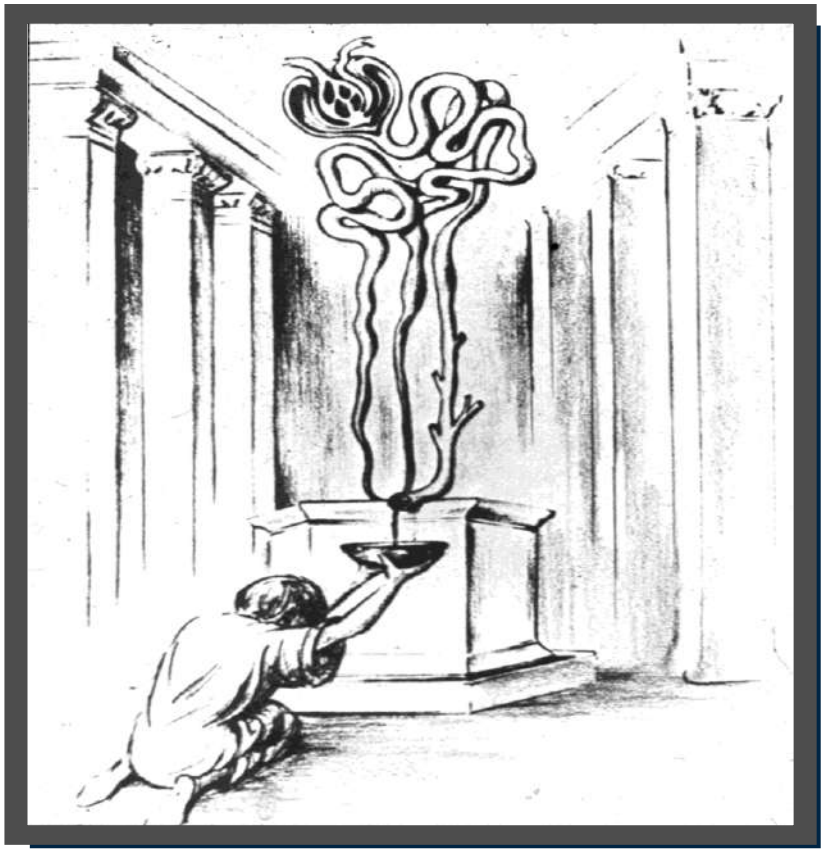
Prescription HD, CAPD complications

Ιωάννης Γ. Γριβέας, MD,PhD

Νεφρολόγος

athens-NEPHROLOGY

Kidney Function



The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

MEDICAL PROGRESS

Uremia

Timothy W. Meyer, M.D., and Thomas H. Hostetter, M.D.

MEDICAL PROGRESS HAS ALTERED THE COURSE AND THUS THE DEFINITION of uremia, which once encompassed all the signs and symptoms of advanced kidney failure. Hypertension due to volume overload, hypocalcemic tetany, and anemia due to erythropoietin deficiency were once considered signs of uremia but were removed from this category as their causes were discovered. Today the term "uremia" is used loosely to describe the illness accompanying kidney failure that cannot be explained by derangements in extracellular volume, inorganic ion concentrations, or lack of known renal synthetic products. We now assume that uremic illness is due largely to the accumulation of organic waste products, not all identified as yet, that are normally cleared by the kidneys.

N Engl J Med 2007;357:1316-25.

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Not all of the illness of a patient undergoing dialysis can be ascribed to uremia. Indeed, the evolution of dialysis has made the effects of uremia more difficult to distinguish, since the severity of classic uremic symptoms is attenuated. Instead, patients undergoing dialysis now have a new illness, which Depner[3] aptly named the "residual syndrome." This illness comprises partially treated uremia; ill effects of dialysis, such as fluctuation in the extracellular fluid volume and exposure to bioincompatible materials; and residual inorganic ion disturbances, including acidemia and hyperphosphatemia. In many patients, the residual syndrome is complicated by the effects of advancing age and systemic diseases that were responsible for the loss of kidney function.

N Engl J Med 2007;357:1316-25.

Table 1. Main known uremic retention solutes

Small water soluble solutes	Protein-bound solutes	Middle molecules
Asymmetric dimethylarginine	3-Deoxyglucosone	Adrenomedullin
Benzylalcohol	CMPF	Atrial natriuretic peptide
β-Guanidinopropionic acid	Fructoselysine	β_2-Microglobulin
β-Lipotropin	Glyoxal	β-Endorphin
Creatinine	Hippuric acid	Cholecystokinin
Cytidine	Homocysteine	Clara cell protein
Guanidine	Hydroquinone	Complement factor D
Guanidinoacetic acid	Indole-3-acetic acid	Cystatin C
Guanidinosuccinic acid	Indoxyl sulfate	Degranulation inhibiting protein I
Hypoxanthine	Kinurenine	Delta-sleep-inducing peptide
Malondialdehyde	Kynurenic acid	Endothelin
Methylguanidine	Methylglyoxal	Hyaluronic acid
Myoinositol	N-carboxymethyllysine	Interleukin 1β
Orotic acid	P-cresol	Interleukin 6
Orotidine	Pentosidine	Kappa-Ig light chain
Oxalate	Phenol	Lambda-Ig light chain
Pseudouridine	P-OHhippuric acid	Leptin
Symmetric dimethylarginine	Quinolinic acid	Methionine-enkepahlin
Urea	Spermidine	Neuropeptide Y
Uric acid	Spermine	Parathyroid hormone
Xanthine		Retinol binding protein
		Tumor necrosis factor alpha

CMPF is carboxy-methyl-propyl-furanpropionic acid.

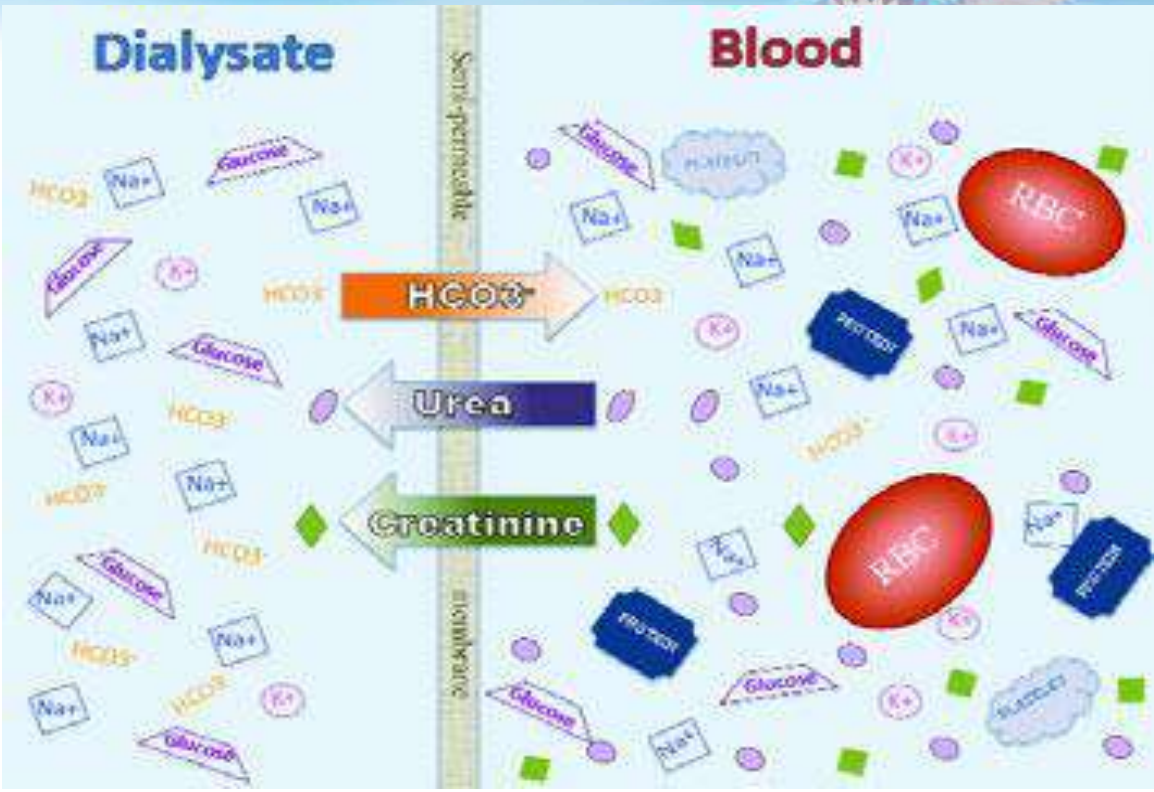
Plasma and /or tissue concentration of the compound should be higher in uremic patients.

The compound should be chemical identified, specific and accurate quantitative analysis

High concentrations should be related to specific uremic symptoms and disappear when the concentration is reduced.

Studying toxicity of the compound , the concentration should be compartable to those found in the body fluids and/or tissues of uremic patients.

www.uremic-toxins.org



Kidney International, Vol. 63, Supplement 84 (2003), pp. S6–S10

New insights in uremic toxins

RAYMOND VANHOLDER, GRIET GLORIEUX, RITA DE SMET, NORBERT LAMEIRE, for the EUROPEAN UREMIC TOXIN WORK GROUP (EUTOX)[1]

Nephrology Section, Department of Internal Medicine, University Hospital, Gent, Belgium

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Table 1. Uremic Solutes.*

Solute Group	Example	Source	Characteristics
Peptides and small proteins	Beta$_2$-microglobulin	Shed from MHC	Poorly dialyzed because of large size
Guanidines	Guanidinosuccinic acid	Arginine	Increased production in uremia
Phenols	p-Cresol sulfate	Phenylalanine, tyrosine	Protein bound, produced by gut bacteria
Indoles	Indican	Tryptophan	Protein bound, produced by gut bacteria
Aliphatic amines	Dimethylamine	Choline	Large volume of distribution, produced by gut bacteria
Furans	CMPF	Unknown	Tightly protein bound
Polyols	Myoinositol	Dietary intake, cell synthesis from glucose	Normally degraded by the kidney rather than excreted
Nucleosides	Pseudouridine	tRNA	Most prominent of several altered RNA species
Dicarboxylic acids	Oxalate	Ascorbic acid	Formation of crystal deposits
Carbonyls	Glyoxal	Glycolytic intermediates	Reaction with proteins to form advanced glycation end products

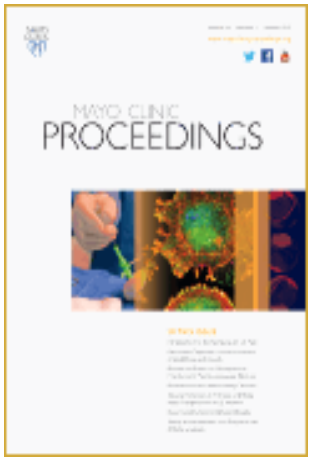
* Uremic solutes may have multiple sources, although only one is listed. MHC denotes major histocompatibility complex, and CMPF 3-carboxy-4-methyl-5-propyl-2-furanpropionic acid.

N Engl J Med 2007;357:1316-25.

Urea is quantitatively the most important solute excreted by the kidney and was the first organic solute detected in the blood of patients with kidney failure.

Early studies indicated
that urea itself causes only a minor part of
uremic illness.

One study showed that uremic
symptoms were relieved by initiation of dialysis,
even when urea was added to the dialysate to
maintain the blood urea nitrogen level at approximately
90 mg per deciliter.



Johnson WJ, Hagge WW, Wagoner RD, Dinapoli RP, Rosevear JW. Effects of urea loading in patients with far-advanced renal failure. Mayo Clin Proc 1972;47: 21-9.

CATEGORIZATION OF SMALL, MIDDLE, AND LARGE MOLECULES

- urea (60), creatinine (113), phosphate (134)
- vitamin B12 (1355), vancomycin (1448), insulin (5200), endotoxin fragments (1000-15000), Parathromone (9425), β2-microgobulin (11818)
- myoglobin (17000), Retinol-Binding Protein (RBP) (21000), EPO (34000), albumin (66000), Transferrin (90000)

- Small molecules <500 (No 68)
- Middle molecules 500-15000 (No 22)
- Large molecules >15000 (No 12)

Small, middle-sized, and large molecules

- **Protein binding No 25**
- Protein intake
- Intestinal bacterial flora
- **Concentrations range from ng/L (methionine-enkephalin) up to g/L (urea).**

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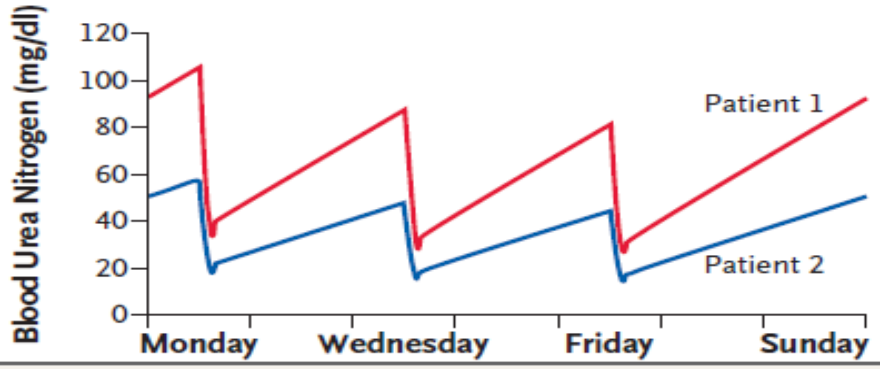


Figure 1. Blood Urea Nitrogen Levels in Two Theoretical Patients Undergoing Conventional Thrice-Weekly Hemodialysis for 3 Hours on Monday, Wednesday, and Friday.

Urea nitrogen levels fall precipitously as urea is rapidly removed during treatment and then rise gradually between treatments, with the highest levels observed after the 3-day interdialytic interval (from Friday after dialysis until Monday before dialysis). Both patients were receiving the same dose of dialysis, as evidenced by the 68% drop in urea levels for both patients with each treatment. This drop constitutes adequate dialysis, according to the current U.S. standard. Patient 1, who had higher absolute plasma urea levels than Patient 2, was presumably eating more protein. To convert the values for blood urea nitrogen to millimoles of urea per liter, multiply by 0.357.

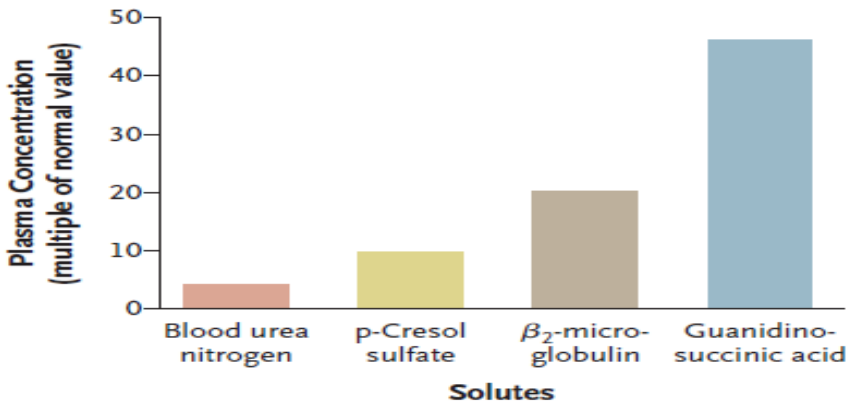


Figure 2. Time-Averaged Plasma Solute Levels in Patients Undergoing Conventional Thrice-Weekly Hemodialysis.

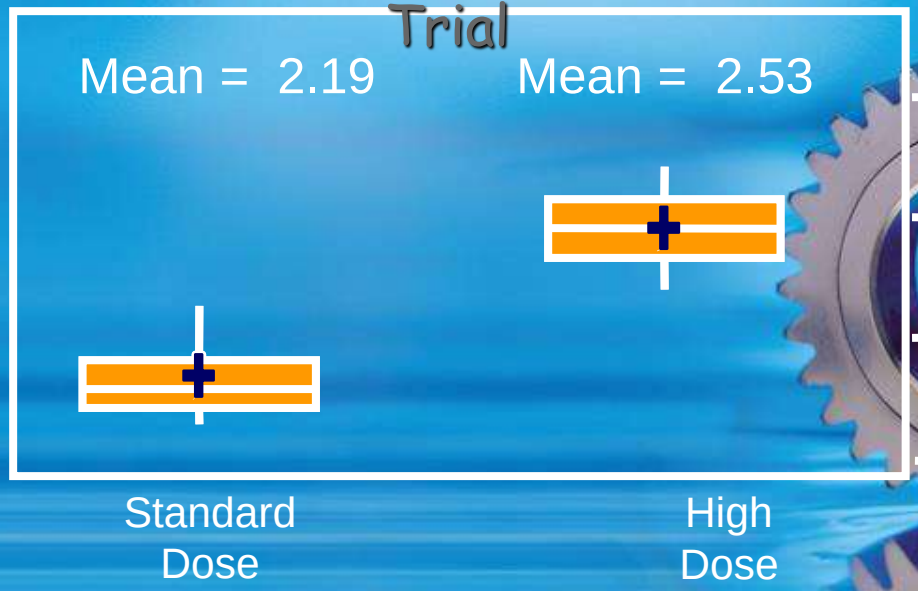
Conventional hemodialysis is prescribed to remove blood urea nitrogen effectively, so that the average urea level in a patient undergoing hemodialysis is only about four times the normal value. But dialysis is much less effective in controlling the levels of other solutes. Binding to albumin limits the dialysis of p-cresol sulfate, and large molecular size limits the dialysis of beta$_2$-microglobulin; as a result, the average levels of these solutes in patients undergoing hemodialysis are about 10 times and 20 times the normal levels, respectively. The plasma level of guanidinosuccinic acid is even higher, averaging more than 40 times the normal value. Guanidinosuccinic acid levels rise this high largely because the production of guanidinosuccinic acid increases in patients with uremia; sequestration within cells impairs the efficiency of dialysis and contributes to the elevation of plasma levels of related guanidines. Solute ratios are approximations based on data from Martinez et al.,[20] Raj et al.,[30] and Eloot et al.[31]

Post-Hoc Analysis of HEMO Study

Limited separation between treatment groups for unified dose measures, such as

Standard Kt/V ≅ [urea generation rate] / [average (C_0)]

Separation in Std Kt/V in HEMO Trial



Only 16% difference in mean Std Kt/V between dose groups

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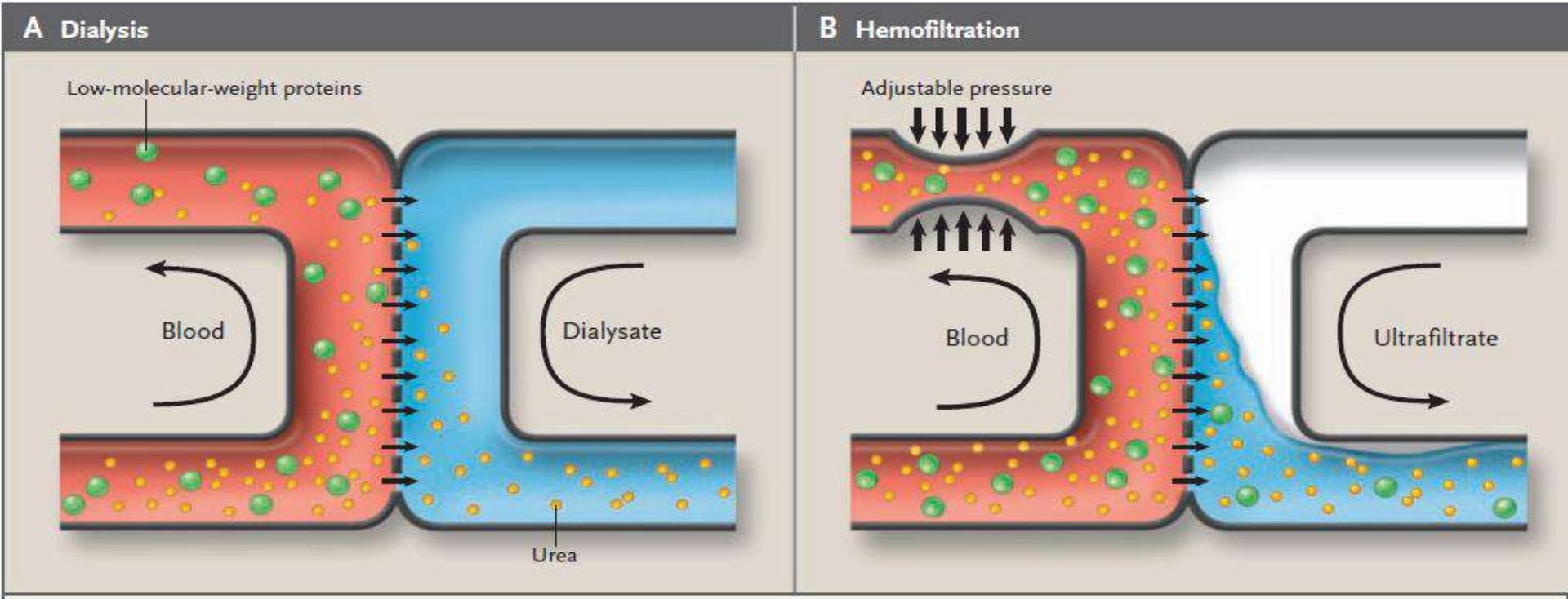
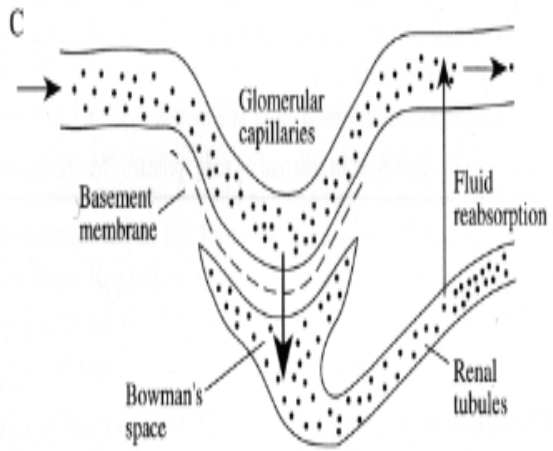
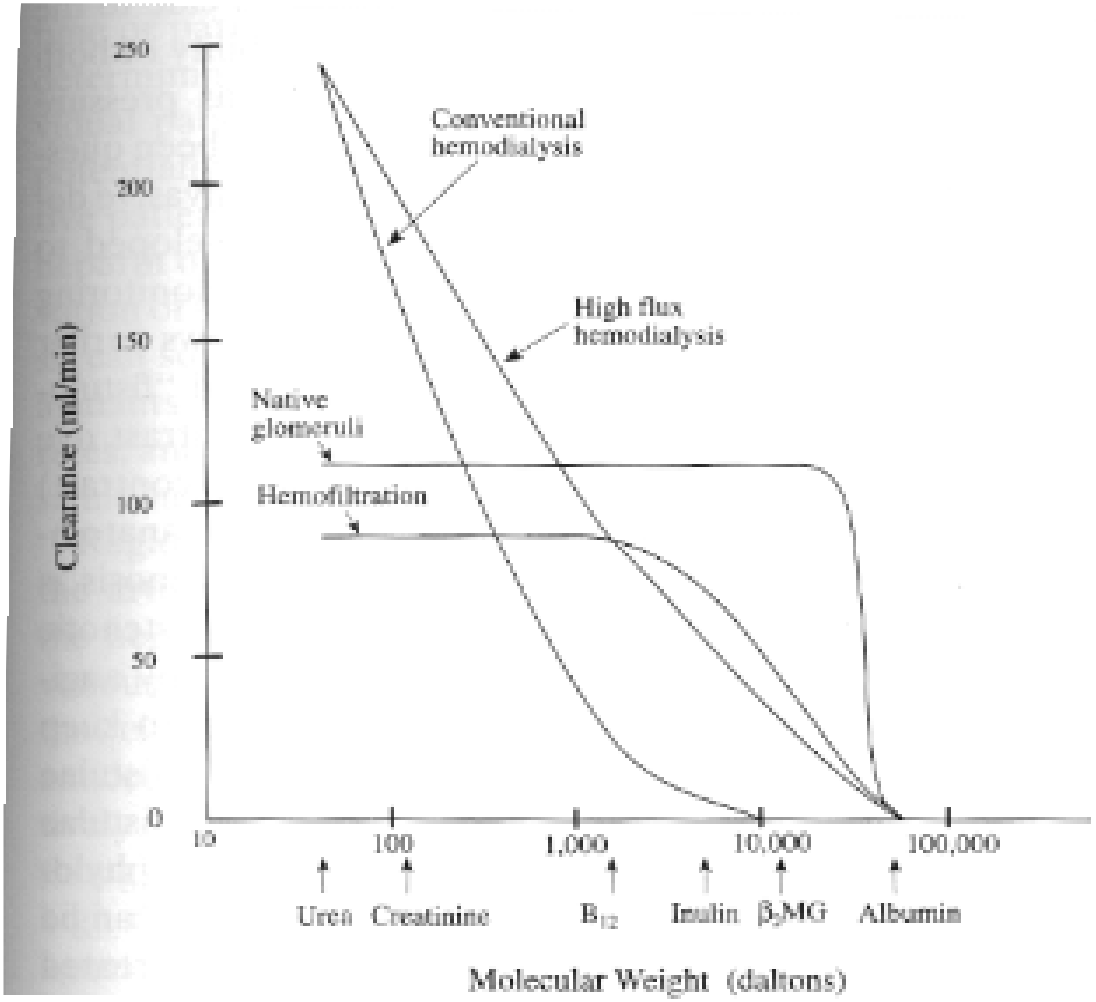


Figure 3. Dialysis versus Hemofiltration.

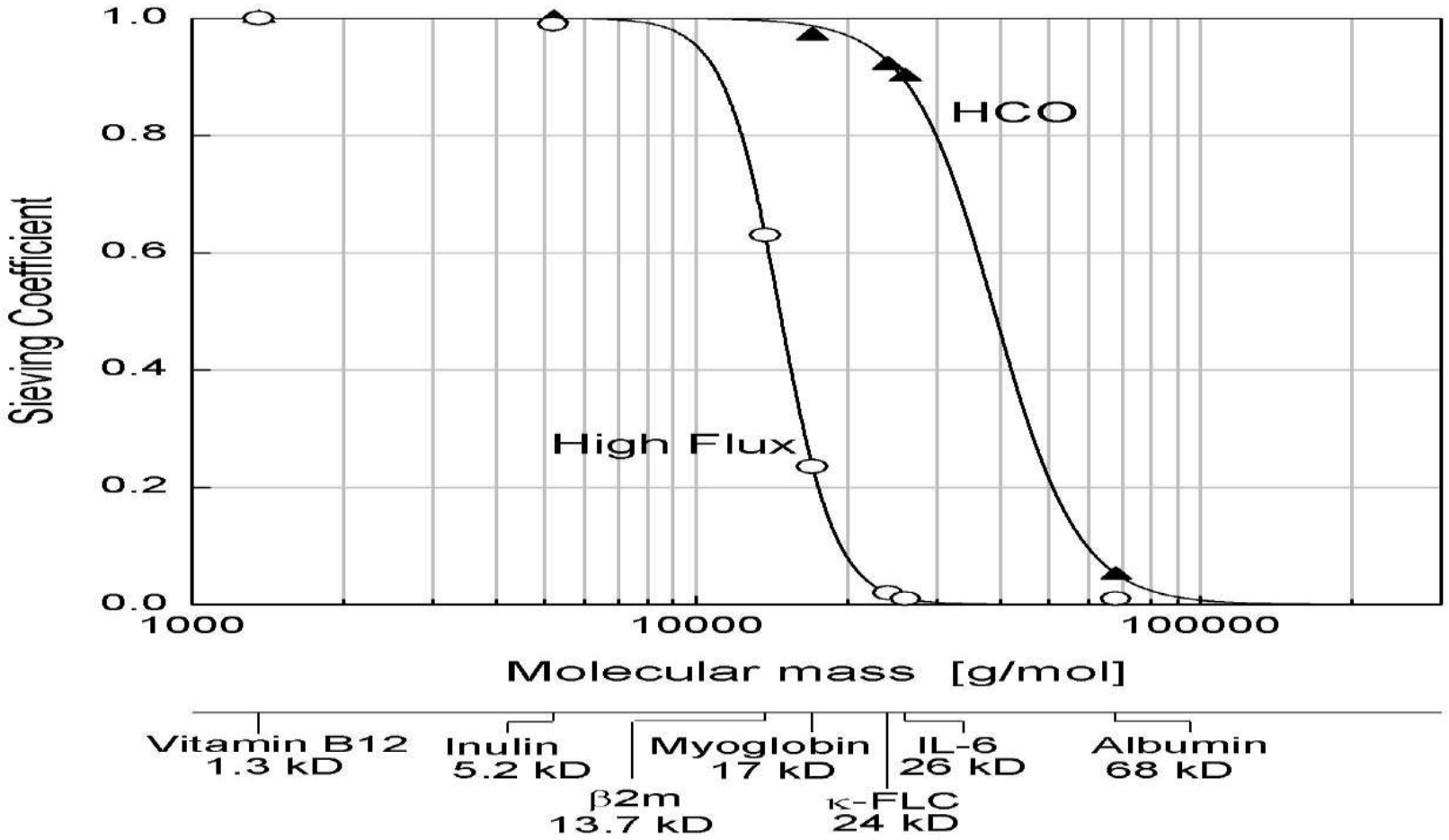
In dialysis (Panel A), solutes diffuse through a thin membrane separating the blood and dialysate, which flow in opposite directions. Small solutes such as urea (small yellow spheres) diffuse readily. Larger solutes, including low-molecular-weight proteins (large green spheres), diffuse less readily and are not cleared as effectively when blood passes through the dialyzer. In hemofiltration (Panel B), fluid is forced through the same membrane by pressure, and solutes are carried with the fluid by convection. As compared with diffusion, convection removes larger solutes at almost the same rate as small solutes. Standard dialysis treatments include some hemofiltration in order to remove the fluid that accumulates with daily intake. The removal of large solutes can be augmented by increasing the amount of ultrafiltration. The combined process of dialysis and high-volume ultrafiltration, which requires the provision of intravenous replacement fluid to offset the ultrafiltration rate, is called hemodiafiltration.

