Charcoal Column Regeneration of CVVHD Fluid to Optimize Clearance of Organic Toxins

ADC 2018
Orlando

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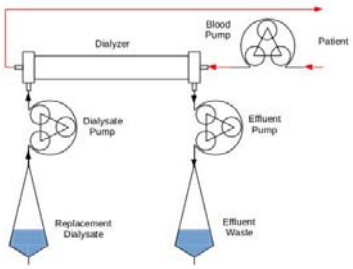
Conventional CVVHD, Flow-Through-To-Drain Dialysate



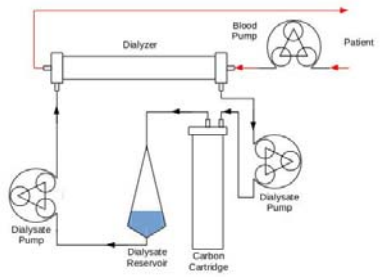
Advantages of CVVHD with Bags of Dialysate

- Continuous therapy
- Physiologic stability
- Maximal UF per day is huge
- Sterile dialysate
- Reasonable middle molecule removal
- Operable by ICU nursing staff

Disadvantages of CVVHD

- Not really continuous-average treatment lasts 20 hours per pack
- Strength and time by staff needed in adding new bags and monitoring patients in the ICU
- Expense of dialysate is very high ($35 or more per bag)
- Designed to produce dialysate-limited clearance; highest clearance of any uremic toxin equals the dialysate flow rate
- Dialysate flow rate is low, 20-40 ml/kg/hour is about 20-40 ml/min
- At dialysate flow suited for organic uremic toxins, removal of simple toxins such as K^+ and H_2PO^{4-} may be excessive, requiring adjustment of dialysate concentrations
- CVVH has better middle molecule clearance but is not done widely in the US, since the dialysate fluid bags are not approved for IV infusion.

Concept of Dialysate Regeneration by Activated Carbon During CVVHD



Advantages of Carbon Regeneration of CVVHD Dialysate

- Dialysate flow can be increased to 400 ml/min, not 20-40 ml/min
- Clearance of important organic uremic toxins would be greatly increased (creatinine, 5-OHIAA, p-cresol, etc.)
- Small or charged toxin removal rate can be separately controlled by frequency of changing dialysate bags as needed (urea, K^+, HCO_3^-, $H_2PO_4^-$)
- Column of 300 grams carbon should last for 72 hours
- Dialysate costs of CVVHD will be decreased in many patients (using 2-3 bags daily rather than 5-6)
- At higher dialysate flows, intrinsic convection of the high-permeability dialyzer will increase MM removal

Clearances of Uremic Markers is Very Low with CVVHD

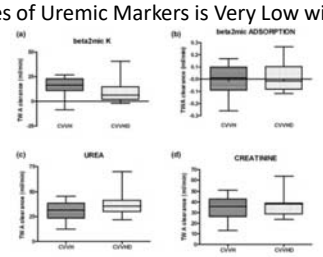


Figure 2
Time weighted average (TWA) clearance of (a) β_2 microglobulin (beta2mic), (c) urea and (d) creatinine by convective and diffusive transport. (b) Beta2mic adsorptive clearance during continuous veno-venous hemofiltration (CVVH) and continuous veno-venous dialysis (CVVHD). Data are expressed as median and interquartile range. None of these comparisons reaches statistical significance.

Solute removal during continuous renal replacement therapy in critically ill patients: convection versus diffusion

Ave Qd = 2150 ml/hr, Ave Qb = 150 ml/min

Creatinine Clearance Increases Proportional to Dialysate Flow Rate

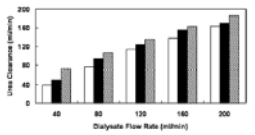


Figure 1. Dependence of urea clearance for dialyzers containing PUREMA membranes on dialysate flow rate at a blood flow rate of 400 ml/min for ultrafiltration flow rates of 0 (white bars), 1 (black bars), and 2 (striped bars) l/h. Standard deviations for all conditions studied were consistently small (individual values not shown) and ranged from 1.7 to 14.0 ml/min. Analysis of variance demonstrated that urea clearance was significantly dependent on both dialysate flow rate ($p < 0.001$) and ultrafiltration flow rate ($p < 0.001$).

