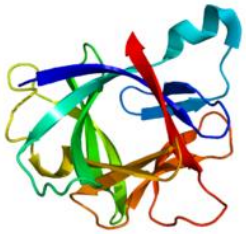

18e Réunion Annuelle des Jeunes Néphrologues
Paris, 17 mars 2018, #Immunity_Report

#PD_inflammation

Johann Morelle, MD, PhD

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Institut de Recherche Expérimentale et Clinique
Université catholique de Louvain, Bruxelles
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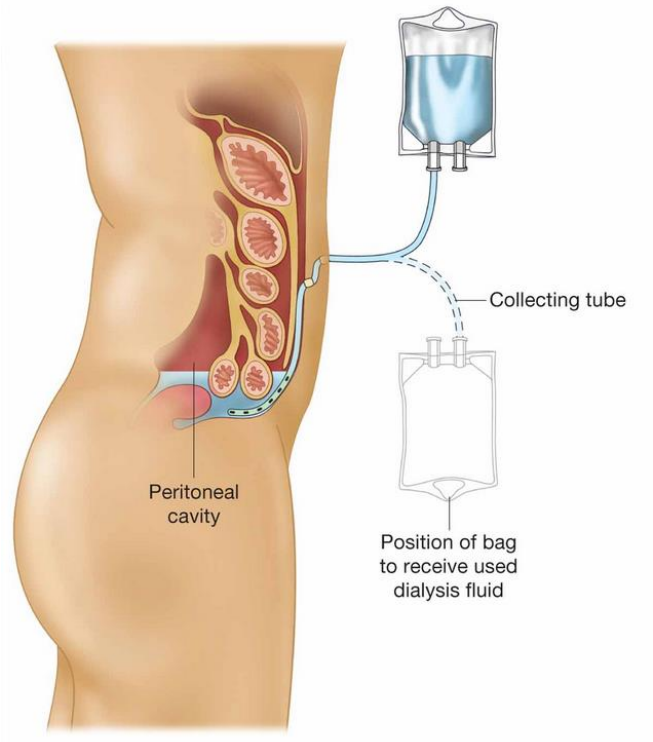
#PD_inflammation

...unfortunately.

Yet, a better understanding of why 'It's a match' may help further improving the safety and efficiency of PD as a unique and valuable form of dialysis for patients with ESRD

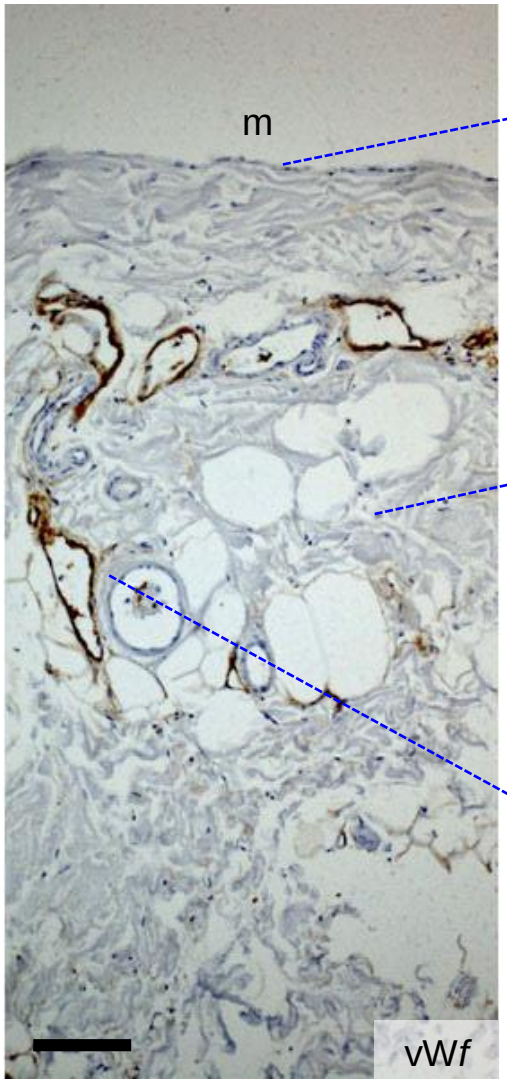
Peritoneal dialysis for the treatment of ESRD



- Main home-based dialysis technique worldwide
- Aims at restoring electrolyte and fluid balance in patients with end-stage renal disease (diffusion and osmosis)
- Uses a natural 'dialysis' membrane, the peritoneum

Mehrotra et al, *J Am Soc Nephrol* 2016

The peritoneal membrane: structure and function



Mesothelium:

- No role in peritoneal transport
- Critical for the protection of the membrane (release of pro-inflammatory/angiogenic/fibrotic cytokines and growth factors)

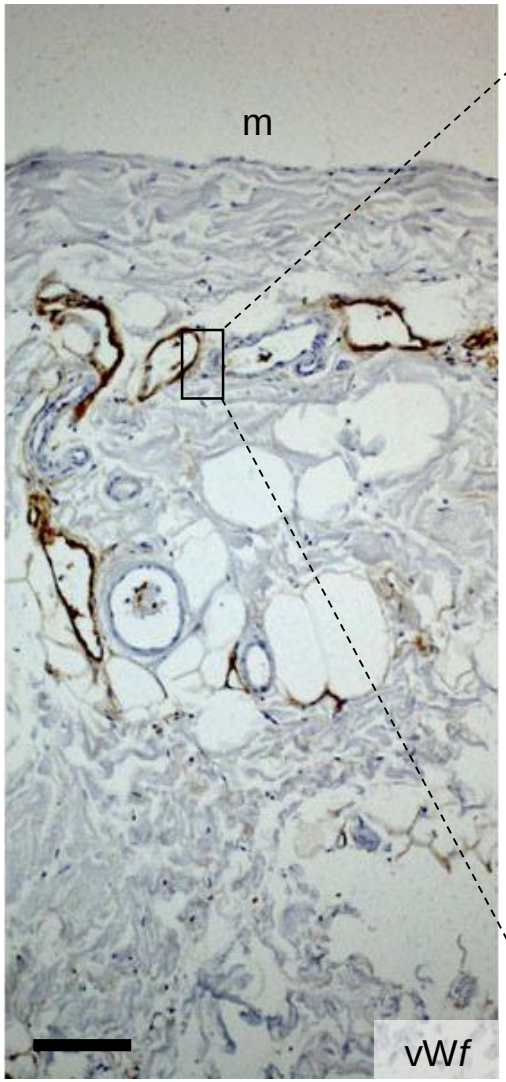
Interstitium:

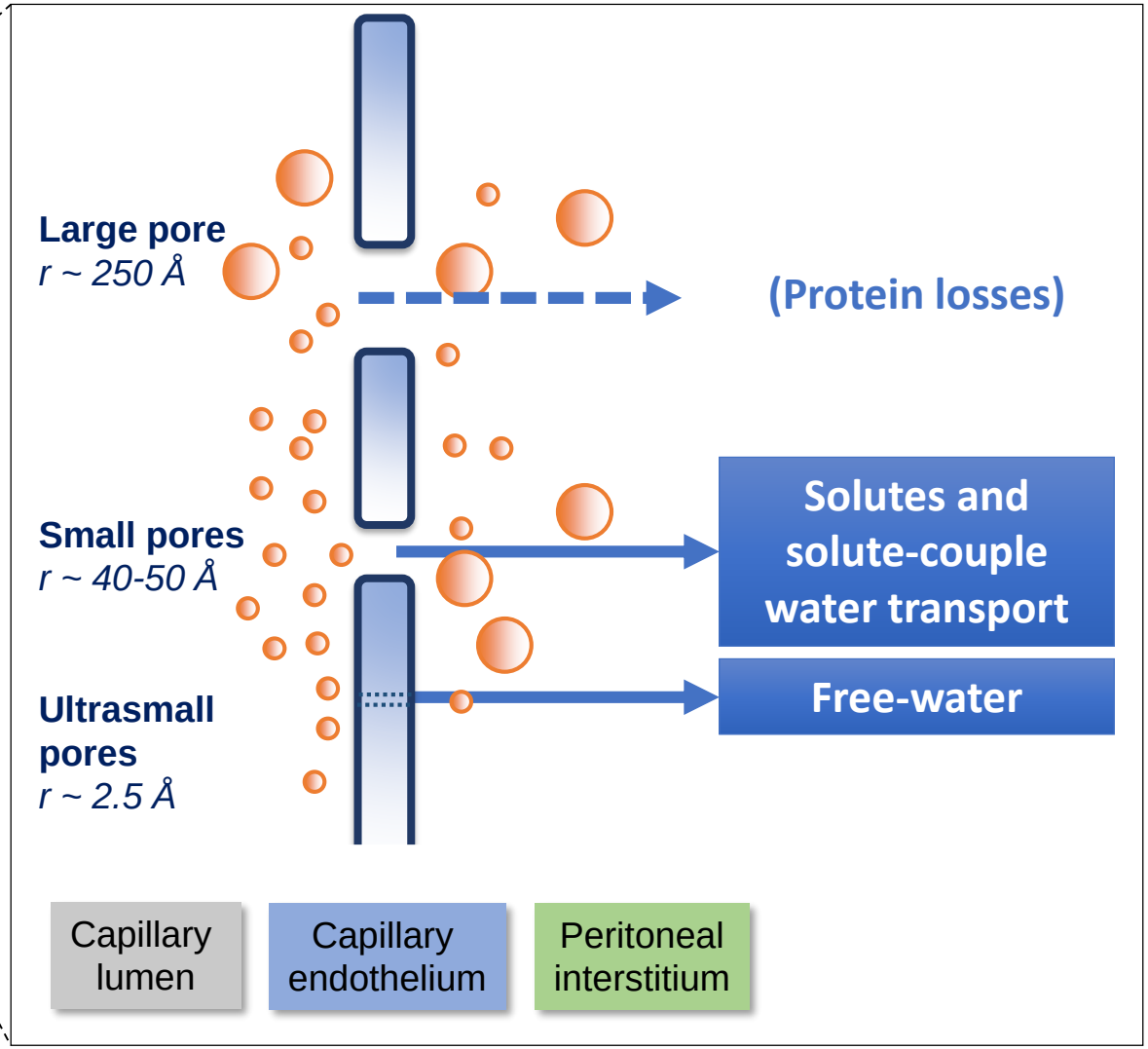
- 'Scaffold'
- Collagen fibres, mucopolysaccharides hydrogel
- Fibroblasts, adipocytes, immune cells (macrophages)

Dense network of capillaries and small vessels:

- Solute and water transport

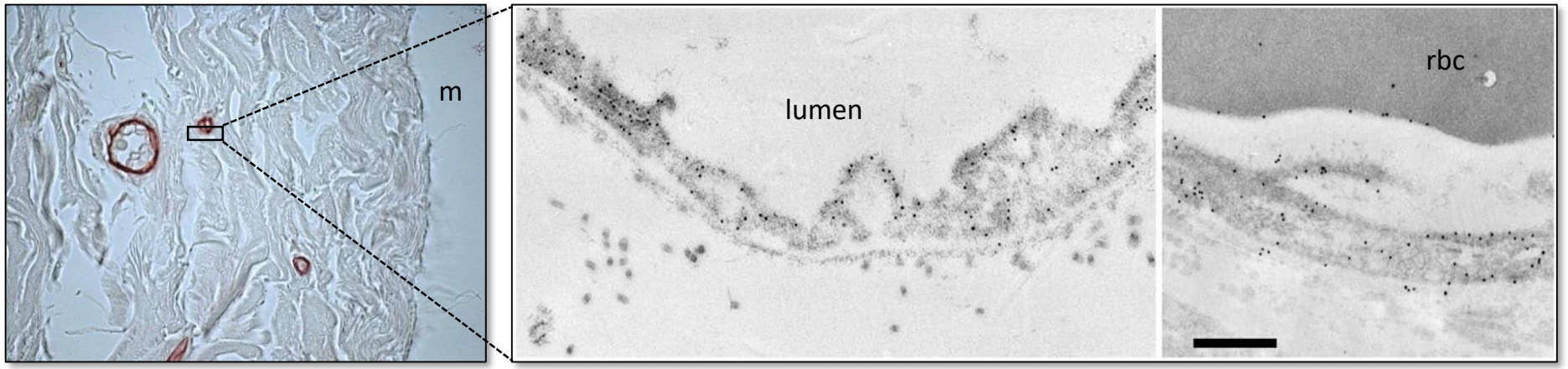
The peritoneal membrane: structure and function

