PART 5: Pharmacotherapy and Pharmacokinetics in Adults: Aminoglycosides and Vancomycin
Objectives

• Define basic pharmacodynamic and pharmacokinetic principles
• Describe the principles of administering and monitoring aminoglycosides and vancomycin
• Demonstrate practical evidence-based dosing of aminoglycosides and vancomycin
Pharmacodynamics

Aminoglycosides Deliver Bactericidal Activity

• Concentration-dependent killing via inhibition of protein synthesis at the ribosome
• Post-antibiotic effect: Bacterial regrowth suppressed even after serum concentrations fall below the minimum inhibitory concentration (MIC)
• Primarily target aerobic gram-negative bacilli
• Limited action against some gram-positive organisms
  • Gentamicin: Combination with a cell-wall-active agent (penicillin or vancomycin) synergistic against strains of Enterococci and Staphylococci
Concentration-Dependent Killing

• Bacterial kill depends on the peak concentrations achieved
  – “High peaks lead to better outcomes”
• Parameters correlating with clinical efficacy: Ratio of maximum peak concentration to MIC (AUC:MIC)
• Peak concentration: MIC ratio
  – At least 8:1
  – “Higher the concentration, greater the kill rate”
  – A ratio of 10:1 may also prevent the emergence of aminoglycoside resistant pathogens
Dosing is Constrained Because of Adverse Events

- Nephrotoxicity <2-10%
  - Careful monitoring and control of serum concentrations may reduce risk
  - Generally reversible upon discontinuation of treatment

- Ototoxicity <2-10%
  - Generally reversible or only partially reversible
  - Can affect cochlear and/or vestibular function
  - Often seen after onset of nephrotoxicity and accumulation of high serum levels
Therapeutic Range

• Peaks concentration targets are based on:
  – Location of infection
  – Severity of infection
  – Aminoglycoside used
• Toxicity concerns with:
  – Gentamicin/Tobramycin
    • Peaks consistently above 12 to 14 mcg/mL
    • Trough consistently greater than 2 mcg/mL
  – Amikacin
    • Peaks consistently above 32 to 34 mcg/mL
    • Trough consistently greater than 8 to 10 mcg/mL
## Patient Population Parameters: Aminoglycosides

<table>
<thead>
<tr>
<th>Agent</th>
<th>CL (ml/min)</th>
<th>Vd (L/kg)</th>
<th>$t_{1/2}$ for CrCl = 80 mL/min &amp; V = 18L</th>
<th>$t_{1/2}$ for CrCl = 10 mL/min &amp; V = 18L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gentamicin</td>
<td>0.95 X CLcr</td>
<td>0.25</td>
<td>2.7</td>
<td>22 hr</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>0.95 X CLcr</td>
<td>0.25</td>
<td>2.7</td>
<td>22 hr</td>
</tr>
<tr>
<td>Amikacin</td>
<td>0.95 X CLcr</td>
<td>0.25</td>
<td>2.7</td>
<td>22 hr</td>
</tr>
</tbody>
</table>
Impact of Disease States on Vd

- Ascites: $V_d$ increases by as much as 25%
- Cirrhosis (critically ill with sepsis): 40% larger volume (L/kg)
- Cystic Fibrosis: $V_d$ increases
- ICU/severely ill: $V_d$ 25% to 50% higher
- Obesity: $V_d$ does not increase proportionally with increasing weight
- Pancreatitis: $V_d$ increase by as much as 25%
- Patent Ductus Arteriosus: $V_d$ increase by 13%
- Postoperative, Mechanical Ventilation: $V_d$ increases
- Postpartum: $V_d$ increases
- Newborn: higher extracellular volume
Compromised Renal Function

- Tissue accumulation occurs in patients receiving aminoglycoside for more than 7 to 10 days
- Serum concentrations should be monitored
- Therapy should be adjusted to prevent excessive tissue accumulation and reduce the risk of toxicity
Hemodialysis