Kidney Function





HCO Membrane - increased permeability for mid-molecules



Convective permeability

Trials

BioMed Central

Study protocol

Open Access

European trial of free light chain removal by extended haemodialysis in cast nephropathy (EuLITE): A randomised control trial

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New insights in uremic toxins

RAYMOND VANHOLDER, GRIET GLORIEUX, RITA DE SMET, NORBERT LAMEIRE, for the EUROPEAN UREMIC TOXIN WORK GROUP (EUTOX)[1]

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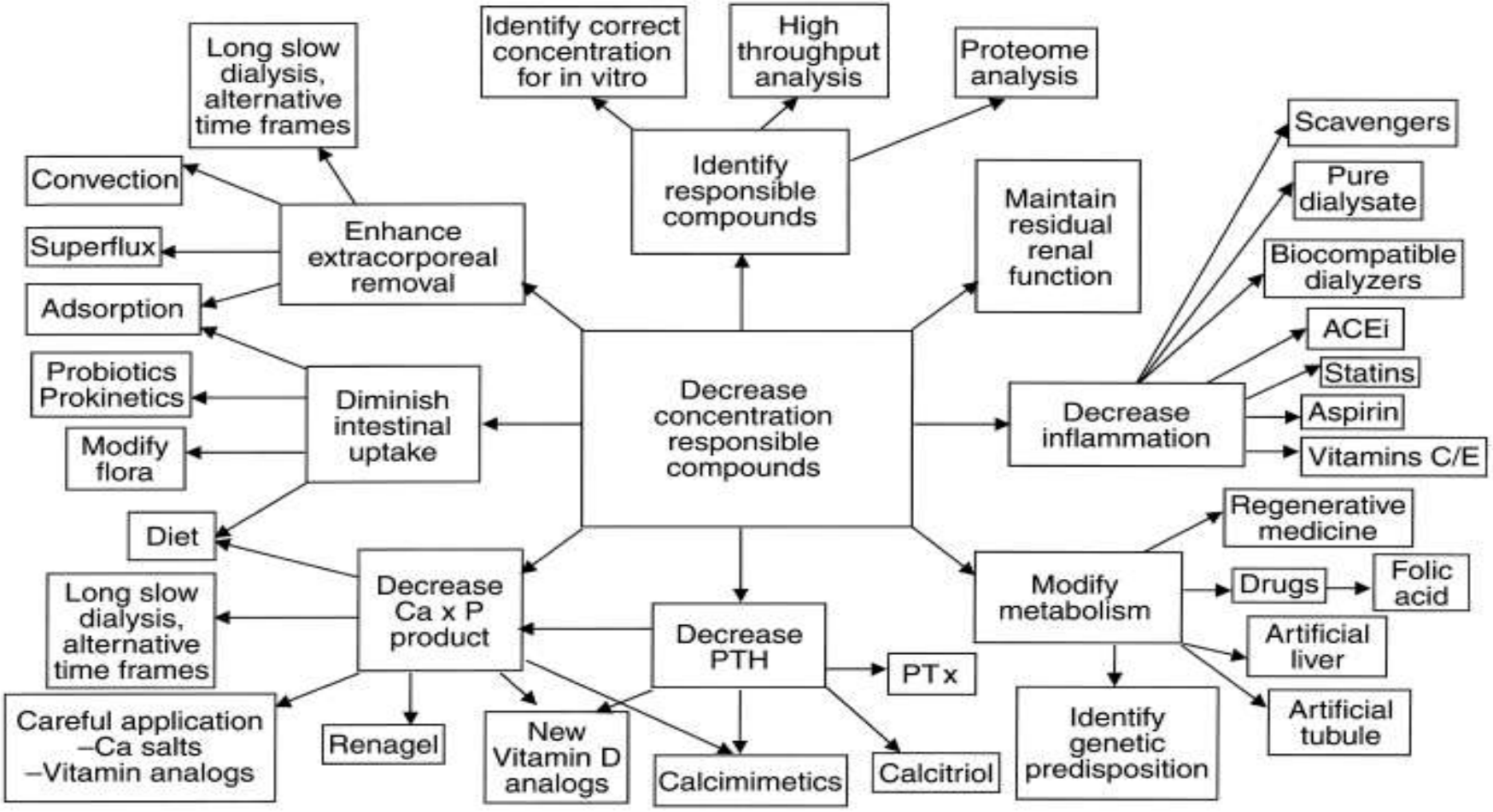

Fig. 1. Possible preventive or therapeutic measures in the context of uremic cardiovascular disease.

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Table 2. Signs and Symptoms of Uremia.

Neural and muscular
Fatigue
Peripheral neuropathy
Decreased mental acuity
Seizures
Anorexia and nausea
Decreased sense of smell and taste
Cramps
Restless legs
Sleep disturbances
Coma
Reduced muscle membrane potential
Endocrine and metabolic
Amenorrhea and sexual dysfunction
Reduced body temperature
Altered amino acid levels
Bone disease due to phosphate retention, hyperparathyroidism, and vitamin D deficiency
Reduced resting energy expenditure
Insulin resistance
Increased protein–muscle catabolism
Other
Serositis (including pericarditis)
Itching
Hiccups
Oxidant stress
Anemia due to erythropoietin deficiency and shortened red-cell survival
Granulocyte and lymphocyte dysfunction
Platelet dysfunction

N Engl J Med 2007;357:1316-25.

- Patients on dialysis have extremely limited exercise capacity, and poor physical functioning has been linked to low quality of life and high mortality in this population.

- The reason for the debility of patients on dialysis is far from clear despite years of study.

- The anemia of chronic renal disease is clearly a contributing factor, but uremic myopathy and resulting decreased muscle oxygen utilization have a significant impact on the physical functioning of patients on dialysis as well

Adv Ren Replace Ther. 1999 Apr;6(2):141-8.

Physical functioning and exercise capacity in patients on dialysis.

Johansen KL

Renal Failure, 27:429–434, 2005

ISSN: 0886-022X print / 1525-6049 online
DOI: 10.1081/JDI-200065200

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CLINICAL STUDY

Relevance of Procalcitonin Levels in Comparison to Other Markers of Inflammation in Hemodialysis Patients

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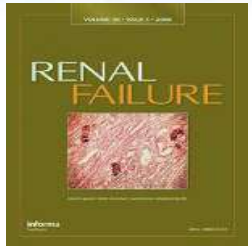

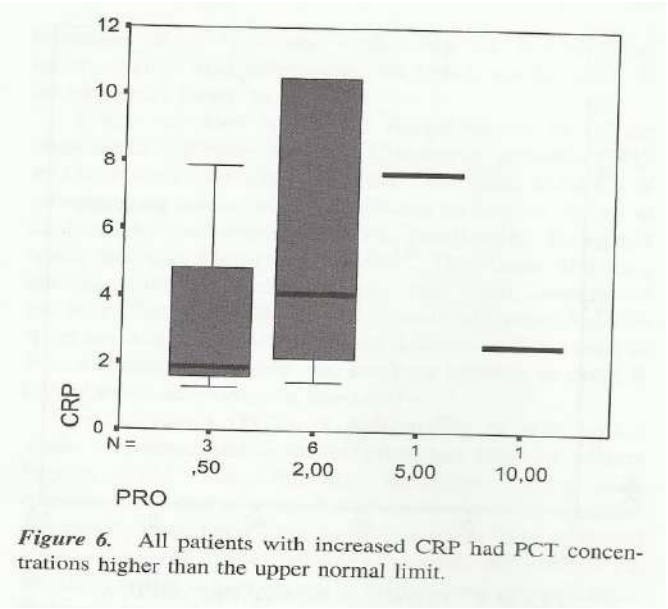

Figure 6. All patients with increased CRP had PCT concentrations higher than the upper normal limit.

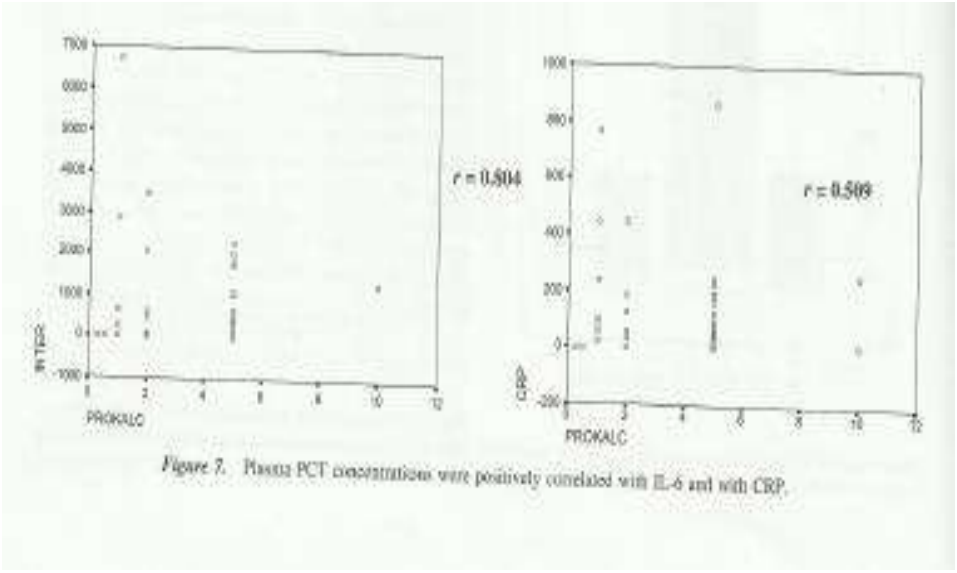

Figure 7. Plasma PCT concentrations were positively correlated with IL-6 and with CRP.

Διαλυτός Υποδοχέας Πλασμινογόνου Ουροκινάσης (suPAR): ένας υποσχόμενος δείκτης φλεγμονής

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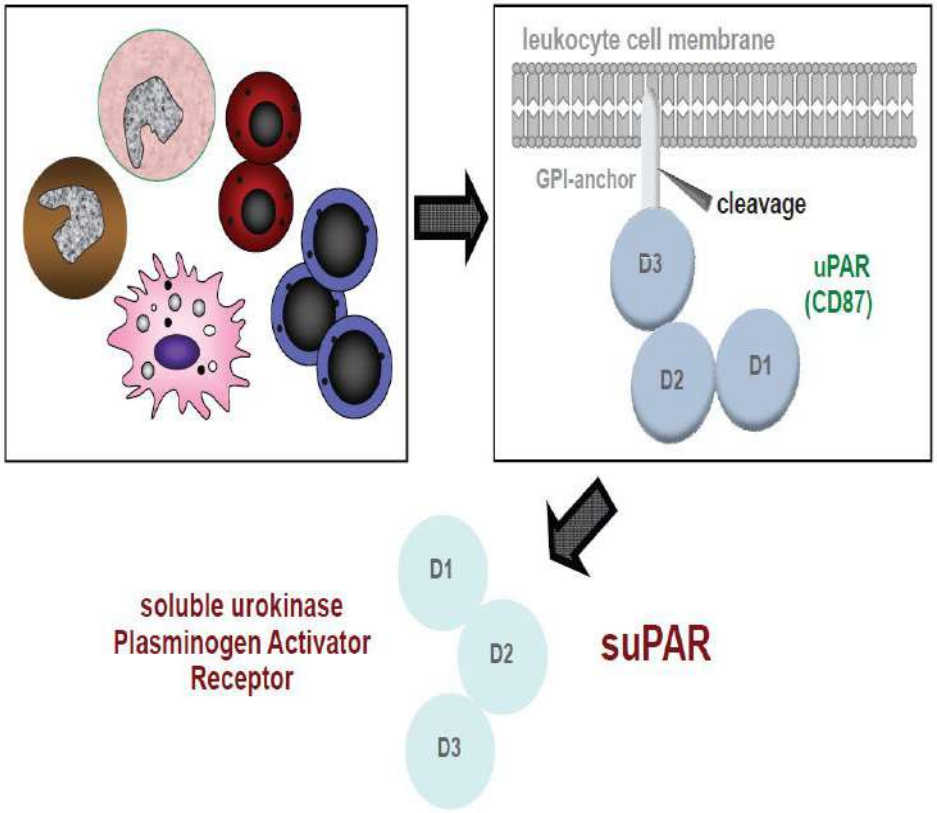
Μονάδα Χρόνιας Αιμοκάθαρσης "Νεφροιατρική"

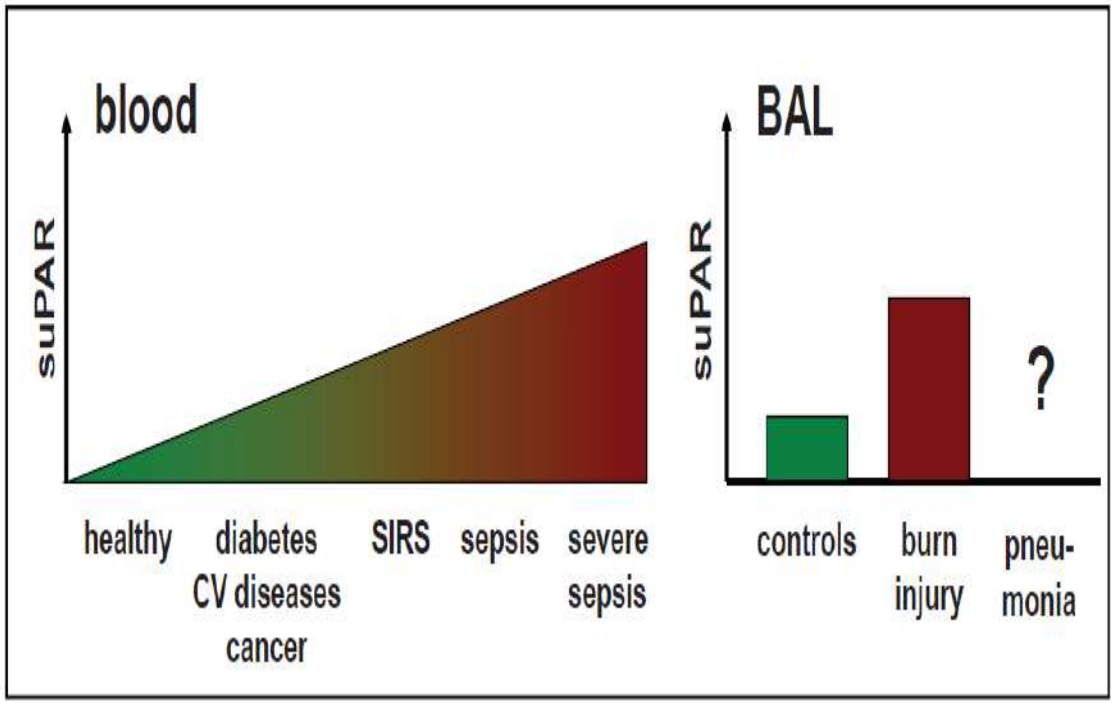
athens-NEPHROLOGY

Συμπεράσματα

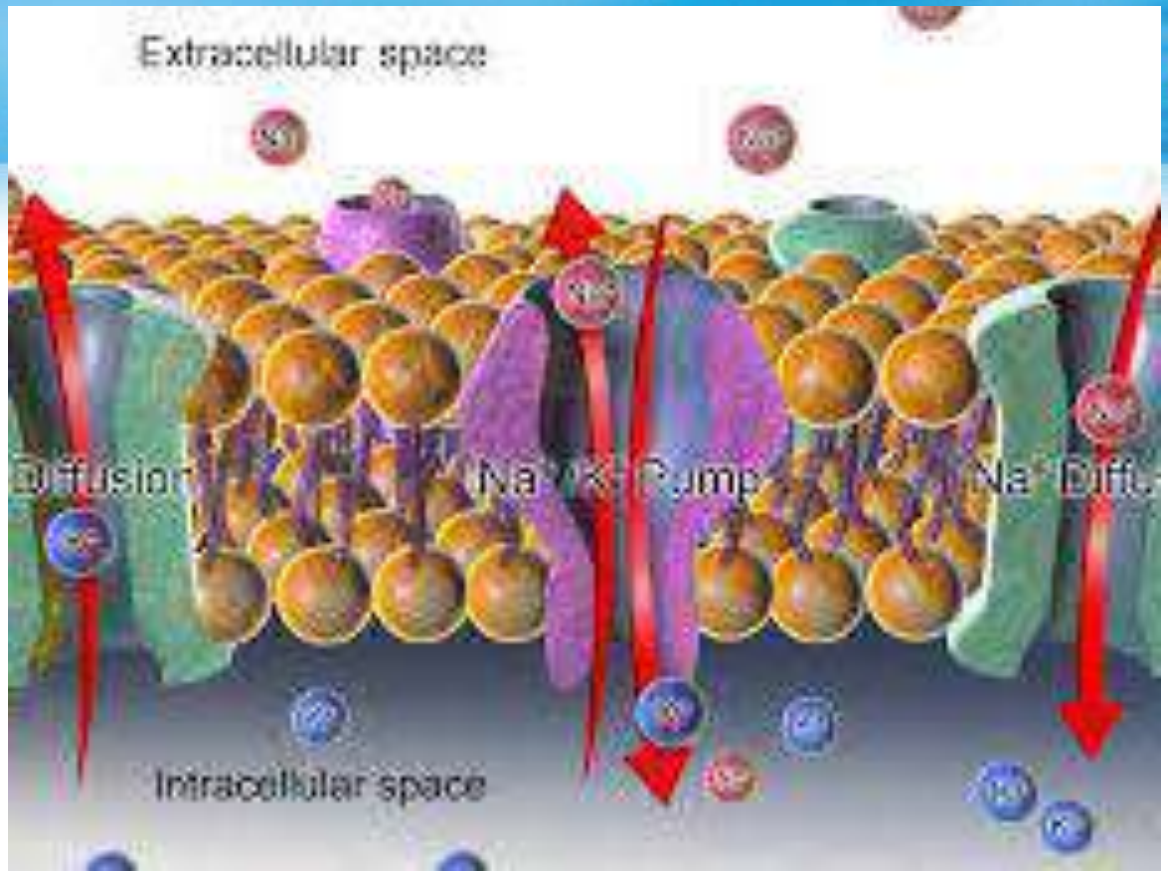
Τα ανωτέρω αποτελέσματα αναδεικνύουν τον δείκτη suPAR ως ένα υποσχόμενο δείκτη φλεγμονής για τον αιμοκαθαιρόμενο πληθυσμό.



Συμπεράσματα



Οι πρώτες ενδείξεις συσχέτισης του με το καθεστώς θρέψης, την αναιμία, την οστική νόσο, την νοσηρότητα και την θνησιμότητα απαιτούν περισσότερες μελέτες για πιο ασφαλή συμπεράσματα.



Cellular Functions

Ελληνική Νεφρολογία 2012; 24 (3): 167 - 173

Ανασκόπηση

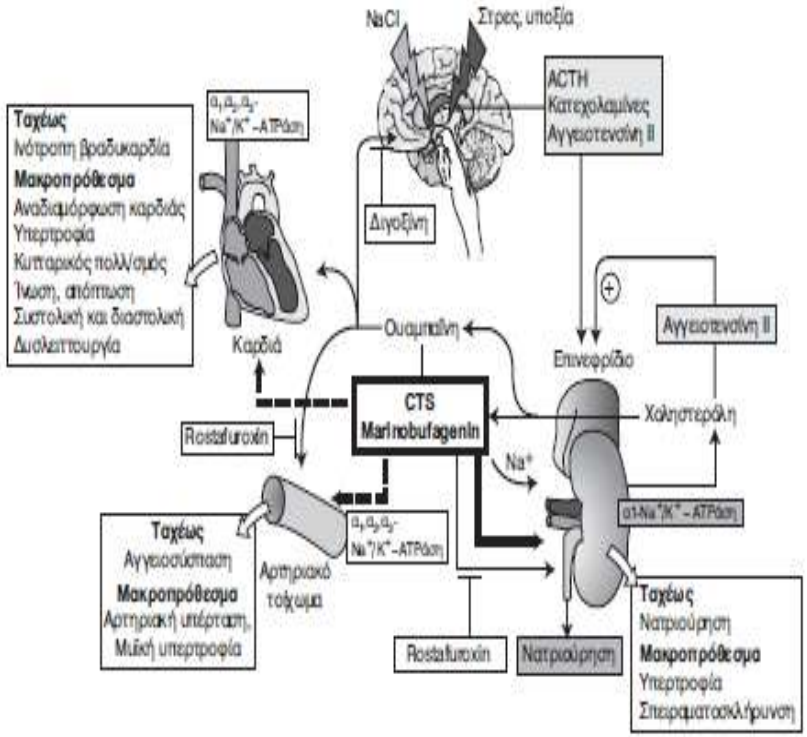
Σηματοδοτικές οδοί της ενδογενούς ουαμπαΐνης και νατριούρηση

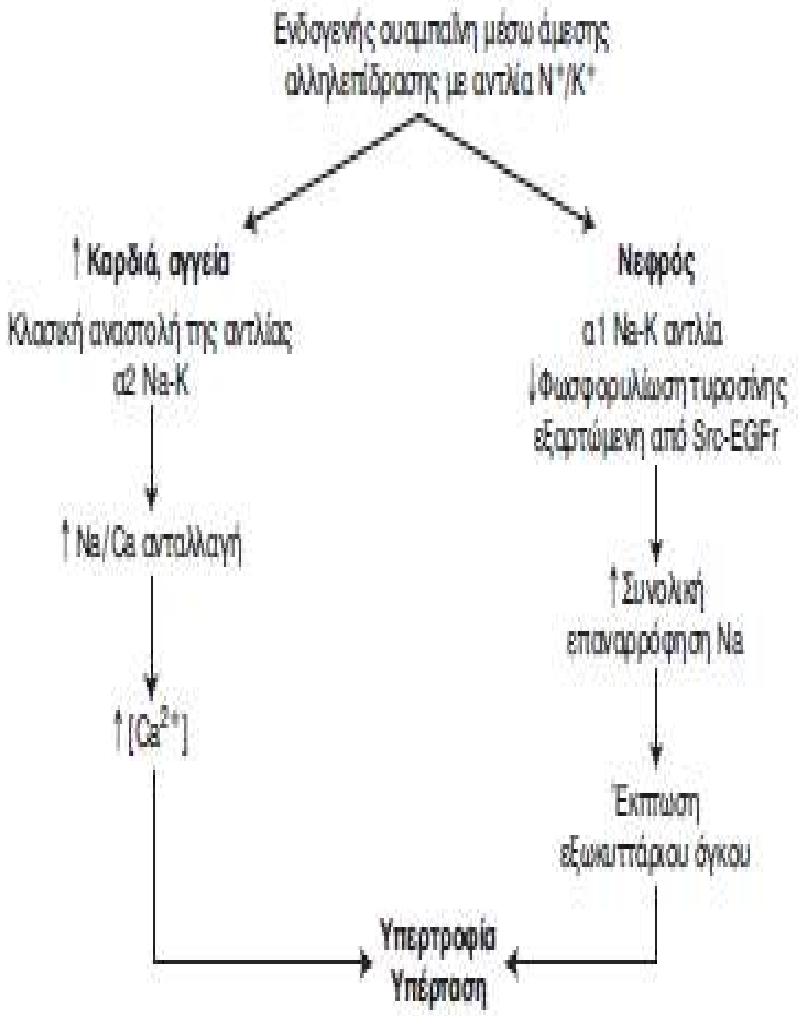
Ι. Γριβέας[1]
Η. Πασαδάκης[2]
Ν. Παπαγαλάνης[3]

Περίληψη

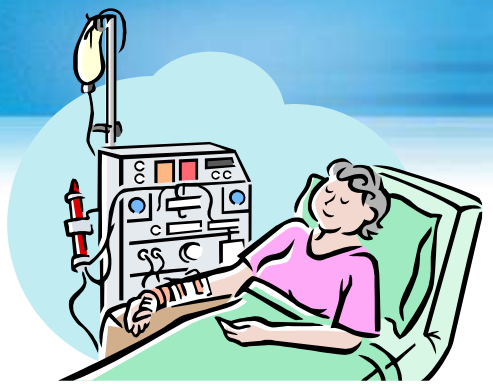
Η παρούσα ανασκόπηση αναφέρεται στην ενδογενή ουαμπαΐνη (ouabain), η οποία ανήκει στα ενδογενή καρδιοτονωτικά στεροειδή (endogenous cardiotonic steroids, CTS), ομάδα γνωστή και ως παράγοντες παρόμοιοι με δακτυλίδα (digitalis-like factors), ή αναστολέας της Na^+/K^+-ATPάσης. Τα CTS αποτελούν σύνδεσμο της διαψωρικής πρόσληψης NaCl και των καρδιαγγειακών και νεφρικών παθήσεων. Αν και η ύπαρξη και η σημασία των παραγόντων αυτών αποτέλεσε αντικείμενο διαμάχης, αξιοσημείωτη είναι η πρόοδος που έχει επιτευχθεί κατά τα τελευταία 15 χρόνια. Υπάρχουν σε υψηλά επίπεδα στο πλάσμα στο 40% περίπου ασθενών με ιδιοπαθή υπέρταση. Οι παράγοντες αιτιοί προκαλούν κατακράτηση άλατος μέσω αύξησης της δραστηριότητας και της έκφρασης της νεφρικής αντλίας νατρίου. Μελέτες τα τελευταία 10 χρόνια έχουν διευκρινίσει πολλές και σημαντικές πρωτεϊνικές αλληλεπιδράσεις της Na^+-K^+-ATPάσης οι οποίες σηματοδοτούν την έναρξη μιας καινούργιας εποχής. Άς σημειωθεί ότι γνωρίζουμε μέχρι σήμερα λίγα για τη συσχέτιση μεταξύ της μεταφοράς ιόντων με βάση τη λειτουργία της Na^+-K^+-ATPάσης και των μηχανισμών της σηματοδότησης στη ρύθμιση των λειτουργιών των κυττάρων.

Λέξεις κλειδιά: *αντλία Na^+, ουαμπαΐνη, υπέρταση.*





Conclusion



Maintenance of life in patients without kidney function is a remarkable achievement of modern medicine. But current treatment with dialysis carries a high price and leaves a persistent burden of disability. Although both the side effects of dialysis and the coexisting conditions in patients receiving this treatment contribute to the residual illness, retained solutes that are poorly cleared by standard treatment are an important part of the problem. A better understanding of uremic solutes and their toxic effects would place dialysis on a more rational basis and should lead to more effective therapy.

Critical Thinking – Inside a Dialysis Machine

National Kidney Foundation®

KDOQI®
Kidney Disease Outcomes Quality Initiative

KDOQI CLINICAL PRACTICE GUIDELINE FOR HEMODIALYSIS ADEQUACY: 2015 UPDATE

Box 2. Summary of Recommendation Statements

Guideline 1: Timing of Hemodialysis Initiation

1.1 Patients who reach CKD stage 4 (GFR < 30 mL/min/1.73 m^2), including those who have imminent need for maintenance dialysis at the time of initial assessment, should receive education about kidney failure and options for its treatment, including kidney transplantation, PD, HD in the home or in-center, and conservative treatment. Patients' family members and care-givers also should be educated about treatment choices for kidney failure. (*Not Graded*)

1.2 The decision to initiate maintenance dialysis in patients who choose to do so should be based primarily upon an assessment of signs and/or symptoms associated with uremia, evidence of protein-energy wasting, and the ability to safely manage metabolic abnormalities and/or volume overload with medical therapy rather than on a specific level of kidney function in the absence of such signs and symptoms. (*Not Graded*)

Guideline 2: Frequent and Long Duration Hemodialysis

In-center Frequent HD

2.1 We suggest that patients with end-stage kidney disease be offered in-center short frequent hemodialysis as an alternative to conventional in-center thrice weekly hemodialysis after considering individual patient preferences, the potential quality of life and physiological benefits, and the risks of these therapies. (*2C*)

2.2 We recommend that patients considering in-center short frequent hemodialysis be informed about the risks of this therapy, including a possible increase in vascular access procedures (*1B*) and the potential for hypotension during dialysis. (*1C*)

Home Long HD

2.3 Consider home long hemodialysis (6-8 hours, 3 to 6 nights per week) for patients with end-stage kidney disease who prefer this therapy for lifestyle considerations. (*Not Graded*)

2.4 We recommend that patients considering home long frequent hemodialysis be informed about the risks of this therapy, including possible increase in vascular access complications, potential for increased caregiver burden, and accelerated decline in residual kidney function. (*1C*)

Pregnancy

2.5 During pregnancy, women with end-stage kidney disease should receive long frequent hemodialysis either in-center or at home, depending on convenience. (*Not Graded*)

Guideline 3: Measurement of Dialysis: Urea Kinetics

3.1 We recommend a target single pool Kt/V (spKt/*V*) of 1.4 per hemodialysis session for patients treated thrice weekly, with a minimum delivered spKt/*V* of 1.2. (*1B*)

3.2 In patients with significant residual native kidney function (Kru), the dose of hemodialysis may be reduced provided Kru is measured periodically to avoid inadequate dialysis. (*Not Graded*)

3.3 For hemodialysis schedules other than thrice weekly, we suggest a target standard Kt/V of 2.3 volumes per week with a minimum delivered dose of 2.1 using a method of calculation that includes the contributions of ultrafiltration and residual kidney function. (*Not Graded*)

Guideline 4: Volume and Blood Pressure Control: Treatment Time and Ultrafiltration Rate

4.1 We recommend that patients with low residual kidney function (< 2 mL/min) undergoing thrice weekly hemodialysis be prescribed a bare minimum of 3 hours per session. (*1D*)

4.1.1 Consider additional hemodialysis sessions or longer hemodialysis treatment times for patients with large weight gains, high ultrafiltration rates, poorly controlled blood pressure, difficulty achieving dry weight, or poor metabolic control (such as hyperphosphatemia, metabolic acidosis, and/or hyperkalemia). (*Not Graded*)

4.2 We recommend both reducing dietary sodium intake as well as adequate sodium/water removal with hemodialysis to manage hypertension, hypervolemia, and left ventricular hypertrophy. (*1B*)

4.2.1 Prescribe an ultrafiltration rate for each hemodialysis session that allows for an optimal balance among achieving euvolemia, adequate blood pressure control and solute clearance, while minimizing hemodynamic instability and intradialytic symptoms. (*Not Graded*)

Guideline 5: New Hemodialysis Membranes

5.1 We recommend the use of biocompatible, either high or low flux hemodialysis membranes for intermittent hemodialysis. (*1B*)

Hemodialysis dose

Components of the dialysis Prescription:

- Type of dialyzer
- Time
- Blood flow rate (Qb)
- Dialysate flow rate (Qd)
- Dialysate composition
- Dialysate temperature
- Ultrafiltration rate
- Anticoagulation
- Dialysis frequency
- Intradialytic medications

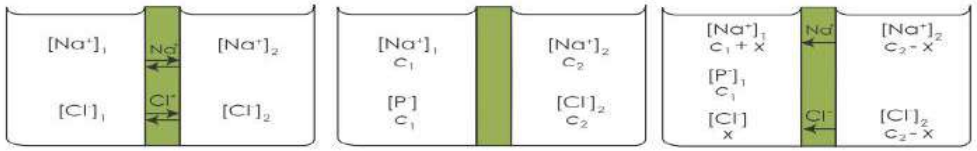


Figure 7.25 (a) Sodium and chloride ions separated by a membrane. (b) Na^+P^- and Na^+Cl^- separated by a membrane: initial conditions. (c) The final Donnan equilibrium conditions arising from (b).

