The Diagnostic Value of Pleural Fluid pH*

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One hundred eighty-three patients had simultaneous blood and pleural fluid pH determinations. Thirty-six effusions were transudates, and 147 were exudates. In 46 effusions, the pleural fluid pH was < 7.30; all 46 were exudates. A pleural fluid pH < 7.30 was associated with the following six diagnoses: (1) empyema; (2) malignancy; (3) collagen vascular disease; (4) tuberculosis; (5) esophageal rupture; and (6) hemothorax. The results of pleural fluid pH determinations are immediately available, narrow the differential diagnosis of the exudate, and may expedite patient management. The pH of pleural fluid should be measured whenever a diagnostic thoracocentesis is performed.

Evaluation of the patient with a pleural effusion is a common medical problem, and despite the use of standard pleural fluid measurements, the etiology remains undetermined in about 20 percent of cases. Since only histocytologic or bacteriologic studies provide a definitive diagnosis, the physician must analyze other pleural fluid characteristics in conjunction with the clinical setting to arrive at a presumptive etiology for the effusion. The traditional classification of pleural fluid into a transudate or an exudate remains helpful, as only a limited number of diagnostic possibilities exist for the transudate. In contrast, however, there are numerous causes of exudative pleural effusions. Recent attempts at improving the clinician's diagnostic capability have included measurement of pleural fluid gas tensions and pH. To date, the most practical application of the pleural fluid pH has been in distinguishing uncomplicated parapneumonic effusions (pH ≥ 7.30) which resolve with antibiotic therapy alone from complicated parapneumonic effusions (pH < 7.30) which usually require chest tube drainage.

With the more routine measurement of the pH of pleural fluid, we have been aware of some confusion in the clinical interpretation of this test. The purpose of this paper is to clarify the meaning of low pleural fluid pH, to review the possible mechanisms responsible for this finding, and to show its value in narrowing the differential diagnosis of the exudative effusion.

Patients and Methods

Between July 1, 1976, and October 1, 1978, 183 patients admitted to the medical and surgical services at the University of Colorado teaching hospitals had simultaneous pleural fluid and arterial blood pH determined as previously described. All samples were collected anaerobically in a glass syringe rinsed with 0.1 ml of heparin (1000 units/ml) ice cooled and transported to the laboratory. Most patients had both pleural fluid and blood determinations for glucose, lactate dehydrogenase (LDH), protein, and amylase. Total and differential leukocyte counts, red blood cell counts, cytologic examination, Gram stain, and routine and mycobacterial cultures were performed on most fluids. The diagnosis of empyema was established by positive culture and/or Gram stain. All malignant effusions had malignant cells demonstrated by either cytology, pleural biopsy, or autopsy. Tuberculous effusions were proven by culture of pleural fluid or tissue. Of the 11 effusions due to collagen vascular disease, five were due to rheumatoid disease, four to systemic lupus, and two resulted from mixed connective tissue disease. All patients with rheumatoid pleurisy were men with rheumatoid nodules. Four of five had high serum rheumatoid factors, pleural fluid glucose < 30 mg/100 ml, and pleural fluid LDH concentrations greater than 800 IU; the fifth patient had rheumatoid nodules demonstrated on pleural biopsy specimen. Two of the lupus effusions were drug-induced and both had LE cells demonstrated in the pleural fluid. The other two patients with lupus effusions had long standing systemic lupus with active disease and high titers of antinuclear antibodies. Two patients had clinical and serologic evidence of mixed connective tissue disease.

Data were analyzed by Student's t-test for independent variables and linear regression analysis.

Results

Of the 183 effusions, 36 were classified as transudates and 147 as exudates based on standard LDH
and protein criteria. Four diagnoses were associated with transudative effusions: congestive heart failure, cirrhosis, nephrotic syndrome, and myxedema. These diagnoses were easily established clinically, and in all, the pleural fluid pH was > 7.30. In contrast, there were 18 causes of exudative pleural effusions (Fig 1). Forty-six of the 147 exudates had a pleural fluid pH < 7.30 (pleural fluid acidosis) and were associated with six diagnoses: (1) empyema; (2) malignancy; (3) collagen vascular disease; (4) tuberculosis; (5) esophageal rupture; and (6) hemothorax. Only one of 46 patients with pleural fluid pH < 7.30 had simultaneous acidemia (blood pH = 7.28/pleural fluid pH = 6.61), and this degree of pleural fluid acidosis was too extreme to be accounted for on the basis of acidemia alone.

Figure 1 shows the range of pleural fluid pH in the 147 exudative effusions. Two-thirds of the empyemas had a pleural fluid pH of < 7.00. Malignant pleural effusions resulted in a pleural fluid pH both above and below 7.30, and those malignant effusions with pH < 7.30 fell into a narrow range from 7.29 to 7.04. All five rheumatoid effusions had pH < 7.30 and ranged from 6.78 to 7.13. Two of the four lupus effusions had a pH < 7.30, one being secondary to hydralazine and the other resulting from active systemic disease. While only two patients with esophageal rupture are included in this study, the mean pH of 6.12 is the lowest of any group. Two of three tuberculous effusions resulted in a low pleural fluid pH, while only one of five patients with uncomplicated hemothorax had pleural fluid pH < 7.30.

