

Prescribing errors in patients with documented drug allergies: comparison of ICD-10 coding and written patient notes

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Abstract *Introduction:* Allergies to drugs are a major cause for hospitalisation and inappropriate prescriptions to patients. However, allergies can be prevented if the patient's history of drug allergy is known and coded. *Objective of the study:* Assessment of the value of the widely used ICD-10 codes for drug-allergies (e.g. Z88, L27) as triggers for decision support in an electronic prescription system and evaluation of the potential impact of such an alert system. We also evaluated the usefulness of manual drug allergy notes recorded in patients' charts in the prevention of prescribing errors due to drug allergies. *Setting:* University hospital providing primary and tertiary care. *Methods:* Using Anatomical Therapeutic Chemical (ATC) classification codes we allocated to drug specifying ICD-10 codes (i.e. Z88) all drugs belonging to the same group of compounds or those known to induce cross-allergy. In a randomly selected cohort of 200 in-patients we then assessed documentation and coding of drug allergies and incident prescribing errors ignoring patients' drug allergies. *Results:* Eighteen of the 200 patients had an allergy-related ICD code in the chart, 51 had a written note, and 13 had both. About 21% of patients with documented drug allergies were prescribed a drug potentially triggering

the allergy. There was no difference in prescribing errors due to drugs potentially inducing allergies when the allergy was only documented as an ICD-10 code or the information was available in the paper record ($P > 0.05$). *Conclusion:* The findings of this study emphasise the necessity of a more precise and efficient documentation system of drug allergies along with the implementation of an electronic CDS for drug allergies that makes physicians aware of patients' drug allergies during the prescribing process.

Keywords Clinical decision support systems · Drug allergy · Germany · Medical order entry systems · Medication errors

Impact of findings on practice

- The charts of a significant fraction of hospitalised patients contain allergy information, yet many of these patients are receiving drugs potentially causing allergic events.
- Although several ICD-10 codes for drug-induced allergies are available these codes are often ambiguous, infrequently used, and therefore of limited value.
- Only for two ICD-10 codes (Z.88.0, Z.88.2) meaningful groups of drugs can be defined that must be avoided in patients with the respective allergy disposition.

Introduction

Drug allergies are immunologically mediated adverse drug reactions (ADR) often caused by IgE- and T-cell-mediated mechanisms [1]. While it is unpredictable who develops a

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drug allergy, recurrence of the allergy in patients with an allergy history is likely upon re-exposure to causative agents or their derivatives [2].

The definite prevalence of drug allergies in hospitals, ambulatory care, or the general population is unknown. However, manifest drug allergies in a hospital occur in 3.6/1000 patients [3] to 22/1000 [4] or 27/1000 [5] if only cutaneous reactions are considered, and in 4.2/1000 [6] for all identified drug allergies. They are a major cause of hospital admissions due to ADR [7]. Because allergies are frequent and often serious, strategies to avoid re-exposure of these patients are important.

Ignoring a patient's drug allergy is a common error concerning about 13% of prescribing errors in a hospital [8]. Seventy-six percent of such errors occur because prescribers are not aware of the patients' allergy history and six percent because physicians neglect the risk of cross-allergy [9]. In systems depending on manual checks, where allergy information is not readily available, patients may receive medications to which they are allergic although an allergy notation was present in the chart [10]. In contrast, inappropriate prescriptions to allergic patients have efficiently been prevented by computerised physician order entry (CPOE) linked to computerised decision support (CDS) systems [11, 12].

However, successful electronic systems depend on three key elements: (1) the reliable coding of a patient's allergy history, (2) the availability of a CPOE-CDS system, and (3) a knowledge base containing allergy-inducing drugs. In Europe diagnoses of hospitalised patients are coded according to the International Classification of Diseases (ICD-10) of the World Health Organisation (WHO). ICD-10 coding is widely used for reimbursement purposes and specifies a number of codes relating to drug allergies (Table 1). It might provide a universal basis for coding drug allergies.

Aim of the study

Our aims were to

- allocate different drugs and drug groups to ICD-10 codes as guidance for allergy alerts to systemically administered drugs,
- evaluate the value of using ICD-10 codes as guidance for allergy alerts to systemically administered drugs in an electronic drug prescribing system, and
- analyse handwritten allergy information in a representative random sample of in-patients' charts to assess the quality of electronic coding and the relationship between prescribing errors and location of allergy documentation in the chart.

