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"CRRT and Hybrid Therapies"

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B.A.M.
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CRRT and Hybrid Therapies

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CRRT and Hybrid Therapies

1) **Why is the correct dosing in AKI important?**
2) **What data are available?**
3) **What are the obstacles in develeoping dosing recommendations?**
4) **What needs to be done**

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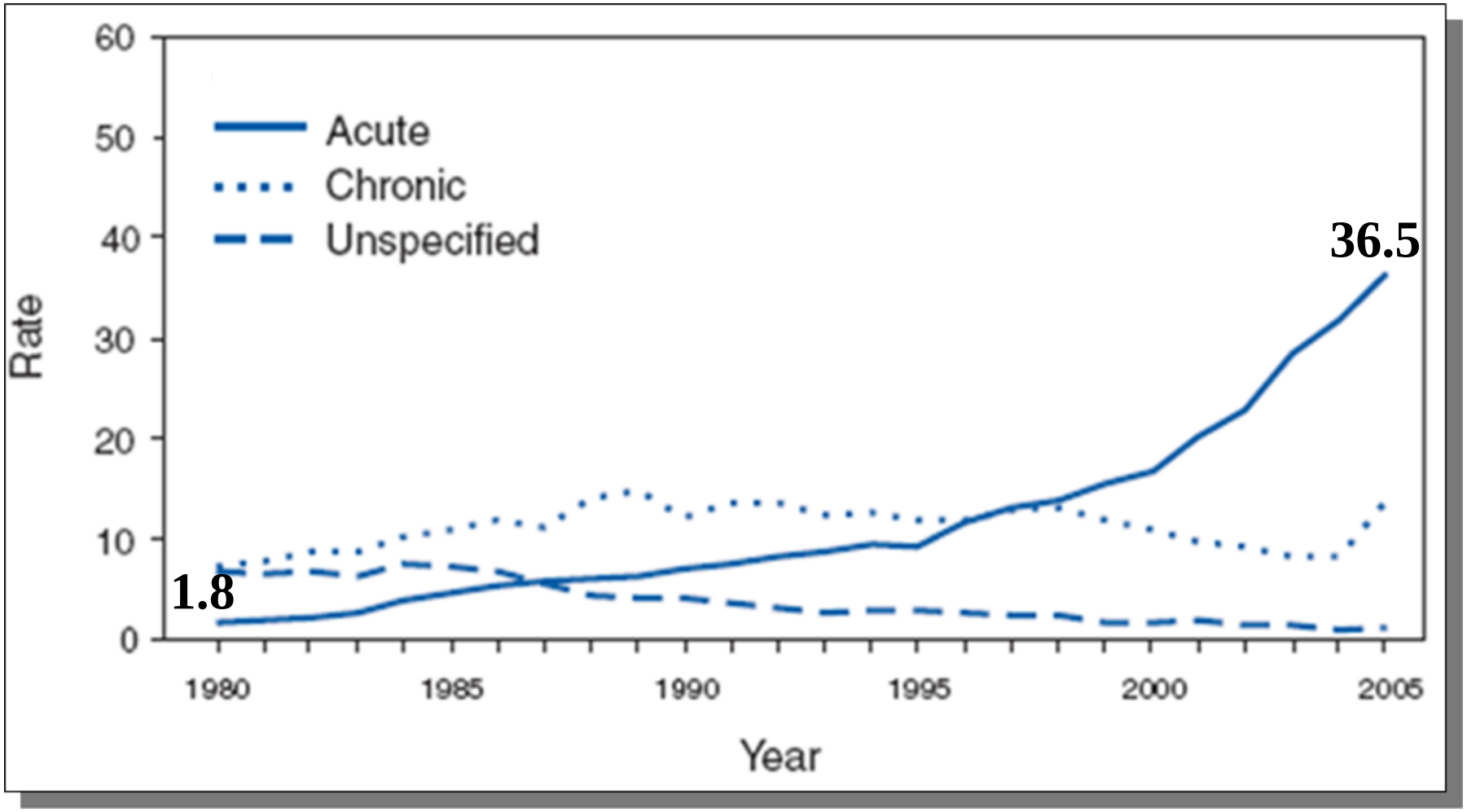
The incidence of AKI is rising

Hospitalization Discharge Diagnoses for Kidney Disease - United States, 1980--2005
Centre for Disease Control *MMWR* 57:309-312, 2008



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Mortality of critically ill patients with AKI remains high

