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REVIEW

Methicillin-resistant *Staphylococcus aureus* bacteremia among liver transplant recipients: epidemiology and associated risk factors for morbidity and mortality

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Abstract: Bacteremia due to *Staphylococcus aureus*, especially methicillin-resistant *S. aureus* (MRSA), complicates the clinical course of liver transplantation and is associated with high morbidity and mortality. Intravascular catheters had been reported to be the most frequent source of MRSA bacteremia. Among bacteremic liver recipients, 26.3%–100% of *S. aureus* were MRSA. Previous studies identified pre-transplant and post-transplant acquired *S. aureus* carriage, greater severity of liver disease, hepatocellular carcinoma and infection with immunomodulatory viruses as predictors of *S. aureus* bacteremia in liver recipients. MRSA bacteremia accompanied by pneumonia and abdominal infections was related to mortality. Vancomycin, as well as daptomycin, is a first-line antibiotic for MRSA bacteremia. The purpose of this review is to better understand the characteristics of MRSA bacteremia by summarizing the epidemiology and antimicrobial resistance of *S. aureus*, the primary source, and related risk factors for morbidity and mortality of MRSA bacteremia. We have also explored the diagnostic, therapeutic and preventive measures for MRSA bacteremia to improve the outcomes of liver recipients.

Keywords: methicillin-resistant *Staphylococcus aureus*, bacteremia, risk factors, morbidity, mortality, liver transplantation

Introduction

Staphylococcus aureus harbors several virulence factors that increase its ability to adhere, colonize and invade tissues and sequentially increase the pathogenicity.[1,2] Liver transplant recipients have a greater propensity to *S. aureus* colonization/infections than other solid organ transplant patients because of the complexity of the surgical procedure and the frequent use of intravascular catheters.[3] *S. aureus* bacteremias represented 23.5% of all *S. aureus* infections and complicated the clinical course of liver transplantation (LT).[4,5] Methicillin-resistant *S. aureus* (MRSA) bacteremias represented 42%–69% of all MRSA infections after LT and increased duration of hospitalization, costs, morbidity and mortality.[3,4,6–8]

The past 2 decades have seen continuous increase of LT practices in People's Republic of China. Since January 1, 2015, organ donation from cardiac death donors has become the only legitimate source of organ transplantations in People's Republic of China, and there were 10,965 patients undergoing LT from January 1, 2015 to December 31, 2017. In our transplant center from January 1, 1999, to December 31, 2017, 18 (6.5%) of 279 consecutive liver recipients underwent 18 episodes of *S. aureus*

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bacteremias, while 13 of 18 *S. aureus* were methicillin resistant. The incidence of *S. aureus* bacteremia was 28.3% (15/53) before March 18, 2005, and thereafter, the rate decreased to 1.3% (3/226) after various strategies being performed. Having witnessed the development of LT and postoperative MRSA, we would like to summarize the epidemiology and antimicrobial resistance of *S. aureus*, the primary source, and related risk factors for morbidity and mortality to better understand the characteristics of MRSA bacteremia in liver recipients. We have also attempted to explore the diagnostic, therapeutic and preventive measures for MRSA bacteremia to improve the outcomes of liver recipients.

Methods

Using the search terms "bloodstream infection", "bacteremia", "septicemia", "infection", "epidemiology", "microbiology", "*Staphylococcus aureus*", "MRSA", "risk factor", "predictor", "mortality", "liver transplantation" and "solid organ transplantation", we searched 4 electronic databases (PubMed, EMBASE, Cochrane library and World Health Organization database-Index Medicus for South East Asia) from the timeframe of 1988 through 2017 for relevant literature published. All searches were augmented by reviewing bibliographic references to confirm potentially relevant studies. During the literature search, no restriction was applied. However, the analysis of drug resistance and mortality rate did not apply to the studies where the sample sizes of patients with S. *aureus*/MRSA bacteremia were <5.

