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 al⁵¹ 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 <i>S. aureus</i> /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 <i>S. aureus</i> 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 <i>S. aureus</i> 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 <i>S. aureus</i> 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 <i>S. aureus</i> /MRSA in all pathogens causing bacteremia in liver recipients), %
Colonna et al ³² /USA	1984–1985	GNB+GPB	<i>S. aureus</i> : 9.1
George et al ²⁹ /USA	1985–1987	GNB+GPB	<i>S. aureus</i> : 3.2
McClean et al ³⁰ /Canada	1990–1992	GNB+GPB+fungi	<i>S. aureus</i> : 19.0
Wade et al ²⁰ /England	1990–1993	GNB+GPB	<i>S. aureus</i> : 13.4
Falagas et al ³¹ /USA	Unknown	GNB+GPB	<i>S. aureus</i> : 14.5
Singh et al ⁴ /USA	1995–1998	GNB+GPB	<i>S. aureus</i> : 46.3; MRSA: 41.4
Torre-Cisneros et al ¹⁵ /Spain	1994–1999	GNB+GPB	<i>S. aureus</i> : 11.8; MRSA: 4.2
Singh et al ³⁷ /USA	1989–2003	GNB+GPB	<i>S. aureus</i> : 41
Munoz-Price et al ²⁸ /USA	1994–1999	GNB+GPB	<i>S. aureus</i> : 10.2
Bedini et al ²⁷ /Italy	2000–2005	GPB	<i>S. aureus</i> : 11.9; MRSA: 11.9
Moreno et al ²¹ /Spain	2003–2005	GNB+GPB+fungi	<i>S. aureus</i> : 7.2
Kawecki et al ⁹ /Poland	2001–2004	GNB+GPB+fungi	<i>S. aureus</i> : 2.9; MRSA: 2.9
Hashimoto et al ⁵ /Japan	1996–2004	GNB+GPB+fungi	<i>S. aureus</i> : 19.2; MRSA: 15.4
Kim et al ¹⁹ /Korea	2005–2007	GNB+GPB+fungi	<i>S. aureus</i> : 7.5; MRSA: 7.5
Bert et al ⁴⁵ /France	1997–2007	GNB+GPB+fungi	<i>S. aureus</i> : 19.8; MRSA: 9.9
Iida et al ⁴⁴ /Japan	2006–2009	GNB+GPB	<i>S. aureus</i> : 16.2; MRSA: 7.7
Shi et al ³⁵ /People's Republic of China	2003–2006	GNB+GPB	<i>S. aureus</i> : 4; MRSA: 4
Lee et al ¹⁸ /USA	1997–2006	GNB+GPB	<i>S. aureus</i> : 15.1; MRSA: 5.8
Karapanagiotou et al ⁴⁷ /Greece	2008–2010	GNB+GPB+fungi	<i>S. aureus</i> : 21.1
Sganga et al ³⁶ /Italy	2008–2011	GNB+GPB	<i>S. aureus</i> : 2.3; MRSA: 2.3
Wan et al ⁴³ /People's Republic of China	2002–2012	GNB+GPB+fungi	<i>S. aureus</i> : 20.8
Yeşilkaya et al ⁴⁸ /Turkey	2004–2012	GNB+GPB+fungi	<i>S. aureus</i> : 7.1
Kim et al ⁴⁶ /Korea	2005–2011	GNB+GPB+fungi	<i>S. aureus</i> : 10.3
Bodro et al ⁵⁰ /Spain	2007–2012	GNB+GPB+fungi	MRSA: 3.1
Doucette et al ⁵¹ /Canada	2009–2012	GNB+GPB	<i>S. aureus</i> : 50 of all donor-derived bacteremias
Ye et al ⁴² /People's Republic of China	2003–2014	GNB+GPB+fungi	<i>S. aureus</i> : 15.1
Bodro et al ⁴⁹ /Spain	2007–2013	GNB+GPB+fungi	<i>S. aureus</i> : 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	<i>S. aureus</i> : 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 al¹⁶ 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 al⁴ 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 al⁴² 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 al³⁴ 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	<i>S. aureus</i> infection including bacteremia	MRSA carriage, MSSA carriage, alcoholic cirrhosis and decreased prothrombin ratio
Singh et al ⁵⁵ /USA	<i>S. aureus</i> bacteremia	<i>S. aureus</i> carriage after transplantation
Singh et al ⁴¹ /USA	<i>S. aureus</i> 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	<i>S. aureus</i> infection including bacteremia	Candidates and recipients with MRSA colonization
Bert et al ⁴⁵ /France	<i>S. aureus</i> bacteremia	Preoperative <i>S. aureus</i> 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	<i>S. aureus</i>	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 <i>S. aureus</i> (26)
Singh et al ⁴ /USA	1995–1998	MRSA (17) responsible for 90% of all <i>S. aureus</i> (19)
Bert et al ³³ /France	1997–2002	21.4% (3/14) was heterogeneous glycopeptide-intermediate <i>S. aureus</i>
