

Drug Allergy in Hospitalized Patients: The Contribution of Allergy Consultation and a Structured Questionnaire

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Key Words

Allergist consultation · Drug allergy · Drug allergy questionnaire

Abstract

Background: Hospitalized patients with an alleged history of drug allergy pose medical and economic concerns when selecting medications for treatment, possibly leading to deviations from standards of care and the use of expensive agents. Accurate history taking and clear documentation of drug allergy are essential for preventing subsequent administration of the offending drug and overdiagnosis of drug allergy. We aimed to evaluate drug allergy-related history taking by internists compared to allergists and to prospectively assess the effect of a simple, structured questionnaire on the accuracy of drug allergy diagnosis. **Methods:** Consenting patients with an alleged drug allergy who were able to give a coherent history were recruited from two internal medicine wards. In both wards, the internists' drug allergy diagnosis was initially compared to that of the allergists. In the second part, in the intervention ward, after the same procedure, the internists completed the structured questionnaire. Their diagnostic conclusions with and without the questionnaire were compared. **Results:** 202 patients labeled

with a medication allergy were enrolled. In the control and intervention wards, 54 and 58% of the patients, respectively, labeled by the internists as allergic, were found not to be allergic by the allergist. In the intervention ward, after using the questionnaire, the percentage of patients tagged by the internists as allergic dropped initially by 31% and finally by 59%. **Conclusions:** Discrepancies between drug allergy diagnosis of internists and allergists are common. Allergist consultation or use of a simple structured questionnaire may be beneficial for accurate diagnosis of drug allergies.

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Introduction

Patient's self-reported drug allergy reaches as high as 25%. Estimates of actual drug allergy rates tend to be much lower and question the accuracy of the patients' report [1, 2]. The discrepancy between true allergy and reported allergy probably represents other adverse effects and unrelated reactions. Hospitalized patients with an alleged history of drug allergy pose a dilemma when medications are prescribed for treatment of the acute situation, as well as the choice of drugs recommended at discharge. This problem comprises both medical and

economic aspects as it can lead to deviations from standard of care and use of more expensive agents.

Detailed history taking and clear documentation of drug reactions suspected to be allergic are essential for minimizing the risk of subsequent administration of the offending drug, as well as overdiagnosis of drug allergy.

Lutomski et al. [3] retrospectively studied antibiotic allergies in medical records of hospitalized patients. Discrepancies between the medical records and meticulous allergy histories were common and the validity of reported allergic reactions was questionable. Incomplete documentation of the drug allergy status of a patient appears to be related mainly to deficient history taking and failure to distinguish between a clinical presentation suggestive of drug allergy and a simple adverse drug reaction, mostly related to the physician's education rather than the patient's ability to provide the information [4, 5]. Various interventions have been suggested in an effort to improve the diagnosis of adverse drug reactions with suspected drug allergy (ADRSA). These include history taking by pharmacists [6–8] as well as means of better documentation [3, 5].

The present study had two parallel prospective components: in the first, we aimed to evaluate drug allergy-related history taking by internal medicine physicians compared to allergy specialists. In the second stage, we prospectively assessed the effect of a simple structured questionnaire on the accuracy of the diagnosis of adverse drug reactions with suspected drug allergy.

Methods

Setting

This prospective comparative study was conducted between September 2008 and January 2010 at a teaching hospital in Kfar Saba, Israel, affiliated with Tel Aviv University. Two internal medicine wards participated. One ward served as a control and the other as the intervention ward.

The study was approved by the local ethics committee.

Patients

Upon admission, every patient was routinely asked whether he had drug allergy. Patients who responded positively were labeled as allergic. During the study period, all consecutive patients labeled as allergic in both wards were eligible for inclusion. Patients were excluded if they were unable to give history or refused to sign an informed consent form as required by the local ethical committee.

Questionnaire

The questionnaire was designed to assist the physician in information gathering. It aimed to help extracting the relevant data in a short time on top of the regular admission procedure. The questionnaire included 3 simple questions: (1) description of the

reaction: signs and symptoms leading to the diagnosis of allergy; (2) time scale: estimation of how long ago the reaction occurred and description of when the reaction occurred in relation to beginning of treatment with the suspected medication. (3) Reexposure: active questions regarding reuse of the suspect drug after the reaction. Conclusion: based on the responses to the questions, the physician had to decide whether the description was compatible with an allergic reaction, a known adverse event or not related to administration of the suspected drug (online suppl. material, www.karger.com/doi/10.1159/000332147).

