How to evaluate the peritoneal membrane?
How to evaluate a hemodialyzer?
How to evaluate a hemodialyzer?

* pore size in microns (µm)
DEFINITIONS OF FLUX, PERMEABILITY, AND EFFICIENCY

**Flux**
- Measure of ultrafiltration capacity
- Low and high flux are based on the ultrafiltration coefficient ($K_{uf}$)
  - Low flux: $K_{uf} < 10 \text{ mL/h/mm Hg}$
  - High flux: $K_{uf} > 20 \text{ mL/h/mm Hg}$

**Permeability**
- Measure of the clearance of the middle molecular weight molecule (e.g., $\beta_2$-microglobulin)
- General correlation between flux and permeability
  - Low permeability: $\beta_2$-microglobulin clearance $< 10 \text{ mL/min}$
  - High permeability: $\beta_2$-microglobulin clearance $> 20 \text{ mL/min}$

**Efficiency**
- Measure of urea clearance
- Low and high efficiency are based on the urea $K_c A$ value
  - Low efficiency: $K_c A < 500 \text{ mL/min}$
  - High efficiency: $K_c A > 600 \text{ mL/min}$

$K_c$—mass transfer coefficient; $A$—surface area.

From: Robert W. Schrier’s Atlas of Diseases of the Kidney
How to evaluate a hemodialyzer?

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K_o — mass transfer coefficient; A — surface area.

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**SOLUTE REMOVAL**

- **pore size**
- **surface area**

**ULTRAFILTRATION**

---

From: Robert W. Schrier’s Atlas of Diseases of the Kidney
Hemodialyzer vs. peritoneum?

+ the effects of intercurrent disease time
glucose exposure

<table>
<thead>
<tr>
<th>Performance Data</th>
<th>REVACLEAR</th>
<th>REVACLEAR 300</th>
<th>REVACLEAR MAX</th>
<th>REVACLEAR 400</th>
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<tbody>
<tr>
<td><strong>Hemodialysis</strong></td>
<td></td>
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</tr>
<tr>
<td>Qb (L/min)</td>
<td>200</td>
<td>300</td>
<td>400</td>
<td>500</td>
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<tr>
<td>Urea</td>
<td>196</td>
<td>271</td>
<td>321</td>
<td>353</td>
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<tr>
<td>Creatinine</td>
<td>196</td>
<td>272</td>
<td>323</td>
<td>356</td>
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<tr>
<td>Phosphate</td>
<td>195</td>
<td>273</td>
<td>324</td>
<td>357</td>
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<tr>
<td>Vitamin B₁₂</td>
<td>144</td>
<td>170</td>
<td>186</td>
<td>197</td>
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<tr>
<td><strong>Membrane</strong></td>
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<tr>
<td>Fiber Dimensions</td>
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<tr>
<td>Wall Thickness</td>
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<tr>
<td>Membrane thickness (µm)</td>
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<tr>
<td>Sterilization agent</td>
<td>Steam</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>Blood flow rate (mL/min)</strong></td>
<td>200-500</td>
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<td>Dialysate flow (mL/min)</td>
<td>800</td>
<td>300-800</td>
<td>600</td>
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<tr>
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**Additional Text:**

Everyone is different.
Peritoneal membrane evaluation

Testing the membrane
## Testing the membrane

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FWT, free water transport; OC, osmotic conductance.

van Biesen et al. Nephrol Dial Transplant 25: 2052-2062, 2010
Peritoneal membrane evaluation

- Testing the membrane
- Understanding PD pathophysiology
- Basic PD Physiology:
  - Functional anatomy
  - Physiology of the peritoneal membrane
‘6 barriers for transport’

Stagnant layers at mesothelial and capillary side: not relevant
Mesothelial cell layer: not relevant
Interstitial tissue: (minor) diffusive resistance
Capillary wall: most important restriction barrier

Capillary wall is the most important restriction barrier and determines the peritoneal membrane’s size-selectivity through a system of pores

→ the “PORE THEORIES”
‘2D membrane with pores’

SOLUTE REMOVAL

ULTRAFILTRATION

pore size

surface area

How to evaluate a hemodialyzer?

