

Received Date : 31-Jul-2012
Revised Date : 27-Aug-2012
Accepted Date : 29-Aug-2012
Article type : Original Article-Epidemiology of Allergic Disease

PROTON PUMP INHIBITORS ARE ASSOCIATED WITH HYPERSENSITIVITY
REACTIONS TO DRUGS IN HOSPITALIZED PATIENTS: A NESTED CASE-
CONTROL IN A RETROSPECTIVE COHORT STUDY

Elena Ramírez¹, Rosario Cabañas², Luis S. Laserna¹, Ana Fiandor², Hoi Tong¹, Nieves Prior²,
Oscar Calderón², Nicolás Medrano¹, Irina Bobolea², Jesús Frías¹, Santiago Quirce²

¹Department of Clinical Pharmacology, Hospital La Paz Health Research Institute (IdiPAZ),
School of Medicine, Universidad Autónoma de Madrid, Madrid, Spain

²Department of Allergy, Hospital La Paz Health Research Institute (IdiPAZ), Madrid, Spain

Corresponding Author:

Elena Ramírez

Address: Arzobispo Morcillo s/n, 28029, Madrid, Spain

Tel/Fax: +34 91 7277559

E-mail address: E Ramírez (elena.ramirez@uam.es)

Keywords: drug allergy; drug hypersensitivity reaction; proton pump inhibitor; hospitalized patients; pharmacoepidemiology; pharmacovigilance

ABSTRACT

Background Previous research has shown that gastric acid suppression by antacid drugs can promote allergic reactions to acid-labile food proteins. No data about whether antacid drugs can promote drug hypersensitivity reactions. The more potent and longer-lasting inhibitor of gastric secretion is provided by proton pump inhibitors. We hypothesized that gastric acid

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/cea.12034

© 2012 Blackwell Publishing Ltd

Accepted Article
suppression by proton pump inhibitors could be causative of drug hypersensitivity reactions during hospitalization.

Objective To estimate the risk of developing drug hypersensitivity reactions during the hospitalization of patients treated with proton pump inhibitors, and other associated factors.

Methods A nested case-control in a retrospective cohort study of hospitalized patients from Sept-2008 to Dec-2010 (70,771 admissions) was conducted using the registry of cases of inter-consultations to the Allergy Department (161 confirmed cases of drug hypersensitivity reactions). 318 controls were matched by first drug suspected in the hypersensitivity reaction, time of admission, age, gender, and hospitalization wards.

Results The relative risk of drug hypersensitivity reaction occurrence during hospitalization of patients treated with PPIs compared with those not treated in the period of study was significant (RR: 3.97; 95% CI: 1.97 - 8.29). After controlling for confounders in the nested case-control cohort, the use of PPIs persists as a predisposing factor (OR: 4.35; 95% CI: 2 - 9.45). Personal history of drug allergy and a long hospitalization time were other predisposing factors of DHR. The hazard that a DHR has occurred during PPI treatment by time was 3.7% per day. The hazard for immediate or accelerated reactions was 1.706 (p=0.003) times that of delayed reactions.

Conclusion and Clinical Relevance In hospitalized patients, the use of proton pump inhibitors was associated with a significant increase risk of drug hypersensitivity reactions along with a personal history of drug allergies and long hospitalization time.

INTRODUCTION

Adverse drug reactions (ADRs) are considered to be among the leading causes of morbidity and mortality. Around 5-25% of hospitals admissions are estimated to be due to ADRs [1,2] and about 6-15% of hospitalized patients experience serious ADRs causing significant prolongation of hospital stay. Adverse drug events, even after excluding prescription errors, are the fourth leading cause of death in the United States, exceeded only by heart disease, stroke and cancer [3,4]. Whereas most ADRs are nonallergic in nature, 6 to 10% may be attributed to an immunologic mechanism [5]. Indeed, the general risk of an allergic reaction to the majority of drugs is between 1% and 3% [6]. It may cause mild symptoms such as skin rash or clinical conditions with high mortality such as toxic epidermic necrolysis [6].

Previous studies have shown that gastric acid suppression by antacid drugs can promote allergic reactions to acid-labile food proteins [7,8]. By increasing the gastric pH, antacid drugs interfere substantially with the digestive function of the stomach, leading to persistence of labile protein during gastric transit increasing the potential of proteins to bind IgE [9] but also acting as a T-helper 2 adjuvant through structural changes in the intestinal epithelium [10,11]. The more potent and longer-lasting inhibitor of gastric secretion is provided by proton pump inhibitors (PPIs) blocking histamine-2-, gastrin-, and cholinergic-mediated sources of acid production and inhibiting gastric secretion at the final common pathway of the H⁺/K⁺ adenosine triphosphatase proton pump [12]. PPIs are the drugs most frequently prescribed during hospitalization; our own data shows that PPIs are prescribed to 83% of hospitalized patients [13]. We hypothesized that this mechanism could also be causative of drug hypersensitivity reactions (DHRs) in hospitalized patients. The objective of the study was to evaluate whether PPIs constitute a risk for developing DHRs, and other associated factors in a nested case-control in a retrospective cohort study of hospitalized patients from Sept-2008 to Dec-2010. We also estimated the incidence rate of DHR in hospitalized patients and the incidence of DHR per drug.

METHODS

Subject population

This is a nested case-control in a retrospective cohort study of hospitalized patients from September 2008 to December 2010. The cohort was comprised by the patients admitted in General and Trauma Wards with at least one prescription for a systemic drug (Farmatools-Dominion, Madrid, ESP) during the period of study. Cases of a DHR that occurred in the cohort were identified and, for each, two matched controls were selected. Controls, those hospitalized patients who did not experience DHRs, were matched to the cases by: first drug suspected in the hypersensitivity reaction, time of admission, age, gender, and hospitalization wards. We analysed the registered cases of inter-consultations from the different hospital units to Allergy department during the period of study. Every case was evaluated and all suspected allergic cutaneous reactions to systemic drugs were collected. Allergic contact dermatitis to topical treatments, chronic itching diseases and other drug-induced cutaneous manifestations such as those linked to antiretroviral drugs (lipodystrophy, etc.), corticosteroids (atrophy, folliculitis) and chemotherapy (alopecia) were excluded. The drug-

induced cutaneous reaction was described and clinical manifestation of severity (high fever, purpura, mucous membrane lesions, blistering) or biological abnormalities (hypereosinophilia, liver cytolysis) were also recorded. The confirmation of diagnosis was based on a convincing clinical history and a clear-cut relationship between drug intake and development of clinical manifestations. In the remaining cases, test to confirm the diagnosis of drug allergy were done. Clinically, allergic reactions to drugs were classified as immediate (less than an hour), accelerated (more than 1h but less than 48 hours), or delayed (more than 48 hours), depending on the time between drug intake and occurrence. Although this classification was developed by Levine [14] based on his study of penicillin allergy, it can be applied to all types of drug allergies. Drugs were categorized by active ingredient using the Anatomical Therapeutics Chemical (ATC) Classification System (ATCCS). First drug suspected was used for analysis. The imputability was performed using the methods of the Spanish Pharmacovigilance System [15]. Two different researches separately evaluated the drug imputability.

