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# Drug Dosing in Extreme Obesity

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## Disclosure of Conflict of Interest

- I have no conflict of interest to declare

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## Objectives

- Describe the global obesity epidemic.
- Discuss methods to classify body size.
- Discuss pharmacokinetic alterations in obesity.
- Discuss methods to estimate creatinine clearance (Cl<sub>cr</sub>) in obese individuals.
- Discuss antimicrobial dosing in extreme obesity, focusing on vancomycin and the aminoglycosides.
- Discuss low molecular weight heparin dosing in extreme obesity.

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## Outline

- Background
- PICO
- Literature Search
- Review of the Literature
  - Antimicrobials
  - LMWH
- Limitations of the Literature
- Summary
- Conclusion

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## Background

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## Obesity: A World-wide Epidemic

- The World Health Organization (WHO)
  - Obesity is now a global pandemic
  - Estimates ~400 million obese people in 2005
  - Estimated projected number to be 700 million in 2015
- Obesity (BMI > 30 kg/m<sup>2</sup>):
  - 23% adults in Canada
  - 39% adults in the U.S.

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## Health Problems Associated with Extreme Obesity

- **Metabolic syndrome (Type 2 DM, Hypertension, Dyslipidemia , CV diseases)**
- Non-alcoholic Fatty Liver Disease (NAFLD)-steatosis, steato-hepatitis, cirrhosis
- Respiratory diseases (OSA, asthma, Restrictive lung disease)
- Cancer
- Osteoarthritis
- Cholelithiasis
- Gynecological Abnormalities (infertility, abnormal menses)
- GERD
- Venous Stasis
- Skin problems (Intertrigo, cellulitis)
- Increased surgical/ pregnancy risk
- Urinary incontinence
- Idiopathic intracranial hemorrhage

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## Treatment for Extreme Obesity

- Weight-loss programs
- Medications for weight loss
- Bariatric surgery
  - From 1996-2002, bariatric surgical procedures increased 7-fold in the US from 3.5-24.0/100,000 population

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## Body Size Classification

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## Body Mass Index

- The WHO has adopted standardized definitions of obesity based on Body Mass Index (BMI):
  - The BMI=  $\text{Weight}/[\text{Height}]^2$ 
    - Where the weight is in kilograms and height is in metres.
    - "Quetelet's Index" developed in 1869 renamed BMI in 1972
    - Does not differentiate adipose from muscle tissue

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## Body Size Classifications Based on BMI

BMI	Weight Status
Below 18.5	Underweight
18.5 – 24.9	Normal
25.0 – 29.9	Overweight
30.0 and Above 30.0-34.9 35.0-39.9 ≥40.0	Obese -Class I -Class II -Class III(Extreme obesity)

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## Morbid Obesity

- **Morbid Obesity** is defined as Class III Extreme obesity ( $BMI \geq 40.0 \text{ kg/m}^2$ ) or Class II Obesity with ( $BMI = 35.0\text{-}39.9 \text{ kg/m}^2$ ) with associated co-morbidities such as Type 2 Diabetes, hypertension, obstructive sleep apnea etc
- Alternately, body size can be classified as a % of ideal body weight (IBW): 80-124% IBW considered "normal" body weight; 125-190% considered obesity; and >190% IBW as morbid obesity

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## Effect of Extreme Obesity on Drug Pharmacokinetics

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## Drug Dosing in Extreme Obesity

- Drug dose requirements in those with extreme obesity have not been well-studied
- An increased dosage may be required for drugs that are well distributed to adipose tissue (e.g. lipophilic drugs) than for drugs that are poorly distributed to adipose tissue (e.g. polar or hydrophilic drugs)

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## Effect of Extreme Obesity on Pharmacokinetic Parameters

- Pharmacokinetics Review
  - Total body Clearance (Cl) (renal and non-renal)
    - mL/minute or mL/hour
  - Volume of Distribution (Vd) (=Dose/Cp)
    - Litres
  - The elimination Constant (k)(dependent variable)(hours<sup>-1</sup>)
    - $k = Cl/Vd$
    - $k = 0.693/t_{1/2}$

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## Volume of Distribution (Vd)

- In Obese Individuals:
  - lipophilic drug distribution favours adipose tissue and Vd correlates better with total body weight (TBW);
  - hydrophilic drug distribution favours lean tissue and Vd correlates better with lean body weight (LBW)
- However...
  - obese individuals have an increased proportion of muscle and connective tissue in proportion to TBW
  - not all excess body weight in obese patients is comprised of adipose tissue.

