Selective bowel decontamination with quinolones and nystatin reduces gram-negative and fungal infections in orthotopic liver transplant recipients

MARGARET J. GORENSEK, MD; WILLIAM D. CAREY, MD; JOHN A. WASHINGTON II, MD; DAVID P. VOGT, MD; THOMAS A. BROUGHAN, MD; MARY KAY WESTVEER, RN

■ Gram-negative and fungal infections are the most important cause of morbidity and mortality after liver transplantation, especially in the first postoperative month. From February 1989 to February 1990, all liver transplant recipients at The Cleveland Clinic Foundation, Cleveland, Ohio, were placed on a selective bowel decontamination regimen employing oral quinolones and nystatin beginning at the time they were put on the active waiting list for transplantation and continuing until the fourth postoperative week. The incidence of gram-negative and fungal infections for these patients was compared against a historical control group. Selective bowel decontamination was well tolerated and highly effective in reducing early serious gram-negative and fungal infections. This regimen may also reduce mortality.

□ INDEX TERMS: LIVER TRANSPLANTATION; DECONTAMINATION; ANTI-INFECTIVE AGENTS, QUINOLONE; NYSTATIN; GRAM-NEGATIVE BACTERIA; MYCOSES □ CLEVE CLIN J MED 1993; 60:139–144

INFECTION IS A COMMON complication after orthotopic liver transplantation.[1–3] Gram-negative and fungal infections remain a major cause of morbidity and mortality in these patients.[2,4,5] Recent studies suggest that selective bowel decontamination (SBD) employing nonabsorbable oral antibacterial and antifungal agents is highly effective in decreasing the incidence of bacterial and fungal infections in the first month after liver transplantation.[6]

Several studies have shown the oral quinolones norfloxacin and ciprofloxacin to be effective agents for SBD; they can prevent gram-negative infections in leukemic patients,[7–10] gram-negative bacilluria in patients undergoing hip replacement,[11] and gram-negative infections in liver transplant recipients.[4]

The purpose of this study was to see whether oral quinolones combined with high-dose nystatin suspension could prevent the development of serious gram-negative and fungal infections in the first month after orthotopic liver transplantation. In addition, it was hoped that SBD could reduce morbidity and mortality in these patients.

From the Department of Infectious Diseases, Cleveland Clinic Florida (M.J.G.), and the Departments of Gastroenterology (W.D.C., M.K.W.), Microbiology (J.A.W.), and General Surgery (D.P.V., T.A.B.), The Cleveland Clinic Foundation, Cleveland.

Address reprint requests to M.J.G., Department of Infectious Diseases, The Cleveland Clinic Florida, 3000 West Cypress Creek Road, Ft. Lauderdale, FL 33309.

MATERIALS AND METHODS

Study population

The study group consisted of 17 consecutive patients who underwent orthotopic liver transplantation at The Cleveland Clinic Foundation, Cleveland, Ohio, between February 1989 and February 1990. These

TABLE 1
DEMOGRAPHICS OF LIVER TRANSPLANTATION PATIENTS

Characteristic	Control group (no SBD, n=34)	SBD* group (n=17)
Age		
Mean	34 years	43 years
Range	19 months to 53 years	26 to 56 years
Pediatric patients	7 (20%)	0
Sex		
Male	17 (50%)	9 (53%)
Female	17 (50%)	8 (47%)
Race		
White	30 (88%)	14 (82%)
Black	3 (9%)	2 (12%)
Asian	1 (3%)	1 (6%)
Underlying liver disease		
Chronic active hepatitis	10 (29%)	7 (41%)
Postnecrotic cirrhosis	5 (14%)	3 (18%)
Chronic active hepatitis B	3 (9%)	0
Wilson's disease	3 (9%)	0
Primary biliary cirrhosis	3 (9%)	2 (12%)
Sclerosing cholangitis	3 (9%)	1 (6%)
Hepatocellular carcinoma	2 (6%)	0
Budd-Chiari syndrome	1 (3%)	0
Alagille's syndrome	1 (3%)	0
Fibropolycystic liver disease	1 (3%)	0
Congenital biliary atresia	1 (3%)	0
Alcoholic cirrhosis	1 (3%)	2 (12%)
Alpha-1 antitrypsin deficiency	0	1 (6%)
Methotrexate toxicity	0	1 (6%)

