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Review

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 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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References

1. Gomes ER, Brockow K, Kuyucu S, et al. Drug hypersensitivity in children: report from the pediatric task force of the EAACI Drug Allergy Interest Group. Allergy 2016; 71: 149-161.
1. Foong RX, Logan K, Perkin MR, du Toit G. Lack of uniformity in the investigation and management of suspected beta-lactam allergy in children. Pediatr Allergy Immunol 2016; 27: 527-32.
2. Smyth RM, Gargon E, Kirkham J, et al. Adverse drug reactions in children-a systematic review. PLoS One 2012; 7: e24061.
3. Rebelo GE, Fonseca J, Araujo L, Demoly P. Drug allergy claims in children: from self-reporting to confirmed diagnosis. Clin Exp Allergy 2008; 38: 191-198.
4. Lange L, Koningsbruggen SV, Rietschel E. Questionnaire-based survey of lifetime prevalence and character of allergic drug reactions in German children. Pediatr Allergy Immunol 2008; 19: 634-638.
5. Orhan F, Karakas T, Cakir M, et al. Parental-reported drug allergy in 6- to 9-yr-old urban schoolchildren. Pediatr Allergy Immunol 2008; 19: 82-85.
6. Erkocoglu M, Kaya A, Civelek E, et al. Prevalence of confirmed immediate type drug hypersensitivity reactions among school children. Pediatr Allergy Immunol 2013; 24: 160- 167.
7. Brockow K, Przybilla,B, Aberer, W et al. Guideline for the diagnosis of drug hypersensitivity reactions. Allergo Journal International 2015; 24: 94-105.
8. Fernandez TD, Torres MJ, Blanca-Lopez N, et al. Negativization rates of IgE radioimmunoassay and basophil activation test in immediate reactions to pennicillins. Allergy 2009; 64: 242-8.
9. Demoly P, Kropf R, Bircher A, Pichler W for the EAACI Interest Group on Drug Hypersensitivity. Drug hypersensitivity: questionnaire. Allergy 1999; 54: 999-1003.

10. Brockow K, Aberer W, Atanaskovic-Markovic M, et al. Drug allergy passport and other documentation for patients with drug hypersensitivity - An ENDA/EAACI Drug Allergy Interest Group Position Paper. Allergy 2016; 71: 1533-1539.
11. Brockow K, Romano A, Blanca M, Ring J, Pichler W, Demoly P. General considerations for skin test procedures in the diagnosis of drug hypersensitivity. Allergy 2002: 57: 45-51.
12. Brockow K, Garvey LH, Aberer W, et al. Skin test concentrations for systemically administered drugs - an ENDA/EAACI Drug Allergy Interest Group position paper. Allergy 2013; 68: 702-12.
13. Caubet JC, Kaiser L, Lemaitre B, Fellay B, Gervaix A, Eigenmann PA. The role of penicillin in benign skin rashes in childhood: a prospective study based on drug rechallenge. J Allergy Clin Immunol 2011; 127: 218-222.
14. Ponvert C, Perrin Y, Bados-Albiero A, et al. Allergy to betalactam antibiotics in children: results of a 20-year study based on clinical history, skin and challenge tests. Pediatr Allergy Immunol 2011; 22: 411-418.
15. Ponvert C, Weilenmann C, Wassenberg J, et al. Allergy to betalactam antibiotics in children: a prospective follow-up study in retreated children after negative responses in skin and challenge tests. Allergy 2007; 62: 42-46.
16. Joint Task Force on Practice Parameters; American Academy of Allergy, Asthma and Immunology; American College of Allergy, Asthma and Immunology; Joint Council of Allergy, Asthma and Immunology. Drug allergy: an updated practice parameter. Ann Allergy Asthma Immunol. 2010; 105: 259-273.
17. Dworzynski K, Ardern-Jones M, Nasser S. Diagnosis and management of drug allergy in adults, children and young people: summary of NICE guidance. Br Med Journal 2014; 349: g4852.
