

Selective Decontamination of the Digestive Tract Helps Prevent Bacterial Infections in the Early Postoperative Period after Liver Transplant

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Abstract

In liver transplant (LTx) recipients, gut-associated bacterial and fungal organisms produce significant postoperative morbidity and mortality. We sought to assess the role of selective digestive decontamination (SDD) in preventing postoperative infections in a large single-center cohort of liver recipients transplanted under two non-simultaneous protocols. In 212 consecutive patients transplanted between 1/1/91 and 7/31/92, SDD (gentamicin 80 mg, polymyxin B 100 mg, nystatin suspension 10 mL) was employed, starting after induction of anesthesia and continued until POD 21 (SDD Group). In 157 consecutive patients transplanted between 1/1/93 and 12/31/93, SDD was not used (non-SDD Group). Both groups received IV vancomycin and cefotaxime prophylaxis. All culture-positive infections within the first 30 days post-LTx were recorded and classified as bacterial or fungal. Infection-related mortality (patients who died of infectious complications without any technical complication) was recorded. Groups did not differ in patient demographics, United Network for Organ Sharing (UNOS) status, use of veno-venous bypass, total/warm ischemia, or length of ICU stay. Infections developed in fewer SDD patients (56/212; 26%) than non-SDD patients (69/157; 44%) ($p < 0.001$). The incidence of gram-negative infection was less in the SDD group (11% vs. 26%, $p < 0.001$) as was gram-positive infection (16% vs. 26%, $p < 0.001$). Among patients who developed infection, there was no difference between groups in infections per patient. Primary graft non-function (PNF) developed in 20 SDD patients (7/20 had infections) and 8 non-SDD patients (6/8 had infections) ($p = 0.06$). There were no differences in incidence of fungal infections or of infection-related mortality between groups. In the SDD group, there were fewer abdominal ($p < 0.001$), lung ($p < 0.001$), wound ($p < 0.01$), and urinary tract infections ($p < 0.05$).

Conclusion: Use of SDD in liver recipients early after transplant was associated with significantly fewer infections in the early postoperative period. **Key Words:** Liver transplantation, selective digestive decontamination, postoperative infection, infection prophylaxis.

Introduction

LIVER TRANSPLANTATION (LTx) is the only therapeutic modality for patients with end-stage liver disease, with one-year survival of 85% (1). Increased experience with candidate selection, refinement of surgical technique, and advances in immunosuppression and organ preservation contribute to successful out-

comes. On the other hand, postoperative infectious complications still remain an important cause of morbidity and mortality. The reported incidence of severe infections after LTx ranges from 53% to 79% (2–3). Endogenous gut-associated bacterial and fungal organisms are the most frequently encountered pathogens (4, 5). Approximately three quarters of bacterial and fungal infections occur in the first month following LTx (4, 6).

Early in our program, between January 1991 and July 1992, selective decontamination of the digestive tract (SDD) was employed routinely. Near the end of this period, we began to see an increasing number of vancomycin-resistant *Enterococcus faecium* infections, and the decision was made to abandon SDD prophylaxis.

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Between January 1993 and December 1993, SDD was not used at all. Because there have been no large studies to evaluate the role of SDD in preventing early postoperative infection in liver allograft recipients, we undertook a retrospective analysis of these two protocols (SDD and non-SDD) to assess whether SDD prevented or decreased the incidence of postoperative infection.

Patients and Methods

A total of 369 liver recipients underwent LTx under these two protocols (SDD vs. non-SDD). Between 1/1/91 and 7/31/92, 212 consecutive patients underwent LTx with use of SDD (SDD group). Between 1/1/93 and 12/31/93, 157 consecutive recipients received no SDD (non-SDD group).

Liver transplantation was performed as described previously (7). Induction immunosuppression was cyclosporine (CsA)-based (CsA, steroid, azathioprine) or FK506-based (FK506 and steroid); OKT3 was used in patients who had renal failure prior to LTx.

The SDD suspension was a mixture of gentamicin, 80 mg; polymyxin B, 100 mg; and nystatin, 2 million units per 10 mL dose. Patients received 10 mL of SDD suspension every 6 hrs, starting after induction of anesthesia, until postoperative day 21 (mechanical bowel preparation was not routinely employed). The SDD suspension was given by nasogastric tube while the patients were intubated, and by mouth after extubation. In addition, a paste (compounded in the hospital pharmacy) consisting of gentamicin 2%, polymyxin-B 2%, and nystatin 100,000 units/gram in Orabase® (Colgate Oral, Canton, MA) was applied to the oral mucosa every 6 hrs during the period of postoperative endotracheal intubation.

All patients in both groups received 48 hr prophylaxis with IV vancomycin, 1 g every 12 hrs, and cefotaxime, 1 g every 8 hrs.

