



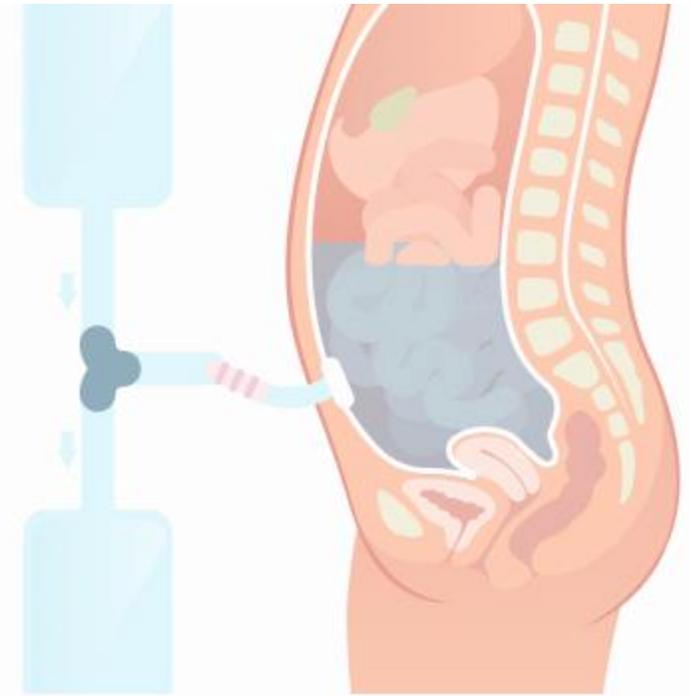
Peritoneal Membrane Structure & Function

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Consultant of Nephrology, Cairo University Hospital

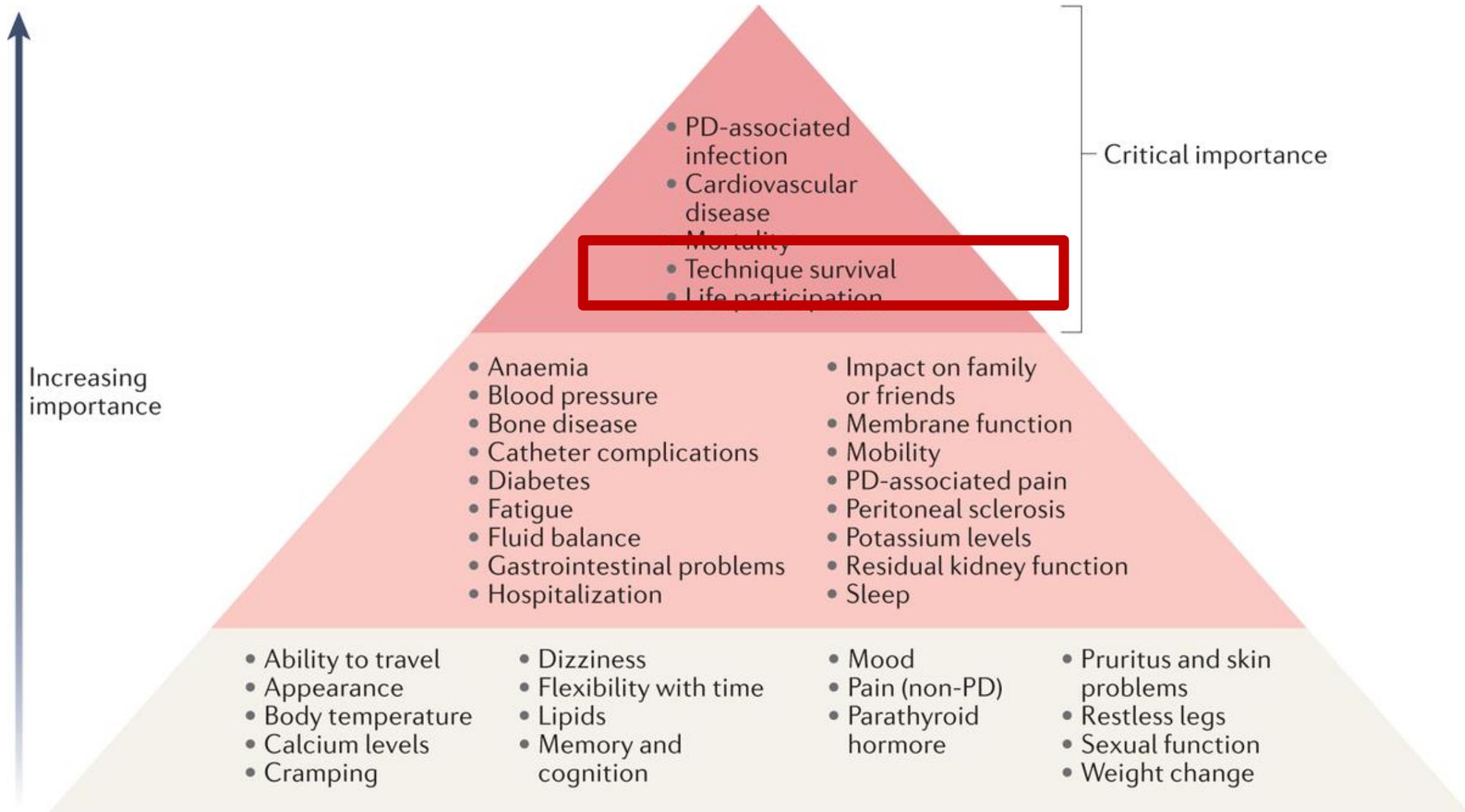
President-Elect & Secretary General IFKF-WKA

President-Elect, Mediterranean Kidney Society

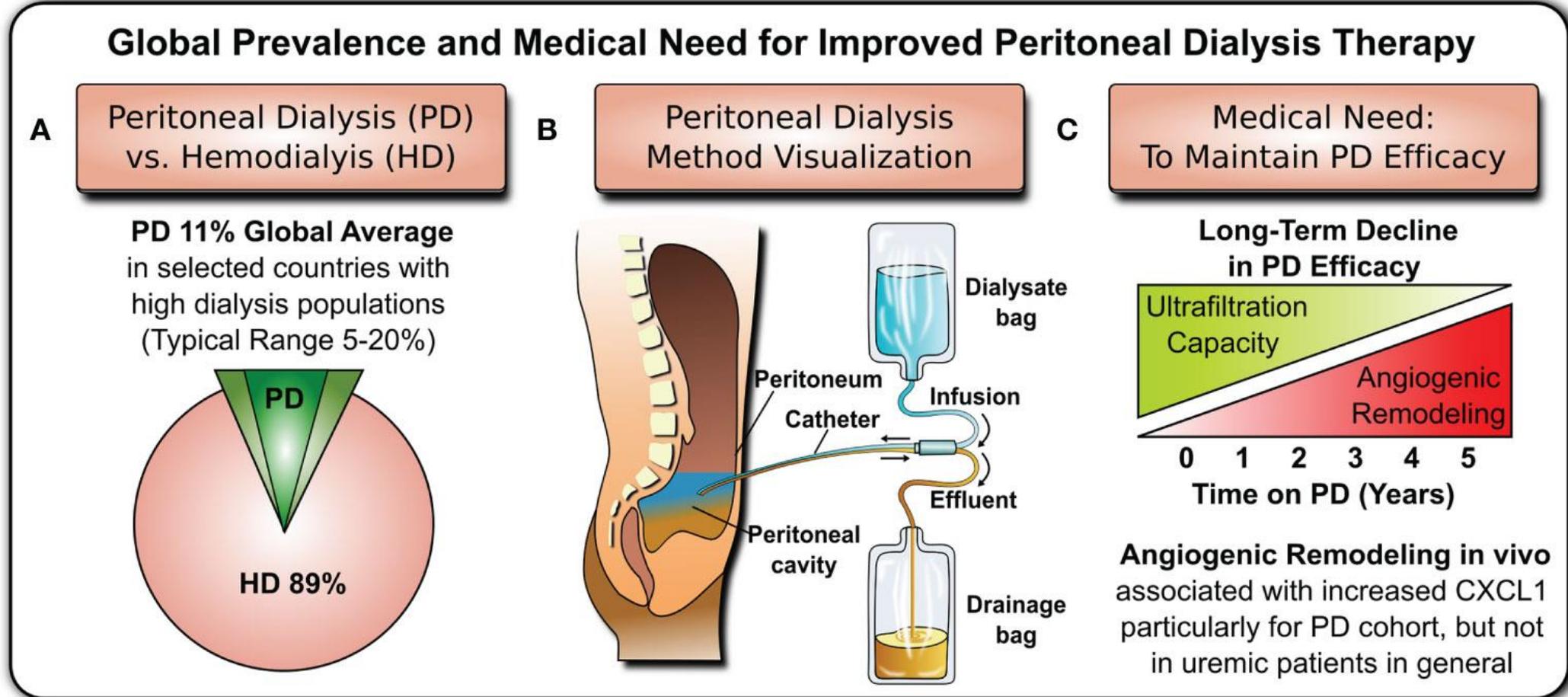


Importance of the Peritoneal Membrane in PD

- Primary Interface for Dialysis
- Home-based Therapy Enabler.
- Residual Kidney Function (RKF) Preservation
- Immunological Role
- Long-term Dialysis Success



Global Prevalence and Need for Improved PD



Have clinical outcomes changed for patients treated with peritoneal dialysis (PD) from 1996 to 2015?

Methods and Cohort



N = 173,533



Medicare
Patients
with ESKD



1996-2014
PD ≥ 1 Day

Findings from 1996 - 2014



Death Rate

48%
decline



Transition to HD

13%
decline

3-Year Follow- Up



2008 -11

vs earlier cohorts

↓ Transition to HD
↓ Risk of Death



Larger program

↓ Transition to HD
↓ Risk of Death



Longer on PD

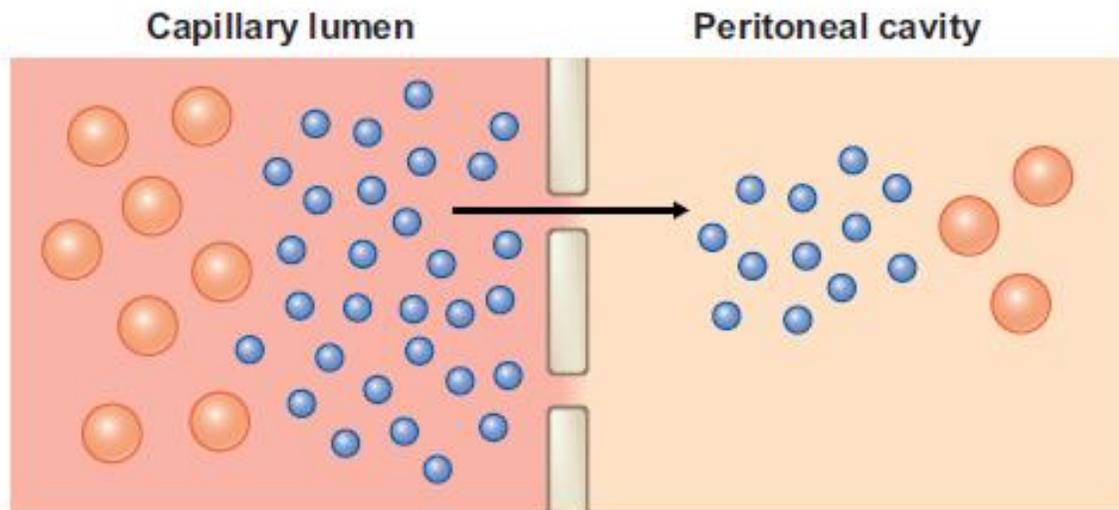
↓ Transition to HD
↑ Risk of Death

Conclusion: Mortality rates and transitions to hemodialysis among PD patients are lower in more recent years and in larger PD programs. Improved technique survival over time warrants further investigation.

Reference: Sukul N, Mukhopadhyay P, Schaubel D et al., Peritoneal dialysis: USRDS trends in mortality, transplantation, and transition to in-center hemodialysis from 1996-2015. *Kidney Medicine*, 2020
Visual Abstract by Caoimhe Costigan, MD.

@CaoimheCostigan

basic principles of PD

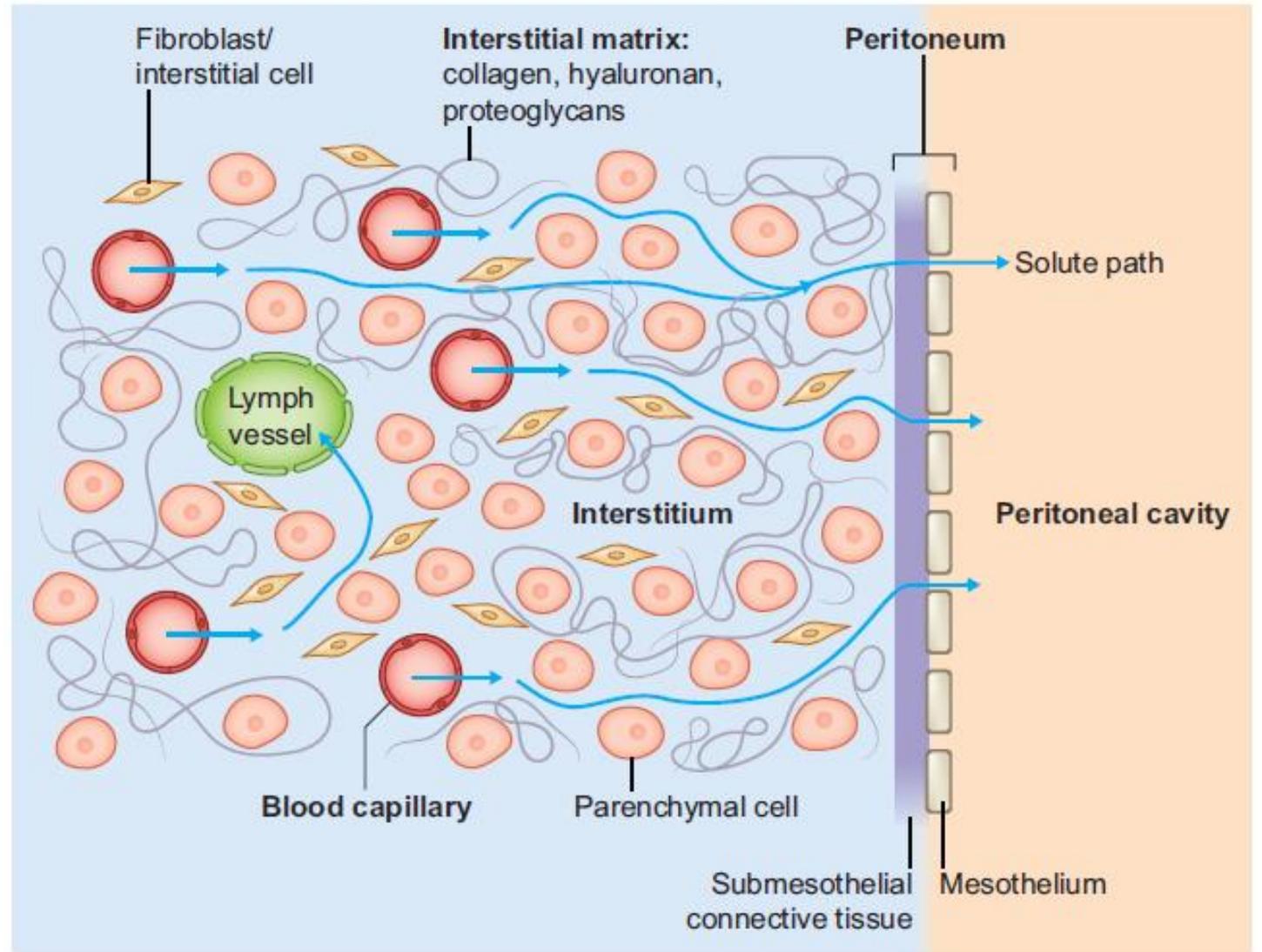


Concentration gradient
(difference higher at start of the dwell)

