Appropriateness of commercially available and partially customized medication dosing alerts among pediatric patients

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ABSTRACT

Objectives To evaluate dosing alert appropriateness, categorize orders with alerts, and compare the appropriateness of alerts due to customized and non-customized dose ranges at a pediatric hospital.

Methods This was a retrospective analysis of medication orders causing dosing alerts. Orders for outpatient prescriptions, patients ≥ 18 years of age, and research protocols were excluded. Patient medical records were reviewed and ordered doses compared with a widely used pediatric reference (Lexi-Comp) and institutional recommendations. The alerted orders were categorized and the occurrence of appropriate alerts was compared.

Results There were 47 181 inpatient orders during the studied period; 1935 orders caused 3774 dosing alerts for 369 medications in 573 patients (median age 6.1 years). All alerted orders had an alert overridden by the prescriber. The majority (86.2%) of alerted orders inappropriately caused alerts; 58.0% were justifiable doses and 28.2% were within Lexi-Comp. However, 13.8% of alerted orders appropriately caused alerts; 8.0% were incorrect doses and 5.8% had no dosing recommendations available. Appropriately alerted orders occurred in 19.7% of alerted orders due to customized ranges compared to 12.8% due to non-customized ranges ($p=0.002$). Preterm and term neonates, infants, and children (2–5 years) had higher proportions of inappropriate alerts compared to appropriate alerts (all $p<0.01$).

Conclusions The vast majority of dosing alerts were presented to practitioners inappropriately, potentially contributing to alert fatigue. Appropriate alerts occurred more often when alerts were due to customized ranges. Advances in dosing alerts should aim to provide accurate and clinically relevant alerts that minimize excessive inappropriate alerting. Medications requiring dosing adjustments based on clinical parameters must be taken into account when designing and evaluating dosing alerts.

BACKGROUND AND SIGNIFICANCE

Pediatric patients are reported to have a threefold higher potential adverse drug event (ADE) rate compared to adults, with a high rate of medication dosing errors.¹ In both the pediatric and adult population, medication prescription has been identified as the source or cause of most medication errors and preventable ADEs.^{1–3} Pediatric dosing is complex and can be error prone due to the dynamic anatomy and physiology, weight based dosing, age based dosing, and the lack of knowledge regarding appropriate medication dosing and

utilization in pediatric patients. While some pediatric medication dosing errors are prevented and do not cause harm, other dosing errors not amended before administration may be fatal.⁴

Computerized provider order entry (CPOE) and dosing related computerized clinical decision support (CDS) functionalities are being used in pediatric institutions to prevent patients from receiving potentially hazardous medication doses.^{5–9} Some institutions have designed their own CDS systems or modified systems designed for the adult population to accommodate pediatric dosing support.^{7–9} Medication information database companies have created pediatric dose ranges, with or without customization options, for use in CPOE systems. Previous studies have suggested decreased dosing errors or ADEs with the use of pediatric dosing rules, although analysis of alert appropriateness was not completed.^{7–10–11} A review of CDS in pediatric patients noted variable effectiveness of CDS functionalities and described the need for additional analysis.¹² Others have also suggested the need for evaluation of CDS alert and response appropriateness.¹³ Evaluation of dosing alert appropriateness may elucidate ways to decrease excessive inappropriate alerting that can cause diminished provider response to appropriate alerts, known as alert fatigue.^{14–15}

OBJECTIVES

The objectives of this study were to evaluate dosing alert appropriateness, categorize medication orders with dosing alerts, and compare the appropriateness of dosing alerts due to customized and non-customized dose ranges at a tertiary pediatric hospital. Secondary objectives included identifying and categorizing the causes of inappropriate dosing alerts.

METHODS

Description of institution and CDS system

This study was conducted at Nationwide Children's Hospital (NCH), an academic pediatric tertiary referral center with over 350 beds, including neonatal and pediatric intensive care units, an emergency department, and other specialized inpatient units. At the time of this study, NCH was utilizing the Epic electronic health record (Epic Systems Corporation, Verona, Wisconsin, USA, 2010). Epic allowed for many CDS functionalities including weight based dosing, infusion calculators, and order sets. The First Databank (FDB) drug information database was uploaded and updated approximately every 3–4 months (First Databank, South

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San Francisco, California, USA). The FDB database provided the drug information necessary for presentation of medication allergy alerts, therapeutic duplication alerts, medication interaction alerts, and medication dosing alerts to practitioners on a daily basis. Multiple dosing alerts can occur for a given order as dosing alerts could be presented to prescribers during order entry into the CPOE system, pharmacists during the order verification process, and nurses before administration of certain medications. Modifications of orders (common with continuous infusions) were also checked by the decision support functionalities. Practitioners could override an alert and continue with the order as written or discontinue the order before providing a digital signature.

