

Optimising Antibiotic use in the Neonatal Intensive Care Unit through Implementation of Antimicrobial Stewardship Program: A Double Cohort Study

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ABSTRACT

Introduction: Inappropriate use of antimicrobials in newborns can lead to serious consequences, including the emergence of multidrug-resistant organisms. Implementing antimicrobial stewardship strategies in neonatal units can reduce indiscriminate antibiotic use and its harmful effects.

Aim: To study the effect of reducing antibiotic usage in newborns admitted to the Neonatal Intensive Care Unit (NICU) by creating a “No Antibiotic Zone” and implementing an Antimicrobial Stewardship Program (ASP).

Materials and Methods: This double-cohort observational study was conducted in a Level III NICU at the Children’s Hospital, GSVM Medical College, Kanpur, Uttar Pradesh, India, from April 2021 to March 2023. During the preintervention period, most neonates were administered antibiotics irrespective of risk factors. During the stewardship period, neonates were assessed for red flags, risk factors and clinical indicators of sepsis. Neonates with minimal or no risk factors or clinical signs of sepsis (n=480) were placed in an aseptic “No Antibiotic Zone” within the NICU under close monitoring. Those who exhibited

early signs of sepsis (n=178) were started on antibiotics and managed according to standard guidelines. Demographic and clinical characteristics, length of hospital stay and outcomes were compared between the preintervention (n=464) and postintervention (n=302) cohorts.

Results: The baseline characteristics of the newborns, including gender, gestational age, birth weight and incidence of various diseases, were comparable between the two cohorts. The mean gestational age and birth weight were 36±2.06 weeks and 2400±500 g, respectively. The mean length of stay before the intervention was 10.1±2.8 days, which decreased to 6.5±2.4 days after the implementation of the ASP (p-value <0.001). Antimicrobial utilisation in the NICU declined by 42% without a corresponding increase in mortality, which was statistically significant (p-value <0.001).

Conclusion: Given the growing threat of antimicrobial resistance, implementation of antimicrobial stewardship strategies—though challenging—can effectively minimise unnecessary antibiotic use in newborns.

Keywords: Antimicrobial resistance, Mortality, Newborns, Risk factors, Sepsis

INTRODUCTION

Antimicrobials are the most commonly used medications in NICUs but are often used inappropriately. In contrast to children and adults, clinical signs of infection in neonates are subtle, non specific and difficult to distinguish from other diseases; hence, antibiotics are frequently administered empirically [1,2]. A risk-based approach, relying on clinical suspicion, is often used to initiate antimicrobial therapy in neonates, resulting in a large number of uninfected infants being inadvertently exposed to antibiotics [2]. The enhanced vulnerability of preterm newborns to infection often precludes discontinuation of initial empiric antimicrobial therapy, even in the absence of positive blood cultures or laboratory findings indicative of sepsis. This leads to the overuse of antibiotics in the NICU setting [1-3].

While timely initiation of antimicrobial therapy is crucial in cases of confirmed bacterial infection, increasing evidence suggests that injudicious and/or prolonged exposure to broad-spectrum antimicrobials may paradoxically increase the risk of mortality and morbidities such as late-onset sepsis, necrotising enterocolitis, retinopathy of prematurity, dysbiosis due to disruption of the developing intestinal microbiome, invasive fungal infections and the emergence of multidrug-resistant organisms [2,3]. These consequences further contribute to an increased healthcare burden. Recent research has also highlighted potentially serious adverse effects in prematurely born infants exposed to antibiotics during early life [4,5].

Given the alarmingly high rates of empiric antibiotic prescriptions in NICUs and the growing threat of multidrug resistance [6], strategies aimed at optimising and reducing indiscriminate antibiotic use in neonates through the implementation of ASP are essential. Although several studies have been conducted previously [7-13] to prevent antibiotic misuse, most have been from high-income countries [9-13]. There is a paucity of data regarding the impact and feasibility of antimicrobial stewardship implementation in NICUs in resource-limited settings with high empirical antibiotic prescription rates. Despite the existence of guidelines issued by the National Neonatology Forum (NNF) [14], which emphasise the judicious use of antibiotics, the antibiotic utilisation rate in NICUs across India remains around 72.4-80% [15], much higher than international figures.

