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Original Article

Effectiveness of a neonatal intensive care unit–specific antimicrobial stewardship program: A ten-year review

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Abstract

Objective: To evaluate the change in consumption of specific antibiotics in a neonatal intensive care unit after the implementation of an antimicrobial stewardship program (ASP).

Design: Retrospective cohort study between January 1, 2010, and December 31,2019.

Setting: The neonatal intensive care unit at British Columbia Women's Hospital (Vancouver Canada), a tertiary-care center.

Patients: Admitted neonates prescribed antibiotics.

Methods: We implemented an ASP with an early implementation phase starting in January 2014 (period 2) and a later phase starting in January 2017 (period 3). Patient demographics were collected, including birth weight, gestational age, history of necrotizing enterocolitis (NEC), and surgical operations from existing databases. Interrupted time-series analysis was used, and comparison of antibiotic days of therapy (DOT) averages were conducted across the preimplementation period (period 1), period 2, and period 3 regarding total patients and subgroups.

Results: We identified 4,512 infants. There was a significant decrease in DOT from 472 (95% confidence interval [CI], 431–517) in period 1 to 405 (95% CI, 367–446) in period 2 to 313 (95% CI, 280–350) in period 3. We detected a significant decrease in the use of ampicillin, aminoglycosides, cloxacillin, and linezolid but not in vancomycin or cefotaxime. Subgroup analyses of infants <1,500 g and those without NEC or surgery showed decreases in the use of cloxacillin, aminoglycosides, and linezolid.

Conclusions: The implementation of an ASP was associated with a significant decrease in the overall DOT and use of certain antibiotics. This study presents important targets for ongoing ASP work.

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Neonates admitted to the neonatal intensive care unit (NICU) are susceptible to a variety of infections. These infections are difficult to differentiate from other pathological processes due to the nonspecific nature of clinical signs and laboratory results in this population. Given the considerable morbidity and mortality associated with invasive infections, timely administration of antibiotics is critical.[1,2] As a result, antibiotics are the most common medication prescribed in the NICU.[3,4]

Over the last decade, the detrimental effects of antibiotic use in preterm neonates have become better characterized from both basic science and clinical research. Antibiotic use can lead to gut dysbiosis and antimicrobial resistance.[5,6] Our group has reported that the increased antibiotic utilization in infants without culture-proven sepsis or necrotizing enterocolitis (NEC) is associated with an increased risk of neonatal morbidities, mortality, and/or adverse neurodevelopmental outcomes at 18–22 months corrected gestational age.[7,8] Cantey et al[9] found that each day of antibiotic use in very low-birthweight (VLBW) infants (<1,500 g) in their first 2 weeks of life was associated with a 1.24 times increased risk of late-onset sepsis, NEC, or death.[9] Thus, it is important to find strategies to reduce antibiotic use in these vulnerable populations.

The challenges associated with identifying and diagnosing true infection in the NICU population leads to difficulty with decisions regarding the initiation, selection, and duration of antimicrobial therapy.[10] Antimicrobial stewardship programs (ASPs) have been implemented in many NICUs to help improve antimicrobial use, with mixed results.[11] These programs usually consist of a multidisciplinary team including neonatologists, infectious disease

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specialists, microbiologists, nurses, and pharmacists.[12] The ASP at British Columbia Women's Hospital (BCWH) was established in 2014.[13] The goals of this study were to measure antibiotic consumption in the BCWH level 3 NICU after implementation of an ASP and to evaluate the time trends of different antimicrobials and their use in different groups of patients over a decade.

Methods

Setting and population

The NICU at BCWH in Vancouver, Canada, serves as the tertiary- and quaternary-care perinatal center for the province of British Columbia and Yukon Territory. It accepts both inborn and outborn neonates, with an admission rate of ~1,400 patients per year. A retrospective audit was performed on all neonates prescribed select antibiotics (ie, ampicillin, gentamicin/tobramycin, cloxacillin, metronidazole, cefotaxime, vancomycin, linezolid, and meropenem) between January 1, 2010, and December 31, 2019, from existing neonatal and pharmacy databases. The study period was divided into 3 phases: before the ASP (period 1, January 2010–December 2013), early after the ASP began (period 2, January 2014–December 2016) and later after the implementation of the ASP (period 3, January 2017–December 2019). For transferred patients, only antibiotics prescribed and days admitted in the BCWH NICU were included.

