BJPS

Brazilian Journal of
Pharmaceutical Sciences

http://dx.doi.org/10.1590/s2175-97902022e20238

Article

Off-label drug use in an adult intensive care unit of a Brazilian hospital

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The objective of this study was to determine the prevalence and describe the factors associated with off-label drug use in an adult intensive care unit (ICU) of a Brazilian hospital. An analytical, cross-sectional, prospective study was conducted in the adult ICU population from March 2018 to May 2018. Off-label use of medication was classified by indication, dosage, route of administration, type and volume of diluent, and duration of administration. Most patients were female (57.89%), non-elderly (56.14%), and had a mean age of 54.44 ± **17.15** years. The prevalence of off-label drug use was 70.31%, but was not associated with the clinical severity of the patients. A statistically significant association was observed between label use of drugs and prescribing potentially inappropriate medicines (PIM). The most common reasons for off-label drug use were therapeutic indication (19.58%) and volume of diluent (23.30%). Drug administration by enteral tubes accounted for the largest number of off-label uses due to route of administration (90.85%). There was a higher prevalence of off-label use of systemic antimicrobials (14.44%) and norepinephrine (9.28%). Our study provided a broad characterization of off-label drug use in an adult ICU and showed why it is important for health professionals to evaluate the specific risks and benefits of this practice.

Keywords: Off-label use. Intensive Care Units. Critical Care. High-alert medication.

INTRODUCTION

The term "off-label" refers to the prescribing and administration of drugs in a different manner to that described in package inserts with regard to factors such as the age of the patient, therapeutic indication, dosage, and frequency (Aronson, Ferner, 2017; Shoulders *et al*., 2017). In some hospital units, such as oncology, pediatrics, and intensive care, the use of drugs for unapproved indications and/or dosages is common, probably due to the lack of comprehensive clinical studies in these fields (Smithburger *et al*., 2015; Casañ *et al*., 2017).

The National Health Surveillance Agency (ANVISA) reviews the registration of medicines in Brazil supported by safety and efficacy studies, which are provided by pharmaceutical companies (Patel *et al.,* 2020). However, neither ANVISA nor the United States Food and Drug Administration (FDA) can regulate medical practice or how these drugs are prescribed, and do not provide guidance on off-label prescribing (Smithburger *et al*., 2015; Carvalho *et al*., 2012).

The off-label use of drugs is not illegal, not necessarily incorrect, and can be predicted and recommended by institutional protocols and international guidelines (Smithburger *et al*., 2015). Nevertheless, prescribers must

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consider several clinical, ethical, and safety aspects (Smithburger *et al.,* 2015; Zheng, Yang, Wu, 2017; Gonçalves and Heineck, 2016). The substantial concerns about off-label drug use are related to the potential adverse effects and/or ineffective therapeutic outcomes of the practice, as well as the lack of strong scientific evidence to support it. (Shoulders *et al*., 2017; Gonçalves *et al.,* 2018; European Medicines Agency, 2004; Eguale *et al.,* 2016).

The prevalence of off-label drug use has been described in hospitalized pediatric and neonatal populations and varies from 26% to 59% in the intensive care units (ICUs) and emergency rooms (Casañ *et al*., 2017; Carvalho *et al.,* 2012; Gonçalves, Heineck, 2016; Gonçalves *et al.,* 2018). Studies conducted in adult ICUs of North American hospitals reported that patients received between 36%–48% of off-label drugs, with gastrointestinal, antibiotic, antiepileptic, and immunological agents being the most prescribed (Smithburger *et al*., 2015; Lat *et al*., 2011).

In the past two decades, several studies have tried to characterize off-label prescribing in pediatrics and neonatology (Gonçalves, Heineck *et al*., 2016; Souza *et al*., 2016; Ferreira *et al*.; 2012). However, specific studies that have evaluated off-label prescribing in adult ICUs of hospitals are scarce (Smithburger *et al.,* 2015; Lat *et al*., 2011). In this context, this study aimed to determine the prevalence of off-label drug use and describe the factors associated with this practice in hospitalized adult ICU patients in Brazil.

MATERIAL AND METHODS

The investigation was an analytical, cross-sectional, and prospective study, performed in a clinical ICU for adult patients admitted at a public university hospital in Fortaleza, Brazil, from March 2018 to May 2018. The study was approved by the Ethics and Research Committee of the Hospital (CAAE: 81729818.5.0000.5045).

The study hospital provides highly complex health care and is integrated into the Brazilian Unified Health System (SUS). The ICU is composed of eight active beds, serves clinical and surgical patients, and has closed medical staff. The ICU multiprofessional team is composed of doctors on duty and day laborers, nurses and nursing technicians, physiotherapists, pharmacists, and nutritionists. In addition, resident professionals from medicine, nursing, pharmacy, and physiotherapy careers integrate into the team. The institution did not have an electronic prescription system at the time of the study.

The study population consisted of patients aged 18 years or older who were admitted to the ICU for at least 48 hours on any day of the week, accompanied by an intensive care pharmacist, with a prescription of at least one drug on each of the evaluation days, and with accessible medical records for data collection. Drugs prescribed to the patients were evaluated from Monday to Friday by a pharmacist through the validation of the patients daily medical prescription. Drugs prescribed over the weekend or on holidays were included in the analysis on the first following business day.

Patient data were collected from medical records and duplicates of drug prescriptions filed in the pharmacy. The demographic and clinical variables collected from patient records included age, sex, weight, reason for admission, and length of stay in ICU. The Acute Physiology and Chronic Health Disease Classification System II (APACHE II) (Knaus *et al*., 1995) and sequential organ failure assessment (SOFA) scores were also collected (Vincent *et al.,* 1996). In general, the APACHE II and SOFA parameters were evaluated immediately after the collection of clinical and laboratory data needed to calculate the scores. This was done within 24 hours of admission into the ICU. Therefore, the APACHE II and SOFA scores were calculated between the issuing of the first and second medical prescriptions in the ICU for most cases, always considering the clinical parameters of the patient at the time of admission to the ICU.

