**THE UNIVERSITY OF MEDICINE AND PHARMACY**

**„CAROL DAVILA", BUCHAREST**

**DOCTORAL SCHOOL**

**FIELD: MEDICINE**

# *Drug hypersensitivity reactions in the elderly: diagnostic and therapeutic features*

**PHD THESIS SUMMARY**

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2022

# Content of the PhD thesis

Published papers:

- Bumbacea, R.S.; **Ali, S**.*; Corcea, S.L.; Jinga, D.C.; Spiru, L. Successful Dabrafenib Desensitization Protocols in a Patient with Metastatic Melanoma. Medicina 2022, 58, 511. https://doi.org/10.3390/medicina58040511. IF = 2,43
  https://www.mdpi.com/1648-9144/58/4/511
    - Chapter 6.5. Chemotherapy-induced hypersensitivity reactions

- Bumbacea RS, **Ali S***, Corcea SL, et al. Omalizumab for successful chemotherapy desensitisation: What we know so far. Clin Transl Allergy. 2021;e12086. https://doi.org/10.1002/clt2.12086. IF = 5,871
  https://onlinelibrary.wiley.com/doi/10.1002/clt2.12086
    - Chapter 3.1. Chemotherapy-induced hypersensitivity reactions

- Bumbacea RS, **Ali S***, Ogneva DO, Motei C, Rusu C, Spiru L. Drug Provocation Testing in the Diagnosis of Symmetrical Drug-Related Intertriginous and Flexural Exanthema (SDRIFE) Induced by Clarithromycin. Maedica (Bucur). 2021 Jun;16(2):297-301. doi: 10.26574/maedica.2020.16.2.297. PMID: 34621355; PMCID: PMC8450659.
  https://www.maedica.ro/articles/2021/2/2021_16(19)_No2_pg297-301.pdf
    - Chapter 6.6. Macrolide-induced hypersensitivity reactions

- **Ali S***, Udrea R, Boustani R, Puiu IA, Corcea SL, Spiru L. Hypersensitivity reactions to nonsteroidal anti-inflammatory drugs: does age matter? Arch Clin Cases. 2022 Jul 7;9(2):80-88. doi: 10.22551/2022.35.0902.10208. PMID: 35813497; PMCID: PMC9262083.
  https://www.clinicalcases.eu/index.php/acc/article/view/703/237
    - Chapter 6.2. NSAIDs-induced hypersensitivity reactions

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## Introduction

Drug hypersensitivity reactions (DHRs) are a subset of adverse drug reactions clinically resembling allergic reactions (1). However, many adverse drug reactions are now labeled as "drug allergies".

Drug allergy not only affects the patient's quality of life, but also can lead to delayed treatment, utilization of alternative, less effective drugs, pointless investigations, increased morbidity and even death. Furthermore, identifying the offending drug is challenging given the multitude of symptoms and signs associated with the reaction.

DHR affects up to 20% of inpatients and approximately 7% of outpatients experience DHR (3). Although there have been paradigm developments in understanding the immunological basis of DHRs over the past 2 decades, clinical practice has lagged behind. Currently, the role of the allergist includes the prevention, diagnosis and treatment of drug hypersensitivity. Developed from studies of the harmful individual and public health consequences of an unverified penicillin allergy label, the term "delabeling" was introduced in 2013 and initiated and promoted a "delabeling" effort in drug allergy (4.5) in the US, subsequently worldwide.

In recent years, the assessment of patients with a history of DHR has undergone exceptional changes. New publications and recommendations have emerged regarding the management of DHRs induced by beta-lactam antibiotics (6), iodinated contrast agents (7), chemotherapy (8) and in the investigation of perioperative anaphylaxis (9). DHRs induced by drugs less known previously as their etiological agents have been described: proton pump inhibitors, macrolide antibiotics, fluoroquinolones. Currently, cross-reactivity between members of these families is being pursued. If in the past the approach was to eliminate the entire class to which the inducer belonged, nowadays, attempts are made to identify safe alternatives from the same therapeutic class, based on the presence or absence of cross-reactivities between the members of the same class.

Elderly patients, due to the presence of several chronic diseases, simultaneously use multiple medications. Moreover, the administration of multiple substances causes an increased risk of side effects that may be related to drug-drug interactions. To evaluate and avoid these side effects, the Beers criteria were proposed and updated (10,11). Unfortunately, DHRs do not fall into this classification. Presently, in Romania, there is limited information on the epidemiology and therapeutic approach of these patients, presented in the form of studies with

a few number of patients, case series or case reports. Also, nationally, there are not many specialized centers in the systematic evaluation of patients with a history of DHRs.

Also, there is no data on the main inducers of DHRs in Romania, as well as on the management and evaluation of these DHRs, even less in the population over 55 years of age, when comorbidities appear and medication use increases.

The concept for this paper came naturally in light of the establishment of the Allergology and Clinical Immunology Department within the Clinical Hospital of Nephrology "Dr. Carol Davila" four years ago, as well as the partnership with the WAO Center of Excellence with a focus on drug allergy in Montpellier, University Clinical Hospital. We adapted the protocols for the DHR assessment, they were approved by the Hospital's Ethics Committee.

The aim of this paper is to evaluate the characteristics of DHRs in a selected population of patients, the differences between two subpopulations divided by age (patients under 55 years of age and patients aged 55 and over), and the influence of comorbidities on patient assessment.

The presumptions behind the selection of the current research topic include the frequency of these adverse drug reactions in primary and specialized medical practice, the complete lack of data on epidemiology, the effect on patients' quality of life, and the evolution after the allergological evaluation.

The research hypothesis is formulated around the in vivo assessment of patients with a history of DHR. I tried to define the main drug classes involved in DHRs in Romania, so that the main research hypothesis was represented by the following question: "Is the main drug class involved in DHRs represented by NSAIDs or beta-lactams?". Secondary objectives were represented by the DHRs features: defining other drug classes involved in DHRs in the studied population, the type of immediate versus late reactions, the underlying mechanisms: IgE-mediated versus non-IgE-mediated, the higher frequency of atopic patients in this population, the influence of comorbidities on the initial reaction, as well as subsequent evaluation. Another question raised in the study was related to the identification of safe alternatives: can recommendations be given to patients outside of medically supervised challenge tests?

# General part

## 1. Drug hypersensitivity reactions - general aspects

Drug hypersensitivity reactions are defined, according to the EAACI, as drug-induced adverse reactions (ADRs) that clinically resemble allergic reactions (1).

The classification of DHRs has over time presented challenges because, for many drugs and clinical manifestations, the underlying mechanisms were poorly understood. However, a general classification based on the length of time between the last drug administration and the onset of DHR symptoms is currently accepted. Thus, DHRs are divided into immediate reactions and delayed or non-immediate reactions (1).

In **immediate reactions**, the onset of symptoms is 1-6 hours after the last administration of the drug. Clinical manifestations vary from isolated symptoms such as urticaria and angioedema, respiratory symptoms (rhinorrhea, sneezing, bronchospasm), digestive symptoms (nausea, vomiting, diarrhea, abdominal cramps) to anaphylaxis or even death. Cutaneous involvement may be absent in 20% of cases of anaphylaxis (17). Immediate reactions are thought to have an IgE-mediated mechanism, although non-IgE-mediated immediate reactions also exist (1).

