Optimizing Therapy in Obese and Frail Patients

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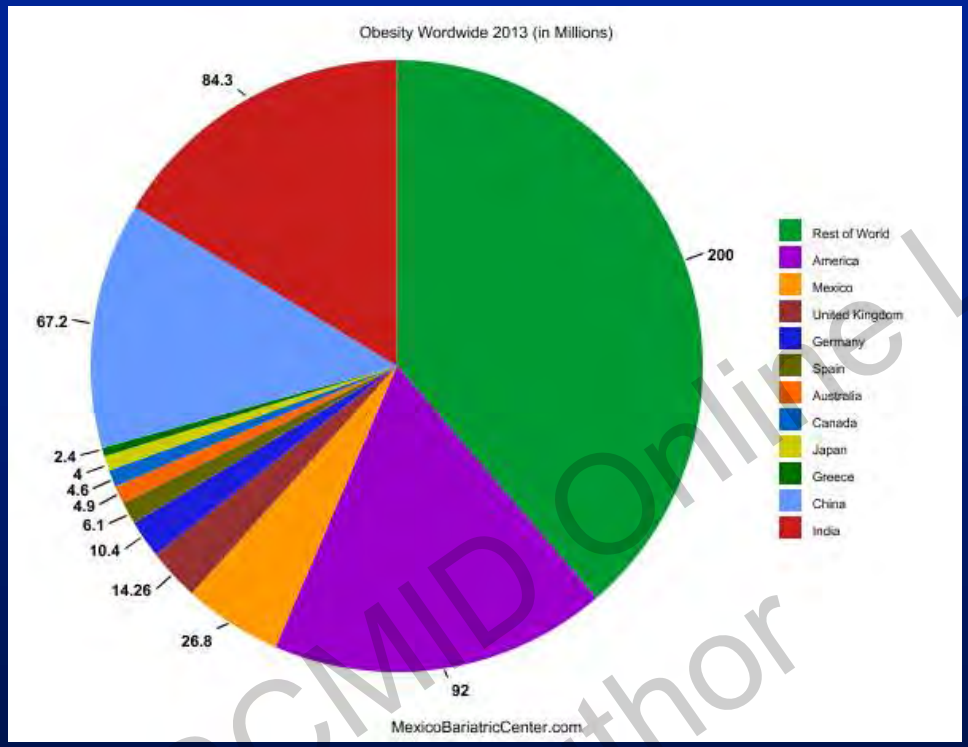
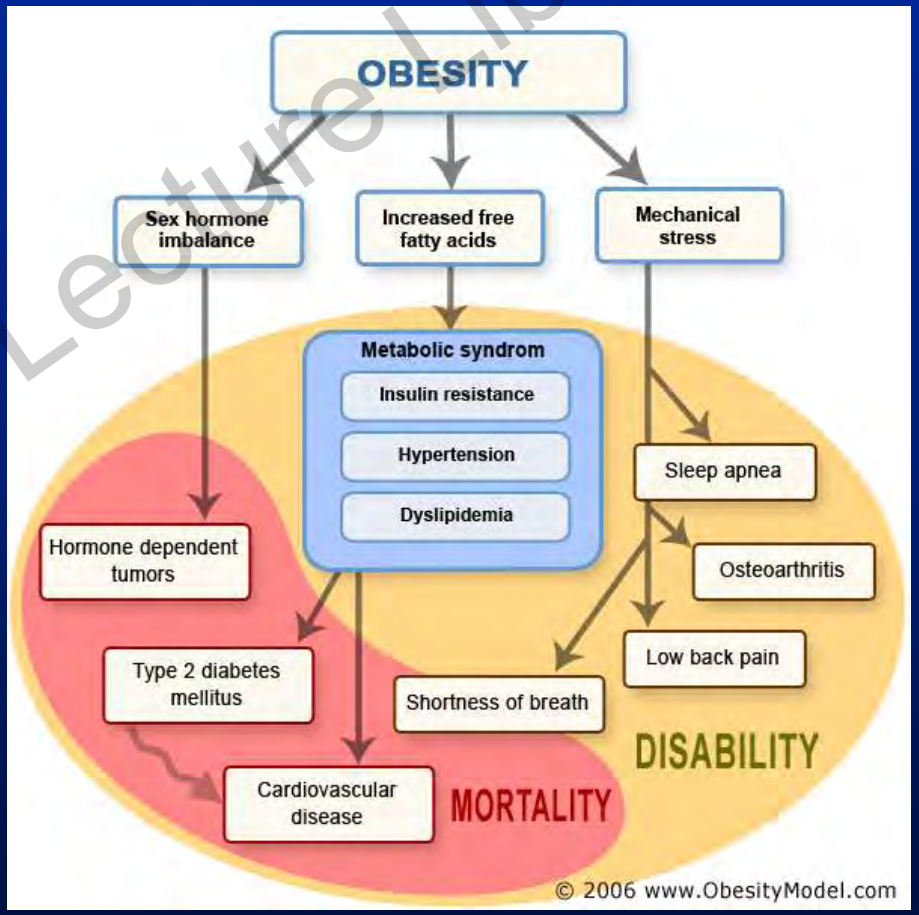
Obesity



	Obesity Class	BMI (kg/m2)
Underweight		<18.5
Normal		18.5-24.9
Overweight		25.0-29.9
Obesity	I	30.0-34.9
	II	35.0-39.9
Extreme obesity	III	More than 40

Preventing and Managing the Global Epidemic of Obesity. Report of the World Health Organization Consultation of Obesity. WHO, Geneva

Obesity



http://bookbing.org/obesity-related-organ-system-disorders-images-powerpoint-presentations/obesity-model/

Pharmacokinetic Changes in Obesity

A
- Effect on parenteral route of administration
- Delayed gastric emptying (gastric dystention)

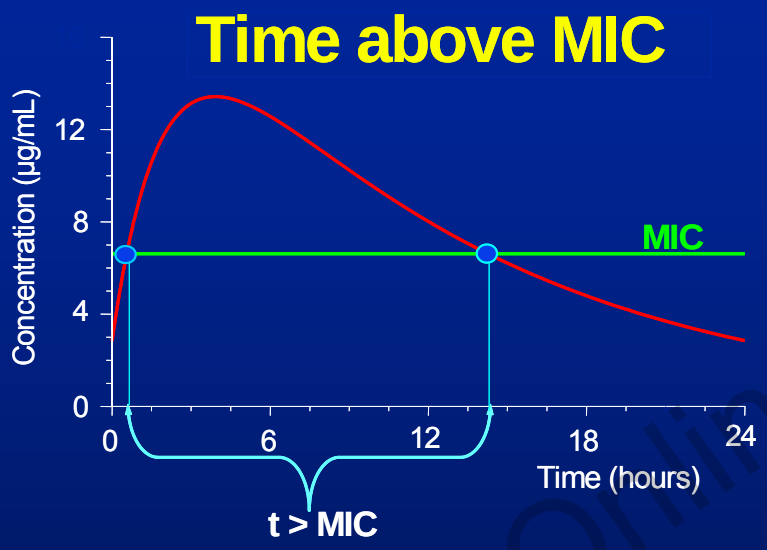
D
- Changes in volume of distribution
- Changes in tissue perfusion
- Change in plasma protein binding

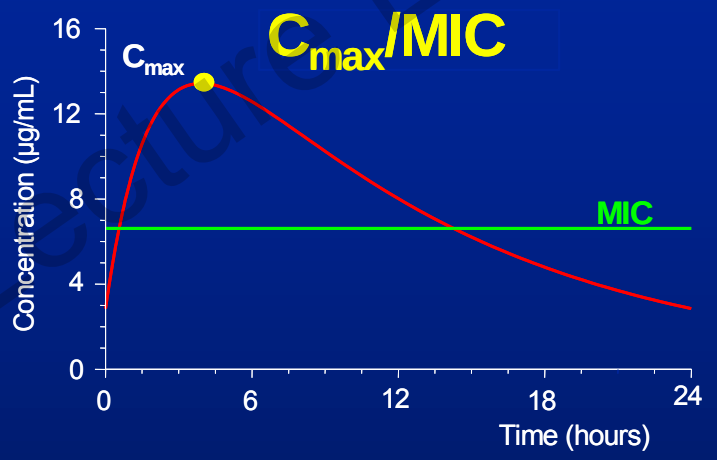
M
- Alteration of CYP mediated metabolism
- Alteration of phase-II metabolism
- Increase in hepatic volume

