



Incidence, etiology, predictors and outcomes of suspected drug hypersensitivity reactions in a tertiary care university hospital's emergency department

A retrospective study

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Received: 11 May 2018 / Accepted: 8 April 2019
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Summary

Background Allergic drug reactions are adverse drug reactions that result from a specific immunologic response to a medication. Considering the epidemiological and clinical importance of drug allergy, this retrospective analysis focused on drug hypersensitivity in a tertiary care university hospital emergency department (ED).

Methods In this study 74,929 ED records obtained from March 2012 to March 2015 were reviewed to determine the incidence, etiology, predictors and clinical features of drug hypersensitivity.

Results The observed incidence of drug hypersensitivity was 0.87% of all ED admissions. It was significantly higher in female patients aged 18–29 years (2.26%; $P < 0.0001$) and during winter months (1.09%; $P = 0.0058$). Most patients had mild to moderate

symptoms which regressed following ED treatment. Only five patients (7 per 100,000 ED visits) were diagnosed with drug-induced anaphylaxis, and only five patients were provisionally diagnosed with severe non-immediate reactions with systemic involvement. No patient died of drug hypersensitivity in the ED, and only a small proportion required subsequent hospitalization. The most common causes of drug hypersensitivity reactions were amoxicillin and paracetamol.

Conclusion Drug hypersensitivity is a common reason for tertiary centre emergency admissions. This is the largest analysis of ED drug hypersensitivity admissions so far. Beta-lactams were identified as the leading cause of drug hypersensitivity requiring ED evaluation, which also explains the peak of drug hypersensitivity cases during winter months when the use of these medications is highest.

Electronic supplementary material The online version of this article (<https://doi.org/10.1007/s00508-019-1499-0>) contains supplementary material, which is available to authorized users.

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Keywords Drug hypersensitivity · Emergency department · Beta-lactam antibiotics · Anaphylaxis · Serious non-immediate reactions with systemic involvement · Adverse drug reaction · Paracetamol

Introduction

Drug hypersensitivity reactions are generally unexpected and unpredicted adverse drug reactions (ADRs) in response to normal therapeutic doses of a drug. They may be of non-immunologic nature, so-called pseudoallergic or intolerance reactions, or of drug-specific immunologic nature. The clinical picture does not enable a safe and proven distinction between them. True allergic drug reactions are ADRs where the immune system is previously involved in a sensitization phase and manifest on a new con-

tact with the drug with clinical symptoms (elicitation phase), such as urticaria, angioedema and anaphylaxis that are caused by drug-specific IgE antibodies and account for 6–10% of ADRs. In contrast, delayed-type immunologic drug hypersensitivity reactions are caused by previously sensitized specific T-cells [1]. As these results are based on the clinical charts without any allergological work-up, the reported drug hypersensitivity reactions cover immediate and delayed-type allergic and pseudoallergic reactions as well as intolerances without clearly proven immunopathogenetic mechanisms.

Since the 1990s ADRs have been the leading cause of both morbidity and mortality and hence pose a significant burden on health care resources [2, 3]. The ADRs are a common cause of emergency department (ED) admissions [4, 5], and a serious health and economic issue in the EDs. Drug hypersensitivity has been observed with almost all drugs, and can manifest as ADRs ranging from mild to severe. Anaphylaxis is a potentially life-threatening type of drug hypersensitivity, and it has been noted that hospitalizations for anaphylaxis are increasing in the United Kingdom [6]. According to the United Kingdom National Institute for Health and Care Excellence (NICE) guidelines, drug hypersensitivity is defined as any reaction caused by a drug with clinical features compatible with an immunological mechanism [7].

This retrospective analysis was conducted to determine the etiology, clinical characteristics, severity and treatment of drug hypersensitivity in the ED of the Department of Internal Medicine at the largest hospital in Croatia, the Clinical Hospital Centre Zagreb, during the first 3 years after the introduction of the electronic hospital information system, in the period from 16 March 2012 to 15 March 2015.

