ORIGINAL ARTICLE

A Decrease in the Number of Cases of Necrotizing Enterocolitis Associated with the Enhancement of Infection Prevention and Control Measures during a *Staphylococcus aureus* Outbreak in a Neonatal Intensive Care Unit

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OBJECTIVE. Most cases of necrotizing enterocolitis (NEC) are sporadic, but outbreaks in hospital settings suggest an infectious cause. Our neonatal intensive care unit (NICU) experienced an outbreak of methicillin-sensitive *Staphylococcus aureus* (MSSA). We aimed to assess whether the enhancement of infection prevention and control measures would be associated with a reduction in the number of cases of NEC.

DESIGN. Retrospective chart review.

SETTING. A 24-bed, university-affiliated, inborn level 3 NICU.

PARTICIPANTS. Infants of less than 30 weeks gestation or birth weight ≤ 1,500 g admitted to the NICU between January 2007 and December 2008 were considered at risk of NEC. All cases of NEC were reviewed.

INTERVENTIONS. Infection prevention and control measures, including hand hygiene education, were enhanced during the outbreak. Avoidance of overcapacity in the NICU was reinforced, environmental services (ES) measures were enhanced, and ES hours were increased.

RESULTS. Two hundred eighty-two at-risk infants were admitted during the study. Their gestational age and birth weight (mean ± SD) were 28.2 ± 2.7 weeks and 1,031 ± 290 g, respectively. The proportion of NEC was 18/110 (16.4%) before the outbreak, 1/54 (1.8%) during the outbreak, and 4/118 (3.4%) after the outbreak. After adjustment for gestational age, birth weight, gender, and singleton versus multiple births, the proportion was lower in the postoutbreak period than in the preoutbreak period ($P < .002$).

CONCLUSION. Although this observational study cannot establish a causal relationship, there was a significant decrease in the incidence of NEC following implementation of enhanced infection prevention and control measures to manage an MSSA outbreak.

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Necrotizing enterocolitis (NEC) is a complex multifactorial illness of unclear etiology affecting primarily the gut of prematurely born infants. Those most at risk are born at less than 30 weeks gestation or no heavier than 1,500 g, with a mean prevalence of 7%.[1,2] Despite early recognition and treatment, NEC accounts for substantial long-term morbidity in survivors; mortality rates are between 15% and 50%, with higher incidence and fatality rates in lower–gestational age (GA) or lower–birth weight (BW) babies.[1,2] A recent review article notes that 20%–30% of infants affected by NEC require surgery.[2] In the 2009 Canadian Neonatal Network, 28% of infants with NEC born at less than 1,500 g required surgery. Other potentially predisposing risk factors, besides prematurity and low BW, include hypoxic-ischemic injury and feeding with formula.[1-3] Feeding regimens may also contribute to the pathophysiology, although large trials with very immature infants are lacking.[4] It is generally believed that most cases of NEC are sporadic, but outbreaks have been documented in the literature.[5,6] Clinical observations during such outbreaks suggest that they are infectious; however, no specific infectious organism has been discovered or linked to outbreak NEC.[5,6] Infection may play an important role in the pathophysiology of NEC by triggering the release of inflammatory mediators, leading to systemic inflammatory response and intestinal cell injury.[2,7] Overcrowding or exceeding capacity in settings such as the neonatal intensive care unit (NICU) may also contribute to outbreaks of NEC, by way of proximity of patients and decreased nurse-to-patient ratio.

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Between October 2007 and February 2008, we experienced an outbreak of methicillin-sensitive *Staphylococcus aureus* (MSSA) in our NICU. An increase in the number of clinical isolates of MSSA was noted between October and December 2007 (in endotracheal secretions [$n = 3$], urine [$n = 1$], discharge from the eye [$n = 1$], and blood [$n = 1$]). This prompted our team to put several measures in place to manage the outbreak, as summarized in Table 1. Ultimately, a total of 26 neonates were affected, the majority (82%) by one of two outbreak strains. Eleven patients were infected (pneumonia and/or bacteremia), while 15 others were colonized.

We observed a decrease in the number of cases of NEC immediately after the MSSA outbreak. The objective of this study was to compare the proportions of NEC before, during, and after the MSSA outbreak to determine whether there was a significant decrease in the incidence of NEC after implementation of enhanced infection prevention and control measures to limit the MSSA outbreak.

