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REVIEW ARTICLE

Drug hypersensitivity in children: report from the pediatric task force of the EAACI Drug Allergy Interest Group

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Abstract

When questioned, about 10% of the parents report suspected hypersensitivity to at least one drug in their children. However, only a few of these reactions can be confirmed as allergic after a diagnostic workup. There is still a lack of knowledge on drug hypersensitivity (DH) epidemiology, clinical spectrum, and appropriate diagnostic methods particularly in children. Meanwhile, the tools used for DH management in adults are applied also for children. Whereas this appears generally acceptable, some aspects of DH and management differ with age. Most reactions in children are still attributed to betalactams. Some manifestations, such as nonsteroidal anti-inflammatory drug-associated angioedema and serum sickness-like reactions, are more frequent among young patients as compared to adults. Risk factors such as viral infections are particularly frequent in children, making the diagnosis challenging. The practicability and validity of skin test and other diagnostic procedures need further assessment in children. This study presents an up-to-date review on epidemiology, clinical spectrum, diagnostic tools, and current management of DH in children. A new general algorithm for the study of these reactions in children is proposed. Data are presented focusing on reported differences between pediatric and adult patients, also identifying unmet needs to be addressed in further research.

Abbreviations
ADR, adverse drug reactions; AGEP, acute generalized exanthemous pustolosis; BAT, basophil activation test; BL, betalactams; DH, drug hypersensitivity; DHR, drug hypersensitivity reactions; DPT, drug provocation test; DRESS, drug reaction with eosinophilia and systemic symptoms; EAACI, European Academy of Allergy and Clinical Immunology; ENDA, European Network for Drug Allergy; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; HIV, human immunodeficiency virus; IDT, intradermal test; LTT, lymphocyte transformation test; MPE, maculopapular exanthema; NMBA, neuromuscular blocking agents; NSAID, nonsteroidal anti-inflammatory drug; RCM, radiocontrast media; SCARs, severe cutaneous adverse reactions; SJS, Stevens–Johnson syndrome; SPT, skin prick test; SSLR, serum sickness-like reaction; TEN, toxic epidermal necrolysis.

When questioned, about 10% of the parents report suspected hypersensitivity to at least one drug in their children (1–5).

However, after a full allergy workup, only a few of the suspected reactions can be confirmed as drug hypersensitivity reactions (DHR) (1, 2).

The drugs prescribed and involved in adverse drug reactions (ADR) and in DH differ between children and adults (6, 7). In the pediatric population, betalactam (BL) antibiotics are the most commonly involved drug group followed by nonsteroidal anti-inflammatory drugs (NSAIDs) and non-BL antibiotics (1–5, 8).

Clinical presentations are diverse, ranging from maculopapular and nonimmediate urticarial exanthemas to life-threatening reactions, such as anaphylaxis and severe cutaneous adverse reactions (SCARs).

Risk factors, comorbidities, and differential diagnoses are age dependent. For instance, viral and bacterial infections with exanthemas, important differential diagnoses for DH, are much more common in young children (9–12).

Traditionally, the same diagnostic algorithms and techniques are used for children and adults, assuming that the general principles applied for adults are also applicable in children. The use of skin tests poses special problems. Particularly, intradermal tests (IDTs), which are more sensitive than prick tests, are painful and can be poorly tolerated by small children. Thus, for nonimmediate reactions, such as mild exanthemas, it has been proposed to perform drug provocation tests (DPT) without prior skin tests (13–16).

Suitable pediatric therapeutic alternatives are lacking for many drugs. For instance, after DHRs to BL and NSAIDs, lifelong avoidance as practiced often in adults is more difficult in children.

This consensus paper of the European Network for Drug Allergy (ENDA) and the EAACI Drug Allergy Interest Group is the result of a task force on pediatric DH, aiming to present an up-to-date review of the available information regarding DH in children with a focus on differences compared to adult patients, to propose a general diagnostic algorithm, and to address controversial issues and unmet needs as well as areas for future investigation.

