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Drug Allergy (MJ Torres Jaén, Section Editor)

How to Manage Drug-Induced Exanthema in Children

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Abbreviations *NSAID* Nonsteroidal anti-inflammatory drugs · *BL* Betalactams · *EBV* Epstein-Barr virus · *DPT* Drug provocation test · *SCARs* Severe cutaneous adverse drug reactions · *AGEP* Acute generalized exanthematic pustulosis · *LAT* Lymphocyte activation test

Opinion statement

Exanthemas are frequently encountered in the pediatric population and often occur while patients concomitantly receive a drug, leading to a high prevalence of suspicion of drug allergy in children. Although the vast majority of these exanthemas are due to the underlying infection, most of those patients are falsely labeled as "drug allergic" without appropriate testing, mostly due to fear of life-threatening reactions. Overdiagnosis of drug allergy constitutes a major public health problem by increasing health costs and by contributing to overall antibiotic resistance. Thus, an accurate diagnosis is considered as a major contribution to cost-effective health care and will be based on a complete allergic workup (i.e., clinical history, skin tests, in vitro tests, and/or drug provocation test). Specific aspects of the management of drug allergy have been highlighted recently, particularly regarding the importance and safety of the drug provocation test as well as the low diagnostic value of skin tests in the diagnosis of betalactam allergy.

Introduction

Exanthemas are frequently encountered in the pediatric population and are mainly caused by viral, or more rarely bacterial, infections. Nonsteroidal anti-inflammatory drugs (NSAID) are often used for fever and pain control during these infections, and antibiotics might be prescribed to control a primary bacterial

infection, or a superinfection of a primary viral infection. Thus, in clinical practice, these exanthemas often occur while patients concomitantly receive a drug, leading to a high prevalence of suspicion of drug allergy in children. It has been shown that up to 10% of the parents claim that their child has an adverse drug reaction, with more than half being a real suspicion of drug allergy [1–4]. However, only 10% of these children will have a drug allergy confirmed by a complete allergic workup [1, 5•, 6•, 7–9, 10•]. Although betalactam (BL) antibiotics and NSAID are the most commonly incriminated drugs in children, overdiagnosis of allergy to vaccines and non-betalactam (non-BL) antibiotics also constitutes a major issue in pediatrics. Thus, the allergic workup is of major importance to confirm or exclude a real drug allergy and will be adapted depending on the drug involved and the type of exanthema. However, the allergic workup is time consuming, not risk-free, and might be difficult to perform in children. In addition, the allergic workup is associated with a relatively high medical cost as it requires a particular setting and an expert team. All these factors may discourage not only parents/patients but also some physicians to investigate a suspicion of drug allergy. From another point of view, a false diagnosis of drug allergy often persists until adulthood, and even in elderly, and it has been shown to be associated with higher medical costs, increased antibiotic resistance rate, higher morbidity, and even higher mortality [11–13].

A simplification of the allergic workup would clearly decrease the number of patients falsely labeled as "drug allergic" in the general population. Recently, major changes in the management of children with suspicion of drug allergy have been proposed [14••]. This is mainly due to specific aspects of drug allergy in children compared to adults, particularly in regards to a higher prevalence of infections in children that may mimic drug allergy, as well as a lower rate of true drug allergy. In addition, the feasibility and interpretations of skin tests in children constitute a very important aspect that should be taken into account when taking care of a child with a suspicion of drug allergy. In this review, we will discuss the specific aspects of the management of children developing an exanthema while concomitantly receiving a drug.

Exanthemas in children

The word exanthema has a Greek origin and means a "breaking out." There is no uniform definition of exanthema, but it generally refers to a skin eruption that is characterized by an abrupt onset and affects several areas of the skin. Different types of exanthemas can be distinguished based on the morphology of primary lesions (i.e., erythematous, papular, vesicular, pustular, or petechial) and distribution [15]. A complete clinical history (prodromal symptoms, previous illness, vaccine administration, contact, drug intake) is of major importance in the process of attribution of the exanthema to a specific disease [16]. Although not routinely performed, blood test (complete blood count, c-reactive protein, procalcitonin, viral PCR, and/or serology) as well as histology may be helpful.

