Clinical and molecular epidemiology of enterococcal bacteremia in a pediatric teaching hospital

Celia Christie, MD, Jeanne Hammond, RN, Shirley Reising, PhD, and Jan Evans-Patterson, MD[a]

From the Department of Infectious Diseases, Children's Hospital Medical Center, Cincinnati, Ohio, and the Departments of Infectious Diseases and Laboratory Medicine, Yale University School of Medicine, New Haven, Connecticut

An apparent increase in the incidence of enterococcal bacteremias from 7 to 48/1000 bacteremias during 1986 to 1991 ($p < 0.01$) prompted this descriptive clinical and molecular epidemiologic study of 83 episodes occurring in 80 children between 1986 and 1992. Most community-acquired cases were in infants, in comparison with nosocomial episodes (24/26 and 34/57; $p < 0.01$); many of them were neonates (10/26 and 6/57; $p < 0.01$). Nosocomial cases were associated with underlying conditions including major surgery 56%, immunosuppression 49%, organ and tissue transplants 30%, and cardiac 32%, pulmonary 25%, renal 21%, and hepatic 21% disorders. Nosocomial episodes developed after a median of 32 days. There were 58 primary and 25 secondary bacteremias. Thirty-two episodes were polymicrobial and 44 organisms were involved. Twenty-six percent of the patients died. In 15%, death was preceded by septic shock, disseminated intravascular coagulation, and polymicrobial bacteremia ($p < 0.01$). Of 75 isolates, 82% were *Enterococcus faecalis* and 14% were *Enterococcus faecium*. Fourteen *E. faecalis* strains produced hemolysin; none produced β-lactamase. Three had high-level resistance to gentamicin and 13 to streptomycin; two *E. faecium* and none of the *E. faecalis* strains were vancomycin resistant at a low level ($p < 0.01$) and one was ampicillin resistant. Pulsed-field gel electrophoresis of whole-cell DNA digested with restriction enzymes *Sma* I and *Eag* I showed five isolates with a homogeneous pattern, two with another homogeneous pattern, and 68 with distinct heterogeneous patterns. The increase in enterococcal bacteremias was not due to a clonal strain dissemination but to an increase in cases of heterogeneous enterococcal strains. We conclude that enterococcal septicemia is now an important cause of serious morbidity and death in critically ill children. (J PEDIATR 1994;125:392-9)

Submitted for publication Oct. 13, 1993; accepted March 3, 1994.

Reprint requests: Celia Christie, MD, Assistant Professor of Pediatric Infectious Diseases and Infection Control Officer, Children's Hospital Medical Center, 3333 Burnet Avenue, Cincinnati OH 45229.

[a]Presently Associate Professor of Medicine, Department of Medicine, University of Texas Health Science Center, San Antonio, TX 78284-7881.

0022-3476/94/$3.00 + 0 **9/20/55722**

Enterococci have emerged as the third leading cause of nosocomial bacteremia in hospitals participating in the National Nosocomial Infections Surveillance System.[1] New chromosomal and plasmid-mediated resistance to β-lactam antimicrobial agents, glycopeptide resistance to vancomycin, and aminoglycoside-modifying enzymatic high-level resistance encoded by plasmid determinants have also developed among the enterococci in this decade.[2-10] Recent descriptive epidemiologic studies of enterococcal bactere-

CHEF	Contour-clamped homogeneous electrical field
EDTA	Ethylenediaminetetraacetic acid
MIC	Minimum inhibitory concentration
PFGE	Pulsed-field gel electrophoresis

mia in adults emphasize its frequent occurrence in hospitals, a high mortality rate, and the association with polymicrobial bacteremia and chronic underlying disease.[11-15] Although we have observed an apparent increase in the incidence of enterococcal bacteremias in recent years, reports of the pediatric spectrum of disease are limited.[16]

This study was therefore designed as a comprehensive overview of the clinical epidemiology of nosocomial and community-acquired episodes of bacteremia caused by enterococci during a 7-year period in our pediatric teaching hospital. Antibiotic resistance patterns to the enterococci were also determined. Finally, we investigated the molecular relatedness of the organisms by whole-cell DNA typing, using the contour-clamped homogeneous electric field technique of pulsed-field gel electrophoresis.

METHODS

Children's Hospital Medical Center is a 361-bed university hospital serving Greater Cincinnati, which has a 2.5 million referral population base. More than 16,000 children are admitted annually to this tertiary care hospital for an average duration of 5.1 days.

