

The large, the small, and the devices: drug dosing in special populations

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Learning Objectives

- Review alterations in pharmacokinetics in obese and underweight patients
- Understand the effect of extracorporeal devices on drug pharmacokinetics
- Discuss potential dosing modifications based on weight and extracorporeal devices

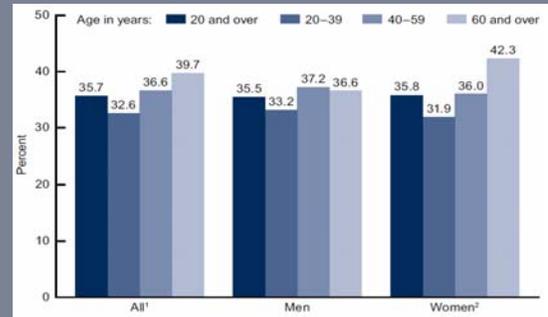
Definitions of Weight

- For African Americans, Caucasians, Hispanics

BMI (kg/m ²)	Weight Status
<16.5	Severely underweight
16.5-18.5	Underweight
18.5-24.9	Normal
25-29.9	Overweight
30-34.9	Class I obesity
35-39.9	Class II obesity
≥40	Class III obesity

*Asians are considered overweight if their BMI is between 23-29.9 kg/m² and obese if BMI is >30 kg/m²

Prevalence of Obesity in adults 2009-2010



NCHS Data brief No 82, Jan 2012.

Medical Costs

- In 2008, medical costs associated with obesity were estimated at \$147 billion; the medical costs for people who are obese were \$1,429 higher than those of normal weight
- 28.6% of adults in Pennsylvania are considered obese
 - Range: Colorado at 21% up to Mississippi at 34%

CDC. <http://www.cdc.gov/obesity/data/adult.html>. accessed July 2013.

New Drug Development

- As new drugs are studied in the design process, overweight and underweight persons are often excluded either due to weight or due to comorbid conditions
- In a review of new drugs approved between 2004-2009
 - 32 had no mention of weight based descriptions
 - 29 mentioned weight based descriptions but didn't define it
 - None of the 84 drugs reviewed had any additional data on obese or lean patients available

Am J Health-Syst Pharm. 2010;67:1948-1950.

Alterations in Pharmacokinetics in Obese Patients

- Absorption
 - No documented changes for orally administered medications
- Distribution – increased volume of distribution
 - Increased
 - Adipose tissue
 - Organ mass
 - Lean body mass
 - Blood volume
 - Alpha-1 acid glycoprotein
 - Dosing modifications based on individual drug properties

Alterations in Metabolism and Elimination

- Increased blood volume seen in obesity, leads to increased blood delivery to the liver and kidneys
- Both phase I and phase II reactions are altered in obesity
 - Trend toward slower clearance of CYP 3A4 medications
 - Faster clearance for 2E1, 2C19, and 2D6, N-acetyltransferase, xanthine oxidase, GFR, and tubular secretion
- Fatty infiltration of the liver may or may not affect drug metabolism

Clin Pharmacokinet. 2012;51:277-304.

Estimating Renal Function

- Dosing can vary widely based on the weight used in Cockcroft-Gault derived CrCl
- For a 51 yo man – 177.8 cm, Scr 2 mg/dL

Dofetilide dosing recommendations			
Weight used	65 kg (normal)	79 kg (overweight)	100 kg (obese)
Actual BW	250 mcg bid	250 mcg bid	500 mcg bid
Ideal BW	NA	250 mcg bid	250 mcg bid
Lean BW	NA	NA	250 mcg bid

Table modified from: Ann Pharmacother. 2013;47:908-909

Estimating Renal Function

- When comparing estimated CrCl to measured CrCl:
 - Lean body weight was found to be the most accurate
- Unfortunately lean body weight is best measured but can be estimated
 - $LBW\ males = (9270 \times TBW) / (6680 + 216 \times BMI)$
 - $LBW\ females = (9270 \times TBW) / (8780 + 244 \times BMI)$
- Other medications like aminoglycosides have also been found to better correlate with LBW instead of adjusted BW

Am J Health-Syst Pharm. 2009;66:642-648.
Antimicrob Agent Chemother. 2011;55:4008-4011.

Dosing Modifications

- Many medications do not offer recommendations for weight based dosing modifications
 - No data
 - Dose modification is not necessary
 - Antidepressants (Unterecker 2011)
 - Dose should not be modified
 - Daptomycin – dosing should be based on total body weight but dosing interval should be based on CrCl using Lean BW or Ideal BW (Pai 2007)

Ther Drug Monit. 2011;33:730-734.
Antimicrob Agent Chemother. 2007;2741-2747.