Dialyzer

Key facets of a dialyzer:

- Capacity for solute clearance
- Capacity for ultrafiltration of fluids
- Nature of dialyzer membrane (biocompatibility)

Ideal dialyzer:

- Low & middle molecular weight molecule clearance
- Vital solutes
- Adequate ultrafiltration
- Low adverse metabolic events
- Low blood volume compartment
- Low Cost
- Reliable
- Low Gibbs-Donnan effects - *in vitro* vs. *in vivo*

Dialyzer 2

- Diffusive vs convective clearance >300Da
  - surface area, thickness, pore size, pore density, and potential to adsorb proteins
- Ultrafiltration co-efficient
- Hollow fiber vs. parallel plate
- Humoral activation pathway clotting vs complement
- Cellular activation pathway
- Reuse
- Types of membranes
  - Cellulosic, Coated, Synthetic
- Biocompatible membranes
- Classification of dialyzers: solute vs water flux

Dialyzer Clearance

Diffusive and convective. Small molecules move principally by diffusion

Mass solute transfer across a dialyzer or diffusive dialyzer clearance
$(K) = Q_b(C_a - C_v) / C_a$
For solutes not present in dialysate $K = Q_{do}(C_{do})/C_a$
Clearance varies with blood flow. Mass transfer coefficient is constant K_oA:

Mass transfer area coefficient $(K_oA) = \frac{Q_b \times Q_d}{Q_b - Q_d} \ln\left(\frac{Q_d(Q_b - K_d)}{(Q_b(Q_d - K_d)}\right)$

K_o (cm/min) may be thought of solute flux /unit area/unit of concentration gradient
K_oA is the most specific constant that describes the efficiency of a dialyzer for removal of a specific solute and represents maximum clearance

FACTORS AFFECTING CLEARANCE

Toxin related	Procedure related	
	LMW	HMW
Size	Dialysate	Flux
Charge	Q_b	Time
Protein binding	Q_d	area
Vol. Distribution	area	Q_b
	Time	Q_d
	Flux	Dialysate

C_a = conc. arterial
C_v = conc. venous
C_{do} = conc dialysate
Q_{do} = flow dialytsate

Water Permeability

Measured by ultrafiltration co-efficient K_{UF}

ml/hr/mmHg of TMP, measured in vitro using bovine blood. Taken from linear part of curve

Directly related to Pore size (power 4) and also size of membrane

Solute and Water permeability do not necessarily correlate
Porosity (i.e. total area of pores) and depth of pores determines small solute transfer whereas pore size affects water flux
Also HMW molecules can adsorb to hydrophobic microdomains, increasing local concentrations

Discrepancy between solute and water flux

Example 1. Cellulose acetate or PS membrane with K_{UF} of 6ml/h/mmHg and 1.1m^2, has B_{12} clearance of 50ml/min and no β_2M clearance

Modified co-polymer membrane has same K_{UF} has B_{12} clearance of 87ml/min and reduces β_2M by 20-30% during 3h dialysis

Example 2.	Membrane	Cellulosic	PS
	K_{UF}	6ml/h/mmHg	8ml/h/mmHg
	A	1.75m^2	1.8m^2
	Thickness	9µm	40µm
	K_oA gentamicin	127ml/min	84ml/min

Dialyzer membrane types

CELLULOSIC	SYNTHETIC
Hydrophilic	Hydrophobic
<protein binds	>protein binds
>C3a, C5a	-ve charge/Contact pathway*
>leukocyte activation	
Thinner 8-15µm (swell)	thicker (20-40µm)
>diffusion of pyrogens	
FORMULATIONS	
Cuprophan	Polysulfone (PS)
Cellulose acetate	Polyether polycarbonate (PC)**
Hemophan	Polyacrylonitrile (PAN) e.g. AN69*
SMC**	PMMA
Cellulose triacetate	Polyethersulfone
Vitamin E	

PPV is required to add hydrophilic domains to synthetic membranes

* Associated with anaphylaxis with ACEI - bradykinin/kallikrein syndrome

** microdomain structure

$C3_a$,$C5_a$ release -->VSMC contraction, vasc perm, MAC,PMN activation

Solute size and clearance

	Size	example	clearance
Small molecule solutes	<200D	urea	Diffusion
Middle molecules	200-12,000D	vitamin B_{12}	Diffusion or below
LMW proteins	12,000-50,000D	β_2M	Conv/Diff/Adsorb

Putative Middle Molecules	Putative LMW toxins
P-cresol	complement factor D
Indoxyl-sulfate	β_2-microglobulin
CMPF (acid)	Granulocyte inhibitory proteins
Hippuric acid	Parathyroid hormone
Guanidines	Advanced glycation end products
Uric acid	Anaphylactoids, C3a, C5a
Homocysteine	Carbamylated proteins
Phenolic acid	
Quinolic acid	
Homocysteine	

Many middle molecules are protein bound

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	Size	example	clearance
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Guanidines	Advanced glycation end products
Uric acid	Anaphylactoids, C3a, C5a
Homocysteine	Carbamylated proteins
Phenolic acid	
Quinolic acid	
Homocysteine	

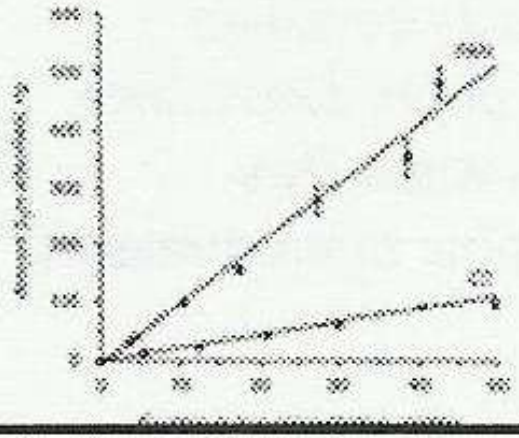
Many middle molecules are protein bound

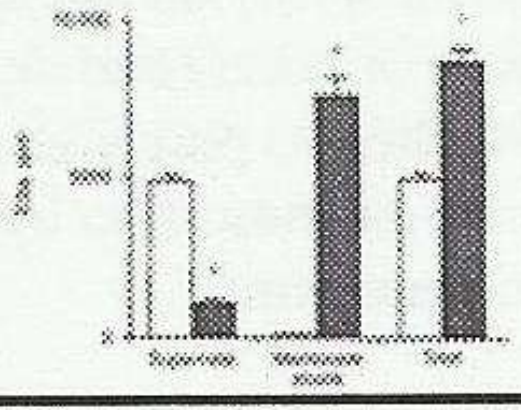
Dialyzer Membrane Permeability

Dialyzer	K_oA_{urea} (ml/min)	K_{UF} water coeff	Hyropilia	Membrane
Low Flux	<450	<10ml/mmHg/h	hydrophilic	Symmetrical
High Efficiency	>450	10-19ml/mmHg/h	Intermediate	Intermediate
High Flux	>450	>15	hydrophobic	Asymmetrical

High Flux Dialyzers

- Pores permit >10kD molecules to pass with K up to 40ml/min (i.e. 40mls of plasma cleared of it per minute)
- High Protein/peptide binding
- Synthetic dialyzers rely more on adsorption to the internal pore structure for clearance
- Cellusolic dialyzers are thinner





Clark et al KI (1999); 56:2235

Use of High Efficiency & High Flux Dialyzers

LMW clearance	Adequate HD in larger pts
HMW Clearance	Better K of middle molecules (300-1500D) & clearance of HMW substances β_2M=11.8kD
Biocompatibility	Reduced complement/leukocyte activation possibly reduced morb/mort
Time	Reduced

Unequivocal data that high flux dialyzers reduce the incidence of β_2M amyloidosis

Several large retrospective studies showing improved mortality using biocompatible dialyzers. However may be confounded by high flux of dialyzers. No prospective studies confirm this.

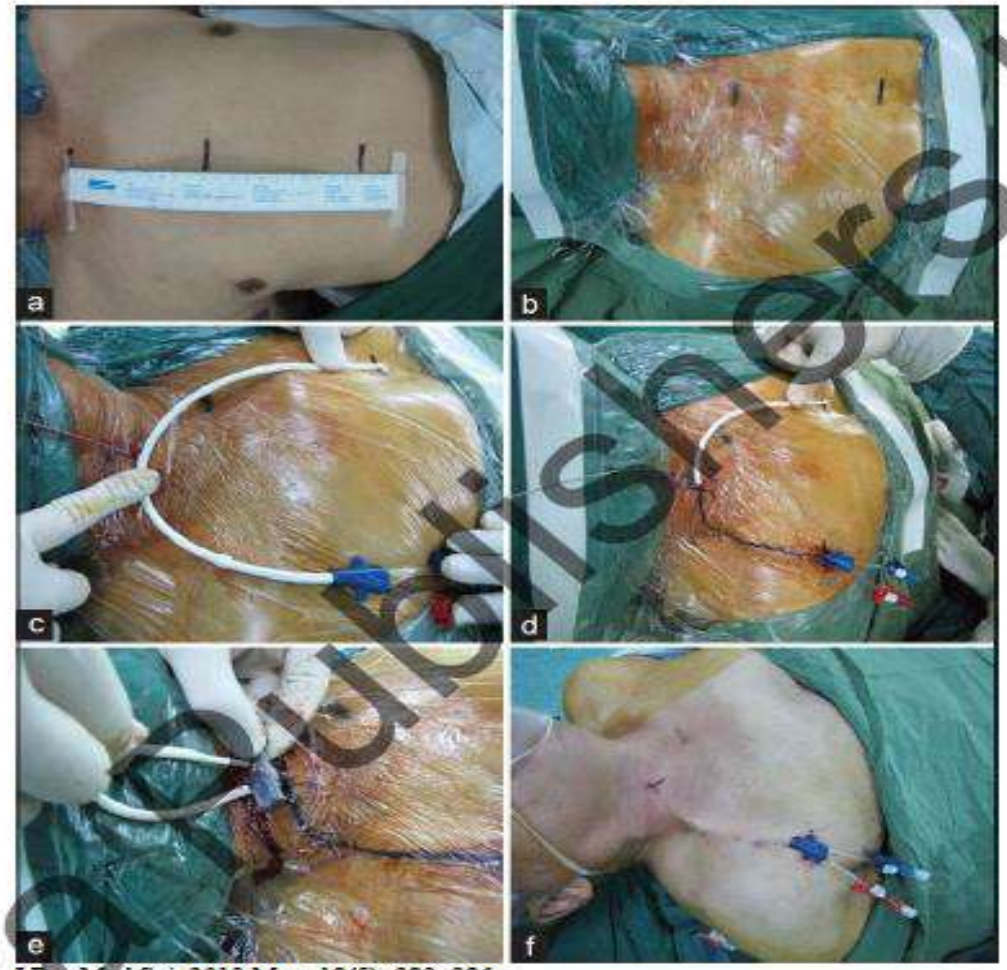
Flow rate

Flow limited mass transfer is part of clearance characteristics

- Resistance/turbulence, Non linear flow
- Boundary layers & streaming effects increased K_oA, maintaining countercurrent gradient
- For hollow fibre dialyzers K_{urea} increases between Q_b 200-300ml/min, and rises less steeply to 400-500ml/min
- Solute removal: Sigdell/Tersteegen dialysate flow max 2 x blood flow
- Recirculation: $R = C_s - C_a / C_s - C_v$. Best C_s is from arterial port where $Q_d = 0$ $Q_b = 50$ml/min. Alternatives, saline/hematocrit or cold bolus/temp probe
- Mismatch of blood/dialysate
- Optimize flow for individuals

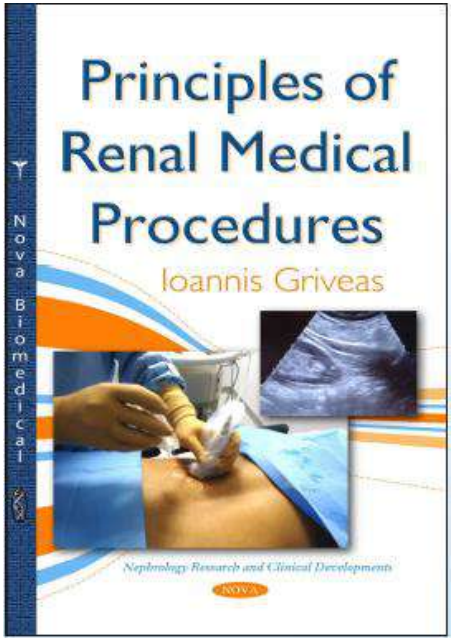
Sigdell & Tersteegen Nephron. 1995;71(4):401-6.

12. Always get a chest x ray (if fluoroscopy was not used) to check position of line and rule out any complications.



J Res Med Sci. 2013 May; 18(5): 383–386.

Figure 1. (a-f) different steps of catheter placement. (a) measurement of insertion depth, (b) creation of the sterile field, (c) insertion of guidewire, (d) creation of tunnel, (e) passing the catheter into the vein, (f) completion of procedure.



Time

- Solute clearance increased with time
- Diminishing returns
- Volume homeostasis and intra-dialytic complications
- Tassin experience
  - 6-8h, BP control, volume control, larger molecule clearance, Phosphate control, best survival, less disparity between prescribed and delivered dialysis
  - Kt/V 1.67 10y survival 88% (35y) 64% (65y) (Cellulosic)
- Daily dialysis experience
- Time as an independent variable?

"What is Kt/V???"

K is simply the clearance of the dialyzer. ***T*** is time. ***V*** is distribution volume of urea.

Kt/V = fractional urea clearance

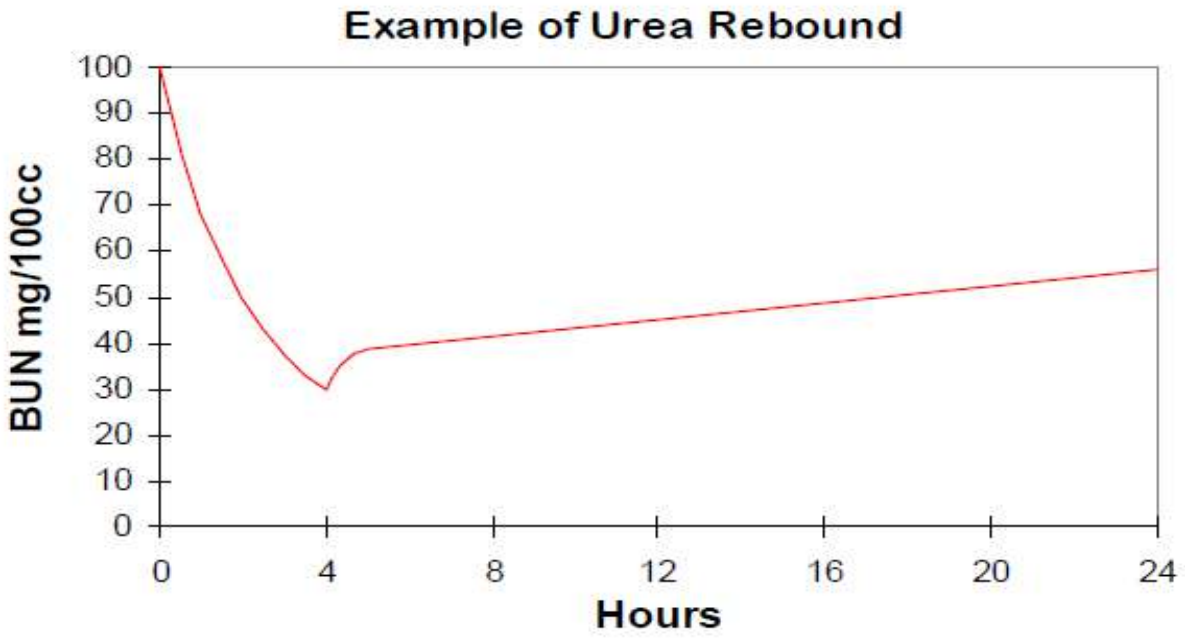
K = dialyzer clearance (ml/min. or L/hr.)
t = time (minute or hour)
V = distribution volume of urea (ml or L)

K x t = L/hr x hr = LITERS
V = LITERS
Kt/V = LITERS/LITERS = ratio

URR = (Pre BUN - Post BUN) / Pre BUN

The resulting fraction is often converted to a percentage by multiplying the result by 100. This latter formula is:

URR = (Pre BUN - Post BUN) / Pre BUN * 100



The problem with V

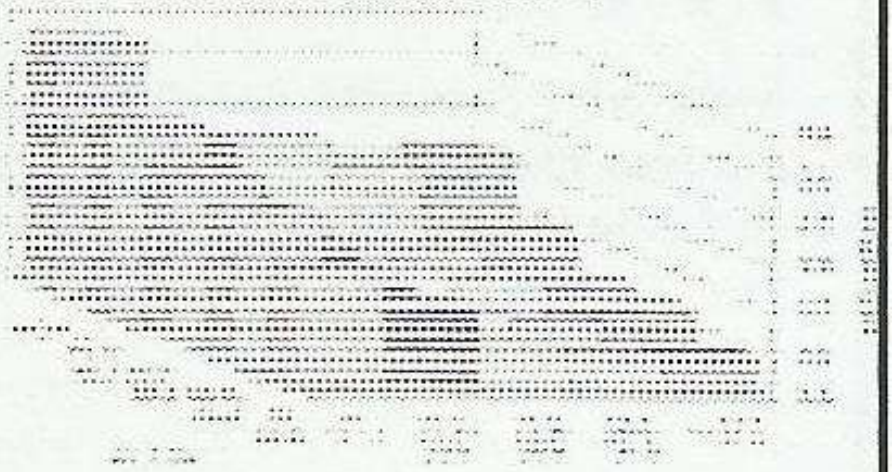
Anthropometric formulas (Watson) vs. kinetic modeling (9-13% lower) vs. bioimpedence vs. dilution

V is an independent predictor of mortality. V predicts low body mass and patients with low body mass on dialysis are more likely to die.

Kt/V assumes that smaller people require less total treatment (Kt) to achieve adequacy. However the survival curve is J shaped

Lowrie et al in a large retrospective study demonstrated that Kt is a predictor of survival and that Kt against survival generates a linear curve not a J curve

Conclusion: In patients with BMI below 24, consider targeting Kt > 50L/*Rx*



Lowrie et al KI (1999); 56:729

Dialysate composition

Sodium: options similar to plasma Na, hyponatric, sodium modeling

•130-135. Used historically Prevents HTN, thirst, wt gain, but high dialysis dysequilibrium, hypotension & cramps interdialytic

•140-144

•>145. Sodium modeling. May reduce symptoms but increased thirst, IDWG, hypertension.

•tailored to patient's plasma Na

Potassium:

•1-2% of 3000-3500mEq is in ECF. Rate largely dependent on predialyisis K.

•Setting K tends to be empirical.

•Evidence that arrhythmias occur in first half of HD during greatest change. Highest sudden death in patients in lowest K bath.

•Consider stepwise approach.

Calcium:

•60% plasma Ca is not protein bountPositive intradialytic calcium balance. Achieved with 3.5mEq/L or 7.0mg/dL)

•2.5-3.0 to prevent hypercalcemia.

•Cardiac contractility/BP/QT dispersion

Dialysate composition

Magnesium:

•Magnesium flux unclear since 1% only is in plasma, 60% is ionic. Most centres use 1mEq/L

Buffers: Acetate- standard for 20y until high flux dialyzers

•Acetate toxicity (nausea, vomiting, headache, fatigue, hypoxemia)

•Bicarbonate. Proportioning systems (single patient) mixes bicarbonate and divalent ions in acid.

•Rarely varied from 30-35

•Can support pathogen growth. Membrane filters on dialysate

Chloride: Major anion. Defined by cation prescription

Glucose:

•Most dialysate used physiological 200mg/dL. Dialysis imposed glucose clamp. Affects K+ removal, dialysis dysequilibruim, post dialysis fatigue

Dialysate temperature

- Dialysate usually maintained between 36.5 and 38C
- Heat generation during HD. Response to heat generation
- Role of pyrogens
- Evidence that dialysate temperature determinant of intradialytic BP, improved contractility, venous tone, complement activation
- Isothermic dialysis

Ultrafiltration Rate

•Definition of dry weight: lowest weight a patient can tolerate without signs or symptoms of hypovolemia. Can be measured but usually determined clinically

•Hematocrit monitoring maybe of use in assessing dry weight

•Achieving dry weight should be accomplished gradually over a number of dialysis treatments (usually over 4 to 12 weeks, but it may require as long as 6 to 12 months) until evidence of fluid overload is in abeyance. May take longer in diabetics

•goal to render the patient euvolemic and normotensive. This includes counseling the patient on sodium and fluid restriction, adequate ultrafiltration, and the use of diuretics in patients with RKF (residual kidney function)

•Study of USRDS cohorts when adjusted for comorbidity, showed that weight gain between dialyses of more than 4.8% (ie, 3.4 kg in a 70 kg person), a reflection of excessive sodium and water intake, is associated with increased mortality

•Some patients require longer time to achieve fluid removal

•Hypotension induced by overzealous UF rate contributes to loss of RKF and coronary, cerebral ischemia and short dialysis times.

National Cooperative Dialysis study

1976-1984 Prospective 160 pts 2x2 factorial trial. Single pool urea kinetics model.

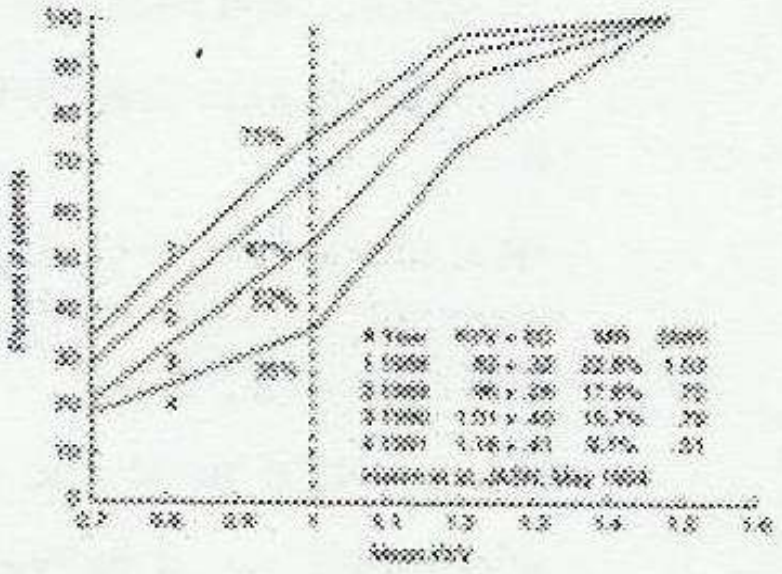
Group I	**Intensive Long TAC_{urea} 52 (Long 269min)**
Group III	**Intensive TAC_{urea} 52 (Short 199min)**
Group II	**Less Intensive TAC_{urea} 89 (long 271min)**
Group IV	**Less Intensive TAC_{urea} 89 (short 194min)**

Group IV discontinued. Groups I, III better survival. TAC_{urea} primary outcome, time much weaker but statistically significant with outcomes

TAC_{urea} depends on UF, dialyzer size, time, flow rate residual renal function etc.

Re-analyzed using single pool
$K_{urea} \times t_d/V_{urea}$ (or spKt/V)
(focusing on intradialytic time)

Kt/V > 0.8 had good outcome

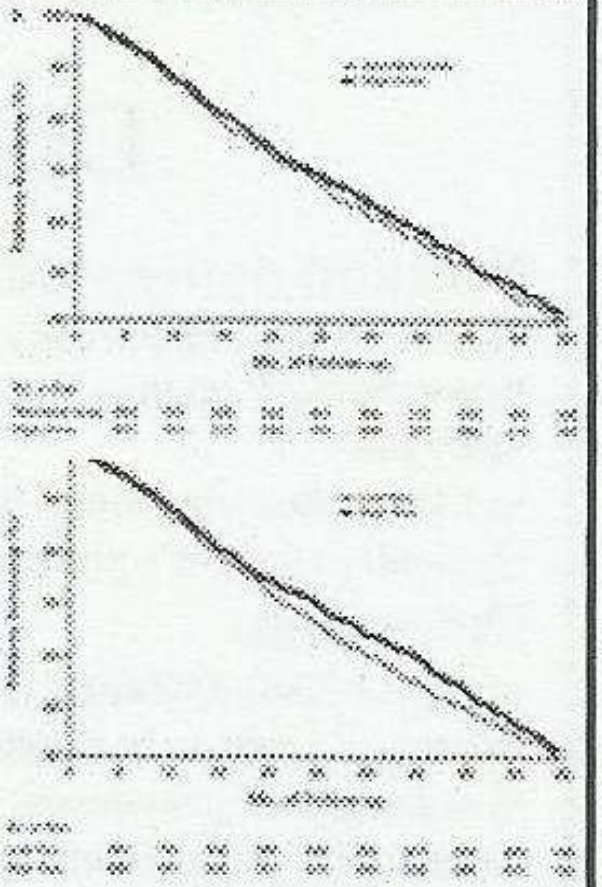


Subsequent retrospective & observational studies (e.g. Hakim et al) showed increasing Kt/V up to 1.2 was associated with increased survival

Hemo study

1846 patients. Prospective 3x a week dialysis, study period 5y. 2x2 factorial design HD dose & membrane flux

1. High dose, high flux
2. High dose, low flux
3. Low dose, high flux
4. Low dose low Flux



- Prescribed equilibrated eKt/V 1.05, (spKt/V 1.25) vs eKt/V 1.45, (spKt/V 1.65)
- Achieved eKt/V 1.16 (sp 1.32) (URR 67%) vs 1.53 (sp1.71) (URR 75%) respectively