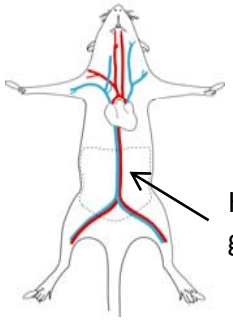


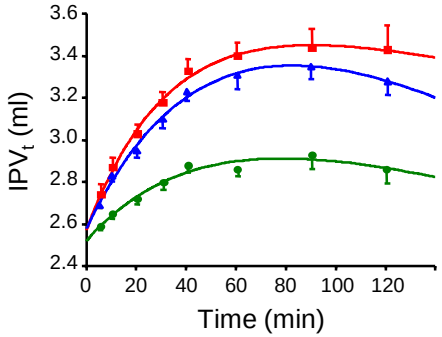


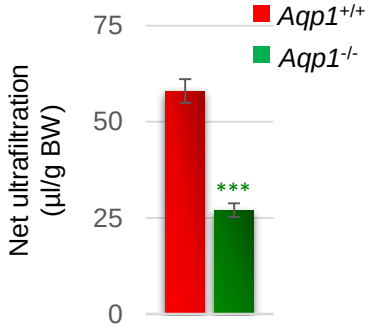
Rippe et al, *Kidney Int* 1991

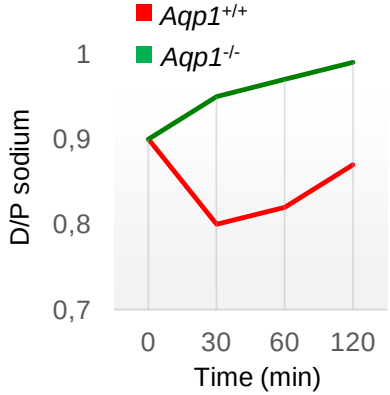
Aquaporin-1 and water transport in PD









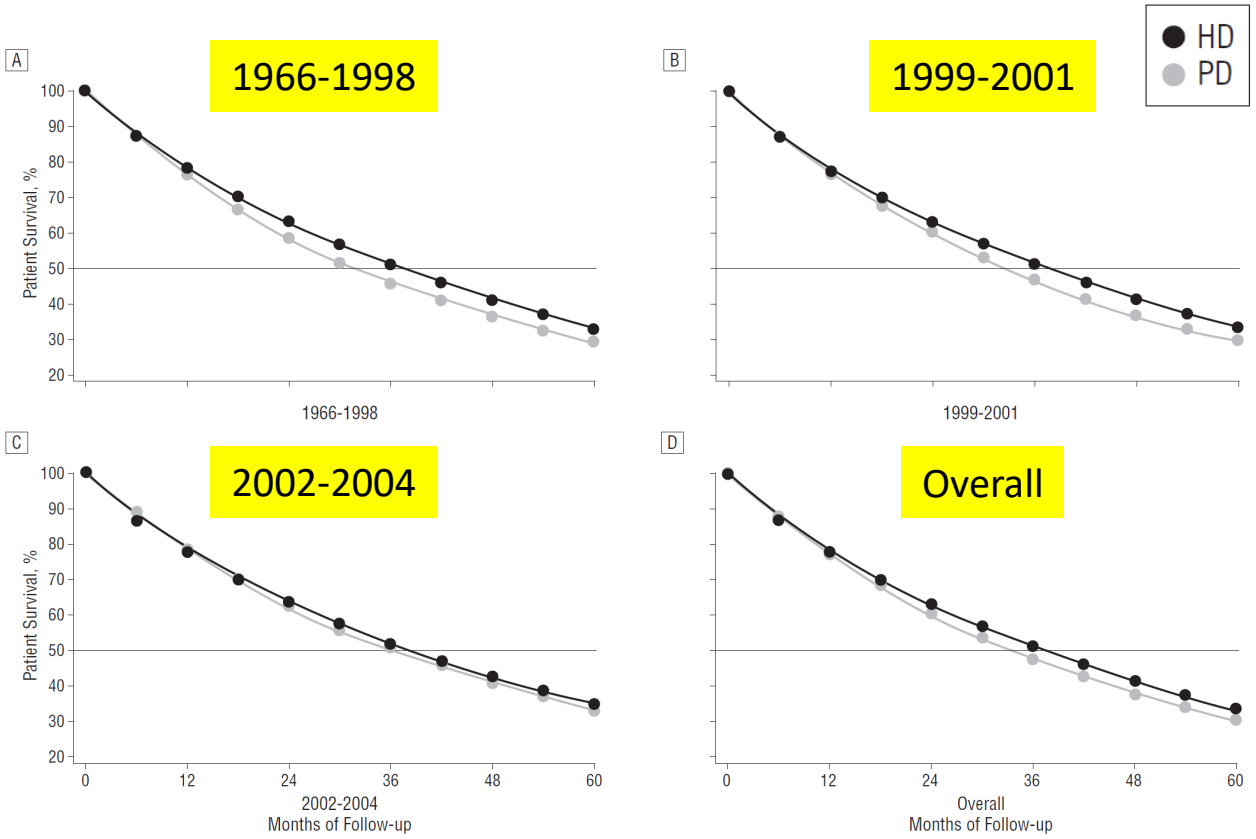


Endothelial AQP1 → ultrasmall pore
50% of water removal in PD

Devuyst et al, *Am J Physiol* 1998 ; Ni et al, *Kidney Int* 2005

Survival rates in PD vs HD

USRDS, 1996-2004 -n = 620 020 patients on HD; 64 406 on PD



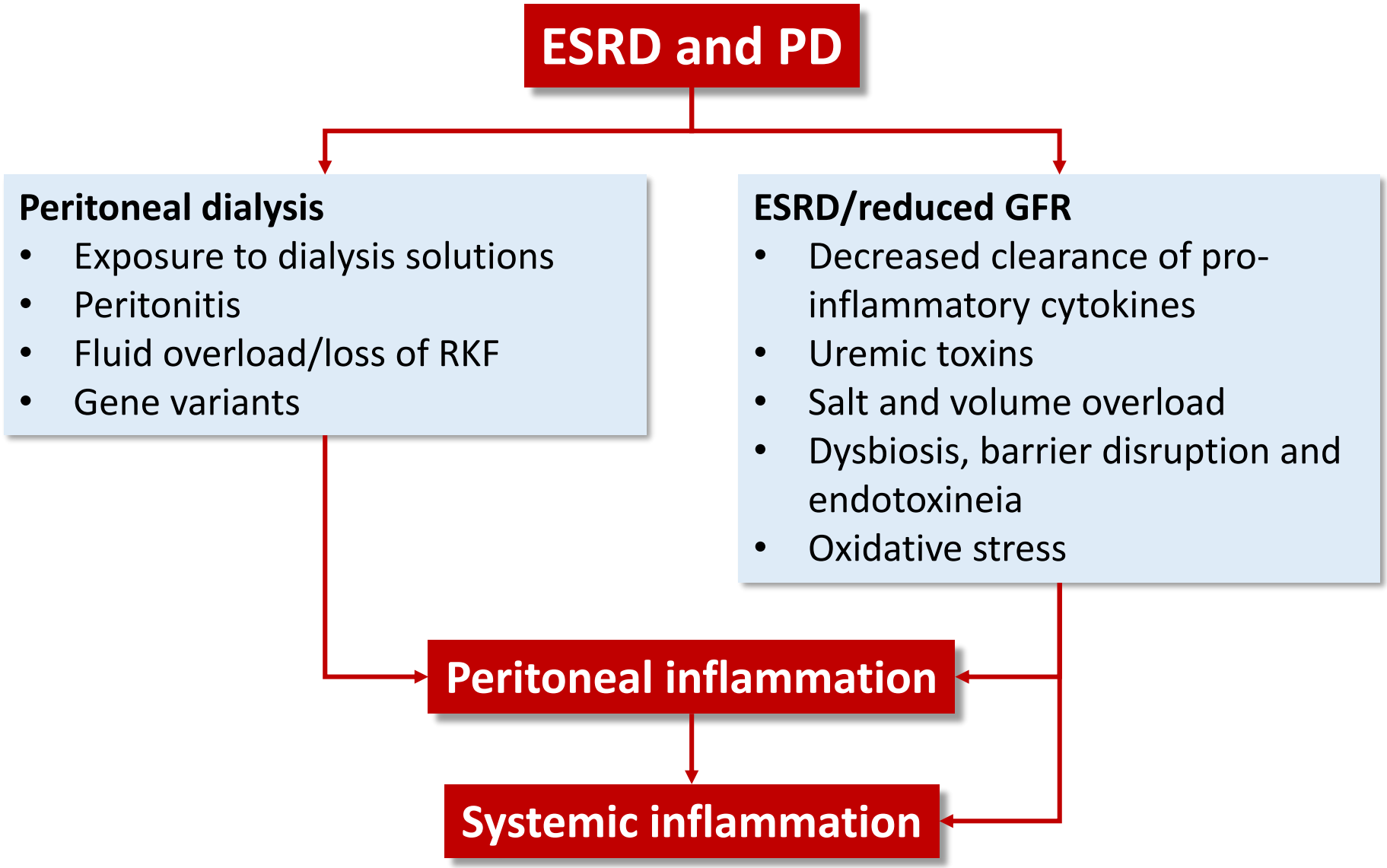
- Similar survival rates - constant improvement for PD
- Specific advantages of PD: flexibility and autonomy, lower costs, safer use

Mehrotra et al, *Arch Int Med* 2011

However, in 2018, PD still has (too many) drawbacks…

1. High prevalence of fluid overload
   (i.e. patients 'fast transporters')
2. Membrane damage, UF/technique failure, and encapsulating peritoneal sclerosis (EPS) in patients on long-term PD
3. Excessive rate of cardiovascular events/mortality

Common link = excess of inflammation


ESRD and PD
Peritoneal dialysis
• Exposure to dialysis solutions
• Peritonitis
• Fluid overload/loss of RKF
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ESRD/reduced GFR
• Decreased clearance of pro-inflammatory cytokines
• Uremic toxins
• Salt and volume overload
• Dysbiosis, barrier disruption and endotoxineia
• Oxidative stress
Peritoneal inflammation
Systemic inflammation

#PD_inflammation

Inflammation, solute transport and the risk of fluid overload

Inflammation, membrane damage and EPS in long-term PD

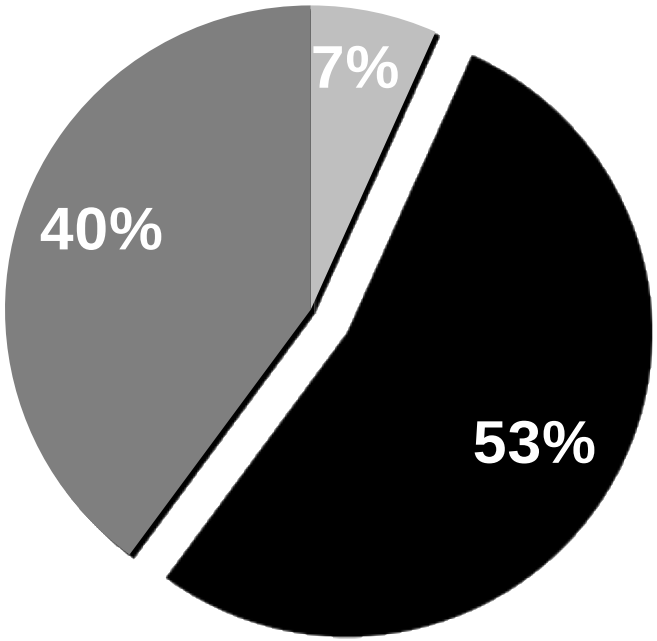
Preventing or modulating peritoneal inflammation to improve outcome in PD

Inflammation and cardiovascular mortality

High prevalence of fluid overload in PD patients

EuroBCM study
639 prevalent PD patients
28 centres, 6 countries

BCM Body Composition Monitor

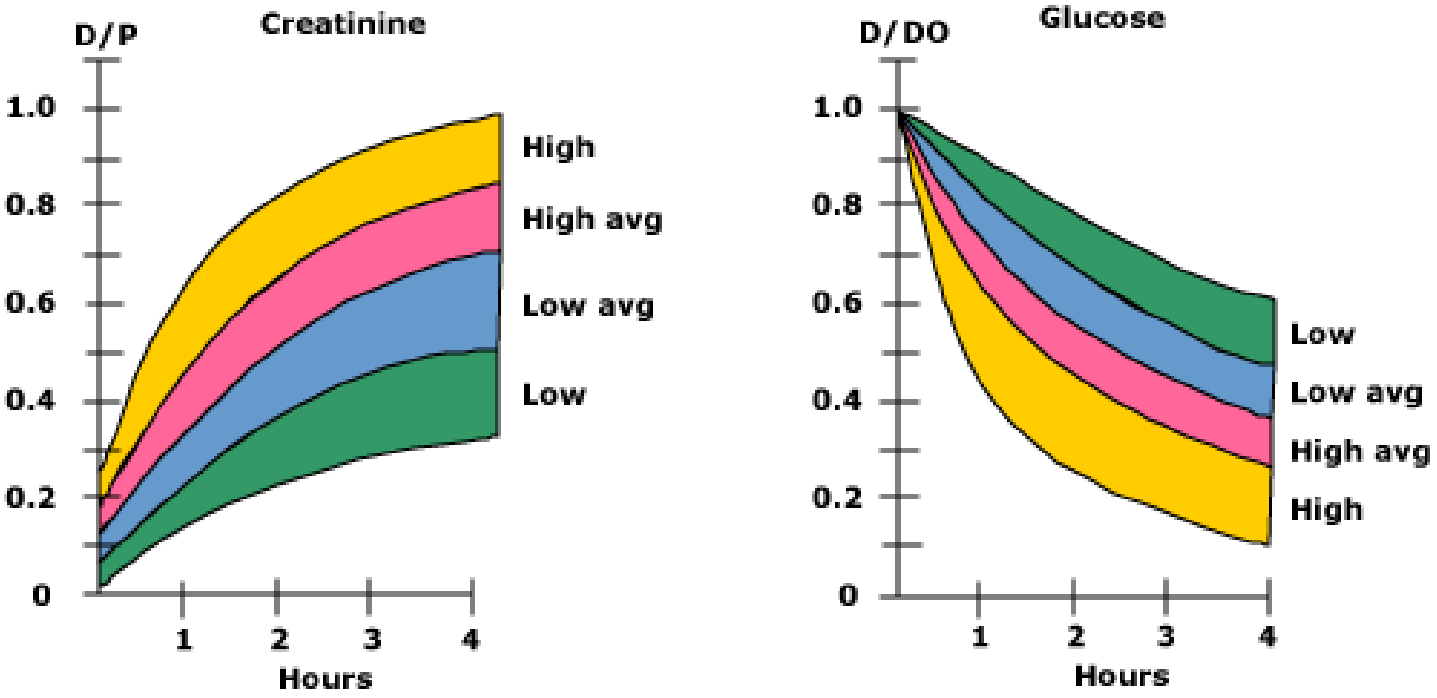


One of the main risk factors to develop hypervolemia:
'fast transport' status

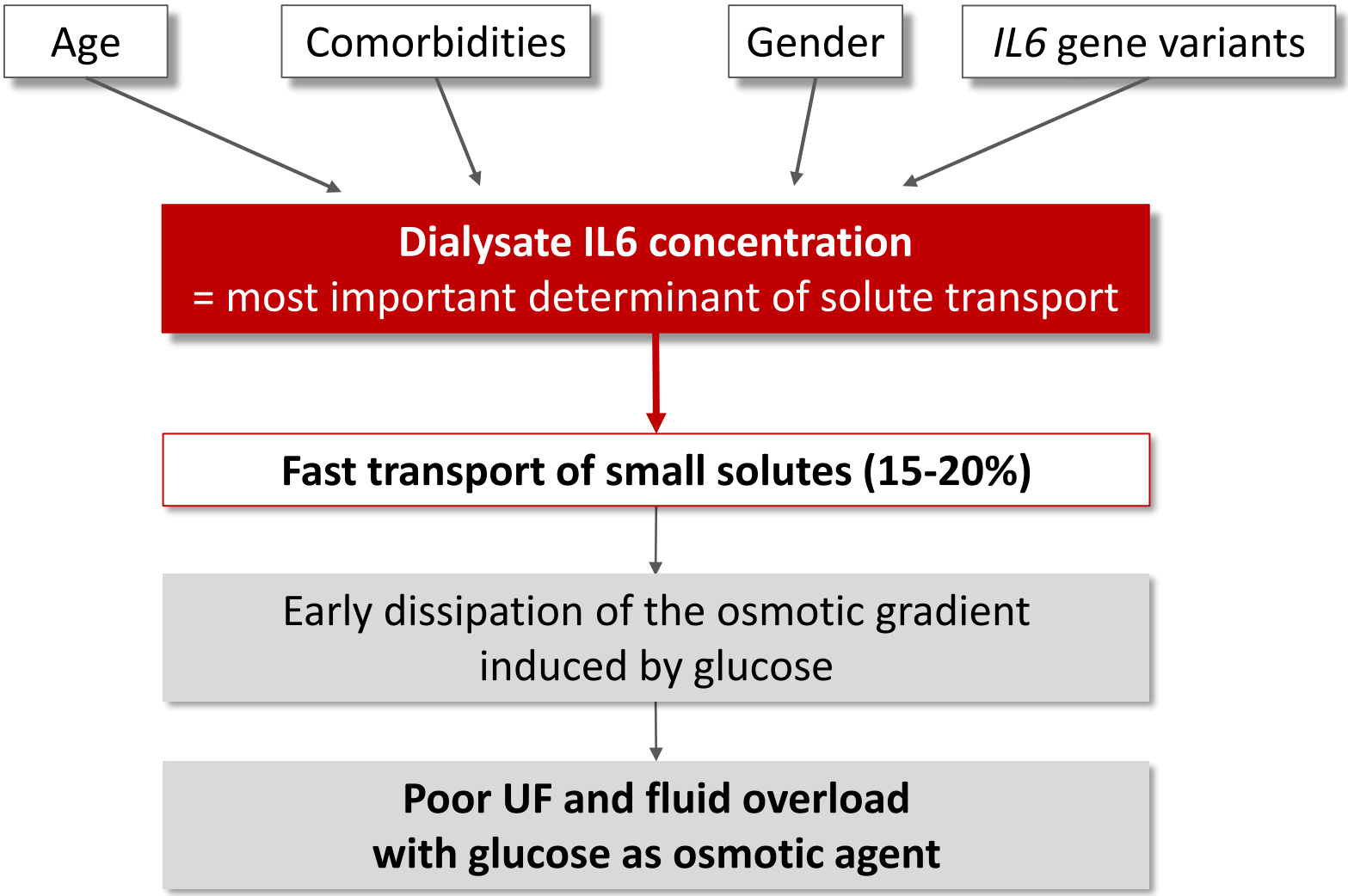
Van Biesen et al, PlosOne 2011

Fast transport status?

Peritoneal equilibration tests → kinetics of D/P_{creat}
to evaluate peritoneal solute transport



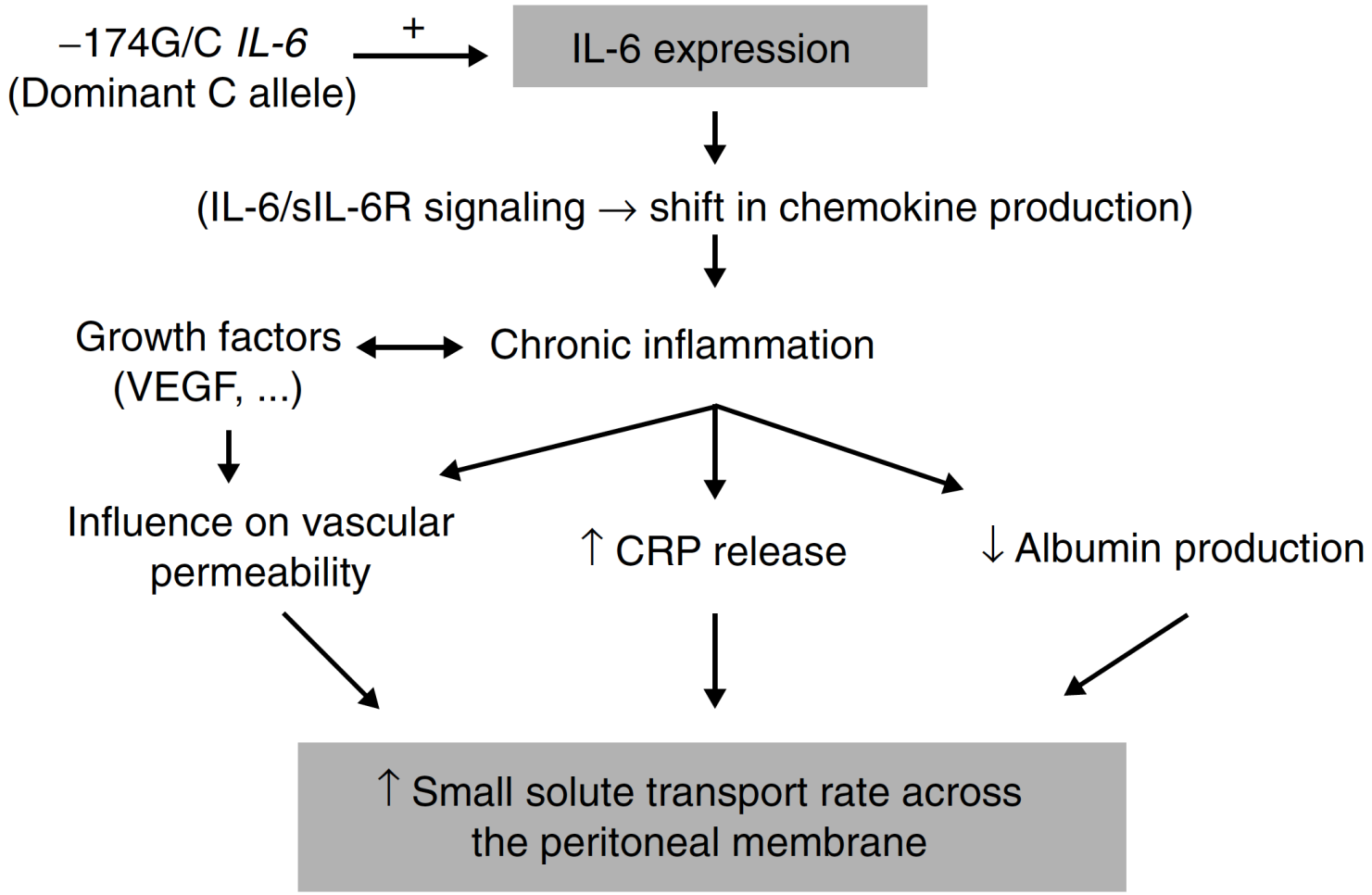
Peritoneal inflammation, solute transport and poor UF



Lambie et al, *J Am Soc Nephrol* 2013

Genetic predisposition to peritoneal inflammation?

