

Risk Factors Associated with Methicillin Resistance in Hospitalized Newborn Infants with *Staphylococcus aureus* Infection

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Background: An increasing number of infections due to methicillin-resistant *Staphylococcus aureus* (*S. aureus*) have been reported worldwide. To explore the risk factors associated with methicillin-resistance among the neonates with confirmed *S. aureus* infections and thereby to help selection of appropriate empirical antibiotics.

Methods: We compared a group of hospitalized neonates with culture confirmed methicillin-resistant *S. aureus* (MRSA) infections to a group with methicillin-sensitive *S. aureus* (MSSA) based on antimicrobial susceptibility reports. We used multivariable regression analysis to determine the risk factors for neonatal MRSA infections.

Results: There was no difference in the ratio of local to systemic infections or mortality between the two groups. However, the total hospitalization days and the medical care expenses in the MRSA group were significantly increased when compared to that of the MSSA group. Prior use of antibiotics for more than 48 hours was an independent risk factor for neonatal acquisition of MRSA infections, while exclusive breast milk feeding was a protective factor against MRSA infections.

Conclusion: Restrictions on antibiotic abuse and promotion of breast milk feeding may protect newborns from MRSA infections. Prior history of antibiotic use and exclusive breast milk feeding may be important factors to consider in the selection of appropriate empirical antibiotics for use in neonates prior to the availability of the results of antimicrobial susceptibility testing.

Keywords: neonates, methicillin-resistant *Staphylococcus aureus*, protective factor, empirical antibiotics

Introduction

Staphylococcus aureus (*S. aureus*) is one of the most common gram-positive pathogens causing neonatal infections.¹ In the last decades, an increasing number of infections due to methicillin-resistant *S. aureus* (MRSA) have been reported worldwide, especially in developing countries. In Asia, more than half of the *S. aureus* infections in neonates were found to be resistant to methicillin.² We have shown previously that MRSA accounted for 59.8% of all *S. aureus* bloodstream isolates in Chinese NICUs.³ Neonatal infections due to *S. aureus*, especially MRSA, continue to be a major cause of neonatal fatality and increased medical expenditure.^{4,5}

Neonates are at high-risk for *S. aureus* infection because of their immature skin and mucosal defense functions, and the high frequency of invasive procedures during hospitalization. To reduce neonatal mortality caused by bacterial infection, when infection is suspected, it is vital to select appropriate empirical antibiotics prior to the availability of culture and antimicrobial susceptibility results, generally avoiding the unnecessary use of broad-spectrum antibiotics. Furthermore, once preliminary culture results are available, it may take up to one or two additional days before the final antimicrobial susceptibility is determined. Therefore, the first-line empirical antibiotic regimen should be selected based on the most common local pathogens and their historical antimicrobial sensitivity patterns. In the current study, we

compared the clinical characteristics of a group of hospitalized neonates with culture confirmed MRSA infection with a group infected with methicillin-sensitive *S. aureus* (MSSA) in order to determine the potential risk factors for MRSA infection among the neonates with confirmed *S. aureus* infections. These results may inform the selection of appropriate empirical antibiotics before the antimicrobial susceptibility results in the future.

Materials and Methods

Data Collection

This was an observational retrospective cohort study which included newborn infants who were admitted into The Children's Hospital of Fudan University, a National Children's Medical Center in Shanghai, China, from 2012 to 2018. The Department of Neonatology, Children's Hospital of Fudan University, is one of the largest neonatology departments in China, responsible for receiving critically ill neonates in the Yangtze River Delta region of China and even the whole country. Neonates requiring mechanical ventilation, surgery, or more complex interventions are frequently transferred to our neonatal unit. All cultures which grew *S. aureus* were identified through our hospital database, and those from blood, cerebrospinal fluid or infected tissue drainage (eg pustules, abscesses, purulent discharge from the umbilical cord) were included for analysis. Detailed clinical data were retrieved from medical records. If the patient had multiple culture positive for *S. aureus* during the hospitalization, only the first result was included to avoid over-representation. Cases with culture specimen sources from sputum, rectal swabs, and other specimen sources (eg Urine, nasal swab, skin, throat swab) which were most likely due to colonization were considered as colonization and excluded for analysis. Cases with incomplete data were also excluded. Cases with culture confirmed *S. aureus* infection were divided into an MRSA group and an MSSA group. Community-acquired *S. aureus* infection was defined as an isolate from either an outpatient, or an inpatient within 48 hours of hospitalization. Those were the babies who had been discharged home and admitted for a variety of reasons.