18. Aberer W, Bircher A, Romano A et al. Drug provocation testing in the diagnosis of drug hypersensitivity reactions: general considerations. Allergy 2003; 58: 854-863.
19. Demoly P, Adkinson NF, Brockow K, et al. International consensus on drug allergy. Allergy 2014; 69: 420-437.
20. Moral L, Caubet JC. Oral challenge without skin tests in children with non-severe beta-lactam hypersensitivity: Time to change the paradigm? Pediatr Allergy Immunol 2017; 28: 724-727.
21. Graham F, Tsabouri S, and Caubet JC. Hypersensitivity reactions to beta-lactams in children. Curr Opin Allergy Clin Immunol 2018; 18: 284-290.
22. Mill C, Primeau MN, Medoff E, et al. Assessing the diagnostic properties of a graded oral provocation challenge for the diagnosis of immediate and non immediate reactions to amoxicillin in children. JAMA Pediatr 2016; 170: e160033.
23. Vezir E, Dibek Misirlioglu E, Civelek E, et al. Direct oral provocation tests in non immediate mild cutaneous reactions related to beta-lactam antibiotics. Pediatr Allergy Immunol 2016; 27: 50-54.
24. Confino-Cohen R, Rosman Y, Meir-Shafrir K, et al. Oral challenge without skin testing safely excludes clinically significant delayed-onset penicillin hypersensitivity. J Allergy Clin Immunol Pract 2017; 5: 669-675.
25. Labrosse R, Paradis L, Lacombe J, et al. Efficacy and safety of five-day challenge for the evaluation of non severe amoxicillin allergy in children. J Allergy Clin Immunol Pract 2018; 6: 1673-1680.
26. Caffarelli C, Franceschini F, Caimmi D, et al. SIAIP position paper: provocation challenge to antibiotics and non-steroidal anti-inflammatory drugs in children. Ital J Pediatr 2018; 44: 147.
27. Korpela K, de Vos WM. Antibiotic use in childhood alters the gut microbiota and predisposes to overweight. Microb Cell 2016; 3: 296-298.
28. Brunser O, Gotteland M, Cruchet S, Figueroa G, Garrido D, Steenhout P. Effect of a milk formula with prebiotics on the intestinal microbiota of infants after an antibiotic treatment. Pediatr Res 2006; 59: 451-456.
29. Mayorga C, Celik G, Rouzaire P, Whitaker P, Bonadonna P, Rodrigues-Cernadas J, et al. In vitro tests for drug hypersensitivity reactions: an ENDA/EAACI Drug Allergy Interest Group position paper. Allergy 2016; 71: 1103-1134.
30. Mockenhaupt M. Severe drug-induced skin reactions: clinical pattern, diagnostics and therapy. J Dtsch Dermatol Ges 2009; 7: 142-162.
31. Shiohara T, Mizukawa T. The immunological basis of lichenoid tissue reaction. Autoimmun Rev 2005; 4: 236-41.
32. Shiohara T. Fixed drug eruption: pathogenesis and diagnostic tests. Curr Opin Allergy Clin Immunol 2009; 9: 316-321.
33. Cho YT, Lin JW, Chen YC, et al. Generalized bullous fixed drug eruption is distinct from Stevens-Johnson syndrome/toxic epidermal necrolysis by immunohistopathological features. J Am Acad Dermatol 2014; 70: 539-48.
34. Paulmann M, Mockenhaupt M. Severe drug-induced skin reactions: clinical features, diagnosis, etiology, and therapy . J Dtsch Dermatol Ges 2015; 13: 625-45.
35. Noguera-Morel L, Hernández-Martín A, Torrelo A. Cutaneous drug reactions in the pediatric population. Pediatr Clin N Am 2014; 61: 403-426.
36. Baldo BA, Fisher MM. Substituted ammonium ions as allergenic determinants in drug allergy. Nature 1983; 306, 262-264.