Vancomycin

- Vancomycin is recommended to be dosed at 15-20 mg/kg every 8-12 h based on total BW
 - A review of 170 adult obese patients:
 - Using 15mg/kg q8-12 h, 55% had trough values >20 mcg/mL
 - Using 10mg/kg q12 h, 59% had trough values of 10-20 mcg/mL
 - In pediatrics, an elevated trough is more likely when using total BW
 - 2% in non-obese vs 19% of obese children had troughs >20mcg/mL
- Close therapeutic monitoring is necessary in obese patients

Am J Health-Syst Pharm. 2012;69:944-950.
Pharmacotherapy. 2013. Ahead of print.

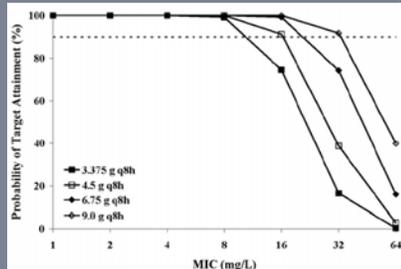
Piperacillin/Tazobactam

- An example of a medication that has a larger Vd and faster clearance

Small study of 14 obese and morbidly obese patients

Mean weight: 161 kg
Mean BMI: 55 kg/m²

Only doses ≥ 4.5 g IV q8h infused over 4h could be used to treat *P. aeruginosa*



Int J Antimicrob Agent. 2013;41:2-56.

Cephalosporins

- Cefepime and ceftazidime also appear to have larger volumes of distribution and faster rates of clearance in obese patients
- In 10 patients with a BMI ≥ 40 kg/m², the most appropriate dose for cefepime was found to be 2 g IV q8h instead of q12h
 - Due to increased clearance 9.09 L/hr vs 7.2 L/hr and shorter half-life 1.92 h vs 2 h

Obese Surg. 2012;22:465-471.
Cefepime package insert.

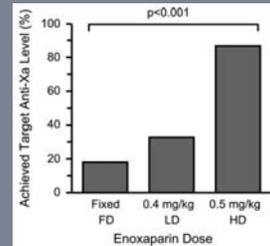
Surgical Prophylaxis

- Cefazolin for surgical prophylaxis
 - Cefazolin 2 g IV re-dosed every 5 h was appropriate for BMI >40 kg/m²
 - Cefazolin 3 g IV, did not achieve a significantly longer time above MIC in patients with a BMI >50 kg/m²
 - Limitations – elective surgery, not fluid overloaded, normal clearance pathways

Surg Infect. 2012;13:33-37.

VTE Prophylaxis

- VTE prophylaxis is very important since obesity itself can be a risk factor for clots



In medically ill patients, enoxaparin 40 mg SQ q24h was compared to 0.4 mg/kg SQ q24h and 0.5 mg/kg SQ q24h

82% of the 40 mg SQ q24h dosing group had an anti-Xa level <0.2 IU/mL

Unfortunately most studies are too small to determine outcomes

Am J Hematol. 2012;87:740-743.

Treatment of VTE

- A database review in Spain, separated patients by weight
 - Patients weighing >100 kg
 - More likely to be treated with UFH instead of LMWH
 - Received lower doses per kg than normal and low body weight patients
 - Had a lower bleeding rate than normal weight patients and no increase in recurrence
 - Limitations
 - Only a 15 day study
 - No further weight categories (<50 , 50-100, >100 kg)

J Thrombosis Haemostasis. 2005;3:703-709.

Summary: dosing in obese patients

- Pharmacokinetics change in obese patients
- Data are lacking for existing medications and new medications
- Inappropriate doses can lead to treatment failures, adverse events, and resistance
 - Linezolid case report: 265kg pt with MRSA pneumonia
 - Peak level 4.13 mcg/mL (15-27 mcg/mL)
 - Trough 1.27 mcg/mL (2-9 mcg/mL)

Ann Pharmacother. 2013;47:e25.

Drug Dosing in Underweight Patients

- Underweight is less well defined than obese
 - Depending on the medication may be <60 kg, <50 kg, or some other break point
- Underweight includes a wide array of patients
 - Small frame patients with "normal" BMIs
 - Undernourished patients
 - Metabolism differences due to illness
 - Ex: cystic fibrosis patients tend to have a larger Vd per kg of weight and their Vd is determined by their nutritional status

Clin Pharmacokinet. 1998;35:437-459.

