Incidence of and Risk Factors For Methicillin-Resistant *Staphylococcus aureus* Bloodstream Infections in a Level III Neonatal Intensive Care Unit

Üçüncü Basamak Bir Yenidoğan Yoğun Bakım Ünitesinde Metisilin Dirençli *Staphylococcus aureus* Kan Dolaşımı Enfeksiyonlarının Görülme Sıklığı ve Risk Faktörleri

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ABSTRACT

Objective: Methicillin-resistant *Staphylococcus aureus* (MRSA) infections are significant causes of morbidity and mortality for the patients in the neonatal intensive care unit (NICU). The identification of risk factors that lead up to the development of MRSA infections is of utmost importance in terms of preventing infections. In this study, we aimed to determine the risk factors of MRSA infections.

Material and Methods: This retrospective study was conducted in a tertiary NICU between 1 st January 2011 and 31 st December 2015. All patients with *S. aureus* isolated in the blood cultures were included. According to the antibiogram pattern, the patients were separated into two groups: MRSA and methicillin-susceptible *Staphylococcus aureus* (MSSA).

Results: Of the 9864 patients admitted to the NICU, 54 had *S. aureus* infection. *S. aureus* infections were more frequent in infants under 1500 g (2.27%) than in infants of 1500 grams and above (0.23%) [OR=10.149, CI: 5.790-17.790, p<0.001]. Forty-three (79.6%) of cases with having *S. aureus* were MSSA and 11 (20.4%) cases were MRSA. Although, MRSA infections were more frequent in infants under 1500 grams, there was no statistically significant association between MRSA and birth weight [OR=1.580, CI: 0.366-6.831, p=0.728]. We found that birth weight, gestational age, sex, SNAPPE score, therapeutic procedures (central venous catheter, total parenteral nutrition, assisted ventilation) and prenatal or empirical antibiotic treatment did not make a significant difference in terms of methicillin resistance.

Conclusion: Very low birth weight is the most important risk factor for *S. aureus* infections in the NICU.

Key Words: Anti-bacterial agents, Central venous catheters, Methicillin resistance, NICU, Very low birth weight

ÖZ

Amaç: Metisilin dirençli *Staphylococcus aureus* (MRSA) enfeksiyonları, yenidoğan yoğun bakım ünitesinde (YYBÜ) izlenen hastalar için önemli bir morbidite ve mortalite nedenidir. MRSA enfeksiyonlarının gelişimine zemin hazırlayan risk faktörlerinin belirlenmesi, enfeksiyonların önlenmesi açısından son derece önemlidir. Bu çalışmada, MRSA enfeksiyonları için risk faktörlerini saptamayı amaçladık.

Gereç ve Yöntemler: Bu retrospektif çalışma, 1 Ocak 2011 – 31 Aralık 2015 arasında üçüncü basamak bir YYBÜ'de yapıldı. Çalışmaya, kan kültürlerinde *Staphylococcus aureus* (*S. aureus*) izole edilen tüm hastalar alındı. Antibiyogram sonucuna göre hastalar iki gruba ayrıldı: MRSA ve metisilin duyarlı *S. aureus* (MSSA). Hastaların demografik özellikleri ile klinik ve laboratuvar bulguları dokümante edildi.

Bulgular: Yenidoğan Yoğun Bakım Üniteleri'ne kabul edilen 9864 hastanın 54'ünde *S. aureus* enfeksiyonu saptandı. *S. aureus* enfeksiyonları, 1500 gr altındaki hastalarda (1542 hastanın 35'i), 1500 ve üzerindeki hastalara (8322 hastanın 19'u) göre daha sık görülmekteydi [p<0.001 IRR=9.94 CI=(5.69 - 17.39)]. Olguların % 79.6'sında (54 hastadan 43'ünde) MSSA, % 20.4'ünde (54 hastanın 11'inde)'ünde ise MRSA suşları tespit edildi. MRSA enfeksiyonları 1500 gr ve altındaki bebeklerde 1500 gr ve üstü bebeklerden daha sık görülmesine rağmen, MRSA enfeksiyonları ile doğum ağırlığı arasında

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Received / Geliş tarihi : 19.03.2019
Accepted / Kabul tarihi : 18.06.2019
Online published : 25.07.2019
Elektronik yayın tarihi
DOI: 10.12956/tchd.542092

istatistiksel olarak anlamlı bir ilişki saptanmadı. Doğum ağırlığı, gebelik yaşı, cinsiyet, SNAPPE skoru, tedavi yöntemleri (santral venöz kateter, total parenteral beslenme, yardımlı ventilasyon) ve kullanılan antibiyotikler (prenatal veya ampirik) metisilin direnci açısından anlamlı bir fark oluşturmadı.

