Rising drug allergy alert overrides in electronic health records: an observational retrospective study of a decade of experience.

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Abstract:
Objective: There have been growing concerns about the impact of drug allergy alerts on patient safety and provider alert fatigue. We aimed to explore the common drug allergy alerts over the last ten years and the reasons why providers tend to override these alerts.
Design: Retrospective observational cross-sectional study (2004-2013).
Materials and Methods: Drug allergy alert data (n= 611,192) were collected from two large academic hospitals in Boston, MA (USA).
Results: Overall, we found an increase in the rate of drug allergy alert overrides, from 83.3% in 2004 to 87.6% in 2013 ($p<.001$). Alarmingly, alerts for immune mediated and life threatening reactions with definite allergen and prescribed medication matches were overridden 72.8% and 74.1% of the time, respectively. However, providers were less likely to override these alerts compared to possible (cross-sensitivity) or probable (allergen group) matches ($p<.001$). The most common drug allergy alerts were triggered by allergies to narcotics (48%) and other analgesics (6%), antibiotics (10%) and statins (2%). Only slightly more than one-third of the reactions (34.2%) were potentially immune mediated. Finally, more than half of the overrides reasons pointed to irrelevant alerts (i.e. Patient has tolerated the medication before, 50.9%) and providers were significantly more likely to override repeated alerts (89.7%) rather than first time alerts (77.4%, $p<.001$).
Discussion and Conclusions: Our findings underline the urgent need for more efforts to provide more accurate and relevant drug allergy alerts to help reduce alert override rates and improve alert fatigue.

INTRODUCTION

Health information technology can play a key role in how we currently diagnose, treat and monitor patients. Electronic health records with computerized provider order entry systems can provide the clinician with real-time guidance and support at the point of prescribing.[1] These systems have been shown to improve the safety and quality of patient care by, for example, reducing the likelihood of medication errors and consequent patient harm.[2] One of the basic drug interaction alert types is a drug allergy checking. This provides the clinicians with an alert or reminder if the patient has a documented allergy in their electronic health record to the prescribed drug. However, clinicians can be exposed to a high number of drug allergy alerts, which can result in them experiencing alert fatigue; clinicians can often ignore or override both clinically important and unimportant alerts.[3, 4] Ignoring alerts can potentially lead to patient harm and other unintended consequences, thus many efforts are underway to improve the accuracy of the alerts and reduce clinicians' alert fatigue.[5, 6] Unfortunately, little is known about the acceptance rates and other aspects of drug allergy alerts presented to providers.

Several factors can potentially affect the providers' tendency to override the drug allergy alerts, for example the nature of the reaction associated with the alert. True immune mediated reactions are rare and can result in hives, severe hypotension, and anaphylaxis.[7] Non-immune mediated reactions and medication intolerances are more common and often present as gastrointestinal upset, nausea, and vomiting, etc.[7] It is currently unclear how often providers override these different types of reactions. Furthermore, drug allergy alerts may not be generated by an *exact* match between the allergy and prescribed medication (e.g. codeine--> codeine), but rather by a *possible* cross-reactivity association between medications that are chemically or structurally related (e.g., codeine--> oxycodone). To the best of our knowledge, no study has specifically looked at how often drug allergy alerts associated with these different types of matches are overridden and whether the quantity of alerts related to non-immune mediated reactions might potentially increase the risk of alert fatigue among providers.

In this study, we aimed to: 1) evaluate providers' drug allergy alert overrides over the last ten years (2004-2013); 2) examine the different types of reactions overridden (immune mediated vs. non-immune mediated; potentially life threatening vs. non-life threatening) and whether these related to definite, probable or possible drug-allergy matches; and 3) examine the reasons why providers chose to override these drug-allergy alerts.

METHODS

In this observational, cross sectional study, we assessed ten years of drug allergy alert records from two large academic medical centers (Brigham and Women's Hospital and Massachusetts General Hospital). Both hospitals are part of Partners Healthcare, an integrated healthcare system in the Boston area. Data were extracted from the Partners Enterprise-wide Allergy Repository (PEAR), a longitudinal allergy database shared within the Partners provider/hospital network.[8] This study is a part of a larger study focused on creating methods for natural language processing of allergy information in the electronic health records (Agency for HealthCare Research and Quality [AHRQ] grant 1R01HS022728-01). For this larger study, a database of a decade of allergy alert override trends was compiled and this data served for this analysis.