Hospital-acquired *S. aureus* infection was defined as culture taken >48 hours after admission. Prior use of antibiotics was defined as having been treated with intravenous antibiotics for more than 48 hours prior to the culture was taken. Transferred from OSH was defined as neonates who were transferred from another hospital to our hospital for further treatment. A waiver for parental consent to review medical records was granted by the Institutional Ethics Committee. Confidential handling of patient data followed the institutional rules strictly and were in compliance with the Declaration of Helsinki.

Bacterial Identification and Drug Susceptibility Testing

S. aureus strain identification was conducted using a MALDI-TOF/MS mass spectrometer (Bruck, Germany) or a VITEK-2 Compact automatic bacterial identification instrument (Mérieux, France). The screen for MRSA and MSSA was either by cefoxitin paper method (30ug, British OXOID) or oxacillin MIC method (AST GP67 Gram-positive bacteria drug sensitivity test card, Mérieux, France). The results were interpreted following the recommendations and definitions of the Clinical and Laboratory Standards Institute (CLSI, 2019). And the quality control strains adopt ATCC29213 and ATCC25923, which were obtained from the Clinical Laboratory Center of Shanghai.

Statistical Analysis

SPSS version 22 (SPSS, Inc., Chicago, Illinois) was used to perform the statistical analysis. Continuous variables were tested for normality using the Kolmogorov–Smirnov test. Non-normally distributed data were expressed by median (25–75 percentile), and the differences between groups were compared by the rank sum test. Categorical data were expressed as numbers or percentages and were analyzed by using the Chi-square test or Fisher's exact test. Multivariable logistic regression was conducted to determine the risk factors associated with infection by a methicillin resistant strain in neonates with confirmed *S. aureus* infection. Factors with $P < 0.1$ in univariate analysis were included in multivariable logistic regression analysis. Before we put these variables into the multivariable logistic regression model, we made a variance inflation factor (VIF), and then all of its VIF are less than 10, indicating that all variables did not have collinearity. Odds ratio (OR) with 95% confidence interval (95% CI) was presented. $P < 0.05$ was considered statistically significant. The goodness-of-fit test of risk factors adopts the Hosmer and Lemeshow test. When $P > 0.05$, it is believed that the risk factors can fit the sample data.

Results

During the study period, a total of 1468 *S. aureus* isolates were identified from specimens sent from our Neonatal Units. Specimens were predominantly from sputum, blood, pus, urine, mucous, and skin swabs. The proportion of MRSA in all *S. aureus* isolates from 2012 to 2018, presented in Figure 1, increased until 2016 when it peaked at 36.8%. After that, the proportion of MRSA decreased gradually and was down to 29.6% in 2018.

After a careful review of the 1468 isolates of *S. aureus* from specimens from newborns, we identified 170 which represented clinical significant infection rather than colonization. Six cases were excluded due to incomplete data, leaving 164 cases that were included for analysis. Among those, 49 were infected with MRSA and 115 were infected with MSSA as the diagram shown in Figure 2. The proportion of MRSA in all *S. aureus* infection was 29.9%, which is similar to the overall proportion of MRSA in all *S. aureus* isolates shown in the Figure 1.

