

Staphylococcus aureus bacteremias following liver transplantation: a clinical analysis of 20 cases

Jiandang Zhou^{1,2}Hui Huang³Shan Liu⁴Ping Yu²Qiquan Wan⁵

¹Department of Clinical Laboratory, the Third Xiangya Hospital of Central South University, ²Department of Immunology, Xiangya School of Medicine, Central South University, ³Nursing Department, the Third Xiangya Hospital of Central South University, Changsha, Hunan, People's Republic of China; ⁴Adelphi University College of Nursing and Public Health, New York, NY, USA; ⁵Department of Transplant Surgery, the Third Xiangya Hospital of Central South University, Changsha, Hunan, People's Republic of China

Background: To describe the incidence, clinical characteristics, and outcomes of *Staphylococcus aureus* bacteremia after liver transplantation and investigate the drug resistance of *S. aureus* to frequently used antibiotics to provide evidence for clinical prevention and therapy.

Materials and methods: In a double-center retrospective study, blood cultures positive for *S. aureus* were obtained from January 1, 2001 to December 31, 2014. The BACTEC 9120 blood culture system and the Vitek-2 system were used to process blood samples and identify species, respectively. We also collected these patients' data to confirm clinical and laboratory characteristics.

Results: Twenty of 275 (7.3%) liver recipients developed *S. aureus* bacteremia during the study period. The median time to the onset of *S. aureus* bacteremias was 6 days after liver transplantation and all episodes of bacteremias were early onset. The lung was the most common source of primary infection, followed by the intra-abdominal/biliary tract. A total of nine (45%) liver recipients died due to *S. aureus* bacteremias. Of these 20 *S. aureus* cases, 80% were methicillin-resistant. *S. aureus* was highly resistant to erythromycin and penicillin (resistance rate >90%). No *S. aureus* resistant to glycopeptides and oxazolidone antibiotics was observed. There were seven (35%) liver recipients with an inappropriate antibiotic therapy. Between the periods of 2001–2007 and 2008–2014, the distribution of methicillin-resistant *S. aureus* was not significantly different ($P=1.000$). Pneumonia as a predominant primary source, a high body temperature, abnormal blood pressure, and decreased platelets, which occurred in the early period after liver transplantation, as well as high morbidity and mortality, were the main characteristics of *S. aureus* bacteremias.

Conclusion: *S. aureus* led to severe bacteremias in liver recipients, with high morbidity and mortality, and the majority of them comprised methicillin-resistant *S. aureus*.

Keywords: liver transplantation, *Staphylococcus aureus*, bacteremia, drug resistance

Introduction

Staphylococcus aureus bacteremia is an important issue complicating the clinical course of liver recipients and has been associated with significant morbidity and mortality, as shown in previous studies with a reported incidence rate of 15%–66% and a mortality rate of 21%.^{1–3} Our previous study revealed that *S. aureus* was responsible for 26% of all pathogens causing bacteremias among liver transplant recipients.⁴

Some researchers have reported a high incidence of methicillin-resistant *S. aureus* (MRSA) in liver transplant recipients.^{3,5,6} The increasing antibiotic-resistant *S. aureus* has emerged as a pivotal factor that influences the prognosis and survival of liver transplant recipients. Herein, we aimed to describe the incidence, clinical and laboratory characteristics, and outcomes of *S. aureus* bacteremias after liver transplantation and to investigate the drug resistance of *S. aureus* to frequently used antibiotics to provide evidence for clinical prevention and therapy.

Correspondence: Qiquan Wan
Department of Transplant Surgery, the
Third Xiangya Hospital of Central South
University, No 138 Tongzipo Road,
Changsha 410013, Hunan, People's
Republic of China
Tel +86 731 8861 8312
Fax +86 731 8861 8312
Email 13548685542@163.com