Relevant morbidity and mortality rates of *S. aureus*/MRSA bacteremia

S. aureus bacteremia has been reported to have an incidence range of 1%–23.5% and has been responsible for 24% of all bacteremias in patients with liver cirrhosis.[9–13] The incidence of *S. aureus* bacteremia increased from 1.2% before LT to 9.6% after LT, which means *S. aureus* bacteremia is easier to occur in liver recipients than in liver cirrhotic patients.[9]

The morbidity of *S. aureus* bacteremia varied from 0.6% to 29% among liver recipients,[5,9,14–36] and for MRSA bacteremia, it was 0.4%–27.4%.[5,6,9,14,15,17,19,22,23,26,35,37–40] According to a study conducted at the Pittsburgh VA Medical Center, of 233 consecutive liver recipients, 3.8% underwent MRSA bacteremia during 1989–1993, 24.5% during 1993–1995, 30% during 1996–1998 and 11.3% during 1998–2003.[37]

The mortality rate in liver recipients with *S. aureus* bacteremia and MRSA bacteremia has been identified to be 20%–46%[34,39,41] and 15%–60%,[4,27,37,38] respectively. For those patients with MRSA bacteremia accompanied by pneumonia and abdominal infections, death rate was up to 86%.[4] The mortality rates of *S. aureus*/MRSA bacteremia among liver recipients are illustrated in Table 1.

Previous studies revealed that *S. aureus* was responsible for 2.3%–46.3%[5,9,14,15,18–20,27–32,35–37,42–49] of all pathogens causing bacteremia among liver recipients and MRSA was 1.6%–41.4%.[5,9,14,15,18,19,27,35,36,44,45,49,50] In a case report, Doucette et al[51] claimed that *S. aureus* accounted for half of four cases wherein donor-derived bacteremias were transmitted to liver recipients, despite appropriate antibiotic prophylaxis. The incidence rates of *S. aureus*/MRSA in all pathogens causing bacteremia among liver recipients are shown in Table 2.

Principle sources of *S. aureus*/MRSA bacteremia

Intravascular catheters were confirmed as the most frequent source of *S. aureus* bacteremia in several studies.[17,20,52,53] A patient's colonized skin is also a usual source of *S. aureus* bacteremia after LT.[54] Other studies reported that the principle sources of *S. aureus* bacteremia in liver recipients included primary infection (including either intravascular catheters or unknown source) (21.4%–57.7%), abdominal or biliary tract (7%–33.6%), lung (6%–55%), urogenital tract

Table 1 Mortality rates of *Staphylococcus aureus*/MRSA bacteremia among liver recipients

Study/country	Study period	Mortality rates due to *S. aureus*/MRSA bacteremia
Singh et al[4]/USA	1990–1998	15% of liver recipients with MRSA bacteremia at 14 days after onset of bacteremia; 23% of liver recipients with MRSA bacteremia at 30 days after onset of bacteremia
Singh et al[37]/USA	1989–2003	27.8% of liver recipients with MRSA bacteremia at 30 days after onset of bacteremia
Singh et al[41]/USA	1995–2005	46.2% of liver recipients with *S. aureus* bacteremia at 1 year after onset of bacteremia
Bedini et al[27]/Italy	2000–2005	60% of liver recipients with MRSA bacteremia at 30 days after onset of bacteremia
Hashimoto et al[5]/Japan	1996–2004	20% of liver recipients with *S. aureus* bacteremia during the study period
Takatsuki et al[38]/Japan	1997–2007	50% of liver recipients with MRSA bacteremia
Zhou et al[34]/People's Republic of China	2001–2014	45% of liver recipients with *S. aureus* bacteremia

Abbreviation: MRSA, methicillin-resistant *S. aureus*.

Table 2 Incidence rates of *Staphylococcus aureus*/MRSA in all pathogens causing bacteremia among liver recipients

