OUTBREAKS OF METHICILLIN RESISTANT *STAPHYLOCOCCUS AUREUS* IN THE NEONATAL INTENSIVE CARE UNIT LOS ANGELES COUNTY, 2004

BACKGROUND

In the early 1980s, the first MRSA infection in a NICU was reported [1]. MRSA infections became a large problem in NICUs in the 1990s worldwide. Recent reports have been published throughout the United States, Israel, and Taiwan [2]. In Japan, 87% of major NICUs suffered from MRSA infections [3]. A study of 60 NICUs in Japan showed infant admissions had an average MRSA infection rate of 5.1%, with the most prevalent causative bacterium of hospital acquired infection being MRSA (41.9%) [4]. Los Angeles County Department of Health Services, Acute Communicable Disease Control (ACDC) has documented multiple MRSA outbreaks in neonatal intensive care units (NICU).

In 2004, ACDC received reports of nine NICU MRSA outbreaks, compared to one NICU MRSA outbreak reported in 2003. ACDC relies on a passive system of outbreak reporting. Once the report of an increase in MRSA disease is received, an investigation is initiated. This requires establishing a diagnosis and a case definition using consistent criteria.

METHODS

The case definition for inclusion as an outbreak in this investigation was the presence of positive cultures of MRSA from two or more infants residing in a NICU. An infant was determined to be infected when there was a positive MRSA test result from a sterile site, and the infant exhibited clinical signs and symptoms of infection with no other etiologic cause; an infant was determined to be colonized when there was a positive MRSA test result from a non-sterile site, and the infant did not exhibit clinical signs or symptoms of infection. A retrospective review of all 2004 NICU outbreaks was initiated. Los Angeles County has 104 licensed acute care hospitals with 26% (n=27) having a NICU with a total of 640 NICU beds. Basic information was gathered during the early stages of each investigation, e.g. patient identifier, culture site and date. As the investigation progressed, additional data were gathered; however, these data were not standardized from outbreak to outbreak. Significant gaps in essential information were filled with the assistance of public health nurses (PHN) by chart extraction or with the help of the hospital infection control professional (ICP).

When possible, isolates were sent to the Public Health Laboratory (PHL) for molecular analysis by pulsed-field gel electrophoresis (PFGE) (Table 1). Individual DNA fingerprint patterns were produced for isolates using the restriction enzymes *Sma*I *and Eag*I. Standard criteria were employed to analyze the DNA fingerprints [5]. Isolates possessing indistinguishable PFGE patterns were assigned identical PFGE pattern designations. Isolates possessing different PFGE fingerprint patterns (>3 band differences from the outbreak strain) were assigned different PFGE pattern designations.

RESULTS

Case Characterization: The cases numbered 47 infants, 41 (87%) of which were hospitalized since birth. The remaining 6 were admitted from home to the pediatric facility. There were six sets of twins and one set of quadruplets. Of the 35 infants with delivery information, 27 (77%) were delivered by cesarean section (c/s) and 8 (23%) were delivered vaginally. Of the 27 infants who were delivered by c/s, fifty-nine percent (n=16) were from a single birth event (as compared to forty-one percent (n=11) delivered by c/s from a multiple birth event). Eighty-one percent (n=38) of NICU admissions were due to preterm birth[1].

[1] Preterm birth is defined as the birth of an infant before 37 weeks of gestation (at least 3 weeks before the "due date") as defined by CDC Maternal and Infant Health Branch and the March of Dimes.

Forty infants (85%) had either low birth weight[2] or very low birth weight[3] upon admission. Twenty-five percent (n=12) of infants experienced respiratory distress at birth and needed mechanical ventilation to assist with breathing; 21 infants were on a ventilator at the time of MRSA diagnosis. Sepsis, rule out sepsis, and patent ductus arteriosus (PDA) were additional admission diagnoses. Eighty-three percent (n=39) of infants had a history of intubation, arterial lines or surgical procedures. Two of forty-seven infants died, one from MRSA sepsis and one from necrotizing enterocolitis.

Of the 47 MRSA positive infants 60% were colonized (n=28) and 38% were infected (n=18) (Table 1). Culture sites included tracheal aspirate, nasopharynx, umbilicus, blood, rectum, axilla, cheek, and breast milk (Figure 1). Blood, rectum, tracheal aspirate and skin accounted for 90% of the sites cultured. Six infants had positive cultures from skin infections.