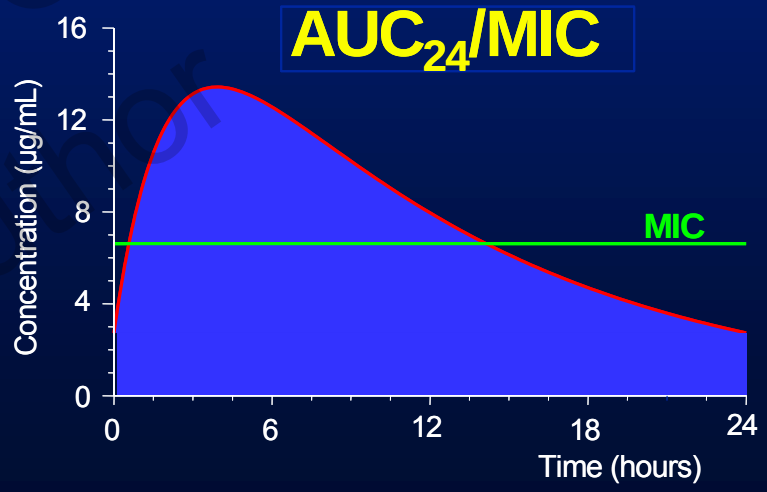
E
- Estimation of glomerular filtration rate using body size descriptors
- Change in glomerular filtration due to increased organ weight
- Change in tubular secretion and reabsorption

Curr Opin Infect Dis 2012, 25 (6): 634-649, Clin Pharm Ther 2011, 90 (1): 77-89

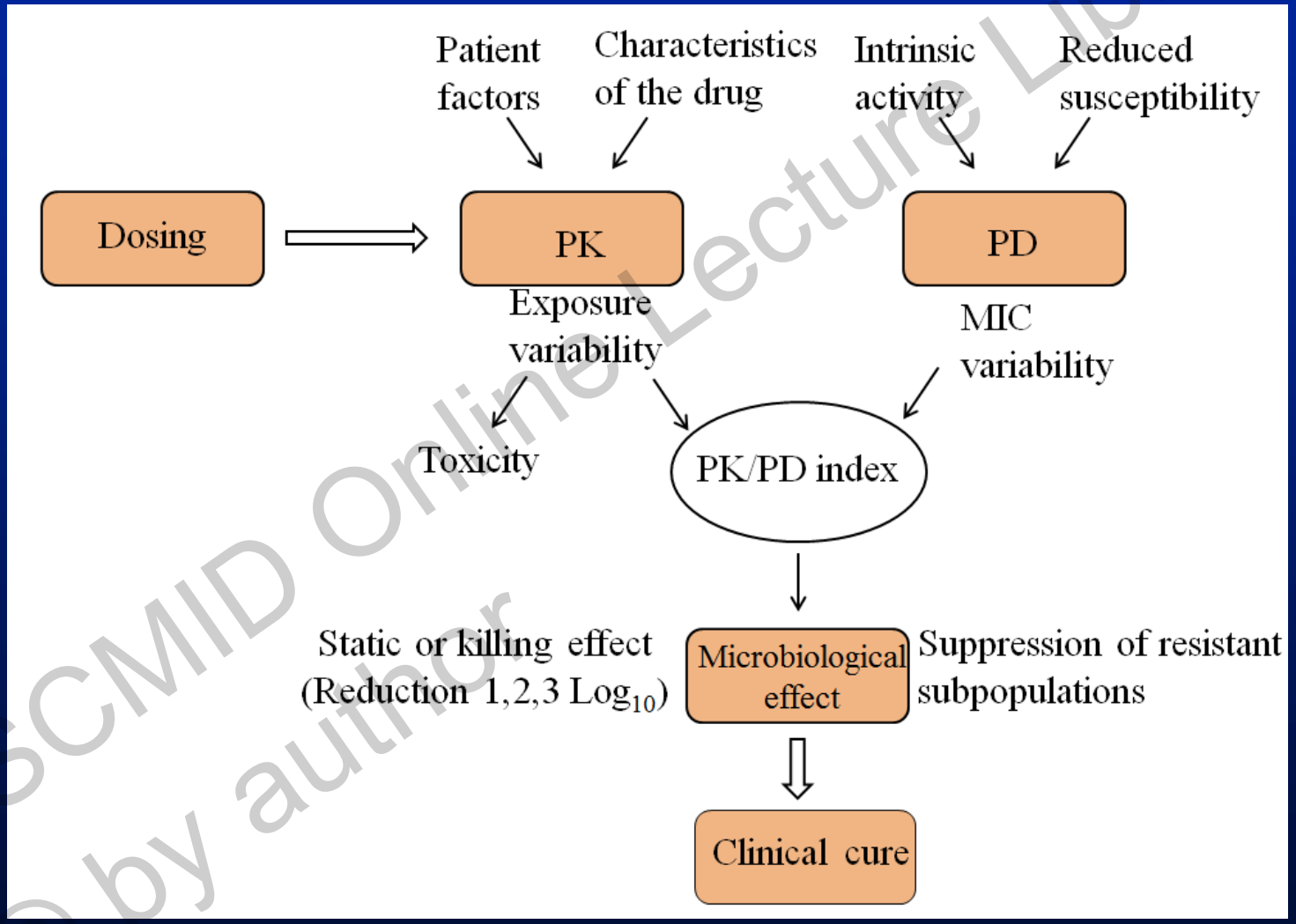
PK/PD indices of antibiotics







Variability and Relationship in PK/PD of Antibiotics in Obesity



Curr Opin Infect Dis 2012, 25 (6): 634-649, Clin Pharm Ther 2011, 90 (1): 77-89

Lipophilicity

- Obese subjects have a higher percentage of body fat
- The effect of body weight on volume of distribution depends on the lipophilicity of the drug

Effects of obesity on volume of distribution

Hydrophilic Drugs:

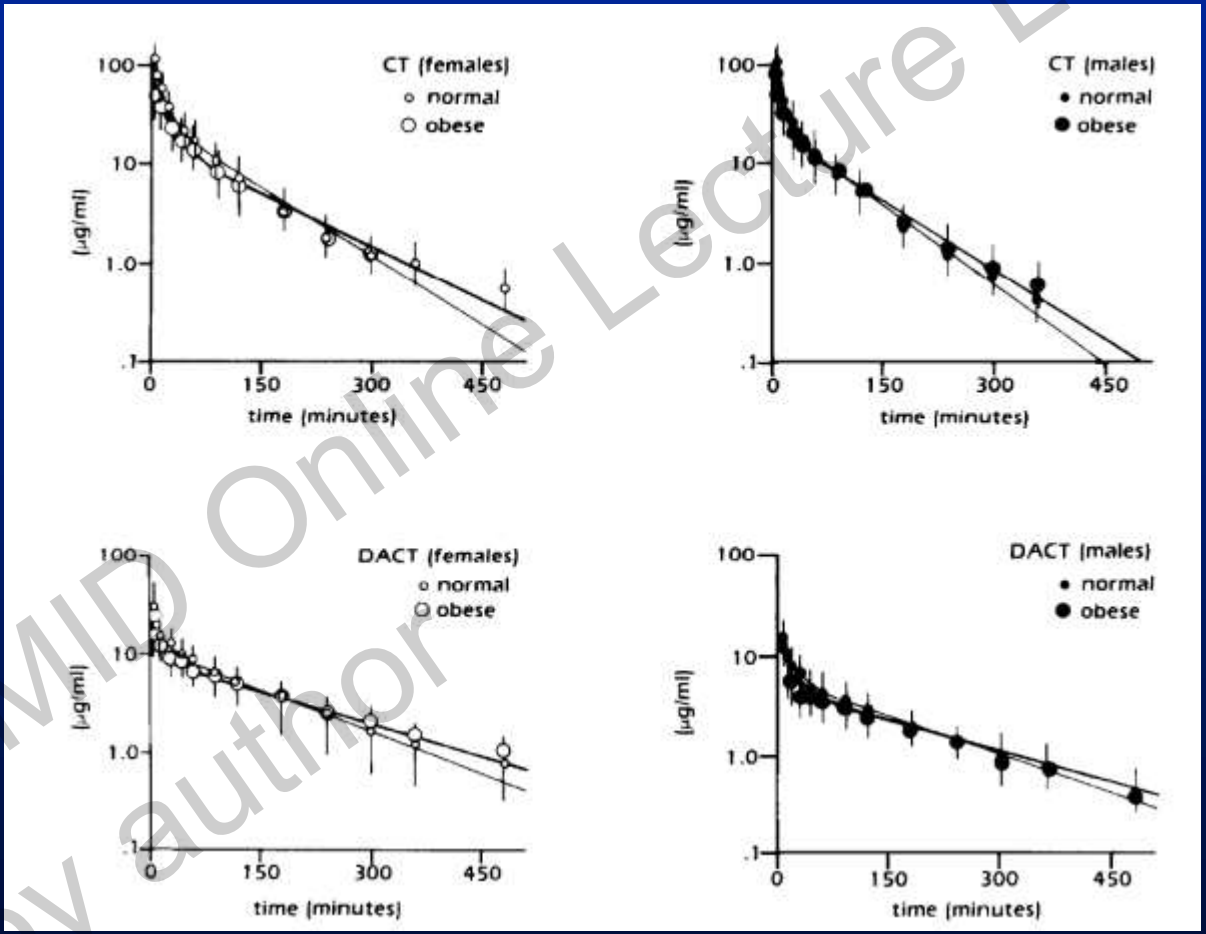
Little change in Vd, decrease in Vd/kg

Lipophilic Drugs:

Increase in Vd, increase in Vd/kg

Disposition of Cefotaxime and its Desacetyl Metabolite in Morbidly Obese Male and Female Subjects

Richard L. Yost and Hartmut Derendorf



Ther Drug Monit 1986, 8 (2): 189-194

Body Weight

Gentamicin

Group I (average weight 55 kg)

Vd = 13 L or 0.24 L/kg

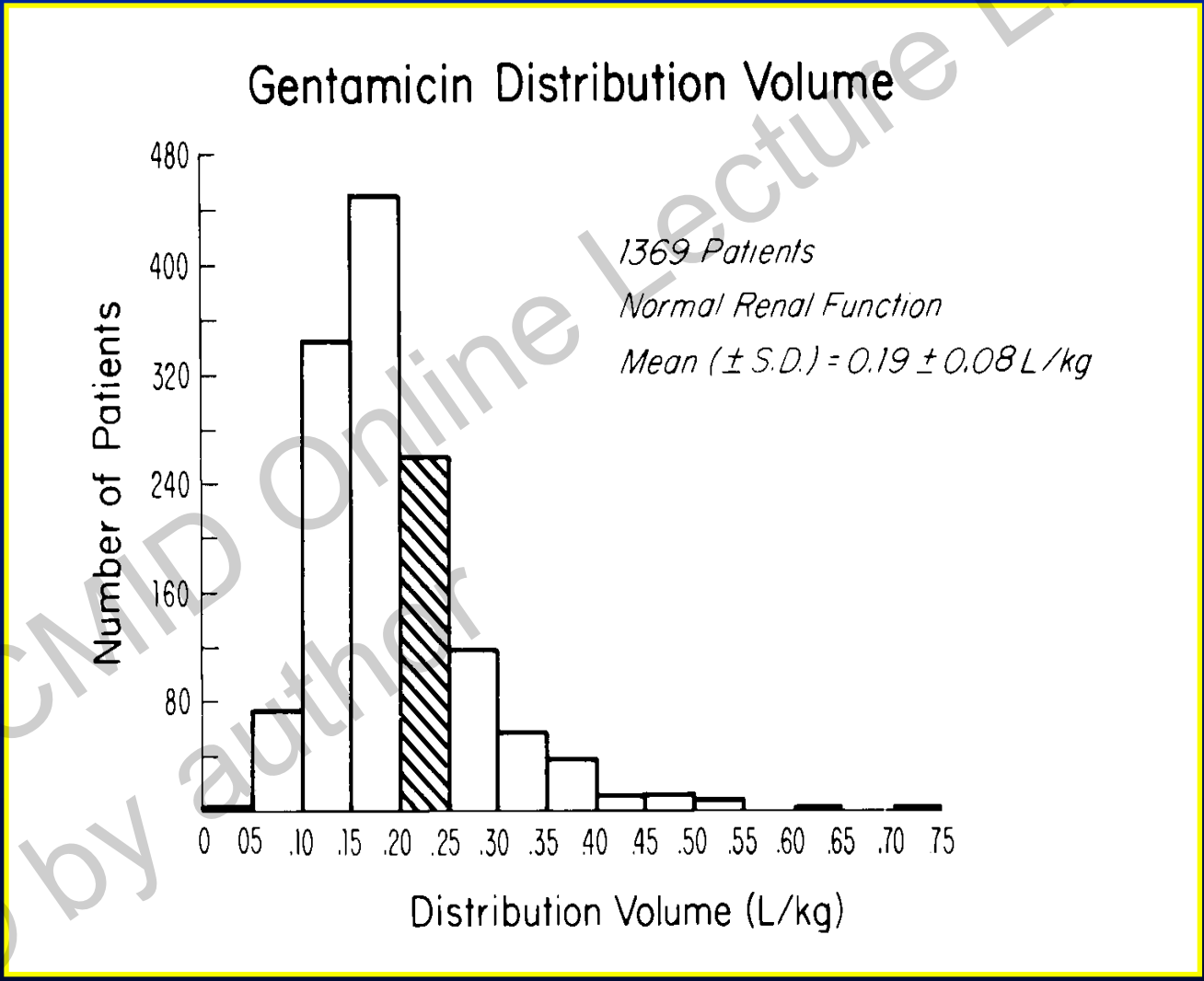
Group II (average weight 104 kg)

Vd = 19 L or 0.19 L/kg

Uptake into excess body mass is about 40 % of uptake into lean body mass Schwartz et al., 1976

Gentamicin

Volume of Distribution



Adjusted Body Weight (Dosing Weight)

Aminoglycosides

$$ABW = IBW + 0.4 \cdot (TBW - IBW)$$

ABW Adjusted Body Weight
IBW Ideal Body Weight
TBW Total Body Weight

Aminoglycosides Vd for Obese and Non-Obese patients

Reference	No. of subjects	Aminoglycoside	%IBW	Volume of distribution		Correction factor
				L/kg TBW	L/kg IBW	
Schwartz et al.	6	Gentamicin	176[a]	0.19 ± 0.03*	0.34 ± 0.09*	0.40
	6		100	0.24 ± 0.05	0.24 ± 0.05	
	7	Tobramycin	161[a]	0.23 ± 0.05*	0.37 ± 0.06*	0.40
	7		100	0.30 ± 0.03	0.30 ± 0.03	
Blouin et al.	9	Tobramycin	225	NR	0.44	0.58 ± 0.22
Bauer et al.	7	Amikacin	255	0.17 ± 0.02	0.42 ± 0.10	0.38 ± 0.18
Korsager	17	Gentamicin	183	NR	NR	0.43
	10		104			
Sketris et al.	30	Gentamicin	151*	0.15 ± 0.04*	0.23 ± 0.08*	0.30
	30		95	0.19 ± 0.06	0.19 ± 0.05	
Bauer et al.	12	Gentamicin	>190	0.17 ± 0.04*	0.41 ± 0.10*	0.45 ± 0.24
	12		NR[b]	0.25 ± 0.04	0.26 ± 0.05	
	10	Tobramycin	>190	0.19 ± 0.03*	0.45 ± 0.08*	0.37 ± 0.19
	10		NR[b]	0.26 ± 0.02	0.26 ± 0.03	
	8	Amikacin	>190	0.18 ± 0.02*	0.44 ± 0.09*	0.42 ± 0.20
	8		NR[b]	0.26 ± 0.03	0.26 ± 0.03	
Leader et al.	100	Gentamicin	151*	NR	NR	0.55
	100		103	NR	NR	
Traynor et al.	524	Gentamicin/tobramycin	>125	0.30 ± 0.12*	NR	0.43
	1119		75-124	0.35 ± 0.11	NR	

Clin Pharmacokinet 2000, 38 (5): 415-426.