Study/country	Study period	Type of organisms	Incidence rates (proportion of *S. aureus*/MRSA in all pathogens causing bacteremia in liver recipients), %
Colonna et al[32]/USA	1984–1985	GNB+GPB	*S. aureus*: 9.1
George et al[29]/USA	1985–1987	GNB+GPB	*S. aureus*: 3.2
McClean et al[30]/Canada	1990–1992	GNB+GPB+fungi	*S. aureus*: 19.0
Wade et al[20]/England	1990–1993	GNB+GPB	*S. aureus*: 13.4
Falagas et al[31]/USA	Unknown	GNB+GPB	*S. aureus*: 14.5
Singh et al[4]/USA	1995–1998	GNB+GPB	*S. aureus*: 46.3; MRSA: 41.4
Torre-Cisneros et al[15]/Spain	1994–1999	GNB+GPB	*S. aureus*: 11.8; MRSA: 4.2
Singh et al[37]/USA	1989–2003	GNB+GPB	*S. aureus*: 41
Munoz-Price et al[28]/USA	1994–1999	GNB+GPB	*S. aureus*: 10.2
Bedini et al[27]/Italy	2000–2005	GPB	*S. aureus*: 11.9; MRSA: 11.9
Moreno et al[21]/Spain	2003–2005	GNB+GPB+fungi	*S. aureus*: 7.2
Kawecki et al[9]/Poland	2001–2004	GNB+GPB+fungi	*S. aureus*: 2.9; MRSA: 2.9
Hashimoto et al[5]/Japan	1996–2004	GNB+GPB+fungi	*S. aureus*: 19.2; MRSA: 15.4
Kim et al[19]/Korea	2005–2007	GNB+GPB+fungi	*S. aureus*: 7.5; MRSA: 7.5
Bert et al[45]/France	1997–2007	GNB+GPB+fungi	*S. aureus*: 19.8; MRSA: 9.9
Iida et al[44]/Japan	2006–2009	GNB+GPB	*S. aureus*: 16.2; MRSA: 7.7
Shi et al[35]/People's Republic of China	2003–2006	GNB+GPB	*S. aureus*: 4; MRSA: 4
Lee et al[18]/USA	1997–2006	GNB+GPB	*S. aureus*: 15.1; MRSA: 5.8
Karapanagiotou et al[47]/Greece	2008–2010	GNB+GPB+fungi	*S. aureus:* 21.1
Sganga et al[36]/Italy	2008–2011	GNB+GPB	*S. aureus*: 2.3; MRSA: 2.3
Wan et al[43]/People's Republic of China	2002–2012	GNB+GPB+fungi	*S. aureus:* 20.8
Yeşilkaya et al[48]/Turkey	2004–2012	GNB+GPB+fungi	*S. aureus:* 7.1
Kim et al[46]/Korea	2005–2011	GNB+GPB+fungi	*S. aureus*: 10.3
Bodro et al[50]/Spain	2007–2012	GNB+GPB+fungi	MRSA: 3.1
Doucette et al[51]/Canada	2009–2012	GNB+GPB	*S. aureus*: 50 of all donor-derived bacteremias
Ye et al[42]/People's Republic of China	2003–2014	GNB+GPB+fungi	*S. aureus*: 15.1
Bodro et al[49]/Spain	2007–2013	GNB+GPB+fungi	*S. aureus*: 6.0; MRSA: 1.6
de Oliveira et al[1]/Brazil	Unknown	GPB	MRSA: 7.8
Berenger et al[131]/Canada	2003–2012	GNB+GPB+fungi	*S. aureus*: 10.7; MRSA: 4

Abbreviations: MRSA, methicillin-resistant *S. aureus*; GNB, Gram-negative bacilli; GPB, Gram-positive bacterium.

(1.3%–17%), gastrointestinal tract (52.8%), endocarditis (3.8%), surgical wounds (1.3%–33%) and donor transmission (1.2%).[4,14,15,21,25,34,35,41,45,46,51,55–57]

Risk factors for MRSA colonization/infection/bacteremia and for *S. aureus*/MRSA infection/bacteremia-related mortality

Liver recipients are at a high risk of MRSA colonization because of multiple hospital admissions, prolonged stay in hospital and recent broad-spectrum antimicrobial use.[58] A number of risk factors for MRSA colonization have been recognized by previous studies, including the severity of patients, prior use of antimicrobial, preoperative use of fluoroquinolones, use of invasive medical devices, postoperative bleeding at the surgical site and prolonged stay in intensive care unit.[24,59,60]

MRSA colonization is generally seen as a factor strongly related to infection in post-LT.[61–64] Other risk factors for MRSA infection after LT are listed as follows: alcoholic cirrhosis, decreased prothrombin ratio, presence of central lines, being intubated, immunosuppressed status, multiple admissions to the intensive care unit, retransplantation and prolonged hospitalization.[4,23,24,40,58,61] Additionally, risk factors such as age 60 years or greater, preoperative use of antimicrobials, operation time (>16 hours) and perioperative dialysis and/or apheresis are also known to increase the risk of MRSA infection. However, postoperative use of fluoroquinolone was negatively associated with acquisition of MRSA.[22,39,58]

