Antibioticoterapia nel paziente obeso

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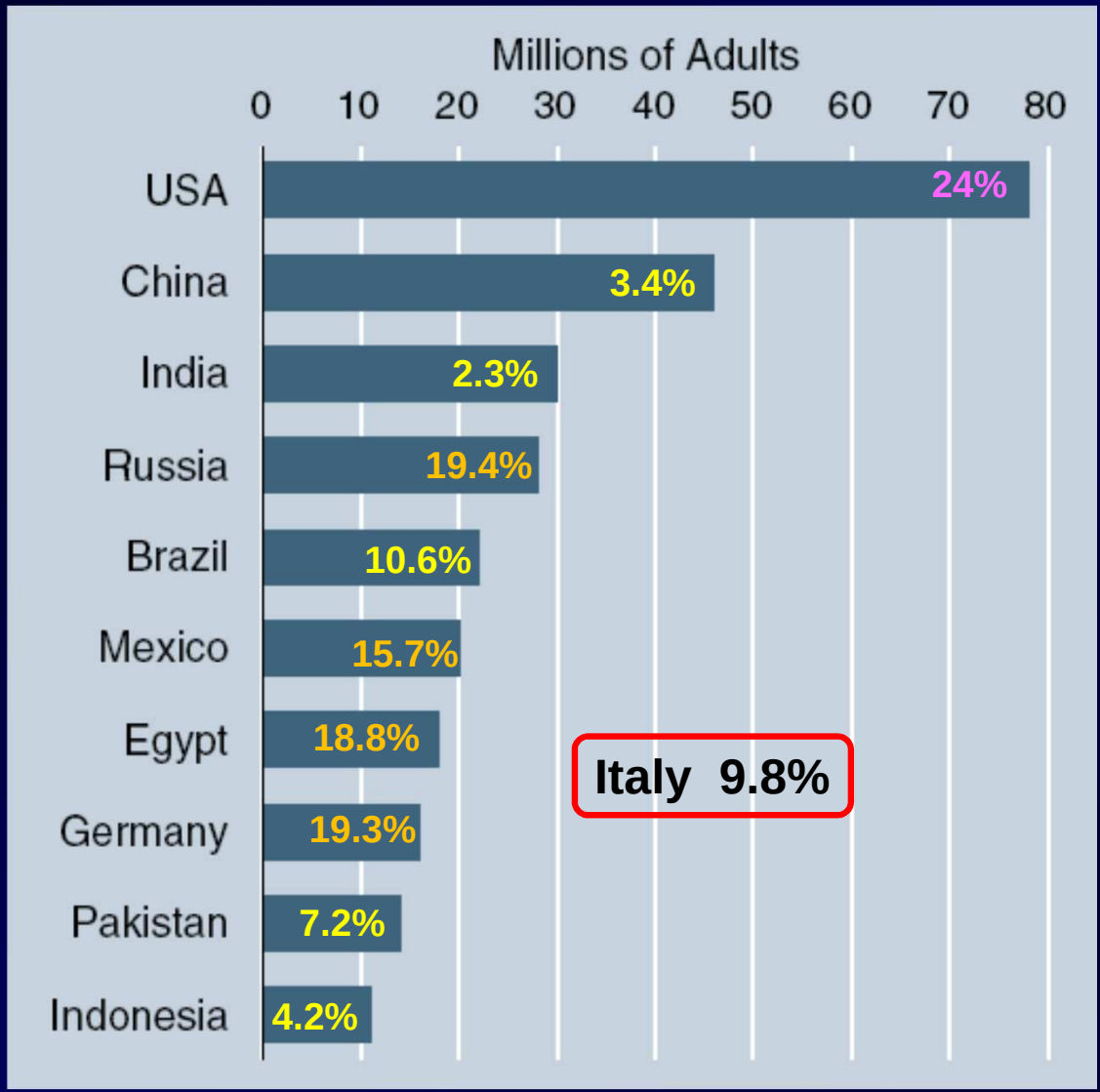
Transparency Declaration

Honoraria or grant support received from:

- **Angelini**
- **MSD**
- **Valeas**
- **Zambon Group**

Top ten countries for obese adults



Pai MP, Curr Opin Pharmacol, 2015, mod

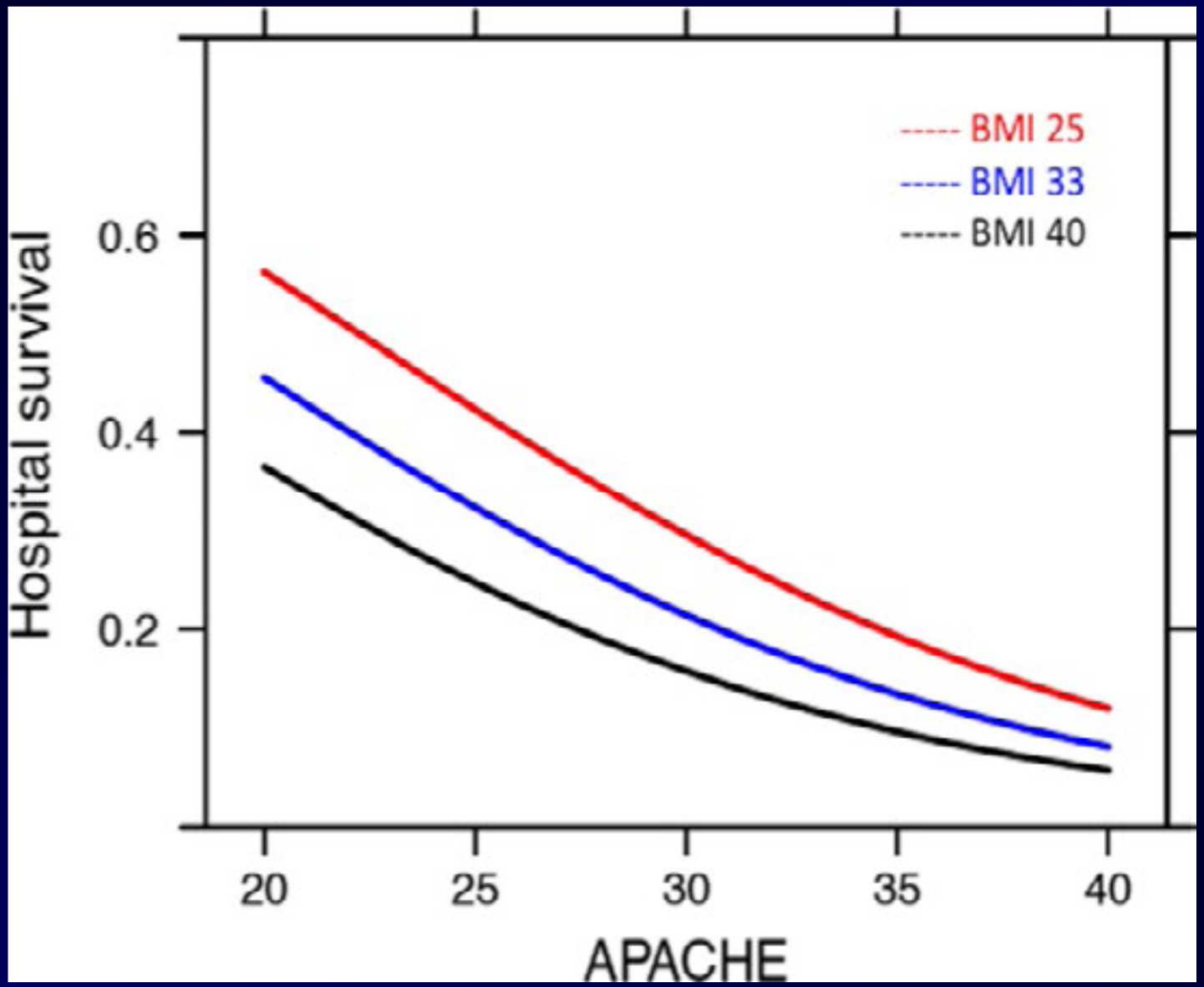
Obesity classification

	BMI	IBW
Underweight	< 18.5	< 80%
Normal weight	18.5 – 24.99	80 – 125%
Overweight	25 – 29.99	126 – 190%
Obese class I	30 – 34.99	126 – 190%
Obese class II	35 – 39.99	126 – 190%
Obese class III or morbid obesity	40 – 49.9	> 190%
Super obesity	> 50	> 190%

BMI = body mass index; IBW = ideal body weight

Al-Dorzi HM et al., Curr Opin Infect Dis, 2014

Predicted survival according to BMI level



Kok B et al., Liver International, 2017

Weight descriptor formulae

BMI = weight in kg/(height in m)^2

IBW for men = 50kg + 2.3 kg for each inch above 60 inches of height
IBW for women = 45.5kg + 2.3kg for each inch above 60 inches of height

ABW = IBW + [(C) x (TBW – IBW)]
C = correction factor, for hydrophilic drugs (0.37 – 0.58), average 0.4

Estimated LBW (kg) for men = (9270 x TBW)/(6680 + 216 x BMI)
Estimated LBW (kg) for women = (9270 x TBW)/(8780 + 244 x BMI)

ABW, adjusted body weight; BMI, body mass index; IBW, ideal body weight; LBW, lean body weight; TBW, total body weight

Al-Dorzi HM et al., Curr Opin Infect Dis, 2014

PK/PD properties that correlate with efficacy

	Pharmacodynamic kill characteristics		
	Time dependent	**Concentration dependent**	**Concentration dependent with time dependence**
Antibiotic	Penicillins Cephalosporins Carbapenems Natural macrolides Clindamycin Oxazolidinones	Aminoglycosides Fluoroquinolones Fosfomycin Metronidazole Daptomycin	Fluoroquinolones Aminoglycosides Fosfomycin Colistin Glycopeptides Semisynthetic macrolides Tetra- and Glycilcyclines Oxazolidinones
Optimal PK/PD index	**T > MIC**	**C_{max}/MIC**	**AUC_{0-24}/MIC**
Objective	Maximise duration of exposure	Maximise concentration	Maximise amount of drug exposure
Measures	Frequent administration or prolonged infusion dosing	Infrequent (once daily) administration of high doses	Administration of a high total daily dose

Osthoff M et al., Swiss Med Wkly, 2016, mod

Antibiotics

Changes in PK parameters

Increased PK parameters

Increased Vd

- Increased excess mass (adipose and lean tissue) – larger change with lipophilic vs hydrophilic drugs
- Hypoalbuminemia*
- Sepsis*
- Third spacing, edema*
- Fluid resuscitation*

Decreased Vd

- Increased renal blood flow
- Increased GFR
- Increased kidney mass
- Augmented renal clearance (ARC)*

NFLD (affects drugs that are substrates of CYP2E1 and undergo xanthine oxidase or N-acetyltransferase reactions)

Decreased CL

- Age or obesity-related nephropathy
- Vascular disease, decreased cardiac output, decreased tissue perfusion
- NFLD (affects drugs that are metabolized by CYP3A4)
- Renal impairment, AKI, RRT*
- Hepatic impairment*