The key intervention in the present study to optimise antibiotic use was the creation of a “No Antibiotic Zone” in the NICU following the strengthening of infection control practices. The primary objective of this study was to determine the effect of reducing antibiotic use in neonates with minimal or no risk factors or clinical signs of sepsis through the implementation of antimicrobial stewardship. As a secondary outcome, the impact of ASP on hospital stay duration and patient outcomes was evaluated.

MATERIALS AND METHODS

This double-cohort observational study was conducted in a 36-bedded Level III NICU at the Children’s Hospital, GSVM Medical

College, Kanpur, Uttar Pradesh, India, over a two-year period from April 2021 to March 2023. The hospital is a tertiary care referral centre with an average of 1,800 admissions annually. The study was approved by the Institutional Ethics Committee (approval number: EC/BMHR/2022/63).

The preintervention period was defined from April 1, 2021, to March 31, 2022, during which the majority of neonates were administered antibiotics irrespective of risk factors. Implementation of ASP began on April 1, 2022, and the postintervention period extended from April 1, 2022, to March 31, 2023.

Inclusion criteria: Neonates with minimal or no perinatal risk factors and no red flags or clinical indicators of sepsis were included in the study.

Exclusion criteria: All neonates were screened on day 1 of admission through a detailed history and physical examination. Those with extreme risk factors (such as chorioamnionitis, foul-smelling liquor, or rupture of membranes lasting more than 72 hours), red flags, clinical signs, or laboratory indicators of sepsis [as per National Institute for Health and Care Excellence (NICE) guidelines] [16] were excluded. Neonates who were started on parenteral antibiotics after sending relevant investigations (blood cultures, lumbar puncture) were also excluded from the study.

Sample size: Assuming an overall reduction in antibiotic use by 46% [17], with an alpha error of 5%, a 95% confidence interval, and an absolute error of 6%, the sample size was calculated using the formula:

$$n = \frac{Z_{(1-\alpha/2)}^2 \times p(1-p)}{d^2}$$

The calculated sample size was 265. Considering a 15% non-response rate, the final sample size was adjusted to 305.

Study Procedure

The study was conducted in the NICU after strengthening infection prevention and control practices, including hand hygiene, sterilisation of equipment, ensuring asepsis during invasive procedures and proper collection of blood cultures. Additional interventions included:

- Framing a policy on rational antimicrobial use
- Revising the antibiotic policy based on the antibiogram
- Conducting regular culture surveillance by a microbiologist
- Performing monthly antibiotic audits
- Enhancing awareness among nursing staff and residents regarding the adverse consequences of unnecessary antibiotic exposure

A dedicated “No Antibiotic Zone” was created in the NICU, where 10 warmers were allocated. Two nursing staff were assigned per eight-hour shift, along with three resident doctors and one fellow every 12 hours. Neonates in this zone were not administered antibiotics but were closely monitored daily by trained staff and resident doctors. Those who developed early signs suggestive of sepsis were started on antibiotics after sending relevant investigations and were subsequently excluded from the study.

Demographics, patient characteristics, duration of stay and outcomes of neonates during the stewardship period were compared with data from the preintervention cohort, obtained from NICU records, which included newborns who had received antibiotics despite having no perinatal risk factors, clinical indicators, or laboratory evidence of sepsis.

STATISTICAL ANALYSIS

Data were compiled and analysed using Statistical Package for the Social Sciences (SPSS) software version 26.0. Categorical variables were expressed as percentages and analysed using Pearson's Chi-square test. Quantitative variables were expressed

as mean±standard deviation and compared using the paired t-test. A p-value <0.05 was considered statistically significant.

RESULTS

During the study period, a total of 2,036 newborns were admitted to the NICU. Of these, 480 newborns had no perinatal risk factors or clinical signs of sepsis. They were not administered antibiotics but were monitored daily by trained staff and doctors. Among these, 178 out of 480 neonates were started on antibiotics during their stay due to the development of clinical signs of sepsis such as feed intolerance, lethargy, or mottling. After applying the inclusion and exclusion criteria, 302 newborns from the postintervention cohort and 464 newborns from the preintervention cohort were included in the final analysis.

The mean gestational age and birth weight were 36±2.06 weeks and 2400±500 g, respectively. The majority of neonates in both cohorts comprised late preterm and term infants. Almost two-thirds of neonates in each cohort were inborn. No statistically significant difference was observed between the preintervention and stewardship cohorts in terms of the frequency of various diseases, gender distribution, gestational age, birth weight, or mode of delivery [Table/Fig-1].