Material and methods

The ED electronic records stored within the hospital information system were used as the source of data in this analysis. The ED diagnoses of all patients admitted to the ED were examined for terms that may be related to hypersensitivity, such as pruritus, rash, blistered rashes, urticaria, angioedema, bronchospasm, hypotension, and anaphylaxis. The standardized medical dictionary for regulatory activities (MedDRA)¹ query (SMQ) for hypersensitivity was used as the basis to compile a list of symptoms and diagnoses that could correspond to drug hypersensitivity reactions. An additional search was performed to identify all patients who received adrenaline, an-

tihistamines, corticosteroids or bronchodilators. The ED records of all patients that met these criteria were further examined to determine whether drug hypersensitivity had been suspected. The World Health Organization (WHO)—Uppsala Monitoring Centre (UMC) system for standardized case causality assessment [8] was used to identify cases with at least a possible causal relationship with any suspected drug or other medicinal product. Cases of drug hypersensitivity identified by this methodology were grouped according to the chemical, pharmacological and therapeutic subgroups of suspected drugs as defined by the anatomical therapeutic chemical (ATC) classification system of the WHO Collaboration Centre for Drug Statistics Methodology [9].

The number of monthly admissions for overall suspected hypersensitivity vs. drug hypersensitivity reactions was analyzed for trends over this 3-year period. Patient demography was also reviewed. The χ^2 statistical method with Yates correction was used to determine the most significant risk factors.

Patients with drug hypersensitivity were further analyzed to determine the clinical presentation and outcome of ED visit (further hospitalization or fatal outcome, both of which would clearly indicate serious drug hypersensitivity). The records of patients with the most serious clinical presentation, suspected anaphylactic reactions and severe non-immediate reactions with systemic involvement were further studied to determine the etiology, existence of any relevant patient history, time to reaction onset and therapy administered during emergency transportation and in the ED. The given therapy was compared with internationally accepted guidelines [10–13]. Finally, it was assessed whether patients with return visits to the ED had a different etiology or severity of clinical presentation, or received different ED treatment, compared with those presenting only once.

Results

Out of 74,929 electronic ED records obtained from the electronic hospital information system during the period covered by this analysis, 71,982 (96%) visits included ED medical examination records and 2947 records (4%) referred to patients who were prescheduled to be admitted to the hospital through the ED (but were not examined in the ED). Suspected hypersensitivity reactions (stated as such in the physician's opinion, or clear symptoms of hypersensitivity treated with adrenaline, antihistamines, corticosteroids and/or bronchodilators) were the reason for 3039 initial visits (4% of all visits) and 43 return visits (0.06% of all visits). Among all diagnoses with suspected allergy the most common cause was insect bites (726 visits; 23.9%). Other suspected etiological factors were drugs and other medicinal products (627 visits; 20.6%), food (230 visits; 7.6%), plants (72 visits; 2.4%), and cosmetic products (46 visits; 1.5%). In the

¹ MedDRA version 20.0 was used. The aim of this SMQ is to retrieve all types of cases possibly related to hypersensitivity reactions. Many terms included in SMQ Hypersensitivity do not permit differentiation between hypersensitivity reactions and other causes for the given event and therefore further analysis of cases retrieved by the SMQ is required.

