

R E V I E W

Pediatric drug hypersensitivity: which diagnostic tests?

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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 pustulosis (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 FcεRI. 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 $\geq 20\%$ 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 *sodium 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

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%

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

Drug	Prick test (mg/mL)	Intradermal test (mg/mL)
Clarithromycin	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.

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

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

(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 is 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 sessions 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, prothamine. 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
Lidocaine	10	1000
Mepivacaine	10	1000
Chlorhexidine	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
Alfentanil	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-propion-

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

ate, 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.

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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