Fecal Emergence of Vancomycin-Resistant Enterococci after Prophylactic Intravenous Vancomycin

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Citation

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Abstract

Purpose: To determine the emergence of vancomycin-resistant enterococci (VRE) in stool after prophylactic intravenous treatment with vancomycin in patients undergoing surgery for congenital heart disease.
Design: Prospective comparative study.
Setting: Multidisciplinary and post-cardiac surgery pediatric intensive care units.
Patients: Forty-one consecutive children aged 3 days to 18 years who underwent cardiac surgery and had not been treated with any antibiotics for 14 days prior to operation. All had positive stool cultures for enterococci. Eighteen children received only intravenous cefuroxime, 75 mg/kg/day for 2 days (control group), and 23 also received intravenous vancomycin, 30 mg/kg/day divided into 2 doses (study group).
Intervention: Stool cultures for enterococci.
Measurements and Results: Stool samples for bacterial culture were obtained before the antibiotic treatment, every day during the treatment, and 2 days after the drugs were discontinued. In cases of growth disappearance, cultures were taken until growth reappearance or discharge. In one of the 18 cefuroxime-treated children, fecal enterococcal growth disappeared one day after prophylactic treatment, and vancomycin-sensitive enterococci reappeared on the third day. In 5 of 23 vancomycin-prophylactic treated children, enterococcal growth disappeared after the second dose of vancomycin. The stool cultures then became positive for vancomycin-sensitive enterococci in 3 of the children and positive for vancomycin-resistant enterococci in one. In the fifth child, findings remained negative.
Conclusions: Perioperative prophylactic treatment with intravenous vancomycin in children undergoing surgical treatment for congenital heart disease does not seem to significantly increase fecal VRE when given over a short period.

INTRODUCTION

The genus Enterococcus, classified in the past as group D Streptococcus, includes at least 12 species. E. fecalis (85%) and E. faecium are the most common species associated with clinical enterococcal infection [1,2]. Currently, enterococcal species are the fourth leading cause of nosocomial infection in the United States [3].

Resistance of E. faecium to vancomycin was first described in 1988 [4]. Since then reports of infection with vancomycin-resistant enterococci (VRE) [5,6,7,8], also in the pediatric population [1,2,9] and in pediatric intensive care units [7,10,11,12], have been steadily increasing. Risk factors for infection with VRE are prolonged hospitalization [13,14], especially in intensive care units, and prolonged treatment with wide-spectrum antibiotics [13,15,16,17,18], mainly cephalosporins, aminoglycosides and vancomycin [19,20]. Recently, Donskey and colleagues reported the promotion of high-density fecal colonization with VRE after antianaerobic antibiotic treatment in 51 patients [21]. VRE infections are difficult to treat and have significant mortality rates.

To control the emergence of VRE infections, especially in light of the possible transference of resistant gene from VRE to Staphylococcus (as observed in vitro)[22], the Hospital Infection Control Practice Advisory Committee (HICPAC) of the Centers for Disease Control and Prevention (CDC) published specific recommendations for antibiotic therapy, especially vancomycin [23]. These include restriction on intravenous vancomycin treatment to: 1) infections by Gram-positive cocci resistant to -lactam antibiotics; 2) infections by Gram-positive cocci in patients with known hypersensitivity to -lactam antibiotics; and 3) therapeutic failure by metronidazole in cases of antibiotic-associated colitis. The recommendations also limit prophylactic intravenous treatment to vascular operations that involve a foreign material such as Gore-Tex, artificial valves or

pacemakers.

Although most of the risk factors for VRE have been recognized, the appearance of VRE in the stool of pediatric patients treated with a relatively short course of prophylactic perioperative vancomycin has not yet been studied.

MATERIALS AND METHODS

STUDY POPULATION

The study included children up to 18 years of age who underwent cardiac surgery at Schneider Children's Medical Center of Israel and were hospitalized in the Pediatric Intensive Care Unit and Post-Cardiac Surgery Unit. Inclusion criteria were positive stool culture for enterococci prior to operation and no antibiotic treatment for at least 14 days prior to operation. Signed informed consent was obtained from all the parents.

The children were divided into two groups: (1) those treated only with intravenous cefuroxime for 2 days, 75 mg/kg/day divided into 3 doses, one dose before surgery and 5 doses after (control group) and (2) those whose repair included use of foreign material (i.e. Gore-Tex, etc.) treated prophylactically in addition with intravenous vancomycin, 30 mg/kg/day divided into 2 doses, one dose before operation and one 12 hours after. Stool specimens were taken prior to operation, during antibiotic treatment and until at least three subsequent positive cultures after discontinuation of antibiotic treatment.

BACTERIOLOGIC EVALUATION

Stool specimens for bacterial cultures were taken before initiation of the antibiotic treatment, every day during treatment, and 2 days after the drugs were discontinued. In cases of growth disappearance cultures were taken until reappearance or discharge. In cases in which there was a suspicion of infection, specimens were also taken from blood, lung secretions and sputum, surgical wounds or sites of central venous line insertions, as necessary.

Swabs were inoculated on selective medium for enterococci, Slanet & Bartly growth cultures (Hy-Laboratories Ltd., Rehovot, Israel) and incubated at 42 C for 24 hours. Colonies suspected of being enterococci were tested on aesculin and 6.5% NaCl containing media (Hy-Laboratories Ltd.) at 37 C for 24 hours. Vancomycin susceptibility was tested by the disk diffusion technique (30 mcg vancomycin, Oxoid Ltd., Basingstoke, England) on blood agar. Resistance was defined as inhibition of bacterial growth of <14 mm diameter. The minimal inhibitory concentration (MIC) of the resistant isolates was tested by E-test (AB Biodisk, Solna, Sweden).