Bedini et al ²⁷ /Italy	2000–2005	MRSA (5) responsible for 100% of all <i>S. aureus</i> (5)
Hashimoto et al ⁵ /Japan	1996–2004	MRSA (4) responsible for 80% of all <i>S. aureus</i> (5)
Saner et al ²⁶ /Germany	2003–2006	MRSA (7) responsible for 70% of all <i>S. aureus</i> (10)
Bert et al ⁴⁵ /France	1997–2007	MRSA (28) responsible for 56% of all <i>S. aureus</i> (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 <i>S. aureus</i> (19)
Shi et al ³⁵ /People's Republic of China	2003–2006	MRSA (13) responsible for 100% of all <i>S. aureus</i> (13)
Lee et al ¹⁸ /USA	1997–2006	MRSA (8) responsible for 38.1% of all <i>S. aureus</i> (21)
Kim et al ⁴⁶ /Korea	2005–2011	MRSA (13) responsible for 92.9% of all <i>S. aureus</i> (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 <i>S. aureus</i> (19)
Zhou et al ³⁴ /People's Republic of China	2001–2014	MRSA (16) responsible for 26.3% of all <i>S. aureus</i> (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 al⁴ 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 al⁴⁰ 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 al³⁸ had introduced their successful experience of salvage therapy with linezolid after teicoplanin failure for systemic severe MRSA infection, while others¹⁰⁷ 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 administered 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 al¹⁶ 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.

References

1. de Oliveira LM, van der Heijden IM, Golding GR, et al. *Staphylococcus aureus* isolates colonizing and infecting cirrhotic and liver-transplantation patients: comparison of molecular typing and virulence factors. *BMC Microbiol.* 2015;15:264.
2. Kobayashi SD, DeLeo FR. An update on community-associated MRSA virulence. *Curr Opin Pharmacol.* 2009;9(5):545–551.
3. Schneider CR, Buell JF, Gearhart M, et al. Methicillin-resistant *Staphylococcus aureus* infection in liver transplantation: a matched controlled study. *Transplant Proc.* 2005;37(2):1243–1244.
4. Singh N, Paterson DL, Chang FY, et al. Methicillin-resistant *Staphylococcus aureus*: the other emerging resistant gram-positive coc-cus among liver transplant recipients. *Clin Infect Dis.* 2000;30(2): 322–327.
5. Hashimoto M, Sugawara Y, Tamura S, et al. Bloodstream infection after living donor liver transplantation. *Scand J Infect Dis.* 2008;40(6–7):509–516.
6. Singh N, Gayowski T, Rihs JD, Wagener MM, Marino IR. Evolving trends in multiple-antibiotic-resistant bacteria in liver transplant recipients: a longitudinal study of antimicrobial susceptibility patterns. *Liver Transpl.* 2001;7(1):22–26.
7. Dummer S, Kusne S. Liver transplantation and related infections. *Semin Respir Infect.* 1993;8(3):191–198.
8. Cosgrove SE. The relationship between antimicrobial resistance and patient outcomes: mortality, length of hospital stay, and health care costs. *Clin Infect Dis.* 2006;42 Suppl 2:S82–S89.
9. Kaweck D, Chmura A, Pacholczyk M, et al. Etiological agents of bacteremia in the early period after liver transplantation. *Transplant Proc.* 2007;39(9):2816–2821.

10. Campillo B, Dupeyron C, Richardet JP, Mangeney N, Leluan G. Epidemiology of severe hospital-acquired infections in patients with liver cirrhosis: effect of long-term administration of norfloxacin. *Clin Infect Dis*. 1998;26(5):1066–1070.
11. Campillo B, Richardet JP, Kheo T, Dupeyron C. Nosocomial spontaneous bacterial peritonitis and bacteremia in cirrhotic patients: impact of isolate type on prognosis and characteristics of infection. *Clin Infect Dis*. 2002;35(1):1–10.
12. Kuo CH, Changchien CS, Yang CY, Sheen IS, Liaw YF. Bacteremia in patients with cirrhosis of the liver. *Liver*. 1991;11(6):334–339.
