

19th Infection and Sepsis Symposium

Porto Palácio
26th-28th February 2014

Antibiotic dosing in the obese patient



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How much?

Antibiotic Goals

- Promote bacteria death
- Prevent the emergence of resistance
- Avoid toxicity

Antibiotic must not only attach to target but must occupy an adequate number of binding sites

That depends on drug concentration within the organism and also on bacteria susceptibility – MIC

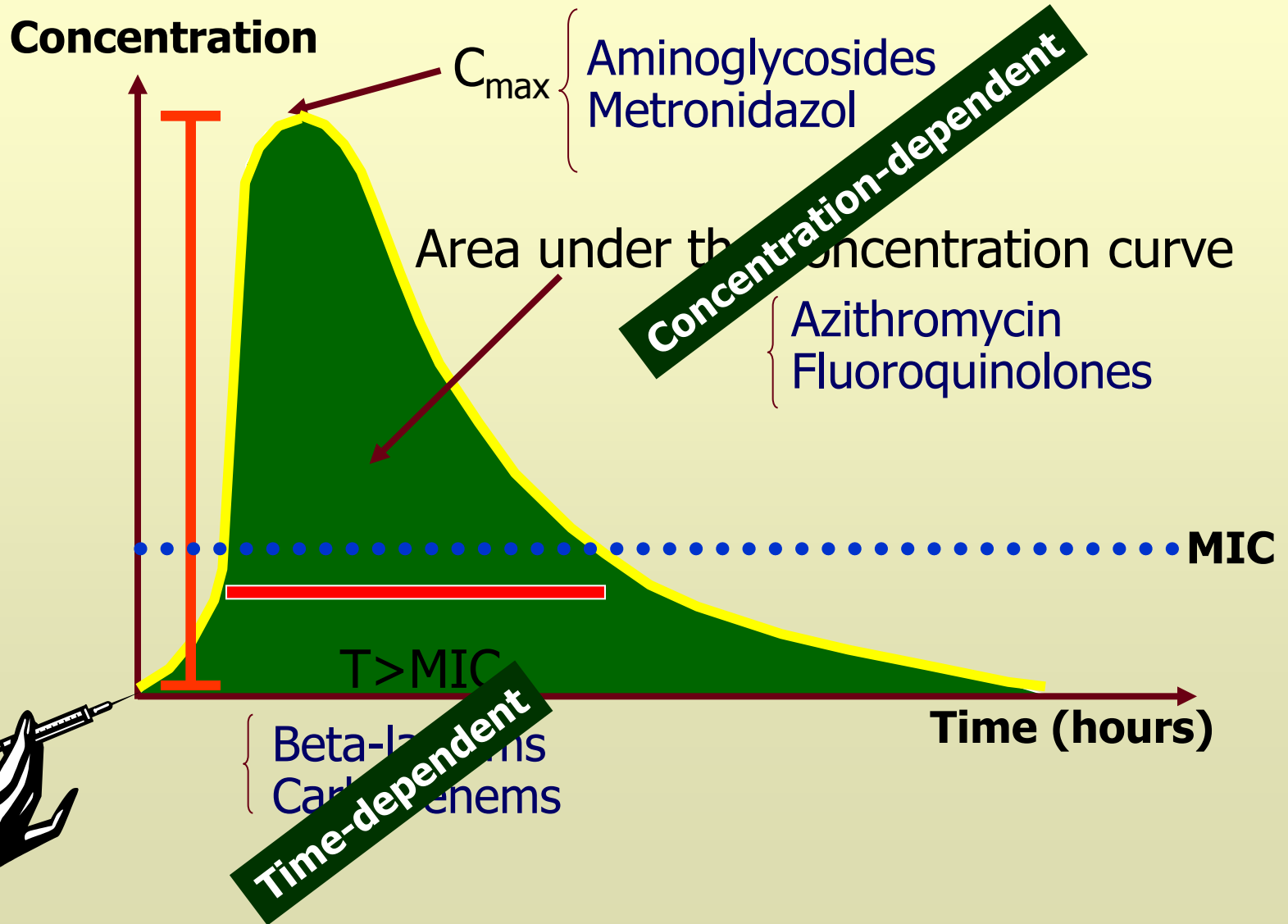
Usually antibiotic concentration must be over 3-5 times MIC