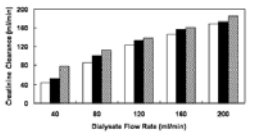


Figure 2. Dependence of creatinine clearance for dialyzers containing PUREMA membranes on dialysate flow rate at a blood flow rate of 400 ml/min for ultrafiltration flow rates of 0 (white bars), 1 (black bars), and 2 (striped bars) l/h. Standard deviations for all conditions studied were consistently small (individual values not shown) and ranged from 0.7 to 15.7 ml/min. Analysis of variance demonstrated that creatinine clearance was significantly dependent on dialysate flow rate ($p < 0.001$) and ultrafiltration flow rate ($p < 0.001$).

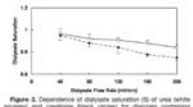


Figure 3. Dependence of dialysate saturation (S) of urea (white squares) and creatinine (black circles) for dialyzers containing PUREMA membranes on dialysate flow rate at blood flow rates of 200 and 400 ml/min and ultrafiltration flow rates of 0 to 2 l/h. Error

Dialyzer Clearances and Mass Transfer-Area Coefficients for Small Solutes at Low Dialysate Flow Rates

Middle Molecule Clearance also Increases Greatly with Higher Dialysate Flow

Clearance * (mL/min)	
Qb=300mL/min, Qd=500mL/min,	
Urea *	271
Creatinine	242
Phosphate	241
Vitamin B_{12}	139
Lysozyme *	74
Qb=400mL/min, Qd=500mL/min,	
Urea *	317
Creatinine	274
Phosphate	272
Vitamin B_{12}	162
Qb=400mL/min, Qd=800mL/min,	
Urea *	332
Creatinine	288
Phosphate	290
Vitamin B_{12}	167
Qb=400mL/min, Qd=900mL/min,	
Urea *	349
Creatinine	302
Phosphate	304
Vitamin B_{12}	173

Clearance about 30 ml/min, with dialysate flow at 33 ml/min

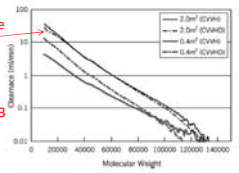


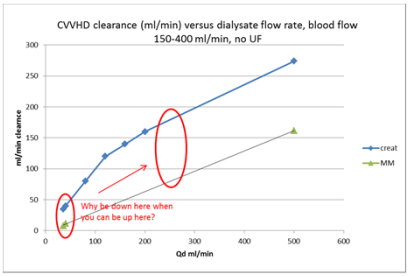
Figure 1. Dialysate-side Ficoll clearance as a function of molecular weight. Y-axis, clearance in ml/min. X-axis, molecular weight. Black lines, 2.0 m^2 dialyser; Gray lines, 0.4 m^2 dialyser; Solid lines, continuous venovenous hemofiltration (CVVH); Dashed lines, con-

Middle-Molecule Clearance in CRRT: *In Vitro* Convection, Diffusion and Dialyzer Area

(Lysozyme=14,300 m.w.)
Optiflux 160 NR, fmcna.com

Much higher clearances possible with dialysate flow of 500 ml/min

Middle Molecule and Creatinine Clearances Increase with Dialysate Flow Rate

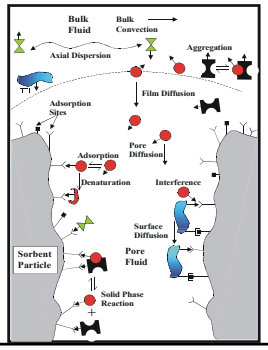


Charcoal Has Been Used to Regenerate Dialysate for Decades, and Use Continues

- Redy™ system and Sorb™ column for AKI and ESRD
- WAK™ device for ESRD (Kolff)
- Sorb column (improved versions) in BioLogic-HD™ and Allient™ machines for AKI and ESRD
- BioLogic-DT™ system for liver failure and HRS (Liver Dialysis™)
- MARS™ system for liver failure and HRS
- OPAL™ system for liver failure (MARS with Hepalbin™ charcoal filters for dialysate)
- WAK™ device for ESRD (Gura)
- AWAK™ peritoneal system for ESRD
- Neokidney™ portable hemodialysis (DKF)

