References


Association between Nasal Carriage of Staphylococcus Aureus and Infection in Liver Transplant Recipients

We reviewed the records of 87 patients who underwent liver transplantation and who were screened by use of nasal swabs on the day before surgery. Twenty-four patients harbored methicillin-susceptible Staphylococcus aureus ( MSSA), and 8 harbored methicillin-resistant S. aureus (MRSA). MSSA infection occurred in 3 (12.5%) of 24 MSSA carriers and in 2 (3.2%) of 63 noncarriers (non-significant). In contrast, MRSA infection occurred more frequently in MRSA carriers (7 [87.5%] of 8) than in MRSA noncarriers (8 [10.1%] of 79; P < .001). Nasal carriage of MRSA is associated with a very high risk of MRSA infection in liver transplant recipients.

Early bacterial infections, which occur within 2 months of transplantation, remain a major cause of morbidity and mortality in liver transplant recipients [1, 2]. Associated risk factors include acute liver failure, preoperative encephalopathy, an elevated bilirubin level, diabetes mellitus, prior hepatobiliary surgery, prolonged duration of surgery, increased operative transfusion requirement, and acute rejection [1, 3–5]. Whereas gram-negative bacilli were previously regarded as the predominant pathogens in these patients [1], Staphylococcus aureus is now recognized as the leading cause of bacterial infection after liver transplantation (LT) [5, 6]. The prevalence of nasal carriage of S. aureus in patients with cirrhosis is higher than that in other patients [7]. A recent study by Chang et al. [8] suggested that preoperative nasal colonization with methicillin-resistant S. aureus (MRSA), but not with methicillin-susceptible S. aureus (MSSA), is a significant predictor of subsequent infection. In other populations, such as patients who reside in intensive care units (ICUs) [10], a higher rate of infection has been reported in MRSA carriers than in MSSA carriers.

The aim of this study was to investigate the relationship between nasal carriage of S. aureus and the risk of infection in liver transplant recipients. In particular, we examined whether this relationship was influenced by resistance to methicillin.

Of the 100 consecutive patients who underwent LT for end-stage liver disease from September 1996 through October 1998 at the Department of Digestive Surgery of Beau-
Table 1. Comparison of methicillin-susceptible *Staphylococcus aureus* (MSSA) carriers and methicillin-resistant *S. aureus* (MRSA) nasal carriers.

<table>
<thead>
<tr>
<th>Variable</th>
<th>MSSA carriers (n = 24)</th>
<th>MRSA carriers (n = 8)</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean y (range)</td>
<td>47.6 (16–65)</td>
<td>47.9 (39–54)</td>
<td>NS</td>
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<tr>
<td>Male:female ratio</td>
<td>15:9</td>
<td>5:3</td>
<td>NS</td>
</tr>
<tr>
<td>Length of hospital stay within previous year, mean d (range)</td>
<td>14.2 (1–45)</td>
<td>46.4 (8–160)</td>
<td>.008</td>
</tr>
<tr>
<td>Patients who stayed &gt;3 days in the ICU during the previous year, no. (%)</td>
<td>1 (4.2)</td>
<td>5 (62.5)</td>
<td>.002</td>
</tr>
<tr>
<td>Child-Pugh score, mean (range)</td>
<td>9.2 (6–13)</td>
<td>10.5 (7–13)</td>
<td>NS</td>
</tr>
<tr>
<td>Underlying liver disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcoholic cirrhosis</td>
<td>6 (25)</td>
<td>5 (62.5)</td>
<td>NS</td>
</tr>
<tr>
<td>Posthepatitic cirrhosis</td>
<td>7 (29.2)</td>
<td>1 (12.5)</td>
<td></td>
</tr>
<tr>
<td>Primary biliary cirrhosis</td>
<td>3 (12.5)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Fulminant hepatitis</td>
<td>3 (12.5)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>5 (21)</td>
<td>2 (25)</td>
<td></td>
</tr>
<tr>
<td>Associated risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal failure</td>
<td>3 (12.5)</td>
<td>2 (25)</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>7 (29.2)</td>
<td>1 (12.5)</td>
<td></td>
</tr>
<tr>
<td>Prior hepatobiliary surgery</td>
<td>4 (16.7)</td>
<td>1 (12.5)</td>
<td></td>
</tr>
<tr>
<td>Pretransplant steroid exposure</td>
<td>2 (8.3)</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

NOTE: Data are no. (%) of patients, unless otherwise indicated. ICU, intensive care unit.

