

In the name of God

VANCOMYCIN & LINEZOLID IN SEPSIS

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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 <i>Staphylococcus aureus</i> 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

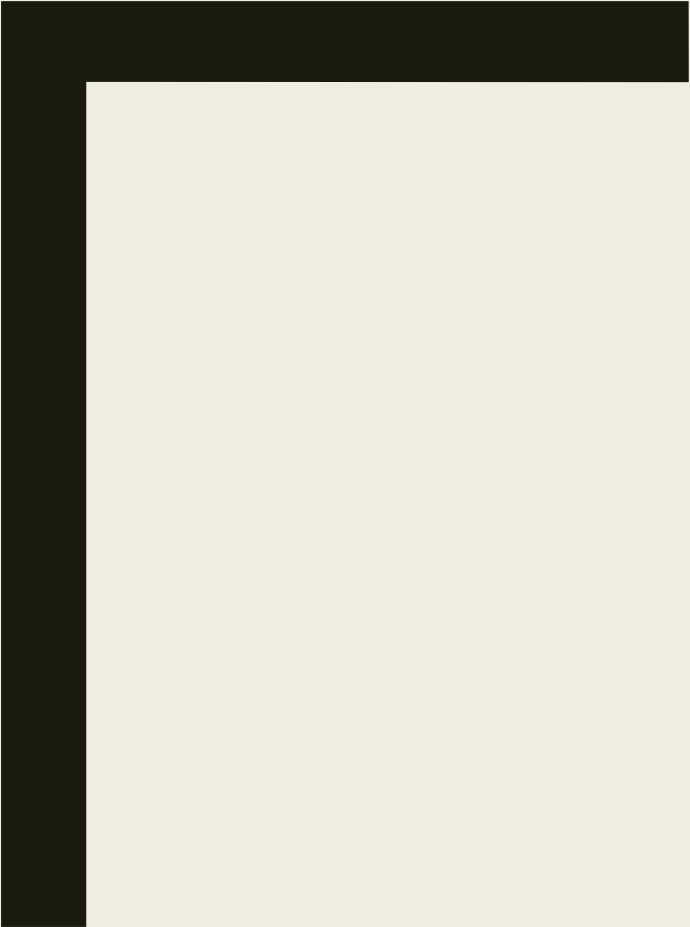
- The mechanism of vancomycin nephrotoxicity involves **apoptosis** induced by accumulation of drug in proximal tubular epithelial cells.
- Factors influencing risk of AKI include dose, host-related factors (**increased weight**, **pre-existing renal dysfunction**, and **critical illness**), and concurrent 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

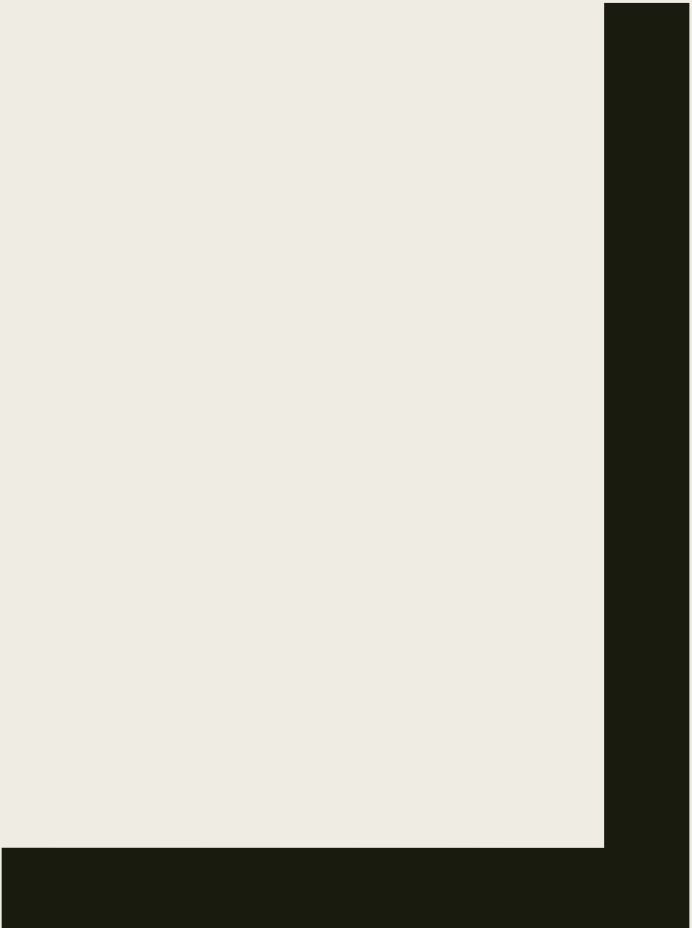
- — It can be difficult to distinguish between drug-induced AKI and other causes of AKI including acute interstitial nephritis. Development of AKI in the setting of vancomycin therapy should prompt discontinuation of the drug.
- Data regarding timeframe for recovery from vancomycin-induced AKI are confounded 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

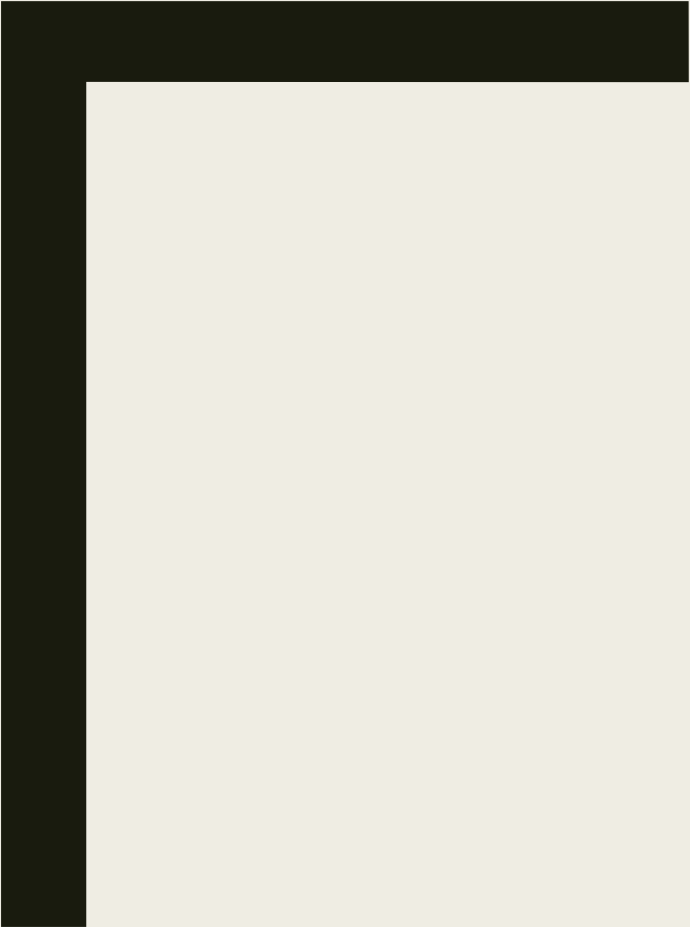
- Among 220 adults with MRSA infection, linezolid and vancomycin had **equivalent clinical cure rates** overall (73 percent) and in the subgroup with MRSA bacteremia (56 and 50 percent, respectively)
- Linezolid resistance has been observed among methicillin-resistant *S. aureus* isolates. The mechanism 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 $\leq$ 2 mcg/mL
 - intermediate = MIC 4 to 8 mcg/mL
 - resistant = MIC $\geq$ 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.
- 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