Underdosing

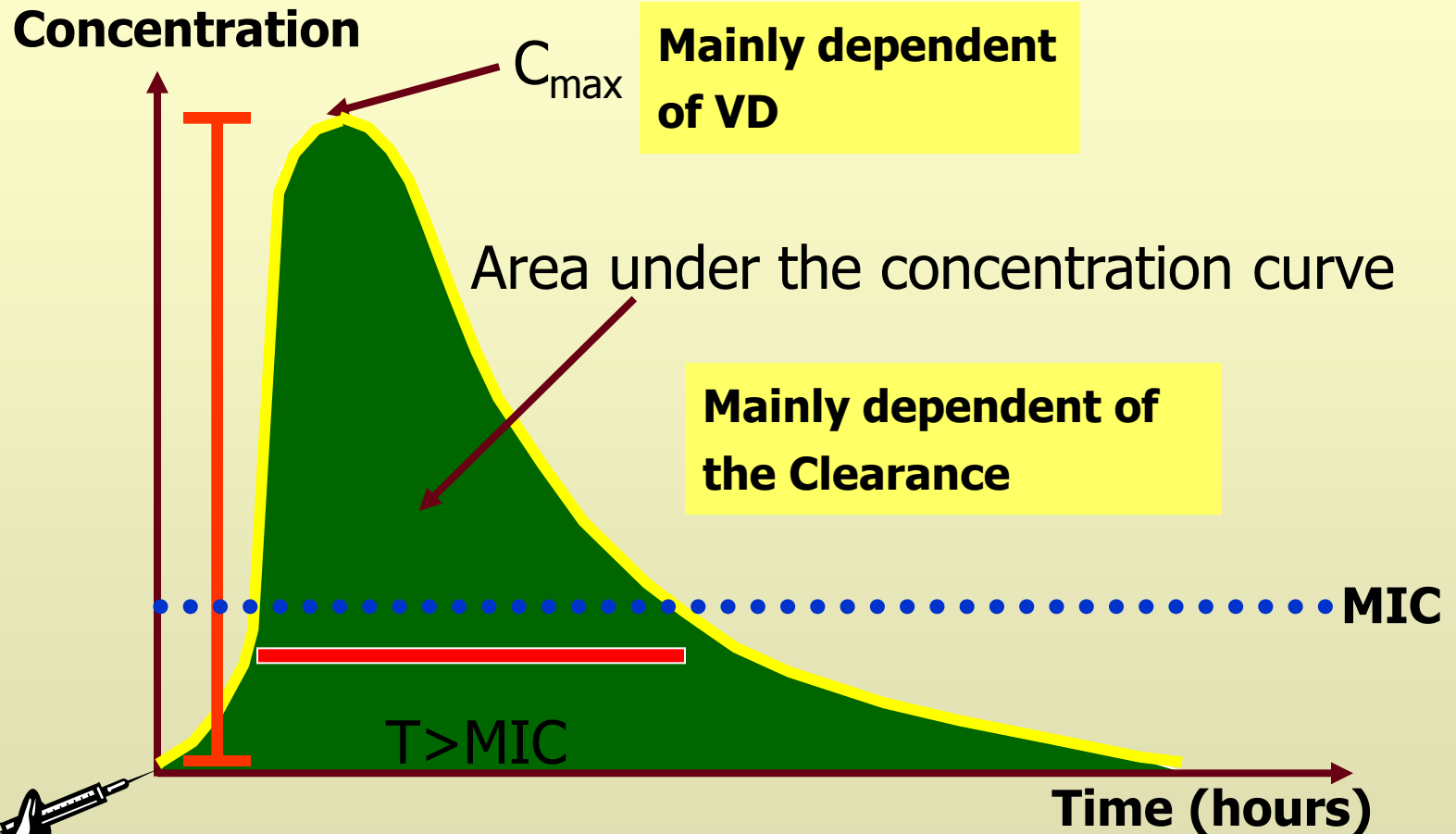
Increase in Volume of distribution

Increase in clearance

Patterns of Antimicrobial Activity



Antimicrobial exposure



Peak Concentration and Volume of Distribution



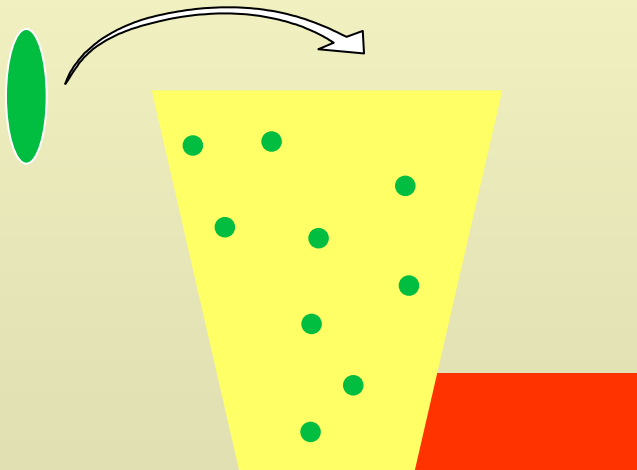
- The apparent **volume of distribution** indicates into how large a volume the drug distributes if it were at the same concentration as that in plasma
- Initial peak concentration is only dependent on dose and volume of distribution

