

Containment of a Methicillin-resistant *Staphylococcus aureus* (MRSA) Outbreak in a Neonatal Intensive Care Unit

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ABSTRACT: **Background:** Methicillin-resistant *Staphylococcus aureus* (MRSA) has emerged as a challenging nosocomial pathogen in the last 50 years.

Objectives: To describe an investigation and containment of an MRSA outbreak in a neonatal intensive care unit (NICU).

Methods: Our NICU is a 25-bed level III unit. Almost 540 neonates are admitted yearly. The index case was an 8 day old term baby. MRSA was isolated from his conjunctiva. Immediate infection control measures were instituted, including separation of MRSA+ carriers, strict isolation, separate nursing teams, and screening of all infants for MRSA. Healthcare workers and parents of positive cases were screened and re-educated in infection control measures. New admissions were accepted to a clean room and visiting was restricted. MRSA isolates were collected for molecular testing.

Results: MRSA was isolated from five infants by nasal and rectal swabs, including the index case. Screening of healthcare workers and families was negative. Two MRSA+ patients already known in the pediatric intensive care unit (PICU) located near the NICU were suspected of being the source. All NICU isolates were identical by pulsed-field gel electrophoresis but were different from the two PICU isolates. The NICU and one of the PICU isolates were defined as ST-5 strain by multilocus sequence typing. One PICU isolate was ST-627. All NICU isolates were Pantone–Valentine leukocidin negative and SCCmec type IV. No further cases were detected, and no active infections occurred.

Conclusions: A strict infection control policy and active screening are essential in aborting outbreaks of MRSA in the NICU.

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KEY WORDS: methicillin-resistant *Staphylococcus aureus* (MRSA), neonatal intensive care unit (NICU), staphylococcus

Methicillin-resistant *Staphylococcus aureus* (MRSA) has emerged as a challenging nosocomial pathogen in the last 50 years, since its description in the early 1960s [1]. The first neonatal case was published almost 20 years later [2]. Since then, rates of nosocomial infections with this pathogen have risen

[3–7]. In 2009, Lessa and colleagues [8] reported a 308% rise in MRSA infections among patients in the neonatal intensive care unit (NICU) during a 10 year period (1995–2004). The transmission rate can be high, as was demonstrated by Song et al. [9], with almost 70% of patients acquiring MRSA in the NICU, and a continuous outbreak for 4 years despite infection control measures. The consequences of colonization with high rates of infection and influence on morbidity and mortality can be devastating for vulnerable preterm neonates [10]. The economic burden of MRSA infections is also high [11].

During a 1 month period in March 2012, our NICU experienced an outbreak of MRSA. In this article, we describe the infection control measures of successful early control and containment of the outbreak by collaboration between the NICU staff, the pediatric infectious diseases unit and the microbiology laboratory, and through implementing aggressive infection control methods.

PATIENTS AND METHODS

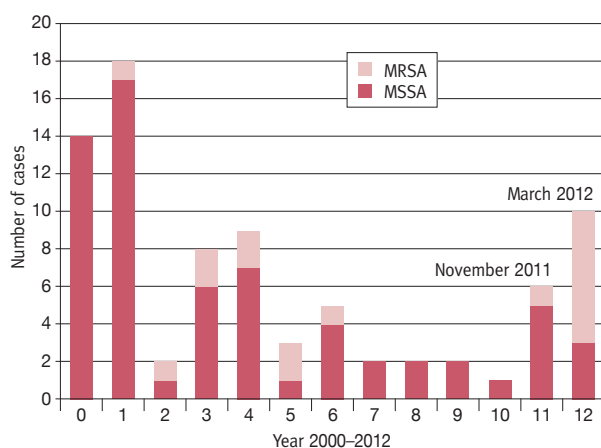
Rambam Health Care Campus is a tertiary hospital in northern Israel. During the outbreak period, its level III NICU had 25 beds and was fully occupied at that time. The unit was composed of three spaces. The main space had nine beds for critically ill neonates. Two rooms with eight beds each served intermediate care cases. Almost 540 neonates are admitted each year, 1% have birth weights less than 500 grams, and 24% weigh less than 1500 grams. There are 45 referrals each year (mainly for major surgery or congenital heart anomalies). Nurse to patients ratio is 1:4 in the intensive care room and 1:5 in the intermediate care room. The index case was an 8 day old term baby. MRSA was isolated from his conjunctiva. There is now a new hospital building and the NICU is arranged differently.

Screening for MRSA is conducted for each admission from another hospital and at admission for patients whose mother had MRSA in the past.

