

These articles have been accepted for publication in the *British Journal of Dermatology* and are currently being edited and typeset. Readers should note that articles published below have been fully refereed, but have not been through the copy-editing and proof correction process. Wiley-Blackwell and the British Association of Dermatologists cannot be held responsible for errors or consequences arising from the use of information contained in these articles; nor do the views and opinions expressed necessarily reflect those of Wiley-Blackwell or the British Association of Dermatologists

Accepted Date : 05-Sep-2011
Article type : Original Article

Is drug allergy less prevalent than previously assumed? A 5-year analysis

L.M. Heinzerling^{1, 2}, D. Tomsitz¹, M.D. Anliker¹

¹ Department of Dermatology and Allergies, Cantonal Hospital St. Gallen, Switzerland

² Department of Dermatology, University Hospital Erlangen, Germany

Running head: AME and drugs

Funding source: None

Disclosure of potential conflict of interest: None of the authors have a potential conflict of interest with any of the content of this article.

The data has not been previously presented.

Corresponding author:

Lucie Heinzerling, MD, PhD, MPH
Department of Dermatology
University Hospital Erlangen
91052 Erlangen, Germany
Tel.: +49-9131-85 33 661
Fax: +49-9131-85 36 175
lheinzer@post.harvard.edu

Abstract

Background: Rashes are a frequent conundrum in clinical practice since they may be reactive, drug-induced or disease-specific. Identification of the culprit drug is important since re-exposure may be harmful or even life-threatening and unnecessary avoidance of 'innocent' drugs leads to limitations of treatment options.

Objective: To objectify the cause of suspected cutaneous drug reactions in a larger patient population.

Method: Over the past 5 years, 612 patients with suspected cutaneous drug reactions were evaluated. Histology was assessed as indicated. About 200 patients were invited for complete work-up with skin tests (prick/intracutaneous testing and scratch/patch as indicated) and, if necessary, lymphocyte transformation tests (LTT). In special cases, drug provocation tests were conducted.

Results: A total number of 141 cases with suspected drug reaction underwent complete work-up (age 6-86 years; 75% female and 25% male). In 107 cases (76%) a drug was identified whereas 34 (34%) were reactive rashes or had other causes. Mostly, cutaneous drug reactions were maculopapular rashes, urticaria/angioedema, less frequently AGEP, DRESS, SDRIFE, TEN, and fixed drug eruptions were present. Of all cutaneous drug reactions investigated, 39.8% were caused by antibiotics, 21.2% by anti-inflammatories, 7.6% by contrast media and 31.4% by others (oral antidiabetics, antimycotics, antipsychotics, antiepileptics and others).

Limitations: Possibly, this study tends to include more severe drug reactions.

Conclusion: Clinical assessment overestimates the role of drug allergies in cutaneous reactions. Assessment of suspected drug reactions can be greatly improved by thorough evaluation including dermatological and allergological work-up with skin testing and essays such as LTT.

Key words: drug reaction, adverse effect, skin test, lymphocyte transformation test, drug rash, exanthema, drug provocation

Capsule summary:

- Cutaneous drug reactions are frequently suspected in clinical practice. Mostly, definitive judgment is based on chronologic criteria and probability.
- Thorough allergologic work-up (including skin tests, lymphocyte transformation tests and drug provocation as needed) of a large patient population narrows down the patients with suspected drug allergies to the cases who really have one by one third.
- Suspected drug allergies should be investigated for definitive diagnosis. Lymphocyte transformation tests are an important tool.

ABBREVIATIONS

AGEP: Acute generalized exanthematous pustulosis

DDD: defined daily doses

DRESS: Drug Reaction with Eosinophilia and Systemic Symptoms

EAACI: European Academy of Allergy and Clinical Immunology

LTT: Lymphocyte Transformation Test

SDRIFE: Systemic Drug-Related Intertriginous and Flexural Exanthema

SJS: Stevens-Johnson-Syndrome

TEN: Toxic Epidermal Necrolysis

INTRODUCTION

Adverse reactions to drugs are frequent. Skin reactions are among the most common undesired effects of drugs occurring in 2 to 3% of medical patients ^(1;2). Besides the immediate type reactions (angioedema/urticaria or anaphylaxis) clinical pictures include maculopapular rash, bullous reactions, acute generalized exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS), vasculitis, fixed drug eruption and Stevens-Johnson-Syndrome (SJS)/Toxic Epidermal Necrolysis (TEN). The attribution of a cutaneous reaction to a particular drug frequently entails a difficult judgment ⁽³⁾, since the clinical picture often gives no clue to the offending drug ⁽⁴⁾, patients receive several drugs simultaneously and are sick so that the skin reaction may also be reactive e.g., induced by an infection (EBV, CMV, HHV6, Parvovirus, B19), toxic or inflammatory (Still's disease). Further differential diagnoses include Graft-vs.-Host disease, and Kawasaki syndrome.

