Observations on the Risk of Resistance With the Extended Use of Vancomycin

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Objective: To document the risk of the development of vancomycin-resistant bacteria in a population of seriously burned patients during a 10-year period of common vancomycin hydrochloride use.

Design: Retrospective study.

Setting: The US Army Institute of Surgical Research, Burn Center, Fort Sam Houston, Tex.

Population and Methods: Microbiology, infection, and antibiotic use records collected during the hospitalization of 2266 consecutively admitted seriously burned patients were reviewed. Vancomycin was the primary therapeutic agent used for gram-positive infections and was also used as a perioperative prophylactic antibiotic during burn wound excision. This policy was established prior to this review because of a high incidence of methicillin-resistant Staphylococcus aureus colonization and an anecdotal association of increased β-lactam resistance in endemic gram-negative pathogens associated with the use of penicillinase-resistant penicillins and cephalosporins.

Main Outcome Measures: Isolation of vancomycin-resistant enterococci (VRE) or other gram-positive organisms resistant to vancomycin.

Results: Examinations of 15,125 gram-positive isolates, including 957 enterococci, for in vitro sensitivity to vancomycin yielded 3 VRE isolates in 3 patients. Vancomycin was used prior to VRE isolation in one of these patients. Resistance was found in 3 other organisms (2 Corynebacterium species, 1 Lactobacillus species). Vancomycin was used prior to these isolations in 2 of 3 patients. None of the vancomycin-resistant organisms was associated with infection and all 6 patients survived. Vancomycin-resistant enterococci or other vancomycin-resistant gram-positive organisms were not found in 663 patients treated with vancomycin for documented gram-positive infections or in 1027 patients where perioperative vancomycin was used.

Conclusion: Use of vancomycin as the primary therapeutic agent in seriously burned patients was not associated with increased risk of VRE isolation or VRE infection.

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Vancomycin is a glycopeptide antibiotic produced by Streptomyces orientalis that has, with rare exception, bactericidal action against pathogenic gram-positive bacteria. Confidence in the utility of vancomycin hydrochloride as the treatment of choice for β-lactam-resistant staphylococci and as a general treatment against gram-positive pathogens in selected hosts was shaken in 1988 by the recognition in Europe of nosocomial infections caused by vancomycin-resistant enterococci (VRE).1 These organisms were recognized in the United States in 1989 and their frequency, when compared with vancomycin-sensitive strains, increased more than 20-fold (0.3%-7.9%) by 1993.2 This change coincided with reported increases in the apparent clinical importance of the enterococci for seriously ill and immunocompromised patients.3,4 Increases in VRE have also been related hypothetically to increased usage of vancomycin as a consequence of an increased frequency of infections caused by β-lactam gram-positive cocci.5

In this article, we present microbiological and infection data from a population of seriously burned patients admitted to a single burn center where vancomycin was the primary therapeutic agent used for gram-positive infections as well as a perioperative antibiotic during burn wound excision. This antibiotic policy was established several years prior to this review because of a high incidence of methicillin-resistant Staphylococcus aureus (MRSA) colonization and the perceived increased β-lactam resistance of endemic Pseudomonas aeruginosa and other gram-negative pathogens thought to be clini-

From the US Army Institute of Surgical Research, Fort Sam Houston, Tex.

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POPCULATION AND METHODS

Microbiological colonization, infection, antibiotic use, and antibiotic sensitivity data for patients admitted to the US Army Institute of Surgical Research’s burn center, Fort Sam Houston, Tex, between 1986 and 1995 were reviewed. All serious burns were treated in a special burn facility with single-room isolation. Microbial surveillance was initiated on admission and multiple weekly wound, sputum, urine, and stool cultures were taken as previously described. As part of the surveillance, antibiotic sensitivity assays were completed on S aureus and P aeruginosa, the predominant organisms at the cultured site, and on all suspected pathogens.

Surveillance data were used to document cross-contamination of resistant organisms and, as a quality improvement tool, to maintain patient isolation during intensive care unit care. Infections and antibiotic use were monitored daily and reviewed monthly by the institute’s Infection Control Committee. Prophylactic antibiotics were not used with the exception of perioperative use as described later. When infection was diagnosed, initial therapeutic antibiotics were selected on the basis of surveillance culture identification of the predominant colonizing organisms at the site prior to infection. The antibiotic selections were confirmed with infection-directed cultures. Blood stream infections were treated on the basis of initial Gram stain results and the selected agents were confirmed when the organism was isolated. Vancomycin was used for gram-positive pathogens whereas gram-negative pathogens were most commonly treated with a ureidopenicillin or amikacin sulfate. Pseudomonas or mixed infections were frequently treated with a combination of the gram-negative agents. Vancomycin dosage was based on the condition of the individual patient and serum levels achieved. Cephalosporins and quinolones were not commonly used. Perioperative antibiotics consisted of vancomycin 1 g intravenously administered, 1 hour before and 12 hours after the surgical procedure, and amikacin, administered 30 minutes before and 8 hours after the operation at a dose individualized to the patient.