Comparisons of the basic clinical characteristics between the two groups are presented in Table 1. As shown in the table, there were no statistically significant differences in gender, birth weight, gestational age, mode of delivery, multiple birth, maternal preeclampsia, maternal chorioamnionitis, infant of diabetic mother (IDM), and history of surgeries between the MRSA group and the MSSA group. However, when compared to the MSSA group, the MRSA group

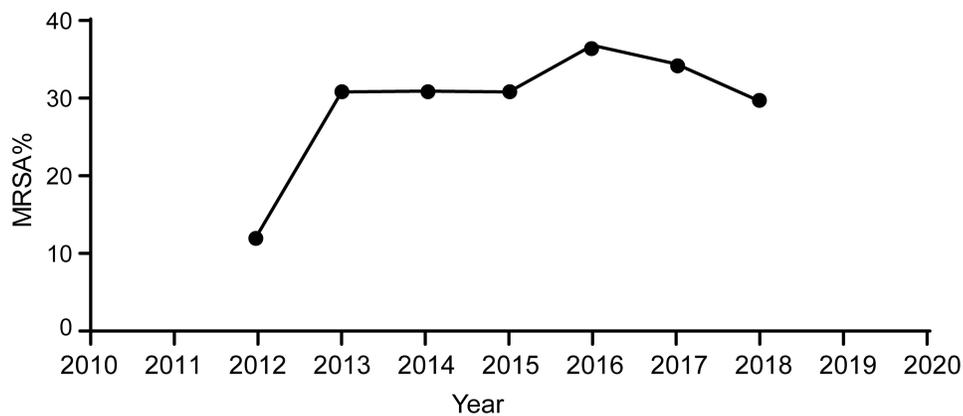


Figure 1 The proportion of MRSA in all *S. aureus* isolates from 2012 to 2018.

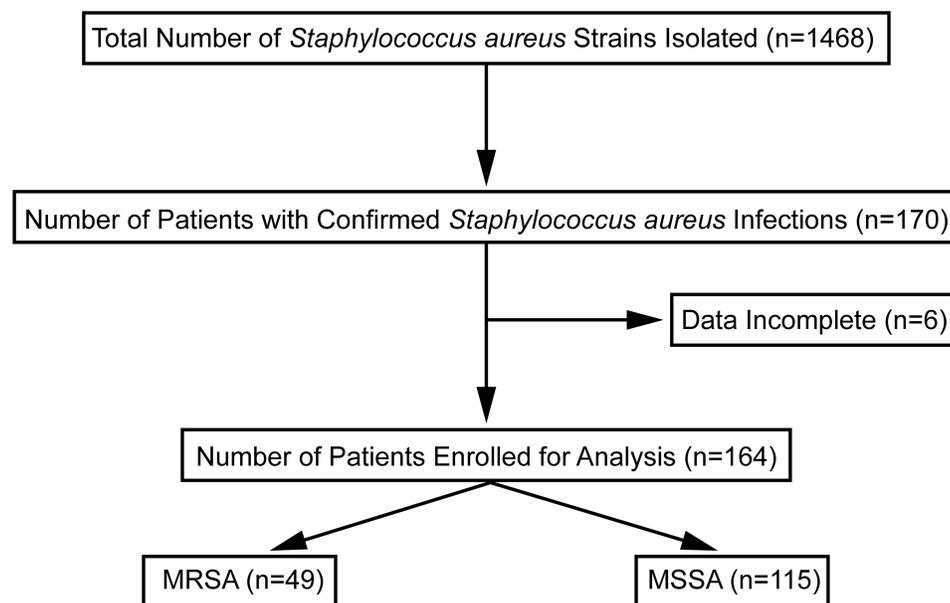


Figure 2 Screening flowchart of research objects.

