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Clinical Investigation

Patterns of Off-Label Prescribing in the Pediatric Intensive Care Unit and Prioritizing Future Research

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OBJECTIVES: To characterize off-label prescribing among US pediatric intensive care units (PICUs), determine characteristics associated with off-label use, and identify medications in highest need for additional study.
METHODS: Medications prescribed for ≥1% PICU patients (age < 18 years) in 2010 were identified from 39 children's hospitals. Use in a patient younger than the Food and Drug Administration (FDA)-approved age for any indication was considered off-label. Hierarchical multivariable modeling was used to identify characteristics associated with off-label use, accounting for center effects. Highest-impact drugs were defined by: 1) high off-label use (off-label use in at least 5% of the PICU cohort), 2) high risk medication, and 3) high priority status by the FDA or Best Pharmaceuticals for Children Act (BPCA).
RESULTS: A total of 66,896 patients received ≥1 medication of interest (n = 162) during their PICU stay. A median of 3 (interquartile range, 2-6) unique drugs per patient were used off-label. Those who received ≥1 drug off-label (85% of the cohort) had longer median PICU (2 days vs 1 day) and hospital (6 days vs 3 days) lengths of stay and higher mortality (3.6% vs 0.7%), p < 0.001. Factors independently associated with off-label drug use included: age 1 to 5 years, chronic conditions, acute organ failures, mechanical ventilation, arterial or venous catheters, dialysis, and blood products. Half of prescribed medications (n = 84) had been used off-label: 26 with significant off-label use, 30 high-risk medications, and 47 with high FDA/BPCA priority. The highest impact medications identified were: dexmedetomidine, dopamine, hydromorphone, ketamine, lorazepam, methadone, milrinone, and oxycodone.
CONCLUSIONS: Most PICU patients are exposed to off-label medication use, with uncertain evidence. Future medication research in this population should focus on medications with high impact potential.

INDEX TERMS: off label use, pediatric intensive care units, pharmacoepidemiology, research priorities, risk factors

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INTRODUCTION

Prior to market release in the United States, prescribed medications must go through a rigorous approval process with the Food and Drug Administration (FDA). This approval process generally includes demonstration of safety and efficacy supported by randomized controlled trials. Such trials, however, are challenging in the pediatric population for a number of reasons including: small sample sizes, low financial incentive, and ethical concerns.[1,2] As a result, a majority of available medications do not have an FDA-approved pediatric indication leading to the widespread and well-recognized practice of off-label prescribing in pediatrics.[3–6]

Pharmacotherapy is an essential part of caring for the critically ill child, whether targeting disease treatment or providing supportive care. In fact, a patient admitted to the pediatric intensive care unit (PICU) may be exposed to a median of 14 different medications (interquartile range [IQR], 9-19) during their PICU admission, and the total number increases with severity of illness and degree of organ failure.[7] With the large number of medications administered to

any single patient, the likelihood of receiving a medication off-label is significant. This is supported by prior single-center studies on off-label medication use in the PICU.[8–13] However, there has been limited data on national off-label prescribing patterns in the PICU and identification of children at highest risk of exposure to medications off-label.

Therefore, we conducted this study to determine the degree of off-label prescribing among US pediatric centers and determine patient characteristics associated with high risk of off-label use. Furthermore, because of the significant number of medications utilized in the PICU, we identified the medications that might have the greatest impact with additional study based on frequency of off-label use, high risk profile, and prioritization by national agencies.

MATERIALS AND METHODS

The Colorado Multiple Institution Review Board determined this study was not human subject research.

Data Source

Data for this study were obtained from the Pediatric Health Information System (PHIS), an administrative database that contains inpatient, emergency department, ambulatory surgery, and observation data from 43 not-for-profit, tertiary care pediatric hospitals in the United States. These hospitals are affiliated with the Children's Hospital Association (Overland Park, KS) and were a mix of stand-alone children's hospitals and hospital-within-a-hospital structures. Data quality and reliability are assured through a joint effort between the Children's Hospital Association and participating hospitals. The data warehouse function for the PHIS database is managed by Truven Health Analytics (Ann Arbor, MI). For the purposes of external benchmarking, participating hospitals provide discharge/encounter data including demographics, diagnoses, and procedures. Certain hospitals also submit resource utilization data (e.g. pharmaceuticals, imaging, and laboratory) into the PHIS database. Data are deidentified at the time of data submission, and data are subjected to a number of reliability and validity checks before being included in the database. For this study, 39 hospitals contributed data.

