Patients treated with Extraneal peritoneal dialysis solution (Baxter Healthcare Corporation, Deerfield, IL, U.S.A.) have a significant decrease in serum amylase activity. The decline is reported to be due to interference of icodextrin in a routinely used laboratory assay. The present study was designed to investigate the kinetics of icodextrin interference in the amylase activity assay and to determine whether assay interference can account for the total decline in amylase activity.

Plasma obtained from healthy volunteers was spiked with 0, 0.21, 0.71, and 3.6 mg/mL icodextrin. Amylase activity was determined using Sigma kit 577-10 (Sigma Diagnostics, St. Louis, MO, U.S.A.). Amylase activity in plasma samples spiked with 3.6 mg/mL icodextrin was also monitored while varying the concentration of the substrate (ET-G7-PNP) from the assay kit.

Amylase activity decreased with increasing amounts of icodextrin and decreasing amounts of assay substrate. A 72.6% decrease in amylase activity was observed in samples spiked with 3.6 mg/mL icodextrin as compared with samples without icodextrin at a substrate level similar to that in the assay kit (0.71 mmol/L). Double reciprocal and Dixon plots indicate competitive inhibition of amylase activity by icodextrin.

Icodextrin functions as a competitive inhibitor in the assay for amylase activity, as predicted by the structural similarities between icodextrin and the amylase assay substrate. The degree of icodextrin interference suggests that the entire decline in amylase activity observed in patients using Extraneal can be accounted for qualitatively by icodextrin interference. The amylase activity decline in patients treated with Extraneal is an artifact attributable to assay interference.

Key words
Icodextrin, amylase, polyglucose, Extraneal, assay interference

Introduction
Amylase, an enzyme produced by the salivary glands, pancreas, and other human tissues, digests polysaccharides specifically at internal α-1,4-glucosidic bonds (1). Amylase typically initiates the hydrolysis of polysaccharides in the mouth as carbohydrates are ingested, and it further degrades the oligosaccharides in the digestive tract to maltose (G2), maltotriose (G3), and other small oligosaccharides. Both the pancreatic and the salivary isoforms of the enzyme are found in the circulation as serum α-amylases. Although the function of circulating amylase is not well understood, measurement of serum amylase activity is useful as a diagnostic tool, because markedly elevated serum amylase levels are associated with pancreatitis (2).

Administration of Extraneal peritoneal dialysis solution (Baxter Healthcare Corporation, Deerfield, IL, U.S.A.) results in a significant decrease in measured serum amylase activity (3—7). Levels of serum amylase activity decline 70%—90% within 1 week of Extraneal administration and remain low (but stable) during continued administration. Upon discontinuing Extraneal, serum amylase levels return to baseline level. No adverse clinical effect has been attributed to the decline in measured serum amylase activity.

Previous reports (4,7) attribute the decline in serum amylase activity to assay interference caused by the presence of icodextrin, or its metabolites, or both, in the serum samples. The current study was designed to investigate the kinetics of that assay interference and to determine whether assay interference can account for the total decline in amylase activity.

Materials and methods
Blood was collected from volunteers and allowed to stand at room temperature for 1 hour to coagulate.
Serum was obtained by centrifugation at 3950g for 30’minutes at 4°C. Serum samples were stored frozen at —80°C until use. An amylase assay reagent kit (no.‘577—10: Sigma Diagnostics, St.’Louis, MO, U.S.A.), employing the substrate 4,6-ethylidene(G7)-p-nitrophenyl(G1)-\(\alpha\)-D-maltoheptaside (ET-G7-PNP), was reconstituted with distilled deionized water in three different proportions to obtain three levels of substrate concentration. Upon mixing with serum and icodextrin, the concentrations of substrate in the final assay samples were 0.55’mmol/L (low), 0.71’mmol/L (medium), and 1.43’mmol/L (high). The medium substrate level was similar to that indicated in the instructions for the Sigma assay’kit.

Icodextrin (ML Laboratories, Birchwood, U.K.) was prepared as a stock solution (100’mg/mL) in distilled deionized water. Icodextrin was spiked into serum samples to yield final concentrations of 0, 0.21, 0.71, or 3.6 mg/mL, where the highest level was similar to levels of icodextrin (minus the primary metabolites maltose, maltotriose, and maltotetraose) typically found in plasma samples from patients using Extraneal. Amylase reagent, icodextrin stock solution, serum and distilled deionized water were combined in the wells of a 96-well plate (#3635: Corning Costar, Corning, NY, U.S.A.) and mixed gently. Absorbance measurements were recorded at 405 nm and 750 nm every 20’seconds for 20’minutes using a Spectramax’250 plate reader (Molecular Devices Corp., Sunnyvale, CA, U.S.A.). Absorbance at 750 nm was subtracted from that at 405 nm to correct for effects such as solution turbidity. The plate reader was equilibrated at 37°C for all assays, and all assays were conducted on the same day.

Results and discussion
Figure’1 contains representative data showing absorbance as a function of enzymatic reaction time. The effects of varying concentrations of icodextrin (0, 0.21, 0.71, and 3.6 mg/mL) are shown for a single substrate concentration (0.71’mmol/L). Following a brief lag phase, absorbance increased linearly. The slope of the response in the linear portion of the absorbance—time curve was used to determine the enzymatic reaction rate. Similar data were obtained at ET-G7-PNP substrate concentrations of 0.55’mmol/L and 1.43’mmol/L.

