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Advances in pediatric drug allergy

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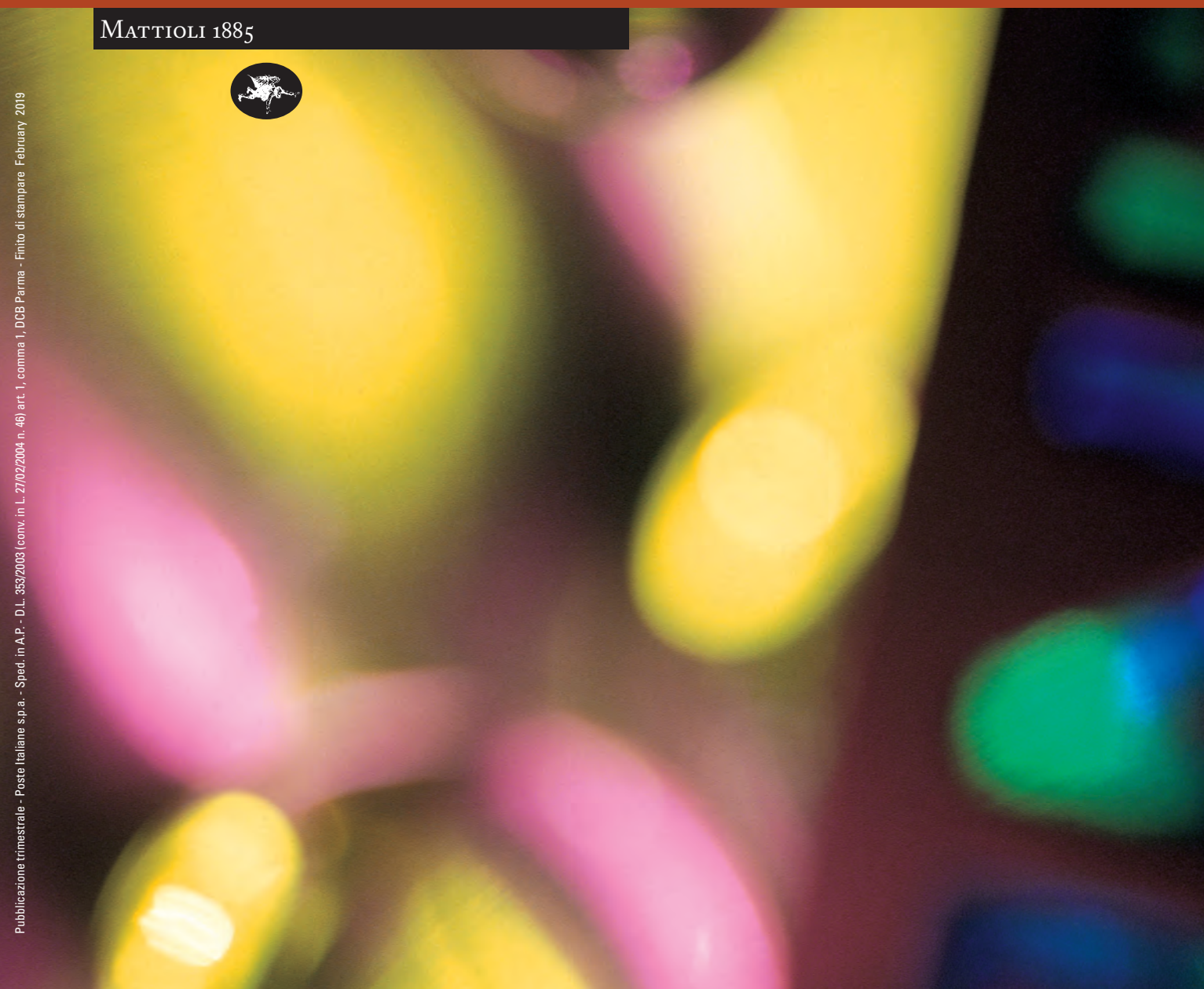

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EDITORIAL OFFICE MANAGER
Anna Scotti
Mattioli 1885 srl - Casa Editrice
Strada di Lodesana 649/sx, Loc. Vaio
43036 Fidenza (PR), Italy
Tel. ++39 0524 530383
Fax ++39 0524 82537
contact@actabiomedica.it

Francesco Covino
Società di Medicina e Scienze Naturali
Azienda Ospedaliero-Universitaria
di Parma - Cattani Building, 2nd floor
Via Gramsci, 14 - Parma, Italy
Tel./Fax ++39 0521 033730
francesco.covino@unipr.it

PUBLISHER
Mattioli 1885 srl Casa Editrice
Strada di Lodesana, 649/sx, Loc. Vaio
43036 Fidenza (PR), Italy
Tel. ++39 0524 530383
Fax ++39 0524 82537
E-mail: edit@mattioli1885.com

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Mattioli 1885
srl- Strada di Lodesana 649/sx
43036 Fidenza (Parma)
tel 0524/530383
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Reviews

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Review

Management of the child with allergy to non-antibiotic drugs

Roberto Bernardini[1], Fabio Cardinale[2], Francesca Mori[3], Francesca Saretta[4], Lucia Liotti[5], Fabrizio Franceschini[6], Giuseppe Crisafulli[7], Silvia Caimmi[8], Paolo Bottau[9], Carlo Caffarelli[10]

[1] Pediatric Unit, "San Giuseppe" Hospital, Empoli, Italy; [2] UOC di Pediatria, Azienda Ospedaliera-Universitaria "Consorziale-Policlinico", Ospedale Pediatrico Giovanni XXIII, Bari, Italy; [3] Allergy Unit, Department of Pediatric Medicine, Anna Meyer Children's University Hospital, Florence, Italy; [4] Pediatric Department, AAS2 Bassa Friulana-Isontina, Palmanova-Latisana, Italy; Pediatric Allergy Unit, Department of Medicine, Udine, Italy; [5] Department of Pediatrics, Senigallia Hospital, Senigallia, Italy; [6] UOC Pediatria, Azienda Ospedaliero-Universitaria "Ospedali Riuniti", Ancona, Italy; [7] UO Allergologia, Dipartimento di Pediatria, Università di Messina, Italy; [8] Pediatric Clinic, Foundation IRCCS Policlinico San Matteo, University of Pavia, Pavia, Italy; [9] Pediatric and Neonatology Unit, Imola Hospital, Imola (BO), Italy; [10] Clinica Pediatrica, Dipartimento di Medicina e Chirurgia, Azienda Ospedaliero-Universitaria, Università di Parma, Italy

Summary. Non-steroidal anti-inflammatory drugs, perioperative drugs, radio contrast media and chemotherapeutics drugs are, after the non-antibiotic drugs, the drugs most commonly responsible for allergic reactions in children. Management is different depending on the drug involved. (www.actabiomedica.it)

Key words: drug allergy, allergy to non-antibiotic drugs, diagnosis

Introduction

According to the World Health Organization, adverse drug reactions (ADRs) are considered as any noxious and unintended response to a medication that occurs at normal doses used for prophylaxis, diagnosis and/or treatment (1). ADRs can be classified as A-type (dose dependent and predictable) and B-type reactions (dose-independent and unpredictable). A-type reactions: toxicity, side effects, interactions with other drugs. B-type reactions: hypersensitivity [a. allergic reactions (immunonological mediated), e.g. IgE mediated or T-cells mediated; b. nonallergic reactions (non immunological mediated), e.g. pseudoallergy, intolerance, idiosyncrasy] (2-3)]. Drug allergies are drug hypersensitivity reactions (DHRs) for which a definite immunological mechanism is demonstrated. When a drug allergic reaction is suspected, DHR is the preferred term. Mechanistically, DHRs can be defined as allergic (Table 1) (4) and non allergic. Allergies to non-antibiotic drugs in child are mainly to non-steroidal anti-inflammatory drugs (NSAIDs), perioperative drugs, radio contrast media, chemotherapeutics drugs (5).

Non-steroidal anti-inflammatory drugs

NSAIDs are commonly used in the pediatric population as antipyretics/analgesics and anti-inflammatory medications. Hypersensitivity (HS) reactions to NSAID in this age group have unique diagnostic and management issues (Table 2, Table 3) (6).

The term selective reactor (SR) (Table 2, Table 3) has been applied for cases in which the clinical manifestation is due to a single drug or single subclass of NSAIDs with good tolerability to other subclasses. In general, this term includes NSAID allergic hypersensitivity reactions.

There are two well-defined phenotypes of selective HS reactions to NSAIDs:

Table 1. Classification of drug allergies

Type of immune response	Physiopathology	Main clinical symptoms	Chronology (after the drug)
IgE mediated	Mast cell, basophil degranulation	Anaphylaxis, angioedema, urticaria, rhinitis, asthma	within 6 hours after the last intake
IgG and complement	IgG and complement-Dependent cytotoxicity	Cytopenia	5-15 days after the start
IgM or IgG and complement or FcR	Deposition of immune complexes	Vaculitis, Serum sickness	7-21 days after the start 7-8 days after the start
Th1 (IFN-γ)	Monocytes inflammation	Dermatitis	within 21 days after the start
Th2 (IL-4 and IL-5)	Eosinophilic inflammation	Maculopapular exanthema DRESS	several days after the start 2-6 weeks after the start
Cytotoxic T cells (perforin, granzyme B, FasL)	Keratinocyte death mediated by CD4 or CD8	SJS/TEN	4–28 days after the start
T cells (IL-8/CXCL8) exanthematous pustulosis	Neutrophil inflammation	Acute generalized	1 to several days

Table 2. Classification of non-steroidal anti-inflammatory hypersensitivity for the child aged (0-10 y) paediatric population

Cross-reactivity	Type	Clinical of reaction	Chronology presentation	Proposed mechanism	Cofactors (influence)
Cross-intolerant reactions (Non-Allergic)	Non-allergic NSAID hypersensitivity (NERD, NECD, NIUAA)	Urticaria, angioedema, dyspnea, rhinitis, conjunctivitis, anaphylaxis	Immediate, usually from minutes to several hours after exposure	COX-1 inhibition	Possible
Non-cross-Intolerant reactions (Allergic)	Selective NSAID-induced urticaria/ angioedema or anaphylaxis (SNIUAA)	Urticaria, angioedema, anaphylaxis	Immediate (<1 h)	IgE-mediated	Unknown
Selective NSAID-induced delayed reactions (SNIDR)	Various symptoms and organs	Delayed onset T- cell-mediated (usually more than 24 h involved after exposure) (e.g., fixed drug eruption, SJN/ TEN, nephritis)		Unknown	

NSAIDs, non-steroidal anti-inflammatory drugs; COX-1, cyclooxygenase 1; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis

Table 3. Classification of non-steroidal anti-inflammatory hypersensitivity for the older paediatric population and adolescents (10-19 y)

Cross-reactivity	Type of reaction	Clinical presentation	Chronology	Mechanism	Cofactors
Cross-intolerant reactions, non allergic	NSAIDs-exacerbated respiratory disease	Bronchial obstruction, dyspnea, nasal congestion, (NERD)	minutes-hours after last intake	COX1-inhibition	Asthma, rhinosinusitis rhinorrhea
	NSAIDs-exacerbated cutaneous disease	wheals and/or angioedema (NECD)	minutes-hours after last intake	COX1-inhibition	Chronic urticaria
	NSAIDs-induced urticaria/angioedema/ anaphylaxis (NIUAA)	wheals and/or angioedema and/or anaphylaxis	minutes-hours after last intake	COX1-inhibition (probably)	Unknown
Non-cross Intolerant Reactions, Allergic	Selective NSAID-induced urticaria/ angioedema or anaphylaxis (SNIUAA)	wheals and/or angioedema and/or anaphylaxis	minutes after last intake	IgE mediated	Unknown
	Selective NSAID-induced delayed reactions (SNIDR)	cutaneous and mucous reactions, complex reactions (e.g. SJS/TEN), organ-specific disorders	delayed onset (usually more than 24 hours after last intake)	T-cell mediated	Unknown

a. Selective NSAID-induced urticaria, angioedema, and/or anaphylaxis (SNIUAA): these are immediate reactions, probably mediated by a specific IgE antibody;

b. Selective NSAID-induced delayed type HS reactions (SNIDR): these are reactions occurring within 24-48 hours after drug intake although the interval can be shorter. They are probably mediated by a specific T-cell response.

The term cross-reactor or according to the current classification, cross-intolerance (CI) reactions (Table 2, Table 3), is used in cases where the clinical manifestations are triggered by more than one subclass of NSAIDs, in which pharmacological mechanisms are the suspected pathophysiology. A combination of the inhibition of COX-1 in conjunction with an intrinsic regulatory defect in arachidonic-acid metabolism triggers a biochemical cascade involving the generation of leukotrienes and the release of mast-cell and eosinophil-derived mediators.

Ibuprofen is a safe alternative antipyretic, in children with a history of reactions to paracetamol as the molecular structure is quite dissimilar. All children with a suspected NSAIDs hypersensitivity reaction should be challenged and re-challenged periodically. COX2-specific medications, although generally not approved in children, have been prescribed and are useful as alternative medications. COX2-specific medications are the best option for all NSAID hypersensitive children. In children with NSAIDs hypersensitivity, a COX2-specific medication can be prescribed without a prior drug provocation test (6). Algorithm for the management of children with non-steroidal anti-inflammatory drugs hypersensitivity reactions has been proposed (6). In case of a confirmed hypersensitivity reaction to a single drug it is possible to use an alternative NSAID even if off label. If is present a cross-intolerance is possible a) use confirmed alternatives NSAID even if off label, b) use alternative drugs, c) use a desensitization in selective cases (6).

Perioperative drugs

Dewachter et al (7) reported an overall incidence for perioperative anaphylaxis in the pediatric population of one in 7741 anesthetic procedures. Rates appear to be higher in selected populations, as in children with congenital malformations, submitted to several interventions (8). In contrast to adults, neuromuscular blocking agents are less commonly incriminated in children, with an estimated incidence at one in 80 000 anesthetic procedures being the second leading cause after latex in this setting (9). Anaphylaxis due to induction agents is rare. Brockow et al recommended drug concentration for skin testing aiming to achieve a specificity of at least 95%. It has been possible to recommend specific drug concentration for perioperative drugs, heparins, platinum salts and radio contrast media (10) (Table 4). For the management of perioperative drug allergy it is necessary to carry out clinical history suggestive for DHR, in vivo and in vitro tests (if available), research of an alternative product, always through in vivo and in vitro tests, possible use of the responsible drug through a desensitization scheme.

Radio contrast media

The overall reported incidence of immediate reactions to intravenous nonionic iodinated radio contrast media in children is lower than in the adult population.

DHR with severe cardiovascular or respiratory involvement has been reported with an incidence of 0.07% for nonionic contrast media in children aged 1–19 years (11). Gadolinium-containing contrast media were associated with DH reactions in 0.04% of the pediatric patients (12-13).

Table 4. Nonirritating test concentrations for main perioperative drugs and selected other drugs

Drug		Skin prick test		Intradermal test	
Generic name	Undiluted Concentration (mg/ml)	Dilution	Maximum concentration (mg/ml)	Dilution	Maximum concentration (mg/ml)
Atracurium	10	1/10	1	1/1000	0.01
Cis-atracurium	2	undiluted	2	1/100	0.02
Etomidate	2	undiluted	2	1/10	0.2
Fentanyl	0.05	undiluted	0.05	1/10	0.005
Propofol	10	undiluted	10	1/10	1
Thiopental	25	undiluted	25	1/10	2.5
Ketamine	10	undiluted	10	1/10	1
Midazolam	5	undiluted	5	1/10	0.5
Sufentanil	0.005	undiluted	0.005	1/10	0.0005
Morphine	10	1/10	1	1/1000	0.01
Mivacurium	2	1/10	0.2	1/1000	0.002
Rocuronium	10	undiluted	10	1/200	0.05
Vecuronium	4	undiluted	4	1/10	0.4
Suxamethonium	50	1/5	10	1/500	0
Carboplatin			10 mg/ml		1 mg/ml
Oxaliplatin			1 mg/ml		0.1 mg/ml
Cisplatin			1 mg/ml		0.1 mg/ml
Adalimumab			50 mg/ml		50 mg/ml
Etanercept			25 mg/ml		5 mg/ml
Infliximab			10 mg/ml		10 mg/ml
Omalizumab			1.25 mcg/ml		1.25 mcg/ml
Chlorhexedine			5 mg/ml		0.002 mg/ml

Chemotherapeutics drugs

Carboplatin and asparaginase are frequent causes of DH among treated children. In one review on children affected by low-grade glioma, 44 of 105 children (42%) developed hypersensitivity to carboplatin (14). Seventeen (9.2%) of the 185 children, affected by different solid tumors and treated with etoposide–carboplatin, presented an allergic reaction to carboplatin: 2% at 6 courses, 11% at 12 courses, and 47% at more than 12 courses (15).

Hypersensitivity reactions to asparaginase have been reported in up to 40% of the treated children (16-17).

It is useful, in case of suspected allergy to Radio contrast media and Chemotherapeutics drugs, follow the same indications given in case of suspected allergy to perioperative drugs.

Conclusions

DHRs in children have a parent-reported prevalence of around 10%, with a much lower real prevalence, and a lower prevalence of confirmed DHRs as compared to adults (5).

Beta lactams (BLs)are the main drugs implicated in DHRs among children and the most common cause of concern. Nonsteroidal anti-inflammatory drugs, non-BL antibiotics, perioperative drugs, anesthetics, radio contrast media, and cytotoxic drugs are also frequently suspected. The most common reactions are nonimmediate maculopapular exanthema and urticaria. Drugs are the third identified cause for anaphylaxis among children. Facial swelling associated with NSAID hypersensitivity appears to be quite specific for children. The diagnostic approach to DHR diagnosis is based on experience in adults, but its adequacy in children has to be further evaluated. For example, drug provocation test without previous skin tests can be considered in children with non-severe maculopapular and nonimmediate urticarial exanthemas (5). Furthermore, there is higher evidence to recommend skin tests in children with suspected drug hypersensitivity to anticonvulsants, chlorhexidine (specific IgE determinations are available and recommended), heparins, neuromuscular blocking agents (specific IgE determinations are available and recommended), platinum salts, radiocontrast media, blue dyes, proton pump inhibitors (5).

Conflict of interest: None to declare

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Correspondence:
Roberto Bernardini, MD
Pediatric Unit, "San Giuseppe" Hospital,
Viale Boccaccio, 50053, Empoli (Florence), Italy
Tel. +39 -0571706452
E-mail: roberto.bernardini@uslcentro.toscana.it

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Review

A practical management of children with antibiotic allergy

Elisabetta Calamelli[1], Carlo Caffarelli[2], Fabrizio Franceschini[3], Francesca Saretta[4], Fabio Cardinale[5], Roberto Bernardini[6], Lucia Liotti[7], Francesca Mori[8], Giuseppe Crisafulli[9], Silvia Caimmi[10], Paolo Bottau[1]

[1] Pediatric and Neonatology Unit, Imola Hospital, Imola (BO), Italy; [2] Clinica Pediatrica, Dipartimento di Medicina e Chirurgia, Azienda Ospedaliero-Universitaria, Università di Parma, Italy; [3] UOC Pediatria, Azienda Ospedaliero-Universitaria "Ospedali Riuniti", Ancona, Italy; [4] Pediatric Department, AAS2 Bassa Friulana-Isontina, Palmanova-Latisana, Italy; Pediatric Allergy Unit, Department of Medicine, Udine, Italy; [5] UOC di Pediatria, Azienda Ospedaliera-Universitaria "Consorziale-Policlinico", Ospedale Pediatrico Giovanni XXIII, Bari, Italy; [6] Pediatric Unit, "San Giuseppe" Hospital, Empoli, Italy; [7] Department of Pediatrics, Senigallia Hospital, Senigallia, Italy; [8] Allergy Unit, Department of Pediatric Medicine, Anna Meyer Children's University Hospital, Florence, Italy; [9] UO Allergologia, Dipartimento di Pediatria, Università di Messina, Italy; [10] Pediatric Clinic, Foundation IRCCS Policlinico San Matteo, University of Pavia, Pavia, Italy

Summary. About 10% of the parents reported that their children are allergic to one drug and the betalactam antibiotics are the most frequently suspected. Even if most of the adverse events following antibiotic prescriptions to children are considered allergic, after a full allergy work-up only a few of the suspected reactions are confirmed. For this reason, many children are incorrectly labelled as "allergic" and this represents an important challenge for the choice of the antibiotic therapy in these "labelled" children, who are frequently improperly deprived of narrow-spectrum antibiotics because considered as allergic. When an allergic reaction is suspected a precise diagnosis and a choice of a safe and effective alternative is essential for the future antibiotic option. In the light of this, the main aim of this paper is to try to provide a practical approach to managing the individuals who have reported adverse reactions to antibiotics. (www.actabiomedica.it)

Key words: antibiotic allergy, betalactam, drug adverse reaction, hypersensitivity reactions, children, skin test, specific IgE, basophil activation test, drug provocation test

Introduction

Data on the prevalence and incidence of antibiotic hypersensitivity reactions (DHRs) are limited, especially in paediatric age and varies around the world (1).

About 10% of the parents reported that their children are allergic to drugs and betalactams (BLs) are the most frequently suspected (2). A prospective study conducted in children and adolescents showed that the rate of adverse drug reactions (ADR) was 10.9% in hospitalized children, 1% in outpatients, and the hospitalizations rate for adverse drug reactions was 1.8% (3). Antibiotics are significantly overused (4) and all classes can be associated with a certain predictable rate of adverse reactions (1). Nowadays, multiple drug-resistant infections are becoming more common (1). Thus, an effective antibiotic stewardship program is important and urgent (5). So, physicians, should be correctly informed on the risks of avoiding certain classes of antibiotics, like narrow-spectrum penicillins, when these are the drugs of choice (1). Physicians should be able to safely and efficiently evaluate and/or refer individuals with reported antibiotic adverse reaction and know when to perform diagnostic testing, drug challenge, or desensitization (6).

Many children are incorrectly labelled as "allergic" (1). The choice of antibiotic therapy in such children represents an important challenge (7). They commonly

receive second-line broad spectrum antibiotics and this increases the risk for infection caused by *Clostridium difficile*, methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *enterococcus* (8). Furthermore, these patients have a prolonged hospital stay, and adverse effects related to second-line antibiotic use (8). This may lead to increase health-care utilization and costs (8,9). Li et al. showed that penicillin allergy was associated with 1.82- to 2.58-fold increase in total antibiotic cost (10).

This review aimed to provide a practical approach in managing the clinical care of individuals who have reported an adverse reaction to antibiotics.

Practical management

Step 1. Make a correct diagnosis

A key point for the management of antibiotic allergy is to establish a correct diagnosis (11).

The first step is to consider that ADRs are classified as type A (predictable by the properties of the drug, and including the toxic side effects, which are dose-dependent and non-immune-mediated) and type B reactions which are unpredictable, not dose-dependent and frequently immune-mediated (11-13). Type B reactions comprise both quick-onset reactions, such as anaphylaxis, bronchospasm, urticaria, angioedema, gastro-intestinal symptoms and late-onset reactions, such as maculopapular exanthema, contact eczema and severe cutaneous adverse reactions (SCARs) including drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) (11-13). Antibiotics trigger type B reactions that should be differentiated from signs/symptoms due to an infectious disease, simultaneously administered drugs, food and airborne allergens, or functional mechanisms (14-21).

In adults, most of ADRs (about 80%) are type A reactions, while type B reactions comprise about 10%–15% of all ADRs (13), while in children, the opposite is true (22). Immunological reactions were classified by Gell and Coombs (types I-IV) and later by Pichler who refined type IV (T-cell-mediated) in type IVa (Monocytic inflammation), IVb (Eosinophilic inflammation), IVc (T cells) and IVd (Neutrophilic inflammation) (23).

Most of the adverse events following antibiotic prescriptions are considered as allergic, but after a full allergic work-up only a few of the suspected reactions can be confirmed (2, 7, 11, 24). Ponvert et al. (25) in their twenty years' experience, found that only 15.9% of 1431 children with suspected allergy to BLs antibiotics were found to be allergic. Caubet et al. (14) showed that the most frequent cause of a benign skin rush during BLs treatment in children, was a viral infection (69.5%) while only 6.8% of children had a positive drug provocation test (DPT) to BLs. Similar results were found by Zambonino et al. (26) that found only 7.9% of 783 patients with suspected allergy to BLs had drug allergy.

A recent paper by Vyles D et al. (27) confirmed the importance of a precise classification and definition of a penicillin adverse reaction. They found that no children with suspected penicillin allergic reaction categorized as low-risk with their allergy questionnaire have a true penicillin allergy (27).

Many studies have showed that penicillin skin testing is useful in increasing BLs use (when indicated by the antibiotic stewardship), and in reducing the use of alternative antibiotics as fluoroquinolones, glycopeptides and other second-line broad spectrum agents, with consequent and relevant cost saving (8, 28, 29). So, many reports called for an incorporation antibiotic allergy-testing program in antimicrobial stewardship (30-32). Raja et al. (33) found that penicillin skin test is useful in adult emergency department for ruling out penicillin allergy. This strategy although useful, appears unfeasible in paediatric emergency department because it is time consuming and costly (27).

Recommendation. Not label a child as allergic to antibiotics without an accurate diagnostic work-up that starts with a precise description of the index reaction and his classification in Type A or Type B reaction.

Step 2: find a safe and effective alternative

Betalactams

BLs are the antibiotics that most frequently cause allergic reactions in childhood (2). The prevalence of

self-reported reactions in children varies from 1.7% to 5.2% (7, 34). A study of 2,375,424 children and adults in Southern California showed that prevalence of allergy to penicillin was 7.9% (34). An European study show that the 0.21% of unselected paediatric outpatients demonstrate positive test for antibiotic allergy and 6.8% of children attending ED for suspected BLs hypersensitivity are allergic (35).

Penicillins are the first line therapy in most paediatric respiratory infections according to many guidelines (36-40). For these reasons when a correct diagnosis of penicillin allergy is done it should be given an alternative well tolerated but equally effective agent. It is important to consider that other classes of antibiotics have limited efficacy for these infection (39, 40). Many studies have found that the avoidance of cephalosporin in penicillin allergy patients causes an increased risk of adverse events, suboptimal treatment of infection and treatment failures (41, 42).

All BLs have a structure that consist in a 4-membered BL ring that in penicillins is attached to a 5-membered thiazolidine ring (44). The side chain distinguishes different penicillins (34, 43, 44). Cephalosporins have a 6-membered sulfur-containing dihydrothiazine ring and two side chains (R1 and R2) (44). Carbapenems (e.g. Imipenem, meropenem) in the 5-member thiazolidine ring contain a carbon double bound instead of sulphur and have a side chain that distinguishes the different carbapenems (44). Monobactams comprise the BL ring without an attached 5-or 6- membered sulphur ring (34, 43, 44) (Fig. 1).

The BL ring, the thiazolidine/ dihydrothiazine rings and the side chains are all potentially immunogenic (28, 38, 39). In the last ten years, the role of side-chain structures as antigenic determinants was widely accepted particularly in hypersensitivity reaction to amoxicillin and cephalosporin (28, 39, 45, 46). Cross-reactivity between BLs seems to be more closely related to side chain identity or similarity than to the central BL ring (34, 43, 44). However, shared epitopes from other parts of the molecule also account for cross-reactivity (34, 43, 44). For instance, ampicillin and cephalexin share an identical side chain with an amino group, as amoxicillin and cefadroxil (40) (Fig. 2). In early studies, cross-reactivity between penicillin and first and early (introduced before 1980) second-

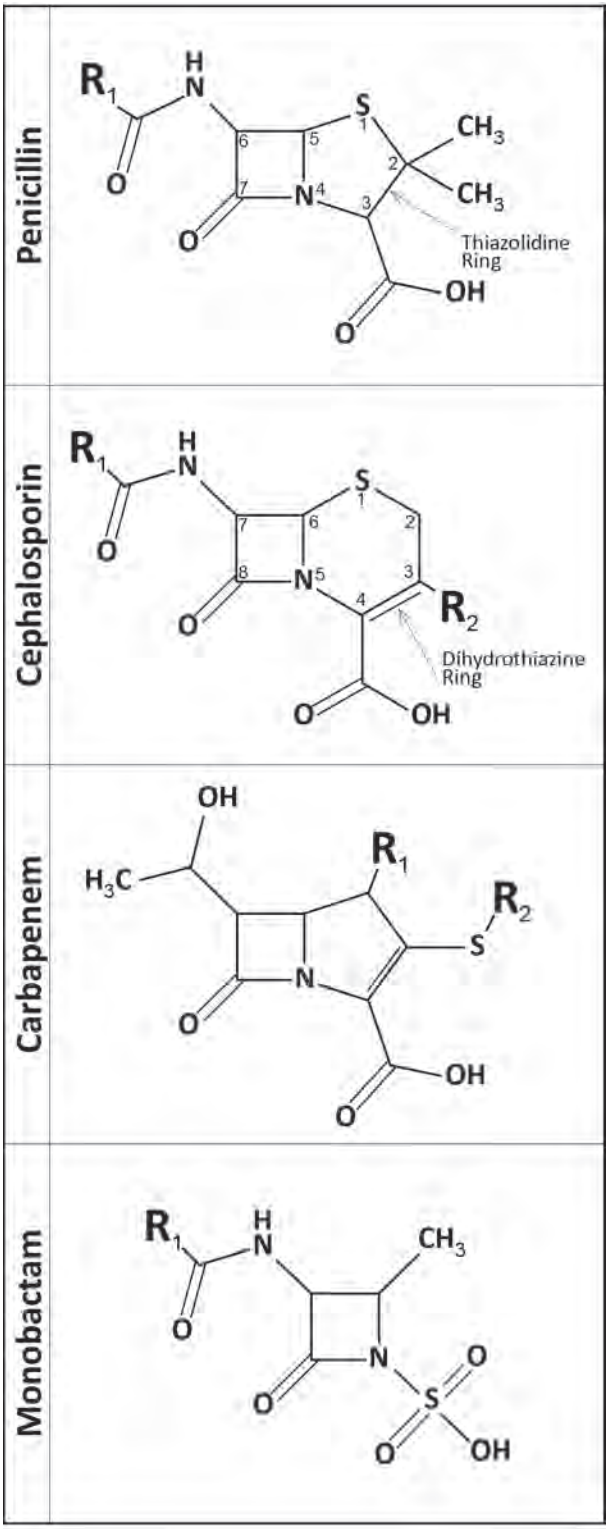


Figure 1. Betalactams chemical structures. "R" indicates side chains

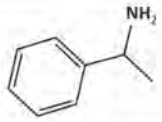
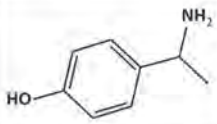
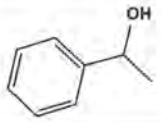
Cephalosporin	R_1 Structure	Penicillin	
		Identical R_1	Similar R_1
Cephalexin Cephaloglycin Cefaclor Loracarbef		Ampicillin	Piperacillin
Cefadroxil Cefatrizine Cefprozil		Amoxicillin	Piperacillin
Cefamandole Cefonicid			Ampicillin Amoxicillin

Figure 2. Penicillin and Cephalosporin side chains (R1): identical or similar structure. Modified by Zagursky RJ and, Pichichero ME (38).

generation cephalosporins has been reported to occur in up to 10% of patients, while for the third-generation ones the rate is lower (2-3% of patients allergic to penicillin) (34, 44). Recent data indicate that the actual rate of cross-reactivity is probably less than 1% (43, 47). The degradation process of cephalosporin leads to a fragmentation of the BL ring as well as the thiazinic group but the R1 side-chain structure of cephalosporins usually remains intact and this is the main factor for cross reactivity between cephalosporins and penicillin (34, 43). The antigenic role of the R2 side-chain is still debated (43). Romano et al. demonstrated that patients with cephalosporin allergy commonly tolerated a cephalosporin with different R1/R2 side chain (48).

