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国外儿科研究  
OVERSEAS PEDIATRIC RESEARCH

## Effects of nosocomial infection trends on neonatal outcomes in preterm infants <33 weeks of gestational age in Canadian NICUs

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**Abstract: Objective** To characterize recent trends of nosocomial infection (NI) among preterm infants admitted to Canadian Level 3 NICUs during 2008-2012, and its association with neonatal outcomes. **Methods** A retrospective observational cohort study was performed including infants born <33 weeks gestational age and admitted to 24 NICU sites participating in the Canadian Neonatal Network<sup>TM</sup> during 2008-2012. NICU sites were classified into three groups according to their baseline NI rates in 2008 [Low NI group ( $\leq 14\%$ ), Medium NI group (14.1%-19%) and High NI group ( $>19\%$ )], and NICU sites were also classified according to their NI trend during 2008-2012 (decreased, null and increased). Trends in NI were further examined for each baseline-NI group. Trends for a composite outcome indicating mortality or severe morbidities (intraventricular hemorrhage grades  $\geq 3$  or periventricular leukomalacia, retinopathy of prematurity stages  $\geq 3$ , bronchopulmonary dysplasia or necrotizing enterocolitis stages  $\geq 2$ ) were examined for each baseline-NI and trend-NI NICU site groups using multivariable logistic regression analyses adjusted for potential confounders. **Results** Baseline high NI group showed significantly decreased trends in NI rates, while for with medium or low baseline NI groups showed no significant trends in NI rates. The composite outcome (mortality during NICU stay or any severe neonatal morbidity such as intraventricular hemorrhage grades 3-4, periventricular leukomalacia, retinopathy of prematurity stages 3-5, bronchopulmonary dysplasia and necrotizing enterocolitis stages 2-3) decreased significantly for sites with decreased ( $OR=0.89$ , 95%  $CI=0.85-0.93$ ) or null ( $OR=0.94$ , 95%  $CI=0.90-0.98$ ) NI trends, but no significant trends in the composite outcome were detected for sites with increased NI rates. **Conclusions** The neonatal outcome is possibly influenced by NI rates and trend. The trend in the mortality and the risk of bronchopulmonary dysplasia, retinopathy of prematurity stage  $\geq 3$  and intraventricular hemorrhage  $>2$  were significantly decreased for sites with decreased NI trend, suggesting that these improved outcomes may be associated with effort to decrease NI rate. [Chin J Contemp Pediatr, 2015, 17(10): 1019-1027]

**Key words:** Nosocomial infection; Outcome; Preterm infant

### 加拿大新生儿重症监护室院内感染及其变化趋势对胎龄 <33 周早产儿预后的影响

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中文概要: 败血症是新生儿重症监护室 (NICU) 的危重病症及造成新生儿死亡的重要原因之一, 根据其发病时间, 可分为早发 (生后 2 d 内) 和晚发 (生后 2 d 后)。其中晚发的新生儿败血症, 一般考虑为院内感染 (NI)。胎龄越小, 出生体重越低, NI 的发生率越高。NI 的发生率在加拿大各 NICU 之间差别较大, 与各中心医护人员的相关诊疗行为密切相关。在国家卫生研究院“基于循证医学的医疗质量改进项目”的推动下, 2003~2009 年间加拿大全国 NICU 总的 NI 率明显下降, 但不同中心各自感染率的变化趋势仍极为不同。本研究纳入了加拿大

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全国共24家NICU在2008~2012年间所有收入院的胎龄<33周的早产儿共18961名,探讨NI率的变化趋势以及其与早产儿预后的关系。

在NICU住院时间超过24h以及在24h内转院或死亡的新生儿都纳入了本研究,但存在严重先天畸形的患儿被排除在本研究外。各中心2008年胎龄<33周早产儿的NI率被定义为基准感染率以进行趋势变化的比较,并根据该年年度NI率,所有NICU被分为低NI组( $\leq 14\%$ ),中NI组( $14.1\sim 19\%$ )以及高NI组( $>19\%$ )。表1和图1列出了各中心的各年年度NI率,以及各自相应的高、中、低NI组别。表2和表3对这些纳入了研究的患儿不同组别之间的临床特征和相关因素进行了分析比较。年度NI率变化趋势的比较采用了Cochran-Armitage趋势检验。各组均采用多元回归分析对可能的干扰因素和高危因素进行了调整。

