Comparison of Mortality Associated with Vancomycin-Resistant and Vancomycin-Susceptible Enterococcal Bloodstream Infections: A Meta-analysis

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Background. Whether vancomycin resistance is independently associated with mortality among patients with enterococcal bloodstream infection (BSI) is controversial. To address this issue, we performed a systematic literature review with meta-analysis.

Methods. Data sources were studies identified using the MEDLINE database (for articles from 1988 through March 2003), the Cochrane Library (for articles published up to March 2003), and bibliographies of identified articles. Inclusion criteria were that the study assessed mortality after enterococcal BSI, compared mortality after vancomycin-resistant enterococci (VRE) BSI with that after vancomycin-susceptible enterococci (VSE) BSI, and adjusted for severity of illness. Study exclusion criteria were as follows: no report of the adjusted measure of effect (adjusted odds ratio [OR], adjusted hazard ratio, or adjusted relative risk) of vancomycin resistance on mortality available and/or its adjusted 95% confidence interval (95% CI). Data in the tables, figures, or text were independently extracted by 2 of the authors. Individual weights were calculated using the 95% CI of the adjusted measures of effect performing both fixed-effect and random-effects models.

Results. Nine studies were eligible (11 studies met the inclusion criteria, and 2 were excluded), with a total of 1614 enterococcal BSI episodes (683 VRE episodes and 931 VSE episodes). Patients with bacteremia caused by VRE were more likely to die than were those with VSE bacteremia (summary OR, 2.52; 95% CI, 1.9–3.4).

Conclusions. Vancomycin resistance is independently associated with increased mortality among patients with enterococcal bloodstream infection.

Enterococcal infections are occurring with increasing frequency among hospitalized patients [1, 2]. Over the past decade, enterococci have emerged as the third or fourth most common cause of nosocomial bloodstream infections (BSIs) [1–3]. In addition, the prevalence of vancomycin resistance among clinical enterococcal isolates has increased rapidly; 14%–25% of all enterococci isolated from patients in North American hospitals are now resistant to vancomycin [3–5]. In 1995, the Centers for Disease Control and Prevention (CDC) published guidelines to prevent transmission of vancomycin-resistant enterococci (VRE) in hospitals [6], and more recently, the Society for Healthcare Epidemiologists of America published guidance for prevention of VRE transmission [7]. Additionally, several pharmaceutical companies have invested heavily in the development of new antimicrobials with activity against multidrug-resistant, gram-positive pathogens, such as VRE [8–10]. Unfortunately, both preventive and therapeutic interventions against VRE can be resource intensive. Some researchers and clinicians have argued that vancomycin resistance has little or no impact on outcome among patients with enterococcal infections [11, 12], and as a result, the cost-effectiveness of implementing additional measures for the prevention and treatment of VRE infections can be questioned [13].

Current literature offers conflicting results on the
clinical impact of vancomycin resistance among patients with enterococcal BSI. Initial investigations suggested that vancomycin resistance contributed to increased attributable mortality, but these studies did not adjust for severity of illness [14]. Several studies that controlled for severity of illness followed, but the conclusions varied. Some studies failed to demonstrate a statistically significant association between vancomycin resistance and mortality [11, 12, 15–18], whereas others concluded that vancomycin resistance was associated with increased mortality [19–23]. These inconsistent findings have contributed to debate regarding the optimal preventive and therapeutic approach to VRE infection [13, 24]. The aim of this study is to determine the clinical impact of vancomycin resistance on the outcome of enterococcal BSI using a systematic literature review and meta-analysis of studies that provide a multivariate comparison of mortality rates associated with both VRE and vancomycin-susceptible enterococci (VSE) BSI that controls for underlying severity of illness.

METHODS

Two independent reviewers (C.A.D. and S.M.Z.) performed a systematic literature review to identify studies that reported mortality rates associated with both VRE and VSE BSI. Studies were identified using the MEDLINE database (for articles published from January 1988 through March 2003), the Cochrane Library (for articles published up to March 2003), and bibliographies of identified papers. The search strategy used the following terms and connectors: “outcome” or “mortality” or “death” AND “Enterococcus” or “enterococcal” AND “bacteremia” or “bloodstream infection.” No language restrictions were used.