• Significantly removes aminoglycoside from serum
• Initial dose: use population-based volume of distribution
• Subsequent doses: individualized using patient-specific parameters calculated from plasma concentrations
Aminoglycoside Administration

• Intermittent infusion over 30 minutes
  – IV push generally avoided

• Distributes to tissue compartment as rapidly as it is being administered

• Slow elimination rate or large volume of distribution alters tissue equilibration
Extended-Interval Dosing (EID) for Aminoglycosides
Extended-Interval Dosing (EID)

- Single-daily high dose therapy
- Do NOT confuse with “traditional” therapy which has been adjusted to a 24 hour dosing interval because of renal dysfunction
Advantages of EID

• Maximize peak levels
  – Avoidance of sub-therapeutic serum concentrations and poor outcomes

• Potentially decrease toxicity
  – Because of low end-of-interval serum levels

• Equally efficacious

• Decrease cost
Post Antibiotic Effect (PAE)

- Post-antibiotic effect (PAE) is partially credited with why EID is acceptable
- PAE allows for persistent suppression of bacterial growth despite negligible serum levels
- Depends on 4 factors
  - Bacterial strain
  - Duration of exposure
  - Inherent antibacterial potency
  - Relative concentration of the aminoglycoside
- Duration of 0.5 to 8 hours
- Higher the concentration of aminoglycoside, the longer the duration of the PAE (thus a longer PAE than with conventional regimens)
- Levels can fall below the MIC without compromising antimicrobial efficacy
EID Adverse Events

• Uptake into the renal tubules and inner ear appears to saturate at relatively low serum levels
• Higher peaks do not necessarily result in greater toxicity
• Duration of exposure appears to be more of a determinant of toxicity than serum level
EID Guidelines: Exclusions

The Pharmacy and Therapeutics Committee recommends EID of the aminoglycosides where appropriate.

All adult patients may be initiated on EID of the aminoglycosides EXCEPT:

• Pregnant patients
• Pediatric patients
• Burns > 20% of body surface area
• Synergy for gram-positive infections (including enterococcus endocarditis)
• CrCl less than 20 ml/min*, patients on dialysis, or patients with rapidly changing renal function

*In CTX, EID is generally used at CrCl of 60 mL/min or above.
EID Guidelines: Cautions

The following types of patients may receive EID if initiated by or approved by prescribing physician (otherwise they should receive traditional dosing):

• Patients with potentially extreme alterations in volume of distribution (anasarca, etc.)
• Neutropenic fever
• History of hearing loss or vestibular dysfunction
• Patients with CrCl 20 to 39 ml/min*
• Other patient populations who may not achieve adequate levels when receiving EID (cystic fibrosis, critically ill, etc.)

*In CTX, EID is generally used at CrCl of 60 mL/min or above
# EID Empiric Dosing Regimen

<table>
<thead>
<tr>
<th>Condition</th>
<th>Gentamicin/Tobramycin</th>
<th>Amikacin</th>
</tr>
</thead>
<tbody>
<tr>
<td>General infections</td>
<td>5 mg/kg IV daily</td>
<td>15 mg/kg IV daily</td>
</tr>
<tr>
<td>HAP/VAP/HCAP or other severe infections</td>
<td>7 mg/kg IV daily</td>
<td>20 mg/kg IV daily</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>CLCR &gt; 60 ml/min</th>
<th>CLCR 40-59 ml/min*</th>
<th>CLCR 20-39 ml/min*</th>
<th>CLCR &lt; 20 ml/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gentamicin/Tobramycin</td>
<td>5-7 mg/kg IV</td>
<td>24 hours</td>
<td>36 hours</td>
<td>48 hours</td>
<td>Patient specific dosing</td>
</tr>
<tr>
<td>Amikacin</td>
<td>15-20 mg/kg IV</td>
<td>24 hours</td>
<td>36 hours</td>
<td>48 hours</td>
<td>Patient specific dosing</td>
</tr>
</tbody>
</table>

*In CTX, EID is generally used at CrCl of 60 mL/min or above.
EID Dosage Recommendations

