In the name of God

VANCOMYCIN & LINEZOLID IN SEPSIS

Dr. Afshin Gharehkhani

Associate Professor of Clinical Pharmacy
Department of Clinical Pharmacy, Faculty of Pharmacy, Tabriz University of Medical Sciences

content

vancomycin

- Dosing
- Intermittent versus continuous infusion
- AUC versus trough-guided monitoring
- Adverse Effects

linezolide

Treatment of MRSA bacteremia

- Management Of MRSA Bacteremia
- Initial antibiotic therapy
- Combination therapy
- Possible combination regimens
- Persistent bacteremia: Salvage therapy

Vancomycin

- Vancomycin is a bactericidal glycopeptide antibiotic that inhibits cell wall synthesis; it is the antibiotic agent for which there is the greatest cumulative clinical experience for treatment of bacteremia caused by MRSA.
- **Tissue penetration** is highly variable and depends on the degree of inflammation.
- Vancomycin has a relatively good safety profile and favorable pharmacokinetics that facilitate convenient administration . Monitoring vancomycin levels is necessary due to the risk of nephrotoxicity

Selecting a dosing/monitoring

method Intermittent versus continuous infusion

- Vancomycin may be administered via intermittent infusion (II) or continuous infusion (CI).
- In general, II is the most common approach; however, CI may be an advantageous alternative in certain circumstances.
- Potential settings for CI include patients with critical illness (particularly those on continuous renal replacement therapy) and patients receiving outpatient antimicrobial therapy.
- Potential advantages of CI include rapid pharmacokinetic (PK) target attainment, less variability in steady-state concentration, ease of serum drug concentration monitoring (given less dependence on sampling time or multiple concentrations to calculate AUC), and lower potential risk of nephrotoxicity.
- Disadvantages include the need for a dedicated intravenous line or compatibility with other agents administered through the same line.*

For patients with known or suspected severe Staphylococcus aureus infection such as bacteremia, our approach to vancomycin dosing is as follows:

- We suggest administration of **a loading dose** (**Grade 2C**), to reduce the likelihood of suboptimal initial vancomycin exposure. We give a loading dose of 20 to 35 mg/kg (based on actual body weight).

- The initial maintenance dose consists of 15 to 20 mg/kg actual body weight (rounded to the nearest 250 mg); the dosing interval is determined by a nomogram. In general, for most patients with normal kidney function, vancomycin dosing consists of approximately 15 to 20 mg/kg/dose (based on actual body weight rounded to the nearest 250 mg) every 8 to 12 hours.

Approach to vancomycin dosing for adults with normal kidney function*

Loading dose (for patients with known or suspected severe *Staphylococcus aureus* infection)¶	Load 20 to 35 mg/kg (based on actual body weight, rounded to the nearest 250 mg increment; not to exceed 3000 mg). Within this range, we use a higher dose for critically ill patients; we use a lower dose for patients who are obese and/or are receiving vancomycin via continuous infusion.
Initial maintenance dose and interval	Typically 15 to 20 mg/kg every 8 to 12 hours for most patients (based on actual body weight, rounded to the nearest 250 mg increment). In general, the approach to establishing the vancomycin dose/interval is guided by a nomogram.Δ
Subsequent dose and interval adjustments	Based on AUC-guided (preferred for severe infection)[1] or trough-guided serum concentration monitoring.◊

- The approach to vancomycin dosing in adults depends on the pathogen, the type and severity of infection, and patient factors including weight and kidney function.

AUC versus trough-guided monitoring

- For subsequent maintenance dosing in patients with stable kidney function, we suggest AUC-guided dosing (rather than trough-guided dosing) (Grade 2C), to maximize clinical efficacy and minimize nephrotoxicity risk; this approach requires the assistance of a pharmacist.
- The optimal pharmacokinetic/pharmacodynamic efficacy target is considered to be an AUC/minimum inhibitory concentration determined by broth microdilution ratio of 400 to 600 mghour/L.

- For patients with unstable kidney function (either worsening or improving) and in settings where it is not feasible to perform AUC-guided dosing, trough-guided dosing is warranted.

- After the loading dose, the initial maintenance dose is determined using a nomogram. Thereafter, the subsequent regimen is guided by a serum vancomycin trough concentration collected near steady state (target 15 to 20 mcg/mL).