Table 1 The Basic Clinical Characteristics Between the Two Groups

| | MRSA Group (n = 49) | MSSA Group (n = 115) | P |
|---|--------------------------------|---------------------------------|----------|
| Gestational Age (weeks) | 38.3 (34.2, 39.9) | 39.0 (38.0, 40.0) | 0.05 |
| Birth Weight (kg) | 3.23 (2.25, 3.68) | 3.36 (2.83, 3.69) | 0.548 |
| Male | 17 (34.7%) | 52 (45.2%) | 0.211 |
| Caesarean Delivery | 27 (55.1%) | 62 (53.9%) | 0.889 |
| Multiples | 5 (10.2%) | 7 (6.1%) | 0.549 |
| IDM | 3 (6.1%) | 8 (7.0%) | 1.000 |
| Preeclampsia | 3 (6.1%) | 6 (5.2%) | 1.000 |
| Chorioamnionitis | 0 (0%) | 7 (6.1%) | 0.179 |
| Age at Infection (day) | 18 (14.0, 28) | 12.5 (7.3, 20.0) | 0.001 |
| Hospitalization Days Prior to Infection | 1 (1, 10.5) | 1 (1, 1) | 0.003 |
| Transferred from OSH | 17 (34.7%) | 23 (20.0%) | 0.045 |
| Community Acquired | 27 (55.1%) | 79 (68.7%) | 0.096 |
| Mechanical Ventilation ^a | 10 (20.4%) | 11 (9.6%) | 0.057 |
| Central Lines | 10 (20.4%) | 13 (11.3%) | 0.003 |
| Surgery | 1 (2.0%) | 4 (3.5%) | 1.000 |
| Antibiotic Use Prior | 21 (42.9%) | 24 (20.9%) | <0.001 |
| Exclusive Breast Milk | 13 (26.5%) | 57 (49.6%) | 0.006 |

Note: ^aMechanical ventilation including CPAP.

Abbreviations: IDM, infant of diabetic mother; OSH, transferred from outside hospitals.

had fewer on exclusive breast milk feeding, more with a history of prior antibiotics use for more than 48 hours, and with an older age and longer hospitalization days prior to infection ($P < 0.01$). Furthermore, the proportion of babies transferred from outside hospitals (OSH) and those with central lines were significantly higher in MRSA group ($P < 0.05$). Community acquired infections appeared to be more often seen in the MSSA group, and the rate of mechanical ventilations including CPAP was higher in the MRSA group, but neither has reached a statistical significance with univariate analysis ($P > 0.05$).

Since the infection site or infection type is closely related to the prognosis of patients, the types of *S. aureus* infection and outcomes were compared between the two groups. As shown in Table 2, there was no difference in the ratio of local to systemic infection between the two groups ($p > 0.05$). Looking into the specific types of infection, other than that the MSSA group had higher percentage of skin infections, there were no percentage differences in other types of infection between the MRSA group and the MSSA group. There was no statistically significant difference in mortality between the

Table 2 Comparison of Infection Sites and Clinical Outcomes Between the Two Groups

| | MRSA Group (n = 49) | MSSA Group (n = 115) | χ^2/ Z Value | p |
|------------------------------|----------------------------|-----------------------------|-------------------------------------|----------|
| Local Infections | 30 (61.2%) | 74 (64.3%) | 0.033 | 0.857 |
| Pustules | 3 (6.1%) | 26 (22.6%) | 6.416 | 0.011 |
| Omphalitis | 23 (46.9%) | 44 (38.3%) | 1.071 | 0.301 |
| Cellulitis/abscess | 4 (8.2%) | 4 (3.5%) | 0.772 | 0.379 |
| Systemic Infections | 19 (38.8%) | 41 (35.7%) | 0.066 | 0.797 |
| Bacteremia | 16 (32.7%) | 39 (33.9%) | 0.024 | 0.876 |
| Osteomyelitis | 2 (4.1%) | 1 (0.9%) | | 0.213 |
| Meningitis | 1 (2.0%) | 1 (0.9%) | | 0.510 |
| Mortality | 2 (4.1%) | 7 (6.1%) | 0.020 | 0.887 |
| Hospitalization (day) | 11 (7, 44) | 8 (5.3, 15.0) | -2.785 | 0.005 |
| Expenses (RMB Yuan) | 14,880 (8394, 72,298) | 8851 (4808, 16,040) | -3.611 | <0.001 |

