Risk factors for wound infection caused by Methicillin Resistant *Staphylococcus aureus* among hospitalized patients: a case control study from a tertiary care hospital in India

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Abstract:

Background: Methicillin Resistant *Staphylococcus aureus* (MRSA) causes infection in hospitals and communities. The prevalence and risk factors of MRSA infection is not homogenous across the globe.

Objective: To find the risk factors of MRSA infection among hospitalized patients.

Methods: Cross-sectional case control study was conducted at a tertiary care hospital in India. The risk factors were collected using checklist from 130 MRSA and 130 Methicillin sensitive *staphylococcus aureus* (MSSA) infected patients. The pathogens were isolated from the wound swabs according to Clinical and Laboratory Standards Institute guidelines.

Results: Both the groups were comparable in terms of age, gender, diabetic status, undergoing invasive procedures, urinary catheterization and smoking (p>0.05). Multivariate logistic regression revealed surgical treatment (OR 4.355; CI 1.03, 18.328; p=0.045), prolonged hospitalization (OR 0.307; CI 0.11, 0.832; p=0.020), tracheostomy (OR 5.298, CI 1.16, 24.298; p=0.032), pressure/venous ulcer (OR 7.205; CI 1.75, 29.606; p=0.006) and previous hospitalization (OR 2.883; CI 1.25, 6.631; p=0.013) as significant risk factors for MRSA infection.

Conclusion: Surgical treatment, prolonged and history of hospitalization, having tracheostomy for ventilation and pressure/venous ulcer were the key risk factors. Therefore, special attention has to be given to the preventable risk factors while caring for hospitalized patients to prevent MRSA infection.

Keywords: MRSA; infection; India.

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Introduction

Methicillin Resistant *Staphylococcus aureus* (MRSA) is a Gram-positive pathogen, having the ability to cause hospital associated infection and/or community acquired infection. Hospital associated MRSA infection is one of the major problems affecting both patients and care providers⁴. MRSA colonization is predominantly present in the nose and skin of humans⁵. Nasal colonization of *Staphylococcus aureus* and MRSA are the independent predictors of MRSA infection⁶. Colonized bacteria may not cause infection. However, it can enter the body through injured skin or mucus membrane and can cause simple skin infection to life threatening bacteremia. The spectrum includes pneumonia, bacteremia, skin and soft tissue infection, pyomyositis, sepsis, osteomyelitis, necrotizing pneumonia and necrotizing fasciitis⁷. Though MRSA can be isolated from blood, nose, wound, urine, respiratory tract, sputum and other body fluids, the prevalence is high in wounds⁸.

Acquiring MRSA infection is multifactorial, and the risk factors described are prolonged post-operative state, emergency admissions and prior treatment with multiple antibiotics⁹. Other notable treatment related factors are emergency surgery, prolonged or multiple hospital stays, use of invasive devices (catheters, surgical drains, gastric/endotracheal tubes), repeated surgeries, treatment with multiple broad-spectrum antibiotics,
MRSA contaminates the hands of healthcare professionals (59.6%)\(^7\). Even the dress of healthcare professionals can spread MRSA. According to the society for Healthcare Epidemiology of America (SHEA) report (2014), HCPs opine that their attire, including footwear, is important in preventing transmission of infection\(^14\). Also, MRSA is found on hospital surfaces, disinfectant areas and reusable equipment\(^19\). Though the cleaning of patient surroundings in ICU has shown a significant reduction in MRSA, after 24 hours of cleaning, the risk of MRSA growth in the patient environment remained high\(^16\).

Although some similar strains of MRSA are seen in many countries depicting international dissemination, the spread is not homogenous around the globe\(^17\). Most of the studies have been conducted in developed countries\(^3,12,18\). No published information on risk factors of MRSA infection is traced in India. Therefore, we aimed at identifying the risk factors of MRSA infection in an Indian hospital to institute appropriate preventive measures.

Methods

Study design

The study has adopted a cross-sectional case control study design (1:1) with a quantitative approach.

