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An EAACI Task Force Report on Allergy to Beta-Lactams in Children: Clinical Entities and Diagnostic Procedures

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ABSTRACT

Beta-lactam (BL) allergy suspicion is common in children and constitutes a major public health problem, with an impact on patient's health and on medical costs. However, it has been found that most of these reactions are not confirmed by a complete allergic workup. The diagnostic value of the currently available allergy tests has been investigated intensively recently by different groups throughout the world. This has led to major changes in the management of children with a suspected BL allergy. Particularly, it is now well-accepted that skin tests can be skipped before the drug provocation test in children with a benign nonimmediate reaction to BL. However, there is still a debate on the optimal allergic workup to perform in children with a benign immediate reaction. In addition, management of children with severe cutaneous adverse drug reactions remains difficult. In this review, based on a selection of the most relevant studies found in the literature, we will review and discuss the diagnosis of different forms of BL allergy in children.

INTRODUCTION

Beta-lactams (BLs) are among the most frequent elicitors of drug hypersensitivity reactions (HSRs) in children. Benzylpenicillin (BP) was the first incriminated BL, followed over the years by other penicillins such as ampicillin, cloxacillin, and amoxicillin (AX), which is nowadays the most frequently involved, and more recently cephalosporins, carbapenems, monobactams (1,2) and clavulanic acid (CLAV) (3,4). To a certain extent, the order in which each BL has been implicated followed the chronological period of release in the market, although the consumption pattern is another factor that contributes to the induction of allergic reaction. In fact, CLAV allergy is surpassing other BL like aztreonam and many cephalosporins (5). The European Network of Drug Allergy (ENDA) classified BLs-HSR into two groups: immediate reactions (IRs), occurring less than 1 hour (h) after the drug intake, and nonimmediate reactions (NIRs), occurring more than 1h and up to several days after the last drug administration (3, 4). The first publication using this terminology was proposed in 1995 based on provocations tests to cases with the so called delayed reactions (6). People responded after BP and AX challenge with a reaction that occurred as soon as 2 to 6 hours after drug provocation (6). However, controversies exist regarding this classification (7-10) and some authors consider IRs as those occurring within 1h and up to 6h

after the drug exposure, and NIR as those occurring at any time greater than 6h, often starting 2 to 5 days later (11-13). More recently, in the AAAAI/WAO 2018 report (13), BLs HSRs were divided into 5 groups, based both on the chronology and the mechanisms of the reaction: 1) Non-immunologically mediated adverse effects; 2) IgE-mediated immediate-onset benign cutaneous reactions; 3) IgE-mediated immediate-onset systemic reactions; 4) T-cell-mediated delayed-onset benign cutaneous reactions and 5) T-cell-mediated delayed-onset severe cutaneous or systemic reactions. It was concluded that these scenarios corresponded to different risks and therefore should guide the diagnostic approach. This manuscript is a comprehensive review of the data published based on the most relevant papers selected from the literature. Throughout it, we will describe our current knowledge regarding the management of paediatric patients presenting one of those clinical entities. Despite this, the controversy continues and a perfect classification has not yet been made.

CLINICAL ENTITIES FOR IMMEDIATE REACTIONS

The clinical entities of IRs extend from mild reactions such as urticaria and/or angioedema to severe reactions such as anaphylaxis and anaphylactic shock. Limited reactions like lip angioedema, dysphonia or isolated bronchospasm may occur, although rather infrequent.

MILD IMMEDIATE REACTIONS (Urticaria/AE)

Most IRs to drugs are isolated cutaneous reactions and are sometimes considered as mild or benign reactions (12). However, any IgE-mediated reaction can be potentially life-threatening because mild symptoms can be due to a low dose, and each treatment, even skin testing (ST), might boost the drug-specific IgE response (14). The estimated prevalence of urticaria/angioedema ranges between 15% and 25% in the general population, being more common in children, in whom the most common causes are acute infections (15,16). A significant proportion of children developing urticaria are concomitantly treated by antibiotics, such as BL, for the underlying infection, and in clinical practice most of them are falsely labelled as allergic (17). This is the main difficulty in the diagnosis of mild HSR in children.