All drug reactions can be classified in immediate and delayed reactions. If allergic the former are IgE-mediated whereas the latter are T-cell dependent. Non-allergic pathomechanisms also exist. Most cutaneous drug reactions are related to drug hypersensitivity, i.e. by a drug-specific activation of the immune response. The drug may act as hapten/antigen as well as similarly to a superantigen ⁽⁵⁾, with a pharmacological interaction of parts of the drug with an immune receptor (p-i concept; ⁽⁶⁾). These latter reactions do not need a sensitization phase - the drug reaction can occur upon the first encounter with the drug. Coombs and Gell have introduced four categories for immunologic reactions with classes I-IV (IgE, cytotoxic, immunoglobuline complexes, T-cell dependent). Furthermore, according to the classification by Pichler *et al.* there are four distinct subtypes within class IV with Th1, Th2, cytotoxic T-lymphocytes and other T-cells being the immune reactants and macrophages (IV a; contact dermatitis), eosinophils (IVb; maculopapular exanthema with eosinophilia), T-cells (IVc; maculopapular and bullous exanthema) and neutrophils (IVd; AGEP) being the effector cells ⁽⁷⁾. These different pathomechanisms explain the large variety in clinical and histological pictures that can be seen.

There have been a number of epidemiologic studies investigating drug-induced cutaneous reactions in hospital patients (reviewed in ⁽⁸⁾). A large study was conducted in the US (Boston Collaborative Drug Surveillance; ^(2;9) with a 7-year monitoring program of 22'227 consecutive medical inpatients that identified 347 patients with suspected drug-induced cutaneous reactions (1.6%). Other studies investigated hospital inpatients in Spain ⁽¹⁰⁾, France ⁽¹¹⁾, Malaysia ⁽¹²⁾, China ⁽¹³⁾, Singapore ⁽¹⁴⁾ and India ⁽¹⁴⁻¹⁶⁾. Switzerland has a report resulting from a computerized drug-monitoring system between 1974 and 1993 ⁽¹⁷⁾ reporting on 1317 cases with definite or probable drug-induced skin reactions out of a total of 48'005 inpatients (2.7%).

Mostly, attribution of the reaction to a drug has been made by probability based on factors like timing of drug intake ⁽¹⁸⁻²⁰⁾.

However, few studies have extensively tested patients to prove diagnosis. This may be misleading since a wide range of skin lesions are not specific for an underlying cause. Allergologic testing and re-exposure can help to underscore the drug as the trigger of the cutaneous reaction as opposed to other possible causes ⁽²¹⁾. In Denmark, a study with allergologic work-up was conducted ⁽²²⁾ which evaluated a total of 194 patients with suspected cutaneous drug reactions but diagnosed a drug reaction in only 65 (33.5%) of these patients. Out of these patients 18 were tested ⁽²³⁾. Drug testing is essential since otherwise diagnosis will be made mainly based on former reports thus overestimating drugs that are known to frequently induce drug reactions and underestimating drugs that have not yet been described as inducers of drug reactions ⁽²⁴⁻²⁸⁾.

The study described here reports on a large number of patients with suspected drug reaction who have been completely evaluated. This is an important overview since the allergologist in clinical practice is often expected to give a first judgment of potential culprit drugs to stop. It sums up the experiences of a tertiary care hospital over the past 5 years.

METHODS

The study was conducted at a large regional hospital (900 beds), the Cantonal hospital St. Gallen in Switzerland with 164'391 hospitalized patients during the time of the study. The department of Dermatology and Allergology has provided consults to a total of 18'273 patients from 2006 until 2010. It serves as a referral center for patients with drug reactions with its specialized allergy clinic. Within this study all patients referred for potential drug reactions from 2006 until 2010 were investigated.

Patients who were suspected to have cutaneous drug-induced skin reactions after consultation by the allergologist were invited for further assessment to identify the culprit drug 6 weeks after the initial reaction. Patients were then evaluated by allergologic testing and if needed drug provocation testing.

Cases were identified by screening our access patient database looking for the search terms drug allergy, drug reaction, exanthema, DRESS, TEN, SJS, Baboon, SDRIFE, drug eruption, and AGEP. All identified patients (n=612) were then analyzed using the patient files for clinical picture, drug history, histologic assessment when present and outcome of the allergologic evaluation. Out of these patients 27 were regarded as reactive exanthemas due to infection and/or histopathologic exclusion of drug allergy, 106 patients showed pseudoallergic/intolerance reactions to anti-inflammatories, which do not produce positive skin tests or LTT, 40 were angioedemas due to other causes (bacterial, histamine, opiates (histamine release), sulfites and others). Others had other dermatological problems (contact dermatitis, exsiccation eczema, etc.). In this study, exclusively patients with suspected drug allergy and complete work-up (n=141) were included.

