "Follow-Up Studies"[Mesh]) OR (histopatholog*[Title/Abstract] OR patholog*[Title/Abstract] OR "pleural fluid*"[Title/Abstract] OR "clinical feature*"[Title/Abstract] OR radiology[Title/Abstract] OR "risk factor*"[Title/Abstract] OR "risk score*"[Title/Abstract] OR prognosis[Title/Abstract] OR prognostic[Title/Abstract] OR diagnos*[Title/Abstract] OR "follow up"[Title/Abstract] OR followup[Title/Abstract]))) NOT (child*[Title/Abstract] OR paediatr*[Title/Abstract] OR pediatr*[Title/Abstract]) Filters: **from 2022 - 2023**

Database: Embase 1974 to present

Search Strategy:

1 (BAPE or "benign asbestos pleural effusion*" or DPT or "diffuse pleural thickening").mp. (4363)

2 exp pathology/ or radiology/ or exp risk factor/ or exp prognosis/ or exp diagnosis/ or follow up/ or histopathology/ (11154501)

3 (histopatholog* or patholog* or "pleural fluid*" or "clinical feature*" or radiology or "risk factor*" or "risk score*" or prognosis or prognostic or diagnos* or "follow up" or followup).ti,ab,kw. (8332398)

4 2 or 3 (13648309)

5 1 and 4 (2052)

6 (child* or paediatr* or pediatr*).ti,ab. (2389108)

7 5 not 6 (1621)

8 7 (1621)

9 limit 8 to yr="2022 -Current" (163)

Cochrane Central Register of Controlled Trials
Issue 6 of 12, June 2023

#1 (BAPE or "benign asbestos pleural effusion*" or "diffuse pleural thickening"):ti,ab,kw 5
#2 (histopatholog* or patholog* or "pleural fluid*" or "clinical feature*" or radiology or "risk factor*" or "risk score*" or prognosis or prognostic or diagnos* or "follow up" or followup):ti,ab,kw 616633
#3 #1 and #2 4
#4 (child* or paediatr* or pediatr*):ti,ab 168037
#5 #3 NOT #4 4
2022-2023

06/06/2023 (2022-2023)

Medline

((BAPE[Text Word] OR "benign asbestos pleural effusion*"[Text Word] OR DPT[Text Word] OR "diffuse pleural thickening"[Text Word]) AND (((((("pathology" [Subheading] OR "Pathology"[Mesh]) OR "Radiology"[Mesh]) OR "Risk Factors"[Mesh]) OR "Prognosis"[Mesh]) OR ("Diagnosis"[Mesh] OR "diagnosis" [Subheading])) OR "Follow-Up Studies"[Mesh]) OR (histopatholog*[Title/Abstract] OR patholog*[Title/Abstract] OR "pleural fluid*"[Title/Abstract] OR "clinical feature*"[Title/Abstract] OR radiology[Title/Abstract] OR "risk factor*"[Title/Abstract] OR "risk score*"[Title/Abstract] OR prognosis[Title/Abstract] OR prognostic[Title/Abstract] OR diagnos*[Title/Abstract] OR "follow up"[Title/Abstract] OR followup[Title/Abstract]))) NOT (child*[Title/Abstract] OR paediatr*[Title/Abstract] OR pediatr*[Title/Abstract]) Filters: **from 2022 - 2023**

Database: Embase 1974 to present

Search Strategy:

1 (BAPE or "benign asbestos pleural effusion*" or DPT or "diffuse pleural thickening").mp. (4363)

2 exp pathology/ or radiology/ or exp risk factor/ or exp prognosis/ or exp diagnosis/ or follow up/ or histopathology/ (11154501)

3 (histopatholog* or patholog* or "pleural fluid*" or "clinical feature*" or radiology or "risk factor*" or "risk score*" or prognosis or prognostic or diagnos* or "follow up" or followup).ti,ab,kw. (8332398)

4 2 or 3 (13648309)

5 1 and 4 (2052)

6 (child* or paediatr* or pediatr*).ti,ab. (2389108)

7 5 not 6 (1621)

8 7 (1621)

9 limit 8 to yr="2022 -Current" (163)

Cochrane Central Register of Controlled Trials
Issue 6 of 12, June 2023

#1 (BAPE or "benign asbestos pleural effusion*" or "diffuse pleural thickening"):ti,ab,kw 5
#2 (histopatholog* or patholog* or "pleural fluid*" or "clinical feature*" or radiology or "risk factor*" or "risk score*" or prognosis or prognostic or diagnos* or "follow up" or followup):ti,ab,kw 616633
#3 #1 and #2 4
#4 (child* or paediatr* or pediatr*):ti,ab 168037
#5 #3 NOT #4 4
2022-2023

Search Results

	05/08/2022 search results	06/06/2023 search results (2022 to 2023 only)
Medline	1123	118
Ovid Embase	1498	163
Cochrane CENTRAL	4	0
Total	2625	281
Total after deduplication	1915	
Unique since 05/08/2022		133

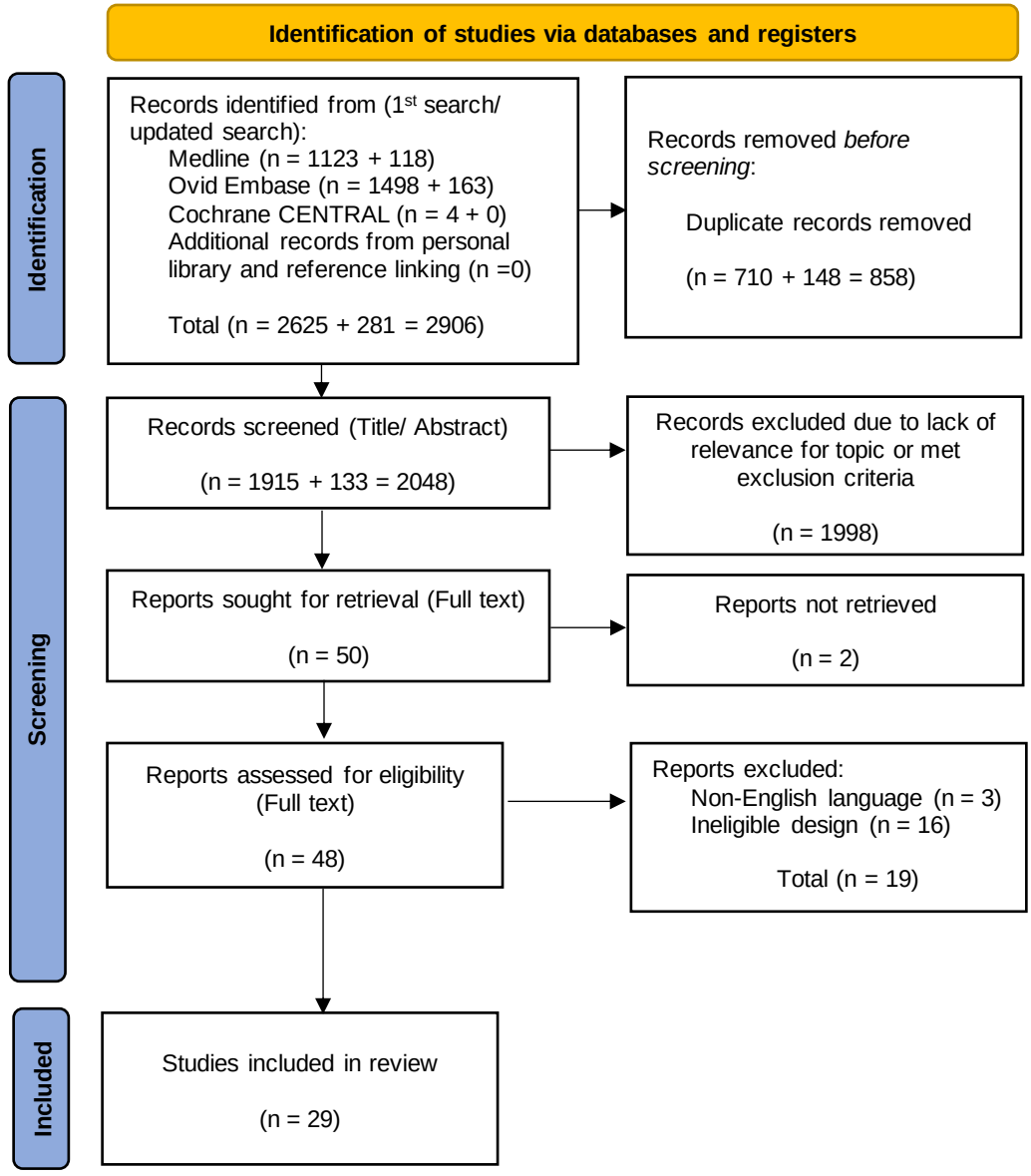
Inclusion/Exclusion criteria

Inclusion criteria	**Exclusion criteria**
Systematic reviews	Paediatric studies
Meta-analysis	Animal studies
RCTs	
Interventional studies (non-randomised)	
Observational studies (retrospective or prospective)	
Case series	
Editorials	
Literature and narrative reviews	
Guidelines	
Case reports	
Conference abstracts	

PRISMA Flowchart

In patients with suspected BAPE/DPT, what are the clinical features that can identify risk factors, diagnose the condition, and identify prognostic features?

In patients with established BAPE/DPT, what are the options for follow up?



From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

Summary of findings (included in manuscript)

In total 2048 studies were screened to identify 29 studies relevant to producing this section. These consisted of 1 editorial or narrative review, 17 retrospective observational studies, 4 prospective observational study, 5 case series or single case reports, 1 systematic review and meta-analysis and 1 trial protocol (see below).
(

Full list of included studies with categorisation

Epler GR, McLoud TC, Gaensler EA. Prevalence and incidence of benign asbestos pleural effusion in a working population. *JAMA* 1982; 247: 617–622.

168. Mastrangelo G, Ballarin MN, Bellini E, Bicciato F, Zannol F, Gioffrè F, Zedde A, Tessadri G, Fedeli U, Valentini F, Scoizzato L, Marangi G, Lange JH. Asbestos exposure and benign asbestos diseases in 772 formerly exposed workers: dose-response relationships. *Am J Ind Med* 2009; 52: 596–602.

169. Fujimoto N, Gemba K, Aoe K, Kato K, Yokoyama T, Usami I, Onishi K, Mizuhashi K, Yusa T, Kishimoto T. Clinical Investigation of Benign Asbestos Pleural Effusion. *Pulmonary Medicine* 2015; 2015: 1–6.

170. Fujimoto N, Kato K, Usami I, Sakai F, Tokuyama T, Hayashi S, Miyamoto K, Kishimoto T. Asbestos-related diffuse pleural thickening. *Respiration* 2014; 88: 277–284.

171. Schwartz DA, Galvin JR, Dayton CS, Stanford W, Merchant JA, Hunninghake GW. Determinants of restrictive lung function in asbestos-induced pleural fibrosis. *J Appl Physiol (1985)* 1990; 68: 1932–1937.

173. Nojima D, Fujimoto N, Kato K, Fuchimoto Y, Kiura K, Kishimoto T, Tanimoto M. Pilot Analysis of Asbestos-induced Diffuse Pleural Thickening with Respiratory Compromise. *Acta Med Okayama* 2015; 69: 261–266.

174. Hara R, Yano Y, Okabe F, Kuge T, Mori M, Urasaki K. Radiographic change over 11 years in a patient with asbestos-related pleural disease. *Respirology Case Reports* [Internet] 2020 [cited 2023 May 2]; 8Available from: https://onlinelibrary.wiley.com/doi/10.1002/rcr2.642.

175. Hillerdal G, Ozesmi M. Benign asbestos pleural effusion: 73 exudates in 60 patients. *Eur J Respir Dis* 1987; 71: 113–121.

177. Robinson BW, Musk AW. Benign asbestos pleural effusion: diagnosis and course. *Thorax* 1981; 36: 896–900.

178. Stephens M, Gibbs AR, Pooley FD, Wagner JC. Asbestos induced diffuse pleural fibrosis: pathology and mineralogy. *Thorax* 1987; 42: 583–588.

179. Allen RKA, Cramond T, Lennon D, Waterhouse M. A retrospective study of chest pain in benign asbestos pleural disease. *Pain Med* 2011; 12: 1303–1308.

180. Luo W, Zeng Y, Shen P, Wu X, Wang J, Zhang X. A multidisciplinary approach for the diagnosis of benign asbestos pleural effusion: a single-center experience. *J Thorac Dis* 2020; 12: 4338–4346.

181. Jeebun V, Stenton SC. The presentation and natural history of asbestos-induced diffuse pleural thickening. *Occupational Medicine* 2012; 62: 266–268.

182. Kishimoto T, Kato K, Ashizawa K, Kurihara Y, Tokuyama T, Sakai F. A retrospective study on radiological findings of diffuse pleural thickening with benign asbestos pleural effusion in Japanese cases. *Ind Health* 2022; 60: 429–435.

183. Fonseka DD, Edey A, Stadon L, Viner J, Darby M, Maskell NA. The physiological consequences of different distributions of diffuse pleural thickening on CT imaging. *Br J Radiol* 2017; 90: 20170218.

184. Metintas M, Ucgun I, Elbek O, Erginel S, Metintas S, Kolsuz M, Harmanci E, Alatas F, Hillerdal G, Ozkan R, Kaya T. Computed tomography features in malignant pleural mesothelioma and other commonly seen pleural diseases. *Eur J Radiol* 2002; 41: 1–9.

