

Effect of Novobiocin-Containing Antimicrobial Regimens on Infection and Colonization with Vancomycin-Resistant *Enterococcus faecium*

Vancomycin-resistant *Enterococcus faecium* (VREF) is a new nosocomial pathogen for which there is no proven effective antimicrobial treatment (3). Novobiocin has good in vitro activity against VREF (5) and attains high concentrations in feces (10). We administered novobiocin-containing antimicrobial regimens to patients with VREF gastrointestinal (GI) colonization (≥ 2 consecutive perianal cultures growing VREF) and to patients with GI colonization and VREF bacteremia (≥ 1 blood culture with VREF).

Prior to treatment, VREF isolates (vancomycin MIC, ≥ 16 $\mu\text{g/ml}$) from 10 patients were susceptible to novobiocin by disk diffusion methods using a 30- μg novobiocin disk (zone, ≥ 23 mm) (1), and 9 isolates tested were susceptible to novobiocin by broth microdilution methods (MIC, ≤ 4 $\mu\text{g/ml}$) (6, 9). Determination of all MICs of novobiocin was performed twice. Isolates were resistant to ampicillin (MIC, ≥ 8 $\mu\text{g/ml}$) and susceptible to tetracycline (MIC, ≤ 2 $\mu\text{g/ml}$) or rifampin (MIC, ≤ 1 $\mu\text{g/ml}$) by the MicroScan type 6 panel (Baxter Diagnostics Inc., West Sacramento, Calif.) (8). Perianal swabs and blood were cultured for VREF by a method similar to that previously reported (7).

Ten patients received novobiocin-containing antimicrobial regimens; six patients had VREF GI colonization alone, and four patients had VREF GI colonization with bacteremia. Nine patients had a hematologic malignancy, and one patient had aplastic anemia; eight patients had a neutrophil count of $< 1,000/\text{mm}^3$. The six colonized patients received novobiocin (500 mg orally [p.o.] every 6 h [q6h]) plus tetracycline (500 mg p.o. q6h) (five patients) or doxycycline (100 mg intravenously [i.v.] q12h) (one patient) for a median of 3.5 days (range, 1 to 6 days). The four bacteremic patients received novobiocin plus doxycycline (100 mg i.v. q12h) (three patients) or rifampin (300 mg i.v. q12h) (one patient) for a median duration of 14 days (range, 7 to 19 days).

VREF could still be recovered from perianal swab culture with seven (88%) of eight patients while they were receiving novobiocin plus tetracycline or doxycycline. The median duration of novobiocin treatment at the time of the last positive perianal culture was 4 days (range, 1 to 15 days). The one patient who converted to negative perianal cultures failed to grow VREF on days 8 and 14 of treatment with novobiocin plus rifampin. The other two patients did not have perianal cultures performed during treatment, but VREF grew from perianal swabs obtained within 3 days after novobiocin was stopped. VREF bacteremia cleared, however, in the four patients receiving the novobiocin-containing regimens.

VREF isolates recovered from perianal culture of five patients after a median of 3 days (range, 1 to 3 days) of novobiocin all remained susceptible to novobiocin (MICs, ≤ 4 $\mu\text{g/ml}$), but one of the five isolates had an increase in the MIC of novobiocin compared with that for the pretreatment isolate (4.0 versus 1.0 $\mu\text{g/ml}$). These five VREF isolates remained susceptible to tetracycline (MIC, ≤ 2 $\mu\text{g/ml}$). Novobiocin was stopped because of intolerability in six patients; two patients could no longer tolerate oral medications, and four patients had increases in total serum bilirubin.

Short courses of novobiocin in combination with tetracycline or doxycycline were ineffective in eradicating GI colonization

with VREF and were poorly tolerated among these severely ill oncology patients. Although bacteremia cleared coincident with novobiocin-plus-doxycycline treatment, stool carriage persisted in bacteremic patients even after 15 days of treatment. Early reports on the use of novobiocin found patient tolerance to be poor (2, 4); however, in a recent study of novobiocin and rifampin for methicillin-resistant *Staphylococcus aureus* colonization, novobiocin was well tolerated (11). The use of novobiocin-containing antimicrobial regimens for the treatment of VREF infection requires further study.

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