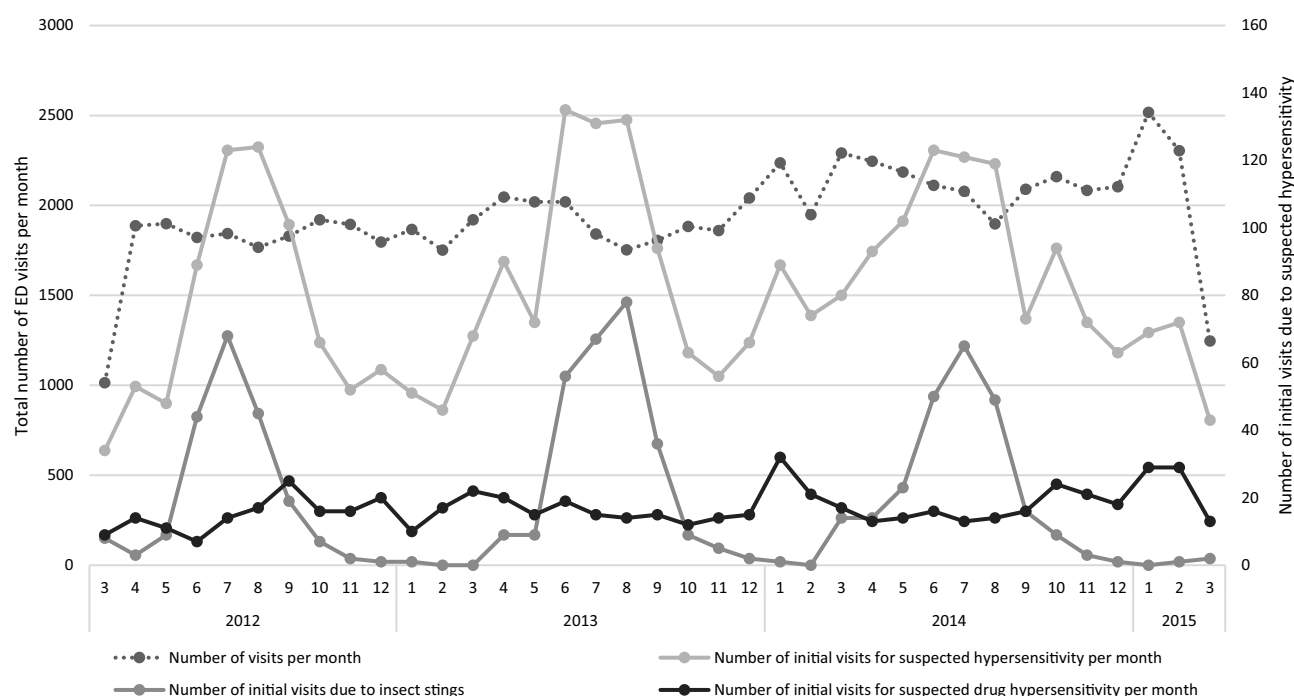


Fig. 1 Number of ED visits per month

remaining 1261 visits (41.5%) no clear cause was suspected. The overall observed incidence of drug hypersensitivity was 0.87% of all ED visits. The number of initial visits due to drug hypersensitivity ranged from 7 to 32 per month, with a mean value of 17 visits per month (standard deviation 5.5).

The time trends of all ED admission causes as well as suspected drug hypersensitivity reaction visits were analyzed. It was found that the peaks of overall suspected hypersensitivity visits occurred during the summer, while the peaks of drug hypersensitivity visits occurred during the winter months (Fig. 1). The likelihood that ED visits in January and February compared to the rest of the year would be due to drug hypersensitivity was found to be highly statistically significant (1.09% vs. 0.82%; $P=0.0058$).

Drug hypersensitivity was mainly suspected in female patients, who accounted for 72% of the sample, which was highly statistically significant ($P<0.0001$). Drug hypersensitivity was most common in women aged 18–29 years: 2.26% of all women in this age group who presented to the ED were suspected to have drug hypersensitivity, this also being highly statistically sig-

nificant ($P<0.0001$). The results of the current analysis clearly show a decrease in incidence of suspected drug hypersensitivity with increasing age. Drug hypersensitivity was least suspected in older patients aged ≥ 75 years, where only 0.2% of both men and women who presented to the ED were suspected to have this diagnosis (Tab. 1).

The most commonly suspected cause of drug hypersensitivity (see supplementary material online Table 1) was anti-infective medications for systemic and topical use (280 visits; 44.7%). These medications were most commonly suspected during the winter (72 out of 280 visits occurred during January and February; $P=0.0442$). The most commonly implicated active substance was amoxicillin (with or without clavulanic acid), which was suspected in 116 (18.5%) of all cases of drug hypersensitivity. It was more likely to be suspected than any other drug taken by the patients analyzed ($P<0.00001$). The second most commonly suspected drug classes were analgesics and nonsteroidal anti-inflammatory drugs (NSAIDs) (117 visits; 18.7%), and the most common in this group was paracetamol (alone or in fixed combination prod-

Table 1 Demographic data of patients with suspected drug hypersensitivity of all ED visits in the named period

Age range (years)	Male, in % (n/N)	Female, in % (n/N)	Total, in % (n/N)
<29	1.24 (37/2995)	2.26 (113/5010)	1.87 (150/8005)
30–39	0.95 (32/3379)	2.16 (97/4496)	1.64 (129/7875)
40–49	0.87 (34/3900)	1.36 (57/4195)	1.12 (91/8095)
50–64	0.40 (35/8746)	1.25 (111/8865)	0.83 (146/17,611)
65–74	0.35 (23/6521)	0.77 (53/6893)	0.57 (76/13,414)
>75	0.20 (14/7165)	0.21 (21/9817)	0.21 (35/16,982)
Total	0.54 (175/32,706)	1.15 (452/39,276)	0.87 (627/71,982)