37. Decuyper II, Mangodt EA, Van Gasse AL et al. In Vitro Diagnosis of Immediate Drug Hypersensitivity Anno 2017: Potentials and Limitations. Drugs R D 2017; 17: 265-278.
38. Ebo DG, Dombrecht EJ, Bridts CH, Aerts NE, De Clerk LS, Stevens WJ. Combined analysis of intracellular signalling and immunophenotype of human peripheal blood basophils by flow cytometry: a proof of concept. Clin Exp Allergy 2007; 37: 1668-1675.
39. Sanz LM, Gamboa PM, De Weck AL. Drug Hypersensitivity; In vitro tests: Basophil activation tests. pg 395. Pichler WJ. Karger Edition 2007.
40. Hausmann OV, Gentinetta T, Bridts CH, Ebo DG. The basophil activation test in immediate-type drug allergy. Immunol Allergy Clin North Am 2009; 29: 555-566.

41. Kepley CL, Youssef L, Andrews RP, Wilson BS, Oliver JM. Sky deficiency in non-releaser basophils. J Allergy Clin Immunol 1999; 104: 279-284.
42. Ebo DG, Leysen J , Mayorga C, Rozieres A, Knol EF, Terreehorst I. The in vitro diagnosis of drug allergy: status and perspectives. Allergy 2011; 66: 1275-1286.
43. Woo-Jung Song, Yoon-Seok Chang. Recent applications of basophil activation tests in the diagnosis of drug hypersensitivity. Asia Pac Allergy 2013; 3: 266-280.
44. Mangodt EA, Van Gasse AL, Decuyper I et al. In vitro Diagnosis of Immediate Drug Hypersensitivity: Should We Go with the Flow? Int Arch Allergy Immunol 2015; 168: 3-12.
45. Laguna JJ, Bogas G, Salas M et al. The Basophil Activation Test Can Be of Value for Diagnosing Immediate Allergic Reactions to omeoprazole. J Allergy Clin Immunol Pract 2018; 6: 1628-36.
46. Nyfeler B, Pichler WJ. The lymphocyte transformation test for the diagnosis of drug allergy: sensitivity and specificity. Clin Exp Allergy 1997; 27: 175-181.
47. Cavkaytar O, Karaatmaca B, Arik Yilmaz E et al. Basal serum tryptase is not a risk factor for immediate-type drug hypersensitivity during childhood. Pediatr Allergy Immunol 2016; 27: 736-742.
48. Sousa-Pinto B, Pinto-Ramos J, Correia C et al. Pharmacogenetics of abacavir hypersensitivity: a systematic review and metaanalysis of the association with HLAB*57:01. J Allergy Clin Immunol 2015; 136: 1092-1094.
49. Mallal S, Phillips E, Carosi G et al. HLA-B*5701 screening for hypersensitivity to abacavir. N Engl J Med 2008; 358: 568-579.
50. Manglani MV, Gabhale YR, Lala MM, Sekhar R, More D . HLA- B*5701 Allele in HIV-infected Indian Children and its Association with Abacavir Hypersensitivity. Indian Pediatr. 2018; 55: 140-141.
51. Rauch A, Nolan D, Martin A, McKinnon E, Almeida C, Mallal S. Prospective genetic screening decreases the incidence of abacavir hypersensitivity reactions in the Western Australian HIV cohort study. Clin Infect Dis 2006; 43: 99-102.
52. Waters LJ, Mandalia S, Gazzard B, Nelson M. Prospective HLA-B*5701 screening and abacavir hypersensitivity: a single centre experience. AIDS 2007; 21: 2533-2534.
53. Zucman D, Truchis P, Majerholc C, Stegman S, Caillat-Zucman S. Prospective screening for human leukocyte antigen-B*5701 avoids abacavir hypersensitivity reaction in the ethnically mixed French HIV population. J Acquir Immune Defic Syndr 2007; 45: 1-3.
54. Amstutz U, Ross CJ, Castro-Pastrana LI et al. HLA-A 31:01 and HLA-B 15:02 as genetic markers for carbamazepine hypersensitivity in children. Clin Pharmacol Ther 2013; 94: 142-9.