Using those data, the effects of icodextrin and substrate concentrations on serum amylase activity were calculated (Table’1). For the medium substrate concentration (0.71’mmol/L), amylase activity decreased by 72.6% in the presence of 3.6’mg/mL icodextrin as compared with the absence of icodextrin. For the high substrate concentration (1.43’mmol/L), the decrease in amylase activity due to 3.6 mg/mL icodextrin was less (58.7%). Analyses of the relationship of the enzymatic rate—1 versus the substrate concentration—1 (double reciprocal plot) and of the enzymatic rate—1 versus the icodextrin concentration (Dixon plot) indicate that the inhibition of amylase activity due to icodextrin is competitive (that is, the intercept for the double reciprocal plot is near zero, indicating competitive inhibition (Figure’2)). Those results accord with previous results reported by Schoennicke et al (7) and Grzegorzewska et al’(4).

Interference with the amylase activity assay by icodextrin is also expected because icodextrin and the substrates commonly used in the amylase activity assay both have identical 1,4-\(\alpha\)-D-glucosidic bonds. As illustrated in Figure’3, amylase hydrolyzes 1,4-\(\alpha\)-D-glucosidic bonds in the substrate (ET-G7-PNP) to form G2-, G3-, and G4-PNP fragments. The \(\alpha\)-glucosidase in the assay kit further hydrolyzes G2-PNP and G3-PNP to yield glucose and p-nitrophenol, the latter producing a yellow color that can be measured at 405 nm. Increase in the absorbance at 405 nm is directly proportional to amylase hydrolytic activity in the sample. When icodextrin is present, amylase hydrolyzes 1,4-\(\alpha\)-D-glucosidic bonds in both the substrate and icodextrin, leading to direct competition for amylase hydrolysis activity. Therefore, the amount of amylase activity in the sample appears to be less than if icodextrin were not present in the assay system.

Caution should be used in the interpretation of assay results using icodextrin spiked into serum or plasma samples. Pre-incubation of the sample may reduce the amount of icodextrin owing to its hydrolysis by amylase, thereby decreasing the degree of icodextrin interference. Our experimental results show that approximately 25% of icodextrin was hydrolyzed to G2, G3, and G4 after 2 hours incubation at 37°C in plasma. As expected, the reduction in amylase activity was found to be 72% at the time of mixing and 57% and 46% after 1 and 2 hours of incubation, respectively, for the same spiked icodextrin concentration. In addition, measured amylase activity may vary if the substrate concentration in the assay kit used is higher or lower, because the degree of icodextrin in-
Interference depends on substrate concentration. For example, the assay kit produced by Boehringer Mannheim (catalog no. 1555685: Boehringer Mannheim, Mannheim, Germany) has a substrate level of approximately 3.55 mmol/L, which is much higher than that of the Sigma kit. As a result, the degree of icodextrin interference may be much lower or unobservable when the Boehringer assay kit is used.

**Conclusion**

Icodextrin functions as a competitive inhibitor in the assay for amylase activity, as predicted by the structural similarities between icodextrin and the amylase assay substrate. The degree of icodextrin interference suggests that the entire decline in amylase activity observed from patients using Extraneal can be accounted for by icodextrin interference. Therefore, the amylase activity decline in patients treated with Extraneal is an artifact due to assay interference.

---

**TABLE I** Effects of icodextrin and substrate concentrations on serum amylase activity

<table>
<thead>
<tr>
<th>Icodextrin concentration (mg/mL)</th>
<th>% Drop&lt;sup&gt;a&lt;/sup&gt; in amylase activity</th>
<th>Substrate concentration (mmol/L)</th>
<th>% Drop&lt;sup&gt;b&lt;/sup&gt; in amylase activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.21</td>
<td>8.2%</td>
<td>0.51</td>
<td>76.8%</td>
</tr>
<tr>
<td>0.71</td>
<td>34.4%</td>
<td>0.71</td>
<td>72.6%</td>
</tr>
<tr>
<td>3.6</td>
<td>72.6%</td>
<td>1.43</td>
<td>58.7%</td>
</tr>
</tbody>
</table>

<sup>a</sup> Substrate concentration was 0.71 mmol/L for the assays with icodextrin concentrations at 0, 0.21, 0.71, and 3.6 mg/mL.

<sup>b</sup> The percentage activity drop was calculated as compared with samples without icodextrin.

<sup>c</sup> The icodextrin concentration was 3.6 mg/mL.

---

**FIGURE 1** Representative data showing absorbance as a function of enzymatic reaction time. Each assay was performed in duplicate. mM<sup>−</sup> = mmol/L.

<table>
<thead>
<tr>
<th>[substrate] = 0.71 mM</th>
</tr>
</thead>
<tbody>
<tr>
<td>w/o icodextrin</td>
</tr>
<tr>
<td>0.21 mg/mL</td>
</tr>
<tr>
<td>0.71 mg/mL</td>
</tr>
<tr>
<td>3.6 mg/mL</td>
</tr>
</tbody>
</table>

---

**FIGURE 2** Double reciprocal and Dixon plots. mM<sup>−</sup> = mmol/L.
References
6 Mistry CD, Gokal R. Single daily overnight (12-h dwell) use of 7.5% glucose polymer (Mw 18700; Mn 7300) +0.35% glucose solution: a 3-month study. Nephrol Dial Transplant 1993; 8:443—7.