Methods

Data sources

Articles in English, German, Italian, French, Portuguese, and Spanish with data on DH in children were identified by searching the databases of MEDLINE (National Library of Medicine) from January 1990 till December 2013. Additional articles were retrieved from archives and reference lists of the identified articles. The experience/expertise of the members of the Task Force panel was considered. We included observational studies, case series, case reports, and personal experience of the members of the group, when another reliable data were lacking. We focused on commonly involved drugs in children, that is, antibiotics, NSAIDs, radiocontrast media (RCM), perioperative, and chemotherapeutics drugs. Of note, hypersensitivity to vaccines will not be discussed in this study, as this is the aim of other ongoing Task Force.

Data extraction and quality grading

The relevance of the articles was evaluated by the authors on the basis of their titles and abstracts. Selected articles were then retrieved, analyzed, and interpreted. For each statement, the quality of evidence and recommendation was graded and discussed by the Task Force members, confirmed, or amended by consensus of the group. Grading for key statements was performed using the GRADE system. Evidence was graded as high, low, or very low. The strength of the recommendations was strong or weak, that is, the grading of low/strong in the text denotes a low quality of evidence and strong strength of recommendation (17).

Epidemiology of drug hypersensitivity in children

Adverse drug reactions consist of any undesired effects that appear in the course of the clinical use of a drug (18). These reactions have been traditionally classified into the following: type A reactions (predictable by the known intrinsic properties of the drug, which include most of the toxic side-effects) and type B reactions (less dose dependent, unpredictable, and corresponding to either allergic or nonallergic hypersensitivity reactions). The term 'drug allergy' is used specifically when immunological mechanisms have been demonstrated (19).

In children, as well as in adults, most epidemiologic studies usually include both types, with a large predominance of type A reactions, which makes it difficult to estimate the prevalence of DH. The reported incidence of ADRs in the pediatric population is generally considered lower as compared to adults. Nevertheless, a recent systematic review of published data on ADRs in children showed that from 0.4% to 10.3% of all pediatric hospital admissions can be ADR-related (2.9% overall incidence) and that 0.6% to 16.8% of all children exposed to a drug during hospital stay can suffer an ADR (20).

These data confirm that ADRs constitute an important medical and public health problem among children (21).

The drugs most commonly reported in association with ADRs, the prescriptions, and the therapeutic options in children may differ from those in adults (weak) (6, 7).

Accurate epidemiological data on DH in general, and particularly in children, are virtually lacking (high). However, some studies indicate that among ADR, DH in children may be more common compared to adults: more than 50% of ADRs among pediatric inpatients and about 35% of ADRs in emergency department visits are supposedly allergic (very low) (6, 22, 23).

Drug hypersensitivity is perceived as an important problem in adults as well as in children (high). When questioned, up to 25% of the general adult population (24) and as much as 10% of parents report their children to be allergic to drugs, with BL antibiotics being the most frequently suspected (1–5). However, the clinical investigation of suspected reactions shows that these numbers are overvalued (high) (1, 2, 25).

Community-based studies and self-reporting generally lead to an overestimation of the rates of DH and drug allergy.

The prevalence of self-reported DH is higher in adults, and it generally increases with age (26, 27).

A Spanish study addressing the reasons for patient referral to allergy departments showed that the suspicion of drug allergy is the third cause, after asthma and rhinitis. It represents 15% of the referrals among adults and 9.8% in children. Betalactams allergy was the motive for referral in 81% of the pediatric cases, but it was suspected in only 47% of the reactions in adults. On the other hand, hypersensitivity to NSAIDs was more frequently reported among adults (24%) than children (13%) (8).

Risk factors and differential diagnosis

Young children appear to be at increased risk for ADRs, when compared to older children (low) (21, 23, 28, 29). The risk increases with the number of drugs taken and off-label prescriptions (low) (21, 29–32). Adverse drug reactions are generally considered to be more common in children with cystic fibrosis, potentially explained by higher levels of exposition to drugs, frequent use of intravenous drugs, and specific immune responses related to cystic fibrosis itself (33). However, a recent study based on systematic full allergic workup showed that although the frequency of proven BL hypersensitivity is high in children with CF, the global prevalence of BL hypersensitivity is lower in children with CF compared to the general pediatric population. These data need to be confirmed by large prospective studies (34). Although an increased risk has been associated with the female gender, particularly for perioperative reactions, this gender pattern has not been documented among children (low) and the age/gender pattern for suspected DH is similar to the one for viral infections (35, 36).

