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Pharmacoepidemiological evaluation of off label and unlicensed prescription in pediatric intensive care units at tertiary care hospitals of Peshawar, Pakistan

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Abstract: Population of pediatric intensive care units are at high risk of receiving off label and unlicensed drug use. Little is known about the characteristics and prevalence of unlicensed and off label prescriptions in pediatric intensive care units (PICUs) at tertiary care settings of Pakistan. Case notes of 420 children were reviewed for unlicensed and off label prescriptions during the one year. Medication profiles were assessed using Micromedex. Logistic regression was applied to calculate the odds-ratios for predictors of unlicensed and off label prescriptions. of the total prescriptions, 29.8% prescriptions were unlicensed from FDA and 42.27% prescriptions were off labelled. Dose (32.79%) was the most common reason for off label prescriptions followed by the indication (26.13%) and indication-dose (13.98%). Multivariate regression analysis revealed no significant association between the unlicensed prescriptions with their predictors. In reference to corresponding category, prescribed medications less than 5 (OR 0.280, 95%CL 0.137-0.570) were significantly less likely to receive off label prescriptions as compared to patients received 6 or more medications. Substantial numbers of children are exposed to unlicensed and off label prescriptions. Standards of drug quality, safety and efficacy should apply equally in adults and in pediatrics under ethical perspective. Suitable clinical interventions must be established by drug manufactures and government agencies for improved pediatric pharmacotherapy.

Keywords: Off label prescribing, pharmacoepidemiology, pediatric intensive care units, unlicensed prescription

INTRODUCTION

Improvements in diagnostic capabilities and pharmacotherapy have enhanced the quality of patient care (Laursen *et al*., 2018). Pharmacotherapy is far more complex for intensive care units (ICUs) patients, both adults and pediatrics. Polypharmacy is regularly employed for these patients, which can be defined as the prescription of five or more medications daily (Masnoon *et al*., 2017). In addition, polypharmacy is also known to be significantly associated with an increased risk of adverse drug reactions (ADRs) (Rieder, 2019). Pediatric patients face unique challenges as specific guidelines for dosing in pediatrics lack worldwide (Cuzzolin *et al*., 2006). Adult guidelines are extrapolated to adjust doses in children (Pasquali *et al*., 2008).

FDA classifies pediatric population into neonates (birth to 1 month), infants (1 month to 2 years), developing children (2-12 years) and adolescents (12-18 years). (Food and Administration, 1998). The pharmacokinetic profile of drugs varies in each pediatric subgroup due to differences in physical size, body composition, physiology and biochemistry (Yaffe and Aranda, 2010). Growth and development occur particularly rapidly during the first 2 years of life (Yaffe and Aranda, 2010) (Alcorn and McNamara, 2002). Body weight typically doubles by 6 months of age and triples by the first year of life. Body surface area (BSA) doubles during the first year (Davis *et al*., 2000).

Pediatric prescription has been much improved after the last legislation passed in 2007 by European Union regarding pediatric clinical drug trials (Kimland and Odlind, 2012). To promote rational drug prescribing in pediatrics choice of appropriate drug regimen, dose, route of administration, duration of regimen, contraindicated drugs and minimum risk of ADRs are important considerations, (Novak and Allen, 2007; Wertheimer, 2011) but unfortunately, still lack of specific guidelines has led to pediatric population being frequently exposed to unlicensed (UL) and off label (OL) drugs (Conroy *et al*., 2000).

UL drug use refers to a drug which has not been authorized for human use by a licensing authority like FDA, while OL drug use is prescribing an authorized drug in a way not mentioned in the product license. (Aronson and Ferner, 2017) Countries like the Spain, Brazil and Netherland not only reported varying prevalence of UL and OL prescriptions (García-Lopez *et al*., 2017; de Abreu Ferreira *et al*., 2012; van der Linden *et al*., 2002) but also reported unlicensed and off label prescribing to be a significant predictor for the occurrence of ADRs (Magalhaes *et al*., 2015; Santos *et al*., 2008).

