A. PHARMACOKINETIC MONITORING/GUIDELINES/PROTOCOLS

6. VANCOMYCIN PROTOCOL

a) Adults: Part I - General Overview

CERTIFICATION
RQHR pharmacists must be certified as per current policy prior to independent utilization of this protocol. Pharmacists not certified must gain approval from a certified pharmacist prior to making any recommendations. Deviations from this protocol must be well substantiated, documented in the patient chart and discussed with the patient’s physician.

PROCEDURE
1. The physician may request the vancomycin monitoring service by writing “Pharmacy consult” or “Pharmacy consult - Full authority” on the patient’s chart. Once consulted, the pharmacist follows the patient’s progress until the vancomycin is discontinued.

2. The pharmacist is responsible for ordering vancomycin levels and other monitoring parameters as indicated in this protocol.

3. Vancomycin is administered by intermittent I.V. infusion with the infusion lasting approximately one hour. Intramuscular injections are not recommended.

4. The pharmacist provides initial dosage recommendations based on dosing guidelines for vancomycin and/or interpretation of serum levels.

5. If the physician writes “Pharmacy consult - Full authority” the pharmacist may change the dosage regimen without contacting the physician, otherwise the pharmacist will first contact the physician to discuss. If the physician is unavailable, however, a chart note is left and the physician contacted the following day.
6. Whether or not a change in the dosage regimen is required, the pharmacist must provide documentation in the patient progress section of the chart.

7. In order to calculate an initial dosing regimen and to monitor therapy optimally, the following information is desirable:
   - Age
   - Sex
   - Height & Weight*
   - Creatinine/Blood urea nitrogen*
   - CBC with differential*
   - Temperature
   - Concomitant antibiotics, ototoxins/nephrotoxins
   - Culture & sensitivity reports
   - Ins and Outs (I/O)

* A pharmacist may order serum creatinine, BUN, body weight and CBC with differential for patients covered under this protocol.

8. Documentation - The pharmacist documents all interventions (dosing, levels, phone calls, etc.) in the patient progress section of the chart.

9. Monitoring – refer to Part II
   - Serum Creatinine/BUN
   - Serum levels - Whenever possible, levels will be ordered at times when the laboratory is well staffed (i.e. 0800-1600 hours)
   - Pharmacy Patient Monitoring Form – a pharmacist completes this for each patient and reviews daily. Additional monitoring parameters are:
     - **Daily**
       - Temperature (highest in last 24h)
       - Ins/Outs
       - Concomitant antibiotics and potential nephrotoxins
     - **Twice weekly**: CBC with differential
     - **Weekly**: Weight

10. Follow-up Therapy
    Follow-up on the patient’s clinical status (i.e. response to therapy, changes in renal function), C & S results and duration of vancomycin therapy.
b) Adults: Part II – Dosing of Vancomycin

Empiric Dosage Regimen

Dose: 15mg/kg* Total Body Weight (Round to the nearest 250mg; Maximum 3g per dose)

* Generally, there is no advantage of giving a **loading dose** as vancomycin kills bacteria in a *time*-dependent manner vs the concentration-dependent manner of aminoglycosides or fluoroquinolones.

**Exceptions:** Give a loading dose of **25mg/kg** (Round to the nearest 250mg; Maximum 3g per dose) in the following patients:

- **Chronic renal failure (CRF) patients** have significantly larger average volumes of distribution; continue empiric dosing as follows:
  - < 75kg, give 500mg in last hour of each dialysis
  - ≥ 75kg, give 750mg in last hour of each dialysis
  Also refer to sections 4.4 and 4.5.

- **Continuous Ambulatory, or Cycling Peritoneal Dialysis (CAPD or CCPD):** Repeat the loading dose of 25mg/kg q5days for 2 – 3 weeks therapy; refer to sections 4.4 and 4.5 for serum level recommendations.  

- **Patients with serious MRSA infections (e.g. endocarditis, septic):** May consider a loading dose, although this is NOT currently supported by large randomized clinical trials. Subsequent dosing and levels as indicated below.