55. Khanna D, Fitzgerald JD, Khanna PP, et al. 2012 American College of Rheumatology guidelines for management of gout. Part 1: systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia. Arthritis Care Res (Hoboken) 2012; 64: 1431-1446.
56. Vultaggio A, Matucci A, Virgili G, et al. Influence of total serum IgE levels on the in vitro detection of beta-lactams-specific IgE antibodies. Clin Exp Allergy 2009; 39: 838-844.
57. Barni S, Mori F, Valleriani C, et al. The utility of the basophil activation test in the diagnosis of immediate amoxicillin or amoxicillin-clavulanate hypersensitivity in children and adults. Ital J Pediatr. 2017; 43: 42-46.
58. Mori F, Fili L, Barni S, et al. Sensitization to amoxicillin/clavulanic acid may underlie severe rashes in children treated for infectious mononucleosis. J Allergy Clin Immunol Pract. 2018; In press https://doi.org/10.1016/j.jaip.2018.06.022
59. Kuyucu S, Mori F, Atanaskovic-Markovic M, et al. Hypersensitivity reactions to non-betalactam antibiotics in children: An extensive review. Pediatr Allergy Immunol 2014: 25: 534-543.
60. Macy E, Poon K-Y. Self-reported antibiotic allergy incidence and prevalence: age and sex effects. Am J Med 2009: 122: 778.e1-7.
61. Blanca-Lopez N, Andreu I, Torres Jaen MJ. Hypersensitivity reactions to quinolones. Curr Opin Allergy Clin Immunol 2011: 11: 285-91.
62. Mori F, Pecoraro F, Pantano A, et al. Azithromycin anaphylaxis in children. Int J Immunopathol Pharmacol 2014: 27: 81-6.
63. Mori F, Barni S, Pucci N, et al. Sensitivity and specificity of skin tests in the diagnosis of clarithromycin allergy. Ann Allergy Asthma Immunol 2010: 104: 417-9.
64. Binenbaum G, Bruno CJ, Forbes BJ et al. Periocular ulcerative dermatitis associated with gentamicin ointment prophylaxis in newborns. J Pediatr 2010; 156: 320-1.
65. Machovcova A. The frequency of contact allergy in children and adolescents in the Czech Republic. Acta Dermatovenerol Croat 2012: 20: 75-9.
66. Le J, Nguyen T, Law AV, Hodding J. Adverse drug reactions among children over a 10-year period. Pediatrics 2006: 118: 555-62.
67. Levy M, Koren G, Dupuis L, Read SE. Vancomycin-induced red man syndrome. Pediatrics 1990: 86: 572-80.
68. Ben Said B, Berard F, Bienvenu J, Nicolas JF, Roziers A. Usefulness of basophil activation tests for the diagnosis of IgE-mediated allergy to quinolones. Allergy 2010: 65: 535-6.
69. Kidon M, Blanca-Lopez N, Gomes E et al. EAACI/ENDA Position Paper: Diagnosis and management of hypersensitivity reactions to non-steroidal anti-inflammatory drugs (NSAIDs) in children and adolescents. Pediatr Allergy Immunol 2018; 29: 469-480.
70. Cousin M, Chiriac A, Molinari N, Demoly P, Caimmi D. Phenotypical characterization of children with hypersensitivity reactions to NSAIDs. Pediatr Allergy Immunol 2016; ;27: 743-748.
71. Gonçalo M, James Ferguson J, Bonevalle A et al. Photopatch testing: recommendations for a European photopatch test baseline series Contact Dermatitis 2013; 68, 239-243.
72. Ariza A, Fernandez TD, Doña I et al. Basophil activation

after nonsteroidal anti-inflammatory drugs stimulation in patients with immediate hypersensitivity reactions to these drugs. Cytometry Part A 2014; 85a: 400-407.
