Antibiotic dosing in the obese patient

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Antibiotic Goals

- Promote bacteria death
- Prevent the emergence of resistance
- Avoid toxicity

Antibiotic must not only attach to target but must occupy an adequate number of binding sites

That depends on drug concentration within the organism and also on bacteria susceptibility – MIC

Usually antibiotic concentration must be over 3-5 times MIC

Underdosing

Increase in Volume of distribution
Increase in clearance
Patterns of Antimicrobial Activity

- Aminoglycosides
- Metronidazol
- Azithromycin
- Fluoroquinolones

Concentration

\[ C_{\text{max}} \]

Time (hours)

MIC

\[ \text{Area under the concentration curve} \]

\[ \text{T} > \text{MIC} \]

Beta-lactams

Carbapenems

Concentration-dependent

Time-dependent
Antimicrobial exposure

- Concentration
  - $C_{\text{max}}$
  - Area under the concentration curve
    - Mainly dependent of the Clearance
  - T$>$MIC

- Time (hours)
  - MIC
  - Mainly dependent of VD

The image illustrates the concentration profile over time, highlighting the main parameters and their dependencies.
Peak Concentration and Volume of Distribution

- The apparent **volume of distribution** indicates into how large a volume the drug distributes if it were at the same concentration as that in plasma.

- Initial peak concentration is only dependent on dose and volume of distribution.
Rate of elimination $= \text{Cl} \times C_{\text{in plasma}}$

$(\text{Amount / Unit of time}) = (\text{Volume / Unit of time}) \times C_{\text{in plasma}}$

Clearance is the volume of plasma completely cleared of the drug per unit of time by all routes - the liver, the kidney...

Elimination of most drugs from the body after therapeutically relevant doses follows first-order kinetics.

$\text{Dose} = 100 \text{ mg}, \text{V}_{d} = 10 \text{ L}, \text{C}_{0} = \frac{\text{Dose}}{\text{Vd}} = 10 \text{ mg/L}$

$\frac{dC}{dt} = -k_{el} \cdot C$

**First order PK**

Amount of drug that is eliminated depends on its initial concentration.

According an increased $\text{Vd}$ usually compensates for an increased $\text{Cl}$. 
Volumes of compartments in relation to Vd

Total body water 0.6 L/kg BW

- Intracellular water 0.4 L/kg BW
- Extracellular water 0.2 L/kg BW
- Plasma 0.04 L/kg BW

\[ V_d \] 0.05 L/kg the drug remains within the blood (heparine)

\[ V_d \] 0.1-0.3 L/kg distribution from blood into extracellular fluid (gentamicin).

\[ V_d \] 0.6 L/kg distribution from blood into intra and extracellular fluid (methotrexate)

\[ V_d \] >> 0.6 L/kg distribution intracellularly and high binding in tissues (amiodarone)

What about fat tissue?
Body Weight Calculations

<table>
<thead>
<tr>
<th>IBW (in kg)</th>
<th>Equation</th>
</tr>
</thead>
<tbody>
<tr>
<td>45.5 kg + 2.3 (inches over 5 feet): women</td>
<td></td>
</tr>
<tr>
<td>50 kg + 2.3 (inches over 5 feet): men</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cockroft-Gault (mL/min)</th>
<th>Equation</th>
</tr>
</thead>
<tbody>
<tr>
<td>(140-age)X TBW/72X Scr (X 0.85, if female)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Salazar-Corcoran (men) (mL/min)</th>
<th>Equation</th>
</tr>
</thead>
<tbody>
<tr>
<td>(137-age)X [(0.285 X TBW)+ (12.1 X Ht^2)/(51X Scr)]</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Salazar-Corcoran (women) (mL/min)</th>
<th>Equation</th>
</tr>
</thead>
<tbody>
<tr>
<td>(146-age)X [(0.287 X TBW)+ (9.74 X Ht^2)/(60X Scr)]</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MDRD (mL/min/1.72m^2)</th>
<th>Equation</th>
</tr>
</thead>
<tbody>
<tr>
<td>(175 X Scr^{-1.154X Age^{-0.203} X (0.742, if female) X (1.210, if black)}</td>
<td></td>
</tr>
</tbody>
</table>