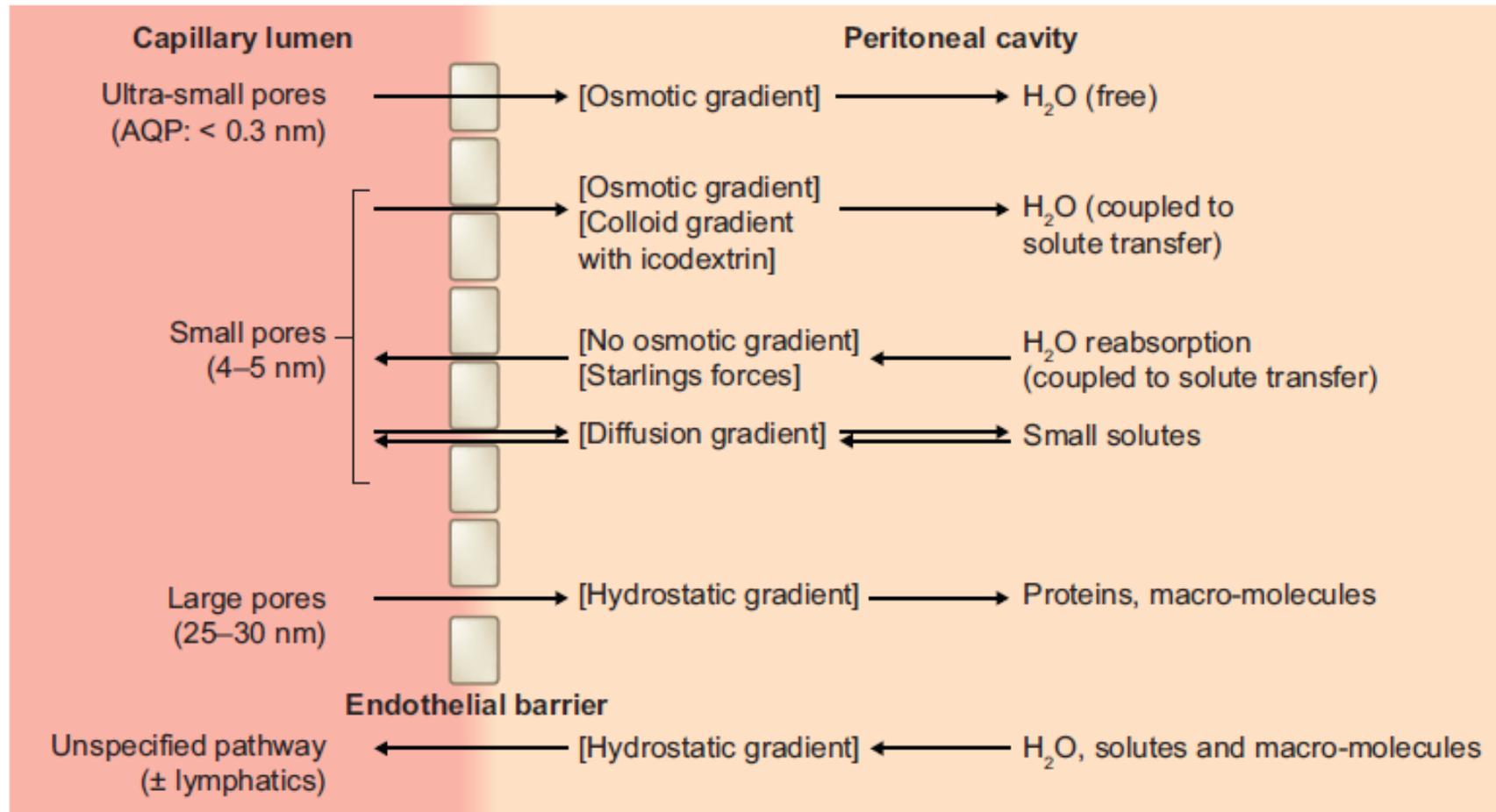
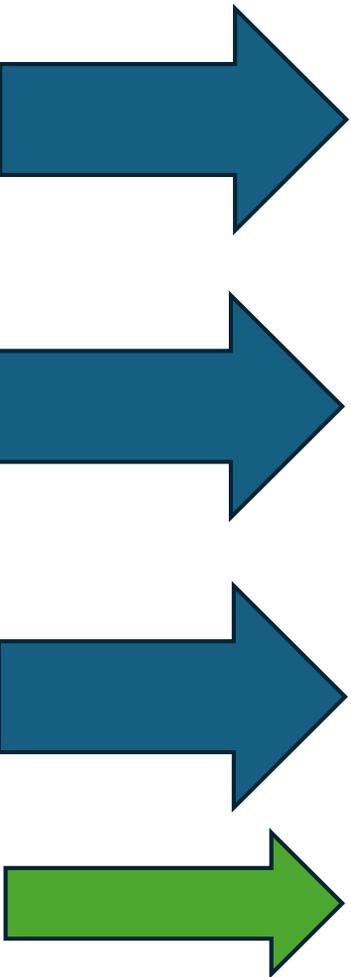
- Molecular weight
- Intrinsic properties of the membrane
- Effective peritoneal surface
- Dwell time

Effective Peritoneal Surface in Solute Transport

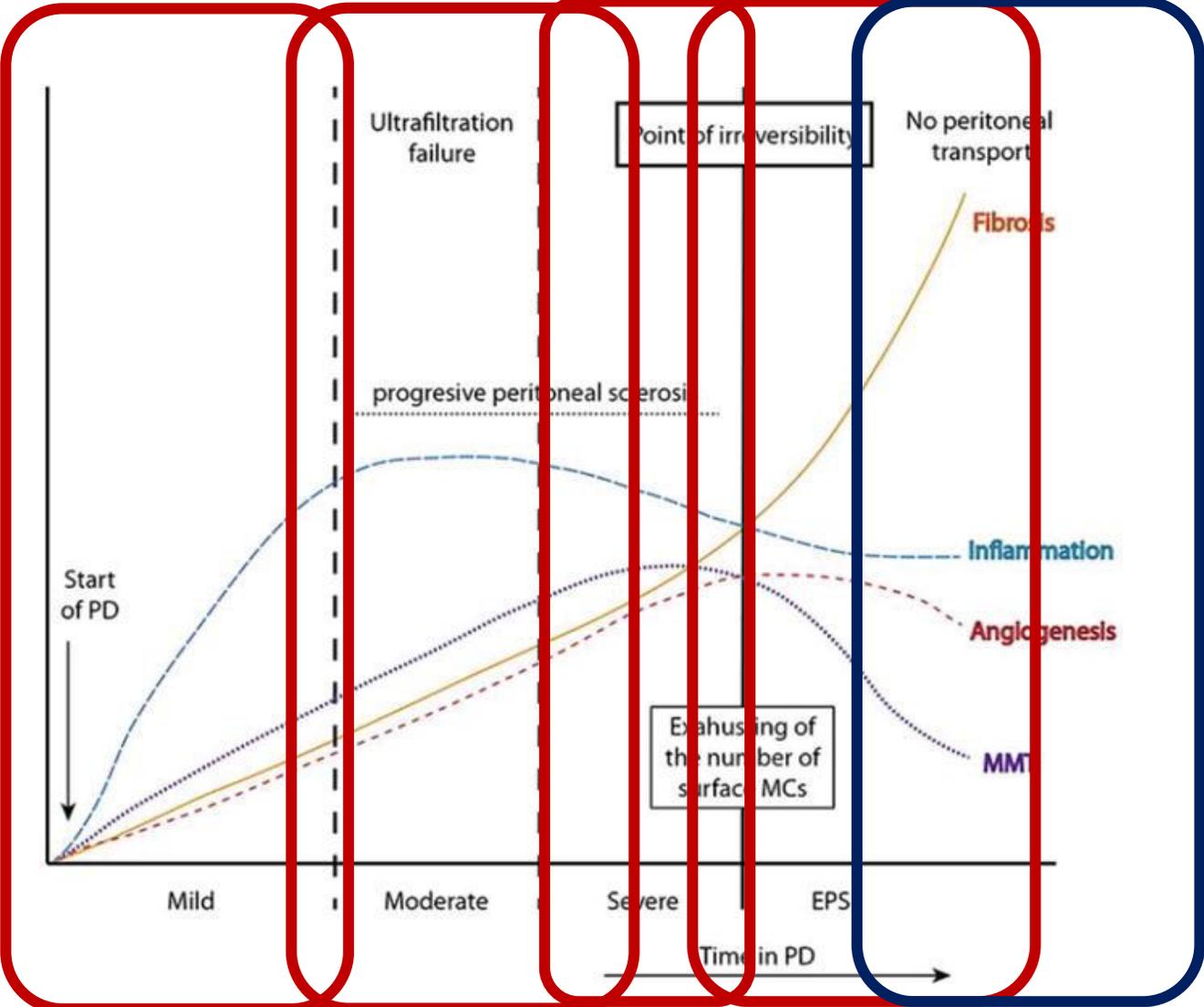
Distributed model of the effective peritoneal surface and influence of blood capillaries and interstitial space on solute transport

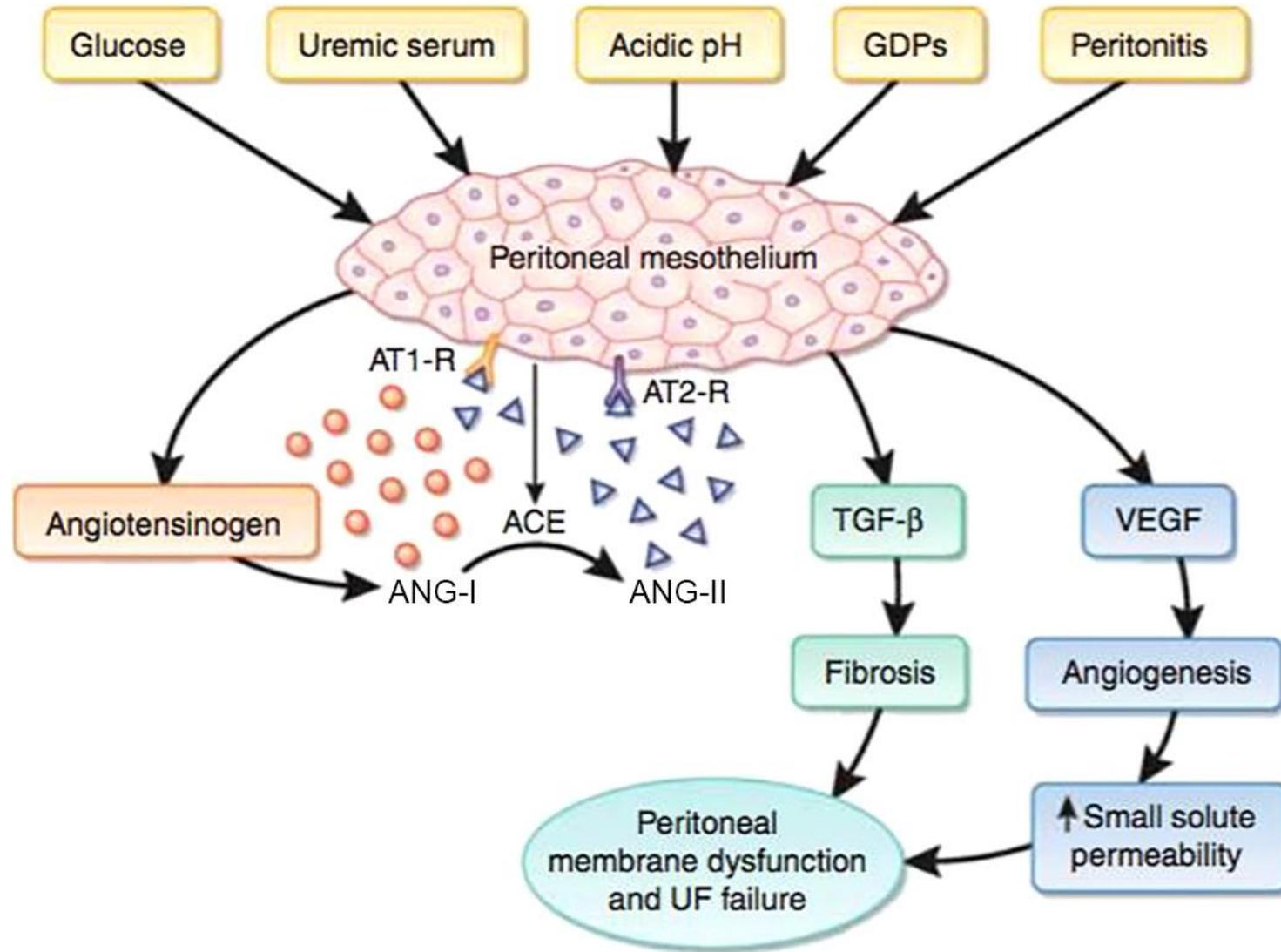


The three-pore model, representing the large pores, small pores and ultrasmall pores