Peak Concentration and Volume of Distribution

$$Vd (L) = \frac{\text{Dose (mg)}}{\text{Conc (mg/L)}}$$

Beta-Lactam

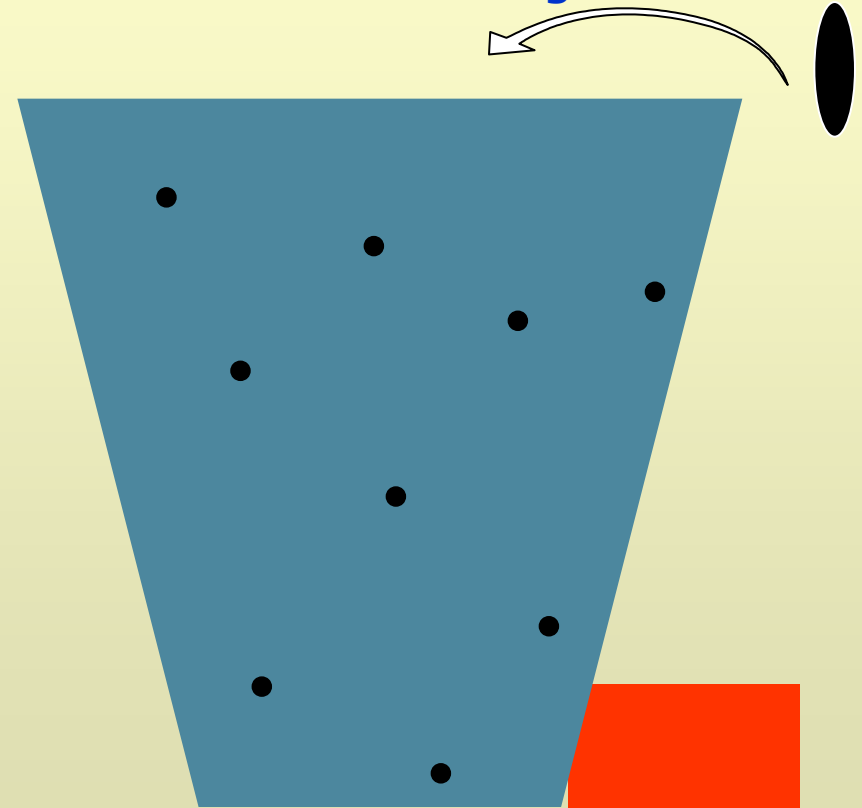
500 mg



Vd 15-20 liters

Fluoroquinolone

500 mg



Vd 80-200 liters

Clearance

Rate of elimination = $Cl \times C_{\text{in plasma}}$

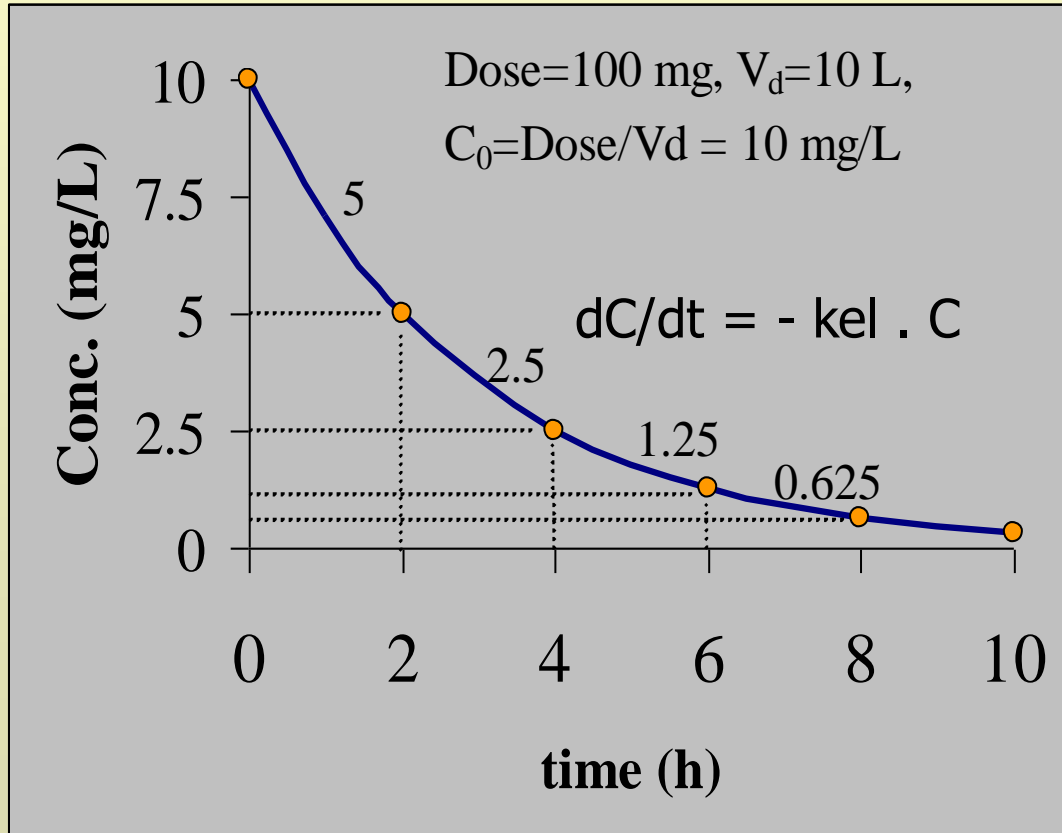
(Amount / Unit of time) = (Volume / Unit of time) $\times C_{\text{in plasma}}$

Clearance is the volume of plasma completely cleared of the drug per unit of time by all routes - the liver, the kidney...

Elimination of most drugs from the body after therapeutically relevant doses follows
first-order kinetics.

Clearance

Elimination of most drugs from the body after therapeutically relevant doses follows **first-order kinetics.**



First order PK

Amount of drug that is eliminated depends of its initial concentration.

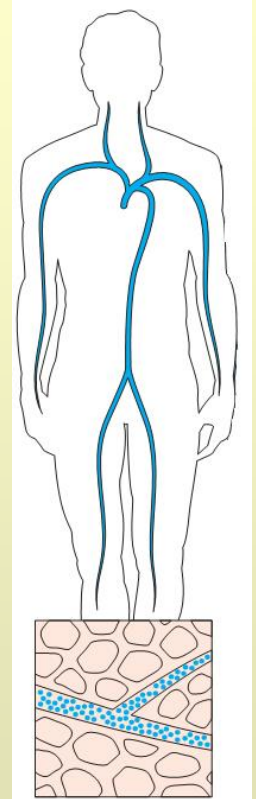
According an increased V_d usually compensates for an increased Cl .

Volumes of compartments in relation to V_d

Total body water 0.6 L/kg BW

- **Intracellular water 0.4 L/kg BW**
- **Extracellular water 0.2 L/kg BW**
- **Plasma 0.04 L/kg BW**

V_d 0.05 L/kg the drug remains in the blood (heparine)



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V_d 0.1-0.3 L/kg distribution from blood into extracellular fluid (gentam)

V_d 0.6 L/kg distribution from blood into intra and extracellular fluid (methotrexate)

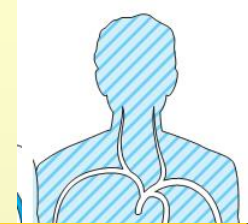
V_d \gg 0.6 L/kg distribution intracellularly and high binding in tissues (amiodarone)



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- **Extracellular**
- **Plasma**