UCHINO et al. *JAMA* 294:813-818, 2005

	No. of Participating Centers (N = 54)	No. of Patients (N = 1738)	Period Prevalence (95% CI), %	Predicted Mortality, %†	Hospital Mortality (95% CI), %
Australia	6	293	6.3 (5.6-7.0)	47.0	53.4 (47.7-59.1)
Belgium	3	163	8.8 (7.5-10.1)	43.2	57.7 (50.1-65.3)
Brazil	4	153	4.8 (4.0-5.5)	43.6	76.8 (70.1-83.6)
Canada	2	93	4.6 (3.7-5.6)	56.8	59.8 (49.8-69.8)
China	2	77	8.8 (6.9-10.7)	48.5	61.0 (50.1-71.9)
Czech Republic	1	21	16.8 (10.2-23.4)	44.6	61.9 (41.1-82.7)
Germany	2	129	3.3 (2.7-3.8)	39.4	61.9 (53.4-70.4)
Greece	1	5	2.4 (0.3-4.5)	62.2	80.0 (44.9-100.0)
Indonesia	1	25	4.4 (2.7-6.1)	41.4	72.0 (54.4-89.6)
Israel	1	10	2.1 (0.8-3.4)	61.3	100.0
Italy	6	109	5.4 (4.4-6.4)	32.0	50.5 (41.1-59.8)
Japan	4	90	5.5 (4.4-6.6)	40.8	64.0 (54.1-74.0)
The Netherlands	2	113	6.1 (5.0-7.2)	49.5	62.5 (53.5-71.5)
Norway	2	50	3.7 (2.7-4.7)	46.6	62.0 (48.5-75.5)
Portugal	2	36	22.1 (15.7-28.5)	53.7	63.9 (48.2-79.6)
Russia	1	14	2.6 (1.3-3.9)	82.6	61.5 (35.1-88.0)
Singapore	2	31	6.3 (4.2-8.4)	59.3	74.2 (58.8-89.6)
Spain	2	16	10.5 (5.6-15.3)	32.2	43.8 (19.4-68.1)
Sweden	1	9	4.7 (1.7-7.7)	25.7	22.2 (0-49.4)
Switzerland	1	26	3.2 (2.0-4.4)	44.3	65.4 (47.1-83.7)
United Kingdom	1	52	20.6 (15.6-25.5)	63.7	73.1 (61.0-85.1)
United States	6	194	8.0 (6.8-9.3)	44.2	52.1 (45.0-59.2)
Uruguay	1	29	12.9 (8.5-17.3)	35.6	65.5 (48.2-82.8)
Overall			5.7 (5.5-6.0)	45.6	60.3 (58.0-62.6)

Overall mortality:

60.3 %

Sepsis is the leading cause for AKI in critically ill patients

UCHINO et al. *JAMA* 294:813-818, 2005

Contributing factors (n = 1726)	
Septic shock	820 (47.5)
Major surgery	592 (34.3)
Cardiogenic shock	465 (26.9)
Hypovolemia	442 (25.6)
Drug-induced	328 (19.0)
Hepatorenal syndrome	99 (5.7)
Obstructive uropathy	45 (2.6)
Other	211 (12.2)

CRRT and Hybrid Therapies

1) Why is the correct dosing in AKI important?
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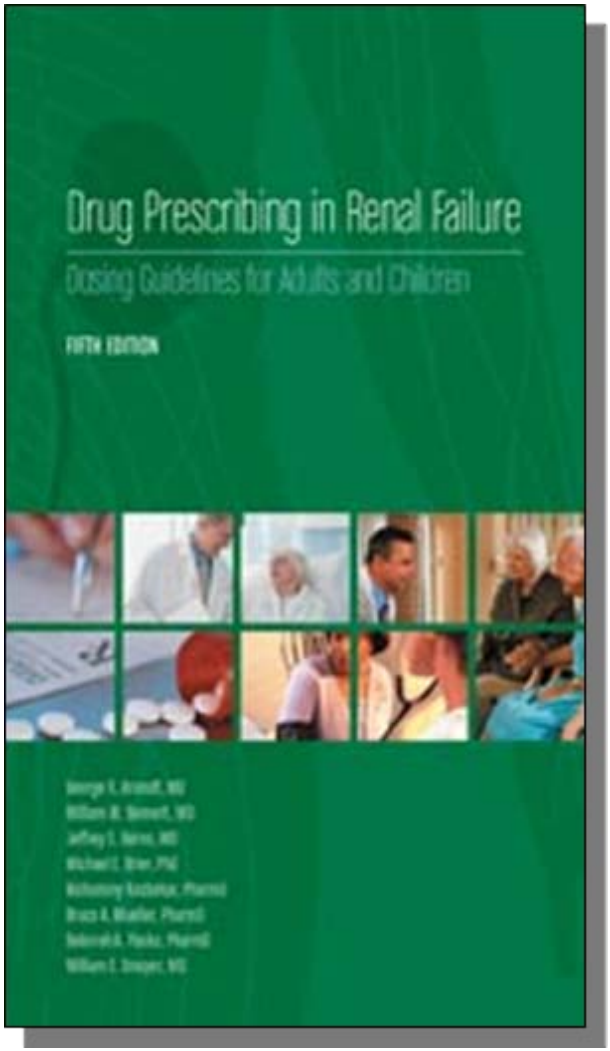
Studies on drugs in CRRT



