MRSA outbreak at a transplantation unit

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ABSTRACT

Methicillin-resistant *Staphylococcus aureus* (MRSA) infections frequently complicate the post-operative course of transplant recipients, and despite nasal carriage and endemic colonization, MRSA outbreaks are not commonly described. This study reports a case of MRSA outbreak and discusses infection control measures and recommendations for this situation.

Keywords: MRSA, outbreak, surgical site infection, liver transplantation, RAPD.

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Abbreviations:
MRSA – methicillin resistant *Staphylococcus aureus*
LT – liver transplantation
ICU – intensive care unit
SSI – surgical site infection
TU – transplantation unit
RAPD – random amplified polymorphic DNA

INTRODUCTION

Bacterial infections are the primary infection complication in patients submitted to solid organ transplantation. In liver transplantation (LT), they generally occur in 30% to 55% of the cases, especially during the first and second months after the procedure, raising morbidity and mortality. Up to 60% of these infections are caused by Gram-positive microorganisms, mainly *Staphylococcus aureus* (*S. aureus*).[1,2] These infections vary according to microorganism virulence and antimicrobial resistance profile.[3]

Many transplanted patients are colonized by *S. aureus*. Colonization can occur in the pre- or post-transplantation period and is associated with several factors, such as surgery duration, altimicrobial use, permanency in the Intensive Care Unity (ICU), drains and catheter use, excessive manipulation, and disease severity.[1,4,5]

S. aureus profile resistance depends on methicillin susceptibility. Methicillin- resistant *S. aureus* (MRSA) displays a *mecA* gene, which orders a modified penicillin-binding protein - PBP-2 that decreases its affinity for penicillin.

MRSA colonization prior to LT occurs in 5.1% to 47.4% of the cases[4-9] and can be associated with a higher risk of infection.[5-7,10]

Although some studies have established a correlation between MRSA colonization and infection with LT patients, outbreaks are not frequent,[5-7,10] possibly due to infection control measures. Singh *et al.* demonstrated reduction in colonization and infection after the adoption of infection control measures, based on the identification of nasal or rectal MRSA carriage by swabs, contact precautions, patient cohort, nasal decolonization with mupirocin, and instructions for patients and visitors.[8] Thus, *S. aureus* identification and dissemination control should be a priority action in transplantation units.[11,12]

The present study describes a MRSA surgical site infection (SSI) outbreak in a transplantation unit (TU) and discusses measures for dissemination control of this microorganism using epidemiological, microbiological, and molecular biology tools.

METHODS

This is a prospective descriptive study that included patients submitted to transplantation who presented with SSI due to MRSA notified

in a TU. The study was performed in a tertiary care medical training center of a university hospital located in Belo Horizonte, Minas Gerais, Brazil, from September 2004 to May 2005, the period defined for case notification, establishment of actions, and surveillance. Outbreak control was defined as four weeks after the last case.

Cases were identified through a daily active search in medical records and laboratory microbiological results. Infection notification was made by National Nosocomial Surveillance System criteria.[13] The process followed local Hospital Infection Control Committee instructions and was monitored via completion of specific forms and a database constructed for this purpose.

The index case was the first post-transplant patient at TU notified with SSI due to MRSA isolated in a surgical wound sample. Cases were defined as all other patients with SSI or colonization due to MRSA after transplantation procedure. Statistical analysis confirmed the outbreak by the event increased frequency, which meant an incidence above the expected number of cases.

During the outbreak, patient nasal and rectal swabs were performed routinely at TU admission and repeated weekly (except if the patient was previously colonized or infected by MRSA). Nasal swabs from healthcare workers were also collected.

Microbiological cultures were performed using commercial media - BioMérieux®. After a 24-hour incubation at 35° C, the staphylococcal colonies suspected by the Gram method were confirmed with enzymatic and biochemical tests. The oxacillin diffusion disk in agar (*Kirby-Bauer*) was used to define methicillin resistance, as per standardization recommended by the Clinical and Laboratory Standards Institute.[14]

MRSA genotypic study was performed using molecular biology techniques. Surgical wound samples isolated during the outbreak and specimens from patients hospitalized in other units were studied by Random Amplified Polymorphic DNA (RAPD) amplification for genetic similarity. Criteria established by Tenover *et al*. were considered for genetic grouping and definition of the same genotypic strain.[15]

Risk factor analysis was performed by matching cases versus controls. Controls were defined as patients who were submitted to transplantation without MRSA SSI. Variables studied were length of stay in the hospital, ICU, and TU hospitalization period prior to MRSA infection or colonization, number of days with central venous catheter, and antimicrobial use. Student's t-test was used for comparison between the groups and statistical significance was considered when $p \leq 0.05$.