In the alert notification screen, the dosing alert provided the CDS system calculated dose (single and/or daily), the percentage over or under the CDS dose limit, and also the CDS suggested dose range or frequency for that medication. Alerts were filtered and not presented to practitioners if the dose was within 10% of the dose range limits, if the alert was for an as needed order exceeding daily dose limits (eg, an every 1 h as needed order in an intensive care unit), and if the alert was because the system was unable to convert dosing units for calculation (eg, with topical products and some intravenous fluids). When the system could not find enough information to determine a dose (eg, weight if the range was based on weight), an alert also occurred. Medications ordered which did not have associated dose ranges within the system created an alert stating 'Dose checking cannot be performed'.

The dose ranges included minimum and maximum doses that could have been written in a weight based or fixed dose format for a one time dose, single dose for maintenance dosing, or cumulative daily dose for maintenance dosing. It was also possible to enter a maximum or minimum daily frequency. A dose range could be specified by age or weight, gestational age at birth, and route of administration. Medications available in different vial sizes or concentrations could have separate ranges (but one range could also be used if desired). Prior to customization, the proprietary FDB database provided pediatric specific dose ranges for over 2000 medications. Practitioners at NCH customized over 600 of the medication dose ranges. Dosing rule customization involved changing or adding any of the rule parameters desired (eg, age or weight range, minimum dose, maximum dose, and route). There were no changes made to the dosing alert rule logic. Any NCH customized range took precedence over the FDB ranges.

Data collection

A report was generated from pharmacy records for all medication orders and all medication dosing alerts occurring during the calendar month of July 2011. Orders were excluded if they were outpatient prescriptions, for patients ≥ 18 years of age, or for patients involved in a research study. Each medication order which caused a dosing alert to be presented to a practitioner (eg, physician, pharmacist, nurse) was identified and reviewed. Each patient's medical record was searched and all clinical information necessary to verify the correctness of a medication order was reviewed (eg, for height, weight, indication, renal function, pharmacokinetics). The medication dose ordered was then assessed in relation to dosing recommendations in the Lexi-Comp Pediatric Dosage Handbook¹⁶ and any institution specific dosing recommendations (eg, guidelines and formulary monographs). We chose Lexi-Comp for comparison because it is among the most widely used pediatric dosing references.

Alerted medication orders were then categorized into one of four categories:

1. Justifiable dose with an inappropriate alert (false positive): the ordered dose was clinically justifiable or within institutional recommendations, although outside of Lexi-Comp ranges.
2. Correct dose with an inappropriate alert (false positive): the dose was clinically appropriate and within the age and/or weight specific Lexi-Comp dose range for an indication.
3. Incorrect dose with an appropriate alert (true positive): the dose was outside of ranges in Lexi-Comp and institutional recommendations without an identifiable clinical justification or was not clinically appropriate.
4. No recommendations available and an appropriate alert (true positive): dosing recommendations were unavailable in Lexi-Comp and institutional recommendations for the patient's age and/or weight and indication.

After categorization, orders were also divided into subcategories based on previously described age groups.¹⁷ Each age group was then broken down by weight categories to best depict the patient characteristics used for pediatric dosing.¹⁶ For each order with a justifiable dose that caused an inappropriate alert, a clinical justification for the dose was provided. For each order with a correct dose that caused an inappropriate alert, there was a reason provided as to why there was an inappropriate alert. After classification, dosing alert ranges were reviewed to determine if the alert occurred due to a customized or non-customized dose range. An alerted order due to a customized range was defined as an alert that only occurred due to customization. All other alerted orders were considered non-customized because they would have occurred if no customization had taken place. This study was deemed exempt by the NCH Institutional Review Board.