Methods

Analysis of drug allergy related codes

We assessed all ICD-10 codes for history of allergic drug reactions (Z88.0–Z88.9). Coding events that were potentially induced by drug allergies such as L27: dermatitis due to substances taken internally, were also included (Table 2). However, we did not include codes that were neither exclusively allergic nor drug-induced in nature.

Classification of prescribed drugs

Because WHO has not commented on the specific meaning of individual Z88 ICD-10 codes we applied drug class definitions published by Goodman and Gilman [13] or as medical subject heading (MeSH) term in Medline [14]. We allocated the corresponding Anatomical Therapeutic Chemical (ATC) classification codes (defined by WHO) of all drugs belonging to the same group of compounds to each of these ICD-10 codes (Table 1). We then screened the literature for detailed information about drugs and drug groups bearing the potential of inducing cross-allergy despite their classification as different therapeutic classes. Cross-reacting drugs were assigned to the respective ICD-10 code but were defined as a separate group (Table 1).

Penicillins were the only well defined drug group (Z88.0). Because of the known cross-reactivity with certain cephalosporins [15] cephalosporins with similar side chains were linked to this group [16, 17] i.e. cephalothin, cephalexin, cefadroxil, cefazolin [18], and carbapenems [19–21]. We further linked β -lactamase inhibitors (e.g. clavulanic acid) as mono-compounds, because they are generally given with penicillins, may cause immunological reactions on their own [22, 23], and may be neglected as causative agent in a patient with penicillin allergy. In contrast the monobactams lacking cross-reactivity were excluded from this group [24].

Code Z88.1 comprised all antibacterial agents including also antitreponemal, antitubercular, and leprostatic agents but not penicillins and sulphonamide antibiotics (MeSH), which were specified in individual codes.

Although sulphonamide moieties are included in many drugs from different therapeutic entities (e.g. loop and thiazide diuretics, sulphonylureas, and cyclooxygenase (COX)-2 inhibitors) Z88.2 was restricted to sulphonamide-antibiotics, the clinically most relevant drug class inducing allergies, while other sulphonamides are immunologically neither related nor prone to cross-reactivity [25–28]. This restriction is also in agreement with the definition of sulphonamides in Goodman and Gilman [13].

According to the MeSH terms local and systemic urinary anti-infectives, systemic antifungal, antiparasitic,

Table 1 ICD-10 codes relating to drug allergies and ATC-codes corresponding to drugs of risk

ICD-10 code	Specification	Related ATC codes	Specification	Linked groups	Classification according to
Z88.0	Personal history of allergy to penicillin	J01C, J01RA01	Penicillins and penicillin combinations	Cephalosporins [16, 17] (J01DB01, J01DB03, J01DB04, J01DB05 [18]), carbapenems [19–21], β -lactamase Inhibitors [22, 23]	[13]
Z88.1	Personal history of allergy to other antibiotic agents	J01A, J01B, J01D, J01F, J01G, J01 M, J01X, J04, G01AA, G01AC, R02AB, A07AA	Tetracyclines, amphenicols, other betalactams, macrolides, aminoglycosides, quinolones, other antibiotics, agents against mycobacterium, antitreponemal and leprostatic agents	Penicillins [16, 17]	MeSH [14]
Z88.2	Personal history of allergy to sulphonamides	J01EB, J01EC, J01ED, J01EE, J01RA02, G01AE, A07AB, J02A, A07AC, A07AX J05, P01, P02	Sulphonamide antibiotics, sulphonamide antibiotic combinations with/and without trimethoprim		[13]
Z88.3	Personal history of allergy to other anti-infective agents		Systemic antimycotics, antiviral, antiparasitic, anthelmintics, antiprotozoal agents		MeSH [14]
Z88.4	Personal history of allergy to anaesthetic agent	N01	Anaesthetics		MeSH [14]
Z88.5	Personal history of allergy to narcotic agent	N02A, R05DA, A07DA02, A07DA52	Opioids, opium and opium alkaloid derivatives, morphine combinations		MeSH [14]
Z88.6	Personal history of allergy to analgesic agent	N02 (except N02A, N02C), M01A, M01B, A03DA	Analgesics and analgesic combinations except opioids & antimigrain agents		MeSH [14]
Z88.7	Personal history of allergy to serum and vaccine	J06, J07, L01XC, L04AA (02, 03, 04, 15, 21, 23, 24), L04AB, L04AC (01, 02), B01AC13	Sera, monoclonal antibodies, and vaccines		MeSH [14]
Z88.8	Personal history of allergy to other drugs, medicaments and biological substances	Any other ATC code			
Z88.9	Personal history of allergy to unspecified drugs, medicaments and biological substances	Unknown drug			