Sonuç: Yenidoğan Yoğun Bakım Üniteleri'nde *S. aureus* enfeksiyonları için en önemli risk faktörü, çok düşük doğum ağırlığına (<1500 gram) sahip olmaktır.

Anahtar Sözcükler: Antibakteriyel ilaçlar, Santral venöz kateter, Metisilin direnci, YYBÜ, Çok düşük doğum ağırlığı

INTRODUCTION

Methicillin-resistant *Staphylococcus aureus* (MRSA) infection is an important cause of morbidity and mortality for infants in the neonatal intensive care unit (NICU) (1-3). It is also one of the common causes of life-threatening, health-care-associated infections in the NICU (4,5). The worldwide prevalence of MRSA infections has been increasing (6). According to the National Nosocomial Infections Surveillance System, between 1995 and 2004, the incidence of late-onset MRSA infections in the NICU increased three times. Many risk factors have been identified for MRSA infections. Immune system immaturity, frequent contact with health care providers, frequent invasive procedures, crowded NICU, and long hospitalization are among these risk factors (7-11). Colonization with MRSA is also a risk factor for infection (4). The identification of the risk factors that lead up to the development of MRSA infections is of utmost importance in terms of prevention.

This study aims to determine the risk factors of MRSA infections in a cohort of neonates, admitted to level-III NICU of a tertiary health care referral center.

MATERIAL and METHODS

This retrospective study was conducted in a tertiary NICU between 1 st January 2011 and 31 st December 2015. The study protocol was approved by the local ethics committee. All patients who were hospitalized between January 1, 2011 - December 31, 2015 and isolated S. aureus in blood culture were included in the study. Patients who had positive blood culture in the presence of clinical features and laboratory findings of infection were given treatment with anti-staphylococcal antibiotics. Patients were divided into two groups as MRSA and methicillin-susceptible *Staphylococcus aureus* (MSSA) according to antibiogram patterns. Demographic characteristics of the patients, and clinical and laboratory information were obtained from the patient files, NICU and electronic medical records. Gestational age, birth weight, gender, birth weight according to gestational age, presence of congenital anomaly, birth mode, multiple pregnancy, resuscitation requirement, Apgar score, score for neonatal acute physiology-perinatal extension (SNAPPE-II), age at positive blood culture for S. aureus, nutritional status, duration of respiratory support, duration of hospitalization, interventional procedures (umbilical catheterization, peripherally placed central catheter insertion, thoracostomy tube placement, and endotracheal intubation), respiratory distress syndrome (RDS), surfactant therapy, patent ductus arteriosus (PDA), intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), premature retinopathy (ROP), bronchopulmonary dysplasia (BPD) were all recorded. On the first day of hospitalization, the SNAPPE-II score was used to assess the disease severity (12).

Positive pressure ventilation (balloon-mask or endotracheal intubation), chest compression, and drug application performed in the delivery room were defined as the need for resuscitation. Infants with a birth weight of less than 10 percentile were accepted as small for gestational age (SGA), infants with a birth weight of above 90 percentile were accepted as large for gestational age (LGA), and infants with a birth weight of between 10 and 90 percentile were accepted as appropriate for gestational age (AGA) (13). Patients with stage 2 or higher disease according to Bell criteria in the presence of specific signs and symptoms were identified as NEC (14). The Papile classification method was used in grading Periventricular - intraventricular hemorrhage (15). According to the National Institute of Child Health and Human Development criteria, patients with a gestational age of <32 weeks at 36 weeks of postmenstrual, and patients with gestational age of ≥32 weeks who were in need of oxygen for longer than 28 days were identified as BPD (16). According to the service protocol, penicillin (Pen G) and aminoglycoside (Gentamycin) treatment were applied for three days until early reproduction signal was reported in the blood cultures, and it was defined as early empirical antibiotic treatment since early-onset neonatal sepsis could not be ruled out in infants under 32 weeks and/or 1500 g. Deaths within 14 days after positive culture were accepted as sepsis related mortality.