La Paz University Hospital is a 1,365-bed tertiary-care teaching facility; 789 beds are located in the General and in the Traumatology wards. The sample size was calculated to detect a specified relative risk (≥ 2.5), with a given power of 80% and a type I error of 0.05. Medical records of each case were reviewed from date of arrival to the hospital until that of discharge. Information was collected according to protocol. A case report form was completed with these details. Approval was obtained from the Institutional Review Board at La Paz University Hospital, protocol PI-1170. Patient consent was not required for this study.

Statistical analysis

A descriptive statistical analysis of the variables was performed. To estimate the relative risk in the cohort we calculated the ratio of the risk of DHR in the exposed group (patients who were receiving PPIs) divided by the risk of DHR in the non-exposed group (patients who were not receiving PPIs). A sensitivity analysis of the “worst scenario” was made for the relative risk estimation. A multiple logistic regression modeling to obtain estimates effects than can be considered adjusted for covariates (age, gender and hospitalization wards) were done in the nested case-control. Length of hospitalization was dichotomized at median in control group. Backwards stepwise model were calculated, with likelihood ratio criteria of

p<0.10 to retain variable. A Cox proportional hazards model was applied to determine which attributes are associated with shorter “time to DHR” in the cases. The in-hospital incidence rate of each drug was calculated by dividing the number of drug hypersensitivity reactions by the number of patients hospitalized during the period of study. Uncertainty of estimation was assessed by calculation of the two-sided Poisson 95% confidence interval. Data analysis was performed using SPSS version 15.0 Statistical Analysis Software (SPSS, Chicago, IL).

RESULTS

During the 28 months of the study, the number of hospital admissions in the target wards was 70,771, of which 81% of cases received PPIs during their hospitalization. Out of 335 inter-consultations to the Allergy department during the period of study, 176 cases of DRH were identified, of which 161 cases occurred during hospitalization. The flow chart (Figure 1) shows the cause of exclusions.

Out of 161 cases of DRH, 152 cases received a PPI and 7 cases did not receive it. In two cases the use of PPI was unknown, so these were considered to be cases of DHR without PPI use (sensitivity analysis). The relative risk of DHR in patients treated with PPIs compared to those not treated with PPIs was 3.97 (CI 95% 1.97–8.29), $p<0.0001$.

A total of 318 controls matched by first drug suspected in the hypersensitivity reaction, time of admission, age, gender, and hospitalization wards were obtained, in one case a dalteparine control and in another, a case of iodinate contrast hypersensitivity reaction could not be obtained. The characteristics of the nested case-control population are showed in table 1. After controlling for these confounders in the nested case-control cohort, the use of PPIs persists as a predisposing factor (OR: 4.35; 95% CI: 2 -9.45). The multiple logistic regression model (Table 2) shows the variables retained in the final model; estimated effect of PPIs, personal history of drug allergies and prolonged hospitalization (>19 days). In 38.64% of the cases, the cutaneous manifestations were exanthematous eruptions and in 30.68% urticaria. In 12.5% of patients it was a severe drug-induced skin reaction such DRESS (8.52%), SJS/TEN (2.27%) or AGEP (1.7%) (Table 3).

Tests to confirm the diagnosis of drug allergy were done in 52% of cases (data not shown). The most common imputable drugs (Table 4) were metamizole in 13.66% of cases followed by piperacillin/tazobactam (9.32%), iodinated contrast (6.83%) and vancomycin (6.21%). The highest incidence rate for Group was J01 of antinfectious drugs (11.69 per 10.000

patients (CI 95%: 6.2 to 19.68)) and for subgroup was J01C and J01D of penicillin and derivatives (7.56 per 10 000 patients (CI 95%: 3.45 to 14.42)) (Table 4). The median (range) of days of treatment from the beginning of PPI treatment and the DHR was 7 days (1-375). The characteristics of use of antacid drugs in the case population are in Table 5. In a Cox Regression procedure, the hazard of a DHR occurred during PPI treatment by time was 3.7% per day ($\text{Exp}(B) = 0.963$, $p < 0.0001$) and the hazard for immediate and accelerated DHRs was 1.706 ($p = 0.003$) times that of delayed DHRs (Overall (score) Chi-square 44.845, $\text{Sig} < 0.0001$) (Figure 2).

DISCUSSION

Pharmacoepidemiology is the study of the use and effects (outcomes) of drugs (exposure) in large population of people. To our knowledge this is the first pharmacoepidemiological study that explores the use of PPIs as a predisposing factor to drug allergies. Several studies have associated the use of PPIs to vitamin B12 deficiency [16], hip fracture [17], spontaneous bacterial peritonitis in cirrhotic patients with ascites [18], increase community-acquired pneumonia [19,20] diarrhoea from *C. difficile* [21,22] and gastroenteritis from *Campylobacter jejuni* [23]. The rationale for examining the association between PPIs and drug allergy emerges from observations concerning the modification of drug allergenicity by gastric acidity. It has been shown that alteration of gastric pH by antacids, H2 antagonists and PPIs can enhance the production of specific IgE antibodies in murine models [24] and in humans [25]. In a murine model, treatment of the mothers with the antacid drug sucralfate induced a T-helper type 2 (Th2) bias in the offspring [26].

