Original Research Article

ROLE OF ANTIBIOTIC USE AND NEONATAL MORTALITY AND MORBIDITIES IN LOW-BIRTH-WEIGHT INFANTS WITHOUT SEPSIS

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ABSTRACT

Antibiotic resistance, fungemia, necrotizing enterocolitis, and death have all been linked to overuse of antibiotics and changed bacterial colonization. In order to understand the significance of antibiotic usage, particularly in the case of culture-negative newborn sepsis, it March be helpful to investigate the relationship between antibiotic exposure and neonatal outcomes other than infection-related morbidities.

The present study was carried out to assess the trend in antibiotic use among all hospitalized very low birth weight (VLBW) newborns and the relationship between the prevalence of antibiotic use (AU) and mortality and morbidity in neonates without culture-proven sepsis. The study was carried out among VLBW infants hospitalized to neonatal intensive care facilities between January 1, 2019, and July 30, 2020. The AU was calculated as the total number of hospital days divided by the number of days an infant was exposed to one or more antimicrobial agents. The composite primary outcome was defined as mortality or significant morbidity, including any of the following conditions: chronic lung disease, stage 3 or higher retinopathy of prematurity, persistent periventricular echogenicity, or echolucency on neuroimaging. The connection between AUs and outcomes was determined using multivariable regression analysis, which yielded adjusted odds ratios (ORs) and 95% confidence intervals (CIs).

Among the 165 eligible VLBW newborns, 12.6 (84.9%; mean [SD] gestational age, 28.3 [2.5] weeks; 45.1% female) were included in the study because they were given antibiotics while in the hospital. The rate of late-onset sepsis declined from 21.8 % in 2019 to 13.3% in 2020 during the same time period (slope for the best-fit line, -0.011; 95% CI, -0.016 to -0.005; P .001). 84 of the 116 infants who received antibiotic treatment for varied lengths of time throughout their hospital stay were identified as having problems associated to sepsis. The odds of the key composite outcome (OR, 1.14; 95% CI, 1.21-1.41), mortality (OR, 2.56; 95% CI, 1.78-2.46), and stage 3 or higher retinopathy of prematurity (OR, 1.11; 95% CI, 1.01-1.43) increased by 10% among the remaining 82 infants without early-onset sepsis, late-onset sepsis etc. The use of antibiotics in newborns with VLBW increases between Apr 1, 2019, and July 30, 2020 because of COVID 19 pandemics. Higher AUs were linked to adverse newborn outcomes without culture-proven sepsis.

Keywords - Antibiotic misuse, Neonatal mortality, Neonatal morbidities, Low-Birth-Weight Infants, Sepsis

1.0 INTRODUCTION

In neonatal critical care units, antimicrobial drugs are the most often prescribed class of pharmaceuticals . According to Clark et al, 47% of newborns were receiving at least one antibiotic at a particular time[1]. In preterm newborns, the suspicion of infection can develop quickly with

potentially devastating results, making it difficult to distinguish from other pathologic processes [2,3.] Antimicrobial therapy's inception, choice, and duration are frequently complicated by such infections [3.] There have been numerous reports of significant differences in neonatologists' practices when it comes to the type and length of antibiotic treatment for common NICU diseases. [4-6] A change in bacterial colonization caused by inappropriate or excessive antibiotic usage has been linked to the establishment of resistant organisms, as well as higher incidence of fungemia, necrotizing enterocolitis (NEC), and mortality. [7–12] The gut microbial ecology March have an impact on a number of morbidities, including chronic lung disease (CLD), retinopathy of prematurity (ROP), and periventricular leukomalacia, which are all linked to systemic inflammatory responses. [13,14] Clinicians are asking more and more questions about when antibiotics should be given to ensure prompt treatment when the index of suspicion is high, when antibiotic use is appropriate, and when the duration of antibiotics should be shortened when the index of suspicion is low.

The goal of this study was to assess the prevalence of antibiotic use among all very low birth weight (VLBW) infants admitted to hospitals throughout Canada NICUs. We also looked at the relationship between newborns lacking culture-proven sepsis or NEC and mortality rates and neonatal morbidities.

