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When Patients Outweigh the Mold: Pharmacotherapy in Pediatric Obesity

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Disclosure

- The program chair and presenters for this continuing education activity have reported no relevant financial relationships.

Objectives

1. Interpret literature on pharmacokinetic alterations & specific dose adjustment tools in the obese population
2. Justify drug dosing for common & high-risk medications in overweight/obese pediatric patients
3. Evaluate dosing strategies for common agents used as continuous infusions

Background

Pediatric Obesity

- Definitions:

BMI Percentile	CDC Definition
< 85th	Healthy weight
85th - 94th	Overweight
≥ 95th	Obese

- Prevalence:
  - 17% of 2-19 years obese (2011-2014)
  - No significant difference between 2005-2006 & 2013-2014

Ogden CL, et al. *JAMA* 2016;315:2292-9.

http://www.cdc.gov/obesity/childhood/defining.html (Accessed 16 Sep 2016).

In-Patient Obese Admissions

Characteristic	Number (%) or Mean ± SD
Males	1448 (50.9)
TCH Admissions	2010 (70.7)
Age (years)	9.8 ± 4.7
Weight (kg)	55.2 ± 31.7
Height (cm)	134.7 ± 28.9
BMI (kg/m2)	27.3 ± 7.1
BMI percentile	98.0 ± 7.1

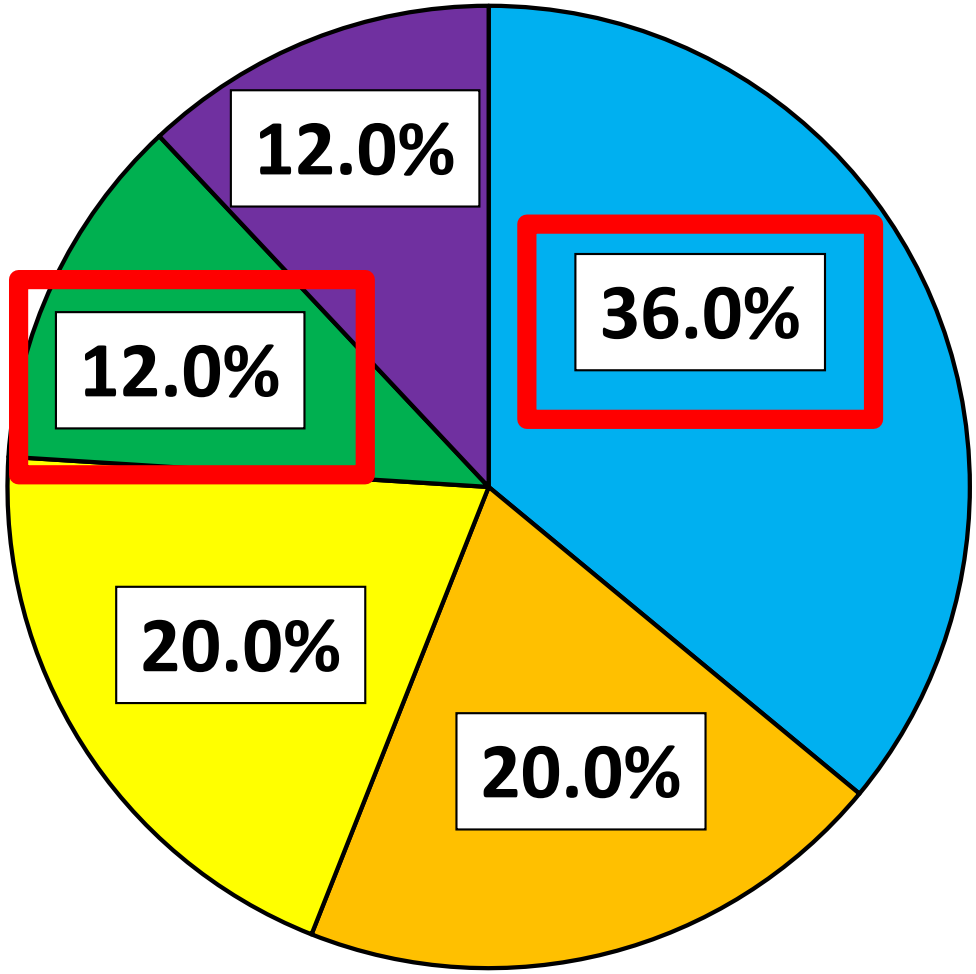
2844 (18.8%) 15,119 admissions 2-17 years

TCH = Texas Children's Hospital

BMI = Body mass index

Johnson PN, et al. *Am J Health-Syst Pharm* 2016;e482-8.

