Vancomycin Revisited: A Reappraisal of Clinical Use

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Over the years, vancomycin has become the mainstay of methicillin-resistant \textit{Staphylococcus aureus} (MRSA) therapy. Although vancomycin is active against a variety of other gram-positive organisms, other antibiotics are preferred to treat infections due to these organisms (Table 1). In critical care medicine, vancomycin has been mainly used to treat infections where MRSA is the presumed cause of infection. These include central intravenous line infections, soft tissue infections, bone infections, shunt infections in hemodialysis patients, bacteremia, and acute bacterial endocarditis. The widespread use of empiric vancomycin has resulted in adverse effects \cite{1–5}.

The initial unpurified formulations of vancomycin were associated with reports of potential nephrotoxicity \cite{6,7}. Subsequently, the purified preparations of vancomycin have been used and have not been associated with nephrotoxicity. There is no evidence for vancomycin monotherapy–associated nephrotoxicity \cite{8,9}. The few reports of potential vancomycin nephrotoxicity described patients receiving vancomycin and known nephrotoxic medications. Vancomycin plus an aminoglycoside does not appear to increase the nephrotoxic potential of the aminoglycoside \cite{10–15}. Endotoxin or cytokine release from gram-negative bacilli treated with an aminoglycoside and vancomycin may be responsible for an increase in creatinine in some cases, which may have been mistakenly ascribed to vancomycin toxicity \cite{16}. Because vancomycin monotherapy is not nephrotoxic, the use of vancomycin serum levels to avoid nephrotoxicity has no basis \cite{3,17,18}. Because vancomycin is renally eliminated by glomerular filtration, vancomycin dosing in renal insufficiency can be accurately dosed based on the creatinine clearance (CrCl), (ie, the daily dose of vancomycin should be reduced in proportion to the
decrease in renal function). In those responding to vancomycin therapy and in those with a normal volume of distribution \( (V_d) \), vancomycin levels are unhelpful, expensive, and unnecessary for vancomycin dosing \([17–21]\). The pharmacokinetic and pharmacodynamic characteristics of vancomycin have been well studied. Vancomycin obeys both “concentration dependent” kinetics at concentrations \( > \text{MIC} \) and “concentration independent” kinetics at concentrations \( < \text{MIC} \) \([1,3,19,22]\). Because nephrotoxicity is not a consideration, high-dose vancomycin (eg, 2 g intravenously every 12 hours \([60 \text{ mg/kg/d}] \)) has been used in special situations, eg, osteomyelitis without nephrotoxicity \([23,24]\). After years of clinical experience, vancomycin side effects have become more fully appreciated. In addition to “red neck” or “red man” syndrome, leukopenia, thrombocytopenia, and, rarely, sudden death have been ascribed to vancomycin \([1,3,25]\).

Extensive vancomycin use over the years has resulted in two major problems. Firstly, excessive use of vancomycin has resulted in an increased prevalence of vancomycin-resistant enterococci (VRE) worldwide. Vancomycin-sensitive enterococci (VSE) represent the main group D enterococcal component of feces. Vancomycin has sufficient anti-VSE activity to decrease VSE in the fecal flora, resulting in a commensurate increase VRE in stools \([26–30]\). Although the spectrum of infection caused by VSE and VRE are the same, the number of antimicrobials available to treat VRE is limited, making the therapy of VRE more difficult than the therapy of VSE \([31,32]\).

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**Table 1**

Vancomycin: clinically useful microbiologic spectrum

<table>
<thead>
<tr>
<th>Clinically effective</th>
<th>Clinically ineffective</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gram-positive aerobic cocci</strong></td>
<td><strong>Gram-negative aerobic cocci</strong></td>
</tr>
<tr>
<td>• Staphylococci (MSSA/MRSA),</td>
<td>• <em>Neisseria meningitidis</em></td>
</tr>
<tr>
<td>• Nonenterococcal streptococci (Groups A, B, C, G)</td>
<td></td>
</tr>
<tr>
<td>• <em>Staphylococcus epidermidis</em> (coagulase negative staphylococci) (MSSE/MRSE)</td>
<td></td>
</tr>
<tr>
<td>• Penicillin-resistant <em>Streptococcus pneumoniae</em></td>
<td></td>
</tr>
<tr>
<td><strong>Gram-positive anaerobic cocci</strong></td>
<td><strong>Gram-negative aerobic bacilli</strong></td>
</tr>
<tr>
<td>• <em>Peptococcus</em></td>
<td>• <em>Escherichia coli</em></td>
</tr>
<tr>
<td>• <em>Peptostreptococcus</em></td>
<td>• <em>Klebsiella pneumoniae</em></td>
</tr>
<tr>
<td><strong>Gram-positive aerobic bacilli</strong></td>
<td><strong>Gram-positive anaerobic bacilli</strong></td>
</tr>
<tr>
<td>• <em>Corynebacterium</em> sp</td>
<td>• <em>Pseudomonas aeruginosa</em></td>
</tr>
<tr>
<td>• <em>Lactobacillus</em> sp</td>
<td></td>
</tr>
<tr>
<td><strong>Gram-positive anaerobic bacilli</strong></td>
<td><strong>Gram-negative anaerobic bacilli</strong></td>
</tr>
<tr>
<td>• <em>Clostridium</em> sp</td>
<td>• <em>Bacteroides fragilis</em></td>
</tr>
<tr>
<td><strong>Group D enterococci</strong></td>
<td><strong>Group D enterococci</strong></td>
</tr>
<tr>
<td>• <em>Enterococcus faecalis</em> (VSE)*</td>
<td>• <em>Enterococcus faecium</em> (VRE)</td>
</tr>
</tbody>
</table>

*Abbreviations: MRSE, methicillin-resistant *Staphylococcus epidermidis*; MSSA, methicillin-sensitive *Staphylococcus aureus*; MSSE, methicillin-sensitive *Staphylococcus epidermidis*; VRE, vancomycin-resistant enterococci; VSE, vancomycin-sensitive enterococci.

a Only when combined with an aminoglycoside (eg, gentamicin).

Data from Refs. [1,3,4].
Another negative effect of vancomycin use over the years has been a relative increase in *S aureus* resistance [33–37]. Vancomycin therapy results in cell-wall thickening of *S aureus* strains, of both methicillin-sensitive *S aureus* (MSSA) and methicillin-resistant *S aureus* (MRSA). Vancomycin-mediated cell-wall thickening results in “permeability mediated” resistance to vancomycin as well as to other anti-MSSA and anti-MRSA antibiotics [38–42]. Vancomycin-induced “permeability-mediated” resistance is manifested microbiologically by increased minimum inhibitory concentrations (MICs) and clinically by delayed resolution or therapeutic failure in treating staphylococcal bacteremias or acute bacterial endocarditis [43–48].

