Usefulness of Data on Albumin and Prealbumin Concentrations in Determining Effectiveness of Nutritional Support

Larry H. Bernstein, Carla J. Leukhardt-Fairfield, Walter Pleban, and Rosser Rudolph

In this ongoing study, albumin and prealbumin (transhthyretin) changes were compared in 40 patients managed with enteral and (or) parenteral support with attainment of caloric/protein goals. The concentration of prealbumin in serum changed rapidly and more accurately reflected current nutritional status of these patients than did that of albumin. We determined concentrations of albumin and prealbumin that reflected significant improvement in nutritional status, using Rudolph's approach based on Shannon information measures. Reference values for albumin and prealbumin in the treatment populations were 25 g/L and 107 mg/L, respectively. A prealbumin concentration of 135 mg/L or greater reflected a return to stable status.

A more sensitive and reliable marker is needed that (a) identifies malnourished patients and (b) effectively monitors the effects of nutritional intervention on the patient's nutritional status, particularly the impact it may have on morbidity and mortality (I-3) and on shortening hospital stay.

It is now well established that anthropometric methods of assessment, measuring losses from the somatic compartment (i.e., triceps skin fold, arm muscle circumference, weight/height ratio), are insensitive measures of protein/calorie malnutrition (4-5). Because these measures are referenced to a population rather than to the individual concerned (6), they are usually reliable only after longstanding changes in protein/calorie malnutrition and often with concurrent changes in the visceral protein compartment.

The most commonly measured indices of nutrition depletion in the visceral protein compartment are the concentrations of albumin and transferrin in serum (3, 7, 8)—also now considered to be insensitive indicators of a patient's nutritional status (9-12). Albumin can be affected by liver or kidney disease and by the hydration state of the patient (11). Total iron-binding capacity, used for a transferrin calculation, is affected by anemia and iron overload (12). Albumin and transferrin concentrations in serum are poorly correlated (13), nor are they correlated with measurements of prealbumin (PAB) and retinol-binding protein concentrations. PAB (10, 14, 15) and retinol-binding protein (15, 16), with only two-day biological half-lives, are considered as sensitive indicators of nutritional status in an ostensibly healthy normal population such as American Red Cross volunteer donors (13). Moreover, the insensitivity of transferrin and albumin is not corrected by using a combined vector variable, the prognostic nutrition index (17, 18). This led to disagreement regarding the advantages of clinical assessment (10) or subjective global assessment (19) vs prognostic nutrition index.

Here we report studies of patients who received enteral or parenteral nutritional support, or both, at Bridgeport Hospi-
ence subset compared with the disease-reference subset treated with nutritional support.

For the calculations involved in this study we used "api" software programs, either written by Dr. Rudolph, or provided by stsc, inc. (Rockville, MD), as "statgraphics" for the IBM XT, as previously described (22). The reference limits of the data set were estimated on the basis of the maximum entropy of the data base, the data entropy, and the difference between the entropies—i.e., the "effective information" of the data set.

We examine the entropy of multivariate data for each variable by setting the binary decision level at the median and measuring the frequency of the binary patterns produced to calculate the entropy of the discrete distribution, the "Bernoulli test" (22). When two variables are used and are randomly independent, they have a flat probability distribution, with an entropy approaching 2 bits. The measured uncertainty is maximum, indicating that no effective information is present. When the data contain effective information, the distribution differs from the flat maximum entropy partition as follows: the all-positive pattern, 00, and the all-negative pattern, 11, usually have a higher frequency than the intermediate patterns, 01 and 10, yielding a measured entropy of less than 2 bits. If information is present, maximum entropy can be mimicked by randomly shuffling the two variables to obtain a flat probability distribution. The difference between the measured entropy of the data base and the expected maximum uncertainty reflects the effective information present (22).

