Drug dosing in patients with acute kidney injury

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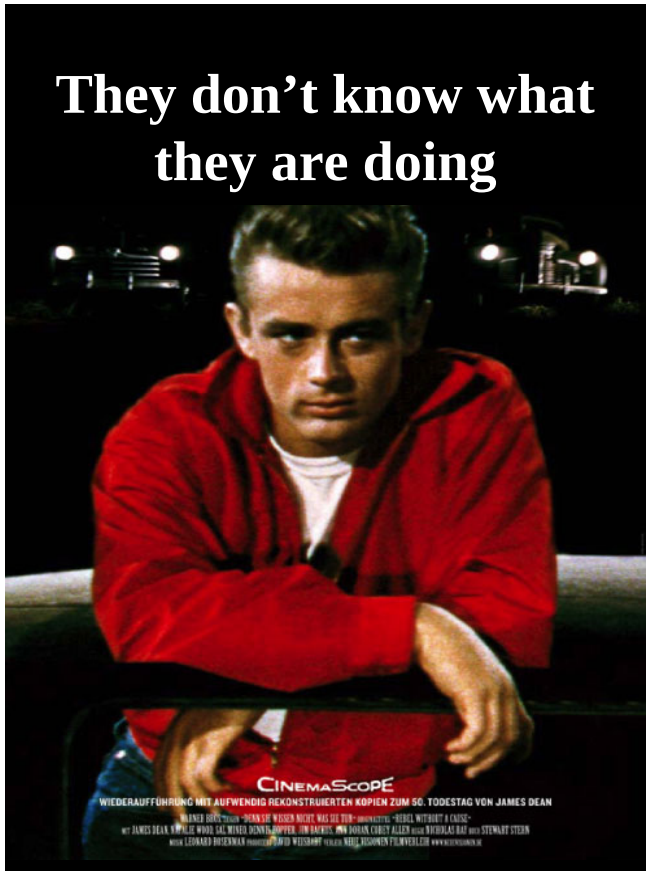

Drug dosing in patients with acute kidney injury

1) Why is it important
2) What is the problem
3) Examples
4) Summary
5) Advice

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Drug dosing in patients with acute kidney injury

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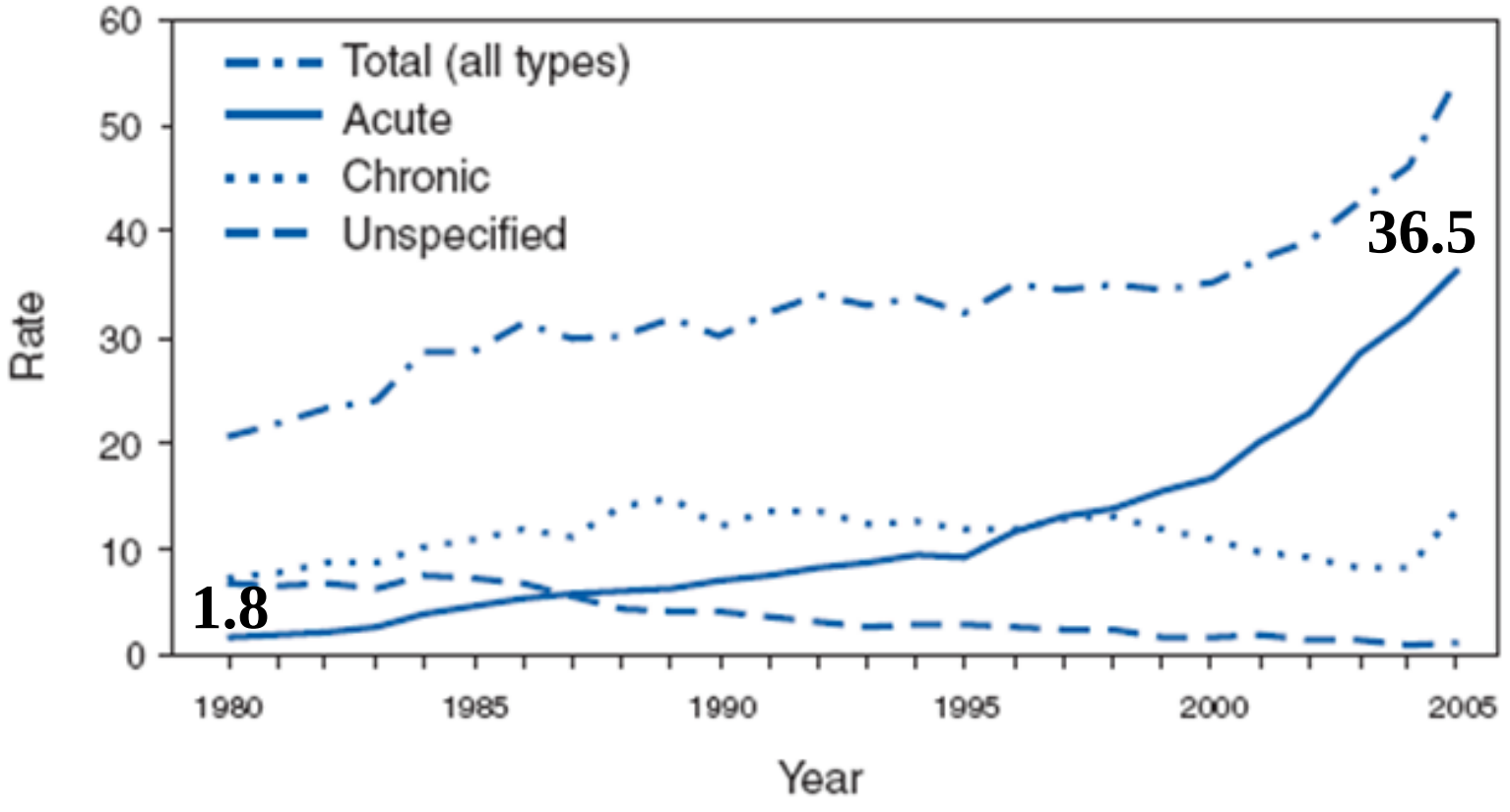
Hospitalization Discharge Diagnoses for Kidney Disease - United States, 1980--2005

CDC *MMWR* 57(12);309-312, 2008

FIGURE 2. Age-adjusted hospitalization rates* for kidney disease,† by type of kidney failure — National Hospital Discharge Survey, United States, 1980–2005



Acute Renal Failure in critically ill patients (n=29,260)
A multinational, multicenter study

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)

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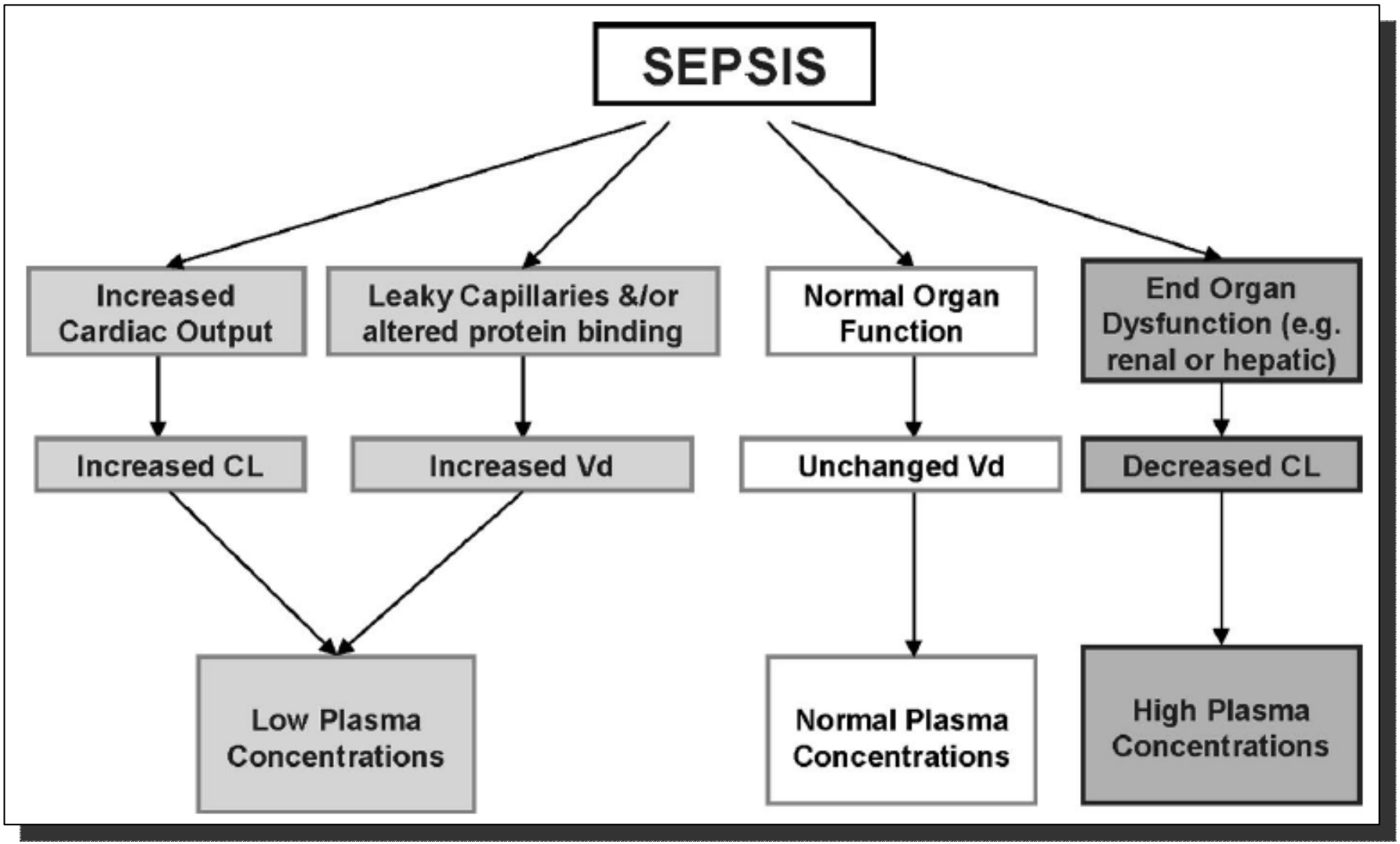
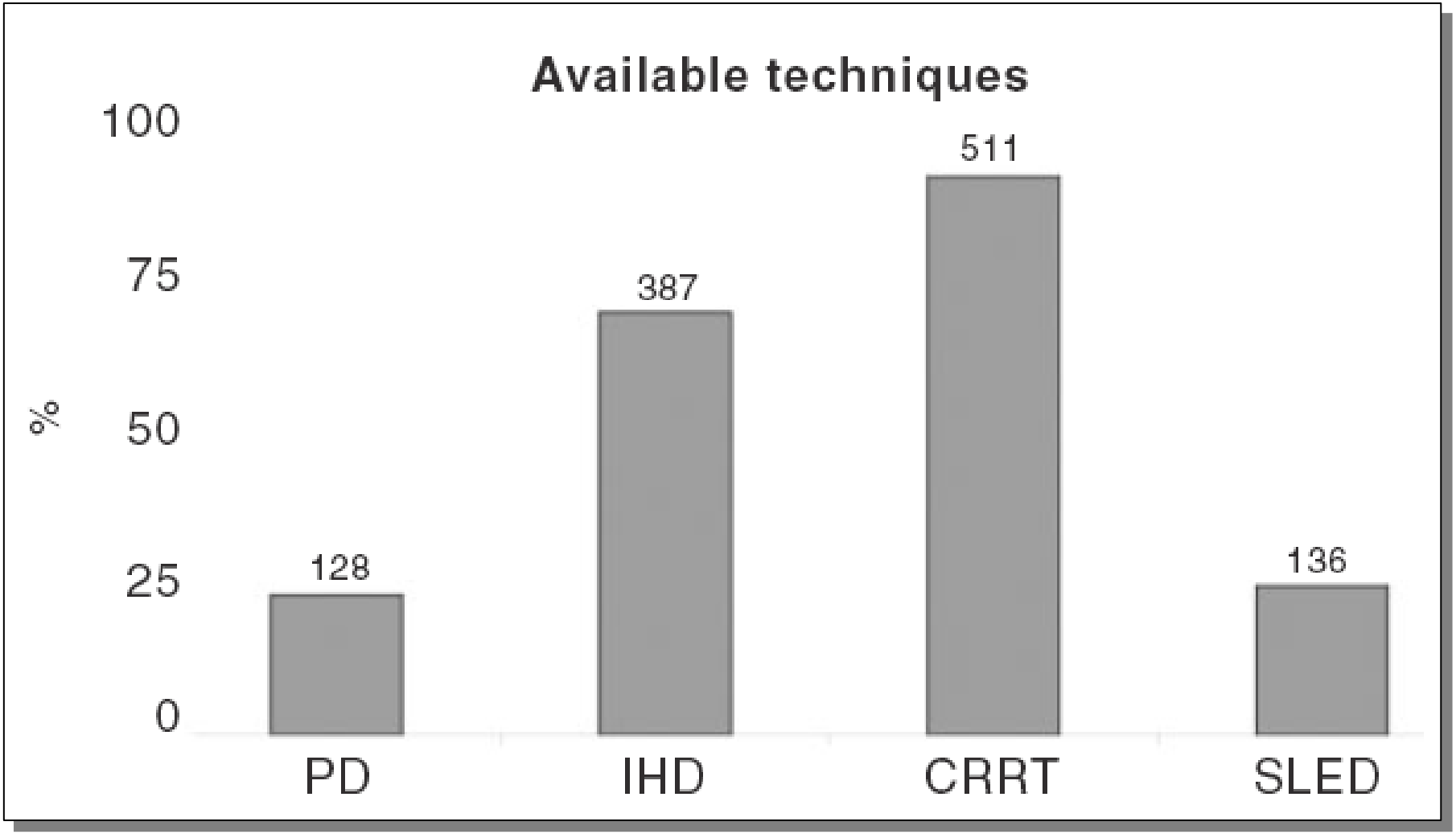
Pharmacokinetic issues for antibiotics in the critically ill patient

