Dosing in Obesity

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Case

65 year old male comes to the ED for new headache, high fevers, and “just not feeling right”.

Yesterday, he felt fine. Wt: 209kg, BMI = 63

Temp 40°C

PE:

+Nuchal rigidity

Labs:

WBC= 14, SCr 1.2

Blood cultures are drawn but LP pending due to BMI

Concern for bacterial meningitis

You are evaluating the following orders:

Ceftriaxone 2g IV q12

Vancomycin 1g IV q12

Acyclovir IV 10mg/kg IV q8h

Ampicillin 2g IV q6h

Are the standard doses appropriate for our patient that weighs 209kg?

WHO Obesity Classification

Body Mass Index (BMI)

BMI: mass(kg)/ (height (m))^2

Classification	BMI (kg/m^2)
Normal weight	18.5-24.99
Overweight	25-29.99
Obese Class I	30-34.99
Obese Class II	35-39.99
Obese Class III (morbid obesity)	$\geq$ 40

Which dosing weight do you use?

- **Total body weight (TBW)**
- **Ideal body weight (IBW), kg:**
  - Men: 50 + 2.3 (inches > 60 inches)
  - Women: 45.5 + 2.3 (inches > 60 inches)
- **Adjusted Body Weight (ABW)**
  - IBW + C* (TBW – IBW)
  - C = correction factor
  - Most commonly C= 0.4 for aminoglycosides

Pharmacokinetics

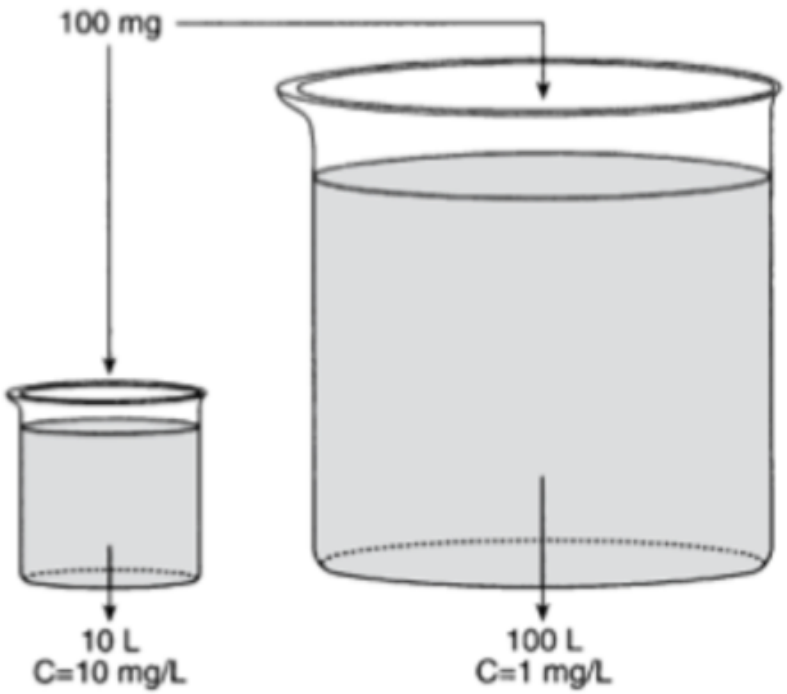
- **Absorption**
  - Maybe altered, lack of data
- **Distribution**
  - Volume of distribution, generally increased
- **Metabolism**
  - Maybe altered, lack of data
- **Excretion**
  - Increased Renal clearance

Volume of distribution

- Altered in obese due to increase in adipose tissue
- BUT can be overestimated by TOTAL body weight if drug does not enter adipose tissue (hydrophilic drugs such as aminoglycosides)