RESULTS

In the 10-year review period (1986-1995), 2266 patients were admitted to the burn center. The average age was 29 years and the average burn size was 21% of the total body surface area. Gross mortality was 8.3%. Of potential microbiologic and epidemiologic interest is the fact that the patients from whom data were collected included individuals transported to San Antonio, Tex, each year by the institute’s burn flight teams after initial care in hospitals throughout the United States as well as Europe, Asia, and Latin America.

A total of 1550 culture-proven infections were documented. The relative frequency of infections were blood (25%); pneumonia (25%); urinary tract (21%); tracheobronchitis (14%); wound invasion (5%); and all other sites of infection (10%). Principal recovered pathogens were S aureus (31%); P aeruginosa (13%); yeasts (11%); Escherichia coli (7%); Klebsiella pneumoniae (7%); Proteus mirabilis (4%); enterococci (2.3%) When segregated by Gram stain results, 51% of bacterial pathogens were gram-positive. Enterococci represented 5% of the gram-positive pathogens. Vancomycin was used as an intravenous therapeutic agent for one or more gram-positive infections in 666 patients. Oral vancomycin was administered in 22 patients for Clostridium difficile enterocolitis. Perioperative vancomycin was used for one or more burn wound excisions and graftings in 1030 patients. More than 88 500 organisms were isolated using our microbial surveillance system. Enterococci represented 3.9% of surveillance isolates. Antibiotic sensitivity panels were completed on 36 712 isolates. Vancomycin sensitivities (gram-positive panel) were completed on 15125 isolates; all staphylococci were found to be sensitive. The frequency distribution of vancomycin inhibition zones (30-µg disk [ie, concentration of drug on disk]) for S aureus are presented in Figure 1. The frequency distribution of vancomycin inhibition zones (30-µg disk) for enterococci are presented in Figure 2. In all, 6 organisms, including 3 VRE, were found to be resistant to vancomycin. Organism and patient data are given in the Table. No infections were caused by vancomycin-resistant organisms and no patient-to-patient contamination with these organisms was observed. Neither VRE nor other vancomycin-resistant gram-positive organisms were found in the other 663 patients treated with vancomycin for gram-positive infections or in the other 1027 patients given perioperative vancomycin. A rationale for vancomycin restriction was not evident during this review.

The recognized importance of enterococci as nosocomial pathogens has paralleled the development of newer generations of broad-spectrum antibiotics and the improvements in medical science’s ability to support critically ill immunosuppressed patients. The propensity of enterococci to have intrinsic resistance to broad-acting antimicrobial agents, eg, cephalosporins, penicillinase-resistant penicillins, ureidopenicillins, and their ability to acquire resistance mechanisms to other agents such as fluoroquinolones, other penicillins, aminoglycosides, and most recently vancomycin, enhances the ability of Enterococcus to cause superinfection. The relatively low pathogenicity of enterococci may be enhanced when repeated successful antibiotic treatments against more virulent nosocomial pathogens in an immunocom-

COMMENT

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promised patient select for overgrowth and infection with a resistant strain. The infection risk of enterococci for a host with the ability to resist more pathogenic community or nosocomial organisms or to recover rapidly after antimicrobial treatments for infection is small.

Enterococci have a multiplicity of genetic transfer mechanisms to donate or acquire resistant genes to and from other gram-positive organisms. These capabilities, in combination with the in vitro demonstration that it is possible to transfer high-level vancomycin resistance (vanA) from *E. faecalis* to *S. aureus*, widely increased apprehension that such transfer would occur in the clinic and render MRSA resistant to vancomycin (VRSA). In response to these concerns, the Centers for Disease Control and Prevention’s Hospital Control Practices Advisory Committee’s subcommittee on Prevention and Control of Antimicrobial-Resistant Microorganisms in Hospitals and a group of selected subject-matter experts published “Recommendations for Preventing the Spread of Vancomycin Resistance,” which focused on the control of VRE. The principal recommendations of that report are (1) prudent use of vancomycin; (2) having an education program on VRE for hospital personnel; (3) establishing routine testing of all enterococci isolated from blood and sterile body sites (except urine) for vancomycin resistance; (4) screening all enterococcal isolates for vancomycin resistance after VRE has been detected in the facility; and (5) establishing appropriate use of isolation of all VRE-infected or colonized patients. These recommendations were supported by a position paper from the Surgical Infection Society. The position paper did, however, question whether the control of the use of vancomycin alone would greatly affect the risk of VRE colonization.

