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Off-Label Medicine Use In Neonatal Intensive Care Unit Of A Secondary Hospital Of Ad Dakhiliyah Governorate Of Oman

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ABSTRACT

Off-label drug use, defined as the prescription of medications for indications, dosages, or routes not sanctioned by regulatory authorities, is prevalent in neonatal intensive care units (NICUs). This prevalence is primarily attributed to the limited availability of evidence-based, regulatory-approved options for neonates. However, such practices raise concerns regarding safety and standardization. In Oman, there is a paucity of data on off-label prescribing within neonatal populations. This study aimed to evaluate the prevalence, patterns, and clinical associations of off-label medication use among neonates admitted to the NICU at Nizwa Hospital. A retrospective cross-sectional analysis was conducted over an 18-month period (January 2023–June 2024), involving neonates aged ≤28 days who received at least one off-label medication. Data were sourced from the hospital's Al Shifa Plus system and the Vigiflow pharmacovigilance platform. Of the 638 NICU admissions, 182 neonates (28.5%) received off-label prescriptions. The primary reasons for off-label use were unapproved routes of administration (47.2%) and age-specific contraindications (22.4%). Frequently used off-label medications included sodium chloride 3% and omeprazole, with 25.9% classified as high-alert drugs. Significant associations were identified between the number of off-label drugs and discharge outcomes ($p = 0.019$), as well as between gender and discharge disposition ($p = 0.012$). No adverse drug reactions were reported. These findings underscore the necessity for neonatal-specific prescribing guidelines, pharmacist-led medication reviews, and enhanced pharmacovigilance and training initiatives to promote safer and more consistent medication use in NICUs.

Keywords: *Off-label prescribing, Neonates, NICU, Medication safety, Oman, High-alert drugs*

1. INTRODUCTION

The treatment of neonates in intensive care units represents one of the most complex and challenging areas of clinical practice, often involving high-risk interventions and multifaceted clinical decision-making. Neonates are especially susceptible to the risks associated with pharmacotherapy due to their physiological immaturity, including underdeveloped organ systems, altered pharmacokinetic profiles, and limited metabolic and excretory capacities (Aagaard & Hansen, 2011; Allen et al., 2018). Off-label prescribing, where licensed medications are used in ways not specified in their regulatory product license, has become a widespread practice in neonatal intensive care units (NICUs) globally. It is no longer considered an exception but rather a routine aspect of neonatal care delivery (Balan et al., 2018; Mazhar et al., 2018).

Current evidence suggests that between 30% and 90% of medications administered to neonates are prescribed off-label or via non-approved routes of administration (Alonso et al., 2019; Koszma et al., 2021). Extended hospitalization in neonatal intensive care units (NICUs) markedly increases the probability of exposure to such medications, with nearly all long-term NICU patients receiving at least one off-label drug (Alonso et al., 2019; Koszma et al., 2021). This prevalent practice is driven by several critical factors. Firstly, there is a significant lack of adequately powered clinical trials in neonatal populations, primarily due to ethical constraints that limit the feasibility of traditional dose-ranging studies in this vulnerable group. Secondly, regulatory gaps persist, as many pediatric formulations lack formal testing or approval (Meng et al., 2022; van der Zanden et al., 2022). In the absence of neonatal-specific evidence, clinicians often extrapolate dosing regimens, routes of administration, and safety data from adult or older pediatric populations, despite well-established differences in neonatal pharmacokinetics and pharmacodynamics (Schrier et al., 2020; Giurin et al., 2022). These challenges highlight the urgent need for neonatal-focused research, regulatory reform, and tailored clinical guidance.

Recent literature underscores the substantial variability in off-label prescribing practices across various institutions and countries, a phenomenon largely attributed to differences in formularies, clinical guidelines, and access to specialized resources (Alyami et al., 2022; Fung et al., 2021). This variability is especially evident in neonatal intensive care units (NICUs), where the complexity of care is further intensified by the frequent use of high-alert medications—drugs that present a significant risk of harm if used improperly (Farajallah et al., 2024). Medications such as aminophylline, omeprazole, and various parenteral anti-infectives are commonly used despite lacking formal approval for neonatal use or being contraindicated in this age group (AlAzmi et al., 2021). The prevalent use of these medications raises critical concerns regarding their safety, efficacy, and the potential for adverse drug reactions (Yackey et al., 2019; Hoon et al., 2019). While there is an increasing global discussion on the epidemiology and determinants of off-label drug use in neonates, there remains a notable gap in region-specific evidence, particularly in Oman and the broader Gulf region. Clinicians in secondary care hospitals in Oman often encounter therapeutic challenges when managing critically ill neonates with a limited formulary, leading to a dependence on off-label medications (Abeer & Jumaa, 2021). Despite the clinical importance of these practices, there is a lack of empirical data to quantify their extent, evaluate associated risks, or guide contextually relevant interventions. This knowledge gap hinders the development of robust prescribing policies, clinical training, and pharmacovigilance mechanisms tailored to the neonatal population (Balan et al., 2018; García-López et al., 2020).