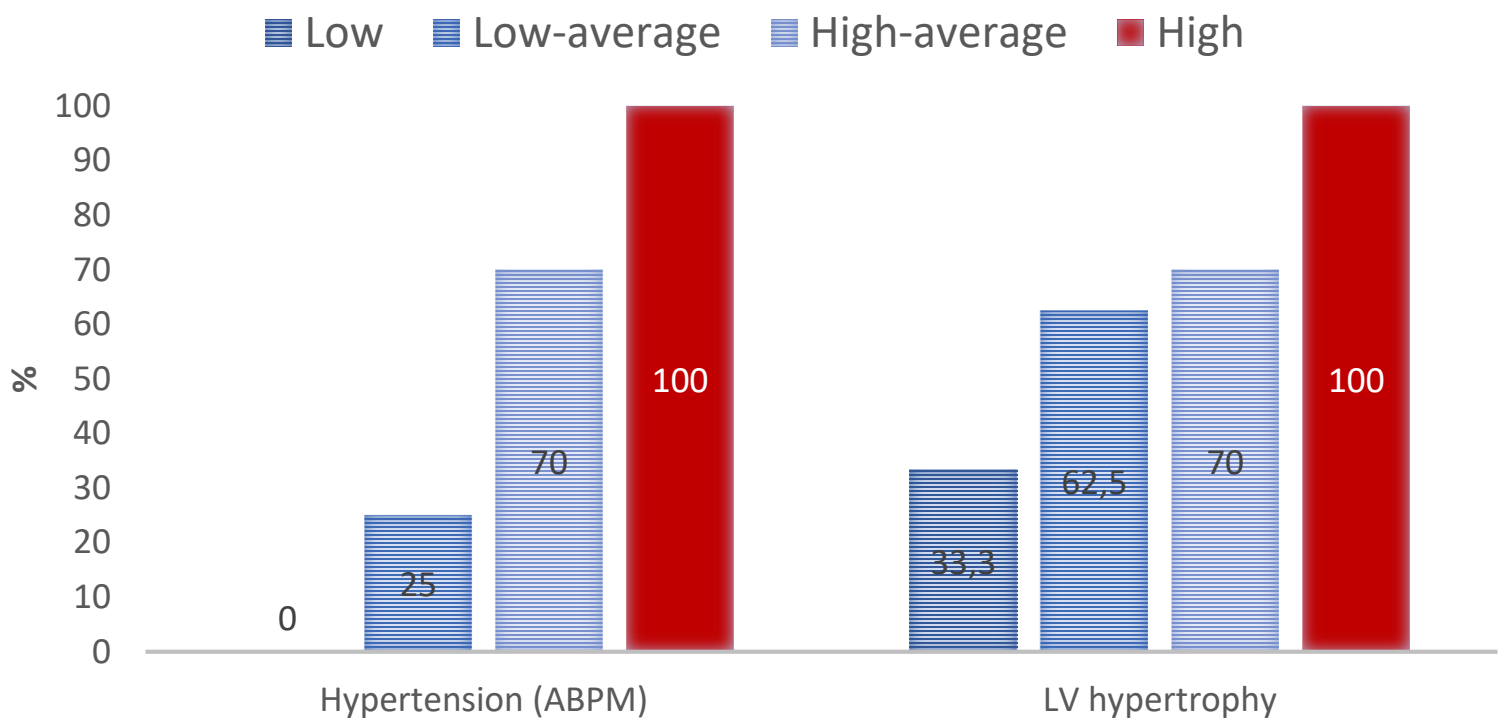
IL6 gene variants and solute transport



Gillerot…Devuyst, *Kidney Int* 2005

Fast transport status leads to fluid overload

Prevalence of hypertension (24-h ABPM) and LV hypertrophy in prevalent PD patients according to transport status

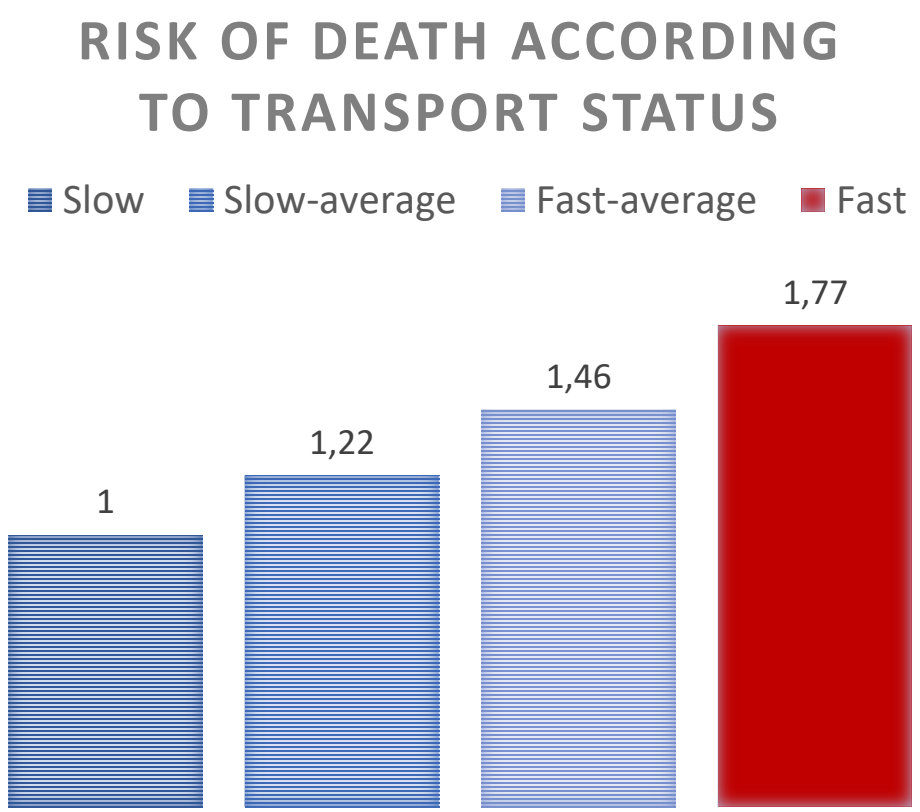


Patients with fast transport status on CAPD
Fluid overload ⟶ Increased risk of death from cardiovascular events

Tongul, *Perit Dial Int* 2003

Impact of baseline peritoneal solute transport on the risk of death

2006 – meta-analysis - 20 observational studies
Mainly CAPD, glucose only

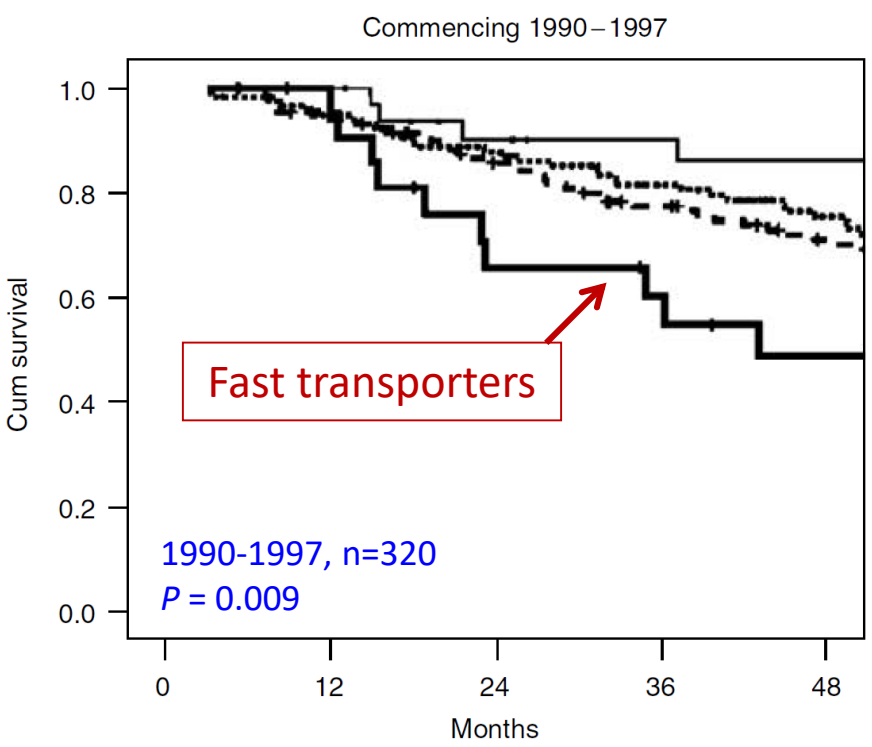


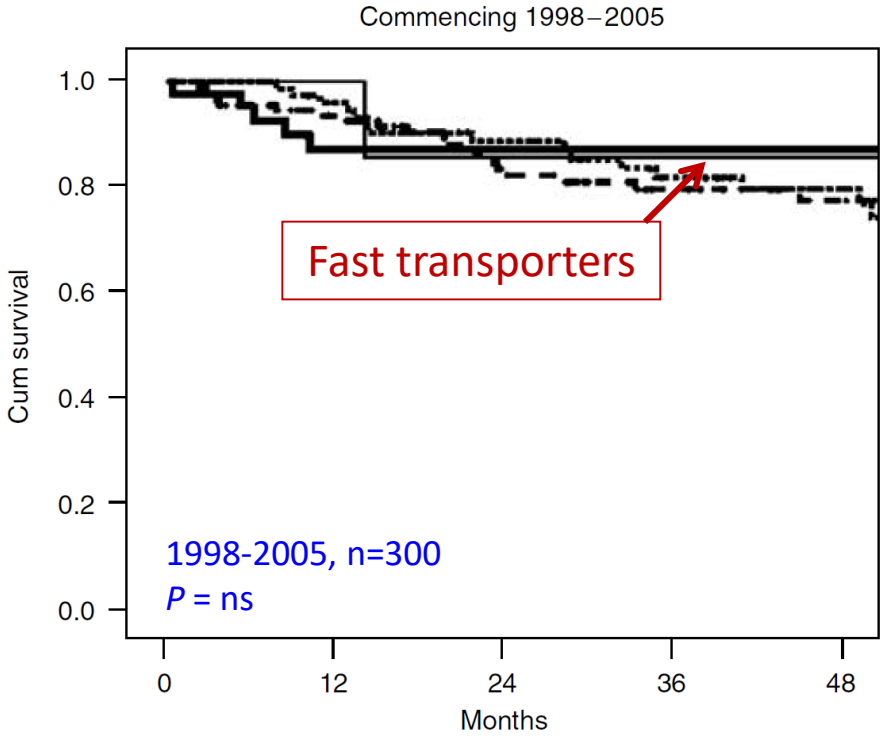
Fast transport status → higher mortality risk

Brimble, *J Am Soc Nephrol* 2006

Individualizing PD prescription improves outcome in fast transporters

Survival on PD according to transport category at the start of treatment (Stoke experience)





CAPD only
Glucose as the only osmotic agent

Automated PD with short dwells
Use of **icodextrin**

Davies, *Kidney Int* 2006

#PD_inflammation

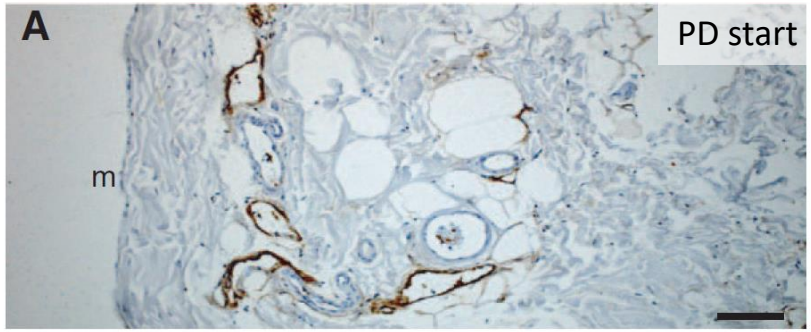
Inflammation, solute transport and the risk of fluid overload

Inflammation, membrane damage and EPS in long-term PD

Preventing or modulating peritoneal inflammation to improve outcome in PD

Inflammation and cardiovascular mortality

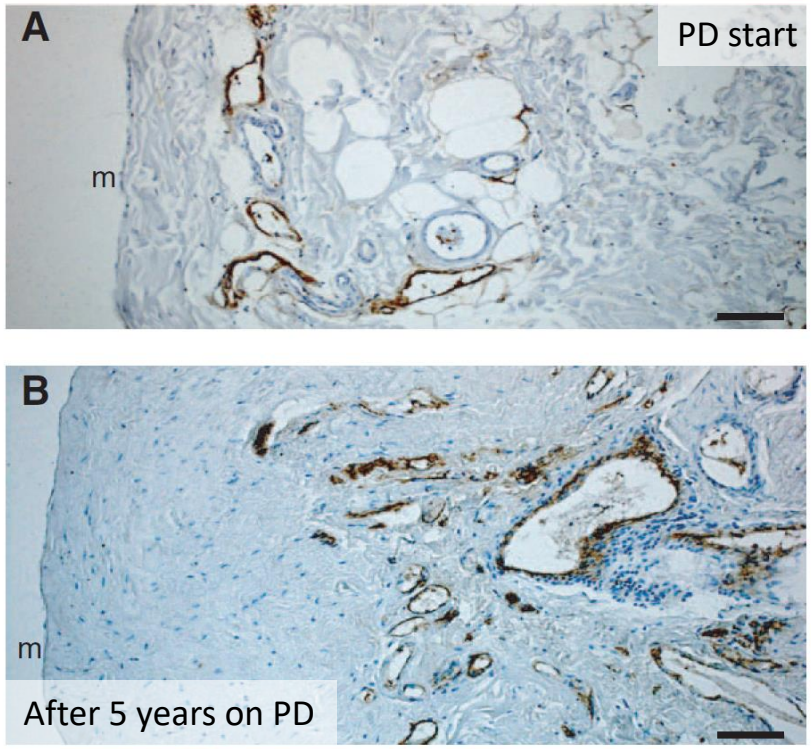
Alterations of the membrane in long-term PD



The peritoneum is a living tissue

Devuyst, *J Am Soc Nephrol* 2010; Davies, *J Am Soc Nephrol* 2004

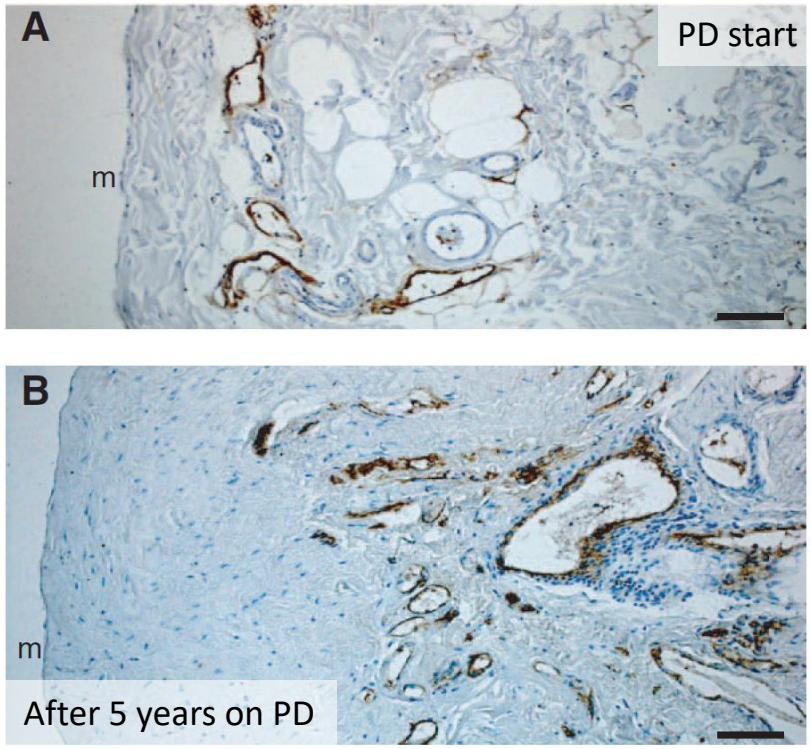
Alterations of the membrane in long-term PD

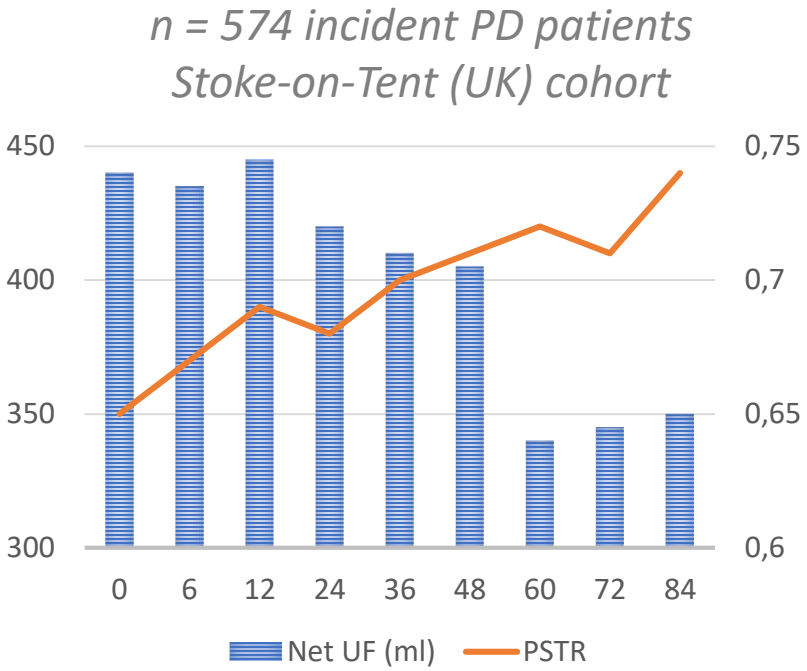


- Loss of mesothelial cell integrity
- Submesothelial fibrosis
- Vascular proliferation/angiogenesis

