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RESEARCH ARTICLE

Pattern of Adverse Drug Reactions and Medication Use in Neonatal Care Units in a Tertiary Care Hospital: A Longitudinal Observational Study

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Abstract: ***Background:*** Neonates represent a uniquely vulnerable population for medication-related harm due to developmental pharmacokinetic variability, multiple drug exposures, and incomplete organ maturation. In neonatal intensive care units (NICUs), polypharmacy is frequent, and monitoring for adverse drug reactions (ADRs) remains challenging. Objective: To identify the pattern, frequency, and severity of adverse drug reactions and to assess overall medication use among neonates admitted to a tertiary care neonatal unit. ***Methods:*** A longitudinal observational study was conducted over three months in the NICU of a tertiary care teaching hospital. A total of 80 neonates receiving at least one systemic medication were enrolled. Drug administration data were recorded daily, and ADRs were actively monitored using the WHO-UMC causality assessment scale and Hartwig's severity criteria. Descriptive statistics were applied for frequency distribution, and chi-square tests were used to determine associations between ADR occurrence and demographic variables such as gestational age and birth weight. ***Results:*** Among 80 neonates, 23 (28.7%) experienced at least one ADR. The most common implicated drug groups were antibiotics (56.5%) and anticonvulsants (21.7%). Cutaneous reactions and feeding intolerance predominated, while serious reactions requiring therapy modification occurred in 9%. Preterm neonates exhibited a higher ADR incidence ($p = 0.02$). The mean number of drugs per neonate was 5.6 ± 1.8, with 42% exposed to at least one off-label medication. ***Conclusion:*** Adverse drug reactions are frequent in neonatal intensive care settings, primarily linked to antibiotics and polypharmacy. Regular pharmacovigilance and rational prescribing are essential to minimize iatrogenic risk in this fragile age group.

Keywords: Neonatal intensive care, Adverse drug reaction, Pharmacovigilance, Antibiotics, Polypharmacy, Causality assessment, India.

INTRODUCTION

Adverse drug reactions (ADRs) are among the most overlooked causes of morbidity in newborns. During the neonatal period, drug handling differs drastically because the liver and kidneys are still developing, and receptor sensitivity continues to evolve. Even small dosing errors or cumulative exposure can lead to toxicity, yet most neonatal medicines are prescribed on extrapolated data rather than age-specific trials [1]. This lack of pharmacological evidence leaves neonates particularly vulnerable to unpredictable adverse effects [2]. Across hospitals, ADR rates among neonates have ranged between 4% and 30%, depending on surveillance methods and patient complexity [3]. Many of these events are predictable, suggesting that careful monitoring and dose adjustment could prevent them [4]. In Indian neonatal intensive care units (NICUs), where multiple drugs are often started empirically, consistent ADR documentation remains a challenge [5]. Polypharmacy, especially with antibiotics, anticonvulsants, and inotropes, further heightens the likelihood of interactions and adverse outcomes. Off-label prescribing is another concern, accounting for almost half of NICU drug use. Such practices are common when clinicians have limited pediatric formulations or stability data for diluted preparations [6]. Neonates metabolize medicines differently because their enzymatic systems, including cytochrome P450 and glucuronidation pathways, mature gradually over weeks. These differences explain why the same drug may be therapeutic in one infant yet harmful in another [7]. Within this context, strengthening pharmacovigilance in NICUs becomes more than an academic goal; it's a patient safety necessity. Systematic observation of prescriptions and adverse events can help identify risky combinations, guide policy, and train staff to anticipate preventable harm [8]. The present longitudinal study, therefore, seeks to describe the pattern of adverse drug reactions and overall medication use among neonates admitted to a tertiary care hospital, providing practical insights for rational drug monitoring in routine neonatal practice.

MATERIAL AND METHODS

Study Design and Setting

This was a longitudinal observational study conducted in the Neonatal Intensive Care Unit (NICU) of Dr. D. Y. Patil Medical College, Hospital and Research Centre, Pune. In the year between December 2024 to September 2025. The unit admits both inborn and referred neonates, providing level III neonatal care. Data collection extended over three consecutive

months, capturing day-to-day medication patterns and any suspected adverse drug reactions.

