Things you will need for these cases:
- SHC Vancomycin Dosing Guide (link)*
- SHC AUC Calculator (link)*
- Weight and CrCl calculator (please use the attached Excel spreadsheet for the purposes of this tutorial)

*These protocols can be found on the Stanford Antimicrobial Safety and Sustainability Program’s website under the “Dosing Protocols” tab for future reference. Type in “Stanford bugs and drugs” in Google to find our website

Principles of vancomycin dosing:
- There are two main protocols used: AUC or trough
  - Specific AUC or trough goals will be dependent on the indication
    - Most indications -> AUC 400-600, trough 10-20**
    - Trough 15-20 ONLY in the following indications:
      - CNS dosing/Meningitis
  - AUC is calculated on the basis of paired peak and trough levels
  - Trough is... well, a trough
- When starting a patient on vancomycin, a loading dose is optional but may be indicated based on the clinical scenario, for example, in seriously ill patients with sepsis.
- Dosing is dynamic!

**You may notice that hospitals outside of Stanford (ie. SCVMC, Palo Alto VA) that still utilize trough-based dosing will aim for a higher or lower trough depending on the severity of indication. For instance, cellulitis may have a goal trough of 10-15 whereas pneumonia has a goal trough of 15-20. Stanford’s current inpatient protocol has a broader trough goal of 10-20, but you will still want to take into account goal trough at the time of discharge if the patient is still on vancomycin (more on this later)
Case 1

A 59 yo Caucasian man with history of diabetes, alcohol use, s/p right BKA for chronic non-healing ulcers, presents with subacute right index finger swelling and erythema. On exam, patient has extensive soft tissue swelling. On X-ray, patient is found to have destruction of the distal phalanx, extensive swelling, and possible foci of soft tissue gas. It is concluded by the clinician that vancomycin should be included in the empiric antibiotic regimen.

The patient has the following characteristics:
- Weight
  - Total body weight (TBW) 114 kg
  - Ideal body weight (IBW) 75 kg
  - Adjusted body weight (ABW) 91 kg
- Height 180 cm (71 in)
- BMI 35.2
- Serum creatinine 0.9, appears stable

***Why are three different types of weights included? The standard formula we use to calculate creatinine clearance (Cockcroft-Gault) can over-estimate creatinine clearance in obese patients if actual body weight is used. Therefore, within this formula, use the following rules:
- Total (actual) Body Weight – Use if TBW is less than IBW
- Adjusted Body weight – Use if obese (BMI > 30)
- Ideal Body Weight – Use this in all other cases

Please also note that this rule applies for calculation of creatinine clearance ONLY. Anywhere else where weight is needed within the vancomycin protocol, just use the total body weight. Also, if you’re using Epic or an online calculator for CrCl calculation, then they will automatically make adjustments for obesity.

What initial regimen of vancomycin do you start, and what dosing regimen do you plan to follow?

We will use AUC-based dosing in this case.

Initial dosing of vancomycin can be calculated with the vancomycin AUC calculator.
- First, obtain his creatinine clearance. In Stanford Epic:
  - You may notice a CrCl column in your patient list with an estimate already provided to you
  - You can also calculate the CrCl using Epic’s provided calculator (Epic tab -> Tools -> Patient Care Tools -> Calculator. Creatinine Clearance can be found under the "Commonly Used" tab.
    - This calculator already takes into account corrections for obesity, so just enter the TBW for patient weight.
    - Please note that Stanford Epic’s calculator may not be reliable for patients who are less than 60 inches tall.
- At hospitals outside of Stanford:
  - Since each hospital EMR may use a different set of equations to estimate Creatinine Clearance, you may notice that other hospitals have a less reliable estimate of Creatinine Clearance.
  - Consider using an online calculator. These calculators will usually list the adjustment made in obese patients separately, so you do not need to worry about using actual vs. ideal vs. adjusted body weight. Just enter TBW. Online calculators we trust include:
    - ClinCalc
    - GlobalRph
For our case:
- Go ahead and use the provided excel spreadsheet.
- For a male patient with his weight, height, and creatinine, use ABW (given obesity) to calculate.
- His estimated CrCl is 113 mL/min.
- Second, input patient parameters into the initial maintenance dose calculator.
  - This calculator uniquely uses the 2020 vancomycin guideline recommendation for a population CL estimate derived from obese patients (Crass et al., JAC 2018). It will help decrease the risk of overdosing them compared to conventional 15mg/kg q12h initial dosing.

