Evaluation of Zinc Bacitracin Capsules versus Placebo for Enteric Eradication of Vancomycin-Resistant Enterococcus faecium

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Patients who are colonized with enteric vancomycin-resistant Enterococcus faecium (VREF) are a major reservoir for transmission of and infection with this organism. In a randomized, controlled study to assess the effectiveness of high-dose bacitracin in the eradication of enteric VREF, 12 patients who were colonized with VREF were randomized to receive placebo \( n = 6 \) or orally administered zinc bacitracin \( n = 6 \) for 10 days. Posttreatment perirectal or stool cultures indicated that after 3 weeks, VREF had been eradicated from the stool of only 2 (33%) of 6 patients in each group. Of the 8 remaining patients who were still VREF-positive at 3 weeks after treatment, 5 (62%) had later evidence of spontaneous enteric eradication at 8 weeks. Further testing of VREF isolates revealed that a significant number \( n = 22, 76\% \) were resistant to bacitracin and that patients may have been colonized with multiple different VREF strains. Although bacitracin was not effective in the enteric eradication of VREF, the high rates of spontaneous eradication suggest that other host and environmental factors are more important in achieving long-term suppression or elimination of VREF colonization.

The emergence of resistance to vancomycin (hereafter referred to as “vancomycin resistance”) among enterococci and widespread colonization of patients with these strains has led to an increased rate of nosocomial infections of the bloodstream attributable to this pathogen. The majority of patients with serious vancomycin-resistant Enterococcus faecium (VREF) infections also have enteric colonization with VREF, now considered the major reservoir for infection and nosocomial transmission [1]. Strategies for the prevention of VREF infection have thus included stringent isolation precautions, antibiotic control policies, and attempts to eradicate enteric VREF colonization.

Two earlier clinical studies assessing the use of orally administered bacitracin for eradicating VREF colonization suggested that it had efficacy [2, 3]. However, both were hampered by lack of control groups and long-term follow-up. A more recent study by Weinstein et al. [4] that used a higher dose of bacitracin with doxycycline showed no significant difference in eradication of VREF among treated patients compared with untreated patients after a longer follow-up period of 4 months. Interestingly, although the majority of treated patients with initial VREF clearance eventually had relapse of VREF colonization, a significant number \( 37.5\% \) of nontreated patients had spontaneous clearance. To further assess the efficacy of high-dose orally administered bacitracin for eradication of enteric VREF, we conducted a pilot study with an 8-week follow-up of study patients.
METHODS

Study design. The study was a randomized, double-blind, placebo-controlled trial of orally administered zinc bacitracin given over a 10-day period to determine the efficacy of this drug in eradicating enteric VREF colonization. During an 8-week follow-up period, patients were also assessed for clinically relevant VREF infections, adverse events, and need for hospitalization or administration of antibiotics other than the study drug.

Patient population. Barnes-Jewish Hospital is a 1287 licensed-bed tertiary-care facility in St. Louis, Missouri. Since the first documentation of clinically significant VREF infection at this institution in 1995, several active surveillance studies have been implemented to identify unit-specific rates of VREF colonization. Outpatients in ambulatory care and those discharged from inpatient care with documented enteric VREF by stool or perirectal culture during these surveillance periods were recruited for study participation. Patients with intolerance to bacitracin, patients who were unable or refused to consent, and patients with repeat stool cultures negative for VREF at enrollment were excluded from the study.

Monitoring and enrollment. Patients were randomized to receive either placebo or zinc bacitracin (50,000 U) by mouth every 6 h for 10 days. Randomization and follow-up drug counts were coordinated by the hospital pharmacist, and outpatients were given the study drug in a bottle for self-administration. Enrollment occurred May 1998–April 1999. All patients had a second stool or perirectal culture performed on the day of enrollment. Baseline assessment of each patient was also performed, which included data on demographics, co-morbidities, immune status, current antibiotics or other medications, recent hospitalization, and laboratory test results. Patients were assessed for efficacy of treatment by means of follow-up stool or perirectal cultures on days 17, 24, 31, and 66 (±4 days) of the study. Monitoring for adverse effects and compliance was also performed during the course of treatment.

Definitions. “Treatment response” was defined as failure to detect enteric VREF by 3 consecutive weekly stool or perirectal cultures. We defined “treatment failure” as detection of VREF in ≥1 of the follow-up stool or perirectal cultures performed on days 17, 24, or 31. Spontaneous enteric eradication or decolonization was considered to have occurred if there was no detection of VREF in stool or perirectal cultures between enrollment and start of therapy or if a patient who had a VREF-positive culture at 3 weeks after treatment subsequently had a VREF-negative culture at 8 weeks after treatment. “Recolonization” was defined as the detection of VREF in stool or perirectal cultures at 8 weeks after treatment in patients who had earlier demonstrated a response to therapy. “Vancomycin resistance” was defined as MIC ≥16 μg/mL. “Bacitracin resistance” was defined as an MIC ≥64 μg/mL. Because there is no standardized defined cutoff for bacitracin resistance, this MIC was arbitrarily chosen on the basis of the concentration of drug in prior studies required to inhibit either VREF or Clostridium difficile obtained from stool as reported in studies elsewhere [2, 3, 5].

