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CLINICAL AND EPIDEMIOLOGICAL STUDY

Staphylococcus aureus infections after liver transplantation

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Abstract
Background More data on the risk factors and outcomes after *Staphylococcus aureus* infections in liver transplantation are needed.
Methods Liver recipients with *S. aureus* infections (cases) were retrospectively identified and compared to gender-, age-, and transplant type-matched (1:2) non-*S. aureus*-infected controls. Risk factors associated with *S. aureus* infections were identified by conditional logistic regression analysis.
Results We evaluated 51 patients (median age 52 years). First *S. aureus* infections developed at a median time of 29 days after transplantation, with 52.94% of them in the first month; 88.24% were nosocomial, 41.18% were polymicrobial, and 47.06% were caused by methicillin-resistant *S. aureus* (MRSA). Surgical site infections represented 58.82% and bacteremia 23.53%. By univariate analysis, patients with *S. aureus* infections were intubated more frequently (odds ratio [OR] 26.92, 95% confidence interval [CI] 3.23–3,504.15, $p = 0.0006$), had a central line (OR 11.69, 95% CI 1.42–95.9, $p = 0.02$), or recent surgery (OR 26.92, 95% CI 3.23–3,504.15, $p = 0.0006$) compared with controls. By multivariate analysis, subjects who underwent surgery within 2 weeks prior to infection had a 26.9 times higher risk of developing *S. aureus* infection (95% CI 3.23–3,504.15, $p = 0.0006$); these results were adjusted for matched criteria. *S. aureus* infections did not affect graft or patient survival, but the study was not powered for such outcomes.
Conclusion Only recent surgical procedure was found to be a significant independent risk factor for *S. aureus* infections after liver transplantation.

Keywords *Staphylococcus aureus* · Liver transplantation · Infection · Risk factors · Outcome

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Introduction

In previous decades, liver transplantation has become increasingly successful, with excellent patient outcomes and limited mortality, offering patients with otherwise poor prognosis the chance for a longer life. Graft and patient survival have continued to improve as a result of developments in medical and surgical management, particularly the introduction of induction therapy and newer immunosuppression regimens. Such drugs are used to prevent or treat rejection by inhibiting the activation of T-lymphocytes through a variety of mechanisms; as a result, infectious complications now represent a common cause of morbidity and mortality after transplantation. Most of the

bacterial infections occur in the immediate post-transplantation period; patients on the waiting list may become colonized with community- (*Aspergillus* spp., *Nocardia* spp., *Cryptococcus*, *Staphylococcus aureus*) or nosocomial-acquired organisms that are often multidrug-resistant, including methicillin-resistant *S. aureus* (MRSA) [1]. Bacterial and fungal infections in the first 6 months after transplantation are generally associated with complications of surgery (i.e., related to incisions, the presence of a central line, or intubation); biliary leak can cause peritonitis or intra-abdominal abscess; early graft injury might become later liver abscess [1]. *S. aureus* has emerged as an important pathogen complicating the clinical course of liver recipients [2, 3]. *S. aureus* is a commensal organism that colonizes the skin and mucosa surfaces, causing infections when the skin or mucosal barriers are disrupted [4].

Some of the previously published studies in liver transplant recipients have investigated the epidemiology and risk factors mainly for MRSA infections [3, 5, 6], while others focused on the effect of these infections on outcomes [2, 7]. These previously assessed risk factors for *S. aureus* infections include underlying liver disease prior to transplantation, methicillin-susceptible *S. aureus* (MSSA) and MRSA colonization, prothrombin time, and the presence of ascites [5, 6, 8]. The goal of our retrospective study was to evaluate several other risk factors for *S. aureus* infections (including both MRSA and MSSA) in the liver transplant patient population and the impact of these infections on their clinical outcome.

Methods

We conducted a retrospective 1:2 matched case–control study at The University of Nebraska Medical Center to determine risk factors for *S. aureus* infections during the first year after liver transplantation and whether these infections had an impact on patient outcome. The matching was based on gender, age (±5 years), and transplantation and re-transplantation type. In addition, the survival time for controls from transplant had to be at least as long as the time from transplantation to the diagnosis of infection in the corresponding cases. The medical records of the patients were reviewed for the first year after liver transplantation. The following data were collected from the patients' medical records: age, gender, ethnicity, cytomegalovirus (CMV) serostatus, type of graft and transplantation, immunocompromised state (induction therapy, immunosuppressant regimen, mean tacrolimus serum level during the 30 days prior to infection), rejection, site of infection, Sequential Organ Failure Assessment (SOFA) score, echocardiogram results, central line and hemodialysis during the 7 days prior to infection, surgery and intubation during the 2 weeks prior to infection, and outcome 1 and 12 months after transplantation and after infection.

