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Concise Communication

Variability in antimicrobial use among infants born at <33 weeks gestational age

Joseph Y. Ting MBBS, MPH[1], Ashley Roberts MD, Med[1], Ayman Abou Mehrem MD[2], Faiza Khurshid MBBS, MSc[3], Christine Drolet MD[4], Luis Monterrosa MD[5], Eugene W. Yoon MSc[6], Prakesh S. Shah MD, MSc[6,7] on behalf of the Canadian Neonatal Network (CNN) Investigators[a]

[1]Department of Pediatrics, University of British Columbia, Vancouver, British Colombia, Canada, [2]Department of Pediatrics, University of Calgary, Calgary, Alberta, Canada, [3]Department of Pediatrics, Queen's University, Kingston, Ontario, Canada, [4]Centre Mère-Enfant Soleil, CHU de Québec, Laval University, Quebec City, Québec, Canada, [5]Department of Pediatrics, Saint John Regional Hospital, Saint John, New Brunswick, Canada, [6]Maternal-infant Care Research Centre, Mount Sinai Hospital, Toronto, Ontario, Canada and [7]Department of Pediatrics, Mount Sinai Hospital and University of Toronto, Ontario, Canada

Abstract

Excessive antimicrobial use is associated with adverse neonatal outcomes. In our cohort of 27,163 infants born at <33 weeks gestational age, the first week after birth accounted for the highest rates of antimicrobial use, and variability across sites persisted after adjustment for patient characteristics correlated with illness severity.

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Antimicrobials are the most commonly prescribed medications in neonatal intensive care units (NICUs).[1] In the Canadian Neonatal Network (CNN), antimicrobial utilization rates (AUR) among infants without culture-proven sepsis or necrotizing enterocolitis (NEC) vary by 6-fold, ranging from 42.2 to 253.7 per 1,000 hospital days for infants born at <29 weeks gestational age (GA).[2]

Evidence-based guidelines and/or consensus on best practices of antimicrobial uses for relatively common conditions in the NICU are lacking. Excessive antimicrobial exposure without evidence of culture-proven sepsis in the neonatal period is associated with increased morbidities, mortality, and/or neurodevelopmental impairment.[3,4] Studies in pediatric intensive care units and children's hospitals have demonstrated extensive variability in antibiotic use unexplained by patient- or hospital-level factors typically associated with the need for antibiotic therapy.[5,6] Substantial variabilities in neonatal antimicrobial use among facilities have been described[7,8]; however, studies on investigating variability in antimicrobial use accounting for patient characteristics across different gestational age groups in the NICU environment are limited.

The objectives of this study were (1) to examine the relationship between antimicrobial use and timing of hospitalization; (2) to explore the variability in antimicrobial use between sites in different GA subgroups (birth at ≤26 weeks, 27–29 weeks, and 30–32 weeks GA); and (3) to assess whether site variability can be explained by patient characteristics correlated with adverse outcomes and illness severity among preterm infants born at <33 weeks GA without culture-proven sepsis or NEC ≥ stage 2.

Methods

Study design and population

We conducted a retrospective cohort study using the CNN database, which represents >90% of tertiary-care NICU admissions in Canada and has been shown to be highly precise and reliable.[9] The study included data from infants born at <33 weeks GA and admitted to participating NICUs between January 1, 2010, and December 31, 2017. Infants who had major congenital anomalies, died within 7 days of birth, or were missing a discharge date were excluded. Those who developed culture-proven sepsis (bacteremia and/or meningitis) or NEC ≥ stage 2 during hospitalization were initially eligible for the study but were then not included in the analysis. Data were abstracted from infant medical records according to standardized definitions and transmitted to the CNN Coordinating Centre in Toronto, Ontario. All sites in the network admit infants needing level 3 NICU care. Data collection and transmission from each site were approved by either local research ethics boards or hospital quality improvement committees. Specific institutional review board approval was obtained for this study from the Children's and Women's Research Ethics Board at the University of British Columbia (no. H18-03380).