Statistical analysis

Non-parametric data were described by median and range. Percentages were used to describe the occurrence of each category of alerted orders. The χ^2 or Fischer's exact test was used to proportionally compare the occurrence of each order type within the alerted orders due to customized versus non-customized dose ranges. The χ^2 or Fischer's exact test was also used to determine differences in distribution of alerted order type among each age and weight category. All statistical tests were completed using SAS V.9.2.

RESULTS

During the study period, there were 91 963 medication orders identified from pharmacy records, involving 47 181 inpatient pediatric orders (figure 1). From the alert database, 1935 medication orders (4.1% of all orders) caused the presentation of 3774 medication dosing alerts to practitioners, with each alerted order having an alert overridden alert by the prescriber (figure 1 and table 1). These medication orders were written for 369 unique medications and 573 unique patients with a median age of 6.1 years (table 1). The majority (86.2%) of alerted orders had inappropriate alerts; 58.0% were for justifiable doses and 28.2% were for correct doses. However, 13.8% of alerted orders had appropriate alerts; 8.0% were incorrect doses and 5.8% did not have dosing recommendations available (figure 1). Examples for each of the alerted order categories are presented in table 2. The occurrence of inappropriately alerted orders was higher than appropriately alerted orders when the orders were for preterm and term neonates, infants, and children 2–5 years (all p values < 0.01). In the neonatal age group, over half of the

Figure 1 Categorization of medication orders.

justifiable doses with inappropriate alerts were for midazolam and morphine continuous infusions, oral morphine, or oral methadone. The occurrence of appropriately alerted orders was higher than inappropriately alerted orders when the orders were for children 6–12 years ($p < 0.001$). There was no difference in the alert appropriateness distribution when the orders were for toddlers 1–2 years and adolescents 13–18 years (table 1).

Figure 2 proportionally compares alerted orders due to customized and non-customized ranges. The occurrence of appropriately alerted orders differed between the alerts due to customized and non-customized ranges (80.3 vs 87.2% for inappropriately alerted orders and 19.7% vs 12.8% for appropriately alerted orders, $p = 0.002$). A lower proportion of alerted orders due to customized ranges were for justifiable doses when compared to non-customized ranges (59.0 vs 51.9%, $p = 0.025$), while the proportion of correct doses with inappropriate alerts was not different. Alerted orders due to customized ranges had a higher proportion of orders with alerts for incorrect doses and orders with alerts for medications without dosing recommendations when compared to non-customized ranges (11.2 vs 7.4%, $p = 0.027$ and 8.5 vs 5.4%, $p = 0.034$, respectively).

Table 3 describes various reasons why 58.0% of alerted orders were for justifiable doses and thus had inappropriate alerts. Thirty-four percent of alerted orders caused inappropriate alerts because the dose was adjusted based on patient specific clinical parameters. This type of alerted order occurred more often when the alerted order was due to non-customized ranges (37.0 vs 17.0%, $p < 0.001$). Dosing titrations for opioids,

benzodiazepines, and corticosteroids were the most common patient specific clinical parameter and occurred in the same proportion regardless of the ranges that caused the alerts. Dosing adjustments based on laboratory values, pharmacologic effect, and symptom severity were also frequent reasons for justifiable orders and occurred less when customized ranges were the cause (all p values ≤ 0.004). Sixteen percent of alerted orders were for justifiable doses because they were correct doses based on institutional recommendations. This type of alerted order occurred more often when alerts were due to customized ranges versus non-customized ranges (21.8% vs 15.2%, $p = 0.005$). Dosing changes required for administration purposes were the reason for 7% of alerted orders and occurred more often when the alert was due to customized ranges (12.9% vs 6.4%, $p < 0.001$).

Table 4 provides the reasons why inappropriate alerts occurred in 28.2% of alerted orders that were within Lexi-Comp recommendations. The majority of orders for correct doses caused inappropriate alerts (14.2% of alerted orders) because the range did not match recommendations from Lexi-Comp. Alerted orders due to customized ranges had the same proportion of correct orders with inappropriate alerts when compared to those due to non-customized ranges (12.9% vs 14.4%, $p = 0.51$). Nearly 4% of alerted orders occurred when a medication order was written for a route of administration not included in the alert ranges. A higher proportion of alerted orders due to a mismatched method of administration occurred when customized ranges caused an alert (9.2% vs 2.6%,

