Vancomycin

Introduction/History
Vancomycin was discovered in a soil sample from Borneo in the early 1950s, and was isolated from Streptomyces orientalis. It belongs to the glycopeptide class of antibiotics and works by inhibiting cell wall synthesis.

Between 1980 and 2000 the use of vancomycin increased 100 fold. Driving forces behind the increased use began with the increased incidence of pseudomembranous enterocolitis; the primary pathogen of which, is Clostridium difficile, but occasionally Staph. aureus. Vancomycin was effective against both organisms; and when taken orally had minimal systemic effect. Widespread use of oral vancomycin was partly responsible for the development of VRE. The increased incidence of MRSA and penicillin-resistant Strept. pneumoniae also led to increased use of vancomycin.

Consensus Guidelines 2009
To aid clinicians in the appropriate use of vancomycin, a consensus panel reviewed the literature and developed recommendations based on available studies.

Consensus Review
All relevant and available peer reviewed studies in the English language between 1958 and 2008 were considered for the review. There were few prospective or randomized trials. Most studies were observational in patients with S.aureus. The review only applied to adult patients.

Summary
-Trough levels are the most accurate and practical method for monitoring efficacy
-Trough should be obtained just prior to the next dose at steady-state (approximately after the fourth dose)
-Vancomycin trough concentrations should always be maintained above 10mg/L to avoid development of resistance. For a pathogen with an MIC of 1mg/L the minimum trough concentration would have to be at least 15 mg/L to attain the target AUC/MIC of 400
-Vancomycin trough concentrations of 15-20 mg/L are recommended to improve penetration, increase the probability of obtaining optimal target serum concentrations, and improve clinical outcomes.
-Daily doses of 15–20 mg/kg (as actual body weight) given every 8–12 hr are recommended for most patients with normal renal function to achieve the suggested serum concentrations when the MIC is =1 mg/L. In patients with normal renal function, the targeted AUC:MIC of >400 is not achievable with conventional dosing methods if the MIC is =2 mg/L in a patient with normal renal function.
-In seriously ill patients, a loading dose of 25–30 mg/kg (based on actual body weight) can be used to facilitate rapid attainment of target trough serum vancomycin concentration.
-Continuous infusion regimens are unlikely to substantially improve patient outcome when compared to intermittent dosing.
-A minimum of two or three consecutive documented increases in serum creatinine concentrations (defined as an increase of 0.5 mg/dL or a ≥50% increase from baseline, whichever is greater) after several days of vancomycin therapy.
-Data do not support using peak serum vancomycin concentrations to monitor for nephrotoxicity.
-Trough monitoring is recommended for patients receiving aggressive dosing (i.e., to achieve sustained trough levels of 15–20 mg/L) and all patients at high risk of nephrotoxicity (e.g., patients receiving concurrent nephrotoxins).
-Monitoring is also recommended for patients with unstable (i.e., deteriorating or significantly improving) renal function and those receiving prolonged courses of therapy (more than three to five days).
-Frequent monitoring (more than one trough before the fourth dose) for short course or lower intensity dosing (to attain target trough concentrations below 15 mg/L) is not recommended.
-All patients on prolonged courses of vancomycin (exceeding three to five days) should have at least one steady-state trough concentration obtained no earlier than at steady state (following the fourth dose) and then repeated as deemed clinically appropriate.
-There are limited data supporting the safety of sustained trough concentrations of 15–20 mg/L. Clinical judgment should guide the frequency of trough monitoring when the target trough is in this range. Once-weekly monitoring is recommended or hemodynamically stable patients. More frequent or daily trough monitoring is advisable in patients who are hemodynamically unstable.
-Monitoring for ototoxicity is not recommended for patients receiving vancomycin monotherapy.
-Monitoring should be considered for patients receiving additional ototoxic agents, such as aminoglycosides.