An early phase of the ASP was implemented in January 2014. This phase involved a designated clinical pharmacist with additional ASP training to review all antimicrobial prescriptions in the NICU during weekdays. Daily real-time feedback on the appropriateness of antimicrobial prescribing was provided to the clinical team. The definition of appropriateness for individual patient cases was at the discretion of the ASP pharmacist based on hospital and external guidelines for the treatment of specific infections based on best available evidence, patient clinical status, dosing protocols and recommendations, and culture and susceptibility results.[13,14] Additionally, an LOS protocol was developed to guide the empiric antibiotic choice, laboratory investigations, recommendations on common specific organisms, and their appropriate treatment (Supplementary Table 1, online). Education seminars on common infections and antimicrobials in the NICU were conducted at nursing education days, as well as the teaching days for both NICU physicians and trainees. The late phase of the project was implemented in January 2017 consisting of the addition of weekly "handshake rounds" with the infectious disease (ID) team, which included an attending ID specialist, fellows, pharmacists, and the NICU medical team to review antibiotic use for appropriateness. This in-person meeting occurred weekly on Monday afternoons and involved discussing every patient on antibiotics regarding appropriateness, indication, and duration. At our institution, empiric antibiotic protocols include ampicillin plus gentamicin for early-onset sepsis (EOS) and cloxacillin plus gentamicin for LOS. During the gentamicin shortage in 2014–2016, tobramycin was used in its place. For LOS of suspected intra-abdominal origin, vancomycin plus cefotaxime is used as empiric therapy. Metronidazole is added if there is concern for bowel perforation. Some other changes in our prescription policies include the following: (1) restricting the prescription of linezolid to those infected by multidrug-resistant gram-positive organisms or those with contraindications to vancomycin and (2) switching to the extended interval aminoglycoside dosing in 2017.

Data collection

Patient demographics were collected from the existing neonatal databases built for clinical care. These included birthweight (BW), gestational age (GA), history of laparotomy and other surgical interventions (extracorporeal membrane oxygenation, thoracotomy, reservoir or drain, ventriculoperitoneal shunt, ostomy, other neurological surgery, other operations or procedures, and patent ductus arteriosus ligation as defined in the Canadian Neonatal Network[15]), presence of NEC, and score for neonatal acute physiology-II (SNAP-II). SNAP II is a validated measure of severity of illness during the first 12 hours of a newborn's admission to the NICU.[16] Subgroup analyses were performed on (1) VLBW (BW <1, 500 g) infants, (2) those who did not have any surgery or culture-proven sepsis or NEC ≥ stage II, and (3) the combination of VLBW and no surgery or culture-proven sepsis or NEC ≥ stage II.

Outcomes

Change in antibiotic use was assessed via antibiotic utilization rate (AUR), days of therapy (DOT), and antibiotic spectrum index (ASI), all of which have been described in the neonatal literature.[17] The AUR is defined as the number of days with ≥1 antibiotic divided by total patient days. DOT is defined as the number of days that a patient receives a particular antibiotic, standardized per 1,000 patient days. Each antibiotic a patient receives on a given day is counted as 1 DOT; thus, 1 day can produce multiple DOT. Total DOT refers to the sum of DOT of ampicillin, cloxacillin, gentamicin, tobramycin, cefotaxime, vancomycin, metronidazole, meropenem, and linezolid. In the ASI, commonly used antibiotics are assigned points ranging from 1 to 13 based on activity against important pathogens, with higher ASI signifying broader spectrum of activity, based on the published criteria.[17] ASI is calculated per antibiotic day using the sum of points allocated to all antibiotics on that day.