PPIs are one of the most commonly prescribed types of drugs [27]. A study quantifying gastro-protective drug consumption in Australia between 1997 and 2006 studied the relationship over time between PPI and non-steroidal anti-inflammatory drugs (NSAID) prescriptions. This study showed an increase in the prescription of PPIs while there was a decrease in prescription of NSAIDs [28]. Although overprescribing could occur mainly in primary care settings [29], evidence of inappropriate use of PPIs in secondary care is abundant. Nardino *et al.* [30], Noguerado Asensio *et al.* [31] and Pham *et al.* [32] (if one considers the history of gastroesophageal reflux disease as an acceptable indication), found that 54%, 72.2% and 71.4% of patients respectively received acid-suppressive therapy during

hospitalization. Being over 64 years of age, with an intake of more than four drugs, plus co-medication (NSAIDs, antiaggregation and anticoagulation) and being hospitalized in certain wards predicted an 83.7% of PPI prescriptions at discharge in our hospital [13]. Therefore the likelihood of hospitalized patients seemed to be an appropriate stage to demonstrate the association between PPI and drug allergies. In the nested study case-control to the cohort, controls were matched to case in addition to in time, with these other variables to control the possible confusion factors with PPI prescription.

Riemer *et al.* [33] described a case of a 60-year-old healthy male patient who suffered from a generalized urticaria following a second course of diclofenac and PPI medication. He had no previous history of allergy or urticaria, but had been using PPIs repeatedly for recurrent gastro-oesophageal reflux disease. The author analysed diclofenac allergy induction but they believed the described mechanism of hypoacidity –associated sensitization could be pertinent to all IgE-mediated NSAID hypersensitivities. Our findings confirm this hypothesis. Metamizole or dipyrone is a pyrazolone drug used in some countries to treat pain and fever; it is banned in others because of an association with life-threatening blood agranulocytosis. It is frequently involved in IgE-mediated hypersensitivity reactions and it has been the most common imputable drug in our study [34]. It was followed in frequency by piperacillin-tazobactam, a beta-lactam drug also capable of producing IgE mediated reaction.

Personal history of drug allergy was another predisposing factor detected in our study; it could suggest genetic susceptibility to allergies and could also explain, as suggested by Riemer *et al.* [33] why millions of patients throughout the world are taking both acid suppressants and NSAID and the incidence of drug reactions are quite low.

Other predisposing factors of drug allergies are gender (women), age (older patients), concomitant diseases (e.g. systemic lupus erythematosus and human immunodeficiency virus infection), ethnicity and pharmacogenetic factors [35]. Drug related factors that affect its immunogenicity include its ability to act as a hapten, a prohaptent or to bind covalently to immune receptors (Pi concept) [36]. Thus, certain classes of drugs tend to be associated with higher frequency of allergic reactions compared with others [37]. Fiszenson-Albala *et al.* [38] in a prospective study among hospitalized patients researched the characteristics of patients with drug allergies. They found that the most frequent associated disorders to drug allergy

was HIV infection. In the nested case-control study the characteristics of patients and HIV infection were significantly associated, but this association was not retained in the logistic model probably because of linearity with the other variables.

The true incidence of drug allergy is not known. The majority of currently available epidemiologic studies have been on ADRs rather than drug allergy specifically [39]. Most studies focus only on selected population groups, e.g. inpatients or outpatients at the emergency departments, general practice clinics or specialist allergy centres; children or adults; cutaneous or severe cutaneous adverse reactions (SCAR) [40], or only patients with anaphylaxis. Case-verification in most studies [41,42] was based on chart review and not on formal patient examination during the actual episode of the reaction, although case-verification was conducted by dermatologists in two reports [43,44]. In our study all the inter-consultations made to the Allergy Department, when drug causality was suspected in cutaneous manifestations, were reviewed. Only cases of confirmed drug allergy by the appropriate allergologic work-up were finally included.

Boston Collaborative Drug Surveillance Programme [42] in a prospective follow-up study in 1980s of 3 years and 8 months found a frequency of cutaneous DHR of 2.2%, incidence rate of 22.02 per 10 000 hospitalized patients (95% CI estimated by Poisson method: 14.58 to 33.31), similar results to those found in our study, such as amoxicillin being the cause of 5.1% of the reactions, ampicillin of 4.5%, and other penicillins of 4.5% of the reactions. In this study the drug most frequently associated was metamizole, not used in the U.S., followed by penicillin and derivatives (30%). In Singapore in 2002, an inpatient network-based electronic drug allergy notification system in a general hospital [45] showed that, out of 366 cases reported from a total of 90 910 admissions during the period of study, 210 cases were verified by an allergist to be due to drug allergies. Cutaneous eruptions were the most common clinical presentation (95.7%), systemic manifestations occurred in 30% and serious adverse reactions such as SJS/TEN and generalized exfoliative dermatitis occurred in 11 (5.2%) patients. The estimated incidence of confirmed drug allergy was 23.10 per 10 000 hospitalizations (95% CI estimated by Poisson method: 15.38 to 34.51). In this study we verified only 4 cases (2.27) of SJS/TEN, but in Asian population the incidence rate of SJS/TEN is higher (1 to 6 cases per million of habitant per year) than in Europe (1 to 2 cases per million of habitant per year) probably because of referral bias, different prescribing habits and high prevalence of some HLA genotypes (HLA B*1502 associated with carbamazepine

induced SJS/TEN in Han Chinese in Taiwan [odd ratio, OR 1357 (95% CI 193 to 8838) - 2504 (95% CI 126 to 49 522) and Hong Kong (OR 71.9), Thais [OR 25.5 (95% CI 2.68 to 242.61)] and Indians but neither in Japanese nor Europeans of non-Asian ancestry; HLA B*1502 associated with phenytoin induced SJS in Han Chinese in Hong Kong (OR 71.9) and Thai (OR 18.5 [95% CI 1.82 to 188.4]) [46, 47, 48, 49, 50] associated to SJS/TEN with carbamazepine and phenytoin.

Strengths and limitations of the study

It is a retrospective study, based on chart review, although all cases were confirmed by allergists.

The study population is limited to adults, so the results cannot be extrapolated to the pediatric population.

It is a single-center study, so that the validity of the results should be confirmed in other hospitals.

Epidemiologists study the factors affecting the health and illness of populations, enabling interventions to be made in the interest of public health and preventive medicine. Our findings emphasize several findings about DHR: The use of PPI increases by 4 the risk of a hypersensitivity reaction to concomitant drugs, along with a personal history of drug allergies and long hospitalization. Thus, PPI treatment is the most preventable risk factor of DHRs.