* Fisher’s exact test was used for proportions, and the Mann-Whitney test was used for means.

During this period, perioperative prophylaxis consisted of iv cefoxitin (2 g given before surgery, followed by 1 g given every 4 h intraoperatively and every 8 h thereafter for 48 h). Patients who were allergic to penicillin received clindamycin and gentamicin. None of the patients received vancomycin. In the early postoperative period, immunosuppression was associated with azathioprine (2 mg/kg/day), corticosteroids, and either ciclosporin or tacrolimus. Doses were adjusted to maintain plasma levels of 300–400 ng/mL for ciclosporin and levels of 10–15 ng/mL for tacrolimus. Administration of iv methylprednisolone was tapered from 5 mg/kg/day to 0.3 mg/kg/day on postoperative days 1–8, and treatment was then switched to oral prednisone (20 mg/day). For prevention of fungal infection, amphotericin B (500 mg) was given q.i.d. via a nasogastric tube.

The characteristics of MSSA carriers and MRSA carriers were compared by use of Fisher’s exact test, for proportions, and by use of the Mann-Whitney test, for means. The association between the carrier status and the occurrence of MSSA and MRSA infection was analyzed by use of Fisher’s exact test.

Of the 87 patients who were included in the study, 32 (36.8%) were nasal carriers. Of these 32 nasal carriers, 24 (27.6%) harbored MSSA, and 8 (9.2%) harbored MRSA. One of the 8 MRSA carriers also harbored MSSA. The characteristics of MSSA carriers and MRSA carriers are compared in table 1. The length of hospital stay in the year prior to transplantation was significantly longer for MRSA carriers than for MSSA carriers. There was a trend toward a greater frequency of alcoholic cirrhosis and a higher Child-Pugh score among MRSA carriers than for MSSA carriers. There was a trend toward a greater frequency of alcoholic cirrhosis and a higher Child-Pugh score among MRSA carriers than among MSSA carriers, although these differences were not statistically significant. The Child-Pugh score was ≥10 in 6 (75%) of 8...
Table 2. Relationship between nasal carriage of *Staphylococcus aureus* and infection in 87 liver transplant recipients.

<table>
<thead>
<tr>
<th></th>
<th>No. of patients with indicated carrier status</th>
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<tbody>
<tr>
<td></td>
<td>MSSA carriers</td>
</tr>
<tr>
<td><em>S. aureus</em> infection</td>
<td>(N = 24)</td>
</tr>
<tr>
<td>MSSA infection (n = 5)</td>
<td>3</td>
</tr>
<tr>
<td>MRSA infection (n = 15)</td>
<td>2</td>
</tr>
<tr>
<td>No <em>S. aureus</em> infection (n = 67)</td>
<td>19</td>
</tr>
</tbody>
</table>

NOTE. by use of Fisher’s exact test for proportions. MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-susceptible *S. aureus*.

MRSA carriers and in 10 (41.7%) of 24 MSSA carriers. The 2 groups were otherwise similar in terms of age, sex, and associated conditions.

Overall, 20 (23%) of 87 patients developed *S. aureus* infection within 2 months after LT. MSSA was involved in 5 cases, and MRSA was involved in 15 cases.

Of the 5 patients who had MSSA infection, 4 had surgical wound infections, and 1 had a lower respiratory tract infection. Onset of infection occurred at a mean of 14.8 days after surgery (range, 4–25 days). One patient was treated with amoxicillin-clavulanate, 1 was treated with oxacillin, and 3 who had superficial wound infections did not receive systemic antibiotics. One patient had *Escherichia coli* urinary infection after surgery, and the 4 other patients did not develop nonstaphylococcal infection. The mean length of hospital stay for MSSA-infected patients was 41.8 days (range, 26–73 days), including 20.6 days of stay in the ICU (range, 11–39 days).

Among the 15 patients with MRSA infection, 6 had several sites of infection. The sites of MRSA infection were the bloodstream (7 patients), the surgical wound (5), the lower respiratory tract (5), the abdominal cavity (4), and the pleural fluid (1). Six of the 7 cases of bacteremia were catheter related. The mean time to the onset of infection was 14.1 days after surgery (range, 2–36 days). Eleven patients were treated with vancomycin, 1 was treated with teicoplanin, and 3 who had superficial wound infections did not receive systemic antibiotics. Within 2 months of surgery, 5 of the 15 patients also developed nonstaphylococcal infection: *Klebsiella pneumoniae* respiratory tract infection and *Clostridium difficile* colitis (1 patient), *Klebsiella oxytoca* bacteremia (1), cytomegalovirus pneumonia (1), *Candida albicans* bacteremia and abdominal infection (1), and *Candida tropicalis* bacteremia (1). The mean length of hospital stay for MRSA-infected patients was 57.3 days (range, 20–119 days), including 38.3 days of stay in the ICU (range, 15–88 days). One patient died during hospitalization, and his death was related in part to the infection.