This study was approved by the Institutional Ethical Committee.

RESULTS

Index case: MRSA SSI was identified on September 27, 2004, and ten other cases have been notified from then until April 14, 2005. A total of 11 patients met the criteria for case definition.

Description of cases: nine (81.8%) patients were submitted to LT; one patient received renal transplantation, and another patient received bone marrow transplantation and required an exploratory laparotomy after a suspicion of appendicitis. Seven cases (63.6%) presented with superficial SSI (six LT patients and one renal transplantation patient). Four other cases (36.4%) presented with deep SSI (three of them after LT and one after bone marrow transplantation).

Genotypic and phenotypic profiles: all 11 *S. aureus* strains identified in transplanted recipients with SSI were oxacillin-resistant, but vancomycin-sensitive. Figure 1 shows 11 *S. aureus* strains studied by RAPD amplification, using three different starters (1A, 1B, 1C). Figure 2 presents a phylogenetic study demonstrating 90% of similarity among MRSA samples with a discriminatory power of D = 0.409.

Figure 1: Genotypic analysis by Random Amplified Polymorphic DNA amplification of MRSA strains from outbreak and other institutional settings.

Figure 1A

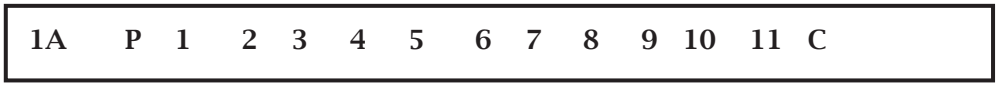


Figure 1B

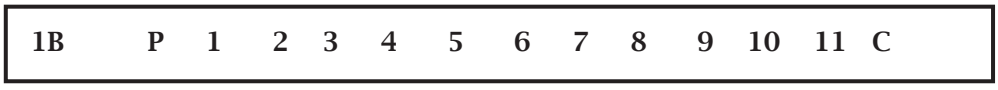
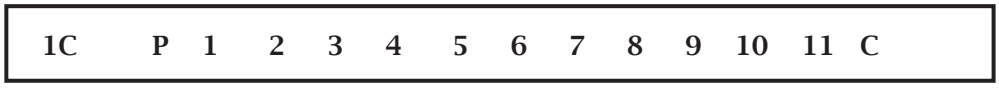


Figure 1C



*P Standard Φ 174/HaeIII; 1 to 11 - Patient samples; C- Negative control s image file number 1

Routine investigation: swab cultures from patients at TU admission did not identify prior colonization. During the outbreak, nasal and rectal swabs were repeated weekly and no patient presented with MRSA colonization before SSI. Healthcare workers also had nasal swabs performed and no carriers were identified. **Risk factors:** none of the risk factors studied showed statistical significance (Table 1). Only the ICU showed a tendency towards MRSA infection ($p = 0.06$). No deaths were notified during the follow-up period.

Outbreak control: chlorhexidine 2% was used for hand hygienization and contact precautions were recommended for care of colonized or infected patients. All infection control measures defined by the Hospital Infection Control Committee are presented on Table 2. After the adoption of the recommendations, this outbreak was controlled on May 17, 2005.

Figure 2: Phylogenetic similarity of MRSA samples from outbreak and other institutional settings.

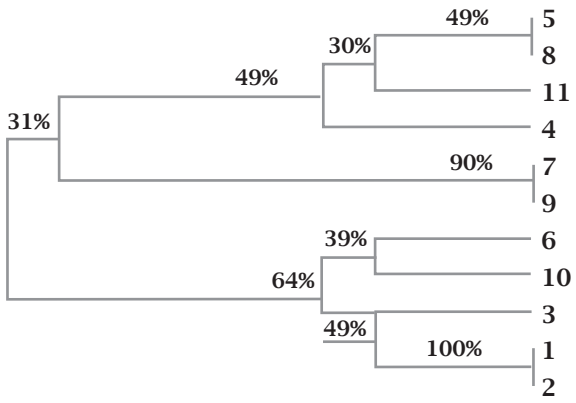


Table 1. Risk factors for patients MRSA colonization or infection

	Patients without MRSA SSI					Patients with MRSA SSI					
	N	Mean	SD	Minimum	Maximum	N	Mean	SD	Minimum	Maximum	p value
Hospital stay before transplantation	39	1.0	1.0	5	0	8	1.0	1.0	2	0	0.53
TU stay	50	5.1	10.5	72	1	7	3.4	1.3	6	2	0.30
ICU stay	9	10.4	8.7	23	0	8	26.7	21.7	66	0	0.06
CVC use (in days)	37	6.3	11.4	63	0	7	3.9	1.3	6	2	0.22
ATM use before MRSA identification (in days)	33	27	3.7	22	1	12	2.7	1.0	4	1	1.00

MRSA: methicillin resistant *S. aureus;* SSI: surgical site infection; TU: transplantation unit; ICU: intensive care unit; CVC: central venous catheter; ATM: antimicrobial.