β_2-M clearance was 3 vs 34 ml/min

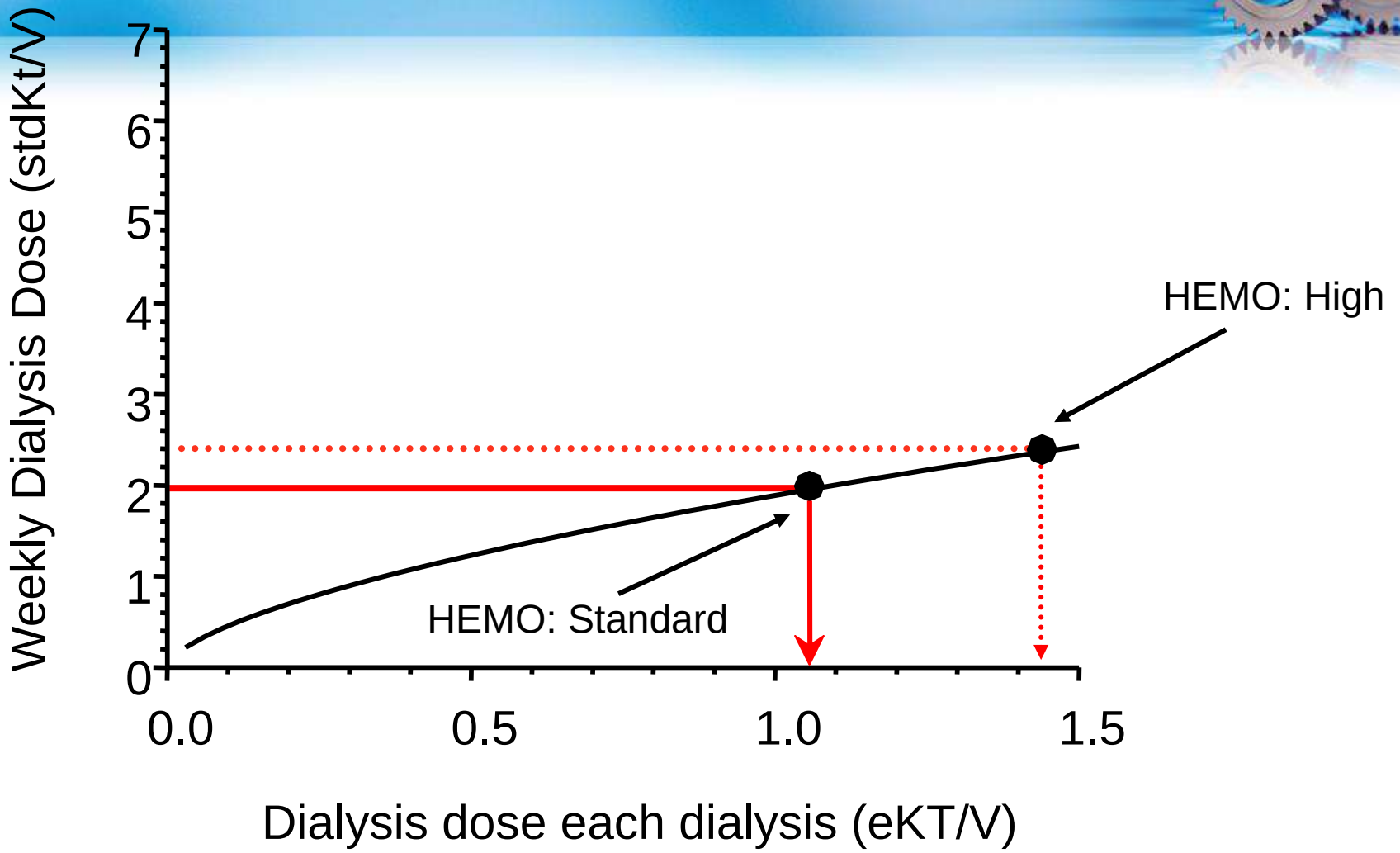
- Primary (death) and secondary outcomes were no different between groups
- Patients on HD for >3.7y had lower mortality with high flux dialyzers (RR 0.68 $P = 0.01$)
- Sub- analysis: high flux lead to fewer hospitalizations or death from cardiac disease, and women had lower mortality with higher dose

Annual mortality rate in USA 20-22%

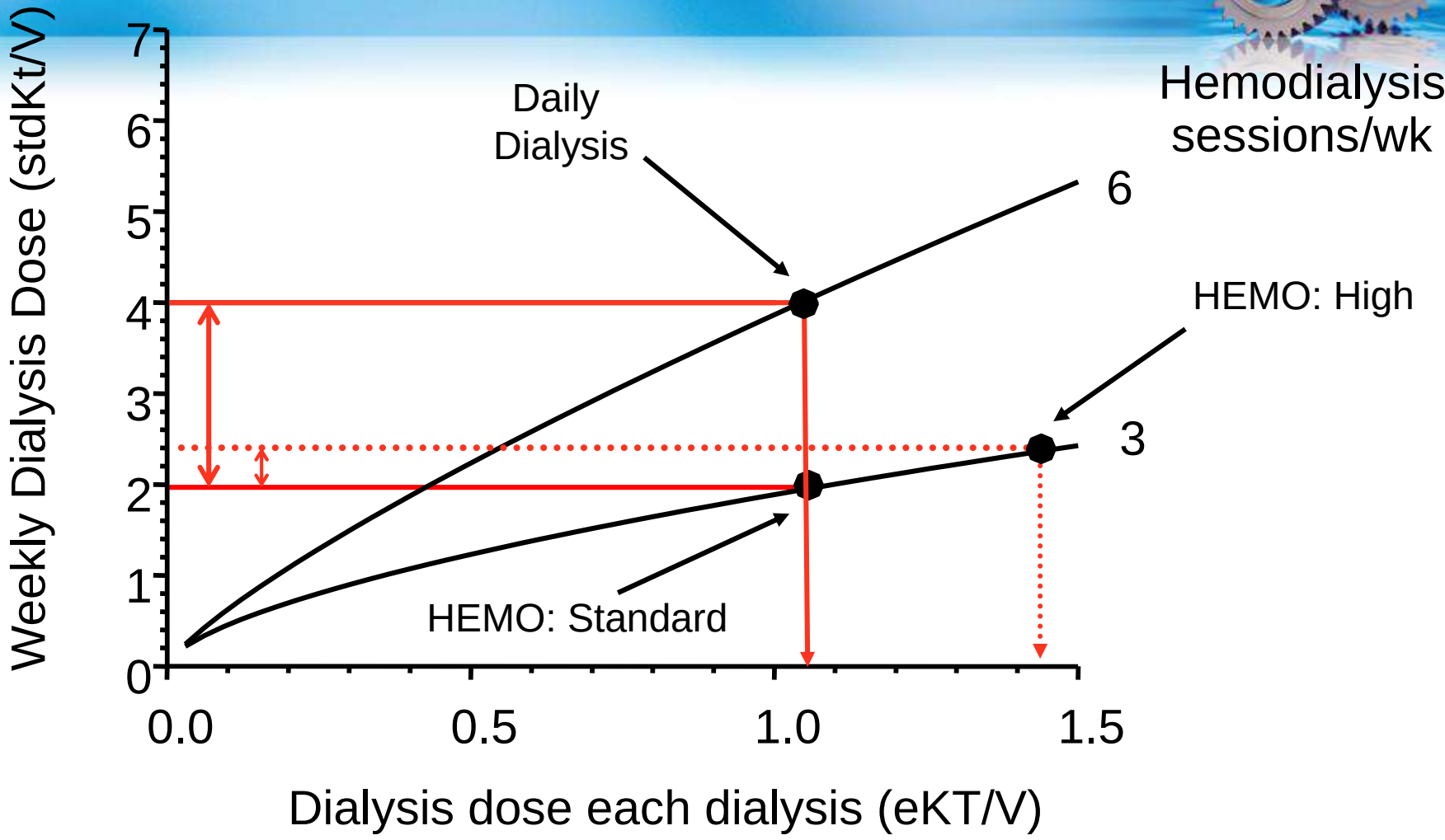
Several large observational studies indicate increasing spKt/V to 1.7 will lead to improvements in mortality

Eknoyan et al NEJM (2002) 347:2010

Effect of increasing length of dialysis Three sessions per week



Effect of increasing number of dialysis sessions per week



Alternatives to the standard 3x weekly prescription

Nocturnal slow dialysis 8h 3 x wkly
Daily short dialysis 2.5-3h 6 x wkly

Small prospective controlled study showing improved (8-10h vs 4h 3x wkly) : Pre-dialysis BP, cardiac LVMI, cardiac FS, phosphate control, increased Hb, decreased Epo resistance, reduction in tablets / anti-hypertensives, reduction in PTH with nocturnal dialysis

Many other non-controlled studies showing improved nutrition, total body nitrogen, QoL, BP control, fluid balance and mortality.
In Tassin France, mortality on >64y was 55% over 10y

Urea kinetic modeling

Single Pool Kt/V: = -ln(R - 0.008 x t) + (4 - 3.5 x R) X UF/W

Double Pool (Equilibrated) Kt/V = single pool Kt/V - 0.6 x K/V + 0.03

$R = C_t/C_o$, UF = UF volume (L), W = post weight (Kg)

Kt/V Daugirdas - single pool

Kt/V Lowrie

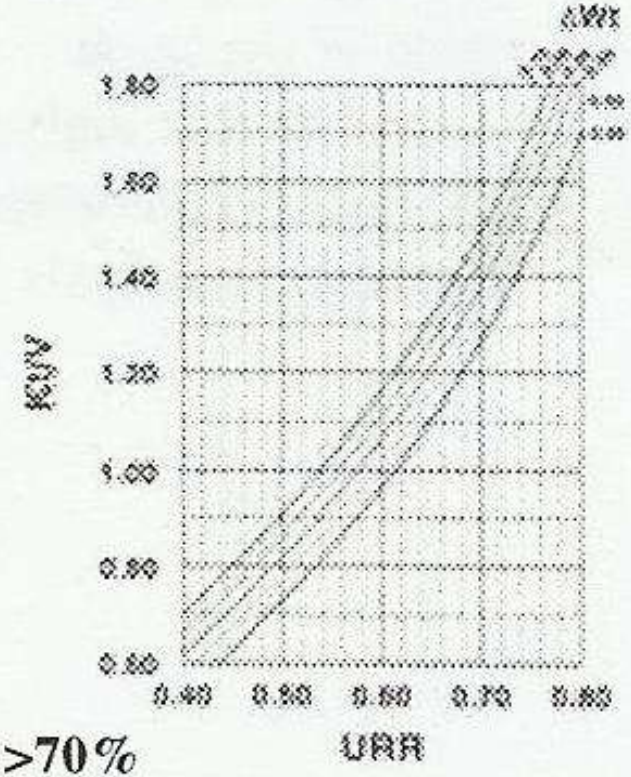
eKt/V Daugirdas double pool

URR = 100 X (1 - C_t/C_o)

UKM (3 and 2 urea samples)

Kt

Relationship between standard weekly Kt/V and intermittent Kt/V



Guidelines: for patients on 3x weekly HD with K_r < 2ml/min/1.73m², targeted spKt/V = 1.4, or URR >70%

Daugirdas et al (1993) JASN 4:1205

1. Method for estimating spKt/V from the natural logarithm of the postdialysis to predialysis BUN ratio.

A linear equation has been developed and been shown to give reliable results for spKt/V when applied to HD administered 3 times per week[138]:

$$spKt/V = -\ln(R - 0.008 \times T) + (4 - 3.5 \times R) \times 0.55 \times \text{Weight loss}/V$$

R is the ratio of postdialysis to predialysis BUN; V is body water volume and Weight loss is expressed in the same units; and T is treatment time in hours.

However, for other schedules including twice or up to 7 treatments per week, the results stray from Kt/V values assessed by formal urea modeling. The errors are largely due to differences in the effect of urea generation between treatments. A recent change to the above established formula accounts for this variable and effectively eliminates these errors:

$$spKt/V = -\ln(R - GFAC \times T) + (4 - 3.5 \times R) \times 0.55 \times \text{Weight loss}/V$$ [149]

This equation differs from the above by substitution of GFAC (G factor) for the constant 0.008. GFAC is a term that reduces R to its estimated value in the absence of urea generation and ranges from 0.0045 to 0.0175, depending on the frequency of treatments, but mostly on the preceding interdialysis interval (PIDI). Values can be obtained from a table in the original publication and can be roughly estimated as 0.175 divided by the PIDI in days.

3. Method for estimating stdKtV from spKt/V.

stdKt/V was conceived by Gotch[145] as a method for downgrading intermittent dialyzer clearances to the equivalent of a continuous clearance by redefining clearance as the urea generation rate (G) divided by the average predialysis BUN (avCpre). The calculation was based on a fixed volume model of urea kinetics during an entire week. The original method was later simplified by Leypoldt[150] and then further enhanced by Daugirdas et al,[146] who included the patient's ultrafiltration rate (Uf) and Kru. As originally defined by Gotch,[145] stdKt/V includes the effects of Uf and Kru. However, when measured using modeled values for G, eKt/V, and avCpre, the contribution of Kru is inappropriately downgraded because G/avCpre assumes that the Kru component also uses the avCpre instead of the average BUN in the denominator. To correct for this error when Kru is included, modeled values for G and V must be used to calculate stdKt/V in the absence of Kru, which can then be added as Kru × 10,080/V.[146]

The following set of equations allow a reasonable approximation of true stdKt/V from spKt/V with accurate contributions by Uf and Kru.[145,146,150]

$$eKt/V = spKt/V(t/(t + 30))$$ [151]

$$stdKt/V = \frac{10{,}080\,\frac{1-e^{-eKt/V}}{t}}{\frac{1-e^{-eKt/V}}{eKt/V} + \frac{10{,}080}{Nt} - 1}$$

Formal Urea Kinetic Modeling

Recommended by K-DOQI. RPA

- Used to prescribe individual hemodialysis treatment
- Checks for errors in dosage
- Approximately take into account residual renal function
- Permits calculation of nPCR (an independent risk factor)

Measure delivered Kt/V by single pool differential equation:

$d(V \times C)/dt = G - (K + K_r) \times C$ (accumulation = generation - loss)

Where G = generation of urea, C = conc urea, V = volume distribution urea, K = urea mass cleared by dialyzer

Incorporate residual renal function as urea clearance $(K_r) = (U_{urea} \times V)/(P_{urea} \times t)$

Corrected $Kt/V = Kt/V_d + 5.5 \times K_r/V$

Complex formulae to derive V(kinetically derived) and G requiring C_o, C_t, C_{o2}, weights pre, post and pre(2), interdialytic interval

Measure prescribed Kt/V using K from: $K_oA = \frac{Q_b \times Q_d}{Q_b - Q_d} \ln\left(\frac{Q_d(Q_b - K_d)}{(Q_b(Q_d - K_d)}\right)$

Protein catabolic rate (PCR) = 9.35G + 0.29V

nPCR = PCR/nBWT (V/0.58)

nPCR enables longitudinal analysis of nutritional status

Estimations and Limitations

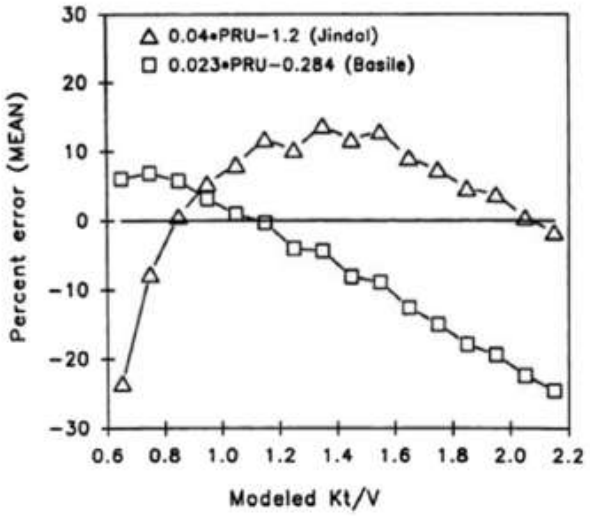


Figure 1. Systematic errors from 2 commonly used linear formulas based on percent reduction in urea concentration (PRU). The formula of Basile et al[136] has less error than the equation of Jindal et al[137] in the usual range, but it overestimates the dose in the critical area of Kt/V < 1.0. Reproduced with permission of the American Society of Nephrology from Daugirdas.[138]

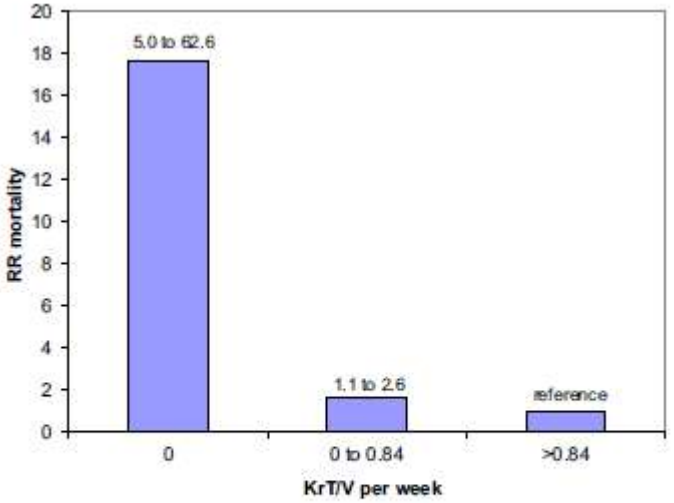


Figure 2. Data from the Netherlands Cooperative Study showing a marked increase in risk of death in patients with no residual native kidney function (KrT/V). Data source: Termorschuizen et al.[140]

Under-delivery of prescribed dialysis

Compromised urea clearance

- Access recirculation
- Inadequate access flow
- Dialyser clotting
- Dialyzer leaks
- Dialysate flow errors

Reductions in treatment time

- Inaccurate time measured
- Interrupted Rx
- Premature discontinuation

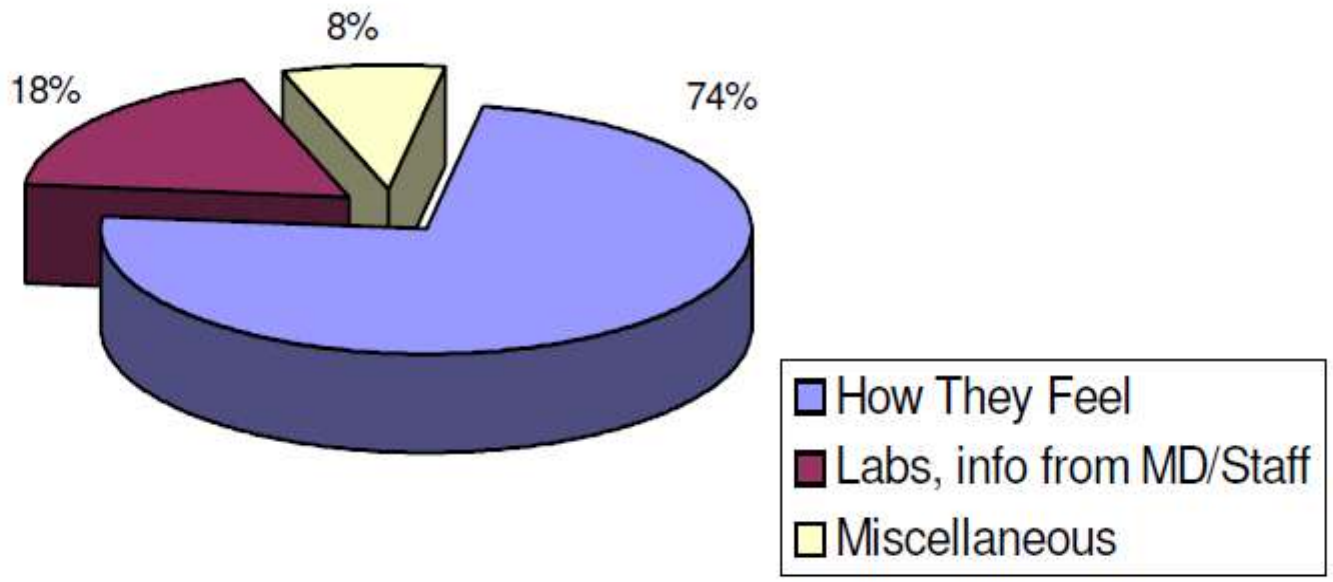
Laboratory or sampling errors

- Dilution of pre-BUN with saline
- Pre-BUN drawn late
- Post BUN drawn early
- Post-BUN drawn late

Six areas of Prescription and Delivery that directly and/or indirectly impact adequacy of hemodialysis are:

- *Weight*
- *Duration (Time)*
- *Kt/V (Technical / Practical)*
- *Blood Flow Rate*
- *Dialysate Flow Rate*
- *Dialyzers*

Basis for How Patients Assess Adequate Dialysis



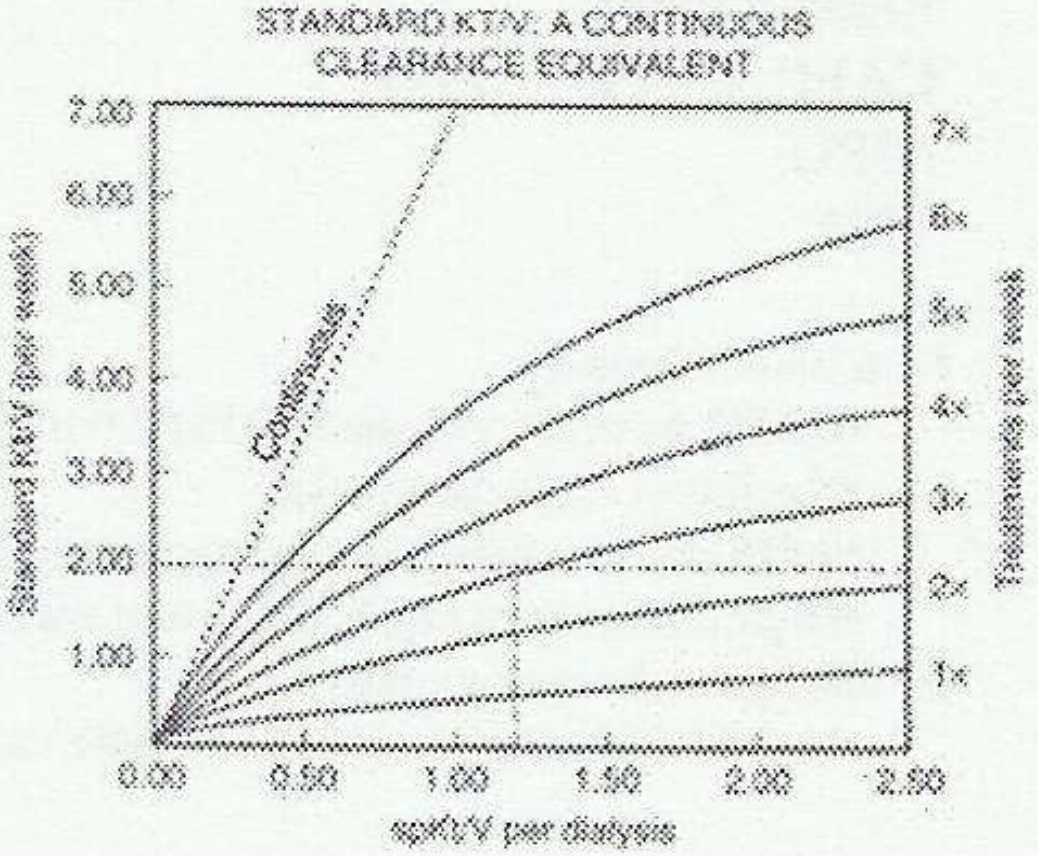
Sehgal et.al., 1997: n=145

QOL should be performed routinely to notice changes in patients' lives or perceptions. It is easier to work proactively in a patient's environment than to work retrospectively.

Standard Kt/V

Methods to compare Kt/V from intermittent treatments and continuous treatments.
Based on TAC_{urea}

Important for adding K_r to K_d in patients with residual renal function > 2ml/min/1.73m^2



Pereira, Sayegh, Blake Chronic Kidney Disease, Dialysis, & Transplantation 2nd Edition

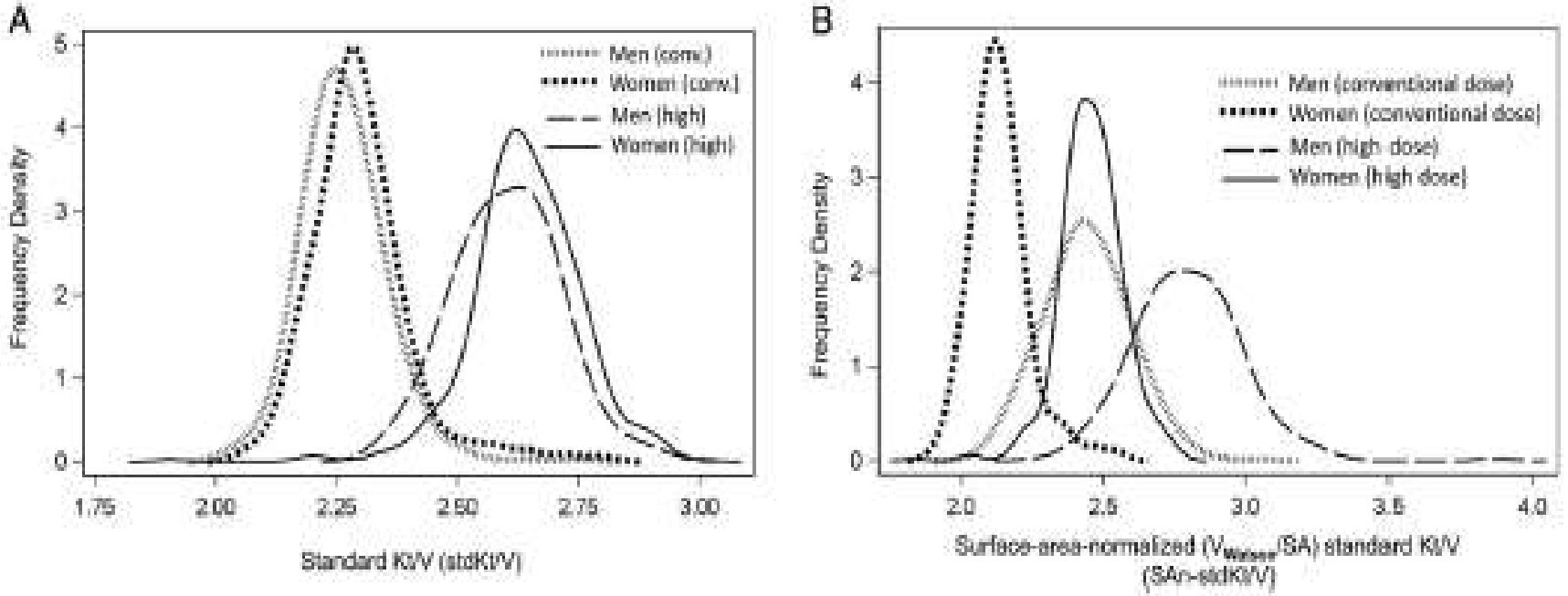


Figure 3. Delivered dialysis doses in the HEMO (Hemodialysis) Study. (A) A clear separation of the delivered dialysis doses expressed as standard Kt/V was achieved for all patients during the HEMO Study. (B) When normalized to BSA, women randomized to the high dose received a dose comparable to the conventional dose in men.[129] Reproduced with permission of the American Society of Nephrology from Daugirdas et al.[147]

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toxins

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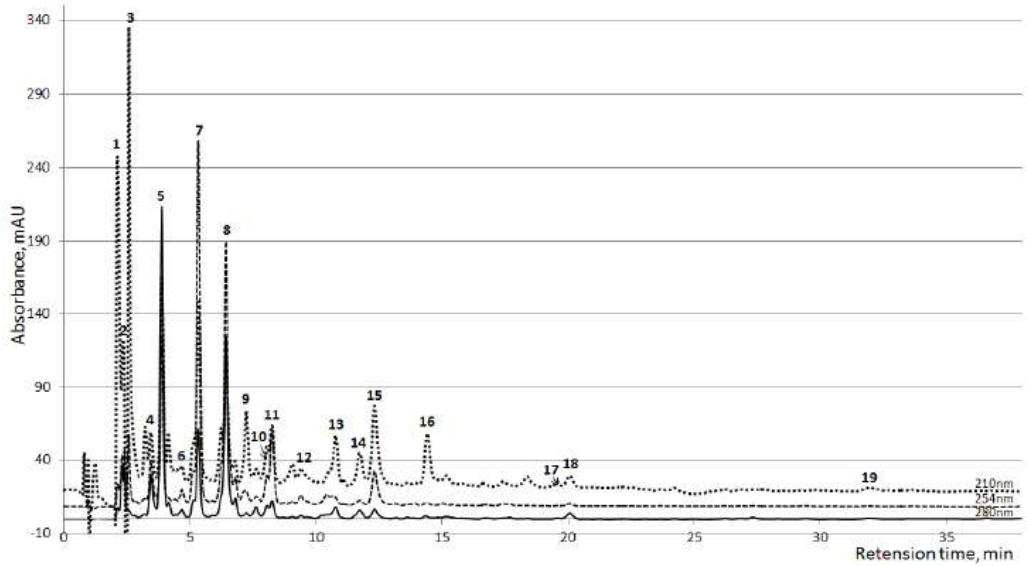
Article

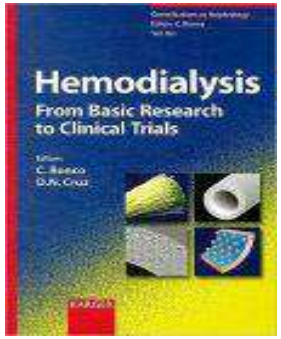
Do Only Small Uremic Toxins, Chromophores, Contribute to the Online Dialysis Dose Monitoring by UV Absorbance?

Jürgen Arund [1,*], Risto Tanner [1,2], Fredrik Uhlin [1,3] and Ivo Fridolin [1]

Figure 1. Averaged HPLC chromatograms of the spent dialysate collected 10 min after the start of the dialysis (n = 24) at three wavelengths. 1,2: Unknown; 3: Creatinine; 4: Unknown; 5: Uric acid; 6: Hypoxanthine; 7: PAR Glucoronide; 8–10: Unknown; 11: PAR Sulfate; 12: Paracetamol (PAR); 13: Tryptophan; 14: Indoxyl Sulfate; 15: Hippuric acid; 16–18: Unknown; 19: Indole-3-acetic acid.



ΑΜΥΝΤΙΚΟΙ ΜΗΧΑΝΙΣΜΟΙ



- Η θεραπεία υποκατάστασης της νεφρικής λειτουργίας με αιμοκάθαρση απαιτεί την χρήση «ξένων» υλικών, όπως οι μεμβράνες, τα οποία όμως με τη σειρά τους επηρεάζουν αρνητικά το ανοσοποιητικό σύστημα.

- Η παθοφυσιολογία της μοναδικής σχέσης μεταξύ λειτουργίας του ανοσοποιητικού συστήματος, της ουραιμίας και της διαδικασίας της αιμοκάθαρσης απαιτεί έρευνα σε βάθος, ώστε να είναι αποτελεσματικές οι οποιεσδήποτε θεραπευτικές παρεμβάσεις.

Coen G, Haag-Weber M, Horl WH. Immune dysfunction in uremia. Kidney Int 1997;52:79-82.

