Vancomycin: A History

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Vancomycin became available for clinical use >50 years ago but was soon discarded in favor of other antibiotics that were deemed to be more efficacious and less toxic. The advent of pseudomembranous enterocolitis, coupled with the spread of methicillin-resistant *Staphylococcus aureus*, led to a resurgence in the use of vancomycin. Almost immediately, concerns arose with regard to its therapeutic utility. In addition, resistance to vancomycin developed, first in enterococci and later in staphylococci. Several types of resistance have now been identified, each with a unique effect on infections treated with vancomycin. Recent studies have rekindled interest in the best way to administer the antibiotic. The findings of future studies may result in a return to measuring levels of vancomycin in serum, to assure a successful therapeutic outcome.

There is greater interest in vancomycin now, 50 years after its discovery, than at any time in its history. Recently published articles about vancomycin reflect parallel increases in both the use of vancomycin and our knowledge about this interesting antibiotic (figure 1). A historical review puts this into perspective. In the 1950s, with few options available to treat penicillin-resistant staphylococcal infections, Eli Lilly and Company initiated a program aimed at discovering antibiotics with activity against these pathogens. In 1952, a missionary in Borneo sent a sample of dirt to his friend Dr. E. C. Kornfield, an organic chemist at Eli Lilly. An organism isolated from that sample (*Streptomyces orientalis*) produced a substance (“compound 05865”) that was active against most gram-positive organisms, including penicillin-resistant staphylococci [1]. Some anaerobic organisms, including clostridia, were also susceptible to compound 05865 [2], as was *Neisseria gonorrhoeae* [3]. In vitro experiments were initiated to determine whether the activity of compound 05865 would be preserved despite attempts to induce resistance. After 20 serial passages of staphylococci from Eli Lilly laboratories, resistance to penicillin increased 100,000-fold, compared with only a 4–8-fold increase in resistance to compound 05865 [4]. Isolates from other laboratories were also tested, and the results were similar [5, 6]. Subsequent animal experiments suggested that compound 05865 might be safe and effective in humans. However, before clinical trials were begun, the compound, dubbed “Mississippi mud” because of its brown color, needed to be purified. A switch from picric acid precipitation to passage over an ion-exchange resin was an improvement, and the resulting drug, which was named “vancomycin” (from the word “vanquish”), was made available for clinical trials.

In studies of volunteers, vancomycin reached therapeutic concentrations in various tissue compartments and resulted in successful treatment of serious staphylococcal infection in 8 of 9 patients, including 1 patient with endocarditis. The sole therapeutic failure occurred in a patient with empyema, in whom an adequate concentration could not be achieved in the empyema pocket [2]. Six patients with endocarditis who had experienced prior therapy failure with other antibiotics were also treated with vancomycin; 5 patients were cured. The therapy failure occurred in a patient who was admitted to the hospital with multiple complications, including shock and intractable heart failure, and who died after receiving treatment for 5 days [7]. As information about vancomycin spread, it was requested for cases for which other drugs had failed. Emergency shipments were made around the clock. Extra supplies at one hospital were shipped to another, if needed. Ultimately, reports of successful treatment were organized and submitted to the US Food and Drug Ad-
ministration, and, in 1958, in the absence of an effective alternative, vancomycin was immediately approved [1]. Later published studies confirmed the efficacy of the drug [8, 9]. However, methicillin, the first semisynthetic penicillin, was also approved in 1958, followed shortly thereafter by cephalothin. Because of perceived toxicity, vancomycin became reserved for patients with serious β-lactam allergies or patients with infections caused by organisms that were resistant to the newer agents.