The blood which was taken from the vein with a sterile needle after the skin disinfection with the antiseptic solution was placed in BacT/ALERT PF culture bottle (bioMérieux, Marcy l'Etoile, France). *S. aureus* infection was defined as a positive culture from blood in the setting of clinical signs of infection and subsequent treatment with appropriate antimicrobial treatment. Identification and antibiotic susceptibility of microorganisms were performed using the Phoenix (BD) automated identification system, and the results were evaluated in accordance with the recommendations of the Clinical and Laboratory Standards Institute (17). The D zone test was performed clindamycin-sensitive and erythromycin-resistant isolates for the inducible clindamycin test. Taking into account the clinical and laboratory findings of the patients, infections that began 48 hours after the

Table I: The demographic characteristics of all patients with *Staphylococcus aureus* bloodstream infection.

	n=54
Birth weight (g)	1297.5 (1030.0 – 1645.0)*
<1500 g	35 (64.8%)
>1500 g	19 (35.2%)
Gestational age (weeks)	$30^{0/7}$ ($28^{0/7}$ – $33^{1/7}$)*
<$37^{0/7}$, preterm	51 (94.4%)
≥$37^{0/7}$, term	3 (5.6%)
Gender	
Female	20 (37.0%)
Male	34 (63.0%)
Age at diagnosis of infections (days)	14 (8 – 20)*
Duration of hospitalization (days)	48.5 (29 – 80)*
Death within 14 Days of Culture	5 (9.3%)

***Median IQR:** interquartile range*

infection occurred in the hospital were defined as nosocomial infection according to the Centers for Disease Control and Prevention (CDC) criteria (18,19). Nosocomial infection surveillance was performed by a physician and a nurse.

Statistical Analysis

Data analysis was performed by using IBM SPSS Statistics 17.0 (IBM Corporation, Armonk, NY, USA). Whether the distributions of continuous variables were normally or not was determined by Kolmogorov Smirnov test. Continuous variables were shown as mean ± standard deviation or median (interquartile range), where applicable. Number of cases and percentages were used for categorical data. While, the mean differences between groups were compared by Student's t test, otherwise, Mann Whitney U test was applied for comparisons of the not normally distributed data. Categorical variables were analyzed by Continuity corrected Chi-square or Fisher's exact test, where appropriate. Multiple Logistic Regression analysis was applied for determining the best predictor(s) which discriminate MSSA and MRSA groups each other after adjustment for all possible confounding factors. Any variable whose univariable test had a p value <0.25 was accepted as a candidate for the multivariable model along with all variables of known clinical importance. Odds ratios, 95% confidence intervals and Wald statistics for each independent variable were also calculated. A p value less than 0.05 was considered statistically significant.

RESULTS

During the study period, 9864 patients were admitted to our NICU and 1542 (15.6%) of them were very low birth weight (VLBW; <1500 g) infants. The cumulative incidence of *S. aureus* BSI for hospitalized infants was 54 cases per 10000 infants. The demographic characteristics of all patients with *S. aureus* are shown in Table I. *S. aureus* infections were more frequent in infants under 1500 g (35 of 1542 infants) than in infants of 1500 g and above (19 of 8322 infants) [OR=10.149, CI: 5.790-17.790, p<0.001] (Table II).

Characteristics of Infected Patients with *S. aureus*

Thirty-four (63.0%) of 54 cases infected with *S. aureus* were male, 20 (37.0%) of them were female, 51 (94.4%) of them were preterm, and 3 (5.6%) of them were term babies. The birth weights of patients were between 680 – 4130 g and gestational ages were between 234/7- 411/7 weeks. The median hospitalization duration of the patients was 48.5 days (IQR, 29-80). One of our patients died because of Conradi-Hünermann

Table II: Distribution of MSSA and MRSA infections according to birth weight.