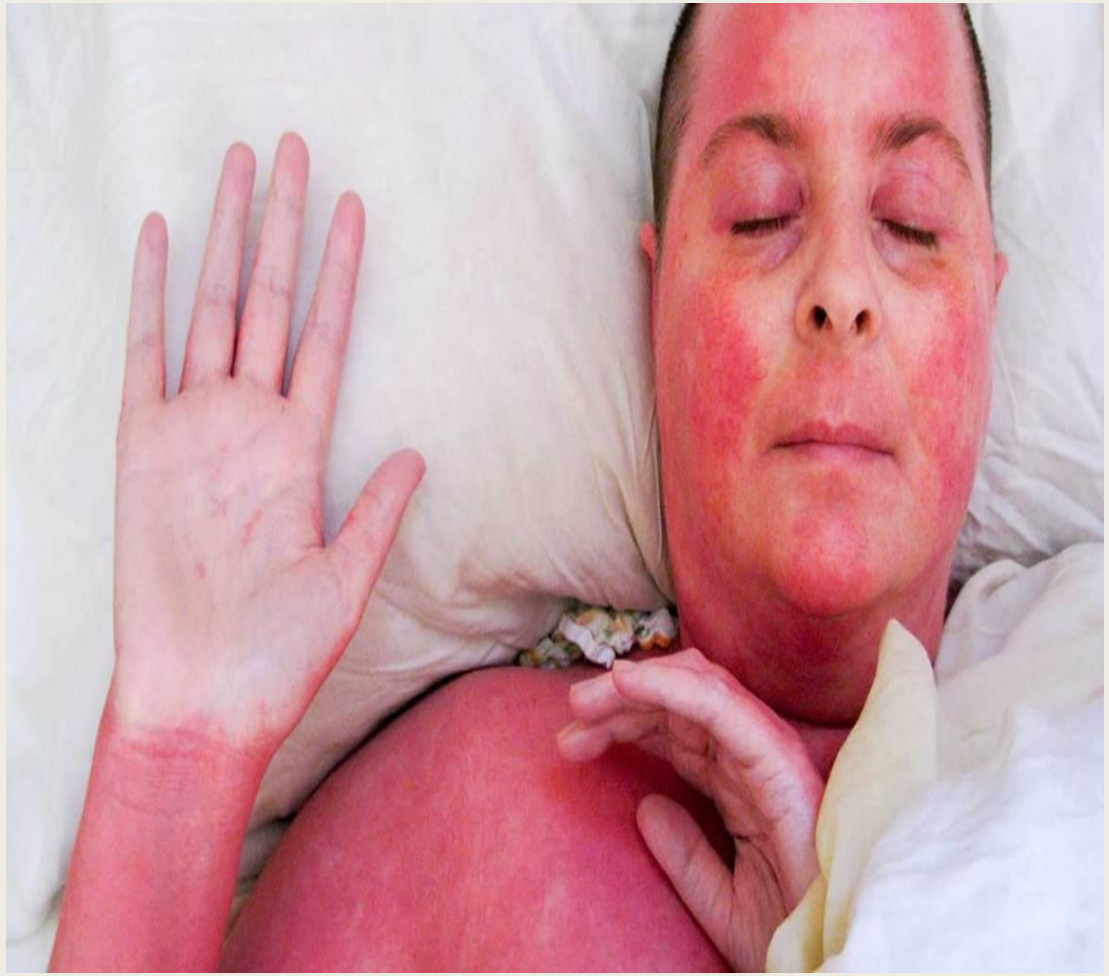
ADVERSE EFFECTS

Infusion-related phlebitis

- Intravenous administration of vancomycin has been associated with low rates of infusion-site phlebitis, given its **acidic pH**.
- Administration of vancomycin via central venous access may minimize such reactions but is not required.
- Additional strategies that may reduce the likelihood of phlebitis include reducing the infusion rate, diluting the drug in higher volumes of fluid, and the use of continuous infusion.

Red man syndrome

- Red man syndrome is a histamine-mediated flushing during or immediately following infusion of vancomycin.
- Flushing usually involves the face and neck but can involve the entire body.
- It may be reduced or eliminated by avoiding excessive doses, prolonging the infusion time (eg, administering the drug at a rate of no more than 500 mg/hour), and administration of antihistamines (prior to or during infusion).
- Some patients require an even slower infusion rate or continuous infusion dosing.