Protocols

Skin preparation in the operating room was done with an iodine-based product, with the exception of allergic patients, in which chlorhexidine preparation was used. Peri-operative prophylaxis was done with cefazolin for 24 h or with vancomycin for patients allergic to cephalosporins, colonized with MRSA, or at risk for MRSA infections. For high-risk liver transplant recipients, fluconazole was administered prophylactically 2 weeks post-transplantation. Infections with MSSA were preferentially treated with oxacillin or cefazolin, while MRSA infections were preferentially treated with vancomycin and alternatively with daptomycin (in patients with acute renal failure or those who were allergic to vancomycin), doxycycline, and trimethoprim/sulfamethoxazole.

Definitions

Patients included were liver or multivisceral (liver–kidney) transplant recipients who were transplanted between January 2005 and December 2008. Patients only colonized with *S. aureus* were excluded from the study. Repeated isolation of *S. aureus* in cultures from the same site within a period of 14 days was treated as a single episode of infection.

Cases were defined as liver transplant recipients who developed *S. aureus* infections during the first year post-transplantation. Cases were identified by querying the computerized information system for liver transplant patients with any positive culture for *S. aureus*. Controls were defined as age-, gender-, and transplant type-matched recipients without *S. aureus* infections.

S. aureus bacteremia was defined as the isolation of the organism from ≥1 set of blood cultures in the presence of clinical signs of infection [6]. Pneumonia was defined as new pulmonary infiltrates in conjunction with clinical symptoms (cough, increased sputum production, fever) and whether *S. aureus* was isolated from sputum, tracheal aspirate, or bronchial aspirate [6]. Intra-abdominal abscess was defined as a collection of fluid, drained intra-operatively or under ultrasound or computer tomography guidance, yielding the growth of *S. aureus*. Peritonitis was diagnosed if the ascitis obtained surgically or by percutaneous aspiration and *S. aureus* grew in the culture, in the absence of an intra-abdominal abscess [6]. Skin and soft

tissue infection was defined by the isolation of *S. aureus* from a purulent fluid drained from a wound [6].

Statistical analysis

The characteristics of patients were compared between case and control groups using non-parametric Wilcoxon rank-sum tests for continuous variables and the Chi-square tests or Fisher's exact tests for categorical variables. Conditional logistic regression, which accounts for the matching between each case and set of two controls, was performed using the SAS (version 9.2 provided by SAS Institute Inc., Cary, NC) procedure PHREG to identify risk factors independently associated with *S. aureus* infection. Only the first infection was used in the risk factor analysis for patients who developed multiple *S. aureus* infections. Odds ratios (ORs) were calculated using the conditional logistic model. When the ORs were estimated as infinite by the conditional maximum likelihood, the estimations were improved by the maximization of a penalized conditional likelihood using Firth's bias correction method [9, 10]. Risk factors and characteristic factors with a p-value <0.2 based on univariate analysis were entered into a multivariable conditional logistic regression model with Firth's bias correction. The backward model selection was terminated until all coefficients were significant at the 0.1 α levels. A value of $p < 0.05$ was considered to be statistically significant.

Results

Demographics

A total of 51 patients were included in our analysis: 17 cases (*S. aureus* culture-positive patients) and 34 controls (*S. aureus* culture-negative patients); the median age at transplantation was 52 years (standard deviation [SD] 15.67, range 9–60); 64.71% of these patients were male. No significant characteristic differences were observed between cases and controls, as can be seen from Table 1. The majority of patients in both groups were white (76.47% of the cases and 70.59% of the controls) with comparable median age (52 vs. 52.5 years). Less than one-fifth of the cases and controls were donor-positive/recipient-negative (D+/R−) CMV recipients. The majority of patients were liver recipients (76.47% isolated liver and 11.76% liver re-transplantation). Induction therapy was administered for 6 cases (35.29%) and 10 controls (29.41%) ($p = 0.67$). Maintenance immunosuppression was based on tacrolimus (88.24% of the cases and 97.06% of the controls), followed by mycophenolate mofetil (29.41% of the cases and 35.29% of the controls). There was an indication of a marginal difference between cases and controls with regard to the severity of illness reflected in the SOFA scores ($p = 0.054$). The cases had a slightly higher median SOFA score compared to controls.