Table 2 Anaphylactic reactions

Patient age and gender	Presenting signs and symptoms	Relevant patient history	Suspected drug	TTO	Outcome of ED visit
56 Y, F	Tongue edema, impaired consciousness, tachycardia	Penicillin hypersensitivity	Amoxicillin	<30 min	Hospitalization
32 Y, F	Unspecified anaphylactic symptoms	Hypersensitivity to amoxicillin/clavulanic acid	Amoxicillin	<1 day	Discharged after symptom regression
45 Y, F	Vomiting, hypotension, malaise, diffuse erythema	Amoxicillin and penicillin hypersensitivity	Amoxicillin/clavulanic acid	<1 day	Discharged after symptom resolution
55 Y, F	Nausea, feeling hot, loss of consciousness	No previous drug hypersensitivity	Paclitaxel	<1 day	Hospitalization
46 Y, F	Dyspnea, diffuse burning sensation, presyncope, hypotension	Earlier anaphylactic reaction to naproxen, but subsequent allergological testing negative	Naproxen	Few hours	Hospitalization
70 Y, F	Pruritus, dyspnea, dizziness	None	Amoxicillin/clavulanic acid	<1 day	Hospitalized to internal medicine department
20 Y, F	Tongue paraesthesia, pruritus, tachycardia, nausea	None	Fixed combination of paracetamol and other analgesics	Not specified	Discharged after symptom resolution
73 Y, F	Rash, angioedema, dyspnea	Hypersensitivity to ACE inhibitors, atopy	Norfloxacin	2 h	Discharged as symptoms already resolved
45 Y, F	Diarrhea, vomiting, somnolence, hypotension	None	Amoxicillin	1–2 h	After regression of symptoms patient decided to leave ED
42 Y, M	Dizziness, dyspnea, malaise, angioedema	Hypersensitivity to pantoprazole	Pantoprazole	<1 day	Discharged as symptoms already resolved
80 Y, M	Hypertension, headache, chills, dyspnea	None	Rituximab	<1 day	Hospitalized to internal medicine department
31 Y, F	Angioedema, diarrhea, rash	Atopy	Clarithromycin, metronidazole	<1 day	Discharged after symptom resolution
82 Y, M	Dyspnea, tachycardia, sweating, pallor	None	Blood transfusion (2nd dose)	Immediate	Hospitalized to intensive care department
68 Y, F	Nausea, vomiting, malaise, syncope, hypotension	None	Rituximab (1st dose)	Immediate	Discharged after symptom regression
52 Y, F	Pruritus, rash, hypotension	Atopy, hypersensitivity to paracetamol and diclofenac	Diclofenac	Immediate	Patient dismissed after symptom regression
29 Y, F	Burning sensation, urticaria, angioedema, dyspnea	Atopy	B complex preparation, herbal medicine	15 min	Dismissed after symptom regression
46 Y, F	Sweating, somnolence, hypotension, chest discomfort	None	Iron, parenteral preparation	Immediate	Dismissed after symptom regression

ACE angiotensin-converting-enzyme, ED emergency department, F female, h hour(s), M male, min minute, TTO time-to-onset (from introduction of suspected drug treatment), Y years

ucts in 38 visits; 6.1%). As for drug hypersensitivity in general, patients presenting with anti-infective-related hypersensitivity reactions were most likely to be women aged 18–29 years ($P=0.0159$). The majority of patients presented with mild to moderate forms of type I hypersensitivity reactions. The presenting signs and symptoms included widespread erythematous maculopapular pruritic rashes or urticaria, with or without angioedema (labial, eyelid or tongue edema). The vast majority (94%) of patients were successfully managed in the ED, and were discharged after res-

olution of symptoms. Only 6% (38 patients) were admitted to the internal medicine department, or referred to another department (mostly dermatology) or another hospital. None of the patients died of drug hypersensitivity in the ED. Of the patients that presented with type I hypersensitivity reactions 17 reported symptoms suggestive of anaphylaxis (Table 2). The incidence of drug-induced anaphylaxis was therefore 2.4 episodes per 10,000 ED visits, and accounted for 2.4% of visits due to drug hypersensitivity.

