Online Appendix C2 BTS Guideline for Pleural Disease

Section C Pleural infection

Question C2 Evidence Review and Protocol

C2 For adults with pleural infection, do pleural fluid or radiology parameters accurately determine which patients should be treated with intercostal drainage?

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Question Evidence Review

C2 For adults with pleural infection, do pleural fluid or radiology parameters accurately determine which patients should be treated with intercostal drainage?

Background

In the absence of purulent pleural fluid, there can be challenges in determining when best to treat patients with parapneumonic effusions (PPE), or suspected pleural infection, by intercostal drainage, in addition to antimicrobial therapy. Various parameters may be available at the point of considering a diagnosis of pleural infection to inform initial decision making as regards to drain or not to drain pleural fluid and therefore classify as complicated (CPPE) or uncomplicated (UPPE) respectively. These include pleural fluid biochemical parameters (pH, lactate dehydrogenase (LDH), glucose) and radiological features such as bedside thoracic ultrasound and CT. Prompt identification of patients with pleural infection who require drainage is necessary to improve patient outcome by potentially prevention of progression to more advanced stages of empyema. This review assesses if pleural fluid or radiology parameters accurately determine which patients should be treated with intercostal drainage.

Outcomes

Identification of patients who need pleural drainage

Evidence review

The initial literature search identified 36 studies of which six met the protocol inclusion criteria. One study was excluded[1] as heparinised syringes were used to collect pleural fluid, a method of sampling known to invalidate pH measurement[2]. Three prospective studies[3-5] and one meta-analysis[6] were ultimately deemed relevant in examining pleural fluid factors and one was relevant in examining radiological factors in the identification of CPPE[7].

Pleural fluid parameters

Two prospective studies reported on the use of pleural fluid factors for determining which pleural infection patients should be treated with intercostal drainage, but each study used different methods of reporting, so meta-analysis was not possible.

Light at al prospectively evaluated 203 consecutive patients with pneumonia for the presence of PPE and performed aspirations on 37/90 patients with PPE identified as large enough for aspirations (>10 mm fluid on lateral decubitus chest x-ray (CXR)).[3] A summary of the results is shown in Table C2a.

Table C2a: Pleural fluid characteristics of parapneumonic effusions

		Pleural fluid parameter (% patients with corresponding parameter)					
		pH		**LDH (IU/L)**		**Glucose (mg/100 ml)**	
PPE classification	**No. patients**	**≤ 7.2**	**> 7.2**	**< 1000**	**> 1000**	**≤ 40**	**≤ 100**
CPPE	10	100%	-	-	100%	80%	100%
UPPE	27	15%	85%	81%	19%	-	56%

CPPE – complicated parapneumonic effusion (defined as PPE where drainage was necessary for its resolution (physician decision to drain)); PPE – parapneumonic effusion; UPPE – uncomplicated parapneumonic effusion

Heffner et al performed a meta-analysis on a number of small studies, (including retrospective studies and some using heparinised syringes) and found that pH had the highest accuracy (over LDH and glucose) for identification of CPPE. A summary of the findings is shown in Table C2b.[6]

Table C2b: Diagnostic accuracy of pH for diagnosing complicated parapneumonic effusions

CCPE risk	pH cut off	Sensitivity	Specificity
"Low risk" patients	≤7.22	0.87	0.90
"High risk" patients	≤7.29	0.93	0.80

CPPE – complicated parapneumonic effusion

As both of these studies[3,6] led to the widespread international practice (American College of Chest Physicians (ACCP)[8] and British Thoracic Society (BTS)[9] guidelines) of employing pH 7.2 as the de facto cut off for drain insertion in suspected CPPE, this subsequently limited the undertaking of further randomised controlled trials to further access the accuracy of using pleural parameters to determine CPPE.