DEFINITION OF AN EPIDEMIC

Between the years 2006 and 2011, MRSA was not isolated from any site in our NICU [Figure 1]. In 2011, there was a single case of MRSA isolated from sputum and later from the nares

Figure 1. *Staphylococcus aureus* in Rambam neonatal intensive care unit, 2000–2012



MRSA = methicillin-resistant *Staphylococcus aureus*, MSSA = methicillin-sensitive *Staphylococcus aureus*

and throat. This infant was immediately transferred to a general pediatric isolation room. No other cases were detected in the NICU for the following 14 months. The cases in the currently described outbreak occurred during one month. No cases were detected within extended periods before or after this period in a range of almost 3 years. Thus, it was defined as an outbreak despite the small number of cases.

INFECTION CONTROL STRATEGY

The infection control team began an immediate investigation and emergency policy, including identifying MRSA positive cases and strict isolation using separate rooms and contact precautions. Gloves and gowns were used only once for each patient and were disposed of after any contact with infants with MRSA. All MRSA-positive neonates were kept in isolation until discharge. A separate nursing team treated the MRSA-positive neonates, without entering other areas of the NICU where other patients were cared for.

Three spaces were created:

1. MRSA-positive cases only
2. Clean room only for patients who were admitted after the first case of MRSA was isolated
3. Intermediate place for children who were together with positive cases, until proven to be negative (3 samples)

The special isolation room was in one of the intermediate rooms and there were no ventilated infants.

SCREENING POLICY

All patients in the NICU were screened for MRSA. Samples were collected using Amies swabs (Copan Italia, Brescia, Italy)

from nares, axilla, groin, and anus for each case. Screening of the umbilical area was not attempted. Swabs were cultured on CHROMAGAR MRSA plates (Hy Laboratories, Rehovot, Israel). Suspected colonies were verified using Vitek 2 (bioMérieux, Marcy l'Etoile, France). Screening was repeated three times weekly until one month after the last colonized infant was discharged. Patients who tested positive were moved to a special isolation space.

All healthcare workers and parents of the index case were screened by nasal swabs when the first case was detected. This was not repeated during the management of the outbreak.

Doctors were asked to treat infants with gowns and gloves. New urgently admitted newborns were placed in a separate space in the NICU. Unconfirmed cases that were in contact with the positive cases but were negative during the first screening round were placed in a separate room with contact precautions but without dedicated nursing staff and were defined as free of MRSA after three consecutive screenings. Re-education of infection control measures and hand hygiene was reinforced on a daily basis by the infection control staff. A daily update was reported to all involved teams and families.

The NICU was intended to be closed for new admissions until all colonized infants were detected and isolated. However, due to limited capacity in other hospitals, new admissions continued throughout the whole period. Visiting was restricted to parents only.

MOLECULAR TYPING

Genetic relatedness was determined by pulsed-field gel electrophoresis (PFGE) [12]. In addition, the corresponding multilocus sequence typing (MLST) clonal complex was assigned [13]. The Panton-Valentine leukocidin (*pvl*) gene was tested by polymerase chain reaction (PCR) [14], and SCCmec typing was assigned according to the *mec* and *ccr* complexes [15].

OUTBREAK SOURCE INVESTIGATION

A search for a common source for the infection was held. Two cases of MRSA were found in the adjacent pediatric intensive care unit (PICU). The first speculation was that MRSA was introduced by common healthcare workers (usually doctors who serve in both units) or by a common non-invasive respirator and common equipment.

USE OF CHLORHEXIDINE AND MUIPIROCIN

Chlorhexidine is not used for premature babies in our institution due to previous reports of toxicity. It was decided that bathing neonates with this agent was not justified. The use of mupirocin was attempted at first, but we found that this material obstructs the very small nostrils and the potential space is too small for any significant instillation of mupirocin, so this procedure was abandoned quickly by the nursing staff.

RESULTS

After a long period with no MRSA cases in our NICU, the first case in the current outbreak was a preterm neonate who was born in our hospital after 33.6 weeks of pregnancy, 2 weeks after premature rupture of membranes with maternal fever. His postpartum screening was negative for bacteria and his general condition was good. On his eighth day of hospitalization, he developed purulent conjunctivitis. A culture from the conjunctival discharge resulted in isolation of MRSA with a pattern of resistance typical for hospital-acquired MRSA (HA-MRSA). It was resistant to oxacillin, gentamicin, clindamycin, and erythromycin and sensitive to vancomycin, linezolid, mupirocin, fusidic acid, rifampin, and trimethoprim/sulfamethoxazole. The patient received local antibiotic treatment for his conjunctivitis and was put in strict isolation. Screening for MRSA from other body sites was positive from the eye, nares, throat, and rectum and negative for axilla and groin [Table 1]. He was discharged 10 days later.