Devuyst, *J Am Soc Nephrol* 2010; Davies, *J Am Soc Nephrol* 2004

Alterations of the membrane in long-term PD

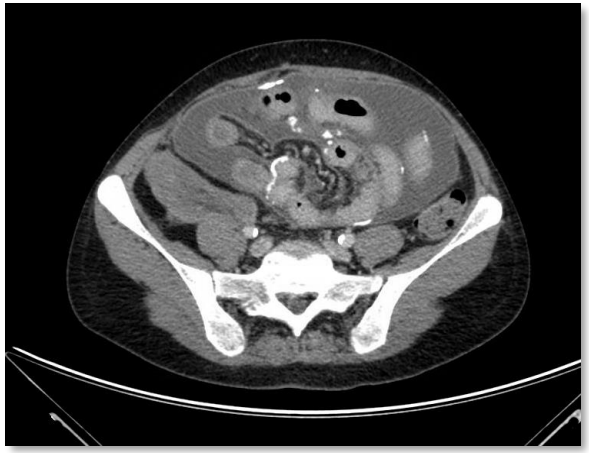
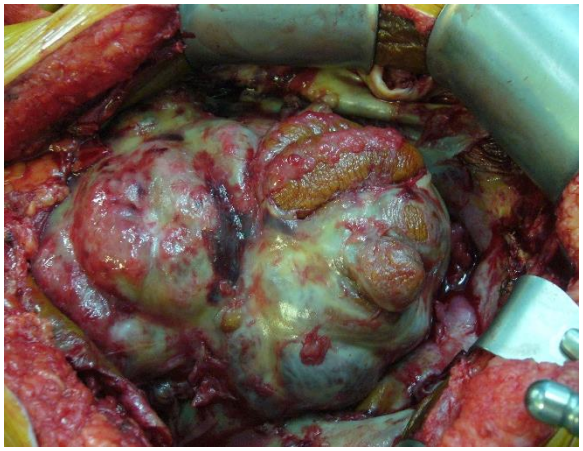
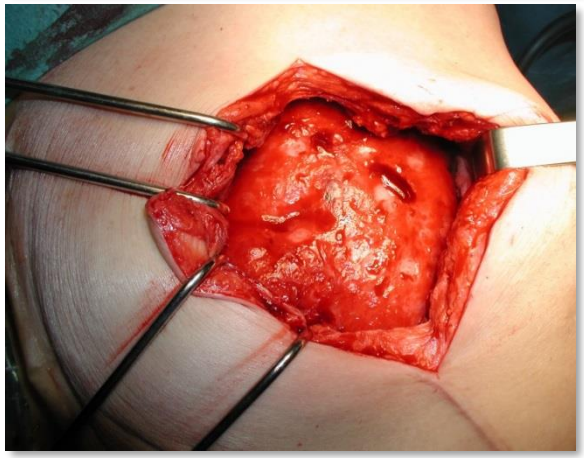




Progressive increase in solute transport
Loss of UF capacity

Devuyst, *J Am Soc Nephrol* 2010; Davies, *J Am Soc Nephrol* 2004

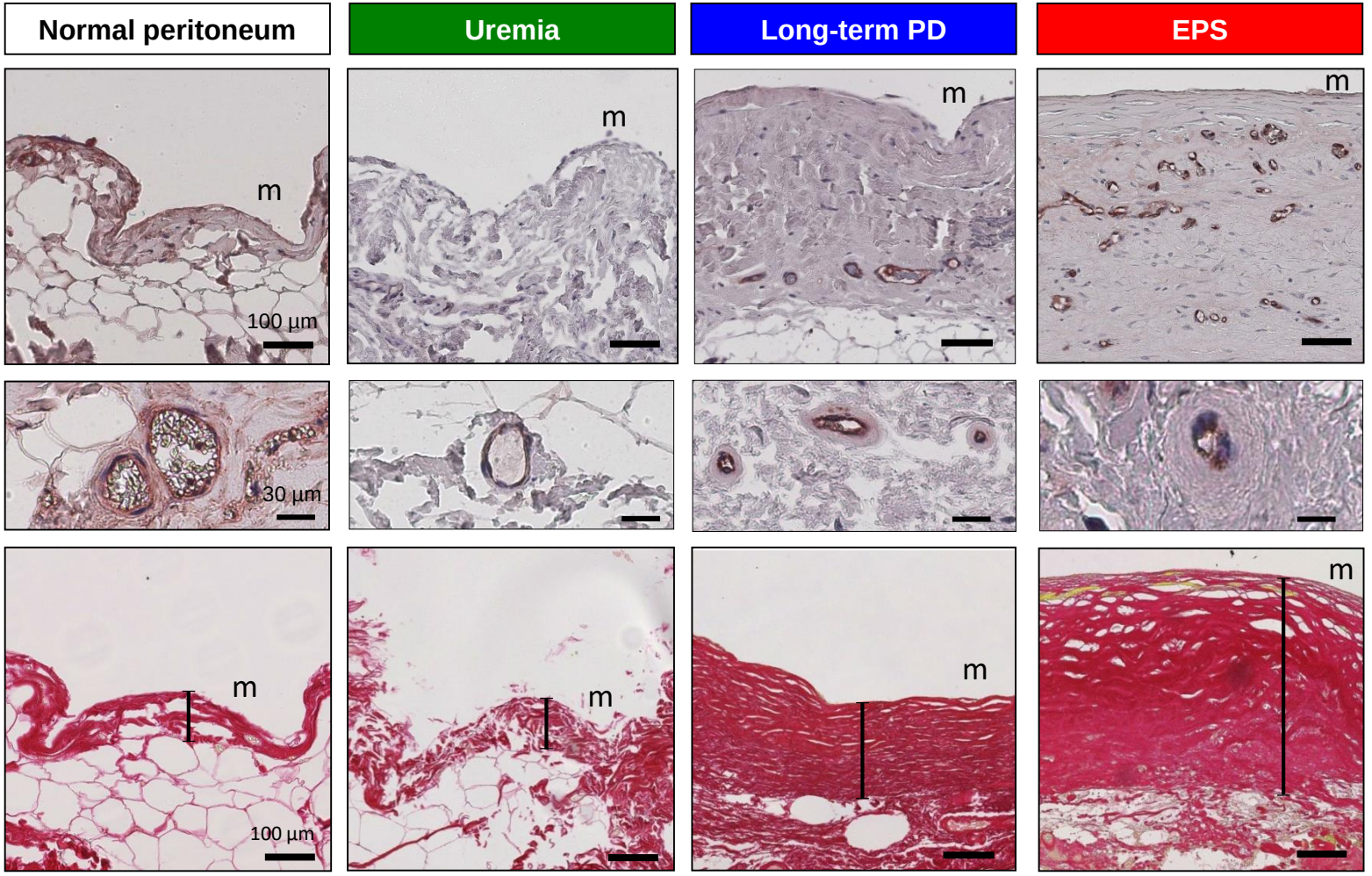
Encapsulating peritoneal sclerosis (EPS)

Very uncommon complication of long-term PD - Excessive fibrogenic response in the peritoneal membrane that encapsulates the bowel, leading to bowel obstruction

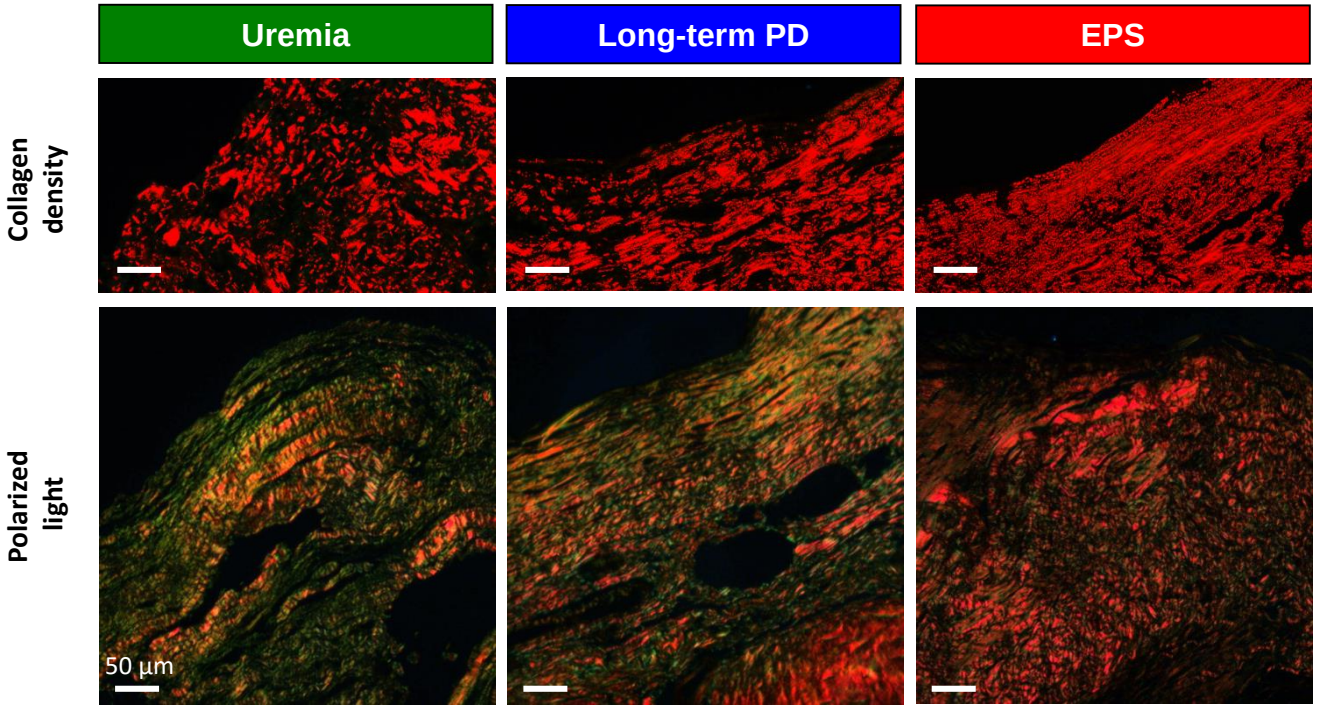
Courtesy Prof. C. Verger, T. Augustine and E. Goffin

Modifications in the membrane of patients with EPS

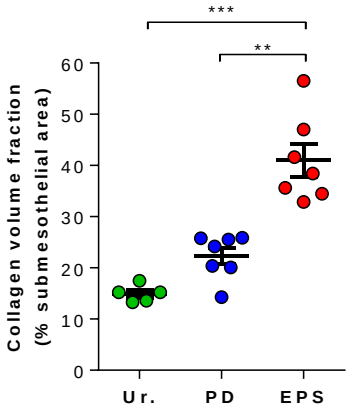


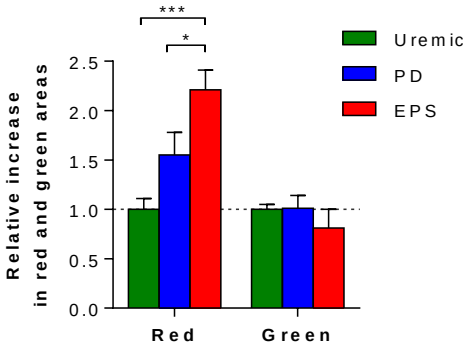
Morelle…Devuyst, Goffin, *J Am Soc Nephrol* 2015

Qualitative changes in the interstitium of patients with EPS



Polarized light	Green	Orange-red
Fiber Ø	20-40 nm	> 60 nm
Collagen	Type III	Type I
Wound-healing	Early stages	Late stages

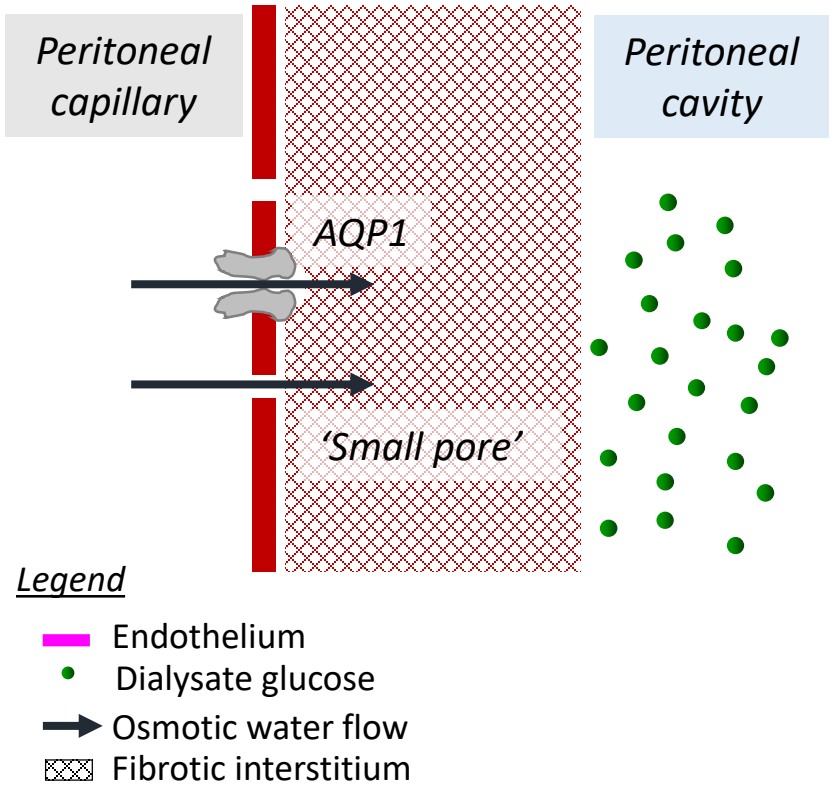


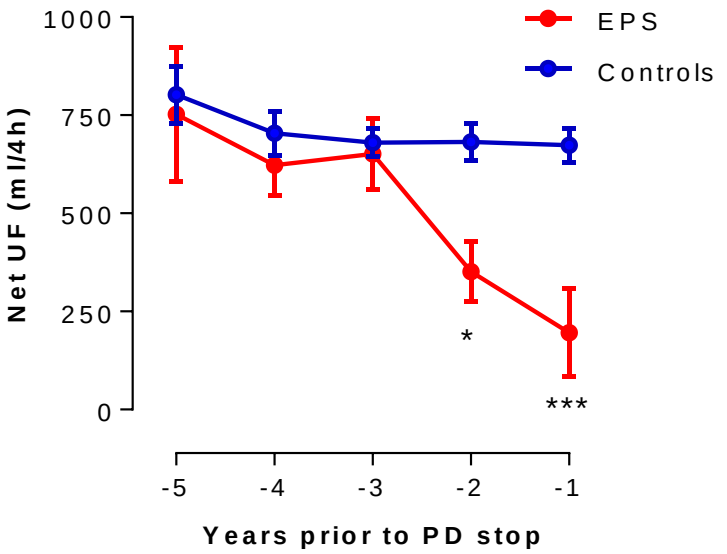


Morelle…Devuyst, Goffin, *J Am Soc Nephrol* 2015

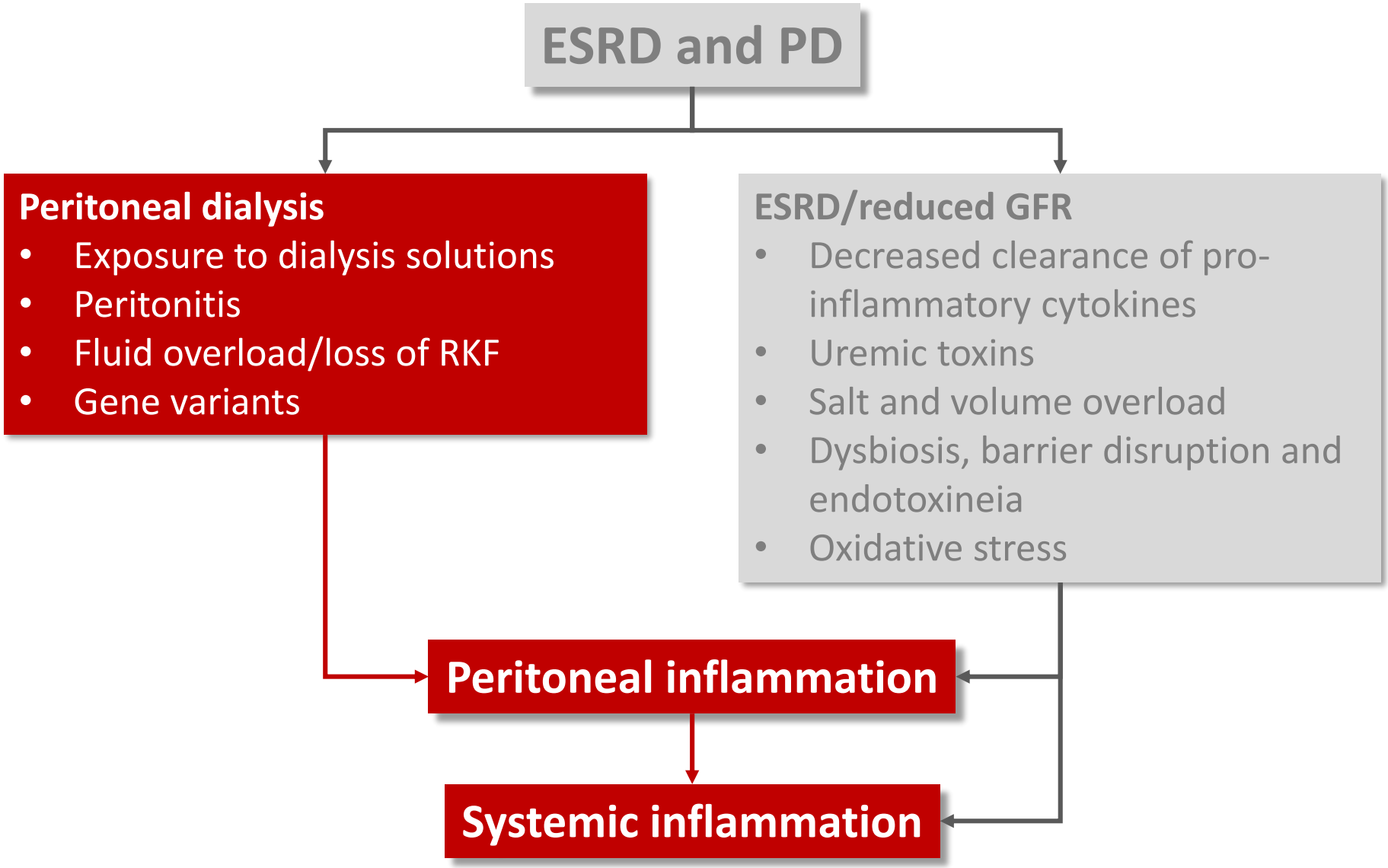
EPS and loss of peritoneal osmotic conductance