However, a third study has also examined the diagnostic utility of pH, LDH and glucose. Jimenez Castro et al prospectively evaluated 238 patients with PPE undergoing thoracocentesis and used receiver operating characteristic (ROC) analysis combined with calculated continuous likelihood ratios to determine the optimum cut off points for pH, LDH and glucose for diagnosing CPPE. pH was found to be the best determinant of CPPE with a value of ≤ 7.15 as the best binary decision threshold for identification of CPPE (sensitivity 0.84, specificity 0.92), but LDH performed poorly as an independent predictor of CPPE. Area under the curve data for pH, LDH and glucose are shown in Table C2c for the whole cohort (n = 238) and patients without empyemas (frank pus) at diagnosis (n = 171).[4]

Table C2c: Relative diagnostic accuracies (AUC) of pleural fluid parameters for diagnosing complicated parapneumonic effusions[4]

Pleural fluid parameter	CPPE optimal cut-off	AUC [95% CIs]	
		Whole cohort (n = 238)	Patients without empyema (n=171)
pH	≤ 7.15	0.93 [0.89, 0.96]	0.76 [0.67, 0.86]
LDH	≥ 865 IU/L	0.82 [0.76, 0.89]	0.68 [0.57, 0.78]
Glucose	≤ 72 mg/dL (equivalent to 4.0 mmol/L)	0.84 [0.77, 0.90]	0.73 [0.63, 0.84]

AUC – are under curve; CIs – confidence intervals; CPPE – complicated parapneumonic effusion; LDH – lactate dehydrogenase

Again pH ≤ 7.15 was found to be best cut off for indicating CPPE in patients without frank pus, but with a less robust AUC (sensitivity and specificity not reported). The highest pH in the CPPE group was 7.38 and only a small number (14/159) with UPPE had pH ≤ 7.2.[4]

It should be noted that only a small number of patients (17) underwent drainage due to persisting fever despite antibiotics and only 11/17 had pH < 7.2. While it is unlikely that clinician's knowledge of fluid parameters biased these results, this group are patients in which there is most uncertainty about need for immediate drainage rather than those with frank pus, loculations or positive gram stain. Hence applying a pH threshold alone in decision making around drain insertion may risk underestimation of CPPE in an at-risk cohort.

One final study (Arnold et al) investigated the role of a novel biomarker, pleural soluble urokinase plasminogen activator receptor (suPAR) alongside pH, LDH and glucose and found that pH performed best in the conventional group in accuracy for predicting need for chest drainage in PPE (AUC 0.82; 95% CI, 0.73–0.90). Pleural suPAR seemed to perform better than pH alone (AUC, 0.93; 95% CI, 0.89–0.98), and, in particular, elevated levels strongly predicted pleural fluid loculations on ultrasound.[5]

Radiology parameters

No studies prospectively evaluated radiological features in the identification of CPPE, but Porcel et al retrospectively examined 150 patients, from a single centre, with PPE who underwent CT scanning prior to potential intercostal drain (ICD) insertion to identify CT features which could predict CPPE. Multivariable logistical regression modelling identified four features as the best predictors of CPPE, which were used to create a CT scoring system (Table C2d)[7] (please also refer to Table B1a in *Supplementary Online Appendix B1*).

Table C2d: CT parameters and scoring system for prediction complicated parapneumonic effusions

CT parameter	OR [95% CIs]	Score
Pleural contrast enhancement	14.0 [4.7, 42.0]	3
Pleural microbubbles	2.2 [1.0, 6.8]	1
Increased attenuation on extrapleural fat	3.1 [1.0, 10.0]	1
Pleural fluid volume ≥ 400mL	2.7 [1.2, 6.4]	1

The scoring system was then applied retrospectively to a validation cohort of 53 patients. The system performed disappointingly in the identification of CPPE in the validation cohort (score ≥4, sensitivity 0.77, specificity 0.65) in comparison to the derivation cohort (sensitivity 0.84, specificity 0.75), but did show high inter-observer agreement and that the presence of pleural contrast enhancement is perhaps the strongest predictor of CPPE.[7] Here, the presence of split pleural sign (thickened parietal and visceral pleural separated by fluid) and pleural fluid volume were the only features predictive of CPPE on multivariate analysis.[10] These two features had shown promise as predictors of CPPE in the Porcel et al study described above[7], but were not identified as able to contribute to the scoring system in the multivariate analysis.