73. Steiner M, Harrer A, Lang R, et al. Basophil activation test for investigation of IgE mediated mechanism in drug hypersensitivity. J Vis Exp 2011; 55: 3263.
74. Gomez E, Blanca-Lopez N, Torres MJ et al. Immunoglobulin E-mediated immediate allergic reactions to dipyrone: value of basophil activation test in the identification of patients. Clin Exp Allergy 2009; 39: 1217-1224.
75. Kowalski ML, Asero R, Bavbek S, et al. Classification and practical approach to the diagnosis and management of hypersensitivity to non-steroidal anti-inflammatory drugs. Allergy 2013; 68: 1219-1232.
76. Man CB, Kwan P, Baum L, et al. Association between HLA-B*1502 allele and antiepileptic drug-induced cutaneous reactions in Han Chinese Epilepsia 2007; 48: 1015-8.
77. Locharernkul C, Loplumlert J, Limotai C, et al. Carbamazepine and phenytoin induced Stevens-Johnson syndrome is associated with HLA-B*1502 allele in Thai population. Epilepsia 2008; 49: 2087-91.
78. Chang CC, Too CL, Murad S, Hussein SH. Association of HLA-B*1502 allele with carbamazepine-induced toxic epidermal necrolysis and Stevens-Johnson syndrome in the multi-ethnic Malaysian population. Int J Dermatol 2011; 50: 221-4.
79. Barbaud A, Gonçalo M, Bruynzeel D, Bircher A, European Society of Contact Dermatitis. Guidelines for performing skin tests with drugs in the investigation of cutaneous adverse drug reactions. Contact Dermatitis 2001; 45: 321-8.
80. Barbaud A. Drug patch tests in the investigation of cutaneous adverse drug reactions. Ann Dermatol Venereol 2009; 136: 635-44.
81. Pinnobphun P, Buranapraditkun S, Kampitak T, Hirankarn N, Klaewsongkram J. The diagnostic value of basophil activation test in patients with an immediate hypersensitivity reaction to radiocontrast media. Ann Allergy Asthma Immunol 2011; 106: 387-93.
82. Salas M, Gomez F, Fernandez TD, et al. Diagnosis of immediate hypersensitivity reactions to radiocontrast media. Allergy 2013; 68: 1203-6.
83. Rosado Ingelmo A, Doña Diaz I, Cabañas Moreno R et al. Clinical Practice Guidelines for Diagnosis and Management of Hypersensitivity Reactions to Contrast Media. J Investig Allergol Clin Immunol 2016; 26: 144-155.
84. Yamaguchi K, Katayama H, Takashima T, Kozuka T, Seez P, Matsuura K. Prediction of severe adverse reactions to ionic and nonionic contrast media in Japan: evaluation of pretesting. A report from the Japanese Committee on the Safety of Contrast Media. Radiology 1991; 178: 363-7.
85. Brockow K, Romano A, Aberer W et al. Skin testing in patients with hypersensitivity reactions to iodinated contrast media - a European multicenter study. Allergy 2009; 64: 234-41.
86. Trcka J, Schmidt C, Seitz CS, Brocker EB, Gross GE, Trautmann A. Anaphylaxis to iodinated contrast material: non-allergic hypersensitivity or IgE-mediated allergy? AJR Am J Roentgenol 2008; 190: 666-70.
87. Torres MJ, Gomez F, Doña et al. Diagnostic evaluation of patients with nonimmediate cutaneous hypersensitivity reactions to iodinated contrast media. Allergy 2012; 67: 929-35.
88. Gomez E, Ariza A, Blanca-Lopez N, Torres MJ. Nonimmediate hypersensitivity reactions to iodinated contrast media. Curr Opin Allergy Clin Immunol. 2013; 13: 345-53.
89. Prieto-García A, Tomás M, Pineda R et al. Skin test-positive immediate hypersensitivity reaction to iodinated contrast media: the role of controlled challenge testing. J Investig Allergol Clin Immunol 2013; 23: 183-9.
