Journal of Cardiovascular Disease Research

ISSN:0975 -3583,0976-2833 VOL14, ISSUE 05, 2023

Correlation between antibiotic use and neonatal mortality and morbidities in Low-Birth-Weight Infants Without Sepsis

Jitendra Kumar Chaudhary[1], Shamsheer Ali Teeto[2]

[1]Jitendra Kumar Chaudhary, Professor and Head, Department of Microbiology, Varun Arjun Medical College and Rohilkhand Hospital, Banthra, Shahjahanpur, U.P., India Pin- 242307.

[2]Shamsheer Ali Teeto, Assistant Professor, Department of Microbiology, Varun Arjun Medical College and Rohilkhand Hospital, Banthra, Shahjahanpur, U.P., India, Pin 242307.

Corresponding author

Shamsheer Ali Teeto, Assistant Professor, Department of Microbiology, Varun Arjun Medical College and Rohilkhand Hospital, Banthra, Shahjahanpur, U.P., India, Pin 242307.

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 may 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 (1500 g) hospitalized to neonatal intensive care facilities between January 1, 2019, and June 30, 2022. 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 132 eligible VLBW newborns, 11 669 (84.9%; mean [SD] gestational age, 27.7 [2.5] weeks; 47.4% female) were included in the study because they were given antibiotics while in the hospital. The rate of late-onset sepsis declined from 19.0% in 2019 to 13.8% in 2022 during the same time period (slope for the best-fit line, -0.011; 95% CI, -0.016 to -0.006; P .01). 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, 2.36; 95% CI, 1.98-2.46), and stage 3 or higher retinopathy of

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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 declined between Jan 2019 and Jun 2021. Higher AUs were linked to adverse newborn outcomes without culture-proven sepsis.

Key words - 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 may 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 Varun Arjun Medical College and Rohilkhand Hospital, Banthra, Shahjahanpur, U.P., which contains information on 95% of 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 January 1, 2019, and June 30, 2021, 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

ISSN:0975 -3583,0976-2833 VOL14, ISSUE 05, 2023

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

Generalized linear models with suitable link functions were fitted to all regression analyses to account for relevant confounders. The rate for the AU annual trend was modified for GA, sex, SNAP-II over 20, and unit size (4 categories defined by the number of beds at each site). The odds ratios were modified for GA, sex, SNAP-II surpassing 20, unit size, admission year, small for GA, multiple births, cesarean section, birth at a non-institution, and maternal use of prenatal corticosteroids when examining the relationship between AUs and neonatal outcomes. In order to take into account correlations among the infants within sites, generalized estimating equations with separate correlation structures were utilized in all regression models. 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 Jan 2019- July 2021
Note - EOS, early-onset sepsis; LOS, late-onset sepsis

Variable	JAN-JUNE 2019 (n = 27)	JULY-DEC2019 (n = 26)	JAN-JUNE2020 (n = 29)	JULY-DEC2020 (n = 38)	JAN2021-JULY2021 (n = 42)
Infant-days	101 .1	109.4	104.6	106.6	108.3
Total antibiotic-days	25.1	32.2	30.3	24.3	21 .1
Days of antibiotic therapy per infant	7 (2-18)	9 (4-19)	6 (2-12)	4 (2-11)	6 (4-15)
EOS(%)	1.9	1.6	1.8	1.6	1.5
LOS (%)	18.8	19.6	16.6	16.9	16.3)
Mortality(%)	7.3	9.1	9.4	6.6	6.1

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4.0 RESULTS

Between 2019 and 2021, 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 18.8% in 2019 to 16.3% in 2021 (P .01), and the yearly adjusted AU among eligible VLBW newborns decreased from 25.1% in 2019 to 21.1% in 2021 (slope for the best-fit line, -0.011; 95% CI, -0.016 to -0.006). (Table 1). The adjusted AU for newborns who did not experience infection-related morbidities during their hospital stay fell from 7.3% in 2019 to 6.1% in 2021 (P .01). (Table 1).

Variable	1 (n = 37)	2 (n = 36)	3 (n = 39)	4 (n = 43)
Antibiotic use rate, range	0.02 to <0.09	0.09 to <0.19	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, 112 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 = 155) 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. Table 2 provides a summary of the distribution

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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 may 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 may be undetected by conventional culture methods. [29-31]

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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 may 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

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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 may spot areas for practice enhancement that can lessen the emergence of unfavorable neonatal outcomes.

