

Title: Methods for detecting pediatric adverse drug reactions from the electronic medical record

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Abstract:

Adverse drug reactions (ADRs) are common, yet are often underreported making them difficult to track and study. Prospective pharmacovigilance programs significantly increase detection and reporting of ADRs. The aim of this pilot study was to apply triggers used by a prospective pharmacovigilance program at a free-standing children's hospital to retrospectively detect ADRs at our institution, therefore determining if these methods could be replicated and provide the basis for implementation of a prospective pharmacovigilance program. In 2019, our institution had 22,000 inpatient admissions and 51,000 emergency room visits and had 21 ADRs voluntarily reported in an electronic medication safety tracking system. Additional ADRs were identified by methods including new or modifications to the patient's allergy profile in the electronic medical record (EMR) and International Classification of Disease (ICD) codes. We identified 754 unique patients with changes to allergy profile and 5,719 ICD codes in 3,966 unique patients to evaluate. These triggers prompted screening of the EMR to validate the ADR, and we identified 280 ADRs occurring in 2019. Eight (2.8%) were identified solely by the electronic medication safety tracking system, 64 (23%) were identified by the allergy list, 110 (39%) were identified only by ICD coding, and the remaining 98 (35%) were identified by multiple methods. The use of triggers followed by review of the EMR identified thirteen-fold more ADRs than were voluntarily reported, illustrating the need for an active pharmacovigilance service and the successful use of multi-modal methods to detect and track ADRs.

Keywords:

Pediatrics, pharmacovigilance, Drug-Related Side Effects and Adverse Reactions, electronic health record, patient safety

Introduction:

The World Health Organization (WHO) describes adverse drug reactions (ADRs) as unintended harmful effects that occur when drugs are given at standard therapeutic doses.¹ Frequently ADRs occur, but are often not reported.² The presence of a pharmacovigilance service has been shown to greatly increase timely documentation of ADRs within the medical record.³⁻⁸ Currently Riley Hospital for Children, Indianapolis, IN, a 350 bed free-standing children's hospital that has approximately 22,000 admissions or observations and

51,000 emergency room visits annually does not have a prospective pharmacovigilance program. Children's Mercy Hospital, Kansas City, MO, a free-standing children's hospital of similar size has an active prospective pharmacovigilance program where ADRs are identified by several hospital specific daily reports and International Classification of Disease (ICD) codes.⁹ These ADRs are then reviewed by a pharmacist and entered into the electronic medical record (EMR).^{8, 10} The aim of this pilot study was to apply triggers used at Children's Mercy Hospital to retrospectively detect ADRs at Riley Hospital for Children and determine if these methods could be replicated to provide the basis for a new prospective pharmacovigilance program.

Methods:

Following Riley Hospital for Children institutional review board exempt approval, triggers used by Children's Mercy Hospital (Table 1) to identify potential ADRs were applied retrospectively at Riley Hospital for Children from January 1- December 31, 2019. In a recent publication by Children's Mercy Hospital, 37% of all ADRs were detected by an automated daily report that pulls any allergy/ADR that had newly been entered into a patient's ADR profile, 15% were identified by an automated daily report that pulled any patient that has an active order on his/her medication administration record, but the same or similar medication in the allergy/ADR profile, 22% were identified by a report generated through EMR utilizing the below billing codes (Table 2), 15% were independently identified by the drug safety service pharmacist, and <3% were identified by diphenhydramine orders, ADR referrals directly to the pharmacovigilance program, or the sedation report.⁸ Because the majority of Children's Mercy Hospital ADRs were identified by allergy/ADR lists and ICD codes, these triggers were used at Riley Hospital for Children to generate lists of possible ADRs for manual EMR review to collect data and confirm the validity of the ADR trigger. Both institutions have the same EMR, yet institutional specific differences exist therefore

unique institution specific reports used at Children's Mercy Hospital were adapted for retrospective review at Riley Hospital for Children (Table 1). The initial ICD codes utilized were those that were included in the Children's Mercy Hospital report, then once true ADRs were identified, all other relevant ICD codes related to that ADR were also recorded. Based on this initial review, a secondary list of ICD codes was added to identify more potential ADRs, these are marked with an asterisk on Table 2.

