Pleural fluid chemical analysis in parapneumonic effusions: a meta-analysis
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Authors' objectives
To compare the relative diagnostic accuracies of pleural fluid pH, glucose and lactate dehydrogenase (LDH) in parapneumonic pleural effusions.

Searching
MEDLINE and reference lists of retrieved articles were searched. Parts of the search strategy were provided.

Study selection
Study designs of evaluations included in the review
Studies of any design were eligible for inclusion.

Specific interventions included in the review
Laboratory assessments of pleural fluid pH, glucose and LDH were eligible. The studies had to report one or more of these for all patients included in the study to be included in the review.

Reference standard test against which the new test was compared
A reference standard was used to group the results as 'uncomplicated' or 'complicated' pleural effusions. 'Uncomplicated' referred to a parapneumonic effusion that successfully resolves with antibiotic therapy alone, without requiring pleural drainage. 'Complicated' described a parapneumonic effusion with any one of the following features: frank purulence; non-purulent fluid that required pleural drainage; non-purulent fluid that was not drained but progressed to purulent fluid. 'Empyema' was defined as the subgroup of complicated effusions that had fluid with the physical characteristics of frank pus. No specific reference standard was specified, but the studies had to report sufficient information to allow the test values to be categorised as 'complicated' or 'uncomplicated'.

Participants included in the review
Patients with parapneumonic pleural effusions.

Outcomes assessed in the review
The studies had to report values in a tabular or dot plot form that allowed the test results for individual patients to be extracted. The outcomes reported in the review were summary receiver operating characteristic (ROC) curves and areas under the curves (AUCs).

How were decisions on the relevance of primary studies made?
One author reviewed the identified articles for possible inclusion.

Assessment of study quality
Study validity was assessed according to the following three criteria.

1. The definition of reference standards: the method by which the patients were categorised, in order to examine the diagnostic accuracy of pleural fluid chemical analysis.

2. The independence of observations: this involves assessing whether the investigators who performed the pleural fluid chemical analyses were blind to the results of the reference standard. The techniques used to blind the clinicians who determined the reference standard to the pleural fluid chemical analysis results were also reviewed.

3. Verification bias: this refers to whether consecutive patients were evaluated equally and fully with both pleural fluid chemical analysis and the reference standard.
Two authors independently assessed each eligible study with respect to the study inclusion criteria. Any disagreements were resolved by independent review by a third author.

**Data extraction**

Values for pleural fluid pH, glucose and LDH were abstracted from tables when absolute values were provided, or from dot plots when figures were the only source of data. Where dot plots were provided, scalar grids were placed over the plots and two authors independently measured the values at the following levels of precision: pH 0.01, glucose 1 mg/dL, LDH 10 IU/mL. The two authors then reviewed the data and resolved any errors in the data abstraction by conferring together over the primary study.

**Methods of synthesis**

How were the studies combined?

The performances of pleural fluid pH, glucose and LDH were evaluated using ROC analysis. A summary ROC plot was produced for each of the three pleural fluid chemical tests by plotting the sensitivity against 1 minus the specificity for multiple test value decision thresholds, using the original discrete test value data. The areas under the ROC plots and their 95% confidence intervals (CIs) were calculated separately for pH, glucose, and LDH plots. The relative diagnostic accuracies of the three tests were determined by comparing their calculated AUC and 95% CIs.

Two examples of decision thresholds (one corresponding to a patient at high risk of pleural infection, the other corresponding to a patient at low risk of the condition) were selected from the ROC plots of each test, by incorporating the ratio of the costs of false results and the prior probability (prevalence) of the predicted event with the following equation:

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slope = \frac{\text{false positive cost}}{\text{false negative cost}} \times \frac{1 - \text{prior probability}}{\text{prior probability}}
\]

Sensitivities, specificities and predictive values were determined for the selected decision thresholds.

How were differences between studies investigated?

A sensitivity analysis was performed whereby the diagnostic accuracy was re-examined after patients with purulent pleural effusions detected at the time of thoracentesis were removed from the ‘complicated’ group.

**Results of the review**

Seven studies were included in the meta-analysis, which provided 251 pleural fluid pH data points, 135 glucose data points and 1,141 LDH data points in 274 patients.

Pleural effusion pH values (n=251): decision thresholds identified complicated parapneumonic effusions to be associated with pleural fluid pH values of less than or equal to 7.29 for patient A (high risk) and less than or equal to 7.21 for patient B (low risk).

Pleural effusion glucose values (n=135): decision thresholds identified complicated parapneumonic effusions to be associated with pleural fluid glucose values of less than or equal to 32 mg/dL for patient A and less than or equal to 94 mg/dL for patient B.

LDH values (n=114): the corresponding figures were greater than or equal to 1,580 IU/L for patient A and greater than or equal to 600 IU/L for patient B.

Pleural fluid pH had the highest diagnostic accuracy for all patients with parapneumonic effusions, as measured by the area under the ROC curve (AUC 0.92, CI: 0.90, 0.94), compared with pleural fluid glucose (AUC 0.84, CI: 0.80, 0.88) or LDH (AUC 0.82, CI: 0.78, 0.86).

After excluding patients with purulent effusions, pleural fluid pH (AUC 0.89, CI: 0.86, 0.92) retained the highest diagnostic accuracy.
The authors highlighted limitations in relation to the quality of the primary studies. In particular, the reference standards varied between the studies; no study blinded the clinicians who determined patient outcome to the results of the pleural fluid analysis; no study blinded the investigators who measured the pleural fluid test results to the clinical outcomes; the degree of patient follow-up not described in any study.

Authors' conclusions
On the basis of the present study, 7.21 should be considered the pleural fluid pH decision threshold for determining the need for chest tube drainage in patients with a low clinical suspicion of pleural infection. Conversely, the decision threshold for high-risk patients is 7.29. The primary studies did not support the use of pleural fluid glucose or LDH as independent predictors of complicated parapneumonic effusions.

CRD commentary
The literature search was limited in that MEDLINE was the only database mentioned, the years and languages searched were not stated, and there was no description of an attempt to locate unpublished material. Only one reviewer examined the bibliography lists derived from the literature search, and the designs of the primary studies were not reported. As the authors mentioned, there were important problems with the quality of the primary studies.

Implications of the review for practice and research
Practice: The authors stated that current evidence suggests that decisions regarding chest tube placement should derive from pleural fluid pH rather than glucose or LDH results. A pH value of 7.29 should be considered the decision threshold for determining the need for chest tube drainage in patients with a low misclassification cost and low clinical suspicion of pleural infection. The decision threshold for 'high-risk' patients is 7.21.

Research: The authors stated that additional studies are required to determine the independence of the three pleural fluid tests and a strategy for their combined use. Additional information is also required to determine the generalisability of pleural fluid analysis. Future studies should particularly consider the establishment of a reference standard, as no errorless 'gold standard' exists.

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