Objectives

The present study was designed to address these gaps through two primary objectives:

1. To investigate the frequency and trends of Off-label medication use in neonates up to 28 days of age admitted to the NICU of a secondary hospital in Oman.
2. To assess the association between off-label prescribing practices and key clinical outcomes, including discharge disposition and the prevalence of high-alert medication use.

2. STUDY DESIGN AND RESEARCH METHODS

2.1 Study Design

A retrospective cross-sectional study was conducted to examine the pattern of off-label drug use among neonates admitted to the Neonatal Intensive Care Unit (NICU) at Nizwa Hospital. This study spanned an 18-month period, from January 2023 to June 2024. The analysis included all neonates aged 28 days or younger who received at least one off-label medication during their hospitalization. Data were extracted from existing historical records available in the hospital's electronic medical record system (Al Shifa Plus 3) and the VigiFlow adverse drug reaction (ADR) reporting system. These sources provided comprehensive information on patient demographics, drug administration records, and safety-related data, facilitating a structured evaluation of prescribing practices within the NICU setting.

2.2 Location of the Study

This research was conducted at Nizwa Hospital, a secondary referral center situated in the Ad Dakhiliyah Governorate of Oman. The hospital comprises multiple specialized departments, including both inpatient and outpatient pediatric services, rendering it an appropriate setting for examining drug prescribing practices among critically ill neonates. The Neonatal Intensive Care Unit (NICU) at Nizwa Hospital manages a diverse patient population, encompassing premature and medically complex neonates, thereby providing a representative and robust sample for evaluating the patterns and extent of off-label medication use in neonatal care.

2.3 Study Population and Sampling

The study utilized a purposive sampling method, guided by predefined inclusion criteria. A review was conducted of all neonates admitted to the Neonatal Intensive Care Unit (NICU) over an 18-month period. Out of 638 hospitalized neonates, 182 who received at least one off-label medication and met the inclusion criteria were selected for analysis, forming the study sample. As no additional randomization or probability-based sampling method was employed, all eligible neonates were intentionally included based on their relevance to the research objective. This approach ensured the inclusion of all pertinent cases to accurately assess the extent and characteristics of off-label drug use in the NICU setting. The prevalence of off-label drug use among NICU admissions was determined to be 28.5%.

2.4 Inclusion and Exclusion Criteria

The study included neonates admitted to the NICU who were undergoing at least one off-label medication and had a gestational age of 0 to 28 days. Exclusion criteria included any neonate that had never been exposed to off-label drugs, children more than 28 days old, or instances where the off-label prescription was solely related to blood products, vaccines, vitamins, or contrast agents.

2.5 Study Period

Data collection was conducted from July 2024 to September 2024. The dataset included medical records of neonates admitted

to the NICU from January 2023 to June 2024, facilitating an 18-month retrospective analysis of off-label drug use during this period.

2.6 Research Tool and Validation

A carefully structured data collection tool was employed to obtain information, developed after an extensive review of the literature and drawing insights from comparable studies, such as the research conducted by AlAzmi et al. (2021). This instrument was divided into three main sections. The first section gathered demographic and clinical information about the neonate, including details such as gender, age, duration of hospitalization, reason for admission, and discharge status. The second section focused on prescription data, detailing the quantity and names of off-label medications, their WHO Anatomical Therapeutic Chemical (ATC) codes, their classification as high-alert drugs, and the specific off-label characteristics (e.g., indication, age, or route/dosage). The third section was dedicated to documenting any adverse drug reactions (ADRs), including their nature, severity, and whether they were reported by healthcare professionals. The content validity and relevance of the tool were evaluated by a panel of experts, comprising a pediatrician, two clinical pharmacists, and two academic researchers, to ensure the instrument's clarity and comprehensiveness.