Top 25 Medications (n=28,234)



Johnson PN, et al. *Am J Health-Syst Pharm* 2016;e482-8.

PK Alterations in Obesity

- Distribution:
  - ↑ Vd_{ss} for lipophillic medications
  - ↓ Vd_{ss} for hydrophillic medications
- Excretion:
  - ↑ kidney size
  - ↑ glomerular filtration rate

Vd_{ss} = Volume distribution at steady state

Lee JB, et al. *Orthopedics* 2006; 29: 984.

Wurtz R, et al. *Clin Infect Dis* 1997; 25: 112-8.

Blouin RA, et al. *Antimicrob Agents Chemother* 1982; 21: 575-80.

Blouin RA., et al. *Applied Therapeutics* 1992; 11.3-11.20.

Pro/Con Debate #1:

Weight-based dosing adjustments

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Pediatric Pharmacists should routinely use weight-based dosing adjustments.

A TRUE

B FALSE

Dose Adjustment Tools:

We <u>should</u> use drug adjustment tools

Dosing Strategies

- Continuous infusion dosing:
  - Fixed-dose (mcg/hr)
  - Weight-based dosing (mcg/**kg**/hr)
- Weight-based dosing:
  - *Total body weight (TBW)*
  - *Body surface area (BSA)*
  - **Ideal body weight (IBW)**
  - **Adjusted body weight (ABW)**
  - **Lean body mass (LBM)**

Johnson PN, et al. *Am J Health-Syst Pharm* 2016;e482-8.

Body Composition

- TBW = FM and FFM
- Fat-free mass:
  - Consists of muscle, bone, vital organs, & ECF
  - Free-fat mass differs from LBM:
    - Lipids in CNS & bone marrow contained in LBM not FFM
    - Differences NOT appreciable
    - FFM interchangeable with LBM

FM = Fat mass

FFM = Free fat mass

ECF = Extracellular fluid

LBM = Lean body mass

Janmahasatian S, et. al. *Clin Pharmacokinet* 2005;44:1051-65.

Body Composition Comparison

Factor	Boys		Girls	
	Obese	Controls	Obese	Controls
	Mean ± SD			
Weight (kg)	65.3 ± 18.2	40.1 ± 12.1	74.9 ± 26.6	39.7 ± 10.2
Total body water (L)	29.7 ± 7.2	24.4 ± 8.5	26.4 ± 7.0	21.0 ± 6.3
Body volume (L)	65.0 ± 18.4	38.2 ± 11.4	75.5 ± 27.5	38.1 ± 9.9
FM (kg)	26.3 ± 10.1	7.7 ± 3.6	34.6 ± 16.0	9.6 ± 3.9
FFM (kg)	39.0 ± 10.0	32.4 ± 11.4	40.2 ± 11.6	30.0 ± 7.6
FFM hydration (%)	76.5 + 1.8	75.3 + 1.7	77.3 + 1.9	75.0 + 1.7

↑ volume, & FFM adjusting for age, sex, & height (p <0.0001)

TBW = Total body water

FM = Fat mass

FFM = Free fat mass

Wells JCK, et al. *Int J Obes* 2006;30:1506-13.

Dosing Considerations

- ↓ Percentage of lean tissue per TBW (kg)
- 30% ↓ in water content in adipose tissue
- Therapeutic alterations:
  - Altered concentrations
  - ↑ or ↓ efficacy
- Alterations in dosing:

Dosing	Hydrophilic	Lipophilic
Loading dose	↓ per TBW (kg)	↑ per TBW (kg)
Maintenance dose	↓ per TBW (kg)	↓ per TBW (kg)

FM = Fat mass

FFM = Free fat mass

TBW = Total body mass

Kendrick JG, et al. *J Pediatr Pharmacol Ther* 2010;15:94-109.

Ross EL, et al. *Am J Health-Syst Pharm* 2015;72:542-56.

Gunderson K, et al. *Am J Clin Nutr* 1966;19:77-83.

Types of Weight-Based Adjustments

Type	Definition	Calculation
IBW	Reflective of indirect assessment of LBM	(50% BMI for age) x (height in m^2)
ABW	Reflective of LBM plus proportion of excess mass determined by cofactor	IBW + Pre-specified cofactor x (TBW – IBW)
LBM	Estimation of lean tissue mass minus adipose tissue	• LBM = IBW + 0.29 (TBW – IBW) • FFM (male) = $\frac{9.27 \times 10^3 \times TBW}{6.68 \times 10^3 + [216 \times BMI]}$ • FFM (female) = $\frac{9.27 \times 10^3 \times TBW}{8.78 \times 10^3 + [244 \times BMI]}$

IBW = Ideal body weight

ABW = Adjusted body weight

LBM = Lean body mass

Ross EL, et al. *Am J Health-Syst Pharm* 2015;72:542-56.

