Clinicians caring for patients on peritoneal dialysis (PD) have relied on a variety of laboratory measures to assess the health of patients and their response to treatment. Traditionally, serum albumin has been an indicator of nutrition status and has therefore been included in monthly blood testing in most centers.

The development of hypoalbuminemia in dialysis patients has been associated with increased mortality and often leads to interventions such as trials of nutritional supplements. In PD, hypoalbuminemia combined with ongoing losses of protein into effluent raise particular concerns with clinicians.

Serum albumin may be affected by a variety of non-nutrition factors such as inflammation, volume status, and comorbidities. Albumin synthesis in the liver exceeds, in most cases, albumin losses in urine or effluent. Interpreting the medical implications of declining serum albumin in PD patients can therefore be a challenge.

This paper reviews protein balance in PD. The nutritional and non-nutritional factors affecting serum albumin are discussed, with specific emphasis on how membrane physiology contributes to dialysate protein losses. A general clinical approach to the PD patient developing hypoalbuminemia is discussed.

**Key words**
Hypoalbuminemia, albumin, protein balance, protein losses, nutrition, inflammation

**Introduction**
Uremic patients initiating peritoneal dialysis (PD) would be expected to experience clinical improvement, with an increase in appetite and nutritional intake. This increase in dietary intake would be expected to favorably affect any underlying nutritional deficits that may have developed in the pre-dialysis interval. And yet, despite the improvement in uremia, some patients develop a progressive decline in serum albumin concentration. The development of hypoalbuminemia in PD patients may represent a complicated interplay of nutrition, non-nutrition, and modality-specific factors such as protein loss into PD effluent.

To further complicate matters, clinicians may now be uncertain about the implications of hypoalbuminemia. Is hypoalbuminemia a marker of nutrition? Is hypoalbuminemia a marker of active comorbid disease, separate from true protein intake? Is hypoalbuminemia purely a marker of volume status and indicative of dilution of the serum albumin concentration? These questions are valid, and clinicians caring for hypoalbuminemic patients may benefit from a clinical algorithm for the assessment and treatment of those patients.

This paper reviews the role of serum albumin as a true marker of nutrition, reviews other processes that may affect serum albumin concentration, discusses protein balance in PD patients, and reviews a clinical approach and treatment strategy for the PD patient developing hypoalbuminemia.

**Discussion**

*Utility of serum albumin as a marker of nutrition*
As eloquently reviewed by Friedman and Fadem, serum albumin may not adequately reflect the true nutritional status of patients (1). Perhaps most illustrative of this fact is an examination of the patient with analbuminemia—a congenital absence of measurable serum albumin (2). This autosomal recessive disorder presents with an absence or marked reduction in serum albumin and is the result of several described mutations in the albumin gene (3). The mutations are felt to disrupt intracellular transport of albumin and to lead to early degradation. Serum oncotic pressure is maintained by increased production of non-albumin proteins such as alpha-2-globulin, beta globulin, and apolipoproteins. Despite unmeasurable serum albumin levels, these patients may have a normal nutritional status and have not been felt to demonstrate serious clinical complications of analbuminemia itself.
Another example of the limited use of serum albumin as an indicator of nutritional status is the condition of marasmus. This condition occurs after longer-term deprivation of adequate nutritional intake, as is seen in starvation. Patients are markedly thin, weak, and listless, and yet may demonstrate a normal serum albumin concentration. Similar observations have been made in patients with anorexia nervosa: despite intentional limitations in nutritional intake, patients may maintain a near-normal serum albumin concentration until the terminal end of the process (4).

Serum albumin is not a sensitive measure of dietary protein intake. For example, protein-restricted diets have been recommended in patients with chronic kidney disease (CKD) to slow disease progression. In the United States, the Modification of Diet in Renal Disease study, published in 1997, studied the impact of dietary protein restriction on the progression of CKD (5). In that study, patients with CKD stages 3 and 4 were randomized to a usual-protein diet of 1.3 g/kg daily or a low-protein or very-low-protein diet of 0.58 g/kg daily. Mean duration of follow-up was 2.2 years. In the low- and very-low-protein groups, serum albumin rose. A French study prescribed supplemented protein-restricted diets that reduced protein intake to 0.43 g/kg from 0.85 g/kg daily. During the study period, serum albumin concentrations were unchanged (6). Those studies demonstrate that, within a range of lower protein intakes, patients with kidney disease have been able to maintain a traditional indicator of nutrition (serum albumin), suggesting that this measure alone is an insensitive marker of true protein intake or requirements.

Serum albumin might therefore not be indicative of nutritional status and might be inferior to other classical measures such as subjective global assessment, mid-arm circumference, and careful dietary histories.

Non-nutrition factors affecting serum albumin concentration

A variety of clinical conditions may affect serum albumin (Table I). Those conditions may be wholly separate and distinct from nutritional intake and may independently alter the serum albumin concentration.