- only 58 of the 475 studied in CRRT
- many were *in vitro* studies

Studies on drugs in ED

Drug	Year	Lead Author	n	ED duration (hr)	Qb (ml/min)	Qd (ml/min)	Filter type & Surface area (m^2)	Dosing Recommendation
Ampicillin/ sulbactam (1)	2009	J. T.Kielstein	1	7.5	180	180	PS, 1.3 m^2	None provided
Anidulafungin (2)	2009	O. Burkhardt	1	8	180	180	PS, 1.3 m^2	No dose adjustment necessary
Daptomycin (3)	2008	O. Burkhardt	1	12	200	100	PS, 1.3 m^2	None provided
Daptomycin (4)	2010	J. Kielstein	10	8	160	160	PS, 1.3 m^2	6 mg/kg daily, 8 hrs prior to SLED
Ertapenem (5)	2009	O. Burkhardt	6	8	160	160	PS, 1.3 m^2	1 gram IV daily
Gentamicin (6)	2003	H. Manley	8	8	200	300	PS, 0.5 m^2	2.0-2.5 mg/kg post SLED*
Levofloxacin (7)	2006	D. Czock	5	8	160	160	PS, 1.3 m^2	None provided- give post SLED
Linezolid (8)	2004	E. Fiaccadori	5	8-9	200	100	PS, 1.6, 1.4 m^2†	None provided- give post SLED
Linezolid (9)	2010	S. Swoboda	10	12-24	110-150	110-150	PS, 1.3 m^2	TDM in patients with liver disease
Meropenem (10)	2005	J. Kielstein	10	8	160	160	PS, 1.3 m^2	0.5-1 gm q8 hrs, depends on weight, illness severity
Moxifloxacin (7)	2006	D. Czock	10	8	160	160	PS, 1.3 m^2	400 mg IV daily post SLED
Vancomycin (11)	2004	J. Ahern	11	24	200	100	PS 0.7, 0.9 m^2†	15 mg/kg load, TDM
Vancomycin (10)	2005	J. Kielstein	10	8	160	160	PS, 1.3 m^2	20-25 mg/kg load, TDM
Vancomycin (12)	2009	L. Golestaneh	10	8	150-200	100-200	PS, 0.7 m^2	TDM
Voriconzole (13)	2010	O. Burkhardt	4	8	180	180	PS, 1.3 m^2	Avoid IV administration due to SBECD accumulation

Dosing regimen from the vinyl age for RRT of the i-Pod era?

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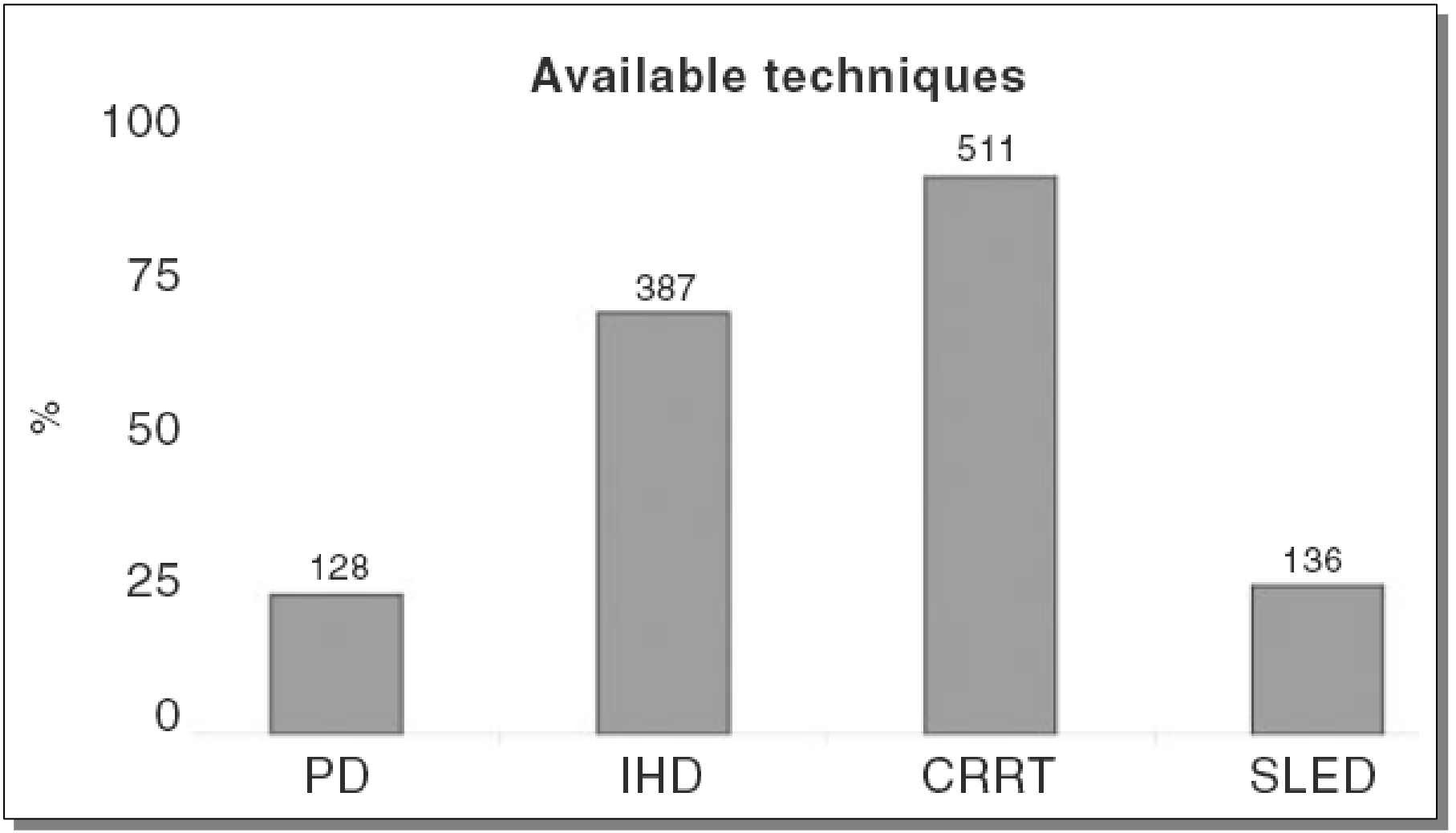
CRRT and Hybrid therapies are frequently used modes of RRT in the ICU