Table 2 Codes of allergic drug reactions considered in patient data analysis [44]

ICD-10 code	Potentially drug-induced allergic event
D59.0	Drug-induced autoimmune haemolytic anaemia
D69.0	Allergic purpura
L10.5	Drug-induced pemphigus
L23.3	Allergic contact dermatitis due to drugs in contact with skin
L25.1	Unspecified contact dermatitis due to drugs in contact with skin
L27.0	Generalised skin eruption due to drugs and medicaments
L27.1	Localised skin eruption due to drugs and medicaments
L50.0	Allergic urticaria
L51	Erythema exsudativum multiforme
L51.1	Bullous erythema multiforme/Stevens–Johnson syndrome
L51.2	Toxic epidermal necrolysis [Lyell]
L51.8	Other erythema multiforme
L51.9	Erythema multiforme, unspecified
L52	Erythema nodosum
L56.1	Drug photoallergic response
L71.0	Perioral dermatitis
M31.0	Hypersensitivity angiitis
M32.0	Drug-induced systemic lupus erythematosus
R50.2	Drug-induced fever
T80.5	Anaphylactic shock due to serum
T88.1	Other complications following immunisation, not elsewhere classified/Rash following immunisation
T88.2	Shock due to anaesthesia
T88.6	Anaphylactic shock due to adverse effect of correct drug or medicament properly administered
T88.7	Unspecified adverse effect of drug or medicament
Z88	Personal history of allergy to drugs, medicaments and biological substances

anthelmintic, antiprotozoal, and antiviral agents, and disinfectants were allocated to Z88.3.

Concerning narcotics (Z88.5) only opioids were included and they were excluded from Z88.4 (anaesthetics) and Z88.6 (all other analgesics). The code Z88.7 was used for immunosera and immunoglobulins, the two main biological drug products being part of the serum, and for vaccines. To this group also monoclonal antibodies were allocated, for which allergic reactions have also been reported [29]. All other drugs were allocated to Z88.8 if they were clearly identified and Z88.9 for drugs not specified in the chart.

Patient data analysis

After approval by the responsible Ethics Committee a random sample [30] of 265 in-patients was drawn from all 54420 admissions to the University Hospital of Heidelberg in 2007. Patients <18 years or with inaccessible charts were replaced until a cohort of 200 patient charts was enrolled. This sample size was deemed appropriate according to similar studies [9, 31] and was a priori not

powered to detect differences in the mode of documentation because no data on this topic was available. The charts were individually screened for actual and past diagnoses or ICD-10 codes alluding to allergy-related diagnoses mentioned in Table 2. Equivocal codes of uncertain allergic origin were excluded (e.g. D70.1: drug induced agranulocytosis and neutropenia). In our hospital patient charts contain different sections where allergy information can be noted (nurses' or physicians' admission records, and medical record containing prescriptions, vital signs, and temperature). These areas were scrutinised for any drug allergy-related entries. Retrospective collection of allergy information was done for the hospital stay of the patient in the index year 2007 and all previous admissions.

Patients were considered allergic if either a pertinent ICD-10 code was documented or drug allergies were mentioned in the corresponding chart sections. Included were documented allergies to drugs occurring after systemic or topical application as were events relating to drug intolerance because the notes were usually not specific

Table 3 Patient demographics and allergy documentation

Variable	Number	Percentage (%)
Gender (male/female)	95/105	47.5/52.5
Drug allergy		
Patients without drug allergy (N)	144	72%
Patients with drug allergy (N)	56	28%
Documented drug allergies		
Involved drug classes		
Penicillin	15	27%
Other antibiotics	6	11%
NSAIDs	7	12.5%
Other drugs	20	36%
Unknown drug	12	21%
Medication error		
Patients with ICD-10 having medication error(s) (frequency)	1/5	20%
Patients with manual documentation having medication error(s) (frequency)	11/51	21.6%

enough to separate the two and because rechallenge of the patient should be avoided in either case.