**Delayed (non-immediate) reactions** begin at least one hour after the last administration of the drug. They usually occur several days after initiation of treatment and are associated with a T-cell-dependent mechanism of delayed hypersensitivity. The most common clinical manifestations are maculo-papular exanthema (MPE) and delayed urticaria (1). Other clinical entities classified as late DHRs are: fixed drug eruption (FDE), vasculitis, drug reaction with eosinophilia and systemic symptoms (DRESS), Acute generalized exanthematous pustulosis (AGEP), symmetrical drug-related intertriginous and flexural exanthema (SDRIFE) , Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). In some delayed reactions, only some internal organs may be affected (hepatitis, renal failure, pneumonitis, anemia, neutropenia, thrombocytopenia) or systemic effects may occur, as in the case of DRESS (1,18).

A new classification of DHRs has been proposed relatively recently (21). Thus, depending on the immune pathogenic mechanisms, they were divided into: allergic, which are defined by the hypothesis of drugs as haptens and can be mediated by IgE, IgG or T-cell type antibodies; ***pharmacological interactions*** (the p-i concept), in which the drug can bind directly to HLA or TCR; and ***pseudoallergic***, when the drug binds directly to receptors or interacts directly with effector cells, in the absence of immunological mechanisms (20).

Although immediate reactions may occur through mast cell activation through IgE-dependent or non-IgE-dependent mechanisms, the symptomatology is similar, determined by the release of mediators such as histamine, tryptase, platelet-activating factor, and cysteinyl-leukotrienes (21).

## 2. Hypersensitivity reactions induced by non-steroidal anti-inflammatory drugs

NSAIDs represent the main class of drugs responsible for DHRs. Depending on the studies, their incidence ranges from 0.5% to 5.7% in the general population (42).

The EAACI guideline (46) on NSAID-induced DHRs classifies these reactions into two main groups, depending on the suspected or demonstrated immunological mechanism:

A. Allergic DHRs (immunologically mediated) and
B. Non-allergic DHRs.

Most patients with NSAID-induced DHRs present with symptoms after administration of several structurally unrelated NSAIDs that share COX-1 inhibition.

They were considered to be "cross-intolerant" and the mechanism is not immunological. In some patients, symptoms may begin after administration of a single NSAID or several NSAIDs belonging to the same structural group, while other NSAIDs are generally well tolerated. These reactions are considered to have an immunological substrate and belong to allergic DHRs (48).

In terms of diagnosis and management, there is no agreement on whether the clinical history is sufficient to diagnose NSAID-induced DHRs (62,63), but the more accurate the history, the easier the diagnosis of NSAID-induced DHRs. Depending on the type of reaction, there are several diagnostic schemes that can be applied to patients.

Urticaria/angioedema or anaphylaxis induced by a single NSAID is probably the only entity in which we find the usefulness of performing skin tests (prick and intradermal). Although they have low sensitivity, the increased specificity (54) allows their use, especially for metamizole, a pyrazolone derivative known for its ability to determine positive skin tests.

## 3. Hypersensitivity reactions induced by beta-lactam antibiotics

Beta-lactam antibiotics, including penicillins, are, according to some studies, the most common cause of DHR (69), probably through their ability to act as haptens through chemical reactivity against proteins (70,71). Penicillins, cephalosporins, carbapenems and monobactams contain a beta-lactam ring, the safety of administration of beta-lactam antibiotics in patients

with a history of penicillin-induced DHR depending on the incidence of cross-reactivity between these sub-classes.

Penicillins consist of a beta-lactam (BL) nucleus to which a thiazolidine ring is attached. Cephalosporins contain the same beta-lactam core but have a dihydrothiazine ring attached. These classes have a side chain, called R1 attached to the BL core. Additionally, cephalosporins contain a second side chain, R2 at the level of the dihydrothiazine ring, whose structure differentiates cephalosporins from one another (72). Carbapenems, including imipenem and meropenem, are similar to penicillins and also contain a bicyclic core with a beta-lactam ring, a double carbon bond, and an R side chain that differentiate them.

Although a large number of patients are labeled as penicillin allergic, more than 95% can tolerate a penicillin after evaluation (73). Cross-reactivity between benzylpenicillin (penicillin G) and semisynthetic penicillins, especially aminopenicillins differs depending on the type of reaction (IgE-mediated or T-cell-mediated). Blanca-Lopez et al (74) diagnosed DHR in 58 patients with a history of immediate post-administration of amoxicillin or amoxicillin/clavulanic acid, with 40 of the patients tolerating subsequent administration of penicillin G and V. Regarding the cross-reactivity rate in case for late, T-cell-mediated reactions between aminopenicillins and penicillin G and/or V, this is between 9.1% and 28.2% (75,76).

Skin testing is based on performing skin prick tests, followed, in case of negativity, by intradermal tests by injecting 0.02 ml of the hapten solution intradermally, with the formation of a papule. The concentrations used vary according to the patient's symptomatology, by performing additional dilutions in accordance with the increase in the severity of the reaction up to the maximum non-irritating concentration (Romano 2018).

## 4. Hypersensitivity reactions induced by iodinated contrast agents

Most frequently, the administration of contrast agents can be associated with dose-dependent toxic reactions that require monitoring and symptomatic treatment, and, less often, hypersensitivity reactions are described, which are unpredictable reactions and do not depend on the dose used (ACR manual 2022; Brockow K - 2014).

According to current data, immediate hypersensitivity reactions were reported in 0.5% to 3% of patients receiving nonionic ICA, and severe reactions were present in 0.02% to 0.04% of intravenous procedures, while Lee et al. reported an overall incidence of HSR for ICA of 1% and of severe reactions of 0.02% (Torres MJ -2021; Lee SY-2017).

Subsequently, the allergological evaluation is indicated to be carried out, according to the latest EAACI position paper, in the first 6 months after the HSR, but not earlier than 2

months, and has as aims the: etiopathogenic diagnosis; assessment of cross-reactivity between contrast agents; identification of safe alternatives. Data from the literature show that if the allergological evaluation is done between 2-6 months after the hypersensitivity reaction, 50% of patients tested show positive results, decreasing to 18% for patients tested for example earlier than 2 months or later than 6 months (Torres MJ -2021).

For immediate HSR, the allergological evaluation involves in vivo exploration - skin prick test, intradermal skin test, challenge test, respectively in vitro - basophil activation test (BAT) (Demoly P-2014). For delayed DHR, the allergological evaluation involves in vivo exploration - intradermal skin test with delayed reading, skin patch test, challenge test, respectively in vitro - lymphoblastic transformation test (LTT) (Demoly P-2014). Allergological evaluation is indicated in patients with a history of maculo-papular exanthema, fixed drug eruption, SDRIFE or AGEP, and in the case of severe bullous skin reactions and in DRESS, only skin testing is recommended, the challenge test being generally contraindicated.

Intradermal skin testing is recommended to be performed with a 1:10 dilution of the standard concentration of ICA, considered the non-irritating variant or with the undiluted substance on the upper forearm or upper back with delayed reading after 48 and 72 hours (Torres MJ -2012). Undiluted ICA testing appears to have greater sensitivity in delayed reactions.