DIAGNOSTIC WORK-UP

Clinical diagnosis was based on consensus definitions (reviewed in ⁽²⁹⁾). Probability judgment was based on parameters from the ALDEN algorithm^{29b}: time lag from initiation of drug intake, drug presence in the body at onset, prechallenge/rechallenge (previously tolerated/previous allergic reaction), dechallenge (regression despite continuation of intake), drug notoriety (probability of drug reaction according to previous literature), other etiological alternatives (e.g., infectious). Diagnostic work-up of patients included as needed a punch biopsy, skin prick and intracutaneous testing

for immediate reactions. Patch testing was performed for delayed reactions ⁽³⁰⁻³³⁾. Histamine HCl 10mg/ml (Stallergenes, Antony, France) was used as positive control, NaCl 0.9% as negative control. Commercial extracts were used for penicillins (Diater, Madrid, Spain). Prick testing (lancets from Stallergenes, Antony, France), intracutaneous testing and scratch testing was performed on the forearm according to guidelines of the European Academy of Allergy and Clinical Immunology EAACI ⁽²⁴⁾. Patch and epicutaneous testing was done using commercial patches (Curatest, Lohmann & Rauscher, Rengsdorf, Germany) according to the recommendations of the European Society of Contact Dermatitis ⁽³⁴⁾. Patch tests were read at 24 and 48 hours. For antibiotics penicillin G (100'000 E/ml), D-penicillamin (50 mg/ml), phenoxymethylpenicillin (100'000 E/ml), amoxicillin/clavulanic acid (50 mg/ml), erythromycin (10 mg/ml), cefuroxim (50 mg/ml) –all in vaseline- and Klacid (500 mg), Augmentin (1 g), Bactrim forte, Tienam, Mandokef (1:100 and 1:10) were included. Tested analgesics included propyphenazon, acetylsalicylic acid, paracetamol (acetaminophen), phenobarbital, novaminsulfon, diclofenac, mefenamic acid, nimesulid, celecoxib, mannitol (placebo), ibuprofen, tramadolhydrochlorid; blood thinners included heparin (5000 IE/0.5 ml), dalteparin (10'000 IE/0.4 ml), enoxaparin (40 mg/0.4 ml), nadroparin (3800 IE/0.4 ml), and fondaparinux (2.5 mg/0.5 ml). For contrast media, ioxaglat-meglumin (320 mg/ml), iopamidol (300 mg/ml), iodixanol (320 mg/ml), ioxithalamat-meglumin (350 mg/ml), iomeprol (300 mg/ml), and iodide (only epicutaneous testing) were tested as described by Brockow et al. (brockow et al. 2009 allergy). Local anesthetics included procain 1%, lidocain 1%, prilocain 1%, prilocain with octapressin, mepivacain 1%, bupivacain 0,5%, articain with adrenalin (rudocain 40mg/5ug), dinatriumsulfite 1%, natriumbenzoate 1%, methylparaben 0.1%, latex, adrenalin (0.1 mg/ml). The narcotics included propofol (10 mg/ml), thiopental, etomidate (20 mg/10 ml), atacuri besilas (25 mg/2.5 ml), midazolam (15

mg/3 ml), rocuronium bromide (50 mg/5 ml) and succinylcholine chloride (100 mg/2 ml). In special cases lymphocyte transformation test and provocation tests were done as previously described^{33b}. Briefly, blood was taken in heparin tubes, peripheral mononuclear cells (PBMCs) were isolated via a gradient (Ficoll/Hypaque, Amersham Bioscience, Uppsala Sweden) and diluted to obtain 2×10^6 cells/ml. In microtitre plates drugs at different concentrations and positive (phytohaemagglutinin) and negative (no drug) controls (all in triplicates) were cultured for 5 days. Then, 3H-thymidine was added for 12 hours, the cells harvested and proliferation measured with a betacounter. Tests were regarded positive if SD between triplicates was less than 30% and the stimulation index (= proliferation with drug/proliferation without drug) was more than 2, based on negative values in exposed but not allergic individuals. A total of 96 LTTs were performed in 31 patients.

In rare cases, drug provocation testing was performed⁽³⁵⁾.

Analysis included frequencies of different culprit drugs, distribution of clinical diagnosis and risk of cutaneous reaction. Data were adjusted to number of doses administered as follows:

Number of cases of adverse cutaneous drug reaction

Number of single doses administered in the hospital

Thus, risks for drug reactions were expressed as risk per 1000 defined daily doses (DDD nach WHO definition), i.e. the risk the patient has of developing a drug-related cutaneous reaction after receiving one day of treatment with the respective drug: $\text{Number of cutaneous reactions} \times 1000 / (\text{DDD over 5 years})$. Prescription information was based on data from the cantonal pharmacy St. Gallen, Switzerland.