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This is an emerging issue in Pakistan and studies are lacking, so the current study addressed this issue and evaluated the prevalence of UL and OL prescription and association with predictors in pediatric intensive care units (PICUs) at public and private tertiary care hospitals.

MATERIAL AND METHODS

This retrospective observational study was conducted in pediatric intensive care units (PICUs) of two tertiary care hospitals [Khyber Teaching Hospital (KTH) and Northwest General Hospital and Research Center (NWGH & RC)] of Khyber Pakhtunkhwa, Pakistan. A cohort of 250 and 170 patients, admitted to the PICU between May 1st 2020 and October 30th 2021 was obtained from the IT department of KTH and NWGH & RC respectively. Stratified random sampling technique was used to select sampling units. Sample size was calculated using the formula for known population (Machin *et al*., 2018). Data of 420 patients who met the inclusion criteria were randomly collected from the each cohort on a predesigned proforma. This proforma comprised of two parts, first contained the demographics and diagnosis, while second contained the drug profiles.

All the data was collected manually from the medication charts of patients from KTH as the hospital lacked electronic health records (EHR) while data from NWGH & RC was collected using EHR of the hospital. Patients of age <18 years admitted in the pediatric intensive care unit for at least 24 hour were included in the study. IV stock's solutions, topical medicines and oxygen therapy were excluded during data collection. The study was approved by the ethical committees of the KTH and NWGH & RC vide letter no 488/pharm and NWGH/Research/02 respectively. Patient drug profiles were evaluated using Micromedex® (Watson health, IBM Corporation) for off label and unlicensed drug use

STATISTICAL ANALYSIS

Descriptive statistics were used to summarize the age groups, gender, number of prescribed drugs, hospital stay of patients and UL and OL drug use. Multivariate binary logistic regression was employed to calculate odds ratio with 95% confidence interval for predictors of UL and OL drug use. Age, gender, number of prescribed drugs and duration of stay were considered as independent variables. While UL and OL drug use were considered as dependent variable. Independent variables (number of prescribed drugs and duration of stay) were stratifies using medians. All the analyses were run in IBM SPSS Statistics for Windows, version 20 (Armonk, NY: IBM Corp.).

RESULTS

Demographics

Of the total 420 patients, 59.52% were admitted to the PICU of KTH and 40.48% were admitted to the PICU of NWGH. Male population (66.43%) was predominant as compared to females in both the hospitals. Mean age of the patients was 29.05±36.58 months and infants (287, 68.33%) were the most common age group observed in PICU. Most of the patients received 4 to 6 drugs (184, 43.81%) and the mean number of prescription per child was 4.13±2.19. Of the total patients, 329 (78.33%) had hospital stay between 1 to 5 days with mean stay of 4.22±5.28. Patient's demographics in PICU are shown in table 1.

Diagnosis

Diagnosis was classified according to ICD 10 disease system. The common reasons for hospital admission in PICUs were pneumonia (11.19%), acute diarrhea (7.86%), acute bronchiolitis (6.67%), lower respiratory tract infection (6.67%), sepsis (5.71%), measles (4.76%), asthma (4.52%), meningitis (4.05%), pulmonary tuberculosis (3.57%) and tubercular meningitis (3.10%).

Drug categories and prescribed drugs

Using the Anatomical Chemical Therapeutic (ATC) classification system, anti-infective for systemic use were reported to be the frequently prescribed drug categories in the PICUs (51.37%), followed by drugs used in respiratory system (9.82%) and central nervous system drugs (8.82%). A total of 96 drugs were prescribed in the PICUs appearing 2453 times in patients admitted to the PICUs. Ceftriaxone (7.38%), ampicillin/cloxacillin (5.87%), captopril (5.58%), Cefotaxime (4.85%), Dexamethasone (4.40%), Salbutamol (3.63%), Cefepime (3.47%), Ceftazidime (3.47%), Ibuprofen (2.85%) and Paracetamol (2.77%) were the most commonly prescribed drugs in PICUs.

