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R E V I E W

Drug allergy in children: focus on beta-lactams and NSAIDs

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Abstract. Drug hypersensitivity reactions (DHRs) are adverse reactions to a drug. In children, most common drugs inducing such reactions include beta-lactams (BLs) and non-steroidal anti-inflammatory drugs (NSAIDs). The aim of the present work was to provide current knowledge on the management of DHRs in the pediatric population, focusing on BLs and NSAIDs hypersensitivity. The clinical feature of DHRs include immediate and non-immediate (delayed and accelerated) reactions, that may be severe or non-severe. A systematic approach to the patient based on the reported clinical history is essential to organize a safe and adapted allergy work-up. Skin tests are the first step to assess a possible DHRs, especially in immediate reactions to BLs. Drugs concentrations for these tests are standardized and validated. The drug provocation test remains the gold standard to reach a firm diagnosis. In selected cases, a therapeutic desensitization protocol may be proposed in children with a confirmed diagnosis of drug hypersensitivity. Clinicians should be aware of the diagnostic and therapeutic options, to provide the best management in children having experienced a history of DHR. (www.actabiomedica.it)

Key words: beta-lactams, children, drug allergy, non-steroidal anti-inflammatory drugs

Introduction

In children, drug hypersensitivity reactions (DHRs), which are adverse reactions to a drug with clinical features of a possible allergy, are frequently reported by parents (1). Indeed, about 10% of the parents report a suspected DHR for their children; nevertheless, whenever a complete allergy work-up is com-

pleted, only a few of the suspected reactions are then confirmed to be associated to the suspected drug (1-3). Therefore, community-based and questionnaire-based studies may lead to an overestimation of the rates of DHR and drug allergy (2). Little data are available today focusing on the confirmed prevalence and incidence of DHRs in children (1). This may be mainly due to the fact that, even in pediatrics, the gold stand-

ard to reach a firm diagnosis remains the drug provocation test (DPT), which is not performed in general settings, but mainly in tertiary specialized hospitals. In prospective studies conducted in children and adolescents, the rate of adverse drug reactions was 10.9% in hospitalized children, 1.0% in outpatients, and the hospitalizations rate for HDRs was of 1.8% (3).

The suspicion of drug allergy is the third cause, after asthma and rhinitis, for consulting in an allergy department, representing 9.8% of all referred pediatric patients (2). The two most frequent classes of drugs reported as responsible of hypersensitivity reactions in children are antibiotics and non-steroidal anti-inflammatory drugs (NSAIDs) (1).

Among antibiotics, beta-lactams (BLs) are the most common trigger involved in children, with an estimated prevalence ranging between 1% and 10% (4). The prevalence of non-BLs allergy has been estimated to range between about 1% and 3%, and, in this group, macrolides and sulfonamides are the most frequently involved pharmacological categories of antibiotics (1,4). As for NSAIDs, a challenge-proven hypersensitivity has been estimated between 8% and 68% in different populations, with ibuprofen, acetaminophen (in young children) and ketoprofen being the most commonly involved drugs involved (4).

The aim of the present paper is to highlight the clinical features of DHRs to BLs and NSAIDs, the clinically validated *in vivo* diagnostic tools, and the possible therapeutic options, in children.

Pathophysiological and clinical features

Adverse reactions to drugs may be classified as type A or type B reactions (Figure 1) (5). Type A reactions are those due the pharmacological activity of the drug, while type B are also known as DHRs. Allergic immune reactions are the classical form of DHR, and they may be mediated by IgE (anaphylaxis, urticaria,...), T cells (maculopapular exanthema), or IgG (hemolytic anemia, immune-complex disease); *p-i* reactions are due to the direct binding between the drug and immune receptors, such as HLA and TCR, and are mediated by T cells only (maculopapular exanthema, generalized acute exanthematous pustulosis (AGEP),

drug eruption with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), hepatitis); in case of pseudo-allergic reactions, the drug binds directly to effector cells through receptors and enzymes: they are not a manifestation of a real allergy, but may clinical evoke it, as in the case of anaphylaxis or urticaria due to the binding of the drug to mast cells vis the MR-PGPRX2, or in the case of a reduced production of cyclooxygenase and increased release of leukotrienes, leading to the appearance of bronchospasm, asthma or urticaria, or in the case of bradykinin-induced angioedema (5).