Study variable definitions

Study variables were defined according to the *CNN Abstractor's Manual*.[10] We defined GA as the best obstetric estimate based on early prenatal ultrasound, obstetric examination, and obstetric history, unless the postnatal pediatric estimate of gestation differed from the obstetric estimate by >2 weeks, in which case the pediatric

Author for correspondence: Joseph Y. Ting, E-mail: yukjosep@ualberta.ca
[a]A full list of CNN investigators and their affiliations is provided in the Acknowledgments.
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estimate of GA was used instead. An infant was considered small for GA if the birth weight was less than the 10th percentile for GA and sex. Version II of the Score for Neonatal Acute Physiology (SNAP-II) is a validated measure of newborn severity of illness that captures physiological status within the first 12 hours of admission to the NICU (lowest blood pressure, lowest temperature, lowest serum pH, pO_2/FiO_2 ratio, seizures, and urine output), with higher scores reflecting increased severity of illness.[11] Culture-proven sepsis was diagnosed by positive pathogenic bacterial, viral, or fungal culture in blood or cerebrospinal fluid from admission to discharge from the NICU. We classified NEC according to modified Bell stage 2 or higher.[12]

Outcomes

For the 3 study objectives, the following 3 outcome indices were used:

1. Proportions of infants who received ≥1 antimicrobial(s) at each postnatal day of age among total infants without culture-proven sepsis or NEC ≥ stage 2 admitted to sites on a given day were calculated for the first 70 days of age.
2. Antimicrobial utilization rate (AUR) was calculated as the number of patient days when infants were exposed to ≥1 antimicrobial(s) divided by total patient days during the period of hospitalization for each CNN participating site.
3. Risk-adjusted AUR was calculated after adjusting for site, small for gestational age, sex, SNAP-II, admission year, multiple birth, delivery mode, and outborn birth.

Statistical analysis

Proportions of infants receiving antimicrobials out of the total numbers of infants at the sites during the first 70 days of age in the 3 GA groups (≤26 weeks, 27–29 weeks, and 30–32 weeks GA) were illustrated graphically. The AUR values were calculated as described for each site. Adjusted AUR values were calculated using a modified Poisson regression model, and the AUR difference across the sites was examined by looking at the site effect in the model. The Poisson model was obtained from a generalized linear model with the log link function and the log of total hospital stay days per patient as the offset. We adjusted for small-for-gestational age, sex, SNAP-II scores >20, multiple births, and outborn deliveries, all of which have been shown to be associated with increased risk of neonatal morbidities or severity of illness. All statistical analyses were conducted using SAS version 9.4software (SAS Institute, Cary, NC). Statistical significance was evaluated using 2-sided P values and a significance level of .05.

Results

Among the 31,925 eligible infants from 30 sites, 27,163 (85%) did not develop any culture-proven sepsis or NEC ≥ stage 2 during their hospitalization and were included in the analysis. The demographic characteristics of the included infants are shown in Table 1.

Proportions of infants receiving antimicrobials in those born at ≤26 weeks, 27–29 weeks, and 30–32 weeks GA were 44%, 21%, and 10%, respectively, on day 7 of age (Fig. 1) These proportions dropped to 29%, 10%, and 4%, respectively, on day 14 of age.

The site-level median AUR values for those without culture-proven sepsis and/or NEC ≥ stage 2 were 0.15 (interquartile range [IQR], 0.08–0.26) for infants born at ≤26 weeks GA, 0.11 (IQR, 0.02–0.22) for infants born at 27–29 weeks GA, and 0.12 (IQR, 0–0.30) for infants born at 30–32 weeks GA, with significant variability across the individual sites in each GA group ($P < .01$) (Table 1). This intersite variability persisted for infants in all 3 GA groups after adjusting for the confounding variables ($P < .01$) (Fig. 2).

Discussion

In this retrospective cohort study, we identified that a substantial proportion of preterm infants without culture-proven sepsis or NEC ≥ stage 2 across CNN sites were still receiving antimicrobials by day 7 of age, especially in groups born at lower GA. We also identified significant variability in antimicrobial use among the sites that persisted after accounting for patient characteristics related to illness severity. To the best of our knowledge, this study is the first to investigate antimicrobial receipt during hospitalization and variability in antimicrobial use accounting for patient characteristics across different GA groups, specifically in the NICU setting.

