Vancomycin is often combined with a second antibiotic, most often rifampin or gentamicin, for the treatment of serious methicillin-resistant Staphylococcus aureus infections. Published data from experiments evaluating these and other vancomycin-based combinations, both in vitro and in animal models of infection, often yield inconsistent results, however. More importantly, no data are available from randomized clinical trials to support their use, and some regimens are known to have potential toxicities. Clinicians should carefully reconsider the use of vancomycin-based combination therapies for the treatment of infection due to methicillin-resistant S. aureus.

Vancomycin is often combined with other antibiotics for the treatment of serious infection due to Staphylococcus aureus, a practice that emerged largely in response to the recognition of important shortcomings of this glycopeptide antibiotic. These shortcomings include poor tissue and intracellular penetration, lack of activity against organisms growing in biofilm, slow bactericidal effect, lack of interference with toxin production, and lack of activity against some S. aureus isolates, including heteroresistant and vancomycin-intermediate S. aureus (VISA) strains [1, 2]. The practice of combination antistaphylococcal therapy, however, deserves close examination.

THEORETICAL BASIS FOR COMBINATION THERAPY WITH VANCOMYCIN FOR S. AUREUS INFECTION

Theoretical reasons for the use of antibiotics in combination with vancomycin for the treatment of serious methicillin-resistant S. aureus (MRSA) infection include the following:

- To broaden coverage to include VISA and heteroresistant VISA and to improve activity against isolates with a minimum inhibitory concentration (MIC) at or approaching the breakpoint for susceptibility
- To prevent the emergence of reduced susceptibility to vancomycin
- To achieve bactericidal synergy
- To provide activity against stationary-phase organisms and organisms growing in biofilm
- To penetrate cells and tissues not reached by vancomycin
- To inhibit toxin production

These theoretical reasons are analyzed in detail below.

Broadening the spectrum of antistaphylococcal activity. Vancomycin therapy is often initiated in patients with suspected staphylococcal bacteremia to provide antibacterial activity against both methicillin-susceptible S. aureus (MSSA) and MRSA. Evidence indicates, however, that vancomycin monotherapy is inferior to β-lactam therapy for the treatment of MSSA bloodstream infection and endocarditis [3–5]. Furthermore, the strategy of switching from vancomycin to a β-lactam when methicillin susceptibility is identified does not ap-
PEAR to overcome this deficit [5]. These observations suggest that a possibly superior approach to the initial empirical treatment of patients with sepsis known or highly suspected to be due to *S. aureus* is the administration of vancomycin together with a cephalosporin or, preferably, a semisynthetic penicillin, followed by the discontinuation of the glycopeptide or the β-lactam when susceptibility data becomes available.

Infections with strains of MRSA that have elevated vancomycin MICs within the range considered susceptible (eg, 2.0 μg/mL) and with strains exhibiting heteroresistance appear to be risk factors for the failure of vancomycin therapy [6–8]. The coadministration of other antibiotics with MRSA activity could potentially provide broader coverage to include these more-recalcitrant strains. This strategy could, however, be defeated if the second agent has a low threshold for the development of resistance, as is the case with rifampin [9].

**Enhancing antibacterial activity.** Vancomycin is subject to an inoculum effect [10] and is poorly active against organisms in the stationary-growth phase [11] as well as against organisms growing in biofilm [12]. The weak bactericidal activity (tolerance) of vancomycin against some MRSA is associated with reduced therapeutic efficacy [13]. Coadministration of certain antibiotics may help overcome some of these deficiencies by, for example, having more-favorable activity against biofilm colonies [12].

**Preventing the emergence of strains with reduced susceptibility to vancomycin.** Prolonged exposure, both in vitro and in vivo, to vancomycin may lead to the emergence of reduced susceptibility to this glycopeptide antibiotic [14–16]. The addition of a second antibiotic that is rapidly bactericidal and that has a high threshold for the development of resistance could narrow the mutant-selection window [17] and has the potential to prevent the emergence of reduced susceptibility to vancomycin.

**Enhancing tissue and intracellular penetration.** Vancomycin penetration into a number of compartments, including the lungs [18, 19], subcutaneous tissue [20], cortical bone [21], and cerebrospinal fluid [22], is limited, as is its intracellular activity [23]. Coadministration of drugs with more-favorable penetrative characteristics, such as rifampin [23], may have the potential to overcome these deficiencies.