本研究发现性别、小于胎龄儿或单胎对基准NI率并无影响。但母亲年纪轻、母孕期高血压、绒毛膜羊膜炎、生后第一天需要氧气或肺表面活性物质、脐静脉置管以及中心静脉置管等因素与高NI率相关。进一步结合感染率变化趋势的分析,发现剖宫产娩出、极早早产(胎龄<28周)、低出生体重、小于胎龄儿、出生在非三级医院、5分钟Apgar评分低于7分、单胎以及中心静脉置管超过两周等因素与NI率变化趋势的增高相关。母亲年纪轻、产前激素或抗生素的使用、短时间全静脉营养、生后第一天需要氧气或无创持续正压通气等与NI率变化趋势的降低相关。性别、母孕期高血压、脐静脉置管或中心静脉置管、生后第一天需要肺表面活性物质等因素与NI率变化趋势无关。此外,高NI组的NICU,接下来数年NI率变化趋势有所下降。但类似的改变,并未在中或低NI组发现。感染率变化趋势降低的NICU其新生儿死亡率及严重疾病的发生率也下降,这些疾病包括支气管肺发育不良、严重的早产儿视网膜病变以及严重的脑室内出血。感染率变化趋势未发生改变NICU新生儿死亡率及支气管肺发育不良的发生率也有所降低。在感染率变化趋势增加的中心,本研究并未发现预后有明显改变。

量化NI对NICU新生儿死亡率和严重疾病发生率的影响,对于指导临床诊疗以改善早产儿预后至关重要。NI在早产儿中发生率很高,有数据显示胎龄<26周的早产儿,NI的发生率可高达50%。患有败血症的极低出生体重早产儿其相关疾病的发生率也会增高,这与感染会导致炎症细胞因子释放,并增加机械通气和氧疗的时间有关。本研究证实NI率下降的中心,支气管肺发育不良、严重的早产儿视网膜病变及三级以上的脑室内出血的发生率也同时下降。这些流行病学证据为我们加强控制NI,改善早产儿预后的努力提供了循证医学的支持。本研究同时发现NI率未发生明显变化的中心,早产儿的部分转归也有所改善,这可能与NICU医务人员在控制NI以外的其他方面的努力有关。另外,在NI率上升的中心,死亡率和严重疾病的发生率并未明显增加,可能是因为这些NICU基准NI率就不高。低NI组在2008年后,NI率上升明显,而高NI组则有明显改善,这可能与高NI组在接下来的数年内积极改进了与NI控制相关的诊疗操作工作有关。

综上所述,各NICU胎龄<33周早产儿的预后与NI的发生率以及NI率的变化趋势相关。伴随NI的下降,早产儿死亡率以及严重疾病的发生率也同时下降。因此,严密监测NI并努力预防,对改善早产儿的预后至关重要。

(摘译:姚跃)

## Introduction

Neonates in the neonatal intensive care units (NICUs), especially those born very preterm, are one of the most vulnerable populations with high risk of developing serious complications, such as intracranial hemorrhage (IVH), bronchopulmonary dysplasia (BPD), infections and even death. Infection is the one of the most common morbidities in neonates admitted to the modern NICUs. Infection could be early or late based on the onset of sepsis. Early onset of sepsis occurring less than two days after birth, or late secondary onset sepsis, which typically occurs after two days of life and is considered nosocomial in origin. Nosocomial sepsis rates can vary greatly between hospitals, regions and countries<sup>[1-3]</sup>. Despite continued efforts, the nosocomial infection (NI) rates in NICUs in Canada remain extremely variable

between units<sup>[4-5]</sup>. The impact of this variability on neonatal outcomes has not been evaluated. Previous studies have shown that NI is associated with higher neonatal mortality and morbidity. Rates of NI increases with decreasing birth weight and gestational age, and often relate directly to the actions of health care workers<sup>[3,6-7]</sup>, which can produce large variability in NI trends among hospitals. The cost of NI and associated morbidities is very high for institutions<sup>[8]</sup> with serious long-term effects on infants' health, such as learning difficulties, cerebral palsy, hearing impairment and visual impairment<sup>[9]</sup>.

*Coagulase-negative staphylococci* (CoNS) are the most common pathogens implicated in late-onset sepsis<sup>[10]</sup>. *Staphylococcus epidermidis* is the primary species of CoNS associated with late-onset sepsis in both adult and pediatric patients<sup>[11-14]</sup>. Methicillin resistant *Staphylococcus capitis* is emerging as a

potentially significant pathogen in NICUs, causing late onset of sepsis in very low birth weight infants (VLBW) infants<sup>[14]</sup>. This pathogen is rarely found in adult patients<sup>[15]</sup> and strains in France have been found to show reduced vancomycin susceptibility<sup>[10]</sup>. Other common pathogens responsible for NI in NICUs include *Staphylococcus aureus*, gram-negative organisms, and candida infections<sup>[16]</sup>.