As mentioned in limited number of studies, pre-transplant and post-transplant acquired *S. aureus* carriage, greater severity of liver disease, hepatocellular carcinoma and infection with immunomodulatory viruses such as cytomegalovirus (CMV) increase the risk of *S. aureus* bacteremia in liver recipients.[23,41,45,55]

CMV does stimulate certain activities of the host immune system by upregulation of specific T- and B-cell alloimmune responses through innate immune mechanisms or stimulation of alloimmunity via cross-reactive viral antigens, but in aggregate the effects of the virus are immune suppressive.[65] Potential mechanisms of CMV-induced immunosuppression included suppression of CD4 T-lymphocyte activation and proliferation, as well as inhibition of the expression of surface-soluble CD14 in alveolar macrophages.[66,67] Table 3 provides an overview of risk factors for *S. aureus*/MRSA infection/bacteremia among liver recipients.

The isolation of *S. aureus*, per se, was a risk factor for mortality in solid organ transplant recipients with bacteremia.[15] In a single-center retrospective study of 2,959 solid organ transplant patients, Malinis et al[16] suggested an association between pulmonary focus and *S. aureus* bacteremia-related mortality. On reviewing the literature it was found that data are scarce focusing on liver recipients with *S. aureus* bacteremia. Only one previous study conducted by Singh et al[4] documented that MRSA bacteremia accompanied by pneumonia and abdominal infections was associated with mortality in liver recipients. Risk factors for associated mortality in liver recipients with *S. aureus/*MRSA infection/bacteremia are displayed in Table 4.

Antimicrobial resistance of *S. aureus*

Previous studies confirmed that, among bacteremic LT, 26.3%–100% of *S. aureus* were methicillin resistant.[4,14,18,26,27,34,35,39,44–46,49] The resistance rates of MRSA to vancomycin, amikacin and ciprofloxacin were 0%, 50% and 53.5%, respectively.[45] Ye et al[42] analyzed the data from 19 episodes and concluded that 52.6% of *S. aureus* were resistant to levofloxacin, 26.3% to amikacin and 5.3% to vancomycin. One study conducted by Zhou et al[34] reported that *S. aureus* was highly resistant to erythromycin and penicillin (resistance rates >90%). Table 5 illustrates the drug resistance rates of *S. aureus*/MRSA causing bacteremia among liver recipients.

Reasons for the high rates and wide ranges of both *S. aureus*/MRSA bacteremia and its related mortality

The great number of *S. aureus*/MRSA bacteremia in LT population is probably explained by a global trend of epidemiology of microbiology, antibiotic prophylaxis such as quinolones for spontaneous bacterial peritonitis, prolonged use of central venous catheters, high immunosuppression required due to the immunity of the allograft and, most importantly, the poor general condition before LT.[10,62,68] The high mortality rate in LT population could be partly explained by virulence of

Table 3 Risk factors for *Staphylococcus aureus*/MRSA bacteremia among liver recipients

Study/country	Microbiology	Risk factors
Singh et al[4]/USA	MRSA infection including bacteremia	Cytomegalovirus seronegativity and primary cytomegalovirus infection
Desai et al[61]/England	MRSA infection including bacteremia	MRSA carriage
Bert et al[24]/France	*S. aureus* infection including bacteremia	MRSA carriage, MSSA carriage, alcoholic cirrhosis and decreased prothrombin ratio
Singh et al[55]/USA	*S. aureus* bacteremia	*S. aureus* carriage after transplantation
Singh et al[41]/USA	*S. aureus* bacteremia	Hepatocellular carcinoma
Hashimoto et al[23]/Japan	MRSA infection including bacteremia	Operation time (>16 hours) and postoperative colonization with MRSA
Hashimoto et al[5]/Japan	MRSA infection including bacteremia	Age (≥60 years); preoperative MRSA colonization, preoperative use of antimicrobials, operation time (>16 hours) and perioperative dialysis and/or apheresis predicted postoperative MRSA acquisition Postoperative use of fluoroquinolones was negatively associated with acquisition of MRSA
Russell et al[40]/USA	*S. aureus* infection including bacteremia	Candidates and recipients with MRSA colonization
Bert et al[45]/France	*S. aureus* bacteremia	Preoperative *S. aureus* nasal carriage
Florescu et al[54]/USA	MRSA infection including bacteremia	Recent surgical procedure prior to infection

Abbreviations: MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-susceptible *S. aureus*.