Corresponding author:
Run Wang, PHD, Advanced Research and Development, Renal Division, Baxter Healthcare Corporation, 1620 Waukegan Road, MPGR-E2, McGaw Park, Illinois 60085 U.S.A.
Peritoneal dialysis (PD), despite being advantageous to patient, physician, and society, has failed to show the growth it deserves. On the contrary, PD utilization has declined. Over the past several years, we have noticed a decline in the number of our home dialysis patients. When compared to the national trend, we find our trend to be not significantly different from other centers across the country. A similar trend has also been noticed in Canada. Although several reasons may exist for the decline, we intend to concentrate on local factors.

In the first quarter of 1996, we had a total of 46 adult and pediatric end-stage renal disease (ESRD) patients on PD. That number decreased to 23 at the end of fourth quarter of the year 2001. The losses in our program far exceeded the gains. We lost our patients mainly to in-center hemodialysis (ICHD) and to transplantation. Peritonitis and membrane failure remained the major grounds for the loss to ICHD.

In our center, geographic location and a lack of structured pre-ESRD education probably played a major role in the decline. Many of our patients are from distant counties that have a contract with University of Texas Medical Branch for providing health care to their indigent population. However, once those patients develop complications, the counties rely on the expertise of local physicians and nephrologists.

Key words
Home dialysis, declining trend, in-center hemodialysis

Introduction
Since peritoneal dialysis (PD) was made available as an alternative to hemodialysis (HD), the PD modality has failed to show the growth it deserves, especially considering that the survival rate and the advantages to patients and nephrologists favor PD (Figure 1). The trend extends worldwide; it is not limited to North America (1—3). Although PD utilization is decreasing worldwide, the United States happens to be among the countries that use the PD modality the least (4).

As PD utilization continues to decrease worldwide, we notice a similar trend at the University of Texas Medical Branch (UTMB). Our institution has a contract with several counties in the state of Texas for providing health care to their indigent populations. For that reason, many patients in our program come from distant areas; unfortunately, in most cases, they are not from the adjacent counties. The adjacent counties are catered to by the institutions and nephrologists from Houston metropolis.

The better way to provide quality health care to distant patients is to offer home dialysis. For that reason, UTMB had one of the largest home dialysis programs. Over the past several years, the home dialysis program has seen a steep decline in patients on PD. We decided to study the reasons for that decline.

Patients and methods
Patients added to our program were automatically entered into the Baxter PD Census (BPDC), Baxter Healthcare Corporation, Deerfield, IL, U.S.A. We retrieved the data for our institution from the BPDC and performed a comparison with the data from the total USRDS 2000.
BPDC. The BPDC data is gathered quarterly and includes both adult and pediatric end-stage renal disease (ESRD) patients. For the present study, we recorded total additions and losses to the program. Among the losses, losses to in-center hemodialysis (ICHD), losses due to death or transplant, and losses due to other causes were recorded. Patients lost to ICHD were further grouped into loss due to peritonitis, catheter loss due to infection or other catheter-related problems, membrane failure or failure to meet adequacy criteria, psychosocial problems, and other medical problems. The adult and pediatric populations were later separately analyzed.

Results
At the beginning of the year 1996, we had a total of 46 PD patients. That number decreased to 21 at the end of the fourth quarter of the year 2001, a decrement of more than 50% (Figure 2). At the end of the 4th quarter of the year 1996, the gross gain was 33 patients against the loss of 35 patients. The trend continued into the year 1997, with a total gain of 18 patients and a total loss of 22. In the years 1998, 1999, 2000, and 2001, the gains were 15, 14, 13, and 12 patients respectively, and the losses were 21, 17, 13, and 9 patients respectively (Figure 3).

Among the losses, 48% were lost to ICHD; 36%, to transplant; 9%, to death; and 7%, to miscellaneous causes [Figure 4(A)]. Among the adult PD patients, 67% were lost to ICHD as compared with 29% among the pediatric patients. Renal transplantation was performed in 19% of the adult PD patients as compared with 64% of the pediatric patients. Of the adult PD patients, 11% died while receiving PD; only 2.4% of the patients in the pediatric PD program died [Figure 4(B)]. In comparing our figures to the overall BPDC [Figure 4(C)], we noted that, although we lost more patients to ICHD, the difference was marginal (48% at UTMB vs. 41% in BPDC). More of our patients underwent transplantation, and that difference was significant (36% at UTMB vs. 15% in BPDC).

Among the UTMB patients lost to ICHD, the indications for the switch were mainly peritonitis (37%) and the need to provide adequate dialysis as per the Dialysis Outcomes Quality Initiative (DOQI) guidelines (34%) [Figure 5(A)]. In comparison, the BPDC data revealed lower percentages for peritonitis (23%) and failure meet adequacy criteria (21%) as the reason for switching to ICHD [Figure 5(B)].

Discussion
Earlier studies had revealed that the survival rate is similar among patients on HD and PD, and some studies even claimed better survival on HD (5—10). However, recent studies have clearly established a survival advantage for patients on PD as compared with patients receiving ICHD (11,12). Patients on PD also seem to have an enhanced sense of satisfaction when compared with ICHD patients, which suggests that PD provides a better quality of life (13—15) yet, despite the advantages, use of the PD modality is declining. The probable factors for the decline are mainly the proliferation of HD facilities, the nature of the incident ESRD patients (older and frailer), and misconceptions about the ability of those incident patients to be maintained on PD for long durations (16,17).