185. Kato K, Gemba K, Fujimoto N, Aoe K, Takeshima Y, Inai K, Kishimoto T. Pleural irregularities and mediastinal pleural involvement in early stages of malignant pleural mesothelioma and benign asbestos pleural effusion. *Eur J Radiol* 2016; 85: 1594–1600.

187. Okten F, Köksal D, Onal M, Ozcan A, Simşek C, Ertürk H. Computed tomography findings in 66 patients with malignant pleural mesothelioma due to environmental exposure to asbestos. *Clin Imaging* 2006; 30: 177–180.

189. Khan AM, Tlemcani K, Shanmugam N, Y D, Keller S, Berman AR. A localized pleural based mass with intense uptake on positron emission tomography scan. *Chest* 2007; 131: 294–299.

190. Yildirim H, Metintas M, Entok E, Ak G, Ak I, Dundar E, Erginel S. Clinical value of fluorodeoxyglucose-positron emission tomography/computed tomography in differentiation of malignant mesothelioma from asbestos-related benign pleural disease: an observational pilot study. *J Thorac Oncol* 2009; 4: 1480–1484.

194. Schaal M, Severac F, Labani A, Jeung M-Y, Roy C, Ohana M. Diagnostic Performance of Ultra-Low-Dose Computed Tomography for Detecting Asbestos-Related Pleuropulmonary Diseases: Prospective Study in a Screening Setting. *PLoS One* 2016; 11: e0168979.

195. Kramer H, Pieterman RM, Slebos D-J, Timens W, Vaalburg W, Koëter GH, Groen HJM. PET for the evaluation of pleural thickening observed on CT. *J Nucl Med* 2004; 45: 995–998.

196. Alì G, Bruno R, Fontanini G. The pathological and molecular diagnosis of malignant pleural mesothelioma: a literature review. *J. Thorac. Dis.* 2018; 10: S276–S284.

197. Hoyle JL, Gudur S. P206 Asbestos related diffuse pleural thickening; Likelihood of progression in the secondary care setting. *Thorax* BMJ Publishing Group Ltd; 2013; 68: A169–A169.

198. Ferguson K, Mercer R, King J, Marshall K, Tsim S, Maskell N, Evison M, Rahman N, Blyth K. S43 Preliminary results of the Meso-ORIGINS feasibility study: retrospective element regarding BAPE-mesothelioma evolution rate. *Thorax* BMJ Publishing Group Ltd; 2021; 76: A28–A28.

199. Ferguson KJ, Blyth KG, Neilson M. S15 Evolution of mesothelioma following initial biopsies showing benign pleural inflammation: a meta-analysis. *Thorax* BMJ Publishing Group Ltd; 2021; 76: A14–A14.

200. Mesothelioma Observational study of RIsk prediction and Generation of benign-meso tissue pairs, Including a Nested MRI Sub-study [Internet]. Health Research Authority [cited 2023 May 3].Available from: https://www.hra.nhs.uk/planning-and-improving-research/application-summaries/research-summaries/meso-origins/.

201. al Jarad N, Poulakis N, Pearson MC, Rubens MB, Rudd RM. Assessment of asbestos-induced pleural disease by computed tomography--correlation with chest radiograph and lung function. *Respir Med* 1991; 85: 203–208.

Kee ST, Gamsu G, Blanc P. Causes of pulmonary impairment in asbestos-exposed individuals with diffuse pleural thickening. *Am J Respir Crit Care Med* 1996; 154: 789–793.

ERS Benign Effusions Taskforce: ESRF

PICO Question 1:

Within the dialysis population what are the management strategies for effusion control in the event of recurrent effusions due to fluid overload?

P - ESRF receiving dialysis

I - Pleural procedures (TxAsp/ IPC/ ICD + Talc/ LATS/ VATS), Renal Interventions (high dose diuretics, aggressive fluid removal at dialysis, salt + fluid restriction, use of hypertonic exchanges, use of icodextrin fluid on PD, switch from PD to HD)

C - Not required

O - Patient reported symptom measures, QoL, Frequency and duration of dialysis sessions, Volume of fluid removed during dialysis (+complications), pleural procedural complications, total # pleural interventions required, # breakthrough pleural interventions required

Literature search methodology

Search strategies run on 04/08/2022 by Eli Harriss, a librarian at the Bodleian Health Care Libraries, University of Oxford, and updated on 05/06/2023.

Methodology

Medline, Ovid Embase, and the Cochrane Central Register of Controlled Trials were searched by an information specialist (EH) on 04/08/2022 and updated on 05/06/2023. The search strategies used text words and relevant indexing to capture relevant literature about End stage kidney disease, pleural effusion and pleural intervention, with no limits applied. The full strategies are available i. All references were exported to Endnote 20 (Thomson Reuters, New York, NY), and duplicates were removed using the Deduklick programme developed by Risklick (https://www.risklick.ch/deduklick/) (04/08/2022) and manually (05/06/2023). The reference lists of included papers were assessed for additional relevant studies, forwards citation searching was conducted via Google Scholar.

Search Strategies

04/08/2022

Medline

((((("Kidney Failure, Chronic"[Mesh]) OR ("Renal Dialysis"[Mesh])) OR ("end stage kidney disease"[Title/Abstract] OR "chronic kidney failure"[Title/Abstract] OR "end stage renal disease"[Title/Abstract] OR "end stage renal failure"[Title/Abstract] OR ESRD[Title/Abstract] OR ESRF[Title/Abstract] OR "chronic renal failure"[Title/Abstract] OR haemodialysis[Title/Abstract] OR hemodialysis[Title/Abstract] OR dialysis[Title/Abstract])) AND (("Pleural Effusion"[Mesh]) OR ("pleural effusion*"[Title/Abstract] OR "pleura effusion*"[Title/Abstract] OR "pleural disease"[Title/Abstract] OR "pleural intervention*"[Title/Abstract])))

Database: Embase 1974 to present

Search Strategy:

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1 exp *chronic kidney failure/ (57813)
2 exp *dialysis/ (94719)
3 ("end stage kidney disease" or "chronic kidney failure" or "end stage renal disease" or "end stage renal failure" or ESRD or ESRF or "chronic renal failure" or haemodialysis or hemodialysis or dialysis).ti,ab. (299151)
4 1 or 2 or 3 (334758)
5 exp pleura effusion/ (71044)
6 ("pleura* effusion*" or "pleural disease" or "pleural intervention*").ti,ab. (44235)
7 5 or 6 (79066)
8 4 and 7 (1445)

Cochrane Central Register of Controlled Trials

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#1 ("end stage kidney disease" or "chronic kidney failure" or "end stage renal disease" or "end stage renal failure" or ESRD or ESRF or "chronic renal failure" or haemodialysis or hemodialysis or dialysis):ti,ab,kw 25808
#2 ("pleural effusion*" or "pleura effusion*" OR "pleural disease" or "pleural intervention*"):ti,ab,kw 2162
#3 #1 and #2 25

05/06/2023 (2022 – 2023 only)

Medline

((((("Kidney Failure, Chronic"[Mesh]) OR ("Renal Dialysis"[Mesh])) OR ("end stage kidney disease"[Title/Abstract] OR "chronic kidney failure"[Title/Abstract] OR "end stage renal disease"[Title/Abstract] OR "end stage renal failure"[Title/Abstract] OR ESRD[Title/Abstract] OR ESRF[Title/Abstract] OR "chronic renal failure"[Title/Abstract] OR haemodialysis[Title/Abstract] OR hemodialysis[Title/Abstract] OR dialysis[Title/Abstract])) AND (("Pleural Effusion"[Mesh]) OR ("pleural effusion*"[Title/Abstract] OR "pleura effusion*"[Title/Abstract] OR "pleural disease"[Title/Abstract] OR "pleural intervention*"[Title/Abstract]))) Filters: **from 2022 - 2023**

Database: Embase 1974 to present

Link to search history:

https://ovidsp.ovid.com/ovidweb.cgi?T=JS&NEWS=N&PAGE=main&SHAREDSEARCHID=2rKQOfF1VYeQy97Dp2fqfyeoMAn7uEit9hMtV1CZ4Z97wxorGlF3lli71F2Zkma3f

Search Strategy:

1 exp *chronic kidney failure/ (65616)

2 exp *dialysis/ (102915)

3 ("end stage kidney disease" or "chronic kidney failure" or "end stage renal disease" or "end stage renal failure" or ESRD or ESRF or "chronic renal failure" or haemodialysis or hemodialysis or dialysis).ti,ab. (320410)

4 1 or 2 or 3 (361449)

5 exp pleura effusion/ (80592)

6 ("pleura* effusion*" or "pleural disease" or "pleural intervention*").ti,ab. (47014)

7 5 or 6 (88739)

8 4 and 7 (1645)

9 limit 8 to yr="2022 -Current" (206)

Cochrane Central Register of Controlled Trials

Issue 6 of 12, June 2023

#1 ("end stage kidney disease" or "chronic kidney failure" or "end stage renal disease" or "end stage renal failure" or ESRD or ESRF or "chronic renal failure" or haemodialysis or hemodialysis or dialysis):ti,ab,kw 28161

#2 ("pleural effusion*" or "pleura effusion*" OR "pleural disease" or "pleural intervention*"):ti,ab,kw 2328

#3 #1 and #2 28

Limited to 2022-2023

Search Results

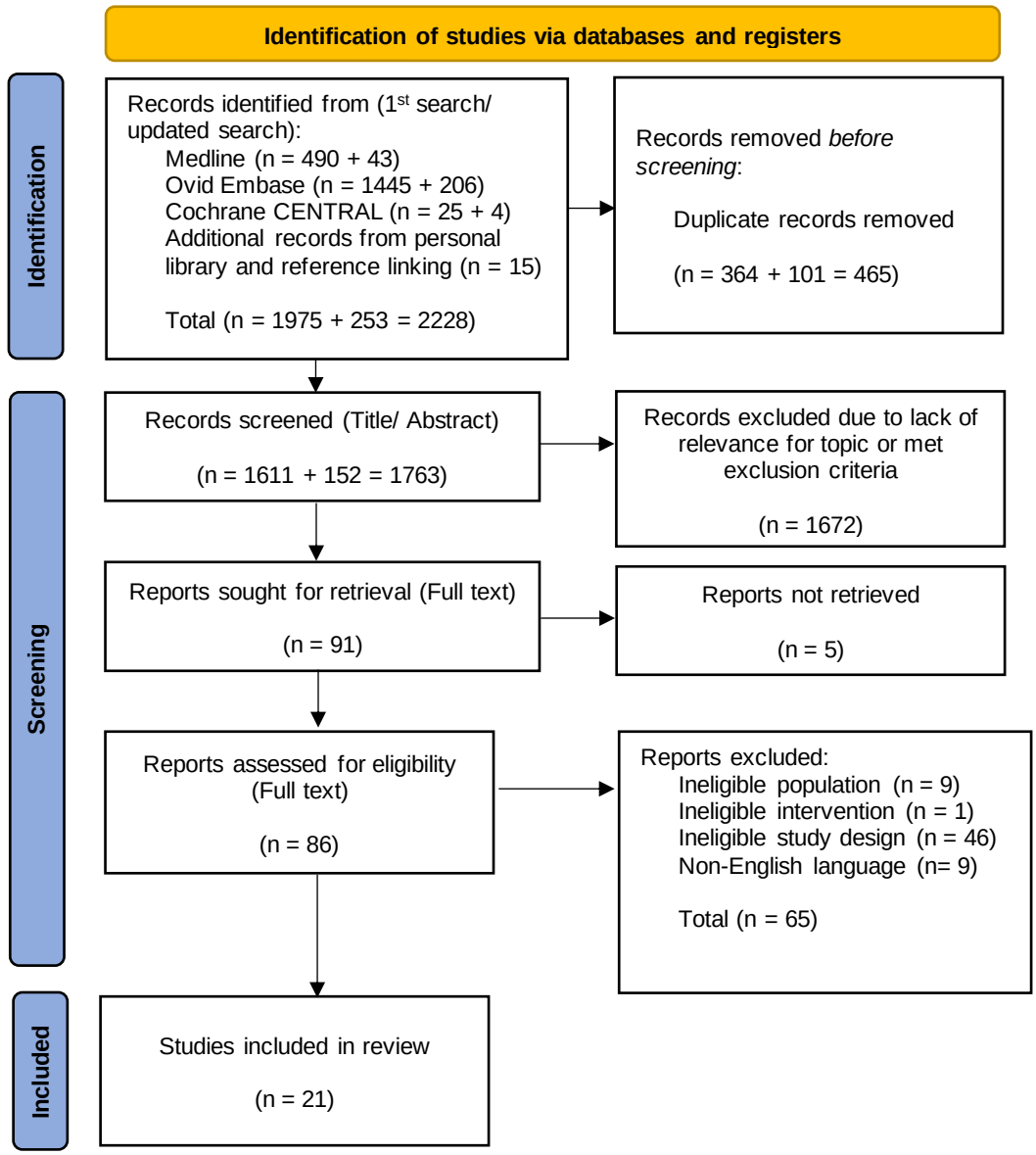
	Search results 04/08/2022 (no limits)	Search results 05/06/2023 (limited 2022-present)
Medline	490	43
Ovid Embase	1445	206
Cochrane CENTRAL	25	4
Total	1960	253
Total after deduplication	1596	
Unique since 04/08/2022		152

Inclusion/Exclusion criteria

Inclusion criteria	**Exclusion criteria**
Systematic reviews	Case reports (n = 1)
Meta-analysis	Conference abstracts
RCTs	Paediatric studies
Interventional studies (non-randomised)	Animal studies
Observational studies (retrospective or prospective)	
Case series	
Editorials	
Literature and narrative reviews	
Guidelines	

PRISMA Flowchart

Within the dialysis population what are the management strategies for effusion control in the event of recurrent effusions due to fluid overload?



