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Randomized Controlled Trial of Selective Bowel Decontamination for Prevention of Infections Following Liver Transplantation

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Nonabsorbable antibiotics for selective bowel decontamination (SBD) sometimes are administered to liver transplant patients to prevent postoperative infections, but the efficacy of SBD is not known. Accordingly, we prospectively studied 69 patients randomly assigned to receive conventional prophylaxis with systemic antibiotics (control patients) or conventional prophylaxis plus oral nonabsorbable antibiotics for SBD (SBD patients). Overall rates of bacterial and/or yeast infections were nearly equal among control patients (42%) and SBD patients (39%). However, the infection rate at SBD key sites (abdomen, bloodstream, surgical wound, and lungs) was lower among patients who received the SBD regimen ≥3 days before transplantation (23%) than among control patients (36%). Administration of the SBD regimen was complicated by gastrointestinal intolerance and noncompliance but not by increased stool colonization with antibiotic-resistant gram-negative bacilli. Practical problems associated with administering an SBD regimen to patients awaiting cadaver liver transplants limit the regimen's usefulness, but we found a trend toward reduced key site infections when the regimen was given ≥3 days before transplantation.

The incidence of bacterial or fungal infection following orthotopic liver transplantation often has exceeded 50% despite perioperative prophylaxis with systemic broad-spectrum antibiotics [1–5]. Aerobic gram-negative bacilli and yeast have been the predominant pathogens, prompting some transplant centers to add oral nonabsorbable antibiotics to the prophylaxis regimen to selectively eliminate these organisms from the alimentary tract [6]. This approach, called selective bowel decontamination (SBD), has yielded low rates of postoperative infection and a paucity of cases of infection due to aerobic gram-negative bacilli at several centers [7–12].

However, rates of infection have remained high among liver transplant recipients at other centers using SBD [13, 14], and SBD has not been uniformly successful for nontransplant patients treated in intensive care units [15–17]. Because of uncertainty about the efficacy of SBD, we conducted a randomized, controlled trial comparing systemic antibiotic prophylaxis with systemic antibiotic prophylaxis plus SBD for liver transplant recipients at the University of Chicago Hospital. In this report, we describe our findings, and we identify factors associated with an increased risk of postoperative bacterial or yeast infection.

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Patients and Methods

Patient Enrollment and Regimens of Antimicrobial Prophylaxis

All patients who had received approval between 1 September 1991 and 31 March 1993 to undergo orthotopic liver transplantation at the University of Chicago Hospital were asked to participate in this study. Patients were eligible if they were not allergic to any of the antibiotics used in this study and if they or their parents were able to give informed consent. Patients were grouped according to donor source (cadaver or living related donor), and the patients within each group were randomly assigned to receive either of two regimens of perioperative antibiotic prophylaxis. Sequentially numbered opaque envelopes, each containing a computer-generated randomized assignment, were prepared for the two groups, and the lowest-numbered remaining envelope in sequence was opened to learn the regimen at the time consent for each patient was obtained.

The first regimen consisted of intravenous cefotaxime and ampicillin administered 30 minutes before surgery, every 6 hours intraoperatively, and then every 8 hours thereafter for 48 hours. Each dose of cefotaxime or ampicillin for adults was 2 g, and the dose for children (younger than 16 years of age) was 40 mg/kg. The second regimen consisted of ampicillin and cefotaxime administered the same as in the first regimen; a suspension of gentamicin (80 mg/10 mL), polymyxin E (100 mg/10 mL), and nystatin (2 million U/10 mL) given orally or per a nasogastric tube every 6 hours; and a paste containing 2% gentamicin, 2% polymyxin E, and 2% nystatin applied to the buccal mucosa every 6 hours while the patient was in the intensive care unit receiving respiratory support [6].

Each dose of the suspension of oral antibiotics for adults was 10 mL; the dose for children ≤10 kg was 2.5 mL, and the dose for children 11–30 kg was 5 mL. Patients who were to receive a cadaver liver were instructed to begin taking the

suspension of oral nonabsorbable antibiotics when active search for a donor began; patients who were to receive a liver segment from a living related donor began taking the suspension of oral nonabsorbable antibiotics 3–5 days before the scheduled date of transplantation. Both groups of patients continued taking oral nonabsorbable antibiotics for 21 days after transplantation unless they were discharged sooner from the hospital.