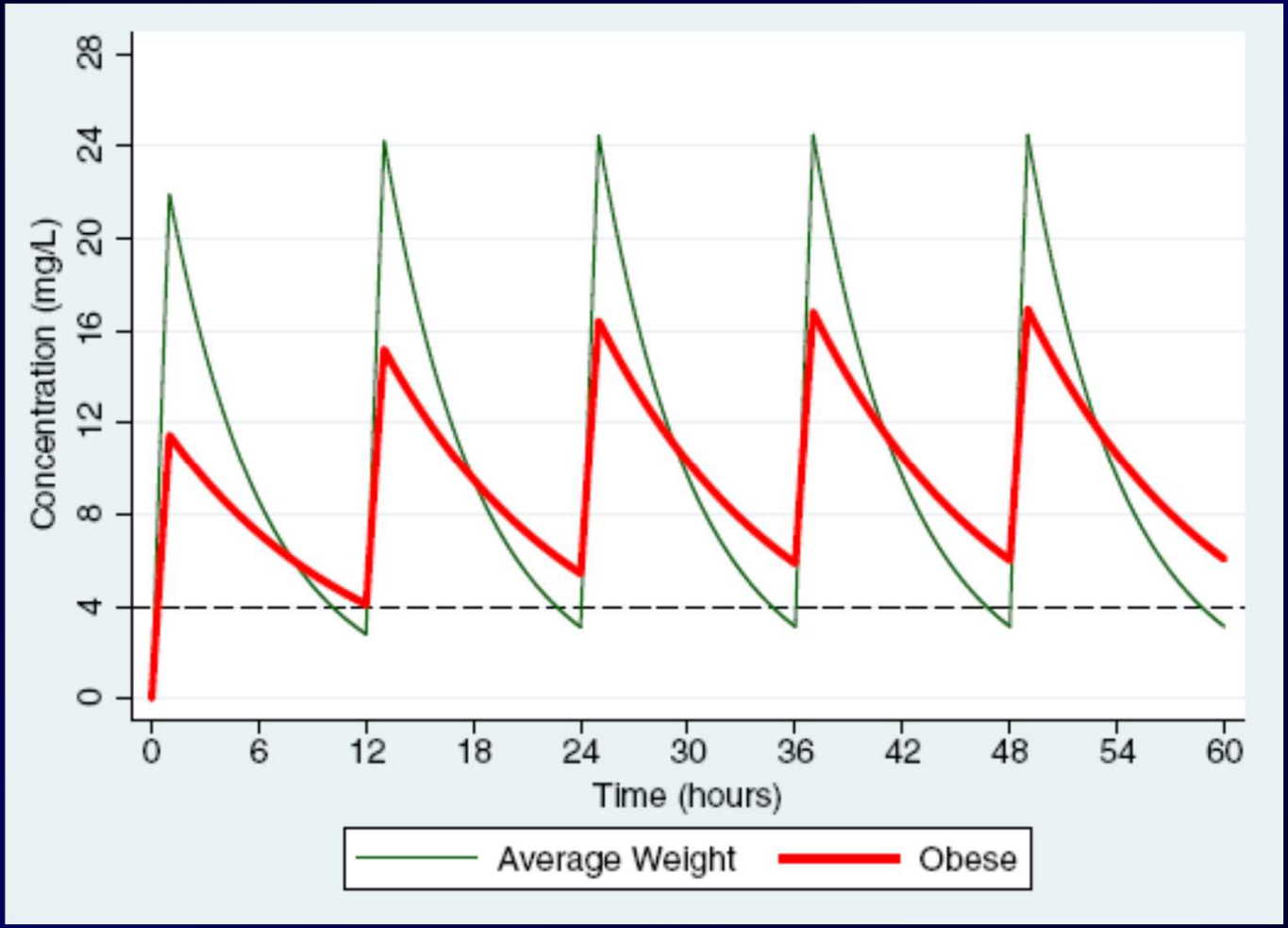
Decreased PK parameters

*Additional factors as commonly described in a critically ill population. AKI = acute kidney injury; NFLD = nonalcoholic fatty liver disease; RRT = renal replacement therapy

Meng L et al., Pharmacotherapy, 2017

Antimicrobial drugs*

Vd 50% increase & no drug clearance change



*** 600mg BID 1h infusion**

Pai MP, Curr Opin Pharmacol, 2015

Obese patients

Altered physiological and pharmacokinetic factors

DISTRIBUTION

Little/no change in volume of distribution expected if

- Large molecular size
- Highly ionized
- Highly protein bound
- Poorly crosses biological membranes

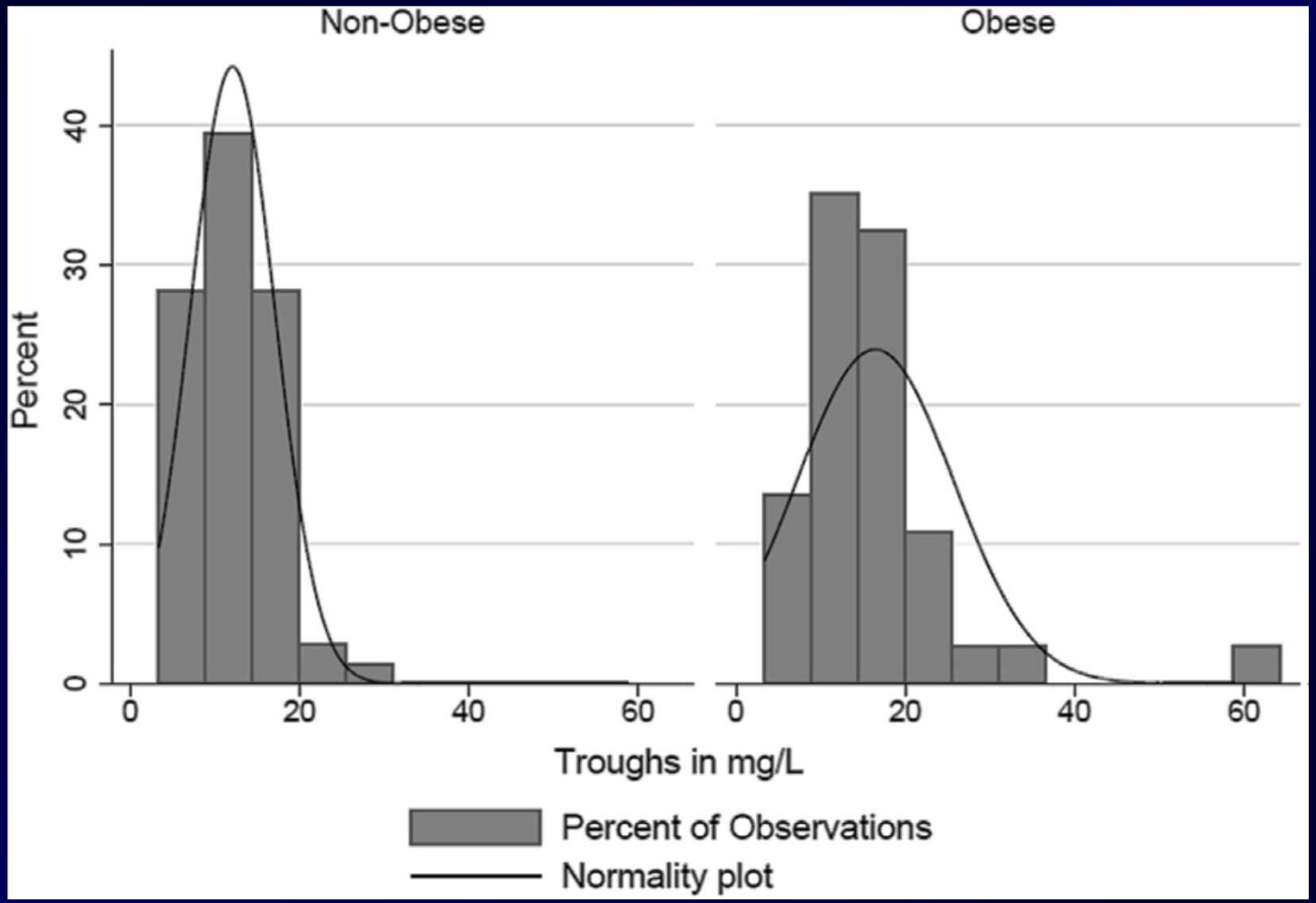
Increase in volume of distribution expected if

- Small molecular size
- Minimally ionized
- Minimally protein bound
- Easily crosses biological membranes

Polso AK et al., J Clin Pharm Ther, 2014

Vancomycin in obese patients

Histogram of trough distributions



Richardson J et al., J Infect Chemother, 2015

Vancomycin in 108 pts

PK characteristics of obese vs non-obese pts

	Obese (n = 37)	Non-obese (n = 71)	*P* value
Trough (mg/l), mean (SD)	16.5 (9.2)	12.1 (5.0)	0.004
Trough < 15 mg/l, n (%)	21 (56.8)	49 (69.0)	0.21
Trough > 20 mg/l, n (%)	7 (18.9)	3 (4.2)	0.03
Dose (mg/kg/day), mean (SD)	23.9 (7.3)	26.0 (8.7)	0.18
Estimated PK parameters, mean (SD)			
Cl_{van} (l/h)	4.7 (1.3)	4.4 (1.4)	0.34
VD (l)	74.4 (14.5)	50.4 (9.3)	< 0.001
T½ (h)	11.8 (3.7)	8.5 (2.5)	< 0.001
Estimated t½ elapsed prior to trough, mean (SD)	5.1 (2.1)	6.6 (2.8)	< 0.001
% steady state achieved, mean (SD)	94.6 (4.4)	97.5 (2.6)	< 0.001

Richardson J et al., J Infect Chemother, 2015

Vancomycin trough concentration

Overweight/obese pediatric patients vs controls

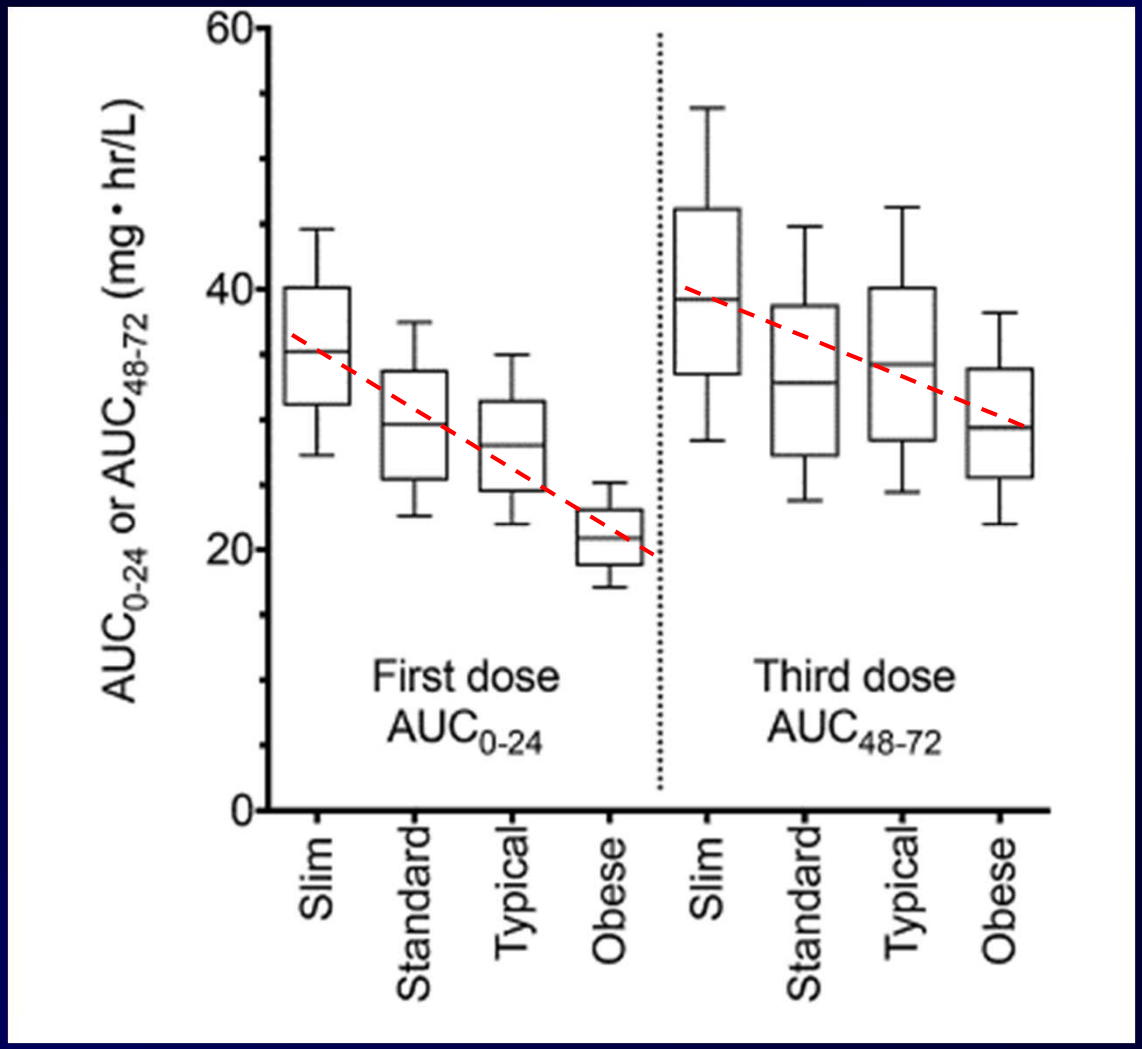
	NBH (%) (n = 84)	Overweight (%) (n = 21)	Obese (%) (n = 21)	*P* value
Below target range (< 10 mg/l)	43 (51)	6 (29)	2 (10)	0.001
Within target range (10 – 20 mg/l)	39 (46)	12 (57)	15 (71)	0.109
Above target range (> 20 mg/l)	2 (2)	3 (14)	4 (19)	0.011

