

# Vancomycin

**D**ue to the emergence of resistant organisms such as VRE, vancomycin is now a "restricted antibiotic". Its use in most hospitals requires the approval of the Infectious Disease Unit.

Vancomycin is a relatively small glycoprotein (Mol Wt ~ 1,450) derived from *Nocardia Orientalis* (formerly known as *Streptomyces Orientalis*).

Vancomycin is active against most Gram positive [G(+)] bacteria including Streptococci, Corynebacteria, Clostridia, Listeria, and Bacillus species. It is bactericidal to most susceptible G(+) bacteria at levels 0.5 - 3 mg/L. Staphylococci including  $\beta$ -lactamase producing and methicillin resistant species are killed at levels <10 mg/L. Resistant mutants are very rare, except for vancomycin resistant enterococcus (VRE).

Vancomycin kills bacteria mainly by inhibiting bacterial cell wall synthesis. However, it also damages the bacterial cell membrane and interferes with bacterial RNA synthesis. No significant post-antibiotic effect (PAE) has been observed for vancomycin and any of the susceptible organisms.

**To treat systemic infections, vancomycin must be given intravenously.** The intramuscular route is not used because of the possibility of tissue necrosis.

When given orally, vancomycin is not absorbed. Oral vancomycin is used only for the treatment of antibiotic-induced pseudomembranous colitis, which is caused by a toxin produced by *Clostridium Difficile*, a spore-forming, G(+) obligate anaerobic bacillus. Metronidazole (250 - 500 mg PO tid x 14 days) is first line therapy for "C dif", while vancomycin (125 - 250 mg po tid or qid x 10 - 14 days) is 2<sup>nd</sup> line (when metronidazole therapy fails or when pt can not tolerate it).

## Appropriate Indications for IV Vancomycin

### I. First-Line Therapy

1. Proven methicillin-resistant (MR) Staph aureus (S.A.) or coagulase-negative Staph (cnStaph)
2. Serious infections where cnStaph is highly suspected (e.g., central line, prosthesis, sternotomy, etc).
3. Endocarditis caused by MR Staph [plus gentamicin and rifampin for prosthetic valve endocarditis caused by cnStaph].
4. Meningitis caused by flavobacteria or PCN-resistant pneumococcus (plus cefotaxime) CNS shunt infection caused by methicillin resistant Staph (+ rifampin)
5. Infections caused by organisms susceptible only to vancomycin (e.g., *Corynebacterium jeikium*)
6. Ampicillin-resistant enterococcal infections.
7. Prophylaxis for major surgical procedures for implantation of prosthetic materials or devices at hospitals with a high rate of infections due to MR Staph. A single dose administered immediately before surgery is sufficient unless the procedure lasts more than 6 hours, in which case the dose should be repeated. prophylaxis should be discontinued after a maximum of two doses.

### II- In pts with true $\beta$ -lactam allergy

1. As alternative therapy for the treatment of Endocarditis caused by diphtheroids, Staph A, cnStaph, Strep bovis or Strep viridans, or Enterococcus (+ gentamicin).
2. Meningitis and CNS shunt infections caused by diphtheroids or G(+) cocci.
3. Severe infections caused by G(+) cocci. For moderate and mild infections, cotrimoxazole (Bactrim<sup>®</sup>) or erythromycin may be used.

## Inappropriate Use of IV Vancomycin

### Avoid using vancomycin for:

1. Routine surgical prophylaxis other than in a patient with a life-threatening allergy to  $\beta$ -lactam antibiotics.
2. Systemic or local prophylaxis for infection or colonization of indwelling central or peripheral intravascular catheters.
3. Empiric therapy for febrile neutropenia unless there is strong evidence that the patient has an infection due to G(+) microorganisms, and the prevalence of MRSA in the hospital is substantial.
4. Treatment in response to a single blood culture positive for coagulase-negative staphylococci if other blood cultures drawn in the same time frame are negative, indicating likely contamination of the specimen.
5. Continued empiric use for presumed infections in patients whose cultures are negative for  $\beta$ -lactamase-resistant G(+) microorganisms.
6. Selective decontamination of the gastrointestinal tract.
7. Eradication of MRSA colonization.
8. Routine prophylaxis of very-low-birth-weight infants
9. Routine prophylaxis for patients on continuous ambulatory peritoneal dialysis or hemodialysis.
10. Treatment (chosen for dosing convenience) of infections due to  $\beta$ -sensitive G(+) microorganisms.
11. Topical application or irrigation.
12. Primary treatment of antibiotic-associated colitis (vancomycin should be used only when organism is resistant to metronidazole).