Table 4 Risk factors of mortality for liver recipients with *Staphylococcus aureus*/MRSA bacteremia

Study/country	Transplantation type	Microbiology	Risk factors for related mortality due to bacteremia
Singh et al[4]/USA	LT	MRSA	Accompanied by pneumonia and abdominal infections
Malinis et al[16]/USA	SOT including LT	*S. aureus*	Pulmonary focus

Abbreviations: MRSA, methicillin-resistant *S. aureus*; LT, liver transplantation; SOT, solid organ transplantation.

Table 5 Drug resistance rates of *Staphylococcus aureus*/MRSA causing bacteremia among liver recipients

Study/country	Study period	Drug resistance rates
Singh et al[4]/USA	1990–1998	MRSA (26) responsible for 100% of all *S. aureus* (26)
Singh et al[4]/USA	1995–1998	MRSA (17) responsible for 90% of all *S. aureus* (19)
Bert et al[33]/France	1997–2002	21.4% (3/14) was heterogeneous glycopeptide-intermediate *S. aureus*
Bedini et al[27]/Italy	2000–2005	MRSA (5) responsible for 100% of all *S. aureus* (5)
Hashimoto et al[5]/Japan	1996–2004	MRSA (4) responsible for 80% of all *S. aureus* (5)
Saner et al[26]/Germany	2003–2006	MRSA (7) responsible for 70% of all *S. aureus* (10)
Bert et al[45]/France	1997–2007	MRSA (28) responsible for 56% of all *S. aureus* (21) 14.3% (8/56) was resistant to gentamicin 50% (28/56) was resistant to amikacin 53.5% (30/56) was resistant to ciprofloxacin 0% was resistant to vancomycin
Iida et al[44]/Japan	2006–2009	MRSA (9) responsible for 47.4% of all *S. aureus* (19)
Shi et al[35]/People's Republic of China	2003–2006	MRSA (13) responsible for 100% of all *S. aureus* (13)
Lee et al[18]/USA	1997–2006	MRSA (8) responsible for 38.1% of all *S. aureus* (21)
Kim et al[46]/Korea	2005–2011	MRSA (13) responsible for 92.9% of all *S. aureus* (14)
Ye et al[42]/People's Republic of China	2003–2014	10.5% (2/19) was resistant to rifampicin 26.3% (5/19) was resistant to amikacin 52.6% (10/19) was resistant to levofloxacin 5.3% (1/19) was resistant to vancomycin 0% was resistant to teicoplanin or linezolid
Bodro et al[49]/Spain	2007–2013	MRSA (5) responsible for 26.3% of all *S. aureus* (19)
Zhou et al[34]/People's Republic of China	2001–2014	MRSA (16) responsible for 26.3% of all *S. aureus* (20) 90% (18/20) was resistant to erythromycin 70% (14/20) was resistant to clindamycin 50% (10/20) was resistant to levofloxacin 75% (15/20) was resistant to trimethoprim-sulfamethoxazole 30% (6/20) was resistant to amikacin 95% (19/20) was resistant to penicillin 10% (2/20) was resistant to rifampicin 80% (16/20) was resistant to oxacillin 0% was resistant to vancomycin or teicoplanin or linezolid

Abbreviation: MRSA, methicillin-resistant *S. aureus*.

S. aureus strains and high frequency of drug resistance.[4,69–71] Furthermore, bacteremia, per se, could also be a marker of other factors related to higher mortality, comprising poor graft function, surgical complications and prolonged intensive care unit stay.[72]

We noticed that there is a wide range of morbidity and mortality of bacteremia between centers, and this phenomenon might result from geographic differences in microbiological environments, along with various diagnostic criteria, severity of the illness, colonization pressure, the frequency of performing active surveillance cultures, immunosuppressive drugs and study designs. As for MRSA bacteremic LT patients, studies differed between the study periods, the follow-up duration, the intrinsic virulence of *S. aureus* strains or between centers performing the different prophylactic and therapeutic antimicrobial strategies, causing the diversity in outcomes.[73,74] The death rate also varied significantly for different sources of bacteremia. Singh et al[4] described that mortality was 67% for bacteremic liver recipients accompanied with pneumonia, 6% for those with abdominal infection and 0% for patients with catheter-related infection or wound and urogenital infections.