Table 3 Serious non-immediate reactions with systemic involvement

Patient age and gender	Presenting signs and symptoms	Provisional diagnosis	Previous patient history	Suspected drug	TTO	Outcome of ED visit
88 Y, F	Maculopapular rash with bullous changes on trunk and extremities, eczema on soles	SJS/bullous pemphigoid	Hypersensitivity to azithromycin	Tramadol/paracetamol	9 days	Unknown (referred to another hospital)
72 Y, M	Dark red erythema with petechiae, bullae and serous secretion between fingers, in axillae, on arms, and in inguinal and pubic region	SDRIFE	COPD, hypersensitivity to sulfamethoxazole/trimethoprim and penicillin	Sulfamethoxazole/trimethoprim	<1 day	Hospitalization
63 Y, M	Generalized rash (erythroderma) with urticarial changes on trunk and extremities, dysphagia, pyrexia, hyperaemia of eyelids and periorbital area, conjunctivitis	SJS	Not provided	Carbamazepine	1 month	Hospitalization
20 Y, F	Tongue and gum edema, urticaria on abdomen and erythematous punctiform perioral lesions, conjunctivitis, dysphagia and dyspnea, pyrexia	SJS	Hypersensitivity to amoxicillin/clavulanic acid	Amoxicillin/clavulanic acid	5 days	Hospitalization
58 Y, M	Pyrexia with chills, generalized pruritus, maculopapulous exanthema, skin edema, eosinophilia	DRESS syndrome	Hypersensitivity to ibuprofen, metamizole, and azithromycin	Sulfasalazine	Not specified	Hospitalization

COPD chronic obstructive pulmonary disease, *DRESS* drug reaction with eosinophilia and systemic symptoms, *ED* emergency department, *F* female, *M* male, *SDRIFE* symmetrical drug-related intertriginous and flexural exanthema, *SJS* Stevens-Johnson syndrome, *TTO* time-to-onset (from introduction of suspected drug treatment), *Y* years

Of the patients that presented as drug hypersensitivity five were provisionally diagnosed with serious non-immediate reactions with systemic involvement. Of these, two were provisionally diagnosed with Stevens-Johnson syndrome (SJS), one with SJS or bullous pemphigoid, one with symmetrical drug-related intertriginous and flexural exanthema (SDRIFE), and one with drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome (Table 3). The incidence of serious non-immediate reactions with systemic involvement was 0.7 per 10,000 ED visits (0.8% of all visits due to drug hypersensitivity).

Using the WHO causality method, the causal relationship between hypersensitivity reactions and suspected drugs was assessed as possible in 594 initial and 7 return visits, and probable in 33 initial visits and 1 return visit (initially also assessed as probably related to the same suspected drug). Of these 33 patients with probable drug hypersensitivity, 13 were due to antibacterial agents for systemic use (mostly amoxicillin) and 9 due to NSAIDs and other analgesics. Of the patients 26 presented with signs and symptoms of immediate-type hypersensitivity.

These were mainly maculopapular rashes, urticaria, angioedema, and dyspnea; however, in 4 of these 26 patients ED physicians made a provisional diagnosis of anaphylaxis, and in 2 patients they made a provisional diagnosis of serious non-immediate reactions with systemic involvement.

Out of eight return visits for drug hypersensitivity six were due to new onset urticaria: one patient with drug hypersensitivity reaction to symptomatic treatment of the common cold returned to the ED twice, two patients possibly had reactions to antibiotic treatment, one patient to NSAID treatment and one to glaucoma treatment. Of the remaining two return visits, one was due to concerns of an unresolved rash and throat tightness (probably related to sulfamethoxazole/trimethoprim), and one female patient returned due to concerns about chest pain although the angioedema possibly caused by moxifloxacin had already resolved. All were given antihistamine and corticosteroid treatment (except one with a milder episode who was only given antihistamine, and the abovementioned patient where angioedema had already resolved). All patients were

discharged on resolution of symptoms, except the patient with a more severe second episode of urticaria (attributed to NSAID treatment), who was referred to the dermatology department.

Discussion

There are only a few relatively recent retrospective reviews that focused on hypersensitivity reactions in the ED. A recent retrospective review of ED visits found that acute hypersensitivity reactions accounted for 1% of all ED visits, and drugs were the most commonly identified trigger accounting for approximately 25% of acute hypersensitivity reactions (therefore responsible for 0.25% of ED visits), yielding a study population of 58 patients with presumed drug hypersensitivity in a 6-month period [14]. This study, published in 2015, is the only methodologically similar study that could be identified in the scientific literature. In the present study an almost four-fold higher incidence of ED visits due to drug hypersensitivity (0.87%) was found. Another two retrospective reviews identified a crude cumulative incidence of 0.9 episodes of anaphylaxis per 1000 emergency episodes [15], and an incidence of 0.53 per 1000 patients per year [16]. In both studies [15, 16] drugs were the second most common suspected cause of anaphylaxis (after food), and the incidence of drug-induced anaphylaxis was approximately 0.25 per 1000 emergency episodes. Suspected drugs were antibiotics and NSAIDs/aspirin. These medicinal products have also been identified as important culprits for drug hypersensitivity in more recent publications [17, 18]. The current analysis identified an incidence of 0.24 possible drug-induced anaphylaxis episodes per 1000 ED visits. Therefore, the observed incidence of drug-induced anaphylaxis in the ED was similar to that observed in the mentioned recent studies.