Infections are common in children, particularly viral ones, and are risk factors or differential diagnoses to DH (high). Most of the skin rashes occurring during BL treatment have been suggested to be due to the infection itself, and DH has been confirmed in <10% of the cases (high) (13, 25, 37, 38).

Underlying viral infections may also act as cofactors in susceptible individuals (low) (39).

In children, aminopenicillins may induce an exanthema especially in patients with Epstein–Barr virus infection, although the incidence is lower than originally reported (40, 41).

HHV-6 reactivation may be a cofactor in drug reaction with eosinophilia and systemic symptoms (DRESS) (42–44). DH is also more common in patients with cytomegalovirus and human immunodeficiency virus (HIV) infection (high) (45, 46).

Atopy, asthma, and chronic urticaria were reported to be significant risk factors for reactions to NSAIDs in children (low) (47–52).

Main elicitors/drugs

Antibiotics

In children, the suspicion of BL allergy is the most common reason for referral to the drug allergy consultation (high) (8). Adverse drug reactions in pediatric patients were reported to be caused in 45% by BL and in 23% by non-BL antibiotics. The estimated prevalence of DH to BL ranges from 1% to 10% (very low) (1, 2, 10, 26, 53).

Macrolides and sulfonamides are also frequently involved, but rarely confirmed in pediatric DHRs (low).The prevalence is closely linked to different prescription habits in different countries (54–56).

Among children, the reported macrolide allergy prevalence ranges from 0.07% to 0.7%, with most reactions being mild cutaneous exanthemas (very low) (3–5, 26).

Suspected allergy to sulfonamide antibiotics in children was reported to range from 0.2% to 2.2% for different age groups (3–5, 26) with the exception of one prospective study reporting an incidence of sulfonamide antibiotic-associated rash of 8.5% among outpatient children (low) (10).

Children infected with HIV have an increased risk of cutaneous reactions from sulfonamide antibiotics, some of which can be very severe (high) (57–59).

Hypersensitivity reactions to quinolones, vancomycin, aminoglycosides, and tetracyclines are rarely reported, partly because of the limited prescription of these drugs in children, except in particular populations, such as cystic fibrosis patients (low) (3–5, 10, 26, 53, 60).

Nonsteroidal anti-inflammatory drugs and analgesics

Nonsteroidal anti-inflammatory drug hypersensitivity in children has not been sufficiently studied. The most commonly used drugs in children are ibuprofen and paracetamol. Drug hypersensitivity to NSAIDs in some adult populations occupies now the first place among self-reported DH (61).

The prevalence is lower among children; however, NSAIDs rank second among drugs suspected to cause DH in pediatric patients (1–5).

Cutaneous and respiratory reactions are the most common manifestations (low). In a study enrolling more than 27 000 children <2 years old, treated with ibuprofen and paracetamol for an acute febrile illness, no hospitalizations occurred secondary to acute anaphylaxis (62). Older studies report a questionnaire-based frequency of NSAID-induced reactions of 0.32% (2 of 618) in children (63).

An increasing rate of NSAID hypersensitivity has been observed with increasing age among consulting atopic children. The estimated rate in this population was 4%, and the most common clinical manifestation was isolated facial and periorbital edema (64).

In a systematic review on prevalence of aspirin-induced asthma, challenge-confirmed ASA hypersensitivity in asthmatic children and adults was estimated to be 5% (0–14%) and 21% (14–29%), respectively (65).

Nonsteroidal anti-inflammatory drugs are known to aggravate chronic urticaria in adults (high), whereas specific data in children are mostly lacking (63). Other cutaneous manifestations include fixed drug eruptions, photosensitivity, and SCARs. In fact, NSAIDs are among the drugs most frequently associated with Stevens–Johnson syndrome (SJS) in children (66, 67).

Perioperative drugs

The study by DeWachter et al. (68) reports an overall incidence for perioperative anaphylaxis in the pediatric population of one in 7741 anesthetic procedures. Rates appear to be higher in selected populations, as in children with congenital malformations, submitted to several interventions (low) (69). In contrast to adults, neuromuscular blocking agents (NMBAs) are less commonly incriminated in children, with an estimated incidence at one in 80 000 anesthetic procedures being the second leading cause after latex in this setting (35). Anaphylaxis due to induction agents is rare (low).