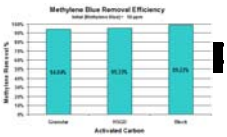
Forms of Carbon: Granular, Powder, Felt, Coated, Uncoated, Sterile, Nonsterile
Contact With: Protein-free dialysate, albumin dialysate, peritoneal fluid

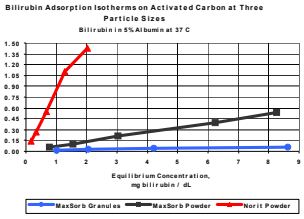
But Carbon Binding of Toxins is Actually a Complicated Phenomenon Involving Macropores, Mesopores and Micropores



Courtesy Prof. N-H-L Wang

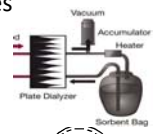
Very Small Particles Greatly Improve Carbon Binding of Larger Organics and Protein-Bound Substances

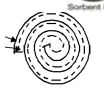


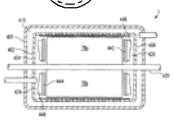


Powdered Carbon Particles are Too Small to Create Packed Bed; Need Other Ways to Restrain the Particles

- Sorbent Suspension Dialyzer (BioLogic-DT)
- Microfiber with embedded charcoal
- Filtration membranes with lots of shear
- Carbon Block



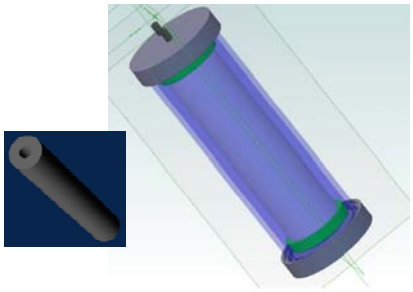




Carbon Block is Created by Mixing Powdered Carbon with Polyethylene and then Extruding as a Tube

Plastic spicules bind carbon particles together without masking the active surface area

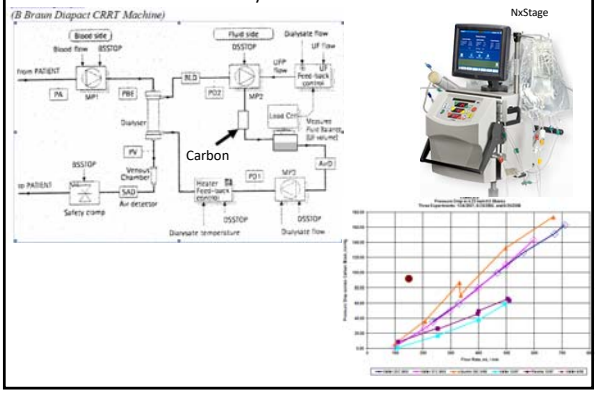
Using a Carbon Block, Creating a Cartridge With Even Flow Distribution is Easy, and Results Predictable



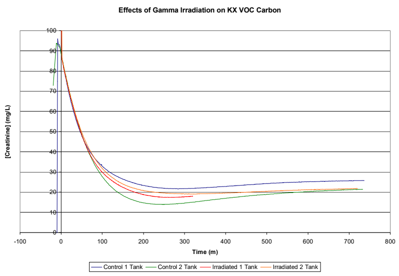
Requirements for Carbon Block Cartridge for Dialysate Regeneration in CVVHD

1. Easily fit in standard CVVHD circuit, minimal pressure drop
2. Maintain sterile dialysate circuit
3. Generate few charcoal fines
4. Maintain purity of dialysate
5. Bind 90% or more of known organic toxins of uremia for 72 hours
6. Avoid generating new chemical species
7. Remove many drugs effectively and predictably
8. Regenerate dialysate with albumin or plasma
9. Remove toxins of hepatic failure
10. Combine with other sorbents easily