• Dosing weight for EID
  – Use actual body weight if using an EID nomogram unless actual body weight is >20% of ideal (obese)
  – If the actual body weight is >20% of the ideal body weight and using EID nomogram then use dosing weight (adjusted body weight)

• Gentamicin and Tobramycin
  – Single dose: 5-7 mg per kg based on indication nomogram used
    • 7 mg/kg dosing per Hartford nomogram used in HAP/VAP/HCAP or other severe infections
    • 5 mg/kg dosing per Ritchie nomogram may be used for less severe infections
  – Order a level
    • For 7 mg/kg dosing per Hartford nomogram, obtain a level 6-14 hours after 1st infusion is STARTED (goal is 10 hours)
    • For 5 mg/kg dosing per Ritchie nomogram, obtain a level 6-14 hours after 1st infusion ENDS (goal is 10 hours)
  – Adjust frequency based on appropriate nomogram

• Amikacin
  – Single dose from 15 to 20 mg/kg
  – For 15mg/kg per Ritchie nomogram, obtain a level 6-14 hours after 1st infusion ENDS (goal is 10 hours)
  – Adjust frequency based on appropriate nomogram
Hartford Nomogram for doing of Gentamicin/Tobramycin (7 mg/kg)
Ritchie et al Nomogram for Gentamicin/Tobramycin (5 mg/kg)
Ritchie Nomogram for Dosing of Amikacin 15 (mg/kg)
Monitoring Extended Interval Dosing

- Baseline serum creatinine (SCr) is necessary before initiating therapy
- Check SCr every 3 to 5 days
- Peak levels should NOT be drawn when using EID therapy
- Troughs are generally not recommended, but could be considered in patients with renal impairment

<table>
<thead>
<tr>
<th></th>
<th>Gentamicin/Tobramycin</th>
<th>Amikacin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Extended Interval</strong></td>
<td>Generally not recommended; consider in patients with renal impairment; less than 1 mcg/ml</td>
<td>Generally not recommended; consider in patients with renal impairment; less than 4 mcg/ ml if ordered</td>
</tr>
</tbody>
</table>
Traditional Aminoglycoside Dosing
Traditional Therapy

- Also known as “multiple-daily dosing” and “conventional dosing”
- Includes patients:
  - Not eligible for EID
  - With documented serious gram-negative infections (e.g. Pseudomonas) in combination with a beta-lactam agent
- Dosing weight for traditional therapy:
  - Use ideal body weight unless actual body weight is >20% of ideal (obese)
  - If the actual body weight is >20% the ideal body weight use dosing weight (adjusted body weight)
Using the BSWH Pharmacokinetic Calculator

• CTX: The calculator is located on the shared pharmacy drive
• NTX: The calculator is located in Allscripts under the ‘Tools’ menu.
  – It is also located on the formulary website under ‘Tools and Calculators’
• For initial traditional dosing use the ‘Empiric Calculation’ tab.
  – Section 1:
    • Enter demographics
    • For SCr and Vd hover over red mark for values (1b)
    • Choose drug you want to dose
  – Section 2:
    • To select weight to calculate Vd, hover over red mark for values (2)
  – Section 3:
    • To select weight to calculate CrCl, hover over red mark for values (3)
    • The following information will populate (4)
      – IBW (Kg), DW (kg), CrCl (mL/min), Ke (hr⁻¹), T₁/₂ (hr), Vd (L)
  – Section 4:
    • Enter desired peak and trough aminoglycoside levels (5)
      » For desired peaks, hover over for range based on indication
      » For target trough, hover over for range based on severity
    – The following information will populate (6)
      » Ideal interval (hr), Ideal dose (mg)
How to use BSWH Pharmacokinetic Calculator (continued)

• Section 5: Enter desired interval and dose based on ideal dose and interval suggested.
  – For gentamicin and tobramycin doses should be in increments of 10 mg
  – For Amikacin, doses should be in increments of 50 mg
• The following information will populate
  – Estimated Cmax (mg/L), Estimated Cmin (mg/L)
Aminoglycoside Level Monitoring

• When traditional dosing is used, both peak and trough serum concentrations should be monitored to ensure that the patient is within the therapeutic range.