Table 1 Study population characteristics

Characteristic	Overall (% alerted orders)	Justifiable dose, inappropriate alert (% alerted orders)	Correct dose, inappropriate alert (% alerted orders)	Incorrect dose, appropriate alert (% alerted orders)	No recommendations, appropriate alert (% alerted orders)
Unique patients with alerted orders					
No. patients*	573	303	294	117	75
Median age (years)	6.1 (0–17.9)	6.1 (0–17.9)	4.8 (0–17.9)	6.9 (0–17.8)	7.0 (0–17.9)
Female*	289	152	147	56	32
Male*	284	151	147	61	43
Alerted orders					
No. medication orders†	1935	1122	545	155	113
No. alerts viewed	3774	2245	1037	255	237
No. medications‡	369	196	156	96	40
Preterm/term neonates (PMA <44 weeks)§	375 (19.4)	250 (22.3)	96 (17.6)	21 (13.5)	8 (7.1)
>0, <5 kg§	360 (18.6)	238 (21.2)	94 (17.2)	20 (12.9)	8 (7.1)
≥5, <10 kg	15 (0.8)	12 (1.1)	2 (0.4)	1 (0.6)	0
Infants (1–11 months)§	364 (18.8)	270 (24.1)	66 (12.1)	14 (9.0)	14 (12.4)
>0, <5 kg§	117 (6.0)	86 (7.7)	25 (4.6)	5 (3.2)	1 (0.9)
≥5, <10 kg§	228 (11.8)	168 (15.0)	41 (7.5)	8 (5.2)	11 (9.7)
≥10, <20 kg§	19 (1.0)	16 (1.4)	0	1 (0.6)	2 (1.8)
Toddlers (12–23 months)	108 (5.6)	56 (5.0)	31 (5.7)	12 (7.7)	9 (8.0)
≥5, <10 kg	50 (2.6)	22 (2.0)	17 (3.1)	8 (5.2)	3 (2.7)
≥10, <20 kg	58 (3.0)	34 (3.0)	14 (2.6)	4 (2.6)	6 (5.3)
Child (2–5 years)§	380 (19.6)	181 (16.1)	153 (28.1)	21 (13.5)	25 (22.1)
≥5, <10 kg	1 (0.1)	0	1 (0.2)	0	0
≥10, <20 kg§	333 (17.2)	154 (13.7)	139 (25.5)	18 (11.6)	22 (19.5)
≥20, <40 kg	44 (2.3)	26 (2.3)	12 (2.2)	3 (1.9)	3 (2.7)
≥40, <70 kg	2 (0.1)	1 (0.1)	1 (0.2)	0	0
Child (6–12 years)§	422 (21.8)	204 (18.2)	119 (21.8)	58 (37.4)	41 (36.3)
≥10, <20 kg§	47 (2.4)	16 (1.4)	18 (3.3)	7 (4.5)	6 (5.3)
≥20, <40 kg§	272 (14.1)	139 (12.4)	74 (13.6)	32 (20.6)	27 (23.9)
≥40, <70 kg§	96 (5.0)	47 (4.2)	24 (4.4)	17 (11.0)	8 (7.1)
≥70 kg	7 (0.4)	2 (0.2)	3 (0.6)	2 (1.3)	0
Adolescent (13–17 years)	286 (14.8)	161 (14.3)	80 (14.7)	29 (18.7)	16 (14.2)
≥20, <40 kg	47 (2.4)	26 (2.3)	9 (1.7)	7 (4.5)	5 (4.4)
≥40, <70 kg	163 (8.4)	98 (8.7)	42 (7.7)	13 (8.4)	10 (8.8)
≥70 kg§	76 (3.9)	37 (3.3)	29 (5.3)	9 (5.8)	1 (0.9)

*Patients and medications could be duplicated in different order categories.

†All alerted orders had an alert overridden by the prescriber.

‡A medication was defined as a different route of administration, formulation, concentration, or active ingredient.

§Significant difference in distribution across alerted order categories using χ^2 analysis or Fisher's exact test ($p < 0.05$).

PMA, post-menstrual age.

$p < 0.001$). The third most common reason for a correctly ordered dose to have an inappropriate alert (3.3% of alerted orders) was that the dose ranges did not include dosing for the desired indication.