ROBERTS & LIPMAN *Crit Care Med* 37(3):926-933, 2009



Practice patterns in the management of acute renal failure in the critically ill patient: an international survey

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



Practice patterns in the management of acute renal failure in the critically ill patient: an international survey

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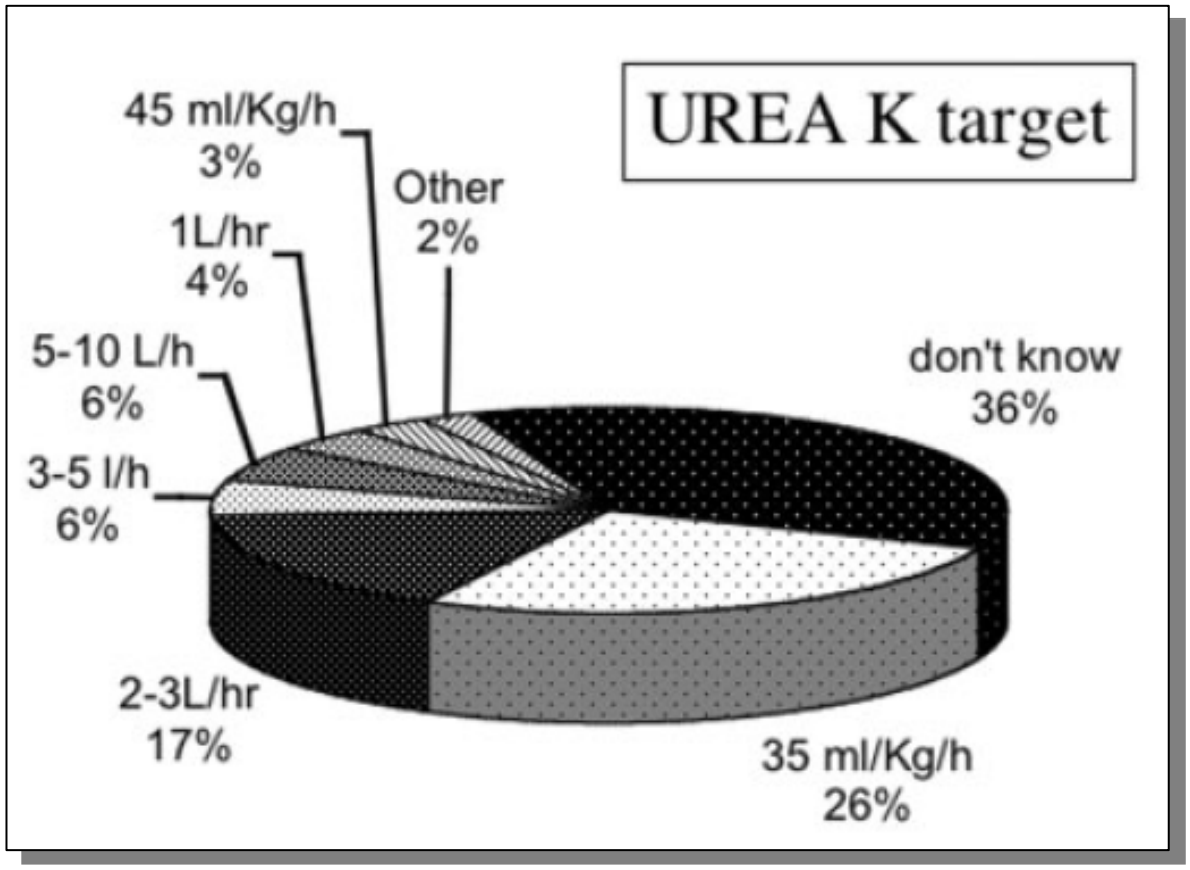
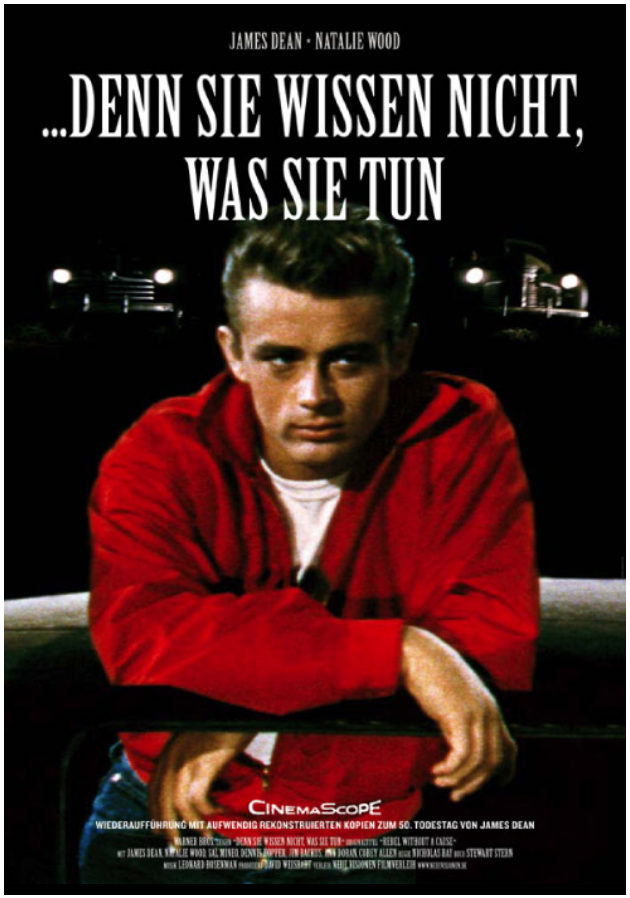
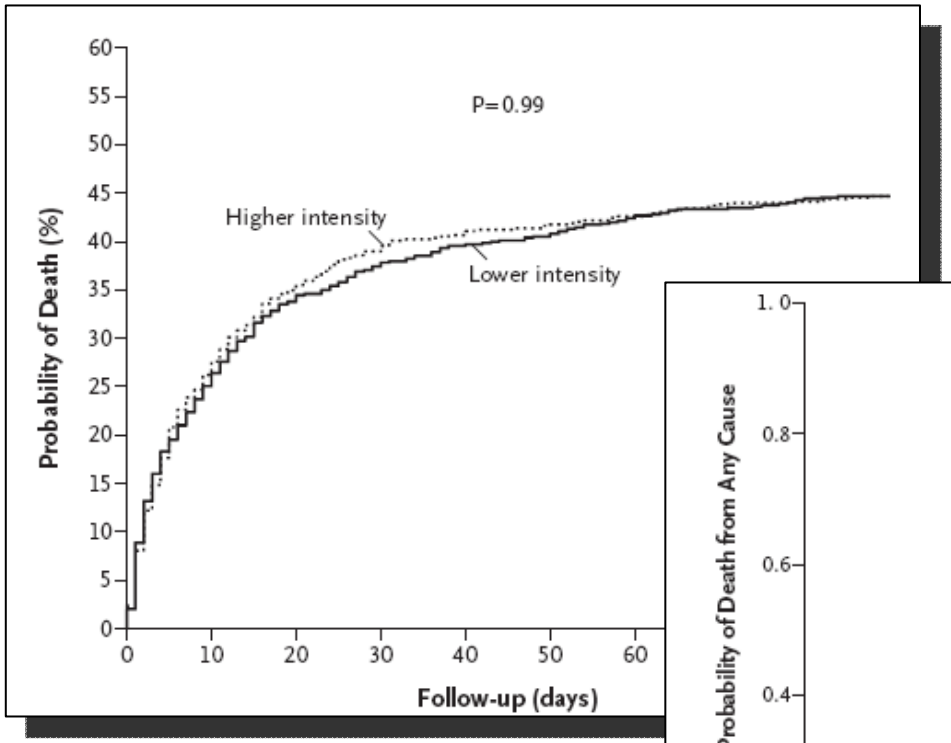


