

The outcomes of methicillin-resistant *Staphylococcus aureus* infection after living donor liver transplantation in a Japanese center.

Mitsuhisa Takatsuki, Susumu Eguchi, Kosho Yamanouchi, Masaaki Hidaka, Akihiko Soyama,  
Kensuke Miyazaki, Yoshitsugu Tajima, Takashi Kanematsu

Department of Surgery, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki,  
Japan

Short running title: MRSA in LDLT

Key words: liver transplantation, living donor, methicillin-resistant *Staphylococcus aureus*

Address correspondence to:

Mitsuhisa Takatsuki, M.D.

Department of Surgery, Nagasaki University Graduate School of Biomedical Sciences,

1-7-1 Sakamoto, Nagasaki 852-8501, Japan

TEL: 81-95-819-7316

FAX: 81-95-819-7319

E-mail: [takapon@net.nagasaki-u.ac.jp](mailto:takapon@net.nagasaki-u.ac.jp)

## Abstract

*Objective.* The objective of this study is to present results from our review of methicillin-resistant *Staphylococcus aureus* (MRSA) infection in living-donor liver transplant (LDLT) recipients.

*Methods.* Seventy patients with primary LDLT between August 1997 and May 2007 were retrospectively reviewed.

*Results.* Overall, 9 patients (12.9%) encountered various kinds of MRSA infection after transplantation (peritonitis (6), bacteremia (6), pneumonia (3), wound infection (3), cholangitis (1)); 4 of these 9 patients died. Of these 4 expired patients, 3 were highly urgent cases with very poor pretransplant status under ventilator support. In one patient, linezolid was effective after teicoplanin failure for severe systemic MRSA infections (bacteremia, peritonitis, cholangitis, pneumonia, and enteritis). Of the 4 patients in whom MRSA was isolated only in a nasal swab before transplantation, none developed MRSA infection after transplantation with a 3-day-course of mupirocin prophylaxis.

*Conclusions.* MRSA infection was a contributing factor in death after transplantation in cases with poor pretransplant status. Linezolid was effective even for treating systemic MRSA infection after LDLT. A short course of mupirocin prophylaxis seemed to be effective, and did not have any adverse effects.

Since methicillin-resistant *S. aureus* (MRSA) was identified in the United Kingdom in 1961 (1), it has been recognized as one of the most troublesome bacteria to manage, including after general abdominal surgery (2,3). In liver transplantation, the risk and severity of MRSA infection might be more serious because of additional immunosuppression. Although MRSA infection has actually been recognized as the leading cause of fatal bacterial infection in liver transplant recipients (4,5), an appropriate strategy to manage it has not yet been established. Especially for nasal carriers, the efficacy of prophylactic treatment is not clear. Bert et al. (6) reported that the nasal carriage of MRSA is an independent risk factor for post-transplant MRSA infection, which indicates that mupirocin prophylaxis would be a reasonable treatment; however, its efficacy in deceased donor liver transplantation is under debate (7). However, in comparison to deceased donor liver transplantation, living donor liver transplantation (LDLT) has an advantage in that we can plan pretransplant elective prophylaxis in the majority of cases. With regard to the treatment of infection after surgery, there are currently several options, including not only glycopeptides, but also linezolid, daptomycin and tigecycline. The aim of this study was to show the outcomes of MRSA infection in our LDLT recipients and to propose an appropriate strategy for treatment.

## Patients and Methods

### *Patients*

This is a retrospective observational study to describe the outcomes of MRSA infection and/or colonization among patients who underwent LDLT in a Japanese hospital. Seventy sequential patients with primary LDLT between August 1997 and May 2007 in a Japanese hospital (Nagasaki Univ. hospital, 869 beds in total) were enrolled in the present study. The medical records of these 70 patients were retrospectively reviewed. During preoperative evaluation, several samples, including nasal swab, urine, and stool samples, were routinely obtained for culture study in the recipients. This screening was not routinely performed in the living donors. In any patients who were MRSA-positive only in the nasal swab before elective LDLT, mupirocin calcium ointment was applied twice daily for 3 days before transplantation without rechecking the nasal culture. For the patients who were MRSA-positive in the stool or urine, oral or intravenous vancomycin was administered until we confirmed the eradication of MRSA before the surgery. In some highly urgent cases, the patients underwent LDLT without checking the results of the culture studies, after clinical signs of infection were carefully ruled out. Basic immunosuppression after transplantation consisted of tacrolimus and steroid. Tacrolimus was begun orally at 0.05 mg/kg twice a day from the day after transplantation. The target trough level was from 10 to 15 ng/ml until one month after surgery, and around 10 ng/ml or less thereafter. Regarding steroids, methylprednisolone was administered