OTHER CASES OF MRSA

Nasal swabs from the parents of positive cases and all NICU staff were negative for MRSA. During a period of 1 month, six other cases were detected. All patients, except the index patient and another one (patient #5) with mild conjunctivitis, were asymptomatic [Table 1].

During the outbreak, 132 neonates were screened and 2010 samples were processed in the 5 month follow-up period after the first case, until the NICU was declared MRSA free again.

MOLECULAR TYPING

PFGE demonstrated the same pattern for all NICU patients, although they were different from that of the PICU patients [Figure 2]. All NICU isolates and PICU patient #2 (a child with burns) were typed as ST-5, while PICU patient #1 was ST-627 type. All isolates in the NICU cases were SCCmec type IV. All isolates were PVL negative. Another three children were found to have unrelated community-acquired MRSA (CA-MRSA) upon admission to the PICU during the screening period.

CONTAINMENT OF THE OUTBREAK

Strict infection control guidelines set for the containment of the MRSA outbreak were maintained for another month after discharge of all MRSA-positive cases. There was no reduction of cases admitted during the same period in the previous year (63 vs. 74). Since then, no MRSA cases have been detected.

DISCUSSION

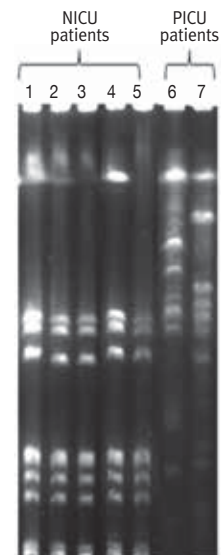
More than 30 years have passed since the first report of MRSA in a NICU. The number of reports has risen through the years, including outbreaks of MRSA colonization and infections [3-8]. Great efforts are made to control the spread of MRSA in the

Table 1. Positive patients (screening) in the NICU and PICU

Patient No.	Nares	Throat	Rectum	Groin	Axilla	Conjunctiva	Other	Date (03/2012)
NICU Patient								
1 (index)	+	+	+			+		4th
2	+	+						6th
3	+	+	+	+				6th
4	+	+	+		+			7th
5		+	+			+		8th
6				+	+			27th
PICU Patient								
1	+	+	+	+	+			
2							Blood, sputum, burn	

NICU = neonatal intensive care unit, PICU = pediatric intensive care unit

Figure 2. Pulsed field gel electrophoresis performed on seven hospital acquired-methicillin-resistant *Staphylococcus aureus* isolates during the outbreak period



NICU = neonatal intensive care unit, PICU = pediatric intensive care unit

NICU due to the huge burden of these infections among highly susceptible patients. Song et al. [11] estimated an increased length of stay and extra charges of \$164,301 per patient with infection compared to those without MRSA. Yet, there have been no specific guidelines for the prevention of this pathogen. In 2006, a research group from the Chicago, IL, USA area published a consensus statement with specific recommendations [7].

We believe that the main issue in outbreak control of MRSA, especially in the NICU, is strict adherence to standard infection control guidelines, without any compromise (i.e., standard precautions on a daily basis and contact precautions when there are indications, as in the case of resistant bacteria). In the current report, our experience in containment of an MRSA outbreak is presented with some aspects that we think may be helpful in halting an outbreak. Early identification of an outbreak is not always easy and depends on the background epidemiology and

alertness of the infection control team. By the time the index case was identified, other cases had already been colonized. This situation reflects the subtle development of clinical cases when the first alert is given.

Teamwork and tight collaboration and communication between the infection control team, NICU staff, microbiology laboratory, and administration is crucial. In the case we present here, a dedicated taskforce was established, including members from the NICU, the pediatric infectious disease unit and infection control, the microbiology laboratory, and administration. Concerned families were transparently updated, and we shared the importance of frequent active screening for seemingly healthy newborns. Concerted activity by a dedicated team is important for control of such outbreaks. Online updates and regular daily communication between teams is also important, as suggested by Gerber and colleagues [7] in their consensus statement.

An optimal screening policy is not known. Using only nasal/rectal cultures would have detected only 66% of our cases, and only 83% of cases would have been detected if we had checked the throat alone. By omitting the groin and axilla, one patient would have been missed in the current series. We did not attempt to sample the umbilical cord area as it was suspected to be heavily colonized by other bacteria. In a cross-sectional study by Matheson and co-authors [16], in a sample of 10,077 cases, 66% were positive using nasal swab alone. Nasal and perineal sites found 82% in combination. In their recommendations, Gerber et al. [7] point out that nasal swabs are sufficient to detect MRSA as a colonizer in the NICU. We agree that frequent screening of multiple sites for a long period of time may not be cost effective or beneficial. It is extremely important to achieve zero tolerance with MRSA colonization, especially in a department free of MRSA, if complete eradication is the goal. Thus, samples were taken frequently from multiple sites to reset a MRSA-free unit as soon as possible.

