

# Off-label drug use in Neonatal Intensive Care Units in China: a descriptive, multicenter study

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## Abstract

**Abstract Aim:** Off-label drug use in neonates remains a global problem. The retrospective, multicenter study was to study the rates and reasons of off-label drug use among representative NICUs in Henan, China. **Methods:** Prescriptions were randomized sampled from eight NICUs. Patient characteristics and diseases were collected. Classifications of off-label drug use including age, frequency, dose, indication and route of administration were analyzed. **Results:** 1770 neonates sampled from eight NICUs were evaluable in the study, with a mean body weight 2.98 kg (SD = 0.80, range 0.78-6.0), 92.03% of whom were exposed to [?] 1 off-label prescription. 5813 prescriptions with 113 drugs were registered, 84.62% of which were off label. 63.03% of the off-label use was in relation to age. **Conclusion:** Off-label drug use among neonates remains fairly prevalent in Henan, China. Initiative and effective implementation is urgently required to improve this situation.

## 1 INTRODUCTION

Off-label drug use is defined as prescribing marketed drugs outside of the authorized age, indication, weight, dose, formulation or route of administration.<sup>1, 2</sup> Drugs have historically been commonly used off label in pediatric population due to the challenge and difficulty to perform clinical trials considering the ethical concerns<sup>1</sup> and the dearth of therapeutic options. Neonates in the neonatal intensive care units (NICUs) are especially prone to off-label drug use.<sup>3-8</sup> Furthermore, neonates are particularly vulnerable and frequently premature in body systems such as drug absorption, metabolism, transportation and elimination, resulting in variations in the pharmacokinetic (PK) and pharmacodynamic (PD) properties and efficacy or toxicity of drugs administered to the infants.<sup>9</sup> For this reason, off-label drug use in neonates has been associated with higher risk of adverse drug reactions.<sup>10</sup> Until recently, there are no consensus guidelines about off-label drug use in global. In China, some expert consensus have been reported and a specific law or regulation for off-label drug use is absent.<sup>11</sup> Rates of off-label drug use varied as reported by studies in Chinese NICUs due to different grades of hospitals and definitions of off-label use.<sup>12-14</sup> We sought to conduct a retrospective, multicenter study including NICUs from regional, representative and different grade hospitals to describe the recent characteristics of off-label prescribing in Chinese neonates.

## 2 METHODS

## 2.1 Study design and setting

17 representative NICUs in each city from Henan province of China were contacted via telephones and requested in 2019 to participate in the retrospective study. All patients admitted to the participating NICUs in February, May, August and November were enrolled. The study was in accordance with Declaration of Helsinki and approved by Zhengzhou Children's Hospital Ethics Committee.

## 2.2 Definitions of off-label drug use

Neonates are defined as infants born to 28 days of age. A prescription was defined as a drug prescribed for a patient regardless of how often it was prescribed. All drugs prescribed to the patients were classified according to Anatomical Therapeutic Chemical (ATC) classification system.

The drugs were classified as label and off-label use. Off-label use is to prescribe a licensed drug for use in an unauthorized way, which differs from the ways specified in the Summary of Product Characteristics (SmPC).<sup>2</sup> The drugs were considered as off label if the drug was used off label for age, dose, frequency, route of administration and clinical indication. Off label for age was defined as (1) prescribed for neonates younger than the approved age for any indication; (2) information for adults and/or pediatrics was available, but information specialized for neonates was unavailable; (3) information for neonates such as 'the safety and efficacy in neonates have not been established', 'use as professionally prescribed', 'please use after consulting physicians or pharmacist' and 'adjust dose according to the disease and age'. The dosage was calculated by body weight or body surface area and the actual dosage within  $\pm 20\%$  standard dosage was not regarded as off label.<sup>15, 16</sup> The prescribed drugs were not further assessed for off-label categories for dose and frequency once they were off label for age.

