Serum Lactate Dehydrogenase (LDH) in 

*Pneumocystis carinii* Pneumonia, Tuberculosis, and Bacterial Pneumonia*

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An increase in serum lactate dehydrogenase (LDH) activity is commonly taken to support the presumptive diagnosis of *Pneumocystis carinii* pneumonia (PCP), although the LDH level may also be increased in other lung infections and in a variety of extrapulmonary disorders. To assess its diagnostic value in patients with fever, lung infiltrates, and a high prevalence of HIV infection, we compared LDH levels in 42 hospitalized patients with PCP, 71 with disseminated tuberculosis (TB), 40 with pulmonary TB, and 37 with bacterial pneumonia. Peak LDH level was higher (p<0.05) in patients with PCP (547±157 U/L) and disseminated TB (509±338 U/L) than in patients with pulmonary TB (258±66 U/L) or bacterial pneumonia (331±139 U/L). However, substantial overlap between groups limited its diagnostic value for individual patients. Expressing LDH as its ratio to simultaneous serum aminotransferases (AST or ALT) did not enhance its discriminatory value. Most patients in each group had abnormalities in other serum enzymes (AST, ALT, alkaline phosphatase, γ-glutamyltransferase), making an isolated elevation of LDH level uncommon (21% of PCP cases). Serum LDH has a high sensitivity for PCP (100% in this series) but must be interpreted with caution given its lack of specificity.

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### Key words:
- bacterial pneumonia; enzyme tests; HIV infection; lactate dehydrogenase; *Pneumocystis carinii* pneumonia; tuberculosis (pulmonary tuberculosis, miliary tuberculosis)

### Methods

Convenience samples of patients hospitalized for PCP, focal pulmonary TB, and bacterial pneumonia were drawn from records of pulmonary consultations and from a computerized listing of hospital discharge diagnoses for 1991 to 1993. Consecutive cases meeting the inclusion criteria were entered until there were approximately 40 in each group. Additionally, we studied a previously described cohort of patients with disseminated TB.8

Patients were included if their medical record contained at least two values for LDH during the acute illness as well as simultaneous values for aspartate aminotransferase (AST) and alanine aminotransferase (ALT). Patients were excluded if they carried a diagnosis associated with raised serum LDH level, including erythrocyte disorders, malignancy, liver disease, shock, rhabdomyolysis, and renal failure. We report the highest LDH value obtained during the first week of hospitalization, as well as the ratios of LDH to the simultaneous AST and ALT. Most patients also had determinations of alkaline phosphatase and γ-glutamyltransferase (GGT) performed within 3 days of the LDH.

The diagnosis of PCP was confirmed by bronchoscopy in all cases. Pulmonary TB was confirmed by culture of *Mycobacterium tuberculosis* from respiratory secretions. Bacterial pneumonia was diagnosed when the patient presented with fever and focal lung consolidation and responded to treatment with an antibiotic(s) other than an aminoglycoside or a fluoroquinolone.

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Human immunodeficiency virus (HIV)-induced immunodeficiency typically leads to secondary infections involving the lungs, of which *Pneumocystis carinii* pneumonia (PCP), bacterial pneumonia, and granulomatous infections (tuberculosis [TB], fungi) are the foremost examples. Definitive diagnosis of these infections, which may entail bronchoscopy or delayed culture results, is often not feasible at presentation. Hence there is considerable interest in noninvasive aids to initial presumptive diagnosis and empiric antimicrobial therapy. PCP has been the main focus of attention, because it is the most common opportunistic pneumonia complicating AIDS and because invasive methods are often required for diagnosis.

The serum lactate dehydrogenase (LDH) activity is increased in more than 90% of AIDS-related cases of PCP,1-4 but it can also be increased in other pulmonary,5,6 and numerous extrapulmonary diseases.6,7 In recent years, we have noted a discordant tendency for physicians to rely on the LDH level to discriminate PCP from other lung infections, even to the point of measuring LDH without considering other serum en...
than trimethoprim/sulfamethoxazole; a bacterial etiology was confirmed by blood culture in 14 of 37 patients (38%; Streptococcus pneumoniae in 12, Haemophilus influenzae in 1, Staphylococcus aureus in 1).

