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The study on antibiotic prophylaxis and surgical site infection

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Abstract
Surgical site infections are common bacterial infections in orthotopic liver transplantation. The purpose of this study was to determine the incidence, timing, location, and risk factors, specifically antibiotic prophylaxis, for surgical site infections. A prospective study was performed that included a population of 1222 consecutive patients (73.0% males) who underwent liver transplantation. One hundred seven patients developed surgical site infections. The predominant infection sites were incisional wound (53 episodes) and peritonitis (40 episodes).
The timing of the organ/space surgical site infections was slightly delayed in comparison with incisional surgical site infections. Enterococcus spp., Escherichia coli, Staphylococcus aureus, and Acinetobacter baumannii were the predominant pathogens. Choledochojejunal or hepaticojejunal reconstruction (odds ratio, 4.2; 95% confidence interval, 1.6-10.7), previous liver or kidney transplant (odds ratio, 2.6; 95% confidence interval, 1.1-6.3), and more than 4 red blood cell units transfused (odds ratio, 2.0; 95% confidence interval, 1.1-3.4) were independently associated with the development of surgical site infections. Biliary reconstruction by choledochojejunostomy or hepaticojejunostomy increases the risk of surgical site infections.

Keywords: antibiotic, prophylaxis, infection

Introduction
The rate of surgical site infection (SSI) after liver transplantation (LT) is generally higher than that following other types of solid-organ transplantation, and SSI remains a major cause of morbidity and mortality [1-4] The high incidence of post-LT infection is related to the technical complexity of the procedure itself, the fact that it is performed in a potentially infected milieu within the abdominal cavity, and the markedly poor medical condition of many recipients [5].
SSIs, including incisional wounds, intra-abdominal abscesses, and peritonitis, are frequent post-LT bacterial infections [5, 6] The purpose of this study was to determine the incidence, timing, location, and risk factors, specifically antibiotic prophylaxis, for SSIs after LT.

Methods
A prospective study was performed that included a population of all consecutive patients who underwent deceased-donor whole LT. serum, plasma, microorganism, and DNA bank are used as research tools. Pretransplant, peritransplant, and follow-up (days 0, 7, 14, 30, 60, 90, 180, 270, 360, and 720 after transplantation) data are prospectively included in the online database, as well as all infections (diagnostic workup, clinical presentation, therapy, and outcome) and rejection episodes.
Centers for Disease Control and Prevention criteria definitions for SSI were adopted and were slightly modified to include infections that developed up to 6 months after surgery, including both wound incisional and organ/space infection, hepatic and intra-abdominal abscess, and peritonitis [8].

Risk Factors for SSIs
In order to assess risk factors for SSI, only patients who developed SSI within the first 30 days after surgery were included. Only the most severe episode of SSI was included for patients who developed more than 1 SSI. The following variables were assessed as risk factors for SSIs: (1) pretransplant variables including age, gender, diabetes mellitus, chronic renal failure, ChildPugh class, elective or emergency surgery, previous transplantation, cause of LT, and cytomegalovirus donor and recipient status and (2) operative and posttransplant variables including duration of transplant surgery, quantity of red blood cell (RBC) transfusions (dichotomized by the median volume transfused), cytomegalovirus disease, type of biliary reconstruction, immunosuppression regimen, and antibiotic prophylaxis regimen.
The number of LTs performed in each hospital during the study period was also included as a risk factor. Participant institutions used fluconazole (100 mg/day) as fungal prophylaxis during the period of hospitalization. Forty-one patients (belonging to a single hospital) received intestinal decontamination with norfloxacin (400 mg orally every day).

Results
Eight hundred ninety patients (73%) were male, with an age range of 18 to 71 years (mean, 53 years). The predominant underlying diseases were alcoholic and hepatitis C cirrhosis, which accounted for more than 50% of the cases. The third most frequent cause of LT was hepatocellular carcinoma (20%); less frequent causes were hepatitis B cirrhosis,

autoimmune liver disease (including autoimmune cirrhosis, primary biliary cirrhosis, and primary sclerosing cholangitis), fulminant hepatitis, and toxic or deposit liver disease (Table 1).