Drug allergy interaction database

In PEAR, medications are stored and encoded using a combination of proprietary (First Databank, Inc.^{TM}) and local (Partners Master Drug Dictionary) terminologies. For patients admitted to the healthcare system, providers enter patient allergy information or indicate no known allergies in the electronic health record. Drugs or drug groups causing allergy are entered as structured data while allergic reactions can be entered as structured or free text information.

The electronic health record system checks every prescribed medication against possible allergies in PEAR. Drug allergy alerts are triggered when a prescribed medication matches the stored allergy as either:

1. **Definite match**: exact match between allergen and prescribed medication (or main medication ingredient), i.e. levofloxacin --> levofloxacin.
2. **Probable match**: prescribed medication matches allergen group of the documented allergen, i.e. ciprofloxacin --> levofloxacin.
3. **Possible match**: the cross-sensitivity group of the patient's allergen matches the cross-sensitivity group of the medication ingredient, i.e. penicillin (penicillins) --> cephalexin (cephalosporins).

The knowledge base has been updated over the years, with some small additions made to some of the match types but no major systematic changes. Drug allergy alerts present several informational components to the providers, including: allergen (e.g., penicillins); the prescribed medication (e.g., amoxicillin); allergy-prescribed medication match type (e.g., definite/probable/possible as explained above); and patient's reaction(s) (e.g., anaphylaxis), if known.

We downloaded all inpatient drug allergy alerts (n= 928,962) from the PEAR database between Jan 2004 and Dec 2013. We then concentrated on the most commonly triggered drug allergy alerts with frequencies higher than 0.1% of total alerts, resulting in 611,192 records (65.8%) which were included in this analysis.

When presented with a drug allergy alert, a provider can either cancel the prescribed medication or override the drug allergy alert. If they decide to override the alert, providers in our inpatient settings are asked to enter a free text override reason. See Figure 1 for a screen-shot of a drug allergy alert. Providers' decisions and alert information are stored in PEAR. In our outpatient electronic health records, five structured override reason categories are offered to providers. These categories include: 1) Patient has tolerated the drug previously; 2) Patient reports no allergy; 3) No reasonable alternative (will monitor for reaction); 4) Patient has sensitivity but will be pre-medicated prior to medication administration; and 5) Other. Consistently with the outpatient structured reasons, we classified the inpatient free text providers' override reasons into those five categories: For example, both free text override reasons 1. "Tolerated the med" and 2. "Previously took the medication with no side effects" were classified as "Patient has tolerated the drug previously". Override reason classification was performed jointly by two study members (the first author and study research assistant) and reviewed by the study team for consistency and accuracy. Overall, there were 284,858 alert override reasons. Reasons were mostly repetitive, with mean override reason frequency appearance of 7.6 times and 23,231 unique reasons presented. All reasons were classified into one of the five abovementioned categories. Of note: at the time of the study, override reason information from only one of the participating sites (Brigham and Women's Hospital) was available, thus the reported override reasons are based on this site data.

Figure 1 (comes around here): Screen-shot of a drug allergy alert in the electronic health record.

Reaction type classification

Each alert warning lists one or more reactions that the patient is at risk of being exposed to, e.g., anaphylaxis. Our research team in collaboration with two allergy specialists (PGW and KGB), reviewed these different types of reactions as well as the current literature[7, 9, 10] and classified them into two main types: 1. Potentially immune mediated (i.e., rash or anaphylaxis) or non-immune mediated (i.e., nausea or vomiting), and 2. Potentially life threatening (i.e. anaphylaxis or bronchospasm) or non-life threatening (i.e. gastrointestinal upset or nausea).

Statistical and other procedures

Microsoft SQL Server Management Studio[11] was used to store and manage all data including allergens, medication groups, and drug allergy alert override rates/reasons. We calculated the frequencies of drug allergy alerts and reactions for the most common medication groups that triggered drug allergy alerts. To generate the medication groups we used a proprietary vocabulary developed and maintained by a vendor serving the healthcare system (First Databank, Inc.). We also examined how many times each drug allergy alert was triggered. Factors associated with drug allergy overrides were analyzed by comparing the frequencies of life threatening and immune mediated allergic reactions. We also queried the PEAR database for allergy-medication match type (i.e., definite, probable, or possible) and then compared the

frequencies of drug allergy alert overrides for immune mediated and life threatening reactions by allergen- medication match type. Statistical procedures included t-tests and chi-square tests, when appropriate. The statistical analysis and group comparisons were conducted in STATA v.11.[12] Override reasons were explored by calculating the frequencies of the drug allergy alerts override reasons recorded by the providers. This study was approved by Partners Institutional Review Board (IRB).

