Evaluating Pleural Fluid

Most clinicians agree that classifying pleural effusions as transudates vs exudates should be the first step in the laboratory evaluation of pleural effusions. The major objective is to identify patients with exudates who require further diagnostic evaluation, especially for conditions with potentially preventable morbidity, such as tuberculosis, complicated parapneumonic effusions, pulmonary emboli, connective tissue diseases, or treatable metastatic malignancies. The converse of this objective is to identify patients with transudates to avoid further costly evaluation.1

Since 1972, Light’s criteria have been used most commonly for this determination.2 Despite reports of lower specificity than in the original data of Light and colleagues, the sensitivity for identifying exudates ranged from 94 to 100%, with an average of 98% in 8 separate patient groups totalling 1,684 patients.3-10 This high sensitivity is to be expected from the combination of multiple tests where any positive result is categorized as disease.

Patients with pleural disease that is considered exudative but is classified as transudative by Light’s criteria are very rare and frequently break the oslerian rule of “one patient, one disease.” That is, they have both a transudative and exudative etiology for their effusion, such as congestive heart failure and malignancy.2,10 Further laboratory evaluation of pleural effusions classified as transudates by Light’s criteria has an extremely low yield.10 Unless the clinical history or examination findings are suspicious for an exudative process, it is appropriate and cost efficient to abandon any further laboratory testing on effusions classified as transudates. In my experience, this is almost never done. Instead, cell count, pH, glucose, amylase, Gram’s stain, bacterial culture, acid-fast bacillus smear, tuberculosis culture, fungal smear, fungal culture, and even cytologic studies are ordered before the results of lactate dehydrogenase (LDH) and total protein are known. Stopping this practice would save more money than making the criteria more specific.

In trying to improve specificity, a number of alternative criteria have been proposed, including the pleural fluid cholesterol,6 the serum-effusion albumin gradient,9 and the combined pleural fluid cholesterol and LDH.3 Although the latter criteria have the best reported combination of sensitivity and specificity (99 and 98%, respectively), they lack the track record of sensitivity that Light’s criteria provide.3 Of specific concern is that the fluid LDH greater than two thirds of the upper normal serum limit had the lowest sensitivity (66%) in a group of 297 patients reported by Romero et al.5 Contrary to the accompanying editorial11 to Costa et al,3 I do not think we should abandon Light’s criteria based on one publication.11 Once established, criteria should be prospectively confirmed on an independent, random population of patients.

The report in this issue of CHEST (see page 97) by Garcia-Pachon and colleagues on the serum cholinesterase ratio for separating transudates and exudates should be evaluated with guarded optimism. As with Light’s criteria, a simultaneous sample of both pleural fluid and serum improved the predictive value of the test and normalized the data from two different hospitals where two different assays were used. Using a cutoff level of 0.23 for the pleural fluid to serum cholinesterase ratio (all ratios greater than 0.23 are exudative), a sensitivity and specificity for exudates of 100 and 94%, respectively, were achieved. The sensitivity and specificity of Light’s criteria were 97 and 74%, respectively. It would be interesting to know how the combination of pleural fluid cholesterol and LDH criteria performed, but those data are not available in the manuscript.

Interesting data on the results of the criteria in undiagnosed pleural effusions are available. Only one previous report by Peterman and Speicher12 provides similar data. In both reports, the majority of undiagnosed pleural effusions are classified as exudates using Light’s criteria (30 of 32 in the present report and 56 of 62 in the Peterman and Speicher10 report). Because most of these patients would then get further testing and/or follow-up, the safety of the two-step laboratory approach (where the second step of further testing on effusions classified as transudates is abandoned) is enhanced. Clinical characteristics that have been associated with tuberculosis or malignancy in these patients include weight loss, fever, positive purified protein derivative, large effusions, and pleural fluid lymphocytosis.12

Aside from the relative obscurity of the serum cholinesterase in pleural effusion, the excellent perfor-
The Problem of Drug Resistance in Tuberculosis

The case report by Weltman and coworkers in this issue of CHEST (see page 279) presents a disturbing scenario, involving the infection of a young nursing assistant by a hospitalized patient with multidrug-resistant tuberculosis and her subsequent death as a result of hepatitis during treatment for disseminated disease. Her management throughout appears to have been marked by what can only be described as a failure of communication. The source case, though known to have resistant pulmonary tuberculosis, was, inexplicably, not placed in isolation. The health-care worker was treated with prophylactic isoniazid by the employee health service of the same hospital, and later with conventional agents, for presumptive tuberculosis, at a second hospital, although the organism in the original case was resistant to all primary drugs. The problem of resistance was finally recognized at a third New York City Hospital, and she was discharged on a self-administered five-drug regimen, including a large dose of rifabutin, and what appears to be inadequate doses of ethionamide and streptomycin, which was also self-administered. Finally she developed progressive hepatotoxicity, not reversed by stopping rifabutin and ethionamide.

Ethionamide, and less likely, rifabutin may have been involved in the hepatitis, but she was also given ofloxacin which has been associated with severe hepatitis. In retrospect, it may have been wise to temporarily stop all medications. Unfortunately, the choice of drugs to treat resistant tuberculosis is limited for the most part to older agents distinguished by toxicity, intolerance, and limited effectiveness. Rifabutin is a potent antimonycobacterial agent, but there is frequent cross resistance with rifampin. The most promising group of drugs is the fluoroquinolones, such as ciprofloxacin, but these have not been adequately tested. The fact is that the pharmaceutical manufacturers show little interest in developing new drugs for tuberculosis or even in maintaining supplies of the existing ones.

The transmission of tuberculosis is unpredictable, and the nursing assistant appears to have been the only one to have been infected among 79 mantoux negative, exposed health-care workers. The Centers for Disease Control, however, has reported conversion rates of 33 and 50%, in health-care workers exposed to multidrug-resistant disease, in addition to at least two cases of active disease, in a survey of four hospitals. Infection of staff members should always be of concern, but the catastrophic results, which can ensue with resistant tuberculosis indicate the importance of isolation, enhanced by such measures as exhaust ventilation, upper room ultraviolet fixtures, and tightly fitting particle masks. Where possible, of course, tuberculosis should be treated on an outpatient basis.

The alarming increase in multidrug-resistant tuberculosis has been related to HIV infection, to the rapid transmission of infection in hospitals and other institutions, and to noncompliance in taking medications. Methods of administering treatment have been reexamined, and directly observed therapy of all patients with tuberculosis has been recommended. It should be noted that the increase in resistance coincides not only with the AIDS epidemic, but also with the widespread use of 6-month regimens. Is there a possibility that such regimens are partly responsible for the development of resistance because of either the short