Study Population

Eighty neonates admitted for more than forty-eight hours and receiving at least one systemic medication were included. Newborns with major congenital anomalies, terminal illness on admission, or those discharged before 48 hours were excluded. Gestational age, sex, birth weight, indication for admission, and duration of stay were recorded for all eligible infants.

Data Collection Procedure

Daily drug administration charts were reviewed by a trained pharmacology postgraduate and NICU resident. Each administered medication was classified by therapeutic group, route, and frequency. Active surveillance for adverse drug reactions was performed through continuous ward visits and staff reports. Suspected ADRs were verified with treating physicians and documented in a pre-validated case report form.

Operational Definitions

- **Adverse drug reaction (ADR):** Any unintended, harmful event occurring at normal therapeutic doses that requires modification, discontinuation, or additional treatment.
- **Polypharmacy:** Concurrent administration of five or more systemic drugs.
- **Off-label use:** Prescription of a drug outside its approved neonatal indication, dose, or route.
- **Preventable ADR:** An event that could have been avoided with appropriate dosing, monitoring, or drug selection.

Causality and Severity Assessment

Each reported ADR was assessed for likelihood using the WHO–UMC causality assessment scale, categorizing reactions as certain, probable, possible, or unlikely. The Hartwig and Siegel severity scale was applied to classify ADRs as mild, moderate, or severe based on the clinical outcome and therapeutic intervention required. Preventability was evaluated through the Schumock and Thornton criteria.

Outcome Variables

Primary outcomes included the incidence rate and pattern of ADRs by drug class and organ system affected. Secondary outcomes included the relationship between ADR occurrence and gestational age, birth weight, polypharmacy status, and off-label use frequency.

Statistical Analysis

Data were entered into Microsoft Excel and analyzed using IBM SPSS version 26. Continuous variables were expressed as mean ± standard deviation, while categorical variables were summarized as percentages. Group comparisons were performed using the chi-square test or Fisher's exact test, and continuous variables were compared using the independent t-test. A p-value < 0.05 was considered statistically significant.

RESULTS AND OBSERVATIONS:

A total of 80 neonates were enrolled and followed throughout their NICU stay. Of these, 47 (58.8%) were male, and 33 (41.2%) were female. The mean gestational age was 34.9 ± 2.8 weeks, and the mean birth weight was 2.1 ± 0.6 kg. Thirty-seven neonates (46.3%) were preterm. The average hospital stay duration was 10.4 ± 4.3 days.

1. Baseline Demographic and Clinical Profile

Table 1 summarizes demographic variables and major diagnostic categories. Respiratory distress, neonatal sepsis, and jaundice were the most frequent causes of admission. No significant differences were observed in age or sex distribution among neonates who experienced ADRs versus those who did not ($p > 0.05$).

Table 1. Baseline characteristics of study participants (N = 80)

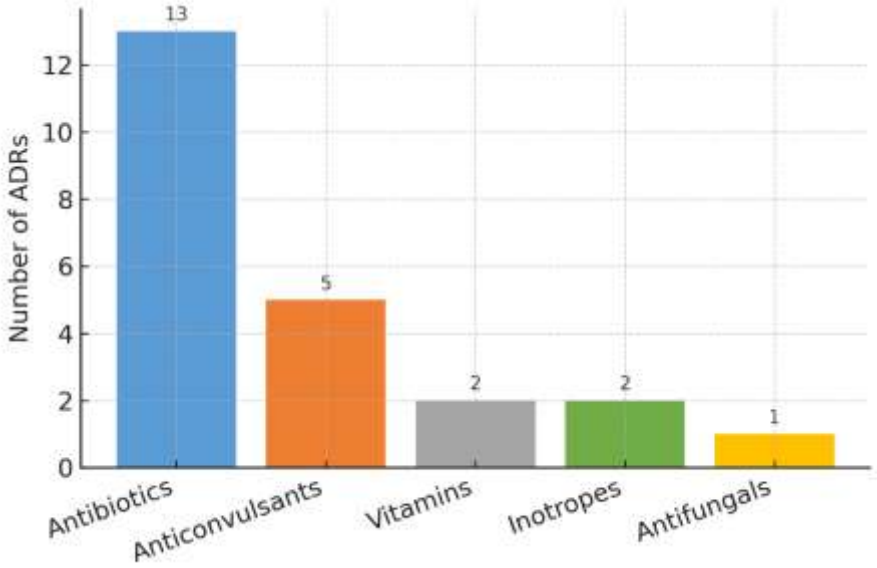
Variable	Frequency (%)	Mean ± SD
Male	47 (58.8)	,
Female	33 (41.2)	,
Gestational age (weeks)	,	34.9 ± 2.8
Birth weight (kg)	,	2.1 ± 0.6
Preterm neonates	37 (46.3)	,
Duration of NICU stay (days)	,	10.4 ± 4.3
Primary diagnosis: Respiratory distress	21 (26.3)	,
Neonatal sepsis	18 (22.5)	,
Neonatal jaundice	13 (16.3)	,
Others	28 (35.0)	,