1. Easily Fits in CVVHD Circuit- Low Hydraulic Resistance

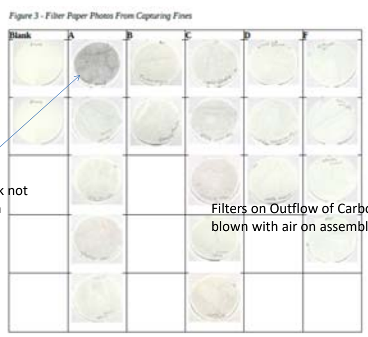


2. Sterility- Gamma Radiation of Charcoal Block Doesn't Affect Physical or Chemical Function



3. Charcoal Fines: With Care in Assembly, No Problem

Figure 3 - Filter Paper Photos From Capturing Fines



4. Purity Carbon Blocks Designed to Purify Water

Table 1 – Cleanliness Results for Heavy Metals

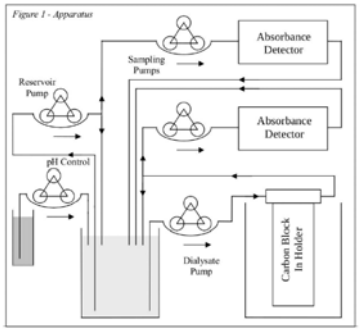
Note: Values reported less than detectable limit are here reported as being present at the limit.

Non-Toxic, Exceeds AAMI
Toxic, Exceeds AAMI
Exceeds HemoCleanse

HemoCleanse Maximum	Metal	AAMI Limit	Units	WL0 (Bagged / Bottled Sterile Water for Injection)	WL1 (Filter Holder After One Hour)	WL2 (KX =5, 15 Minutes)	WL3 (KX =5 5 Hours)	WL4 (KX =1 15 Minutes)	WL5 (KX =1 5 Hours)
0.2	ALUMINUM	0.000-0.010	mg/L	0.001	0.001	0.010	0.041	0.008	0.024
0.12	ANTIMONY	0.0000-0.0060	mg/L	0.0005	0.0005	0.0005	0.0005	0.0005	0.0005
0.1	ARSENIC	0.0000-0.0050	mg/L	0.0005	0.0005	0.0007	0.0008	0.0005	0.0005
2	BARIUM	0.000-0.100	mg/L	0.001	0.001	0.004	0.002	0.275	0.279
0.008	BERYLLIUM	0.0000-0.0004	mg/L	0.00005	0.00005	0.00005	0.00005	0.00005	0.00005
0.02	CADMIUM	0.0000-0.0010	mg/L	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001
40	CALCIUM	0.000-2.000	mg/L	0.1	0.1	0.2	0.1	9.5	8.1
0.28	CHROMIUM	0.000-0.014	mg/L	0.001	0.001	0.001	0.001	0.001	0.002
2	COPPER	0.000-0.100	mg/L	0.001	0.001	0.001	0.001	0.001	0.001
4	FLUORIDE	0.0-0.2	mg/L	0.1	0.1	0.1	0.1	0.1	0.1
	IRON		mg/L	0.025	0.025	0.025	0.025	0.025	0.025
0.1	LEAD	0.0000-0.0050	mg/L	0.0005	0.0005	0.0005	0.0005	0.0005	0.0005
80	MAGNESIUM	0.000-4.000	mg/L	0.1	0.1	0.3	0.8	2.8	3.8
	MANGANESE		mg/L	0.001	0.001	0.002	0.001	0.038	0.021
0.004	MERCURY	0.00000-0.00020	mg/L	0.00002	0.00002	0.00002	0.00002	0.00002	0.00002
	NICKEL		mg/L	0.001	0.001	0.001	0.002	0.008	0.003
40	NITRATE	0.0-2.0	mg/L	1	1	1	1	1	1
100	POTASSIUM	0.000-8.000	mg/L	0.1	0.1	8.4	11.7	0.7	0.8
1	SELENIUM	0.000-0.090	mg/L	0.001	0.001	0.001	0.001	0.001	0.001
0.1	SILVER	0.0000-0.0050	mg/L	0.0005	0.0005	0.0005	0.0005	0.0005	0.0005
1400	SODIUM	0.00-70.00	mg/L	0.1	0.1	4.7	5.7	12.4	13.7
2000	SULFATE	0.0-100.0	mg/L	2	2	2	2	POSITIVE	4.4
0.04	THALLIUM	0.0000-0.0020	mg/L	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001
2	ZINC	0.000-0.100	mg/L	0.004	0.009	0.001	0.001	0.001	0.001
	CONDUCTIVITY		uS/cm	1.3	1.3	81.2	100.1	190.9	223.0
	PH			5.05	4.28	6.30	6.82	6.03	6.47

Note: The level that triggers "Positive" for sulfate is not known, but is assumed to be minimal, less than the 4.4 that was numerically reported.