In daily practice, antimicrobials are administered shortly after birth to most preterm infants due to risk of overt infection and the difficulty in differentiating respiratory immaturity from infection in extremely preterm infants with respiratory distress. The strongest single predictor of early-onset sepsis (EOS) is GA, and most preterm births occur in the setting of other factors associated with risk of EOS.[13] Certain birth characteristics, such as lack of evidence of chorioamnionitis and cesarean birth in the absence of labor onset, may be used to identify those with significantly lower incidences of EOS and limit prolonged early antimicrobial use.[14] In our previous work, we identified that prolonged empirical antimicrobial exposure for >3 days within the first week after birth in very low birth weight (VLBW) infants was associated with increased odds of the composite outcome of mortality or severe morbidity.[15] In this study, we identified that antimicrobials were given by 7 days of age without culture-proven sepsis and/or NEC ≥ stage 2 to almost 1 in every 2 infants born at ≤26 weeks GA, 1 in 5 infants born at 27–29 weeks GA, and 1 in 10 infants born at 30–32 weeks GA. This could be an important ASP target to decrease antimicrobial exposure in preterm infants who do not have infections.

Our work confirmed the previous findings of antimicrobial use variability between sites among large population studies like those from the Premier Perspective Database and Vizient Clinical Database/Resource manager[7,16] and, beyond that, we provided evidence that the variability persisted after accounting for patient characteristics associated with adverse neonatal outcomes and severity of illness. Evidence-based guideline or consensus on best practices are lacking, and the management of commonly encountered conditions like culture-negative sepsis, urinary tract infection and ventilator associated pneumonia remains controversial in daily clinical practice. Early signs of infections are often indistinguishable from other commonly encountered prematurity-related morbidities and can result in rapid deterioration, which results in sepsis evaluations and empirical antimicrobial usage and/or prolonged broad-spectrum antibiotic usage among the most prematurely born infants. The personal preferences of attending physicians and teams likely also contribute to patterns of antimicrobial use,[17] and the acknowledgment of such biases in the context of data like ours will be an important step forward in rationalizing antimicrobial use.

A key strength of our study was that it involved a Canada-wide, representative, population-based cohort. However, our study also had several limitations. First, due to the limits of the existing

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Table 1. Demographic Characteristics of Infants Without Culture-Proven Sepsis or Necrotizing Enterocolitis Stage 2 or Above

Variable	Gestational Age at Birth			*P* Value[a]
	≤26 Weeks (n=3,599)	27–29 Weeks (n=7,963)	30–32 Weeks (n=15,601)	
Antimicrobial utilization rates, median (IQR)	0.15 (0.08–0.26)	0.11 (0.05–0.22)	0.12 (0–0.30)	<.01
Infant characteristics				
Birth weight, mean g (SD)	811 (175)	1,173 (252)	1,645 (353)	<.01
Small for gestational age, no. (%)	228 (6)	678 (9)	1,615 (10)	<.01
Version II Score for Neonatal Acute Physiology >20, no. (%)	1,249 (35)	964 (12)	767 (5)	<.01
Multiple births, no. (%)	827 (23)	2,229 (28)	5,473 (35)	<.01
Outborn, no. (%)	627 (17)	1,288 (16)	2,131 (14)	<.01

Note. IQR, interquartile range; SD, standard deviation.
[a]AUR, *P* value was from a Poisson regression model, where the GA category effect was tested under the hypothesis that AUR was the same across all GA categories. Birth weight: *P* value was from one-way ANOVA. For all other variables (all categorical variables): *P* value was from χ^2 tests.

