The Association Between Antecedent Vancomycin Treatment and Hospital-Acquired Vancomycin-Resistant Enterococci

A Meta-analysis

Yehuda Carmeli, MD, MPH; Matthew H. Samore, MD; W. Charles Huskins, MD, MPH

Background: The association between vancomycin hydrochloride treatment and vancomycin-resistant enterococci (VRE) has been investigated in numerous studies with variable results.

Objectives: To conduct a meta-analysis to estimate the magnitude of the association between vancomycin treatment and individual risk of VRE and to identify study characteristics that accounted for heterogeneity in study results.

Methods: Studies were identified using MEDLINE with index terms “Enterococcus,” “Enterococcus faecalis,” or “Enterococcus faecium” and “vancomycin,” “drug resistance,” “drug resistance, microbial,” or “drug resistance, multiple or risk factors.” Reports from conferences and reference lists of recent reviews were used. A total of 420 published reports and 98 conference reports were reviewed; 20 studies described in 15 published reports were included in the analysis. We recorded study period, hospital setting, case and control definitions, length of hospital stay, method of adjustment for differences in length of stay, and data on treatment with vancomycin. The odds ratio (OR) of vancomycin treatment provided the measure of association analyzed. A random-effects model was used to estimate the pooled OR.

Results: When results from all 20 studies were combined, the pooled OR was 4.5 (95% confidence interval, 3.0-6.9), but the test for heterogeneity was highly significant (P<.001). The 5 studies that used patients with vancomycin-susceptible enterococci as controls found a stronger association (pooled OR, 10.7; 95% confidence interval, 4.8-23.8) than the 15 studies that used controls who had no VRE isolated (pooled OR, 2.7; 95% confidence interval, 2.0-3.8). After restricting the analysis to the latter studies only, no heterogeneity was evident in the unadjusted study results. Patients with VRE had stayed in the hospital much longer than control patients. Studies that adjusted for this difference found only a small and nonsignificant association between vancomycin treatment and VRE (pooled OR, 1.4; 95% confidence interval, 0.74-2.60). We also detected publication bias, favoring report of studies that found a large measure of association.

Conclusions: The reported strong association between vancomycin treatment and hospital-acquired VRE results from the selection of the reference group, confounding by duration of hospitalization, and publication bias. Studies that accounted for these factors found only a small and nonsignificant association.

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From the Divisions of Infectious Diseases, Beth Israel Deaconess Medical Center (Drs Carmeli and Samore), Children’s Hospital (Dr Huskins), and Harvard Medical School (Drs Carmeli, Samore, and Huskins), Boston, Mass. Dr Carmeli is now with the Division of Infectious Diseases, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel.

First isolated in 1987,1,2 vancomycin hydrochloride-resistant enterococci (VRE) have rapidly become established as important nosocomial pathogens in the United States. In some hospitals, VRE are responsible for greater than 20% of enterococcal infections.

Initial epidemiological studies3,4 identified therapy with vancomycin as a risk factor for VRE infection or colonization. The emergence of VRE was also coincident with dramatic increases in global vancomycin use in the 1980s and early 1990s. For example, investigators5 in a large university hospital documented a 20-fold increase in the use of intravenous vancomycin during the 10-year period from 1981 to 1991.

These data were widely interpreted as indicating that vancomycin treatment facilitated acquisition of VRE by individual patients and that increased use of vancomycin played a major role in the emergence and dissemination of VRE in the United States. This conclusion was consistent with the broader concept that antibiotic treatment exerts selection pressure that promotes resistance. Consequently, interventions to facilitate “prudent vancomycin use” were emphasized strongly in recommendations for preventing the spread of VRE published by the Hospital Infection Control Practices Ad-
MATERIALS AND METHODS

IDENTIFICATION OF RELEVANT LITERATURE

We defined a report as a printed document by an organization or group of authors. We defined a study as an analysis of data from case and control (comparison) patients. An individual report could describe more than 1 study.