Birth weight (gram)	NICU admissions N (% of total admissions)	Number of infections (% of admissions by birth weight)	
		MSSA (n=43)	MRSA (n=11)
<750	152 (1.5%)	3 (2.0%)	0
750 – 999	404 (4.0%)	7 (1.7%)	1 (0.3%)
1000 – 1499	986 (9.9%)	17 (1.7%)	7 (0.7%)
1500 – 2499	3536 (35.4%)	14 (0.4%)	2 (0.1%)
≥ 2500	4918 (49.2%)	2 (0.04%)	1 (0.02%)

***MSSA:** Methicillin-susceptible Staphylococcus aureus, **MRSA:** Methicillin-resistant Staphylococcus aureus, **NICU:** Neonatal intensive care unit*

Table III: The clinical characteristics of patients with MSSA vs MRSA.

	MSSA (n=43)	MRSA (n=11)	p
Gestational age, weeks, (n (%))			
Median (IQR)	30^{0} (26^{6} – 33^{1})	30^{0} (28^{2} – 33^{1})	0.683†
<29	14 (32.6)	3 (27.3)	>0.999‡
29^{0} – 33^{6}	21 (48.8)	7 (63.6)	0.590¶
34^{0} – 36^{6}	6 (14.0)	0 (0.0)	0.327‡
37^{0} – 41^{6}	2 (4.7)	1 (9.1)	0.502‡
Birth weight, (n (%))			
Median (IQR)	1320 (1020 – 1682.5)	1130 (1105 – 1460)	0.830†
<1000 g	10 (23.3)	1 (9.1)	0.426‡
1000-1499 g	17 (39.5)	7 (63.6)	0.186‡
1500-2499 g	14 (32.6)	2 (18.2)	0.474‡
2500-3999 g	1 (2.3)	1 (9.1)	0.369‡
≥4000 g	1 (2.3)	0 (0.0)	-
Male gender, (n (%))	28 (65.1)	6 (54.5)	0.728‡
Born by cesarean delivery, (n (%))	28 (65.1)	10 (90.9)	0.144‡
Birth weight adjusted for gestational age			
Small for gestational age, (n (%))	6 (14.0)	1 (9.1)	>0.999‡
Appropriate for gestational age, (n (%))	35 (81.4)	10 (90.9)	0.667‡
Large for gestational age, (n (%))	2 (4.7)	0 (0.0)	>0.999‡
APGAR score at 5 min. (n (%))			
<7	11 (25.6)	4 (36.4)	0.475‡
≥7	32 (74.4)	7 (63.6)	
SNAPPE score, median (IQR)	17 (9.5 – 32.5)	28 (13.5 – 35.0)	0.311†
Need for resuscitation, (n (%))	22 (51.2)	7 (63.6)	0.688¶
Congenital anomaly, (n (%))	3 (7.0)	2 (18.2)	0.266‡
Frequency of invasive procedures, (n (%))	27 (62.8)	8 (72.7)	0.728‡
Ventilator support, median (IQR)			
Invasive (hours)	24 (24 – 240)	24 (24 – 72)	0.735†
Non-invasive (hours)	96 (48 – 180)	24 (24 – 192)	0.181†
Starting time of enteral nutrition (days), median (IQR)	2 (1 – 3)	2 (1 – 3)	0.845†
Length of parenteral nutrition (days), median (IQR)	15 (10 – 26)	26 (13.5 – 29.3)	0.231†
Age at first positive culture, (days), No (%)	14 (7 – 19)	17 (9 – 24)	0.491†
Median stay of hospitalization (days), (IQR)	46 (28 – 76)	66 (29 – 86)	0.446†
Empirical antibiotics treatment (n (%))	25 (58.1)	7 (63.6)	>0.999‡
Mother Age (year)	27.8 (±6.4)	28.7 (±7.0)	0.671$
Nulliparity (n (%))	23 (53.5)	3 (27.3)	0.224¶
Death within 14 days of culture (n (%))	7 (16.3)	2 (18.2)	>0.999‡
Age at death (days), median (IQR)	16.0 (14-37)	16.5 (4-29)	0.56†
Multiple pregnancy (n (%))	10 (23.3)	1 (9.1)	0.426‡
Prenatal antibiotics treatment (n (%))	4 (9.3)	1 (9.1)	>0.999‡
Antenatal steroid administration (minimum ≥2doses) (n (%))	19 (44.2)	4 (36.4)	0.741‡
Blood transfusion administration	27 (62.8)	6 (54.5)	0.733‡
Clinical presentations			
Skin and soft tissue	17 (39.5)	3 (27.3)	0.510‡
Apnea	15 (34.9)	4 (36.4)	>0.999‡
Fever	8 (18.6)	3 (27.3)	0.676‡
Septic arthritis	1 (2.3)	1 (9.1)	0.369‡
Other site of infection	2 (4.7)	0 (0.0)	>0.999‡