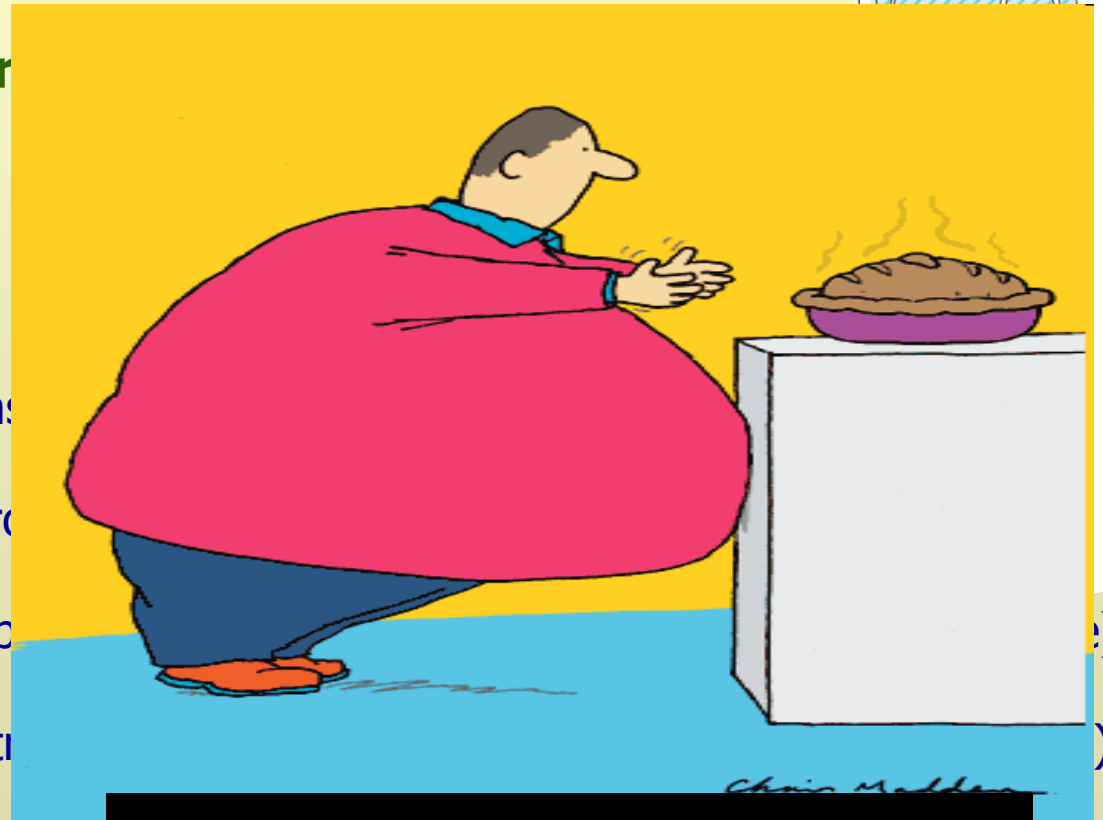


V_d 0.05 L/kg the drug remains

V_d 0.1-0.3 L/kg distribution from

V_d 0.6 L/kg distribution from b

V_d >>0.6 L/kg distribution into



What about fat tissue?

Body Weight Calculations



Table 2: Formulas

	Equation
IBW (in kg)	45.5 kg + 2.3 (inches over 5 feet): women 50 kg + 2.3 (inches over 5 feet): men
Cockcroft-Gault (mL/min)	$140 - \text{age} \times \text{TBW} / 72 \times \text{Scr}$ (X 0.85, if female)
Salazar-Corcoran (men) (mL/min)	$(137 - \text{age}) \times [(0.285 \times \text{TBW}) + (12.1 \times \text{Ht}^2)] / (51 \times \text{Scr})$
Salazar-Corcoran (women) (mL/min)	$(146 - \text{age}) \times [(0.287 \times \text{TBW}) + (9.74 \times \text{Ht}^2)] / (60 \times \text{Scr})$
MDRD (mL/min/1.72m ²)	$175 \times \text{Scr}^{1.154} \times \text{Age}^{-2.03} \times (0.742, \text{ if female}) \times (1.210, \text{ if black})$

- <25 Normal
- 25-30 Overweight
- >30 Obese
- >35 Morbidly obese
- >55 Super-morbidly obese

➤ Pharmacokinetic changes in obesity in general

– Absorption

- Little data exists on differences -> maybe delayed gastric emptying

– Distribution

- **Lipophilic medications** should be dosed on total body weight due to higher distribution volumes
- **Hydrophilic medications** should be dosed on ideal body weight or adjusted body weight due to lower volumes of distribution

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- **Metabolism**
 - CYP3A4 has lower drug clearance; CYP2E1 and most phase 2 enzyme systems have higher clearance; CYP1A2, CYP2C9, CYP2C19 and CYP2D6 trend towards higher clearance
- **Excretion**
 - Obesity results in **an increase in baseline renal clearance**, but has a higher incidence of renal dysfunction from hypertension or diabetes

- **To achieve therapeutic concentrations rapidly loading doses are recommended**
- **Recommend giving high end of normal loading dose (or even higher dose)**
 - Example: Vancomycin (normal patient Vd ~0.7 L/kg)
 - 100kg septic shock patient
 - **Recommended loading dose for complicated infections in seriously ill patients is 25-30 mg/kg based on actual body weight**

– Am J Health-Syst Pharm 2009;66:82-98

Loading Dose	Estimated Vd	Estimated Peak level (mcg/mL)
1 gram	~0.7 L/kg	14
15 mg/kg ABW	~0.7 L/kg	21
15 mg/kg ABW	~1 L/kg due to fluid resuscitation	15
25 mg/kg ABW	~1 L/kg due to fluid resuscitation	25

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Results—Data were collected on a random sampling of 421 patients, stratified by body mass index, who met the inclusion criteria. Most patients in each body mass index category received a fixed dose of vancomycin 2 grams daily divided into two doses (underweight 82%, normal weight 90%, overweight 86%, obese 91%). Adequate initial dosing (≥ 10 mg/kg/dose) was achieved for 100% of underweight, 99% of normal weight, 93.9% of overweight, and 27.7% of obese patients ($p < 0.0001$).