Radiocontrast media

The overall reported incidence of immediate reactions to intravenous nonionic iodinated RCM in children is lower than in the adult population. In the large study by Katayama et al., DHR with severe cardiovascular or respiratory involvement has been reported with an incidence of 0.07% for nonionic contrast media in children aged 1–19 years (70). Other large studies have reported incidences of 0.18% (20 of 11 306) and 0.46% (57 of 12 494) for all DHR (71–73). Gadolinium-containing contrast media were associated with DH reactions in 0.04% of the pediatric patients (74–76).

Chemotherapeutics drugs

Carboplatin and asparaginase are frequent causes of DH among treated children. Drug hypersensitivity to carboplatin is associated with repetitive therapeutic courses (77–79). In one review on children affected by low-grade glioma, 44 of 105 children (42%) developed hypersensitivity to carboplatin (78). Seventeen (9.2%) of the 185 children, affected by different solid tumors and treated with etoposide–carboplatin, presented an allergic reaction to carboplatin: 2% at 6 courses, 11% at 12 courses, and 47% at more than 12 courses (79). Hypersensitivity reactions to asparaginase have been reported in up to 40% of the treated children (80, 81). Incidence seems to depend on the different types of asparaginase preparations, the regimens used, and the route of administration (82, 83). Reports about DHR due to other chemotherapeutic drugs are sparse.

Clinical manifestations of drug hypersensitivity in children

Dermatological presentations

Maculopapular exanthema (MPE) is considered to be the most common skin reaction (low) (84). Maculopapular exanthema and nonimmediate urticarial exanthemas are particularly observed in children treated with BL (high) and further to non-BL antibiotics, NSAIDs, and nervous system medication (85, 86). Immediate cutaneous reactions such as urticaria, pruritus, and erythema are also frequently attributed to BL antibiotics, sulfonamides, NSAIDs, and NMBAs (low) (86). Regarding DH to NSAIDs, facial angioedema manifests in <5% of infants and toddlers, but in up to 20% of adolescents and young adults (very low). More than 80% of hypersensitive children may cross-react upon challenge with another NSAID (very low) (51, 87–89).

Fixed drug eruption in children has mostly been associated with sulfonamides, and rare reports are found concerning other antibiotics, NSAIDs, and antihistamines (low) (90, 91).

Far less common cutaneous reactions in children include DRESS, acute generalized exanthematic pustulosis (AGEP), and SJS/toxic epidermal necrolysis (TEN). DRESS is reported to occur in approximately 1 : 1000 to 1 : 10000 of exposures to aromatic anticonvulsants, which are the most frequent cause (low). Drugs such as allopurinol, antibiotics, aspirin, and lamotrigin have been less frequently implicated in pediatric DRESS (92–98).

Acute generalized exanthemous pustolosis has been observed in children treated with BL, but also with other drugs and in the course of viral and bacterial infections (97–103). Regarding SJS/TEN, a pooled analysis of medications in 80 pediatric patients (<15 years) and 216 matched controls showed that sulfonamides, anticonvulsants, paracetamol, and NSAIDs were frequent culprit medications (low) (66).

Respiratory presentations

Symptoms include either isolated respiratory reactions (mostly restricted to NSAIDs) or, more frequently, respiratory symptoms as part of an anaphylactic reaction (low) (104). The risk is higher among asthmatic children (low). Delayed respiratory hypersensitivity reactions, such as drug-induced pneumonitis, are rare in children with any type of medication except chemotherapeutic drugs (low).

Anaphylaxis

In a recent review, Hompes et al. (105) reported that DH was the cause of anaphylaxis in 8% of children. There is insufficient data on the culprit drugs, but there is no reason to believe that the situation would be different from adults, where BL and NSAIDs are the most common triggers (very low) (106).

Serum sickness-like reactions

Serum sickness-like reaction (SSLR) is uncommon and mostly restricted to young children (107).

Cefaclor has been the major culprit drug, with an estimated incidence of 0.024% in controlled trials and 0.5% in published reports, but other BL have been increasingly implicated (16, 108–113). Trimetoprim–sulfamethoxazole administration has a reported SSLR incidence of 5 per 5597 courses of treatment (108).