**Reducing staphylococcal toxin production.** Production of at least some toxins is reported to be increased by β-lactam antibiotics and to be diminished by clindamycin and linezolid, whereas vancomycin has no significant effect [24, 25]. These findings have led to suggestions that a toxin-inhibiting antibiotic be added to vancomycin for the treatment of selected infections.

**Empirical basis for some combination therapies with vancomycin for *S. aureus* infection**

**Vancomycin plus rifampin.** Rifampin has a number of characteristics that make it potentially effective when used in combination with vancomycin, including its potent bactericidal activity [26], modest activity against nongrowing cells [27], and ability to penetrate cells [28, 29] and a variety of tissues and compartments, such as bone [30] and cerebrospinal fluid [31]. Rifampin is reported to enhance the activity of vancomycin against *S. aureus* in biofilm [12, 32] and against *S. aureus* that have been ingested by polymorphonuclear leukocytes [23]. In addition, subinhibitory concentrations of rifampin inhibit PVL production by *S. aureus* [24].

Evaluation of the antistaphylococcal activity of the combination of rifampin and vancomycin in vitro is dependent on methodology [33–35]. Separate studies have concluded that both synergy [26] and antagonism [36] represent their dominant interaction against *S. aureus*, but a recent extensive review examining published studies concluded that in vitro studies most often demonstrated indifference [34]. A number of studies, however, have found vancomycin and rifampin to be synergistic against MRSA growing in biofilm [37].

The effect of methodology is illustrated by the finding that the combination of vancomycin and rifampin is more effective than either agent alone in the treatment of experimental endocarditis in a rabbit model of MRSA infection caused by a strain for which antagonism had been demonstrated by the checkerboard method, whereas synergy was observed by time-kill analysis [34]. In a rabbit model of endocarditis, the addition of rifampin did not significantly reduce the bacterial load in heart valves but did significantly reduce bacterial density in several organs [38]. Other investigators have also failed to identify a benefit from the addition of rifampin to vancomycin in the treatment of experimental MRSA endocarditis [39]. In an experimental model of osteomyelitis due to MRSA, rifampin alone was as effective as the combination of rifampin and vancomycin, and the combination did not reliably prevent the emergence of resistance to rifampin [40], an observation that could be predicted from in vitro results [41]. Rifampin resistance, however, may not be all bad, because the associated rpoB mutations cause reduced fitness of *S. aureus* [42]. A recent review concluded that experiments in animal models suggested that the addition of rifampin to vancomycin in the treatment of endocarditis or meningitis had no benefit, whereas there was a possible benefit for osteomyelitis and an apparent benefit for abscesses [35].

In contrast to the large number of preclinical studies, there is only a single published randomized clinical trial examining the efficacy of the combination of vancomycin and rifampin. In that study, 42 patients with native-valve MRSA endocarditis

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(right-sided in 34) were treated with vancomycin and were randomized to also receive either rifampin or no additional antibiotic [43]. Although there was no difference in clinical outcomes between the 2 treatment groups, the addition of rifampin was associated with prolongation of bacteremia by 2 days: the median duration of bacteremia was 7 days (range, 3–8 days) among those who received vancomycin alone and was 9 days (range, 3–10 days) among those treated with the combination. It should be noted, however, that follow-up was incomplete for 21 patients who refused planned phlebotomies or who absconded, so that the final outcome analysis was based only on the remaining 21 patients.

Rifampin use may also have adverse effects. A recent retrospective cohort study analyzed 84 patients with native-valve *S. aureus* endocarditis (78.6% of which was caused by MRSA), half of whom received rifampin in addition to a cell wall–active agent (vancomycin in 83.3%) [44]. Although rifampin administration was associated with more-prolonged bacteremia and other adverse outcomes, confounding factors precluded a conclusion with regard to efficacy. Rifampin administration was associated with drug-drug pharmacokinetic interactions in 22 (52%) of 24 patients and with hepatotoxicity in 9 (21%), whereas only 1 patient (2%; *P* < .014) receiving vancomycin alone developed hepatotoxicity. All patients with hepatotoxicity, however, had preexisting chronic hepatitis C virus infection. Rifampin resistance emerged in 9 (21%) of recipients of this drug, with all instances occurring in patients who still had bacteremia at the time rifampin was added, among whom it occurred in 56%.

