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PERSPECTIVES

# Approaching 65 Years: Is It Time to Consider Retirement of Vancomycin for Treating Methicillin-Resistant *Staphylococcus aureus* Endovascular Infections?

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Vancomycin was introduced nearly 65 years ago and remains the standard antibiotic for serious methicillin-resistant *Staphylococcus aureus* (MRSA) infections. *Staphylococcus aureus* remains highly susceptibility to vancomycin (>97%). Despite this, MRSA treatment failure with vancomycin is high in complicated bacteremia. Additionally, vancomycin can cause nephrotoxicity, leading to new therapeutic drug monitoring guidance. This demonstrates how difficult it is to dose vancomycin in a way that is both efficacious and safe, especially during long courses of therapy. Often underappreciated are the cost, resources, and complexity of vancomycin care at a time when alternative antibiotics are becoming cost comparable. This perspective highlights a bigger picture of how the treatment repertoires of many other diseases have changed and advanced since vancomycin's introduction in the 1950s, yet the vancomycin MRSA treatment standard remains. While vancomycin can still have a role, 65 years may be a practical retirement age for vancomycin in highly complex endovascular infections.

**Keywords.** bacteremia; efficacy; glycopeptide; MRSA; toxicity.

Vancomycin is an important antimicrobial for clinicians and patients throughout the healthcare continuum. However, physicians and pharmacists continue to grapple with many of its disadvantages that can be avoided with alternative antibiotics, most notably its dosing conundrums and toxicities. Introduced in 1958, vancomycin will celebrate its 65th birthday in 2023, widely considered a target retirement age for many working adults in the United States. Therefore, the time may be ripe to consider vancomycin's future role in the antibiotic repertoire; specifically in the context of today's complex patient with medical devices (eg, pacemakers, implantable cardioverter-defibrillator, prosthetic joints, indwelling ports/lines) and vancomycin's suboptimal performance in treating serious types of infection [1]. In this perspective, we highlight contemporary vancomycin practice issues surrounding efficacy, toxicity, cost, and complexity of care at a time when potentially more viable alternative antibiotics are becoming cost comparable.

## VANCOMYCIN EFFICACY

Vancomycin has been a workhorse antibiotic for decades as empiric and definitive treatment of serious, β-lactam–resistant gram-positive infections. For methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia and endocarditis, vancomycin represents 1 of the 2 accepted standards of care, along with daptomycin [2]. However, recent studies indicate that when given the choice between these 2 treatments against MRSA bacteremia, >96% of clinicians choose vancomycin [3]. It is remarkable that, despite being on the market for nearly 65 years, vancomycin "susceptibility" among *S aureus* remains stable, with a recent global surveillance estimate showing that nearly 97% of *S aureus* isolates are susceptible by the Clinical and Laboratory Standards Institute definition (minimum inhibitory concentration [MIC] ≤2 mg/L) [4]. Despite this, MRSA persistence and treatment failure with vancomycin are high in complicated bacteremia. Studies report approximately 5%–20% persistent bacteremia (>4 days duration) rates in patients treated with vancomycin, with high inoculum sources such as endocarditis associated with persistent bacteremia rates closer to 20% [5, 6]. Recent data have shown the relatively slow blood culture clearances of MRSA (eg, typically with vancomycin therapy), while others also note excess mortality associated with each day-by-day persistence of blood culture positivity [7, 8]. Source control remains key to antibiotic success and improved survival. As with most infections, any patients who fail initial antibiotic therapy will be at higher risk of treatment failure with alternative options. It is likely that many patients who fail vancomycin therapy despite a susceptible MIC will

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then go on to fail alternative anti-MRSA therapy.

In vitro and in vivo, vancomycin is established as a slowly bactericidal antibiotic, often only reaching bactericidal (>3 $\log_{10}$ colony-forming units/mL killing) threshold by 24–72 hours. However rapidly bactericidal antibiotics, such as β-lactams and daptomycin, achieve this activity within a few hours. Although the importance of bactericidal antibiotics has been debated [9], it is well established that patients with serious methicillin-susceptible *S aureus* (MSSA) infections should receive an antistaphylococcal β-lactam over vancomycin due to their superior efficacy [2]. This recommendation likely rests on the superiority of the β-lactam class over non-β-lactam antibiotics rather than the degree of in vitro bactericidal activity. Driven by favorable clinical data, nafcillin is universally preferred over vancomycin for serious MSSA infections despite being >20-fold higher in cost [10].