Study setting

The study was carried out in a tertiary care hospital in South India. The hospital has almost all the super specialties with 2032 beds and provides both in-patient and outpatient healthcare services. It caters to the health needs of a large population. It is a private university hospital meeting the teaching needs of many health science courses such as medical, dental, nursing and other allied health courses. The hospital had more than 80% occupancy during the study period. The hospital is certified by the International Organization for Standardization, (ISO) 14001: 2015 ISO 50001:2011 and accredited by National Accreditation Board for Hospitals & Healthcare Providers (NABH).

Participants and sample size

Hospitalized patients infected with MRSA were the cases. Patients with Methicillin Sensitive Staphylococcus aureus (MSSA) infections were considered as controls.

The sample size for identifying the risk factors of MRSA infection was calculated based on the previous study reports by using the following formula\(^19\).

\[
n = \left\{ \frac{Z_{1-\alpha/2}^2pq + Z_{1-\beta}\sqrt{pq(1-p)q_1 + p_2q_2}}{(p_1 - p_2)^2} \right\}^2
\]

The proportion at baseline was 0.73 and the expected outcome set was 0.53 (based on the previous hospitalization as the risk factor)\(^19\). The measured confidence interval was 95% with 80% power, and the calculated sample was 88 in each group. Considering the presence of skin ulcers (baseline 0.33 and expected outcome 0.18)\(^19\) the calculated sample size was 129. The study included 130 patients with MRSA infection (cases) and 130 patients with MSSA infection (controls). Hospitalized patients who had MRSA grown in their wound culture were considered as cases, whereas hospitalized patients with MSSA grown in the wound swabs were taken as controls. We recruited both male and female adult patients (18 years and above) of general wards, medical and surgical intensive care units. The wards included were medical, surgical, dermatology, orthopedics, cardiology, Ear, nose and throat (ENT) specialties. The patients who were hospitalized for more than two days (>48 hours) as in-patients were included. Patients with immunosuppressive with human immunodeficiency virus, cancer and on immunosuppression therapy were excluded from the study. However, patients with agranulocytosis, leukocytosis and mild autoimmune disorder were not excluded.

Risk assessment checklist

There was no standardized tool available for identifying the risk factors of MRSA infection. Hence, a checklist of risk factors for MRSA infection was developed after an extensive literature search and discussion with microbiologists and Hospital Infection Control Committee (HICC) members. The checklist had 31 dichotomous items with ‘yes’ or ‘no’ options. The content validity was done by nine experts from different healthcare professionals (members of HICC, microbiologists, physicians, faculty of nursing and a policymaker). Content validity index was 0.94. The reliability of the tool was established by the rater-inter-rater method, and the calculated ‘r’ was 0.974.

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Ethical consideration
Ethical permission was obtained from the Institutional Ethics Committee (IEC). The study was registered at ‘clinical trial registry – India’ (CTRI/2018/01/011510). Administrative approval was taken from the Medical Superintendent and Chief Operating Officer of the hospital. Informed written consent from study participants was obtained.

Data analysis
The data were coded and entered in Statistical Package for Social Sciences (SPSS 16.0) version and the analysis was performed using logistic regression. The demographic characteristics are given in frequency and percentage.

Data collection procedure
We collected the data from June 2017 to May 2018. The hospitalized patients, whose wound swab grew MRSA or MSSA were approached as presented in the flow diagram (figure 1). After obtaining the consent, investigators collected information from the patients and the medical records using a risk assessment checklist. A total of 260 (130 MRSA infected and 130 MSSA infected) patients were recruited.

Figure 1: Flow diagram of patient recruitment and data collection
Results
Both MRSA and MSSA infection groups were comparable in terms of age, gender, admission status, immunity, diabetes mellitus, smoking status, having undergone invasive diagnostic procedures, presence of a catheter, feeding tubes and duration of surgery as shown in Table 1. The mean duration of hospital stay was 9.9 days (range: 1-38 days) for the MRSA infected patients and 9.7 days (range: 1-30 days) for the MSSA infected patients.