5. Bind Uremic Toxins for long time- Automated Testing Setup for Organic Binding



Use the following standard solution for dialysate:

Compound	Standard Value	Value for 40 L
1. NaCl	7.650 g	306 g
2. Na2HPO4, anhyd	0.724 g	29 g
3. NaH2PO4, anhyd	0.185 g	7.4 g
4. Distilled water qs	1000 mL	40 L

Table 2 - Marker Data

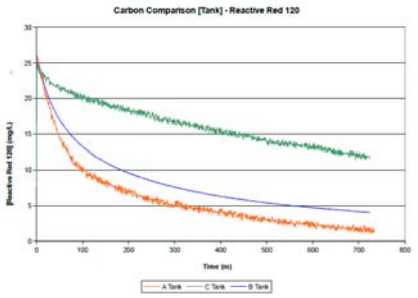
Marker	Optical Abs. Pk. (nm)	MW	Conc. (mg/L)	Molarity (µMoles)
Creatinine	235	114	100	877
Reactive Red 120	510	1469	25	17
Methylguanidine	205	73	23	311

Columns Tested

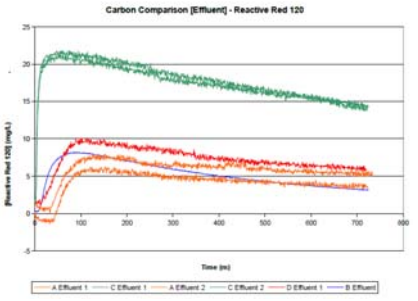
Table 3 - Summary of Results

Trial No.	Carbon Block	Marker	Initial [Tank] (mg/L)	Final [Tank] (mg/L)	% Tank Marker Removed	Final [Out] (mg/L)	Effluent Break-Through Time (min)	Remarks
1	F	Creatinine	100	26	74	35	19	Creatinine -- Creatol
2	F	Creatinine	100	21	79	31	16	Creatinine -- Creatol
3	D	Creatinine	100	23	77	37	126	Creatinine -- Creatol
4	D	Creatinine	100	18	82	31	85	Creatinine -- Creatol
5	A	Creatinine	100	9	91	20	240	Creatinine -- Creatol
6	A	Creatinine	100	9	91	20	242	Creatinine -- Creatol
7	C	Creatinine	100	7	93	18	18	Creatinine -- Creatol
8	C	Creatinine	100	7	93	17	18	Creatinine -- Creatol
9	A	Creatinine	100	9	91	20	261	Creatinine -- Creatol
10	A	R. Red	25	2	92	5	35	[Tank] uncertain - Instrument issue
11	C	R. Red	25			14	1	[Tank] uncertain - Instrument issue
12	A	R. Red	25	0	100	3	42	[Tank] uncertain - Instrument issue
13	C	R. Red	25			14	1	[Tank] uncertain - Instrument issue
14	D	R. Red	25			2	16	[Tank] uncertain - Instrument issue
15	C	MG	23				5	Poor data quality
16	A	MG	23				30	Poor data quality
17	B	R. Red	25	4	16	3	10	
18	B	Creatinine	100	16	84	29	90	
19	B	MG	23				49	Poor data quality

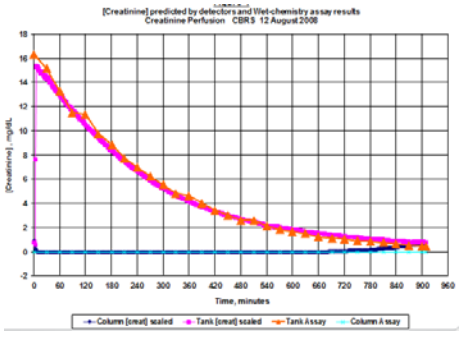
Reactive Red Removal from Tank; Marked Differences in Various Columns



