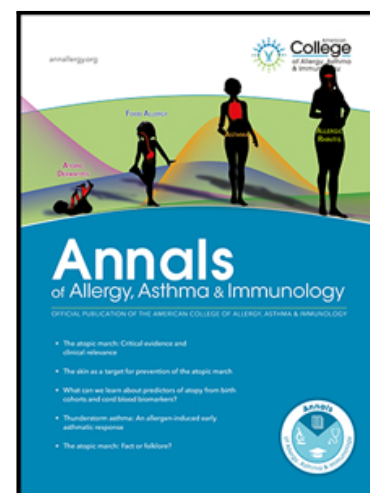


Accepted Manuscript

Proven Immunologically-Mediated Drug Hypersensitivity in Children with A History of Multiple Drug Intolerances

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PII: S1081-1206(18)31193-1
DOI: <https://doi.org/10.1016/j.anai.2018.09.447>
Reference: ANAI 2690



To appear in: *Annals of Allergy, Asthma Immunology*

Received date: 12 July 2018
Revised date: 31 August 2018
Accepted date: 5 September 2018

Please cite this article as: H. Guvenir MD , E. Dibek Misirlioglu MD Professor , M. Toyran MD Associate Professor , E. Civelek MD Associate Professor , B. Buyuktiryaki MD Associate Professor , T. Ginis MD , C.N. Kocabas MD Professor , Proven Immunologically-Mediated Drug Hypersensitivity in Children with A History of Multiple Drug Intolerances, *Annals of Allergy, Asthma Immunology* (2018), doi: <https://doi.org/10.1016/j.anai.2018.09.447>

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Full title: Proven Immunologically-Mediated Drug Hypersensitivity in Children with A History of Multiple Drug Intolerances

Running title: Multiple Drug Hypersensitivity in Children

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Conflicts of interest: none

Funding Source: none

Trial registration: Not applicable

Keywords: children; multiple drug hypersensitivity; drug provocation test

Abbreviations:

ASA: Acetyl Salicylic Acid,

BLA: Beta lactam antibiotic

DPT: Drug provocation test

IQR: Interquartile range

min-max: minimum-maximum

MPE: Maculopapular eruption

MDH: Multiple drug hypersensitivity

NSAID: Nonsteroidal anti-inflammatory drug

SD: Standard deviation

Abstract

Background: Children may be referred to pediatric allergy clinics for reactions to multiple drugs. Multiple drug hypersensitivity (MDH) is defined as immunologically-mediated hypersensitivity to two or more chemically different drugs.

Objective: The aim of this study is to report the allergy work-up results of children who had a history of potential hypersensitivity reactions to two or more unrelated drugs.

Methods: This study was conducted in the Pediatric Allergy and Immunology department of our hospital. Children who described hypersensitivity reactions to two or more drugs were included and were evaluated by allergy work-up (skin and/or provocation tests) between January 2011 and July 2016.

Results: During the study period, 886 children were evaluated for a history of drug intolerance. Of these children, 73 (8.2%) had a history of drug reactions to two or more chemically different drugs. The median age of the children who had a history of reactions to two or more drugs was 7.8 (min-max: 2.5-16.4) years, and 59% (n=43) were male. Among the suspected drugs, antibiotics (65.9%) ranked first and non-steroid antiinflammatory drugs (34.1%) were the second. All 73 children were evaluated with skin and/or provocation tests with the suspected drugs, and MDH was confirmed in only two (2.7%) children.

Conclusion: Multiple drug hypersensitivity is uncommon in children. The incidence and prevalence of MDH may vary with the specific population studied. Evaluating children with a

history of MDH, by performing drug hypersensitivity testing, will help avoid the morbidity associated with unnecessary drug avoidance.