Every patient reporting a suggestive history or who have a diagnosis of penicillin allergy may receive cephalosporins, especially the third generation, as a replacement, with the exception of those showing R1 side-chain similarity (34, 36, 43, 45, 47). It is still debated if in these occasions, a skin test should precede the administration of cephalosporin through a graded challenge (42). In figure 3 were listed many of the major drugs used nowadays and whether the R1 or R2 side chains are identical or similar.

Prospective studies on carbapenems and monobactams suggest that cross reactivity with penicillins/cephalosporins is very unlikely or absent (34, 43, 44, 49), with the exception of ceftazidime which shares an identical R1 side chain with aztreonam (50).

Recommendations:

- Third generation cephalosporins can be used in patients with mild nonimmediate penicillin allergy. In case of SCARs, antibiotic class avoidance is the preferred management (11, 45).
- In patients with immediate reactions to penicillins who required cephalosporins, it is useful to perform skin tests with a cephalosporin of second or third generation with different side chains and if negative, administer the drug in a gradual and controlled challenge (34, 43-45, 47).
- In patients with immediate reactions to cephalosporins who required cephalosporin or penicillins, it is useful to perform skin tests with a cephalosporin or penicillins with different side chains and if negative, administer the drug in a gradual and controlled challenge (34, 43-45, 47).
- Subjects allergic to penicillin who required carbapenems or monobactams should undergo skin tests and when negative, the drug should be administered in a gradual and controlled challenge (11, 43-45, 51).

Non-betalactam antibiotics

The prevalence of allergic reactions to non-betalactam antibiotics (NBLs) is estimated to be 1-3% of the general population and represents about 10% of the DHRs in children (47). Viral infections can provoke skin eruptions such as maculopapular exanthemas that is also the most common symptom of allergic reactions to NBLs (51). Therefore, it is difficult to differentiate DHRs from skin symptoms due to infections (51). The main classes involved in NBLs DHRs in children are sulphonamides, macrolides, glycopeptides, aminoglycosides and quinolones (1, 52). There is a lack of studies on hypersensitivity reactions to NBLs (52).

*Macrolides***.** Macrolides are classified according to the number of carbon atoms in their lactone ring: 14 membered (e.g. erythromycin, clarithromycin), 15 membered (azithromycin), and 16 membered (spiramycin, rokitamycin, josamycin) (52). Hypersen-

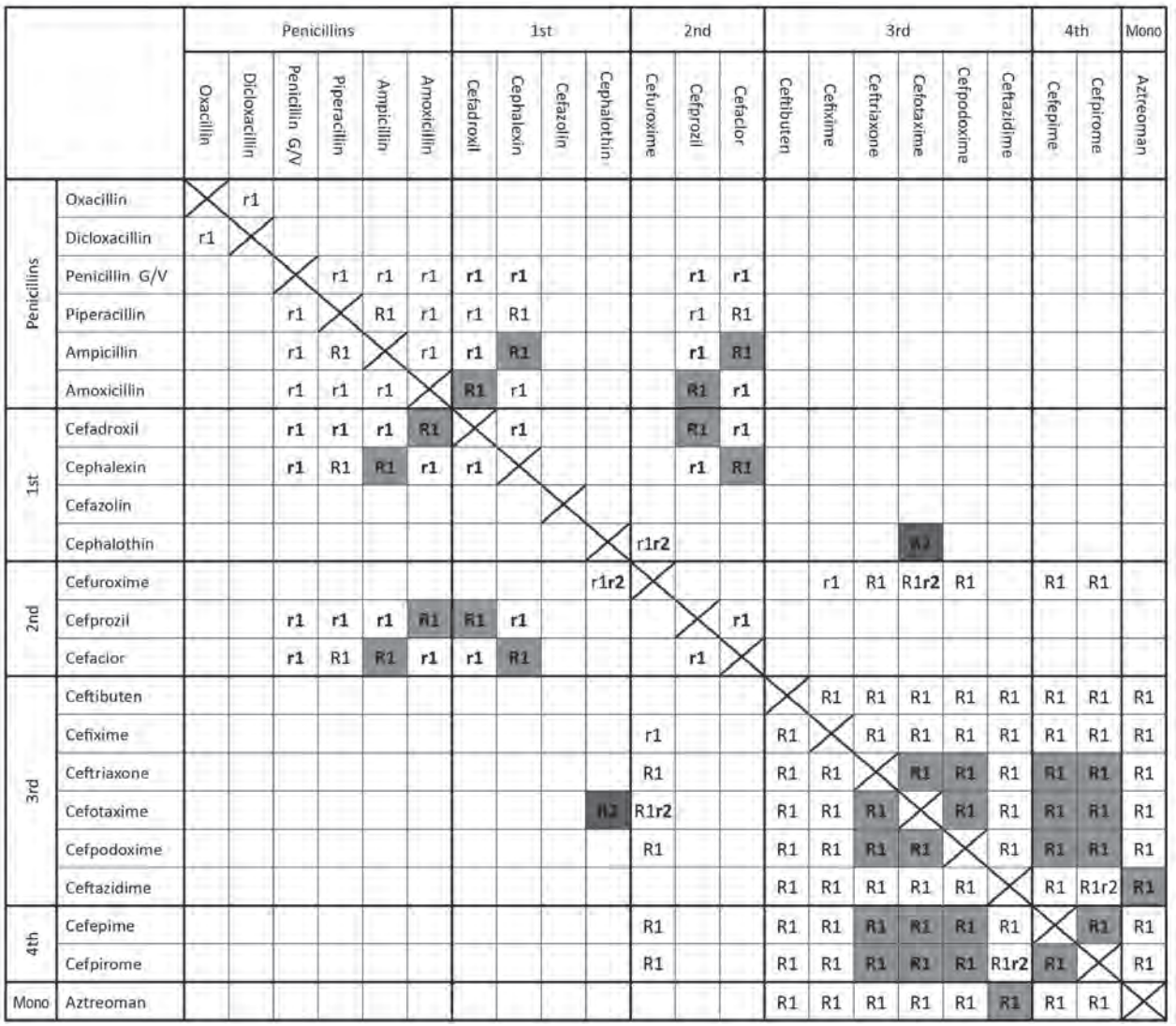


Figure 3. Comparison of penicllins and cephalosporins side chain. Bolded R1 or R2 (gray cell) indicate total identical R1/R2 side chain; regular R1 or R2 indicate only in part identical R1/R2 side chain; bolded r1 or r2 indicate total similar r1/r2 side chain; regular r1 or r2 indicate only in part similar r1/r2 side chain. Modified by Zagursky RJ and, Pichichero ME (38)

sitivity reactions to macrolides occur in 0.4% to 3% of treatments (53). DHRs to azithromycin appear to be more frequent than to clarithromycin (54). Allergy to macrolides is difficult to diagnose because of poor standardization of skin tests as well as lack of accurate in vitro tests (1, 55). In a study by Mori at al. on sixty-four children with a history of hypersensitivity reactions to clarithromycin, the sensitivity and specificity of intradermal test (IDT) to clarithromycin at the concentration of 0.5 mg/ml were 75% and 90%, respectively (56). In children, few data are available on non-irritant concentrations, therefore the interpretation of a positive skin test result to macrolides is uncertain (1, 57). Thus, DPT is the only reliable diagnostic test (52, 55), even in the absence of any standardized protocol for macrolides. It should be taken into account that anaphylactic reactions can be induced by the systemic administration of allergens including drugs (51), and foods (58, 59) during challenge tests. So, challenges should be performed under medical surveillance by trained personnel and materials for treating anaphylaxis should be available (51).

It has been suggested that macrolide allergies are unlikely to be a class allergy (1, 60). However, cross reactivity may occur between different macrolides, at least regarding anaphylaxis (61).

Aminoglycosides. Aminoglycosides are classified in two groups: (A) streptidine group: e.g., streptomycin; (B) desoxystreptamine group: e.g. amikacin, gentamicin, tobramycin, neomycin (60). Aminoglycosides hypersensitivity is uncommon except for some risk groups such as patients with cystic fibrosis (52). Contact dermatitis from topical aminoglycosides is the most frequent clinical manifestation, since neomycin, gentamicin and tobramycin are widely used as cream, ointment, and eye or ear drops (60, 62). Anecdotal cases of positive skin prick test to tobramycin, gentamicin, and streptomycin (63) have been observed. However, in vivo tests are not validated for the diagnosis of immediate reactions to aminoglycosides (51). Patch tests with reading at 72 and 96 hours have been performed for the diagnosis of non-immediate reactions (64).

Cross-reactivity between aminoglycosides is common (50%) (1, 65), so aminoglycosides should be avoided in patients with a diagnosis of hypersensitivity (60).

*Sulphonamides. C*otrimoxazole is frequently used for prophylaxis and eradication of opportunistic infection in serious diseases, such as AIDS or hematologic malignancies, and for community infections in same regions of the world (47).

Sulfonamides are most commonly associated with non-immediate manifestations, such as maculopapular rashes, and SCARs (66, 67). Among antibiotics, sulfonamides have the more frequent cause of benign rash and of SYS/TEN (1). Most allergic sulfonamide-associated adverse reactions appear to be T-cell-mediated (1). The rash rate is even higher in individuals with active untreated or acutely treated HIV infection with low CD4 T-cell counts (67).

The best management strategy in a patient with sulfonamide hypersensitivity is to use a different drug, but in some clinical settings, especially in patients with HIV infection or hematologic malignancies, where no equally effective alternative exists (52).

In case of mild or moderate non-immediate reactions (without mucosal signs or systemic symptoms) different strategies have been proposed (60). It is possible to continue cotrimoxazole administration at the same doses, to discontinue the drug over a few months, usually 6 months, and then cotrimoxazole can be resumed after a graded challenge or a "desensitization" protocol (47). A meta-analysis involving 268 adults with HIV infection and mild or moderate hypersensitivity reactions to cotrimoxazole found that the desensitization protocol was the most beneficial for preventing severe skin reactions, when it is performed after 6 months of drug discontinuation (68).

Glycopeptides. Vancomycin, a glycopeptide, has been often used in infections with BL resistant Gram-positive organisms or in BL allergic patients (52, 60).

The most common hypersensitivity reaction associated with vancomycin is the red man syndrome (RMS) (52, 60). Vancomycin causes a variety of DHRs; nonimmediate DHRs are more common than immediate one, with linear IgA bullous dermatosis being most frequent (69).

In patients with suggestive clinical history, positive immediate-reading IDTs (0.1 mg/ml or lower dilution) may identify immediate hypersensitivity reactions, and positive patch tests (at concentration of 0.005%) delayed hypersensitivity reactions (52).

Severe RMS can mimic IgE-mediated anaphylaxis and requires immediate diagnosis and management (60). In contrast to true allergic hypersensitivity reactions, slowing the infusion rate of vancomycin to 500 mg given over one hour usually reduces the chance of developing RMS (60). There are few studies regarding the effectiveness of antihistamines as premedication to prevent RMS (60).

Despite its chemical affinity, no cases of RMS and very few cases of allergic reactions were reported with teicoplanin (70) in children with previous reactions to vancomycin. However, when possible, an alternative drug should be used or a desensitization protocol should be performed (51).

Quinolones. Quinolones can be classified according to their generation: first (e.g. nalidixic acid), second (e.g. ciprofloxacin), third (levofloxacin), and fourth (1).

In Spain, quinolones are the third cause of confirmed DHR, after anti-inflammatory drugs and BLs, having an increase in incidence from 0.53% in 2005 to 5.96% in 2009 (71). A paediatric study on ciprofloxacin involving 16,184 patients ≤17 years, gave an estimated risk of 0.046 suspected DHRs every 100 patients (72). The rate of allergic and non-allergic anaphylaxis between immediate hypersensitivity reactions to quinolones are similar among different quinolones (52). Allergic reactions to quinolones can be immediate or delayed (73). Anaphylaxis and maculopapular exanthema are respectively the most frequent clinical entities (73).

Skin prick tests and IDTs are not recommended for the diagnosis of hypersensitivity to quinolones because they can induce direct mast cells activation, leading to false positive results (1, 73). DPT remains the reference standard for the diagnosis even if not without risk (1, 52, 73). Cross-reactivity between quinolones is difficult to predict due to the small number of patients included in the few published studies (73). Some studies in adults showed that the level of cross-reactivity can be important (52, 73). Patients with hypersensitivity to quinolones should avoid these drugs and when quinolones are the only therapeutic option, desensitization is necessary (73). Cross-reactions between quinolones, BLs and neuromuscular blocking agents have been also described (74).

Conclusion

Antibiotic hypersensitivity is a frequent problem for physicians in particular for the future use of antibiotics. Firstly, it should be determined if the reaction associated with antibiotic intake was a type A or Type B reaction. In case of a Type B reaction, it is mandatory an appropriate diagnostic work-up for ascertaining the causal role of the drug. This is the first step for a correct management of antibiotic allergy. It is important not to "label" a child as allergic without an appropriate diagnostic work-up. When a diagnosis of antibiotic allergy is done, the second step is to find a safe and effective alternative. Unfortunately, the allergic work-up and the evaluation of cross reactivity is well structured only for BLs. Up to now, evidences on diagnostic tests for NBL allergy in children are limited.

Conflict of interest: None to declare

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Correspondence:
Paolo Bottau, Pediatric and Neonatology Unit, Imola Hospital, Via Montericco, 4 - 40026 Imola (BO) Italy
Tel. +390542662805
Fax +390542662810
E-mail: p.bottau@ausl.imola.bo.it

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Review

Drug desensitization in allergic children

Silvia Caimmi[1], Carlo Caffarelli[2], Francesca Saretta[3], Lucia Liotti[4], Giuseppe Crisafulli[5], Fabio Cardinale[6], Paolo Bottau[7], Francesca Mori[8], Fabrizio Franceschini[9], Roberto Bernardini[10], Gian Luigi Marseglia[1]

[1] Pediatric Clinic, Foundation IRCCS Policlinico San Matteo, University of Pavia, Pavia, Italy; [2] Clinica Pediatrica, Dipartimento di Medicina e Chirurgia, Azienda Ospedaliero-Universitaria, Università di Parma, Italy; [3] Pediatric Department, AAS2 Bassa Friulana-Isontina, Palmanova-Latisana, Italy; Pediatric Allergy Unit, Department of Medicine, Udine, Italy; [4] Department of Pediatrics, Senigallia Hospital, Senigallia, Italy; [5] UO Allergologia, Dipartimento di Pediatria, Università di Messina, Italy; [6] UOC di Pediatria, Azienda Ospedaliera-Universitaria "Consorziale-Policlinico", Ospedale Pediatrico Giovanni XXIII, Bari, Italy; [7] Pediatric and Neonatology Unit, Imola Hospital, Imola (BO), Italy; [8] Allergy Unit, Department of Pediatric Medicine, Anna Meyer Children's University Hospital, Florence, Italy; [9] UOC Pediatria, Azienda Ospedaliero-Universitaria "Ospedali Riuniti", Ancona, Italy; [10] Pediatric Unit, "San Giuseppe" Hospital, Empoli, Italy

Summary. Drug allergy is an increasing problem worldwide, affecting all populations and races, children and adults, and for which diagnosis and treatment are not well standardized yet. Besides classical treatments, new drugs have been developed, especially for patients suffering from malignancies and chronic inflammatory diseases, that specifically target the cause of the disease. For those patients requiring such molecules, it is sometimes difficult to find an alternative drug when hypersensitivity reactions occur. Desensitization is therefore the best option whenever no alternative therapy is available but also when alternative treatments are considered therapeutically inferior and or more toxic. Despite its clinical success, little is known about the mechanisms and molecular targets of drug desensitization. Desensitization protocols use a gradual dose escalation to allow the safe administration of a treatment to which a patient previously presented a hypersensitivity reaction. The procedure requires special training and coordination of an allergy team, including physicians, nurses, and pharmacists, working together to safely and successfully implement desensitization protocols when appropriate. There is no difference in desensitization protocol between adults and children, except for the final cumulative dose of the administered drug. (www.actabiomedica.it)

Key words: children, drug allergy, drug desensitization, hypersensitivity reactions, premedication

Background

Drug hypersensitivity reactions may occur after intake of any kind of drug. Antibiotics are among the most common molecules associated to such reactions. Drug hypersensitivity may affect any organ or system, and manifestations range widely in clinical severity from mild pruritus or urticaria (1) to anaphylaxis (2, 3). In most cases, the suspected drug is subsequently avoided. The decision to desensitize should not be taken lightly since it is an expensive and time-consuming procedure, possibly associated to severe reactions. Potential indications to undergo a desensitization protocol should include the lack of a viable alternative, or the lower efficacy and/or a greater toxicity of available alternative. This seems to be particularly important when dealing with patients suffering from chronic conditions, for which few effective drugs have been approved (4). When treating patients presenting with an infectious disease, physicians may usually select a safe antibiotic alternative. Nonetheless, in some cases, no alternative treatment exists for optimal therapy,

such as in multi-resistant patients with cystic fibrosis or tubercolosis, or in patients needing chemotherapic agents, monoclonal antibodies, anti-epileptic drugs, or vaccines. Indeed, in patients with multi-resistant infections or with a history of multiple drug allergy a desensitization protocol may outweigh the risks (5). Desensitization protocols have been developed only for therapeutic purposes to safely administer a drug to which the patient has a proven or highly suspected hypersensitivity reactions.

They consist of administration of increasing doses of the drug with a pre-determined time schedule. When tolerance to the required dose of the drug is reached, such molecule will be accepted by the patient's immune system, for the whole course of the therapy. On the other hand, if the treatment is stopped, patients will require to undergo a new desensitization before starting any further course of treatment using the same drug (6,7). Such approach allows to protect patients from experiencing unexpected anaphylactic reactions, and to optimize the clinical outcomes.

The aim of the present paper is to focus on possible drug desensitization protocols in children. An evidence-based review is currently not feasible, because there is a lack of controlled studies in children.

Drug desensitization

The drug desensitization is a process through which a patient's immune response to a drug is modified to generate impermanent tolerance, taking advantage of well characterized inhibitory pathways (8).

In contrast to desensitization through allergen immunotherapy to aeroallergens or hymenoptera venoms (9), drug desensitization only provides a temporary state of tolerance, being sustained only for the time the drug remains in the patient's system (3-4 half-lives).

Rosa et al. (10) reported a 11 years-old girl, who had previously experienced a hypersensitivity reaction to recombinant human erythropoietin, and failed a 2-days desensitization protocol with epoetin alfa, while tolerating the drug after a 17-days protocol. Two months later, the patient developed a systemic reaction after intravenous injection of the molecule, but she had actually been missing several doses of epoetin alfa. In fact, desensitization protocols require that the drug is regularly administered (usually at least once a day). In case of treatment discontinuation, drug reactions may occur again if the molecule is re-administered at standard dose. Therefore, patients should undergo a desensitization protocol for each course of drug. Desensitization has been used to induce tolerance not only in patients with a proven (or a strongly suspected) IgE-mediated allergy, but also in those presenting with non IgE-mediated reactions. Most protocols require a one-day hospitalization to be effective, but some patients need slower protocol, over a few days, to reach tolerance to a drug. Such consideration strengthens the fact that desensitization should be tailored to the patient's reaction and that a single protocol may not fit all possible occasions.

Mechanisms

Since the first case of drug desensitization was published by Peck et al. (11), many Authors have been trying to have a better understanding of the immunological basis of drug desensitization. Nevertheless, the exact mechanisms remain poorly understood. Rapid drug desensitization is a process through which mast cells and possibly basophils become hypo-responsive to a drug allergen, providing therefore temporary tolerance in drug hypersensitive patients (12). In sensitized patients, drug exposure causes the quick release of inflammatory mediators from activated mast cells, leading to the systemic allergic reaction. In the early phase of mast cells activation, the release of mediators is quickly followed by an increased synthesis of prostaglandins (PGD2) and leukotrienes (LTC/D4 and LTB4) that play an additional role in the clinical expression of the allergic reaction (13). During the late phase of mast cell activation, cytokines such as TNFα and IL-6 are released along with chemokines and other factors. Mast cells are key effector cells in IgE-dependent immediate hypersensitivity because they express large amounts of a high-affinity tetrameric receptor (FceRI) for the Fc region of IgE. Multivalent allergen activates mast cells through binding to IgE and aggregating IgE–FceRI complexes. FceRI-mediated signaling induces the activation of Src family

tyrosine kinases Lyn and Fyn followed by the recruitment and activation of tyrosine kinase Syk. Phosphorylation of LAT by Syk induces the recruitment and activation of PLCc, leading to calcium mobilization and mast cell degranulation (14).

In desensitization, a central role is played by the downregulation of the expression of mast cells and basophils. Three non-mutually exclusive hypotheses explaining how RDD could impair mast cell activation have been suggested: (1) depletion of activating signal transduction components such as syk kinase; (2) sub-threshold depletion of mediators; and (3) internalization of FcεRI through progressive cross-linking at a low antigen concentration. On the other hand, basophils downregulation causes the activation of SHIP; the processing of syk by ubiquination; the degradation and loss of FcεR1 receptors; and the resorting of receptors in the cell membrane. The desensitization process also seems to be related to the inhibition of the release of mediators such as β-hexosaminidase, prostaglandins and leukotrienes (15).

The precise mechanism of desensitization in cell-mediated reactions is only supposed in studies focusing on phenytoin. In these cases, the process seems to be mediated by the activation of T regulatory cells, demonstrated by the simultaneous reduction in skin lesions and skin recruitment of Foxp3+ regulatory T cells (16,17). Other studies on desensitization to allopurinol, showed similar results (18).

Indication and contraindication

The general rules for drug desensitization in adults are also applied to children. Drug desensitization is indicated when no alternative drug is available; when the prescribed drug is more effective than other possible alternatives; if there are no comorbidities putting the patient at increased risk during the procedure; and when the reported drug reaction was not a severe, life-threatening immune-toxic reaction, vasculitis or bullous skin disease such a Stevens-Johnson syndrome/ toxic epidermal necrolysis (SJS/TEN) or drug induced hypersensitivity syndrome (DIHS). Desensitization in type II and type III hypersensitivity reactions is contraindicated, because the interaction between the antigen and the antibody may possibly lead to the activation and consumption of the complement system (19).

In patients with history of severe hypersensitivity reaction, an alternative may not be available, which makes it difficult to decide to rule out the possibility of a desensitization. In 2018, Saripassorn et al. (20) showed a success rate of 62% of drug desensitization in adults with previous history of severe allergic reactions, such as SJS, TEN, DRESS. Corrado-Chagoya et al. (21) reported that a 6 years-old boy experienced a SJS/TEN overlap syndrome to the anti-tuberculosis (TB) drugs, and he tolerated the anti-TB drugs after undergoing a desensitization protocol with premedication. Witcher et al. showed that a 5 years-old boy was successfully desensitized to phenobarbital, after having presented a DRESS syndrome (22). Other cases of successful desensitization protocols in adults with history of severe hypersensitivity reactions are reported in Table 1 (23, 24).

An individual risk/benefit evaluation should be assessed, before performing any procedures (25). Physicians and patients (and their caregivers) should be aware that desensitization may be associated with a possible risk of acute hypersensitivity reaction during the procedure.

Table 1. Case reports of patients experiencing severe allergic reactions, but tolerating desensitization protocols

Author	Year	Number of patients	Age	Reaction	Drug
Corrado-Chagoya (21)	2018	1	Pediatric	SJS	Anti-TB
Witcher (22)	2018	1	Pediatric	DRESS	Phenobarbital
Thong (24)	2014	2	Adult	SJS	Anti-TB
Thong (24)	2014	5	Adult	DIHS	Anti-TB
Minor (23)	2012	1	Adult	SJS	Veramufanib

Legend - SJS: Stevens-Johnson syndrome; DRESS: drug reaction with eosinophilia and systemic symptoms; DIHS: drug induced hypersensitivity syndrome; Anti-TB: anti-tuberculosis drugs

Desensitization protocols

Choosing a specific desensitization protocol depend on the patient's medical disease requiring the specific drug, the presence of atopy and other comorbidities, and the type of adverse hypersensitivity reaction presented in the clinical history (26). Generally, it should be advisable to use protocols previously published and validated on few patients. However, many times and for specific reasons, protocols may have to be tailored on single patient. A few studies on drug desensitization in children have been performed. So, it has been suggested that protocols applied for adults should be adapted in children (26, 27). In general, protocols in children differ from those in adults only in the cumulative dose, which should be the daily dose used for adequate therapy (5).

At baseline, patients should be in a stable clinical condition and any concomitant medication used for treating underlying diseases must be continued, with the only exception of beta-blockers, that should be discontinued, if the cardiologist allows it, since they may interfere with the treatment of a severe hypersensitivity reaction. Caution and surveillance by well-trained specialists and nurses are mandatory in all cases, with continuous monitoring of the child (28). Caregivers should be taught to recognize early signs and to notify the nurse or doctor. Desensitization for more severe reactions, like anaphylaxis, should be carried out in the intensive care unit (25). An informed and signed consent, by parents and/or tutors, is required (25).

It is still debated the role of premedication with corticosteroids and antihistamines. Premedication is supposed to reduce the risks for a hypersensitivity reaction occurring during desensitization. Premedication regimens vary from one center to the other and aim to prevent or minimize the severity of any allergic reactions. In some studies, authors advise to administer, 20 minutes before starting desensitization, diphenhydramine (1 mg/kg), famotidine (20 mg iv in patients of at least 12 years of age) and/or ranitidine (1,5 mg/kg). Others include a dose of dexamethasone (10 mg/m^2, maximum 20 mg) that should be taken the night before the protocol and the same morning, especially when desensitizing patients to chemotherapeutic agents. In patients who previously failed a desensitization protocol, or in those having experienced flushing reactions, montelukast (10 mg orally for children > 14 years old, 5 mg for children 6-14 years old; 4 mg for children 2-5 years old) and/or acetylsalicilic acid (10-15 mg/kg) 1 hour before desensitization may be considered as additional premedication. In patients requiring desensitization to monoclonal antibodies, a premedication with paracetamol/acetaminophen (15 mg/kg) and antihistamines is advised, to reduce reactions due to possible cytokine release (4). Nevertheless, the European Network of Drug Allergy (ENDA) and the European Academy for Allergy and Clinical Immunology (EAACI) interest group on drug hypersensitivity claim that premedication with systemic corticosteroids and antihistamines is not necessary and may mask early signs of a hypersensitivity reaction (27). Such consideration may be relevant in research settings, but it is probably less important when the target is to achieve the possibility to administer a drug to a needing patient.

Route of administration and dosing scheme

The drug should be administered though the same route required for therapeutic purposes. Both oral and parenteral routes may be used in the procedure and they both seem equally effective. Regarding drugs that may be administered both orally and parenterally, the oral route seems to be safer, easier and less expensive. In some protocols both routes may be combined for the same patient (27). Specific protocols for parental routes have been developed and have been widely used for many drugs, including beta-lactams, insulins, chemotherapeutic agents and monoclonal antibodies.

The starting dose should be determined considering the severity of the reported reaction: in patient with severe anaphylaxis the initial dose should be between 1/1.000.000 and 1/10.000 of the full therapeutic dose. In patients with a positive skin test to a non-irritating concentration of a drug, the starting dose may be determined based on the endpoint titration. This concept is applicable only in patients with positive skin prick test performed according to available guidelines (29, 30) and using recommended concentrations (30). In patient with a very low endpoint titration value and/or with previous severe reactions, the protocol should

be accordingly modified, by either reducing the initial dose, or decreasing the rate of infusion, or increasing the time interval between doses, or increasing the total number of doses. Most protocols increase doses by doubling, others by tripling the dose, compared with the previously administered one. Incremental step ranges from two-times to ten-times the previous dose (2) and the total amount of steps goes from 12 to 20. Time interval between two steps ranges from 15 minutes to 120 minutes and total duration of desensitization from 2 hours (rapid desensitization protocol) to a few weeks (slow desensitization schemes).

The protocol by Demoly et al., starts at a 1/1.000.000 of the therapeutic dose, and, through a total of 13 steps, they triple each time the previous dose, to reach the final cumulative dose (31,32). In protocols developed by Castells et al. for chemotherapeutics and monoclonal antibodies, the final step entails both a much larger dose (around 17-30 times greater than the previous one), and a much longer time of administration (5, 17). It is probably for such reason that the same Authors showed a greater rate of adverse reactions occurring during the administration of the last dose.

The Brigham and Women's Hospital Rapid Drug Desensitization Program (BWH) assessed a 12- to 20-step standard protocol based on an in vitro mouse mast cell model, in which unresponsiveness to a triggering antigen dose was achieved by delivering doubling doses of antigen at fixed time intervals starting at 1/1000 the final dose (33). The most commonly used protocol has 12 steps, using three solutions at escalating rates. Patients who have had severe anaphylactic reactions to the agent of choice or who have reacted early in the standard 12-step desensitization may experience fewer symptoms if desensitized using a 16-step protocol, which adds another bag containing 1/1000th of the full dose. The use of a 16-step (four bags) or a 20-step (five bags) protocol is reserved for high-risk patients. It was also observed that 70% of reactions during desensitization occurred during the 12th and the final step using standard 12-step protocol (34).