To avoid selecting out heteroresistant vancomycin-intermediate *S aureus* (hVISA), vancomycin use should be minimized and other MRSA antibiotics should preferentially be used instead (eg, minocycline, daptomycin, linezolid, or tigecycline) [1,31,32].

**Vancomycin pharmacokinetics and pharmacodynamics**

Although available orally and intravenously, vancomycin is primarily administered via the intravenous route in the critical care setting. Oral vancomycin is the preferred therapy for *Clostridium difficile* diarrhea because it is not absorbed, is active against *C difficile*, and achieves high intraluminal concentrations in the colon [1,3,32]. Because intravenous vancomycin does not penetrate into the bowel lumen, intravenous vancomycin has no role in the treatment of *C difficile* diarrhea or colitis [1,3,5,49].

Vancomycin is usually administered as 1 g (intravenous) every 12 hours. After a 1-g intravenous dose, vancomycin serum concentrations are predictably \( \geq 25 \, \mu g/mL \) [1,3,5,50]. High dose of vancomycin (eg, 2 g intravenously every 12 hours) has been used in the treatment of central nervous system (CNS) infections to overcome the relatively poor cerebrospinal fluid (CSF) penetration of vancomycin (CSF penetration with noninflamed meninges is 0% and with inflamed meninges is only 15% of simultaneous serum concentrations) and osteomyelitis (achieves serum trough levels \( \geq 15 \, \mu g/mL \) [1,32,51,52]. For cardiopulmonary bypass (CBP) prophylaxis, use 1 g intravenously preoperatively because vancomycin is rapidly removed during CBP [53,54]. Burn patients have increased \( V_d \) and may require higher doses of vancomycin. Intravenous drug abusers (IVDAs) have higher vancomycin renal clearances than do non-IVDAs, and may require higher doses (Box 1) [1].

Vancomycin is not removed by hemodialysis [1,3]. In anuric patients a 1 g (IV) dose results in peak serum concentrations of about 48 mg/mL. Vancomycin’s mean elimination half-life is 7.5 days (vancomycin serum concentration is 3.5 mg/mL after 18 days) [1,32,55,56]. In patients using new “high flux” membranes for hemodialysis, about 40% of vancomycin is removed. Therefore, a post-“high flux” hemodialysis dose (eg, 500 mg intravenously, which is \( \sim 50\% \) of the anuric dose) should be administered post-hemodialysis [57].
Peritoneal dialysis (PD) removes no vancomycin. Therefore, after an initial 1-g intravenous dose, vancomycin should be dosed for a CrCl less than 10 mL/min and no post-PD dose is necessary [1,32]. For patients with peritonitis on chronic ambulatory peritoneal dialysis (CAPD), vancomycin may be added to peritoneal dialysis fluid. A 1-g intravenous loading dose of vancomycin may be given to such patients after dialysis, followed by the renally adjusted maintenance anuric dose [1,32]. In addition, to maintain equilibrium between the dialysate fluid and the serum compartment,
vancomycin may also be given intraperitoneally (2–30 mg of vancomycin per liter of dialysis fluid) with each CAPD [1,32]. Vancomycin has been used to treat CNS infections, but CNS penetration of vancomycin is variable. Vancomycin administered intravenously achieves only about 15% of simultaneous serum levels in the CSF in patients with meningitis. If high CSF concentrations are desired for treatment of gram-positive shunt infections, give 2 g intravenously every 12 hours until shunt removal. Intravenous vancomycin may be supplemented by intrathecal doses (ie, vancomycin 10–20 mg/d intrathecally), preferably administered via Omaya reservoir [1,3,32,58].

With normal renal function, about 90% of intravenous vancomycin is eliminated unchanged in the urine during the first 24 hours. After a single 1-g intravenous dose of vancomycin, urine concentrations are ~500 µg/mL, which are maintained for 24 hours [1,3]. Intravenously administered vancomycin does not concentrate well into bile (30%), synovial fluid, pleural fluid, or lung parenchyma [1,58–62].

Intravenous vancomycin diffuses well into most other body compartments except feces, aqueous humor, and CSF [1,60]. While vancomycin penetrates poorly into CSF, it penetrates well into brain tissue (Box 2) [1,6,32,51,52,58].

Vancomycin levels

Vancomycin is eliminated by glomerular filtration. The serum half-life of IV vancomycin is 6 hours with normal renal function, and 7 days in anuria [1,6,56,62]. Many approaches to vancomycin dosing for various degrees of renal insufficiency have been devised and all are based on CrCl [1,6,21]. Formerly, vancomycin was administered as 500 mg intravenously every 6 hours. Today vancomycin is usually administered as 1 g intravenously every 12 hours (for adults with a normal Vd and CrCl) [22,63,64]. For serious systemic infections due to susceptible organisms, is to administer vancomycin 1 g intravenously every 12 hours (15 mg/kg/d) or 2 g intravenously every 12 hours (30 mg/kg/d) [1,3,32]. Even when used in prolonged high doses for special situations, such as for MRSA osteomyelitis (2 g intravenously every 12 hours [30 mg/kg/d]), there has been no nephrotoxicity [23,24].

Since vancomycin was thought to be nephrotoxic, vancomycin dosing was based on vancomycin levels [65,66]. However, vancomycin has no nephrotoxic potential. Thus, there is no rationale for using routine vancomycin levels to dose patients to avoid nephrotoxicity. Accurate vancomycin dosing is readily achieved more quickly, simply, less expensively, and without risk of nephrotoxicity by dosing vancomycin based on CrCl rather then by vancomycin levels [67–72]. It has been shown that vancomycin levels do not reduce nonexistent toxicity but vancomycin levels often result in unnecessary vancomycin dosing changes [73–78].
There is often considerable delay between the time vancomycin peaks and troughs are reported [70,74–76]. Two or more days have usually elapsed when dosing adjustments are made, which means adjustments in vancomycin dosing are based on previous, but no longer relevant estimates of renal function (CrCl) [70,76]. The other practical difficulty with vancomycin serum peak and trough levels is in the timing of the samples which influences interpretation of the levels. This, in addition, causes unnecessarily frequent changes in vancomycin dosing, which serve no clinical purpose [1,6,32,70–78].