## Pharmacokinetic Parameters

Volume of distribution (Vd) $\cong$ 0.7 L/kg	Ke = 0.00083 CLcr + 0.0044
Protein binding $\cong$ 55%	
Elimination: >90% renal	Half-life $\cong$ 7 hrs (w/ normal CLcr)
Vancomycin is not removed to any significant extent by conventional HD. However, significant fraction is removed by the newer high-flux HD membranes as well as by CVVH.	

## Dosing and Monitoring Guidelines

- /// Initial individual Dose = 15 mg/kg (based on actual body weight)
- /// For adult patients, the dose should be rounded to the nearest 250 mg (500, 750, 1000, 1250, 1500, 1750, 2000, etc)
- /// Dilute dose in D5W (maximum conc.  $\cong$  5 mg/mL and infuse over at least one hours. Slower infusion rates should be used in patients who develop "red man syndrome". Doses  $\geq$  1.5 grams should be infused over 90 – 120 min in all patients.
- /// Vancomycin may be given as a continuous infusion in special circumstances.
- /// The initial dosing frequency depends on the estimated creatinine clearance (CLcr) and the **target vancomycin trough level**
- /// CLcr may be estimated by using either the Cockcroft (for most pts) or the Sanaka equations (for elderly pts with muscle atrophy).

CLcr	≥ 75	40 - 74	30 - 39	CVVH	20 - 29	<20 (HD)	
Frequency	q12h	q24h	q48h	q48h	q72h	q5days	

- /// The dosing interval is then adjusted to achieve and maintain a trough level between 8 and 20 mg/L depending on the severity and location of the infection (the higher targets may be necessary for the treatment of CNS and bone infections). If necessary, the dosing interval may be as short as q6h. Continuous vancomycin infusion has been used successfully in special cases (see references below). When the higher levels are indicated, the Infectious Disease team should specify at least a target trough.
- /// If the trough level is below the target, shorten the dosing interval (e.g., from q12h to q8h). The opposite is also true.
- /// Peak levels should be < 45 mg/L. However, monitoring vancomycin peaks has little or no clinical value and many centers have abandoned this practice

### **Hemodialysis Patients**

- /// Hemodialyzed pts may be dosed at 15-20 mg/kg. A level is then taken 2-3 hrs after the next hemodialysis. Dosage will have to be individualized according to the level obtained and the severity of infection.
- /// Because the commonly used assays (EMIT or FPIA) do not differentiate between vancomycin and its metabolites, the reported vancomycin level in HD patients may be falsely elevated (by 10 to 40% ). A trough level of 15 - 25 mg/L may be more appropriate in these patients.
- /// Most patients will require dosing every other dialysis.
- /// Peritoneal Dialysis: Start with 15-20 mg/kg IV, and repeat dose once every 7 - 10 days.
- /// Oliguric / Anuric ARF Patients Who Are Not on Dialysis Yet: Start with 15-20 mg/kg. Draw a random levels every 2-3 days, and re-dose if level < 10 mg/L.
- /// Oliguric / Anuric ARF Patients on continuous venovenous hemofiltration (CVVH): Give a loading dose of 15 mg/kg followed by 10 mg/kg q24h. Monitor trough level; should be maintained > 8 mg/L.

### **Pediatric Patients**

- /// Vancomycin must be used only to treat severe infections.
- /// Infants < one wk old: 30 mg/kg/day (q12h).
- /// Infants 1 - 4 wks: 30 - 42 mg/kg/day (q8h).
- /// Infants more than one month and children: the initial dosage is 10 mg/kg q6h.

### **Adverse Drug Reactions**

- /// The side effects of iv vancomycin include a histamine-mediated erythematous flushing of the face, neck and trunk, a reaction that occurs during the infusion, and may be associated with hypotension.
- /// Nephrotoxicity and ototoxicity may occur in < 1% of pts especially those receiving other drugs like aminoglycosides.
- /// A relationship between vancomycin level and nephrotoxicity or ototoxicity has not been established. It is now widely believed that the earlier reports of nephrotoxicity may have been related to impurities in the product.
- /// The other side effects (neutropenia, thrombocytopenia, and hypersensitivity) are very rare.

## References

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