*Selective bowel decontamination

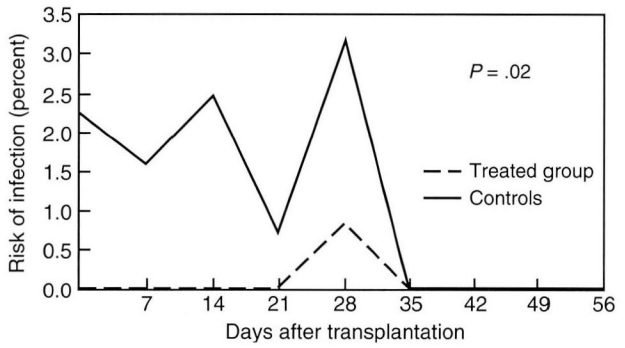

FIGURE 1. Risk of infection in the first month after liver transplantation was significantly lower (P = .02) in patients treated with selective bowel decontamination than in control patients.

patients had been placed on SBD beginning at the time they were put on the active waiting list for transplantation and continuing until 1 month after transplantation. They were followed prospectively for evidence of gram-negative and fungal infections. The incidence of gram-negative and fungal infections in the first month after liver transplantation in this group of patients was then compared with a historical control group consisting of the initial 34 patients who had undergone liver transplantation in our center; these patients had not received SBD.[12] The groups were similar, except that the SBD group included no pediatric patients and had a slightly higher incidence of chronic active hepatitis (*Table 1*).

Bowel decontamination regimen

The SBD regimen consisted of norfloxacin, 400 mg po bid, and nystatin suspension, 2 million units po qid. The regimen was initiated when the patients were put on the active waiting list for liver transplantation and continued orally up to the time of transplantation. The regimen was maintained via nasogastric tube during the postoperative period while the patient was not taking medication po, and then was continued po for 4 weeks after transplantation. During the hospital stay, ciprofloxacin, 250 mg po bid, was substituted for norfloxacin because norfloxacin was not available on the hospital formulary. In addition, during the period of intubation, a special hydrocortisone acetate topical paste consisting of polymyxin 2%, gentamicin 2%, and nystatin 2% was swabbed around the endotracheal tube and in the oropharynx qid. Perioperative antibiotics, usually consisting of a third generation cephalosporin plus metronidazole, were administered for 5 days after transplantation.

Immunosuppression

Immunosuppression consisted of tapering dosages of corticosteroid and cyclosporine in the standard liver transplantation protocol, with close monitoring of cyclosporine levels. Azathioprine was used in patients who required additional maintenance immunosuppression, or who could not tolerate cyclosporine. Rejection, as diagnosed on routine liver biopsies, was treated with a 5-day cycle of increased levels of corticosteroid or, in refractory cases, with 10- to 14-day courses of Minnesota antilymphocyte globulin or muromonab-CD3 (OKT3).

Prospective infection surveillance

All patients were followed prospectively from the time of organ transplantation for evidence of infection. Twice-weekly surveillance cultures were taken of urine and sputum, as well as from any abdominal or other drainage tube in the first 4 weeks after transplantation. In addition, when clinically indicated, additional cul-

tures were obtained from blood, ascitic, pleural, or peritoneal fluid, abscess material, or other tissue. Specimens were examined microscopically with stains for bacteria, fungi, and (when indicated) mycobacteria, and they were cultured for bacteria, fungi, viruses, and mycobacteria (when indicated). Tissue specimens were also submitted for histopathologic analysis.

TABLE 2
INFECTIONS IN LIVER TRANSPLANT PATIENTS: EFFECT OF SELECTIVE BOWEL DECONTAMINATION

Infectious agent	Number of infections	Associated clinical problems
Control group		
Acinetobacter anitratus	3	Pneumonia, perihepatic abscess, biliary sepsis
B-hemolytic Streptococcus	1	Pneumonia
Candida albicans	13	Esophagitis, sepsis, peritonitis, pneumonia, cholangitis, fungemia, wound infection, urinary tract infection
Candida tropicalis	2	Urinary tract infection, peritonitis
Citrobacter freundii	4	Peritonitis, sepsis, liver abscess
Coagulase-negative Staphylococcus	5	Bacteremia, sepsis, subhepatic abscess
Enterobacter aerogenes	2	Liver abscess, cholangitis
Enterobacter cloacae	1	Peritonitis
Enterococcus	4	Peritonitis, perihepatic abscess
Escherichia coli	4	Cholangitis, sepsis, urinary tract infection, peritonitis
Pseudomonas maltophilia	2	Bacteremia, biliary sepsis, peritonitis, pneumonia
Pseudomonas aeruginosa	10	Pneumonia, cholangitis, bacteremia, sepsis, peritonitis, urinary tract infection
Serratia marcescens	3	Pneumonia, bacteremia, sepsis
Staphylococcus aureus	1	Pneumonia
Torulopsis glabrata	3	Fungemia, peritonitis, sepsis, subhepatic abscess
Selective bowel decontamination group		
Pseudomonas aeruginosa	1	Cholangitis, peritonitis