Diagnostic value of in vivo and in vitro tests

The most important first step is a detailed standardized history, which should include data about the symptoms presented, the drug/s involved, the dose, duration of treatment, the time interval between drug administration and the reaction, treatment administered and time to recovery, as well as previous episodes and drugs tolerated after the reaction. However, published studies show mismatches between the clinical history and allergy tests results (18-22). The next step is to perform in vitro immunoassays, which can be useful to avoid a severe IgE-mediated reaction when drug provocation test (DPT) is performed. The recommended algorithm for IR to BLs includes skin prick testing (SPT) first and, if negative, intradermal tests (IDT), with major and minor determinants, penicillin G, amoxicillin (AX) and/or the culprit BL. Of note, some reference centres start directly with IDT, skipping SPT, due to the low risk of systemic reaction during IDT in children (9). According to paediatric BL studies, IRs are more likely to have positive ST than NIR. However, positive predictive values of ST were not determined in most of them (2,10,23,24). Benzylpenicilloyl-poly-Lysine-PPL (PPL, Pre-Pen®, AllerQuest LLC, Plainville, CT, US) and benzylpenicilloyl-octa-L-lysine (BP-OL, 0.04 mg/mL, DAP®, Diater laboratories, Madrid, Spain) are the commercially available major determinants used today (4, 25, 26), while benzylpenicillin and sodium benzylpenilloate (MD, 0.5 mg/mL, DAP®) are the minor determinants, both only commercialized in Europe (26). It should be emphasized that the formulation for the previous MDM has changed in Diater kits (Diater Laboratories, Madrid, Spain) and since 2006 only comprises benzylpenicilloate (MD, 0.5 mg/mL, DAP®) (11,27). Hence, penicillin G, an important minor determinant, should also be included in the BL testing panel if minor determinants quoted above are negative (4,28-30). Recent studies have highlighted the role of CLAV, so it has also been recommended to test this antibiotic (CLV, Diater®) (4,31,32).

If the results of STs and/or in vitro assay are negative, then a DPT should be considered (4,12,28,33,34).

Although there is no agreement on the optimal doses and intervals between the doses, in most mild IRs DPT is usually started with 1/100 or 1/10 of the single therapeutic dose, with increasing doses at 30 to 60 min intervals given until the full therapeutic single dose is reached (3,12,33). Recent reports suggest that fewer challenge steps (less than 4-5 steps; e.g. 10%-20%-70% of the full single dose) could be employed safely avoiding the potential inadvertent desensitization by too many doses and small dosing increments (11,21,34-37). It must be underlined that although

in most instances symptoms induced by DPT are similar to the index reaction (27, 33), a few reactions during DPT may be more severe than the index one (21). Although some studies have shown that up to 20% of cases with IR history turned positive on prolonged (5-7 days) DPT, this approach is still controversial (2,8,20,23,35,38-40).

Skipping skin testing in patients with immediate benign reaction

While many authors recommend a classical approach in evaluating IRs to BLs, paradigm changing studies have been published giving rise to DPT without ST in mild IRs to BLs in children. In a study carried out by Mill et al., a total of 800 children (12,5% with mild IR) suspected of AX allergy were directly challenged without performing ST. The results showed that 94% tolerated amoxicillin, 2% had IRs and 4% NIRs, all of which were mild (38). In another study carried out by Vyles et al. including 100 children with low-risk symptoms of BL allergy (both NIR and IRs), a DPT was safely completed in all patients regardless of ST findings. Nevertheless, a selection bias could exist because only one-third of the participants agreed to perform testing (39). In a similar study, Labrosse et al. included 130 children with a history of mild IR and/or NIR to AX or AX/CLAV, all of whom underwent a DPT with AX, independently of ST. From the total only 2.3% had a positive DPT, all with mild reactions (40). In another Australian study including children with a suspicion of BL allergy, including anaphylaxis, the outcomes of different diagnostic approaches were compared: 73 cases underwent direct DPT without ST and 103 cases ST plus DPT. Authors found that a prior history of anaphylaxis did not necessarily predict IRs and that a direct DPT could be safe, even in those with history of anaphylaxis (41).