intravenously at 10 mg/kg for pediatric cases and 1 g for adult cases just after reperfusion during surgery. In the postoperative period, we administered a 0.5 mg/kg i.v. four times a day for the first 3 postoperative days, followed by 0.5 mg/kg twice a day for the next 3 days. Thereafter, we switched to oral prednisolone at 0.5 mg/kg once a day at 7 days after transplantation, and the steroid was discontinued by 6 months, when the liver function was stable, after a staged reduction. In selected cases, additional mycophenolate mofetil or azathioprine was used. For patients with hepatitis C-related cirrhosis, tacrolimus was converted to microemulsified cyclosporine when the patients started receiving anti-viral therapy after transplantation. Post-transplant antibiotic prophylaxis consisted of cefazolin and ampicillin at 1 g each, four times a day, for 3 days. After surgery, samples were obtained from the nares, respiratory secretions, urine, stool, ascites and bile (when applicable) for the surveillance culture weekly, for each patient after transplantation.

#### *Definition of MRSA infection*

Each sample was plated onto mannitol-salt agar. After incubation at 37°C for 24 to 48 hours, *S. aureus* was identified by microscopic and growth characteristics, the coagulase test, and DNA hydrolysis. Methicillin resistance was determined by the disk diffusion method on Mueller-Hinton agar plates (Becton Dickinson Co.) containing 5 µg of oxacillin, incubated at 30°C for 24 to 48 hours. The medical records were retrospectively reviewed and MRSA infections were defined as follows.

Bacteremia was defined as the isolation of MRSA in at least one blood culture with obvious clinical signs of infection (high fever and/or elevation of serum level of C-reactive protein (CRP)).

Pneumonia was defined as a new pulmonary infiltrate developed on radiographic studies in conjunction with clinical signs (high fever and/or elevation of serum level of CRP, with purulent sputum), and MRSA was isolated from a respiratory secretion. Cholangitis was defined as the elevation of serum bilirubin, and the isolation of MRSA in bile obtained from biliary drainage (if applicable) with clinical signs of infection (high fever and/or elevation of CRP). Peritonitis was diagnosed if MRSA was isolated from ascites obtained intra- or post-operatively with clinical signs of infection (abdominal pain, high fever and/or elevation of CRP). Wound infection was defined as the isolation of MRSA from a purulent fluid drained from the wound. Even if MRSA was isolated from various kinds of specimens, it was defined as the carrier when there were no clinical signs of infection.

## Results

### *The characteristics of the patients*

The 70 patients with primary LDLT during the study period consisted of 40 males and 30 females, with a median age of 52 (range, 0.5-67). The original diagnoses included hepatitis C-related cirrhosis in 20 patients (14 with hepatocellular carcinoma), hepatitis B-related cirrhosis in 15 (11 with

hepatocellular carcinoma), acute liver failure in 10, biliary atresia in 9, primary biliary cirrhosis in 5, cryptogenic cirrhosis in 5, alcoholic cirrhosis in 2, and other diagnoses in 4. With regard to preoperative status, the median Model for End-Stage Liver Disease (MELD) score was 18 (range, 7-41) in the adult cases older than 12 years.

#### *Isolation of MRSA before LDLT*

The characteristics of the MRSA infection are shown in Table 1.

MRSA was isolated in 10 samples from 8 patients (11.4%) before transplantation (nasal swab (6), respiratory secretion (2), and stool (2)). The 2 patients with MRSA in respiratory secretions were highly urgent cases under mechanical ventilation, and we finally performed transplantation after clinical signs of infection were carefully ruled out. Of these 8 patients, 3 (37.5%) developed MRSA infection after transplantation, which was a contributing factor in the death of 2 of the patients. Both of these patients encountered septic shock with MRSA peritonitis, followed by multiorgan failure.