Thus, although rifampin has a number of theoretically beneficial characteristics as a companion agent to vancomycin, empirical results obtained in the laboratory are often contra-
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at the time rifampin was added, among whom it occurred in Wall–active agent (vancomycin in 83.3%) [44]. Although rifampin administration was associated with more-prolonged bacteremia and other adverse outcomes, confounding factors precluded a conclusion with regard to efficacy. Rifampin administration was associated with drug-drug pharmacokinetic interactions in 22 (52%) of 24 patients and with hepatotoxicity in 9 (21%), whereas only 1 patient (2%; *P* < .014) receiving vancomycin alone developed hepatotoxicity. All patients with hepatotoxicity, however, had preexisting chronic hepatitis C virus infection. Rifampin resistance emerged in 9 (21%) of recipients of this drug, with all instances occurring in patients who still had bacteremia at the time rifampin was added, among whom it occurred in 56%.

Thus, although rifampin has a number of theoretically beneficial characteristics as a companion agent to vancomycin, empirical results obtained in the laboratory are often contradictory, and there are no clinical trial results that support the use of rifampin coadministration.

**Vancomycin plus gentamicin.** A number of studies have demonstrated in vitro synergy between gentamicin and vancomycin against many MRSA isolates [45], although this phenomenon was not detected with any of 3 VISA strains in an in vitro pharmacodynamic model [46]. Gentamicin enhanced the bactericidal activity of vancomycin against MRSA in an in vitro model of infected fibrin-platelet clots [47]. Using an in vitro pharmacodynamic model with simulated endocardial vegetations, Tsuji and Rybak [48] found evidence that a single 5 mg/kg dose of gentamicin enhanced early killing of MRSA by vancomycin and resulted in 99.9% killing at 32 h. Findings such as these, as well as evidence that combinations of gentamicin and a β-lactam shorten the duration of bacteremia in animal models of MSSA endocarditis and in patients with right-sided endocarditis due to MSSA (albeit at the price of nephrotoxicity) [49], have contributed to the use of the combination of vancomycin and gentamicin by many clinicians.

There are no published randomized clinical trials comparing the combination of vancomycin alone to vancomycin plus an aminoglycoside in patients with serious MRSA infections. However, the combination of vancomycin plus gentamicin (given for the first 4 days of therapy) was numerically inferior to daptomycin alone in the treatment of MRSA bacteremia and endocarditis in a randomized trial, although statistical significance was not achieved [50]. Unfortunately, even the low dose of gentamicin (1 mg/kg every 8 h) and the short duration in that study was associated with significant nephrotoxicity [51, 52]. Netilmicin may be less nephrotoxic than gentamicin, but the addition of the former to vancomycin therapy in a rabbit model of MRSA endocarditis provided no advantage [39].

It can be concluded from the foregoing that the administration of gentamicin with vancomycin for the treatment of MRSA infection is associated with potential toxicity in the absence of evidence of clinical benefit, making its use difficult to justify [53].

**Vancomycin plus rifampin and gentamicin.** Current guidelines for the treatment of prosthetic valve endocarditis (PVE) due to MRSA recommend the use of the 3-drug combination of vancomycin, rifampin, and gentamicin, with the aminoglycoside administered for only the first 2 weeks of therapy [54]. In contrast, the guidelines do not recommend the 3-drug combination in the treatment for MRSA PVE appears to be an extrapolation from the recommendation for the treatment of PVE due to *S. epidermidis* [54], which, apparently, is predominantly based on a retrospective analysis of a total of 26 patients receiving various regimens, with or without concomitant surgical therapy (table 1) [55]. In that study, 19 of the 26 patients received combined medical and surgical therapy, leaving only 7 for whom antibiotic therapy was assessable—only 1 of whom received vancomycin monotherapy. All 3 patients who received vancomycin plus rifampin were cured, as were all 3 who received all 3 antibiotics, whereas the single recipient of vancomycin alone experienced therapy failure.

A recent publication analyzed 86 adults with PVE due to coagulate-negative staphylococci (two-thirds methicillin resistant), most of whom were treated with vancomycin together with rifampin and/or gentamicin [56]. In-hospital mortality did not vary significantly among groups, with rates of 27% among those treated with vancomycin alone (*n = 15*), 33% among those given vancomycin plus rifampin (*n = 12*), 20% among those given vancomycin plus gentamicin (*n = 16*), and 19% among those given all 3 antibiotics (*n = 16*).

Thus, the evidence for the recommendation of 3-drug therapy for PVE due to MRSA—which carries with it the potential for increased risk of adverse reactions—is, at best, unconvincing.