More recently, a large paediatric multicentre Spanish study reported the results of 732 children with a suspicion of non-severe BL allergy including both IR and NIR, all of whom prospectively underwent the same diagnostic work-up including SPT, IDT, in vitro assay, and DPT regardless of the ST results. DPT confirmed penicillin allergy in only 35 (4.8%) children, and all the reactions induced were mild or moderate. Interestingly, allergy was not confirmed in any children with an IR history, while 17% of patients with skin reactions showed an IR during DPT (18). Although all the studies mentioned above mostly include children with mild reactions, the evidence to support DPT without ST in mild IRs remains still limited, since only approximately 10% of patients studied had IR history. Most of the reactions described during DPT were mild, although

anaphylactic reactions were also reported (18, 41). In addition, the time interval between the index reaction and testing was more than one year in some studies (39-41), which can lead to natural waning of specific IgE. Some studies included only infants or preschool children (38), of whom the drug allergy characteristics may differ from older children and adolescents. Unfortunately, analysis of results considering these factors was not performed.

SEVERE IMMEDIATE REACTIONS (Anaphylaxis/Anaphylactic shock):

Anaphylaxis is a systemic HSR characterized by a rapid onset of and multiorgan symptoms that can be life-threatening (42). These reactions mostly occur less than 1h after drug exposure, although sometimes a short time later (43). Drugs are one of the main causes of anaphylaxis in children (44,45) including fatal anaphylaxis (46-48), especially BLs (45,49-53) such as AX, cephalosporins (1,54) and CLAV (55). However, the risk of fatality with an oral exposure is extremely low. According to a survey published only one case of fatal anaphylaxis was reported in approximately 100 million treatment courses of AX given throughout 35 years (56). The proportion of drug-induced anaphylaxis cases increases with age, drugs being the major causative agents after 7-12 years (45,57). According to different studies, the percentage of drug-induced anaphylaxis is higher than 30% over the age of 7 years, while in children younger than 6 it is about 15% (45,57). In the general population, the frequency of BL-induced anaphylaxis has been reported between 0,015% to 0,004% (58), with few studies focusing on the paediatric population. According to different studies in paediatrics, the reported drug-induced anaphylaxis in true allergic patients ranges from 0.1%-10.2% (59,60) with no data concerning only BLs.

Regarding clinical symptoms in children, alarming signs for a systemic reaction can be easily overlooked, because of misperception by the child and parents (61). However, identifying severe IRs is important because they are rapidly progressive, potentially fatal, and tend to become more severe with repeated exposures (3,62).

Some features to be considered in severe IR are: first, very small amounts are sufficient to allow interaction and crosslinking of receptor-bound IgE molecules inducing severe reactions, so that even ST may elicit systemic symptoms in up to 10% of cases tested (3,63); secondly, about 50% of patients deny any prior contact with the drug (64), although inadvertent exposures may sensitise

or resensitize (14). And thirdly, there are some conditions such as a previous history of anaphylaxis, family history of drug allergy and co-existent atopic diseases that have been proposed as major risk factors for a severe anaphylactic reaction (58,65-67), although among children results are contradictory (45,50,68,69).

Diagnostic value of in vivo and in vitro tests

As occurs with any kind of drug allergic reaction and mentioned above in mild IRs, the diagnosis of severe IRs requires a complete work-up that includes clinical history, in vitro test, STs, and DPT when indicated. Important data for the clinical history are a description of the symptoms, the drug/s involved and the dose, the time interval between drug administration and the reaction, treatment administered and time to recovery, as well as previous episodes and drugs tolerated after the reaction. Unfortunately, as a rule, the clinical history alone is insufficient for establishing a diagnosis, and discrepancies between history and test results is frequent (8,18-21,70,71).

In vitro tests, such as quantification of tryptase, determination of sIgE or basophil activation test (BAT), can be useful in severe IRs (4,12,25,33). Some authors recommend to perform them before ST in order to avoid risks (4,33,72,73). The methodology for ST is the same as described for mild IRs, however, diluent concentrations are required for safety. When both in vitro tests and ST are positive, the risk of a positive DPT is high (74). DPT is nowadays the gold standard for the diagnosis, although there is no standardized protocol (25). In severe IRs It is only indicated when no other safe alternative drug exist (66). As a general rule, it has been recommended to start in severe IR with 1:10000 to 1:1000 of the full dose (33), with escalating doses administered every 30-60min (11,21,36,75). Nevertheless, in very severe IRs such as anaphylactic shock, only in vitro tests and ST can be considered, avoiding a DPT with the culprit drug.