Interval: based on the patient’s estimated creatinine clearance

**Note:** If patients are borderline to an interval change, repeat serum creatinine to ensure a shorter interval is not more optimal – e.g. patients who may be dehydrated on admission, once hydrated will clear vancomycin faster

<table>
<thead>
<tr>
<th>Clcr* (mL/min)</th>
<th>Interval</th>
<th>&lt; 25mL/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 80</td>
<td>q12h</td>
<td>Order 1st dose as above; dosing interval based on trough level</td>
</tr>
<tr>
<td>50 - 79</td>
<td>q24h</td>
<td></td>
</tr>
<tr>
<td>35 - 49</td>
<td>q36h</td>
<td></td>
</tr>
<tr>
<td>25 - 34</td>
<td>q48h</td>
<td></td>
</tr>
<tr>
<td>&lt; 25mL/min</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Estimated Clcr (140 - age) x 90 ÷ Scr (mmol/L); x 0.85 for females

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2. Infusion Rate

**Maximum Rate of Infusion: 15mg/min** to minimize thrombophlebitis and red man syndrome

<table>
<thead>
<tr>
<th>Dose</th>
<th>Minimum Infusion Time*</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤1g</td>
<td>1 h</td>
</tr>
<tr>
<td>1.25 - 1.5g</td>
<td>1.5 h</td>
</tr>
<tr>
<td>1.75 - 2g</td>
<td>2 h</td>
</tr>
<tr>
<td>2.25 - 3g</td>
<td>3 h</td>
</tr>
</tbody>
</table>

* May increase infusion time if patient has a reaction

Renal patients: if administering during last hour of dialysis, the dose is administered in a syringe via a Bard pump (Refer to Bard guidelines on Intranet, under Nursing/Pharmacy Committee)

3. Concentration

**Maximum Concentration 5mg/mL** to minimize infusion-related side effects such as thrombophlebitis and red man syndrome. Suggested concentrations:

- ≤ 500mg in 100mL
- > 500mg - 1.25g in 250mL
- 1.5 - 2.5g in 500mL

4. Monitoring

4.1 Serum Creatinine

- Baseline, then at least ONCE weekly while in hospital, or every 1-2 weeks if therapy continues at home, and if patient not on an aminoglycoside or other nephrotoxic agent. If stable and patient to be on therapy indefinitely, may decrease to qmonthly.
- More frequent Scr monitoring required if changing renal function or concomitant nephrotoxic agent(s)

4.2 Vancomycin Serum Levels

**NOTE:** There is no evidence to suggest peak serum concentrations have any bearing on efficacy as vancomycin exhibits time-dependent killing of bacteria. Peak levels are difficult to determine due to slow distribution into peripheral tissues and are not supported.
Vancomycin trough levels should be obtained for the patients/situations listed below. To ensure steady state has been achieved, draw a trough level ≤ 30 minutes prior to 4th dose (i.e. after the 3rd dose), unless otherwise indicated.

- Concurrent aminoglycoside, or other nephrotoxic agents (e.g. some chemotherapy regimens, amphotericin, cyclosporine A, etc.)
- Anticipated therapy > 5 days
- Infants & children with serious infections (e.g. meningitis, osteomyelitis)
- Cerebrospinal fluid shunt infections, meningitis
- Deteriorating/unstable renal function (e.g. ↑ Scr >25% above baseline) For dialysis patients, refer to Sections 4.4 and 4.5.
- Patients with rapid clearance of drug (e.g. cystic fibrosis, burns >20% BSA)

In the following situations, obtain a serum trough level before 2nd dose (i.e. after the 1st dose) to avoid overestimation in obese patients, and to ensure trough level is likely to be >10-15mg/L; repeat trough level at steady state (e.g. after 3 or 4 doses)

- Morbidly obese patients (≥ 190% IBW)
- Patients receiving ≥ 4g vancomycin per day, or ≥ 3g per dose
- Patients with a desired target trough concentration of 15 - 20mg/mL

Additional trough vancomycin levels should be obtained ONCE weekly for hemodynamically stable inpatients and q1 – 2 weeks for outpatients. If stable and on therapy indefinitely, may decrease levels to qmonthly, but ensure to regularly confirm patient’s weight.

4.3 Adjustments Based On Vancomycin Serum Levels
Previous literature suggested trough concentrations of 5 – 10mg/L were desirable for optimal therapeutic response, however, recent evidence suggests trough levels should always be maintained above 10mg/L to avoid the development of resistance. This coincides with the 2006 Clinical and Laboratory Standards Institute (CLSI) lowering vancomycin’s susceptibility breakpoint to isolates with a MIC ≤ 2mg/L (previously ≤4mg/L).
Less seriously ill patients, refer to the following table:

(NOTE: Refer to next page for patients requiring a higher target range)

<table>
<thead>
<tr>
<th>Serum Trough (C_min)</th>
<th>Dosage Adjustment*</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10 mg/L and interval greater than q12h</td>
<td>Decrease interval by 12h increment (e.g. if q36h, change to q24h; if q24h, change to q12h)</td>
</tr>
<tr>
<td>&lt;10 mg/L and on q12h</td>
<td>Increase interval to q8h, or consider alternative therapy if possible</td>
</tr>
<tr>
<td>10 – 15 mg/L</td>
<td>No change (desired level)</td>
</tr>
<tr>
<td>&gt;15mg/L</td>
<td>Increase interval by 12h increment (e.g. if q12h, change to q24h; level will be approx. halved), or consider alternate therapy if possible</td>
</tr>
</tbody>
</table>

