Pleural Fluid to Serum Bilirubin Concentration Ratio for the Separation of Transudates from Exudates*

Simecha Meisel, M.Sc., M.D.; Arie Shamiss, M.D.; Michael Thaler, M.D.; Naomi Nussinovitch, M.D.; and Talma Rosenthal, M.D.

Whether fluid accumulating in the pleural space is a transudate or an exudate is determined by the widely used criteria of the pleural fluid to serum LDH and protein concentration ratios. Such a distinction is important for limiting the extent of the differential diagnosis of possible causes for this condition. We have found that a pleural fluid to serum total bilirubin ratio can serve the same purpose. The correlation of a bilirubin concentration ratio of 0.6 or more with the presence of an exudate as determined by established criteria is statistically highly significant; and its sensitivity, specificity, positive predictive accuracy, and overall accuracy in relation to etiology and LDH or protein criteria (Light’s criteria) are about 90 percent. Hence, the bilirubin criterion is statistically equivalent to the widely accepted LDH and protein criteria. (Chest 1990; 98:141-44)

CHF = congestive heart failure; CRF = chronic renal failure

The distinction between a transudative process and an exudative one causing accumulation of fluid in the pleural cavity is based on diagnostic criteria established by Light et al. These authors have advocated one of three characteristics for the identification of most exudates: (1) a pleural fluid to serum protein ratio greater than 0.5; (2) a pleural fluid LDH greater than 200 units/L; and (3) a pleural fluid to serum LDH ratio greater than 0.6. While examining the composition of pleural fluid specimens, we serendipitously discovered that the pleural fluid to serum total bilirubin concentration ratio could serve as an alternative criterion for the separation of transudates from exudates. The purpose of this preliminary study was to evaluate this criterion for statistical significance and accuracy in relation to established etiology and widely accepted LDH and protein pleural fluid to serum ratios.

MATERIALS AND METHODS

Fifty-one specimens of pleural fluid from 51 different patients were obtained consecutively on our medical ward at the Sheba Medical Center between Feb 1, 1987 and Aug 15, 1989. The fluid specimens were analyzed prospectively by SMA 12.

To optimally determine the etiology of the pleural effusion and to place the patient in the most probable diagnostic category (exudate or transudate), we adopted the criteria of Light et al., with minor modifications.

The diagnosis of malignant effusion required biopsy, cytopathologic findings, or autopsy as proof of malignant tissue in the serous cavity, or unequivocal CT demonstration of a malignant process involving or contiguous to the pleura.

The diagnosis of congestive heart failure as the cause of the pleural effusion had to meet the following four criteria: (1) an enlarged heart on the chest roentgenogram; (2) an elevated central venous pressure or distended jugular veins and pitting edema or ventricular cardiac gallop; (3) the absence of pulmonary infiltrates, purulent sputum, thrombophlebitis, pleuritic chest pain, or early signs of ARDS; (4) clearing of the effusion in response to a therapeutic regimen or postmortem evidence of uncomplicated congestive heart failure.

Other miscellaneous exudates were effusions clearly caused by the postpericardiotomy syndrome, collagen vascular disease, or various rare etiologies of exudative pleural effusion. Other transudates were those due to cirrhosis, nephrosis, or fluid overload.

Samples of fluid and serum were obtained within an hour of each other and were immediately centrifuged. Protein, LDH, and bilirubin measurements were undertaken soon after by SMA 12 analysis.

Those effusions whose etiology could not be determined were termed “undetermined” and were evaluated for concordance of their bilirubin criterion with established protein or LDH criteria.

The pleural fluid to serum ratio of LDH, total protein, and bilirubin (LDH, protein, and bilirubin criteria, respectively) were calculated.

The diagnostic accuracy of the bilirubin criterion with reference to contended etiology was evaluated for sensitivity, specificity, positive predictive accuracy, and overall accuracy. Statistical significance was determined by the χ² method with Yates correction.

RESULTS

The types and causes of pleural fluid specimens are detailed in the following tabulation:

<table>
<thead>
<tr>
<th>Transudates</th>
<th>CHF</th>
<th>Fluid overload</th>
<th>Cirrhosis</th>
<th>Chronic renal failure</th>
<th>Exudates</th>
<th>Malignancy</th>
<th>Tuberculosis</th>
<th>Parapneumonic</th>
</tr>
</thead>
<tbody>
<tr>
<td>23</td>
<td>19</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>23</td>
<td>15</td>
<td>1</td>
<td>1</td>
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*From the Hypertension Unit, Department of Internal Medicine D, Chaim Sheba Medical Center, Tel Hashomer, Israel (affiliated with Tel Aviv University, Sackler School of Medicine, Tel Aviv, Israel).

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Reprint requests: Dr. Meisel, Hypertension Unit, Chaim Sheba Medical Center, Tel Hashomer, Israel 52621.

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Figure 1 displays the distribution of the 46 fluid specimens with established etiology according to ratio and type (transudate or exudate) for the three criteria. It is readily seen that a pleural fluid to serum bilirubin ratio of 0.6 or more distinguishes exudates from transudates in almost all cases.

Table 1 summarizes the sensitivity, specificity, positive predictive accuracy, and overall accuracy of the bilirubin criterion in relation to etiology (established in 46 fluid specimens as outlined in the previous section) and to LDH or protein criteria in all fluid specimens (criteria of Light et al).