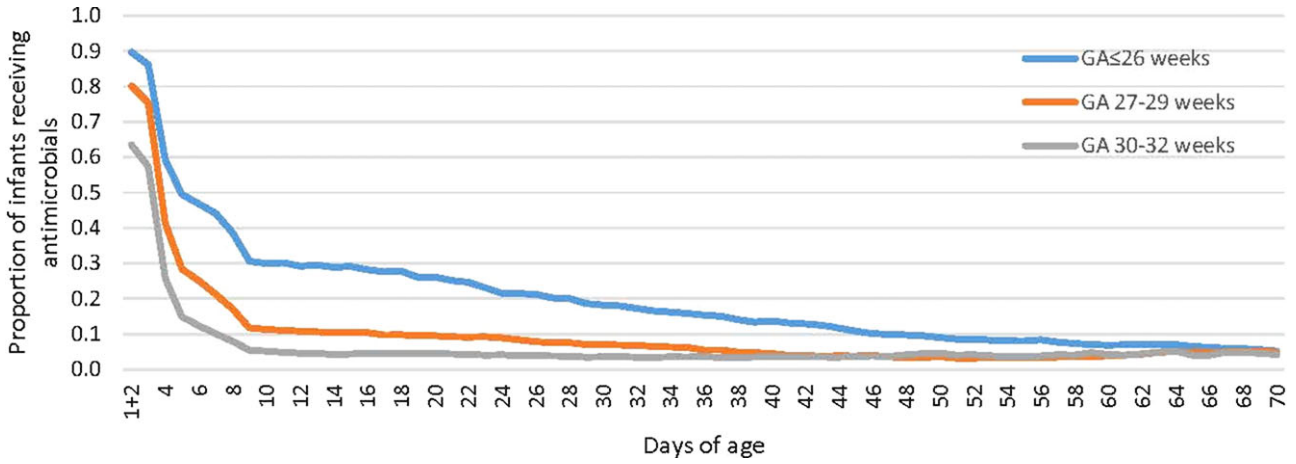

Fig. 1. Proportions of infants receiving antimicrobials by gestational age group. Note. GA, gestational age; GA ≤26, ≤26 weeks gestational age at birth; GA 27–29, 27–29 weeks gestational age at birth; GA 30–32, 30–32 weeks gestational age at birth.

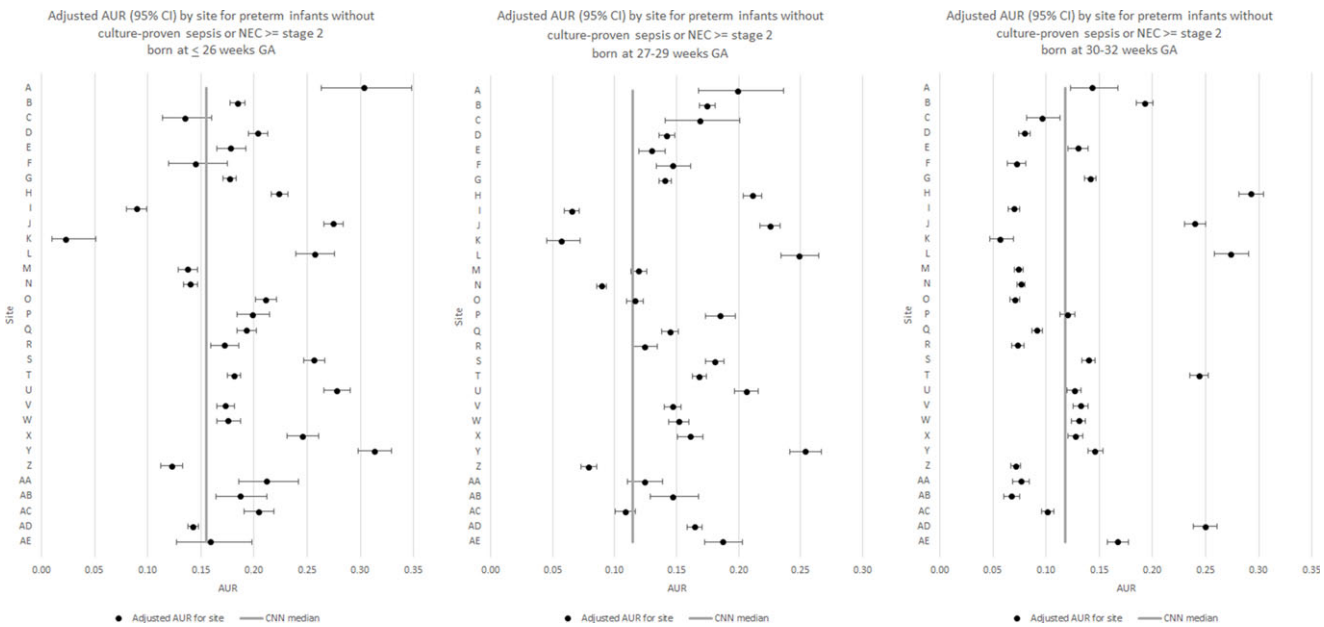

Fig. 2. Adjusted antimicrobial utilization rates across canadian neonatal network sites in the 3 gestational age groups. Note. AUR, antimicrobial utilization rate; CI, confidence interval; CNN, Canadian Neonatal Network; GA, gestational age; NEC, necrotizing enterocolitis.

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database design, we could not investigate secular trends and variations in the use of specific broad-spectrum antimicrobials. Second, in the calculation of AUR, the denominator (length of stay) only included the stay in participating NICUs. Since some preterm infants are transferred to level 2 hospitals prior to discharge home, we may have overestimated the AUR. Third, our analyses of AUR among infants without evidence of sepsis or NEC may have included some infants with other potential infections (eg, urinary tract infections or pneumonia); however, standardized definitions for urinary tract infections or pneumonia in preterm neonatal populations are lacking.[18,19] Fourth, although patient characteristics associated with adverse neonatal outcomes and increased severity of illness during hospitalization were included in the adjustment models, the issue of residual confounding remains.