Diagnostic approach to drug hypersensitivity in children

The main differential diagnosis of DH in children is a viral infection. The diagnosis relies on a complete allergy workup, ideally performed 1–6 months after complete recovery of the

initial reaction (low, strong) (Fig. 1). The diagnostic methods for pediatric patients are the same as for adults and consist of clinical history, skin tests, laboratory tests (if available and validated), and DPTs (strong).

Clinical history

The diagnostic workup should start with a complete and precise clinical history (114).

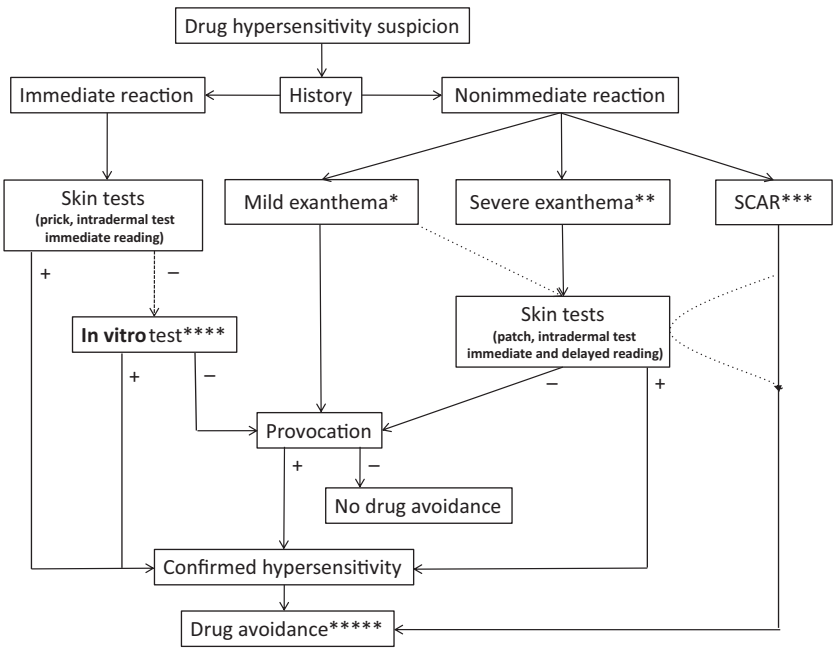
The history is often taken from the caregivers, which may lead to inaccurate or exaggerated pictures. Difficulties may also arise from the fact that children are generally less able to express themselves. The use of photos (e.g., by cell phone) to get a better description of the skin lesions at the acute phase should be encouraged as well as searching for danger signs as is advised in adults (115).

Skin tests

Skin tests include skin prick test (SPT), IDT, and patch tests. Regarding their diagnostic value, few pediatric studies have been published so far (Table 1) (13, 37, 113, 116–121). Published limitations and contraindications of skin testing in adults also apply for children (122).

Skin tests with drugs are considered relatively safe in children, with a reported rate of systemic reactions ranging between 0.3% and 1.2%; no fatalities among children could be found in the literature (13, 37, 123).

However, skin tests, especially IDT, are painful and less tolerated by children. Thus, in a query among ENDA members, 8 of 11 responders (73%), experienced with both adults and children, declared to use less IDT in children (unpublished data).



* Non severe uncomplicated exanthemas. If there is any doubt, skin tests should be performed before drug provocation test

** More severe exanthemas, such as those with high extent and density of skin lesions and long duration, complications or danger signs.

*** Acute generalized exanthematic pustulosis, drug reaction with eosinophilia and systemic symptoms, Stevens–Johnson Syndrome or toxic epidermal necrolysis. In specific cases, skin tests may be considered for identification of culprit among several used drugs

**** Validated in vitro tests recommended before skin tests if history of severe reactions or if skin tests are not possible or refused. They may confirm hypersensitivity only together with convincing history and/or other tests. Practically, specific IgEs are mainly used for suspicion of hypersensitivity to BL antibiotics or NMBAs .

*****In selected cases consider drug desensitization (e.g. in cystic fibrosis)

Figure 1 Algorithm for the diagnosis of immediate and nonimmediate drug hypersensitivity in children.