RICCI et al. *Nephrol Dial Transpl*, 21: 690–696, 2006

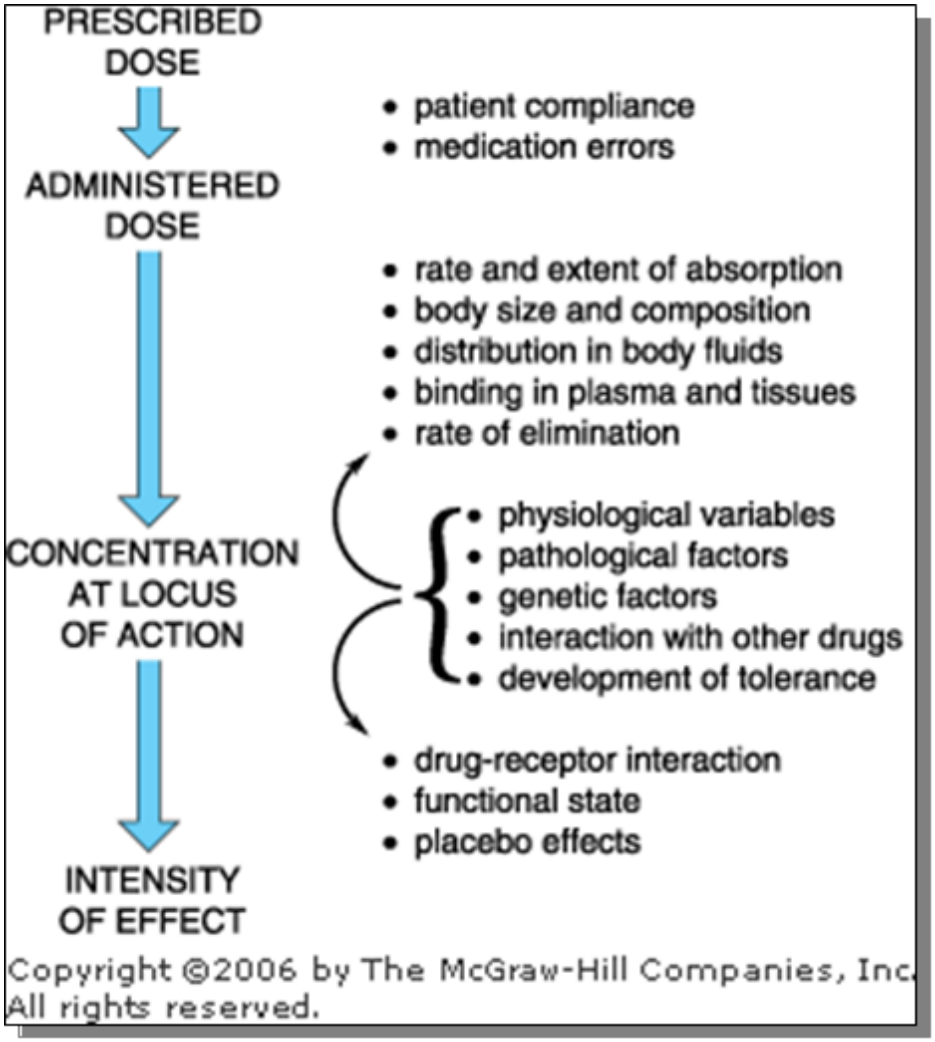


Main coordinates of RRT are not standardized

Goodman & Gilman's The Pharmacological Basis of Therapeutics, 11th Edition