Materials and methods

Study population and clinical isolates

This study was conducted both at the Third Xiangya Hospital, an 1,800-bed teaching hospital, affiliated with the Central South University, Changsha, People's Republic of China, with an active transplantation program (annual average of 30 liver transplants and 150 kidney transplants) and Zhongnan Hospital, a 1,200-bed teaching hospital, affiliated with Wuhan University, Wuhan, People's Republic of China, with an active transplantation program (annual average of 40 liver transplants and 100 kidney transplants). Liver recipients with an episode of *S. aureus* bacteremia, between January 1, 2001 and December 31, 2014, were identified from the microbiology laboratory database. Maintenance immunosuppression was based on calcineurin inhibitor (cyclosporine or tacrolimus) and corticosteroids, with or without mycophenolate mofetil. Cyclosporine was administered to three patients, and tacrolimus was prescribed in the remaining 17 patients. Doses of cyclosporine were adjusted to obtain trough plasma levels of 200–300 ng/mL during the first month and 100–150 ng/mL later on. The initial dose of oral tacrolimus was 0.05 mg/kg twice a day and adjusted to achieve a targeted trough level of 8–10 ng/mL for the first 3 months and 5–6 ng/mL thereafter. Mycophenolate mofetil was prescribed in four patients at a dose of 1 g per day, and the dose was adjusted in response to adverse events. All patients received steroids at a dose of 500 mg/day via intravenous on transplant day 0 then tapered to 5 mg per day, leading to steroid-free maintenance after 6 months.

The prophylactic antibiotics used during liver transplantation included second- or third-generation cephalosporins, semisynthetic penicillins/beta-lactamase inhibitors, and carbapenems according to susceptibility patterns of the bacteria isolated before operation. Clinical characteristics including age, sex, body temperature at bacteremia onset, time of bacteremia onset, nosocomial origin, site of primary infection, inappropriate antimicrobial use, the number of MRSA cases, septic shock, and laboratory data were collected for the analysis. The laboratory data were collected in the first 24 hours after the blood culture was drawn, including serum creatinine levels, serum albumin levels, white blood cell count, platelet count, and lymphocyte count. The present study was approved by the two hospitals' ethics committees.

Definitions

Bacteremias were defined according to Centers for Disease Control and Prevention criteria.⁷ An episode of bacteremia was defined by at least one positive blood culture with

S. aureus in the presence of clinical signs of infection. The source of bacteremia was determined if focal signs or symptoms of infection were present, and the same microorganism was found in the blood isolate, as well the infected site.⁸ Appropriate antimicrobial therapy was defined as the use of an in vitro susceptible antibiotic against *S. aureus* within 24 hours of the first positive blood culture.⁹ Nosocomial bacteremia was defined as a positive blood culture obtained from patients who had been hospitalized for 48 hours or longer.¹⁰ We identified a microorganism as the same microorganism when the same biotype and the same antibiotype were identified in both the blood and the primary infected site, without molecular analysis being performed. Fisher's exact test was used to compare the distribution of MRSA between the period of 2001–2007 and 2008–2014, and a two-sided value of $P < 0.05$ was considered significant.

Microbiologic studies

A 10 mL blood sample was injected into each bottle of a set of aerobic and anaerobic blood culture bottles, and they were immediately transported to the clinical microbiology laboratory for bacterial culture and identification. The BACTEC™ 9120 blood culture system (BD, Franklin Lakes, NJ, USA) and the VITEK® 2 system (bioMérieux, Craponne, France) were used to process blood samples and identified species, respectively. The Kirby–Bauer disk diffusion method was used for determining antimicrobial susceptibility and agar dilution for measuring the minimum inhibitory concentration. For amikacin, levofloxacin, trimethoprim-sulfamethoxazole, penicillin, erythromycin, clindamycin, oxacillin, and rifampicin, the Kirby–Bauer disk diffusion method was used. The oxacillin disk was a reference method for the identification of MRSA strains. Resistance of vancomycin, teicoplanin, and linezolid was defined by minimum inhibitory concentration determination. According to Zhang,¹¹ the agar dilution of vancomycin and teicoplanin was applied.

S. aureus 25923, which belonged to American Type Culture Collection strains (Manassas, VA, USA), was used to perform quality control. The results were interpreted according to the National Committee for Clinical Laboratory Standards manual,¹² which was suitable for 2001–2003 and the Clinical Laboratory Standards Institute criteria,¹³ which was suitable for 2004–2014. Intermediate susceptibility to the antibiotics was classified as resistance.

Antibiotics for bacteria

Amikacin, levofloxacin, trimethoprim-sulfamethoxazole, penicillin, erythromycin, clindamycin, oxacillin, rifampicin,

vancomycin, teicoplanin, and linezolid were products of Oxoid Ltd (Hampshire, UK). The powder of vancomycin and teicoplanin was also obtained from Oxoid Ltd (Hampshire, UK).