Weight Calculation in Obesity

Measure	Formula
BMI	$BMI = TBW/[Ht(m) \times Ht(m)]$
IBW (Devine)	$IBW = 45.4 + [0.89 \times (Ht(cm) - 152.4)]$ (+4.5 if male)
EBW	$EBW = TBW - IBW$
LBW (Janmahasatian)	Males: $LBW = (9270 \times TBW) / [6680 + (216 \times BMI)]$ Female: $LBW = (9270 \times TBW) / [8780 + (244 \times BMI)]$
FFM	Males: $FFM = (TBW \times 0.285) + [12.1 \times Ht(m)^2]$ Females: $FFM = (TBW \times 0.287) + [9.74 \times Ht(m)^2]$
ABW	$ABW = IBW + [DWCF \times (TBW - IBW)]$ $ABW = IBW + (DWCF \times EBW)$
PNW	Males: $PNW = (TBW \times 1.57) - (TBW \times BMI \times 0.0183) - 10.5$ Females: $PNW = (TBW \times 1.75) - (TBW \times BMI \times 0.0242) - 12.6$
BSA Dubois and Dubois	$BSA = TBW^{0.425} \times Ht(cm)^{0.725} \times 0.007184$
BSA Mosteller	$BSA = \sqrt{[(Ht(cm) \times Wt)/3600]}$

ABW, adjusted body weight; DWCF, dosing weight correction factor; EBW, excess body weight; FFM, fat-free mass; Ht(cm), height (in centimetres); Ht(m), height (in metres); IBW, ideal body weight; LBW, lean body weight; PNW, predicted normal weight; TBW, total body weight; Wt, weight.

Curr Opin Infect Dis 2012, 25 (6): 634-649

Creatinine Clearance Calculations

CL_{CR} method	Equation
Cockcroft and Gault	$\frac{[(140 - age) \times TBW]}{(72 \times S_{CR})}$
Modified Cockcroft and Gault	$\frac{[(140 - age) \times IBW]}{(72 \times S_{CR})}$
Modified Cockcroft and Gault (C = 0.4)	$\frac{(140 - age) \times [IBW + C \times (TBW - IBW)]}{(72 \times S_{CR})}$
Salazar-Corcoran	Males: $\frac{(137 - age) \times [(0.285 \times TBW) + (12.1 \times Ht^2)]}{(51 \times S_{CR})}$
	Females: $\frac{(146 - age) \times [(0.287 \times TBW) + (9.74 \times Ht^2)]}{(60 \times S_{CR})}$
Jelliffe	Males: $(\frac{100}{S_{CR}}) - 12$
	Females: $(\frac{80}{S_{CR}}) - 7$

Clin Pharmacokinet 2000, 38 (5): 415-426.

Estimated GFR (eGFR) from MDRD Study

(Modification of Diet in Renal Disease)

- Derived from 1628 men and women with CKD
- GFR adjusted to BSA-accounts for different body sizes
- Standardized serum creatinine values

$$eGFR(ml/\min/1.73m^2) =$$

$$175 \cdot SCr_{std}^{-1.154} \cdot age^{-0.203} \cdot 0.742(female) \cdot 1.212(African-Americ$$

- Several versions available

SCr_{std}: serum creatinine from a standardized assay

Body Weight

Diazepam

Group I (average weight 61 kg)

Vd = 91 L or 1.5 L/kg

Group II (average weight 104 kg)

Vd = 292 L or 2.8 L/kg

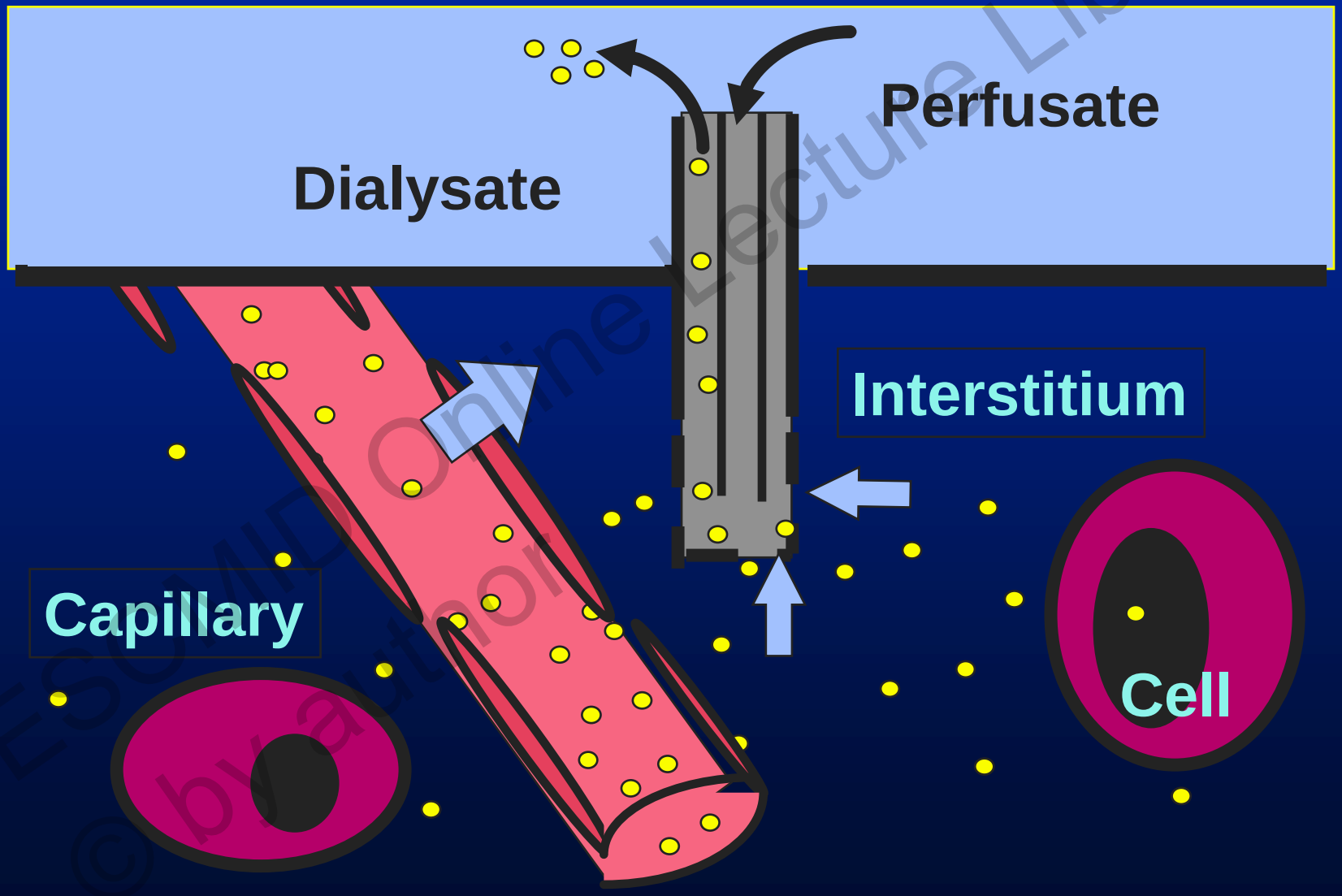
Uptake into excess body mass is much higher than uptake into lean body mass