Table 1 Summary of studies including only children on the diagnosis of immediate and/or nonimmediate drug hypersensitivity to antibiotics

Authors	No. of patients	No. of patients with positive results (%) Immediate reactions	No. of patients with positive results (%) Nonimmediate reactions	No. of patients with positive results (%) Not specified
Betalactams				
Pichichero & Pichinchero (116)	247	84 (34)	20 (8.1)	
Ponvert et al. (113)	325	24 (7.4)	15 (4.6)	
Atanaskovic-Markovic et al. (117)	1170	682 (58.3)		
Romano et al. (118)	148	34 (79) of 43	1 (0.9) of 105	
Ponvert et al. (37)	1431	50 (30.9) of 162	177 (16.7) of 1087	227 (15.9)
Atanaskovic-Markovic et al. (119)	245	14 (43.7) of 32	19 (59.4) of 32	32 (13)
Caubet et al. (13)	88	6 (6.8)		
Macrolides				
Mori et al. (120)	64	14 (21.8)		
Atanaskovic-Markovic et al. (119)	115	1 (0.8)	2 (1.7)	
Sulfonamides				
Adegbidi et al. (121)	21			11 (52.38)
Atanaskovic-Markovic et al. (119)	37	1 (2.7)	5 (13.5)	

Skin tests in DH have been mainly standardized in adult populations, and test accuracy can only be extrapolated from mixed adult/pediatric studies (Table 2) (124). As there are no specific guidelines for children, general recommendations for adults have been applied (122, 125).

Due to the paucity of reliable data, it is difficult to assess the real value of skin tests to drugs in children, because most publications reporting skin test results are older, have neither used actual recommended protocols, nor have included DPTs and have validated their results only against the clinical history. Recent reports showed that the evidence to date does not clearly lean in favor or against skin testing in children (126–128).

It is also impossible to say whether test concentrations that are currently used are also optimal for children (very low) and there are some publications recommending different concentrations especially for cephalosporins (117, 129, 130).

However, the limited number of available studies indicates that using the same concentrations in similar clinical settings, the sensitivity seems to be comparable for adults and children (131–133).

Table 2 Level of certainty to recommend skin tests in children with suspected drug hypersensitivity

Higher evidence	Lower evidence
Anticonvulsants	Biologicals
Betalactam antibiotics*	Local anesthetics
Chlorhexidine*	Hormones
Heparins	Insulins
Neuromuscular blocking agents*	Nonbetalactam antibiotics
Platinum salts	Nonpyrazolone NSAIDs
Radiocontrast media	Opioids
Blue dyes	
Proton pump inhibitors	

*In addition, specific IgE determinations are available and recommended for these drugs.

Most of the studies focusing on pediatric patients evaluating the performance of skin tests concern antibiotics (Table 1). While the diagnostic value of those tests (SPT and IDT) is relatively high for immediate reactions (meaning reactions occurring up to one hour after drug administration) mainly concerning BL, several recent pediatric studies have confirmed a low sensitivity of skin tests (IDT and/or patch tests) to diagnose nonimmediate hypersensitivity in children (13, 14, 16, 25, 37, 134, 135).

Patch tests have been suggested to be especially useful to diagnose nonimmediate hypersensitivity to anticonvulsants and NSAIDs, but further large studies are needed to evaluate their diagnostic value (38, 119, 136).

In vitro testing

Due to the lack of sufficient comparative data, the same general principles and rules are considered applicable for both children and adults, although there is a considerably less available experience in children. The most commonly applied procedure is quantification of IgE antibodies, mainly relevant for BL, particularly the benzyl penicilloyl and the amoxicilloyl determinants. However, sensitivity is limited and comparison of commercial tests versus in house-produced tests indicates important differences in sensitivity (low) (137). In severe anaphylactic reaction involving BL antibiotics or NMBA, specific IgE measurement for the suspected culprits and cross-reactive drugs is recommended by some authors before skin testing if available. The rest of commercial available drugs for quantification of IgE antibodies are other low molecular weight compounds such as penicilloyl V, ampicilloyl, cefaclor, clorhexidine, suxamethonium, morphine and pholcodin, or protein/polymers like insulin, bovine gelatin, adrenocorticotrphic hormone, protamine, tetanus toxoid, and chymopapain.

Additional tests, such as basophil activation test (BAT), measurement of sulfidoleukotrienes, the lymphocyte transformation test (LTT), and the ELISPOT assay, have predominantly been used in adults, and the value in children cannot be estimated (very low) (138, 139).