Figure 1 . MRSA Culture Site (N=47)

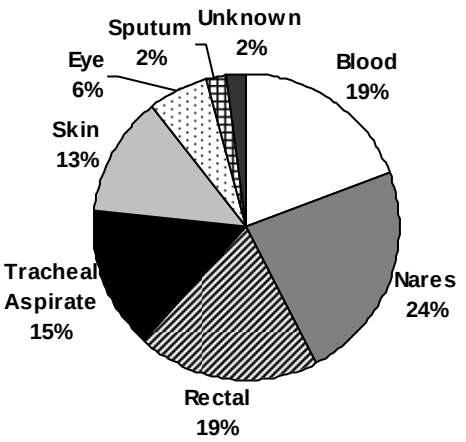

Table 1. Demographic Characteristics of MRSA Case-Patients (N=47)

	n	%
Gender		
Male	21	45%
Female	25	53%
Unknown	1	2%
Gestation		
Term	4	9%
Pre-term	38	81%
Unknown	5	10%
Weight at birth		
Low birth weight	12	25%
Very low birth weight	28	60%
Unknown	7	15%
Invasive Procedures and Lines		
Present	39	83%
Absent	3	7%
Unknown	5	10%
Respiratory Distress at Birth		
Present	12	25%
Absent	4	9%
Unknown	31	66%
MRSA status		
Infection	18	38%
Colonization	28	60%
Unknown	1	2%

The time from NICU admission to positive culture ranged from 2 to 151 days. The reason for culture varied. Most often, a culture was ordered when an infant became symptomatic. If positive, surveillance cultures were ordered on neighboring infants in the unit. At each facility, infants were housed in close proximity to each other. It was not uncommon for infants to be moved from bay to bay within the unit in order to accommodate staffing needs, especially on weekends and during the holiday season. The use of "float" nursing personnel also contributed to patients being relocated.

In addition, two mothers associated with infant cases were breast milk culture positive for MRSA in respective outbreaks. Mother 1 is a 35 year old gravida 2 para 1 who delivered quadruplets via c/s at 29 weeks gestation. She had in vitro fertilization with this pregnancy and the prior pregnancy two years previous. She reported a history of a rash and inflammation of her breasts one day after beginning milk production that reportedly progressed to a lump and was diagnosed as mastitis two weeks after the initial MRSA reports. She also had a methicillin-sensitive Staphylococcus aureus cesarean site infection. Four frozen breast milk specimens, one collected at the hospital on the day of discharge and three collected at home, were MRSA culture positive. Mother 2 is a 28 year old primigravida with an uneventful prenatal course. She was admitted with preterm labor, had spontaneous rupture of the membranes with foul

[2] Low birth weight is between 1501 grams to 2500 grams.
[3] Very low birth weight is 1500 grams or less.

smelling green fluid and had a normal vaginal delivery at 29 3/7 weeks gestation. Breast milk collected the day of delivery was culture positive for MRSA.

MRSA Characterization: The PFGE strain from one of six outbreaks was indistinguishable from the prevailing Los Angeles County CA-MRSA strain, pulsed-field types (PFT) USA 300 (Table 2). At Hospital 1, the MRSA isolate pattern has not been seen previously in the United States and was not common to PFT USA 100-800 [6], but further subtyping at the Centers for Disease Control and Prevention (CDC) showed isolates contain the SCC*mec* IVc gene and PVL toxin. Isolate susceptibility/sensitivity patterns were available for 5 of the 9 outbreaks.

Seasonality: Four of the nine outbreaks had an onset date from September through December 2004.

Maternal Risk Factors: Of the available data, thirty-four comorbidities were identified and categorized as pregnancy-related conditions, infectious processes and general medical conditions. Half were pregnancy related, e.g. gestational diabetes, pregnancy induced hypertension, multiple gestation, and pre-eclampsia. Nine mothers (26%) had an infectious process, including group B Streptococcus infection (n=4), unspecified skin lesions (n=2), and surgical site infection. 8 of 34 had other medical conditions, such as hypertension, pleural effusion and chronic diabetes.

