Peritoneal Dialysis:
A Viable Renal Replacement Therapy Option

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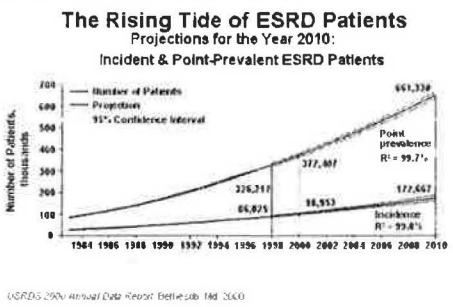
Areas of interest:
Autoimmune glomerulonephritis
Critical care nephrology

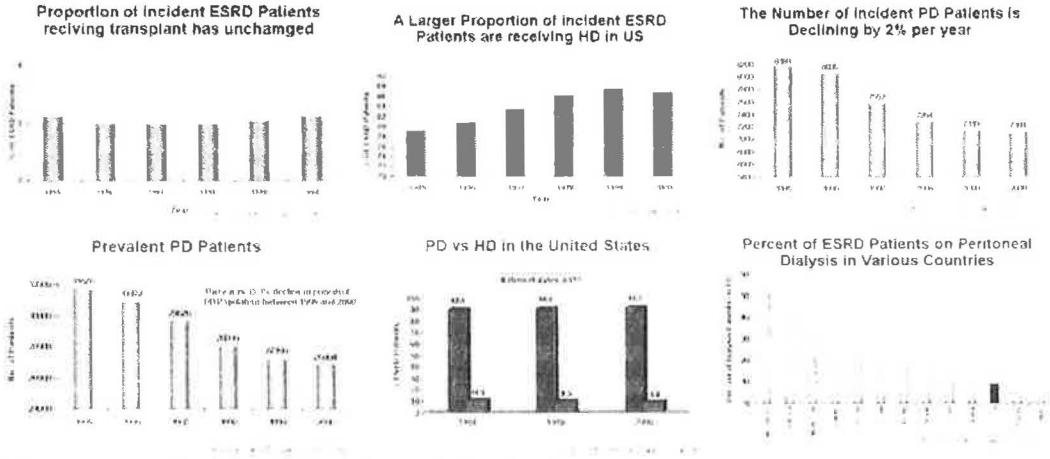
Background

The population of the United States is experiencing an escalating burden of end stage renal disease (ESRD). The recent annual data report (ADR) of the United States Renal Data System (USRDS) indicates that by the end of year 2001, there were over 400,000 ESRD patients with an annual percent growth of more than 4% (1). With this growth rate, the projected ESRD population will grow to more than 650,000 by the year 2010. The cost of providing care to the ESRD population was close to $ 23 billion in 2001. About 7% of the Medicare budget is spent on the ESRD program (1). The rising tide of ESRD population is just a tip of the iceberg. For each ESRD patient there are 100 folds more patients with various degree of renal dysfunction (2). Given the enormous burden of patients with chronic kidney disease (CKD), increasing emphasis is now being paid on early detection of CKD and slowing down the progression of the disease (2). Additionally, when the patient reaches stage 4 of CKD, it is strongly recommended to implement measures to prepare the patient for the renal replacement therapy (RRT).



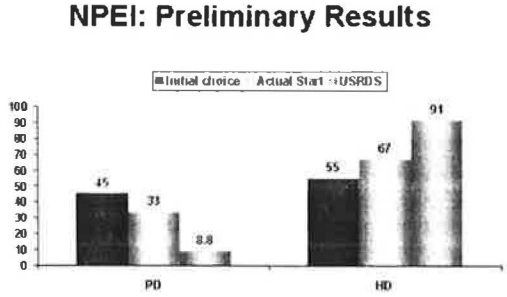
USRDS 29th Annual Data Report Bethesda Md 2006

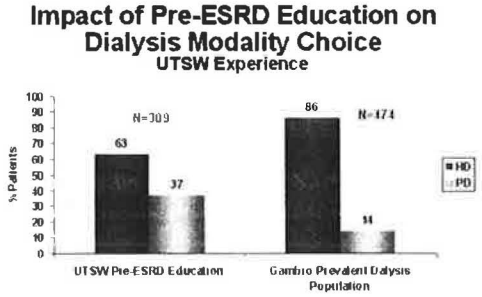
Currently there are 3 options for RRT, renal transplant, hemodialysis (HD) and peritoneal dialysis (PD). While renal transplant is the treatment of choice for stage 5 CKD, the proportion of ESRD patients receiving renal transplant has not changed considerably over the last decade (1). Thus, with the growing burden of ESRD population, the onus for their treatment falls on the two dialysis modalities, HD and PD. One would expect a proportionate utilization of the two modalities. However, this is not the case in the United States. While, there has been increasing utilization of HD in the past decade, there has been a steady decline in the utilization of PD. By the end of year 2001, only 8.8% of total dialysis patients in the USA were receiving PD (3). This is, however, not a worldwide phenomenon. PD is being utilized in a much larger proportion of ESRD population in most developed countries across the world, with some countries like UK and New Zealand having more than 50% of the dialysis patients on PD (3).



The reasons for low utilization of PD in the USA are complex, but seem to be influenced by psychosocial and economic factors, physician bias and inadequate pre-ESRD education to the patient. Analysis of the USRDS Dialysis Morbidity and

Mortality Study Wave 2 (DMMS 2) revealed that among new ESRD patients, the selection of PD over HD was significantly associated with younger age, white race and fewer co-morbid conditions (4). Furthermore, PD is more often used in the patients who are employed, married and more educated (4). Besides, a recent study highlighted the lack of adequate exposure to PD during nephrology fellowship training in the USA (5). A practicing nephrologist, who did not have an adequate PD training, will be reluctant to offer this therapy to the patients. The importance of patient education is underscored by the preliminary results of the National Pre-ESRD Education Initiative (NPEI) where 45% of the patients who received pre-ESRD





education opted for PD and 33% actually started PD (6). Another contributing factor is the timing of referral to the nephrologists. Patients referred earlier to a nephrologist (>4 months) and seen more frequently by a nephrologist (>2 visits) in the pre-ESRD period have greater utilization of PD (4). Conceivably, patients who are referred early and have chance to get pre-ESRD counseling and active participation in decision making are more likely to be placed on PD. Thus greater effort should be paid in improving PD education during the fellowship training. Moreover, delivery of pre-ESRD education to the patients needs to be strongly emphasized in order to improve utilization of PD in the USA.

Introduction

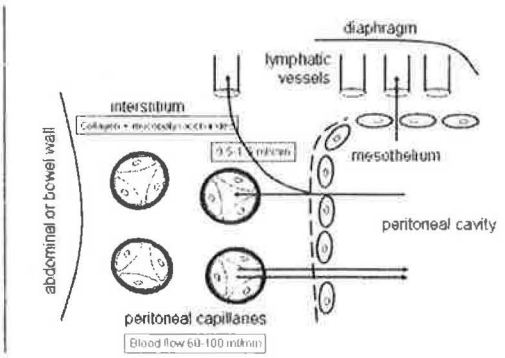
Peritoneal dialysis is achieved by introducing dialysis solution into the peritoneal cavity using a silastic catheter that is inserted through the patient's abdominal wall. This catheter is tunneled under the skin for stability and terminates in the peritoneal space deep in the pelvis. Using this catheter, the dialysis solution is drained into the peritoneal space by gravity and is removed from the cavity by the same means. The natural membrane lining the peritoneal cavity acts as a dialysis membrane through which waste products and excess water from the body can pass through into the peritoneal dialysate fluid. This waste containing dialysate solution is drained out of the abdomen into a plastic bag and is discarded and a new quantity is reintroduced. Each exchange, that is draining of the old solution and replacing it with fresh solution, takes about 30-45 minutes. Interestingly, when abdominal cavity is filled with dialysis solution via an abdominal catheter, ancient phylogenic conditions are recreated. In certain fish, Dobbie showed that the peritoneal cavity is full of liquid and communicates with external environment through a small passage (7). In CAPD patients, that passage corresponds to the peritoneal catheter and functions as a conduit for elimination of waste products.

The Technique of Peritoneal Dialysis

The essential elements of PD are:

- A viable peritoneal cavity lined by a functional membrane
- Access to the peritoneal cavity, usually by means of indwelling catheter
- Dialysis fluid and delivery mechanisms.

The Peritoneal Cavity



The peritoneal cavity represents the largest serosal cavity in the body. In normal circumstances, the closed peritoneal cavity contains 50-100 ml of fluid at any given time (8). It is lined by a continuous, thin, translucent serous membrane, the peritoneum. It consists of a simple squamous mesothelial monolayer resting upon a thin basement membrane, underneath which is a connective tissue interstitium. It covers the inner surface of the abdominal wall (parietal peritoneum) and the majority of visceral organs (visceral peritoneum). The total surface area of peritoneum is approximately similar to the total body surface area (about 2 m^2). About 10-15% of the peritoneum consists of parietal peritoneum while the remaining 85-90% consists of visceral peritoneum. Nevertheless the relative contributions of visceral and parietal peritoneum in PD may not necessarily correlate to the anatomic surface area. Studies in eviscerated rats suggest that the contribution of visceral peritoneum is much less than what would be predicted from the anatomic surface area (13). Visceral peritoneum seems to contribute only about 30% of the total exchange during PD.