Hall. Am J Med. 2008; 121: 515–518



Predictors of antibiotic failure



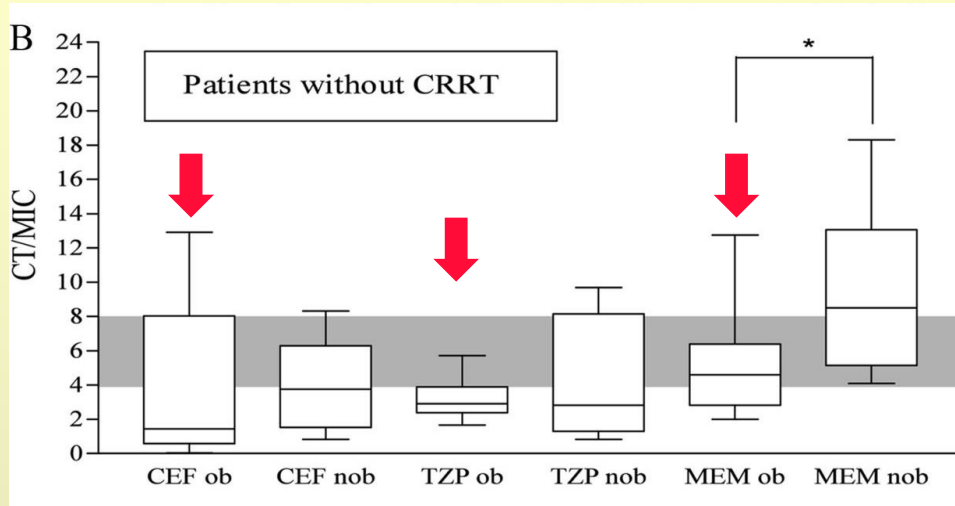
Hospital
Vila Franca de Xira

Variable	Adjusted	
	OR (95% CI)	P-Value
1. Sex (Reference: Male)	0.88 (0.76–1.03)	0.106
2. Age		
20–34 yrs	1.00 (0.78–1.27)	0.974
35–49 yrs	1.03 (0.84–1.26)	0.812
50–64 yrs	0.99 (0.82–1.20)	0.954
65–70 yrs (Reference)	–	–
3. Socioeconomic Status		
Low Income	1.00 (0.85–1.18)	0.960
Middle Income (Reference)	–	–
High Income	0.78 (0.56–1.08)	0.127
4. BMI Category		
Normal (Reference)	–	–
Overweight	1.06 (0.89–1.26)	0.504
Obese	1.26 (1.03–1.52)	0.022
5. Alcohol Consumption		
Non-drinker	1.20 (1.01–1.42)	0.036
Moderate (Reference)	–	–
Heavy	0.98 (0.72–1.33)	0.889
6. MRSA	2.33 (1.78–3.06)	<0.001
7. History of Antibiotic Use	1.27 (1.08–1.50)	0.003

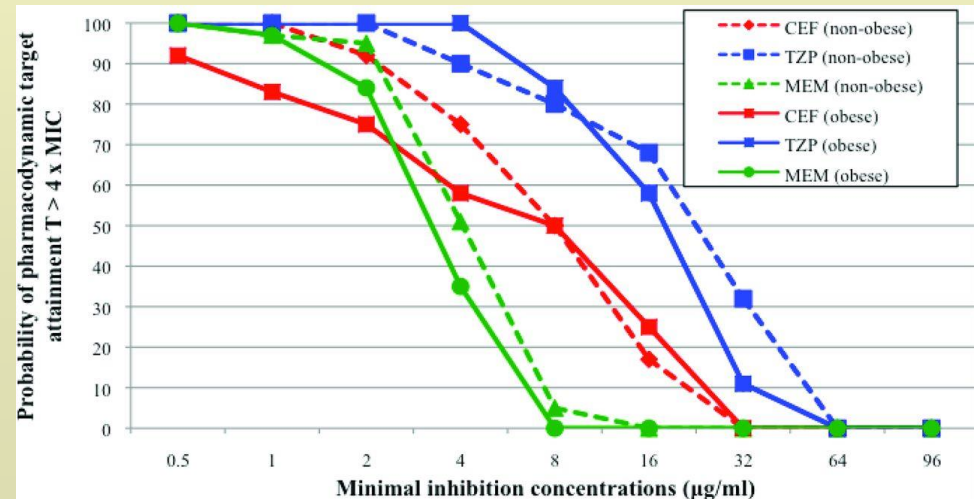
KEY POINTS

- Of the 828 (13.4%) persons who suffered an antibiotic treatment failure (ATF) event, nearly 64% were either overweight or obese.
- Significant predictors of ATF were obesity, antibiotic resistance, recent history of antibiotic use, and being a non-drinker
- Alternative antibiotic dosing strategies may be necessary when treating obese patients for acute infections as a means of reducing the risk of ATF.

Serum drug concentrations obtained in obese and nonobese patients

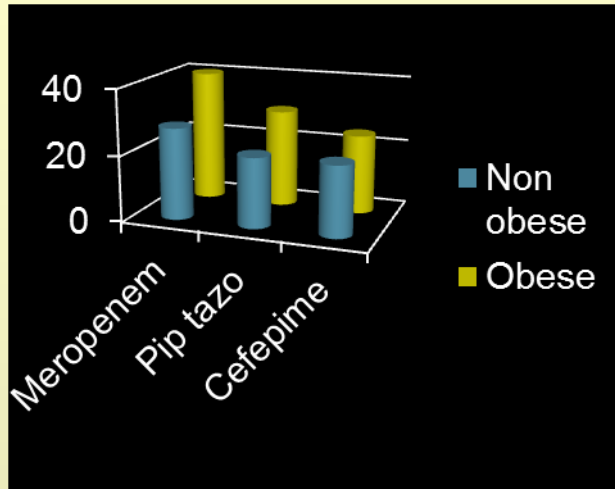


In obese patients without renal failure the probability of target attainment was lower

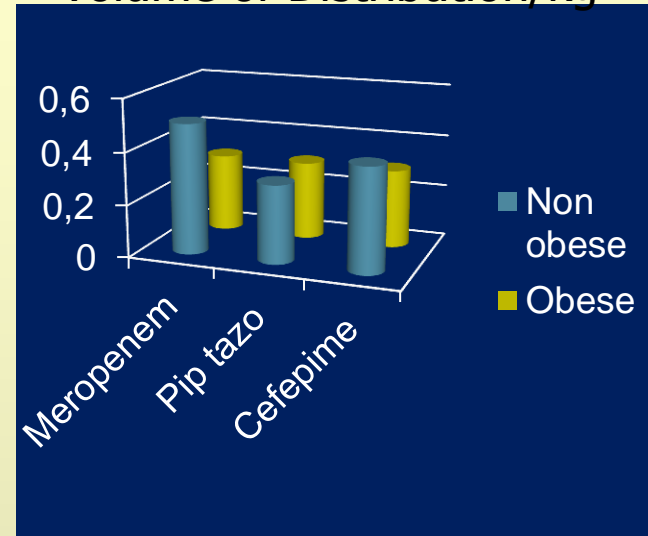


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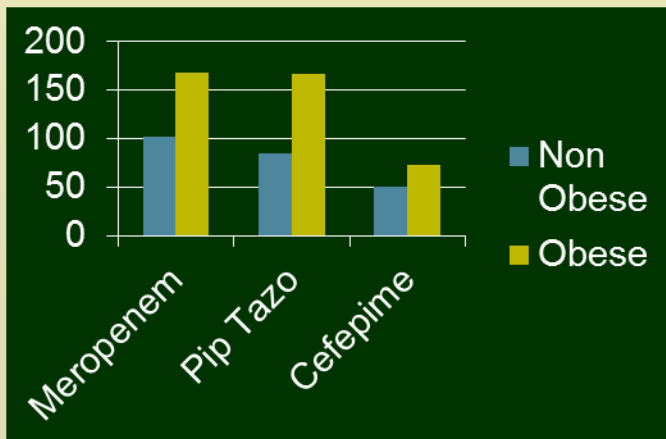
Volume of Distribution