Statistical analysis

Comparisons of averages among phases were conducted using Poisson regressions on the total AUR, DOT, or ASI for each period within each subgroup. They were calculated monthly as well as total over each period: before implementation (period 1), early during implementation (period 2), and later after implementation (period 3). An interrupted time-series (ITS) model was constructed with breaks at the beginning of periods 2 and 3. Univariate comparisons were made using the Pearson χ^2 test for dichotomous data, and analysis of variance (ANOVA) or the Kruskal–Wallis test was used for continuous data. This analysis was performed within each subgroup for AUR, DOT, ASI, and the DOT for each antibiotic. $P < .05$ was regarded as statistically significant. The Children's and Women's Research Ethics Board at the University of British Columbia reviewed the application and agreed that this was a quality assurance project and did not require ethics approval.[18]

Results

In total, 4,512 infants were included between January 2010 and December 31, 2019 (Table 1). Their mean GA was 33 weeks (SD, ±5) and the mean BW was 2,215 g (SD, ±1,054). The infants in periods 2 and 3 had higher average birth weights (2,300 vs 2,159 g; $P < .01$), compared to infants in period 1.

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Table 1. Demographic Characteristics of Study Infants.

Variable	Total (n=4,512)	Study Period			*P* Value
		Period 1, Before Implementation (n=1,869)	Period 2, Soon After Implementation (n=1,371)	Period 3, Later After Implementation (n=1,272)	
Birthweight, mean g (SD),	2,215 (1,054)	2,159 (1,038)	2,213 (1,049)	2,300 (1,079)	<.01
Birthweight <1500 g, no. (%)	1410 (31)	619 (33)	420 (31)	371 (29)	.04
Gestational age, mean weeks (SD),	33.4 (5.1)	33.2 (5.0)	33.3 (5.1)	33.7 (5.2)	.04
SNAP-II score ≤20, no. (%)	2,709 (60)	1,117 (60)	822 (60)	770 (61)	.91
NEC, no. (%)	85 (1.9)	41 (2.2)	19 (1.4)	25 (2.0)	.24
History of surgical procedures, no. (%)	428 (10)	191 (10)	129 (9)	108 (9)	.27

Note. SD, standard deviation; NEC, necrotizing enterocolitis; SNAP, score for neonatal acute physiology.

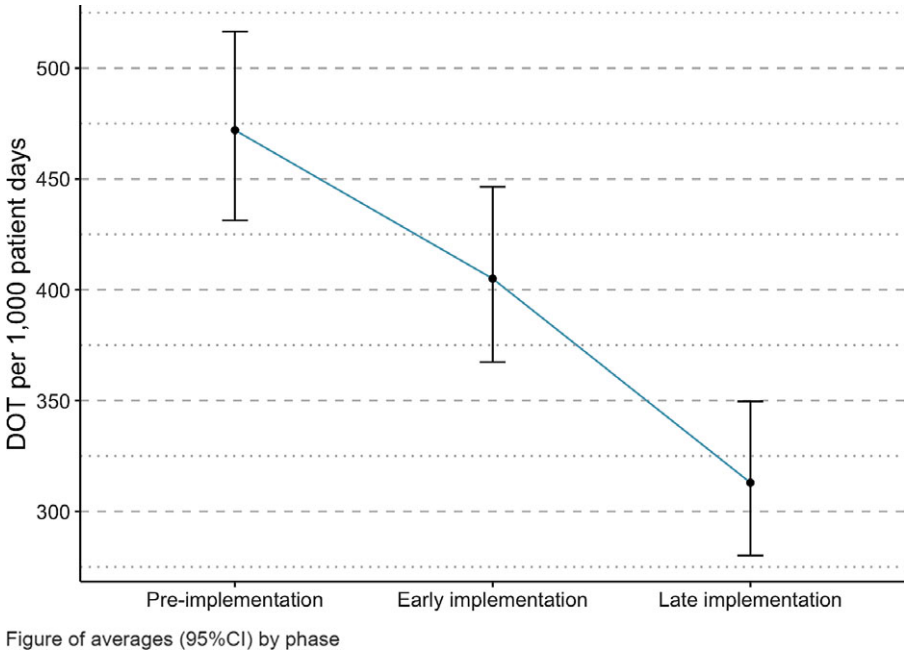

Fig. 1. Days of therapy (per 1,000 patient days) across the 3 phases for all participants.