Results

Figure 1 illustrates the ALB and PAB changes in a cancer patient who received nutritional support but died 36 days after admission. These changes are plotted for the first 27 days of hospitalization, and they are compared with the attainment of calorie and protein needs. The serum ALB decreased by 5 g/L and the PAB (already severely depressed at 25 mg/L) did not change during the first five days after admission, when the patient was fasting. The serum ALB decreased by a further 1 g/L during the next three days, despite aggressive feeding meeting 90% of nutritional needs. The PAB increased by 85 mg/L during the remaining 22 days of treatment. The ALB did not increase more than 1 g/L over this same interval. The daily increase in PAB averaged about 3.8 mg/L. A successful course of therapy is accompanied by a usual daily increase in PAB of not less than 9 mg/L.

Figure 1 illustrates the correlation of PAB increase with a change reflecting attainment of calorie and protein needs. The serum PAB changes more rapidly and more accurately reflects the current nutrient status of the patient than does ALB.

Figure 2 shows a plot of the data representing the course of a patient who was maintained with adequate nutritional support during a month. Not only are the changes in PAB and ALB correlated, they also increase with nutritional support meeting at least 50% of estimated requirements as seen from the plot (during which the PAB was assayed more frequently than the ALB). This patient's PAB and albumin values both increased as feeding was improved according to estimated nutritional needs, the response of ALB being the more gradual. An ALB value that reaches 34 99/L and a PAB value that reaches 180 mg/L is expected to accompany a good clinical response.

Figure 3 shows a plot of the data representing a patient who responded poorly to nutritional support. This poor response is reflected in the slight increase only in PAB during 13 days of feeding that met 100% of estimated needs. The PAB increase did not exceed 110 mg/L on day 9 and subsequently decreased to 70 mg/L, whereas the ALB decreased to 22 g/L.

Figure 4 shows a plot of changes in PAB concentration vs nutrient intake as percent of needs; it is based on data for at least 40 patients. There are two major clusters with a mean increase in PAB of 60 mg/L corresponding to a nutrient intake meeting 85% of needs and a mean decrease of PAB of 40 mg/L, corresponding to attainment of 22% of nutrient goals. No change or a decrease in PAB is seen within a range of nutrient intake between 40% and 60% of needs.

Examination of the frequency distribution and normal probability plots of serum PAB for the hospitalized population showed that an assumption of normality does not coincide with the values for PAB because of the frequency with which PAB was <80 mg/L. Of the PAB values in the population, 95% are <230 mg/L. The median of these values is 130 mg/L.

To determine the best values for ALB and PAB to use for decision limits, we plotted the effective information for ALB and PAB, using 27 g/L and 107 mg/L to determine the
maximum entropy of the randomized data base and the data entropy, respectively. The effective information is the difference between the maximum entropy and the data entropy. The entropies at ALB 31 g/L and PAB 129 mg/L are information obtained at the medians of the population data. There is information at ALB 20 g/L. This is significant because of the known poor survival at ALB below 20 g/L. The maximum effective information is at ALB 27 g/L and PAB 107 mg/L.

Table 1 shows frequency distribution and cumulative information of the patterns created by the decision levels for ALB and PAB at 27 g/L and 107 mg/L, respectively.

Table 2 shows the occurrence of patterns that are not 00 or 11, separated by ALB at 27 g/L and PAB at 107 mg/L. If the decision level for ALB were at 31 g/L, there would be 10 patients in group A. Actually, the frequency of the 11 pattern would be decreased from 33 to about 22 patients at 31/107. If the decision levels were changed to 27/129 there would be 10 patients in group B with ALB exceeding 27 g/L and PAB below 129 mg/L (pattern 2).

We re-investigated the information maxima by combining several sets of data, substantially enlarging the data base, including a healthy data base replicated and added for the study. The results obtained were decision values for ALB of 25 and 35 g/L and for PAB of 107 and 135 mg/L, with medians at 31 g/L and 145 mg/L, respectively.

The studies of information maxima with the new data base were compared with a more familiar sort of study in which statistical methods are used. This study was limited to a series of 10 patients for whom our data on PAB, ALB, and nutrient intake during the entire hospitalization were complete. These patients were individually classified according to the changes in protein markers and in nutrient intake. The variables used for classifying were analyzed. Simple regression with analysis of variance showed correlations between PAB and intake ($F(48) = 13.61; P = 0.007$), between PAB and ALB ($F(48) = 20.15; P = 0.0001$), and no correlation between ALB and intake. Kruskal–Wallis analyses of the data for PAB and ALB, by patient, were significant at $P < 0.001$.

