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Clinical evaluation of early acquisition of *Staphylococcus aureus* carriage by newborns

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ABSTRACT

Background: Little is known about neonatal *Staphylococcus aureus* carriage. Sites and clinical outcomes of *S. aureus* colonization during the first month of life were evaluated in this study.
Methods: A cohort of 279 infants born at term to 277 mothers was included. Maternal *S. aureus* colonization status was examined before labor. Newborns were screened for nasal, auricular, umbilical, and rectal colonization, one to three times within 100 h after birth, and infants of carrier mothers were re-screened at 1 month. Medical data were recorded from the medical charts at discharge and at the 1-month follow-up interview.
Results: Overall 43 out of 279 (15.4%) infants acquired *S. aureus* within the first days of life. The only two predictors of *S. aureus* carriage in the postnatal period were maternal *S. aureus* carriage (odds ratio 7.905, 95% confidence interval 3.182–19.638) and maternal antibiotic treatment during labor (odds ratio 0.121, 95% confidence interval 0.016–0.949). Among colonized children, the nose (56%) and rectum (40%) were more frequently colonized, while ear (26%) and umbilicus (16%) colonization were less common. Co-colonization at two sites was rare (4%), but always predicted carriage at 1 month of age. Maternal and neonatal characteristics, including neonatal outcomes, were similar between *S. aureus* carrier and non-carrier infants during the first month of life.
Conclusions: Maternal carriage is the major predictor of neonatal *S. aureus* carriage. The nose and rectum are the main sites of neonatal carriage. *S. aureus* carriage was not associated with neonatal complications throughout the first month of life. The long-term significance of early *S. aureus* carriage is yet to be determined.

Introduction

Staphylococcus aureus nasal colonization is considered the source of endogenous infections, including skin and soft tissue infections, as well as invasive infections (Huang et al., 2006; Kluytmans and Wertheim, 2005). Carriage is also the source of transmission between individuals in the community and in hospitals. While *S. aureus* carriage in adults has been studied widely, data on carriage by healthy infants are scarce. Particularly, data on colonization sites, as well as the clinical significance of early *S. aureus* colonization, are lacking.

Studies published more than 50 years ago indicated rapid acquisition of nasal *S. aureus* colonization followed by skin and intestinal colonization in the first days of life (Williams, 1963). The present authors and others have shown that the major source of newborn acquisition of *S. aureus* carriage is maternal *S. aureus* carriage (Peacock et al., 2003; Mitsuda et al., 1996; Regev-Yochay et al., 2009; Huang et al., 2009; Bourgeois-Nicolaos et al., 2010; Chatzakis et al., 2011). It was previously shown by this study group that 42.6% of infants born to *S. aureus* carrier mothers were colonized by 72–100 h after birth, and nearly 70% were colonized

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by 1 month of age; most of them were colonized by the same strain as was carried by the mother (Leshem et al., 2012).

The aims of the current study were specifically to assess *S. aureus* acquisition at different body sites and its role in predicting later carriage in infants, as well as to determine predictors and clinical outcomes of early postnatal *S. aureus* acquisition and carriage at 1 month of age.

Methods

Study population

The study population included a cohort of 279 infants born at term or late preterm (gestational age 35–42 weeks) to 277 mothers at the Sheba Medical Center in Israel, between March 2009 and January 2015. In order to compare children of carrier mothers to those of non-carrier mothers, equal groups of carrier and non-carrier women were recruited.

Screening for Staphylococcus aureus *carriage*

Pregnant women were enrolled in the study and were screened for nasal and vaginal *S. aureus* colonization during routine late pregnancy (third trimester) follow-up and on arrival for delivery. Newborns were screened within 12 h of birth, again at between 12 and 24 h after delivery, and again before discharge (between 24 and 100 h).

Infant screening included nasal, ear, umbilical, and rectal swabs. Screening was performed using a cotton-tipped swab placed in Amies transport medium (Copan Innovation, Brescia, Italy). A mother or an infant was defined as being an *S. aureus* carrier if *S. aureus* was isolated in culture at any of the screening times or sites. Infants of carrier mothers were re-screened for nasal and rectal carriage at their homes at 1 month of age.