Study Population and Off-Label Medication Status

Subjects were included in the study if they were: 1) less than 18 years of age at hospital discharge, 2) had at least 1 day in a non-neonatal intensive care unit during the year 2010, and 3) had pharmacy charges submitted by their hospital during the study year. Demographic information (age, sex, and race), discharge diagnoses, procedures performed, and outcomes were obtained for each subject meeting inclusion criteria. Complex chronic conditions (CCCs) and acute organ dysfunction were identified by International Classification of Diseases, Ninth Revision (ICD-9) codes and were categorized based on previously developed algorithms.[14–17]

All unique pharmacy charges with a date occurring within the subjects' intensive care unit (ICU) stay were obtained. We excluded intravenous fluids, electrolyte replacements, topical medications, vitamins, vaccines, and inhaled anesthetics. Because the regulatory process differs for over-the-counter medications as compared to prescribed medications, over-the-counter medications were further excluded from the analysis. High use medications (defined as prescribed in at least 1% of the PICU cohort) were then identified and analyzed for off-label use, defined as use in a subject younger than the FDA-approved age for any indication.[18]

Schema for Prioritization

Medications of interest, as identified above, were first categorized by: 1) frequency of off-label use, 2) high-risk status, and/or 3) high priority status by the FDA or the Best Pharmaceuticals for Children Act (BPCA). High off-label use was defined as off-label use in at least 5% of the PICU cohort. If a medication was identified by the Institute for Safe Medication Practices (ISMP) as a "high alert" medication, it was categorized as high risk in our study.[19] ISMP defines their "high alert" medications as those that "bear a heighted risk of causing significant patient harm when used in error," irrespective of the frequency of actual medication error. FDA or BPCA high-priority status was determined by either: 1) a written request to the manufacturer by the FDA for pediatric studies, or 2) presence on the BCPA therapeutic priority list.[20] Presence on either list was taken as a proxy for lack of pediatric data for a particular medication.

Medications under more than 1 category (fre-

quency of off-label use, high risk, or high priority) were then identified, and those drugs present in all 3 categories were considered to be of potentially highest impact with future research efforts.

Statistical Analyses

The ICU cohort and patterns of off-label use were characterized using descriptive statistics. Subject outcomes (ICU and hospital lengths of stay, death) were compared using Wilcoxon rank sum testing (for the non-normally distributed lengths of stay) and chi-squared analysis. Logistic regression was used to measure the associations between patient characteristics and the receipt of at least 1 medication off-label. Variables with an alpha ≤ 0.05 on bivariate analysis were candidate variables for the multivariable model. Candidate variables with potential for significant collinearity were assessed using Pearson's correlation coefficient. To account for potential center effects, all regression analyses were performed using mixed modeling with PROC GLIMMIX.[21] Risk estimates were presented as odds ratios with 95% confidence intervals (CIs). All analyses were performed using STATA 9.2 (Stata Corp, College Station, TX) or SAS 9.3 (SAS Institute, Cary, NC).

RESULTS

Cohort Characteristics and Outcomes

In 2010, among the 39 centers, 66,896 subjects met inclusion criteria and received at least 1 of the frequently prescribed medications (n = 163 unique drugs) during their ICU stay. Among the cohort, 56,968 (85%) had received at least 1 of these medications off-label. The average number of off-label medications a patient was exposed to was 4.5 (median, 3; IQR, 2-6). The average age of the cohort was 5.4 ± 5.7 years with a slight male predominance (55%). The most common identified races were white (64%) and black (17%). Over half had at least 1 CCC present during their hospitalization. The average PICU and hospital lengths of stay were 6 days (median, 2; IQR, 1-5) and 12 days (median, 5; IQR, 3-12). The overall hospital mortality rate for the entire ICU cohort was 3%.

Risk Factors for Receiving Off-Label Medications

In the unadjusted analysis, many characteristics were significantly associated with an increased risk of receiving a medication off-label (Table 1). Children age 5 years and younger were more likely to receive a drug off-label as were patients from the Asian/Pacific Islander race. Additionally, children who had received a medication off-label were more likely to have at least 1 CCC as compared to those who had not received any medications off-label. They were also more likely to have at least 1 organ failure and require critical care interventions. Similarly, children who had been exposed to at least 1 medication off-label had longer median PICU and hospital lengths of stay (2 days vs 1 day, and 6 days vs 3 days, respectively, $p < 0.001$) and more frequent deaths (3.6% vs 0.7%, $p < 0.001$).