Eight percent of alerted orders were categorized as incorrect doses with an appropriate alert and all had an alert overridden by the prescriber. Customization provided 33 additional appropriate alerts that would not have occurred with non-customized ranges. The main area of enhancement was with underdoses, where there was a higher proportion of alerted orders due to customized ranges when compared to non-customized ranges (7.8% vs 3.7%, $p = 0.001$). The majority of these additional appropriate alerts were due to the addition of minimum dose ranges for one time doses, which were not present in the proprietary ranges.

Six percent of the alerted orders did not have recommendations available and thus appropriate alerts. Customization added 25 additional appropriate alerts that would not have occurred

with non-customized ranges. The most common reason for orders with no dosing recommendations available to cause an alert was the lack of dosing information in institutional recommendations and Lexi-Comp for the desired age group.

DISCUSSION

Our data illustrate that practitioners were inappropriately alerted in the vast majority of the orders with dosing alerts at our institution. The majority of inappropriate alerts occurred because the medication doses were being adjusted based on patient specific parameters, because the dose ordered was within our institution's recommendations, and because the dose ranges that caused the dosing alerts were inaccurate. Preterm and term neonates, infants, and children (2–5 years) were identified as groups with higher proportions of inappropriate alerts compared to appropriate alerts. Excessive inappropriate alerting potentially contributed to the inappropriate overrides of alerts for incorrect orders, known as alert fatigue.

Table 2 Examples of alerted orders

Alerted order category	Medication, patient, and indication	Ordered dose(s)	Lexi-Comp range	Alert limit
Justifiable dose, incorrect alert, within institutional recommendations	Magnesium sulfate intravenous; 5-year old, 19 kg; status asthmaticus	20 mg/kg/h (institutional range 20 mg/kg/h and titrate)	25–75 mg/kg once, no continuous dose	Maximum: 8.33 mg/kg/hr
Justifiable dose, incorrect alert, with a changed dose due to administration purposes	Hydrocortisone oral tablet; 7-month old, 0.54 m ² and 8.1 kg; congenital adrenal hyperplasia	5 mg qAM + 2.5 mg (0.3 mg/kg, 4.6 mg/m ²) at lunch and qPM as 3 separate orders (18.5 mg/m ² /day)	10–20 mg/m ² /day divided into 3 doses	Minimum: 0.5 mg/kg/day
Correct dose, inappropriate alert, where alert range did not match references	Cefotaxime intravenous; 17-day old, 3.4 kg, full term; rule out meningitis	50.5 mg/kg/dose q6h	100–200 mg/kg/day divided 3–4 times	Maximum: 180 mg/kg/day
Correct dose, inappropriate alert, because range did not specify an indication	Vasopressin intravenous; 4-month old, 5.6 kg female; vasodilatory shock	0.6 milliunits/kg/min	0.3–2 milliunits/kg/min	Minimum: 2 milliunits/kg/min (dosing for gastrointestinal hemorrhage)
Incorrect dose, appropriate alert	Calcium chloride intravenous; 9-day old, full term, 4.1 kg; cardiac arrest	1 mg once	20 mg/kg once	Minimum: 10 mg/kg/dose* (no minimum if not customized)
No recommendation available, appropriate alert	Acetazolamide oral suspension; 7-year old, 22 kg; increased intracranial pressure	17 mg/kg/dose four times a day	No dosing available for this indication	Maximum: 50 mg/kg/day*

*Customized range.

The customized CDS dose ranges used at our institution caused a higher proportion of appropriately alerted orders compared to non-customized ranges (figure 1). As noted in table 3, this difference was likely because our institution was able to identify some medications which were commonly used outside of dosing recommendations in Lexi-Comp, such as medications requiring serum concentration monitoring or dose titrations, and changed the minimum and maximum ranges to prevent inappropriate alerts for justifiable doses. There was no difference in the occurrence of inappropriate alerts for correct doses when comparing alerted orders due to customized and non-customized ranges. At least part of this issue was because our institution did not create a dosage range for the continuous infusion of midazolam, resulting in inappropriate alerts. In addition, this also suggests that there are alert rule logic issues

which are not amendable by customization. Others implementing dosing alert ranges should be aware of the limitations of the currently available dosing alert systems when customizing dose ranges.