Clinically, DHRs are classified as immediate, non-immediate/delayed, or accelerated reactions. While immediate reactions typically occur within one hour after the last drug administration, delayed ones appear at least 1 h afterwards; accelerate and delayed reactions are overlapping, since accelerated ones are recorded between 1 and 6 h after the last drug intake (3). If immediate reactions are mainly due to direct mast cell activation, or IgE-mediated hypersensitivity, delayed ones are generally caused by antigen-specific IgG production, complement activation or are T-cells mediated; as for accelerated reactions, they may be secondary to either IgE-related or T-cells mediated mechanisms (3).

In children, non-immediate reactions are more frequent than immediate ones, and skin manifestations are the most frequently reported symptom (1). This fact relates to one of the major problem in clinical practice: without performing an allergy evaluation, it is difficult to differentiate an infectious rash from a DHR. For this reason, in case of reported history or unavailable data on patient's serology during the appearance of the clinical symptom, the allergy work-up is often the only way to prove or exclude the responsibility of the drug to the reaction.

BLs are the most commonly prescribed antibiotics in children, and most pediatric patients consulting for a suspected DHRs reported a history of reactions to this category of antibiotics (1). Reported reactions mainly include maculopapular exanthema and urticaria/angioedema (3).

Immediate manifestations typically include urticaria/angioedema, rhinitis, conjunctivitis, anaphylaxis