In conclusion, when doses are too high and delivered too fast, the state of unresponsiveness may be delayed; this can explain breakthrough reactions during desensitization. Also, a certain time interval between doses of the drug antigen is needed to achieve maximum tolerance of the therapeutic dose (12).

Desensitization to antibiotics

Desensitization protocols to antibiotics seem to be very successful especially in some patients, such as HIV-positive patients with a sulfonamide hypersensitivity or cystic fibrosis patients with any antibiotic hypersensitivity, showing efficacy rates of above 80%. However, in most published cases, a pre-existent sensitization and allergy have not been proven by positive skin tests and/or drug challenge. Therefore, in some reported cohorts, successful re-administration may be achieved in non-allergic patients (19). On the other hand, adverse reactions to cotrimoxazole in HIV-positive patients are rarely IgE mediated. Therefore, while skin tests may be useful for diagnosing IgE-mediated reactions, allergy to cotrimoxazole is usually diagnosed on medical history. Once an adverse reaction to cotrimoxazole occurs, a desensitization protocol is the management strategy of choice as it has proven to be more beneficial and less risky than a drug challenge to prescribe the drug for prophylaxis purposes (35). In most cases of cotrimoxazole allergy, the same symptoms occur on several administrations of the drug. So, the causative link between drug administration and hypersensitivity symptoms makes the challenge an unnecessary step to reach a diagnosis of drug allergy (36). Nagarajan et al. (37) successfully performed a 7-h desensitization protocol to cotrimoxazole in 4 of 5 HIV-positive children. After a 10-month follow-up, all patients continued to tolerate cotrimoxazole. Based on a paper by Moreno-Ancillo et al. (36), Gomez-Traseira (38) performed a successful 28-days desensitization protocol on a 5 years-old girl, after she had presented mild reactions during a faster desensitization procedure. A variety of cotrimoxazole desensitization protocols have been performed in HIV patients in adulthood, but there is still a lack of validated protocols for such drug in children (38).

Several specific protocols for penicillin desensitization have been widely published, but the one described by Sullivan et al. (39) seems to be the most applied in clinical practice. For penicillin-derived antibiotics, the oral route seems to be safer, because it is

less prone to expose patients to multivalent penicillin conjugates, which play a key role in IgE- mediated reactions. It is the preferable route in children too (Table 2). Protocol for oral and intravenous desensitization to penicillin usually starts with 1/10.000 to 1/1.000 of the target dose, and doses have a two-folds increase at each step. Doses are administrated every 15-20 min, over the course of several hours, until the therapeutic dose is reached. Intravenous protocols and protocols with mixed routes are also available. In patients with severe anaphylaxis, the initial dose should be 1/1.000.000 to 1/10.000 of the full therapeutic dose (17).

There are some cases in the literature of successful desensitization to other non-penicillin beta-lactams such as meropenem, cefotaxime, ceftriaxone and ceftazidime. Most of the reactions reported with these molecules are IgE mediated. Most studies on desensitization to such agents are reported in patients suffering from cystic fibrosis. Protocols differ in initial doses, dose increments, number of steps (6-12 steps), use of premedication, and success rates, that range from 75% to 100% (25).

Hypersensitivity reaction to anti-TB drugs ranging from maculopapular or urticarial rush to severe reactions, have been reported in 4% to 5% of patients (21). If an adverse drug reaction occurs in a child taking multiple drugs simultaneously, a careful clinical assessment should be performed to determine a possible allergic mechanism causing the adverse event. After stopping all drugs, they should be re-administered one at the time, with a 4-5 days-interval to detect the responsible drug (25). Thereafter, patients may be desensitized to the culprit drug. There are only some pediatric case reports with rapid desensitization in suspected IgE mediated allergy and with slow desensitization in T- cell mediated allergy.

Table 2. Oral Penicillin desensitization protocol. The time between doses is every 15-20 minutes (39)

Step	Penicillin mg/ml	Amount (ml)	Dose (mg)	Cumulative dose
1	0.5	0.1	0.05	0.05
2	0.5	0.2	0.1	0.15
3	0.5	0.4	0.2	0.35
4	0.5	0.8	0.4	0.75
5	0.5	1.6	0.8	1.55
6	0.5	3.2	1.6	3.15
7	0.5	6.4	3.2	6.35
8	5.0	1.2	6.0	12.35
9	5.0	2.4	12.0	24.35
10	5.0	5.0	25.0	49.35
11	50.0	1.0	50.0	100.0
12	50.0	2.0	100.0	200.0
13	50.0	4.0	200.0	400.0
14	50.0	8.0	400.0	800.0

Desensitization to vaccines

Immunization with DTP vaccine (diphtheria, tetanus and pertussis) is a part of the vaccination calendar for children. Adverse allergic reactions vary from minimal urticarial reactions to life-threatening anaphylaxis. In infancy, these reactions usually interrupt the vaccination calendar, but immunization with tetanus-vaccine in these children should still be assured. Desensitization to tetanus-vaccine is performed using a 9-step graded dosing schedule with the tetanus toxoid vaccine (40) (Table 3).

Desensitization to MMR-vaccine is performed by subsequent subcutaneous administration of 0.05 ml of a 1/100 dilution, 0,05 ml of a 1/10 dilution, and 0,05 ml of the non-diluted vaccine up to the 0,5 ml dose (41,42).

Desensitization to chemotherapeutics and monoclonal agents

Chemotherapeutics and monoclonal antibodies are expensive, and they often are the best treatment option for those patients requiring such treatment. So, over the last 15 years, attention has been focused on desensitization to chemotherapeutics and monoclonal antibodies. In most cases desensitization has

Table 3. Desensitization protocol to tetanus vaccine; injections should be performed every 20 minutes (40)

Dose number	Volume (ml)	Dilution	Route
1	0.2	1:1000	Intradermal
2	0.2	1:100	Intradermal
3	0.2	1:100	Intradermal
4	0.2	1:10	Subcutaneous
5	0.10	1:10	Subcutaneous
6	0.05	Non-diluted	Subcutaneous
7	0.10	Non-diluted	Subcutaneous
8	0.15	Non-diluted	Subcutaneous
9	0.20	Non-diluted	Subcutaneous

been shown to be effective and safe (6). As chemotherapeutics are usually dosed per meter squared, the full therapeutic dose differs for each child. Intravenous desensitization with carboplatin starts at dose of 0.01-1 mg, infused over 1 min. Dose increments are made every 15 minutes, by prolonging the infusion time, while holding the infusion rate constant. When a dose of 15-22.5 mg administered over 15-22.5 minutes is well tolerate, the infusion rate may be increased to 100 mg/h for 1 h and then to 200 mg/h for the remaining dose (5).

Confino-Cohen et al. (43) published a protocol, including patients' premedication, that starts with the administration of 1/1.000 of the total dose over 90 minutes, followed by 1%, 10%, and 89% of the total therapeutic dose, each perfused over 90 minutes.

Several large case series describing desensitization regimens have been published in adults with hypersensitivity to carboplatin (5, 37-40). Most of them include a premedication with 10 to 20 mg of dexamethasone, associated with an antihistamine. Leukotriene receptor antagonists such as zileuton or Montelukast have also been used. Desensitization protocols start with 1/1.000 or 1/100 of the total dose and increase to full dose over 6 to16 hours. Success rates range from 79% to 99% (8, 43-46).

Small case series in children reported that desensitization was largely unsuccessful (47, 48). The reason for the difference between children and adults is not clear yet, as the mechanism determining hypersensitivity reactions to carboplatin (49). Hypersensitivity reactions have been reported to all platinum-containing chemotherapeutics. The Canadian Pediatric Brain Tumor Consortium reported a 42% rate carboplatin hypersensitivity in children and very different outcomes after re-challenge (50). Other platinum compounds may act as haptens to stimulate the development of specific IgE antibodies which, in subsequent infusions, generate a type I hypersensitivity. In support of a type I IgE mediated hypersensitivity are the rising incidence of hypersensitivity reactions after repeated injections of these drugs and the occurrence of positive skin prick tests to platinum compounds. A possible non-IgE mediated mechanism may be due to a direct complement activation on the mast cell membrane causing histamine release (49).

L-Asparaginase is an immunogenic compound in humans and is often associated to allergic reactions. Even if the pathogenesis of hypersensitivity to L-Asparaginase has not been fully explained, some studies showed that the immunological mechanism may be either IgE mediated or related to complement activation mediated by IgG or IgM complexes with L- Asparaginase (51).

L-Asparaginase is administrated intramuscularly, but intravenous desensitization had been described starting at a 1 IU dose, that is then doubled every 10 minutes (52).

Intravenous desensitization to methotrexate is started at 1/1000 of the full dose over 1.5 hour, followed by 1/10 over 6 hours and by the remaining dose over 24 hours, for every therapeutic cycle (53,54). This procedure may necessitate a dose reduction due to increased toxicity secondary to a prolonged exposure to the agent (53).

Several protocols have been successfully applied to monoclonal agents, such as infliximab, trasduzumab, rituximab, omalizumab, natalizumab, basiliximab, abciximab and cetuximab (14, 55). An important feature of these protocols is that premedication with diphenhydramine and famotidine, aspirin, montelukast or glucocorticoids is usually included to considerably reduce adverse reactions.

Rapid desensitization protocols were reported in pediatric patients for rituximab (56), infliximab (31, 57), and alemtuzumab (58).

Conclusions

Drug desensitization induces a temporary tolerance to the drug that previously caused a hypersensitivity reaction, allowing the administration of the same drug, when there are no alternative treatments, or only fewer effective ones. Drug desensitization protects against anaphylaxis and activates inhibitory mechanisms which need further research and comprehension. Desensitization is dose and drug dependent, and therefore patient dependent. Unfortunately, it is not persistent, and when drug intake is discontinued, tolerance is lost over hours or days. Therefore, for patients needing several courses of the same treatment,

desensitization protocols must be performed before the beginning of every single course. Probiotics induce a Th1 response instead of Th1 which is associated with allergy (59, 60). Probiotics have been successfully used as adjuvants in desensitization to peanuts (61) and aeroallergen (62), and they may be a a promising means of enhancing unresponsiveness induced by drug desensitization. Desensitization is a high-risk procedure and should be performed only by well- trained allergy teams in selected patients, after assessing a personalized risk/ benefit profile. The literature lacks cohort studies on drug desensitization in children and the availability of validated protocols is crucial for the success of this procedure. Both successful and unsuccessful outcomes should be published to establish the most efficient and safer protocols.

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Correspondence:
Caimmi Silvia
Pediatric Clinic, Foundation IRCCS
Policlinico San Matteo, University of Pavia,
Pavia, Italy
Tel. +39.0382.502878.
Fax +39.0382502876.
E-mail: s.caimmi@smatteo.pv.it

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Review

Drug-induced anaphylaxis in children

Fabio Cardinale[1], Doriana Amato[1], Maria Felicia Mastrototaro[1], Carlo Caffarelli[2], Giuseppe Crisafulli[3], Fabrizio Franceschini[4], Lucia Liotti[5], Silvia Caimmi[6], Paolo Bottau[7], Francesca Saretta[8], Francesca Mori[9], Roberto Bernardini[10]

[1] UOC di Pediatria, Servizio di Allergologia e Pneumologia Pediatrica, Azienda Ospedaliera-Universitaria "Consorziale-Policlinico", Ospedale Pediatrico Giovanni XXIII, Bari, Italy; [2]Clinica Pediatrica, Dipartimento di Medicina e Chirurgia, Azienda Ospedaliero-Universitaria, Università di Parma, Italy; [3] UO Allergologia, Dipartimento di Pediatria, Università di Messina, Italy; [4] UOC Pediatria, Azienda Ospedaliero-Universitaria "Ospedali Riuniti", Ancona, Italy; [5] Department of Pediatrics, Senigallia Hospital, Senigallia, Italy; [6] Pediatric Clinic, Foundation IRCCS Policlinico San Matteo, University of Pavia, Pavia, Italy; [7] Pediatric and Neonatology Unit, Imola Hospital, Imola (BO), Italy; [8] Pediatric Department, AAS2 Bassa Friulana-Isontina, Palmanova-Latisana, Italy; Pediatric Allergy Unit, Department of Medicine, Udine, Italy; [9]Allergy Unit, Department of Pediatric Medicine, Anna Meyer Children's University Hospital, Florence, Italy; [10] Paediatric Unit, "San Giuseppe" Hospital, Empoli, Italy

Summary. Anaphylaxis represents one of the most frequent medical emergencies in childhood. However, as compared to adults, drugs are less common triggers of anaphylaxis in children, with a frequency which is increasing from infancy to adolescence. Deaths seldom occur, maybe because of the paucity of comorbidities in children. Antibiotics and non-steroidal anti-inflammatory drugs (NSAIDs) are the main elicitors in drug-induced anaphylaxis in children. Both immune-mediated (mainly IgE-mediated) and non immune-mediated may be involved. IgG-mediated and complement-mediated mechanisms has been also hypothesized. Correct management relies on a right diagnosis and prompt therapy. A proper work-up is also important to prevent further potentially fatal re-exposures to the same drug or other structurally similar molecules but also unnecessary avoidance of medications not representing the culprit of the episode. (www.actabiomedica.it)

Key words: epidemiology, drugs, anaphylaxis, MRGPRX2

Introduction

Anaphylaxis is an acute systemic allergic reaction which could be life-threatening and also fatal. Diagnostic criteria has been established since 2006 but still many cases remain underdiagnosed and undertreated all over the world (1). Food, insect stings and medications are the main triggers across all ages (2-5). Less common triggers include animal dander, latex, contrast media, environmental allergens, and exercise or temperature. In as much as 10-35% of cases a plausible trigger cannot be identified (i.e. in idiopathic anaphylaxis) (1, 5). Differences however exist in anaphylaxis between adulthood and childhood regarding the relative proportion of eliciting triggers, clinical presentation and even mortality. Drugs in adults are the most frequent etiological agents in fatal anaphylaxis in most regions were data are available (3). Data on drug-induced anaphylaxis in children are scarce and mostly limited to case series including adult populations. Aim of the present review is to provide the reader some insights into the etiology, pathophysiological mechanisms and management of drug-induced anaphylaxis in children.

Epidemiology

The frequency of anaphylaxis varies widely across studies, with an incidence ranging from 3 to 112 episodes per 100,000 person-years, and a lifetime prevalence of 0.05 to 5.1%. Such wide variations me be

explained by the strength of the definitions used, genetics, geographical patterns, and other still undefined factors (6, 7). The incidence in children aged 0-4 years is almost 3 times higher than that of other age groups, with higher figures in boys than in girls until age 10-15 years. According to the raising prevalence of atopy, the frequency of anaphylaxis has also been increased since late 1990s, maybe reflecting also a better diagnostic capacity and guidelines implementation among care providers worldwide (6, 8).

Much less is known about the prevalence of drug-induced anaphylaxis. The frequency of self reported drug hypersensitivity is very high in the general population, even in childhood. Systematic reviews and metanalysis report a prevalence of self-reported drug allergy of 10.0% in adults, and 5.1% in children, with a higher frequency in hospital settings (9). However, when properly investigated, only a few of these reactions can be confirmed after a diagnostic work-up (10). Noteworthy, drugs represent one of the "big three" elicitors in etiological ascertained anaphylaxis and the first causative factor in perioperative anaphylaxis (1-3, 5-8). Recent electronic health database reports found an unexpected high prevalence of drug-induced anaphylaxis, occurring in approximately in 1% of adults in the United States (11). Time trend in the same populations seemed to be relatively stable, but year peaks for unexplained reasons were recorded (11).

Drugs are also the main cause of hospital admission for anaphylaxis in adults with an expected rate of 1 in 3.000 hospitalized patients and the leading causative factor in severe or fatal anaphylaxis in adulthood in most regions. Death approximately occurs in 0.3% to 2% of severe anaphylaxis (6). The incidence of fatal drug-induced anaphylaxis may be increasing (12). The patent of many new biotechnological drugs for different human diseases and the approval from regulatory agencies of newly discovered life-saving therapies in critically ill patients could be a major culprit in this expected temporal trend. However, in UK no increase in fatal-anaphylaxis was found for any cause, including drugs, between 1992 and 2012 despite an increase in rate of hospitalization (13). Indeed, in Australia drug-induced fatal anaphylaxis had increased by 300% between 1995 and 2004, despite an increasing rate of hospital admission of only 150% (14). A small but not significant increase of drug-induced fatal anaphylaxis has been also reported in the same country from 2004 onward (15).

Little is known about the epidemiology of drug-induced anaphylaxis in children. The frequency of self-reported drug allergy, including anaphylaxis in children and adolescents is almost half of that reported in adults in most regions of the world (2, 9, 16). As in adults, also in children only a few cases of suspected drug hypersensitivity are really allergic to certain drugs, with the likelihood of a true allergy increasing with the severity of the reaction (17). Medications, including allergen-specific immunotherapy (SIT), have been reported with a proportion ranging from 8%. to 33.1% of all causes in case series of anaphylaxis in children (2, 17-23). However, drugs were the eliciting triggers in only 101 out of 1970 (5%) cases of anaphylaxis registered among patients under 18 years reported in the European Anaphylaxis Registry (24). Of those, 50 out of 101 (50%) were attributed to SIT. In this population sample however only 1.3% patients had grade IV / fatal reactions. It is worth mentioning that the proportion of medication-induced anaphylaxis in adolescence (13-17 years) almost doubled as compared to earlier ages, probably reflecting age-dependent sensitization and/or different attitude to use specific therapeutic products. Indeed, in infants and toddlers the frequency of drug-induced anaphylaxis seems to be to 4- 5-fold lower than in children > 12 months of age (20).

Fortunately, deaths very seldom occur because of drug-induced anaphylaxis in children. In general the mortality because of anaphylaxis is age-dependent and is much less in children than in adults, maybe as an epiphenomenon of the lack of major comorbidites, less use of medications interfering with treatment and high adult supervision (3, 6). In a large French survey on 1603 cases of fatal anaphylaxis (of whom 63% were iatrogenic) only 2.4% occurred in children (25). Further in a pharmacovigilance study from China collecting 91 cases of drug-induced anaphylaxis in children, only one death was recorded, with a frequency of severe anaphylaxis being more then 15 time lower in children 0-5 years than children 13-17 years old (26). However, even if uncommon, drugs account for most of pediatric anaphylaxis fatalities in both Europe and United States (27, 28)

Etiology and risk factors of drug-induced anaphylaxis in children

Anaphylaxis has been described as an adverse affect virtually of all medications, including anti-allergic drugs and corticosteroids across all ages (19, 26, 29, 30). Antibiotics and non-steroidal anti-Inflammatory drugs (NSAIDs) represent the major culprit in almost all studies on drug-induced anaphylaxis in children. NSAIDs, whether or not combined with exercise, are also major potentiating factors in the so called cofactor augmented food-induced anaphylaxis (31). However, specific immunotherapy (SIT) represented the most frequent etiology of medication-induced anaphylaxis in a multi-center data-collection survey from Turkey (19). Other medications, including opiates, anesthetics, hormones, radiocontrast agents, probiotics and chemotherapics may also represent a significant issue. In a recent survey from China, biologics and chemotherapics covered 10% of all cases of drug-induced anaphylaxis in children (26).

In general, asthma and atopy seem not to be a risk factors for drug-induced anaphylaxis (19, 30, 32). However, an atopic status seems to be a risk factor for NSAIDs hypersensitivity reactions (33). Atopy has been also associated to cross-intolerance to NSAIDS, at least in adults (34).

Female sex has been also reported to be associated with a three-fold higher risk of medication-induced anaphylaxis in some studies (19). Other studies have also reported a higher risk of actual drug-induced anaphylaxis in children with a history of systemic illnesses or concomitant regular assumption of other medications (30). High level of exposition and the frequent use of intravenous route as occurs in cystic fibrosis may be also predisposing factors (35).

Mastocytosis may also be a risk factor for drug-induced anaphylaxis, particularly in the perioparative period (36, 37). Triggers may be NSAIDs, opioids, beta-lactams, contrast media, or other medications, including anesthetics. Approximately 4% of children with mastocytosis may develop an episode of mast cell activation with systemic symptoms under different anesthetic procedures (38). However, high levels of basal tryptase are uncommon in drug-induced anaphylaxis and only a minority of cases with medication-induced anaphylaxis are associated with mastocytosis (36).

Mechanisms of drug-induced anaphylaxis in children

Drug-induced anaphylaxis may occur as a consequence of both immune-mediated (mainly IgE-mediated) and non immune mediated mechanisms (7, 35). As many drugs have a low-molecular weight, thay act as aptens, i.e. they require the binding to a high molecular weight protein carrier to be recognized by antigen-presenting cells to induce an IgE or non IgE-mediated immune response. Non immune mechanisms may include direct mast cell activation or an imbalance of eicosanoids metabolism with up-regulation of leukotrienes production and inhibition of prostaglandins synthesis, including prostaglandin E2 (PGE2). PGE2 acts through the EP2 receptor, which stabilizes mast cells, and therefore the decrease in PGE2 occurring as a downstream effect of COX-1 inhibition by NSAIDS might lead to abrupt mediator release from inflammatory cells and the development of systemic symptoms in susceptible subjects (39). Non immune mediate mechanisms seem to be the main mechanism of anahylaxis induced by certain medications such as NSAIDs, opiates, neuromuscolar blockers and some antibiotics, such as vancomicin or fluorochinolones (35, 39, 40). New insights into the pathophysiology of some anaphylactoid (or "psudoallergic") reactions have been provided by the discovery that a single receptor in mouse, named Mrgprb2, the orthologue of the human G-protein-coupled receptor MRGPRX2, can induce direct mast cell activation leading to histamine release, inflammation and airway contraction (41). This receptor seems to be the target for some small-molecule drugs (such as quinolones, neuromuscular blocking agents, and icatibant) and other cationic substances collectively called basic "secretagogues" which can induce adverse reactions by non immune mechanisms. Acetyl salicylic acid has also been shown to facilitate direct mast cell activation by an increase in Syk kinase phosphorylation of the FcεRI signalling complex, with an affect which could have a genetic basis related to FcεRIa subunit gene polymorphisms (42, 43).

Immune mechanisms may be IgE mediated or non IgE-mediated. Under a condition of antigen-excess, as occurs when large amount of drugs are administered by the intravenous route, a IgG-mediated may be involved, with a mechanism which has been described in mouse as «passive systemic anaphylaxis» (40). This has been demonstrated in patients treated with aprotinin, dextran but also in intravenous immunoglobulin-treated IgA-deficient individuals, von Willebrand factor-deficient subjects under substitutive therapy, and also in patients treated with a variety of chimeric, humanized, and even fully human mAb (40, 44). Again, genetic factors may play a role in these non IgE-mediated adverse reactions to medications. For example, some studies haves shown a higher frequency of mutant alleles associated with a gain-of-function of the stimulatory FcγRIIA in patients with hypogammaglobulinemia who developed anaphylaxis because of IgG anti-IgA antibodies after intravenous immunoglobulin infusion (45). Mouse models indicate that probably in drug-induced IgG-mediated anaphylaxis different cell types from mast cells, such as activated monocytes/macrophages, basophils, or neutrophils are involved (40, 44).

Notably, the existence of a complement-mediated anaphylaxis has been also hypothesized, which could explain some non IgE-mediated anaphylaxis triggered by non proteic micellar drugs, lipid carriers, liposomes and polyethylene glicol (40).

Management of drug-induced anaphylaxis

Drug-induced anaphylaxis is an emergency. The median times to cardiorespiratory arrest after a medical intervention-induced anaphylaxis is only 5 minutes, as compared to 30 minutes after food-induced anaphylaxis (1). The premise for proper treatment is a correct diagnosis, which in most cases may be made independently from the confirmation of the etiological role of a drug through a proper diagnostic work-up. Indeed, the diagnosis of anaphylaxis relies on a combination of history and a well defined set of symptoms established from international guidelines (1, 4). According to guidelines, two out of three criteria require the exposure to a likely or known allergen or other trigger. Therefore, unless the first criteria is respected, if a trigger could be not properly identified, by history alone and/or in vivo or in vitro test results, a diagnosis of drug-induced anaphylaxis could not be made. This occurs quite seldom in drug-induced anaphylaxis, as the brief time lapse between exposure to the suspected trigger and the beginning of symptoms makes the cause-effect relationship often undoubtful. Sometimes clinical history is so clear that performing in vivo or in vitro tests aimed to demonstrate an immune or non immune mechanism upon which the suspected drug had induced reported symptoms may be useless or even contraindicated. This is not the case of anaphylaxis occurring during the periperative period, as many drugs and diagnostic or therapeutic interventions are administered at the same time during anesthetic procedures.

An increase of serum tryptase concentrations in comparison with basal levels between 15 min and 2 h after a reaction is highly suggestive of anaphylaxis, but his absence does not exclude it (46). Regarding emergency treatment, guidelines recommend adrenaline intramuscularly as first-line option. Intravenous fluids and bronchodilators may be required. Second-line options include antiH1-antihistamines and glucocorticoids.

The identification of the offending drug is necessary to prevent further, potentially fatal, episodes and unnecessary avoidance of a drug not etiologically related to the episode. Appropriate tests are skin tests and detection of IgE to the suspected drug The drug provocation test is considered the diagnostic gold standard. However, it should be taken into account that risks and benefits must be carefully considered before performing a challenge test to the relevant drug in children with anaphylaxis (35, 47). Further, children with anaphylaxis to drug and their families should be prescribed adrenaline autoinjector and they should be instructed on how they should use it.

Conclusions

Further studies are warranted on the prevalence of drug induced anaphylaxis in childhood. A correct diagnosis is critical for preventing further anaphylactic reactions. Avoidance of the offending drug and knowledge of adrenaline use for treatment of anaphylaxis are the cornerstone of the management of anaphylaxis.

Conflict of interest: None to declare

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Correspondence:
Fabio Cardinale
Unità Operativa Complessa di Pediatria
Servizio di Allergologia e Pneumologia Pediatrica
Azienda Ospedaliero-Universitaria
"Policlinico-Giovanni XXIII"
Via Amendola 207 - Bari, Italy
Tel. ++39 080 5596586
E-mail: fabiocardinale@libero.it

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Review

Mild cutaneous reactions to drugs

Giuseppe Crisafulli[1], Fabrizio Franceschini[2], Silvia Caimmi[3], Paolo Bottau[4], Lucia Liotti[5], Francesca Saretta[6], Roberto Bernardini[7], Fabio Cardinale[8], Francesca Mori[9], Carlo Caffarelli[10]

[1] UO Allergologia, Dipartimento di Pediatria, Università di Messina, Italy; [2] UOC Pediatria, Azienda Ospedaliero-Universitaria "Ospedali Riuniti", Ancona, Italy; [3] Pediatric Clinic, Foundation IRCCS Policlinico San Matteo, University of Pavia, Pavia, Italy; [4] Pediatric and Neonatology Unit, Imola Hospital, Imola (BO), Italy; [5] Department of Pediatrics, Senigallia Hospital, Senigallia, Italy; [6] Pediatric Department, AAS2 Bassa Friulana-Isontina, Palmanova-Latisana, Italy; Pediatric Allergy Unit, Department of Medicine, Udine, Italy; [7] Paediatric Unit, "San Giuseppe" Hospital, Empoli, Italy; [8] UOC di Pediatria, Azienda Ospedaliera-Universitaria "Consorziale-Policlinico", Ospedale Pediatrico Giovanni XXIII, Bari, Italy; [9] Allergy Unit, Department of Pediatric Medicine, Anna Meyer Children's University Hospital, Florence, Italy; [10] Clinica Pediatrica, Dipartimento di Medicina e Chirurgia, Azienda Ospedaliero-Universitaria, Università di Parma, Italy

Summary. Adverse reactions to drugs are not frequent in childhood. Cutaneous reactions are the most frequent in this age group. Mild cutaneous reactions are immediate or delayed adverse reactions that do not seriously compromise the clinical condition of children. The patients usually early improve and recover the state of health. Although it is difficult to define the prevalence accurately, we could affirm that the rate adverse reaction to drugs are often over estimated by both the families and the physicians. Therefore, children may be prone to loss of school days and inappropriate or sub-optimal treatments. However, the identification of a true adverse reaction to drugs allows adequate treatment and alert to further exposure to harmful drugs. (www.actabiomedica.it)

Key words: drug hypersensitivity reactions, children, skin test, specific IgE, drug provocation test, exanthema, urticaria

Introduction

An adverse drug reaction (ADR) is defined by the World Health Organization as "a response to a medicine which is noxious and unintended and which occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease, or for the modification of physiological function" (1). Cutaneous adverse drug reaction (CADR) may be defined as an undesirable manifestation of the skin resulting from administration of a drug. CADRs are reported as type of ADRs (2) in either adult population and pediatric population (1). CADRs represent about 35% of all suspected ADRs in children (3). It could be estimated that 2.5% of children who are treated with a drug, and up to 12% of children treated with an antibiotic, will experience a CADR (4). Reactions are more frequently reported following intake of antimicrobials, neurology drugs, and dermatological agents (3). CADRs can be divided into different classes based on pathogenesis and clinical morphology. On the basis of pathogenesis, they are divided into 2 categories. Type A ("augmented") reactions are related to the pharmacologic effects of a drug and are dose dependant, predictable or expected, mild to moderate in severity. Type B ("bizarre") reactions are not related to the pharmacologic effects of a drug, are not dose dependent (occurring with low doses of medication too), unpredictable, idiosyncratic,

Table 1. Mild cutaneous adverse drug reaction

Exanthematous Drug Eruptions
- Maculopapular rash (morbilliform, scarlatiniform rubelliform eruptions)
- Eczematoid-like pattern
- Psoriasiform-like pattern
- Lichenoid-like pattern
Urticaria
Fixed Drug Eruptions
Photosensitivity Reactions
- Phototoxic reactions
- Photoallergic reactions
Other
- Serum Sickness–Like Reactions
- Acneiform eruptions

often severe (5, 6). Such reactions have been categorized as immunologic hypersensitivity (allergic) reactions, pseudo-allergic, and idiosyncratic (5,7). At variance from adults, type B reactions are more common in children. CADRs can also be identified on the basis of the clinical presentation. Distribution, morphology, configuration, and progression of the lesions should be adequately described. At least 29 mild to rarely severe clinical presentation of cutaneous drug reactions have been identified (8-12). We will discuss only mild cutaneous reactions in childhood (Table 1).

Exanthematous Drug Eruptions

Exanthematous drug eruptions (EDEs) include maculopapular rash (morbilliform, scarlatiniform rubelliform eruptions), eczematoid/psoriasiform/ lichenoid-like pattern (based on similarity with infectious or inflammatory diseases) (13). They are the most common CADR in children (8, 14) and occur in 1-5 % of cases at first drug exposure (15).

