THE PERITONEAL TRANSPORT BARRIER:

The peritoneal barrier is made up of the ‘anatomic peritoneum’ and its underlying tissue space.

This underlying tissue space contains parenchymal cells, interstitial cells, interstitial matrix, pericytes and endothelial cells of the microvessels that traverse the space. In clinical parlance the entire barrier is called the ‘peritoneal membrane’ (PM), although in strict anatomic terms, the peritoneal membrane or peritoneum consists only of the mesothelium and underlying connective tissue.
The anatomic peritoneum is not a significant barrier to small solute, macromolecule and water transport. It is the blood vessel wall and surrounding interstitium that constitute the major barrier to transport.

Although the mesothelium and its underlying connective tissue are not a significant transport barrier, the mesothelium is important in the maintenance and transformation of the barrier that occurs with long-term peritoneal dialysis. In long-term peritoneal dialysis, (after ~ 6 years of PD), chronic fibrosis and vasculopathy occur in the subperitoneal tissue, resulting in major changes in transport function.

**PERITONEAL DIALYSIS:**

A glucose-based solution is instilled into the peritoneal cavity, allowed to dwell for an interval (usually hours), after which it is drained, in a cycle of 'fill-dwell-drain'.

This cycle is repeated a number of times per day.

1.) Small solutes (<1000 Da) move passively, mainly by diffusion, from blood circulating in the subperitoneal microcirculation into the dialysate in the peritoneal cavity.
2.) Some solute molecules also move into the peritoneal cavity by convection i.e. “dragged with water”; this is particularly relevant for macromolecules.

3.) Water alone, without solute, (free water), moves from blood into the peritoneal cavity by osmosis – osmotic filtration.

THE THREE-PORE MODEL OF Rippe et.al.:

As previously stated, the major anatomic barrier to the movement of small solutes and macromolecules within the peritoneum lies in the walls of the blood vessels, not the mesothelium and its underlying connective tissue.

Rippe et.al. hypothesized that transport of solutes and water across the peritoneal membrane occurs through 3 types of ‘pores’ located in the capillary endothelium.

1.) ‘small pores’ (radius 40-50 angstroms), correspond to the clefts between capillary endothelial cells and account for ~95% of the hydraulic conductance of the membrane. (UF coefficient, $L_pS$). Thus, these ‘small pores’ account for most of the total pore surface area, and are the principal route for the diffusion of small solutes such as urea, creatinine, and glucose.
2.) ‘large pores’ (radius 250 angstroms), are thought to correspond to the venular interendothelial gaps and account for 5% of the UF coefficient. Although they represent only 0.01% of the total number of pores, they mediate an important part of UF via fluid convection from blood to the peritoneal cavity. These pores are involved in the transport of macromolecules (proteins, immunoglobulins)

These ‘small’ and ‘large pores’ may be described as ‘solute pores’. The concept of ‘solute pores’ is currently being replaced by that of a ‘pore-matrix’ in which a glycocalyx, 0.4-0.5 µm thick, lines the spaces between endothelial cells and is a determinant of permeability. This glycocalyx layers the luminal side of the endothelial cells and the interendothelial space, and restricts the passage of molecules across the endothelium according to molecular size, charge and structure.

Hyaluronic acid is a major part of the glycocalyx endothelial barrier. Cytokines, such as tumor necrosis factor-α (TNF-α), and vascular mediators such as nitric oxide (NO), alter the glycocalyx and result in increased permeability to macromolecules. Thus, this endothelial coating, responsive to cytokines and vascular mediators, enables the modulation of peritoneal membrane permeability.

3.) Water-specific ‘ultra-small pores’ located in the endothelial cells which correspond to aquaporin 1 (AQP1). Transport through the aquaporins is transcellular. It accounts for only 1-2% of the hydraulic conductance i.e. an almost insignificant contribution to the overall UF
coefficient. However, because ‘ultrasmall pores’ reject solutes and facilitate the transport of water, they are extremely important during crystalloid osmosis. Data obtained from AQPI transgenic mouse models have confirmed that ‘ultrasmall pores’ mediate ~50% of the UF, as well as ‘sodium seiving’ (i.e. the rapid fall in dialysate sodium concentration during a dwell with hypertonic glucose). According to the three-pore model, the ‘ultrasmal pore’ is located in the endothelium lining the peritoneal capillaries and post-capillary venules, where most of the water movement during PD occurs.

VOLUME CONTROL AND ULTRAFILTRATION IN PERITONEAL DIALYSIS:

Volume overload is an important problem in PD patients, especially when residual renal function is decreasing.