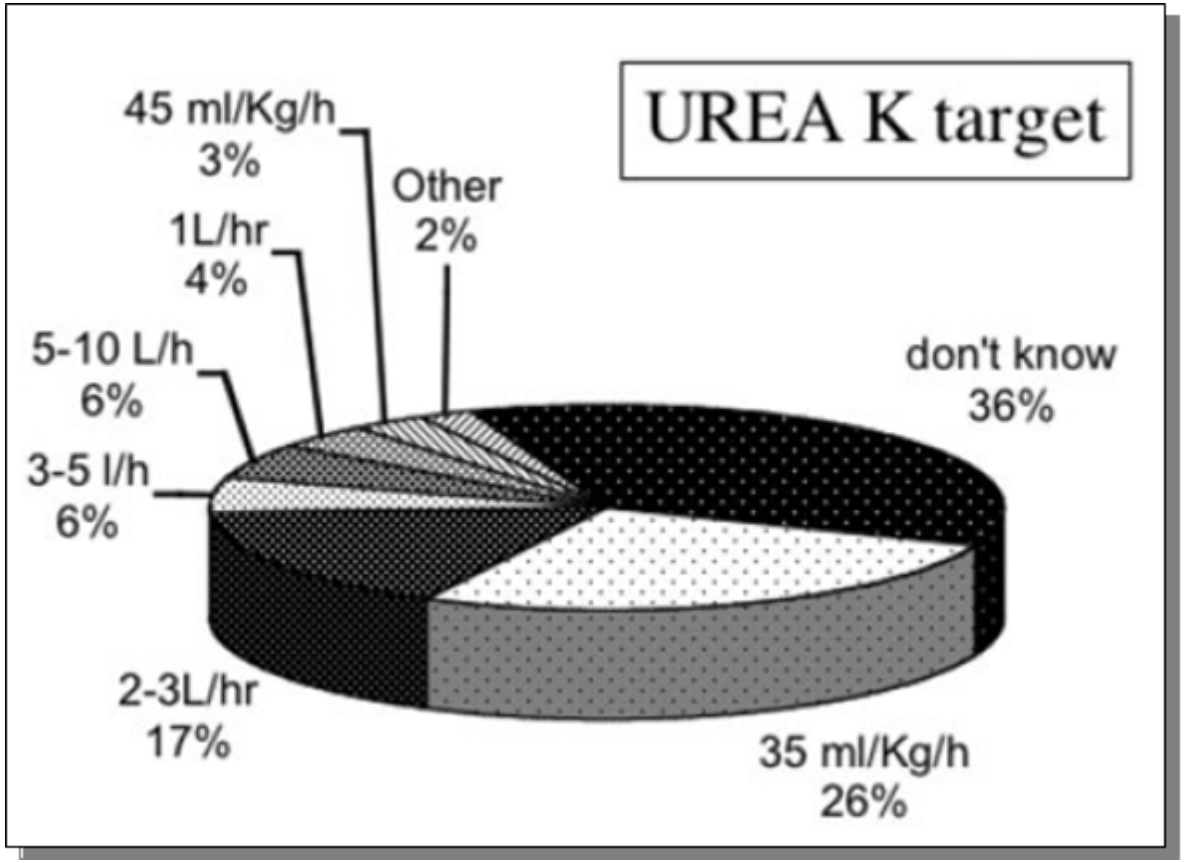
Specifics of RRT:

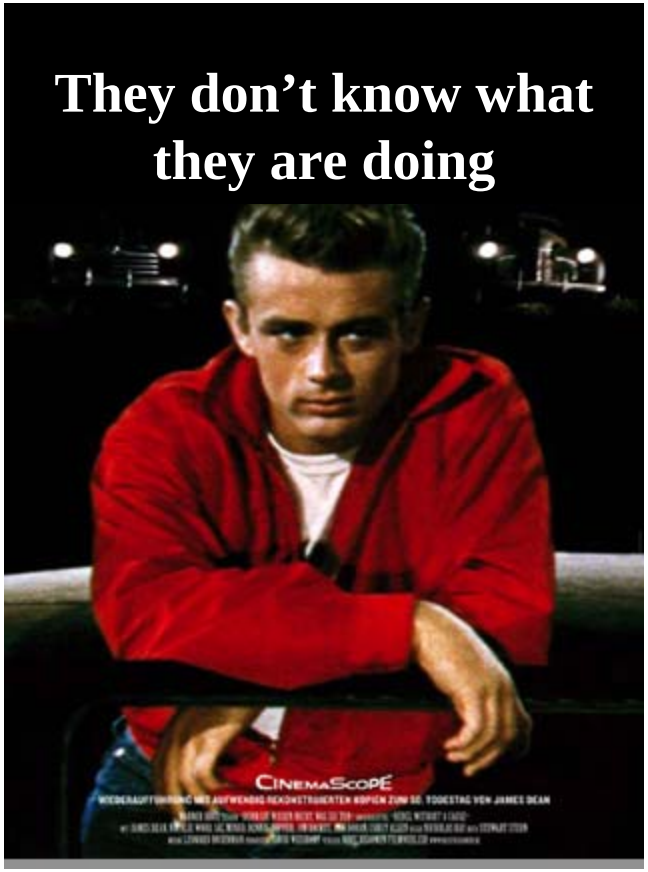
- treatment mode
- blood flow
- dialysate flow
- treatment time
- filter type
- ultrafiltration rate