INTRODUCTION

PChildren may be referred to pediatric allergy clinics for reactions with multiple drugs used simultaneously or sequentially. In order to prevent unnecessary drug prohibitions, these children need to be evaluated for drug hypersensitivity with appropriate tests.¹ Multiple drug intolerance syndrome or multiple drug hypersensitivity is considered in patients with reaction history to more than one drug. While multiple drug intolerance syndrome is defined as non-immunologic reactions to three or more drug classes², multiple drug hypersensitivity (MDH) is defined as hypersensitivity to two or more chemically different drugs.³ There are two types of MDH. The first type includes hypersensitivity developing to different drugs administered simultaneously, and the second type includes sensitivity reactions developing sequentially, sometimes years apart.³ The main responsible drugs are antibiotics and nonsteroidal anti-inflammatory drugs (NSAIDs). Clinical manifestations can occur as immediate or non-immediate reactions.^{4,5}

The pathogenesis of MDH is not well known. However, the underlying pathological mechanism is thought to be T-cell mediated.⁶⁻⁸ It is suggested that immunostimulation during the first drug hypersensitivity reaction, like that of viral infections, may lower the threshold of T-cell reactivity to drugs and facilitate the immune response to the second drug.⁶⁻⁸

There is limited data about allergy work-up proven MDH in childhood. Therefore, actual incidence and prevalence are unknown.⁹ In the literature, there is only one study of children with suspected multiple drug hypersensitivity, who have been tested with detailed allergic tests and provocation tests. Among suspected children, the rate of confirmed multiple drug hypersensitivity was reported as 2.5%, in this study.¹⁰

The aim of this study is to report the outcomes in children with a history of multiple drug intolerance who underwent allergy work-up.

METHODS

This study was conducted in the Pediatric Allergy and Immunology department of our hospital. We included children with ≤ 18 years, who described hypersensitivity reactions to at least two drugs and were evaluated by skin and/or provocation tests between January 2011 and July 2016. The local ethics committee approved the study design and protocol.

Prior to the allergy work-up, the parents of all the children received information about the possible risks of skin and challenge tests, and written informed consent was obtained.

The initial drug allergy workup started with the standardized European Network of Drug Allergy questionnaire on drug allergy.¹¹ The suspicious drugs, used at simultaneously or sequentially, a detailed history included the spectrum and timing of symptoms, dose and route of administration and a list of concomitant medications, history and timing of previous hypersensitivity reactions, coexisting chronic diseases, and a family history of allergic diseases. Reactions occurring within the first hour were labeled as ‘immediate reactions’, mostly manifesting clinically as urticaria, angioedema, rhinitis, bronchospasm and anaphylaxis; the ones occurring later (after 1 h) were labeled as ‘nonimmediate reactions’, manifesting clinically as maculopapular eruptions and delayed appearing urticaria/angioedema.

If the history of suspected reaction was compatible with drug hypersensitivity, then skin tests (prick test and intradermal test) and oral provocation test with the drug (suspected or alternative) were proposed. These tests were performed at least 1 month after the initial reaction. Use of antihistamine medications and other drugs that could affect skin tests or drug provocations were ceased a week before the test.

Evaluation of drug hypersensitivity

PSkin tests

Children were subjected to prick and intradermal skin testing with the suspected drugs. Isotonic saline solution was used for dilution. All the drugs were initially tested on the volar forearm skin with the prick method, and reactions were considered positive when a wheal diameter 3 mm larger than the negative control, with surrounding erythema, was present 20 minutes later. When prick tests yielded negative results, 0.02 mL of the relevant agent was injected intradermally on volar forearm skin. Readings were made 20 minutes after injections. Results were considered positive when an increase of larger than 3 mm in the wheal diameter occurred, accompanied by erythema. Histamine at 10 mg/mL and 0.9% NaCl were used as positive and negative controls, respectively. When a skin test result was positive, the patient was considered to be hypersensitive to the tested drug, and the procedure was ceased.¹²

If the suspicious drug is a NSAID, then skin tests were performed with the culprit drug by using the suggested concentration (paracetamol 10 mg/mL, metamizole 0.1 mg/mL).¹³

If immediate-type beta lactam antibiotic (BLA) hypersensitivity was suspected, skin tests included the classic penicillin test (benzylpenicilloypoly-L-lysine, minor determinant mixture, and penicillin G [10,000 IU/mL]), amoxicillin-clavulanate (20 mg/mL), and the suspected drug. If the suspicious drug is a cephalosporin, then skin tests were performed with the culprit drug by using the suggested concentration (2 mg/mL).¹³