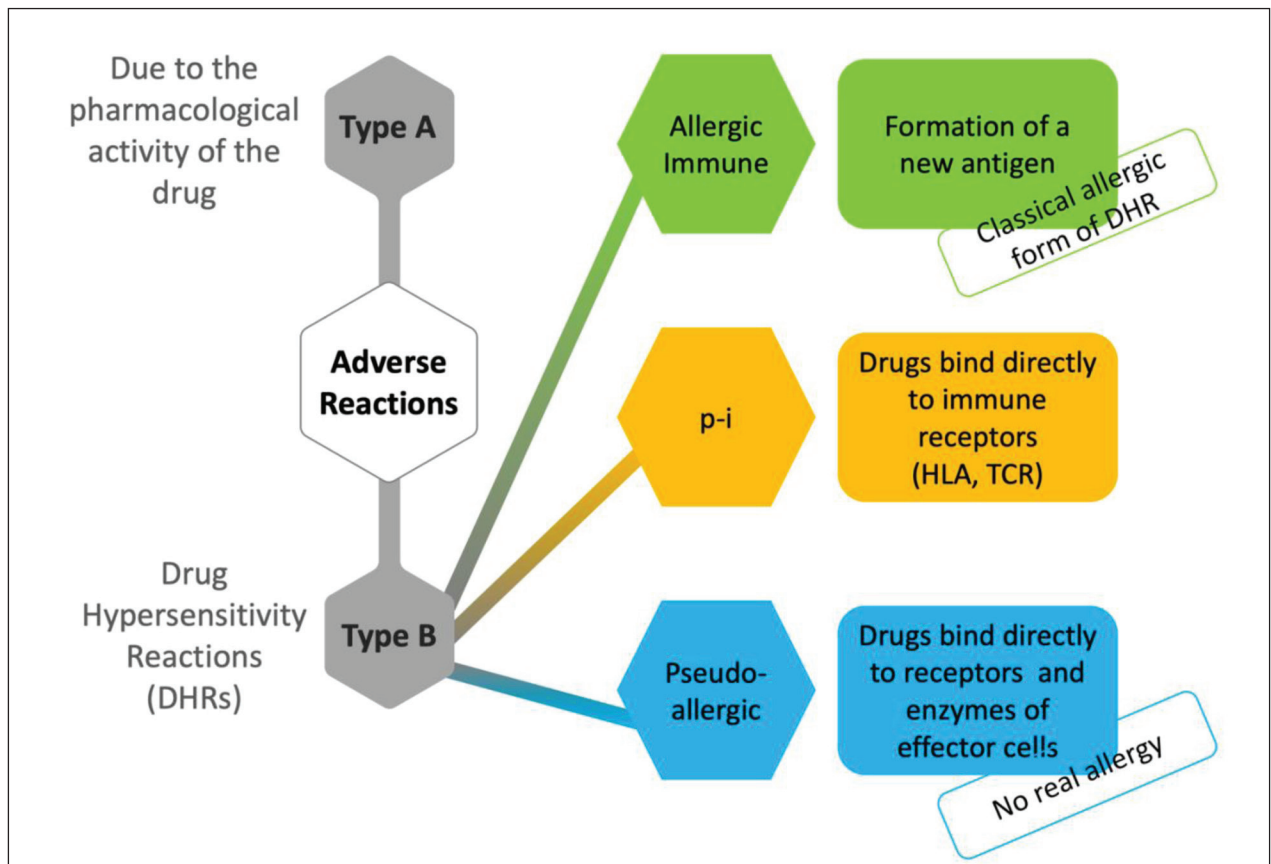


Figure 1. Drugs adverse reactions, based on the molecule mechanism of action. Adapted from (5)

(and anaphylactic shock), bronchospasm, and gastrointestinal symptoms (6). It should be noted that it is extremely rare that an immediate drug reaction may induce an isolated respiratory or digestive symptom: skin symptoms are the most frequent ones and they may be associated with other clinical manifestations (6).

Most common mild cutaneous non-immediate reactions are maculopapular exanthema, eczema, delayed urticaria and/or angioedema (3).

Delayed severe cutaneous adverse reactions (SCAR) include erythema multiforme major (EMM), AGEP, DRESS, SJS, TEN (3). Serum Sickness-Like Reactions (SSLRs) are very rare in children (0.02 to 0.2%) and mostly related to first generation cephalosporins (3).

Delayed severe organ reactions include nephritis, pneumoniae, haemolytic anaemia, cytopenia, hepatitis,

vasculitis and serum sickness, with or without cutaneous symptoms, and are rare in pediatrics. In children, drugs severe reactions seem to be more frequently associated with BLs, as recently reported by an Italian study, run in a specialized tertiary center (1). Hypersensitivity reactions to NSAIDs in children may be immune-mediated (through IgE or T-cells) and specific to one single molecule (7). Nevertheless, in most cases, patients present not immune-mediated reactions to several different molecules (7,8). These patients are defined as cross-intolerants or cross-reactors, while the first group is referred to as selective reactors (8). Cutaneous symptoms such as urticaria and angioedema are the most frequent reactions appearing during NSAID induced DHRs in children (9). One important clinical feature is isolated facial angioedema especially localized on lips or eyelids, and it seems to be more frequent in cross-intolerant patients (9).

One specific feature of non-allergic reactions due to NSAIDs hypersensitivity is the appearance of respiratory symptoms, such as bronchospasm (9). In most cases, this reaction is due to the pharmacological activity of these drugs: NSAIDs inhibit cyclooxygenase enzymes (COX-I and COX-II), that act in the synthesis of prostanoids (prostaglandins, prostacyclin, and thromboxane A₂ from arachidonic acid). Through this mechanism they may possibly cause a bronchial constriction, inducing the clinical symptom (6,9). Possibly, all the clinical features reported for BLs, may also be associated to NSAIDs hypersensitivity reactions. Compared to BLs, NSAIDs, and especially ibuprofen, are more often associated to anaphylaxis in children (1).