2.7 Data Collection Process

Data was pulled out of Al Shifa Plus 3, the electronic medical record system in the hospital, and the VigiFlow ADR reporting database. The collection process was completed over three months. The entire information, such as the demographic characteristics, prescribing details, was methodically captured on the data collection sheet. To verify the off-label status of each drug, authoritative sources in pediatric pharmacology were consulted, including Harriet Lane Handbook (Tschudy & Arcara, 2021), Pediatric and Neonatal Lexicomp (Lexicomp, 2022), Micromedex (IBM Watson Health, 2023), and the British National Formulary for Children (BNFC, 2023).

2.8 Data Analysis

The data collected were systematically entered and coded using Microsoft Excel, followed by a comprehensive analysis with the Statistical Package for the Social Sciences (SPSS), version 20.0. Descriptive statistics, such as frequencies and percentages, were employed to effectively summarize demographic characteristics and drug prescription patterns. To investigate associations between categorical variables, Fisher's Exact Test and Chi-square Test were utilized as appropriate. The strength of these associations was quantified using Cramer's V coefficient, with the following interpretive thresholds: weak association (≤ 0.2), moderate association (0.2–0.6), and strong association (> 0.6). For analyses involving continuous variables, such as the duration of NICU stay and the number of off-label medications, non-parametric tests were applied. Specifically, the Kruskal-Wallis test was used for comparisons involving more than two groups, while the Mann-Whitney U test was employed for two-group comparisons. Throughout the analysis, a p-value < 0.05 was considered indicative of statistical significance.

2.9 Ethical Considerations

Ethical approval for this research was secured from the Institutional Research Committee (Ref. No: CHS/S/24/2023-24), the Research and Studies Committee of the Directorate General of Health Services (DGHS), Al Dakhiliyah Governorate, and the Hospital Administration of Nizwa Hospital, under the Ministry of Health, Oman. The confidentiality and anonymity of patient data were rigorously upheld. All data collected were utilized solely for the study's purposes. Electronic data were stored in password-protected files on secure systems, and all datasets were archived in accordance with institutional data management policies.

3. RESULTS

A total of 638 neonates were admitted to the NICU between January 2023 and June 2024. Among them, 182 neonates (28.5%) received at least one off-label medication.

3.1. Demographic Characteristics

More than half of the neonates were male, and the majority were admitted during the first week of life. The mean NICU stay was 13.05 days (SD ±18.8). Table 1 summarizes the demographic profile of the study population, highlighting that 95.1% were admitted between 1–7 days of age, and most (83%) stayed less than two weeks. Figure 1 illustrates the gender distribution, showing a slightly higher proportion of male neonates. Figure 2 depicts the predominance of admissions within the first week of life.

Table 1. Demographic Characteristics of Neonates Receiving Off-Label Medications

Demographic Characteristics		Frequency (n)	Percentage (%)
Gender	Male	98	53.8
	Female	84	46.2
Age Group at Admission	1–7 days	173	95.1
	8–14 days	2	1.1
	15–21 days	4	2.2
	22–28 days	3	1.6
Length of Stay	1–14 days	151	83.0
	15–30 days	14	7.7
	>30 days	17	9.3

Figure 1. Gender Distribution of Neonates Receiving Off-Label Medications

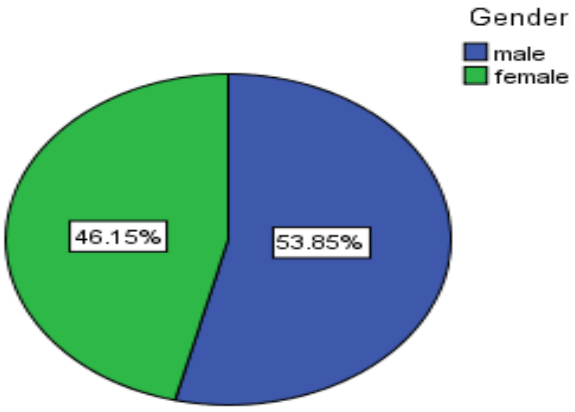
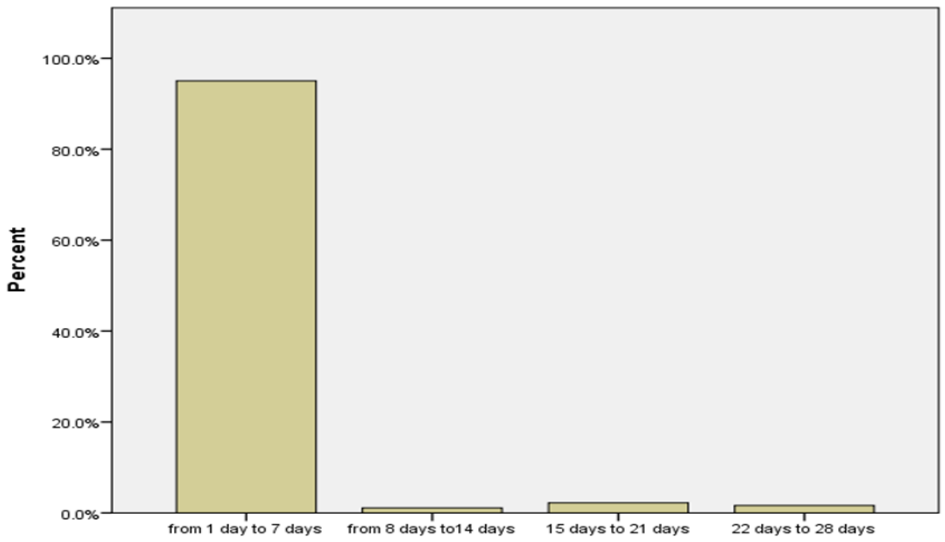