The UTMB is located on Galveston Island, which is situated approximately 40 miles southeast of the metropolitan city of Houston (Figure 6). The population of the island of Galveston is approximately 60,000. The adjacent counties to the north of Galveston County form the southern part of the greater Houston area, which has several university and major hospital—based nephrology groups and many practicing nephrologists. However, many counties surrounding the Houston metropolitan area have a contract with UTMB to provide medical care to the indigent populations of those counties.

Patients from the indigent population either consult a physician too late or (more commonly) present to the nearest hospital when in need of emergent dialysis and are then transferred to UTMB for management of renal failure. That situation perpetually results in initiation of HD and subsequent placement in an outpatient dialysis facility closer to their residence. If such patients are referred early, they are offered dialysis education and a choice to select the dialysis modality. If they decide to select home dialysis, they are offered assistance for their stay on Galveston Island for the duration of the training period. Most patients who opt for PD are not hesitant to travel long distance for their monthly visits.

Loss to ICHD
As mentioned earlier, our center provides health care to several distant counties. The patients are indigent, and once they develop complications, some of them tend to go to the nearest hospital. Because of the distance involved, many delay going to hospital; but, as
the severity of their complications increases, they present to the nearest hospital. Not all of the hospitals may have nephrologists who are comfortable in treating PD patients especially when those patients have complications related to PD. We had to switch some of our patients to ICHD when the criteria for adequacy of peritoneal dialysis could not be met. Our loss to ICHD was therefore probably disproportionately high.

**Loss to transplantation**

The transplantation rate among our PD patients is quite high. As cited earlier, our loss to transplantation is 36%, which is more than twice the BPDC rate of 15%.
We can only speculate on the reason: perhaps the patients appear so healthy that they go on the list more quickly and receive a transplant graft faster. A large proportion are pediatric patients, who have a higher transplantation rate of 64% [Figure 4(B)].

**Failure to meet adequacy criteria**

We have noted that patients on automated peritoneal dialysis (APD) have a tendency to avoid manual ex-

![Figure 3](image1.png)

**Figure 3**  Additions to, and losses from, the peritoneal dialysis program at the University of Texas Medical Branch. The dotted line represents the number of patients exiting the program. The x’ axis represents quarters of years, beginning with the first quarter of the year 1996 and ending with the last quarter of the year 2001. The y’ axis represents the absolute number of patients.

![Figure 5](image2.png)

**Figure 5**  (A) The reasons for switching from the peritoneal dialysis program at the University of Texas Medical Branch to in-center hemodialysis. The numbers are percentages. (B) The reasons for switching from a peritoneal dialysis program to in-center hemodialysis per the Baxter national peritoneal dialysis census. The numbers are percentages.

![Figure 4](image3.png)

**Figure 4**  (A) The percentage of patients exiting the peritoneal dialysis program at the University of Texas Medical Branch (UTMB) for various reasons. (B) The number of patients exiting the pediatric peritoneal dialysis program at UTMB for various reasons. (C) The percentage of patients exiting the Baxter national peritoneal dialysis census for various reasons.
changes. We noted that, the more manual exchanges added, the lower the satisfaction (and hence compliance) among the patients especially among those who are employed.

Inadequate gains
Our center had lacked a structured pre-ESRD education program. Studies have shown that structured pre-ESRD education helps more patients to select the dialysis modality of their choice in a timely manner (18). We concur with those authors, because we have seen sustained growth since we started pre-ESRD education in our institution. Also, one important cause for the loss of patients to ICHD was catheter failure. Such losses were not included in the BPDC data, because those patients were never enrolled into our PD program owing to primary failure or non function of the PD catheter after the surgery.

Primary catheter failure
We have data only from March 1997 until the end of 2001 on primary catheter failure. During that time, 46 patients were referred for placement of a PD catheter. In 33 patients, the catheter was successfully placed, for a success rate of 72% and a failure rate of 28%. Some patients were sent for catheter placement despite a prior history of abdominal surgery.

Conclusion
We analyzed our data to determine the cause of a declining trend in the utilization of PD at our institution. We conclude that the decline is in keeping with a global trend. The decline in our PD program is mainly due to a lack of aggressive recruitment: fewer patients were added to the program than left the program. Although our findings are similar to those of the BPDC, our losses are due mainly to ICHD and to transplantation, as opposed to ICHD and death as recorded in the BPDC. The discrepancy between our data and the BPDC data may be due to the inclusion of pediatric patients, who constitute a sizable proportion of our total PD population and who are likely to have a higher transplantation rate and lower mortality. Loss to ICHD was due mainly to peritonitis and failure to meet the DOQI criteria for adequacy. Another speculation for the lower death rate may be the switch to ICHD as the patient becomes sicker. The death rate would then be reported under ICHD, which may also explain our higher rate of loss to ICHD. The distance from our patients’ residences to our hospital probably plays a major role in our losing them to ICHD. Finally, primary catheter failure was also a significant factor for poor recruitment to our PD program.

References
17 Oreopoulos DG, Blake P. Declining utilization of peritoneal dialysis: time to stop imposing our biases on the patients and let them be dialyzed with the modality of their choice. ASAIO J 2001; 47:312—15.

