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Concise Communication

Antibiotic use in Canadian neonatal intensive care units: a national survey for developing antimicrobial stewardship targets

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Abstract

A survey was conducted among Canadian tertiary neonatal intensive care units. Of the 27 sites who responded, 9 did not have any form of antimicrobial stewardship, and 11 used vancomycin for empirical coverage in late-onset-sepsis evaluations. We detected significant variations in the diagnostic criteria for urinary tract infection and ventilator-associated pneumonia.

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Antibiotic prescribing practices vary widely among neonatal intensive care units (NICUs), and they do not correlate well with the burden of proven infection.[1] A study from the Canadian Neonatal Network (CNN) revealed significant variability in antibiotic prescription among infants without culture-proven sepsis or necrotizing enterocolitis (NEC) across Canadian tertiary NICUs, even after adjustment for patient characteristics correlated with illness severity.[2]

Prior to the development of a nationwide antimicrobial stewardship program (ASP), we conducted a national cross-sectional survey to understand the current practices of empirical antimicrobial coverage and diagnostic criteria for commonly encountered infections.

Methods

In this cross-sectional study, we utilized a web-based survey sent in Fall–Winter 2019 by the CNN Coordinating Center in Toronto to each participating CNN unit, which includes all tertiary NICUs across Canada. It consisted of 12 questions, focused on the following aspects: availability of an ASP in their NICU, screening practices for antibiotic-resistant organisms (AROs), empirical coverage for late-onset sepsis (LOS) and NEC, and criteria for the diagnosis of urinary tract infection (UTI) and ventilator-associated pneumonia (VAP) (Supplementary Material online).

Descriptive statistics were used to summarize the results. Ethics approval was obtained from the University of British Columbia and Children's and Women's Health Research of British Columbia Research Ethics Board (no. H19-01531).

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Results

Of 31 Canadian NICUs contacted, 27 (87.1%) completed the survey. Of these, 11 NICUs (40.7%) received regular reports from their infection control practitioners or microbiology departments regarding the proportion of AROs among bacterial isolates.

ASPs in Canadian NICUs

Overall, 9 units (33.3%) did not have any form of ASP. Of the 27 responding NICUs, 25 (92.6%) expressed interest in participating in a national collaborative program to examine antibiotic utilization and prevalence of AROs across Canada.

Screening practices for AROs

Of 27 NICUs, 17 (63.0%) which performed routine screening for ARO at admission, and sometimes with repeated rectal or surface swabs. Among these, all 17 (100%) screened for methicillin-resistant *Staphylococcus aureus* (MRSA), 11 screened (64.7%) for vancomycin-resistant enterococci (VRE), and only 2 (11.8%) screened for extended-spectrum β-lactamase (ESBL)–producing or third-generation cephalosporin-resistant organisms.

Antimicrobial prescription practice: Empirical coverage for LOS

With respect to empirical coverage for LOS, vancomycin was used in infants without central in 8 units (29.6%) and in infants with catheters in situ in 11 units (40.7%) (Table 1). Aminoglycosides

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Table 1. Empirical Antimicrobial Coverage in NICU Sites for Suspected Late-Onset Sepsis and Queried Necrotizing Enterocolitis

Choice of Empirical Antibiotics	Sites Using Indicated Antibiotics, No. (%)
Suspected late-onset sepsis with no central catheter in situ	
Cloxacillin and gentamicin-tobramycin	7 (25.9)
Ampicillin and gentamicin-tobramycin	5 (18.5)
Vancomycin and gentamicin-tobramycin	4 (14.8)
Vancomycin and cefotaxime	4 (14.8)
Ampicillin and cefotaxime	1 (3.7)
Cefotaxime	1 (3.7)
Piperacillin-tazobactam	1 (3.7)
Others[a]	4 (14.8)
Suspected late-onset sepsis with central catheter in situ	
Cloxacillin and gentamicin-tobramycin	7 (25.9)
Vancomycin and gentamicin-tobramycin	6 (22.2)
Vancomycin and cefotaxime	4 (14.8)
Vancomycin and piperacillin-tazobactem	1 (3.7)
Ampicillin and gentamicin-tobramycin	1 (3.7)
Others[b]	8 (29.6)
Suspected or confirmed necrotizing enterocolitis	
Ampicillin and gentamicin-tobramycin	9 (33.3)
Vancomycin and gentamicin-tobramycin	3 (11.1)
Vancomycin and cefotaxime	3 (11.1)
Piperacillin-tazobactam	3 (11.1)
Cloxacillin and gentamicin-tobramycin	2 (7.4)
Ampicillin and cefotaxime	1 (3.7)
Ampicillin and clindamycin	1 (3.7)
Ampicillin and clindamycin & gentamicin-tobramycin	1 (3.7)
Clindamycin and gentamicin-tobramycin	1 (3.7)
Others[c]	3 (11.1)

