UWTASP tele-antimicrobial stewardship program | echo

April 2, 2024

PK/PD

- Zahra Kassamali Escobar, PharmD

Agenda

- Defining Terms
- PK/PD Dosing Principles
- Application: Obesity

Defining Terms: Pharmacokinetics

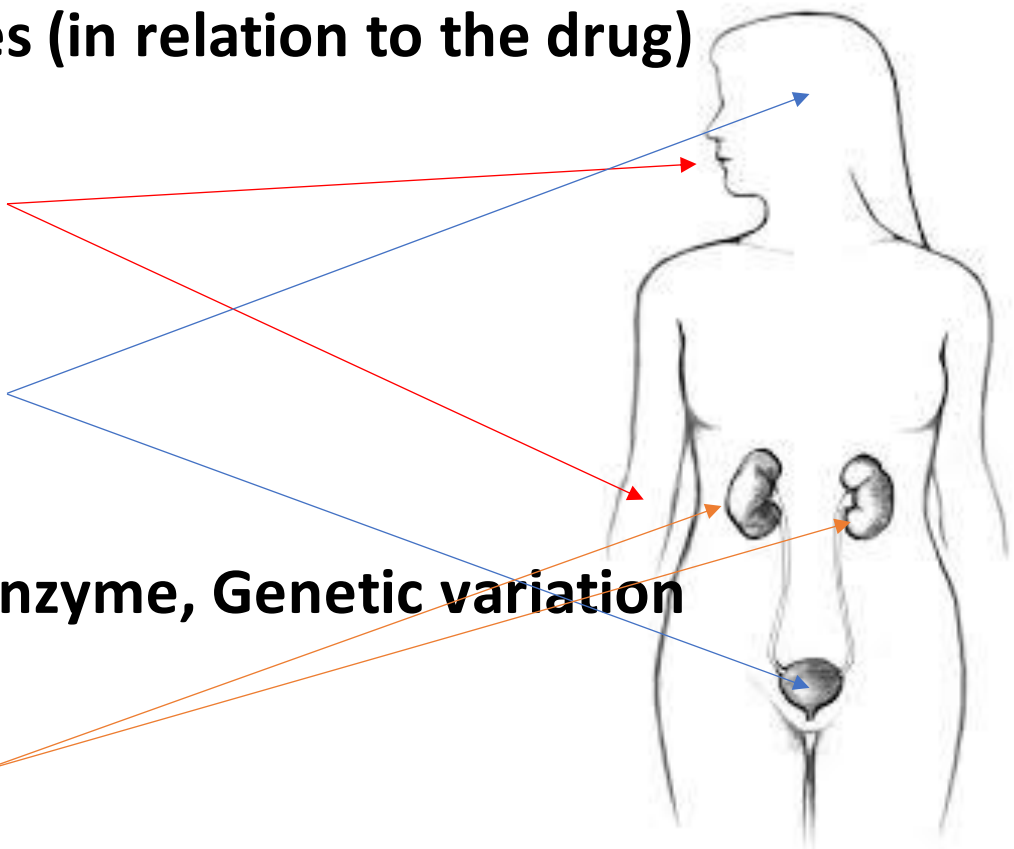
What the body does (in relation to the drug)

ABSORPTION:

DISTRIBUTION:

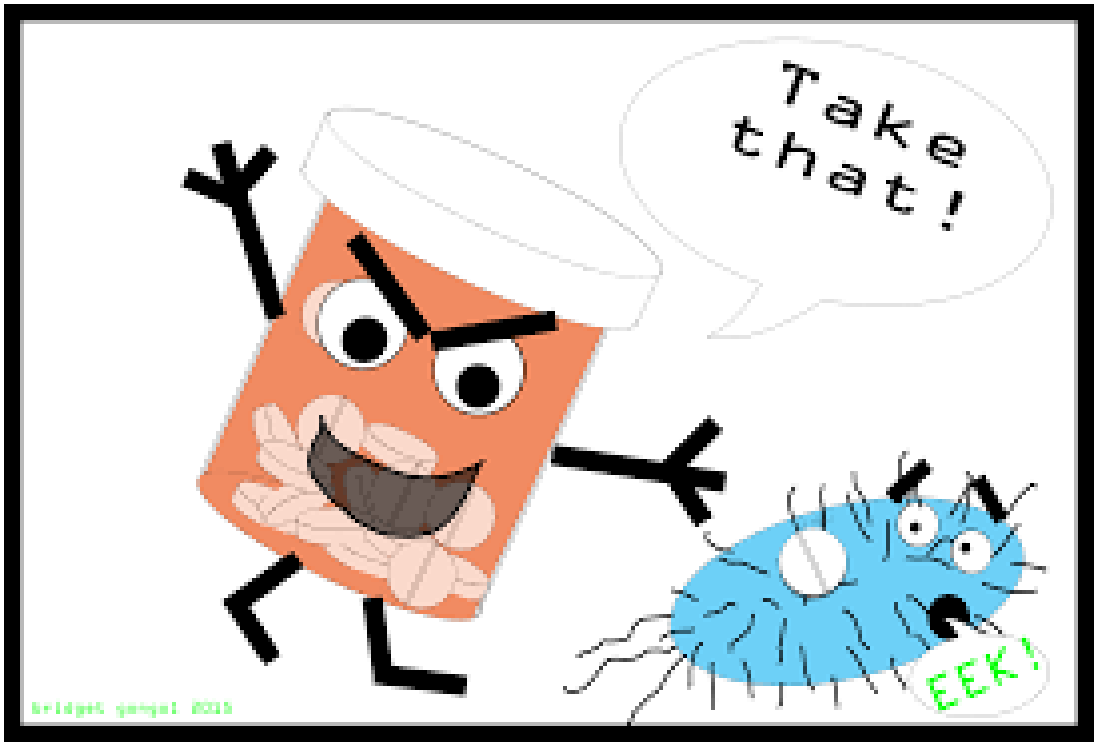
METABOLISM: **Enzyme, Genetic variation**

ELIMINATION:



Defining Terms: Pharmacodynamics

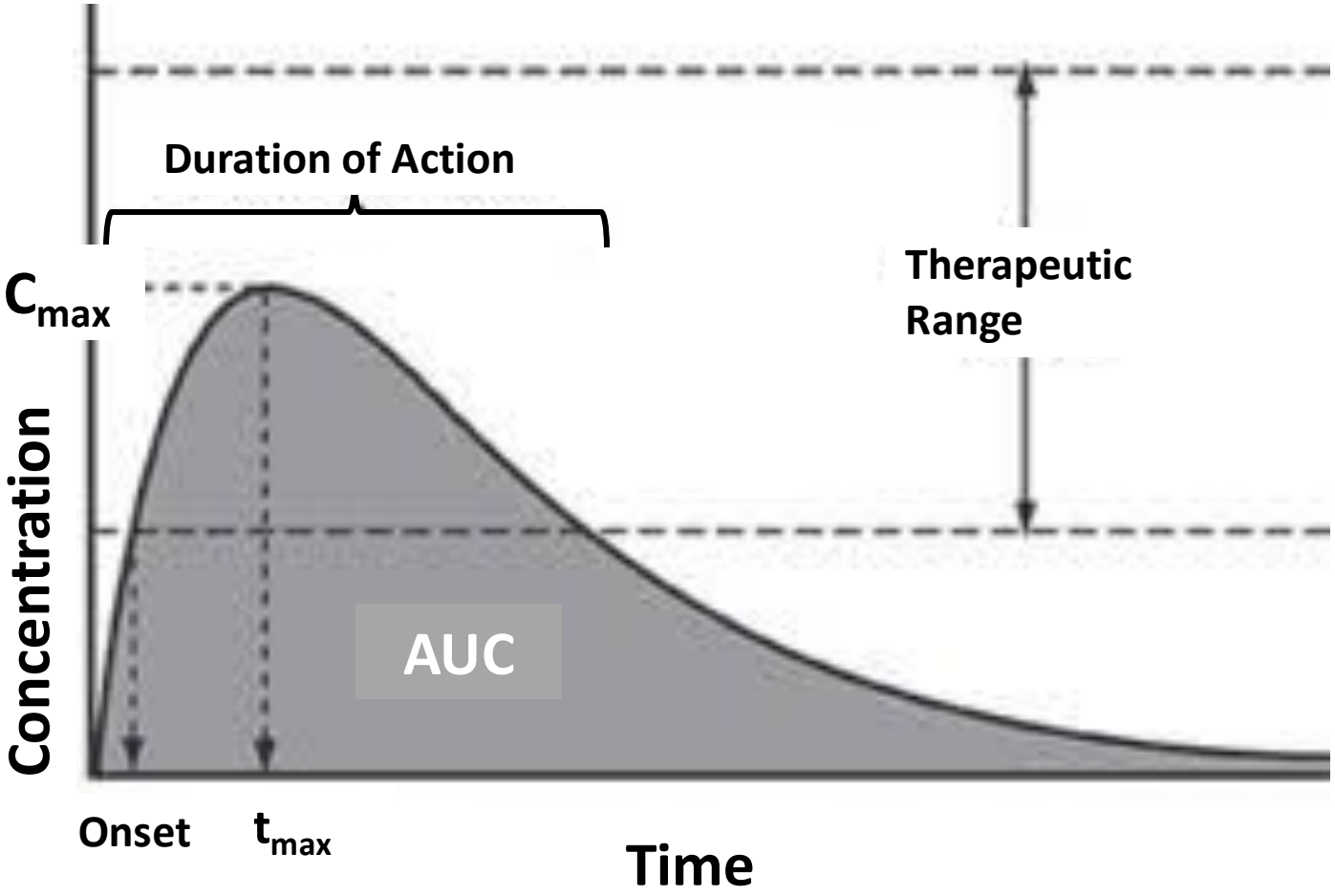
What the drug does (in relation to the body)



Efficacy of Antibiotics is directly related to how we dose them

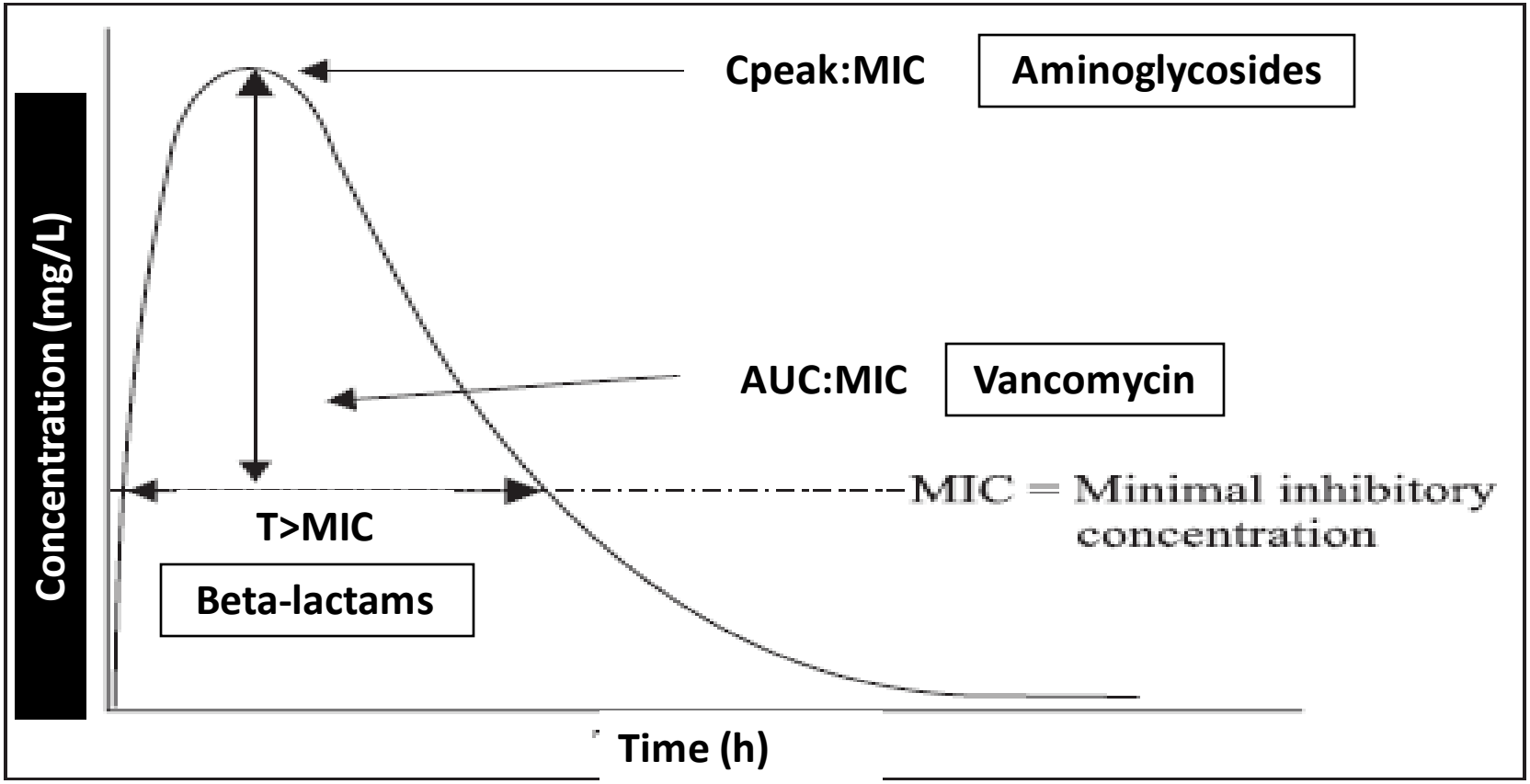
Defining Terms: Pharmacodynamics

What the drug does (in relation to the body)



PK/PD Dosing Principles:
Managing antibiotic dose in relation to bacteria

What the drug does (in relation to the body)



