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Risk factors for allergy documentation in electronic health record: a retrospective study in a tertiary health center in Switzerland.

THESE

préparée sous la direction du Professeur Camillo Ribi

et présentée à la Faculté de biologie et de médecine de
l'Université de Lausanne pour l'obtention du grade de

DOCTEUR EN MEDECINE

par

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Médecin diplômé de la Confédération Suisse
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Risk factors for allergy documentation in electronic health record: a retrospective study in a tertiary health center in Switzerland

sans se prononcer sur les opinions exprimées dans cette thèse.

Directeur	Professeur Camillo Ribi
Vice-directeur de l'Ecole doctorale	Professeur John Prior

Lausanne, le 10.10.2023

pour Le Doyen
de la Faculté de Biologie et de Médecine

Monsieur le Professeur John Prior
Vice-Directeur de l'Ecole doctorale

Résumé du travail de thèse

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Risk factors for allergy documentation in electronic health record: A retrospective study in a tertiary health center in Switzerland

Maxime Ringwald, Prof. Dr. Med. Camillo Ribi

Les réactions indésirables aux médicaments (RIM) sont définies par l'Organisation Mondiale de la Santé comme une réaction nocive et non voulue sur un principe actif, se produisant aux posologies normales utilisées chez l'homme pour la prophylaxie, le diagnostic, le traitement d'une maladie ou la modification d'une fonction physiologique. Parmi les causes les plus fréquentes de RIM figure l'hypersensibilité aux médicaments (allergie médicamenteuse dans le langage courant). La plupart des hôpitaux utilisent un dossier médical informatisé pour informer les professionnels de la santé d'une hypersensibilité médicamenteuse ou autres allergies. Des enregistrements erronés ou imprécis peuvent entraîner une surcharge du système, résultant en des évictions injustifiées de molécules et finalement une augmentation des coûts de la santé.

A travers notre étude, nous nous sommes intéressés aux hypersensibilités documentées chez les patients hospitalisés au Centre Hospitalier Universitaire Vaudois (CHUV). Pour ce faire, nous avons mené une étude rétrospective sur les patients hospitalisés au moins 24 heures au CHUV entre 2011 et 2021. Après accord de la commission d'éthique du canton de Vaud, les données anonymisées ont été obtenues. Du fait de la possibilité de renseigner les allergies en utilisant une liste prédéfinie ou manuellement, les données ont été harmonisées à l'aide d'une base de données harmonisée des principaux allergènes. L'analyse statistique a été effectuée par la suite.

Parmi les 192'444 patients répondant aux critères d'inclusion, 16% avaient au moins une allergie référencée. Les allergies médicamenteuses représentaient 60% de toutes les alertes, principalement les antibiotiques béta-lactames (30%), les AINS (11%) et les produits de contraste iodés (7%). L'âge médian lors de la première hospitalisation et la durée d'hospitalisation étaient plus élevés dans le groupe des patients allergiques. Il y avait également plus de femmes dans ce groupe (ratio 2:1). Les réactions étaient limitées à la peau dans la majorité des cas et compatible avec une anaphylaxie dans 6% des cas. Chez ceux considérés comme allergiques aux béta-lactames, le coupable était mentionné dans 19% des cas autrement référencé comme « allergique à la pénicilline ». Il était impossible de différencier si la documentation se basait sur l'anamnèse ou suite à un bilan spécialisé.

Finalement, il découle de l'étude qu'un âge avancé, une durée d'hospitalisation plus longue et le sexe féminin augmentent le risque d'avoir une documentation d'allergie dans le dossier médical informatisé. Cette étude vise à établir un état des lieux concernant l'épidémiologie de l'allergie médicamenteuse dans une population hospitalière suisse. Les retombées sont multiples tant au niveau institutionnel qu'au niveau de la pratique médicale. Ce projet s'inscrit dans une volonté d'harmoniser la documentation des allergies sur le plan national et de faciliter l'échange de ces données entre les différents centres médicaux. Ainsi, nous espérons contribuer à une diminution de la morbidité et mortalité liés à une information inconstante et souvent non transmise entre les différents intervenants.

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Original Article

Risk factors for allergy documentation in electronic health record: A retrospective study in a tertiary health center in Switzerland

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Abbreviations:
ADR, adverse drug reaction; AGEP, acute generalized exanthematous pustulosis; BLA, beta-lactam antibiotics; CHUV, Lausanne University Hospital; DH, drug hypersensitivity; DRESS, drug rash with eosinophilia and systemic symptoms; EHR, electronic health record; ER, emergency room; EPR, electronic patient record; HDM, house dust mites; ICD, international common denomination; ICM, iodinated contrast media; IQR, interquartile range; NERD, NSAID-exacerbated respiratory disease; SJS, Stevens-Johnson Syndrome; TEN, Toxic Epidermal Necrolysis; WHO, World Health Organization

ABSTRACT

Background: Most hospitals use electronic health records (EHR) to warn health care professionals of drug hypersensitivity (DH) and other allergies. Indiscriminate recording of patient self-reported allergies may bloat the alert system, leading to unjustified avoidances and increases in health costs. The aim of our study was to analyze hypersensitivities documented in EHR of patients at Lausanne University Hospital (CHUV).