TOXICITY

In the initial trials, little toxicity was observed in association with vancomycin use. Venous irritation, chills, and rash were reported but were considered to be infusion related. Ototoxicity was observed, usually presenting as tinnitus, but was attributed to elevated serum concentrations found in patients with renal failure. These problems occurred more frequently in association with the use of early preparations of vancomycin and were considered to be the result of impurities in the compound. Reports of ototoxicity described patients who were also receiving known ototoxic drugs. Traber and I [10] reported the acute onset of tinnitus and documented hearing loss 7 days after beginning therapy with vancomycin for a patient who was receiving no other ototoxic drugs. His peak serum vancomycin concentration was 49.2 μg/mL, and an audiogram revealed a profound high-frequency sensorineural hearing loss that slowly improved, despite continued treatment with vancomycin at a lower dose [10]. Nevertheless, subsequent studies indicated that vancomycin-induced ototoxicity was an infrequent occurrence [11, 12]. Infusion-related chills seemed to be eliminated by use of the purified commercial product, and skin rash, which was described in early reports, has not been a persistent problem [7]. In a retrospective analysis of patients receiving vancomycin between 1974 and 1981, auditory toxicity was not seen. Fever and rash were uncommon (1%–3% of patients). Phlebitis affected 13% of patients and necessitated discontinuation of therapy for 2% of patients. Nephrotoxicity was infrequent (5% of patients) and reversible, but it possibly was potentiated by concomitant aminoglycoside therapy. Neutropenia occurred in 2% of patients but was rapidly reversible [13]. Thrombocytopenia associated with the use of vancomycin has been studied [14, 15], as has the nephrotoxic potential of vancomycin [16–18]. Vancomycin rarely causes interstitial nephritis [16], and the combination of vancomycin and aminoglycosides has been reported to cause renal failure, especially in adults who are receiving prolonged therapy and whose trough serum vancomycin concentrations are >10 μg/mL [17, 18]. Notably, the combination does not appear to cause nephrotoxicity in children [19, 20].

Rapid infusion of vancomycin has been associated with the “red man,” or “red neck,” syndrome. This syndrome, which is characterized by a combination of erythema, pruritis, hypotension, and angioedema, is a histamine-like response to rapid infusion, but was not a feature of early reports. Rybak et al. [21] compared the incidence of red man syndrome in patients taking either vancomycin or teicoplanin (a glycopeptide antibiotic with an antimicrobial spectrum similar to that of vancomycin) with the incidence of red man syndrome in healthy control subjects given vancomycin or placebo. For both patients and control subjects, vancomycin infusions lasted 60 min and were administered via infusion pumps with identical tubing. Nine of 10 control subjects who received vancomycin experienced symptoms, versus none of the patients who received either vancomycin or teicoplanin (P<.001) [21]. Interestingly,
there was no difference in serum histamine levels between patients and control subjects, which could be explained only by the hypothesis that infection blunts the effect of glycopeptides. No matter how much toxicity is truly related to vancomycin, many researchers were convinced that problems could be avoided by careful monitoring of serum concentrations.

**MONITORING**

Measuring vancomycin levels in serum might be helpful to prevent toxicity and to assure an adequate therapeutic drug concentration. However, there are no definitive studies relating serum concentrations of vancomycin to treatment outcome. Indeed, the standard regimens of 500 mg of vancomycin every 6 h or 1 g of vancomycin every 12 h appear to have been arbitrary. However, many clinicians preferred to know whether the regimen they prescribed achieved an expected serum concentration, especially if dosage adjustments were necessitated by renal failure. Thus, to assure a desired concentration without actually measuring serum levels, several investigators constructed nomograms, several of which became popular [22, 23]. Other investigators compared individualized dosing based on the actual serum concentration with dosing based on data from nomograms and found the individualized method to be superior [24, 25]. However, by 1994, without data to support either a therapeutic or a toxic range, Cantu et al. [26] questioned the value of monitoring serum concentrations of vancomycin. Moeller [27] agreed but recommended monitoring of serum levels in certain situations—for example, when patients receive vancomycin/aminoglycoside combinations, when anephric patients undergoing hemodialysis receive infrequent doses of vancomycin, and when patients receive higher-than-usual doses of vancomycin. With no clear consensus, many clinicians chose to dose according to nomogram data, whereas others measured serum concentrations in every case. Currently, the issue is being reconsidered, as will be discussed later in this article.