Skin tests

Traditionally, the same diagnostic algorithms and techniques are used both in children and adults, assuming that the immune system reacts in the same way at any age (2,10). Skin tests are usually the first *in vivo* step performed to diagnose DHRs: several standardized concentrations have been published, for different classes of drugs (6). DPT should not be routinely performed if patients present a history of severe cutaneous or severe organ delayed reaction (2). In case of a reported immediate reaction to BLs, skin prick tests (SPT) and intradermal tests (IDT) should be performed. In case of non-immediate reactions, a delayed-reading IDT could be performed, with evaluation of the local reaction up to 1 or 2 weeks after the test is performed (6). Patch tests could also be proposed for non-immediate reactions, but they show a low sensitivity (3). At any rate, whenever possible, clinicians should wait at least 1 month and maximum to 6 months to perform the allergy work-up after the allergic reaction (3). Skin tests to BLs are validated and their negative predictive value is high for immediate reactions, while their sensitivity is low for non-immediate ones (1,3). There is currently a debate concerning non-severe delayed reactions (especially maculopapular exanthema) in children. In fact, the use of skin tests poses special problems: particularly, IDTs, which are more sensitive than prick tests, are painful and may be poorly tolerated by small children (2). While some

authors advise to avoid skin tests in non-severe delayed reactions (11), others continue to highlight the importance of performing this procedure before exposing children to DPTs (10). Today, for non-severe non-immediate reactions, such as mild exanthemas, it has been proposed to perform drug provocation tests (DPT) without prior skin tests (2). For sure, in immediate reactions, skin tests should be performed. For BLs, the drug concentration should be of 20 mg/ml for both penicillins and cephalosporins. More detailed concentrations are shown in Table 1. In case of a reported NSAIDs hypersensitivity reaction, SPT, IDT, patch test, photo-patch test could be proposed as a first step in the allergy-work-up. In literature, skin testing has been used for the diagnosis of immediate reactions to metamizole, dipyrone, and paracetamol in children (8). In Table 1, we reported proposed concentrations and formulations of metamizole/dipyrone, and paracetamol for skin and intradermal testing proposed in literature (8,12). Even though it seems like intradermal test may be more sensitive, these tests are not standardized, and their overall sensitivity remains low (3). Therefore, the standard use of skin testing for the diagnosis of NSAIDs hypersensitivity cannot be recommended nowadays (8).

Drug Challenge

DPTs are the gold standard to diagnose DHR; ideally, a double-blind placebo DPT should be performed, but, in clinical setting, in most cases, an open challenge is proposed. The main problem related to a non-confirmed diagnosis of DHR is that, until a complete allergy work-up is not performed, patients risk to avoid without a reason specific drugs that are usually common and very useful in pediatrics: the DPT not only allows to diagnose a hypersensitivity to a molecule, but also permits to exclude its possible implication in the reported reaction, and to find a safe alternative in case of a proven DHR, avoiding non-optimized treatments (1). DPT is useful in both immediate and non-immediate reactions. DPT should always be supervised by personnel trained to promptly recognize and treat acute allergic reactions, including anaphylaxis (3). Patients should not be sick the day of the test

Table 1. Validated concentrations for skin prick tests (SPT) and intradermal tests (IDT) for beta-lactams and Non-Steroidal Anti-Inflammatory Drugs. Adapted from (8,12)

Hapten / Drug	SPT concentration	IDT concentration
Benzylpenicilloyl-poly-L-lysine	6.0×10^{-5} mol/L	6.0×10^{-5} mol/L
Benzylpenicilloyl-octa-L-lysine	8.64×10^{-5} mol/L	8.64×10^{-5} mol/L
Sodium benzylpenilloate	1.5×10^{-3} mol/L	1.5×10^{-3} mol/L
Benzylpenicillin	10,000 IU/mL	10,000 IU/mL
Amoxicillin and other semi-synthetic penicillins	20-25 mg/mL	20-25 mg/mL
Cefepime	2 mg/mL	2 mg/mL
Other cephalosporins	20 mg/mL	20 mg/mL
Clavulanic acid	20 mg/mL	20 mg/mL
Aztreonam	2 mg/mL	2 mg/mL
Imipenem-cilastatin	0.5 mg/mL	0.5 mg/mL
Meropenem and ertapenem	1 mg/mL	1 mg/mL
Paracetamol	10 mg/mL	1 mg/mL
Metamizole sodium	40- 400 mg/mL	0.4-4-40 mg/mL