90. Schrijvers R, Breynaert C, Ahmedali Y, Bourrain JL, Demoly P, Chiriac AM. Skin testing for suspected iodinated contrast media hypersensitivity. J Allergy Clin Immunol Pract 2018; 6: 1246-1254.
91. Dillman JR, Ellis JH, Cohan RH, Strouse PJ, Jan SC. Frequency and severity of acute allergic-like reactions to gadolinium-containing IV contrast media in children and adults. Am J Roentgenol 2007; 189: 1533-1538.
92. Dillman JR, Strouse PJ, Ellis JH, Cohan RH, Jan SC. Incidence and severity of acute allergic-like reactions to IV nonionic iodinated contrast material in children. Am J Roentgenol 2007; 188: 1643-1647.
93. Callahan MJ, Poznauskis L, Zurakowski D, Taylor GA. Nonionic iodinated intravenous contrast material-related reactions: incidence in large urban children's hospital-retrospective analysis of data in 12,494 patients. Radiology 2009; 250: 674-81.
94. Mertes PM, Laxenaire MC, Lienhart A et al. Reducing the risk of anaphylaxis during anesthesia: guidelines for clinical practice. J Invest Allergol Clin Immunol 2005; 15: 91-101 .
95. Hsu Blatman KS, Hepner DL. Current knowledge and management of hypersensitivity to perioperative drugs and radiocontrast media. J Allergy Clin Immunol Pract 2017; 5: 587-92.
96. Takazawa T, Mitsuhata H, Mertes PM. Sugammadex and rocuroniuminduced anaphylaxis. J Anesth 2016; 30: 290-297.
97. Krishna MT, York M, Chin T et al. Multicentre retrospective analysis of anaphylaxis during general anaesthesia in the United Kingdom: aetiology and diagnostic performance of acute serum tryptase. Clin Exp Immunol 2014; 178: 399-404.
98. Mertes PM, Moneret-Vautrin DA, Leynadier F, et al. Skin reactions to intradermal neuromuscular blocking agent injections: a randomized multicenter trial in healthy volunteers. Anesthesiology 2007; 107: 245-52.
99. Mertes PM, Aimone-Gastin I, Gueant-Rodriguez RM, et al. Hypersensitivity reactions to neuromuscular blocking agents. Curr Pharm Des 2008; 14: 2809-25.
100. Ewan PW, Dugue P, Mirakian R, Dixon TA, Harper JN, Nasser SM. BSACI guidelines for the investigation of sus-

pected anaphylaxis during general anaesthesia. Clin Exp Allergy 2010; 40: 15-31.
101. Harboe T, Johansson SGO, Florvaag E, Öman H. Pholcodine exposure raises serum IgE in patients with previous anaphylaxis to neuromuscular blocking agents. Allergy 2007; 62: 1445-50.
102. Ebo DG, Venemalm L, Bridts CH, et al. Immunoglobulin E antibodies to rocuronium. Anesthesiology 2007; 107: 253-9.
103. Sharma V, Harper NJN, Garcez T, Arkwright PD. Allergic reaction to mepivacaine in a child. Br J Anaesth 2013; 110: 1059-61.
104. Allen G, Chan D, Gue S. Case report: investigation and diagnosis of an immediate allergy to amide local anaesthetic in a paediatric dental patient. Aust Dent J 2017; 62: 241-245.
105. Kvisselgaard AD, Krøigaard M, Mosbech HF, Garvey LH. No cases of perioperative allergy to local anaesthetics in the Danish Anaesthesia Allergy Centre. Acta Anaesthesiol Scand 2017; 61: 149-155.
106. Malinovsky JM, Chiriac AM, Tacquard C, Mertes PM, Demoly P. Allergy to local anesthetics: reality or mith? Presse Med 2016; 45: 753-7.
107. Bhole MV, Manson AL, Seneviratne SL, Misbah SA. IgE-mediated allergy to local anaesthetics: separating fact from perception: a UK perspective. Br J Anaesth 2012; 108: 903-11.