7.0 REFERANCES-

1. Clark RH, Bloom BT, Spitzer AR, Gerstmann DR. Reported medication use in the neonatal intensive care unit: data from a large national data set. *Pediatrics*. 2006;117(6):1979-1987.
2. Fanaroff AA, Korones SB, Wright LL, et al; National Institute of Child Health and Human Development Neonatal Research Network. Incidence, presenting features, risk factors and significance of late onset septicemia in very low birth weight infants. *Pediatr Infect Dis J*. 1998;17(7): 593-598.
3. Cantey JB, Patel SJ. Antimicrobial stewardship in the NICU. *Infect Dis Clin North Am*. 2014;28(2): 247-261.
4. Engle WD, Jackson GL, Sendelbach D, et al. Neonatal pneumonia: comparison of4vs 7 days of antibiotic therapy in term and near-term infants. *J Perinatol*. 2000;20(7):421-426.
5. W6jkowska-MachJ,R6zahskaA, Borszewska-Kornacka M, et al. Necrotising enterocolitis in preterm infants: epidemiology and antibiotic consumption in the Polish Neonatology Network neonatal intensive care units in 2009. *PLoS One*. 2014;9(3):e92865. doi:10.1371/journal .pone.0092865
6. Cotten CM. Antibiotic stewardship: reassessment of guidelines for management of neonatal sepsis. *Clin Perinatol*. 2015;42(1): 195-206, x.
7. Bizzarro MJ, Gallagher PG. Antibiotic-resistant organisms in the neonatal intensive care unit. *Semin Perinatol*. 2007;31(1):26-32.
8. Saiman L. Risk factors for hospital-acquired infections in the neonatal intensive care unit. *Semin Perinatol*. 2002;26(5):315-321.
9. Saiman L, Ludington E, Dawson JD, et al; National Epidemiology of Mycoses Study Group. Risk factors for *Candida* species colonization of neonatal intensive care unit patients. *Pediatr Infect Dis J*. 2001;20(12):1119-1124.
10. Kuppala VS, Meinzen-Derr J, Morrow AL, Schibler KR. Prolonged initial empirical antibiotic treatment is associated with adverse outcomes in premature infants. *J Pediatr*. 2011;159(5):720-725.
11. Cotten CM, Taylor S, Stoll B, et al; NICHD Neonatal Research Network. Prolonged duration of initial empirical antibiotic treatment is associated with increased rates of necrotizing enterocolitis and death for extremely low birth weight infants.
Pediatrics. 2009;123(1):58-66.
12. Cotten CM, McDonald S, Stoll B, Goldberg RN, Poole K, Benjamin DK Jr; National Institute for Child Health and Human Development Neonatal Research Network. The association of third-generation cephalosporin use and invasive candidiasis in extremely low birth-weight infants. *Pediatrics*. 2006;118(2):717-722.
13. Neu J, Douglas-Escobar M, Lopez M. Microbes and the developing gastrointestinal tract. *Nutr Clin Pract*. 2007;22(2):174-182.
14. Douglas-Escobar M, Elliott E, Neu J. Effect of intestinal microbial ecology on the developing brain. *JAMA Pediatr*. 2013;167(4):374-379.
15. Canadian Neonatal Network. Abstractor's manual. http://www.canadianneonatalnetwork.org /Portal/LinkClick.aspx?fileticket=U4anCYsSN20 %3D&tabid=69. Published September 19, 2011. Accessed September 15, 2016.
16. Kramer MS, Platt RW, Wen SW, et al; Fetal/Infant Health Study Group of the Canadian Perinatal Surveillance System. A new and improved population-based Canadian reference for birth weight for gestational age. *Pediatrics*. 2001;108(2): E35.
17. Richardson DK, Corcoran JD, Escobar GJ, Lee SK. SNAP-II and SNAPPE-II: simplified newborn illness

ISSN:0975 -3583,0976-2833 VOL14, ISSUE 05, 2023

severity and mortality risk scores. *J Pediatr*. 2001;138(1):92-100.

18. Bell MJ, Ternberg JL, Feigin RD, et al. Neonatal necrotizing enterocolitis: therapeutic decisions based upon clinical staging. *Ann Surg*. 1978;187(1): 1-7.

19. Kwon SH, Vasung L, Ment LR, Huppi PS.
The role of neuroimaging in predicting neurodevelopmental outcomes of preterm neonates. *Clin Perinatol*. 2014;41(1):257-283.

20. Jasani B, Nanavati R, Kabra N. Mechanisms and management of retinopathy of prematurity. *N Engl J Med*. 2013;368(12):1161-1162.

21. Baraldi E, Filippone M. Chronic lung disease after premature birth. *NEnglJ Med*. 2007;357(19): 1946-1955.

22. Lee SK, Shah PS, Singhal N, et al; Canadian EPIQ Study Group. Association ofa quality improvement program with neonatal outcomes in extremely preterm infants: a prospective cohort study. *CMAJ*. 2014;186(13):E485-E494. doi:10.1503/cmaj.140399

23. Schulman J, Dimand RJ, Lee HC, Duenas GV, Bennett MV, Gould JB. Neonatal intensive care unit antibiotic use. *Pediatrics*. 2015;135(5):826-833.