NBH = normal body habitus

Heble DE et al., Pharmacotherapy, 2013

Moxifloxacin

Effect of BW on AUC values

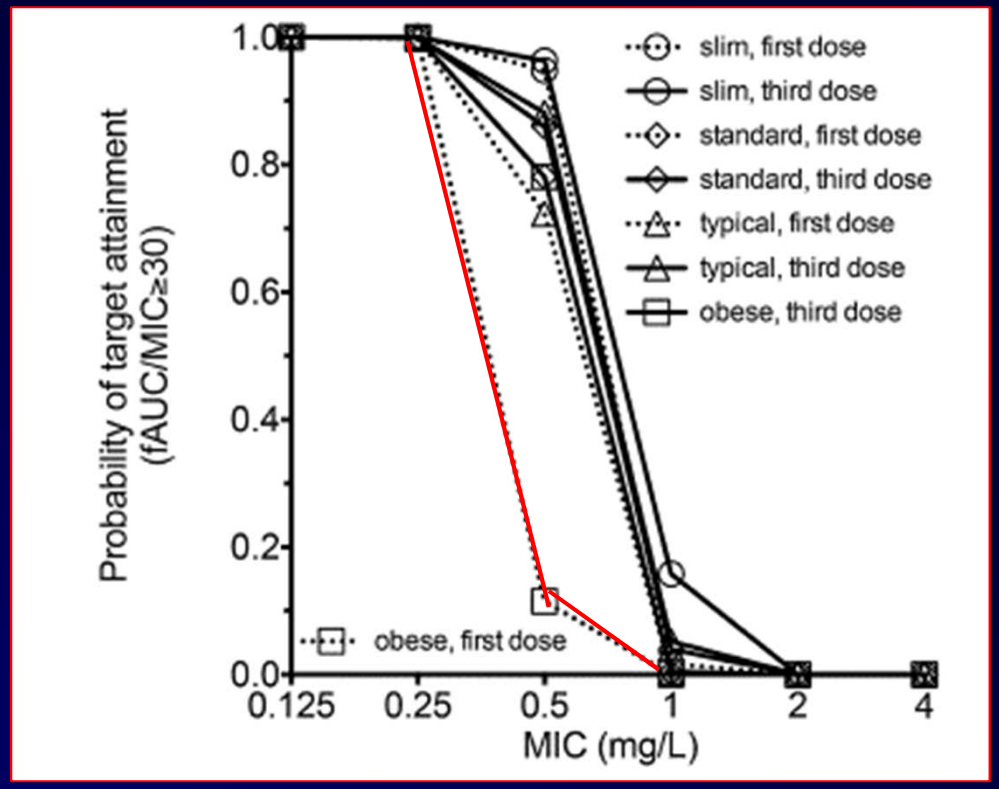


Wicha SG et al., J Clin Pharmacol, 2015

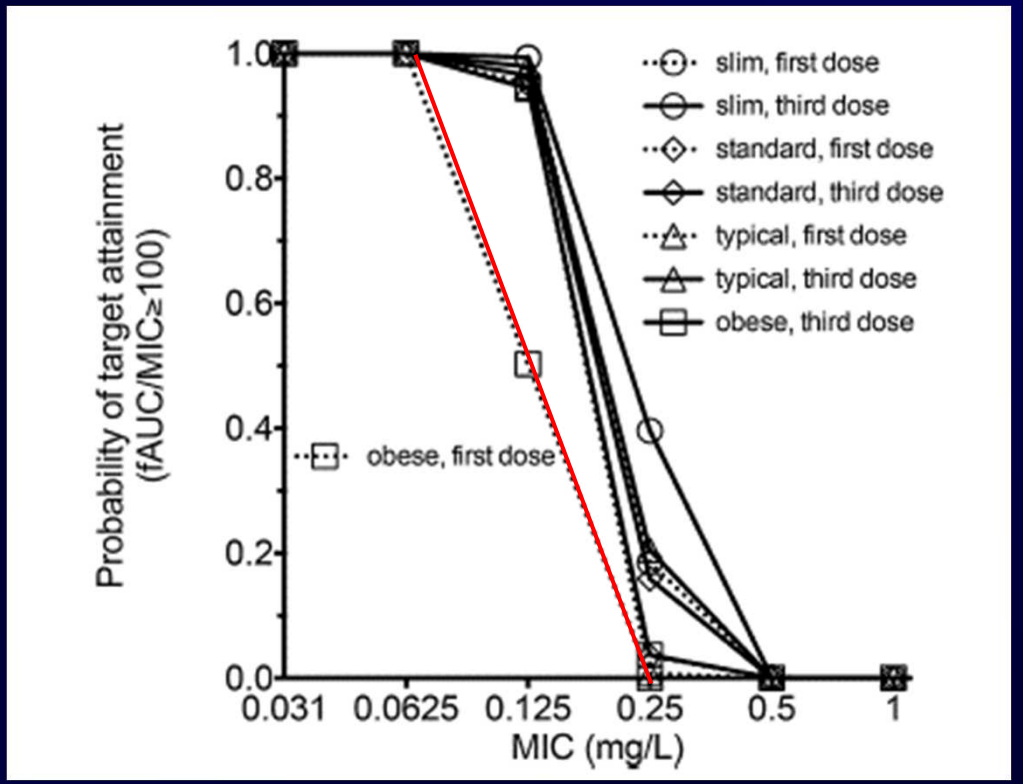
Moxifloxacin

Effect of BW on PTA values

Gram-positive



Gram-negative



Wicha SG et al., J Clin Pharmacol, 2015

	Hydrophilic antibiotics	Lipophilic antibiotics
Pharmacokinetics	• Generally low Vd • Primarily cleared in kidneys • Lower intracellular and tissue penetration	• Generally high Vd • Primarily cleared in the liver • Higher intracellular and tissue penetration
Changes in obesity	• Little effect on the antibiotic Vd • Renal clearance generally increased unless renal impairment is present	• Increase of the antibiotic Vd • Variable effects on hepatic clearance
Dosing in obesity	• Ideal or adjusted body weight is generally used for dosing	• Total body weight is generally recommended for dosing
Examples of antibiotics	• β-lactams (penicillins, cephalosporins, carbapenems) • Aminoglycosides • Vancomycin • Colistin	• Fluoroquinolones • Macrolides • Tigecycline

Al-Dorzi HM et al., Curr Opin Infect Dis, 2014

Obese patients

Altered physiological and pharmacokinetic factors

METABOLISM

Increased fatty infiltration of liver

- Altered blood flow and metabolism ; Change in activity level of cytochrome P450 enzymes

ELIMINATION

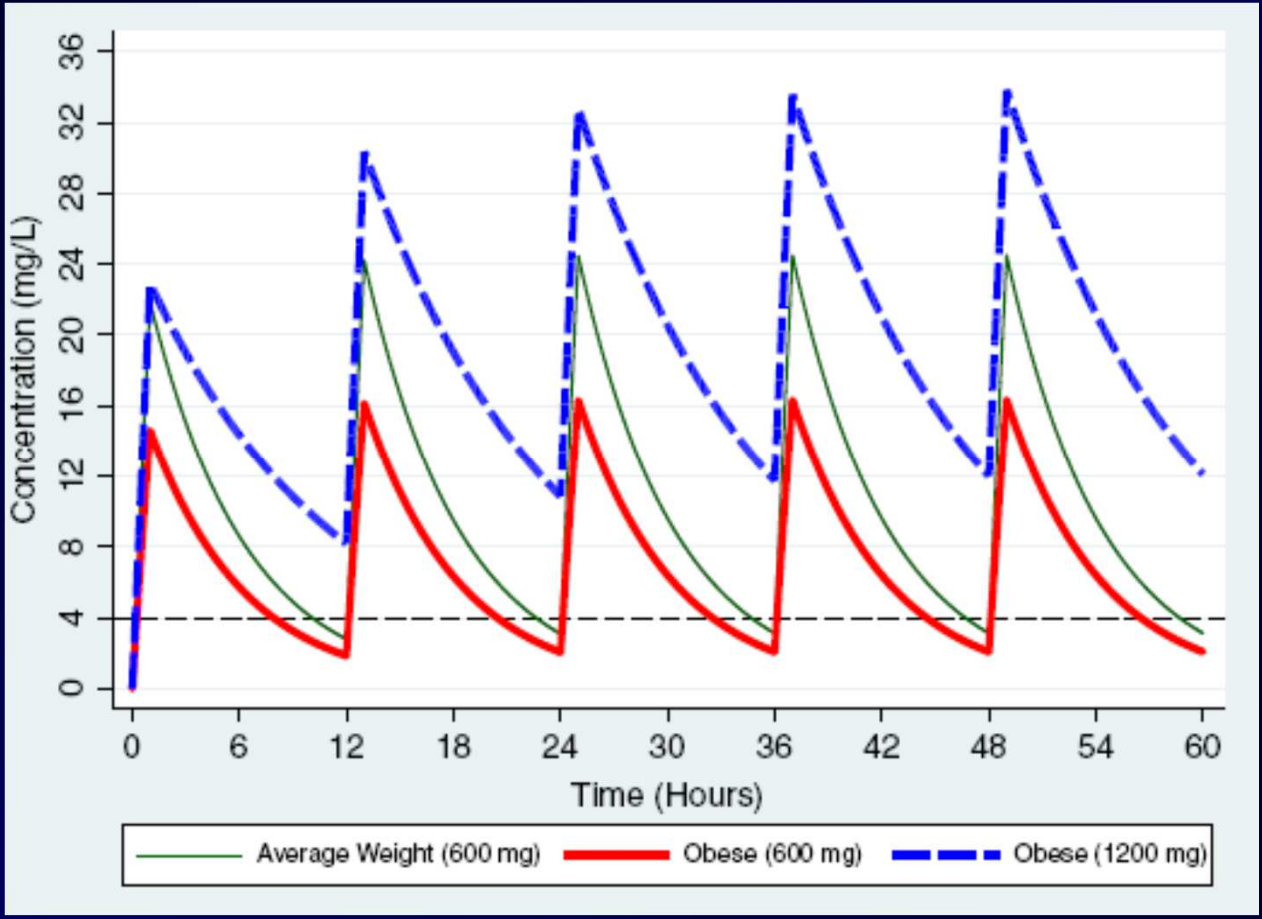
Variable effects on kidney function

- Increased glomerular filtration rate in healthy obese patients
- Possible kidney dysfunction with comorbid conditions