States of overhydration have classically been described as causing hypoalbuminemia because of dilution. Dilutional hypoalbuminemia can be seen in a variety of overhydration states such as congestive heart failure or CKD. Volume depletion has the opposite effect, causing elevated albumin because of plasma volume contraction. Volume status may therefore independently affect serum albumin.

Albumin is a negative acute-phase reactant, meaning that, in states of inflammation, serum albumin is depressed. Inflammatory states can affect the levels of a variety of plasma constituents, increasing them (acute-phase reactants) or lowering them (negative acute-phase reactants) (8). The putative role of the negative acute-phase response is to reduce production of some proteins to conserve amino acids, shifting those substrates to the production of other hepatic proteins that can augment the immune system during infection or inflammation. This negative acute-phase response of albumin is, therefore, generally independent of nutritional intake.

These non-nutritional factors affecting serum albumin concentration may explain the unpredictable response in patients on dialysis to nutritional supplements administered in an attempt to increase this laboratory value (9).

Protein balance in PD

Albumin and protein stores in the PD patient are determined by dietary protein intake, rates of hepatic synthesis of albumin and other proteins, protein losses into effluent, and urinary losses in patients with residual kidney function (Table II). In the stable PD patient, recommendations for dietary protein intake are 1.2 – 1.3 g/kg daily (10). Protein losses into effluent are typically 5 – 15 g daily (11). Urinary protein losses are also a possibility. To offset those losses, the rate of albumin synthesis in the liver is 12 – 15 g daily. In PD patients, Kaysen (7) demonstrated an increase in the albumin synthesis rate proportional to external albumin losses. This compensatory increase in albumin synthesis typically maintains normal plasma albumin concentrations during PD therapy and explains why peritoneal albumin and protein losses into dialysate are, themselves, not predictive of outcome (13). Further investigations in PD patients determined that states of inflammation directly suppress hepatic albumin synthesis, preventing compensatory increases in albumin production (12). The development of hypoalbuminemia in most PD patients therefore appears to be characterized by a combination of the acute-phase response, with a reduction in serum albumin, combined with a true decrease in albumin synthesis to compensate for protein losses into effluent.
Determinants of protein losses into peritoneal effluent

Protein loss into peritoneal effluent has been noted to vary widely from patient to patient and from day to day in a single patient (14). The main determinant of effluent protein loss is the large-pore flux across the peritoneal capillary lumen (15). In the 3-pore model of peritoneal permeability, the large pores allow for the flux of proteins into dialysate, with some loss of smaller proteins across the small pores (16). As mentioned earlier, daily protein losses into effluent are typically 5 – 15 g, with the variation reflecting differences in the capillary density of the peritoneal membrane.

Capillary density and surface area are the main determinants of the peritoneal membrane transport category, as described in the classical peritoneal equilibration test [PET (17)]. Peritoneal membrane transport categories—originally described as low, low-average, high-average, and high—actually reflect the capillary surface area of the peritoneal membrane. Low-transport membranes are less vascular, and high-transport membranes typically reflect increased vascular density because of the individual’s underlying baseline anatomy or as a consequence of neovascularization during longer-term exposure to dialysate (18,19). The migration of PET results toward higher transport characteristics over time is presumed to be a result, in part, of the elaboration of vascular endothelial growth factor, which induces capillary neovascularization (20). Additionally, patients may transiently demonstrate increased vascular permeability during peritoneal inflammation—as in peritonitis, for example. Episodes of peritonitis are associated with increased small-solute clearance across the membrane and increased protein losses into effluent because of vasodilation of the capillary bed, which

### Table I
Evidence suggesting that serum albumin is not a pure marker of nutrition

<table>
<thead>
<tr>
<th>Evidence</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital analbuminemia has been described, and many patients appear to develop normally and to have a normal nutrition status.</td>
<td>1,2</td>
</tr>
<tr>
<td>Albumin can shift from the plasma space to the interstitial space in sepsis or burns.</td>
<td>1</td>
</tr>
<tr>
<td>Severe anorexia nervosa is often accompanied by normal serum albumin.</td>
<td>4</td>
</tr>
<tr>
<td>Patients with marasmus may maintain normal serum albumin.</td>
<td>1</td>
</tr>
<tr>
<td>The Modification of Diet in Renal Disease study examined reduction in protein intake as low as 0.3 g/kg daily and noted no decline in levels of serum albumin.</td>
<td>5</td>
</tr>
<tr>
<td>Serum albumin may be affected by volume status (dilutional hypoalbuminemia)</td>
<td>7</td>
</tr>
<tr>
<td>Albumin is a negative acute-phase reactant; lower serum levels are seen in the setting of systemic inflammation</td>
<td>8</td>
</tr>
</tbody>
</table>

### Table II
Protein balance in peritoneal dialysis (PD)

<table>
<thead>
<tr>
<th>Contributor to protein balance</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommended daily dietary protein intake in PD is 1.2–1.3 g/kg</td>
<td>10</td>
</tr>
<tr>
<td>Daily protein losses in dialysate are typically 5–15 g</td>
<td>11</td>
</tr>
<tr>
<td>Daily albumin losses in dialysate are 3–6 g/1.73 m²</td>
<td>12</td>
</tr>
<tr>
<td>In patients with residual kidney function, protein may be lost in urine</td>
<td></td>
</tr>
<tr>
<td>The daily albumin synthesis rate is 12–15 g</td>
<td>7</td>
</tr>
<tr>
<td>The albumin catabolic rate is depressed in dialysis patients</td>
<td>7</td>
</tr>
</tbody>
</table>
increases pore diameter and flux (21). Increased capillary vessel numbers implies an increased number of large pores and increased peritoneal losses of protein across those large pores. Peritoneal protein losses into effluent are therefore a function of the vascularity of the peritoneal membrane. However, that theory remains somewhat controversial, because not all studies have demonstrated this association (22).