We identified reports published in journals using a computerized literature search (MEDLINE). We used medical subject headings in the following search strategy: “Enterococcus,” “Enterococcus faecalis,” or “Enterococcus faecium” and “vancomycin,” “drug resistance,” “drug resistance, microbial,” or “drug resistance, multiple or risk factors.” We limited the search to reports on human subjects with an abstract in English published between January 1987 and March 1998. This search identified 420 published reports.

We identified reports from conferences by searching the official conference proceedings of the 1996 and 1997 annual meetings of the Infectious Diseases Society of America, the Interscience Conference on Antimicrobial Agents and Chemotherapy, and the Society for Healthcare Epidemiology of America. This search identified 98 conference reports.

We compared the list of reports identified by these searches with the reference lists of recent reviews. No additional reports were identified.

INCLUSION AND EXCLUSION CRITERIA

We defined criteria for the inclusion and exclusion of studies before reviewing specific reports.

We included studies that (1) provided data regarding antecedent vancomycin therapy among patients who were infected or colonized with VRE and a concurrent control group of patients selected from the same general population at risk (eg, same hospital or unit or same primary diagnosis) and (2) were performed in hospitals in the United States. The latter criterion was based on the observation that the epidemiological features of VRE in Europe have been distinctly different from those in the United States regarding spread in the community compared with hospitals.

Since our intent was to examine the association of antecedent vancomycin therapy with infection or colonization with VRE at the level of the patient, we excluded studies examining the correlation between global vancomycin use and rates of infection or colonization with VRE. We also excluded studies that focused on enterococcal strains in which vancomycin resistance was shown to be conferred by the VANC gene or Enterococcus species in which vancomycin resistance is generally due to the VANC gene (Enterococcus casseliflavus, Enterococcus gallinarum, and Enterococcus flavescens) because the epidemiological characteristics of infection or colonization with these microorganisms differ substantially from those in which resistance is conferred by the VANA or VANB genes.

Two of us (Y.C. and W.C.H.) independently reviewed the abstracts of all reports identified by the searches described above. Abstracts describing studies performed in hospitals outside the United States and studies focused solely on the results of antimicrobial susceptibility testing and/or molecular mechanisms of resistance among enterococci were not reviewed further. The entire text of the remaining reports was independently reviewed by both investigators who recorded predetermined information relevant to the inclusion and exclusion criteria. The investigators compared their evaluations, discussing discrepancies and reviewing studies again until they reached a consensus regarding satisfaction of these criteria.

RESULTS

Twenty case-control analyses examining the association of vancomycin treatment and VRE were described in 15 published reports that met the inclusion criteria. One report described 2 studies using part of the same case group but different control groups. For the purpose of this analysis, we considered these 2 studies to be independent. Characteristics of the studies are outlined in the table and discussed further. Twenty-three other relevant publications not meeting the study criteria and the main reason for noninclusion are listed in the “Suggested Reading” section.

All of the studies included were designed to examine simultaneously several possible risk factors for VRE, such as location in the hospital, length of hospital stay, comorbidities, and exposure to antibiotics, including vancomycin. Vancomycin exposure was predominantly treatment with intravenous vancomycin. Studies were performed between 1990 and 1995 and included various patient populations; 8 were hospital-wide studies, 7 were...
DATA EXTRACTION

Two of us (Y.C. and W.C.H.) extracted the following information regarding each study, independently using a data extraction form: year of publication, period of study, hospital unit or primary diagnosis of the study population, method used to identify case patients, method used to select control patients, method used to adjust for length of hospital stay, the total number of case and control patients and the number who were exposed to vancomycin, the odds ratio (OR) and confidence intervals (CIs) (crude and adjusted, if reported) for antecedent vancomycin therapy, the average number of days in the hospital (before a culture for VRE was obtained) for case patients, and the day of inclusion for controls. In the few reports in which the number of patients treated with oral vancomycin was reported separately from the number of patients treated with intravenous vancomycin, only the number of patients treated with intravenous vancomycin was used in the analysis. The investigators compared their evaluations, discussed discrepancies, and reviewed studies again together as necessary. Authors of the original reports were contacted for clarification when incomplete or ambiguous data were reported.