Data collected from the prescriptions included therapeutic indication, presentation, dosage, frequency, route of administration, and if applicable, diluent, volume of dilution, and method of administration, as well as whether drugs were prescribed before or after admission to the ICU. In cases of doubt or missing information on a prescription, the pharmacist consulted the prescribing team for further clarification. Volume replacement solutions, parenteral nutrition, blood transfusion products, oxygen, and oral hygiene products were not included in the study. In addition, drugs prescribed as "if necessary"

or "at medical discretion" and bolus injections of sedative drugs were not included in the study due to lack of data, specifically regarding the exact therapeutic indications.

Adequacy analyses of the prescriptions were performed using the information contained in the package insert of the reference drug approved by ANVISA. Therapeutic drug classification was performed using the Anatomical Therapeutic Chemical (ATC) database. In addition, PIM were defined according to the Brazilian Institute for the Practice of Safe Medication (ISMP), a non-governmental, independent, and non-profit organization that promotes safe practices during the use of medicines and health products (WHO, 2018; ISMP; 2018). The workflow of the study is summarized in Figure 1.

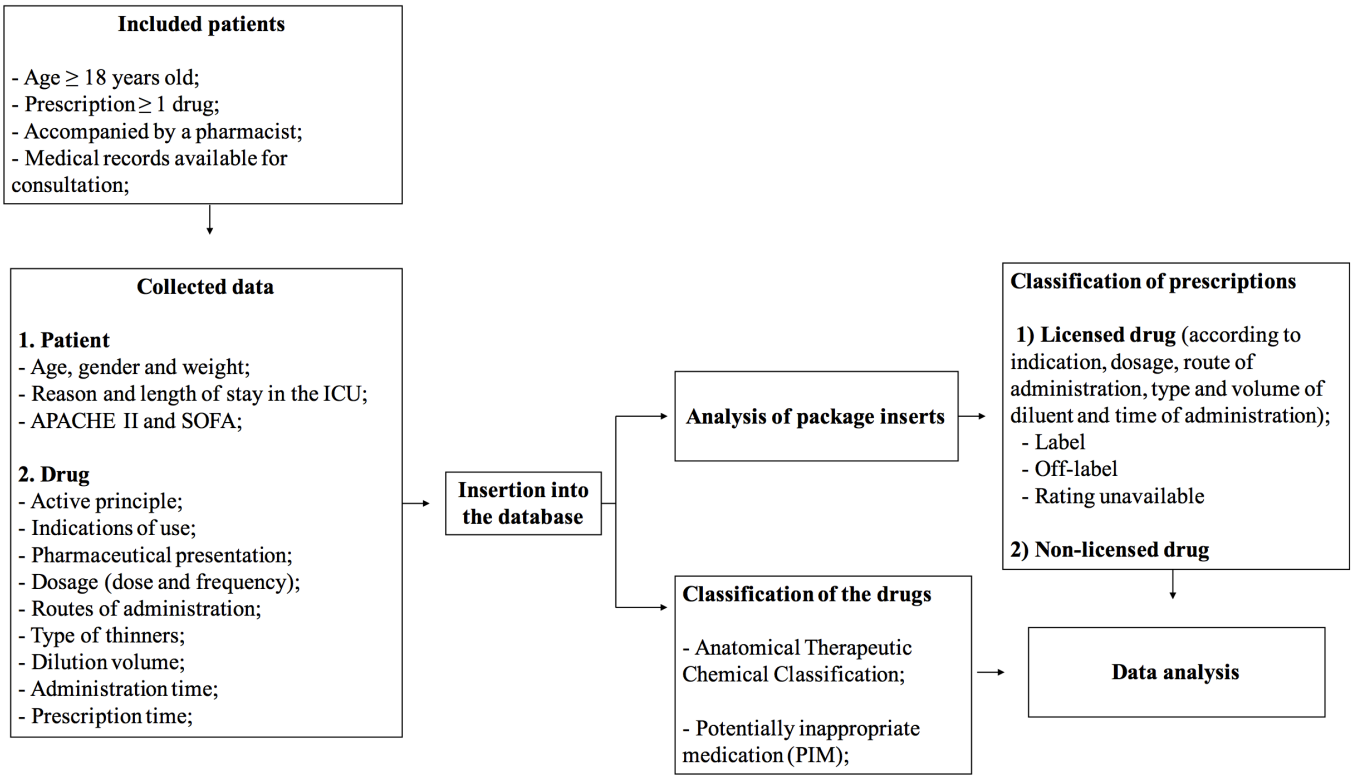

FIGURE 1 - Workflow of the study protocol: Selection and enrollment of patients, drug information with further analysis of package inserts, and drug classification.

Drug prescriptions were classified into four groups: label, off-label, non-licensed, and non-defined. All drugs used for which the prescription showed a discrepancy with at least one of the indications found in the package inserts were considered off-label and divided into subcategories: 1) therapeutic indication, 2) dosage, 3) route of administration, and if applicable, 4) type of diluent, 5) volume of diluent, and 6) duration of administration for intravenous drugs. Non-licensed drug prescription classification was applied to extemporaneous preparations manufactured at the hospital or external laboratories that are not registered by ANVISA. Non-defined group classification included drug prescriptions with at least one missing instruction, such as diluent or volume of diluent, which reflected an error in the prescription. Prescription data were collected with an indication of the start and end dates of each prescription. The final date indicated the point at which therapy ended, with complete supporting information, such as therapeutic indication, dose and frequency (dosage), route of administration, diluent, volume of dilution, and route of administration.

Data were collected and inserted into Excel® sheets (version 2016). Numerical variables are shown as mean and standard deviation, while categorical variables are presented as frequencies of factors associated with off-label drug use. The significance level was set at 5%. When analyzing the association between variables, Fisher's exact test was performed using Graph Pad Prism software, version 7.0d.

RESULTS

Characterization of the population

A total of 71 patients were admitted to the ICU and received prescriptions with at least one drug. Of these, 57 (80.28%) patients were included in the study. The remaining patients were excluded based on the following criteria: stayed in the ICU for less than 48 h (n = 12; 16.90%), were < 18 years old (n = 1; 1.41%), and had missing data (n = 1; 1.41%). There were 92 days of patient follow-up, with an average of 19 patients per month.