Callaghan LC, et al. *Anaesthesia* 2015;70:176-82.

Janmahasatian S, et al. *Clin Pharmacokinet* 2005;44:1051-65.

Summary Pro: Use Adjustments

- Obese kids have altered body composition
- Weight-based dosing may lead to ↑ adverse events
- Utilize weight-based adjustments:
  - Validated approaches
  - Work in obese adults

Dose Adjustment Tools:

We <u>should NOT</u> use drug adjustment tools

Summary Con: Don't Use Adjustments

- Outcomes
- Therapeutic Drug Monitoring
- Technology Limitations

Patient Outcomes

- No clear data on improved patient outcomes when adjusting medications for body habitus.

- Propofol use in morbidly obese pediatric patients
  - Patients required a lower dose for sedation

- Esophagogastroduodenoscopy, colonoscopy, or both
  - Airway obstruction (1%), cough (0.9%), and laryngospasm (0.6%).
  - 5 years old or younger, American Society of Anaesthesiologists greater than or equal to 2, esophagogastroduodenoscopy ± colonoscopy, and coexisting medical conditions of obesity and lower airway disease were independent predictors of higher adverse event

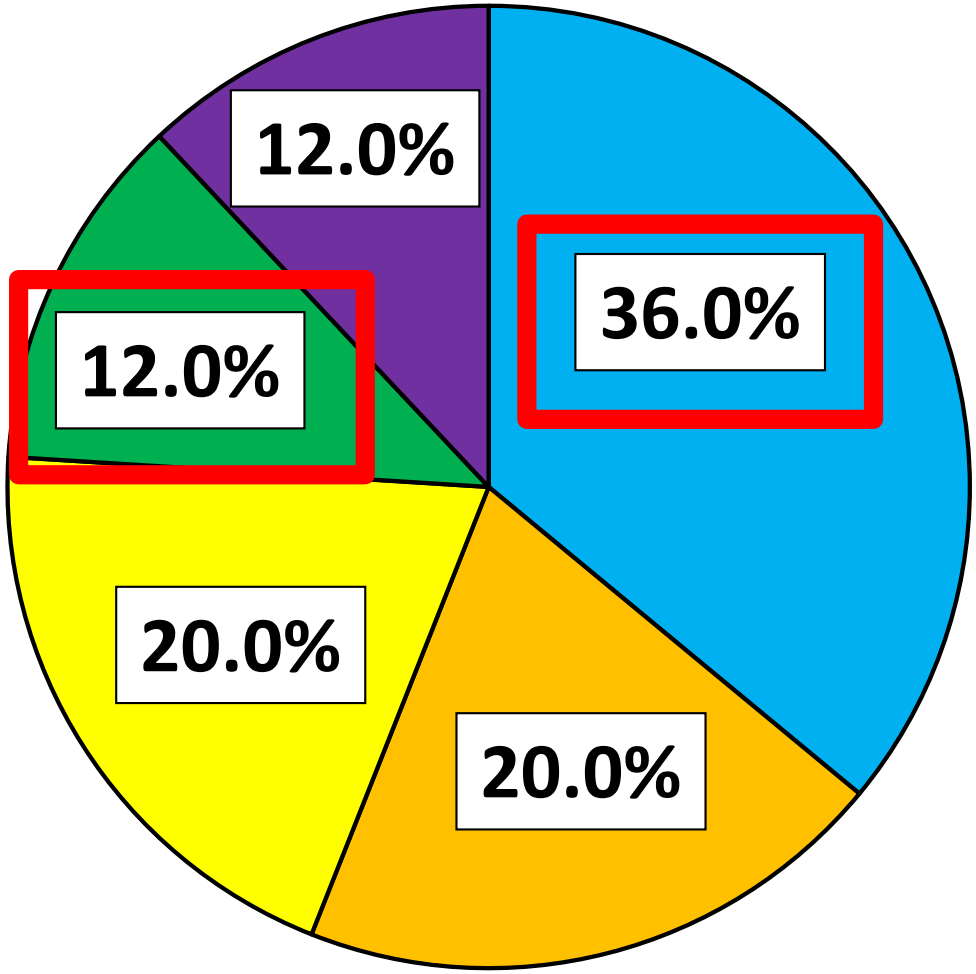
- TNA surgery
  - Weight < 14 kg (underweight) associated with complications

Anesth Analg 2012;115:147-53.

Pediatr Crit Care Med 2015;16:e251-9.

Paediatr Anaesth 2015;25:392-9.

Top 25 Medications (n=28,234)



Johnson PN, et al. *Am J Health-Syst Pharm* 2016;e482-8.