Surveillance Cultures

Swab specimens of stool or rectum from each patient were obtained initially within 24 hours of surgery and then weekly for 3 weeks. The swabs were held in aerobic transport medium (Culturette; Microdiagnostics, Lombard, IL) and within 2 hours were plated onto MacConkey agar and Sabouraud dextrose agar with gentamicin (Remel, Lenexa, KS) by means of the four-quadrant streaking technique [18]. Plates were incubated aerobically at 35°C for up to 72 hours, and aerobic gram-negative bacilli on MacConkey agar were recognized by characteristic morphology and gram-stained appearance. Identification of genus and species was determined by an automated photometric in vitro testing system (VITEK Model 240; bioMérieux Vitek, Hazelwood, MO). Susceptibilities of aerobic gram-negative bacilli to gentamicin, polymyxin E, cefotaxime, and ampicillin were tested by the Kirby-Bauer disk diffusion method [19].

Colonies growing on Sabouraud dextrose agar with gentamicin were identified as yeast based on colony morphology and gram-stained appearance. Colonies resembling *Candida* were inoculated into tubes containing horse serum that were incubated for 2 hours at 35°C and inspected for germ tube production. If the inspection was negative, further identification was carried out with a commercial biochemical system (API 20 C^R System; Analytab Products, Plainview, NY). The quantity of aerobic gram-negative bacilli and yeast on the primary plating media was recorded as few if growth was confined to the first quadrant only, as moderate if growth was present on the first and second quadrants, and as heavy if growth extended to the third quadrant.

Detection of Infection

During hospitalization, all patients were evaluated for bacterial or fungal infection twice each week by one of the investigators (G.C.C. or R.Z.). A definite infection was considered to be present when standard clinical criteria [20] were met and cultures of a specimen from the infected site yielded a bacterial or fungal pathogen. The diagnosis of cholangitis required isolation of the same organism from blood and purulent drainage from a T tube or isolation of an organism from blood alone when there was histologic evidence of cholangitis in a liver biopsy specimen and no other apparent source of infection. Patients were considered to have suspected infection if at least two of the following criteria were present without other explanation: a single oral temperature of >38.5°C or a temperature of >38.3°C on at least two occasions during a 24-hour period >2 days after transplant surgery, an oral temperature of <35.6°C, an unexplained WBC count of >12,000/mm^3 or a differential WBC count of >10% band forms, a sustained decrease in systolic blood pressure of >40 mm Hg or a systolic blood pressure of <90 mm Hg, or unexplained progressive respiratory failure.

Demographic and Clinical Information

The following information was collected to characterize each patient: before transplantation—age, sex, body weight, major diagnosis, serum creatinine level, serum bilirubin level, previous liver transplants, and systemic antibiotic treatment during the preceding week; during transplant surgery—type of donor, duration of surgery, blood products administered, and type of biliary drainage constructed; and after transplant surgery—primary immunosuppressive regimen, number of rejection episodes, surgical complications (intraabdominal bleeding, bile leak, portal vein thrombosis, hepatic artery thrombosis, or failure of the transplanted liver), infections, antimicrobial treatment, and outcome. Primary endpoints were bacterial or yeast infections during the first 28 days following transplantation. Infections involving the following key sites were considered to be potentially preventable by SBD: abdomen, surgical wound, bloodstream (without an apparent primary source), and lungs.

Statistical Methods

A study sample of 90 patients was to be selected on the basis of calculations that this sample size would provide a 70% power for detecting a 50% decrease in the rate of bacterial or fungal infections from 50% among the control patients (α level, 0.05). Patients who had been enrolled in the study were excluded from the evaluation if they died before transplantation, withdrew from the study, or received an alternative prophylactic regimen.

Continuous variables were compared by the two-sample t test, and sample proportions were compared by the χ^2 test or Fisher's exact test [21]. All P values were two-sided. A multivariate analysis of risk factors for infection was performed with the following variables: demographic and clinical information cited in the preceding section, results of initial surveillance cultures of stool, and the prophylactic regimen. Variables first were examined by the χ^2 test, and those with P values of $\leq .15$ were tested simultaneously by logistic regression [22]. Variables were included in the final model if they significantly improved the fit ($P \leq .05$) on the basis of the likelihood ratio test. The prophylactic regimen and the presence of aerobic gram-negative bacilli in the initial stool specimen were examined for inclusion as variables in the final model even though they had not met earlier inclusion criteria.