Analysis of prescriptions

For in-patients most drugs were prescribed manually whereas a large fraction of prescriptions for ambulatory patients attending clinics or in-patients at discharge are electronically issued using a hospital wide drug information system (AiDKlinik®). This web-based system is run on all 5500 clients of the hospital's intranet, contains information on >60000 different brands marketed in Germany, and is equipped with decision support modules (e.g. information on drug interactions, dosing in renal failure, prevention of overdoses, duplicate prescription, inappropriate tablet splitting, and incompatibilities). All prescriptions (electronic and handwritten) to patients with drug allergies (coded and/or documented) were evaluated for the presence of drugs likely causing allergic reactions upon (re)exposure as specified in Tables 1 and 2. Generally, clinically meaningful prescribing errors occur “when, as a result of a prescribing decision or prescription writing process, there is an unintentional significant (1) reduction in the probability of treatment being timely and effective or (2) increase in the risk of harm when compared with generally accepted practice” [32]. In our study a prescribing error was defined as (i) the same culprit drug or (ii) a cross-reacting drug being prescribed to the patient in the same or a subsequent medical record and/or electronic prescription after the drug allergy was noted in the patient's charts either as a written note or an ICD-10 code. Each contraindicated drug prescribed to a patient with a documented allergy was counted as one medication error. If an allergy was coded for the first time in

the chart and the patient was receiving the culprit drug within the same hospital stay, drug administration was not considered as an error unless documentation unambiguously revealed that the allergy was known before drug exposure.

Statistics

Data are reported as frequencies with 95%-confidence intervals (95%-CI) or mean $\pm$ SD. Frequencies of prescribing errors between groups were compared using Fisher's exact test. A *P*-value < 0.05 was considered significant.

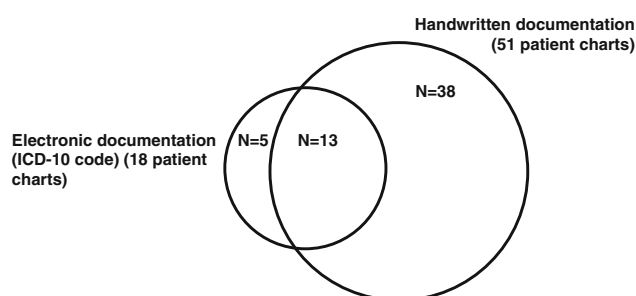
Results

Patient population

The average patient age was 59 (± 17) years (range 19–96) and 53% were female. Patients were admitted mainly due to cancer (37.5%), central nervous system disorders (12.5%), hepatic diseases (10.5%), and 6.5% for cerebral infarction (Table 3). Fifty-six patients (28%) of the total cohort had an allergy either documented or coded in their charts. In five of these 56 patients (9%; 95%-CI: 2.96–19.6%) allergy information was only available as an ICD-10 code, in 38 patients (68%; 95%-CI: 45.4–79.7%) only written in the chart, and in thirteen patients (23%; 95%-CI: 13–36.4%) allergies were both documented and coded (Fig. 1). Fifty-one patients had handwritten allergy notes in their chart. When the place of the allergy warning section was analysed, nine patients had entries in nurses' admission records, 28 in the medical record, and only two patients had a documented allergy in physician admission

Table 4 Potentially inappropriately prescribed drugs in the patient cohort

Patient number	Type of allergy	Type of documentation	Prescribed drug	Type of prescription
1	Acetylsalicylic acid	Chart	Metamizole	Written
2	Penicillin	ICD-10	Amoxicillin + clavulanic acid, amoxicillin	Written
3	Ciprofloxacin	Chart	Ciprofloxacin (thrice), levofloxacin (twice)	Written
4	Levofloxacin	Chart	Ciprofloxacin	Written
5	Ciprofloxacin	Chart	Ciprofloxacin	Written
6	Metamizole	Chart	Metamizole (twice)	Written, electronic
7	Acetylsalicylic acid	Chart	Metamizole, ibuprofen	Written
8	Metamizole	Chart	Metamizole	Written
9	Metamizole	Chart	Metamizole (thrice)	Written
10	Moxifloxacin	Chart	Ciprofloxacin	Electronic
11	Metamizole	Chart	Metamizole	Written
12	Diclofenac	Chart	Diclofenac, ibuprofen, paracetamol	Written