Table 2 - Infection control measures adopted during MRSA SSI outbreak

Control measures
Hand hygienization with 2% chlorhexidine for healthcare workers.
Contact precautions for all colonized or infected patients (gloves and gowns in contact with patient); patient and healthcare worker cohort.
Nasal and rectal swab cultures (excluding those with known prior colonization).
Nasal swab cultures of health assistance team.
Frequent meetings with assistance team and Hospital Infection Control Committee.

MRSA: methicillin resistant *S. aureus*; SSI: surgical site infection.

DISCUSSION

S. aureus is an important agent related to infection in solid organ transplantation, especially in LT recipients. The most common form of acquisition is prior colonization or nosocomial cross-transmission associated with antimicrobial use and invasive procedures. Although MRSA colonization or infection is common in solid organ transplantation recipients, outbreaks are not frequently described. The approach and management of this situation usually focuses on individual aspects. This study allows a discussion of systematic practices and infection control/prevention measures based on a multidisciplinary board.

Outbreak investigation

During an outbreak, case definition is recommended. In this study, case was defined as a transplanted patient admitted to the TU with MRSA isolation in a swab or in any sample associated with site infection. After that, to identify the

total number of cases, transplanted patients underwent nasal and rectal swab monitoring; MRSA isolation in any sample was also considered. Infection control protocols usually include hand hygiene, precautions with gowns and gloves, in addition to environment and equipment cleansing.

Despite of *S. aureus* colonization high frequency in transplanted patients, in this particular unit MRSA isolation was a rare occurrence, probably because our institution maintains a low *S. aureus methicillin* resistance rate. Outbreak confirmation requires an increase of a specific infection or complication above the background rate. During two years before this outbreak, no patients presented with MRSA SSI at the TU, and so MRSA isolation in more than one patient demanded our attention.

The outbreak involved 11 patients over a six-month observation period. A case versus control study was performed and the source investigation comprised MRSA carrier admission, healthcare workers contamination during surgery, and cross-transmission in the ICU, TU, or other hospital units. From all variables studied, only the ICU stay showed a tendency for MRSA infection ($p = 0.06$), suggesting a cross-transmission that might occur in this setting. At our transplantation service, patients are assisted in the ICU for at least 48 hours after the procedure. MRSA-colonized patients presented a mean TU stay of 26.7 days compared to 10.4 days for patients without MRSA SSI.

Swab cultures are routinely performed before surgery and in the ICU when patients stay for seven days or more. As no patient was identified as having MRSA at TU or ICU admission, posterior colonization was considered due to broken barriers. It is noted that swab sensitivity varies enormously, depending on the number of samples collected, and it is not possible to exclude MRSA cross-transmission in the ICU.

All stains demonstrate the same antibiogram pattern, with resistance to all antimicrobials tested, except for vancomycin. Genotypic analysis by RAPD included eleven samples (MRSA from institucional settings and outbreak strains) and confirmed the hypothesis of genetic correlation (with 90% similarity, besides micro heterogeneity among samples - Figure 2). Genotypic analysis by Pulsed Field Gel Electrophoresis, Restriction Fragment Length Polymorphism, or RAPD should be used whenever possible with this purpose. However, these techniques present different primers and lack of interpretation standardization. RAPD showed quicker results as has been demonstrated by several studies.[16,17] The combination of three different starters in this study improved the discriminatory power ($D = 0.409$), and this low value could be justified by a high genetic correlation among the samples.

Clinical aspects

S. aureus nasal or rectal colonization is frequent in transplanted patients, and *S. aureus* systemic infections, especially sepsis, still remain as an important cause of serious complications.[8] Additionally, cirrhotic patients show greater *S. aureus* colonization rates,[18] and the association between staphylococcal colonization and infection has been discussed in several studies.