As Table 1 shows, the various statistical tests for evaluating the bilirubin criterion according to etiology (a bilirubin ratio ≥0.6 for an exudative etiology and a bilirubin ratio <0.6 for a transudative one) yielded values in the order of 90 percent and higher. In four patients who had jaundice and in whom the etiology was transudative (CHF in two), the bilirubin ratio was valid.

Figures 2 and 3 depict pleural fluid to serum bilirubin concentration ratio in relation to corresponding LDH and total protein ratios, respectively.

Only one false-positive result was detected for a specimen with a bilirubin ratio greater than 0.6, despite a transudative etiology. This misclassified specimen came from an elderly patient with CHF and a pleural effusion, who died suddenly. As we are dealing with a varied population of patients, some of them elderly and suffering from multiple underlying

<table>
<thead>
<tr>
<th>Test</th>
<th>R_{eti} vs: Etiology</th>
<th>R_{eti} or R_{pr}</th>
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<tbody>
<tr>
<td>Sensitivity</td>
<td>0.96</td>
<td>0.9</td>
</tr>
<tr>
<td>Specificity</td>
<td>0.83</td>
<td>0.82</td>
</tr>
<tr>
<td>Positive predictive accuracy</td>
<td>0.85</td>
<td>0.87</td>
</tr>
<tr>
<td>Overall accuracy</td>
<td>0.8</td>
<td>0.86</td>
</tr>
</tbody>
</table>
diseases, this patient, and those with mismatched LDH and protein criteria, might have had more than one active disease process.

The statistical significance of the association of a bilirubin ratio of 0.6 or greater with an exudative fluid according to established etiology was estimated by applying the χ² test with the Yates correction. The obtained χ² value corresponded to p<0.001 and so proves a highly significant statistical relation.

DISCUSSION

It is generally accepted that an effusion due to pleural disease more closely resembles plasma (exudate), whereas that occurring in the presence of a normal pleural membrane is due to hemodynamic aberrations or oncotic changes and is an ultrafiltrate of the plasma (transudate).

Effusions that occur with involvement of the pleura in infectious, neoplastic, vascular, or inflammatory processes are due to increased permeability of the pleural membrane and subjacent capillaries or of the capillary bed within the pulmonary parenchyma, as in ARDS. One exception to the above is a pleural effusion that accumulates due to lymphatic obstruction. Since the only route for reabsorption of protein from the pleural space is through the lymphatic system, such an obstruction will result in a high concentration of protein in the fluid, despite an intact pleural membrane.

Historically, transudates were separated from exu-
dates by specific gravity. Leuallen and Carr claimed that the protein level of the fluid might better be used to separate transudates from exudates, since using the specific gravity as a criterion misclassified about 30 percent of effusions. This was in contrast to Luetscher’s report 14 years previously, that it was impossible to apply the total protein criterion without encountering frequent exceptions. He suggested that the pleural fluid to serum protein ratio was a more discriminating criterion. Wroblewski and Wroblewski first observed in 1958 that the pleural fluid level of LDH of malignant effusions was higher than the simultaneous serum LDH level. Since then, several observations have suggested that pleural fluid LDH might also be high in other exudative effusions, but it was Light et al who rigorously based the separation of transudates from exudates on the fluid to serum protein and LDH ratios and fluid level of LDH.

Considering the aforementioned pathogenesis, it is not surprising that exudative pleural fluid contains increased concentrations of LDH and protein, which are similar in their biophysical behavior. Any inflammation of a serous membrane will increase the permeability of underlying capillaries and enable diffusional transport of high-molecular-weight molecules according to a concentration gradient. Transudation of plasma through intact serous membrane results in the transport of water and low-molecular-weight ions or molecules (eg, sodium, glucose, and urea) but prevents permeation of protein molecules through intercellular pores of normal endothelium and mesothelium. Hence, unexpected was our fortuitous finding that bilirubin of a molecular weight of about 584 behaved similarly to high-molecular-weight proteins with respect to its concentration distribution between serum and pleural fluid. Such behavior may be attributed to stereochemical and electrical properties of bilirubin, but it seems that it cannot be based on sound biochemical reasoning other than the plausible mechanism of protein binding.

The association between a bilirubin ratio greater than 0.6 and an exudate according to etiology was found to be of high statistical significance. The accuracy of this criterion in terms of sensitivity, specificity, positive predictive accuracy, and overall accuracy in relation to etiology and LDH or protein criteria is about 90 percent (Table 1). The bilirubin criterion, therefore, is equivalent to the well-accepted LDH and protein criteria and may serve as another condition to distinguish an exudate from a transudate. This is important since, as succinctly put by Light et al in their original article: "A single chemical test, or a set of chemical tests is rarely 100% effective in separating two populations, but increasing the number of tests results in a more reliable separation." Furthermore, the bilirubin method possesses the advantages of being more cost-effective in terms of laboratory processing and is more readily available even when LDH and protein measurements are not performed.

An ongoing effort is underway to pursue this issue further beyond this preliminary study in a larger population of patients. For the present, it seems that a pleural fluid to serum bilirubin ratio greater than 0.6 strongly indicates that the fluid is an exudate.

REFERENCES