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Evaluation of KIDs List Compliance at a Children's Hospital Within a Large Academic Medical Center

Alexandra Cooper, PharmD; Shannon Lyons, PharmD; Lisa Thames, PharmD; Timothea Scott, PharmD; Ansley Gayle, PharmD; Alexandra Lehman, PharmD; and Tara Higgins, PharmD

OBJECTIVES In 2020, a list of Key Potentially Inappropriate Drugs in Pediatrics, known as the "KIDs List," was published. The objective of this analysis was to evaluate institutional compliance with the recommendations in this publication and identify areas for improvement.

METHODS Medications in the KIDs List were compared to the institutional formulary at a large academic medical center caring for pediatric and adult patients. Medications listed in the formulary were then evaluated for order comments and restrictions related to their use in pediatric patients. Oral liquid products and a group of commonly used intravenous (IV) medications were reviewed for potentially inappropriate excipients through available manufacturer information. The pediatric clinical specialists were then solicited to review and make recommendations for medications that had not been addressed.

RESULTS Of the 67 medications or classes listed in the KIDs List, 47 (70.1%) of the medications are listed in our formulary and available for use. Of these 47 medications, 4 (8.5%) included warnings related to their use in pediatric patients. Of the 270 oral liquid medications reviewed, 206 (76.3%) contained at least 1 potentially inappropriate excipient. Of the 20 commonly used IV medications, 3 (15%) contained at least 1 potentially inappropriate excipient.

CONCLUSIONS This review found that many medications listed in the KIDs List are included in our institution's formulary and that few have warnings for pediatric patients built into the institutional electronic health record. Further review of medications in the formulary will be conducted to determine the next steps to implementing KIDs List recommendations.

ABBREVIATIONS ADE, adverse drug event; EHR, electronic health record; IV, intravenous; KIDs, Key Potentially Inappropriate Drugs in Pediatrics

KEYWORDS adverse drug reaction; excipient; formulary; medication safety; medications; pediatrics; potentially inappropriate medication list

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Introduction

More than 2 decades ago, studies demonstrated that potential adverse drug events (ADEs) are approximately 3 times higher in the pediatric population compared with adults (1.1% vs 0.35%) in the hospital setting.[1] In addition, evidence using focused trigger tool methodology to identify medication-related harm in US children's hospitals demonstrated an even higher rate of ADEs, at 11.1 per 100 patients, with 22% of the events being deemed preventable.[2] There are many known risk factors for pediatric ADEs, including but not limited to the lack of available dosage forms, excipients, and concentrations appropriate for administration in pediatrics.[3]

Similarly, the geriatric population, defined as patients 65 years and older, are at increased risk of ADEs for different reasons. To mitigate the risk and prevent ADEs, a list was created nearly 30 years ago of inappropriate drugs for the geriatric population; it is widely known today as the "Beers Criteria." The Beers Criteria list has become standard of care and is updated on a 3-year cycle by the American Geriatric Society.[4,5]

In 2020, the Pediatric Pharmacy Association commissioned a group of pediatric pharmacists to create a similar list for the pediatric population.[6] The Key Potentially Inappropriate Drugs in Pediatrics "KIDs List" serves as a guide to highlight the risk of ADEs with key medications and excipients when used in the pediatric population.

The publication of the KIDs List led to the review of practices at a large academic medical center caring for adult and pediatric patients. The aims of this analysis were to evaluate the KIDs List and determine which medications and/or excipients were on the inpatient formulary, document if any restrictions and/or warnings

were in place for pediatric patients, and determine if adjustments were necessary to comply with the KIDs List recommendations.