Results

Enrollment and Characteristics of Patients

During 19 months, 86 patients were enrolled in the study and were randomly assigned to receive either systemic antibiotic prophylaxis (38 control patients) or systemic antibiotic prophylaxis and oral nonabsorbable antibiotics for SBD (48 SBD patients). Seventeen of the 86 patients subsequently were excluded because they died before transplantation (9), withdrew either without explanation (2) or because of severe gastrointestinal symptoms attributed to the initial doses of oral nonabsorbable antibiotics (4), or received an alternative regimen of perioperative antibiotic prophylaxis (2). Sixty-nine patients were able to take their assigned regimen and were evaluated. The baseline characteristics, parameters of transplant surgery, and immunosuppressive regimens of the 36 SBD patients were similar to those of the 33 control patients (table 1).

Administration of Antibiotic Prophylaxis

Systemic cefotaxime and ampicillin were administered to the 69 evaluated patients in accordance with the study protocol. Twenty-eight of the 36 SBD patients reported taking their preoperative regimen as directed. For these 28 patients, the median duration of SBD therapy before transplantation was 14 days (range, 2–100 days); 26 of these patients received the SBD regimen for at least 3 days. The eight other SBD patients had not taken oral nonabsorbable antibiotics during the week before transplantation; of these eight patients, three underwent transplantation on the same day that they consented to participate in the study, and five had stopped taking oral nonabsorbable antibiotics during the 12- to 171-day period (median, 110 days) that they waited for a donor liver.

Outcome

During the first 28 days after transplantation, 37 bacterial and/or yeast infections occurred in 28 (41%) of the 69 evaluated patients. The most common sites were the abdomen (12 cases), bloodstream (7 cases from an infected intravascular catheter and 6 cases without an apparent primary source), and surgical wound (6 cases). Twenty-nine infections were caused by bacteria alone, 5 were caused by yeast alone, and 3 were caused by bacteria and yeast. The predominant bacterial pathogens were coagulase-negative *Staphylococcus* (10 cases), *Enterococcus* species (7), *Escherichia coli* (6), *Staphylococcus aureus* (6), and *Pseudomonas aeruginosa* (3). All yeast infections were caused by *Candida albicans* (8 cases).

Of the 36 SBD patients, 39% (14) had at least one bacterial and/or yeast infection, and 33% (12) had at least one bacterial infection. Of the 33 control patients, 42% (14) had at least one bacterial and/or yeast infection, and 39% (13) had at least one bacterial infection. There was no statistically significant difference between the two treatment groups in the proportion of patients with bacterial and/or yeast infections ($P = .76$; χ^2 test; 95% CI for the difference, −19.7–26.7) or the proportion of patients with bacterial infection ($P = .60$; χ^2 test; 95% CI for the difference, −16.6–28.8). The risk of bacterial and/or yeast infection at key sites (where prophylaxis with oral nonabsorbable antibiotics is expected to be of benefit) was

Table 1. Characteristics of liver transplant recipients receiving either systemic antibiotic prophylaxis (control patients) or systemic antibiotic prophylaxis and oral nonabsorbable antibiotics for SBD (SBD patients).