[a]These 4 sites used various other combinations of ampicillin, cloxacillin, cefazolin, vancomycin, cefotaxime and gentamicin-tobramycin.
[b]These 8 sites used various other combinations of ampicillin, cloxacillin, clindamycin, vancomycin, linezolid, cefotaxime and gentamicin-tobramycin. Among these, 6 of 8 sites used gentamicin-tobramycin consistently for empirical coverage.
[c]These 3 sites used various other combinations of ampicillin, cloxacillin, cefazolin, clindamycin vancomycin, cefotaxime and gentamicin/ tobramycin. Among these, 1 of 3 sites used gentamicin-tobramycin consistently for empirical coverage.

were used for empirical coverage in infants without central catheter in-situ in 16 units (59.3%) and in infants with catheters in situ in 20 units (74.1%).

The most common combinations of antibiotics were cloxacillin and gentamicin- tobramycin (25.9%), vancomycin and gentamicin-tobramycin (22.2%), and vancomycin and cefotaxime (14.8%) with central intravascular catheter.

Antimicrobial prescription practice: Empirical coverage for NEC

Regarding the empirical coverage for NEC, the most common combinations of antibiotics were ampicillin and gentamicin-tobramycin (33.3%), vancomycin and gentamicin-tobramycin (11.1%), vancomycin and cefotaxime (11.1%), and piperacillin-tazobactam (11.1%). Moreover, 11 units (40.7%) started anaerobic coverage for stage I/II NEC without evidence of peritonitis or perforation.

Table 2. Diagnostic Criteria Applied for VAP and UTI the NICU

Diagnostic Criteria	Sites Using Indicated Criteria, No. (%)[a]
Urinary tract infection (UTI)	
Catheterized urine sample with $>10^6$ per CFU growth of pathogen per mL ($>10^9$ per L)	1 (3.7)
Catheterized urine sample with $>10^5$ per CFU growth of pathogen per mL ($>10^8$ per L)	17 (63.0)
Catheterized urine sample with $>10^4$ per CFU growth of pathogen per mL ($>10^7$ per L)	7 (25.9)
Suprapubic sample with any growth	8 (28.6)
Any growth in any sample in a symptomatic neonate	2 (7.4)
Patient dependent	5 (7.4)
Ventilator-associated pneumonia (VAP)	
In an infant on ventilator >48 h	11 (40.7)
Any positive tracheal aspirate culture	10 (37.0)
Temperature instability	11 (40.7)
Increase in MAP >4 cm H_2O	8 (29.6)
Increase in FiO_2 >25%	9 (33.3)
Any radiological evidence	13 (48.1)
Use of antimicrobials for at least 4 days	3 (11.1)
Physician dependent	14 (51.9)
We do not label VAP as we do not have strict criteria	3 (11.1)
Others[b]	8 (29.6)

[a]Multiple criteria allowed.
[b]Others: different cut-off for MAP and FiO_2; relied on hematological markers, etc.Note. UTI, urinary tract infection; VAP, ventilator-associated pneumonia; MAP, mean airway pressure; FiO_2, fraction of inspired oxygen.

Diagnostic criteria for UTI and VAP

Overall, 17 (63.0%) of 27 NICUs defined the microbiological cutoff for a single pathogen growth in catheterized urine sample as 10^5 colony-forming unit (CFU)/mL, whereas others interpreted CFU and growth of organisms in urine samples differently (Table 2).