Before the beginning of the study, all physicians in the intervention unit were instructed how to use the questionnaire. The guiding principles were that all patients reporting the following symptoms: rash or shortness of breath or anaphylactic shock that had begun during the first 3 days of treatment should be regarded as allergic. Combination of one of the above symptoms with vomiting/abdominal pain/diarrhea or with pruritus within the same time frame or abdominal symptoms with pruritus was also considered an allergic reaction. Itching without rash or abdominal discomfort alone was not regarded as an allergic reaction. When the patient reported rash suspected to be erythema multiforme, it was considered an allergic reaction in order to avoid reintroducing a drug to patients with a suspected history of Stevens-Johnson syndrome. Likewise, when the patient had no recollection of the event classifying him as allergic to the drug and reexposure could not be proven – he was regarded as having drug allergy (although arbitrary – safer for the patient). Undefined, mild rashes, limited to less than 10% of the skin area, not involving mucous membranes and appearing 72 h after the beginning of treatment were considered a nonallergic side effect. Symptoms that were not linked in time to the consumption of the medication were considered unrelated (for example, fine maculopapular rash appearing 5 days after the injection of contrast media).

When a patient described symptoms suggesting a previous allergic reaction and could provide a firm documentation of reuse of the same drug afterwards without a reaction, he/she was considered not allergic.

Procedure (fig. 1)

Part 1: Observation

In both wards, the admission process includes taking a drug allergy history. This part of history taking is mandatory and done by the attending physician. Once the physician is convinced that the patient has a drug allergy, he or she notes this information on the chart and on a red sticker which is placed on the patient's chart and bed. In both groups, all consenting patients were interviewed by an allergist who also completed the structured questionnaire and calculated the Naranjo adverse drug reaction probability score (see below). These parts of history taking, data collection and allergist interview continued throughout the study period independent of whether the patient belonged to the control or intervention groups.

All the questionnaires completed by the allergist were reviewed by a second unbiased experienced allergist. Based on the data in the questionnaire, this allergist determined whether the patient had a drug allergy, side effect, or whether the description was unrelated to the culprit drug.

Part 2: Intervention

In the intervention ward, all consenting patients were reinterviewed by one of the ward physicians who, simultaneously, also

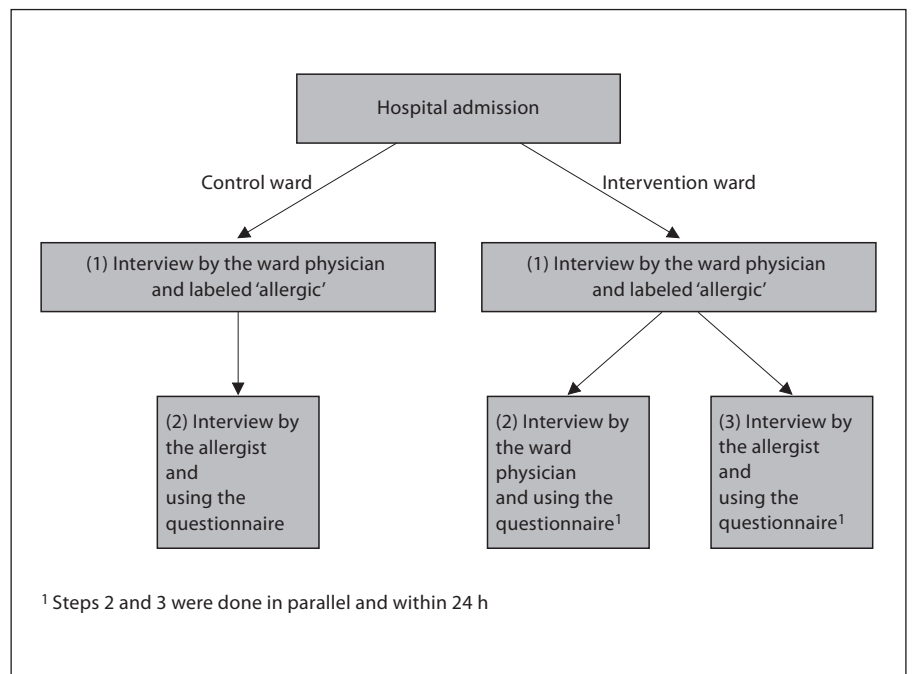


Fig. 1. Description of the study procedure.

completed the study questionnaire. Based on the questionnaire findings, this physician had to decide if the patient should still be classified as having a drug allergy, a side effect, or an unrelated problem.