RESULTS

A total of 612 patients were referred to the Department of Dermatology and Allergies for suspected cutaneous drug reactions in the past 5 years. Out of these a total of 141 cases were suspected to have had a cutaneous drug reaction by an allergologist and had a complete diagnostic work-up. The clinical manifestations seen most often were maculopapular exanthema and urticaria/angioedema as depicted in Figure 1. Another 173 patients had intolerance reactions or infectious exanthemas and 298 did not receive a complete work up with skin tests or were not biopsied due to refusal or because the situation did not allow further investigation. Out of the 141 cases 107 patients were diagnosed with a drug reaction (69.4%) whereas 29 cases (27.1%) were not drug-related and 5 (3.5%) remained of unknown cause even after complete work-up. The non-drug related skin reactions were parainfectious (15; 10.6%), reactive to other causes (7; 5.0%), EBV-associated (3; 2.1%), Id reactions (2; 1.4%), or caused by other triggers. Cases with drug reactions showed a striking preponderance of female patients with 84 out of 107 cases (78.5%) being female. A total of 76 cases were identified by positive reactions to skin tests, 19 cases were identified by positive LTT, and 6 patients were identified with drug provocations (3 with intolerance to non-steroidal drugs and 3 with drug reactions to antibiotics). Seven cases were identified without skin testing with severe drug reactions (LYELL/TEN; n=4), clear causality (DRESS; n=1) and other reasons (n=2).

Causing drugs were mostly antibiotics, anti-inflammatories/analgesics and contrast media with 47 (39.8%), 25 (21.2%) and 9 (7.6%) cases, respectively (Table 1). For the most severe reactions TEN, Lyell syndrome and Stevens-Johnson-Syndrome acetylsalicylic acid, ampicillin, carbamazepine, ciprofloxacin/vancomycin, ethambutol, nevirapine and lamotrigine were identified as culprit drugs. LTT identified the

following culprit drugs in patients who had previously remained negative in skin tests: antibiotics (cefmandol, ceftriaxon, amoxicillin, PTV, clavulanic acid, vancomycin, cefazolin, penicillin G/V, imipenem, clarithromycin), analgesics (ASS, piroxicam), contrast media (hexabrix, visipaque), esomeprazol, prednisolon, methylphenidate, copaxone. All drugs by clinical presentation are presented in Table 2.

Risks of drug reactions per 1000 defined daily doses are calculated with the data from the Cantonal pharmacy. This has a certain bias since it does not include all prescriptions. It shows striking differences with very high risks for some drugs like levofloxacin, nadroparin and tolperison (see Table 3).

DISCUSSION

This is a five-year longitudinal study of drug rashes and the evaluation of the causative drugs. This study purposefully excluded cutaneous drug reactions like injection site reactions to any drugs and all drug reactions that occurred during specific immunotherapy as well as cutaneous reactions to blood and blood products since these are easily traceable to the causing drug.

Out of a total of 612 patients 141 cases with suspected drug allergy were completely evaluated with allergy testing. Interestingly, out of the tested subjects with suspected drug reaction one third could not be confirmed by objective testing and skin changes were tracked to another trigger. This confirms former data from other studies that found also only part of the suspected drug reactions to finally be confirmed. Borch et al. ⁽²³⁾ confirmed 27% of suspected cases after testing, and Surtees et al. ⁽²⁸⁾ who screened patients with only a history of drug allergy confirmed only 3% of suspected cases. Thus, depending on the prescreening the role of drugs in sudden exanthema is over-estimated. All of these 141 cases would have been attributed as drug reactions had it not been for the testing and work-up. However, only rigorous testing

(and provocation) can rule out or confirm the drug reaction and finally identify the culprit drug. Interestingly, it was by means of a LTT that one fifth of the cases were identified which thus represents an important tool shown to have a sensitivity of 78%^{35b} even though this methodology is often considered experimental. To specify sensitivity and specificity of LTT in comparison to that of skin tests for each substance further studies are needed.

This study has tested a large number of patients with suspected drug allergy to diagnose them with certainty. It shows that in clinical practice the majority of drug reactions are still caused by antibiotics and non-steroidal anti-inflammatories. For the severe drug reactions (TEN/Lyell/SJS), anticonvulsants and antivirals also play a role. Potential biases of the data include the avoidance of applying drugs to which patients are known to be allergic. Furthermore, this study potentially excluded less severe, immediate or transient drug reactions since only cases that were reported to the Department of Dermatology and Allergies are included. This might be further accentuated by the fact that only patients with a complete work-up were included in the final analysis and more severe cases could be more likely to complete the investigations. However, if at most the 298 patients without or incomplete testing would be presumed to have drug allergy plus the confirmed 107 it would amount to a maximum of 405 cases with drug allergy. Thus, 202 out of 612 (33%) did not present with drug allergy, who were primarily referred with this suspected diagnosis and 0.25% of the hospitalized patients in this time period would have been affected. To our knowledge this is the report with the largest number of tested cases for delayed-type drug hypersensitivity (n=141). In the Danish study, 18 cases were tested⁽²³⁾. Other studies have not included drug testing^(9-13;17;36-38) and the large French study with rigorous drug testing only included immediate drug allergy⁽³⁹⁾. Thus, despite the often stated usefulness⁽⁴⁰⁾ testing is often not included in larger patient populations.