**Fig. 1** Venn diagram illustrating the different locations of drug allergy documentation in 56 patients with allergy information documented in the chart

records. The remaining twelve patients had the allergy note registered in more than one section. Hence, 78% ($N = 40$; 95%-CI: 65–88.7%) of patients with documented allergies had a drug allergy note in their actual or previous medical records. The other 22% ($N = 11$) had their drug allergies mentioned in either the nurses' or physicians' admission records.

Prescription analysis

Out of the 56 patients with documented drug allergies twelve (21%; 95%-CI: 12–34.4%) were prescribed twenty-three times an allergy-inducing drug either as the same culprit drug ($N = 12$, 52%) (95%-CI: 31–73%) or as a cross-reacting compound ($N = 11$, 46%) (95%-CI: 26–69%) (Table 4). There was no difference in the risk of being prescribed a drug potentially inducing an allergy whether the allergy was only documented as an ICD-10 code (1 in 5 patients) or documented in the paper record (11 in 51 patients) ($P = 1.0$).

About 20% ($N = 10$) (95%-CI: 9.8–33%) of all patients with written allergy entries ($N = 51$) received potentially allergy-inducing or cross-reacting drugs, although the

allergy was noted in their medical record, and two percent ($N = 1$) (95%-CI: 0.5–10.5%) when the allergy was registered elsewhere (i.e. in nurses' or physicians' admission records). There was also no significant difference in the prevalence of prescribing a contraindicated drug when the allergy information was mentioned in the medical record as compared to those registered elsewhere ($P = 0.42$). Most of the medication errors occurred in written patient charts, while 17% of the prescribing errors occurred in electronic prescription.

Discussion

This study revealed a remarkable number of hospitalised patients with documented allergies receiving potentially allergy-causing drugs. It is in accordance with the 13% error rate found in earlier reports when only prescribing errors are considered [8]. Surprisingly patients were not less likely to be exposed to high-risk drugs if allergies were documented in the medical paper record instead of only being available in electronic form (i.e. ICD-10 code). Hence, although information was available in charts, patients were prescribed drugs that may elicit allergic events emphasising the importance of supporting physicians with pertinent information.

In about half of the cases physicians ignored potential cross-reactions with the noted culprit suggesting that knowledge support in this regard may be essential. For instance, in the cohort two patients allergic to the nonsteroidal anti-inflammatory drug (NSAID) acetylsalicylic acid were prescribed another NSAID (ibuprofen, metamizole) for pain relief. Although they are not structurally related, as non-specific COX inhibitors the prescribed drugs were likely to cause adverse events in these patients [33] who had risk factors like allergic asthma and chronic obstructive

pulmonary disease. In addition, in many instances physicians prescribed antibiotics from the same group to which the patient was allergic.

Differences between coded and documented drug allergies were large with coded information being about 7-times less prevalent. In accordance with studies using ICD-10 codes to identify adverse drug events mandating action [34, 35], also in this study ICD-10 codes detected risks undetected otherwise. However, in contrast to these studies many of our patients had allergy information both coded and documented in paper charts, which is in agreement with other studies [36]. The large variability in frequency of electronic coding of adverse drug reactions or risk situations is likely due to differences in coding policies between different countries, the relevance of the event for reimbursement, and skills and tasks of non-clinical staff involved in the coding process.