RESULTS

Exploring the drug allergy alerts

Figure 2 shows the most common medication groups that triggered drug allergy alerts. The most common medication group was narcotics (Figure 1). Of the 611,192 drug allergy alerts, almost half (48%) were triggered by narcotics, 10% by antibiotics, 6% other analgesics and statins (2%) (Figure 1). On average, drug allergy alerts were repeated 2.3 times after the first warning.

Figure 2 (comes around here): Medication groups associated with the most commonly triggered drug allergy alerts.

Table 1 shows the 15 most common reactions (n=438,509, 91.2% of all 627,000 reactions) presented to the provider in the drug allergy alerts. Only about one third (34.2%) of all the reactions were potentially immune mediated while 44.5% were potentially non-immune mediated and 21.3% were unknown (Table 1). In addition, the majority of alerts were triggered by potentially non-life threatening reactions (68.2%) while only 10.5% had potentially life threatening reactions and the rest (21.3%) were reactions documented as "Unknown". On average, drug allergy alerts examined in this study were associated with 1.03 allergic reactions.

Table 1: Common allergic reactions associated with drug allergy alerts in inpatient settings.

Reaction	Reaction frequency*	% Reaction out of total	Potentially immune mediated reactions	Potentially life threatening reactions
Hives or rash	128,288	20.5	Yes	No
Gastrointestinal upset	100,074	15.9	No	No
Itching	46,596	7.4	Yes	No
Vomiting	31,520	5	No	No
Nausea	28,796	4.6	No	No
Mental status change	28,001	4.5	No	Yes
Anaphylaxis	26,716	4.3	Yes	Yes
Swelling	10,573	1.7	Yes	Yes
Shortness of breath	8,036	1.3	Yes	Yes
Angioedema	7,945	1.3	Yes	Yes
Myalgia	6,066	1	No	No
Headaches	5,889	0.9	No	No
Bronchospasm or wheezing	4,709	0.8	Yes	Yes
Hypotension	3,440	0.6	Yes	Yes
Seizures	1,860	0.3	No	Yes
Other reactions (small #)	55,101	8.5	---	---
Unknown**	133,390	21.5	---	---
Total	627,000	100	214,562	65,837

*The total frequency of allergic reactions is larger than unique drug allergy alerts triggered since each unique drug allergy alert could have more than one associated reaction.
**A reaction entry documented by providers as 'Unknown' in the allergy entry section of the electronic health record.

Most of the drug allergy alerts (74.8%, n=457,316) were triggered by a probable match while the rest were based on either definite (12.2%, n=74,720) or possible (13%, n=79,156) matches.

In the analyzed common drug allergy alert subset, the override rate was 86.3%, which is slightly higher than the overall override rate of 83.9%. Interestingly, providers were less likely to override first time drug allergy alerts (77.4% overrides, n= 132,314) while repeated alerts that appeared two or more times were overridden more frequently (89.7%, n= 394,891, p< .001). In general, the rate of overrides has increased, from 83.3% in 2004 to 87.6% in 2013.

Drug – allergy match types

Overall, definite allergy-medication match type was overridden significantly less frequently (74.6%) than possible (80.7%) and probable (89.1%) match types (p<.001) (Figure 3). Potentially life threatening reactions were overridden slightly less frequently (83.6%) than unknown (85.6%) or non-life threatening (86.9%) reactions (p<.001).

Figure 3 (comes around here): Drug allergy alert override rates by allergy-prescribed medication match type, immune mediated status and life threatening status reactions.

Providers were significantly more likely to override *probable* matches for both life threatening (89.5%) and non-life threatening (87.3%) reactions whereas *definite* matches were overridden less frequently (74.1% life threatening, 75.1% non-life threatening, p<.001) (Table 2). Similar trends were identified in potentially immune mediated reactions.

Table 2: Inpatient drug allergy alert overrides by allergen-prescribed medication match types.