FDA approved and OL use of drugs

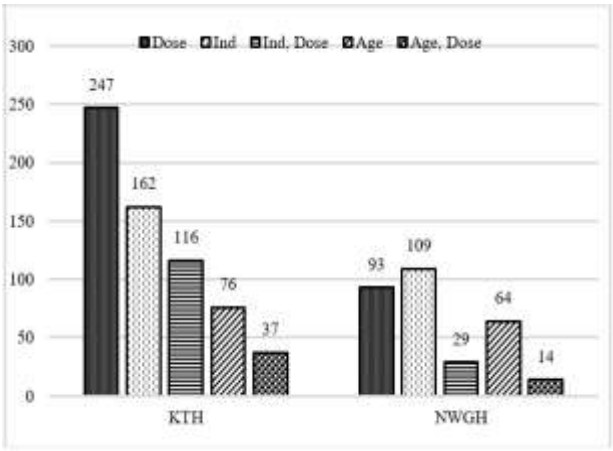
Of the total prescriptions, 29.8% were UL and 42.27% were OL. Overwhelming total of 97.38% patients (n-409) received at least one UL drug and 88.33% of the patients (n=371) received at least one OL drug (table 1).

Off Label categories

Dose [340 (32.79%)] was the prevalent reason for OL prescriptions and was present across all age groups and hospitals, followed by the indication [271 (26.13%)] and indication-dose [145 (13.98%)] as shown in fig. 1 and 2. Ceftriaxone, ampicillin and captopril were the frequently prescribed drugs in OL categories. Frequencies of frequently prescribed drugs and their OL categories are presented in fig. 3.

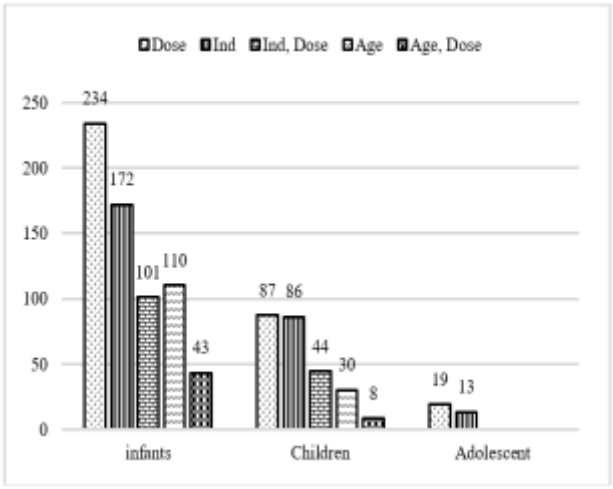
Predictors for Unlicensed and off label drug use

Multivariate regression analysis reported that patients with < 5 prescribed drugs (OR 0.280, 95%CI 0.137-0.570) were significantly less likely to receive OL prescriptions as compared to patients with ≥5 drugs. Other predictors including gender, age and hospital stay had no significant effect on OL prescriptions. Additionally, no significant relationship between UL drug uses was observed with any of the predictors (table 2).



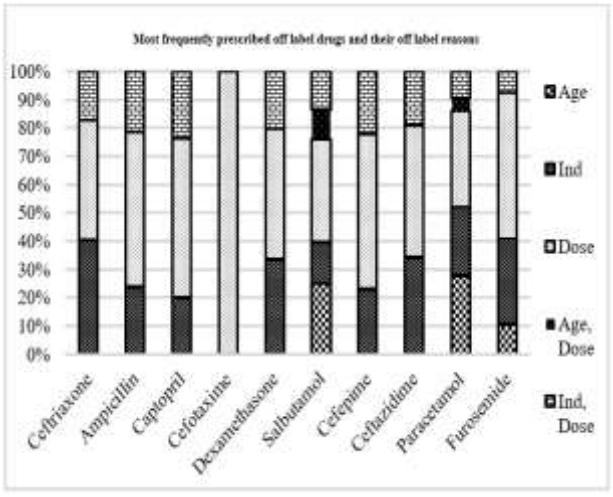
*Ind represents indication; KTH represents Khyber Teaching Hospital; NWGH represents Northwest General Hospital

Fig. 1: Prevalent off label categories in both hospitals.