Although drug allergies are known they are not always coded and if they are it is not commented on the culprit drug. For instance, a drug-induced generalised skin eruption would be coded as L27.0 without commenting on the causing agent even if it were known. Therefore coding of allergic events in our setting appears incomplete. This may partly be due to the demand that ICD-10 codes relating to allergies are only reclaimable for reimbursement if the actual treatment was complicated by an allergy or treatment had to be modified because of the patient's history of allergy. Since reimbursement is a major incentive for coding, codes relevant only for optimum care of a patient may not as strictly be coded. Another reason may be the insecurity of physicians when classifying adverse drug reactions as allergy without results of diagnostic tests that usually follow only four to six weeks after occurrence. Finally, in this and other hospitals coding is not always done by a physician and therefore important clinical information may not be accurately coded. This stresses the necessity of using a more specific coding system in a CDS for drug allergies that gives each culprit a unique code leading to more specific alerts.

In this study prescribing the same or cross-reacting drug(s) happened frequently, indicating how important physicians' education or alerting in this regard will be. This emphasises the necessity of implementing an electronic tool for drug allergies, which advises physicians during the prescribing process against prescribing the same or any cross-reacting substance.

Another major finding of this study is that Z88 ICD-10 codes for drug allergies are ambiguous and have limited usefulness in identifying patients at risk. For instance, allergy to penicillins (Z88.0) does not include cephalosporins and therefore cross-reacting drugs are not allocated to the same class. However, with a cross-reactivity rate of 4.4% [15] the risk is considerable particularly with

cephalosporins with similar side chains like penicillins [16, 17]. It is therefore often, although not always [37, 38], recommended to strictly avoid cephalosporins in patients with a history of penicillin allergy [39, 40].

Another example of ambiguity is that the term "sulphonamides" is of little value unless it is restricted to antibacterials because only this group is indeed prone to cross-allergic reactions whereas other chemical entities with sulphonamide moieties are considered safe in patients allergic to sulphonamide antibiotics [25, 28]. In addition to ambiguities with respect to chemical structure there are also ambiguities in the therapeutic classification of drugs. As an example opioid analgesics may be allocated to more than one code (Z88.5 or Z88.6). In clinical practice a coding system can only be useful if its codes act as links to meaningful clinical situations. Given the numerous challenges in drug safety and the difficulty of assuring quality without electronic support, such systems should be tailored to the needs of CPOE-CDS systems to ensure effective prevention of potentially serious prescription errors.

From a clinical point of view the current ICD-10 coding system allows the meaningful definition of only two codes (Z88.0, Z88.2) without labelling too many patients not being at risk. Assuming that both codes were used unequivocally it may be expected that about 6.9% of cutaneous drug reactions [5] or ~34% of all drug-induced allergies [6] are labelled. However, even if all currently available codes were used not all drug induced allergies would be covered because a significant fraction is caused by additives [41], which are not part of the current coding system and would therefore be classified as Z88.9. In those patients allergies may recur with apparently unrelated brands and it might then be better to consider drugs at the level of brand names or codes relating to them [42].

Moreover, clinically useful CDS might also include situations of drug intolerance and cross-intolerance caused by non-immunological mechanisms but frequently presenting with similar symptoms. They may better be described as anaphylactic reaction, which serves as a more general term for allergic and pseudoallergic reactions. One example is aspirin and other NSAIDs that may induce pseudoallergic reactions e.g. aggravation of asthma in predisposed patients. These intolerance reactions are ascribed to the inhibition of COX and are thus prone to cross-reactivity with all drugs sharing this mechanism of action [43].

It was our primary goal to analyse the suitability of ICD-10 codes for allergy prevention and to assess their use in clinical practice. While we were able to identify a substantial fraction of patients with documented allergies and potentially dangerous exposure to drugs causing the allergy, the study was not powered to analyse the impact of the documentation on the occurrence of prescribing errors.

However, the findings of this study may indicate that if differences were present they were not very large. Another limitation of this study is its retrospective design that precluded checking whether the physicians truly neglected a documented drug allergy or were well aware of it, but deliberately prescribed the drug after balancing the likelihood of an allergic reaction with available treatment options.

Conclusion

In conclusion, although drug allergies are considered major and often neglected risks in drug therapy important obstacles obviate consequent and comprehensive prevention. This analysis suggests that a multidisciplinary intervention is required to improve the situation specifying available codes, optimising the coding system, and encouraging health care providers to report and code allergies electronically. Without these modifications efficient prevention of prescribing errors appears futile and over-alerting is likely to occur because of the lack of specificity of current alerts.

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