Nephrotoxicity Review
Nephrotoxicity associated with high dose vancomycin
-Literature search 2010-Aug 2012
-nephrotoxicity in regimens designed to attain a trough level of 15-20 mg/L.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Design</th>
<th>Patients</th>
<th>Intervention</th>
<th>Nephrotoxicity</th>
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<tr>
<td>Reynolds et al.</td>
<td>R, C</td>
<td>Obese patients</td>
<td>15 mg/kg q8-12 n=64 vs. 10 mg/kg q12, or 15mg/kg q24 n=74</td>
<td>3.1% HD 2.7% LD p=ns</td>
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<tr>
<td>Kullar et al.</td>
<td>R, QE</td>
<td>Adult bacteremic n=200</td>
<td>Tr target of &lt;15 (pre) vs. Tr target 15-20 (post)</td>
<td>15% pre (12.3mg/L) p=0.85 18% post (15.8 mg/L) Post had 60% clinical success vs 45% pre</td>
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<tr>
<td>Cano et al.</td>
<td>R, O, MC</td>
<td>Adult ICU pneumonia (HAP, VAP, HCAP) n=188</td>
<td>Only tr levels were monitored No specific dosing info No data on contrast dye No info on shock or pressor use</td>
<td>15.4% tr&gt;/= 15 p=0.001 AG use p=0.03 Duration p=0.02 were assoc. w/ nephrotoxicity</td>
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<tr>
<td>Wunderink et al.</td>
<td>P, DB, PC, MC</td>
<td>HA-MRSA pneumonia Linezolid n=172 Vanco n=176</td>
<td>15mg/kg q12 tr adjusted dose vs. linezolid 600mg q12</td>
<td>18.2% vanc 8.4% linezolid</td>
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<tr>
<td>Prabaker et al.</td>
<td>R, C</td>
<td>Adult VA patients n=348</td>
<td>Preperiod tr=9.7 Postperiod tr=13.2</td>
<td>Overall 8.9% Pre 8% Post 10.2% Contrast dye OR 4.01 p=&lt;0.001 Trend toward associated nephrotoxicity With tr15 p=0.082</td>
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<tr>
<td>Bosso et al.</td>
<td>P, MC</td>
<td>Adult n=288</td>
<td>Dosing was not controlled</td>
<td>tr≤ 15 8.9% tr&gt;15 29.6% tr&gt;15 nephrotoxicity OR 3.643 p=0.01</td>
</tr>
<tr>
<td>Kullar et al.</td>
<td>P, MC</td>
<td>Adult pts n=200</td>
<td>Dosing nomogram to achieve tr=15-20 Excluded pts &gt;110kg</td>
<td>4.5% nephrotoxicity</td>
</tr>
<tr>
<td>Walraven et al.</td>
<td>R,C</td>
<td>Adult pts n=200</td>
<td>Goal tr 15-20</td>
<td>11.1% in cured group 29.9% in failure group Avg tr cure 15.6 Avg tr fail 21.4 No correlation between tr and nephrotoxicity p=ns</td>
</tr>
<tr>
<td>Minejima et al.</td>
<td>P, O</td>
<td>Adult n=227</td>
<td>Loading dose and maintenance dose to tr 15-20</td>
<td>19% developed nephrotoxicity ≥15 24% &lt;15% 17% tr&gt;15 was not found to be a predictor of nephrotoxicity p=ns</td>
</tr>
<tr>
<td>Pritchard et al.</td>
<td>R, C</td>
<td>Adult Phase 1 n=1504</td>
<td>Evaluation of the association between vanc levels and nephrotoxicity</td>
<td>Vanc tr214, duration ≥7d, baseline scr&lt;1.7 independent predictors of nephrotoxicity p&lt;0.001</td>
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<tr>
<td>McKamy et al.</td>
<td>R,C</td>
<td>Pediatric N=167</td>
<td>tr≥15 compared to a low tr goup</td>
<td>14% nephrotoxicity High tr 28% p=0.0001 Low tr 7.3% High tr, icu stay, furosemide pts more likely to have nephrotoxicity</td>
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<tr>
<td>Hermsen et al.</td>
<td>R,C</td>
<td>Adult pts with msra pneumonia, endocarditis, or osteomyelitis N=39 low dose N=16 high dose</td>
<td>Compared low vs. High dose (≥15)</td>
<td>10% low 31% high Though not significant, trend toward increased nephrotoxicity for tr≥15 p=ns</td>
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Mean HD nephrotoxicity = 17.8% (excluding pediatric)
Vancomycin Meta-Analysis

Reviewed literature from 1950 to Sept. 2011.

Fifty-three trials comparing vancomycin with linezolid, daptomycin, quinupristin-dalfopristin, tigecycline, ceftaroline, ceftobiprole, telavancin, teicoplanin, iclaprim, and dalbavancin were included in the meta-analysis.

Individual antibiotics were as effective as vancomycin, except for linezolid, which was more effective than vancomycin for the treatment of skin and soft tissue infections (odds ratio [OR], 1.61; 95% confidence interval [CI], 1.07-2.43).

Comparators were as effective as vancomycin in the intent-to-treat population (OR, 1.08; 95% CI, 0.98-1.18) but were more effective in the clinically evaluable population (OR, 1.14; 95% CI, 1.02-1.27) when all infections were pooled. When available data from all trials were pooled, no differences were noted when patients with febrile neutropenia (OR, 1.07; 95% CI, 0.82-1.39), pneumonia (OR, 1.10; 95% CI, 0.87-1.37), bacteremia (OR, 1.05; 95% CI, 0.76-1.45), and skin and soft tissue infections (OR, 1.11; 95% CI, 0.89-1.39) were studied.

Comparators were more effective in open-label (OR, 1.28; 95% CI, 1.08-1.50) but not in double-blind trials (OR, 1.04; 95% CI, 0.90-1.20).

Total adverse events attributed to studied antibiotics (OR, 1.07; 95% CI, 0.90-1.28) and patients withdrawn from trials (OR, 0.86; 95% CI, 0.68-1.09) were similar in the compared groups.

REFERENCES