METHODS

We performed a retrospective chart review on infants with GA < 30 weeks or BW ≤ 1,500 g admitted to our NICU between January 2007 and December 2008 with a diagnosis of NEC during their admission. Cases were first identified by our unit database, which is part of the Canadian Neonatal Network. The NICU at the Ottawa Hospital, General Campus, is a 24-bed, university-affiliated, inborn level 3 unit with approximately 700 admissions per year. This 2-year study was broken down into three distinct time periods: January–September 2007, before the outbreak occurred (period 1); October 2007–February 2008, during the outbreak, when infection prevention and control measures were enhanced (period 2); and March 2008–December 2008, after the outbreak, during which enhanced infection prevention and control measures continued (period 3). For the purpose of the study, infants transferred to our institution with a preexisting diagnosis of NEC were excluded.

The primary outcome of our study was the proportion of NEC in the at-risk study population (infants with GA < 30 weeks or BW ≤ 1,500 g) before, during, and after the MSSA outbreak. For the purpose of our study, NEC was defined as either (1) confirmed NEC, with pneumatosis intestinalis or portal vein gas on an abdominal X-ray (AXR) in a patient with compatible clinical signs, or (2) clinical diagnosis of NEC (or presumed NEC) based on history, clinical signs, and a physical exam (apneic spells, feeding intolerance, lethargy, and/or frank blood in the stools) in the presence of an equivocal AXR, with medical treatment (nil-per-mouth and intravenous antibiotics) instituted for at least 7 days. The clinical definition was included in the outcome because this scenario is a frequent occurrence in many NICUs, wherein the diagnosis of NEC is suspected but not definitive but babies are treated as if they have NEC. Secondary outcomes included severity of NEC according to modified Bell's staging criteria in the three time periods,[9] the need for a surgical intervention for NEC, mortality, and the length of stay in the NICU.

Sample Size

The study used a convenience sample covering a total of 2 calendar years.

TABLE 1. Description of the Methicillin-Sensitive *Staphylococcus aureus* (MSSA) Outbreak

Time line	Infection prevention and control measures
November 2007	Active surveillance for MSSA began
	Cultures for MSSA from nares, umbilicus, rectum, wounds, and trachea (if ventilated) of all admitted infants
	Alcohol-based hand rub made available at each bedside and at each door of the unit
December 2007	Cohorting of cases (infected and colonized infants); contact precautions for each case (gowns, nonsterile gloves)
	Increased dedicated housekeeping hours (from 8 to 12 hours per day) with a specific focus on the cleaning of patient space after a discharge or transfer
	Enhanced environmental cleaning measures: twice-daily cleaning of surfaces and medical equipment (intravenous pumps, ventilators, and monitors) with a hospital-grade disinfectant (2% hydrogen peroxide, Virox)
	Nasal screening cultures of all staff in the neonatal intensive care unit (NICU), looking for MSSA colonization; 35% of the staff were colonized and were treated with topical mupirocin in an attempt to decolonize them
	Strict adherence to the policy of 24 NICU admissions with a maximum of 26 infants admitted at any time (allowing for short-term observation patients to be briefly admitted) was applied (a review of the bed space allocation in the NICU compared to the 2007 Report of the Seventh Consensus Conference on Newborn ICU Design[8] revealed insufficient bed space for the occupancy levels)
January 2008	One-time thorough environmental cleaning of the entire NICU, including wall-to-wall cleaning of the bed spaces, drawers, floors, and ceilings
	Unused incubators and beds relocated away from the NICU to declutter the unit
	Follow-up cultures of all colonized staff after antibiotic treatment, with a second attempt at decolonization for those with persistently positive cultures
	Temporary relocation of the observation area, for infants admitted for short-term observation
February 2008	Closure of the NICU to any new admissions
March 2008	End of the outbreak with reopening of the NICU

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Statistical Analysis

Baseline characteristics of the included patients were summarized as mean and standard deviation (SD) for continuous variables, as median and range for ordinal variables, and as frequency and percentage for dichotomous variables. As a preliminary step, an unadjusted analysis of the primary outcome (proportion of NEC) was performed with Fisher's exact test. To account for differences in BW and GA, a logistic regression analysis of the proportion of infants who developed NEC was used. With this model, the primary analysis was a test of the hypothesis that the proportion of NEC was different in periods 1 and 3. The study was approved by the Ottawa Hospital Research Ethics Board.

