Pleural Effusions: The Diagnostic Separation of Transudates and Exudates

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In this prospective study of 150 pleural effusions, the utility of pleural-fluid cell counts, protein levels, and lactic dehydrogenase (LDH) levels for the separation of transudates from exudates was evaluated. According to preset diagnostic criteria, 47 of the effusions were classified as transudates and 103 as exudates. Three characteristics were found, each of which was associated with over 70% of the exudates and, at most, one of the transudates: [1] a pleural fluid-to-serum protein ratio greater than 0.5; [2] a pleural fluid LDH greater than 200 IU; and [3] a pleural fluid-to-serum LDH ratio greater than 0.6. Moreover, all but one exudate had at least one of these three characteristics, whereas only one transudate had any of the three. The simultaneous use of both the pleural-fluid protein and LDH levels better differentiates transudates from exudates than does the use of either of these values individually.

PLEURAL EFFUSIONS are classically divided into “transudates” and “exudates” (1). A transudate occurs when the mechanical factors influencing the formation or reabsorption of pleural fluid are altered. Increased plasma osmotic pressure or elevated systemic or pulmonary hydrostatic pressure are alterations that produce transudates (2). The pleural surfaces are thought not to be involved by the primary pathologic process (3). In contrast, an exudate results from inflammation or other disease of the pleural surface, such as occurs in tuberculosis, pneumonia with effusion, malignancy, pancreatitis, pulmonary infarction, or systemic lupus erythematosus.

A pleural-fluid protein level of 3.0 g/100 ml is frequently used to separate transudates from exudates; however, this dividing line has consistently led to the misclassification of many effusions. Carr and Power (4) found that 8% of their exudates and 15% of their transudates were misclassified by this criterion. Recently, Chandrasekhar and colleagues (5) have proposed that the absolute level of the pleural-fluid lactic dehydrogenase (LDH) can separate transudates from exudates more effectively than the pleural-fluid protein level. The purpose of the present study is to compare the utility of the pleural-fluid protein level, the pleural-fluid LDH level, and the pleural-fluid cell counts for the separation of transudates from exudates.

Patients and Methods

One hundred and fifty pleural fluids from 150 different patients from the medical wards of The Johns Hopkins Hospital and The Good Samaritan Hospital were studied prospectively, between 1 April 1970 and 1 October 1971. The following precise criteria were established before beginning the study, to place the patients in various diagnostic categories.

The diagnosis of malignant effusion required that malignant tissue in the pleural cavity be shown by pleural biopsy, cytopathology, or autopsy. When a pleural effusion in a patient with proved malignancy was believed to be caused by the tumor but could not be documented in these ways, it was excluded from the series.

The diagnosis of congestive heart failure as the cause of the pleural effusion required that all four of the following criteria be satisfied: [1] an enlarged heart; [2] an elevated central venous pressure or distended neck veins and pitting edema or ventricular cardiac gallop; [3] the absence of pulmonary infiltrates, purulent sputum, thrombophlebitis, and pleuritic chest pain; and [4] clearing of the effusion in response to a therapeutic
cardiac regimen or evidence of uncomplicated congestive heart failure by the autopsy report.

The diagnosis of tuberculous pleuritis required: [1] Mycobacterium tuberculosis, shown by culture of pleural fluid or pleural tissue or [2] granulomas on pleural biopsy (open or closed). The diagnosis of pneumonia with effusion required that there be an acute febrile illness, with purulent sputum and pulmonary infiltrates, in association with a unilateral pleural effusion and uncomplicated congestive heart failure.

The category, "other exudates," encompasses those effusions that were clearly caused by pancreatitis, collagen vascular disease, pulmonary emboli, postmyocardial infarction (Dressler's) syndrome, or various rare but well-documented causes of exudative pleural effusions. The diagnosis of pulmonary infarction required arteriographic demonstration of pulmonary emboli. The effusions classified as "other transudates" are those clearly owing to cirrhosis or nephrosis.

Samples of pleural fluid and venous blood were obtained within 30 minutes of one another for LDH and protein analysis. Both samples were immediately centrifuged. The protein and LDH measurements were done on the supernatant within 48 hours. The LDH was measured with the Boehringer Mannheim kit, according to the procedure of Wroblewski and LaDue [6], and expressed in international units (IU). The upper normal limit for serum is 300 IU. Protein was measured by the biuret method. A white blood cell count and red blood cell count were done on each pleural fluid.

Results

The causes of the 150 effusions are shown in Table 1. Only those effusions that fit the diagnostic requirements are shown; the 33 effusions that did not meet the criteria were excluded. The most probable diagnoses for the omitted patients were probable malignancy (8 patients with known malignancy and pleural effusions but with no malignant cells shown in the pleural cavity); viral pleuritis—7 patients; postoperative effusion—5 patients; congestive heart failure plus purulent sputum—4 patients; probable congestive heart failure (no autopsy)—2 patients; probable tuberculosis—3 patients; probable pulmonary infarction—3 patients; and uremic pleuritis—1 patient.