Table 1 Comparison between the characteristics of cases and controls included in our study

Variables	Cases ($n = 17$)	Controls ($n = 34$)	p-value
Median age at the first infection (range)	52 (12, 60)	52.5 (9, 60)	0.87
Male sex, *n* (%)	11 (64.71)	22 (64.71)	0.99
Number of patients with D+/R− CMV serostatus (%)	3 (17.65)	6 (18.18)	0.99
Type of graft, *n* (%)			
Liver	13 (76.47)	26 (76.47)	0.99
Liver–kidney	2 (11.76)	4 (11.76)	
Liver–liver	2 (11.76)	4 (11.76)	
Number of cadaveric donors (%)	17 (100.00)	32 (94.12)	0.55
Ethnicity (%)			
Black	2 (11.76)	4 (11.76)	0.99
Hispanic	1 (5.88)	3 (8.82)	
Other	1 (5.88)	3 (8.82)	
White	13 (76.47)	24 (70.59)	
Induction therapy (%)	6 (35.29)	10 (29.41)	0.67
Tacrolimus, *n* (%)	15 (88.24)	33 (97.06)	0.25
Number of patients on MMF and Rapamune (%)			
MMF	4 (23.53)	11 (32.35)	0.72
Rapamune	2 (11.76)	2 (5.88)	
Both	1 (5.88)	1 (2.94)	
None	10 (58.82)	20 (58.82)	
Median SOFA score (range)	1 (0, 17)	0 (0, 18)	0.054

D+/R− donor-positive/recipient-negative, *CMV* cytomegalovirus, *MMF* mycophenolate mofetil, *SOFA score* Sequential Organ Failure Assessment score (the day when the cultures were drawn)

Infections

Of the 447 patients who underwent liver transplantation during the study period, only 17 patients developed *S. aureus* infection in the first year after transplantation (incidence 3.80%). There were a total of 19 episodes of *S. aureus* infection, of which two were recurrent infections. First infections developed at a median time of 29 days (range 2–259) after transplantation. The first infection and all infections (combined first and recurrent infections) are described in Table 2. Of the 17 first infections, 9 (52.94%) had developed in the first month after transplantation and 13 (76.47%) during the first 3 months. For all 19 infections (first episode and recurrent infections), 9 (47.37%) developed in the first month and 14 (73.68%) in the first 3 months. From Table 2, it can be seen that there was an almost equal distribution between MSSA and MRSA infections. The majority of infections were nosocomial (88.24% of the first infections and 89.47% of the total infections), and about half were polymicrobial (41.18% of the first infections and 47.37% of all *S. aureus* infections). Approximately half of the first infections were surgical site infections (35.29% skin infections and 23.53% intra-abdominal infections). Bacteremia represented 23.53% of the first infections; no cases of infective endocarditis were diagnosed (Table 2).

Risk factors

Univariate analysis of risk factors for *S. aureus* infections was performed using several variables: age at first transplantation, tacrolimus level, and steroid administration 4 weeks prior to infection; rejection; D+/R− CMV mismatch; CMV infections 4 weeks prior to infection; presence of a central line; and hemodialysis 7 days prior, surgery and/or intubation 2 weeks prior to infection (Table 3). The cases group had a higher proportion of central lines in place 7 days prior, intubation 2 weeks prior, and surgery 2 weeks prior compared to the controls group. By univariate analysis, there was a difference between cases and controls with regard to the presence of central line 7 days prior to infection ($p = 0.02$), intubation 2 weeks prior ($p = 0.0006$), and surgery 2 weeks prior ($p = 0.0006$). Steroid maintenance therapy was more commonly administered to controls (34 patients, 100%) than cases (15 patients, 88.24%) while the tacrolimus level in the 4 weeks prior to infection was not significantly different between the two groups (10.7 ng/ml for cases and 8.7 ng/ml for controls, $p = 0.56$). D+/R− CMV serostatus was similar between the cases and controls (17.65 vs. 18.18%). CMV reactivation was diagnosed in two controls (5.88%); no cases were diagnosed with the CMV reactivation.

