Measurement of Pleural Fluid Cholesterol and Lactate Dehydrogenase*

A Simple and Accurate Set of Indicators for Separating Exudates From Transudates

Marina Costa, MD; Teresa Quiroga, MD; and Edgardo Cruz, MD

Objectives: To evaluate the usefulness of diverse combinations of pleural cholesterol concentration, pleural or serum protein, and lactate dehydrogenase (LDH) levels for the differentiation of pleural exudates and transudates.

Design: Prospective laboratory study of pleural effusions.

Setting: Medical school hospital.

Patients: One hundred eighty consecutive internal medicine ward patients in whom the etiologic diagnosis of their pleural effusion was confirmed.

Measurements: Cholesterol concentration in pleural fluid and protein and LDH both in pleural fluid and blood serum.

Results: According to their etiology, 49 (27.2%) of the effusions were transudates and 131 (72.7%) were exudates. Using a cutoff point of 45 mg for pleural cholesterol and values for protein and LDH of Light et al, the best diagnostic power corresponded to the combination of pleural cholesterol and LDH: cholesterol level over 45 mg/dL and/or LDH over 200 IU/L identified exudates with a sensitivity of 99% and a specificity of 98%. All the other combinations showed inferior values and the criteria of Light et al reached 98 and 82%, respectively.

Conclusions: The measurement of pleural cholesterol and LDH permits the separation of pleural exudates from transudates with an accuracy similar to the original report of Light et al, with the advantage of requiring only two laboratory determinations and no simultaneous blood sample.

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LDH = lactate dehydrogenase

Key words: pleural cholesterol concentration; pleural effusion; pleural LDH

The current criteria for differentiating exudates from transudates in pleural effusions, through the measurement of protein and lactate dehydrogenase (LDH) levels in serum and pleural fluid, were established by Light et al1 in 1972. Sensitivity and specificity, calculated from their data, were 99 and 98%, respectively. However, these results have not been fully reproduced by other investigators who have reported specificities between 70 and 86%.2-5

In 1987, Hamm et al6 showed that cholesterol concentration increases in exudative pleural effusions and, by using a cutoff point of 60 mg/dL, they correctly labeled 95% of 62 pleural fluid samples. Quiroga et a7 using 45 mg/dL of cholesterol as the cutoff in 80 patients, reported a sensitivity of 83% and a specificity of 100%. In the same patients, the criteria of Light et al1 showed a sensitivity of 98% an a specificity of 86%. As the samples misclassified by one method were correctly identified by the other one, the authors suggested that their simultaneous use could be useful. Since this combination requires both pleural and blood samples, and five chemical measurements, we decided to determine whether a similar result could be obtained by combining cholesterol with only one or two of the individual indicators of Light et al,1 thus simplifying the diagnostic procedure and lowering the cost. Our results show that these aims are satisfactorily attained by measuring only LDH and cholesterol concentrations in pleural fluid.

Methods

Considering the etiology of the effusion as the gold standard for the classification of pleural fluid, we selected, from 551 consecutive inpatients who underwent a thoracentesis at the internal medicine ward, all those who met the following conditions: (1) a confirmed diagnosis of a disease which, when causing a pleural effusion, is invariably associated with an exudate or with a transudate; patients with pulmonary embolism and renal insufficiency, which may be accompanied both by exudates or transudates,8 were excluded; (2) absence of other diseases capable of causing a pleural effusion or of modifying its nature; and (3) measurement of pleural cholesterol

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concentration and the indicators of Light et al in the same pleural effusion sample and blood sample for protein and LDH determination, obtained within 8 h of the thoracentesis.

This last requirement meant the exclusion of 263 patients, while 105 had to be left out because the diagnosis was considered presumptive or the patient had more than one disease. This left 180 patients for analysis.

The diagnosis of the disease causing the effusion was considered to be confirmed when the following conditions were met: (1) congestive heart failure: presence of an enlarged heart with clinical or echocardiographic evidence of cardiac disfunction, and one or more of the following alterations: elevated venous pressure, edema, tachycardia, or ventricular gallop. Patients suspected of having respiratory infections, pulmonary embol, or persistence of the effusion after adequate treatment of the cardiac insufficiency, were excluded; (2) liver cirrhosis: clinical and laboratory evidence of hepatic damage with portal hypertension or hypoalbuminemia; (3) pleural malignancy: cytologic or histologic demonstration of pleural involvement; (4) tuberculosis: presence of tuberculomas in pleural biopsy specimen or positive smear or culture of acid-fast bacilli; (5) parapneumonic effusion: clinically and radiologically confirmed pneumonia with no direct or indirect evidence of bacterial invasion of the effusion; and (6) complicated parapneumonic effusion: pneumonia with one or more of the following indicators of bacterial invasion of the effusion: pus cells, bacteria in Gram's stain smear or culture, and pH under 7.0 or progressively decreasing to under 7.20.