Characteristic	Control patients*	SBD patients†
No. of patients	33	36
No. of pediatric/adult patients	16/17	20/16
No. of males/females	15/18	15/21
No. (%) with underlying liver disease		
Biliary atresia	10 (30)	10 (28)
Viral hepatitis	5 (15)	7 (19)
Other	18 (55)	19 (53)
No. (%) with transplant urgency		
UNOS status 2	7 (21)	11 (31)
UNOS status 3‡	12 (36)	10 (28)
UNOS status 4‡	8 (24)	7 (19)
Not reported (living related donor)	6 (18)	8 (22)
Mean serum creatinine level ± SD (mg/dL)	0.83 ± 0.77	0.92 ± 1.01
No. (%) with serum creatinine level of ≥1.5 mg/dL	4 (12)	4 (11)
Mean serum bilirubin level ± SD (mg/dL)	13.8 ± 14.1	15.0 ± 12.9
No. (%) with serum bilirubin level of ≥12 mg/dL	14 (42)	17 (47)
No. (%) received prior liver transplant	2 (6)	3 (8)
No. (%) received systemic antibiotics during prior 2 w	6 (18)	8 (22)
No. received cadaver liver/living relative liver	27/6	28/8
Mean operative time ± SD (h)	7.8 ± 2.3	8.2 ± 2.5
No. (%) with operative time of ≥8 h	14 (42)	20 (56)
Mean amount of transfused blood ± SD (vol)	2.3 ± 1.9	2.4 ± 2.0
No. (%) received ≥2 vol of transfused blood	14 (42)	13 (36)
No. (%) underwent biliary reconstruction		
Choledochojejunostomy	24 (73)	27 (75)
Choledochocholedochostomy	9 (27)	9 (25)
No. (%) received immunosuppressive regimen§		
Cyclosporine	23 (70)	31 (86)
Tacrolimus	5 (15)	3 (8)
Azathioprine	5 (15)	2 (6)

NOTE. The distribution of characteristics was compared in the two groups of patients by the t test for means and either Fisher's exact test or the χ^2 test for proportions. All P values were ≥.4. SBD = selective bowel decontamination; UNOS = United Network for Organ Sharing.

* Received intravenous cefotaxime and ampicillin.

† Received intravenous cefotaxime and ampicillin plus topical and oral gentamicin, polymyxin E, and nystatin.

‡ Patients who required hospital care while awaiting transplantation.

§ All patients also received methylprednisolone.

Table 2. Rates of bacterial and/or yeast infection in patients receiving either systemic antibiotic prophylaxis (control patients) or systemic antibiotic prophylaxis and oral nonabsorbable antibiotics for SBD (SBD patients) following liver transplantation.

Type of infection	No. (%) of patients with infection		
	Control patients (n = 33)	SBD patients	
		≤2 d* (n = 10)	≥3 d* (n = 26)
Infection by bacteria and/or yeast			
All body sites	14 (42)	3 (30)	11 (42)
Key sites†	12 (36)	3 (30)	6 (23)
Infection by bacteria			
All body sites	13 (39)	3 (30)	9 (35)
Key sites	12 (36)	3 (30)	5 (19)
Infection by aerobic gram-negative bacilli and/or yeast			
All body sites	8 (24)	2 (20)	4 (15)
Key sites	6 (18)	2 (20)	2 (8)
Infection by aerobic gram-negative bacilli			
All body sites	7 (21)‡	2 (20)	0‡
Key sites	6 (18)‡	2 (20)	0‡

NOTE. SBD = selective bowel decontamination.

* Days of administration of oral nonabsorbable antibiotics before transplantation. Administration of the regimen for ≥3 days was considered necessary for successful SBD.

† Sites at which prophylaxis with oral nonabsorbable antibiotics is expected to reduce the risk of infection: abdomen, surgical wound, bloodstream (without an apparent primary source), and lungs.

‡ $P < .05$ for each comparison of the rate of aerobic gram-negative bacilli infection in control patients with the rate of infection in SBD patients who received the regimen ≥3 days before transplantation (Fisher's exact test). $P > .4$ for all other comparisons of infection rates.

considered to be the most appropriate measure of SBD efficacy. This risk was lower among SBD patients (25%) than among control patients (36%), but the difference was not statistically significant ($P = .31$; χ^2 test; 95% CI for the difference, −10.3–33.0). Overall mortality during hospitalization was 8% (3 deaths) among 36 SBD patients and 9% (3 deaths) among 33 control patients.

For further analysis, SBD patients were divided into two groups: those who received the regimen ≥3 days before transplantation (adequate duration for SBD) and those who received the regimen ≤2 days before transplantation (inadequate duration for SBD). SBD patients in the latter group were similar to control patients in terms of risk of infection (table 2) and predominant sites and pathogens (table 3). When SBD patients who received the regimen ≥3 days before transplantation were compared with control patients, rates of infection caused by various pathogens at key sites and infection caused by aerobic gram-negative bacilli and/or yeast in the SBD patients were at least one-third lower (table 2). For example, bacterial and/or yeast infection at key sites occurred in 36% of control patients and in 23% of SBD patients whose regimen was started ≥3 days before transplantation ($P = .42$; Fisher's exact test; 95% CI for the difference, −9.8–36.3). The only differences that were statistically significant ($P < .05$) were in rates of infection by aerobic gram-negative bacilli at all sites or at key sites.