Corresponding author:
Mahendra Agraharkar, MD, FACP, Nephrology Division, Department of Medicine, 4.200 John Sealy Annex, University of Texas Medical Branch, 301 University Boulevard, Galveston, Texas 77555-0562 U.S.A.
High transporters are defined based on the peritoneal equilibration test. Peritoneal transport rate changes over time, inflammation and angiogenesis affecting the total pore area. Factors influencing the neovascularization process are described.

High transporters have distinctive clinical and laboratory features. The incidence of high transporters varies among different populations.

Unfortunately, high transporters have the worst clinical outcomes. Mechanisms proposed to explain the adverse prognosis including hypoalbuminemia, chronic fluid overload, malnutrition, and chronic inflammation are discussed.

We suggest dividing baseline high transporters into two groups: sick and healthy high transporters. The two types of high transporters have different baseline characteristics and different clinical outcomes. Hopefully, further studies will better define the appearance of the two groups of high transporters.

Key words
High transporters, high peritoneal transport, hypoalbuminemia, malnutrition-inflammation-atherosclerosis syndrome

Introduction
Since its description in the mid-1980s by Twardowski et al (1), the peritoneal equilibration test (PET) has been widely used to characterize peritoneal dialysis (PD) patients according to peritoneal transport status. Based on the dialysate-to-plasma ratio of creatinine (D/P Cr) or the dialysate-to-initial-dialysate ratio of glucose (D/D0), or both, patients can be classified as high, high-average, low-average, and low transporters. High transporters have the highest rates of creatinine diffusion and glucose absorption. After a 4-hour dwell time, they achieve a D/P Cr ratio above 0.8, while their D/D0 decreases below 0.3.

From: Division of Nephrology, Department of Internal Medicine, University of Missouri, Columbia, Missouri, U.S.A.

**Discussion**

Peritoneal membrane evolution over time
Among the various transport resistances that constitute the peritoneal membrane, the vascular component represented by the capillary wall is the most important barrier to solute transport (2). Thus, theoretically, the transport capacity of the peritoneal membrane depends on the two characteristics of the vascular site: the effective peritoneal surface area (total number of pores present in perfused capillaries) and the membrane permeability (size of the pores). Over time, the effective peritoneal surface area can increase, as seen with neoangiogenesis, leading to higher mass transfer-area coefficients (MTCs) for low and high molecular weight molecules. The intrinsic membrane permeability can potentially be altered by a change in the diameter of the large pores, but clinical changes in transport are predominantly in total pore area (2). A recent study (3) tried to address the relative importance of peritoneal fibrosis and angiogenesis in peritoneal membrane dysfunction. The authors compared the response to intraperitoneal lipopolysaccharide-induced inflammation in two groups of genetically altered animals. In one group, production of decorin, a proteoglycan inhibitor of transforming growth factor-β, reduced collagen production. In the other genetically altered group, the high production of angiostatin showed a significant reduction in vessel density. They demonstrated better ultrafiltration preservation in animals producing abundant angiostatin as compared with animals producing high decorin, suggesting that the blood vessel density, and not the collagen concentration, is responsible for peritoneal membrane dysfunction.

A cross-sectional study (4) evaluating the histology of parietal peritoneal tissue obtained by biopsy in 22 continuous ambulatory peritoneal dialysis (CAPD) patients found a strong correlation between the relative capillary area and the D/P Cr. That finding indicated that increased capillary surface area is actually involved in the mechanism of high transport during PD. The same group of researchers analyzed the relat-
tionship between vascular endothelial growth factor (VEGF), known for its angiogenic action, and peritoneal membrane transport status (5). The positive correlation between the growth factor and peritoneal transport suggested that VEGF might be responsible for the hypervascularization associated with a high peritoneal transport rate. Free plasma VEGF levels have been found to be high in pre-dialysis patients and may contribute to vascular endothelial dysfunction (6). Leptin, another angiogenic substance, has been implicated in the peritoneal hypervascularization that characterizes high transporters (7).

With the initiation of PD, the peritoneal membrane undergoes structural and functional changes. During the first 2 weeks of PD, in 35.3% of patients, a slight increase in peritoneal transport characteristics tends to occur (8). For that reason, Rocco et al recommend performing the baseline PET one month after the initiation of PD.

Long term, and in the absence of recurrent episodes of peritonitis, peritoneal transport tends to remain stable in most patients (9). However, several studies have shown that high transporters tend slowly toward a decrease in peritoneal membrane transport over time, while the low and low-average groups demonstrate reciprocal changes (10,11).

Incidence
The incidence of baseline high transport status varies among different populations.

The CANUSA study (12) documented an incidence of 15.3% high transporters among patients initiating PD in the United States and Canada. That incidence is similar to the incidence reported in northern European (13) and Latin (14) populations. A much higher incidence (around 50%) has been found in Asian Indians (15) and in Greeks (16). In Australians and New Zealanders, the incidence of high transporters commencing PD is 32% or higher (17).

Clinical and laboratory features specific for high transporters
Compared with other transport types, high transporters have more rapid increases in D/P Cr (18). As a result, small-solute clearance targets can easily be reached unless the patient is very large. The glucose osmotic gradient dissipates relatively rapidly owing to the high rate of glucose absorption. During long dwells, net ultrafiltration (UF) ceases when the glucose osmotic gradient declines to the point where lymphatic reabsorption exceeds the rate of ultrafiltration. Maximum UF is captured within the first 2 hours of a dwell (18); long dwells (>4—6 hours) may have little or negative UF. As a result, in the absence of residual renal function, patients may run into problems with volume control and hypertension. To maximize clearances and UF, short-dwell therapies such as nightly intermittent peritoneal dialysis (NIPD) or daily automated peritoneal dialysis (DAPD) are recommended.