However, desired trough levels may need to be higher in patients with new, worsening, or persistent signs/symptoms of infection (e.g. fever, leukocytosis) receiving at least 5 days of vancomycin, or in seriously ill patients (e.g. bacteremia, endocarditis, osteomyelitis, meningitis, and hospital-acquired pneumonia caused by *S. aureus*). However, larger vancomycin doses (4 or more grams per day) are associated with increased nephrotoxicity and benefits should outweigh the risks. Reference: Lodise et al. Antimicrobial Agents & Chemotherapy 2008 (April); 52 (4):1330-1336.

Alternatively, other agents should be considered. (e.g. as per C&S results, or linezolid if indicated).
For patients requiring HIGHER target trough levels, use the following table:

<table>
<thead>
<tr>
<th>SERUM TROUGH (C_{MIN})</th>
<th>DOSAGE ADJUSTMENT*</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 15mg/L and interval greater than q12h</td>
<td>Decrease interval by 12h increment</td>
</tr>
<tr>
<td></td>
<td>(e.g. if q36h, change to q24h; if q24h, change to q12h, however, please note</td>
</tr>
<tr>
<td></td>
<td>the subsequent trough level will approx. double)</td>
</tr>
<tr>
<td>&lt; 15mg/L and on q12h</td>
<td>Increase interval to q8h, or</td>
</tr>
<tr>
<td></td>
<td>consider alternative therapy if possible</td>
</tr>
<tr>
<td>15 – 20mg/L</td>
<td>No change (desired level)</td>
</tr>
<tr>
<td>&gt;20 mg/L</td>
<td>Depending on clinical situation and response, consider increasing interval</td>
</tr>
<tr>
<td></td>
<td>by 12h increment</td>
</tr>
<tr>
<td></td>
<td>(e.g. if q12h, change to q24h, however please note the subsequent trough level</td>
</tr>
<tr>
<td></td>
<td>will be approx. halved), or consider alternate therapy if possible</td>
</tr>
</tbody>
</table>

4.4 Renal Failure Patients - NOT Critically Ill
As previously indicated, patients with renal failure have significantly larger volumes of distribution and their limited clearance necessitates the use of higher than usual serum levels to ensure adequate killing of the organism. If possible, consider alternative, less toxic agents if required long term (e.g. >10 days).

### Hemodialysis
- No levels required unless no improvement on empiric dosing. If required, draw a pre-dialysis level and adjust as follows:
  - **< 10mg/mL**, increase dose during last hour of dialysis by 250mg
  - **10 - 15mg/L**, no change
  - **> 15mg/L**, decrease dose during last hour of dialysis by 250mg

### Continuous Ambulatory or Cycling Peritoneal Dialysis (CAPD or CCPD)
- Draw a level on Day 5 with morning blood work and adjust as follows:
  - **< 12mg/L**, increase frequency to every 3 days
  - **12 - 25mg/L**, no change
  - **> 25mg/L**, decrease frequency to every 7 days

### Unstable renal function and NOT on scheduled hemodialysis
- Draw random vancomycin level q2 - 3days. Re-dose with 15mg/kg dose when random level **<12mg/L**.

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4.5 Renal Failure Patients

(e.g. patients with fulminant infection, septic, on inotropes, etc. resulting in need for intermittent or abbreviated dialysis).

Critically ill patients may temporarily require continuous renal replacement therapy (CRRT), or hemodialysis on a daily or prn basis and may switch between the various dialysis modalities. These patients may have changes in protein binding, blood pH, renal function, fluid status, etc. requiring more frequent monitoring to ensure vancomycin levels remain optimal as much as is possible.

NOTE: Given the molecular weight and variability in protein binding of vancomycin, it is assumed all forms of CRRT more effectively remove vancomycin than conventional hemodialysis.

The various forms of CRRT are:

- **Slow Continuous Ultrafiltration (SCUF)** and **Continuous Venovenous Hemofiltration (CVVH)** utilize only a convective process and are relatively inefficient at clearing vancomycin and other drugs.