In anuria, on chronic hemodialysis, vancomycin peak serum concentrations are predictable and vancomycin serum levels are unnecessary. In

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**Box 2. Vancomycin tissue concentrations**

<table>
<thead>
<tr>
<th>Bone concentrations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortical bone</td>
</tr>
<tr>
<td>Uninfected: ~5%</td>
</tr>
<tr>
<td>Infected: ~10%</td>
</tr>
<tr>
<td>Cancellous bone</td>
</tr>
<tr>
<td>Uninfected: ~5%</td>
</tr>
<tr>
<td>Infected: &lt;5%</td>
</tr>
</tbody>
</table>

| Synovial fluid concentrations |
| Uninflamed synovial fluid: ~20% |

<table>
<thead>
<tr>
<th>Urine Concentrations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uninfected urine: 100% (normal renal function)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stool concentrations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feces:</td>
</tr>
<tr>
<td>Intravenous: 0%</td>
</tr>
<tr>
<td>Orally: 1000%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CSF concentrations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uninflamed meninges: 0% (prophylaxis of CSF seeding)</td>
</tr>
<tr>
<td>Inflamed meninges: 15% (therapy of acute bacterial meningitis)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Heart concentrations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac valves: 20%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lung concentrations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung parenchyma: &lt;10%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Bile concentrations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unobstructed bile: ~50%</td>
</tr>
</tbody>
</table>

| Ascitic fluid concentrations |
| Ascites: <10%               |

* Relative to simultaneous serum levels
patients receiving vancomycin on “high flux” hemodialysis, a posthemodialysis dose should be given to replace the vancomycin removed. Since about 40% of vancomycin is removed by “high flux” hemodialysis, a 500-mg intravenous posthemodialysis dose should be given [57].

Vancomycin serum concentrations may be used to assess adequacy of therapy in patients with unusual V_d, such as burn patients, or in those patients not responding to appropriately dosed vancomycin (ie, patients showing vancomycin “tolerance” or resistance). For these purposes, vancomycin serum levels should be obtained. Except to assess therapeutic efficacy or “apparent therapeutic failure” there is no rationale for obtaining vancomycin serum levels [69–78].

Vancomycin microbiologic activity and efficacy

Anti-staphylococcal activity

Staphylococcus epidermidis

The main use of parenteral vancomycin over the years has been in the treatment of Staphylococci epidermidis, (ie, coagulase-negative staphylococci (CoNS) infections, methicillin-sensitive S epidermidis (MSSE), and methicillin-resistant S epidermidis (MRSE) infections). CoNS infections are usually related to prosthetic implant materials (ie, infections involving prosthetic joints, prosthetic heart valves, and CNS shunts). These infections are difficult to eradicate with antimicrobial therapy alone because antibiotics are unable to eradicate these organisms in the glycocalyx on prosthetic materials.

Methicillin-resistant Staphylococcus aureus

Vancomycin has been used to treat serious staphylococcal infections, especially MRSA. The prevalence of MRSA has increased during the past several decades with three clinical variants recognized. Two of these are hospital-acquired MRSA (HA-MRSA) and community-onset MRSA (CO-MRSA). CO-MRSA strains originate in the hospital, circulate in the community, and subsequently have their onset in the community before being readmitted to the hospital. A third is community-acquired (CA-MRSA), a term often mistakenly applied to CO-MRSA because both come from the community.

However, CA-MRSA infections have two distinctive clinical presentations readily differentiating them from CO-MRSA strains, which represent the majority of MRSA admitted from the community (community onset) to the hospital. CA-MRSA infections usually present either as severe pyoderma or as necrotizing/hemorrhagic CAP. Although still rare, these two clinical CA-MRSA syndromes are recognizable by their clinical presentations. Strains of CA-MRSA, particularly those with the Panton-Valentine leukocidin gene (PVL positive), are unusually virulent with a high degree of cytotoxic
activity, which accounts for their extensive tissue destruction and two unique clinical presentations. While these strains are genetically distinctive (ie, Staphylococcal chromosome cassette [SCC] mec IV), most hospital laboratories cannot perform studies to identify PVL positive strains. Clinicians must rely on the clinical presentation to identify CA-MRSA strains versus the great majority of MRSA strains from the community, which are nearly all CO-MRSA. In spite of the increased virulence of CA-MRSA PVL positive strains, these organisms are surprisingly sensitive to older antibiotics, such as doxycycline, clindamycin, and trimethoprim-sulfamethoxazole (TMP-SMX), but these antibiotics are not effective against HA-MRSA strains. Vancomycin, linezolid, daptomycin, minocycline, and tigecycline are active against HA-MRSA, CO-MRSA, and CA-MRSA strains. For CA-MRSA necrotizing pyodermas, treat with surgical debridement and a HA-MRSA/CO-MRSA antibiotic, such as vancomycin, linezolid, daptomycin, or tigecycline. For CA-MRSA CAP with influenza-like illness, treat with influenza antivirals and linezolid [79,80].

**Group D enterococci**

Since vancomycin was the initial antibiotic effective against MRSA, its excessive use over time has resulted in two major clinical problems. Firstly, extensive intravenous (not oral) vancomycin use has resulted in an increase in the prevalence of *E faecium* (VRE), as well as increased vancomycin resistance [81]. The increase in VRE isolates is explained by the activity of vancomycin against the VSE component in the fecal flora, which is the predominant enterococcal species in the fecal flora. By decreasing VSE in the fecal flora, there is a commensurate increase in VRE in feces. There has been an increase worldwide in VRE prevalence due to vancomycin overuse. Instead, other anti-MRSA antibiotics that do not have this effect should be used [26,81,82].

**Vancomycin tolerance and resistance**

**Enterococci**

Enterococci and, to a lesser extent, staphylococci may develop “tolerance” to vancomycin. “Tolerance” may be defined as a minimum bactericidal concentration (MBC) of ≥32 times the MIC of an antibiotic. Vancomycin “tolerance” may account for some cases of delayed or blunted therapeutic response with enterococci or staphylococci [1,83–85].

Vancomycin is a heptapeptide and is bactericidal for most gram-positive organisms, including staphylococci but is bacteriostatic against enterococci. Resistance to vancomycin is mediated by alterations in the permeability of outer membrane porins in *S aureus*. Vancomycin binds rapidly and irreversibly to cell walls, inhibiting cell-wall synthesis. Interfering with peptidoglycan
cross-linkages causes defective cell-wall synthesis, resulting in bacterial cell-wall lysis. Enterococci resistance to vancomycin may be of the high- or low-grade variety. High-level (Van A) vancomycin resistance (MIC ≥ 64 μg/mL) is mediated by plasmids and is inducible and transferable. Low-level (Van B) resistance (MIC: 32–64 μg/mL) is nontransferable and chromosomally encoded [1,85].