Table 1 lists the characteristics of the 46 pleural fluids found to have a pH < 7.30. Values for pleural fluid glucose, LDH, and total protein were not helpful in further narrowing the differential diagnosis. In these 46 effusions, the pH correlated directly with glucose (P < 0.05), i.e., the lower the pleural fluid pH, the lower the PF glucose. This observation has been documented previously.

The LDH concentrations were high in all effusions with pH < 7.30, especially empyema, and the pleural fluid LDH correlated inversely with pleural fluid pH (P < 0.05). While mean leukocyte counts were highest in empyema fluids, there was a wide range (200 to 150,000), as well as considerable overlap with other diagnoses which limited the usefulness of this pleural fluid test. As expected, the

![Figure 1](image-url)

**Figure 1.** The pH of 147 exudative pleural effusions. Only six diagnoses were associated with pleural fluid pH < 7.30. All empyemas had pH < 7.30. Acidic malignant effusions fell into a narrow range from 7.29 to 7.04. Pleural fluid pH < 7.00 was found with three diagnoses—empyema, collagen vascular disease, and esophageal rupture.
percentage of polymorphonuclear leukocytes was significantly higher in empyemas than in malignant effusions (P < 0.01). There was no correlation between types of organisms and degree of pleural fluid acidosis. Similarly, the type of malignancy (e.g., squamous cell carcinoma, adenocarcinoma, or lymphoma) did not correlate with pleural fluid pH.

**DISCUSSION**

The finding of a low pleural fluid pH (< 7.30) in the absence of acidemia should alert the clinician that a process resulting in substantial pleural inflammation or infiltration has occurred. The small quantity of pleural fluid present in normal man has a pH around 7.64, and we have demonstrated a similar pleural fluid pH (7.66) in the normal rabbit. When a pleural effusion develops, the pH of this fluid usually approaches that of blood. However, in those effusions associated with a pH of < 7.30, the pathophysiologic process must result in a substantial accumulation of hydrogen ion within the pleural space.

While the pathogenesis of pleural fluid acidosis has not been defined precisely, it appears to result from a combination of acid production by pleural fluid or pleura, inadequate buffering capacity of pleural fluid, and an efflux block to H⁺ by the rheumatoid pleura is a more important factor. Low pH malignant effusions could result from increased acid production by malignant cells both in the fluid and infiltrated pleura, but recent CO₂ transfer studies suggest that impaired efflux of H⁺ due to pleural thickening by the tumor is the major pathophysiologic factor. The low pleural fluid pH of esophageal rupture has been thought to result from reflux of gastric acid into the pleural space. However, recent data from our laboratory suggest that infection, resulting in mediastinitis and empyema, is the predominant mechanism.

One of our five patients with a hemothorax had pleural fluid pH of 7.27, while another had a pleural fluid pH of 7.32. These values continued to rise over the next 24 hours (7.43 and 7.45, respectively). Light et al. described one patient with a massive hemothorax of ten hours' duration and a pleural fluid pH of 7.17, and another with a bloody effusion secondary to pulmonary infection with a pH of 7.29. Most likely, in hemothoraces with high hematocrit values, excess acid production from red cell glucose metabolism overwhelms H⁺ efflux and results in a low pleural fluid pH. In bloody effusions with a lower number of red blood cells, an efflux block to H⁺ due to an altered pleural membrane must play a substantial role in H⁺ accumulation as red cell glycolysis proceeds at a rate of 500 to 600 times slower than that of the leukocyte.

To our knowledge, the only other cause of a pleural fluid pH < 7.30 was reported by Funahashi et al. who described a patient with a pancreatic pseudocyst and a pleural fluid pH of 7.28. Since pancreatic effusions due to direct transdiaphragmatic communication are associated with the highest pleural fluid amylases, a high concentration of enzyme could cause marked pleural damage with enhanced glucose metabolism and an efflux block to H⁺.

**Table 1—Pleural Fluid Characteristics in the 46 Patients with Low pH Effusions**

<table>
<thead>
<tr>
<th>Etiology (n)</th>
<th>pH</th>
<th>Glucose (mg/100 ml)</th>
<th>LDH (IU/ml)</th>
<th>Protein (gm/100 ml)</th>
<th>WBC (/cu mm)</th>
<th>Polys (percent)</th>
<th>RBC (/cu mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emphyema (22)</td>
<td>6.83±.08*</td>
<td>37±8</td>
<td>1576±351</td>
<td>3.79±.3</td>
<td>42,622±13,103</td>
<td>90±3</td>
<td>27,444±9,405</td>
</tr>
<tr>
<td>Malignancy (12)</td>
<td>7.16±.02</td>
<td>38±7</td>
<td>617±114</td>
<td>4.0±.3</td>
<td>6,732±2,883</td>
<td>22±5</td>
<td>66,365±39,886</td>
</tr>
<tr>
<td>Collagen vascular (7)</td>
<td>7.06±.05</td>
<td>47±22</td>
<td>978±450</td>
<td>4.3±.5</td>
<td>2,224±1,345</td>
<td>56±13</td>
<td>2,388±787</td>
</tr>
<tr>
<td>Esophageal rupture (2)</td>
<td>6.12±.08</td>
<td>22±20</td>
<td>369±73</td>
<td>3.9±.8</td>
<td>2,430±1,470</td>
<td>—</td>
<td>4,600±400</td>
</tr>
<tr>
<td>Tuberculosis (2)</td>
<td>7.17±.12</td>
<td>54±2</td>
<td>640±250</td>
<td>5.1±.2</td>
<td>3,350±860</td>
<td>29±3</td>
<td>—</td>
</tr>
<tr>
<td>Hemothorax (1)</td>
<td>7.27</td>
<td>101</td>
<td>1044</td>
<td>3.7</td>
<td>4,480</td>
<td>87</td>
<td>1×10⁴</td>
</tr>
</tbody>
</table>