Severity of ADRs was reviewed and assigned to mild, moderate, or severe according to a modified Hartwig's Severity Assessment Tool.¹¹ A mild reaction is when the drug was continued without any treatment, a moderate reaction was when the drug was stopped and/or required additional treatment, and a severe reaction caused hospital admission, increased level of care (if already hospitalized), permanent disability, delayed discharge, or was life threatening.^{10, 11} Adverse drug reaction validation was performed by reading clinician progress notes, nursing assessment notes, review of medication administration records, and comments in the allergy profile. Detailed information of ADR treatment and implemented drug were recorded and any ADR that was in question was independently reviewed by a pharmacist in order to confirm that the ADR should be included. In addition to the allergy and ICD code trigger lists, we also ran a report for all ADRs voluntarily reported in the hospital medication safety and adverse event reporting system.

Once an ADR was validated, data were recorded for the implicated drug, drug class, detailed reaction, general type of reaction, severity, place where medication was administered and where ADR was treated, the addition or absence of the drug on the patient allergy profile, and any ICD codes associated with that date or admission that were used to describe the ADR, therefore multiple ICD codes could be used for a single ADR. The patient allergy profile is part of the electronic medical record and allows the clinician to document allergies or ADRs and include detailed reactions and severity, yet these details are not required for completion.

Results:

In 2019, 21 ADRs were reported in the electronic medication safety tracking system. All were validated by manual chart review as ADRs. A data query identified 1048 new or modified allergies entered into the allergy profile of 754 unique patients, 162 (21%) of these were validated as ADRs. A report of ICD codes identified 5,719 codes in 3,966 unique patients and 203 (5%) were verified and confirmed as ADRs (Table 2). Of the 203 ADRs identified by ICD codes, 97 were coded by multiple ICD codes. The sensitivity of individual ICD code to detect an ADR ranged from 0-100%, with a median of 9%.

Eight of the 280 ADRs were detected by all three methods (electronic medication safety tracking system, ICD, and allergy list), 85 were detected by both ICD codes and allergy lists, and 5 were detected by both the event reporting and allergy lists. Collectively using all of the above triggers, we identified 280 ADRs at Riley Hospital for Children in 2019 and only 21 of these ADRs (7.5%) were voluntarily reported in the hospital event reporting system (Figure 1). The most common reason for the false positive in detecting the ADRs within our study period of 2019 was that the allergy actually occurred prior to 2019 but it was newly entered, or comments were edited during this hospital encounter.

Out of the total 280 ADRs identified, 39 were classified as mild, 150 as moderate, and 91 were classified as being severe ADRs based on the modified Hartwig's Severity Assessment Tool. Of the 21 ADRs were reported in the electronic medication safety tracking system 6 were mild, 7 were moderate, and 8 were severe.

Discussion:

We report the feasibility of integrating the approaches of an existing prospective pharmacovigilance program to identify ADRs at our institution. Specifically, our results

highlight three key findings: 1) voluntary reporting systems for ADRs result in low ADR detection highlighting the need for active pharmacovigilance, 2) ICD codes are not specific for ADRs and often ineffective for ADR capture, and 3) review of new and modifications to patient allergy profiles greatly enhance ADR detection.

As shown in many previous studies, voluntary reporting of ADRs is low in the absence of an active pharmacovigilance program.^{3, 5, 6, 8, 10} In 2019, only 21 ADRs were reported in the Riley Hospital for Children electronic medication safety tracking system. After this extensive review of more than 4,700 EMRs and applying multiple detection methods, we identified 280 ADRs. This is 13-fold higher than what was voluntarily reported. Both Riley Hospital for Children and Children's Mercy Hospital are of similar size (~350 bed) free-standing children's hospitals, therefore the number of ADRs would be expected to be similar. In an 8-year period from 2010 – 2018, 3,065 total ADRs or approximately 383 ADRs per year were reported at Children's Mercy Hospital.⁸ As previously noted, triggers related to the allergy profile and selected ICD codes accounted for 75% of the Children's Mercy Hospital ADRs. Using similar methods to detect changes in allergy profile and a more extensive list of ICD codes to retrospectively detect ADRs at Riley Hospital for Children we identified 280 ADRs. This number is reassuring and within the expected range of ADRs for a hospital our size. Interestingly, ADR severity did not seem to be a factor in voluntary reporting. As one might expect and as previously shown, severe ADRs would be more likely to be reported than mild ADRs,^{8, 12} however this was not the case with voluntary electronic medication safety tracking system at Riley Hospital for Children in 2019. Voluntary reported ADRs at Riley Hospital for Children were fairly equally distributed with 6 mild, 7 moderate, and 8 severe. Additionally, we identified 83 severe ADRs that occurred at Riley Hospital for Children in 2019 that were not voluntarily reported.