Acute kidney injury

- The mechanism of vancomycin nephrotoxicity involves **apoptosis** induced by accumulation of drug in proximal tubular epithelial cells.

- Factors influencing risk of AKI include dose, host-related factors (increased weight, pre-existing renal dysfunction, and critical illness), and concurrent administration of nephrotoxic agents (such as aminoglycosides, loop diuretics, amphotericin B, intravenous contrast dye, and vasopressors)

- Coadministration of vancomycin and select beta-lactams (notably piperacillin-tazobactam and flucloxacillin) has been associated with increased risk for AKI.

Management

- — It can be difficult to distinguish between drug-induced AKI and other causes of AKI including acute interstitial nephritis. Development of AKI in the setting of vancomycin therapy should prompt discontinuation of the drug.
- Data regarding timeframe for recovery from vancomycin-induced AKI are confounded by presence of additional risk factors for AKI. In one review, improvement or resolution was noted in approximately three quarters of patients

Ototoxicity

- Ototoxicity has been observed in association with vancomycin administration; ototoxicity attributable to vancomycin should prompt discontinuation of the drug.
- Potential risk factors for vancomycin induced ototoxicity include pre-existing hearing abnormalities and underlying renal dysfunction.
- Ototoxicity associated with vancomycin is more common in **older patients.**
- In the absence of tinnitus or ataxia, clinical detection of vancomycin ototoxicity is challenging; in the absence of audiometric testing, high-frequency hearing loss may not be detected and when it occurs, reversibility is unknown. In addition, older adults at greatest risk often suffer high-frequency hearing loss in the absence of vancomycin therapy

LINEZOLID

Linezolid

- Linezolid is a bacteriostatic oxazolidinone that inhibits initiation of protein synthesis at the 50S ribosome
- This drug class may have enhanced efficacy against strains producing toxins such as Panton-Valentine leukocidin, alpha-hemolysin, and toxic shock syndrome toxin 1.
- Linezolid and tedizolid are bacteriostatic (vancomycin, daptomycin, ceftaroline, and telavancin are bactericidal), and toxicity limits prolonged use.
- Monitoring of blood counts and serum chemistries should be performed at least weekly.

Linezolid

- Among 220 adults with MRSA infection, linezolid and vancomycin had **equivalent clinical cure rates** overall (73 percent) and in the subgroup with MRSA bacteremia (56 and 50 percent, respectively)
- Linezolid resistance has been observed among methicillin-resistant *S. aureus* isolates. The mechanism appears to be via the bacterial *cfr* gene, which resides in a potentially mobile genetic element.

Linezolid

- Safety concerns limit the extended use of linezolid. Adverse effects include thrombocytopenia, anemia, lactic acidosis, peripheral neuropathy, serotonin toxicity, and ocular toxicity.
- Linezolid can reversibly inhibit monoamine oxidase; when administered with serotonergic agents (particularly selective serotonin reuptake inhibitors), it can induce the serotonin syndrome.
- Thrombocytopenia appears to occur more frequently with more prolonged therapy and in the setting of end stage kidney disease and typically resolves after **discontinuation** of the drug.
- Peripheral neuropathy and lactic acidosis appear to occur more frequently in the setting of prolonged linezolid administration and may not resolve after drug discontinuation.

Dosing in Bloodstream infection:

- *Empiric therapy or pathogen-directed therapy for vancomycin-resistant enterococci:* Oral, IV:
  - 600 mg every 12 hours; treat uncomplicated bacteremia for 7 to 14 days from day of first negative blood culture, with longer courses warranted for endocarditis or metastatic sites of infection (IDSA)

- *Empiric therapy or pathogen-directed therapy for methicillin-resistant Staphylococcus aureus (alternative agent) (off-label use):*
  - Oral, IV: 600 mg every 12 hours; treat uncomplicated S. aureus bacteremia for ≥14 days from day of first negative blood culture, with longer courses warranted for endocarditis or metastatic sites of infection (IDSA).