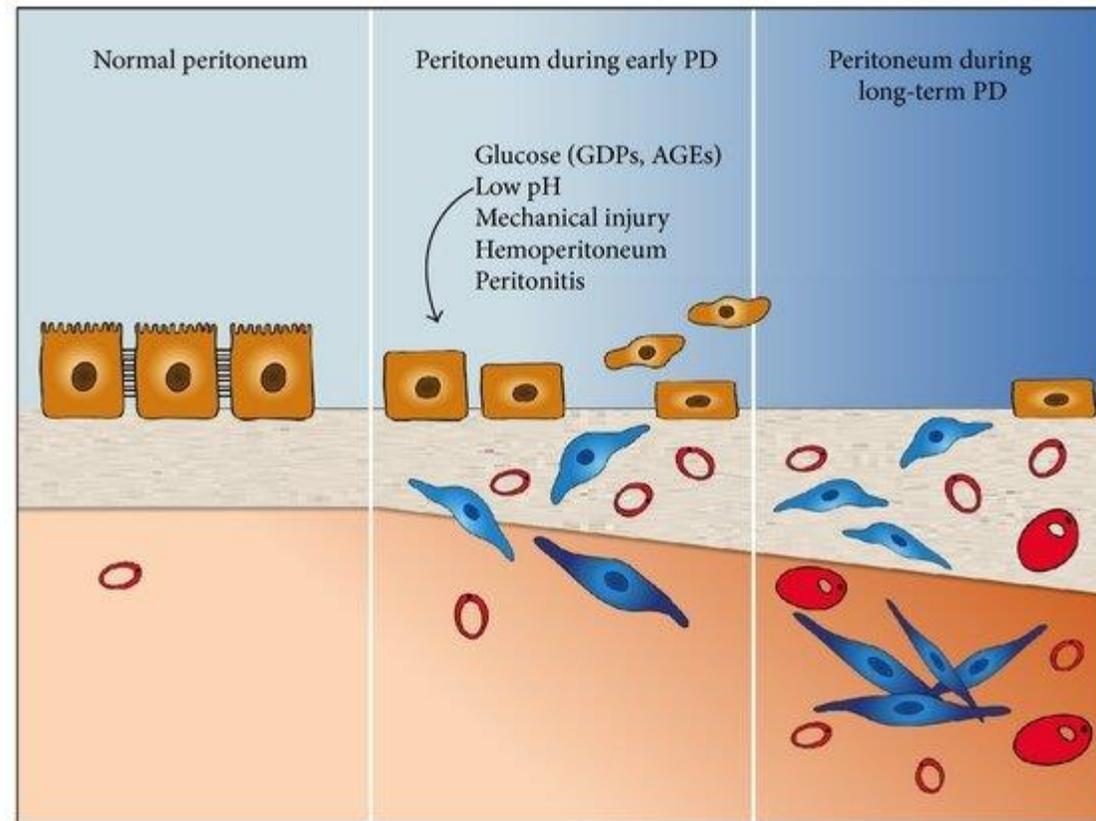


Natural history of peritoneal membrane changes



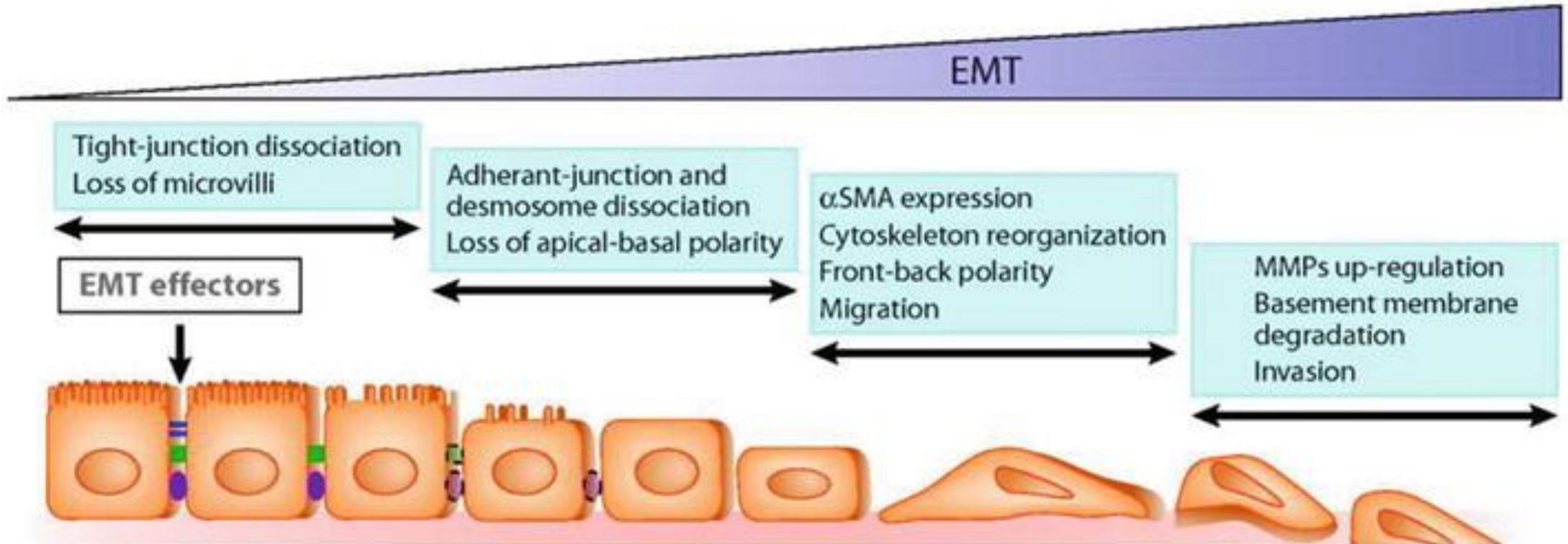


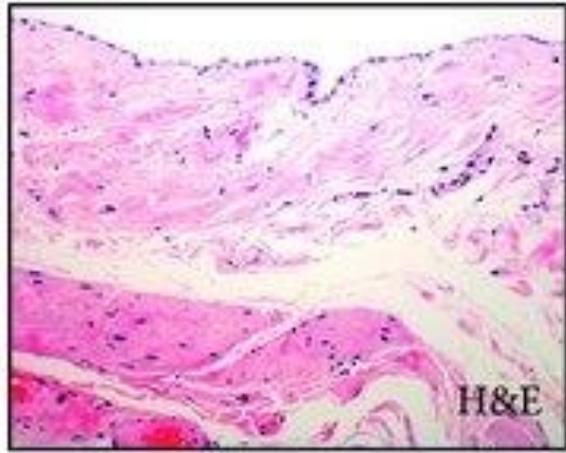
progressive structural changes in the peritoneal membrane



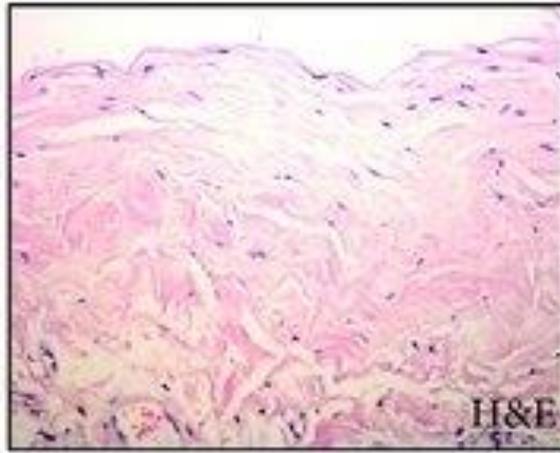
- Mesothelial cell
- Myofibroblast
- Vessel
- Vessel vasculopathy

Epithelial-to-mesenchymal transition (EMT)

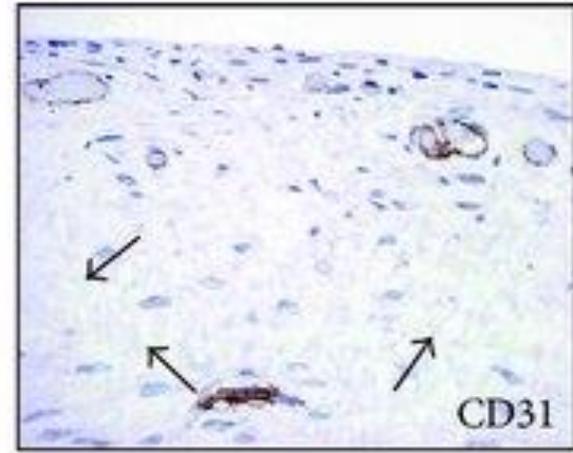




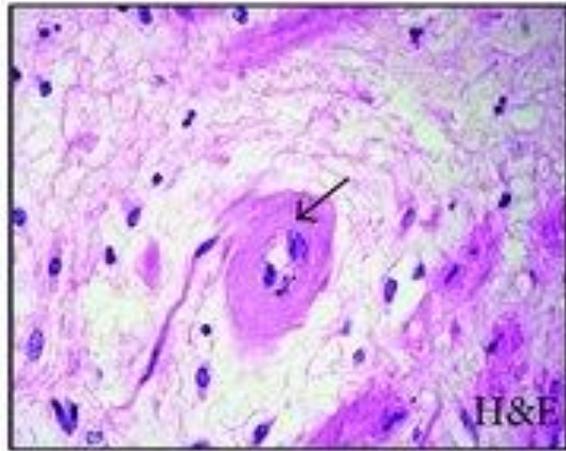
(A)



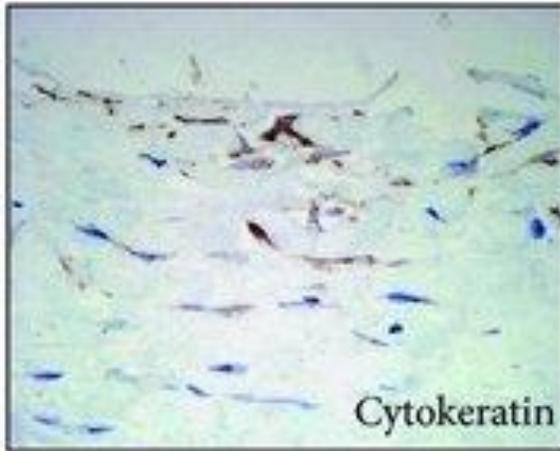
(B)



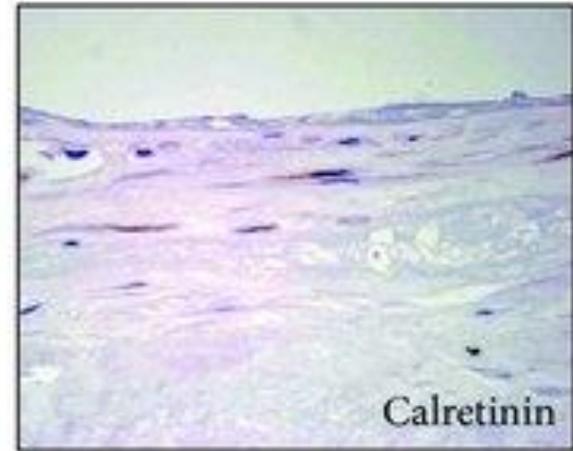
(C)



(D)



(E)



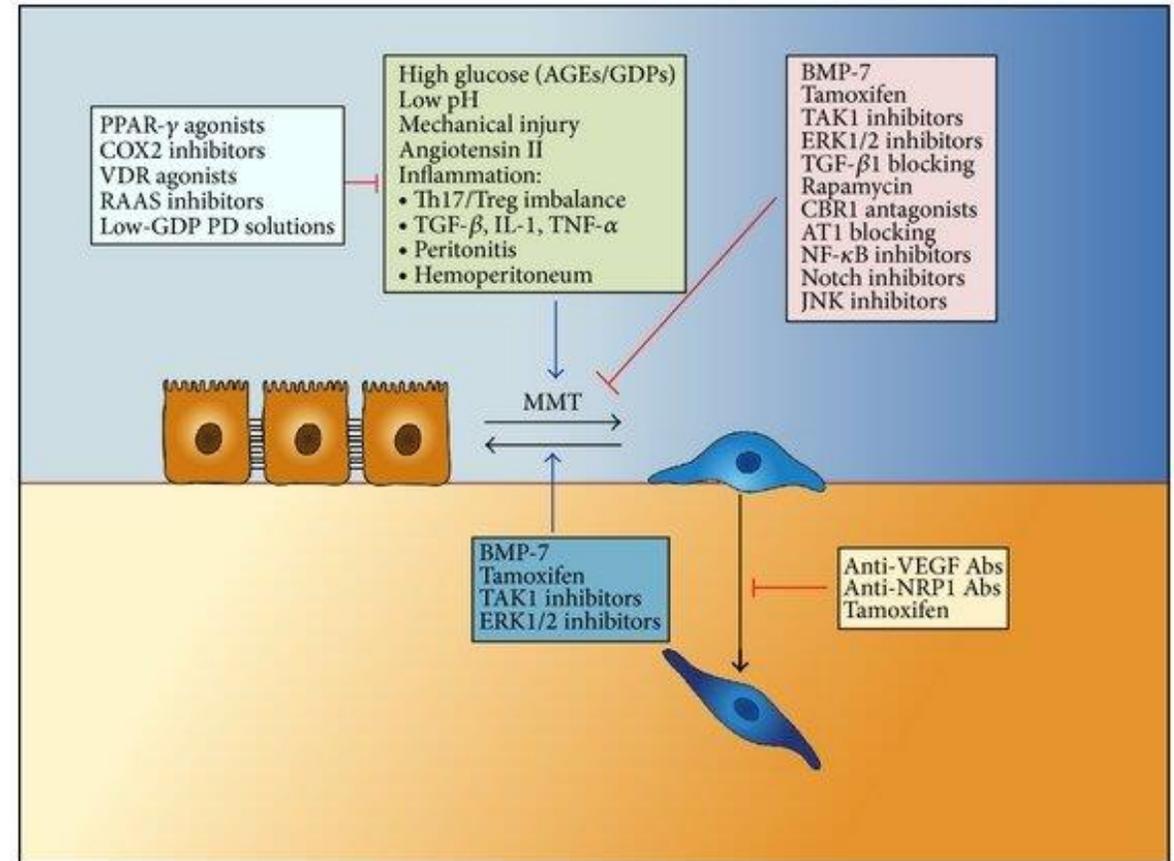
(F)

key challenges and factors contributing to membrane deterioration over time

1. Chronic Exposure to Glucose-Based Solutions
2. Oxidative Stress and Inflammation
3. Recurrent Episodes of Peritonitis
4. Epithelial-to-Mesenchymal Transition (EMT)
5. Angiogenesis and Increased Vasculature
6. Loss of Aquaporin-1 (AQP1) Function
7. Genetic and Individual Variability
8. Encapsulating Peritoneal Sclerosis (EPS)
9. High Transport Status

The therapeutic strategies

The therapeutic strategies may be designed either to prevent or reverse the MMT itself, to decrease the MMT-promoting stimuli, or to treat MMT-associated effects to avoid their accumulation in the compact zone.



Strategies to Address These Challenges:

1. Optimizing the PD Prescription

1. Use of Biocompatible Solutions:

1. Minimizing Glucose Exposure

1. Early Detection of Membrane Dysfunction

1. Management of Peritonitis

1. Preserving Residual Kidney Function

1. Research on Cytoprotective Agents



HOME DIALYSIS – FUNDAMENTALS AND BEYOND

Delivering Person-Centered Peritoneal Dialysis

Corbett, Richard W.¹; Beckwith, Hannah²; Lucisano, Gaetano¹; Brown, Edwina A.¹

[Author Information](#) ⓘ

Clinical Journal of the American Society of Nephrology 19(3):p 377-384, March 2024. | DOI: 10.2215/CJN.0000000000000281

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HOME DIALYSIS – FUNDAMENTALS AND BEYOND

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Clinical Journal of the American Society of Nephrology 19(3):p 377-384, March 2024. | DOI:

10.2215/CJN.0000000000000281

Table 2. Factors suggesting need to change peritoneal dialysis prescription

Uremic symptoms	Increasing tiredness, loss of appetite, nausea, loss of weight
Declining residual kidney function	Decrease in urine output Biochemical evidence of rising plasma creatinine and phosphate Decrease in kidney removal of solute measured during the clearance test
Volume overload	Decrease in urine output Address whether this arises from poor ultrafiltration or high fluid intake?
Plasma biochemistry	High creatinine, urea, phosphate, and potassium particularly if rising and therefore suggesting decline in residual kidney function
Small solute clearance tests	Measure dose of dialysis and not target. Low or decline in measurements would suggest need for increased prescription if supported by other factors

Initial prescription

Usually CAPD x2–3 exchanges x5–6 days/week

Clinic review (nursing or medical)

Assess patient well-being:

- Symptom burden
- Volume status and ultrafiltration volume
- Biochemistry
- Residual kidney function
- Clearance tests

Is there any concern that more dialysis would be of benefit?