The transfer and stable expression of enterococcal resistance mechanisms to a more virulent organism, as in a VRE-based transformation of MRSA into VRSA, is a real concern. The clinical appearance of a virulent VRSA could lead to a return of the midcentury hospital staphylococcal epidemics. The Hospital Control Practices Advisory Committee’s recommendations for restriction of vancomycin to control VRE are designed to minimize the risk of such an event.

The intrinsic resistance of enterococci to broad-spectrum antibiotics such as penicillinase-resistant penicillins (nafcillin, oxacillin, etc) and cephalosporins, in combination with the acquired resistance to vancomycin found in VRE strains, questions the value of intravenous β-lactam agents over vancomycin for treatment of β-lactam-sensitive staphylococci. In fact, it could be argued that the gut permeability of β-lactam antibiotics and their activity spectra, that includes many enteric anaerobes, would be more likely to select VRE overgrowth by direct selection of the intrinsic resistances of enterococci and the indirect selection of acquired vancomycin resistance. Another obviously important but undocumented concern is how often a superinfection with VRE occurs when a VRE-colonized patient requires vancomycin treatment for serious MRSA infection. This concern has certainly become a reality many times in hospitals in which there are both endemic VRE and MRSA.

Does use of vancomycin in this situation truly increase the later risk of VRE infection and with enough exposures will VRSA become a reality? This review was conducted in a nonendemic VRE situation, but the results do document that extensive vancomycin use per se has

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**Organisms Found to Be Resistant to Vancomycin**

<table>
<thead>
<tr>
<th>Organism</th>
<th>Recovery Site</th>
<th>Diagnosis</th>
<th>Patient Age, y</th>
<th>% Burn*</th>
<th>Postburn Day</th>
<th>Prior Vancomycin</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Corynebacterium</em></td>
<td>Blood</td>
<td>Contaminant</td>
<td>5</td>
<td>53</td>
<td>26</td>
<td>Yes</td>
<td>Died</td>
</tr>
<tr>
<td><em>Corynebacterium</em></td>
<td>Sputum</td>
<td>No infection</td>
<td>44</td>
<td>53</td>
<td>2</td>
<td>No</td>
<td>Died</td>
</tr>
<tr>
<td><em>Lactobacillus</em></td>
<td>Blood</td>
<td>Contaminant</td>
<td>76</td>
<td>13</td>
<td>64</td>
<td>Yes</td>
<td>Died</td>
</tr>
<tr>
<td><em>Enterococcus</em></td>
<td>Urine</td>
<td>No infection</td>
<td>42</td>
<td>26</td>
<td>9</td>
<td>No</td>
<td>Died</td>
</tr>
<tr>
<td><em>Enterococcus</em></td>
<td>Urine</td>
<td>No infection</td>
<td>67</td>
<td>37</td>
<td>48</td>
<td>Yes</td>
<td>Died</td>
</tr>
<tr>
<td><em>Enterococcus</em></td>
<td>Sputum</td>
<td>No infection</td>
<td>74</td>
<td>32</td>
<td>41</td>
<td>No</td>
<td>Died</td>
</tr>
</tbody>
</table>

*% Burn indicates the percentage of body surface burned.*

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not been associated with difficulties with the Enterococcus organism in the treatment of more than 2000 immunocompromised burn patients.

The risk or the existence of the development of vancomycin-resistant S aureus in the clinic is not established. In 40 years of use, acquired mutational resistance has not been described. If transfer of a resistance mechanism from another organism occurs, this transfer is not likely to be vancomycin dependent and, like MRSA, VRSA will most likely have a clonal pattern of dissemination.

The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.


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REFERENCES


Joseph S. Solomkin, MD, Cincinnati, Ohio: Your study is of considerable importance in raising the issue, of some importance to this Society, of the value of drug restriction in limiting resistance. The argument in favor of restricting vancomycin is fairly weak. It is based on case-controlled studies done in epidemic settings that document a very strong association between vancomycin usage and the occurrence of the infection. Certainly that is not logically connected, as you point out very well, with the potential virtue of restricting the drug.