108. Matura G. Contact allergy to corticosteroids. Allergy 2000; 55: 698-704.
109. Baeck M, Marot L, Nicolas JF, Pilette C, Tennstedt D, Goossens A. Allergic hypersensitivity to topical and systemic corticosteroids: a review. Allergy 2009: 64: 978-94.
110. Klein-Gitelman MS, Pachman LM. Intravenous corticosteroids: adverse reactions are more viable than expected in children. J Rheumatol 1998; 25: 1995-2002.
111. Peng YS1, Shyur SD, Lin HY, Wang CY. Steroid allergy: report of two cases. J Microbiol Immunol Infect 2001; 34: 150-4.
112. Nahum A, Garty BZ, Marcus N, Shoenfeld T, Levy Y. severe hypersensitivity reactions to corticosteroids in children. Pediatr Emerg Care 2009; 25: 339-341.
113. De Sousa G, Santa-Marta C, Morais-Almeida M. Systemic corticosteroid hypersensitivity in children. J Investig Allergol Clin Immunol 2010; 20: 529-532.
114. Otani IM, Banerji A. Immediate and delayed hypersensitivity reactions to corticosteroids: evaluation and management. Curr Allergy Asthma Rep 2016; 16: 18-26.
115. Patel A, Bahna S. Immediate hypersensitivity reactions to corticosteroids. Ann Allergy Asthma Immunol 2015; 115: 178-182.
116. Nowak-Wegrzyn A, Shapiro G, Beyer K, Bardina L, Sampson H. Contamination of dry powder inhalers for asthma with milk proteins containing lactose. J Allergy Clin Immunol 2004; 113: 558-60.
117. Caglayan Sozmen S, Povesi Dascola C, Gioia E, Mastrorilli C, Rizzuti L, Caffarelli C. Diagnostic accuracy of patch test in children with food allergy. Pediatr Allergy Immunol 2015; 26: 416-22.
118. Boffa MJ, Wilkinson SM, Beck MH. Screening for corticosteroid contact hypersensitivity. Contact Dermatitis 1995; 33: 149-51.
119. Warshaw EM, Belsito DV, Taylor JS, et al. North American Contact Dermatitis Group patch test results: 2009 to 2010. Dermatitis 2013; 24: 50-9.
120. Matura M, Lepoittevin JP, Arbez Gindre C, Goossens A. Testing with corticosteroid aldehydes in corticosteroid sensitive patients (preliminary results). Contact Dermatitis 1998; 38: 106-8.
121. Dooms-Goossens A. Corticosteroid contact allergy: a challenge to patch testing. Am J Contact Dermat 1993; 4: 120-122.
122. Ruggiero A, Triarico S, Trombatore G, et al. Incidence, clinical features and management of hypersensitivity reactions to chemotherapeutic drugs in children with cancer. Eur J Clin Pharmacol 2013; 69: 1739-46.
123. Cernadas JR. Reactions to cytostatic agents in children. Curr Opin Allergy Clin Immunol 2017; 17: 255-261.
124. Lafay-Cousin L, Sung L, Carret AS, et al. Carboplatin hypersensitivity reaction in pediatric patients with low-grade glioma: a Canadian Pediatric Brain Tumor Consortium experience. Cancer 2007; 112, 892-899.
125. Dodgshun AJ, Hansford JR, Cole T, Choo S, and Sullivan MJ. Carboplatin hypersensitivity reactions in pediatric low grade glioma are protocol specific and desensitization show poor efficacy. Pediatr Blood Cancer 2016; 63, 17-20.
126. Ruggiero A, Rizzo D, Catalano M, Attinà G, Riccardi R. Hypersensitivity to Carboplatin in Children with Malignancy. Front. Pharmacol 2017; 8: 201.
127. Zanotti KM, Rybicki LA, Kennedy AW et al. Carboplatin skin testing: a skin-testing protocol for predicting hypersensitivity to carboplatin chemotherapy. J Clin Oncol 2001; 19: 3126-3129.