From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

Summary of findings (included in manuscript)

In total 1763 studies were screened, and 21 studies were of relevance in producing this section. These consisted of 16 retrospective observational studies, 3 prospective observational studies, 2 case series (see below). (

13. Jarratt MJ, Sahn SA. Pleural effusions in hospitalized patients receiving long-term hemodialysis. *Chest* 1995; 108: 470–474.

14. Coşkun M, Boyvat F, Bozkurt B, Agildere AM, Niron EA. Thoracic CT findings in long-term hemodialysis patients. *Acta Radiol* 1999; 40: 181–186.

15. Bakirci T, Sasak G, Ozturk S, Akcay S, Sezer S, Haberal M. Pleural Effusion in Long-Term Hemodialysis Patients. *Transplantation Proceedings* 2007; 39: 889–891.

16. Lakadamyali H, Lakadamyali H, Ergun T. Thorax CT Findings in Symptomatic Hemodialysis Patients. *Transplantation Proceedings* 2008; 40: 71–76.

17. Ray S, Mukherjee S, Ganguly J, Abhishek K, Mitras S, Kundu S. A cross-sectional prospective study of pleural effusion among cases of chronic kidney disease. *Indian J Chest Dis Allied Sci* 2013; 55: 209–213.

18. Rashid-Farokhi F, Pourdowlat G, Nikoonia M-R, Behzadnia N, Kahkouee S, Nassiri A-A, Masjedi M-R. Uremic pleuritis in chronic hemodialysis patients. *Hemodial Int* 2013; 17: 94–100.

19. Potechin R, Amjadi K, Srour N. Indwelling pleural catheters for pleural effusions associated with end-stage renal disease: a case series. *Ther Adv Respir Dis* 2015; 9: 22–27.

20. Kumar S, Agarwal R, Bal A, Sharma K, Singh N, Aggarwal AN, Verma I, Rana SV, Jha V. Utility of adenosine deaminase (ADA), PCR & thoracoscopy in differentiating tuberculous & non-tuberculous pleural effusion complicating chronic kidney disease. *Indian J Med Res* 2015; 141: 308–314.

21. Qureshi SQ, Idrees MK, Ahmad S, Ahmed E. Pleural effusion among patients on maintenance hemodialysis at SIUT Karachi, Pakistan. *Rawal Medical Journal* Pakistan Medical Association Rawalpindi Islamabad Branch, Rawalpindi, Pakistan; 2016; 41: 11–11.

22. Colella S, Fioretti F, Massaccesi C, Primomo GL, Panella G, D'Emilio V, Pela R. Usefulness of Medical Thoracoscopy in the Management of Pleural Effusion Caused by Chronic Renal Failure. *J Bronchology Interv Pulmonol* 2017; 24: 285–289.

23. Hamada S, Sano T, Nagatani Y, Tsukino M. Pleural effusion negatively impacts survival of patients undergoing maintenance hemodialysis. *Pulmonology* 2019; 25: 58–60.

24. Uzan G, İkitimur H. Pleural Effusion in End Stage Renal Failure Patients. *Sisli Etfal Hastan Tip Bul* 2019; 53: 54–57.

25. Pant P, Baniya S, Jha A. Prevalence of Respiratory Manifestations in Chronic Kidney Diseases; A Descriptive Cross-sectional Study in A Tertiary Care Hospital of Nepal. *JNMA J Nepal Med Assoc* 2019; 57: 80–83.

26. Jabbar A, Qureshi R, Nasir K, Dhrolia M, Ahmad A. Transudative and Exudative Pleural Effusion in Chronic Kidney Disease Patients: A Prospective Single-Center Study. *Cureus* 2021; 13: e18649.

27. Shaik L, Thotamgari SR, Kowtha P, Ranjha S, Shah RN, Kaur P, Subramani R, Katta RR, Kalaiger A mukhtadir, Singh R. A Spectrum of Pulmonary Complications Occurring in End-Stage Renal Disease Patients on Maintenance Hemodialysis. *Cureus* 13: e15426.

28. Wu J, Lin L, Jiang X, Xiao G, Chen Z, Li M, Wang C. Characteristics and negative impacts of pleural effusion in hospitalized patients undergoing maintenance hemodialysis. *Am J Transl Res* 2022; 14: 7494–7503.

140. Berger HW, Rammohan G, Neff MS, Buhain WJ. Uremic pleural effusion. A study in 14 patients on chronic dialysis. *Ann Intern Med* 1975; 82: 362–364.

146. Walker SP, Morley AJ, Stadon L, De Fonseka D, Arnold DT, Medford ARL, Maskell NA. Nonmalignant Pleural Effusions: A Prospective Study of 356 Consecutive Unselected Patients. *Chest* 2017; 151: 1099–1105.

147. Goodkin DA, Bragg-Gresham JL, Koenig KG, Wolfe RA, Akiba T, Andreucci VE, Saito A, Rayner HC, Kurokawa K, Port FK, Held PJ, Young EW. Association of comorbid conditions and mortality in hemodialysis patients in Europe, Japan, and the United States: the Dialysis Outcomes and Practice Patterns Study (DOPPS). *J Am Soc Nephrol* 2003; 14: 3270–3277.

148. DeBiasi EM, Pisani MA, Murphy TE, Araujo K, Kookoolis A, Argento AC, Puchalski J. Mortality among patients with pleural effusion undergoing thoracentesis. *Eur Respir J* 2015; 46: 495–502.

151. Horita Y, Noguchi M, Miyazaki M, Tadokoro M, Taura K, Watanabe T, Nishiura K, Harada T, Ozono Y, Kohno S. Prognosis of Patients with Rounded Atelectasis Undergoing Long-Term Hemodialysis. *NEF* Karger Publishers; 2001; 88: 87–92.

PICO Question 2:

What is the optimal investigation and management of a PD associated pleuro-peritoneal leak

P - Patients receiving PD

I - Ix: PF analysis according to defined cut-off values, peritoneal injected contrast agents, trial of cessation from PD

Mx: Pleural interventions (Pleurodesis via slurry, poudrage, surgical), Renal interventions (permanently cease PD, temporary pause of PD)

C - Not required

O - Diagnostic accuracy, time to diagnosis, efficacy (resolution of pleural effusion), complications, cost

Literature search methodology

Search strategies run on 04/08/2022 by Eli Harriss, a librarian at the Bodleian Health Care Libraries, University of Oxford, and updated on 05/06/2023

Methodology

An information specialist (EH) searched the following databases on 04/08/2022 and updated the searches on 05/06/2023: Medline; Ovid Embase; and the Cochrane Central Register of Controlled Trials. The search strategies used text words and relevant indexing to capture relevant literature about End stage kidney disease, peritoneal dialysis, pleural effusion and pleural intervention, with no limits applied. The full strategies are available in the appendix. All references were exported to Endnote 20 (Thomson Reuters, New York, NY), and duplicates were removed using the Deduklick programme developed by Risklick (https://www.risklick.ch/deduklick/), and manually for the updates. The reference lists of included papers were assessed for additional relevant studies, forwards citation searching was conducted via Google Scholar.

Search Strategies

04/08/2022

Medline

((((("Kidney Failure, Chronic"[Mesh]) OR ("Renal Dialysis"[Mesh])) OR ("end stage kidney disease"[Title/Abstract] OR "chronic kidney failure"[Title/Abstract] OR "end stage renal disease"[Title/Abstract] OR "end stage renal failure"[Title/Abstract] OR ESRD[Title/Abstract] OR ESRF[Title/Abstract] OR "chronic renal failure"[Title/Abstract] OR haemodialysis[Title/Abstract] OR hemodialysis[Title/Abstract] OR dialysis[Title/Abstract])) AND (("Pleural Effusion"[Mesh]) OR ("pleural effusion*"[Title/Abstract] OR "pleura effusion*"[Title/Abstract] OR "pleural disease"[Title/Abstract] OR "pleural intervention*"[Title/Abstract])))

Database: Embase 1974 to present
Search Strategy:
---
1 exp *chronic kidney failure/ (57813)
2 exp *dialysis/ (94719)
3 ("end stage kidney disease" or "chronic kidney failure" or "end stage renal disease" or "end stage renal failure" or ESRD or ESRF or "chronic renal failure" or haemodialysis or hemodialysis or dialysis).ti,ab. (299151)
4 1 or 2 or 3 (334758)
5 exp pleura effusion/ (71044)
6 ("pleura* effusion*" or "pleural disease" or "pleural intervention*").ti,ab. (44235)
7 5 or 6 (79066)
8 4 and 7 (1445)

Cochrane Central Register of Controlled Trials
Issue 7 of 12, July 2022
#1 ("end stage kidney disease" or "chronic kidney failure" or "end stage renal disease" or "end stage renal failure" or ESRD or ESRF or "chronic renal failure" or haemodialysis or hemodialysis or dialysis):ti,ab,kw 25808
#2 ("pleural effusion*" or "pleura effusion*" OR "pleural disease" or "pleural intervention*"):ti,ab,kw 2162
#3 #1 and #2 25

05/06/2023 (2022-2023 only)

Medline

((("Kidney Failure, Chronic"[Mesh]) OR ("Peritoneal Dialysis"[Mesh])) OR (("end stage kidney disease"[Title/Abstract] OR "chronic kidney failure"[Title/Abstract] OR "end stage renal disease"[Title/Abstract] OR "end stage renal failure"[Title/Abstract] OR ESRD[Title/Abstract] OR ESRF[Title/Abstract] OR "chronic renal failure"[Title/Abstract]) OR ("peritoneal dialysis"[Title/Abstract] OR "peritoneal leak*"[Title/Abstract] OR "pleuroperitoneal leak*"[Title/Abstract] OR "pleuroperitoneal fistula*"[Title/Abstract]))) AND (("Thoracentesis"[Mesh]) OR ("pleural procedure*"[Title/Abstract] OR "pleural intervention*"[Title/Abstract] OR thoracocentes*[Title/Abstract] OR thoracentes*[Title/Abstract] OR pleurocentes*[Title/Abstract] OR "pleural aspiration*"[Title/Abstract] OR "chest aspiration*"[Title/Abstract] OR "intercostal

drain*"[Title/Abstract] OR "indwelling pleural catheter*"[Title/Abstract])) Filters: **from 2022 - 2023**

Database: Embase 1974 to present

Link to search history:
https://ovidsp.ovid.com/ovidweb.cgi?T=JS&NEWS=N&PAGE=main&SHAREDSEARCHID=1w5Vwio2vY2DeaqXvrXUjexXQwZ3NzV7XQxUcVIRtYP78kFvQdabet5rc8QfkU1Yz

Search Strategy:

1 exp chronic kidney failure/ (150019)

2 exp peritoneal dialysis/ (49400)

3 ("end stage kidney disease" or "chronic kidney failure" or "end stage renal disease" or "end stage renal failure" or ESRD or ESRF or "chronic renal failure" or "peritoneal dialysis" or "peritoneal leak*" or "pleuroperitoneal leak*" or "pleuroperitoneal fistula*").ti,ab. (147111)

4 1 or 2 or 3 (266150)

5 thoracocentesis/ (11333)

6 ("pleural procedure*" or "pleural intervention*" or thoracocentes* or thoracentes* or pleurocentes* or "pleural aspiration*" or "chest aspiration*" or "intercostal drain*" or "indwelling pleural catheter*").ti,ab. (8200)

7 5 or 6 (14028)

8 4 and 7 (397)

9 limit 8 to yr="2022 -Current" (60)

Cochrane Central Register of Controlled Trials
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#1 ("end stage kidney disease" or "chronic kidney failure" or "end stage renal disease" or "end stage renal failure" or ESRD or ESRF or "chronic renal failure" or "peritoneal dialysis" or "peritoneal leak*" or "pleuroperitoneal leak*" or "pleuroperitoneal fistula*"):ti,ab,kw 14001
#2 ("pleural procedure*" or "pleural intervention*" or thoracocentes* or thoracentes* or pleurocentes* or "pleural aspiration*" or "chest aspiration*" or "intercostal drain*" or "indwelling pleural catheter*"):ti,ab,kw 364
#3 #1 and #2 4
Limited 2022-2023