One of the most impactful antimicrobial stewardship interventions over the last few years has been de-labeling "penicillin allergies" in patients (either by the quality of the clinical history or via empiric oral challenge of a β-lactam such as single-dose amoxicillin) so they can receive β-lactam antibiotics for serious infections over inferior agents such as vancomycin [11, 12]. If we readily acknowledge avoiding vancomycin in favor of a more effective antibiotic for serious MSSA infection, why should we not also consider this direction in MRSA? To date, there has only been 1 randomized controlled trial (RCT) directly evaluating daptomycin for use in MRSA bacteremia (Table 1) [13]. This trial found daptomycin to be noninferior to the combination of vancomycin and gentamicin. Both treatment regimens in this study are now considered outdated by many, given that daptomycin 6 mg/kg monotherapy has been replaced by higher dose and combination regimens in practice. Furthermore, this RCT fell far short of capturing higher-risk patients with *S aureus* bacteremia where the medical need of advancing the status quo heavily lies. About 25% of enrolled subjects had catheter-related bacteremia, the lowest risk category, and definitive endocarditis was present in <20% of each study arm.

More recently, retrospective cohort studies using higher doses of daptomycin have demonstrated a reduction in 30-day mortality when using daptomycin over vancomycin (Table 1) [14–16]. Data supporting the use of ceftaroline in MRSA bacteremia are mostly limited to case series, and no direct comparison to vancomycin is available [17]. A recent retrospective cohort study, however, demonstrated similar clinical efficacy between daptomycin and ceftaroline in the treatment of MRSA bacteremia [18]. While ideally there would be RCTs supporting the use of vancomycin alternatives in MRSA bacteremia, the evidence provided by these retrospective studies is substantial.

Recent studies have provided some explanation about the discordance between vancomycin "susceptibility" in vitro and "resistance" in vivo driving clinical failure. Indeed, mutations have been detected in *S aureus* under vancomycin selective pressure that do not confer resistance using standard clinical microbiology laboratory media, but which compromise the activity of vancomycin in physiological media [19]. Antibiotic in vitro activity in physiological media has been shown to better predict activity in vivo compared to standard bacteriologic media [20].

### Vancomycin Nephrotoxicity

In addition to its questionable efficacy, we must consider the hazards associated with vancomycin therapy, specifically nephrotoxicity. There is large variation in reported vancomycin-associated acute kidney injury (AKI) rates, but studies frequently report rates in the range of 5%–35% [21–23]. Despite this high risk of kidney injury, the package insert contains only a brief mention of nephrotoxicity [24]. In contrast, aminoglycosides (which have a reported rate of nephrotoxicity around 25%) carry a Food and Drug Administration (FDA) black box warning [25]. It is unclear why 2 drugs with similar reported AKI rates do not carry similar warnings; however, a few factors may be considered. First,

**Table 1. Studies Comparing the Treatment Outcomes of Daptomycin Versus Vancomycin or Ceftaroline for Methicillin-Resistant *Staphylococcus aureus* Bacteremia[a]**

| Study | Design | No. of Patients | Treatment | Outcome |
|---|---|---|---|---|
| Zasowski et al, 2021 [18] | Retrospective cohort | 278 | DAP vs CPT[b] | 10.7% vs 14.5% 30-d all-cause mortality |
| Schweizer et al, 2021 [15] | Retrospective cohort | 108 | VAN vs switching to DAP[c] within 3 d | 17.4% vs 8.3% 30-d all-cause mortality |
| Claeys et al, 2016 [14] | Retrospective cohort | 262 | VAN vs DAP[d] | 15.3% vs 6.1% 30-d all-cause mortality |
| Murray et al, 2013 [16] | Retrospective cohort | 170 | VAN vs DAP[e] | 12.9% vs 3.5% 30-d mortality |
| Fowler et al, 2006 [13] | RCT | 124 | VAN + GEN vs DAP[f] | 10.8% vs 11.3% mortality at 42-d follow-up |

Abbreviation: CPT, ceftaroline; DAP, daptomycin; GEN, gentamicin; RCT, randomized controlled trial; VAN, vancomycin.

[a]Studies include only adult patients.

[b]Median DAP dose: 7.7 mg/kg total body weight (8.5 mg/kg adjusted body weight).

[c] Ninety-three percent of patients received DAP ≥5 mg/kg.

[d]Median DAP dose: 8.2 mg/kg total body weight.

[e]Median DAP dose: 8.4 mg/kg.

[f]DAP dose: 6 mg/kg.

vancomycin was FDA approved 25 years before the first aminoglycoside. It is likely that FDA labeling changed during that time and raises the question of what labeling would be required if vancomycin were approved today. In addition, the nephrotoxicity seen with vancomycin is likely exacerbated by the increase in use of other nephrotoxins. Piperacillin-tazobactam, aminoglycosides, loop diuretics, angiotensin-converting enzyme inhibitors, intravenous contrast, and vasopressors have all been shown to increase the risk of AKI when used concomitantly with vancomycin [22]. These medications were not utilized when vancomycin was initially approved, but now some are used frequently, especially within intensive care units where patients may already have tenuous kidney function.