Epidemiologic data are scarce, but the estimated prevalence of exanthema in children is 158.3/10000 (CI 142.3–174.4) [17]. Although exanthemas can be caused by drug or autoimmune disease, they generally refer to an infectious disease. At the beginning of the twentieth century, six classic infectious exanthemas have been described, i.e., measles, scarlet fever, rubella, Duke's disease that no longer exist, erythema infectiosum, and exanthema subitum. The term "atypical exanthemas" has been proposed for exanthema not included in the previous category. They are often associated with fever and upper respiratory or gastrointestinal infection. Thus, Goodyear et al. confirm a concomitant infection in 65% of children presenting with an exanthema and fever, and virus, bacteria, or both, were incriminated in 72, 23, and 3% of the cases, respectively

[18]. Non-polio enteroviruses are the most common cause of exanthema during summer, while rhinovirus, adenovirus, parainfluenza virus, respiratory syncytial virus, and influenza virus are more frequent causes during winter [19]. Epstein-Barr Virus (EBV) is also a common cause of exanthema, and has been identified for a long time as a potential co-factor in developing drug allergy [20•]. Although the virus may have a direct cytopathogenic effect, the exanthema may also result from a paraviral mechanisms, i.e., the virus causing an immune response leading to the exanthema response (i.e., Gianotti-Crosti syndrome) [16]. In addition to Streptococcus, several bacteria can be responsible for an exanthema, particularly Mycoplasma and Chlamydia [15]. These atypical exanthemas usually consist of macules, papules, or a combination of both (maculopapular), and more rarely of vesicules or pustules that might be combined with macules. They are characterized by lesions usually persisting several days. Of note, some maculopapular exanthemas might have an urticarial aspect, with single lesion persisting more than 24–48 h, resulting from a cell infiltrate process. Maculopapular exanthemas should be distinguished from urticaria, which results from mast cells degranulation, which is characterized by transient lesions lasting usually 24 h (maximum 36 h) with a typical feature such as wheals. Urticaria is viewed by dermatologists as a distinct entity, and is not usually included in the exanthema category. In this review, we will discuss urticaria separately, as it is a common problem in pediatrics and often leads to suspicion of drug allergy. While drug-induced maculopapular exanthemas are classified as non-immediate, urticaria is a usual manifestation of immediate reaction and can be associated with symptoms of anaphylaxis [21••].

Exanthemas and concomittant drug intake

Children developing an exanthema often have associated symptoms, and consequently most of them concomitantly take one or several drug(s) mainly to control associated pain and fever (i.e., NSAID) or the infection itself (i.e., antibiotics). Although the most common cause of an exanthema in children is an infectious disease, when a drug is taken concomitantly, the differential diagnosis of the exanthema includes a drug allergy. An interaction between the drug and the viral and/or bacterial infection has also been suggested as a potential cause of the exanthema [20•, 22, 23]. This has been particularly suggested for concomitant EBV infection in patients treated by ampicillin [20•]. In a study by Caubet et al. based on 88 children developing a non-immediate exanthema during a BL treatment, it has been shown that the majority of children with a negative oral drug provocation test (DPT) (i.e., drug allergy not confirmed) tested positive for a viral infection, mainly enterovirus and herpes viruses [5•]. Recently, Atanaskovic-Markovic et al. have found similar results by showing that a significant proportion of exanthemas occurring during a BL treatment is mainly from viral origin [24]. In this study, the authors also highlighted Mycoplasma as a common cause of urticaria in children treated with antibiotic [24].

Around 10% of suspected non-immediate drug allergy will be confirmed by a positive allergic workup [5•, 6•, 10•, 24–28], while the proportion is higher for suspected immediate reaction (around 30% for BL) [6•]. In order to decrease overdiagnosis, but at the same time, to avoid life-threatening reactions, it

is important to exclude or confirm a drug allergy in such patients. Unfortunately, no test is currently available to distinguish between a viral exanthema and a drug-induced exanthema during the acute phase. Measurement of serum FAS ligand has been suggested to be useful in one study, but these data have not been confirmed [29]. Testing for virus is not useful in the acute phase to determine the cause of the exanthema, as a positive test will not exclude an allergic reaction [14••]. Indeed, it has been shown that a significant proportion of patients with a positive DPT (i.e., allergy confirmed) tested positive for a viral infection during the acute phase of the reaction, and the opposite is also true [5•]. After exclusion of typical childhood exanthemas characterized by pathognomonic lesions and autoimmune disease (such as Kawasaki disease), distinction will be based mainly on a complete allergic workup that should be adapted depending on the type of drug allergy suspected, i.e., immediate or non-immediate (Fig. 1). Identification of danger signs during the acute phase