#### *MRSA infection after LDLT*

Overall, 9 patients (12.9%) encountered various kinds of MRSA infection after transplantation (peritonitis in 6 patients, bacteremia in 6, pneumonia in 3, wound infection in 3, cholangitis in 1); 4 of these 9 patients died. Of the 4 expired patients, 3 were highly urgent cases with very poor

pretransplant status under ventilator support, including the 2 patients mentioned above. Another patient had systemic MRSA infections (bacteremia, peritonitis and pneumonia) followed by hemophagocytic syndrome possibly due to cytomegalovirus viremia; this patient finally died 48 days after transplantation. In this patient, linezolid was started, but discontinued and replaced by teicoplanin because of severe thrombocytopenia (nadir platelet count,  $4000/\text{mm}^3$ ) due to hemophagocytic syndrome. One patient, a 60-year-old female, also developed severe systemic MRSA infections (bacteremia, peritonitis, cholangitis, pneumonia), which were promptly resolved by linezolid after ineffective treatment with teicoplanin. In this case, trough level of teicoplanin was maintained therapeutic range, around  $10\ \mu\text{g}/\text{mL}$  or greater. As shown in Table 1, the patients who were defined as carriers did not require any treatment; this was true not only for nasal carriers, but also for the patients with MRSA isolated in respiratory secretions, stool or bile. The median MELD score in adult cases (older than 12 years) was not significantly different between the groups with or without MRSA infection (19 (range, 8-40) vs 18 (range, 7-41), Mann-Whitney test). Although there were no statistic differences in MELD score between the patients who died or survived after MRSA infection, 2 of the 4 expired patients revealed high MELD score greater than 30 (40 and 36, respectively; Table 1).

## Discussion

Although MRSA infection is well recognized as a life-threatening complication after liver transplantation, the criteria for transplant indication and appropriate prophylaxis have not yet been established. Several studies have indicated that nasal carriers are at a high risk of post-transplant MRSA infection (3,4), which means that mupirocin prophylaxis is reasonable, but Paterson and colleagues showed the lack of efficacy of this strategy in a deceased donor liver transplantation series (7). However, in deceased donor liver transplantation, appropriate elective prophylaxis is difficult, and mupirocin resistance is of great concern with the prolonged or repeated use of an elective prophylaxis (8). In LDLT, an elective protocol can be established, and a short course of mupirocin prophylaxis was adapted in our series. In our study, there were 4 nasal carriers in whom MRSA was isolated in the nasal swab only, but none of them had any MRSA infection after transplantation. Accordingly, we adopted a 3-day course of mupirocin prophylaxis for elective cases because this course can be undergone safely, without any adverse effects. Although a randomized and controlled study is needed to show the efficacy of mupirocin prophylaxis in LDLT, we propose it as one possible effective strategy.

Currently, there are several prophylaxis and treatment options for MRSA infection, including mupirocin, glycopeptides (vancomycin, teicoplanin), linezolid, and more recently, daptomycin and tigecycline (9). Glycopeptides are widely used, but their current use to treat MRSA infections has

been the subject of much debate because they have a modest effect despite showing in vitro sensitivity, especially in pulmonary infection (10). Based on our experience of successful salvage therapy with linezolid after teicoplanin failure for systemic severe MRSA infection, our current policy is to adopt linezolid as the rescue treatment for MRSA infection. In principle, glycopeptides should still be the first-line for MRSA infection, because majority of the cases could be controlled by these drugs as shown in this study. Linezolid can be an alternative for glycopeptides, but indications should be considered carefully, because several studies demonstrated treatment failure (11) and severe adverse effects such as myelosuppression (12). However, we recommend using linezolid as a second-line treatment in liver transplant recipients with MRSA infection, who easily tend to fall into critical condition because of immunosuppression.