and should not be taking any drug possibly interfering with the results of the challenge. DPT should not be performed if patients present a history of severe cutaneous or severe organ delayed reaction (2). DPT consists in administration of increasing doses of the tested drug, at predetermined time intervals, up to a cumulative daily therapeutic dose. The appearance of objective hypersensitivity symptoms correlates to a diagnosis of hypersensitivity to the tested drug. Whenever such symptoms appear, the DPT should be stopped, and the reaction properly treated. If no reaction appears during the test, a surveillance period is mandatory to verify if no symptom is noted after the end of the challenge. The duration of the surveillance period depends on the tested molecule and on the clinical history reported by the patient.

Beta lactams are a class of antibiotics considered essential for patients. For such reason, excluding these drugs from the possible therapeutic options for a child could lead to increased risk or lack of chance for a patient. DPT should be proposed in case of negative skin tests, in patients with a clinical history of a possible DHR. Whenever skin tests are positive, allergists

should look for an alternative drug (12). A possible protocol for DPT is shown in Table 2 (3,12).

In case of a hypersensitivity reaction to a NSAID, clinicians should first assess if the patient presented the reaction only to one molecule or to more. This aspect may help differentiating cross-intolerants from selective reactors patients. There is debate on whether a first DPT should be performed with aspirin or not. If a patient reacts to aspirin, he's more likely cross-intolerant, and an alternative drug should be found (13). Nevertheless, such diagnostic procedure might increase the number of DPTs needed to reach a diagnosis and potentially find an alternative, since, in most cases, reported reactions are not due to the suspected NSAID (14). The best option in pediatrics remains to test the culprit drug and, in case of a positive challenge, to find an alternative. In cross-intolerant patients, or whenever a safe alternative seems impossible to find, anti-COX-II specific preparations may be prescribed, even though not approved in children, to assure a possible anti-inflammatory drug in case of inflammation, fever, pain or need for general anesthesia (EAACI). Possible protocols for DPTs to NSAIDs are shown in Table 2 (3,15).

Table 2. Possible protocols to perform drug provocation tests for beta-lactams and Non-Steroidal Anti-Inflammatory Drugs, in children. Adapted from (3,12,15).

<i>Possible protocols</i>		<i>Interval between doses</i>
Drug Provocation Test for Beta Lactams		
Immediate reactions	(0.1)-(1)-10-40-50% of total daily dose.	30-60 minutes
	(1)-10-20-70% of total daily dose.	30-60 minutes
Non-immediate reactions	Same protocol as for immediate reactions. Afterwards, daily TD once a day, at home, for 5-7 days.	30-60 minutes
	Full-dose challenge. Afterwards, daily TD once a day, at home, for 5-7 days.	
Drug Provocation Test for Non-Steroidal Anti-Inflammatory Drugs		
Aspirin	4 doses of 2.5 mg/kg	60 minutes
	20-30-50% of the TD of 50 mg/kg	60 minutes
Ibuprofen	4 doses of 2.5 mg/kg	60 minutes
	20-30-50% of the TD of 50 mg/kg	60 minutes
Paracetamol	4 doses of 5 mg/kg	60 minutes
	10-25-65% of the TD of 60 mg/kg	60 minutes

Legend – TD: total dose.