Most of the patients were female (57.89%; n = 33) and non-elderly (56.14%; n = 32). The mean age of the study population was 54.44 ± 17.15 years (range: 21-85 years old). Some patients (15.79%; n = 9) came from external health institutions while 84.21% (n = 48) patients were transferred from inpatient units of the study hospital, with 47.37% (n = 27) from clinical wards and 36.84% (n = 21) from surgical ICUs.

The most prevalent reasons for admission to the ICU were septic shock (38.60%; n = 22), sepsis (22.81%; n = 13), decreased level of consciousness (14.04%; n = 8), and cardiogenic shock (10.53%; n = 6). With regards to comorbidities, systemic arterial hypertension (63.16%; n = 36), diabetes mellitus (36.84%; n = 21), and renal dysfunction (36.84%; n = 21) were predominant. The assessment of severity / organ dysfunction scores showed an average of 19.16 ± 7.97 points (range: 2-34 points) for APACHE II and 6.05 ± 3.50 (range: 1-17 points) for SOFA. The average length of stay in the ICU was 11.89 ± 10.22 days (median, 9 days; range, 2-55 days), and hospital discharge was the most common outcome (71.93%; n = 41).

Prevalence of off-label drug use and associated factors

A total of 660 prescriptions were analyzed and included in the study, with an average of 11.58 prescriptions per patient. These prescriptions accounted for a total of 2,309 drugs. The prescribing of drugs classified as non-licensed use was observed six times (0.26%) and was restricted to papain, a drug contained in a cream extemporaneously prepared in a pharmacy. Licensed drug use was present in 2,284 cases, with 29.68% (n = 678) of these drugs being for their approved clinical use while 70.31% (n = 1,606) were for off-label use. The average number of off-label drugs per patient was 28.18, and all patients received at least one drug for off-label use. Non-defined classification was present in 19 cases (0.82%) (Table I).

TABLE I – General indicators of prescriptions, drugs and off-label drug use prevalence among the 57 patients of the study

Prescriptions	**N (%)**
Prescriptions total number	660 (94.42)
Average of prescriptions per patient	11.58
Drugs	**N (%)**
Total number of prescribed drugs	2,309
Non-licensed drugs	6 (0.26)
Licensed drugs	2,284 (98.92)
Licensed drugs with off-label use	1,606 (70.31)
Licensed drugs with label use	678 (29.68)
Licensed drugs with non-defined classification	19 (0.82%)
Mean ± SD[a] of the number of times of off-label drug prescriptions per patient	28.18 ± 21.37
Moment of drug prescription at admission	**N (%)**
Before ICU[b]	**323 (100)**
Before ICU as label use	91 (28.17)
Before ICU as off-label use	232 (71.83)
After ICU[b]	**318 (100)**
After ICU as label use	111 (34.91)
After ICU as off-label use	207 (65.09)

TABLE I – General indicators of prescriptions, drugs and off-label drug use prevalence among the 57 patients of the study

Prescriptions	**N (%)**
Potentially Inappropriate Medicines (PIM)	**N (%)**
Different prescribed PIM	33
Number of times that PIMs were prescribed	1.015 (43.96)
Number of PIMs prescribed as off-label (proportion to total number of prescribed drugs)	681 (29.49)

[a] Standard Deviation. [b] Intensive Care Unit.

Evaluation of patient prescriptions at the time of admission to the ICU showed that 71.83% of the drugs (n = 232) that were prescribed prior to ICU admission were for off-label use. Analysis of drugs prescribed during ICU admission showed that 65.09% (n = 207) of them were for off-label use. Thirty-three different drug classes of PIM were prescribed, with the following five drugs being the most frequent: norepinephrine (14.68%; n = 149), potassium chloride (11.53%; n = 117), fentanyl (11.03%; n = 112), midazolam (9.26%, n = 94), and heparin (8.18%, n = 83). PIM accounted for 43.96% (n = 1,015) of the total drugs that were prescribed, with 29.53% (n = 681) of them being for off-label use (Table II).

TABLE II – Comparison of off-label and label drug use regarding demographic and clinical data and prescription of Potentially Inappropriate Medicines (PIM)

Factors	**Total = 2,284 N (%)**	*Off-label (n=1,606)*	*Label (n=678)*	p^a	**Odds ratio**	$\mathbf{CI_{95\%}}^b$
		N (%)	***N (%)***			
Female	1,408 (61.65)	982 (61.15)	426 (62.83)	0.4517	0.9309	0.77-1.12
Male	876 (38.35)	624 (38.85)	252 (37.17)			
Elderly[c]	1,139 (49.87)	793 (49.38)	346 (51.03)	0.4921	0.9359	0.39-1.12
Non-elderly	1,145 (50.13)	813 (50.62)	332 (48.97)			
APACHE II ≤ 25[d]	1,851 (81.04)	1,291 (80.39)	560 (82.60)	0.2426	0.8636	0.34-1.09
APACHE II > 25[d]	433 (18.95)	315 (19.61)	118 (17.40)			
SOFA ≤ 12[e]	2,226 (97.46)	1,563 (97.32)	663 (97.79)	0.5638	0.8224	0.45-1.45
SOFA > 12[e]	58 (2.54)	43 (2.68)	15 (2.21)			
Alta	1,717 (75.18)	1,189 (74.03)	528 (77.88)	0.0563	0.8100	0.32-1.00
Death	567 (24.82)	417 (25.97)	150 (22.12)			
PIM no	1,269 (55.56)	925 (57.60)	344 (50.74)	0.0027	1.3190	0.55-1.58
PIM yes	1,015 (44.44)	681 (42.40)	334 (49.26)			

[a] Fisher's exact test; $p<0.05$. [b] CI 95%: confidence interval of 95%. [c] In Brazil, elderly are subjects aging 60 years old or more. [d] *Acute Physiology and Chronic Health Evaluation*. APACHE II stratification was applied randomly, considering mortality risk above 50% for values above 25.[14] [e] *Sequential Organ Failure Assessment*. SOFA stratification was applied randomly, considering organ failure above 50% for values above 12.[15]

An investigation into whether off-label drug use could be associated with gender, age, severity and organ dysfunction scores (APACHE II and SOFA), and prescription of PIM was conducted (Table II). Fisher's exact test showed a significant association between label drug use and prescribing PIM; however, the association was of a low magnitude (p = 0.0027; odds ratio = 1.319; CI 95%: 0.55–1.58). In addition, the other variables tested had

no statistically significant associations. Due to the high use of antimicrobial drugs, the analysis of the association between label use and PIM was also performed after exclusion of these drugs, and yielded similar findings (p = 0.0248; odds ratio = 1.112; 95% CI: 1.015–1.214).