Volume control is essential and PD fluid removal needs to be adequate.

Volume overload may be caused by:

Mechanical catheter problems – catheter dislocation, occlusion, omental wrap…

Subcutaneous leaks of dialysate …
Peritoneal membrane failure

PERITONEAL MEMBRANE FAILURE

A diagnosis of peritoneal membrane failure is made when the net UF volume is <400ml after a standardized 4 hr. dwell using 3.86% glucose solution, after mechanical problems have been ruled out.

Peritoneal membrane-related UF failure can be caused by different membrane mechanisms:

1.) The presence of a large vascular surface area (this is characterized with the PET, by a high dialysate/plasma creatinine ratio), is the major cause of UF failure. It leads to high absorption rates of low MW osmotic agents, e.g. glucose, and therefore a rapid disappearance of the osmotic gradient.

2.) A high effective lymphatic absorption rate.

3.) Impaired ‘free water’ transport, the result of decreased osmotic filtration.
4.) Rarely, a very small vascular surface area, e.g. secondary to adhesions, with very limited peritoneal membrane surface available for dialysis.

5.) A combination of the above.

**SMALL SOLUTE TRANSPORT:**

The small solute transport rate depends on the effective peritoneal surface area (EPSA), which is determined by the amount of perfused capillaries within the peritoneal membrane, the blood flow and the surface area of the membrane in contact with dialysate.

The peritoneal equilibration test (PET), provides an indirect measure of small solute transport rate.

In the PET, D/P creatinine and Dt/Do glucose reflect this effective peritoneal surface area.

**PERITONEAL EQUILIBRATION TEST:**

The PET, using a 2.27% glucose solution over a 4 hour dwell, assesses small solute transport rate, and thus the transport function of the ‘small pores’. The following measurements are made:

1.) D/P creatinine (dialysate and plasma creatinine concentrations at specified times during the dwell).
2.) \( \text{D}_t/\text{D}_0 \) (dialysate glucose concentration at specified times during the dwell divided by dialysate glucose concentration at time ‘0’)

3.) Net UF

Based on the D/P creatinine, patients are classified as:

1.) low transporters (L)
2.) low-average transporters (LA)
3.) high-average transporters (HA)
4.) high transporters (H)

This is usually not a ‘fixed’ membrane property, but can change. Thus there is a need to monitor the patient’s ‘transport type’ – L, LA, HA, or H.

For example,

1.) During peritonitis, vasoactive substances will lead to an enhanced perfusion and to vasodilatation of the peritoneal vessels, Solute transport will therefore increase and, owing to a rapid decrease in osmotic gradient, net UF will be lower. This change in transport is reversible after recovery of peritonitis.

2.) During long-term PD treatment, longitudinal studies have shown an increase in solute
transport and a decrease in UF volume, with duration (years) of PD treatment. Peritoneal biopsy studies have shown a functional enlargement of the peritoneal vascular surface area, that corresponds with this increase in solute transport rate.

This suggests a possible role of non-physiologic PD fluids in the etiology of neoangiogenesis and other structural and functional changes of the peritoneal membrane.

3.) The preceding dwell can influence small solute transport rate and net UF significantly. D/P creatinine was significantly higher after a long dwell with icodextrin, compared with a dwell with 2.27% glucose, even when the test was preceded by a rinsing procedure with glucose. This was also observed for net UF. Therefore it seems important to note with which solution the patient performed the exchange the night before the test or that the patient be instructed to always use glucose-base dialysate on the night before the PET.

**WHAT ARE THE CLINICAL DETERMINANTS OF THE BASELINE SMALL SOLUTE PERITONEAL TRANSPORT RATE?**

The CANUSA study (1988; 606 patients) showed that older age, male gender, diabetes and low serum albumin
concentration were all independent risk factors associated with a high transport status (high D/P creatinine) at the start of peritoneal dialysis. Other studies have confirmed these observations. Additional factors associated with high transport status include:

- Treatment with ACEIs and ARBs
- Higher comorbidity
- Higher body surface area (BSA)

It is possible that systemic inflammation, associated with comorbid states and hypoalbuminemia as surrogate marker, may result in structural changes such as neoangiogenesis, leading to a high transport state.

Caution should be exercised in relating hypoalbuminemia to transport status. Hypoalbuminemia may:

- be a marker of inflammation
- may reflect fluid overload related to high transport status
- may reflect increased albumin losses in the dialysate

These known independent clinical variables, however, account for only ~20% of the individual variability of solute transport. Thus other factors, not yet known or measured routinely play a role in determining the baseline functional characteristics of the peritoneal membrane.
ARE THERE GENETIC DETERMINANTS OF SMALL SOLUTE TRANSPORT RATES OF THE PERITONEAL MEMBRANE?