**Vancomycin plus a β-lactam.** Although this combination...
is not used for definitive therapy, vancomycin is often administered together with an antistaphylococcal \(\beta\)-lactam antibiotic during the initial empirical phase (when the methicillin susceptibility of the infecting pathogen remains undetermined) without concern regarding their potential interaction. Favorable antistaphylococcal interactions between these 2 antibiotics have, however, been frequently identified in vitro. Thus, cefepime and vancomycin are often synergistic in vitro against both MSSA and MRSA [57], and cefazolin and imipenem are each frequently synergistic with vancomycin in vitro against MRSA [58], as is ceftobiprole and vancomycin [59]. The carbapenems doripenem, panipenem, meropenem, and imipenem were each synergistic with vancomycin by the checkerboard method against 92% of 27 strains of MRSA [60]. Synergy was observed for 46% of 50 MRSA isolates by the checkerboard method and for 5 of 5 by time-kill analysis with the combination of vancomycin and cefotaxime, whereas antagonism was not detected [61]. Ceftobiprole, which itself has activity against MRSA, was synergistic with vancomycin against a vancomycin-resistant strain of MRSA, markedly lowering the vancomycin MIC [62]. In an in vivo study, the addition of nafcillin to vancomycin was significantly more effective than either agent alone in experimental endocarditis due to a vancomycin-resistant strain of \(S.\ aureus\) carrying the \(vanA\) gene complex [63].

The interaction may also operate in the reverse direction, because reduced vancomycin susceptibility achieved by serial passage of MRSA in the presence of the glycopeptide antibiotic is associated with increased susceptibility to methicillin [64]. Consistent with these observations, the combination of a \(\beta\)-lactam antibiotic and vancomycin is reported to be synergistic against MRSA with reduced susceptibility to vancomycin [65]. MRSA with reduced susceptibility to vancomycin have altered penicillin-binding proteins, including down-regulation of PBP2a, potentially providing an explanation for increased susceptibility to \(\beta\)-lactam antibiotics [66]; loss of the \(mecA\) gene has also been reported [67]. Synergy could not, however, be demonstrated in vivo in a murine model of infection [68].

Although these experimental studies all report a beneficial interaction between vancomycin and \(\beta\)-lactams, \(\beta\)-lactam exposure has also been reported to cause reduced susceptibility of some strains of MRSA to vancomycin [69]. Furthermore, although vancomycin has no effect on staphylococcal toxin production [24], subinhibitory concentrations of \(\beta\)-lactams enhance their production [24, 25] and, as a result, could have a detrimental effect on therapy in some cases.

Overall, these results suggest that, in addition to possibly being preferable for initial empirical therapy before methicillin susceptibility results are available, the combination of vancomycin with a \(\beta\)-lactam antibiotic may provide benefit in definitive therapy for serious MRSA infection. In the absence of clinical trials confirming these results, however, the combination cannot be recommended for this purpose.

**Vancomycin plus clindamycin, linezolid, or quinupristin-dalfopristin.** The ability of subinhibitory concentrations of clindamycin and linezolid to diminish production of several toxins by \(S.\ aureus\) [24, 25] has led to their use in combination with vancomycin. It is reported, however, that clindamycin frequently antagonizes the antistaphylococcal activity of vancomycin [70, 71]. Although linezolid and vancomycin are reported to be indifferent when studied by the checkerboard method [70], by the time-kill method it was found that the addition of linezolid decreased the rate of vancomycin killing of MRSA by 100–1000-fold [72]. Antagonism between these 2 antibiotics was also found by another group of investigators using time-kill analysis [73, 74].

The observed in vitro interaction between quinupristin-dalfopristin (QD) and vancomycin has been variable, ranging from frequent antagonism to frequent synergy [75]. QD has been reported to reduce the bactericidal activity of vancomycin against macrolide-lincosamide-streptogramin B (MLSB)–resistant \(S.\ aureus\) [76] but, in contrast, to enhance the bactericidal activity of vancomycin in time-kill studies and in a rabbit model of endocarditis, regardless of the presence or absence of constitutive MLSB resistance [77]. An open-label, nonrandomized prospective study reported that patients treated with the combination of vancomycin and quinupristin-dalfopristin who had been selected because of persisting infection experienced more-

### Table 1. Retrospective Analysis of Treatment Outcomes among Patients with Prosthetic-Valve Endocarditis Due to *Staphylococcus epidermidis* Infection