STATISTICS

Comparison between the study and control groups was performed by Fisher exact test for small numbers, using the SPSS 9.0 package for Windows (SPSS Inc., Cary, NC, USA).

RESULTS

The study population included 41 children aged 3 days to 18 years (median, 26.4 months); 18 were male and 23 female.

The study group included 23 children treated prophylactic with cefuroxime and vancomycin. In 19 patients, treatment with vancomycin was given for 2 doses according to the protocol. Vancomycin treatment was continued for another 1, 2, 7 and 17 days in four children because of suspected or proven bacterial infection. The cefuroxime treated group (control group) comprised 18 children.

The follow-up period for enterococcal growth was 5 to 28 days (median, 7 days). Cultures from 1/18 children (5.5%) treated with cefuroxime only and from 5/23 children (21.7%) treated also with vancomycin, became negative for enterococci after initiation of antibiotic treatment. The difference between the groups was not statistically significant ($p>0.05$).

In one child from the cefuroxime group whose stool culture became negative on the second day of antibiotic treatment it then became positive for vancomycin-sensitive enterococci on the third day.

In the five children from the vancomycin group, the stool became negative for enterococcal growth after the second dose of vancomycin. In one of those children who was treated with vancomycin for 8 days, cultures remained negative for 15 days of follow-up (discharged). In the other four children, the stool became positive again after 2 to 24 days – for vancomycin-sensitive enterococci in 3 children, and for vancomycin-resistant E. faecium in one; the MIC of the isolates resistant to vancomycin was 256 mcg/ml. The latter child had been treated with 2 doses of vancomycin. Details of the disappearance and reappearance of enterococci in the stools of the children treated with vancomycin are shown in Table l.

Of the 23 children treated with vancomycin, only one (4.3%) acquired VRE in the stool.

Enterococci were not isolated from any other site (blood, urine, sputum, or surgical wound).

Figure 1

Table l: Enterococcal Fecal Growth after Vancomycin Treatment

Patient No.	Duration of Treatment with Vancomycin (days)	Days of Antibiotic Treatment to Enterococcal Disappearance	Duration of Disappearance (days)
1	1	2	3
2	1	2	2
3	1	2	5
4	8	2	Throughout
5	18	2	25

Patient No.	Day of Reappearance (from day 1 of treatment)	Duration of Follow-up (days)	Vancomycin Susceptibility
1	5	7	Susceptible
2	4	7	Susceptible
3	7	8	Resistant
4	-	15	-
5	27	28	Susceptible

DISCUSSION

The present study was prompted by the rising rates of VRE-induced nosocomial infections among the pediatric population and the sparse data available on perioperative intravenous vancomycin as a risk factor for the emergence of VRE infection. To the best of our knowledge, this is the first study of the emergence of VRE in stool, the major source of resistant enterococcus, after short-term prophylactic intravenous treatment with vancomycin for cardiac surgery in infants and children.

In our study, all fecal enterococcal isolates obtained prior to the antibiotic treatment were vancomycin-susceptible. A similarly low prevalence of VRE in the community has also been previously reported [24]. The emergence of enterococci in the stool of children who tested negative for enterococci prior to hospitalization may be explained by nosocomial infection in the intensive care unit. Gordts and colleagues [19] identified hospitalization, prolonged stay in a hematology ward and prior vancomycin treatment as risk factors for gastrointestinal tract colonization with VRE. Similar results were reported by other investigators [25,26,27]. None of these studies, however, focused on short-term, prophylactic, intravenous vancomycin as a risk factor. We found that of 18 children treated with cefuroxime, enterococci disappeared from the gastrointestinal tract for a short time in only one; soon afterwards, vancomycin-sensitive enterococci reappeared. By contrast, of 23 children treated with vancomycin, the enterococci disappeared in 5; yet, with only a single reappearance of VRE.

The difference between the rates of enterococcal disappearance between the groups was not statistically significant which may be due to the relative small study population, and a future larger study is warranted.. Nevertheless, our findings highlight a problematic aspect of short-term, prophylactic intravenous vancomycin treatment. Vancomycin apparently depresses the enterococcal flora of the gastrointestinal tract, thereby enabling the emergence of vancomycin-resistant species of enterococci. The reports of Boyce and colleagues [5], Frieden and colleagues [6] and CDC [23] showing that stool is the reservoir of enterococci that can cause infections point to the possible risk posed by even short-term, prophylactic intravenous vancomycin treatment, at least in children. It appears that although the short-term vancomycin caused disappearance of the enterococci from the stool, the treatment duration was not long enough to cause the emergence of VRE. The effect of vancomycin on enterococcal growth emphasizes the need for the earliest possible withdrawal of the drug.

We conclude that treatment with intravenous vancomycin does not significantly increase VRE in the stool and therefore does not increase the risk of VRE infection if given over a short period. Our study highlights the need for a large, prospective, comparative study that would evaluate the safety of the short-term prophlactic use of vancomycin in post cardiac surgery children. Our findings also support the HICPAC recommendations for perioperative intravenous vancomycin prophylaxis.

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