Evidence statements

Pleural fluid pH appears to have a high specificity and high sensitivity for identifying patients who will undergo a complicated clinical course (complicated parapneumonic effusion (CPPE)) and thus require intercostal drainage (**Ungraded**)

In the context of clinically suspected pleural infection:

- Pleural fluid pH > 7.38 appears to indicate a very low risk of CPPE (**Ungraded**)
- Pleural fluid pH ≤ 7.15 appears to indicate a high risk of CPPE (**Ungraded**)
- Pleural fluid pH between 7.16 and 7.38 appears to indicate a decreasing risk of CPPE/pleural infection with increasing pH, especially with pH > 7.22 (**Ungraded**)
- Pleural fluid LDH or glucose measurements appear to be less accurate as pH in initial, independent prediction of which PPE patients should be treated with intercostal drainage (**Ungraded**)
- Pleural fluid pH and glucose are highly correlated, and thus where immediate or accurate pH measurement is not possible, an initial glucose of 4.0 mmol/L (in the non-diabetic patient) indicates a moderate – high likelihood of CPPE (**Ungraded**)

CT pleural fluid contrast enhancement may improve detection of CPPE (**Ungraded**)

Recommendations

- For patients with parapneumonic effusion (PPE) or suspected pleural infection, where diagnostic aspiration does not yield frank pus, immediate pH analysis should be performed (**Strong** – by consensus)
- For patients with suspected CPPE:

- If pleural fluid pH ≤ 7.2 this implies a high risk of CPPE or pleural infection and an intercostal drain (ICD) should be inserted if the volume of accessible pleural fluid on ultrasound makes it safe to do so (**Strong** – by consensus)
- If pleural fluid pH is > 7.2 and < 7.4 this implies an intermediate risk of CPPE or pleural infection. Pleural fluid lactate dehydrogenase (LDH) should be measured and if >900 IU/L intercostal drainage should be considered, especially if other clinical parameters support CPPE (specifically ongoing temperature, high pleural fluid volume, low pleural fluid glucose (72 mg/dL ≤ 4.0 mmol/L), pleural contrast enhancement on CT or septation on ultrasound (**Strong** – by consensus)
- If pleural fluid pH ≥ 7.4 this implies a low risk of CPPE or pleural infection and there is no indication for immediate drainage (**Strong** – by consensus)

  (a summary of Recommendation 2 is shown in Table C2e)

➢ In the absence of readily available immediate pleural fluid pH measurement, an initial pleural fluid glucose < 3.3 mmol/L may be used as an indicator of high probability of CPPE / pleural infection and can be used to inform decision to insert intercostal drain in the appropriate clinical context. (**Strong** – by consensus)

Table C2e: Suggested drainage options according to pleural pH in cases of suspected pleural infection

Initial pH	**Level of risk for CPPE / pleural infection**	**Initial action regarding drainage**
≤ 7.20	**High risk**	**Insert ICD, assuming ultrasound demonstrates safe volume of accessible pleural fluid**
> 7.2 to < 7.4	**Intermediate risk**	**Check LDH and review other parameters which may support CPPE / pleural infection. Consider ICD insertion if LDH > 900, especially if any of the following:** • **Large pleural fluid volume** • **Low pleural fluid glucose (72 mg/dL / ≤ 4.0 mmol/L)** • **Pleural contrast enhancement on CT** • **Septation on ultrasound**
≥ 7.40	**Very low risk**	**No indication for immediate ICD**

Good Practice Points

✓ Clinicians should be mindful of alternative diagnoses that can mimic parapneumonic effusion (PPE) with a low pH and potential for loculations, e.g. rheumatoid effusion, effusions due to advanced malignancy/ mesothelioma