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From: Robert W. Schrier’s Atlas of Diseases of the Kidney
The THREE pore theory

Small pores with constant radius 40-50Å
majority
for transport of low molecular weight solutes

Large pores with various radii, average > 150Å
minority (less than 0.1% of total pore count)
for transport of macromolecules

Ultra-small pores with radius 3-5Å
for transport of water only
accounts for 1/2 of transcapillary water transport
The THREE pore theory

The pore theory explains the “classical” mechanisms of transmembrane transport of molecules.

**DIFFUSION**

movement of solutes along their concentration gradient

**SOLUTE REMOVAL**

Bammens Semin Nephrol 31: 127-137, 2011
Diffusive transport

\[ J_s = \frac{D_f}{\Delta x} \cdot A \cdot \Delta C \]  

(Fick’s first law of diffusion)

diffusive permeability (membrane- and solute-specific)
Diffusive transport

\[ J_s = \frac{D_f \Delta A}{\Delta x} \Delta C \]  

(Fick’s first law of diffusion)

diffusive permeability (membrane- and solute-specific)

surface area (membrane-specific)
Diffusive transport

\[ J_s = \frac{D_f}{\Delta x} \cdot A \cdot \Delta C \]

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diffusive permeability (membrane- and solute-specific)

surface area (membrane-specific)

concentration difference between plasma and dialysate
Diffusive transport

\[ J_s = \frac{D_f \cdot A \cdot \Delta C}{\Delta x} \]  

(Fick’s first law of diffusion)

diffusive permeability (membrane- and solute-specific)
surface area (membrane-specific)

mass transfer area coefficient (MTAC)
Diffusive transport

\[ J_s = \frac{D_f \cdot A \cdot \Delta C}{\Delta x} \] (Fick’s first law of diffusion)

\[ J_s = MTAC \cdot \Delta C \]

Transport of small molecules up to MW of $\beta_2M$ (118 kDa)
NOT limited by size of the pores

MTAC for a given solute ONLY determined by effective vascular peritoneal surface area (number of pores)
The THREE pore theory

The pore theory explains the “classical” mechanisms of transmembrane transport of molecules.

CONVECTION

movement of solutes along with fluid as it moves across the membrane (solvent drag)
Convective transport

\[ J_s = J_v \cdot \bar{C} \cdot (1 - \sigma) \]
Convective transport

\[ J_s = J_v \cdot \bar{C} \cdot (1 - \sigma) \]

water flux (membrane-specific)
Convective transport

\[ J_s = J_v \cdot \bar{C} \cdot (1 - \sigma) \]

- water flux (membrane-specific)
- mean solute concentration in the membrane \((P+D)/2\)
Convective transport

\[ J_s = J_v \cdot \bar{C} \cdot (1 - \sigma) \]

water flux (membrane-specific)

mean solute concentration in the membrane \((P+D)/2\)

Staverman’s reflection coefficient
= how difficult it is for a solute to be transported by solvent drag across a semi-permeable membrane
(membrane- and solute-specific)
Convective transport

$\sigma$  Staverman’s reflection coefficient

= how difficult it is for a solute to be transported by solvent drag across a semi-permeable membrane

$S$  sieving coefficient

= how easy it is for a solute to be transported by solvent drag across a semi-permeable membrane
For a semi-permeable membrane, $S$ and $\sigma$ are expected to be perfectly interchangeable concepts!

\[ S = 1 - \sigma \]
Convective transport

$\sigma$ Staverman’s reflection coefficient

= how difficult it is for a solute to be transported by solvent drag across a semi-permeable membrane

= fraction of maximal osmotic pressure a solute can exert across a semi-permeable membrane

$S$ sieving coefficient

= how easy it is for a solute to be transported by solvent drag across a semi-permeable membrane

= fraction of maximal solute transport by solvent drag across a semi-permeable membrane
Convective transport

For a semi-permeable membrane, $S$ and $\sigma$ are expected to be perfectly interchangeable concepts!