<table>
<thead>
<tr>
<th>Antibiotic therapy</th>
<th>Medical and surgical</th>
<th>Medical only</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin</td>
<td>3/5</td>
<td>0/1</td>
<td>3/6</td>
</tr>
<tr>
<td>Vancomycin plus rifampin</td>
<td>4/5</td>
<td>3/3</td>
<td>7/8</td>
</tr>
<tr>
<td>Vancomycin plus aminoglycoside</td>
<td>5/5</td>
<td>0/0</td>
<td>5/5</td>
</tr>
<tr>
<td>Vancomycin plus rifampin and aminoglycoside</td>
<td>3/4</td>
<td>3/3</td>
<td>6/7</td>
</tr>
<tr>
<td>Total</td>
<td>15/19</td>
<td>6/7</td>
<td>21/26</td>
</tr>
</tbody>
</table>

**NOTE.** Data are from Karchmer et al [55].

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rapid clearance of MRSA than did those who continued receiving vancomycin alone [78]. The study is, however, available only in abstract form, and the lack of adequate public information precludes confidently drawing conclusions from it.

Miscellaneous antibiotics, biologicals, and physical agents.
In vitro synergy with vancomycin against S. aureus has been detected with levofloxacin [59] and with moxifloxacin [79]. Killing of MRSA and VISA strains by vancomycin was modestly reduced by the addition of tigecycline [80] but, in contrast, this glycyglycine enhanced the activity of vancomycin against S. aureus in biofilm [12]. Other agents that have been reported to improve the activity of vancomycin against S. aureus growing in biofilm include clarithromycin [81] and fusidic acid [32], with the 3-drug combination of vancomycin, rifampin, and fusidic acid being among the most potent in an extensive study [32]. Coexposure to trimethoprim-sulfamethoxazole enhances the bactericidal activity of vancomycin against S. aureus that have been ingested by polymorphonuclear leukocytes [23]. Clinical data on the use of these miscellaneous agents in combination with vancomycin are almost nonexistent except for the occasional case report, such as that of successful salvage therapy with a combination of daptomycin, vancomycin, and rifampin in 2 patients with recurrent osteoarticular infections who had experienced failure of prior therapy with either daptomycin alone or the combination of vancomycin and rifampin [82].

Administration of granulocyte colony-stimulating factor did not improve the survival of mice with experimental MRSA sepsis treated with vancomycin [83], but other biologicals show promise. The antistaphylococcal activity of the endopeptidase lysostaphin is additive to that of vancomycin [84], and a favorable interaction was observed in eradicating MRSA growing in biofilm [85]. The combination of the 2 agents was modestly more effective than either agent alone in a murine model of MRSA infection [86], and lysostaphin enhanced the activity of vancomycin in a rabbit model of MRSA endocarditis [87]. The α-helical peptides cercopin A and magainin II were each synergistic with vancomycin in vitro against a VISA strain and significantly improved survival, relative to that achieved with each of the 3 given alone, in a murine model of MRSA infection [88]. Therapy with the combination of the cationic peptide BMP-28 and vancomycin was superior to that with either alone in a rat model of MRSA ureteral stent infection [89]. Cloned lysin encoded by the S. aureus bacteriophage ΦMRII was synergistic with vancomycin against VISA in vitro [90]. The interaction between vancomycin and antibody has also been investigated. Tefibazumab, a monoclonal antibody recognizing clumping factor A on the surface of S. aureus, enhanced the activity of vancomycin in an experimental model of endocarditis [91]. Aurograb (NeiTec Pharma), a human recombinant single-chain antibody fragment (scFv) that binds to GrfA, an ABC transporter on the surface of S. aureus, is synergistic with vancomycin [92]. Finally, exposure to a electrical current (2000 μA) significantly enhanced the activity of vancomycin against MRSA growing in biofilm [93].

Conclusion
In a recent survey, infectious disease clinicians were asked how they would manage a patient who was apparently experiencing failure of vancomycin therapy for a bacteremic illness caused by MRSA with a vancomycin MIC of 2 μg/mL [94]. In response, 72% indicated they would continue vancomycin but would add a second antibiotic, most often rifampin or gentamicin. The available data reviewed here, however, would not appear to provide support for this approach, nor do they provide support for the use of such combinations for initial definitive treatment of MRSA infection. The optimal therapy for serious MRSA infection is undetermined and will remain so in the absence of randomized clinical trials.

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