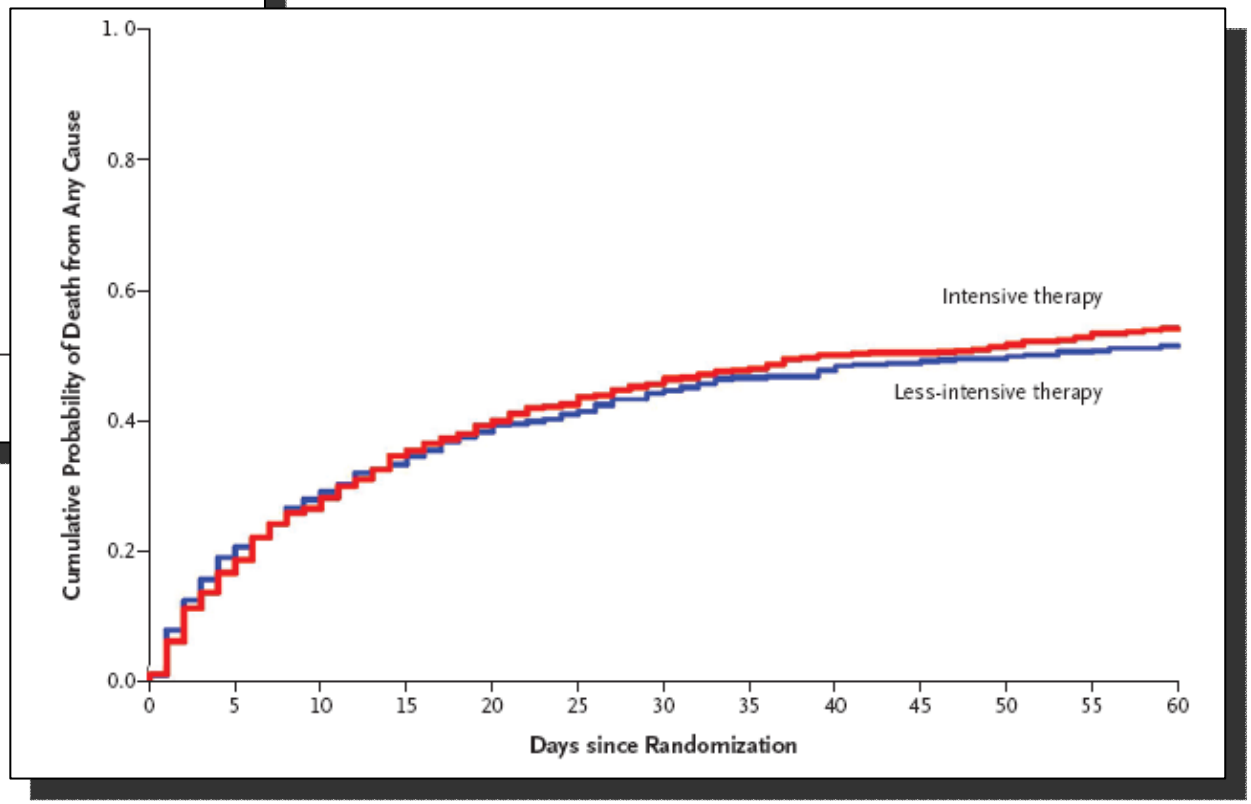


Drug dosing regimens identical in each group. Was Intensive CRRT group underdosed with Abx?

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

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





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

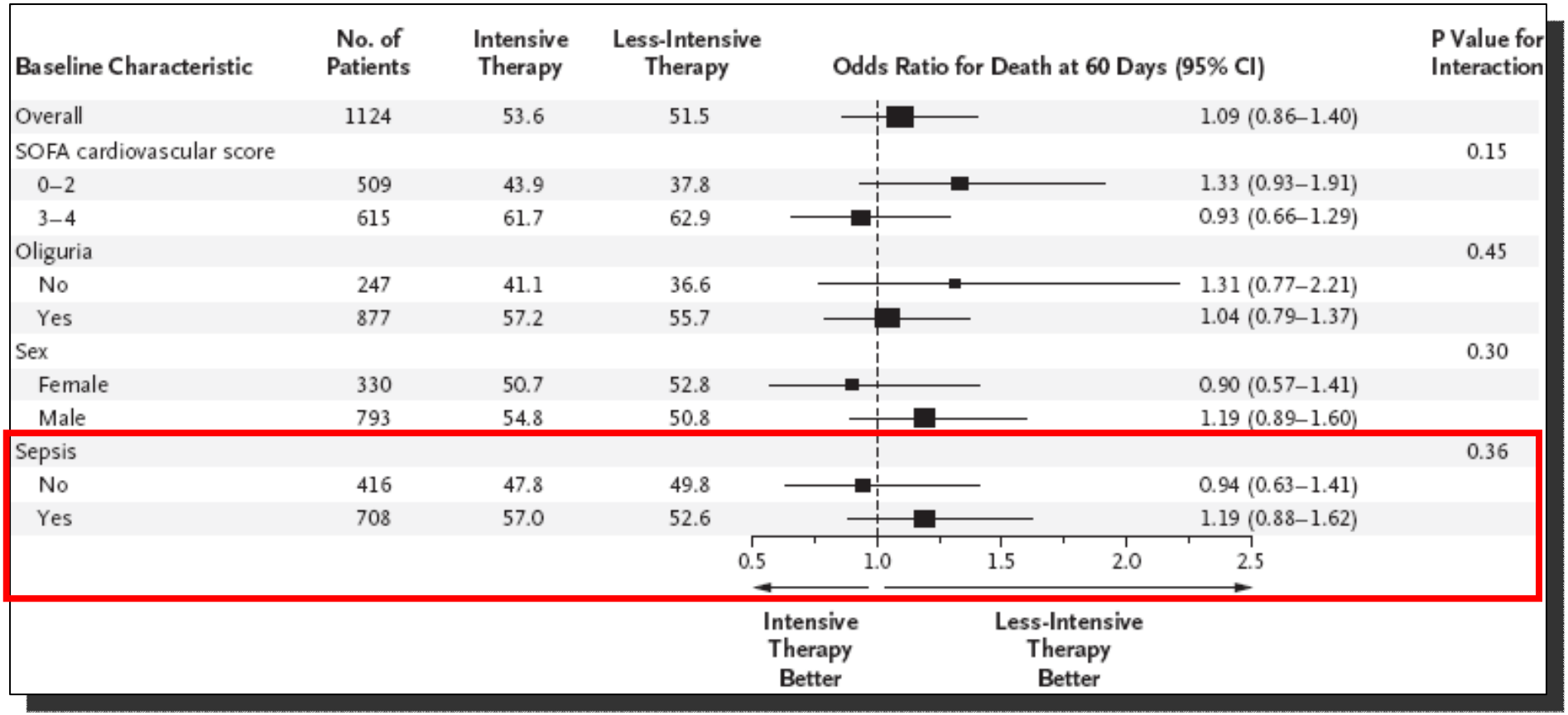
Table 4. Summary of Complications Associated with Study Treatment.

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

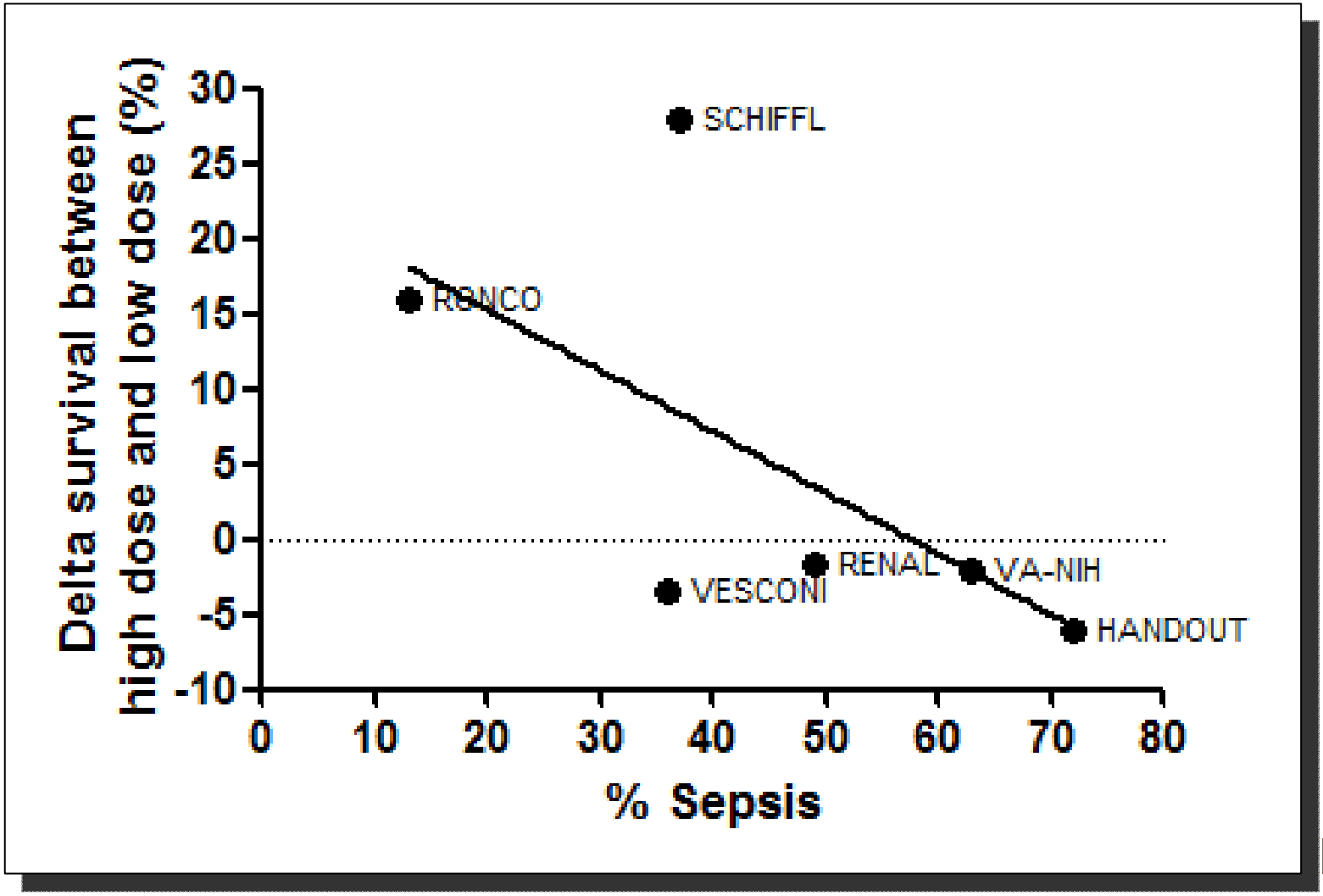
The RENAL Replacement Therapy Study Investigators *NEJM* 361:1627-38 ,2009