## 5. Chemotherapy-induced drug hypersensitivity reactions

CHT-induced RHMs can be defined as unexpected signs and symptoms that are not consistent with a toxicity reaction. The mechanisms responsible for RHM are not fully understood and may vary between: IgE-mediated, non-IgE-mediated, or unclear pathogenic events (7). Depending on the risk of generating DHR, it is possible to divide the CHT agent into three groups: drugs with high, intermediate or low potential to cause DHR. Reactions can be caused by the parent compound, its metabolites or by the solvent. According to this classification, the problem of CHT-induced DHR is notable for patients treated with platinum compounds, taxanes, L-asparaginase, epipodophyllotoxins and is lower for others (7).

In clinical practice, if the first-line treatment resulted in an DHR, the oncologist might switch to a second-line therapy that may be less effective and lead to significant morbidity (29). However, if the culprit drug is associated with increased life expectancy and increased quality of life, or if there is no therapeutic alternative, the physician must weigh the benefit of continuing treatment against the risk of a potentially fatal anaphylactic reaction during the next administration of chemotherapy (7). Premedication programs are performed to prevent DHR; these include the administration of corticosteroids and antihistamines prior to chemotherapy

infusion. Occasionally, if premedication fails or if the procedure cannot be implemented, a desensitization protocol to the required drug may be recommended. The rapid desensitization protocol is the best option for mast cell-mediated DHR, regardless of whether the mechanism involved is IgE-mediated or not (29).

In the General Part of the PhD thesis, DHR induced by other drug classes are also reviewed, such as macrolides, quinolones, proton pump inhibitors, general and local anesthetics, and paramagnetic contrast agents.

# Special part

## 6. Working hypotheses and general objectives

The main objective of the personal part of the thesis is the study of RHM induced by NSAIDs and beta-lactams, as the main inducer of RHM in the studied population. We also characterized the profile of the type of reactions (immediate or delayed), we studied the differences between the age categories (under 55 years and over 55 years) both from the point of view of the inducer and the allergological evaluation. Another objective was related to atopy as a risk factor for RHM.

The same points were followed for other drug classes, such as iodinated and paramagnetic contrast agents, macrolides, quinolones, proton pump inhibitors, general and local anesthetics.

The present study is a retrospective, descriptive one, which included patients hospitalized in the Department of Allergology and Clinical Immunology of the Clinical Hospital of Nephrology "Dr. Carol Davila", Bucharest, Romania during 01.01.2019 - 03.31.2022.

General patient data as well as specific data related to patient-described DHR and specific allergy procedures were recorded in the translated and adapted ENDA questionnaire (30).

## 7. Results

### 7.1. Global descriptive analysis

We included in the study a number of 417 patients. Among them, 76 (18.23%) are male, and 341 (81.77%) are female. Regarding the age distribution, of the total analyzed patients, 225 (53.96%) are younger than 55 years old, and 192 (46.04%) are older than or equal to 55 years old.

Regarding the DHR inducers of the patients included in the study, they were: non-steroidal anti-inflammatory drugs, beta-lactam antibiotics, iodinated and paramagnetic contrast agents, fluoroquinolone antibiotics, macrolides, cytostatic drugs, medication used for general and local anesthesia, proton pump inhibitors and other drugs. The frequency of DHR induced by each drug class is found in Table 6.1. The first three classes of drugs involved in RHM in the studied group were represented by NSAIDs, beta-lactam antibiotics and iodinated contrast agents. These data are consistent with studies from other countries (6,17,31).

Table 7.1. The main drug classes involved in RHM in the studied group.

| The incriminated class of drugs | Number of patients (%) |
|---|---|
| | |
| NSAID | 135 (32,37%) |
| Beta-lactam antibiotics | 125 (29,97%) |
| Iodinated constrast agents | 43 (10,31%) |
| Local anesthetics | 15 (3,6%) |
| General anesthetics (perioperative anaphylaxis) | 13 (3,12%) |
| Chemotherapy | 11 (2,64%) |
| Fluoroquinolones | 10 (2,4%) |
| Proton pump inhibitors | 8 (1,92%) |
| Paramagnetic contrast agents | 7 (1,68%) |
| Macrolides | 6 (1,44%) |
| Other antibiotics | 4 (0,96%) |
| Other drugs | 40 (9,59%) |

Other antibiotics were represented by: concurrently administered streptomycin and isoniazid, clindamycin, nalidixic acid and metronidazole, each being implicated in one episode of DHR. In the group of "Other drugs" we included substances that are not found in the other groups of drugs, but which were incriminated in few reactions, not allowing the creation of a statistical analysis group for each substance. These are: low molecular weight heparins (fraxiparin, enoxaparin), antithrombotic medication (dabigatran, apixaban), corticosteroids (hydrocortisone hemisuccinate, dexamethasone, budesonide, methylprednisolone), oral antidiabetics (gliquidone, glycalzide, glibenclamide, metformin, ripaglinide, metformin) , thiamazole, levothyroxine, monoclonal antibodies (etanercept, bevacizumab, infliximab, bortezomib, trastuzumab), romiplostim, injectable or oral iron, drotaverine, sulodexide, allopurinol, codeine, leflunomide, ranitidine, progesterone, and eye drops (brinzolamide, latanoprost/timolol , flumetholone).

From the point of view of the atopic status defined by the total IgE value above 100 KU/l, 93 patients (out of the 417 in which this parameter was determined) had elevated values.

### 7.2. NSAID-induced drug hypersensitivity reactions.

We included in the study a number of 135 patients with a history of NSAID-induced DHR. Of these, 88 patients were under 55 years of age and 55 patients were over 55 years of age at the time of the allergological evaluation.

One of the variables studied was the length of time between the time of the initial reaction and the actual allergy assessment. A Mann-Whitney test (p-value = 0.0429) showed that there were statistically significant differences regarding the length of time between the first reaction and the assessment and age of the patients. Thus, the duration of time between the first reaction and the evaluation is longer in the case of patients aged 55 years or older (average duration = 6.87 years), than in the case of patients younger than 55 years (average duration of average time = 3.77 years).

Immediate reactions predominated in both groups: 94 patients in total (69.63%). 17 patients (12.59%) developed symptoms more than 6 hours after taking the drug. 24 patients (9 patients from the first group, respectively 15 from the second) could not recall the length of time between NSAID administration and the onset of the reaction. Among the delayed reactions, in the group of patients under 55 years old, 3 patients experienced MPE and 1 developed SDRIFE, while only 1 patient over 55 years of age had a history of MPE. Also, among the patients older than 55 years, one presented FDE and one SJS. These data are illustrated in Figure 7.1.