The celiac, superior mesenteric and inferior mesenteric arteries supply the visceral peritoneum, whereas circumflex, iliac, lumbar, intercostal and epigastric arteries supply the parietal peritoneum. The venous drainage of visceral peritoneum occurs in portal vein, while that of parietal peritoneum occurs in systemic veins. This is important because drugs introduced intraperitoneally will be partly subjected to hepatic metabolism during the first pass to portal circulation.

Lymphatic drainage from the peritoneal cavity is mainly through specialized lymph stomata of a size up to 20μm located in the sub-diaphragmatic peritoneum. About 80% of the lymphatic drainage is returned to the venous circulation via the right lymphatic duct. In addition to the sub diaphragmatic stomata, a rich network of lymphatic vessels is observed in the interstitium of both parietal and visceral peritoneum. These drain mainly to the thoracic lymph duct.

Ultrastructure of the peritoneum

The peritoneal serous membrane consists of a monolayer of flat cells on a basement membrane (mesothelial cells) and a layer of connective tissue, of variable thickness and structure, containing cells, blood vessels, lymphatic and nerve fibers immersed in a connective tissue matrix. The peritoneum is very thin, about 40 μm in thickness (9).

The Mesothelium: It is a single layer of flattened elongated cells of 0.6-2.0 μm thickness, lining the peritoneal membrane. The luminal side of the mesothelial cells has numerous microvilli. A thin layer of glycocalyx is distributed on the surface of microvilli and on the cell surface between the microvilli. Microvilli are more numerous in the peritoneal region covering the internal organs than elsewhere. It has been hypothesized that mesothelial microvilli have the function of increasing the cell surface area to facilitate the exchanges between cells and the peritoneal fluid and to trap the peritoneal fluid, mainly the phospholipids, to reduce the friction between the moving organs. This is supported by the fact that microvilli are more numerous where there is more friction between the abdominal organs. In addition to microvilli, it is sometimes possible to observe a single cilium on the surface of mesothelial cells. These cilia have a structure of typical motile cilia with 9 peripheral doublets and a single pair of central microtubules. Their function is not yet known.
The mesothelial cytoplasm is extraordinarily rich in organelles. It contains numerous mitochondria and a prominent rough endoplasmic reticulum. In addition, it contains numerous pinocytic vesicles and prominent lamellar bodies that are involved in secretion of phospholipids analogous to secretion of surfactant by type II pneumocytes. The mesothelial cells are secretory in nature and have been shown to synthesize phospholipids, collagen, elastin, proteoglycans, fibronectin, interleukins, growth factors, prostaglandins and others. The secretion of many substances demonstrates the importance of mesothelium not only as a lining cell but also as a structure involved in formation of underlying connective tissue, vasomotor regulation and host defense.

The submesothelial layer: The interstitial connective tissue has a few cells immersed 7in a matrix of collagen and elastic fibers and a gel containing macromolecules. The collagen fibers mainly consists of types I and III collagen. In addition the interstitium contains a small number of fibroblasts, mast cells, macrophages, leukocytes and adipocytes as well as blood and lymphatic vessels. Furthermore, hyaluronic acid and proteoglycans form a gel-like substance that behaves like a filter. The submesothelial layer is less than 50μm in thickness (median thickness 40μm).

Peritoneal Dialysis Access

Access to the peritoneal cavity can readily be achieved through the use of one of many commercially available catheters. Most of the PD catheters are designed after Tenckhoff's original cuffed straight or curled catheter (10). The design and selection of materials is a compromise between the biocompatibility required for a long-lasting implantable devise and the biocompatibility necessary to assure tissue growth for anchoring and sealing the opening between the catheter and the abdominal wall. A variety of catheters are available for PD including the traditional one or two cuff-straight or curled (pigtail) Tenckhoff, the swan neck varieties which incorporate a permanent bend for the subcutaneous segment of the catheter, those with disks and balloons designed to repel bowel loops and omentum around the intra-abdominal segment of the catheter and catheters offering larger pore size and surface area designed to enhance dialysate flow. Both silastic and polyurethane catheters are available.
Each PD catheter is comprised of three parts

- Intra-abdominal segment

- Subcutaneous tunnel segment
- External segment

The intra-abdominal segment has multiple small holes and an open terminal end. The subcutaneous segment usually has two cuffs, the outer cuff is placed just under the skin, about 3-4 cm from the exit site and the deep cuff is placed just external to the fascia covering parietal peritoneum.

The intra-abdominal segment of the catheter should preferably be directed towards the left lower quadrant and specifically into the rectovesical pouch, which is normally the most dependent location in the pelvis. Placement in the right lower quadrant often leads to transposition of the catheter to upper abdominal quadrants through peristaltic forces. An arcuate subcutaneous tunnel with a caudad-oriented exit is recommended in order to facilitate drainage of the exit site, prevent accumulation of sweat, bacteria and debris, and thus reduce exit site infections. It is best to wait 2 weeks following insertion of the catheter before commencing PD to assure good healing and to prevent dialysate leaks.

The complications resulting from the catheter insertion include peri-catheter dialysate leaks, catheter cuff extrusion, exit site infection, tunnel infection, blood vessel or visceral perforation, hernia formation, scrotal or labial edema, hemorrhoids, hydrothorax and catheter obstruction. Catheter obstruction can be total (inflow and outflow), or limited only to outflow failure. The latter is the most common. This is usually the consequence of peritoneal wrapping around the intra-abdominal segment of the catheter resulting in a ball-valve effect.

Peritoneal Dialysis Fluids

Conventional PD fluids consist of an aqueous solution of electrolytes designed to normalize the plasma electrolyte profile, a bicarbonate precursor (usually lactate) to maintain acid base balance and a primary osmotic agent, glucose. The compositions of some commercially available PD solutions are shown in the following table. The solutions are dispensed in plastic bags of various sizes (from 0.5 L to 6.0 L).

Current PD Solutions

	PD1	PD2	PD4
Dextrose (g/dl)	1.5,2.5,4.25	1.5,2.5,4.25	1.5,2.5,4.25
Sodium (mEq/L)	132.0	132.0	132.0
Chloride (mEq/L)	102.0	96.0	96.0
Calcium (mEq/L)	3.5	3.5	2.5
Magnesium (mEq/L)	1.5	0.5	0.5
Lactate (mEq/L)	35.0	40.0	40.0
Osmolality (mmol/L)	346-485	346-485	346-485
pH	5.2	5.2	5.2

As solution dwells in the peritoneal cavity, toxic substances and metabolites diffuse across the peritoneal membrane into the dialysate. In addition, due to hyperosmolarity created by glucose, there is a net movement of fluid from blood to the dialysate.

The original PD solution contained sodium lactate at a concentration of 35 mEq/L, but this was later increased to 40 meq/L to improve acid base balance. It was observed that increasing lactate concentration to 40 mEq/L lead to weight gain, an increase in mid-arm muscle circumference, decreased days of hospitalization and better overall acid-base control (11).

In conventional PD fluids, varied concentrations of dextrose (1.5%, 2.5%, 4.25%) are used to produce fluids of different osmolality. Glucose is widely accepted as an osmotic agent for PD because it is considered relatively safe (at least till recently), and is inexpensive. Furthermore, it has been used in other clinical situations for long and its metabolism is well understood. One disadvantage of glucose as an osmotic agent is its small size (molecular weight 180 Daltons). During a dwell, there is rapid absorption of glucose from the dialysate into blood with, a progressive loss of osmotic

gradient and long-term metabolic consequences from glucose load, described elsewhere in the protocol.

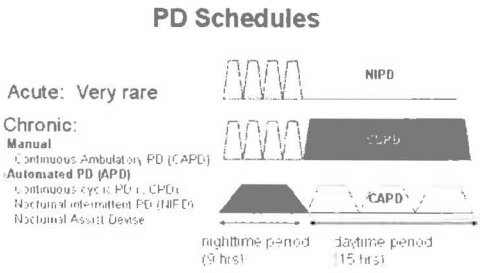
Delivery Mechanism

Delivery of fluid from the dialysate bag to the PD catheter is usually accomplished by using a transfer set, of which two main types are in common use.

Straight transfer sets: This comprises a straight piece of tubing, one end of which is connected to the catheter, the other end to the PD dialysate bag. The patient connects a full bag, opens the clamps and instills the fluid into the abdominal cavity, rolls up the empty bag and carries it with him/her. At the end of the dwell time, the patient unrolls the empty bag, drains the fluid out into this bag, disconnects and discards the bag, connects a new full bag and repeats the process. The transfer sets are changed once every 3 months.

Y-sets: This sets comprises a Y tube with one empty and one full bag connected to the two arms of the Y set. The third arm is connected to an extension tube that is connected to the catheter. This configuration allows the patient to disconnect the empty and remove the empty bag. Utilization of the Y-set with flush before fill technique has been reported to decrease the incidence of peritonitis (12).