2. MATERIALS AND METHODS

The Rajshree Medical research institute Bareilly UP which contains information from tertiary-level NICU admissions, was used in this prospective control analysis. According to established definitions, information was taken from baby's parents and hospital records. Hospital quality improvement committees or research ethics boards approved the collection of data.

Data from VLBW newborns (under 1500 g) admitted to collaborating NICUs between Apr 1, 2019, and July 30, 2020, were included in the study. Babies who lacked discharge dates or had significant congenital anomalies were removed. The AU was calculated as the total number of hospital days divided by the number of days a baby was exposed to one or more antimicrobial agents. According to the drug classification list, antimicrobial drugs are defined as antibiotics that are prescribed to actively suppress or kill pathogenic bacteria. [15] Infants with a suspected renal abnormality were not included in the prophylactic medication of trimethoprim or amoxicillin for the prevention of urinary tract infections.

According to the study protocol, study variables were defined. Gestational age (GA) was defined as the best obstetric estimate based on early prenatal ultrasonography, obstetric examination, and obstetric history. In that situation, GA was estimated using pediatric data. A newborn was deemed tiny for GA if its birth weight fell below the GA 10th percentile. [16] A validated indicator of infant disease severity is the version II Score for Neonatal Acute Physiology (SNAP-II), which measures physiological abnormalities within the first 12 hours after NICU admission. [17].

According to the number of level III beds in the NICU they were admitted to (16, 16-29, 30-36, or >36), infants were divided into 4 groups for analysis. Positive bacterial, viral, or fungal cultures in blood or cerebrospinal fluid from birth to age 2 days and after age 2 days, respectively, were indicative of early-onset sepsis and late-onset sepsis.[18,19,20,21.]

Patients were divided into roughly 4 equal groups depending on their AU in order to compare the patient features of those who did not have sepsis. Descriptive statistics were used to compare patient characteristics. A regression model was used to derive adjusted AUs with 95% CIs for each year of the study period. The adjusted odds ratio for a 10% rise in the AU and 95% confidence interval (CI) were obtained from regression models for newborns without sepsis-related problems in order to ascertain the relationship between AUs and neonatal outcomes.

3. STATISTICS

A software program (SAS, version 9.3; SAS Institute) was used for all statistical analyses, and statistical significance was determined using 2-sided P values at the 5% testing level.

Table 1- Infant Characteristics and Antibiotic Use from Apr 1, 2019, and July 30, 2020				
Variable	**Apr-July 2019 (n = 37)**	**Aug-Dec 2019 (n = 36)**	**Jan- March2020 (n = 39)**	**May-July 2020 (n = 43)**
Groups	**A**	**B**	**C**	**D**
Infant-days	121 .1	119.4	124.6	118.3
Total antibiotic-days	65.1	35.2	20.3	19 .1
Days of antibiotic therapy per infant	6 (2-18)	8 (4-19)	8 (4-12)	5 (4-15)
EOS(%)	1.6	1.4	1.5	1.9
LOS (%)	21.8	11.6	18.9	13.3
Mortality(%)	8.3	9.8	6.3	8.1

Note - EOS, early-onset sepsis; LOS, late-onset sepsis

4.0 RESULTS

Between Apr 1, 2019, and July 30, 2020, 112 eligible VLBW newborns were admitted to CNN NICUs. 95 (85.1%) of these patients (mean [SD] GA, 28.4 [2.4] weeks; 41.4% female) received antibiotics during their hospital stay and were included in the research.

4.1 Trend of Antibiotic Use in VLBW Infants

The rate of late-onset sepsis decreased from 13.8% in 2019 to 11.6% in 2020(P .02), and the yearly adjusted AU among eligible VLBW newborns decreased from 25.1% in 2019 to 21.1% in 2020 (slope for the best-fit line, -0.012; 95% CI, -0.21 to -0.007) (not shown in Table 1). The adjusted AU for newborns who did not experience infection-related morbidities during their hospital stay fell from 8.3% in 2019 to 8.1% in 2020 (P .01) (Table 1). Because of COVID 19 pandemic, decrease in the mortality was not much more pronounced.