2. Incidence and General Pattern of Adverse Drug Reactions

Out of 80 neonates, 23 (28.7%) developed at least one ADR, accounting for a total of 23 distinct events. The overall incidence rate was 28.7 ADRs per 100 neonates. Most reactions occurred within the first week of therapy.

Antibiotics were the most frequently implicated class, responsible for more than half of all events, followed by anticonvulsants, vitamins, and inotropes. The complete drug-class distribution is shown in **Figure 1**.

Figure 1 depicts that antibiotics contributed to 13 ADRs (56.5%), while anticonvulsants accounted for 5 (21.7%). Other classes were less frequently involved.



3. System Organ Classification of ADRs

When classified by affected organ systems, cutaneous reactions (35%) were the most common, followed by gastrointestinal disturbances (30%) such as feeding intolerance and vomiting. Hematological abnormalities such as thrombocytopenia were less frequent. The relative proportion of each system is illustrated in **Figure 2**.

Figure 2. ***Pie chart showing the system organ classification of observed ADRs (skin and gastrointestinal systems predominate).***

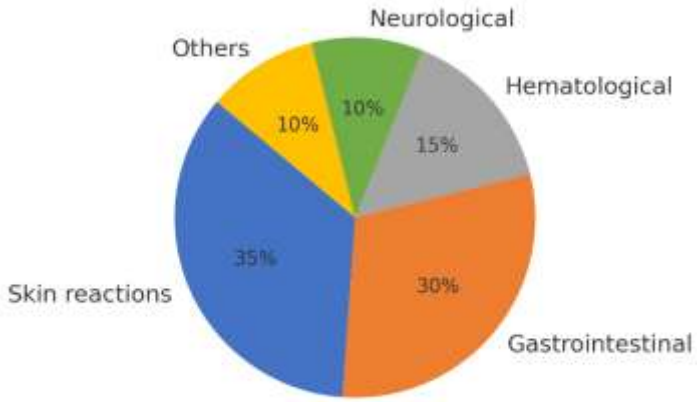


Table 2. Pattern of adverse drug reactions by system involvement (N = 23)