The on/off label status were evaluated via the Mcdex (version 3) database developed by Sichuan Mcdex Pharmaceutical Software Research and Development Company and Committee of Experts on Rational Drug Use National Health and Family Planning Commission of The People's Republic of China, which contained labels of all drugs marketed by State Administration for Market Regulation. We also assessed the on/off label status of the drugs according to the Chinese National Formulary Chemical and Biological Products for Children (CNFC) 2013.

## 2.3 Data collection and statistical analysis

### Sample Size Calculation

The equation  $n = (Z_{\alpha/2}^2 \cdot pq) / d^2$  was used to figure out the sample size required for each NICU. The lowest rate of off-label drug use with 25.61% in a Chinese NICU was chosen as the assumed rate. The sample size of 1116 in each NICU was expected with a 95% confidence interval. The final sample size was increased to 2400 considering that injection liquid including 0.9% sodium chloride injection, 5% or 10% glucose injection, and sterilized liquid for injection, would be excluded from further study.

### Sampling method

The drugs prescribed to neonates admitted to each NICU in February, May, August and November were totally collected by hospital information system. 600 prescriptions were randomly decided and sampled in each of the four months, respectively. The random number of sampling was produced using SPSS 19.0.

## 2.4 Data analysis

Demographic data of the patients including birth, sex, body weight and diagnosis were collected. Drug information such as dose, frequency, route of administration and indication for use were also retrieved from the electronic medical records of each hospital. Prescriptions with incomplete data, electrolytes, contrast media, total parental nutrition, traditional Chinese medicine, intravenous infusions such as glucose and chloride and transfusion were excluded in this study. Data were collected, combined and analyzed in Excel for Windows using standard descriptive methods for demographics and prescriptions.

## 3 RESULTS

### 3.1 Characteristics of the patients

Eight NICUs (6 level III NICUs and 2 level II NICUs, comprising 1 children's hospital, 2 maternal and child health hospitals and 5 comprehensive hospitals), including 6 of the 17 NICUs we contacted and 2 NICUs who contacted us, participated in the retrospective, multicenter study. In total, 2051 newborns admitted to the participating hospitals were sampled and enrolled, 1770 of whom were evaluable and 281 were excluded due to incomplete demographic data (10 neonates) and unqualified prescriptions (271 neonates) (Table 1). Among the evaluable patients, 1035 (58.47%) were male and 735 (41.53%) were female. The mean body weight was 2.98 kg (SD = 0.80, range 0.78-6.0) and the majority of patients (68.14%) resulted to be the normal body weight ( $2.5 < 4.0$  kg). Of the patients, 41.52% were diagnosed with suspected/proven infections, followed by gastrointestinal diseases (25.88%) and respiratory diseases (7.57%). Intravenous injection was the most common route of administration, accounting for 73.11% of all the prescriptions, followed by oral administration (11.89%) and intramuscular injection (10.39%).

### 3.2 Prescribed drugs

A total of 5813 prescriptions with 113 drugs according to the Anatomical Therapeutic Chemical Classification system (Supplemental Information, Supplemental Table 1) were analyzed. The median prescriptions administrated to each neonate was 2 (range:1-38). According to drug categories (ATC level I), systemic anti-infectives were most prescribed to neonates (1716 prescriptions), followed by drugs acting on blood and blood forming organs (1184 prescriptions), alimentary tract and metabolism (1145 prescriptions), and cardiovascular system (843 prescriptions).

The most often prescribed drugs and off-label using drugs overall were listed in rank order (from 1 to 10) in Table 2. Among the anti-infectives (1716 prescriptions), piperacillin-tazobactam (212 prescriptions), cefoperazone-sulbactam (203 prescriptions) and ceftazidime (191 prescriptions) were the most prescribed drugs. Aminoglycoside antibiotics such as levofloxacin (2 prescriptions) and tobramycin (3 prescriptions) were rarely prescribed in our NICUs. Drugs for blood and blood forming organs (1184 prescriptions) were predominantly comprised of phylloquinone (699 prescriptions), etamsylate (162 prescriptions) and heparin (112 prescriptions). Among the drugs acting on alimentary tract and metabolism, vitamins were most commonly used, accounting for 82.79%. Among the cardiovascular drugs (843 prescriptions), phosphocreatine (425 prescriptions) and dopamine (136 prescriptions) were most frequently administrated.