Even within a given treatment modality the treatment intensity (if known) varies up to an order of magnitude

RICCI et al. *Nephrol Dial Transpl*, 21: 690–696, 2006





Considerable variation of operational characteristics in extended dialysis

FLISER & KIELSTEIN *Nat Clin Pract Nephrol* 2006;2:32-9

Author	Dialysis machine	Blood/dialysate flow (ml/min)	Prescribed treatment time (h)	Nocturnal treatment
Fiaccadori *et al.*[24]	AK200® Ultra	200/100	8–9	No
Kielstein *et al.*[21]	Genius®	200/100	12	Yes
Kielstein *et al.*[43]	Genius®	150–200/150–200	8	Yes
Kumar *et al.*[18]	2008H®[a]	200/300	6–8	No
Lonnemann *et al.*[19]	Genius®	70/70	18	Not reported
Marshall *et al.*[20]	2008H®[a]	200/100	12	Yes
Marshall *et al.*[22]	2008H®[a]	200/100	12	Not reported
Marshall *et al.*[22]	4008S ArRT-Plus	250–350/200	8	No
Morgera *et al.*[33]	Genius®	180–200/180–200	4–6	No
Naka *et al.*[51]	Not reported	100/200	6–8	Not reported
Ratanarat *et al.*[25]	Not reported	200–250/67–150	6–12	Not reported
Schlaeper *et al.*[17]	2008H®[a]	100–200/100–300	8–24	Yes

[a]Modified for SLED treatment mode.

Hypophosphatemia as a surrogate marker for inadequate drug dosing ?

The VA/NIH Acute Renal Trial network *NEJM* 359:7-20, 2008

The RENAL Replacement Therapy Study Investigators *NEJM* 361:1627-38 ,2009

Table 4. Summary of Complications Associated with Study Therapy.*

Event	Intensive Strategy (N = 563)	Less-Intensive Strategy (N = 561)	P Value
	no. of patients (%)		
Hypokalemia	42 (7.5)	25 (4.5)	0.03
Hypophosphatemia	99 (17.6)	61 (10.9)	0.001

Table 4. Summary of Complications Associated with Study Treatment.

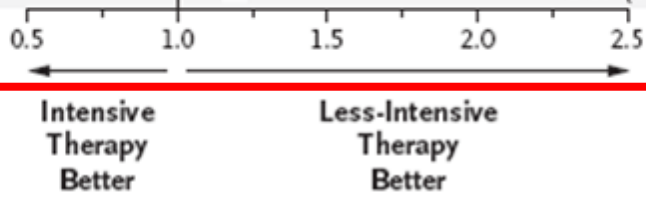
Complication	Higher-Intensity CRRT	Lower-Intensity CRRT	P Value
Hypophosphatemia*			
No. of patients/total no.(%)	461/708 (65.1)	396/733 (54.0)	<0.0001
No. of episodes	1495	1059	—
Hypokalemia*			
No. of patients/total no. (%)	168/718 (23.4)	180/737 (24.4)	0.34
No. of episodes	297	308	0.93