RESULTS

During the study period (January 2007–December 2008), 282 infants with GA < 30 weeks or BW ≤ 1,500 g were admitted to the NICU: 110 between January and September 2007 (period 1), 54 between October 2007 and February 2008 (period 2), and 118 between March and December 2008 (period 3). Their GA (mean ± SD) was 28.2 ± 2.7 weeks, and their BW (mean ± SD) was 1,031 ± 290 g. Baseline characteristics (GA, BW, gender, singleton vs multiple birth) did not differ significantly between periods 1 and 3.

The proportion of infants with NEC was 18/110 (16.4%) in period 1, 1/54 (1.8%) in period 2, and 4/118 (3.4%) in period 3. The proportion was significantly lower in period 3 than in period 1 ($P < .001$) and remained so after adjustment for GA, BW, gender, and singleton versus twin or higher-order multiple birth ($P = .002$; Figure 1). Five cases of NEC were diagnosed on clinical grounds in period 1, 1 in period 2, and none in period 3. The median age (interquartile range) of onset of NEC was 14 (8–19) days in period 1 and 28 (11–65) days in period 3 ($P = .25$).

There were significantly fewer cases of definitive NEC (Bell stage ≥ 2) in period 3 (4/118) than in period 1 (13/110; $P = .021$; Figure 2) This observation remained significant after adjustment for GA, BW, singleton versus twin or higher-order multiple birth, and gender ($P = .021$). There were no significant differences in mortality (1.7% vs 4.5%; $P = .27$), need for surgery for NEC (2 cases vs 3; $P = .68$), or length of NICU stay (54.8 ± 50.6 vs 56.4 ± 28.6 days; $P = .77$) between periods 3 and 1.

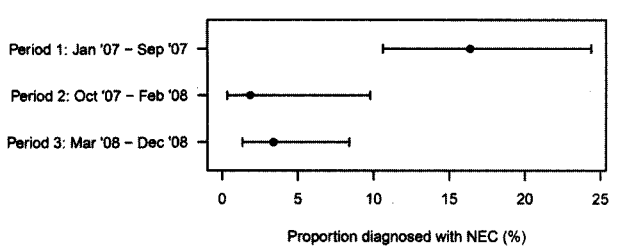


FIGURE 1. Proportion of necrotizing enterocolitis (NEC) in the study periods.

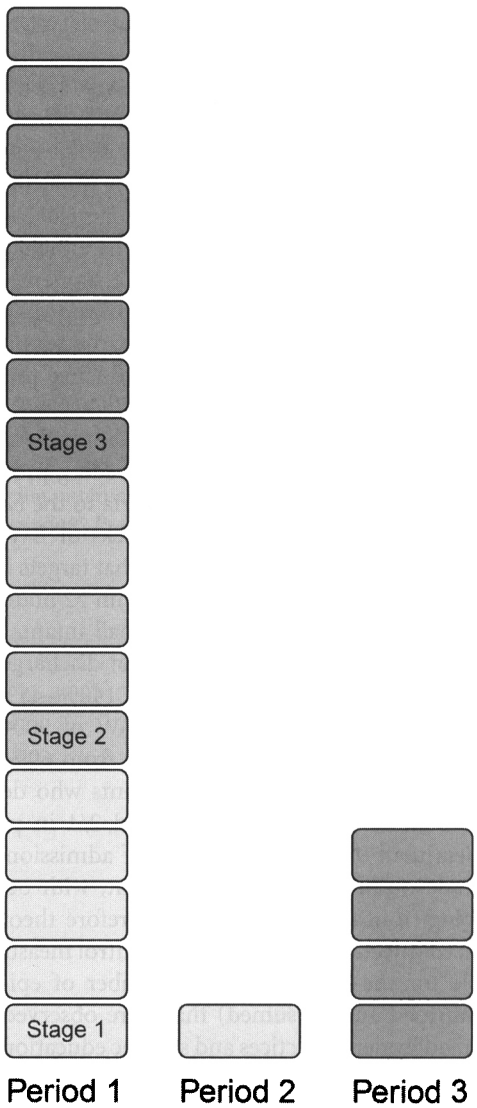


FIGURE 2. Severity of necrotizing enterocolitis during the study periods.