MRSA IN ADULTS

Treatment of bacteremia

- Vancomycin MIC breakpoints for *S. aureus* are defined as follows (preferably determined by E-tests):

  - susceptible = MIC ≤2 mcg/mL
  - intermediate = MIC 4 to 8 mcg/mL
  - resistant = MIC ≥16 mcg/mL

MANAGEMENT OF MRSA BACTEREMIA

- Treatment of MRSA bacteremia consists of:
  1. prompt source control (such as removal of implicated vascular catheters and/or drainage of purulent collections if present), which is crucial for a successful therapeutic outcome.
  2. antibiotic therapy

Initial antibiotic therapy

- **Vancomycin susceptible isolates**

- For initial treatment of a documented MRSA bacteremia, we are in agreement with the 2011 guidelines issued by IDSA, which recommend vancomycin or daptomycin.
- Vancomycin is the agent for which there is the greatest cumulative clinical experience for the treatment of MRSA bacteremia.
- Due to risk of nephrotoxicity, vancomycin requires **serum concentration monitoring**, particularly in the setting of renal dysfunction.
- Daptomycin is an acceptable alternative to vancomycin for treatment of MRSA bacteremia, particularly in the setting of known or suspected high vancomycin minimum inhibitory concentration (MIC >1 mcg/mL); it is more costly than vancomycin and is associated with myopathy, so it requires **serum creatine kinase monitoring.**

Combination therapy

- Combination therapy with beta-lactam agents lacking activity against MRSA are not recommended.In
- a randomized trial : addition of an antistaphylococcal beta-lactam (intravenous flucloxacillin, cloxacillin, or cefazolin) to standard antibiotic therapy (intravenous vancomycin or daptomycin) was not associated with significant improvement in the primary composite end point of 90-day mortality, persistent bacteremia at day 5, relapse, or treatment failure
- **Nephrotoxicity** occurred more frequently among patients treated with combination therapy (23 versus 6 percent), primarily in those receiving flucloxacillin or cloxacillin, leading to early termination of the trial. Further study of combination therapy with daptomycin and ceftaroline is needed.

Combination therapy

- Combination therapy with vancomycin and gentamicin or rifampin has also been associated with adverse effects.
- vancomycin-gentamicin has been associated with an increased risk of nephrotoxicity.
- vancomycin-rifampin has been associated with hepatic adverse effects, drug interactions, and emergence of rifampin resistance

Borderline vancomycin susceptibility

- Some studies suggest a **worse clinical outcome** associated with vancomycin therapy for infection due to MRSA with vancomycin MIC ≥2 mcg/mL, while others do not*.
- A retrospective cohort study including 170 patients with MRSA bacteremia with vancomycin MICs 1.5 to 2 mcg/mL compared the **efficacy of vancomycin with daptomycin** . Vancomycin was associated with a higher rate of treatment failure (24 versus 11 percent) and a higher rate of renal complications (23 versus 9 percent).

Clinical approach

- In general, if the vancomycin MIC approaches the limit of the susceptible range (2 mcg/mL) and there is a poor initial clinical response (eg, persistent bacteremia), vancomycin should be discontinued and therapy switched to daptomycin.
- For patients with infection due to *S. aureus* isolates approaching the limit of the susceptible range (2 mcg/mL) who are not responsive to or are intolerant of vancomycin and daptomycin, there are several potential alternative agents. In such circumstances, the approach to antibiotic selection is uncertain; definitive trials are lacking. It is unknown whether combination therapy or monotherapy is warranted.

Possible combination regimens

- Daptomycin plus ceftaroline
- Vancomycin plus ceftaroline or other beta-lactams
- Daptomycin plus trimethoprim-sulfamethoxazole
- Ceftaroline plus trimethoprim-sulfamethoxazole

Possible regimens

- Possible monotherapy regimens include telavancin, ceftaroline, and linezolid.
- Telavancin monotherapy may prove effective for treatment of MRSA bacteremia (thus far, data are limited); in a phase II trial of telavancin for treatment of bacteremia including 17 patients, cure rates were comparable for telavancin and standard therapy (88 versus 89 percent).
- Linezolid and tedizolid are bacteriostatic (vancomycin, daptomycin, ceftaroline, and telavancin are bactericidal), and toxicity limits prolonged use.
- There is no role for use of quinupristin-dalfopristin, tigecycline, or fluoroquinolones for treatment of *S. aureus* bacteremia.

Persistent bacteremia: Salvage therapy

- Patients with persistent MRSA bacteremia (≥3 days) are at increased risk of metastatic infections and death.

- In these patients, we favor combination therapy with daptomycin (dosed at 8 to 10 mg/kg rather than 6 mg/kg intravenously daily) and ceftaroline

Thanks for your attention