13. Munita S JM, Araos BR, Pérez GJ, et al. Bacteriemia en daño hepático crónico [Bacteremia in patients with liver cirrhosis]. *Rev Chilena Infectol*. 2011;28(1):35–39. Spanish [with English abstract].
14. Singh N, Paterson DL, Gayowski T, Wagener MM, Marino IR. Predicting bacteremia and bacteremic mortality in liver transplant recipients. *Liver Transpl*. 2000;6(1):54–61.
15. Torre-Cisneros J, Herrero C, Cañas E, Reguera JM, De La Mata M, Gómez-Bravo MA. High mortality related with *Staphylococcus aureus* bacteremia after liver transplantation. *Eur J Clin Microbiol Infect Dis*. 2002;21(5):385–388.
16. Malinis MF, Mawhorter SD, Jain A, Shrestha NK, Avery RK, van Duin D. *Staphylococcus aureus* bacteremia in solid organ transplant recipients: evidence for improved survival when compared with non-transplant patients. *Transplantation*. 2012;93(10):1045–1050.
17. Bert F, Galdabart JO, Zarrouk V, et al. Association between nasal carriage of *Staphylococcus aureus* and infection in liver transplant recipients. *Clin Infect Dis*. 2000;31(5):1295–1299.
18. Lee SO, Kang SH, Abdel-Massih RC, Brown RA, Razonable RR. Spectrum of early-onset and late-onset bacteremias after liver transplantation: implications for management. *Liver Transpl*. 2011;17(6):733–741.
19. Kim SI, Kim YJ, Jun YH, et al. Epidemiology and risk factors for bacteremia in 144 consecutive living-donor liver transplant recipients. *Yonsei Med J*. 2009;50(1):112–121.
20. Wade JJ, Rolando N, Hallar K, Philpott-Howard J, Casewell MW, Williams R. Bacterial and fungal infections after liver transplantation: an analysis of 284 patients. *Hepatology*. 1995;21(5):1328–1336.
21. Moreno A, Cervera C, Gavalda J, et al. Bloodstream infections among transplant recipients: results of a nationwide surveillance in Spain. *Am J Transplant*. 2007;7(11):2579–2586.
22. Hashimoto M, Sugawara Y, Tamura S, et al. Acquisition of methicillin-resistant *Staphylococcus aureus* after living donor liver transplantation: a retrospective cohort study. *BMC Infect Dis*. 2008;8:155.
23. Hashimoto M, Sugawara Y, Tamura S, et al. Impact of new methicillin-resistant *Staphylococcus aureus* carriage postoperatively after living donor liver transplantation. *Transplant Proc*. 2007;39(10):3271–3275.
24. Bert F, Bellier C, Lassel L, et al. Risk factors for *Staphylococcus aureus* infection in liver transplant recipients. *Liver Transpl*. 2005;11(9):1093–1099.
25. Wagener MM, Yu VL. Bacteremia in transplant recipients: a prospective study of demographics, etiologic agents, risk factors, and outcomes. *Am J Infect Control*. 1992;20(5):239–247.
26. Saner FH, Olde Damink SW, Pavlakovic G, et al. Pulmonary and blood stream infections in adult living donor and cadaveric liver transplant patients. *Transplantation*. 2008;85(11):1564–1568.
27. Bedini A, Codeluppi M, Cocchi S, et al. Gram-positive bloodstream infections in liver transplant recipients: incidence, risk factors, and impact on survival. *Transplant Proc*. 2007;39(6):1947–1949.
28. Munoz-Price LS, Slifkin M, Ruthazer R, et al. The clinical impact of ganciclovir prophylaxis on the occurrence of bacteremia in orthotopic liver transplant recipients. *Clin Infect Dis*. 2004;39(9):1293–1299.
29. George DL, Arnow PM, Fox AS, et al. Bacterial infection as a complication of liver transplantation: epidemiology and risk factors. *Rev Infect Dis*. 1991;13(3):387–396.
30. McClean K, Kneteman N, Taylor G. Comparative risk of bloodstream infection in organ transplant recipients. *Infect Control Hosp Epidemiol*. 1994;15(9):582–584.
31. Falagas ME, Snyderman DR, Griffith J, Werner BG. Exposure to cytomegalovirus from the donated organ is a risk factor for bacteremia in orthotopic liver transplant recipients. Boston Center for Liver Transplantation CMVIG Study Group. *Clin Infect Dis*. 1996;23(3):468–474.
32. Colonna JO 2nd, Winston DJ, Brill JE, et al. Infectious complications in liver transplantation. *Arch Surg*. 1988;123(3):360–364.