The most common type of EDEs is maculopapular rash (MPR) that is characterized by erythematous macules evolving in papules from 1 to 5 mm in diameter and may coalesce in plaques. MPR involves face, neck, or upper trunk and tipically spreads bilaterally and symmetrically toward the limbs. MPR could be accompanied by pruritus and mild fever (16). MPR is self-limiting and resolves within 7-14 days after stopping the drug. With resolution, lesions may become brownish and desquamation may occur. EDEs are usually considered delayed-type hypersensitivity reactions, although evidence of such a mechanism is rare. There is a distinguishing timing of occurrence of lesions (17). At the first drug exposure, lesions appear after a sensitization phase, 5-14 days after the start of therapy and sometimes after drug discontinuation (8). In previously sensitized patients, skin lesions develop following re-exposure to the same drug in 6 hours to 5-7 days. The most common implicated drugs include beta-lactams, sulfonamides, and antiepileptic medications (18). EDE develops in 5% to 10% of patients treated with ampicillin. This frequency increases substantially during a viral infection. Children who are infected with the Epstein-Barr virus are at increased risk of rash (19). In EDE, patch test and provocation test should be used to identify the culprit drug (20, 21). The management of EDE is supportive. Pruritus can be treated with topical steroids, emollients, oral antihistamines. Second generation H1 blockers are associated with fewer sedative effects when compared with first generation H1 blockers (22, 23). A post-inflammatory hypopigmentation or hyperpigmentation may follow which vanishes over months or years, and sun avoidance or protection should be advised (24). The choice of suspending the offending drug must be made on individual basis. It is unclear whether continuation of a drug can lead to Steven-Johnson Syndrome (25). Topical steroids and emollients are therapeutic options in children with eczematous reactions (26).

Urticaria

Drug-induced urticaria is one of the most common drug eruption along with EDEs and represents approximately 5% of all cutaneous drug eruptions (27, 28, 29).

Urticaria is characterized by wheals due to swelling of the dermis and/or angioedema due swelling of lower dermis and subcutis or mucous membranes (30). Wheal are characterized by central swelling surrounded by an erythematous area and pruritus (rarely burning) (30). Each wheal resolves in 24 hours but new

lesions may appear. Urticaria caused by drugs is usually acute, and rarely chronic (>6 weeks) (31). Acute urticaria is triggered by drugs in about 7% of children and beta-lactams followed by non-steroidal anti-inflammatory drugs (NSAIDs) are the most common causative drugs (32). Drug-induced urticaria is due to mediators, including histamine, and citokines released by activated mast-cells (31). Mast-cells can be degranulated by an IgE-mediated mechanism or directly by the drug (33). NSAIDs usually elicit a nonimmune mediated urticaria and should be cautiously administered in children with chronic urticaria since it may aggravate symptoms (34).

In acute urticaria, skin prick test should be used to identify the offending drug. Drug provocation test should be performed when it is appropriate (21, 30) in a setting where personnel and emergency treatment is available (35). Treatment includes discontinuation of the causative drug and administration of 2nd generation H1-antihistamines (32). If there are sleeping problems caused by pruritus, sedative antihistamines could be used at night, but do not improve control of symptoms (36). Oral corticosteroids in addition to antihistamines may be beneficial (37). The problem arises when the causative drug cannot be halted and urticaria is not controlled by reliever medications. In these cases, probiotics that are mainly used in the prevention of infectious diseases (38, 39), seem to be promising in reducing symptoms (40).

Fixed Drug Eruptions

Fixed drug eruptions (FDEs) are common in children, accounting for approximately 10-14% of cases of drug eruptions (41, 42). FDEs begin as soon as 30 minutes-8 hours after drug intake and as long as 2 months after drug exposure (8, 13). Lesions are characterized by well-demarcated, solitary or multiple papules or plaques. Their colour varies from dusky red to violet. They can be intensely pruritic (8). Lesions resolve in 7-10 days but hyperpigmentation can persist for years (24). The sites of lesions include lips, trunk, legs, arms, and genitals. Genitals are affected particularly in adolescents. Most reactions occur in multiple sites (43-48). Multiple lesions are rarely associated with systemic symptoms including malaise, high fever, nausea, and arthralgia (49-52). In previously sensitized patients, a flare develops at the same site following re-exposure (8, 53) to the offending drug within 1-8 hours (54). In the pediatric population, the most common drugs that cause FDEs are: antimicrobials (amoxicillin, teicoplanin, vancomycin, co-trimoxazole), NSAIDs (paracetamol, ibuprofen, nimesulide, naproxen, metamizol), barbiturates, sulphonamides (55).

The exact pathogenic mechanisms remain unknown. However, there is evidence that it is a CD8+ T-cell mediated reaction. The offending drug may induce local reactivation of memory CD8+T-cell lymphocytes localized in epidermal and dermal tissues and targeted initially by the viral infection and protect against the virus (53, 56). FDEs are probably underdiagnosed in primary care (57). The gold standard for diagnosis of FDEs is re-challenge, depending on the severity of the initial reaction (13). The cornerstone of the treatment is discontinuation of the causal drug that can worse the lesions (8). Management of FDE is supportive and is based on topical steroids.

Photosensitivity Reactions

Drug-induced photosensitivity refers to the development of cutaneous disease due to the interaction between a given chemical agent and sunlight (58). Exposure to either the chemical or the light alone is not enough to induce the disease. When photoactivation of the chemical occurs, one or more cutaneous manifestations may arise. In general population up to 8% of cutaneous drug eruptions are photosensitivity reactions (59), in infants and children the prevalence is quite low because of the restricted use of causal drugs. such as: hydrochlorothiazide and doxycycline. Based on their pathogenesis, they can be classified as phototoxic or photoallergic drug eruptions, although in many cases it is not possible to determine whether a particular eruption is due to a phototoxic or photoallergic mechanism (60).

Drug-induced phototoxicity occurs when photoradiation interacts with a chemical within the skin to generate free radicals, which induces host cytotoxic effects. The site of the eruption coincides with sun-

exposed areas of the skin. Phototoxic reactions are non-immunologic and dose dependant and often occur soon after initial ingestion of the drug. There are 3 general variations of phototoxic reactions (61). The first is an intense and delayed erythema and edema that occurs 8 to 24 hours after exposure to sunlight. This reaction can involve hyperpigmentation and be a darker red than sunburn. Hydrochlorothiazide is an example of a trigger for this first type of phototoxic reaction. A second, more-immediate variation can occur within 30 minutes after light exposure and can last for a day or two. In this variant, erythema occurs without edema and is accompanied by local burning and pruritis. This more-immediate variation is often associated with doxycycline and the coal-tar derivatives such as anthracene and acridine. The third variant is associated with porphyrins and manifests as a rapid, transient, urticarial-like eruption that can be activated by room lighting.

In contrast, photoallergic reactions occur after a period of sensitization and can reoccur with small doses of the offending drugs. The reactions may appear with papulovesicular eruption, pruritis, and eczematous dermatitis 1 to 14 days after exposure to sunlight. Photoallergic reactions should be differentiated from lupus, solar urticaria (61-65).

Phototesting and photopatch testing can be useful for achieving the diagnosis. The mainstay of management is prevention, including informing patients of the possibility of increased sun sensitivity and the use of sun protective measures. Moisturizes and emollients can be useful to treat the burning. In severe cases, topical antibiotic can be considered for vesicles and blisters. Oral antihistamines and topical corticosteroids can provide symptomatic relief of skin lesions due to photoallergic reactions (13, 61).

Other forms

Serum Sickness-Like Reactions (SSLRs) are characterized by fever, pruritis, urticaria, and arthralgias (13). Lymphadenopathy and eosinophilia may be present. Unlike the "true serum sickness reaction", SSLRs do not exhibit immune complexes, hypocomplementemia, vasculitis, or renal lesions (25). They have claimed mostly associated with cefaclor therapy. The development of bacterial resistance to cefaclor has limited its utility in the treatment of pediatric infections (66). For this reason, SSLRs might be less common now than in the past. Cross-reaction of cefaclor with other beta-lactam antibiotics is rare and, in general, other cephalosporins are well tolerated (67). However, some physicians recommend that all beta-lactam antibiotics should be avoided in patients who have experienced cefaclor induced SSLR (68).

Other drugs that have been implicated include biological agents (efalizumab, omalizumab, rituximab, infliximab) (69-73), antibiotics (meropenem, minocycline, ciprofloxacin, rifampicin) (73-79), antimycotics (griseofulvin, itraconazole) (80, 81) and other agents such as bupropion (82), clopidogrel (83), fluoxetine (84), insulin detemir (85), immunoglobulin (86), mesalamine (87), or streptokinase (88).

SSLRs usually occur 1-3 weeks after drug exposure and resolve soon after drug discontinuation (25). The suspected drugs should be avoided by patients who had SSLRs. The underlying cause of SSLRs remains unknown. Therefore, treatment is symptomatic, consisting in identification and discontinuation of the offending drug. Antihistamines are prescribed in case of urticaria and NSAIDs in case of persistent arthralgia and/or arthritis. It is unclear whether a short course of systemic glucocorticoids improves SSLRs (89).

Acneiform eruptions are pustular induced eruptions by drugs that often affects the arms and legs at variance from acne vulgaris. The lesions are usually monomorphous and heal without scarring. They occur with iodides, bromides, adrenocorticotropic hormone, corticosteroids, isoniazid, androgens, lithium, actinomycin D, and phenytoin. Topical medications that are oil-based could be the cause of a type of acne known as pomade acne. Sometimes corticosteroids worsening testosterone-induced acne within 2 weeks by the beginning of treatment. The risk appears to be directly proportional to the dose and duration of the therapy and severity of pre-existent acne (90). Treatments is the same as acne vulgaris and include topical benzoyl peroxide, topical antibiotics, and topical tretinoin (25).

Conclusions

CADRs are a frequent reason of primary care visit (91). In childhood there is a misattribution of cutaneous drug reactions. Diagnosis could be difficult because CADRs can closely mimic other diseases (e.g., viral infections); the identification of the causative drug can become complex especially in the patient on treatment with more than one drug.

CADRs are confirmed with a drug challenge in a very low number of cases (92, 93). Furthermore, the anxiety of parents could mislead the clinician to consider the child "allergic" to a drug (7). In the case of a true allergy the drug involved should be avoided. On the other hand, an incorrect diagnosis can limit therapeutic options and increase the risk of using more toxic, less effective and more expensive drugs (94). A detailed history is necessary in order to evaluate the real occurrence of the adverse reaction. Therefore, good management of suspected CADRs requires an efficient method of estimating the probability of the drug reaction. Causality assessments based on clinical history, such as the Naranjo assessment (94), have proven to be a valid method of estimating the probability of ADR (18, 95-100) but provocation test is the gold standard in the diagnosis of ADR (21).

Conflict of interest: None to declare

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Correspondence:
Giuseppe Crisafulli
Allergy Unit, Department of Pediatrics, University of Messina, Via Consolare Valeria 1, Messina, Italy
Tel. 0039 90 2213156
Fax: 0039 90 2213162
E-mail: crisafullig@unime.it

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Review

Mechanisms of hypersensitivity reactions induced by drugs

Fabrizio Franceschini[1], Paolo Bottau[2], Silvia Caimmi[3], Fabio Cardinale[4], Giuseppe Crisafulli[5], Lucia Liotti[6], Francesca Saretta[7], Roberto Bernardini[8], Francesca Mori[9], Carlo Caffarelli[10]

[1] UOC Pediatria, Azienda Ospedaliero-Universitaria "Ospedali Riuniti", Ancona, Italy; [2] Pediatric and Neonatology Unit, Imola Hospital, Imola (BO), Italy; [3] Pediatric Clinic, Foundation IRCCS Policlinico San Matteo, University of Pavia, Pavia, Italy; [4] UOC di Pediatria, Azienda Ospedaliera-Universitaria "Consorziale-Policlinico", Ospedale Pediatrico Giovanni XXIII, Bari, Italy; [5] UO Allergologia, Dipartimento di Pediatria, Università di Messina, Italy; [6] Department of Pediatrics, Senigallia Hospital, Senigallia, Italy; [7] Pediatric Department, AAS2 Bassa Friulana-Isontina, Palmanova-Latisana, Italy; Pediatric Allergy Unit, Department of Medicine, Udine, Italy; [8] Paediatric Unit, "San Giuseppe" Hospital, Empoli, Italy; [9]Allergy Unit, Department of Pediatric Medicine, Anna Meyer Children's University Hospital, Florence, Italy; [10]Clinica Pediatrica, Dipartimento di Medicina e Chirurgia, Azienda Ospedaliero-Universitaria, Università di Parma, Italy

Summary. Adverse drug reactions include drug hypersensitivity reactions (DHRs), which can be immunologically mediated or non-immunologically mediated. The high number of DHRs unconfirmed and/or self-reported is a frequent problem in daily clinical practice, with considerable impact on future prescription choices and patient health. It is important to distinguish between hypersensitivity and non-hypersensitivity reactions by adopting a structured diagnostic approach to confirm or discard the suspected drug, not only to avoid life-threatening reactions, but also to reduce the frequent over-diagnosis of DHRs. (www.actabiomedica.it)

Key words: drug allergy, prevention, beta lactam hypersensitivity, NSAIDs hypersensitivity, hypersensitivity reactions, children, skin test, specific IgE, drug provocation test

Introduction

Adverse drug reactions (ADRs) affect 10-20% of hospitalized patients and over 7% of the general population (1). Data on prevalence and incidence of drug hypersensitivity reactions (DHRs) are limited, especially in pediatric age and varies around the world. Allergic reactions can manifest as immediate IgE-mediated or non-immediate T cell-mediated reactions.

About 10% of the parents reported that their children are allergic to drugs (2). Beta-lactam hypersensitivity is suspected in the majority of children, the most frequently suspected beta-lactams being amoxicillin and clavulanate, and, to a lesser extent, third-generation cephalosporins (3). A meta-analysis (4) found that just 3% of patients with penicillin allergy in their medical records had a confirmed diagnosis of hypersensitivity reactions by skin or drug provocation tests. The difference appears to be even more striking in the pediatric population, in whom penicillin allergy diagnoses based solely on clinical history are more common (5). According to the above-mentioned meta-analysis, the frequency of confirmed immediate reactions to penicillin is less than 2% in children (4). Overdiagnosis of beta lactams allergy is associated with a greater use of alternative antibiotics, which are usually less effective, less safe, and more expensive; they also usually have a broader spectrum of activity, which can increase the risk of infections by *Clostridium difficile* and multiresistant agents. There may also be economic and management consequences, including higher hospitalization costs, increased readmissions, and longer hospital stays (2). Hospitalizations of children labelled as allergic to penicillins are associated

with longer hospital stays, more comorbidities, and a tendency towards higher hospitalization costs. An accurate diagnosis of penicillin allergy based on clinical history and confirmatory tests is therefore essential in all paediatric patients (6).

Non-steroidal anti-inflammatory drugs (NSAIDs) are the second most frequent type of drug to cause hypersensitivity reactions in children. The overall prevalence of NSAID hypersensitivity has been reported as being between 0.6 and 5.7% in the general population (7). A questionnaire-based frequency of NSAID-induced reactions reported a frequency of 0.3% in children (8). However, in populations at risk (such as asthma or chronic urticaria sufferers) NSAID hypersensitivity prevalence may be higher (9, 10). In studies assessing tolerance for both NSAIDs and acetaminophen is reported that the prevalence of acetaminophen hypersensitivity in children reporting allergy to NSAIDs is 4-25% (11). The frequency of lgE-mediated anaphylactic reactions to NSAIDs in perioperative period was 1 in 2100 operations (12).

In the pediatric population, cutaneous reactions constitute 35% of adverse drug reactions and between 2% to 6.7% of cutaneous reactions can develop into severe and potentially life-threatening clinical syndromes. (2), The most common cutaneous reactions in children are maculopapular rashes (MPR; 20%-80%), urticaria/angioedema (20%-30%) (13), while eczema is rare (14). Serum sickness-like reactions (SSLRs) occur in 0.02%-0.2% of children, especially in young children treated with first-generation cephalosporins (15). Severe cutaneous adverse reactions (SCARs), including erythema multiforme major (EMM), Stevens-Johnson syndrome (SJS), acute generalized exanthematic pustulosis (AGEP), toxic epidermal necrolysis (TEN), and drug-induced reaction/rash with eosinophilia and systemic symptoms (DRESS) are rare, although they may represent up to 10% of the patients explored for suspected DHRs (16-18).

Classification

The classification of DHRs relies on the clinical presentation of typical symptoms and their timing, and were originally described by Gell and Coombs: namely Type I, IgE mediated reactions, Type II, antibody mediated cytotoxicity reactions, Type III, immune complex-mediated reactions, and Type IV, delayed hypersensitivity.

Recently phenotypes, endotypes, and genotypes for DHRs are being elucidated and applied to provide personalized approaches to treating and managing DHRs. Phenotypes in drug allergy focus on symptoms and timing of the reactions. The clinical presentations of each phenotype are mediated by different immunological mechanisms which are defined endotypes. Biomarkers are used to identify endotypes (Table 1) (19).

Phenotypes

DHRs phenotypes may be classified as immediate or nonimmediate/delayed reactions. Immediate reactions typically occur within one hour after the last drug administration and they are often caused by direct mast cell activation or IgE-mediated hypersensitivity. Delayed reactions occur from 1 hours after drug administration and may result from antigen-specific IgG production, complement activation or a T-cell mediated response. Reactions occurring between 1 and 6 hours after the last drug intake are called accelerate and can be caused both by an IgE-mediated and T-lymphocyte mediated response. There is an overlap between accelerate and delayed reactions (20).

However, the cut-off point of 1 h is arbitrary for different reasons. The exact occurrence of initial signs of a drug allergy might be hard to pinpoint in the clinical history, the route of administration can influence the time interval in which the reaction starts (e.g. antibiotics can elicit severe anaphylaxis within a few minutes after parenteral administration, but can take up to 1–2 h to do so after oral intake), drug metabolites may take some hours to be formed and therefore an IgE-mediated immediate reaction can start later than 1 h after drug intake (21).

DHRs phenotypes may be classified according to clinical presentation. Cutaneous Adverse Reactions are the most common manifestation of drug allergy and may be clinically classified in Mild Cutaneous Allergic Reactions (MCAR) and Severe Cutaneous adverse reactions (SCARs). The common culprit drugs to induce

Table 1. Drug hypersensitivity reactions: phenotypes, endotypes, biomarkers

Phenotype		Endotype	Biomarkers
Immediate:	Urticaria/angioedema, Anaphylaxis, Laringeal edema, Bronchospasm	I, IgE mediated Direct mast cell-basophil activation - Complement activation - Mrgx-2	Skin testing, Specific IgE, Basophil activation test, Tryptase
Immediate:	Aspirin exacerbated respiratory disease, Aspirin exacerbated cutaneous disease	COX-1 inibition	
Delayed:	Anemia, agranulocytosis Thrombocytopenia Autoimmunity (SLE, pemphigus)	II, IgG cytotoxic and complement	Patch test, LTT, HLA, Viral antibodies
Delayed:	Serum sickness-like reactions, Vasculitis, urticaria, Organ reactions	III, immune-complex, IgG mediated complement	
Delayed:	Contact eczema	IVa, Th1 (IFN-gamma), Infiltrated monocytes	
Delayed:	DRESS/DIHS	IVb, Th2 (IL-4, IL-5), Infiltrated eosinophils	
Delayed:	SYS/TEN, EM bullous/pustular	IVc, T cell cytotoxic	
Delayed: AGEP		IVd, T cell (IL-8, CXCL-8)	

SCARs include aromatic anti-epileptic drugs, allopurinol, NSAIDs, and antibiotics (22).

Endotypes

Multiple endotypes exist for DHRs, including immunologic reactions (mostly IgE-mediated reactions and T-cell mediated reactions) and non immunologic reactions (pharmacologic interactions, pseudoallergic reactions).

Immunologic Reactions. The term drug allergy refers to a specific immune response to a drug acting as an allergen, mostly linked to endogenous proteins or peptides. In majority of cases drugs or drug metabolites are too small (molecular weight <800 KD) to elicit a specific immune response on their own. Only if they bind *covalently* to endogenous proteins a new antigen is generated (apten-protein complex) (23). The covalent link is resistant on intracellular processing and transform an autologous protein to a novel drug modified protein (2). Autologous proteins may be soluble (e.g. albumin, transferrin) or cell bound protein (e .g. integrin, selectins). The typical immune response to such antigens is a T cell-dependent antibody formation. The sensitization takes time (>4 days). It occurs at therapeutic drug concentrations and it is often clinically unapparent. In T cell mediated reactions, however, symptoms may appear directly following sensitization, namely when the amount of reactive T cells is high enough and homes to the affected organs (mainly the skin) (18, 24). The fact that IgE mediated reactions con occur already al minimal doses does not mean the reaction is dose dependent. The final response is dependent on the type of sensitization. An immune-mediated mechanism linked to certain clinical phenotypes is the basis for the Coombs and Gell classification. The immediate appearing symp-

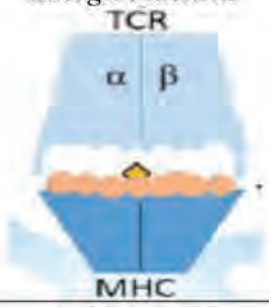
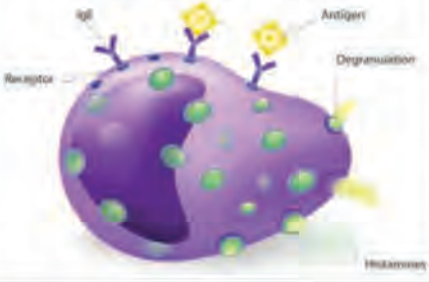
toms (urticaria, anaphylaxis) were classified as being due to IgE (type I) and the delayed appearing symptoms (e.g. exanthemas, eczema, hepatitis) as dependent on T-cell activation (and rarely antibody involvement, especially IgG) (25). In eczematous reactions it is possible to have increased inflammatory biomarkers (26) In immunologic reactions the extent of cross reactivity is dependent on structural similarity and affinity of the drugs to the available immune receptors, T cell receptor (TCR), human leukocyte antigen (HLA), IgE. (26). Immune reactions to drugs may be linked to an autoimmune reactions. The altered peptide repertoire model suggests that a drug could bind strongly and specifically to the HLA protein to alter the selection of self-peptides which in turn results in polyclonal T cell proliferation (26,27) (Table 2).

Non Immunologic Reactions. The pharmacological interaction with immune receptors (p-i concept) proposes that a drug/metabolite may directly, reversibly bind to the TCR and/or HLA protein but not the antigenic peptide (28). According to the "p-i" theory, the antigen-processing pathway in antigen presenting cells is bypassed. This drug binding to immune receptors is a typical off-target effect and is based on noncovalent bonds like van der Waals forces, hydrogen bonds, and electrostatic interactions. The interaction with HLA or TCR is often *selective* for a particular HLA molecule or a particular TCR, as only certain amino-acid sequences and 3D structures allow relatively strong, noncovalent drug binding (29). This is particularly well illustrated by abacavir and its association with HLA-B*57:01 allele. Individuals with this allele have approximately a 50% chance of developing abacavir hypersensitivity syndrome, while no one without this allele is predicted to develop an immunologically confirmed hypersensitivity reaction (30). This occurs only in *some* individuals, and persons at risk can be identified by carrying the risk allele. The majority of high risk alleles were HLA class I, but some less stringent associations were also found for HLA class II alleles (31, 32). In p-i reactions cross reactivity may be important and is based on pharmacologics properties of the drug. For example, the carbamazepine binding HLAB*15:02 protein binds carbamazepine, some carbamazepine metabolites and possibly even other anticonvulsants like lamotrigine and phenytoin (33). Clinical symptoms in p-i reactions typically appear > 5-7 days after the initiation of treatment and only after T cell expansion and migration into tissues. In p-i reactions drug concentrations are important for eliciting T cell reactions, but in some cases lower amounts of the drug may be sufficient to cause symptoms if a massive expansion of drug reactive T cells has already taken place (18).

The p-i concept implies important clinical consequences: reactions are dose dependent, if many clones are stimulated symptoms could appear rapidly, if few clones are stimulated symptoms appear days or weeks after. Moreover p-i concept justifies unelessness of skin tests in diagnosis of many delayed drug allergic reactions (29). In vitro analysis of T cells of patients suggests that p-i reactions may be involved MPR, but most frequently in severe hypersensitivity reactions like AGEP, drug-induced liver injury , SJS/TEN and DRESS (29-31).

Pseudo allergic reactions (PARs) do not require prior sensitization or cell expansion. Symptoms can appear after the first dose. The pathomechanisms of PARs are not yet completely clarified. PARs are characterized by the following properties which differentiate them from allergic reactions. (35). The symptoms of PARs are qualitatively different from the pharmacological response of a drug and are not related to adverse reactions connected with its pharmacological and toxicological profile. PARs are not specific with regard to the chemical structure of the triggering agent in contrast to allergic reactivity. The pseudo-allergic reactivity is not acquired but genetically predetermined. Symptoms of PARs are like those of allergic reactions and are typical of certain substances like NSAIDs, radiocontrast media, muscle relaxants, quinolones, and vancomycin. Reactions usually appear at standard or high doses, which is an important distinction to sensitized individuals having IgE reactions (36). Some of these effects appear to be linked to a single receptor on mast cells, known as MRGPRX2 (Mas-related G-protein-coupled receptor member X2). This receptor which recognize common chemical motif was found to be crucial for IgE independent, direct mast cell stimulation (37). Most PARs are mild (acute urticaria), but anaphylaxis even lethal may occur. In NSAID related pseudo allergic reactions

Table 2. Immune reaction to drugs

Immunologic reactions	***Pathogenesis***	***Need of sensitization***	***Dose dependence***	***Cross reactivity***
Allergic reactions 	Drug modified peptide derived from intracellular haptenated protein	YES	NO	Based on affinity of immune receptors
p-i reactions 	Drug bind to the TCR or to HLA molecules outside of the antigen-binding groove through noncovalent interaction	NO	YES	Based on pharmacol-ogic properties and type or HLA or TCR
Reactions by altered repertoire model 	Drugs bind within the antigen-binding groove of specific HLA molecules altering the repertoire of endogenous peptide ligands	NO	YES	Based on pharmacol-ogic properties
Pseudoallergic reactions 	Reactions related to mast cell or eosinophil activation	NO	YES	Based on ligands on mast cells or eosinophils

the underlying inflammation and effector cell hyperreactivity influences the clinical severity (38).

Cofactors

Most patients who suffer from urticaria and angioedema induced by NSAIDs are females and atopy predisposes to more severe reactions (39). DHRs are also frequently associated with viral infections and in most cases the drug is blamed for the exanthema that occurs. Sometimes this is true and the patient has a persistent delayed type allergy to aminopenicillins. However, the reaction does not often recur on re-administration of the drug. The rash in this case may be caused by a lowering of the T cell threshold for drug reaction during the infection, or from infection-induced alterations in drug metabolism or virally-induced polyclonal T cell activation. An interaction between viral infections and drug-induced hypersensitivity has been most often associated with ampicillin-induced exanthema in patients with infectious mononucleosis caused by Epstein Barr virus. Exanthematous eruptions occur in approximately 10% of patients with infectious mononucleosis, but this rate can increase to 70% in adults and 100% in children receiving ampicillin (40). Currently, there is on-going debate as to whether this is true hypersensitivity. The lymphocyte transformation test assay has helped to demonstrate the immune mechanism of the disease (41). Another well known example of a relationship between viral infection and an increased risk of developing drug-induced skin rashes, including SJS and TEN, has been observed in HIV-positive patients. Clinical observations and several studies showed that the incidence of severe adverse reactions to drugs such as co-trimoxazole was much higher in HIV patients than in the general population (42). Viral infections have been suggested as a potential trigger for hypersensitivity reactions. This is particularly the case with human herpes virus-6 HHV-6 infection and anticonvulsant-induced hypersensitivity (43). It has been suggested that since HHV-6 reactivation can only be detected in hypersensitivity syndrome and not in other drug reactions, it can be utilized as a diagnostic test for hypersensitivity. Indeed, in Japan, HHV-6 reactivation seems to be a gold standard test for drug-induced hypersensitivity syndrome (44). In addition, slow resolution of DRESS is thought to be linked to HHV-6 reactivation and hypogammaglobulinaemia which can occur during treatment with certain drugs, in particular anticonvulsants (45). The herpes group family of DNA viruses including EBV, cytomegalovirus, HHV-6, HHV-7 and herpes simplex virus, have not only been implicated in drug-induced hypersensitivity reactions but also in SJS, where viral DNA has been identified in the blood of patients (46). These viruses are important opportunistic pathogens, which can induce massive expansions of cross-reactive memory T-cells. Viruses can interact with the immune system at several points: during drug metabolism, during the presentation of a drug to lymphocytes by dendritic cells, and during the production of cytokine and chemokine in the effector response (47). On the other hand, certain microbes may prevent infection (48, 49). Furthermore, probiotics reduce Th2 cytokines and enhanced Th1 cytokines production and specific IgE and IgG1 (50). Therefore, it has been hypothesized that probiotics may reduce the risk for DHRs.

Conclusions

DHRs include immediate and delayed reactions that are potentially life-threatening. It remains to be understood the mechanisms of the reactions and the interactions between drug's pharmacological characteristics and variables related to the patients' health conditions and to patients' microbes. All these factors contribute to the occurrence of the DHRs.