Polso AK et al., J Clin Pharm Ther, 2014

Antimicrobial drugs*

Vd and Cl changes



*** 600 or 1200mg BID 1h infusion**

Pai MP, Curr Opin Pharmacol, 2015

Vancomycin median 1500mg/24h in a non-critical care setting

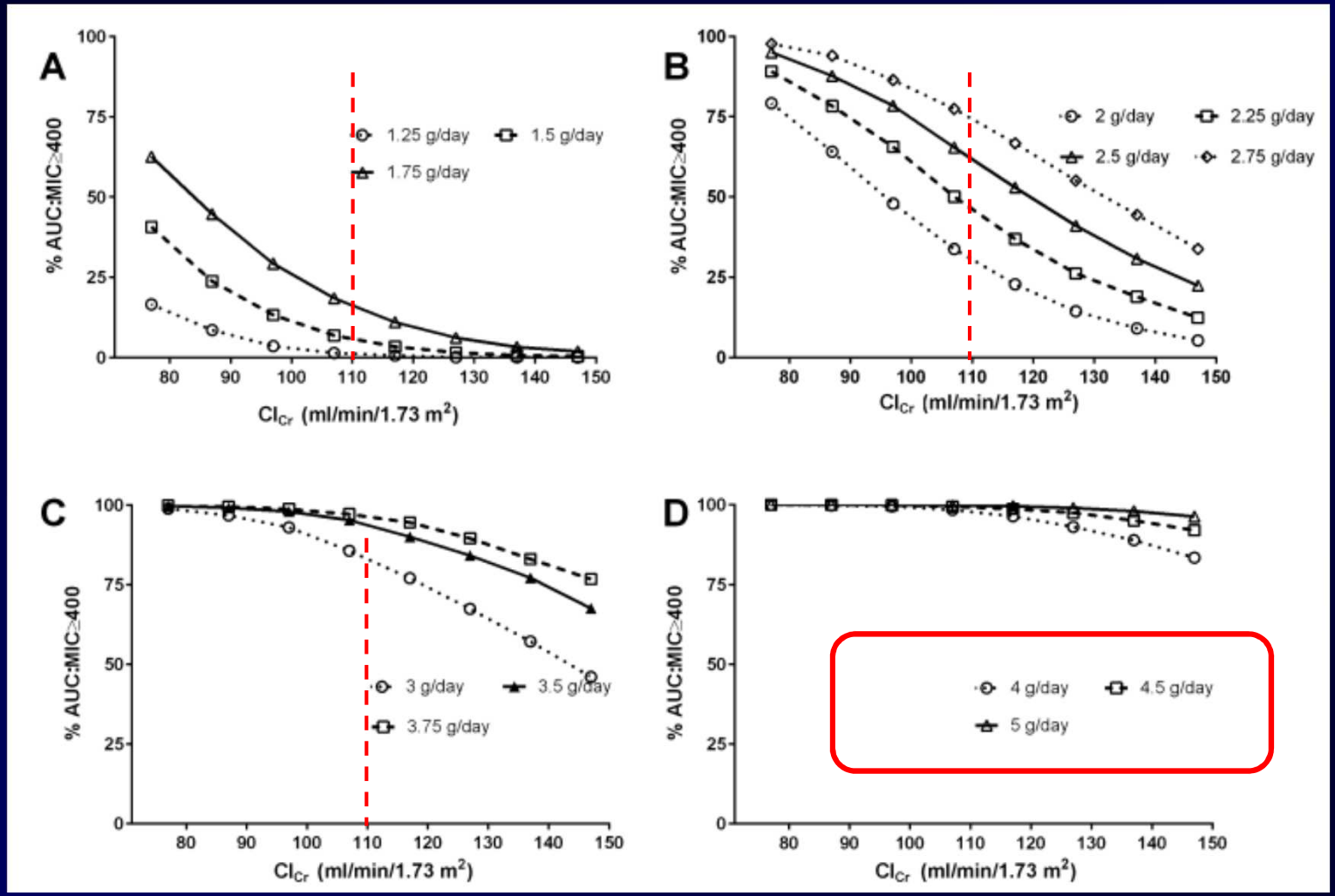
Monte Carlo Simulation (1000 pts)

Patients	AUC/MIC (mean ± SD)	Pts with AUC/MIC ≥ 400
Normal (16)	524 ± 174	75%
Overweight (8)	479 ± 108	75%
Obese (6)	320 ± 74	17%

Rawson TD et al., J Infect, 2017

Vancomycin

% AUC/MIC > 400 with different doses in extremely obese patients



Adane ED et al., Pharmacotherapy, 2015

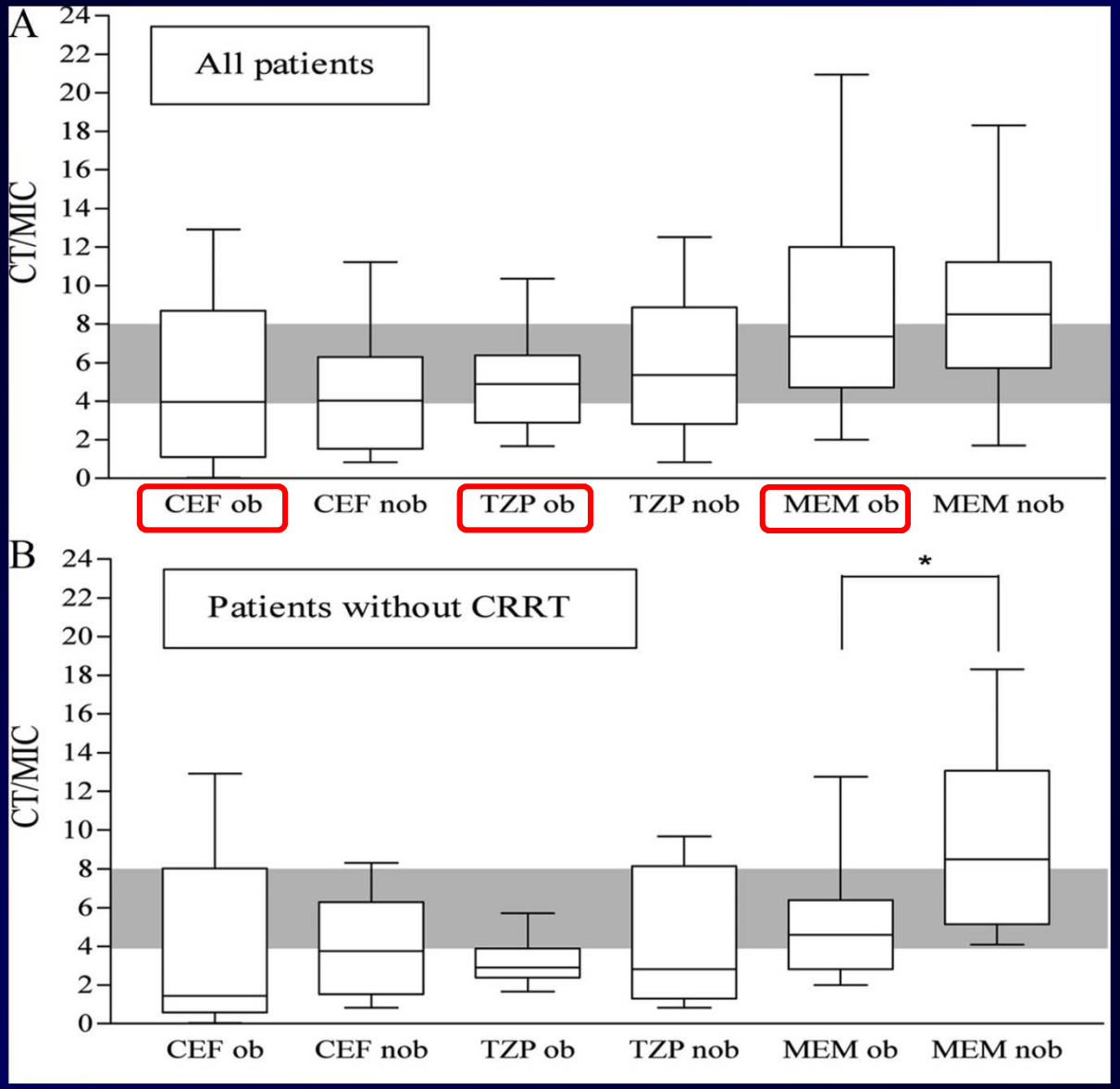
Dosing recommendations of commonly used antibiotics in obese patients with pneumonia

Aminoglycosides	The loading dose should be based on adjusted or lean body weight with subsequent dose and interval based on kidney function and drug level
Vancomycin	The loading dose is 25 – 30 mg/kg of TBW in seriously ill patients. Maintenance dose is 15 – 20mg/kg of TBW every 8 – 12h, not to exceed 2g per dose for pts with normal kidney function. Trough level should be measured prior to the 4th or 5th dose. Target trough concentrations of 15 – 20mg/l are recommended. Doses >1.5 g should be infused over ≥ 1.5 h
Colistin	Dosing colistin using ideal body weight is recommended. Loading doses are suggested

Al-Dorzi HM et al., Curr Opin Infect Dis, 2014

Betalactams

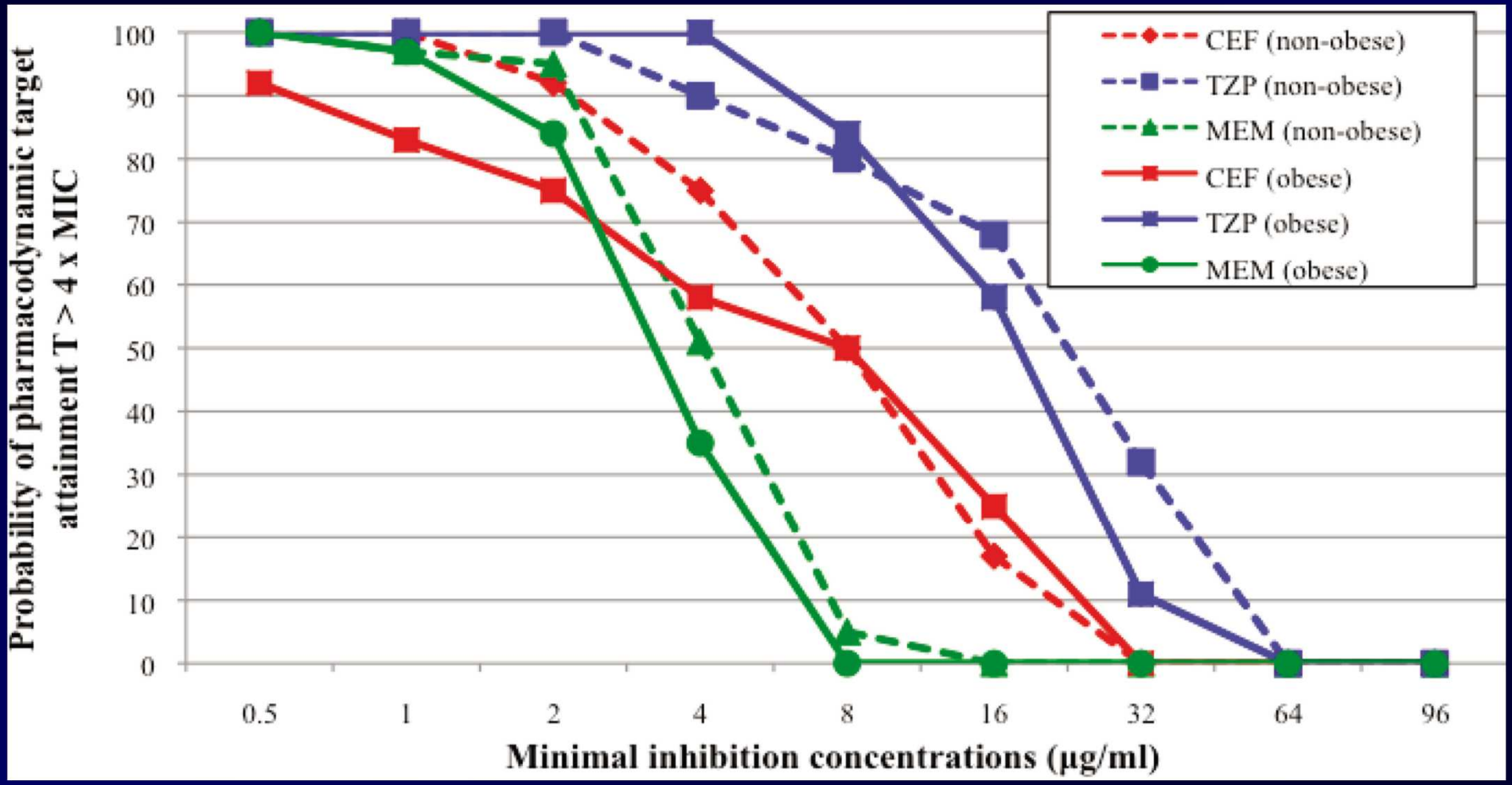
Serum drug concentrations in obese and non obese patients with standard regimens