*Ind represents indication

Fig. 2: Prevalent off label categories in age groups.



*Ind represents indication

Fig. 3: Most prevalently prescribed off label drugs and their off label reasons.

DISCUSSION

Tragedies observed in the last century like drugs affected developing fetuses (thalidomide) and newborns (chloramphenicol) give rise to the phenomenon of drug licensing to ensure the safety and efficacy of drugs used in clinical practice (O'Donnell *et al*., 2002). UL and OL prescribing in pediatric pharmacotherapy cannot be ignored as limited approved drugs are available for the treatment of children. The lack of pediatric drug data is due to insufficient clinical drug trials for pediatric population. Due to this reason pharmacotherapy of pediatric patients in ICUs becomes more challenging for physicians (Conroy *et al*., 2000). With best of our knowledge, this is the first study which analyzes the UL and OL drug use at PICUs in Pakistan.

A High prevalence of UL prescriptions (29.80%) was observed at the PCIUs in our study. Turner *et al* published a report from a PICU in United Kingdom which reported a similar prevalence of UL prescriptions (31%) (Turner *et al*., 1996). An eight week study conducted in Malaysia also reported 27.3% of UL prescriptions (Lee *et al*., 2013). However, other studies from Spain, Brazil and Palestine reported a lower prevalence of UL prescriptions. (García-López *et al*., 2017; de Abreu Ferreira *et al*., 2012; Khdour *et al*., 2011). The improved culture of drug prescribing after legislation passed in 2007 by European Union reduced UL drug use in Europe. Presence of EHR and high funding for pediatric researches in developed countries could be the other reason of low prevalence of UL prescription in their children. In spite of that reason for high prevalence of UL drug use in our region is lack of pediatric drug information in national formulary of Pakistan.

The prevalence of OL drug use at PICUs observed was 42.27%. Comparable finding have been observed in Malaysian and Palestinian reports which revealed prevalence of 35.3% and 34.1% of OL prescriptions respectively (Lee *et al*., 2013; Khdour *et al*., 2011). A cross-sectional study carried out in PICU of tertiary care hospital of Brazil revealed a low prevalence (23.4%) of OL drug use (de Abreu Ferreira *et al*., 2012). On the contrary, two studies performed at PICUs in Spain reported a high prevalence of OL prescriptions, 53.9% and 52% respectively (García-López *et al*., 2017), (Blanco-Reina *et al*., 2016). A much higher prevalence (70.5%) was also reported in an Indian study, (Bavdekar *et al*., 2009). The wide differences in the literature can be attributed to variations in the definitions of off label drugs used and heterogeneity in the studied patient population. In addition, variation in prevalence may be due to different nature of methodologies of these studies.

Dose (32.79%) was reported as the prevalent category for OL prescriptions. The second most frequently observed category for OL prescription was indication (26.13%).

