Risk factors related to methicillin-resistant *Staphylococcus aureus* infection among inpatients at Prof. dr. R. D. Kandou general hospital Manado

H T Utomo*, A Nugroho¹, and P N Harijanto¹

¹Tropical & Infection Disease Division, Departement of Internal Medicine, Faculty of Medicine, Sam Ratulangi University – Prof. dr. R. D. Kandou General Hospital, Manado, North Sulawesi, Indonesia

*Corresponding author: gran4marin3@gmail.com

**Abstract.** Methicillin-resistant *Staphylococcus aureus* (MRSA) presents nosocomial infection problems in hospitals. Identification of risk factors related to MRSA infection is a concern among healthcare provider. A retrospective case-control study was conducted to identify MRSA infection proportion among isolates, also to identify risk factors among inpatients at Prof. dr. R. D. Kandou General Hospital, Manado. Data were from the medical record, from patient’s culture isolates with positive *Staphylococcus aureus* infection from January-December 2015. Case subject isolated cultures of MRSA and control subject isolated cultures of non-MRSA. Bivariate analysis were performed in 10 independent variables (age, length of stay, prior use of antibiotics before cultures, history of HIV infection, prior use of corticosteroid, history of malignancy, history of chronic disease, prior use of medical tools (catheter, ventilator, etc), history of invasive medical procedure, history of hospitalization before). All variables with a *p*-value<0.05 were into multivariate analysis with forward stepwise logistic regression. Mean subjects age were 48.13 ± 2.05 years old and length of stay were 8.65 ± 0.25 days, and only prior antibiotic use-variable were considered statistically significant (*p* = 0.017; OR 1.889; 95%CI 1.595 – 2.238).

1. **Background**

*Staphylococcus aureus* is a leading cause of health-care associated infections. These isolates are generally resistant to multiple antibiotics, thus make available therapeutic options are limited. Methicillin-resistant *Staphylococcus aureus* (MRSA) is a formidable bacterial pathogen responsible for a variety of infections commonly seen in patients at all ages.[1] MRSA have acquired resistance to methicillin and other beta-lactam antibiotics via the mecA and mecC genes.[2] MRSA presents major nosocomial infection problems in hospitals, which may increase patient’s mortality and morbidity numbers.[3] In the past two decades, there has been a dramatic change in the epidemiology of MRSA. Prevalence of MRSA-strain in isolates among inpatients in many American and European hospitals is an increase from 29 – 35%. [4] The most impact from these events rising in antibiotics control program and hospital-excess cost.[5] In Indonesia, MRSA prevention data in hospitals were also rarely reported.[6] Identification of risk factors related to MRSA infection in patients is an important concern among healthcare provider. The purpose is to make some efforts also to prevent and manage those risk factors related to these MRSA infections.[7]
Risk factors related to MRSA infection are patients in advanced age, previous hospitalization, length of stay, admitted intensive care unit, chronic medical illness, prior and prolonged antibiotic treatment, prior surgery, and presences of using the invasive-indwelling medical device.[8] Only a few clinical studies related to these risk factors were conducted in Indonesia, also in other countries still remain controversial.[6] Hence, become our goal in these study to identify risk factors related to MRSA infection in our hospital. The aim of this study was to measure MRSA infection isolates proportion also to identify risk factors in patients who admit to Prof. dr. R. D. Kandou General Hospital, Manado.

2. Methods
This retrospective study used case-control methods. Data were collected from patient’s medical record also from isolate cultures with positive-Staphylococcus aureus infection data from January until December 2015. Case subjects were isolated cultures of MRSA (resistant to methicillin, oxacillin, and cephalotin), and control subjects were cultures of non-MRSA. Data were normalized first with Kolmogorov-Smirnov test. Fisher Exact test were by performing SPSS version 20.0 in 10 independent risk factors-variables (age, length of stay, prior use of antibiotics before cultures, history of HIV infection, prior long time use of corticosteroid medication, history of malignancy, history of chronic disease, presence of using invasive-indwelling medical devices (catheter, ventilator, etc), history of invasive medical procedure, and prior hospitalization before). A p-value of <0.05 was considered statistically significant. All variables with a p-value <0.05 in bivariate analysis were selected in a forward stepwise logistic regression model for multivariate analysis.