Patients. All enterococcal blood isolates for the period from 1986 to 1992 were identified through a review of our hospital's microbiology laboratory data bank. Simultaneously, all cases of nosocomial enterococcal bacteremia that were identified prospectively from the hospital-wide surveillance program during this period were extracted from the NOSO-3 version 2.2a database (Epi-Systematics, Inc., Fort Myers, Fla.). Hospital charts were reviewed for all the cases. Factors that were evaluated included patient demographics, underlying disease conditions, device use, invasive and other procedures, previous antibiotic therapy and other therapeutic modalities, clinical presentation, sites of infection, copathogens, antibiotic therapy, clinical outcome, and autopsy records.

Criteria. The definitions developed by the Centers for Disease Control and Prevention, Atlanta, Ga., were used to classify nosocomial and community-acquired infections.[17] These included primary bacteremia, secondary bacteremia, endocarditis, peritonitis, meningitis, cholangitis, urosepsis, deep surgical wound infections, and skin and soft tissue infections. "Line sepsis" was further defined as a positive blood culture finding in the presence of an infection at the intravascular catheter insertion site, a culture positive for enterococcus infection at the catheter tip, thrombus, or catheter insertion site. Bacteremia documented on admission in a patient who had a central line placed within the previous 30 days was also designated as nosocomial. Other bacteremias that were present on admission were designated as community acquired. Disseminated intravascular coagulation was defined as a bleeding disorder with prolongation of the prothrombin and partial thromboplastin times, low platelet count, and an elevated concentration of fibrin split products. Antibiotic regimens considered acceptable for enterococcal bacteremia included ampicillin, penicillin, vancomycin, or aminoglycoside monotherapy, or combinations of the aminoglycosides with any of the aforementioned antibiotics.

Microbiology. Enterococcal blood isolates were identified by bile-esculin reduction and growth in 6.5% sodium chloride[18] and then stored in whole sheep blood agar at −70° C. Isolates were thawed in 1992 and were reconfirmed with Rapid Positive Identification (Baxter Healthcare Corp., MicroScan Division, West Sacramento, Calif.). β-Lactamase production was determined with the use of nitrocefin.[19] Hemolysin production was assessed after growth of the organisms on human blood agar.[18] Antimicrobial susceptibility testing was performed with the National Committee for Laboratory Standards methods[20] for the agar plate dilution and the MicroScan microbroth dilution (Baxter Healthcare). Ampicillin resistance was defined at a standard breakpoint of a minimal inhibitory concentration >16 μg/ml. For this study, high-level resistance to gentamicin was defined at a cutoff point of MIC >500 μg/ml, and high-level resistance to streptomycin was determined at a cutoff point of >1000 μg/ml.[6] Such resistance was detected by agar dilution. Low-level resistance and high-level resistance to vancomycin were defined at MICs >8 to 16 μg/ml and >512 μg/ml, respectively.

Molecular studies. All enterococcal isolates were further characterized by the CHEF electrical fields modification of PFGE. Genomic DNA was prepared by the methods of Smith and Cantor[21] and Murray et al.[22] Bacterial agarose plugs were incubated overnight at 37° C in lysis buffer (Tris, 6 mmol/L; EDTA, 100 mmol/L; sodium chloride, 1.0; Brij-58 solution, 0.5%; deoxycholate, 0.2%; sarcosine, 0.5%; ribonuclease, 20 μg/ml; lysozyme, 1 μg/ml; pH, 7.6). The slices were washed at 37° C in TE (Tris, 10 mmol/L; EDTA, 0.1 mmol/L; pH 7.5) and then stored at 4° C. Whole-cell DNA was digested by incubation of the agarose plug in a buffered solution containing the restriction endonuclease *Sma* I according to the manufacturer's specifications (Bethesda Research Laboratories, Gaithersburg, Md.). We analyzed DNA using the CHEF device (CHEF-DR II; Bio-Rad Laboratories, Chemical Division, Richmond, Calif.). The pulse time was increased from 5 to 35 seconds in an 18-hour period at 198 volts for *Enterococcus faecalis*, whereas the pulse times were increased from

Table I. Associated factors for enterococcal bacteremia

	Total cases (n = 83)		Nosocomial cases (n = 57)		Community-acquired cases (n = 26)		
	No.	%	No.	%	No.	%	p
Age							
<1 mo	16	19	6	11	10	38	<0.01
<3 mo	41	49	20	35	21	81	<0.01
<1 yr	58	70	34	60	24	92	<0.01
1-6 yr	20	24	18	32	2	8	<0.01
6-12 yr	1	1	1	2			
>12 yr	4	5	4	7			
Underlying illness	67	81	57	100	10	38	<0.01