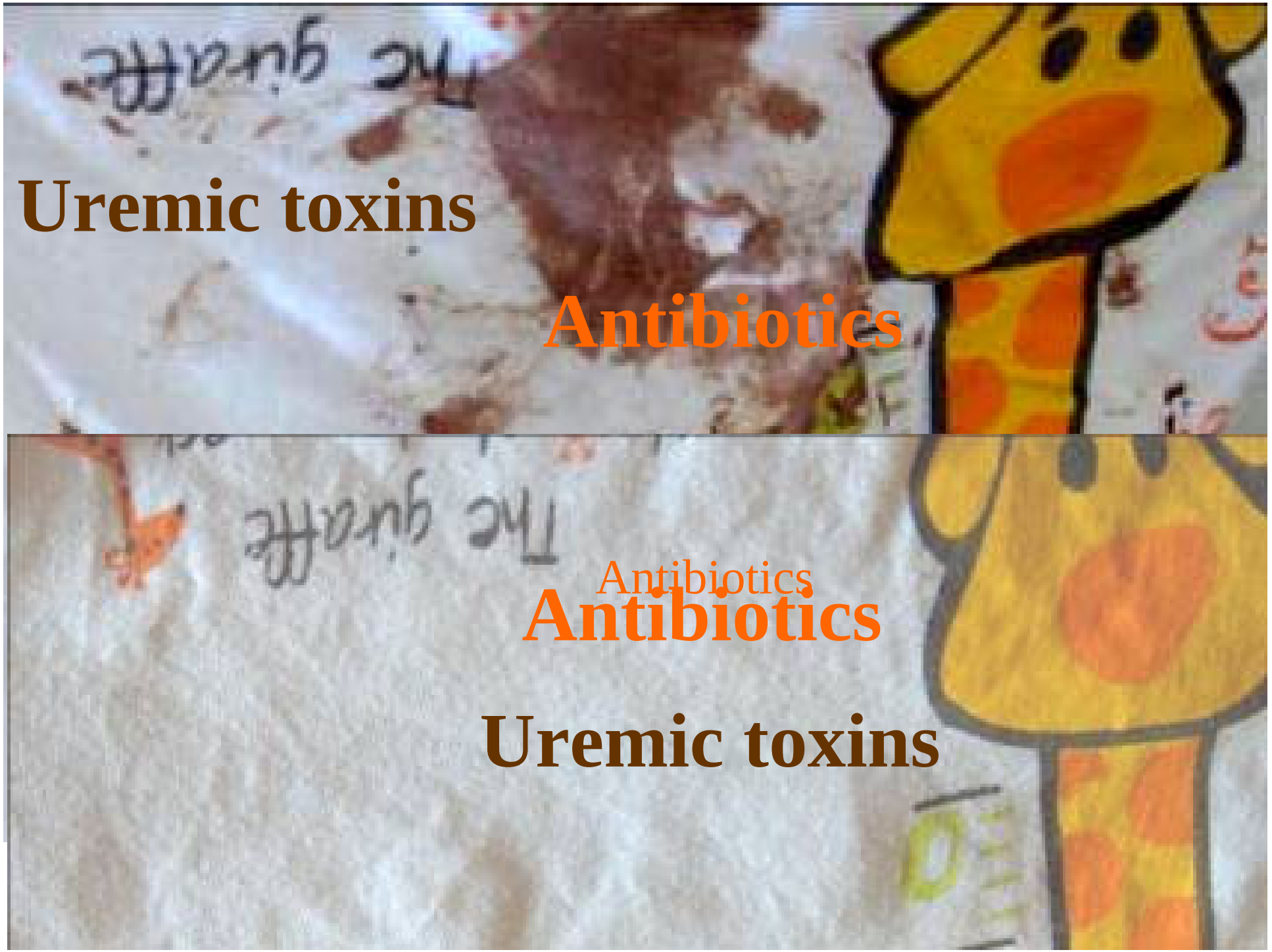


Baseline Characteristic	No. of Patients	Intensive Therapy	Less-Intensive Therapy	Odds Ratio for Death at 60 Days (95% CI)	P Value for Interaction
Overall	1124	53.6	51.5	1.09 (0.86–1.40)	
SOFA cardiovascular score					0.15
0–2	509	43.9	37.8	1.33 (0.93–1.91)	
3–4	615	61.7	62.9	0.93 (0.66–1.29)	
Oliguria					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)	

Effect in higher RTT on mortality and its relation to the number of septic patients in the study

Kielstein, unpublished




Uremic toxins
Antibiotics
Antibiotics
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Uremic toxins

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Vancomycin

Indication: invasive gram-positive infections

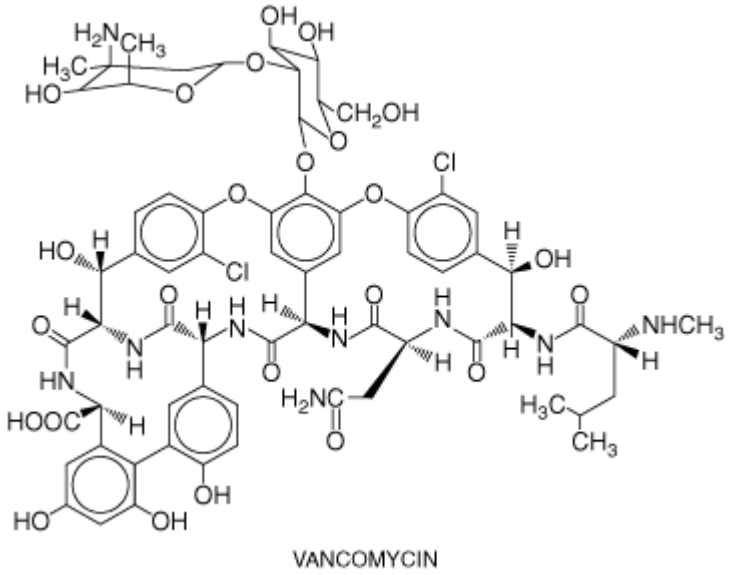
MW: 1449 Da

Protein bndg: 10-50%

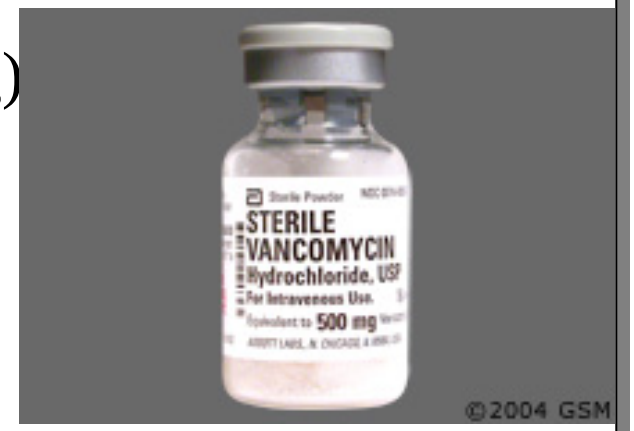
VOD: 0.6 L/kg

Elimination: urine
(80% to 90% as unchanged drug)