Of note, the risk of resensitization had been sparsely investigated, but has been found to be low (76). However, considering IRs and especially the more severe ones, it is important to consider a re-evaluation some time later following the same protocol indicated above in patients with clear

history but negative STs, in vitro assays and/or DPTs (3). Further large studies are still needed to determine the utility of a boost test in the pediatric population, particularly by including a DPT.

CLINICAL SPECTRUM OF NON-IMMEDIATE REACTIONS

The clinical entities included in NIRs extend from mild reactions such as maculopapular exanthema (MPE) or non-immediate urticaria to severe cutaneous adverse reactions (SCAR).

MILD NON-IMMEDIATE REACTIONS: non-immediate urticaria/(MPE)

Most NIR are mild, with MPE occurring in 5-10% of children prescribed amoxicillin (70).

Diagnostic value of in vivo and in vitro tests

Concerning ST in mild NIR, IDT and patch test have been found to have a low sensitivity (around 2-10%) and lack optimal standardization, particularly in the paediatric population. Thus, it has been demonstrated that delayed reading intradermal tests seem to have low sensitivity and poor negative predictive value, although when the test is positive the predictive value is high (35,77).

Because they are non-invasive and more suitable in children, patch tests have been proposed for the diagnosis of NIR to BLs, with a sensitivity ranging from 7-10% with BP to 37% with AX (78, 79). However, these tests have not been validated in the paediatric population and their diagnostic value remains to be determined, particularly by a DPT in children with a positive patch test as it has been done for IDT. Different European guidelines have been published about how to perform patch tests (79,80). A concentration of 10% of active compound in petrolatum and a maximum 30% concentration for commercial drugs are the most widely accepted standards.

In addition to DPT and ST, ex vivo assays, such as IFN- γ ELISpot, and in vitro assays, such as the lymphocyte transformation test (LTT), have many challenges. Studies report a sensitivity of LTT of 56.1% in adults, with limited evidence in children (35). Their negative predictive value is currently not adequate to justify unsupervised rechallenge with potentially implicated drugs in most settings (81). More recent works suggest that combining laboratory-based ex vivo and/or in

vitro assays with delayed IDT and patch testing might significantly increase the diagnostic sensitivity, though more studies enrolling children are needed (77,82,83).

Role of the DPT in benign nonimmediate reaction

Due to the low sensitivity of IDT in MPE or non-immediate urticaria associated with BLs, and taking into account the difficulty of performing painful IDT in children, several studies confirm the safety of DPTs without previous ST in children who developed a benign exanthema or delayed urticaria (84, 85). Indeed, all the studies describing a direct DPT without previous ST in mild NIR report only mild reactions to the DPT, confirming the safety of this procedure (Table 1).

DPT is considered the gold standard, being necessary for the diagnosis and management of these reactions. Recently, several paediatric studies have reported a percentage of confirmatory diagnosis ranging from 5 to 10% (34,37,38,86-89). As discussed above for IRs, there is general agreement that DPT should be performed with the culprit drug by administering a graded dose challenge. On the contrary, there is no consensus for performing DPTs in NIRs. Indeed, some protocols have proposed to administer the initial full dose all at once (100% or 150% of the standard dose), or by a graded challenge with equal or incremental doses (23,24,90,91). While some authors propose to administer only one dose or the same number of doses according to the index reaction, others suggest a full treatment course. Thus the length of DPT in mild NIR varies greatly among different studies, going from as short as 1 day to as long as 20 days. A summary of the principal studies published are shown in Figure 1.

Summarizing the results of the major paediatric studies in which in vivo tests have been performed to diagnose mild NIR (Table 2), we found that positivity of ST (ID and patch test) varies between 0-12.5% (mean value 2.9%), positivity of DPT with the culprit BL varies between 0-15% (mean value 5.9%) depending on the consistence and number of episodes of the reactions, ST sensitivity varies between 0-50% (mean value 6.2%), and that in a high percentage of cases patients had negative ST with positive DPT [ranges 77.8-100% (mean value 94.9%)].

It has been recently suggested that a large proportion of children might outgrow their nonimmediate benign allergy to BL (76). Further studies including a large number of patients in different centers are urgently needed to assess the utility of challenging children with a positive DPT after 2-3 years, to confirm these data. Of note, the utility of booster DPT in children with a suspicion of nonimmediate reaction who had a negative DPT appears to be negligible (76).