Reaction type	Allergy/ Medication match*	Alert Overridden N (%)**	Overall N (%)***
Immune mediated reactions			
Potentially non-immune mediated reactions	Definite	29233 (76.2)	38382 (6.3)
	Possible	8676 (83.1)	10444 (1.7)
	Probable	195315 (90.3)	216222 (35.4)
Potentially immune mediated reactions	Definite	15900 (72.8)	21827 (3.6)
	Possible	36240 (80)	45308 (7.4)
	Probable	129273 (87.7)	147427 (24.1)
Unknown reactions	Definite	10605 (73.1)	14511 (2.4)
	Possible	18961 (81)	23404 (3.8)
	Probable	83002 (88.6)	93667 (15.3)
Life threatening reactions			
Potentially non-life threatening	Definite	39,221 (75.1)	52,223 (8.5)
	Possible	37,431 (82.1)	45,603 (7.5)
	Probable	281,875 (89.5)	314,781 (51.5)
Potentially life threatening	Definite	5,887 (74.1)	7,949 (1.3)
	Possible	7,259 (73.3)	9,899 (1.6)
	Probable	41,904 (87.3)	47,989 (7.9)
Unknown	Definite	10,630 (73.1)	14,548 (2.4)
	Possible	19,187 (81.1)	23,654 (3.9)
	Probable	83,811 (88.6)	94,546 (15.5)
Total		527,205 (86.3)	611,192

* Possible types of allergy-medication matches: 1) **Definite match**: exact match between allergen and prescribed medication (or main medication ingredient), i.e. levofloxacin --> levofloxacin; 2) **Probable match**: prescribed medication matches allergen group of the documented allergen, i.e. ciprofloxacin --> levofloxacin; 3) **Possible match**: the cross-sensitivity group of the patient's allergen matches the cross-sensitivity group of the medication ingredient, i.e. penicillin (penicillins) --> cephalexin (cephalosporins).
** Percentage of alerts overridden out of total alerts for this allergy/medication match.
*** Percentage of alerts out of total alerts.

The most overridden drug allergy alerts were for statins (n=18,541, 88.3%) and narcotics (n=300,286, 88.7%) (Figure 4). Salicylate analgesics (e.g., aspirin) and penicillin alerts were overridden the least (n=16,971, 78.2% and n=49,167, 74.3%, respectively).

Figure 4 (comes around here): Drug allergy alert override rates by allergy medication group.

Table 3 shows examples of the 10 most and 10 least overridden allergy-prescribed medication combinations. Similarly to the trends presented in Table 2, the most frequently overridden alerts were triggered by *probable* allergy-prescribed medication matches while *definite* matches were overridden less frequently.

Table 3: Examples of the 10 most and 10 least overridden drug allergy alerts in inpatient settings.

Allergy	Prescribed medication generic name	Allergy-prescribed medication match	# Overrides	% Overrides***	Total alerts	% Overall alerts
10 most overridden drug allergy alerts						
Percocet	Hydromorphone 0.5 mg/ml	Probable	603	98.05	615	0.1
Morphine Controlled Release	Hydromorphone Hcl	Probable	1857	96.82	1918	0.3
Opioids - Morphine Analogues	Hydromorphone Hcl	Probable	1192	95.13	1253	0.2
Simvastatin	Rosuvastatin	Probable	1093	94.71	1154	0.2
Oxycodone 5 mg/ Acetaminophen 325 mg	Hydromorphone Hcl	Probable	1200	94.71	1267	0.2
Simvastatin	Pravastatin	Probable	1009	94.65	1066	0.2
Oxycodone Controlled Release	Hydromorphone Hcl	Probable	1686	94.61	1782	0.3
Percocet	Hydromorphone Hcl	Probable	15037	94.53	15907	2.6
Atorvastatin	Pravastatin	Probable	1743	94.47	1845	0.3
Ibuprofen	Acetylsalicylic Acid (Aspirin)	Probable	2822	92.2	3061	0.5
10 least overridden drug allergy alerts						
Penicillins	Ampicillin/Sulbactam	Probable	405	48.91	828	0.1
Meperidine	Meperidine Hcl	Definite	726	48.02	1512	0.3
Simvastatin	Simvastatin	Definite	313	47.86	654	0.1
Demerol	Meperidine Hcl	Definite	487	47.10	1034	0.2
NSAIDs	Ibuprofen	Probable	607	45.13	1345	0.2
Penicillins	Ampicillin	Probable	715	42.87	1668	0.3
Sulfa (Sulfonamide Antibiotics)	Trimethoprim/ Sulfamethoxazole Double Strength	Probable	249	40.69	612	0.1
Ibuprofen	Ibuprofen	Definite	341	39.51	863	0.1
Sulfa	Trimethoprim/Sulfamethoxazole double strength	Probable	563	39.43	1428	0.2
Percocet	Oxycodone 5 mg/ Acetaminophen 325 mg	Definite	549	37.09	1480	0.2