33. Bert F, Clarissou J, Durand F, et al. Prevalence, molecular epidemiology, and clinical significance of heterogeneous glycopeptide-intermediate *Staphylococcus aureus* in liver transplant recipients. *J Clin Microbiol*. 2003;41(11):5147–5152.
34. Zhou J, Huang H, Liu S, Yu P, Wan Q. *Staphylococcus aureus* bacteremias following liver transplantation: a clinical analysis of 20 cases. *Ther Clin Risk Manag*. 2015;11:933–937.
35. Shi SH, Kong HS, Jia CK, et al. Coagulase-negative *Staphylococcus* and *Enterococcus* as predominant pathogens in liver transplant recipients with gram-positive coccid bacteremia. *Chin Med J (Engl)*. 2010;123(15):1983–1988.
36. Sganga G, Spanu T, Bianco G, et al. Bacterial bloodstream infections in liver transplantation: etiologic agents and antimicrobial susceptibility profiles. *Transplant Proc*. 2012;44(7):1973–1976.
37. Singh N, Wagener MM, Obman A, Cacciarelli TV, de Vera ME, Gayowski T. Bacteremias in liver transplant recipients: shift toward gram-negative bacteria as predominant pathogens. *Liver Transpl*. 2004;10(7):844–849.
38. Takatsuki M, Eguchi S, Yamanouchi K, et al. The outcomes of methicillin-resistant *Staphylococcus aureus* infection after living donor liver transplantation in a Japanese center. *J Hepatobiliary Pancreat Sci*. 2010;17(6):839–843.
39. Hashimoto M, Sugawara Y, Tamura S, et al. Methicillin-resistant *Staphylococcus aureus* infection after living-donor liver transplantation in adults. *Transpl Infect Dis*. 2008;10(2):110–116.
40. Russell DL, Flood A, Zaroda TE, et al. Outcomes of colonization with MRSA and VRE among liver transplant candidates and recipients. *Am J Transplant*. 2008;8(8):1737–1743.
41. Singh N, Wannstedt C, Keyes L, et al. Hepatic iron content and the risk of *Staphylococcus aureus* bacteremia in liver transplant recipients. *Prog Transplant*. 2007;17(4):332–336.
42. Ye Q, Ma Y, Wan Q, Zhou J. The distribution and resistance of pathogens causing blood stream infections following liver transplantation: a clinical analysis of 69 patients. *Hepatogastroenterology*. 2014;61(136):2311–2314.
43. Wan QQ, Ye QF, Ming YZ, Ma Y, Zhou JD, Qiao BB. The risk factors for mortality in deceased donor liver transplant recipients with bloodstream infections. *Transplant Proc*. 2013;45(1):305–307.
44. Iida T, Kaido T, Yagi S, et al. Posttransplant bacteremia in adult living donor liver transplant recipients. *Liver Transpl*. 2010;16(12):1379–1385.
45. Bert F, Larroque B, Paugam-Burtz C, et al. Microbial epidemiology and outcome of bloodstream infections in liver transplant recipients: an analysis of 259 episodes. *Liver Transpl*. 2010;16(3):393–401.
46. Kim HK, Park YK, Wang HJ, et al. Epidemiology and clinical features of post-transplant bloodstream infection: an analysis of 222 consecutive liver transplant recipients. *Infect Chemother*. 2013;45(3):315–324.
47. Karapanagiotou A, Kydonia C, Papadopoulos S, et al. Infections after orthotopic liver transplantation in the intensive care unit. *Transplant Proc*. 2012;44(9):2748–2750.
48. Yeşilkaya A, Azap OK, Demirkaya MH, Ok MA, Arslan H, Akdur A. Bloodstream infections among solid organ transplant recipients: eight years' experience from a Turkish university hospital. *Balkan Med J*. 2013;30(3):282–286.
49. Bodro M, Sabé N, Tubau F, et al. Extensively drug-resistant *Pseudomonas aeruginosa* bacteremia in solid organ transplant recipients. *Transplantation*. 2015;99(3):616–622.
50. Bodro M, Sabé N, Tubau F, et al. Risk factors and outcomes of bacteremia caused by drug-resistant ESKAPE pathogens in solid-organ transplant recipients. *Transplantation*. 2013;96(9):843–849.
51. Doucette KE, Al-Saif M, Kneteman N, et al. Donor-derived bacteremia in liver transplant recipients despite antibiotic prophylaxis. *Am J Transplant*. 2013;13(4):1080–1083.

52. Singh N, Gayowski T, Wagener MM, Marino IR. Bloodstream infections in liver transplant recipients receiving tacrolimus. *Clin Transplant*. 1997;11(4):275–281.