Through multivariable modeling, many of the same characteristics were identified as independently associated with the receipt of at least 1 medication off-label (Table 1). The highest risk age group was 1 to 5 years, while race and gender were not associated with a difference in risk. All of the CCC except metabolic remained significantly associated with an increased risk estimate. The CCCs with the strongest associations were in the categories of oncologic, cardiovascular, neuromuscular, and congenital or genetic syndromes. Children with respiratory, cardiovascular, or renal failure were at increased risk, while those with neurological failure had a slightly decreased risk. Requirement for mechanical ventilation, venous or arterial catheterization, and dialysis and blood products were all independently associated with an increased risk of receiving an off-label medication.

Medications Prescribed, Off-Label Status, and Prioritization

For the entire cohort, 163 individual drugs met inclusion criteria and were considered "high use" medication in the ICU population. Most of these drugs came from the therapeutic categories of neurological (24%), antimicrobial (22%), and cardiovascular (18%). Of these medications, 84 (52%) had been prescribed off-label in at least 1 subject (Table 2). Approximately half (46/84) of the medications prescribed off-label did not have any FDA-approved pediatric indications, with the remainder having at least 1 FDA-approved indication for *some* less than 18 years of age. The largest number of unique drugs that had been prescribed off-label came from the cardiovascular (20/84, 24%) and neurological (22/84, 26%) therapeutic categories.

Table 1. Patient Characteristics Associated With Receiving at Least 1 Medication Off-Label

Patient Characteristic	Unadjusted Odds Ratio (95% CI)	Adjusted Odds Ratio† (95% CI)
Age at admission		
<1 yr	Reference*	Reference
1-5 yr	0.99 (0.93-1.06)	1.49 (1.36-1.62)
6-12 yr	0.64 (0.60-0.68)	1.07 (0.99-1.16)
13-17 yr	0.69 (0.65-0.73)	1.08 (1.00-1.16)
Sex		
Male	Reference	Reference
Female	1.03 (0.98-1.07)	1.04 (0.99-1.10)
Race		
White	Reference*	Reference
Black	0.95 (0.88-1.01)	1.05 (0.97-1.13)
Asian/Pacific Islander	1.21 (1.02-1.44)	1.16 (0.97-1.39)
Native American	1.05 (0.76-1.45)	1.03 (0.74-1.45)
Other	1.06 (0.98-1.15)	1.00 (0.92-1.08)
Missing		
Complex chronic conditions		
Cardiovascular	3.64 (3.41-3.90)*	2.94 (2.70-3.20)*
Respiratory	2.63 (2.33-2.97)*	1.99 (1.72-2.30)*
Neuromuscular	1.77 (1.63-1.92)*	2.08 (1.89-2.30)*
Gastrointestinal	3.23 (2.56-4.09)*	2.03 (1.53-2.69)*
Hematologic or immunologic	2.62 (2.12-3.24)*	1.49 (1.14-1.95)*
Oncologic	2.29 (2.05-2.57)*	2.78 (2.42-3.20)*
Metabolic	1.48 (1.31-1.66)*	0.95 (0.82-1.11)
Renal	2.84 (2.26-3.56)*	1.54 (1.16-2.03)*
Other congenital or genetic defect	2.54 (2.31-2.80)*	2.32 (2.07-2.62)*
Organ failure diagnoses		
Respiratory	3.81 (3.53-4.12)*	1.95 (1.76-2.16)*
Cardiovascular	3.32 (2.97-3.70)*	1.44 (1.25-1.66)*
Neurologic	1.02 (0.93-1.12)	0.86 (0.76-0.97)*
Hematologic	3.45 (2.98-4.01)*	0.94 (0.78-1.14)
Hepatic	2.92 (1.81-4.70)*	0.68 (0.36-1.26)
Renal	4.33 (3.49-5.37)*	1.38 (1.06-1.80)*
Procedures		
Mechanical ventilation	4.05 (3.77-4.35)*	1.79 (1.63-1.97)*
Non-invasive ventilation	1.67 (1.49-1.88)*	1.12 (0.92-1.37)
Venous catheterization	7.29 (6.57-8.08)*	3.79 (3.34-4.92)*
Arterial catheterization	6.81 (5.76-8.06)*	1.74 (1.41-2.15)*
CPR	5.14 (3.43-7.67)*	0.71 (0.45-1.11)
ICP monitoring	2.57 (1.77-3.73)*	1.35 (0.88-2.07)
Dialysis	12.71 (7.49-21.57)*	5.89 (3.27-10.61)*
Received blood products	7.33 (6.60-8.14)*	3.58 (3.16-4.06)*