• Draw a peak and a trough level around the 3rd dose to determine if dosing interval adjustment is needed:
  – Order trough to be drawn 30 minutes prior to the 3rd infusion
  – Order peak to be drawn one hour after the start of the 3rd infusion

• Peak concentrations should be based on the infection site

• The next slides outline general guidelines for goal peaks and troughs based on selected indications.
  – Peak and trough concentrations should be obtained at steady state and every 5 or 7 days once levels are in the desired range with stable renal function.

• These concentrations should be used in the PK calculator to calculate a new dosage if necessary.
## Peak Concentrations: Traditional Dosing Only

<table>
<thead>
<tr>
<th>Condition</th>
<th>Gentamicin/Tobramycin</th>
<th>Amikacin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cystic Fibrosis</td>
<td>8 to 12 mcg/mL</td>
<td>25 to 40 mcg/mL</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>8 to 10 mcg/mL</td>
<td>28 to 35 mcg/mL</td>
</tr>
<tr>
<td>Biliary Tract Infection</td>
<td>8 to 10 mcg/mL</td>
<td>25 to 35 mcg/mL</td>
</tr>
<tr>
<td>Peritonitis</td>
<td>8 to 10 mcg/mL</td>
<td>25 to 35 mcg/mL</td>
</tr>
<tr>
<td>Sepsis</td>
<td>8 to 10 mcg/mL</td>
<td>28 to 35 mcg/mL</td>
</tr>
<tr>
<td>FUO with Neutropenia</td>
<td>6 to 8 mcg/mL</td>
<td>20 to 25 mcg/mL</td>
</tr>
<tr>
<td>Cellulitis</td>
<td>6 to 8 mcg/mL</td>
<td>20 to 25 mcg/mL</td>
</tr>
<tr>
<td>Diverticulitis</td>
<td>6 to 8 mcg/mL</td>
<td>20 to 25 mcg/mL</td>
</tr>
<tr>
<td>Pyelonephritis</td>
<td>6 to 8 mcg/mL</td>
<td>20 to 25 mcg/mL</td>
</tr>
<tr>
<td>Wound Infection</td>
<td>6 to 8 mcg/mL</td>
<td>20 to 25 mcg/mL</td>
</tr>
<tr>
<td>Cystitis-UTI</td>
<td>4 to 6 mcg/mL</td>
<td>15 to 20 mcg/mL</td>
</tr>
<tr>
<td>Synergy against Gram-positive organisms</td>
<td>4 to 6 mcg/mL (Gentamicin)</td>
<td>NA (Tobramycin)</td>
</tr>
</tbody>
</table>
**Traditional Dosing Goal Trough Concentrations**

<table>
<thead>
<tr>
<th></th>
<th>Gentamicin/Tobramycin</th>
<th>Amikacin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Traditional Dosing</td>
<td>&lt;1 mcg/mL for moderate infections and &lt;2 mcg/mL for severe infections</td>
<td>&lt;10 mcg/mL</td>
</tr>
</tbody>
</table>
Adjusting Aminoglycoside Dose Based on Levels

• If you have obtained aminoglycoside trough or peak levels that are not within range adjust dosing based on pharmacokinetic calculations

• Using the BSWH Pharmacokinetic calculator:
  – Make sure to maximize window as there is an ‘Empiric Calculation’ tab and then a ‘Steady State Calculation’ tab. To adjust doses you want to use the ‘Steady State Calculation’ tab.
    • Section 1: Choose drug you are adjusting and enter current dosage (mg), dosing interval (hr), infusion duration (hr), and time of last dose given as MM/DD/YYYY HH:MM (military time).
    • Section 2: Enter patient’s weight (kg)
    • Section 3: Enter the time (also MM/DD/YYYY HH:MM) that peaks and troughs were drawn
    • Section 4: This will populate automatically and show patient specific calculations:
      • True interval from last dose to trough (Δt)
      • Elimination rate (ke) and Half-life (t₁/₂)
      • Vd (both as L and L/kg)
      • Cmax (mg/L) and Cmin (mg/L)
    • Section 5: Enter desired peak and trough levels as done during empiric calculations (based on indications)
      • Ideal dose and interval populates
      • Enter a practical desired dose and interval to populate estimated Cmax and Cmin in the next box - Keep adjusting numbers until you get desired peak/trough
Synergy Dosing with Gentamicin
Synergy Dosing