* HMG CoA: 3-hydroxy-3-methylglutaryl-coenzyme

** COX: cyclooxygenase

*** Percentage of alerts overridden out of total alerts for this allergy/medication combination.

Drug allergy alerts override reasons

The most common override reason was related to whether the patient had previously tolerated the medication (n=145,112, 50.9%), while (n=9,930, 3.5%) reported that patients reported that they had no allergy (Table 4). The "other" reasons (n=88,015, 30.9%) were presented as other ambiguous free-text entries, such as a single letter (e.g., "a", "D"), "pain protocol" or "OK with patient/ family". Since half of the cases were indicated as either previously tolerated or no existing allergy, we compared the rates of possibly life threatening reactions overrides without those two override groups within the hospital site where the override reasons data were available. Override trends (not shown) were similar to those presented in Table 2.

Table 4: Inpatient drug allergy alerts override reasons.

Override reason	**Override reason frequency**	**% out of total override reasons**
Patient has tolerated the drug previously	145,112	50.9
Patient reports no allergy	9,930	3.5
No reasonable alternative- will monitor for reaction	37,465	13.1
Patient has sensitivity but will be pre-medicated prior to administration	3,596	1.3
Other	88,015	30.9
Unknown	740	0.3
Total	284,858	

DISCUSSION

The goals of this study were to identify the most common drug allergy alerts over the past decade and examine factors associated with providers' tendency to override those alerts. We also examined the override reasons for the common drug allergy alerts, and identified areas for further investigation and lessons learned to potentially improve the clinical utility of the drug allergy alerting.

Exploring the drug allergy alerts

Our results suggest that, in hospital settings, almost half of the drug allergy alerts are triggered by medications from the narcotic analgesics group (i.e. morphine, codeine, etc.). Previous studies from one of the institutions analyzed here (Brigham and Women's Hospital) present an interesting trend of general increase in the rate of opioid alerts over the years: between 1995-99, one-third (32.9%) of the alerts were for narcotics;[13] followed by 39% of alerts in 2002; [14] and reaching a peak of 48% in this study. Evidence from other sites indicates that narcotic analgesics alerts can constitute up to 69% of all drug allergy alerts.[15] This trend might be

partially explained by the consistent increase in the opioid drug prescription rates over time in inpatient and outpatient settings. For instance, several recent studies have reported that opioid prescriptions increased as high as three-fold in the past two decades in the US.[16-19] In practice, this finding underlines the critical importance of managing opioid related allergies information appropriately within the computerized provider order entry systems and allergy repositories to avoid potential over-alerting.

Other common drug allergy alerts were triggered by antibiotics (especially penicillins), other analgesics and statin (HMG CoA inhibitors), responsible in total for about one-fifth of the drug allergy alerts. Those trends are similar to the previously reported findings with some minor differences.[13-15, 20] For example, we found that statins are becoming an increasingly prevalent trigger for drug allergy alerts (2% of all alerts) whereas previous studies found only minute instances of this alert. This finding is consistent with the increasing rates of statin prescriptions reported in the literature.[21]

We identified potentially life threatening and immune mediated reactions in our dataset through a series of allergy/immunology specialist consultations and relevant literature sources [7, 9, 10]. Although our approach to classifying reactions without evaluating detailed lab/pathology information has its limitations, only slightly more than one-third of the reactions were potentially immune mediated (i.e. IgE mediated or T-cell mediated reactions such as anaphylaxis or rash) and one-tenth of the reactions were potentially life threatening (i.e. anaphylaxis or angioedema). Also, only about one-tenth of the alerts were based on the definite match between the allergy and prescribed medication, while the rest were based on either the cross-sensitivity or allergy group. In practice, these findings suggest that the majority of the drug allergy alerts present adverse sensitivity or side effect information to a related medication rather than true immune mediated reactions for the medication prescribed. These findings are similar to the previously reported trends.[13, 14]