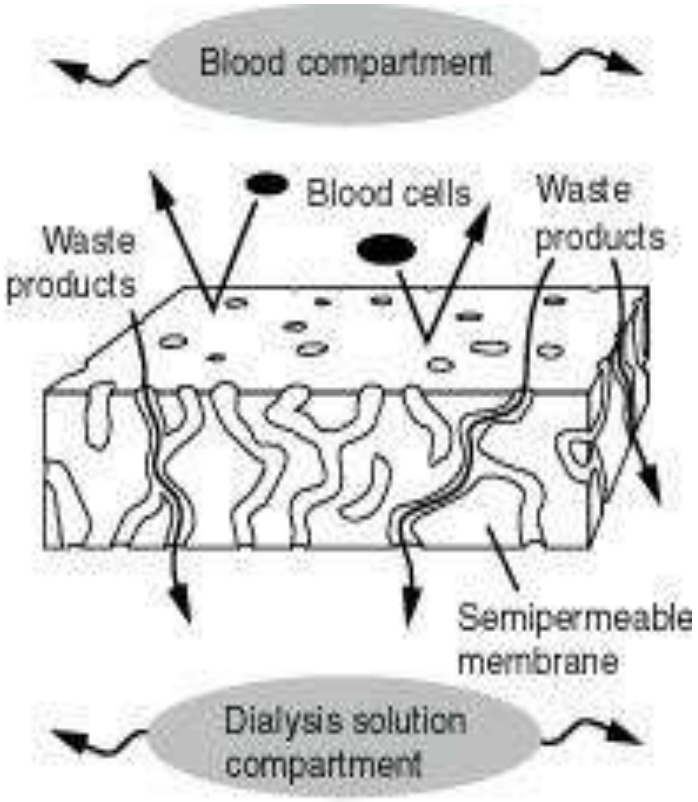
ΚΛΙΝΙΚΗ ΒΙΟΛΟΓΙΑ ΤΗΣ ΘΕΡΑΠΕΙΑΣ ΥΠΟΚΑΤΑΣΤΑΣΗΣ

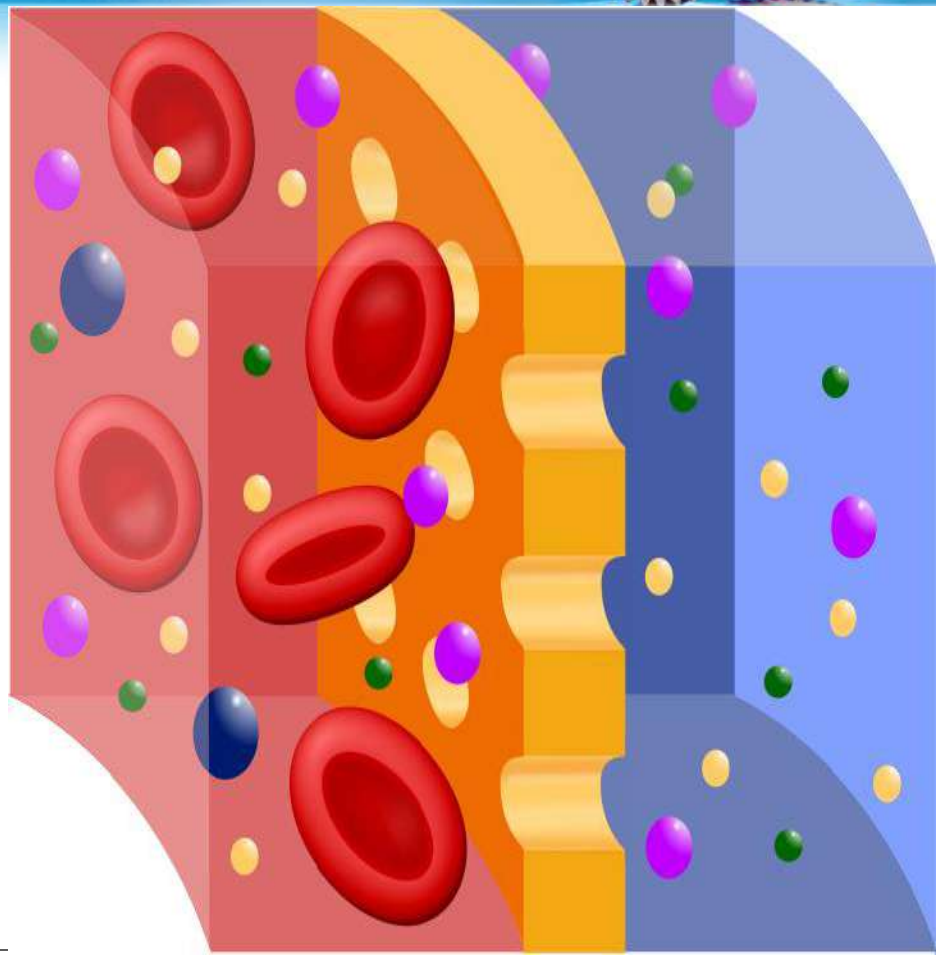
Αλληλουχία βιολογικών γεγονότων στην πορεία από το φυσιολογικό στο παθολογικό. Όταν έρθει ο οργανισμός σε επαφή με ένα παθογόνο παράγοντα (βακτήριο, ιός, φυσικός ή χημικός εισβολέας, αλλεργιογόνος, τοξικός η οποιοσδήποτε παράγοντας «ξένος» προς τον οργανισμό) η βιολογία του αλλάζει ή τροποποιείται.

Όταν ακολούθως απαιτηθεί κάποιας μορφή θεραπεία (αντιβίωση για βακτήριο) τότε μιλάμε για θεραπευτική κλινική βιολογία.

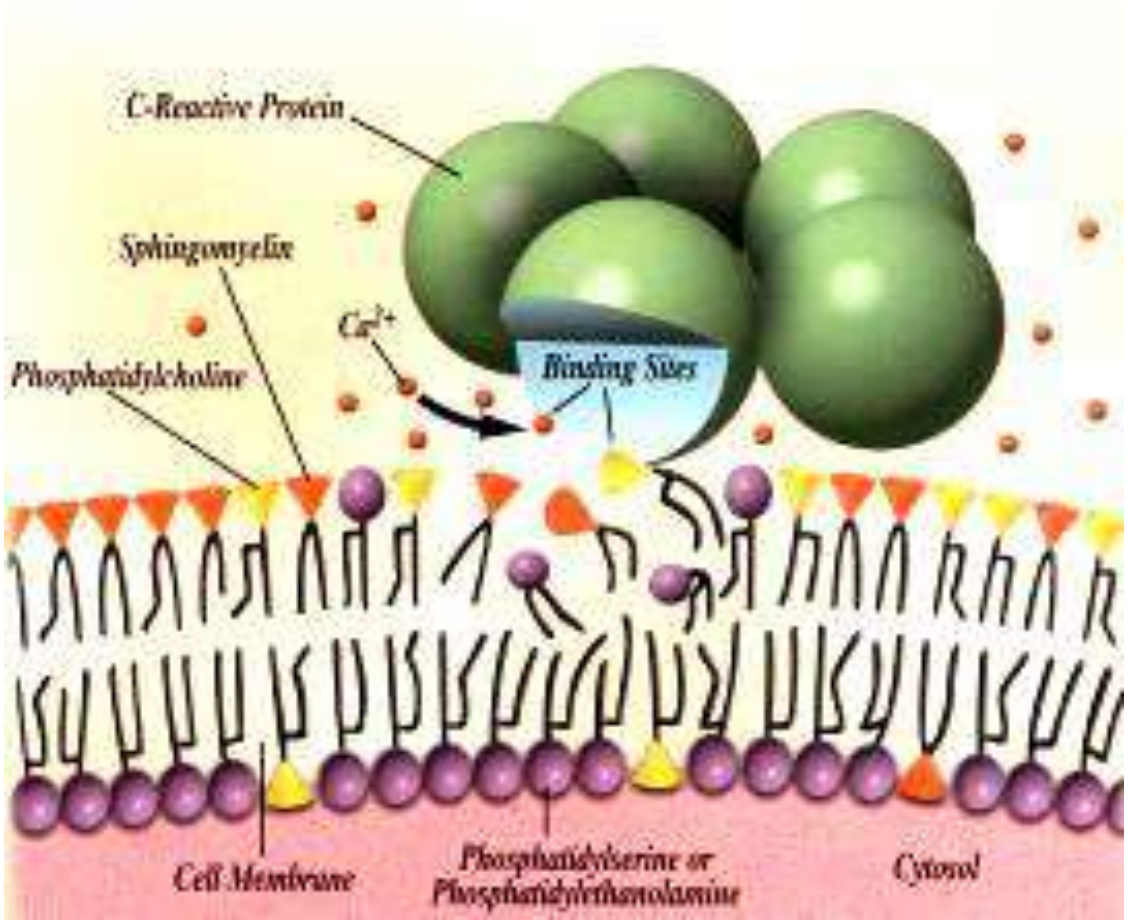
Stefoni s, La Manna G, Perna c, et al. Clinical biology of artificial organ substitution. Nephrol Dial Transplant 1998;13:51-54.

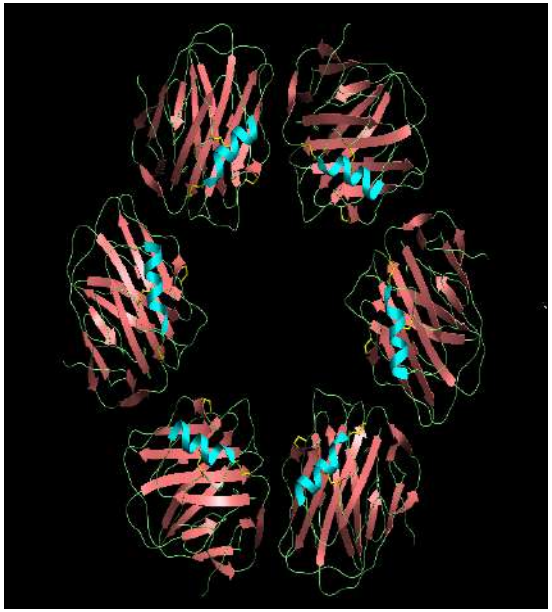
ΚΛΙΝΙΚΗ ΒΙΟΛΟΓΙΑ ΤΗΣ ΘΕΡΑΠΕΙΑΣ ΥΠΟΚΑΤΑΣΤΑΣΗΣ





Stefoni s, La Manna G, Perna c, et al. Clinical biology of artificial organ substitution. Nephrol Dial Transplant 1998;13:51-54.


C-Reactive Protein
Sphingomyelin
Ca^{2+}
Phosphatidylcholine
Binding Sites
Cell Membrane
Phosphatidylserine or
Phosphatidylethanolamine
Cytosol



Τι είναι η βιοσυμβατότητα;

- Κάθε μεμβράνη χαρακτηρίζεται από την ***απόδοσή της***, την ικανότητά της δηλαδή να απομακρύνει ουραιμικές τοξίνες και υγρά από τον ανθρώπινο οργανισμό, χωρίς την απώλεια απαραίτητων ουσιών, και από την ***βιοσυμβατότητα*** της, δηλαδή την ικανότητά της να προκαλεί τις λιγότερες δυνατές ανεπιθύμητες αλληλεπιδράσεις κατά την επαφή της με τα στοιχεία του αίματος.

- **Η ιδανική μεμβράνη ΑΜΚ έχει υψηλή απόδοση και πολύ καλή βιοσυμβατότητα.**

Τι είναι η βιοσυμβατότητα;

- Το θέμα της βιοσυμβατότητας μπορεί να διαχωρισθεί σε δύο ειδών αλληλεπιδράσεις:

  α) την αλληλεπίδραση αίματος και μεμβράνης στο σύστημα εξωσωματικής κυκλοφορίας και

  β) την αλληλεπίδραση αίματος και ενδοθηλίου.

- Ο διαχωρισμός αυτός υπενθυμίζει ότι μόνο όταν η αλληλεπίδραση αίματος-ενδοθηλίου διαταραχθεί γίνονται αντιληπτές οι όποιες διαταραχές από την αλληλεπίδραση αίματος-μεμβράνης αιμοκάθαρσης.

Hakim RM. Clinical implications of hemodialysis membrane biocompatibility. Kidney Int 1993;44:484

Δείκτες Βιοσυμβατότητας

- Ενεργοποίηση συμπληρώματος
- Ενεργοποίηση των λευκών αιμοσφαιρίων
- Ενεργοποίηση της πήξης
- Ενεργοποίηση των αιμοπεταλίων
- Ενεργοποίηση μονοπυρήνων
- Λεμφοκύτταρα

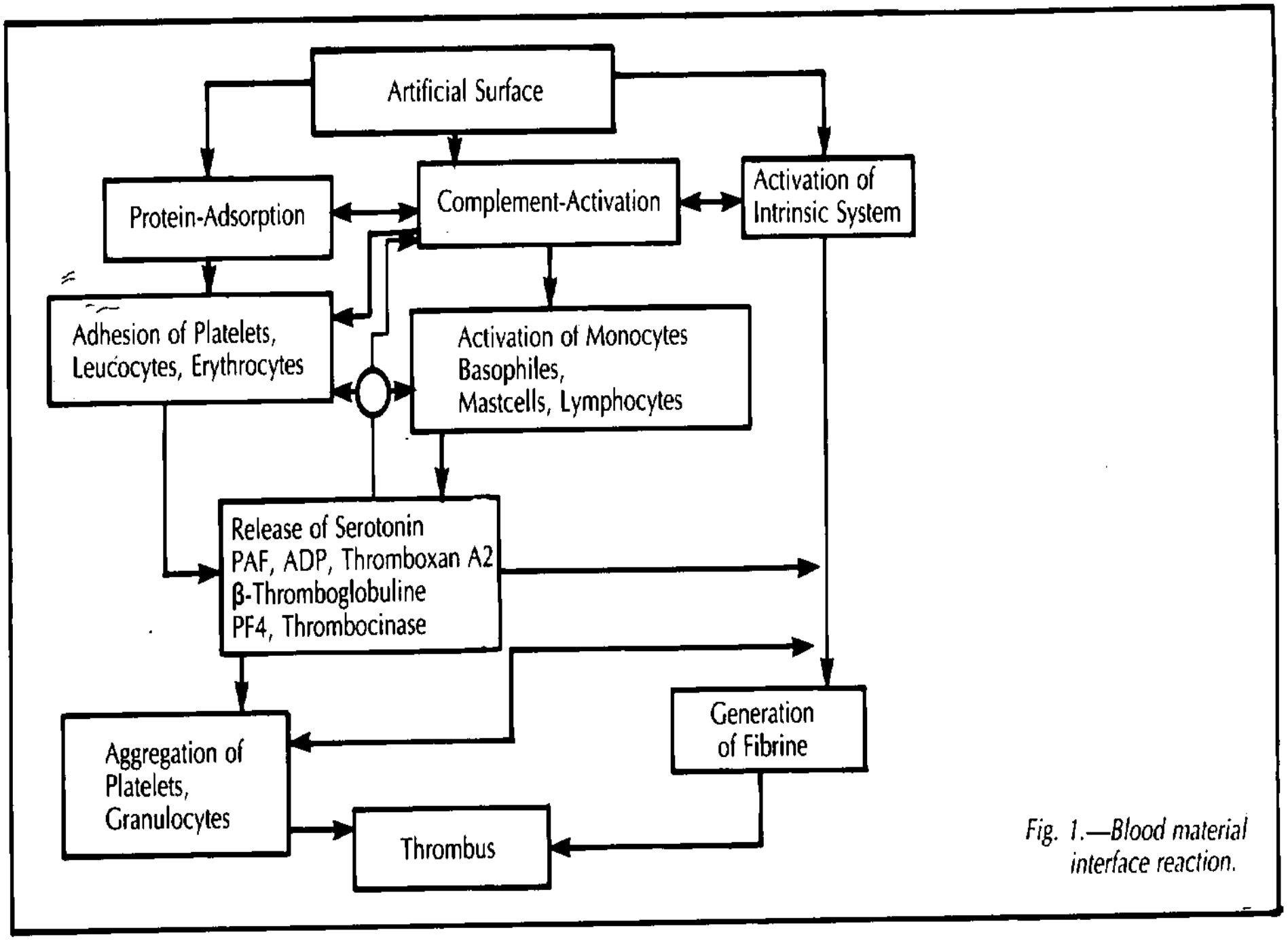


Fig. 1.—Blood material interface reaction.

Kidney International, Vol. 44 (1993), pp. 484–494

EDITORIAL REVIEW

Clinical implications of hemodialysis membrane biocompatibility

Table 1. Types of hemodialysis membranes

Membrane type	Membrane structure
Cellulosic	
Cellulose	Polysaccharide units with hydroxyl groups formed from cotton fibers
Derivatized cellulosic	
Cellulose acetate	Cellulose with 4 out of 5 hydroxyl groups replaced with acetate
Hemophane	Cellulose with 1.5% hydroxyl groups replaced by diethylaminoethyl radicals
Synthetic polymers	
Polyetherpolycarbonate	Hydrophilic synthetic
Ethylvinyl alcohol	Hydrophilic synthetic
Polysulfone (PS)	Hydrophobic synthetic
Polyamide	Hydrophobic synthetic
Polymethylmethacrylate (PMMA)	Hydrophobic synthetic
Polyacrylonitrile (PAN)	Hydrophobic synthetic

Table 2. Sequelae of complement activation (alternative pathway)

1. Release of anaphylatoxins (C3a, C5a) leading to:
   - Smooth muscle contraction
   - Increased vascular permeability
   - Release of histamine from mast cells
2. Formation of membrane attack complex (C5b-9)
3. Activation of neutrophils
   - —Degranulation and release of granulocyte enzymes (such as, proteases)
   - —Production of reactive oxygen species (ROS)
   - —Increased expression of adhesion receptors
   - —Enhanced arachidonic acid metabolism (LTB_4) and PAF
4. Activation of monocytes
   - —Increased transcription of IL-1β and TNF-α

Table 3. Surface potential of hemodialysis membrane[a]

Membrane	Charge
Cuprophane®	~0
Cellulose acetate	−3.4
Polyacrylonitrile	−153.9

[a] Methylene blue dye method

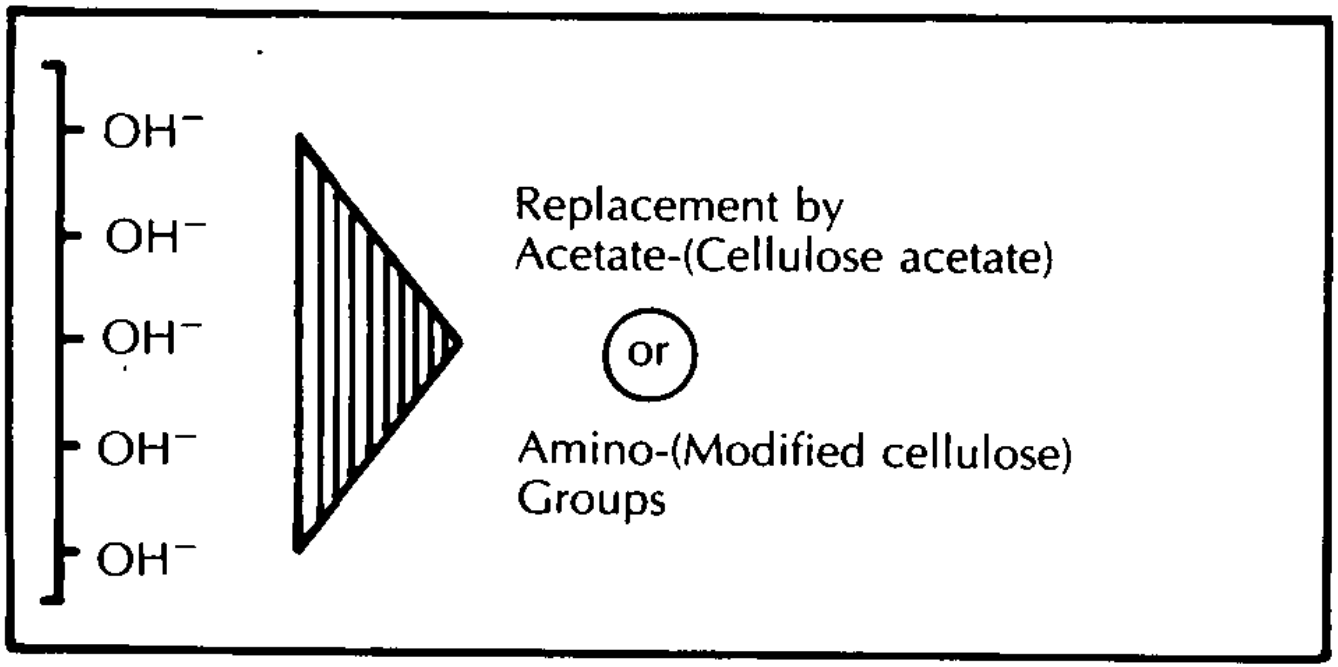


Fig. 2.—Membrane modification.

EDITORIALES

Clinical relevance of biocompatibility. «The material cannot be divorced from the device»

H. Klinkmann (1), D. Falkenhagen (1) and J. H. Courtney (2)
(1) Klinik für Innere Medicine, W-Pieck University Rostock. República Democrática de Alemania. (2) Bioingineering Unit, University of Strathclyde. Glasgow, Reino Unido.

Table I. Definition of biocompatibility

Biocompatibility
No: — Thrombogenic toxic, allergic, inflammatory reaction.
— Destruction of formed elements.
— Changes in plasma-proteins and enzymes.
— Immunologic reactions.
— Carcinogenic effect.
— Deterioration of adjacent tissues.

EDITORIALES

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Table VIII. Main factors influenting the biocompatibility of a dialyzer

Biocompatibility of a dialyzer:

- Membrane.
- Sterilization.
- Flow-geometry.
- Material.
- ?
- ?

Table VII. Influence of different dialysis membranes and anticoagulants on beta-thromboglobulin (BTG) release

Membrane	Anticoagulant	BTG (ng/ml.) 3 min.	6 min.	9 min.
Cuprophan	None	70	101	154
Cuprophan	Heparin (1 IU/ml.)	89	102	103
Cuprophan	Citrate (15 mmol/l.)	42	40	37
An 695	None	74	105	205
An 695	Heparin (1 IU/ml.)	61	71	85
An 695	Citrate (15 mmol/l.)	44	38	48

EDITORIALES

Clinical relevance of biocompatibility. «The material cannot be divorced from the device»

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(1) Klinil für Innere Medicine, W-Pieck University Rostock. República Democrática de Alemania. (2) Bioingineering Unit, University of Strathclyde. Glasgow, Reino Unido.

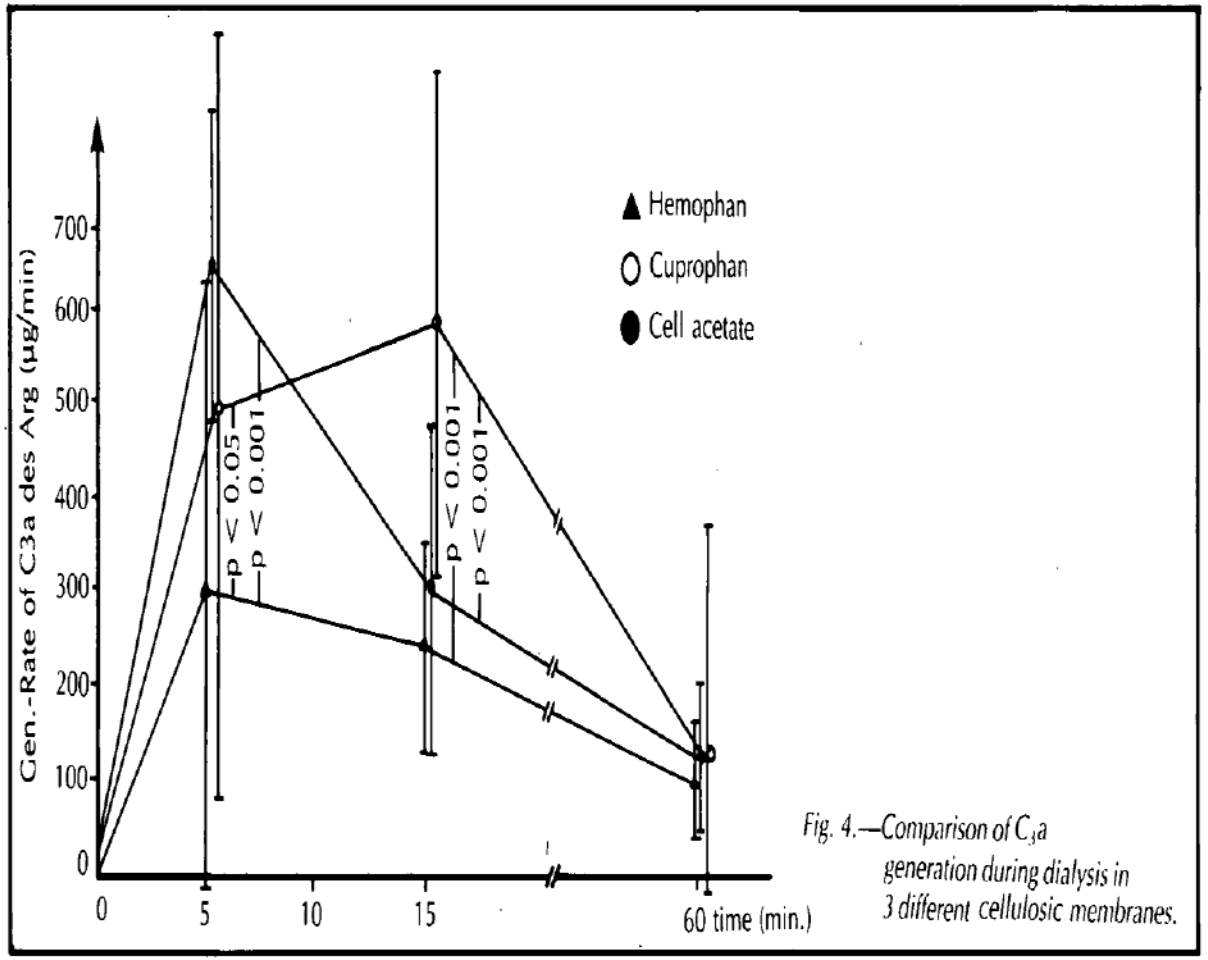

Fig. 4.—Comparison of C_3a generation during dialysis in 3 different cellulosic membranes.

ΑΝΑΚΕΦΑΛΑΙΩΣΗ

- α) υπάρχουν πολλά συστήματα αξιολόγησης της βιοσυμβατότητας των μεμβρανών ΑΜΚ που κάθε ένα από αυτά έχει μειονεκτήματα,
- β) δεν υπάρχουν πολλές μελέτες που να συγκρίνουν μεγάλο αριθμό μεμβρανών μεταξύ τους,
- γ) για λόγους τεχνικούς οι μελέτες αυτές δεν έχουν μεγάλο αριθμό αρρώστων,
- δ) η εκτίμηση του «φαινομένου» βιοσυμβατότητα και η επίδραση του στην κλινική κατάσταση των ασθενών δεν είναι πλήρως κατανοητό στην ολότητα του και
- ε) ως φαινόμενο η βιοσυμβατότητα δεν είναι μονοσήμαντο και επομένως το όποια συμπεράσματα σε πολλές περιπτώσεις ελέγχονται.

Renal Failure, 28:493–498, 2006
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DOI: 10.1080/08860220600781336

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healthcare

CLINICAL STUDY

Biocompatibility Study Based on Differential Sequestration Kinetics of CD14+CD16+ Blood Monocyte Subsets with Different Dialyzers

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Ploumis Passadakis, Ilias Thodis, and Vasilios Vargemezis
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Immunology Department, Papageorgiou General Hospital, Thessaloniki, Greece

The immune defect in hemodialysis (HD) patients is associated with a monocyte dysfunction, including an increase in the production of proinflammatory cytokines. Blood membrane contact leads to an increase in cellular activation and sequestration into the capillary bed of the lung. The influence of the sequestration on the number of mature monocytes was studied by analyzing the fate of monocytes, particularly, the CD14+CD16+ subpopulation, during HD treatment.

In thirty stable HD patients, the distinct cell populations were determined by differential blood counts and flow cytometry. Patients with diabetes or systemic vasculitis, those showing evidence of infectious complications or malignancy, or those taking immunosuppressive medications were excluded from the study. Cells from this study population were analyzed before the start, 30 min thereafter, and at the end of HD treatment, each time using a different dialyzer: hemophan, methylmethacrylate (PMMA), triacetate membrane, cuprophane/vitamin E, acrylonitrile, and sodium methallylsulfonate polymer (AN69).

The CD14+CD16+ subset decreased at 30 min and remained suppressed for the course of dialysis. To examine whether currently used biocompatible membranes differ in their effect on the sequestration of monocyte subpopulations, temporal monocytic changes were comparatively analyzed during HD with a different dialyzer. The drop in the first 30 min until the end of HD treatment was significant ($p<0.05$), very uniform, and sharp in all patients, and was independent upon membrane type.

The CD14+CD16+ monocyte subpopulation showed increased and longer margination from the blood circulation during HD. Given the fact that CD14+CD16+ monocytes represent a sensitive marker for inflammation or cellular activation, the depletion of these cells may offer an easily accessible parameter that is more sensitive than complement activation for biocompatibility studies on forthcoming, improved dialyzer membranes.

Keywords biocompatibility, CD14+CD16+ monocytes, hemodialysis, dialyzers

INTRODUCTION

Since its early observation in the first minutes of hemodialysis (HD) by Kaplow and Goffinet,[1] the issue of transient leukopenia has undergone extensive investigation. Several studies have shown that neutropenia and monocytopenia take place during HD procedures when cellulosic membranes are used.[2–9] Leukocyte margination and adhesion is associated with complement activation during HD with cellulosic dialyzers such as cuprophane. During the HD process, the direct contact of plasma with the dialyzer membrane initiates the alternative pathway of complement activation, leading to the generation of the active peptides C3a and C5a, which can then induce responses in neutrophils.[6,7] However, synthetic membranes that show a higher biocompatibility (e.g., polyacrylonitrile) markedly reduced complement and granulocyte activation as well as subsequent granulocytopenia.[3,8]

Most studies have focused on the pathophysiology of granulocytes during HD. However, the HD process also influences monocytes. In addition, monocytes also express many of the same complement and adhesion receptors expressed by neutrophils (e.g., CD11b and CD11c). It has been suggested that neutrophils and monocytes are activated during dialysis even before they pass the dialyzer.