Of the 4 expired patients in this study, 3 had a very poor preoperative status under mechanical ventilation, and 2 revealed high MELD score greater than 30. It is well recognized that preoperative status affects the outcome of transplantation. The leading cause of death is infection, which means that liver transplantation might be contraindicated even for carriers when a patient's status is poor. In regard to the risk factors of MRSA infection after LDLT, Hashimoto and colleagues (13, 14) showed that independent predictive factors included preoperative MRSA colonization, preoperative use of antimicrobials, prolonged operation time, and postoperative apheresis, none of which were seen as predictive factors in our study (data not shown), possibly because of our smaller number of cases. In

regard to preoperative MRSA colonization, none of the patients in whom MRSA was detected only in a nasal swab during preoperative evaluation developed MRSA infection after transplantation. Mupirocin prophylaxis might be effective in these cases, but we have to follow such cases carefully after transplantation in order to monitor them for signs of MRSA infection.

It is unclear whether we should treat carriers in whom MRSA is isolated without any clinical signs of infection after transplantation. In our series, not only nasal carriers, but patients with MRSA isolated in respiratory secretions, bile or stool did well and did not require any treatment. Although such isolated MRSA might lead to subsequent severe infection in an immunosuppressive state, it seems that we can safely follow such patients with close observation. Another concern is that of possible MRSA transmission from the living donors (15). Although such cases are probably rare, routine MRSA screening in the living donors might be recommended.

In conclusion, MRSA infection is life-threatening in LDLT recipients, especially for patients with a poor pre-transplant clinical condition. Linezolid is an effective option for reversing even critical infections, and we therefore recommend it as the second line of treatment for MRSA infection after LDLT. A short course of mupirocin prophylaxis seemed to be effective for elective cases, although a prospective and randomized study is needed to fully determine its efficacy.

## References

1. Benner EJ, Morthland V. Methicillin-resistant *Staphylococcus aureus*. Antimicrobial susceptibility. *N Engl J Med*. 1967;277:678–680.
2. Giamarellou H. Fourth generation cephalosporins in the antimicrobial chemotherapy of surgical infections. *J Chemother*. 1999;11:486-93.
3. Emmerson AM, Garau J. Postoperative complications due to methicillin-resistant *Staphylococcus aureus* (MRSA) in an elderly patient: management and control of MRSA. *J Hosp Infect*. 1992;22 Suppl A:43-50.
4. Dummer S, Kusne S. Liver transplantation and related infections. *Semin Respir Infect*. 1993;8:191-8.
5. Singh N, Paterson DL, Chang FY, Gayowski T, Squier C, Wagener MM, et al. Methicillin-resistant *Staphylococcus aureus*: the other emerging resistant gram-positive coccus among liver transplant recipients. *Clin Infect Dis*. 2000;30:322-7.
6. Bert F, Galdbart JO, Zarrouk V, Le Mee J, Durand F, Mentre F, et al. Association between nasal carriage of *Staphylococcus aureus* and infection in liver transplant recipients. *Clin Infect Dis*. 2000;31:1295-9.

7. Paterson DL, Rihs JD, Squier C, Gayowski T, Sagnimeni A, Singh N. Lack of efficacy of mupirocin in the prevention of infections with *Staphylococcus aureus* in liver transplant recipients and candidates. *Transplantation*. 2003;75:194-8.
8. Vasquez JE, Walker ES, Franzus BW, Overbay BK, Reagan DR, Sarubbi FA. The epidemiology of mupirocin resistance among methicillin-resistant *Staphylococcus aureus* at a Veterans' Affairs hospital. *Infect Control Hosp Epidemiol*. 2000;21:459-64.
9. Saner FH, Heuer M, Rath PM, Gensicke J, Radtke A, Druhe N, et al. Successful salvage therapy with tigecycline after linezolid failure in a liver transplant recipient with MRSA pneumonia. *Liver Transpl*. 2006;12:1689-92.
10. Lamer C, de Beco V, Soler P, Calvat S, Fagon JY, Dombret MC, et al. Analysis of vancomycin entry into pulmonary lining fluid by bronchoalveolar lavage in critically ill patients. *Antimicrob Agents Chemother*. 1993;37:281-6.
11. Vernadakis S, Saner FH, Rath PM, Kaiser GM, Mathe Z, Treckmann J, Paul A. Successful salvage therapy with daptomycin after linezolid and vancomycin failure in a liver transplant recipient with methicillin-resistant *Staphylococcus aureus* endocarditis. *Transpl Infect Dis*. 2009 May 21. [Epub ahead of print]
12. Gorchynski J, Rose JK. Complications of MRSA Treatment: Linezolid-induced myelosuppression presenting with pancytopenia. *West J Emerg Med*. 2008;9:177-8.