Table 3 Multivariate Regression Analysis of Risk Factors for MRSA Infection

| | β | SE | Wald | P | OR | 95% CI |
|---|---------|-------|-------|-------|-------|--------------|
| Gestational Age (weeks) | -0.016 | 0.078 | 0.044 | 0.834 | 0.984 | 0.845–1.146 |
| Age at Infection (day) | 0.028 | 0.024 | 1.375 | 0.241 | 1.028 | 0.982–1.076 |
| Hospitalization Days Prior to Infection | 0.010 | 0.032 | 0.098 | 0.754 | 1.010 | 0.949–1.075 |
| Transfer from OSH | -0.232 | 0.529 | 0.192 | 0.662 | 0.793 | 0.281–2.239 |
| Community Acquired | -0.110 | 0.441 | 0.063 | 0.803 | 0.896 | 0.377–2.126 |
| Mechanical Ventilation ^a | -0.684 | 0.906 | 0.571 | 0.450 | 0.504 | 0.085–2.978 |
| Central Lines | 0.166 | 0.885 | 0.035 | 0.851 | 1.180 | 0.208–6.688 |
| Antibiotic Use Prior | 1.371 | 0.506 | 7.331 | 0.007 | 3.939 | 1.460–10.625 |
| Exclusive Breast Milk | -1.007 | 0.409 | 6.076 | 0.014 | 0.365 | 0.164–0.814 |

Note: ^aMechanical Ventilation including CPAP.

Abbreviation: OSH, transferred from outside hospitals.

two groups ($P = 0.887$). However, the total hospitalization days and the medical care expenses in the MRSA group were significantly higher than those of the MSSA group ($P < 0.01$).

To determine the risk factors associated with methicillin-resistant strain in newborns with *S. aureus* infection, a multivariable logistic regression analysis was performed. All associated variables with $P < 0.1$ in the univariate analysis were included into the model. As shown in Table 3, the prior use of antibiotics for more than 48 hours was an independent risk factor for methicillin resistance in hospitalized newborn infants with *S. aureus* infection (OR = 3.939, 95% CI:1.460–10.625, $P = 0.007$), while exclusive breast milk feeding was a protective factor against MRSA infection (OR = 0.365, 95% CI:0.164–0.814, $P = 0.014$). None of the other variables were statistically significant in the multivariable regression model.

Discussion

Although numerous antibiotics have been developed to overcome the challenge presented by pathogenic bacteria, infection with *S. aureus*, especially MRSA, in newborns remains an important problem faced by clinicians.⁶ In hospitalized newborn infants, whenever *S. aureus* infections are suspected, appropriate selection of empirical antibiotics is very important to improve the prognosis. Previous studies have shown that the incidence of MRSA correlates with the neonates' history of having received medical therapy.^{7,8} In the current study, we collected data of hospitalized neonates with *S. aureus* infection, and analyzed the risk factors associated with MRSA infection among the neonates with confirmed *S. aureus* infection. We demonstrate that prior antibiotic usage is a strong and independent risk factor for methicillin resistance of *S. aureus* isolated from a neonate, while exclusive breast milk feeding is a protective factor against methicillin resistance.

An increasing number of MRSA are being isolated as the pathogens in neonatal infections in China.³ The current study from one of the largest children's medical centers in China suggests that the proportions of MRSA in either *S. aureus* colonization or serious infection are about 30%. When the clinical differences between the MRSA and MSSA infections were compared, we found that neonates in the MRSA group had longer length of hospitalization days prior to the onset of infection, higher chance of being transferred from OSH, more with central lines, higher percentage of CPAP or mechanical ventilation, and more with prior antibiotic use. As the results, the treatment of MRSA group was associated with higher total expenses for hospitalization, although no significant differences were found in overall infection types as well as mortality between the two groups.