About half of NICU-acquired infections manifest as bloodstream infections but they can also appear as lower respiratory tract, ear-nose-throat and urinary tract infections<sup>[17]</sup>. Complications of prematurity, which can lead to increased rates of NI, include patent ductus arteriosus (PDA), prolonged ventilation, prolonged intravascular access, BPD and necrotizing enterocolitis (NEC)<sup>[16]</sup>. Interventions associated with increased risk of bloodstream infections include central intravascular catheters and receiving total parenteral nutrition (TPN)<sup>[17]</sup>.

Numerous interventions, including more stringent and sterile protocols for placing and maintaining indwelling venous catheters, have been implemented to decrease NI rates associated with medical care and procedures within NICUs in Canada through the Evidence-based Practice for Improving Quality (EPIQ) through CIHR research projects. Implementation of evidence-based guidelines for the prevention of hospital-acquired infections has resulted in reduced overall NI rates in Canadian NICUs from 2003-2009<sup>[18]</sup>. Although the overall NI rate has decreased, Canadian Neonatal Network (CNN) data reveal significant variations in NI trend among Canadian NICUs. Further research is warranted to characterize these trends in NI rates, gain new knowledge about factors contributing to NI, and further delineate the associations of NI to mortality/morbidities in Canadian NICUs.

While surveillance of NI trends in ICUs has been documented for adults, this information cannot be extrapolated to neonates<sup>[17,19-20]</sup>. The objective of this study was to characterize recent trends of NI among preterm infants admitted to Canadian Level 3 NICUs

during 2008-2012, and its association with neonatal outcomes.

## Materials and methods

This observational study examined data from very preterm infants born with gestational age (GA) <33 weeks and admitted to NICUs affiliated to the CNN during 2008 to 2012. At all CNN participating sites, patient information was extracted by trained personnel using standard definitions according to the CNN Data Abstractor Manual. Information was entered into the database and was electronically pooled, stored and checked periodically for accuracy at the CNN Coordinating Center.

For this study, an admission was defined as a stay of >24 hours or death/transfer to another facility within 24 hours. Infants were excluded if born with major congenital anomalies, declared moribund (a decision was made at birth not to provide resuscitative care). We further excluded infants from NICUs with less than 15 infants admitted during any year during the study period.

Early onset of sepsis was defined as when sepsis occurring less than two days after birth, or late secondary onset sepsis, which typically occurs after two days of life and is considered nosocomial in origin.

A composite outcome was defined to indicate mortality (all causes during NICU stay) or any severe neonatal morbidity (intraventricular hemorrhage grades 3-4 or periventricular leukomalacia, retinopathy of prematurity stages 3-5, bronchopulmonary dysplasia or necrotizing enterocolitis stages 2-3).

## Statistical analyses

NICU sites were classified into three groups with equal number of sites according to baseline NI rates during 2008: Low ( $\leq 14\%$ ), Medium (14.1%-19%) or High ( $>19\%$ ) NI groups. The pattern of NI rates was evaluated within each NICU site using the Cochran-Armitage trend test, and NICU sites were

also classified according to their NI trend: decreased [Cochrane-Armitage test  $P \leq 0.2$ ], null [ $P > 0.2$ ] or increased [ $P \leq 0.2$ ]. Since the number of infants with GA  $< 33$  weeks admitted to each site for each year may be too small to be able to detect the trend at the significance level of 0.05, therefore we used 0.2 as the cut-off to group the sites with similar pattern of NI rate. Infant characteristics and treatment procedures were summarized across baseline-NI and trend-NI groups and tested for association using the Pearson Chi-square test and the ANOVA  $F$ -test for categorical variables and continuous measures, respectively.

For each of the three baseline-NI groups [Low group ( $\leq 14\%$ ), Medium (14.1%-19%) and High group ( $> 19\%$ )] and NI trends (decreased, null and increased), NI rates were evaluated using multivariable logistic regression with adjustment for potential confounders and important risk factors. Trends in the composite outcome and each of its components

were tested within each trend-NI group separately using multivariable logistic regression analyses. All statistical analyses were performed using the SAS software, version 9.3 (SAS Institute Inc. Cary, NC), with statistical significance evaluated using 2-sided  $P$  values at the 5% testing level.