AUC = Area under the curve, MIC = Minimal inhibitory concentration, T = Time

Santos Filho L et al. Braz J Microbiol. 2007 Apr/June;38(2):183-193.
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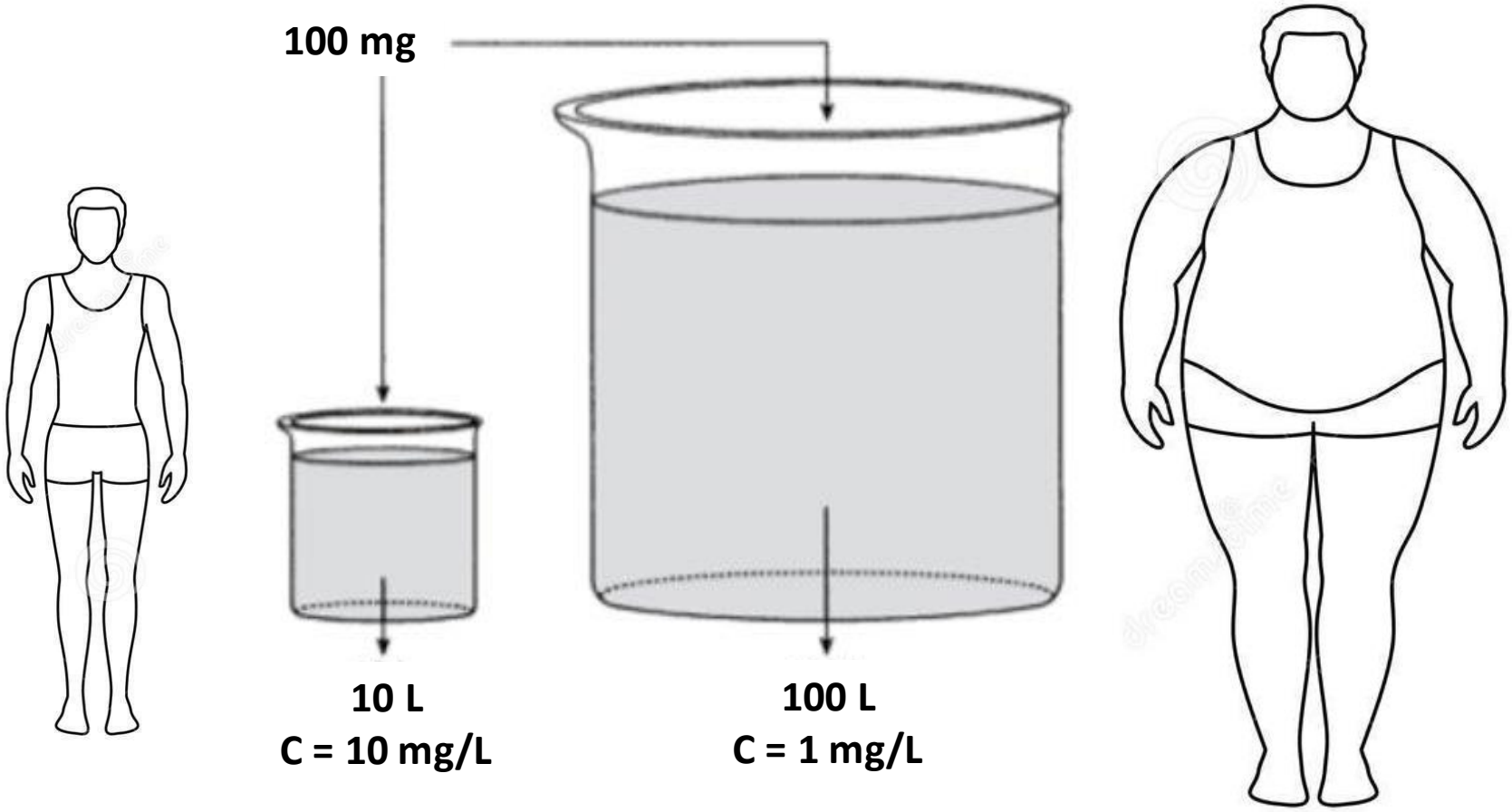
Craig WA. Infect Dis Clin North Am. 2003 Sep;17(3):479-501.

PK Practical Applications:

Dosing in Obese Patients – Bigger Volume



Bauer LA, Applied Clinical Pharmacokinetics 2nd Edition

ADME & Obesity: Pharmacokinetics

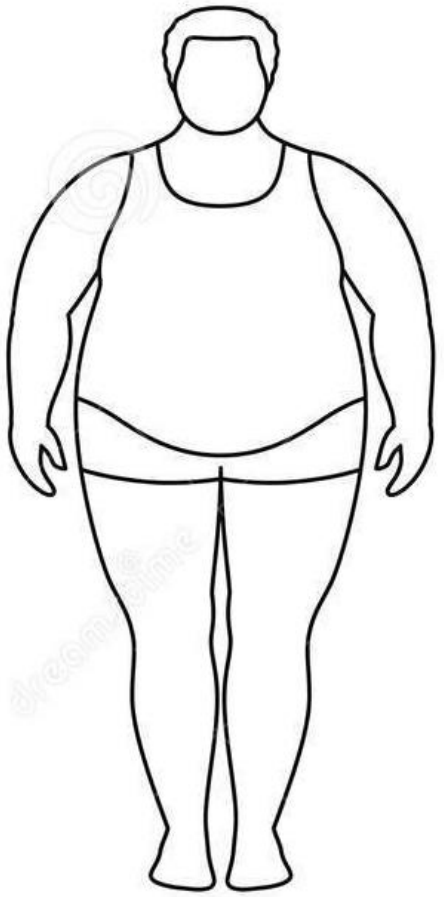
What the body does (in relation to the drug)

ABSORPTION: ✗

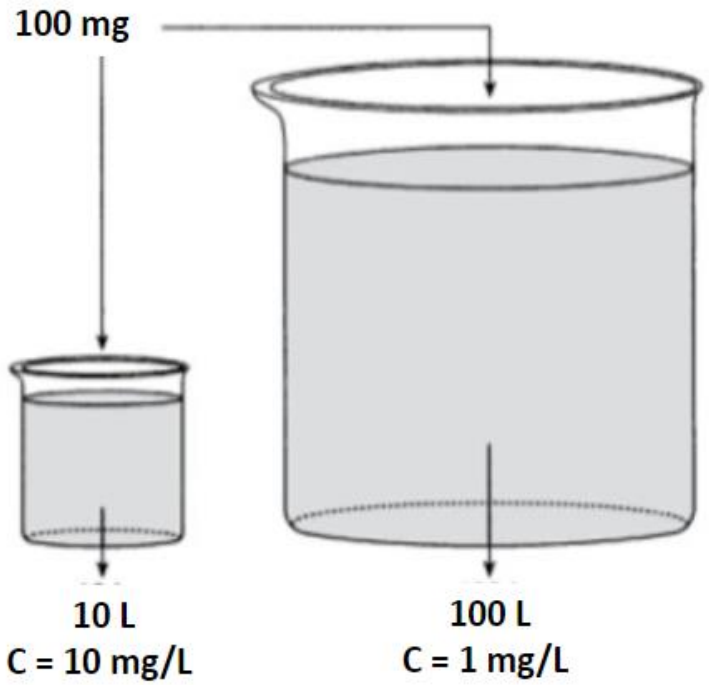
DISTRIBUTION: ✓

METABOLISM:

ELIMINATION:



PK Practical Applications:
Dosing in Obese Patients – Bigger Volume of Distribution