Drug provocation tests

European Network of Drug Allergy guidelines for all drug DPTs were carefully respected.¹⁴ The suspected drug was administered at divided doses every 30 minutes, until a cumulative dose close to the age- and weight-adjusted daily dose of the drug was achieved. The test is discontinued in the event of any reaction. The provocation test was not blinded, and an open challenge was performed by a physician with full resuscitation backup. The DPT result was considered positive if any objective symptoms or signs were documented. After the last dose had been administered without a reaction, the patient was kept under surveillance for at least 2 hours. The children were asked to contact the physician in order to inform whether a reaction occurred after the provocation test.¹⁴

Aspirin Provocation Test: On the first day, three placebo capsules were administered at 1.5-hour intervals. On the second day, four increasing doses (27 mg, 44 mg, 117 mg, and 312 mg) were given at 1.5-hour intervals until a maximum dose of 500 mg was reached or until the cumulative dose of 10 mg/kg was reached. Forced expiratory volume in 1 second was measured by spirometry at the beginning of the test and every 30 minutes during the provocation.¹⁵

Skin prick tests for the evaluation of atopy

Skin-prick tests were performed with mites (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*), molds (*Alternaria*, *Cladosporidium*, and *Aspergillus*), pollens (grass mix, cereal mix, weeds, and trees), cockroach, and cat and dog epithelia for the children (Stallergenes, Paris, France).

Definition of multiple drug hypersensitivity

Children who had positive hypersensitivity test results to at least two drugs with different chemical structure were defined as MDH. When two drugs had similar chemical structures, the reaction was labeled as a single drug hypersensitivity, even if both reactions were confirmed to be hypersensitivity with allergy work-up. Because NSAIDs may cause a reaction related to their pharmacological properties, children with reactions to more than one NSAID are generally accepted to be hypersensitive to this group of drugs and are not accepted to have MDH.^{3,7}

RESULTS

During the study period, 886 children were evaluated for drug hypersensitivities as outpatients. Of these children, 98 (11%) had a history of hypersensitivity reactions to two or more drugs and 73 (8.2%) had a reaction with two or more chemically different drugs, and MDH was considered in these children.

The median age of the children was 7.8 (min-max: 2.5-16.4) years, and 59% (n=43) were male. Fourteen (19.2%) children had an allergic disease (8 asthma, 2 asthma+allergic rhinitis, 2 allergic rhinitis, 1 atopic dermatitis, and 1 vesicular allergy) and 8 (11%) children had a family history of allergic disease. There was not family history of MDH in the study group. The suspicious drugs most frequently involved were amoxicillin clavulanate (30%, n=51), paracetamol (15.8 %, n=27), clarithromycin (15.3%, n=26), and ibuprofen (14.7%, n=25) (Table 1).

Sixty-six (90.4%, 66/73) children had a history of reactions to two different chemically drugs while 7 (9.6%, 7/73) children had a history of reactions to three different chemically different drugs. In 50.7% (n = 37) of children, reactions with suspected drugs occurred simultaneously, whereas 49.3% (n = 36) occurred at different times (Table 2).

11 73 children with suspected MDH were evaluated with allergy work-up (skin and/or provocation tests by the suspected drug). As a result of the tests, drug hypersensitivity was confirmed in 7 (9.6%) children. Characteristics of children who had confirmed drug hypersensitivity is given in Table 4. Two (2.7%) children had a confirmed MDH; other five children had confirmed single drug hypersensitivity. Both of the children with MDH had used these drugs at different times. Among children with simultaneous use of the drugs, none of the children was confirmed to have MDH; only one child was confirmed to have single drug hypersensitivity (Table 3).

Characteristics of the children with a history of allergies to ≥ 2 similar chemically drugs (n=25) is given in eTable 1.

The flow chart of the study is summarized in Figure 1.