In the current analysis women aged 18–29 years had the highest observed incidence of drug hypersensitivity as well as hypersensitivity to anti-infective medications (drug hypersensitivity was suspected in 2.26%, and hypersensitivity to anti-infectives was suspected in 1.0% of all ED visits in this patient group). This is in line with a recent analysis of antibiotic challenge reactions in patients reporting a history of antibiotic associated immediate-type hypersensitivity, where challenge-reactive patients were significantly younger ($P=0.007$), and more often women ($P=0.036$) [19]. In another recent retrospective review, penicillin hypersensitivity was almost twice as common in women than in men [20]; however, this significantly higher number of women with drug hypersensitivity that was also observed in current analysis could also be caused by a lower threshold of symptoms prompting women to present to the ED [21].

In general, drugs most commonly implicated in type I reactions include beta-lactams (mainly penicillins and cephalosporins), neuromuscular blocking

agents, quinolones, platinum-containing chemotherapeutic agents (such as carboplatin and oxaliplatin), and foreign proteins (including chimeric antibodies, such as cetuximab and rituximab) [17, 22–25].

In a cross-sectional study penicillins and other beta-lactams (penicillin G or V, followed by amoxicillin and clavulanic acid) were the most common causes of self-reported drug hypersensitivity (4.5%), and NSAIDs (led by aspirin and ibuprofen) were placed second (1.9%) [23]. These results are similar to the present study, with the main difference of hypersensitivity to amoxicillin and clavulanic acid or amoxicillin alone being much more common than hypersensitivity reactions to penicillin V (116 vs. 24 cases). This is probably due to the fact that penicillin V is much less prescribed in Croatia.

Of the other drugs well-known to cause drug hypersensitivity, in this study no events were attributed to neuromuscular blocking agents. This can be explained by the fact that reactions to these drugs would mostly be expected perioperatively (after initiation of anesthesia). Therefore such patients would not be referred to the ED, but managed within the anesthesiology department [26, 27].

The summer peaks of all suspected hypersensitivity visits in the current study can be explained by the highest number of insect bites during this time of the year [28]. The winter peaks of drug hypersensitivity can be explained by the highest antibiotic use (for treatment of respiratory infections) during this season [29]. All drugs causing serious non-immediate reactions with systemic involvement observed in this analysis (Table 3) are drugs known to cause such reactions, according to their respective summaries of product characteristics (SmPCs).

Limitations of this analysis

A limitation of the study is the fact that in some of the suspected drug hypersensitivity reactions the disease itself, and not the drug, is the etiological agent responsible for symptoms and/or signs of the presumed allergy. For example, a skin rash can be caused by an infection rather than antibiotic treatment. This is a source of bias and probably caused some degree of overestimation of the incidence of suspected drug hypersensitivity reactions in the ED. Due to its retrospective nature, this study may have underestimated the incidence of drug-related ED visits as a result of missing or inaccurately documented information in the ED records. Any such incompleteness of records might have also caused type II errors in identifying patients at increased risk. Due to the nature of ED records, no information about the social status of the patients was available, which was therefore not considered among the potential risk factors. Some of the ADRs classified in this review as drug hypersensitivity, might have in fact been pseudoallergic drug reactions, also called non-immunological hypersensitivity

reactions [30]. Pseudoallergic reactions are difficult to distinguish clinically because they are similar or identical in clinical presentation to true allergic reactions. Some pseudoallergic reactions arise from direct (rather than immunologic) activation of immune and inflammatory cells, so the final steps in pathogenesis and the resultant clinical features are indistinguishable from those of true allergic reactions. Furthermore, the mentioned tendency of female patients to present to the ED with milder symptoms might have led to a type I error inflation. Additionally, the results of the WHO causality assessment depend on the partially subjective assessment performed by authors based on data available in ED records (due to the nature of ED visits, confounding factors might have been incompletely documented). It is possible that some of the drug hypersensitivity reactions were later excluded based on objective results of allergy testing. Moreover, since all information was gained only from electronic records of ED visits, additional important data such as associated infections (e.g. pneumococcal pneumonia, herpes virus infections), skin biopsy findings and other important clinical details as well as subsequent allergologic work-up (e.g. patch-test results), were not available. Therefore, the definite conclusions about the causative agents in patients with the provisional diagnoses of SJS and DRESS (Table 3) are not guaranteed. Finally, the observed proportion of drug hypersensitivity and respective suspected drugs in this largest Croatian hospital may not be representative of Croatia or Europe in general.