Methods: We conducted a retrospective study on patients admitted at least 24 h to CHUV between 2011 and 2021. After ethical clearance, we obtained anonymized data. Because culprit allergen could be either manually recorded or selected through a list, data was harmonized using a reference allergy database before undergoing statistical analysis.

Results: Of 192,444 patients, 16% had at least one allergy referenced. DH constituted 60% of all allergy alerts, mainly beta-lactam antibiotics (BLA) (30%), NSAID (11%) and iodinated contrast media (ICM) (7%). Median age at first hospitalization and hospitalization length were higher in the allergy group. Female to male ratio was 2:1 in the allergic group. Reactions were limited to the skin in half of patients, and consistent with anaphylaxis in 6%. In those deemed allergic to BLA, culprit drug was specified in 19%, 'allergy to penicillin' otherwise. It was impossible to distinguish DH based on history alone or resulting from specialized work-up.

Conclusions: Older age, longer hospital stays, and female sex increase the odds of in-patient allergy documentation. Regarding DH, BLA were referenced in 4% of inpatient records. Specific delabeling programs should be implemented to increase data reliability and patient safety.

Introduction

The World Health Organization (WHO) defines adverse drug reactions (ADR) as harmful, unintended reactions to medicines that occur at doses normally used for treatment. Amongst others, drug hypersensitivity (DH, or simply drug allergy in everyday use) is the leading cause of ADR. In the United States of America (USA), up to one over 300 patients dies from an ADR, with DH implication around 10%.[1] DH can be further classified according to their pathophysiological mechanisms. DH can be either of immune type (drug allergy) or of non-immune type (pharmacological effects for example). Frequency of the later can be reduced by using preventive methods such as reducing the infusion rate in vancomycin administration (vancomycin is known to induce mast cell

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degranulation, historically called the "red man syndrome"). Iodinated contrast media (ICM) reaction can be prevented in most cases by antihistamine premedication.[2]

Nowadays, the most frequently reported drugs responsible for hypersensitivity reactions are beta-lactam antibiotics (BLA) and non-steroidal anti-inflammatory drugs (NSAIDs). Back in 2018, an American survey estimated drug hypersensitivity prevalence as high as 13%, with hypersensitivity to penicillin accounting for 30% of cases.[3] In 2014, a European consortium assumed a prevalence of drug hypersensitivity close to 7% in general population. Most publications agree on the fact that drug hypersensitivity is a major public health issue.[4–8]

Since 2010, Lausanne University Hospital (CHUV), which is a tertiary health care center, uses electronic health records (EHR) in order to document patients' medical records. An allergy alert system allows users to integrate information on potential allergies that are reported by the patients themselves or obtained from their medical files. Besides the culprit substance responsible for allergies, other information such as type and severity of the reaction may also be reported. This tool is meant to prevent contact with allergens such as latex during hospital stay, as well as alert during prescription of drugs to which the patient is allergic. However, such numeric alert systems present intrinsic and extrinsic flaws. Our daily practice reminds us how difficult it is to obtain precise and detailed past medical events during patient history. Correct assessment of the severity and the type of reaction by untrained personnel is often difficult. Finally, correct documentation of hypersensitivity reactions in EHR is tricky, as is the integration of alerts in modules for electronic prescription. An American study indicates that medical staff simply ignored 90−95% of system alerts related to electronic prescription.[9]

It is important not to re-expose a patient to a drug that has previously elicited hypersensitivity, unless there is no other choice and precautionary measures such as tolerance induction or pre-medication are in place. Thus, incorrect documentation of hypersensitivities can have various consequences. On the one hand, if a previous hypersensitivity reaction remains undocumented, a patient might be re-exposed to the culprit drug and experience recurrent hypersensitivity. On the other hand, unqualified reporting of poorly documented adverse events may lead to unjustified avoidance of first-line drugs, with use of second-line or third-line treatment, responsible for increase in health costs, adverse events and, in case of BLA avoidance for example, to increased antibiotic resistance. The same is true with radiocontrast agents, were incorrect documentation of hypersensitivity reactions may result in delay or avoidance of important diagnostic procedures.

As authorities and health care providers struggle to find a solution to integrate data on hypersensitivity in the planned electronic patient health record, we decided to analyze the allergy data included during the past decade in CHUV. The aim of our study is to analyze type and severity of allergies in patients hospitalized at least 24 h on the last ten years in CHUV, focusing mainly on drug hypersensitivity.

Methods

Population studied

Single-center retrospective study on patients hospitalized in CHUV for at least 24 h between June 2011 and June 2021. Soarian® (formerly Siemens AG, now Cerner, North Kansas City, Missouri, USA) is used as EHR since 2010 in CHUV. It allows documentation of medical records for in- and outpatients. Any health care professional involved in management of in-patients has access to the EHR with the possibility of recording allergies. The local ethics committee (CER-VD 2021-01784) approved the study.