- **Continuous Venovenous Hemodialysis (CVVHD)** and **Continuous Venovenous Hemodiafiltration (CVVHDF)** combine convective and diffusive techniques to remove solutes and fluid. In critically ill patients renal therapies may include CRRT or hemodialysis on a daily or prn basis and patients may switch between the various dialysis modalities during the course of their treatment. Generally speaking, critically ill patients receiving CRRT have larger volumes of distribution (Vd) than non-ICU patients or ICU patients with normal renal function. Critically ill patients also have variable protein binding, changes in blood proteins, frequent fluid shifts and pH changes. Due to these factors steady state vancomycin serum levels are unlikely to be achieved. As well, patients on CRRT and hemodialysis may accumulate vancomycin requiring lower doses over time. Based on this, vancomycin levels in these patients are monitored frequently to ensure the troughs remain high enough without being excessively high.
1. Calculate loading dose of vancomycin 25mg/kg (Round to the nearest 250mg; Maximum 3g per dose)
2. Write an order in the chart for “Vancomycin level daily with morning blood work. Pharmacist to order vancomycin dose based on daily level.”
3. Enter in Pharmacy computer system as “Vancomycin as Per Daily Pharmacist Order”
4. Based on the daily level, order vancomycin as indicated in table below.

<table>
<thead>
<tr>
<th>Daily Vanco Level</th>
<th>Hemodialysis* (HD)</th>
<th>CRRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 15mg/L</td>
<td>75kg: 750mg x1</td>
<td>Re-dose immediately with 20mg/kg x1</td>
</tr>
<tr>
<td></td>
<td>≥ 75kg: 1g x1</td>
<td></td>
</tr>
<tr>
<td>15 - 20 mg/L</td>
<td>If HD expected in next 24h: 75kg: 500mg x1</td>
<td>15mg/kg x1</td>
</tr>
<tr>
<td></td>
<td>≥ 75kg: 750mg x1</td>
<td></td>
</tr>
<tr>
<td>&gt; 20 mg/L</td>
<td>No dose required</td>
<td>No dose required</td>
</tr>
</tbody>
</table>

* It is NOT necessary to administer the vancomycin during the last hour of hemodialysis as this is not always possible. **NOTE:** Once a patient’s dialysis routine has stabilized (i.e. 96 hours with same dialysis plan), daily vancomycin levels can stop and Section 4.4 followed thereafter.

**NOTE to RQHR Pharmacists:** Use the Pharmacy [CRRT Antibiotic Monitoring form](#) and document in the chart as follows:

- An initial progress note must be written by the pharmacist for patients starting CRRT. Thereafter, a daily vancomycin order will be written prior to 16h, whether or not a dose is required (eg: “No vancomycin today” or “Give vancomycin 1g IV x1 today”, etc.

**c) Pediatrics (Infants & Children ≤12yo): Part I - General Overview**

**Note:** There is no official RQHR Pediatric protocol, however, the following is offered as a guideline for those with normal renal function.
1. The physician may request the vancomycin monitoring service by writing “Pharmacy consult” or “Pharmacy consult - Full authority” on the patient’s chart. Once consulted, the pharmacist follows the patient’s progress until the vancomycin is discontinued.

2. The pharmacist will first contact the physician to discuss any issues which arise re: vancomycin dosing. If the physician is unavailable, however, a chart note is left and the physician contacted the following day.

3. **Documentation:** Whether or not a change in the dosage regimen is required, the pharmacist must provide documentation in the patient progress section of the chart.

4. **Monitoring:**
   - Serum Creatinine/BUN
   - Serum levels - Whenever possible, levels will be ordered at times when the laboratory is well staffed (i.e. 0800-1600 hours)
   - Pharmacy Patient Monitoring Form – a pharmacist completes this for each patient and reviews daily.

5. **Follow-up Therapy:**
   Follow-up on the patient’s clinical status (i.e. response to therapy, changes in renal function), C & S results and duration of vancomycin therapy.

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**d) Pediatrics (Infants & Children ≤12yo): Part II – Dosing of Vancomycin**

1. **Empiric Dosage Regimen (Round to nearest 25mg)**
   - Mild – Moderate Infections: 10mg/kg q6h (i.e. 40mg/kg/day ÷ q6h)
   - Serious Infections: 10 -15mg/kg q6h (i.e. 40 - 60mg/kg/day ÷ q6h)
   - CNS Infections: 15mg/kg q6h (i.e. 60mg/kg/day ÷ q6h)
2. Infusion Rate
   ♦ Refer to BARD infusion chart
   ♦ *Maximum Rate of Infusion: 15mg/min* to minimize thrombophlebitis and red man syndrome
   ♦ May increase infusion time if patient has a reaction

3. Concentration
   ♦ Refer to BARD infusion chart
   ♦ *Maximum Concentration: 5mg/mL* to minimize infusion-related side effects such as thrombophlebitis and red man syndrome.