- <25 Normal
- 25-30 Overweight
- >30 Obese
- >35 Morbidly obese
- >55 Super-morbidly obese
Pharmacokinetic changes in obesity in general

- **Absorption**
  - Little data exists on differences -> maybe delayed gastric emptying

- **Distribution**
  - **Lipophilic medications** should be dosed on total body weight due to higher distribution volumes
  - **Hydrophilic medications** should be dosed on ideal body weight or adjusted body weight due to lower volumes of distribution

Curr Opin Infect Dis 2012;25:634-49
Clin Pharmacokinetic 2012;51:277-304
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- **Metabolism**
  - CYP3A4 has lower drug clearance; CYP2E1 and most phase 2 enzyme systems have higher clearance; CYP1A2, CYP2C9, CYP2C19 and CYP2D6 trend towards higher clearance

- **Excretion**
  - Obesity results in an increase in baseline renal clearance, but has a higher incidence of renal dysfunction from hypertension or diabetes

*Curr Opin Infect Dis* 2012;25:634-49
*Clin Pharmacokinetic* 2012;51:277-304
To achieve therapeutic concentrations rapidly loading doses are recommended

Recommend giving high end of normal loading dose (or even higher dose)
- Example: Vancomycin (normal patient Vd ~0.7 L/kg)
  - 100kg septic shock patient

<table>
<thead>
<tr>
<th>Loading Dose</th>
<th>Estimated Vd</th>
<th>Estimated Peak level (mcg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>25 mg/kg ABW</td>
<td>~1 L/kg due to fluid resuscitation</td>
<td>25</td>
</tr>
</tbody>
</table>

Results—Data were collected on a random sampling of 421 patients, stratified by body mass index, who met the inclusion criteria. Most patients in each body mass index category received a fixed dose of vancomycin 2 grams daily divided into two doses (underweight 82%, normal weight 90%, overweight 86%, obese 91%). Adequate initial dosing (≥10 mg/kg/dose) was achieved for 100% of underweight, 99% of normal weight, 93.9% of overweight, and 27.7% of obese patients (p < 0.0001).

Predictors of antibiotic failure

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR (95% CI)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Sex (Reference: Male)</td>
<td>0.88 (0.76–1.03)</td>
<td>0.106</td>
</tr>
<tr>
<td>2. Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20–34 yrs</td>
<td>1.00 (0.78–1.27)</td>
<td>0.974</td>
</tr>
<tr>
<td>35–49 yrs</td>
<td>1.03 (0.84–1.26)</td>
<td>0.812</td>
</tr>
<tr>
<td>50–64 yrs</td>
<td>0.99 (0.82–1.20)</td>
<td>0.954</td>
</tr>
<tr>
<td>65–70 yrs (Reference)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>3. Socioeconomic Status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low Income</td>
<td>1.00 (0.82–1.20)</td>
<td>–</td>
</tr>
<tr>
<td>Middle Income (Reference)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High Income</td>
<td>0.78 (0.61–1.00)</td>
<td>–</td>
</tr>
<tr>
<td>4. BMI Category</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal (Reference)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Overweight</td>
<td>1.06 (0.87–1.28)</td>
<td>–</td>
</tr>
<tr>
<td>Obese</td>
<td>1.26 (1.02–1.57)</td>
<td>–</td>
</tr>
<tr>
<td>5. Alcohol Consumption</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-drinker</td>
<td>2.20 (1.80–2.68)</td>
<td>–</td>
</tr>
<tr>
<td>Moderate (Reference)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Heavy</td>
<td>0.98 (0.90–1.06)</td>
<td>–</td>
</tr>
<tr>
<td>6. MRSA</td>
<td>2.33 (1.97–2.75)</td>
<td>–</td>
</tr>
<tr>
<td>7. History of Antibiotic Use</td>
<td>1.27 (1.13–1.43)</td>
<td>–</td>
</tr>
</tbody>
</table>

**KEY POINTS**
- Of the 828 (13.4%) persons who suffered an antibiotic treatment failure (ATF) event, nearly 64% were either overweight or obese.
- Significant predictors of ATF were obesity, antibiotic resistance, recent history of antibiotic use, and being a non-drinker.
- Alternative antibiotic dosing strategies may be necessary when treating obese patients for acute infections as a means of reducing the risk of ATF.