TABLE 1. Main Diagnosis and Risk of Surgical Site Infection in the Liver Transplant Cohort

Demographic and Diagnostic Characteristics	Patients [n (%)]†
Main diagnosis	
Cirrhosis	
Hepatitis B virus	58 (4.8)
Hepatitis C virus	276 (22.6)
Alcoholic	410 (33.6)
Autoimmune	28 (2.3)
Hepatocarcinoma	247 (20.2)
Fulminant hepatitis	33 (2.7)
Toxic	2 (0.2)
Deposit	6 (0.4)
Other	160 (13.1)
Surgical site infections*	127 (10.4)
Incisional	53 (4.3)
Organ/space	74 (6.1)
Hepatic	13 (1.1)
Intra-abdominal abscess	21 (1.7)
Peritonitis	40 (3.3)

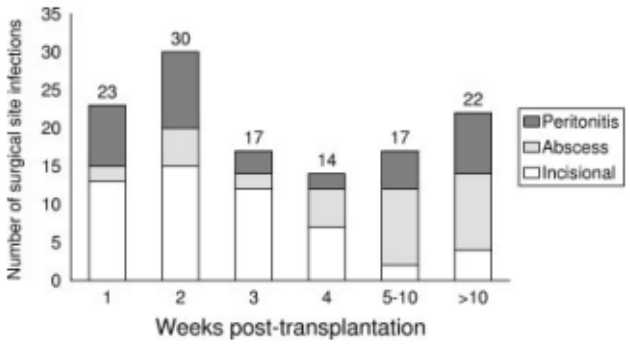

Figure 1. Time of onset of incisional and organ/space surgical site infections after liver transplantation.

Surgical Site Infections (SSIs)

One hundred twenty-seven episodes of SSIs were recorded in 107 transplant patients. Eighty-one patients developed SSI within the first 30 days after surgery. The risk of developing at least 1 SSI was 8.8 (107/1222) per 100 patients, and the cumulative incidence of SSI was 10.3 episodes per 100 transplanted patients (95% CI, 8.4-12.2%). The predominant infection sites were incisional SSI (42%) and peritonitis (39%), with intra-abdominal abscess (16%) and hepatic abscess (10%) occurring less frequently (Table 1).

The SSI rate in ChildPugh class A, B, and C patients showed a linear trend, with SSI rates of 9.8%, 12.8%, and 14.3%, respectively, but they did not reach statistical association (chisquare for trend, 2.44; P 0.119). Case fatality risk ranged from 8.3% (95% CI, 0.2%- 38.5%) for intra-abdominal abscess to 16.1% (95% CI, 5.5%-33.7%) for peritonitis, with no significant differences by SSI type.

Time of Occurrence

Seventy-six percent of the SSIs occurred during the first 4 weeks after surgery. The incidence declined progressively after the second postoperative week. Seventy-six percent (40/53) of the incisional SSIs occurred within 3 weeks after surgery. The timing of the organ/space SSIs was slightly delayed in comparison to that of incisional SSIs (Fig. 1), organ/space infections being 43% and 75% of the infections that developed during and after the first 3 postoperative weeks, respectively.

Pathogens

One hundred twenty-four organisms were recovered from 85 episodes of SSI, with 21 (17%) of the episodes being polymicrobial infections. Thirty-eight percent of pathogens recovered were gram-positive cocci, 52% were gram-negative rods, and 8% were Candida spp. Enterococcus spp., Escherichia coli, Staphylococcus aureus, and Acinetobacter baumannii were the most frequent pathogens isolated (Table 2). No differences in the site frequencies of microorganisms were found for the majority of pathogens, with the exception of S. aureus, which was more frequent in incisional SSIs (28% versus 8%), and Enterococcus spp, which was more frequent in the deepest infections (28% versus 20%; Table 2).