Volume of Distribution/kg

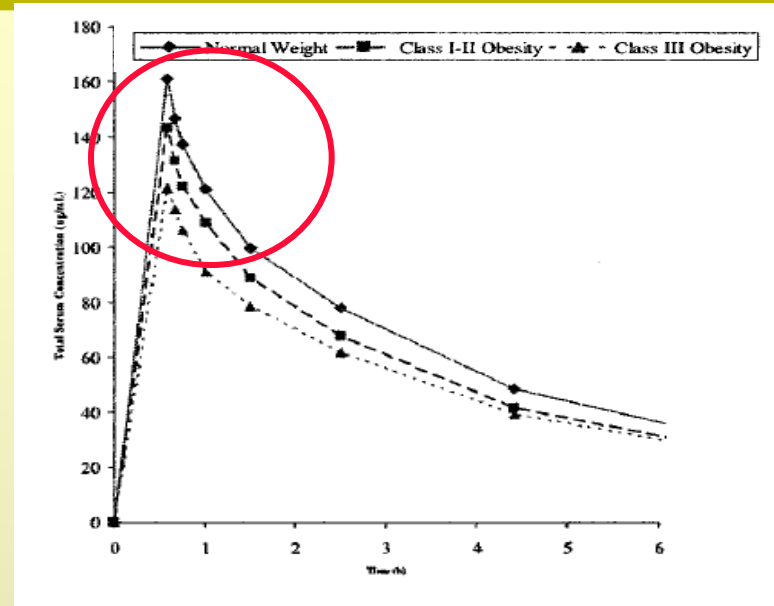
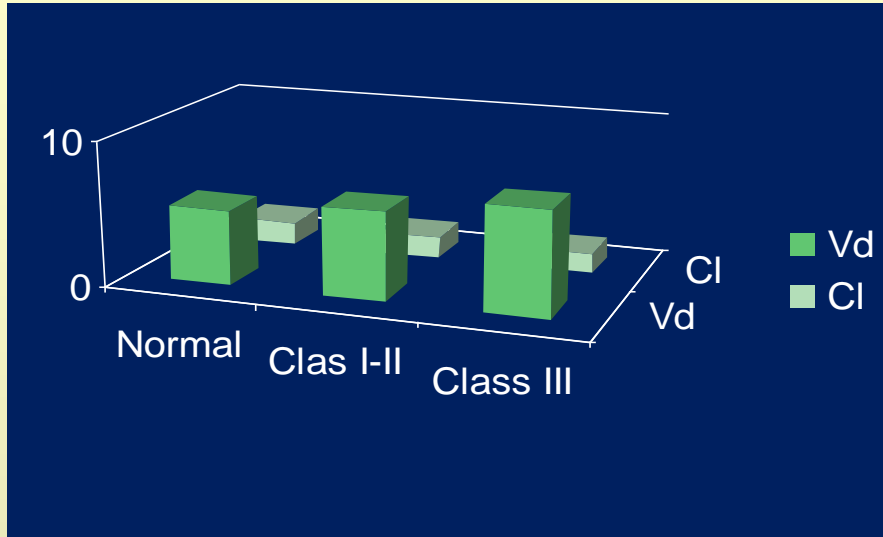


Clearance



In obese patients the total Vd is higher but the Vd/kg is lower

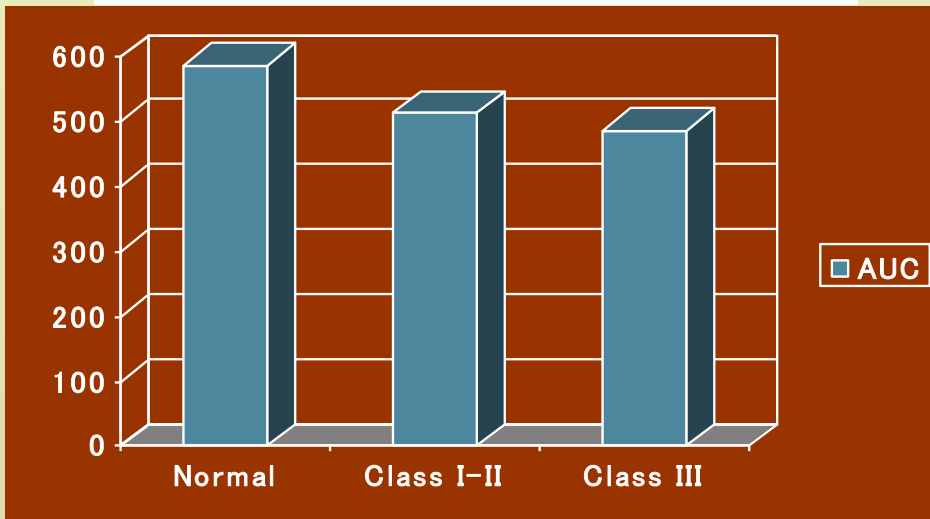
Pharmacokinetics and total concentration of ertapenem versus time profile over 6 h according to weight