234 incident PD patients, 1994-2013, Saint-Luc Academic Hospital, Brussels
7 patients with EPS *versus* 28 (4:1) matched controls – yearly 3.86% glucose-based PET





Morelle…Devuyst, Goffin, *J Am Soc Nephrol* 2015


ESRD and PD
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ESRD/reduced GFR
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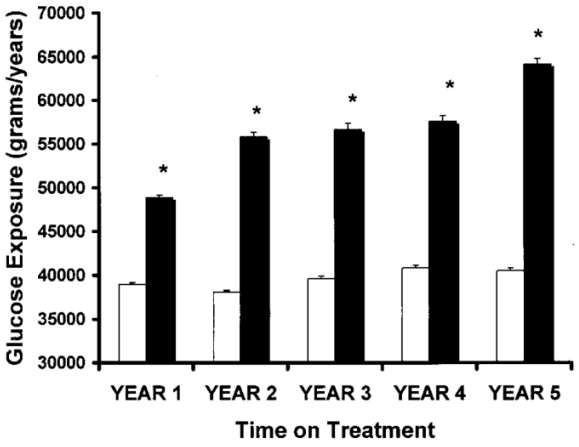
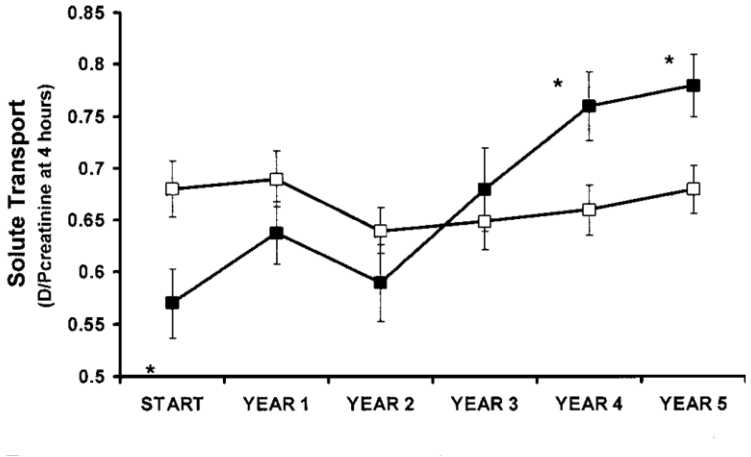
Peritoneal inflammation
Systemic inflammation

Exposure to glucose and ‘bio-incompatible’ solutions

Excessive glucose exposure



Acceleration of solute transport

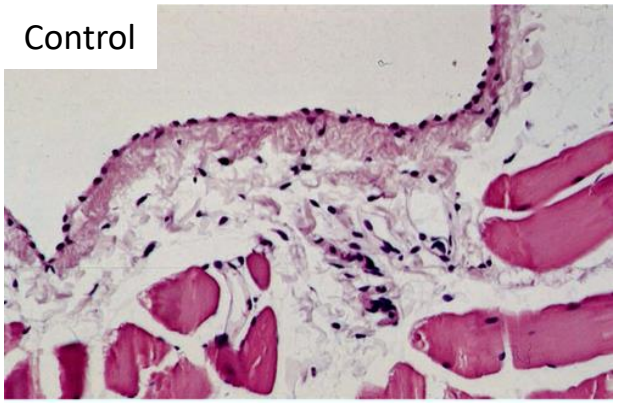


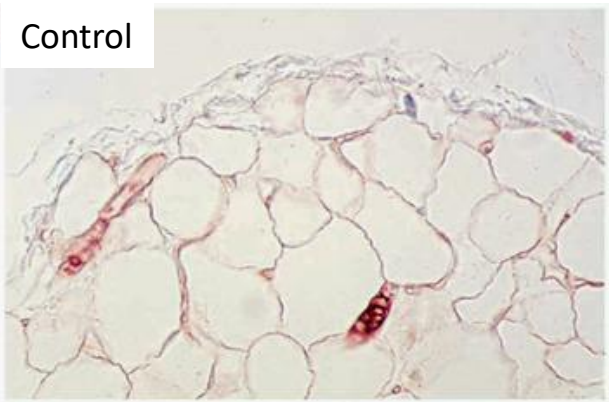
Bio-incompatibility
of ‘conventional’
dialysis solution

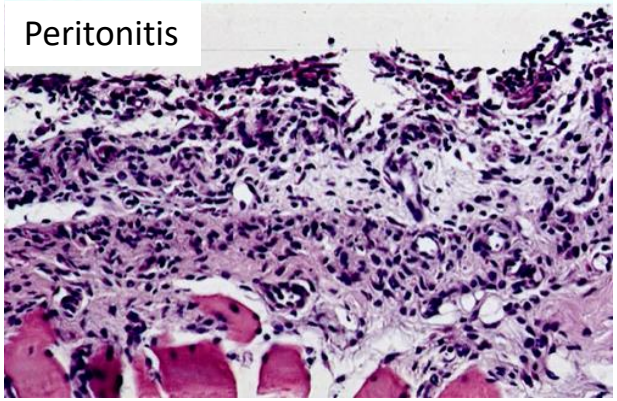
- **High glucose concentration**
- **Acidic pH/lactate buffer**
- **GDPs et AGEs (heat sterilization)**

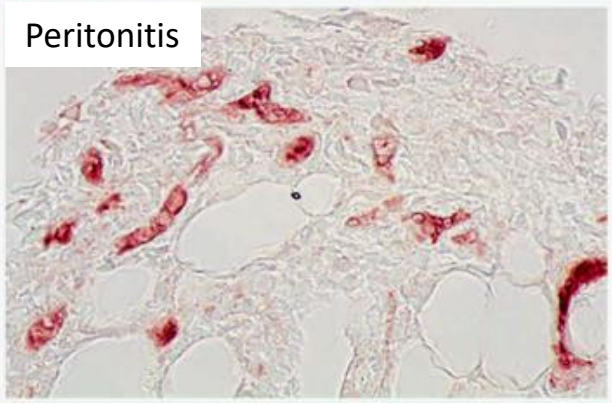
Davies et al, *J Am Soc Nephrol* 2001

PD-associated peritonitis









Inflammatory infiltrate

Vascular proliferation

Staph. epidermidis-induced peritonitis (5 days)

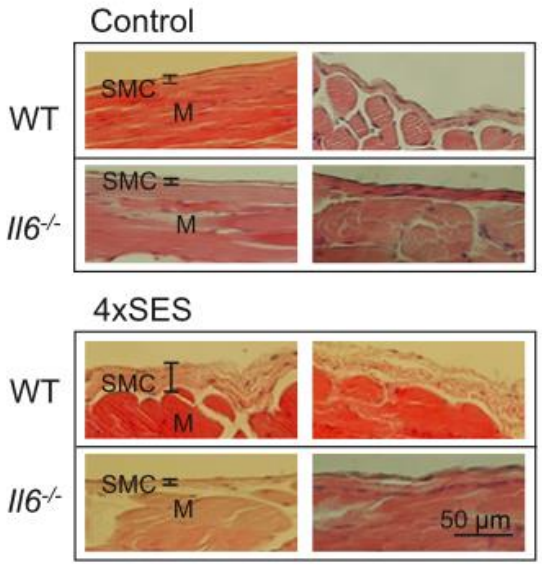
- Fast solute transport
- Loss of UF
- Increased morbidity and mortality

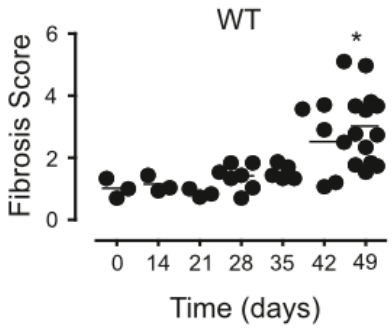
Combet et al. JASN 10: 2185-96, 1999

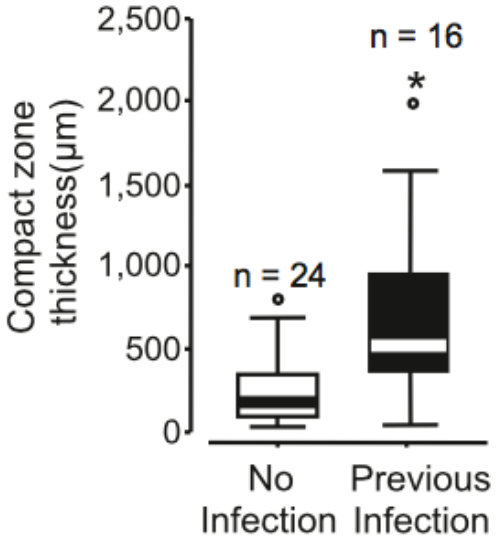
Repeat episodes of peritonitis, inflammation and fibrosis

i.p. *staph. epidermidis*

Repeat



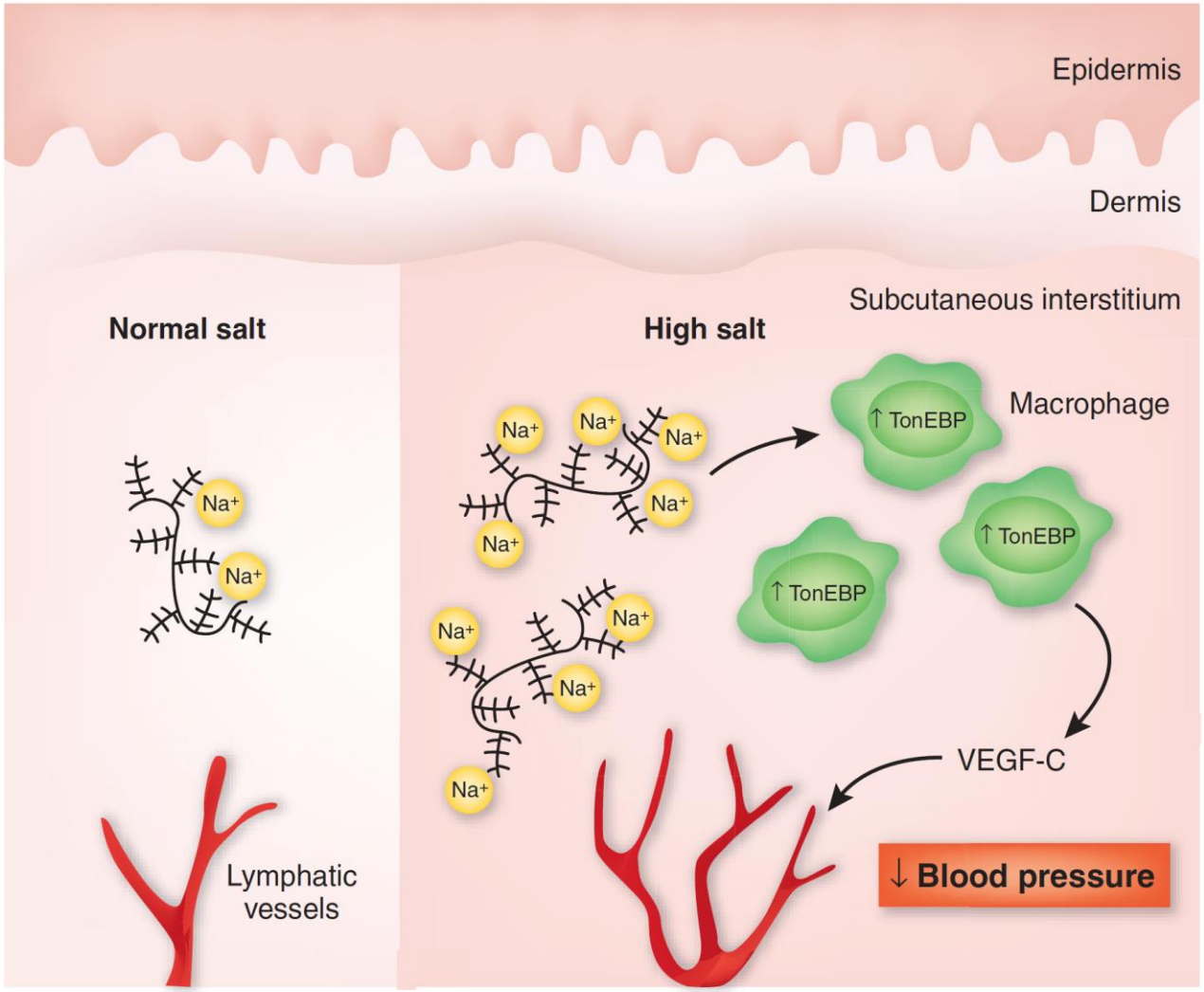




Repeat/severe episodes of peritonitis⟶ peritoneal fibrosis (IL-6 dependent)

Fielding, Jones…Topley, Jones, *Immunity* 2014

Accumulation of salt, osmo-sensing and inflammation



Positive salt balance

↓

Accumulation of sodium in subcutaneous interstitium

↓

Osmosensing by macrophages

↓

Inflammation and vascular proliferation

↓

'Buffer compartment' to prevent/reduce high BP

Machnik et al, *Nat Med* 2009

Nephrol Dial Transplant (2010) 25: 1688–1696
doi: 10.1093/ndt/gfq036
Advance Access publication 11 February 2010

Preliminary Communication

NDT
Nephrology Dialysis Transplantation

Salt intake induces epithelial-to-mesenchymal transition of the peritoneal membrane in rats

High salt diet
(non-uremic rats)

↓

Release of TGFβ and IL-6

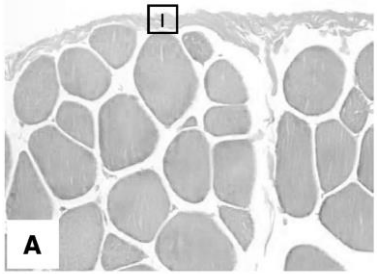
↓

Peritoneal inflammation

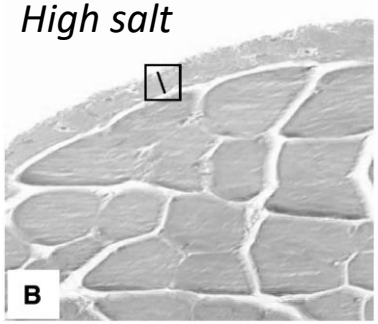
↓

Peritoneal angiogenesis
and fibrosis

Normal

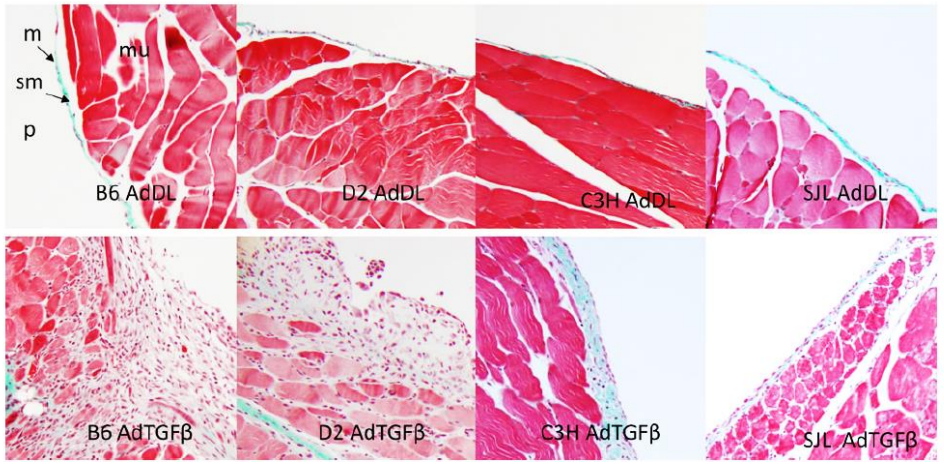


High salt



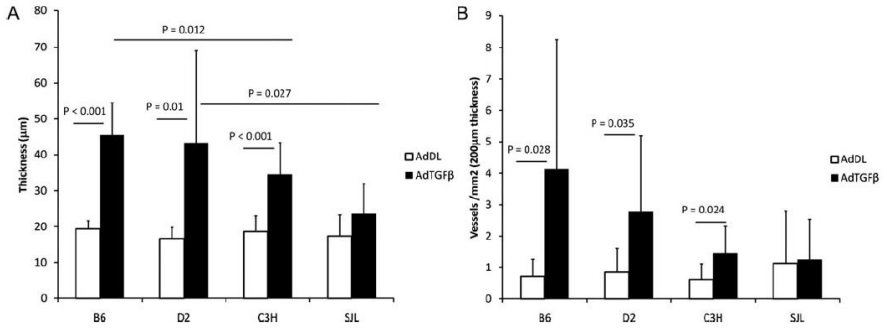
Pletinck et al, *Nephrol Dial Transplant* 2010