**Staphylococci**

Widespread vancomycin use has increased staphylococcal resistance to vancomycin manifested as increased MICs. Clinically, vancomycin resistance is manifest as delayed resolution of infection or therapeutic failure. It has long been appreciated that patients with MRSA bacteremia/endocarditis often do not respond to vancomycin therapy [86–92]. This cannot be ascribed to underdosing vancomycin. Even with optimal vancomycin dosing, persistent MRSA bacteremias and therapeutic failures are not uncommon in clinical practice. Vancomycin therapy increases staphylococcal cell-wall thickening, particularly in hVISA strains. Cell-wall thickening results in “permeability-mediated” resistance to vancomycin as well as to other antistaphylococcal antibiotics. For these reasons, vancomycin may no longer be the preferred antibiotic for treatment of serious systemic MRSA infections. Other effective MRSA antibiotics are available and may be used in place of vancomycin (eg, minocycline, linezolid, tigecycline, and daptomycin). The empiric use of vancomycin to treat MRSA-colonized patients should be minimized to avoid further increases in VRE prevalence and MRSA resistance [1,6,32,93].

**Vancomycin: clinical uses**

Methicillin-sensitive *Staphylococcus aureus* and methicillin-resistant *Staphylococcus aureus* bacteremias

The finding of *S aureus*, either of the MSSA or MRSA variety, is common in blood culture reports. Because MSSA and MRSA often colonize the skin, these organisms are frequently introduced into blood cultures during venipuncture. *S epidermidis*, (CoNS), are also common blood culture contaminants. Approximately 20% of blood cultures are contaminated by MSSA, MRSA, or CoNS. Clinicians should not equate-positive blood cultures with bacteremia.

Some organisms have clinical significance whenever present in blood cultures (ie, *Listeria monocytogenes, Brucella* sp, *Streptococcus pneumoniae*). The clinical significance of gram-positive cocci in blood cultures must be assessed by the degree of blood culture positivity and considered in the appropriate clinical context. Ordinarily, four blood cultures should be obtained. This usually allows the clinician to clearly differentiate between blood
culture positivity and bacteremia when dealing with blood culture reports positive for MSSA, MRSA, or CoNS. One or two out of four positive blood cultures usually represent blood culture contamination rather than infection. High-grade blood culture positivity—three of four or four of four—is usually indicative of bacteremia. If it is established that the patient has bacteremia, the clinician’s next task is to determine whether it is a transient or sustained bacteremia. Staphylococci bacteremia is said to be persistent when MSSA or MRSA is present repeatedly in consecutive blood cultures demonstrating high blood culture positivity (ie, three of four or four of four). One out of four or two of four blood cultures with CoNS almost always represents blood culture contamination. Conversely, persistent high-grade blood culture positivity with CoNS, particularly in the presence of implanted prosthetic materials, usually indicates a prosthetic material- or device-associated infection [2,32,94,95].

Much empiric vancomycin is used to “cover” “gram positive cocci in clusters” in preliminary blood culture reports rather than bacteremia. The most common cause of high-grade MSSA, MRSA, or CoNS bacteremia are central venous catheter (CVC)–related infections. Empiric vancomycin used to “cover” the staphylococcal bacteremia or the “catheter” should be discouraged. If CVC line infection is suspected, the line should be removed and the diagnosis confirmed by semiquantitative catheter tip cultures. Treatment for CVC line–associated bacteremia is catheter removal, not just antibiotic therapy. Overuse of empiric vancomycin for suspected or known CVC-line infections has increased the prevalence of VRE. If CVC access is necessary after CVC removal for semiquantitative catheter tip culture, another line may be replaced over a guide wire without risk of pneumothorax, pending catheter tip results. If the semiquantitative catheter tip cultures are later reported as negative, the new catheter placed over a guide wire may remain in place. If catheter tip cultures are positive (ie, ≥ 15 colonies of the same organism as causing the bacteremia), then the line replaced over the guide wire should be removed and a new CVC placed in a different anatomic location (Boxes 3 and 4) [96,97].

Continuous Methicillin-sensitive Staphylococcus aureus and methicillin-resistant Staphylococcus aureus bacteremias

Patients presenting with a sustained or persistent MSSA or MRSA bacteremia should be treated empirically with an agent that offers a high degree of activity against MSSA or MRSA, depending upon the hospital’s predominant S aureus type (ie, MSSA versus MRSA) while a workup to determine the cause of the persistent bacteremia is undertaken. The most common underlying causes of persistent MSSA or MRSA bacteremia are intravascular infections (ie, CVC-related infections) or acute bacterial endocarditis or paravalvular abscess, and less commonly are due to persistent bacteremias from non-cardiac staphylococcal abscesses and, even less commonly, bone infections [47,97–101].
Methicillin-sensitive *Staphylococcus aureus* and methicillin-resistant *Staphylococcus aureus* central intravenous line infections

The majority of intravenous line infections related to CVCs are due to skin organisms (ie, MSSA, MRSA, MSSE, or MRSE). Because vancomycin is active against these skin pathogens, it is frequently used as empiric monotherapy for presumed CVC line infections. There are two problems with this approach. In institutions where the predominant pathogen causing CVC line infections is MSSA, rather than MRSA, other agents should be used in preference to vancomycin. After MSSA and MRSA, aerobic gram-negative bacilli are the next most important pathogens in CVC line infections. The use of vancomycin empirically for CVC infections has two hospital-wide consequences [96,97,101].

Firstly, vancomycin increases institutional prevalence of VRE. Secondly, exposure to vancomycin has the effect of increasing cell-wall thickness among staphylococci. Vancomycin-induced thickened bacterial cell walls

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**Box 3. Vancomycin: appropriate prophylactic and therapeutic uses**

**Prophylaxis**
- Prosthetic (orthopaedic/cardiovascular) implant surgery
- MSSA/MRSA infections in hemodialysis patients
- Subacute bacterial endocarditis for:
  - Oral and upper respiratory tract procedures (*Streptococcus viridans*) (in penicillin allergic patients)
  - Gastrointestinal and genitourinary procedures (*E faecalis*, VSE) procedures in patients with previous subacute bacterial endocarditis or prosthetic valve endocarditis (plus gentamicin)

**Therapy**
- MRSA, CoNS CNS shunt (ventriculo-atrial, ventriculo-peritoneal) infections
- MRSA hemodialysis catheter infections
- Endocarditis
  - *Streptococcus viridans* subacute bacterial endocarditis (in penicillin-allergic patients)
  - CoNS prosthetic valve endocarditis due to MSSE or MRSE
  - VSE subacute bacterial endocarditis

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* a Preferred therapy (eg, linezolid).
* b Preferred therapy (eg, daptomycin or linezolid).
* c Alternative therapy preferred.
* d Combined with gentamicin.