The distribution of infections in control patients and SBD patients who received the regimen ≥3 days before transplantation differed by site and pathogen (table 3). Eighty-three percent of the infections in control patients occurred at key sites, compared with 47% of infections in SBD patients ($P = .06$; Fisher's exact test; 95% CI for the difference, 6.1–67.2), and aerobic gram-negative bacilli were recovered from 56% of infections in control patients compared with none of the infections in SBD patients ($P < .01$; Fisher's exact test). The number of infections caused by gram-positive bacteria remained nearly the same in SBD patients and control patients.

The mean interval ± SD from transplantation until onset of bacterial and/or yeast infection was 12.7 ± 4.0 days for control patients, 11.0 ± 4.0 days for SBD patients who received the regimen ≤2 days before transplantation, and 11.1 ± 7.8 days for SBD patients who received the regimen ≥3 days before transplantation. Enterococci were isolated from three infections in two control patients and from four infections in three SBD patients who received the regimen for ≥3 days. Antibiotic susceptibility testing was performed only on two enterococcal isolates from two different sites of infection in an SBD patient.

Table 3. Distribution of infections in liver transplant recipients receiving either systemic antibiotic prophylaxis (control patients) or systemic antibiotic prophylaxis and oral nonabsorbable antibiotics for SBD (SBD patients).

Site of infection	Total no. of infections (no. due to all bacteria, aerobic gram-negative bacilli, yeast)		
	Control patients (n = 33)	SBD patients	
		≤2 d* (n = 10)	≥3 d* (n = 26)
Key sites†			
Bloodstream, primary infection	4 (4, 2, 0)	1 (1, 1, 0)	1 (1, 0, 1)
Abdomen	6 (6, 4, 2)	2 (2, 2, 0)	4 (3, 0, 1)
Wound	4 (4, 2, 0)	1 (1, 0, 0)	1 (1, 0, 0)
Lungs	1 (1, 1, 0)	0	1 (1, 0, 0)
Other sites			
Bloodstream, intravascular catheter infection	2 (1, 0, 1)	0	5 (4, 0, 1)
Urinary tract	1 (1, 1, 0)	0	3 (1, 0, 2)

NOTE. SBD = selective bowel decontamination.

* Days of administration of oral nonabsorbable antibiotics before transplantation.

† Sites at which prophylaxis with oral nonabsorbable antibiotics is expected to reduce the risk of infection: abdomen, surgical wound, bloodstream (without an apparent primary source), and lungs.

Table 4. Eradication of aerobic gram-negative bacilli from stool specimens from liver transplant recipients receiving either systemic antibiotic prophylaxis (control patients) or systemic antibiotic prophylaxis and oral nonabsorbable antibiotics for SBD (SBD patients).

	Percentage of patients with no aerobic gram-negative bacilli in stool (no. with negative culture/no. tested)		
		SBD patients	
Week	Control patients	≤2 d*	≥3 d*
0	19 (6/31)	30 (3/10)	58 (15/26)
1	17 (5/30)	80 (8/10)	81 (21/26)
2	24 (6/25)	83 (5/6)	87 (20/23)
3	24 (4/17)	75 (3/4)	84 (16/19)

NOTE. SBD = selective bowel decontamination.

* Days of administration of oral nonabsorbable antibiotics before transplantation.

Both isolates were *Enterococcus faecalis* and were resistant to vancomycin and ampicillin.

Complications

When SBD patients who received the regimen for ≥3 days were compared with control patients, there were no statistically significant differences (all P values, >.1) in the following post-transplant complications or therapies: rate of suspected infection (31% vs. 30%, respectively), rate of rejection (46% vs. 36%, respectively), rate of surgical complications (58% vs. 39%, respectively), or mean duration ± SD of systemic antibiotic therapy (16.6 ± 19 days vs. 10.4 ± 10.8 days, respectively). When SBD patients who received the regimen for ≤2 days were included in an analysis with either of the other two groups, all P values remained >.1.