Table 2. Summary of PFGE results by MRSA Outbreak

Hospital	No. NICU Beds	No. Cases	No. Infected	No. Colonized	No. Deaths	Strain Type	Comments
1	52	5	1	4	1	A*, B	*New PFGE pattern in U.S.
2	13	5	3	2	0	C	PFGE Pattern indistinguishable to LAC CA-MRSA PFT 300 strain.
3	33	6	3	3	0	----------	PFGE not performed
4	15	6	5	1	0	D	
5	27	9	1	8	0	----------	PFGE not performed
6	45	2	0	2	0	----------	PFGE data unavailable for pattern comparison
7	9	7	4	3	0	E	
8	6	2	1	1	0	F	
9	10	5	3	2	1	3 G, 2 H	
Total	**210**	**47**	**21**	**26**	**2**		

Treatment/Decolonizations: Decolonization was conducted in only one outbreak (hospital 1). Although none of the household members was confirmed by culture to be colonized, decolonization treatment with mupirocin was completed (mother, father, sibling and cousin) at the request of the family.

Mode of Transmission: We believe that MRSA transmission occurred from mother to infant through breast milk in two outbreaks (Table 1, hospitals 1 and 2), as determined by PFGE testing. We were unable to determine the primary source of transmission in the remaining outbreaks.

Recommendations: All the NICUs implemented standard infection control measures for MRSA (cohorting, dedication of staff and equipment, staff education, contact isolation, strict hand hygiene, proper cleaning procedures, etc.) during the course of the outbreaks. Additional control recommendations included the use of single dose medication vials and dedicated ointments or creams. strict adherence to aseptic technique when doing invasive procedures, and proper cleaning and maintenance of equipment.

DISCUSSION

The number of reported outbreaks of MRSA within NICUs has grown dramatically in Los Angeles County. Since outbreaks are traditionally underreported [7, 8], we estimate that MRSA has become well

established in the NICU population. The literature has identified low birth weight, young gestational age and multiple gestation as risk factors for MRSA colonization and infection in this population [9].

Community-associated MRSA strains have emerged as a significant cause of infection in neonates in the NICU and have caused disseminated infection with substantial morbidity and mortality [10]. Of the four outbreaks reported with molecular subtyping, only one MRSA outbreak strain was indistinguishable from the CA-MRSA prevalent in Los Angeles County (LAC) in such populations as jail inmates and college sports teams, Another outbreak strain carried the PVL toxin and SCC*mec* IV markers consistent with CA-MRSA, though not the common LAC strain. The majority of neonates in the NICU are hospitalized since birth and represent a unique patient population with limited environmental exposure. In two of the reported outbreaks, the index cases probably acquired MRSA through their mothers' breast milk. It is unknown if the index cases in the other outbreaks acquired MRSA from their mother, visitors, or healthcare workers. Since breast milk feedings and skin-to-skin contact between mother and baby are encouraged in the NICU, and these neonates are a vulnerable population, risk factors for CA-MRSA should be assessed for all neonates and their mothers entering the NICU.

In all of the outbreaks described, regardless of the method of acquisition of the index case, the outbreak was probably propagated to other infants within the NICU through poor infection control practices, with the organism being spread by the hands of healthcare workers. Several areas needing improvement were identified including the use of multi-dose medication vials, lapses in asepsis, and improper cleaning of equipment. Proper hygiene procedures need to be emphasized.

Two ACDC recommendations, in collaboration with the ICPs, resulted in permanent hospital policy change. One facility implemented a policy and procedure on breast milk collection, storage, and utilization after breast milk was implicated as the source of transmission. Another facility initiated a review of its eye medication procedure during the outbreak investigation; it looked at multi-use solutions used to prepare the medication and changed the process from multi-use solutions to preparing individual doses.

CONCLUSION

This retrospective study describes nine MRSA outbreaks in NICUs within a twelve month period in Los Angeles County. It is the initial endeavor to document an emerging trend seen in this fragile population. Although the primary source of transmission was not identified in seven of nine outbreaks, research shows that subsequent transmission is usually the result of poor infection control practices by health care workers. Molecular epidemiological tests such as PFGE may characterize *S. aureus* strain patterns and help differentiate between hospital acquired and community-associated MRSA [11]. This distinction provides crucial guidance to clinical practitioners in diagnosis and treatment modalities, and directs future MRSA prevention efforts. Further studies that incorporate the complex factors that impact MRSA infection -- prenatal care and history of skin lesions, household history of skin lesions, labor and delivery, multiple gestation, post-partum infections, breast milk transmission, etc. – are needed.

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