Patients were considered to have HIV disease if they (1) had a confirmed positive serologic test for HIV, (2) met the 1987 Centers for Disease Control and Prevention (CDC) case surveillance definition for AIDS, or (3) had a risk factor for HIV infection together with a CD4 count <400 cells per microliter and a CD4/CD8 ratio <1.0.

All data are presented as the mean±SD. Intergroup differences for each enzyme variable were assessed by one-way analysis of variance followed by the Scheffé procedure (SPSS). The relationship of LDH to the aminotransferases was assessed by analysis of covariance, using AST and ALT as multiple covariates; the adjusted LDH means were compared by the Scheffé procedure.

RESULTS

Lactate dehydrogenase level was increased in 100% of patients with PCP, but it was also increased in most patients in each of the other groups (Table 1, Fig 1). The mean values were nearly identical in patients with PCP and disseminated TB, both groups showing higher levels than those with bacterial pneumonia or pulmonary TB (Table 2).

The chest radiographs of patients with disseminated TB showed a miliary pattern in 54%, focal lung lesion(s) in 14%, and clear lungs in 32% at presentation (intrathoracic lymphadenopathy was visible in 9 of 23 with clear lungs). There were no significant differences in LDH levels at the time of the radiographs among these subgroups (mean LDH=559, 490, and 507 respectively; p=0.71).

Among all patients combined, LDH showed independent linear correlations with AST and ALT (r=0.66 and 0.38, respectively; p<0.01). The aminotransferase levels together accounted for a substantial portion of the variability in LDH (r²=0.44; multiple regression, p<0.0001), due largely to its correlation with AST. The mean LDH values adjusted for AST and ALT (analysis of covariance) remained higher in patients with PCP (579 U/L) and disseminated TB (507 U/L) than in patients with bacterial pneumonia (344 U/L) or pulmonary TB (326 U/L) (p<0.05). Thus the high LDH values in disseminated TB were not explained solely by injury to tissues that also release aminotransferases proportionately, eg, liver necrosis.

Since the elevation of serum LDH level in patients with PCP is thought to occur independently from other commonly measured enzymes, we hypothesized that the ratio of LDH to AST or ALT would improve discrimination of PCP from other causes of increased LDH. Both ratios tended to be higher in patients with PCP than in the other groups (Table 2), but the considerable overlap made them unreliable for diagnosis of PCP in individual patients (Fig 2).

Most patients, regardless of group, exhibited mild to moderate increases of at least one enzyme other than LDH (AST, ALT, alkaline phosphatase, GGT; Table 1, Fig 3). In only 21% of patients with PCP was the peak LDH level accompanied by normal aminotransferase levels. Levels of GGT and alkaline phosphatase were both higher in patients with disseminated TB than in the other three groups (data not shown), probably reflecting granulomatous lesions of liver and other extrapulmonary sites.

DISCUSSION

Our main finding is that serum LDH activity is increased in most patients requiring hospitalization for all four conditions studied. Prior reports have suggested a diagnostic role for LDH in PCP but included relatively few patients with other forms of pneumonitis for comparison.4-7 We have found LDH levels to be increased in patients with infections that sometimes mimic PCP (or vice versa) and that frequently enter its differential diagnosis. Thus, our results confirm the high sensitivity of the serum LDH level for PCP, but suggest that its specificity in this clinical setting is limited.

Pneumocystis carinii pneumonia is considered to produce an isolated elevation of serum LDH level, lung parenchyma being the putative source;5 although prior studies have not examined simultaneous values of other enzymes. Lactate dehydrogenase is a ubiquitous enzyme, and serum levels increase in a wide variety of diseases. Some, such as hepatic, hematologic, and neoplastic disorders, occur frequently in the setting of AIDS. Isolated elevation of LDH level proved to be uncommon in our patients with PCP, possibly because background disorders such as chronic viral hepatitis or
fatty liver often coexist and contribute to enzyme abnormalities.