Figure 1 shows the protein concentration of the effusions, grouped by diagnostic category. Each point represents one pleural fluid. In general, transudates had a lower protein than did exudates, but considerable overlap is noted. When a protein level of 3.0 g/100 ml is used as the dividing line between transudates and exudates, 4 transudates and 11 exudates are placed in the wrong category. Moreover, 19% (8 of 43) of the malignant effusions are incorrectly grouped with the transudates.

The ratios of pleural-fluid protein to the serum protein, again grouped by diagnostic category, are shown in Figure 2. Transudates are seen to have lower ratios than exudates, but overlap still occurs. If a value of 0.50 for the ratio of pleural-fluid protein to serum protein is used as the dividing line, only 1 of 47 transudates is placed in the exudative range, compared with 4 when a protein level of 3.0 g/100 ml is used. Nevertheless, this dividing line still places 10 exudates in the transudative range.

Exudates tended to have higher erythrocyte counts than did transudates, but only a red blood cell count
greater than 100,000 is highly suggestive that a fluid is an exudate (Figure 3, Left). Since less than 20% of the exudates had red blood cell counts this high, this measurement is of very limited use. It is seen (Figure 3, Right) that a leukocyte count greater than 10,000/mm$^3$ is virtually always associated with an exudative effusion. A leukocyte count greater than 2500/mm$^3$ suggests that a fluid is an exudate. Nevertheless, since more than 40% of exudates have a leukocyte count less than 2500/mm$^3$, this measurement also seems to be of limited use for the separation of exudates from transudates.

Figure 4 depicts the LDH levels of the effusions. No transudate had an LDH level of more than 200 IU, whereas most exudates (71%) exceeded this level. Figure 5 summarizes the ratios of pleural fluid to serum LDH. It is seen that only 2% of transudates had LDH ratios greater than 0.6, whereas 86% of the exudates exceeded this value.

From the above results three characteristics can be singled out, each of which is associated with more than 70% of the exudates and, at most, one of the transudates: [1] a protein ratio greater than 0.5; [2] a pleural-fluid LDH greater than 200 IU; and [3] an LDH ratio greater than 0.6. The data were then analyzed to determine whether a combination of these individual characteristics might better separate transudates from exudates. Figure 6 shows that the simultaneous use of any two of these measurements was indeed more useful than the best individual measurement. For example, 90% of the exudates had either an LDH level greater than 200 IU or an LDH ratio greater than 0.6, but only one of the transudates met either of these criteria. The best set of two measurements in this series is a protein ratio of 0.5 in combination with a pleural-fluid LDH value of 200 IU; 97% of exudates had one of these characteristics—only one of the transudates had either one.

When all three measurements were used simultaneously, at least one of the three characteristics of exudates was found in all but one exudative effusion. On the other hand, only one of the transudates had even one of these characteristics.

The one effusion in this series that was classified as an exudate by the preset criteria but that did not have at least one of the characteristics of exudates developed in a patient with metastatic breast carcinoma while she was in severe congestive heart failure. The protein level of the fluid was 1.9 g/100 ml, and the pleural fluid-to-serum protein ratio was 0.34. The LDH level of the pleural fluid was 54 IU, and the LDH ratio was 0.26. The pleural effusion disappeared completely with only diuretic therapy, but the cytological examination of the fluid showed malignant cells. It seems probable, in retrospect, that the development of the effusion in this case was dependent on the congestive heart failure, rather than the pleural metastases.

The one effusion classified as a transudate by the preset criteria but that had two of the characteristics of exudates occurred in a patient who met the criteria for congestive heart failure. The pleural-fluid protein was 3.1 g/100 ml, the protein ratio was 0.57, the pleural-fluid LDH was 184 IU, and the LDH ratio was 0.96. The pleural fluid was bloody, with an erythrocyte count of 72,000/mm$^3$. Since there was no clinical evidence of pulmonary emboli, no lung scan was done; however, because of the very high pleural-fluid erythrocyte count and the relatively high LDH and protein levels, the possibility of pulmonary infarction remains.

**Discussion**

In the evaluation of a pleural effusion, its classification as either a transudate or an exudate is the first diagnostic step. If an exudative effusion is present, further diagnostic procedures are imperative, such as cytopathology, pleural biopsy, and sometimes even thoracotomy, so that a definitive diagnosis can be made and specific therapy for the pleural disease may
be instituted. On the other hand, if the fluid is clearly a transudate, one need not worry about therapeutic maneuvers directed at the pleura and need treat only the congestive heart failure, nephrosis, cirrhosis, or hypoproteinemia.