Drug Metabolism in Smaller Adults

- Smaller adults do NOT metabolize medications in the same manner as children
 - Children have immature enzyme systems
 - Enzymes like CYP2A6, 2C19, 2D6 do not mature until around age 12 yo and flavin-containing monooxygenases may not mature until 18 yo
 - Many smaller adults are also elderly or ill and may have age related decline in enzymatic function
 - Plasma aspirin esterase is known to decline in both frail and elderly patients

Drug Discov Today. 2007;12:599-610.

Drug Dosing in Smaller Adults

- For medications where there is adult data on weight based dosing, actual body weight should be used
 - Patients should still be monitored closely for adverse events
 - From a database review of anticoagulation in Spain, patients <50 kg
 - Received higher weight based doses compared to normal weight pts
 - Had a higher total bleeding and minor bleeding risk than normal weight patients and mortality rate during the study

J Thromb Haemostasis. 2005;3:856-862.

Drug Dosing in Smaller Adults

- Clinical trial data may provide some insight into the lower limit of weight studied

Medication	Normal dose	Dose adjustment for weight
Apixaban	For Afib: 5 mg BID	If 2 or more of the following: ≥ 80 yo, ≤ 60 kg or Sc ≥ 1.5 mg/dL use 2.5 mg BID
Fondaparinux	Treatment of DVT: 50-100 kg: 7.5 mg Daily >100 kg: 10 mg Daily	Treatment of DVT: <50 kg: 5 mg Daily
Prasugrel	Maintenance dosing: 10 mg daily with aspirin	Maintenance dosing <60 kg: 5 mg daily*

*Clinical outcomes only available for medical management

Summary: Dosing in Underweight Adults

- Currently there is a lack of data to support dosing recommendations for most medications in smaller adults
- Pediatric dosing may or may not be appropriate for small adults
- Close monitoring is necessary to ensure efficacy and prevent adverse events



<http://www.tmsackett.com/2011/02/10/whos-better-big-ht-or-small-ht/>

Drug Dosing in Renal Replacement Therapies

- Renal replacement therapies can be intermittent or continuous
- ICU patients are frequently unable to tolerate intermittent therapy

Considerations during RRT

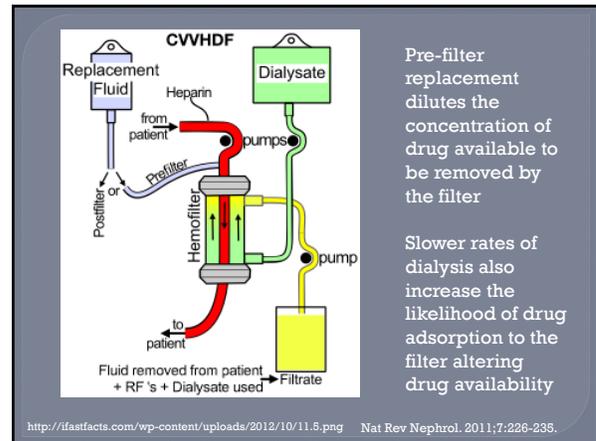
	Both	IHD	CRRT
Volume of distribution	Molecular weight	Drug redistribution	Plasma protein build up on filters
Lipid solubility	Filter properties		
Blood and dialysate flow rates	Protein binding		

Seminars in Dialysis. 2011;24:176-182.

Continuous Renal Replacement Therapies

- CRRT therapies vary greatly
 - CVVHD vs CVVHDF vs SLED
 - Filter type
 - Placement of fluid replacement – pre or post filter
 - One study reviewing dosing of CRRT found that only 52% of studies included enough information to calculate the dose of CRRT and only 58% specified when the fluid replacement was done
 - Techniques have also changed in the last 10 yrs so older studies may not be applicable

Acta Anaesthesiol Scand. 2012;56:147-157.
Nat Rev Nephrol. 2011;7:226-235.



Pre-filter replacement dilutes the concentration of drug available to be removed by the filter

Slower rates of dialysis also increase the likelihood of drug adsorption to the filter altering drug availability

<http://fastfacts.com/wp-content/uploads/2012/10/11.5.png> Nat Rev Nephrol. 2011;7:226-235.

Continuous Renal Replacement

- When starting a patient on CRRT
 - Determine the dose of CRRT
 - Consult references to determine if a reference exists that used that dose of CRRT
 - Ex. Drug Prescribing in Renal Failure 2007 edition uses an effluent rate of 2L/hr for dosing
 - Consider drug dose calculation if appropriate
 - CRRT clearance estimate = free fraction x CRRT dose (ml/kg/hr) x 1h/60 min x weight (kg) = ml/min
 - Use therapeutic drug monitoring if available

Adv Chronic Kid Dis. 2013;20:89-93.
Seminars in Dialysis. 2011;24:176-182.