Figure 2. Age Group Distribution



3.2. Clinical Reasons for NICU Admission

The most frequent reason for admission was respiratory system disorders (33.7%), followed by infectious diseases (23.6%). Table 2 provides a breakdown of the various clinical indications leading to NICU admissions.

Table 2. Reasons for NICU Admission

Reason for Admission	Frequency (n)	Percentage (%)
Respiratory system disorders	70	33.7
Infectious diseases	49	23.6
Digestive system disorders	37	17.8
Endocrine, nutritional, and metabolic	23	11.1
Circulatory system	13	6.2
Nervous system	12	5.8
Injury	3	1.4
Musculoskeletal system	1	0.5

This distribution underscores that respiratory and infectious causes were the primary drivers of critical care needs.

3.3. Off-Label Prescribing Patterns

Most neonates received either one or two off-label medications, with unapproved routes of administration being the most common reason for off-label use. Table 3 details the number of off-label prescriptions per patient and the types of off-label status identified.

Table 3. Off-Label Medication Patterns

Off-Label Patterns		Frequency (n)	Percentage (%)
Number of Off-Label Drugs received per Neonate	1	115	63.2
	2	56	30.8
	3	9	4.9
	4	2	1.1
Off-Label Status	Unapproved route of administration	173	47.2
	Age-related unapproved use	82	22.4
	Contraindication	79	21.6
	Other indication	32	8.7

3.4. WHO ATC Classification of Off-Label Drugs

Anti-infectives, blood and blood-forming agents, and alimentary tract medications were the most frequently used drug classes. Table 4 shows the distribution by WHO ATC Level 1 classification.

Table 4. ATC Classification of Prescribed Off-Label Medications

ATC Level 1 Class	Frequency (n)	Percentage (%)
Anti-infectives for systemic use (J)	59	22.3
Blood and blood-forming organs (B)	53	20.1
Alimentary tract and metabolism (A)	49	18.6

Respiratory system (R)	40	15.2
Sensory organs (S)	23	8.7
Nervous system (N)	16	6.1
Cardiovascular system (C)	15	5.7
Systemic hormonal preparations (H)	4	1.5
Genito-urinary system (G)	3	1.1
Musculoskeletal system (M)	2	0.8

This classification highlights the reliance on anti-infectives and hemostatic agents in neonatal care.

3.5. Frequently Prescribed Off-Label Medications

The most commonly used off-label medication was sodium chloride 3% infusion (19.7%), followed by omeprazole (14.4%) and aminophylline (13.3%). Table 5 lists the top prescribed off-label drugs.

Table 5. Common Off-Label Medications in the NICU

Drug	Frequency (n)	Percentage (%)
Sodium chloride 3% infusion	52	19.7
Omeprazole injection	38	14.4
Aminophylline injection	35	13.3
Vancomycin injection	23	8.7
Atropine eye drops	20	7.6

3.6. High-Alert Medications and Prevalence of ADR

The study identified that 25.9% of the off-label medications prescribed in the NICU setting were classified as high-alert drugs known to carry a heightened risk of causing significant harm if used in error. These included medications such as hypertonic saline and aminophylline, which require stringent monitoring protocols due to their narrow therapeutic indices and potential for adverse outcomes in neonates. Despite the prevalence of such high-risk medications in the prescribing pattern, no adverse drug reactions (ADRs) were documented within the study population during the review period.