Peritoneal Dialysis Schedules:



Peritoneal dialysis can be done manually or can be done with automated devises. It can be continuous (fluid in the abdominal cavity 24 hours a day) or intermittent (when abdominal cavity is dry for a part of the day). The intermittent schedules are utilized in patients with considerable residual renal functions. The various schedules for peritoneal dialysis are as follows:

- Manual
  - Continuous ambulatory peritoneal dialysis (CAPD)
- Automated
  - Continuous cycler assisted peritoneal dialysis (CCPD)
  - Nocturnal intermittent peritoneal dialysis (NIPD)
  - CAPD with a single nocturnal exchange using a nocturnal assist devise

Continuous Ambulatory Peritoneal Dialysis: This requires only connecting tubes and bags of solutions (2 to 3 liters) using gravity to fill and empty the peritoneal cavity. The most commonly used method employs four exchanges per day but in some patients, especially those who are anuric and have a high body mass index, five exchanges are necessary. A small number of patients (low BMI, excellent residual renal functions) may require only three exchanges per day, but this is inadequate in majority of patients with ESRD. The night dwell in CAPD is long (8-10 hours). Sometimes, enhancement of solute removal with CAPD can be accomplished by performing additional 1-2 nocturnal exchanges using night time assist devise such as Quantum devise (Baxter) or a mini cycler (Fresenius).

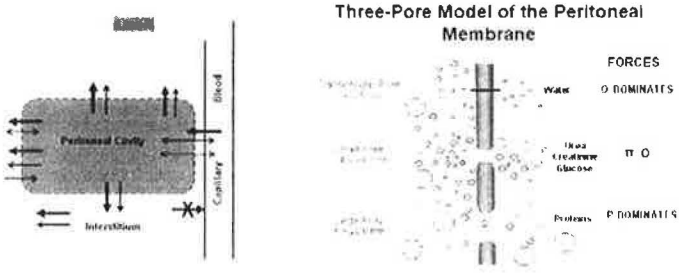
Continuous Cycling Peritoneal Dialysis (CCPD): In this technique, the patient loads the bags of solutions on to a cycler and connects the catheter to the cycler at bedtime. The cycler is programmed to do 3-5 (or more) exchanges during the night. In the morning, 2-2.5 L of fluid is left in the abdomen for the long daytime dwell. During the day period, usually there is no exchange and the procedure is repeated at night. Occasionally, an additional exchange is done during the day to improve clearance or ultrafiltration.

Nocturnal Intermittent Peritoneal Dialysis: NIPD is a cycler assisted nightly procedure as described above except that the peritoneal cavity is left empty during the day. It is usually offered to patients with excellent residual renal functions.

Physiology of Peritoneal Dialysis

In PD, the peritoneal membrane is utilized as an endogenous dialyzing membrane for removal of uremic toxins and excess body water. Various mathematical models of peritoneal membranes have been proposed to explain the transport of solutes and water between the blood and peritoneal dialysate (14, 15). The three-pore model is the most widely accepted model to explain solute and water transport across the peritoneal membrane (16,17).

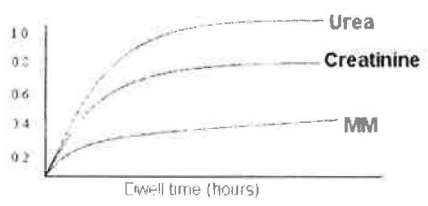
Experimental studies have shown mesothelial layer not being an important barrier to solute transport in PD (18). The barrier function of interstitial tissue is not very well known. The capillary wall is likely the most important barrier to solute transport during PD (16-18). According to the three-pore model, the solute transport across the peritoneal capillaries ensues through a system of pores. These pores include a large number of small pores (40-60 A^{o} radii), together with a small number (less than 0.1% of total number) of large pores (200-300 A^{o} radii) that permit the transport of macromolecules. In addition, an abundance of transendothelial ultrasmall pores (radius 3-5 A^{o}) have been assumed that allow the transport of water but not other solutes. The small pores are likely represented by the tortuous intercellular clefts between the endothelial cells. Recently, aquaporin-1 was demonstrated in the peritoneal vasculature of CAPD patient. It is likely that aquaporin-1 represents the transendothelial ultrasmall pores (19-21). The nature of the large pores is largely unknown. It is possible that they represent specialized intercellular clefts with large radii. Alternatively, they may represent fused plasmalemmal vesicles forming large transcellular canals. Computer simulation hypothesizes that about one half the volume filtered across the endothelium during PD with dextrose occurs through transcellular pores.



Two major mechanisms, diffusion and convection, are involved in transport of solutes from peritoneal capillaries to dialysate (22).

Diffusion Curves

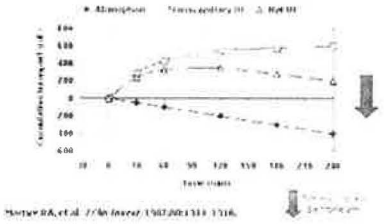
Dialysate to plasma (D/P) ratios



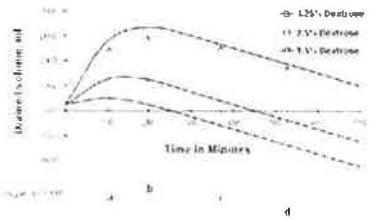
Diffusion: Diffusion is the most important transport mechanism for low molecular weight solutes. Diffusion of small solutes is bi-directional and occurs through the small pore system. The rate of diffusion depends upon the concentration gradient of the solutes, the effective peritoneal surface area, the intrinsic permeability of the membrane and the time allowed for the transport. Furthermore, rate of diffusion decreases as the molecular weight of the solute increases (e.g. urea diffuses faster than the creatinine).

The permeability of the peritoneum to the transport of low molecular weight solutes is traditionally investigated by performing a standardized peritoneal equilibration test (PET). The test is performed using a 2.0-liter of 2.5% dextrose dialysate (23). The dialysate is drained after 4 hours. A blood sample at 2 hours is taken for determination of creatinine, urea and glucose concentration. Dialysate samples are taken at time 0 and then at 2 and 4 hours to determine dialysate glucose, urea and creatinine. The dialysate to plasma (D/P) ratios of urea and creatinine at 4 hours and the ratio of dialysate glucose at 4 hours to its initial concentration at time zero (D_4/D_0) are used to study the peritoneal permeability to small solutes. The D/P ratio of creatinine at 4 hours is clinically used to classify the peritoneum into four transport categories: Low, Low-average, High-average and High. Patients who exhibit high transport character will rapidly equilibrate creatinine and urea and achieve excellent small solute clearance. However, they will also rapidly absorb glucose from the peritoneal cavity and therefore rapidly lose osmotic gradient leading to poor ultrafiltration. In contrast, patients who are low transporters will have poor urea and creatinine clearance but excellent ultrafiltration.

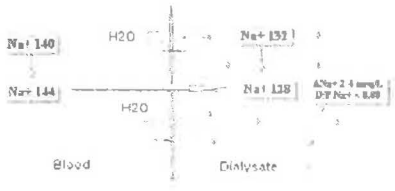
Net UF: Balance of opposing forces



Determinants of UF Profile:
Dextrose Strength, Duration and Drain Volume



Transcellular Water Transport:
The Concept of Sodium Sieving



Ultrafiltration: In clinical setting, ultrafiltration is achieved by using hypertonic glucose to create crystalloid osmotic pressure gradient between dialysate and blood. The transcapillary UF rate depends upon the hydraulic permeability of the peritoneum, its effective surface area and the hydrostatic, colloid osmotic and crystalloid osmotic pressure gradients (24). In PD using conventional solutions, glucose is used to create crystalloid osmotic pressure gradient for UF. The effectiveness of glucose as an osmotic agent depends upon the resistance the peritoneal membrane exerts to glucose transport. This is expressed as the osmotic reflection coefficient. It can range from 1 (no passage, ideal osmotic agent) to 0 (no hindrance, not an effective osmotic agent). The reflection coefficient of glucose across small pores is very low, but is close to 1.0 across the ultra-small pores. This explains why glucose is

an effective osmotic agent despite its small size. The concentration of glucose is maximal during the beginning of dialysis but decreases during the dwell because of diffusion into blood across the small pores. The glucose absorption averages 60% of the instilled quantity during a 4 hour dwell. Consequently, the UF rate is maximal at start but decreases during the PD dwell.

Sodium sieving: It has been observed for years that the concentration of sodium in the dialysate decreases during the initial phase of the dwell using dialysis with hypertonic glucose, followed by a gradual rise. The minimum values are reached after about 1-2 hours. This so-called "sodium sieving" is likely caused by transcellular water transport through ultra-small pores (24). Water transport rates are high during the initial phase of a hypertonic exchange leading to sodium dilution in the dialysate. This implies that during short dwells using hypertonic dialysate, much more water than sodium is removed from blood, which can lead to hypernatremia. The gradual rise during the subsequent hours is likely caused by diffusion of sodium across the small pores. By using 4.25% dextrose for PET and estimating D/P Na^+ or degree of Na^+ dilution in the dialysate, ΔNa^+ at 60 minutes, one can roughly assess aquaporin mediated water transport. Absence of Na^+ dilution or one hour D/P $Na^+ > 0.88$ would suggest impaired aquaporin mediated water transport (24, 25).

Fluid reabsorption: In addition to diffusion and convection, peritoneal fluid is being reabsorbed at a relatively constant rate of 1-1.5 ml/min. The fluid is either reabsorbed directly into the sub-diaphragmatic lymphatics at a rate of 0.2-0.3 ml/min or into the interstitium and thereafter to interstitial lymphatics at a rate of about 1-1.2 ml/min. The lymphatic reabsorption can be measured either as the disappearance rate of intraperitoneally administered macromolecules (such as dextran) or its appearance rate in circulation (such as radiolabeled iodinated albumin). The disappearance overestimates lymphatic absorption because the tracer is also transported across the mesothelial layer into the interstitium. The appearance underestimates the lymphatic absorption because only 40-50% of albumin is intravascular (24).