Before commencement of the study, physicians from both wards were encouraged to access the patients' written and computerized records including the computerized list of drugs dispensed by the pharmacy over the 2 years preceding the index admission.

The Naranjo adverse drug reaction probability scale [9] was applied to all questionnaires. This scale is an accepted and validated tool designed to assess the likelihood that a specific drug caused the reaction (a score of 5 or higher means probable or highly probable adverse drug reaction. Scores between (–3) and 4 indicate a possible or doubtful adverse drug reaction).

Statistical Analysis

Differences between the two wards were analyzed by the χ^2 test. Within the intervention ward, the differences between the allergist and internist, and the differences with and without the use of the questionnaires were analyzed by the McNemar test. Specificity and negative predictive values were calculated.

A p value <0.05 was considered statistically significant. Statistical analysis was performed using SPSS version 18.0 software.

Results

A total of 202 patients from both wards were recruited to this study, 86 from the control ward and 116 from the intervention ward. The two groups were comparable in

their demographic data and in the drugs suspected of causing allergy (table 1). Antibiotics and NSAIDs comprised 70–80% of the drug-related reactions in both groups.

Part 1

By definition, all study patients were considered by the treating wards to have a drug allergy. At the observation stage, in the intervention ward, 63 patients (54.3%) who were tagged as allergic by the ward physicians were labeled nonallergic by the allergist. In 13 (11%), the history was compatible with simple side effects and in 50 (43%), the history was unrelated to medication. Similarly, in 50 control group patients (58%) classified as allergic, the allergist found no support for this diagnosis. Eight (9%) had a history implying side effects and in 42 (49%), the history was unrelated to the use of the culprit drug. In most cases, 36 (57%) in the intervention ward, and 35 (70%) in the control group, the allergist could definitely rule out the diagnosis of allergy supported by the pharmacy prescription documentation and/or by the patient declaring safe reuse of the suspected drug. In the remaining cases, the history was not suggestive of drug allergy and the patient's symptoms were classified as not drug related. This was supported by a Naranjo adverse drug reaction probability score of less than 4 in all non-drug related cases (table 2).

Table 1. Patients' demographics and characteristics of suspected drugs and reactions

Demographics	Control ward	Intervention ward
Patients, n	86	116
Mean age $\pm$ SEM, years	70 $\pm$ 15	67 $\pm$ 17.5
Category of drugs suspected as the cause of reaction, n		
Antibiotics	45 (52)	60 (52)
NSAIDs	22 (26)	24 (21)
Contrast media	9 (10)	15 (13)
Antihypertensive drugs	2 (2)	8 (7)
Other drugs	8 (9)	9 (8)
Description of the reaction, n		
Rash	21 (24)	34 (29)
Pruritus	12 (14)	21 (18)
Shortness of breath	5 (6)	9 (8)
Angioedema	7 (8)	10 (9)
Vomiting/abdominal pain	6 (7)	13 (11)
Anaphylaxis	0	0
General discomfort/nonspecific complaints	35 (40)	29 (25)

n = Number of patients; figures in parentheses are percentages.

Table 2. Allergist's evaluation of patients regarded as allergic by the admitting wards

Classification	Intervention ward (n = 116)	Control ward (n = 86)
Allergic reaction, n	53 (46)	36 (42)
Side effect, n	13 (11)	8 (9)
Nonrelated, n	50 (43)	42 (49)
Naranjo score ¹ <4	50 (43)	42 (49)
Readministration of the suspect drug, n	35 (57)	35 (70)

n = Number of patients; figures in parentheses are percentages.

¹ Naranjo adverse drug reaction probability score (≥ 5 : probable or highly probable adverse drug reaction, ≤ 4 : possible or doubtful adverse drug reaction).