Table 1: General characteristics of patients in PICU

Variables	n % KTH	n % NWGH	Total
Gender			
Male	157 (37.38)	122 (29.05)	279 (66.43)
Female	93 (22.14)	48 (11.43)	141 (33.57)
Total	250 (59.52)	170 (40.48)	420 (100)
Age groups			
≤ 23 months	172 (40.95)	115 (27.38)	287 (68.33)
24 to 143 months	69 (16.43)	51 (12.14)	120 (28.57)
≥ 144 months	9 (2.14)	4 (0.95)	13 (3.1)
Total	250 (59.52)	170 (40.48)	420 (100)
Mean ± S.D	26.29 ± 36.52	25.69 ± 36.17	29.05 ± 36.58
Range	166.88 (1.12-168)	215.97 (0.03-216)	215 (0.03-216)
Prescribed drugs			
1 to 3 drugs	88 (20.95)	74 (17.62)	162 (38.57)
4 to 6 drugs	123 (29.29)	61 (14.52)	184 (43.81)
7 or more drugs	39 (9.29)	35 (8.33)	74 (17.62)
Total	250 (59.52)	170 (40.48)	420 (100)
Mean ± S.D	4.31 ± 2.05	4.12 ± 2.38	4.23 ± 2.19
Range	8 (1-9)	8 (1-9)	8 (1-9)
Hospital stay			
1 to 5 days	190 (45.24)	139 (33.1)	329 (78.33)
6 to 10 days	48 (11.43)	23 (5.48)	71 (16.9)
11 or more days	12 (2.86)	8 (1.9)	20 (4.76)
Total	250 (59.52)	170 (40.48)	420 (100)
Mean ± S.D	4.54 ± 6.33	3.76 ± 3.12	4.22 ± 5.28
Range	44 (1-45)	24 (1-25)	44 (1-45)
Patients received at least one unlicensed drug			
Y	244 (58.1)	165 (39.29)	409 (97.38)
N	6 (1.43)	5 (1.19)	11 (2.62)
Total	250 (59.52)	170 (40.48)	420 (100)
Patients received at least one unlicensed drug			
Y	223 (53.1)	148 (35.24)	371 (88.33)
N	27 (6.43)	22 (5.24)	49 (11.67)
Total	250 (59.52)	170 (40.48)	420 (100)

PICU; Pediatric Intensive care unit, KTH; Khyber Teaching Hospital, NWGH; Northwest General Hospital,

Table 2: Predictors of unlicensed drug and off label prescriptions in PICUs

S.No.	Variables	Unlicensed		OR (95% CI)	*p* value
		Present (n=409)	Absence (n=11)		
1	Gender Male Female	 273 136	 6 5	 1.004 (0.641-1.574) Reference	 0.986
2	Age Groups ≥ 23 months 24 to 143 months ≤ 144 months	 277 119 13	 8 2 1	 1.180 (0.734-1.899) 1.924 (0.304-3.449) Reference	 0.495 0.969
3	Length of Stay Less than 5 days 5 or More days	 321 88	 8 3	 1.162 (0.701-1.925) Reference	 0.561
4	Prescribe Drugs Less than 5 drugs 5 or More drugs	 298 111	 7 4	 1.127 (0.704-1.803) Reference	 0.618
		Off label			
		Present (n=371)	Absence (n=49)		
1	Gender Male Female	 246 125	 33 16	 1.081 (0.643-1.818) Reference	 0.768
2	Age Groups ≥ 23 months 24 to 143 months ≤ 144 months	 251 110 10	 36 10 3	 1.155 (0.665-2.006) 0.330 (0.98-1.111) Reference	 0.610 0.073*
3	Hospital Stay Less than 5 days 5 or More days	 281 91	 38 11	 0.501 (0.249-1.007) Reference	 0.052*
4	Prescribe Drugs Less than 5 drugs 5 or More drugs	 256 115	 41 6	 0.280 (0.137-0.570) Reference	 0.000***

*significant at p <0.1 **significant at p < 0.05 ***significant at *p < 0.01* OR= Odds Ratio, CI= Confidence interval

Similar findings were reported from Spain: dose and indication as most common OL categories (Blanco-Reina *et al*., 2016). An Indian study also reported dose as the most common OL category (Bavdekar *et al*., 2009). A report published from Brazil also observed dose as the prevalent OL category (de Abreu Ferreira *et al*., 2012). However, another study conducted in Spain showed indication, age followed by dose as most frequent OL categories in their findings (García-López *et al*., 2017). If drug is prescribed under dosed there may be no pharmacological effect and overdosing may lead to toxicity. Furthermore these both (Under dosing and overdosing) effect carries a risk of ADRs.