Conflict of interest: None to declare

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Correspondence:
Fabrizio Franceschini, MD
Department of Pediatrics, Salesi Children's Hospital,
via Corridoni 11, Ancona, Italy
Tel. 0719715949
Fax 0715962234
E-mail: allped@libero.it

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Review

Clinical features, outcomes and treatment in children with drug induced Stevens-Johnson syndrome and toxic epidermal necrolysis

Lucia Liotti[1], Silvia Caimmi[2], Paolo Bottau[3], Roberto Bernardini[4], Fabio Cardinale[5], Francesca Saretta[6], Francesca Mori[7], Giuseppe Crisafulli[8], Fabrizio Franceschini[9], Carlo Caffarelli[10]

[1] Department of Pediatrics, Senigallia Hospital, Senigallia, Italy; [2] Pediatric Clinic, Foundation IRCCS Policlinico San Matteo, University of Pavia, Pavia, Italy; [3] Pediatric and Neonatology Unit, Imola Hospital, Imola (BO), Italy; [4] Paediatric Unit, "San Giuseppe" Hospital, Empoli, Italy; [5] UOC di Pediatria, Azienda Ospedaliera-Universitaria "Consorziale-Policlinico", Ospedale Pediatrico Giovanni XXIII, Bari, Italy; [6] Pediatric Department, AAS2 Bassa Friulana-Isontina, Palmanova-Latisana, Italy; Pediatric Allergy Unit, Department of Medicine, Udine, Italy; [7] Allergy Unit, Department of Pediatric Medicine, Anna Meyer Children's University Hospital, Florence, Italy; [8] UO Allergologia, Dipartimento di Pediatria, Università di Messina, Italy; [9] UOC Pediatria, Azienda Ospedaliero-Universitaria "Ospedali Riuniti", Ancona, Italy; [10] Clinica Pediatrica, Dipartimento di Medicina e Chirurgia, Azienda Ospedaliero-Universitaria, Università di Parma, Italy

Summary. Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), which can be considered a late-onset allergic reaction, can cause serious long-term sequelae. SJS/TEN are considered a spectrum of life-threatening adverse drug reactions. They have the same clinical manifestations and the only difference is in the extent of epidermal detachment. These conditions are associated with high mortality, although incidence of SJS/TEN is rare in children. SJS/TEN is an adverse drug reaction influenced by genes that involve pharmacokinetics, pharmacodynamics and immune response. Infective agents are additional influencing factors. Anticonvulsants and antibiotics, and especially sulphonamides and non-steroidal anti-inflammatory drugs, are among the drugs that were predominantly suspected of triggering SJS/TEN. No evidence-based standardized treatment guidelines for SJS or TEN are currently available. The usual treatment is mainly founded on the withdrawal of the suspected causative agent and supportive therapy. In pediatric patients, the specific therapeutic strategies are controversial and comprise systemic corticosteroids and the use of intravenous immunoglobulin (IVIG). More recently, new therapeutic approaches have been used, such as immunosuppressive therapies, including cyclosporine and TNF-α inhibitors. (www.actabiomedica.it)

Key words: drug adverse reaction, Stevens-Johnson Syndrome, toxic epidermal necrolysis**,** hypersensitivity reactions, children, skin test, specific IgE, basophil activation test, drug provocation test

Introduction

Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe cutaneous adverse reactions (SCAR) that belong to type IV hypersensitivity, mediated by immunological effect (1). SJS and TEN, which were reported for the first time in 1922, are part of the same spectrum of disease and have similar aetiology. There are differences in the extent of detached or detachable skin. SJS affects <10% of the body surface area with, SJS/TEN overlap 10%-30% of the body surface and TEN >30% (2, 3). SJS/TEN

is a severe disease, which is often life-threatening and usually drug-induced. Because of its rarity, there is a lack of epidemiologic and prospective studies. The reported incidences of SJS and TEN in adults are 3.96 to 5.3/1,000,000 for SJS and 0.4 to 1.45/1,000,000 for TEN (4, 5). Pediatric data only refer to small case series and retrospective studies (6, 7). Nevertheless, a higher incidence in pediatric age has been recently reported by a US study. The incidence was 6.3/100,000 for SJS, 0.7/100,000 for SJS/TEN overlap syndrome, and 0.5/100,000 for TEN. Children aged 11-15 years recorded the highest incidence ($p<0.001$). The highest mortality was seen in children aged 0-5 years and in children with TEN (8). The reported mortality rates at 6 weeks are comprised between 7.5% and 23% (7, 9). The increasing incidence of SJS/TEN with age is likely a result of more frequent drug prescriptions and comorbidities that modify the drug effects.

TEN and SJS/TEN overlap syndrome is associated with longer hospitalization, greater mortality, and higher hospital charges compared to SJS. The mortality associated with SJS and TEN in adults is higher than in pediatric populations (5), which are affected by long-term complications in more than half of the cases. Children show a high recurrence rate of SJS, 1 in 5 in the study by Finkelstein et al. (6), suggesting vulnerability and potential genetic predisposition.

How to recognize SJS/TEN

In several studies, prodromal non-specific symptoms lasting 1 to 7 days precede the onset of the SJS/TEN disease. They include discomfort, dysphagia and ocular pruritus, followed by high fever, respiratory symptoms and rashes with blisters or lesions causing mucosal inflammations. Skin lesions are usually preceded by a few days by inflammation and dryness of the mouth and genitalia. The oral, ocular and genital mucous membranes are gradually affected by erythema, erosion, and pseudomembranes. Patients are severely ill and bullous lesions develop fast both on skin and mucous membranes (10), often within 12 hours.

Skin lesions have variable severity and change into vesicles, bullae and extended detachable skin necrosis. When erythema is the main cutaneous finding, the diagnosis may be guided by the Nikolsky sign, in spite of not being exclusive of SJS/TEN. The Nikolsky sign (11) is defined as an epidermal detachment caused by the application of a tangential pressure on erythematous, non-blistering skin. Despite the highest involvement of the skin, multiple organ systems, such as cardiovascular, pulmonary, gastrointestinal, and urinary systems can also be affected. Several different complications are reported in SJS and TEN patients, the most common being secondary skin infection. Bacterial infection is inevitable because of epidermal detachment. Severely ill patients show various complications, such as pneumonia, hepatitis, and septicemia, and they determine the major cause of morbidities and mortalities.

Mucocutaneous complications occur in about 90% of cases and the ocular surface is one of the most frequently affected mucosal surfaces in TEN (50-67%) (12). Patients surviving from the often fatal acute stage of the disease are usually affected by major ocular sequelae, which include bilateral blinding caused by corneal scarring, and vascularization in severe cases. The complications are more severe in TEN than in SJS, except for ocular complications, such as corneal ulcerations, that were equally distributed between SJS and TEN. Furthermore, there is no correlation between the severity of skin detachment and the severity of ocular findings. In view of the persistent ocular complications, prompt eyes examination with appropriate treatment is recommended in all SJS and TEN patients (13, 14).

SJS/TEN is a very severe form of drug-induced reaction. Its differential diagnosis includes various diseases, such as drug induced linear IgA and DRESS. A drug-induced maculo papular exanthema should also be excluded, being the most common cutaneous adverse drug reaction. The Staphylococcal scalded skin syndrome (SSSS) and the erythema multiforme must be also taken into consideration.

Triggers for SJS/TEN

SJS/TEN is induced by drugs in about 60%-90% of children (6, 15, 16). A limited number of drugs are responsible for the majority of cases, especially in chil-

dren, even if more than 100 drugs have been associated with this disease (6, 7). Anticonvulsants, antibiotics and non-steroidal anti-inflammatory drugs (NSAIDs) are the more common triggers. In order to consider SJS/TEN as drug related, the affected patients must be exposed to the suspected drug within 8 weeks prior to the occurrence of the rash. The largest pediatric cohort, which was reported by Levi et al., included 80 patients and 216 matched controls below the age of 15 years. The study shows that the most frequent causative drugs were sulphonamides and anticonvulsants (phenobarbital, lamotrigine, and carbamazepine) (7). In this study, the exposure to the offending agent was reduced to 7 days before the onset of the cutaneous lesions. Because of its longer half-life, this window was extended to 3 weeks for phenobarbital. Techasatian et al. (13) have showed that antiepileptics were the most common cause (60%), followed by antibiotics (26.6%) and other drugs, such as NSAIDs and chemotherapy drugs. The most common drug in the antiepileptic drug group was carbamazepine (26.6%) followed by phenytoin, phenobarbital and levetiracetam. The antibiotic drug group included erythromycin, cefotaxime, trimethoprim-sulfamethoxasone, cloxacillin, and amoxycillin. According to the authors, the latent period from drug exposure to diagnosis was comprised between 1 and 31 days, with a mean of 10.7 days. The longest latent period was recorded for anticonvulsivants in comparison to antibiotics or other drugs (13). In a retrospective study, Egunsola et al. found that valproic acid (VPA) increases the risk of SJS/TEN in pediatric patients receiving lamotrigine (LTG). VPA inhibits hepatic glucuronidation that results in a reduced LTG metabolism and plasma levels (17). Children with SJS/TEN due to azithromicyn (18) and vancomycin (19) have been reported. In children, various pathogens, especially Mycoplasma pneumoniae and Herpes virus have been found to induce SJS (6, 15, 20) in 5%-31% of cases. Infections caused by virus (influenza, Epstein-Barr, cytomegalovirus, coxsakie, human herpes virus 6 and 7, parvovirus), bacteriae (streptococcus β-haemolyticum, group A), mycobacterium, and rickettsia are also associated with pediatric SYS/TEN (16). Infections can also act as potential cofactors. SYS/TEN has been reported to be idiopathic in 5%-18% of children and in 25-50% of adults (6, 16, 21).

Pathogenic mechanisms and genetic aspects

A full understanding of the pathogenesis is still lacking. Drug-induced SJS/TEN may be caused by dysregulation of cellular immunity. Cytotoxic T lymphocytes (CTLs) and natural killer (NK) cells (22, 23) may recognize unmodified drugs or offending drugs or their metabolites (24) presented by human leukocyte antigen (HLA) class I molecules on keratinocytes (24). When these immune cells are activated, various cytotoxic signals, including Fas/Fas ligand, perforin/granzyme B (25) and granulysin (26) are released to mediate keratinocyte apoptosis and detachment of skin and mucous membranes. T lymphocytes, particularly CD8+ lymphocytes, are present in a large amount in blister fluids and exhibit drug specific cytotoxicity in patients affected by TEN (27). Moreover, skin lesions, blister fluids/cells, peripheral blood mononuclear cells, or plasma of patients with SJS/TEN contained an increased number of cytokines that are responsible for proliferation and activation of T cells (25, 28). They include IFN-g, IL-2, IL-5, IL-6, IL-10, and IL-13. Tumor necrosis factor-alpha (TNF-alpha) is released by keratinocytes and macrophages in plasma and blister fluids and it may induce keratinocyte apoptosis (29, 30).

In the last 15 years, associations between drug-induced SJS/TEN (31) and Class I and II HLA alleles of the major histocompatibility complex (MHC) have been demonstrated by pharmacogenomic studies. In order to explain how drugs are recognized by T cells in an MHC-dependent manner, several models have been suggested, including the hapten concept/prohapten model and the p-i model (pharmacological interaction of drugs with immune receptors) (32). Moreover, a major role in the onset of SJS/TEN is played by genetic susceptibility. Carbamazepine-induced SJS is associated with HLA-B15:02 genotyping in a Han Chinese population (33), whereas an association between HLA-B58:01 and allopurinol-induced SJS/TEN has been found in a Japanese population (34). However, such association was not reported in European population. Therefore, the risk of SJS/TEN is related both to the exposure to high-risk drugs and to a genetic predisposition (27). Moreover, many genetic polymorphisms in detoxifying enzymes have

been founded, especially in the CYP450 family, that is deeply involved in drug kinetics and toxicity. Furthermore, a low N-acetylating capacity has been identified in some patients with SJS/TEN, and this aspect exposes them to the risk of SCARs (35).

Diagnostic approach

Although the diagnosis of SJS/TEN is mainly based on clinical signs and symptoms. Skin biopsy showing a typical full epidermal thickness necrosis associated with a scarce dermal inflammatory infiltrate is not always required for diagnosis.

It may be difficult to identify the exact causative agent because there is no definitive laboratory test to confirm the role of triggers. In case of a suspected diagnosis of SJS/TEN, it is necessary to obtain a detailed medical history, with a list of all new medications taken during the 8 weeks prior to the onset of the cutaneous lesions. The ALDEN score can be calculated to identify suspected culprit medications (36). The algorithm considers five items, that is to say index day, half-life, prechallenge/rechallenge, dechallenge, and notoriety.

Moreover, different serological tests and polymerase chain reaction (PCR) for diagnosing infections caused by herpes simplex virus 1 and 2, varicella-zoster virus, Epstein-Barr virus, cytomegalovirus, human herpes virus 6 and 7, parvovirus and M pneumoniae (20) should be carried out.

In spite of being useful for diagnostic purposes, a biopsy can prove to be an invasive and time-consuming procedure. Cytokine determination might be a feasible test for diagnosing SJS before performing a skin biopsy. Cytokines may be potentially important for diagnostic purposes, for prognosis and as a possible therapeutic target. Granulysin expression in CD4+ cells by flow cytometry, granzyme B production by ELISpot assay, and IFN-γ levels in cell supernatant by cytokine bead array have been investigated. Several studies have reported that patients with early-stage SJS have a higher level of serum granulysin than patients with other drug-induced skin reactions (37). The granulysin rapid test by immunochromatographic assay is a non-invasive procedure, with the additional advantage of rapid diagnosis within 15 min (19, 38 ,39). Fujita et al. found that the granulysin rapid test was helpful for an early diagnosis of SJS/TEN (38). Lin et al (39) showed that the granulysin rapid test had a sensitivity of 80% and a specificity of 95.8% for SJS/TEN at the very first stages of the disease. It must be pointed out that the prognostic role of cytokines in SJS/TEN has not been completely explained yet. Su et al. demonstrated that the progression and fatality of the illness were correlated with increased levels of IL-15 that may be used to evaluate the prognosis of SJS/TEN (40).

The lymphocyte transformation test (LTT) can be used for identifying the offending drug. It is a safe and reproducible test but its reliability is a controversial issue because it shows many false positive and negative results. In SJS/TEN it has to be performed within the first week after the onset of the rash (41). It has been recently proposed that the T-cell activation assay can be used as an alternative for the LTT to identify the culprit drugs, with a sensitivity of 80% (95%CI: 52-96%) and a specificity of 96% (95%CI: 80-99%) (42). Patch testing (43) are not considered useful in SJS and TEN. It is not indicated to perform drug challenges with suspected drugs in SJS and TEN because second episode can be extremely dangerous (44).

A severity-of-illness score for TEN (SCORTEN) is a clinically predictive score based on 7 prognostic factors and it is used to assess the risk of mortality in TEN patients. In order to obtain a better assessment of the risk of mortality, SCORTEN should be calculated within 24 hours after admission. However, SCORTEN has not received full validation in children (45).

Management and therapy in SJS/TEN children

The management of SJS and TEN is mostly conservative and requires multidisciplinary skills (Table 1). It is important to immediately discontinue the causative drug and start supportive care. It comprises monitoring of fluid balance and electrolytes, respiratory and nutritional support. An important aspect is the nutritional needs of children with SJS/TEN. The energy requirements of SJS/TEN pediatric patients are increased, and a 30% factor to resting energy requirements should be applied when calculating nutritional

Table 1. Suggested multidisciplinary approach for the management of SJS/TEN [modified from White KD et al. (71)]

support (46). Pain management includes administration of analgesics and topical anesthetics. With the aim of reducing the complications of the loss of barrier function, wound treatment is necessary and includes debridement of broken blisters, removal of necrotic skin, topical antiseptics or antibiotics, bandages (47, 48) and a warm environment (28°C). Admission to a specialized burn unit when skin involvement is > 25-30% is correlated to decrease morbidity and mortality rates (40). When clinical signs of infection occur, systemic antibiotics should be administered, always guided by systematic cultures of skin, mucosae, catheters and urine (49). An eye visit may be necessary. Psychosocial attention is necessary for a full patient care.

There is insufficient evidence that there is an effective treatment of SJS/TEN. Randomized controlled studies for the treatment of SJS/TEN are lacking because it is a rare disease, often associated with a high rate of mortality. The therapeutic role of intravenous immunoglobulin (IVIG) is related to the direct inhibition of FAS/FAS ligand interaction (50). Many studies showed that patients treated with high dose (2-4 g/kg) in the first 4 days after the beginning ok skin lesions had a better recovery and a higher survival rate (51-53). On the other hand, other studies did not found such an improvement on mortality rates (54). The therapeutic role of corticosteroids (e.g. prednisolone, methylprednisolone and dexamethasone) has also been evaluated. On one side, some studies found that corticosteroids, particularly high doses of dexamethasone were effective, especially when they are used at the beginning of the disease (55). Other studies, underlined a higher risk of complications, such as gastrointestinal hemorrhage and sepsis, and a loss of efficacy (13, 55-58). In fact, the timing for corticosteroid systemic administration, the corticosteroid type, dose and the treatment duration are still not clearly defined.

Studies in adults showed that intensive supportive care was the only therapeutic measure that reduced mortality rates (50). However, a metanalysis did not find any difference between corticosteroid, IVIG and supportive care in reducing mortality (59). Although the literature is poor, patients treated with steroids and IVIG seemed to have a better outcome (54). In recent years it has become widely suggested to administer IVIG at high dose (2-4 g/kg) for 4 days followed by corticosteroids (16), especially in case of TEN or SJS/TEN overlap (60).

Other specific treatments include cyclosporine, plasmapheresis, TNF-α inhibitors or a combination of different drugs.

Recent studies evidenced that the use of immunosuppressive treatment with TNF-α inhibitors can be useful. Infliximab and etanercept have shown to be effective at halting disease progression (61, 63, 64). In moderate-to-severe SJS-TEN patients, a TNF-α antagonist etanercept in a randomized trial showed some advantages towards corticosteroids, including a significant shorter time for skin healing and a lower incidence of gastrointestinal bleeding (65).

Patients with SJS/TEN can be effectively treated with ciclosporine (3mg/kg/die for 7 days followed by 1.5 mg/kg/die) that may improve reepithelization, prevent onset of new lesions, reduce lenght of hospitalization. Both in adults and children cyclosporine reduces mortality (66-68) compared to high dose IVIG (15, 69).

Conclusions

Studies on children with SJS/TEN are scarsely reported and limited to small case series and retrospective studies. Therefore, a definition of SJS/ TEN in children requires further work. Incidence of severe drug reactions including SYS/TEN or anaphylaxis (70) is low in children, but SYS/TEN is associated with high mortality.

Rates of mortality are lower in children in comparison with adults, but a high rate of long-term complications is reported in pediatric population. Important progress has been recently acquired in the immunogenomics and immunopathogenesis of SJS/TEN. Nevertheless, several clinical and research gaps remain (71). Biomarkers for early diagnosis and prognosis are needed. They may be detected not only in serum but also in exhaled breath, a non invasive method for the assessment of inflammation (72-74). Guidelines based on high quality trials or metananalysis (75) for the therapeutic management and genetic predictors for most drugs that cause SJS/TEN are lacking. Furthermore, the reason why only a small percentage of population (<10%) with an HLA risk allele will develop SJS/TEN after exposure to the culprit drugs is still unclear (23). In conclusion, with the aim of ensuring an early diagnosis and an effective treatment, more studies are needed for a deeper understanding of the pathogenesis of SJS/TEN.

Conflict of interest: None to declare

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Correspondence:
Lucia Liotti
Department of Pediatrics, Senigallia Hospital,
Via Cellini 1 - 60019 Senigallia (AN), Italy
Tel. +3907179092751
Fax +3907179092762
E-mail: lucialiotti@libero.it

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Review

Chronic urticaria and drug hypersensitivity in children

Carla Mastrorilli[1], Roberto Bernardini[2], Lucia Liotti[3], Fabrizio Franceschini[4], Giuseppe Crisafulli[5], Silvia Caimmi[6], Paolo Bottau[7], Francesca Mori[8], Fabio Cardinale[9], Francesca Saretta[10], Giovanni Simeone[11], Marcello Bergamini[12], Carlo Caffarelli[1]

[1] Clinica Pediatrica, Dipartimento di Medicina e Chirurgia, Azienda Ospedaliero-Universitaria, Università di Parma, Italy; [2] Paediatric Unit, "San Giuseppe" Hospital, Empoli, Italy; [3] Department of Pediatrics, Senigallia Hospital, Senigallia, Italy; [4] UOC Pediatria, Azienda Ospedaliero-Universitaria "Ospedali Riuniti", Ancona, Italy; [5] UO Allergologia, Dipartimento di Pediatria, Università di Messina, Italy; [6] Pediatric Clinic, Foundation IRCCS Policlinico San Matteo, University of Pavia, Pavia, Italy; [7] Pediatric and Neonatology Unit, Imola Hospital, Imola (BO), Italy; [8] Allergy Unit, Department of Pediatric Medicine, Anna Meyer Children's University Hospital, Florence, Italy; [9] UOC di Pediatria, Azienda Ospedaliera-Universitaria "Consorziale-Policlinico", Ospedale Pediatrico Giovanni XXIII, Bari, Italy; [10] Pediatric Department, AAS2 Bassa Friulana-Isontina, Palmanova-Latisana, Italy; Pediatric Allergy Unit, Department of Medicine, Udine, Italy; [11] Primary care Pediatrician, Local Health Unit of Brindisi, Brindisi, Italy; [12] Generalist Pediatrician, Local Health Unit of Ferrara, Ferrara, Italy

Summary. The cause of chronic urticaria remains often elusive. The association between chronic urticaria and intake of medications have been reported in children. However, the causative role of drugs has been rarely ascertained by onset of symptoms on drug provocation test. Chronic urticaria can be mediated by immunologic and nonimmunologic mechanisms. The diagnostic work-up of chronic urticaria includes a comprehensive evaluation of triggering factors such as drugs. A diagnosis is necessary in order to permit a safely administration of drugs in children with chronic urticaria. (www.actabiomedica.it)

Key words: drug hypersensitivity reactions, children, urticaria, skin test, specific IgE, basophil activation test, drug provocation test

Introduction

Chronic urticaria (CU) is a common dermatologic disease, defined as the sudden development of transient wheals and/or angioedema recurring at least two times a week and lasting longer than 6 weeks. CU affects up to 5% of the general population and it is more frequent in adults (1). Depending on whether the lesions appear spontaneously or are induced by specific triggers, current classification distinguishes spontaneous CU (sCU) and inducible CU (2). CU is considered a mast cell-driven disease that may be triggered by infections, food or drug intolerance, activation of the coagulation cascade, genetic disposition, or autoimmunity (3). Within the inducible subtype, there are physical and non-physical urticarias (4). Although, drugs are occasionally implicated in CU and they may be causative factors or aggravate CU (5). In the last years, urticaria has increasingly attracted notice to patients and their families, last but not least inspired by the involvement of allergy and adverse reactions to drugs, foods or additives. This report attempts to summarize the evidence on the role of drugs in eliciting CU in childhood. English-language studies published from 1978-November 2018 in PubMed and the Cochrane central register of controlled Trials were searched by using the following keywords: "children", "chronic urticaria", "drug allergy", "etiology", "ACE inhibitors", "nonsteroidal anti-inflammatory drugs", and "drug-induced urticaria". Systematic reviews, guidelines, clinical trials, cohort and cross-sectional studies were considered. Case reports and abstracts were

excluded. References from selected papers were also examined to find additional related articles. Identified papers were discussed and relevant articles were included in this review.

Frequency of drug-induced chronic urticaria

The association between CU and intake of medications has been investigated in several studies. However, the diagnosis has not been always demonstrated by drug provocation test that is the gold standard (6,7). In a systematic review, etiological factors of CU in children have been analyzed, mentioning drug allergy from 0 to17% of cases (Table 1) (8-12). Kozel et al (13) showed that 9% of 220 patients from secondary and tertiary referral centers had CU or angioedema caused by an adverse drug reaction that was confirmed by positive drug challenge and urticaria was cured by permanent elimination of the drug use. In a population-based study, drug intake caused CU in 1.8% of children (14). Moreover, CU was caused by drug allergy in 1/44 and 22/92 Turkish children aged 6-15 years in two different studies (15, 16). Furthermore, drugs were suspected as precipitating factors for CU among 423 patients in 7.3% of cases (17). In an observational study including 369 patients aged 5-74 years, a history of CU triggered by various medications was positive in 28.6% of patients (18). However, urticaria improved in only three cases after withdrawing the suspect medication. In a Turkish cohort of 222 children with CU, drugs were found to be the triggering factors by clinical history in 18 patients, but they were not confirmed by skin tests, if available, and drug provocation tests (19).

Which drugs?

Several drugs have reported to trigger CU in children. Volonakis et al (10) described the type of drugs, penicillin and phenobarbital, which provoked CU. Sánchez-Borges et al (17) showed that the most frequent drugs involved in CU were nonsteroidal anti-inflammatory drugs (NSAIDs) (4.2%), ACE inhibitors (1.1%), radiocontrast media (0.4%), oral contraceptives (0.2%), glyburide/metformin (0.2), losartan (0.2%), penicillin (0.2%), lorazepam (0.2%), oxcarbazepam (0.2%). Desferal was reported as offending drug by Sahiner et al (15). Sublingual immunotherapy (20), perioperative drug (21), probiotics (22,23) have not been related to CU.

Commonly, CU in adults is considered "allied" to particular conditions, such as the multiple drug allergy syndrome (MDAS) and hypersensitivity to multiple NSAIDs (24,25). Patients with MDAS report a history of reactions to several chemically unrelated antibiotic and nonantibiotic drugs. The clinical classification of cross-intolerant hypersensitivity reactions to NSAIDs includes two different cutaneous manifestations: NSAIDs-exacerbated cutaneous disease (NECD), urticaria and/or angioedema occurring in

Table 1. Characteristics of included studies on the etiologic role of drug allergy in children with chronic urticaria

Authors, year	Country	Study population (n)	Age (range, years)	Prevalence of drug allergy (%)	Diagnosis of drug allergy
Kauppinen et al. 1984 (9)	Finland	55	6 months – 16 y	0	Challenge
Volonakis et al. 1992 (10)	Greece	226	1-14	17	Challenge
Kozel et al. 1998 (13)	Netherlands	220		9	Challenge
Sackesen et al. 2004 (11)	Turkey	17	1-19	17	Clinical history
Jirapongsananuruk et al. 2009 (12)	Thailand	94	4-15	0	Clinical history
Sahiner et al. 2011 (15)	Turkey	25	0.7-17.2	1	Clinical history
Sánchez-Borges et al. 2014 (17)	Venezuela	423	2-85	7.3	Clinical history
Colgecen et al. 2015 (18)	Croatia	369	5-74	28.6	Clinical history
Uysal et al. 2016 (16)	Turkey	92	6-15	23.9	Clinical history
Lee et al. 2017 (14)	Korea	57	9.12±1.68	1.8	Clinical history
Yilmaz et al. 2017 (19)	Turkey	222	4.6-12.3	0	Skin test, Challenge

patients with a history of sCU and NSAIDs-induced urticaria/angioedema (NIUA), wheals and/or angioedema occurring in otherwise healthy children. Although NECD has been occasionally reported in patients affected by physical urticaria with persistent dermatographism, it is primarily defined in patients with sCU (26). Aspirin hypersensitivity has been reported in 24% of 58 children and adolescents with CU, performing single-blind placebo-controlled challenge (26). Aspirin caused CU or exacerbated CU in 10% to 40% of patients (27, 28).

Regarding the role of additives, allergic or pseudo-allergic reactions can be provoked by benzoic acid, butylated hydroxytoluene, sulfites, aspartame, coloring, tartrazine, and preservatives. The prevalence of reaction to food and drug additives ranges from 2%-68%. In this regard, Rajan et al (29) challenged 100 patients with CU, aged 14-67 years, to 11 different colored additives and preservatives, and found two positive responses on single-blind challenge. No patient had a positive urticarial response on double-blind placebo-controlled challenge.

Mechanisms

CU can be mediated by both type I (IgE mediated) and type II (autoantibodies) hypersensitivity reactions (30) and by nonimmunologic mechanisms. Several studies showed that up to 60% of patients with sCU had a positive intradermal autologous serum test. In these patients, serum histamine-releasing activity has been endorsed to the presence of circulating IgG autoantibodies specific either for the high-affinity IgE receptor, FceRI, or for IgE. Circulating autoantibodies would be responsible for histamine release from both basophils in healthy donors and human mast cells *in vitro* (3). The autoreactivity observed in most patients might also represent a pathogenic mechanism for allergic and pseudo-allergic reactions induced by drugs. Several studies reported that leukotriene antagonists were of benefit not only in asthmatics by perhaps reducing radical induced by peroxidation of arachidonic acid in the cell membrane such as 8-isoprostane (31) but also in patients with CU, especially due to NSAID intolerance (32), suggesting that the inhibition of cyclooxygenase (COX)-1 pathway may play a role in these drug-induced reactions (33, 34). This hypothesis was supported by the tolerance of selective COX-2 inhibitors by most patients. However, other mechanisms could be involved, and a pathogenic role may be sustained by the presence of circulating histamine-releasing factors (35,36). It may be hypothesized that offending drugs may increase or help the activity of circulating histamine-releasing factors, whereas such factors alone might not be enough to provoke symptoms.

Diagnostic work-up and management

It is challenging to ascertain a cause-effect correlation between CU and drug allergy only on the basis of history, especially at the emergency department (37). The approach to CU includes a comprehensive evaluation. It is essential to identify, when possible, the triggering factors of CU by clinical assessment. Thus, in the clinical history it must be taken into consideration the use of drugs (e.g., NSAIDs), injections, immunizations, hormones, laxatives, suppositories, ear and eye drops, and alternative remedies. Diagnostic tests to drugs (cutaneous, serum specific IgE, challenge) should be considered in case of convincing relationship between drug consumption and symptoms occurrence (38). If there is a suspicion that a medication has induced urticaria, international guidelines recommend as routine diagnostic tests a trial of withholding the drug (2). The suspected drug should be substituted by another class of agents if necessary (39). A correct diagnostic approach can be reached up after symptoms' improvement during the exclusion period and onset of symptoms on drug provocation test. Tests aimed at searching IgE sensitization to additives and pseudo-allergens are not useful (40). A diet without additives and colorants in foods and drugs additive-free diet should be recommended only when there is an history of additives ingestion associated with symptoms occurrence, or when diagnostic work-up does not allow the identification of other etiologies. If the diet is successful, an open challenge should be performed initially. If there is any objective evidence of reaction, then double-blind placebo-controlled challenge should be performed to

confirm the diagnosis (41). CU in children is often a self-limited disease, but the long-term natural history of drug hypersensitivity in children is unknown. There is no data on the evolution of drug allergy after the resolution of CU in children (42).

Conclusions

Drugs account only for a few cases of CU, but it is important to be recognized as a possible cause. Patients with CU should be asked whether they take ACE inhibitors, aspirin, and non-steroidal anti-inflammatory drugs which are the most common eliciting agents. A rapid diagnosis is necessary to permit that drugs are safely given to children with CU.