Considerations and caveats
- For most indications, target AUC is 400-600. Exceptions are meningitis; given lack of AUC data in this infection type, target a trough between 15-20.
- Remember, dosing interval should be at least 1.0-1.5x the half-life to avoid dose-stacking. Initial half-life estimate of 7 hours.
- Note that the daily dose of Vancomycin may be split up throughout the day, usually in intervals ranging from Q24H to Q8H, with a maximum of 4.5 grams given within a 24 hour period. The individual doses given range anywhere from 750 to 2000 grams per dose given. Options for individual doses include: 750 mg, 1 g, 1.25g, 1.5g, 1.75g, and 2g.
- Using a goal AUC 400-600 (note that the Excel calculator defaults to target a goal AUC of 500), estimated daily dose for BMI 35 will be 2866 mg. This rounds to 3000 mg daily. Given that the estimated half-life is 7.1 hours, 1500 mg q12h is a reasonable starting dose.

If you desire a loading dose, you may refer to dosing tables detailing standard (25 mg/kg) and modified (20-25 mg/kg) loading doses (See SHC Vancomycin dosing guide, Section C). In this obese patient with BMI>30, a modified loading dose corresponds to 1750 mg.****

In this case, patient was started on vancomycin 1750 mg IV q12h.
Please note that the right side of the maintenance dosing table explains the optimal timing of when you obtain your peak and trough levels. Ideally, you want the vancomycin to reach a steady state before you check levels, so it is important to communicate to the team exactly when levels should be obtained.

**Note:** the modified loading dose is based on 2020 vancomycin guidelines and is notably more conservative than loading dose recommendations of 20-35mg/kg for the general population. Dosing weight for vancomycin is always total or actual body weight.

Orthopedics is consulted. In the OR, patient is found to have significant tendon and tissue necrosis consistent with flexor tenosynovitis and osteomyelitis of the distal phalanx. Patient underwent DIP amputation. Intra-operative cultures grow 1+ coagulase-negative Staph and 1+ MRSA. Vancomycin MIC is 1 ug/mL. Blood cultures are negative.

The following levels are obtained when he is on vancomycin 1750 mg q12h, with each infusion over 120 minutes (each 1000 mg of vancomycin is administered over 60 minutes):
- Last dose of vancomycin given at 0500 and completed at 0700
- Peak level 30.4 at 0900 (2 hours after completion of dose)
- Trough level 14.6 at 1800 (13 hours later, prior to the next dose)

What dose of vancomycin do you continue?

Ideally, per protocol, a peak level is to be drawn 1 hour after the completion of a dose, and trough 30 minutes before a dose. In general, at least 1 half-life should elapse between the 2 levels drawn to improve accuracy. In this case, the peak was drawn late but should not significantly impact our PK and AUC estimates (Half-life ~8.5h; levels were drawn 9 hours apart).

The goal AUC for this patient is 400-600.

The current AUC can be calculated using the vancomycin AUC calculator.

Calculated AUC is 593, which is within goal. Additionally, at Stanford, our pharmacists have noted that obesity is frequently associated accumulation of the drug. In this case, an astute pharmacist decreased the dose slightly from 1750 mg to 1500 mg IV q12h to account for this issue, particularly since the AUC was already at the upper end of the target range.