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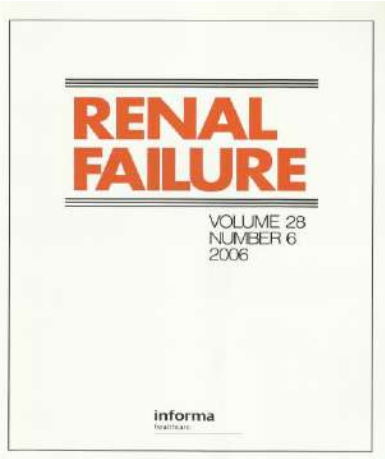


ΟΝΟΜΑΣΙΑ (Αποστείρωση)	ΟΓΚΟΣ (ml)	ΕΠΙΦΑΝΕΙΑ (m^2)	ΠΑΧΟΣ (μ)	UF (ml/mmHg/hr)
1. Αιμοφάνη (GFS-PLUS 16) Ατμός	95	1,7	8	9,4
2. Κουπροφάνη/Βιτ Ε (CLC15NL) Ατμός	90	1,5	22	7,1
3. Τριοξεική κυτταρίνη (SUPERFLUX 170G) γ ακτιν/ΕΤΟ	105	1,7	15	11,8
4. PMMA B3-1,3A γ ακτιν	76	1,3	20	8,8
5. AN69 (FILTRAL 16 HF) γ ακτιν/ΕΤΟ	122	1,7	50	48

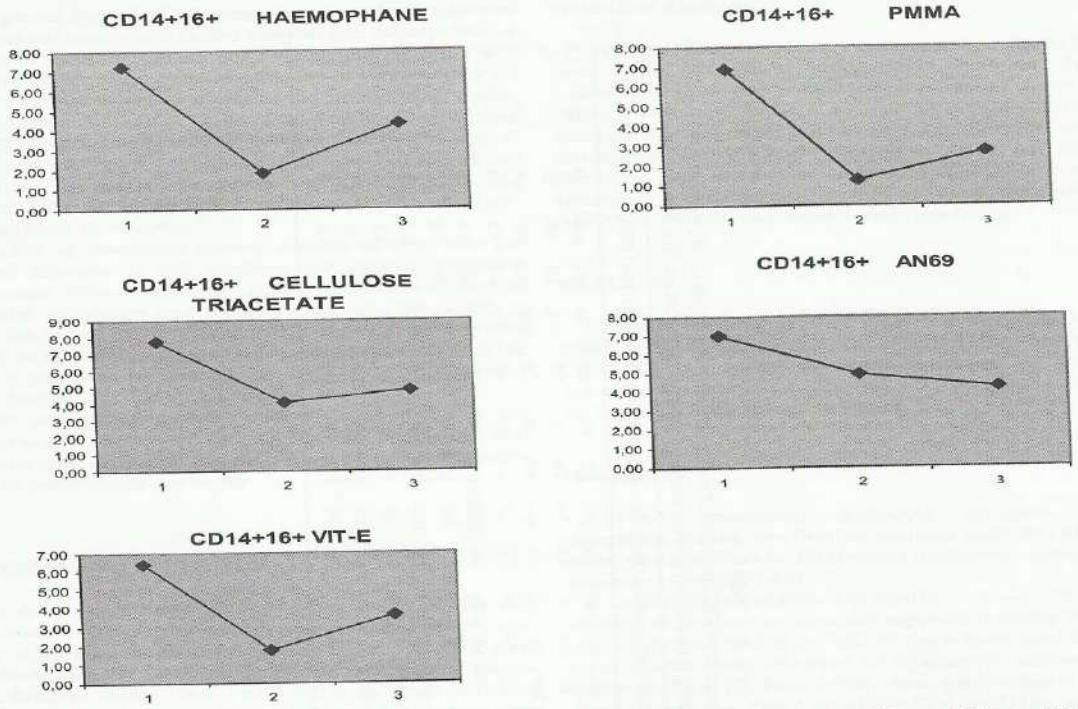


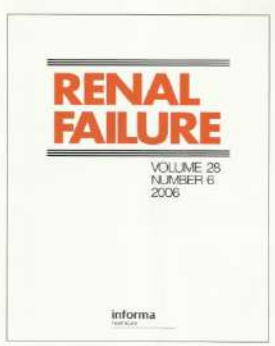
Figure 1. Differential sequestration kinetics of CD14+CD16+ blood monocyte subsets with different dialyzers (1) before the beginning of the session (t=0), (2) 30 min from the beginning of the session (t=30), and (3) at the end of the session (t=240).

The drop of the CD14+CD16+ subpopulation after 30 min of dialysis was striking and detectable in all patients ($p<0.05$), and this population then started to rise during ongoing dialysis. At the end of the session, the levels of CD14+CD16+ monocytes remained suppressed significantly compared to pre-dialysis levels ($p<0.05$). The CD14+CD16+ subset decreased to 73.70% of pre-dialysis level at 30 min and to 55.64% of pre-dialysis level at 240 min. The percentage of NK remained significantly suppressed until the end of the session ($p<0.05$).

Cellulose Triacetate (CTA)

The total circulating leukocyte numbers strongly decreased during the first 30 minutes ($p<0.05$) of a treatment session and then started to rise. Within 240 min of treatment, white blood cells remained suppressed ($p<0.05$). The percentage of monocytes increased during the first 30 min of dialysis ($p<0.05$) and at the end of the session was nearly at pre-dialysis levels ($p=0.526$).

The drop of the CD14+CD16+ subpopulation after 30 min of dialysis was also striking and detectable in all patients ($p<0.05$), and this population also started to rise during ongoing dialysis. At the end of the session, the levels of CD14+CD16+ monocytes remained suppressed significantly compared to pre-dialysis levels ($p<0.05$). The CD14+CD16+ subset decreased to 23.47% of pre-dialysis level at 30 min and to 13.04% of pre-dialysis level at 240 min. The percentage of NK remained significantly suppressed until the end of session ($p<0.05$).



Ελληνική Νεφρολογία 2007; 19 (4): 00 - 00

Πρωτότυπη εργασία

Φαγοκυτταρική ικανότητα και αναπνευστική έκρηξη σε ασθενείς υπό αιμοκάθαρση με δύο διαφορετικές μεμβράνες*

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Περίληψη

Σκοπός: *Σκοπός της παρούσας μελέτης ήταν ο έλεγχος της φαγοκυτταρικής ικανότητας (ικανότητα των φαγοκυττάρων να προσλαμβάνουν τα μικρόβια) και της αναπνευστικής έκρηξης (ικανότητα των φαγοκυττάρων να τα θανατώνουν) σε ασθενείς, που υποβάλλονται σε αιμοκάθαρση με δύο διαφορετικές μεμβράνες.*

Ασθενείς – Μέθοδοι: *Μελετήθηκαν 30 αιμοκαθαιρόμενοι ασθενείς από 47 έως 74 ετών (μέση ηλικία: 60,1±8,7 έτη, M±SD), (διάρκεια αιμοκάθαρσης: 24,1±14,3 μήνες, M±SD). Διενεργήθηκε δοκιμασία ελέγχου φαγοκυττάρωσης (phago test) και αναπνευστικής έκρηξης (burst test) πριν από τη συνεδρία αιμοκάθαρσης, 15 λεπτά μετά και στις 3 ώρες από την έναρξή της, με αιμοφάνη και με πολυακρυλονιτρίλη/νατριούχο μεθαλυλοθειϊκή (AN69).*

Αποτελέσματα: *Κατά τη συνεδρία με αιμοφάνη, η φαγοκυτταρική ικανότητα των μονοκυττάρων παρουσίασε σημαντική αύξηση στα 180 λεπτά ($p<0,05$), ενώ τόσο η φαγοκυτταρική ικανότητα των πολυμορφοπυρήνων όσο και η αναπνευστική έκρηξη των μονοκυττάρων δεν παρουσίασαν σημαντικές μεταβολές. Η αναπνευστική έκρηξη των πολυμορφοπυρήνων αυξήθηκε σημαντικά στα πρώτα 15 λεπτά ($p< 0,05$) και στα 180 λεπτά της συνεδρίας ($p<0,05$). Κατά τη συνεδρία με AN69, η φαγοκυτταρική ικανότητα των μονοκυττάρων και των πολυμορφοπυρήνων δεν παρουσίασε σημαντικές μεταβολές. Αντίθετα, η αναπνευστική έκρηξη τόσο των μονοκυττάρων όσο και των πολυμορφοπυρήνων αυξήθηκε σημαντικά στα 15 λεπτά ($p<0,05$) και στα 180 λεπτά της συνεδρίας ($p<0,05$). Η σύγκριση των τιμών των επιμέρους παραμέτρων μεταξύ των δύο μεμβρανών, στις διάφορες χρονικές στιγμές, δεν αποκάλυψε στατιστικά σημαντικές διαφορές.*

Συμπεράσματα: *Ο έλεγχος της φαγοκυτταρικής ικανότητας και της αναπνευστικής έκρηξης λειτουργεί συμπληρωματικά στην εκτίμηση του βαθμού βιοσυμβατότητας των μεμβρανών αιμοκάθαρσης, ενώ ανοίγει νέους ορίζοντες για περαιτέρω έρευνα στα αίτια, τον επιπολασμό και την κατάληξη των λοιμώξεων σε αιμοκαθαιρόμενους ασθενείς.*

* Προφορική Ανακοίνωση στο 14ο Πανελλήνιο Συνέδριο Νεφρολογίας. Πόρτο Καράς, Χαλκιδική, 31/5-3/6/2006.

Πίνακας 4. *Ο έλεγχος της φαγοκυτταρικής ικανότητας και της αναπνευστικής έκρηξης.* [1. χρόνος πριν την έναρξη της συνεδρίας, 2.15 λεπτά από την έναρξη της συνεδρίας, 3.180 λεπτά από την έναρξη της συνεδρίας].

α/α	ΜΕΜΒΡΑΝΗ	NK 1	NK-like 1	NK 2	NK-like 2	NK 3	NK-like 3	PHAGO MONO 1
1	ΑΙΜΟΦΑΝΗ	17,36+/-6,37	4,41+/-4,87	11,83+/-4,96	4,26+/-5,30	10,83+/-4,19	3,36+/-4,04	79,38+/-9,67
2	AN 69	19,40+/-7,32	4,05+/-4,53	13,49+/-5,57	3,84+/-4,58	13,38+/-5,31	3,23+/-4,09	80,46+/-7,38

α/α	ΜΕΜΒΡΑΝΗ	MFI MONO 1	PHAGO MONO 2	MFI MONO 2	PHAGO MONO 3	MFI MONO 3	PHAGO NEU 1	MFI NEU 1
1	ΑΙΜΟΦΑΝΗ	17,70+/-1,66	78,49+/-10,9	16,27+/-1,55	83,18+/-8,55	19,60+/-8,29	92,15+/-8,23	25,37+/-11,67
2	AN 69	18,92+/-5,17	83,23+/-5,63	18,50+/-5,49	83,65+/-6,87	20,45+/-7,82	94,29+/-0,97	27,29+/-8,61

α/α	ΜΕΜΒΡΑΝΗ	PHAGO NEU 2	MFI NEU 2	PHAGO NEU 3	MFI NEU 3	BURST MONO 1	MFI MONO 1	BURST MONO 1 HIGH
1	ΑΙΜΟΦΑΝΗ	91,32+/-8,76	24,28+/-10,40	91,26+/-8,89	28,15+/-12,91	78,55+/-15,39	1,78+/-0,75	91,82+/-11,73
2	AN 69	93,72+/-1,24	26,97+/-8,20	93,41+/-4,85	28,87+/-8,96	79,83+/-11,34	1,61+/-0,61	91,09+/-8,03

Πίνακας 4. *(Συνέχεια)*

α/α	ΜΕΜΒΡΑΝΗ	MFI MONO 1 HIGH	BURST MONO 2	MFI MONO 2	BURST MONO 2 HIGH	MFI MONO 2 HIGH	BURST MONO 3	MFI MONO 3
1	ΑΙΜΟΦΑΝΗ	2,89+/-1,44	82,64+/-14,50	2,12+/-0,80	91,29+/-13,72	5,16+/-9,62	83,32+/-11,92	2,24+/-1,05
2	AN 69	3,35+/-4,37	87,11+/-7,23	1,99+/-0,77	94,26+/-4,50	2,95+/-1,67	87,75+/-9,30	2,65+/-1,45

α/α	ΜΕΜΒΡΑΝΗ	BURST MONO 3 HIGH	MFI MONO 3 HIGH	BURST NEU 1	MFI NEU 1	BURST NEU 1 HIGH	MFI NEU 1 HIGH	BURST NEU 2
1	ΑΙΜΟΦΑΝΗ	90,27+/-12,25	2,24+/-1,05	94,65+/-4,96	8,82+/-6,50	98,27+/-2,23	16,45+/-10,27	97,05+/-2,94
2	AN 69	87,75+/-9,30	2,95+/-1,67	95,06+/-5,02	7,97+/-4,72	98,03+/-2,74	16,51+/-11,29	97,17+/-3,34

α/α	ΜΕΜΒΡΑΝΗ	MFI NEU 2	BURST NEU 2 HIGH	MFI NEU 2 HIGH	BURST NEU 3	MFI NEU 3	BURST NEU 3 HIGH	MFI NEU 3 HIGH
1	ΑΙΜΟΦΑΝΗ	12,90+/-10,56	99,07+/-0,89	23,77+/-14,37	93,46+/-7,27	12,54+/-12,02	98,32+/-2,44	19,96+/-18,15
2	AN 69	12,22+/-9,46	99,05+/-0,93	23,63+/-13,86	94,01+/-7,23	13,41+/-12,31	98,11+/-2,90	21,98+/-20,10

PHAGO. Φαγοκυτταρική ικανότητα
BURST. Αναπνευστική έκρηξη
MONO. In vivo
High. Με διεγέρτη
MFI. Μέση ένταση φθορισμού, η οποία εκφράζει την οξειδωτική ικανότητα
NEU. Πολυμορφοπύρηνα
MONO. Μονοκύτταρα

- Οι παρατηρήσεις τόσο οι δικές μας όσο και της διεθνούς βιβλιογραφίας συμφωνούν ότι παρά την γνωστή διαφορά στην βιοσυμβατότητα μεταξύ των δύο μεμβρανών η φαγοκυτταρική ικανότητα μάλλον δεν παρουσιάζει σημαντικές διαφορές.

- ✓ Η δυσαρμονία μεταξύ φαγοκυτταρικής ικανότητας και αναπνευστικής έκρηξης την ίδια χρονική στιγμή είναι κάτι που έχει παρατηρηθεί σε μελέτη με βιοασύμβατες μεμβράνες (κουπροφάνη), πρώτη ουσιαστικά προσέγγιση της φαγοκυτταρικής δραστηριότητας ως δείκτη βιοσυμβατότητας.

Ward R, McLeish K. Hemodialysis with cellulose membranes primes the neutrophil oxidative burst. Artificial Organs 1995;8:901-807.

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Φαγοκυτταρική ικανότητα και αναπνευστική έκρηξη σε ασθενείς υπό αιμοκάθαρση με δύο διαφορετικές μεμβράνες*

κτική. Η πιο σοβαρή μελέτη που θέτει τον προβληματισμό του χρόνου ΑΜΚ είναι αυτή των Pereira και συν.[27] το 2004, που έγινε στα πλαίσια της HEMO study, και συνέκρινε κουπροφάνη, πολυσουλφόνη και αναγεννημένη κυτταρίνη. Δε διαπιστώθηκε διαφορά στη φαγοκυτταρική δραστηριότητα, ενώ στο θέμα της αναπνευστικής έκρηξης, η μεμβράνη από αναγεννημένη κυτταρίνη είχε χαμηλότερες επιδόσεις. Δεν υπάρχει, όπως αναφέρθηκε, ικανοποιητικός αριθμός αξιόπιστων ερευνών, αλλά στη μελέτη αυτή τίθεται ο προβληματισμός, χωρίς να μπορεί να δοθεί συγκεκριμένη απάντηση, ότι ο χρόνος των συνεδριών με μία συγκεκριμένη μεμβράνη ίσως να έχει κάποιο ρόλο τόσο στις διαταραχές του μεταβολικού προφίλ όσο και στην αποκατάσταση τους.

Σύγχρονες οδηγίες

- Οι συνθετικές μεμβράνες κυριαρχούν στην καθημερινότητα της ΑΜΚ στον δυτικό κόσμο (το χαμηλό κόστος έχει συμβάλλει σε αυτήν την πραγματικότητα) και σίγουρα τα στοιχεία υπέρ της καλύτερης βιοσυμβατότητας τους οδηγεί τον νεφρολόγο σε αυτήν την επιλογή.

Συσχέτιση με νοσηρότητα και θνητότητα

Θεωρείται από πολλούς ερευνητές ότι η αιμοκάθαρση με high flux μεμβράνες, η αιμοδιήθηση και η αιμοδιαδιήθηση είναι πιο 'βιοσυμβατές' από την κλασική αιμοκάθαρση.

- ✓ Η καλύτερη βιοσυμβατότητα σχετίζεται όχι μόνο με τα οξέα συμβάματα (καρδιαγγειακή αστάθεια, υποξαιμία, αλλεργικές αντιδράσεις) αλλά και με απώτερες επιπλοκές (αμυλοείδωση, αθηρωσκλήρυνση) όπως και διαταραχές του ανοσιακού συστήματος (λοιμώξεις, κακοήθειες).

Locatelli F. Influence of membranes on morbidity. Nephrol Dial Transplant 1996;2:116-120.

- Συμπερασματικά, διάφορες μη τυχαιοποιημένες αναδρομικές μελέτες έχουν αναφέρει ελάττωση στην θνητότητα από 15-20% σε 9-11% χρησιμοποιώντας συνθετικές μεμβράνες αντί κουπροφάνης.
- Ωστόσο, σε τέτοιου τύπου μελέτες η ανάλυση των αποτελεσμάτων πρέπει να γίνει με πολλή προσοχή γιατί πολλές φορές δεν συνυπολογίζονται διάφοροι παράγοντες.
- Τα αποτελέσματα μεγάλων μελετών, ακόμα και του NIH, έχουν αντικρουόμενα αποτελέσματα, γεγονός που κάνει δύσκολη την ακριβή συσχέτιση των μεμβρανών αιμοκάθαρσης με την νοσηρότητα και την θνητότητα των ασθενών σε πρόγραμμα περιοδικής αιμοκάθαρσης.

Locatelli F. Influence of membranes on morbidity. Nephrol Dial Transplant 1996;2:116-120.

Προοπτικές

Table 1 | Improvements in hemodialysis membranes

Traditional membranes

1. *Biocompatibility*: New materials and chemical modifications of side chains
2. Refining pore dimensions to enhance hydraulic permeability and middle molecule clearance

Innovative membranes

1. Microfluidics and membraneless systems
2. Nanofabrication with synthetic channels
3. Nanofabricated silicon membranes with slit pores

Living membranes

1. Endothelial cell-lined membranes for hemocompatibility and durability
2. Tubule cell-lined membranes for active transport and metabolic activities

http://www.kidney-international.org mini review

The future of hemodialysis membranes

HD Humes[1], WH Fissell[1] and K Tiranathanagul[1]

[1]*Department of Internal Medicine, Division of Nephrology, University of Michigan School of Medicine, Ann Arbor, Michigan, USA*

Blood Purification

Blood Purif 2007;25:12–17
DOI: 10.1159/000096391

Published online: December 14, 2006

Dialysis and Nanotechnology: Now, 10 Years, or Never?

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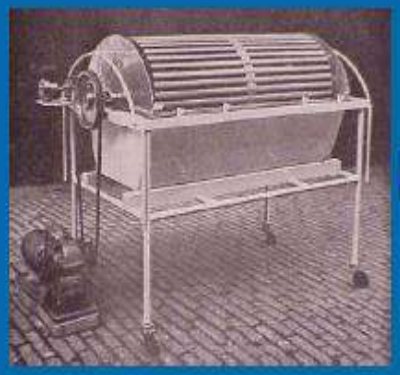
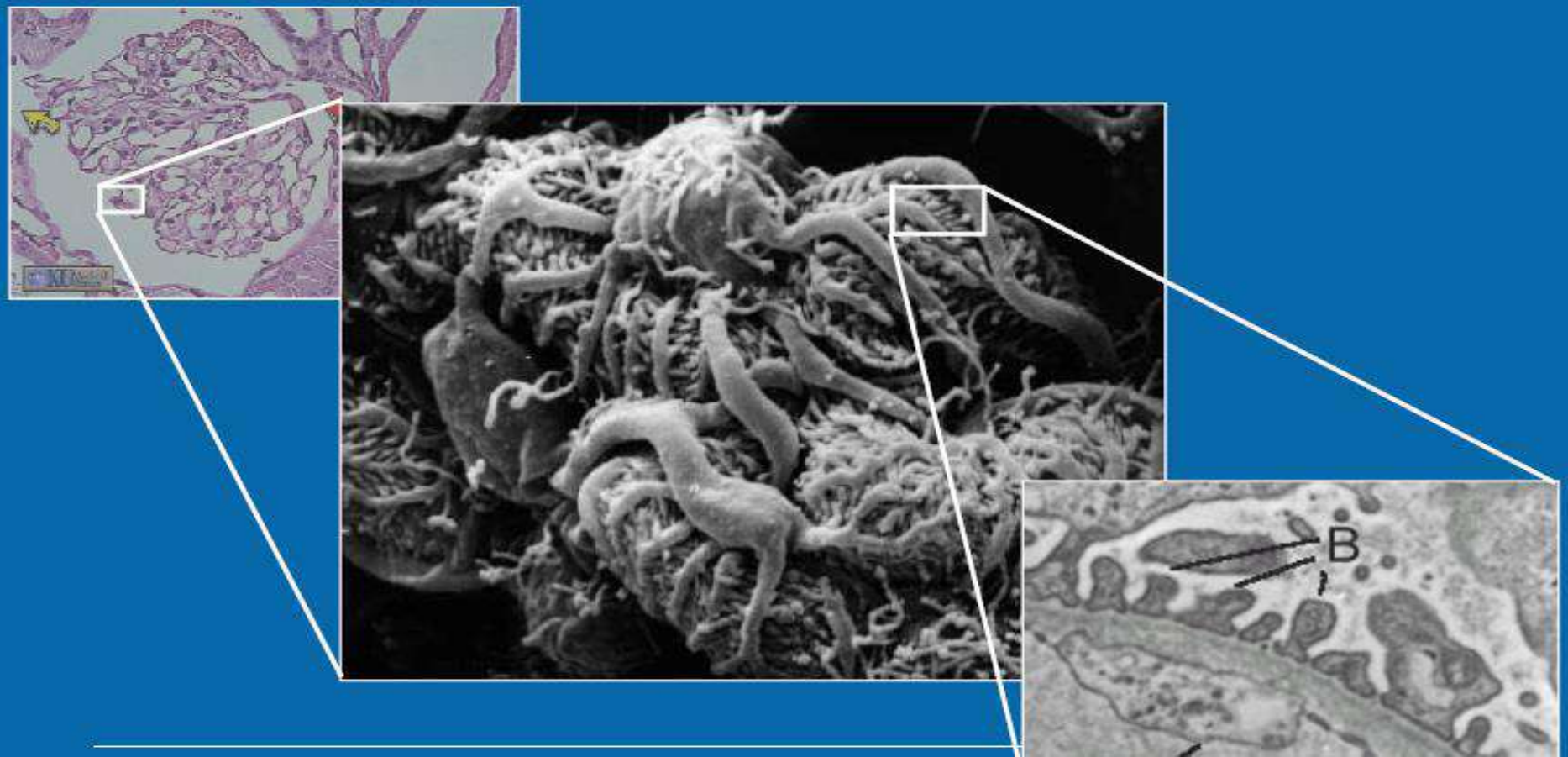
[a]Department of Internal Medicine, University of Michigan, Ann Arbor, Mich., and [b]BioMEMS Laboratory, Cleveland Clinic, Cleveland, Ohio, USA

Arrythmia Care as a Paradigm for the 21st Century

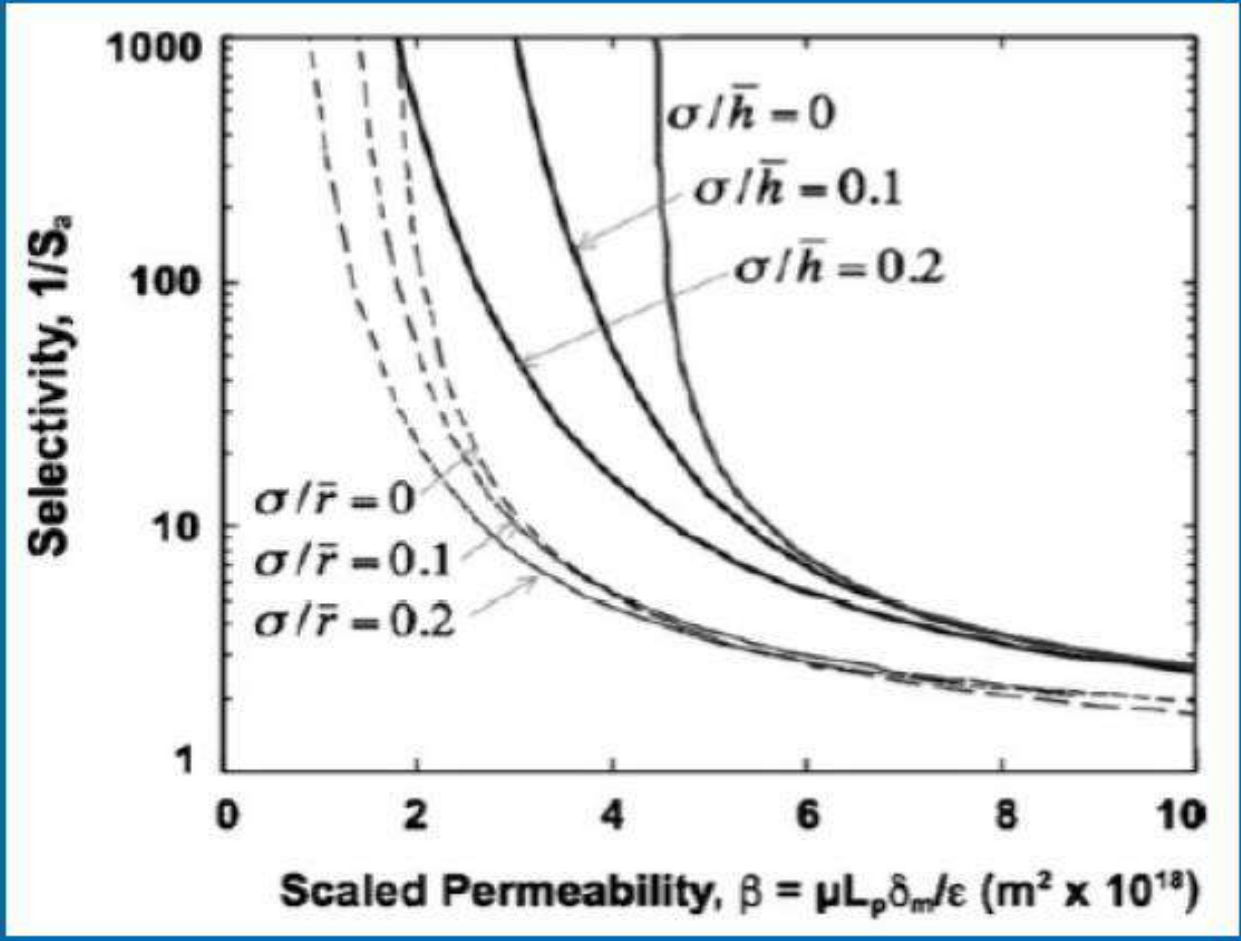


?