3.7. Discharge Disposition

Among neonates receiving off-label drugs, 75.3% were discharged, 13.2% died, and 11.5% were referred to tertiary care. Table 6 summarizes discharge outcomes by gender.

Table 6. Discharge Disposition

Outcome	Male (n)	Female (n)	Total (n)	Percentage (%)
Discharged	82	55	137	75.3
Referred to tertiary care	6	15	21	11.5
Died	10	14	24	13.2

3.7. Statistical Associations

The analysis identified significant associations between clinical and demographic variables. A moderate association was found between discharge disposition and gender ($p = 0.012$, Cramér's $V = 0.220$), suggesting gender may influence discharge outcomes. A significant relationship existed between discharge disposition and off-label drug prescriptions ($p = 0.019$, Cramér's $V = 0.239$), indicating increased exposure to off-label medications may affect outcomes. The use of ATC Level B drugs was significantly associated with age group ($p = 0.035$, Cramér's $V = 0.212$). No significant associations were found between high-alert medication use and gender ($p = 0.288$) or age group ($p = 0.099$). Length of NICU stay showed no significant association with discharge disposition ($p = 0.149$) or gender ($p = 0.620$). These findings highlight factors that may influence prescribing patterns and clinical outcomes in the NICU.

4. DISCUSSION

The study analysed the prevalence, patterns, and clinical implications of off-label use of medicines in neonates admitted to the Neonatal Intensive Care Unit of Nizwa Hospital. The findings suggest that the practice of prescribing off-label medications is prevalent, indicating a notable trend not only within the specific region but also internationally.

The current study's finding of a 28.5% prevalence of off-label medication use is consistent with existing regional data. For instance, Mazhar et al. (2018) reported off-label usage rates between 30% and 42% in neonatal intensive care units (NICUs) throughout Saudi Arabia, whereas Koszma et al. (2021) observed even higher rates, surpassing 60%, in European NICU environments. These variations in estimates can be attributed to differences in national regulatory frameworks and the availability of pediatric-specific drug formulations. The limited access to age-appropriate formulations is a persistent issue in numerous healthcare systems (Balan et al., 2018; Alyami et al., 2022). The significant prevalence of off-label prescribing identified in this study highlights the necessity for context-specific modifications in neonatal pharmacotherapy, especially in settings where approved dosing guidelines for neonates are limited (Meng et al., 2022).

Among neonates administered off-label medications, a slight male predominance was noted, with 53.8% being male. This distribution aligns with regional NICU admission trends documented in previous studies (Alonso et al., 2019). A statistically significant association was identified between gender and discharge disposition ($p = 0.012$; Cramér's $V = 0.220$), indicating a moderate relationship. Notably, female neonates exhibited higher rates of mortality and referrals to tertiary care centers compared to their male counterparts. This observation is consistent with existing literature suggesting sex-based biological vulnerabilities in neonates, including differences in immune function and susceptibility to complications such as respiratory distress syndrome (Koszma et al., 2021; Mazhar et al., 2018). While further research is warranted to explore these gender-related disparities in greater depth, the findings underscore the importance of considering gender as a potential determinant of neonatal health outcomes in clinical and pharmacological decision-making.

In terms of prescribing patterns, approximately **47.2%** of off-label drugs were administered via **unapproved routes,** while **22.4%** were prescribed to neonates outside the **recommended age range**, and **21.6%** were used in **contraindicated clinical situations.** This distribution closely mirrors the findings of Schrier et al. (2020), who identified **route of administration and dosing** as key factors contributing to off-label prescribing practices in European neonatal intensive care settings. Furthermore, the present study found that **25.9%** of all off-label prescriptions involved **high-alert medications**, significantly raising the risk of medication-related adverse events. Previous literature has emphasized the serious safety implications associated with the use of high-alert drugs, particularly when administered without adequate clinical safeguards or monitoring systems (Allen et al., 2018; AlAzmi et al., 2021). These findings highlight the critical need for structured pharmacovigilance and the development of clear guidelines to minimize harm in vulnerable neonatal populations.