There is accumulating evidence that growth factors such as vascular endothelial growth factor (VEGF) and cytokines such as interleukin-6 (IL-6), together with the release of nitric oxide (NO) by endothelial cells, play a central role in the regulation of vascular density and permeability of the peritoneal membrane. Other mediators of angiogenesis and fibrosis such as transforming growth factor-β (TGF-β) and plasminogen activator inhibitor-1 (PAI-1) are involved in peritoneal transport. Several polymorphisms within the regulatory region of the genes coding for VEGF, IL-6, eNOS, and PAI-1 are being studied.
Peritoneal Dialysis Adequacy
PERITONEAL DIALYSIS UREA CLEARANCE:

\[ \text{Dialysate}_{UN} \times \text{Dialysate}_{vol} / \text{BUN} \] (in L/week)

e.g. Consider an anuric 70 kg patient with:

\[ \text{Dialysate}_{UN} = 60 \text{ mg/dl} \]
\[ \text{Dialysate}_{vol} = 10 \text{ L/day (10,000 ml/day)} \]
\[ \text{BUN} = 80 \text{ mg/dl} \]
\[ \text{Urea clearance} = 60 \text{ mg/dl} \times 10/80 \text{ mg/dl} \]
\[ = 7.5 \text{L/day} \]
\[ = 52.5 \text{L/week} \]

If we “normalize” this clearance to the volume of distribution of urea (total body water), which is 42L in this patient we have a “normalized” urea clearance or “fractional” urea clearance of 52.5L/42L = 1.3

\[ Kt/V = 1.3 \]

Creatinine clearance on the contrary is normalized to body surface area – 1.73 m²

e.g. if the same patient had a BSA of 2.0 m²,

\[ \text{dialysate creatinine} = 8 \text{ mg/dl} \]
\[ \text{dialysate volume} = 10 \text{L/day} \]
\[ \text{serum creatinine} = 10 \text{ mg/dl} \]
dialysis creat. clearance = 8mg/dl x 10L/10mg/dl
    = 10L/day
    = 70L/week
normalized creat. Clearance = 70L x 1.73/2.0
    = 60.55L/week

NOTE: Kt/V is normalized to volume of
distribution of urea (total body water) while
creatinine clearance is normalized to BSA
DISCREPANCIES BETWEEN Kt/V and CREATININE CLEARANCE.

Total Kt/V and total creatinine clearance usually correlate; there is no data to suggest that one index is better than the other.

In ~20% of patients, however, there is significant discrepancy between the two. There are many possible reasons for these discrepancies:

1.) The amount of RRF and its relative contribution to the total Kt/V and creatinine clearance. Creatinine clearance is relatively greater at low GFRs than urea clearance—tubular secretion of creatinine as compared to tubular reabsorption of urea. This factor disappears when the patient becomes anuric.

2.) The difference in peritoneal transport of urea and creatinine. Urea, a smaller molecule than creatinine, diffuses more rapidly across the peritoneal membrane; thus peritoneal clearance of urea is higher than that of creatinine. This difference is more pronounced in low transporters. The difference is more pronounced in APD, when dwell times are shorter and
disappears with the long dwell times of CAPD. Thus $K_t/V_{urea}$ and $C_{Cr}$ are well correlated in CAPD but less so in APD (where the relationship is more variable and depends on the APD regimen (dwell times... and peritoneal transport characteristics). Therefore, in CAPD, a separate target for $C_{Cr}$ (besides $K_t/V_{urea}$) is less necessary. In APD, the additional $C_{Cr}$ target is more important (currently at 45L/week).

3.) The influence of patient size on normalization. The patient’s weight has a different impact on $V$ and BSA, and for male and female. The relationship of $V$ and BSA is affected by gender and obesity. Further, $V$ is affected differently by weight gain due to ‘obesity as opposed to edema fluid, or weight loss due to amputation.

The use of different size indicators for $K_t/V$ urea and Cr Cl is the cause of and artificial discrepancy.

a.) As a consequence, women with adequate $K_t/V$ urea may be at risk of a low Cr Cl., while men with
adequate Cr Cl may be at risk of a low Kt/V urea.

b.) Underweight individuals with adequate Kt/V urea may be at risk of inadequate Cr Cl, while obese subjects with adequate Cr Cl may be at risk of a low Kt/V.