Search Results

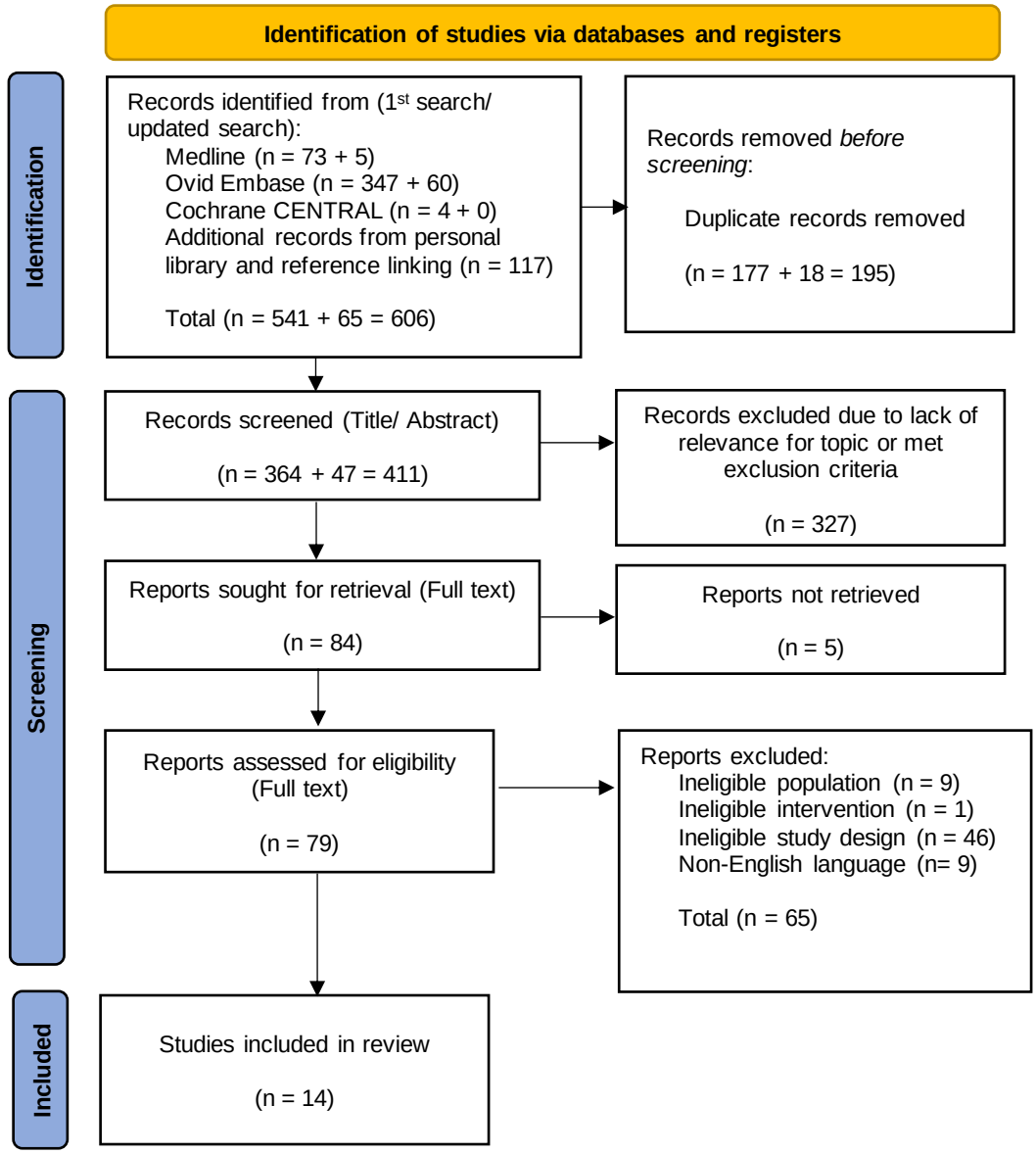
	Search results 04/08/2022	Search results 05/06/2023 (2022 to date only)
Medline	73	5
Ovid Embase	347	60
Cochrane CENTRAL	4	0
Total	424	65
Total after deduplication	364	
Unique since 04/08/2022		47

Inclusion/Exclusion criteria

Inclusion criteria	**Exclusion criteria**
Systematic reviews	Case reports (n = 1)
Meta-analysis	Conference abstracts
RCTs	Paediatric studies
Interventional studies (non-randomised)	Animal studies
Observational studies (retrospective or prospective)	
Case series	
Editorials	
Literature and narrative reviews	
Guidelines	

PRISMA Flowchart

What is the optimal investigation and management of a PD associated pleuro-peritoneal leak



From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

Summary of findings (included in manuscript)

In total 411 studies were screened, and 14 studies were of relevance in producing this section. These consisted of 1 Editorial, 11 retrospective observational studies, 2 case series (see below). (

Full list of included studies with categorisation

154. Chow KM, Szeto CC, Li PK-T. Review Articles: Management Options for Hydrothorax Complicating Peritoneal Dialysis: MANAGEMENT OF HYDROTHORAX IN CAPD. *Seminars in Dialysis* 2003; 16: 389–394.

155. Nomoto Y, Suga T, Nakajima K, Sakai H, Osawa G, Ota K, Kawaguchi Y, Sakai T, Sakai S, Shibat M, Takahashi S. Acute Hydrothorax in Continuous Ambulatory Peritoneal Dialysis – A Collaborative Study of 161 Centers. *AJN* Karger Publishers; 1989; 9: 363–367.

157. Ramon RG, Carrasco AM. Hydrothorax in Peritoneal Dialysis. *Perit Dial Int* SAGE Publications Ltd STM; 1998; 18: 5–10.

159. Chow KM, Szeto CC, Wong TY-H, Li PK-T. Hydrothorax Complicating Peritoneal Dialysis: Diagnostic Value of Glucose Concentration in Pleural Fluid Aspirate. *Perit Dial Int* SAGE Publications Ltd STM; 2002; 22: 525–527.

160. Momenin N, Colletti PM, Kaptein EM. Low pleural fluid-to-serum glucose gradient indicates pleuroperitoneal communication in peritoneal dialysis patients: presentation of two cases and a review of the literature. *Nephrology Dialysis Transplantation* 2012; 27: 1212–1219.

161. Harry L, Nyakale N, Tinarwo P. Scintigraphic peritoneography in the diagnosis of pleuroperitoneal leak complicating peritoneal dialysis: A comparison with conventional diagnostic methods. *Medicine* 2020; 99: e21029.

162. Matsuoka N, Yamaguchi M, Asai A, Kamiya K, Kinashi H, Katsuno T, Kobayashi T, Tamai H, Morinaga T, Obayashi T, Nakabayashi K, Koide S, Nakanishi M, Koyama K, Suzuki Y, Ishimoto T, Mizuno M, Ito Y. The effectiveness and safety of computed tomographic peritoneography and video-assisted thoracic surgery for hydrothorax in peritoneal dialysis patients: A retrospective cohort study in Japan. *PLOS ONE* Public Library of Science; 2020; 15: e0238602.

163. Inanaga R, Oda M, Asahina K, Muraki N, Jimbo M, Shiga K, Hamanaka R, Shinozaki M. The new method to make diagnosis and identify the location of leakage of pleuroperitoneal communication in peritoneal dialysis patients. *CEN Case Rep* 2022; 11: 471–476.

164. Prasad N, Patel MR, Kushwaha R, Behera MR, Yachcha M, Kaul A, Bhadauria D, Kumar S, Gupta A. Modalities of diagnosis and management of peritoneal dialysis-related hydrothorax including videothoracoscopy-assisted repair: A single-center experience. *Indian Journal of Nephrology* 2021; 31: 574.

165. Nemeth A, Mustafi M, Friedel G, Sayer M, Heyne N, Schlensak C, Artunc F, Steger V. Thoracoscopic mesh implantation as a definitive treatment approach for peritoneal dialysis-associated hydrothorax. *Updates Surg* 2022; 74: 2011–2017.

166. Chen H-YM, Chan H-YH, Chan H-MH, Cheung H-L. Surgical management of pleuro-peritoneal fistula in chronic renal failure patient—safety and effectiveness. *Journal of Thoracic Disease* [Internet] AME Publishing Company; 2021 [cited 2022 Sep 15]; 13Available from: https://jtd.amegroups.com/article/view/51126.

32. Benz RL, Schleifer CR. Hydrothorax in Continuous Ambulatory Peritoneal Dialysis: Successful Treatment With Intrapleural Tetracycline and a Review of the Literature. *American Journal of Kidney Diseases* 1985; 5: 136–140.

35. Mak S, Nyunt K, Wong P, Lo K, Tong GMW, Tai Y, Wong AKM. Long-term follow-up of thoracoscopic pleurodesis for hydrothorax complicating peritoneal dialysis. *Ann Thorac Surg* 2002; 74: 218–221.

36. Tang S, Chui WH, Tang AWC, Li FK, Chau WS, Ho YW, Chan TM, Lai KN. Video-assisted thoracoscopic talc pleurodesis is effective for maintenance of peritoneal dialysis in acute hydrothorax complicating peritoneal dialysis. *Nephrol Dial Transplant* 2003; 18: 804–808.

ERS Benign Pleural Effusions Taskforce Heart Failure:

PICO Questions

What are the management options for refractory heart failure related effusions?

P - Patients with refractory heart failure related effusions

I - Pleural interventions (TxAsp/ IPC/ ICD + Slurry/ Poudrage/ VATS), Cardiological interventions (Diuresis, Fluid restriction, CRTD, Valvular surgery, Dialysis)

C - Not required

O - Patient reported outcome measures on QoL, VAS dyspnoea scores, hospital attendance rates, complications from pleural interventions (eg bleeding, infection), complications to planned surgery as a result of pleural interventions (ie due to pleurodesis)

What are the optimal investigations for investigating a unilateral effusion in a patient with known cardiac failure?

P - Patients with known (decompensated) cardiac failure and presenting with a unilateral effusion

I - Stratification to conservative management or invasive diagnostics according to clinical algorithms (using non-invasive tests: serum BNP, TUS)

C - Not required

O - Complications arising from invasive investigations (bleeding, infection, pneumothorax), Outcomes (mortality, risk of circulatory or respiratory failure), delayed diagnosis of clinically relevant differential diagnosis (eg malignant pleural effusion, pleural infection)

Literature search methodology

Search strategies run on 05/08/2022 by Eli Harriss, a librarian at the Bodleian Health Care Libraries, University of Oxford, and updated on 05/06/2023

Methodology

Medline, Ovid Embase, and the Cochrane Central Register of Controlled Trials were searched by an information specialist (EH) on 05/08/2022 and updated on 06/06/2023. The search strategies used text words and relevant indexing to capture relevant literature by combining terms and phrases for Heart Failure and Pleural Effusion. This search strategy uses the Scottish International Guidelines' Network search filter for Diagnostic Studies, available from: https://www.sign.ac.uk/what-we-do/methodology/search-filters/. The full strategies are available below. All references were exported to Endnote 20 (Thomson Reuters, New York, NY), and duplicates were removed using the Deduklick programme developed by Risklick (https://www.risklick.ch/deduklick/) and manually for the updates. The reference lists of included papers were assessed for additional relevant studies, forwards citation searching was conducted via Google Scholar.

Search Strategies

05/08/2022

Medline

((("Heart Failure"[Mesh]) OR ("cardiac failure"[Title/Abstract] OR "heart decompensation"[Title/Abstract] OR "heart failure"[Title/Abstract] OR "myocardial failure"[Title/Abstract])) AND (refractory[Title/Abstract] OR end-stage*[Title/Abstract] OR endstage*[Title/Abstract] OR advanced[Title/Abstract] OR decompensated[Title/Abstract])) AND (("Pleural Effusion"[Mesh]) OR (effusion*[Title/Abstract]))

Database: Embase 1974 to present
Search Strategy:
---
1 ((cardiac* or heart* or myocardial) adj6 (refractory or end-stage* or endstage* or advanced or decompensated)).mp. (47844)
2 exp pleura effusion/ (71050)
3 effusion*.ti,ab,kw. (86119)
4 2 or 3 (118265)
5 1 and 4 (757)

Cochrane Central Register of Controlled Trials
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#1 ((cardiac* or heart* or myocardial) near/6 (refractory or end-stage* or endstage* or advanced or decompensated)):ti,ab,kw 3482
#2 effusion*:ti,ab,kw 4749
#3 #1 and #2 23

05/06/2023 (2022-present only)

Medline

((("Heart Failure"[Mesh]) OR ("cardiac failure"[Title/Abstract] OR "heart decompensation"[Title/Abstract] OR "heart failure"[Title/Abstract] OR "myocardial failure"[Title/Abstract])) AND (refractory[Title/Abstract] OR end-stage*[Title/Abstract] OR endstage*[Title/Abstract] OR advanced[Title/Abstract] OR decompensated[Title/Abstract])) AND (("Pleural Effusion"[Mesh]) OR (effusion*[Title/Abstract])) Filters: **from 2022 - 2023**

Database: Embase 1974 to present

Search Strategy:

1 ((cardiac* or heart* or myocardial) adj6 (refractory or end-stage* or endstage* or advanced or decompensated)).mp. (51798)

2 exp pleura effusion/ (80592)

3 effusion*.ti,ab,kw. (91780)

4 2 or 3 (130444)

5 1 and 4 (859)

6 5 (859)

7 limit 6 to yr="2022 -Current" (136)

Cochrane Central Register of Controlled Trials
Issue 6 of 12, June 2023

#1 ((cardiac* or heart* or myocardial) near/6 (refractory or end-stage* or endstage* or advanced or decompensated)):ti,ab,kw 3709

#2 effusion*:ti,ab,kw 5081

#3 #1 and #2 28

Limited: 2022-2023

Search Results

	Search results 05/08/2022	Search results 05/06/2023 (2022-present only)
Medline	291	41
Ovid Embase	757	136
Cochrane CENTRAL	23	5
Total	1071	182
Total after deduplication	924	
Unique since 05/08/2022		100