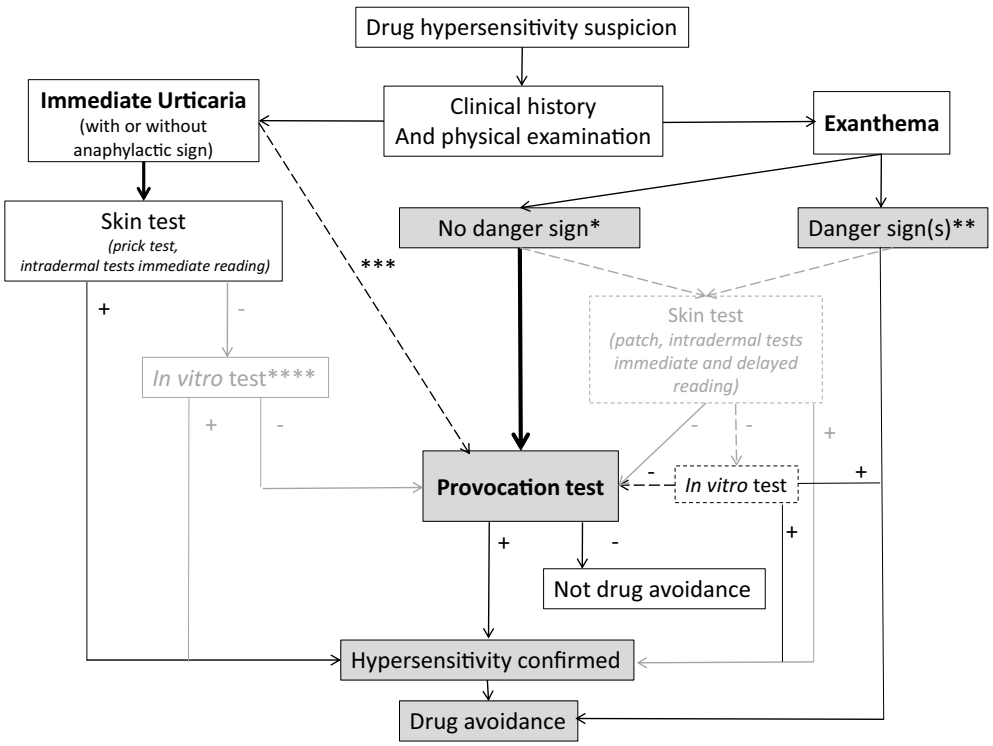

Fig. 1. General algorithm for the diagnosis of immediate and non-immediate drug hypersensitivity reaction in children (adapted with authorization from Gomes ER et al., Allergy, 2016).

based on detailed morphological diagnosis of symptoms and signs, as well as some laboratory tests to detect involvement of internal organs, are of major importance in excluding severe cutaneous adverse drug reactions (SCARs) [21••, 30]. If those signs are present, the drug should be stopped immediately, and the allergic workup will be initiated (Fig. 1) [21••].

Drug-induced benign maculopapular exanthema

The drugs most commonly involved in drug-induced exanthema in children are BL antibiotics and NSAID [14••]. The high prevalence of BL- and/or NSAID-induced exanthema is most likely related to the relatively high frequency of prescription of these drugs in the pediatric population.

Betalactam antibiotics

Betalactam antibiotics can lead to different types of hypersensitivity reactions, but one of the most common manifestation in children is isolated benign maculopapular exanthema (i.e., without any associated danger signs), which might have an urticarial aspect [5•, 6•, 24]. Those reactions occurred typically more than 1 h after drug intake and are classified as non-immediate [21•, 31]. From a pathophysiological point of view, a T cell-mediated immune mechanism has been suggested by histopathology studies and in vitro tests (i.e., lymphocyte transformation tests (LTT) and lymphocytes activation test (LAT)) [32]. As mentioned above, a complete allergic workup, ideally performed 6 to 8 weeks after the initial reaction, remains essential to confirm or exclude a BL allergy (Fig. 1).