Diagnosis of MRSA colonization and infection

In the past, the isolation of pathogens by traditional cultures used to take 96 hours, whereas with new methods using the GeneOhm™ MRSA polymerase chain reaction test and GeneXpert MRSA/SA test, only 27.6 and 21.4 hours are required, respectively.[75] Rapid molecular diagnostics within hours rather than days enable the prompt pre-emptive treatment of *S. aureus* carriers when appropriate.[76,77]

Molecular characterization allows clinicians to know if there is a resistance gene related to antimicrobials, such as mupirocin, or antiseptics such as chlorhexidine in MRSA isolates to propose a future intervention study.[78,79] Thanks to advances in molecular methods, we are now able to evaluate MRSA isolates and to develop strategies to control and prevent colonization and infection (for example, chlorhexidine baths and treatment with nasal mupirocin). The methods include staphylococcal chromosome cassette mec by polymerase chain reaction, multilocus sequence typing, whole-genome sequencing, pulsed-field gel electrophoresis and *Staphylococcus* protein A typing.[69,80,81] Staphylococcal chromosome cassette mec typing and pulsed-field gel electrophoresis are helpful for understanding the molecular epidemiology of MRSA with the latter one showing a greater discriminatory power, whereas *Staphylococcus* protein A typing is useful for both investigation of hospital outbreaks and studies of molecular evolution of MRSA preventive measures for MRSA bacteremia.[1,81,82]

The aforementioned results of high morbidity and mortality among liver recipients highlight the urgency to curtail the incidence of MRSA bacteremia. There are some measures to prevent MRSA bacteremia in liver recipients the same as those in nonimmunosuppressed hospitalized patients, including source control, preservation of kidney function, restriction of the use of invasive devices and equipment, removing all unnecessary catheters at the earliest possible time and minimizing postoperative length of stay in intensive care unit.

MRSA colonization before LT occurred in 5.1%–47.4% of the cases.[23,55] Up to 87.5% of colonized patients developed MRSA infections, which contained bacteremia.[4,24,39,61,78,83–85] Thus, we should keep a close eye on MRSA colonization. Preoperative and postoperative screening for MRSA nasal carriage is crucial, and control measures of eliminating nasal carriage of *S. aureus* should be taken. Furthermore, medical workers should take actions to prevent transmission of MRSA from patient to patient, such as hand washing with hydroalcoholic solutions.[17,24,86,87] Intranasal mupirocin 2% ointment with or without a combination of chlorhexidine gluconate body wash could be used to eradicate both methicillin-susceptible *S. aureus* (MSSA) and MRSA in liver recipients with *S. aureus* carriage, but mupirocin resistance may exist.[88–91]

Catheter-related bacteremia caused by MRSA was preventable with appropriate prevention strategies.[72] Strict adherence to the principles of intravascular catheter management established by CDC sharply reduced its incidence.[92–94] Skin antisepsis with chlorhexidine gluconate or daily skin cleansing with 2% chlorhexidine gluconate can also control this type of bacteremia well.[95] Other studies have reported the efficacy of antibiotic impregnated catheters.[96]

When serious MRSA infections occur, it is suggested to reduce or remove immunosuppressive agents to elevate host reactivity and to prevent the onset of MRSA bacteremia. Corticosteroids can block transcription of cytokine genes and nonspecific inhibition of T lymphocytes and macrophages. Maintenance treatment without prednisone, therefore, can decrease the development of MRSA bacteremia.

The treatment for donors with *S. aureus* colonization and/or infections and a surveillance of liver recipients of organs from donors with *S. aureus* bacteremia were also needed, since *S. aureus* may be transferred in the donated organs and appropriate prophylaxis did not eliminate the risk of transmission.[51,97–99] However, the addition of vancomycin or teicoplanin should be reserved for confirmed MRSA sepsis rather than for decolonization therapy for MRSA carriers, because overuse of these glycopeptide antibiotics could be associated with other potential problems such as superinfection.[100]

Effects of infection control measures on reducing colonization/infection rates and mortality

The prevalence of newly detected MRSA colonization by active surveillance cultures declined from 8.0% to 5.4%.[40] Russell et al[40] found that the rate of health care-associated MRSA infection declined from 4.1 per 1,000 patient days during 2001–2003 to 1.2 per 1,000 patient days during 2004–2006, as a result of active surveillance cultures in all liver service units since 2002. Another previous study at a university hospital also reported that despite the number of MRSA-colonized patients went up during a 3-year period, the proportion of MRSA infection cases decreased from 50% to 6% after the successful use of active surveillance cultures, barrier precautions and decolonization therapy for carriers.[87] The incidence of hospital-acquired MRSA cases significantly decreased after a successful hand hygiene promotion program in a district hospital in the UK.[101] In London, researchers at St George's hospital reported that reductions in MRSA rates were strongly associated with reducing the prescribing of cephalosporins and ciprofloxacin.[102]