We classified the method for identifying case patients into 1 of 3 categories: (1) clinical cultures—case patients detected through clinical cultures ordered by clinicians as part of patient care, (2) surveillance—case (and control) patients identified through systematic surveillance cultures (cross-sectional identification), and (3) acquisition—case patients who underwent serial culturing and had a negative VRE culture result followed by a positive culture result (incident cases).

We classified the method for selection of control patients as either “no VRE” or “vancomycin-susceptible enterococci (VSE).” No VRE was defined as control patients who were not identified as colonized or infected with VRE by the methods described above. Control patients in these studies typically represented a sample of the hospital or unit population. Vancomycin-susceptible enterococci was defined as control patients who were infected or colonized with vancomycin-susceptible strains of enterococci.

We classified the method of adjustment for length of hospital stay as either “adjustment” or “no adjustment.” Adjustment was defined as either matching of case and control patients regarding length of hospital stay or use of multivariable analysis to adjust for differences in length of hospital stay. No adjustment was defined as the use of neither of these 2 methods.

DATA AND STATISTICAL ANALYSES

We managed reports using computer software (EndNote, version 3.0; Niles Software, Inc, Berkeley, Calif). We calculated the crude OR and 95% CIs by the Woolf approximation using the primary data reported for the study. One case was added to empty cells to allow calculation of the OR. If the primary data were not reported, we used the OR and 95% CIs reported for the study.

We used the DerSimonian and Laird15 random-effect model to obtain pooled estimates of the OR and 95% confidence limits for a group of studies. We tested for heterogeneity in the results of different studies using the Q statistic and considered heterogeneity to be significant if P<.25.

Publication bias was evaluated by plotting the point estimate against the percentage weight of the study (1/variance, a measure of the power of the study) and constructing a funnel diagram originating from the pooled OR of the studies that weighted more than the average study weight, and included as many studies as possible.

The Egger et al16 regression asymmetry test and the Begg and Mazumdar17 adjusted rank correlation test were used to test for publication bias. Paired t tests were used to test the differences in length of hospitalization between case and control patients.

CRITERIA FOR SELECTING
THE CONTROL GROUP

Two different strategies were used for the selection of controls. Five studies used controls who had vancomycin-resistant enterococci isolated from their cultures. Fifteen other studies used controls who had no VRE isolated from their cultures. The pooled OR for the first group of studies was substantially higher (pooled OR, 10.7; 95% CI, 4.8-23.8) than that of the group of 15 studies that used controls who had no VRE isolated (pooled OR, 2.7; 95% CI, 2.0-3.8) (Figure 2).

CASE PATIENT IDENTIFICATION

We also examined the hypothesis that the association for exposure to vancomycin would vary with case definition. Studies were divided into 3 groups based on case definitions: clinical cultures, surveillance, and acquisition. The method of case identification appeared to account for part of the heterogeneity in results; studies identifying case patients based on clinical culture results found a stronger association between vancomycin and VRE (pooled OR, 6.2; 95% CI, 3.2-12.2) than studies identifying case patients by...
### Summary of Studies Included in the Meta-analysis

<table>
<thead>
<tr>
<th>Study No./Source/Period</th>
<th>Setting</th>
<th>Case Definition</th>
<th>Mean Hospital Stay, d</th>
<th>Vancomycin Therapy*</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Case Patients</td>
<td>Controls</td>
<td></td>
</tr>
<tr>
<td>1/Anil et al. /10/94-2/95</td>
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<td>Clinical</td>
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<td>Clinical</td>
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<td>5.0</td>
</tr>
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</tr>
<tr>
<td>7/Henderson et al. /92-3/91</td>
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<td>Surveillance</td>
<td>No VRE</td>
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</tr>
<tr>
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<td>Acquisition</td>
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<td>Clinical</td>
<td>VSE</td>
<td>18/45</td>
</tr>
</tbody>
</table>