Serum sickness like reaction

Serum sickness like reactions (SSLR) are characterized by a skin eruption (usually urticaria or MPE) accompanied by systemic symptoms such as fever and joint manifestations (arthritis, arthralgia) usually within 7 to 21 days of exposure to the causative agent and without evidence of systemic vasculitis (92-102). The pathogenesis is not well-known and circulating immune complexes are typically not found. It has been suggested that it might be an inflammatory response to drug metabolites after hepatic biotransformation (92). It is commonly seen in children younger than five-year-old (93). Antibiotics, especially BLs (94-96), are one of the main drugs involved. Classically cefaclor is the most frequently associated BL, with an incidence of 0.14-0.2 % per course of treatment (96,97), with the symptoms more likely observed during the second and third courses (98). This clinical entity was rarely described in association with other BLs with a reported incidence of 0.007% with AX and 0.04% with penicillin V, though in the last decade most paediatric reports seem to involve aminopenicillins.

Treatment includes nonsteroidal anti-inflammatory drugs for fever, antihistamines for pruritus and short course of systemic corticosteroids in the case of extensive rash and/or joint involvement (94, 98, 102).

The study of such reactions is difficult, as no biomarkers exist. The diagnosis is mainly clinical and a drug allergy diagnostic workup is seldom performed. Positive specific IgE and STs for BLs have been proposed, although the exact meaning of the positive results is far from clear considering that SSLR do not fit a classic IgE-mediated IRs. DPT is not usually done in this context so most time diagnosis lacks confirmatory proof. In a study including 23 patients with a history of SSLR, 3 patients had a confirmed diagnosis of SSLR based on positive ST and 4 based on a positive DPT

(94). In another study concerning suspected NIRs to aminopenicillins in children, 14 patients with SSLR were included. None of them had positive STs but 7 had positive DPTs and were diagnosed as having HSR (103).

The lymphocyte-based cytotoxicity assay can also be useful to confirm the BL responsible for SSLR and exclude cross-reactivity, although further validation are needed (104). Patients with SSLR to a certain BL should be investigated as they may not require avoiding others (34).

SEVERE NON IMMEDIATE REACTIONS (SCARs)

SCARs are life-threatening adverse drug HSR associated with hospitalization, mortality and severe sequelae. SCAR include Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), acute generalized exanthematous pustulosis (AGEP) and drug reaction with eosinophilia and systemic symptoms (DRESS) (105).

SJS/TEN are characterized by blistering skin lesions of various severities due to the detachment of necrotic epidermis often progressing from cranial to caudal and haemorrhagic erosions of mucous membranes of which oral cavity is most commonly involved (106-108). Prodromal symptoms lasting 1–7 days concern fever, malaise difficulty in swallowing and ocular pruritus (109,110). Skin biopsy reveals necrotic keratinocytes and vacuolization of the basement membrane leading to subepidermal blistering (111). In a population based paediatric study, the incidence was 6.3/100000 for SJS and 0.5/100000 for TEN; the highest incidence was in those aged 11-15 years (38.4/100 000) (112). Antibiotics, mainly BLs, are the most important eliciting drugs of SJS/TEN in children. Both aminopenicillins (amoxicillin, amoxicillin/clavulanate, ampicillin sulbactam) and cephalosporins (cefixime, cefdinir, cefazolin, cefuroxime, ceftriaxone) are reported to induce SJS/TEN (113-115). Infectious agents such as herpes simplex virus, mycoplasma pneumonia may be responsible for SJS/TEN making the diagnosis more complex (109).

Concerning DRESS, it is a severe DHR that frequently presents with MPE, involvement of internal organs (mainly hepatitis and nephritis), fever and lymphadenopathy. Hematologic manifestations

reveal eosinophilia, leukocytosis and atypical lymphocytes (17). In large cohorts of children with symptoms suggestive of hypersensitivity to BLs, the diagnosis of DRESS is very rare (0-0.07%) (23,24). Although antiepileptics are the most common causative drugs of DRESS, BLs (mostly amoxicillin $\pm$ clavulanate) are also responsible for 6.9-17.6% of pediatric DRESS cases (116, 117). However, in a tertiary care pediatric hospital setting, antibiotics are shown to be most frequent culprit drug in DRESS and BLs account for 25% of cases (118). Patch testing with the offending BL should be preferred as the first line of diagnostic approach at least 6 months after the disappearance of the rashes and in absence of reactivation of herpes group viruses (25). The sensitivity and specificity of lymphocyte transformation test for BL induced DRESS is demonstrated as 73% and 100%, respectively (119). The major treatment strategy involves withdrawal of the culprit drug and use of systemic corticosteroids. Nevertheless, severe pediatric DRESS cases respond to IVIG therapy (120).