Antibiotics in Obesity

	Hydrophilic antibiotics	Lipophilic antibiotics
Pharmacokinetics	• Generally have low volume of distribution. • Are primarily cleared in kidneys. • Have lower intracellular and tissue penetration.	• Generally have high volume of distribution. • Are primarily cleared in the liver. • Have higher intracellular and tissue penetration.
Changes in obesity	• Obesity has little effect of the antibiotic volume of distribution. • Renal clearance is generally increased in obesity unless renal impairment is present.	• Obesity increases the antibiotic volume of distribution. • Obesity have variable effects on hepatic clearance.
Dosing in obesity	Ideal or adjusted body weight is generally used for dosing[a].	Total body weight is generally recommended for dosing[a].
Examples of antibiotics	β-lactams (penicllins, cephalosporins, carbapenems) Aminoglycosides Vancomycin Colistin	Fluoroquinolones Macrolides Tigecycline

Curr Opin Infect Dis 2013, 27 (2): 165-173

Microdialysis



Soft tissue penetration of cefuroxime determined by clinical microdialysis in morbidly obese patients undergoing abdominal surgery

April Barbour[a,1], Stephan Schmidt[a,1], W. Robert Rout[b], Kfir Ben-David[b], Olaf Burkhardt[c], Hartmut Derendorf[a,*]

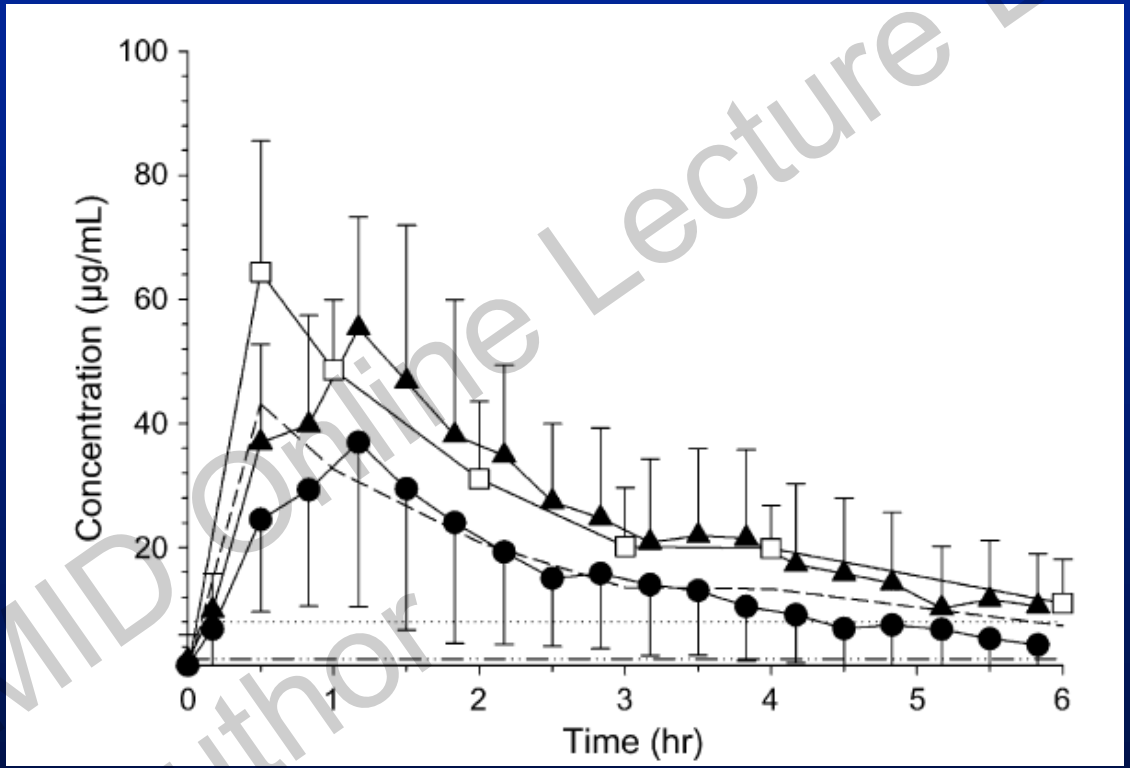
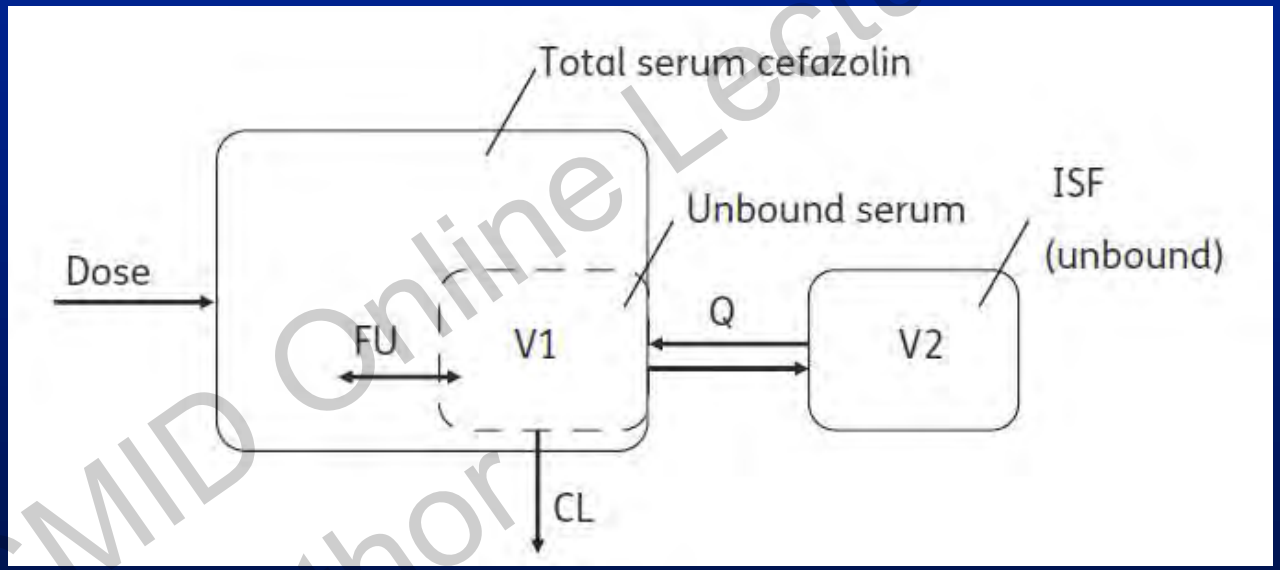


Figure: Mean concentration–time profile in plasma (square, solid line), free plasma (dashed line) and in the interstitial space fluid (free) of skeletal muscle (triangle, solid line) and subcutaneous adipose tissue (circle, solid line) of cefuroxime administered as a 1.5 g short-term intravenous infusion within 1 h of incision.