Table 1: Comparison of demographic characteristics among both the groups of MRSA and MSSA infected patient

| Characteristics                  | Categories         | MRSA (n=130) | MSSA (n=130) | OR and 95% CI | p Value |
|----------------------------------|--------------------|--------------|--------------|---------------|---------|
| Age                              | Above 60 years     | 28 (21.54%)  | 29 (22.31%)  | 0.96 (0.53, 1.72) | 0.881   |
|                                  | Below 60 years     | 102 (78.5%)  | 101 (77.7%)  |               |         |
| Gender                           | Female             | 34 (26.15%)  | 34 (26.15%)  |               |         |
|                                  | Male               | 96 (73.85%)  | 96 (73.85%)  | 1 (0.58, 1.74) | 1.00    |
| Emergency Admission              | Present            | 29 (22.31%)  | 23 (17.69%)  | 1.34 (0.73, 2.46) | 0.35    |
|                                  | Absent             | 101 (77.69%) | 107 (77.31%) |               |         |
| Immunosuppression status         | Immunosuppressed   | 27 (20.77%)  | 27 (20.77%)  |               |         |
|                                  | Non-immunosuppressed | 103 (79.33%) | 103 (79.33%) | 1 (0.55, 1.82) | 1       |
| Presence of Diabetes Mellitus    | Diabetic           | 35 (26.9%)   | 38 (29.2%)   | 1.20 (0.71, 2.02) | 0.503   |
|                                  | Non diabetic       | 95 (73.1%)   | 92 (70.8%)   |               |         |
| Smoking                          | Smoker             | 39 (30%)     | 49 (37.69%)  | 1.44 (0.84, 2.37) | 0.19    |
|                                  | Non smoker         | 91 (70%)     | 81 (62.31%)  |               |         |
| Presence of other infections     | Present            | 30 (23.08%)  | 33 (25.38%)  |               |         |
|                                  | Absent             | 100 (76.92%) | 97 (74.62%)  | 1.13 (0.64, 2.0) | 0.664   |
| Invasive diagnostic procedure    | Performed          | 30 (23.08%)  | 30 (23.08%)  |               |         |
|                                  | Not performed      | 100 (76.92%) | 100 (76.92%) | 1 (0.562, 1.78) | 1       |
| Presence of urinary catheter     | Catheterized       | 17 (13.1%)   | 17 (13.1%)   |               |         |
|                                  | Non catheterized   | 113 (86.9%)  | 113 (86.9%)  | 1 (0.486, 2.057) | 1       |
| Ryle’s tube feeding              | NG feed            | 13 (10%)     | 12 (9.23%)   | 1.09 (0.48, 2.50) | 0.833   |
|                                  | No NG feed         | 117 (90%)    | 118 (90.77%) |               |         |
| ICU admission                    | ICU admitted       | 14 (10.77%)  | 20 (15.38%)  | 1.51 (0.73, 3.13) | 0.272   |
|                                  | No ICU admission   | 116 (89.33%) | 110 (84.62%) |               |         |
| Duration of surgery (>3 hours)   | More than 3 hours  | 24 (18.46%)  | 30 (23.08%)  | 1.33 (0.73, 2.42) | 0.359   |
|                                  | Less than 3 hours  | 106 (76.92%) | 100 (76.92%) |               |         |

Both the MRSA and MSSA infected patients were comparable (Table 1) as the odds ratio was not significant at p<0.05. Hence, the groups were considered for further statistical analysis to identify the risk factors.