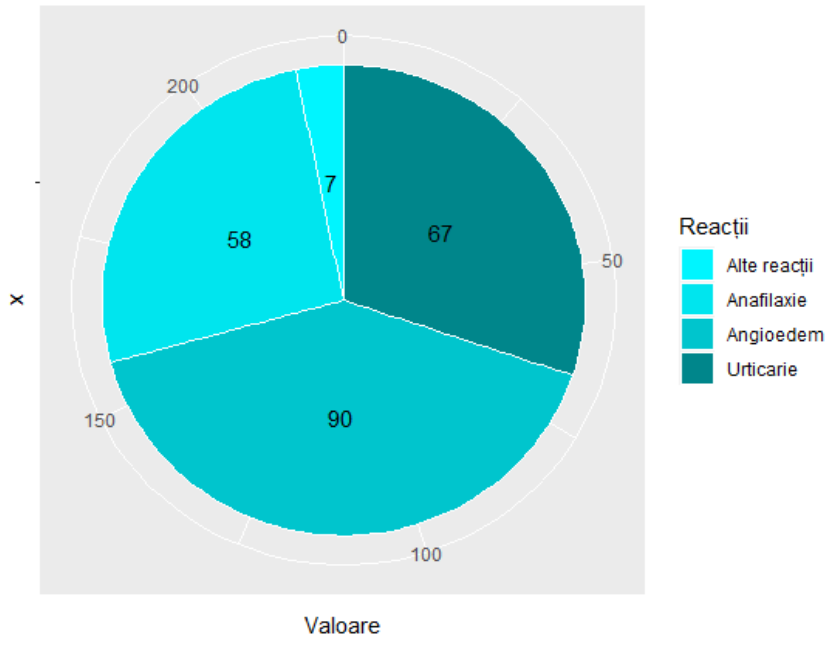


Figure 7.1. Frequency of NSAID-induced reactions*.

*Other reactions include: maculo-papular exanthema (5 patients), fixed drug eruption (1 patient), Stevens-Johnson syndrome (1 patient).

Of the total 135 patients, 114 (84.44%) had a history of NSAID-induced anaphylaxis. The number of patients in the two age groups and their distribution according to the severity of anaphylaxis are graphically represented in Figure 7.2.

We characterized the patients as atopic and non-atopic, according to the total IgE value and according to the presence of at least one skin prick test to an aeroallergen. We did not identify statistically significant differences (p-value = 0.2203) regarding the average value of the patients' IgE depending on the degree of anaphylaxis.

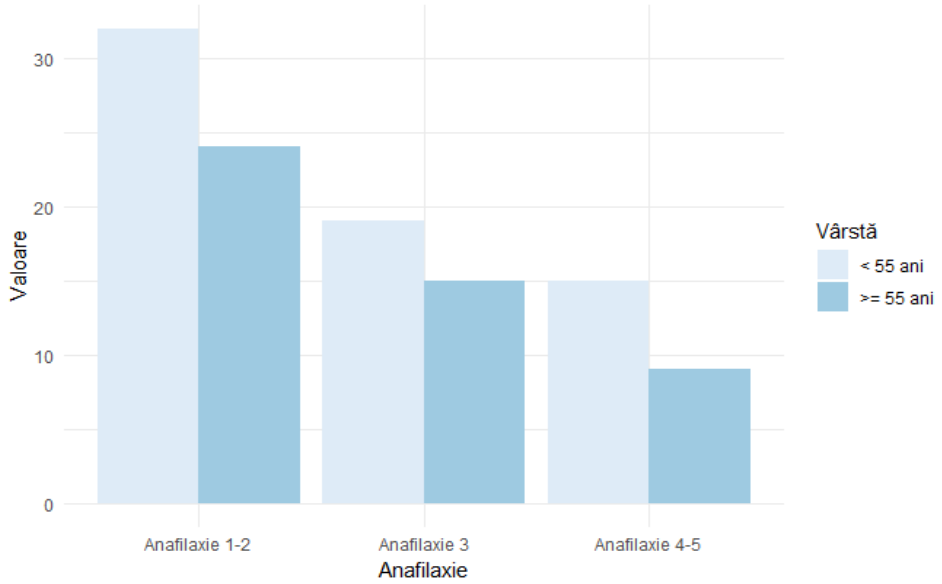


Figure 7.2. Distribution of the two age groups according to the severity of anaphylaxis

We identified the drug agents involved in NSAID-induced DHR. Figure 7.3 shows the main chemical classes of DHR inducers. The most frequent inducers, both in the general group and in the group of patients under 55 years of age, were metamizole, ibuprofen and paracetamol. In the senior group, metamizole was also most frequently incriminated, followed by acetylsalicylic acid and diclofenac.

Diclofenac ranked third in frequency among patients over 55 years of age (p-value = 0.001189), and ibuprofen was second in frequency among young people (p-value = 0.03801), the differences between the two groups having statistical significance. This could also be related to the NSAID usage habits in the two patient groups.

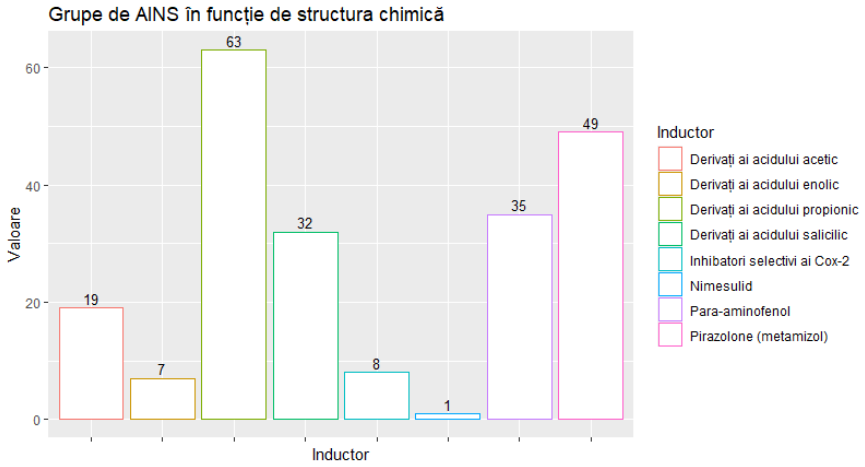


Figure 7.3. Main NSAID drug classes that induced DHR in the study population

A total of 59 (43.7%) patients reported symptoms to 2 or more chemically unrelated drugs. This is in accordance with the data provided by Demir et al. (32), who reported a cross-reactivity of 50.3% in a cohort of patients with NSAID-induced hypersensitivity reactions, and by Angeletti et al. (33) whose group reported that 60.6% of patients who developed symptoms on more than one NSAID. In another study (34), only about a quarter of patients reported the same reactions.

In order to investigate the IgE-mediated component of the reactions compatible with this type of mechanism, we performed skin prick testing, then intradermal to the offending substance, as well as to therapeutic alternatives.

A total of 40 patients were skin tested for paracetamol. All tests were negative. Fifty-one patients were tested for metamizole. One patient had a positive skin prick test and in 13 cases (25%) the metamizole intradermal test was positive. Two patients had a positive ketoprofen intradermal test in the absence of ketoprofen monosensitization. The results of the skin tests, as well as the substances that were tested, can be found in Table 7.2.

Table 7.2. Results of the performed skin prick and intradermal tests.

| Substance tested | prick CT | | intradermal CT | | Total patients tested |
|---|---|---|---|---|---|
| | Pozitive | Negative | Pozitive | Negative | |
| Metamizol | 1 | 37 | 13 | 37 | 51 |
| Ketoprofen | 0 | 35 | 2 | 35 | 37 |

| | | | | | |
|---|---|---|---|---|---|
| Paracetamol | 0 | 40 | 0 | 40 | 40 |
| Meloxicam | 0 | 2 | 0 | 2 | 2 |

Another 5 patients with positive metamizole skin tests had only IgE-mediated sensitization to metamizole, being able to tolerate other NSAIDs, but the remaining 7 also reacted to other NSAIDs. This fact may raise the suspicion of a dual mechanism of the reaction induced by metamizole, both through an IgE-mediated mechanism and through COX-1 inhibition.