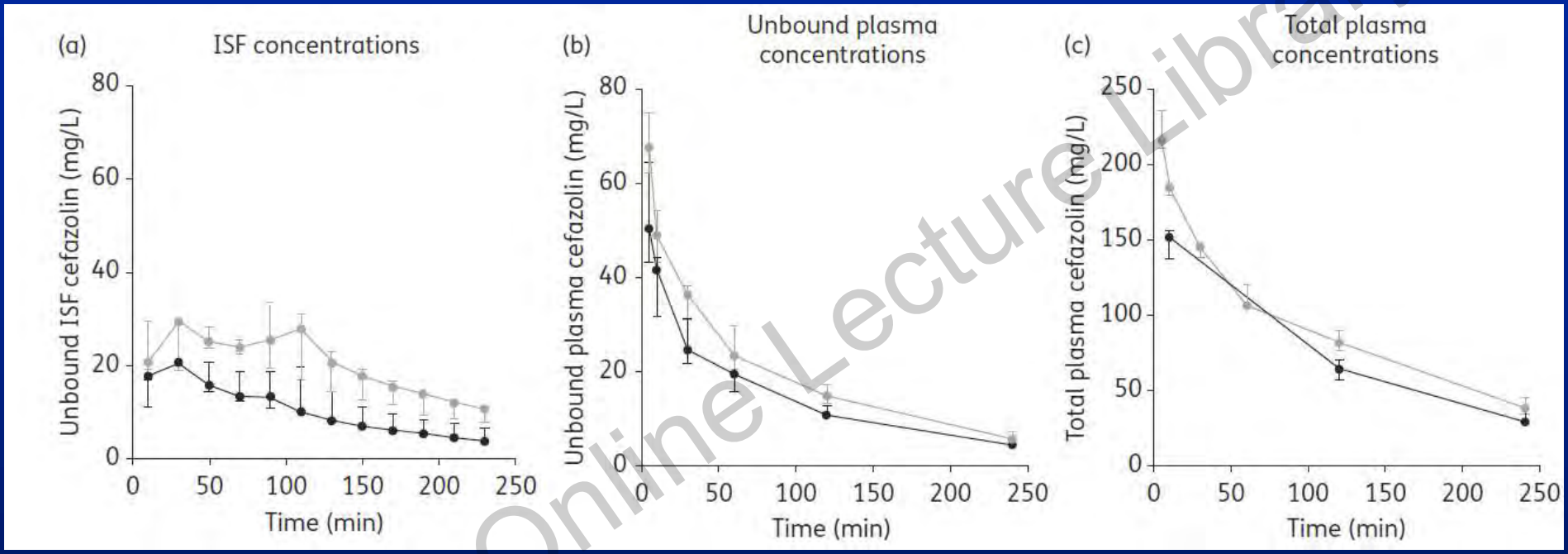
Int J Antimicrob Agents 2009, 34: 231-235

Reduced subcutaneous tissue distribution of cefazolin in morbidly obese versus non-obese patients determined using clinical microdialysis

Margreke J. E. Brill[1,2], Aletta P. I. Houwink[3], Stephan Schmidt[4], Eric P. A. Van Dongen[3], Eric J. Hazebroek[5], Bert van Ramshorst[5], Vera H. Deneer[2], Johan W. Mouton[6] and Catherijne A. J. Knibbe[1,2]*



J Antimicrob Chemother 2014; 69: 715–723

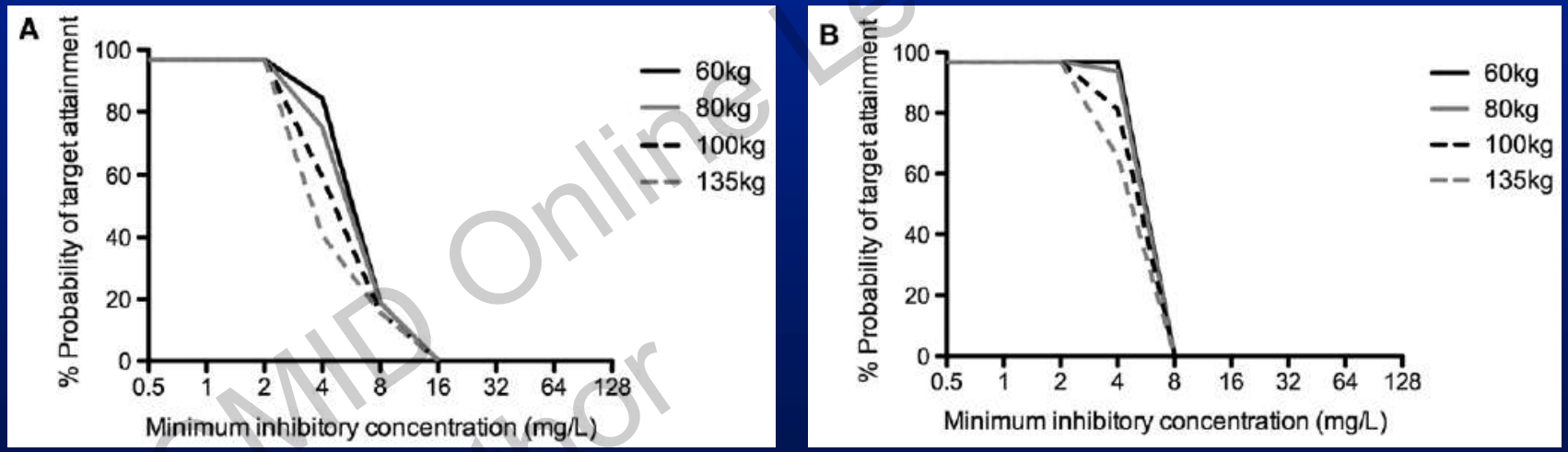


Observed cefazolin concentrations (median+IQR) in **morbidly obese (black symbols)** and **non-obese (grey symbols)** in (a) Subcutaneous ISF cefazolin. (b) Unbound plasma cefazolin. (c) Total plasma cefazolin.

J Antimicrob Chemother 2014; 69: 715–723

Optimal Doripenem Dosing Simulations in Critically Ill Nosocomial Pneumonia Patients With Obesity, Augmented Renal Clearance, and Decreased Bacterial Susceptibility*

Jason A. Roberts, PhD[1,2,3]; Jeffrey Lipman, FCICM, MD[1,3]