Off-label categories and associated drugs

Among all drug uses, 23.30% (n = 538) were classified as off-label due to the volume of the diluent, which resulted in more concentrated solutions than recommended, and 19.58% (n = 452) were due to therapeutic use. Some drugs were classified as off-label for more than one reason – the sum of the reasons for off-label use exceeded the absolute value of off-label drugs (Figure 2). Among the off-label drug use due to route of administration, 90.85% (n = 318/350) were related to the administration of drugs using enteral tubes.

Analysis of the drugs using the ATC code showed the presence of 50 different therapeutic classes. Systemic antimicrobials (n = 232; 14.44%), cardiac therapy drugs (n = 202; 12.58%), and psycholeptics (n = 192; 11.96%) were the top prescribed agents for off-label use (Figure 3).

The most prescribed drugs for off-label use were norepinephrine (n = 149; 9.28%), due to differences in the type and volume of the diluent; potassium chloride (n = 116; 7.22), due to the route of administration when considering syrup formulations, and volume of the diluent; fentanyl (n = 112; 6.97%), mainly due to therapeutic indication and duration of administration (Figure 4). The most frequently prescribed systemic antimicrobials for off-label use were meropenem (n = 56; 3.49%) and polymyxin B (n = 56; 3.49%), while midazolam (n = 94; 5.85%) was the most frequently prescribed psycholeptic.

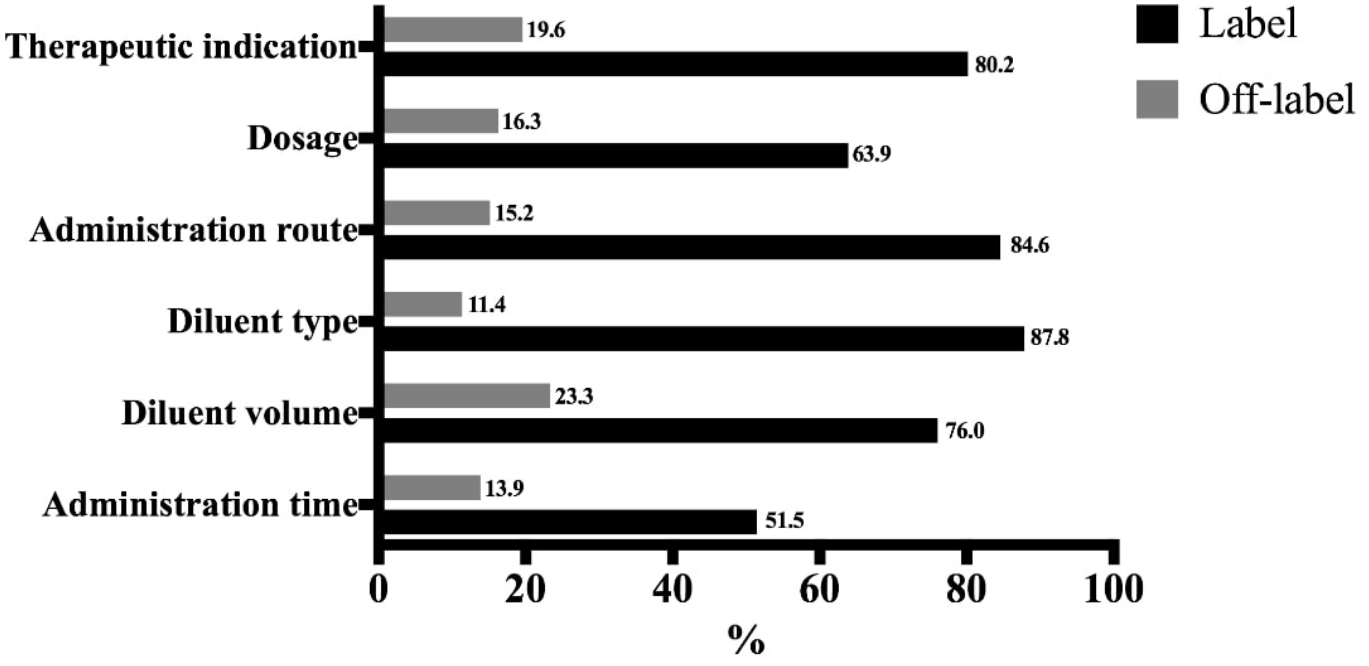

FIGURE 2 - Prevalence of off-label and label drug use for each of the categories assessed: therapeutic indication, dosage, route of administration, type and volume of diluent, and duration of administration.

Dosage category was only assessed for licensed drugs which were prescribed for use as per their therapeutic indication. Non-licensed drugs were identified in 0.26% of the prescriptions (n = 6). Non-defined drug use was

identified in the following categories: type of diluent (0.52%, n = 12), volume of diluent (0.39%, n = 9), and duration of administration (1.86%, n = 43). The duration of administration was only evaluated for intravenous drugs.