4. Monitoring
   4.1 Serum Creatinine
   ♦ Baseline, then ONCE weekly while in hospital, or every 7-14 days if therapy continues at home *and if* patient is not on an vancomycin or other nephrotoxic agents. May decrease to qmonthly if stable & patient on therapy indefinitely.

   ♦ More frequent Scr monitoring required if changing renal function or concomitant nephrotoxic agents

   ♦ Additional monitoring parameters, if possible are:
      Daily:
      - Temperature (highest in last 24h)
      - Ins/Outs
      - Concomitant antibiotics and potential nephrotoxins
      Twice weekly: CBC with differential
      Weekly: weight
4.2 Vancomycin Serum Levels

Suggested for the following patients*:

- On concurrent aminoglycoside
- Anticipated therapy >2 weeks
- Infants & children with serious infections
- Cerebrospinal fluid shunt infections, meningitis
- Deteriorating/unstable renal function (e.g. ↑ Scr >25% above baseline)
- Patients with rapid clearance of drug (e.g. cystic fibrosis, burns >20% BSA)
- Selected dialysis patients only (see Adults section)

* To ensure steady state has been achieved, draw trough level ≤ 30 minutes prior to 4th dose

- **Trough**:  5 - 12mg/L
  - May increase to 15mg/L for CNS infections
  - Additional trough vancomycin levels ONCE weekly for inpatients and q7-14 days for outpatients. If stable and on indefinite therapy, may decrease to qmonthly.

- In serious infections may also obtain a peak level 1h after infusion completed.

- If required, **Desired Peak** = 20 - 40mg/L


- No need for loading dose as vancomycin kills bacteria in time-dependent manner vs. the concentration-dependent manner of aminoglycosides or fluoroquinolones.

- Minimum infusion time is 1 hour to minimize infusion-related side effects such as thrombophlebitis and red man syndrome
The following regimen is based on adequate renal function (urine output >2mL/kg/h). In infants with poor renal function the dosing interval may need to be increased.

- **DOSE** = 10mg/kg

- **INTERVAL** based on postconceptual (PCA) and postnatal age (PNA) as indicated below:

<table>
<thead>
<tr>
<th>PCA (weeks)</th>
<th>PNA (days)</th>
<th>Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 29</td>
<td>0 - 14</td>
<td>q18h</td>
</tr>
<tr>
<td></td>
<td>&gt; 14</td>
<td>q12h</td>
</tr>
<tr>
<td>30 - 36</td>
<td>0 - 14</td>
<td>q12h</td>
</tr>
<tr>
<td></td>
<td>&gt; 14</td>
<td>q8h</td>
</tr>
<tr>
<td>37 - 44</td>
<td>0 - 7</td>
<td>q12h</td>
</tr>
<tr>
<td></td>
<td>&gt; 7</td>
<td>q8h</td>
</tr>
<tr>
<td>≥ 45</td>
<td>All</td>
<td>q6h</td>
</tr>
</tbody>
</table>

**Monitoring:**

**Vancomycin Serum Levels**
- Peak & trough levels day 3 of therapy
  - Trough: 0 - 60 minutes prior to administration of the next dose.
  - Peak: At least 60 minutes following the end of a 1-hour infusion
- If earlier levels are required, peak and trough levels may be drawn around the 4th dose
- Repeat peak & trough levels should be drawn on 3rd day following a dosage change. If earlier levels are required, they may be drawn around the 4th dose following the change.
- In stable infants on vancomycin for long-term therapy (≥10 days) additional trough vancomycin levels may be drawn once weekly. Peak levels may be drawn if desired when the trough level falls outside the desired range.

<table>
<thead>
<tr>
<th><strong>Target Trough Levels</strong></th>
<th><strong>Target Peak Levels</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>5 – 12 mg/L</td>
<td>20 - 40 mg/L</td>
</tr>
</tbody>
</table>

- Trough levels as high as 15 mg/L may be desired in patients with CNS infections or with a second positive blood culture

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Additional Monitoring Guidelines:

<table>
<thead>
<tr>
<th>Monitoring Parameter</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>BP</td>
<td>Pre, mid, &amp; post infusion</td>
</tr>
<tr>
<td>Urine output (mL/h)</td>
<td>Daily</td>
</tr>
<tr>
<td>Serum Creatinine &amp; BUN</td>
<td>Baseline, then consider q3 days</td>
</tr>
</tbody>
</table>

♦ More frequent monitoring of serum creatinine may be indicated if changing renal function or concomitant nephrotoxic agents (i.e. vancomycin, indomethacin).

♦ Consider repeating CBC with differential based on patient status.
REFERENCES


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