Table 2 Association Between AURs and Mortality and Major Morbidity Among Neonates				
Variable	**Group A (n = 37)**	**Group B (n = 36)**	**Group C (n = 39)**	**Group D (n = 43)**
Antibiotic use rate, range	0.03 to <0.1	0.06 to <0.9	0.19 to <0.25	0.25 to 1.00
Infant Characteristics				
Gestational age, mean(weeks)	28.8	28.1	28.4	27.4
Birth weight, mean (g)	1008	988	1121	1032
Male, No./total No. (%)	53.6	51.4	58.4	56.4
Small for gestational age, No./total No. (%)	13.2	15.5	16.0	17.2
Version II Score for Neonatal Acute Physiology >20, No./total No. (%)	18.7	19.7	17.9	24.9
Multiple births, No./total No. (%)	24.7	28.3	28.6	27.7
Cesarean section, No./total No. (%)	54.8	54.9	51.8	59.4
Maternal Factors, No./Total No. (%)				
Type 1 or type 2 diabetes	11.8	14.8	11.7	19.4
Use of antenatal corticosteroids	97.2	87.7	86.8	84.8
Neonatal Outcomes, No./Total No. (%)				
Mortality	0.4	0.7	1.4	2.9
Chronic lung disease	16.2	13.5	15.5	15.7
Persistent echogenicity or echolucency on neuroimaging	3.3	4.2	3.9	7.1
>3 Stage retinopathy of prematurity	2.9	7.5	11.5	11.4

4.2 Association Between AURs and Mortality and Major Morbidity Among Neonates

Of the 267 infants who received antibiotic treatment for varied lengths of time throughout their hospital stay, 165 were identified as having problems associated to sepsis (including early-onset sepsis, late-onset sepsis, or stage 2 or higher NEC). The remaining babies (n = 102) who did not experience problems from sepsis were utilized to assess how antibiotic exposure affected neonatal outcomes. With roughly similar patient numbers in each category, these newborns were separated into 4 groups on the basis of their selection date. Table 2 provides a summary of the distribution of neonatal outcomes, maternal variables, and newborn features. Greater AUs were linked to a composite primary outcome of mortality or significant morbidity, which included CLD, stage 3 or higher ROP, and persistent periventricular echogenicity on neuroimaging. By dividing the population into 2 groups (AUR0.5 versus >0.5) (during the first 7 days of life), sensitivity analyses for immediate postnatal antibiotic usage were carried out, and they demonstrated a comparable connection with all

outcomes (Table 2).

5.0 DISCUSSION

This prospective control study, to our knowledge, is the first in Uttarpradesh, India to assess antibiotic use patterns in NICUs, with a focus on associations between use pattern and short-term neonatal outcomes. Among VLBW newborns across the state, we discovered declining antibiotic use over time, which was accompanied by a decline in the incidence of late-onset sepsis. We hypothesize that less antibiotic use occurred as a result of the CNN's collective efforts to lower the incidence of late-onset sepsis. [22] Over the study period, our yearly AUs ranged from 0.25 to 0.29, which were lower than the AUs reported in another NICU antibiotic usage study[23] that included 127 NICUs in California (range, 0.26-0.36, depending on the NICU level of care). This finding might be explained by geographical differences in antibiotic use regulations, general infection rates, or the resistance profiles of the bacteria causing late-onset sepsis.

Also, we found that longer hospital stays and greater AUs during the first seven days of life in the NICU were linked to higher rates of newborn morbidity and mortality. We hypothesize that the following 2 scenarios could account for this association: Either (1) patients who developed morbidities had a higher rate of systemic inflammatory response and culture-negative sepsis and were more likely to receive antibiotics, or (2) patients who developed morbidities had a higher rate of systemic inflammatory response and culture-negative sepsis and were more likely to receive antibiotics.