Results

Clinical manifestation

Twenty of 275 (7.3%) liver recipients developed *S. aureus* bacteremias from January 1, 2001 to December 31, 2014, involving 19 (95%) male and one (5%) female patients aged 15–67 years (the average age was 42.7 ± 14.5 years). A total of 19 (95%) patients had central vein catheters at the onset of *S. aureus* bacteremias. Sixteen patients experienced extensive exposure to broad-spectrum antibiotics in the pretransplant phase. The median time of hospitalization prior to transplantation was 25 days (range: 2–121 days). We elaborated upon the clinical manifestation of liver recipients with *S. aureus* bacteremias as follows. First, there was fever and abnormal blood pressure. The majority of recipients had a fever and there were 12 (60%) episodes of bacteremias accompanied by a body temperature of 38°C or greater. A total of nine (45%) liver recipients developed septic shock at the onset of *S. aureus* bacteremias. Second, 20 (100%) episodes of *S. aureus* bacteremias were nosocomial infection. Third, the onset occurred in the early period after liver transplantation. The median time to the onset of *S. aureus* bacteremias after liver transplantation was 6 days (interquartile range: 4–9 days) and all bacteremias were early onset (within 1 month of transplantation). Fourth, 17 (85%) episodes of bacteremias were secondary to other infections. The most common site of primary infection was the lung (55%; number [n]=11), followed by the intra-abdominal/biliary tract (30%; n=6) and unknown sources (15%; n=3). Fifth, there was a high rate of inappropriate antibiotic therapy. Among these 20 liver recipients, two, three, and eight received levofloxacin, linezolid, and glycopeptide antibiotics, respectively, which had in vitro activity against *S. aureus* at the onset or within 1 day of *S. aureus* bacteremias. Ceftazidime, cefepime, and meropenem, all of which did not have in vitro activity against *S. aureus*, were prescribed in two patients each at the onset or within 1 day of *S. aureus* bacteremias, and piperacillin–tazobactam was prescribed in one patient with inappropriate antimicrobial use. Finally, there was high mortality. A total of nine (45%) liver recipients died within 1 month after they were diagnosed with *S. aureus* bacteremias. Among these 20 patients with *S. aureus* bacteremias, 13 patients experienced polymicrobial bacteremias and seven patients who expired belonged to this group. The clinical and

demographic characteristics of 20 liver transplant patients with *S. aureus* bacteremias are outlined in Table 1.

Laboratory data

White blood cell count increased obviously. The amount of white blood cells in 40% of patients (8/20) with *S. aureus* bacteremias was more than $15 \times 10^9/L$, and the highest could reach $32.5 \times 10^9/L$. Platelets dropped markedly. The amount of platelets in 50% of patients with bacteremia was less than $50 \times 10^9/L$, and it could decrease to $3 \times 10^9/L$. Lymphocyte count decreased obviously. The amount of lymphocyte count in six (30%) patients was less than $300/mm^3$, and the lowest could reach $0.05 \times 10^9/L$. Procalcitonin elevated highly. The highest serum level of procalcitonin was more than 10 ng/mL. The laboratory data of these 20 liver recipients with *S. aureus* bacteremias are also illustrated in Table 1.

Drug resistance to *S. aureus*

Of these 20 *S. aureus* cases, MRSA (80%; n=16) was the predominant bacterium. *S. aureus* was highly resistant to erythromycin and penicillin (resistance rate >90%).

Table 1 Demographic, laboratory, and clinical characteristics of 20 liver recipients with *Staphylococcus aureus* bacteremias

| Characteristics | Value |
|---|-----------------|
| Age, mean years \pm standard deviation | 42.7 \pm 14.5 |
| Sex, number of males/number of females | 19/1 |
| Temperature of 38°C or greater | 12/20 |
| Nosocomial origin | 20/20 |
| Inappropriate antimicrobial use | 7/20 |
| Septic shock | 9/20 |
| Site of primary infection, number of cases (%) | |
| Lung | 11 (55) |
| Intra-abdominal/biliary | 6 (30) |
| Unknown | 3 (15) |
| Time of bacteremia onset (post-transplant), number of cases (%) | |
| \leq 2 weeks | 16 (80) |
| >2 weeks | 4 (20) |
| MRSA, number of cases (%) | |
| Yes | 16 (80) |
| No | 4 (20) |
| Type of organisms, number of cases (%) | |
| Monomicrobial | 7 (35) |
| Polymicrobial | 13 (65) |
| Laboratory variables, number of cases (%) | |
| Platelet count $< 50,000/mm^3$ | 10 (50) |
| Lymphocyte count $< 300/mm^3$ | 6 (30) |
| Albumin level < 30 mg/dL | 3 (15) |
| WBC count $> 15,000/mm^3$ | 8 (40) |
| Creatinine level > 1.5 mg/dL | 5 (25) |
| Related mortality | 9 (45) |

Abbreviations: MRSA, methicillin-resistant *Staphylococcus aureus*; WBC, white blood cell.