Clinical presentation varied as previously documented ⁽⁴¹⁾ and included mostly maculopapular exanthema (65.4%) while SJS/TEN/Lyell represented only 6.5% of cases. This distribution is similar to other studies in the field. The distribution of clinical presentations is comparable to the 10 months-cohort study of Hernandez-Salazar et al. with a similar strong representation of maculopapular exanthema whereas SJS, DRESS or TEN being rarer events ⁽¹⁰⁾. Gerson also reports about 94% of “morbilliform”-type rashes in a 5-year study in Miami, Florida ⁽⁹⁾. In the study from Malaysia however, the percentage of severe drug reactions (SJS/TEN) was much higher (33.8%; ⁽¹²⁾. The differences in cutaneous drug reactions between different populations have been documented previously ^(11;15;22;42;42).

Allergic drug reactions are complex to assess and rates vary greatly depending on the setting. Confirmation of a suspected allergic reaction requires early assessment by a dermatologist, evaluation of histology by a pathologist and a rigorous work-up by the allergist.

CONCLUSION

This study shows that after complete work-up part of the suspected cutaneous drug reactions are actually reactions to other causes. Thus, allergologic testing is essential to not exclude drugs for patients who are not allergic to them. Assessment of allergic reactions to drugs can be greatly improved by evaluation including a dermatological and allergological work-up with skin testing and laboratory essays such as LTT.

Acknowledgements:

We thank our great nursing staff for continuously performing our skin tests and Werner Pichler who has conducted all lymphocyte transformation tests. We thank Dieter Schilling and Farideh Loher for providing the drug utilization data. Samuel Henz has kindly given critical input for the manuscript.

LEGENDS

Table 1: Drugs implicated in cutaneous drug reactions by substance. Some patients reacted to more than one drug. Thus, a total of 118 drugs in a total number of 107 cases were identified.

Table 2: Drugs implicated for specific types of clinical drug reaction. Since some patients showed more than one reaction pattern the number (n=113) is higher than the number of cases (n=107)

Table 3: Risk of cutaneous drug reaction by drug as calculated in relation to the frequency of application in reactions per 1000 defined daily doses.

Figure 1: Patient flow within study

Figure 2: Distribution of cutaneous reaction patterns from patients with suspected drug reaction and final diagnosis. Since some patients had different symptoms the total number of clinical diagnosis (n=150) is higher than the number of cases (n=141). SJS=Stevens-Johnson-Syndrome, TEN=Toxic Epidermal Necrolysis, LYELL=Lyell syndrome, AGEP=Acute Generalized Exanthematous Pustulosis, DRESS= Drug Reaction with Eosinophilia and Systemic Symptoms.

References

- (1) Jick H, Miettinen OS, Shapiro S, Lewis GP, Siskind V, Slone D. Comprehensive drug surveillance. JAMA 1970; 213(9).
- (2) Bigby M, Jick S, Jick H, Arndt K. Drug-induced cutaneous reactions. A report from the Boston Collaborative Drug Surveillance Program on 15,438 consecutive inpatients, 1975 to 1982. JAMA 1986; 256(24).
- (3) Friedmann PS, Pickard C, Ardern-Jones M, Bircher AJ. Drug-induced exanthemata: a source of clinical and intellectual confusion. Eur J Dermatol 20(3).
- (4) Ramdial PK, Naidoo DK. Drug-induced cutaneous pathology. J Clin Pathol 2009; 62(6).
- (5) Pichler WJ. Delayed drug hypersensitivity reactions. Ann Intern Med 2003; 139(8):683-93.
- (6) Schnyder B, Pichler WJ. Mechanisms of drug-induced allergy. Mayo Clin Proc 2009; 84(3).
- (7) Pichler WJ. Drug hypersensitivity reactions: Classifications and relationships to T-cell activation. In: Pichler WJ, editor. Basel: Karger, 2007.
- (8) Gomes ER, Demoly P. Epidemiology of hypersensitivity drug reactions. Curr Opin Allergy Clin Immunol 2005; 5(4).
- (9) Gerson D, Sriganeshan V, Alexis JB. Cutaneous drug eruptions: a 5-year experience. J Am Acad Dermatol 2008; 59(6).
- (10) Hernandez-Salazar A, Rosales SP, Rangel-Frausto S, Criollo E, Archer-Dubon C, Orozco-Topete R. Epidemiology of adverse cutaneous drug reactions. A prospective study in hospitalized patients. Arch Med Res 2006; 37(7).