The criteria for inclusion and exclusion were established by the investigators before reviewing the literature. Studies were considered for inclusion if they assessed mortality after enterococcal BSI, compared mortality after VRE BSI with that of VSE BSI, and adjusted for underlying severity of illness. Studies were excluded if the adjusted measure of effect (adjusted OR or adjusted HR) of vancomycin resistance on mortality and/or if the adjusted 95% CI were not provided. Before we excluded the studies, authors of such studies were contacted in an effort to obtain missing data. Differences between reviewers regarding appropriateness for inclusion or exclusion were resolved by consensus. Publication bias was assessed using the funnel plot method [25].

Individual study validity was assessed, with exploration for selection bias and misclassification bias. Confounding was assessed at the time of study selection, because the main confounding variable (severity of illness) had to be controlled for a study to be included. An evaluation of the definition of enterococcal BSI for each study was performed to assess the possibility of selection bias. Definitions used to classify exposure (VRE BSI episodes vs. VSE BSI episodes) for each individual study were appraised to evaluate the possibility of exposure misclassification bias. Because the outcome was objective (death vs. survival), misclassification of outcome was evaluated by assessing patient follow-up for each study (i.e., attrition bias assessment).

Analysis was performed using Revman software, version 4.2 (Cochrane collaboration). Fixed-effect models (inverse variance) and random-effects models (DerSimonian and Laird) were performed [26]. A test of heterogeneity was used to assess for significant differences among study estimates. A sensitivity analysis was performed to explore changes in the summary measures of effect by study subgroups [27].

RESULTS

The initial search yielded 114 studies, all of which were assessed using the abstract and/or the full-text manuscript for inclusion

Table 1. Studies of enterococcal bloodstream infection (BSI) eligible for meta-analysis.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study type</th>
<th>No. of BSI episodes</th>
<th>VRE</th>
<th>VSE</th>
<th>Total</th>
<th>Study population</th>
<th>Severity of illness criteria</th>
<th>Method of adjustment</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>[11]</td>
<td>R-cohort</td>
<td>72 188 260</td>
<td></td>
<td></td>
<td></td>
<td>Mixed</td>
<td>Determined by the authors</td>
<td>Logistic regression</td>
<td>.244</td>
</tr>
<tr>
<td>[15]</td>
<td>R-cohort</td>
<td>46 23 69</td>
<td></td>
<td></td>
<td></td>
<td>Mixed</td>
<td>APACHE II score, OSFI, SIRS</td>
<td>Logistic regression</td>
<td>.39</td>
</tr>
<tr>
<td>[16]</td>
<td>R-cohort</td>
<td>46 46 92</td>
<td></td>
<td></td>
<td></td>
<td>Mixed</td>
<td>APACHE II score</td>
<td>Logistic regression</td>
<td>.11</td>
</tr>
<tr>
<td>[17]</td>
<td>R-cohort</td>
<td>93 101 194</td>
<td></td>
<td></td>
<td></td>
<td>Mixed</td>
<td>APACHE II score</td>
<td>Logistic regression</td>
<td>.063</td>
</tr>
<tr>
<td>[19]</td>
<td>R-cohort</td>
<td>53 53 106</td>
<td></td>
<td></td>
<td></td>
<td>Mixed</td>
<td>APACHE II score</td>
<td>Logistic regression</td>
<td>.02</td>
</tr>
<tr>
<td>[20]</td>
<td>RP-cohort</td>
<td>150 150 300</td>
<td></td>
<td></td>
<td></td>
<td>Mixed</td>
<td>APACHE II score</td>
<td>Logistic regression</td>
<td>.001</td>
</tr>
<tr>
<td>[21]</td>
<td>P-cohort</td>
<td>147 251 398</td>
<td></td>
<td></td>
<td></td>
<td>Mixed</td>
<td>APACHE II score</td>
<td>Logistic regression</td>
<td>.02</td>
</tr>
<tr>
<td>[22]</td>
<td>R-cohort</td>
<td>54 48 102</td>
<td></td>
<td></td>
<td></td>
<td>LT recipients</td>
<td>Shock/liver failure</td>
<td>Logistic regression</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>[23]</td>
<td>R-cohort</td>
<td>22 61 83</td>
<td></td>
<td></td>
<td></td>
<td>Neutropenic patients</td>
<td>APACHE II score</td>
<td>Cox PH Modeling</td>
<td>.026</td>
</tr>
</tbody>
</table>

NOTE. LT, liver transplant; mixed, immunocompromised and nonimmunocompromised patients, as well as medical and surgical patients; OSFI, organ system failure index; P-cohort, prospective study cohort; PH, proportional hazard; R-cohort, retrospective cohort study; RP-cohort, retrospective and prospective cohort study; SIRS, systemic inflammatory response evaluation; VRE, vancomycin-resistant enterococci; VSE, vancomycin-susceptible enterococci.