On the other hand, I would have to question whether your data really address the same types of issues, because, first, those studies were done in epidemic settings, yours were not, and vancomycin’s usage may in fact be important in an epidemic setting, and I wonder if you would comment on that.

The other issue is whether the usage of vancomycin in your hands was really comparable to what occurs in nonburn patients. I would characterize your usage as relatively low intensity, most of it prophylactic, and I would ask you if you could comment on the duration of treatment for patients who were given the drug therapeutically. How many patients received repetitive treatment courses? I think that is another issue.

The other point that has been raised and that for us has been a real problem is the use of oral vancomycin for C difficile. We had an epidemic problem at our VA hospital; giving the drug orally was associated with 65% conversion to positive carriage for VRE. Realizing you had a small number of patients treated with oral vancomycin, I would ask if any of these had stool cultures done to look for a similar phenomenon.

Would you speculate on the issue of how much restriction do you really need to affect resistance rates? My sense is that you almost have to eliminate the drug from the environment to do that.

Dr McManus: With reference to the question of endemic vs nonendemic situations, as I pointed out, we do not have endemic VRE. I am sure that most of you involved with patient care in tertiary referral services where VRE is not endemic have in the past and continue to use vancomycin without problems. I was unable to find data on the relationship of extensive use of vancomycin and the development of an endemic VRE situation. The commonly assumed effect of vancomycin use and the related appearance of VRE is a motivation for preparing use and the related appearance of VRE as a motivation for preparing for an epidemic setting. Certainly that is not logically connected, as you point out very well, with the potential virtue of restricting the drug.

As far as the repeated use of prophylactic vancomycin, large burns commonly require 5 or more excisions, and vancomycin was used at each operation. There was repeated use of vancomycin.

As far as treatment, I would say 10 days on average was the most common duration of treatment. With oral use, I cannot say that the patients who received oral vancomycin were specifically cultured for VRE in stools. They did, however, have stool cultures as part of the surveillance program. This went on at a time mostly prior to 1993 when the Enterococcus really was not considered much of a problem. As far as relative pathogenesis is concerned, enterococci are really not that big an issue in our experience.

Donald E. Fry, MD, Albuquerque, NM: Thank you for the opportunity to discuss this paper, which I think is a very provocative one. Our experience in a critical care setting has certainly been very different from Dr McManus’. In cultivating intensive care unit [ICU] patients in a surgery ICU after 5 days of intravenous vancomycin, 50% of those patients will have a VRE culturable from their stool even though a very, very small number of those patients actually end up with clinical infection. Our experience, however, with cephalosporin use has been dramatically greater than that which Dr McManus has presented, and that indeed may be a very major issue, as he has identified.

On the other hand, one of the critical issues in the evolution of resistance in any clinical setting is how one doses any
given antibiotic. Subtherapeutic dosing of antibiotics is probably the most significant way that one can encourage resistant organisms in any intensive care unit, and we have been subject to this cost-saving feeding frenzy right now of using smaller doses at longer treatment intervals, and in fact stretching vancomycin treatment out to longer treatment intervals probably provides the patient with a longer period of time for subtherapeutic concentrations to be floating around.

So I would ask Dr McManus if they have had any particular strategy relative to the aggressiveness with which they treat the patients with their IV antibiotics? I would surely say that 1 g every 12 hours, for example, is a treatment strategy that is certainly inviting resistance to occur in an ICU setting. Thank you.

Dr McManus: Dr Fry, it is interesting to have you talk about the enterococcus as a pathogen after all these years.

Dr Fry: I didn't say that. Look at the mortality rate in your own data, Albert, nobody died from it.

Dr McManus: As far as a 50% incidence after vancomycin use, once the organism is present, as I tried to say, selection for any of the resistances, which include all of the β-lactam agents, especially cephalosporins, could result in the selection of overgrowth. Well, I am asking you questions. I speculate that if you did not use vancomycin that your incidence, because of cephalosporin use, would also be 50%. I don’t know.

As far as dosing goes, I believe our most common dose is still 2 g a day, and we have not seen a problem with the enterococci. I didn’t mention the most common mechanism of spread of resistance of VRE. It is clonal. There are actually very few strains—when people look at their endemics in their hospitals, these are not new resistances that are popping up because of vancomycin use in virgin populations. These are resistant strains introduced into the hospital, spread by cross-contamination among the patients and then selected for overgrowth by antibiotic use. Restrictions of antibiotics are not going to prevent VRE. It is the old hand-washing, isolation problem that is really at issue here.