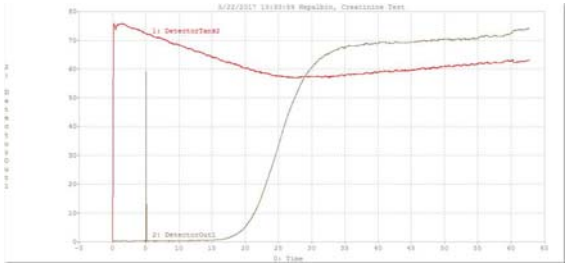
Reactive Red Effluent



Creatinine Removal with 4.25” Diameter Carbon Block, 250 ml/min Flow

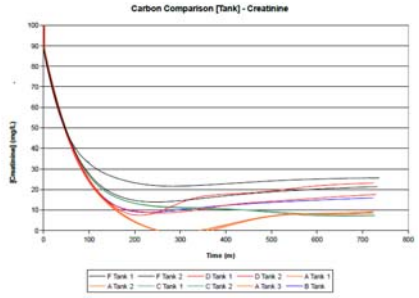


Hepalbin™ carbon filters absorb bilirubin very well, but not creatinine

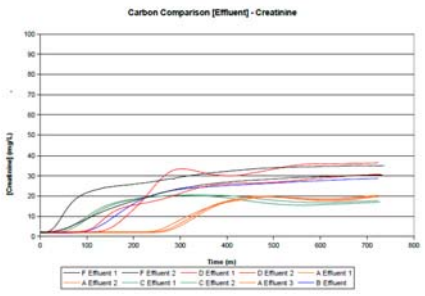


(made to remove bilirubin, not general organics)

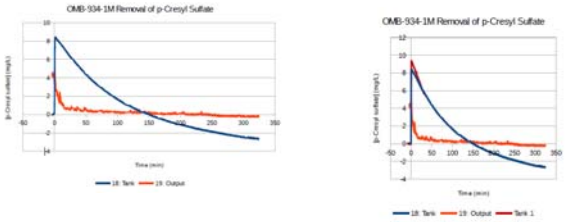
Optical Measure of Creatinine Removal from Tank, 2.5” Diameter Column, 400 ml/min



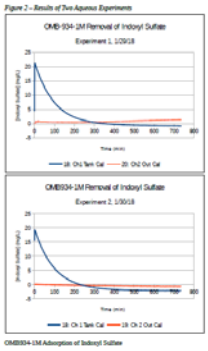
Effluent from Column as Measured at Creatinine Absorption Wavelength



Middle Molecule Removal-PCS



Indoxyl Sulfate



Beta-2 Microglobulin (WAK with Carbon Column)

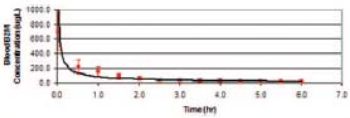


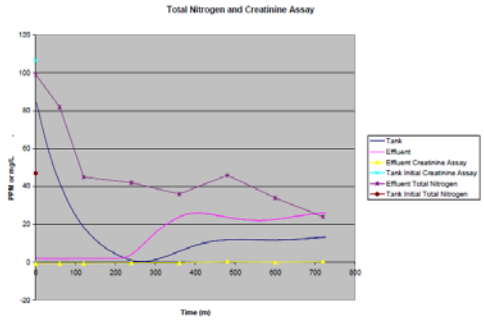
Figure 7. Removal of β2M from healthy human blood by WAK system is shown to be most effective in the first half-hour.