In the past, transudates were separated from exudates by the specific gravity, the cell count, and the presence or absence of clotting of the fluid (1). It was soon found, however, that it was often difficult to classify a given fluid. Paddock (1) in a retrospective review of 863 pleural effusions, in which no criteria for the various diagnoses were recorded, found that 10% of 350 effusions secondary to congestive heart failure, cirrhosis, or nephrosis had specific gravities greater than 1.016, whereas 10% of the effusions secondary to tuberculosis and more than 40% of those caused by malignancy had specific gravities of less than 1.016. He found that the pleural-fluid protein level was no more helpful than the specific gravity in differentiating transudates from exudates.

Luetscher (7) found that it was impossible to draw any dividing line between exudates and transudates, from the total-protein content, without encountering frequent exceptions. He suggested that the ratio of the pleural-fluid protein to the serum protein was more discriminating than was any protein concentration but that some exceptions still occurred.

Leuallen and Carr (8) reported that 28.1% of 32 pleural effusions caused by congestive heart failure had a specific gravity of 1.016 or more and that 27% of 137 fluids caused by neoplasm or tuberculosis had specific gravities of less than 1.016. They suggested that the protein level of the fluid might better be used to separate transudates from exudates. In a subsequent publication Carr and Power (4) reported that only 16% of effusions secondary to congestive heart failure had proteins of more than 3.0 g/100 ml and that only 7.2% of 167 fluids caused by malignancy and none of 20 tuberculous fluids had protein levels of less than 3.0 g/100 ml.

Our findings concerning the separation of transudates from exudates by the use of protein measurements are in general agreement with those reported previously. The use of a pleural-fluid protein level of 3.0 g for separation of transudates from exudates resulted in erroneous classification of 8% of the transudates and 11% of the exudates. Moreover, 19% of the malignancies were misclassified. A dividing line based on a pleural-fluid-to-serum protein ratio of 0.5 yielded a somewhat better separation than the protein level of 3.0 g, and only one of the transudates was incorrectly placed. But 10% of the exudates were still misclassified. There is no reason to believe that measurements of specific gravity would better separate transudates from exudates, since their usefulness is apparently related to their correlation with protein count. The specific gravity is probably less helpful than the protein concentration because it is measured with the commonly available hydrometer, which gives unreliable results (9).

It might be presumed that any pleural fluid that appears bloody would be an exudate, although some exudates might be serous. The present study shows that this is not true, since 15% of the transudates had red cell counts greater than 10,000/mm³. These results are very similar to those reported by previous authors. Paddock (1) found that 12% of transudates
had red blood cell counts greater than 10,000/mm$^3$. Tinney and Olsen (10) found that 24% of transudates were bloody. The occurrence of bloody transudates is probably related to the fact that it takes only 10,000 RBC/mm$^3$ to give a bloody appearance to a fluid. The leakage of but 2 millilitres of normal blood into 1000 millilitres of pleural fluid would result in such a count.

It might also be presumed that the white blood cell count of the pleural fluid would be helpful in separating exudates from transudates. Figure 3 (Right) shows that more than 80% of the transudates had white blood cell counts of less than 1000/mm$^3$, whereas more than 80% of the exudates had white blood cell counts greater than 1000/mm$^3$. Transudates rarely had white blood cell counts greater than 2500/mm$^3$, but only 57% of the exudates exceeded this value. These results are in close agreement with those of Paddock [1], who found that 12% of transudates had white blood cell counts greater than 1000/mm$^3$, that 30% of exudates had white blood cell counts greater than 5000/mm$^3$. Nevertheless, any separation effected by the total white cell count of the fluid is definitely inferior to the one effected by a protein ratio of 0.5.

Wróblewski and Wróblewski (11) first observed that malignant neoplastic cells in tissue culture contribute increasing amounts of LDH to the medium that bathes the cells. He found that the pleural-fluid LDH from effusions containing malignant cells was higher than was the simultaneous serum-LDH. Since that time several observations have suggested that the pleural-fluid LDH might be high in other exudative effusions. Rabinowitz and Dietz (12) found that stimulation of normal lymphocytes with phytohemagglutinin resulted in increased amounts of LDH in the cells. A similar mechanism may be operative in the hypersensitivity pleuritis that follows postprimary tuberculosis. Evans and Karnovsky (13) found that phagocytosis, by either guinea-pig polymorphonuclear leukocytes or peritoneal macrophages, was associated with a markedly increased lactic acid production, apparently related to a TPN-linked LDH. Most exudative effusions have either polymorphonuclear leukocytes or macrophages actively phagocytizing. Blonk, Schaberg, and Willighaven (14) observed that pleural mesothelial cells and macrophages from humans have strongly positive cytochemical LDH reactions.