The BAT and sulfidoleukotriene release test may be applied when specific IgE to a drug is negative or not available, although only small series have been reported (weak) (139–141).

Most of the validated data exist on BL antibiotics in adults, where the reported sensitivity of the BAT is <60% (142).

Lymphocyte transformation test may be applied for the diagnosis of nonimmediate allergic drug reactions (weak), but the test has mostly been used in research settings (to explore the involved immunological mechanisms) rather than in clinical practice (143–146).

The ELISPOT assay applied to the diagnosis of drug allergy is based on the quantification of cytokines or other T-/B-cell products in peripheral blood. There are studies for T-cell-dependent reactions. In cases with MPE and Steven–Johnson reactions, it has been shown that this procedure is more sensitive than the classical LTT assay (147, 148). Particularly, the combination of the quantification of more than one cytokine and other proteins such as granzyme B provides a higher sensitivity (148). However, overall the number of cases evaluated is rather small and more studies are needed to confirm these data.

Drug provocation tests

Provocation tests are particularly important in children, as the main culprits (i.e., BL antibiotics, ibuprofen and paracetamol) will often be needed again in future treatments, and in many cases, DH cannot be excluded by other means. General recommendations for DPT, including indications and contraindications, also apply for children (149).

Many schemes for DPT in children have been proposed, and the optimal protocol is debatable. First, for each child, the therapeutic single and daily dose has to be calculated according to age/weight. As a general rule, we recommend to start with approximately 1/10 of a single dose and proceed to half and a full dose (weak). In severe reactions, a lower starting dose, sometimes as low as 1 : 10000 to 1 : 1000 of the maximum therapeutic dose, should be used (weak). The cumulative daily dose should not be exceeded. The intervals have to be chosen according to the time course of the clinical manifestations of the initial reaction and the drug involved. Various intervals for incremental doses have been described, ranging from 20 min to 1 week (150). For example, an interval of 30 min to 2 h is generally appropriate for immediate reactions, whereas for nonimmediate exanthemas, longer intervals may be considered (weak) (14, 15, 37, 123, 132, 133, 149, 151–154).

The aim of the DPT is to confirm or exclude a reaction or to find safe alternative treatments, in case of confirmed DH to the culprit drug. Whereas the risk for future reactions can be further reduced by giving a full daily dose, or even 3, 5, and 7-day administration, the members of the Task Force panel believe that exposing on full single therapeutical dose is sufficient for most cases (weak) (113, 151, 155, 156).

Drug provocation tests have been reported to have a good negative predictive value both in children and in adults (123, 157–159). Taking into account the difficulty of performing painful IDT in children and the low sensitivity of these skin tests in mild nonimmediate skin reactions, several investigators suggested a physician-supervised DPT without previous skin testing provided that the patient has been observed at the acute phase by an experienced physician who confirms that the reaction was not severe (13–16, 160).

Studies have shown that this approach in mild MPE or nonimmediate urticarial exanthemas has not been associated with severe reactions during DPT (low). Based on the available data and the experience of the members of the Task Force panel, a general diagnostic algorithm for DH evaluation in children is proposed (Fig. 1), where a DPT without previous skin test (ST) in the case of nonimmediate reactions manifesting as mild cutaneous exanthemas (which are the most prevalent ones in childhood) can be considered (14, 15).

Provocation tests should be performed in a hospital setting under strict surveillance by a trained team according to the published guidelines (149). Of note, Ponvert et al. (37, 113) have performed prolonged challenge at home with exceedingly rare severe reactions in patients with a history of mild nonimmediate reactions during betalactam treatment. However, these data need to be confirmed in different populations in large prospective studies. An open oral DTP seems to be sufficient in most pediatric cases, and only a few studies refer to blinded placebo-controlled tests (weak) (13–16, 37, 48, 87, 117, 118, 151, 153, 161, 162).

The investigation of suspected reactions using the available methods allows the exclusion of DH in the vast majority of the suspected cases (25, 118, 151, 161–164).