Due to the lack of pediatric data, the allergic workup performed in children was based on adults' guidelines for a long time [33]. Thus, it included systematic, delayed-reading intradermal testing, even in children developing a benign skin eruption [33]. However, several recent pediatric studies have demonstrated the low sensitivity of skin tests for diagnosis of benign non-immediate allergic reactions to BL in children. Thus, Caubet et al. investigated the diagnostic value of intradermal tests and patch tests by challenging 88 children developing a rash during a BL treatment, independently of the results of the skin tests. The authors found a low sensitivity for intradermal tests (66.7%) with a positive predictive value of only 36.4% [5•]. Of note, patch test were negative in all included patients [5•]. Other pediatric studies did not include systematic DPT in patients with positive intradermal test. However, Ponvert et al. found that around 70% of non-immediate allergic reactions to BL in children were diagnosed based on a DPT and only one third based on skin tests [6•]. Zambonino et al. found that 96.2% of the included children needed a DPT to confirm diagnosis of non-immediate benign allergy to BL [10•]. Mori et al. found similar results [34]. Of note, no severe reaction has been reported after DPT in these cohorts of patients, confirming the safety of DPT in children developing an isolated benign exanthema [5•, 6•, 10•, 24–26, 34, 35]. However, large multicentric studies are still needed to confirm the safety of omitting skin tests before the DPT [5•, 26].

Recently, Atanaskovic-Markovic et al. evaluated 1026 children with a suspicion of non-immediate reaction to BL. Although the authors found a similar percentage of confirmed allergy by a complete allergic workup (7.6%), 75% of

those patients were diagnosed based on skin tests and only 25% based on the DPT [24]. But from another point of view, the investigators had to test 1026 children to identify only 57 children (5.5%) diagnosed based on positive skin tests. In addition, children with positive skin tests were not challenged, although a relatively high rate of false positive reaction has been suggested in previous studies [5•].

Several factors need to be taken into account to draw conclusion based on these recent data. First, it is important to take into account the difficulty to perform intradermal tests in children, due in part to pain, but more importantly the lack of standardization in the pediatric population. Indeed, the skin in children, and particularly in infant, is significantly different compared to adults, and this leads to difficulty in interpreting skin tests. Second, it is important to note that a DPT has to be performed regardless in children with negative intradermal tests to formally exclude an allergy, and that all reactions observed during a DPT in those studies were benign. Based on these considerations, several authors recommend skipping skin tests and performing a DPT directly. This recommendation has been recently suggested in the guidelines of the European Academy of Allergy and Clinical Immunology (EAACI) for the management of drug hypersensitivity in children [14••]. Large multicentric studies would be useful to confirm the safety of this recommendation in different populations and encourage allergists to change their protocol, as it will clearly decrease the number of children falsely labeled as allergic. Indeed, a DPT without skin testing first is very well accepted by children and parents, and in our experience, it increases the number of patients having an allergic workup that leads to a final diagnosis.

Unfortunately, the protocol of DPT for children with a suspicion of non-immediate hypersensitivity reaction has not been standardized, particularly regarding the length of the test, which can range from a one dose protocol to 10-day protocol [5•, 6•, 34, 36]. It has been shown that the vast majority of BL allergic children will be identified after the first dose challenge, and longer protocol has been associated with only a limited increase of the negative predictive value of the DPT [5•, 6•, 10•]. The delay between the initial reaction and the allergic workup probably plays a major role. Large well-conduct prospective studies are needed to determine the optimal length of DPT, taking into account the risk-benefit analysis of prolonged exposition to the antibiotic. Of note, although promising data has been shown in adults, in vitro testing (i.e., LTT or LAT) seems to have a low diagnostic value for the diagnosis of benign non-immediate allergic reactions to BL in children [37–39].

The natural history of those reactions remains unknown. Thus, prospective studies including a follow-up DPT in patients with a confirmed benign non-immediate reaction need to be performed in order to evaluate this important aspect.

Non-betalactams antibiotics

As any other drugs, non-BL antibiotics can be responsible for hypersensitivity reactions. Similarly to BL antibiotics, the most common manifestations of non-BL hypersensitivity are maculopapular exanthema, which might have an urticarial aspect [40••]. Macrolide and sulfonamides are the most frequently involved non-BL antibiotics in hypersensitivity reaction, probably related to

the higher levels of prescription compared to the others [3, 4, 41–43]. Quinolones and tetracycline are rarely responsible for non-immediate reaction in children [44–47]. Maculopapular exanthemas are the most common reactions reported with antituberculosis drugs, currently including isoniazid, rifampicin, pyrazinamide, ethambutol, and streptomycin [48–53]. Concomitant HIV infection has been associated with a higher risk of both sulfonamide and antituberculosis drug hypersensitivity [50]. The incidence of non-BL drug hypersensitivity remains not well defined as most studies are retrospective and do not take into account systematic allergic workup in evaluating all adverse drug reactions.