For VAP, in 14 units (51.8%), the diagnosis was made at the discretion of physicians, whereas 10 units used variable diagnostic criteria and 3 units did not label VAP because they did not have strict criteria. Only 8 NICUs (29.6%) included the increase in MAP >4 cm H_2O and 9 NICUs (33.3%) included the increase in FiO_2>25% in their diagnoses of VAP [according to the Centre for Disease Control (CDC) criteria].

Discussion

Our cross-sectional survey revealed wide variation in the clinical practices of antimicrobial use and screening policies in Canadian NICUs, and out results provide insight into potential targets for neonatal ASPs.

In the NICU, vancomycin is commonly used for empirical coverage of coagulase-negative *Staphylococcus* (CoNS), the most

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common bacteria in central-line–associated blood stream infections (CLABSIs). Ericson et al[3] reported that there was lack of survival benefit with empirical vancomycin versus delayed vancomycin therapy (1–3 days after first positive blood culture) for CoNS bloodstream infection in a cohort of 4,364 infants from 348 NICUs. It is intriguing to find that, in cases of suspected LOS without a central intravascular catheter, almost one-third of NICUs were still using vancomycin in their empirical regimen.

The Infectious Diseases Society of America (IDSA) recommends combinations of antibiotics and potentially an antifungal for empirical therapy for NEC, but they do not recommend a specific regimen.[4] After propensity score matching, an observational retrospective study involving 2,780 preterm infants from 348 centers suggested that among those with stage 2 NEC (without need for surgical intervention), anaerobic coverage was not associated with lower mortality but resulted in an increased risk of intestinal strictures.[5] Our finding of more than half of NICUs providing empirical anaerobic coverage for infants with stages I/II NEC should be reviewed further.

In recent CNN data, *Staphylococcus aureus* was the second most common pathogen after CoNS in causing hospital-associated infections.[6] Swabbing infants at birth and placing MRSA-colonized neonates under contact precautions has been shown to prevent transmission and outbreaks in the NICU.[7] Screening asymptomatic carriers in NICUs for other AROs is less well described. Screening priorities should be based on local colonization rates, prevalence of infection and hospital financial resources.[8]

Lack of consensus in diagnostic criteria and management of common neonatal conditions (ie, neonatal UTI and VAP) has caused problematic variation in antibiotic use across NICUs. Not surprisingly, the definitions applied in our NICUs were very heterogenous. The current diagnostic criteria for VAP for infants of <1 year of age from the CDC are extrapolated from pediatric guidelines, which intrinsically pose difficulties for direct applications to the preterm populations.[1] Noninfective conditions, like bronchopulmonary dysplasia, cannot be confidently distinguished from VAP on the chest radiographs. The gold standard of obtaining lower-respiratory-tract specimens can be risky in preterm neonates with high ventilatory settings, and positive tracheal aspirates that cultures may just represent colonization.

The existing UTI guidelines published by the American Academy of Pediatrics (AAP) are targeted at patients >2 months old.[9] The diagnosis of UTI requires both pyuria and $\geq 5\times10^7$ CFU/L of a single uropathogen in an appropriately collected specimen of urine.[9] Because there is no reference standard to prove which infants have a UTI, the thresholds for laboratory values diagnosis for UTI vary significantly across the neonatal literature.[1]

One strength of this study is the 87% participation rate by tertiary NICUs across Canada. It provides useful information to identify relevant targets in our nationwide ASP development.[10] Areas for further imporvement include decreasing use of vancomycin in empirical coverage for LOS, avoidance of anaerobic coverage for stage 1 and 2 NEC and development of standard VAP and UTI diagnostic criteria for preterm population.

This study had several limitations. Cross-sectional surveys are limited by the depth and scope of the questionnaire. CNN site investigators were not able to elaborate on their answers, and in-depth explanations were not captured. Second, site investigators self-reported their units' practices, and our survey was not designed to identify substantial intra-NICU variation.

In conclusion, this national survey revealed a wide variation of existing antimicrobial prescription practices in Canadian NICU, which highlights potential targets for national neonatal ASP.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/ice.2023.112

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