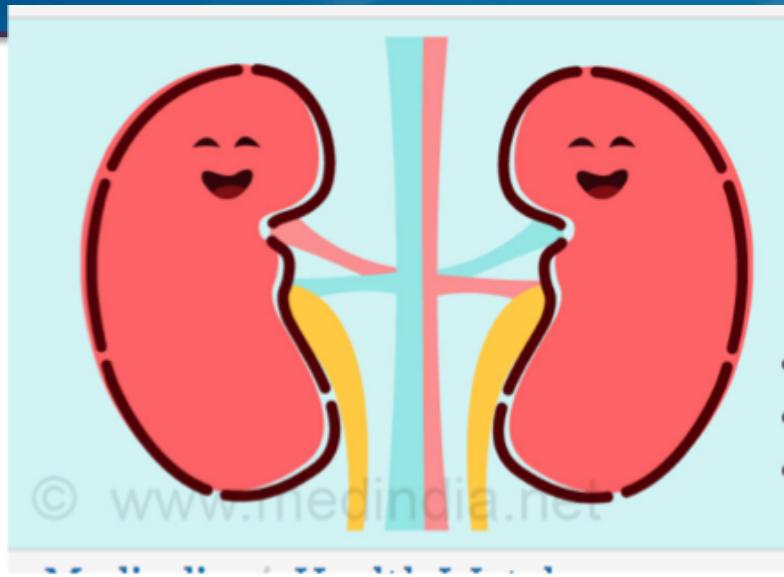
Hydrophilic vs Lipophilic Drugs

- Hydrophillic: Adipose is composed of 30-40% of water
- Lipophilic: Fat “loving” compounds can accumulate



Bauer LA, Applied Clinical Pharmacokinetics 2nd Edition

Renal Clearance



- Increased in obesity
  - Enlarge kidney size
  - Increased renal perfusion
- Decreased
  - Acute kidney injury
  - Age or obesity-related nephropathy

Estimation of GFR: Cockcroft-Gault vs Salazar-Corcoran vs ???

- Try using Adjusted BW 40% in CCG

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Cephalosporins

- Hydrophilic agents with high degree of protein binding, so little penetration into adipose tissue
- Ceftriaxone has 85-95% protein binding, not specifically studied in obesity

- Cefazolin has been studied in pre-op setting with mixed results
  - high saturable protein binding and good correlation with Vd and decreased SQ concentrations

Pharmacotherapy 2017;37(11):1415–1431

Ampicillin

- Only one case study with 6 patients
- Increased Vd, but Cl remained unchanged

- Recommendation:
  - No definitive data published
  - Use upper limit of normal dosing interval

Pharmacotherapy 2017;37(11):1415–1431

Vancomycin

- Increased volume and clearance relative to non-obese
- Weight normalized Vd is not linear at BMI ≥40
  - Lower loading doses needed at higher BMI

Recommendation:

Load with 20-25 mg/kg (based on TBW)—max 2.5g

10-15 mg/kg q12, then adjust based on TDM

More levels the better!

Try q8h dosing

Pharmacotherapy 2017;37(11):1415–1431

Acyclovir

- Original package insert: use IBW for obese patients
- Recent study comparing PK of obese (avg: BMI 45) compared to non-obese (avg: BMI 22.5) were given 5mg/kg based on IBW for obese and TBW for non-obese.
  - Increased clearance (19.4 vs 14.3 L/h, p = 0.047)
  - Exposure was lower (AUC) for obese (15.2 vs 24 mg*h/L, p=0.011)
  - Author's Conclusion: Use an adjusted body weight (although not studied!)

Antimicrob Agents Chemother 2016 Mar 60(3): 1830

Summary

Antibiotics	Comments
Ceftaroline, ceftolazane-tazobactam, ceftazidime-avibactam, doripenem, Ertapenem,Imipenem, moxifloxacin, linezolid, tedizolid, dalbavancin, oritavancin, tigecycline=	• Do no require dose adjustment based on obesity alone • Extended infusions maybe considered for meropenem or doripenem
Aminoglycosides and polymixin B	• Use adjusted body weight (0.4), as a dosing weight
Colistin	• Use IBW as the dosing weight
Vancomycin	• Doses do not scale linearly with body weight • Two measurement would increase accuracy of exposure (AUC
Amoxicillin, nafcillin, piperacillin-tazobactam, cefazolin, cephalexin, ceftazidime,	• Data inadequate and/or conflicting; Dose at the upper range would be reasonable for severe or deep-seated infections

Summary

- Serum concentrations may be altered in obese patients compared to non-obese patients
- Dose adjustments are necessary for some antimicrobials
- Dose adjustments should be considered based available data especially in life-threatening infections