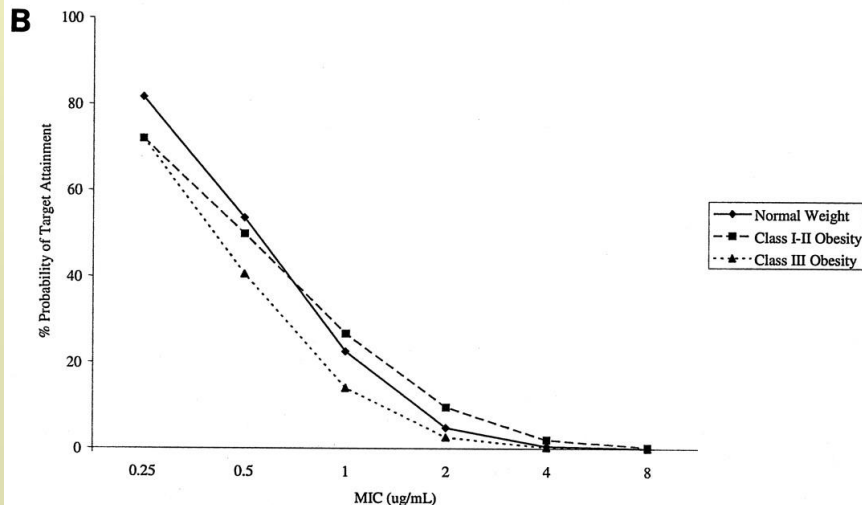
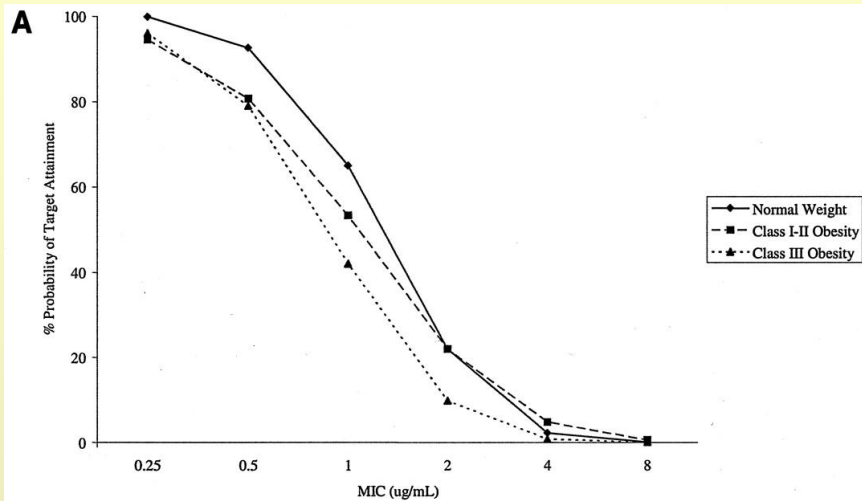
Vd (l) and Cl (l/1,73m²)

Vd increase with weight whilst Vd/kg decreases

Decrease AUC with increasing weight and Vd



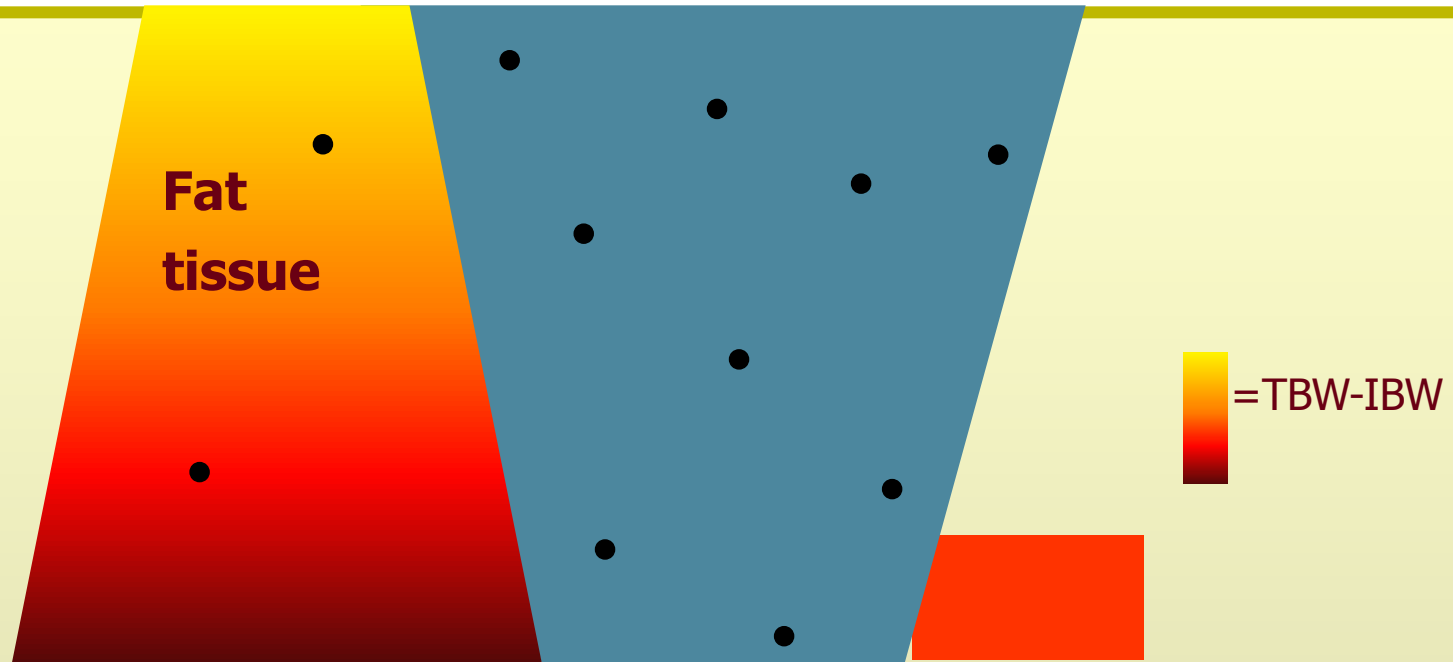
Pharmacokinetics and total concentration of ertapenem versus time profile over 6 h according to weight



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 $\mu g/ml$ in normal-weight, class I-II obese, and class III obese groups.