Half life: -4-6 h in healthy subjects
-200-250 h in ESRD

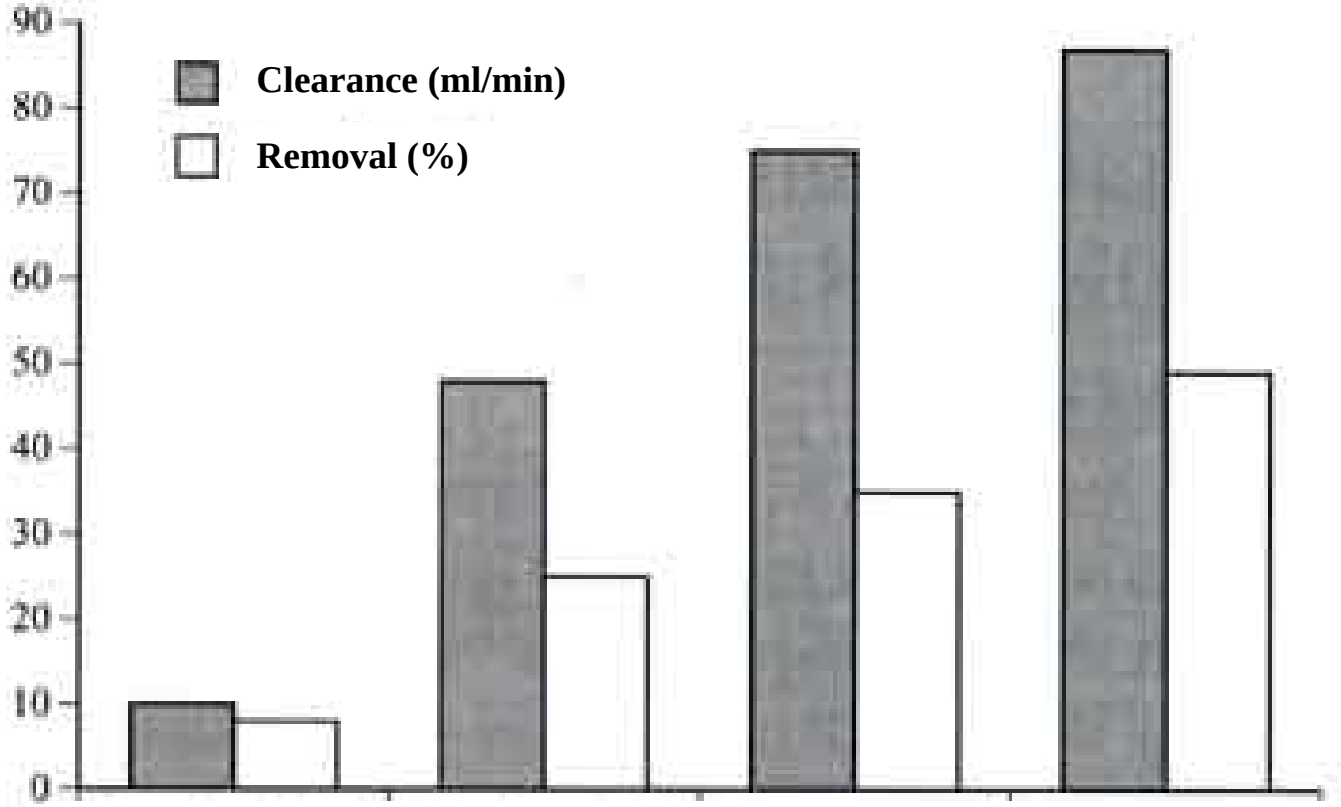


VANCOMYCIN



Markedly increased clearance of vancomycin during hemodialysis using polysulfone dialyzers

LANESE et al. *Kidney Int* 35(6):1409-12, 1989



Use of vancomycin in high-flux hemodialysis: experience with 130 courses of therapy

BARTH et al. *Kidney Int* 50(3):929-36, 1996

We conclude that in high-flux hemodialysis, a **20 mg/kg loading dose of vancomycin** followed by **500 mg doses after each dialysis treatment** achieves predictable, adequate and safe therapeutic levels, does not lead to unacceptably high peaks, and does not accumulate during long treatment courses. **By contrast, once-weekly vancomycin dosing resulted in subtherapeutic serum levels after five to seven days, and should be abandoned in the high-flux setting.**

Higher Renal Replacement Therapy Dose Delivery Influences on Drug Therapy

MUELLER et al. *Artificial Organs* 27(9):808–814, 2003

TABLE 1. *Comparison of calculated daily maintenance drug requirements (mg/day) for 70 kg anuric patient with ARF using two published dosing methods*

(Not meant to be dosing recommendations to be used in patients.)

Drug Dose for normal RF†/ Dose for CKD†	Assumed SA/SC	Dialysate/Ultrafiltrate Production Rates					
		1 L/hr		3 L/hr		6 L/hr	
		Method 1	Method 2	Method 1	Method 2	Method 1	Method 2
Vancomycin 1000 mg Q12 1000 mg Q120 hr	0.8	400 mg/day	1,587 mg/day	1,100 mg/day	4,167 mg/day	2,137 mg/day	6,667 mg/day

† Doses taken from (4).

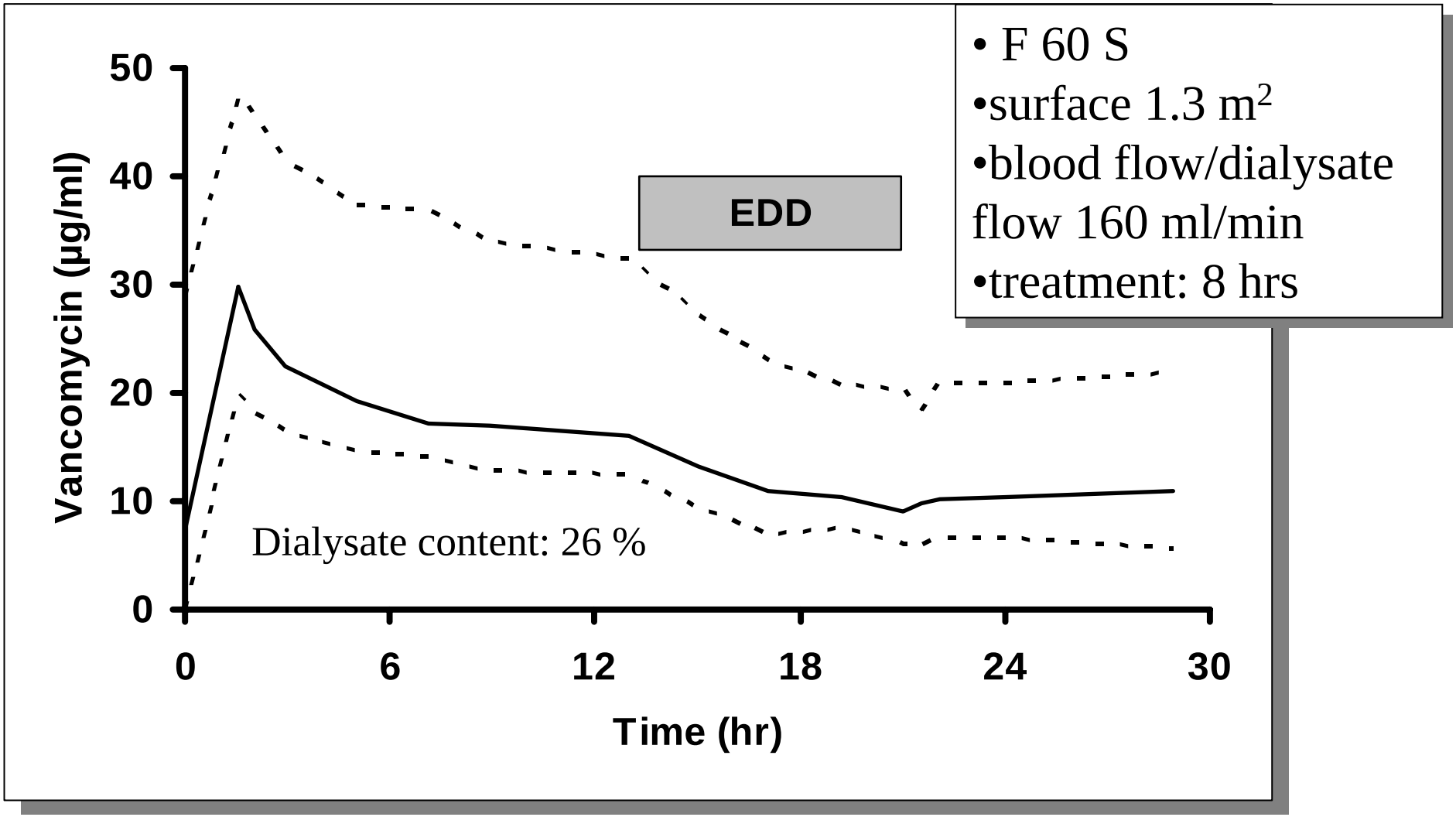
Shaded boxes are not doses recommended by the authors; they are simply results of calculations using published dosing algorithms. All dosing should be guided by serum concentration monitoring when possible.

Method 1: Begin with dose for patients with normal renal function and adjust (20,37).

Method 2: Begin with dose for patients with chronic kidney disease and adjust (16,17).

Pharmacokinetics and total elimination of meropenem and vancomycin in ICU patients undergoing EDD

KIELSTEIN et al. *Critical Care Medicine* 34(1):51-56, 2006



Therapeutic monitoring of vancomycin in adult patients: A consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists

MICHAEL RYBAK, BEN LOMAESTRO, JOHN C. ROTSCHAFER, ROBERT MOELLERING JR., WILLIAM CRAIG, MARIANNE BILLETER, JOSEPH R. DALOVISIO, AND DONALD P. LEVINE

Summary and recommendations: *Based on the potential to improve penetration, increase the probability of optimal target serum vancomycin concentrations, and improve clinical outcomes for complicated infections such as bacteremia, endocarditis, osteomyelitis, meningitis, and hospital-acquired pneumonia caused by* S. aureus, *total trough serum vancomycin concentrations of 15–20 mg/L are recommended. Trough serum*

Vancomycin

	UpToDate ONLINE	University of Pennsylvania Health System	PubMed www.pub
No renal impairment	20-45 mg/kg/d	20-45 mg/kg/d	20-45 mg/kg/d
IHD + after HD	15-20 mg/kg 1 g	-	15-20 mg/kg 1 g
CVVH	15-20 mg/kg 1 g / d	-	15-20 mg/kg 1 g / d
SLED	-	-	15-20 mg/kg 1 g / d