✓ Pleural fluid samples taken for pH measurement should not be contaminated with local anaesthetic or heparin (e.g. by extruding all heparin from an arterial blood gas syringe) as this lowers pleural fluid pH. Delays in obtaining a pleural fluid pH or residual air in the sampling syringe will also increase pleural fluid pH

✓ In patients where a clinical decision is made not to insert an intercostal drain (ICD) at initial diagnostic aspiration, regular reviews should be performed and repeat thoracocentesis considered to ensure that complicated parapneumonic effusion (CPPE) is not missed

Research Recommendations

- Further research is needed into the role of radiological features (both ultrasound and CT) for predicting complicated parapneumonic effusion (CPPE), especially in patient with an indeterminate risk of CPPE or pleural infection on initial pH measurement
- The role of novel biomarkers (in particular suPAR), in pleural infection and their ability to inform immediate management in PPE requires further prospective validation

References

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Question Protocol

Field	Content
Review Question	For adults with pleural infection, do pleural fluid or radiology parameters accurately determine which patients should be treated with intercostal drainage?
Type of review question	Prognostic review
Objective of the review	Patients presenting with pleural infection may have fluid which requires drainage or may respond to antibiotic treatment only. Are there reliable criteria (radiology, biochemistry) at baseline which allow prediction of this (sometimes referred to as “complicated” versus “uncomplicated” parapneumonic effusion)
Eligibility criteria – population / disease / condition / issue / domain	Adults (18+) with pleural infection
Eligibility criteria – exposure(s)	Pleural fluid pH Pleural fluid purulence Pleural microbiology pleural fluid glucose pleural fluid LDH US parameters CT parameters CXR parameters
Eligibility criteria – reference(s)	Opposite of exposures
Outcomes and prioritisation	Identification of patients who need pleural drainage
Eligibility criteria – study design	Prospective comparative studies Case series of >100 patients
Other inclusion /exclusion criteria	Non-English language excluded unless full English translation Conference abstracts, Cochrane reviews, systematic reviews, reviews Cochrane reviews and systematic reviews can be referenced in the text, but **DO NOT** use in a meta-analysis
Proposed sensitivity / subgroup analysis, or meta-regression	None

Selection process – duplicate screening / selection / analysis	Agreement should be reached between Guideline members who are working on the question. If no agreement can be reached, a decision should be made by the Guideline co-chairs. If there is still no decision, the matter should be brought to the Guideline group and a decision will be made by consensus

Methodology will depend on data type. If sensitivity / specificity data, follow as below, if tabulated data, use a narrative approach and further instruction will be given

Data management (software)	RevMan5	Pairwise meta-analyses (if data in the correct format) Evidence review/considered judgement. Storing Guideline text, tables, figures, etc.
	Gradeprofiler	Quality of evidence assessment
	Gradepro	Recommendations
Information sources – databases and dates	MEDLINE, Embase, PubMED, Central Register of Controlled Trials and Cochrane Database of Systematic Reviews No date restriction	
Methods for assessing bias at outcome / study level	RevMan5 prognostic review template (follow instructions in '*BTS Guideline Process Handbook – Prognostic Review (May 2019)'*)	
Methods for quantitative analysis – combining studies and exploring (in)consistency	If 3 or more relevant studies: RevMan5 for meta-analysis, heterogeneity testing and forest plots (if data appropriate) Contact BTS to discuss best method for combining data if not suitable for meta-analysis (follow instructions in '*BTS Guideline Process Handbook – Prognostic Review (May 2019)'*)	
Meta-bias assessment – publication bias, selective reporting bias	GRADEprofiler	Intervention review quality of evidence assessment for each outcome
	(follow instructions in '*BTS Guideline Process Handbook – Prognostic Review (May 2019)'*)	
Rationale / context – what is known	Low pleural fluid pH (<7.2), low pleural fluid glucose (<2mmol/L in non-diabetic patients), pleural purulent fluid and pleural fluid positive microbiology are traditionally used to diagnose established pleural infection, where bacteria have translocated in to pleural fluid and which require drainage. No radiological parameters are known to predict which patients have established pleural infection. What is the evidence guiding current practice?	