These types of discrepancies would be eliminated if both clearances were normalized by the same size parameter.

**WHICH INDEX OF SMALL SOLUTE CLEARANCE IS TO BE PREFERRED - Kt/V or C\textsubscript{Cr}?**

There is no data to suggest that one or the other is ‘superior’. There will be patients in whom it is not possible or ‘easy’ to achieve the target clearances in both indexes. When only one of the two reaches target, the patient should be followed closely for clinical evidence of uremia especially nutrition, serum albumin ...
**KDOQI GUIDELINES:**

**MINIMUM RECOMMENDATIONS FOR DIALYSIS DOSE (1997):**

Recommendations by ad hoc committee on adequacy of peritoneal dialysis, based on literature as of mid-1997

Implicit in the guidelines, although unproven, was the assumption that one unit of peritoneal small solute clearance, expressed as $Kt/V$, was equivalent to one unit of $Kt/V$ by residual renal function; that both are interchangeable and can be added at will without consequence for the outcome of the patient

The Canada-United States (CANUSA) Study was the basis for these recommendations

**CAPD:**

$$Kt/V \geq 2.0 \text{ per week}$$

Creatinine clearance:

- $\geq 50 \text{ L/week}/1.73\text{m}^2 \text{ BSA}$ (low/low average transporters);
- $\geq 60 \text{ L/week}/1.73 \text{ m}^2 \text{ BSA}$ (high/high average transporters).

**CCPD:** (less ‘continuous’ than CAPD – solute transport stops relatively earlier in long day dwell)
$Kt/V \geq 2.1 \text{ per week}$

Creatinine clearance $\geq 63 \text{ L/week/1.73 m}^2 \text{ BSA}$

**NIPD, DAPD (INTERMITTENT PD)**

$Kt/V \geq 2.2 \text{ per week}$

Creatinine clearance $\geq 63 \text{ L/week/m}^2 \text{ BSA}$

Reanalysis of the CANUSA Study showed that the improved survival noted with increased small solute clearances was more attributable to RRF than to peritoneal clearance.

**ADEMEX STUDY**

*(JASN 13: 1307-1320, 2002):*

A randomized, controlled study to investigate the effect of PD dose on clinical outcome in CAPD patients.

2 levels of PD dose were evaluated.

RRF, but not peritoneal clearance predicted clinical outcome.

An increase in PD dose from 1.8 to 2.27 $Kt/V$ did not improve patient survival or technique survival.
It is possible that above a certain threshold, increasing small solute clearances will not provide additional benefit to the patient. However, there are no patient survival studies on the influence of peritoneal small solute clearances, which are markedly in excess of the recommended DOQI guidelines.

To put things in perspective, peritoneal creatinine clearances in the intervention group was 4.3 ml/min, and the difference in creatinine clearance between control and intervention groups amounted to only 1 ml/min.


3 levels of total Kt/Vurea in patients with small degrees of RRF; lowest group was randomized to a total Kt/V of 1.5 to 1.7.

Result: no difference in survival

NOTE: In these 2 studies:
1. homogeneity of patient population
2. possible effects of cultural attitudes to compliance when compared to the USA.
KDOQI GUIDELINES FOR PERITONEAL DIALYSIS:
CURRENT (2006) PERITONEAL DIALYSIS SOLUTE CLEARANCE TARGETS:

AJKD, 48, No 1, Suppl 1 (July), 2006: pp S103-S116

For patients with RRF – urine volume > 100 ml/day:

Minimal “delivered” dose of total solute clearance should be a total (peritoneal + renal) Kt/v urea of at least 1.7 per week.

Measure Kt/Vurea (total i.e. peritoneal + residual renal) within the first month after start of chronic dialysis and at least q 4 months thereafter.

MONITOR RRF CLOSELY:
Measure 24 hour urine volume and residual renal Kt/Vurea at least q 2 months

IF RESIDUAL RENAL FUNCTION IS NOT SIGNIFICANT i.e. urine volume < 100 ml/day:

Minimal “delivered “ peritoneal Kt/Vurea should be at least 1.7 per week, measured within the first month of initiation of chronic dialysis and check at least q 4 months.
The International Society for Peritoneal Dialysis (ISPD) Guidelines;  
The Canadian Guidelines for Adequacy and Nutrition in PD (2003);  
The Australian PD guidelines (2006);  
The Renal Association (UK) Guidelines (2002);  
The European Best Practice Guidelines for PD (2005)  
are all similar to the KDOQI Guidelines.
A REDEFINITION OF “DIALYSIS ADEQUACY”:

The term “adequacy” should now be defined more broadly, and not refer only to small solute clearances.
Adequate dialysis needs to include consideration of:

- the preservation of RRF,
- volume status,
- appetite and nutritional status,
- blood pressure control and other cardiovascular risk reduction
- control of uremic symptoms
- anemia control and responsiveness to erythropoietin
- electrolyte and acid base balance
- calcium/phosphate homeostasis

Additional risk factors include:

- middle molecule clearances
- comorbidities
PRESERVATION OF RRF:

**AVOID:**

1.) Nephrotoxic drugs –
   NSAIDs,
   aminoglycosides,
   intravascular contrast agents (use N-acetylcysteine when contrast studies are done).