### 3.3 Off-label drug prescriptions

According to the Mcdex (version 3), 4920 (84.64%) out of the 5813 prescriptions were classified as off label. Off-label use for age (3665 prescriptions) was most frequent, followed by indication (2742 prescriptions), dose (528 prescriptions), frequency (244 prescriptions) and route of administration (54 prescriptions). (Table 3) The majority of neonates (92.03%) were exposed to at least one off-label prescription. The most frequently prescribed drugs in off-label manner were phosphocreatine (425 prescriptions) and phylloquinone (416 prescriptions) (Table 2). Of note, inhalation of ambroxol for injection were the main reason of the off-label use for route of administration, due to the unavailability of ambroxol for inhalation in China.

However, some prescribed drugs were not found in CNFC 2013, such as caffeine, adenosine and biapenem. According to CNFC 2013, 3789 prescriptions were prescribed off label. The main reasons for off-label drug use were age (2276 prescriptions), indication (2207 prescriptions), dose (492 prescriptions), frequency (396 prescriptions) and route of administration (54 prescriptions), which were different from the results derived from Mcdex (version 3).

## 4 DISCUSSION

In this study, drug prescriptions were evaluated in NICUs of Henan, China. To the best of our knowledge, this is the first large-scale multicenter study conducted in China and the data would be representative of the regional distribution of Henan, demonstrating high rates of off-label use in neonates.

Due to lack of evidence on drug use in neonates and therapeutic alternatives, off-label drug use is widespread

in NICUs throughout the world<sup>3-8, 17, 18</sup>, with a incidence rate ranging from 14% in an academic Dutch Children's hospital<sup>17</sup> to 95.6% in a level III NICU in Brazil<sup>4</sup>. Regulations and guidelines related to off-label drug use are different in global. For example, the rational off-label drug use is allowed in United States, France, Japan and UK,<sup>2, 19-21</sup> but is abandoned in India<sup>22</sup>. Laws and regulations related to off-label drug use are unavailable in China. *Chinese Expert Consensus of Pediatric Off-Label Drug Use* was established to regulate pediatric off-label drug use in 2016 by Chinese Journal of Pediatrics with great efforts of Chinese pediatric healthcare experts.<sup>11</sup> However, there are still barriers to implement the Chinese expert consensus of pediatric off-label drug use in clinical practice,<sup>23</sup> resulting in high prevalence for off-label drug use. The percentage of prescriptions found to be off label in our study was 84.62%, which was higher as compared to previous reports ranging from 25.61% to 78.52% in China.<sup>12-14</sup>

Among the 5813 prescriptions, 63.03% was off label in relation to age. In an Italian multicenter study, the proportion of off-label prescriptions in relation to age was 34.4%.<sup>6</sup> The study performed in Germany showed that only 38% had information regarding the use in patients aged less than 1 month in their SmPC among the 102 prescribed drugs.<sup>24</sup> In the current study, 76.11% (86/113) of the prescribed drugs are in the absence of information for neonates, leading to the higher prevalence of off-label prescriptions associated with neonatal age. Historically, clinical trials evaluating the safety and efficiency of drugs and published information such as journal articles, practice guidelines, consensus statements in neonates are always unavailable.<sup>20</sup> Indeed, a large number of policies have been implemented to encourage the clinical evaluation in pediatric population, resulting in more than 500 pediatric labeling changes and the increase of prospective pediatric drug testing.<sup>20, 25</sup> Despite this, less than 50% of products had pediatric information in labeling, indicating that labeling with pediatric information is still insufficient.<sup>26</sup> Additionally, as a vulnerable subpopulation, neonates are always excluded from studies under the incentive legislative measures. Therefore, neonatal information such as safety, efficiency and appropriate dose in labeling is especially scarce.<sup>27</sup> Between 1997 and 2010, only forty-one studies referred to 28 drugs in neonates were completed resulting in 24 related labeling changes.<sup>27</sup> Consequently, numerous efforts are still required to overcome the current limitations and improve the efficiency in neonatal drug evaluation,<sup>28</sup> thus increasing the scientific evidence of drug use and alleviating the situation of off-label drug use in this population.