Conflict of interest: None to declare

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Correspondence:
Carlo Caffarelli
Clinica Pediatrica, Dipartimento di Medicina e Chirurgia,
Azienda Ospedaliero-Universitaria, Università di Parma,
Via Gramsci 14 - Parma, Italy
Tel. 0521702207
Fax 0521702830
E-mail: carlo.caffarelli@unipr.it

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Review

Drug reaction with eosinophilia and systemic symptoms (DRESS) in children

Francesca Mori[1], Carlo Caffarelli[2], Silvia Caimmi[3], Paolo Bottau[4], Lucia Liotti[5], Fabrizio Franceschini[6], Fabio Cardinale[7], Roberto Bernardini[8], Giuseppe Crisafulli[9], Francesca Saretta[10], Elio Novembre[1]

[1] Allergy Unit, Department of Pediatric Medicine, Anna Meyer Children's University Hospital, Florence, Italy; [2] Clinica Pediatrica, Dipartimento di Medicina e Chirurgia, Azienda Ospedaliero-Universitaria, Università di Parma, Italy; [3] Pediatric Clinic, Foundation IRCCS Policlinico San Matteo, University of Pavia, Pavia, Italy; [4] Pediatric and Neonatology Unit, Imola Hospital, Imola (BO), Italy; [5] Department of Pediatrics, Senigallia Hospital, Senigallia, Italy; [6] UOC Pediatria, Azienda Ospedaliero-Universitaria "Ospedali Riuniti", Ancona, Italy; [7] UOC di Pediatria, Azienda Ospedaliera-Universitaria "Consorziale-Policlinico", Ospedale Pediatrico Giovanni XXIII, Bari, Italy; [8] Paediatric Unit, "San Giuseppe" Hospital, Empoli, Italy; [9] UO Allergologia, Dipartimento di Pediatria, Università di Messina, Italy; [10] Pediatric Department, AAS2 Bassa Friulana-Isontina, Palmanova-Latisana, Italy; Pediatric Allergy Unit, Department of Medicine, Udine, Italy

Summary. Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) is a severe reaction to drugs. Incidence of DRESS in children is not well known and the mortality rate seems to be lower than 10%. Anticonvulsants are the main drugs involved both in adults and in children. The treatment of choice is intravenous immunoglobulins and corticosteroids used in synergy. Today there are not controlled clinical trials regarding DRESS treatment in children. Anyway, the prompt withdrawn of the offending drug is of paramount importance for a better prognosis. DRESS sequels may occur, consequently, follow-up visits are required at least until the first year after the reaction. (www.actabiomedica.it)

Key words: children, drug reaction with eosinophilia and systemic symptoms, severe cutaneous adverse reactionst

Epidemiology

Drug reaction with eosinophilia and systemic symptoms (DRESS) is a serious and potentially fatal adverse reaction to therapeutic medications. Over the last 80 years, the nomenclature of this disease has been changing from drug-induced pseudolymphoma, anticonvulsant hypersensitivity syndrome, drug induced hypersensitivity syndrome (DIHS), drug induced delayed multiorgan hypersensitivity syndrome to DRESS. DRESS is classified among severe cutaneous adverse reactions (SCARs) and in 1966 Bocquet et al. (1) identified it as a distinct clinical syndrome. Moreover, the meaning of "R" in DRESS acronym has been changed from Rash to Reaction due to the heterogeneity of skin eruptions (2). Initially, DRESS was thought to affect only adults, later it was diagnosed also in children (3).

The incidence of DRESS due to antiepileptics is in the range of 1:1000 to 1:10.000 in general population (4) and of 0.4:1000 (5) in hospital settings. In younger children the incidence of DRESS seems to be lower than in adults, although the real incidence is not known (6,7). Anyway, DRESS is more frequent than other severe immediate drug-induced reactions such as anaphylaxis (8), or exercise-induced anaphylaxis (9) but less common than food-induced anaphylaxis (10,11). The overall mortality rate is of 10% with a lower percentage in children than in adults (12-13).

Pathogenesis

DRESS is the result of a complex interplay of genetic factors [ethnic predisposition in people with certain human leucocyte antigen (HLA) alleles], immunological response, abnormalities in metabolic pathways (such as a deficiency or abnormality in epoxide hydroxylase, an enzyme that detoxifies the metabolites of aromatic amine anticonvulsants) and associated reactivations of herpes virus family members (HHV-6 and HHV-7, EBV and CMV) (14). In this context, African Americans are most likely to develop DRESS syndrome after initiation of aromatic anticonvulsants drugs whereas the Han Chinese are most likely to develop DRESS after allopurinol intake (15).

In fact, it has been found that DRESS syndrome is associated with certain human leukocyte antigens (HLAs), such as, HLA A*31:01 (aromatic anticonvulsant-induced DRESS); HLA A* 24:02 (lamotrigine-induced DRESS); HLA B*51:01, HLA B*15:13 and CYP2C9*3 (phenytoin-induced DRESS); HLA-B*57:01 and DRB1*01:01 and HLAB*35:05 (abacavir-induced DRESS) and HLA-B*58:01 (allopurinol-induced DRESS); HLA C*04:01 (nevirapine-induced DRESS) (16-19).

Apart from HLA, cytochrome P4502C9 marker has been reported to be involved in phenytoin induced SCARs (20-21).

Moreover, being a slow acetylator of drugs is thought to be a risk factor for DRESS syndrome (22).

Drugs may act as foreign antigens, binding to HLA/peptide/TCR complex and inducing hypersensitivity reactions. DRESS is a delayed type reaction according to Gell and Coombs classification (23).

There are four hypotheses regarding drug presentation mechanisms that have been suggested to explain how small drug molecules might interplay with HLA and TCR in drug hypersensitivity: (1) the hapten theory, (2) the pharmacological interaction with immune receptors (p-i) concept (i.e. carbamazepine directly interacts with HAL B*15:02) (3) the altered peptide repertoire model (i.e. abacavir binds to the F-pocket of HLA B*57:01), and (4) the altered TCR repertoire model (i.e. sulfamethoxazole directly interacts with TCR).

In delayed type reactions such as DRESS syndrome, drug antigens may activate specific T lymphocytes or natural killer cells with production of various cytokines/chemokines (i.e. TNF-α, IFN-γ, IL-2, IL-4, IL-5, TARC/CCL17, IL-6, IL-15, and IL-13) (16).

Furthermore, viruses have also been proposed to be involved in HLA/drug/TCR interactions and play an important role in drug hypersensitivity reactions, representing a source of exogenous peptides for drug presentation (24).

So far, the role of viruses in the pathogenesis of DRESS is unclear: a) Viral reactivation may be provoked by a cytokine storm secondary to an immune response against the drug (25); b) DRESS is a consequence of a strong immune response against an early viral reactivation (26). CD4+ and CD8+ drug-specific T cells proliferate after encountering the drug, but also anti-viral specific T cell can be cross-activated by drugs. In conclusion, the most common hypothesis is that the immunologic response to drugs induces a boost viral reactivation, consequently T lymphocytes and monocytes/macrophages release viruses that represents as an early marker of stimulation of these cells, rather than the triggering event in the pathogenesis of DRESS (27). In particular, toxic drug metabolites accumulation provoke an immunosuppression of B cells with hypogammaglobulinemia and subsequent viral re-activation (28). For example, in Asia and Europe the detection of HHV-6 copies in DRESS cases has been commonly reported with a frequency of 70-80%, making this data as an available diagnostic test (29, 30).

Clinical manifestations

The time onset of DRESS symptoms ranges from 2-6 weeks after initiation of treatment (2), anyway latency periods up to 105 days have been described (31).

Retrospective studies have found that the average age of occurrence of DRESS syndrome is 9 years of age in children (7,13). The most common clinical feature is fever, which is usually high grade ranging from 38-40°C. The second most common feature is macular erythema. This kind of rash later evolves in more violaceous and papular lesions with or without pruritus (Figure 1), and over time, the eruption becomes potentially exfoliative. Consequently, although

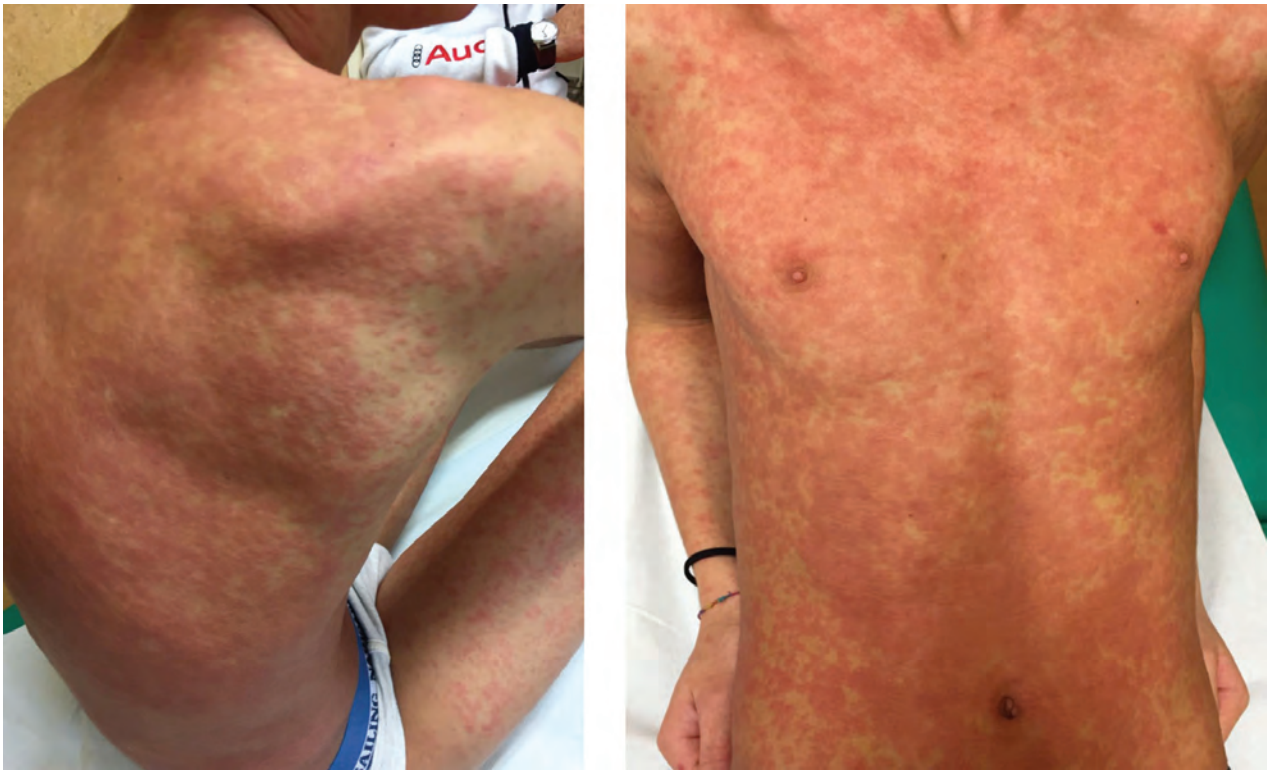

Figure 1. Acute Rash in DRESS syndrome

a maculopapular rash is the most common initial cutaneous manifestation other eruptions may be described, including targetoid, urticarial, pustular, blistering, lichenoid, exfoliative, and eczematous lesions. The skin eruption typically begins on the face associated to facial oedema and then involves the upper trunk progressively spreading at lower extremities. The skin can be involved from less than 50% of body surface to diffuse erythroderma, making consistent the cutaneous distribution of the eruption. Moreover, mucosal involvement has been frequently (>50%) described (i.e. conjunctivitis, oral mucositis and/or genital lesions) in DRESS (7).

The eruption can persist for months after the offending drug has been discontinued. Lymphadenopathy is the third most common presentation, which is seen in 70-75% of patients (32).

Haematological abnormalities, such as leucocytosis, eosinophilia, atypical lymphocytosis, thrombocytopenia and agranulocytosis commonly occur in DRESS.

Eosinophilia is typically reported in DRESS studies from both Asia and Europe with percentages ranging from 48 to 95% of patients (2, 7, 33).

Among visceral organ, liver (i.e. hepatitis) is involved in 50-80% of patients, followed by kidney (i.e. nephritis with haematuria or acute renal failure) in 11-28% of patients. Unfortunately, in some patients, hepatic injury can progress to widespread hepatic necrosis and fulminant liver failure (29, 34, 35) and it represents the leading cause of mortality in these patients (36).

Lungs (i.e. pneumonitis) are involved in 2.6-5% patients, but also muscle (myositis), gastrointestinal (i.e. colitis) heart (i.e. myocarditis), pancreas (i.e. pancreatitis), brain (i.e. encephalitis), thyroid (i.e. thyroiditis) and conjunctiva (i.e. conjunctivitis) involvements have been described (31 37). In table 1 are reported the clinical features of DRESS syndrome (29, 35, 36, 38-44). Clinical manifestations were similar between children and adults, with the exception of pulmonary involvement (excluding asthma), which was more

Table 1. Most common clinical features of DRESS syndrome and percentages of organ involvement

Fever (>38°C)	86.5%	(38)
Acute Rash	85%	(38)
Facial Swelling with periorbital involvement	27%	(38)
Lymphadenopathy	70%	(38)
Eosinophilia	60-80%	(29, 30, 38)
Liver: Hepatomegaly and/or increase liver enzymes (AST/ALT) and/or hyperbilirubinemia; elevated Alkaline phosphatase (30)	51-84%	(35, 36, 40-41)
Kidney: Elevation in creatinine Decrease in glomerular filtration rate (GFR) Proteinuria Haematuria *Allopurinol is most commonly implicated with renal involvement (36)	11-57%	(35, 40-41)
Lungs: Interstitial pneumonitis Pneumonia Pleural effusion Acute respiratory distress Syndrome (ARDS) *Minocycline, Allopurinol, Abacavir are most commonly implicated with lung involvement (26, 37)	2.6-5%	(29, 36)
Non specific Gastrointestinal Symptoms: Colitis Diarrhoea with or without electrolyte abnormalities	8%	(35, 42)
Heart: Late onset Myocarditis (Troponin and CKMB elevated)	4-27%	(43,44)
Tachycardia, arrhythmias, chest pain, non specific ECG changes, gross ST segment, elevation or depression, decrease in LV ejection fraction * Ampicillin is most commonly implicated with heart involvement		

frequent in adults, and gastrointestinal involvement, which was more frequent in children (42).

Drugs Involved

More than 40 medications have been described as triggers of DRESS and among various drugs, aromatic antiepileptics are reported to be the most common cause followed by antibiotics. Moreover, aromatic anticonvulsants show cross-reactivity in 40-80% of cases while non aromatic anticonvulsants are well tolerated as alternative choice in case of reactions to aromatics. Anyway, data about DRESS in children are scarce and mostly come from case reports. In the study of Misirlioglu et al (45), antibiotics were the most common (50%) medication in the aetiology; 87.5% of the suspected antibiotics were beta-lactams, and 12.5% were macrolides. Antiepileptics were second (37.5%, n. 6) most common class of drugs in the aetiology. In Table 2 we reported the drugs most frequently involved in DRESS syndrome in children in the last ten years. Studies where children were included but not clearly specified in terms of age and culprit drugs, were excluded.

Table 2. Most frequently reported drugs causing DRESS syndrome in children

Single case or less than 10 children (mean age 7,6 years) (46-114)	• carbamazepine 14/103 (13.6%) • phenytoin 12/103 (11.7%) • phenobarbital 9/103 (8.8%) • valproic acid 6/103 (5.9%) • vancomycin 5/103 (5%) • lamotrigine 4/103 (4%) • cefotaxime 4/103 (4%) • trimethoprim-sulfamethoxazole 4/103 (4%) • ceftriaxone 3/103 (3%) • levetiracetam 3/103 (3%) • dapsone 3/103 (3%) • clindamycin 2/103 (2%) • piperacillin-tazobactam 2/103 (2%) • azithromycin 2/103 (2%) • oxacarbamazepine 2/103 (2%) • minocycline 2/103 (2%) • sulfadiazine 2/103 (2%) • oxacilline 2/103 (2%) • penicillin 2/103 (2%) • cefixime 1/103 (0.9%) • naproxen 1/103 (0.9%) • canakinumab 1/103 (0.9%) • amoxi-clav 1/103 (0.9%) • anakinra 1/103 (0.9%) • tobramycin 1/103 (0.9%) • ibuprofen 1/103 (0.9%) • acetylsalicylic acid 1/103 (0.9%) • griseofulvine 1/103 (0.9%) • sulthiame 1/103 (0.9%) • infliximab 1/103 (0.9%) • fluoxetina 1/103 (0.9%) • cefepime 1/103 (0.9%) • allopurinol 1/103 (0.9%) • perampanel 1/103 (0.9%) • cefditoren-pivoxil 1/103 (0.9%) • paracetamol 1/103 (0.9%) • Ethambutol+rifampin+pyranzinamide 1/103 (0.9%) • pyrimethamine 1/103 (0.9%) • rufinamide 1/103 (0.9%)
32 children (mean age 8,9 y) (13)	• 13 carbamazepine • 12 phenytoin • 5 phenobarbital • 5 lamotrigine • 1 primidone • 1 oxcarbamazepine
33 children (mean age 5,8 y) (115)	• 18 phenobarbital • 15 phenytoin

(continued)

Table 2 ***(continued)*****.** Most frequently reported drugs causing DRESS syndrome in children

29 children (mean age 11 y) (116)	• 10 trimethoprim-sulfamethoxazole • 3 phenytoin • 3 amoxicillin • 2 cefalosporins • 2 lamotrigine • 2 minocyclin • 2 macrolids • 2 oxcarbamazepine • 1 carbamazepine • 1 clindamycin • 1 zonisamide
11 children (mean age 6,6 y) (117)	• 4 lamotrigine • 1 cefotaxime • 2 carbamazepine • 1 phenytoin + phenobarbital • 3 amoxi-clav
16 children (mean age 8,2 y) (45)	• 3 amoxi-clav • 1 ampicillin-sulbactam • 2 cefdinir • 1 cefotaxime • 1 clarythromycin • 3 carbamazepine • 1 lamotrigine • 1 phenytoin • 1 phenobarbital • 1 sulfasalazine • 1 oxymetazoline nasal spray

Diagnosis

Due to the variability of its presentation, DRESS is known as "the great mimicker" making difficult the diagnosis (118). In particular, DRESS symptoms resemble those of cutaneous and systemic infectious diseases and can appear up to 3 months after the initial culprit drug exposure. The allergy work-up should start with a detailed record of clinical history by focusing on the chronology of drug assumptions and physical examination. Laboratory testing is fundamental, it should include liver, and kidney functions, search for viral infections, complete blood count and coagulation testing.

There are no clear and specific histopathological patterns in skin biopsy that are characteristic of DRESS Syndrome. Maculopapular exanthema (MPE) may be the initial presentation of SCARs including DRESS (119-120). When comparing DRESS with MPE, skin biopsies showed differences in terms of inflammatory infiltrate, atypical lymphocytes, keratinocyte damage, dermal involvement and leukocytoclastic vasculitis, these characteristics being more frequently observed in DRESS cases than in MPE cases (86, 121). Few necrotic keratinocytes were associated with non-severe DRESS cases, otherwise high amount of necrotic keratinocytes with confluent necrotic areas were associated with severe DRESS, respectively. Anyway, the role of skin or lymph node biopsies remains controversial (119).

Eosinophilia is a diagnostic criterion for DRESS. In physiologic conditions, eosinophils are not present in skin, liver, lungs or other internal organs otherwise in DRESS, eosinophils are typically increased in blood, in skin and in involved organs. Eosinophils infiltrate

organs in response to cytokines and chemokines including eotaxin-1, TARC, IL-5 and granule release representing key factors of tissue damage (122).

The discovery of biomarkers of drug hypersensitivity could be useful for the diagnosis of DRESS syndrome. In DRESS cases, serum TARC levels have been reported to be significantly higher than those in patients with Steven-Johnson Syndrome (SJS)/Toxic epidermal necrolysis (TEN) and MPE during the acute phase and to be correlated with skin eruptions (122). For this reason, TARC could be considered a potential biomarker for the early phase and disease activity of DRESS syndrome.

Re-challenging with the offending drug has been considered the gold standard to diagnose drug eruptions, but in suspected DRESS cases, it should not be used because of the life-threatening nature of this syndrome (2, 123). Patch tests can be useful to prove a drug-specific immune response in DRESS syndrome (124). On the contrary, patch tests to different allergens such as foods have a low diagnostic accuracy (125). In vivo patch tests represent a low-risk method for reproducing delayed hypersensitivity by re-exposing patients to low amount of suspected offending drugs. Anyway, the sensitivity and specificity of patch tests are different according to the drug tested.

The lymphocyte transformation/activation test (LTT/LAT) measures the proliferation of T cells to a drug (126, 127). Unfortunately, it is not standardized for many medications and it is difficult to perform. Furthermore, it usually yields a negative result early in the course of the syndrome, and lacks sensitivity. A positive LTT/LAT is useful to confirm the diagnosis due to very low false positive results (only 2%), however a negative test cannot exclude the diagnosis (128). All these factors prevent widespread use of this test.

For the diagnosis of DRESS syndrome different criteria can be used such as Bocquet's criteria (1), The European Registry of Severe Cutaneous Adverse Reactions to Drugs and Collection of Biological Samples (RegiSCAR) criteria (7) and the Japanese group of Severe Cutaneous Adverse Reactions to Drugs (SCAR-J) criteria (Table 3). The RegiSCAR is most often used to diagnose DRESS (129), it is based on seven independent parameters and three of them are required for the diagnosis of DRESS. According to RegiSCAR, the diagnosis of DRESS can be definite (score >5), probable (score 4-5), possible (score 2-3) and no (score <2) DRESS syndrome.

Differential Diagnosis

DRESS should be differentiated from viral exanthemas especially EBV infectious mononucleosis, staphylococcal and streptococcal shock syndrome, meningococcemia, non infectious drug eruptions (e.g. SJS/TEN), autoimmune diseases (e.g. hypereosinophilic syndrome, Kawasaki disease, Stills diseases), urticaria vasculitis (130), neoplastic diseases (e.g. leukemia cutis, pseudolymphoma, mycosis fungoides), serum sickness like reaction, and atopic eritrodermia. In the last, for example, nephritis and hepatitis are lacking, being caused by bacterial infections (131).

Depending on organs involved, the differential diagnosis also includes viral hepatitis (liver), parasitic infection (gastrointestinal tract) and bacterial, viral and fungal pathogens (lung) (36).

Treatment

So far, there have been no prospective clinical trials on treatment of DRESS syndrome. Current recommendations are based on case reports and expert opinion (132). The first and most important step in treatment of DRESS is withdrawal of the causative drug, because a better prognosis is associated with an earlier discontinuation of the drug.

In mild forms, treatment is mainly supportive and symptomatic, consisting of topical steroids, systemic anti-H1 antihistamines and emollients for rash and itching. In patients with exfoliative dermatitis a prompt and appropriate fluid, electrolyte and nutritional support is of primary importance. In moderate cases without visceral involvement, corticosteroids are usually adequate (133).

In case of organ involvement, such as liver (transaminases >5 times upper limit of normal), kidney, lungs or heart, the expert opinion of French Society of Dermatology recommended to administer corticosteroid (prednisone, 1 mg/kg/day per os). Several aspects

Table 3. Three proposed diagnostic criteria of DRESS syndrome

	Bocquet et al. (1)	RegiSCAR (7)	J-SCAR (129)
Requirement for diagnosis	≥3 criteria	≥3 criteria of the following asterisk marks	all 7 criteria = typical without 2 asterisk marks = atypical
History		- hospitalization - reaction suspected to be drug related	- symptoms persisting at least 2 weeks after drug discontinuation
Fever		- fever ≥38°C*	- fever ≥38°C
Cutaneous finding	- acute drug eruption	- acute rash	- macular rash developing 3 weeks after starting offending drug
Hematologic abnormalities	- eosinophilia >1.5×109/L or atypical lymphocytosis	one of the following hematologic abnormalities - eosinophilia over laboratory limits - lymphocyte count over and under normal limits - thrombocytopenia under laboratory limits	one of the following hematologic abnormalities - leucocytosis (>11×109 /L) - atypical lymphocytes (>5%) - eosinophilia (>1.5×109 /L)
Other organ involvements	- lymphadenopathy ≥2 cm in diameter - hepatitis with liver transaminases ≥2 times of the normal values - interstitial nephritis - interstitial pneumonitis - carditis	- lymphadenopathy involving ≥2 sites* - at least 1 internal organ involvement*	- lymphadenopathy* - liver abnormalities (ALT >100 U/L)
Viral reactivation			- HHV-6 reactivation*

(i.e. optimal dose, route of administration, duration of treatment, and rapidity of dose tapering) of steroid treatment have not been compared in controlled trials (119). Tapering should take three to six months of time because rapid taper can be associated with relapse of DRESS (119, 134, 135). Systemic steroid therapy is advised to treat cases of moderate to severe disease taking into account the dramatic improvement in symptoms and frequent relapses of DRESS associated with quick prednisone taper. For all these reasons, intravenous pulses of methylprednisolone (1 g/d) are recommended especially in patients worsening despite adequate doses of oral corticosteroids (52).

Proposed mechanism by which corticosteroids benefit the patient is inhibition of IL-5, which attracts eosinophils, which are responsible for visceral organ damage by accumulation in DRESS syndrome (35). For the same reason, some authors proposed the use of mepolizumab (anti IL-5) in the treatment of DRESS (136).

Today, cyclosporine may be considered a second-line therapy for patients with severe organ involvement who do not respond to systemic corticosteroids and for patients in whom corticosteroids are contraindicated (137). Intravenous immunoglobulins (IVIG) have been reported to be useful in a few patients with DRESS and detrimental in others (138). Periodical controls (both clinical and laboratory parameters) are necessary to check progression of the skin eruption and/or development of clinical fatal life-threatening signs, which include hemophagocytosis with bone marrow failure, encephalitis, severe hepatitis, renal

failure, and respiratory failure requiring treatment with steroids generally administered at a dose of 2 g/kg over 5 days with IVIG. The largest series of paediatric patients have been described by Marcu N et al. (62) who reported 7 patients with severe DRESS in whom treatment with IVIG (1-2 gr/kg) in addition to systemic corticosteroids was successful. One possible explanation is that IVIG preparations contain antiviral neutralizing antibodies that help clear the viral infection/reactivation found to be fundamental in the pathophysiology of DRESS. Anyway, IVIG should not be administered in the absence of steroids.

Due to the fact that there is a major viral reactivation along with presence of life-threatening signs, it has been proposed to administer anti-viral medications (e.g. ganciclovir) in combination with steroids with or without IVIG but the efficacy is unclear (139).

In severe and corticosteroid-resistant cases, more potent immunosuppressant medications including cyclosporine, azathioprine, rituximab, infliximab and mycophenolate have been used, sometimes alongside adjunctive treatment with IVIG and plasmapheresis (42, 66, 140, 141). N-acetyl cysteine (NAC), which acts as detoxifying drug, can also be used in DRESS.

Finally, the treatment of DRESS syndrome should be started immediately after diagnosis, even if the result of viral markers are still ongoing. Further studies with appropriate designs (i.e. randomized controlled trials) are needed to establish a standard of care in DRESS. Such studies should also assess the potential application of anti-viral drugs or probiotics for treating infections (142, 143, 144).

Prognosis

After withdrawal of the causative drug, most of the patients need some weeks to completely recover. The prevalence of sequelae is unknown. Long-term sequelae may be renal failure, chronic anaemia, autoimmune diseases (autoimmune thyroid disease, diabetes mellitus type I, systemic lupus erythematous (SLE), systemic sclerosis, adrenal insufficiency and autoimmune haemolytic anaemia). For example, thyroiditis has been reported in the 12.5% of children with a previous DRESS (7).

Moreover, recurrence of DRESS with unrelated drugs can be observed in 25% of cases, whereas very little or no flares are reported in patients after SJS/TEN (145, 146).

Those manifestations can occur months to years following the initial episode and awareness of association with a drug administration is crucial to promptly recognise and treat a possible DRESS. Follow-up visits at 2, 3, 4, 5, 6, 12 months and then once a year are recommended (146, 148).

Conflict of interest: None to declare

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Correspondence:
Mori Francesca, M.D.
Allergy Unit, Anna Meyer Children's Hospital,
Department of Pediatrics, University of Florence
Viale Pieraccini, 24 - 50139 Florence, Italy
Tel. +39-055-5662034
Fax +390555662902
E mail: f.mori@meyer.it

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Review

Hypersensitivity reactions to food and drug additives: problem or myth?

Laura Andreozzi[1], *Arianna Giannetti*[1], *Francesca Cipriani*[1], *Carlo Caffarelli*[2], *Carla Mastrorilli*[2], *Giampaolo Ricci*[1]

[1] Pediatric Unit, Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy; [2] Clinica Pediatrica, Azienda Ospedaliero-Universitaria, Dipartimento di Medicina e Chirurgia, Università di Parma, Parma, Italy

Summary. *Background and aim of the work:* The possibility of an allergic reaction or an intolerance to additives is frequently suspected by parents, especially for chronic illness with frequent exacerbations such as atopic dermatitis or chronic urticaria. For more than 50 years, potential adverse reactions to additives have been suggested, but to date data are conflicting. The purpose of this article is to provide the clinicians with general information about additives and adverse reactions to them and to suggest a practical approach to children suspected to have reactions to food additives. *Methods*: We performed an extensive research on all English-language Medline articles, case reports and reviews published online until December 2018. Used search terms were: food additives, food dye, adverse reactions, food allergy, food hypersensitivity, intolerance, drugs, children. *Results*: There are only few case reports of adverse reactions in childhood with a clear involvement of additives. In this review article we reported the associations between additives and adverse reactions described in literature, in order to inform the pediatrician about the potential clinical manifestations. *Conclusions*: Prior to suspect an adverse reaction to additives, it is important to rule out other possible causes: the diagnostic process is complicated and rarely conclusive. The gold standard is the double-blind placebo controlled oral challenge after an exclusion diet. (www.actabiomedica.it)

Key words: food additives, food dye, adverse reactions, food allergy, food hypersensitivity, intolerance, drugs

Introduction

Additives are substances used in the food industry for many purposes, such as to preserve food, to improve its taste or appearance. The earliest record of a food additive date from the ancient Egypt, around 1500 BC, when natural extracts were added to candies to make them more appealing (1).

The Food and Drug Administration (FDA) updates an online list of these food additives that nowadays includes more than 3000 substances (*https://www.fda.gov/food/ingredientspackaginglabeling/foodadditivesingredients/ucm094211.htm*). Prior their use in foods, they must pass a premarket safety evaluation in accordance with a specific food additive regulation from specific government agencies, such as the FDA in the United States or the European Food Safety Authority (EFSA) in Europe (2).