Technical Breakthroughs in the Wearable Artificial Kidney (WAK)

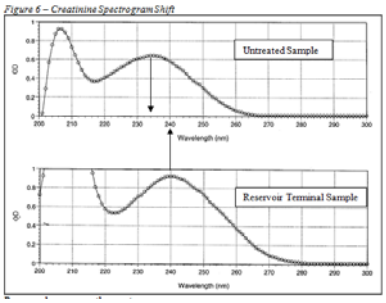
Victor Gura,* Alexandra S. Macy,† Masoud Beizai,‡ Carlos Enon,‡ and Thomas A. Golper§
*Cedars-Sinai Medical Center, Los Angeles, California; †UCLA Geffen School of Medicine, Los Angeles, California; ‡Xenomed Inc., Los Angeles, California; §Vanderbilt University Medical Center, Nashville, Tennessee

Clin J Am Soc Nephrol ●●: ●●●–●●●, 2009.

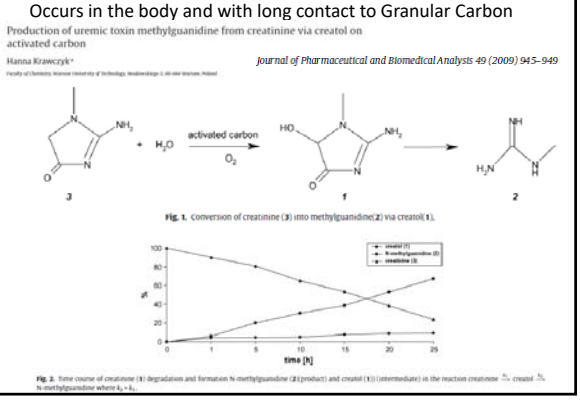
6. Avoid generating new chemical species-
What is Coming Out is *not* Creatinine, but not *New*



Outlfow Product of Contact with Carbon has Wavelength Shift vs. Creatinine



Oxidation of Creatinine to Creatol and then MG is *Known*-
Occurs in the body and with long contact to Granular Carbon


Production of uremic toxin methylguanidine from creatinine via creatol on activated carbon

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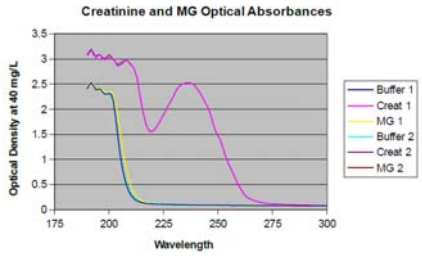
Journal of Pharmaceutical and Biomedical Analysis 49 (2009) 945–949

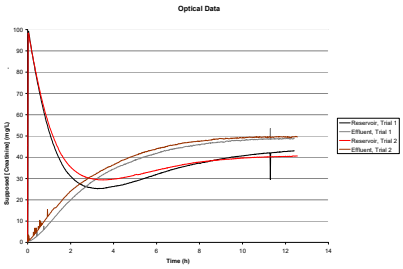
Fig. 1. Conversion of creatinine (3) into methylguanidine(2) via creatol(1).

Fig. 2. Time course of creatinine (3) degradation and formation N-methylguanidine (2)(product) and creatol (1)) (intermediate) in the reaction creatinine $\xrightarrow{k_1}$ creatol $\xrightarrow{k_2}$ N-methylguanidine where $k_2 > k_1$.

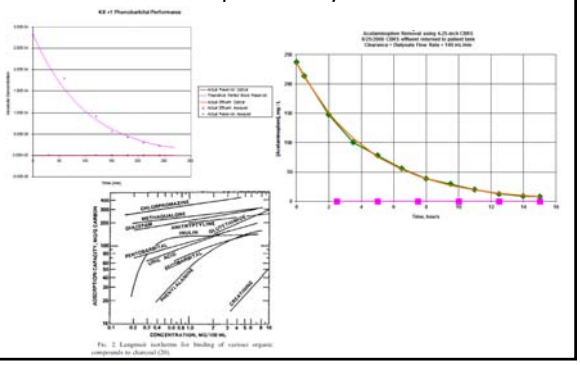
Outflow of Column Contains Creatol, and probably some MG
(MG analysis requires sophisticated techniques)



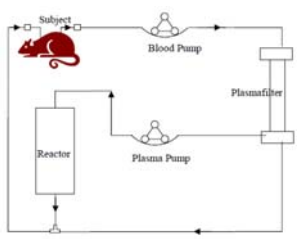
Redy (Sorb) column carbon also generates creatol when highly loaded with creatinine (more so than carbon block)