Because the dose of vancomycin was changed, you again want to wait for steady state before rechecking peak and trough levels. This means ideally checking a peak level ~1 hour...
after the 4th dose is finished, as well as checking a trough level ~30 minutes before the 5th dose is given.

Patient returns to the OR for repeat wash-out on hospital day 4; due to continued presence of purulent material, revised amputation of the PIP is performed. Cultures grow rare MRSA.

The following levels are obtained when he is on vancomycin 1500 mg q12h, with each infusion over 90 minutes:
- Last dose of vancomycin given at 2100 and completed at 2230
- Peak level 26.5 at 2300 (30 minutes after completion of dose)
- Trough level 15.4 at 0600 the next day (7.5 hours later)

What dose of vancomycin do you continue?

Again using the vancomycin AUC calculator:

<table>
<thead>
<tr>
<th>Initial dosing</th>
<th>Calculated values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial dose (mg)</td>
<td>Vd (L)</td>
</tr>
<tr>
<td>1500</td>
<td>84.9</td>
</tr>
<tr>
<td>Initial dosing frequency (hr)</td>
<td>ke (hours-1)</td>
</tr>
<tr>
<td>12</td>
<td>0.07754</td>
</tr>
<tr>
<td>Infusion duration (hr)</td>
<td>t1/2 (hr)</td>
</tr>
<tr>
<td>1.5</td>
<td>8.9</td>
</tr>
<tr>
<td></td>
<td>true peak</td>
</tr>
<tr>
<td></td>
<td>27.5</td>
</tr>
<tr>
<td></td>
<td>true trough</td>
</tr>
<tr>
<td></td>
<td>12.2</td>
</tr>
</tbody>
</table>

Calculated AUC is 455, which is at goal. It would be reasonable to continue the current dose, which is what was done in this case.

Once a stable dose is determined, with target AUC achieved, then monitoring can become less frequent. At this time, our protocol would recommend checking a trough level every 2-5 days. The repeat trough should ideally remain within ~25% of the last trough obtained (unless the AUC was already at the limits of normal range). Levels should be checked sooner in certain clinical scenarios, such as if the patient’s clinical status changes, their renal function changes significantly, or if there is concern for risk of drug accumulation.

Due to presence of continued skin necrosis, patient then undergoes another wash-out and revision amputation at the metacarpophalangeal joint on hospital day 8. Cultures are negative and pathology is pending at the time of discharge.

What is the target trough for the patient after discharge?

- Using Stanford’s protocol, you may continue targeting the trough associated with the last therapeutic AUC +/- 2 if the SCr remains stable.
- If SCr changes by >25%, we recommend reassessing the situation. A repeat peak and trough are warranted but may not be easily done in the outpatient setting without trained staff. Without further AUC calculations, one may revert to goal troughs from 2009 Vancomycin consensus guidelines PMID: 1910634, i.e.
10-15 or 15-20 depending on infection type/source. Here is an example from SHC’s previous trough-based protocol based on 2009 guidelines:

<table>
<thead>
<tr>
<th>Goal Trough (mcg/mL)</th>
<th>Indication**</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 – 15</td>
<td>Cellulitis, skin/soft tissue infections not penetrating bone</td>
</tr>
<tr>
<td>15 – 20</td>
<td>Pneumonia, <em>Staphylococcus Aureus</em> bacteremia, endocarditis, osteomyelitis, deep seated infections, meningitis, sepsis, necrotizing fasciitis, febrile neutropenia (for suspected/proven MRSA or severe infection)</td>
</tr>
</tbody>
</table>

- Alternatively, the total daily dose may be converted to a continuous infusion. Target a random level between 20-25 to approximate an AUC between 400-600. This will require a pump. Ensure insurance coverage for this via case manager. If multiple IV infusions are planned as an outpatient, compatibility may be a barrier. This method will be valid even if SCr changes significantly.