Markers of Peritoneal Transport

A number of locally produced substances are present in the peritoneal effluent. Among these are various cytokines but also phospholipids, glycoproteins and glycosaminoglycans. The phospholipids in effluent largely consist of phosphatidylcholine (55-85%). They are mainly, but not exclusively synthesized in mesothelial cells (26). Glycosaminoglycans, consisting of hyaluronans and proteoglycans are also mainly but not exclusively synthesized in mesothelial cells (27, 28). Cancer antigen, CA 125 is a 220 KD glycoprotein synthesized exclusively by mesothelial cells in the peritoneal tissue (29). CA 125 concentration in peritoneal effluent represents mesothelial cell mass in stable peritoneal dialysis patient (29-31). The following further supports this conclusion: 1. A positive relationship is present between the number of mesothelial cells and CA125 level in the peritoneal effluent. 2. CA 125 is not synthesized by other cells present in peritoneal tissue or by leukocytes (29-31).

During processing of procollagen I and III to collagen, procollagen I C terminal peptides (PICP) and procollagen III N terminal peptide (PIIINP) are split off. Dialysate concentration of PICP and PIIINP could be used as markers of collagen synthesis in peritoneum (32).

Pros and Cons of Peritoneal Dialysis

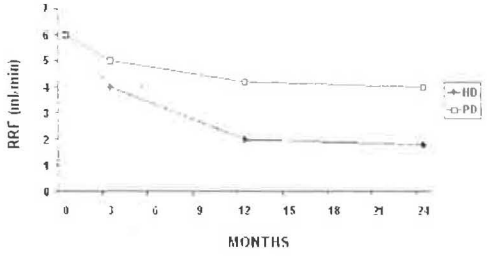
PD offers several advantages over HD in the management of ESRD patients. Unlike saw tooth treatment with HD, PD being a slow continuous therapy delivers steady state treatment. This avoids wide fluctuations of plasma volume, electrolytes and other solutes and is generally better tolerated by the patients with cardiovascular compromise. In addition, PD provides a flexible schedule (unlike HD, where dialysis shifts are generally fixed) and therefore provides patients the opportunity to work, travel and participate in daytime activities. Unlike HD where the patients experience great anxiety at the thought of being stuck with needles and having a negative impact on the quality of life, PD is needle-less. This also helps to preserve sites for arterio-venous access for future HD. Additionally risk of acquiring Hepatitis C, which is rampant in HD population, is significantly reduced in PD population. PD also facilitates preservation of residual renal function (RRF) much longer as compare to HD (33,34). There is growing evidence that preserved RRF is directly related to adequacy of dialysis, better endocrine function, better clearance of middle molecules, better control of volume status and hypertension and better survival outcomes (35,36). PD may also be beneficial in patients waiting for kidney transplant. Recent data suggests that compared to HD patients, PD patients have significantly lower incidence of delayed graft function and a significantly lower requirement of dialysis in the post-transplant period. This may have impact on long-term allograft survival (37-39).

Despite the numerous advantages of PD listed above there are certain drawbacks of PD. PD being a continuous therapy requiring four to six exchanges a day with no "off" days may be inconvenient and can lead to patient fatigue in long-term. Some patients may have concern with the presence of a permanent external catheter and the body image changes resulting from the catheter and the fluid in the abdomen. Moreover there are always risks of infection and mechanical complications like hernias, catheter leaks and catheter malfunction. Furthermore, unlike HD where health professionals give care, PD requires self-care with patient and the family assuming most of the responsibilities for the dialysis treatment and administration of medications like erythropoetin. To some patients this can be overwhelming.

Residual Renal Function and Peritoneal Dialysis

The residual renal function (RRF) progressively declines in virtually all patients with CKD, both before and after initiation of dialysis. There is ample clinical data to support that RRF declines more slowly in the patients receiving PD than in patients on HD (33-35). The reasons for these differences between HD and PD have not been fully defined but several mechanisms have been suggested. PD patients have more hemodynamic stability with less abrupt volume and osmolar shifts. As a consequence, glomerular capillary pressure remains relatively stable glomerular ischemia is minimized. Additionally, potential nephrotoxic inflammatory mediators that are generated by the bioincompatible extracorporeal circuit of HD are not observed in PD. Another

Effect of Dialysis Modality on RRF



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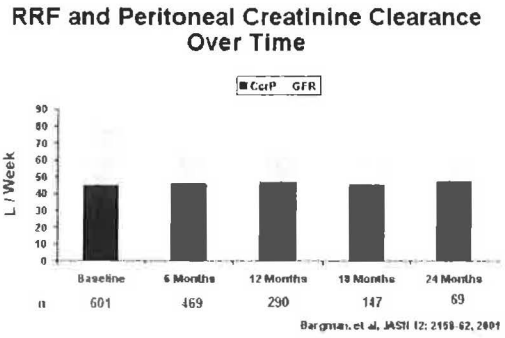
important factor in better preservation of RRF in PD is mild, constant volume expanded state of these patients.



While dialyzer membrane in HD and peritoneum in PD provide the major route for elimination of fluids and solutes, the importance of RRF is increasingly recognized. Higher RRF at the initiation of dialysis and maintenance of RRF throughout the course of renal replacement therapy has been associated with improved outcomes and reduced patient mortality. The reanalysis of CANUSA (Canadian, USA study) data revealed that the patients on PD who died or transferred to HD had a higher rate of decline of GFR as well as a significantly lower GFR at dialysis initiation (35). Preserved RRF may also reduce cardiovascular morbidity by controlling volume homeostasis. Better preservation of RRF may have other important clinical associations, including preserved endocrine functions (with better erythropoetin production and better activation of vitamin D), and elimination of middle molecules like β_2-microglobulin. Studies have shown that patients with preserved RRF have better nutritional status (35, 40,41).

Thus preservation of RRF is an important goal in the management of patients with PD. Risk factors for faster decline of RRF include diabetes mellitus, left ventricular dysfunction, higher rates of peritonitis, frequent use of aminoglycosides, use of radiocontrast agents and use of non-steroidal analgesics (NSAIDs). Furthermore, HD during the break-in period can be associated with a greater decline in RRF compared to the patients who start directly on PD (42).

Given, significant benefits RRF confers, every effort to preserve RRF must be pursued diligently. It is important to avoid nephrotoxic drugs like aminoglycosides and NSAIDs, limit the use of radiocontrast agents and avoid delay in initiation of PD (thus avoiding the break-in period with HD) (43) Some studies suggest that use of angiotensin converting enzyme inhibitors (or angiotensin receptor blockers) may help to preserve RRF (44). Finally, every effort should be made to prevent peritonitis and if it happens, all attempts should be made to avoid aminoglycosides.

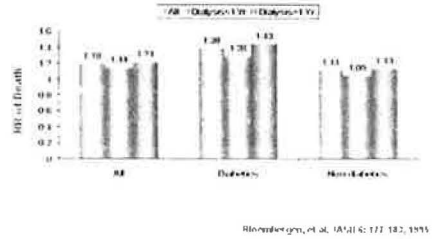
Lastly, in view of the fact that PD preserves RRF better than HD, PD should be the modality of choice in patients with renal failure where there is any possibility of renal recovery (45).

Peritoneal Dialysis Outcome Studies.

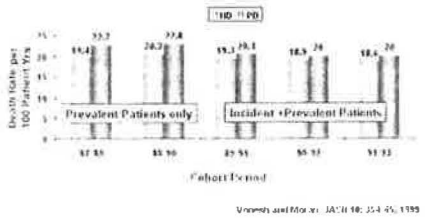
Several studies have been undertaken to compare the outcomes of PD and HD. Analysis of earlier studies published from 1988-1992 comparing relative risk of death on PD as compared with HD by and large found the mortality risks to be equal for HD and PD patients (46-48). Thereafter came a report by Bloembergen, et al (49), which was based on the USRDS data on prevalent patients (1987, 1988, 1989) and showed that PD patients had a 19% higher risk of mortality compared to HD patients. The risk was not significant in patients less than 55 years old and increasingly large and significant for ages >55 years. In addition, the higher relative risk for PD patients was significantly accentuated among diabetics and females, although it was also present in non-diabetics and males > 55 years. However, the mortality risk was significantly

lower in patients who were on PD less than 1 year compared to those treated for more than 1 year. This was met with considerable dismay in the USA and probably did the therapy a major disservice. A subsequent analysis of Canadian incident hemodialysis and peritoneal dialysis patients from 1990-1994 found that the relative risk of mortality for PD relative to hemodialysis was 27 % lower (RR 0.73, 95% CI 0.68-0.78) (50). Moreover, it was observed that the increased mortality in HD compared to PD was concentrated in the first two years of the treatment with subsequently no difference up to 4 years. The lower risk of death was observed regardless of age or diabetes status. An analysis of US Medicare incident patients between 1994 and 1997 by Collins, et al yielded results similar to the Canadian study by Fenton, et al (51). It showed that in the first two years of therapy, PD is associated with superior outcomes compared with HD at all ages except in elderly women and diabetics. Interestingly, a reanalysis of the USRDS data from the periods 1987-1993 (which included the USRDS cohort 1987-88 analyzed by Bloembergen, et al (52), Vonesh and Moran found no difference in mortality between HD and PD when both incident and prevalent patients were included from periods 1989 onwards. For the periods 1987-1989, results similar to that of Bloembergen, et al (49) were obtained, as this period (1987-1989) included only prevalent patients (USRDS started reporting incident and prevalent dialysis patients from 1989 onwards. Prior to that, patients starting dialysis in the middle of the year were not reported for that year, but reported the next year). A further analysis of 17,000 PD patients from the Canadian Organ Replacement Registry database (1981-1997) showed a significant decrease in mortality rates during this period (53). Furthermore, a recent study from Denmark using registry data from periods (1990-1999) revealed a survival advantage for PD during first 2 years of treatment (54). The recent USRDS data comparing adjusted 5-year survival for PD and HD for two different cohorts (1987-1991, 1992-1996) showed no difference between the modalities (Fig.) (1). Recent analysis of Medicare database from periods between 1995-1997 showed that although the overall mortality risk of PD and HD was similar, incident patients with coronary artery disease (CAD) on PD had a higher risk of mortality than those on HD (55). Of note, the patients with coronary artery disease were significantly older (mean age 54 years in patients without vs. 65 years with CAD) and had higher prevalence of diabetes (34.7% without and 52.6% with