Meropenem / Meronem ®

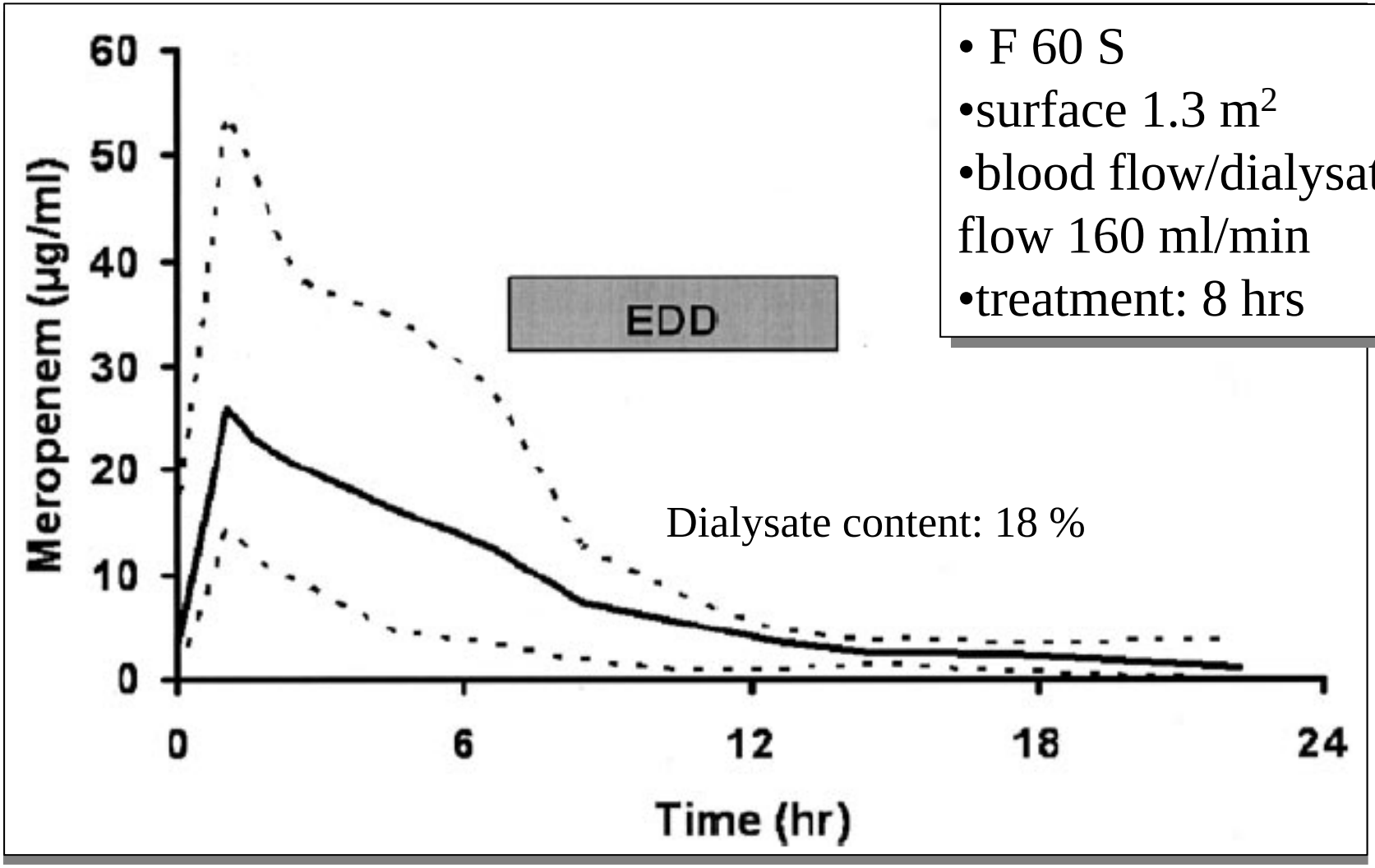
Indication: invasive gram-positive and gram negative infections ß—lactamase producers and pseudomonas aeruginosa

MW: 437 Da
Protein bndg: 2 %
VOD: 0.21 L/kg

Elimination: 65% - 80% in urine as unchanged drug (glomerular filtration and tubular secretion)
Half life: 0.9 h in healthy volunteers
6.8 h in ESRD

Pharmacokinetics and total elimination of meropenem and vancomycin in ICU patients undergoing EDD

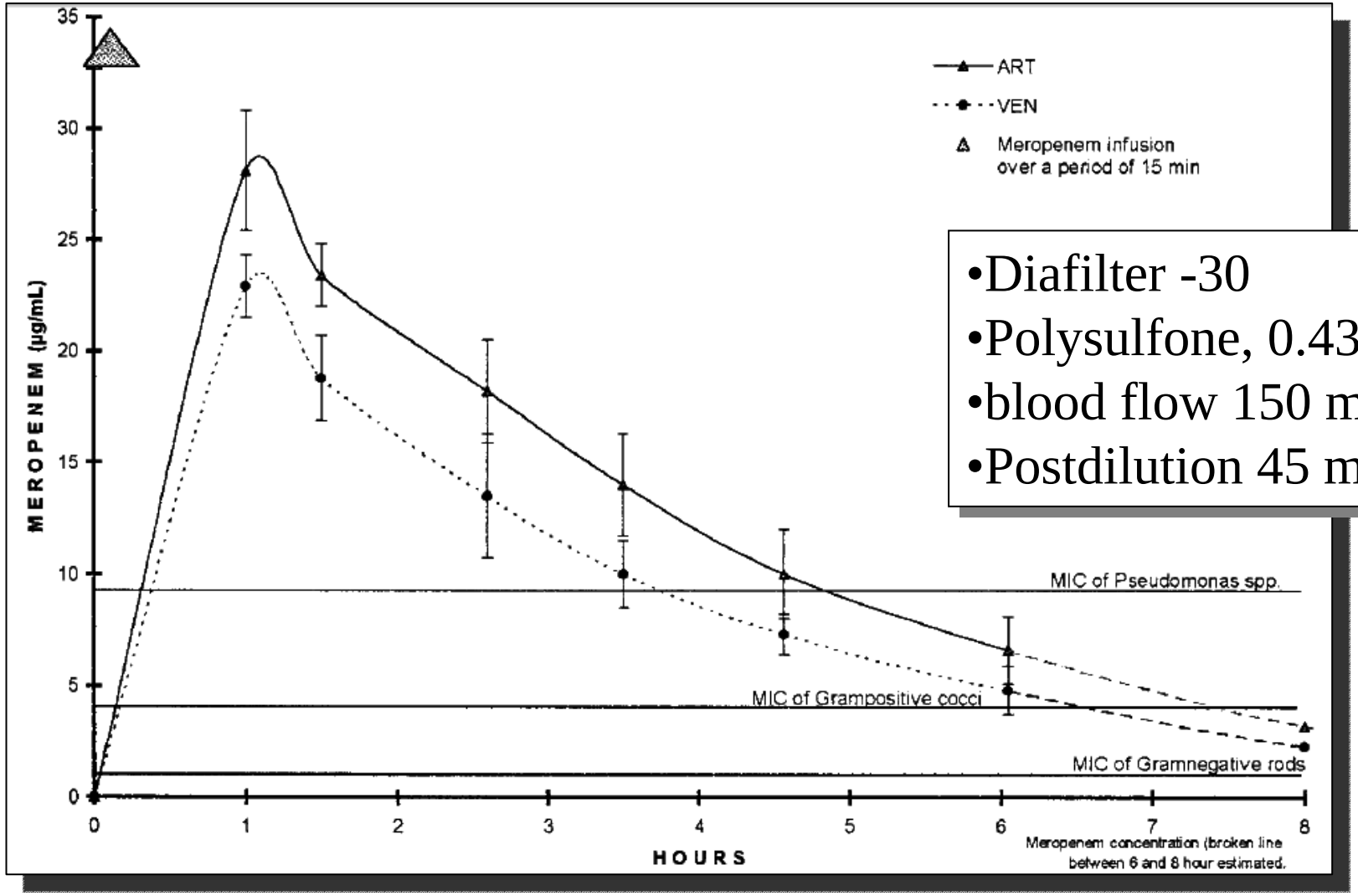
KIELSTEIN et al. *Critical Care Medicine* 34(1):51-56, 2006



- F 60 S
- surface 1.3 m^2
- blood flow/dialysate flow 160 ml/min
- treatment: 8 hrs

Single-Dose Pharmacokinetics of Meropenem during Continuous Venovenous Hemofiltration

THALHAMMER et al. *Antimicrob Agents Chemother* 42:2417–2420, 1998



- Diafilter -30
- Polysulfone, 0.43 m^2
- blood flow 150 ml/min
- Postdilution 45 ml/min

Meropenem / Meronem ®

	UpToDate ONLINE	University of Pennsylvania Health System	PubMed www.pub
No renal impairment	1g / 8 h	1g / 8 h	1g / 8 h
IHD + after HD	0.5 g / 24 h 0.5 g	0.5 g / 24 h 0.5 g	0.5 g / 24 h 0.5 g
CVVH	1g / 12 h	-	1g / 8 h
SLED	-	-	1g / 12 h

Would you like to buy a car for 10.000 € ?

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

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Daptomycin / Cubicin ®

Indication: -skin and skin-structure infections
-right heart endocarditis
-MRSA, sepsis

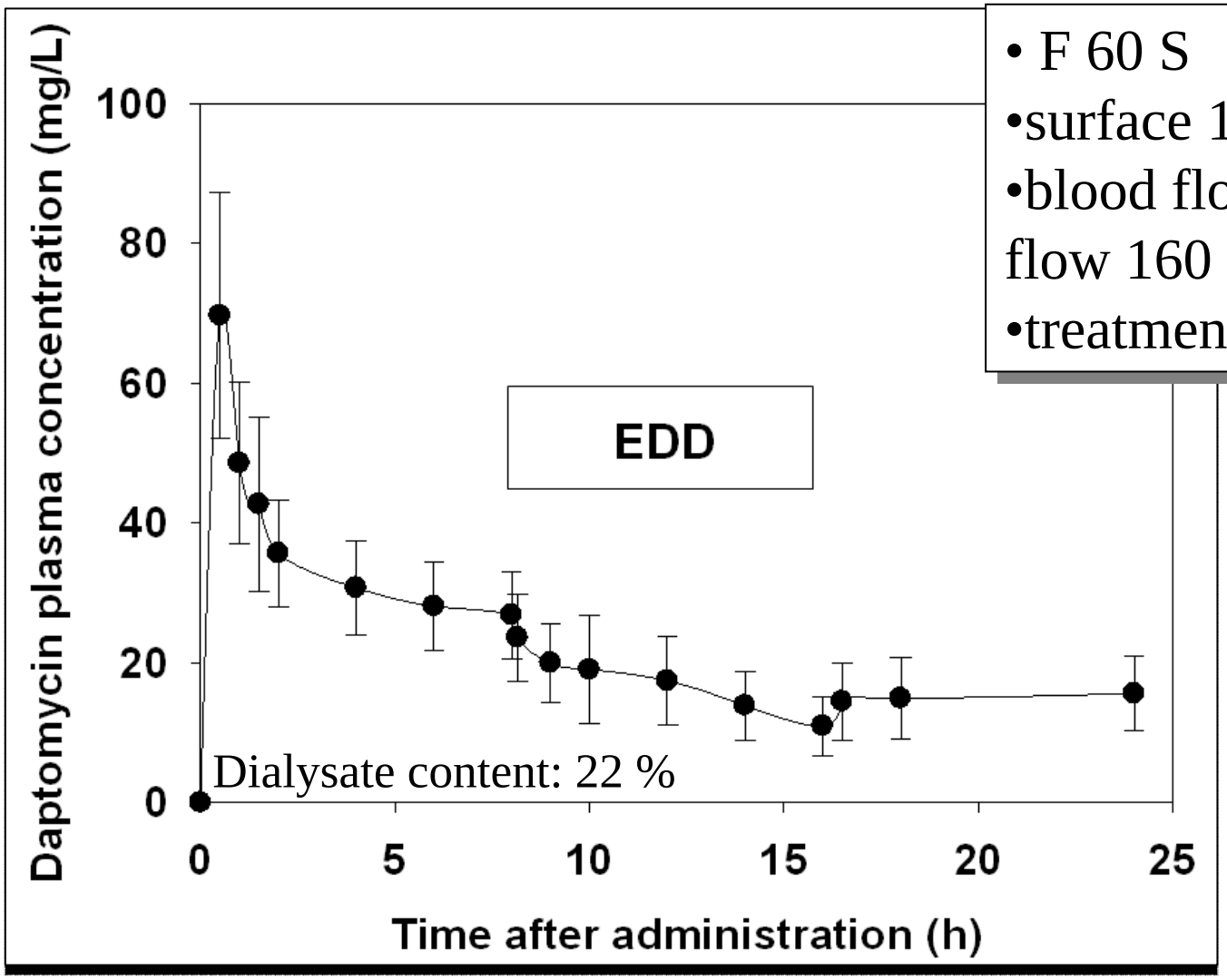
MW: 1620 Da
Protein bndg: 92 %
VOD: 0.01 L/kg