CI, confidence interval; CPR, cardiopulmonary resuscitation; ICP, intracranial pressure

* $p < 0.05$

† Multivariate analysis adjusted for other variables

Table 2. Most Frequently Prescribed Medications During PICU Stay (Received by at Least 1% of Patients) With Off-Label Use

	Percent of All Subjects Who Received Medication (n = 66,896)	Percent of Subjects Who Received Medication Off-Label
Antimicrobials		
Azithromycin	7	92
Metronidazole	5	100
Ampicillin/sulbactam	4	23
Ciprofloxacin	3	15
Amphotericin B	1	100
Ganciclovir	1	100
Levofloxacin	1	100
Oseltamivir	1	25
Voriconazole	1	
Respiratory		
Albuterol	29	44
Ipratropium	9	86
Levalbuterol	6	64
Dornase alpha	4	61
Salmeterol/fluticasone	1	9
Terbutaline	1	84
Cardiovascular		
Dopamine	18	100
Milrinone	15	100
Clonidine	6	100
Norepinephrine	4	100
Amlodipine	3	43
Captopril	3	100
Hydralazine	3	100
Nicardipine	3	100
Nitroglycerin	3	100
Sildenafil	3	100
Amiodarone	2	100
Dobutamine	2	100
Ephedrine	2	100
Esmolol	2	100
Labetalol	2	100
Nifedipine	2	100
Propranolol	2	100
Atenolol	1	100
Isoproterenol	1	100
Lisinopril	1	28
Neurologic		
Fentanyl	53	44
Lorazepam	26	100
Dexmedetomidine	15	100
Ketamine	12	94
Oxycodone	12	100
Levetiracetam	10	94

PICU, pediatric intensive care unit

Table 2. Most Frequently Prescribed Medications During PICU Stay (Received by at Least 1% of Patients) With Off-Label Use (*cont.*)

	Percent of All Subjects Who Received Medication (n = 66,896)	Percent of Subjects Who Received Medication Off-Label
Bupivacaine	9	77
Hydromorphone	9	100
Methadone	6	100
Fosphenytoin	5	100
Etomidate	4	70
Baclofen	3	69
Caffeine	2	96
Gabapentin	2	13
Meperidine	2	100
Oxcarbazepine	2	15
Topiramate	2	22
Valproic acid	2	7
Lamotrigine	1	2
Ropivacaine	1	100
Gastrointestinal		
Ondansetron	38	29
Glycopyrrolate	19	93
Pantoprazole	10	50
Sucralfate	2	100
Ursodiol	2	100
Lactulose	1	100
Hematological		
Protamine	10	100
Aminocaproic acid	6	100
Enoxaparin	4	100
Warfarin	1	100
Endocrine		
Insulin aspart	2	5
Insulin glargine	2	16
Insulin lispro	2	100
Renal		
Mannitol	13	84
Chlorothiazide	8	100
Spironolactone	6	100
Acetazolamide	4	89
Bumetanide	3	100
Metolazone	2	100
Oxybutynin	1	27
Other		
Neostigmine	12	100
Budesonide	9	24
Fluticasone	7	38
Beclomethasone	2	64
Promethazine	2	1
Mometasone	1	36
Sodium polystyrene sulfonate	1	100

PICU, pediatric intensive care unit

Prioritization by Frequency, Risk, and the FDA/BPCA

Seventy of the 84 medications (83%) that had been used at least once in an off-label manner met at least 1 category of prioritization (significant off-label use, high risk category, or high prioritization by the FDA or the BPCA; Table 3). Twenty-six of the 162 medications of interest had been used off-label in at least 5% of the PICU cohort, with half having been used in at least 10% of the cohort. Eleven medications (42%) were of the neurological category. Thirty medications were considered as high-risk medication by ISMP, most of which are within the cardiovascular (12/30, 40%) or neurological categories (11/30, 37%). Forty-seven medications had already been identified by the FDA and/or BPCA as a high priority drug for pediatric research with cardiovascular and neurologic medications as the most commonly identified.