Diagnostic value of in vivo and in vitro tests and treatment recommendations

Diagnosis is mainly clinical and histological (121). Nikolsky's sign is positive (lateral expansion of a blister with delicate pressure from a finger). However this sign is positive in other bullous disorders (17). Laboratory tests may exhibit lymphopenia, thrombocytopenia, transient neutropenia, mild cytolysis and transient liver or renal enzyme increase (12,121). Although sensitivity is low, patch tests with the offending BL can be used as first line of investigation after 6 months and should be evaluated at least at two consecutive times: 48 h and 72h (79,121-123). In case of patch test negativity, the BL should be initially tested with the highest dilution for IDT (78). DPT are contraindicated in severe life-threatening DHRs including SJS/TEN (12) and is mainly used in case of low suspicion, to exclude an allergy. However, Lezmi et al performed DPT with culprit BL in 5 children who had a history of SJS which yielded negative results (85). Those data are based on a limited number of patients should be confirmed by further studies as the risk of life-threatening reaction during DPT in this situation is potentially high. There is no definite treatment of the condition. Early withdrawal of the causative drug is essential. Supportive care including ocular supervision, fluid replacement therapy, cutaneous and mucous membrane care

and nutritional support (112,121,124). Use of immunomodulatory drugs (IVIG, corticosteroids) is controversial (125). IVIG treatment may shorten disease progression, increase survival rate and lead complete re-epithelization (125). Glucocorticosteroids and cyclosporine treatments were associated with encouraging survival benefit (126). In a recent study, both IVIG and/or glucocorticoids did not affect duration of hospitalization or need for mechanical ventilation (127). Prognostic factors of mortality have been determined and incorporated in a severity-of-disease score called SCORTEN (128). It has been found that survival in children with SJS/TEN is better compared to adults (129). TEN was shown to be associated with higher mortality (3.23%) compared with SJS (0.13%) (127). The recurrence rate of SJS/TEN was demonstrated to be 7.1-18% in children (130).

CONCLUSION

There is a wide spectrum of HRS to BLs in children but the most common manifestation is a nonimmediate mild skin reaction, either maculopapular rash or delayed urticaria. In these mild NIRs, a DPT is almost universally advocated and there is now enough evidence that skin test can be skipped in this situation. However, this approach should take into account variables such as reliability of the history, age of the child, the time interval between index reaction and testing and underlying comorbidities that can increase the risk for the patient. Most importantly, a more clear definition of a mild, or low risk, index reaction should be made. The optimal protocol for the DPT still needs to be defined. In addition, more studies are needed to confirm the safety of performing a direct DPT in children with mild immediate BL reactions. Finally, recent reports suggest that a subset of children with mild nonimmediate hypersensitivity to BL outgrow their allergy. Further large multicentric studies are needed to investigate the natural history of BL allergy.

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Table and Figure Legends

Table 1. Principal pediatric studies that perform direct DPT without previous skin tests in case of history of mild cutaneous reactions to BLs.

In the table we provided homogeneously the results.

We specified that we presented only pediatric studies in children with history of mild reactions to beta-lactams antibiotics.

Table 2. Results of the major pediatric studies in which in vivo tests have been performed to diagnose mild NIR

Percentages are calculated on the total number of tests

*Results after the first DPT

HSRs= Hypersensitivity reactions

NIRs= Non immediate reactions

DPT= Drug Provocation tests

ST= Skin Tests

PT= Patch Tests

Figure 1. Variations in the lengths of DPT among the different studies published in the literature.

Few studies have two different DPT (Drug Provocation test) lengths because duration of DPT depends on the timing of the index reaction.

Moreover, in the study from Pichichero et al. the DPT length was of 10 days in case of reaction to only one antibiotic and it was of 5 days with an antibiotic and of 5 more days with a different antibiotic, after a three-days wash out period, in case of reactions to different antibiotics.