The ICD codes used in this review detected nearly 73% of the total ADRs, but nearly 4,000 EMRs were manually reviewed in order to identify these. The lack of sensitivity of ICD codes make identifying ADRs very labor intensive. Seven ICD codes had sensitivity of \geq

75%, yet these ICD codes only accounted for 22 ADRs. Three ICD codes included in our methods did not detect any ADRs. The lack of sensitivity of ICD codes for detecting ADRs has been previously described as having high rates of miscoding resulting in lack of cause and effect.¹³ Aside from general ICD codes such as R21 (rash and other nonspecific skin eruption) not being drug related, the most common false positive was when a medication allergy was charted in an admission note and was then coded during that admission even though the reaction occurred at an earlier date, therefore if the goal of the pharmacovigilance program is to detect new ADRs, this method would need to be refined as not to capture all historic ADRs or allergies. As machine learning and medical informatics improve and as ICD coding expands, these may be more useful for ADR detection in the future.

The EMR allergy profile is not limited to only ADRs, so the allergy list also resulted in a low sensitivity. Although this may not be true for all institutions, at our institution, often the allergy profile is used to list drugs that should be avoided when the potential risk for drug-drug or drug-disease interactions are high, and no ADR occurred. For example, many patients on immunosuppression post-solid organ transplant have erythromycin added to the allergy profile so that computer decision support alerts will fire for this serious drug interaction with concomitant immunosuppressive agents. Because this is listed as an allergy, in our review, we discovered that this was coded with ICD codes such as Z88.1, allergy status to antibiotic. Additionally, clinicians may add nephrotoxic medications to the allergy profile of patients with chronic kidney disease or add propofol to the allergy profile of a patient with a particular metabolic disease as a way to be more cautious and have confidence that computer decision support alerts would pick-up this potential interaction to prevent drug administration.

In a recent study evaluating the accuracy of EMR drug safety and computer decision support alerts in 41 pediatric hospitals, the authors report potential drug errors were detected in an average of 62% of test scenarios, but that ranged from 23 – 91%.¹⁴ This highlights the

limitations of computer decision support alerts and how some clinicians take extra steps to document drugs in the allergy list as computer decision support may miss disease specific or clinical circumstance that could result in an adverse event. Although the allergy profile is not the place for these preventative strategies for avoiding drug errors, if the allergy profile is used, there is a need for detailed notes so that the particular reaction or contraindication is clear. Because of these flaws in the EMR, a manual review is necessary as an automated process may fail to capture ADRs in the absence of detailed descriptions for avoidance of drugs. Additionally, in our report methods, we included both new and modifications to the allergy profile, so if an allergy or reaction was modified, this would occur on a report. Although this method is useful in not missing any new reactions to the same medication, this also resulted in many false positives, detecting ADRs that had occurred in the years prior to the study inclusion.

There may not be a “perfect equation” for active pharmacovigilance but including drug specific ICD codes and ICD codes for severe reactions such as anaphylaxis should be included. General ICD codes such as R21 are not sensitive to ADRs, but coupled with other codes, modifications to allergies, and potentially other medications, it may be possible to use machine learning to extract potential ADRs with a high degree of sensitivity and specificity.

Conclusion:

Voluntary reporting is not effective for tracking and studying ADRs. The sensitivity of ICD codes for ADRs are highly variable. Applying multifactorial methods including computer-generated reports of specific ICD codes and new and modified allergies coupled with manual EMR review resulted in a 13-fold increase of ADRs in a pediatric hospital.

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Figure legend:

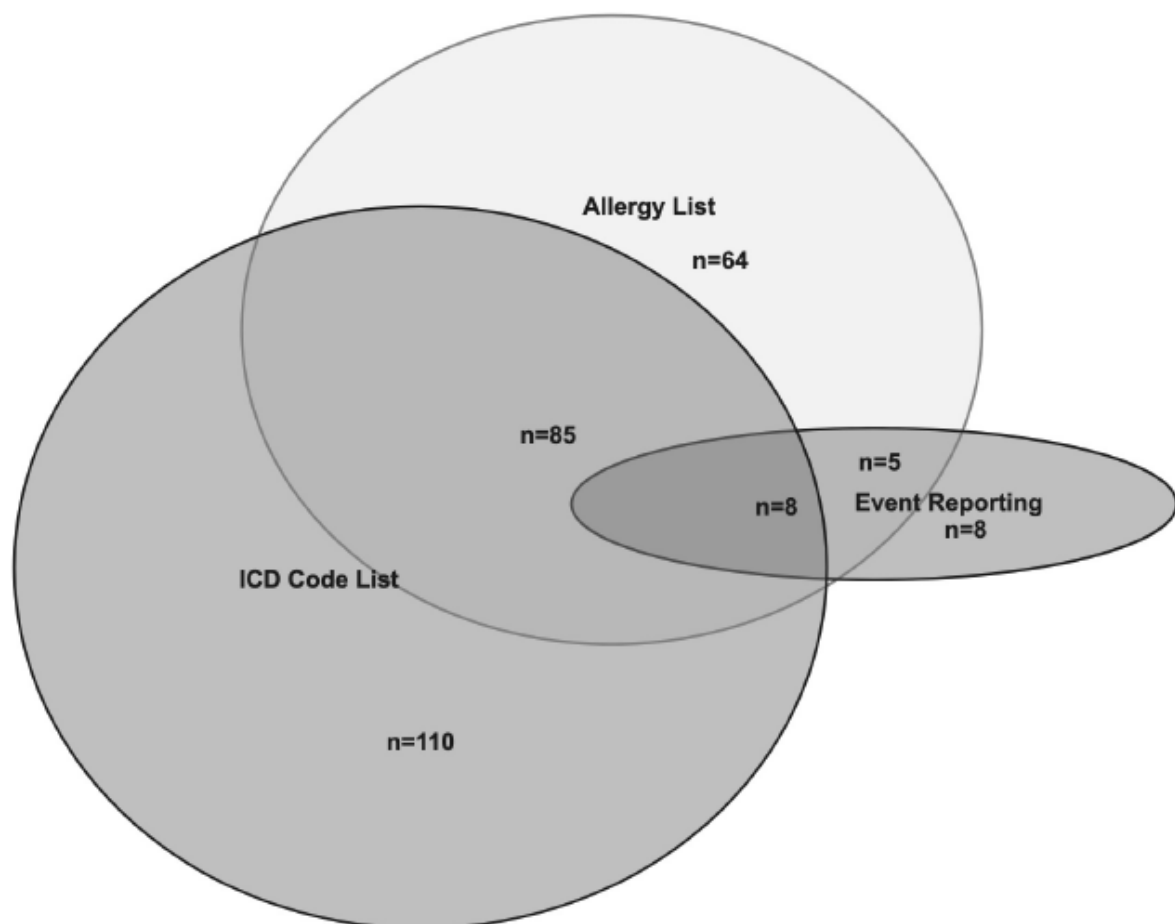


Figure 1: Identification methods for ADR detection

This diagram illustrates the overlap of multiple methods for identifying ADRs. The three detection methods were voluntarily reported in an electronic medication safety tracking system (event reporting), new additions or modifications to the electronic medical record allergy profile (allergy list), and selected ICD codes (ICD code list).

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TABLE 1: Adverse drug reactions detection triggers

Children's Mercy Hospital Report with Description	Riley Hospital for Children Retrospective Approach
Newly entered ADR: Automated daily report that pulls any ADR that has newly been entered into a patient's ADR profile	Reviewed all newly entered and modifications to patient allergy profile
Discontinued due to ADR: Automated daily report that pulls any patient that has an active order on his/her medication administration record, but the same or similar medication in the ADR profile	
ICD code: Report generated through electronic medical record utilizing selected billing codes	Reviewed all billing codes included on Children's Mercy Hospital report (Table 2)
ADR Referral: Voluntary notification built within EMR, sends a notification to the drug safety service pharmacist	Collected and reviewed all incidences of ADRs that were voluntarily reported into the online event reporting system
Diphenhydramine trigger: Any patient that has a diphenhydramine order on his/her medication administration record	5,332 completed orders for IV diphenhydramine. This was not feasible to retrospectively review.
Sedation report: Nursing sedation documentation form, question asking if ADR occurred during procedure	Not available in EMR, Riley Hospital for Children uses paper sedation documentation