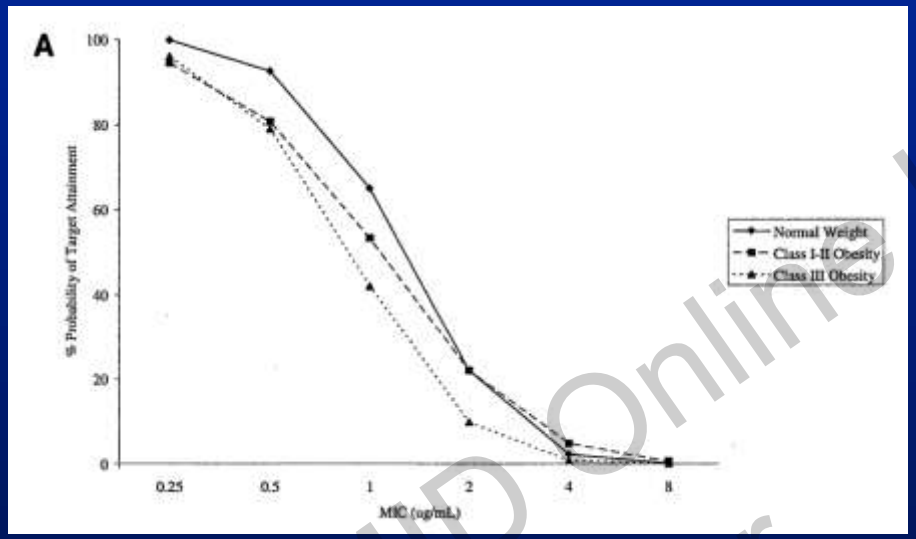


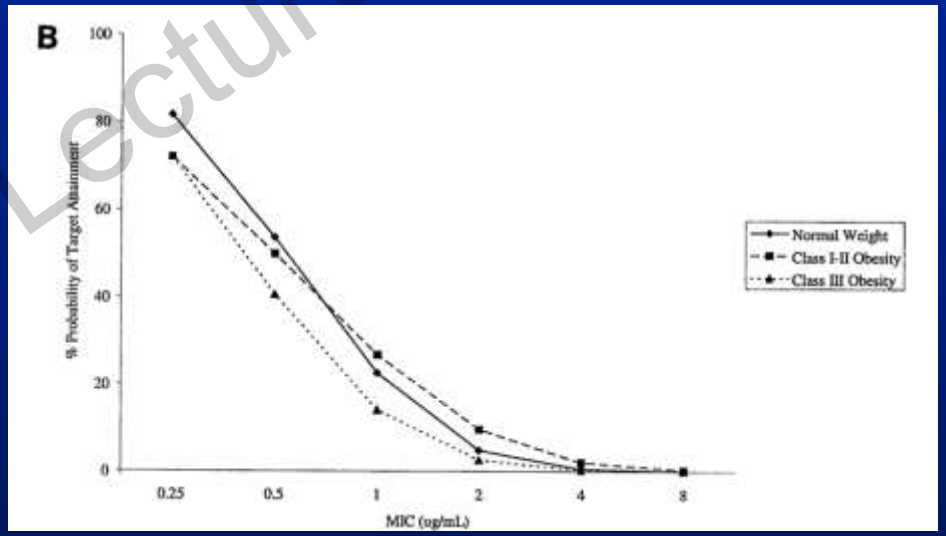
The probability of target attainment for achieving 40% *f* T>MIC for various simulated patient weights for 500 mg IV doripenem doses administered as **(A) 1-hr infusion** or **(B) 4-hr infusion** to patients with a glomerular filtration rate of 100 mL/min against a theoretical minimum inhibitory concentration range.

Crit Care Med 2013; 41 (2): 489-495

Comparative Pharmacokinetics and Pharmacodynamic Target Attainment of Ertapenem in Normal-Weight, Obese, and Extremely Obese Adults

M. Chen,[1,2] A. N. Nafziger,[1,2] G. L. Drusano,[3] L. Ma,[3] and J. S. Bertino, Jr.[1,2]*





Percent probability of attaining the **target of 20% (A)** or **40% (B) for fT >MIC** with a single 1-gram dose of ertapenem at MICs of 0.25, 0.5, 1, 2, 4, and 8 g/ml in normal-weight, class I-II obese, and class III obese groups.

Antimicrob Agents Chemother 2006, 50: 1222-1227

Vancomycin PK Parameters in Obese and Non-Obese Patients

Reference	No. of subjects	TBW (kg)	IBW (kg)	Volume of distribution		Clearance		
				L/kg TBW	L/kg IBW	ml/min	ml/min/kg IBW	ml/min/kg TBW
Blouin et al	6	165.7[a]	63.5[a]	0.26 ± 0.03	0.68 ± 0.07	187.50 ± 64.69	2.90 ± 0.61	1.11 ± 0.16
	4	74.6[a]	72.7[a]	0.39 ± 0.06	NR	80.78 ± 11.28	1.09 ± 0.07	1.09 ± 0.07
Ducharme et al.	108	94.3*	59.7*	0.56*	0.89*	74.4[b]	NR	NR
	559	70.4	69.0	0.64	0.65	81.0		
Bauer et al.	24	165 ± 46**	63 ± 14	0.32 ± 0.05**	0.83 ± 0.08**	197 ± 77**	3.1 ± 0.7**	1.2 ± 0.2[b]
	24	68 ± 6	64 ± 9	0.68 ± 0.24	0.64 ± 0.26	77 ± 22	1.0 ± 0.4	1.1 ± 0.3

a Calculated from data presented in original manuscript.

b Not significantly different from group immediately below ($p > 0.05$).

IBW = ideal bodyweight; **NR** = not reported; **TBW** = total bodyweight; * $p \leq 0.05$ compared with group immediately below; ** $p \leq 0.001$ compared with group immediately below.

Vd=0.178·age+0.22·TBW+15 [L]

Clin Pharmacokinet 2000, 38 (5): 415-426.

Vancomycin Pharmacokinetics in Normal and Morbidly Obese Subjects

ROBERT A. BLOUIN,[1] LARRY A. BAUER,[3]* DELWYN D. MILLER,[1] KENNETH E. RECORD,[1] AND WARD O. GRIFFEN, JR.[2]

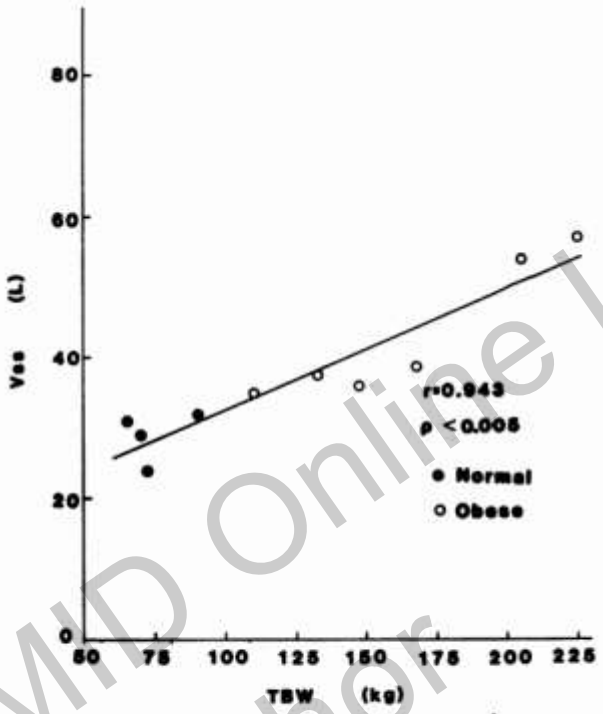


FIG. 1. Relationship between V_{ss} of vancomycin and TBW in morbidly obese and normal patients. The equation for the regression line is: V_{ss} = 0.173 (TBW) + 15.1.

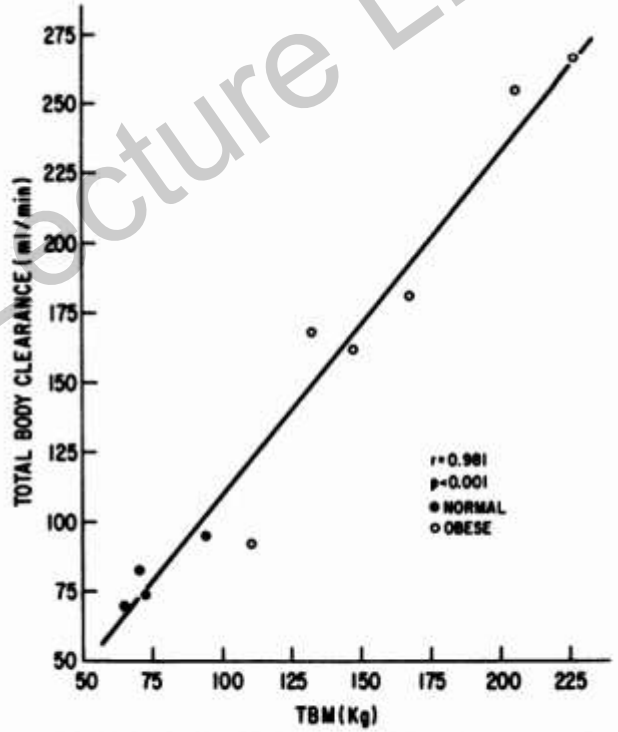


FIG. 2. Relationship between Cl_T of vancomycin and TBW in morbidly obese and normal patients. The equation for the regression line is: Cl_T = 1.251 (TBW) − 16.84.