Twenty-six off-label medications had overlap in at least 2 categories, with only 8 meeting the criteria of significant frequency, high risk, and FDA/BPCA priority status. These medications were dexmedetomidine, dopamine, hydromorphone, ketamine, lorazepam, methadone, milrinone, and oxycodone. All but 1 (methadone) had been used in at least ~10% of the ICU cohort. All of the highest priority drugs were cardiovascular or neurological medications, and none other than ketamine (approved for ages 16 years and above) had FDA approval for use in patients younger than 18 years for any indication at the time of our analysis.

DISCUSSION

In this multicenter evaluation of off-label medication use, we found that a majority of patients received at least 1 medication in an off-label manner during their PICU admission. These patients were more likely to be young, have existing chronic complex conditions, more frequent organ failures, and require more intensive support. They were also more likely to have longer lengths of stay and higher mortality. Of the most frequently prescribed medications, over half had been used in an age group younger than that approved by the FDA for any indication. Based on frequent off-label use, high-risk status, and national prioritization, most of these off-label medications met at least 1 criterion for high prioritization with almost half meeting more than 1. Eight drugs met all 3 criteria, all of which were in cardiovascular or neurological therapeutic categories.

Our findings of high off-label medication exposure in the PICU population are consistent with prior single-center studies.[8,9,11,12] There are certainly benefits to off-label use of medications.[22] Off-label use has allowed access to potentially therapeutic benefits not otherwise available to pediatric patients. Additionally, using medications for other non-approved indications has led to innovative new therapies for certain pediatric diseases.[23] Yet, using a medication off-label may mean prescribing with limited information about drug dosing, effectiveness, and side effects, although this is not always the case. In the field of pediatrics, medication dosing is often extrapolated from adult studies. This strategy, however, may not be appropriate for the developing child with varying ability for drug metabolism and elimination.[1,24] This can be further complicated by the disturbed physiology of the critically ill child, often with multiorgan failure, who was at greatest risk of receiving an off-label medication in our study. These differences can then result in under or overdosing of a medication and the associated risk of therapeutic failures or adverse events.

Not surprisingly, the medications used off-label with greatest frequency were from the cardiovascular or neurological therapeutic categories. Aside from antimicrobials, these are some of the most frequently used medications in the ICU in both a therapeutic as well as supportive manner. The implications of off-label use, however, may be more significant given the potential for immediate adverse events as well as longer-term ones.[25–27] Cardiovascular medications, if under- or overdosed, may result in hemodynamic instability and/or impaired oxygen delivery. Neurological medications, similarly, could result in acute instability in cardiopulmonary status as well as neurologic. Furthermore, as evidence has been emerging on the potential for longer-term adverse effects of sedatives, unclear dosing or unknown therapeutic benefits raises additional questions about the risk-vs-benefit profile of certain neurological medications.[28,29] These concerns, in addition to the high frequency of use, make these drugs particularly good targets for additional pediatric studies.

Pediatric patients have frequently been

Table 3. Top Medications Used Off-Label in the Pediatric Intensive Care Unit (PICU) and Suggested Prioritization Based on High Off-Label Use (Off Label Use in at Least 5% of the Cohort), High Risk Status (As Identified by the Institute of Safe Medication Practices) and High Regulatory Priority (As Identified by Either the US Food and Drug Administration or Through the Efforts Under the Best Pharmaceuticals for Children Act [BPCA])

Category A	Category B			Category C		
High Off-Label and High Risk and BPCA/FDA Priority	**High Off-Label and High Risk**	**High Off-Label and BPCA/FDA Priority**	**High Alert and BPCA/FDA Priority**	**High Off-Label Only**	**High Risk Only**	**BPCA/FDA Priority Only**
Dexmedetomidine	Bupivacaine	Albuterol	Amiodarone	Aminocaproic acid	Amphotericin	Acetazolamide	Levofloxacin
Dopamine	Fentanyl	Azithromycin	Enoxaparin	Chlorothiazide	Dobutamine	Amlodipine	Lisinopril
Hydromorphone		Ketorolac	Esmolol	Clonidine	Ephedrine	Atenolol	Mometasone
Ketamine		Levetiracetam	Insulin aspart	Glycopyrrolate	Etomidate	Baclofen	Oseltamivir
Lorazepam		Metronidazole	Insulin glargine	Ipratropium	Insulin lispro	Beclomethasone	Oxcarbazepine
Methadone		Ondansetron	Labetalol	Mannitol	Isoproterenol	Budesonide	Oxybutynin
Milrinone		Pantoprazole	Nicardipine	Neostigmine	Meperidine	Ciprofloxacin	Salmeterol
Oxycodone			Propranolol	Protamine	Nitroglycerin	Fosphenytoin	Sildenafil
			Ropivacaine	Spironolactone	Norepinephrine	Gabapentin	Topiramate
					Promethazine	Lamotrigine	Ursodiol
					Warfarin	Levalbuterol	Valproic acid
							Voriconazole