One of the largest transplant centers reported an impact of an aggressive infection control strategy in liver recipients, which decreased the rate of *S. aureus* bacteremia from 26% to 4%, including positive screening for nasal and rectal colonization, effective isolation strategies and decolonization with intranasal mupirocin therapy.[55] Various strategies could lead to a decline in the proportion of MRSA bacteremia.[37] According to Hashimoto et al,[5] following infection control policies and standard perioperative prophylaxis aimed at decreasing either the risk of MRSA colonization or infection, only 2.1% (5/242) of liver recipients developed *S. aureus* bacteremia and of these 242 patients, only 1 (0.4%) (1/242) died of bacteremia.

Clinical management of *S. aureus* bacteremia

Choosing empirical antibiotic therapy while awaiting for the results of blood cultures must take into account susceptibility changes of *S. aureus* causing bacteremia and the high frequency of MRSA. Currently, glycopeptides (vancomycin, teicoplanin), linezolid, daptomycin, quinupristin-dalfopristin and, more recently, tigecycline are several treatment options for MRSA infection.[103–105] The standard treatment for MRSA is glycopeptide, which has been widely used, but its current administration to treat MRSA infections has been in great debate because it has a modest effect despite showing in vitro sensitivity.[106] Takatsuki et al[38] had introduced their successful experience of salvage therapy with linezolid after teicoplanin failure for systemic severe MRSA infection, while others[107] demonstrated that none of them was proven to work as good as vancomycin against MRSA.

Vancomycin and daptomycin are the only two FDA-approved agents for the treatment of MRSA bacteremia in the US. Therefore, a recent review still recommended them as the first-line antibiotic therapy for MRSA bacteremia.[108] As far as concentrations of vancomycin were concerned, trough monitoring was recommended to achieve target concentrations of 15–20 μg/mL.[109] It is important to note that vancomycin is less effective for the treatment of MSSA bacteremia and endocarditis when compared with β-lactam agents.[110,111] Patients receiving empirical vancomycin who are found to have catheter-related bacteremia due to MSSA should be switched to cefazolin.[112]

MRSA treated with vancomycin is associated with reduced vancomycin susceptibility and treatment failure.[113] The prevalence of heteroresistant vancomycin-intermediate *S. aureus* is also increasing; antibiotics with in vitro activity against it comprised linezolid, daptomycin, ceftaroline, tigecycline and quinupristin/dalfopristin.[114] However, drug resistance of *S. aureus* to these antibiotics is described.[115] Furthermore, according to the black box warning by FDA, tigecycline, which can increase the risk of death, should be reserved only for situations in which alternative treatments are not suitable.[108]

Telavancin is a novel lipoglycopeptide antibiotic with potential activity against MRSA. It was successful in treating MRSA bacteremia in some case reports.[116–118] Nonetheless, in a study involving 73 patients with bacteremic pneumonia, telavancin was not related to a significant difference in cure rate when compared with vancomycin.[119]

It is notable that combination therapy for MRSA bacteremia appeared no more effective and was even more harmful than vancomycin monotherapy. Adding gentamicin, rifampin or both to vancomycin offers no meaningful benefit and may confer harm for treating MRSA bacteremia.[120,121] The addition of a β-lactam antibiotic to vancomycin or daptomycin for treating MRSA bacteremia has unproven benefit.[122] The mortality on day 30 was 41% among those who received combination therapy compared with 7% (1/14) among those who received vancomycin monotherapy in liver recipients with MRSA bacteremia.[4]

As far as duration of antibiotic use is concerned, when organs are utilized from donors with *S. aureus* bacteremia, recipients should receive a relatively long (2–4 weeks) antibiotic course.[51,123] Based on published guidelines and observational studies, MRSA bacteremia should be administrated intravenous (IV) antibiotic therapy of ≥14 days for uncomplicated bacteremia or ≥28 days for complicated bacteremia.[88,108,112] Transplant patients with *S. aureus* catheter-related bacteremia should receive 4–6 weeks of antimicrobial therapy.[112] For adults with infective endocarditis, IV vancomycin or daptomycin 6 mg/kg/dose IV once daily for 6 weeks is recommended.[109]