As shown in table 1, age and weight played an important role in determining the appropriateness of pediatric dosing alerts. The older patients (≥ 6 years of age) had more appropriate alerts compared to inappropriate alerts, while the children < 6 years of age had more inappropriate alerts (except for toddlers). These data illustrate the limitations in both the dosing rule logic capabilities and drug information resources in neonates, infants, and young children. Post-menstrual age was not accounted for in the dosing alert rule logic capabilities, but this age classification is used commonly to determine dosing for premature neonates.¹⁶ This may explain some of the 17.6% of correct doses

Figure 2 Proportion of alerted order types due to customized and non-customized ranges. ^a χ^2 test for differences in distribution. ^b χ^2 test for alerted order type versus all other types for customized and non-customized ranges.

Table 3 Clinical justifications for doses with inappropriate alerts (n=1122)

Clinical justification	No. overall orders (% alerted orders*)	No. orders due to non-customized rules (% alerted orders*)	No. orders due to customized rules (% alerted orders*)	p Value†
Dose adjusted or titrated for patient needs	657 (34.0)	607 (37.0)	50 (17.0)	<0.001
Opioid, benzodiazepine, or steroid titrated/weaned	216 (11.2)	184 (11.2)	32 (10.9)	0.87
Adjusted based on blood or serum lab value (eg, blood glucose, aPTT, PK)	200 (10.3)	193 (11.8)	7 (2.4)	<0.001
Titrated/weaned based on pharmacologic effect (eg, BP, fluid balance)	160 (8.3)	158 (9.6)	2 (0.7)	<0.001
Initial dose based on patient symptom severity	36 (1.9)	36 (2.2)	0	0.004‡
Patient controlled on home dose	29 (1.5)	24 (1.5)	5 (1.7)	0.79‡
Organ function adjustment	16 (0.8)	12 (0.7)	4 (1.4)	0.29‡
Dose within institutional guidelines	313 (16.2)	249 (15.2)	64 (21.8)	0.005
Dose adjusted for practical administration purposes	143 (7.4)	105 (6.4)	38 (12.9)	<0.001
Sum of multiple orders provides correct dose	51 (2.6)	33 (2.0)	18 (6.1)	<0.001
Dose administered differed from entered dose	44 (2.3)	39 (2.4)	5 (1.7)	0.47
Rounded for administration	29 (1.5)	17 (1.0)	12 (4.1)	<0.001
Interval unspecified in Lexi-Comp	19 (1.0)	16 (1.0)	3 (1.0)	0.94
Other	9 (0.5)	8 (0.5)	1 (0.3)	0.73

*n=1935 overall alerted orders, 1641 due to non-customized and 294 due to customized ranges.

† χ^2 test for clinical justification versus all other clinical justifications for customized and non-customized ranges.

‡Fisher's exact test.

aPTT, activated partial thromboplastin time; BP, blood pressure; PK, pharmacokinetics.

with inappropriate alerts that were ordered for neonatal patients. The large proportion of incorrect alerts for justifiable doses in neonates and infants (22.3% and 24.1%, respectively) associated with medications commonly titrated represents both rule logic and drug information deficiencies. For example, neonatal midazolam dosing recommendations only included initial continuous infusion recommendations and then stated the medication should be titrated based on response. Dose ranges created to mirror these initial dosing recommendations did not account

for titration and caused excessive inappropriate alerts to occur. This can create more inappropriate alerts in neonates compared to other age groups because neonatal dosing recommendations have narrower dosing recommendations.¹⁶ Other analgesics and sedatives had similar limitations causing inappropriate alerts in neonates and infants.

The high percentage (58%) of orders with inappropriate alerts for justifiable doses in our study highlights the importance of patient specific dosing in the clinical setting. It is important

Table 4 Reasons why correct doses caused inappropriate alerts (n=545)