* For exploration of significance of association between vancomycin resistance and mortality.
Table 2. Population details for studies included in a meta-analysis of enterococcal bloodstream infection.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Neutropenia</th>
<th>Other IS</th>
<th>Renal failure</th>
<th>Dialysis</th>
<th>Malignancy</th>
<th>Liver failure</th>
<th>Enterococcus species</th>
<th>Type of bacteremia</th>
</tr>
</thead>
<tbody>
<tr>
<td>[11]</td>
<td>30 (11.5)</td>
<td>36 (13.8)</td>
<td>56 (21.5)</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>[15]</td>
<td>NS</td>
<td>32 (46)</td>
<td>...</td>
<td>9 (13)</td>
<td>...</td>
<td>...</td>
<td>69 (100)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>[16]</td>
<td>27 (29.3)</td>
<td>...</td>
<td>...</td>
<td>52 (56.5)</td>
<td>...</td>
<td>...</td>
<td>40 (43.5)</td>
<td>NS</td>
</tr>
<tr>
<td>[17]</td>
<td>NS</td>
<td>66 (34)</td>
<td>...</td>
<td>63 (32.5)</td>
<td>...</td>
<td>...</td>
<td>126 (64.9)</td>
<td>71 (36.6)</td>
</tr>
<tr>
<td>[19]</td>
<td>NS</td>
<td>11 (10.4)</td>
<td>18 (17)</td>
<td>...</td>
<td>17 (16)</td>
<td>21 (20)</td>
<td>45 (42.4)</td>
<td>60 (56.6)</td>
</tr>
<tr>
<td>[20]</td>
<td>NS</td>
<td>67 (22.3)</td>
<td>...</td>
<td>51 (17)</td>
<td>16 (5.3)</td>
<td>...</td>
<td>120 (40)</td>
<td>48 (16)</td>
</tr>
<tr>
<td>[21]</td>
<td>NS</td>
<td>119 (29.9)</td>
<td>...</td>
<td>72 (18)</td>
<td>29 (7.3)</td>
<td>...</td>
<td>148 (37)</td>
<td>239 (60)</td>
</tr>
<tr>
<td>[22]</td>
<td>3 (2.9)</td>
<td>...</td>
<td>...</td>
<td>22 (21.6)</td>
<td>30 (29.4)</td>
<td>...</td>
<td>102 (100)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>[23]</td>
<td>83 (100)</td>
<td>78 (94)</td>
<td>...</td>
<td>80 (96.4)</td>
<td>...</td>
<td>...</td>
<td>36 (43.4)</td>
<td>32 (38.6)</td>
</tr>
</tbody>
</table>

NOTE. Data are no. (%) of patients. IS, immunosuppression; NS, not specified.

* Excluding catheter as the source.
* Including bone marrow transplant recipients.