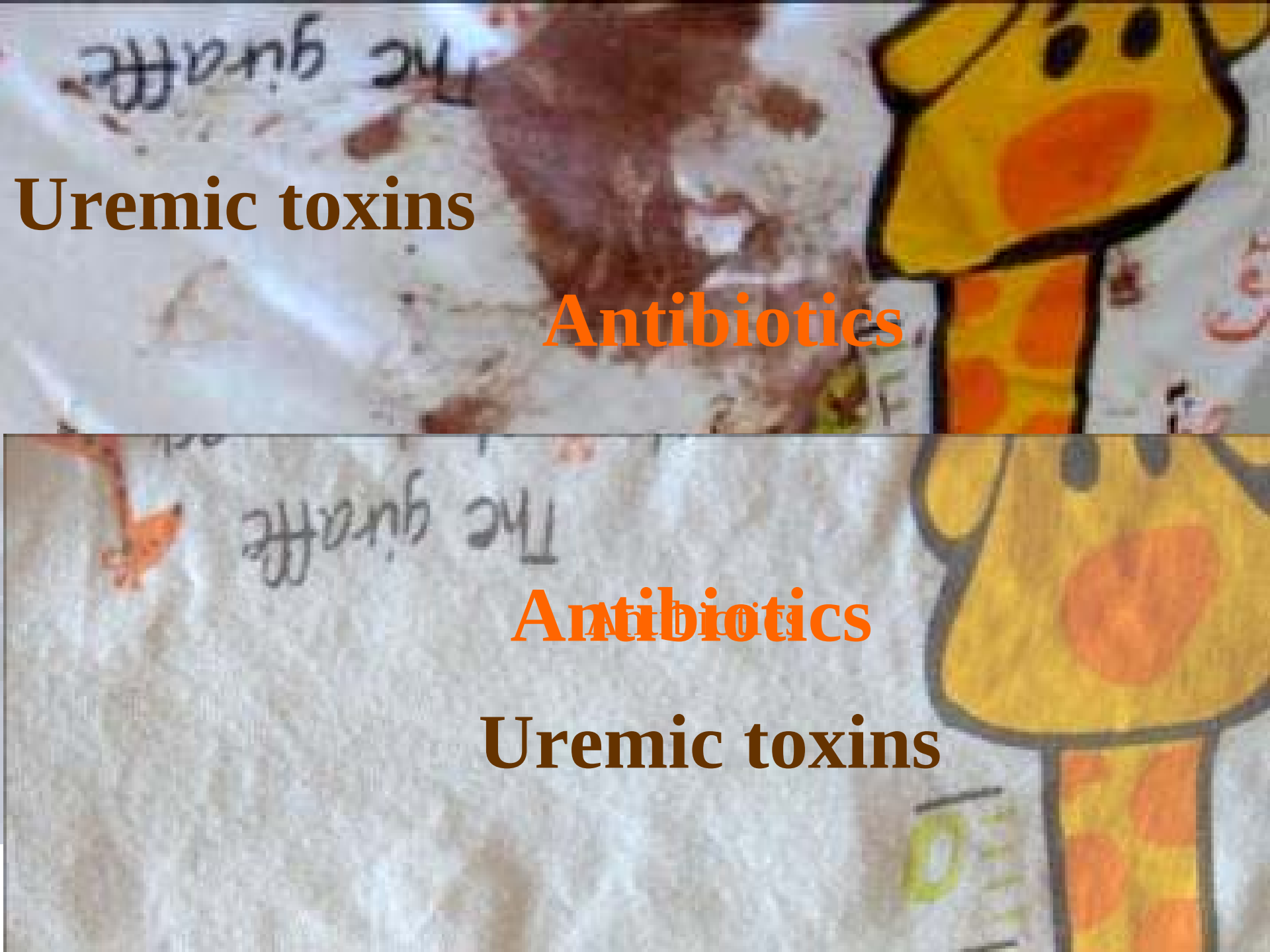
Intensity and renal support in critically ill patients with acute kidney injury

The VA/NIH Acute Renal Trial network *NEJM* 359:7-20, 2008

The RENAL Replacement Therapy Study Investigators *NEJM* 361:1627-38 ,2009

Baseline Characteristic	No. of Patients	Intensive Therapy	Less-Intensive Therapy	Odds Ratio for Death at 60 Days (95% CI)	P Value for Interaction
Overall	1124	53.6	51.5	1.09 (0.86–1.40)	
SOFA cardiovascular score					0.15
0–2	509	43.9	37.8	1.33 (0.93–1.91)	
3–4	615	61.7	62.9	0.93 (0.66–1.29)	
Oliguria					0.45
No	247	41.1	36.6	1.31 (0.77–2.21)	
Yes	877	57.2	55.7	1.04 (0.79–1.37)	
Sex					0.30
Female	330	50.7	52.8	0.90 (0.57–1.41)	
Male	793	54.8	50.8	1.19 (0.89–1.60)	
Sepsis					0.36
No	416	47.8	49.8	0.94 (0.63–1.41)	
Yes	708	57.0	52.6	1.19 (0.88–1.62)	