Drug Dosing in CRRT

- ARF and CRRT can alter the kinetics of drugs beyond just altering renal clearance
 - For midazolam the free fraction of drug increases to 6.5% in renal failure compared with 3.9% in healthy volunteers
 - In one study this led to an increased total body clearance of midazolam compared to general ICU patients (8.6 L/hr vs 11.3 L/hr)

Am J Kidney Dis. 2005;45:360-371.

Drug Dosing in CRRT

- Empiric dosing regimens frequently do not achieve levels adequate to treat resistant organisms
- Roberts et al. found that 25% of patients receiving meropenem, piperacillin/tazobactam, vancomycin and ciprofloxacin did not achieve the target trough concentration

Crit Care Med. 2012;40:1523-1528.

Drug Dosing in CRRT

Probability of achieving target time above MIC (%)

MIC (mcg/mL)	Meropenem 1g q12	Cefepime 2g q12	Ceftazidime 2g q12	Piperacillin/tazobactam 4.5g q6
8	0	0	53	90
2	81	90	100	100
1	100	100	100	100

Adapted from Crit Care. 2011;15:R137

- Variability: time off therapy? Dosing ranges used? Patient factors?

Patient Characteristics

- Patient characteristics can also complicate dosing in AKI
 - Fluid related weight gain
 - In a review of piperacillin/tazobactam the Vd was more closely related to weight gain since admission than actual weight at the time the drug was started
 - Amikacin may require dosing at 25 mg/kg in patients on CRRT to ensure adequate peak levels
 - Tubular secretion and reabsorption are also impaired
 - Fluconazole dosing is the same or higher for CRRT and normal renal function (target dose 800 mg/day)

Nat Rev Nephrol. 2011;7:226-235. Int J Antimicrob Agent. 2011;37:531-535. Clin J Am Soc Nephrol. 2012;7:452-457. Seminars in Dialysis. 2011;24:176-182.

Patient Characteristics

- Patient characteristics can also complicate dosing in AKI
 - Extra renal metabolism is not decreased as much in AKI as in ESRD and many dosing recommendations are based on ESRD patients or extrapolations
 - Udy et al. recently were not able to determine a significant relationship between RRT and vancomycin dosing and levels

Int J Antimicrob Agent. 2013;41:564-568.

Patient Case

- RD is a 42 yo man started on CRRT due to worsening acid/base disorder secondary to sepsis
- Received cefepime 2 g x1
- Starting CRRT at 25 ml/kg/hr
- Start piperacillin/tazobactam 4.5 g IV x1, then 3.375 g IV q6 h
- Start vancomycin 20 mg/kg x1
 - Consider checking a level in 12 h
 - Dosing may be 10-15 mg/kg q12h or q24h depending on CRRT rate

Patient Case

- Alternatives
 - Continuous infusions of beta-lactams
 - Daptomycin 8 mg/kg q48h
 - Linezolid may also require dose adjustment
 - Aminoglycosides
 - Patients may require up to 6 mg/kg IBW to reach a target peak due to enlarged Vd
- Loading doses should be used and therapeutic drug monitoring when possible

<http://imgc.allpostermages.com/images/P-473-483-90/88/8889/A3P00002/posters/drew-demavich-this-is-a-teaching-hospital-new-yorker-cartoon.jpg> Chemother. 2012;24:107-112. Am J Kidney Dis. 2006;47:e83-86.

Intermittent Hemodialysis

- Many resources available for dosing estimates in IHD
- Limitations
 - Age of the reference – filters have changed; MICs have changed
 - Extra-renal clearance
 - Residual renal clearance
 - Patient specific characteristics
 - “weekend” dialysis intervals

Intermittent Hemodialysis

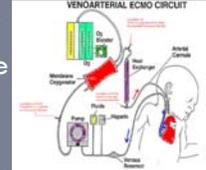
Drug	Normal	CrCl 30-50ml/min	IHD
Atenolol	25-100 mg q24h	50 mg q24h	50 mg q48h after IHD or give 25mg extra after IHD
Hydralazine	10-50 mg q6-8h	10-50 mg q8h	10-50 mg q12-24h
Pregabalin	300 mg bid	150 mg bid	Max 75 mg daily with extra 25-150 mg given after IHD
Levetiracetam	500-1000 mg bid	250-750 mg bid	500-1000 mg daily with extra 250-500 mg after IHD
Gabapentin	300-600 mg tid	300 mg q12-24h	Load 300 mg, then 200-300 after IHD
Famotidine	20-40 mg daily	10-20 mg daily	10 mg given after IHD