Overall, we report a 34% decrease in the total DOT over the 10-year period ($P < .01$) (Fig. 1). The mean DOT for each period were 472 (95% confidence interval [CI], 431.3–516.6) in period 1, 405 (95% CI, 367.4–446.4) in period 2, and 313 (95% CI, 280.2–349.7) in period 3. This trend was observed within all subgroups, namely infants without culture-proven sepsis or NEC ≥ stage II or surgery, VLBW infants, and VLBW infants without NEC ≥ stage II and/or culture-proven sepsis and/or surgery (all $P < .01$) (Fig. 2).

We detected a significant reduction in DOT for gentamicin-tobramycin ($P < .01$), ampicillin ($P = .03$), cloxacillin ($P < .01$), and linezolid ($P < .01$) (Fig. 3). These antibiotic changes were consistent in all subgroups, except for ampicillin, which showed a nonsignificant decrease across all subgroups (Supplementary Figs. 1–3 online).

We detected a nonsignificant reduction in overall AUR over the 3 periods, with a mean AUR of 27% (95% CI, 18.5–39.4) in period 1, 23% (95% CI, 15.3–34.6) in period 2, and 19% (95% CI, 12.1–29.8) in period 3 ($P = .50$) (Fig. 4).

There was no significant decrease in all-participants mean ASI and subgroup ASI across the 3 periods, with a mean ASI of 7 (95% CI, 3.3–14.7) in period 1, 7 (95% CI, 3.3–14.7) in period 2, and 6 (95% CI, 2.7–13.4) in period 3 (Fig. 5).

Discussion

The implementation of ASP initiatives was associated with a reduction in antibiotic usage of 34% in total DOT over a decade. To our knowledge, this is one of the largest studies in a tertiary- and quaternary-care NICU to examine the effects of an ASP, both by number of patients and intervention period. Additionally, the primary driver of these changes was a reduction in the use of ampicillin, aminoglycosides, and cloxacillin, which are empiric therapies for early- and late-onset sepsis.

The goal of the ASP is to provide standardized, evidence-based recommendations for hospital antimicrobial use.[19] The decrease in DOT could be attributed to the increased awareness of judicious use of antibiotics among our healthcare providers through efforts

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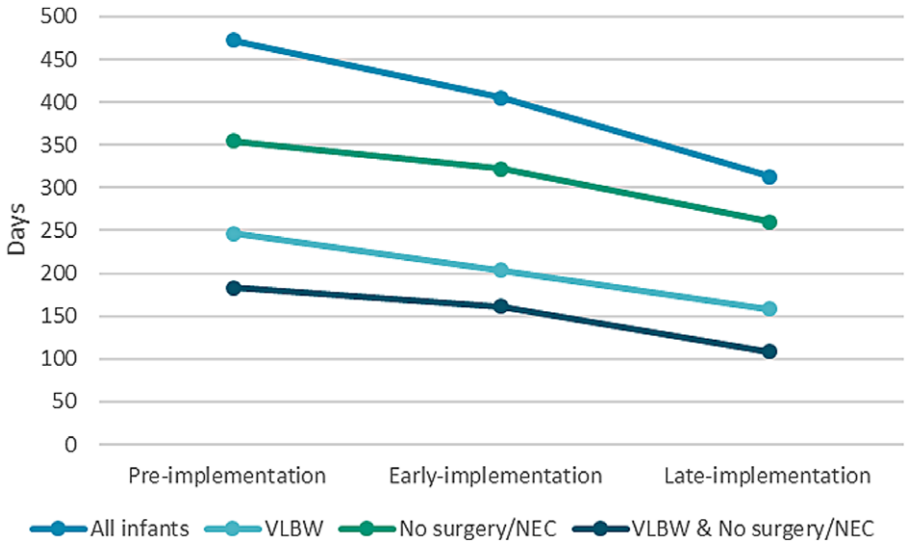

Fig. 2. Days of therapy (per 1,000 patient days) by subgroup.