Methicillin-sensitive *Staphylococcus aureus* and methicillin-resistant *Staphylococcus aureus* central intravenous line infections

The majority of intravenous line infections related to CVCs are due to skin organisms (ie, MSSA, MRSA, MSSE, or MRSE). Because vancomycin is active against these skin pathogens, it is frequently used as empiric monotherapy for presumed CVC line infections. There are two problems with this approach. In institutions where the predominant pathogen causing CVC line infections is MSSA, rather than MRSA, other agents should be used in preference to vancomycin. After MSSA and MRSA, aerobic gram-negative bacilli are the next most important pathogens in CVC line infections. The use of vancomycin empirically for CVC infections has two hospital-wide consequences [96,97,101].

Firstly, vancomycin increases institutional prevalence of VRE. Secondly, exposure to vancomycin has the effect of increasing cell-wall thickness among staphylococci. Vancomycin-induced thickened bacterial cell walls
are manifested as an increase in MICs, delayed resolution of infection, or therapeutic failure. Staphylococci with thickened cell walls represent a permeability barrier to vancomycin as well as to other antibiotics. This is manifested clinically in the microbiology laboratory as “MIC drift.” The increase in MICs, often observed during vancomycin therapy, is reflective of cell-wall thickening. A preferred approach to the empiric treatment to CVC line infections pending CVC removal is to use meropenem in institutions where CVC infections are more frequently due to MSSA/GNBs than to MRSA. In institutions where the reverse is true, and MRSA is an important CVC pathogen, empiric therapy with tigecycline is preferable to combination therapy with vancomycin plus an anti–GNB antibiotic (Box 5).

Methicillin-sensitive *Staphylococcus aureus* and methicillin-resistant *Staphylococcus aureus* hemodialysis catheter infections

The treatment of hemodialysis catheter infections in hemodialysis patients has been a major area of vancomycin usage because vancomycin is eliminated by glomerular filtration. The increased half-life of vancomycin in anuria may be used to a therapeutic advantage in patients with MSSA/MRSA infections in end stage renal disease on hemodialysis. As with other foreign body infections due to gram-positive organisms, shunt removal is usually necessary for elimination the infection. Vancomycin has been used prophylactically and therapeutically in hemodialysis patients to treat dialysis catheter infections due to MSSA and MRSA [32,102–104].

**Box 4. Clinical situations in which vancomycin should be avoided**

*Prophylaxis*
- General surgical procedures
- MSSA/MRSA neurosurgical shunts
- MSSA/MRSA chest tubes
- MSSA/MRSA intravenous lines
- MSSA/MRSA in febrile leukopenia

*Therapy*
- MRSA colonization of respiratory secretions, wounds, or urine (avoid treating colonization; treat only infection)
- Most serious systemic MRSA infections
  - Preferentially use other anti-MRSA antibiotics
  - Intravenous MRSA antibiotics: linezolid, daptomycin, tigecycline, minocycline
  - Oral MRSA antibiotics: linezolid, minocycline
Methicillin-sensitive *Staphylococcus aureus* and methicillin-resistant *Staphylococcus aureus* acute bacterial endocarditis

The diagnostic approach to persistent *S. aureus* bacteremia is relatively straightforward. First, in patients with CVCs, this source of infection should be ruled out first because since CVC infections are readily diagnosable and easily treated by CVC removal. If there is no CVC in place, or if the removed CVC semiquantitative catheter tip cultures are negative, then endocarditis should be the next diagnostic consideration. MSSA or MRSA endocarditis presents as acute bacterial endocarditis (ABE). Except for IVDAs, patients presenting with MSSA or MRSA acute bacterial endocarditis, usually present with fever of 102°F or higher. In addition, MSSA or MRSA acute bacterial endocarditis usually presents without a heart murmur early in the infectious process. Later, when there is valvular destruction, a new or rapidly changing murmur becomes apparent.

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**Box 5. Diagnostic clinical pathway: persistent *S aureus* (MSSA, MRSA) bacteremias**

Differentiate *S aureus* blood culture positivity (1/4 or 1/2) from bacteremia.

With *S aureus* bacteremia, differentiate low-intensity intermittent bacteremia (1/2 or 2/4 positive blood cultures) from continuous high-intensity bacteremia (3/4–4/4 positive blood cultures).

**Determine the source of *S aureus* bacteremia.**
- Abscesses
- Central intravenous lines
- Implanted prosthetic devices/materials
- Acute bacterial endocarditis
- Soft tissue and bone infections

**Review antibiotic-related factors.**
- Determine drug dose/dosing interval.
- Determine MIC/MBCs.
- Evaluate in vivo versus in vitro effectiveness.
- Evaluate potential of permeability-related resistance due to vancomycin cell-wall thickening.

With high-intensity continuous *S aureus* bacteremia, obtain a transthoracic or transesophageal echocardiogram to diagnose or rule out acute bacterial endocarditis.

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In patients with subacute bacterial endocarditis and positive blood cultures due to subacute bacterial endocarditis pathogens, cardiac echocardiography is indicated in patients who have a heart murmur. Cardiac echocardiography may be the transthoracic (TTE) or the transesophageal (TEE) variety. For screening purposes, TTE is preferred to TEE. For detection of prosthetic valve endocarditis and myocardial abscess TEE is preferred. In patients with subacute bacterial endocarditis, the indication for a TTE or a TEE is the presence of continuous bacteremia due to a known subacute bacterial endocarditis pathogen plus fever and a heart murmur [105–107].