While β-lactams are often considered one of the safest antimicrobial drug classes, concomitant use of some with vancomycin has been associated with nephrotoxicity. Based on available data, this toxicity risk appears to be linked to hydrophobic β-lactams (eg, nafcillin, piperacillin-tazobactam) with affinity to organic anion transporter 3 [26]. Replacement with alternative antibiotics such as hydrophilic β-lactams (eg, most cephalosporins, carbapenems, ampicillin) would mitigate the AKI risk when β-lactams are used in combination in empiric antimicrobial coverage [26].

To minimize the risk of nephrotoxicity, many institutions have abandoned vancomycin trough-based monitoring in favor of area under the concentration time curve (AUC)–based monitoring strategies, as now recommended by current guidelines [27]. The targeted pharmacokinetic/pharmacodynamic parameter with AUC-based monitoring is an AUC/MIC of 400–600, a threshold derived from a prospective study and concurred among some retrospective studies in MRSA bacteremia [21, 27]. While this exposure target is believed to confer a lower risk of treatment failure, higher vancomycin exposure leads to a higher rate of AKI. Hodiamont et al found that critically ill patients who achieved a vancomycin $AUC_{0\text{-}24}$ ≥400 mg × hour/L had a significantly higher risk of AKI (39.0% vs 14.8%; $P = .031$) compared to those who failed to meet this pharmacokinetic parameter [28]. Studies have also demonstrated that the risk of AKI increases with longer durations of vancomycin therapy [21, 22]. These results demonstrate how difficult it is to dose vancomycin in a way that is both efficacious and safe, especially when long courses of therapy are required. Other MRSA agents, like daptomycin and ceftaroline, are not associated with a high risk of AKI and should be considered safer options, especially when using for long-term therapy. Moreover, these 2 antibiotics do not require therapeutic drug monitoring.

## COST AND COMPLEXITY OF CARE OF VANCOMYCIN

At the beginning of the 21st century, recommending vancomycin as the standard of care for MRSA bacteremia made sense because alternative antibiotics were limited, vancomycin experience was extensive, its drug acquisition costs were minimal, and its narrow therapeutic window could be targeted using evolving drug monitoring strategies [29]. However, given antibiotic drug development, treatment experience, and changes in microbiology of *S aureus* over the last 20 years, the risk-benefit balance of vancomycin needs to be reassessed. The last 2 decades saw the emergence of MRSA infections in community settings to the point where MRSA exceeded MSSA infections. However, MRSA rates have fallen and the majority of *S aureus* bacteremia in the United States and European Union are now due to MSSA [30–32].

Additionally, and possibly due to the opioid epidemic and injection drug use, an increasing number of MRSA bacteremia patients are younger and severely ill with endocarditis, frequently with metastatic foci of infection [33, 34]. As discussed earlier, vancomycin is a poor antibiotic choice for these types of infections, with clear dosing strategies muddled by dynamic renal function and by potential augmented renal clearance of acute illness. Recent guidance recommends vancomycin AUC-based monitoring, adding a level of care complexity under the auspices of safety rather than efficacy [27, 35]. Injection drug users often have dynamic organ function, including augmented vancomycin clearance making vancomycin serum level target attainment challenging, if not impossible [36]. Vancomycin alternatives historically shunned due to high cost, such as daptomycin, ceftaroline (although off-label), and various antibiotic combinations, have promising effectiveness requiring further study validation for MRSA bacteremia without the associated drug monitoring and renal hazards associated with vancomycin therapy [37]. In combination with source control, it is prudent to consider high-dose daptomycin (eg, 8–10 mg/kg) for patients with MRSA bacteremia secondary to injection drug use, and likely all patients with MRSA bacteremia [14, 16, 17, 38–41]. A possible exception includes those with uncomplicated MRSA bacteremia (low inoculum, catheter-related MRSA bacteremia patients who defervesce quickly following source control without repeat positive blood cultures) [37, 42]. When treating a 75-kg patient with preserved renal function for MRSA bacteremia today, the cost balance between vancomycin and daptomycin actually tips in favor of daptomycin (Table 2). In fact, we were surprised to find that the wholesale drug costs are not much different today: $4.16/day vs $30.15/day for vancomycin and daptomycin, respectively. If utilizing 2-level AUC determinations, the cost of daptomycin is even more favorable, although some have demonstrated that the laboratory costs of AUC and trough-based monitoring are not appreciably different [43]. This assessment does not even account for the proportion of patients who will develop AKI (21%) despite even the best AUC monitoring