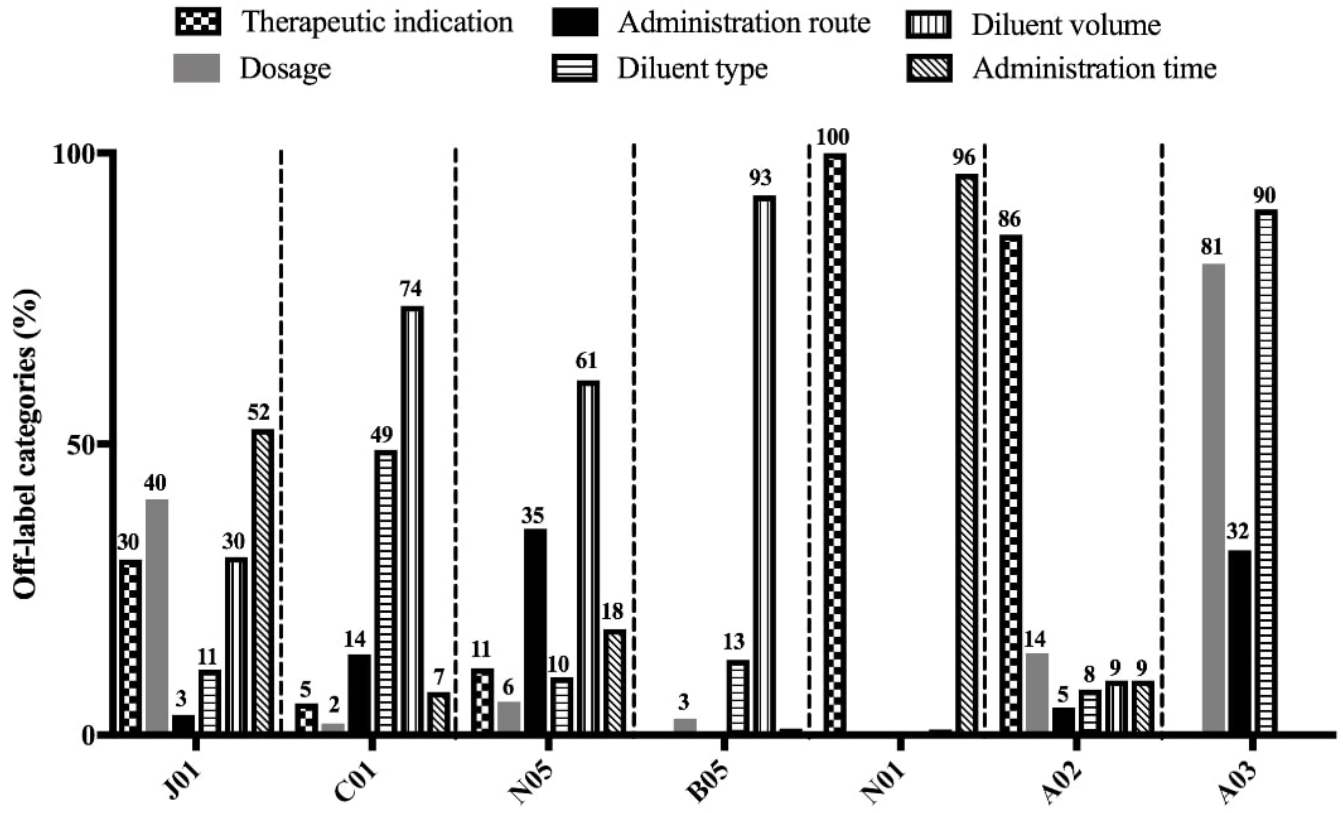

FIGURE 3 - Prevalence of off-label drug use categories by therapeutic class according to the ATC classification.

The proportion was calculated from a total of 1,606 prescribed off-label drugs. Dosage category was assessed only for licensed drugs which were prescribed for label use, that is, according to their therapeutic indication. J01 - Antiinfectives for systemic use; C01 - Cardiac therapy; N05 - Psycholeptics; B05 - Blood substitutes and perfusion solutions; N01 - Anesthetics; A02 - Drugs for acid related disorders; A03 - Drugs for functional gastrointestinal disorders.

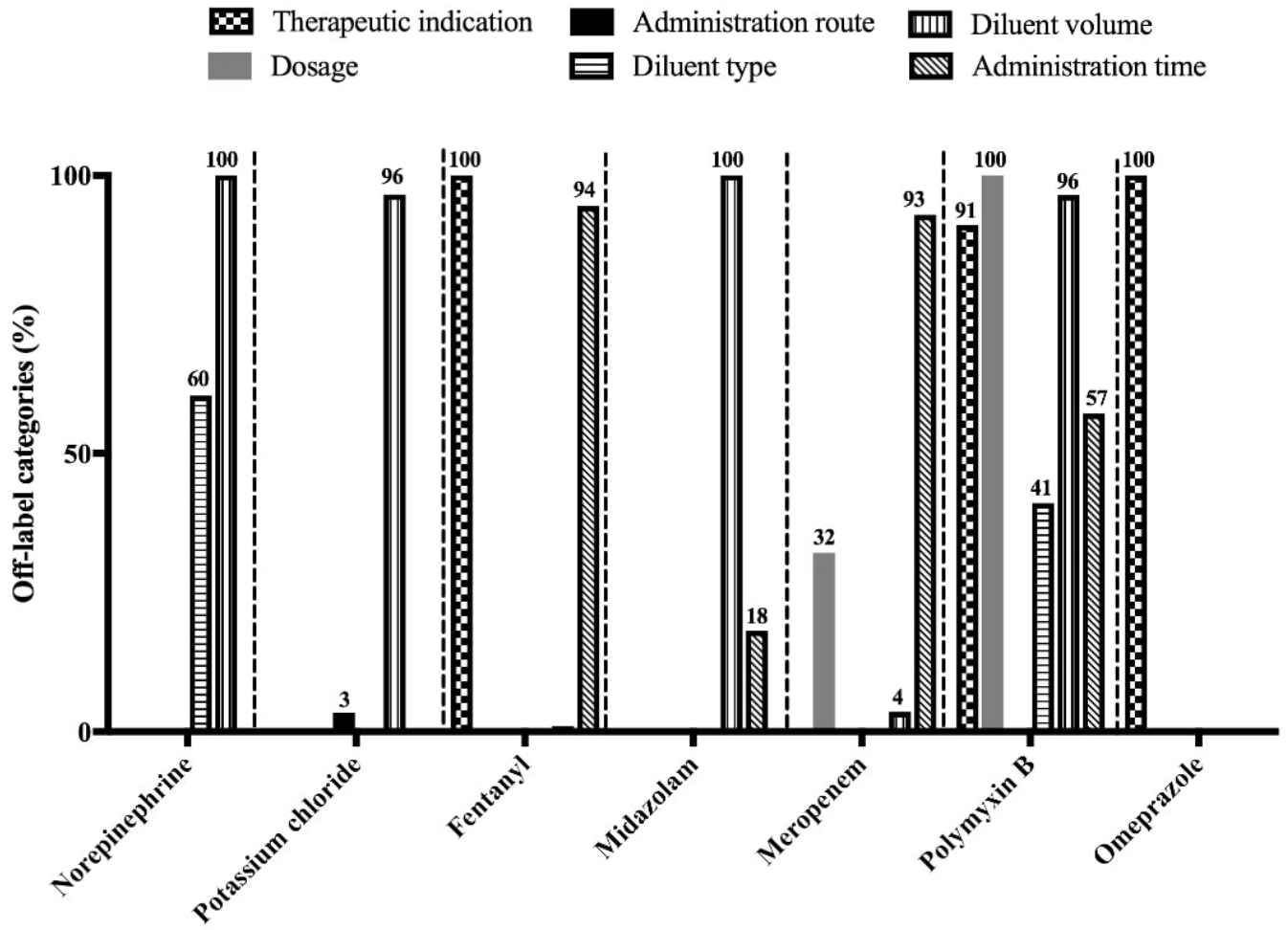

FIGURE 4 - Most prescribed drugs for off-label use and their respective category rates.