Transforming growth factor β-induced peritoneal fibrosis is mouse strain dependent*



Fibrotic response to TGF-β1

Genetic background influences angiogenic and fibrotic responses in the peritoneal membrane



Margetts et al, *Nephrol Dial Transplant* 2013

Peritoneal inflammation precedes encapsulating peritoneal sclerosis: results from the GLOBAL Fluid Study

Nested, case-control study, 11 EPS cases vs. 26 matched PD controls (centre and PD duration), GLOBAL fluid study

Dependent variable	EPS	
	Coefficient (95% CI)	P-value
Dialysate		
IL-6	0.79 (0.03, 1.56)*	0.043
IL-1β	1.06 (−0.11, 2.23)	0.075
IFN-γ	0.62 (−0.06, 1.29)	0.073
TNF-α	0.64 (0.23, 1.05)*	0.002
Plasma		
IL-6	0.42 (0.07, 0.78)*	0.020
IL-1β	0.66 (−0.65, 1.97)	0.33
IFN-γ	−0.30 (−0.69, 0.09)	0.14
TNF-α	0.13 (−0.13, 0.39)	0.31
Solute transport		
D/PCr	0.024 (−0.054, 0.102)	0.55

Lambie et al, *Nephrol Dial Transplant* 2016

#PD_inflammation

Inflammation, solute transport and the risk of fluid overload

Inflammation, membrane damage and EPS in long-term PD

Preventing or modulating peritoneal inflammation to improve outcome in PD

Inflammation and cardiovascular mortality

ISPD statement

Length of Time on Peritoneal Dialysis and Encapsulating Peritoneal Sclerosis: Position Paper for ISPD – Update 2017

Edwina A Brown, Joanne Bargman, Wim van Biesen, Ming-Yang Chang, Frederic O Finkelstein, Helen Hurst, David W Johnson, Hideki Kawanishi, Mark Lambie, Thyago Proença de Moraes, Johann Morelle, Graham Woodrow

Peritoneal Dialysis International 2017

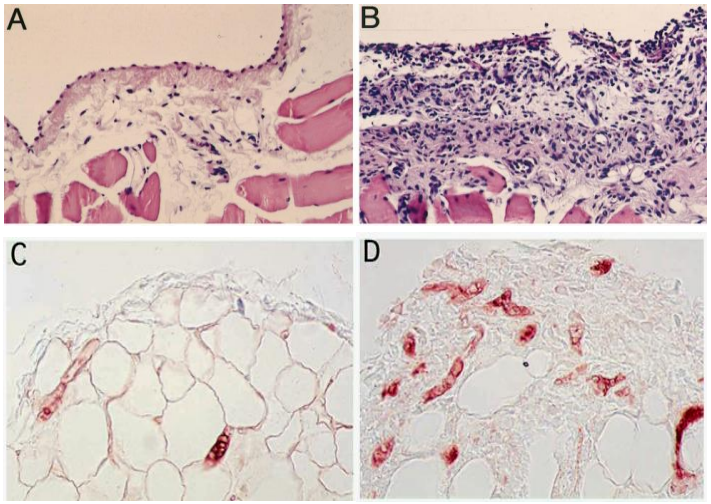
SUMMARY STATEMENTS

5. **No single strategy to reduce risk of EPS has been proven in clinical trials, but there is some evidence to support the following:**
    1. **Minimising dialysate glucose exposure, although it is important to ensure that fluid volume status is not compromised as a result**
    2. **Preventing acute PD-related peritonitis using interventions recommended by the ISPD Peritonitis Guidelines**
    3. **Use of neutral pH, low glucose-degradation product dialysis solutions (low-grade evidence only)**

Peritoneal Dialysis International 2017

Modulating the inflammatory response during peritonitis to improve outcome?

In PD-associated peritonitis, the inflammatory response is a ‘double-edged sword’



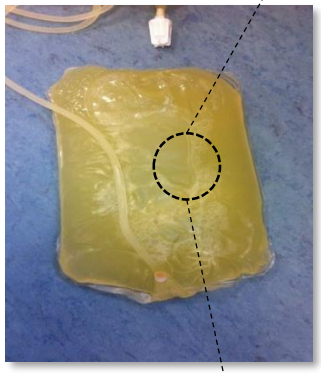
Inflammation helps clearing pathogens…

…but also contributes to the burden of peritonitis

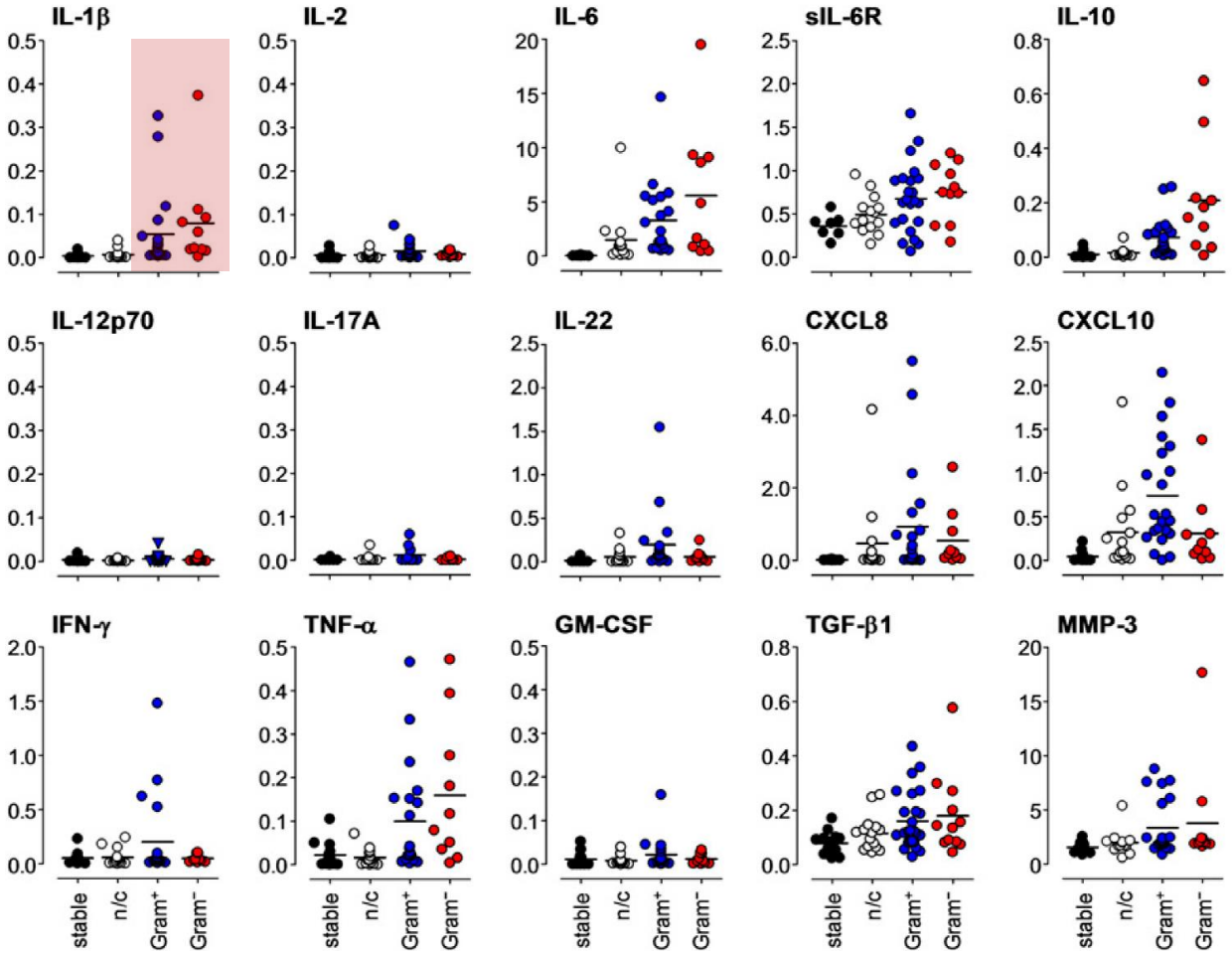
- Excess mortality
- Damage to the peritoneal membrane
  - Acute phase: angiogenesis, inflammatory infiltration and loss of ultrafiltration
  - Long-term: peritoneal fibrosis, membrane and technique failure

Too much inflammation → harmful

IL-1β release during PD-associated peritonitis



Peritoneal levels in stable PD patients and on day 1 of acute peritonitis

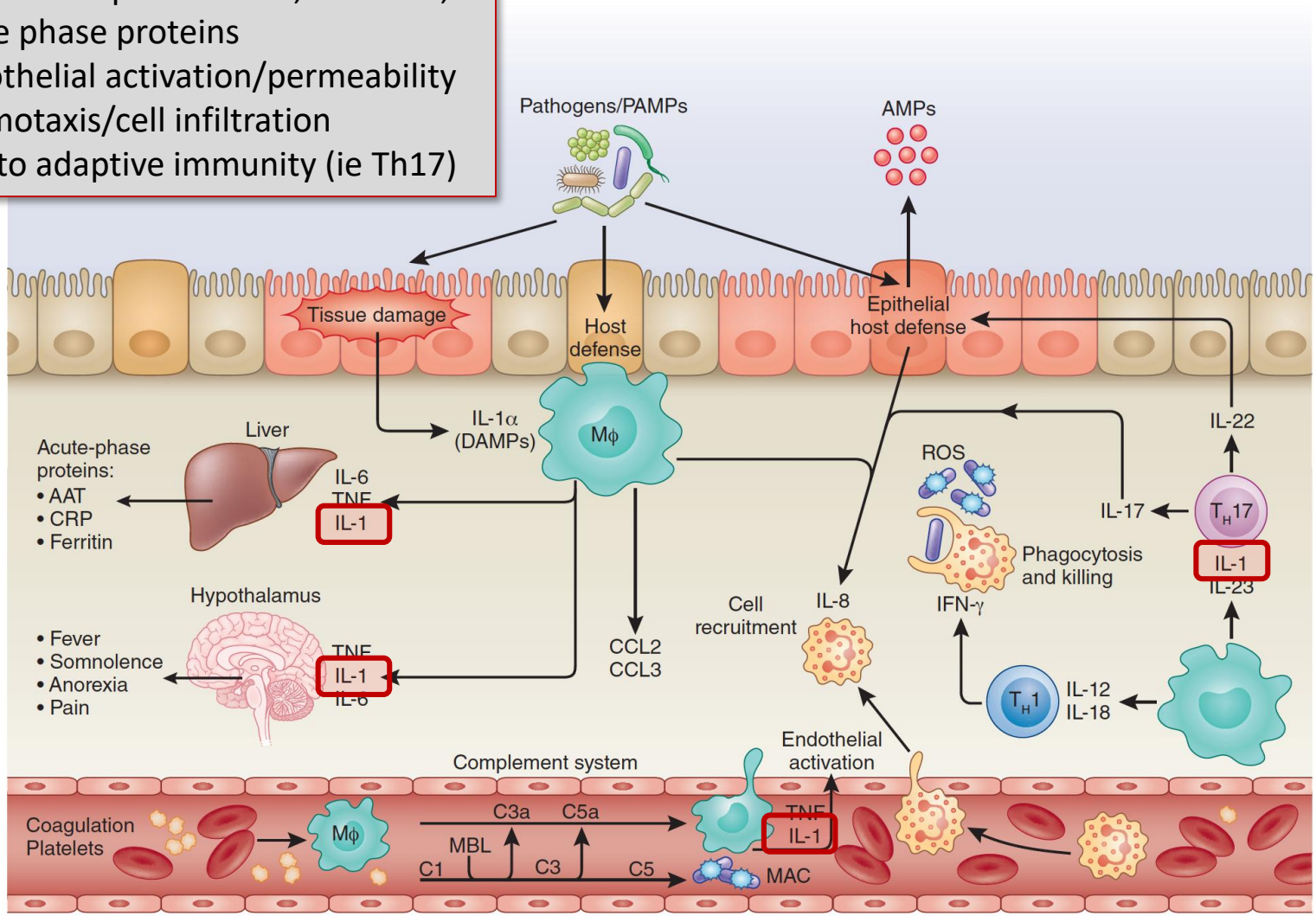


Lin et al, *J Am Soc Nephrol* 2013

Central role of IL-1 in the inflammatory response

Effects of IL-1β

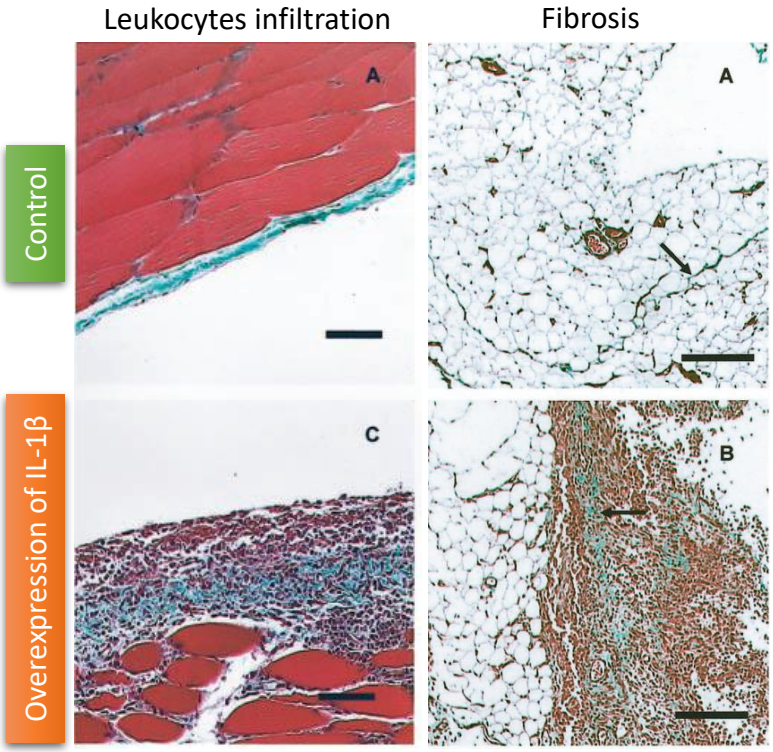
- Systemic response: fever, anorexia, acute phase proteins
- Endothelial activation/permeability
- Chemotaxis/cell infiltration
- Link to adaptive immunity (ie Th17)