Validity of individual studies was considered to be adequate overall. Definitions of enterococcal BSI varied to some extent from study to study. Four studies [11, 15, 21, 22] used a definition of enterococcal BSI episode that required $\geq 2$ positive blood culture results or 1 positive blood culture result and a positive result of a culture of a sample from the presumptive primary site. In comparison, 5 studies [16, 17, 19, 20, 23] used a definition that required only 1 positive blood culture result. The standardized definition for BSI used by the CDC [28] does not consider Enterococcus species to be common skin contaminants and, therefore, does not require 2 positive blood culture results. Nevertheless, the CDC definition is intended to be used for surveillance purposes, and it may lead to overestimation of the real frequency of infection. On the other hand, strict definitions for which $\geq 2$ blood cultures are required may exclude some real enterococcal BSI episodes. Therefore, the risk of selection bias in individual studies can be classified as moderate. Exposure misclassification bias (vancomycin resistance vs. vancomycin susceptibility) was considered very unlikely, because studies used internationally accepted definitions and cutoff points for vancomycin resistance in enterococcal isolates. Most studies used in-hospital mortality as the outcome of interest. Three studies [20, 21, 23] assessed mortality during a follow-up period of specified duration, regardless of hospital admission status. For studies using in-hospital mortality as the main outcome of interest, the risk of attrition bias is moderate, because some patients may have died soon after discharge and may therefore have been misclassified as survivors. For studies assessing mortality at a specific follow-up time, the risk of attrition bias is low. Therefore, the overall risk of attrition bias can be classified as moderate, and the overall risk of misclassification of outcome can be classified as low to moderate.
The 9 studies included a total of 1614 enterococcal BSIs (683 were caused by VRE, and 931 were caused by VSE). Four of the studies found no significant association between vancomycin resistance and mortality, and 5 found a significant association. The point estimates for all 9 studies fell to the right side of the null value (figure 2). The summary OR for the effect of vancomycin on mortality in this meta-analysis was 2.52 (95% CI, 1.9–3.4). The results obtained using fixed-effect and random-effects models were identical.

Despite a negative heterogeneity test result, we considered the possibility that results of the meta-analysis may have been influenced by the inclusion of 2 studies that exclusively examined immunocompromised populations, in whom the clinical impact of vancomycin resistance may be more pronounced than it is in immunocompetent populations. To address this concern, we performed a sensitivity analysis by repeating the meta-analysis after excluding these 2 studies. This meta-analysis included 7 studies, with a total of 1429 enterococcal BSI episodes (607 VRE episodes and 822 VSE episodes). Four of the included studies found no significant association, and 3 found a significant association. Again, the point estimates were consistently distributed to the right side of the null value (data not shown). The summary OR for the second meta-analysis was 2.32 (95% CI, 1.7–3.2), which was not meaningfully different than the results found by the first meta-analysis.

**DISCUSSION**

Our results indicate that vancomycin resistance is an independent predictor of death among patients with enterococcal BSI. The odds of death among patients with VRE BSI are more than double that for patients with VSE BSI after controlling for underlying severity of illness. The consistency of the point estimates above the null value, the negative heterogeneity test result, and the lack of a meaningful change after a sensitivity analysis strongly suggests that vancomycin resistance has a true impact on mortality in patients with enterococcal BSI.

The conflicting results of previous reports may be explained in part by lack of sufficient power among several studies to detect a statistically significant association between vancomycin resistance and mortality. The aggregate crude mortality for patients with VSE BSI for the studies included in our meta-analysis was 20%. With use of this figure as the expected mortality rate among patients with VSE BSI, the sample size needed to detect a significant association would be 252 patients (84 patients with VRE BSI and 168 patients with VSE BSI), assuming power of 80%, an α level of 5%, a ratio of patients with VSE BSI to patients with VRE BSI of 2:1, and an expected OR of 2.4 for VRE BSI. Two of the studies with positive findings had a sample size this large [20, 21], and both found a significant independent association between vancomycin resistance and death. All but 1 of the studies with negative findings [11] had smaller sample sizes (table 1). Differences in the magnitude of impact of vancomycin resistance among distinct patient populations may have further contributed to the inconsistency in the existing literature. Two of the 5 studies that reported significant associations were performed exclusively among severely immunocompromised populations [22, 23]. If the risk of death due to VRE bacteremia in immunocompromised patients is especially high, then studies focusing on this population may have had greater statistical power to detect an association between mortality and vancomycin resistance. Our systematic review and meta-analysis allowed us to aggregate
individual cohort studies, thereby overcoming deficiencies in sample size, and to explore the change in the summary measure of effect according to differences in study populations using a sensitivity analysis. The results suggest that the most likely explanation for inconsistent conclusions in the current literature is the lack of statistical power of small sample studies.

There are several biologically plausible explanations for the association between vancomycin resistance and increased mortality among patients with enterococcal BSI. These include suboptimal activity against VRE among the antimicrobials used to treat VRE BSI in these studies, a systematic delay in the initiation of antimicrobial agents active against VRE among study subjects, and differences in intrinsic virulence among vancomycin-resistant and vancomycin-susceptible species of enterococci.