Elimination: urine
(80% to 90% as unchanged drug)

Half life: -7.8 hrs in healthy subjects
-29.3 hrs in ESRD

Elimination of daptomycin in septic patients in the ICU with acute kidney injury undergoing ED

KIELSTEIN et al., *Nephrol Dial Transplant*, 25: 1537–1541, 2010



- F 60 S
- surface 1.3 m^2
- blood flow/dialysate flow 160 ml/min
- treatment: 8 hrs

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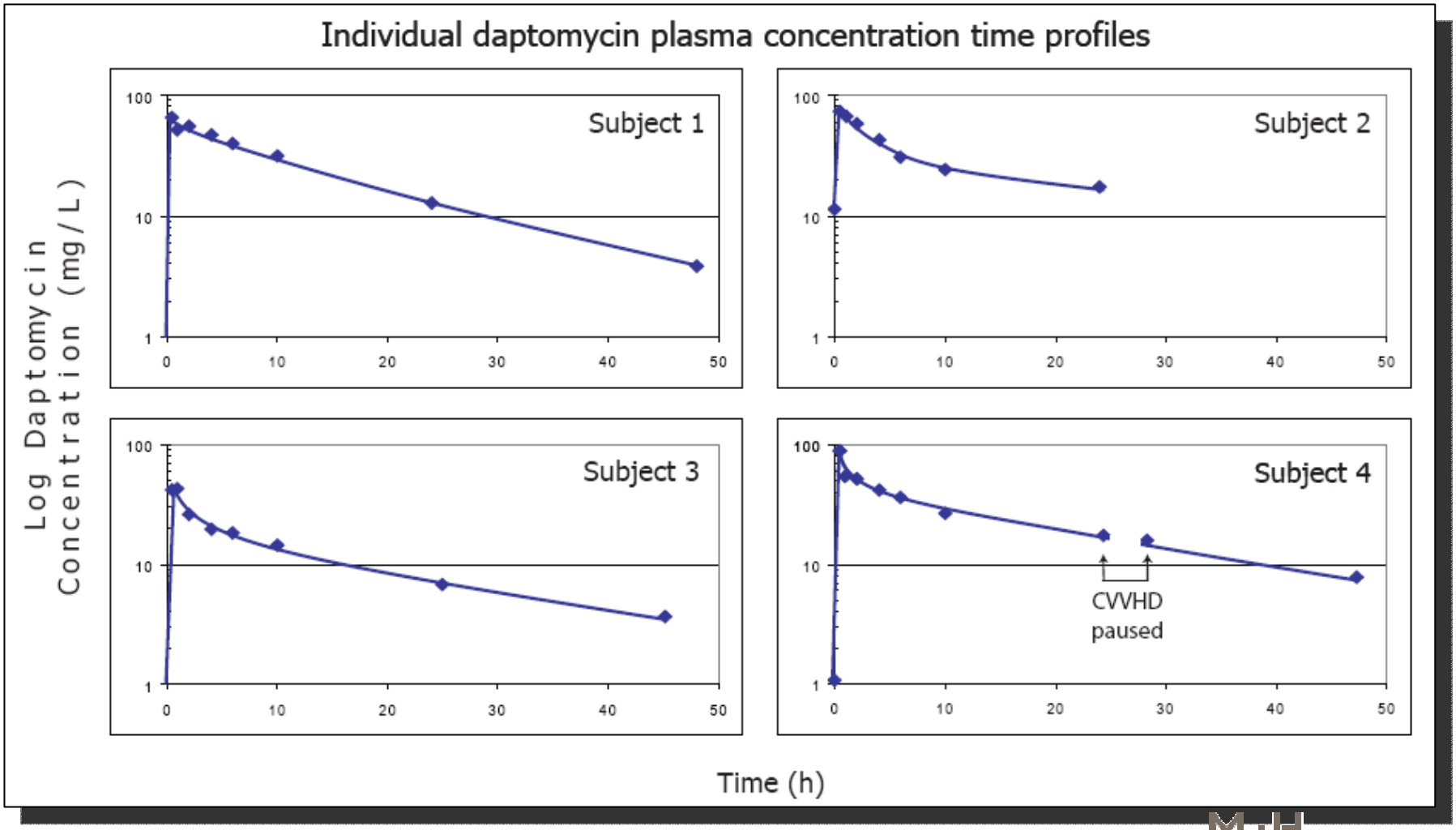
Daptomycin PK in patients treated with CVVHD

(1.6 m^2 high-flux polysulfone dialyzer,Qb150-200 mL/min, Qd=2 L/h, Quf=500-700 mL/h)

VILAY et al., JASN. 2008 (Abstract)



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Daptomycin / Cubicin ®

	UpToDate ONLINE	University of Pennsylvania Health System	PubMed www.pub
No renal impairment	6 mg/kg/24 h	6 mg/kg/24 h	6 mg/kg/24 h
IHD	6 mg/kg/48h	6 mg/kg/48h	7-9 mg/kg post HD
CVVH	-	-	6 mg/kg/24 h
SLED	-	-	6 mg/kg/24 h

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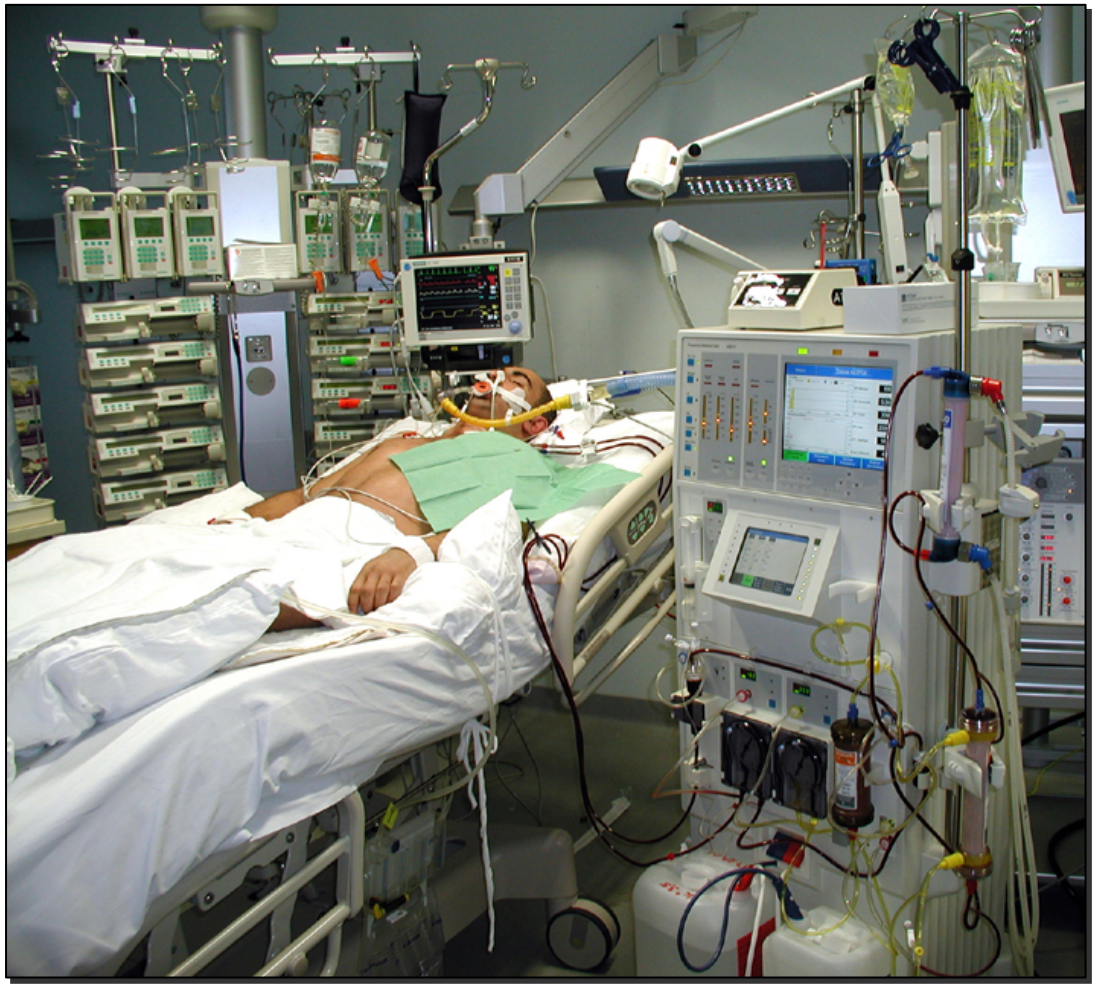
Pharmacokinetics and total elimination of meropenem and vancomycin in ICU patients undergoing EDD