**CLINICAL USE**

As noted above, shortly after being introduced, vancomycin was eclipsed by antibiotics that were considered to be less toxic and equally or more efficacious. Beginning in the early 1980s, a dramatic increase in vancomycin use occurred, with a 100-fold increase occurring over the next 2 decades [28] (figure 2). Two events were primarily responsible for this dramatic resurgence. The first was the advent of pseudomembranous enterocolitis. Prior to its release, vancomycin was used to treat an entity called “postoperative micrococal colitis” [2]. The response to vancomycin was excellent, and the presence of this disease, also called “acute staphylococcal ileocolitis,” became an indication for the use of vancomycin [29]. Although *Clostridium difficile* is the primary agent of pseudomembranous enterocolitis, *Staphylococcus aureus* is clearly an occasional cause of the disorder [30]. Because vancomycin is active against both pathogens and is poorly absorbed from the intestinal tract, it became the drug of choice for treating pseudomembranous enterocolitis [31]. However, widespread vancomycin use, especially via the oral route, was responsible, at least in part, for the development of vancomycin-resistant enterococci (VRE) (discussed below) [32]. With the recent interest in intracolonic administration of vancomycin, VRE will likely remain a growing problem [33, 34].

The second event leading to increased vancomycin use was the widespread appearance of resistant pathogens: first, methicillin-resistant *S. aureus* (MRSA), and, then, penicillin-resistant *Streptococcus pneumoniae*. Known for decades as a cause of
nosocomial infection [35], MRSA appeared suddenly in community isolates in Detroit and, later, throughout the world [36–38]. With its predictable activity against MRSA, vancomycin was the drug of choice, thus beginning a new era in the history of the antibiotic.

In 1982, Sorrell et al. [39] described 19 patients with MRSA infection, including 10 with bacteremia. Vancomycin was equally as effective against MRSA as standard therapy was against methicillin-susceptible S. aureus, but the results may have been influenced by adjunctive therapy with aminoglycosides, rifampin, or trimethoprim-sulfamethoxazole. In addition, although patients had peak and trough vancomycin levels, which conformed to previously recommended ranges (18.0–47.0 μg/mL and 4.8–12.9 μg/mL, respectively), tinnitus, rash, neutropenia, and possible nephrotoxicity were observed. At the same time, my colleagues and I described 24 patients with infective endocarditis due to MRSA infection [40]. Most patients received other antibiotics in addition to vancomycin, so the mean duration of bacteremia (9.2 days) must be interpreted in that light. One patient, the index case patient, remained bacteremic for 68 days without vancomycin therapy before undergoing tricuspid valve excision. Prior to surgery, she was given a variety of different regimens, and, each time, she appeared to respond initially. Therapy with vancomycin would have been started sooner, but the treating physician was reluctant to use it because of concerns about toxicity.

With the increased use of vancomycin came data suggesting that vancomycin might not be equivalent to β-lactams. For example, some patients with septic thrombophlebitis had persistent bacteremia, despite receiving treatment with heparin and vancomycin. It was found that heparin causes vancomycin to precipitate when administered through the same tubing, leading to subtherapeutic concentrations of vancomycin [41]. Small and Chambers [42] studied S. aureus isolates recovered from patients who experienced failure of vancomycin therapy and found that, compared with nafcillin, vancomycin resulted in delayed bacterial eradication in vitro.

In an effort to address the question of the efficacy of vancomycin, my colleagues and I studied patients with endocarditis due to MRSA. We planned to compare vancomycin monotherapy with combination therapy involving vancomycin plus either rifampin or gentamicin. However, clinicians were reluctant to participate, fearing that the vancomycin-gentamicin combination would prove to be too toxic. Thus, the final study consisted of only 2 treatment arms: vancomycin monotherapy or vancomycin plus rifampin [43]. Vancomycin monotherapy resulted in prolonged bacteremia (9.0 days), which is consistent with the results of our previous report but nearly 3 times as long as the duration observed with nafcillin therapy [44]. Of equal importance, 6 (14%) of 43 patients experienced therapy failure; 3 died, and 3 required valve replacement or excision. Surprisingly, patients receiving vancomycin plus rifampin remained bacteremic longer than did those receiving vancomycin alone, although the data were not statistically significant. In studies of coagulase-negative staphylococci, vancomycin and rifampin are usually synergistic in vitro [45, 46]. The combination is less predictable against S. aureus, and antagonism has been reported [47, 48]. Whether antagonism played a role in our study is unknown. In a search for better alternatives, Markowitz et al. [49] found vancomycin to be superior to trimethoprim-sulfamethoxazole in treating patients infected with either MRSA or methicillin-susceptible S. aureus, although the main difference was in patients infected with methicillin-susceptible S. aureus.