Laboratory parameters			
Leukopaenia (<5 000/mm^3)	2 (4.7)	0 (0.0)	>0.999‡
Leukocytosis (>15 000/mm^3)	24 (55.8)	6 (54.5)	>0.999‡
Thrombocytopaenia (<150 000/mm^3)	12 (27.9)	3 (27.3)	>0.999‡
Elevated CRP (>0.5mg/dL)	38 (88.4)	11 (100.0)	0.571‡
Highly elevated CRP (>20 mg/dL)	20 (46.5)	7 (63.6)	0.499¶
Morbidity			
Patent ductus arteriosus	12 (27.9)	3 (27.3)	>0.999‡
Intraventricular haemorrhage (Grade 3 and 4)	4 (9.3)	2 (18.2)	0.590‡
Necrotising enterocolitis (Stage ≥2)	2 (4.7)	0 (0.0)	>0.999‡
Bronchopulmonary dysplasia	7 (16.3)	2 (18.2)	>0.999‡
Retinopathy of prematurity	6 (14.0)	1 (9.1)	>0.999‡

SNAPPE-II:*Score for Neonatal Acute Physiology, Perinatal Extension, Version II.,* ***†:*** *Mann Whitney U test,* ***‡:*** *Fisher's exact test,* ***¶:*** *Continuity corrected Chi-square test,* ***$:*** *Student's t test,* ***MSSA:*** *Methicillin-susceptible Staphylococcus aureus,* ***MRSA:*** *Methicillin-resistant Staphylococcus aureus,* ***CRP:*** *C-reactive protein,* ***IQR:*** *Interquartile range*

Table IV: The results of multiple logistic regression analysis.

	OR	95% CI		p
		Lower	Upper	
Cesarean delivery	4.291	0.409	45.006	0.225
Multiparity	8.513	0.834	86.896	0.071
Parenteral nutrition	1.049	0.970	1.134	0.228
Duration of non-invasive ventilator support	0.995	0.988	1.003	0.257

OR: *Odds ratib,* ***CI:*** *Confidence interval.*

Table V: Antimicrobial resistance pattern of MSSA vs MSSA.

Antimicrobial agents	Resistant n (%)	
	MSSA (n=43)	MRSA (n=11)
Penicillin	39 (90.7%)	11 (100.0%)
Clindamycin	7 (16.3%)	5 (45.5%)
Erythromycin	11 (25.6%)	5 (45.5%)
Gentamicin	7 (16.3%)	5 (45.5%)
Ciprofloxacin	1 (2.3%)	5 (45.5%)
Cefazolin	7 (16.3%)	8 (72.7%)
Tetracycline	6 (14.0%)	4 (36.4%)
Trimethoprim - sulfamethoxazole	2 (4.7%)	2 (18.2)
Vancomycin	0	0

MSSA: *Methicillin-susceptible Staphylococcus aureus,* ***MRSA:*** *Methicillin-resistant Staphylococcus aureus*

Syndrome at the age of four days. The longest hospitalized patient in the study group was admitted to ventilator therapy due to subglottic stenosis. The median age of initial positive blood culture was 14 days (IQR, 8-20).

Twenty of patients (37.1%) had soft tissue infections (abscess, cellulitis, phlebitis, etc.), 19 (35.2%) had apnea, 11 (20.4%) had fever, 2 (3.7%) had septic arthritis and 2 (3.7%) had other findings (see Table III). The most common invasive procedures were intubation (59.3%) and umbilical vein catheterization (16.7%).

It was determined that during birth, twenty-nine (53.7%) patients underwent aggressive resuscitation, 25 (46.3%) patients received surfactant treatment with due to RDS, 35 (64.8%) patients underwent invasive procedures, 43 (79.6%)

patients needed mechanical ventilation. PDA was detected in 15 (%27.8) of the patients, grade 3 - 4 IVH in 6 (%11.1), stage ≥2 NEC in 2 (3.8%), ROP in 7 (% 13.0) and BPD in 9 (16.7%). Nine (16.7%) of 54 patients died in the study group.