The risk factors given in Table 2 were considered for multiple logistic regression since the univariate analysis indicated statistical significance. The risk factors along with the odds ratio and 95% confidence interval are given in Table 2.
The risk factors for MRSA infection which showed significance such as prolonged hospitalization, undergoing surgical procedures, surgical drain, previous use of antibiotics, presence of open wounds, having endotracheal and tracheostomy tubes, presence of intravenous access, presence of vascular/pressure ulcers and recent previous hospitalization were considered for further multiple logistic regression. Multiple logistic regression was adjusted with the age (advanced age) and gender (female), as these two factors are biologically significant and adjusted odds ratios are given in Table 3.

| Characteristics                  | Categories                        | MRSA (n=130) | MSSA (n=130) | OR and 95% CI      | p Value |
|----------------------------------|-----------------------------------|--------------|--------------|-------------------|---------|
| Surgical procedure performed     | Surgery done                      | 96 (73.85%)  | 87 (66.9%)   | 0.717 (4.20, 1.24)| 0.021   |
|                                  | No surgery done                   | 34 (26.2%)   | 43 (33.1%)   |                   |         |
| Prolonged hospitalization        | Early discharge                   | 34 (26.2%)   | 14 (10.8%)   | 2.94 (1.49, 5.78) | 0.001   |
|                                  | History of recent antibiotic use  | 63 (48.46%)  | 44 (33.85%)  |                   |         |
| Prior Antibiotic usage           | No history of recent antibiotic   | 67 (41.54%)  | 86 (66.15%)  | 0.473 (0.285, 0.785) | 0.004   |
|                                  | use                                |              |              |                   |         |
| Presence of open wound           | Had open wounds                   | 64 (49.23%)  | 46 (35.38%)  | 1.77 (1.08, 2.91) | 0.024   |
|                                  | No open wounds                    | 66 (50.77%)  | 84 (64.66%)  |                   |         |
| Presence of surgical drain       | Surgical drain present           | 54 (41.54%)  | 34 (26.15%)  | 2.0 (1.19, 3.39)  | 0.009   |
|                                  | No surgical drains                | 76 (58.46%)  | 96 (73.85%)  |                   |         |
| Presence of endotracheal tube    | Presence of endotracheal tube     | 6 (4.62%)    | 1 (0.77%)    | 8.46 (1.04, 68.64) | 0.046   |
|                                  | Endotracheal tube absent          | 124 (95.38%) | 129 (99.23%) |                   |         |
| Presence of tracheostomy tube    | Presence of tracheostomy          | 16 (12.31%)  | 6 (4.62%)    | 2.90 (1.10, 7.67) | 0.032   |
|                                  | No tracheostomy                   | 114 (87.69%) | 124 (95.38%) |                   |         |
| Intravenous lines                | Presence of peripheral IV lines   | 115 (88.46%) | 103 (79.23%) | 0.498 (.251, .987) | 0.046   |
|                                  | Absence of IV lines               | 15 (11.54%)  | 27 (20.77%)  |                   |         |
| Presence of vascular/pressure ulcer | Presence of vascular or pressure ulcer | 23 (17.69%) | 9 (6.92%) | 2.68 (1.14, 6.33) | 0.011   |
|                                  | Absence of any ulcers             | 107 (82.31%) | 221 (93.08) |                   |         |
| Previous recent hospitalization  | Had recent hospitalization         | 77 (59.23%)  | 52 (40%)     | 2.18 (1.33, 3.58) | 0.002   |
|                                  | No recent hospitalization          | 53 (40.77%)  | 78 (60%)     |                   |         |

Significance considered as p<0.05 level
Out of the above risk factors, surgery as a treatment option (OR 4.355; CI 1.03, 18.328; p=0.045), prolonged hospitalization (OR 0.307; CI 0.11, 0.832; p=0.020), presence of tracheostomy tube (OR 5.298; CI 1.16, 24.298; p=0.032), presence of pressure/venous ulcer (OR 7.205; CI 1.75, 29.606; p=0.006) and recent hospitalization (OR 2.883; CI 1.25, 6.631; p=0.013) were significant risk factors for causing MRSA infection among hospitalized patients.

The prevalence of MRSA infection is high among emergency admission patients. In the present study, 34.9% of patients were admitted from the trauma center and have undergone emergency surgeries. Usually, emergency surgeries are not well prepared like elective surgeries. However, emergency admission was not a significant determinant in our study.