## Results

There were a total of 18961 infants that met the inclusion criteria from 24 NICU sites participating in the CNN. Table 1 and Figure 1 reports yearly NI rates of each NICU site during the study period, and indicates the classification of each site according to baseline-NI rate in 2008 and trend-NI during the study period. Tables 2 and 3 show the distribution of infant characteristics and treatments among NICU site groups defined according to baseline-NI rate and the trend-NI, respectively.

**Table 1 NI rates and trends for each participating NICU** [%( $n/N$ )]

Site code	Admission year					Baseline-NI group	$P$ value (trend test)	Trend-NI group
	2008	2009	2010	2011	2012			
A	15.5(9/58)	37.7(23/61)	30.6(19/62)	10.4(7/67)	3.3(3/92)	Medium	$< 0.0001$	Decreased
B	30.5(18/59)	10.5(6/57)	25.0(14/56)	20.3(14/69)	12.1(8/66)	High	0.08	Decreased
C	22.6(40/177)	19.1(37/194)	14.5(25/172)	10.8(20/185)	10.5(19/181)	High	$< 0.0001$	Decreased
D	22.0(27/123)	16.3(21/129)	15.2(19/125)	10.7(13/122)	10.3(13/126)	High	0.004	Decreased
E	16.4(18/110)	20.2(20/99)	14.5(16/110)	13.8(12/87)	8.7(8/92)	Medium	0.06	Decreased
F	20.8(22/106)	12.0(10/83)	11.8(10/85)	11.9(10/84)	11.8(8/68)	High	0.09	Decreased
G	23.3(21/90)	18.0(16/89)	16.9(14/83)	19.5(16/82)	13.5(14/104)	High	0.13	Decreased
H	19.8(49/247)	15.2(42/277)	12.7(35/276)	7.5(22/294)	12.3(48/389)	High	0.001	Decreased
I	18.0(27/150)	27.2(37/136)	21.9(40/183)	20.3(31/153)	11.3(17/150)	Medium	0.06	Decreased
J	20.2(26/129)	22.6(28/124)	21.6(32/148)	17.5(18/103)	12.7(16/126)	High	0.07	Decreased
K	19.4(46/237)	23.8(50/210)	13.6(35/257)	8.6(22/255)	12.2(31/255)	High	$< 0.0001$	Decreased
L	14.0(19/136)	12.4(18/145)	13.8(19/138)	11.2(16/143)	9.2(14/153)	Low	0.2	Decreased
M	10.9(29/266)	12.8(33/257)	11.9(40/337)	18.0(50/278)	7.5(21/281)	Low	0.76	Null
N	5.6(4/71)	2.5(2/81)	4.7(3/64)	4.8(3/62)	4.3(3/70)	Low	0.99	Null
O	15.6(49/315)	12.8(42/327)	16.4(64/391)	19.7(70/356)	12.9(46/357)	Medium	0.83	Null
P	10.0(35/351)	8.5(28/328)	10.0(35/349)	9.7(35/361)	10.2(34/334)	Low	0.77	Null
Q	11.2(26/233)	11.2(24/215)	12.6(27/215)	9.1(19/208)	12.1(25/207)	Low	0.97	Null
R	14.1(26/185)	15.2(34/224)	16.4(35/214)	11.1(18/162)	15.8(28/177)	Medium	0.97	Null
S	16.1(15/93)	11.1(11/99)	9.9(12/121)	16.5(19/115)	18.9(18/95)	Medium	0.31	Null
T	0(0/26)	22.2(10/45)	22.6(7/31)	10.8(4/37)	15.4(6/39)	Low	0.62	Null
U	14.8(19/128)	16.2(22/136)	16.7(16/96)	23.5(23/98)	21.0(21/100)	Medium	0.08	Increased
V	16.0(29/181)	29.9(20/67)	34.4(22/64)	49.3(33/67)	22.9(36/157)	Medium	0.02	Increased
W	6.5(2/31)	6.5(2/31)	3.1(1/32)	21.4(6/28)	10.0(3/30)	Low	0.2	Increased
X	3.6(7/192)	10(31/311)	13.7(43/314)	19.0(52/273)	15.3(43/281)	Low	$< 0.0001$	Increased



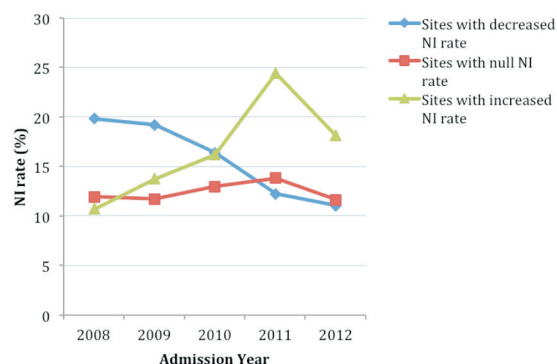


Figure 1 Trends of NI rates for three NI site groups

This figure shows the trends for each of the three NI site groups: sites with decreased NI rate ( $P<0.001$ ), sites with null NI rate ( $P=0.58$ ) and sites with increased NI rate ( $P<0.001$ ).