Yes

No

Shared decision making

Consider ways of increasing PD prescription that support the person's lifestyle

No change to prescription

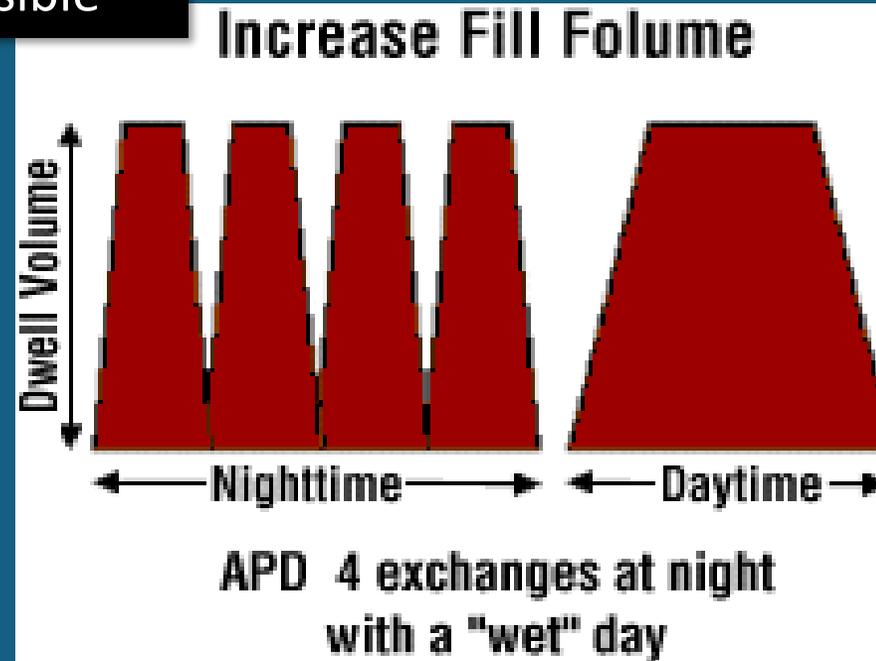
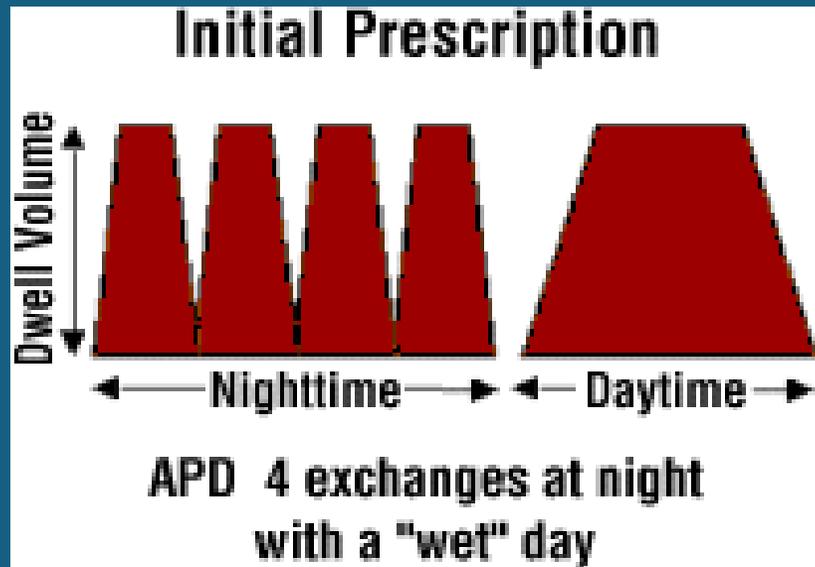
Opportunity to discuss how PD prescription could change if loss of residual kidney function

New prescription

- CAPD: Increase days or exchanges
- APD: Increase days or regime

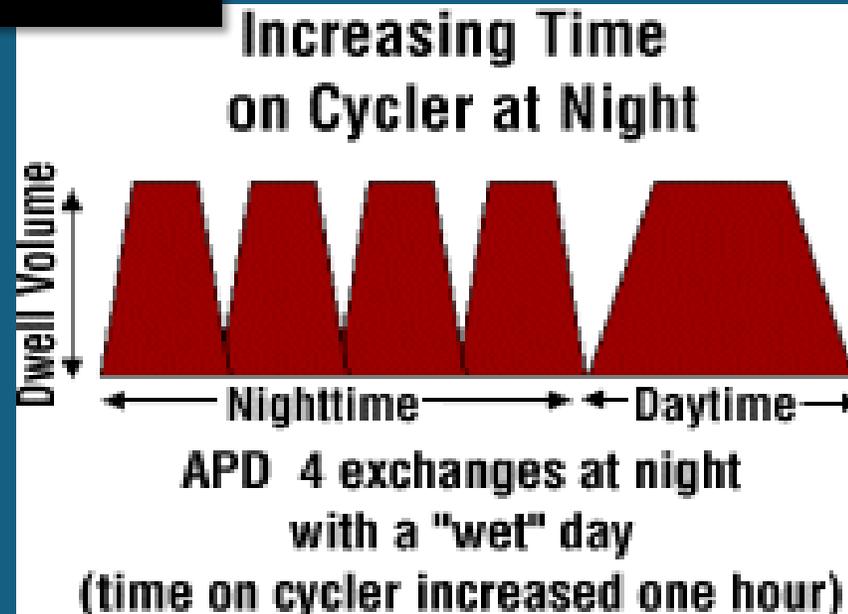
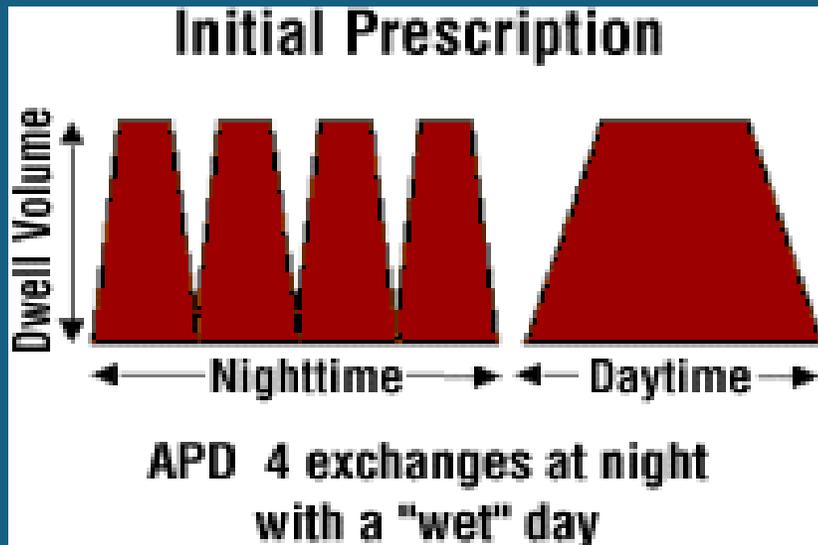
Prescription Modification

- Effective means of improving clearance
- Minimum impact on patient lifestyle
- Adjust nighttime exchanges first
- Use 2.0L or greater whenever possible



Prescription Modification

- Cyclor time can be extended to 10 hours
- Increasing cyclor time with a constant number of exchanges increases dwell time which increases clearance

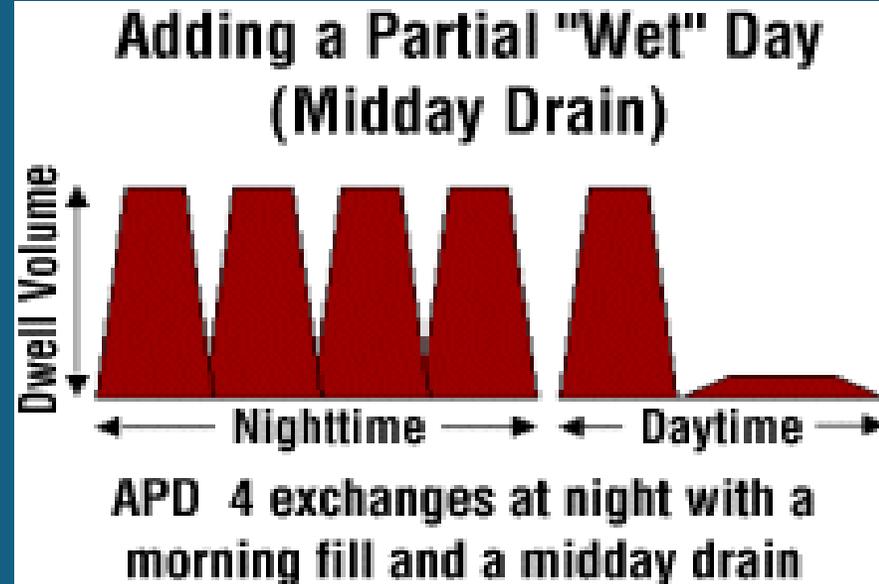
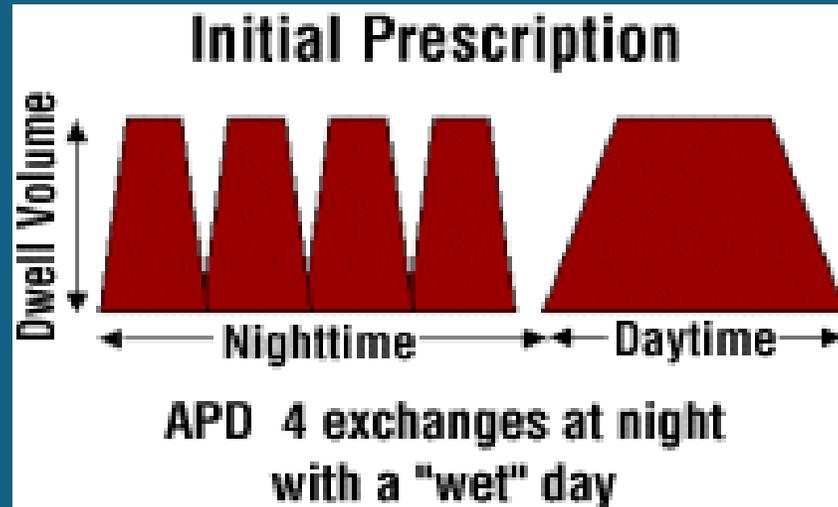


Increase Number of Nighttime Exchanges

- May increase clearance, but only if time on cyclor is also increased

Prescription Modification

- This is a very effective means of improving clearance
- Machine can be programmed to deliver the midday exchange



Causes of hypervolaemia due to insufficient daily UF.



Non-dialysis-related causes



Reduced RKF



Salt and water ingestion



Cardiovascular disease



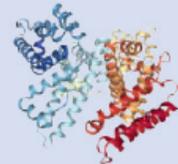
Dialysis-related causes



Wrong prescription
Non-adherence



Hyperglycaemia

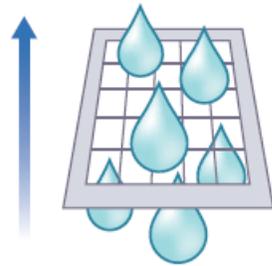


Hypoalbuminaemia



Mechanical dysfunction
Peritoneal leak

Strategies to maximize volume status control.



-  **1. Increase diuresis**
-  **2. Reduce salt and water intake**
-  **3. Use of icodextrin**
-  **4. Maximize concentration gradient**
 -  Increase volume
 -  Reduce dwell time
 -  Increase tonicity

Optimizing PD prescription for the type of peritoneal transport.



Fast transporters

- Fast diffusion of small solutes
- Early loss of osmotic gradient



- Preferred APD
- Short and frequent dwells
- Icodextrin for long dwells



Slow transporters

- Slow diffusion of small solutes



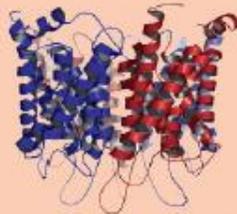
- Preferred CAPD
- APD with one or two diurnal dwells