To provide safe alternatives, we performed challenge tests for other drugs. A total of 210 NSAID challenge tests were performed. Paracetamol was the most frequently tested drug. It was tolerated in the total dose of 1000 mg by 86 patients, 2 reacted during the challenge test, developing angioedema. Drug challenge tests are summarized in Table 7.3.

Table 7.3. Challenge tests performed for therapeutic alternatives.

| Substance administered / total dose administered | Well tolerated | Reaction | Was not performed |
|---|---|---|---|
| Paracetamol 1000 mg | 86 | 2 | 47 |
| Nimesulide 200 mg | 39 | 1 | 95 |
| Celecoxib 200 mg | 48 | 1 | 86 |
| Etoricoxib 60 mg | 16 | 1 | 118 |

Special attention was paid to patients with a history of DHR induced by coxibs and the preferential COX2 inhibitor, nimesulide. Of the 5 patients who responded to etoricoxib, one tolerated celecoxib, 4 tolerated paracetamol and one tolerated meloxicam. All 3 patients with a history of celecoxib-induced DHR tolerated paracetamol. One of them tolerated nimesulide following a drug challenge test, and one tolerated meloxicam and etoricoxib. The patient with a history of nimesulide-induced angioedema tolerated paracetamol.

Regarding patients sensitized to coxibs, there is little evidence of tolerance to other NSAIDs. In our cohort we demonstrated celecoxib tolerance in one patient with etoricoxib-induced DHR and paracetamol tolerance in 4 others.

### 7.3. Beta-lactam-induced drug hypersensitivity reactions

We included in the study a number of 125 patients with a history of beta-lactam-induced DHR. Of these, 73 patients were under 55 years of age and 52 patients were over 55 years of age at the time of the allergological evaluation.

We classified patients according to the onset of symptoms versus drug administration. This classification is presented in Table 6.4. Immediate reactions predominated in both groups: 101 patients in total (80.80%).

We looked at the prevalence of certain symptoms such as urticaria and angioedema among patients with a history of beta-lactam-induced RHM. The frequency of the main types of beta-lactam-induced reactions is illustrated in Figure 7.4.

Table 7.4. Classification of patients according to the type of reaction: immediate/delayed.

| Reaction type | < 55 years old | ≥ 55 years old | Total |
|---|---|---|---|
| Immediate (< 6 hours) | 58 (46,40%) | 43 (34,40%) | 101 (80,80%) |
| Delayed (≥ 6 hours) | 10 (8,00%) | 4 (3,20%) | 14 (11,20%) |
| Cannot specify | 5 (4,00%) | 5 (4,00%) | 10 (8,00%) |

The most frequent inducers (illustrated in Figure 7.5), both in the general group and in the group of patients aged less than 55 years old, were amoxicillin alone or in combination with clavulanic acid, penicillin and cefuroxime. In the senior group, amoxicillin alone or in combination with clavulanic acid was also most frequently incriminated, followed by penicillin and ampicillin.

Table 7.5 shows the sensitivities according to the class to which the RHM inducer belongs, differentiated by the two age classes.

In the evaluation of patients with a history of DHR induced by beta-lactam antibiotics, we followed the EAACI recommendations (5). The results of the skin tests, as well as the substances that were tested, can be found in Table 7.6.

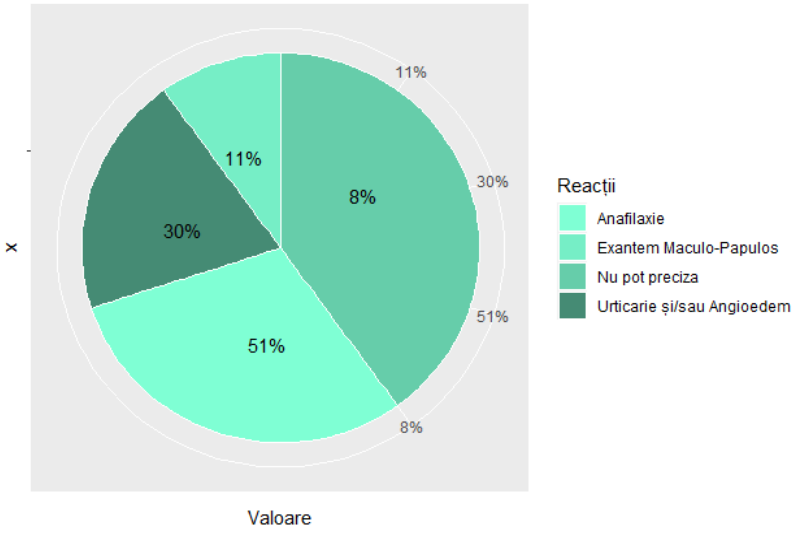


Figure 7.4. Frequency of beta-lactam-induced reactions*.

* Anaphylaxis includes grades 3, 4 and 5 according to the WAO classification.

Table 7.5. DHR inducers in the study population

| Beta-lactams | < 55 years old | ≥ 55 years old |
|---|---|---|
| Penicillins | 48 (38,40%) | 49 (39,20%) |
| Cephalosporins | 30 (24%) | 11 (8,80%) |
| Cannot specify the antibiotic | 3 (2,40%) | 2 (1,60%) |

Statistical analysis of beta-lactam skin test positivity and aeroallergen sensitization showed a positive and significant association of aeroallergen-positive prick CT and penicillin prick CT (p-value = 0.01546), cefuroxime prick CT (p-value = 2.571e- 05), ceftriaxone prick CT (p-value = 7.661e-06), id CT to ceftriaxone (p-value = 9.351e-05), id CT to cefoperazone-sulbactam (p-value = 0.00181). TCP to common environmental aeroallergens does not show a dependency relationship with the rest of the analyzed substances or inducers.

Skin prick testing confirmed IgE-mediated sensitization in 2 (2%) of the total 97 patients with a history of penicillin-induced DHR, and in 9 (21.95%) of the 41 patients with a history of cephalosporin-induced DHR. Also, id CT identified the inducer in 26 (27.37%) of the 95 patients tested. The identification of sensitization allowed the avoidance of oral challenge tests in sensitized patients, as well as the development of a hypersensitivity reaction during oral challenge tests.