*Mean ± SEM
†Excludes 2 diabetics

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**DIAGNOSTIC VALUE OF PLEURAL FLUID pH** 57
In addition to the finding of a pleural fluid pH < 7.30, the degree of pleural fluid acidosis may be of further diagnostic value. Malignant effusions with a pH < 7.30 fell within a narrow range between 7.29 and 7.04. A pleural fluid pH of less than 7.00 was found with only three diagnoses: empyma, collagen vascular disease, and esophageal rupture. The latter diagnosis usually is associated with a pleural fluid pH approaching 6.00.

The leukocyte differential of the low pH effusions was of additional value in limiting the diagnostic possibilities. A mononuclear predominance was found with pH < 7.30 due to malignancy, tuberculosis, or chronic rheumatoid disease, while the polymorphonuclear predominance were found in empyema, esophageal rupture, and acute rheumatoid or lupus pleuritis.

While there was a direct correlation between pleural fluid pH and glucose, there were instances where pleural fluid glucose was normal (with normal serum glucose) with a low pleural fluid pH. In two patients with empyema and one each with malignancy and systemic lupus, pH values were all < 7.20, while pleural fluid glucose concentration varied from 60 to 113 mg/100 ml, suggesting that pleural fluid pH is an earlier and more sensitive indicator of pleural inflammation.

Care must be exercised in both obtaining and transporting pleural fluid for pH analysis. Pleural fluid should be aspirated anaerobically into a syringe rinsed with heparin (1,000 units/ml), placed in ice, and transported to the laboratory. The pH value is stable for up to two hours if kept at 0°C. A false low pH value will be obtained if the sample is allowed to remain at room temperature due to in vitro glycolysis. A falsely elevated pH will occur if the sample is allowed to equilibrate with room air.

The following cases illustrate how pleural fluid pH may be useful to the clinician:

**Case 1**

A 49-year-old woman with massive malignant effusion (pH < 7.19) had a therapeutic thoracocentesis for dyspnea. She returned 12 hours later with pleuritic pain, low grade fever, and peripheral leukocytosis. Repeat thoracocentesis revealed an exudate with 300 leukocytes/cu mm, 100 percent polys, pH of 6.40, and negative Gram stain. Pleural fluid culture subsequently grew Clostridial perfringens.

**Comment**

Since malignant effusions rarely are associated with a pH < 7.00 and there had been a marked fall in pH over 12 hours from 7.19 to 6.40, it was clear that despite a negative gram stain and low cell count, that this patient had an iatrogenic empyema. Antibiotic therapy and chest tube drainage were instituted immediately while waiting 24 to 48 hours for the culture results.

**Case 2**

An 80-year-old woman was admitted with bilateral pleural effusions (large on the left and small on the right), cardiomegaly, and a diagnosis of congestive heart failure. A left thoracocentesis showed pleural fluid/serum protein ratio of 0.50 and LDH ratio of 0.62, leukocyte count 100/cu mm, 75 percent mononuclear cells, and pH of 7.18. Results of cytologic examination of pleural fluid were suspect. Closed pleural biopsy was done promptly and showed adenocarcinoma.

**Comment**

The cellular and chemical composition of the fluid, excluding the pH, was consistent with chronic congestive heart failure. However, because of the pleural fluid pH of 7.18 and the mononuclear predominance, the differential diagnosis was narrowed to cancer or tuberculosis. Early pleural biopsy was performed establishing the diagnosis of cancer.

In our experience, a low pleural fluid pH (< 7.30) limits the differential of the exudative effusion to the six following diagnoses: (1) empyema; (2) malignancy; (3) collagen vascular disease; (4) tuberculosis; (5) esophageal rupture; and (6) hemothorax. This finding should alert the clinician to perform those histocytologic, bacteriologic, and biochemical studies which will establish the etiology of the effusion. While the degree of pleural fluid acidosis does not establish a diagnosis, the lowest pHs are associated with pleural space infection.

Pleural fluid pH is a simple and rapid determination which provides the clinician with immediate results and should be done whenever a diagnostic thoracocentesis is performed.

**References**

8. Potts DE, Levin DC, Sahn SA: Pleural fluid pH in...