Interestingly gender, small for gestational age (SGA) or singleton status has no impact on the baseline NI rates in NICUs (Table 2). However, preterm infants born to younger mothers or mothers with hypertension or with chorioamnionitis or infants who needed oxygen or surfactant on day one of life or required umbilical venous or peripherally inserted central catheter (PICC) line were more likely to have high risk of baseline NI in NICUs (Table 2).

Table 2 Distribution of characteristics among baseline-NI rate site groups

Characteristics	Site groups by baseline-NI rate in 2008			P value $\Delta$
	Low ( $\leq 14\%$ )	Medium (14.1%-19%)	High ( $>19\%$ )	
Sites (infants) (n)	8(6 983)	8(5 935)	8(6 043)	
Cesarean [n(%)]	4 235(60.9)	3 316(57.2)	3 530(58.5)	0.0001
Steroid use [n(%)]	5 841(86.9)	4 796(85.2)	5 067(85.7)	0.0244
Maternal hypertension [n(%)]	1 236(18.0)	1 041(18.3)	1 223(20.5)	0.0037
Chorioamnionitis [n(%)]	965(15.6)	663(14.8)	804(18.6)	<0.0001
Antenatal antibiotics use [n(%)]	4 236(62.3)	3 095(55.2)	3 839(66.0)	<0.0001
Maternal age ( $\bar{x}\pm s$ , year)	31 $\pm$ 6	31 $\pm$ 6	30 $\pm$ 6	<0.0001
Birth weight ( $\bar{x}\pm s$ , g)	1 359 $\pm$ 448	1 290 $\pm$ 455	1 334 $\pm$ 456	<0.0001
Gestational age [median (IQR), weeks]	30(27-31)	29(27-31)	30(27-31)	<0.0001
22-28 weeks [n(%)]	2 422(34.7)	2 451(41.3)	2 273(37.6)	<0.0001
29-32 weeks [n(%)]	4 562(65.3)	3 484(58.7)	3 769(62.4)	<0.0001
Gender (male) [n(%)]	3 805(54.6)	3 243(54.8)	3 294(54.6)	0.9759
SGA [n(%)]	673(9.7)	613(10.4)	574(9.5)	0.2476
Apgar score <7 at 5 min [n(%)]	1 866(27.0)	1 524(26.5)	1 348(22.5)	<0.0001
Score for neonatal acute physiology-II >20 [n(%)]	1 104(15.9)	1 058(18.1)	819(13.6)	<0.0001
Singleton [n(%)]	4 712(67.5)	4 076(68.9)	4 067(67.3)	0.1396
Outborn [n(%)]	949(13.6)	1 238(20.9)	907(15.0)	<0.0001
CPAP at day 1 [n(%)]	3 145(45.0)	2 024(34.1)	2 547(42.2)	<0.0001
Oxygen support at day1 [n(%)]	3 333(47.7)	2 991(50.4)	3 374(55.8)	<0.0001
Ventilation at day1 [n(%)]	3 002(43.0)	3 025(51.0)	2 882(47.7)	<0.0001
Surfactant use at day1 [n(%)]	2 726(83.3)	2 594(85.5)	2 740(87.1)	0.0001
Umbilical vein duration [n(%)]				
None	3 590(51.6)	3 060(51.6)	2 945(48.8)	<0.0001
1-14 days	3 267(47.0)	2 820(47.6)	3 056(50.6)	
>14 days	95(1.4)	48(0.8)	39(0.7)	
PICC duration [n(%)]				
None	4 096(59.6)	3 754(63.4)	3 607(59.7)	0.0001
1-14 days	1 571(22.9)	1 030(17.4)	1 410(23.3)	
>14 days	1 203(17.5)	1 136(19.2)	1 023(16.9)	
Total arental utrition duration [n(%)]				
None	2 667(38.2)	2 745(46.3)	2 729(45.2)	0.0001
1-14 days	2 910(41.7)	1 779(30.0)	2 216(36.7)	
>14 days	1 405(20.1)	1 410(23.8)	1 095(18.1)	

Note:  $\Delta$  Chi-square test for categorical variables and the  $F$  test using ANOVA for continuous variables or Kruskal-Wallis test as appropriate. n(%): The denominator for calculating the percentage value is not always the same as the total number of infants in the groups due to missing cases.