CONCLUSIONS

To conclude, the relative risk of occurrence of DHR during hospitalization in patients treated with PPIs compared with those not treated in the period of study was significant (RR 3.97, 95%CI: 1.97-8.29). After controlling for confounders in the nested case-control cohort study, the use of PPIs persists as a predisposing factor (OR 4.35; 95%CI: 2-9.45). Personal history of drug allergy and a long hospitalization were other predisposing factors of DHR. The hazard ratio that a DHR has occurred during PPI treatment by time was 3.7% per day. The hazard ratio for immediate and accelerated reactions was 1.706 (p=0.003) times that of delayed reactions. The incidence of hospitalized patients DHR was of 22.75 per 10 000 patients (95 CI Poisson: 14.58 to 33.33), being metamizole the drug most commonly

incriminated. The incidence of DHR per group and subgroup, were the anti-infective for systemic use J01 therapeutic group, and the subgroup J01C and J01D of the ATC.

Acknowledgements We are grateful to R. Lubomirov, of the Clinical Trial Unit Phase I of the School of Medicine, for his technical advice on statistic analysis.

Funding Part of results of this study were included in the master's degree thesis of Luis S. Laserna, School of Medicine, Universidad Autónoma de Madrid, Madrid, Spain

Contributorship

Program concept and design: ER and RC.

Data acquisition and entry of data: LL, HT, NM, NP, OC, IB.

Analysis and interpretation of data were carried out independently by LL, HT and NM verified by ER and AF.

Drafting of the manuscript: ER, RC, AF, NP, OC, IB.

Critical revision of the manuscript for important intellectual content: SQ and JF.

Conflicts of interest

Elena Ramírez: None to declare

Rosario Cabañas: None to declare

Luis Santiago de la Serna: None to declare

Ana Fiandor: None to declare

Hoi Tong: None to declare

Nieves Prior: None to declare

Oscar Calderón: None to declare

Nicolás Medrano: None to declare

Irina Bobolea: None to declare

Sonsoles Hernández: None to declare

Jesús Frías: None to declare

Santiago Quirce: None to declare

Figure 1 Flow Chart of inter-consultations to Allergy Service. DHR, Drug Hypersensitivity Reaction

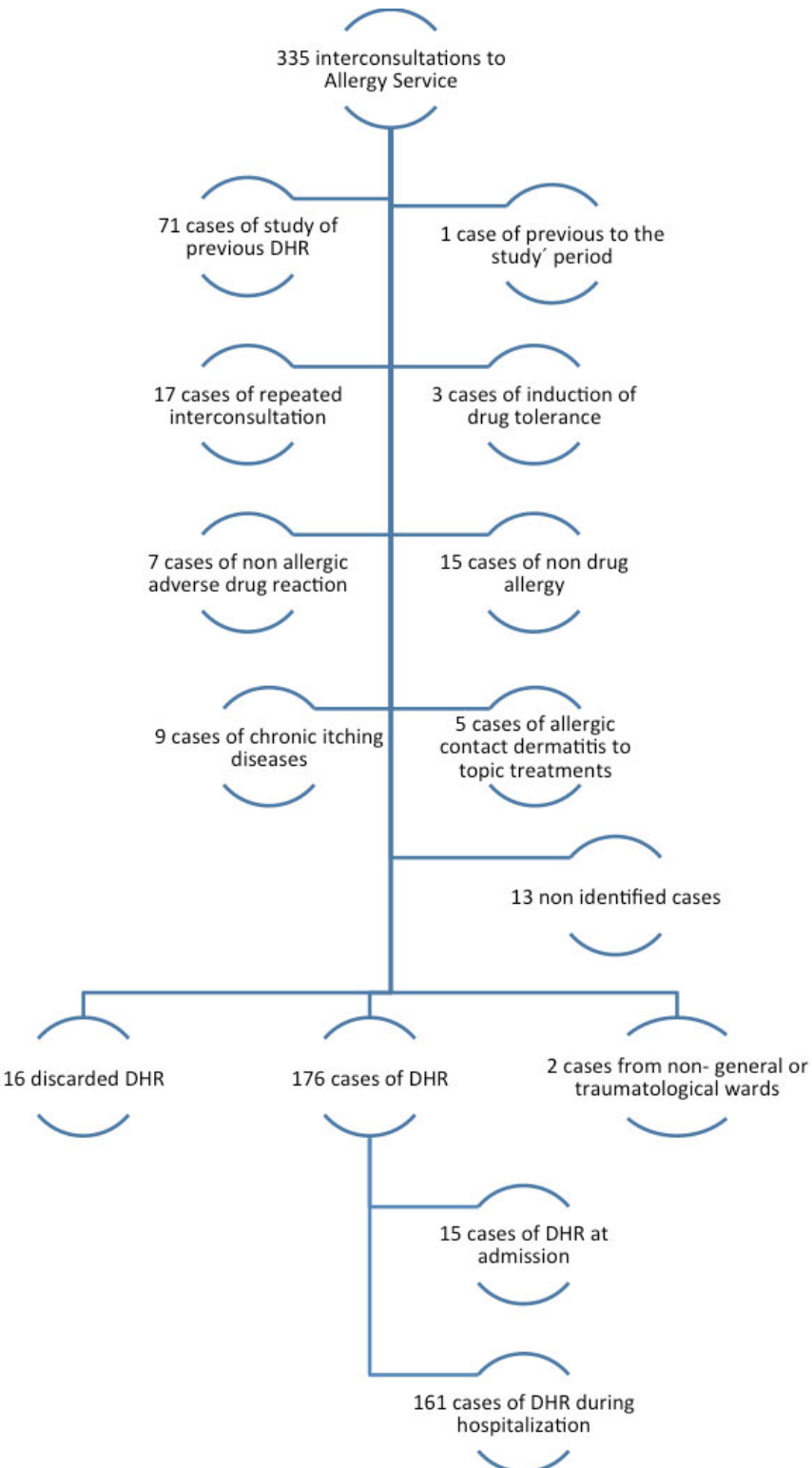


Table 1 Comparison of Population Characteristic of case-control in the cohort study.