The following variables were recorded and compared: (1) patient demographics; (2) pretransplant United Network for Organ Sharing (UNOS) status; (3) primary disease; (4) incidence of pretransplant spontaneous bacterial peritonitis (SBP); (5) intraoperative use of veno-venous bypass (i.e., bypass circuit used during the anhepatic phase to carry venous blood from lower torso and portal circulation into the heart through the axillary vein); (6) warm and total ischemia times (i.e., interval from cross-clamping of the aorta in the donor to reperfusion in the recipient [total ischemic time]; and interval during which har-

vested organ is not cold-preserved [warm ischemic time]); (7) total operative time; (8) intraoperative blood use; (9) technique of bile duct reconstruction; (10) occurrence of primary graft non-function (PNF); (11) induction immunosuppression regimen; (12) length of ICU stay; and (13) cost of SDD.

All culture-positive infections during the first 30 days post-LTx were recorded and classified as bacterial (gram-positive or gram-negative) or fungal. The number of methicillin-resistant *Staphylococcus aureus* (MRSA) infections and vancomycin-resistant *E. faecium* (VREF) infections were also recorded in each group. Definitions of infections appear in Table 1. Infection-related mortality (i.e., death related to infectious complications without any technical complication) was recorded as well.

Chi square, T test, and Mantel-Haenszel test were used for statistical analysis. $P < 0.05$ was considered significant.

Results

In the SDD group, 212 recipients underwent 237 LTx; 24 recipients received more than one LTx (23 patients had 2, 1 patient had 3 liver transplants). In the non-SDD group, 177 LTx were performed in 157 patients; 15 recipients received more than one LTx (11 had 2, 3 had 3, and 1 patient had 4 transplants). There was significant no difference between groups in primary disease (Table 2), patient demographics, UNOS status at transplant, or SBP. Groups were also similar in warm ischemia, total ischemia, total operative time, intraoperative blood use, technique of bile duct reconstruction, occurrence of PNF, and ICU stay (Table 3). In the SDD group, veno-venous bypass was used more frequently than in the non-SDD group ($p < 0.001$). As outlined in Table 4, infection rates for bypass and non-bypass patients

TABLE 1
Definitions for the Diagnosis of Clinical Infection

Clinical signs of infection
Pyrexia $> 38.5^{\circ}\text{C}$
WBC $> 15,000$
Culture of organism within 72 hours
Lung infection
New infiltrate with clinical signs
Culture of organisms from sputum
Wound infection
Redness/induration and the presence of pus on exploration
Positive wound culture
Sepsis
Clinical signs with a positive blood culture
Urinary tract infection (105 cfu/hpf)

TABLE 2
Indication for Liver Transplantation

	SDD* n=212	Non-SDD* n=157
Alcoholic	39	18
Autoimmune	9	9
Biliary atresia	12	9
Cryptogenic	18	16
Fulminant hepatitis	16	11
Viral hepatitis	58	56
Cholestatic	48	27
Others	12	11

* The differences between the two groups are not statistically significant.

TABLE 3
Patient Demographics, Operative and Postoperative Data

	SDD* n=212	Non-SDD* n=157
Age	43.9 (8 mos–71 yr)	45.2 (9 mos–70 yr)
UNOS 3-4	133	90
UNOS 1-2	104	87
SBP	6	8
Warm ischemia time (min)	52±10.3	50±11.4
Total ischemia time (hrs:min)	12:20±6:00	10:9±7:10
Total operative time (hrs:min)	9:00±5:34	7:20±4:50
Packed red blood cells (PRBC) (unit)	15.8±17.2	11±15.4
Fresh frozen plasma (FFP) (unit)	15.5±14.2	12±11.9
Bile duct anastomosis		
Duct-Duct	187	105
Roux-Y	50	52
Mean ICU stay (days)	4±12	4±14.5
PNF	20	9

* The differences in the two groups are not statistically significant.

in both the SDD and non-SDD groups were essentially the same by Mantel-Haenszel test.

Bacterial infections developed in significantly fewer patients in the SDD group than in the non-SDD group ($p < 0.001$) (Table 5). There was no difference in the incidence of fungal infections between groups. As shown in Table 6, in the SDD group there were fewer abdominal ($p < 0.001$), lung ($p < 0.001$), wound ($p < 0.01$), and urinary tract infections (UTI) ($p < 0.05$); there was no statistical difference between groups regarding sepsis. Between our two groups, there was no difference in the incidence of MRSA infection (14 cases in the SDD group vs. 11 cases in the non-SDD group). The incidence of VREF infections was significantly higher in the non-SDD group (19/157, vs. 11/212 cases in the SDD group, $p = 0.02$). There were 7 infection-related deaths in the SDD group vs. 11 in the non-SDD group ($p = ns$).