For each drug, the proportions of off-label categories were calculated from the total times the drug was prescribed. Dosage category was assessed only for licensed drugs which were prescribed for label use. Total number of times each drug was prescribed: Norepinephrine: 149; Potassium chloride: 116; Fentanyl: 112; Midazolam: 94; Meropenem: 56; Polymyxin B: 56; Omeprazole: 55.

DISCUSSION

To our knowledge, this is the first study to evaluate off-label drug use in severely ill adult patients in Brazil, as previous studies have focused on pediatric and neonatal populations at either primary or hospital care levels (Gonçalves et al., 2016; Souza *et al.,* 2016; Loureiro *et al.,* 2013).

This study reinforces the high prevalence of off-label drug use in critically ill adult patients. All included subjects received at least one off-label drug, which corroborates findings from a study performed on critically ill adult patients in American hospitals (Lat *et al.*, 2011). Another study conducted by intensive care practitioners from China indicated that poor medical prognosis, reports of new therapeutic regimens with strong scientific evidence, and limited indications in package inserts are major reasons for off-label drug use in ICUs (Lin *et al*., 2018), which were also observed in the current study.

Our data showed that 70.31% of the drugs were prescribed for off-label use, while other studies reported rates of 36% and 48% (Smithburger *et al.,* 2015; Lat *et al.,* 2011). Such discrepancies can be attributed to the

variations in the off-label categories assessed. The type and volume of diluent and the duration of administration for intravenous drugs were the off-label categories assessed in the present study, which were not assessed in the aforementioned studies. This could explain the lower prevalence rates of off-label drug use in those studies when compared with our data. Of note, the assessment of the off-label categories in the current study are critically important because they closely influence the effectiveness and safety of drug therapy (Ministério da Saúde, 2014).

In the current study, prescriptions of PIM were associated with the increased label use of drugs. Although the magnitude of this association was low, this finding suggests a higher concordance with the package inserts when using PIM in comparison with other medicines, which helps to prevent off-label drug use. PIM have an increased risk of causing severe medical consequences to patients if used incorrectly (Cajanding, 2017). Therefore, these drugs are potentially subjected to greater institutional surveillance, and their use in unregulated conditions (off-label) tends to be less frequent in clinical practice.

With regards to the clinical scores analyzed in the study (APACHE II and SOFA), there were no associations between the scores and off-label drug use, which is in contrast with the findings of Lat *et al.* (2011). Our data indicates that overall off-label prescribing in the study population was similarly distributed between clinically severe and non-severe patients. Further research is necessary to elucidate the clinical impact of off-label drug use in the study population.

We also analyzed the moment at which drugs were prescribed for off-label use. More than half of the prescriptions (71.83%) originated from the unit that originally admitted the patient. This indicated that off-label drug use was not only restricted to the ICU, but rather a common practice in the wards of the study hospital. In contrast, Barletta *et al.* (2015) found that only 12% of off-label drug use was initiated before ICU admission. However, the authors only evaluated drugs with gastrointestinal action with regard to the therapeutic indication category. Thus, it is difficult to compare these data, as our study was more comprehensive with regard to the therapeutic classes assessed.

Among the drugs with off-label use status in this study, the proportion of off-label due to therapeutic indication not described in package inserts was 19.58%. Other studies from ICUs of American hospitals found higher rates of 36.2% and 81.6% (Smithburger *et al.,* 2015; Lat *et al.,* 2011). This can be explained by the differences in the therapeutic arsenal and clinical protocols available to each institution, as well as the numbers and profiles of patients in each study. Moreover, the absence of off-label category preparation and duration of drug administration in the current studies may also help to explain the lower incidence of off-label uses due to therapeutic indication.

This study reports high rates of off-label drug use due to a different route of administration from that recommended in the package insert. This was mostly attributed to the use of enteral tubes. The use of this route is expected in ICU settings given that the patients usually cannot use the oral route due to their critical clinical status and common instability (Matysiak-Luśnia, Łysenko, 2014). On the other hand, pharmaceutical industries commonly do not provide guidance for the use of drugs via enteral tubes in package inserts. Thus, the administration of most drugs via enteral tubes is often classified as off-label. This finding helps to explain the high prevalence of off-label drug use in critically ill adult patients, indicating that the use of enteral tubes is an important contributing factor.

The most prescribed therapeutic class in the off-label use of drugs was systemic antimicrobials (14.44%), which corroborates studies performed in ICUs of American hospitals (17%) (Shoulders *et al.,* 2017). Lat et al. (2011) indicated that the low number of drugs approved by the FDA for treatment of sepsis is a major reason for the off-label use of antimicrobial drugs. Sepsis is a fatal inflammatory response that occurs in 10% of patients admitted to the ICU (Dummitt *et al*., 2018; Mayr *et al*., 2014). Consequently, increased rates of off-label use in ICUs due to therapeutic indications may occur in patients with sepsis. Moreover, antimicrobials are often prescribed for off-label use because of increased antimicrobial resistance (Tansarli *et al.,* 2012; Dhaese *et al*., 2018). In the current study, the most commonly prescribed antimicrobials for off-label use were meropenem and polymyxin B, both with

a broad spectrum of activity and considered as reserve antimicrobials in the study institution.