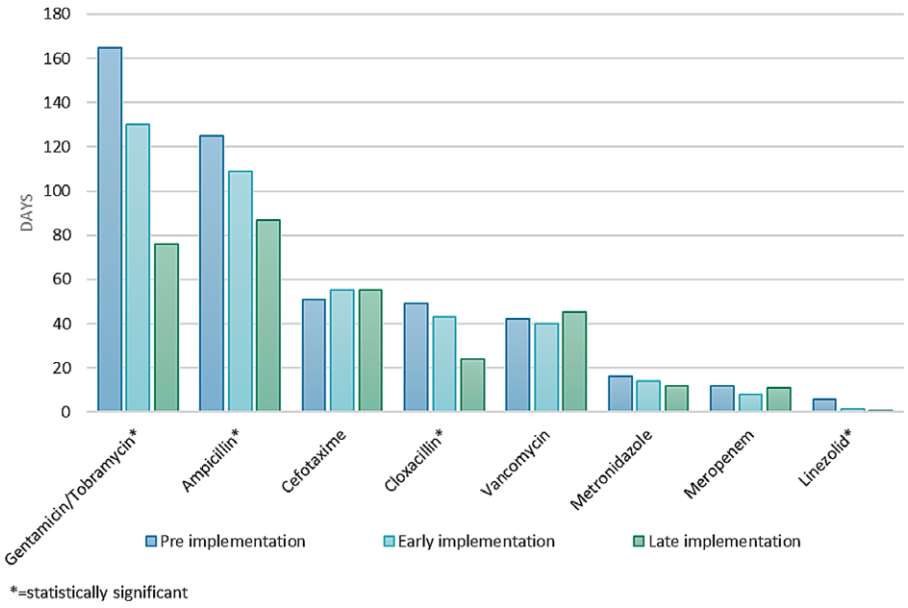

Fig. 3. Days of therapy implementation period (per 1,000 patient days) by antibiotic.

of the ASP team. It could also be related to changes in our practice policies. For example, in 2017, our unit switched to extended-interval aminoglycoside dosing, which contributed to the significant drop in its DOT for this agent.

Our findings are comparable with previously studied initiatives. Nzegwu et al[20] analyzed antibiotic use in a 54-bed NICU and reported a nonsignificant decrease in DOT over 5 years, with a significant decrease in ampicillin use but not other antibiotics. In a recent study by Thampi et al,[21] DOT decreased by 14% after ASP implementation, without a change in clinical outcomes.[21] Finally, Cantey et al[22] analyzed antibiotic usage in 2,502 infants over 1 year and reported an overall decrease in DOT by 27% through the use of stewardship initiatives.[22] A recent systematic review examining premature infants and the impacts of ASP supported its use, especially when multifactorial and tailored measures were used.[23] Although we detected a significant decrease in DOT, this metric does have some limitations, including that DOT decreases can occur with increased use of broad-spectrum monotherapy.[17] However, we did not see a compensatory increase in broad-spectrum antibiotic use in our study from our analysis of ASI. No significant decline was seen with cefotaxime and vancomycin, which could be due to their use as empiric coverage for intra-abdominal infections or the relatively small sample size. These agents will be a target for future ASP efforts.

As with most other NICU-focused studies, we examined antibiotic consumption using DOT, though we also employed AUR which is a newer metric in the NICU field.[17,26] Makri et al[24] reported a reduction in AUR of 43%, and the largest effect was driven by limiting the duration of antibiotics in culture negative sepsis and by not initiating antimicrobials in low-risk, well babies. Similar methods were used in a 2020 study by Meyers et al,[25] who reported a 43% decrease in AUR using clinical guidelines and automatic discontinuation of antibiotics at 36 hours with culture-negative sepsis. AUR measurement has some limitations. It does not account for multiple antibiotics used in 1 day; it relies on admission lengths and thus gives more weight to shorter lengths of stay, and it may be subject to significant interhospital variation.[17] The decrease in DOT but nonsignificant reduction in AUR in our unit might