Source data

In order to document an allergy in the EHR, the user (physician/nurse) has to go through three steps, or scrolling menus. The first scrolling menu selects the culprit in a defined compound list, the second the clinical symptoms presented (cutaneous reaction, eczema, urticarial, asthma, angioedema, gastrointestinal symptoms, rhino conjunctivitis and anaphylactic shock) and the third the severity of the reaction (mild/moderate/severe). Of note that the severity of the reaction is suggested by the system but can be overruled by user. When an EHR is generated, no mandatory action is needed regarding the allergy alert system. It is set by default as "no known allergy". It relies upon the contributors to the EHR to inquire and document known allergies, as per good clinical practice. The Soarian® drug database allows for introduction of multiple choices corresponding to the same active principle according to the International Common Denomination (ICD), for example, terms as 'Bactrim 200/40 syrup', 'BACTRIM', 'Bactrim forte 800/160 cpr' or 'sulfamethoxazole with trimethoprim'. Some may be listed as 'XXXX'. It is also possible to list the culprit as free text, if the textual keyboard input is not present in the reference list (e.g., 'Vampire' or 'Penizilin'). Free text entries are not taken over to the reference list. In addition, drugs entered as free text in the EHR do not trigger an alert when further electronically prescriptions are made (interaction analysis process, treatment duration …).

Data obtained from the EHR were: age of subjects, number and length of hospitalization stays over the analyzed period, medical ward and administrative responsibility, frequency of documented allergy, substances involved, type of reaction and severity.

Data processing

We compared the extracted raw allergy data to a reference harmonized allergy database containing only ICD using a Python script. The algorithm replaced free text entries of drugs in the EHR by their ICD equivalent if Levenshtein distance (comparing minimum number of character editing) was ≤ 1 or if the later character chain was contained in the former.[10]

Date and time variables were transformed to a uniform format (yyyy/mm/dd). Date unit was years, rounded up to the next integer.

For each patient fulfilling the inclusion criteria, we obtained data from all hospitalizations situated within the time frame of the study. Patients that were admitted to the Emergency Room (ER) for 24 h or more and then left the hospital were considered as having ER stays. Those merely transiting through the ER to a hospitalization ward were considered as having one stay in the given ward. For a better understanding, patients having allergies referenced in their medical records will be referred to as "the allergic group", while those without allergies as "the non-allergic group".

Substances typically eliciting respiratory symptoms such as grass or tree pollens, molds, house dust mites (HDM) and other allergens such animal dander were attributed to the aeroallergen group.

Statistics

Data analysis was performed using IBM® SPPS Statistics (Chicago, IL) and its Python add-on module. General statistics (mean, median, standard deviation, Chi-squared test and p-values) were obtained with IBM® SPPS Statistics (Chicago, IL).

Microsoft Excel and GraphPad-Prism were used to obtain data graphical representation.

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Descriptive statistics

Descriptive statistics were conducted using IBM® SPPS Statistics (Chicago, IL). Because our values were not distributed on a normal distribution, we performed a non-parametric test using a Mann–Whitney U test. Mean, median and values as interquartile range (IQR) were used for further comparison. Finally, all data were compute using a binary logistic regression process.

We performed a logistic regression using the same software. The single binary variable was whether the patient was referenced as allergic or not (0: non-allergic, 1: allergic). Independent variables were patient sex (0: male, 1: female) age at first hospitalization (expressed as years), the total number of hospitalized days and finally whether the patient transited only through the emergency room or was transferred to another ward (0: transit through ER to another inward service, 1: ER only).

Results

Of the 279,952 patients screened, 192,244 fulfilled the inclusion criteria (Fig. 1). Of these, 30,942 (16%) had at least one allergy alert, while no allergy was mentioned in 161,302 (84%).

Demographic and epidemiological characteristics of both allergic and non-allergic patients are shown in Table 1. Median age at first hospitalization was 53 (33–78) years old in the allergic population vs 36 (9–64) years in the non-allergic group ($p < 0.005$). Female to male ratio was 2:1 in the allergic group vs 1:1 in the non-allergic group ($p < 0.005$). The median number of hospitalizations per patient was 2 (1–3) in allergic vs 1 (1–2) in non-allergic patients ($p < 0.005$). The median duration of hospitalization was higher in the allergic group, being 4.25 days (3–9.25). In the non-allergic group, the median was 3 days and the corresponding IQR 4 (3–7) days. Of note, mean duration of hospitalization was slightly higher in allergic group (7.62 vs 7.39 days). ER was the most frequent hospitalization ward in both groups. The other frequent hospitalization wards are listed in Table 1.

The 51,044 substances listed in the 30,942 allergic patients were categorized in five main groups: drugs (including contrast medias used for diagnostic purposes), respiratory allergens (pollens, animal dander), insect venom (hymenoptera venom), foods (or edible substances), and contact allergens (including metals and fragrances). Substances that did not fit into the five categories were classified as 'Other'. Substance categories are listed in Figure 2. The most frequently listed allergens are displayed in Table 2.