Table II. Sites of enterococcal infection

Infection sites	Total (n = 83)		Nosocomial (n = 57)		Community-acquired (n = 26)		
	No.	%	No.	%	No.	%	p
Primary bacteremia	58	70	36	63	22	85	<0.08
"Line sepsis"	18	22	18	32	0		<0.02
Secondary bacteremia	25	30	21	37	4	15	<0.05
Urosepsis	8	10	7	12	1		<0.05
Deep surgical wound	8	10	8	14	0		<0.05
Peritonitis	6	7	6	11	0		<0.20
Meningitis	5	6	4	7	1		0.90
Cholangitis	3	4	3	5	0		0.50
Endocarditis	4	5	4	7	0		0.30
Skin and other soft tissue	4	5	3	5	1		0.80
Necrotizing enterocolitis	3		2		1		
Tracheitis	2		2		0		
Pericarditis	2		2		0		
Polymicrobial episodes	32	39	24	42	8	31	0.50

1 to 20 seconds in a 15-hour period at 198 volts for *Enterococcus faecium*. Gels were then stained with ethidium bromide, 1 μg/ml, and photographed with ultraviolet illumination. Homogeneity among isolates was confirmed by repeat digestion with the restriction endonuclease *Eag* I (New England BioLabs Inc., Beverly, Mass.). Isolates were considered to be distinct if DNA patterns differed by two or more bands.

Data analysis. Data on the patient demographics, clinical presentations, microbiology, and molecular epidemiology were entered into the statistical program EPI INFO (version 5.1)[23] and analyzed by univariate analysis with the Fisher Exact Test (two tailed).

Table III. Copathogens with the enterococcus in 32 patients with polymicrobial bacteremia

Copathogen*	Organisms (No.)
Staphylococcus epidermidis	11
Escherichia coli	8
Klebsiella pneumoniae	7
Enterobacter aerogenes	4
Pseudomonas aeruginosa	2
Other pathogens	12
TOTAL ORGANISMS	44

RESULTS

Seventy-nine nosocomial and community-acquired enterococcal blood isolates were identified through the microbiology data bank, and 38 nosocomial bacteremias were identified from surveillance records of 1986 to 1992. Four episodes were deleted: two were identified by postmortem blood cultures, and two charts were not found. The study included 83 evaluable episodes of enterococcal bacteremia in 80 patients. There were 44 boys (55%).

Community-acquired bacteremia. Twenty-six episodes (31%) were community acquired. None of the patients with community-acquired bacteremia was transferred from another hospital. Most episodes occurred in infants and newborn infants without underlying disease, in comparison with those who had nosocomial bacteremia (Table I).

Nosocomial bacteremia. Fifty-seven episodes (69%) were nosocomial. Patients with nosocomial bacteremia were more likely to be older than 1 year of age than were those with community-acquired bacteremia (Table I). The period of hospitalization preceding nosocomial bacteremia was up to 816 days (median, 32 days; first quartile, 13 days; third quartile, 63 days; some were not hospitalized). Those with nosocomial bacteremia had serious underlying conditions. These conditions included major surgery (56%), immunosuppression (48%), organ and tissue transplantation (30%), and cardiac (32%), pulmonary (25%), renal (21%), and hepatic (21%) disorders.

Solid-organ transplants included liver (8), kidney (2), and heart (1). One of the six patients with bone marrow transplants had bacteremia after receiving bone marrow contaminated with the enterococcus. All six episodes of neonatal bacteremia were associated with serious underlying illnesses. Other major conditions were failure to thrive in 11 patients, congenital heart disease requiring cardiac surgery in 10, complicated disorders from the neonatal period in 12, and miscellaneous conditions in 7.

Table IV. Microbiology of enterococcal blood isolates

	Total	*E. faecalis*	*E. faecium*	*E. avium*	*E. durans*
Total	75	60(80%)	13 (17%)	1	1
Nosocomial infection	53 (71%)	42(79%)	10	0	1
CA infection	22 (29%)	18(82%)	3	1	0
Deaths	16 (21%)	13	3	0	0
β-Lactamase production	0	0	0	0	0
Hemolysin production	14 (19%)	14	0	0	0
Ampicillin R	1 (1%)	1	0	0	0
Gentamicin HLR	3 (4%)	2	1	0	0
Streptomycin HLR	13 (17%)	12	1	0	0
Vancomycin LLR	2 (3%)	0	2	0	0
Vancomycin HLR	0	0	0	0	0

CA, Community-acquired; *R*, resistance; *HLR*, high-level resistance; *LLR*, low-level resistance.