The cost effectiveness of a screening policy was addressed by Chhangani and colleagues [17], who found 4/2031 screened cases (0.2%) that were positive. Two of these would have been screened with no relation to the study, suggesting that it is not cost-effective. However, missing colonized infants may lead to unrecognized spread and, in time, uncontrolled outbreaks and active infection among vulnerable preterm infants. As Song et al. [11] demonstrated, this situation can lead to high costs and increased morbidity. Another study by Schultz and co-authors [18] compared 59 colonized neonates with 1701 non-colonized neonates [18]. There was no difference in the cost of each hospitalization day, but the colonized patients had longer hospitalization periods and the total excess cost was \$6,901,180.

Isolating patients in a separate space with dedicated nurses 24 hours a day, and setting an intermediate-care room for neonates at risk of being in contact with positive cases was implemented immediately for the current outbreak. The number of people

visiting patients was restricted to parents only. Strict isolation is fundamental to the successful eradication, not only of MRSA, but also of other resistant bacteria. One of the main problems was recruiting sufficient nursing staff, as the NICU is maintained by a very limited number of nurses and the nurse/patient index is very low compared to other developed countries.

In their recommendations, Gerber and colleagues [7] suggested the option of using mupirocin for decolonization. The use of mupirocin is not universally helpful and is usually accompanied by other infection control measures [3,19-24]. In practice, the use of mupirocin was attempted in the first days but soon rejected due to technical problems reported by the nursing team. It was found to be too difficult to use for most premature babies who have small nares and are obligatory nasal breathers; some were already on non-invasive nasal ventilation.

Although the exact source of infection was not identified, molecular typing has demonstrated how complicated the epidemiological situation may be. The first impression was that the source was patients who were heavily colonized and situated in the PICU, very close to the NICU. Yet, PFGE analysis showed that the NICU isolates were identical, as would be expected in a common source outbreak situation, but were completely different from isolates identified in the PICU which were, in fact, different from each other as well.

PFGE is considered highly discriminatory for distinguishing strains of MRSA, but other more convenient technologies have been described, such as spa typing [19] and MLST technology. All of the isolates in the NICU and one case belonging to a child with extensive burns treated in the PICU were ST5. Another isolate from the PICU was ST627. All these HA-MRSA strains were SCCmec type IV and PVL negative. These results also demonstrate the need for more than one test for confirmation of a common source outbreak and meticulous efforts to discriminate between similar isolates, especially during an investigation in an outbreak setting.

CONCLUSIONS

We report on the containment of an outbreak of MRSA in a tertiary NICU using known infection control measures, and with maximal adherence to those guidelines, stressing the need for communication, working in a multidisciplinary team, and using maximal efforts to diagnose and isolate each positive case, without using any decolonization. In summary, strict infection control policy and active screening are essential in aborting outbreaks of MRSA in the NICU.

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Capsule

Flares after withdrawal of biologic therapies in juvenile idiopathic arthritis: clinical and laboratory correlates of remission duration

Simonini and colleagues assessed the time in remission after discontinuing biologic therapy in patients with juvenile idiopathic arthritis (JIA). The authors enrolled 135 patients followed in three tertiary care centers. The primary outcome was to assess, once remission was achieved, the time in remission up to the first flare after discontinuing treatment. Mann-Whitney U test, Wilcoxon's signed rank test for paired samples, chi-square tests, and Fisher's exact test were used to compare data. Pearson's and Spearman's correlation tests were used to determine correlation coefficients for different variables. To identify predictors of outcome, Cox regression model and Kaplan-Meier curves were constructed, each one at the mean of entered covariates. The majority of enrolled patients flared after stopping treatment with biologics (102 of 135, 75.6%) after a median follow-up time in remission off therapy of 6 months (range 3–109 months). A higher probability of maintaining

remission after discontinuing treatment was present in systemic-onset disease compared to the rest of the JIA patients (Mantel-Cox chi-square = 8.31, $P < 0.004$). In analysis limited to children with JIA with polyarticular and oligoarticular disease, patients who received biologics more than 2 years after achieving remission had a higher probability of maintaining such remission off therapy (mean \pm SD 18.64 \pm 3.3 months vs. 11.51 \pm 2.7 months, $P < 0.009$, Mantel-Cox chi-square = 9.06, $P < 0.002$). No other clinical variable was significantly associated with a long-lasting remission. The authors concluded that children with oligoarticular and polyarticular JIA who stop treatment before 2 years from remission have a higher chance of relapsing after biologic withdraw.

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