The high transporter group includes higher proportions of children (19), older men, and patients with diabetes (12).

Acid—base status might also be influenced by peritoneal membrane transport characteristics. In a cross-sectional study of 143 stable PD patients (20), lactate and dialytic base gains were significantly higher in high transporters, leading to increased pH and bicarbonate levels.

Several studies have found lower serum albumin in the high transporters as compared with other groups (12,21,22). That observation was linked to higher dialysate protein losses (12,21) and fluid overload owing to poor UF. The gastrointestinal tract might contribute to an additional protein loss. Protein-losing enteropathy, determined by the fecal clearance of α1-antitrypsin, is more frequent in patients with high urea and creatinine MTCs (23).

Unfortunately, high transporters have the worst clinical outcomes. They are at increased risk of death (2-year survival is 71% versus 91% in low transporters in the CANUSA study) and technique failure (12—14,24).

Clinical outcomes and proposed mechanisms
To explain the adverse prognosis found in high transporters, various mechanisms have been postulated (25).

It is now widely recognized that hypoalbuminemia is associated with higher mortality rates among patients on dialysis (26). On the other hand, hypoalbuminemia is more common in high transporters. Is the high peritoneal transport status leading to hypoalbuminemia? Can hypoalbuminemia alone explain the increased mortality risk seen in high transporters?

Although protein loss is greater in the high transport group after initiation of PD, that high loss cannot
explain why some of the patients have lower baseline serum albumin levels (12). Moreover, it has not yet been demonstrated that hypoalbuminemia per se is the direct cause of high mortality, rather than being a marker of underlying comorbidities (25).

Some researchers have related adverse outcomes in high transporters to poor UF and chronic fluid overload. Although the thesis is not fully proved, there are data to support it: high transporters have higher body weights and diastolic blood pressures (13). Patients with symptomatic fluid retention on CAPD are 3.7 times more likely to be high transporters rather than low transporters (27).

Repeated use of hypertonic exchanges may increase the carbohydrate load, possibly suppressing appetite and reducing protein intake. Additionally, increased dialysate protein losses may contribute to malnutrition and further high risk of mortality. But does the literature contain evidence to support malnutrition in high transporters?

Although initial cross-sectional studies showed lower net protein catabolic rate (nPCR), lean body mass (LBM), and daily creatinine production in the high transporters, suggesting malnutrition (21), further studies did not confirm those observations (12,24,28,29). Aside from hypoalbuminemia, the CANUSA study (12) showed no differences among the transport groups in other estimates of nutrition status, including subjective global assessment, LBM, and PCR. When nutrition status was comprehensively assessed by means of 24-hour dietary recall together with a nutrition index (calculated based on eight clinical, biochemical, and anthropometric parameters), no correlation with peritoneal transport rate was found (28).

Those results lead us to examine an intriguing hypothesis: that high transport status, hypoalbuminemia, and adverse outcomes are the result of underlying comorbidities, perhaps related in many patients to the MIA (malnutrition, inflammation, atherosclerosis) syndrome (30).

Through cytokine dysregulation, the chronic inflammation that accompanies uremia might cause higher peritoneal transport (via neovascularization and maybe other mechanisms) in the peritoneal membrane, and an increased risk of cardiovascular diseases and hypoalbuminemia (30). However, the literature data to support that hypothesis are conflicting. A cross-sectional study (31) performed on 39 PD patients found no correlation between peritoneal transport rate and chronic inflammation as measured by blood levels of hyaluronan, interleukin-1β, tumor necrosis factor-α, and C-reactive protein (CRP). On the other hand, the same group later reported (11) that during the first year on PD, changes in peritoneal transport rate appeared to be linked to inflammation (as suggested by a high CRP) and a decrease in residual renal function (RRF). Those findings are compatible with the possibility that two types of high transporters might exist at baseline: one subgroup with evidence of chronic inflammation, lower baseline RRF, and a faster loss of RRF during the first year; and another subgroup that would include patients diagnosed with a high transport status at baseline, without much evidence of inflammation and with better, preserved RRF.

Evidence for a major role of inflammation and neovascularization comes from a prospective study by Chung et al (32). They followed 213 PD patients and found the same poor survival in some baseline high transporters as was documented by previous studies. The 2-year patient survival in the baseline high transport group was significantly lower as compared with the other groups combined (57.1% vs. 79.5%, \( p = 0.009 \)). However, when patients with comorbid diseases were censored from the analysis, the survival in the baseline high transporters without comorbid conditions was not different compared with the other transport groups combined. That study brings weight to the hypothesis that high transporters can be grouped into two types: with and without comorbid diseases associated with inflammation.