Intrinsic fast transporters



Genetic features



Aquaporins



Acquired fast transporters



Peritonitis



Dialysis
time



Early loss
of RKF



Exposure
to glucose

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graph TD; A[Initiate Therapy] --> B[Measure Clearances]; B --> C[Adjust Therapy];
```

Initiate Therapy

Measure Clearances

Adjust Therapy

Monitoring frequency

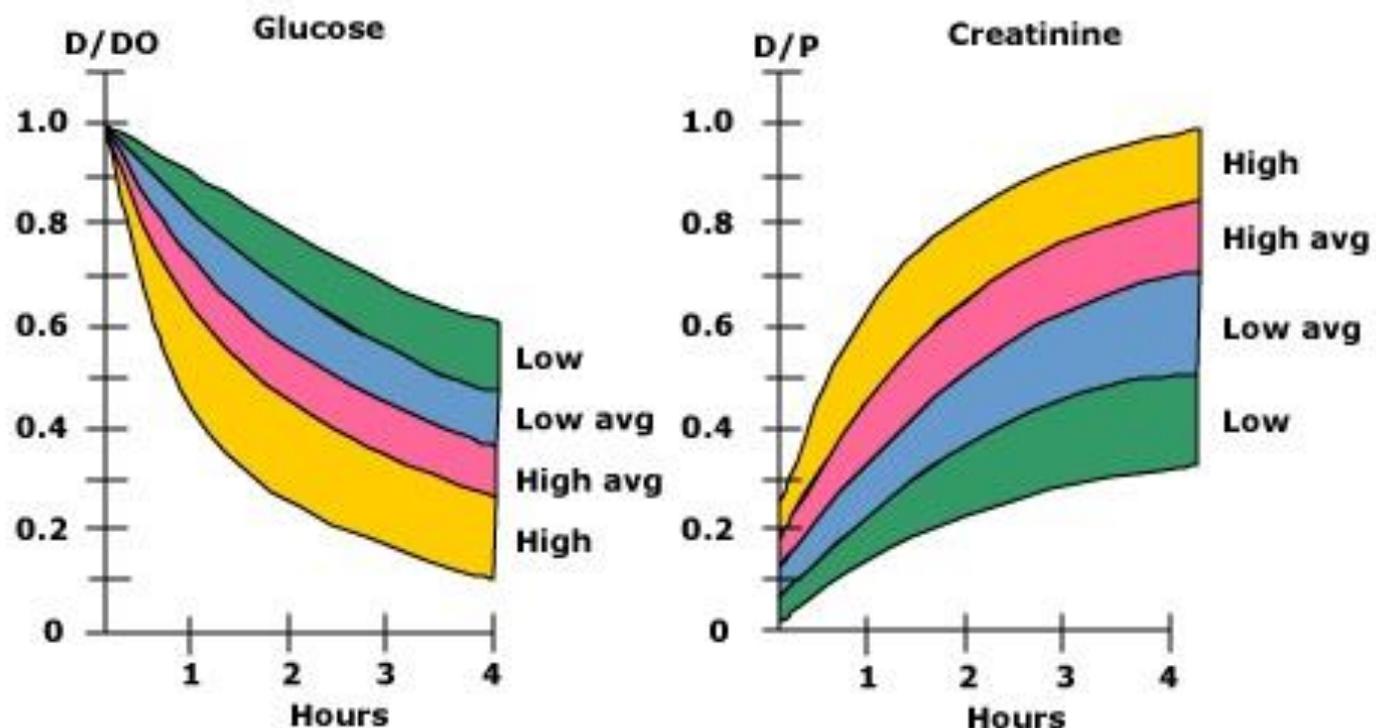
KT/V and Ccl:

- Within 6-8 weeks after commencing dialysis
- Every subsequent 6 month
- If patients clinical status changes unexpectedly, or if prescription is altered, take supplemental clearance measurements

PET

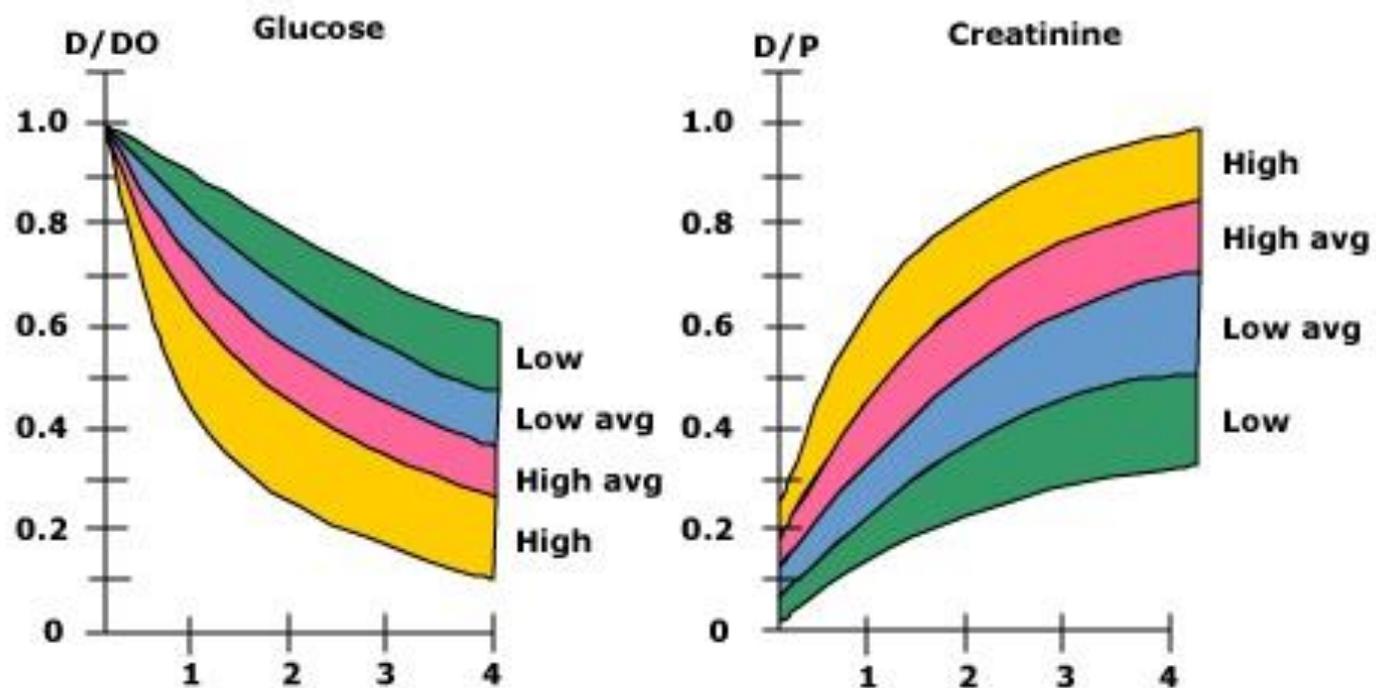
- Within 6 weeks of initiating PD
- Repeat if unexpected changes in peritoneal UF occur

Peritoneal Equilibration Test (PET)



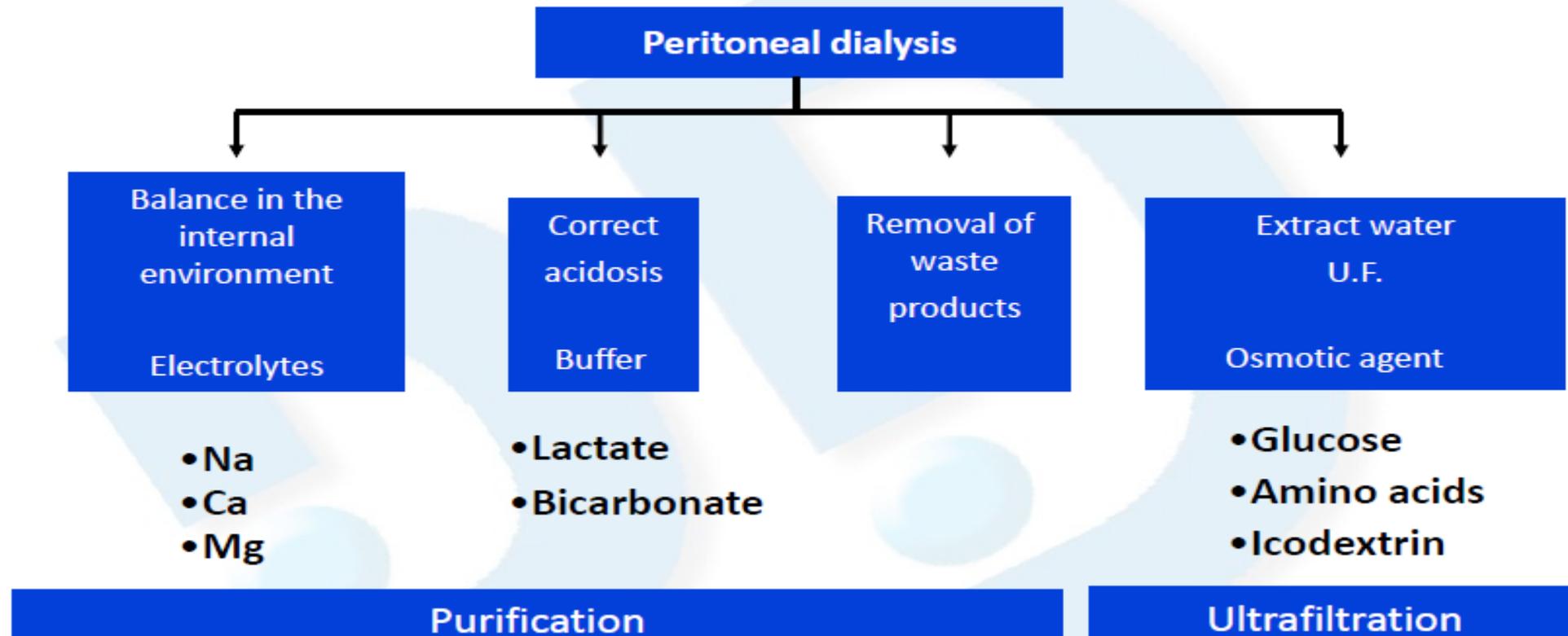
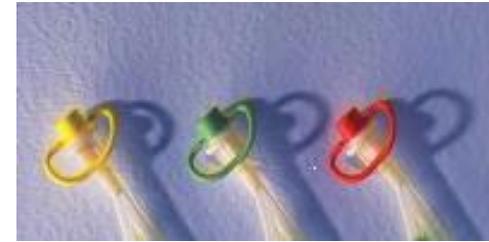
This should be done early in the course dialysis treatment (between 6 weeks and 12 weeks) (**GRADE 1A**) and subsequently when clinically indicated. (**practice point**)

Peritoneal Equilibration Test (PET)



Socioeconomic considerations: When resource constraints prevent the use of routine tests, consideration of membrane function should still be part of the **clinical management** and may be inferred from the **daily UF** in response to the prescription. (**practice point**).

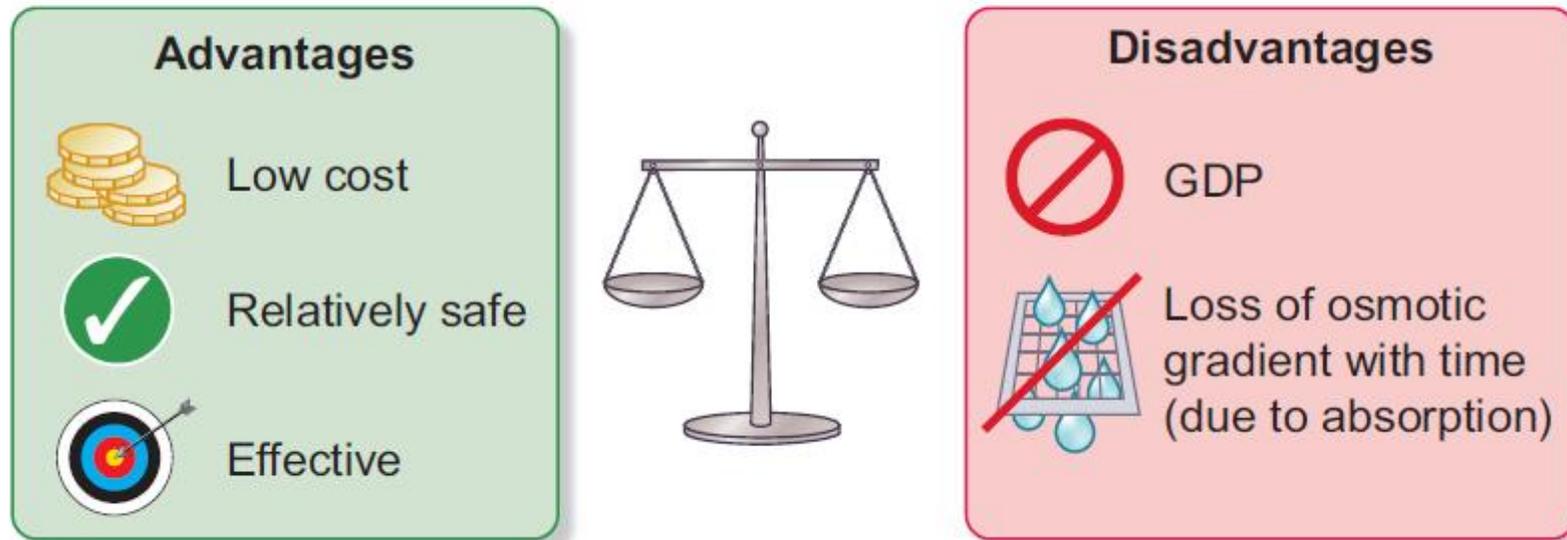
PD solutions



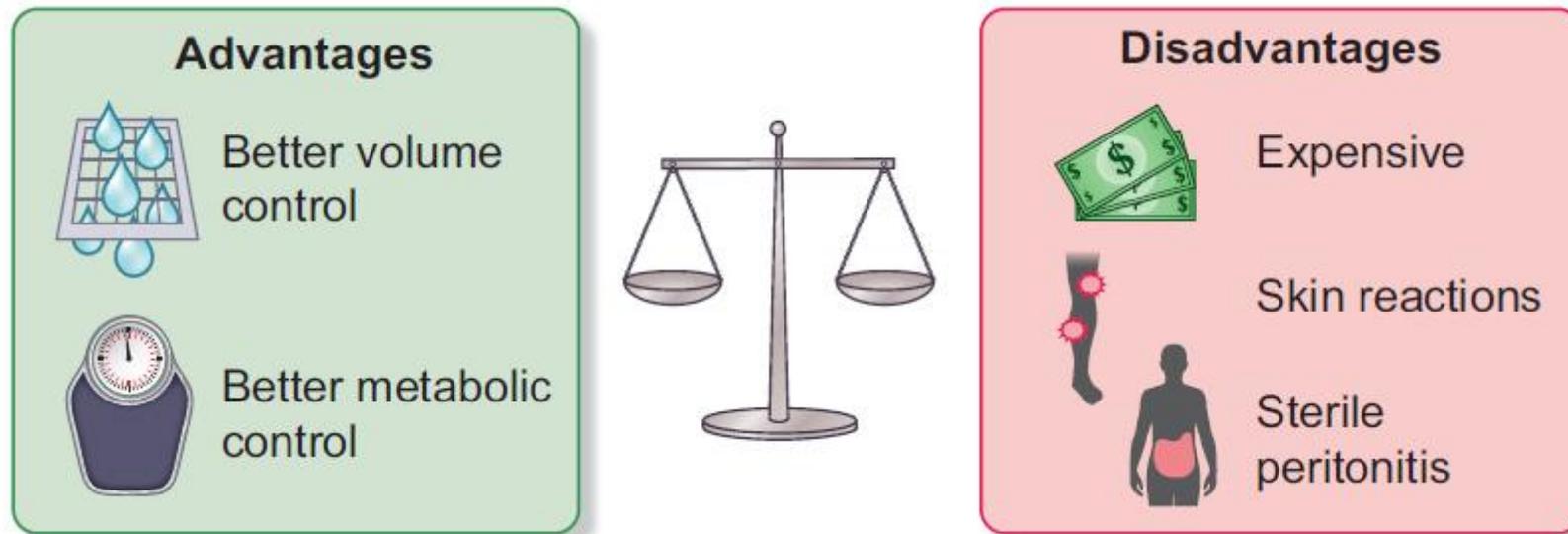
PD Solutions

	Dextrose	Amino acid	Icodextrin
Osmolality (mOsm/kg)	346, 396 and 485	365	282
Molecular Weight (Dalton)	182	100-200	20,000
Advantages	Well studied Most commonly used for a long time Side effect profile well known to most of the nephrologists	Can improve nutritional status in malnourished diabetic and/or patients with recurrent peritonitis	Sustained ultrafiltration for many hours Decreased solute absorption
Disadvantages	Short lived ultrafiltration Metabolic complications like hyperinsulinemia, hyperglycemia, hyperlipidemia, and weight gain	Expensive May increase nitrogen waste product in blood May cause/worsen acidosis	Increases serum levels of maltose, maltotriose, and oligopolysacharides
Indications	first line peritoneal dialysis solution in all patients	Malnourished diabetic patients or Malnourished patients with recurrent peritonitis	<ul style="list-style-type: none"> • Patients who lose UF • to achieve sustained UF • increased solute and fluid removal In diabetic patients

Advantages and disadvantages of glucose-based solutions.



Advantages and disadvantages of icodextrin.



False results in serum glucose and amylase tests

- Toxic effects of maltose not fully known
- Mild translocational hyponatremia

Biocompatible fluids

Solution (manufacturer)	pH	Chambers	Buffer	Glucose degradation products (3-desoxyglycosone) [20, 53, 54]
Conventional PD fluids				
Dianeal (Baxter)	5.2	Single	Lactate (35–40 mmol/L)	↑↑↑ (525 μmol/L)
Stay-safe (Fresenius)	5.5	Single	Lactate (40 mmol/L)	↑↑ (172–324 μmol/L)
Biocompatible PD fluids				
Physioneal (Baxter)	7.4	Double	Lactate (10–15 mmol/L)/bicarbonate (25 mmol/L)	↓ (253 μmol/L)
Balance (Fresenius)	7.0	Double	Lactate (35 mmol/L)	↓↓ (42 μmol/L)
BicaVera (Fresenius)	7.4	Double	Bicarbonate (34/39 mmol/L)	↓↓ (42 μmol/L)
Gambrosol Trio (Fresenius)	6.5	Triple	Lactate (39–41 mmol/L)	↓↓ (65 μmol/L)

Physioneal –
Baxter



Balance –
Fresenius



Key Features of Biocompatible PD Fluids

Neutral or Near-Neutral pH

- Traditional PD fluids often have a low pH (~5.5) to improve shelf-life, but this acidity can cause peritoneal irritation and inflammation.
- Biocompatible fluids are buffered with lactate or bicarbonate to maintain a neutral or near-neutral pH, reducing peritoneal inflammation.

Low Levels of Glucose Degradation Products (GDPs)

- GDPs are by-products of glucose sterilization in traditional solutions, which are toxic to peritoneal cells and contribute to membrane damage.