Surveillance Cultures

Stool or rectal specimens for culture were obtained on at least one occasion from 68 study patients. As shown in table 4, aerobic gram-negative bacilli had been eradicated at the time of transplantation (week 0) from most of the SBD patients who received the regimen ≥3 days before transplantation but from few of the other patients. Following transplantation, the proportion of specimens free of aerobic gram-negative bacilli increased substantially in the two subgroups of SBD patients but not in the group of control patients. The quantity of aerobic gram-negative bacilli in culture-positive specimens was lowest for SBD patients who received the regimen ≥3 days before transplantation. Fifty-five percent (12) of 22 specimens from these patients had moderate or heavy growth of aerobic gram-negative bacilli, compared with 89% (8) of the nine culture-positive specimens from SBD patients given the regimen ≤2 days before transplantation and 90% (74) of the 82 culture-positive specimens from control patients.

The total number of isolates of aerobic gram-negative bacilli from surveillance cultures was 40 for the 26 SBD patients given the regimen ≥3 days before transplantation, 16 for the 10 SBD patients given the regimen ≤2 days before transplantation, and 159 for the 33 control patients. In each group, the proportion of isolates resistant to cefotaxime and the proportion of isolates resistant to gentamicin were as follows: 14% and 5%, 25% and 19%, and 22% and 3%, respectively. Only two isolates were resistant to both gentamicin and polymyxin E. One of these isolates, *Proteus mirabilis,* was recovered at transplantation from a SBD patient who had received the regimen for 60 days. The other isolate, *Burkholderia cepacia,* was recovered 1 week after transplantation from a SBD patient whose regimen had been started 10 days before transplantation. No isolates of aerobic gram-negative bacilli were resistant to ampicillin, cefotaxime, gentamicin, and polymyxin E.

Risk Factors

Multivariate analysis showed that two factors, pediatric age group (P = .001) and surgical complications (P = .01), were significantly associated with bacterial infection. When yeast infections were included in the analysis, the same two factors remained significant (both P values, <.02). The risk of bacterial infection in pediatric patients with surgical complications was about sevenfold greater than that of bacterial infection in adults with no surgical complications (table 5).

Randomization to SBD, treatment with the SBD regimen for at least 3 days before transplantation, and having no aerobic gram-negative bacilli or yeast in the stool specimen obtained within 1 day of transplantation each significantly decreased the risk of infection by aerobic gram-negative bacilli (all P values, <.03). These characteristics did not significantly reduce the risk of bacterial infection or bacterial and/or yeast infections (all P values, >.2).

Discussion

On the basis of the epidemiology of infections following transplantation, there is a logical rationale for the use of SBD

Table 5. Risk of bacterial infection related to age group and surgical complications in liver transplant recipients receiving either systemic antibiotic prophylaxis or systemic antibiotic prophylaxis and oral nonabsorbable antibiotics for selective bowel decontamination.

Risk category	Percentage of patients with bacterial infection (no. infected/no. at risk)
Adult without surgical complication	11.5 (3/26)
Adult with surgical complication	42.9 (3/7)
Child without surgical complication	46.7 (14/30)
Child with surgical complication	83.3 (5/6)

in liver transplant patients. First, the SBD regimen is directed against aerobic gram-negative bacilli and yeast, the principal pathogens that cause infection during the first month after transplantation [1–5]. Second, the most common sites of infection are the abdomen, bloodstream, lower respiratory tract, and surgical wound [1–5]. The pathogens that cause infections at these sites presumably arise from the gastrointestinal tract or oropharynx, the target sites of SBD. Third, infections may be initiated by events, such as enterotomy [23], that occur during surgery or by postoperative events, such as translocation [24] or aspiration of pharyngeal secretions [25, 26]. Therefore, it may be of benefit to extend prophylaxis for ≥1 week after transplantation, and the SBD regimen seems more appropriate than systemic antibiotics for this use. These considerations, together with favorable reports of SBD in other settings [27–29], have prompted many transplant centers to add SBD to their prophylactic regimen.