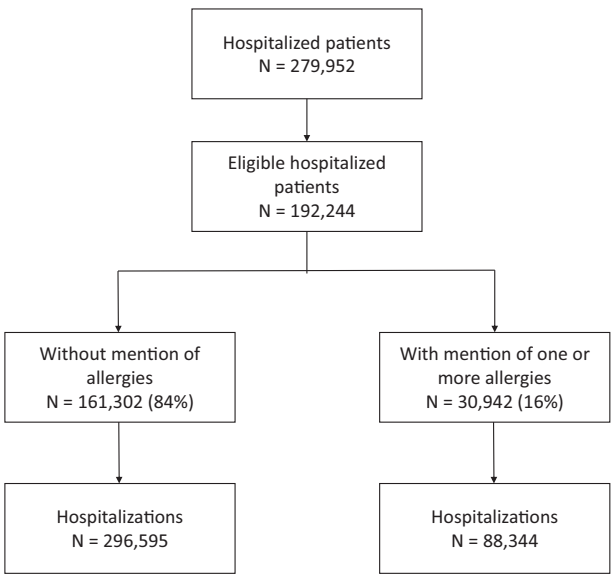

Fig. 1. Study flowchart. The inclusion period runs from June 2011 to June 2021. Eligible patients were hospitalized at least 24 h in CHUV.

Of the 30,942 allergic patients, 35% had more than one allergy referenced. There were no double entries. The most frequently referenced secondary allergens were pollens (16%), NSAIDs (5%), opioids, penicillin and bandage adhesives (4% each).

Drug hypersensitivity

Molecules

Drugs represented the largest category of allergens listed; accounting for 59% of allergy alerts (Fig. 2). BLA constitutes the most important group of drug allergens, listed in 28% of individuals with allergy alerts and 4% of all hospitalized patients. Most patients were tagged as being 'allergic to penicillin', without distinction, whether it applied to the molecule or a BLA subfamily. In 19% cases, specific molecules other than penicillin were listed (Table 3).

Hypersensitivity to NSAID is mentioned in 10% of all allergic and 1.5% of all hospitalized patients. Of note, only two generic terms were used, being 'NSAID' and 'salicylates'. Concerning ICM, it represented 6% of allergic and 1% of hospitalized patients. The generic term 'ICM' is used in more than 80% of cases, while in the remaining cases the commercial denomination is mentioned (e.g., Visipaque™, Accupaque™, etc.). Finally, opioid analgesics (including morphine, fentanyl, and tramadol) were found in 5% of the allergic and 1% of all hospitalized patients.

Reaction types

'Cutaneous symptoms' is by far the most frequently listed symptom complex in the EHR, accounting for 40% of cases. Subcategories were listed in half of cases and encompass 'cutaneous reaction' in 72%, 'exanthema' in 11%, 'eczema' in 9%, 'urticarial rash' in 8%. Angioedema is defined as a swelling beneath the skin or the mucosa, resulting from various etiologies and referenced in 2% of patients having 'cutaneous symptoms', In patients tagged as allergic to BLA, NSAID and ICM, 'Cutaneous symptoms' (as symptom complex) were described in more than 60% of cases (Fig. 3).

'Anaphylactic shock' was listed in 2647 alerts (7% of all DH reactions, Fig. 3). Leading causes of anaphylactic shock were ICM (11% of cases), penicillin (7% of cases) and NSAIDs (7% of cases).

Non-drug hypersensitivity

Allergens

Respiratory allergens were the second largest substance category, accounting for 22% of allergy tags. The main allergens were pollens (either tree or grass pollen, without further specifications), corresponding to 19% of allergic patients. Other frequent allergens encountered were cat and HDM (4.5% and 3.6% of allergic patients, respectively).

Food allergens accounted for 11% of allergy tags. Fruits (sic) were mentioned in 4% of allergic patients, followed by shellfish (2%). Contact allergens were listed in 5% of allergy tags (adhesives, latex and nickel in general). Finally, 1.5% had allergy to insect venom, mainly to honeybee and wasp stings.

Reaction types

Rhino conjunctivitis (3% of patients) and asthma (2% of patients) were the two main respiratory symptoms listed. In both conditions, pollens were the leading cause of symptoms. The generic term 'Gastrointestinal symptoms' was referenced in 3178 patients (1% of patients). The type of symptoms was not specified.

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Table 1
Characteristics of 192,244 patients admitted for at least 24 h in Lausanne University Hospital between 01.06.2011 and 30.06.2021.

	All (N = 192,244)	Without documented allergies (N = 161,302)	With documented allergies (N = 30,942)	p-value
Females, no. (%)	101,449 (52)	81,605 (51)	19,844 (64)	<0.005
Age at first hospitalization, median (IQR) years	40 (49)	36 (54)	53 (35)	<0.005
Duration of hospitalization, median (IQR) days	3 (7)	3 (4)	4.25 (6.25)	<0.005
Hospitalizations, no. (median, IQR)	384,939 (2, 2)	296,595 (1, 77)	88,344 (2, 84)	<0.005
Ward type, no. (%)				
Emergency room	68,286 (18)	51,340 (17)	16,946 (19)	
Obstetrics	56,107 (14)	49,508 (17)	6599 (8)	
Pediatrics	21,957 (5)	19,494 (6)	2463 (3)	
Orthopedics	23,307 (6)	16,449 (5)	6858 (8)	
Visceral surgery	16,414 (4)	10,909 (4)	5505 (6)	
Internal Medicine	15,248 (4)	10,591 (4)	4657 (5)	
Other	183,620 (49)	138,304 (46)	45,316 (51)	

Severity score

For each allergy referenced in the EHR, one can chose the severity of the reaction between 'severe', 'moderate', and 'mild'. As previously mentioned, the reaction severity is suggested by the system (referred to as 'Default') and has to be validated by user. Apart from the cutaneous (unspecified) category, users did not change the system suggestion. Around 10% reactions did not bear any severity grade (Table 4).