ADR, adverse drug reaction

TABLE 2. Identification of ADRs by ICD codes

ICD Code	Description	5719 codes in 3966 unique patients [†]	Confirmed ADRs (N, %)	Confirmed ADRs captured by multiple ICD codes (N, %) ^{††}	Confirmed ADRs Identified on both ICD list & allergy list (N, %) ^{††}
B09	Unspecified viral infection characterized by skin and mucous membrane lesions	234	5, 2%	4, 80%	3, 60%
D59.9	Acquired hemolytic anemia, unspecified	16	0, 0%	0, 0%	0, 0%
D70.1	Agranulocytosis secondary to cancer chemotherapy	153	6, 4%	3, 50%	5, 83%
G24.02	Drug induced acute dystonia	11	5, 45%	2, 40%	2, 40%
L23.3*	Allergic contact dermatitis due to drugs	3	1, 33%	1, 100%	1, 100%
L27.0*	Drug rash	76	31, 41%	24, 77%	12, 39%
L27.1	Localized skin eruption due to drugs and medicaments taken internally	25	1, 4%	1, 100%	1, 100%
L50.0	Allergic urticaria	21	2, 10%	1, 50%	1, 50%
L50.8*	Urticaria, chronic or periodic	93	7, 8%	7, 100%	4, 43%
L50.9	Urticaria, unspecified	314	11, 4%	10, 91%	1
L51.1*	Stevens-Johnson Syndrome	4	3, 75%	3, 100%	2, 67%
L51.2*	Toxic epidermal necrolysis	4	1, 25%	1, 100%	1, 100%
L51.9*	Erythema multiforme, unspecified	23	4, 17%	4, 100%	3, 75%
R21	Rash and other nonspecific skin eruption	2434	80, 3%	50, 63%	28, 35%
T36.0X5A	Adverse effect of local antifungal, anti-infective and anti-inflammatory drugs, initial encounter	4	4, 100%	3, 75%	1, 25%
T36.95XA*	Adverse effect of unspecified systemic antibiotic	54	5, 9%	4, 80%	2, 40%
T37.0X5A*	Adverse effect of sulfonamides, initial encounter	2	2, 100%	2, 100%	1, 50%
T37.1X5A*	Adverse effect of antimycobacterial drugs initial encounter	5	4, 80%	1, 25%	4, 100%
T40.2X5A*	Adverse effect of other opioids, initial encounter	60	5, 8%	2, 40%	4, 80%
T42.1X5A*	Adverse effect of other opioids, subsequent encounter	2	0, 0%	-	-
T42.6X5A*	Adverse effect of other antiepileptic and sedative-hypnotic drug	26	9, 35%	1, 11%	3, 33%
T43.4X5A*	Adverse effect of butyrophenone and thiothixene neuroleptics, initial encounter	3	3, 100%	3, 100%	3, 100%
T45.1X5A*	Adverse effect of antineoplastic and immunosuppressive drugs, initial encounter.	161	12, 7%	6, 50%	9, 75%
T46.5X5A*	Adverse effect of calcium-channel blockers, initial encounter.	3	3, 100%	3, 100%	2, 67%
T49.0X5A	Adverse effect of local antifungal, anti-infective and anti-inflammatory drugs, initial encounter	2	1, 50%	0, 0%	1, 100%
T50.905A*	Adverse effect of unspecified drugs, medications, or biological substances	31	13, 42%	4, 31%	9, 69%
T78.2XXA	Anaphylactic shock, unspecified, initial	55	2, 4%	0, 0%	1, 50%

	encounter				
T78.3XXA	Angioneurotic edema, initial encounter	22	2, 9%	1, 50%	1, 50%
T78.40XA*	Allergy, unspecified, initial	496	19, 4%	13, 68%	1, 5%
T78.49XA	Other allergy, initial encounter	3	0, 0%	-	-
T80.69XA*	Serum reaction due to other serum, initial encounter	27	12, 44%	8, 67%	1, 8%
T88.6XXA*	Anaphylactic reaction due to adverse effect of correct drug or medicament properly administered, initial encounter	3	3, 100%	3, 100%	2, 67%
T88.7XXA*	Unspecified adverse effect of drug or medicament, initial encounter.	12	1, 8%	1, 100%	0, 0%
Z88.0*	Allergy status to penicillin	391	9, 2%	9, 100%	5, 56%
Z88.1*	Allergy status to antibiotic	550	32, 6%	10, 31%	28, 88%
Z88.2*	Allergy status to sulfonamides	56	3, 5%	3, 100%	1, 33%
Z88.5*	allergy status to narcotic agent	94	6, 6%	2, 33%	6, 100%
Z88.6*	Allergy status to analgesic agent	160	4, 3%	3, 75%	3, 75%
Z88.7*	allergy status to serum and vaccine	7	1, 14%	1, 100%	0, 0%
Z88.8*	Allergy status to other drugs, medicaments and biological substances	72	4, 6%	2, 50%	4, 100%
Z88.9*	Allergy status to unspecified drugs, medications, biological substances	22	5, 23%	4, 80%	1, 20%

*Codes added based on other billing codes discovered during documented ADRs

† Some patients had multiple ICD codes

†† Percentages are based on confirmed ADRs and not total ICD codes screened