This study indicates that most exudative pleural effusions (Figure 3, Right) have a relatively high LDH level. These findings contrast with those of Wróblewski (11), DeTorregrosa (15), Erickson (16), and Wu and Sung (17), who reported that an elevated pleural-fluid LDH was characteristic of malignant effusions and that nearly all benign effusions had low LDH levels. But the benign effusions in all 4 series were mainly transudates. Kirkeby and Prydz (18) first suggested that elevated pleural-fluid LDH may be characteristic of all inflammatory
conditions of the pleura. Chandresekar and his associates (5) more recently concluded that the absolute level of pleural-fluid LDH served better than the protein level in differentiating exudates from transudates; this conclusion contrasts with our results, which show (Figure 6) that the use of the protein ratio is better than either the absolute LDH or the LDH ratio for separating transudates from exudates. Although red blood cells contain a large amount of LDH, there was no correlation between the pleural-fluid LDH level and the red blood cell count, making it unlikely that hemolysis contributed significantly to the elevated LDH in exudates.

In Figure 6 it is seen that either a pleural fluid-to-serum protein ratio greater than 0.5 or a pleural-fluid LDH level greater than 200 IU, or a pleural fluid-to-serum LDH ratio greater than 0.6 misclassified more than 10% of the exudates but only one of the transudates. Since any of these three characteristics was associated with a misclassification of only one transude, it is reasonable to question whether the same exudates were misclassified by the individual variables. Figure 6 shows that, in fact, each of the characteristics misclassifies different exudates. Fewer exudates were misclassified with any pair of characteristics than with any one characteristic by itself. Moreover, when all three variables were used simultaneously, the chance of misclassification became exceedingly small. Only one of the exudates and one of the transudates were classified incorrectly.

Both of the misclassified effusions quite possibly were placed in the wrong category by the preset criteria. Although the pleural fluid of the misclassified "exudate" contained malignant cells, the cause of the effusion appeared to be congestive heart failure. Meyer (19) has observed that more than 40% of patients with pleural metastases do not have an associated pleural effusion at autopsy. A transudative pleural effusion in such a case could contain malignant cells. The "transudate" placed in the exudative category by two different characteristics was from a patient who definitely had congestive heart failure but who quite possibly also had pulmonary emboli.

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. For the separation of pleural transudates from pleural exudates, the simultaneous use of the protein and the LDH levels is more effective than the use of either one by itself. The presence of any one of the following three characteristics indicates that a fluid is an exudate: [1] a pleural fluid-to-serum protein ratio greater than 0.5; [2] a pleural-fluid LDH level greater than 200 IU; or [3] a pleural fluid-to-serum LDH ratio greater than 0.6.

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References


Gastrointestinal Absorption of Iron

DEMONSTRATION has already been made of the facts that: (1) under basal conditions of iron intake and utilization, hourly variations in the serum iron level are comparatively slight; and (2) following the oral administration of a single large dose of various of the iron salts, there is a prompt rise in the serum iron fraction. This increase is apparent within the first half hour, reaches its maximum in 2½ to 5 hours, and then gradually falls to approximate the basal level by the end of 12 hours. The serum iron increase is not associated with a rise in the serum bilirubin content. Hemoglobin and "easily split-off" iron fractions do not participate in the change. By following the serum iron responses to graded amounts of orally administered iron salts, therefore, under contrasting states of gastric acidity, during varying states of hematopoietic activity, and with experimentally altered conditions of intestinal motility and absorption, it should be possible theoretically to obtain considerable information about those factors which influence and control iron absorption. The present communication presents the results of such a study.

... From the data available in the literature and that which this communication presents, the following picture of iron absorption may tentatively be constructed. When ingested iron reaches the stomach, it is subjected to the influences of the prevailing acidity. The free hydrochloric acid normally present apparently has two functions: (1) to ionize and dissolve iron not already present in solution nor in an ionized state; and (2) to delay the formation of insoluble and undissociated iron compounds. Since these form at a pH above 5.0, the change to them would tend to occur to some degree, at least, in the stomachs of patients with achlorhydria. When the iron is delivered to the duodenum, it is subjected to two influences: the alkaline intestinal juices and certain reducing agents. The latter tend to reduce any trivalent iron to the ferrous form before the change to non-ionizable salts has occurred. Iron is absorbed from the intestinal tract largely, if not entirely, as ferrous iron. The degree to which ferric salts are assimilated would seem to depend upon the capacity of the intestinal contents to reduce them. It is the consensus of opinion that absorption takes place largely in the upper portion of the small intestine. When iron is absorbed, it passes directly into the blood plasma and is not to any extent collected by the intestinal lymph channels. As more data are accumulated, this working hypothesis based on information now available will undoubtedly be altered and enlarged.