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## How Vd affects Drug Dosing

- Loading dose =  $Vd * C_{pmax}$ 
  - Therefore, an increased Vd will increase the LD required to achieve a desired  $C_{pmax}$
- With Multiple dosing:
  - $Dose = Vd * k * C_p(\text{average}) * T$ 
    - Therefore, an increased Vd will favour an increased MD to achieve a desired average  $C_p$

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## Total Body Clearance (Cl)

- Total body Clearance
  - $Cl = Cl_R + Cl_{NR}$
  - Where R=renal clearance and NR=non-renal clearance (e.g. hepatic clearance)
- In obesity
  - Renal Clearance is generally increased
    - Obese kidney donors have significantly higher glomerular planar surface area than non-obese donors

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## Estimating Creatinine Clearance in Obesity-Iohexol Cooperative Study (1998)

- Evaluated 10 Clcr estimate equations to a measure Clcr (using a 24-hour urine collection) in cardiac patients who were elderly or had low albumin, chronic renal insufficiency, low serum creatinine, or were obese
- In obese patients:
  - the Salazar-Corcoran Equation was the only unbiased method and was the most precise;
  - The Cockcroft-Gault Equation (using total body weight) was less biased than all the equations except the Salazar-Corcoran Equation

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## Estimating the Clcr in Obesity

- Salazar-Corcoran Equation was developed for calculation of Clcr in obese patients.
  - For Men:  
$$\frac{[137 - \text{age}] \times [(0.285 \times \text{weight}(\text{kg})) + (12.1 \times \text{height}(\text{m})^2)]}{(51 \times \text{SCr})}$$
  - For Women:  
$$\frac{[146 - \text{age}] \times [(0.287 \times \text{weight}(\text{kg})) + (9.74 \times \text{height}(\text{m})^2)]}{(60 \times \text{SCr})}$$
- Units: Weight: kg Height: meters Scr: mg/dL
- A Salazar-Corcoran equation calculator can be found at <http://www.globalrph.com/salazar.htm>

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## Estimating Clcr in Obesity

- Recommendation
  - Use the Salazar-Corcoran (preferred)

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## Example of Estimation of Clcr in Extreme Obesity

- 60 year old female
- 5'5" and 125 kg
- BMI=45.9 Kg/m<sup>2</sup>
- Scr=75 umol/L

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## Creatinine Clearance

- Cockcroft and Gault
  - Using IBW=63 ml/min.
  - Using TBW=137 ml/min.
  - Using Adjusted body weight=95 ml/min.
- Using 4-variable MDRD
  - 73 ml/min./1.73 m<sup>2</sup>
- Using Salazar-Corcoran
  - 112 ml/min.

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## Hepatic Clearance

- Effect on hepatic clearance is variable:
  - Obesity can result altered activity of hepatic enzymes resulting in increased glucuronidation, sulfation and cytochrome p450 biotransformations (except 3A4).
  - Obesity can cause in fatty liver deposits Non-alcoholic Fatty Liver Disease (NAFLD)-steatosis, steato-hepatitis, cirrhosis which may reduce clearance of hepatically metabolized medications

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## Effect of Increased Cl and Vd on Drug Dosing

- $K=Cl/Vd$ 
  - $T_{1/2}=0.693/K$
- $T=ln(Cpmax-Cpmin)/k$
- Therefore,
  - an increased Cl would favour a larger K and shorter T
  - An increased Vd would favour a smaller K and longer T
  - An increased Cl and Vd would favour a neutral K and neutral T (or unpredictable effect)

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## Antimicrobial Dosing in Extreme Obesity

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## Search strategy-Antimicrobial Dosing in Extreme Obesity

Database (all 1950 to October)	Pubmed	Embase	Cochrane
MESH & keywords	Obesity/Morbid Obesity and dosing	Obesity/Morbid Obesity and dosing	Obesity/Morbid Obesity and dosing
Hits	180	262	5
Results (Trials)	4 review articles 1 NR controlled 14 case-controlled 7 cases	1 more review article	0 new articles
<b>For review</b>	<b>27 trials</b>		

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## Clinical question

<b>P</b>	In adult patients with extreme obesity,
<b>I</b>	are higher antimicrobial doses required,
<b>C</b>	compared to normal weight patients,
<b>O</b>	for treatment and prophylaxis of infection?