Hites M et al., Antimicrob Agents Chemother, 2012

Betalactams

PTA in obese and non obese patients



Hites M et al., Antimicrob Agents Chemother, 2012

Steady-state pharmacokinetics and pharmacodynamics of meropenem in morbidly obese patients hospitalized in an intensive care unit

Cheatham SC, Fleming MR, Healy DP, Chung EK, Shea KM, Humphrey ML and Kays MB

- 9 pts hospitalized in ICU with a BMI ≥40 kg/m^2 received meropenem 500 mg or 1 g q6h, infused over 0.5h. PK parameters were estimated, and Monte Carlo simulations were performed for 5 dosing regimens (500 mg q8h, 1 g q8h, 2 g q8h, 500 mg q6h, 1 g q6h) infused over 0.5 and 3h.

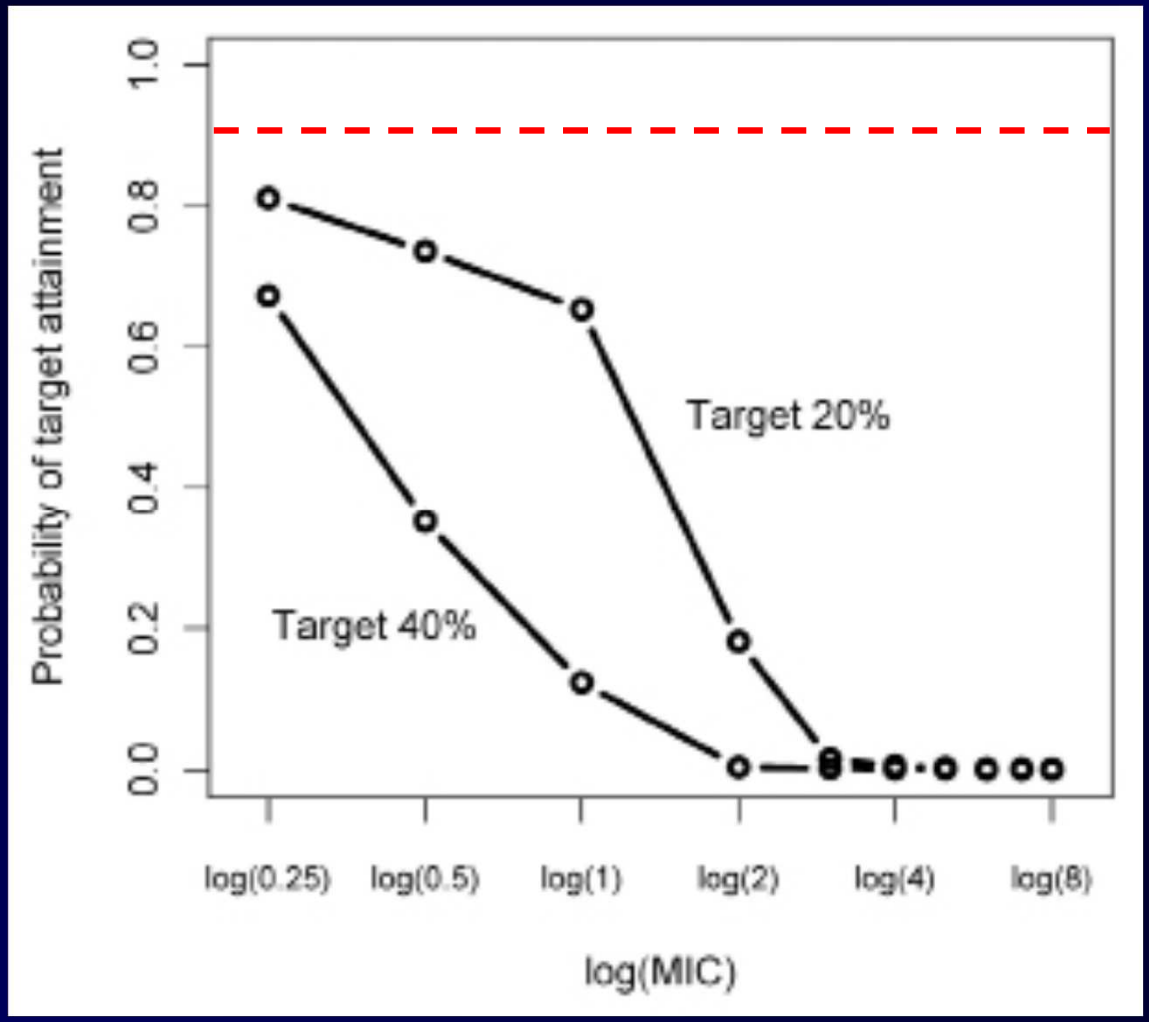
- Volume of distribution at steady state was **37.4 ± 14.7 L**, and systemic clearance was **10.2 ± 5.0 L/h**.

- Standard doses achieve **adequate exposures** for susceptible bacteria at a **PD target of 40% fT>MIC**. Higher doses or prolonged infusion regimens are needed at the higher pharmacodynamic target

The Journal of Clinical Pharmacology, 54(3) 324–330, 2013

Ertapenem 1g IV

PTA* in 10 class III obese female patients



*** Monte Carlo simulation**

Borracci T et al., Minerva Anestesiol, 2014

Journal of Antimicrobial Chemotherapy
JAC

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

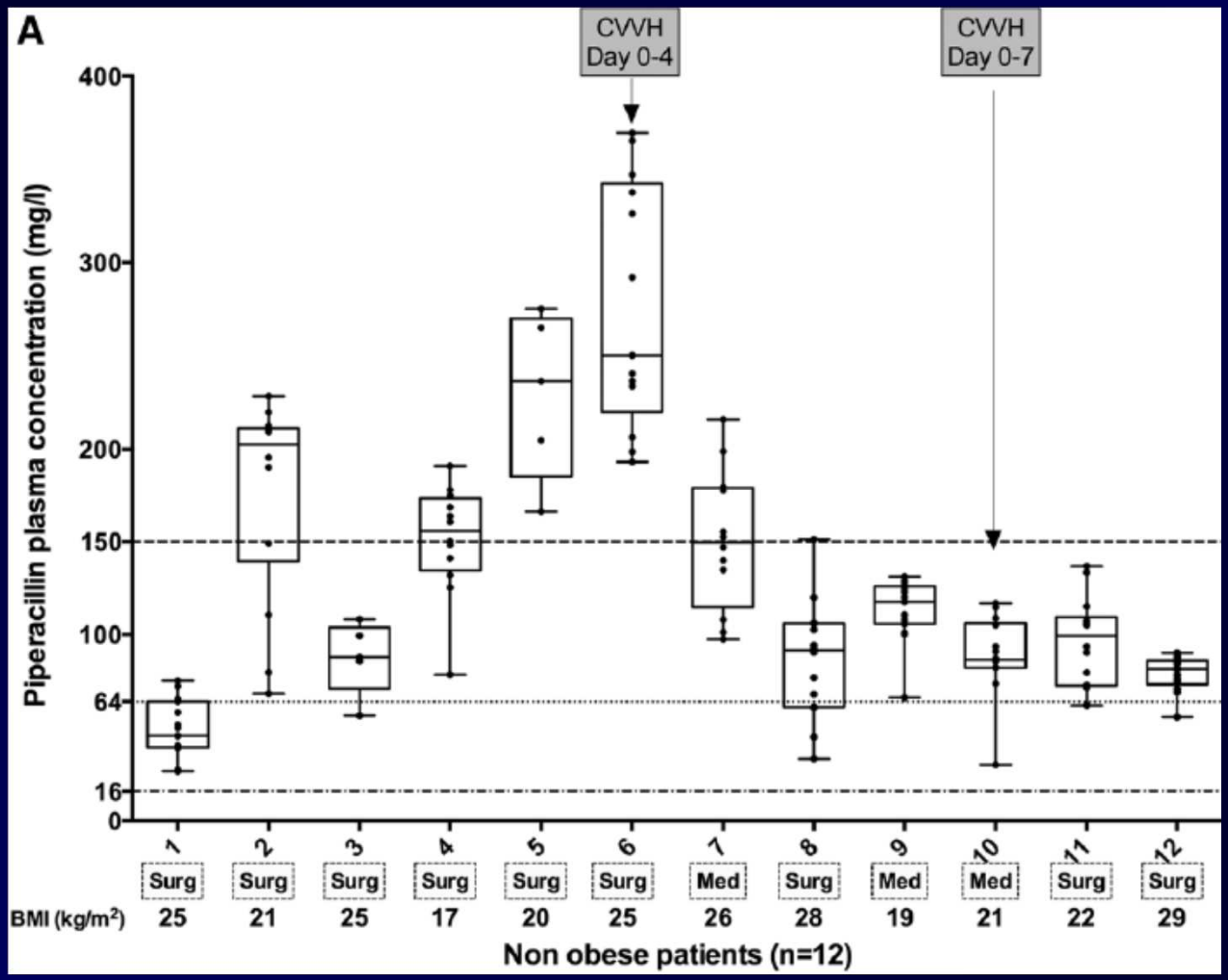
Brill MJE, Houwink API, Schmidt S, Van Dongen EPA, Hazebroek EJ, van Ramshorst B, Deneer VH, Mouton JW and Knibbe CAJ

- ***Methods***: 9 patients BMI 47 ± 6 kg/m^2, and 7 non-obese pts (BMI 28 ± 3 kg/m^2) received cefazolin 2 g IV before surgery.
- ***Results***: The free cefazolin ISF penetration ratio (fAUC$_t$/fAUC$_p$) was 0.70 (range 0.68–0.83) in obese pts vs 1.02 (range 0.85–1.41) in non-obese pts ($P < 0.05$).
- Cefazolin distribution to the ISF compartment proved dependent on body weight. Monte Carlo simulations showed reduced PTA for obese pts for MIC values of 2 and 4 mg/L.
- ***Conclusions***: Cefazolin tissue distribution is lower in obese pts and reduces with increasing body weight. Dose adjustments are required in this patient group.