A specific group of food additives named "Generally Recognized As Safe" (GRAS) includes about 1000 substances that are considered safe by experts and are exempted from the usual tolerance requirements (3).

The widespread use of additives has caused concern among consumers about the possibility of adverse reactions, but few scientific data are available. Recently, the American Academy of Pediatrics (AAP) has given rise to doubts regarding the safety of GRAS in children (4).

The purpose of this article is to provide the reader with general information about food and drug additives and adverse reactions to these substances and to suggest a practical approach to children suspected to have reactions to additives.

Definitions of food additives and classification

Food additives are defined according to their specific functions. Several definitions are available, that are similar to each other (Table 1).

According to the Joint FAO/WHO Expert Committee on Food Additives (JECFA), an international expert scientific committee administered jointly by the Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO), food additives are "substances added to food to maintain or improve its safety, freshness, taste, texture, or appearance".

The definitions used by the FDA and the EFSA point out that these substances are added to food intentionally.

Food additives generally have the following characteristics: 1- synthetic and natural substances; 2- they cannot be consumed alone as food themselves; 3- the purpose of addition is to improve the quality, color, fragrance, flavor of food, and to meet the demands of preservation, freshness and processing (1).

More than 3000 food additives are listed by the FDA, and they can be classified into different groups according to their function and property: preservatives, sweeteners, color additives, flavors and spices, flavor enhancers, fat replacers, nutrients, emulsifiers, stabilizers and thickeners, binders, texturizers, pH control agents and acidulants, leavening agents, anti-caking agents, humectants, yeast nutrients, dough strengtheners and conditioners, firming agents, enzyme preparations, gases.

Some substances used as food additives can also be contained in some medications or cosmetics. Children suspected to have an adverse reaction to a food additive might need to avoid medicines and cosmetics that contain them.

Additives can be found in all kinds of food and beverages (Table 2). In 2011, EFSA provided a list of food in which additives cannot be used (Table 3) (5).

Epidemiology

To date, few studies have investigated the prevalence of adverse reactions to food additives. Contrary to the general public perception, the prevalence of these reactions seems to be rather low.

According to some studies the prevalence in adults is estimated to be less than 1%, while it seems to be higher in children (1-2%) (6-8). Atopic children appear to be more likely to have adverse reactions to food additives (7, 9).

The estimated low prevalence of adverse reactions to food additives contributes to make the diagnosis a true challenge for the clinician.

Table 1. Main definitions of food additives by different government agencies

Last updated on January 31, 2018	United States	JECFA www.who.int	Substances added to food to maintain or improve its safety, freshness, taste, texture, or appearance.
Last updated on February 7, 2018	United States	FDA www.fda.gov	Any substance the intended use of which results or may reasonably be expected to result - directly or indirectly - in its becoming a component or otherwise affecting the characteristics of any food.
Last updated on November 30, 2018	Europe	EFSA www.efsa.europa.eu	Food additives are substances added intentionally to foodstuffs to perform certain technological functions, for example to colour, to sweeten or to help preserve foods.
Last updated on March 18, 2012	Europe	EAACI www.eeaci.org	Food additives are a large and varied group of substances added to food to, for example, prevent growth of microorganisms, give colour or flavour, improve texture or prevent browning.

Table 2. Main additives in foods and beverages

Substances	Foods and beverages
Food colorants[§]	
Carmine*	Cheese, fruit and vegetable preparations, jams, chewinggum, breakfast cereals, meat products (salami, sausages), processed fish and fishery products, soups, sauces, dietary products, desserts, snacks, alcoholic and non-alcoholic drinks.
Annatto*	Cheese, breakfast cereals, processed fish and fishery products, desserts, jams, processed potato products, meat products, soups, sauces, noodles.
Tartrazine	Cheese, canned or bottled fruit or vegetables, soups, processed fish or fishery products, pickles, desserts, sauces, seasonings, flavoured processed cheese, dietary products, non-alcoholic flavoured drinks.
Spices*	Pudding and pie fillings, gelatin dessert mixes, cake mixes, salad dressings, candies, soft drinks, ice cream and sauces, Asian dishes
Saffron	Soups, bouillabaisse, sauces, rice dishes (paella, "risotto alla milanese"), cakes, cheese, liqueurs
Preservatives	
Butylated Hydroxyanisole, Butylated Hydroxytoluene[§]	Cereal-based snack foods, cereals, soups, sauces, dehydrated meat, dehydrated potatoes, chewing gum, seasonings and condiments, fats and oils, cake mixes
Sulfites*[§]	Dried fruits, fresh fruits, frozen fruits, canned or bottled fruit and vegetables, fruit and vegetable preparations, jam, processed potato products, cereals, starches, meat preparations (sausages), processed fish and fishery products, seasoning and condiments, snacks, desserts, fruit juices, flavored drinks, wine, beer, other alcoholic drinks.
Sweeteners	
Aspartame[§]	Canned or bottled fruit and vegetables, jam, chewing gum, breakfast cereals, processed fish and fishery products, soups, sauces, dietary foods, beer and malt beverages, soft drink, diet soda, desserts, snacks.
Flavor Enhancers	
Monosodium glutamate (MSG)	Processed cheese, fats and oils, fruit and vegetable preparations, processed potato products, cocoa and chocolate products, chewing gum, breakfast cereals, gluten-free and hypoproteic pasta, noodles, bread and rolls, processed fish and fishery products, processed eggs and egg products, seasonings and condiments, soups, sauces, dietary foods, glute-free products, non-alcoholic and alcoholic beverages, desserts, meat products.

[§] These additives can also be found in medications.
* These additives can also be found in cosmetics.

Reactions to food additives

Food hypersensitivity is defined as an adverse reaction to food or a food additive and can be mediated by two different mechanisms: immunologic and non-immunologic.

Immunologic reactions are divided into 3 groups: IgE-mediated (allergic reactions), non-IgE mediated (cell-mediated) or both.

On the contrary, non-immunologic reactions do not involve the immune system and they are also defined "food intolerances". They subtend metabolic, pharmacological, toxic and undefined mechanism.

IgE-mediated reactions are quite uncommon but can be severe and life-threatening. Natural additives contain molecules of sufficient molecular weight to induce an IgE-mediated response (10). On the contrary, synthetic additives are more likely to act like haptens, because of their low molecular weight. Haptens can induce an IgE-mediated response only if they are attached covalently to a large carrier molecule (10).

Table 3. Foods in which the presence of an additive may not be permitted according to EFSA (EU Commission 2011) (5)

"Unprocessed foods" (a food which has not undergone any treatment resulting in a substantial change in the original state of the food, for which purpose the following in particular are not regarded as resulting in substantial change: dividing, parting, severing, boning, mincing, skinning, paring, peeling, grinding, cutting, cleaning, trimming, deep- freezing, freezing, chilling, milling, husking, packing or unpacking)
Honey
Non-emulsified oils and fats of animal or vegetable origin
Butter
Unflavoured pasteurised and sterilised (including UHT) milk and unflavoured plain pasteurised cream (excluding reduced fat cream)
Unflavoured fermented milk products, not heat-treated after fermentation
Unflavoured buttermilk (excluding sterilised buttermilk)
Natural mineral water and spring water and all other bottled or packed waters
Coffee (excluding flavoured instant coffee) and coffee extracts
Unflavoured leaf tea
Sugars
Dry pasta, excluding gluten-free and/or pasta intended for hypoproteic diets

Clinical manifestations

The spectrum of clinical manifestations is variegated. Most of the studies investigated adverse reactions to food in adult population and little is known about these manifestations in children.

Food additives can be responsible of the onset of new symptoms, ranging from *mild* manifestations (i.e. flushing or rhinorrhea) to life-threatening situations (i.e. anaphylaxis), or can be the cause of worsening pre-existent diseases, such as atopic dermatitis (AD).

The manifestations caused by a specific food additive can vary from patient to patient.

Food dyes are usually added to food, beverages, medications and cosmetics to make them more appealing and/or to enhance their color. They have been associated with many adverse reactions, mainly described in adults. Few studies are available about these reactions in children.

Carmine, a natural red dye, has been implicated in urticaria/angioedema, recurrent intermittent bouts of generalized systematized dermatitis (11), asthma (12, 13, 14) and anaphylaxis (15-17) in adults.

Two studies (11, 18) reported carmine as cause of intermittent flares of atopic eczema (AE) in children.

Annatto is a deep yellow or orange food coloring which is added to food and cosmetics. To our knowledge, only two studies have reported adverse reactions to this additive in children, consisting both in urticaria and angioedema (19, 20). In adults, the potential role of Annatto in inducing anaphylaxis has been described (21).

Tartrazine has been frequently linked to different illnesses such as Chronic Idiopathic Urticaria (CIU), recurrent intermittent flares of AE and fixed drug eruption in children (22-25). In 2003 Nettis et al. found that, in adults, the percentage of acute urticaria and/or angioedema induced by tartrazine, investigated with a Double Blind Placebo Controlled Food Challenge (DBPCFC), is very low (about 1%) (26).

The ingestion of tatrazine was also associated with irritability, restlessness and sleep disturbance in some children, with a dose-response effect (27).

Spices are usually added to pudding and pie fillings, gelatin dessert mixes, cake mixes, salad dressings, candies, soft drinks, ice cream and sauces.

Exposure to spices is highest in adults than in children with a particular frequency in certain occupa-

tions, such as spice factory workers, butchers, bakers, chefs, restaurant workers, and florists (28).

In adults, spices seem to be responsible of: a) irritant effects (i.e. irritant contact dermatitis, sneezing, rhinorrhea, ocular itching, conjunctival injection, tearing, or cough); b) IgE-mediated reactions (i.e. rhinoconjunctivitis, asthma, urticaria, angioedema, anaphylaxis, gastrointestinal symptoms); c) Non IgE-mediated immunologic reactions (i.e. allergic contact dermatitis) (28).

Spices-induced angioedema and anaphylaxis have been described in children (29-31) and spices seem to be also responsible of exacerbations of AE in children (32).

Saffron, which is widely used as spice or as coloring agent, was associated to symptoms of allergic rhinoconjunctivitis (sneezing, rhinorrhea, nasal obstruction, and conjunctivitis) in a 12-year-old boy, after performing a DBPCFC (33).

Preservatives are commonly added to prevent food spoilage and changes in food color, flavor and texture. Butylated Hidroxyanisole (BHA) and Butylated Hydroxytoluene (BHT) are useful preservatives due to their antioxidant capacity. They have been associated with exacerbations of CIU in studies involving adult patients (34-36). BHT can also be found in some medications, such as multivitamin (oral suspension) or in resin-based dental sealants (37, 38). To our knowledge there are no studies or case reports about adverse reactions to BHA or BHT in children.

Sulfiting agents in the form of sodium salts (i.e. sodium metabisulfite) and potassium salts (i.e. potassium bisulfite) are used as preservatives in the food and pharmaceutical industries. They reduce microbial spoilage and act as an antioxidant in some medications.

Sulfite sensitivity occurs more often in asthmatic patients (39). In adults, dermatologic, respiratory and gastrointestinal manifestations have been described, such as contact dermatitis (40), bronchoconstriction (41) and abdominal cramps with diarrhea (42). Bronchoconstriction has been described, with a greater frequency in adults than children (39, 43, 44). Recently, recurrent events of urticaria and angioedema following sodium metabisulphite ingestion in a five-year-old female has been described (45). Sulfites contained in medicines and cosmetics can be also responsible of adverse reactions (37, 46).

Sweeteners are food additives used to improve sweetness with or without extra calories. Aspartame is an artificial sweetener present in several sugar-free products, as well as in some medications and vitamin supplements. A case study conducted in a 11-years-old patient, demonstrated the resolution of Systemic Contact Dermatitis (SCD) after dietary restriction, cessation of montelukast chewable tablets (which contained aspartame) and all personal health products containing aspartame (47). Studies in adults showed a correlation between daily aspartame intake and chronic headache, but this was not confirmed among children (48, 49, 50). A recent study found a correlation between consumption of aspartame in artificially sweetened soft drinks and early menarche (51).

Monosodium Glutamate (MSG) is a flavor enhancer and it is used in many processed foods. It is included in the GRAS group by the FDA classification. In 2017, EFSA re-assessed the safety of glutamates used as food additives and derived an acceptable daily intake (ADI) (*https://www.efsa.europa.eu/en/efsajournal/pub/4910*).

In 1968, MSG was associated to the well-known 'Chinese restaurant syndrome' characterized by several symptoms, such as tightness, burning or numbness in the face, neck and upper chest (52).

MSG have been considered responsible of many manifestations in adults, such as exacerbations of unstable asthma (53) or CIU (54, 55). Over the last two decades, some studies investigated the relation between MSG ingestion and asthma or bronchospasm in adults, but with conflicting results (56). No studies have been conducted on children about the role of MSG in exacerbate chronic asthma. In 2012 a Cochrane review about MSG and chronic asthma in adults and children concluded that there is no evidence to support the avoidance of MSG in all patients (57).

MSG has been associated with CIU not only in adults, but also in children (22, 58). In 2000, Simon demonstrated that MSG is an unusual (<3% at most) exacerbant of CIU in adults (59).

Table 4. Most common food additives and their adverse reactions in children.

Food colorants	
Carmine	Recurrent intermittent flares of atopic eczema (11, 18)
Annatto	Urticaria/angioedema (19, 20)
Tartrazine	Recurrent intermittent flares of atopic eczema (24) Chronic Urticaria (22, 23) Fixed drug eruption (25) Irritability, restlessness and sleep disturbance (27)
Spices	Angioedema and anaphylaxis (29; 30; 31) Exacerbations of AE (32).
Saffron	Allergic rhinitis (33)
Preservatives	
Butylated Hidroxyanisole, Butylated Hydroxytoluene	No studies in children.
Sulfites	Bronchoconstriction (43, 44) Urticaria and anaphylaxis (45)
Sweeteners	
Aspartame	SCD (47) Chronic headache (not confirmed in children) (48, 49, 50) Early menarche (51).
Monosodium glutamate	CIU (22, 58)

Reactions to drug additives

Additives can also be added to medicinal products as excipients. An excipient is any component of the medicinal product other than the active substance. Excipient can be found in any medicinal product and every excipient can be responsible of hypersensitivity reactions to the specific drugs.

Food dyes can be easily found in many drugs. Tartrazine is a food dye that has been associated with hypersensitivity reactions. The first report of a reaction to drugs containing tartrazine was in 1959 (60). It is thought that these reactions, occur most commonly in patients with acetylsalicylic acid (ASA) sensitivity (61). As it is described for tartrazine added to food, this food dye contained in medications can cause urticaria and/or angioedema (60-62).

A fixed drug eruption to tartrazine in children has been also described (25).

One of the most widely used drug excipient is lactose. It is used as a stabilizing agent, for example in inhaled corticosteroids, daily used for patients diagnosed with asthma. Even if rarely, a life-threatening event can occur after using one of these medications containing lactose in patients with cow's milk protein allergy (63). In literature, only one case describes anaphylaxis after the use of lactose-containing inhaled corticosteroids (64). More recently a case of refractory asthma exacerbation in a child with cow's milk protein allergy resulting from a hypersensitivity reactions to lactose-containing medications, has been described (63).

Among sweeteners, aspartame can be used as an excipient in some medications such as montelukast chewable tablets. A case study conducted in a 11-years-old patient, demonstrated the resolution of Systemic Contact Dermatitis (SCD) after dietary restriction, cessation of montelukast chewable tablets and all personal health products containing aspartame (47).

Parabens are aliphatic esters of parahydroxybenzoic acid and include methyl, ethyl, propyl, and butyl parabens. Sodium benzoate is a closely related sub-

stance usually reported to cross-react with the other compounds noted above. These agents are widely used as preservatives in foods and drugs and are clearly recognized as causes of severe contact dermatitis (65). There are three reports (66-68) of hypersensitivity reactions to parabens in the medical literature, a concern purported sensitivity to local anesthetics. Other studies (69-72), supported by clinical data, have shown the relevance of benzoates in adverse drug and food reactions such as eczema, asthma, urticaria and skin contact reactions. Balatsinou et al. (69) reported two cases of sensitivity to benzoates. The first patient (5 years old, male) had also shown adverse reactions (asthma, urticaria, angioedema) after drinking beverages such as "Coca-Cola" and orange-juice or eating mayonnaise and had several asthma attacks usually after taking drugs (syrups or suppositories) prescribed for colds. The second child presented a similar history of asthma worsened by oral formulation of anti-asthmatic or anti-inflammatory drugs usually prescribed for cold or flu and persistence or worsening of asthma after oral betamethasone.

In both cases the reactions were associated with ingestion of these additives. In fact, challenge with benzoate-containing formulations (paracetamol-syrup, flurbiprofen-syrup, erythromycin-suspension, amoxicillin-drops, ibuprofen-drops) induced asthma attacks, while the same molecules administered by benzoate free compounds (paracetamol-suppositories, flurbiprofen-suppositories, erythromycin-packets, amoxicillin-soluble tablets, ibuprofen-effervescent tablets) did not.

Sulfiting agents are used widely by the pharmaceutical industry as antioxidants. Some of the medications that contain sulfites are: bronchodilatator solutions, epinephrine, local anesthetics, corticosteroids, antibiotics, antiarrhythmics, analgesics, pressors, eye drops, solutions for total parentereral nutrition and dialysis, thorazine and others. Sulfites are also known to be present in some oral tablet formulations, but the amounts present are incapable of provoking reactions. When compared with the concentrations of sulfite in foods, most pharmaceuticals contain small amounts of sulfite (0.25% to 1%). Unfortunately, a small amount of sulfite may produce grave consequences in rare patients when inhaled directly into the tracheobronchial tree or injected parenterally (73). Twarog and Leung (74) have described a patient with asthma who experienced generalized pruritus, throat discomfort, and respiratory failure 2 minutes after receiving isoetharine by inhalation. Similar symptoms also developed after the intravenous administration of metoclopramide. Bisulfite was the only common chemical found in both agents.

Diagnostic approach

The diagnosis of an adverse reaction to food additives in children can be a true challenge for the clinician.

A *detailed medical history* is essential and a careful collection of the symptoms should be done. Because atopic children appear to be more likely to have adverse reactions to food additives, manifestations of atopy should be investigated.

Suspicion should be directed to food additives when there is an history of: 1- adverse reactions to several unrelated foods; 2- adverse reactions to a commercially prepared food but not when it is prepared at home; 3- aggravation of a pre-existing disease (i.e. AD) without explanation.

The next step is to rule out a "hidden" food allergen. The most common cause is unintentional contamination in the processing steps, but there are many ways for allergens to be hidden in food (75). One of the first record of hidden allergen in food allergy was reported in 1928 by Balyeat who described asthma symptoms in two peanut-allergic children after they had drunk milk from a cow fed on peanut plants (76).

A "Food and Symptoms Diary" can be useful in the diagnostic process. It helps to rule out a hidden food allergen and, checking the food labels, it can help to find out the common additive contained in suspected food that can be responsible of the patient's symptoms.

Diagnosis

Skin Prick Test (SPT) and *laboratory testing* detecting specific IgE can be used only for some natural

colorants (i.e. annatto, saffron, carmine, mannitol and vegetable gum).

The *Atopy Patch Test (APT)* can be used to find out delayed-type hypersensitivity reactions to foods and aeroallergen in atopic eczema (18). Catli et al. demonstrated that in a cohort of children with AE, positive APT results for Carmine were significantly higher in the AE than the control group suggesting a possible role of this natural colorant in AE. The authors conclude that the cost-effectiveness, safety, and practicability of the APT makes it a useful diagnostic tool for detecting delayed hypersensitivity to food additives in AE, especially with regard to late-phase clinical reactions (18). In a recent case report, APT was successfully used to find out an association between the consumption of foods containing Carmine and flares of AE in children with a history of AE (11).

The *DBPCFC* is considered the gold standard for the diagnosis of hypersensitivity to food and food additives (8, 10, 36).

Before performing the DBPCFC, adhesion to an additive-free diet (no more than 4 weeks) can be considered, to confirm the suspicion of an adverse reaction to food additives, if the patient's symptoms or manifestations improve (10, 36, 77). An example of an additive-free diet, according to EFSA regulations (5), is shown in Table 5.

The next step is an initial trial with multiple additives in order to reduce the number of challenge. If there is a positive reaction, the components of the challenge mixture should be tested separately, in order to identify the food additive responsible of the clinical manifestations (10, 36, 77). Protocols of oral challenge vary considerably among different studies (10, 78, 79) and to date there is not a consensus about the doses that should be used for the challenges.

Treatment

After performing the diagnostic tests, if a food additive is considered to be responsible of the clinical manifestations, the exclusion of the specific additive from the patient's diet is the effective treatment. The patients and the caregivers should be provided with all the names of the specific additive and should be aware about all the products (food, beverages, cosmetics and medicines) that might contain the culprit.

For patients with severe reactions (i.e. anaphylaxis) an appropriate action plan should be developed.

These patients must be provided with a medical identification tag and emergency medications (i.e.

Table 5. Example of an additive-free diet

Pasta	Any kind. *Avoid gluten-free and hypoproteic pasta.*
Meat	Beef, chicken, lamb, turkey, veal (fresh or frozen) *Avoid cold cuts and canned meat.*
Fish	Fresh or frozen fish. *Avoid processed fish and fishery products.*
Fruit and Vegetables	Fresh fruit and vegetable. *Avoid canned or bottled fruit and vegetables.*
Cheese	Mozzarella, Parmesan cheese.
Condiments	Honey, salt, pepper, sugar. *Avoid sauces, commercially prepared condiments.*
Beverages	Coffee, milk, tea, water. *Avoid alcoholic beverages, fruit juices, energy drinks, canned or bottled drinks.*

ephinefrine autoinjector) available all the time. To date, no studies have demonstrated a role for desensitization with food additives.

Conclusion

Additives are substances widely used in food industry, such as in cosmetics and medicines production processes.

A recent study conducted in USA, showed that the realistic level of daily exposure to food additives is deeply lower than ADI in children (80). This low exposure contributes to make adverse reactions to additives quite uncommon events and the diagnosis a real challenge for the clinician.

The diagnosis should be suspected in the presence of a suggestive clinical history. In this case the diagnostic process should be initiated. A IGE-mediated mechanism can be demonstrated only for a small number of additives in particular food dyes. The double-blind placebo controlled oral challenge after an exclusion diet represents the gold standard for diagnosis. If the suspicion is confirmed, an exclusion diet, without the culprit additive, is the only possible therapeutic approach.

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Correspondence:
Prof Giampaolo Ricci
Pediatric Unit, Department of Medical and Surgical Sciences, University of Bologna, S. Orsola-Malpighi Hospital
Via Massarenti, 11 - 40138 Bologna, Italy
Tel. + 39 0512143075
Fax +39 0512143075.
E-mail: giampaolo.ricci@unibo.it

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Review

Allergic reactions to cow's milk proteins in medications in childhood

Angelica Santoro[1], Laura Andreozzi[2], Giampaolo Ricci[2], Carla Mastrorilli[1], Carlo Caffarelli[1]

[1] Clinica Pediatrica, Azienda Ospedaliero-Universitaria, Dipartimento di Medicina e Chirurgia, Università di Parma, Parma, Italy; [2]Pediatric Unit, Department of Medical and Surgical Sciences, University of Bologna, S. Orsola-Malpighi Hospital, Bologna, Italy

Summary. *Introduction:* Cow's milk is a frequent trigger of allergic reactions in childhood. Cow's milk proteins can be present in pharmaceutical excipients. *Methods:* We have analyzed paediatric literature on allergic reactions to cow's milk proteins in medication, focusing on the different routes of administration (inhaled, parental and oral). *Results:* Dry-powder inhalers may contain lactose as excipient. Lactose can be rarely contaminated with milk proteins and it may induce allergic reactions in patients with cow's milk allergy. Case reports have described immediate hypersensitivity reactions to methylprednisolone sodium succinate 40 mg injection, a formulation that contains lactose as excipient. Some cases of anaphylaxis after receiving diphteria-tetanus-pertussis vaccine injection in children allergic to milk have been reported. Cow's milk proteins can be detected also in oral polio vaccine, certain probiotics and lactulose syrup. *Conclusions:* We suggest caution in administration of pharmaceuticals containing milk allergens in children allergic to milk. (www.actabiomedica.it)

Key words: cow's milk allergy, drug allergy, probiotics, vaccine, skin prick test, anaphylaxis, patch test, challenge test, lactose

Introduction

Cow's milk is a frequent trigger of allergic reactions, including anaphylaxis, in childhood (1). Diagnosis of cow's milk allergy (CMA) is based on skin prick tests and measurement of serum IgE (2) while patch tests are useless (3) and oral challenge to cow's milk is the diagnostic gold standard (4). Patients with CMA have to make their best to avoid common food and non-food products containing offending proteins. However, this is not easy when cow's milk proteins are present in pharmaceutical excipients. The prevalence of reactions to cow's milk allergens in medications has not been investigated in sensitized patients. Generally, it appears to be low but rising. The purpose of this review is to provide an overview on the role of cow's milk proteins contained in pharmaceuticals as a cause of allergic reactions.

Inhaled milk allergens

Dry-powder inhalers (DPIs) may contain lactose as excipient. Lactose is a carbohydrate that should not be considered allergenic since it is free of milk proteins and it is safe in children with CMA (5). However, lactose contained in dry-powder inhalers can rarely be contaminated by milk proteins. It has been demonstrated that in children with CMA, inhalation of milk proteins may precipitate severe allergic reactions (6, 7). Accordingly, in children with asthma, anaphylaxis has been elicited by inhaling dry powder containing fluticasone/salmeterol (8) or lanimavir (9) and lactose contaminated with molecules of milk. Even if, in rare cases, milk allergen contamination of lactose-containing DPIs may induce allergic reactions in patients with CMA, patients allergic to milk usually do not have allergic reactions to lactose in DPI (10).

Parental route

Case reports have detailed immediate hypersensitivity reactions to methylprednisolone sodium succinate and diphtheria-tetanus-pertussis vaccine (DTP) in children with CMA.

Several children with high-level CMA have been reported to develop urticaria and anaphylaxis following intravenous methylprednisolone sodium succinate 40 mg injections that contain lactose as excipient (11-14). This methylprednisolone formulation with lactose may also contain milk proteins (15). In patients with CMA who reacted to methylprednisolone, skin prick test or intradermal test resulted positive only to methylprednisolone sodium succinate 40 mg but not to different methylprednisolone formulation that are free of lactose (11, 14). These reports have led to contraindicate the use of methylprednisolone injections containing lactose in patients with CMA or suspected to be allergic to cow's milk proteins (15). Allergic reactions to methylprednisolone injections containing lactose have been reported mainly in asthmatic children (15). However, physicians should always consider that clinical hypersensitivity reactions to corticosteroids can occur also when lactose-free preparations are given (16). Therefore, in selected cases drug provocation challenge may be required to reach a firm diagnosis (17).

Caseins have been found by ELISA at low concentration (8.1 and 18.3 ng/mL) in culture media of DTP (18). Along this line, it has been reported that 6 out of 8 children with anaphylaxis after receiving DTP injection have had immediate allergic reactions to milk proteins (19). However, it is reassuring that the Vaccine Adverse Event Reporting System database does not record reactions caused by DTP in patients with CMA (18).

Oral route

Cow's milk protein can be detected in oral polio vaccine (OPV), probiotics and lactulose. OPV provoked immediate severe allergic reactions in 4 children with positive skin prick test result and positive serum IgE antibodies to milk. Children had also positive skin prick test to OPV. Alfa-lactalbumin was found in OPV by ELISA (20).

Adverse reactions to probiotics have been rarely reported (21, 22). Anaphylaxis to a probiotic compound has been described in an infant allergic to milk with acute gastroenteritis (23). Subsequently, in the probiotic preparation it has been detected beta-lactoglobulin binding IgE from patients with CMA (24). Another study showed that 10 out of 11 probiotics contained cow's milk proteins (25). Lactulose is synthetically prepared from lactose. It has been demostrated by oral challenge that lactulose syrup elicited rhinoconjunctivitis and wheezing in a child with high-level CMA. Authors hypothesized that milk proteins might have contaminated the medication and induced the reaction (26). Overall, these case reports raise the question whether tablets or oral solutions containing lactose are safe in children with severe CMA.

Conclusions

Patients with CMA have been sparsely reported to develop allergic reactions following administration of pharmaceuticals that have been contaminated with milk proteins with unpredictable lot-to-lot variability. We feel that it is unnecessary to avoid the administration of products that might be potentially contaminated with milk proteins in children with anaphylactic reaction to milk with the exception of methylprednisolone injections containing lactose of bovine origin (15). However, the risk of developing severe reactions suggests caution when such children receive medications that may potentially contain milk allergens. For example, a 1-hour surveillance should be performed at the office following administration of OPV or DPT (18). Finally, it is desirable that manufacturers remove or measure residual allergen content in the medications. This is necessary to definitively prevent allergic hypersensitivity reactions in patients with CMA.

Conflict of interest: None to declare

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Correspondence:
Carlo Caffarelli
Clinica Pediatrica, Azienda Ospedaliero-Universitaria,
Dipartimento di Medicina e Chirurgia, Università di Parma,
Via Gramsci 14 - Parma, Italy
Tel. 0521702207
Fax 0521702830
E-mail carlo.caffarelli@unipr.it

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Review

Pediatric drug hypersensitivity: which diagnostic tests?