We compared the performance of the prediction variables by carrying out a multiple linear regression with stepwise selection of variables. This resulted in elimination of intake and ALB from the model and selection of PAB as the best variable for predicting class. We used the PAB and ALB as variables in a discriminant function for class selection, obtaining: eigenvalue, 0.8478; canonical correlation, 0.6774; Wilks lambda, 0.5412; chi-square, 28.24. Using the discriminant function analysis model, we estimated the separation between the classes at a PAB concentration at 123 mg/L and ALB concentration of 26 g/L, but the PAB concentration was revised to 117 mg/L when we used the linear regression model. Nevertheless, studies of the distribution of these data showing a log normal and a normal distribution for the PAB and ALB, respectively, explain problems inherent from distributional assumptions about the data ($24, 25$). The Kolmogorov–Smirnov test gave lower values for PAB and ALB concentrations to separate the groups, 105 mg/L and 25 g/L, respectively, like the results obtained from information measures. Consequently, the studies using information and statistical methods with an enlarged set of data indicate serum concentrations of ALB and PAB at 25 g/L and 107 mg/L to separate patients treated with protein/calorie malnutrition into two treatment groups.

### Table 1. Classification Matrix at the Decision Level:

<table>
<thead>
<tr>
<th>Pattern</th>
<th>Number</th>
<th>Frequency</th>
<th>Entropy</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>24</td>
<td>0.3529</td>
<td>0.5303</td>
</tr>
<tr>
<td>1</td>
<td>6</td>
<td>0.0862</td>
<td>0.8393</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>0.0735</td>
<td>1.1162</td>
</tr>
<tr>
<td>3</td>
<td>33</td>
<td>0.4853</td>
<td>1.6224</td>
</tr>
</tbody>
</table>

That there are binary patterns with a predominance of 0 and 3 shows the presence of information because of the presence of malnutrition in the population.

### Table 2. Intermediate Patterns of Separation by ALB/PAB = 27/107

<table>
<thead>
<tr>
<th>A</th>
<th>B</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALB</td>
<td>PAB</td>
</tr>
<tr>
<td>26</td>
<td>150</td>
</tr>
<tr>
<td>27</td>
<td>198</td>
</tr>
<tr>
<td>27</td>
<td>186</td>
</tr>
<tr>
<td>21</td>
<td>129</td>
</tr>
<tr>
<td>25</td>
<td>190</td>
</tr>
<tr>
<td>24</td>
<td>162</td>
</tr>
</tbody>
</table>

Albumin and prealbumin results contributed by patterns of 1 and 2 using albumin and prealbumin decision points.

![Graph showing the relationship between nutritional requirements and ALB/PAB](image)

**Fig. 3.** PAB and ALB changes reflecting lack of sustained response to feeding

The serum PAB increased to more than 110 mg/L and subsequently declined with 100% of feeding requirements met, a response reflecting the nutrient status of the patient.

![Graph showing change in PAB concentration](image)

**Fig. 4.** Changes in PAB concentration with nutrient intake as percent of nutrient needs met for various patients.

**CLINICAL CHEMISTRY, Vol. 35, No. 2, 1989** 273
Discussion

This study demonstrates that PAB, a sensitive protein marker for determining protein/calorie malnutrition losses in the visceral compartment, reflects changes more rapidly and reflects attainment of nutritional requirements better than do changes in serum ALB. However, it was of considerable interest to find that PAB changes become significant when nutrient intake increases to exceed 50% of estimated needs. This study shows most markedly the effects on PAB of changes with repletion of protein mass.

The study shows the relative usefulness of values for ALB and PAB where there is effective information on the population in terms of decision levels. There is most effective separation of the malnourished patients who improve with nutritional support to attain stable status. We find decision points at ALB 25 g/L and PAB at 107 mg/L, respectively. Using Shannon information measures to examine data sets that include a healthy population indicates the decision levels for ALB/PAB to be 35 g/L and 135 mg/L, below which there is significant risk of protein/calorie malnutrition-related complications.

References