Characteristics of Infected Patients with MSSA vs MRSA

Forty-three (79.6%) cases of *S. aureus* were MSSA and 11 (20.4%) cases were MRSA. Although MRSA infections were more frequent in infants under 1500 g, there was no statistically significant association between MRSA and birth weight [OR=1.580, CI: 0.366-6.831, p=0.728]. The lack of a relationship between MRSA and birth weight may be due to insufficient number of patients. Although the occurrence of MSSA infection was earlier but it was not statistically significant (p=0.491).

Patients with MSSA and MRSA had similar characteristics such as gestational age, birth weight and gender, small for gestational age status or cesarean birth rate (Table III). When the risk factors such as early empirical antibiotic therapy, invasive procedure, blood transfusion ventilator and parenteral nutritional supports were evaluated, there were no significant difference between MRSA and MSSA. Possible risk factors, identified in the univariate statistical analysis, to be effective in distinguishing the MSSA and MRSA groups were then entered into a multivariate logistic regression analysis. None of these factors were found to be independent risk factors (p> 0.05) (Table IV).

There was not significant difference between the two groups in terms of combined morbidity and mortality such as PDA, IVH, stage 2 and 3 NEC, BPD, and ROP (Table III). C-reactive protein levels and white cell numbers were similar in both of the groups (p = 0.571 and p = 0.999, respectively).

Antimicrobial Susceptibility

Resistance rates of the strains to various antimicrobials were shown in Table V. Penicillin resistance was considerably high in both MRSA and MSSA strains (100% vs. 90.7%). A significant number of MRSA strains (72.7%) were also resistant to cefazolin. The resistance to clindamycin, erythromycin, gentamicin and ciprofloxacin was also significantly high in MRSA strains (45.5%).

DISCUSSION

This study is one of the few recent studies investigating the risk factors of MRSA infections in the NICU patients. The prevalence of MRSA infections ranges from 0.6% to 8.4%, depending on the prevalence of MRSA in the community, the MRSA colonization in the NICU and the success of infection control programs (3). We found that the prevalence of MRSA was 0.11% and we did not investigate MRSA colonization, which is a limitation of the study.

In the current study, we found that the proportion of patients with MRSA was 20.4%, a finding that is in accordance with the literature that states an 8% of the proportion in the United Kingdom, and 33% in the United States (20). Limited number of patients and unknown MRSA colonization rates constitute the restraints of this study.

S. aureus is the second most common cause of late-onset sepsis in VLBW infants with birth-weight less than 1500 grams (2). It is also known that VLBW infants are prone to both MSSA and MRSA infections (21-23). Again, consistent with the literature, we found that *S. aureus* infections were more common in infants weighing under 1500 grams. We did not, however, found a significant correlation between birth weight and methicillin resistance.

The more the severity of the disease increases, the more the risk of invasive procedures increases (24). Thaden et al. (1) found that infants with more severe disease to be infected with MRSA at an earlier age. Similarly, in our study, patients with MRSA were found to have higher SNAPPE scores and higher rates of invasive procedures. But they were not statistically significant.

We found that birth weight, gestational age, sex, SNAPPE score, therapeutic procedures (central venous catheter, total parenteral nutrition, assisted ventilation) and antibiotic treatment (prenatal or empirical) did not make a significant difference in terms of methicillin resistance. We need multicenter, large-scale studies to determine the risk factors for MRSA infections. Possible risk factors, identified in the univariate statistical analyzes, to be effective in distinguishing between the MSSA and MRSA groups were then entered into a multivariate logistic regression analysis. None of these factors were found to be independent risk factors. We believe that a larger study sample size may reveal different results.

In bloodstream infections related to *S. aureus*, the mortality ranged from %1 to %17, and our study had a pre-discharge mortality rate of 16.7% (7, 25-28). Thaden et al. (1), reported 3339 infants with *S. aureus* bloodstream infection, and showed that inadequate empirical antibiotic therapy was associated with an increased risk of mortality on day 30. The high rate of mortality at day 30 in our study may be due to inadequate empirical antibiotic therapy.

In conclusion, *S. aureus* infections, especially MRSA infections remain a significant source of morbidity in the NICU population. Very low birth weight is the most important risk factor for S. aureus infections.

Financial Support: No financial support was provided for our study by any sponsoring organization or any for-profit product companies.The authors declare no conflict of interest.

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