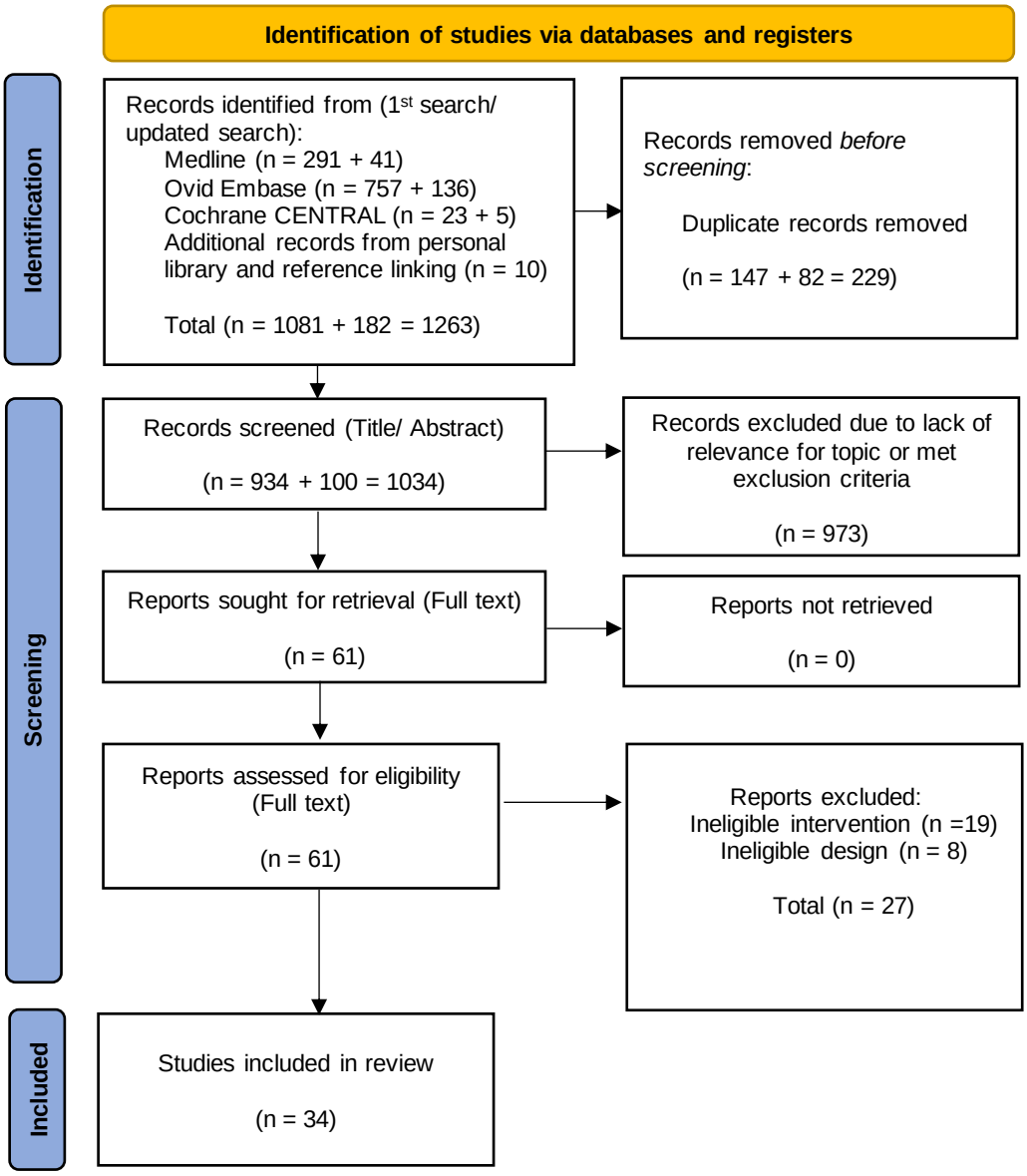
Inclusion/Exclusion criteria

Inclusion criteria	**Exclusion criteria**
Systematic reviews	Case reports (n = 1)
Meta-analysis	Conference abstracts
RCTs	Paediatric studies
Interventional studies (non-randomised)	Animal studies
Observational studies (retrospective or prospective)	
Case series	
Editorials	
Literature and narrative reviews	
Guidelines	

PRISMA Flowchart

What are the management options for refractory heart failure related effusions?

What are the optimal investigations for investigating a unilateral effusion in a patient with known cardiac failure?



From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

Summary of findings (included in manuscript)

In total 1034 studies were screened to identify 34 studies relevant to producing this section. These consisted of 2 editorials or narrative reviews, 2 guidelines, 12 retrospective observational studies, 6 prospective observational studies, 4 non-randomised interventional (comparator) studies, 3 RCTs, 2 Case series, and 3 systematic reviews and meta-analyses (see below).

Full list of included studies with categorisation

56. Walker SP, Bintcliffe O, Keenan E, Stadon L, Evison M, Haris M, Nagarajan T, West A, Ionescu A, Prudon B, Guhan A, Mustafa R, Herre J, Arnold D, Bhatnagar R, Kahan B, Miller RF, Rahman NM, Maskell NA. Randomised trial of indwelling pleural catheters for refractory transudative pleural effusions. *Eur Respir J* 2022; 59: 2101362.

57. Krishnan M, Cheriyath P, Wert Y, Moritz TA. The Untapped Potential of Tunneled Pleural Catheters. *Ann Thorac Surg* 2015; 100: 2055–2057.

58. Harris K, Chalhoub M. The use of a PleurX catheter in the management of recurrent benign pleural effusion: a concise review. *Heart Lung Circ* 2012; 21: 661–665.

59. Chalhoub M, Harris K, Castellano M, Maroun R, Bourjeily G. The use of the PleurX catheter in the management of non-malignant pleural effusions. *Chron Respir Dis* SAGE Publications Ltd STM; 2011; 8: 185–191.

60. Patil M, Dhillon SS, Attwood K, Saoud M, Alraiyes AH, Harris K. Management of Benign Pleural Effusions Using Indwelling Pleural Catheters: A Systematic Review and Meta-analysis. *Chest* 2017; 151: 626–635.

61. Frost N, Ruwwe-Glösenkamp C, Raspe M, Brünger M, Temmesfeld-Wollbrück B, Suttorp N, Witzenrath M. Indwelling pleural catheters for non-malignant pleural effusions: report on a single centre's 10 years of experience. *BMJ Open Respir Res* 2020; 7: e000501.

62. Murthy SC, Okereke I, Mason DP, Rice TW. A simple solution for complicated pleural effusions. *J Thorac Oncol* 2006; 1: 697–700.

63. Aboudara M, Maldonado F. Indwelling pleural catheters for benign pleural effusions: what is the evidence? *Curr Opin Pulm Med* 2019/03/14 ed. 2019; 25: 369–373.

64. Majid A, Kheir F, Fashjian M, Chatterji S, Fernandez-Bussy S, Ochoa S, Cheng G, Folch E. Tunneled pleural catheter placement with and without talc poudrage for treatment of pleural effusions due to congestive heart failure. *Annals of the American Thoracic Society* 2016; 13: 212–216.

65. Bhatnagar R, Reid ED, Corcoran JP, Bagenal JD, Pope S, Clive AO, Zahan-Evans N, Froeschle PO, West D, Rahman NM, Chatterji S, Sivasothy PR, Maskell NA. Indwelling pleural catheters for non-malignant effusions: a multicentre review of practice. *Thorax* BMJ Publishing Group Ltd; 2014; 69: 959–961.

66. Freeman RK, Ascioti AJ, Dake M, Mahidhara RS. A propensity-matched comparison of pleurodesis or tunneled pleural catheter for heart failure patients with recurrent pleural effusion. *Ann Thorac Surg* 2014/04/15 ed. 2014; 97: 1872–1876; discussion 1876-7.

67. Srour N, Potechin R, Amjadi K. Use of Indwelling Pleural Catheters for Cardiogenic Pleural Effusions. *Chest* 2013/06/29 ed. 2013; 144: 1603–1608.

68. Herlihy JP, Loyalka P, Gnananandh J, Gregoric ID, Dahlberg CGW, Kar B, Delgado III RM. PleurX® catheter for the management of refractory pleural effusions in congestive heart failure. *Tex. Heart Inst. J.* 2009; 36: 38–43.

69. Li P, Hosseini S, Zhang T, Amjadi K. Clinical Predictors of Successful and Earlier Removal of Indwelling Pleural Catheters in Benign Pleural Effusions. *RES* Karger Publishers; 2019; 98: 239–245.

70. Lazarevic A, Dobric M, Goronja B, Trninic D, Krivokuca S, Jovanic J, Picano E. Lung ultrasound-guided therapeutic thoracentesis in refractory congestive heart failure. *Acta Cardiol* 2020; 75: 398–405.

71. Ekpe EE, Essien IO, Idongesit U. Significant pleural effusion in congestive heart failure necessitating pleural drainage. *Nigerian Journal of Cardiology* 2015; 12: 106–110.

76. Steger V, Mika U, Toomes H, Walker T, Engel C, Kyriss T, Ziemer G, Friedel G. Who gains most? A 10-year experience with 611 thoracoscopic talc pleurodeses. *Ann Thorac Surg* 2007; 83: 1940–1945.

77. Glazer M, Berkman N, Lafair JS, Kramer MR. Successful talc slurry pleurodesis in patients with nonmalignant pleural effusion. *Chest* 2000; 117: 1404–1409.

78. Little AG, Kadowaki MH, Ferguson MK, Staszek VM, Skinner DB. Pleuro-peritoneal shunting. Alternative therapy for pleural effusions. *Ann Surg* 1988; 208: 443–450.

79. Artemiou O, Marta G-M, Klepetko W, Wolner E, Müller M-R. Pleurovenous shunting in the treatment of nonmalignant pleural effusion. *Ann Thorac Surg* 2003; 76: 231–233.

80. Morales-Rull JL, Bielsa S, Conde-Martel A, Aramburu-Bodas O, Llàcer P, Quesada MA, Suárez-Pedreira I, Manzano L, Barquero MM-P, Porcel JM, RICA Investigators group. Pleural effusions in acute decompensated heart failure: Prevalence and prognostic implications. *Eur J Intern Med* 2018; 52: 49–53.

82. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, Burri H, Butler J, Čelutkienė J, Chioncel O, Cleland JGF, Coats AJS, Crespo-Leiro MG, Farmakis D, Gilard M, Heymans S, Hoes AW, Jaarsma T, Jankowska EA, Lainscak M, Lam CSP, Lyon AR, McMurray JJV, Mebazaa A, Mindham R, Muneretto C, Francesco Piepoli M, Price S, Rosano GMC, Ruschitzka F, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2021; 42: 3599–3726.

85. Rosmini S, Seraphim A, Knott K, Brown JT, Knight DS, Zaman S, Cole G, Sado D, Captur G, Gomes AC, Zemrak F, Treibel TA, Cash L, Culotta V, O'Mahony C, Kellman P, Moon JC, Manisty C. Non-invasive characterization of pleural and pericardial effusions using T1 mapping by magnetic resonance imaging. *Eur Heart J Cardiovasc Imaging* 2022; 23: 1117–1126.

86. Li H, Chen J, Hu P-X. Cardiopulmonary ultrasound correlates of pleural effusions in patients with congestive heart failure. *BMC Cardiovasc Disord* 2022; 22: 198.

87. Via G, Hussain A, Wells M, Reardon R, ElBarbary M, Noble VE, Tsung JW, Neskovic AN, Price S, Oren-Grinberg A, Liteplo A, Cordioli R, Naqvi N, Rola P, Poelaert J, Guliĉ TG, Sloth E, Labovitz A, Kimura B, Breitkreutz R, Masani N, Bowra J, Talmor D, Guarracino F, Goudie A, Xiaoting W, Chawla R, Galderisi M, Blaivas M, Petrovic T, et al. International evidence-based recommendations for focused cardiac ultrasound. *J Am Soc Echocardiogr* 2014; 27: 683.e1-683.e33.

88. Maw AM, Hassanin A, Ho PM, McInnes MDF, Moss A, Juarez-Colunga E, Soni NJ, Miglioranza MH, Platz E, DeSanto K, Sertich AP, Salame G, Daugherty SL. Diagnostic Accuracy of Point-of-Care Lung Ultrasonography and Chest Radiography in Adults With Symptoms Suggestive of Acute Decompensated Heart Failure: A Systematic Review and Meta-analysis. *JAMA Netw Open* 2019; 2: e190703.

89. Miger KC, Fabricius-Bjerre A, Maschmann CP, Wamberg J, Winkler Wille MM, Abild-Nielsen AG, Pedersen L, Lawaetz Schultz HH, Damm Nybing J, Nielsen OW. Clinical Applicability of Lung Ultrasound Methods in the Emergency Department to Detect Pulmonary Congestion on Computed Tomography. *Ultraschall Med* 2021; 42: e21–e30.

90. Kataoka H, Takada S. The role of thoracic ultrasonography for evaluation of patients with decompensated chronic heart failure. *J Am Coll Cardiol* 2000; 35: 1638–1646.

91. Gallard E, Redonnet J-P, Bourcier J-E, Deshaies D, Largeteau N, Amalric J-M, Chedaddi F, Bourgeois J-M, Garnier D, Geeraerts T. Diagnostic performance of cardiopulmonary ultrasound performed by the emergency physician in the management of acute dyspnea. *Am J Emerg Med* 2015; 33: 352–358.

92. Pivetta E, Goffi A, Lupia E, Tizzani M, Porrino G, Ferreri E, Volpicelli G, Balzaretti P, Banderali A, Iacobucci A, Locatelli S, Casoli G, Stone MB, Maule MM, Baldi I, Merletti F, Cibinel GA, Baron P, Battista S, Buonafede G, Busso V, Conterno A, Del Rizzo P, Ferrera P, Pecetto PF, Moiraghi C, Morello F, Steri F, Ciccone G, Calasso C, et al. Lung Ultrasound-Implemented Diagnosis of Acute Decompensated Heart Failure in the ED: A SIMEU Multicenter Study. *Chest* 2015; 148: 202–210.

93. Arvig MD, Laursen CB, Jacobsen N, Gæde PH, Lassen AT. Monitoring patients with acute dyspnea with serial point-of-care ultrasound of the inferior vena cava (IVC) and the lungs (LUS): a systematic review. *J Ultrasound* 2022; 25: 547–561.

94. Anderson KL, Jenq KY, Fields JM, Panebianco NL, Dean AJ. Diagnosing heart failure among acutely dyspneic patients with cardiac, inferior vena cava, and lung ultrasonography. *Am J Emerg Med* 2013; 31: 1208–1214.