Therapy

Avoidance of the culprit and cross-reactive drugs is the treatment of choice for DHR. In children, this may be more difficult to achieve, compared to adults, because the choice of alternative drugs is more limited (due to prescription restrictions). For example, BL antibiotics are the first-line treatment for most infections in children, and widely used antibiotic alternatives for adults, such as tetracyclines and quinolones, are contraindicated. The same applies to paracetamol and ibuprofen. COX-2 inhibitor use is limited by their delay of action and, moreover, they are not approved in infants/young children in most countries. In addition, 'lifelong avoidance' implies a stronger restriction in children as their expected lifespan is much longer compared to that of adults. In selected cases, desensitization can be considered, even though experience in children is more limited compared to adults (165, 166).

Unmet needs

High-quality epidemiologic data, with precise phenotyping and full allergy workup, are lacking in children. Thus, the

incidence and prevalence of DH to specific drugs and for specific clinical manifestations is unknown. Studies comparing feasibility and validity of the adult DH diagnostic procedures in children are required; current practice is mostly extrapolating adult experience to pediatric populations with a very limited number of confirmatory studies. The available guidelines for drug allergy diagnosis for adults should be further evaluated in children, especially regarding sensitivity of skin tests and DPT. The development of commercially available sensitive laboratory tests would be of particular interest in pediatric settings, as in this population, pain and fear can limit the use of skin tests. It has to be further studied in which clinical manifestations the skin test may be avoidable before performing DPT. A test allowing distinguishing DH from infectious exanthemas would be helpful. Standardization of DPT in children is necessary, as there is a great diversity of protocols making it difficult to compare published results. An agreement on desensitization procedures in pediatric ages is also needed as sometimes therapeutical alternatives do not exist or are clearly less effective. Multicenter studies with standardized protocols for different drugs are required.

Conclusions

Drug hypersensitivity in children has a parent-reported prevalence of around 10%, with a much lower real prevalence, and a lower prevalence of confirmed DH as compared to adults.

Betalactams are the main drugs implicated in DH among children and the most common cause of concern.

Nonsteroidal anti-inflammatory drugs, non-BL antibiotics, perioperative drugs, anesthetics, RCM, and cytotoxic drugs are also frequently suspected. Atopy and infections are the most important risk factors to consider especially regarding reactions to NSAIDs and antibiotics.

The most common reactions are nonimmediate MPE and urticaria. Drugs are the third identified cause for anaphylaxis among children. Facial edema associated with NSAID hypersensitivity and SSLD appear to be quite specific for children. The diagnostic approach to DH diagnosis is based on our experience in adults, but its adequacy in children has to be further evaluated. For example, DPT without previous skin tests can be considered in children with nonsevere maculopapular and nonimmediate urticarial exanthemas.

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Author contributions

Eva Gomes contributed to conception of the review, general structure of the paper, analysis and writing on data concerning epidemiology and diagnostic provocation tests, general writing of the paper, diagnostic algorithm elaboration and approval, management of references, and chair of the Task force; Knut Brockow to general structure of the paper, analysis of data on skin manifestations, critical reviewing and evidence grading, and diagnostic algorithm approval; Semanur Kuyucu to acquisition, analysis, interpretation, and writing on data concerning main elicitors, critical reviewing, and diagnostic algorithm approval; Francesca Saretta to acquisition, analysis, interpretation, and writing on data concerning main elicitors, critical reviewing, and diagnostic algorithm approval; Francesca Mori to acquisition, analysis, interpretation, and writing on data concerning main elicitors, critical reviewing, and diagnostic algorithm approval; Natalia Blanca-Lopez to acquisition, analysis, interpretation, and writing about laboratory data and critical reviewing; Hagen Ott to acquisition, analysis, interpretation, and writing on data concerning cutaneous manifestations; Marina Atanaskovic-Markovic to acquisition, analysis, interpretation, and writing on data related to diagnostic tests, diagnostic algorithm elaboration and approval, and critical reviewing; Mona Kidon to acquisition, analysis, interpretation, and writing on data concerning NSAIDs and on respiratory manifestations, critical reviewing, and evidence grading; Jean-Christoph Caubet to acquisition, analysis, interpretation, and writing on data concerning risk factors and diagnostic provocations, diagnostic algorithm elaboration and approval, management of references, and critical reviewing; Ingrid Terreehorst to general structure of the paper, analysis on data regarding clinical manifestations and writing clinical manifestations section, diagnostic algorithm elaboration and approval, management of references, critical reviewing, and secretary of the Task force.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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