DISCUSSION

In this study, MDH was confirmed in only two of 73 (2.7%) children who had a history of potential hypersensitivity reactions associated with two or more chemically unrelated drug groups. One of the children had hypersensitivity to a BLA and a NSAID, and the other child had hypersensitivity to two antibiotics from different chemical groups (BLA and macrolide).

Drug hypersensitivities can cause significant morbidity and mortality for all age groups. The reactions against a single drug are more common.¹ However, reactions against two or more chemically unrelated drug groups, which is called MDH, have also been reported. It is important to determine whether patients who had reactions against more than one drug have really MDH by performing in vivo and/or invitro allergy tests.^{3,5,7}

Reactions to more than one NSAID are usually related to pharmacologic properties of the drug (cyclooxygenase inhibition).^{16,17} Therefore, in our study, NSAID-related reactions were evaluated in a separate group. In our study, 15 children had reported a reaction with more than one NSAID and two of them (13.4%) had positive OPT with more than one NSAID.

In the literature, MDH related data generally comes from adult patients. The first data on this subject was published by Sullivan et al,¹⁸ who have shown that 1% of 437 patients with penicillin allergy developed a reaction against non-BLAs. However, this study was observational and there was no allergic evaluation. In recent retrospective cohorts, the incidence of MDH was reported as 0.6% when assessed by allergy tests in adult patients with a history of drug hypersensitivity.¹⁹

There are only 4 studies evaluating MDH in children.^{10,20-22} Two of these studies [(Kamada et al,²⁰ and Park et al.²¹)] evaluated parent reported MDH reactions with antibiotics. The incidence of reported multiple antibiotic hypersensitivities was found to be 11%²¹ and 20%.²⁰ In studies proving hypersensitivity with allergy tests, lower frequencies were reported. Buonomo et al.²² performed skin prick tests to children with a history of allergic reactions to more than one drug and found the incidence of MDH in children as 2.2%, OPT were not performed for children with negative SPT.

In the study conducted by Atanaskovic-Markovic et al,¹⁰ all children with a history of MDH were evaluated with hypersensitivity by a whole allergy work-up. In this study, of 928 children, ages between 2-14 years, 32.1% had a history of reactions with multiple drugs and MDH was confirmed in 7 children (2.5%). In accordance with their results, the verified incidence of MDH was found to be 2.7% in our study.

The most common causes of MDH are antibiotics, NSAIDs, antiepileptics, and local anesthetics.⁹ In our study, amoxicillin-clavulanate and clarithromycin were found in one of the 2 children confirmed with MDH, and amoxicillin-clavulanate and paracetamol allergies

were found in the other patient. In the study conducted by Atanaskovic-Markovic et al,¹⁰ antibiotics, NSAIDs and antiepileptics were among the susceptible drugs.

Reactions that occur due to multiple drug hypersensitivities can be immediate or delayed type reactions.^{4,5} In our study, 3 out of 4 reactions belonging to 2 children who were confirmed to have MDH were immediate and 1 was non-immediate reaction. In the study conducted by Atanaskovic-Markovic et al,¹⁰ 11 out of 15 reactions belonging to 7 children confirmed with MDH were delayed.