J Antimicrob Chemother 2014; 69: 715–723

Piperacillin/tazobactam

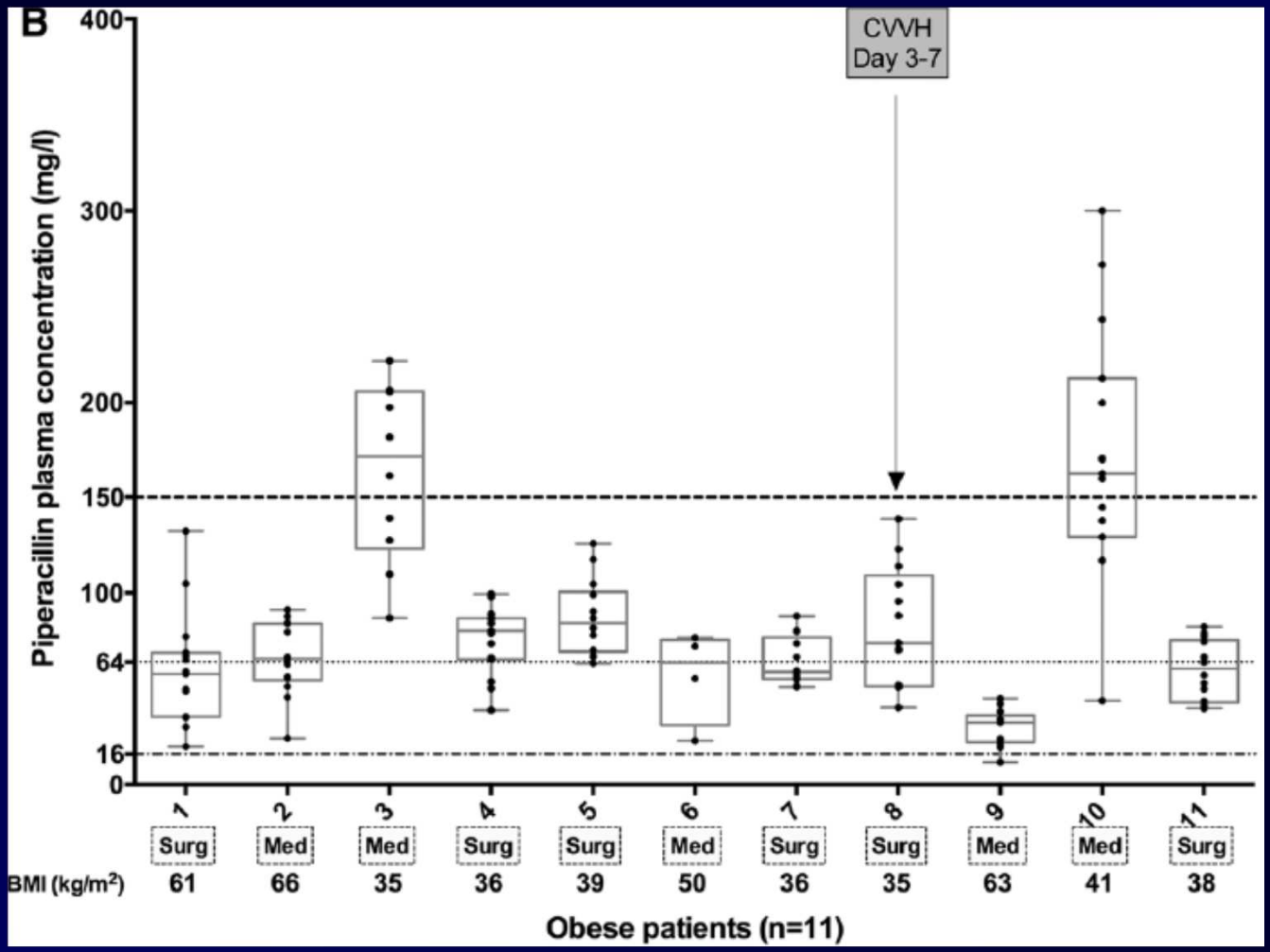
Plasma concentrations in 12 non obese patients



Jung B et al., Crit Care Med, 2017

Piperacillin/tazobactam

Plasma concentrations in 11 obese patients



Jung B et al., Crit Care Med, 2017

Piperacillin/tazobactam

PTA with different dosing regimen*

Targeted MIC (mg/l)	Probability of Traget Attainment (%)					
	4.0/0.5g every 8h		4.0/0.5g every 6h		4.0/0.5g every 4h	
	Obese	Nonobese	Obese	Nonobese	Obese	Nonobese
16	90	100	100	100	100	100
32	88	100	91	100	100	100
64	21	65	44	98	75	100
150	0	8	12	27	18	42

* Monte Carlo simulation

Jung B et al., Crit Care Med, 2017

Betalactams

Proposed classification depending on antimicrobial mechanisms

Class (example)	Essential PBP saturation	CFU/ml Log_{10} reduction	Biomass increase	PAE (h)	Inoculum effect	Endotoxin release
A (imipenem)	At least two	3 logs in 6h	Absent (*PIOD concentration-dependent*)	> 3	Small	Negligible
B (ceftazidime)	No more than two	3 logs in 12h	Transient or negligible (*PIOD intermediary*)	2	Moderate	Little
C (piperacillin)	Only one prevailing	Little or none	Progressive and remarkable (*PIOD concentration-independent*)	< 1	Considerable	Yes

Periti P & Nicoletti P, J Chemother, 1999

β-lactam–β-lactamase inhibitors against *E. coli* strains

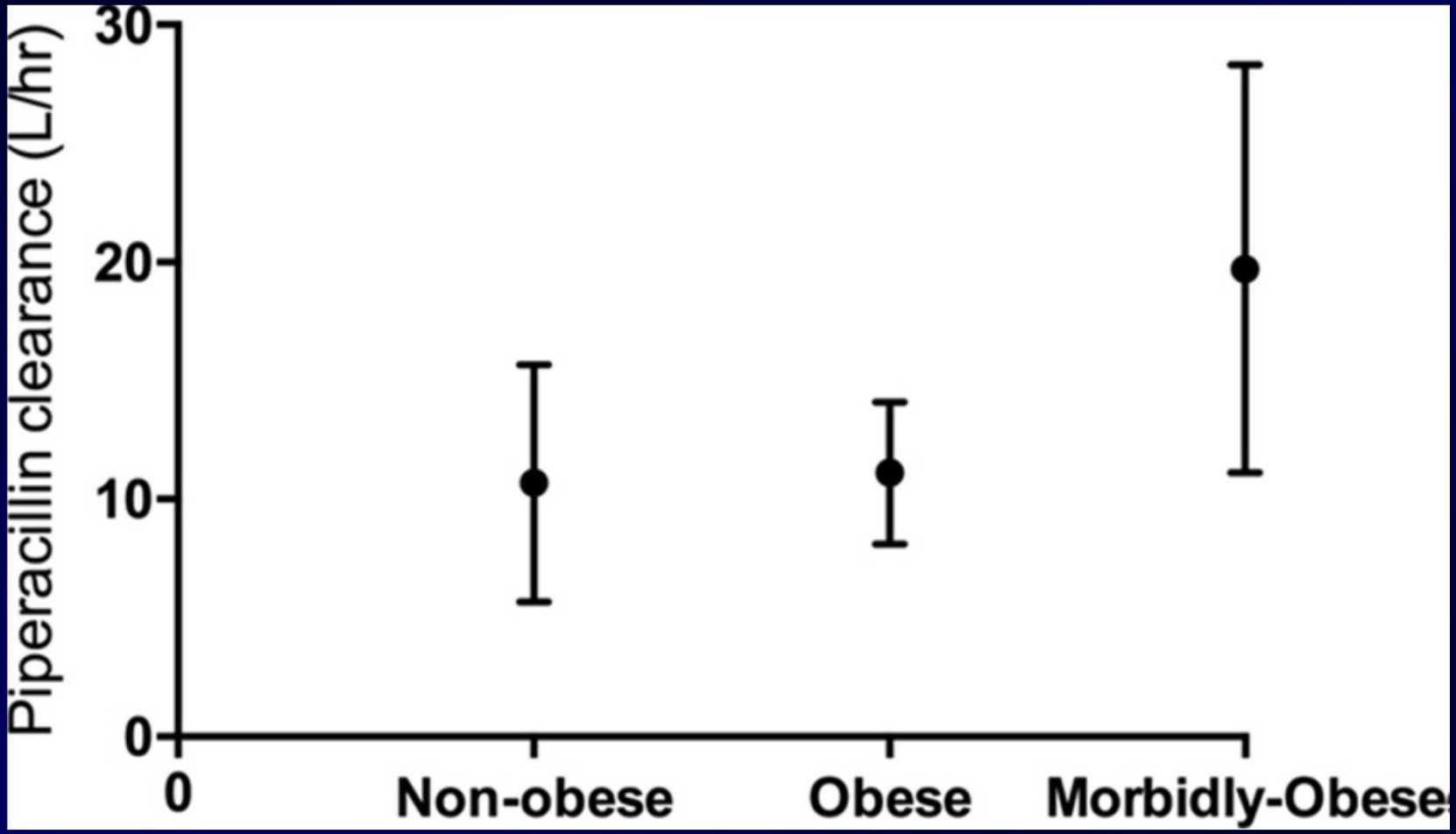
Type of β-lactamase	MIC (mg/l) of antimicrobial combinations							
	Amoxycillin-clavulanate				Piperacillin-tazobactam			
	2 : 1		4 : 1		8 : 1		Tazobactam 4 mg/l	
	S	H	S	H	S	H	S	H
CTX-M group	2 – 16	4 – 16	4 – 8	4 – 16	1 – 8	16 → 256	1 – 4	64 – 256
SHV group	4 – 16	4 – 16	4 – 16	4 – 16	1 – 16	64 → 256	1 – 8	64 – 256
TEM group	4 – 8	8 – 16	4 – 8	8 – 16	4 – 16	64 → 256	1 – 4	256

S = standard inoculum for every method according to CLSI guidelines;
H = 100-fold standard inoculum

López-Cerero L et al., Clin Microbiol Infect, 2010

Piperacillin

Effect of BMI on clearance



Alobaid AS et al., Antimicrob Agents Chemother, 2017

Piperacillin

Effect of BMI on volume of distribution

Alobaid AS et al., Antimicrob Agents Chemother, 2017

Dosing recommendations of commonly used antibiotics in obese patients with pneumonia

Penicillins	Higher doses of piperacillin and tazobactam and longer infusion time of up to 4 h
Cephalosporins	The upper limit of normal doses is recommended
Carbapenems	The upper limit of normal doses with extended infusions over approximately 3 – 4 h is recommended

Al-Dorzi HM et al., Curr Opin Infect Dis, 2014

Obese patients

Altered physiological and pharmacokinetic factors

DISTRIBUTION

Little/no change in volume of distribution expected if

- Large molecular size
- Highly ionized
- Highly protein bound
- Poorly crosses biological membranes