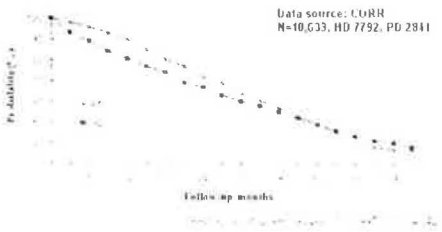
RR of Death Higher in Prevalent PD Patients



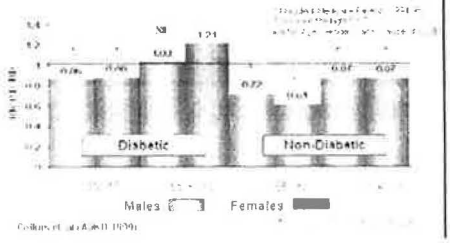
Trends in Adjusted All-cause DR for HD and PD Patients: USRDS Cohorts



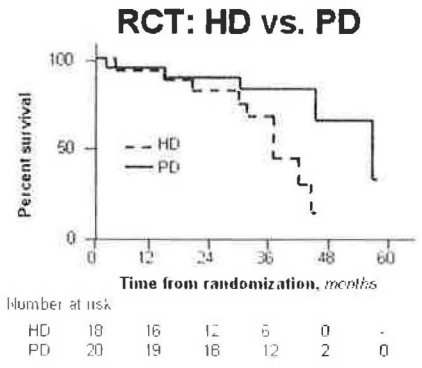
Patient Survival Probability for Patients Initiating Dialysis with PD Compared to HD (1990-94)



Relative Risk PD vs. HD

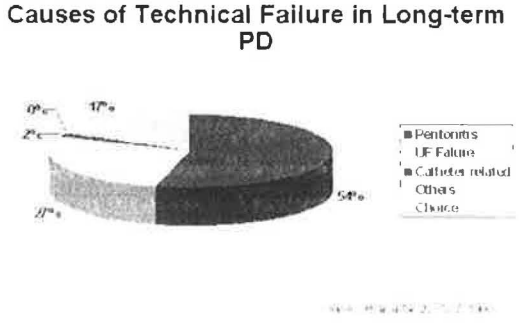


CAD). Another study examined the impact of dialysis modality on incident patients with congestive heart failure (CHF) using the same data (Medicare, 1995-1997) (56). Again, the risk of mortality was found to be significantly higher in PD patients with CHF. No information of the severity of CHF, PD prescription, PET status or residual renal functions was available. Similar to patients with CAD, patients with CHF were older (63.5 years vs. 54.3 years) and had higher prevalence of diabetes (60.4% vs. 41.7%). Previous studies have noted higher mortality risks in elderly PD patients with diabetes, which may be due to a higher incidence of CAD and CHF in such population.



So far, the studies comparing outcomes of PD with HD have been observational and based largely upon registry data. The mortality results from these studies should be viewed with caution since other unmeasured co-morbid factors and severity of the reported co morbidities may be unevenly distributed between the two treatment groups. Whether the difference in mortality risks between the two modalities is a modality effect per se or due to unmeasured patient selection, residual renal function, dialysis adequacy or severity of the co morbidity requires further investigation. There is a great need for a randomized controlled trial (RCT) to address these issues, but the challenge to carry out such a study is underscored by the only RCT done so far and published recently (57). This multi-center RCT from Netherlands to compare survival and health-related quality of life on HD and PD patients was discontinued prematurely because very few patients (38 patients over an inclusion period of more than 3 years) could be randomized. Interestingly, during the recruitment period, 773 patients were initiated on dialysis, but 735 of them refused participation in the study. However, by their own choice, 48% preferred to start on PD and 52% on HD. Notwithstanding the small sample size, the study showed a significant survival benefit for PD over HD in the first 4 years of the treatment.

Taken together, the results from the aforesaid studies suggest that overall mortality is at least similar in HD and PD. PD may offer survival benefit in the first two years of the treatment. On the other hand there may be a higher risk of mortality among elderly diabetic patients on PD, which may, in turn, be related to higher prevalence of coronary artery disease and congestive heart failure in such population. Furthermore, higher mortality risk among PD patients with CHF may not be a consequence of dialysis modality but a result of sub-optimal fluid management.



Current Problems with Peritoneal Dialysis

Peritoneal dialysis has been a successful and effective form of therapy since it was introduced about 25 years ago. There have been dramatic improvements in the outcomes in the patients treated with

PD. PD is now a major form of therapy for end stage renal disease worldwide. Currently more than 125,000 patients with end stage renal disease utilize PD as a dialysis modality globally. As described above, there is growing evidence to suggest PD provides at least an equal if not superior mode of dialysis to HD. The benefit of PD is however limited to first three or four years and majority of patients shift to HD because of technique failure. In an analysis by Davies, et al, technique survival in seven studies in the 1990s was 30-50% at 5 year (58). Long-term PD survival is usually less than 20% at 10 years. In data from Japan, the median long-term survival from a cohort of 242 patients was 5.5 years (59). The causes of treatment failure are multifactorial and include recurrent episodes of peritonitis, loss of residual renal function, inadequate solute clearance and loss of peritoneal membrane function (58-60). With the improvement of PD the connection technology, there have been a dramatic reduction in the episodes of peritonitis. Additionally, with the introduction of the automated PD (APD), there have been improvements in solute clearance especially in large anuric patients. However, one of the leading causes of non-achievement of long-term PD that needs to be addressed is related to the ongoing changes in the peritoneal membrane structure and function leading to membrane failure.

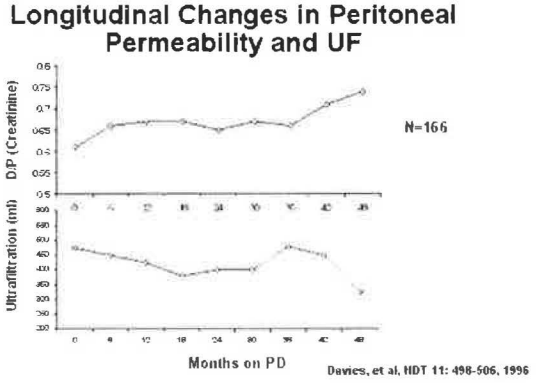
Structural changes in the peritoneum during peritoneal dialysis

During peritoneal dialysis, the peritoneum is continuously exposed to peritoneal dialysate, which is hyperosmolar, has low pH and contains lactate and high levels of glucose. In addition during sterilization and storage of dialysate, a large quantity of glucose degradation products (GDPs) are formed. All these features make peritoneal dialysate bio-incompatible. During PD, the peritoneum is forced to adopt a foreign mode in which surface-active phospholipids are replaced by dialysis solution along with all its problems of bio-incompatibility leading to changes in the peritoneal tissue. The current understanding of peritoneal morphology during long term PD rests heavily on the compilation of information derived from peritoneal biopsies taken during various events. Because the peritoneal membrane is not easily accessible, biopsies are generally taken during insertion or removal of a catheter, during an unrelated abdominal surgery or during renal transplantation (61).
Before the start of PD, the mesothelium in non-diabetic and diabetic patients has a normal morphology. After several months on PD there is gradual reduction in the number and finally, by 8-10 months, total disappearance of microvilli. The intercellular junctions start opening up leading to separation of mesothelial cells from each other. In addition, by 4 months, the mesothelial basement membrane starts showing signs of replication similar to the changes in the capillary basement membrane. Eventually the mesothelial cells become nonviable and are exfoliated off from the peritoneum (62). In addition to the changes in the mesothelium, striking changes in the submesothelial interstitium, including variable degree of expansion are observed during PD. The interstitial tissue becomes edematous with dissociation of bundles of collagen and elastic fibers. Gross irregularities in the distribution of collagen fibers characterized by increased deposition of type IV collagen are observed in long term PD (62). The median thickness of peritoneal membrane in normal individuals is 40μm with a range of 30-70μm. The thickness of sub-mesothelial layer increases in uremic patients (median thickness 150μm) who have never been on PD. However, there is gradual increase in the thickness of this layer progressing from 180μm in patients on PD for less than 24 months to up to 600μm in patients who have

been on PD for more than eight years (61). In addition, the number of cells in the interstitium also increases during PD (62) . Peritoneal mesenchymal cells entrapped in the in the interstitial stroma have historically been considered to be the primary cells involved in the peritoneal fibrosis. Alternatively, mesothelial cells may transdifferentiate from an epithelial phenotype to profibrotic mesenchymal phenotype and play an active role in peritoneal fibrosis (63). Along with changes in mesothelium and the submesothelial connective tissue matrix, there are changes observed in the peritoneal vasculature. The basement lamina of peritoneal capillaries is normal before treatment in non-diabetics, but features doubling after a few months on PD. Later, multiple reduplications-even exceeding 5 layers-can be seen. In diabetic patients, the reduplication of capillary basement membrane is already present in the initial biopsy and aggravates upon exposure to dialysate. Rarely, after many months of PD (usually more than 36 months), the layers unite to give appearance of a thickened membrane. The thickness of the capillary membrane increases as dialysis goes on, until the capillary is completely occluded. These pathologic changes were reported to occur more frequently in patients with recurrent peritonitis, but the data is sparse and inconclusive (61,62). In addition to structural changes, the number of blood vessels per unit length of the peritoneal surface also increases with the duration of PD (62).