DISCUSSION

To our knowledge, this study is the first to report a decrease in the number of cases of NEC after the enhancement of infection prevention and control measures to manage an outbreak, in this case of MSSA, in an NICU. The etiology of NEC is not completely understood, but it appears to be multifactorial, with intestinal immaturity, hypoxia-ischemia, and microbial colonization mainly contributing to the pathophysiology.[2,10,11] Previous studies suggest the possibility of a role for an infectious agent in the pathogenesis, particularly in outbreaks of NEC, although no single organism has been found to be associated with NEC.[5,7,12,13] Several studies have

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examined possible causative organisms in the context of NEC episodes (sporadic and clusters): coagulase-negative staphylococci, *Clostridium difficile* toxin, other Clostridia species, various gram-negative organisms, and viruses (astrovirus, rotavirus, and norovirus) have been described as possible causative organisms.[5,7,12-14] Recent preliminary studies evaluating fecal microbiota of preterm infants by using molecular methods suggest that NEC is associated with unusual intestinal microbial species.[2,15,16] We speculate that the enhanced infection prevention and control measures we implemented led to decreased colonization of infants (skin and/or gastrointestinal tract) by pathogenic bacteria and a better balance of commensal bacteria in the gut, thus reducing the risk of invasion by pathogens and subsequent NEC.

During the time of the study, basic management (resuscitation, cardiorespiratory support, and feeding protocol) of very-low-BW infants and admission criteria to the NICU did not change. All infants with GA < 30 weeks or BW ≤ 1,500 g are fed according to a feeding protocol that targets increases in feeds of 20–30 mL/kg/d with early (within 72 hours of life) trophic feeds. The proportion of very small infants (<900 g at birth) receiving expressed breast milk at discharge did increase in 2008 (80%), as compared to 2007 (40%–45%); however, the proportion of infants with a BW of 900–1,500 g receiving expressed breast milk decreased from 60% to 50% between 2007 and 2008. Half of the infants who developed NEC in the study (9/18 in period 1 and 2/4 in period 3) weighed less than 900 g. The number of admissions before and after the outbreak remained constant, with occupancy rates ranging from 86% to 96%. We therefore theorize that the enhanced infection prevention and control measures were responsible for the decrease in the number of episodes of NEC (confirmed and presumed) that were observed.

Good hand hygiene practices and specific education around what constitutes the infant's environment in an NICU (isolette, monitors, and equipment attached to the infant) in order to clarify opportunities for hand hygiene were central to our enhanced infection prevention and control measures. The definition of the patient environment is less intuitive in the NICU setting, where there are 3 large areas partitioned by doors, with 4–6 isolettes per area, than in most adult or pediatric inpatient settings. Therefore, specific educational tools were created to educate all healthcare team members as to what constitutes the infant's environment. We speculate that these measures likely reduced transmission of skin bacteria or other pathogens from caregivers' hands to vulnerable infants, who have immature immune systems, immature skin, and foreign bodies (endotracheal tubes, intravenous catheters) as part of their supportive treatment. Likewise, enhanced housekeeping measures and decluttering of the NICU environment might lead to reduced opportunity for equipment colonization by pathogenic organisms. Finally, avoidance of overcrowding and overcapacity, which results in higher nurse-to-patient ratios and decreased proximity between infant beds, reduces the opportunity for transmission of pathogens from one patient to the other via healthcare workers.

The decline in the number of cases was more striking in clinical (or presumed) NEC (5 of 18 cases of NEC in period 1 vs none of the 4 cases in period 3). It is possible that some of these cases were, in fact, missed sepsis rather than NEC. Regardless, the end point is clinically very relevant: after the enhancement of infection prevention and control measures, fewer infants received antibiotics and total parenteral nutrition and intravenous access (often central) while not being fed, for gastrointestinal and other nonspecific signs and symptoms for suspected NEC.

One limitation of this study is the absence of data relating to illness severity scores between the periods, which might have accounted for differences in the baseline risk of developing NEC. The two main risk factors for NEC, GA and BW, were similar in all the periods studied, although we did not account for previous exposure to antibiotics. Another limitation is the retrospective nature of the data, with its inherent potential biases (selection bias, missing data, and undetected changes in practices over time). However, we used strict definitions for NEC, and the time periods covered a relatively short time span, limiting the potential for such biases. A third limitation is that we do not have complete data on the proportion of infants receiving expressed breast milk when they were most at risk of developing NEC, which is around 3–4 weeks of age, or a GA of 31 weeks corrected.

Although this observational study cannot establish a causal relationship, there was a significant decrease in the incidence of NEC following implementation of enhanced infection prevention and control measures to manage an MSSA outbreak.

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