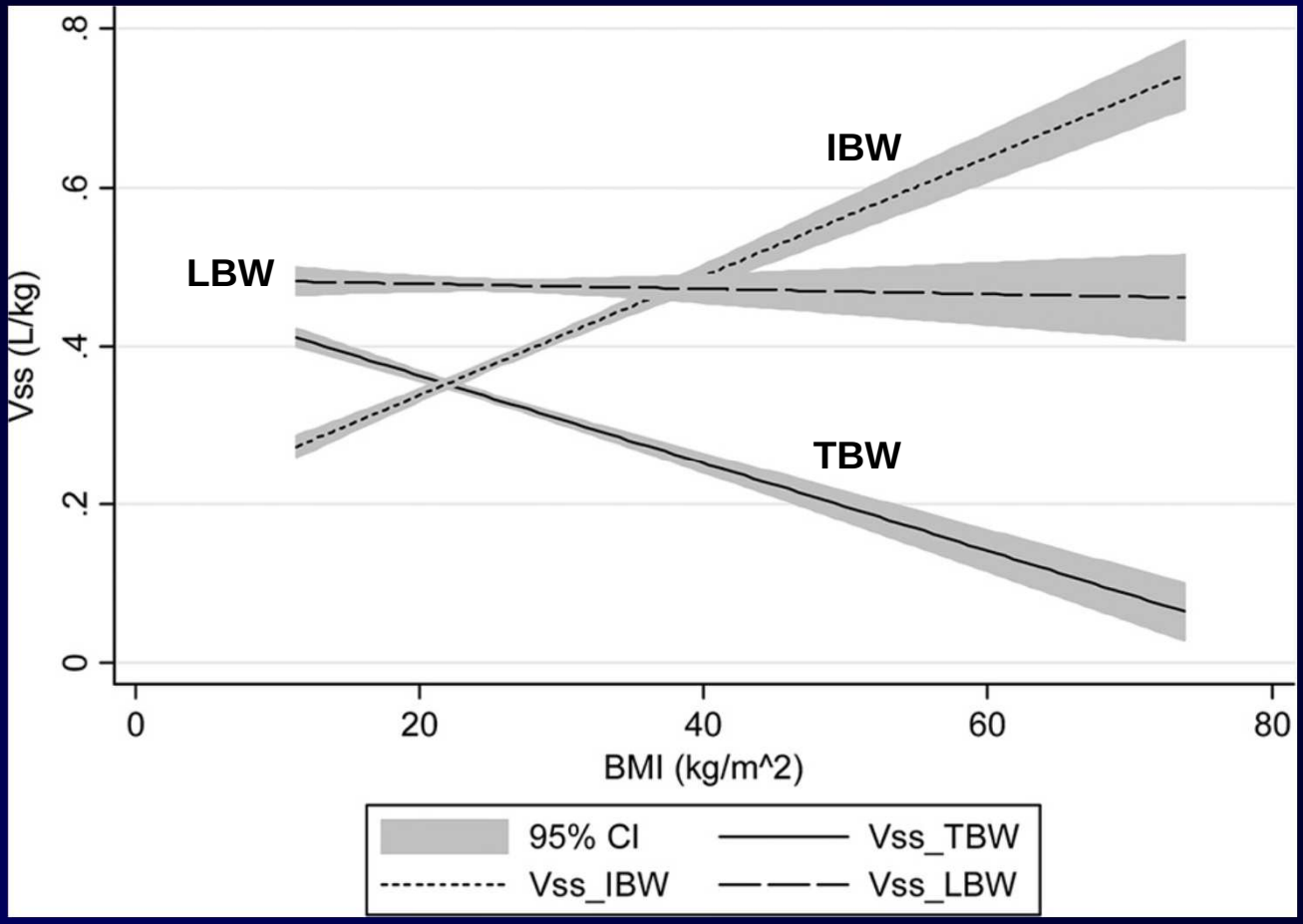
Increase in volume of distribution expected if

- Small molecular size
- Minimally ionized
- Minimally protein bound
- Easily crosses biological membranes

Polso AK et al., J Clin Pharm Ther, 2014

Aminoglycosides

*V*ss (l/kg) plot to TBW, IBW, and LBW



Pai MP et al., Antimicrob Agents Chemother, 2011

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Colistin	Dosing colistin using ideal body weight is recommended. Loading doses are suggested

Al-Dorzi HM et al., Curr Opin Infect Dis, 2014

Therapeutic drug monitoring of aminoglycosides

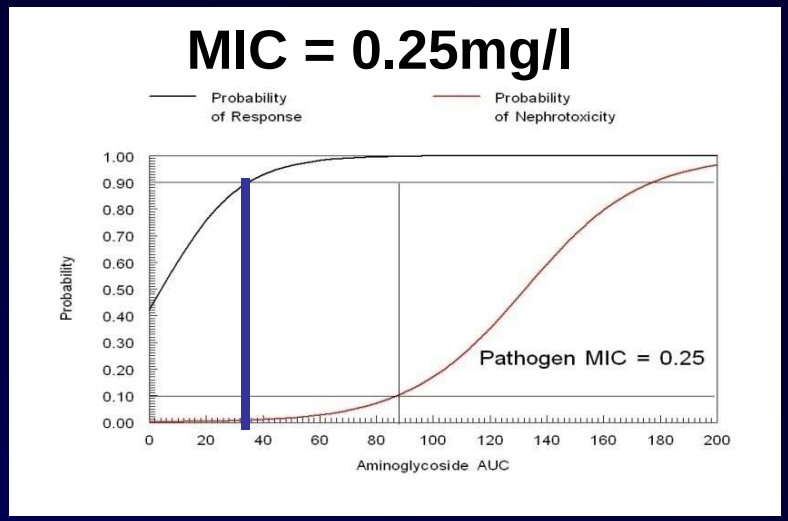
(appropriate loading and maintenance dose regimen)

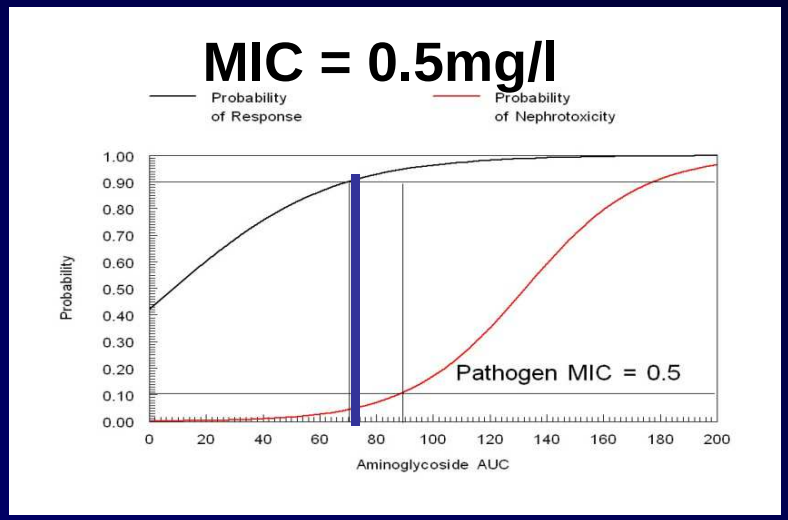
- Elderly
- Renal impairment
- Infants and neonates
- Severe burns or trauma victims
- Cystic fibrosis
- Sepsis
- Malignancy
- Total parenteral nutrition
- Obesity

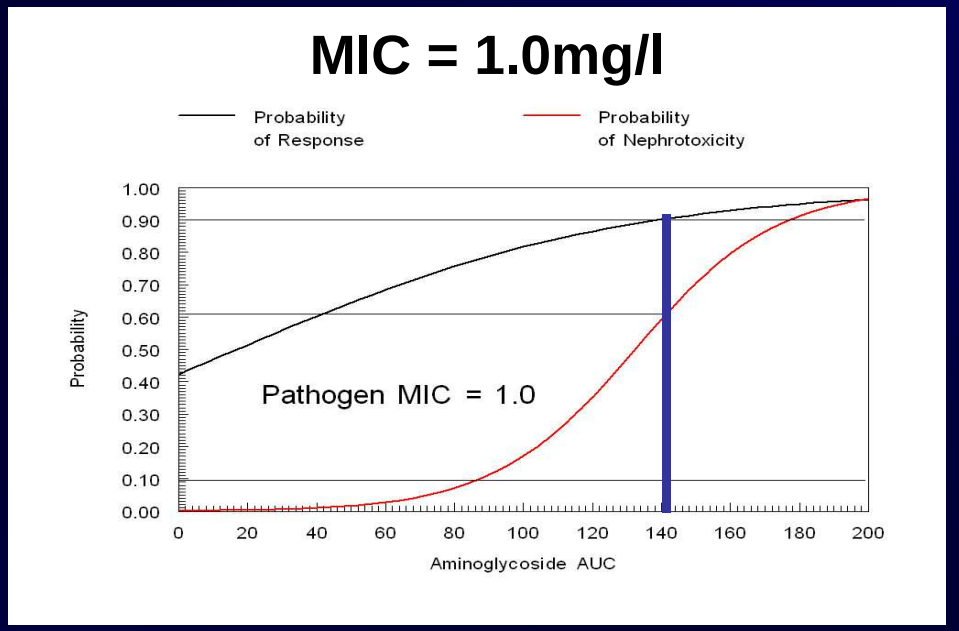
Lorthalary O et al., Med Clin N A, 1995; Begg EJ et al., Br J Clin Pharmacol, 2001

Aminoglycosides

Therapeutic/Toxic Window







Courtesy of G.L. Drusano

Dosing recommendations of commonly used antibiotics in obese patients with pneumonia

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Al-Dorzi HM et al., Curr Opin Infect Dis, 2014

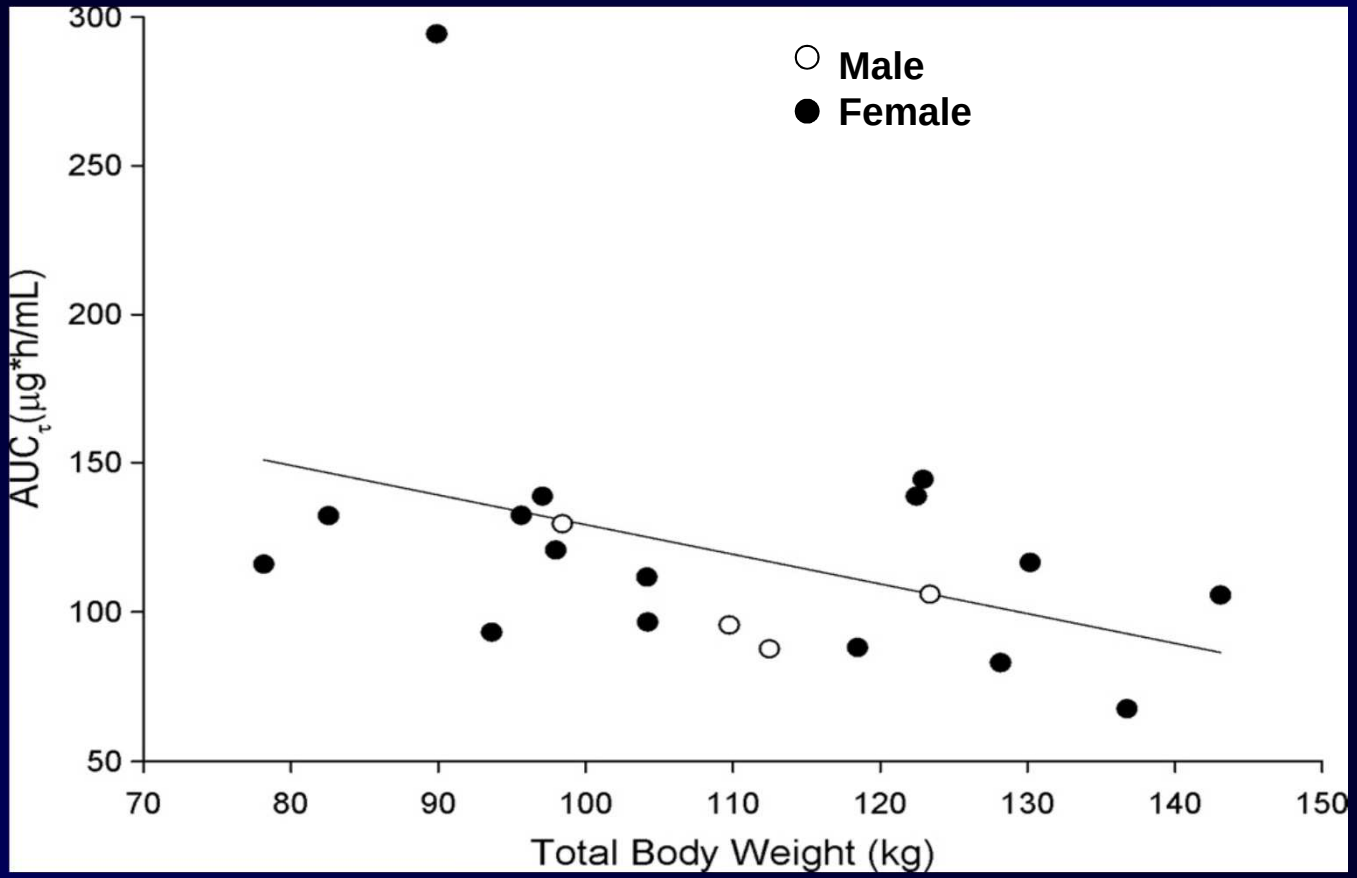
Colistin

Multivariate analysis for independent predictors for associated NTX

Parameter	OR	95% CI	*P* value
BMI ≥ 31.5 kg/m^2	3.1	1.15 – 8.35	0.025
Diabetes	2.11	0.84 – 5.29	0.112
Length of stay (days) prior to CMS	1.04	0.99 – 1.08	0.078
Age (yr)	1.08	1.00 – 1.17	0.045