(11) Fiszenson-Albala F, Auzerie V, Mahe E, Farinotti R, Durand-Stocco C, Crickx B et al. A 6-month prospective survey of cutaneous drug reactions in a hospital setting. *Br J Dermatol* 2003; 149(5).

(12) Ding WY, Lee CK, Choon SE. Cutaneous adverse drug reactions seen in a tertiary hospital in Johor, Malaysia. *Int J Dermatol* 49(7).

(13) Huang HY, Luo XQ, Chan LS, Cao ZH, Sun XF, Xu JH. Cutaneous adverse drug reactions in a hospital-based Chinese population. *Clin Exp Dermatol*.

(14) Lee HY, Tay LK, Thirumoorthy T, Pang SM. Cutaneous adverse drug reactions in hospitalised patients. *Singapore Med J* 2010; 51(10):767-74.

(15) Pudukadan D, Thappa DM. Adverse cutaneous drug reactions: clinical pattern and causative agents in a tertiary care center in South India. *Indian J Dermatol Venereol Leprol* 2004; 70(1).

(16) Sehgal S, Balachandran C, Shenoi SD. Clinical study of cutaneous drug reactions in 80 patients. *Indian J Dermatol Venereol Leprol* 2003; 69(1).

(17) Hunziker T, Kunzi UP, Braunschweig S, Zehnder D, Hoigne R. Comprehensive hospital drug monitoring (CHDM): adverse skin reactions, a 20-year survey. *Allergy* 1997; 52(4).

(18) Moore N, Biour M, Paux G, Loupi E, Begaud B, Boismare F et al. Adverse drug reaction monitoring: doing it the French way. *Lancet* 1985; 2(8463):1056-8.

(19) Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981; 30(2):239-45.

(20) Nebeker JR, Barach P, Samore MH. Clarifying adverse drug events: a clinician's guide to terminology, documentation, and reporting. *Ann Intern Med* 2004; 140(10):795-801.

(21) Torres MJ, Mayorga C, Blanca M. Nonimmediate allergic reactions induced by drugs: pathogenesis and diagnostic tests. *J Investig Allergol Clin Immunol* 2009; 19(2).

(22) Borch JE, Andersen KE, Bindslev-Jensen C. Cutaneous adverse drug reactions seen at a university hospital department of dermatology. *Acta Derm Venereol* 2006; 86(6).

(23) Borch JE, Andersen KE, Bindslev-Jensen C. The prevalence of acute cutaneous drug reactions in a Scandinavian university hospital. *Acta Derm Venereol* 2006; 86(6).

(24) Brockow K, Romano A, Blanca M, Ring J, Pichler W, Demoly P. General considerations for skin test procedures in the diagnosis of drug hypersensitivity. *Allergy* 2002; 57(1).

(25) Seitz CS, Brocker EB, Trautmann A. Allergy diagnostic testing in clindamycin-induced skin reactions. *Int Arch Allergy Immunol* 2009; 149(3):246-50.

(26) Seitz CS, Brocker EB, Trautmann A. Diagnostic testing in suspected fluoroquinolone hypersensitivity. *Clin Exp Allergy* 2009; 39(11):1738-45.

(27) Schubert B, Grosse Perdekamp MT, Pfeuffer P, Raith P, Brocker EB, Trautmann A. Nonsteroidal anti-inflammatory drug hypersensitivity: fable or reality? *Eur J Dermatol* 2005; 15(3):164-7.

(28) Surtees SJ, Stockton MG, Gietzen TW. Allergy to penicillin: fable or fact? *BMJ* 1991; 302(6784):1051-2.

(29) Mockenhaupt M. Severe drug-induced skin reactions: clinical pattern, diagnostics and therapy. *J Dtsch Dermatol Ges* 2009; 7(2).

29b Sassolas B, Haddad C, Mockenhaupt M, Dunant A, Liss Y, Bork K, Haustein UF, Vieluf D, Roujeau JC, Le Louet H. ALDEN, an algorithm for assessment of drug

causality in Stevens-Johnson Syndrome and toxic epidermal necrolysis: comparison with case-control analysis. Clin Pharmacol Ther. 2010 Jul;88(1):60-8.

(30) Osawa J, Naito S, Aihara M, Kitamura K, Ikezawa Z, Nakajima H. Evaluation of skin test reactions in patients with non-immediate type drug eruptions. J Dermatol 1990; 17(4).

(31) Bruynzeel DP, Maibach HI. Patch testing in systemic drug eruptions. Clin Dermatol 1997; 15(4).

(32) Calkin JM, Maibach HI. Delayed hypersensitivity drug reactions diagnosed by patch testing. Contact Dermatitis 1993; 29(5).

(33) Romano A, Quaratino D, Di Fonso M, Papa G, Venuti A, Gasbarrini G. A diagnostic protocol for evaluating nonimmediate reactions to aminopenicillins. J Allergy Clin Immunol 1999; 103(6).