Small difference but no dosage adjustment was recommended

Obesity and Volume of Distribution



Lipophilic drugs  +  (TBW)

Hydrophilic drugs  + $K * \img alt="yellow-to-red gradient square" data-bbox="616 751 667 801"/>$ (ABW)

K depends on water content and tissue affinity – usually 0,37-0,58

No fat distribution  (IBW)

Dosing Recommendations

Table 1: Dosing Guidelines

Agent	Suggested dosing weight (for dosing or Vd calculation)	Additional dosing recommendation
Antibacterial agents		
Aminoglycosides (amikacin, gentamicin, tobramycin)	Adjusted body weight= IBW+ 0.4 (TBW-IBW)	
Azithromycin		No dose adjustment recommended.
Ampicillin		No dose adjustment recommended; use normal recommended dose, adjusted for renal function.
Aztreonam		No dose adjustment recommended.
Beta-lactam drugs (without other specific recommendations)	Adjusted body weight= [IBW+ 0.3 (TBW-IBW)]	No specific recommendations; base dose on VD calculated off of adjusted body weight.
Carbapenems		No dose adjustment recommended, use normal recommended dose, adjusted for renal function.
Cefazolin		For surgical prophylaxis, increase dose to 2 g.
Ceftazidime, cefuroxime		No dose adjustment recommended; use normal recommended dose, adjusted for renal function.

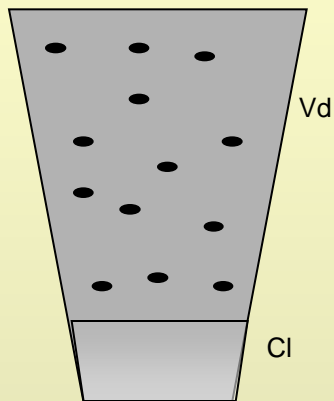
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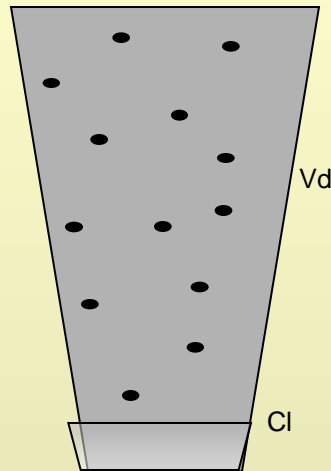
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Aztreonam		No dose adjustment recommended.
Beta-lactam drugs (without other specific recommendations)	Adjusted body weight= [IBW+ 0.3 (TBW-IBW)]	No specific recommendations; base dose on VD calculated off of adjusted body weight.
Carbapenems		No dose adjustment recommended, use normal recommended dose, adjusted for renal function.
Cefazolin		For surgical prophylaxis, increase dose to 2 g.
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Ciprofloxacin	Adjusted body weight= [IBW+ 0.45 (TBW-IBW)]	No specific recommendations; base dose on VD calculated off of adjusted body weight.
Clindamycin		No data.
Daptomycin	TBW	Consider reducing final dose by 25%.
Doxycycline		No data.
Erythromycin	IBW	
Linezolid		No dose adjustment recommended.
Metronidazole		No data.
Nafcillin		May need to increase dose to 3 g q6h.
Penicillin G		No dose adjustment.
Quinolones (levofloxacin and moxifloxacin)		No dose adjustment recommended; use normal recommended dose, adjusted for renal function as appropriate.
Quinupristin-dalfopristin	TBW	
Sulfamethoxazole-trimethoprim		No data.
Tigecycline		No dose adjustment.
Vancomycin	TBW	A more frequent dosing interval may be required; use TDM to guide dosing.
Antifungal agents		
Amphotericin B	TBW for conventional preparation IBW for lipid preparations	
Echinocandins		No data.
Fluconazole		Consider higher doses in obese patients.
Echinocandins		No data.
Antiviral agents		
Acyclovir	IBW	
Cidofovir		No data.
Foscarnet		No data.
Ganciclovir		No data.

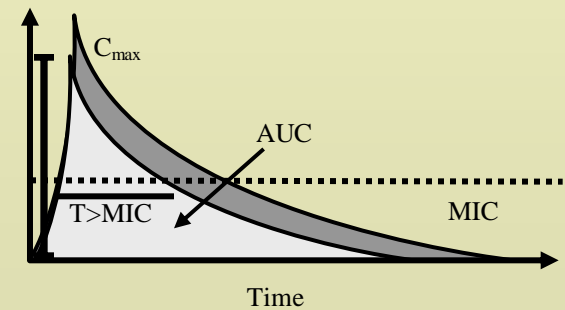
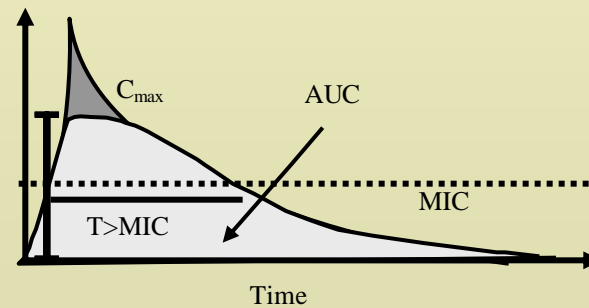
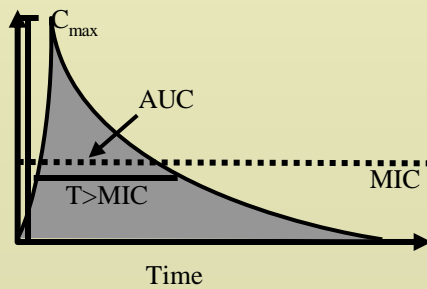
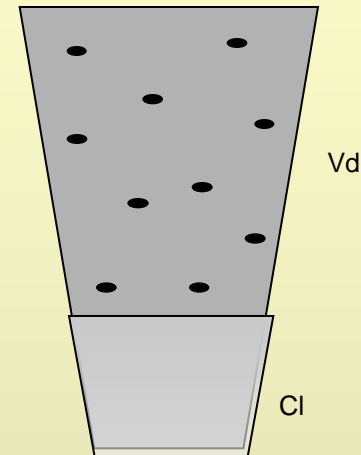
Healthy



Organ Failure



Sepsis



Obese Population

- ➡ Always use high loading doses – according to ABW or TBW

 - ➡ Adjust maintenance dose according to Pharmacodynamics and Clearance (especially peak dependent drugs)
 - Steady state concentration most likely not affected

 - ➡ Consider renal function and augmented renal clearance
 - 65,1% of patients with normal creatinine
- Udy, Crit Care Med 2014; 42:520–527
-
- ➡ In unstable obese patients use therapeutic drug monitoring whenever possible
 - Alternative: population pharmacokinetics



V-FIB

GODS Ctrl/Alt/Delete