UK guidelines have been removed because we show results of different studies and not recommendation obtained from guidelines.

The percentage of Poussel G has been corrected because there was a mistake 3% has been changed into 14.2%. At last we added information regarding the type of DPT and the mean age of the children tested, according to the reviewers suggestions.

Table 1. Principal pediatric studies that perform direct DPT without previous skin tests in case of history of mild cutaneous reactions to BLs.

	Mattheij 2011 (131)	Moral 2011 (84)	Vezir 2015 (89)	Mill 2016 (38)	Iammatteo 2018 (132)	Koosakulchai 2018 (133)	Prieto 2018 (134)	Rodriguez 2019 (135)	Pouessel 2019 (136)	Diaferio 2019 (9)
Patients with history of NIRs	33	50	119	818	155	31	67	97	91	208
Range or Mean Age	10 months- 16.4 years	6.7 years	4.3 years	1.7 years	5.11 years	5.9 years	1-14 years	<14 years	6.9 years	5 years
Type of DPT	skin contact;lip contact; mucosal contact; 1/3 of half day dose; 2/3 of half day dose (30 minutes intervals)	1/50;1/5;usual single dose (1 hour interval)	2 half doses	1/10; 9/10 of the therapeutic dose	About 1/10- 9/10 of the therapeutic dose	2 half doses	1 single dose	1/4; 1/2; full dose (30 minutes intervals)	2 half doses	1/10;/10;7/10 (30 minutes intervals)*
DPT + (n); %	(4) 12.1%	(1) 2%	(4) 3,4%	(48) 5.8%	(4) 2.6%	(1) 3.2%	(6) 9%	(14) 14.4%	(13) 14.2%	(5) 2.4%

Table 2. Results of the major pediatric studies in which in vivo tests have been performed to diagnose mild NIR

Studies	Patients with history of NIRs	ST + (n); %	DPT + (n); %	ST+/DPT+ (sensitivity)	ST-/DPT+ (false negative)
<i>Romano 1997 (137)</i>	82	(4); 4.9	(0/49); 0	/	
<i>Blanca Lopez 2009 (103)</i>	20 confirmed HSRs 20 control group	(1); 0.05	(19); 95	(0); 0	(19); 100
<i>Ponvert 2011 (23)</i>	1269	(60); 4.7	(117); 9.2	/	
<i>Caubet 2011 (90)</i>	88	(11); 12,5	(6); 6.8	(4); 66,6	(2); 33.3
<i>Zambonino 2014 (24)</i>	783 (717 NIRs)	(2); 0.28	(51); 7.1	/	(51); 100
<i>Mori 2015 (87)</i>	200 (152 NIRs)	(6); 3.9	(14); 9.9	(2); 14,3	(12); 85.7
<i>Barni 2015 (138)</i>	352	(3); 0,08	(25); 7.4	(2); 8	(23); 92
<i>Caubet 2015 (35)</i>	250 (14 confirmed HSRs)	(7); 50	(14); 5.6	(7); 50	(14); 100
<i>Atanaskovic 2016 (139)</i>	1026	(57); 5.5 PT (18); 1.7	(19); 1.8	/	(19); 100
<i>Manuyakorn 2016 (140)</i>	86	(3); 3.5	(4); 4.6	/	(4); 100
<i>Vyles 2017 (39)</i>	100	(3); 3	0	/	/
<i>Faitelson 2017 (141)</i>	133 (101 NIRs)	(0); 0	(10); 9.9	(0); 0	(10); 100
<i>Lezmi 2018 (85)</i>	550	(9); 1.6 PT (12); 2.1	(43); 8.2	/	(43); 100
<i>Ibanez 2018 (18)</i>	732 (694 NIRs)	(3); 0.4	(34*); 4.8	(3); 0.4	(31); 91.2
<i>Diaferio 2019 (9)</i>	229 (208 NIRs)	(6); 2.6	(6); 2.7	/	(6); 100
<i>Vila 2019 (142)</i>	229 (154 NIRs)	(2); 1.3	(17); 11.2	/	(17); 100

Figure 1. Variations in the lengths of DPT among the different studies published in the literature.

*ENDA (European Network on Drug Allergy) guidelines