99. Torres-Macho J, Cerqueiro-González JM, Arévalo-Lorido JC, Llácer-Iborra P, Cepeda-Rodrigo JM, Cubo-Romano P, Casas-Rojo JM, Ruiz-Ortega R, Manzano-Espinosa L, Lorenzo-Villalba N, Méndez-Bailón M. The Effects of a Therapeutic Strategy Guided by Lung Ultrasound on 6-Month Outcomes in Patients with Heart Failure: Results from the EPICC Randomized Controlled Trial. *J Clin Med* 2022; 11: 4930.

100. Araiza-Garaygordobil D, Gopar-Nieto R, Martinez-Amezcua P, Cabello-López A, Alanis-Estrada G, Luna-Herbert A, González-Pacheco H, Paredes-Paucar CP, Sierra-Lara MD, Briseño-De la Cruz JL, Rodriguez-Zanella H, Martinez-Rios MA, Arias-Mendoza A. A randomized controlled trial of lung ultrasound-guided therapy in heart failure (CLUSTER-HF study). *Am Heart J* 2020; 227: 31–39.

ERS Benign Effusions Taskforce: Hepatic Hydrothorax

PICO Questions

What are the therapeutic options in patients with symptomatic refractory hepatic hydrothorax (HH)?

P - Patients with decompensated chronic liver disease, who are eligible for liver transplant and have refractory hepatic hydrothorax

I - Pleural interventions (TxAsp/ IPC/ ICD + Slurry/ Poudrage/ VATS), Hepatological interventions (TIPS, Albumin infusion, Abdominal paracentesis, Diuresis)

C - Not required

O - Dyspnea, Quality of life, Need for re-intervention, Hospital LoS, Survival

Complications

Literature search methodology

Search strategies run on 09/07/2022 by Eli Harriss, a librarian at the Bodleian Health Care Libraries, University of Oxford, and updated on 08/06/2023.

Methodology

Medline, Ovid Embase, and the Cochrane Central Register of Controlled Trials were searched by an information specialist (EH) on 09/07/2022 and were updated on 08/06/2023. The search strategies used text words and relevant indexing to capture relevant literature about chronic liver disease, pleural effusion and pleural intervention, with results limited to exclude case reports, paediatric studies, and were limited by language to English only. The full strategies are available in the appendix. All references were exported to Endnote X9 (Thomson Reuters, New York, NY), and duplicates were removed using the Deduklick programme developed by Risklick (https://www.risklick.ch/deduklick/). The reference lists of included papers were assessed for additional relevant studies, forwards citation searching was conducted via Google Scholar.

Search Strategies

09/07/2022

Medline

((((((((("Liver Failure"[Mesh:NoExp]) OR "End Stage Liver Disease"[Mesh]) OR "Liver Cirrhosis"[Mesh]) OR "Hypertension, Portal"[Mesh]) OR ("Liver Transplantation"[Mesh])) OR (("end-stage liver disease"[Title/Abstract] OR cirrhosis[Title/Abstract] OR "liver fibrosis"[Title/Abstract] OR "portal hypertension"[Title/Abstract] OR "chronic liver disease*"[Title/Abstract] OR "decompensated liver disease*"[Title/Abstract]) OR ("non-malignant effusion*"[Title/Abstract] OR "benign effusion*"[Title/Abstract] OR "liver transplant*"[Title/Abstract] OR "liver graft*"[Title/Abstract] OR "hepatic transplant*"[Title/Abstract] OR "liver failure"[Title/Abstract]))) AND ((("Hydrothorax"[Mesh]) OR "Pleural Effusion"[Mesh]) OR (hydrothorax[Title/Abstract] OR "pleural effusion*"[Title/Abstract]))) AND ((((((((((("Thoracentesis"[Mesh]) OR "Chest Tubes"[Mesh]) OR "Pleurodesis"[Mesh]) OR "Thoracic Surgery, Video-Assisted"[Mesh]) OR "Portasystemic Shunt, Transjugular Intrahepatic"[Mesh]) OR "Paracentesis"[Mesh:NoExp]) OR "Diuresis"[Mesh]) OR "Albumins"[Mesh]) OR ("therapy" [Subheading] OR "Therapeutics"[Mesh])) OR "Palliative Care"[Mesh]) OR (Thoracentes*[Title/Abstract] OR "pleural aspiration*"[Title/Abstract] OR "chest aspiration*"[Title/Abstract] OR Thoracocentes*[Title/Abstract] OR Pleurocentes*[Title/Abstract] OR "indwelling pleural catheter*"[Title/Abstract] OR "intercostal catheter*"[Title/Abstract] OR "chest drain*"[Title/Abstract] OR "chest tube*"[Title/Abstract] OR pleurodesis[Title/Abstract] OR VATS*[Title/Abstract] OR "video-assisted thoracic surger*"[Title/Abstract] OR TIPS[Title/Abstract] OR TIPSS[Title/Abstract] OR "Transjugular Intrahepatic Portasystemic Shunt*"[Title/Abstract] OR paracentes*[Title/Abstract] OR "puncture and aspiration*"[Title/Abstract] OR centesis[Title/Abstract] OR centeses[Title/Abstract] OR "puncture and drainage"[Title/Abstract] OR culdocentes*[Title/Abstract] OR diuresis[Title/Abstract] OR diureses[Title/Abstract] OR albumin*[Title/Abstract] OR "diaphragmatic defect repair*"[Title/Abstract] OR "thoracoscopic repair*"[Title/Abstract] OR management[Title/Abstract] OR treat*[Title/Abstract] OR therap*[Title/Abstract] OR palliat*[Title/Abstract]))) NOT ("case report*"[Text Word] OR child*[Text Word] OR paediatr*[Text Word] OR pediatr*[Text Word]) Filters applied: English

Database: Embase 1974 to present
Search Strategy:

---

1 liver failure/ or chronic liver failure/ or end stage liver disease/ (54399)
2 exp liver cirrhosis/ (176978)
3 exp portal hypertension/ (35211)
4 exp liver transplantation/ (129930)
5 ("end-stage liver disease" or cirrhosis or "liver fibrosis" or "portal hypertension" or "chronic liver disease*" or "decompensated liver disease*" or "non-malignant effusion*" or "benign effusion*" or "liver transplant*" or "liver graft*" or "hepatic transplant*" or "liver failure").ti,ab. (317848)
6 1 or 2 or 3 or 4 or 5 (401996)
7 hydrothorax/ (4610)
8 exp pleura effusion/ (70722)
9 (hydrothorax or "pleural effusion*").ti,ab. (44860)

10 7 or 8 or 9 (81275)
11 thoracocentesis/ (10451)
12 exp chest tube/ (12403)
13 pleurodesis/ (5943)
14 video assisted thoracoscopic surgery/ (15024)
15 transjugular intrahepatic portosystemic shunt/ (5110)
16 paracentesis/ (9003)
17 exp diuresis/ (31169)
18 exp albuminoid/ (278217)
19 exp therapy/ (9579379)
20 exp palliative therapy/ (128543)
21 (Thoracentes* or "pleural aspiration*" or "chest aspiration*" or Thoracocentes* or Pleurocentes* or "indwelling pleural catheter*" or "intercostal catheter*" or "chest drain*" or "chest tube*" or pleurodesis or VATS* or "video-assisted thoracic surger*" or "video assisted thoracoscopic surger*" or TIPS or TIPSS or "Transjugular Intrahepatic Portasystemic Shunt*" or paracentes* or "puncture and aspiration*" or centesis or centeses or "puncture and drainage" or culdocentes* or diuresis or diureses or albumin* or "diaphragmatic defect repair*" or "thoracoscopic repair*" or management or treat* or therap* or palliat*).ti,ab. (11543993)
22 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 (15813995)
23 6 and 10 and 22 (4018)
24 ("case report*" or child* or pediatr* or paediatr*).ti,ab,kw. (2765641)
25 23 not 24 (3047)
26 25 (3047)
27 limit 26 to english language (2882)

Cochrane Database of Systematic Reviews
Issue 7 of 12, July 2022
Cochrane Central Register of Controlled Trials
Issue 7 of 12, July 2022
#1 ("end-stage liver disease" or cirrhosis or "liver fibrosis" or "portal hypertension" or "chronic liver disease*" or "decompensated liver disease*" or "non-malignant effusion*" or "benign effusion*" or "liver transplant*" or "liver graft*" or "hepatic transplant*" or "liver failure"):ti,ab,kw 15798
#2 (hydrothorax or "pleural effusion*"):ti,ab,kw 1700
#3 (Thoracentes* or "pleural aspiration*" or "chest aspiration*" or Thoracocentes* or Pleurocentes* or "indwelling pleural catheter*" or "intercostal catheter*" or "chest drain*" or "chest tube*" or pleurodesis or VATS* or "video-assisted thoracic surger*" or "video assisted thoracoscopic surger*" or TIPS or TIPSS or "Transjugular Intrahepatic Portasystemic Shunt*" or paracentes* or "puncture and aspiration*" or centesis or centeses or "puncture and drainage" or culdocentes* or diuresis or diureses or albumin* or "diaphragmatic defect repair*" or "thoracoscopic repair*" or management or treat* or therap* or palliat*):ti,ab,kw 1215971
#4 #1 and #2 and #3 51

08/06/2023 (2022 – present only)

Medline

((((((((("Liver Failure"[Mesh:NoExp]) OR "End Stage Liver Disease"[Mesh]) OR "Liver Cirrhosis"[Mesh]) OR "Hypertension, Portal"[Mesh]) OR ("Liver Transplantation"[Mesh])) OR (("end-stage liver disease"[Title/Abstract] OR cirrhosis[Title/Abstract] OR "liver fibrosis"[Title/Abstract] OR "portal hypertension"[Title/Abstract] OR "chronic liver disease*"[Title/Abstract] OR "decompensated liver disease*"[Title/Abstract]) OR ("non-malignant effusion*"[Title/Abstract] OR "benign effusion*"[Title/Abstract] OR "liver transplant*"[Title/Abstract] OR "liver graft*"[Title/Abstract] OR "hepatic transplant*"[Title/Abstract] OR "liver failure"[Title/Abstract]))) AND ((("Hydrothorax"[Mesh]) OR "Pleural Effusion"[Mesh]) OR (hydrothorax[Title/Abstract] OR "pleural effusion*"[Title/Abstract]))) AND ((((((((((("Thoracentesis"[Mesh]) OR "Chest Tubes"[Mesh]) OR "Pleurodesis"[Mesh]) OR "Thoracic Surgery, Video-Assisted"[Mesh]) OR "Portasystemic Shunt, Transjugular Intrahepatic"[Mesh]) OR "Paracentesis"[Mesh:NoExp]) OR "Diuresis"[Mesh]) OR "Albumins"[Mesh]) OR ("therapy" [Subheading] OR "Therapeutics"[Mesh])) OR "Palliative Care"[Mesh]) OR (Thoracentes*[Title/Abstract] OR "pleural aspiration*"[Title/Abstract] OR "chest aspiration*"[Title/Abstract] OR Thoracocentes*[Title/Abstract] OR Pleurocentes*[Title/Abstract] OR "indwelling pleural catheter*"[Title/Abstract] OR "intercostal catheter*"[Title/Abstract] OR "chest drain*"[Title/Abstract] OR "chest tube*"[Title/Abstract] OR pleurodesis[Title/Abstract] OR VATS*[Title/Abstract] OR "video-assisted thoracic surger*"[Title/Abstract] OR TIPS[Title/Abstract] OR TIPSS[Title/Abstract] OR "Transjugular Intrahepatic Portasystemic Shunt*"[Title/Abstract] OR paracentes*[Title/Abstract] OR "puncture and aspiration*"[Title/Abstract] OR centesis[Title/Abstract] OR centeses[Title/Abstract] OR "puncture and drainage"[Title/Abstract] OR culdocentes*[Title/Abstract] OR diuresis[Title/Abstract] OR diureses[Title/Abstract] OR albumin*[Title/Abstract] OR "diaphragmatic defect repair*"[Title/Abstract] OR "thoracoscopic repair*"[Title/Abstract] OR management[Title/Abstract] OR treat*[Title/Abstract] OR therap*[Title/Abstract] OR palliat*[Title/Abstract]))) NOT ("case report*"[Text Word] OR child*[Text Word] OR paediatr*[Text Word] OR pediatr*[Text Word]) Filters: **English, from 2022 - 2023** Sort by: **Most Recent**

Database: Embase 1974 to present

Link to search history:

https://ovidsp.ovid.com/ovidweb.cgi?T=JS&NEWS=N&PAGE=main&SHAREDSEARCHID=3VQfHdqQsQQ0EA1RWjPGbyvW9mAmJLSE0FRJ1DlatsN9wn6JZ4IInd07s1iYcKuBe

Search Strategy:

1 liver failure/ or chronic liver failure/ or end stage liver disease/ (58159)

2 exp liver cirrhosis/ (191310)

3 exp portal hypertension/ (37572)

4 exp liver transplantation/ (139615)

5 ("end-stage liver disease" or cirrhosis or "liver fibrosis" or "portal hypertension" or "chronic liver disease*" or "decompensated liver disease*" or "non-malignant effusion*" or "benign effusion*" or "liver transplant*" or "liver graft*" or "hepatic transplant*" or "liver failure").ti,ab. (343836)