- Includes patients with serious gram-positive infections (e.g. endocarditis) being treated with a beta-lactam or vancomycin

- Gentamicin: 1 mg/kg/dose every 8 hours

- Tobramycin/amikacin not recommended for synergy
Vancomycin
Indications

• Treatment of documented, serious infections due to beta-lactam-resistant gram-positive microorganisms

• Treatment of infections due to gram-positive microorganisms in patients with a serious documented allergy to beta-lactam antimicrobials

• When antibiotic-associated colitis (AAC) fails to respond to metronidazole therapy, OR if AAC is SEVERE and potentially life-threatening (oral vancomycin only)

• Empiric therapy for presumed gram-positive infection in patients at high risk of resistant organisms, while awaiting culture and sensitivity results (limited number of doses)
Indications

• Prophylaxis, as recommended by the American Heart Association, for endocarditis following certain procedures in patients at high risk for endocarditis with documented, *serious* allergy to penicillin:
  – Prosthetic cardiac valves, including bioprosthetic and homograft valves (Physicians may choose to administer prophylactic antibiotics even for low-risk procedures that involve the lower respiratory, genitourinary, or gastrointestinal tracts)
  – Previous bacterial endocarditis, even in the absence of heart disease
  – Most congenital cardiac malformations
  – Rheumatic and other acquired valvular dysfunction, even after valvular surgery
  – Hypertrophic cardiomyopathy
  – Mitral valve prolapse with valvular regurgitation, particularly men > 45 years of age

• Prophylaxis for major surgical procedures involving implantation of prosthetic materials or devices, (e.g., cardiac and vascular procedures and total hip replacements), at institutions with a high rate of infections due to methicillin-resistant *Staphylococcus aureus* (MRSA) or methicillin-resistant *Staphylococcus epidermidis* (MRSE). A single dose administered 120 minutes before surgery.
Pharmacodynamics

- Vancomycin is generally bactericidal with time-dependent killing
  - Peak values should be 5 to 8 times the MIC
  - Trough values should be 2 to 4 times the MIC
  - If Staphylococcus aureus and the MIC >1 minimum trough concentration goal should be 15 mg/L, if MIC ≥ 2 use of vancomycin strongly discouraged, consider alternative agents*
  - Concentration of vancomycin should exceed MIC for at least 40% to 50% of the dosing interval
- To generally decrease risk of toxicity
  - Peaks are kept below 40 mg/L

*Note MIC based vancomycin use recommendations based on studies in Staphylococcus aureus, not applicable to coagulase-negative staphylococcus (CoNS)
Absorption

• Not well absorbed orally
  – Used orally for the treatment of pseudomembranous colitis

• Intramuscular injection associated with extreme pain

• Usually administered via IV intermittent infusions
  – Generally infused at 10 mg/minute
Distribution

• Very pronounced
  – Can be described using one-, two-, or three-compartment models

• Initial distribution phase
  – First 1 to 3 hours
  – Plasma drug concentrations are high

• After initial phase
  – Plasma drug concentrations rapidly decline over short period of time

• Approximately 30% to 55% of vancomycin is bound to plasma proteins depending on patient’s albumin concentration

• Therapeutic concentrations found in pleural, pericardial, ascites and synovial fluids, lung, lymph, bile and feces
Elimination

• Primarily cleared by glomerular filtration
• May be eliminated by renal tubular secretion or non-renal routes
• 80% to 90% recovered unchanged in the urine
  – Dosage adjustments necessary for patients with disease or age related alterations in renal function
• Typical half-life: 4.7 hours
Vancomycin in the Morbidly Obese