Conclusion

Drug-related hypersensitivity reactions constituted the second most common cause, after insect bites, amongst all cases of hypersensitivity reactions at the ED of the largest Croatian hospital in a 3-year period. The drug hypersensitivity incidence was 0.87% of all ED visits, and female patients aged 18–29 years were identified as the population at highest risk. Drug hypersensitivity was suspected almost three times more commonly than food hypersensitivity, but slightly less commonly than insect bite hypersensitivity reactions. No specific cause was identified in over 40% of ED visits due to hypersensitivity. The vast majority of drug hypersensitivity reactions were mild to moderate, and regressed following ED (mostly systemic antihistamine and fluid replacement) treatment. During this 3-year period, drug-induced anaphylaxis occurred in only 12 ED patients (0.24 per 1000 ED visits). No patient died of drug hypersensitivity in the ED, and only a small proportion (6%) required subsequent hospitalization. The most common causes of drug hypersensitivity were antibiotics (mostly beta-lactam antibiotics), which also explains the peak of drug hypersensitivity visits during winter months when the use of these medications is highest. A more structured, comprehensive and standardized docu-

mentation of ED records could provide very valuable insights into causes, risk factors, management practices and outcomes of patients presenting with drug hypersensitivity reactions, as well as enable faster detection of potential drug safety signals.

Author contribution CB wrote the article and performed data analysis, while LB and RL designed the study, performed data acquisition and critical review of the article.

Acknowledgements The authors thank Ružica Jurakić-Tončić, a specialist in dermatology and allergology, for advice on making provisional diagnoses in patients with serious non-immediate reactions with systemic involvement. We thank Prof. Aleksandra Žmegač-Horvat, a professional proof reader in medical English, for revising the manuscript.

Conflict of interest C. Bielen, L. Bielen, and R. Likić declare that they have no competing interests.

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Table 1 Suspected medications for drug hypersensitivity reactions grouped by their therapeutic indication

2nd level in the ATC classification system / INN (or description)	Number of individual ED visits
Antibacterials for systemic use (J01)	275
Amoxicillin and enzyme inhibitor	79
Amoxicillin	37
Phenoxymethylpenicillin	24
Azithromycin	23
Clindamycin	22
Cefuroxime	18
Sulfamethoxazole and trimethoprim	11
Clarithromycin	9
Nitrofurantoin	9
Norfloxacin	6
Cefalexin	5
Metronidazole	5
Ciprofloxacin	4
Moxifloxacin	4
Unspecified antibiotic	3
Levofloxacin	2
Doxycycline	2
Cefixime	2
Erythromycin	1
Clarithromycin, metronidazole	1
Ciprofloxacin and clindamycin	1
Nitrofurantoin and azithromycin	1
Cotrimoxazole, rabeprazole	1
Flucloxacillin	1
Cefazolin	1
Amoxicillin, metronidazole	1
Nitrofurantoin, cefuroxime	1
Amoxicillin/clavulanic acid, clindamycin	1
Analgesics (N02)	62
Acetylsalicylic acid	21
Paracetamol, combinations excl. psycholeptics	17
Paracetamol	14
Tramadol and paracetamol	5
Unspecified analgesic	3
Unspecified antipyretic	1
Tramadol	1
Anti-inflammatory and antirheumatic products (M01)	55
Ibuprofen	23
Ketoprofen	14
Diclofenac	11
Indometacin	2
Piroxicam	1
Combined NSAID	1
Naproxen	1
Ibuprofen and diclofenac	1
Unspecified NSAID	1
Contrast media (V08)	16
X-ray contrast media, iodinated	15
Gadopentetic acid	1
Various (V)	14
Herbal medicine	7