Part 2

In the intervention arm, within 24 h after admission, the ward physicians reevaluated the diagnosis of drug allergy, guided this time by the structured questionnaire. During the whole study period, 59 out of 116 patients

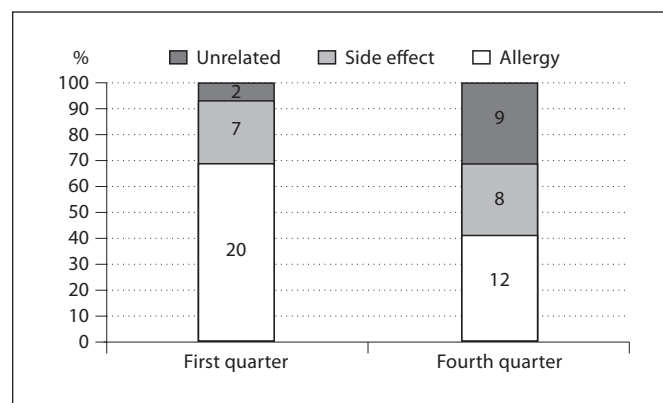


Fig. 2. Comparison of the negative predictive value, specificity and drug allergy diagnosis during the first and last quarters of using the questionnaire. Negative predictive value and specificity: 0.556 (first quarter) and 0.765 (last quarter).

(51%) initially tagged as allergic by the ward physicians were considered, by the same staff, not allergic after using the questionnaire. Twenty-seven of the descriptions (23%) were compatible with side effects and the complaints of 30 patients (26%) were evaluated as nonrelated to the culprit drug. When using the questionnaire, the more it was used, the more the ward physicians' diagnosis agreed with that of the allergist: in the first quarter of the study period (defined as the first 25% of enrolled patients), when using the questionnaire, 9 out of 29 patients (31%) first tagged as allergic, were eventually tagged as not allergic. Their complaints were defined as a side effect in 7 (24%) and nonrelated in 2 (7%). In most of them (66%), there was a documentation of reuse of the suspected drug without adverse effect. In the 2 patients defined as unrelated, the diagnosis was also based on a Naranjo score of less than 4. After practicing the use of the questionnaire, during the last quarter of the study period (defined as the last 25% of enrolled patients), this diagnosis was rejected in 17 patients (59%) initially regarded as allergic. The initial diagnosis of allergy was reclassified as side effect in 8 patients (28%) and unrelated in 9 (31%). In these 9 patients, the Naranjo score was less than 4. In 11 of the 17 patients (65%), there was a documentation of reuse of the suspected drug without an allergic reaction. The specificity of the drug allergy diagnosis during the first quarter of practicing this questionnaire was 0.556 and it rose to 0.765 in the last quarter. The negative predictive value of this diagnosis changed comparably (fig. 2).

Discussion

Taking drug allergy history is an integral part of any medical admission. It is important to extract from the patient's report previous adverse drug reactions and allergies as these data directly influence drug selection and therapeutic decisions. Unfortunately, the reliability of self-reported allergies is questionable and although these details are repeatedly asked by physicians and nurses, they are often recorded in a perfunctory or inaccurate way [10].

In the present study, we aimed to compare drug-related history taking by internists and allergy specialists and to find a simple objective tool that would help improve the accuracy of obtaining and recording this important information.

In the first part of the study, 202 patients were defined by internists as having ADRSA. In most of these patients, this diagnosis was ruled out when the allergist's took the history. Nevertheless, once the patient is labeled as having drug allergy readministration of the culprit drug is practically impossible. Different approaches have been proposed to solve this important issue. For example, a recent work by Caubet et al. [11] showed that in children, β -lactam allergy is clearly overdiagnosed because the skin rash is only rarely reproducible (6.8%) by a subsequent challenge. Similarly, in our study, the label of drug allergy could be removed safely as it was supported either by documentation obtained from the pharmacy or by a definite report of harmless reuse of the same drug. The allergist's diagnosis of an unrelated reaction was also supported by a low probability of adverse drug reaction, as defined by the Naranjo score. The current results support data previously reported by Lutomski et al. [3] that showed significant discrepancies between medical records and in-depth allergy history taking. A similar study by MacPherson et al. [5] clearly demonstrated that the patients' self-reported drug allergies are unreliable and when taken as a fact they cause medical treatment to deviate from standard of care. Taken together, the data collected from the first part of the current study strongly suggest the need for better allergy history taking in order to eliminate overdiagnosis of drug allergy and distinguish between allergy, anticipated side effects and other nonrelated reactions.