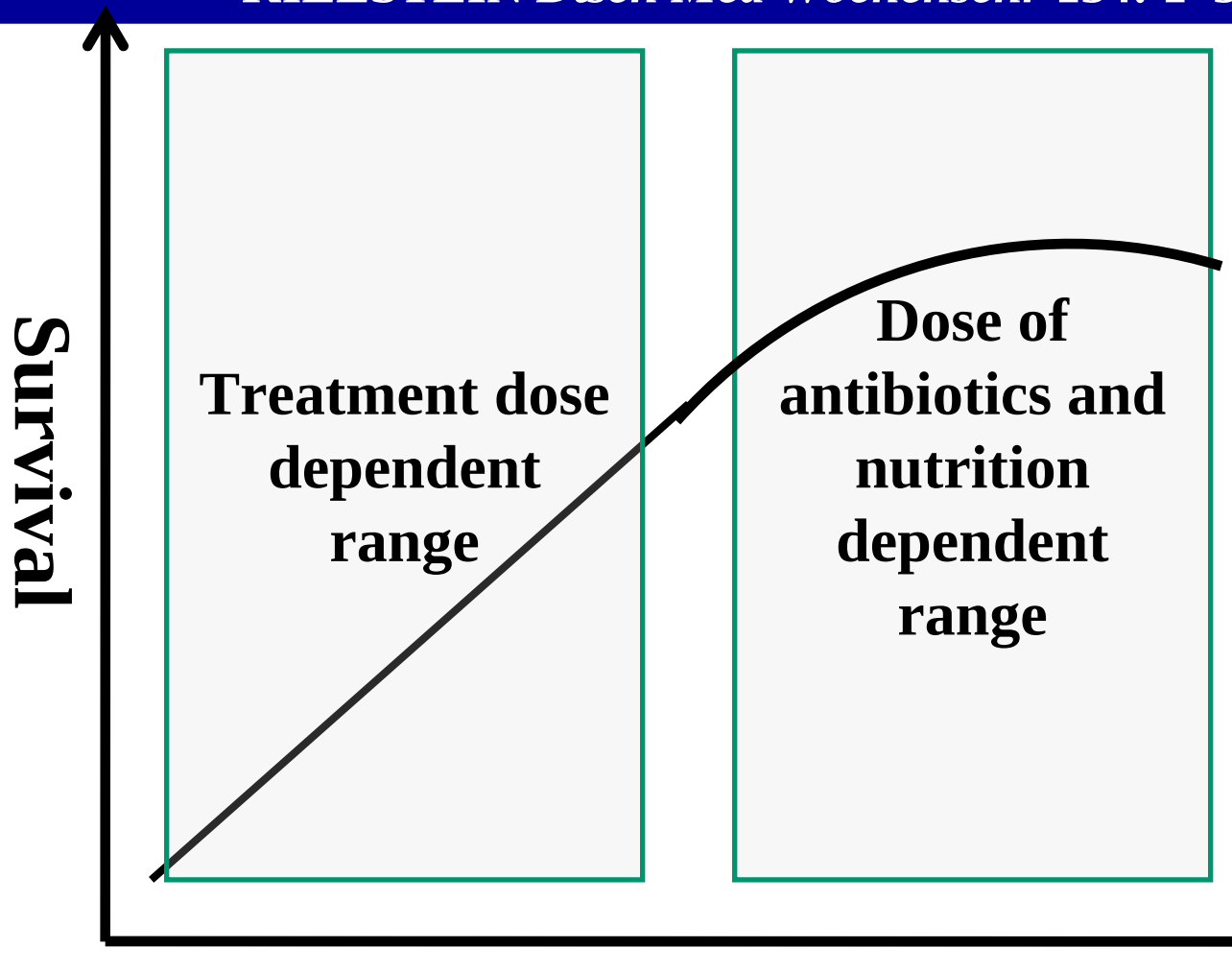



Uremic toxins
Antibiotics
Antibiotics
Uremic toxins

Autor	RRT	N	Überleben LD	Überleben HD	% Sepsis
Ronco 2000	CVVH	435	41 % 20 ml/kg/h	57 % 35 ml/kg/h	13
Schiffl 2002	IHD	160	44 % wKt/V 3,0	72 % wKt/V 5,8	37
Bouman 2002	CVVH	106	72 % 19 ml/kg/h	74% 48 ml/kg/h	-
Saudan 2006	CVVH/DF	206	39 % 23 ml/kg/h	59 % 48 ml/kg/h	60
Tolwani 2008	CVVHDF	200	56 % 20 ml/kg/h	49 % 35 ml/kg/h	54
Palevsky 2008	IHD,EDD CVVH	112 4	48 % 20 ml/kg/h	46% 35 ml/kg/h	63
Faulhaber 2009	EDD	156	61 % Urea 20-25	55 % Urea < 15	72

Dose of renal replacement therapy in acute kidney injury

KIELSTEIN *Dtsch Med Wochenschr* 134: 1–3, 2009



CRRT and Hybrid Therapies

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Ideal Data Set for RRT Pharmacokinetic Trials

Drug-related	Antibiotic assayed
	Specified target concentration
	Dose recommendation
Patient-related	Age
	Weight
	Severity of illness
	Number of patients in study
	Residual renal function
	Hepatic dysfunction
Basic pharmacokinetics	Volume of distribution (Vd)
	Total, CRRT, and non-CRRT clearances
	Protein binding/serum albumin
CRRT clearance	Membrane type/surface area
	Mode of CRRT
	Pre-filter/post-filter fluid replacement (if applicable)
	If pre-filter replacement: Hct, predilution replacement rate
	Sieving/saturation coefficients
	Dialysate/ ultrafiltration effluent rates
	Blood flow rates

How to improve current practice

-analyse whether current data for drug dosing in RRT can be used for current treatment coordinates (filter, intensity…)

-contact publishing bodies and distributing companies that reprint outdated dosing lists

-compile a central data source to allow easy access to known PD and PK parameters of currently used drugs

-request that package inserts of older drugs be updated to reflect RRT practices, as many resources recommend doses based on outdated RRT modes (continuous arteriovenous hemofiltration)

What should be done

-further pharmacokinetic studies in RRT must be conducted

-assessment of non-renal clearance changes in AKI and how RRT affects non-renal clearance must be performed

-drug dosing recommendations on a mg/kg basis should be

-new technologies that could greatly simplify drug dosing efforts should be developed

-most helpful and large-scale recommendation by far would be a standardize a worldwide RRT technology and dosing corridor in research and practice

-it should be requested that package inserts of older drugs be updated

-the FDA and EMEA can be convinced to encourage drug manufacturers to conduct CRRT/Hybrid RRT pharmacokinetic trials