13. Hashimoto M, Sugawara Y, Tamura S, Kaneko J, Matsui Y, Moriya K, et al.  
  
Methicillin-resistant *Staphylococcus aureus* infection after living-donor liver transplantation in adults. *Transpl Infect Dis.* 2008;10:110-6.
  
14. Hashimoto M, Sugawara Y, Tamura S, Kaneko J, Matsui Y, Togashi J, et al. Acquisition of methicillin-resistant *Staphylococcus aureus* after living donor liver transplantation: a retrospective cohort study. *BMC Infect Dis.* 2008;8:155.
  
15. Obed A, Schnitzbauer AA, Bein T, Lehn N, Linde HJ, Schlitt HJ. Fatal pneumonia caused by Panton-Valentine Leucocidine-positive methicillin-resistant *Staphylococcus aureus* (PVL-MRSA) transmitted from a healthy donor in living-donor liver transplantation. *Transplantation.* 2006;81:121-4.

Table 1  
Characteristics of MRSA infection

Case No	Gender/Age	Diagnosis	MELD	Isolation of MRSA before Tx.	Isolation of MRSA after Tx	Definition	Treatment	Outcome
3	M/5	BA	NA		Nasal swab	Carrier	None	Alive
17	M/45	PBC	17		Bile	Carrier	None	Alive
20	M/58	C-LC	23		Respiratory secretion	Carrier	None	Alive
21	M/57	C-LC/HCC	40		Blood, Pleural fluid, Ascites	Bacteremia, Pneumonia, Peritonitis	VCM	Died
28	F/0	BA	NA	Respiratory secretion	Ascites	Peritonitis	None	Died
32	M/65	B-LC	36	Nasal swab, Respiratory secretion	Blood, Ascites, Wound	Bacteremia, Peritonitis, Wound infection	TEIC	Died
39	F/60	C-LC/HCC	11	Nasal swab, Stool	Nasal swab, Blood, Ascites, Bile, Pleural fluid, Stool	Bacteremia, Peritonitis, Cholangitis, Pneumonia	Linezolid	Alive
44	M/59	B-LC/HCC	19		Blood, Ascites	Bacteremia, Peritonitis	TEIC	Alive
45	M/53	B-LC	24	Stool		Carrier	None	Alive
47	F/11	BA	NA		Wound	Wound infection	None	Alive
51	F/55	C-LC/HCC	8	Nasal swab		Carrier	None	Alive
52	M/57	C-LC/HCC	22		Nasal swab, Blood, Ascites, Respiratory secretion	Bacteremia, Peritonitis, Pneumonia	TEIC <sup>1</sup>	Died
55	F/62	C-LC	14	Nasal swab		Carrier	None	Alive
56	M/52	FHF	23		Ascites, Wound	Peritonitis, Wound infection	Linezolid	Alive
60	M/68	B-LC/HCC	25	Nasal swab		Carrier	None	Alive
61	M/37	Cryptogenic-LC	16	Nasal swab		Carrier	None	Alive
68	M/58	B-LC/HCC	13		Respiratory secretion	Carrier	None	Alive
69	M/63	B-LC/HCC	9		Blood	Bacteremia	Linezolid	Alive

M, male; F, female; BA, biliary atresia; PBC, primary biliary cirrhosis; C-LC, hepatitis C virus-related liver cirrhosis; HCC, hepatocellular carcinoma; B-LC, hepatitis B virus-related liver cirrhosis; FHF, fulminant hepatic failure; NA, not applicable; VCM, vancomycin; TEIC, teicoplanin

<sup>1</sup>Linezolid was discontinued because of severe thrombocytopenia due to hemophagocytic syndrome