33b Pichler WJ, Tilch J. The lymphocyte transformation test in the diagnosis of drug hypersensitivity. Allergy 2004; 59:809-820.

(34) Barbaud A, Goncalo M, Bruynzeel D, Bircher A. Guidelines for performing skin tests with drugs in the investigation of cutaneous adverse drug reactions. Contact Dermatitis 2001; 45(6).

(35) Aberer W, Bircher A, Romano A, Blanca M, Campi P, Fernandez J et al. Drug provocation testing in the diagnosis of drug hypersensitivity reactions: general considerations. Allergy 2003; 58(9).

35b Nyfeler B, Pichler WJ. The lymphocyte transformation test for the diagnosis of drug allergy: sensitivity and specificity. Clin Exp Allergy. 1997 Feb;27(2):175-81.

(36) Fattinger K, Roos M, Vergeres P, Holenstein C, Kind B, Masche U et al. Epidemiology of drug exposure and adverse drug reactions in two swiss departments of internal medicine. Br J Clin Pharmacol 2000; 49(2):158-67.

(37) Thong BY, Leong KP, Tang CY, Chng HH. Drug allergy in a general hospital: Results of a novel prospective inpatient reporting system. Ann Allergy Asthma Immunol 2003; 90(3):342-7.

(38) Classen DC, Pestotnik SL, Evans RS, Burke JP. Computerized surveillance of adverse drug events in hospital patients. JAMA 1991; 266(20):2847-51.

(39) Messaad D, Sahla H, Benahmed S, Godard P, Bousquet J, Demoly P. Drug provocation tests in patients with a history suggesting an immediate drug hypersensitivity reaction. Ann Intern Med 2004; 140(12):1001-6.

(40) Romano A, Viola M, Gaeta F, Rumi G, Maggioletti M. Patch testing in non-immediate drug eruptions. Allergy Asthma Clin Immunol 2008; 4(2).

(41) Roujeau JC. Clinical heterogeneity of drug hypersensitivity. Toxicology 2005; 209(2).

(42) Raksha MP, Marfatia YS. Clinical study of cutaneous drug eruptions in 200 patients. Indian J Dermatol Venereol Leprol 2008; 74(1):80.

Table 1

Culprit drugs	Number of cases (%)
Antibiotics	47 (39.8)
Penicillins (co-amoxiclav: 9, penicillin: 6, amoxicillin: 4, ampicillin: 1, phenoxymethylpenicillin: 1)	20 (17.8)
Cephalosporins (cefamandol: 4, cefuroxime: 1, cefazolin: 1, ceftriaxone: 1)	7 (5.9)
Carbapenems (imipinem: 4)	4 (3.4)
Fluoroquinolones (ciprofloxacin: 2, levofloxacin: 1)	3 (2.5)
Macrolides (clarithromycin: 2)	2 (1.7)
Sulphonamides (co-trimoxazol: 2)	2 (1.7)
Beta-lactamase inhibitor (clavulanic acid: 1)	1 (0.8)
Glycopeptide antibiotics (vancomycin: 3)	3 (2.5)
Others (polymyxin B, tobramycin, clindamycin, ethambutol: 1 each)	4 (3.4)
NSAIDs and analgesics	25 (21.2)
Metamizole sodium	15 (12.7)
Diclofenac	5 (4.2)
Acetylsalicylic acid	2 (1.7)
Acemetacin/indometacin, ibuprofen, piroxicam: 1 each	3 (2.5)
Contrast media	9 (7.6)

Iodixanol	5 (4.2)
Meglumine oxitalamate	2 (1.7)
Iomeprol, ioxaglate: 1 each	2 (1.7)
Anticoagulants	4 (3.4)
Dalteparin	2 (1.7)
Heparin, nadroparin: 1 each	2 (1.7)
Anticonvulsants	5 (4.2)
Carbamazepine	2 (1.7)
Lamotrigin, flurazepam, phenobarbital: 1 each	3 (2.5)
Antimalarials	3 (2.5)
Hydroxychloroquine	2 (1.7)
Chloroquine	1 (0.8)
Antifungals	3 (2.5)
Clotrimazole	2 (1.7)
Terbinafine	1 (0.8)
Glucocorticoids	2 (1.7)
Prednisolone	2 (1.7)
Antihypertensives	2 (1.7)
Propanolol, valsartan: 1 each	2 (1.7)
Proton pump inhibitors	2 (1.7)

Pantozol, esomeprazol: 1 each	2 (1.7)
Others (betadine: 3, additives: 2, amiodarone, atorvastatin, glatiramer acetate, metformin, nevirapine, Pretuval®, tolperisone, trimipramine, venlafaxinum, methylphenidate, atracuri besilas: 1 each)	16 (13.6)
	118 (100.0)