3. Results
Between January until December 2015, there were 1466 isolates were collected among inpatients at Prof. dr. R. D. Kandou General Hospitals. From these isolates, 126 isolates with Staphylococcus aureus-positive were in this study. Then, we divided subjects into two groups, 70 MRSA-isolates as case group and 56 Non-MRSA-isolates as a control group (Figure 1). Mean subjects age were 48.13 ± 2.05 years old and mean length of stay were 8.65 ± 0.25 days.

There are many ward section in our hospital, however, we divide into four major hospital ward category (Intensive Care, Intermediate Care, Emergency Departement and Common Hospital Ward). In case of groups, the following numbers of isolates are 2 (2.8%) isolates from Intensive Care, 4 (5.7%) isolates from Intermediate Care, 8 (11.4%) from Emergency Departement, and 56 (80%) from other wards. In control groups, the following numbers of isolates are 4 (7.1%) isolates from Intensive Care, 0 (0%) isolates from Intermediate Care, 2 (3.6%) isolates from Emergency Departement, and 50 (89.3%) isolates from other wards (Table 1).

Number isolates were also drawn from patient’s blood, urine, pus, stool, and other samples cultures. In case of groups, the following numbers of isolates are 39 (55.7%) isolates from blood cultures, 1 (1.4%) isolate from pus culture, 25 (35.7%) isolates from urine cultures, 4 (5.7%) isolates from stool cultures, and 1 (1.4%) isolates from other cultures. In control groups, the following numbers of isolates are 42 (75%) isolates from blood cultures, 0 (0%) isolate from pus culture, 0 (0%) isolates from urine cultures, 12 (21.4%) isolates from stool cultures, 2 (3.6%) isolates from other cultures (Table 1).
Bivariate analysis was performed and stepwise logistic regression using an odds ratio of risk factors were measured to identify which risk factor is the most associated with MRSA infection. The result was shown in Table 2. Since a couple of risk factors component (length of stay and presences of using invasive-indwelling medical devices) are unable to be analyzed. All study subjects have length of stay ≥2 days, also using invasive medical tools (e.g. catheter, intravenous catheter-line, or nasogastric tube insertion, etc), we excluded these couple risk factors from our study. The rest. Independant risk factors-variables (age, prior use of antibiotics before cultures, history of HIV infection, prior use of longtime corticosteroid medication, history of malignancy, history of chronic disease, history of invasive medical procedure, prior hospitalization before) were analyzed then. As the final result, only prior antibiotic use-variable were considered statistically significant (p = 0.017) with OR 1.889; 95% CI: 1.595 – 2.238, among other risk factors.

| Risk Factors | Component | Isolates | Odds Ratio | 95% Confidence Interval | p-value |
|--------------|-----------|----------|------------|-------------------------|---------|
| Age, n (%)   | <60 years old | 52 (74.3%) | 32 (57.1%) | 0.462 | 0.217 – 0.980 | 0.057 |
|              | ≥60 years   | 18 (25.7%) | 24 (42.9%) |           |         |         |
4. Discussion
In this study, among the Staphylococcus aureus-positive isolates, we found that MRSA isolates proportion (55.5%) are higher than non-MRSA (44.4%). Stenstrom et al. reported that MRSA isolates proportion are also higher than non-MRSA-isolates.[9]

Intensive care wards are among the most affected areas, which serves as reservoirs for the dissemination of colonized or infected patients within the hospital.[10] However, from this study, we found only a few isolates with MRSA positives were collected from intensive care ward (ICU, ICCU, and PICU), 2 (2.8%) isolates in the case group and 4 (7.1%) in control group, rather than other ward rooms. It is due to our intensive care ward only have a limited bed, rather than other ward room. Blood isolates were also considered become the most common predisposition for staphylococcal infection, 39 (55.7%) isolates in case groups and 42 (75%) in control group, since as our regulation that these culture isolates, were considered to be first taken among our hospital inpatients with evidence of systemic infection. The first limitation of this study was we were unable to find the source of MRSA acquired the infection, whether it is community-acquired nor is hospital-acquired. Due to we have to conduct a genetic and phenotype test using genomic-sequence typing to determine its source, which still unable to be conducted in our hospital.[10]

In this study, sex is not included as risk factors, whether in some studies, it did not become risk factors for MRSA infection.[11] There are also many risk factors related to MRSA infections appear in some study (e.g. history of contact with MRSA patients before, ethnicity, etc).[12,13] However, these risk factors are unable to be obtained in our study, due to limited data in our medical records.