In contrast, in patients with possible acute bacterial endocarditis, the indications for a TTE or TEE are fever and a sustained high-grade MSSA or MRSA bacteremia. A heart murmur is not usually present in acutely in patients presenting with acute bacterial endocarditis. If cardiac echocardiography is negative for vegetations, acute bacterial endocarditis is effectively eliminated from further consideration. If the high-grade continuous MSSA or MRSA bacteremia continues, the echocardiography should be reviewed for a potential paravalvular myocardial abscess. If a myocardial abscess is suspected, TEE, is the preferred echocardiographic modality to demonstrate a perivalvular septal, or myocardial abscess. In patients with potential staphylococcal prosthetic valve endocarditis (PVE), a TEE is preferred to demonstrate vegetations. Patients with prosthetic valve(s) should be suspected of having prosthetic valve endocarditis if there is fever and a continuous high-grade bacteremia with a known endocarditis pathogen. Fever is usually present, but murmurs are difficult to appreciate because of the sounds generated by the prosthetics valve. Subacute bacterial endocarditis, acute bacterial endocarditis, and prosthetic valve endocarditis may be accompanied by peripheral findings associated with endocarditis (Box 6; Tables 2 and 3) [97,101,106,107].

**Staphylococcal central nervous system infections**

Vancomycin has been used to treat CNS shunt infections, which are usually due to CoNS of the MSSE or MRSE variety. CNS shunt infections usually require shunt removal. If suppression is desired, vancomycin may be given parenterally and, if necessary, CSF concentrations may be further increased by intraventricular administration. Usually the best way to administer intrathecal vancomycin is via an Ommaya reservoir. Vancomycin CSF levels may be obtained in patients to assure adequate CSF levels, but resolution of shunt infections almost always requires shunt removal. It is preferable to use an antibiotic with good CSF penetration (eg, linezolid) [1,31,32].

**Febrile neutropenia**

Recently, some clinicians have added vancomycin to regimens to treat febrile neutropenia in compromised hosts receiving chemotherapy. The increased incidence of gram-positive infections in febrile neutropenia are not due to neutropenia per se, but are due to central line catheters or
Box 6. Diagnostic clinical pathway: MSSA/MRSA acute bacterial endocarditis

Differentiate *S aureus* blood culture positivity (1/2 or 1/4 positive blood cultures) from bacteremia (3/4–4/4 positive blood cultures).

With *S aureus* bacteremia, differentiate low-intensity intermittent bacteremia (1/2 or 2/4 positive blood cultures) from continuous high-intensity bacteremia (3/4–4/4 positive blood cultures).

Acute bacterial endocarditis is not a complication of low-intensity/intermittent *S aureus* bacteremia. TTE/TEE unnecessary, but will verify no vegetations.

If continuous high-grade MSSA/MRSA bacteremia, obtain a TTE or TEE to document cardiac vegetations and/or paravalvular abscess and confirm diagnosis of acute bacterial endocarditis.

Diagnostic criteria for MSSA/MRSA acute bacterial endocarditis

**Essential features**
- Continuous high-grade MSSA/MRSA bacteremia
- Cardiac vegetations on TTE/TEE
- No other source

**Nonessential features**
- Fever ≥102°F (non-IVDAs)
- Cardiac murmur

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*With early MSSA/MRSA, a murmur is not present. Later, a new murmur in acute bacterial endocarditis indicates a vegetation or valvular destruction.*


chemotherapy infusion devices in these patients. Depending upon the geography/epidemiology of the balance between MSSA versus MRSA strains in patients in the community, empiric treatment with an anti-MSSA or an anti-MRSA agent may be desired until the temporary or semipermanent catheter is removed or replaced. For patients presenting with febrile neutropenia treated with an antibiotic effective against *Pseudomonas aeruginosa* with good anti-MSSA activity, additional antistaphylococcal therapy is usually unnecessary. Antibiotics commonly used empirically in febrile neutropenia (eg, levofloxacin, meropenem) have anti-MSSA activity. In febrile neutropenia, fungal infections usually present after 10 to 14 days of antibiotic therapy and are clinically manifested as an otherwise unexplained recrudescence of fever in patients who have responded to empiric anti-*P aeruginosa* therapy. If fungal infection can be ruled out, a temporary or semipermanent central line infection should be suspected. If blood cultures are persistently positive (high-grade positivity) with MRSA, then anti-MRSA therapy should
be given until the device is removed. The routine use of vancomycin in combination therapy with an anti-
P. aeruginosa antibiotic for febrile neutropenia should be discouraged to minimize further increases in VRE prevalence and permeability-mediated resistance [1,32,108].

**Penicillin-allergic patients**

Vancomycin has been used in penicillin-allergic patients to treat Streptococcus viridans and enterococcal endocarditis. Vancomycin monotherapy has been used successfully over the years to treat S. viridans subacute bacterial endocarditis. Because vancomycin is bacteristatic against E. faecalis, combination therapy with aminoglycoside (eg, gentamicin) has been used to treat VSE endocarditis. Strains demonstrating high-level gentamicin resistance may be treated with vancomycin plus ceftriaxone or, alternatively, another antibiotic with bactericidal antienterococcal activity may be used (eg, daptomycin) (see Box 4) [32,109].

**Vancomycin: therapeutic alternatives**

The empiric therapeutic approach to central intravenous line–related infections has been discussed. Empiric therapy during the workup for

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Delayed resolution or failure of vancomycin therapy of MSSA or MRSA bacteremia and acute bacterial endocarditis</th>
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<tbody>
<tr>
<td><strong>Failure rates</strong></td>
<td><strong>Duration of bacteremia</strong></td>
</tr>
<tr>
<td><strong>MSSA bacteremia</strong></td>
<td>Nafcillin: 4%</td>
</tr>
<tr>
<td></td>
<td>Vancomycin: 20%</td>
</tr>
<tr>
<td><strong>MSSA acute bacterial endocarditis</strong></td>
<td>Nafcillin: 1.4%–26%</td>
</tr>
<tr>
<td></td>
<td>Vancomycin: 37%–50%</td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td><strong>MRSA acute bacterial endocarditis</strong></td>
<td>Nafcillin: Not applicable</td>
</tr>
</tbody>
</table>

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<tr>
<th>Table 3</th>
<th>Combination therapy for MSSA and MRSA acute bacterial endocarditis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antibiotic combinations</strong></td>
<td><strong>Comments</strong></td>
</tr>
<tr>
<td><strong>MSSA acute bacterial endocarditis</strong></td>
<td>Outcomes same without gentamicin</td>
</tr>
<tr>
<td>Nafcillin + gentamicin</td>
<td></td>
</tr>
<tr>
<td>Vancomycin + gentamicin</td>
<td></td>
</tr>
<tr>
<td><strong>MRSA acute bacterial endocarditis</strong></td>
<td>Duration of bacteremia: 7 days</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>Duration of bacteremia: 9 days (antagonistic; not synergistic)</td>
</tr>
<tr>
<td>Vancomycin + rifampin</td>
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</table>
ABE should consist of antistaphylococcal antibiotic that has a high degree of activity against the presumed pathogen, does not cause resistance, does not cause the emergence of other organism (eg, VRE), and has a good safety profile. In the treatment of MSSA bacteremias, vancomycin has been shown to be inferior to vancomycin in terms of delayed resolution of bacteremia. If MSSA is the pathogen in bacteremia or endocarditis, vancomycin should not be used as therapy in these patients and preferably another agent should be used. In penicillin-allergic patients, vancomycin is often used empirically to treat MSSA or MRSA bacteremias. However, there are many alternative antibiotics available that do not cross-react with penicillins or cephalosporins and that are effective to treat MSSA or MRSA bacteremias.