**Table 2. Vancomycin and Daptomycin Cost Comparison for a 75-kg Adult With Methicillin-Resistant *Staphylococcus aureus* Bacteremia**

| Drug/Intervention | Item Cost | Item Frequency | Duration of Therapy | | |
|---|---|---|---|---|---|
| | | | 14 Days | 28 Days | 42 Days |
| VAN 1 g | $1.94[a] | 2 g load, then 1 g twice daily | $56.26 | $110.58 | $164.90 |
| VAN serum level monitoring, trough only [43] | $141[b] | Three times every 2 wk (conservative) | $423 | $846 | $1692 |
| VAN serum level monitoring, 2-level AUC [43] | $141[b] | Three times every 2 wk (conservative) | $846 | $1692 | $3384 |
| Pharmacist coordinating, interpreting, and documenting TDM, trough only | $60/h | 15 min, $15 × 3 | $45 | $90 | $135 |
| Pharmacist coordinating, interpreting, and documenting TDM, 2-level AUC[c] | $60/h | 20 min[d], $20 × 3 | $60 | $120 | $180 |
| Total cost[e] of vancomycin (range based on PK monitoring strategy) | | | $524–$962 | $1045–$1923 | $1992–$3729 |
| Daptomycin 500 mg | $25.31[a] | 600 mg (~8 mg/kg) once daily[f] | $425.20 | $850.42 | $1275.62 |
| Total cost[e] of daptomycin | | | $425 | $850 | $1276 |

Estimates for drug costs are based on actual wholesale price due to variability in patient/third-party payer costs.

Abbreviations: AUC, area under the curve; PK, pharmacokinetic; TDM, therapeutic drug monitoring; VAN, vancomycin.

[a]Average average wholesale price from 2 institutions.

[b]Average laboratory cost from 2 institutions.

[c]AUC can be estimated using a single level with Bayesian software. The cost of purchasing and deploying such software is variable and beyond the scope of this cost analysis.

[d]Twenty minutes instead of 15 minutes used because of time needed to coordinate the second level.

[e]Rounded to the nearest dollar.

[f] Based on 75 kg patient weight.

efforts, which comes at a substantial cost to the patient and hospital [21, 44].

## THE INTANGIBLES

While we have outlined some key issues with vancomycin use that suggest alternative antibiotics may be better suited for treating severe MRSA infections, a bigger picture reflection at how the treatment repertoires of our colleagues in other specialties have changed since the 1950s may offer a different perspective on the situation with vancomycin. Other than aspirin and some opiates, which have been around since the antiquity of medicine, how many other prescription drugs from the 1950s are still in use today? Take, for example, hypertension, the most common comorbidity in the United States. How many patients do we see on hydralazine, reserpine, chlorothiazide, or guanethidine? While derivatives of the diuretic chlorothiazide are still in use, they are deployed for the simplest-to-manage cases of hypertension [45]. We should examine our patient medication list from time to time and consider how many of the medications still warrant clinical use. Even more recently, our patients with human immunodeficiency virus rarely see zidovudine in their antiretroviral therapy cocktails. Yet, when presenting with MRSA bacteremia, with endocarditis or some other confirmed life-threating endovascular infection—a disease where one-quarter of patients die—we approach our patients with a medication from the era of hydralazine and reserpine. Even nafcillin, the traditional standard treatment for invasive MSSA since the 1970s, is now questioned for replacement by many in favor of cefazolin due to its similar efficacy and improved safety profile [46]. It would be understood if some of us sense a bit of embarrassment in such cases, knowing what we have available, what our colleagues in other subspecialties are prescribing, and knowing deep down that we can do better. Those who cite registrational trials showing newer drugs like daptomycin or ceftaroline to be noninferior to vancomycin as a justification that we have yet to show there are better treatments are off target. Such trials lack the robustness or granularity to detect differences in drugs in a way analogous to assessing differences in cardiovascular fitness by walking a city block on level ground. It is evident better and bolder trials of MRSA bacteremia treatments are needed. Until then, the available data, while limited in scope and quality of evidence, suggest that alternatives to vancomycin for MRSA bacteremia are preferable, under the auspices of safety and, likely, effectiveness.

## CONCLUSIONS

Infectious diseases are dynamic through emergence of novel organisms and in evolution of well-established pathogens in host interactions and resistance to treatments. Indeed, these factors have been at the center of the world stage for the last 2 years. Our success in treating infectious diseases rests on keeping pace with better therapies and prevention. Vancomycin has served us well for decades. Its durability, low rates of vancomycin "resistance" defined microbiologically, and low costs may have lulled us into a state of complacency. Clear signals have emerged that we can do better for some patients using antibiotics introduced in the last 20 years. We should continue to call for

bolder, high-quality RCTs of vancomycin alternatives in high-risk MRSA bacteremia patients (ie, endovascular sources). However, alternatives to vancomycin may be helpful not only in improving outcomes in endovascular MRSA infections, but also in streamlining care of less complex acute bacterial skin and skin structure infections and pneumonia. While vancomycin can still have a role, 65 years may mark not only a traditional, but also a practical retirement age for vancomycin in highly complex endovascular infections.

## Notes

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