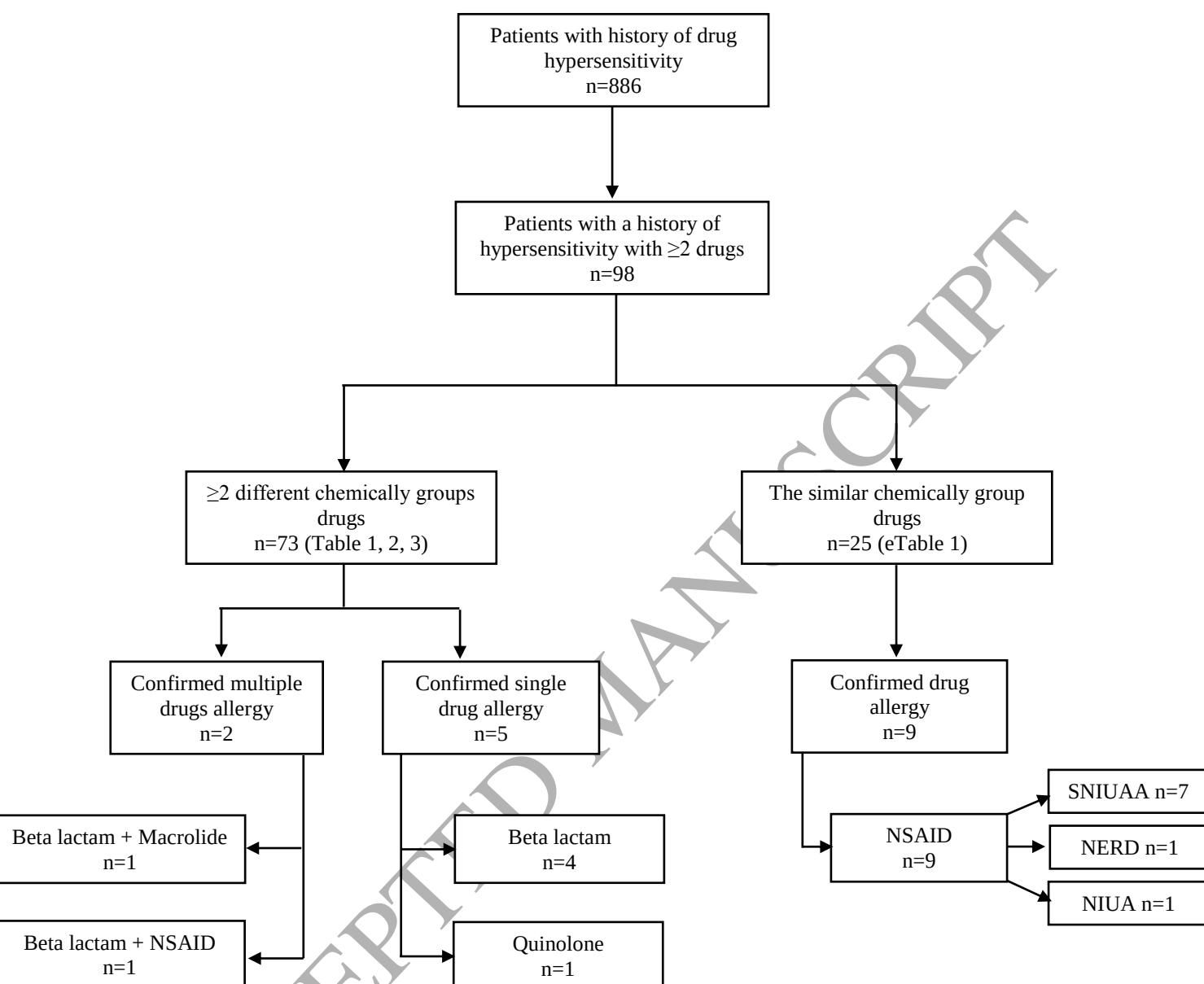
In patients with a history of MDH, it is important to determine whether the drugs used have been taken concurrently or at different times.³ Antibiotics and NSAIDs can often be used concurrently or sequentially during infections and the developing skin rash may be related to drug hypersensitivity as well as infection. Thus, it can be predicted that children with multiple drug hypersensitivities may be more likely to develop against concomitant drugs. In our study, however, suspicious drugs were used concurrently in 50.7% and at different times in 49.3% of the children. In both of the two children diagnosed with MDH, reactions occurred after the use of suspected drugs at different times. In the study conducted by Atanaskovic-Markovic et al, all children with MDH has been using concurrent or consecutive suspicious drugs.¹⁰

In conclusion, multiple drug reactions are frequently reported but most of the reported cases are not confirmed when evaluated with allergy work-up. In these children, the chemical structures of the suspected drugs and their usage times (concurrent or different time), as well as characteristics of the drug reaction, should be questioned in detail and definitely confirmed with allergy testing. Drug options for children are more limited than adults. Therefore, it is important to correctly diagnose MDH. In this manner, it will be possible to prevent unnecessary drug withdrawal.