Functional Changes in Peritoneal Membrane with Long-term PD

In addition to the structural changes, long-term exposure of peritoneal membrane to bio-incompatible dialysate leads to its functional alterations. Cleary some patients on PD survive for extended periods in absence of significant changes in peritoneal function, suggesting that individual susceptibility to as yet unidentified factors plays a role. Evidence is mounting that ultrafiltration capacity of peritoneal membrane is progressively lost with time on PD and that the problem becomes apparent after 4 or more years of treatment (58,64,65). Furthermore, growing number of studies indicate that small solute transport rates tend to increase progressively with time on PD at least in a proportion of patients. Small solute transport across the peritoneum depends upon the effective surface area of the peritoneal membrane. Accordingly, elevated transport of small solutes with time would thus imply increase in the surface area. While, increase in the size of peritoneum is unlikely, an increase in effective surface area must be due to increase in the number of capillaries that contribute to small solute transport, either by recruitment of previously underperfused capillaries or by formation of new capillaries. Consequently, a stable increase in small solute transport rate points towards the presence of peritoneal neoangiogenesis.



Altered peritoneal membrane functions have a significant impact on both technique and patient survival (58, 61-65). Next to peritonitis, ultrafiltration failure is the most common cause of technique dropout. Loss of ultrafiltration capacity accounts for up to 25-30% cases technical failure (58,59). As prevalence of ultrafiltration failure increases with time on PD, it becomes the predominant reason for drop out in long-

term PD patients. Kawaguchi, et al (59), reported a 23.5% overall incidence of ultrafiltration failure in 224 patients, but 51.4% such failure in those who had spent more than 6 years on PD. High transport characteristics have consistently been associated with low survival rates, a finding that can be ascribed to various mechanisms (66-68). The most important element is the reduced ultrafiltration capacity, which leads to a chronic volume overload state with resultant congestive heart failure and cardiovascular mortality. Poor ultrafiltration can also lead to low drain volumes and consequently to poor solute clearance and thus lower dialysis adequacy. In addition, the nutrition status of high transporters is poor. A proposed mechanism is that high transport patients experience rapid absorption of glucose from the dialysate (with inhibition of appetite) and a greater loss of proteins in the dialysate. Both these factors contribute to poor nutritional status (66-68).

Potential causative factors for peritoneal membrane changes in long-term PD

As noted earlier, continuous exposure to unphysiologic dialysis solutions in an important pathogenic element involved in the structural and functional changes of the peritoneal membrane in long-term PD. Conventional peritoneal dialysis solutions are hyperosmolar, have low pH, have high glucose content and contain high concentration of lactate buffer. As if this were not enough, it has also been demonstrated that during heat sterilization and storage, some of the glucose in PD fluid is degraded to reactive substances referred to as glucose degradation products (GDPs). Any of the aforesaid elements can be potentially toxic to the peritoneal membrane.

Low pH and Lactate

Conventional PD solutions are based on a 5.2 pH and 40 mmol/L lactate formulation. Infusion pain is the most direct and immediate clinical consequence of low pH (69,70). Neutralized solutions are known to reduce discomfort during infusion (69,70). Furthermore, in vitro studies have demonstrated the toxic effects of low pH on mesothelial cells as well as on peritoneal host defense (71). It has been observed that raising the pH of dialysate to 6.5 or higher prevents impairment of many cell functions (72). Simultaneous exposure of polymorphonuclear leukocytes (PMN) to high lactate concentration and low pH results in a rapid and profound lowering of intracellular pH (71). In contrast, fluids of low pH in absence of lactate showed a much slower rate of reduction of intracellular pH. In fluids of neutral pH, the presence of lactate did not influence the intracellular pH. The drop in intracellular pH may be one of key pathophysiological factors in the cytotoxicity of conventional peritoneal dialysis fluids (71). The long-term effects of neutralized, lactate-containing dialysate used in CAPD were evaluated in 8 well-controlled patients. Sodium bicarbonate (12 mL, 8.4%) was added to conventional acidic lactate containing dialysate immediately before every administration. The final pH was 6.8. Patients were treated with neutralized dialysate for five months. Total leukocyte counts in the effluent decreased, and the leukocyte viability increased. Abdominal distension, abdominal pain during instillation, nausea and headache improved (73).

Glucose

For more than 20 years, glucose has been used successfully as an osmotic agent in PD fluids. In order to generate effective osmotic pressure, the glucose concentrations must typically be 15-40 times physiological levels (1370-3860 mg/dL). Absorption of glucose may be associated with metabolic problems such as hyperglycemia, hyperinsulinemia, hyperlipidemia and obesity (74,75). Furthermore, glucose may not only have direct effects on cellular parameters but also may indirectly influence cell functions through hyperosmolarity, glucose degradation products (GDPs) and advanced glycation end product (AGE) mediated reactions.

Various studies show that exposure of human peritoneal mesothelial cells to high glucose leads to generation of reactive oxygen species, enhanced expression of genes such as TGF-β, fibronectin, laminin, and MCP-1 and increased apoptosis (76). A recent study showed that high glucose and to a lesser extent high osmolality inhibited mesothelial cell migration (77). This effect on migration combined with glucose-mediated damage to the intercellular junction suggests that chronic exposure to glucose could promote membrane damage by interfering with remesothelialization of the membrane after injury.

Experimental data also suggests that high glucose/hyperosmolarity reduce leukocyte viability, phagocytosis, bactericidal activity and cytokine production. Furthermore, presence of glucose also increases the rate of fibroblast proliferation with concomitant increase in the synthesis of procollagen III peptide, indicating a potential role of glucose in expansion of the extracellular matrix in the peritoneal interstitium (77-79). Finally, high glucose up regulates the synthesis of vascular endothelial growth factor (VEGF), by rat peritoneal endothelial cells suggesting its possible role in dialysis-mediated changes in the vasculature and peritoneal permeability (76).

Glucose Degradation Products

It has been demonstrated that during heat sterilization and storage, some of the glucose in PD fluid is degraded to reactive substances referred to as glucose degradation products (GDPs). Even though this reaction has been well known from the fields of carbohydrate chemistry, it took a long time before it was realized to be a problem in the PD fluids (80). The presence and toxicity of GDPs in PD fluids was first demonstrated in vitro in a mouse cell line (81). Since then, the general nature of these results has been confirmed using a large variety of endpoints and different human cells (82). Most GDPs are of small molecular weight, including reactive aldehydes such as 5-HMF (5-hydroxymethylfuraldehyde), formaldehyde, acetaldehyde and 2-furaldehyde. Other compounds currently identified are methylglyoxal, glyoxal, 3-deoxyglucosone (3-DG) and 3,4-dideoxyglucosone-3-ene (3,4-DGE) (83). However, the number of identified GDPs represents only a fraction of a large number of degradation products that can be generated from glucose. All of the GDPs are highly reactive carbonyl compounds, known to be extremely toxic, but the most recently identified GDP, 3,4-DGE, has been reported to be the most biologically active of all GDPs and is presently the main candidate responsible for most of the cytotoxicity (84). It has been shown that GDPs impair the proliferation and wound healing capacity of mesothelial cells. It has been observed that peritoneal dialysate concentration of CA125, a marker of mesothelial cell mass, is higher in dialysate from patients using fluids with low levels of GDPs (85). Furthermore, the dialysate concentration of CA125 increases within a few weeks when the patients are

switched from fluids with GDPs to the fluids without GDPs. Finally, mesothelial cells from patients using fluids with low GDPs have improved ex vivo proliferative capacity (86). Thus presence of GDPs in PD fluid seems to be a major factor responsible for mesothelial cell loss observed during the course of peritoneal dialysis (87). Apart from their inherent toxic effects, GDPs have also been shown to participate in glycosylation of amino groups, thus forming Amadori products and irreversibly glycosylated proteins, called advanced glycosylated end products (AGEs). AGEs are known to accumulate over time and are considered to participate in remodeling and fibrosis of the peritoneal membrane (88). It is now recognized that GDPs are much stronger promoters of AGEs than glucose *per se*. GDPs exert their action not only within the peritoneal cavity, but are also transported into blood stream and contribute to systemic accumulation of AGEs. Indeed, increased plasma levels of circulating reactive carbonyl compounds and AGEs have been reported from clinical studies with GDP-containing PD fluids.