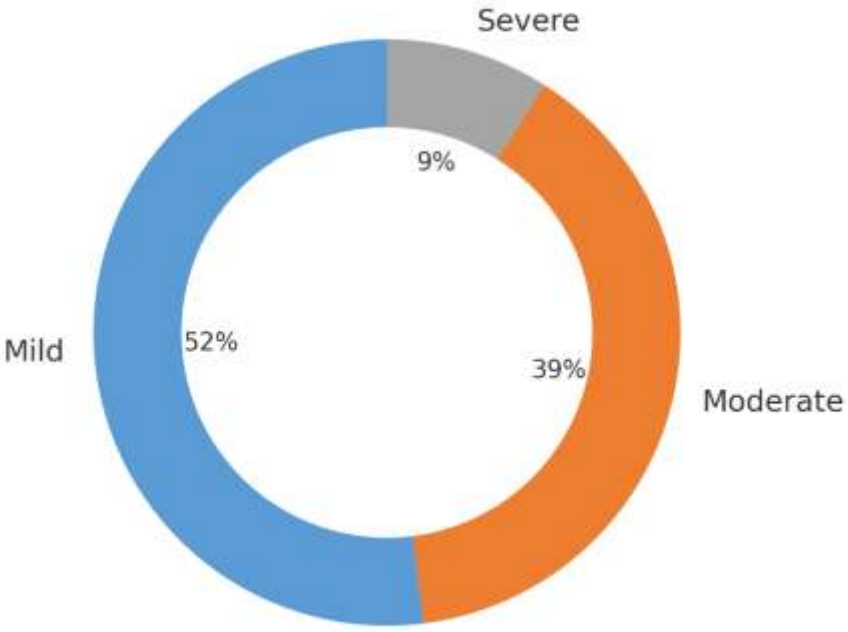
Organ/System Involved	Frequency (%)	Common Presentation
Skin	8 (34.8)	Maculopapular rash, erythema
Gastrointestinal	7 (30.4)	Feeding intolerance, vomiting
Hematological	3 (13.0)	Thrombocytopenia, anemia
Neurological	2 (8.7)	Tremors, irritability
Others	3 (13.0)	Local injection site induration

4. Severity and Preventability of ADRs

According to Hartwig's criteria, 52% of ADRs were mild, 39% moderate, and 9% severe. The donut chart **(Figure 3)** visualizes this distribution. Most reactions required only observation or dose adjustment, while two severe cases (one antibiotic-associated thrombocytopenia, one phenytoin-induced rash) required therapy discontinuation and drug substitution.

Preventability assessment revealed that 65% of ADRs were possibly preventable, mainly due to modifiable factors such as prolonged antibiotic use and lack of dose revision in preterm infants.

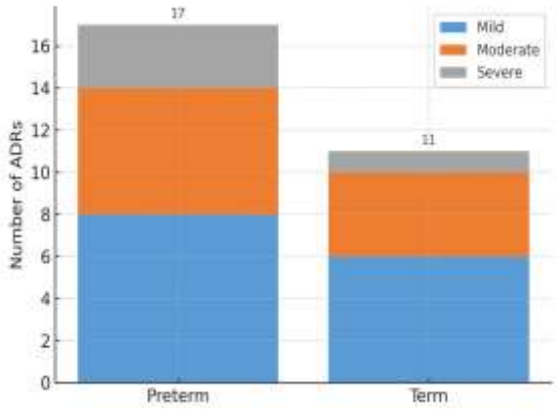
Figure 3. ***Donut chart representing the severity distribution of ADRs (majority mild in nature).***



5. ADR Distribution by Gestational Age

When stratified by gestational maturity, preterm neonates experienced a higher incidence of ADRs (17 out of 37; 45.9%) compared to term neonates (6 out of 43; 13.9%), a statistically significant difference ($p = 0.02$). The majority of severe reactions were also observed in preterm infants, as illustrated in **Figure 4**.

Figure 4. ***Stacked bar chart showing ADR severity by gestational category (preterm vs. term)***



6. Medication Use Pattern

Across all neonates, the mean number of prescribed medications per patient was 5.6 ± 1.8. The highest frequency of use was observed for antibiotics, followed by fluids and supplements. Nearly 42% of neonates received at least one off-label medication, most commonly aminoglycosides and phenobarbital.

Table 3. Medication use profile among study participants (N = 80)

Drug Category	Neonates Exposed (%)	Common Drugs Used
Antibiotics	71 (88.7)	Ampicillin, Gentamicin, Cefotaxime
Fluids/Electrolytes	62 (77.5)	Dextrose, Normal saline
Anticonvulsants	27 (33.8)	Phenobarbital, Phenytoin
Vitamins and Minerals	45 (56.3)	Vitamin K, Calcium gluconate
Inotropes	11 (13.8)	Dopamine, Dobutamine
Others	19 (23.8)	Antifungals, Proton pump inhibitors

Summary of Key Findings

1. ADR incidence: 28.7% of neonates experienced at least one reaction.
2. Antibiotics were implicated in more than half of all ADRs.
3. Cutaneous and gastrointestinal systems were most affected.
4. Preterm neonates showed significantly higher susceptibility.
5. Mild ADRs predominated, and two cases required therapy modification.
6. Polypharmacy and off-label use were common contributors.