Materials and Methods

The KIDs List was reviewed to determine the medications associated with potential ADEs in pediatric patients (Table 1 in the KIDs List publication) and then was compared to our institution's drug formulary. Medications that were not available in the institution's formulary were excluded from this analysis. Each KIDs List medication available in the formulary was evaluated for any restrictions, warnings, or comments for the ordering provider or verifying pharmacist to assess when a new order is placed in the electronic health record (EHR). Order restrictions, warnings, and comments were recorded. These were considered to be addressed if the content of the restriction, warning, or comment was consistent with the recommendation and rationale provided in Table 1 of the KIDs List. If there were no restrictions, warnings, or comments in the EHR consistent with the recommendation of the KIDs List it was deemed unaddressed. This evaluation also included the 10 excipients listed in the KIDs List (Table 2 in the KIDs List publication) with known or potential harm when used in pediatric patients, including benzyl alcohol, sodium benzoate, benzoic acid, ethanol/ethyl alcohol, isopropyl alcohol, methylparaben, propylparaben, phenylalanine, polysorbate 80, and propylene glycol. All commercially manufactured oral solutions, hospital compounded oral solutions, and a list of commonly used intravenous (IV) medications in pediatric patients were included in the review of excipients. For the manufactured oral solutions and suspensions, package inserts were individually investigated to determine what inactive ingredients and excipients are present in these products. Institution-compounded oral liquid recipes were evaluated to determine the presence of excipients, including Ora-Plus, Ora-Sweet, sterile water, cherry syrup, simple syrup, or propylene glycol, which are often used as vehicles in nonsterile compounding. A similar process was repeated for the 20 most frequently ordered IV medications among the pediatric and neonatal population at our institution based on use during a 3-month period. Drug manufacturer(s) for each product were identified using our purchasing inventory software, and excipient data were extracted from the National Library of Medicine's DailyMed searchable database. Intravenous agents evaluated included acyclovir, ampicillin/sulbactam, bivalirudin, caffeine citrate, cefepime, ceftazidime, clindamycin, cefazolin, dexamethasone, dexmedetomidine, epinephrine, famotidine, fluconazole, fentanyl, hydrocortisone sodium succinate, magnesium sulfate,

Table 1. Key Potentially Inappropriate Drugs in Pediatrics (KIDs List) Medication Review

	Value
KIDs List medication review, all (N = 67)	
Formulary status, n (%)	
Formulary	47 (70.1)
Nonformulary	20 (29.9)
KIDs List recommendation	
Caution in specific patients	21 (31.3)
Avoid in specific patients	33 (49.3)
Caution or avoid based on patient population	13 (19.4)
KIDs List medication review, formulary (n = 47), n (%)	
Appropriate restriction criteria or warnings in place	4 (8.5)
No associated restriction criteria or warnings	43 (91.5)

Table 2. Existing Alerts/Warnings in Electronic Health Record (EHR) Consistent With Key Potentially Inappropriate Drugs in Pediatrics (KIDs List) Recommendations

KIDs List Medications	Existing Alerts and/or Warnings Present in EHR
Ceftriaxone injection	Use in patients 21 days or younger is restricted to a 1-time dose for gonorrhea prophylaxis in patients without high-intermediate–risk to high-risk hyperbilirubinemia (per American Academy of Pediatrics) OR recipient of intravenous calcium within 48 hr of ceftriaxone administration. Consider cefotaxime as alternative therapy. May use empirically in febrile patients 22 days or older who are well-appearing, born at least 37 wk gestation, and discharged home after birth as supported by the American Academy of Pediatrics.
Promethazine injection	Best practice alert "WARNING! This patient is not 2 years of age. Please DO NOT order this medication."
Propofol injection	Contains recommended dosage ranges and titration parameters.
Tramadol tablet	This product is contraindicated in patients younger than 12 years hard-stop alert with suggested alternatives.

methylprednisolone sodium succinate, pantoprazole sodium, piperacillin-tazobactam, and vancomycin.

Results

Of the 67 medications or medication classes listed in the KIDs List, 47 (70.1%) of the medications are on our institution's formulary and available to be ordered on an inpatient basis (Table 1). Of the 47 medications on formulary, 4 medication orders (8.5%; ceftriaxone, promethazine, propofol, and tramadol) have warnings or order comments regarding use in pediatric patients (Table 2). Warnings and/or order comments correlate warning with age restrictions.