The patient has an uneventful post-operative recovery and is discharged on vancomycin. In this case, 1500mg q12h was converted to 3g/24 hour continuous infusion. Target random level 20-25. The case manager reports that the patient’s insurance will not cover a pump. You change the discharge order to 1500mg IV q12h to complete a total of 4-6 weeks of IV therapy with a target trough 10-15.

**Case 2**

A 67 yo man with a history of type B aortic dissection s/p repair (2010) with persistent thoracoabdominal aortic aneurysm (6.8 cm) undergoes open repair and graft placement. Post-operatively, he is admitted to the ICU on pressors, with continued bleeding and coagulopathy. The team orders vancomycin out of concern for a purulent cellulitis on his leg.

The patient has the following characteristics:
- Weight
  - Total body weight (TBW) 147 kg
  - Ideal body weight (IBW) 79.5 kg
  - Adjusted body weight (ABW) 106.5 kg
- Height 185 cm
- BMI 43
- Baseline creatinine (pre-operative) 1.2

**What initial regimen of vancomycin do you start?**

If we use the same approach using AUC-based dosing, as in case 1:
- His pre-operative GFR is 90 mL/min.
- Using the initial dose calculator with goal AUC 400-600, total daily dose will be 2326mg (1250 mg q12h).
If we want to use a loading dose, for patients >120 kg, both standard and modified loading dose is 2000 mg. This is also the maximum dose to be given at one time using the SHC protocol****. (Maximum dose per day is 4500 mg.)

However, in this case, dosing by level may be more appropriate due to his critical illness and anticipated fluctuations in his creatinine. Thus, it would be reasonable to give a one-time dose, for example, 2000 mg, then re-assess.

**** SHC guidelines use a lower maximum modified loading dose of 2g in special populations such as obesity (rather than 3g in national guidelines). This is based on internal QA/QI.

Patient receives a 2000 mg dose of vancomycin. Due to increasing abdominal distension, he is taken back to the OR for, and found to have hemoperitoneum. He receives another dose of 2000 mg vancomycin intra-operatively (thus receiving a total of two 2000 mg doses in the last 24 hours.) His abdomen is packed and left open, with plans to return to the OR.

Unfortunately, patient develops oliguric renal failure. His serum creatinine rises from 1.2 to 1.8. Nephrology is consulted, and patient will be started on CRRT.

What vancomycin dosing protocol do you plan to follow?

We can continue to monitor using AUC-based protocol after he is stabilized on CRRT. During the transition to CRRT, if supratherapeutic levels are suspected in the setting of AKI, dose-by-level may be considered temporarily. In addition, he has received multiple doses of vancomycin within the last 24 hours, both intra-operatively and on the floor, so it would be prudent to monitor levels closely.

<table>
<thead>
<tr>
<th>Creatinine Clearance (mL/min)</th>
<th>Dose &amp; Frequency Total body weight (TBW)</th>
<th>TDD Range</th>
<th>Timing of Peak/Trough Levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRRT*</td>
<td>Initial: 20-25 mg/kg x 1 (max 2gm)</td>
<td>N/A</td>
<td>Q24H: Peak 1 hr after 2nd or 3rd dose; Trough 30 min before 3rd or 4th dose, respectively</td>
</tr>
<tr>
<td></td>
<td>Maintenance: 10-15 mg/kg Q24H</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Following this protocol, an initial dose is given, then subsequent maintenance doses are given while monitoring drug levels.

- Initial dose (15-20 mg/kg) for this patient is still 2000 mg, as it is the maximum dose. He has already received multiple 2000 mg doses, so we can skip this step.
- Maintenance dose (10-15 mg/kg q24) is ~1500-2000 mg.

Target AUC of 400-600. A peak should be obtained 1 hour after the 2nd or 3rd dose; a trough should be obtained 30 minutes before the 3rd or 4th dose.