Therapeutic Drug Monitoring

- Vancomycin
  - Obese (6.9 ± 4.30 µg/mL) versus nonobese children (4.8 ± 3.08 µg/mL; P = 0.052)

- Aminoglycosides
  - Higher values in obese pediatric patients
  - Monitoring is standard anyway
  - Dose limits and prescribing practices saw no differences

Clin Pediatr 2011;50:442-6.

Pediatr Infect Dis J 2011;30:347-9.

Therapeutic Drug Monitoring

- What about drugs with no monitoring?
  - Corticosteroids
  - Gastrointestinal medications
  - Analgesic / Sedative medications
- Risk versus Benefit
- Overdosing vs underdosing

Technology Limitations

Type	Definition	Calculation
IBW	Reflective of indirect assessment of LBM	(50% BMI for age) x (height in m^2)
ABW	Reflective of LBM plus proportion of excess mass determined by cofactor	IBW + Pre-specified cofactor x (TBW – IBW)
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Which one do you use?

Seriously, who is going to calculate this?

IBW = Ideal body weight

ABW = Adjusted body weight

LBM = Lean body mass

Ross EL, et al. *Am J Health-Syst Pharm* 2015;72:542-56.

Callaghan LC, et al. *Anaesthesia* 2015;70:176-82.

Janmahasatian S, et al. *Clin Pharmacokinet* 2005;44:1051-65.

Summary Con: Don't Use Adjustments

- No data suggest improved outcome
- Obesity doesn't always mean reduce the dose
- Calculations are labor intensive and have not had clinical evaluation
- Current guidelines prevent errors

Pediatric Pharmacists should routinely use weight-based dosing adjustments.

A TRUE

B FALSE

Pro/Con Debate #2:

Dosing for high-risk meds (anti-coagulants)

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Patient Case #1

- 9 year-old Male (68 kg; 147 cm) admitted for multiple bowel perforations:
  - Ulcerative colitis
  - Obesity (99th percentile for age, height, gender)
- HD 1: Transferred to PICU
- HD 12:
  - Abdominal ultrasound revealed portal vein thrombosis
  - Normal renal function

What dose of SQ enoxaparin should be used?

HD = Hospital day

Dosing Controversies for High-Risk Medications:

We <u>should</u> make empiric dose adjustments for anti-coagulants

Summary Pro: Use An Adjustment

- Unfractionated Heparin
  - Lower doses required in obese patients
  - Initial Doses: 17.4 vs 20.2 U/kg/hour; P = 0.013
  - Maintenance dose: 19.1 vs 24.3 U/kg/hour; P = 0.033
  - Xa: 0.45 vs 0.29 unit/mL; P = 0.045

- Enoxaparin
  - Anti-Xa: 0.67 ± 0.27 vs 0.53 ± 0.24 unit/mL, P = 0.028
  - Lower doses were required over time

J Pediatr 2013;163:150-3.

J Pediatr 2013;162:293-6.

Summary Pro: Use An Adjustment

- Warfarin
- Max Initial Dose of Warfarin: 0.2 mg/kg/dose (5 mg per day)
  - Initial and maximum doses of warfarin per kg significantly lower in obese patients (P<0.05).
- Time to therapeutic INR value was twice as long in obese patients
  - Median=6 [range, 4 to 28 d] vs median=3 [range, 1 to 10 d]; P<0.01).

J Pediatr Hematol Oncol 2014;36:e487-9.

Summary Pro: Use Adjustments

- Clinically relevant endpoints are different for obese patients
- Risk of overdosing
  - Increased monitoring
- Risk of increasing length of stay

Dosing Controversies for High-Risk Medications:

We <u>should not use empiric adjustments</u> (use total body weight) & follow therapeutic concentrations to adjust dosing

Heparin & Warfarin

- Heparin:
  - Rarely used outside of CV surgery population
  - Titrate to effect due to post-operative bleeding
- Warfarin:
  - Drug interactions & PG affect dosing
  - Obese adults cap dose—5-10 mg
- Recommendations:
  - Dose using TBW & cap at adult dosing
  - Monitor vigilantly & titrate to effect

PG = Pharmacogenomics

TBW = Total body weight

Enoxaparin Prophylaxis in Kids

Patient	Weight (kg)	Enoxaparin Dose	Enoxaparin Dose (mg/kg/day)	Anti-Factor Xa Value (IU/mL)
1	358.6	40 mg SQ daily	0.11	< 0.02
	338.6	40 mg SQ bid	0.24	0.06
	336.4	60 mg SQ bid	0.36	0.05
	324.5	90 mg SQ bid	0.55	0.15
	324.5	95 mg SQ bid	0.59	0.17
	302.3	100 mg SQ bid	0.66	0.21
	285	100 mg SQ bid	0.7	0.29
2	277	40 mg SQ daily	0.14	*
	277	40 mg SQ bid	0.29	0.05
	277	45 mg SQ bid	0.32	0.13
3	81.5	40 mg SQ daily	0.49	*
	81.5	40 mg SQ bid	0.49	0.14

Prophylaxis anti-Xa range: 0.1-0.3 IU/mL

Lewis TV, et al. *Pediatrics* 2011;127:e787-90.