The hypothesis that the observed association between mortality and vancomycin resistance resulted from suboptimal antimicrobial activity of the regimens used in these studies is supported by the findings in 1 report that showed that the effect of vancomycin resistance on mortality was dependent on the duration of bacteremia [23]. In this study, the effect of vancomycin resistance was strongly associated with failure to rapidly clear bacteremia, and when the duration of bacteremia was controlled for by including this variable in a multivariate mathematical model, there was no observable association between resistance and mortality, suggesting that duration of bacteremia is an important determinant of mortality in this setting. Similarly, the study by Bhavnani et al. [20] found that patients with VRE BSI and persistently positive blood culture results (defined as ≥1 positive follow-up blood culture results) are more likely to die.

Delays in initiating antimicrobial therapy active against VRE may have contributed to the increase in mortality associated with VRE BSI. If vancomycin resistance is not suspected when a patient is found to have bacteremia caused by gram-positive cocci, the administration of antimicrobial agents with activity against VRE may be delayed until susceptibility testing is complete. In the study by Vergis et al. [21], failure to administer active antimicrobial therapy within 48 h after onset of bacteremia was associated with increased mortality.

Enterococcus faecium is more frequently associated with vancomycin resistance than is Enterococcus faecalis, and some in vitro studies indicate that there may be a difference in virulence among enterococcal species [29–32]. However, 1 epidemiologic study failed to show a significant association between enterococcal species and relevant clinical outcomes [23]. Additionally, 2 other studies included in our meta-analysis were restricted to E. faecium BSI [15, 22], suggesting that the association between mortality and vancomycin resistance is independent of species.

A separate meta-analysis addressing the outcomes associated with VRE BSI was previously published by Salgado et al. [33]. This study examined several outcomes, including the monetary cost of VRE bacteremia, the impact on length of hospital stay, and the case-fatality rate. The authors analyzed 14 studies that compared case-fatality rates for VRE BSI and VSE BSI, but 7 of these studies did not provide a measure of effect that was adjusted for underlying severity of illness [18, 34–39]. We excluded these studies from our meta-analysis, and we included 2 additional studies not included in Salgado and colleagues’ assessment of mortality [11, 23]. The inclusion criteria, data extraction, and statistical methods used by Salgado and colleagues were different than the ones used in our study. They concluded that vancomycin resistance was associated with higher overall mortality. Our meta-analysis expands upon and strengthens their findings, demonstrating that the effect on mortality is consistent, even after controlling for severity of illness.

Our study has several limitations. It is a systematic review of cohort studies, only 2 of which had prospective components. Because of possible incomplete or inaccurate collection, data quality in retrospective studies can be questioned, and the same applies for an aggregate of such studies. As mentioned above, individual studies may have selection biases as a result of not having standardized definitions of enterococcal BSI. The resulting aggregate may have the same bias. Because the total number of eligible studies is small, the possibility of publication bias cannot be completely excluded, even though there was no clear evidence of this, as assessed by the funnel plot method.

Most of the studies included in this meta-analysis were conducted before the widespread availability of newer antimicrobial agents with activity against VRE, such as the streptogramins or the oxazolidinones recently approved for use by the US Food and Drug Administration. It is possible that use of such agents to treat VRE bacteremia might alter the observed association between vancomycin resistance and mortality, but this hypothesis has not been tested. Nevertheless, the observed association between mortality and resistance highlighted in this meta-analysis has important implications for the future regarding VRE and other drug-resistant organisms. It confirms that the emergence of antimicrobial-resistant organisms can have an important, deleterious impact on clinical outcome. Although new drug development may ameliorate the problem in the short term, there is no guarantee that potential clinical advantages offered by newly developed agents will be long-lasting. Resistance to newer antimicrobials is already being reported [40–44], and there are few new drugs in the developmental pipeline to replace them should they be rendered ineffective by widespread emergence of resistance [45]. These uncertainties suggest that, rather than relying solely on new drug development to address the problem of antimicrobial resistance, we should redouble our efforts to prevent transmission...
of antimicrobial-resistant organisms in the health care setting and to promote judicious antimicrobial use.

We conclude that vancomycin resistance is an independent predictor of death in patients with enterococcal BSI. Increased efforts to prevent nosocomial VRE infections and the further emergence of antimicrobial resistance among enterococci are warranted.

Acknowledgments

Potential conflicts of interest. All authors: no conflicts.

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