$S = 1 - \sigma$

$\sigma_{\text{glucose}}$ very low!

SMALL (and large) PORES
For a semi-permeable membrane, $S$ and $\sigma$ are expected to be perfectly interchangeable concepts!

However, the water-only channels make the peritoneal membrane “more than a semi-permeable membrane”!

\[ \text{Apparent } \sigma_{\text{glucose}} = \text{higher} \]

\[ \sigma_{\text{glucose}} = 0.03 \]
The THREE pore theory

Ultra-small pores with radius 3-5Å

AQUAPORIN-1

Fig. 1. Schematic model representing CHIP integral membrane protein within the membrane lipid bilayer. Notable features include 1) homotetrameric complex with 1 subunit bearing a polylactosamino glycan, 2) minimal polypeptide mass extending above or below the lipid bilayer, and 3) possible individual water pore within each subunit.

The THREE pore theory

ULTRAFILTRATION

Davies Kidney Int 70 (Suppl 103): 76-83, 2006
The THREE pore theory

ULTRAFLTRATION

Davies Kidney Int 70 (Suppl 103): 76-83, 2006
Ultrafiltration

\[ \text{NUF} = \Delta \text{IPV} = \text{TCUF} - \text{ELA} \]
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Peritoneal membrane evaluation

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van Biesen et al. Nephrol Dial Transplant 25: 2052-2062, 2010
Peritoneal membrane evaluation

CARI Guidelines 2005

Canadian Society of Nephrology, PDI 31: 218-239, 2011


UK Renal Association, Guidelines 2010 (review due 2013)
SOLUTE REMOVAL

3. For small solute removal, the total (renal + peritoneal) Kt/V urea should not be less than 1.7 at any time (Evidence level A). That means, in anuric patients, peritoneal Kt/V urea has to be above 1.7. In the presence of residual renal function, the contributions of renal and peritoneal clearances may be added for practical purposes, although, as mentioned previously, renal and peritoneal clearances may not be truly additive (Opinion). Solute removal above this level should not be equated with “adequate dialysis.” Knowledge of the transport characteristics of the patient’s peritoneal membrane by peritoneal equilibration test or other tests may help to optimize the prescription to meet this target.
**ISPD GUIDELINES/RECOMMENDATIONS**

**EVALUATION AND MANAGEMENT OF ULTRAFILTRATION PROBLEMS IN PERITONEAL DIALYSIS**

Recommendations:

- Adherence to sound physiologic principles in the design and implementation of PD prescriptions is essential to prevent the emergence of fluid overload. The most frequently ignored principles in PD that lead to UF difficulties, are the need to avoid long dwells in high transporters, and balancing glucose concentration and dwell time. Prescription setting must take these into account.
### Peritoneal membrane evaluation

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FWT, free water transport; OC, osmotic conductance.
(D/P creatinine reflects effective vascular surface area, rather than the intrinsic permeability of the membrane!)