Enoxaparin Treatment in Kids

Data	Obese (n = 30)	Non-obese (n = 30)	*P*-value
	Mean ± SD or Number (%)		
Age (years)	11.6 ± 4.4	11.4 ± 4.3	NA
Initial dose (mg/kg)	0.93 ± 0.16	0.98 ± 0.19	0.22
Therapeutic dose (mg/kg)	0.81 ± 0.12	1.1 ± 0.14	0.005
Dose changes:			0.12
Increases	26 (38%)	35 (52%)	
Decreases	42 (62%)	32 (48%)	
Supratherapeutic anti-Xa concentration:			
Patients	21 (70%)	14 (47%)	0.12
Concentration (IU/mL)	1.12 + 0.17	1.08 + 0.08	<0.01

Both groups required dose ↑'s & ↓'s

Question other affects on clearance

Richard AA, et al. *J Pediatr* 2013;162:293-6.

Summary Con: Use TBW

- Case series suggest ↑ dosing for prophylaxis
- ↓ dosing needed for treatment in obese group:
  - Similar age groups
  - All groups needed dose adjustments
  - Unclear affect of other factors on clearance
- Data unclear so dose using TBW & monitor anti-Xa concentrations

TBW = Total body weight

What Dose of SQ Enoxaparin Should be Used?

A. Use ABW & monitor anti-Xa concentrations
B. Use IBW & monitor anti-Xa concentrations
C. Use LBM & monitor anti-Xa concentrations
D. Use TBW & monitor anti-Xa concentrations

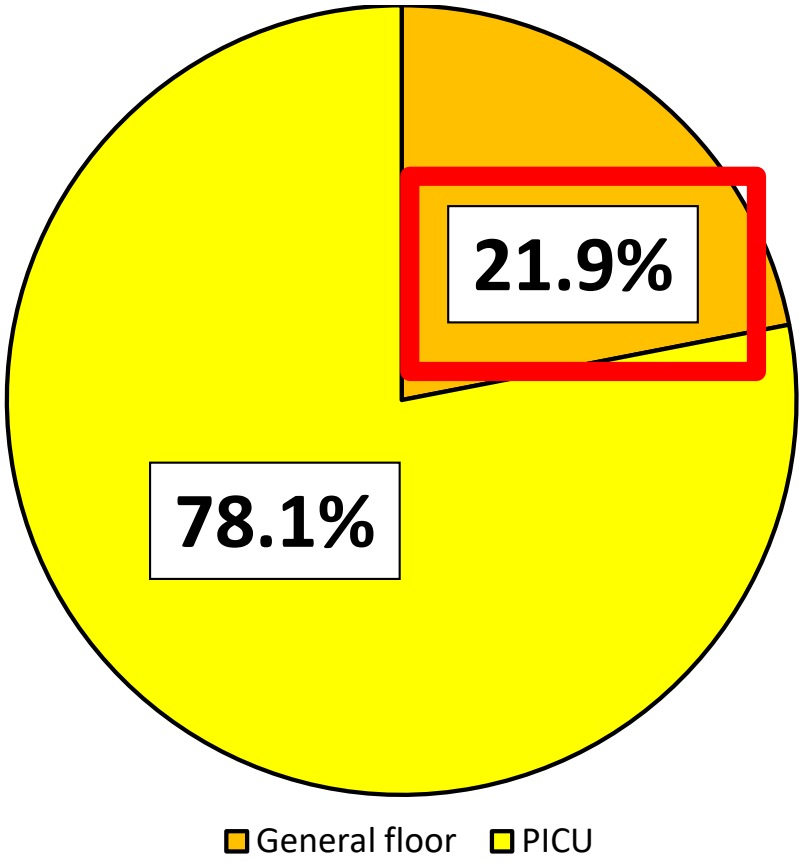
Patient Case # 1 Summary:

- 9 year-old
- Wt = 68 kg
- Normal renal function

Pro/Con Debate #3:

Continuous infusion dosing

PICU Obese Admissions (n=834)



Represent 12.8% of all PICU admissions

Johnson PN, et al. *Ann Pharmacother* (Under Review)