Variable	No DRH (n=318)	DHR (n=161)	P value
Age. mean (SD)	63 (17)	61 (18)	0.53
Women (%)	51	53	0.435
Hospitalization			
Surgery wards	64 (20.13)	33 (20.50)	0.924
Intensive Care Units	20 (6.29)	10 (6.21)	0.973
Medicine	200 (62.89)	101 (62.73)	0.973
Traumatology	34 (10.69)	17 (10.56)	0.964
Geographical origin			
Africa	3 (0.94)	2 (1.24)	0.761
Spain	300 (94.34)	148 (92.55)	0.31
Europe. rest	6 (1.89)	4 (2.48)	0.666
Latin America	9 (2.83)	6 (3.73)	0.595
Days of hospitalization			
Mean (SD)	29 (3)	34.57 (32.13)	0.02 (*)
Median (range)	19 (1-179)	23 (1-171)	
Family History of allergy	20 (6.29)	14 (8.70)	0.595
Personal History of drug allergy	54 (17)	56 (34.78)	<0.0001 (*)
Drugs allergy			
Penicillins and derivates	28 (8.81)	29 (18.01)	0.004 (*)
NSAID	28 (8.81)	28 (17.39)	0.006 (*)
Quinolones	8 (2.52)	8 (4.97)	0.158
Iodinated contrast	4 (1.26)	5 (3.11)	0.160
Procaine	2 (0.63)	4 (2.48)	0.085
Acetaminophen	1 (0.31)	4 (2.48)	0.027 (*)
Aminoglycosides	2 (0.63)	3 (1.86)	0.210
Glycopeptides	2 (0.63)	3 (1.86)	0.210
Macrolides	7 (2.20)	3 (1.86)	0.807
Sulfonamides	4 (1.26)	3 (1.86)	0.602
Others	30 (9.43)	32 (19.88)	0.001 (*)
More than one drug subgroup of ATCCS	18 (4.40)	13 (8.07)	0.301
Comorbid conditions	167 (52.51)	100 (62.11)	0.046 (*)
HIV	0 (1.57)	3 (1.86)	0.015 (*)
Immunosuppression	17 (5.35)	16 (9.94)	0.061
Solid organ transplant	7 (2.20)	4 (2.48)	0.845
Autoimmune disease	20 (3.14)	12 (7.45)	0.630
Cancer	65 (20.44)	33 (20.50)	0.988
Chemotherapy	20 (6.29)	12 (7.45)	0.630
GORD	20 (6.29)	10 (6.21)	0.973
Peptic or gastric ulcer	9 (2.83)	4 (2.48)	0.826
Dyspepsia	9 (2.83)	6 (3.73)	0.595
A02 treatment at admission	133 (41.82)	75 (46.58)	0.321
PPI	89 (27.99)	53 (32.92)	0.264
H2 RA	2 (0.63)	2 (1.24)	0.486
Others	3 (0.94)	2 (1.24)	0.761
PPIs during hospitalization	258 (81.1)	152 (94.4)	<0.0001 (*)

Anatomical Therapeutic Chemical Classification System (ATCCS); Drugs for acid related disorders (A02) of ATC Classification System; Gastro-oesophageal reflux disease (GORD); H2 receptor antagonists (H2RA); Non-steroidal anti-inflammatory drug (NSAID); Proton Pump Inhibitors (PPIs); (*) P-value significant

Table 2 Variables retained in the multimodal logistic regression model after controlling for confounders in the nested case-control cohort.

VARIABLE	OR	95% CI	P value
PPIs	4.35	2 – 9.45	<0.0001
Personal history of drug allergy	2.55	1.62 – 4.02	<0.0001
> 19 days of hospitalization (*)	1.6	1.06 – 2.35	<0.05
Proton pump inhibitors (PPIs); Significance of the statistic analysis (P); (*) Median of days of hospitalization in controls			

Table 3 Types of DHR at admission and during hospitalizations from September 2008 to December 2010.

Type	DHR At admission (n=15)	DHR During hospitalization (n=161)	DHR Total (n=176)
Immediate and accelerated (0 to 48hours)	3 (20)	71 (44.10)	74 (42.05)
Urticaria	.	54 (33.54)	54 (30.68)
Angioedema	1 (6.67)	7 (4.35)	8 (4.55)
Anaphylaxis	2 (13.33)	10 (6.21)	12 (6.82)
Delayed (more than 48hours)	12 (80)	90 (55.90)	92 (52.27)
Erythema	-	10 (6.21)	10 (5.68)
Maculopapular exanthema	2 (13.33)	66 (40.99)	68 (38.64)
Fixed drug eruption	-	1 (0.62)	1 (0.57)
Erythema multiforme	1 (6.67)	-	1 (0.57)
DRESS	4 (26.67)	11 (6.83)	15 (8.52)
AGEP	1 (6.67)	2 (1.24)	3 (1.70)
SJS/TEN	4 (26.67)	-	4 (2.27)
Acute generalized exanthematic pustulosis (AGEP); Drug Rash with Eosinophilia and Systemic Symptoms (DRESS); Stevens-Johnson syndrome (SJS); Toxic epidermal necrolysis (TEN)			

Table 4 Breakdown by first suspected drug of DHR during hospitalization between September 2008 and December 2010.

Drug	Nº (%) of cases at admission	Nº (%) of cases During hospitalization	Incidence rate of all cases (per 10.000 inpatients)	Confidence interval of incidence rate (per 10.000 inpatients) (*)
Metamizole	5 (33.33)	22 (13.66)	3.82	1.09 to 8.88
Piperacillin/tazobactam		15 (9.32)	2.12	0.62 to 7.25
Iodinated contrast		11 (6.83)	1.55	0.24 to 5.57
Vancomycin		10 (6.21)	1.41	0.24 to 5.57