In obese patients without renal failure the probability of target attainment was lower.
Serum drug concentrations obtained in obese and nonobese patients

In obese patients the total Vd is higher but the Vd/kg is lower

Pharmacokinetics and total concentration of ertapenem versus time profile over 6 h according to weight

Vd (l) and Cl (l/1,73m²)

Vd increase with weight whilst Vd/kg decreases

Decrease AUC with increasing weight and Vd

Pharmacokinetics and total concentration of ertapenem versus time profile over 6 h according to weight

Percent probability of attaining the target of 20% (A) or 40% (B) for fT>MIC with a single 1-gram dose of ertapenem at MICs of 0.25, 0.5, 1, 2, 4, and 8 μg/ml in normal-weight, class I-II obese, and class III obese groups.

Small difference but no dosage adjustment was recommended

Obesity and Volume of Distribution

Lipophilic drugs $+ \ (TBW)$

Hydrophilic drugs $+ \ K \ * \ (ABW)$

K depends on water content and tissue affinity – usually 0.37-0.58

No fat distribution $\ (IBW)$

Fat tissue

$= \text{TBW-IBW}$
# Dosing Recommendations

## Table 1: Dosing Guidelines

<table>
<thead>
<tr>
<th>Agent</th>
<th>Suggested dosing weight (for dosing or Vd calculation)</th>
<th>Additional dosing recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antibacterial agents</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aminoglycosides (amikacin, gentamicin, tobramycin)</td>
<td>Adjusted body weight = IBW + 0.4 (TBW-IBW)</td>
<td>No dose adjustment recommended.</td>
</tr>
<tr>
<td>Azithromycin</td>
<td></td>
<td>No dose adjustment recommended.</td>
</tr>
<tr>
<td>Ampicillin</td>
<td></td>
<td>No dose adjustment recommended; use normal recommended dose, adjusted for renal function.</td>
</tr>
<tr>
<td>Aztreonam</td>
<td></td>
<td>No dose adjustment recommended.</td>
</tr>
<tr>
<td>Beta-lactam drugs (without other specific recommendations)</td>
<td>Adj. body weight = [IBW + 0.3 (TBW-IBW)]</td>
<td>No specific recommendations; base dose on VD calculated off of adjusted body weight.</td>
</tr>
<tr>
<td>Carbapenems</td>
<td></td>
<td>No dose adjustment recommended, use normal recommended dose, adjusted for renal function.</td>
</tr>
<tr>
<td>Cefazolin</td>
<td></td>
<td>For surgical prophylaxis, increase dose to 2 g.</td>
</tr>
<tr>
<td>Ceftazidime, cefuroxime</td>
<td></td>
<td>No dose adjustment recommended; use normal recommended dose, adjusted for renal function.</td>
</tr>
</tbody>
</table>

**Notes:**
- Final dose by 25%.
- Use dose to 3 g q6h.
- For surgical prophylaxis, increase dose to 2 g.
- Use adjusted dose, adjusted for renal function.
- For the initial dose, 1 g q6h.
- Dosing interval may be longer than standard.
- No data.

**Special Considerations:**
- For patients with renal impairment, adjust dose based on renal function.
- For chronic renal failure, consider using a different agent.
- Use caution when dosing children, elderly, or patients with hepatic impairment.
Antibiotics Pharmacokinetics

Gonçalves-Pereira. Crit Care 2011, 15:R206
Always use high loading doses – according to ABW or TBW

Adjust maintenance dose according to Pharmacodynamics and Clearance (especially peak dependent drugs)
  • Steady state concentration most likely not affected

Consider renal function and augmented renal clearance
  • 65.1% of patients with normal creatinine

In unstable obese patients use therapeutic drug monitoring whenever possible
  • Alternative: population pharmacokinetics

Udy, Crit Care Med 2014; 42:520–527
V-FIB
GODS Ctrl/Alt/Delete