As patient has received multiple doses of vancomycin in the setting of declining kidney function, it can be helpful to have a random vancomycin level drawn to see if the patient has a supratherapeutic level, in which case you would want to wait a little longer before re-dosing vancomycin. His initial random vancomycin level is 23.3. Another level is drawn 4 hours later to ensure appropriate clearance and returns at 18.3. You confirm that he is on stable CRRT settings. He is then started on 2000 mg q24h.
A vancomycin peak is drawn 1 hour after the 3rd dose and returns at 27; a trough is drawn before the 4th dose and returns at 12.

**What do you do next?**

Per protocol, AUC is therapeutic. We can then check another level every 2 to 5 days if routine; or, sooner if clinically indicated (especially in changes in renal function, dialysis status, or clinical status.) We should in the meantime, check that CRRT settings remain stable.

**How to you monitor CRRT settings?**

The most accurate/real-time data is located on the “TDM” snapshot flowsheet. Look for “Effluent dose”. All SHC machines have been changed to run CVVHDF as of Aug 2020.
Case 3

62 Y female with HIV (dx early 90s, most recent CD4 130 and poorly compliant with bictegravir/emtricitabine/tenofovir alafenamide) with h/o PCP pneumonia (1998) and recurrent CAP, HTN, tobacco abuse, and anal invasive squamous cell carcinoma s/p chemotherapy and radiation, admitted for surgical management of her rectal CA with abdominoperineal resection and rectus abdominus myocutaneous flap reconstruction. ID consulted for postoperative fevers, team starts vancomycin and cefepime, with concern for post-operative or surgical site infection.

The patient has the following characteristics:
- Weight
  - Total body weight (TBW) 57.6 kg
  - Ideal body weight (IBW) ?
  - Adjusted body weight (ABW) ?
- Height unknown
- BMI 22.5
- Baseline creatinine (pre-operative) 0.5

What initial regimen of vancomycin do you start?

We will use AUC-based dosing in this case.
- For our case:
  - Go ahead and use the provided excel spreadsheet.
  - Her estimated CrCl is 119 mL/min.
- Second, input patient parameters into the initial maintenance dose calculator.

<table>
<thead>
<tr>
<th>Input patient parameters</th>
<th>Calculated values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chosen goal (AUC_{24})</td>
<td>500</td>
</tr>
<tr>
<td>(\text{CrCl (mL/min)})</td>
<td>119</td>
</tr>
<tr>
<td>Total Body Weight (kg)</td>
<td>57.7</td>
</tr>
<tr>
<td>CNS infection? Use trough 15-20</td>
<td>no</td>
</tr>
<tr>
<td>Obese: BMI (\geq 30)? (yes/no)</td>
<td>no</td>
</tr>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>SCR</td>
<td></td>
</tr>
<tr>
<td>Sex (male = 1, female = 0)</td>
<td></td>
</tr>
</tbody>
</table>

**Loading Dose:** ~26mg/kg x1 or modified load 16-25mg/kg x1 (if preferred in critically ill patients with suspected or documented serious MRSA infection. Use of and magnitude of LD should be driven by the severity of infection and the urgency)

<table>
<thead>
<tr>
<th>Maintenance Dose</th>
<th>AUC-based dosing (preferred)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimated DAILY dose (if BMI 30-39.9) (mg)</td>
<td>n/a</td>
</tr>
<tr>
<td>Estimated DAILY dose (if BMI (\geq 40)) (mg)</td>
<td>n/a</td>
</tr>
<tr>
<td>Estimated DAILY dose (non-obese) (mg)</td>
<td>2084</td>
</tr>
</tbody>
</table>

*Recommended dosing frequency: at least 1-1.5x the half-life*
In this case, patient was started on vancomycin 1000 mg IV q12h.

Ideally, you want the vancomycin to reach a steady state before you check levels, so it is important to communicate to the team exactly when levels should be obtained.