Antimicrob Agents Chemother 1982, 21:575-580

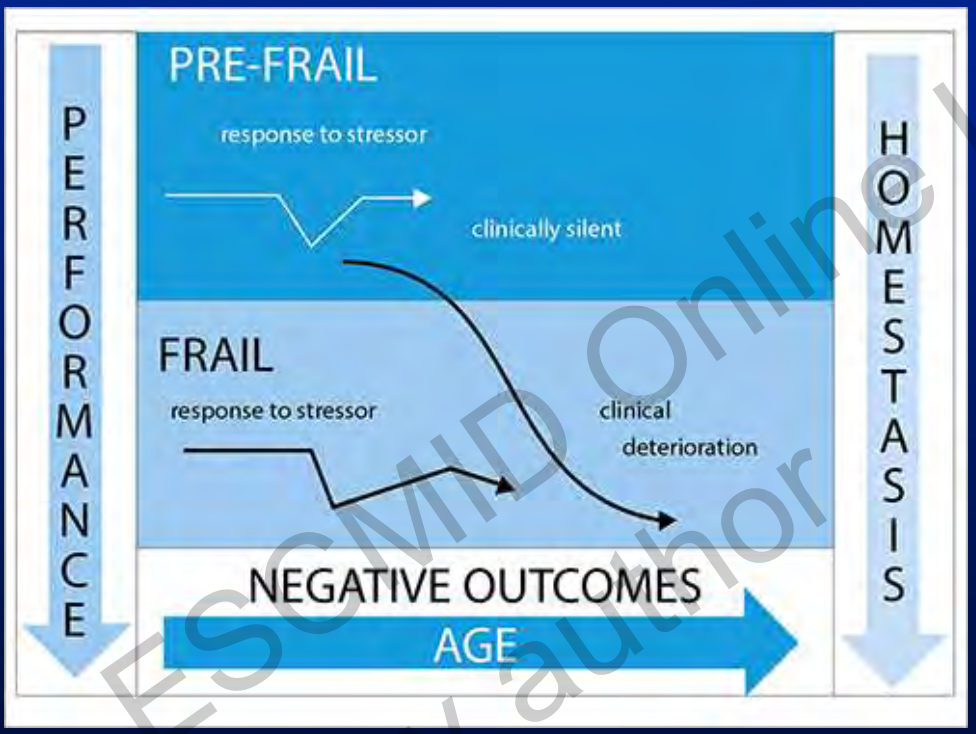
Dose Adjustment in Obese Patients

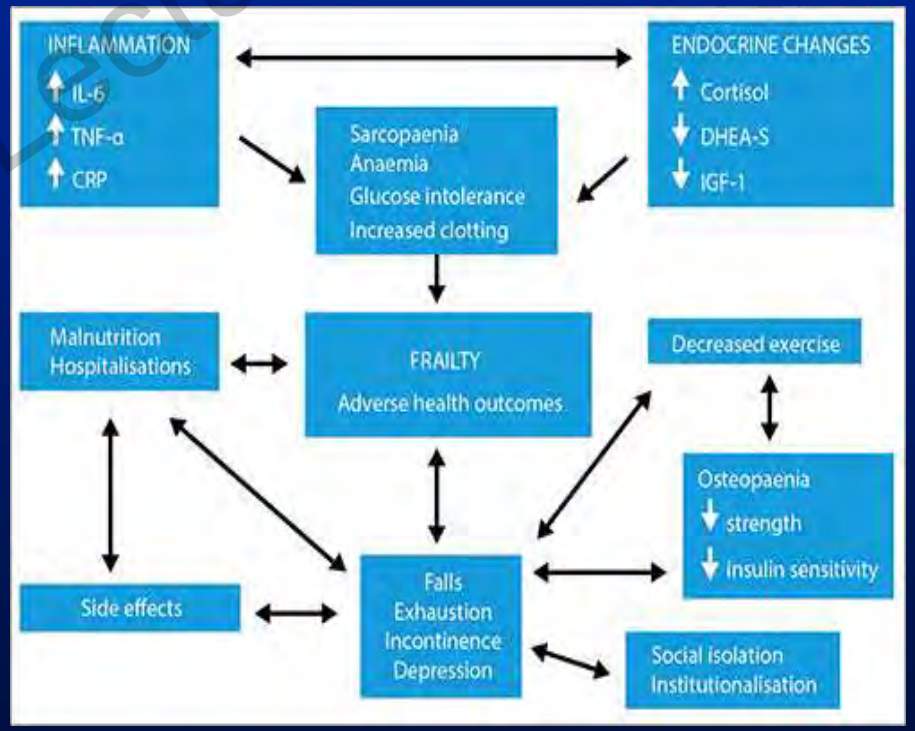
Class	Antibiotic	PK/PD-Index	Obese / Normal Doses
Aminoglycosides	Gentamicin	C_{max}/MIC	**540 mg/d / 380 mg/d**
Glycopeptides	Vancomycin	AUC_{24h}/MIC	**15-20 mg/kg / 5-7 mg/kg**LD
Penicillins	Piperacillin	T>MIC	**4.5-5 g q6h / 3-4 g q6h**
Cephalosporins	Cephazolin	T>MIC	**2 g q4-5 h / 1 g q4-5 h**
Carbapenems	Ertapenem	T>MIC	**>1 g/day / 1 g/day**
Lipopeptides	Daptomycin	AUC_{24h}/MIC	**6 mg/kg** / 4 mg/ kg
Fluoroquinoliones	Ciprofloxacin	AUC_{24h}/MIC	**800 mg q12h / 400 mg q12hr**

Curr Opin Infect Dis 2012, 25 (6): 634-649

Frailty

"Is a state of 'weakness' where there is an increased vulnerability to adverse outcomes and where minor physiological stressors can lead to progressive deterioration".





PK Changes in Frail Patients - Use of Antibiotics

Volume of distribution

- Prolonged half life
- Increased plasma concentration
- Changes in protein binding changes

Drug metabolism

- Half life changes for hepatically cleared drugs
- Enzyme induction/inhibition

Renal drug elimination

- Half life changes
- Drug accumulation in the plasma

Dose Optimization

Drugs Aging 2007; 24 (4): 275-292

Dose Adjustment of Antibiotics in Patients with Pneumonia and Impaired Renal Functions

Antibiotic	Renal function	
	Moderately compromised (CLCr 30–50 mL/min)	Severely compromised (CLCr <30 mL/min)
Azitromicin	500 mg q24 h	500 mg q24 h
Cefotaxime	2 g q6–8 h	1 g q6–8 h
Ceftazidime	1 g q8–12 h	0.5 g q12 h
Cefepime	1 g q8–12 h	0.5 g q12 h
Ceftriaxone	2 g q12–24 h	2 g q12–24 h
Ciprofloxacin	400 mg q8 h, 600 mg q12 h IV, 750 mg q12 h OS	400 mg q8 h, 600 mg q12 h IV, 750 mg q12 h OS
Claritromicin	500 mg q12 h	250 mg q12 h
Imipenem	250 mg q6 h or 500 mg q8 h	125 mg q6 h or 250 mg q8 h
Levofloxacin	500 mg q24 h	500 mg q48 h
Linezolid	600 mg q12 h	600 mg q12 h
Meropenem	250 mg q6 h or 500 mg q8 h	125 mg q6 h or 250 mg q8 h
Metronidazole	500 mg q8 h	500 mg q8 h
Moxifloxacin	400 mg q24 h	400 mg q24 h
Piperacillin/tazobactam	3/0,375 g q6 h	2/0.25 g q6 h
Teicoplanin	LD 12 mg/kg q12 h for 3 doses → 2–4 mg/kg q12 h	LD 12 mg/kg q12 h for 3 doses → 2–4 mg/kg q24 h
Vancomycin	LD 15 mg/kg → 7.5–15 mg/kg/die	LD 15 mg/kg → 5–7.5 mg/kg/die

Intern Emerg Med 2012, 7: 415-424

Challenges and Limitations

- **Obesity**
  - Difficult dosing extrapolation between healthy obese and sick obese patient population or critically ill patients
  - Dosing differences between different classes of obese patients
  - Type or location of infection may require change in dosing of the antibiotics
  - Development of resistance due to inadequate dosing regimens
- **Frailty**
  - Resistant bacterial strains due to inadequate use of antibiotics
  - Previous antibiotic history
  - Polypharmacy and number of physiological changes