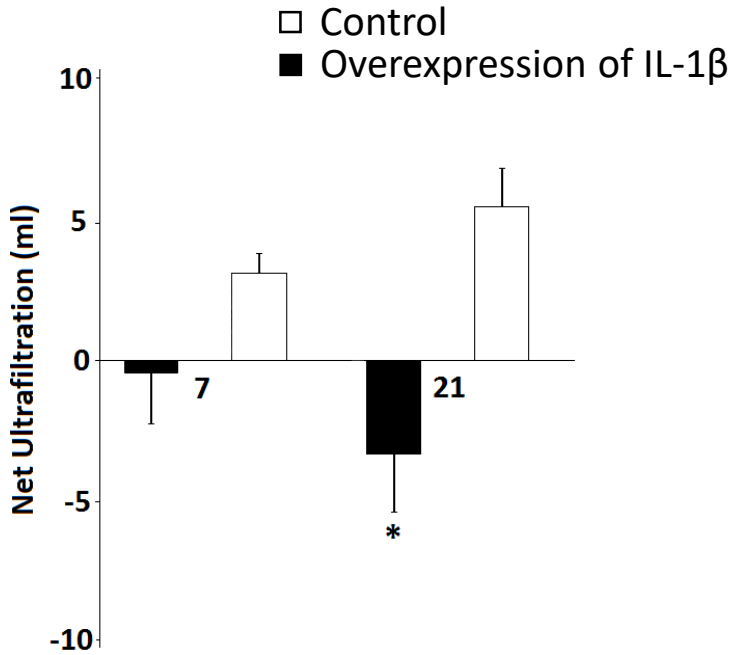


Netea…Dinarello, *Nat Immunol* 2017

Detrimental effects of IL-1β on the membrane

Adenovirus-mediated transfection of *IL1β* gene to the rat peritoneal membrane

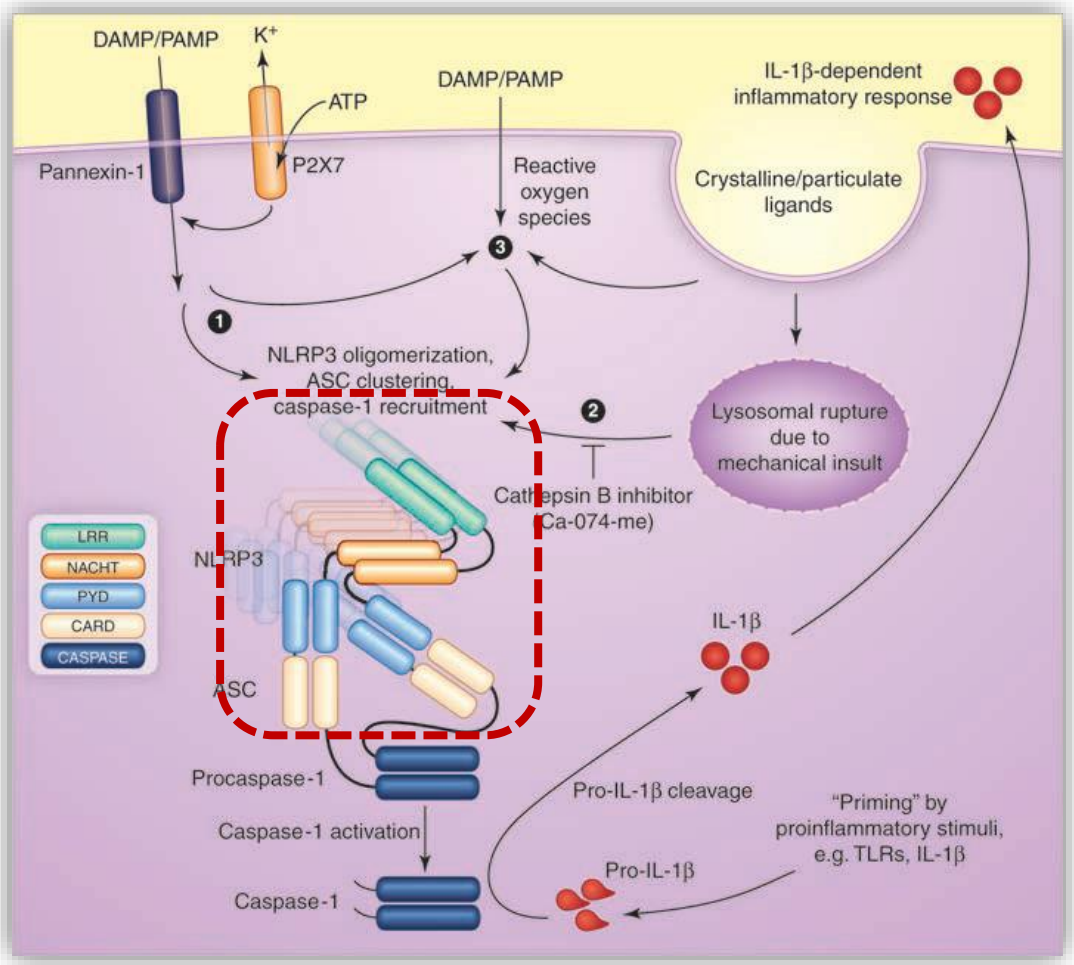




IL-1β ⟶ leukocytes infiltration, fibrosis and loss of ultrafiltration

Modified from Margetts et al, *Am J Pathol, 2002*

Activation of IL-1β is mediated by the inflammasome



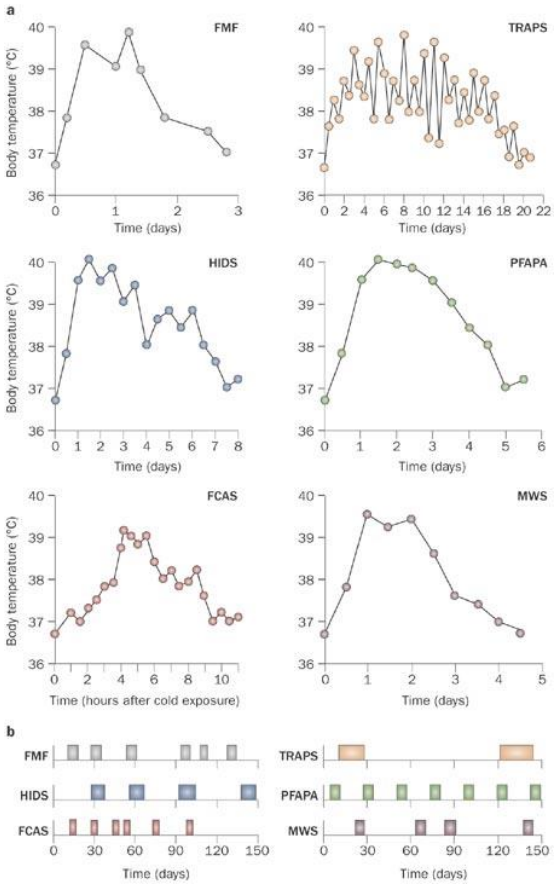
- Multiprotein platform
- Cytosol of immune cells
- Innate immune sensor
- Translates a microbial or metabolic stress into a potent inflammatory response
- Autocleavage and activation of caspase-1, which in turn cleaves pro-IL-1β into IL-1β

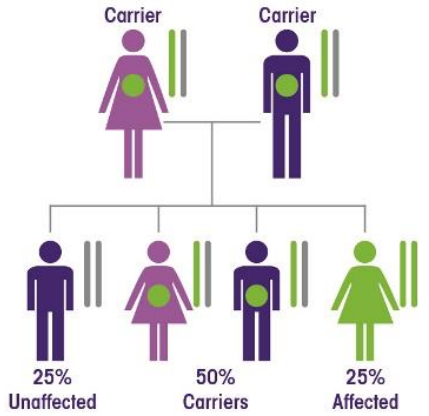
Schroder et al, *Science* 2010

Genetic dysregulation of the inflammasome

Cryopyrinopathies

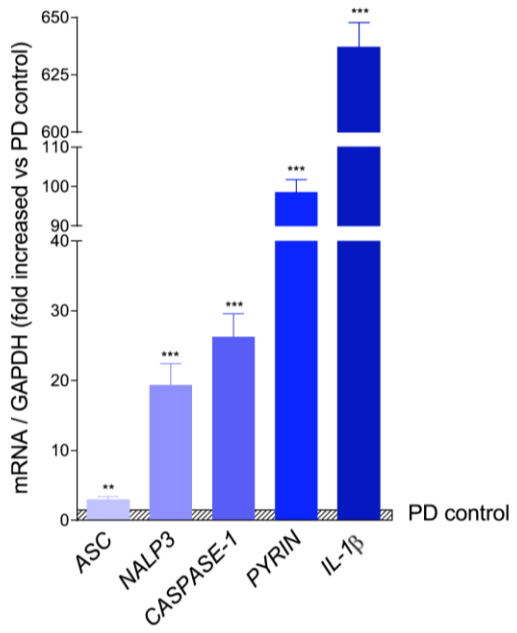
- Auto-inflammatory diseases
- Familial Mediaterranean Fever, TRAPS, Muckle-Wells,…
- Recurrent and spontaneous episodes of inflammation
- Periodic fever
- Systemic manifestations such as skin rash and peritonitis



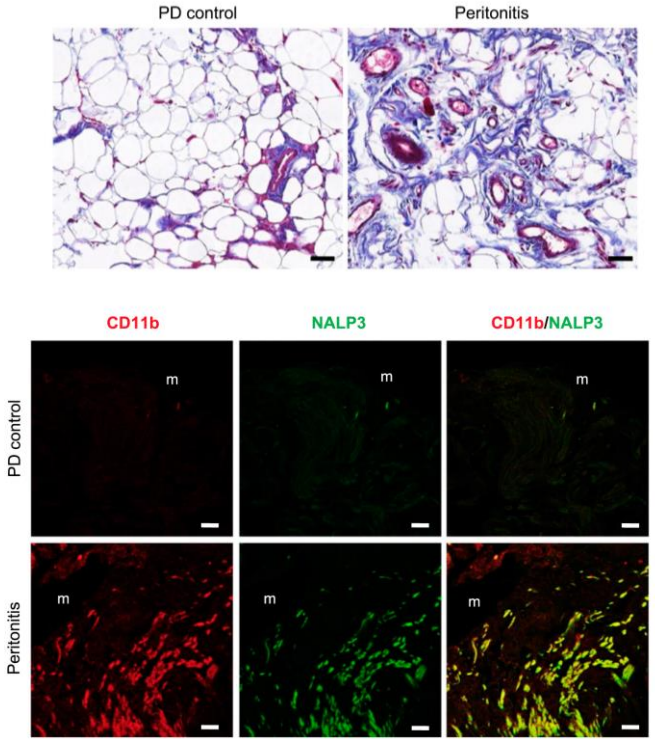


A role for the inflammasome in PD-associated peritonitis?

RT-PCR on total leukocytes
from PD patients with peritonitis (n=5) vs controls (n=3)



NLRP3 expression in the membrane
of a patient with PD-associated peritonitis vs PD control

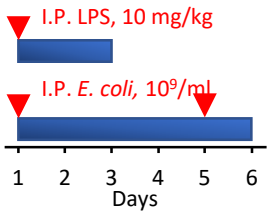


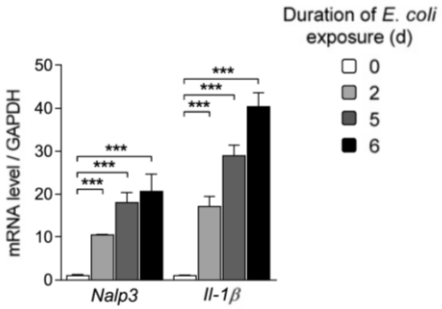
Peritonitis → upregulation of inflammasome components in immune cells of the peritoneal membrane

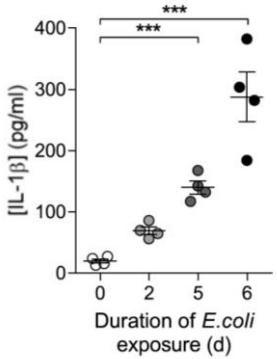
Hautem*, Morelle*…Devuyst, *J Am Soc Nephrol* 2017

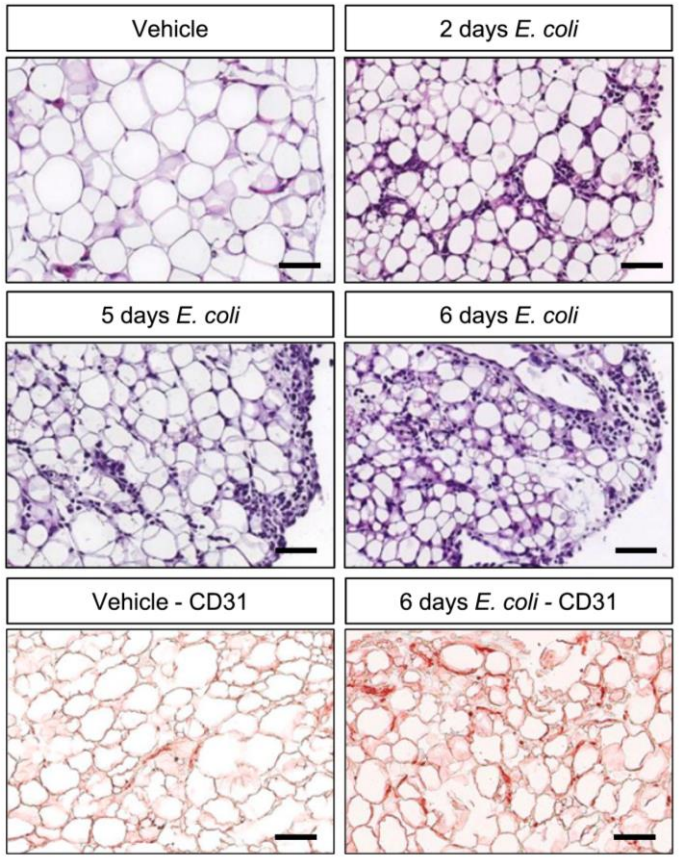
Mouse models of acute PD-associated peritonitis

Intraperitoneal LPS or *E. coli*









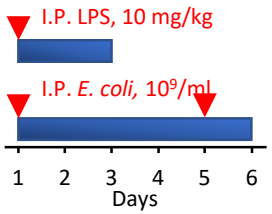
Acute peritonitis in mice

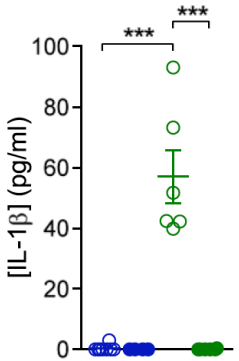
- Upregulation of inflammasome components
- Maturation and release of IL1β
- Peritoneal inflammation and angiogenesis, increased PSTR and loss of UF

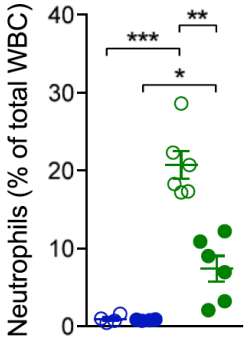
Hautem*, Morelle*…Devuyst, *J Am Soc Nephrol* 2017

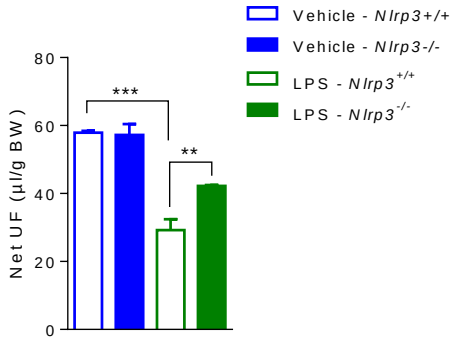
Mouse models of acute PD-associated peritonitis

Intraperitoneal LPS or *E. coli*









Nlrp3 knockout

↓

No IL-1beta maturation & release

↓

Reduction of peritoneal infiltrate

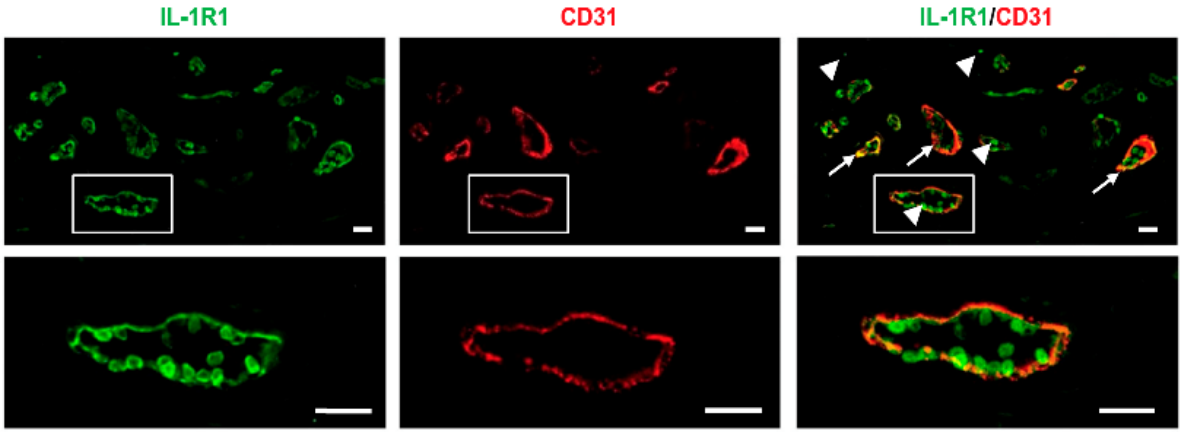
↓

Protection against peritoneal transport defects, incl. loss of UF

Hautem*, Morelle*…Devuyst, *J Am Soc Nephrol* 2017

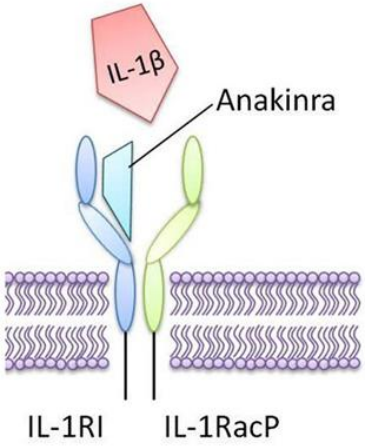
Pharmacological modulation of the NLRP3/IL1β axis?