Reason	No. overall (% alerted orders*)	No. due to non-customized ranges (% alerted orders*)	No. due to customized ranges (% alerted orders*)	p Value†
Ranges did not match available dosing recommendations	274 (14.2)	236 (14.4)	38 (12.9)	0.51
Ranges written for a different method of administration (eg, intermittent vs continuous infusion)	69 (3.6)	42 (2.6)	27 (9.2)	<0.001
Ranges did not allow indication specification	64 (3.3)	58 (3.5)	6 (2.0)	0.22‡
Ranges did not account for multiple patient characteristics (eg, combination of age and weight)	31 (1.6)	30 (1.8)	1 (0.3)	0.07‡
Weight written in chart, but not entered into electronic medical record	28 (1.4)	28 (1.7)	0	0.02‡
Ranges did not take into account appropriate dosing based on age, weight, or body surface area	28 (1.4)	23 (1.4)	5 (1.7)	0.60‡
Calculated dose did not appropriately fit clinical situation	23 (1.2)	22 (1.3)	1 (0.3)	0.24‡
Patient was <18 years of age, but reached adult maximum dosing	20 (1.0)	16 (1.0)	4 (1.4)	0.53‡
Others	8 (0.4)	7 (0.4)	1 (0.3)	1.00‡

*n=1935 overall alerted orders, 1641 due to non-customized and 294 due to customized ranges.

† χ^2 test for alerted order reason vs all other reasons for customized and non-customized ranges.

‡Fisher's exact test.

to note that patient specific dose adjustments or titrations resulted in inappropriate alerts (table 3), although the same dose ranges also appropriately caused alerts in other patients who were unintentionally ordered too low or too high doses. The currently available dosing rule logic cannot adequately describe dose adjustments made for patient specific reasons (eg, dose titrations and adjustments based on renal function) that are outside of dosing recommendations. Alternative approaches must be developed to provide decision support for medications commonly used outside of referenced dose ranges for a justifiable purpose, particularly high risk medications such as analgesics and sedatives.

The justifiable doses that were within institutional dose ranges depict the potential for differing dosing practices present at our institution compared to other institutions. Collaboration among physicians, nurses, and pharmacists in the customization of dose ranges at a particular institution may prevent unnecessary alerts at the institution level. However, customization may require substantial time and resources as previously described with the creation of alert based systems.¹⁸ Although alerted orders due to customized ranges overall had more appropriate alerts (figure 2), alerted orders due to customized ranges had a higher proportion of orders within our institution's recommendations that were inappropriately alerted (table 3). This may suggest that our institution was not able to identify ranges requiring customization or inappropriately customized them.

Additional enhancements in medication alert rule logic are needed to prevent inappropriate alerts for 7% of alerted orders (table 3). For example, 2.6% of alerted orders would not have caused alerts if the system had the ability to detect concurrent dosing regimens used to create a daily dose. Dose rounding limits could also be set at different levels for medications commonly rounded before administration (eg, acetaminophen suppositories) and prevent the orders that were inappropriately alerted for this reason. Medication specific dose rounding has been suggested for use in pediatric patients.¹⁹

Inconsistency between created dose ranges and a common dosing reference was illustrated in the 28% of orders that had inappropriate alerts for correct doses. There was no difference in the occurrence of inappropriate alerts for correct doses when comparing alerted orders due to customized and non-customized ranges. Potential explanations for these findings may include the lack of continual dosage range updates, different dosing interpretations by range creators and practitioners, and/or the inability of the current dosing alert rule logic to describe pediatric dosing regardless of the dose ranges entered into the system. Some of these issues are potentially amendable by ensuring dose range accuracy compared with accepted dosing references. The 4% of alerted orders due to the lack of different routes of administration in the ranges are also amendable by changing or adding the desired route of administration. Three percent of alerted orders caused an alert because the CDS ranges did not include all indications available for the medication. This can result in both false positive and false negative alerts, potentially allowing for inappropriate dosing of high risk medications such as vasopressin and heparin. This was potentially an underestimate of this problem as many of the medications in our dataset were not used for all of their indications. Inappropriate alerts due to lack of indication specific dosing rules are not amendable by customization and require further improvements in dosing alert rule logic.

The other two categories in this study, representing only 14% of the alerted orders, illustrate appropriate alerts (true positives) and the impact dosing alerts could have on ensuring appropriate

medication dosing. These appropriately alerted orders occurred in a greater proportion when the alert was due to customized ranges compared to non-customized ranges (figure 2). The 8% of orders with appropriate alerts for incorrect doses should not have been overridden by any practitioners, but indeed were, indicating alert fatigue may have been present at our institution. The incorrect doses with appropriate alerts due to customized ranges may represent an increase in potential dosing error detection. These appropriately alerted orders were mostly underdoses that were not present in proprietary dose ranges, but could be clinically important. This may corroborate previous statements in medication interaction literature suggesting customization should be available to interpret the relationship between information databases and clinical practice.^{20–22} Six percent of our alerted orders did not have recommendations available, and may require searching primary literature or alternative consultation to determine dosing appropriateness. These alerted orders illustrate how the dosing alert functionality may be used as a tool to identify new areas of research and increase the available knowledge for medication use in pediatrics.