2nd level in the ATC classification system / INN (or description)	Number of individual ED visits
Honey-based medicine	3
Dietary supplement	2
Propolis	2
Antacids (A02)	12
Pantoprazole	8
Ranitidine	2
Esomeprazole	2
Antihypertensives acting on the renin-angiotensin system (C09)	11
Ramipril	5
Perindopril and diuretics	2
Ramipril and amlodipine	1
Ramipril and diuretics	1
Enalapril	1
Fosinopril and diuretics	1
Antineoplastic agents (L01)	10
Rituximab	5
Lapatinib, capecitabine	1
Temozolomide	1
Sorafenib	1
Oxaliplatin, capecitabine	1
Paclitaxel	1
Cough and cold preparations (R05)	9
Bromhexine	5
Acetylcysteine	3
Pholcodine	1
Antiepileptics (N03)	8
Lamotrigine	4
Carbamazepine	2
Pregabalin	1
Oxcarbazepine	1
Thyroid therapy (H03)	7
Thiamazole	5
Levothyroxine sodium	2
Blood substitutes and perfusion solutions (B05)	7
Blood plasma	2
Other blood products	2
Erythrocytes	2
Thrombocytes	1
Anaesthetics (N01)	7
Local anaesthetic	2
Mepivacaine	2
Lidocaine, combinations	1
Lidocaine	1
Unspecified anaesthetic	1
Vitamins (A11)	6
Vitamins	5
Multivitamins and other minerals, incl. combinations	1
Antidiarrhoeals, intestinal anti-inflammatory/anti-infective agents (A07)	4
Sulfasalazine	2
Bismuth preparations	1
Lactic acid producing organisms	1
Sex hormones (G03)	3
Drospirenone and ethinylestradiol	2

2nd level in the ATC classification system / INN (or description)	Number of individual ED visits
Dienogest	1
Psycholeptics (N05)	3
Promazine	1
Olanzapine	1
Quetiapine	1
Immune sera and immunoglobulins (J06)	3
Immunoglobulins, normal human, for intravascular adm.	3
Antianæmic preparations (B03)	3
Folic acid, combinations	1
Ferrous gluconate	1
Iron, parenteral preparations	1
Antihypertensives (C02)	3
Moxonidine	2
Multiple antihypertensives	1
Corticosteroids, dermatological preparations (D07)	3
Mometasone	2
Dexamethasone and antibiotics	1
Calcium channel blockers (C08)	3
Diltiazem	1
Lercanidipine	1
Amlodipine	1
Psychoanaleptics (N06)	3
Escitalopram	1
Trazodone	1
Venlafaxine	1
Cardiac therapy (C01)	3
Amiodarone	1
Trimetazidine	1
Isosorbide mononitrate	1
Antigout preparations (M04)	2
Allopurinol	1
Unspecified gout medicine	1
Urologicals (G04)	2
Tamsulosin and dutasteride	1
Tamsulosin	1
Gynaecological anti-infectives and antiseptics (G01)	2
Clotrimazole	1
Povidone-iodine	1
Antifungals for dermatological use (D01)	2
Ketoconazole	1
Miconazole	1
Drugs for constipation (A06)	2
Bisacodyl	2
Immunostimulants (L03)	2
Glatiramer acetate	2
Antithrombotic agents (B01)	2
Nadroparin	1
Dabigatran etexilate	1
Antihistamines for systemic use (R06)	2
Fexofenadine	1
Desloratadine	1
Immunosuppressants (L04)	2
Methotrexate	1

2nd level in the ATC classification system / INN (or description)	Number of individual ED visits
Infliximab	1
Throat preparations (R02)	2
Dichlorobenzyl alcohol	1
Benzalkonium	1
Drugs used in diabetes (A10)	1
Metformin	1
Drugs for treatment of bone diseases (M05)	1
Strontium ranelate	1
Preparations for treatment of wounds and ulcers (D03)	1
Dexpanthenol	1
Nasal preparations (R01)	1
Fluticasone	1
Diuretics (C03)	1
Indapamide	1
Antihemorrhagics (B02)	1
Phytomenadione	1
Antibiotics for dermatological use (D06)	1
Mupirocin	1
Ophthalmologicals (S01)	1
Fluorescein	1
Vasoprotectives (C05)	1
Diosmin, combinations	1
Antiseptics and disinfectants (D08)	1
Unspecified antiseptic	1
Muscle relaxants (M03)	1
Botulinum toxin	1
Multiple medications	56
Unspecified medication(s)	10
Grand Total	627

Abbreviations: ATC = anatomical therapeutic chemical (classification system); INN = international non-proprietary name;
NSAID = non-steroid anti-inflammatory drug.