The emergence of penicillin-resistant S. pneumoniae presented new therapeutic challenges, especially for the treatment of meningitis. Vancomycin was well-established therapy for shunt-related meningitis, but there always was concern about its penetration across the blood-brain barrier. Because penicillin-resistant S. pneumoniae may also be cephalosporin resistant, vancomycin plus a third-generation cephalosporin is the standard initial empirical regimen for known or suspected cases of pneumococcal meningitis. Studies show variable penetration in adults, but results are favorable if high doses of vancomycin are used. However, concomitant steroid therapy, which is also standard for acute meningitis in adults, may prevent adequate vancomycin levels in CSF. In pediatric patients, the combination of vancomycin plus steroids does not appear to be harmful [50].

**RESISTANCE AND ITS IMPACT**

With the accelerated use of vancomycin that began in the 1980s, it was inevitable that resistance would occur. VRE were reported in Europe by 1986 and in the United States by 1987 [51]. Six resistance patterns (designated “VanA” through “VanE,” and, most recently, “VanG”) have been reported [52, 53]. VanA-type strains are inducibly resistant to high levels of vancomycin (MIC, ≥64 μg/mL) and teicoplanin (MIC, ≥16 μg/mL). VanB-type strains are also inducibly resistant to vancomycin (MIC, 4 to >1024 μg/mL) but retain susceptibility to teicoplanin [54]. VanC, which is found in Enterococcus casseliflavus/Enterococcus flavescens and Enterococcus gallinarum, is constitutive and confers low-level resistance to vancomycin (MIC, 4–32 μg/mL) but not to teicoplanin [55]. VanD is also constitutive and has been found in only a few isolates [55]. Like the Van A, VanB, and VanD types, the VanE type appears to be acquired and also confers low-level resistance to vancomycin only (MIC, 16 μg/mL), as does VanG (MIC, 12–16 μg/mL). Multiple genes are responsible for these different phenotypes, but they produce resistance by only one or the other of 2 common pathways. The target for vancomycin is the terminal D-alanyl-D-alanine of the growing peptidoglycan chain. In vancomycin-resistant organisms, these peptidoglycan intermediates are altered to either D-alanyl-D-lactate (VanA,
VanB, and VanD) or d-alanyl-d-serine (VanC, VanE, and VanG). These altered targets have reduced affinity for vancomycin, resulting in much higher MICs.

Depardieu et al. [52] contributed much to the understanding of resistance to vancomycin and helped to characterize the clinical significance of each glycopeptide-resistant phenotype. Using a strain of VanB-resistant Enterococcus faecalis, Aslangul et al. [54] were able to prevent the emergence of resistance by combining teicoplanin with gentamicin; monotherapy with either vancomycin or teicoplanin induced resistance. Later experiments with a VanB isolate proved that a 2-step mechanism is required for the development of resistance to the combination of teicoplanin and gentamicin [56]. VanE strains responded to high doses of glycopeptides, whereas standard doses led to treatment failure in the rabbit model of endocarditis. Notably, because such strains may be indistinguishable from other types of resistant enterococci in clinical practice, Lafaurie et al. [57] recommended the routine use of combination therapy with gentamicin. Finally, Lefort et al. [58] found VanD strains to be affected by a significant inoculum effect. Detection of such strains is important, because standard doses of vancomycin or teicoplanin might result in mutants with high-level glycopeptide resistance in infections with high bacterial density.