Due to the lack of pediatric data, management of suspected non-BL hypersensitivity in children is largely empiric [40••]. The DPT remains the gold standard, and similarly to BL, skin tests can be skipped before the DPT in children with a suspicion of benign non-immediate allergy to non-BL [40••]. Although skin tests for this type of reaction have been poorly evaluated in the pediatric population, their diagnostic value is probably limited [54••]. Moreover, the lack of standardization of skin tests in children combined with irritating properties of non-BL antibiotics render the testing difficult. Therefore, the diagnosis relies mainly on DPT (Fig. 1) [45, 55, 56]. Regarding in vitro tests, the real diagnostic values of LTT and LAT remain to be determined in large pediatric studies [40••].

Nonsteroidal anti-inflammatory drugs

NSAID are commonly prescribed in children and have been shown to be safe in a large number of children [57–59]. Similar to BL antibiotics, the vast majority of children developing an exanthema during a NSAID treatment are due to an underlying viral infection [22, 60]. A true hypersensitivity will be confirmed more frequently in adult than in children presenting with an exanthema during NSAID treatment [8], and it will be classified as single-NSAID-induced delayed reactions (SNIDR) [61, 62••]. These reactions typically occur more than 24 h following drug exposure and are heterogeneous, ranging from mild maculopapular exanthema that might have an urticarial aspect to SCARs [61, 62••]. Due to low prevalence, data regarding these reactions are rather scarce [62••]. They are believed to be T cell-mediated, are likely to require NSAID binding to proteins, that might be preceded by generation of active metabolites [63–65]. Propionic acid derivatives, diclofenac, pyrazolones, and paracetamol, are the most frequently involved drug in this type of NSAID hypersensitivity [62••].

Diagnosis of delayed reaction to NSAID is mainly based on the clinical history and a DPT (Fig. 1) [61, 62••, 66]. No standardized protocol is currently available, with various protocols ranging from one single dose protocol to administration of incremental dose every 24–48 h [9]. However, most pediatricians use a single dose protocol or 3 doses regimen (10%/20%/70%) at 30–60 min interval to investigate mild reaction [67–70]. As for other drugs, the DPT has to be performed in a secure setting with a trained team [21••]. Regarding fixed drug eruption (FDE), a DPT is mainly useful to identify the culprit in patients receiving multiples drugs at the time of the reaction [71, 72]. Delayed-reading intradermal tests and patch tests have been proposed, but these tests are not standardized. Furthermore, their diagnostic value has been poorly

investigated and thus remains unknown, particularly in the pediatric population [61, 62••]. Regarding in vitro tests, LTT has been suggested to be useful, but data are currently lacking to recommend its use in clinical practice for this type of reaction in children [37].

Severe cutaneous adverse drug reactions

SCARs should be suspected in children developing an exanthema associated with danger signs while concomitantly taking a drug (Fig. 1). These reactions include acute generalized exanthematic pustulosis (AGEP), drug-induced hypersensitivity syndrome (DIHS), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN). Diagnosis is mainly based on typical clinical manifestations, laboratory tests, and/or histopathology data [73]. In children with suspicion of SCARs, the drug should be avoided and a DPT is contraindicated in patients presenting with danger signs indicating a SCAR [21•, 61]. If the drug is considered the only option, an allergic workup can be discussed. Of note, skin tests in patients with suspicion of SCARs are associated with a potential risk of severe systemic reaction [73]. Usually, patch tests are used as a first line, and in case of negativity, intradermal tests are performed starting with the lowest concentration to decrease the risk of systemic reaction [21•]. However, due to evident ethical reason, the real diagnostic value of those tests remains unknown.

Vaccines

Adverse events after vaccination constitute a major public health problem, as most of these relatively common reactions are benign, but are often associated with an excessive fear of a severe reaction during subsequent vaccination. The consequence is a decreased rate of vaccination coverage in the general population. After local reactions, one of the most common reactions after immunization is exanthema that can lead to suspicion of allergy to vaccine [74, 75•]. Clinical history and physical examination are again crucial in management of suspected vaccine allergy. The chronology and morphological aspect are particularly important, for example, to exclude an exanthema related to viral replication in attenuated live vaccines (such as morbiliform exanthema after measles, mumps, and rubella (MMR) vaccine occurring in 5% of the children) [76]. But the most common type of exanthema after vaccine administration includes nonspecific maculopapular exanthema (with or without an urticarial aspect), typically occurring a few hours after vaccine administration. Of note, isolated delayed urticaria is also common. These skin eruptions have been reported in 5 to 13% of patients after vaccination [77–82]. Although the exact pathomechanisms remain unknown, they are unlikely to result from a hypersensitivity reaction, but from a nonspecific inflammation as well as nonspecific degranulation of mastocytes [83]. This hypothesis is mainly based on the fact that subsequent administration of the incriminated vaccine is generally well tolerated [75•, 84••]. Thus, no allergic workup is recommended and the vaccine can be given without any precaution [75•, 84••]. Some authors recommend giving an antihistamine before the booster dose in order to prevent recurrence of these reactions, although this approach has not been proven to be effective [75•].