Bert *et al.* showed that 87.5% of MRSA infections occurred in previously colonized patients compared to 10.1% of non-colonized patients ($p < 0.001$).[6] Desai *et al.* describe a greater risk for MRSA sepsis in previously colonized patients compared to non-colonized individuals ($p = 0.002$).[7] In a retrospective cohort, sensitive or resistant *S. aureus* colonization was also an independent factor for post-transplantation infection, according to multivariate analysis ($p = 0.0004$ and $p < 0.0001$; respectively).[4] Hashimoto *et al.* demonstrated that patients colonized by MRSA after the transplant showed higher infection rates compared to those non-colonized ($p=0.001$).[10] Also according to Hashimoto *et al.*, higher MRSA infection rates occurred in patients with prior colonization ($p = 0.04$ and odds ratio: 3.5).[5]

Swab monitoring: some authors recommend swab monitoring at admission and periodically after transplantation, considering increased infection rates in previously colonized patients. Coia *et al.* suggest that swabs must be repeated weekly or monthly, depending on local prevalence.[19] The identification of colonized individuals could allow contact precautions, patient cohorts, decolonization, and educational information for patients and their visitors.[5,7,8,10] In accordance with British guidelines, swab monitoring or active surveillance cultures should be considered according to hospital epidemiological profile and MRSA prevalence for patients from Critical Care Units, including TU.[19] Moreover, other variables must be observed, such as prior colonization, hospital admissions and transfers from hospitals with a high MRSA prevalence. In the present study, swabs from transplanted patients and healthcare workers aimed at carrier identification. Our results showed that no patient was considered as previously colonized and no professional was considered a MRSA carrier. Nevertheless, swab monitoring is still controversial, especially in institutions with a high endemic MRSA prevalence, because the impact of monitoring measures, in this situation, is reduced. Harbarth *et al.*, comparing different periods with and without MRSA swab monitoring by PCR, showed no statistical difference among MRSA infection rates ($p = 0.29$).[9]

Site colonization: transplanted patients could present concomitant nasal and rectal colonization rates up to 25.5%,[20] as they show a higher infection risk when compared to those with only nasal colonization ($p = 0.025$ and odds ratio = 23.9). We highlight the fact that *S. aureus* decolonization is difficult due to the intestinal reservoir, and mere nasal decolonization could be

useless. In the present study, no patient was recognized as having prior rectal colonization, but rectal swab sensitivity is no more than 70%, which limits carrier identification and restricts preventive measures to avoid dissemination.

Mortality: although high mortality rates associated with *S. aureus* infections are described in several studies,[1,2,11,12] no deaths associated with MRSA SSI occured during this outbreak. The majority of SSI were superficial, presenting low severity with better treatment response. In a study of 165 liver transplant patients, Singh *et al.* described vascular catheter infection as the main site (n = 15), followed by SSI and the abdominal site (n = 7 each), in addition to five pulmonary infections.[11] Higher mortality (86%) was observed in patients with abdominal or pulmonary infections. Torre-Cisneros *et al.*, in a study with 405 patients submitted to LT, defined *S. aureus* as the only independent variable associated with mortality.[12]

Prophylaxis: MRSA identification contributes to surgical prophylaxis definition. In our Transplantation Service, the surgical prophylaxis protocol included cefotaxime plus ampicillin during the first 48 hours. This allows a good coverage, with adequate levels at the surgical site and relative safety. Considering a MRSA prevalence of approximately 35% at our hospital, glycopeptides as antimicrobial prophylaxis are indicated only for patients previously colonized by MRSA or who display hypersensitivity to first-choice drugs. During this outbreak, glycopeptides prophylaxis was discussed, but not used, since no previously colonized patients were identified. Furthermore, there is a selective advantage enjoyed by MRSA in the presence of antimicrobial exposure that facilitates patient-to-patient cross-transmission.

Decolonization: MRSA decolonization for LT candidates is controversial. In a meta-analysis by van Rijem *et al.*, nasal mupirocin reduced decolonization and *S. aureus* infection after transplantation (p = 0.02, RR 0.55, and 95% CI 0.34-0.89).[21] Although routine MRSA decolonization is supported by literature, in this outbreak its use was not indicated due to high recolonization rates, especially for patients with an intestinal reservoir or frequent and prolonged hospital admissions. In one study, 27 patients colonized by *S. aureus* used mupirocin and 37% recolonized.[22] Seven of these patients, previously colonized by sensitive *S. aureus*, were recolonized by MRSA. The authors emphasized that intestinal MRSA could be a source that cannot be eliminated by nasal mucopirocin and chlorhexidine bath. Besides, mupirocin resistance has been described.

Prevention: standard and contact precautions are necessary and should be followed by all professionals and visitors, including in home care. Instructions, such as hand washing, contact precautions, swab monitoring, patient cohorts, and regular meetings with the assistance team were efficient in controlling this outbreak (Table 2). However, transmission control among special patients brings up new challenges. Transplanted liver patients are immunosuppressed, and have a possible *S. aureus* gastrointestinal reservoir and an extended surgical area.