6 1 or 2 or 3 or 4 or 5 (433995)
7 hydrothorax/ (4937)
8 exp pleura effusion/ (80643)
9 (hydrothorax or "pleural effusion*").ti,ab. (47974)
10 7 or 8 or 9 (91495)
11 thoracocentesis/ (11337)
12 exp chest tube/ (14452)
13 pleurodesis/ (6306)
14 video assisted thoracoscopic surgery/ (16601)
15 transjugular intrahepatic portosystemic shunt/ (5798)
16 paracentesis/ (9732)
17 exp diuresis/ (32974)
18 exp albuminoid/ (301933)
19 exp therapy/ (10310516)
20 exp palliative therapy/ (141081)
21 (Thoracentes* or "pleural aspiration*" or "chest aspiration*" or Thoracocentes* or Pleurocentes* or "indwelling pleural catheter*" or "intercostal catheter*" or "chest drain*" or "chest tube*" or pleurodesis or VATS* or "video-assisted thoracic surger*" or "video assisted thoracoscopic surger*" or TIPS or TIPSS or "Transjugular Intrahepatic Portasystemic Shunt*" or paracentes* or "puncture and aspiration*" or centesis or centeses or "puncture and drainage" or culdocentes* or diuresis or diureses or albumin* or "diaphragmatic defect repair*" or "thoracoscopic repair*" or management or treat* or therap* or palliat*).ti,ab. (12476118)
22 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 (17007083)
23 6 and 10 and 22 (4408)
24 ("case report*" or child* or pediatr* or paediatr*).ti,ab,kw. (2983777)
25 23 not 24 (3331)
26 25 (3331)
27 limit 26 to english language (3148)
28 27 (3148)
29 limit 28 to yr="2022 -Current" (294)

Cochrane Central Register of Controlled Trials
Issue 6 of 12, June 2023

#1 ("end-stage liver disease" or cirrhosis or "liver fibrosis" or "portal hypertension" or "chronic liver disease*" or "decompensated liver disease*" or "non-malignant effusion*" or "benign effusion*" or "liver transplant*" or "liver graft*" or "hepatic transplant*" or "liver failure"):ti,ab,kw 17025

#2 (hydrothorax or "pleural effusion*"):ti,ab,kw 1856

#3 (Thoracentes* or "pleural aspiration*" or "chest aspiration*" or Thoracocentes* or Pleurocentes* or "indwelling pleural catheter*" or "intercostal catheter*" or "chest drain*" or "chest tube*" or pleurodesis or VATS* or "video-assisted thoracic surger*" or "video assisted thoracoscopic surger*" or TIPS or TIPSS or "Transjugular Intrahepatic Portasystemic Shunt*" or paracentes* or "puncture and aspiration*" or centesis or centeses or "puncture and drainage" or culdocentes* or

diuresis or diureses or albumin* or "diaphragmatic defect repair*" or "thoracoscopic repair*" or management or treat* or therap* or palliat*):ti,ab,kw 1311697
#4 #1 and #2 and #3 54
2022-2023

Search Results

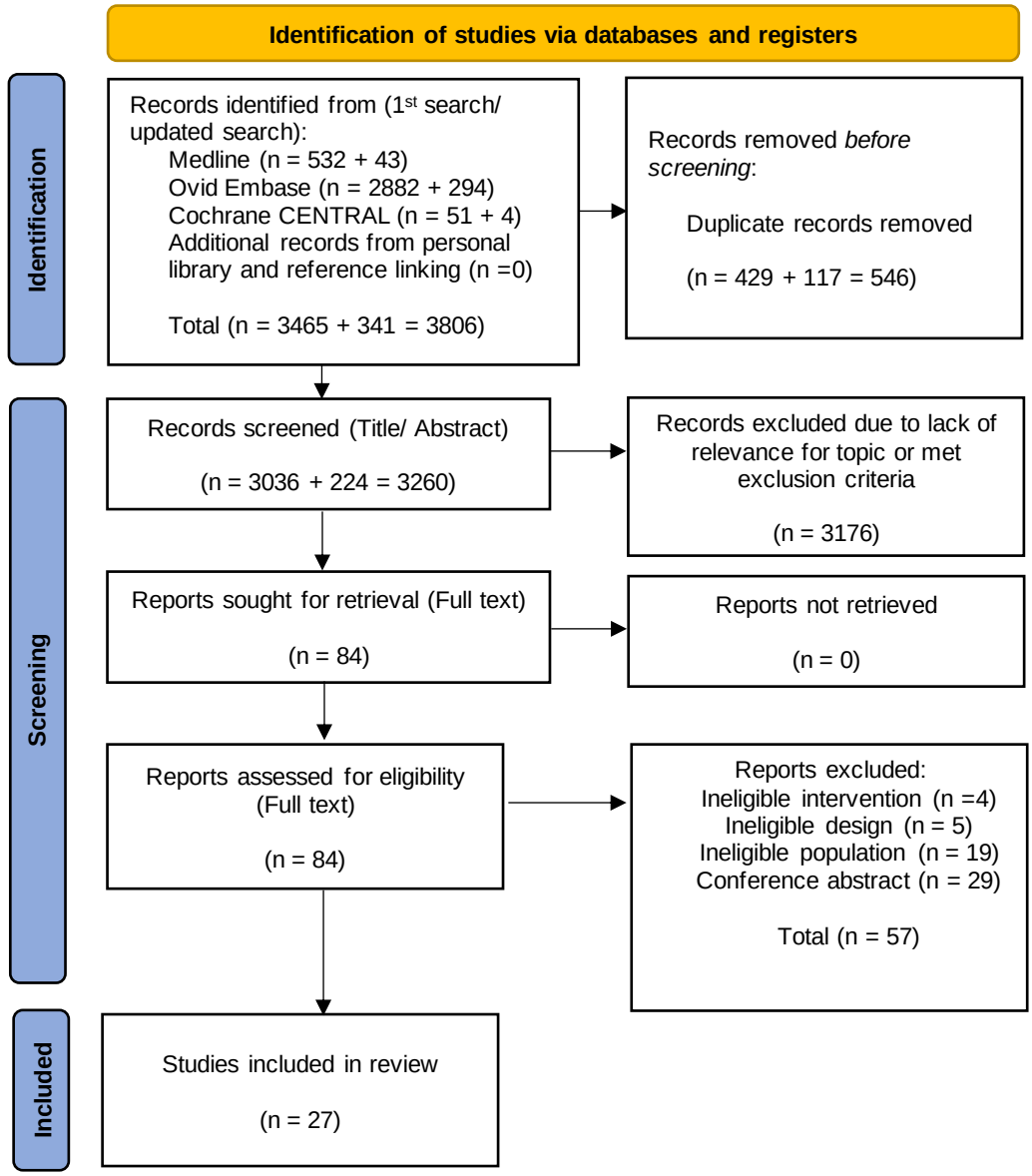
	Search results 09/07/2022	Search results 08/06/2023 (2022-present only)
Medline	532	43
Ovid Embase	2882	294
Cochrane CENTRAL	51	4
Total	3465	341
Total after deduplication	3026	
Unique since 09/07/2022		224

Inclusion/Exclusion criteria

Inclusion criteria	**Exclusion criteria**
Systematic reviews	Case reports (n = 1)
Meta-analysis	Conference abstracts
RCTs	Paediatric studies
Interventional studies (non-randomised)	Animal studies
Observational studies (retrospective or prospective)	
Case series	
Editorials	
Literature and narrative reviews	
Guidelines	

PRISMA Flowchart

What are the therapeutic options in patients with symptomatic refractory hepatic hydrothorax (HH)?



From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

Summary of findings (included in manuscript)

In total 3260 studies were screened to identify 27 studies relevant to producing this section. These consisted of 3 editorials or narrative reviews, 19 retrospective observational studies, 1 prospective observational study,
, 1 RCT, (see below).

Full list of included studies with categorisation

56. Walker SP, Bintcliffe O, Keenan E, Stadon L, Evison M, Haris M, Nagarajan T, West A, Ionescu A, Prudon B, Guhan A, Mustafa R, Herre J, Arnold D, Bhatnagar R, Kahan B, Miller RF, Rahman NM, Maskell NA. Randomised trial of indwelling pleural catheters for refractory transudative pleural effusions. *Eur Respir J* 2022; 59: 2101362.

102. Walker SP, Morley AJ, Stadon L, De Fonseka D, Arnold DT, Medford ARL, Maskell NA. Nonmalignant Pleural Effusions: A Prospective Study of 356 Consecutive Unselected Patients. *Chest* 2017; 151: 1099–1105.

103. Singh A, Bajwa A, Shujaat A. Evidence-based review of the management of hepatic hydrothorax. *Respiration* 2013; 86: 155–173.

104. Hung T-H, Tseng C-W, Tsai C-C, Hsieh Y-H, Tseng K-C, Tsai C-C. Mortality Following Catheter Drainage Versus Thoracentesis in Cirrhotic Patients with Pleural Effusion. *Dig Dis Sci* 2017; 62: 1080–1085.

105. O'Leary JG, Rajender Reddy K, Tandon P, Biggins SW, Wong F, Kamath PS, Garcia-Tsao G, Maliakkal B, Lai JC, Fallon M, Vargas HE, Thuluvath P, Subramanian R, Thacker LR, Bajaj JS. Increased Risk of ACLF and Inpatient Mortality in Hospitalized Patients with Cirrhosis and Hepatic Hydrothorax. *Dig Dis Sci* 2021; 66: 3612–3618.

106. Castellote J, Xiol X, Cortés-Beut R, Tremosa G, Rodríguez E, Vázquez S. Complications of thoracentesis in cirrhotic patients with pleural effusion. *Rev Esp Enferm Dig* 2001; 93: 566–575.

107. Shojaee S, Khalid M, Kallingal G, Kang L, Rahman N. Repeat Thoracentesis in Hepatic Hydrothorax and Non-Hepatic Hydrothorax Effusions: A Case-Control Study. *Respiration* 2018; 96: 330–337.

108. Adlakha N, Russo MW. Outcomes After Transjugular Intrahepatic Portosystemic Shunt in Cirrhotic Patients 70 Years and Older. *J Clin Med* 2020; 9: 381.

109. Badillo R, Rockey DC. Hepatic hydrothorax: clinical features, management, and outcomes in 77 patients and review of the literature. *Medicine (Baltimore)* 2014; 93: 135–142.

110. Bisht RU, Liu MC, Koblinski JE, Kang P, Wong MN, Little EC. Is 70 the new 50? Complications and outcomes of transjugular intrahepatic portosystemic shunt in older versus younger patients. *Abdom Radiol (NY)* 2021; 46: 2789–2794.

111. Dhanasekaran R, West JK, Gonzales PC, Subramanian R, Parekh S, Spivey JR, Martin LG, Kim HS. Transjugular intrahepatic portosystemic shunt for symptomatic refractory hepatic hydrothorax in patients with cirrhosis. *Am J Gastroenterol* 2010; 105: 635–641.

112. Jindal A, Mukund A, Kumar G, Sarin SK. Efficacy and safety of transjugular intrahepatic portosystemic shunt in difficult-to-manage hydrothorax in cirrhosis. *Liver Int* 2019; 39: 2164–2173.

113. Young S, Bermudez J, Zhang L, Rostambeigi N, Golzarian J. Transjugular intrahepatic portosystemic shunt (TIPS) placement: A comparison of outcomes between patients with hepatic hydrothorax and patients with refractory ascites. *Diagn Interv Imaging* 2019; 100: 303–308.

114. Deltenre P, Zanetto A, Saltini D, Moreno C, Schepis F. The role of transjugular intrahepatic portosystemic shunt in patients with cirrhosis and ascites: Recent evolution and open questions. *Hepatology* 2023; 77: 640–658.

115. Mahmoud EM, Anwar MIA. Comparison of tigecycline and bleomycin pleurodesis by pigtail catheter in hepatic hydrothorax with liver cirrhosis. *The Egyptian Journal of Chest Diseases and Tuberculosis* 2020; 69: 98.

116. Lee WJ, Kim HJ, Park JH, Park DI, Cho YK, Sohn CI, Jeon WK, Kim BI. Chemical pleurodesis for the management of refractory hepatic hydrothorax in patients with decompensated liver cirrhosis. *Korean J Hepatol* 2011; 17: 292–298.

118. Kniese C, Diab K, Ghabril M, Bosslet G. Indwelling Pleural Catheters in Hepatic Hydrothorax: A Single-Center Series of Outcomes and Complications. *Chest* 2019; 155: 307–314.

119. Shojaee S, Rahman N, Haas K, Kern R, Leise M, Alnijoumi M, Lamb C, Majid A, Akulian J, Maldonado F, Lee H, Khalid M, Stravitz T, Kang L, Chen A. Indwelling Tunneled Pleural Catheters for Refractory Hepatic Hydrothorax in Patients With Cirrhosis: A Multicenter Study. *Chest* 2019; 155: 546–553.

120. Alhabeeb FF, Carle-Talbot K, Rakocevic N, Zhang T, Mitchell M, Amjadi K, Kwok C. Indwelling tunneled pleural catheters in patients with hepatic hydrothorax: A single-center analysis for outcomes and complications. *Canadian Journal of Respiratory, Critical Care, and Sleep Medicine* Taylor & Francis; 2023; 7: 4–9.

121. Romero S, Lim AK, Singh G, Kodikara C, Shingaki-Wells R, Chen L, Hui S, Robertson M. Natural history and outcomes of patients with liver cirrhosis complicated by hepatic hydrothorax. *World J Gastroenterol* 2022; 28: 5175–5187.

122. Han S-K, Kang S-H, Kim M-Y, Na S-K, Kim T, Lee M, Jun B-G, Kim T-S, Choi D-H, Suk K-T, Kim Y-D, Cheon G-J, Yim H-J, Kim D-J, Baik S-K. Outcome of Intermittent Thoracentesis versus Pigtail Catheter Drainage for Hepatic Hydrothorax. *J Clin Med* 2022; 11: 7221.