The original 2.27% PET test
The original 2.27% PET test

**ULTRAFILTRATION**

**SOLUTE TRANSPORT**

---

The original 2.27% PET test

ULTRAFILTRATION

SOLUTE TRANSPORT

## Fast/slow: need a test?

**Table 1. Peritoneal membrane transport types and their consequences for clinical management**

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<th>Properties</th>
<th>Recommendations</th>
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| Fast transporter  | Fast, hyperbolic, equilibration of creatinine, typically with 
                   | a $D/P_{\text{creat}} > 0.80$ after 4 h            | Short dwells, preferably shorter than 180 min       |
|                  | Fast dissipation of glucose from the peritoneal cavity, with negative    | Icodextrin to be considered for longest dwell,      |
|                  | ultrafiltration in dwells with 1.36% glucose longer than 180 min        | unless sufficient residual diuresis                |
|                  | Limited sodium sieving, with 3.86% PET and small (<5 mmol/l) delta $D_{\text{sodium}}$ (difference between the $D_{\text{sodium}}$ at start and after 1 h) | Check inflammatory status (peritoneal protein loss). |
|                  | Moderate fast appearance of osmotic agent.                               | When negative, check transport status using larger |
|                  | Fast disappearance of osmotic agent.                                      | fill volumes                                       |
|                  | Negative ultrafiltration only in too long dwells (>240 min)              | Too short (<120 min) and too long dwells (>300 min) |
|                  | Slow, semi-linear equilibration of creatinine, typically with $D/P_{\text{creat}} < 0.55–0.60$ after 4 h | should be avoided, except for one exchange/day (the ‘long dwell’) |
|                  | Sustained ultrafiltration even in dwells longer than 240 min              | Use larger volumes rather than more dwells         |
|                  | Important sodium sieving, with 3.86%-PET and substantial delta $D_{\text{sodium}}$ (>5 mmol/l) after 1 h (the peak of delta $D_{\text{sodium}}$ could occur later in the dwell) | Icodextrin probably not necessary for longest dwell |

- **FAST**
- **AVERAGE**
- **SLOW**

Can be derived from clinical observation without need of formal testing!
The original 2.27% PET test

ULTRAFILTRATION

![Graph showing ultrafiltration volume over time with different pathways: Net UF, Small pores, Aquaporins, Large pores, Lymphatics.](image)
The aquaporins?

ULTRAFILTRATION

Davies Kidney Int 70 (Suppl 103): 76-83, 2006
With a hypertonic dialysate solution, dialysate $\text{Na}^+$ concentration will decrease initially due to water-only transport across aquaporins.

= SODIUM SIEVING

Time profile $D/P_{\text{sodium}}$, $D_{\text{sodium}}$ (or $D/D_0$ or $\Delta D_{\text{sodium}}$ at 1 hour) can be used to assess the contribution of aquaporin transport to ultrafiltration.

ISPD definition of UF failure = $< 400\text{ml UF after 4 hours of 3.86% glucose}$
Modified (3.86%) PET test

BUT:
A flat SODIUM SIEVING profile may have different meanings! (at least theoretically)

aquaporin deficiency
“very very fast” small solute transport (small pores)
BUT:
A flat SODIUM SIEVING profile may have different meanings! (at least theoretically)

aquaporin deficiency
“very very fast” small solute transport (small pores)
fibrotic peritoneal interstitium (“closed membrane”, uncoupling)
Pore models: interstitium?

Morphological changes in peritoneal membrane
THICKNESS OF SUBMESOTHELIAL COMPACT ZONE

Normal  After 9 years of PD

Pore models: interstitium?

the serial three-pore membrane/fiber matrix model

A. Three pore membrane with a normal ("loose") serial fiber matrix

\[ \varepsilon = 0.995 \]
\[ r_f = 6 \text{ (Å)} \]

\[ L_p \sigma_g = 3.66 \text{ µL/min/mmHg} \]
\[ PS_g = 9.30 \text{ mL/min} \]
\[ \sigma_g = 0.047 \text{ mL/min/mmHg} \]
\[ L_p S = 0.078 \text{ mL/min/mmHg} \]

B. Three pore membrane with a fibrotic ("dense") serial fiber matrix

\[ \varepsilon = 0.96 \]
\[ r_f = 7.5 \text{ (Å)} \]

\[ L_p \sigma_g = 3.02 \text{ µL/min/mmHg} \]
\[ PS_g = 13.46 \text{ mL/min} \]
\[ \sigma_g = 0.039 \text{ mL/min/mmHg} \]
\[ L_p S = 0.078 \text{ mL/min/mmHg} \]
Pore models: interstitium?