Gauthier TP et al., Antimicrob Agents Chemother, 2012

Linezolid in obese patients*
AUC vs TBW



* Moderately to morbidly obese adults

Bhalodi AA et al., Antimicrob Agents Chemother, 2013

Linezolid 600 mg IV BID in 2 obese patients

	Patient 1 Weight = 116 kg BMI = 40 kg/m^2	Patient 2 Weight = 102 kg BMI = 35 kg/m^2
$AUC_{tot0\text{-}24h}$ (mg·h/l)	78.8	60.4
PI (ELF/serum)	115%	113%
AUC/MIC (2 mg/l)	39.4	30.2
T_{free} > MIC (2 mg/l)	48.8%	29.3%

De Pascale G et al., Minerva Anestesiol, 2012

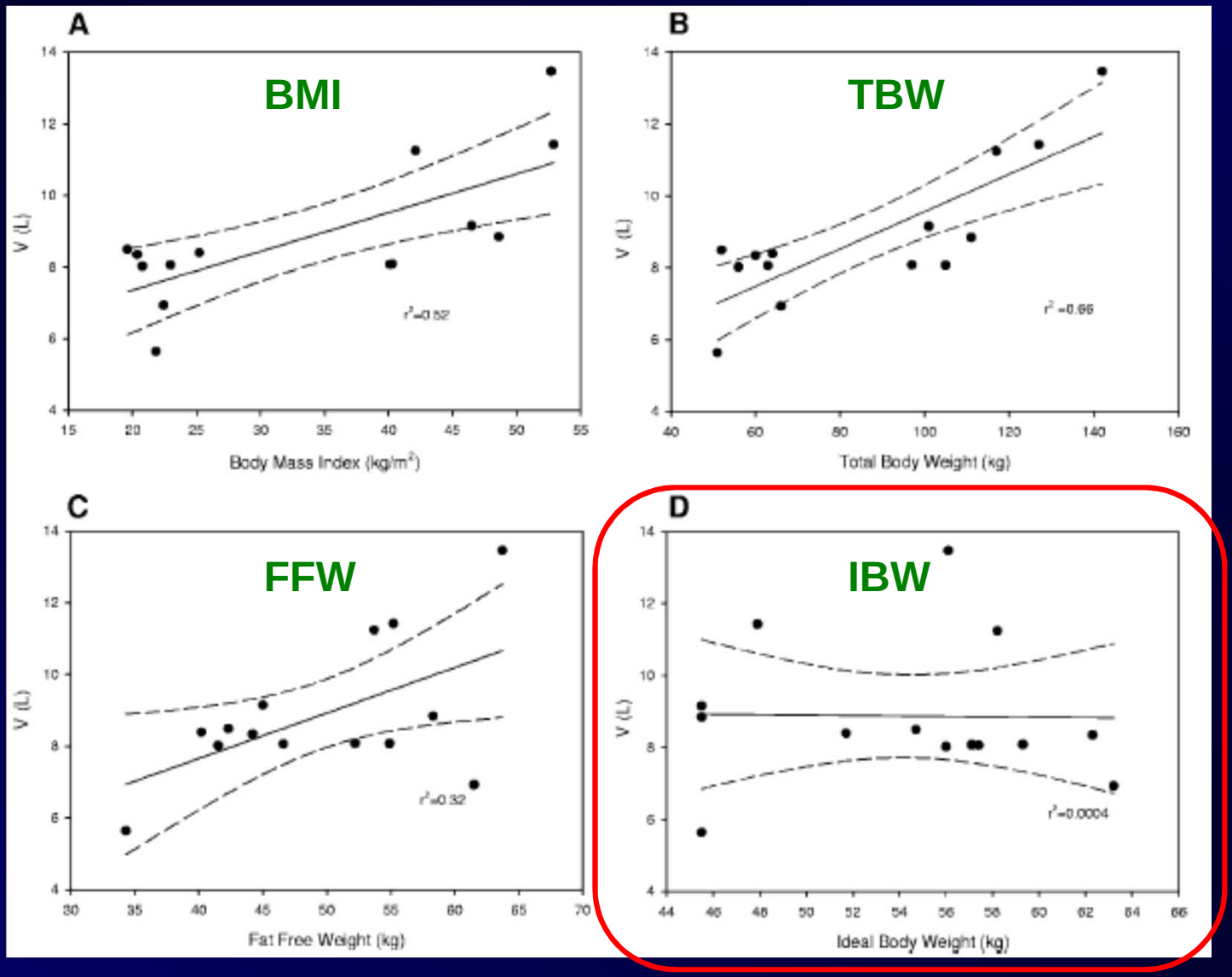
Dosing recommendations of commonly used antibiotics in obese patients with pneumonia

Linezolid	**Standard linezolid dosing with consideration of continuous infusion is recommended**
Macrolides	Standard doses are recommended. Whether higher doses and longer durations should be used remains uncertain
Fluoroquinolones	Dose adjustment is probably not warranted for levofloxacin and moxifloxacin. Doses of up to 800mg every 12h of ciprofloxacin should be considered in morbidly obese patients

Al-Dorzi HM et al., Curr Opin Infect Dis, 2014

Daptomycin

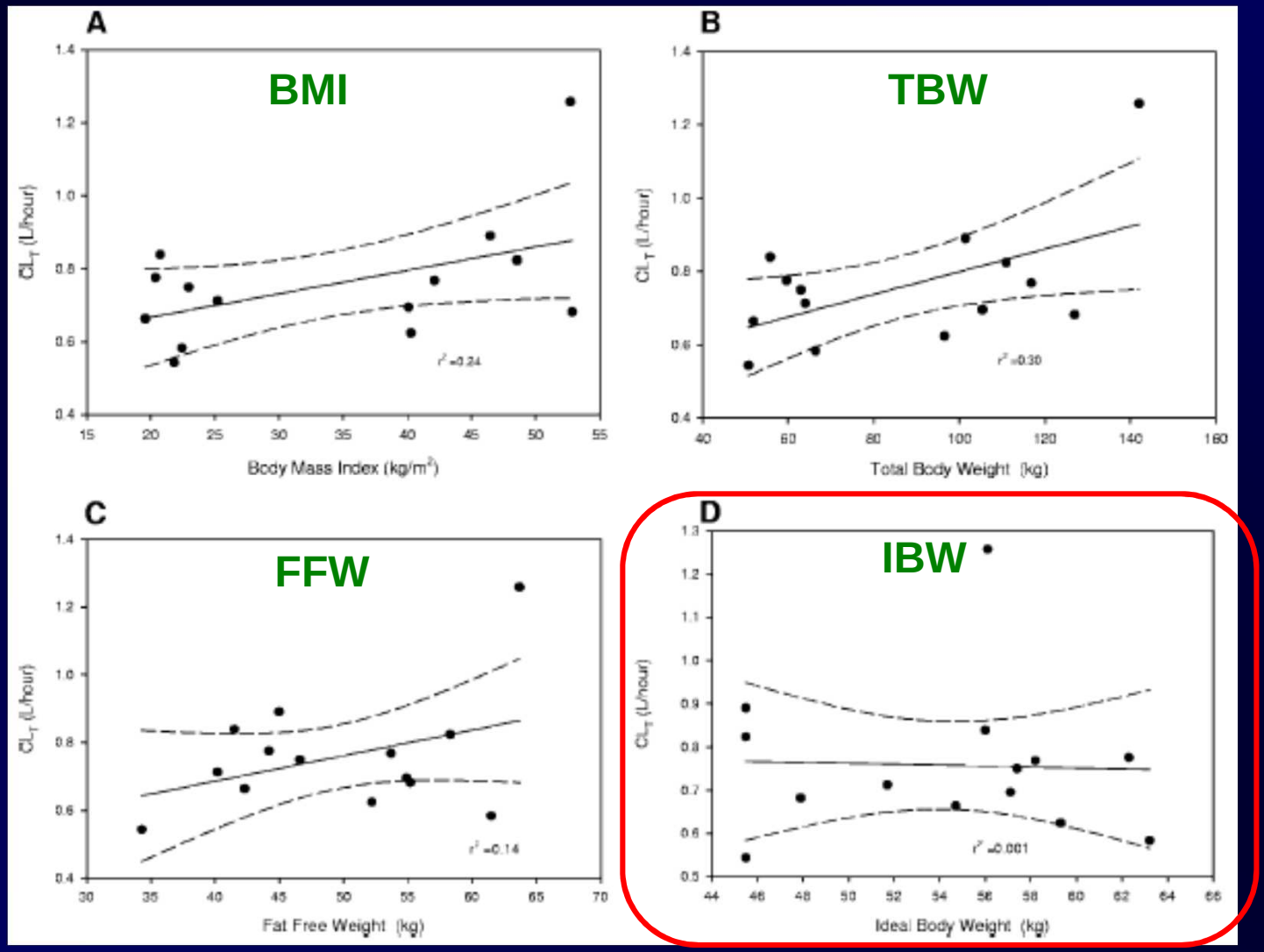
Relationships of Vd to weight



Pai MP et al., Antimicrob Agents Chemother, 2007

Daptomycin

Relationships of CLT to weight



Pai MP et al., Antimicrob Agents Chemother, 2007

Pharmacokinetics of daptomycin in special populations

- **LIVER IMPAIRMENT**

  Subjects with moderate liver impairment do not require an adjustment in daptomycin dose or dose regimen

- **OBESITY**

  In obese subjects exposure to daptomycin (C_{max}, AUC) was increased ~ 30%. However, no adjustment in daptomycin dose or dose regimen should be required based solely on obesity.

Dvorchik B et al., J Clin Pharmacol, 2004; Dvorchik B and Damphousse D, J Clin Pharmacol, 2004

Daptomycin

Mean dose 8mg/kg/day for a median of 25 days (range 14-82 d) in 61 pts (29 M and 32 F, mean age 66,6 yrs)

3/58* (5.2) **CPK levels > 10 times upper normal limit (grade 3) with muscoloskeletal symptoms after 24 days of therapy**

*** 2/3 pts were morbidly obese (BMI grade III)**

Figueroa DA et al, Clin Infect Dis, 15 July 2009

Key points

- Obesity is associated with several alterations in antibiotic pharmacokinetics and pharmacodynamics
- Data on antibiotic dosing in obese patients are limited and come mainly from observational studies
- Obesity should be considered when dosing both hydrophilic and lipophilic compounds

Al-Dorzi HM et al., Curr Opin Infect Dis, 2014, MOD

TDM MIGHT BE VERY USEFUL FOR OPTIMAL DOSING