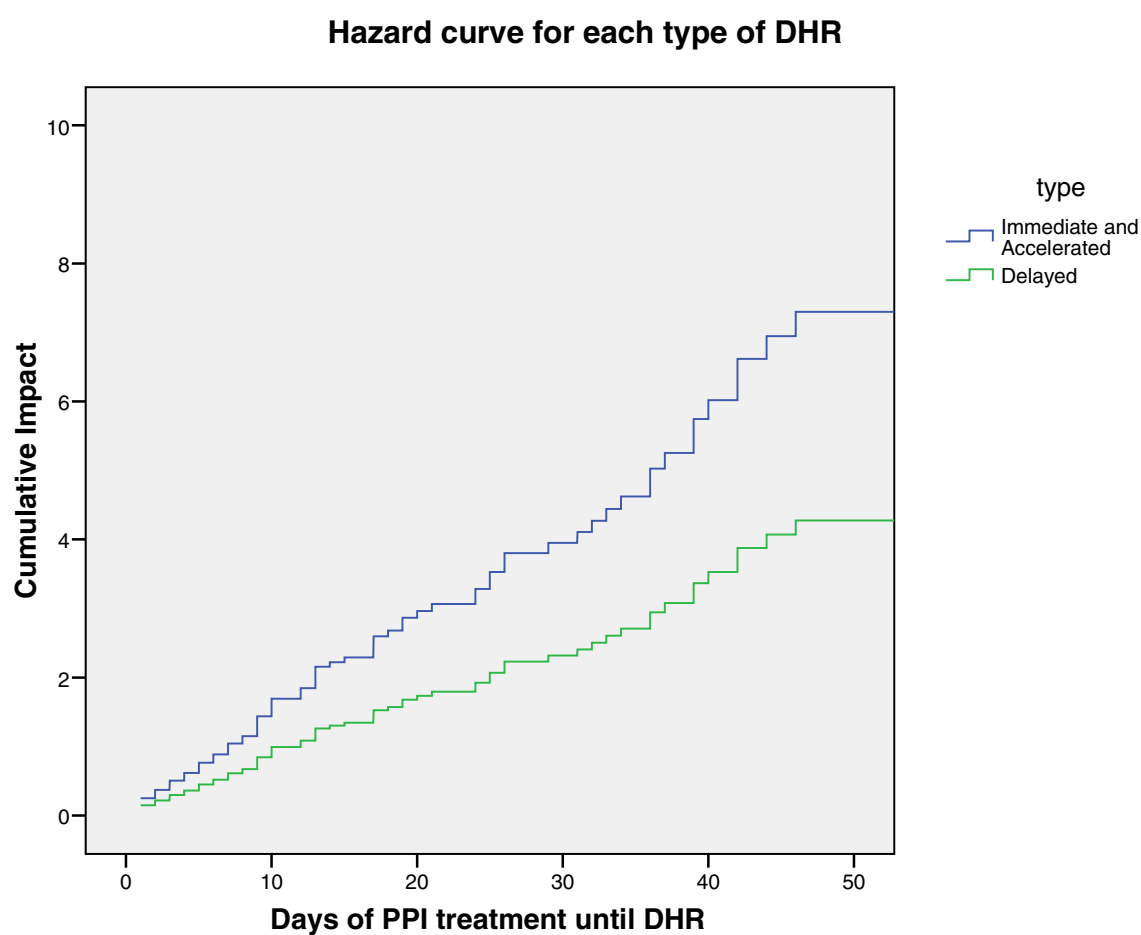
Meropenem		9 (5.59)	1.27	0.24 to 5.57
Amoxicillin clavulanate	1 (6.66)	6 (3.73)	0.99	0.03 to 3.69
Ceftriaxone		6 (3.73)	0.85	0.03 to 3.69
Cloxacillin		6 (3.73)	0.85	0.03 to 3.69
Levofloxacin		6 (3.73)	0.85	0.03 to 3.69
Aztreonam		4 (2.48)	0.57	0.03 to 3.69
Dexketoprofen		4 (2.48)	0.57	0.03 to 3.69
Rifampicin		4 (2.48)	0.57	0.03 to 3.69
Teicoplanin		4 (2.48)	0.57	0.03 to 3.69
Allopurinol		3 (1.86)	0.42	0.03 to 3.69
Cefazolin		3 (1.86)	0.42	0.03 to 3.69
Ciprofloxacin		3 (1.86)	0.42	0.03 to 3.69
Phenytoin	2 (13.33)	3 (1.86)	0.71	0.03 to 3.69
Furosemide		3 (1.86)	0.42	0.03 to 3.69
Cefotaxime		2 (1.24)	0.28	0.03 to 3.69
Ceftazidime		2 (1.24)	0.28	0.03 to 3.69
Enalapril		2 (1.24)	0.28	0.03 to 3.69
Imipenem		2 (1.24)	0.28	0.03 to 3.69
Metronidazole		2 (1.24)	0.28	0.03 to 3.69
Sulfametoxazole trimethopim	1 (6.66)	2 (1.24)	0.42	0.03 to 3.69
Others	6 (40)	27 (16.77)	4.66	1.62 to 10.24
Total	15 (100)	161 (100)	22.75	14.58 to 33.31
(*) Two-sided Poisson 95% confidence interval				

Table 5 Characteristics of use of antacid drugs in the case population.

A02 Drugs	n	Days of treatment to the DHR Median (range)	Daily dose until DHR Median –units- (range)
One drug			
PPIs	150	6 (1-360)	-
Pantoprazole	145	6 (1-360)	40 –mg- (20-120)
Omeprazole	5	13 (5-19)	20-mg- (-)
H2RA			
Ranitidine	2	3 (1-5)	300-mg-(-)
Others			
Almagate	2	11.5 (3-17)	3-gr (-)r
Two drugs			
PPIs			
Pantoprazole	2	22.5 (9-27)	60-mg- (40-80)
H2RA			
Ranitidine	2	5 (1-360)	150-mg- (50-300)
Sucralfate	1	11 (-)	1-gr- (-)
Three drugs			
Almagate	2	34 (31-37)	3-gr- (-)

Antacid drugs defined as drugs for acid related disorders (A02) of ATC Classification System; H₂ receptor antagonists (H₂RA); Grams (gr); Milligrams (mg); Proton pump inhibitors (PPIs);