There were 270 oral liquid formulations evaluated for potentially inappropriate excipient content (Table 3). Of those, 156 were manufactured oral solutions or suspensions available on formulary and 114 were institution-specific nonsterile compounded oral liquid recipes. Overall, 206 liquid formulations (76.3%) contained at least 1 potentially inappropriate excipient, with 90 products (33.3%) containing more than 1 potentially inappropriate excipient. Of the manufactured solutions, 82.1% (n = 128) had at least 1 excipient listed on the KIDs List with known or potential harm when used in pediatric patients. Of the compounded solutions, 100% (n = 114) had at least 1 excipient listed in the KIDs List with known or potential harm when used in pediatric patients. This is due to the fact that OraSweet, OraSweet Sugar Free, or OraPlus is used in all of our institution-specific compounding recipes. Both OraSweet and OraPlus contain methylparaben, and OraSweet Sugar Free contains both methylparaben and propylparaben.

Of the top 20 IV medications examined (Table 4), 15% (n = 3) had at least 1 potentially inappropriate excipient listed in the package insert, with 2 products (10%) containing more than 1 excipient. The 3 products containing potentially inappropriate excipients were clindamycin, gentamicin, and lorazepam.

The list of potentially inappropriate excipients also contains recommendations on maximum milligrams or percent volume of excipients recommended for pediatric patients. Many of the package inserts did not report these values, with an exception for products containing ethanol or ethyl alcohol. To determine if the drug manufacturers maintain this information, the researchers reached out to a random selection of 5 drug manufacturers electronically to inquire about the amount of excipient in these products. Of the 5 electronic communications, 2 manufacturers responded. One of the responding manufacturers provided the percent and milligrams of excipient used in the oral solution. The other responding manufacturer stated this was proprietary information and did not provide the amount of excipient included.

Table 3. Excipient Review in Oral Liquids

Oral Formulation Excipient Data	Oral Liquids (N = 270)
Commercially available products, n (%)	156 (57.8)
Compounded oral liquids, n (%)	114 (42.2)
Number (%) of oral liquids with at least 1 potentially inappropriate excipient	206 (76.3)
Number (%) of potentially inappropriate excipients in oral liquids	
Zero	63 (23.3)
One	117 (43.3)
Two	59 (21.9)
Three	20 (7.4)
Four	11 (4.1)
Number (%) of oral liquids containing each excipient	
Benzyl alcohol	6 (2.2)
Sodium benzoate	54 (20)
Benzoic acid	2 (0.7)
Ethanol/ethyl alcohol	24 (8.9)
Isopropyl alcohol	0
Methylparaben	123 (45.6)
Propylparaben	61 (22.6)
Phenylalanine	0
Polysorbate 80	20 (7.4)
Propylene glycol	49 (18.2)

Discussion

The landmark KIDs List publication has prompted pediatric institutions to reevaluate their formulary products for safety and the potential to cause ADEs. Some medications are well known for causing ADEs in pediatric patients. As an example, many are aware of the association of chloramphenicol with Gray Baby Syndrome in neonates and ceftriaxone being

Table 4. Excipient Review in Commonly Used Intravenous (IV) Medications

IV Formulation Excipient Review	IV Medications (n = 20)
Number (%) of IV medications with at least 1 potentially inappropriate excipient	3 (15.0)
Number (%) of IV medications containing each excipient	
Benzyl alcohol	2 (10.0)
Sodium benzoate	0
Benzoic acid	0
Ethanol/ethyl alcohol	0
Isopropyl alcohol	0
Methylparaben	1 (5.0)
Propylparaben	1 (5.0)
Phenylalanine	0
Polysorbate 80	0
Propylene glycol	1 (5.0)

associated with kernicterus. There are alternatives to these medications for the specific patient population they affect. This is also the case for certain excipients, such as propylene glycol. Unfortunately, some medications may not have a therapeutic alternative and their benefit has to be established over the risk associated with them.