In the present study, which, to our knowledge, is the largest reported randomized, controlled trial of the use of SBD in liver transplant recipients, we found that SBD was not of substantial benefit in reducing overall rates of bacterial and/or yeast infections. However, when SBD patients whose regimens were given for ≤2 days (inadequate duration for eliminating aerobic gram-negative bacilli from the alimentary tract) [8, 27, 30] were excluded from the analysis, SBD was associated with a moderate decrease in the rate of infections at key sites (the most common and serious infections in control patients). Our ability to detect a statistically significant benefit of SBD was hampered by the low power associated with a modest sample size and by the small number of SBD patients who received the regimen ≥3 days before transplantation.

Our findings are not as favorable as those reported by Badger et al. [12] in an interim analysis of a randomized, controlled trial of SBD in liver transplant recipients. These investigators detected bacterial and/or yeast infections in only two of 14 SBD patients compared with eight of 16 control patients. However, they monitored patients for no more than 15 days after transplantation, an interval that would have detected only about one-half of the infections in the present study. In addition, the low rate of infection in their SBD patients is surprising, because the SBD regimen was not started until a donor organ was identified. In other studies in which SBD was begun on the day of transplantation, rates of infection were relatively high [13, 14, 31], and eradication of aerobic gram-negative bacilli from the alimentary tract was delayed [13, 30].

Emergence of bacteria resistant to the oral nonabsorbable antibiotics used for SBD is an important concern with this therapy. Selection of antibiotic-resistant aerobic gram-negative bacilli has occurred in patients given SBD for brief periods in intensive care units [17, 32, 33], and this occurrence could be an even greater hazard for liver transplant patients treated for weeks to months. Surprisingly, we found infrequent colonization of SBD patients by gentamicin-resistant and polymyxin E–resistant aerobic gram-negative bacilli, no infections by these bacteria, and a marked reduction in cefotaxime-resistant aerobic gram-negative bacilli in stool. There did not appear to be any substantial effect of SBD on gram-positive bacteria. As has been noted in other controlled trials [12, 31], the number of infections caused by gram-positive bacteria did not increase. We did not attempt to learn whether SBD promoted the emergence of vancomycin-resistant gram-positive bacteria, but this problem has been reported both from centers using SBD [34] and from centers that do not [35, 36].

The present study illustrates several practical problems that may limit the usefulness of SBD for liver transplant recipients. First, the oral nonabsorbable antibiotics caused immediate, severe gastrointestinal upset that prompted withdrawal from the study by four (8%) of the 48 patients initially randomized to SBD. Mild gastrointestinal upset has been described in at least one-third of patients at two other centers [31, 37], but the patients apparently continued taking the SBD regimen. Second, compliance with the regimen lapsed completely in five (18%) of our 28 SBD patients who survived the often lengthy wait for a cadaver liver. Patient compliance at other centers reportedly has been good but was not quantified [11, 37]. It is possible that better motivation or the substantially shorter wait for a donor liver [6] may have enhanced compliance. Third, the regimen could not be initiated before transplantation for three of our SBD patients, because they had fulminant hepatic failure and received a cadaver liver within 1 day.

Starting the SBD regimen several days before transplantation appears desirable for eliminating aerobic gram-negative bacilli from stool [30] and probably confers an optimal benefit [7, 9–11]; however, our experience suggests that compliance with this regimen cannot be reliably achieved except with scheduled transplantations of organs from living related donors.

The cost of the SBD regimen is not a major consideration. Our pharmacy cost for 10 mL of the oral suspension was $1.10, and the cost of 15 g of the antibiotic paste was $4.33. Thus, the cost of the SBD regimen for an adult patient given the oral suspension for 5 weeks (starting 2 weeks before transplantation) and the antibiotic paste for 2 days was about $160.

In summary, this study shows that there are practical problems associated with administering an SBD regimen preoperatively to liver transplant patients and that these problems limit the usefulness of the regimen. Nonetheless, in the subgroup of SBD patients given the regimen ≥3 days before transplantation, there appears to be moderate benefit in preventing infections at key sites.

Additional randomized, controlled trials are warranted to assess the efficacy of SBD for liver transplant patients and their compliance. These studies probably should focus on patients whose preoperative duration of the SBD regimen will be brief, i.e., patients who are scheduled to receive a liver segment from a living related donor and patients whose urgent United Network for Organ Sharing status is likely to limit their wait for a cadaveric liver. Finally, these studies should include microbiological monitoring to learn if the

SBD regimen promotes the emergence of antibiotic-resistant gram-positive or gram-negative bacteria.

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