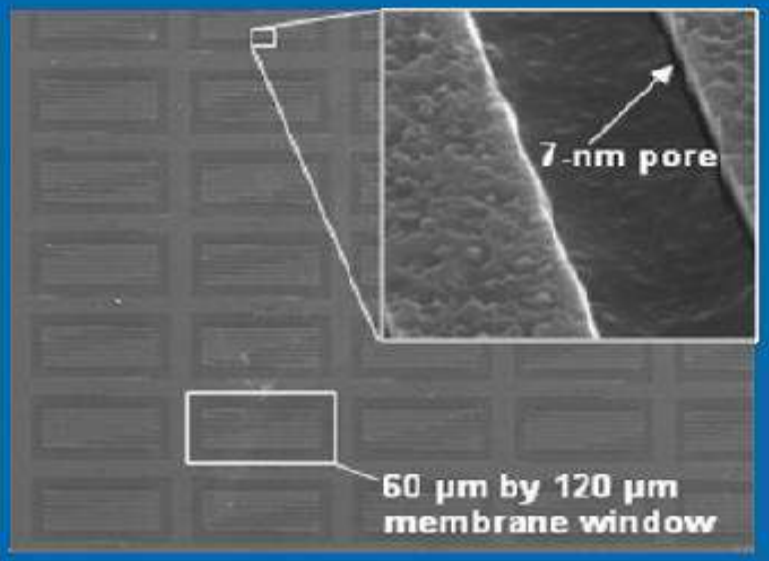
The Kidney's Natural Hemofilter

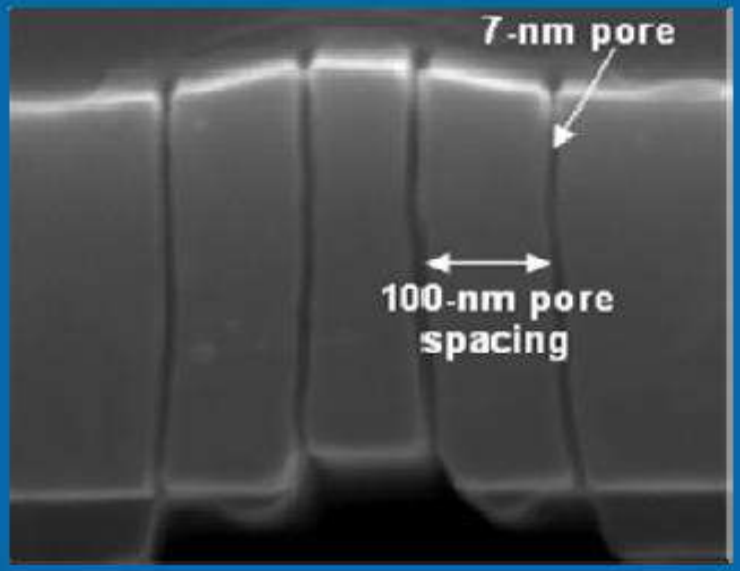


Uniformity of Pores and Shape of Pores Control Selectivity

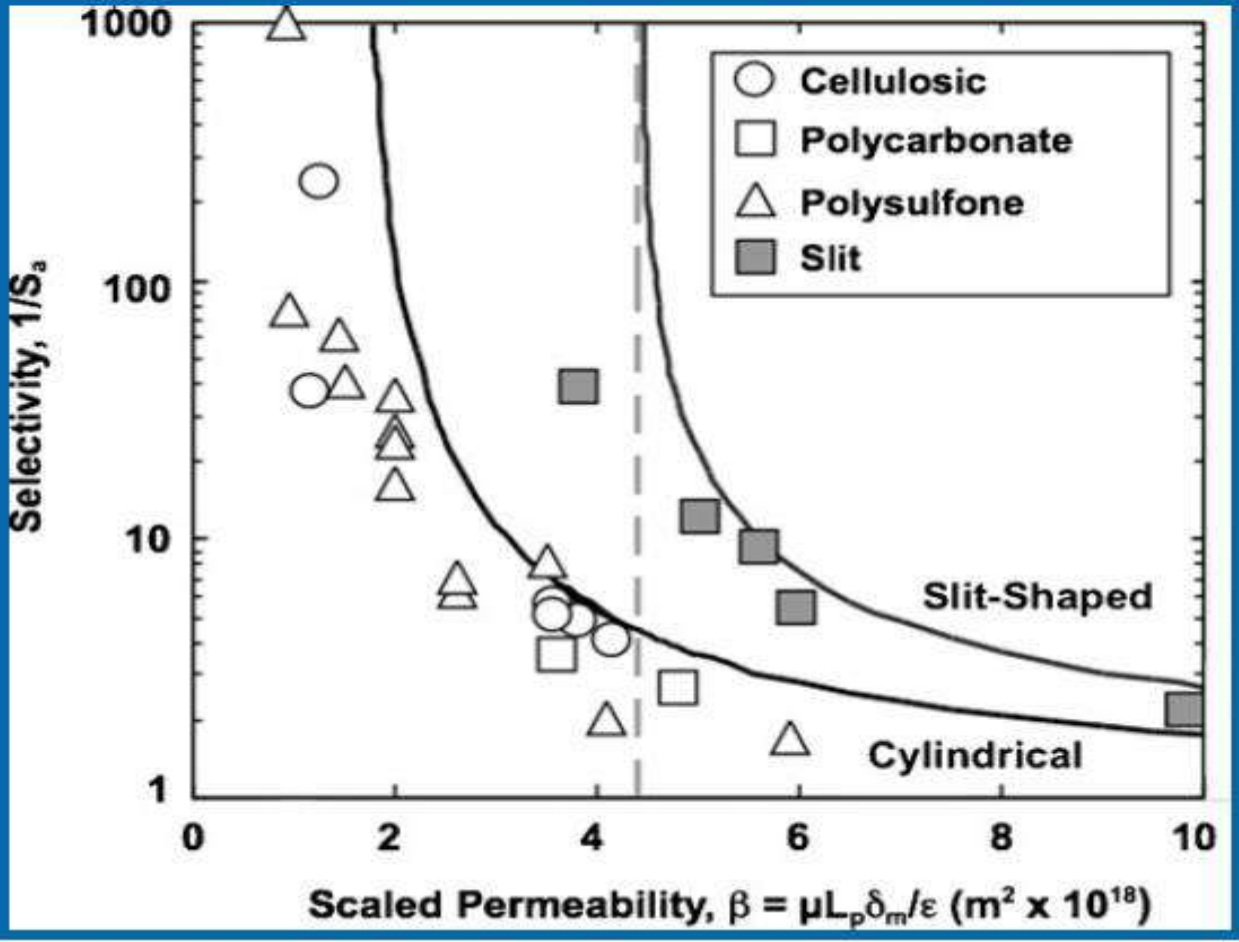


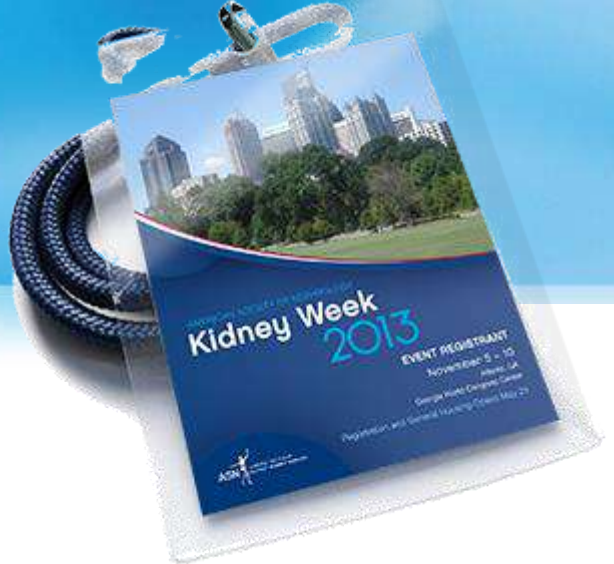
Silicon Nanopore Membrane





Enhanced Selectivity of Slit Pores



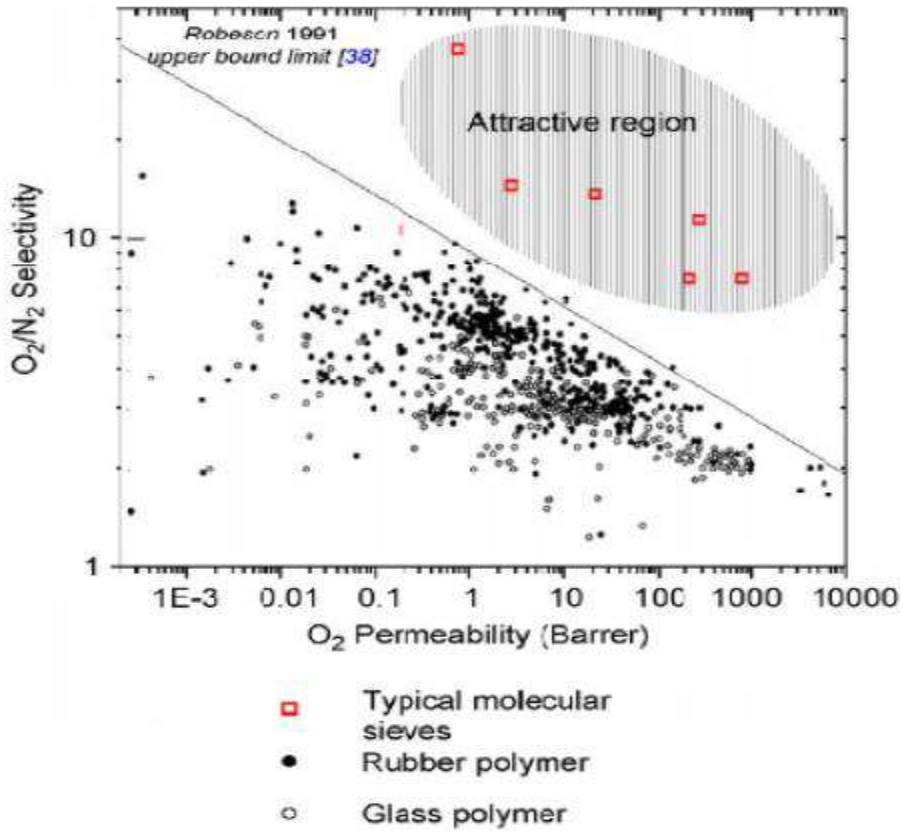


Beyond the nanometric scale ?

Nanometric size increases the specific surface, which is often used to enhance well established properties at macrocale:

- Bacteriostatic properties of silver nanoparticles
- Catalysis of oxidation reactions in fuel cells

Beyond the nanometric scale: the nanometric structure



Particles with a controlled nanostructured have much better properties than standard ceramic or polymer films

T.-S. Chung et al. / Prog. Polym. Sci. 32 (2007) 483–507

Mixed matrix (nanocomposite) membranes

A. Galve et al. / Journal of Membrane Science 370 (2011) 131–140

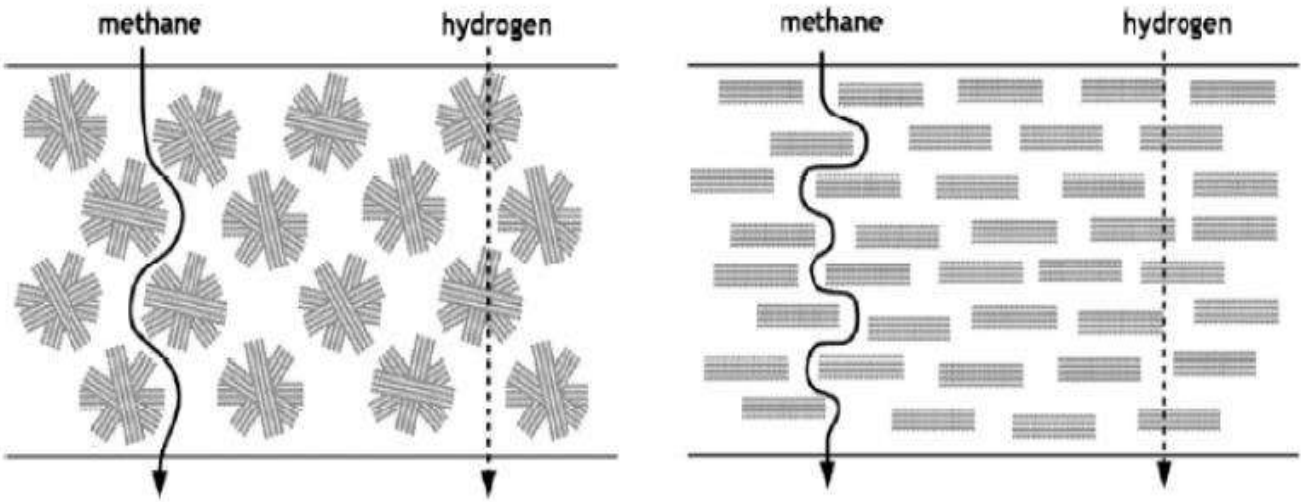
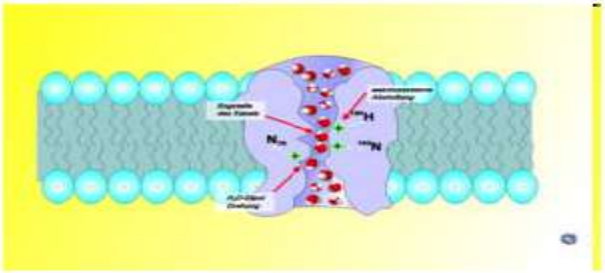


Fig. 3. Scheme of the approach for MMMs using sheet-shaped inorganic materials with horizontal orientation.

Mimicking natural beauty…



Aquaporins= water channel through bilipidic bi-layers

Agre P, Preston GM, Smith BL, Jung JS, Raina S, Moon C, Guggino WB, Nielsen S (1 October 1993). *Am. J. Physiol.* **265** (4 Pt 2): F463–76.

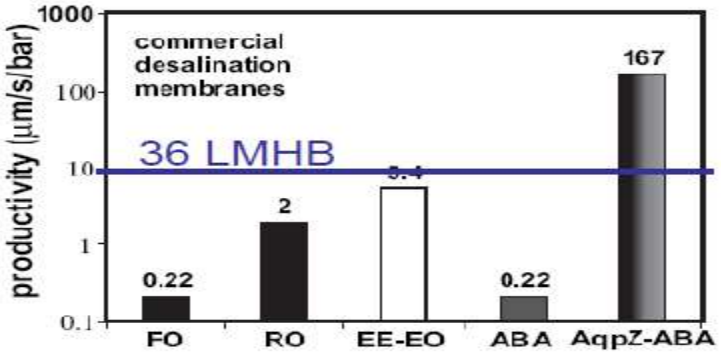
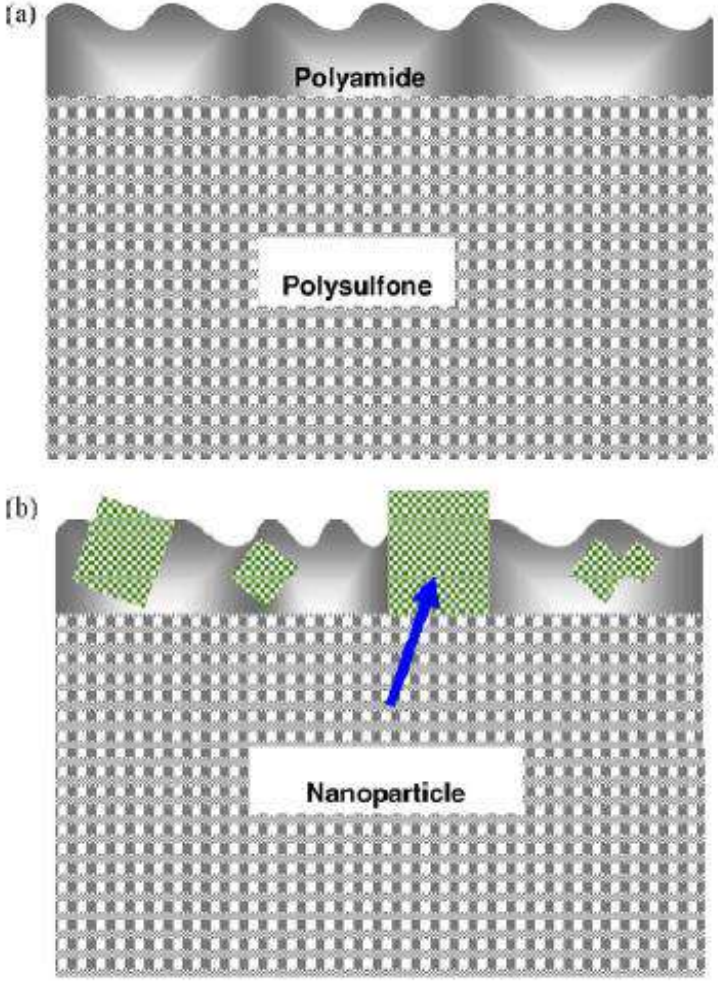


Fig. 5. Comparison of reported permeability values for polymeric membranes to those obtained in this study. FO is a commercial forward-osmosis membrane with data from McCutcheon and Elimelech (37) at 20°C. RO is a commercial reverse-osmosis desalination membrane with data fromMatsura (38) at room temperature (assumed 25°C). EE-EO is a polyethylethylene-polyethylene oxide diblock polymer with data from Discher *et al.* (13) at 20°C. ABA represents the polymer vesicles used in this study with permeability calculated at 20°C. AqpZ-ABA represents the polymer vesicles with incorporated AqpZ at 1:50 molar ratio used in this study at 20°C. Data for ABA and AqpZ were obtained at 5.5°C and calculated at 20°C by using E_a values.

M. Kumar, M. Grzelakowski, J. Zilles, M. Clark, W. Meier, PNAS,,104(52) (2007) 20723–20728

Nanostructured particles: ideal candidate for desalination membranes ?



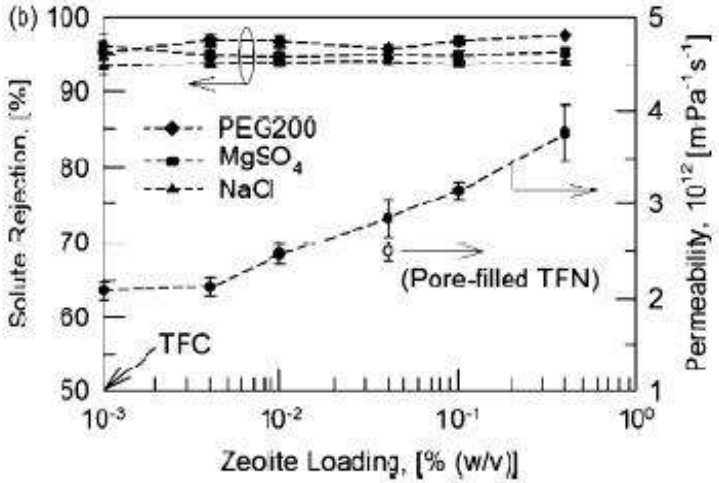
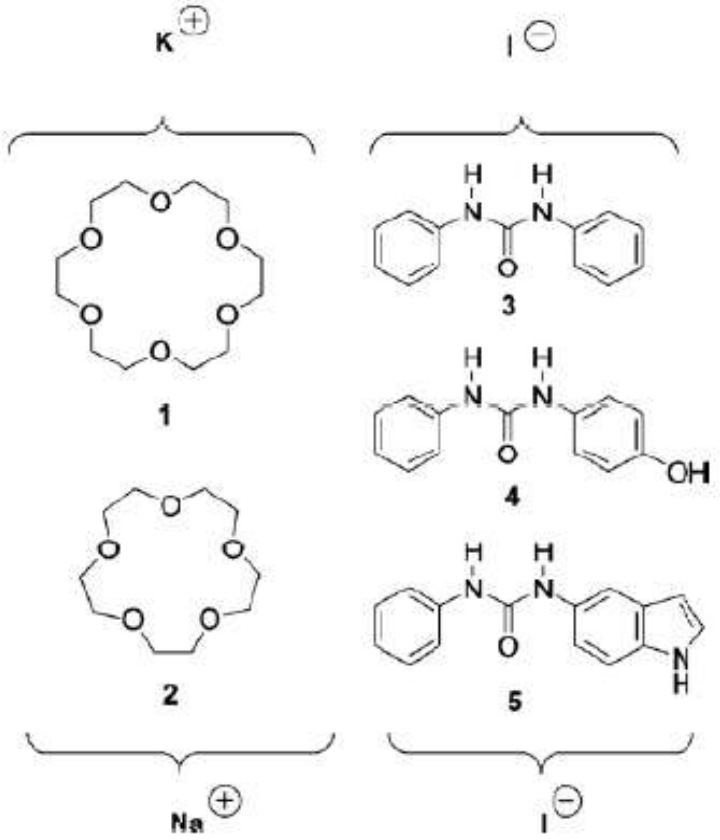


Fig. 5. Effect of zeolite loading on (a) surface properties and (b) separation performance of synthesized TFC and TFN membranes. *Note*: TFC data are plotted at 10^{-3} for convenience.

Jeong B.-H., Hoek E.M.V., Yan Y., Subramani A., Huang X., Hurwitz G., Ghosh A. K., Jawor A., *J. Membr. Sci.*, 294 (2007) 1–7.

Design of ion channels by supramolecular chemistry



Scheme 1. Structures of the cation-carriers 18-crown-6, **1** and 15-crown-6, **2** M_1–M_3 and of the phenylureidoarene anion-carriers **3**–**5**.

Mixed supramolecular cation-carrier and anion-carrier facilitated transport for the selective alkali cations transport, C. Arnal-Hérault, M. Michau, M. Barboiu, JMS (321) 2008.

Beyond the nanometric scale: Let's scale-up!

An interesting example at the University of Twente… at the microscale

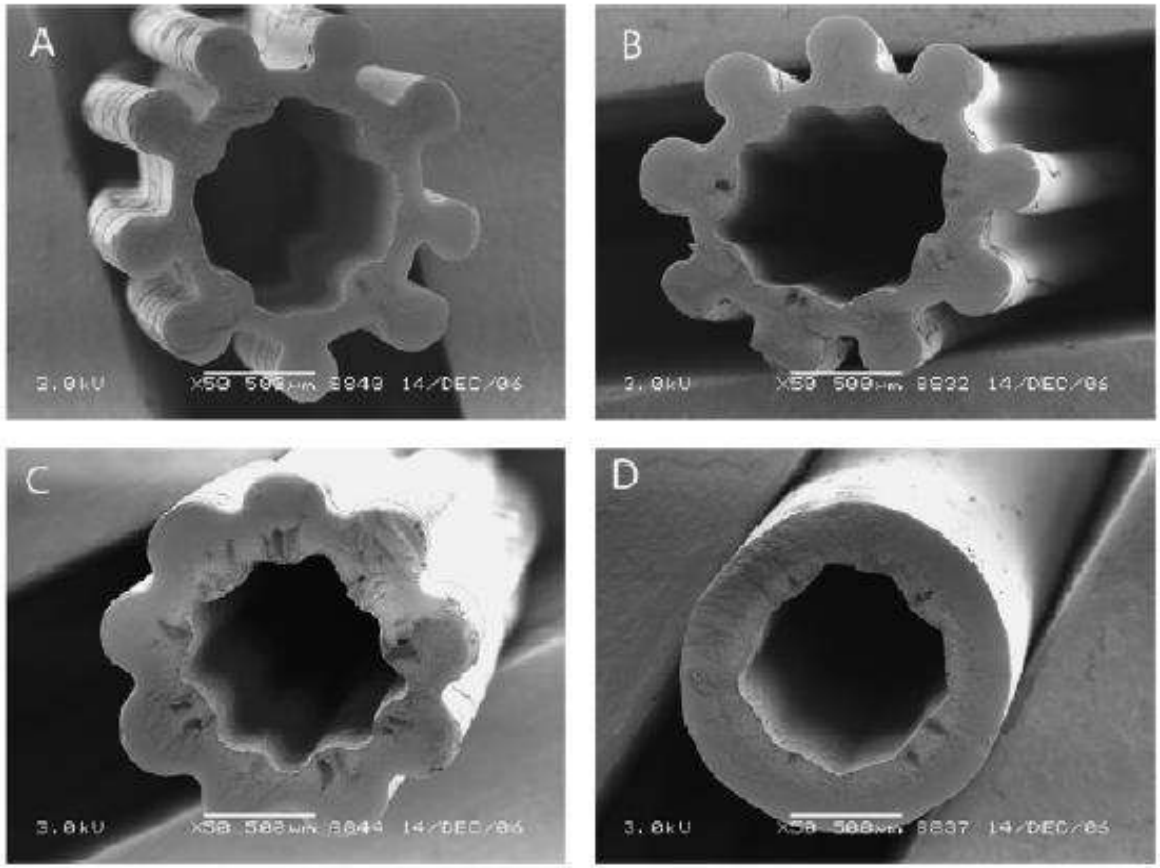


Fig. 2. Fibers spun with dope D1, using air gaps of (a) 5 mm, (b) 12 mm, (c) 32 mm and (d) 58 mm.

Microstructured hollow fibers for ultrafiltration, P. Zeynep C¸ulfaz, E. Rolevink, C. van Rijn, R. G.H. Lammertink, M. Wessling, Journal of Membrane Science 347 (2010) 32–41

Concluding remarks

- Membrane technologies are at the nanometric scale
- Membranes not yet involved in (litterally) “nanotechnology”
- The interest of the “Membrane community” for nano* is still growing fast.
- Papers on membranes in sensors or “lab-on-chip” (the smallest scale devices so far in operation) are published elsewhere (Small, Lab-on-Chip, Nano, …)
- Promising perspective for membrane technology:
  - Properties of nanometric particles
  - Self assembling molecules or supramolecular architecture.
- Next challenges are CO2 capture / Water supply and treatment / Gas purification / Fuel cells for ground transportation etc…:
  - ⇒ **mass production is the issue**

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Editorial Review

Dialysis adequacy today: a European perspective

Francesco Locatelli[1] and Bernard Canaud[2]

Table 2. Clinical studies examining the influence of haemodiafiltration on patient survival

First author/year of publication	Study design	Type of study	No. of patients	Survival between treatment modalities	Comments
Locatelli *et al.*/1996 [58]	LF-HD versus HF-HD versus HDF	Prospective, randomized multicentre	380	No difference	Primary aim to compare LF polysulfone and cuprophan
Locatelli *et al.*/1999 [59]	HD versus HDF versus HF	Historical, prospective multicentre	6444	10% reduction in relative risk	Non-significant trend towards better survival
Wizemann *et al.*/ 2000 [60]	LF-HD versus HDF	Prospective randomized single centre	44	No difference	
Bosch *et al.*/2006 [61]	HE-HD versus HF-HD versus HDF	Prospective observational, single centre	183	Improved survival with HDF than national average	Standardized mortality ratio relative to USRDS data
Canaud *et al.*/2006 [52]	LF-HD versus HF-HD versus HDF (Low-/ High-efficiency)	Historical prospective observational, multicentre	2165	35% improvement	Survival improvement observed for high-efficiency HDF versus LF-HD
Jirka *et al.*/2006 [62]	LF-HD versus HF-HD versus HDF	Prospective observational, multicentre	2564	35% improvement	Study part of European Clinical Database (EuClid)
Schiffl/2007 [63]	HF-HD versus HDF	Prospective randomized, single centre	76	No difference	Ultrapure fluids used for both HF-HD and HDF groups
Panichi *et al.*/2008 [64]	LF-HD versus HDF	Prospective observational multicentre	757	15% improvement	Improved survival independent of dose
Vilar *et al.*/2009 [65]	HF-HD versus HDF	Retrospective observational, monocentre	858	34% improvement	Incident patients studied over 18-year period
Tiranathanagul *et al.*/2009 [66]	HF-HD versus HDF	Prospective observational, single centre	22	No difference	Study evaluated tolerance and patient acceptance
Locatelli *et al.*/2010 [53]	LF-HD versus HF-HD versus HDF	Prospective, randomized	146	No difference	Primary aim cardiovascular stability

Criteria used to include the published studies reported in this table: all studies dealing with survival involving high-flux haemodiafiltration, irrespective of study type, design or sample size.

http://www.kidney-international.org

Novel techniques and innovation in blood purification: a clinical update from Kidney Disease: Improving Global Outcomes

Christopher T. Chan[1], Adrian Covic[2], Jonathan C. Craig[3,4], Andrew Davenport[5], Bertram L. Kasiske[6], Martin K. Kuhlmann[7], Nathan W. Levin[8], Philip K.T. Li[9], Francesco Locatelli[10], Michael V. Rocco[11] and David C. Wheeler[5]

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Table 2 | Research recommendations

- Observational data from registries providing additional information about the risks and benefits of more frequent hemodialysis. At a minimum, registries should collect prescription data that include the frequency of dialysis per week and the number of hours per hemodialysis session. Combining this data with laboratory information and patient outcome data, including hospitalizations, change in modality, and death, would provide much needed information on patient outcomes, even accounting for the potential selection bias of patients who are capable of choosing frequent hemodialysis.
- Clinical trials in more frequent hemodialysis could allow for meta-analyses of specific frequent modalities. It is also not known whether providing dialysis either four times a week or every other day would provide some or most of the benefits shown with six times per week dialysis, but at a lower cost.
- All studies should include careful baseline and periodic measurement of residual kidney function.
- Much work needs to be done to provide a less complex method for performing hemodialysis at home. Factors that are likely to limit the number of patients who perform home hemodialysis include the need to troubleshoot dialysis machines, the need for an appropriate partner at home, acceptance of a complex piece of machinery, avoiding hypotension, and avoiding access complications. More funding is needed to develop a simpler, more user-centric hemodialysis machine that will minimize the time needed for setup and take down, and further decrease the risks of having an adverse event while performing hemodialysis at home.

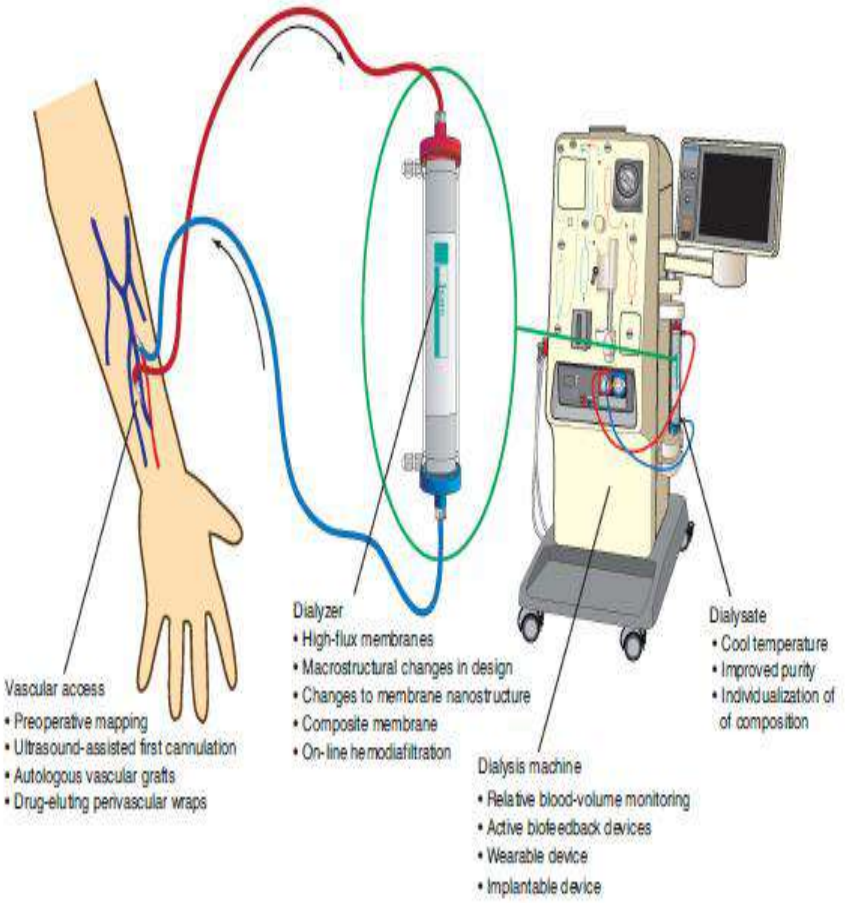


Figure 1 | Innovations in hemodialysis technology.