Callejo et al. and Sun et al. reported that the risk factors of MRSA infection were advanced age (above 65 years), traumatic injuries, admitted from a long-term care facility, presence of a urinary catheter, previous antibiotic treatment and skin-soft tissue or post-surgical superficial skin infections. Patients with an open fracture tend to get infected more (14.7%) than a closed fracture (4.2%) or open injuries. In contrast, none of these factors were significant in the present study. Therefore, it can be inferred that the risk factors of MRSA infection differ around the globe.

In the present study, undergoing surgery, prolonged hospitalization, presence of tracheostomy tube, pressure/venous ulcer and recent hospitalization were the significant independent risk factors causing MRSA infection among hospitalized patients.

### Table 3: Multiple logistic regression with adjusted Odds Ratio on risk factors of MRSA infection

| Risk factors                        | β coefficient | Adjusted OR | 95% CI Lower | 95% CI Upper | P     |
|-------------------------------------|---------------|-------------|--------------|--------------|-------|
| Performing surgery                  | 1.471         | 4.355       | 1.03         | 18.328       | 0.045 |
| Prolonged hospitalization           | -1.182        | 0.307       | 0.11         | 0.832        | 0.020 |
| Prior Antibiotic use                | -0.709        | 0.492       | 0.20         | 1.204        | 0.120 |
| Presence of open wound              | 0.292         | 1.339       | 0.58         | 3.089        | 0.494 |
| Presence of surgical drain          | -0.223        | 0.800       | 0.35         | 1.85         | 0.601 |
| Presence of ET                      | -2.427        | 0.088       | 0.01         | 1.305        | 0.077 |
| Presence of TT                      | 1.667         | 5.298       | 1.16         | 24.298       | 0.032 |
| Intravenous lines                   | -0.058        | 0.944       | 0.22         | 4.134        | 0.939 |
| Pressure/venous ulcer               | 1.975         | 7.205       | 1.75         | 29.606       | 0.006 |
| Recent hospitalization              | 1.059         | 2.883       | 1.25         | 6.631        | 0.013 |
| Constant                            | -2.482        |             |              |              |       |

Odds ratio adjusted to age and gender

Logistic regression model: log (odds of MRSA) = -2.482 + 1.471 (performing surgery) + -1.182 (prolonged hospitalization) + 1.667 (presence of tracheostomy tube) + 1.975 (presence of pressure/venous ulcer) + 1.059 (Recent hospitalization)

Out of the above risk factors, surgery as a treatment option (OR 4.355; CI 1.03, 18.328; p=0.045), prolonged hospitalization (OR 0.307; CI 0.11, 0.832; p=0.020), presence of tracheostomy tube (OR 5.298, CI 1.16, 24.298; p=0.032), presence of pressure/venous ulcer (OR 7.205; CI 1.75, 29.606; p=0.006) and previous recent hospitalization (OR 2.883; CI 1.25, 6.631; p=0.013) were significant risk factors for causing MRSA infection among hospitalized patients.

### Discussion

*Staphylococcus aureus* remains the most common pathogen causing infection in wounds. World Health Organization has stressed that MRSA is one of the high priority multidrug-resistant organism. MRSA infection is high in Asia and the region is considered as ‘hospital associated MRSA endemic area’.