Our findings indicate an alarming trend of increasing drug allergy alert overrides over the last 10 years. Two previous studies from one of the institutions in this study (Brigham and Women's Hospital, which introduced one of the first computerized provider order entry systems over two decades ago) have shown that override rates increased from about 50% in 1995[13] to about 80% in 2002,[14] culminating in 86.3% in this study. This might suggest a general trend of increasing alert fatigue; providers are overwhelmed with frequent interruptive alerts and pay increasingly less attention to new alerts over time.[3, 4] Recent studies from other sites have also identified similar or higher drug allergy alert override rates. For example, in their study of 643 alerts Hunteman et al. found that the overall drug allergy alert override rate was 97% and alerts were overridden with a frequency of 89% in a study of 2,676 opiate drug allergy alerts.[15]

Drug class and reaction characteristics associated with provider's tendency to override drug allergy alerts

Exploring factors affecting drug allergy alert override rates, we found that alerts based on the definite match between allergy and prescribed medication were overridden significantly less frequently than non-definite type matches. Similarly, alerts with potentially immune mediated and life threatening reactions were overridden less than others. Interestingly, there was only minute difference (of about 3%) between overrides of potentially life threatening vs. non-life threatening reactions. Providers were least likely to override alerts triggered by definite match for either potentially immune mediated or life threatening reactions. Although the general alert override rates were high for either type of reactions, our findings confirm the findings of the previous studies[14, 22] and indicate that providers pay attention to the nature of the reaction and type of match between the prescribed medication and allergy. Those results also underline a critical need for further investigation - potentially using qualitative methods- to better understand providers' reasons to override even the most alarming drug allergy alerts.

Providers were more likely to override drug allergy alerts for certain medication groups more frequently than others. For example, narcotic analgesic and statin alerts were overridden in 9 out of 10 cases. Salicylate analgesic (aspirin) and penicillin alerts were among the least overridden. This might be because both of those medication groups are frequently associated with more severe reactions (i.e. NSAIDs are commonly associated with angioedema, and penicillins with anaphylaxis) than other medications.[7] Consistent with the previous literature on the topic,[14] these results suggest that future drug allergy alerts can be presented differently (i.e. non interruptive vs. interruptive manner) for different medication groups to decrease the alert fatigue.

Drug allergy alerts override reasons

We found that more than half of the alerts were triggered for medications that patients have either previously tolerated or had no allergy to and each alert was fired more than twice after its first appearance. These results are similar to Hunteman et al. study findings indicating that 49% of overrides are for medications previously tolerated by patients. [15] In addition, providers were significantly more likely to override repeated alerts that were triggered twice or more times rather than first time alerts. This indicates that providers were overriding repeated alerts rather than removing the allergy from patients' allergies lists in the electronic health records. Also, about one-third of the override reasons were classified as 'others', including single letters and other ambiguous entries. These entries are likely to be indicative of providers trying to save time and "click-out" of the time consuming tasks, such as providing free text alert override.

In order to improve the quality and safety of patient care, providers should be encouraged to update the allergy list of their patients, which includes the removal of inaccurate allergies. In fact, our outpatient electronic health record system allergy module prompts providers to remove previously tolerated allergies from patient's allergy list and similar practices should be applied in other settings/systems. However, based on the anecdotal evidence from our health system's physicians, inpatient drug allergy alerting systems might need to differ from the outpatient systems. For example, several inpatient physicians suggested that they did not feel that they

knew their patients well enough to be able to remove allergies from the list and felt that this should be done by their primary care physicians. Our team is currently involved in a qualitative study of alert overrides that is likely shed light on these questions.

Clearly, computerized provider order entry systems user interfaces must evolve to identify medications patients have no allergy to or tolerated in the past so providers are not inundated with highly irrelevant alerts.[2] Alerts to previously tolerated medications might be presented in a non-interruptive fashion (e.g., warning). Future systems should pay more attention to storage of override reason data while potentially triggering and encouraging providers to provide accurate override reasons.

Solutions to high drug allergy alert override rates may be informed by drawing on our previous experiences with drug-drug interaction tiering. For example, our health system was one of the first to develop and implement a comprehensive approach to differentiating drug–drug interaction alerts by level of severity, also called "alert tiering". Each drug-drug interaction alert was classified as: a) Level 1 alert - considered to be life threatening and the clinician is required either to cancel the order he or she is writing or discontinue the pre-existing drug order (a "hard stop"); b) Level 2 alert - less serious, but still requires action by the clinician in that the clinician is required to discontinue one or the other drug, or to select an override reason; and c) Level 3 alert - least serious alerts and are informative only, requiring no action from the clinician.[23] This tiering approach was shown to decrease the drug-drug interaction alert override rates dramatically (e.g., 0% overrides at tiered hospital vs 66% at non-tiered hospital for severe alerts and 71% vs 90% for moderate alerts, respectively).[24]