Table 2

Clinical diagnosis	Number of cases (%)	Culprit drugs
Maculopapular eruption	69 (61.1)	Metamizole sodium: 11, co-amoxiclav: 9, cefamandol: 4, iodixanol: 4, diclofenac: 3, penicillin: 3, acetylsalicylic acid: 2, amoxicillin: 2, betadine: 2, co-trimoxazol: 2, clarithromycin: 2, clavulanic acid: 2, clotrimazol: 2, hydroxychloroquine: 2, meglumine oxitalamate: 2, prednisolone: 2, acemetacin: 1, additives: 2 (1 colour of bilol tablets), atorvastatin: 1, atracuri besilas: 1, cefazolin: 1, ceftriaxone: 1, chloroquine: 1, clindamycin: 1, esomeprazol: 1, flurazepam: 1, heparin: 1, imipinem: 1, indometacin: 1, iomeprol: 1, ioxaglate: 1, levofloxacin: 1, metformin: 1, nadroparin:1, phenobarbital: 1, pretuval: 1, piroxicam: 1, polymyxin B:1, tolperisone: 1, vancomycin: 1
Urticaria	12 (10.6)	Amoxicillin: 2, iodixanole: 2, penicillin: 2, acetylsalicylic acid: 1, ciproxin: 1, imipenem: 1, metamizole sodium: 1, terbinafine: 1, valsartan: 1
TEN/LYELL/SJS	7 (6.2)	Acetylsalicylic acid: 1, ampicillin: 1, carbamazepin:1, ciprofloxacin+vancomycin: 1, ethambutol: 1, lamotrigine: 1, nevirapine: 1
Vasculitis	4 (3.5)	Amiodarone:1, diclofenac: 1, ibuprofen: 1, trimipramine: 1
AGEP	5 (4.4)	Imipenem: 1, metamizole sodium: 1, methylphenidate: 1, penicillin: 1, venlafaxin: 1
Bullous eruption	4 (3.5)	Betadine: 1, diclofenac: 1, metamizole sodium: 1, pantozol: 1
Pustular eruption	3 (2.7)	Metamizole sodium: 2, unknown drug: 1

Erythema only	3 (2.7)	Diclofenac: 1, metamizole sodium: 1, phenoxymethylpenicillin: 1
DRESS	2 (1.8)	Carbamazepin: 1, imipinem/vancomycin: 1
Fixed drug eruption	1 (0.9)	Propanolol: 1
Miscellaneous	3 (2.7)	Dalteparin: 1, glatiramer acetate: 1, nadroparin: 1
	113 (100)	

Table 3

	Active ingredient(s)	Trade name(s)	Risk of reaction 1000 Day-doses (Dd)	Number of drug-related cutaneous reactions in 5 years	Utilization Day-doses per year
Contrast media	Iodixanol	Visipaque	0.16	5	6297
	Iomeprol	Iomeron	0.10	1	2016
	Ioxithalamat-Meglumin	Telebrix	0.07	2	5851
	Ioxaglat-Meglumin	Hexabrix		1	
Non-steroidal antiphlogistics	Novaminsulfon	Novalgin	0.01	15	350827
	Diclofenac	Voltaren, Brufen, Olfen	0.01	5	83845
	Ibuprofen	Brufen, Algifor, Dolo-Spedifen, Nurofen	0.01	1	37486
	Acetylsalicylsäure	Aspegic, Aspirin	0.01	2	56738
Antibiotics	Levofloxacin	Tavanic	10.00	1	20

	Vancomycin	Vancocin	0.48	3	1244.7
	Penicillin	Penicillin	0.40	6	2977.7
	Tobramycin	Obracin	0.19	1	1075
	Cefamandol	Mandokef	0.14	4	5710
	Cefazolin	Kefzol	0.12	1	1654.7
	Clarithromycin	Klacid	0.12	2	3360
	Cefuroxim	Zinat, Zinacef	0.11	1	1826.5
	Clindamycin	Dalacin	0.07	1	3025
	Imipinem	Tienam	0.06	4	12926
	Amoxicillin/Clavulanic acid	Augmentin	0.06	9	30828.7
	Trimethoprim+Sulfamethoxazol	Bactrim	0.06	2	7222.5
	Ceftriaxon	Ceftriaxon	0.03	1	7064
	Amoxicillin	Augmentin	0.03	4	30828.7
	Ciprofloxacin	Ciproxin	0.02	2	16354
	Clavulansäure	Augmentin	0.01	1	30828.7
Anticoagulants	Nadroparin	Fraxiparin	7.62	2	52.5
	Heparin	Heparin	0.02	1	13144.5
	Dalteparin	Fragmin	0.00	1	152967

Miscellaneous	Chloroquin	Nivaquine	2	1	100
	Tolperison	Mydocalm	1.43	1	140
	Metformin	Metformin	0.05	1	3976
	Prednison	Prednison, Prednisolon	0.05	2	8866
	Hydroxychloroquin	Plaquenil	0.02	2	18888