24. Cordero L, Ayers LW. Duration of empiric antibiotics for suspected early-onset sepsis in extremely low birth weight infants. *Infect Control Hosp Epidemiol*. 2003;24(9):662-666.

25. Spitzer AR, Kirkby S, Kornhauser M. Practice variation in suspected neonatal sepsis: a costly problem in neonatal intensive care. *J Perinatol*. 2005;25(4):265-269.

26. Patel SJ, Oshodi A, Prasad P, et al. Antibiotic use in neonatal intensive care units and adherence with Centers for Disease Control and Prevention 12-Step Campaign to Prevent Antimicrobial Resistance. *Pediatr Infect Dis J*. 2009;28(12): 1047-1051.

27. Flenady V, Hawley G, Stock OM, Kenyon S, Badawi N. Prophylactic antibiotics for inhibiting preterm labour with intact membranes. *Cochrane Database Syst Rev*. 2013;12(12):CD000246.

28. Ng PC, Ma TP, Lam HS. The use of laboratory biomarkers for surveillance, diagnosis and prediction of clinical outcomes in neonatal sepsis and necrotising enterocolitis. *Arch Dis Child Fetal Neonatal Ed*. 2015;100(5):F448-F452.

29. Connell TG, Rele M, Cowley D, Buttery JP, Curtis N. How reliable is a negative blood culture result? volume of blood submitted for culture in routine practice in a children's hospital. *Pediatrics*. 2007;119(5):891-896.

30. Schelonka RL, Chai MK, Yoder BA, Hensley D, Brockett RM, Ascher DP. Volume of blood required to detect common neonatal pathogens. *J Pediatr*. 1996;129(2):275-278.

31. Verani JR, McGee L, Schrag SJ; Division of Bacterial Diseases, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention (CDC). Prevention of perinatal group B streptococcal disease: revised guidelines from CDC, 2010. *MMWR Recomm Rep*. 2010;59(RR-10):1-36.

32. Clark RH, Bloom BT, Spitzer AR, Gerstmann DR. Empiric use of ampicillin and cefotaxime, compared with ampicillin and gentamicin, for neonates at risk for sepsis is associated with an increased risk of neonatal death. *Pediatrics*. 2006;117(1):67-74.

33. Faa G, Gerosa C, Fanni D, Nemolato S, van Eyken P, Fanos V. Factors influencing the development ofa personal tailored microbiota in the neonate, with particular emphasis on antibiotic therapy. *J Matern Fetal Neonatal Med*. 2013;26(suppl 2):35-43.

34. Schumann A, Nutten S, Donnicola D, et al. Neonatal antibiotic treatment alters gastrointestinal tract developmental gene expression and intestinal barrier transcriptome. *Physiol Genomics*. 2005;23(2):235-245.

35. Fouhy F, Guinane CM, Hussey S, et al. High-throughput sequencing reveals the incomplete, short-term recovery of infant gut microbiota following parenteral antibiotic treatment with ampicillin and gentamicin.
Antimicrob Agents Chemother. 2012;56(11): 5811-5820.

36. Arboleya S, Sanchez B, Milani C, et al. Intestinal microbiota development in preterm neonates and effect of

ISSN:0975 -3583,0976-2833 VOL14, ISSUE 05, 2023

perinatal antibiotics. *J Pediatr*. 2015;166 (3):538-544.

37. Goldstein EJ. Beyond the target pathogen: ecological effects of the hospital formulary. *Curr Opin Infect Dis*. 2011;24(suppl 1):S21-S31.

38. Singh N, Patel KM, LegerMM, et al. Riskof resistant infections with Enterobacteriaceae in hospitalized neonates. *Pediatr Infect Dis J*. 2002;21 (11):1029-1033.

39. Lee JH, Hornik CP, Benjamin DK Jr, et al. Risk factors for invasive candidiasis in infants >1500 g birth weight. *Pediatr Infect Dis J*. 2013;32(3):222-226.

40. de Man P, Verhoeven BA, Verbrugh HA, Vos MC, van den Anker JN. An antibiotic policy to prevent emergence of resistant bacilli. *Lancet*. 2000;355(9208):973-978.

41. Arshad M, Seed PC. Urinary tract infections in the infant. *Clin Perinatol*. 2015;42(1):17-28, vii.

42. Pramanik AK, Rangaswamy N, Gates T. Neonatal respiratory distress: a practical approach to its diagnosis and management. *Pediatr Clin North Am*. 2015;62(2):453-469.