The other factors like cesarean-section, premature infants (22-28 weeks), low birth weight, SGA, outborn, Apgar score <7 at 5 minutes, singleton and PICC line duration >14 days had increased trend of NI (Table 3). In contrast, babies born to younger mothers, receipt of antenatal corticosteroids or antibiotics, shorter duration of TPN, need of oxygen or use of CPAP on day one of life had decreased trend of NI in various NICUs (Table 3). However, there

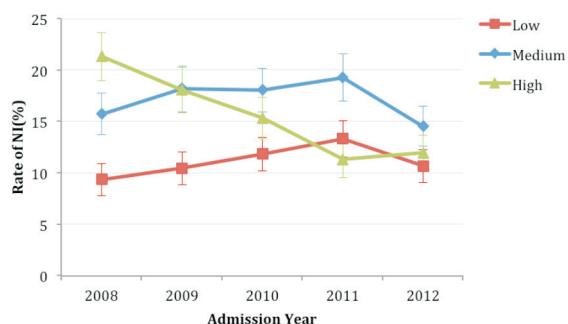
was no effect of maternal hypertension, duration of umbilical venous lines or PICC line catheters or use of surfactant on day one or gender on trend of NI in NICUs affiliated with the CNN (Table 3).

For sites with high baseline NI rates, the trend in NI during subsequent years was decreased; however no significant NI trends were detected for sites with low or medium baseline NI rates (Figure 2).

**Table 3 Characteristics among NI-trend groups**

Characteristics	Site groups by trend in NI rates 2008-2012			P value <sup>△</sup>
	Site with decreased NI rate	Site with Null NI rate	Sites with increased NI rate	
Sites (infants)	12(8368)	8(7967)	4(2617)	
Maternal age ( $\bar{x} \pm s$ , year)	30.4±5.9	31.2±6.0	30.2±5.4	<0.0001
Cesarean [n(%)]	4873(58.5)	4601(58.1)	1607(63.2)	<0.0001
Antenatal steroid use [n(%)]	6893(85.2)	6865(88.1)	1946(81.9)	<0.0001
Maternal hypertension [n(%)]	1594(19.6)	1442(18.4)	464(19.1)	0.1518
Chorioamnionitis [n(%)]	1149(18.8)	1090(15.8)	193(9.2)	<0.0001
Antenatal antibiotics use [n(%)]	5233(65.4)	4657(59.7)	1280(52.8)	<0.0001
Birth weight ( $\bar{x} \pm s$ , g)	1349±458	1321±448	1291±452	<0.0001
Gestational age [median (IQR), weeks]	30(27-31)	30(27-31)	29(27-31)	<0.0001
22-28 weeks	3025(36.2)	3006(37.7)	1115(42.6)	<0.0001
29-32 weeks	5342(63.9)	4971(62.3)	1502(57.4)	<0.0001
Gender (male) [n(%)]	4547(54.4)	4393(55.2)	1402(53.7)	0.3874
SGA [n(%)]	766(9.2)	797(10.0)	297(11.4)	0.0027
Apgar score <7 at 5 min [n(%)]	1975(23.9)	2032(25.7)	731(29.5)	<0.0001
Score for neonatal acute physiology-II >20 [n(%)]	1076(12.9)	1425(18.1)	480(18.5)	<0.0001
Singleton [n(%)]	5721(68.4)	5286(66.4)	1848(70.8)	0.0001
Outborn [n(%)]	1265(15.2)	1108(13.9)	721(27.6)	<0.0001
Umbilical vein duration [n(%)]				
None	4618(55.2)	3345(42.1)	1632(62.4)	
1-14 days	3698(44.2)	4491(56.6)	954(36.5)	<0.0001
>14 days	47(0.6)	104(1.3)	31(1.8)	
PICC duration [n(%)]				
None	5373(64.3)	4585(58.4)	1499(57.3)	
1-14 days	1644(19.7)	1854(23.6)	513(19.6)	<0.0001
>14 days	1344(16.1)	1413(18.0)	605(23.1)	
TPN duration [n(%)]				
None	3778(45.2)	2997(37.6)	1366(52.2)	
1-14 days	2992(35.8)	3229(40.5)	684(26.1)	<0.0001
>14 days	1593(19.1)	1750(21.9)	567(21.7)	

Note: <sup>△</sup> Chi-square test for categorical variables and the *F* test using ANOVA for continuous variables or Kruskal-Wallis test as appropriate. n(%): The denominator for calculating the percentage value is not always the same as the total number of infants in the groups due to missing cases.