In our study, the abnormal diagnosis such as 'preterm' was common (14.29%), which was defined as off label for indication. In addition, the clinical diagnosis was incomplete, for example, phosphocreatine for neonatal respiratory distress syndrome, phenobarbital for acid reflux, fructose diphosphate sodium for pneumonia. Therefore, 47.17% of the prescriptions resulted off label for indication.

Obviously, the exposure to antibiotics is very common in hospitalized neonates. In a one-day point prevalence study of the Antibiotic Resistance and Prescribing in European Children project, 31% (532/1712) of the neonates were exposed to antibiotics, ranging from 19.9% in a general neonatal ward to 39% in a neonatal intensive care setting.<sup>29</sup> In the current study, systemic anti-infectives were most prescribed to neonates, which was quite similar to the results of recent studies by Neubert et al<sup>24</sup>, de Souza et al<sup>4</sup> and Costa et al<sup>3</sup>. However, a great variation regarding the anti-infective drugs prescribed in each NICU has been widely observed. Aminoglycosides such as gentamicin and amikacin, the preferred empirical treatment of suspected neonatal sepsis,<sup>30, 31</sup> were most frequently prescribed in UK<sup>32</sup>, Australia<sup>8</sup>, USA<sup>33</sup>, Italy<sup>34</sup> and Brazil<sup>4</sup>. In contrast, our data indicated that beta-lactam antibiotics including piperacillin-tazobactam, cefoperazone-sulbactam and cefotaxime were most prescribed antibiotics. This heterogeneity indicates that neonatologists prescribed antibiotics to the extensive variability in NICUs across globe, due to the lack of consensus regarding empirical antibiotic regimens in neonatal infections. To rationally use antibiotics, different and important aspects such as the pathogens and the resistance pattern, the PK and PD characteristics of antibiotics, and the neonatal pharmacology, should be considered.<sup>35</sup>

The analysis of off label based on CNFC exhibited a lower rate (65.16%) compared to Mcdex (84.62%) due to the differences of drug information between CNFC and Mcdex. For example, Mcdex recommend aminophylline for the treatment of asthma rather than neonatal apnea, while CNFC does. These results indicated that pediatricians are prone to making therapeutic decisions guided by the available evidence and

the benefit for the individual patient in their medical practice, thus adhering to CNFC.

Undoubtedly, this study had some limitations. First, as a retrospective study, detailed demographic information of neonates such as the gestational ages was unavailable, due to lack of corresponding data collected from hospital information system. However, recent studies have shown that a higher proportion of off-label prescriptions were associated with increased postmenstrual age.<sup>5, 34</sup> Second, off-label conditions were analyzed according to Mcdex database rather than country-specific licensing information in the package leaflets, regardless of the difference from different pharmaceutical enterprises with different trade names, leading to heterogeneity. Third, participating NICUs in this study were from a specialized region in China. Prospective, large sample, multicenter and nationwide studies would be required to understand the status of off-label drug use in neonates in the future.

## 5 CONCLUSION

We have demonstrated that neonates were exposed to high rates of off-label drug use in Henan, China. The most frequently prescribed category of off-label use was anti-infectives for systemic use and most frequently prescribed drugs in an off-label manner were phosphocreatine and phylloquinone. Efforts are still in urgent need to ensure the safety and efficiency of drug therapy for neonates, such as the publication and implementation of guidelines, the clinical pharmacokinetic and pharmacodynamic research, and the design and development of pediatric formulations.

## CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest relevant to this article.

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## FINANCIAL DISCLOSURE

The authors have no financial relationships relevant to this article to disclose.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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