Previously published studies proposed different ways to resolve these discrepancies. Carter et al. [6] found that pharmacist's medication histories are more complete than those of other health professionals. Yu-Hor Thong et al. proposed verification of drug allergy diagnosed by the hospital nurses and doctors to be reevaluated by an

allergist/immunologist to enable more accurate determination of drug allergy [12]. However, although the proposed systems were efficient, they all involve specialized personnel that are not always available. Moreover, in an in-hospital setting where acutely ill patients are admitted around the clock and drug-related decisions may need to be taken immediately, instant consulting of an allergist is impractical. Naranjo et al. [9] previously published a method for estimating the probability of an adverse drug reaction [9]. This algorithm, although reliable and sensitive in monitoring adverse drug reactions, does not differentiate between allergic reactions and other side effects [13].

Considering these limitations, we developed a short questionnaire that consists of three simple steps designed to help extract a drug reaction history and differentiate between drug-induced allergy, side effects and unrelated conditions.

When designing the questionnaire, we assumed that physicians knew the difference between an allergic reaction and anticipated side effect, but were too occupied to actively implement this knowledge. In concordance with this assumption, in the second part of this study, we found that use of the questionnaire by the ward physician on the day of admission helped to rule out drug allergy in a significant proportion of patients initially tagged as having a drug allergy.

Initially, a drug allergy diagnosis was omitted in a third of patients, and after a short period of practicing the questionnaire, this diagnosis was excluded in as many as 59% of patients initially regarded as allergic. One can argue that these data imply a better understanding of the differences between drug allergy and side effects. However, we assume that it better represents the ability to learn how to use the questionnaire. This is supported by the fact that repeatedly, in a given admission of the same patient, within 24 hours, the diagnosis of drug allergy decreased significantly if the history was taken using the questionnaire.

Our questionnaire is short and easy to use. The addition of short guidelines in the case of suspected allergy to antibiotics or NSAIDs provided the admitting physician with a basic valuable tool in assessing as many as 80% of the reported drug allergies. An additional advantage of our questionnaire over those presented by previous authors is that it helped to differentiate between allergic and nonallergic reactions. Theoretically, the words 'drug allergy' should be used solely when immunologic mechanisms have been demonstrated [14]. In clinical practice, most cases of drug allergy are defined as such following

a suggestive history without further tests or challenges. Nevertheless, the label of 'drug allergy' needs to be applied with caution. Physicians are expected to understand that unnecessarily labeling a patient as allergic can result in future use of less adequate medications. Our solution of a simple questionnaire responds to this complexity: the questionnaire is available for use at all times by the admitting physician and has very high specificity. Along with using it, we suggest replacing the 'drug hypersensitivity' rubric in the admission chart by an 'adverse drug

reaction box'. This should be further divided to 3 categories: (1) Drug allergy – reserved for strict, well-defined allergic reactions; (2) Side effect – describing simple, known side effects, and (3) Unrelated – describing concomitant reactions that cannot be attributed to the use of a specific medication.

Widespread use of these definitions may help in the implementation of a uniform terminology for adverse drug reactions. The use of consistent language is essential for better communication and improving patient care.

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1 Online Supplementary Material: Drug Allergy Questionnaire

2

3 Patient name Age..... ID No..... Date.....

4

Name of suspected drug	
Description of the reaction (circle the relevant items, more than one if needed)	1.Rash- (urticaria? Other?) 2.Pruritus 3.Shortness of breath 4.Vomiting/abdominal pain/diarrhea 5. Anaphylactic shock 6.Don't remember 7.Other
When did the reaction begin? (circle the relevant item, possible more than one)	1.After the first dose 2.After the dose 3.After days of treatment 4.After the end of the treatment
How many years have passed since the reaction	
Have you used similar medications after the reaction? (names)*, **	If yes – when
Conclusion(circle one) 1.allergy 2. side effect 3. non-related	

5

6

7*, **: Guidelines for the physician interviewing the patient.

8*When reporting penicillin allergy, inquire about using ampicillin, amoxycillin, 9cloxacilin.

10 **When reporting NSAID's allergy, inquire about using other commercial 11brand-names of the same generic drug.