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## Vancomycin

- Effect of Obesity on Vancomycin Pharmacokinetic Parameters- 2 case controlled studies
- Similar study design: compared vancomycin PK in morbidly obese patients to matched controls
- Bauer targeted peak concentration of 25-35 ug/mL and trough concentrations of 5-10 ug/mL
- Blouin studied vancomycin PK with multiple sampling after one dose (1 g)
- Bauer calculate Clcr using the Salazar-Corcoran eqn. in the morbidly obese patients and Cockcroft-Gault Eqn. in controls

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## Vancomycin in Extreme Obesity

Study	Blounin (n=6)(n=4 controls)	Bauer (n=24)(n=24 controls)
Vd	0.26 ±0.03 L/kg (obese) vs 0.68 ±0.07 L/kg (control)	0.32 ±0.05 L/kg (obese) vs 0.68 ± 0.24L/kg (control)
Clearance (total)	187.5 mL/min. (obese) vs 80.78 mL/min.(control)	197 ±77mL/min. (obese) vs 77 ±22 mL/min. (control)
Creatinine Clearance	Not reported	209 ±35 mL/min. (obese) vs 110 ±17 mL/min. (control)
Half-life	3.2 h (obese) vs 4.8 h (control)	3.3 ±0.8 (obese) vs 7.2 ±2.2 (control)

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## Vancomycin in Extreme Obesity

- Recommendations PK studies:
  - Doses to achieve a peak of 25-35 mg/L and trough 5-10 mg/L were 30 mg/kg/day using total body weight
    - Bauer found morbidly obese patient required 31.2 ±6.3 mg/kg-day based on total body weight
  - Shorter half-life (3.2-3.3 h) results in more frequent dosing i.e. q8h dosing
    - Bauer found 20/24 morbidly obese patients required q8h dosing (mean dose of 1948±549 mg iv q8h) to achieve target concentrations; 4/20 achieved adequate concentrations using q12h dosing (mean dose of 1250±289 mg iv q12h)

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## Key Points

- Extrapolation of study results to extremely obese patients with "normal" renal function:
  - Vancomycin 30 mg/kg/day based on TBW is suggested
  - The loading dose can be omitted
    - Loading dose to achieve 30-35 mg/L
    - =Vd\*Cpmax=0.32L/kg\*35 mg/L~10 mg/kg
  - An increased renal clearance results in a shorter half-life and requiring q8h dosing

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## Example of Vancomycin Dosing Extreme Obesity

- JG -55 year old male
- Height=5'9"
- Weight=346 lb (157 kg)
- BMI=51.1kg/m<sup>2</sup>
- Scr=75 umol/L
- Clcr=165 mL/min. (Salazar-Corcoran)
- Suggested initial vancomycin Dose=1500 mg IV q8h (10 mg/kg) (omit LD)
- Check pre- and 3-h post dose levels at SS



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## Vancomycin Dosing in RF and Extreme Obesity

- Vancomycin dosing in RF and extreme obesity has not been studied

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## The Aminoglycosides in Extreme Obesity

- polar drugs that distribute into
  - the extracellular fluid compartment (the lean body mass)
  - water portion of adipose tissue and to increased muscle mass and connective tissue present that support the excess weight

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## Aminoglycosides in Extreme Obesity

- Effect of Extreme Obesity on Aminoglycoside Pharmacokinetic Parameters- 1 case controlled study
- Study design: compared aminoglycoside PK in morbidly obese patients (n=20) to matched controls (n=20)
- Targeted peak concentration:
  - Gentamicin/Tobramycin 5-8 ug/mL
  - Amikacin 20-30 ug/mL
- Targeted trough concentrations:
  - Gentamicin/tobramycin <2 ug/mL
  - Amikacin <5 ug/mL

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## Aminoglycosides in Extreme Obesity