Data collection

Data were collected from the medical files and included maternal data and infant data. Maternal data included previous deliveries, antibiotic treatment during pregnancy, prolonged rupture of the membranes (PROM) of >18 h before delivery, meconium-stained amniotic fluid, and delivery mode (partum spontaneous, cesarean section, or instrumental delivery). Infant data included gestational age, birth weight, sex, Apgar score, and overall post labor neonatal complications such as respiratory distress, or cardiac or gastrointestinal manifestations.

At 1 month of age, data were collected from the mother using a standardized questionnaire, which included information about their infant's health during this time period. Specifically, mothers were asked whether the infant had presented any clinical manifestations such as respiratory disease, rash, or diarrhea, and whether the infant had required a medical examination (except well-baby check) or medical treatment.

Staphylococcus aureus *identification and characterization*

All specimens were streaked on CHROMagar *S. aureus* plates (HiLabs, Rehovot, Israel) and incubated for 24–48 h. Suspected colonies were further identified by Gram staining. Gram-positive cocci were tested for catalase and by Staphylase test (PASTOREX STAPH-PLUS, BioRad, France). All isolates were frozen in brain–heart infusion medium with 30% glycerol at −80 °C within 24 h. To determine genetic relatedness between maternal and newborn strains, isolates were thawed and characterized using pulsed field gel electrophoresis (PFGE), as described previously (Leshem et al., 2012). Briefly, digested DNA with SmaI was electrophoresed in 1% agarose gels for 21 h using a CHEF DRII system (Bio-Rad Laboratories).

Spa-typing was performed for 62 of the cases for which PFGE was not available. For spa-typing, DNA was extracted and amplified using the following primers: spaF AGA CGA TCC TTC GGT GAG C, spaR GCT TTT GCA ATG TCA TTT ACT G. PCR products were purified (Gene JET PCR DNA Purification Kit; Fermentas) and Sanger sequencing of the *spa* gene was performed by Hy Laboratories Ltd (Rehovot, Israel). Sequences were analyzed using the Fortinbras SpaTyper (http://spatyper.fortinbras.us/) and Ridom Spa Server (Harmsen et al., 2003).

Maternal strain acquisition by the newborn was defined as acquisition of an *S. aureus* strain that was identical (by PFGE or spa-type) to the maternal strain.

Institutional review board (IRB) and patient consent

The study was approved by the Institutional Review Board of Sheba Medical Center. Written informed consent was given by the mother for herself and for her newborn.

Statistical analysis

Comparisons were performed between carrier mothers and non-carrier mothers, and between carrier infants and non-carrier infants in the postnatal hospitalization period, as well as at 1 month of age. The Mann–Whitney test and Chi-square test or Fisher's exact test were used, as applicable.

To determine independent predictors of infant *S. aureus* carriage in the postnatal period, as well as at 1 month, multiple logistic regression models were applied using a general method of entering variables that were significant in the univariate models (up to a threshold of $p < 0.2$). In addition, to adjust for antimicrobial treatment, this was also included in the logistic models. The following variables were included in the final model for infant carriage in the postnatal hospitalization period: maternal antibiotic treatment during labor, maternal *S. aureus* carriage, and newborn antibiotic treatment during the postnatal period.

In the model for infant carriage at 1 month after birth, the following variables were included: antibiotic treatment for the infant in the postnatal period and in the first month of life, infant's sex, infant's birth weight, and post labor neonatal complications. All statistical analyses were conducted using SAS 9.4.

Results

A total of 295 pregnant women were enrolled during the study period, of whom 277 were included in the final analysis. Eighteen women were excluded because newborn cultures were not available, either because they had delivered at other institutes, or because of missed screening. Initially, carrier mothers were compared to non-carrier mothers (Table 1). The only maternal variable that differed between the two groups was that PROM (>18 h) was more common among carrier mothers. However, a sub-analysis of vaginal *S. aureus* carriage as a predictor of PROM was not significant. The infants born to carrier mothers did not differ from those of non-carrier mothers for any of the variables that were compared. Infant complications were rare and included one infant of a non-carrier mother presenting polycythemia and three infants of carrier mothers, one with transient tachypnea of the newborn and two with polycythemia. None of the four infants with postnatal complications were *S. aureus* carriers in the postnatal screenings.

Overall 43 out of 279 infants (15.4%) screened at least once in the postnatal period (first 100 h of life) acquired *S. aureus* (Table 2). Within the first 12 h of life, 10/202 (5%) infants had acquired *S.*