**Figure 2 Trends of NI rates within site groups classified according to baseline-NI rate** NI rate decreased over time for High baseline-NI rate site group ( $P<0.0001$ ); NI rate increased over time for Low baseline-NI rate site group ( $P=0.045$ ); No increased or decreased in NI rate over time for Medium baseline NI rate group. After adjustment for gestational age, gender, small (<10th percentile birth weight) for gestational age, Apgar score < 7 at 5 min, score for neonatal acute physiology-II, singleton, outborn status, cesarean delivery, maternal hypertension, antenatal steroid use, maternal antibiotic use and maternal age, only the trend in NI rate for High baseline-NI rate site group remained (adjusted  $OR$ : 1.02 (0.96, 1.09), 0.94 (0.89,1.00) and 0.79 (0.74, 0.84) for Low, Medium and High baseline-NI rate site groups respectively).

Table 4 shows the trends in the adverse neonatal outcomes within each of the three site groups classified according to the trend in NI rate. For example, the trend in the composite mortality/morbidity and BPD significantly decreased for sites with decreased NI trend ( $OR$  of composite outcomes=0.88, 95%  $CI$ =0.84-0.92) or null NI trend ( $OR$  of composite outcomes=0.93, 95%  $CI$ =0.89-0.98). No significant trend in the composite outcome was detected for sites with increased NI rates (Table 4). Similarly, the trend in severe retinopathy of prematurity (ROP) and severe IVH (IVH grade 3) also decreased significantly for sites with decreased NI rate (Table 4).

**Table 4 Trends in mortality, morbidities and the composite outcome within sites classified according to the trend in NI rates** [%( $n/N$ )]

Outcome	Trend-NI Site groups	Admission year					$P$ value $\Delta$	$OR(95\%CI)^*$
		2008	2009	2010	2011	2012		
Mortality	Decreased	7.0(109/1 622)	6.1(98/1 604)	4.4(74/1 695)	6.0(100/1 644)	6.6(118/1 802)	0.91	0.97(0.90,1.05)
	Null	6.2(95/1 540)	5.9(93/1 576)	8.5(147/1 722)	6.8(107/1 579)	6.3(98/1 560)	0.58	0.88(0.81,0.95)
	Increased	7.3(39/532)	7.9(43/545)	10.3(52/506)	13.5(63/466)	8.8(50/568)	0.04	1.13(0.99,1.28)
BPD	Decreased	14.6(223/1 523)	15.0(228/1 514)	16.6(270/1 624)	12.4(192/1 546)	12.2(207/1 693)	0.006	0.91(0.86,0.96)
	Null	19.7(284/1 444)	19.6(290/1 481)	24.7(384/1 557)	22.0(324/1 472)	18.0(263/1 458)	0.81	0.92(0.87,0.97)
	Increased	20.9(95/455)	28.4(142/500)	25.7(118/459)	23.6(96/406)	16.6(86/517)	0.01	0.94(0.87,1.03)
Severe ROP	Decreased	9.5(68/717)	9.3(66/713)	9.6(78/814)	7.3(53/724)	7.8(58/745)	0.1	0.87(0.79,0.96)
	Null	11.3(59/521)	9.9(48/487)	11.0(60/541)	11.7(59/505)	10.9(54/496)	0.84	0.93(0.83,1.03)
	Increased	5.7(15/262)	11.5(33/287)	8.9(26/292)	8.5(22/259)	4.3(12/276)	0.22	0.91(0.77,1.08)
Severe IVH	Decreased	14.4(187/1 294)	15.8(204/1 291)	10.2(142/1 390)	11.4(154/1 355)	11.9(170/1 428)	0.001	0.90(0.85,0.95)
	Null	10.8(112/1 039)	11.5(124/1 077)	12.3(161/1 311)	11.9(151/1 261)	15.6(197/1 265)	0.001	1.09(1.01,1.16)
	Increased	10.3(47/457)	11.4(57/498)	14.2(64/452)	10.5(45/427)	10.5(56/535)	0.86	1.00(0.90,1.12)
NEC	Decreased	4.3(70/1 618)	4.3(68/1 588)	3.7(63/1 690)	4.0(66/1 641)	3.8(69/1 795)	0.42	0.95(0.87,1.03)
	Null	5.0(77/1 522)	5.3(81/1 546)	5.0(86/1 719)	4.1(65/1 573)	4.7(74/1 558)	0.31	0.93(0.85,1.01)
	Increased	7.3(39/532)	9.0(49/543)	8.3(42/504)	9.0(42/464)	5.2(29/558)	0.2	0.92(0.82,1.03)
Composite outcome	Decreased	29.1(472/1 622)	29.3(470/1 604)	27.2(461/1 695)	25.7(422/1 644)	24.4(439/1 802)	<0.0001	0.88(0.84,0.92)
	Null	30.3(466/1 540)	31.3(493/1 576)	36.1(622/1 722)	33.6(530/1 579)	30.9(482/1 560)	0.34	0.93(0.89,0.98)
	Increased	33.5(178/532)	42.0(229/545)	39.9(202/506)	41.0 (191/466)	30.8(175/568)	0.24	0.97(0.90,1.05)