There was a significant association between the preoperative carrier status and the occurrence of infection after surgery (*P* < .001; table 2). MSSA infection occurred in 3 (12.5%) of 24 MSSA carriers versus 2 (3.2%) of 63 MSSA noncarriers (NS). In contrast, MRSA infection developed more frequently in MRSA carriers (7 [87.5%] of 8) than in MRSA noncarriers (8 [10.1%] of 79; *P* < .001). The mean time to the onset of MRSA infection tended to be shorter for MRSA carriers (8.1 days) than for noncarriers (14.6 days), although statistical significance was not attained. Infection occurred within 10 days of transplantation in 6 (85.7%) of 7 infected carriers versus 3 (37.5%) of 8 infected noncarriers.

PFGE patterns of MRSA isolates from the 7 infected carriers are shown in figure 1. For 3 patients (patients A, D, and G), the isolate from the nose and the isolate from the infected site had similar patterns. For 2 patients (patients B and C), the 2 isolates were considered to be closely related, because the patterns differed by only 2 or 3 bands. For the remaining 2 patients (patients E and F), the 2 isolates had quite distinct patterns, differing by >3 bands. For patient F, the infecting strain was similar to that recovered from another infected patient hospitalized in the unit during the same period (figure 1).

Six PFGE patterns were identified among the 8 MRSA isolates that infected the noncarriers. One pattern was shared by 3 patients, and the remaining 5 patterns were found in only 1 patient each.

The present study indicates that preoperative nasal carriage of MRSA is associated with a very high risk of subsequent MRSA infection among liver transplant recipients. The majority of these carriers developed infection within 10 days.
days of transplantation. Molecular typing showed that the infection was more frequently the result of endogenous reactivation than of environmental acquisition, because, in 5 of the 7 infected carriers, the isolate was either identical or closely related to that previously recovered from the nose. During the postoperative period, the remaining 2 carriers, for whom the pair of isolates did not match, presumably acquired the infecting strain as a result of horizontal spread from other patients. Our results amplify those of Chang et al. [8], who reported a similar association between MRSA colonization and infection in liver transplant recipients. Because of the small number of patients in the group of MRSA carriers, larger studies would be useful to confirm these findings. Whereas, in the study by Chang and colleagues, infection occurred exclusively in MRSA nasal carriers, 8 of our patients who did not harbor MRSA before surgery developed infection, which indicates that the strain was acquired during hospitalization after LT.

Compared with MRSA carriers, MSSA carriers were not significantly more likely than noncarriers to develop MSSA infection. Likewise, not a single case of MSSA infection was observed in the study by Chang and colleagues [8]. Therefore, as reported for other groups of patients [9, 10], nasal carriage of MSSA is associated with a lower risk of infection than is nasal carriage of MRSA in liver transplant recipients. This finding cannot be ascribed only to the differences in the intrinsic virulence of S. aureus strains, because there is no evidence that MRSA strains are more virulent than MSSA strains [13, 14]. Antibiotics given for perioperative prophylaxis, which were active against MSSA but not against MRSA, probably contributed to the prevention of MSSA infection in the early postoperative period. Differences in the rates of infection could also be the result of differences in host characteristics. Indeed, a greater severity of illness favors the acquisition of MRSA because hospitalization is required before LT, and it also increases the risk of subsequent bacterial infection.

Comparison of the characteristics of MRSA carriers with those of MSSA carriers revealed that MRSA carriers had a significantly greater length of preoperative hospital stay than did MSSA carriers. For 5 of the 8 MRSA carriers, the hospital stay in the year prior to LT included ≥3 days of stay in the ICU, where the risk of acquisition of MRSA is greater. In addition, there was a trend toward a higher Child-Pugh score and a greater frequency of alcohol-induced cirrhosis among MRSA carriers, although these differences were not statistically significant; they were probably a result of the low number of patients in the group of MRSA carriers. Previous studies have shown that there is a lower incidence of acute rejection and a higher incidence of bacterial infections in patients undergoing LT for alcoholic cirrhosis, which indicates a reduced immune responsiveness [15]. Our findings suggest that, compared with MSSA carriers, MRSA carriers have a poorer preoperative clinical condition, which may predispose them to infection. This result is corroborated by a recent report indicating that a higher Child-Pugh score is independently associated with MRSA carriage in patients with cirrhosis [16].