The treatment of MSSA or MRSA bacteremia is optimal with a single agent. Clinicians often assume there is benefit in adding a second drug for enhanced antistaphylococcal activity. It has been shown that vancomycin plus gentamicin offers no benefit in the treatment of MSSA bacteremias. Another common misconception is that the addition of rifampin or other drugs to vancomycin will enhance the antistaphylococcal activity of the primary anti-MSSA/MRSA agent. It has been shown the rifampin is likely to be antagonistic, not synergistic, against *S aureus* [110]. While rifampin has a high degree of in vitro activity against *S aureus*, rifampin monotherapy should not be used because of resistance. The practice of adding an aminoglycoside or rifampin to antistaphylococcal antibiotics has no benefit and may have a negative effect on outcomes (see Tables 2 and 3) [1,3–5,31,32,110].

In penicillin-allergic patients, the treatment of serious systemic infections due to MSSA (ie, CVC line infections, acute bacterial endocarditis, prosthetic valve endocarditis, and so on), may be treated with antibiotics other than vancomycin (ie, meropenem, TMP-SMX, daptomycin). As with MSSA, there are numerous therapeutic alternatives to vancomycin for the treatment of serious MRSA infections. Useful antibiotics to treat all MRSA types (HA-MRSA, CO-MRSA, CA-MRSA) include daptomycin, linezolid, tigecycline, and minocycline [1,32].

If possible, vancomycin should be avoided in therapy of most serious systemic infections due to MSSA/MRSA for two principal reasons. Prolonged vancomycin exposure selects out heteroresistant strains (hVISA). These strains are the ones that have thickened cell walls as the result of vancomycin exposure. Thickened cell walls are manifested as an increase in MICs and decreased cell-wall permeability to vancomycin as well as to other antibiotics. The other untoward side effect of vancomycin use is increased VRE prevalence [37–43].

In conclusion, vancomycin should be used selectively for the parenteral treatment of serious systemic infections due to MSSA, MRSA, or CoNS. Available therapeutic alternatives do not increase the prevalence of VRE and do not result in cell-wall thickening and permeability-mediated resistance. Alternative agents more quickly resolve MSSA/MRSA...
bacteremias than vancomycin. The addition of gentamicin or rifampin to vancomycin does not enhance antistaphylococcal activity and may have a negative effect (ie, antagonism) [47,98–100,111–117].

**Vancomycin: reassessment of use**

The main role of vancomycin has been in the therapy of serious systemic MRSA infections [1,118]. The widespread use of vancomycin over the years has resulted in increased prevalence of VRE in institutions worldwide. Recently, it has been shown that vancomycin induces cell-wall thickening among staphylococci, resulting in “permeability-mediated” resistance. To avoid these problems associated with vancomycin, it is preferable to use other anti-MRSA antibiotics in place of vancomycin. Fortunately, several other anti-MRSA agents are available. Antibiotics with excellent anti-MRSA activity include minocycline, linezolid, daptomycin, and tigecycline. Although vancomycin is available as an oral formulation for *C difficile* infections, it is ineffective to treat systemic infections. For the parenteral treatment of serious systemic MRSA infections, minocycline, daptomycin, and linezolid are effective alternative anti-MRSA antibiotics. For the oral therapy of MRSA, minocycline or linezolid may be used (Boxes 7 and 8) [1,32,119,120].

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**Box 7. Vancomycin: use in serious systemic infection**

**Clinical advantages**
- Extensive clinical experience
- Not nephrotoxic

**Clinical disadvantages**
- Adverse side effects
  - Red neck (red man) syndrome
  - Thrombocytopenia
  - Leukopenia
  - Sudden death
  - Increased VRE prevalence
  - Related to volume of intravenous (not oral) use
- *S. aureus* infections: delayed resolution, therapeutic failures
  - MSSA/MRSA bacteremias
  - MSSA/MRSA acute bacterial endocarditis
- *S. aureus* infections: permeability-mediated resistance (increased MICs)
  - Cell-wall thickening; decreased *S. aureus* penetration of antibiotics (vancomycin and other anti-*S. aureus* antibiotics)
- Not inexpensive
Box 8. Suboptimal uses of vancomycin

- Empiric treatment of central intravenous line infections
  - In locations where MSSA/GNBs > MRSA CVC pathogens
  - Remove intravenous line as soon as possible
- Therapy of MRSA bacteremia/acute bacterial endocarditis
  - Delayed clinical responses
  - Therapeutic failures
- Intraperitoneal therapy of *S. aureus*/CoNS CAPD peritonitis
  - Intravenous therapy achieves therapeutic concentration in ascitic fluid. Requires another antibiotic for anti-gram-negative bacillary coverage.
- Monotherapy of VSE
  - Bacteriostatic if monotherapy used.
  - Adequate anti-VSE activity only if given with an aminoglycoside (eg, gentamicin)
- *S. aureus* chronic osteomyelitis
- Prevention of *S. pneumoniae* CSF “seeding” (2° to CAP pneumococcal bacteremia)
  - Unnecessary when using antibiotics that achieve therapeutic CSF concentrations (eg, ceftriaxone)


For the therapy of gram-positive CNS infections, other agents are pharmacokinetically preferable to vancomycin. Linezolid, available orally and intravenously, achieves high CSF levels when given in the usual dose (ie, 600 mg intravenously or orally every 12 hours). Minocycline using the usual dose (100 mg intravenously or orally every 12 hours) also achieves therapeutic CSF levels. No data are available regarding treatment of CNS infections with or tigecycline [1,32].