Analysis using multivariate regression revealed no significant predictor regarding UL drug use. In case of gender similar association was reported by cross-sectional study conducted in Brazil. (de Abreu Ferreira *et al*., 2012). Contrary results to our findings were published from Malaysia which demonstrated that infant's age group, hospital stay more than 8 days and number of prescribed drugs on every unit was found to be significant predictors for UL prescription (Lee *et al*., 2013). Unsymmetrical pattern of therapies in PICU for critical pediatrics could be cause of insignificant relationship among UL prescriptions and their predictors.

Prescribed medications less than 5 drugs had significantly low chance of exposure to OL prescriptions. Similar results were showed by research conducted at intensive care unit, based on 194 pediatrics in Malaysia. Another significant predictor was term infant for use of OL prescriptions, which was found insignificant risk factor in our study (Lee *et al*., 2013).

Anti-infective for systemic use was the most frequent prescribed therapeutic drug category in current report. A study conducted in Spain also complies with our finding (Blanco-Reina *et al*., 2016). A research conducted in Brazil also stated anti-infective for systemic use as most common prescribed therapeutic category (de Abreu Ferreira *et al*., 2012). A pilot study conducted in Spain revealed drugs used in nervous system as frequent prescribed therapeutic category, which was observed as 3rd most frequent therapeutic drug category in our findings (García-López *et al*., 2017). According to World health organization report (2019) Global child mortality rate was 15% due to pneumonia under 5 years of age (Organization, 2019). Recent review article indicates that the incidence of clinical pneumonia and severe pneumonia increased in Pakistan by about 50% from the year 2000 to 2015 (McAllister *et al*., 2019). Several factors likely contribute to the high prevalence of pneumonia in pediatric in developing region of world. These include the high burden of viral etiologies of pneumonia, the use of antibiotics before culture, the limited sensitivity of culture-based methods and also limited resources with high burden of patients in tertiary care setups.

PICUs patients were prescribed ceftriaxone and ampicillin as major part of their therapy in both hospitals. Ampicillin was also described as the most frequent drug prescribed to patients admitted in PICU of Spain (Blanco-Reina *et al*., 2016). Cefotaxime was reported mostly prescribed in PICU of India, however, cefotaxime was the fourth most common drug in our study (Bavdekar *et al*., 2009). While a study revealed fentanyl as most frequent drug in PICU of Spain (García-López *et al*., 2017). But the fentanyl was not used in PICU nor even in any pediatric department in our study. As general anesthesia is the only condition in which fentanyl is approved by FDA in children above 2 two years (Mellon *et al*., 2007). High prevalence of bacterial infections (pneumonia, diarrhea and sepsis) in PICUs in our region is the primary cause of frequent prescription of these antibiotics. An overview about cefotaxime also prefers to prescribe cefotaxime along with ampicillin as compared to other antibiotics for better clinical outcomes in pediatric infectious diseases (Payne and Ericson, 2019).

In critical situations it is responsibility of prescriber to assess the situation and condition of the patient, where the children are already seriously ill and when researches already reported that off-label use is associated with higher risk of adverse drug reactions (Horen *et al*., 2002; Neubert *et al*., 2004).

Pharmacoepidemiological studies are the primary need for improved prescribing culture for safe and efficacious clinical outcomes for pediatrics. Moreover, the studies in multicenter settings are lacking worldwide especially in developing countries. However, the study did not identified categories for UL prescribing and was also limited to PICUs. Therefore, the results need to be generalized with caution in other pediatric community.

CONCLUSION

Substantial numbers of children are exposed to UL and OL prescriptions. Standards of drug quality, In order to improve health care in pediatric population in developing countries health regularity agencies must introduce new therapeutic practice protocols followed in developed region. Furthermore, safety and efficacy of drugs should apply equally in adults and in pediatrics under ethical perspective.

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