Rarely, generalized eczematiform exanthema has been reported after vaccine injection [85, 86]. In those patients, an allergic workup to confirm or

exclude a delayed hypersensitivity to adjuvants/preservatives is important to prevent potential reactions with products containing these components in the future. However, it is important to highlight that a positive patch test is not a contraindication to administer the vaccine following a risk-benefit analysis [75•].

Drug-induced urticaria

As mentioned above, urticaria is not usually classified as an exanthema due to its distinct clinical aspect, although it fulfilled all the criteria. As it is a common manifestation of suspicion of drug hypersensitivity and represents a major issue in clinical practice, it has been included in this review. Delayed-appearing urticaria is a manifestation of non-immediate allergic reaction and the management will be similar to exanthemas as discussed in the previous section. Urticaria with or without angioedema typically occurring within 1 to 6 h after the last drug administration may be part of anaphylaxis, and is classified as immediate allergic reaction. We will discuss the management of patients developing immediate urticaria while taking concomitantly a drug.

Betalactams

Immediate allergic reactions to BL are rare with an incidence ranging between 1 and 4 episodes per 10,000 administrations [87, 88]. Diagnosis is based on immediate-reading skin tests (prick and intradermal tests) to a combination of PPL (the penicillin major determinant benzylpenicilloyl conjugated to poly-L-lysine), MDM (mixture of minor determinants), and side-chain structures (i.e., amoxicillin or the culprit drug such as cephalosporins) (Fig. 1) [31, 33, 89–92]. Recently, selective hypersensitivity to clavulanic acid has been increasingly reported, and this substance should be tested in case of suspicion (i.e., reaction to amoxicillin-clavulanic acid and negative to the classic reagents) [6•, 93•, 94]. Nonirritating concentration for skin tests evaluated mainly in the adult population are used in children due to the lack of pediatric data [14••, 54••]. Of note, in order to limit the number of painful intradermal tests, most pediatrician start with the highest concentration directly, as the risk of systemic reaction after skin testing is very low in children (ranging from 0.3 to 1.2%) [6•]. Data on the real diagnostic value of those tests is limited. Indeed, the positive predictive value remains not well defined, as it is considered unethical to perform a DPT in patients with positive skin tests [95]. However, some data mainly in the adult population shows that the positive predictive value ranges between 30 and 100% [5•, 96–100]. The negative predictive value of skin tests has been found to be high and no serious immediate reactions has been reported after DPT in patients with negative skin testing [5•, 6•, 101, 102]. However, the negative predictive value is not 100%, highlighting the importance in performing a DTP in children with negative skin tests (Fig. 1) [33]. Similar to non-immediate reaction, the protocol of DPT for suspicion of immediate reaction to BL has not been standardized. Recently, the Task force of the EAACI on drug allergy in children recommends as a general rule a 3-dose regimen (i.e. start with 10% of a single dose, and then half and a full dose that should be administered every 30 min to 2 h) [14••]. In patients with history of severe anaphylactic reaction,

low starting dose should be used (i.e., 1:10,000 to 1:1000) [14••].

Of note, the utility of skin tests in patients developing benign isolated urticaria has been recently questioned [26, 103]. Indeed, some authors consider benign skin eruption as a general entity without distinction between immediate and non-immediate benign reaction. From a practical point of view, it is important to note that this distinction is often difficult to establish. Indeed, the parents often give the dose before the child goes to bed and the eruption is noticed the day after when the child wakes up. However, further large prospective studies are needed to confirm the safety of this approach, and skin tests are still recommended in this situation [14••].

Regarding in vitro tests, serum specific IgE are mainly used in adults as a first line in patients with history of severe immediate reaction in order to decrease the risk of systemic reaction during intradermal test [33]. However, those tests are rarely performed in the pediatric population due to the low risk of systemic reaction during skin testing in children, and also because of the lack of data on their diagnostic value in children [5•, 6•, 14••, 104]. Thus, the use of specific IgE to BL in children is restricted to selected children with history of severe reaction and negative skin tests before proceeding to the DPT (Fig. 1) [14••]. Basophils activation test (BAT) has been suggested to be useful in the diagnosis of immediate reaction to BL. However, large-scale pediatric studies are needed to confirm data shown in adults suggesting a high specificity [105].