124. Assouad J, Barthes FLP, Shaker W, Souilamas R, Riquet M. Recurrent pleural effusion complicating liver cirrhosis. *Ann Thorac Surg* 2003; 75: 986–989.

126. Milanez de Campos JR, Filho LO, de Campos Werebe E, Sette H, Fernandez A, Filomeno LT, Jatene FB. Thoracoscopy and talc poudrage in the management of hepatic hydrothorax. *Chest* 2000; 118: 13–17.

127. Xiol X, Tremosa G, Castellote J, Gornals J, Lama C, Lopez C, Figueras J. Liver transplantation in patients with hepatic hydrothorax. *Transpl Int* 2005; 18: 672–675.

ERS Benign pleural effusions Taskforce: Post-surgical

PICO Question

Optimal treatment of post-surgical pleural effusions: thoracentesis/chest drain vs. conservative treatment.

P – Adults (>18 years of age) with post-surgical pleural effusions after cardiac or thoracic surgery

I – Effusion drainage by thoracentesis or chest drain insertion

C – Medical management or observation

O – Re-admission, length of stay, symptom scores, recurrence of effusion, radiological improvement, complications, quality of life, mortality

Literature search methodology

Search strategies run on 29/09/2022 by Eli Harriss, a librarian at the Bodleian Health Care Libraries, University of Oxford, and updated on 08/06/2023.

Methodology

Medline, Ovid Embase, and the Cochrane Central Register of Controlled Trials were searched by an information specialist (EH) on 29/09/2022 and updated on 08/06/2023. The search strategies used text words and relevant indexing to capture relevant records by combining terms and phrases for treatments for post-surgical pleural effusion. No limits were applied. The full strategies are available below. All references were exported to Endnote 20 (Thomson Reuters, New York, NY), and duplicates were removed using the Deduklick programme developed by Risklick (https://www.risklick.ch/deduklick/). The reference lists of included papers were assessed for additional relevant studies, forwards citation searching was conducted via Google Scholar.

Search Strategies

29/09/2022

Medline

((((("Pleural Effusion"[Mesh]) OR ("pleural effusion*"[Title/Abstract] OR "pleura effusion*"[Title/Abstract])) AND (("Postoperative Period"[Mesh]) OR (post-surg*[Title/Abstract] OR postoperat*[Title/Abstract] OR post-operat*[Title/Abstract]))) AND (("Thoracentesis"[Mesh]) OR (thoracocentes*[Title/Abstract] OR thoracentes*[Title/Abstract] OR pleurocentes*[Title/Abstract] OR aspiration*[Title/Abstract] OR "drain insert*"[Title/Abstract] OR "intercostal drain*"[Title/Abstract] OR "indwelling pleural catheter*"[Title/Abstract]))) AND ((("Thoracic Surgical Procedures"[Mesh]) OR "Thoracic Surgery"[Mesh]) OR ((thoracic*[Title/Abstract] OR cardiac*[Title/Abstract] OR heart*[Title/Abstract] OR cardiothoracic*[Title/Abstract] OR chest*[Title/Abstract] OR thorax*[Title/Abstract] OR cardiac-thoracic*[Title/Abstract]) OR (cardio-thoracic*[Title/Abstract])))

Database: Embase 1974 to present
Search Strategy:
---

1 exp pleura effusion/ (72033)
2 "pleura* effusion*".ti,ab,kw. (44406)
3 1 or 2 (79504)
4 exp postoperative period/ (577929)
5 (post-surg* or postoperat* or post-operat*).ti,ab,kw. (989689)
6 4 or 5 (1321843)
7 thoracocentesis/ (10653)
8 (thoracocentes* or thoracentes* or pleurocentes* or aspiration* or "drain insert*" or "intercostal drain*" or "indwelling pleural catheter*").ti,ab,kw. (143708)
9 7 or 8 (148977)
10 exp thorax surgery/ (676690)
11 ((thoracic* or cardiac* or heart* or cardiothoracic* or chest* or thorax* or cardiac-thoracic* or cardio-thoracic*) adj6 (surg* or operat* or procedur*)).ti,ab,kw. (225923)
12 10 or 11 (761186)
13 3 and 6 and 9 and 12 (800)

Cochrane Central Register of Controlled Trials
Issue 9 of 12, September 2022
#1 ("pleura effusion*" OR "pleural effusion*"):ti,ab,kw 2188
#2 (post-surg* or postoperat* or post-operat*):ti,ab,kw 149039
#3 (thoracocentes* or thoracentes* or pleurocentes* or aspiration* or "drain insert*" or "intercostal drain*" or "indwelling pleural catheter*"):ti,ab,kw 10216
#4 ((thoracic* or cardiac* or heart* or cardiothoracic* or chest* or thorax* or cardiac-thoracic* or cardio-thoracic*) near/6 (surg* or operat* or procedur*)):ti,ab,kw 32968
#5 #1 and #2 and #3 and #4 27

08/06/2023 (2022-2023)

Medline

((((("Pleural Effusion"[Mesh]) OR ("pleural effusion*"[Title/Abstract] OR "pleura effusion*"[Title/Abstract])) AND (("Postoperative Period"[Mesh]) OR (post-surg*[Title/Abstract] OR postoperat*[Title/Abstract] OR post-operat*[Title/Abstract]))) AND (("Thoracentesis"[Mesh]) OR (thoracocentes*[Title/Abstract] OR thoracentes*[Title/Abstract] OR pleurocentes*[Title/Abstract] OR aspiration*[Title/Abstract] OR "drain insert*"[Title/Abstract] OR "intercostal drain*"[Title/Abstract] OR "indwelling pleural catheter*"[Title/Abstract]))) AND ((("Thoracic Surgical Procedures"[Mesh]) OR "Thoracic Surgery"[Mesh]) OR ((thoracic*[Title/Abstract] OR cardiac*[Title/Abstract] OR heart*[Title/Abstract] OR cardiothoracic*[Title/Abstract] OR chest*[Title/Abstract] OR thorax*[Title/Abstract] OR cardiac-thoracic*[Title/Abstract]) OR (cardio-thoracic*[Title/Abstract]))) Filters: **from 2022 - 2023**

Database: Embase 1974 to present
Link to search history:
https://ovidsp.ovid.com/ovidweb.cgi?T=JS&NEWS=N&PAGE=main&SHAREDSEARCHID=6o0FTEykEBvlhFO2SZPZkUzWFg3S3cTTqQbAtnP4ydCc3ytd7Y7wflaq9wXMJko4W
Search Strategy:
1 exp pleura effusion/ (80643)
2 "pleura* effusion*".ti,ab,kw. (46818)
3 1 or 2 (88148)
4 exp postoperative period/ (615402)
5 (post-surg* or postoperat* or post-operat*).ti,ab,kw. (1057929)
6 4 or 5 (1410648)
7 thoracocentesis/ (11337)
8 (thoracocentes* or thoracentes* or pleurocentes* or aspiration* or "drain insert*" or "intercostal drain*" or "indwelling pleural catheter*").ti,ab,kw. (150995)
9 7 or 8 (156596)
10 exp thorax surgery/ (678938)
11 ((thoracic* or cardiac* or heart* or cardiothoracic* or chest* or thorax* or cardiac-thoracic* or cardio-thoracic*) adj6 (surg* or operat* or procedur*)).ti,ab,kw. (238428)
12 10 or 11 (770488)
13 3 and 6 and 9 and 12 (888)
14 13 (888)
15 limit 14 to yr="2022 -Current" (98)

Cochrane Central Register of Controlled Trials
Issue 9 of 12, September 2022
#1 ("pleura effusion*" OR "pleural effusion*"):ti,ab,kw 2188
#2 (post-surg* or postoperat* or post-operat*):ti,ab,kw 149039
#3 (thoracocentes* or thoracentes* or pleurocentes* or aspiration* or "drain insert*" or "intercostal drain*" or "indwelling pleural catheter*"):ti,ab,kw 10216
#4 ((thoracic* or cardiac* or heart* or cardiothoracic* or chest* or thorax* or cardiac-thoracic* or cardio-thoracic*) near/6 (surg* or operat* or procedur*)):ti,ab,kw 32968
#5 #1 and #2 and #3 and #4 27
2022-2023 only

Search Results

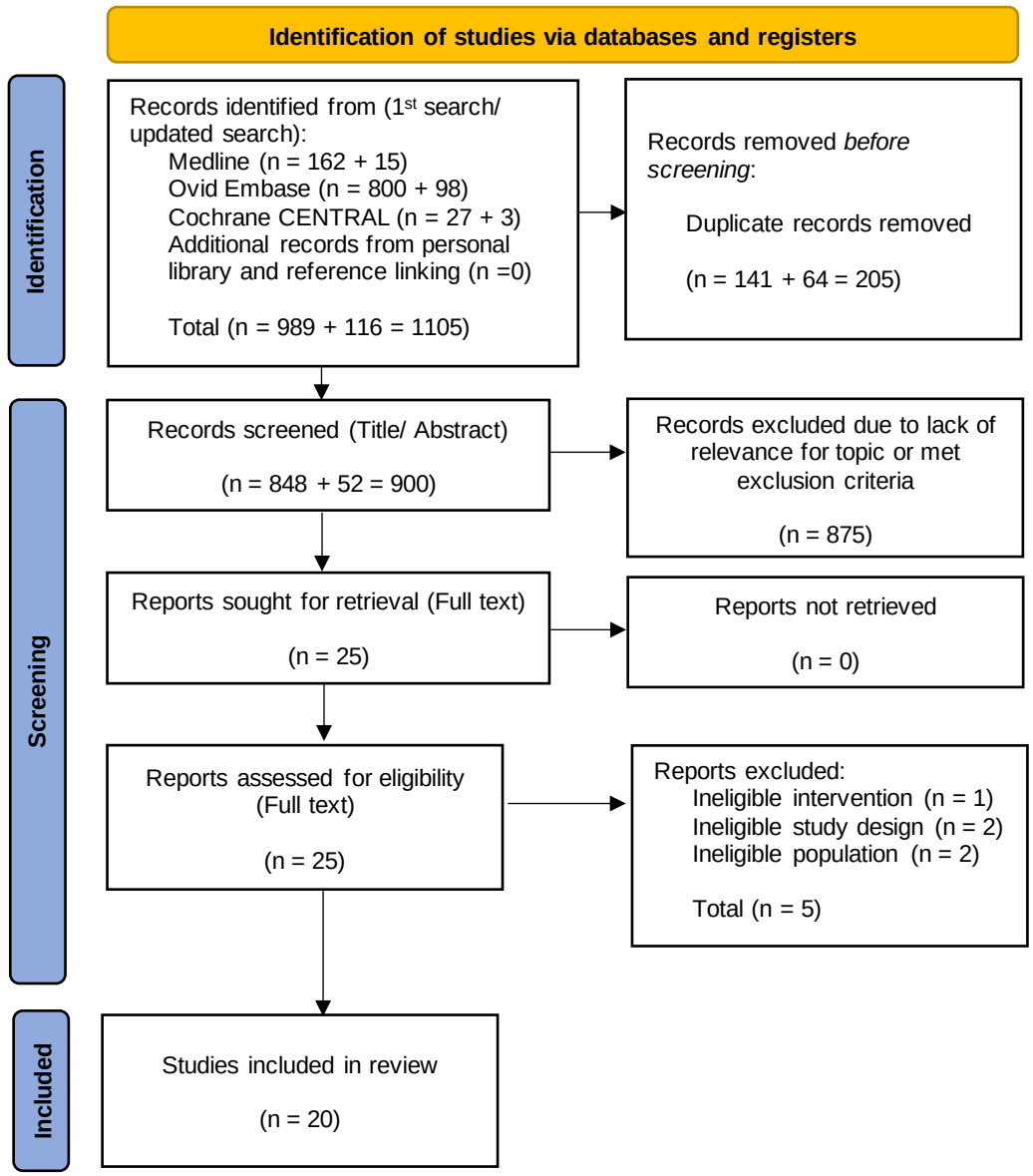
	Search results 29/09/2022	Search results 08/06/2023 (2022 to present only)
Medline	162	15
Ovid Embase	800	98
Cochrane CENTRAL	27	3
Total	989	116
Total after deduplication	848	
Unique since 29/09/2022		52

Inclusion/Exclusion criteria

Inclusion criteria	**Exclusion criteria**
Systematic reviews	Paediatric studies
Meta-analysis	Animal studies
RCTs	Case reports
Interventional studies (non-randomised)	Conference abstracts
Observational studies (retrospective or prospective)	
Case series	
Editorials	
Literature and narrative reviews	
Guidelines	

PRISMA Flowchart

Optimal treatment of post-surgical pleural effusions: thoracentesis/chest drain vs. conservative treatment.



From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

Summary of findings (included in manuscript)

In total 900 studies were screened to identify 20 studies relevant to producing this section. These consisted of 3 editorials or narrative review, 8 retrospective observational studies, 5 prospective observational studies, 1 non-randomised comparative study, 3 RCTs (see below)

Full list of included studies with categorisation

Fischer M-O, Brotons F, Briant AR, Suehiro K, Gozdzik W, Sponholz C, Kirkeby-Garstad I, Joosten A, Nigro Neto C, Kunstyr J, Parienti J-J, Abou-Arab O, Ouattara A. Postoperative Pulmonary Complications After Cardiac Surgery: The VENICE International Cohort Study. *Journal of Cardiothoracic and Vascular Anesthesia* 2022; 36: 2344–2351.

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