53. Singh N, Arnow PM, Bonham A, et al. Invasive aspergillosis in liver transplant recipients in the 1990s. *Transplantation*. 1997;64(5):716–720.
54. Florescu DF, McCartney AM, Qiu F, et al. *Staphylococcus aureus* infections after liver transplantation. *Infection*. 2012;40(3):263–269.
55. Singh N, Squier C, Wannstedt C, Keyes L, Wagener MM, Cacciarelli TV. Impact of an aggressive infection control strategy on endemic *Staphylococcus aureus* infection in liver transplant recipients. *Infect Control Hosp Epidemiol*. 2006;27(2):122–126.
56. Al-Hasan MN, Razonable RR, Eckel-Passow JE, Baddour LM. Incidence rate and outcome of Gram-negative bloodstream infection in solid organ transplant recipients. *Am J Transplant*. 2009;9(4):835–843.
57. Linares L, García-Goez JF, Cervera C, et al. Early bacteremia after solid organ transplantation. *Transplant Proc*. 2009;41(6):2262–2264.
58. Kim YJ, Kim SI, Choi JY, Yoon SK, You YK, Kim DG. Clinical significance of methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci colonization in liver transplant recipients. *Korean J Intern Med*. 2015;30(5):694–704.
59. Marshall C, Harrington G, Wolfe R, Fairley CK, Wesselingh S, Spelman D. Acquisition of methicillin-resistant *Staphylococcus aureus* in a large intensive care unit. *Infect Control Hosp Epidemiol*. 2003;24(5):322–326.
60. Asensio A, Guerrero A, Quereda C, Lizán M, Martínez-Ferrer M. Colonization and infection with methicillin-resistant *Staphylococcus aureus*: associated factors and eradication. *Infect Control Hosp Epidemiol*. 1996;17(1):20–28.
61. Desai D, Desai N, Nightingale P, Elliott T, Neuberger J. Carriage of methicillin-resistant *Staphylococcus aureus* is associated with an increased risk of infection after liver transplantation. *Liver Transpl*. 2003;9(7):754–759.
62. Dupeyron C, Campillo SB, Mangeney N, Richardet JP, Leluan G. Carriage of *Staphylococcus aureus* and of gram-negative bacilli resistant to third-generation cephalosporins in cirrhotic patients: a prospective assessment of hospital-acquired infections. *Infect Control Hosp Epidemiol*. 2001;22(7):427–432.
63. Chang FY, Singh N, Gayowski T, Wagener MM, Marino IR. *Staphylococcus aureus* nasal colonization in patients with cirrhosis: prospective assessment of association with infection. *Infect Control Hosp Epidemiol*. 1998;19(5):328–332.
64. Romanelli RM, Clemente WT, Lima SS, et al. MRSA outbreak at a transplantation unit. *Braz J Infect Dis*. 2010;14(1):54–59.
65. Kaminski H, Fishman JA. The cell biology of cytomegalovirus: implications for transplantation. *Am J Transplant*. 2016;16(8):2254–2269.
66. Fornara O, Odeberg J, Khan Z, et al. Human cytomegalovirus particles directly suppress CD4 T-lymphocyte activation and proliferation. *Immunobiology*. 2013;218(8):1034–1040.
67. Hopkins HA, Monick MM, Hunninghake GW. Cytomegalovirus inhibits CD14 expression on human alveolar macrophages. *J Infect Dis*. 1996;174(1):69–74.
68. Patel J, Everly M, Chang D, Kittleson M, Reed E, Kobashigawa J. Reduction of alloantibodies via proteasome inhibition in cardiac transplantation. *J Heart Lung Transplant*. 2011;30(12):1320–1326.
69. Chang FY, Singh N, Gayowski T, Drenning SD, Wagener MM, Marino IR. *Staphylococcus aureus* nasal colonization and association with infections in liver transplant recipients. *Transplantation*. 1998;65(9):1169–1172.
70. Howden BP, Ward PB, Charles PG, et al. Treatment outcomes for serious infections caused by methicillin-resistant *Staphylococcus aureus* with reduced vancomycin susceptibility. *Clin Infect Dis*. 2004;38(4):521–528.
71. Kim SH, Kim KH, Kim HB, et al. Outcome of vancomycin treatment in patients with methicillin-susceptible *Staphylococcus aureus* bacteremia. *Antimicrob Agents Chemother*. 2008;52(1):192–197.
72. Karvellas CJ, McPhail M, Pink F, et al. Bloodstream infection after elective liver transplantation is associated with increased mortality in patients with cirrhosis. *J Crit Care*. 2011;26(5):468–474.