How can GDPs be avoided?

It is well known that pH, glucose concentration and presence of catalyzing substances affect degradation. For standard PD solution, hydrochloric acid is added to reach pH 5.0-5.5, and although GDPs are still formed, the compromise has for many years been considered satisfactory. Further lowering of pH has not been possible because of poor tolerance due to infusion pain and compromise of host defense. Recently, multi-compartment bags have been developed in which one compartment contains a very high concentration of glucose (50%) with very low pH (3.2) while the other compartment contains the buffer and other electrolytes (89). When the PD fluid under these conditions is heat sterilized, few GDPs are generated. Mixing the fluids of the compartment just prior to infusion results in a final solution with a pH close to the physiologic value (7.4) and a minimal GDP concentration.

Another approach to avoid GDP is to sterilize the solution without heat, using stepwise ultrafilters, to remove bacteria and pyrogens. Some GDPs are still generated. This method is not yet in commercial use (90).

Finally, one obvious approach would be to avoid using glucose and to select alternative osmotic agents. Among alternative agents available today or in clinical trials, no candidate has appeared to replace glucose completely. Amino acids and icodextrins are indicated in certain cases but usually for only one dwell per day (91). Besides, icodextrin, being a glucose polymer, also contains some GDPs after heat sterilization.

Advanced glycation end products (AGEs)

Glucose can also contribute indirectly to peritoneal membrane alterations through formation of AGEs. These are a great variety of individual compounds that are formed during non-enzymatic reactions between side chains of proteins, in particular lysine and arginine residues and reactive carbonyl compounds such as glucose or glucose degradation products (GDPs). This complex reaction was first described in 1912 by Louis-Camille Maillard, who report browning reactions that occur when aqueous solutions containing amino acids and reducing sugars are heated (92). Within last 20 years, it has been realized that the Maillard reaction (non-enzymatic glycation) also occurs under physiologic conditions in human body. The Maillard reaction is generally divided into 3 stages. The "early" stage is characterized by the formation of aminoketoses, the so called Amadori compounds or sugar amino acids, resulting from

the reaction of a reactive carbonyl compound such as GDPs or reducing sugars such as glucose and an amino group of an amino acid, a peptide or a protein. Depending on the time and temperature of the incubating conditions, the initially formed aminoketoses are degraded in the "advance" stage to highly reactive α-dicarbonyl compounds, which, afterwards, in the "final" stage induce the formation of a large number of AGEs (93). AGEs have been implicated in various activities that can adversely affect peritoneal membrane, including protein cross linking, inflammation, angiogenesis, vascular smooth muscle proliferation and increased nitric oxide production (94-96). However, up till now no individual AGE has been linked to any biological effect on a cellular or molecular basis. A recent histochemical analysis of peritoneal membrane biopsy demonstrated co-localization of AGEs with TGF-β, VEGF and M-CSF, suggesting that AGE-receptor binding activates signaling pathways leading to development of peritoneal fibrosis and neovascularization (97). Furthermore, AGEs have been shown to reduce the mesothelial cell viability and increase VCAM-1 and plasminogen activator inhibitor-1 (PAI-1) expression in mesothelial cells (98,99). These studies suggest that AGEs play a significant role in peritoneal membrane alteration in long-term PD. Recent studies suggest that newly developed bicarbonate/lactate based solutions with neutral pH have a decreased potential for AGEs formation in vivo (mainly due to decreased GDP formation), which would minimize membrane damage and preserve membrane structure and function in long-term PD (89).

New Solutions for Peritoneal Dialysis

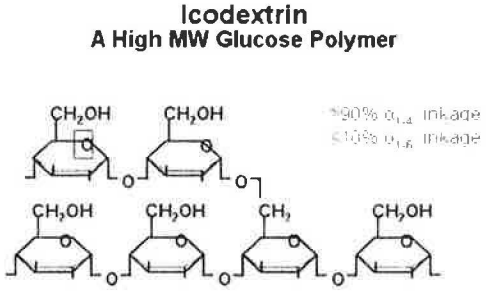
The development of new PD solutions has focused on both the acute and chronic effects related to bioincompatibility of conventional PD solutions. Pain upon infusion is considered to reflect bioincompatibility and, to date is probably the only measurable acute clinical effect of PD solution bioincompatibility. Loss of ultrafiltration and impaired host defense are chronic effects attributed to bioincompatibility of PD solutions. In addition to these local effects, various systemic effects of conventional PD solutions must be considered:

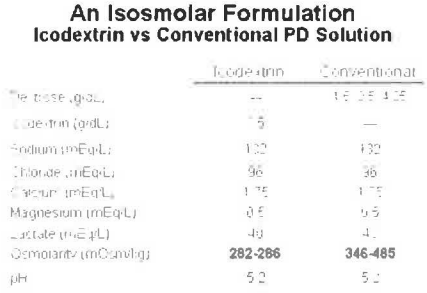
- Nutritional effects, such as malnutrition may be aggravated by the dialysis procedure
- Systemic inflammation (a contribution to malnutrition, atherosclerosis, and premature cardiovascular disease) may be aggravated by the dialysis procedure.

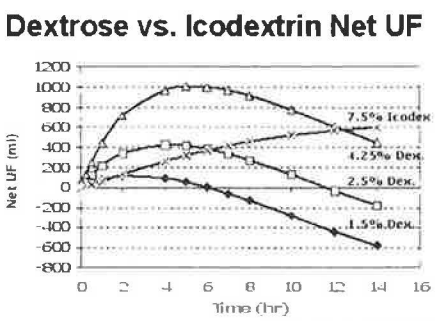
The three new PD solutions described below address the clinical requirement to improve the acute and chronic local effects of bioincompatible PD solutions. In addition, the new PD solutions may also have more favorable systemic effects.

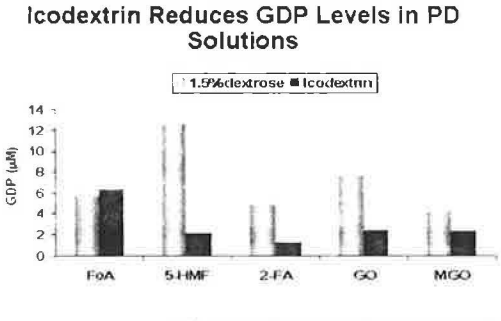
Icodextrin-Based Solution: Icodextrin is a polymer of glucose produced by the hydrolysis of cornstarch (100). The solution contains a spectrum of icodextrin molecules with average molecular weight of 16,200 Daltons. The polymer consists of glucose units linked predominantly by α 1-4 glucosidic bonds, with a small proportion (< 10%) of branches linked by α 1-6 glucosidic bonds. After absorption, the polymers are degraded to disaccharides, maltose, and eventually, glucose. Icodextrin 7.5% PD solution is iso-osmolar to plasma (284 mOsm/kg), and its pH is 5.2 – 5.6. Icodextrin employs colloidal, rather than crystalloid, osmotic pressure to yield a sustained ultrafiltration profile that is beneficial for long dwells, and thus allows the use of a solution that is iso-osmolar with plasma. Compared to glucose,

icodextrin produces a continuous increase in ultrafiltration over 12 hours. The ultrafiltration generated by a 7.5% icodextrin PD solution used for the 8-12 hour long dwell in CAPD and APD patients is equivalent to, or better than that of 4.25% dextrose solution and may therefore also yield better solute removal in patients with high peritoneal small-solute transport rate (High-transporters) and patients with peritonitis. Long-term clinical experience with icodextrin now extends over many







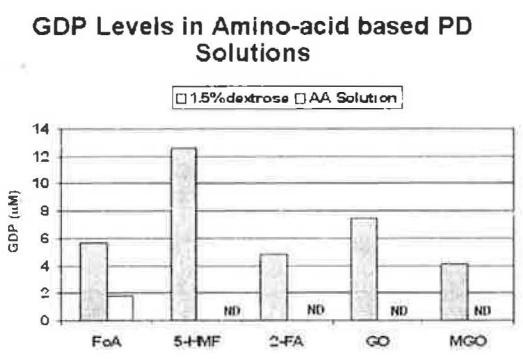


years in Europe, and Icodextrin has been demonstrated to possibly extend PD technique survival in patients with UF failure (102). Several ex vivo studies have demonstrated improvements in both peritoneal and mesothelial cell function in patients using icodextrin-based dialysis solution. In addition to these local effects, icodextrin solution may also have a positive systemic effects related to improved fluid removal in patients with increased peritoneal surface area (High-transporters). Icodextrin has been used successfully during peritonitis, and can prevent the temporary decline in UF resulting from the increased absorption of glucose from glucose-based solutions. Icodextrin has been demonstrated to exert no long-term toxicity. Some studies suggest that it is more biocompatible to peritoneum than glucose because it is iso-osmolar and the concentration of GDPs in icodextrin-based dialysis solution is much lower compared to glucose-based solutions. Furthermore emerging data demonstrates a significant reduction in cell cytotoxicity and AGE formation with icodextrin solution compared to conventional PD dialysate (101). Icodextrin usage is accompanied by a sustained rise in plasma oligosaccharides, particularly maltose, though no clinical related clinical adverse effects have been reported even after several years of continuous use. Levels return to baseline after cessation of treatment. A decline in serum amylase level in patients treated with icodextrin has been observed. It is likely due to interference by maltose or icodextrin metabolites on amylase assay. It is therefore recommended not to rely on serum amylase alone in diagnosing pancreatitis in patients on icodextrin. Some adverse effects, especially skin reactions, with use of icodextrin, have been reported. In a total

of 4045 patients, the incidence of skin reaction was 2.5%. The rash usually resolves after discontinuation of icodextrin (102).
In summary, icodextrin is recommended as an alternative osmotic agent for the long dwell in CAPD overnight and APD during the day, as it may increase UF in patients with high small solute transport rate (High-transporters) and in peritonitis. While icodextrin provides increased UF and clearances during long dwells, it avoids the problems connected with excessive glucose absorption, which may be an advantage in obese and diabetic patients. Finally, icodextrin may enhance biocompatibility and may extend PD technique survival in patients with ultrafiltration failure.