Definition of infection

Infection was defined as recovery of a pathogen or potential pathogen from a generally sterile body site or in significant quantity from another body site where it was determined to be causing clinical disease. Major infection was defined as an infection with the potential for serious morbidity or mortality and requiring specific therapy. Major infections included bacteremia, peritonitis, pneumonia, intra-abdominal abscess, wound infection, and symptomatic urinary tract infection.

Pneumonia was defined by a characteristic clinical picture, changes on chest radiography, and a positive sputum or bronchoscopic culture or special stain for microorganisms. Bacteremia was defined by a positive blood culture for an organism with a consistent clinical picture. Urinary tract infection was defined by a characteristic clinical picture, with pyuria and bacteriuria greater than 100 000 CFU/mL on urine culture. Peritonitis was defined by a characteristic clinical picture and positive ascitic fluid cultures. Cholangitis was defined by a characteristic clinical picture and biliary cultures positive for a predominant organism. Intra-abdominal abscess was defined by a characteristic clinical picture and by identification of a localized collection of purulent fluid that yielded a microorganism when cultured. Invasive fungal infection was defined by a positive fungal culture from tissue or from a body fluid (not just urine alone), or when special stains showed fungal invasion with characteristic histopathologic appearance (ie, presence of *Aspergillus*).

Statistical analysis

Fisher's exact test was used to determine significant association of (1) the incidence of infection with the treatment group and (2) the incidence of mortality within 1 month with the treatment and no-treatment groups.[13] Long-term survival was analyzed using the Kaplan-Meier survival analysis technique; the percentage risk of infection for the first month was calculated by standard life table techniques.[14]

RESULTS

Occurrence of infection

Only 1 of 17 patients (6%) treated with SBD developed a gram-negative infection in the first month after liver transplantation; no fungal infections occurred. In contrast, 18 of 34 patients (53%) who did not undergo SBD developed gram-negative or fungal infections in this same time period ($P = .002$). *Figure 1* shows the increased risk of gram-negative and fungal infections in the non-SBD group vs the SBD group.

The types of infections observed in this first month are listed in *Table 2*. Gram-negative infections included predominantly enteric organisms such as *Escherichia coli*, *Klebsiella*, *Citrobacter*, *Enterobacter*, *Acinetobacter*, and *Pseudomonas* species, and were seen

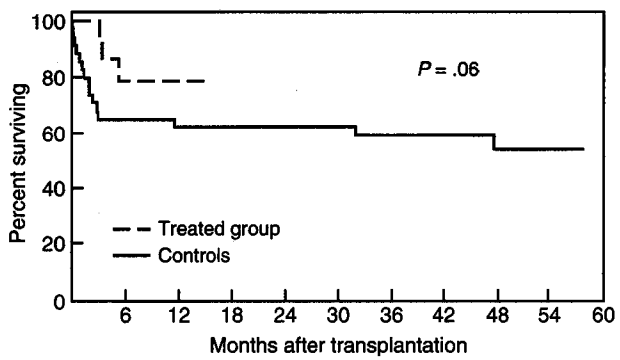

FIGURE 2. Survival for patients treated with selective bowel decontamination was higher (P = .06) than for control patients.

in 14 of 34 patients (41%) in the non-SBD group; the one patient in the SBD group developed infection with *Pseudomonas aeruginosa*. None of the 17 SBD patients developed fungal infection in the first month after transplantation, compared with 13 of 34 patients (38%) in the non-SBD group (P = .002). Nine of these 13 patients had both gram-negative and fungal infections. The differences between the two groups were all statistically significant.

Morbidity and mortality

The SBD group showed a trend toward increased short-term survival: no SBD patient died in the first month after transplantation, whereas 4 of 34 patients (12%) in the control group died (P = .14). The 4 deaths were all related to infection: 3 patients had a gram-negative or fungal infection; the fourth patient died from sepsis due to methicillin-resistant *Staphylococcus aureus*.

Long-term survival (after 1 month) also appeared better in the SBD group, though the difference was not statistically significant. In the control group, 15 of 34 patients (44%) died vs 3 of 17 (18%) in the SBD group (P = .06) (*Figure 2*). In all cases, infection contributed significantly to death; disseminated cytomegalovirus was also a major factor in many infection-related deaths.