Free text and codified information

Roughly, 5600 various substances are listed in the allergy tags. Precise proportion of free text entry is unknown as no dedicated label exists. By looking at metadata, it seems around 20–30% of entries were manually saved and were more frequently documented in early version of EHR system. As we could not access earlier versions, our estimations could not be confirmed.

Logistic regression analysis

Patients were grouped according to the median age at first hospitalization (0: age at first hospitalization inferior to 40 years old, 1: age at first hospitalization superior to 40 years old). Being a woman increased the risk of being tagged as allergic by an OR of 1.9 (95% CI 1.85–1.95, $p < 0.05$). In addition, older age at first hospitalization increased the risk of being allergic by an OR of 2.1 (95% CI 2.06–2.17, $p < 0.05$). The longer the hospital stay, the greater the

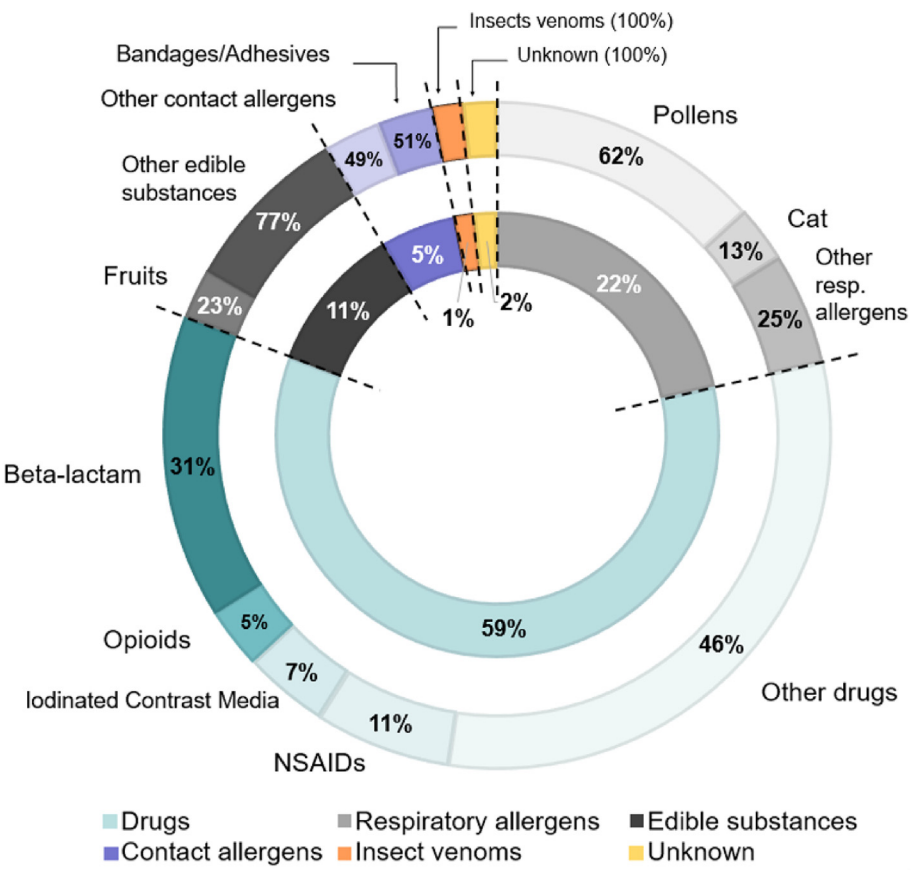

Fig. 2. Allergy categories according to 51,044 allergy tags found in 30,942 hospitalized patients. The inner circle corresponds to allergen categories as defined by the electronic health record allergy module. The outer circle shows principal allergens by category. Contrast media such as iodinated contrast media are listed under 'drugs'.

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Table 2
The top ten allergens listed as alerts in the electronic health records of 30,942 patients.

Allergen	Category	Number (%) of allergy alerts (51,044)	Number (%) of allergic patients (30,942)	Percentage of all patients (192,244)
Beta-lactam antibiotics	Drugs	9237 (18)	8621 (28)	4%
Pollens	Respiratory allergens	6770 (13)	6013 (19)	3%
NSAID	Drugs	3371 (7)	3035 (10)	2%
Iodinated contrast media	Drugs	2094 (4)	1995 (6)	1%
Opioids	Drugs	1517 (3)	1306 (4)	<1%
Cat	Respiratory allergens	1405 (3)	1364 (4)	<1%
Bandage adhesives	Contact allergens	1401 (3)	1376 (4)	<1%
Fruits	Edible substances	1251 (2)	1224 (4)	<1%
House dust mites	Respiratory allergens	1061 (2)	1021 (3)	<1%
Shellfish	Edible substances	919 (2)	895 (3)	<1%

Table 3
Beta-lactam antibiotics listed as responsible for drug hypersensitivity in 30,627 hospitalized patients.