Summary: Drug Dosing in Renal Replacement Therapies

- Consider the use of medication not known to be cleared renally
- Therapeutic drug monitoring should be used whenever possible
- Have a high suspicion of over-dosing and under-dosing patients
 - Cefepime induced seizures [Crit Care Resusc. 2012;14:312-315]
 - Vancomycin subtherapeutic levels [Clin Nephrol. 2012;77:329-331]

Drug Dosing During ECMO Therapy

- Extracorporeal membrane oxygenation (ECMO) can be used as a bridge to
 - Recovery
 - Long term mechanical support
 - Transplantation
- ECMO has been used more extensively in infants
 - Infant data cannot be used for dosing adults



http://www.pitt.edu/~gartner/04_GROUPS/ECMO_alarm/Sub_pages/ECMO_alarm_circuit.html

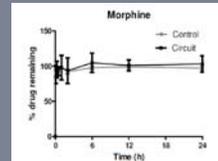
Pharmacokinetic Changes During ECMO

- Alterations in volume of distribution
 - The volume of the ECMO circuit itself minimally increases the volume of distribution of an adult
 - The ability of the ECMO circuit to sequester medications has a significant effect on the volume of distribution of medication
 - Can also lead to medications "leaking" back into the patient once therapy is stopped
 - Drug sequestration also appears to increase the longer a circuit is in use

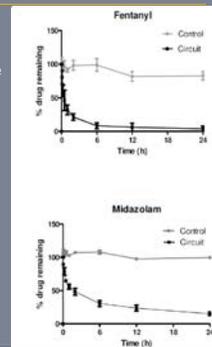
J Crit Care. 2012;27:741.e18.

Drug Sequestration

- In an ex vivo model:
 - Fentanyl and midazolam are rapidly sequestered, while morphine is less affected



Crit Care. 2012;16:R194.



Drug Sequestration

- This sequestering is dependent upon the make up of the pump and oxygenator
 - Midazolam 63% removed by centrifugal pump with polypropylene hollow fiber vs 0.62% with silicon membrane and roller pumps
 - Fentanyl loss was 80%, 86%, 83% with no oxygenator, polypropylene Quadrox D oxygenator and membrane oxygenator respectively

J Crit Care. 2012;27:741.e18.

Drug Sequestration

- Extent of sequestering is also dependent on the fluids used to prime the cannula if therapy was started prior to insertion
 - Priming with blood instead of crystalloids increased the losses of phenytoin, fentanyl, and heparin
- Drug sequestering also affects antibiotics
 - Meropenem is degraded and sequestered within 4-6 hours

Crit Care. 2012;16:R194.
J Crit Care. 2012;27:741.e13.

Medication Clearance

- It is unknown if pulseless perfusion of the kidney will decrease GFR
 - Use of CRRT during ECMO is common but not characterized in the literature due to variations in techniques
- Regional blood flow to the liver may alter clearance but this has also not been studied in adults
 - Characterization in children is limited due to developmental differences

J Crit Care. 2012;27:741.e13.

Dosing Recommendations in ECMO

- In a small study, oseltamivir 75 mg BID had levels comparable to ambulatory patients in adults
 - Drug levels correlated with renal function so renal dose adjustment is still necessary
 - Children may require higher doses to maintain adequate serum concentrations
- A case report involving caspofungin
 - Caspofungin 70 mg daily maintained adequate peak concentrations for 4 days

Anaesth Int Care. 2013;41:66-73.
J Antimicrob Chemother. 2009;63:767-770.

Drug Dosing Recommendations in ECMO

- A case report on voriconazole
 - Trough levels were elevated by day 3 of ECMO therapy
 - The delay in elevated troughs may be due to saturation of sequestering binding sites
 - May be due to extended half-life and a dose increase when ECMO was started
 - May be due to worsening hepatic function (bilirubin rise from 3.36mg/dL to 6.94mg/dL)

J Antimicrob Chemother. 2009;63:767-770.

Summary: Drug Dosing in ECMO

- There is a lack of data available on drug dosing in ECMO especially when patients are also receiving CRRT
- ECMO circuits are able to sequester large quantities of medications and possibly nutrients and hormones
- Hydrophilic medications may require less dose adjustments
- Close monitoring and altered medication regimens are necessary to ensure safety and efficacy

ASAIO J. 2004;50:68-67.

Drug Dosing in Special Populations

- Special patient populations are understudied
- Within group variations limit applicability to all groups
- Further research into these areas will benefit future care
- Currently, care should be closely monitored to ensure positive outcomes and safety

Questions???

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