Figure 2 Cox survival analysis



REFERENCES

- ¹ Johnson, J.A., Bootman, J.L. Drug-related morbidity and mortality; a cost of illness model. *Arch. Intern. Med* 1995; **155**: 1949-56.
- ² Pirmohamed, M., James, S., Meakin, S., Green, C., Scott, A.K., Walley, T.J, Farrar, K., Park. B.K., Breckenridge, A.M. Adverse drug reactions as a cause of admission to hospital: prospective analysis of 18 820 patients. *BMJ* 2004; **329**:15-9.
- ³ Classen, D.C., Pestotnik, S.L., Evans, R.S., Loyds, J.F., Burke, J.P. Adverse drug events in hospitalized patients. Excess length of stay, extra cost, and attributable mortality. *JAMA* 1997; **277**: 301-6.
- ⁴ Lazarou, J., Pomeranz, B.H., Corey, P.N. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. *JAMA* 1998; **279**: 1200-5.
- ⁵ DeShazo R, Kemp S. Allergic reactions to drugs and biologic agents. *JAMA* 1997; **278**: 1895-906.
- ⁶ Demoly, P., Hillaire-Buys, D. Classification and epidemiology of hypersensitivity drug reactions. *Immunol. Allergy Clin N Am* 2004; **24**: 345-56.
- ⁷ Untersmayr E, Jensen-Jarolim E. The role of protein digestibility and antacids on food allergy outcomes. *J Allergy Clin Immunol* 2008; **121**:1301-8; quiz 1309-10.
- ⁸ Untersmayr E, Schöll I, Swoboda I, Beil WJ, Förster-Waldl E, Walter F, Riemer A, Kraml G, Kinaciyan T, Spitzauer S, Boltz-Nitulescu G, Scheiner O, Jensen-Jarolim E. Antacid medication inhibits digestion of dietary proteins and causes food allergy: a fish allergy models in BALB/c mice. *J Allergy Clin Immunol* 2003; **112**:616-23.
- ⁹ Untersmayr E, Bakos N, Schöll I, Kundi M, Roth-Walter F, Szalai K, Riemer AB, Ankersmit HJ, Scheiner O, Boltz-Nitulescu G, Jensen-Jarolim E. Anti-ulcer drugs promote IgE formation toward dietary antigens in adult patients. *FASEB J* 2005; **19**:656-8.
- ¹⁰ Brunner R, Wallmann J, Szalai K, Karagiannis P, Altmeppen H, Riemer AB, Jensen-Jarolim E, Pali-Schöll I. Aluminium per se and in the anti-acid drug sucralfate promotes sensitization via the oral route. *Allergy* 2009; **64**:890-7.
- ¹¹ Pali-Schöll I, Yildirim AO, Ackermann U, Knauer T, Becker C, Garn H, Renz H, Jensen-Jarolim E, Fehrenbach H. (2008) Anti-acids lead to immunological and morphological changes in the intestine of BALB/c mice similar to human food allergy. *Exp Toxicol Pathol* 2008; **60**:337-45.
- ¹² Pisegna JR. Pharmacology of acid suppression in the hospital setting: focus on proton pump inhibition. *Crit Care Med* 2002; **30**(6 Suppl):S356-61.
- ¹³ Ramirez E, Lei SH, Borobia AM, Piñana E, Fudio S, Muñoz R, Campos A, Carcas AJ, Frias J. Overuse of PPIs in patients at admission, during treatment, and at discharge in a tertiary Spanish hospital. *Curr Clin Pharmacol* 2010; **5**(4):288-97.
- ¹⁴ Levine BB. Immunologic mechanisms of penicillin allergy: a haptenic model system for the study of allergic diseases of man. *N Engl J Med* 1966; **275**:1115-25.
- ¹⁵ Capellá, D. & Laporte, J.R. La notificación espontánea de reacciones adversas a medicamentos. In Principios de Epidemiología del Medicamento 2nd edn. (eds. Laporte, J.R. & Tognoni, G.) 147-170 (Masson-Salvat, Barcelona 1993).
- ¹⁶ Hirschowitz BI, Worthington J, Mohnen J. Vitamin B12 deficiency in hypersecretoris during long-term acid suppression with proton pump inhibitors. *Alimen Pharmacol Ther* 2008; **27**:1110-21
- ¹⁷ Yang YX, Lewis JD, Epstein S, Metz DC. Long-term proton pump inhibitors therapy and risk of hip fracture. *JAMA* 2006; **296**:2947-53.
- ¹⁸ Bajaj JS, Zadornova Y, Heuman DM, Hafeezullah M, Hoffmann RG, Sanyal AJ, Saeian K. Association of proton pump inhibitor therapy with spontaneous bacterial peritonitis in cirrhotic patients with ascites. *Am J Gastroenterol* 2009; **104**: 1130-4.