### Notes
- ICU indicates intensive care unit; SICU, surgical intensive care unit; MICU, medical intensive care unit; VRE, vancomycin-resistant enterococci; VSE, vancomycin-susceptible enterococci; ellipses, data not applicable; and minus sign, data not available.
- Median number of days.
- Control matched for length of stay.
- Part of the data received by personal communication.
- Bacteremia.
- Combination of surveillance and infection.
- Urinary tract infection.
- Adjusted for time using survival analysis.
- Adjusted for time using logistic regression.
- One case was added to the empty cell to allow calculation of the odds ratio.
- Acquired immunodeficiency syndrome, SICU, and oncology wards.
- Nine percent of case patients and 60% of controls stayed in the ICU less than 6 days.

Since the study design of using controls with VSE was the major source of heterogeneity and appeared to be associated with distorted effects, such studies were excluded from further analyses.

### Adjustment for Length of Hospitalization

In the remaining group of 15 studies, we compared the strength of the association between exposure to vancomycin and VRE in 2 groups of studies: 10 studies that did not adjust for length of hospitalization and 5 studies that did adjust for length of hospitalization by design or by analysis (Figure 4). The pooled OR for studies that did not adjust for length of hospitalization was 3.1 (95% CI, 1.8-5.3); for studies that did adjust for length of hospitalization, 1.4 (95% CI, 0.74-2.60). The results of the studies that adjusted for length of stay were not homogeneous (P = 0.03).

Seven of the 10 studies that did not adjust for the length of stay nevertheless reported specific data on duration of hospital stay for case and control patients. In these studies, a substantial difference in the duration of hospital stay between case and control patients was found. Case patients were hospitalized until study inclusion was due to the association between use of controls with VSE and use of case patients detected by clinical culture results. When the studies using controls with VSE were excluded, this method of case identification gave similar results to the other methods (pooled OR, 2.0; 95% CI, 1.2-3.5), and no heterogeneity was found between the combined unadjusted results (Figure 3).

Since the study design of using controls with VSE was the major source of heterogeneity and appeared to be associated with distorted effects, such studies were excluded from further analyses.

### Publication Bias

We examined the relation between the weight of the studies (a combination of the study size and the number of outcomes, a measure of the power of the study) and the unadjusted OR reported by the study. Low-weight studies (low power) were more likely to report high ORs and
significant results than large studies (high power). The pooled OR was 4.4 (95% CI, 2.7-7.1) for the 11 studies with less than 7% weight (the average study weight), whereas the pooled OR was 1.8 (95% CI, 1.2-2.7) for the 4 studies with a weight greater than 7%. Figure 5 demonstrates that small studies with modest effects appear missing from the left lower quadrant of the funnel graph. The regression asymmetry test and the adjusted rank correlation test were compatible with the presence of publication bias ($P = .01$ and $P = .13$, respectively).

**COMMENT**

The rationale for conducting this meta-analysis of the association between antecedent vancomycin treatment and hospital-acquired VRE was that results of previous studies have been inconsistent and that many have had relatively small sample sizes. The subject of nosocomial VRE and its relation to vancomycin is one of intense interest in the medical community, as evidenced by the large number of studies that have been conducted during a relatively short time. The postulated causal relation between vancomycin treatment and VRE has largely motivated efforts to devise effective means of reducing vancomycin use.6,33,34
The main findings of this meta-analysis were the following: (1) although the crude analysis of all published studies appeared to provide strong support for the association between vancomycin and VRE, there was significant heterogeneity among studies results; (2) the major sources of heterogeneity were related to study design regarding selection of controls and lack of adjustment for confounding by length of stay; (3) once confounding and other sources of heterogeneity were taken into account, the association between vancomycin and VRE was small and not statistically significant; and (4) a lack of small studies with modest effect sizes was discerned, suggesting the presence of some degree of publication bias. Studies of low power with nonsignificant results may have been less likely to be published, or if published, less likely to report in detail the association between vancomycin and VRE.