Nosocomial bacteremia was preceded, in 98% of the 57 patients, by the use of a device, procedure, or therapeutic modality: central lines (71%), chemotherapy and immunotherapy (33%), ventilator support (31%), arterial lines (23%), urinary catheters (16%), chest tubes (10%), tracheostomies (10%), and peritoneal dialysis and hemodialysis (8%). Forty-six percent were admitted to the intensive care unit. Seventy-seven percent of the patients with nosocomial bacteremia and 11% of those with community-acquired bacteremia were treated with antibiotics during the 3-month period preceding their bacteremia ($p < 0.01$). Forty percent of the nosocomial episodes were preceded by the use of a third-generation cephalosporin.

Sites of infection. Primary bacteremia occurred in 85% of community-acquired episodes and 70% of nosocomial episodes (Table II). "Line sepsis" complicated insertion of the following: central lines (11), arterial lines (4; 2 were for hemodialysis), umbilical catheter (1), peripheral line (1), and extracorporeal membrane oxygenation catheter (1). Two patients had two episodes each. Three cases of thrombophlebitis were associated with clot cultures positive for enterococcus. Secondary bacteremias were commonly seen with nosocomial bacteremias (Table II). Thirty sites with culture positive for enterococci accounted for 21 nosocomial episodes of secondary bacteremia.

Clinical features. Clinical features of enterococcal bacteremia included 61 patients (78%) with fever >38.3° C (31 of them were infants) and 31 patients (44%) with documented elevation in their leukocyte counts $>12 \times 10^9$/L ($12{,}000/mm^3$). Septic shock occurred in 10 patients (12%), and disseminated intravascular coagulation complicated five episodes (6%). Two patients had cyanosis and pallor. One neonate with community-acquired bacteremia had septic shock and disseminated intravascular coagulation complicating group B streptococcal septicemia and meningitis.

Outcome. Ninety percent of the patients (75 episodes) were treated with antibiotics; 48% received ampicillin with an aminoglycoside and 17% received ampicillin alone. A combination of vancomycin and an aminoglycoside, or vancomycin alone or an aminoglycoside alone, was given to 8% each. A penicillin analog or a cephalosporin was given to 5% each. Antibiotics were usually given intravenously for 7 to either 10 or 14 days in uncomplicated cases. Of those who were not treated with antibiotics, two ambulatory patients and one inpatient were already doing well when reexamined for a positive blood culture result. Their subsequent clinical course was benign. Five patients died before appropriate antibiotic therapy was commenced. Other therapeutic modalities included central line changes (seven patients), flushing of the central line with urokinase (one patient), or exploration of the central line (one).

Of the 80 children, 21 died; the crude mortality rate was 26%. In 12 children (15%) death was attributed to enterococcal bacteremia and 11 had underlying illnesses. Predictive factors for death included the presence of septic shock (9/10 vs 1/73; $p < 0.001$), disseminated intravascular coagulation (4/5 vs 1/78; $p < 0.001$), and polymicrobial bacteremia (6/12 vs 6/71; $p < 0.001$). The six polymicrobial episodes were associated with nine gram-negative enteric pathogens. Four polymicrobial episodes were associated with serious gastrointestinal conditions. Five patients with fulminating septicemia died, two of them in the outpatient department before appropriate antibiotic therapy for the enterococcus infection could be commenced. Five others died within 2 to 5 days of serious enterococcal sepsis while receiving appropriate antibiotic therapy. Nine children died of unrelated conditions 1 to 5 months after recovery.

Changing incidence. The incidence of total nosocomial and community-acquired enterococcal bacteremia was 7 of 1000 total episodes of bacteremia in 1986 and 48 of 1000 episodes of bacteremia in 1991 ($p < 0.002$). The incidence of nosocomial enterococcal bacteremia was 4% (3/79) in 1986, compared with 10% (10/101) in 1991. The incidence