Treatment

Whenever a diagnosis of DHR is reached, the drug should be avoided, and a possible alternative found. Nevertheless, if a patient has a proven drug hypersensitivity and a type I or type IV mechanism with non-severe clinical reaction has been highlighted, and the clinical history requires the use of an irreplaceable drug a drug desensitization protocol is indicated (4). A desensitization protocol provides a temporary tolerance to the drug, that is usually reached in 4 to 12 hours, and lasts only for 3-4 half-lives of the drug, this means that the drug will be accepted by the patient's immune system, for the whole course of a therapy, but, for each further treatment, the protocol needs to restart from the beginning (4). In pediatrics, there are few indications to prescribe a desensitization, including, for BLs, children suffering from severe and chronic infection diseases (tuberculosis, HIV, cystic fibrosis), and, for NSAIDs, children presenting with chronic inflammatory diseases (4).

Several protocols to perform desensitization have been described in the scientific literature for BLs, prov-

ing to be safe and effective (4). One of the more common protocol is the penicillin one, in which the concentration is doubled every 15-20 minutes, as shown in Table 3. The oral route of administration seems not only to be safer, but it also represents the preferred route in children (4).

Even though in most cases of NSAIDs hypersensitivity in children, reactions are not-allergic, desensitization protocols seem to be effective (4). Nevertheless, there are no publications specifically for children for aspirin, ibuprofen, or paracetamol desensitization, and today there is a lack of experience from clinicians, therefore recommendations cannot be made for the pediatric age (8).

Conclusions

Drug hypersensitivity reactions in children are an important topic of debate. The allergy work-up should always start with a complete collection of data from the patient's clinical history. Being able to differentiate immediate from non-immediate reactions and severe

Table 3. Possible protocols for drug desensitization to penicillins. Patients should be observed for 30 minutes, then full therapeutic dose should be administered. From (4)

Step	Oral				Intra-venous			
	Penicillin concentration (mg/ml)	Amount (ml)	Dose (mg)	Cumulative dose (mg)	Penicillin concentration (mg/ml)	Flow-rate (ml/h)	Dose (mg)	Cumulative dose (mg)
1	0.5	0.1	0.05	0.05	0.01	6	0.015	0.015
2	0.5	0.2	0.1	0.15	0.01	12	0.03	0.045
3	0.5	0.4	0.2	0.35	0.01	24	0.06	0.105
4	0.5	0.8	0.4	0.75	0.1	50	0.125	0.23
5	0.5	1.6	0.8	1.55	0.1	10	0.25	0.48
6	0.5	3.2	1.6	3.15	0.1	20	0.50	1.0
7	0.5	6.4	3.2	6.35	0.1	40	1.0	2.0
8	5.0	1.2	6.0	12.35	0.1	80	2.0	4.0
9	5.0	2.4	12.0	24.35	0.1	160	4.0	8.0
10	5.0	5.0	25.0	49.35	10.0	3	7.5	15.0
11	50.0	1.0	50.0	100.0	10.0	6	15.0	30.0
12	50.0	2.0	100.0	200.0	10.0	12	30.0	60.0
13	50.0	4.0	200.0	400.0	10.0	25	62.5	123.0
14	50.0	8.0	400.0	800.0	10.0	50	125.0	250.0
15					10.0	100	250.0	500.0
16					10.0	200	500.0	1000.0

from non-severe ones is crucial to decide the clinical approach for each patient. In case of SCAR, the drug should be avoided. In case of a suspected hypersensitivity reaction to BLs, if an immediate reaction was recorded, skin tests should be performed, prior to a DPT. The challenge remains the gold standard to reach a diagnosis, and, in selected patients, a drug desensitization protocol may be proposed. In patients with a history of DHR to NSAIDs, even though in most cases reactions are non-immune mediated, the DPT is the only test able to confirm or exclude a possible hypersensitivity, in both selective-reactors and cross-intolerant patients. Not only specialists, but also primary care physicians should be aware of the possible diagnostic and therapeutic options in children with a history of DHRs, in order to reduce misdiagnosis and to optimize patients' management, especially in children.

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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