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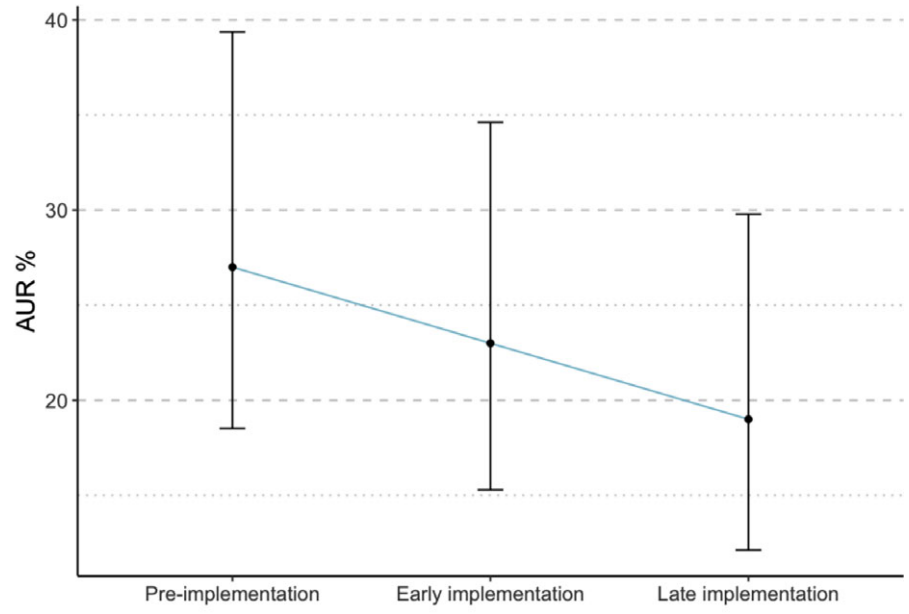

Fig. 4. Antibiotic utilization rate across the three phases for all participants.

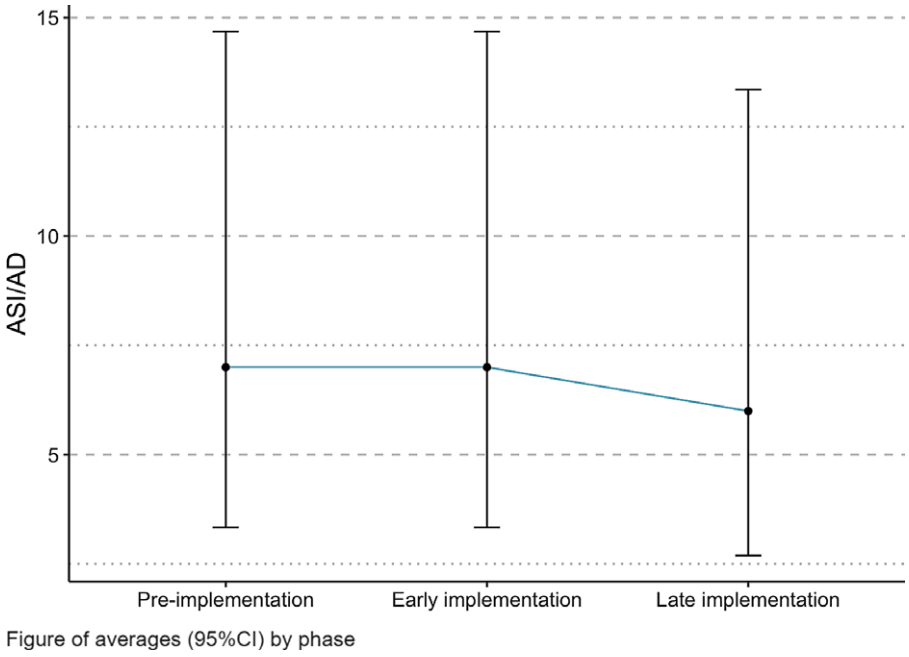

Fig. 5. Antibiotic spectrum index (ASI) across the three phases for all participants.

indicate that infants were exposed to a smaller number of antibiotics but not necessarily less days of exposure to the antibiotics. This finding is important to consider when planning the next stage of our ASP.