Effusions associated with congestive heart failure and liver cirrhosis were classified as transudates and the rest were classified as exudates.

The first sample of pleural fluid obtained in each patient was considered for analysis. Protein was measured by the biuret method; LDH by UV spectrophotometry at 37°C and 340 nm and cholesterol with the Boehringer-Mannheim enzymatic method CHOD-PAP.

For the laboratory classification of pleural fluids, protein and LDH were interpreted according to the criteria of Light et al and a cutoff point of 45 mg/dL was adopted for cholesterol.

The operating characteristics of the measured indicators and their different combinations were assessed through their sensitivity and specificity in relation to the etiologic-based classification of the pleural fluids. These indices were compared using McNemar's exact test for correlated proportions.

Table 1—Causes of 180 Pleural Effusions

<table>
<thead>
<tr>
<th>Causes</th>
<th>No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transudates (49)</td>
<td></td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>30</td>
</tr>
<tr>
<td>Liver cirrhosis</td>
<td>19</td>
</tr>
<tr>
<td>Exudates (131)</td>
<td></td>
</tr>
<tr>
<td>Pleural malignancy</td>
<td>55</td>
</tr>
<tr>
<td>Pleural tuberculosis</td>
<td>22</td>
</tr>
<tr>
<td>Simple parapneumonic effusion</td>
<td>21</td>
</tr>
<tr>
<td>Complicated parapneumonic effusion</td>
<td>22</td>
</tr>
<tr>
<td>Rheumatologic diseases</td>
<td>11</td>
</tr>
</tbody>
</table>

Table 2—Accuracy of Criteria of Light et al in the Classification of 180 Pleural Effusions

<table>
<thead>
<tr>
<th>Exudates (131)*</th>
<th>Transudates (49)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Correctly classified</td>
<td>129</td>
</tr>
<tr>
<td>Misclassified</td>
<td>2</td>
</tr>
</tbody>
</table>

*Etiologic classification.

Table 3—Sensitivity and Specificity of Different Combinations of Indicators for the Identification of Pleural Exudates

<table>
<thead>
<tr>
<th>Criteria of Light et al</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol &gt;45 mg/dL</td>
<td>98</td>
<td>82</td>
</tr>
<tr>
<td>Cholesterol-criteria of Light et al</td>
<td>100*</td>
<td>95</td>
</tr>
<tr>
<td>Cholesterol+LDH &gt;200 IU/L</td>
<td>99</td>
<td>98*</td>
</tr>
<tr>
<td>Cholesterol+Pr P/S &gt;0.5§</td>
<td>98</td>
<td>92</td>
</tr>
<tr>
<td>Cholesterol+Pr P/S &gt;0.5§+LDH &gt;0.6</td>
<td>99</td>
<td>86</td>
</tr>
<tr>
<td>Cholesterol+Pr P/S &gt;0.5§+LDH &gt;200 IU/L</td>
<td>100</td>
<td>90</td>
</tr>
</tbody>
</table>

*Significantly lower than criteria of Light et al (p<0.05).
†Significantly higher than criteria of Light et al (p<0.01).
‡Significantly higher than criteria of Light et al (p<0.02).
§Pr P/S=protein pleural/serum ratio.

RESULTS

According to the causal disease, 49 pleural fluid samples were labeled as transudates and 131 were labeled as exudates (Table 1). In Table 2, classification based on the application of the criteria of Light et al is compared with the etiologic classification, considered as the gold standard. It may be observed that 2 of the 131 exudates were misclassified as transudates (sensitivity 98%) and 9 of the 49 transudates were erroneously labeled as exudates (specificity 87%). The two misclassified exudates correspond to complicated parapneumonic effusions and of the erroneously classified transudates, seven were secondary to congestive heart failure and two to liver cirrhosis.

When the concentration of cholesterol in pleural fluid, with a cutoff point of 45 mg/dL, was used for classification, 13 of the 131 exudates were misclassified (Table 3), with a sensitivity of 88%, while all the transudates were correctly labeled (specificity 100%). If the cutoff point of 60 mg/dL proposed by Hamm and coworkers was used, sensitivity fell to 73% and specificity remained 100%.