- $V_{dss}$ is significantly higher in morbidly obese patient compared to non-obese patient
  - Morbid obesity is defined as weight greater than 20% over Ideal Body Weight (IBW)
- Obese patient with large Vd will have an prolonged half-life compared to lean patient with similar CrCl rate.
- Calculations
  - Use actual body weight for initial dosing
  - Initial doses over 4000 mg per day in the obese patient should be avoided
Adverse Events

• Nephrotoxicity
  – Frequency has decreased to 0% to 5% due to more purified preparations
  – Associated with longer courses of therapy and elevated serum levels
  – Concomitant aminoglycoside use
    • Additive toxicity
    • Incidence reported to be as high as 35%

• Ototoxicity
  – Incidence <2%; reversible
  – Most frequently associated with serum concentrations > 80mg/L
Goals of Therapy

• Peak levels should NOT be routinely drawn
• Trough concentration is target

<table>
<thead>
<tr>
<th>Level mcg/ml</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 – 15</td>
<td>General infections (cellulitis, UTI, etc.)</td>
</tr>
<tr>
<td>10 – 20</td>
<td>End stage renal disease</td>
</tr>
<tr>
<td>15 – 20</td>
<td>MRSA-, hospital-, ventilator-, or health-care associated pneumonia, bacteremia, osteomyelitis, endocarditis, bacterial meningitis</td>
</tr>
</tbody>
</table>
Initial Loading Dose for Vancomycin

• For seriously ill patients, with suspected MRSA meningitis, pneumonia, sepsis or infective endocarditis, a loading dose of 25-30 mg/kg can be considered. (Max dose of 2000mg)

• A loading dose may not be needed if patient has cellulitis without suspected bacteremia
Vancomycin Nomogram

- Alternative method utilizing weight and CrCl for initial dosing
- Less patient specific than using the pharmacokinetic calculator
- Allows for prompt initial dosing!
- Vancomycin troughs are used to determine dose adjustments

**IV Vancomycin Dosing Nomogram**

1. Calculate Initial Maintenance Dose: 15mg/kg based on actual body weight (can go up to 20mg/kg) with maximum dose 2000mg (round calculated dose to the nearest 250mg increment)

2. Choose initial dosing interval based on CrCl:

<table>
<thead>
<tr>
<th>CrCl (ml/min)</th>
<th>Dosing Interval (hours)</th>
<th>Goal Trough 10-15 &amp; Goal Trough 15-20 in patients &gt; 65yo</th>
<th>Goal Trough 15-20 in patients ≤ 65 years old</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 70</td>
<td>12</td>
<td></td>
<td>8*</td>
</tr>
<tr>
<td>45-69</td>
<td>24</td>
<td></td>
<td>12</td>
</tr>
<tr>
<td>30-44</td>
<td>36</td>
<td></td>
<td>24</td>
</tr>
<tr>
<td>20-29</td>
<td>48</td>
<td></td>
<td>36</td>
</tr>
<tr>
<td>&lt; 20 &amp; dialysis patients</td>
<td>PULSE DOSING</td>
<td>Single dose 15-20 mg/kg, re-dose based on serum concentrations</td>
<td>PULSE DOSING</td>
</tr>
</tbody>
</table>

(*when choosing initial interval of Q8hr, do not exceed 1500mg per dose)
Vancomycin Serum Level Monitoring

• Peak levels should NOT be routinely drawn
• Trough levels should be obtained for longer courses of therapy
• Troughs should be drawn prior to the 4th dose unless otherwise indicated
• In the following situations, obtain a serum level before 2nd dose (repeat trough level at steady state (i.e prior to 4th or 5th dose)
  – Morbidly obese patients (≥ 190% IBW) and receiving ≥ 4g vancomycin per day
Serum Level Monitoring