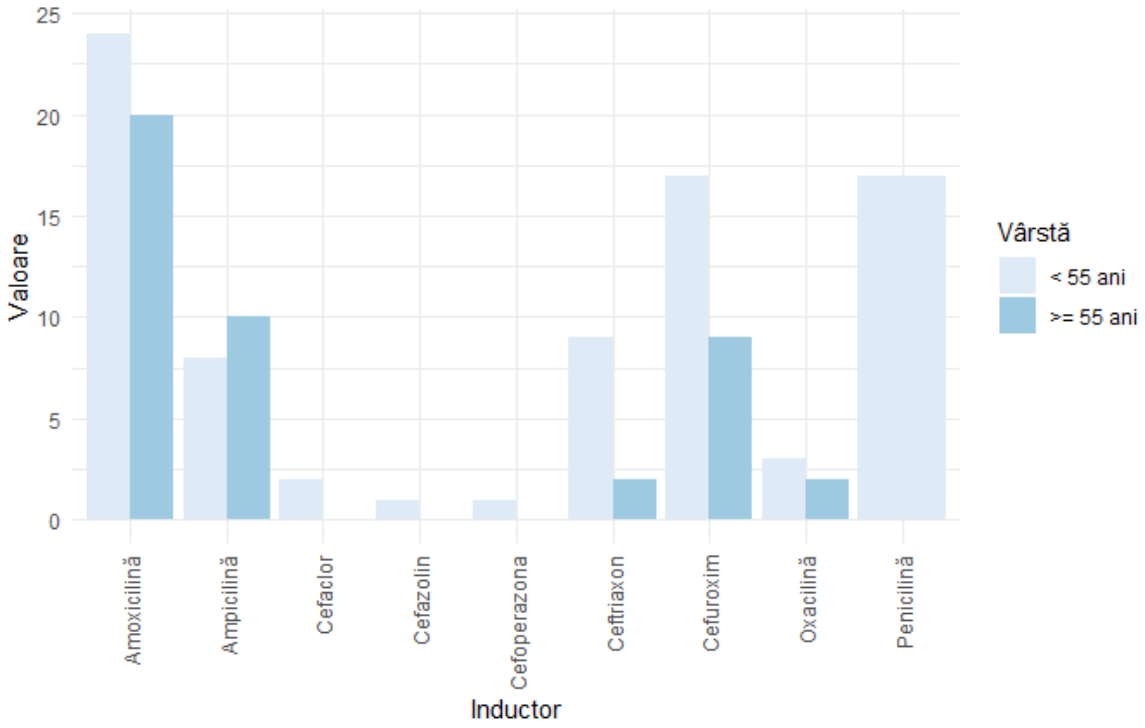


Figure 7.5. Distribution by inducers of patients with a history of beta-lactam-induced DHRs.

Table 7.6. Beta-lactam antibiotics skin tests performed.

| | Prick cutaneous test | | | Intradermal cutaneous test | | |
|---|---|---|---|---|---|---|
| The substance tested | Pozitiv | Negativ | Ne-efectuat | Pozitiv | Negativ | Ne-efectuat |
| Penicillin | 0 | 113 (90,4%) | 12 (9,6%) | 6 (4,80%) | 107 (85,60%) | 12 (9,60%) |
| Amoxicillin/clavulanic acid | 2 (1,60%) | 111 (88,80%) | 12 (9,60%) | 20 (16%) | 91 (72,80%) | 14 (11,20%) |
| Cefuroxime | 9 (7,20%) | 111 (88,80%) | 5 (4%) | 4 (3,20%) | 108 (86,40%) | 13 (10,40%) |
| Ceftriaxone | 0 | 120 (96%) | 5 (4%) | 6 (4,8%) | 114 (91,20%) | 5 (4%) |
| Cefoperazone/sulbactam | 0 | 1 (0,8%) | 124 (99,2%) | 1 (0,8%) | 0 | 124 (99,2%) |

Regarding delayed reactions, 4 patients had positive id CT at the 24-hour reading. No patient had positive patch CT for amoxicillin (concentration 20%).

After skin testing, we performed oral or intravenous challenge tests with one or more of the substances that had negative skin tests. In total, we performed 108 oral challenge tests for beta-lactam antibiotics. In 25 patients we denied DHRs to the suspected antibiotic, the patients tolerating the inducer. Where sensitization to both penicillins and cephalosporins was suspected, we performed skin tests, followed by intravenous challenge tests with penems (meropenem or imipenem) or directly with therapeutic alternatives (antibiotics structurally unrelated to beta-lactams). The oral challenge tests are summarized in Table 7.7.

Also, 2 patients had double sensitization, both to penicillins and to cephalosporins. One of the patients had a history of amoxicillin-induced DHRs manifested by urticaria and angioedema onset approximately 30 minutes after the amoxicillin dose, with cefuroxime and ceftriaxone skin testing. Developed the same type of reaction during the oral challenge test to cefuroxime. The second patient had a history of WAO 5 anaphylaxis that started 30 minutes after the amoxicillin/clavulanic acid dose.

Skin test evaluation revealed sensitization to both amoxicillin/clavulanic acid and cefuroxime by prick CT positivity to both substances at the maximum non-irritant concentration.

Table 7.7. Oral challenge tests performed in patients with a history of beta-lactam-induced DHRs.

| The substance administered | < 55 ani | ≥ 55 ani |
|---|---|---|
| Amoxicillin/clavulanic acid | 26 (20,80%) | 15 (12%) |
| Cefuroxime | 33 (26,40%) | 34 (27,20%) |
| Penemy | 4 (3,20%) | 0 |
| Structurally unrelated antibiotics | 11 (8,80%) | 5 (4%) |

### 7.4. Drug hypersensitivity reactions induced by iodinated contrast agents

We included in the study a number of 43 patients with a history of DHR induced by ICA. Of these, 11 patients were under 55 years of age and 32 patients were over 55 years of age at the time of allergy evaluation.

We classified the patients according to the onset of symptoms versus the administration of ICA. This classification is presented in Table 7.8. Immediate reactions predominated in both groups: 35 patients in total (81.40%). 5 patients (11.63%) developed symptoms more than 6 hours after taking the drug. 3 patients could not recall the length of time between the administration of ICA and the onset of the reaction.

Tabelul 7.8. Classification of patients according to the type of reaction: immediate/delayed.

| Reaction type | < 55 years old | ≥ 55 years old | Total |
|---|---|---|---|
| Immediate (< 6 h) | 8 (18,60%) | 27 (62,79%) | 35 (81,40%) |
| Delayed (≥ 6 h) | 2 (4,65%) | 3 (6,98%) | 5 (11,63%) |
| Cannot be specified | 1 (2,33%) | 2 (4,65%) | 3 (6,98%) |

Regarding the type of reaction, immediate versus delayed, the chi-square test (p-value = 0.372) showed that this is not dependent on the two age categories.

The frequency of damage to organs and systems is illustrated in Figure 7.6.

We studied the correlation between the atopic status defined by an increased value (over 100 KU/l) of total IgE on the severity of anaphylaxis. Thus, we identified four patients with a history of anaphylaxis of WAO grade 3 or higher. The Kruskal-Wallis test (p-value = 0.3618) does not indicate significant differences regarding the mean value of total IgE of the patients according to the degree of anaphylaxis (3, 4 or 5).

The positivity of skin prick tests to common environmental aeroallergens, respectively mites, is presented in Table 7.9. We hypothesized the appearance of the rash after ICA administration in atopic patients. The lack of an association between atopic status (defined by sensitization to an aeroallergen) and the occurrence of rash (chi-square test p-value = 0.6323) and also between sensitization to house dust mites and the occurrence and of the rash in the DHR induced by ICA (chi-square test p-value = 0.5117).

Neoplasias were present in a number of 27 patients (62.79%), respectively 5 (11.63%) patients under 55 years of age and 22 (51.16%) patients over 55 years of age. The high percentage of neoplasias among these patients is observed, which may also be correlated with repeated administration of ICM.