Variables	Preintervention cohort (n=464)	Postintervention cohort (n=302)	p-value
Gender			
Male	265 (57)	190 (63)	0.110*
Females	199 (43)	122 (37)	
Gestational age (weeks)			
24-30	24 (5.1)	14 (3.0)	0.743*
30-34	101(21.7)	74 (24.5)	
34-37	186 (40)	109 (36)	
37-42	135 (29)	90 (29.8)	
>=42	18 (3.8)	15 (4.9)	
Birth weight (grams)			
<1000	7 (1.5)	6 (1.9)	0.531*
1000-1499	121 (26.0)	73 (24)	
1500-2499	247 (53.2)	169 (55.9)	
>= 2500	89 (19)	54 (17.8)	
Mode/place of delivery			
Inborn	283 (61)	193 (64)	0.416*
Caesarean delivery	274 (59)	160 (53)	0.465*
Diagnosis			
RDS†	143 (30.8)	96 (31.7)	0.735*
HIE‡	116 (25.0)	79 (26.1)	
Transient tachypnoea	75 (16.1)	43 (14.2)	
MAS°	55 (11.8)	36 (11.9)	
Neonatal jaundice	53 (11.4)	31 (10.2)	
Neonatal seizures††	9 (1.9)	6 (1.9)	
CHD‡	7 (1.5)	6 (1.9)	
Others™	6 (1.2)	5 (1.6)	

[Table/Fig-1]: Demographic and disease characteristics of the study population in the preintervention and stewardship periods (values expressed as n (%)).

*not significant at p<0.05 †RDS respiratory distress syndrome, ‡HIE hypoxic ischemic encephalopathy, § MAS meconium aspiration syndrome, ¶ congenital heart disease ††aetiology other than perinatal asphyxia **Others include haemorrhagic disease of newborn, congenital anomalies

A significant variation (p-value <0.0001) was observed in the duration of hospital stay between the two cohorts. The length of stay was notably shorter among neonates who were not given antibiotics. Out of 302 newborns who were not administered antibiotics, 172 (57%) were discharged within one week after the implementation of the ASP, in contrast to those who received antibiotics, among

whom 148 (32%) had a prolonged hospital stay. A significant reduction in the mean duration of stay was observed, particularly among preterm infants, and the least reduction was noted in cases of meconium aspiration syndrome.

The mean duration of hospital stay before the intervention was 10.1±2.8 days, which decreased to 6.5±2.4 days after the implementation of the ASP. This represents a 35.6% reduction in the mean NICU stay, which was statistically significant according to the paired t-test (p-value <0.001) [Table/Fig-2].

Disease	Mean duration of preintervention	Stay (days)* postintervention	Decrease in stay (%)	p-value
MAS†	13.4±3.4	11.2±2.9	16.4	0.03
RDS*	10.3±2.5	7.7±1.9	25.2	0.002
HIE*	12.0±2.8	7.5±1.7	37.5	<0.001
Prematurity	13.5±2.8	7.1±1.8	47.4	<0.001
Transient tachypnoea	6.7±1.4	4.5±0.9	32.8	0.001
Neonatal jaundice	6.5±0.9	3.8±0.4	41.5	<0.001
Neonatal seizures	11.2±2.5	6.1±1.5	45.5	<0.001
CHD††	10.5±2.4	7.6±1.9	27.6	0.004
Others**	7.1±0.8	3.4±0.6	52.1	<0.001
Mean duration of hospital stay	10.1±2.8	6.5±2.4	35.6	<0.001

[Table/Fig-2]: Mean duration of stay in various diseases before and after Intervention.

*Values expressed as Mean±SD; †MAS meconium aspiration syndrome, †RDS respiratory distress syndrome, †HIE hypoxic ischemic encephalopathy, ††congenital heart disease

**Others include haemorrhagic disease of newborn, congenital anomalies

Out of 480 newborns who were not administered antibiotics, 302 (63%) were discharged without having received any antibiotics, as compared to the preintervention period, where almost 79% received empirical antibiotics at admission. A total of 37% of infants were initiated on antibiotic therapy due to the development of clinical signs such as feed intolerance (35%), temperature instability (23%), lethargy, prolonged capillary refill, mottling, and cyanosis, and were therefore excluded from the final analysis. Among these, 19% had positive blood cultures, while 57.8% showed an abnormal sepsis screen. The overall mortality during the stewardship period was 11.7%, compared to 26.3% during the preintervention period, and this difference was found to be statistically significant (p-value <0.05) [Table/Fig-3].