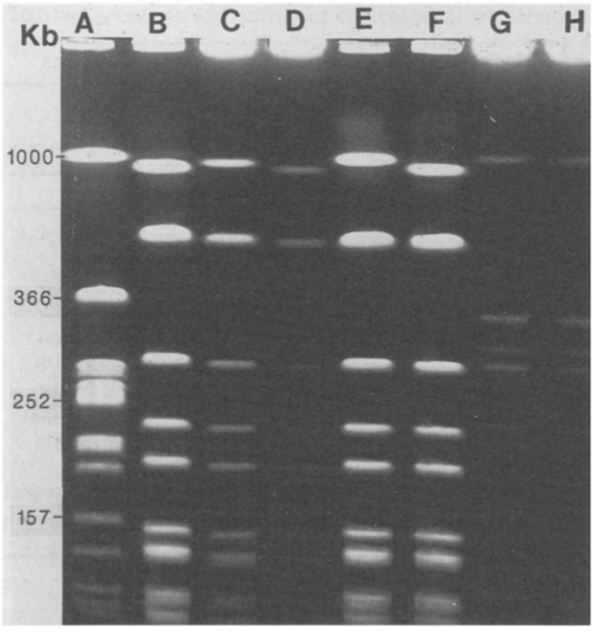

Fig. 1. Homogeneous enterococcal blood isolates, patterns A and B. *Lane A* shows the size standard, MG 1655. *Lanes B to F* show homogeneous isolates of *E. faecalis* with pattern A isolated from patients with nosocomial and community-acquired bacteremia. *Lanes G and H* show homogeneous isolates of *E. faecalis* pattern B isolated from patients with nosocomial bacteremia who were treated in the intensive care unit.

was 27 of 1000 total episodes of bacteremia in 1992 and represented 7% of all episodes of nosocomial bacteremia. Enterococci accounted for 7% (38/573) of episodes of nosocomial bacteremias during the 7 years (1986 to 1992) of prospective hospital-wide surveillance.

Polymicrobial bacteremia. Of the 80 patients, 30 (38%) had 32 episodes of polymicrobial enterococcal bacteremia caused by a total of 44 organisms (Tables II and III). Although 61% of the organisms were gram-negative aerobes, *Staphylococcus epidermidis* was the next most common isolate. Of the 32 polymicrobial episodes, 17 were associated with a primary polymicrobial site from which the same pathogenic organisms were isolated.

Microbiology. There were 75 enterococcal isolates available for further microbiology studies; 62 (83%) were subspeciated as *E. faecalis*, 11 (15%) were *E. faecium*, and there was one isolate each of *Enterococcus avium* and *Enterococcus durans*. Antibiotic resistance and β-lactamase and hemolysin production are tabulated (Table IV).

Molecular epidemiology. Whole-cell DNA CHEF PFGE typing of 75 enterococcal strains revealed 70 heterogeneous banding patterns: 5 *E. faecalis* isolates had a homogeneous pattern, 2 *E. faecalis* isolates had another homogeneous pattern, and 68 isolates had distinct heterogeneous patterns (Figs. 1 and 2).

DISCUSSION

Enterococci were previously considered organisms of low virulence, rarely capable of producing life-threatening infections. This pediatric study confirms reports that emphasize the increasing importance of the enterococcus as a significant pathogen in serious invasive infections with high attributable morbidity and mortality rates in adults.[1, 11-15, 24-27] Enterococci were the third most common cause of bacteremia in malnourished infants.[28]

Community-acquired enterococcal bacteremia in newborn infants and children is rarely described.[16, 29] Twenty-six episodes were identified in this study, compared with nine in the only other descriptive study of pediatric patients outside the neonatal period.[16] Our cases were predominantly community-acquired episodes in infants less than 3 months of age and without underlying illnesses, whereas the literature focuses on small numbers of neonates with underlying conditions and on nosocomial bacteremia.[16, 30-33] This difference is partly explained by our system of regionalization of neonatal care. Newborn infants are managed in general hospitals, where most nosocomial cases occur, whereas our pediatric hospital captures most episodes of community-acquired neonatal sepsis.

Underlying illnesses were present in our patients and also in the majority of adults with enterococcal sepsis.[11, 14] Major categories in adults were genitourinary disease and malignancies,[11] whereas our patients had immunosuppression, solid-organ or bone marrow transplants, and congenital heart disease requiring surgery.

Prior invasive procedures and antibiotic usage were common associated factors in adults.[11, 14] Serious enterococcal superinfections were reported in 42% to 77% of adult patients who were pretreated with broad-spectrum antibiotic agents.[13, 27] Pretreatment with third-generation cephalosporins, which have little activity against the enterococcus, has been proposed as a predisposing factor for enterococcal infection in adults.[26] There are no corresponding data in the pediatric literature. In our study, the majority of children were pretreated with antibiotics, and most received third-generation cephalosporins. Most nosocomial cases developed in the pediatric and neonatal intensive care units and the bone marrow transplant unit, where broad-spectrum antibiotic use is exceedingly high. Immunosuppressive therapy, device use, or invasive procedures were prevalent in our study.