Risk Factors

Eighty-one patients who developed SSI within 30 days after surgery were included and compared by univariate analysis. Patients who had received a previous liver or kidney transplant were found to have a significantly greater risk of SSI. Surgical reconstruction by choledochojejunostomy was also found to be associated with a greater risk of SSI than choledochocholedochostomy anastomosis.

Patients receiving transplants in low-volume LT hospitals, which were defined as hospitals in which fewer than 50 LTs were performed per year, also had an increased risk of SSI (Table 3). The most frequently used immunosuppressive regimens were double therapy with steroids and calcineurin inhibitors: tacrolimus (44%; 95% CI, 41%-47%) or cyclosporine (18%; 95% CI, 15%-20%). The use of mycophenolate mofetil in triple-association prophylaxis was associated with a higher risk of SSI in comparison with the double regimen (7.9% versus 4.7% and 10.7% versus 4.8%; crude odds ratio, 2.1; 95% CI, 1.2-3.5).

More than 8 types of antibiotics or antibiotic combinations were used for surgical prophylaxis, with the most common being amoxicillin-clavulanate (19%) and combinations of glycopeptide and antipseudomonal penicillin (16%) and glycopeptide and aztreonam (10%). The risk of SSI associated with different antibiotics ranged from 1.7% for the combination glycopeptide/ aztreonam to 17.1% for cefazolin alone (odds ratio, 12.3%; CI, 2.6-114; Table 3).

No other variables showed statistical association in the univariate analysis. After we controlled by Child-Pugh class and center, antibiotic prophylaxis no longer remained associated with SSI risk. Nevertheless, choledochojejunal reconstruction, previous solid organ transplant, and RBC transfusion greater than 4 units were found to be independently associated with the development of SSI by the unconditional multiple logistic regression model (Table 4).

Discussion

SSIs occurred in 8.8% of patients, and this figure is within the range of those previously reported but much lower than the risk found by Iinuma *et al* [10] in patients receiving living-donor

liver transplant. Some of the differences found among studies could be due to the use of different SSI definitions, the duration of SSI surveillance, and technical improvements in recent years.[10-14] Most SSIs occurred during the first 2-3 weeks, as noted in previous reports, and could be related to contamination of the abdominal cavity during the transplant procedure [12-16]. Although SSI infections carried a high mortality in the 1980s [17]. in the present series, fatality related to this complication occurred only in 11 patients (10%).

TABLE 2. Organisms Recovered from Incisional and Organ/Space Surgical Site Infections (SSIs) After Liver Transplantation

	All SSIs		Incisional SSIs		Organ/Space SSIs	
Microorganism	n	%	n	%	n	%
Escherichia coli	23	18.5	10	21.7	13	16.7
Acinetobacter baumannii	16	12.9	7	15.2	9	11.5
Pseudomonas aeruginosa	8	6.4	0	0.0	8	10.2
Enterobacter spp.	5	4.0	2	4.3	3	3.8
Enterococcus faecalis	14	11.3	5	10.9	9	11.5
Enterococcus faecium	17	13.7	4	8.7	13	16.7
Staphylococcus aureus	19	15.3	13	28.2	6	7.7
Bacteroides spp.	4	3.2	0	0.0	4	5.1
Klebsiella pneumoniae	4	3.2	2	4.3	2	3.1
Morganella morganii	3	2.4	0	0.0	3	2.6
Citrobacter freundii	1	0.8	0	0.0	1	1.3
Candida albicans	6	4.8	1	2.2	5	6.4
Candida glabrata	4	3.2	2	4.3	2	2.6
Total	124	100	46	100.0	78	100.0

Rapid advances in surgical techniques and antimicrobial therapy during recent years could have induced improved prognoses in these patients.[18] Most SSIs were caused by gram-negative aerobic bacteria, which are inhabitants of the digestive tract, as has been reported in previous studies.[2,14] Fungal infection by Candida spp. occurred in 10 cases (8%). Invasive candidiasis after LT usually presents as an intraabdominal abscess, peritonitis, catheter-related fungemia, or fungemia of unknown origin [10-12]. A number of approaches toward antifungal prophylaxis have been proposed [4].