Clinicians are familiar with mild elevations of serum LDH levels in cases of non-PCP pneumonia. In bacterial pneumonia the injured lung might be the source, but the concomitant abnormalities in “liver enzymes” suggest that alternative mechanisms may often play a role, such as the hepatic dysfunction associated with bacterial sepsis and/or other coexisting disorders.

To our knowledge, LDH in TB has not received emphasis in the literature. Tissue necrosis, a characteristic feature of tuberculous granulomas, provides a ready explanation for elevated LDH values. Necrosis was observed in most tissue samples from disseminated cases and was no doubt usually present in pulmonary cases as well, as evidenced by radiographic cavities in a third of patients. Frank necrosis of lung (or other organ) parenchyma may not be required to raise the serum LDH level, however, as suggested by the examples of PCP and pulmonary alveolar proteinosis, in which lung architecture is often preserved.

Patients with localized pulmonary TB had normal or mildly increased LDH levels, never exceeding 400 U/L. Patients with disseminated TB often showed striking elevations of LDH, exceeding 500 U/L in 41%. The higher levels in disseminated TB might reflect a greater total-body burden of tuberculous lesions,

Table 2—Serum Enzyme Activities in Units per Liter (Mean±SD)*

<table>
<thead>
<tr>
<th></th>
<th>LDH</th>
<th>AST</th>
<th>ALT</th>
<th>LDH/AST</th>
<th>LDH/ALT</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCP</td>
<td>547±157</td>
<td>65±34</td>
<td>44±41</td>
<td>10.4±5.6</td>
<td>21.2±16.3</td>
</tr>
<tr>
<td>DTB</td>
<td>569±338</td>
<td>118±117</td>
<td>65±64</td>
<td>6.8±4.0</td>
<td>13.3±13.8</td>
</tr>
<tr>
<td>PTB</td>
<td>258±66</td>
<td>45±33</td>
<td>35±22</td>
<td>7.9±4.2</td>
<td>11.7±10.4</td>
</tr>
<tr>
<td>BACT</td>
<td>331±139</td>
<td>76±85</td>
<td>47±44</td>
<td>8.4±7.1</td>
<td>15.8±18.1</td>
</tr>
</tbody>
</table>

*DTB=disseminated TB; PTB=pulmonary TB; BACT=bacterial pneumonia.

Normal ranges: LDH 80-250, AST 0-40, ALT 0-40.

Statistical differences (ANOVA, Scheffé procedure, p<0.05):
- LDH: PCP>DTB>PTB, BACT.
- AST: DTB>PCP, PTB.
- ALT: DTB>PTB.
- LDH/AST: PCP>DTB.
- LDH/ALT: PCP>PTB.
greater access of LDH to the circulation from small miliary lesions, a greater propensity of certain extra-pulmonary organs (eg, liver, spleen, bone marrow) to release LDH when involved, or other unidentified factors. LDH values exceeding 1,000 U/L were observed only in patients with disseminated TB and were a sign of poor prognosis; 6 of 11 died. Such extreme elevations of LDH level probably reflect the widespread necrotizing lesions of overwhelming miliary disease.

In our experience, the initial working diagnosis of acute lung disease in patients with known or suspected HIV infection is guided by clinical observations but rests mainly on the pattern of radiographic abnormality. This study does not permit a formal estimate of the specificity or positive predictive accuracy of LDH level in diagnosing PCP, but suggests that LDH, like hypoxemia, is too nonspecific to hold discriminative value in individual patients. While its positive predictive accuracy would improve if one took twice the upper limit of normal (500 U/L) as the diagnostic threshold, this would greatly reduce its sensitivity (Fig 1), especially for cases that are not full-blown radiographically. A prospective study is needed to determine whether knowledge of the serum LDH level substantially improves the accuracy of a clinician’s presumptive diagnosis. Meanwhile, our data caution against undue reliance on the LDH level alone in forming a diagnostic impression. A normal serum LDH level may be useful in excluding PCP (at least in cases with definite lung infiltrates), but elevated values remain nonspecific and must be interpreted with due consideration of coexisting diseases and other serum enzyme abnormalities.

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REFERENCES