There are no comparable pediatric data that separate primary and secondary enterococcal bacteremias.[16] Seventy percent of our patients had primary bacteremia. Cen-

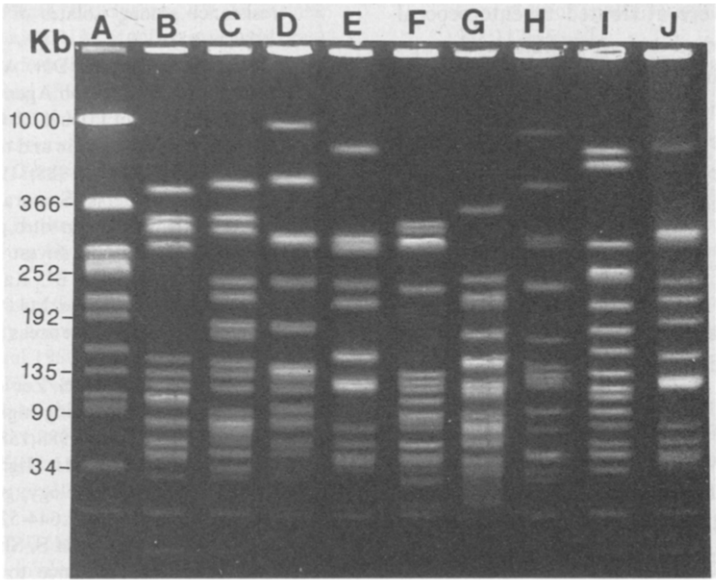

Fig. 2. Heterogeneous enterococcal blood isolates. *Lane A* shows the size standard, MG 1655. *Lane B* shows isolates from a 1-month-old infant in the neonatal intensive care unit with nosocomial acquisition of *E. faecalis*. *Lane C* shows isolates from a 9-month-old infant in the neonatal intensive care unit with nosocomial acquisition of *E. faecalis*; he died. *Lane D* shows isolates from a 17-day-old infant with Omen syndrome, with nosocomial acquisition of *E. faecalis* on the hematology-oncology service; he died. *Lane E* shows isolates from a 5-month-old infant with necrotizing enterocolitis; with nosocomial acquisition of *E. faecalis* in the pediatric intensive care unit; he died. *Lane F* shows isolates from an 18-year-old patient with angiosarcoma with nosocomial acquisition of *E. faecalis* in the pediatric intensive care unit; he died. *Lane G* shows isolates from an achondroplastic dwarf with community-acquired *E. faecium* bacteremia. *Lane H* shows isolates from a 2-month-old infant with respiratory distress syndrome and nosocomial *E. faecalis* bacteremia. *Lane I* shows isolates from a 1-month-old infant with community-acquired *E. faecalis* bacteremia. *Lane J* shows isolates from a 6-day-old infant with community-acquired *E. faecalis* bacteremia.

tral line insertion sites were the most frequent portal of entry for the enterococcus in this study, whereas this site accounted for 5% in an adult series.[11] Serious infection with enterococcus at intraabdominal sites included liver abscess, peritonitis, cholangitis, and enterocolitis, especially in the liver transplant population. This pattern, as in adults, suggested the colon or biliary tree as the portal of entry for the enterococcus.[24] In other adult studies the genitourinary system was the most common portal of entry.[12, 13]

Polymicrobial episodes were similar (35% to 38%) to those in adult series.[11, 13] In adults, enteric Enterobacteriaceae from the intestinal tract and biliary tree were the most common isolates.[25] In comparison, our cases had a high proportion of staphylococcal species as copathogens, reflecting central line–associated septicemias. Serious metastatic foci of bloodstream invasion of the enterococcus included meningitis, endocarditis, and pericarditis, although enterococcal endocarditis is rarely reported in children.[16]

Our proportion of *E. faecium* strains is higher than that reported in many series. This is important because *E. faecium* is often more resistant than *E. faecalis*; two of our strains of *E. faecium* had low-level resistance to vancomycin. Enterococci are intrinsically resistant to many antimicrobial agents.[2-8] High-level resistance to aminoglycosides caused by aminoglycoside-modifying enzymes was first reported in the United States in 1983 and is now global.[34] Such resistance is usually mediated by plasmids that are transferable. High-level gentamicin resistance was lower than expected and may be more representative of a pediatric institution. Rates of more than 55% have been reported in adults.[35]

Optimal antibiotic therapy of enterococcal bacteremia remains controversial.[11, 12, 14, 16, 35] The effect is also difficult to determine because of the high prevalence of severe underlying diseases and varied definitions of enterococcal bacteremia.[11, 13, 14, 27] In our study, community-acquired episodes (which were not associated with secondary foci of infection) were treated successfully with monotherapy. This concurs with adult reports that one antibiotic may be sufficient for bacteremia without endocarditis.[11, 14] Nosocomial cases with severe underlying diseases or secondary foci of infection were treated with combination therapy or van-

comycin. Twelve deaths were attributed to enterococcal bacteremia: five patients died before antibiotic therapy could be commenced and five died within 5 days of appropriate combination antibiotic therapy, which did not reverse their fulminating course. Because of increasing instances of isolation of resistant enterococcal strains, antibiotic therapy should be carefully reviewed when sensitivity patterns become available.