Morbidity associated with SBD was very low. One patient on SBD developed a reversible interstitial nephritis, possibly related to ciprofloxacin therapy. No other complications from the SBD regimen were noted: the regimen was generally well tolerated, and patient compliance was good.

DISCUSSION

Despite the advent of cyclosporine, improvements in surgical techniques, and significant advances in immunosuppressive therapy, bacterial and fungal infections remain a major cause of morbidity and mortality in patients undergoing orthotopic liver transplantation.[1–6,15–21] Recent series in which cyclosporine was used document a 50% to 80% incidence of gram-negative and fungal infections associated with an approximately 33% mortality rate.[1,2,6,16,18]

Most gram-negative and fungal infections occur within 2 months after surgery. Numerous risk factors have been identified[5,6,9] and are in large part related to the nature of the transplant operation (which often takes place in an already contaminated surgical field) and to subsequent surgical complications (such as thrombosis of the hepatic artery and leakage of the biliary anastomosis, leading to peritonitis, cholangitis, and intra-abdominal abscess).[1,2,5,6,9] Increased risk of subsequent infection is associated with duration of the transplant operation beyond 12 hours, increased number of abdominal operations, the type of biliary drainage (particularly choledochojejunostomy), older age, increased steroid and antibiotic administration, increased initial serum creatinine, other vascular and gastrointestinal complications, need for dialysis, prolonged ventilatory dependency, and a stay in the intensive care unit.[2,5,17,18,20] Much of the overall morbidity and mortality due to these infections seems to occur in the immediate postoperative period, so efforts to prevent infections should be focused on that period.

Since most gram-negative bacterial and fungal infections are thought to arise from the endogenous microflora of the oropharynx and gastrointestinal tract, then eliminating colonization of the gastrointestinal tract by these potentially pathogenic organisms should decrease the subsequent risk of infection.[6]

SBD is not a new concept. Bowel decontamination using preoperative oral neomycin and erythromycin to decrease both the gram-negative and the anaerobic bacterial flora in patients undergoing colorectal surgery is well established and has significantly reduced the occurrence of postoperative infections.[22–24] Based on this principle, SBD selectively decreases aerobic gram-negative bacteria (those that normally reside in the intestinal tract, and other potentially pathogenic aerobic gram-negative organisms), while allowing the resident gram-positive flora and anaerobic bacteria to remain and thereby fulfill their protective role in "colonization resistance," as defined by Van der Waaij.[25]

SBD very effectively decreases the incidence of gram-negative infections in neutropenic leukemic patients during their period of maximum neutropenia.[26] Trimethoprim-sulfamethoxazole and vancomycin preparations have been used most commonly. However, recent studies have shown that oral quinolones are also very effective agents for SBD.[27–29] Rapid decrease in gram-negative colonization of the gastrointestinal tract has been well documented by quantitative culture counts in numerous studies using the quinolones for SBD.[27–29]

Fungal infections are also a serious problem in liver transplant recipients. Weisner et al[6] expanded the concept of SBD to include antifungal activity. Adding an oral nonabsorbable antifungal agent (nystatin) to an SBD regimen consisting of polymyxin and gentamycin produced rapid decrease (by quantitative culture counts) of gram-negative, yeast, and fungal colonizations. They claimed a subsequent decrease in the incidence of gram-negative and fungal infections during the first month after liver transplantation, although no historical or concurrent control data were provided.[6] These results were similar to earlier studies of SBD that included oral amphotericin B in patients with multiple trauma.[30]

CONCLUSION

Our study shows that using oral quinolones and high-dose nystatin suspension reduces the occurrence of gram-negative and fungal infections during the first month after liver transplantation ($P = .002$). Mortality was not significantly different ($P = .14$), probably because the sample size was too small. SBD tended to increase both 1-month survival ($P = .14$) and longer-term survival ($P = .06$), although a larger study group will be needed to answer this with confidence. Our SBD regimen was well tolerated: only one complication may have been associated with the therapy (one case of interstitial nephritis, possibly related to quinolone use).

Other factors that may have contributed to the difference in infections noted between the study group and the control group include the experience of the surgical team, unidentified underlying host factors, the condition of the donor liver, and the intensity and duration of immunosuppressive therapy. However, none of these factors appeared to be significant in our patients.

We believe SBD is effective in reducing gram-negative and fungal infections in the first month after orthotopic liver transplantation. Further studies are needed to demonstrate the effectiveness of this regimen in decreasing mortality.

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