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NSAID: Non-steroidal antiinflammatory drug, SNIUAA: Single NSAID-induced urticaria/angioedema or anaphylaxis, NERD: NSAIDs-exacerbated respiratory disease, NIUA: NSAIDs-induced urticaria/angioedema

Figure 1. The flow chart of the study

Table 1. Distribution of suspected drugs in patients with multiple drug hypersensitivity

	n (%)
Antimicrobial agents	112 (65.9%)
Beta lactam antibiotics	75 (44.1%)
<i>Penicillins</i>	56 (32.9)
Amoxicillin clavulanate	51 (30)
Ampicillin sulbactam	5 (2.9)
<i>Cephalosporins</i>	19 (11.2)
Cefdinir	6 (3.5)
Cefixime	6 (3.5)
Cefuroxime	4 (2.4)
Ceftriaxone	2 (1.2)
Cefprozil	1 (0.6)
Macrolides	28 (16.5%)
Clarithromycin	26 (15.3)
Azithromycin	2 (1.2)
Quinolones	3 (1.8%)
Ciprofloxacin	3 (1.8)
Sulfonamides	2 (1.2%)
Co-trimoxazole	2 (1.2)
5-nitroimidazoles	2 (1.2%)
Metronidazole	2 (1.2)
Aminoglycosides	1 (0.6%)
Gentamicin	1 (0.6)
Lincosamides	1 (0.6%)
Clindamycin	1 (0.6)
Nonsteroidal anti-inflammatory drugs	58 (34.1%)
Paracetamol	27 (15.8)
Ibuprofen	25 (14.7)
Naproxen	3 (1.8)
Metamizole	3 (1.8)

Table 2. Patients with a history of allergies to ≥ 2 different chemically drugs (n=73)

	n	Used at simultaneously	Used at different times	MDH	Single drug hypersensitivity
2 different chemically drugs	66	35	31		
BLA + NSAID	37	30	7		
Amoxicillin clavulanate + Paracetamol	11	7	4	1	
Amoxicillin clavulanate + Ibuprofen	6	5	1		
Amoxicillin clavulanate + Paracetamol + Ibuprofen	6	6	-		
Ampicillin sulbactam + Naproxen	2	2	-		
Cefdinir + Ibuprofen	2	2	-		

Cefdinir + Paracetamol + Ibuprofen	1	1	-		
Cefdinir + Metamizole	1	1	-		
Cefixime + Ibuprofen	1	1	-		
Cefixime + Paracetamol	1	1	-		
Ceftriaxone + Paracetamol	1	1	-		1 (with Ceftriaxone)
Cefuroxime + Paracetamol	1	1	-		
Cephuroxime + Ibuprofen	1	1	-		
Ampicillin sulbactam + Paracetamol	1	1	-		
Amoxicillin clavulanate + Cefixime + Ibuprofen	1	-	1		
Amoxicillin clavulanate + Ibuprofen + Metamizole	1	-	1		
BLA + Macrolides	21	2	19		
Amoxicillin clavulanate + Clarithromycin	15	1	14	1	2 (with Amoxicillin clavulanate)
Amoxicillin clavulanate + Azithromycin	1	-	1		
Ceftriaxone + Clarithromycin	1	1	-		
Cefdinir + Clarithromycin	1	-	1		
Amoxicillin clavulanate + Cefixime + Cefdinir + Clarithromycin	1	-	1		
Amoxicillin clavulanate + Cephuroxime + Clarithromycin	1	-	1		
Ampicillin sulbactam + Cefprozil + Clarithromycin	1	-	1		
Macrolides + NSAID	2	-	2		
Clarithromycin + Ibuprofen	1	-	1		
Clarithromycin + Paracetamol + Ibuprofen	1	-	1		
BLA + Sulfonamide	2	1	1		
Amoxicillin clavulanate + Cotrimoxazole	2	1	1		
BLA + Quinolone	1	-	1		
Amoxicillin clavulanate + Ciprofloxacin	1	-	1		1 (with Ciprofloxacin)
BLA + 5-nitroimidazole	1	-	1		
Amoxicillin clavulanate + Metronidazole	1	-	1		
Quinolone + NSAID	1	1	-		
Ciprofloxacin + Naproxen	1	1	-		
Quinolone + Clindamycin	1	1	-		
Ciprofloxacin + Clindamycin	1	1	-		
3 different chemically drugs	7	2	5		
BLA + Macrolides + NSAID	5	1	4		
Amoxicillin clavulanate + Azithromycin + Ibuprofen	1	-	1		
Amoxicillin clavulanate + Cefixime + Clarithromycin + Ibuprofen	1	-	1		
Amoxicillin clavulanate + Clarithromycin + Paracetamol + Ibuprofen	1	-	1		
Amoxicillin clavulanate + Clarithromycin + Paracetamol	1	1	-		
Cephuroxime + Clarithromycin + Paracetamol	1	-	1		
BLA + 5-nitroimidazoles + NSAID	1	1	-		
Cefixime + Metronidazole + Ibuprofen	1	1	-		
BLA + Aminoglycosides + NSAID	1	-	1		
Ampicillin sulbactam + Gentamicin + Paracetamol + Metamizole	1	-	1		1 (with Ampicillin sulbactam)
Total	73	37 (50.7%)	36 (49.3%)	2 (2.7%)	5 (6.8%)