Five variables, central line within 7 days prior, intubation within 2 weeks prior, surgery within 2 weeks prior, steroids within 4 weeks prior to infection, and SOFA score, were entered into a multivariable conditional logistic regression model. The final model included only surgery 2 weeks prior to infection as a significant risk factor. The subjects with recent surgery had a 26.9 times higher odds of having infection than those subjects without it, adjusting for matched criteria.

Outcome

No grafts (0%) were lost in the cases group, while only one (2.94%) graft was lost in the controls group in the first year after transplantation ($p = 0.99$). Mortality 12 months after transplantation was 2 (11.76%) recipients in the cases group versus 1 (2.94%) recipient in the controls group

Table 2 Description of the first and all (first and recurrent) *Staphylococcus aureus* infections after liver transplantation

Variables	First infections ($n = 17$) (%)	Total infections ($n = 19$) (%)
Cases with MSSA	9 (52.94)	10 (52.63)
Cases with MRSA	8 (47.06)	9 (47.37)
Sites of infection description		
Abscess/peritoneum	4 (23.53)	4 (21.05)
Blood	4 (23.53)	4 (21.05)
Lung/pleura	3 (17.65)	4 (21.05)
Skin/wound	6 (35.29)	7 (36.84)
Median time to infection after transplant in days (range)	29 (2, 259)	31 (2, 285)
Number of monomicrobial infections (%)	10 (58.82)	10 (52.63)
Number of polymicrobial infections (%)	7 (41.18)	9 (47.37)
Number of nosocomial infections (%)	15 (88.24)	17 (89.47)
Number of community-acquired infections (%)	2 (11.76)	2 (10.53)
Number of cases with echocardiogram (%)	6 (35.29)	7 (36.84)
Number of cases with vegetations (%)	0 (0)	0 (0)

MSSA methicillin-susceptible *Staphylococcus aureus*, *MRSA* methicillin-resistant *Staphylococcus aureus*

Table 3 Risk factors for *S. aureus* infection after liver transplantation evaluated by univariate analysis

Variables	Cases ($n = 17$)	Controls ($n = 34$)	Odds ratio (95% confidence interval)	p-value
Median age at the first infection (range)	52.0 (12, 60)	52.5 (9, 60)	0.93 (0.81–1.06)	0.25
Median tacrolimus levels 4 weeks prior (range)	10.7 (3.1, 14.5)	8.7 (0, 14.6)	1.06 (0.87–1.31)	0.56
Patients on steroids 4 weeks prior (%)	15 (88.24)	34 (100.00)	0.1 (0.001–1.23)	0.07
Number of clinical rejections (%)	3 (17.65)	4 (11.76)	2.0 (0.28–14.2)	0.49
Number of patients with D+/R− CMV serostatus (%)	3 (17.65)	6 (18.18)	1.0 (0.23–4.35)	0.99
Number of patients with CMV infection 4 weeks prior (%)	0 (0.00)	2 (5.88)	0.4 (0.003–4.92)	0.52
Number of patients with central line 7 days prior (%)	9 (52.94)	6 (17.65)	11.69 (1.42–95.9)	0.02
Number of patients on hemodialysis 7 days prior (%)	2 (11.76)	2 (5.88)	2.0 (0.28–14.2)	0.49
Number of patients intubated 2 weeks prior (%)	11 (64.71)	9 (26.47)	26.92 (3.23–3,504.15)	0.0006
Number of patients with surgery 2 weeks prior (%)	11 (64.71)	9 (26.47)	26.92 (3.23–3,504.15)	0.0006

($p = 0.25$). Post-*S. aureus* infection mortality at 1 month was 1 patient (5.88%) and at 12 months, it was 2 patients (11.76%).