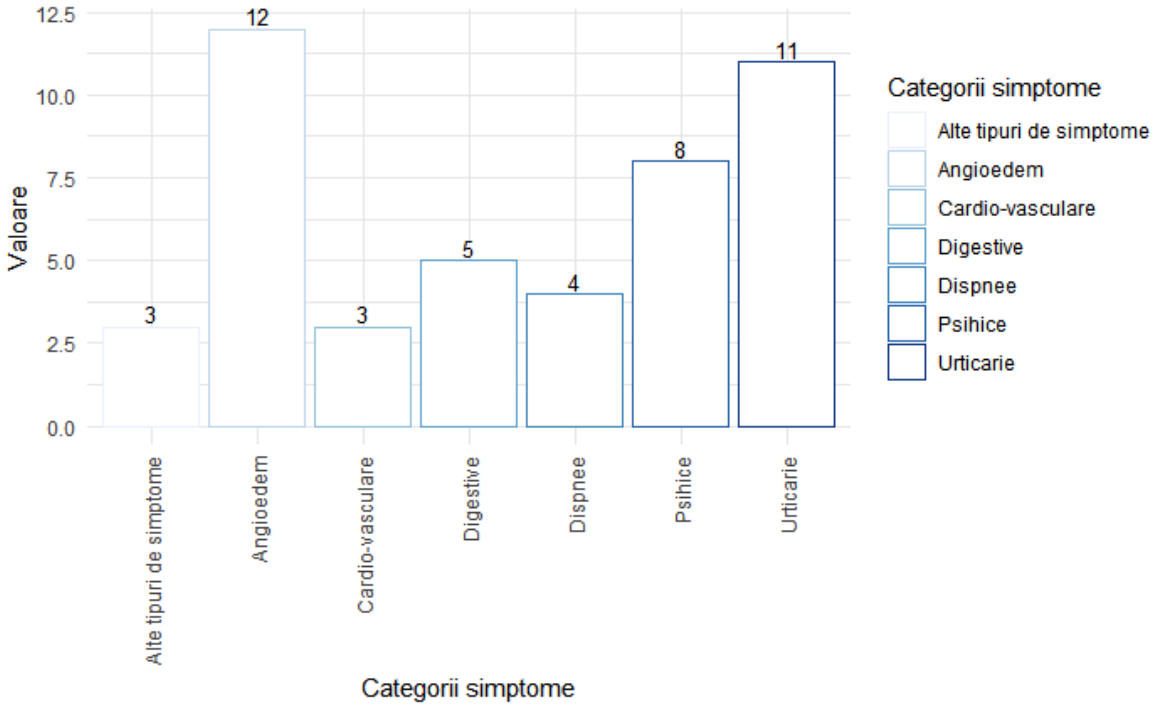


Figure 7.6. Frequency of involvement of different organs and systems in ICA-induced DHR*.

*Other types of symptoms include: chills, chest pain, sphincter incontinence.

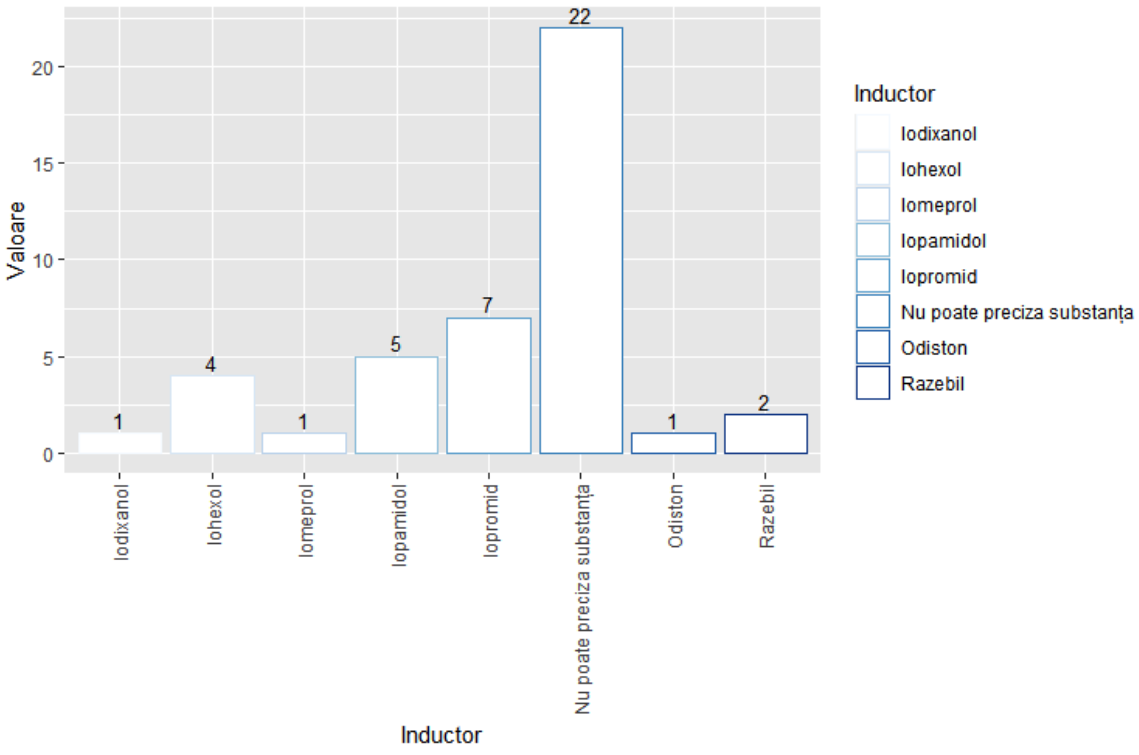


Figure 7.7. The main ICA that induced DHRs in the studied population

We identified drug agents involved in ICA-induced DHR. These data are presented in Figure 7.7. A high percentage of patients (22 patients, 51.16%) were unable to specify the substance administered.

For the evaluation of these patients we performed skin prick and intradermal testing on a panel of ICA. All skin prick tests were negative. Of the id CT performed, 15 were positive. For immediate reactions, we obtained positive id CT tests for: iopromide (5 patients), iopamidol (1 patient) and iohexol (3 patients). In case of delayed reactions, id CT was positive for iopamidol (1 patient), iopromide (2 patients) and iohexol (1 patient).

In the case of **iopamidol**, the id CT results were positive in a number of 2 patients, one with a history of DHR immediately after the administration of iodinated contrast agent, without being able to specify the substance, respectively a case of maculo-papular exanthema after the administration of iohexol. This finding raises the possibility of cross-reactivity between iopamidol and iohexol in delayed reactions.

Regarding id CT to **iopromide**, they were positive in 9 cases, of which 7 had a history of immediate DHR, and 2 cases of delayed DHR. 2 of the patients with positive CTs to iopromide also had positive CTs to iopamidol, showing the possibility of cross-reactivity between the two compounds. Among patients with IgE-mediated sensitization to iopromide, the substances that had been administered prior to the reaction are: Iopromide (4 patients), Razebil (1 patient), Iodixanol (1 patient), Iohexol (2 patients). Only one patient could not specify the administered substance.