The findings of this review demonstrated a high number of KIDs List medications on formulary, with few having restrictions or warnings in place. There were only 4 of 47 medications on formulary that had restrictions or a warning related to pediatric patients. Of the warnings and restrictions noted in the EHR, they are broken down by age restrictions, which would be beneficial to consider in any future reviews. This does not seem to be a common practice at our institution; however, based on review by clinical specialists, minimal warnings are warranted. A major challenge with institutions is a lack of dosage forms available that can be used by pediatric patients. Some drugs are only available in solid dosage forms that do not allow for consumption by many pediatric patients because of their inability to swallow tablets or capsules. Although some manufacturers have made efforts to provide medications consumed by pediatric patients in liquid dosage forms, some of them still contain excipients in increased amounts that may cause ADEs.

At our institution, the oral liquid preparations had a high likelihood of containing potentially inappropriate excipients, whereas commonly used IV medications evaluated did not. The review of oral liquids did include all oral liquid preparations, not just those specifically marketed for pediatric patients, as well as those that are compounded products. The amount of oral liquid excipients in each product may be hard to determine if not defined in the package insert. Manufacturing companies may not have medical science liaisons assigned to generic products or may be reluctant to disclose this information for commercially available products. For compounded products, nearly all recipes contained ingredients with potentially inappropriate excipients. Because of this, preparation and use of oral liquid products without these potentially inappropriate excipients may be difficult.

Upon review of the IV medications on our institution's formulary by the pediatric clinical specialists, there were recommendations for an additional warning and education. A recommendation was made to add a warning to prochlorperazine to indicate it should not be ordered in patients younger than 2 years. This recommendation was accepted because of prochlorperazine being prescribed when the preferred agent is unavailable. It was also suggested that the KIDs List publication, highlighting the formulary medications along with the risk and rationale for each recommendation, be shared with the pediatric pharmacists upon annual competency assessment and also made available as an electronic reference. This information will also be evaluated in the annual assessment. Education should also be provided to the institutional purchaser to ensure any new medications brought into the organization are reviewed for appropriateness in the context of the KIDs List, including the presence of excipients. Especially during times of shortages, it may be necessary to purchase from a different manufacturer, which may contain different excipients. In addition, it should be noted that the presence of a medication or excipient on the KIDs List does not necessarily mean that it should not be on the formulary of a pediatric hospital or eliminated from solutions altogether, but it should be evaluated in the context of the patient and clinical situation.

Future directions include examining the formulary agents further for possible removal from pediatric use or removal from formulary, if feasible. Medications that cannot be removed from pediatric use will be investigated for implementation of restrictions or warnings as well as age-based order presentations within the EHR based on strength of recommendation and quality of evidence. Appropriate implementation of restrictions for formulary products as it relates to excipients will require periodic reevaluation because of manufacturer-specific excipients and the potential for institutional supply containing products from multiple manufacturers as a result of medication shortages (e.g., fentanyl, dexmedetomidine). Further integration into order entry to alert providers of potential risk is an option and would necessitate a similar reevaluation process and alert adjustments based on the most current manufacturer(s) and excipients. For the medications that currently have warnings, it will be prudent to inspect the effectiveness of these warnings to determine the most appropriate warning to implement for future KIDs List medications. Another area that will need to be further explored is all IV medications used in pediatrics for excipients because this project was limited to the most frequently prescribed medications.

Limitations to our evaluation include an inability to completely assess the impact of the excipients because the amount was not consistently listed in the package inserts. Another limitation is that only the manufacturers available at the time of review in the hospital were evaluated. Last, fully elucidating the amount of the listed inappropriate excipients is difficult to determine because of a lack of transparency in package inserts and manufacturers sharing details that may be considered proprietary information.

Conclusion

In conclusion, there are several medications listed in the KIDs List that are included in our institution's formulary, a large academic medical center caring for pediatric and adult patients. It was found that minimum warnings associated with their use in pediatric patients are built into the EHR. The products used for all oral

solutions and suspensions compounded at our facility contain at minimum 1 excipient with warnings for pediatric patients; therefore, eliminating the use of these products would not be feasible. Implementing recommendations from the KIDs List is a multistep process that will likely require many cycles of review to fully evaluate an institution's formulary.

Article Information

Affiliation. UF Health Shands Children's Hospital (AG, SL, LT, TS, TH, AL, AG), Gainesville, FL.

Correspondence. Alexandra Cooper, PharmD; amg45040@gmail.com

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