Conclusion: MRSA outbreaks in transplant recipients have rarely been described. The present study demonstrates the importance of epidemiologic and molecular tools in outbreak investigation. Infection control measures were effective to limit dissemination, although no source of infection had been identified. Colonization monitoring allows carrier identification and facilitates decisions, contact precautions, decolonization and antimicrobial prophilaxis. A specific protocol including infection control recommendations would facilitate handling with future similar events.

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REFERENCES

1. Souza MV, Barth AL, Álvares-da-Silva MR, Machado AR. Infections after liver transplantation in adults: data from a university hospital in southern Brazil (1996-2000). Arq Gastroenterol 2007; 44(2):128-32.
2. Bedini M, Codeluppi S, Cocchi G *et al.* Gram-positive bloodstream infections in liver transplant recipients: incidence, risk factors, and impact on survival. Transplant Proc 2007; 39(6):1947-9.
3. Siegel JD, Rhinehart E, Jackson M, Chiarello L. The Healthcare Infection Control Practices Advisory Committee. Center of Diseases Control and Prevention (CDC). Management of Multidrug-Resistant Organisms in Healthcare Settings, November 2006. Access: www.cdc.gov/ncidod/dhqp/pdf/ar/mdroguideline2006.pdf
4. Bert F, Bellier C, Lassel L *et al.* Risk factors for Staphylococcus aureus infection in liver transplant recipients. Liver Transpl 2005; 11(9):1093-9.
5. 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):3271-5.
6. Bert F, Galdbart JO, Zarrouk V *et al.* Association between nasal carriage of Staphylococcus aureus and infection in liver transplant recipients. Clin Infect Dis 2000; 31(5):1295-9.
7. 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):754-9.
8. 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):122-6.

9. Harbarth S, Fankhauser C, Schrenzel J *et al*. Universal screening for methicillin-resistant Staphylococcus aureus at hospital admission and nosocomial infection in surgical patients. JAMA 2008; 299(10):1149-57.
10. 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):110-6.
11. Singh N, Paterson DL, Chang FY *et al*. Methicillin-resistant Staphylococcus aureus: the other emerging resistant gram-positive coccus among liver transplant recipients. Clin Infect Dis 2000; 30(2):322-7.
12. 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):385-8.
13. Horan TC, Gaynes RP. Nosocomial surveillance of infections. In: Mayhall CG. Epidemiology of hospital and infection control. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2004:1659-1702.
14. Clinical Laboratory Standard Institute (CLSI). Performance Standards for Antimicrobial Susceptibility Testing; Seventeenth Information Suplement - M100s15. Access: www.clsi.org/source/orders/free/m100-s15.pdf
15. Tenover FC, Arbeit RD, Goering RV *et al*. Interpreting chromosomal DNA restriction patterns produced by pulsed-field gel electrophoresis: criteria for bacterial strain typing. J Clin Microbiol 1995; 33(9):2233-9.
16. Olmos A, Camarena JJ, Nogueira JM, Navarro JC, Risen J, Sánchez R. Application of an optimized and highly discriminatory method based on arbitrarily primed PCR for epidemiologic analysis of methicillin-resistant Staphylococcus aureus nosocomial infections. J Clin Microbiol 1998; 36(4):1128-34.
17. Tambic A, Power EG, Talsania H, Anthony RM, French GL. Analysis of an outbreak of non-phage-typeable methicillin-resistant Staphylococcus aureus by using a randomly amplified polymorphic DNA assay. J Clin Microbiol 1997 Dec; 35(12):3092-7.
18. Chapoutot C, Pageaux GP, Perrigault PF *et al*. Staphylococcus aureus nasal carriage in 104 cirrhotic and control patients. A prospective study. J Hepatol 1999; 30(2):249-53.
19. Coia JE, Duckworth GJ, Edwards DI *et al*. Joint Working Party of the British Society of Antimicrobial Chemotherapy; Hospital Infection Society; Infection Control Nurses Association. Guidelines for the control and prevention of methicillin-resistant Staphylococcus aureus (MRSA) in healthcare facilities. Hosp Infect 2006; 63 Suppl 1:S1-44.
20. Squier C, Rihs JD, Risa KJ *et al*. Staphylococcus aureus rectal carriage and its association with infections in patients in a surgical intensive care unit and a liver transplant unit. Infect Control Hosp Epidemiol 2002; 23(9):495-501.
21. van Rijen MM, Bonten M, Wenzel RP, Kluytmans JA. Intranasal mupirocin for reduction of Staphylococcus aureus infections in surgical patients with nasal carriage: a systematic review. J Antimicrob Chemother 2008; 61(2):254-61.
22. 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):194-8.