4 patients had positive CTs to iohexol: 2 patients with a history of immediate DHR, one with a delayed reaction and one could not specify the length of time between administration and onset of symptoms. Also, 2 of patients had received iohexol during the investigation with iodinated contrast substance, one had received iopromide, and the fourth could not specify the administered substance.

### 7.5. Chemotherapy-induced drug hypersensitivity reactions

We included in the study a number of 11 patients with a history of CHT-induced DHRs. The inductors in the case of DHRs at CHT are summarized in Table 7.9.

Of the patients with a history of carboplatin-induced DHR, all had carboplatin-negative prick CT (concentration 10 mg/ml) and -negative id CT (concentration 1 mg/ml). One of the patients had developed the reaction during a desensitization procedure, which is why we decided to change the premedication and increase the administration time, increasing the time

duration of each dose escalation step. The other two received carboplatin treatment with H1 and H2 antihistamine premedication, corticosteroids, and slower infusion.

Table 7.9. Chemotherapy medication implicated in hypersensitivity reactions.

| Inducer | Number of cases, % |
|---|---|
| *Platinum salts* | |
| Carboplatin | 3 (27,27%) |
| Oxaliplatin | 2 (18,18%) |
| *Taxanes* | |
| Paclitaxel | 1 (9,09%) |
| Docetaxel | 1 (9,09%) |
| *Other chemotherapy* | |
| Fulvestrant | 2 (18,18%) |
| Dabrafenib | 1 (9,09%) |
| Total | 11 |

In patients with oxaliplatin-induced DHR, one had negative prick CT (concentration 5 mg/ml) and id (concentration 0.5 mg/ml) and the second had positive id CT 1/100 (concentration 0.05 mg /ml) . For the patient with negative CT, we opted for a protocol with premedication and slow administration of chemotherapy. In the second case with proven IgE-mediated sensitization, we opted for a desensitization protocol adapted from the 12-step protocol described by M. Castells (29) .

In the case of fulvestrant, due to the fact that there is not much data in the literature, we opted for the administration of a premedication 12 hours and 2 hours prior to the administration of the medication. All patients tolerated the administration after adjusting the previously administered corticotherapy dose.

A special case, which I also published, was represented by the desensitization to dabrafenib, in the case of a patient with metastatic melanoma who developed hives, chills, cough and altered general condition on the 14th day of drug administration (35). We described a hypersensitivity reaction to dabrafenib for which we successfully used two desensitization protocols: one rapid (3 days) and one slow (14 days).

### 7.6. Macrolide-induced drug hypersensitivity reactions

The sample of patients with a history of macrolide-induced DHRs includes a total of 6 patients, all of them female. The frequency of the 3 inductors is shown in Table 7.10.

Table 7.10. Substances involved in macrolide-induced DHRs

| Inducer | Number of reactions, % |
|---|---|
| Erythromycin | 2 (28,57%) |
| Clarithromycin | 2 (28,57%) |
| Azithromycin | 3 (42,85%) |
| Total reactions | 7 |

Depending on the cutaneous involvement, 3 patients presented urticaria, one case of rash, one case of maculo-papular exanthema and one case of SDRIFE. Overall, the reported reactions were mild-moderate in severity, consistent with other reports in the literature (36) .

We performed prick CT to clarithromycin 25 mg/ml (37) in 4 patients. Prick CT was positive in one of the cases. Id CT (maximum concentration 1 mg/ml) were performed in 3 patients and were negative.

Subsequently, we performed oral challenge tests with clarithromycin in 5 patients. 3 of the patients with a history of azithromycin-induced DHR (one of them had also reacted to the administration of clarithromycin) tolerated the administration without side effects. One patient developed digestive adverse reactions (nausea, diarrheal stools), and one patient developed a rash compatible with the diagnosis of SDRIFE, a case published in Maedica magazine (38) .

Because the cohort included a small number of patients, no statistical analysis could be performed, but the results are consistent with those of other studies regarding the utility of oral challenge test in the diagnosis of macrolide-induced DHRs, as well as demonstrating the absence of cross-reactivity between members same class (36) .

## 8. Personal contributions and conclusions

The main objective of the personal part of the thesis was to determine the main inducer of DHR in a defined population of patients with a history of DHR, who were referred for evaluation in a tertiary Allergology and Clinical Immunology Service, with special interest in drug allergy.

The primary inducer of RHM in the study population was identified as NSAIDs. Thus, 135 patients (32.37%) out of a total of 417 evaluated between January 1, 2019 and March 31, 2022, declared NSAIDs as the primary etiological agent of DHR. Patients with a history of beta-lactam-induced DHR were on the second place, with a total of 125 patients, representing 29.97%, while patients with a history of ICM-induced DHR took third place, with 43 patients (10.31%) being evaluated.

The majority of the reactions described by the patients were immediate: 94 cases (69.63%) in the NSAID-induced DHR group, 101 cases (80.80%) in the betalactam-induced DHR, and 35 cases (81.40%) with a history of ICM-induced DHR.

In the group of patients with a history of NSAID-induced DHR, metamizole, ibuprofen and paracetamol were the most frequent inducers, both in the general group and in the group of patients under 55 years of age. In the elderly group, metamizole was also the most frequently incriminated, followed by acetylsalicylic acid and diclofenac. Diclofenac ranked third in frequency among patients over 55 years of age (p-value = 0.001189) and ibuprofen was second in frequency among younger people (p-value = 0.03801), the differences between the two groups having statistical significance.

The value of total IgE above 100 KU/l did not influence the severity or occurrence of DHR for any category of drugs. Sensitization to aeroallergens was statistically correlated only with IgE-mediated sensitizations to certain penicillins and cephalosporins (skin prick test to penicillin, to cefuroxime, and to ceftriaxone, and intradermal test to ceftriaxone, and cefoperazone-sulbactam).

Although rare, double sensitization to both penicillins and cephalosporins can occur, so tolerance to the other class should be tested by initial skin testing followed by drug provocation test.

In the case of NSAIDs, metamizole skin testing may have a role in determining IgE-mediated sensitization and proving mono-sensitization by challenge tests. However, metamizole can also induce DHR through COX inhibition.

In the evaluation of patients with a history of ICM-induced DHR, skin tests are useful for identifying the inducer as well as safe alternatives and avoiding premedication.

The most common chemotherapeutics involved in DHR in the studied group were represented by platinum salts, fulvestrant and taxanes. The rarely encountered DHR inducers give the paramountey to this group. In the case of platinum salts and taxanes there are published desensitization protocols adapted by our center as well. In the case of dabrafenib, we proposed a new desensitization protocol and implemented one published by another collective.

Our study showed a multitude of possible etiological agents of DHR, in addition to the 3 classes most commonly involved. That is why, in front of a patient with a possible RHM, a detailed anamnesis must be acquired and then a correct evaluation in order not to remove useful drugs from the therapeutic arsenal.

This paper describes a group of patients that has been little studied nationally to date, namely patients with a history of DHR, who were evaluated in a tertiary Allergology and Clinical Immunology Center. It is the first work of this type in Romania, and I believe that we have achieved the objectives proposed at the beginning of the work. It paves the way for new research in the field, and the conducted studies can be continued by further registering new patients.

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