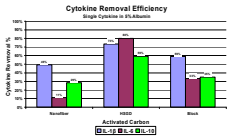


7. Remove many drugs effectively and predictably

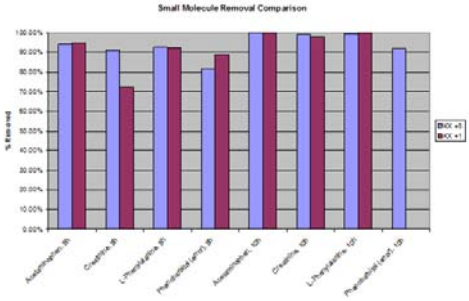


8. Regenerate dialysate with albumin or plasma-
Carbon Block Allows Plasma Regeneration in Sepsis Study

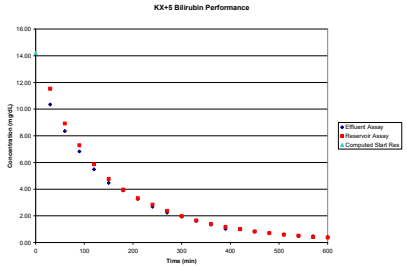




9. Remove toxins of hepatic failure-
Compounds Without Strong Protein Binding Are Removed Well



Bilirubin binding is effective but slow, however



Same slow bilirubin removal occurs regardless of sorbent type (e.g. in MARS, Prometheus, Liver Dialysis

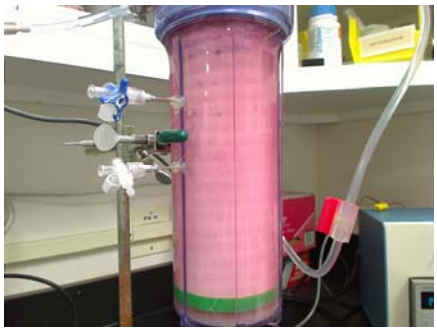
10. Combine with other sorbents easily

Lightweight Powdered Sorbents Can Form a Filtration Bed Around Carbon Block

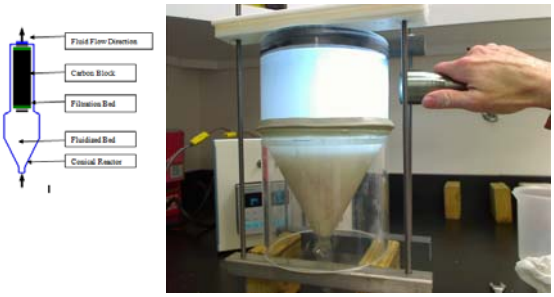
Figure 18 – Calcium Phosphate Powder Without Fluid Flow (left) and With Fluid Flow (right)

Calcium Phosphate powder dissolves/precipitates to maintain phosphate and calcium levels in dialysate during Whole Body Hyperthermia

Flow Through Suspended Filtration Bed is Uniform, Resulting in Effective Chemical Function of Powdered Sorbents



Heavier Sorbents Can Be Perfused in a Conical Reactor Below Carbon Block (Fines Form Filtration Bed Around Carbon)



Examples: CaPhos granules, Zirconium Phosphate, Zirconium Cyclo-Silicate

Conclusions

- Carbon block columns effectively remove the most important toxins of uremia (organics, middle molecules)
- Carbon block column in a CVVHD circuit allows dialysate flow rate to be increased, improving clearance of organic toxins, and possibly improving clinical response
- Frequency of bag changes will determine clearance of small, charged uremic toxins
- Cost and effort of CVVHD will be diminished
- Other applications of CVVHD will be improved, including treatment of drug overdose, acute-on-chronic hepatic failure, hepato-renal failure, etc.
- Other powdered or granular sorbents may be combined with the carbon block in the future.
- Carbon block can effectively regenerate albumin solutions and plasma, so there may be applications in treatment of sepsis, immune diseases and hepatic failure (though bilirubin removal is slow)
- If there were an effective oral sorbent to bind many small and charged uremic toxins in the gut, then regenerating dialysate could be done by carbon alone, for HD and PD applications

Thanks for your attention and support…