Once at steady state, consider more frequent monitoring:
• Vancomycin/aminoglycoside combinations
• Concomitant nephrotoxic or ototoxic agents
• Unstable renal function or hemodynamic status
• Extremes of body weight (an initial peak may be useful)
• CHF
• Intravenous drug abuse
• Burns
• Higher than standard doses (as in abscesses or meningitis)
• Greater than 3 weeks of continued therapy or > 3 grams per 70 kg patient per 24 hours
• Documented or reported decline in hearing
• Acute renal failure or CKD
The BSWH Pharmacokinetic Calculator

• Can also be used for vancomycin dosing
  – Vancomycin desired peak ’35’,
  – For target trough enter 15 in ‘desired trough’
  – Vancomycin doses should be in increments of 250mg
Adjusting Vancomycin Dose Based on Levels

There are several ways to approach adjusting doses once you have obtained trough and peak levels that are not within range:

Use clinical judgment:

• Often times if the levels are close to therapeutic then adjusting the dose up or down incrementally using clinical judgment may be all that is needed. For example, if a vancomycin trough level comes back at 21 when the goal is 15-20, then lowering the dose by 250mg and keeping the same interval may be all that’s required to get it into range.

• Usually if the level returned is not close to the target range adjusting the interval may be required in order to get into the target range. Sometimes when adjusting the interval the dose may also need to be adjusted so that the change is not overshooting the target.

• For levels not close to therapeutic please use the calculator to formulate dose adjustment such as described on the next slide.
Adjusting Vancomycin Dose Based on Levels and the Pharmacokinetic Calculator

Make sure to maximize window as there is an ‘Empiric Calculation’ tab and then a ‘Steady State Calculation’ tab. To adjust doses you want to use the ‘Steady State Calculation’ tab.

- **Section 1:** Choose drug you are adjusting and enter **current** dosage (mg), dosing interval (hr), infusion duration (hr), and time of last dose given as MM/DD/YYYY HH:SS (military time).
- **Section 2:** Enter patient’s weight (kg)
- **Section 3:** Enter the time (also MM/DD/YYYY HH:MM) that peaks and troughs were drawn
  - In the instance where no peak is drawn (ex. Vancomycin troughs) approximate the peak by either using projected peak from empiric calculations, using clinical judgment or use ’35’ as a peak
- **Section 4:** This will populate automatically and show patient specific calculations:
  - True interval from last dose to trough (Δt)
  - Elimination rate (ke)
  - Half-life (t1/2)
  - Vd (both as L and L/kg)
  - Cmax (mg/L)
  - Cmin (mg/L)
- **Section 5:** Enter desired peak and trough levels as done during empiric calculations (for vancomycin peak use ’35’, for target trough 10-15 enter 13 in ‘desired trough’ or for target trough 15-20 enter 15 in ‘desired trough’)
Pulse Dosing of Vancomycin

• Indications:
  • Patients on dialysis (hemodialysis (HD) or peritoneal dialysis (PD))
  • Any patient is estimated CrCl less than 20 ml/min

• Initial Dose:
  • Loading dose of 15 mg/kg actual body weight (Round to the nearest 250 mg; Max 2 g per dose)

• Maintenance Dose/Monitoring dialysis:
  • Order a vancomycin blood level to be drawn as an “AM collection” for the day of the next HD or next day if unknown
  • For PD or acute renal failure draw with AM labs (allow at least ~ 24 hours between dose and lab draw)

• Dose adjustment
  • HD - Re-dose vancomycin after dialysis session to achieve a target serum concentration of 20-25 mcg/ml using Cp = Dose/Vd equation
  • Others- Re-dose vancomycin when serum level is less than goal (either 13 or 18 mcg/ml based on indication)
Pulse Dosing

Initial Dosing:
• Loading dose of 15 mg/kg Total Body Weight (Round to the nearest 250 mg; Max 2 g per dose)
• May Give a loading dose of 25 mg/kg in patients with serious infections (Round to the nearest 250 mg; Max 2 g per dose)