The patient is spiking daily fevers. After a few doses of vancomycin, peak and trough measurements are taken which give an AUC of 308. Given the AUC goal of 500, an increase in vanc frequency is recommended:

<table>
<thead>
<tr>
<th>SHC Adult Vancomycin AUC calculator v5/29/2020</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use this section to estimate AUC based on 2 levels at steady state</td>
</tr>
<tr>
<td><strong>Initial dosing</strong></td>
</tr>
<tr>
<td>Initial dose (mg)</td>
</tr>
<tr>
<td>Initial dosing frequency (hr)</td>
</tr>
<tr>
<td>Infusion duration (hr)</td>
</tr>
<tr>
<td><strong>AUC assessment based on paired levels drawn after a dose</strong></td>
</tr>
<tr>
<td>Date/time of dose preceding peak/trough</td>
</tr>
<tr>
<td>Measured Level 1 (&quot;peak&quot;)</td>
</tr>
<tr>
<td>Date/time of Level 1</td>
</tr>
<tr>
<td>Measured Level 2 (&quot;trough&quot;)</td>
</tr>
<tr>
<td>Date/time of Level 2</td>
</tr>
<tr>
<td>Calculated AUC₂₄</td>
</tr>
</tbody>
</table>

The pt is placed on 1g q8h for a couple days, then new peak/trough measurements are taken. Unfortunately, the Cr rose a little to 0.6 the day before, and now on the day the troughs are drawn has risen to 1.15.

What is the new CrCl?

Using the Epic clinical CrCl calculator, it is 46 ml/min.

What would the initial dose have been if this had been her CrCl up front?
So the total daily dose would have been much less.

A vanc peak is measured as 46.5 at 0131. A trough is measured as 29.3 at 0634. The last dose of vanc was at 2300.

What is the AUC?

It is calculated at 907.

Is this accurate?

Take a look at the ½ life. On the “initial” calculator it is 16 hrs. Based on the peak/trough measurements, the ½ life was calculated at 7.6 hrs. One principle is that the peak and trough levels should have been drawn at least one half-life apart. They were drawn 5 hrs apart, in the setting of a rising SCr. The second principle is that AUC dosing needs to be done in steady
state. So it is very hard to know what the AUC really is given these data. All we know is that it is likely too high.

So what do you do with the vanc dosing/schedule?

Hold the vanc, and trend SCr and vanc levels. Dose vanco based on trough levels until a steady state re-emerges.

**Case 4**

58 Y postmenopausal female with stage IIIb squamous cell carcinoma of the cervix admitted for vaginal bleeding which was found to be from the necrotic cervical mass. She was treated with 1U PRBCs and IR embolization as well as continued radiation therapy. On hospital day 2 she developed a new leukocytosis to 15 and febrile to 38.2. Cultures are drawn and she is empirically started on vancomycin and pip/tazo.

The patient has the following characteristics:
- Weight
  - Total body weight (TBW) 58 kg
  - Ideal body weight (IBW) 50.1 kg
  - Adjusted body weight (ABW) ?
- Height 5’2”
- BMI 23
- Baseline creatinine 0.65

What initial regimen of vancomycin would you start?

When should a vancomycin peak be drawn?

When should a vancomycin trough be drawn?

The 4th dose of vancomycin is given at 0900, Vancomycin peak drawn at 1000 is 35 and trough drawn at 1930 is 15.

Calculate any needed dose adjustment based on these values.
**Answers**

What initial regimen of vancomycin would you start?

We will use AUC-based dosing in this case.
- We will use the TBC 58 kg
- Her estimated CrCl is 104 mL/min

In this case, patient was started on vancomycin 1000 mg IV q12h.

**When should a vancomycin peak be drawn?**
- Peak vanc level should be drawn 1 hour after the end of infusion of the 4th dose

**When should a vancomycin trough be drawn?**
- Trough should be drawn 30 min prior to 5th dose

Use the AUC calculator to calculate any needed dose adjustment based on the peak and trough levels.
The calculated AUC is 568, which is near the target of 500. No dose adjustment is needed at this time and the patient is continued on 1g q12hr.