Outcome	Postintervention	Preintervention	p-value
Shifted to antibiotics	178 (37)	NA*	
Sepsis screen positive	103 (57.8)	-	
Culture positive LOS†	34 (19)	-	
Culture negative LOS	144 (81)	-	
Discharged without receiving antibiotics	302 (63)	NA	
Mortality	56 (11.7)	122 (26.3)	<0.001

[Table/Fig-3]: Outcome of newborns who were not administered antibiotics (n=480) compared to the pre-intervention cohort (n=464).

Values expressed as no. (percentage), *not applicable, †late onset sepsis

DISCUSSION

The distinctive characteristics of infection in neonates necessitate the empirical use of antibiotics in the majority of infants admitted to the NICU, resulting in a large proportion of uninfected newborns being inappropriately exposed to antibiotics. One of the key measures to reduce indiscriminate antibiotic use and its adverse outcomes is the implementation of ASPs [18-20].

ASPs include a set of coordinated interventions designed to promote the appropriate use of antimicrobials by ensuring the selection of the

optimal drug regimen, dose and duration to achieve the best clinical outcomes with minimal adverse effects, including the prevention of antimicrobial resistance [14,19].

This prospective double-cohort study, undertaken to optimise antibiotic use through stewardship strategies in a Level 3 NICU, resulted in a 42% reduction in unnecessary antimicrobial utilisation over a 12-month period. Additionally, a 35.6% decrease in the mean duration of hospital stay was observed, which was statistically significant and consistent with findings from previous studies [7-12]. Importantly, sepsis-related mortality during the stewardship period was significantly lower, indicating that ASPs can be effectively implemented in neonatal units without increasing adverse events.

A large proportion of neonates in the NICU were outborn and referred cases with severe sepsis, who were already receiving broad-spectrum antibiotics. The culture-positive sepsis rate in the NICU was approximately 20%. Additionally, a significant number of admissions involved neonates with congenital anomalies who had undergone surgery, necessitating antibiotic use. Empiric antibiotic utilisation in the NICU during the preintervention period was high.

Nevertheless, a substantial reduction in antibiotic use was achieved during the stewardship period, primarily through the restriction of antibiotics in culture-negative and preterm neonates with minimal risk factors or clinical indicators of sepsis. Prior to the implementation of the ASP, the majority of preterm infants received empiric antibiotics regardless of risk factors. A significant decrease in empiric antibiotic prescription in preterm infants was achieved through judicious antimicrobial use guided by standard algorithms [16], adherence to aseptic practices and close monitoring for early indicators of sepsis.

Similar observations were reported by Berardi A et al., who showed that antibiotic stewardship in very low birth weight infants led to a significant decrease in antibiotic use and a 29% decline in Days of Therapy (DOT) per 1000 patient days [13]. Recent studies indicate that safe strategies combining quantitative risk estimates and serial clinical evaluation can reduce unnecessary antibiotic use in preterm neonates with gestational ages below 34 weeks, suggesting that antimicrobial stewardship is feasible even in this vulnerable population [21-23]. However, close vigilance is essential to determine when to initiate or discontinue antibiotic therapy.

Additional strengths of present study include the effective implementation of stewardship in a resource-limited hospital and the cost benefits achieved due to reduced length of stay and decreased consumption of higher antibiotics such as carbapenems and vancomycin.

Limitation(s)

One of the major limitations of present study was that most newborns were critically ill referred cases already receiving multiple antibiotics at the time of admission, making their inclusion in the study infeasible. Additionally, the study did not evaluate the impact of stewardship practices on antimicrobial resistance patterns of culture isolates obtained from the NICU. Further studies are warranted to explore this correlation.

CONCLUSION(S)

Despite strict guidelines for rational antibiotic use from the National Neonatology Forum (NNF), World Health Organisation (WHO) and other professional bodies, antibiotic usage rates in NICUs remain high. Present study reinforces the importance of adhering to these guidelines to restrict indiscriminate antibiotic use, as this reduces hospital stay, NICU burden and neonatal morbidity and mortality. Further research, including genomic sequencing studies, may be undertaken to explore the effects of unnecessary antibiotic exposure on the gut microbiome of neonates.

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