BLA: Beta lactam antibiotic, MDH: Multiple Drug Hypersensitivity, NSAID: Nonsteroidal Antiinflammatory Drug

Table 3. Characteristics of patients who had confirmed drug hypersensitivity

Patient No	Gender	Atopic disease	Atopic disease in family	Age at time of reaction	Drug timing	Suspicious drugs in history	Reaction in history	Reaction type	Skin test with suspicious drugs	DPT with suspicious drugs	Classification
1	Girl	None	Penicillin allergy	6	given different times	Amoxicillin clavulanate	Urticaria	Immediate	Negative with Amoxicillin clavulanate, penicillin major and minor determinant	Urticaria+Angioedema	Multiple drug hypersensitivity
				8		Clarithromycin	MPE	Non-immediate	Negative	MPE	
2	Boy	AR	None	12	given different times	Paracetamol	Urticaria	Immediate	Negative	Urticaria+Angioedema	Multiple drug hypersensitivity
				10		Amoxicillin clavulanate	Urticaria	Immediate	Negative with Amoxicillin clavulanate, penicillin major and minor determinant	Urticaria	
3	Girl	None	None	11.5	given simultaneously	Ceftriaxone	Urticaria	Immediate	Positive with ceftriaxone Negative with Amoxicillin clavulanate, penicillin major and minor determinant	-	BLA hypersensitivity
						Paracetamol	Angioedema	Immediate	Negative	Negative	
4	Girl	None	None	9.3	given different times	Amoxicillin clavulanate	Urticaria	Immediate	Positive with penicillin minor determinant	-	BLA hypersensitivity
				10.8		Clarithromycin	MPE	Non-immediate	Negative	Negative	
5	Boy	None	None	9.8	given different times	Amoxicillin clavulanate	Urticaria	Immediate	Negative with Amoxicillin clavulanate, penicillin major and minor determinant	Urticaria	BLA hypersensitivity
				12.4		Clarithromycin	MPE	Non-immediate	Negative	Negative	
6	Girl	Asthma	Asthma	10.5	given different times	Amoxicillin clavulanate	Urticaria	Immediate	Negative with Amoxicillin clavulanate, penicillin major and minor determinant	Negative	Quinolone hypersensitivity
				12.9		Ciprofloxacin	Urticaria	Non-immediate	Negative	Anaphylaxis	
7	Boy	None	None	14.4	given different times	Ampicillin sulbactam	Urticaria + Angioedema	Immediate	Positive with penicillin minor determinant	-	BLA hypersensitivity
				13.8		Gentamicin	Urticaria	Immediate	Negative	Negative	
				12.5		Paracetamol	Angioedema	Immediate	Negative	Negative	
				5.2		Metamizole	MPE	Immediate	Negative	Negative	

BLA: Beta lactam antibiotic, MPE: Maculopapular eruption, DPT: Drug provocation test