73. Zumla A. Superantigens, T cells, and microbes. *Clin Infect Dis*. 1992;15(2):313–320.
74. Paterson DL, Singh N, Gayowski T, Marino IR. Rapidly fatal bacteremia due to *Staphylococcus aureus* producing both enterotoxins A and B in a liver transplant recipient. *Clin Infect Dis*. 1997;25(6):1481–1482.
75. Wassenberg M, Kluytmans J, Erdkamp S, et al. Costs and benefits of rapid screening of methicillin-resistant *Staphylococcus aureus* carriage in intensive care units: a prospective multicenter study. *Crit Care*. 2012;16(1):R22.
76. Francois P, Pittet D, Bento M, et al. Rapid detection of methicillin-resistant *Staphylococcus aureus* directly from sterile or nonsterile clinical samples by a new molecular assay. *J Clin Microbiol*. 2003;41(1):254–260.
77. Paule SM, Pasquariello AC, Hacek DM, et al. Direct detection of *Staphylococcus aureus* from adult and neonate nasal swab specimens using real-time polymerase chain reaction. *J Mol Diagn*. 2004;6(3):191–196.
78. van der Heijden IM, de Oliveira LM, Brito GC, et al. Virulence and resistance profiles of MRSA isolates in pre- and post-liver transplantation patients using microarray. *J Med Microbiol*. 2016;65(10):1060–1073.
79. Centers for Disease Control and Prevention. Public health dispatch: vancomycin-resistant *Staphylococcus aureus*. *MMWR*. 2002;51:565–567.
80. Altman DR, Sebra R, Hand J, et al. Transmission of methicillin-resistant *Staphylococcus aureus* via deceased donor liver transplantation confirmed by whole genome sequencing. *Am J Transplant*. 2014;14(11):2640–2644.
81. Zhang K, McClure JA, Elsayed S, Louie T, Conly JM. Novel multiplex PCR assay for characterization and concomitant subtyping of staphylococcal cassette chromosome mec types I to V in methicillin-resistant *Staphylococcus aureus*. *J Clin Microbiol*. 2005;43(10):5026–5033.
82. Shopsin B, Gomez M, Montgomery SO, et al. Evaluation of protein A gene polymorphic region DNA sequencing for typing of *Staphylococcus aureus* strains. *J Clin Microbiol*. 1999;37(11):3556–3563.
83. von Eiff C, Becker K, Machka K, Stammer H, Peters G. Nasal carriage as a source of *Staphylococcus aureus* bacteremia. Study Group. *New Engl J Med*. 2001;344(1):11–16.
84. Davis KA, Stewart JJ, Crouch HK, Florez CE, Hospenthal DR. Methicillin-resistant *Staphylococcus aureus* (MRSA) nares colonization at hospital admission and its effect on subsequent MRSA infection. *Clin Infect Dis*. 2004;39(6):776–782.
85. 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(2):194–198.
86. Muto CA, Jernigan JA, Ostrowsky BE, et al; SHEA. SHEA guideline for preventing nosocomial transmission of multidrug-resistant strains of *Staphylococcus aureus* and *enterococcus*. *Infect Control Hosp Epidemiol*. 2003;24(5):362–386.
87. Tomic V, Svetina Sorli P, Trinkaus D, Sorli J, Widmer AF, Trampuz A. Comprehensive strategy to prevent nosocomial spread of methicillin-resistant *Staphylococcus aureus* in a highly endemic setting. *Arch Intern Med*. 2004;164(18):2038–2043.
88. Gould FK, Brindle R, Chadwick PR, et al; MRSA Working Party of the British Society for Antimicrobial Chemotherapy. Guidelines (2008) for the prophylaxis and treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) infections in the United Kingdom. *J Antimicrob Chemother*. 2009;63(5):849–861.
89. Henkel T, Finlay J. Emergence of resistance during mupirocin treatment: is it a problem in clinical practice? *J Chemother*. 1999;11(5):331–337.
90. Kaur DC, Narayan PA. Mupirocin resistance in nasal carriage of *Staphylococcus aureus* among healthcare workers of a tertiary care rural hospital. *Indian J Crit Care Med*. 2014;18(11):716–721.
91. WHO Guidelines approved by the Guidelines Review Committee. Global Guidelines for the prevention of surgical site infection. Geneva: World Health Organization; 2016.