the serial three-pore membrane/fiber matrix model

**A** Three pore membrane with a normal ("loose") serial fiber matrix

- $\mathcal{E} = 0.995$
- $r_f = 6$ (Å)
- $L_pS\sigma_g = 3.66$ μL/min/mmHg
- $PS_g = 9.30$ mL/min
- $\sigma_g = 0.047$
- $L_pS = 0.078$ mL/min/mmHg

$S = 1$

**B** Three pore membrane with a fibrotic ("dense") serial fiber matrix

- $\mathcal{E} = 0.96$
- $r_f = 7.5$ (Å)
- $L_pS\sigma_g = 3.02$ μL/min/mmHg
- $PS_g = 13.46$ mL/min
- $\sigma_g = 0.039$
- $L_pS = 0.078$ mL/min/mmHg

$S = 1.8$
The Osmotic Conductance to Glucose

= the ability of glucose to exert an osmotic pressure sufficient to cause transperitoneal ultrafiltration

= \( L_p . S . \sigma \) (\( \mu l/min/mmHg \))

OCG: the Dummy’s view

$L_p S \sigma \ (\mu l/min/mmHg)$

- Reflection coefficient of glucose
  - lower in case of aquaporin dysfunction
  - lower in case of increased small solute transport

- Surface area
  - higher in case of increased small solute transport

- Hydraulic conductivity
  - lower in case of fibrosis
**OCG: the Dummy’s view**

A flat SODIUM SIEVING profile may have different meanings! (at least theoretically)

- **L_{p}.S.σ (μl/min/mmHg)**

Aquaporin deficiency

“very very fast” small solute transport (small pores)

**Fibrotic peritoneal interstitium** (“closed membrane”, uncoupling)

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<thead>
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(double) mini-PET

A flat SODIUM SIEVING profile may have different meanings! (at least theoretically)

- aquaporin deficiency
- "very very fast" small solute transport (small pores)
- fibrotic peritoneal interstitium ("closed membrane", uncoupling)

**Mini-PET added value:**
quantitative assessment of free water transport and small pore water transport

**Double mini-PET added value:**
quantitative assessment of free water transport and small pore water transport
+ assessment of osmotic conductance to glucose
Mini-PET
1 hour of 3.86%

assessment of $D/P_{\text{creatinin}}$, $D/P_{\text{glucose}}$, $D/D_0$ or $\Delta D_{\text{sodium}}$
calculation of free & small pore water transport

Free water transport (FWT):

$$FWT \ (ml) = UFT \ (ml) - UFSP \ (ml)$$

Ultrafiltration over the small pores (UFSP) is assessed using the Na clearance:

$$UFSP \ (ml) = [\text{NaR} \ (\text{mmol}) \times 1000]/\text{Na}_p \ (\text{mmol/l})$$

$\text{NaR} \ (\text{mmol})$ is the Na removed during the second part of the test with the 3.86% solution. NaR is calculated as follows:

$$\text{NaR} \ (\text{mmol}) = [\text{Drained dialysate volume (l) \cdot Na concentration (mmol/l) in the drained dialysate}] - [\text{Volume of dialysate before infusion (l) \cdot Na concentration (mmol/l) in dialysate before infusion}]$$

$$\text{Na}_p = \text{plasma sodium}.$$
Mini-PET

1 hour of 3.86%

assessment of \( \frac{D}{P}_{\text{creatinine}} \), \( \frac{D}{P}_{\text{glucose}} \), \( \Delta \frac{D}{D_0} \) or \( \Delta \frac{D}{D_{\text{sodium}}} \)

calculation of free & small pore water transport

Free water transport (FWT):

\[
\text{FWT (ml)} = \text{UFT (ml)} - \text{UFSP (ml)}
\]

Ultrafiltration over the small pores (UFSP) is assessed using the Na clearance:

\[
\text{UFSP (ml)} = \frac{[\text{Na}_R \text{ (mmol)1000}]}{\text{Na}_p \text{ (mmol/l)}}
\]

\( \text{Na}_R \text{ (mmol)} \) is the Na removed during the second part of the test with the 3.86% solution. \( \text{Na}_R \) is calculated as follows:

\[
\text{Na}_R \text{ (mmol)} = [\text{Drained dialysate volume (l)} \cdot \text{Na concentration (mmol/l) in the drained dialysate}] - [\text{Volume of dialysate before infusion (l)} \cdot \text{Na concentration (mmol/l) in dialysate before infusion}]
\]

\( \text{Na}_p = \text{plasma sodium} \).