Study	Bauer (n=20)(20 matched controls)
Volume of Distribution (Control Vd=0.25-0.26 L/kg IBW or TBW)	Gentamicin 0.17 ±0.04 L/kg TBW and 0.41 L/kg IBW Tobramycin 0.19 ±0.03 (TBW) vs 0.45 ±0.08 L/kg IBW Amikacin 0.18 ±0.02 (TBW vs 0.44 ±0.02 L/kg IBW)
Clearance (total) (Control Cl=1.31-1.43)	Gentamicin 1.02 ±0.24 ml/min/kg TBW Tobramycin 1.11 ±0.22 ml/min/kg TBW Amikacin 1.07 ±0.26 ml/min/kg TBW
Half-life (Control Half-life= 2.1-2.2 h)	Gentamicin 2.2 ±0.4 h Tobramycin 1.9 ±0.4 h Amikacin 2.0 ±0.4 h

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## The Aminoglycosides

- Effect of Obesity on AMG PK parameters
  - Volume of Distribution (Vd) correlated to both lean body mass and adipose tissue mass
    - The relationship between TBW and Vd was quantified using  $Vd=0.26(IBW+CF[TBW-IBW])$  with  $CF\sim 0.4$  in this study:
      - 0.45 for gentamicin
      - 0.37 for tobramycin
      - 0.42 for amikacin

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## The Aminoglycosides

- Study Conclusions:
  - Vd is higher than those of normal weight and can be estimated using  $0.26(IBW+ 0.4[TBW-IBW])$
  - Clearance was higher than in normal weight patients, likely reflecting higher renal clearance
  - Half-life was similar normal weight patients (~2 hours)
  - Mean doses were higher than in normal weight patients: (divided q8h)
    - Gentamicin 540 mg/day
    - Tobramycin 690 mg/day
    - Amikacin 1970 mg/day

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## Key Points

- In patients with extreme obesity and normal renal function, the AMG should be dosed using conventional dosing
  - Single daily aminoglycoside dosing using the Hartford nomogram should not be used
- Can use Salazar-Corcoran equation to estimate Clcr and the elimination constant (k) using population PK
- Vd can be estimated using  $0.26(IBW+ 0.4[TBW-IBW])$

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## Example of Gentamicin Dosing Extreme Obesity

- 55 year old male
- Height=5'9"
- Weight=346 lb (157 kg)
- BMI=51.1kg/m<sup>2</sup>
- Scr=75 umol/L
- Clcr=165 mL/min. (Salazar-Corcoran)



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## Example of Gentamicin Dosing - Extreme Obesity

- Pharmacokinetic Parameters:
  - Estimated  $K=0.429h^{-1}$
  - Estimated  $t_{1/2}=1.6 h$
  - Estimated  $V_d$  (using  $0.26 L/kg DBW$ )= $27.3 L$
- Suggested Dose= $200 mg IV q8h$  to achieve at peak  $6.2 mg/L$  and trough  $0.31 mg/L$
- Obtain 30-minute pre-dose and 1-h post dose serum concentrations at SS and analyze

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## Other Antimicrobial Drug Dosing in Extreme Obesity

- Aside from the aminoglycosides and vancomycin, few studies on dosing antimicrobials in extreme obesity
- To determine the most appropriate dose consider:
  - Patient response
  - Antimicrobial dose-related toxicity/side effects
  - Need to adjust dose in renal dysfunction
- Can try using upper end of usual dose in patients with extreme obesity if no data available

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## Review of the Drug Dosing in Extreme Obesity Tables

- Antimicrobial agents studied:
  - Cefazolin- Use  $2 g IV$  pre-op prophylaxis
  - Cefuroxime-Use  $1.5 g iv$  pre-op prophylaxis (gram positive infections only; higher doses may be need for gram-negative infections)
  - Ciprofloxacin-Calculate  $V_d$  using Adjusted body weight= $0.45(TBW-IBW)+IBW$
  - Daptomycin-Dosing using TBW resulted a  $C_{max}$  and AUC  $\sim 60\%$  higher than normal subjects-further study need to determine optimal dose
  - Fluconazole-use up to  $1200 mg/day$  for *C. albicans* necrotizing fasciitis
  - Linezolid-use usual dose
  - Meropenem-use usual dose

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## LMWH Dosing in Extreme Obesity

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## Low-molecular Weight Heparin