TABLE 4
Bypass Status and Infection Rate

Bypass	Infection	SDD* n=210#	Non-SDD* n=157
Yes	Yes	49 (26.2%)	36 (51.4%)
	No	138 (73.8%)	34 (48.6%)
No	Yes	7 (30.4%)	33 (37.9%)
	No	16 (69.6%)	54 (62.1%)

Data on two patients are missing.

* The differences between the two groups are not statistically significant.

TABLE 5
*Comparison of Incidence and Type of Infection Between Groups**

	SDD (n=212)	Non-SDD (n=157)	p value
Patients with infection	56 (26%)	69 (44%)	<0.001
Gram-negative	22 (11%)	38 (26%)	<0.001
Gram-positive	32 (16%)	41 (28%)	<0.01
Fungal	10 (5%)	11 (7%)	NS

* Some patients had more than 1 type of infection.

TABLE 6
*Site of Infection**

	SDD n=212	Non-SDD n=157	p value
Abdomen	11 (5%)	30 (19%)	<0.001
Lung	13 (6%)	28 (18%)	<0.001
Sepsis	17 (8%)	22 (14%)	0.06
Wound	23 (11%)	32 (20%)	<0.01
UTI**	2 (1%)	7 (4%)	<0.05

* Some patients had more than 1 type and site of infection.

**UTI = urinary tract infection.

For each treated patient, the daily cost of SDD was \$7. The mean total cost per patient (for a 3-week course) was \$161.

Discussion

Infectious complications following liver transplantation result in long-term hospitalization, especially in the ICU, and are the leading cause of morbidity and mortality. Responsible pathogens are usually intestinal in origin. In recent studies, up to 74% of bacterial and fungal infections occurred during the first 4 weeks after liver transplantation (4, 6). The concept of a reduction of gut-associated bacterial and fungal sepsis in liver recipients with use of SDD appears very appropriate.

Wiesner (8) has shown a reduction in the incidence of gram-negative and fungal sepsis after using SDD in liver transplant recipients, with SDD initiated from days to weeks prior to LTx and continued for 3 weeks post-LTx. We deemed

this approach impractical, however, since waiting time in our patient population is always more than 5 months. Thus, we elected to start SDD immediately prior to surgery.

In our study, we found no difference in the incidence of fungal infections between groups. In a randomized prospective study of 36 pediatric liver recipients, Smith et al. (9) found significantly fewer gram-negative infections among patients who received SDD and no difference in gram-positive infections, but mortality was not significantly affected. In our patients, with the use of SDD, we were able to decrease the incidence of both gram-negative and gram-positive infections.

We could find no correlation between bypass use and infection rate. In our SDD group, infection rates for bypass and non-bypass patients were similar. In the non-SDD group, the bypass patients had a higher incidence of infection than those patients who did not have bypass, although the difference did not reach statistical significance. Whether or not the use of bypass in the non-SDD group promoted the occurrence of infectious complication is not amenable to further analysis in our study (10).

Miller et al. (7) have shown that SDD may cause an increase in the incidence of gram-positive infections, especially MRSA. Between our two groups of patients, there was no difference in the incidence of MRSA infection. However, SDD was associated with a significant reduction in the incidence of gram-positive infection in our study (16% vs. 28%, $p < 0.01$).

In addition to the reduction in overall incidence of infection, SDD was associated in our study with a reduction in infections involving the abdomen, lung, wound, and urinary tract.

Unfortunately, our study suffers from a number of limitations common to most retrospective reviews. We did not perform routine surveillance cultures, nor did we control for pretransplant use of immunosuppressive drugs or prior abdominal surgery. However, patients in both groups were well matched for pretransplant risks, including diagnosis and UNOS status. In our series, the incidence of fungal infections in the SDD group (5%) and in the non-SDD group (7%) were lower than in other reported series (4, 5, 9). We have no explanation for this difference.

Although we abandoned our original SDD protocol because it was felt to be associated with an increasing number of VREF infections, our retrospective analysis showed us that SDD

did not increase the incidence of VREF infection. In fact, the incidence of these infections was higher under the non-SDD protocol. One explanation for the occurrence of VREF infections in both groups could be our prophylactic use of vancomycin.

Based on these results, since January 1994 we have resumed the use of a modified SDD protocol in our recipient population. In this modified protocol, our SDD suspension and the oral paste remain unchanged, but the duration of administration of the SDD suspension is limited to 7 days, and vancomycin is no longer administered prophylactically. Results with our use of this newer protocol have yet to be published.

We conclude that use of SDD after liver transplantation resulted in a significant reduction in the incidence of infections. SDD did not, however, decrease the number of fungal infections, the length of ICU stay, or overall and infection-related mortality.

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