- ¹⁹ Laheij RJ, Sturkenboom MC, Hassing RJ, Dieleman J, Stricker BH, Jansen JB. Risk of community-acquired pneumonia and use of gastric acid-suppressive drugs. *JAMA* 2004; **292**: 2012–13.
- ²⁰ Laheij RJ, Van Ijzendoorn MC, Janssen MJ, Cansen JB. Gastric acid-suppressive therapy and community-acquired respiratory infections. *Aliment Pharmacol Ther* 2003; **18**:847–51.
- ²¹ Yearsley KA, Gilby LJ, Ramadas AV, Kubiak EM, FOne DL, Allison MC. Proton pump inhibitor therapy is a risk factor for Clostridium-difficile associated diarrhoea. *Aliment Pharmacol Ther* 2006; **24**:613–19.
- ²² Dial S, Delaney JA, Barkun AN, Suissa S. Use of gastric acid suppressive agents and the risk of community acquired Clostridium difficile associated disease. *JAMA* 2005; **294**: 2989–95.
- ²³ Neal KR, Scott HM, Slack RC, Logan RF. Omeprazole as a risk factor for Campylobacter gastroenteritis: case-control study. *BMJ* 1996; **312**: 414–15.
- ²⁴ Untersmayr E, Scholl I, Swoboda I, Beil WJ, Förster-Waldl E, Walter F, Riemer A, Kraml G, Kinaciyan T, Spitzauer S, Boltz-Nitulescu G, Scheiner O, Jensen-Jarolim E. Antacid medication inhibits digestion of dietary proteins and causes food allergy: a fish allergy models in BALB/c mice. *J Allergy Clin Immunol* 2003; **112**:616–23.
- ²⁵ Untersmayr E, Bakos N, Scholl I, Kundi M, Roth-Walter F, Szalai K, Riemer AB, Ankersmit HJ, Scheiner O, Boltz-Nitulescu G, Jensen-Jarolim E. Anti-ulcer drugs promote IgE formation toward dietary antigens in adult patients. *FASEB J* 2005; **19**:656–8.
- ²⁶ Scholl I, Ackermann U, Ozdemir C, Blümer N, Dicke T, Sel S, Sel S, Wegmann M, Szalai K, Knittelfelder R, Untersmayr E, Scheiner O, Garn H, Jensen-Jarolim E, Renz H. Anti-ulcer treatment during pregnancy induces food allergy in mouse mothers and a Th2-bias in their offspring. *FASEB J* 2007; **21**:1264–70.
- ²⁷ Batuwitage BT, Kingham JG, Morgan NE, Bartlett RL. Inappropriate prescribing of proton pump inhibitors in primary care. *Postgrad Med J* 2007; **83**: 66–8.
- ²⁸ Barozzi N, Tett SE. Gastroprotective drugs in Australia: utilization patterns between 1997 and 2006 in relation to NSAID prescribing. *Clin Ther* 2009; **31**: 849–61.
- ²⁹ De Burgos Lunar, Novo del Castillo S, Llorente Díaz E, Salinero Fort MA. Study of prescription indication of proton pump inhibitors. *Rev Clin Esp* 2006; **206**:266–70.
- ³⁰ Nardino R, Vender RJ, Herbert PN. Overuse of acid-suppressive therapy in hospitalised patients. *Am J Gastroenterol* 2000; **95**: 3118–22.
- ³¹ Noguerado Asensio A, Rodríguez Barrientos R, Zelaya Castro P, Sánchez Sempere A, Antuña Blanco F, Lutz García E, Quintana de la Cruz, Estellés Píera F, Alcázar MS. [Use of acid-suppressive medications in hospitalized patients]. *An Med Interna* 2002; **19**: 557–60.
- ³² Pham CQD, Regal RE, Bostwick TR, Knauf KS. Acid suppressive therapy use on an inpatient internal medicine service. *Ann Pharmacother* 2006; **40**:1261–6.
- ³³ Riemer AB, Gruber S, Pali-Schöll I, Kinaciyan T, Untersmayr E, Jensen-Jarolim E. (2010) Suppression of gastric acid increases the risk of developing immunoglobulin E-mediated drug hypersensitivity: human diclofenac sensitization and a murine sensitization model. *Clin Exp Allergy* 2010; **40**:486–93.
- ³⁴ Gómez E, Blanca-Lopez N, Torres MJ, Requena G, Rondon C, Canto G, Blanca M, Mayorga C. Immunoglobulin E-mediated immediate allergic reactions to dipyrone: value of basophil activation test in the identification of patients. *Clin Exp Allergy* 2009; **39**: 1217–24.
- ³⁵ Thong, BY, Tan, TC. Epidemiology and risk factors for drug allergy. *Br J Clin Pharmacol* 2011; **71**:684–700.
- ³⁶ Schneck J, Fagot JP, Sekula P, Sassolas B, Roujeau JC, Mockenhaupt M. Effects of treatments on the mortality of Stevens-Johnson syndrome and toxic epidermal necrolysis: a retrospective study on patients included in the prospective EuroSCAR Study. *J Am Acad Dermatol* 2008; **58**: 33–40.
- ³⁷ Pichler WJ. Delayed drug hypersensitivity reactions. *Ann Intern Med* 2003; **139**: 683–93.
- ³⁸ Fiszenson-Albala F, Auzeir V, Mahe E, Farinotti R, Durand-Stocco C, Crickx B, Descamps V. A 6-month prospective survey of cutaneous drug reactions in a hospital setting. *Br J Dermatol* 2003; **149**:1018–1022.
- ³⁹ Demoly P, Viola M, Gomes ER, Romano A. Epidemiology and causes of drug hypersensitivity. In: Drug Hypersensitivity, ed. Pichler WJ. Basel: Karger, 2007; 2–17.

- ⁴⁰ Mockenhaupt M. Epidemiology and causes of severe cutaneous adverse reactions to drugs. In: Drug Hypersensitivity, ed. Pichler WJ. Basel: Karger, 2007; 18–31.
- ⁴¹ Allain H, Chevrant-Breton J, Beneton C, Bousser AM, Bentue-Ferrer D, Mazeas D, Van der Driessche J. Undesirable dermatologic results of drugs. Results of a drug monitoring survey (French). *Ann Med Interne (Paris)* 1983; **134**: 530–6.
- ⁴² Bigby M, Jick S, Jick H, Arndt K. Drug-induced cutaneous reactions. A report from the Boston Collaborative Drug Surveillance Programme on 15 438 consecutive patients, 1975 to 1982. *JAMA* 1986; **256**: 3358 – 63.
- ⁴³ Rademaker M, Oakley A, Duffill MB. Cutaneous adverse drug reactions in a hospital setting. *N Z Med J* 1995; **108**: 165–6.
- ⁴⁴ 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**: 388–93.
- ⁴⁵ 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**: 342–47.
- ⁴⁶ Man CB, Kwan P, Baum L, Yu E, Lau KM, Cheng AS, Ng MH. Association between HLA-B*1502 allele and antiepileptic drug-induced cutaneous reactions in Han Chinese. *Epilepsia* 2007; **48**: 1015–8.
- ⁴⁷ Locharernkul C, Loplumlert J, Limotai C, Korkij W, Desudchit T, Tongkobpetch S, Kangwanshiratada O, Hirankarn N, Suphapeetiporn K, Shotelersuk V. Carbamazepine and phenytoin induced Stevens-Johnson syndrome is associated with the HLA-B*1502 allele in a Thai population. *Epilepsia* 2008; **49**: 2087–91.
- ⁴⁸ Mehta TY, Prajapati LM, Mittal B, Joshi CG, Sheth JJ, Patel DB, Dave DM, Goyal RK. Association of HLA-B*1502 allele and carbamazepine-induced Stevens-Johnson syndrome among Indians. *Indian J Dermatol Venereol Leprol* 2009; **75**: 579–82.
- ⁴⁹ Kaniwa N, Saito Y, Aihara M, Matsunaga K, Tohkin M, Kurose K, Sawada J, Furuya H, Takahashi Y, Muramatsu M, Kinoshita S, Abe M, Ikeda H, Kashiwagi M, Song Y, Ueta M, Sotozono C, Ikezawa Z, Hasegawa R, JSAR research group. HLA –B locus in Japanese patients treated with antiepileptic or antimicrobial agents. *Pharmacogenomics* 2008; **9**: 1617–22.
- ⁵⁰ Lonjou C, Thomas L, Borot N, Ledger N, de Toma C, LeLouet H, Graf E, Schumacher M, Hovnanian A, Mockenhaupt M, Roujeau JC, RegiSCAR Group. A marker for Stevens-Johnson syndrome: ethnicity matters. *Pharmacogenomics J* 2006; **6**: 265–8.