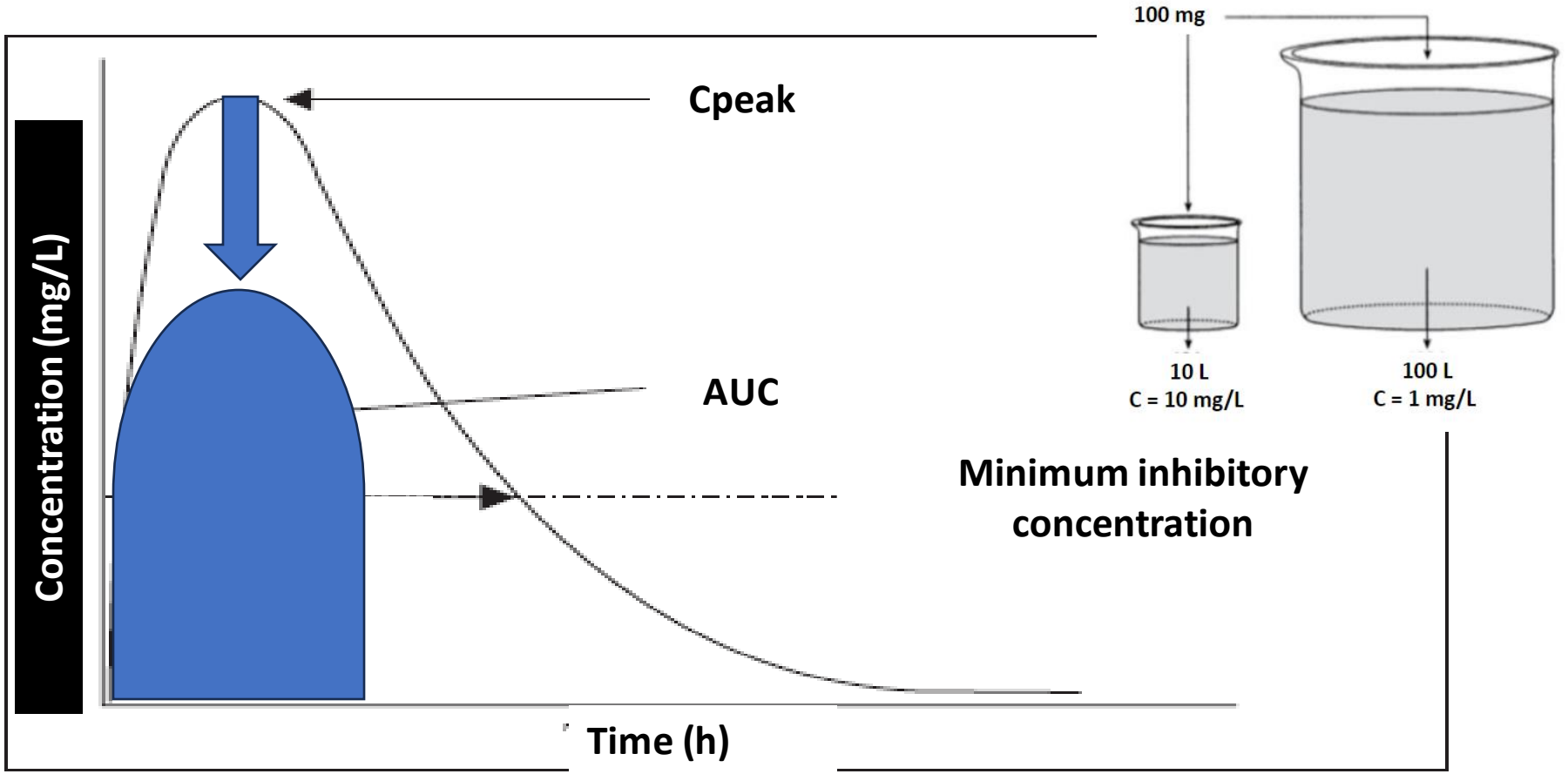


- ✓Hydophilic/ Hydrophobic
- ✓Drug delivery system
- ✓Mechanism of action

Meng L et al. Pharmacotherapy 2017;37(11):1415–1431) doi: 10.1002/phar.

What does Bigger volume of distribution mean?

Give the first dose based on total body weight



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ADME and Obesity: Pharmacokinetics

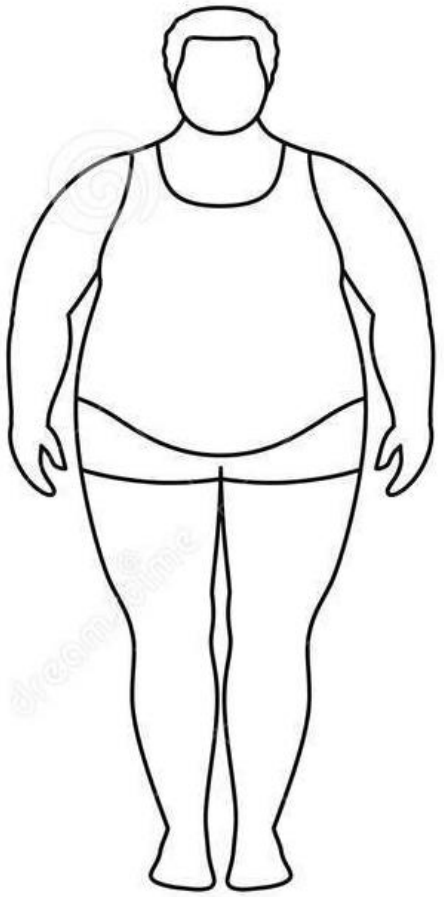
What the body does (in relation to the drug)

ABSORPTION: ✗

DISTRIBUTION: ✓

METABOLISM: ?

ELIMINATION:



Metabolism and Obesity:

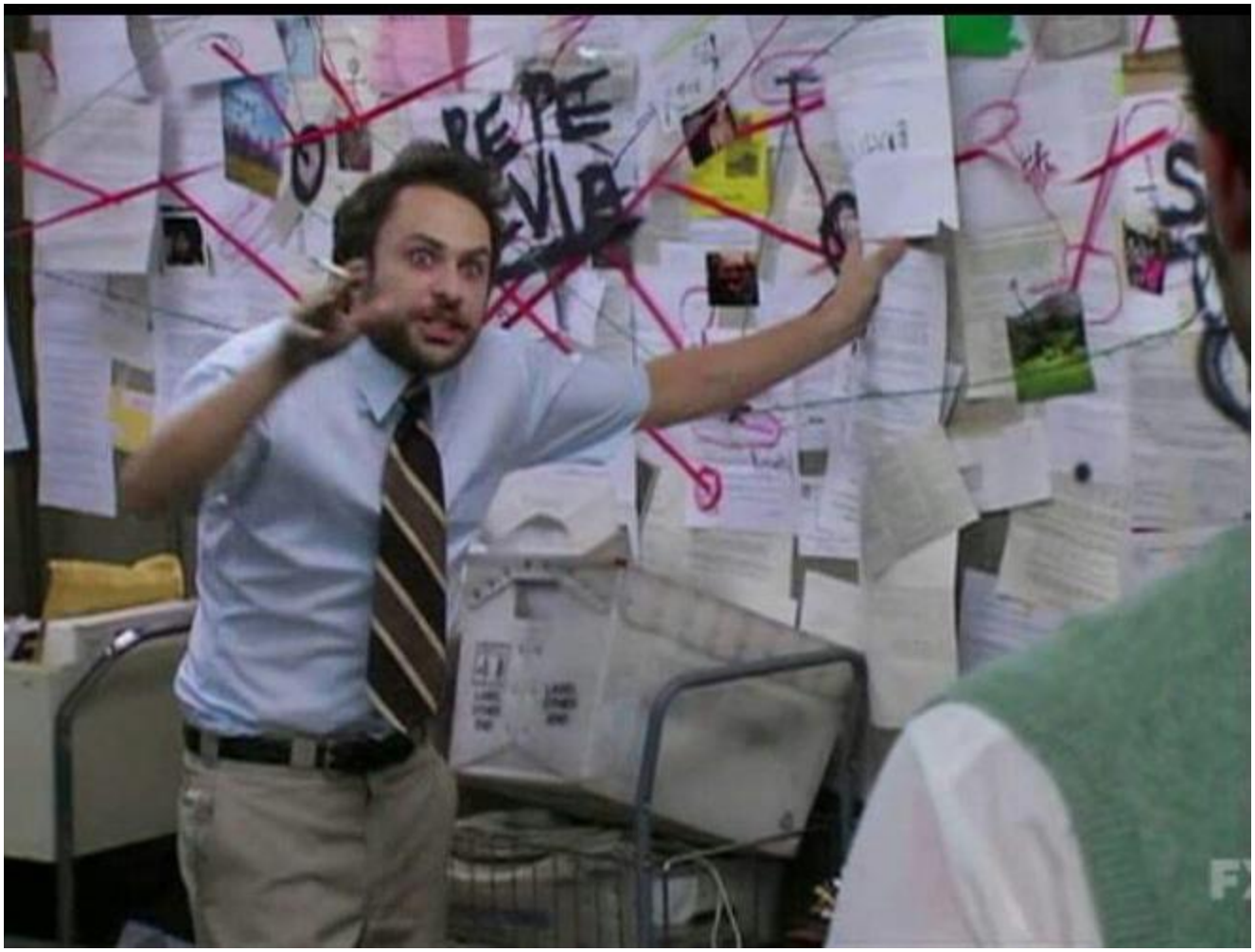
Impact of Obesity on Drug Metabolism and Elimination in Adults and Children

Margreke J.E. Brill,[1,2] Jeroen Diepstraten,[1] Anne van Rongen,[1] Simone van Kralingen,[3] John N. van den Anker[4,5] and Catherijne A.J. Knibbe[1,2]

Clearance of cytochrome P450 (CYP) 3A4 *substrates is* **lower in obese** *as compared with non-obese patients. In contrast, clearance of drugs primarily metabolized by uridine diphosphate glucuronosyltransferase (***UGT***), glomerular filtration and/or tubular-mediated mechanisms, xanthine oxidase,* **N-acetyltransferase or CYP2E1** *appears* **higher in obese** *versus non-obese patients. Additionally, in obese patients,* **trends indicating higher clearance** *values were seen for drugs metabolized via* **CYP1A2, CYP2C9, CYP2C19 and CYP2D6**, *while studies on high-extraction-ratio drugs showed somewhat inconclusive results.*

Clin Pharmacokinet.2012 May 1;51(5):277-304.
doi: 10.2165/11599410-000000000-00000.

Metabolism and Obesity:



ADME and Obesity: Pharmacokinetics

What the body does (in relation to the drug)

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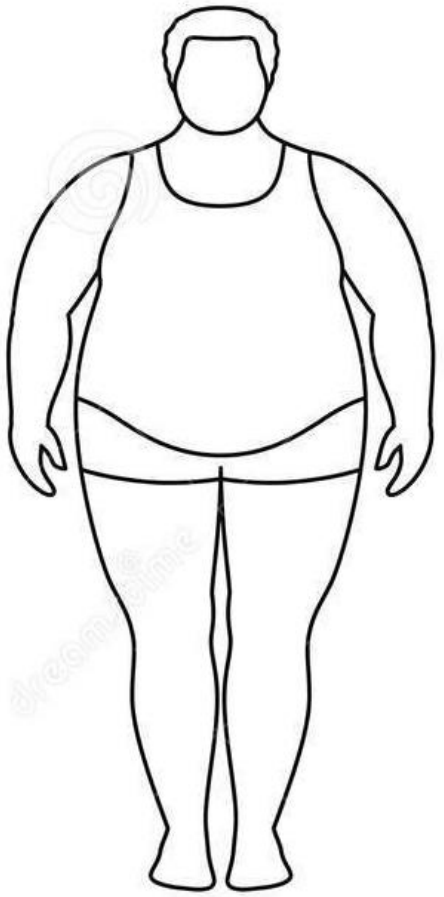
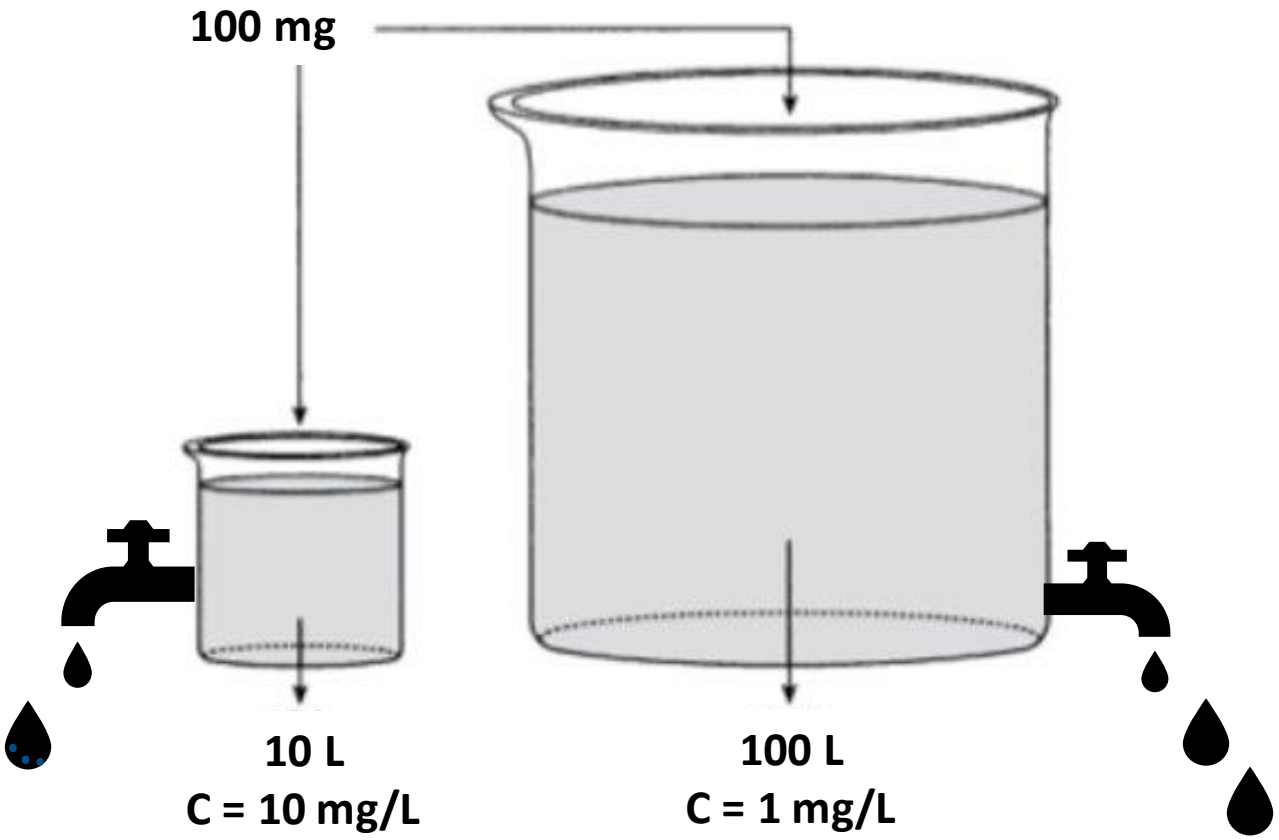
METABOLISM: ?