From this study, only one risk factor (prior antibiotic use) are considered being related to MRSA infection. Oztoprak et al. show that from their study previous antibiotic use become the most risk factor related to MRSA infection (p = 0.037; OR 2.337; 95%CI 1.326 – 4.119).[14] However, we were unable to obtain data for what antibiotic had been being used before, due to limited data from themedical record. Some studies, also, show that treatment of MRSA colonization to decrease the risk of MRSA infection still remain controversial. Prophylactic treatment and eradication of the carrier state were shown to decrease the incidence of infection, however, it may increase the prevalence of more drug-resistant Staphylococcus infections.[15]

5. Conclusion
Risk factor related to MRSA infection among inpatients at Prof. dr. R. D. Kandou General Hospital, Manado is prior antibiotic use. Identification of this risk factor may help us to decrease the rate of MRSA infection, also to show whether the antibiotic-stewardship regulation is effective or not in our hospital. Finally, there is still a lot limitation from this study, which further investigation or more study needs in the future.
References

[1] Chambers H F 2001 The changing epidemiology of Staphylococcus aureus? Emerg. Infect. Dis. 7 178–82
[2] Lowy F D 2015 Staphylococcal infections Harrison’s principles of internal medicine 19th edition pp 954–63
[3] David M Z, Glikman D, Crawford S E, Peng J, King K J, Hostetter M A, Vavra S B and Daum R S 2008 What is community-associated methicillin-resistant Staphylococcus aureus 197 1235–43
[4] Panlilia A L, Culver D H and Gaynes R P 1992 Methicillin-resistant Staphylococcus aureus in US hospitals Infect. Control Hosp. Epidemiol. 13 582–6
[5] Aliberti S, Reyes L F, Faverio P, Sotgiu G, Dore S, Rodriguez A H, Soni N J and Restrepo M I 2016 Global initiative for methicillin resistant Staphylococcus aureus pneumonia (GLIMP): an international, observational cohort study Lancet Infect. 16 30267
[6] Putra M I H, Suwanto S, Loho T and Abdullah M 2014 Faktor risiko methicillin-resistant Staphylococcus aureus pada pasien infeksi kulit dan jaringan lunak di ruang rawat inap Indonesia Internal Med. J. 1 3–14
[7] Price J R, Cole K, Bexley A, Kostiou V, Eyre D W, Golubchik T, Wilson D J, Crook D W, Walker A S, Peta E, Korkmaz A, Eren E and Paul J 2017 Transmission of Staphylococcus aureus between health-care workers, the environment, and patients in intensive care unit: a longitudinal cohort study based on whole-genome sequencing Lancet 17 207–14
[8] Haddadin A S, Fappiano S A and Lipsett P A 2002 Methicillin-resistant Staphylococcus aureus (MRSA) in the intensive care unit Postgrad. Med. J. 78 385–92
[9] Stenstrom R, Grafstein E, Romney M, Fahimi J and Harris D 2009 Prevalence of and risk factors for methicillin-resistant Staphylococcus aureus skin and soft tissue infection in a canadian emergency departement Clin. J. Emerg. Med. 11 430–8
[10] Nicole L E, Dyck B and Thompson G 1999 Regional dissemination and control of epidemic methicillin-resistant Staphylococcus aureus Infect. Control Hosp. Epidemiol. 20 202–4
[11] Grudmann H, Hori S, Winter B, Tami A and Austin D J 2002 Risk factors for the transmission of MRSA in an adult intensive care unit (ICU): fitting a model to the data J. Infect. Dis. 185 481–8
[12] Huang S S and Platt R 2003 Risk of methicillin-resistant Staphylococcus aureus infection after previous infection or colonization Clin. Infect. Dis. 36 281–5
[13] Coello R, Glyn J R, Gaspar C, Picazo J J and Fereres J 1997 Risk factors for developing clinical infection with methicillin-resistant Staphylococcus aureus (MRSA) amongst hospital patient initially only colonized with MRSA J. Hosp. Infect. 37 39–46
[14] Oztoprak N, Cevik M A, Akinci E, Korkmaz M, Erbay A, Eren S S, Balaban N and Bodur H 2006 Risk factors for ICU-acquired methicillin-resistant Staphylococcus aureus infections Am. J. Intens. Care 34 1–5
[15] Coello R, Jimenez J and Garcia M 1994 Prospective study of infection, colonization of carriage of MRSA in an outbreak affecting 990 patients Eur. J. Clin. Microbiol. Infect. Dis. 13 74–81