The analysis revealed a noteworthy link between prescribing practices and clinical outcomes. Specifically, the frequency of off-label drug administration per neonate showed a significant association with discharge disposition ($p = 0.019$; Cramér's $V = 0.239$), indicating a moderate relationship. Neonates receiving multiple off-label medications were more prone to adverse outcomes, such as mortality or the need for referral to tertiary care centers. This observation is in line with previous studies that have highlighted the increased risk of adverse drug reactions, dosing errors, and drug–drug interactions in neonatal populations subjected to polypharmacy (Mazhar et al., 2018; Koszma et al., 2021). These findings emphasize the critical need for cautious and evidence-based prescribing practices in NICU settings to minimize the potential risks associated with off-label medication use.

A statistically significant association was identified between age group and the prescription of blood and blood-forming agents (ATC Level B) ($p = 0.035$; Cramér's $V = 0.212$), indicating a modest yet meaningful association. These medications were predominantly administered to younger neonates, particularly within the first week of life, a period characterized by a heightened incidence of conditions such as anemia, coagulopathy, and other hematological complications frequently encountered in the immediate postnatal period (Alonso et al., 2019; Schrier et al., 2020). This age-specific prescribing pattern underscores the necessity for developing treatment protocols tailored to different age groups to ensure the safe and effective management of neonatal hematologic disorders, thereby minimizing the risk of inappropriate dosing and adverse outcomes.

A notable portion (25.9%) of off-label medications utilized in the NICU were identified as high-alert drugs, which inherently present an elevated risk of significant harm if not used correctly. While no adverse drug reactions (ADRs) were reported, this lack of documentation may stem from underreporting or limited detection capabilities rather than an actual absence of such events. In contrast, no statistically significant associations were observed between the administration of high-alert medications and demographic factors such as gender ($p = 0.288$) or age group ($p = 0.099$), suggesting these variables did not affect prescribing trends. Moreover, the length of NICU stay did not exhibit any significant association with discharge outcomes or gender, indicating it was not a determinant of outcomes in this cohort. The total absence of recorded ADRs and pharmacist interventions during the study period, while possibly indicative of effective clinical practices, more likely points to underreporting and shortcomings in pharmacovigilance—an issue previously highlighted in neonatal care settings (Allen et al., 2018; Schrier et al., 2020; Mazhar et al., 2018).

Inadequate ADR monitoring represents a critical gap in ensuring medication safety, especially in neonatal populations where

high-alert medications and off-label prescribing are prevalent. These findings underscore the urgent need for system-level interventions. Specifically, the significant associations observed suggest that enhanced monitoring is warranted for neonates receiving multiple off-label medications and those prescribed blood-forming agents in the early neonatal period. Developing evidence-based clinical guidelines tailored to the Omani healthcare context could standardize prescribing practices and reduce reliance on empirical dosing decisions (Meng et al., 2022). Additionally, integrating dedicated clinical pharmacists into NICU teams and establishing multidisciplinary review committees could strengthen medication safety practices and promote rational prescribing (AlAzmi et al., 2021; Alyami et al., 2022). Ultimately, this study contributes to the existing literature by reinforcing the notion that while off-label prescribing in neonates may be unavoidable, it must be accompanied by robust safety surveillance, uniform treatment protocols, and ongoing professional education to minimize preventable harms and optimize patient outcomes.

This study is subject to several limitations. Firstly, the analysis was conducted on a relatively small sample size, which may constrain the generalizability of the findings and may not adequately represent the broader patterns of off-label drug use in neonatal care. Secondly, data retrieval was influenced by the recent renaming of the unit—from the Special Care Baby Unit to the Neonatal Intensive Care Unit—just two months prior to the study period. This transition may have resulted in incomplete records or data inconsistencies, potentially affecting the comprehensiveness of the dataset. While efforts were made to verify and reconcile the data, this limitation should be considered when interpreting the findings.

5. CONCLUSION

This study provides the first structured analysis of off-label drug use in neonatal intensive care units in Oman, offering valuable insights into prescribing patterns over an 18-month period. Nearly one-third of NICU admissions involved at least one off-label medication, with the majority related to unapproved routes of administration, age-specific contraindications, and the use of high-alert drugs. Beyond documenting current practices, the study establishes a replicable framework based on standard definitions and the WHO ATC classification, enabling other institutions to monitor and evaluate their prescribing trends. The findings underscore the urgent need for neonatal-specific prescribing guidelines, strengthened pharmacovigilance systems, and integration of medication data into electronic health records. This research lays the groundwork for future quality improvement initiatives, regional collaborations, and prospective studies aimed at enhancing medication safety, clinical outcomes, and evidence-based practice in neonatal care across Oman and similar healthcare settings.

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