ELIMINATION: ✓



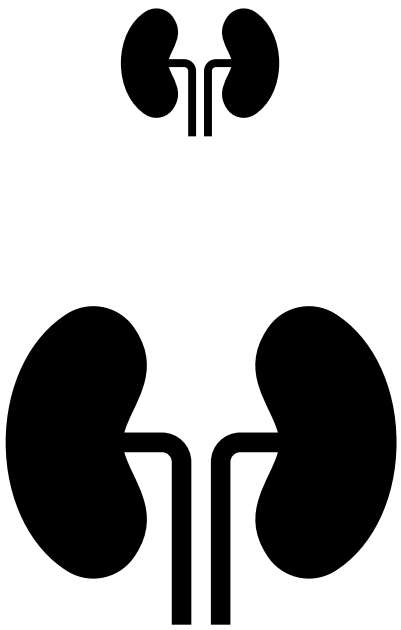
PK Practical Applications:

Dosing in Obese Patients – Is there greater clearance?



Bauer LA, Applied Clinical Pharmacokinetics 2nd Edition

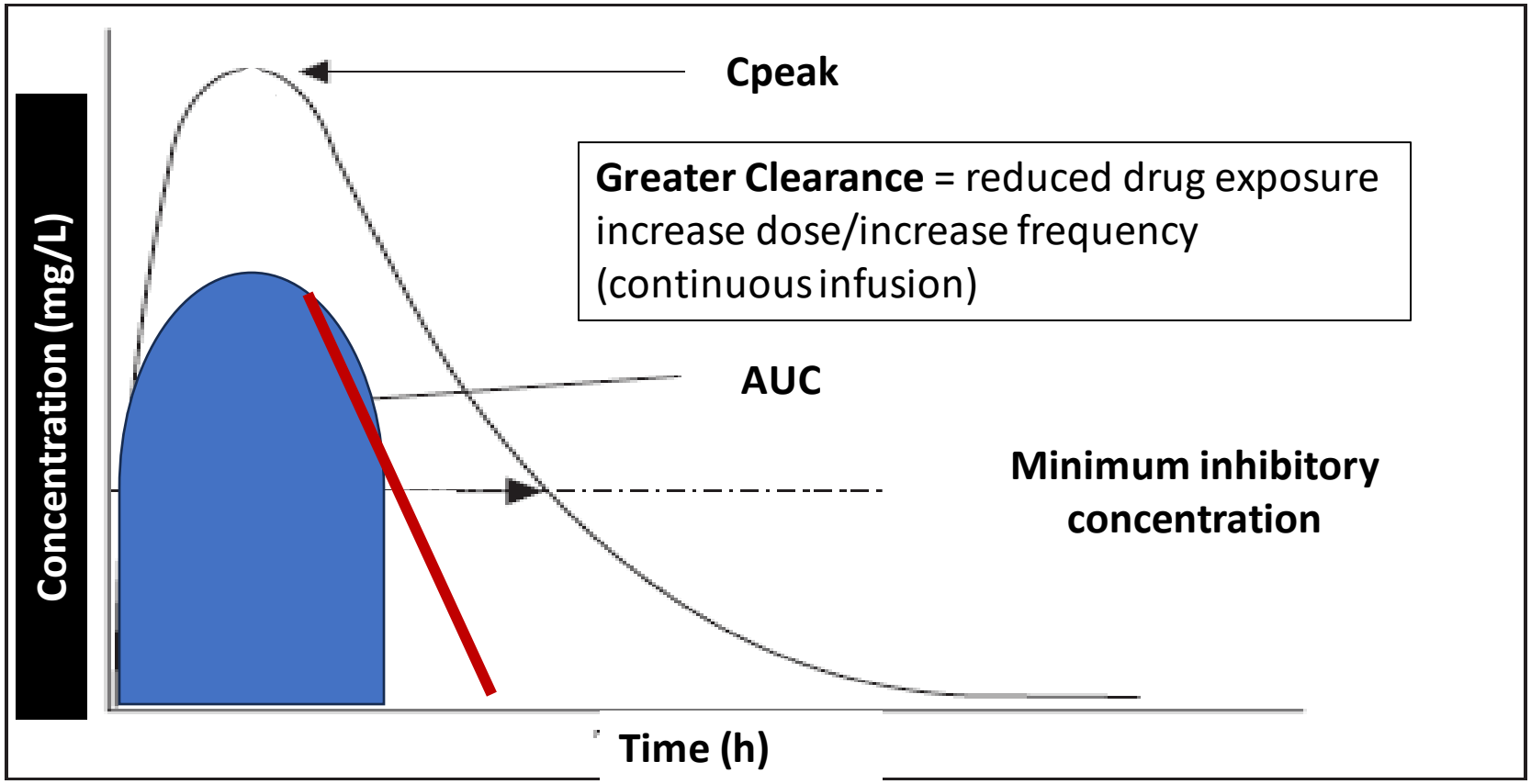
Big Human = Big Beans



- ✓Increased renal blood flow
- ✓Increased GFR
- ✓Increased kidney mass

Meng L et al. Pharmacotherapy 2017;37(11):1415–1431) doi: 10.1002/phar.