Most of the meropenem prescriptions were indicated for off-label use because the infusion period differed from that recommended in the package insert. The literature reports an optimization of pharmacodynamic profiles and increased cure rates in patients who received meropenem as an extended infusion instead of a rapid injection or slow infusion, as per the package insert (Falagas *et al*., 2013). Polymyxin B use was classified as off-label in all categories, especially due to therapeutic indication, dosage, and volume of the diluent. This drug is indicated for urinary tract, meningeal, and blood infections, as per the package insert, with recommended dose adjustment for renal function. However, several studies have recommended the use of high doses of polymyxin B in severe infections from other topographies, without dose adjustment for renal function (Rigatto *et al*., 2016; Yapa *et al.,* 2014; Sandri *et al.,* 2013). Therefore, the current study indicates that updates to the package inserts of these systemic antibiotics are necessary.

The high prevalence in prescribing drugs for cardiac therapy was attributed to norepinephrine, specifically due to the type and volume of the diluents used when administering the drug. The stability of concentrated norepinephrine preparations in saline and glucose solutions is well documented in literature, as there is a great interest in developing strategies to reduce excess fluid infusion in critically ill patients (Closset *et al.,* 2017; Walker *et al.,* 2010). Fluid overload is associated with increased morbidity and mortality, and a possible way to prevent this is to use more concentrated solutions, which are considered off-label (Ogbu et al., 2015; Besen *et al*., 2015). Therefore, the need for an update to the package insert of this drug is evident.

The high frequency of off-label drug use may prevent pharmaceutical companies from conducting well-designed clinical trials thus hindering the necessary updates to package inserts of drugs (Lat *et al.,* 2011). In addition, the lack of regulatory guidelines regarding off-label drug use worsens the situation (Shoulders *et al.,* 2017*;* Eguale *et al*., 2016; Lat *et al*., 2011; Wittich, Burkle, Lanier, 2012). In this context, our findings help to better understand off-label drug use in ICUs, potentially helping to increase prescriber awareness about the importance of this practice, which should be based on strong scientific evidence.

There are concerns regarding the safety associated with off-label drug use due to the increased occurrences of adverse reactions associated with such practices, especially in ICU settings. A recent prospective and multicenter study conducted in critically ill adult patients from the US reported that adverse events were not more frequent in patients taking off-label medication, although these patients were at increased risk for adverse events with each addition of an off-label drug. The authors pointed out the need for physicians to be aware of the association between off-label drug use and adverse reactions, especially in cases of insufficient scientific evidence (Smithburger *et al*., 2015). Limited medical knowledge on therapeutic indications approved by regulatory agencies is a contributing factor for off-label drug use (Lat *et al.,* 2011).

Our study provides useful knowledge regarding off-label drug use in critically ill patients. However, this study had some limitations. Firstly, these findings cannot be generalized to community or rural hospitals, institutions without the daily presence of a pharmacist in the ICU, and non-adult ICU populations. In addition, this was a unicentric study performed in a short period of time that focused only on the extension of off-label drug use in critically ill patients, rather than on the evaluation of benefits and adverse effects associated with off-label drug use. However, we were able to rigorously evaluate and classify off-label drug use according to several categories, including the type of preparation and duration of drug administration, which are usually not included in other studies. Furthermore, we provided data on off-label drug use in critically ill adult patients, which has never been described in Brazil. Future research should explore these issues in other health centers.

CONCLUSIONS

Our study provided a broad characterization of off-label drug use in an adult ICU, showing high rates of this practice. The major findings were that there was

no association between off-label drug use and clinical severity scores, while off-label drug use had an inverse correlation with the use of PIM. The therapeutic indication and volume of the diluent, including frequent use of enteral probes for drug administration were major reasons for off-label drug use. Moreover, systemic antibiotics and norepinephrine were found to be the most prescribed therapeutic class and drug for off-label use, respectively. Therefore, health professionals must carefully evaluate the benefits and risks associated with off-label drug use and request for periodic updates of package inserts from pharmaceutical companies.

ACKNOWLEDGEMENTS

The authors acknowledge the contribution of the physicians and pharmacists at the Walter Cantídio University Hospital who participated in this project.

FUNDING

No funding was received for the study.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

REFERENCES

Aronson JK, Ferner RE. Unlicensed and off-label uses of medicines: definitions and clarification of terminology. Br J Clin Pharmacol. 2017;83(12):2615–25.

Barletta JF, Lat I, Micek ST, Cohen H, Olsen KM, Haas CE. Off-label use of gastrointestinal medications in the intensive care unit. J Intensive Care Med. 2015;30(4):217-25.

Besen BA, Gobatto AL, Melro LM, Maciel AT, Park M. Fluid an electrolyte overload in critically ill patients: an overview. World J Crit Care Med. 2015;4(2):116-29.

Cajanding JMR. Administering and monitoring high-alert medications in acute care. Nurs Stand. 2017;31(47):42–52.

Carvalho CG, Ribeiro MR, Bonilha MM, Jr. MF, Procianoy RS, Silveira RC. Use of off-label and unlicensed drugs in the neonatal intensive care unit and its association with severity scores. J Pediatr. 2012;88(6):465–70.

Casañ VA, Escribano BC, Garrido-Corro B, De la Cruz Murie P, Blázquez Álvarez MJ, De la Rubia Nieto MªA. Off-label and unlicensed drug use in a Spanish Neonatal Intensive Care Unit. Farm Hosp. 2017;41(3):371–81.

Closset M, Hecq JD, Soumoy L, Simar J, Gonzalez E, Charlet L, et al. Physical stability of highly concentrated injectable drugs solutions used in intensive care units. Ann Pharm Fr. 2017;75(3):185–8.

Dhaese SAM, Farkas A, Colin P, Lipman J, Stove V, Verstraete AG, et al. Population pharmacokinetics and evaluation of the predictive performance of pharmacokinetic models in critically ill patients receiving continuous infusion meropenem: a comparison of eight pharmacokinetic models. J Antimicrob Chemother. 2018;74(2):432-41.

Dummitt B, Zeringue A, Palagiri A, Veremakis C, Burch B, Yount B. Using survival analysis to predict septic shock onset in ICU patients. J Crit Care. 2018;48:339–44.

Eguale T, Buckeridge DL, Verma A, Winslade NE, Benedetti A, Hanley JA, et al. Association of off-label drug use and adverse drug events in an adult population. JAMA Intern Med. 2016;176(1)55–63.