Table 2 Resistance of *S. aureus* to eleven antibiotics

| Antibiotics | ERY | CC | LVF | SXT | AN | PEN | RA | OX | VAN | TEC | LZD |
|-----------------------|---------|---------|---------|---------|--------|---------|--------|---------|-------|-------|-------|
| <i>S. aureus</i> (20) | 18 (90) | 14 (70) | 10 (50) | 15 (75) | 6 (30) | 19 (95) | 2 (10) | 16 (80) | 0 (0) | 0 (0) | 0 (0) |

Notes: Data presented as number of cases (%).

Abbreviations: *S. aureus*, *Staphylococcus aureus*; ERY, erythromycin; CC, clindamycin; LVF, levofloxacin; SXT, trimethoprim-sulfamethoxazole; AN, amikacin; PEN, penicillin; RA, rifampicin; OX, oxacillin; VAN, vancomycin; TEC, teicoplanin; LZD, linezolid.

The D-test-positive rate of inducible resistance to clindamycin was 50% in four cases of *S. aureus*, which were erythromycin resistant and clindamycin sensitive by individual disk diffusion test. None of the *S. aureus* strains was resistant to glycopeptides and oxazolidinone antibiotics. All but two *S. aureus* strains were susceptible to rifampicin. The drug resistance of *S. aureus* to the eleven antibiotics investigated could be seen in Table 2. No significant differences in the frequency of MRSA were observed between 2001–2007 and 2008–2014 (80% [12/15] versus 80% [4/5], respectively; $P=1.000$).

Discussion

S. aureus bacteremias, especially MRSA bacteremia, are still a cause of morbidity and mortality in liver recipients so far. In the present study, all episodes of *S. aureus* bacteremias were early onset (within 1 month after liver transplantation), which was consistent with the findings in a previous study,¹⁴ which reported that the majority of the Gram-positive bacteremias occurred within 30 days after liver transplantation.

In the present study, the drug susceptibility test showed that the resistance rate of *S. aureus* to the eleven antibiotics investigated was relatively low, although MRSA was the predominant bacterium. *S. aureus* was highly susceptible to glycopeptides and oxazolidinone antibiotics in our present study.

A high incidence (80%) of MRSA was noted in this study when compared with methicillin-susceptible *S. aureus*, in line with other studies which confirmed that, among bacteremic liver transplantation, more than 90% of *S. aureus* strains were MRSA.^{15,16} This is most likely explained by the presence of known risk factors related to MRSA, such as intravenous catheters, hospitalization, and antibiotic exposure, which are also present in our study group.^{17,18} MRSA represents a serious problem among bacteremic liver recipients.^{14,19,20}

We found that *S. aureus* strains causing bacteremias after liver transplantation had low drug resistance ($\leq 50\%$) to the majority (6/11) of antibiotics investigated. There were no episodes of glycopeptide- or oxazolidinone-resistant *S. aureus*. All but two episodes were susceptible to rifampicin. The possible explanations to this finding include evolving trends of Gram-positive bacteria toward multiple-antibiotic-resistant

bacteria are slowly, when compared with Gram-negative bacteria.²¹ Physicians can choose glycopeptides alone or oxazolidinone antibiotics alone for empirical therapy in patients that are highly suspected to have *S. aureus* bacteremia when awaiting confirmation of the bacterial identity and susceptibility pattern. It is notable that combination therapy for MRSA bacteremia appears to be no more effective than vancomycin monotherapy. Adding rifampicin to vancomycin offers no meaningful benefit and may confer harm for treating MRSA bacteremia.²² Furthermore, there is no clinical rationale to refer to rifampicin after liver transplantation, as it is known that it may eliminate calcineurin inhibitors.

Conclusion

In conclusion, *S. aureus* led to severe bacteremias in liver recipients, with high morbidity and mortality. Although the majority of the strains comprised MRSA, *S. aureus* had relatively low drug resistance to the majority of antibiotics investigated.

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Disclosure

The authors report no conflicts of interest in this work.

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