The high incidence of candidiasis in this study is remarkable because many of the participant institutions used fluconazole (100 mg/day) prophylaxis during the period of hospital admission [16, 18]. However, a recent meta-analysis of fungal prophylaxis studies in LT showed that a higher dose of fluconazole (400 mg/day) and a more prolonged duration of prophylaxis are associated with a lower incidence of invasive fugal infection [19, 20] Forty percent of isolated species were Candida glabrata, which could have emerged after fluconazole usage.

No prophylactic antibiotic regimen has been definitively established for LT in the medical literature [13]. This could be due to the lack of randomized controlled studies comparing the efficacy of different antimicrobial prophylactic regimens. In fact, second-generation or third-generation cephalosporin alone is used in many institutions [4] and also in hospitals with a high frequency of SSI due to enterococci [10].

An antibiotic prophylaxis regimen, specifically the use of cefazolin, was found to be associated with the risk of SSI in the univariate analysis; however, this association did not remain after we controlled by center effect and Child-Pugh class. The use of cefazolin was found to be associated with a specific center with high rates of SSI, so our study could not identify whether the use of cefazolin itself or some other unmeasured factor associated with that center was responsible for the high increase of SSI. Nevertheless, this study suggests that the use of cephalosporin as a unique prophylactic agent is inadvisable and highlights the importance of enterococci as the main microbiological agents. Furthermore, one study found a significantly higher incidence of enterococcal infections under cefotetan prophylaxis than under ampicillin-sulbactam administration [10].

The rationale for this fact could be a difference in the pathogenicity of enterococci in LT compared to other abdominal surgical procedures. In addition, isolation of enterococci in intraoperative cultures in LT patients has been demonstrated to increase the risk of early postoperative enterococcal infection [12]

Amoxicillin-clavulanate, or the combination of a third-generation cephalosporin plus amoxicillin, could be a reasonable antibiotic prophylaxis regimen in LT in institutions with a low incidence of penicillin-resistant and vancomycin-resistant enterococci. In hospitals with a high incidence of methicillin-resistant S. aureus postoperative infections, vancomycin could be included in the prophylactic antibiotic regimen. However, the normally good prognosis of patients with SSI must be pointed out. Stool and urine cultures, performed prior to LT, may be useful in detecting multiresistant enterococci, which have become a nosocomial problem in transplant units during recent years and could justify an appropriate prophylactic regimen.

The greatest risk factor for SSI was choledochojejunal reconstruction. This risk factor has frequently been identified in previous studies. Opening the jejunum increased enteric organism contamination of the surgical field with a resultant increased risk of infection. In fact, prolonged prophylaxis (more than 2 days) has been recommended in cases involving jejunostomy.

Perioperative blood transfusion has also been considered a risk factor for bacterial infections but was weakly related to SSI in this study. The use of mycophenolate mofetil was associated with SSI at univariate analysis. This medication has been considered a risk factor for wound infections in kidney transplantation because it is a powerful immunosuppressive

drug that inhibits the proliferation of T and B cells. Nevertheless, no increased risk of bacterial infection in LT patients treated with mycophenolate mofetil has been observed in other studies.

It is also remarkable that no other known SSI risk factors, such as duration of the operation and repeat surgery were detected in our study. Other risk factors, such as retransplantation, were detected only in the univariate analysis.