However, the tiering solutions developed so far have only limited applicability to the allergy domain. For example, level 1 "hard-stop" alerts may not be applicable to allergy because some patients can undergo drug desensitization that will potentially allow them to take the medications they were once allergic to. Also, severity of the drug allergy alert should be based on the patient reaction: life-threatening reactions (e.g, anaphylaxis or angioedema) should likely trigger interruptive alerts (level 2) while other less severe non-immune mediated reactions (e.g., nausea or myalgia) should trigger non-interruptive alerts (level 3). Further research is critically needed to better understand and develop a tiering structure for drug allergy alerts in addition to educating providers on the intricacies of accurate documentation of allergies and adverse sensitivities in EHRs.[25, 26]

Limitations

This study has several limitations. First, although we analyzed the largest dataset of drug allergy alerts reported so far, our data was limited to two large academic hospitals in Boston, which limits the generalizability of our findings. In addition, although based on the literature and expert panel discussions, our classification of potentially life threatening and potentially immune mediated reaction is an estimation based on the captured patient reactions rather than a

conclusive statement based on patient lab/ pathology or allergy tests. Also, drug allergy alert override reasons were available from only one of the study sites, which somewhat limits our inference for this data. Lastly, due to the large size of our dataset, we did not perform chart review on the patients whose drug allergy alerts were overridden to draw definitive conclusions about safety of current override practices.

CONCLUSIONS

This study examined one of the largest reported allergy datasets for trends in the most commonly triggered drug allergy alerts in inpatient settings. The most common drug allergy alerts were triggered by allergies to narcotics (almost half of the alerts) and other analgesics, several antibiotic groups, and statins. Only slightly more than one-third of the reactions were potentially immune mediated. Over the past decade, we identified an alarming trend of constantly increasing rate of drug allergy alert overrides, culminating in 87.6% in 2013. The drug allergy alert override rates were high for both potentially immune mediated or life threatening reactions. Overall, definite allergy and prescribed medication matches were overridden less frequently compared to probable or possible matches. The most overridden medication groups were the narcotic analgesics and statins. Finally, more than half of the overrides reasons pointed to irrelevant alerts (i.e. Patient has tolerated the medication before) and providers were significantly more likely to override repeated alerts rather than first time alerts. Our findings underline the urgent need for more efforts focused on providing more accurate and relevant drug allergy alerts for providers to decrease alert overrides and alert fatigue. Finally, further investigation is needed into providers' reasons for overriding drug allergy alerts.

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REFERENCES

1. ONC. Computerized Physician Order Entry (CPOE) for Medication Orders: Office of National Coordinator for Health IT; 2014. Available from: http://www.healthit.gov/providers-professionals/achieve-meaningful-use/core-measures/cpoe-meaningful-use.

2. Kuperman GJ, Bobb A, Payne TH, Avery AJ, Gandhi TK, Burns G, et al. Medication-related clinical decision support in computerized provider order entry systems: a review. Journal of the American Medical Informatics Association : JAMIA. 2007;14(1):29-40.

3. Nanji KC, Slight SP, Seger DL, Cho I, Fiskio JM, Redden LM, et al. Overrides of medication-related clinical decision support alerts in outpatients. Journal of the American Medical Informatics Association : JAMIA. 2014;21(3):487-91.

4. Smithburger PL, Buckley MS, Bejian S, Burenheide K, Kane-Gill SL. A critical evaluation of clinical decision support for the detection of drug-drug interactions. Expert opinion on drug safety. 2011;10(6):871-82.

5. Harrington L, Kennerly D, Johnson C. Safety issues related to the electronic medical record (EMR): synthesis of the literature from the last decade, 2000-2009. Journal of healthcare management / American College of Healthcare Executives. 2011;56(1):31-43; discussion -4.

6. Kesselheim AS, Cresswell K, Phansalkar S, Bates DW, Sheikh A. Clinical decision support systems could be modified to reduce 'alert fatigue' while still minimizing the risk of litigation. Health affairs. 2011;30(12):2310-7.

7. Burks AB, W; Holgate, ST; Lemanske, RF; O'Hehir, RE; Adkinson, NF; Bochner, BS Middleton's Allergy: Principles and Practice. 8 ed: Elsevier Health Services; 2013.