In access catheter graft infections in chronic hemodialysis patients, daptomycin, linezolid, or tigecycline may be used. Vancomycin can be used to treat *S. viridans* subacute bacterial endocarditis in penicillin-allergic patients, but other agents are preferable to vancomycin for this use. Vancomycin monotherapy is “bacteriostatic” against VSE. Therefore, for VSE subacute bacterial endocarditis, an aminoglycoside should be added to vancomycin to achieve bactericidal anti-VSE activity alternate therapy for VSE subacute bacterial endocarditis (eg, meropenem, linezolid, or daptomycin) is available [3,32,119,120].

Aside from increased prevalence of VRE and increasing resistance among staphylococci, there are other reasons to avoid or minimize vancomycin use. Because vancomycin is an older drug, it is often thought of as an inexpensive
<table>
<thead>
<tr>
<th>Clinical uses</th>
<th>Disadvantages, problems</th>
<th>Therapeutic alternatives</th>
<th>Advantages of alternative antibiotics</th>
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<tbody>
<tr>
<td><strong>Monotherapy</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>• Central IV catheter (CVC) infections “that may be due to MRSA”</td>
<td>• Increased VRE prevalence</td>
<td>• Removal of CVC</td>
<td>• High-degree MRSA activity</td>
</tr>
<tr>
<td></td>
<td>• Increased permeability-mediated resistance</td>
<td>• Daptomycin (6 mg/kg IV every 24 hours)</td>
<td>• Also covers MSSA, VSE</td>
</tr>
<tr>
<td></td>
<td>• MIC “drift”</td>
<td>• Linezolid (600 mg IV every 12 hours)</td>
<td>• No increased resistance/VRE</td>
</tr>
<tr>
<td>• MRSA bacteremias, acute bacterial endocarditis</td>
<td>• Increased permeability-mediated resistance</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Delayed therapeutic response (persistent bacteremia)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• MIC “drift”</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• MRSA osteomyelitis</td>
<td>• Vancomycin: often delayed response with 30 mg/kg/d; better results with 60 mg/kg/d</td>
<td>• Linezolid (600 mg IV every 12 hours)</td>
<td>• Most rapidly bactericidal MRSA antibiotic</td>
</tr>
<tr>
<td></td>
<td>• Increased permeability-mediated resistance</td>
<td></td>
<td>• Effective in vancomycin “treatment failures”</td>
</tr>
<tr>
<td></td>
<td>• Increased MICs during therapy</td>
<td></td>
<td>• Also available orally for prolonged therapy</td>
</tr>
<tr>
<td></td>
<td>• MIC “drift”</td>
<td></td>
<td>• No increased resistance/VRE</td>
</tr>
<tr>
<td>• MRSA nosocomial and ventilator associated pneumonia (rare)</td>
<td>• Essential to avoid “covering” MSSA/MRSA respiratory secretion colonization</td>
<td>• Linezolid (600 mg IV/orally every 12 hours)</td>
<td>• Inexpensive and also available orally for prolonged therapy.</td>
</tr>
<tr>
<td></td>
<td>• Increases permeability-mediated resistance</td>
<td>• Minocycline (100 mgIV/orally every 12 hours)</td>
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<tr>
<td></td>
<td>• MIC “drift”</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• Effective in rare cases of bona fide MRSA nosocomial pneumonia and ventilator-associated pneumonia</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• Therapeutic parenchymal lung concentrations</td>
</tr>
</tbody>
</table>
### Combination Therapy

- **Vancomycin and ceftriaxone** to prevent “seeding” of CSF from bacteremic *S. pneumoniae* (PRSP) CAP
  - “Double drug” therapy unnecessary. Vancomycin: relatively low CSF concentrations
  - Ceftriaxone (1–2 g IV every 12 hours)
  - Good CSF penetration prevents PRSP “seeding” of CSF
  - Ceftriaxone monotherapy provides adequate CSF concentrations if PRSP seeding of CSF

- **Vancomycin plus gentamicin therapy** of *E. faecalis* (VSE) subacute bacterial endocarditis
  - Vancomycin alone “bacteriostatic” against VSE
  - Vancomycin bactericidal only when combined with an aminoglycoside (eg, gentamicin)
  - Vancomycin plus gentamicin therapy
  - Daptomycin (6 mg/kg IV every 24 hours)
  - MICs for VSE/VRE greater than those for MSSA/MRSA
  - Use 12 mg/kg IV every 24 hours for VSE endocarditis
  - Available orally for prolonged therapy of VSE subacute bacterial endocarditis
  - Bacteriostatic but effective in subacute bacterial endocarditis

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*Abbreviations: IV, intravenous; PRSP, penicillin-resistant *S. pneumoniae.*
antibiotic. However, because vancomycin must be administered intravenously, the cost of intravenous administration and monitoring must be added to the actual cost of vancomycin use. If serum vancomycin levels are used to guide therapy, the cost of such levels plus the cost of serial serum creatinine levels must also be included in the actual cost of administering parenteral vancomycin. For patients requiring long-term parenteral therapy with vancomycin, peripherally inserted central catheters (PICCs) are often used. The use of a PICC line to administer vancomycin increases antibiotic cost because other charges related to surgical insertion, radiological verification of PICC line placement, and the cost of home intravenous agencies must be added to vancomycin cost. While the cost of administering parenteral antibiotics via PICC lines for vancomycin is similar to that for other antibiotics, most infections for which vancomycin is administered parenterally may be treated equally effectively with oral linezolid which is much less expensive (see Boxes 4 and 5, Table 4).

Summary

The reassessment of vancomycin use today is based on an evaluation of the advantages and disadvantages of vancomycin alternatives for the therapy of MRSA. Other antibiotics exist as alternative therapy for VSE infections as well as for preventing the “seeding” of the CNS by penicillin-resistant \( S \) \( \text{pneumoniae} \) from bacteremic pneumococcal CAP. Clinicians should appreciate the limited role of vancomycin today in MRSA therapy. Clinicians should also realize vancomycin has limited activity against MSSA and VSE. Other antibiotics are preferable against MSSA and VSE. Presently, clinicians should consider alternatives to vancomycin because of the negative effects of vancomycin therapy (ie, increased VRE prevalence and increasing resistance among staphylococci), and also because better therapeutic alternatives are available with little or no resistance potential, no increase in VRE prevalence, better pharmacokinetics and lower cost (eg, linezolid) (see Box 6). For the reasons mentioned, clinicians should use vancomycin sparingly and consider other antibiotic alternatives for MSSA, MRSA, CoNS, and VSE infections [32,119,120].

References