According to our results, candidates for LT should systematically be screened for nasal carriage of MRSA, and a strategy aimed at the prevention of subsequent infection is warranted for nasal carriers. The addition of vancomycin to the preoperative prophylactic regimen may prevent infection at the surgical site, but its impact on the emergence of S. aureus strains with reduced susceptibility to glycopeptides is questionable [17]. An alternative strategy is to try to eliminate the carrier state before the patient undergoes LT. Mupirocin is a topical antibiotic that has been recommended for eradication of nasal carriage of MRSA in hospitalized patients [18]. It has been reported to be effective in decreasing the incidence of bacteremias in patients undergoing hemodialysis [19] and the incidence of surgical site infection in those undergoing cardiothoracic surgery [20]. Further investigations are needed to evaluate the impact of the use of mupirocin for preoperative eradication of nasal carriage on the rates of MRSA infection among liver transplant recipients.

References

8. Chang FY, Singh N, Gayowski T, Drenning SD, Wagener MM, Marino IR. Staphylococcus aureus nasal colonization and association with
Trichosporon beigelii Funguria in Renal Transplant Recipients

Trichosporon beigelii funguria in renal transplant recipients is usually benign and is seldom associated with invasive or deep-seated infections.

Trichosporon beigelii is frequently found in the environment and may colonize the human flora [1]. In immunocompromised hosts, it frequently causes invasive fungal infections [2]. Gastrointestinal and urinary tract colonization usually precedes invasive infections. In renal transplant recipients, the clinical significance of positive urine cultures with T. beigelii is largely unknown.

From 1992 through 1999, 11 renal transplant recipients experienced T. beigelii funguria at our institution (Hôpital Maisonneuve-Rosemont, Université de Montréal, Quebec, Canada) (table 1). All patients were receiving immunosuppressive therapy consisting of either prednisone and/or azathioprine and/or cyclosporine. The majority of cases occurred during the early postengraftment period (<6 months after engraftment), and results of urine cultures were repeatedly positive for T. beigelii in all patients except for patients 4, 5, 7, and 11. Five patients had urinary tract indwelling devices, and 6 patients were treated with broad-spectrum systemic antibacterial therapy when a positive urine culture for T. beigelii funguria was obtained. Seven of the 11 patients had clinical signs of infection. Three of the 7 symptomatic patients complained of symptoms of urinary tract infection, and 4 patients experienced only fever. Two patients (patients 8 and 10) had invasive urinary tract infections caused by T. beigelii.

Patient 8 developed a vesicoureteral stenosis shortly after receiving a renal cadaveric allograft, and he had a ureteral stent installed. After receiving, for 14 days, antibiotic therapy for Pseudomonas aeruginosa infection of the site of a peritoneal dialysis catheter tunnel, repeated urine cultures yielded T. beigelii. The MICs against the isolate were as follows: for amphotericin B, 1 mg/L; for 5-fluorocytosine, 8 mg/L; for ketoconazole, 1 mg/L; for itraconazole, 0.5 mg/L; and for fluconazole, 4 mg/L. The ureteral stent was removed, and the patient was treated with ketoconazole. After 7 days of therapy, the urine cultures remained positive for T. beigelii, and ketoconazole therapy was switched to fluconazole therapy. On day 3 of fluconazole therapy, the results of urine cultures became negative. While receiving fluconazole, the patient underwent pyelovesicostomy with removal of the ureteral stent. The patient did not experience any fungal infection at follow-up 1 month after discontinuation of fluconazole therapy.

Patient 10 was admitted with progressive dysfunction of a renal cadaveric allograft. Results of repeated urine cultures revealed T. beigelii urinary infection, which was initially treated with itraconazole followed by daily intravesical instillations of amphotericin B. Despite the antifungal therapy, the urine cultures remained positive for T. beigelii. At the time of the renal transplantation, a fungus ball at the surgically reconstructed ureter was discovered on cystoscopy and was partially removed. Direct calcofluor examination of the material removed was positive, and culture yielded T. beigelii. The MICs against this isolate were as follows: for amphotericin B, 0.5 mg/L; for 5-