Continuous Infusions in Obese Kids (n=94)

Rank Order	Agent	Number (%)	Rank Order	Agent	Number (%)
1	Fentanyl	12 (12.8)	11	Furosemide	3 (3.2)
2	Regular insulin	12 (12.8)	12	Cisatricurium	2 (2.1)
3	Milrinone	12 (12.8)	13	Nitropruside	2 (2.1)
4	Epinephrine	11 (11.7)	14	Norepinephrine	2 (2.1)
5	Midazolam	10 (10.6)	15	Propofol	2 (2.1)
6	Dopamine	6 (6.4)	16	Vasopressin	2 (2.1)
7	Dobutamine	5 (5.3)	17	Aminophyllline	1 (1.1)
8	Remifentanyl	5 (5.3)	18	Amiodarone	1 (1.1)
9	Aminocaproic acid	4 (4.3)	19	Morphine	1 (1.1)
10	Dexmedetomidine	4 (4.3)	20	Phenylephrine	1 (1.1)

35% for sedation, analgesia, and NMB

40% for hemodynamic support

Johnson PN, et al. *Ann Pharmacother* (Under Review)

Patient Case #2

- 11 year-old Male (81.5 kg; 165 cm) admitted for septic shock secondary to pneumonia:
  - Ulcerative colitis
  - Obesity (99th percentile for age, height, gender)
- HD 1: Admitted to PICU
- HD 2:
  - Intubated in PICU
  - Team wishes to initiate fentanyl infusion

What dose of fentanyl should be used (mcg/kg/hr or mcg/hr)?

HD = Hospital day

Dosing Strategies for Continuous Infusions:

We <u>should</u> use non-weight based dosing

Summary Pro: *Non-weight Based Dosing*

- Overdosing Risk
- Titration
- Other medications

Summary Pro: *Non-weight Based Dosing*

- Fentanyl
- 1 mcg/kg/hr = 81.5 mcg/hr

- Severe pain, intermittent: 25-35 mcg
- Infusion: 25 to 100 mcg bolus followed by an initial rate of 25 to 200 mcg/**hour**

Drugs 2003;63:755-67.

Summary Pro: *Non-weight Based Dosing*

- Titration of continuous infusions
- Difficult due to multiplying scale
- Titrating by 10%
  - 1.1 mcg/kg/hour, 1.2 mcg/kg/hour…
  - Used to larger increments

Summary Pro: *Non-weight Based Dosing*

- Other medications:
  - Vasopressin
  - Norepinephrine

- Weight, as a pharmacokinetic variable, is not as relevant once patients achieve adult size.

Arch Dis Child 2013;98:737-44.

Summary

- Initiation and titration using weight based dosing will result in greater than expected changes in dose
- Pharmacokinetics don't support the inclusion of weight as a variable once a patient has reached 'adult' size
- Adult patients receive adult doses at adult hospitals regardless of weight

Dosing Strategies for Continuous Infusions:

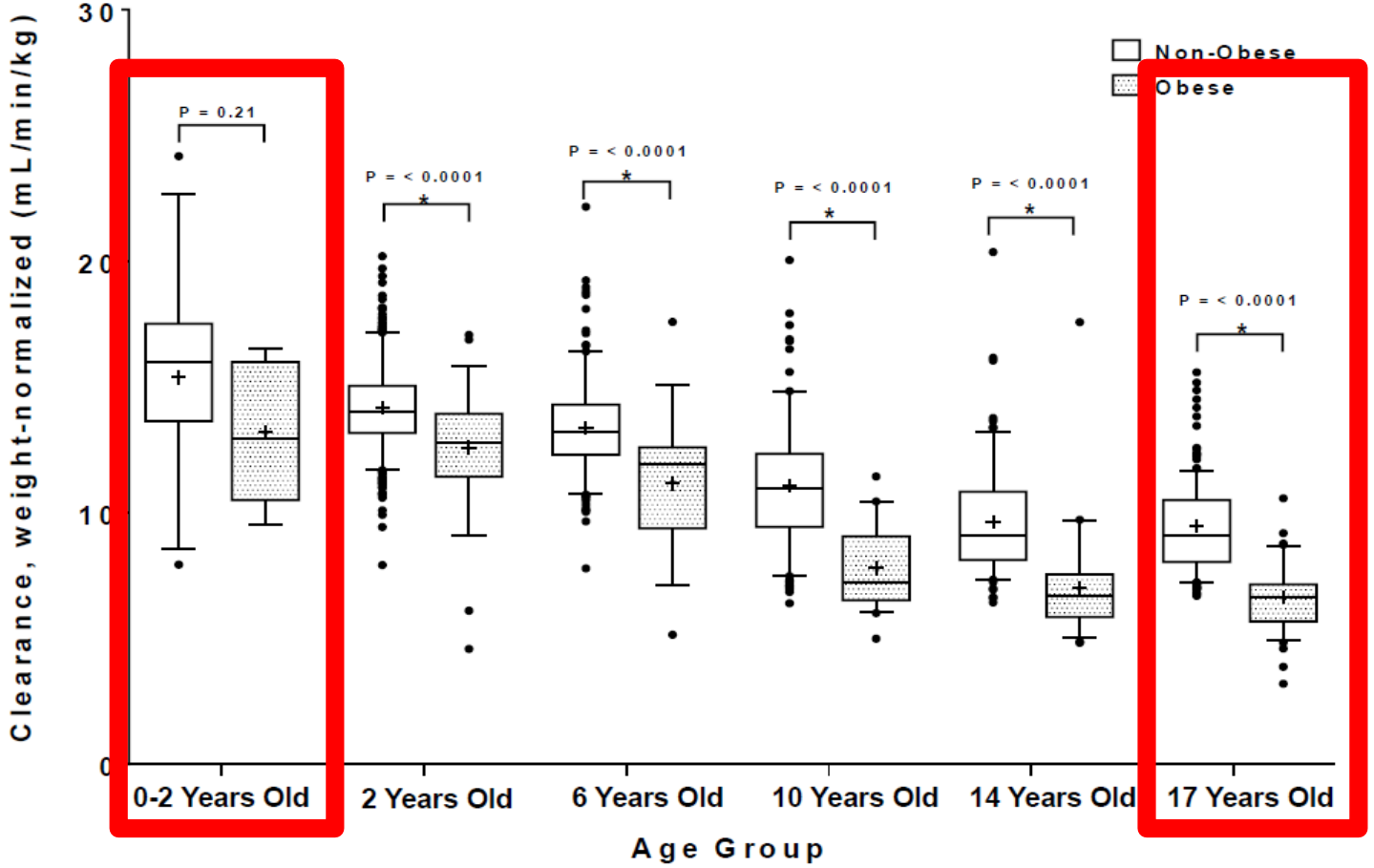
We should use fixed-dosing or weight-based dosing depending on the patient or drug

Not A Straightforward Answer

- Depends on degree of lipophilicity & compartment type (zero, 1st, 2nd, 3rd)
- Variability in weight-based clearance vs clearance differences based on age

Lim SY, et al. (Unpublished data)

Fentanyl Clearance: Obese vs Controls



N = 4,376

11-30% ↓ clearance in all obese groups

Lim SY, et al. (Unpublished data)

Fentanyl Pharmacokinetics

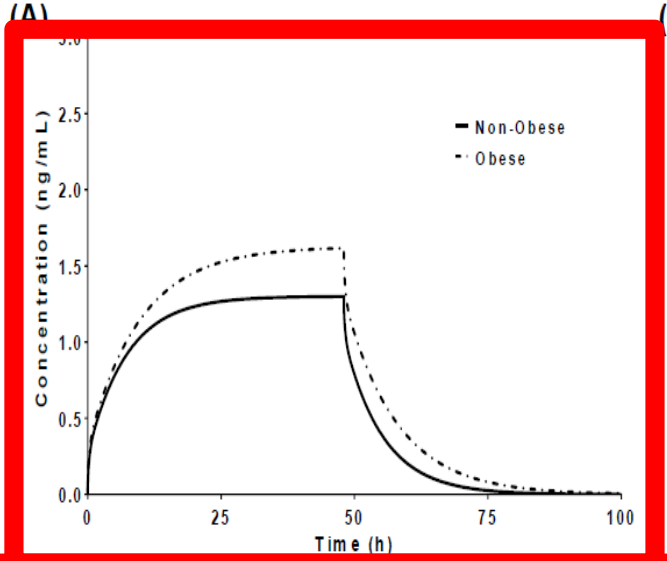
- Vd_{ss} values ↑ 50% in obese vs non-obese children > 10 years
- ↑ C_{ss} using weight-based dosing in obese vs non-obese children:
  - 4 YO: 25%
  - 9 YO: 77%
  - 15 YO: 50%