Discussion

S. aureus is an important pathogen after transplantation. *S. aureus* infections have been documented in 20–25% of patients who have undergone liver transplantation, with 30-day mortality rates of up to 21% [11]. The incidence of infections in our liver transplant recipients in the first year after transplantation was low (~4%), similar to the data reported by Singh et al. (~4%) [11], and much lower than the rate reported by other authors (10–23%) [3, 6, 12–14]. The most common sites of infection were the surgical site (~59%) and bacteremia (~24%). *S. aureus* from the patient's colonized skin is the usual source of infection for bacteremia and for the surgical site infections. With surgical procedures involving the biliary duct, the pathogens causing surgical site infections would reflect the endogenous flora, including *S. aureus* (and MRSA) if the patient underwent procedures prior to transplantation; such infections are typically polymicrobial. The presence of foreign bodies (surgical sutures, stents, and clips) would increase the risk of infection because of the lower requirement for bacterial inoculum to cause an infection [15]. The immune defense of the host is also impaired, which further increase the risk of infections. Chronic liver disease and alcohol consumption are associated with impaired humoral and cell-mediated immunity, since the reversal of immune dysfunction is progressive after the cessation of alcohol consumption [6, 16–18]. Also, neutrophil chemotaxis and superoxide production are affected by post-operative steroid administration and by anesthetic-induced hypothermia [19].

The first episode of *S. aureus* infection occurred within a median of 29 days following liver transplantation in our study, similar to the data which we reported in kidney recipients (article in press). Almost half of the infections occurred in the first month after transplantation. It is not surprising that most of the infections in liver (as in kidney) transplantation developed in the early post-operative period. This is the time when the skin and mucosal integrity are broken, central lines are present, hemodialysis is sometimes performed, and patients are intubated; neutrophil function is also impaired due to liver disease prior to transplantation and to steroid administration after transplantation. Since most of the infections were associated with intra-vascular access and surgical procedures, they were classified as nosocomial (~88% of the first infections, ~89% of all infections).

Liver transplant recipients have multiple risk factors for developing *S. aureus*, and, in particular, MRSA infections: immunosuppressed status, prolonged hospitalization, and multiple admissions to the intensive care unit increase the risk of colonization with *S. aureus*. From the variables we assessed in the univariate analysis, only intubation, surgery, and presence of a central line were significantly associated with *S. aureus* infections. We expected that D+/R− CMV serostatus and prior CMV disease would be risk factors for *S. aureus* infections, knowing the indirect immunomodulatory effects of CMV [2]; however, these factors likely were not associated with infection probably because of the small number of events and patients in the study. In the multivariate analysis, only surgery remained an independent predictor of *S. aureus* infections. Although renal replacement therapy has been previously reported as a risk factor of MRSA infections after living-related liver transplantation [3], it was not a risk factor in our study.

A high mortality rate from *S. aureus* infections, in particular, bacteremia, has been previously described in

several studies, and it has been particularly associated with methicillin resistance [2, 7, 20]. Hashimoto et al. [3] reported a low mortality rate (0.4%), but the data were reported only at 3 months after liver transplantation. Our study could not confirm that *S. aureus* infection had a major impact on the mortality of liver transplant patients; likely, this finding is multifactorial: low event rates; the strict adherence to standard peri-operative prophylaxis; the measures aimed at reducing the incidence of bacteremia (proper insertion and handling of intra-vascular catheters); and the infection control policies that prevented the cross-transmission of bacteria (especially MRSA) probably all contributed to the low mortality rate observed in patients with *S. aureus* infections.

Limitations of the present study are inherent to the retrospective design and data collection. In addition, the small sample size did not allow us to draw firm conclusions regarding risk factors and outcome associated with *S. aureus* infections after liver transplantation. We did not investigate *S. aureus* colonization as a risk factor for infection since routine pre- or post-operative screening for MRSA colonization followed by MRSA decolonization is not performed at our institution. We did not independently assess several risk factors for *S. aureus* infections that occur in the operative and peri-operative period (i.e., wound class, length of surgery, hypoxia, hypothermia, hypoglycemia, hyperglycemia, and blood transfusions); these factors were described in another study published by our group, showing the association of various intra- and peri-operative factors with the development of infections (article in press). However, given the limited data of *S. aureus* infections in this population, we believe that our study provides relevant and useful clinical information.

Conclusion

In contrast with previously published studies in liver transplant recipients which demonstrated that most of the *Staphylococcus aureus* infections are caused by methicillin-resistant strains and are associated with high mortality rate, our data showed only a 50% MRSA rate of infection. Most of the infections were considered to be nosocomial-acquired (88%) and developed early after transplantation, with more than 50% being diagnosed in the first month post-transplantation. Surgical site infections represented almost 60% of the infections and surgical intervention remained in our analysis as the only significant independent risk factor for *S. aureus* infections after liver transplantation.

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Conflict of interest The authors have no conflict of interest to disclose.

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