- Biocompatible fluids are processed to minimize GDP formation, improving membrane biocompatibility.

Improved Osmotic Agents

- Some biocompatible fluids use alternative osmotic agents (e.g., icodextrin or amino acids) or low-glucose concentrations to reduce metabolic and peritoneal side effects.

Benefits of Biocompatible PD Fluids

1.Reduced Peritoneal Inflammation

- Neutral pH and low GDPs decrease mesothelial cell damage and local inflammation.

Preservation of Peritoneal Membrane Function

- Lower risk of long-term membrane failure due to less fibrosis and sclerosis.

Improved Patient Outcomes

- Reduced pain during exchanges due to neutral pH.
- Lower risk of systemic complications such as hyperglycemia or metabolic acidosis.

Enhanced Ultrafiltration

- Alternative osmotic agents like icodextrin improve ultrafiltration in patients with membrane dysfunction or fluid overload.

Comparison of longitudinal membrane function in peritoneal dialysis patients according to dialysis fluid biocompatibility

STUDY POPULATION



251 incident PD patients

Conventional
n=135

Follow-up, 2.3 yrs
Peritonitis, 1.1 per yr

More biocompatible
n=116

Follow-up, 2.2 yrs
Peritonitis, 0.9 per yr

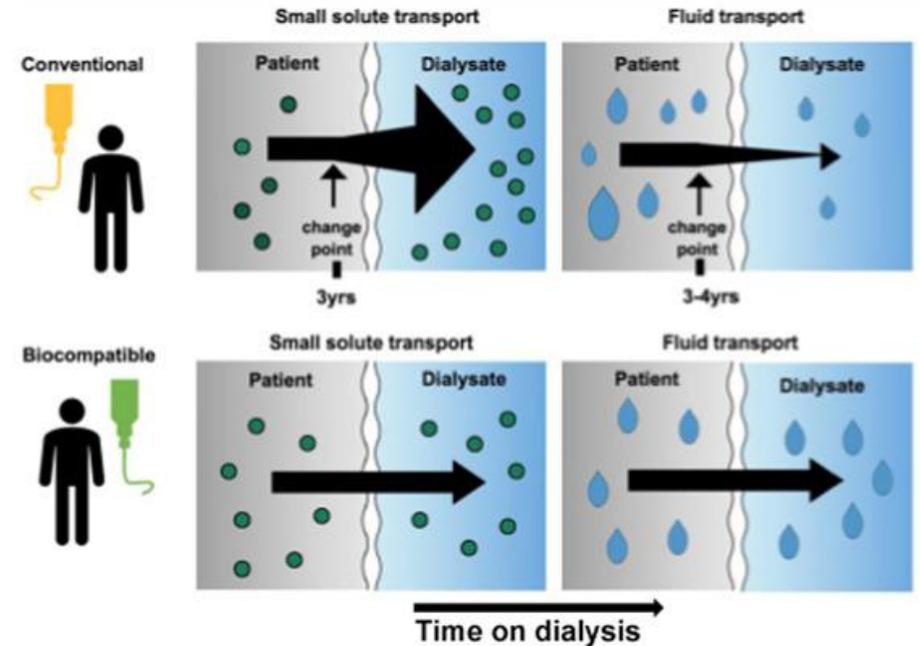
METHODS

Observational cohort study
A longitudinal comparison was performed between the course of peritoneal solute and fluid transport during treatment with conventional and more biocompatible solutions.

Yearly transport and peritonitis data were prospectively collected.

Linear mixed models were used. Interaction with peritonitis was examined.

RESULTS

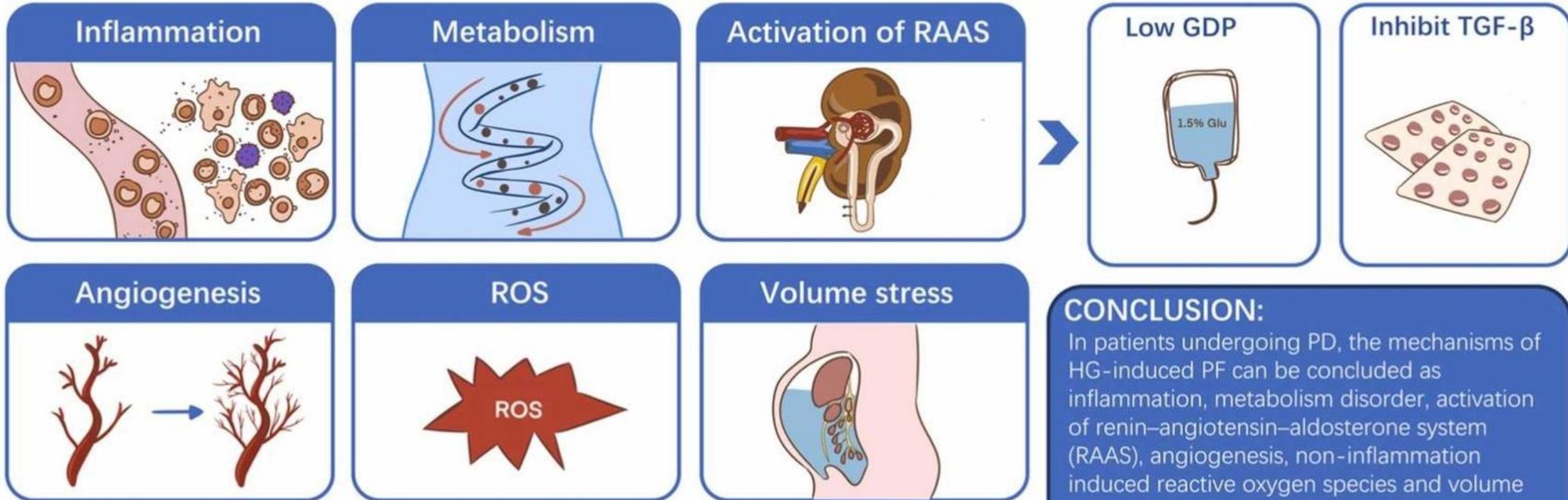


The width of the arrow represents the alteration of peritoneal alteration over time as well as its transport direction over the peritoneal membrane.

CONCLUSION:

This study emphasizes the detrimental association between conventional dialysis solutions, their potential synergistic interaction with peritonitis and the acceleration of the changes in peritoneal membrane function during PD.

High glucose dialysate – induced peritoneal fibrosis: pathophysiology, underlying mechanisms and therapy strategies.



CONCLUSION:
In patients undergoing PD, the mechanisms of HG-induced PF can be concluded as inflammation, metabolism disorder, activation of renin–angiotensin–aldosterone system (RAAS), angiogenesis, non-inflammation induced reactive oxygen species and volume stress. The main prevention and treatment strategies include low-GDP PD solutions and inhibitors of TGF- β 1/Smad pathway.

Associations of neutral pH, low GDP peritoneal dialysis solutions with patient survival, transfer to haemodialysis and peritonitis

Are neutral pH, low GDP PD solutions associated with clinical benefits?

Methods



Incident adult PD patients in Australia and New Zealand



Retrospective cohort (ANZDATA Registry)

Results

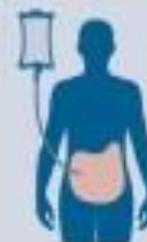
Neutral pH, low GDP solution (n=2,282) vs. conventional solution (n=10,532)



All-cause mortality*

0.67

(0.61–0.74)



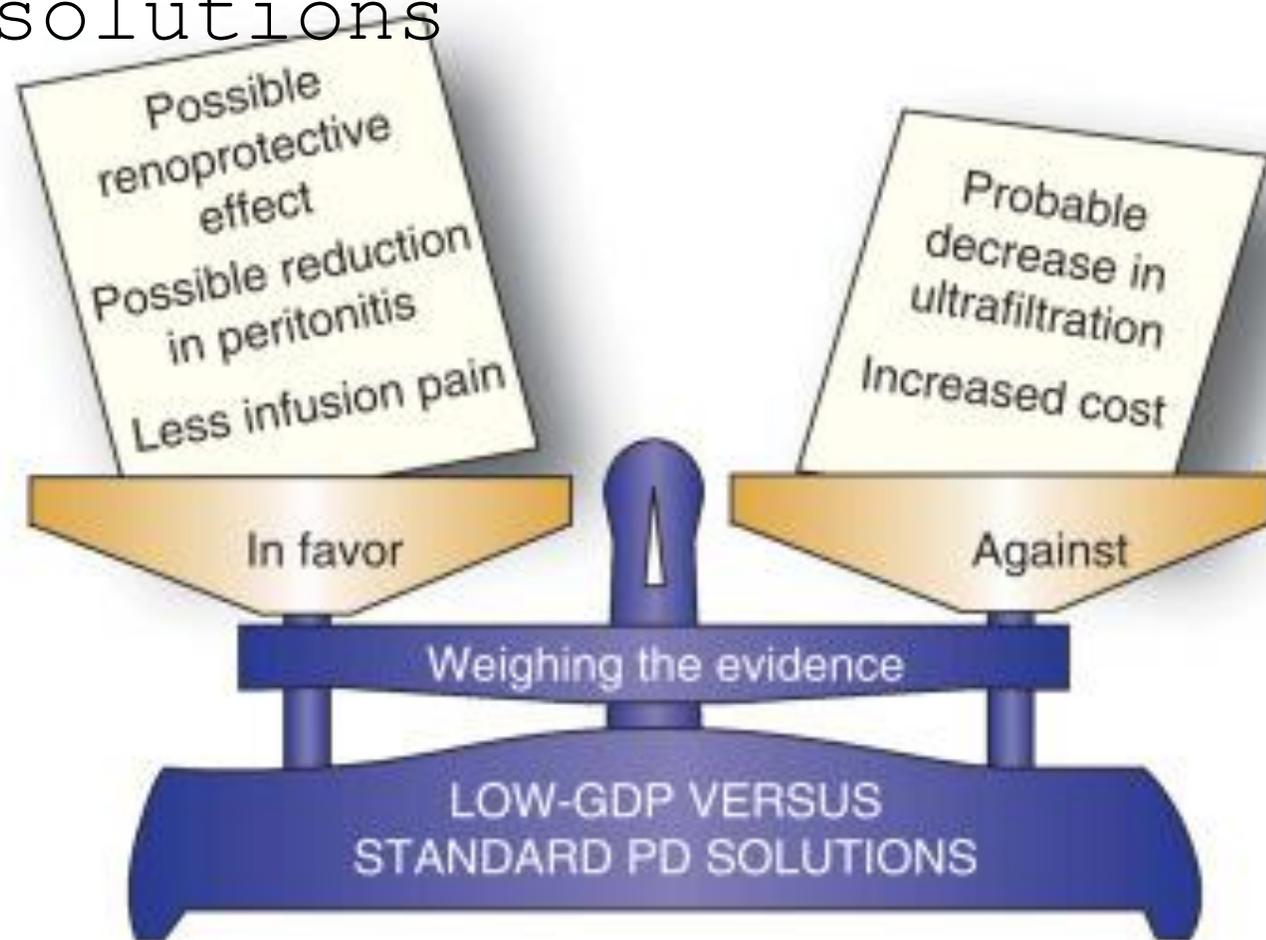
PD peritonitis*

1.16

(1.07–1.26)

*Adjusted hazard ratio (95% CI)

Weighing the evidence on biocompatible peritoneal dialysis solutions



Monitoring frequency

KT/V and Ccl:

- Within 6-8 weeks after commencing dialysis
- Every subsequent 6 month
- If patients clinical status changes unexpectedly, or if prescription is altered, take supplemental clearance measurements

PET

- Within 6 weeks of initiating PD
- Repeat if unexpected changes in peritoneal UF occur



Incremental peritoneal dialysis

Peter G Blake¹, Jie Dong^{2,3,4,5} and Simon J Davies⁶

Peritoneal Dialysis International
2020, Vol. 40(3) 320–326
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DOI: 10.1177/0896860819895362
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- (1) less than standard “full-dose” PD is initially prescribed in recognition of the value of residual renal function;
- (2) peritoneal clearance is initially less than the individualized clearance goal but the combination of peritoneal plus renal clearance achieves or exceeds that goal clearance