All the transudates that were erroneously classified by the criteria of Light et al were correctly identified through cholesterol level and, inversely, all exudates that were misclassified by cholesterol were correctly identified by the measurements of Light et al.

Table 3 shows the sensitivity and specificity calculated for the criteria of Light et al, for cholesterol alone and for all the possible combinations of cholesterol and the individual components of the set of Light et al. It may be observed that cholesterol has a higher sensitivity (p<0.05) but a lower specificity (p<0.01) than the criteria of Light et al and that their combined use improves sensitivity but not specificity. Of the six alternatives that combine cholesterol and one or two of the indicators of Light et al, only that of cholesterol level greater than 45 mg/dL and LDH level greater than 200 U/L exhibit a better diagnostic yield than the triad of...
Light et al, and this is due to a significantly higher specificity (p<0.02).

Figure 1 illustrates the distribution of individual results. It may be observed that all but one of the transudates fell in area A with both LDH and cholesterol concentrations below the cutoff points. The only transudate that fell outside this area corresponds to an effusion caused by congestive heart failure that fell in area C because of an LDH value of 210 IU/L. Most exudates (71%) are located in area B, with both LDH and cholesterol above normal limits, while 8% showed only abnormal LDH concentration (area C) and 19.8% showed only abnormal cholesterol level (area D). Only one exudate, corresponding to a complicated parapneumonic effusion, fell in area A, originating a false diagnosis of a transudate.

**Discussion**

Our results show that the combination of an increased concentration of cholesterol level greater than 45 mg/dL and/or LDH level greater than 200 U/L in pleural fluid constitutes a useful tool for separating exudates from transudates. The diagnostic yield of this combination is similar to that obtained by Light et al in their original investigation and superior to those reported by other authors and what is observed in the present study using the same diagnostic criteria in similar patients.

Our initial assumption, based on a previous study, that the simultaneous use of the criteria of Light et al and cholesterol would be complementary, was not confirmed, since the specificity of this combination was, in our patients, as low as that of the criteria of Light et al alone. This could be interpreted as a lack of a contributory effect of cholesterol, but Table 3 shows that the combinations which include pleural-serum protein ratio are the ones that exhibit the lowest specificity, while the combination of cholesterol and LDH shows the highest. This misleading effect of protein ratio is present in all the studies that report low specificities. Most of the errors were observed in congestive heart failure, and protein ratio was the deceiving index in most cases. This aspect has been recently addressed by Chakko et al who demonstrated that the treatment of heart failure may change the chemistry of pleural fluid probably by withdrawing water and, thus, concentrating proteins. Considering that previous treatment of heart failure is neither registered in the present nor the cited articles, it is reasonable to speculate that this uncontrolled factor may explain the wide variations of specificity reported in literature for the criteria of Light et al. If this is so, the interpretation of protein ratio in heart failure would depend on previous treatment, which is a variable that is difficult to standardize. This would mean that this indicator is not suitable in patients with heart failure and, probably, in those with liver cirrhosis in whom diuretics have been used. As most transudates considered for differential diagnosis correspond to those etiologies, it seems reasonable to abandon this low-specificity indicator.

Roth et al showed that this limitation of the criteria of Light et al could be overcome by measuring the serum-effusion albumin gradient which, when over 1.2 mg/dL, indicated a transudate. Replacing the serum-effusion protein ratio by this other indicator undoubtedly increases the specificity of the criteria of Light et al, but a simultaneous blood sample is still required.

After our study was finished, Romero et al, using the criteria of Light et al in 297 patients, reported the same sensitivity found by us (98%) and a slightly lower specificity (77 vs 82%). They propose a modification of the cutoff points of Light et al that increases specificity to 93% with a slight decrease of sensitivity to 94%. Despite the improvement, these values are lower than those obtained with the combined use of cholesterol and LDH.

We conclude that simultaneous measurement of LDH and cholesterol in pleural fluid permits the identification of exudates through the elevation of either one or both of these indicators, with an accuracy similar to the best that has been reported with the criteria of Light et al. The proposed combination has the advantages that a contemporary blood sample is not required and that chemical tests are reduced from four to two, thereby, lowering the cost of the diagnostic procedure.

**References**

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8 Light RW. Pleural diseases. Philadelphia: Lea & Febiger, 1983; 146