Predicting Clearance
Scenario 1 – the athlete



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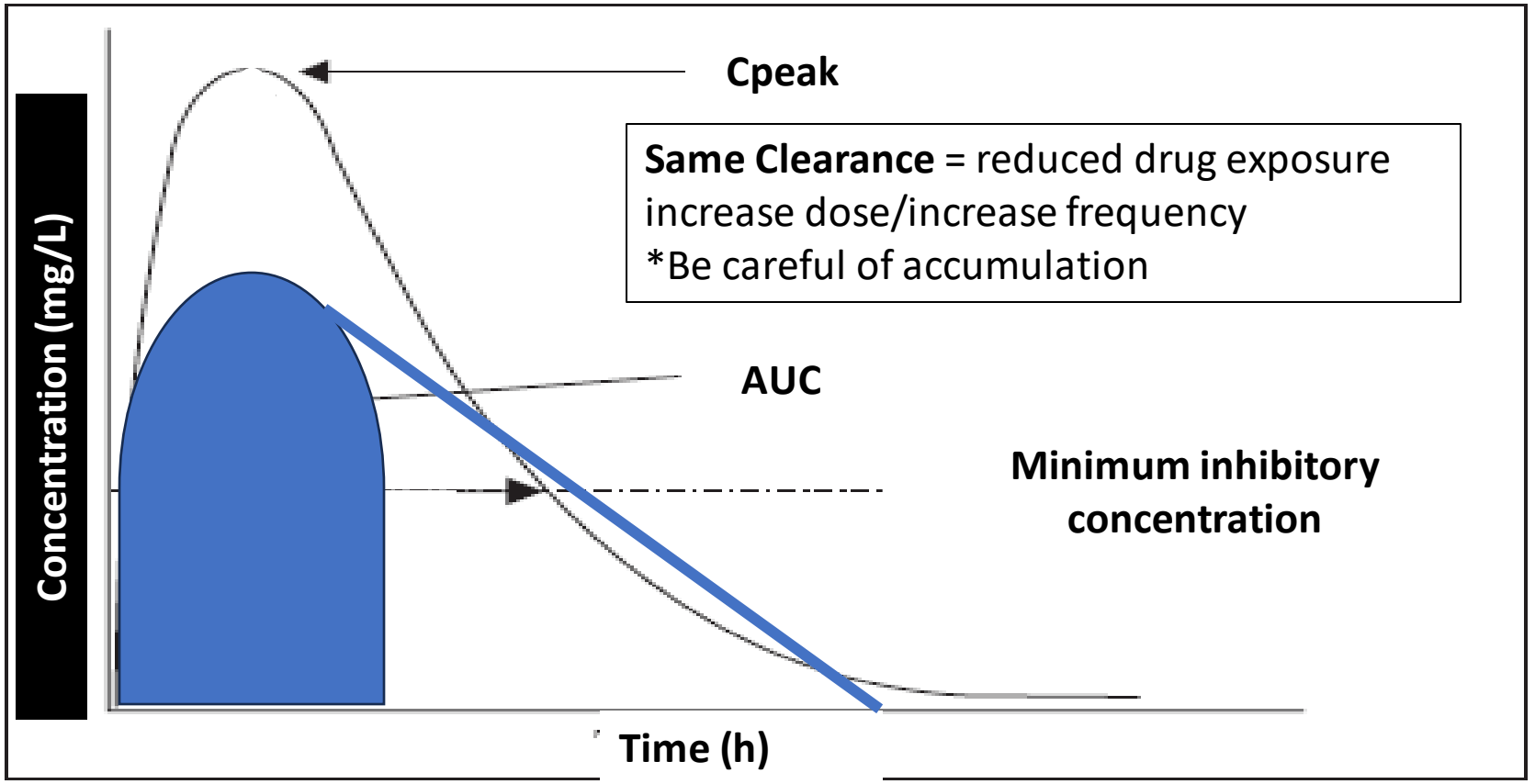
Predicting Clearance
Scenario 2



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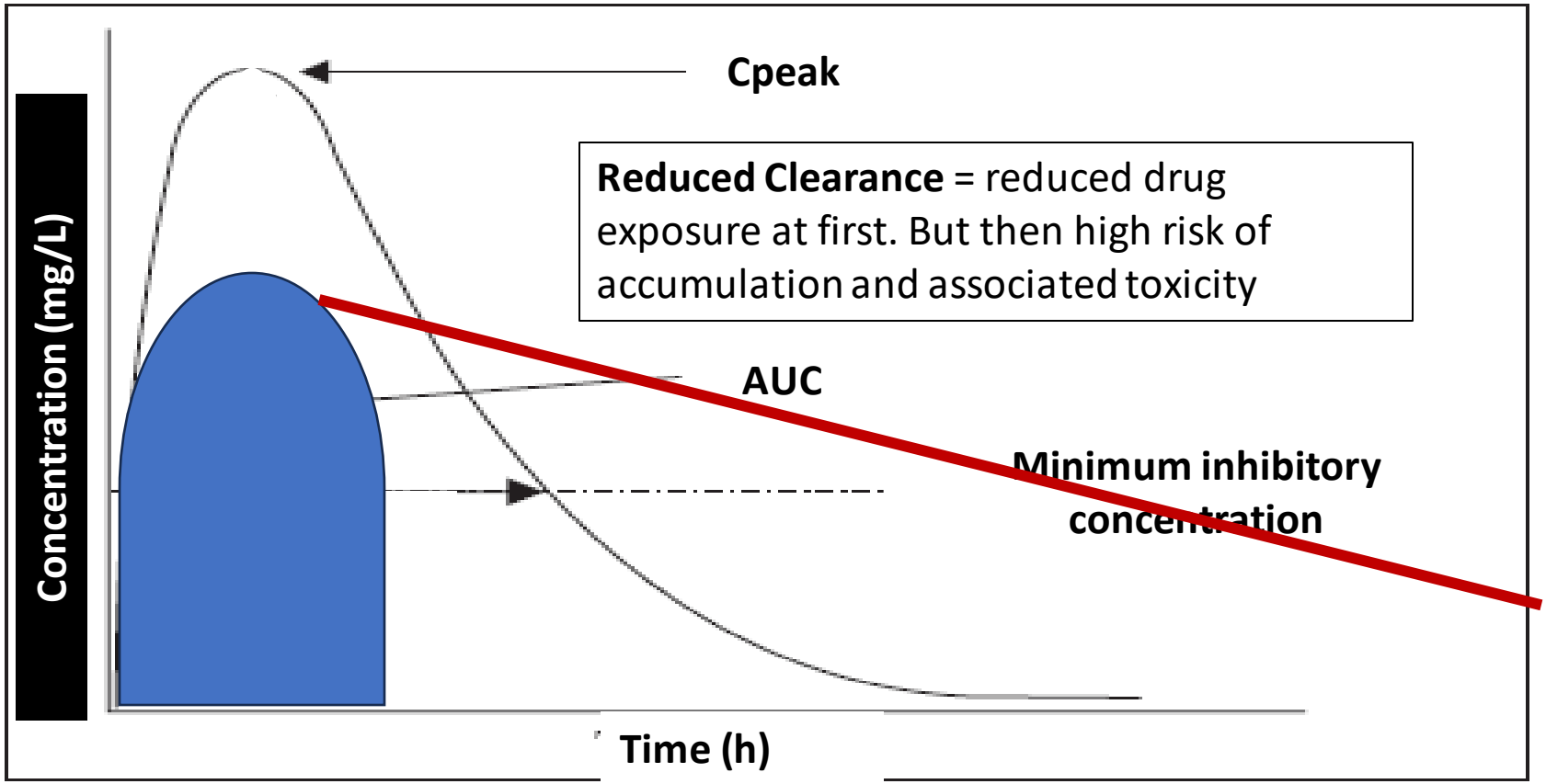
Predicting Clearance
Scenario 3- Obese and Comorbid