The vascular density hypothesis: sick and healthy high transporters

Based on current literature evidence, we suggest dividing baseline high transporters into two groups (Figure 1). Sick high transporters have evidence of inflammation before initiating dialysis. Through its neoangiogenic action, inflammation leads to abundant peritoneal capillaries. Patients at risk of falling into this category display baseline low serum albumin, higher CRP, lower RRF, and lower protein equivalent of nitrogen appearance (PNA). The baseline lower RRF further predisposes to inflammation (11), which in turn accelerates the loss of RRF. For these patients with comorbid diseases, evidence of chronic inflam-
information, and decreased RRF at baseline, a high peritoneal transport status is a predictor of increased mortality and morbidity while on PD.

Baseline high transporters without associated comorbidities or inflammation the healthy baseline high transporters most likely have a genetically inherited increased vascular density. Their lack of significant inflammation might be quantified by normal/low serum albumin, normal CRP, better RRF, and more normal PNA. Upon initiation of PD (lower portion of Figure 1, below dashed line) and in the absence of angiogenic stimuli, the healthy high transporters and the non high transporters (assuming that they don’t have other associated comorbidities) have better survival and less evidence of inflammation (no elevation in CRP, normal/low serum albumin). On the other hand, over time, their peritoneal vascular density can increase and change their outcomes if they acquire inflammation and neovascularization. The change in solute transport is heralded by an increase in D/P Cr. When that happens, their mortality and morbidity (malnutrition, ath-

croscclerosis) approaches the level seen in baseline high transporters with evidence of pre-dialysis inflammation.

Conclusions
We speculate that there are two types of high transporters: sick and healthy high transporters. Dividing the high transporters into two subgroups and acknowledging their dynamics might help to explain the controversial results seen in various studies. It might also explain why different populations have higher proportions of baseline high transporters [as seen in Australians, New Zealanders (17), Greeks (16), and Asian Indians (15)]; why Greeks don’t have the poor outcomes (16) documented in most other studies; and why, by 6—12 months of follow-up, only 22.4% of Australian high transporters had maintained significant RRF (17).

For future studies, it might be important to document whether baseline high transport status is associated with chronic inflammation or comorbidities (or both) and whether the high transport status was acquired at baseline or during follow-up. The differences can be quite significant. In one retrospective study (10), for example, 16 patients were defined as high transporters based on baseline PET. The final PET recorded 8 high transporters. Of the initial 16 high transporters, only 3 patients remained for the final count. The rest (5 patients) acquired the high peritoneal status over time.

For both subgroups, short dwell-time therapies such as NIPD or DAPD maximize small-solute clearances and UF.

Further studies will hopefully better define the appearance of the two types of high transporters.

References


30 Bergstr m M, Lindholm B. Malnutrition, cardiac


Corresponding author: Ramesh Khanna, MD, Division of Nephrology, MA436 Health Sciences Center, One Hospital Drive, Columbia, Missouri 65212 U.S.A.
The use of antibiotic prophylaxis before peritoneal dialysis (PD) catheter insertion has been a matter of great interest for both the surgical and the nephrology community. No uniform consensus exists on the timing, duration, or choice of antibiotic prophylaxis. The exact incidence of early postoperative peritonitis is unknown. The impact of the use of antibiotic prophylaxis in the prevention of early PD peritonitis and in long-term catheter survival is not clear. In that respect, many retrospective and prospective studies have been undertaken in the past, and they have shown conflicting results. Based on extensive data from the surgical and nephrology literature, and also based on our experience, we present a review of the use of antibiotic prophylaxis before peritoneal dialysis catheter insertion.

Key words
Catheter, antibiotic, prophylaxis

Introduction
The true incidence of early postoperative peritonitis after peritoneal catheter insertion is unknown. Postoperative infections can lead to infection of the tunnel and exit site, and may cause recurrent peritonitis and catheter loss.

Discussion
Principles of antibiotic use
Initial use of antibiotic prophylaxis before or at the time of peritoneal dialysis catheter placement has been based mainly on data extrapolated from similar surgical interventions (1—4). Surgical wounds have been traditionally classified into clean operations without foreign implants, clean operations with foreign body implants, clean contaminated wounds, contaminated wounds, and dirty wounds (1,5). The incidence of wound infection increases progressively from clean (2.9%), through clean contaminated (3.9%) and contaminated (8.5%), to dirty/infected (12.6%) (6). High-risk patients (Table 1) with multiple medical problems have a higher incidence of wound infections (5—8).

The operation for insertion of a peritoneal dialysis catheter can be classified as clean surgery with implantation of a foreign body. Patients requiring such catheters are at high risk, especially those with multiple medical problems and malnutrition. The use of low-pH, high glucose, lactate-containing peritoneal dialysis solutions has been shown to reduce the phagocytic activity of macrophages in the peritoneum (9).

The surgical literature contains abundant and convincing evidence for the use of antibiotic prophylaxis for clean operations utilizing foreign body implants (1,3,5,6,10). In fact, the current trends even advocate the use of antibiotic prophylaxis in clean surgery without implants (11).

Studies in peritoneal dialysis patients
Numbers of published studies have looked at whether the use of antibiotic prophylaxis before peritoneal dialysis catheter insertion makes any difference to the incidence of early postoperative peritonitis.

Using the Cox proportional hazards model, the U.S. Renal Data System (USRDS) 1992 Data Report (12) showed, in 3366 patients, no difference between patients receiving antibiotic prophylaxis and those not receiving it. But the study was retrospective, and the timing and duration of antibiotic administration was not clearly defined.

Golper et al, in the Network’9 study (13), showed a 39% reduction in the risk of peritonitis and a 38% reduction in combined peritonitis and exit-site/tunnel infection. No difference was seen in the time to first peritonitis.