Once an immediate reaction to BL is confirmed by a complete allergic workup, identification of well-tolerated alternative BL is important due to potential cross-reactivity between BL that share the same ring and potentially similar side chain. Most of the studies assessed the tolerance of cephalosporin in adult patients with a confirmed allergy to penicillin. Only 2 to 3% of those patients will also react to cephalosporins, the rate of cross-reactivity being higher for first-generation cephalosporins while most second- or third-generation cephalosporins are well tolerated as they have different chemical structures [106–109]. Most of the cross-reactions are linked to identical side chains located at the R1 position [110–112]. Thus, patients with a confirmed immediate allergy to amoxicillin should not receive cephalexin, cefaclor, and cephadine. Similarly, ceftazidime should not been prescribed in patients allergic to aztreonam [32, 113, 114]. The rate of cross-reactivity between monobactams (i.e. aztreonam) and other BL has been shown to be low and therefore these drug can be prescribed safely in patients with penicillin allergy [32, 115, 116]. Similary, the degree of cross-reactivity between penicillin and carbapenems is relatively low [117, 118]. From another point of view, it has been shown that 25% of patients with a confirmed immediate hypersensitivity to a cephalosporin will react to penicillin, 3.1% to azteronam, 2% to imipenem, and 1% to meropenem [119].

Pediatric studies evaluating cross-reactivity between BL antibiotics are sparse. Based on 1170 children, Atanaskovic-Marcovic et al. found a rate of cross-reactivity between cephalosporins and penicillin to be 0.3 and 23.9% [106]. As expected, the rate of cross-reactivity among different generations of cephalosporins was higher for the first- and second-generation cephalosporin and 0% for third-generation cephalosporins [106]. Based on these data, in a child with confirmed immediate hypersensitivity to penicillin, skin testing with the alternative BL (cephalosporin, carbapenem, and aztreonam) should be performed, and if negative, a DPT should be done.

Non-betalactam antibiotics

Immediate allergic reactions to non-BL antibiotics remain rare in the pediatric population [40••]. Thus, sulfonamides and macrolides, which are relatively commonly prescribed in children, are rarely responsible of urticaria and/or anaphylaxis [40••, 120]. The most common hypersensitivity reaction induced by glycopeptides antibiotics is the red man syndrome (flush, erythematous rash, and/or urticaria) typically occurring at the end of a vancomycin injection with an estimated incidence of 1.6 to 35% [121, 122]. It has been linked to a nonspecific mast cell degranulation [123]. Although several risk factors have been identified, a high infusion rate is probably one of the main risk factor to develop a red man syndrome [122, 124]. Of note, although rare, real immediate hypersensitivity reaction to vancomycin has been reported mainly in the adult population [125]. In pediatrics, aminoglycosides as well as quinolones are used in patients with cystic fibrosis particularly, and these may rarely cause immediate allergic reactions (estimated incidence in children of 1/1000) [126, 127]. Cross-reactivity among quinolones as well as among sulfonamides has been described [126, 127]. Diagnosis relies mainly on skin tests (nonirritating concentration has been published), and if negative, a DPT (Fig. 1). However, the diagnostic value of skin tests remains not well defined and those tests have not been standardized in the pediatric population. Specific IgE are of limited diagnostic value for the diagnosis of non-BL immediate hypersensitivity [40••]. Some recent studies show promising results for BAT, but further pediatric studies are needed to confirm these data [40••, 128].

Nonsteroidal anti-inflammatory drugs

NSAID-induced urticaria can be due to a specific immunological mechanism (i.e., IgE mediated) and is classified as single-NSAID-induced urticaria/angioedema or anaphylaxis (SNIUAA) [61, 62••, 66]. More frequently, NSAID-induced urticaria is related to the mechanism of the drug itself, with an imbalance of the arachidonic acid pathway [68, 70, 129••]. This type of reaction is classified as non-allergic hypersensitivity or cross-intolerance (CI) reactions, and the patients will react to different NSAID [61, 66, 129••]. In the currently used classification, patients with or without underlying urticaria are distinguished as NSAID-exacerbate cutaneous diseases (NECD) or NSAID-induced urticaria/angioedema (NIUA), respectively. It has been found that approximately one third of patients with chronic urticaria will have an exacerbation after NSAID intake [130]. However, in the pediatric population, chronic urticaria is rare and NIUA is thus more common [131]. Isolated angioedema linked to NSAID intake is the most common manifestation in children, followed by generalized urticaria [68, 132]. The term blended reaction is used for patients with both respiratory and cutaneous involvement due to CI and are relatively common in children and adolescents [61, 66, 69, 129••, 132, 133].