2.) Hypercalcemia from vitamin D and its analogues

3.) Dehydration/Hypotension from excessive UF
   intercurrent illness – febrile illnesses, surgery, gastrointestinal illnesses
   over-aggressive control of hypertension

4.) Judicious evaluation of “dry weight” – the patient does not need to be “as dry as possible”, as a way to preserve RRF.

5.) The theoretical fear of ACE-Is and ARBs does not appear justified; these agents actually preserved RRF in PD patients. Thus the use ACE-Is and ARBs is encouraged in ESRD.

   These agents should be considered where possible even in patients without hypertension.
6.) Consider "incremental" and "sequential" (PD first, then HD) approach as a way to preserve RRF.

**MONITOR AND MEASURE RRF FREQUENTLY:**
CAUSES OF INADEQUATE DIALYSIS:

1.) Body size considerations:

The large patient:

CAPD cannot deliver the total fill volumes required by a large patient. Such a patient will need APD and likely with a day dwell ± one or more day exchanges (PD plus).

Anuria in such a patient may force a switch to HD.

The underweight, malnourished patient:

Pay attention to the need to increase dialysis dose as patient gains weight.

Malnutrition and small size may themselves be the result of underdialysis.

Such a patient may need an increased dose of dialysis.

2.) Fluid overload:
This may affect the accuracy of estimates of the normalized clearances. The anthropomorphic methods of estimating V and BSA do not
distinguish between true weight gain and weight gain from edema.
In edematous patients, delivered dialysis (Kt/V) is overestimated – <40% of true weight gained adds to V, while 100% of edema fluid gained adds to V.
This can be corrected if ‘dry weight' is known and used to estimate V.
Calculation of Kt/V urea, using the corrected V results in values much lower than Kt/V urea values obtained with the use of the uncorrected anthropomorphic formulas in PD subjects with substantial fluid overload.

The error created by fluid overload on BSA has not been estimated.

ADVERSE EFFECTS OF FLUID OVERLOAD:

Hypertension
LVH
CHF
Inadequate dialysis – overestimation of Kt/V.

3. PD TRANSPORTER STATUS:

In CAPD, solute transport status has a profound effect on peritoneal creatinine
clearance, but a negligible effect on urea clearance.

An anuric CAPD patient with low or low-average, or even high-average transport status who achieves a Kt/V urea of 2.0 cannot achieve a Cr Cl of 60L/1.73 m².

4.) SHORT DWELL TIME:

Shortening of dwell time has more pronounced effects on Cr Cl than on Kt/V urea because creatinine equilibration across the peritoneal membrane is slower than that of urea.

This is more evident and clinically relevant in low transporters.

Thus, when the dose of PD is increased by adding APD exchanges, patients may achieve the target Kt/V urea but not the target Cr Cl.

5.) PROBLEMS OF FAULTY TECHNIQUE:

Errors in measurement of clearances:

Improper mixing of sample from long and short dwell time bags.
Errors in sampling of blood in PD plus or NIPD

Analytical errors (mainly interference of glucose with certain creatinine assays)

Errors in 24 hour urine collection; there is a relative large daily variation in urine volumes; errors in urine collection have a greater effect on Cr Cl than on Kt/V (in subjects with low urine flow rates and infrequent voiding, urine collection accuracy may be enhanced by using 48-hr. instead of 24 hr. collections).

6.) PATIENT ERRORS:

Sampling errors:
Wrong number of bags
Aliquot methods have their own problems.

Noncompliance:
Omission of one or more exchanges
Poor timing so that dwell times are too short in some exchanges and too long in others
Inordinate long infusion or drain times
“dumping” of part of dialysate bag before filling
leaving abdomen ‘dry’ for excess time periods
Noncompliance is a major cause of dialysis inadequacy

Causes include psychological and medical reasons – hostility to authority, depression, memory impairment, financial problems, language, impaired mobility, male gender, ethnic barrier, young age