IL1-R1 expression
in the peritoneal membrane



- Microvascular endothelium ($CD31^{+}$)
- Immune cells ($CD31^{-}$)

Anakinra
(IL-1R antagonist)

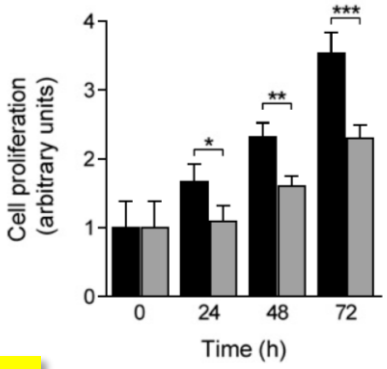


Interruption
of signal transduction

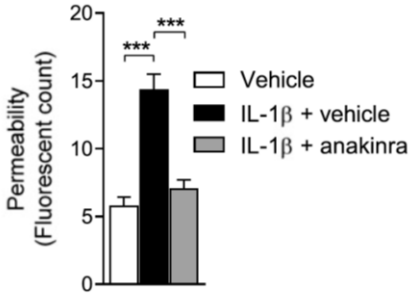
Hautem*, Morelle*…Devuyst, *J Am Soc Nephrol* 2017

Effects of IL-1β and anakinra on endothelial cells

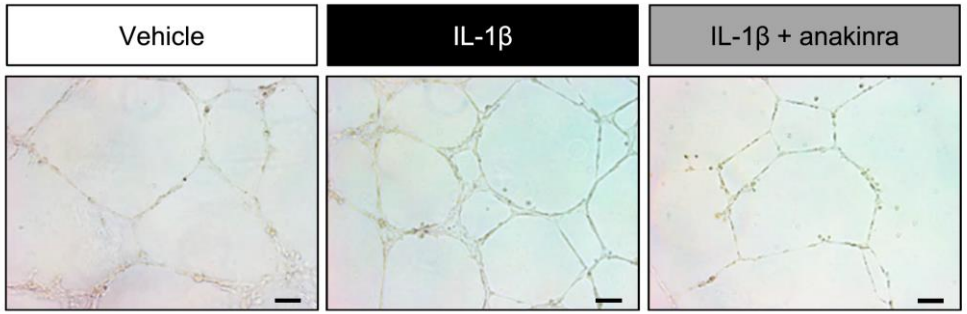
Cell proliferation

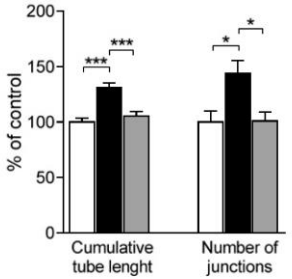


Permeability



Angiogenesis





IL-1β → endothelial cell proliferation and vascular permeability
Anakinra → protection against microvascular alterations

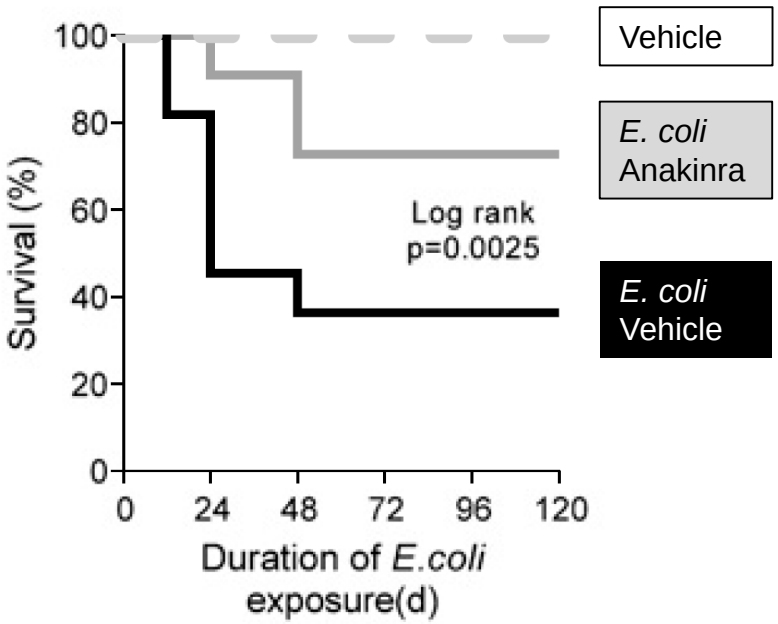
Hautem*, Morelle*…Devuyst, *J Am Soc Nephrol* 2017

Beneficial effects of anakinra *in vivo*

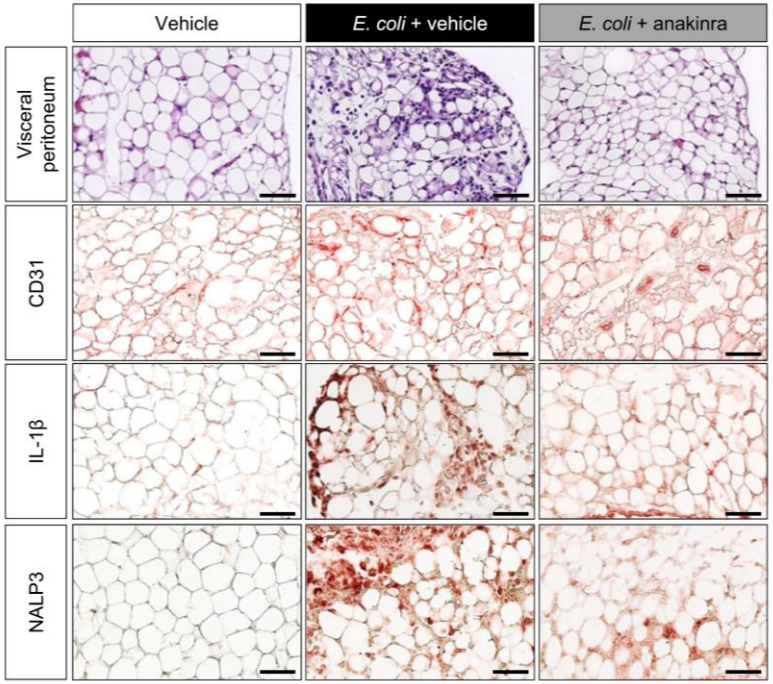
I.P. *E. coli*, 10^9/ml

I.P. anakinra, 50 mg/kg

Survival

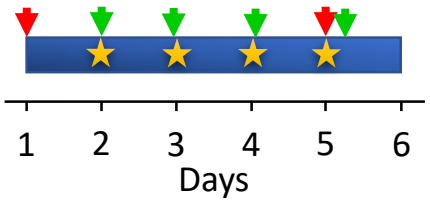


Membrane



Hautem*, Morelle* et al, *J Am Soc Nephrol* 2017

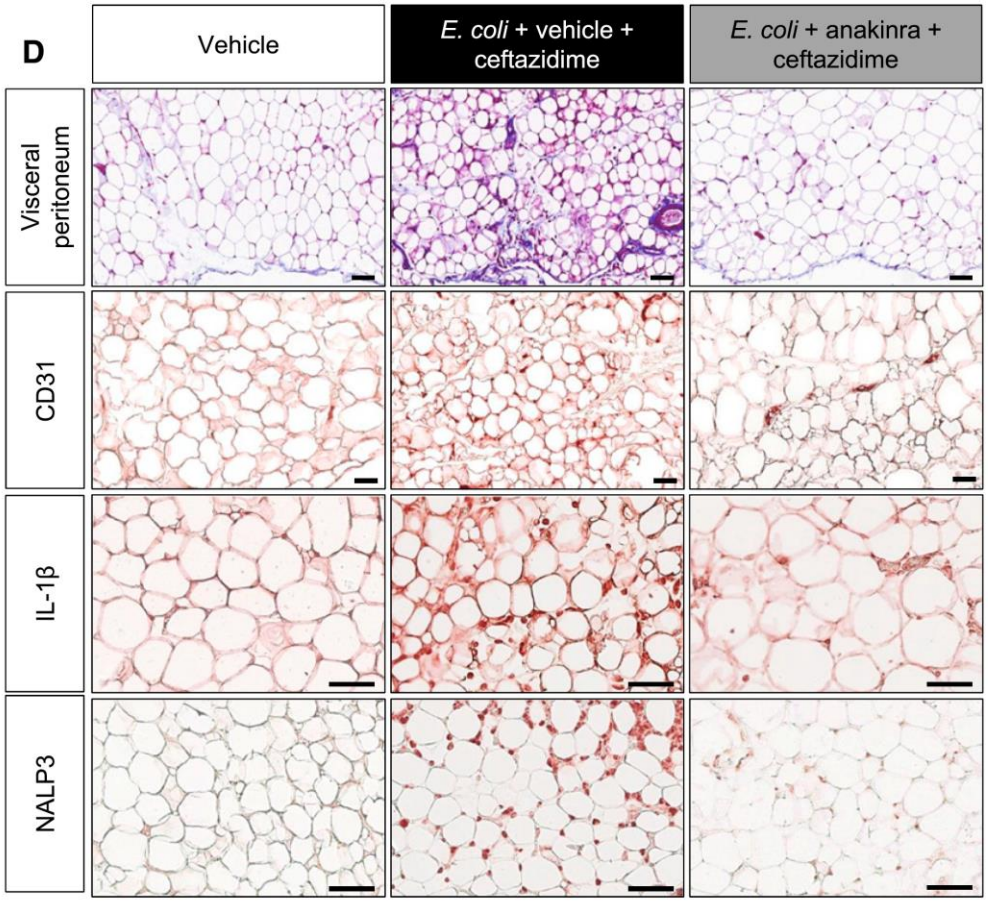
Beneficial effects of anakinra *in vivo* - on top of antibiotics

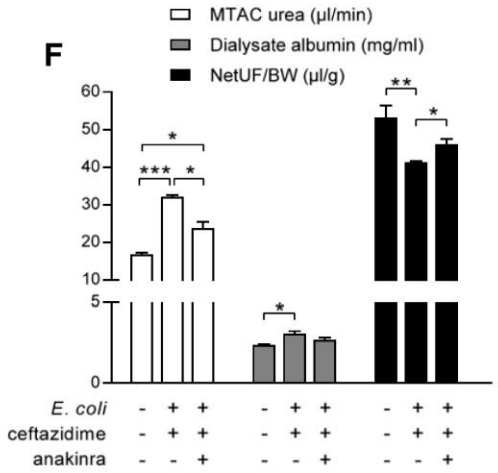


I.P. *E. coli*, 10^9/ml

I.P. anakinra, 50 mg/kg

I.P. ceftazidime, 40 mg/kg





Anakinra (antag. IL-1R)

- ↓ inflammatory infiltrate
- ↓ vascular proliferation
- Preservation of UF

Hautem*, Morelle* et al, *J Am Soc Nephrol* 2017

#PD_inflammation

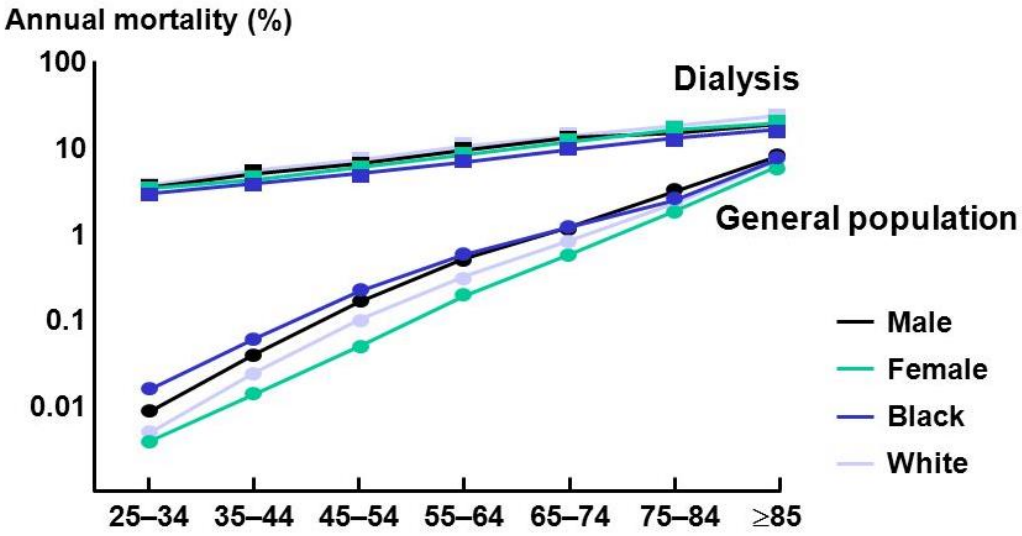
Inflammation, solute transport and the risk of fluid overload

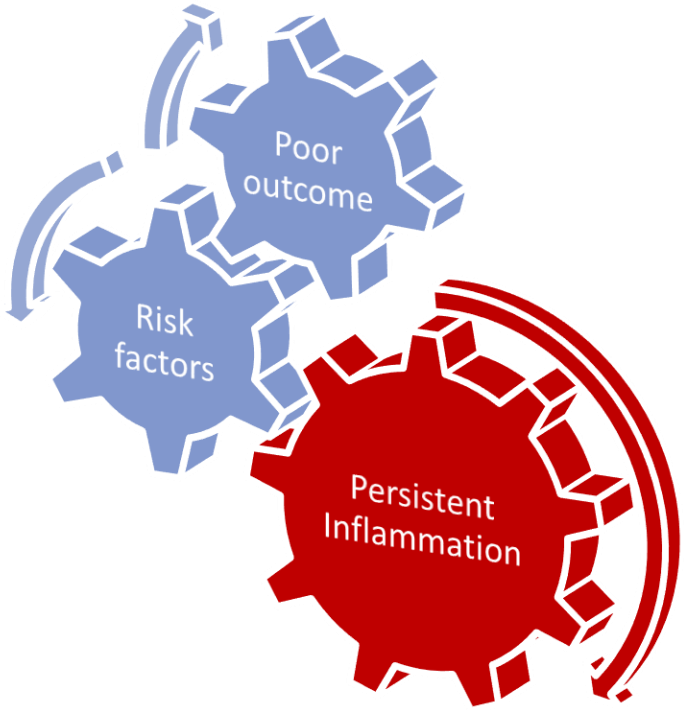
Inflammation, membrane damage and EPS in long-term PD

Preventing or modulating peritoneal inflammation to improve outcome in PD

Inflammation and cardiovascular mortality

Cardiovascular disease and the 'inflammation catalyst' hypothesis in ESRD





Unacceptably high risk of cardiovascular events in patients on dialysis
Catalyst effect of persistent systemic inflammation

Carrero and Stenvinkel, *Clin J Am Soc Nephrol* 2009

Table 1. Association Between Inflammatory Markers and Clinical Outcomes of Dialysis Patients

Study	Subjects	Inflammatory marker	Follow-up duration	Results	95% CI
Wang et al,[12] 2003	246 prevalent PD patients	hs-CRP (median, 2.84 mg/L)	24 mo (median)	All-cause mortality: HR, 1.02 (per mg/L)	1.01-1.04
				Cardiovascular mortality: HR, 1.03 (per mg/L)	1.01-1.05
Ducloux et al,[13] 2002	240 incident PD patients	CRP (median, 7 mg/L)	41 mo (median)	All-cause mortality: RR, 5.20 (4th quartile versus 1st quartile of CRP)	1.37-12.94
				Cardiovascular event: RR, 4.66 (4th quartile versus 1st quartile of CRP)	1.69-12.85
Liu et al,[14] 2014	402 prevalent PD patients	hs-CRP (mean, 9.0 mg/L)	24 mo	All-cause mortality: RR, 1.02 (per mg/L)	1.00-1.03
				Technique failure: RR, 1.01 (per mg/L)	1.00-1.02
Pecoits-Filho et al,[18] 2002	99 incident PD and 74 incident HD patients	IL-6 (mean, 6.4 pg/mL)	37 mo (mean)	All-cause mortality: HR, 3.31 (per log ng/mL)	1.07-10.6
Lambie et al,[19] 2013	575 incident PD patients	IL-6	63 mo (median)	All-cause mortality: HR, 2.15 (per log IL-6)	1.22-3.78
	384 prevalent PD patients	IL-6	61 mo (median)	All-cause mortality: HR, 2.68 (per log IL-6)	1.28-5.58
Cho et al,[20] 2015	175 incident PD patients	IL-6 (mean, 1.56 pg/mL)	24 mo	Cardiovascular event: IRR, 1.06 (per pg/mL)	1.02-1.10

Abbreviations: CI, confidence interval; HR, hazard ratio; IRR, incidence rate ratio; RR, relative risk.

Systemic inflammation (CRP, IL-6)
→ poor outcome in ESRD patients

Li et al, *Semin Nephrol* 2017

Beneficial effects of modulating inflammation on the risk of CV events…in the non-ESRD population

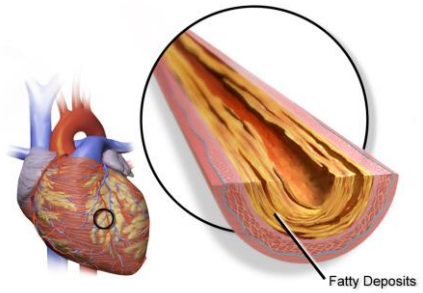
The NEW ENGLAND JOURNAL of MEDICINE

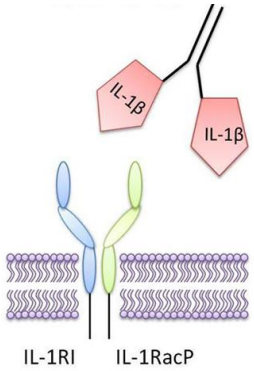
ORIGINAL ARTICLE

Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease

CANTOS

Canakinumab **An**ti-inflammatory **T**hrombosis **O**utcomes **S**tudy





10,061
patients

Previous myocardial infarction
hsCRP level ≥ 2 mg/l

Canakinumab
vs. placebo (4-y follow-up)

Canakinumab ⟶ 15-20% reduction in the risk of severe cardiovascular events

Ridker et al, *N Engl J Med* 2017

#PD_inflammation

- Peritoneal and systemic inflammation
  - Drives membrane damage and transport defects
  - Contributes to the excess mortality of ESRD patients treated with PD
- Prevention and treatment of inflammation in PD is a realistic option in clinical practice
- Understanding the causes and mechanisms of PD-associated inflammation will help (further) improving the safety and efficiency of PD

Acknowledgements

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- Olivier Devuyst
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- Yves Pirson
- Nathalie Demoulin
- Laura Labriola
- Nada Kanaan
- Arnaud Devresse
- Valentine Gillion

Extramural Grant

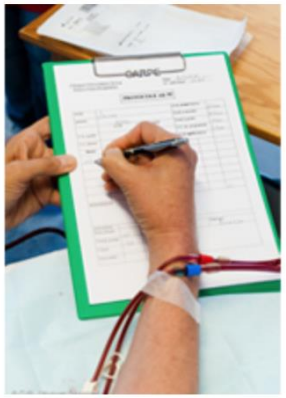
self-care dialysis
symposium

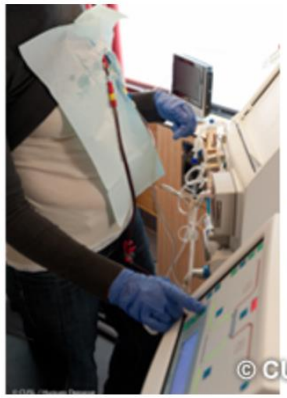
En collaboration avec le RDPLF

4ème Symposium de Dialyse Extra-Hospitalière

Les 6 et7 juin 2018

Square-Brussels Meeting Centre





Contactez-nous !

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