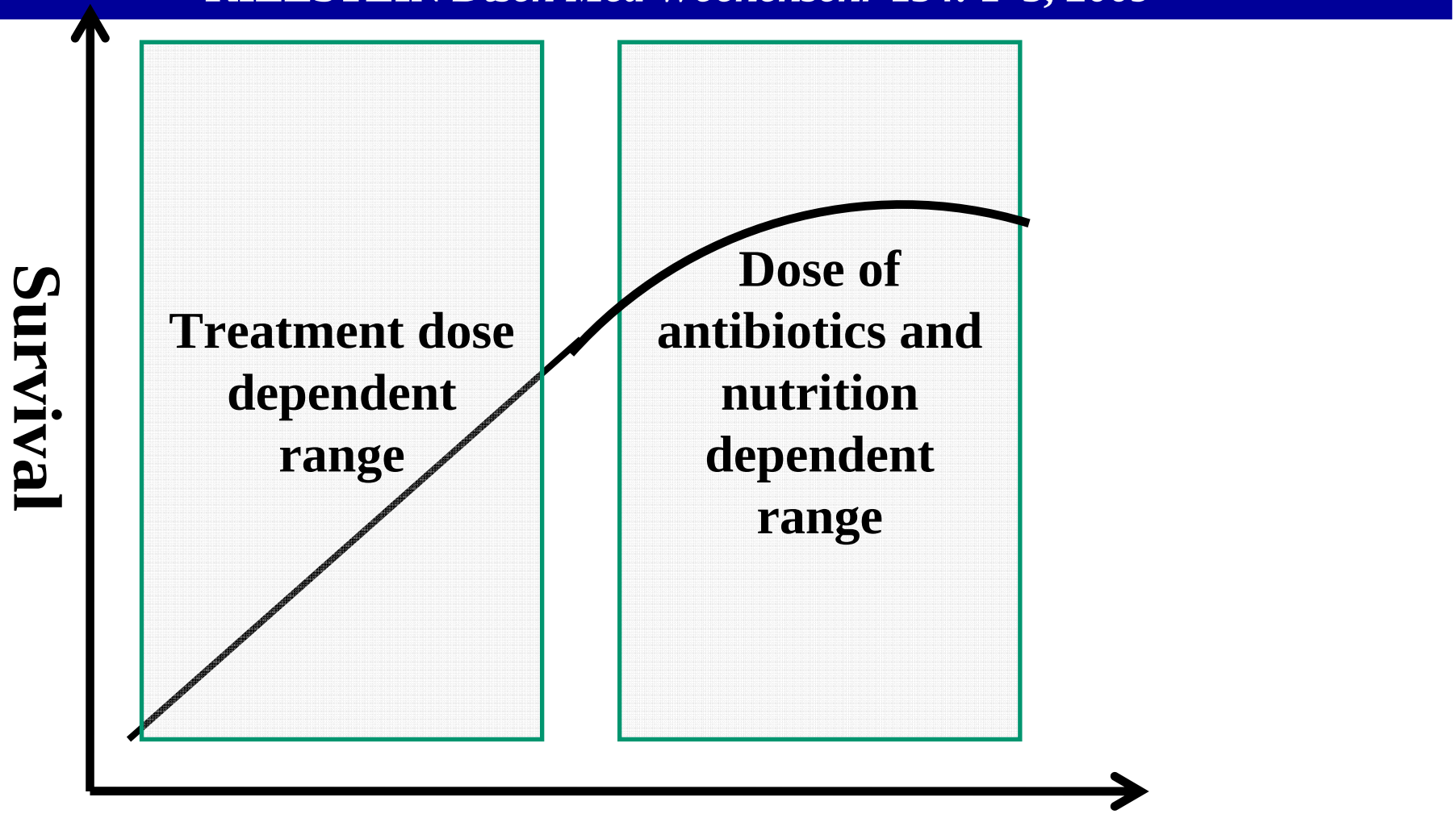
KIELSTEIN et al. *Critical Care Medicine* 34(1):51-56, 2006

The use of high dose renal replacement therapy mandates adjustment of current dosing regimens to avoid the risk of significant under-dosing, which may have detrimental effects on critically ill patients with life-threatening infections.



Dose of renal replacement therapy in acute kidney injury

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



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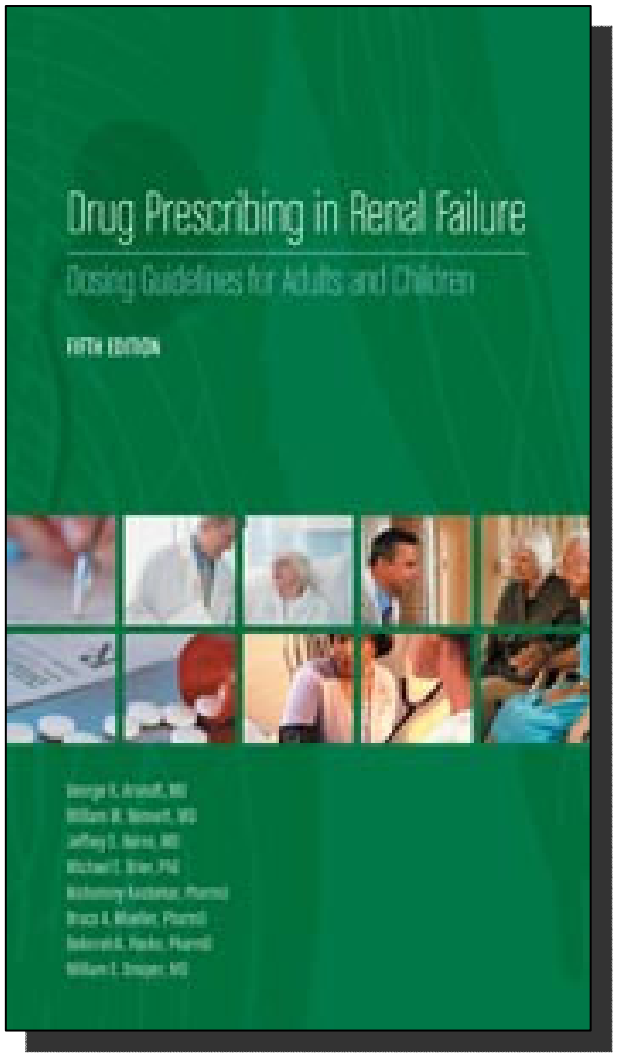
Studies on drugs in CRRT



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

Advice

1. **Be aware of the problem!**
2. **Dont blindly trust online and other resources! READ!**
3. **Create institutional guidelines depending on the type of RRT**
4. **Drugs that are not renally excreated (almost) never require dose adjustment**
5. **Drugs that are renally (> 30 %) excreated do require dose adjustment**
6. **Dosage adjustment is especially important in drugs with a narrow therapeutic window**
7. **Drugs with MW <5000 Da, low plasma protein binding and a small volume of distribution will be removed effectively**
8. **Use therapeutic drug monitoring!**

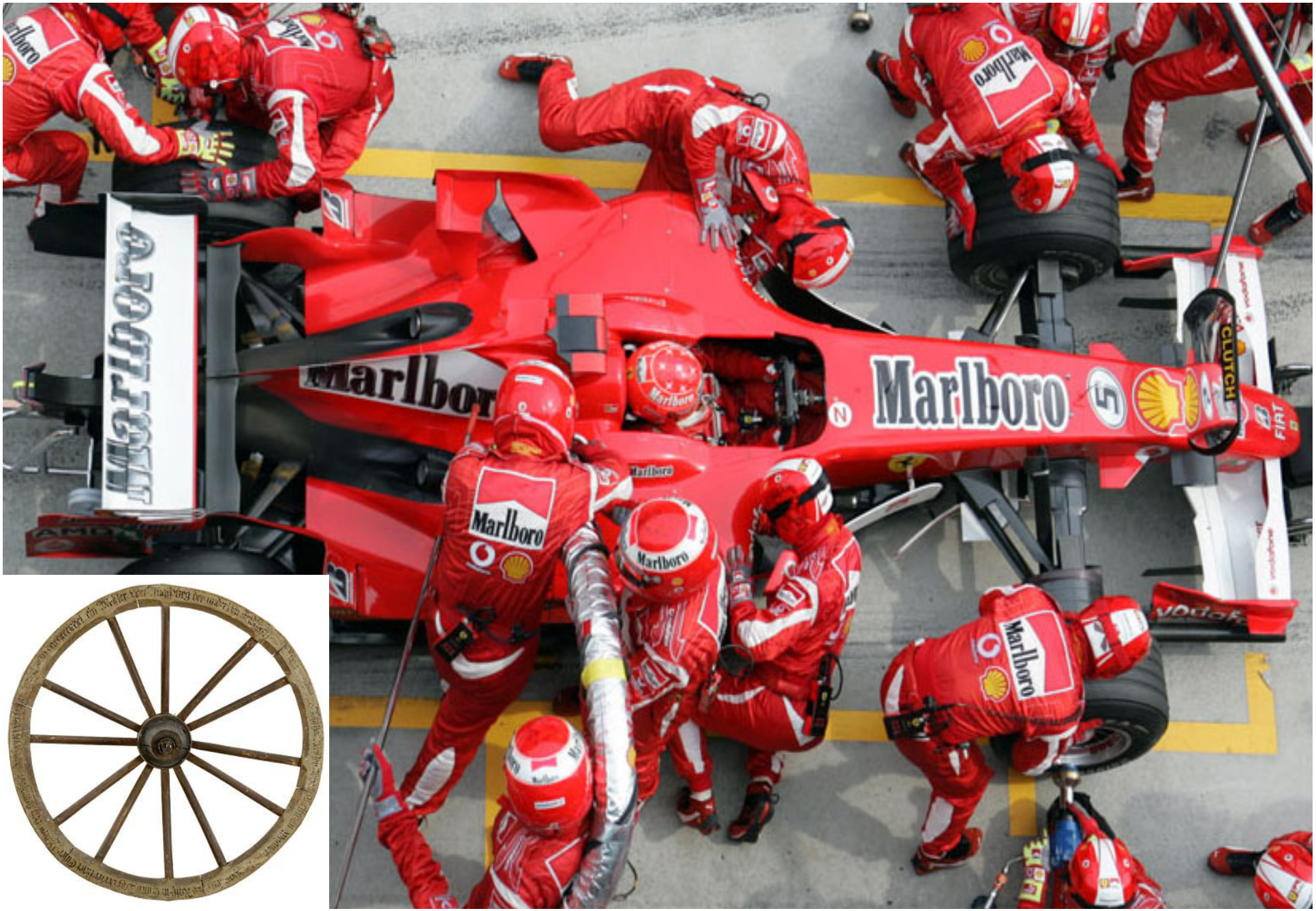
Drug Prescribing in Kidney Disease: Initiative for Improved Dosing

Drug Removal by Continuous Renal Replacement Therapy (CRRT) and Hybrid Therapies

Section Leaders:

Jan T. Kielstein and Bruce A. Mueller

Kidney Disease: Improving Global Outcomes



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