FDA, Food and Drug Administration

referred to as "therapeutic orphans" because of the limited pediatric data on a majority of medications. Recognizing this, there has been national and legislative efforts to improve our knowledge of medications used in pediatrics. Significant legislative efforts to advance pediatric drug research have included the Pediatric Research Equity Act (previously Pediatric Final Rule), the Pediatric Exclusivity Provision, and the BPCA.[30] These legislative changes support increased financial incentives to industry, increase power by the FDA to require pediatric studies on drugs with high likelihood of pediatric use, and provide a mechanism to study pediatric medications outside of the manufacturer's purview. Such efforts have led to increased pediatric clinical studies but the progress can be slow.[24,31,32]

One highly promising effort is the Pediatric Trials Network (PTN; pediatrictrials.org), sponsored by the National Institute of Child Health and Human Development.[33] The PTN is a network of clinical research sites within the United States that is "studying the formulation, dosing, efficacy, and safety, of drugs…used in pediatric patients." One example of an on-going study that may directly involve critically ill children is the Pharmacokinetics of Understudied Drugs Administered to Children Per Standard of Care (PTN_POPS). This study is specifically interested in obtaining pharmacokinetic information on medications that are understudied in pediatric patients and special populations such as obese patients or those requiring extracorporeal support. Currently, 7 of the actively studied medications in the PTN_POPS study met at

least 1 criterion for high priority in our study, 1 (methadone) of which was identified as particularly high impact in our study (personal communication: Peter Mourani, Children's Hospital Colorado, June 4, 2013). The findings from such studies and others will hopefully lead to more safe and effective use in our patients.

Several limitations to our study deserve acknowledgement. First, we used an administrative database in which a medication charge was used as proxy for actual receipt of medication. While this allowed for a large national sample, this could increase the risk of misclassification. However, we believe the likelihood of this occurring would be sufficiently low to not impact our findings. We also were unable to determine whether certain medications (e.g. non-intravenous medications) were initiated with the PICU or were continued from outpatient (reflecting outpatient rather than PICU off-label prescribing). Additionally, because we did not have the indications for prescribed medications, we were limited to using age only as an indicator for off-label use. Therefore, the estimated rate of off-label use in our study could have been an underestimate if medications were used for a different indication than that approved for a particular pediatric age range, resulting in a different prioritization list. Furthermore, the data only came from pediatric centers, limiting the generalizability of our findings to children cared for in non-pediatric centers. Finally, our prioritization scheme was developed empirically and did not include costs as a consideration. Other approaches may result in a different set of identified medications for high-impact future research.

CONCLUSIONS

Off-label prescribing remains a challenging reality for pediatric providers, and the decision-making becomes even more difficult with critically ill children. Although they comprise only a small percentage of the pediatric population, children who require ICU support are a uniquely vulnerable population deserving of special attention. They often have underlying vulnerability related to chronic conditions, which may be further exacerbated when critically ill.[34] Additionally, as seen in our study, they are exposed to multiple different medications, often in an off-label manner. It is unreasonable to expect that off-label prescribing cease, for children deserve access to potentially beneficial therapies. However, this practice mandates careful consideration of risk vs benefit in medical decision-making by providers based on the existing evidence including expert guidelines. Parents and children, alike, trust their health care professionals to make the best decision in this respect.[35,36] Furthermore, as stated by the American Academy of Pediatrics Committee on Drugs, "Physicians who choose to prescribe a medication with limited pediatric data have a public and professional responsibility to assist in the systematic development of the information about that drug for the benefit of other patients."[3] Hopefully, our findings serve as a starting point for focusing our attention on which lines of drug research might have the greatest impact on safe and effective use in critically ill children.

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Abbreviations BPCA, Best Pharmaceuticals for Children Act; CCC, complex chronic condition; CI, confidence interval; FDA, Food and Drug Administration; ICU, intensive care unit; ISMP, Institute for Safe Medication Practices; IQR, interquartile range; PHIS, Pediatric Health Information System; PICU, pediatric intensive care unit; PTN, Pediatric Trials Network; PTN_POPS, Pharmacokinetics of Understudied Drugs Administered to Children Per Standard of Care

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