The most important goal of multidisciplinary ASP is to optimize antimicrobial therapy and not simply to curtail antimicrobial therapy. Reduction of high rates of antimicrobial use at early postnatal age, particularly among lower GA infants at very low risk of developing EOS by applying 36- or 48-hour automatic stop order and regular audit and feedback can be important ASP strategies. Standardizing and auditing the practice by developing nationwide NICU-specific ASP may help reduce interfacility variability in the long run.[20]

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Canadian Neonatal Network (CNN) site investigators: Prakesh S Shah, MD, MSc (Director, Canadian Neonatal Network and Site Investigator), Mount Sinai Hospital, Toronto, Ontario; Marc Beltempo, MD, (Associate Director, Canadian Neonatal Network and Site Investigator), Montreal Children's Hospital at McGill University Health Centre, Montréal, Québec; Jaideep Kanungo, MD, Victoria General Hospital, Victoria, British Columbia; Joseph Ting, MD, British Columbia Women's Hospital, Vancouver, British Columbia; Zenon Cieslak, MD, Royal Columbian Hospital, New Westminster, British Columbia; Rebecca Sherlock, MD, Surrey Memorial Hospital, Surrey, British Columbia; Ayman Abou Mehrem, MD, Foothills Medical Centre, Calgary, Alberta; Jennifer Toye, MD, and Khalid Aziz, MBBS, Royal Alexandra Hospital, Edmonton, Alberta; Carlos Fajardo, MD, Alberta Children's Hospital, Calgary, Alberta; Jaya Bodani, MD, Regina General Hospital, Regina, Saskatchewan; Lannae Strueby, MD, Royal University Hospital, Saskatoon, Saskatchewan; Mary Seshia, MBChB, and Deepak Louis, MD, Winnipeg Health Sciences Centre, Winnipeg, Manitoba; Ruben Alvaro, MD, St. Boniface General Hospital, Winnipeg, Manitoba; Amit Mukerji, MD, Hamilton Health Sciences Centre, Hamilton, Ontario; Orlando Da Silva, MD, MSc, London Health Sciences Centre, London, Ontario; Mohammad Adie, MD, Windsor Regional Hospital, Windsor, Ontario; Kyong-Soon Lee, MD, MSc, Hospital for Sick Children, Toronto, Ontario; Eugene Ng, MD, Sunnybrook Health Sciences Centre, Toronto, Ontario; Brigitte Lemyre, MD, The Ottawa Hospital, Ottawa, Ontario; Thierry Daboval, MD, Children's Hospital of Eastern Ontario, Ottawa, Ontario; Faiza Khurshid, MD, Kingston General Hospital, Kingston, Ontario; Ermelinda Pelausa, MD, Jewish General Hospital, Montréal, Québec; Keith Barrington, MBChB, Anie Lapoint, MD, and Guillaume Ethier, NNP, Hôpital Sainte-Justine, Montréal, Québec; Christine Drolet, MD, and Bruno Piedboeuf, MD, Centre Hospitalier Universitaire de Québec, Sainte Foy, Québec; Martine Claveau, MSc, LLM, NNP, Montreal Children's Hospital at McGill University Health Centre, Montréal, Québec; Marie St-Hilaire, MD, Hôpital Maisonneuve-Rosemont, Montréal, Québec; Valerie Bertelle, MD, and Edith Masse, MD, Centre Hospitalier Universitaire de Sherbrooke, Sherbrooke, Québec; Roderick Canning, MD, Moncton Hospital, Moncton, New Brunswick; Hala Makary, MD, Dr. Everett Chalmers Hospital, Fredericton, New Brunswick; Cecil Ojah, MBBS, and Luis Monterrosa, MD, Saint John Regional Hospital, Saint John, New Brunswick; Julie Emberley, MD, Janeway Children's Health and Rehabilitation Centre, St. John's, Newfoundland; Jehier Afifi, MB BCh, MSc, IWK Health Centre, Halifax, Nova Scotia; Andrzej Kajetanowicz, MD, Cape Breton Regional Hospital, Sydney, Nova Scotia; Shoo K Lee, MBBS, PhD (Chairman, Canadian Neonatal Network), Mount Sinai Hospital, Toronto, Ontario.

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