The high crude mortality rate of 26% was evidence of the severe nature of the premorbid illnesses in the patient population. The bacteremia-associated death rate (15%) compares with the 12% to 44% documented in adult medical series.[11, 13, 15] Septic shock or disseminated intravascular coagulation or both were present in 75% of the patients who died, and were positive predictive factors for death. The mortality rate was significantly higher in nosocomial cases. This was probably a reflection of the more serious underlying diseases, immunosuppression, and other sites of serious enterococcal infection. Polymicrobial bacteremia was also a predictive factor for death.

The CHEF PFGE typing was very useful in determining enterococcal strain identity. Our molecular epidemiologic patterns suggest that the increased rate of enterococcal bacteremias is not due to a clonal strain dissemination or cross-transmission in an outbreak, but to acquisition of infections with heterogeneous enterococcal strains, probably related to selection in the hospital environment (cephalosporins, devices). This heterogeneity supports the use of PFGE typing in an analysis of nosocomial transmission of enterococci and other bacteria.[36]

We recommend that hospitals monitor invasive enterococcal diseases, speciate enterococci, and screen for aminoglycoside and vancomycin resistance, while practicing judicious selection of antibiotics. This practice should facilitate the early recognition of emerging resistant enterococcal strains and implementation of the appropriate treatment and containment strategies.

We thank Martin Myers, MD, past director of infectious diseases, for his encouragement. We acknowledge the assistance of Mary Marx, Danita Carter, Katherine Quinn, and Patricia Farrell. We are grateful to the doctors and nurses who cared for these patients and to Walter Hierholzer, MD, who reviewed the manuscript. Celia Christie, MD, was a visiting scholar in hospital and molecular epidemiology at Yale University School of Medicine during September to December 1992.

REFERENCES

1. Banerjee SN, Emori TG, Culver DH, et al [National Nosocomial Infections Surveillance System]. Secular trends in nosocomial primary bloodstream infections in the United States, 1980–1989. Am J Med 1991;91(suppl 3B):86-9.
2. Bush LM, Calmon J, Cherney CL, et al. High-level penicillin resistance among isolates of enterococci. Ann Intern Med 1989;110:515-20.
3. Herman DJ, Gerding DN. Antimicrobial resistance among enterococci. Antimicrob Agents Chemother 1991;35:1-4.
4. LeClerq R, Derlot I, Duval J, Courvalin P. Plasmid-mediated resistance to vancomycin and teicoplanin in *Enterococcus faecium*. N Engl J Med 1988;319:157-61.
5. Murray BE, Mederski-Samoraj. Transferable beta-lactamase: a new mechanism for in vitro penicillin resistance in *Streptococcus faecalis*. J Clin Invest 1983;72:1168-71.
6. Patterson JE, Masecar BL, Kauffman CA, Schaberg DR, Hierholzer WJ Jr, Zervos MJ. Gentamicin-resistant plasmids from diverse geographic areas are heterogeneous. J Infect Dis 1988;158:212-6.
7. Patterson JE, Colodny S, Zervos MJ. Serious infection due to beta-lactamase producing high-level resistant *Streptococcus faecalis*. J Infect Dis 1988;158:1144-5.
8. Patterson JE, Zervos MJ. High-level gentamicin resistance in *Enterococcus*: microbiology, genetic basis and epidemiology. Rev Infect Dis 1990;12:644-52.
9. Williamson R, Al-Obeid S, Shlas JH, Goldstein FW, Shales DM. Inducible resistance to vancomycin in *Enterococcus faecalis*. J Infect Dis 1989;159:1095-104.
10. Zervos MJ, Kauffman CA, Therasse PM, Bergman AG, Mikesell TS, Schaberg DR. Nosocomial infection in gentamicin-resistant *Streptococcus faecalis*: an epidemiologic study. Ann Intern Med 1987;106:687-91.
11. Gullberg RM, Homann SR, Phair JP. Enterococcal bacteremia: an analysis of 75 episodes. Rev Infect Dis 1989;11:74-85.
12. Graninger W, Ragette R. Nosocomial bacteremia due to *Enterococcus faecalis* without endocarditis. Clin Infect Dis 1992;15:49-57.
13. Malone DA, Wagner RA, Myers JP, Watanakukorn C. Enterococcal bacteremia in two large community hospitals. Am J Med 1986;67:601-6.
14. Maki DG, Agger WA. Enterococcal bacteremia: clinical features, the risk of endocarditis, management. Medicine (Baltimore) 1988;67:248-69.
15. Rimailho A, Lampl E, Riou B, Richard C, Rottman E, Auzepy P. Enterococcal bacteremia in a medical intensive care unit. Crit Care Med 1988;16:126-9.
16. Boulanger JM, Ford-Jones EL, Matlow AG. Enterococcal bacteremia in a pediatric institution: a four-year review. Rev Infect Dis 1991;13:847-56.
17. Garner JS, Jarvis WR, Emori TG, Horan TC, Hughes JM. CDC definitions for nosocomial infections, 1988. Am J Infect Control 1988;16:128-40.
18. Facklam RR, Washington JA. Streptococcus and related catalase-negative gram-positive cocci. In: Balows A, ed. Manual of Clinical Microbiology. 5th ed. Washington, D.C.: American Society for Microbiology, 1991:238-57.
19. Patterson JE, Masecar BL, Zervos MJ. Characterization and comparison of two penicillinase-producing strains of *Streptococcus (Enterococcus) faecalis*. Antimicrob Agents Chemother 1988;32:122-4.
20. National Committee for Laboratory Standards. Approved standard: M7-A2—methods for dilution antimicrobial susceptibility tests for organisms that grow aerobically; vol 10, No. 8. 2nd ed. Villanova, Pennsylvania: The Committee, 1990.
21. Smith CL, Cantor CR. Purification, specific fragmentation and separation of large DNA molecules. Methods Enzymol 1987;155:449-67.