Peritoneal Dialysis dose

- Peritoneal dialysis adequacy indices
- Peritoneal membrane characteristics
- Dialysate composition
- Dwell time
- Mode of delivery
- Volume status
- Nutrition
- Electrolytes
- Outcomes

Indices of dialysis adequacy

- Urea clearance normalized to body water (Kt/V)
- Creatinine clearance normalized to body surface area
- Both include dialytic and residual components
- Residual function is a greater component in PD patients and lasts longer
- Samples from PD effluent. In CAPD any time, but in APD blood samples at mid-afternoon
- V derived from anthropometric Watson formula and BSA from DuBois Formula
- In patients with wt. loss from malnutrition suggest using desirable body weight for V

Measure PD adequacy in first 2-4 weeks then 2x in first 6 months, then 4 monthly. Residual RF should be measured with same regularity until Kt/V <0.1 (<100ml/24h)

Guidelines: Minimum Kt/V(total) of 1.7. Current guidelines do not include weekly CrCl. Consider minimum UF 1L/24h, consider higher Kt/V in APD/CCPD.
Note limited data in anuric patients. Consider min total CrCl of 50L/wk. Consider 24h dialysis in all anuric patients.

PD techniques and parameters

Manual PD,
Rapid cycling
CAPD, CCPD (APD)
NIPD
TPD

To achieve adequacy:

- •CAPD Increase volume (CAPD 2.0 to 2.5L)
- •Nocturnal exchange device
- •APD: dwell volume, no. exchanges, total time, no. daytime dwells
- •High transporters rapid cycle short dwell

To manage technique symptoms:

- •Use tidal PD, vary exchange volume vs. exchange frequency

Volume Status

- Evidence that PD patients have poor volume status
- Patients with poor volume status but better clearance have increased mortality
- Urine volume and K_r both important. ACEI and ARB preserve K_r
- Diuretics preserve urine volume

Studies of PD patient survival

	% survival by transport group			
Pts	L	LA	HA	H
503	91	80	72	71
123	100	89	91	71
46	100	90	63	16
303	70	57	46	42
202	72	66	60	31

Causes of volume overload

Membrane causes	Nonmembrane causes
Type I - high effective	Excess salt + water
Membrane area	Decline in UO
Type II - inadequate	Non compliance
Effective membrane area	Wrong solution tonicity
Type III - excessive PD	Peritoneal leak
fluid absorption	Poor catheter function
Other	Hyperglycemia

Nutrition

PD dialysate protein losses (9g/d) (higher than HD), impaired gastric emptying, anorexic effect of dialysis glucose absorption, peritonitis episodes
Protein intake 1.0-1.2g/Kg/day
Peritoneal Kt/V >1.7
Consider amino acid dialysate
nPNA and Kt/V may be coupled
In prospective studies nPNA may rise as Kt/V rises possibly reflecting increased DPI (daily protein intake)
As in HD, Kt/V may mask malnutrition (remember V)

To calculate PCR (g/day) = 10.76 X (G_{un} + 1.46)

G_{un} = urea nitrogen generation in mg/min which can be calculated from 24h dialysate collection

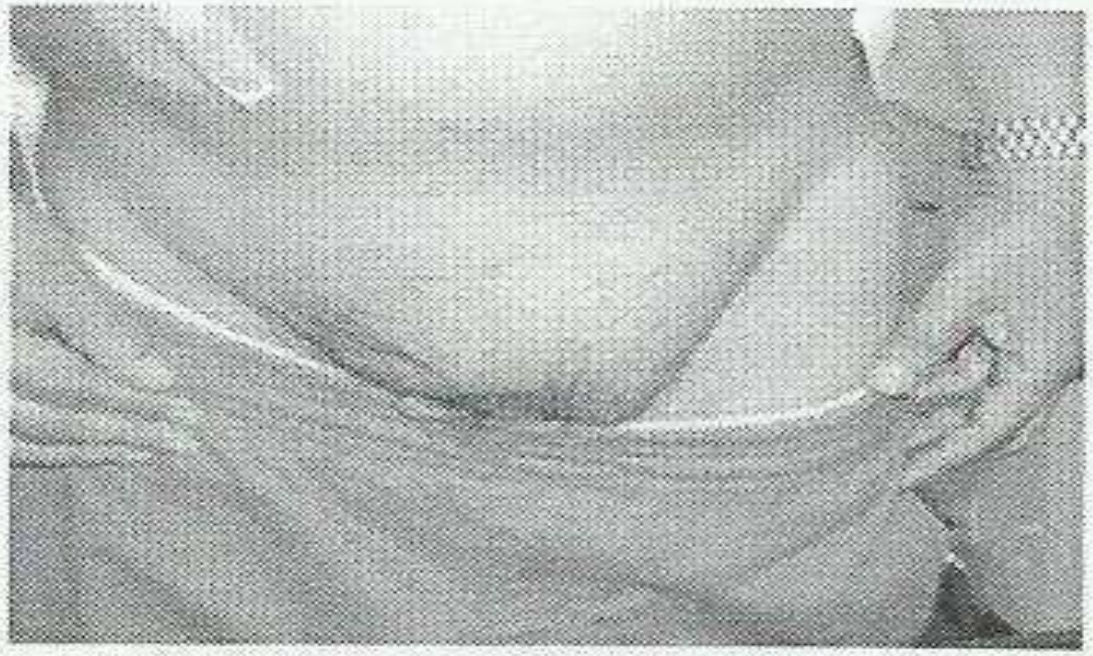
Calculate nPCR from BUN and Kt/V. nPCR can be used to determine a patient's nitrogen balance

Residual Renal Function

ACEI/ARB indicated.
Consider diuretics for volume only
Avoid:

- Contrast
- Aminoglycosids
- NSAIDS
- Volume depletion
- Urinary track obstruction
- Hypercalcemia
- Withdrawal of transplant immunosuppression

Horton and his Hernia



PD and Increased Intra-abdominal Pressure (IAP)

- instillation of dialysate into the peritoneal cavity leads to increased IAP
- the magnitude of the increase depends upon:

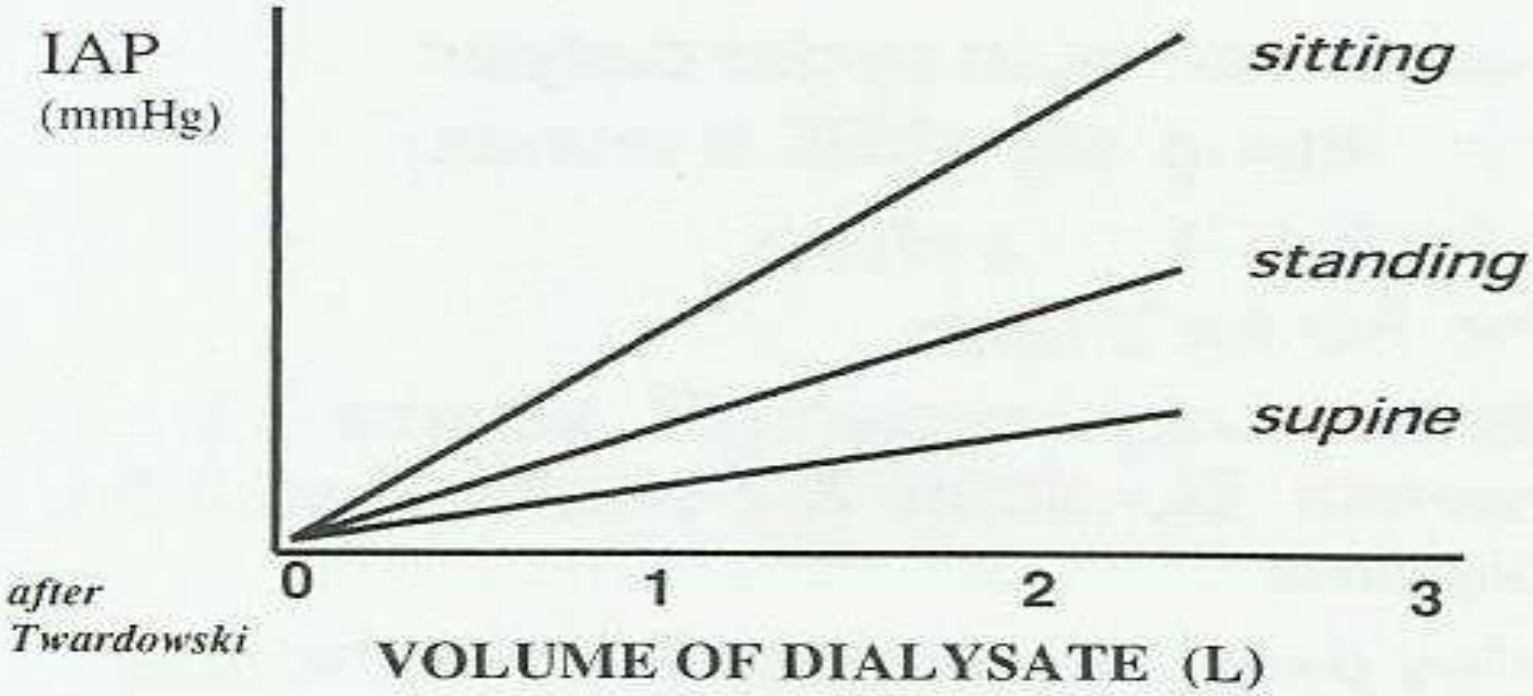
  -volume of dialysate instilled

  -position of the patient (*sitting>standing>supine*)

  -age, body mass index

  -coughing, lifting, straining at stool, aerobics class (!), chopping wood (!)

Relationship among Intra-Abdominal Pressure (IAP), Position & Dialysate Volume



after Twardowski

Hernias

Clinical Presentation:

- lump or swelling that may be tender
- bowel incarceration or strangulation
- rarely, peritonitis (if associated bowel strangulation)

Hernias *(cont'd)*

Treatment:

- warn patient about signs of incarceration
- surgical repair:

  -dialysis around repair depends on renal function and condition of the patient

  -don't usually have to put them on HD !

  -reintroduce PD with low volumes, supine posture, increase volume over 2 weeks

So What Happened to Horton?

- continued night cycler dialysis
- dry during day (RRF 8 ml/min)
- elective hernia repair
- no PD for 2 days
- back to night cycler 1.5L volume X 2 weeks, 2Lvolume X 2 weeks, then 2.5 L volume
- day dwell re-introduced 2 months later

Abdominal Wall and Genital Edema

Presentation:

- abdominal swelling or bogginess, scrotal or labial edema
- diminished effluent return
- weight gain without peripheral edema
- pericatheter leak: wetness or swelling at exit site

Abdominal Wall & Genital Edema

Diagnosis:

- physical exam (have patient stand in front of you)
- unchanged PET results
- CT scan
- pericatheter leak: ultrasound around exit site

Abdominal Wall and Genital Edema

Diagnosis by CT Scanning:

- add 100-150 ml Omnipaque to dialysis bag
- infuse dialysate into patient
- * have patient ambulatory for 30 to 60 minutes to increase intra-abdominal pressure
- * send for CT scan - discuss with the radiologist !

Abdominal Wall & Genital Edema

Management:

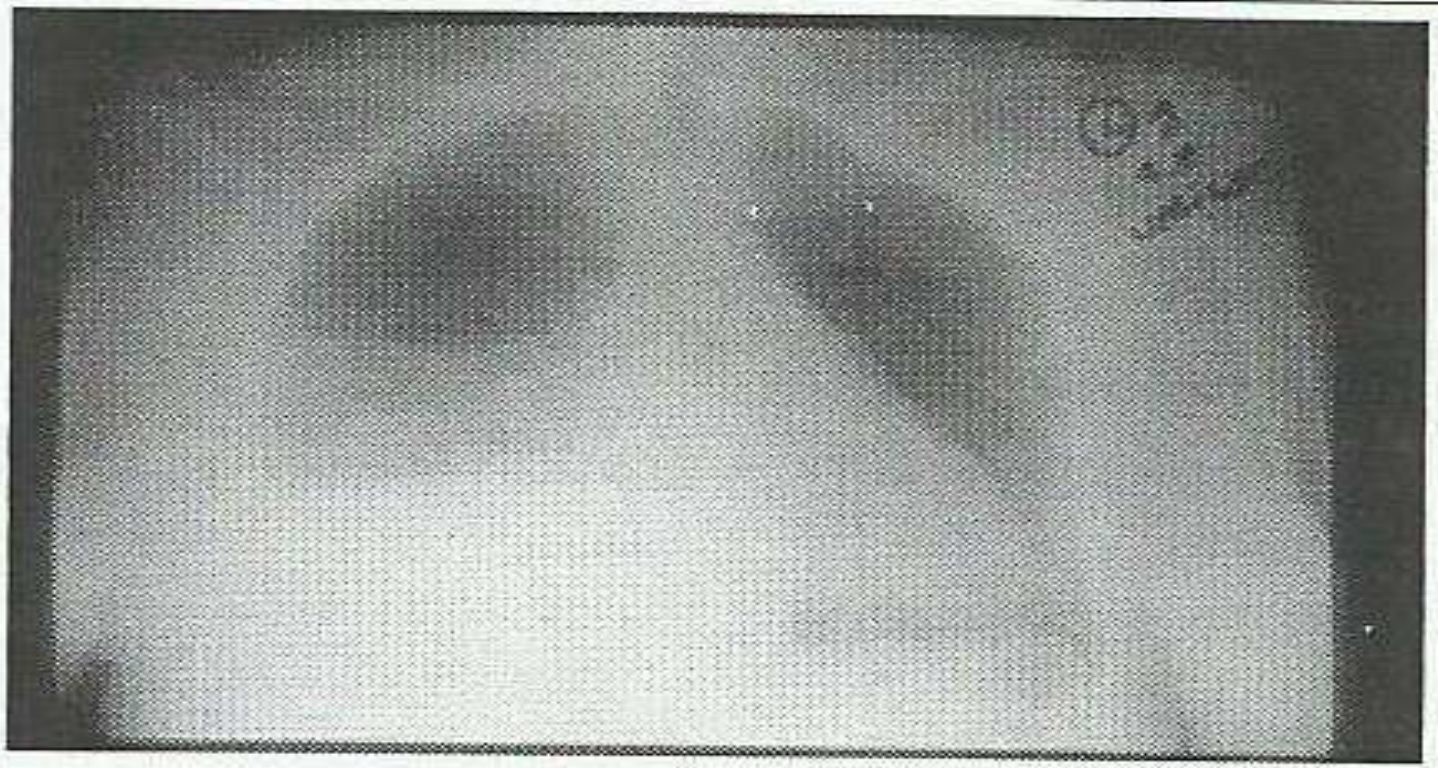
- reintroduce low pressure PD (eg APD with low volumes)
- temporary HD to allow healing
- Abdominal wall: CT scan for occult hernia
- Genital: CT scan for patent processus vaginalis, which is easily repaired

Ms. F.M. Gets SOB *(cont'd)*

She comes for home peritoneal dialysis training 2 weeks later. This goes well and she is discharged on 2L exchanges TID. Residual GFR is 10 ml/min.

One week later she calls the unit that she has become progressively short of breath over the past 3 days. There is no cough, wheeze or sputum production. She is 1 kg above her target weight.

Ms. F.M. Gets SOB



Hydrothorax

Definition: The presence of peritoneal dialysis fluid in the pleural cavity

Incidence: Probably < 5%

Pathogenesis: Movement of dialysate, under increased intra-abdominal pressure, from peritoneal to pleural cavity through congenital or acquired defects in the diaphragm

Hydrothorax (cont'd)

Presentation:

- may be asymptomatic
- shortness of breath
- worsening SOB with hypertonic dialysate
- diminished effluent return
- right-sided pleural effusion on CXR

Hydrothorax

Diagnosis:

- thoracentesis for relief of symptoms and/or diagnosis
- pleural fluid analysis:

  -transudate

  - high glucose concentration (*usually, but not always*)

  -cell count variable

Hydrothorax

Treatment:

- thoracentesis may be helpful if very SOB
- stop PD
- temporary hemodialysis, if dialysis necessary

Hydrothorax

Treatment

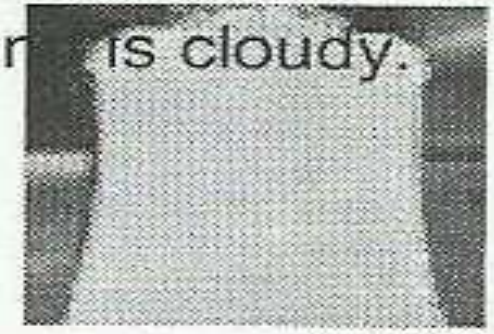
- trial of re-introducing "low pressure" PD *(the dialysate in pleural cavity may have functioned as a sclerosing agent)*
- pleurodesis (talc, tetracycline, bleomycin, autologous blood)
- operative or pleuroscopic repair (diaphragmatic defects identified and patched or oversewn)

The Cloudy Bag *(cont'd)*

He presents to the emergency department with 12 hours of progressive abdominal pain, anorexia and nausea.

On examination, he is afebrile and normotensive. There is diffuse abdominal tenderness and diminished bowel sounds.

The day bag is drained out ar is cloudy.



Peritonitis - Diagnosis

- The diagnosis of peritonitis requires at least 2 of the following 3 features:
  - peritoneal fluid leukocytosis (>100/mm^3, and at least 50% polymorphonuclear cells)
    - the fluid should dwell 2 to 4 hours
  - abdominal pain
  - positive culture of the dialysis effluent

Peritonitis - *Differential* Diagnosis (*cont'd*)

- pancreatitis
- ischemic bowel
- pyelonephritis
- nephrolithiasis
- constipation
- strangulated hernia

Peritonitis - *Differential* Diagnosis (*cont'd*)

- Also, surgical causes can lead to *secondary* peritonitis:
  - strangulated hernia
  - diverticulitis
  - appendicitis
  - ruptured viscus

Careful physical examination needed !

How Does Bacteria Gain Entry Into the Peritoneal Cavity?

- during catheter connection for the exchange
- tracking around the catheter from the exit site, through the tunnel, to the peritoneal cavity
- across the bowel wall (*eg diverticulosis*)
- transvaginal (*rare*)
- hematogenous (*rare*) (*but even rarer is for peritonitis to cause bacteremia*)

Complications of Peritonitis

- hospitalization
- technique failure
- transient problems with ultrafiltration
- peritoneal adhesions
- malnutrition
- death

Peritonitis - Principles of Treatment

- start antibiotic treatment quickly
- cover for both gram positive and gram negative organisms until cultures available
- adjust antibiotics according to culture results
- re-evaluate the treatment if no improvement* in 36-48 hours
  - ** improvement: less abdominal pain, falling peritoneal fluid WBC count*

Peritonitis - Principles of Treatment

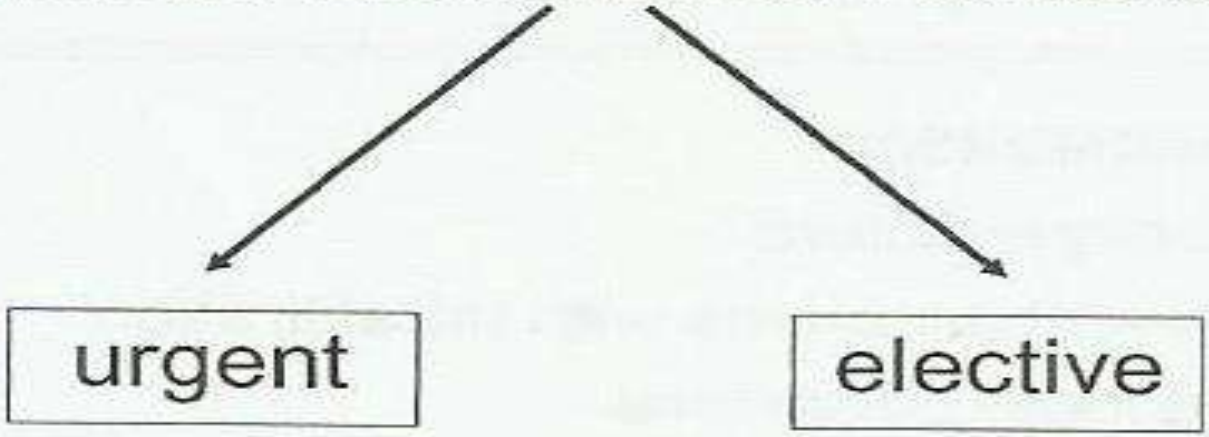
- consider removal of the PD catheter if little or no improvement in 4-5 days *(especially if staph. aureus or pseudomonas)*
- fungal peritonitis: catheter removal as soon as possible
- watch for acute problems with UF

don't let peritonitis drag on for days !

Peritonitis – Special Situations

IF:	THEN CONSIDER:
abdominal pain is *localized*	appendicitis or diverticulitis
tender hernia	strangulation
patient very hypotensive	toxigenic *s.aureus*

Catheter Removal for Peritonitis



Peritonitis -Indications for Catheter Removal

- Urgent:
  - unresolving or worsening peritonitis after 3 -5 days
  - "surgical" peritonitis (eg bowel perforation)
  - unresolving peritonitis associated with exit site or tunnel infection
  - fungal peritonitis

Fungal Prophylaxis – Prophylaxis

- oral anti-fungals administered concomitantly with any antibiotic regimen
- start at the onset of antibiotic treatment
- continue throughout therapy and for up to one week after antibiotics
- candidates - those on immunosuppressives, diabetics, all PD patients?

Indications for Catheter Removal

- Elective:
  - relapsing or recurrent peritonitis with same organism
  - continuing culture positivity of PD fluid
  - ongoing exit site infection, especially if recent peritonitis with same organism

The Mucky Exit Site

A 31 yo Type I diabetic starts on home cycler peritoneal dialysis. He does very well, but about 6 months later complains of discharge and discomfort at the PD catheter exit site.

On examination there is erythema and pus at the catheter exit site. The catheter tunnel appears swollen, and pus can be milked from the tunnel to the exit site.

A swab of the pus grows *Staph aureus*.

Exit Site and Tunnel Infections

- Diagnosis of exit site infection
  - erythema around exit site +/- seropurulent drainage
  - *don't culture a normal-looking exit site*
- Diagnosis of tunnel infection
  - edema and tenderness along catheter tunnel
  - may need ultrasound

Exit Site and Tunnel Infections

- best treatment is *prevention*
  - careful perioperative care
  - good exit site maintenance care
  - immobilization of catheter
  - treatment of *staph. aureus* nasal carriage (difficult)
  - intranasal or exit site mupirocin (reduces risk by about 50%)
  - recent study suggests gentamicin cream may be even more effective

Exit Site and Tunnel Infections

- Treatment (*cont'd*):
  - local antiseptic agents
  - antibiotics (topical or systemic)
  - shave distal cuff if protruding, or revise tunnel
  - catheter removal and replacement
  - *nothing*

The Mucky Exit Site *(cont'd)*

Part II

The patient comes to the emergency 1 week later with abdominal pain and cloudy fluid.

On examination, the exit site and tunnel appear unchanged from the week before. There is generalized abdominal pain and rebound tenderness. The bowel sounds are quiet.

The PD fluid is cloudy. Cell count is 6000 X 10^6/L with > 90% neutrophils. Gram stain shows Gram positive cocci in clusters.

Transient "Rapid Transporter" Status During PD Peritonitis

the "***leakier***" the peritoneal membrane (2º to hyperemia of inflammation)

⇩

the faster glucose will diffuse out of the peritoneal cavity

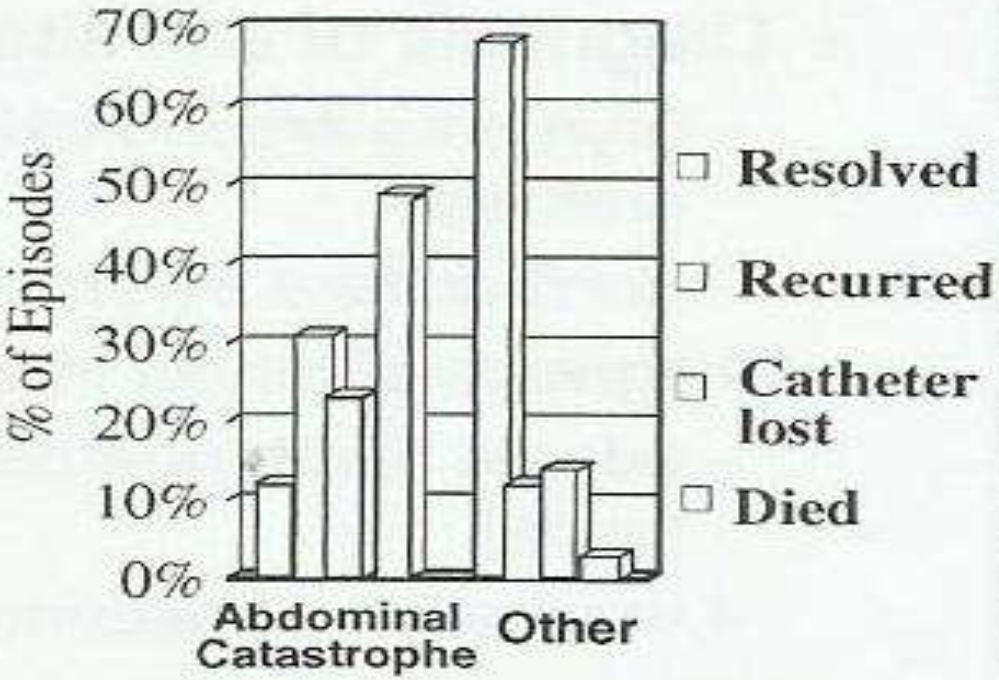
⇩

the faster the osmotic gradient will dissipate

Peritonitis: Visceral Leakage

Harwell et al. *Perit Dial Int*, 1997

- Etiology:
  - **appendicitis 4**
  - **cholecystitis 3**
  - **ischemic bowel 11**
  - **diverticulitis 6**
  - **perforated ulcer/ endoscopy 3**



Slide courtesy Dr. T. Golper

Encapsulating Peritoneal Sclerosis

Incidence: rare

Presentation: recurrent bowel obstruction
abdominal pain
hemoperitoneum

***** May present when a patient is no longer on PD (transplanted, HD)***

Encapsulating Peritoneal Sclerosis *(cont'd)*

Diagnosis:

- recurrent bowel obstruction
- patient may no longer be on PD
- Consider especially if PD was stopped because of severe, unresolving peritonitis
- characteristic CT appearance

Many gastroenterologists, surgeons and radiologists are unaware of this entity!

Encapsulating Peritoneal Sclerosis

Treatment:

- nutritional support (eg pureed food, TPN)
- surgical dissection of fibrous tissue
- anti-inflammatory/immunosuppressive meds
- tamoxifen, sirolimus

Hemoperitoneum

Definition:

- Bloody peritoneal effluent

Presentation:

- scary ! (*not as bad as it looks*)
- must consider "benign" and "serious" causes

Hemoperitoneum *(cont'd)*

"Benign" Causes:

- menstruation
- ovulation
- ruptured renal or ovarian cysts
- trauma
- coagulopathy

Hemoperitoneum *(cont'd)*

Serious Causes:

- ischemic bowel
- colon cancer
- pancreatitis
- encapsulating peritoneal sclerosis
- urologic cancer

Hemoperitoneum *(cont'd)*

Treatment:

- IP heparin to avoid clotting of catheter
- flushes
- dialysate at room temperature
- investigations depend on whether benign or serious type of presentation

During training, warn females in advance of this complication!

Summary Points (I)

- hernias are unsightly, enlarge with time, and pose a risk for leaks and incarceration
- they can usually be repaired operatively without putting the patient on hemodialysis
- patients at risk should be on a “low pressure” PD regimen

Summary Points (II)

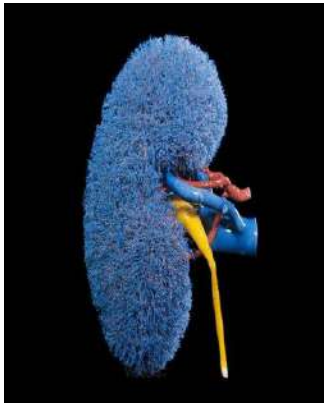
- edema of the abdominal wall and genitals is through a leak of dialysate
- often this resolves with "low pressure" dialysis
- fixed defects, such as hernias or patent processus vaginalis should be surgically repaired

Summary Points (III)

- it is important to be aware of hemoperitoneum and encapsulating peritoneal sclerosis as complications of PD
- think of encapsulating peritoneal sclerosis if a (present or former) PD patient presents with bowel obstruction
- commonest cause of hemoperitoneum is menstruation, and is benign

" If I have seen further it is because I have stood on the shoulders of Giants"

Sir Isaac Newton



“One must not stay within the lines”- Eric Carle