In the present study, undergoing surgery, prolonged hospitalization, presence of tracheostomy tube, pressure/venous ulcer and recent hospitalization were the significant independent risk factors causing MRSA infection among hospitalized patients.
1.4-8.8, p=0.008) were at risk of developing recurrent MRSA infection. Vascular ulcer increases the risk of MRSA infection. In agreement to this, the presence of vascular ulcer in the present study was one of the significant risk of causing MRSA infection. Vascular ulcer reduces the blood flow to distal areas. In the absence of oxygen, wound healing is delayed. Non-healing of the ulcer increases the risk of infection. In the current study, bed occupancy was more than 80%. The studies have proven that the occupancy rate in the hospital is directly proportional to the incidence of HAIs. The previous hospitalization is a proven cause of MRSA bacteremia. Recent hospitalization (OR 2.883; CI 1.25, 6.631; p=0.013) within a year was a significant cause of MRSA infection. Both prolonged hospitalization and repeated hospitalization increases the risk. The previous history of nursing home admission (OR 8.42; 1.06–66.43) is another threat of acquiring MRSA infection. Hospital is a source of multiple pathogens, and transmission of such pathogens from the hospital to the host is common. MRSA is seen in hospital environmental surface (38.9%) which increases the risk of causing infection. The ICU environment (67.3%) is an additional well-known risk factor of getting MRSA infection. MRSA was detected in ventilators (33%), ultrasound transducers (17%) and endoscopes used in the hospital. Also, MRSA is detected on the hands of 59.6% healthcare professionals.

Old age and nursing home residences are found to be independent risk factors of MRSA infection related death. Pre-prosthetic infection with MRSA is increasing (44%) among orthopedic surgery patients and arthroplasty patients have a higher risk (OR 0.11; 0.02–0.56) than internal fixation which also increases the treatment costs. Most of the time, removal of the prosthesis is the treatment for prosthetic infection and this infection indicates the failure of treatment. MRSA infection can have an adverse effect on the life of infected patients. The consequence of the infection can be repeated hospitalization, increased healthcare cost, increased mortality and morbidity. A retrospective study carried out in Texas showed that 21% MRSA infected patients developed recurrent infection. A two year retrospective study of amputated patients showed 7.3% re-hospitalization due to stump infection. Among the re-admitted patients, MRSA was the leading pathogen causing infection and the most common cause of death. The occurrence of surgical site infection with MRSA among orthopedic and transplant surgery patients is in late post-operative days compared to general surgical patients. This indicates that a longer duration of hospitalization is a threat for the development of infection. Longer hospitalization not only causes wound infection but also can result in MRSA bacteremia. In the present study, prolonged hospitalization (OR 0.307; CI 0.11, 0.832; p=0.020) was a significant contributing factor of MRSA infection. The mean duration of the hospitalized MRSA infected patients was 9.9 days. The duration of the hospitalization differs for each disease condition. However, for patients with minor surgeries, more than three days of hospitalization and more than seven days for major surgeries were considered as prolonged hospitalization. For patients, without surgical procedures (only medical treatment) the duration of hospitalization was compared with our hospital policy.

In the present study, undergoing surgery emerged as a risk factor. As surgical procedure disrupts the integrity of the skin, a pathogen can enter into the body easily. It is also noted that, more personnel in the operation room increases the risk of infection. However, the operating room team is bigger in teaching hospitals as students are posted in the operation room to develop surgical skills. Therefore, additional measures need to be implemented to reduce risk.

Presence of endotracheal or tracheostomy tubes and vascular ulcers result in infection. Though ulcers can be prevented, managing the patient with endotracheal or tracheostomy is unavoidable in many situations. Therefore, additional emphasis is needed for infection control. These patients need to stay for a longer time in the hospital. A systematic review revealed that the cost of treating MRSA infection is high. Though hospitalization cannot be completely eliminated, the hospital must take necessary measures to reduce the duration of hospitalization and avoid repeated admissions.

Limitation
The study conducted at a single center with convenient sampling lacks the generalizability. Perhaps further studies are required covering diverse geographical and clinical areas which may help in developing appropriate guidelines to prevent MRSA infection.

Conclusion
We identified that the damage to the skin and mucosal barriers such as undergoing surgical procedures and the existence of pressure or venous ulcers increase the risk of acquiring MRSA infection. Prolonged length of hospital stay and the history of recent hospitalization...
are the other risk factors. In addition, tracheostomy escalates the threat of MRSA infection in wounds of patients admitted to the hospital. Hence, controlling these risk factors may help in reducing the burden of infection.

Conflict of interest
The authors declare that they have no conflict of interests.

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