22. Murray BE, Singh KV, Heath JD, Sharma BR, Weinstock GM. Comparison of genomic DNAs of different enterococcal isolates using restriction endonucleases with infrequent recognition sites. J Clin Microbiol 1990;28:2059-63.
23. Dean JA, Dean AG, Brendel KA. EPI INFO. Version 5: word processing, database and statistics system for epidemiology on microcomputers. Atlanta, Georgia: Centers for Disease Control, 1991.
24. Blenkhorn JI, Blumgart LH. Streptococcal bacteremia in hepatobilliary operations. Surg Gynecol Obstet 1985;160:139-41.
25. Klimek JJ, Ajeman E, Gracewski J, et al. Enterococcal infections in a large community hospital, with emphasis on bacteremia. Am J Infect Control 1980;8:58-61.
26. Maghnuissen CR, Cave JC. Nosocomial enterococcal infections: association with use of third-generation cephalosporin antibiotics. Am J Infect Control 1988;16:241-5.
27. Barrall DT, Kenney PR, Slotman GJ, Burchard KW. Enterococcal bacteremia in surgical patients. *Arch Surg* 1985; 120:57-63.
28. Christie CD, Heikens GT, Golden MG. Coagulase-negative staphylococcal bacteremia in severely malnourished Jamaican children. Pediatr Infect Dis J 1992;11:1030-6.
29. Dagan R, Sofer S, Phillip M, Shachak E. Ambulatory care of febrile infants younger than 2 years of age classified as being of low risk for having serious bacterial infections. J PEDIATR 1988;112:355-60.
30. Buchino J, Ciambarella E, Light I. Systemic group D streptococcal infection in newborn infants. Am J Dis Child 1979; 133:270-3.
31. Luginbuhl L, Rothbart H, Facklam R, Roe M, Elliott J: Neonatal enterococcal sepsis: case-control study and description of an outbreak. Pediatr Infect Dis J 1987;6:1022-30.
32. Dobson S, Baker C. Enterococcal sepsis in neonates: features by age of onset and occurrence of focal infection. Pediatrics 1990;85:165-71.
33. Bavikatte K, Schreiner RL, Lemons JA, Gresham EL. Group D streptococcal septicemia in the neonate. Am J Dis Child 1979;133:493-6.
34. Zervos MJ, Kauffman CA, Therasse PM, Bergman AG, Mikesell TS, Schaberg DR. Nosocomial infection caused by gentamicin-resistant *Streptococcus faecalis*: an epidemiologic study. Ann Intern Med 1987;106:687-91.
35. Hoge CW, Adams J, Buchanan B, Sears SD. Enterococcal bacteremia: to treat or not to treat—a reappraisal. Rev Infect Dis 1991;13:600-5.
36. Maslow JN, Mulligan ME, Arbeit RD. Molecular epidemiology: application of contemporary techniques to the typing of microorganisms. Clin Infect Dis 1993;17:153-64.