Beta-lactam designation	Percentage of BLA-allergic patients (N = 9237)	Percentage within all reported allergies (N = 30,627)
'Penicillin'	81	25
Amino-/Ureido-penicillins[†]	12	4
Cephalosporins[‡]	6	2
Carbapenems[§]	0.9	0.2
Monobactam	0.01	<0.001

[†] Includes: amoxicillin, amoxicillin-clavulanate, piperacillin-tazobactam and flucloxacillin.
[‡] Includes ceftriaxone, cefuroxim, cefepim, cefpodoxim, cefazolin, ceftazidim, cefaclor and the generic term 'cephalosporins'.
[§] Includes: imipenem, meropenem, ertapenem and the generic term 'carbapenem'. BLA, Beta-lactam antibiotics.

chance of being tagged as allergic, with an OR of 1.002 (95% CI 1.002−1.003, $p < 0.05$) per hospitalization day. Besides being of shorter duration, ER hospitalization were independently associated with a lower risk of allergy tags, with an OR of 0.833 (95% CI 0.807−0.860, $p < 0.05$).

Discussion

We found that 16% of inpatients had at least one allergy tag. Independent risk factors for allergies were older age, female sex and longer hospital stays. These findings are consistent with the literature.[11]

Repeated exposure to drugs in the outpatient and hospital setting may bear the risk of becoming allergic. This may explain the observation that allergies are more frequent with longer hospitalization. Another explanation could be the repeated use of the EHR in this patient and the increase of chances to document allergies. In this regard, we question the utility to set 'no known allergies' by default in an EHR, without requiring confirmation by the documenting health care professional. Being older also increases the probability of allergies in particular to drugs and this is a known issue in an ageing population. The increased incidence of anaphylaxis in females and drug allergy in general is multifactorial. Hormonal and genetic factors, epigenetic may account for this difference. Some of these assumptions have already been made in past studies.[12] Estrogens for example are believed to enhance mast cells activation and imbalance the immune system.[13,14] Data on the female preponderance in anaphylaxis/drug allergies is rather scare and further studies are needed.[15]

DH represents 60% of total labeled allergies, with BLA being the most frequent. Around a quarter of patients with allergy tags were listed as being allergic penicillin, representing 4% of the in-hospital patient population. This observation is similar to a Belgian study relating the prevalence of antibiotic allergy labels in a tertiary center.[16] The prevalence of confirmed BLA after specialized work-up is much lower.[17] Among all in-hospital patients with allergies, less than 5% benefited from an appointment in our allergy outpatient ward over the same 10 years period. Unfortunately, we do not have data regarding specialized work-up performed in private practice or other hospitals.

DH was responsible for the vast majority of cutaneous reaction, angioedema and anaphylactic shock. Cutaneous reactions may reflect immediate-type hypersensitivity (e.g., IgE-mediated) or delayed reactions (T cell-mediated), the latter being much more frequent. Unless the cutaneous reaction was documented by qualified observers at the time of occurrence, it is most of the time impossible to differentiate in retrospect between immediate- and delayed-type hypersensitivity. The information on the culprit substance and the time between exposition and symptom onset is more easily obtained in an outpatient setting, while in inpatient hypersensitivity reaction often occur after exposure to multiple new drugs, which makes identification of the culprit and time of exposure more complicated.[18]

The reported food allergies were mostly to fruits, suggesting pollen-food syndrome in population with high prevalence of sensitization to pollen allergens.[19] Frequently reported allergies were to fish and shellfish, which is in accordance with other observations in the country.[20,21] One could argue on the utility to list food allergies in allergy alerts in an EHR for in-hospital patients. This would make sense if the information were transmitted to the meal providers, in order to avoid exposure of in-patients to known food allergens. However, the information regarding food allergies is not collected systematically in the EHR, nor is information about dietary restrictions shared with dieticians and hospital chefs. Integration of such alerts should lie within the scope of future EHR.

Concerning allergic rhinitis and/or conjunctivitis, prevalence is around 20% in Switzerland, compared to the 3% listed in our records.[22–24] We would argue that information on allergic rhinoconjunctivitis is of little value in hospitalized patients. However, would this information be systematically registered in the EHR, it could help distinguish food allergens as likely part of cross-reactions to aeroallergens and characterize potential asthma triggers.

Severe asthma is indeed an important risk factor for hypersensitivity reactions within the hospital setting, especially if uncontrolled.[25–27] Prevalence of asthma is around 7% in Western Switzerland.[23] This contrasts with the observed prevalence of 2% in our study population. Together with the observed frequency of other respiratory and food allergies in our population, these low prevalence rate of asthma hints at unsystematic history taking.