La Milia et al. Kidney Int 68: 840-846, 2005
(double) mini-PET

Double mini-PET
1 hour of 1.36%, followed by 1 hour of 3.86%

From the 3.86% hour:
assessment of $D/P_{\text{creatinin}}$, $D/P_{\text{glucose}}$, $D/D_0$ or $\Delta D_{\text{sodium}}$
calculation of free & small pore water transport

From the two consecutive dwells of 1 hour:

Osmotic Glucose Conductance (OCG)
(ml/min/mmHg)

$$OCG = \left( \frac{V_{3.86} - V_{1.36}}{19.3(G_{3.86} - G_{1.36})60} \right)1.7$$

Double mini-PET

\[ \frac{D}{P_{\text{creatinin}}}, \frac{D}{P_{\text{glucose}}} \]
cannot be extrapolated to the classical or modified PET result

Ultrafiltration volume after 1 hour 3.86%
cannot be referenced to the ISPD definition of UF failure

Uni-PET

1 hour of 1.36%, followed by 4 hours of 3.86%, but with temporary drainage after 1 hour.
OCG: the Dummy’s view

A flat SODIUM SIEVING profile may have different meanings! (at least theoretically)

- **OCG**
- **Free water transport**
- **Small pore water transport**

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OCG: what does it mean?

increasing/fast small solute transport ≠ low osmotic conductance to glucose
OCG: what does it mean?

ULTRAFILTRATION

normal OCG

low OCG

OCG: what does it mean?

Low osmotic conductance to glucose is particularly seen in late ultrafiltration failure.

A flat SODIUM SIEVING profile may have different meanings! (at least theoretically)

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\[ L_pS_\sigma (\mu l/min/mmHg) \]

- aquaporin deficiency
- “very very fast” small solute transport (small pores)
- fibrotic peritoneal interstitium (“closed membrane”, uncoupling)

‘isolated aquaporin dysfunction probably non-existent’ (Rippe a.o.)
OCG: what does it mean?

Double mini-PET test

OCG: what does it mean?

The peritoneal osmotic conductance is low well before the diagnosis of encapsulating peritoneal sclerosis is made

Mark L. Lambie¹,², Biju John¹,², Lily Mushahar¹,², Christopher Huckvale¹,² and Simon J. Davies¹,²

Lambie et al. Kidney Int 78: 611-618, 2010
OCG: what does it mean?

Interstitial Fibrosis Restricts Osmotic Water Transport in Encapsulating Peritoneal Sclerosis

Johann Morelle,* Amadou Sow,* Nicolas Hautem,* Caroline Bouzin,† Ralph Crott,‡ Olivier Devuyst,*§ and Eric Goffin*

OCG: what does it mean?

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OCG: what does it mean?

Ultrafiltration Failure and Impaired Sodium Sieving During Long-Term Peritoneal Dialysis: More Than Aquaporin Dysfunction?

The THREE pore theory

ULTRAFILTRATION

Davies Kidney Int 70 (Suppl 103): 76-83, 2006
1.36% glucose solution + Dextran 70 (1g/L)

allows calculation of

- MTAC (i.e. D/P) of creatinin, urea, urate glucose absorption rate
- net ultrafiltration

but also

- effective lymphatic absorption rate
- clearances of other molecules (β₂M, IgG,...)
Now you know how to evaluate the peritoneal membrane!

BUT…

...IS IT NOT USEFUL ANYMORE?

...IS IT STILL MANDATORY?

WHO KNOWS THE ANSWER?
How to evaluate the peritoneal membrane?