92. Mermel LA. Prevention of intravascular catheter-related infections. *Ann Intern Med*. 2000;132(5):391–402.
93. Garner JS, Jarvis WR, Emori TG, Horan TC, Hughes JM. CDC definitions of nosocomial infections, 1988. *Am J Infect Control*. 1988;16(3):128–140.

94. Pronovost P, Needham D, Berenholtz S, et al. An intervention to decrease catheter-related bloodstream infections in the ICU. *New Engl J Med*. 2006;355(26):2725–2732.
95. Bleasdale SC, Trick WE, Gonzalez IM, Lyles RD, Hayden MK, Weinstein RA. Effectiveness of chlorhexidine bathing to reduce catheter-associated bloodstream infections in medical intensive care unit patients. *Arch Intern Med*. 2007;167(19):2073–2079.
96. Veenstra DL, Saint S, Saha S, Lumley T, Sullivan SD. Efficacy of antiseptic-impregnated central venous catheters in preventing catheter-related bloodstream infection: a meta-analysis. *JAMA*. 1999;281(3):261–267.
97. Johnston L, Chui L, Chang N, et al. Cross-Canada spread of methicillin-resistant *Staphylococcus aureus* via transplant organs. *Clin Infect Dis*. 1999;29(4):819–823.
98. Cerutti E, Stratta C, Romagnoli R, et al. Bacterial- and fungal-positive cultures in organ donors: clinical impact in liver transplantation. *Liver Transpl*. 2006;12(8):1253–1259.
99. Patel G, Rana MM, Huprikar S. Multidrug-resistant bacteria in organ transplantation: an emerging threat with limited therapeutic options. *Curr Infect Dis Rep*. 2013;15(6):504–513.
100. Philpott-Howard J, Burroughs A, Fisher N, et al. Piperacillin–tazobactam versus ciprofloxacin plus amoxicillin in the treatment of infective episodes after liver transplantation. *J Antimicrob Chemother*. 2003;52(6):993–1000.
101. MacDonald A, Dinah F, MacKenzie D, Wilson A. Performance feedback of hand hygiene, using alcohol gel as the skin decontaminant, reduces the number of inpatients newly affected by MRSA and antibiotic costs. *J Hosp Infect*. 2004;56(1):56–63.
102. Knight GM, Budd EL, Whitney L, et al. Shift in dominant hospital-associated methicillin-resistant *Staphylococcus aureus* (HA-MRSA) clones over time. *J Antimicrob Chemother*. 2012;67(10):2514–2522.
103. Chen SL, Zhu CY, Zhou H, Yang Q, Shen YH, Zhou JY. [Efficacy and safety of linezolid among patients with methicillin-resistant *Staphylococcus aureus* bacteremia]. *Zhonghua Yi Xue Za Zhi*. 2017;97(14):1084–1088. Chinese [with English abstract].
104. Saner FH, Heuer M, Rath PM, et al. Successful salvage therapy with tigecycline after linezolid failure in a liver transplant recipient with MRSA pneumonia. *Liver Transpl*. 2006;12(11):1689–1692.
105. Rice LB. Unmet medical needs in antibacterial therapy. *Biochem Pharmacol*. 2006;71(7):991–995.
106. Lamer C, de Beco V, Soler P, et al. Analysis of vancomycin entry into pulmonary lining fluid by bronchoalveolar lavage in critically ill patients. *Antimicrob Agents Chemother*. 1993;37(2):281–286.
107. Arias CA, Murray BE. Antibiotic-resistant bugs in the 21st century – a clinical super-challenge. *N Engl J Med*. 2009;360(5):439–443.
108. Holland TL, Arnold C, Fowler VG Jr. Clinical management of *Staphylococcus aureus* bacteremia: a review. *JAMA*. 2014;312(13):1330–1341.
109. Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the infectious diseases society of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children. *Clin Infect Dis*. 2011;52(3):e18–e55.
110. Stryjewski ME, Szczech LA, Benjamin DK Jr, et al. Use of vancomycin or first-generation cephalosporins for the treatment of hemodialysis-dependent patients with methicillin-susceptible *Staphylococcus aureus* bacteremia. *Clin Infect Dis*. 2007;44(2):190–196.
111. Chang FY, Peacock JE Jr, Musher DM, et al. *Staphylococcus aureus* bacteremia: recurrence and the impact of antibiotic treatment in a prospective multicenter study. *Medicine (Baltimore)*. 2003;82(5):333–339.
112. Mermel LA, Allon M, Bouza E, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2009;49(1):1–45.
113. Zheng X, Berti AD, McCrone S, et al. Combination antibiotic exposure selectively alters the development of vancomycin intermediate resistance in *Staphylococcus aureus*. *Antimicrob Agents Chemother*. 2018;62(2):e02100–e02117.