Anaphylaxis and severe anaphylaxis (anaphylactic shock) are life-threatening conditions that need immediate medical care such as adrenaline administration and supportive measures. Over the

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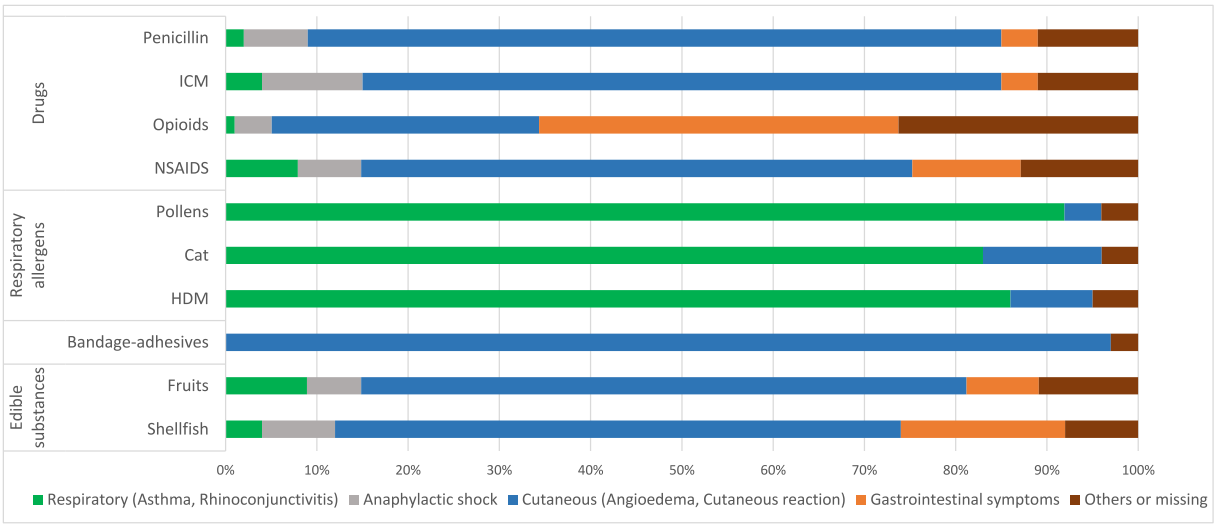

Fig. 3. Reaction types according to the ten more frequently listed allergens in 30,627 hospitalized patients. For better visibility, reaction types listed as 'cutaneous (unspecified)', 'urticaria', 'exanthema', 'eczema', as well as 'angioedema' were regrouped in a single 'cutaneous' category. *HDM, house dust mite; NSAID, nonsteroidal anti-inflammatory drugs; ICM, iodinated contrast media.*

Table 4
Severity grading according to the reported reaction type in 30,627 hospitalized patients.

	By default	Mild	Moderate	Severe	Total
Cutaneous (unspecified)	Severe	2033 (13%)	5779 (40%)	6972 (46%)	14,784
Angioedema	Severe	178 (3%)	846 (13%)	5433 (84%)	6457
Anaphylactic shock	Severe	37 (1%)	149 (6%)	2453 (93%)	2639
Unknown reaction	Severe	207 (9%)	562 (25%)	1356 (60%)	2125
Urticaria	Moderate	121 (8%)	1408 (82%)	152 (9%)	1681
Exanthema	Moderate	170 (7%)	1968 (84%)	201 (9%)	2339
Eczema	Moderate	150 (10%)	1455 (85%)	93 (5%)	1698
Rhinoconjunctivis	Mild	4830 (80%)	1108 (18%)	140 (2%)	6078
Asthma	Moderate	438 (10%)	3570 (80%)	447 (10%)	4455
Gastrointestinal symptoms	Moderate	383 (10%)	2956 (76%)	542 (14%)	3881
Missing	Unknown				4907

Information on reaction severity was missing in 4907 allergy tags.

ten years period, severe anaphylaxis was tagged in 2647 patients. It is not known whether the tag corresponds to the current hospital stay or from a previous medical record. By considering, all 'sever anaphylaxis' to have happened during hospital stays, a calculated pseudo-prevalence could be around 9/1000 patients/year. Rate varies between studies from 3.2 per 100,000 per year to as high as one per 100 per year in general population.[28–31] Our data seems highly overestimated but prevalence of severe anaphylaxis in hospitalized patients is unknown. Our starting hypothesis is certainly wrong, meaning most patients experienced severe anaphylaxis before their hospital stays. Selection bias could also explain this difference.

Regarding the severity of hypersensitivity reactions, the information was found to be subject to system- and user-based bias. We were unable to obtain information concerning the type of health care provider documenting allergies in the EHR (physicians, nurses, other health care providers), which would have been interesting to compare. Upon entering the type of reaction, the system suggests a severity grade in the adjacent field. The person entering the information in the allergy alert has the option to change the proposed severity grading in a scrolling menu, but is not obligated to do so in order to record the allergy alert. Another issue is the severity grading in listed allergies. More than 30% of all allergy tags (not limited to DH) were listed as 'severe' hypersensitivity. This is in contrast with most reactions being listed as cutaneous, which in our clinical experience are only rarely severe. Listing reported hypersensitivity by default as severe may reflects apprehension of patients and non-specialist health care provider regarding the risk of in-hospital allergic reactions. On the other hand, the system used did not allow specifying a history of severe delayed-type drug reactions, such as drug reaction with eosinophilic and systemic symptoms (DRESS), acute generalized exanthematous pustulosis (AGEP), Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). In our opinion, a history of severe delayed-type reactions deserves as much attention in an EHR allergy alert system than prior anaphylaxis.