8. Kuperman GJ, Marston E, Paterno M, Rogala J, Plaks N, Hanson C, et al. Creating an enterprise-wide allergy repository at Partners HealthCare System. AMIA Annual Symposium proceedings / AMIA Symposium AMIA Symposium. 2003:376-80.

9. DeDea L. Prescribing opioids safely in patients with an opiate allergy. JAAPA : official journal of the American Academy of Physician Assistants. 2012;25(1):17.

10. Joint Task Force on Practice P, American Academy of Allergy A, Immunology, American College of Allergy A, Immunology, Joint Council of Allergy A, et al. Drug allergy: an updated practice parameter. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology. 2010;105(4):259-73.

11. Microsoft SQL Server Management Studio. Microsoft; 2008.

12. STATA. 11 ed: StataCorp; 2010.

13. Abookire SA, Teich JM, Sandige H, Paterno MD, Martin MT, Kuperman GJ, et al. Improving allergy alerting in a computerized physician order entry system. Proceedings / AMIA Annual Symposium AMIA Symposium. 2000:2-6.

14. Hsieh TC, Kuperman GJ, Jaggi T, Hojnowski-Diaz P, Fiskio J, Williams DH, et al. Characteristics and consequences of drug allergy alert overrides in a computerized physician order entry system. Journal of the American Medical Informatics Association : JAMIA. 2004;11(6):482-91.

15. Hunteman L, Ward L, Read D, Jolly M, Heckman M. Analysis of allergy alerts within a computerized prescriber-order-entry system. American journal of health-system pharmacy : AJHP : official journal of the American Society of Health-System Pharmacists. 2009;66(4):373-7.

16. Daubresse M, Chang HY, Yu Y, Viswanathan S, Shah ND, Stafford RS, et al. Ambulatory diagnosis and treatment of nonmalignant pain in the United States, 2000-2010. Medical care. 2013;51(10):870-8.

17. Jena AB, Goldman D, Weaver L, Karaca-Mandic P. Opioid prescribing by multiple providers in Medicare: retrospective observational study of insurance claims. Bmj. 2014;348:g1393.

18. Manchikanti L, Helm S, 2nd, Fellows B, Janata JW, Pampati V, Grider JS, et al. Opioid epidemic in the United States. Pain physician. 2012;15(3 Suppl):ES9-38.

19. Mazer-Amirshahi M, Mullins PM, Rasooly I, van den Anker J, Pines JM. Rising opioid prescribing in adult U.S. emergency department visits: 2001-2010. Academic emergency medicine : official journal of the Society for Academic Emergency Medicine. 2014;21(3):236-43.

20. Rimawi RH, Cook PP, Gooch M, Kabchi B, Ashraf MS, Rimawi BH, et al. The impact of penicillin skin testing on clinical practice and antimicrobial stewardship. Journal of hospital medicine : an official publication of the Society of Hospital Medicine. 2013;8(6):341-5.

21. Ward S, Lloyd Jones M, Pandor A, Holmes M, Ara R, Ryan A, et al. A systematic review and economic evaluation of statins for the prevention of coronary events. Health technology assessment. 2007;11(14):1-160, iii-iv.

22. Ariosto D. Factors Contributing to CPOE Opiate Allergy Alert Overrides. AMIA Annual Symposium proceedings / AMIA Symposium AMIA Symposium. 2014.

23. Shah NR, Seger AC, Seger DL, Fiskio JM, Kuperman GJ, Blumenfeld B, et al. Improving acceptance of computerized prescribing alerts in ambulatory care. Journal of the American Medical Informatics Association : JAMIA. 2006;13(1):5-11.

24. Paterno MD, Maviglia SM, Gorman PN, Seger DL, Yoshida E, Seger AC, et al. Tiering drug-drug interaction alerts by severity increases compliance rates. Journal of the American Medical Informatics Association : JAMIA. 2009;16(1):40-6.

25. Campbell EM, Sittig DF, Ash JS, Guappone KP, Dykstra RH. Types of unintended consequences related to computerized provider order entry. Journal of the American Medical Informatics Association : JAMIA. 2006;13(5):547-56.

26. AHRQ. Computerized Provider Order Entry - Inpatient: Agency for Healthcare Research and Quality; 2013. Available from: http://healthit.ahrq.gov/ahrq-funded-projects/emerging-lessons/computerized-provider-order-entry-inpatient.