Infectious disease consultation is nowadays a great concern. It is likely that the reduction in all-cause mortality in patients with *S. aureus* bacteremia is via improved quality measures of management, including removal of infectious foci, repeat blood culture, echocardiography, appropriate antibiotic therapy and administration of prolonged treatment of complicated infections.[124,125] A large multicenter cohort study suggested that in the non-transplant population with *S. aureus* bacteremia, infectious disease consultation is associated with better adherence to quality measures, reduced in-hospital mortality and earlier discharge.[126] In a single-center retrospective study, Malinis et al[16] reported that infectious disease consultation, as one of contributing factors in reducing mortality, was obtained in 65 of 70 (93%) solid organ transplant patients.

Source control by eliminating and/or debriding primary sites of bacteremia was recommended and additional blood cultures 2–4 days after initial positive cultures were needed, especially when vancomycin treatment failed and MRSA bacteremia was persistent.[109] Within the liver, Kupffer cells are optimally positioned within the vasculature to encounter circulating bacteria, which are critical for their clearance from the bloodstream during steady state and during sepsis.[127–129]

Kupffer cells contribute to neutrophil recruitment and their dysfunction is a risk factor for post-LT bacteremia.[130] It can be explained by Kupffer cell dysfunction if any case of otherwise unexplained persistent MRSA bacteremia occurs in a post-LT patient, despite having been treated with an appropriate anti-microbial agent.

Prolonged therapy and early evaluation for valve replacement surgery are recommended if prosthetic valve infective endocarditis is confirmed.[109] In addition, all liver recipients with *S. aureus* bacteremia should be evaluated with echocardiography, preferably by transesophageal echocardiography unless the patient meets criteria for being at low risk.[16,108]

Future research

Given the considerable morbidity and mortality in liver recipients with MRSA bacteremia, considerably more work will need to be done to explore more intensive prophylactic measures and effective treatments.

Data are lacking with regard to the risk factors for the development of MRSA bacteremia, particularly its associated mortality, after LT. In addition, most of the literature studies provided just a general comment about preventive measures and did not specifically focus on LT with MRSA bacteremia. The safety and outcomes linked with donor-transmitted MRSA infections are controversial.[4,14,51] Chlorhexidine resistance has not been frequently described in MRSA isolates. However, the efficacy of mupirocin prophylaxis on MRSA infection in LT is debatable.[17,38] Evidence from well-controlled studies, therefore, is needed to better confirm the risk factors for MRSA bacteremia and its related mortality, and to better confirm the efficacy of mupirocin in this population thus to form specifically preventive strategies.

Treatment data specific to liver recipients with *S. aureus* bacteremia are also limited. Since inadequate empirical therapy has been identified as a significant risk factor for bacteremia-related mortality, more funding and clinical trials are urgently needed to explore therapeutic options for MRSA. Data were also particularly scarce regarding the proportion of liver recipients with *S. aureus* bacteremia who received infectious disease consultation. A future challenge will be to ensure that this patient population benefit from this expert advice and improved care.

Recommendation for prevention and management of *S. aureus*/MRSA colonization/infection/bacteremia

The incidence of *S. aureus* bacteremia decreased from 28.3% to 1.3% in our liver recipients when appropriate measures were taken. Our recommendations for management of *S. aureus* colonization and infection for now are as follows: 1) removing the risk factors for *S. aureus*/MRSA colonization/infection/bacteremia such as reducing broad-spectrum antibiotics for prophylaxis and using invasive medical devices and central lines, and minimizing postoperative length of stay in the intensive care unit and hospital; 2) improving surgical techniques and reducing intraoperative bleeding and transfusions; 3) using molecular methods to diagnose MRSA colonization and infection; 4) controlling source by eliminating and/or debriding primary sites of bacteremia; 5) preventing transmission of MRSA from patient to patient such as strict hand hygiene measures and effective isolation strategies; 6) treating donors with *S. aureus* colonization and/or infections; 7) preoperative and postoperative screening and decolonization therapy for *S. aureus*/MRSA carriers in liver recipients; and 8) using vancomycin and daptomycin as the first-line antibiotic therapy for MRSA bacteremia.

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Disclosure

The authors report no conflicts of interest in this work.

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