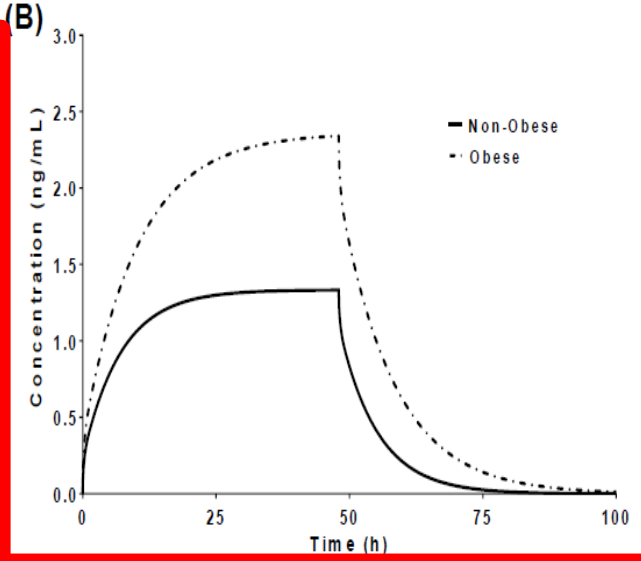
Vd_{ss} = Volume of distribution at steady state

C_{ss} = Steady state concentration

Lim SY, et al. (Unpublished data)

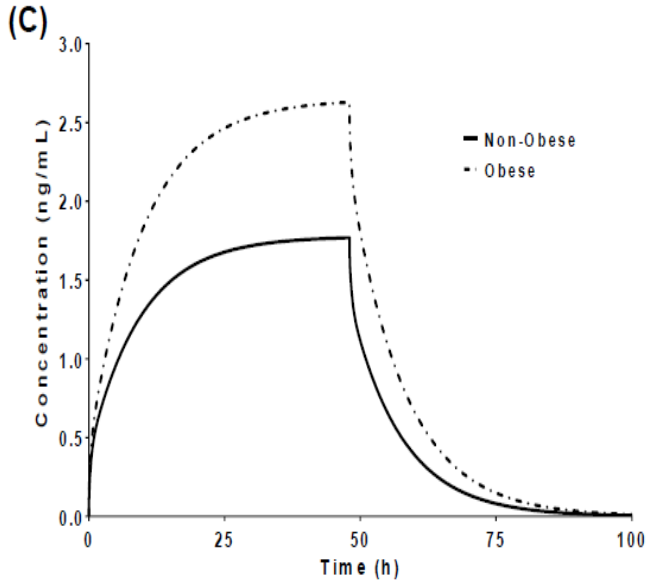
4 YO:
1 mcg/kg/hr

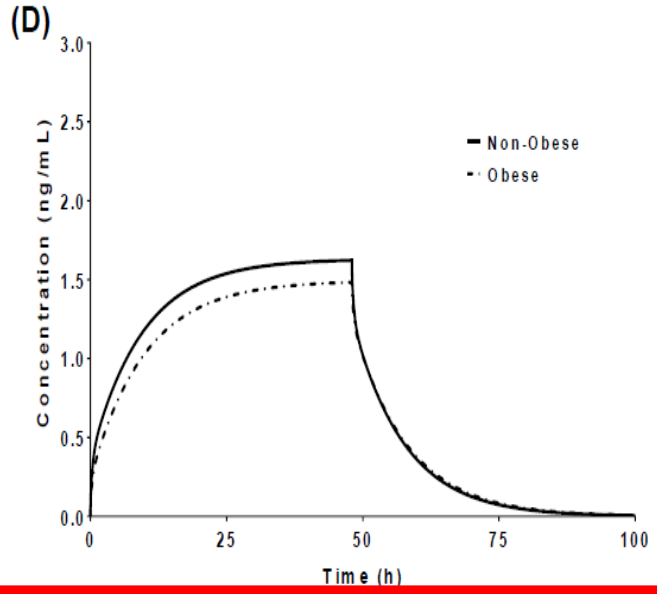




9 YO:
1 mcg/kg/hr

15 YO:
1 mcg/kg/hr





15 YO:
50 mcg/hr

Lim SY, et al. (Unpublished data)

Summary Con: *Always* Fixed-Dosing

- Not one-sized fits all answer
- Use weight-based dosing based on TBW
- Utilize pharmacodynamic target & adjust dosing:
  - Sedation scores
  - Mean arterial pressure
  - Urine output (mL/kg/hr)

TBW = Total body weight

What Dosing Units Should Be Used (mcg/kg/hr OR mcg/hr)?

- A Use mcg/kg/hr based on TBW
- B Use mcg/kg/hr based on IBW
- C Use mcg/kg/hr based on ABW
- D Use mcg/hr
- D None of the above

Patient Case # 2 Summary:

- 11 year-old
- Wt = 81.5 kg
- Intubated & placed on fentanyl infusion

Key Takeaways

1. Number of obese children hospitalized children are ↑'ng
2. Dosing in obese children is **NOT** straightforward
3. Consider pharmacokinetic analysis & employ monitoring with pharmacodynamic targets

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