Subgroup analyses were performed for several reasons. VLBW infants are thought to be the most susceptible to the negative impact of antibiotics.[7,27] Higher AUR in this population is associated with an increased risk of mortality or major morbidity (eg, persistent periventricular echogenicity or echolucency on neuroimaging, stage 3 or higher retinopathy of prematurity, and chronic lung disease).[7] The confirmation of significant decline in total DOT was a valuable finding for the VLBW group. Those with surgical conditions, NEC, and sepsis were assessed because these were the infants with more justification to be exposed to prolonged antibiotics. It is reassuring to find the decrease of DOT in all subgroups.

In our cohort, DOT in all infants appeared to be higher than those of the VLBW subgroup. Infants of lower GA and lower BW are in general more likely to receive more antibiotics for prophylaxis or treatment due to their less mature immune system and more exposure to invasive procedures. Our paradoxical finding was likely to be explained by the referral pattern. Once infants are stabilized, they would be transferred from our tertiary- or quaternary-care beds to the level II units as soon as possible. Their duration of stay in the lower-level unit would not be captured by our existing database system. In other words, transferred term

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infants would have a relatively short stay in our unit compared to those born prematurely, yet many were receiving the empiric antibiotics for possible sepsis during most of their stay, that is, relatively high DOT and AUR.

It is reassuring to see a persistence in significant reduction of DOT between the early and late phases of ASP implementation because the new intervention between those periods was "handshake rounds." The impact of handshake rounds has not been well studied in the NICU population; however, handshake rounding is an innovative and effective method to reduce inappropriate antibiotic use in pediatrics.[28] Our study supports this collaborative approach in the NICU to further ASP goals and reduce antibiotic use.

This study is one of the few that have investigated the impact of an ASP on antibiotic use in NICU patients and using subgroups based on birthweight. We did see areas of improvement, but we recognize that continued focus is needed on the most vulnerable lower birthweight infants, those with NEC and/or surgery, and broad-spectrum antibiotic use.

Our study had several limitations. It is challenging to diagnose sepsis in such a vulnerable population, and there is no clear consensus on the management of common conditions such as culture-negative sepsis, pneumonia, and urinary tract infection.[1,2,29] We were not able to determine the proportion of the antimicrobial use that was inappropriate. The infants in periods 2 and 3 had slightly higher average birth weights, compared to infants in period 1. This difference may have had some impact on the antibiotic consumption throughout the study period. We did not examine clinical outcomes in this audit; thus, we were unable to determine whether the ASP resulted in any change in outcomes or reduction of multidrug-resistant organisms isolated in the unit. However, this factor has been assessed in other ASP studies, which have shown no change in mortality or morbidity with similar decreases in DOT/AUR.[21,24] Alternatively, these benefits could also be due to other interventions such as continuing medical education, new research, improvements in diagnostic tools, etc. Additionally, we only considered the most common antibiotics used and thus could have missed the potential effect of less frequently employed antimicrobials such as cefazolin, cefoxitin, piperacillin-tazobactam, etc.

Our study has highlighted the need for future ASP goals. Primarily, we will work toward significantly decreasing unnecessary broad-spectrum antibiotic use, particularly the use of vancomycin and cefotaxime. Additionally, it would be beneficial to correlate antibiotic decline with clinical outcomes, such as evaluating the resurgence of sepsis after stopping antibiotics. It is equally important to conduct retrospective antibiotic audits to identify the proportion of inappropriate antibiotic use and identify the targets of stewardship.[20]

Our study has demonstrated a significant decline in antibiotic usage through DOT across a decade in level 3 NICU in Canada. This change was persistent across VLBW and those without NEC or sepsis or surgical conditions. This study has highlighted several future improvement goals, with a specific focus on reducing the use of broad-spectrum antibiotics.

Supplementary material. To view supplementary material for this article, please visit https://doi.org/10.1017/ice.2022.318

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