- (3) there is a clear intention to increase dose of PD as renal clearance declines and/or symptoms appear.

Incremental PD lessens the workload of dialysis for those doing PD

Reduces cost and exposure of the

COMPLEMENTARY APPLICATION OF DIALYSIS



**Adequate
dialysis**

**Preservi
ng RKF**



Incremental Versus Standard (Full-Dose) Peritoneal Dialysis

Direct outcomes

- Fewer connections
- Reduced dialysate use
- Reduced glucose exposure

Potential Clinical Implications

- Improved quality of life
- Reduced peritonitis risk
- Reduced financial cost
- Reduced environmental waste
- RKF preservation
- Peritoneal membrane preservation
- Reduced systemic complications of glucose

ADVANTAGES

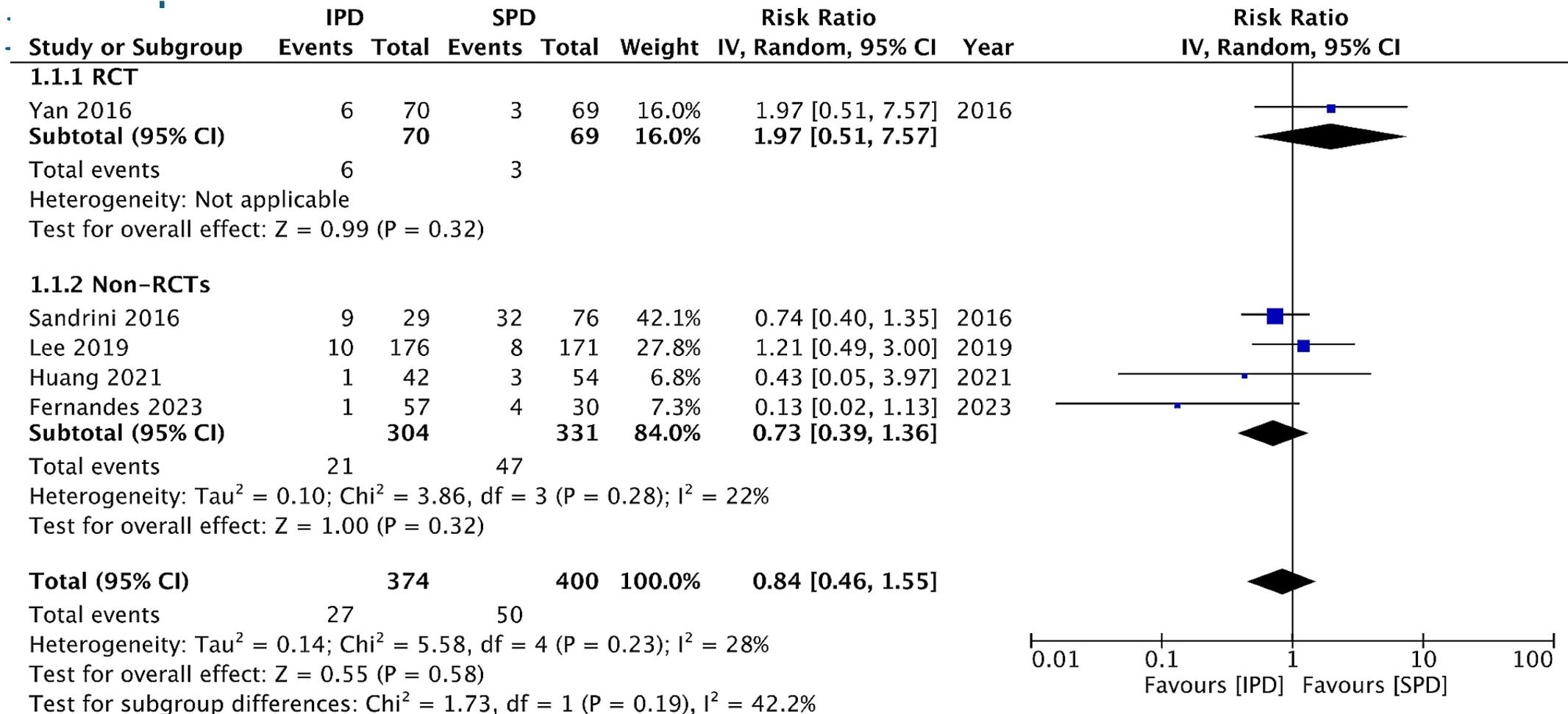
INCREMENTAL PERITONEAL DIALYSIS

DISADVANTAGES

- Reduced small solute clearance
- Reduced ultrafiltration
- Risk of therapeutic inertia

- Poorer patient survival
- Increased risk of fluid overload

Comparison of outcomes of incremental vs. standard peritoneal dialysis: a systematic





Outline



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REVIEW ARTICLE

Incremental Peritoneal Dialysis—Definition, Prescription, and Clinical Outcomes

Fernandes, Adriana¹; Matias, Patrícia²; Branco, Patrícia²

[Author Information](#) ☺

Kidney360 4(2):p 272-277, February 2023. | DOI: 10.34067/KID.0006902022



- The potential benefits for RKF preservation and the lower risk of peritonitis
- There are some concerns regarding this strategy, such as inadequate clearance of uremic toxins and/or severe electrolyte disturbances due to undetected loss of RKF, lower clearance of medium-sized molecules (such as β -2-microglobulin), which primarily depends on the total PD dwell time, and patients' reluctance to dose adjustments.
- Current clinical evidence is based on moderate-quality to low-quality studies and suggests that the outcomes of IPD will be at least identical to those of a full dose.

Strategies to Minimize Peritonitis in PD Patients



1. Proper Catheter Insertion and Maintenance

Rigorous Hand Hygiene and Aseptic Technique

Prophylactic Antibiotics

Antimicrobial Exit-Site Protocols

Use of Disconnect Systems

Early Identification and Management of Infections

Nutritional Support and Immune Health

Prophylactic Antifungals with Antibiotics

Telemonitoring and Follow-Up

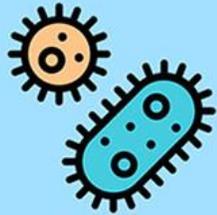
Vaccination

ISPD Peritonitis Guideline Recommendations: 2022 Update on Prevention and Treatment



PERITONEAL
DIALYSIS
INTERNATIONAL

Definitions and measurement of peritonitis



- Cause-specific peritonitis
- Time-specific peritonitis
- Outcomes-specific definitions

Prevention of peritonitis



- Catheter placement
- Exit-site care
- Contamination of PD system
- Invasive G.I. and Gynecological procedures
- Training program
- Domestic pet and zoonotic infections

Treatment of peritonitis: initial and subsequent



- Identification of causative organisms
- Empiric antibiotic selection
- Dosage of antibiotics
- Antibiotic delivery and stability

Monitoring response to peritonitis treatment

(including indications for catheter removal)



- Refractory peritonitis
- Relapsing, recurrent and repeat peritonitis

Return to PD after cessation of PD

(due to peritonitis-related catheter removal)

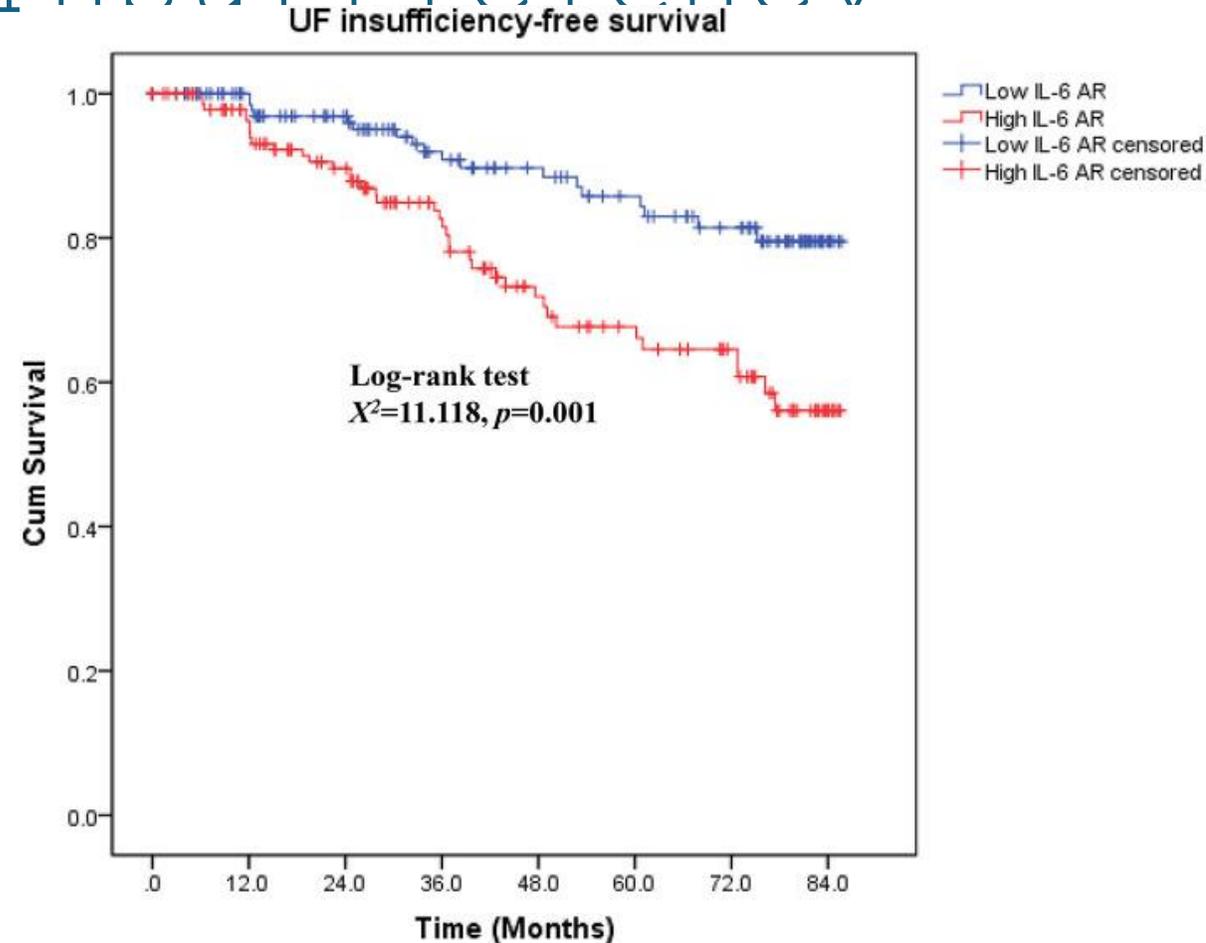


These recommendations are evidence-based where evidence is available, and if multiple reports are available, findings from the more recent publications have been incorporated by the committee.

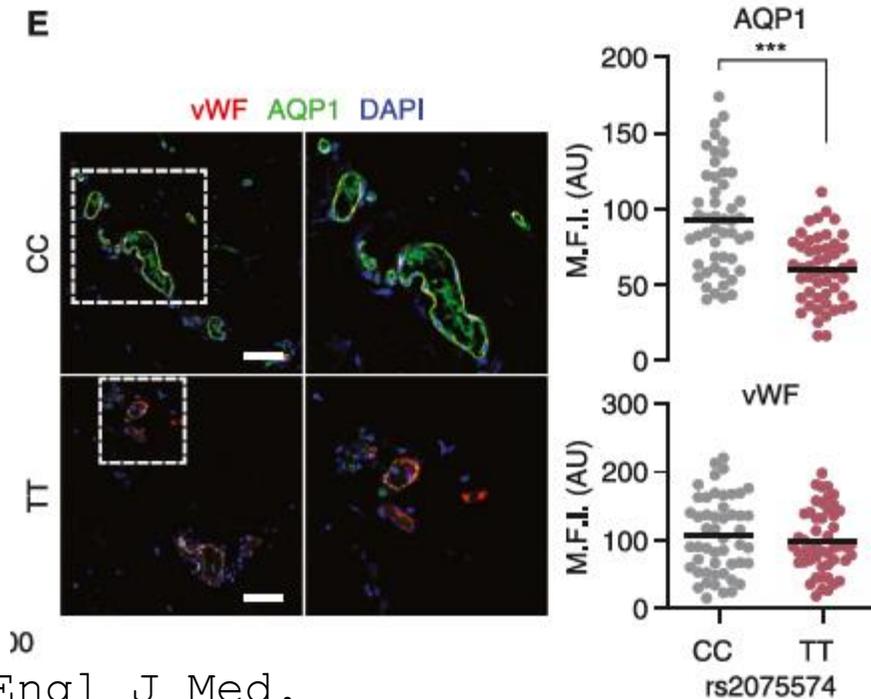
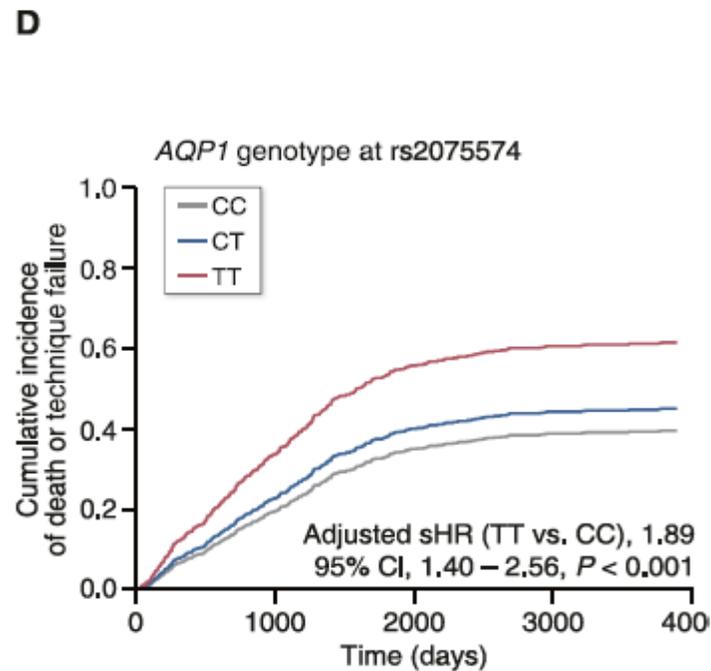
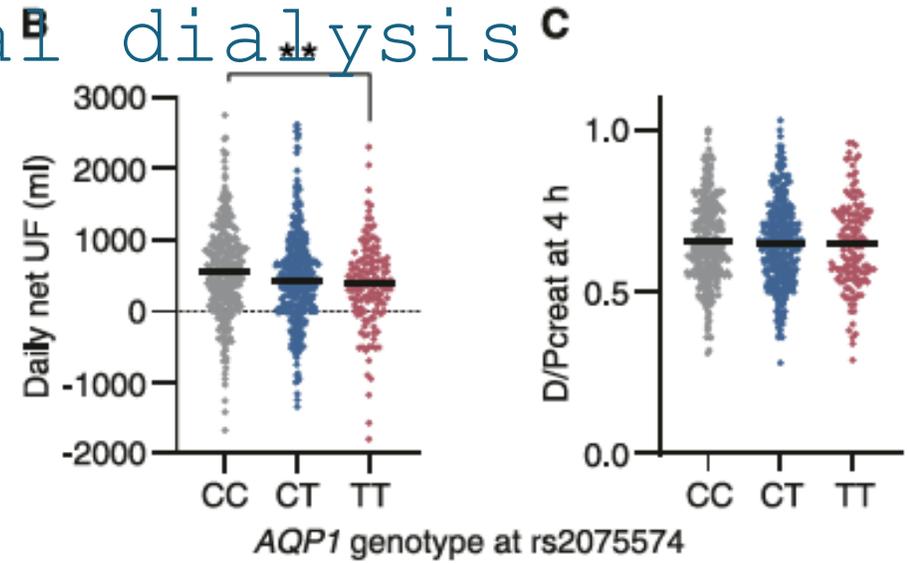
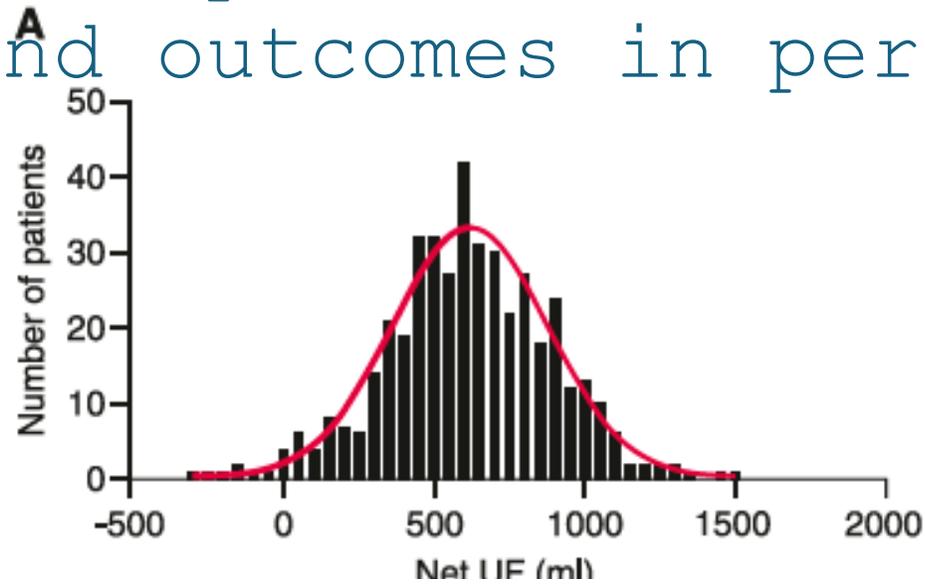
Philip Kam-Tao Li, Kai Ming Chow, Yeoungjee Cho, et al. *ISPD Peritonitis Guideline Recommendations: 2022 Update on Prevention and Treatment*. *Perit Dial Int*. DOI:10.1177/08968608221080586
Visual Graphic by Edgar Lerma, MD