Several factors that were significantly different between the MRSA and MSSA groups by using univariate analysis were confounding factors. Using a multivariable regression analysis, we found that prior use of antibiotics for more than 48 hours was the only independent risk factor for methicillin resistance in hospitalized newborn infants with *S. aureus* infection. *S. aureus* is an opportunistic pathogen,⁹ which is a conditional pathogen that causes infection when human immune function is low or disturbed. The use of antibiotics may act as a selective factor, increasing the risk of infection of resistant strains. The abuse of antibiotics in China has been relatively serious in the past decades, resulting in an

increasing rate of MRSA colonization and infection.^{10,11} In recent years, the country began to pay attention to the abuse of antibiotics, and antibiotic stewardship is being implemented in our hospital. Possibly as a result, the MRSA proportion of *S. aureus* isolates has peaked as demonstrated in our data. However, the incidence of community-related MRSA infections worldwide continues to gradually increase, so restrictions on the unnecessary use of antibiotics require more effort.^{12–14}

Our data demonstrate that exclusive breast milk feeding is a protective factor against MRSA infection. Our results are consistent with the recent findings by others that breastfeeding is an independent preventive factor for MRSA colonization and that MRSA colonization is an independent risk factor for neonatal MRSA infection.^{15,16} In addition to essential nutrients, breast milk also contains a wide range of immune cells and bioactive ingredients with anti-inflammatory, anti-infection and probiotic effects.^{17,18} Breast milk can promote the development of a healthy infant microbiota and immune system through various mechanisms, prevent various infections and reduce the symptoms.¹⁹ Indeed, recent trials from both Finland²⁰ and France²¹ have proven that breastfeeding is closely related to the reduction of antibiotic use, and there is an inverse relationship between the duration of breastfeeding and the frequency of antibiotic use in infants. Decreased colonization by MRSA may be the reason that exclusive breastfeeding is a protective factor against MRSA infection in newborn infants.

Several molecular mechanisms have been elucidated for methicillin resistance of *S. aureus*.^{22,23} We did not perform molecular analysis on any of the isolated MRSA strains. Apart from the commonly known synthesis of modified PBP2a, *S. aureus* resistance to methicillin may also be determined by other mechanisms.^{24,25} One example is the staphylococcal strains referred to as borderline oxacillin-resistant *S. aureus* (BORSA), which do not carry modified PBP2a encoded by the *mecA* or *mecC* gene.²⁶ In our study, BORSA strains, with oxacillin MIC of ≥ 4 $\mu\text{g/mL}$, can fall into the MRSA group. There are other limitations of our study. Due to the nature of an observational retrospective cohort study, the risk factors selected for analysis were not comprehensive enough to include all possible factors. Furthermore, this study is a single-center study with a limited sample size, which may cause bias. It is hoped that a related multi-center study can be conducted in the future.

Conclusions

Our research shows that a prior use of antibiotics for more than 48 hours is an independent risk factor for methicillin resistance in neonates with *S. aureus* infection, while, on the other hand, exclusive breast milk feeding is associated with a lower risk for MRSA infection. The prior history of antibiotic use and exclusive breast milk feeding may be important factors to be considered for appropriate antibiotic selection prior to availability of the antimicrobial susceptibility results. To reduce the risk of MRSA infections in neonatal intensive care units, we need to restrict the abuse of antibiotics in neonates. Furthermore, we should promote breastfeeding for all infants to protect newborns from MRSA infections.

Abbreviations

MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*; NICU, neonatal intensive care unit; CLSI, clinical and Laboratory Standards Institute; VIF, variance inflation factor; OR, odds ratio; CI, confidence interval; IDM, infant of diabetic mother; OSH, outside hospitals.

Data Sharing Statement

The datasets generated during and analysed during the current study are not publicly available due to patient privacy protection but are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

The study was approved by the ethical committee of Children's Hospital of Fudan University, Shanghai, China. This study was conducted in accordance with the Declaration of Helsinki. The data are anonymous, and the requirement for informed consent was therefore waived.

Consent for Publication

Written informed consent for publication was obtained from all authors.

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Author Contributions

All authors made significant contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically important intellectual content; gave final approval for the version to be published; agreed to submit to the current journal; and agreed to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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