114. Swartz TH, Huprikar S, Labombardi V, et al. Heart transplantation in a patient with heteroresistant vancomycin-intermediate *Staphylococcus aureus* ventricular assist device mediastinitis and bacteremia. *Transpl Infect Dis*. 2013;15(5):E177–E181.
115. Kelley PG, Gao W, Ward PB, Howden BP. Daptomycin non-susceptibility in vancomycin-intermediate *Staphylococcus aureus* (VISA) and heterogeneous-VISA (hVISA): implications for therapy after vancomycin treatment failure. *J Antimicrob Chemother*. 2011;66(5):1057–1060.
116. Joson J, Grover C, Downer C, Pujar T, Heidari A. Successful treatment of methicillin-resistant *Staphylococcus aureus* mitral valve endocarditis with sequential linezolid and telavancin monotherapy following daptomycin failure. *J Antimicrob Chemother*. 2011;66(9):2186–2188.
117. Marcos LA, Camins BC. Successful treatment of vancomycin-intermediate *Staphylococcus aureus* pacemaker lead infective endocarditis with telavancin. *Antimicrob Agents Chemother*. 2010;54(12):5376–5378.
118. Nace H, Lorber B. Successful treatment of methicillin-resistant *Staphylococcus aureus* endocarditis with telavancin. *J Antimicrob Chemother*. 2010;65(6):1315–1316.
119. Stryjewski ME, Barriere SL, Rubinstein E, et al. Telavancin versus vancomycin for bacteraemic hospital-acquired pneumonia. *Int J Antimicrob Agents*. 2013;42(4):367–369.
120. Levine DP, Fromm BS, Reddy BR. Slow response to vancomycin or vancomycin plus rifampin in methicillin-resistant *Staphylococcus aureus* endocarditis. *Ann Intern Med*. 1991;115(9):674–680.
121. Cosgrove SE, Vigliani GA, Fowler VG Jr, et al. Initial low-dose gentamicin for *Staphylococcus aureus* bacteremia and endocarditis is nephrotoxic. *Clin Infect Dis*. 2009;48(6):713–721.
122. Dhand A, Bayer AS, Pogliano J, et al. Use of antistaphylococcal beta-lactams to increase daptomycin activity in eradicating persistent bacteremia due to methicillin-resistant *Staphylococcus aureus*: role of enhanced daptomycin binding. *Clin Infect Dis*. 2011;53(2):158–163.
123. Fischer SA, Avery RK; AST Infectious Disease Community of Practice. Screening of donor and recipient prior to solid organ transplantation. *Am J Transplant*. 2009;9(Suppl 4):S7–S18.
124. Jenkins TC, Price CS, Sabel AL, Mehler PS, Burman WJ. Impact of routine infectious diseases service consultation on the evaluation, management, and outcomes of *Staphylococcus aureus* bacteremia. *Clin Infect Dis*. 2008;46(7):1000–1008.
125. Honda H, Krauss MJ, Jones JC, Olsen MA, Warren DK. The value of infectious diseases consultation in *Staphylococcus aureus* bacteremia. *Am J Med*. 2010;123(7):631–637.
126. Bai AD, Showler A, Burry L, et al. Impact of infectious disease consultation on quality of care, mortality, and length of stay in *Staphylococcus aureus* bacteremia: results from a large multicenter cohort study. *Clin Infect Dis*. 2015;60(10):1451–1461.
127. Crispe IN. The liver as a lymphoid organ. *Annu Rev Immunol*. 2009;27:147–163.
128. Deng M, Scott MJ, Loughran P, et al. Lipopolysaccharide clearance, bacterial clearance, and systemic inflammatory responses are regulated by cell type-specific functions of TLR4 during sepsis. *J Immunol*. 2013;190(10):5152–5160.
129. Lee WY, Moriarty TJ, Wong CH, et al. An intravascular immune response to *Borrelia burgdorferi* involves Kupffer cells and iNKT cells. *Nat Immunol*. 2010;11(4):295–302.
130. McDonald B, Jenne CN, Zhuo L, Kimata K, Kubes P. Kupffer cells and activation of endothelial TLR4 coordinate neutrophil adhesion within liver sinusoids during endotoxemia. *Am J Physiol Gastrointest Liver Physiol*. 2013;305(11):G797G806.
131. Berenger BM, Doucette K, Smith SW. Epidemiology and risk factors for nosocomial bloodstream infections in solid organ transplants over a 10-year period. *Transpl Infect Dis*. 2016;18(2):183–190.

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