TABLE 3. Risk of Surgical Site Infection (SSI) by Potential Risk Factors: Univariate Analysis

Variable	SSI Risk [n/N (%)]	Odds Ratio (5% Confidence Interval)	*P* Value*
Age (mean ± standard deviation)			
SSI patients	52.8 ± 11.6		0.580
Patients without SSI	53.5 ± 10.2		
Gender			
Male	62/892 (7.0)	1.2 (0.7–2.2)	0.458
Female	19/330 (5.8)		
Cytomegalovirus status			
Donor+/recipient+	51/737(6.9)	1.3 (.5–4.4)	0.699
Donor+/recipient−	25/376 (6.6)	1.2 (0.4–4.1)	
Donor−/recipient+	5/94 (5.3)	Reference	
Donor−/recipient−	0/15 (0)	Undetermined	
Type of surgery			
Emergency	10/108 (9.3)	1.5 (0.7–3.0)	0.223
Elective	71/1108 (6.4)		
Previous transplant			
No	67/1139 (5.9)	1	<0.001
Liver	11/70 (15.7)	3.0 (15–5.9)	
Kidney	3/13 (23.1)	4.8 (1.3–17.9)	
Diabetes mellitus			
Yes	19/262 (7.3)	1.1 (0.6–1.8)	0.692
No	63/960 (6.6)		
Chronic renal failure			
Yes	5/71 (7.0)	1.1 (0.37–2.9)	0.885
No	76/1151 (6.6)		
Biliary derivation			
Choledochojejunostomy	11/43 (25.6)	5.5 (2.6–11.3)	<0.001
Choledochocholedochostomy	70/1179 (5.9)		
Duration of surgery (mean ± standard deviation)			
Patients with SSI	6.0 ± 2.2		0.673
Patients without SSI	5.8 ± 2.2		
Amount of blood transfused			
>4 red blood cell units	43/463 (9.3)	1.9 (1.2–3.1)	0.004
≤4 red blood cell units	38/758 (5.0)		
Immunosuppression regimen			
Steroids/cyclosporine	10/214 (4.7)	1	0.020
Steroids/cyclosporine/mycophenolate mofetil	11/140 (7.9)	1.7 (0.7–4.2)	
Steroids/tacrolimus	26/537 (4.8)	1.0 (0.5–5.2)	
Steroids/tacrolimus/mycophenolate mofetil	19/178 (10.7)	2.4 (1.0–5.4)	
Other	15/153 (9.8)	2.2 (1.0–5.1)	
Antibiotic prophylaxis			
Glycopeptide/aztreonam	2/121 (1.7)	1	<0.001
Quinolones/glycopeptide	1/51 (2.0)	1.2 (.01–13.4)	
Quinolones/amoxicillin-clavulanate	3/81 (3.7)	4.6 (0.5–44.8)	
Ampicillin/third-generation cephalosporin	4/98 (4.1)	5.1 (0.6–46.1)	
Amoxicillin-clavulanate	13/231 (5.6)	3.6 (0.8–16.0)	

TABLE 4. Risk Factors for Surgical Site Infection: Multivariate Analysis Controlling by Child-Pugh Class and Center Effect

	Odds Ratio	95% Confidence Interval	*P* Value
Choledochocholedochostomy	4.2	1.6–10.7	0.003
Previous liver or kidney transplant	2.6	1.1–6.3	0.029
Red blood cell transfusion > 4 units	2.0	1.1–3.4	0.019

In addition, the number and timing of repeat doses during surgery were not recorded and therefore were unavailable for the analysis. Moreover, some important risk factors, such as ABO incompatibility, treatment of early rejection, use of monoclonal antibody, immune modulators, and evidence of infection prior to SSI, were not assessed, so their importance was not evaluated and could constitute a difficulty in its generalizability. Despite these limitations, these results provide some insight into the risk of SSI in relation to previous transplantation, choledochojejunal reconstruction, and RBC transfusion, which could motivate new studies to aid in the understanding of the pathogenesis of SSI in LT.

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