Clinical utility of serum albumin in the care of the PD patient

Figure 1 shows a proposed algorithm, adapted from the work of Heaf and associates (15), for interpreting serum albumin concentration in PD patients.

In the patient approaching end-stage renal disease, serum albumin may decline into the lower ranges of normal, possibly reflecting the onset of anorexia and diminished nutritional intake. The concentration may be further depressed because of dilution from worsening kidney function and edema. With the initiation of PD, the concentration of serum albumin can be followed for one of three responses:

- Serum albumin may be noted to improve because of improvement in uremic symptoms and appetite, and reduction in edema with dialysis.
- Other patients have been noted to demonstrate stable serum albumin.
- The third response is a further precipitous fall in serum albumin after the initiation of PD. This third presentation is most concerning and places the patient in a group that may be at highest risk of morbidity and technique failure.

With those possibilities in mind, serum albumin can be used in the care of PD patients as a screening tool so that the clinical team can triage their patients and identify those who are potentially at highest risk and in need of interventions.

In the PD patient demonstrating significant hypoalbuminemia, a variety of clinical interventions may be indicated. The dietician can evaluate dietary history to determine if any component of the hypoalbuminemia may be a result of inadequate protein intake. A trial of supplements can be considered. The care team should recognize that the hypoalbuminemia may be largely attributable to systemic inflammation and the negative acute-phase response. A focused examination of the patient should attempt to identify any source of inflammation that could be addressed. Examples include periodontal disease, foot ulcers, active peripheral vascular disease, colonic bacterial overgrowth with constipation, active comorbidities, or inflammation because of a PD-related process such as exit-site or tunnel infection or indolent peritonitis.

In addition to considering a trial of dietary supplements and treatment of any source of inflammation that may be suppressing compensatory hepatic albumin synthesis, the clinical team can assess peritoneal protein losses. In patients demonstrating higher transport properties, the team should consider the possibility of higher peritoneal protein losses. Protein losses in higher transporters may be lessened by a change in the PD prescription to automated PD. Elimination of the longer day dwell in higher transporters may allow for a temporary reduction in peritoneal protein losses without significant compromise in small-solute clearance (23). Conversion to a dry day with ongoing monitoring of total solute clearance to maintain adequacy parameters can be considered in an attempt to improve hypoalbuminemia.

Patients on PD who demonstrate worsening hypoalbuminemia despite attempts at interventions in nutrition, in detecting and addressing sources of inflammation, and in changing the therapy prescription to minimize peritoneal protein losses will be at higher risk of morbidity and mortality. The underlying
comorbidities contributing to inflammation may not be improved by a change in modality, but the clinical team should discuss whether a conversion to hemodialysis (HD) may be indicated. Conversion eliminates the contribution of peritoneal protein losses to refractory hypoalbuminemia and might be attempted in this high-risk population. However, the patient remaining hypoalbuminemic on HD remains at significant risk of higher mortality. In an extensive review of hypoalbuminemia as a predictor of mortality, Mehrotra and colleagues (24) determined that, at any level of serum albumin reduction, mortality was higher on HD than PD, documenting the increased risk of hypoalbuminemia across these dialysis modalities.

Summary
Hypoalbuminemia in PD patients can be multifactorial and might reflect increased systemic inflammation, untreated volume excess with dilution, ongoing peritoneal and urinary losses of protein, and impaired compensatory hepatic synthesis of albumin. Nutritional supplementation can be attempted on the understanding that hypoalbuminemia is not simply reflective of decreased dietary protein intake. Caregivers should attempt to identify and treat any source of inflammation and to assess peritoneal membrane function to determine whether a prescription change might be indicated to reduce peritoneal protein losses while maintaining adequate total solute clearance targets. The PD patient developing hypoalbuminemia during PD therapy should be evaluated with the clinical algorithm proposed here.

Disclosures
SG is an employee of Baxter Healthcare Corporation.

References
19 Davies SJ, Phillips L, Naish PF, Russell GI. Peritoneal glucose exposure and changes in membrane solute


Hypoalbuminemia in Peritoneal Dialysis Patients

Corresponding author:
Steven Guest, MD, Baxter Healthcare Corporation, 1 Baxter Parkway, Mailstop DF5 2-W, Deerfield, IL, U.S.A.

E-mail: steven_guest@baxter.com