European Medicines Agency. Evidence of harm from off-label or unlicensed medicines in children. 2004. http://www.ema.europa.eu/docs/en_GB/…/Other /…/WC500 00402 1.pdf. Accessed 14 March 2018.

Falagas ME, Tansarli GS, Ikawa K, Vardakas KZ. Clinical outcomes with extended or continuous versus short-term intravenous infusion of carbapenems and piperacillin/tazobactam: A systematic review and meta-analysis. Clin Infect Dis. 2013;56:272-82.

Ferreira AL, Ibiapina CC, Machado MGP, Fagundes EDT. A alta prevalência de prescrições de medicamentos off-label e não licenciados em unidade de terapia intensiva pediátrica brasileira. Rev Assoc Med Bras. 2012;58(1):82-7.

Gonçalves AC de S, Reis AMM, Marçal ACG, Bouzada MCF. Use of unlicensed and off-label drugs in neonates in a Brazilian university hospital. Braz J Pharm Sci. 2018;53(3):1–10.

Gonçalves MG, Heineck I. Frequency of prescriptions of off-label drugs and drugs not approved for pediatric use in primary health care in a southern municipality of Brazil. Rev Paul Pediatr. 2016;34(1):11–17.

Instituto para Práticas Seguras no Uso de Medicamentos. Medicamentos Potencialmente Perigosos de Uso Hospitalar e Ambulatorial - Listas Atualizadas 2015. Boletim ISMP Brasil. 2015;4(3). Disponível em: <http://www.ismp-brasil.org/site/wp-content/uploads/2015/12/V4N3.pdf>. Accessed 12 Out 2018.

Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med. 1995;13(10):818-29.

Lat I, Micek S, Janzen J, Cohen H, Olsen K, Haas C. Off-label medication use in adult critical care patients. J Crit Care. 2011;26(1):89–94.

Lin Liu, Hong-Yu Yang, Yan Lou, Jing Miao, Xiao-Yang Lu, Qing-Wei Zhao, et al. Off-label prescriptions in intensive care unit: the Chinese experience. Ther Clin Risk Manag. 2018;14:195–202.

Loureiro CV, Loureiro CV, Néri EDR, Mascarenhas MBJ, Fonteles MMF. Uso de medicamentos *off-label* ou não licenciado para pediatria em hospital público brasileiro. Rev Bras Farm Hosp Serv Saude. 2013;4(1):17–21.

Matysiak-Luśnia K, Łysenko L. Drug administration via enteral feeding tubes in intensive therapy – terra incognita? Anaesth Intens Care. 2014;46(4)307–11.

Mayr FB, Yende S, Angus DC. Epidemiology of severe sepsis. Virulence. 2014;5(1):1-11.

Ministério da Saúde (BR), Fundação Oswaldo Cruz, Agência Nacional de Vigilância Sanitária. Documento de referência para o Programa Nacional de Segurança do Paciente. Brasília (DF): Ministério da Saúde; 2014.

Ogbu OC, Murphy DJ, Martin GS. How to avoid fluid overlaod. Curr Opin Crit Care. 2015;21(4):315-21.

Patel P, Cerqueira DM, Santos GML, de Lima Soares R, Sousa VD, Liberti L, et al. A Baseline Analysis of Regulatory Review Timelines for ANVISA: 2013-2016. Ther Innov Regul Sci. 2020;54(6):1428-35.

Rigatto MH, Falci DR, Lopes NT, Zavascki AP. Clinical features and mortality of patients on renal replacement therapy receiving polymyxin B. Int J Antimicrob Agents. 2016;47(2):146–50.

Sandri AM, Landersdorfer CB, Jacob J, Boniatti MM, Dalarosa MG, Falci DR, et al. Population pharmacokinetics of intravenous Polymyxin B in critically Ill patients: implications for selection of dosage regimens. Clin Infect Dis. 2013;57(4):524-31.

Shoulders BR, Smithburger PL, Tchen S, Buckley M, Lat I, Kane-Gill SL. Characterization of Guideline Evidence for Off-label Medication Use in the Intensive Care Unit Ann Pharmacother. 2017;51(7):529–42.

Smithburger PL, Buckley MS, Culver MA, Sokol S, Lat I, Handler SM, et al. A multicenter evaluation of off-label medication use and associated adverse drug reactions in adult medical ICUs. Crit Care Med. 2015;43(8):1612–21.

Souza AS, Dos Santos DB, Rey LC, Medeiros MG, Vieira MG, Coelho HLL. Off-label use and harmful potential of drugs in a NICU in Brazil: A descriptive study. BMC Pediatrics. 2016;16(1):1–10.

Tansarli GS, Rafailidis PI, Kapaskelis A, Falagas ME. Frequency of the off-label use of antibiotics in clinical practice: a systematic review. Expert Rev Anti Infect Ther. 2012;10(12):1383-92.

Vincent JL, Moreno R, Takala J, Willatts S, De Mendonça A, Bruining H, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. Intensive Care Med. 1996;22(7):707-10.

Walker SE, Law S, Garland J, Fung E, Iazzetta J. Stability of Norepinephrine Solutions in Normal Saline and 5% Dextrose in Water. Can J Hosp Pharm. 2010;63(2):113–18.

Wittich CM, Burkle CM, Lanier WL. Ten common questions (and their answers) about off-label drug use. Mayo Clin Proc. 2012;87(10):982–90.

World Health Organization (WHO). The anatomical therapeutic chemical classification system with defined daily doses (ATC/DDD). Norway: WHO. 2006. https://www.whocc.no/atc_ddd_index/. Accessed 01 Jan 2018.

Yapa WS, Li J, Patel K, Wilson JW, Dooley MJ, George J, et al. Pulmonary and systemic pharmacokinetics of inhaled and intravenous colistin methanesulfonate in cystic fibrosis patients: targeting advantage of inhalational administration. Antimicrob Agents Chemother. 2014;58(5):2570–79.

Zheng Z, Yang M, Wu J. Ethical Off-label Drug use: Need for a Rethink? Indian Pediatr. 2017;54(6):447-50.

Received for publication on 01st April 2020
Accepted for publication on 03rd January 2021