- LMWH Dosages often capped in obese patients with DVT/PE:
  - Dalteparin  $200 units/kg$  capped at  $18000 units$  daily for weights  $>83 kg$
  - Enoxaparin  $1.5 mg/kg$  capped at  $180 mg/day$
  - Tinzaparin  $175 units/kg$  daily capped at  $18000 units$  for weights  $>105 kg$
  - Nadroparin  $171 units/kg$  daily capped at  $17100 units$  for weights  $>90 kg$
- However...
  - Total body weight and adjusted body weight correlate better with antifactor Xa activity when compared to lean body weight suggesting weight based dosing should be used in obese patients

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## Search strategy-LMWH Dosing in Extreme Obesity

Database (all 1950 to October)	Pubmed	Embase	Cochrane
MESH & keywords	Obesity/Morbid Obesity and dosing	Obesity/Morbid Obesity and dosing	Obesity/Morbid Obesity and dosing
Hits	180	262	5
Results (Trials)	3 review articles 3 case-controlled 3 observational cohort studies	0 new articles	0 new articles
<b>For review</b>	<b>9 articles</b>		

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## Clinical question

<b>P</b>	In adult patients with extreme obesity,
<b>I</b>	Should LMWH doses be capped or dosed by total body weight
<b>C</b>	compared to normal weight patients,
<b>O</b>	for treatment of deep vein thrombosis and pulmonary embolism?

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## LMWH Dosing in Obesity

- Safety of LMWH in obese patients:
  - Hemorrhage rates with in 193 obese patients treated with dalteparin dosed with 100 units/kg q12h or 200 units/kg TBW daily for VTE –none experienced major bleeding in the 1<sup>st</sup> 2 weeks after diagnosis and treatment
  - Retrospective analysis of obese and non-obese patients from TIMI 11b and ESSENCE trials treated with enoxaparin 1 mg/kg q12h TBW for ACS found no significant differences in major bleeding between groups

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## LMWH Dosing in Obesity

- Antifactor Xa levels
  - Antifactor Xa levels in obese patients receiving therapeutic doses of dalteparin (using TBW):
    - therapeutic levels achieved 6/10 patients subtherapeutic levels achieved in 4/10 receiving daily dosing
    - therapeutic levels achieved 9/11 patients; subtherapeutic levels achieved in 2/10 receiving q12h dosing
  - Antifactor Xa levels in overweight or obese compared to normal weight patients receiving therapeutic doses of enoxaparin (using TBW):
    - Mean antifactor Xa levels were 1.56 U/mL in overweight and obese patients compared to 1.49 U/mL in normal weight patients (both within desired range)

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## LMWH Dosing in Obesity

- Antifactor Xa levels in overweight or obese compared to normal weight patients receiving therapeutic doses of enoxaparin (using TBW):
  - Similar obese and normal weight patients had subtherapeutic, supratherapeutic and desired antifactor Xa levels

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## LMWH Dosing in Obesity

- Frequency of Administration
  - Obese patients receiving enoxaparin daily therapeutic doses 37% had subtherapeutic Antifactor Xa levels compared to 2% who received q12h therapeutic dosing
  - In another study, 4/10 patients receiving enoxaparin daily had subtherapeutic antifactor Xa levels compared to 0/12 who received q12h dosing

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## Study Limitations

- Studies not exclusively performed in patients with extreme obesity
- Only a small number of patients >150 kg enrolled in studies
  - Retrospective review of obese patients >150 kg receiving enoxaparin 1 mg/kg q12h for ACS had a higher bleeding risk than those who received a lower dose based on adjusted body weight
- Studies did not include patients with renal dysfunction
  - Should avoid LMWH in obese patients with Cl<sub>cr</sub><30mL/min. –further studies need in these patients

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## Key Points

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- In obese patients 90-150 kg, with thromboembolic disorders, LMWH should be dosed using total body weight
  - In patients >150 kg, unfractionated heparin should probably be used; if LMWH is used antifactor Xa levels should be monitored
  - Enoxaparin should be dosed at 1 mg/kg q12h to avoid subtherapeutic antifactor Xa levels
- LMWH heparin should be avoided in obese patients with  $Cl_{cr} < 30$  mL/min.

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## Example of LMWH Dosing in Obesity

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- KA-58 year old female
- Height=5'8"
- Weight=228 lb (113 kg)
- BMI=34.7kg/m<sup>2</sup>
- Multiple plane trips to Hollywood to promote new reality TV show resulted in a dVT
- Tinzaparin 175 units/kg sc daily for DVT =20000 units sc daily (bridging therapy)



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■ Questions.....

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