Diagnosis of NSAID hypersensitivity is difficult and is more frequently misdiagnosed compared to hypersensitivity to other drugs [134]. Currently, the clinical history plays a major role in the diagnosis, although its diagnostic value is debated [70, 135, 136]. The use of skin tests in this type of NSAID hypersensitivity remains limited and is controversial, mainly due to a large variability of the diagnostic value of those tests in the literature, particularly in the pediatric population (Fig. 1) [61, 66, 129••]. Considering in vitro tests, data

regarding the diagnostic value of specific IgE and BAT are generally lacking, and those tests are not routinely performed for this type of reaction [61, 66, 129••]. The DPT is used to confirm the diagnosis if the suspicion is low and for mild reaction, or more commonly, to assess tolerance to an alternative NSAID (Fig. 1). There is no consensus regarding the optimal protocol for the DPT [62••, 129••]. However, the most common pediatric protocols include drug administration every 30 to 60 min starting at 10% of the age appropriate standard dose. Similar to antibiotics, if the patient has a history of severe reaction, this protocol should be adapted by starting with lower doses (i.e., 1:1000 to 1:10000). Of note, testing with an alternate NSAID is important for diagnosis of CI versus SNIUAA [62••, 129••, 137].

Vaccines

As opposed to exanthema, isolated immediate allergic reactions after vaccine administration are rare, with an estimated incidence of 1–3 case per million injections [138, 139]. This type of reaction has been linked to IgE-mediated sensitization to one component of the vaccine (preservatives, stabilizers, and adjuvants) and more rarely, to the microbial component itself [75•, 84••]. As for other immediate reactions, the diagnosis is based on an accurate clinical history, particularly including the differential diagnosis of urticaria and/or anaphylaxis (i.e., mainly viral- or bacterial-induced urticaria, vasovagal malaise, vocal cord dysfunction, occuloglobular syndrome) [84••]. Skin testing with prick test (full dose or one tenth in case of severe anaphylactic reactions) as well as IDR (1/100) should be performed with the incriminated vaccine but also to the single components (egg, gelatin, yeast, formaldehyde, and latex). Specific IgE are of limited value for the vaccine itself, but might be useful for some vaccine components such as egg, gelatin, or latex [75•, 84••]. Of note, an allergic workup should be performed, not only to increase vaccination coverage, but also to decrease the risk of reaction to some common components that might be present in other vaccines or foods [75•, 84••]. A negative allergic workup will lead to administration of full dose of vaccine. Administration in graded dose might be recommended in case of history of severe anaphylactic reaction. In case of positive skin test to vaccine, vaccine injection is still possible after risk-benefit analysis [75•, 84••], by using the protocol proposed by the American Academy of Pediatrics [140]. In this case, a monovalent vaccine should then be preferred. Measurement of vaccines antibodies (i.e., IgG) might be helpful to make a decision.

Conclusion

Exanthema is a common cause of consultation in pediatrics, and the main differential diagnosis includes infection. When a drug is taken concomitantly (mainly antibiotics and NSAID), the differential diagnosis expands to include a drug allergy. In this case, an allergic workup should be performed. Indeed, an accurate diagnosis will lead to decreased number of children falsely labeled as drug allergic. For suspected non-immediate allergic reactions, skin tests are of limited diagnostic value and a DPT can be performed directly in children. In case of exanthema occurring after vaccine administration, there is no contraindication to administer a booster dose, and a premedication with antihistamines

might be recommended. Regarding immediate urticaria with or without anaphylactic signs, the current guidelines include skin testing to the incriminated drug or vaccine. If skin tests are negative, a DPT can be performed to confirm or exclude an immediate hypersensitivity. Recently, the utility of skin tests has been questioned in patients with isolated benign urticaria during a BL treatment, but currently the evidence is low and those tests are still recommended. Thus, DPT is the gold standard and important in the management of children with a suspicion of drug allergy. However, it is time consuming, and further studies are needed to identify biomarkers, particularly during the acute phase, to not only to improve the diagnosis of drug allergy but also to decrease the overdiagnosis of drug allergy, which has been associated with increased mortality and morbidity.

Compliance with Ethical Standards

Conflict of Interest
Dr. Jean-Christoph Caubet declares that he has no conflicts of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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