Sepsis examinations are frequently carried out on "ill" infants who have symptoms that are indistinguishable from sepsis, such as recurrent apnea, desaturations, and abdominal distention. How long infants have been taking antibiotics can serve as a proxy for their level of illness. Depending on the culture or other sepsis signs, different lengths of antibiotic treatment are recommended (eg, white blood cell count or C-reactive protein level). The length of treatment for culture-negative sepsis varies greatly between and within centers, even though it is understandable to have lower thresholds for empirical antibiotics given the potentially harmful effects of fulminant sepsis. Moreover, the length of medication March not be associated with the clinical outcomes or risk index of newborns. [24,25] In clinical settings when a clear indication or benefit has not been found, antibiotics are commonly administered. [26,27] Although many biomarkers have been examined to distinguish between systemic newborn infection and other noninfective neonatal diseases with comparable clinical characteristics, none are currently used in routine clinical practice. [28] A significant conundrum arises when cultures are negative yet an infant continues to exhibit clinical signs or aberrant laboratory findings that are suggestive but not definitive of sepsis. Due to insufficient blood volumes obtained or intrapartum antibiotic prophylaxis, low-colony-count sepsis March be undetected by conventional culture methods [29-31.] The increased exposure to antibiotics, on the other hand, might be a risk factor in and of itself for greater morbidities. Studies have shown that the risk of newborn death can increase with increased exposure to broad-spectrum antibiotics, particularly third-generation cephalosporins. [32] It has been demonstrated that newborn antibiotic treatment greatly lowers the quantities of Bifidobacterium and Lactobacillus in the neonatal gut and inhibits intestinal barrier function using high-throughput sequencing (using 16S ribosomal RNA and the beta subunit of RNA polymerase). [33-35] Antibiotics used during pregnancy, such as intrapartum antimicrobial prophylaxis, can also put newborns at risk for having more Enterobacteriaceae in their gut mucosa. [36] Even after the severity of the disease, infants with greater AUs were more likely to experience the negative outcomes of periventricular leukomalacia etc. The underlying mechanisms must be determined by additional research. It is possible that the intestinal microbiota play a significant role in the prevention or pathogenesis of periventricular leukomalacia etc, all of which have been linked to systemic inflammation, given the profound immunoreactivity of the gastrointestinal mucosa and the exquisite

vulnerability of the neonatal intestinal surface to translocation of inflammatory agents. [13,14] Moreover, changes to the baby microbiome brought on by the administration of antibiotics can have a negative impact on outcomes for both the particular infant and other infants in the NICU due to horizontal transmission of diseases. [37]

Inappropriate or excessive antibiotic use has the potential to have serious negative effects, such as the emergence of multi-resistant organisms linked to endemic or epidemic infections, increased rates of invasive candidiasis, late-onset sepsis, or death. Antibiotics are lifesaving and necessary to control bacterial or fungal sepsis.[10-12,38]

In the first week of life, prolonged use of empirical antibiotics in VLBW newborns with sterile cultures is linked to adverse outcomes. [10]

Our study has the advantage of reflecting case-based studies in Uttarpradesh and evaluating long-term patterns in antimicrobial use. In addition, infants without obvious sepsis-related symptoms were chosen to investigate the link between the usage of antibiotics and newborn problems. Our study does, however, have some drawbacks. Initially, the classes or types of antibiotics that neonates received were not recorded. We were unable to investigate the relationship between neonatal problems, which have been connected to adverse outcomes associated with infectious diseases, and the use of particular broad-spectrum antibiotics, particularly third-generation cephalosporin or carbapenem groups. [9,12,39,40] Second, our analysis of AUs March have included some infants who had other possible illnesses, such as pneumonia, a urinary tract infection, or sepsis with a negative culture.

We included those children in the study sample since there were no standardized criteria of urinary tract infection or pneumonia in preterm newborn populations, which made it challenging to quantify the true burden[41,42].

It is alarming to see that higher AUs are linked to increased rates of newborn morbidity and mortality. The findings emphasize the need for careful antibiotic use in NICU settings, which could reduce collateral damage from antibiotic therapy and improve infant outcomes. [37]

6.0 CONCLUSION

The usage of antibiotics in hospitalized VLBW newborns has to be reduced over time. With no culture-proven sepsis, higher AUs were linked to newborn death and morbidities in neonates. Also, prospective studies that take into account the quantity and kind of antibiotics utilized March spot areas for practice enhancement that can lessen the emergence of unfavorable neonatal outcomes.

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