Note:  $\Delta$  Cochran-Armitage trend test; \* Adjusted for gestational age, gender, small (<10th percentile birth weight) for gestational age, Apgar score < 7 at 5 min, score for neonatal acute physiology-II, singleton, outborn status, cesarean delivery, maternal hypertension, antenatal steroid use, maternal antibiotic use and maternal age.

## Discussion

It remains important to quantify the relative contribution of NI and other neonatal care practices to mortality/morbidity to identify target interventions that will provide the greatest improvement in outcomes of preterm infants. The effect of NI baseline rates and NI trend on the short term and long term outcome is not well studied and recognized. As we strive to improve outcomes in the vulnerable population in NICUs, we need all the tools necessary in our hands to affect change and improve quality of life in this population.

NI is common among preterm infants admitted to NICU. In fact up to 50% of preterm infants < 26 weeks get NI during their stay in NICU<sup>[16]</sup>. Klinger et al<sup>[21]</sup> showed that VLBW infants with sepsis were at increased risk of BPD [OR: 1.74 (95%CI: 1.24-2.43)], severe intraventricular hemorrhage (IVH) [OR: 2.24 (95%CI: 1.67-3.00)], and severe ROP [OR: 2.04 (95%CI: 1.32-3.16)]. The increased risk of IVH, BPD and ROP in infants with sepsis is associated with a direct bacterial effect by cytokine-mediated inflammatory response, increased exposure of infants with sepsis to mechanical ventilation and exposure to prolonged oxygen therapy. In this study based on national database, we found that the rates of BPD, severe ROP, and IVH grade3 were all significantly decreased in sites with decreasing NI rate possibly due to reduced inflammatory response.

Overall mortality in this group was not changed significantly. This study revealed improved outcomes in sites with null trend in NI, the composite outcome showed greater change in the sites with decreased NI rates. This correlation provides us with evidence that our efforts to decrease NI rates is contributing to improved quality of life in neonates due to lower rates of major morbidities. We found decreased rates of mortality and major morbidities also in sites with null trend in NI. This is likely due to improved techniques and treatments in NICUs unrelated to NI rates. No decrease or increase trend for mortality and morbidity

was observed in the site group with increased NI rate. The sites with low baseline NI rate may not target to improve their NI rate but may conduct the interventions targeting to improve other morbidities. Instead, the sites with high baseline NI rates may conduct interventions to decrease the rate. This may explain why NI rate decreased for those sites with high baseline NI rate. This also may have been mitigated by the same improvements in treatment and techniques leading to improved outcomes in the group with no changes in NICU rate.

When subdivided by baseline NI rate, we found that the trend of NI rate was impacted significantly. For example, in the low baseline NI rate group, NI rate increased significantly (although not significant when adjusted), while in high baseline NI rate group, NI rate decreased significantly, even after adjustment. No increase or decreased trend was observed for the average baseline NI rate group. We believe that these trends are partly a result of large scale interventions aimed at decreasing the NI rates. These interventions had the greatest impact on hospitals with high baseline NI rates and brought them closer to the rates of other hospitals, which were likely already, implementing stringent infection control protocols.

In conclusion, the neonatal outcome is influenced by NI rates and trend. The trend in the composite mortality and the risk of BPD, severe ROP and IVH were significantly decreased for site group with decreased NI rate. These decreased outcomes were associated with effort to decrease NI rate and may also lead to a decrease in other adverse neonatal outcomes.

Based on our findings, these efforts have led to improvements in sites with previously higher than average NI rates. Therefore, we must continue to monitor NI rates in nurseries and continue to strive to maintain low rates of NI in order to improve quality of life in this vulnerable population. Future studies of NICU outcomes should take this into account in planning, data gathering and doing statistical calculations.



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