Microbiological methods. Isolation of VREF from stool or perirectal specimens was performed by streaking cotton-tipped swabs onto bile esculin agar plates supplemented with 6 μg/mL of vancomycin. Enterococci growing on this agar were further characterized by level of vancomycin resistance and genotype by measuring the size of the vancomycin inhibitory zone. Confirmed strains were then subjected to zinc bacitracin susceptibility testing by E-test (AB Biodisk) and detection of VanA or VanB resistance by use of PCR [6].

RESULTS

Nineteen patients had VREF-positive results of stool cultures and were randomized to receive placebo or bacitracin. Twelve patients completed the study (6 patients in the bacitracin group and 6 in the control group; table 1). Seven patients were excluded from the evaluation because they withdrew from the study (n = 1, day 2) or because they did not have follow-up stool cultures performed (n = 6). No patients were withdrawn because of adverse effects of bacitracin or lack of compliance. Eight (66%) of the 12 patients were women, 4 (33%) of the 12 patients had received an antibiotic during the 8-week post treatment follow-up, and all had been hospitalized within the previous 3 months. Four patients required hospitalization during the study period, with 3 of these patients subsequently receiving antimicrobial therapy and 3 having persistent VREF colonization at final follow-up. Surveillance culture results revealed that after 3 weeks of consecutive cultures (day 31), only 2 (33%) of 6 patients in the bacitracin group had negative VREF stool cultures, compared with 2 (33%) of 6 patients in the placebo group. After longer follow-up at 66 days, one of the successfully treated patients was recolonized, as demonstrated by a stool culture positive for VREF. Additionally, of the 8 remaining patients who still had VREF-positive cultures at day 31, 5 (62%) of 8 had negative results of stool cultures by day 66. None of the patients had any known history of exposure to another antibiotic with activity against VREF during the study.

At the end of the study, 29 of the 33 total VREF-positive stool specimens were characterized as to Van genotype and bacitracin susceptibility. Twenty-five (86%) were characterized as VanA, 1 (3%) as VanB, and 3 (10%) as neither (which were therefore assumed to be VanC). Twenty-two specimens (76%) were resistant to bacitracin, including 18 (72%) of the VanA...
strains and all VanB and VanC strains. All patients except one (in the bacitracin group) had ≥1 VREF samples resistant to bacitracin.

**DISCUSSION**

Despite the use of a high dose of bacitracin, there was no significant difference in the rate of colonization with VREF between the 2 study groups at final follow-up. Our findings thus complement those of the earlier study by Weinstein et al. [4], demonstrating recolonization of VREF among adequately treated patients and significant spontaneous eradication or de-colonization among nontreated patients. Although short-term suppression of VREF with bacitracin may still be possible, it is unlikely to offer a significant durable effect.

Interestingly, the patients in our study had VREF stool samples with much higher MICs to bacitracin, on average, than in studies elsewhere [2, 3, 5]. Bacitracin has been a good candidate drug for eradication of VREF from stool given its poor systemic absorption, high fecal concentrations, and in vitro activity against VREF. However, more recent in vitro studies have shown bacitracin activity against VREF to be variable at best [3, 7]. Unfortunately, our sample size was too small to detect any correlation between increasing resistance to bacitracin and drug treatment or duration of VREF colonization. It is possible that many patients with negative results of stool cultures really had VREF colonization that was simply undetectable by current laboratory methods. Nonetheless, there was a large variance of bacitracin MICs and the existence of ≥1 genotype for many of the patients, suggesting that patients may have successfully eradicated or suppressed one VREF strain, only to reacquire or express a different strain. Given the high bacitracin MICs exhibited in our patient population, it would be helpful to determine the bactericidal concentration in stool of any drug used in potential future studies involving long-term eradication of VREF colonization.

Many studies have examined the risk factors for acquisition and transmission of VREF, but, to our knowledge, no study has been performed to examine the natural history of persistent colonization with VREF. Our study followed patients for 8 weeks with no surveillance cultures beyond this time period; thus the long-term durability of our observations remains unclear. The study was also too limited to further explore the factors that may have contributed to spontaneous loss of VREF colonization. Infection with VREF and colonization with VREF have been associated with previous extensive antibiotic use, prolonged hospitalization, severity of illness, high colonization pressure, comorbidities, and person-to-person transmission [8–10]. A complex intermingling of such host and environmental factors likely determines the initial acquisition and later potential eradication of VREF. A large observational study of such patients would be necessary to further assess all of the potential determinants for eradication of VREF. Our results support such a study as being more clinically useful than further antibiotic trials for eliminating carriage of VREF.
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References