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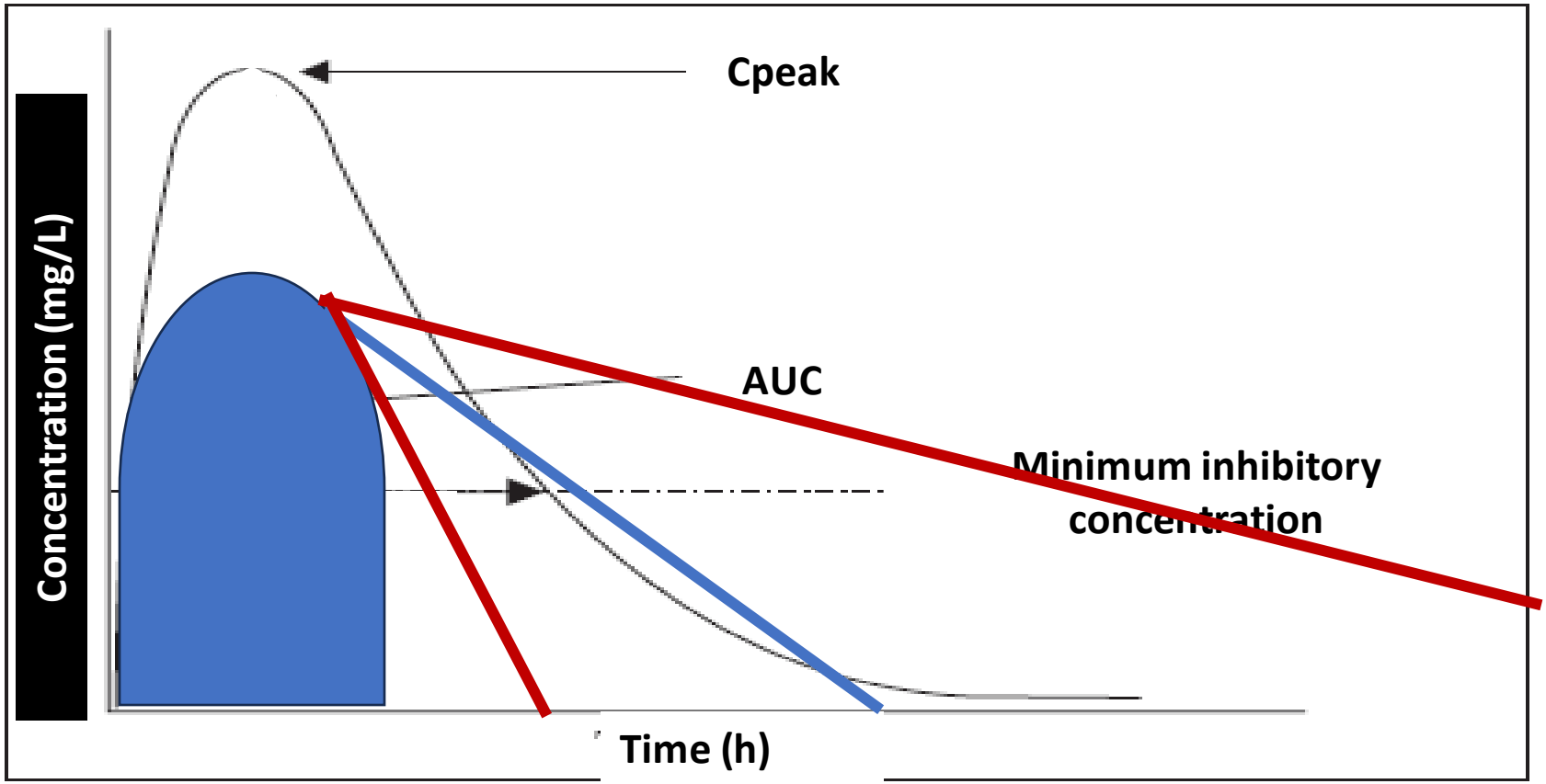
Craig WA. Infect Dis Clin North Am. 2003 Sep;17(3):479-501.

How do I predict Clearance?
The same way you always have, carefully & clinically



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How to adjust clinical practice?

Drug/Class	PK Change	Dosing Suggestions
Piperacillin/tazobactam	↑ Vd ↑ Clearance	Prolonged infusion strategies
Cefazolin (surgical prophy)	↑ Vd	Higher doses (3g) in patients ≥120kg
Levofloxacin	↔	No change
Vancomycin	↑ Vd ↑ Clearance	Therapeutic drug monitoring

Other Drugs? See this paper:

Comprehensive Guidance for Antibiotic Dosing in Obese Adults

Lina Meng,[1,2*] Emily Mui,[1,2] Marisa K. Holubar,[2,3] and Stan C. Deresinski[2,3]

citations

Resource: Stanford obesity dosing guide

https://med.stanford.edu/content/dam/sm/bugsanddrugs/documents/antimicrobial-dosing-protocols/SHC-ABX-Obesity-Dosing-Guide.pdf

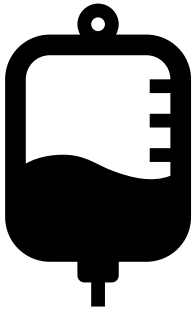
Table 1.[1,153] Recommended Antibiotic Dosing in Obesity (BMI ≥ 30 kg/m²)

Drug	Dose[a]	Study Type[b]			Comments
		Case studies	PK/PD studies	Clinical outcomes	
Acyclovir[146-148, 162]	Use ideal or adjusted body weight		•	•	- PK study: 5mg/kg IV x1 showed that dosi based on IBW in obese patients led to lov AUC than dosing by TBW in normal-weigl patients. Authors suggest using AdjBW - Renal function may be a more important consideration than weight-based dosing i obese patients - No difference in AKI rates with AdjBW compared to IBW dosing[162]
Amoxicillin ± clavulanate	Amoxicillin: 1g PO every 8 hours Amoxicillin/clavulanate: 875mg/125mg PO every 8 hours or 2000mg/125mg XR PO BID		•		
Cefazolin[15-21]	Insufficient data	•	•	•	- Consider upper limit of normal dosing in severe infections, e.g. up to 2 g q8h (option for continuous infusion)[22], or 1.5-2 g q6h intermittent dosing - In post-trauma critically ill patients, data suggests 2g q6h if CrCl > 215 ml/min.[23]

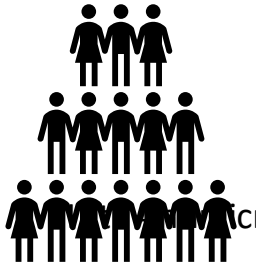
Does it matter? Sometimes

STUDY	ANALYSIS	OUTCOMES

Cefepime ≥ 24h

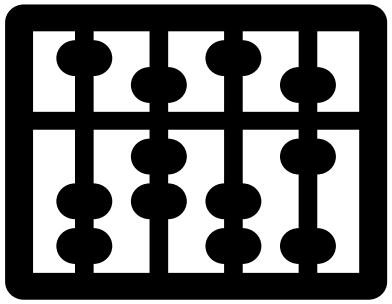


N = 180 patients with GNR bacteremia



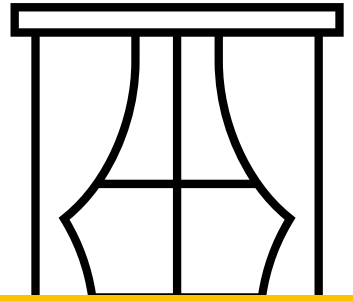
PK Model

$T_{>MIC}$ = 74%



Too Healthy
APACHE II score <9

JUST RIGHT
APACHE II (9-22)



Goldilocks Window

Too Sick
APACHE II score >22

Probability of Survival

icrob Agents. 2017 Sep;50(3):487-490. doi: 10.1016/j.ijantimicag.2017.04.023.

Summary

PK/PD Dosing Principles

To optimize antibiotic activity (i.e. pick a dose) consider

-How the body acts on the drug (PK)

-How the drug acts on the body/bacteria (PD).

Application: Obesity

Bigger volume = lower Cmax = ?potentially delayed onset of action or shorter duration of activity

Bigger kidneys = higher CL if no comorbidities = shorter duration of activity

Dose Dosing Matter?

Sometimes in some people.