DISCUSSION

In this longitudinal NICU study, about one-third of neonates experienced at least one adverse reaction to medication. The figure, though modest, echoes the pattern observed across many Indian hospitals where empirical treatment and multi-drug exposure are common [9]. The finding highlights that even with cautious prescribing, neonatal pharmacotherapy still carries considerable iatrogenic risk.

Comparison with Reported Trends

International reports show lower ADR frequencies, often because developed centres rely on electronic dose-checking systems and pharmacy cross-verification [10]. Manual record-keeping, still the norm in Indian NICUs, may overlook early, subtle reactions but capture more overt ones, thereby influencing apparent prevalence. In this series, antibiotics were the main contributors to ADRs, mirroring other South Indian data where these drugs account for roughly half of all reactions [11]. Gentamicin and cefotaxime remain first-line choices for suspected sepsis, and their recurrent appearance among ADR sources simply reflects their wide usage rather than unsafe practice.

Gastrointestinal and skin reactions predominated, findings consistent with the profile documented by Le and colleagues, who noted similar organ involvement in hospitalized infants receiving antimicrobials [12]. Anticonvulsants ranked next; phenobarbital and phenytoin frequently produced transient tremors or rash, as also noted in German multicentre neonatal surveillance [13].

The extent of off-label use in this cohort, around 40%, reaffirms that neonatal therapy still depends heavily on formulations developed for adults. Because metabolic enzymes such as CYP3A4 mature gradually, dosage adjustments become uncertain, making unlicensed or extrapolated use unavoidable [14].

Nature, Severity, and Preventability

Most ADRs were reversible and mild, yet a few required drug substitution. The 9% severe-reaction proportion parallels results reported in paediatric systematic reviews [15]. Nearly two-thirds of the observed ADRs were classed as potentially preventable. This underlines that safer scheduling, therapeutic monitoring, and dose review, especially in premature infants, could avert many such outcomes [16].

Preterm neonates showed a significantly higher reaction rate ($p = 0.02$). Immature organ systems, low albumin binding, and prolonged elimination half-lives collectively explain their heightened sensitivity. Similar trends have been documented in European and Brazilian NICU studies [17,18]. Hence, gestational maturity must remain a central consideration whenever empirical regimens are planned.

Medication Exposure and Practice Implications

Each neonate received an average of 5–6 medications, which aligns with the prescribing pattern reported by the ICMR surveillance network [19]. The dominance of antibiotics, followed by fluids and supplements, depicts current NICU realities where prophylactic coverage often overrides targeted therapy. Integrating stewardship protocols, pharmacist feedback, and fixed audit schedules could rationalize such practices without compromising infection control.

A structured pharmacovigilance mechanism, preferably integrated within hospital electronic systems, could strengthen early detection. Including parents in simple ADR awareness, supported by post-discharge tele-

follow-up, would further extend vigilance beyond the hospital stay.

Limitations and Way Forward

The limited sample and three-month follow-up constrain external validity, and delayed or cumulative reactions may have been missed. Moreover, causality and preventability assessments, though standardized, still depend on individual judgment. Future multicentre collaborations using digital ADR reporting platforms could provide a larger evidence base. Pharmacogenomic correlation may also help identify neonates at elevated risk, guiding truly individualized dosing strategies.

CONCLUSION

Adverse drug reactions remain an important concern in neonatal intensive care, particularly where multiple drugs and empirical antibiotic regimens are common. In this longitudinal observation, nearly one-third of neonates experienced at least one ADR—most mild, some preventable, and a few severe. Preterm infants were notably more susceptible, emphasizing the need for dose adjustments tailored to gestational maturity. The consistent predominance of antibiotics and off-label drug use underscores an urgent call for structured neonatal pharmacovigilance, rational prescribing, and antibiotic stewardship within tertiary care systems. Integrating real-time ADR monitoring, clinician training, and parental awareness could markedly enhance medication safety for this fragile population.

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