the role of intraperitoneal interleukin-6 (IL-6) as a predictor of UF insufficiency

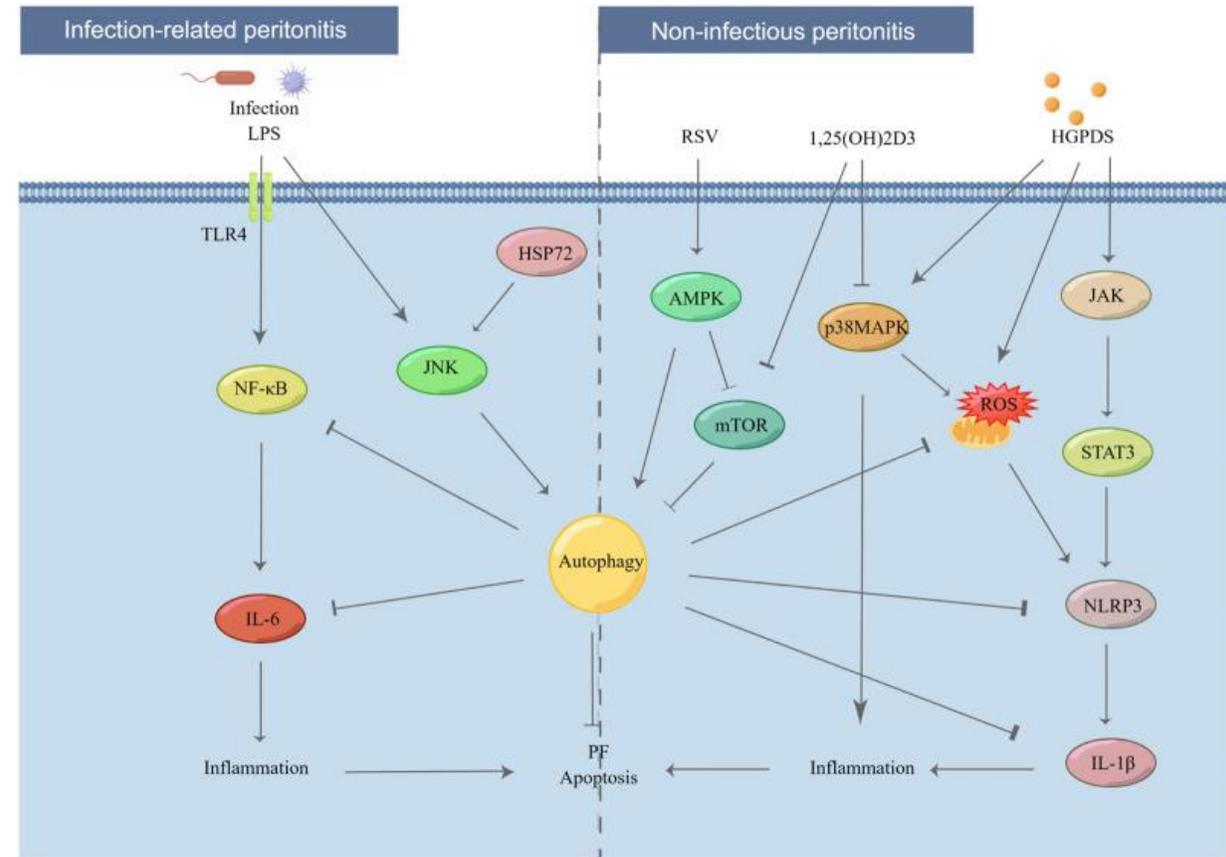
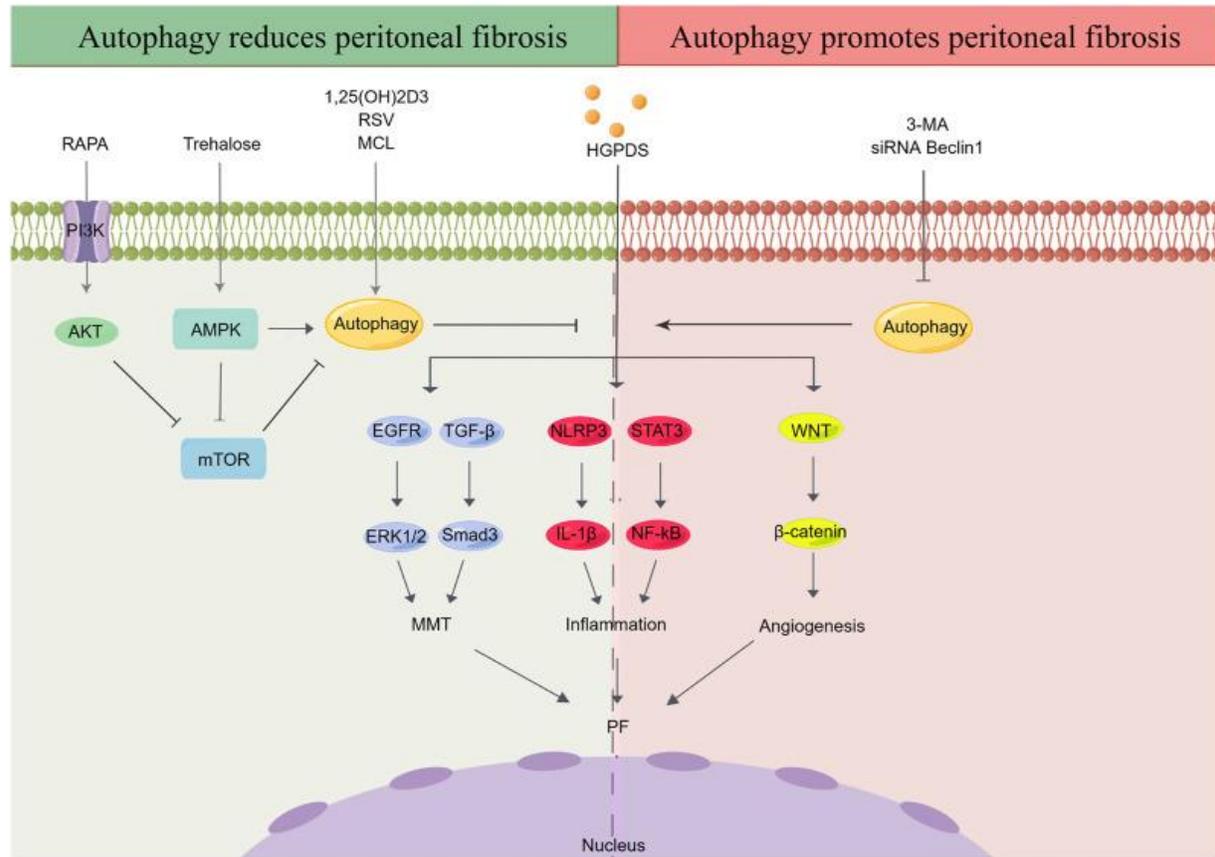
- Patients with high IL-6 AR have a significantly lower UF insufficiency-free survival compared to those with low IL-6 AR.
- This supports the conclusion that elevated intraperitoneal IL-6 levels may predict UF insufficiency in PD patients.



AQP1 promoter variant, water transport, and outcomes in peritoneal dialysis



Autophagy in peritoneal fibrosis



Potential MMT modulators untested IN PD.

Antifibrotic agents	Mechanism of action
1) Tetrapeptide	TGF β inhibition
2) Dipyridamole	TGF β inhibition
3) Pentoxifylline	Inhibition of ECM production
4) Emodin	Inhibition of ECM production
5) Simvastatin	Increases fibrinolytic activity
Antiangiogenic	
1) Anecortave acetate	Inhibits VEGF production
2) Pegaptanib	Inhibits VEGF-VEGFR binding
3) Anti-VEGFR2	Blocks receptor VEGFR2
4) TNP 470	Decreases VEGF expression
Inhibition of EMT	
1) Rho-ROCK inhibitor (Y27632)	TGF- β /Smads inhibitors
2) Anti-oxidant agent	NF- κ B inhibition
3) Notch inhibitors	Inhibit the induction of snail and repression of VE-cad
4) JNK inhibitors (PS600125)	Inhibition of both ZEB and Rho pathway
5) CBR1 antagonists	TGF- β /Smads inhibitors

phaphuli LK. IntechOpen. 2023.

<https://doi.org/10.5772/intechopen.111586>

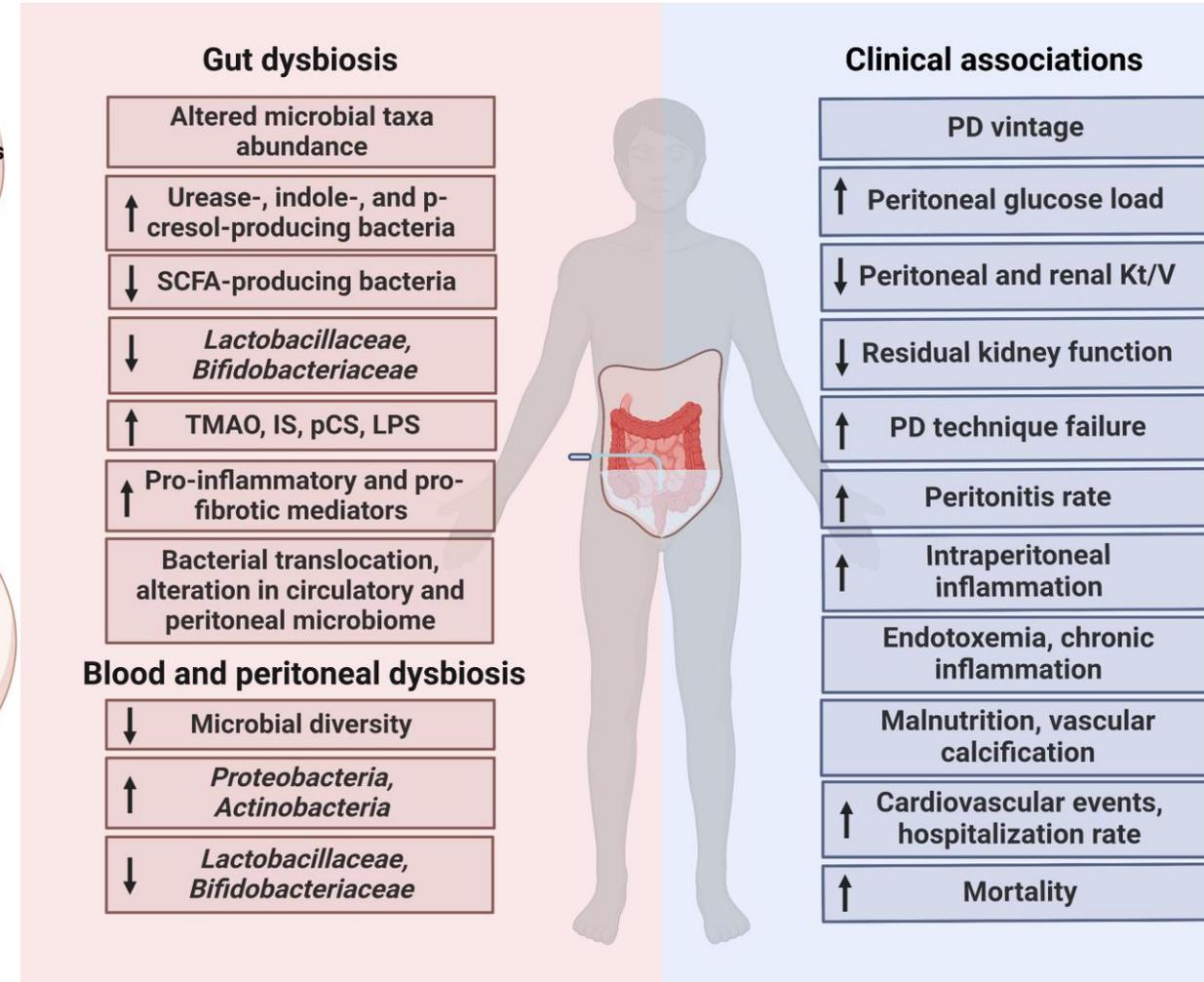
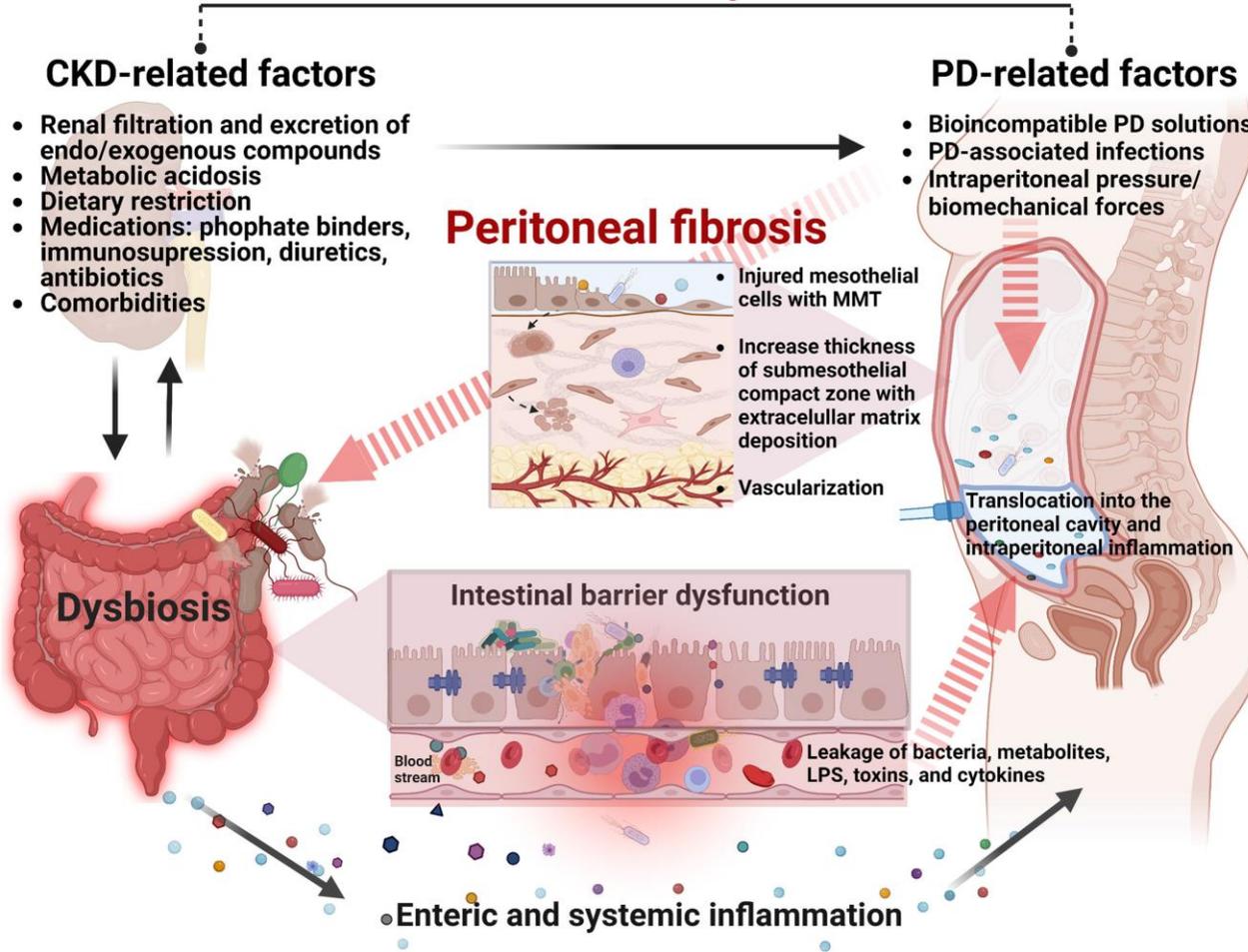
Gut dysbiosis

Wang H, et al. *Kidney Med.*

2023;5(1):100645.

<https://doi.org/10.1016/j.xkme.2023.100645>

Gut microbiota dysbiosis



What are the key ISPD recommendations to prescribing high-quality goal-directed peritoneal dialysis?



Conclusion-The aim of high-quality goal-directed dialysis is to provide the best health outcome possible for an individual on PD in terms of maintaining their clinical well-being, quality of life, ability to meet life goals and at the same time minimize treatment burden.

Residual kidney function should be determined for all individuals doing PD and management should focus on preserving this function (practice point).

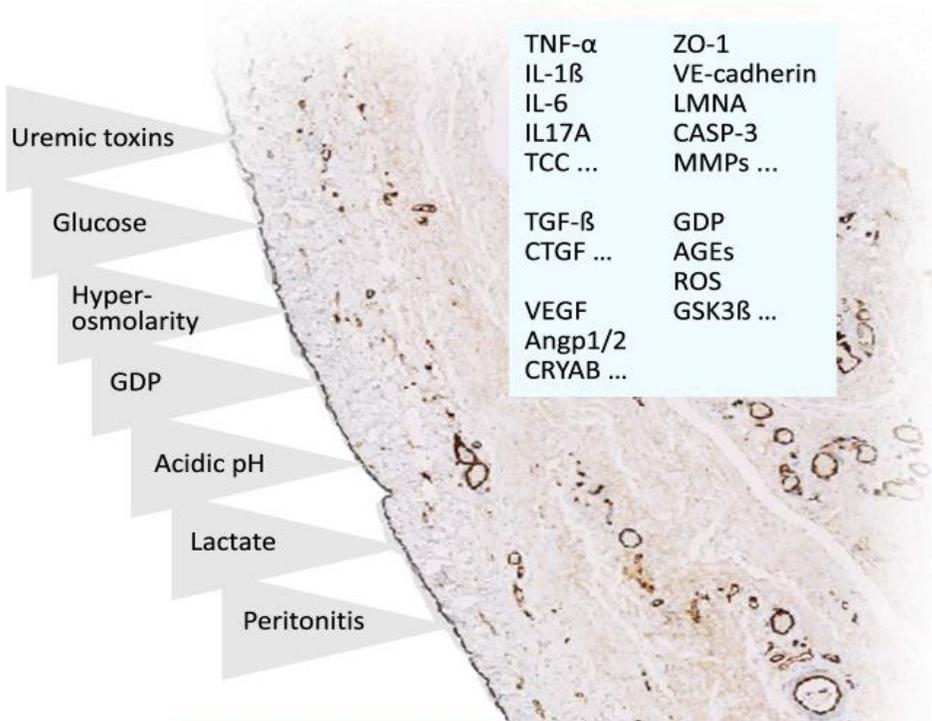


Take Home Message

- In conclusion, PF is a complex process, and many factors contribute to the formation of fibrosis.
- PD solutions with high glucose content, chronic inflammation, inflammatory cytokines, angiogenesis, and mesothelial to mesenchymal transition are factors contributing to the fibrosis of the peritoneum.
- Although most of the experimental models are promising in preventing or delaying PD-related fibrosis, most of these recommended treatment options require further research.
- The lack of sufficient data from real PD patients and many inconclusive data make clinicians depend on conservative treatment such as PD holidays, discontinuation of PD, and nutritional support.

Take Home Message

Damage factors Peritoneal membrane Molecular mediators



- ### Strategies to preserve peritoneal and systemic health
- GDP-free PD fluids
 - Glucose replacing osmolytes – icodextrin, AA, xylitol, L-carnitine
 - *Protective supplements – AlaGln, LiCl ...*
 - *Individual PD patient risk stratification*
 - *Comprehensive molecular understanding and modulation of peritoneal membrane transport function*

Peritoneal alterations
Mesothelial cell loss
Inflammation
MMT, EndMT
Hypervascularization
Vascular hyperpermeability
Submesothelial fibrosis
Vascular damage (endothelial cell loss, lumen narrowing)

Clinical consequences
Increased solute clearance
Ultrafiltration decline
Encapsulating peritoneal sclerosis
Systemic toxicity (residual renal function decline, vascular disease, glucose metabolic sequelae)



Thank You



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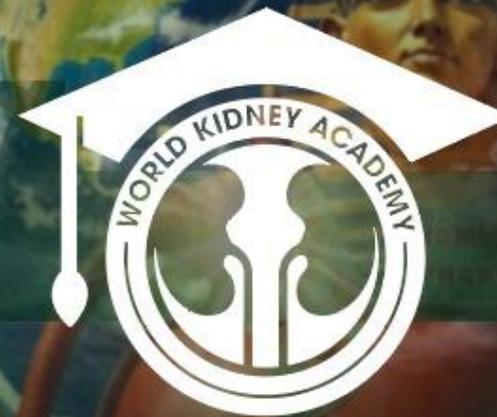
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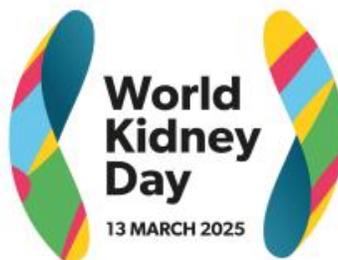
19TH- 20TH FEBRUARY 2025

AL-MONTAZA HALL



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