Studies that used controls with VSE showed a substantially stronger association for antecedent vancomycin treatment compared with other studies (pooled OR, 10.7 vs 2.7). We believe that a study design that uses patients with VSE as controls has inherent shortcomings regarding identification of causal risk factors. Control patients with VSE likely represent a biased sample of the source population of hospitalized patients, at least regarding exposures that may influence the development of VSE. Treatment with vancomycin probably reduces the likelihood of subsequent infection with VSE, thus lowering the frequency of antecedent vancomycin exposure in these patients relative to the general hospital population and inflating the magnitude of vancomycin effect in studies that used this group as controls.

The other major factor that gave rise to an exaggerated association between vancomycin and VRE was confounding by length of hospital stay. Five studies that adjusted for length of hospital stay exhibited a pooled OR of 1.4, with the lower bound of the 95% CI extending to 0.74. In studies that did not adjust for length of stay but nevertheless provided detailed data, case patients with VRE had substantially longer lengths of stay than controls. This is expected based on the relation...
between days in the hospital and cumulative risk of acquisition of a nosocomial pathogen such as VRE. Conversely, in contrast to our a priori hypothesis, we did not observe heterogeneity in ORs as to whether case patients were identified by clinical culture, surveillance, or acquisition.

One implication of this meta-analysis is that if vancomycin is not a significant causal factor in nosocomial VRE, curtailment of vancomycin use may have relatively little impact on incidence rates of VRE infection or colonization. Other antibiotics, such as cephalosporins or antianaerobic agents, may play an equally if not more important role in promoting the spread of VRE within institutions. Given the complex genetic machinery required to confer vancomycin resistance, de novo emergence of resistance is unlikely in an individual patient. Thus, newly detected VRE may represent either acquisition of resistant organisms or expansion of pre-existing but undetected populations of VRE. Therefore, antibiotics may facilitate detection of VRE largely through effects on competing gastrointestinal flora, for which the action of vancomycin may be less prominent than other antibiotic agents.

We focused our analysis on only a few study characteristics. Other characteristics, such as the methods used to determine the susceptibility of enterococcal strains to vancomycin or variation in the source patient population, were not explored. The homogeneity found in the unadjusted study results, after excluding the studies that used controls with VSE, suggests that we accounted for the most important areas of heterogeneity. Most important, results of studies did not vary according to case definition, despite the different microbiologic methods used in these different types of studies.

Intravenous vancomycin constituted the vast majority of vancomycin use and, therefore, insufficient data existed to specifically examine the effect of oral vancomycin. Similarly, lack of available data prevented an examination of the effect of duration of vancomycin exposure. Furthermore, an analysis of the effects of antibiotics other than vancomycin was precluded by the limited amount of data and was beyond the scope of this study.

The results of this analysis do not abrogate the notion that vancomycin played a crucial role in the initial emergence of vancomycin resistance. Moreover, antibiotic selection pressure may have different effects during various stages of an epidemic. We also acknowledge that this meta-analysis was limited to studies conducted in the United States and, therefore, the findings may not be generalizable to countries where patterns of spread have been distinctly different. Finally, vancomycin treatment may have indirect effects on the transmission and acquisition of VRE that might be detectable only in ecological, population-level studies.

In summary, our results suggest that the reported association between antecedent vancomycin treatment and VRE is distorted by the method of selection of the control group, lack of adjustment for duration of hospitalization, and publication bias. After taking these factors into account, the pooled association between vancomycin and VRE is of modest size and not statistically significant. Thus, we conclude that, at most, vancomycin has a small degree of association with hospital-acquired VRE when examined at the level of the individual patient.

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Reprints: Yehuda Carmeli, MD, MPH, Division of Infectious Diseases, Tel Aviv Sourasky Medical Center, 6 Weizman St, Tel Aviv 64239, Israel (e-mail:yycarmeli@mailx.com).

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