Amino Acid Based Solutions:

Amino acid-based dialysis solution is designed to replace losses of amino acids and proteins during PD, thereby improving nitrogen balance in patients with malnutrition. Malnutrition, already present in pre-dialysis patients, is aggravated by a daily peritoneal loss of 6-9 g protein and 1-2 g amino acids. It is observed that among CAPD patients, about 33% have mild to moderate and 8% severe malnutrition (103). Various amino acid solutions have been proposed as an alternative osmotic agent to glucose. Total transperitoneal absorption ranges from 60-80% during a 4-hour dwell, and reaches 90% after a 6-hour dwell, so that one exchange with a 1.1% solution results in the absorption of about 13-20 g amino acids (104). Several studies have indicated that amino acid solutions can deliver clearance of small solutes equivalent to those achieved with glucose solutions, and that the intraperitoneal administration of amino acids is safe. Furthermore, the capacity of amino acid based solutions to remove waste products and water has been confirmed by several groups. The use of amino acids can improve nitrogen balance, increase concentration of plasma proteins and serum amino acid pattern and improve the overall nutritional status. Furthermore, the glucose load with conventional dialysis solution is reduced, which may be advantageous in diabetic patients. At present no amino acid PD solution is available in USA. On the other hand, an amino-acid solution, Nutrineal (Baxter Healthcare Corp.) is commercially available in Europe. It contains mainly essential amino acids, with some non essential and semi essential amino acids, buffered in lactate with a pH of 6.2 (less acidic than conventional dextrose based solutions). The effects of amino acid based solutions on intra-abdominal defense mechanisms and peritoneal membrane alteration may be less detrimental than those of glucose based PD solutions, owing to more physiologic pH and reduced exposure of peritoneum to glucose. However, the use of amino acid solution results in increased generation of urea and acid, owing to increased absorption and metabolism of delivered amino acids. As a consequence, serum urea level increases and bicarbonate level decreases. To prevent unacceptable levels of urea and acidosis, only one daily exchange, or a maximum two exchanges of 1.1% amino-acid solution is recommended (104).



In summary, the use of amino acid based solutions may provide an amino acid supplement for malnourished patients, replace peritoneal amino-acid and protein loss,

avoid glucose absorption and increase biocompatibility because of the lower pH and lack of glucose and GDPs.

Bicarbonate-Buffered PD Solutions

During PD using conventional lactate based dialysate, endogenous bicarbonate is lost across the peritoneal membrane. The lactate flux from PD solution not only compensates for metabolic acid production but also for the bicarbonate loss during PD. Thus large buffer fluxes are required to achieve a small gain in the control of metabolic acidosis. Owing to difficulties in heat sterilizing bicarbonate in the presence of other dialysate constituents, particularly calcium and magnesium, a dual bag system is used. One chamber contains glucose, calcium chloride and magnesium chloride at a PH of 3.5, while the other chamber contains sodium chloride and sodium bicarbonate with or without lactate. The two components are mixed just before the inflow (89). Various bicarbonate-based solutions have been studied including a 34

Dual-Chambered Bicarbonate Dialysates

- Dextrose separation during sterilization, storage at ~ pH 3.0 - 4.0
- Calcium and Magnesium salts separated from buffer to prevent precipitation
- Target pH 7.4 after mixing two chambers

Dialysate Composition

Component	HD	Conventional	Dual-chambered
Sodium (mM)	135-155	132	132
Potassium (mM)	0-4.0	0	0
Calcium (mM)	0-2.0	1.25-1.75	1.25-1.75
Magnesium (mM)	0-0.75	0.25-0.75	0.25
Chloride (mM)	97-120	95-96	95-96
Dextrose (g/dl)	0-0.20	1.5-4.25	1.5-4.25
Bicarbonate (mM)	25-40	--	25
Lactate (mM)	--	35-40	15

Parsons, NEJM 338:1428-1437, 1998

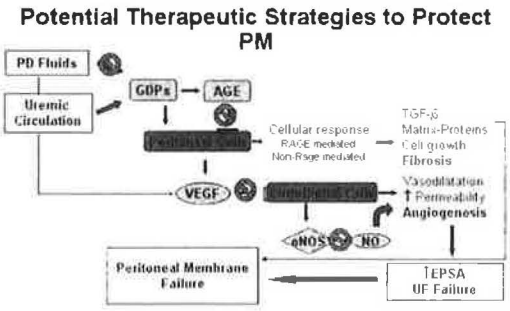
mmol/L, and a 39 mmol/L bicarbonate solution and a solution containing a mixture of bicarbonate (25 mmol/L) and lactate (15 mmol/L) with a pH of 7.4. The rationale for combining bicarbonate with lactate was the high pCO_2 (with potential risk for intracellular acidosis) associated with solutions containing only bicarbonate at a concentration of 35-40 mmol/L (105,106). Several studies have shown that the neutral pH, bicarbonate/lactate-buffered or bicarbonate buffered solutions have better biocompatibility than conventional, acidic, lactate-buffered solutions with regards to mononuclear cytokine release and viability and improvement of bactericidal activities of neutrophils, macrophages, and mesothelial cells. Moreover, bicarbonate/lactate or bicarbonate buffered solutions are effective in reducing infusion pain. Reduced GDPs are also observed with these solutions. Increased CA 125 in PD effluent while using bicarbonate-based solutions showed an impact on biocompatibility (89, 106,107).
In summary, bicarbonate or bicarbonate/lactate solutions provide a buffer system with neutral pH and a reduced concentration of GDPs. Clinical studies indicate that the control of acidosis is at least as good as that with conventional PD solutions and that the new solutions may have a favorable impact on peritoneal membrane integrity. Experimental studies show that the bicarbonate or bicarbonate/lactate solutions have a significantly improved biocompatibility profile as compared with the conventional lactate solutions. Finally, these solutions are superior to lactate buffered solutions in relieving pain associated with infusion of dialysis fluid.

Future strategy for use of PD solutions

Conventional PD solutions were formulated for maintenance of fluid and electrolyte balance and removal of electrolytes. Recent emphasis has been on improving biocompatibility to enhance peritoneal membrane integrity, reduce glucose load, correct nutritional and metabolic abnormalities and improve cardiovascular and long-term outcomes. No currently available PD solution meets all requirements of an ideal solution: effective ultrafiltration, long-term preservation of peritoneal membrane, and correction of nutritional and metabolic abnormalities. However, using the new PD solutions in combination may help to achieve these goals. Preliminary evidence suggests that a combination of 2 or all of the 3 new solutions provides equal or superior efficacy to a standard glucose regimens. A prospective multi-centered European study is ongoing to address these issues by comparing the efficacy of combination of newer PD solutions (Icodextrin for the long dwell, one dwell of amino acid solution and remaining dwells with bicarbonate, lactate solution) with conventional glucose/lactate based solution. The results are awaited.

Long-term Prospects

While the novel PD solutions appear to offer an improvement in the biocompatibility of the PD fluids, they do not completely abolish the formation of GDPs and the long-term effect on the peritoneum is not yet known. The putative mechanisms by which RCOs and AGEs initiate a number of cellular responses including stimulation of VEGF and TGF b expression and interaction of VEGF with eNOS and NO to stimulate angiogenesis, evoke new therapeutic strategies that might protect peritoneal membrane against the consequences of long-term PD. One approach would be to add inhibitors of AGE formation such as aminoguanidine or OPB-9195 to the PD fluid. Clinical use of these inhibitors is, however, hampered by their neurotoxicity (108). Another approach would be to inhibit the L-arginine-NO pathway to decrease vascular proliferation and peritoneal permeability. The L-arginine analogues [such as NG-monomethyl-L-arginine (L-NMA) and its prodrug NG-nitro-L-arginine methyl ester (L-NAME)] that compete with L-arginine to bind with NOS are well-characterized NOS inhibitors (109). However, risks and benefits of inhibiting such a ubiquitous mediator like NOS remain to be seen. A third approach could be to modulate angiogenesis with agents that inhibit the growth of endothelial cells. Although numerous anti-angiogenesis compounds have been tested in anti-cancer trials, their use in non-cancerous diseases are limited thus far (110). Finally, the levels of GDPs like methyl glyoxal and glyoxal can be lowered by addition of glutathione and glyoxalase. In this respect it has been suggested that gene therapy may increase the availability of glyoxalase in the peritoneum (111). It remains to be seen if these approaches would prove clinically beneficial.



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