The detailed analysis of dosing alert appropriateness presented in our study was not well described in previous pediatric studies. In previous CPOE implementation studies in the pediatric population, the appropriateness of dosing alerts was unclear.^{5 6 8} Authors have described the implementation of a dosing support system which provided recommendations before order entry. Although decreases in harmful ADEs were reported after implementation, it was unclear if the dosing recommendations were regularly accepted or aided in ADE prevention.⁷ Outside of the USA, decision support dosing alerts were shown to have an impact on prescribing errors independent of CPOE implementation. Minimal information was provided regarding the percent of overrides.^{10 11} Using an institutionally derived system, 32% of dosing suggestions for the top 200 pediatric medications were accepted in a pediatric ward, and only 10% in the neonatal intensive care unit, suggesting inaccuracy of ranges, insufficient dosing rule logic, or differences in dosing based on clinical scenarios.¹⁸ This study was limited by the number of medication ranges studied and because it did not use a commercial vendor supplied system. These limitations make it difficult to apply the results of this study in other institutions. Our study used a commercially available information database system and may be applicable to other institutions.

The use of hard stops, which prevents the ordering of a dose outside of a desired range, has been described.^{6 23} The majority of the alerts in our study were for clinically justifiable doses outside of the reference range. The use of hard stops in our patients may have caused delays in care as described previously.²⁴ This strategy should only be used for specific medications with absolute and well documented maximum or minimum doses. Sensitivity of dosing alerts has also been questioned, as only 2 of 19 non-intercepted serious dosing errors reported after CPOE and CDS implementation had associated alerts.⁹ Analysis of the sensitivity and specificity of dosing alert systems for dosing errors and ADEs requires further evaluation. Identifying all dosing errors and determining which dosing errors had alerts would allow for sensitivity and specificity determination. Utilizing this information, one could also perform a number needed to alert analysis when comparing multiple CDS systems (eg, customized vs non-customized).

Our study has a few limitations to note. It was retrospective, and all clinical decisions may not have been captured by the retrospective medical record review. Although many of the issues identified in this study would likely occur in other

institutions, results may vary somewhat between institutions. The authors categorized institutionally appropriate orders as justifiable orders with alerts to illustrate areas that our data may differ from other institutions. Multicenter studies may account for differences between institutions. The authors chose a widely used and published dosing reference to improve external validity, but other dosing references may provide different dose ranges. Seasonal variation in medication use and a potential learning curve for medical residents may affect alert outcomes and needs further evaluation. This study may have underestimated the number of dosing alert ranges that did not coincide with published dosing references, because each dose range was analyzed based on the order found in our alert database, not all possible orders for a given medication.

Despite some limitations, our data suggest that an increase in the clinical appropriateness of dosing alerts is needed to decrease the potential for alert fatigue. Improved accuracy of dose range information in CDS systems along with the development and evaluation of dosing support for medications commonly adjusted based on clinical parameters should be the focus of improvements for the CDS dosing support functionality. Continual analysis of dosing alert appropriateness can identify areas for enhancement. Some improvements can be made at the institutional level by customization, while others require changes from different or multiple areas of the decision support infrastructure (eg, electronic health record and drug information database providers). Interaction between clinical practitioners at and among pediatric institutions, information technology personnel, and information technology companies is needed to make these improvements. Without further advancement in these areas, the CDS dosing alert functionality may fail to prevent unsafe or ineffective medication dosing among pediatric patients.

CONCLUSIONS

The vast majority of dosing alerts occurring at our institution were presented to practitioners inappropriately, potentially contributing to alert fatigue. Appropriate alerts occurred more often when alerts were due to customized dose ranges. Preterm and term neonates, infants, and children (2–5 years) had higher proportions of inappropriate alerts compared to appropriate alerts. Continual evaluation and improvements in dosing alerts for use in pediatric institutions is needed.

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