Lye et al (14), using single-dose cefazolin and gentamicin, showed no significant benefit of antibiotic prophylaxis. Bennett—Jones et al (15), using
gentamicin at the time of catheter insertion, showed a reduction in the incidence of peritonitis from 46% (no antibiotic) to 8% (antibiotics). Sardegna et al (16), in a retrospective study, showed significant benefit using multiple antibiotics in a pediatric dialysis population.

Wikdahl et al (17), in a prospective study using intravenous (1.5 g, 0.5—2 hours before surgery) and intraperitoneal (250 mg in 1-L bag starting perioperatively) cefuroxime (a second-generation cephalosporin), showed a beneficial role for preoperative antibiotics. Active therapy was associated with a lower incidence of microbial growth in the dialysate (0 of 18 patients vs. 6 of 20 patients, \( p = 0.021 \)) during a 10-day follow-up period.

In a recent large prospective randomized trial conducted over a 6-year period (18), 221 patients were randomly assigned either to group I (vancomycin, 1 g intravenously, 12 hours before the procedure), group II (cefazolin, 1 g intravenously, 3 hours before the procedure), or group III (no antibiotics). At 2 weeks, the groups given antibiotics showed a significantly lower incidence of peritonitis (1%, 7%, and 12% for groups I, II, and III, respectively). All the catheters in that study were placed peritoneoscopically.

**Timing of antibiotic administration**

The timing of the prophylactic antibiotic administration before a surgical procedure has been extensively studied in several prospective randomized trials (2,4,19). Most studies have concluded that, to prevent infections, antibiotics should already be present in adequate concentrations when the tissues are exposed to contaminating bacteria. The rate of infection increases for each hour that antibiotics are delayed after the start of the operation (2). The explanation for that observation is that, when an incision is made, the body’s inflammatory process immediately mobilizes and begins to isolate the wound. By the time the operation is completed, the wound contaminated by the skin microbial flora has been completely isolated, and systemic antibiotics cannot reach the wound.

**Duration of antibiotic prophylaxis**

The total duration of antibiotic prophylaxis is still being debated, although the use of antibiotic therapy beyond 24 hours has shown no benefit and may lead to a rise in antibiotic resistance (20—22). A single-dose intravenous antibiotic before surgery has been shown to be effective in most procedures of approximately 0—2 hours (1,2,5). Procedures lasting longer than 3—4 hours may require an additional effective dose (5).

When compared with one shot antibiotic regimens, longer courses of antibiotics have not resulted in any statistical difference with regard to the incidence of postoperative infection (23). The focus is on maintaining adequate antibiotic levels in the tissues continuously from the time of incision to a time after wound closure sufficient to cover the lag phase of the contaminating organisms (approximately 6 hours for a 2-hour operation), but not longer (2).

**Choice and route of antibiotic administration**

The first-generation cephalosporins continue to be the most frequently used antibiotics in the context of peritoneal dialysis catheter placement. Cefazolin, with its prolonged half-life in renal failure (normal: 90—150 minutes) and its time to peak serum concentration of 0.5—2 hours (intramuscular administration), offers a valuable coverage. The effective dose should be governed by the patient’s weight. The intravenous route of administration is preferred.

The role of topical antimicrobials and oral antibiotics in prophylaxis remains to be determined. The routine use of vancomycin as a prophylactic agent should be discouraged to avoid the development of
resistant micro-organisms such as vancomycin-resistant enterococci and staphylococci. Maintaining a local, up-to-date hospital analysis of the microbial susceptibilities of wound isolates is also important for detecting important shifts in patterns of resistance. Changes can then be made accordingly.

**Conclusion**

To summarize, reports conflict regarding the use of prophylactic antibiotics for peritoneal dialysis catheter replacement. The largest prospective clinical trial in peritoneal dialysis patients (18) showed a significant benefit of antibiotic prophylaxis in reducing early postoperative peritonitis. The surgical literature also contains abundant and convincing evidence for the use of antibiotic prophylaxis in clean operations utilizing foreign body implants.

The timing of antibiotic administration is crucial to its effectiveness, and the antibiotic should be given immediately before surgery so that adequate tissue concentration has been achieved at the time of incision. A single-dose first-generation cephalosporin, given intravenously 1—2 hours before the procedure, is a good first-line prophylactic antibiotic. At the University of Missouri—Columbia, we use cefazolin 1.5 g, intravenously, 2 hours before the procedure.

Use of vancomycin as a routine prophylactic agent should be discouraged.

According to USRDS, only 43% of patients receive antibiotic prophylaxis before catheter insertion. Whether the widespread use of prophylactic antibiotics will make a significant difference to the overall incidence of peritonitis remains to be seen (24). To achieve good results, a well-thought-out prophylactic regimen needs to be supplemented by exquisite surgical technique and competent post-surgical management.

**References**

1 Nichols RL. Surgical wound infection. Am J Med 1991; 91:54S—64S.
17 Wikdahl AM, Engman U, Stegmayr BG, Sorensen JG. One-dose cefuroxime i.v. and i.p. reduces microbial growth in PD patients after catheter insertion.


Corresponding author:
Atul Katyal, MD, Division of Nephrology, MA436 Health Sciences Center, University of Missouri, One Hospital Drive, Columbia, Missouri 65212 U.S.A.