It is also impossible to distinguish within the allergy alert system of the EHR whether patients with allergies had been subject to a specialized work-up. We estimate this number to be very low. BLA features among the most frequent DH and is a major public health issue. Indiscriminate avoidance of BLA increases health costs and microbial resistance. A specialized work-up including skin testing, in vitro assays and challenges to the alternative drugs is need to de-labeling unjustified allergy warnings. Such programs may be cost-effective.[32,33] In order to implement a de-labeling program, it is important to identify patients with DH that were not subject to a specialized work-up. Thus, implementing within the EHR whether a specialist assessed the reported allergy would not only improve the accuracy of the information gathered, but also pave the way to systematic work-up after the hospital stay.

Our study has several limitations, linked to its retrospective design and potential biases. Our analysis is limited to in-hospital patients, which were the ones having their medical data integrated in the EHR. We cannot extrapolate the findings to the outpatient population. We also applied a Levenshtein distance algorithm to identify allergens that were misspelled. Extensively misspelled substances may not be identified by this method. This however underlines the importance of avoiding free-text entries for substance-based allergy alerts in EHR, which is a major recommendation based on our findings. While the extracted data did not offer the possibility to discriminate between substances chosen from the integrated drug database or entered as free text, it appeared that a substantial number of substances were not referenced. When applying the algorithm to exclude simple misspells in free-text entries, we observed up to 400 entries for the

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same drug compound. We estimated manual input to account for 20% of listed substances, and probably the same amount within the drug category. Non-referenced allergens, that is not listed within the integrated database and introduced as free text in the allergy tag may not trigger alerts. This is an important issue for integrated prescription systems, which need to prevent administration of listed allergens to inpatients.

Pharmacopoeia varies from country to country, as does national institutions and corresponding laws. There is a need of standardized and simplified drug databases (i.e., only one possible choice for each molecule) which suits regional and international needs.

The strength of our study lies in the large number of patients included and the detailed information obtained by the EHR allergy alert system.

In our opinion, a modern allergy alert system should take into account groups of substances that are known to trigger cross-reaction in a sensitized subject. Thus, we believe that it is important to include a hierarchical classification of drug substances, in order to organize compounds according to their chemical structure and/or known allergic cross-reactivity. As mentioned earlier, the most frequently listed allergen is 'penicillin'. In the vast majority of cases, it is not possible to determine whether the term 'penicillin' refers to the molecule itself, the subfamily of amino-penicillin or the BLA in general. Today, allergic cross-reactivity between penicillin and other BLA is known to be limited and it appears important to list the specific culprit, whenever possible.[34] It is not only important to distinguish between single molecules and substance classes in drug hypersensitivity reactions according to Gell & Coombs, but also in other types of hypersensitivity. For example, angioedema induced by Angiotensin-converting enzyme inhibitors warrants avoidance of all representatives of this drug family.[35] Another example is NSAID exacerbated respiratory disease (NERD), in which all non-selective cyclooxygenase-inhibitors should be avoided.[36] Future substance databases implemented in an EHR should be able to search not only for single substances, but also for substance groups. These alerts should be enforced by algorithms taking into account the risk of cross-reactions and warn prescribers accordingly. Comorbidities such as asthma, cardiac failure and systemic mastocytosis should also be taken into account in risk stratification. A comprehensive user interface with scroll-down menus, an up-to-date list of allergens and indications whether an allergy was subject to work-up should improve the quality of stored information and generated alerts.

Allergic reactions are notoriously difficult to document, most of the time due to the absence of information regarding the type, severity and culprit involved. However, guidelines on how to recording hypersensitivity reactions and guidance by the EHR during the documentation process could improve the quality of information gathered by non-specialists. Accurate data are essential for algorithms preventing exposure to culprit allergens or cross-reactive substances in integrated prescription systems. Systematically recorded food allergies and dietary restrictions in the EHR and transmission of this information to meal providers could further improve in-patient safety. National implementation of electronic patient records (EPR) encounters difficulties in many countries, related to various issues such as the choice of interchangeable data format, confidentiality and third-party implementation. We believe that hospitals and their EHR providers should play a leading role in improving allergy documentation, which ultimately will extend to the EPR. Our next steps would be to compare our findings with other tertiary health centers and to agree on common practices in recording allergies, including EHR and EPR developers. Ultimately, patient-reported allergies not subject to a specialized work-up could benefit from de-labeling programs, which were shown to reduce health costs and other issues with unjustified second-choice treatments.

Conclusion

We retrieved data of 192,444 hospitalized patients over a 10-year period, of which 16% had an allergy alert in electronic medical record. We showed older age, long hospital stays and female sex to be major independent odds factors for in-patient allergy documentation. Among allergy alerts, 'drugs' was the major category representing 60% of allergy alerts. Within this category, BLA scored first, being referenced in 4% of studied population. Specific delabeling programs should be implemented to increase data reliability and patient safety, as well as decreasing health costs. Indeed, self-reported allergy triggers unnecessary avoidance and increase microbial resistance in the case of BLA.

Conflict of interest

The authors have no conflict of interest to declare.

Authors' contributions

MR and CR conceived of the presented idea. AW provided with data extractions. MR performed the computations and statistical analysis. MR wrote the manuscript with support from CR. CR supervised the project. All authors discussed the results and commented on the manuscript.

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