Francesca Saretta[1], Francesca Mori[2], Fabio Cardinale[3], Lucia Liotti[4], Fabrizio Franceschini[5], Giuseppe Crisafulli[6], Silvia Caimmi[7], Paolo Bottau[8], Roberto Bernardini[9], Carlo Caffarelli[10]

[1] Pediatric Department, AAS2 Bassa Friulana-Isontina, Palmanova-Latisana, Italy; Pediatric Allergy Unit, Department of Medicine, Udine, Italy; [2] Allergy Unit, Department of Pediatric Medicine, Anna Meyer Children's University Hospital, Florence, Italy; [3] UOC di Pediatria, Azienda Ospedaliera-Universitaria "Consorziale-Policlinico", Ospedale Pediatrico Giovanni XXIII, Bari, Italy; [4] Department of Pediatrics, Senigallia Hospital, Senigallia, Italy; [5] UOC Pediatria, Azienda Ospedaliero-Universitaria "Ospedali Riuniti", Ancona, Italy; [6] UO Allergologia, Dipartimento di Pediatria, Università di Messina, Italy; [7] Pediatric Clinic, Foundation IRCCS Policlinico San Matteo, University of Pavia, Pavia, Italy; [8] Pediatric and Neonatology Unit, Imola Hospital, Imola (BO), Italy; [9] Pediatric Unit, "San Giuseppe" Hospital, Empoli, Italy; [10] Clinica Pediatrica, Dipartimento di Medicina e Chirurgia, Azienda Ospedaliero-Universitaria, Università di Parma, Italy

Summary. Along with the anamnesis and clinical evaluation, diagnostic tests are one of the mainstream key points in the evaluation and management of drug hypersensitivity reactions (DHR). A wide knowledge gap, both in diagnosis and management of pediatric DHR, must be filled. Only a few published studies evaluated sensitivity and specificity of skin and *in vitro* tests in children. However, selected case series show that diagnostic work-up for adults could be useful, with some limitations, in pediatric age. Indeed, despite improvement in *in vivo* and *in vitro* diagnosis, drug provocation test remains the gold standard in pediatric age, too. Unmet needs in children include multi-centric studies on incidence of DHR, utility and feasibility of *in vivo* and *in vitro* diagnostic tests and specifically dedicated guidelines for the diagnosis and management of DHR in children. (www.actabiomedica.it)

Key words: Drug hypersensitivity reactions, children, skin test, specific IgE, basophil activation test, drug provocation test

Introduction

A wide knowledge gap needs to be filled in pediatric drug hypersensitivity reactions DHR, both in diagnosis and management (1). Along with history and clinical evaluation, diagnostic tests are the cornerstone for the evaluation and management of DHR. Most diagnostic studies involve adults or mixed adult/children populations, while only a few papers are targeting the pediatric age. Indeed, despite improvement in *in vivo* and *in vitro* tests, drug provocation test (DPT) remains the gold standard in pediatric age. In recent years, it has been underlined a lack of uniformity in allergy work-up in childhood (2).

Up to 10.3% of children admitted to hospital could present a DHR (with an overall 2.9% incidence) (3). Although parents report a general prevalence of 10% (4-6), only few reactions are true DHR (4, 7). These DHR are often mild and non-immediate, but severe cutaneous adverse reactions (SCAR) could occur as well. Therefore, the clinical history must be carefully evaluated to choose the appropriate diagnostic steps. For example, in SCAR the DPT is contraindicated and in cross-intolerant non-steroidal anti-inflammatory drugs (NSAIDs) allergy diagnostic tests are recommended since the reactions are not immune mediated.

It is suggested that diagnostic tests should be conducted within 4 weeks to 6 months after the resolution of the drug reaction to ensure the better sensitivity and specificity of the tests (8). It has been demonstrated that there is a reduction of sensitivity and specificity of diagnostic tests over time (9).

In 1999 the ENDA (European Network for Drug Allergy) group has proposed a questionnaire, available in different languages on the EAACI website (10). The questionnaire comprises all the information that must be collected when a DHR is evaluated: patient data, clinical history, characteristics of the reaction, results of *in vivo* and *in vitro* tests, DPT outcome and interpretation of data. Skin test procedures should be reported in order to standardize them. This questionnaire could be used also in children. The EAACI/ENDA group also suggests delivering a Drug Allergy Passport (11) to be kept together with health documentation, to avoid accidental exposure to culprit drugs and unnecessary alternative therapies.

Skin tests

Although widely used in other allergic diseases, skin tests to drugs have not been completely validated yet in childhood (12, 13). No commercial extracts are available for most drugs but penicillin. DAP®Kit (Diater, Madrid, Spain) offers benzylpenilloyl-octa-L-lysine for major determinants and sodium benzylpenicilloate for minor determinant. All other skin tests need to be prepared immediately before use.

All skin tests (prick tests PT, intradermal tests IDT, patch test PaT) could be, however, performed in children and, in specific cases, they could suffice to guide the decision on performing additional tests. Skin tests to drugs have been proved to be safe, and systemic reactions following skin tests occur in 0.3%-1.2% of children (14-16). The EAACI pediatric task force has conducted an unpublished survey between members and, in most cases, IDT are not performed to avoid unnecessary painful procedures in children (1). Concerning data from studies on skin tests, only a few of them enrolled children. Skin tests (PT and IDT) are endowed with a relatively high diagnostic value in immediate reactions but with a low sensitivity for non-immediate ones. Although PaTs seem to be useful in the diagnosis of non-immediate DHR to anti-epileptic drugs (AEDs), more pediatric studies are needed to confirm these data (1). No guidelines recommend skin tests to drugs in pediatric age (1, 17, 18). However, in children, skin tests have a higher diagnostic value for AEDs, beta-lactams (BLs), chlorhexidine, heparins, neuromuscular blocking agents (NMBA), platinum salts, radio contrast media (RCM), blue dyes and proton pump inhibitors (PPI), and a lower value for biologicals, local anesthetics, hormones, insulins, non beta-lactams (nBLs), non pyrazolone anti-inflammatory drugs and opioids (1).

Drug provocation test

Due to the paucity of studies and the limits of both skin tests and *in vitro* tests in pediatric populations, the DPT remains the gold standard for the diagnosis of DHR. General recommendations (indications, contraindications, settings and equipment) for performing DPT apply to children as well (19). Although no international consensus on DPT protocols has been achieved yet, the EAACI pediatric task force has given the following general suggestions (1):

a) for each child, an appropriate age/weight dose must be calculated
a) start with approximately 1/10 of the single dose, followed by half and, then, the full dose; the cumulative daily dose should not be exceeded
b) in severe reactions, start with a lower dose (1:10,000 to 1:1,000 of maximum therapeutic dose)
c) dose intervals and observation should be decided according to clinical history, considering a prolonged DPT at home for non-immediate DHR and for NSAIDs
d) in most cases a single therapeutic dose should be given. In the United States a DPT with 3 or more steps is thought to possibly lead to an unintentional desensitization.

Moreover, the ICON on Drug Allergy (20) has suggested to avoid DPT if skin tests are positive, if the reactions were severe (as severe cutaneous reactions or anaphylaxis), if there are concomitant diseases or pregnancy, or if the culprit drug will be no longer needed by the patient. Usually none of these contraindications are observed in the pediatric age and most published papers on DPT are focused on antibiotics and NSAIDs, which account for a large percentage of

DHR in children. Recently, some Authors have proposed, in selected mild non-immediate DHR to antibiotics, to proceed with DPT without performing skin and *in vitro* tests (21, 22). Authors underline that, in those studies where no skin or *in vitro* tests have been performed, no severe reactions have occurred (14, 23-26), but larger studies are needed to confirm these observations. Moreover, there is no agreement on the duration of DTP (22, 27). Protocols span between 1 dose to 10 days, and many clinicians adapt the length of DPT to the clinical history of the patient. However, parents are often not reliable in reporting timing and clinical history of DHR. Furthermore, the overlapping of symptoms appearance with drug administration are not always clear. Besides sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV), other issues should be considered. The number needed to harm to get those patients reacting on extended DPT is 95 healthy children exposed to an unnecessary course of antibiotics (22). Furthermore, prolonged exposure to antibiotics (even multiple times) could lead to microbial resistance and to disturbances of the gut microbiota which has been linked to obesity (28,29).

In vitro tests

Recently, the Drug Allergy Interest Group of EAACI has published a position paper on the diagnostic use and value of *in vitro* test in DHR (30). Regarding *in vitro* tests, we report some considerations that could be generally applied to children.

Skin biopsy

Macular papular exanthema (MPE) and urticaria are the most frequent cutaneous reactions in children. They are usually mild to moderate in severity, show a benign clinical course and usually no skin biopsy is performed. In other cutaneous DHR such as SCAR, skin biopsies can be useful to diagnose and differentiate the DHR since other skin tests and DPT are not recommended (31). Several pediatric case reports of fixed drug eruption (FDE) have been published but in most cases biopsy consent was not given; FDE biopsy shows a lichenoid reaction with pigmentary incontinence with the typical melanin accumulation (32). The role of intraepidermal CD8+T cells in FDE has been proved in evoking the local tissue damage (33). Generalized bullous FDE (GBFDE) shows some histologic features like those observed in Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) (31). However, in GBFDE the clinical course is usually milder and there is no mucosal involvement (34). In acute generalized exanthematous pustolosis (AGEP) biopsy usually shows the formation of a typical spongiform subcorneal and/or intraepidermal pustule, a perivascular infiltrate containing neutrophils and papillary edema (35). In drug reaction with eosinophilia and systemic symptoms (DRESS) could present with different histological findings, often within the same sample, with a superficial atypical lymphocyte infiltrate and a perivascular involvement containing eosinophils (36). Biopsies of SJS/TEN show epidermal necrosis with sub-epidermal blistering, due to the vacuolar detachment of the basement membrane and extensive keratinocyte apoptosis. A perivascular lymphohistiocytic infiltrate with eosinophils could be also observed. It could be helpful to perform the Tzanck smear of the blister fluid: To distinguish TEN from staphylococcal scalded skin syndrome (SSSS). In SSSS, epithelial cells show a small nucleus/cytoplasm ratio, while in TEN, cuboidal cells present a large cell nucleus/cytoplasm ratio. Moreover, in SSSS, the skin separation is in the subcorneal stratum, while in TEN, it occurs in the spinosum (31).

Specific IgE

Specific serum IgE antibodies to drugs could be detected by using enzyme-linked immunosorbent test or immunoassay test. Specific IgE to a limited number of drugs are commercially available: ampicilloyl, amoxicilloyl, cephaclor, chlorhexidine, chymopapain, gelatin (bovine origin), insulin (human, bovine and porcine origin), morphine, penicilloyl G, penicilloyl V, pholcodine and suxamethonium. For research purposes, other extracts are available, such as tetanus toxoid and adrenocorticotrophic hormone (ACTH). In 1983, Baldo and Fisher (37) have used the epoxy-activated sepharose 6 B radioimmunoassay for determining spe-

cific serum IgE. Although this test has been improved over the following years, it is only used for research, and its specificity and sensitivity are not validated yet.

Basophil activation test (BAT)

Although basophils account for usually less than 1% of circulating leukocytes, they could represent a useful source of information in DHR. Drug can activate basophils by both IgE-dependent and IgE-independent mechanisms (38). Few specific markers have been identified to evaluate activation of basophils upon allergic stimulation: CD63, CD123/HLA-DR, CCR3 (CD193)/CD3, CD203c, and MAPK (mitogen-activated protein kinase). The phosphorylation state of the latter seems to be tightly linked to CD63 up-regulation (39). In BAT, CD63 and CD203 are commonly used as marker of basophil activation. A correct stimulation protocol and index are fundamental to obtain acceptable sensitivity and specificity, although these depend both on the analyzed population and drug (40, 41). Usually 5-10% of subjects are not reactive to a specific positive stimulation and are identified as non-responders, possibly due to a defect in SYK tyrosin kinase (42) that is involved in transducing the signals occurring downstream the cross-linking between specific IgE and basophils FceRI. Furthermore, BAT could offer the possibility to study cross-reactivity between drugs from the same class without performing the DPT. Sensitivity and specificity vary depending on drug, population, timing of reactions (immediate vs nonimmediate), BAT procedure (CD63 vs CD203) (43-46). Most studies have been conducted in adults (table 1).

Table 1. Sensitivity and specificity of Basophil Activation Test (data from 45)

Drug	Sensitivity	Specificity
Beta-lactam	22-55	79-100
Non beta-lactam	0-100	70-100
NSAIDs	0-100	20-100
RCM	42-63	89-100
NBMA	36.1-91.7	93-100
L-asparaginase	75	82
Methylprednisolone	75	100
Gelofusine	100	87.5
Omeprazole	66.7	100

Lymphocyte transformation test (LTT)

LTT evaluates proliferative response of T cells upon allergen stimulation (47). Sensitivity and sensibility show a wide variability, depending on the tested allergen. LTT is more frequently used for non-immediate cutaneous reactions such as MPE, FDE, DRESS and TEN, with a sensitivity ranging from 60% to 70% and specificity from 85% to 93% (43). LTT is still considered a research tool.

Tryptase

Tryptase is a serine protease, contained in mast cells and basophils, that could be released upon allergic and nonallergic stimulation. It has two isoforms. Alpha-tryptase is constantly released in the bloodstream, thus representing the basal levels of the enzyme in the plasma, while beta-tryptase is released upon mast cells degranulation. However, commercially available assays measure both isoforms. In acute DHR, tryptase must be measured at onset, between 30-120 minutes and after 24 hours, and these levels must be compared to baseline levels. The normal level of tryptase are usually below 11.4 ng/mL. An increase ≥20% above baseline level plus 2 ng/mL within 4 h from the occurrence of the reaction, could be clinically significant. Tryptase sensitivity ranges from 30% to 94.1% and specificity from 92.3% to 94.4% (30). Concomitant mast cells disorders could increase basal and acute tryptase levels. A recent study analyzing a pediatric population with food and hymenoptera allergy showed that baseline tryptase levels are not a risk factor for immediate-type DHR (48).

HLA haplotyping

Specific HLA haplotypes have been demonstrated to be associated to DHR. The EAACI Interest group on Drug Allergy (30) has given the following suggestions:

- *abacavir* induced DHR are associated to HLA-B*57:01 with a sensitivity of 45.5-80%, a specificity of 97.6-99%, a NPV of 100% and a PPV of 55-58% (49, 50). This association has been observed also in children (51). A screening is suggested since it has been shown

that reduce the prevalence of DHR from 12-7.5% to 3-0% (52-54);

- *carbamazepine* DHR association to HLA-B*15:02 has been observed in children (55) underlining the possible utility for identifying children at risk;

- *allopurinol* DHR have been associated to HLA-B*58:01 and the screening has been recommended by the American College of Rheumatology in high risk individuals (56).

Antibiotics

BLs

Skin tests (PT and IDT) could be performed in children using the nonirritating concentrations suggested for adults. For BLs, Diater (Madrid, Spain) offers a ready-to-use DAP®Kit which contains *benzylpenilloyl-octa-L-lysine* for major determinants and s*odium benzylpenicilloate* for minor determinant. For other BLs PT, IDT and PaT maximum concentrations have been reported (13) (Table 2).

In immediate DHR to BLs, sIgE show a low sensitivity (0-85%) and a fair specificity (52-100%) (38). In patients with total IgE>200 kU/l, an increased sensitivity with a lower threshold from 0.35 to 0.1 kUA/l, with a decreased specificity have been shown (57). BAT have been used in different studies to assess antibiotics hypersensitivity in adults. In children, Barni et al have evaluated 18 children with a suspect immediate reaction to amoxicillin or amoxicillin-clavulanate. In this study, no correlation has been observed between results of BAT and DPT (58). LTT has also demonstrated sensitization to amoxiclavulanate in a pediatric population with Epstein-Barr Virus infection (59).

nBLs

nBLs induce roughly 10-20% of DHR (17, 60). A self-reported survey (61**)** on DHR to antibiotics in pediatric age, found that sulfonamides were the second most frequent cause of DHR (0.5%-2.2% according to age), followed by macrolides and cephalosporins. The incidence of DHR to nBLs is correlated with the frequency of their use. In Spain quinolones are at the third rank after NSAIDs and BLs, with an incidence increased from 0.53% in 2005 to 5.96% in 2009 (62). No data on incidence in children are available for most nBLs and, usually, skin tests are performed following the maximum concentrations given for adults (Table 3). In vitro tests, especially BAT and LTT have been mostly studied in adult populations.

Macrolides rarely cause anaphylaxis (63) and IDT has shown a sensitivity of 75% and specificity of 90% at concentration of 0.5 mg/mL (64). Aminoglycosides are mainly used in neonatal sepsis and in cystic fibrosis and, although uncommon, adverse reactions have been reported even in the newborn (65). DHRs to aminoglycosides seem to be frequent in cystic fibrosis patients. In immediate DHR, skin tests could be used, monitoring the irritant concentration, since no specific data for children have been provided yet. PaT could also be used to evaluate contact dermatitis. However, a positive PaT to neomycin have been shown in 11.5% of asymptomatic children (66). Among glycopeptides, vancomycin was the most common cause of DHR in a pediatric study (67), and it is also cause of red man syndrome due to mast cells degranulation (68). For skin tests, nonirritant concentrations determined in adults could be used for children and both BAT and LTT

Table 2. Maximum concentration of prick, intradermal and patch test for beta-lactams (modified from 13)

Drug	Prick test	Intradermal test	Patch test
Ampicillin	20 mg/mL	20 mg/mL	5%
Amoxicillin	20 mg/mL	20 mg/mL	5%
Benzylpenicillin	10.000 UI	10.000 UI	5%
Cephalosporin	2 mg/mL	2 mg/mL	5%

Table 3. Maximum concentration of prick and intradermal test for non beta-lactams (modified from 60)

Drug	Prick test (mg/mL)	Intradermal test (mg/mL)
Claritromycin	50	0.05-0.5
Azithromycin	100	0.01
Clindamycin	150	15
Gentamycin	40	4
Tobramycin	40	4
Levofloxacin	5	25
Vancomycin	50	5
Cotrimoxazole	80	0.8

could be performed. Since sulfonamides often cause nonimmediate reactions, delayed IDT reading, PaT for fixed drug eruptions and LTT have been studied, showing a low sensitivity but a good specificity (60). BAT has been used to evaluate immediate quinolones DHR with a specificity of 100% and sensitivity from 28.9% to 71.1% in adults (69). The pathogenesis of DHR to antituberculosis drugs is still not completely known, therefore no diagnostic guidelines have been provided. Nonirritant concentrations for skin test have been suggested for rifampicin and isoniazide, and both BAT and LTT have been studied.

NSAIDs

Skin tests and *in vitro* tests show a limited value for the diagnosis of different phenotypes of NSAIDs hypersensitivity in children, So, DPT remains the gold diagnostic standard (70, 71). In cross-intolerants including patients with NSAIDs-exacerbated respiratory disease (NERD) and NSAIDs-exacerbated cutaneous disease (NECD), there is no indication for allergy tests since the reactions are not immune mediated (70,71). In patients with selective NSAID-induced urticaria/angioedema or anaphylaxis (NIUA), skin tests to paracetamol, metamizole and dipyrone have been evaluated in pediatric age case series. IDTs could be performed as well, but negative results need to be confirmed by DPT. In children, skin tests concentrations have not yet been validated (Table 4). Until now, no data are available on skin tests in children with selective NSAID-induced delayed reactions (SNIDR). A recent guideline (72) has not recommended PaT to NSAIDs in children. *In vitro* tests to NSAIDs are not yet validated. BAT has shown low specificity and sensitivity in cross intolerants and children were not often enrolled in the studies (45, 73-75). In immediate NSAIDs hypersensitivity, BAT had a sensitivity between 22-55% and specificity between 20-100% (38). Sensitivity varies between 30-78% for NERD, between 37-100% for NECD and NIUA while specificity varies from 40% to 83% for NERD and between 31-90% for NECD and NIUA (30). The cellular allergen stimulation test (CAST) evaluates the release of basophil-derived leukotrienes, CAST has been suggested for the diagnosis of selected phenotypes of NSAIDs hypersensitivity, although it is not recommended in clinical practice (76) especially in children with no available specific data.

Table 4. Maximum concentration of prick and intradermal test for NSAIDs (modified from 70)

Drug	Skin test	Intradermal test
Acetaminophen	10 mg/mL	1 mg/mL
Metamizole sodium	40-400 mg/mL	0.4-4 mg/mL

AEDs

The diagnostic value of skin and *in vitro* tests to AEDs is unclear since DPT has not been performed in most studies. HLA haplotype polymorphisms could be useful in predicting hypersensitivity reactions to AEDs, especially for carbamazepine in Eastern populations (77-79).

In immediate reactions, PaT and IDT could be performed, although non-irritating concentrations have not been evaluated or reported in childhood (13). In nonimmediate reactions, diagnosis relies on delayed-reading IDT, PaT, LTT and/or a DPT (13, 20). The maximum recommended concentration for PaT is 10% in petrolatum for pure substances and 30% in PET for commercialized forms of AEDs, not exceeding 20% for carbamazepine. If a severe cutaneous adverse reaction is suspected, it is recommended to start with a concentration of at least 1% (80, 81). PaT could be performed if there is a low suspicion or to find alternative drugs in SCAR.

Radio contrast media (RCM)

The diagnostic evaluation for DHR to RCM has not reached an international consensus yet. European guidelines (13) suggest performing skin tests, while American guidelines do not recommend any allergy tests (17). This discrepancy is probably due to the emerging evidence that immediate reactions to RCM could be due to an IgE mediated mechanism. Positive results of skin and *in vitro* tests (tryptase and BAT) support this hypothesis (82, 83). Different mechanisms include complement activation, mast cells activation, direct membrane effect and bradykinin involvement

(84). The previous concept/attitude of RCM pre-test administration, as a proof of possible hypersensitivity, is not recommended and it could even evoke severe and fatal reactions (85).

Skin tests, whose sensitivity varies from 4.2% to 73%, could be performed in immediate reactions (83, 86, 87). Undiluted RCM could be used for prick test and a 1/10 dilution for IDT, starting with even higher dilutions in case of severe reactions. In nonimmediate reactions, PaT could be useful, even though it has a lower sensitivity compared to IDT (88, 89). No commercial assay is available to detect IgE to RCM, and the diagnostic value of this test in unknown. In RCM hypersensitivity, BAT showed a sensitivity of 46-63% and a specificity of 89-100%, but only a few studies are available (38). LTT shows a sensitivity between 13% and 75% in nonimmediate reactions (89). Some Authors suggest performing DPT with increasing doses at 30-45-minute intervals for immediate reactions and 1-hour intervals for nonimmediate reactions (83, 90), and in case of severe nonimmediate reactions in 2 separate session with 1-week interval (88).

In a very recent study on 597 adults (91), among which some teenagers, skin tests were positive in 80 patients (13.4%), 70% of patients had immediate reactions, 25% nonimmediate reactions, and 5% unknown timing. When DPT is performed, NPV of skin tests was 93.1%, 94.2% for immediate reactions and 86.1% for nonimmediate reactions. The median interval between reaction and evaluation was 52 months (4.5-215.9 IQR). Large studies in pediatric patients (92-94) showed a low incidence of DHR in children, but no allergy tests were performed.

Perioperative drugs

Perioperative anaphylaxis is common (95). In perioperative DHR the most essential step is to accurately record all used drugs, including RCM, disinfectants, latex, colloids and plasma expanders, since all of them could be the primary responsible for the observed reaction. According to a recent review, the most common cause in the United States is the use of antibiotics, while NMBA is more common in Europe. Chlorhexidine and blue dye are an emerging cause, as well as sugammadex (96, 97).

Serum tryptase concentration could be useful to identify possible anaphylaxis during anesthesia. According to a recent study (98), a tryptase value >15.7 ng/mL has a sensitivity of 75%, specificity of 68.4%, PPV of 82% and NPV of 59% for IgE-mediated anaphylaxis during general anesthesia.

It should be firstly performed skin tests, that are more sensitive, and available *in vitro* tests. For most perioperative drugs, PT and IDT maximum concentrations have been proposed, but there are no data in children (13, 80, 99-101) (Table 5)

It is possible to determine IgE to pholcodine, morphine, chlorhexidine, succinylcholine, latex, protamine. Pholcodine, an antitussive agent, is a marker for sensitization to NMBA (102) and in a recent study appears to have a higher sensitivity (88%) compared to rocuronium, suxamethonium, and specificity was 100% (104). Sensitivity of IgE to NMBA is between 14.2%-97%, specificity between 85.7%-100%, depending on population and type of NMBA, while sensitivity of BAT is between 36-92% and specificity between 81-100%.

In childhood, a frequent issue is possible DHR to local anesthetics (LA) that are classified as either

Table 5. Maximum concentration of prick and intradermal test for perioperative drugs (modified from 95)

Drug	Prick test (mg/mL)	Intradermal test (mcg/mL)
Bupivacaine	2.5	250
Lidocaina	10	1000
Mepicavaina	10	1000
Chlorexidine	2%	0.0002%
Etomidate	2	200
Midazolam	5	500
Propofol	10	1000
Thiopental	25	2500
Atracurium	1	10
Cisatracurium	2	20
Pancuronium	2	200
Rocuronium	10	100
Vecuronium	4	400
Sugammadex	10	100-1000
Alfentanyl	0,5	50
Fentanyl	0,05	5
Remifentanyl	0,05	5
Sufentanyl	0,005	0,5
Morphine	1	10
Methylene blue	10	100

ester or amide. IgE mediated reactions to ester LA (exceptionally to amide LA) account for less than 1% of reported reactions to LA. Delayed contact hypersensitivity to ester seems to be more common in children (104, 105). In 162 patients, including some children, evaluated for suspected IgE mediated reactions to LA no reaction occurred during subcutaneous drug provocation test, even when skin tests resulted positive (106). Adjuvants must be tested too (such as potassium metabisulphite and disodium edetate). Skin tests can be used to investigate both immediate and delayed allergic reactions, although rarely positive (107), and could be useful to evaluate cross-reactivity between LA (common within esters) (108).

Corticosteroids

Most DHR to systemic corticosteroids (CS) occur during topical administration, with a prevalence ranging from 0.2% to 5% (109). The prevalence of systemic immediate reactions has been estimated to be 0.1-0.3% (110). Some pediatric case-series have been reported (111-114). CSs most commonly implicated in DHR are methylprednisolone (41%), prednisolone (20%), triamcinolone (14%), and hydrocortisone (10%) (115),

For immediate reactions, PT and especially IDT must be performed, since patients with negative PT, may subsequently have a positive IDT (116). IDT has a NPV of 88% and a specificity of 97% (115). Additives contained in the CS preparation, such as polyethylene glycol or carboxymethylcellulose, must be tested, too. Indeed, a pediatric case of inhaled CS DHR was due to lactose contamination of dry powder (117). Maximum concentrations for PT and IDT are reported in Table 6. Other *in vitro* tests could be performed, such as sIgE, LTT and BAT, but no specific data on large series and in children are available (110).

Ready-to-use PaTs (118) can be used in delayed reactions. Drugs, concentrations and vehicles are reported in Table 7. TRUE test (US) which comprises budesonide ad tixocortol-21-pivalate could identify up to 91.3% of patients (119), but, recently, the North American Contact Dermatitis group suggests adding hydrocortisone-17-butyrate, clobetasol-17-propionate, and triamcinolone acetonide to the tested drugs (120). Although European Series includes more CSs, sometimes additional CSs need to be tested, as well as the vehicle, for example ethanol could provoke the reaction (121). In reading PaT results, two side effects of topical CS must be evaluated: the so-called early "edge effect" and the blanching/erythema. The first is due to the higher CS concentration in the center of patch, that exerts an anti-inflammatory effect, that, however, disappears at late reading. The latter is due to a primary blanching for vasoconstriction followed by erythema due to vasodilation (122).

If all diagnostic tests are negative (including testing for cross-reactive CSs), a DPT must be performed, but no standardized protocols have been published.

Table 6. Maximum concentration of prick and intradermal test for corticosteroids (modified from 115)

Drug	Prick test (mg/mL)	Intradermal test (mg/mL)
Betamethasone sodium phosphate	4	4
Betamethasone acetate	6	6
Dexamethasone sodium phosphate	4	0,04-4
Hydrocortisone sodium succinate	100	1-10-25
Methylprednisolone (acetate and sodium succinate)	40	0,4-4
Prednisone	30	NA
Prednisolone	10	NA
Triamcinolone acetonide	40	0,4-40

Table 7. Drugs, concentrations and vehicles in available patch test for corticosteroids

Drug	Patch series	Concentration/ Vehicle
Budesonide	TRUE test USA	0,01/petrolatum
Tixocortol-21-pivalate	TRUE test USA	0,1%/petrolatum
Amcinonide	Europe	0,1%/ethanol
Bethametasone-17-valerate	Europe	0,12%/ethanol
Budesonide	Europe	0.1%/ethanol
Clobetasol-17-propionate	Europe	0,25%/ethanol
Hydrocortisone	Europe	0,1%/ethanol
Hydrocortisone-17-butyrate	Europe	1%/ethanol
Prednisone	Europe	1%/ethanol
Tixocortol-21-pivalate	Europe	0,1%/petrolatum
Triamcinolone acetonide	Europe	0,1%/ethanol

Antineoplastic drugs

Among antineoplastic drugs, the more frequently involved in DHR are platinum compounds, L-asparaginase, and methotrexate (123, 124). There are some pediatric series in which hypersensitivity reactions to carboplatin have been described, with a reported incidence from 7% to 47% (125-127). For adults, it has been proposed to perform an IDT test with carboplatin 30 minutes before therapy, which could identify patients at risk of DHR with NPV of 99% (128-129) but this must be confirmed in children.

For L-asparaginase, skin tests could be performed before the first dose and any time thereafter, to identify patients at risk due to the high rate of DHR, with the systemic route. The suggested concentration for IDT is 20 UI/mL (125). Specific serum IgE to L-asparaginase could be detectable and could be responsible for DHR, together with complement activation, and IgG or IgM complexes (130, 131). Some case reports have been reported in children (132-136) and they focused on desensitization rather than on the diagnostic work-up, in which PT were performed at 10mg/mL concentration, while IDT was done at 0.1-1-10 mg/mL concentration.

Monoclonal antibodies

No standardized concentrations for skin tests have been published yet, but some have been proposed as nonirritant. PT should be done undiluted, and if negative, IDT could be performed using 1:100 and 1:10 dilution (137-138).

Regarding cetuximab, it is important to remind that IgE-mediated reactions have occurred even at the first dose, due to a previous production of IgE against galactose-alpha-1,3-galactose (alpha-gal). This is an oligosaccharide whose exposure occurs after ingestion of red meat and/or after tick bites, and that could be responsible for delayed onset of urticaria or anaphylaxis to red meat, even in children (139, 140). Diagnosis could be made with positive skin tests to cetuximab or positive serum IgE to alpha-gal.

Conclusions

Although DHR in children are less frequent than in adults, in recent years it has been observed an increased interest in this topic. However, there are several unmet needs in children. Multicenter studies assessing frequency of different causes of DHR are needed. The investigation of mechanisms of drug hypersensitivity might be of importance for discovering new diagnostic tests such as assessment of biomarkers in exhaled breath (141-144). Utility and feasibility of diagnostic tests (*in vivo* and *in vitro)* should be clarified (145). Finally, guidelines for the diagnosis and management of DHR in children are warranted.

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Correspondence:
Francesca Saretta
Pediatric Department, AAS2 Bassa Friulana-Isontina,
Via Natisone - 33057 Palmanova (UD), Italy
Tel. +390432921414
Fax +390432921320
E-mail: francescasaretta@gmail.com