Maintenance Dosing:
• Unstable renal function and NOT on scheduled hemodialysis
  – Draw random vancomycin level every 2 – 3 days. Re-dose with 15 mg/kg dose when random level < 15mg/L.
• Hemodialysis

<table>
<thead>
<tr>
<th>Empiric Maintenance dose (No Levels)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 75kg</td>
</tr>
<tr>
<td>≥ 75kg</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Maintenance dose (Pre- HD levels)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 10mg/mL</td>
</tr>
<tr>
<td>10 – 20 mg/L</td>
</tr>
<tr>
<td>&gt; 20mg/L</td>
</tr>
</tbody>
</table>
Example of pulse dosing:

- Random vancomycin blood level for an HD patient is 18.6 mcg/ml.
- The estimated post dialysis vancomycin level (assuming 30% removal) is calculated to be 13 mcg/ml (18.6 mcg/ml x 0.7 = 13 mcg/ml).
- The approximate increase in serum concentration provided by 500 mg dose is 10.2 mcg/ml
  - Patient is 70 kg, VD= 49L (70kg x 0.7L/kg).
  - Cp = Dose/Vd equation
  - Dose/Vd = 500 mg ÷ 49 L = 10.2 mcg/ml
- Therefore, an order is written for a 500 mg vancomycin dose.
- This will result in an estimated new serum vancomycin concentration of ~ 23.2 mcg/ml
  - 13 mcg/ml + 10.2 mcg/ml = 23.2 mcg/ml.
Vancomycin Monitoring

Hemodialysis

• Serum drug concentrations should be measured on dialysis days
• Daily random drug levels not warranted (every 2-5 days, weekly once stable)
• If using post dialysis levels, order levels 4 hours later to allow for redistribution
Pharmacokinetic Management Documentation

North Division

- North Division pharmacists are to document pharmacokinetic management activities using the Pharmacokinetic structured notes in Allscripts.
- Use pre-populated pharmacokinetic parameters
- Select lab values and culture results (if desired)
- Meets documentation requirements and expectations of physicians
- Click on ‘Enter Document’ icon
- Type the word ‘Pharm’ in the field as shown below → Pharmacokinetic Initial Note and Pharmacokinetic Follow-Up Note will populate
- Select ‘Pharmacokinetic Initial Note’ or ‘Pharmacokinetic Follow-Up Note’ then click ‘Open’
Pharmacokinetic Management Documentation
Central Division

• Calculations and recommendations are recorded in a NOTE in EPIC
Sample Language for Documentation of “Plan”

• **EXAMPLE of an INITIAL NOTE PLAN:**
  Patient received a vancomycin loading dose of 2gm (25mg/kg) x1 in ED. Will dose vancomycin at 1500mg Q12H for a predicted trough level of ~14mg/L based on calculated pharmacokinetic parameters. Will check trough level around the ~3 - 4th dose, or sooner if clinically indicated. Pharmacy will follow and adjust as clinically indicated. Thank you for the consult.

• **EXAMPLE of a FOLLOW – UP NOTE PLAN (Therapeutic):**
  Vancomycin trough level is therapeutic on 1gm Q12H. Will continue with same dose and will re-check level in 5 - 7 days, or sooner if clinically indicated. Pharmacy to follow.

• **EXAMPLE of a FOLLOW – UP NOTE (Sub or Supra - Therapeutic):**
  Will increase vancomycin to 1250 mg iv q12hrs given subtherapeutic trough level; Will monitor SCr closely and repeat trough in 2 - 3 days, or sooner if clinically indicated. Thank you for this consult.
Concluding Note - Approach to Care

• In serious infection, the prompt administration of a first dose of antibiotics may be crucial

• A “generally acceptable” dose administered promptly may be life-saving compared to a “meticulously calculated” dose that is delayed

• Take Home Message – Do not allow dose calculations to unnecessarily delay initial therapy

• Assure follow-up processes are coordinated across shifts and weekends
Please Complete Quiz

Part 5: Pharmacotherapy and Pharmacokinetics in Adults: Aminoglycosides and Vancomycin