Perhaps the greatest concern about VRE is the potential for resistance to spread from enterococci to other pathogens, in particular to S. aureus. Enterococci possess several systems, including plasmids and transposons, that enable the transfer of genetic material to other bacteria. Although the transfer of resistance from enterococci to S. aureus was demonstrated in vitro in 1992 [59], some researchers questioned whether it could occur in natural conditions. Intermediate resistance to vancomycin had already been reported among staphylococci, but it was not caused by transfer of genetic material from enterococci. The first staphylococcal strain with reduced susceptibility to vancomycin were reported from Japan in 1997 [60, 61]. VanE strains reportedly responded to high doses of glycopeptides, whereas standard doses led to treatment failure in the rabbit model of endocarditis. Notably, because such strains may be indistinguishable from other types of resistant enterococci in clinical practice, Lafaurie et al. [57] recommended the routine use of combination therapy with gentamicin. Finally, Lefort et al. [58] found VanD strains to be affected by a significant inoculum effect. Detection of such strains is important, because standard doses of vancomycin or teicoplanin might result in mutants with high-level glycopeptide resistance in infections with high bacterial density.

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from a foot lesion; this is a noteworthy fact because, by this time, Enterococcus faecium had largely supplanted E. faecalis as the predominant species found in hospital settings. It appears that the staphylococcus acquired the VanA gene from the VRE [77, 78]. A second VRSA strain was soon isolated from a patient in Pennsylvania, who also had received intermittent courses of vancomycin, but none during the 5 years prior to developing VRSA infection [79]. She was colonized with VRE and MRSA, both of which were isolated on multiple occasions. As in the Michigan case, it appears that the MRSA acquired VanA from the VRE, even though the patient was not being treated with vancomycin at the time [80, 81].

In April 2004, a third VRSA strain (vancomycin MIC, 64 μg/mL) was isolated from a patient in New York [82]. This strain was found to be vancomycin susceptible, as determined by standard automated antimicrobial susceptibility testing. The observation that automated techniques might misinterpret antibiotic susceptibility among staphylococci prompted the Centers for Disease Control and Prevention to publish new guidelines for laboratory testing of S. aureus isolates [83].

As we advance further into the era of vancomycin resistance, it is important to recall that failure of vancomycin therapy may still occur in infections due to susceptible organisms. Fowler, Jr. et al. [84] found vancomycin therapy to be an independent risk factor for recurrent S. aureus bacteremia, and, in another study, vancomycin treatment was cited as a potential reason for increased mortality among patients with MRSA infection [85]. Recent evidence suggests that outcomes might be determined by even slight differences in the MIC. In a recent study by Fowler, Jr. et al. [76], patients with bacteremia due to MRSA with an MIC of ≤0.05 μg/mL had a 55.6% success rate, compared with a 9.5% success rate among patients whose bacteremia was due to MRSA with an MIC of 1–2 μg/mL (P = .03). Such a result might be avoided if there were reliable data indicating what serum vancomycin level predicts therapeutic success (i.e., the therapeutic concentration). Knowledge of the therapeutic concentration and the MIC of the pathogen might overcome the intrinsic deficiencies of the drug and improve its utility. As an example, the serum vancomycin level was noted to play a role in the treatment of pneumonia. Penetration of vancomycin into lung tissue is poor [86], resulting in therapeutic failure in patients with pneumonia [87]. However, when the serum concentration was maintained at a level sufficiently above the MIC of the infecting organism, the outcome was significantly improved. Moise et al. [88] showed that 78% of the patients being treated for pneumonia who achieved an area under the inhibition curve of >345 survived, versus 24% of the patients with an area under the inhibition curve of ≤345. Future studies must address whether specific therapeutic ranges can be determined for different types of infections. A return to monitoring serum levels, a practice almost abandoned long ago, might be required, but it might also extend the useful life of this antibiotic. After 50 years, we are learning more about vancomycin than ever before, and this knowledge may lead us to a much more successful approach to patient care. Even after 50 years, there is still much to add to the history of vancomycin.

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References