128. Markman M, Zanotti K, Peterson G, Kulp B, Webster K, Belison J. Expanded experience with an intradermal skin test to predict for the presence or absence of carboplatin hypersensitivity. J Clin Oncol 2003; 21: 4611-4614.
129. Körholz D, Wahn U, Jürgens H, Wahn V. Allergic reactions in treatment with L-asparaginase. Significance of specific IgE antibodies. Monatsschr Kinderheilkd 1990; 138: 23-25.
130. Soyer OU, Aytac S, Tuncer A, Cetin M, Yetgin S, Sekerel BE. Alternative algorithm for L-asparaginase allergy in children with acute lymphoblastic leukemia. J Allergy Clin Immunol 2009; 123: 895-899.
131. Caldeira T, Costa V, Silva I, Oliva T, Norton L. Anaphylactoid reaction to high-dose methotrexate and re-administration after a successful desensitization. Pediatr Hematol Oncol 2008; 25: 131-4.
132. Bouchireb K, Dodille A, Ponvert C, Gouraud F, Dubrel M, Brugieres L. Management and successful desensitization in methotrexate-induced anaphylaxis. Pediatr Blood Cancer 2009; 52: 295-297.

133. Oulego-Erroz I, Maneiro-Freire M, Bouzón-Alejandro M, Vázquez-Donsión M, Couselo JM. Anaphylactoid reaction to high-dose methotrexate and successful desensitization. Pediatr Blood Cancer 2010; 55: 557-559.
134. Scott JR, Ward DA, Crews KR, Panetta JC, Navid F. Hypersensitivity reaction to high-dose methotrexate and successful rechallenge in a pediatric patient with osteosarcoma. Pediatr Blood Cancer 2014; 61: 373-375.
135. Dilley MA, Lee JP, Dioun Broyles A. Methotrexate hypersensitivity reactions in Pediatrics: evaluation and management. Pediatr Blood Cancer 2017; 64: e26306.
136. Picard M, Galvao VR. Current knowledge and management of hypersensitivity reactions to monoclonal antibodies. J Allergy Clin Immunol Pract 2017; 5: 600-9.
137. Brennan PJ, Bouza T, Hsu IF, Sloane DE, Castells MC. Hypersensitivity reactions to mAbs: 105 desensitizations in 23 patients, from evaluation to treatment. J Allergy Clin Immunol 2009; 124: 1259-66.
138. Commins SP, Platts-Mills TAE. Delayed Anaphylaxis to Red Meat in Patients with IgE Specific for Galactose alpha-1,3-Galactose (alpha-gal). Curr Allergy Asthma Rep 2013; 13: 72-77.
139. Kennedy JL, Stallings AP, Thomas Platts-Mills TAE, et al. Galactose-a-1,3-galactose and delayed anaphylaxis, angioedema, and urticaria in children. Pediatrics 2013; 131: e1545-e1552.
140. Corradi M, Zinelli C, Caffarelli C. Exhaled breath biomarkers in asthmatic children. Inflamm Allergy Drug Targets 2007; 6: 150-9.
141. Caffarelli C, Dascola CP, Peroni D, Ricò S, Stringari G, Varini M, Folesani G, Corradi M. Airway acidification in childhood asthma exacerbations. Allergy Asthma Proc 2014; 35: 51-6.
142. Caffarelli C, Calcinai E, Rinaldi L, Povesi Dascola C, Terracciano L, Corradi M. Hydrogen peroxide in exhaled breath condensate in asthmatic children during acute exacerbation and after treatment. Respiration 2012; 84: 291-8.
143. Zinelli C, Caffarelli C, Strid J, Jaffe A, Atherton DJ. Measurement of nitric oxide and 8-isoprostane in exhaled breath of children with atopic eczema. Clin Exp Dermatol 2009; 34: 607-12.
144. Caffarelli C, Dondi A, Povesi Dascola C, Ricci G. Skin prick test to foods in childhood atopic eczema: pros and cons. Ital J Pediatr 2013; 31; 39:48.

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