Management of Suspected Antibiotic Reactions in Children

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EPIDEMIOLOGY

To date, the actual incidence of drug allergy in the pediatric population is not well known. Epidemiologic studies report that drug allergy affects more than 10% of children and adolescents; although when these children are fully investigated <10% are confirmed to be truly allergic to the suspected drug. Until a few years ago, penicillin allergy was the most frequently reported drug allergy with a prevalence rate of 5%–10% in adults and children. Today amoxicillin allergy is more prevalent than penicillin allergy in children. Non-β-lactam allergy is rare in children and estimated to affect 1%–3% of this population following β-lactams and nonsteroidal anti-inflammatory drugs. As regards the most frequently reported reactions to non-β-lactam drugs, sulphonamides and macrolides are among the most commonly implicated antibiotics.[1]

These so-called allergic reactions are rather common in children, most likely because of the frequency of rashes that occur during antibiotic treatment for a viral infection and reluctance to test to confirm allergy.

Nowadays, it is mandatory to rigorously confirm or exclude a diagnosis of antibiotic allergy to improve patient safety by using the most appropriate antibiotic depending on the infection to be treated and avoid alternative often more expensive, favoring antibiotic resistance.

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MECHANISMS OF ANTIBIOTIC ALLERGY

According to the time interval between the last drug intake and the onset of symptoms, 2 main clinical phenotypes have been described:

1. Patients with immediate reactions (IRs) that occur within 1–6 hours after exposure to the drug and are possibly induced by an IgE–mediated mechanism. They manifest as cutaneous, respiratory, gastrointestinal symptoms or anaphylaxis.
2. Patients with non-IRs (NIRs) observed within days to weeks after drug administration with a wide range of clinical symptoms from maculopapular exanthemas (MPEs), urticaria, exfoliative dermatitis and fixed drug eruption, to severe cutaneous adverse reactions (SCARs) such as acute generalized exanthematous pustulosis, Stevens-Johnson Syndrome/toxic epidermal necrolysis and drug reaction with eosinophilia and systemic symptoms. They are often associated with a delayed T-cell mediated mechanism. MPEs are the most frequent, although life-threatening reactions may occur with a mortality rate of 1%–5% in Stevens-Johnson Syndrome, up to 25%–35% in toxic epidermal necrolysis, and of 10% in drug reaction with eosinophilia and systemic symptoms.[2] Symptoms because of type II and III hypersensitivity according to Gell and Coombs Classification are not always isolated to one organ and can cause interstitial nephritis, pneumonitis, hepatitis and vasculitis with or without signs of serum sickness, cytopenias (hemolytic anemia, thrombocytopenia and neutropenia).

ASSESSMENT OF HYPERSENSITIVITY REACTIONS TO ANTIBIOTICS

A detailed clinical history including the type of reactions, time elapsed between drug exposure and onset of clinical symptoms, and time latency between the clinical reaction and allergy work-up is of paramount importance to choose specific allergy tests for IRs or NIRs.

In case of IRs, diagnostic skin prick tests (SPTs) and intradermal tests (IDTs) are mainly validated for β-lactams [major (benzylpenicilloyl-poly-L-lysine) and minor (benzylpenicillin, sodium benzylpenilloic acid, benzylpenicilloic acid) determinants], while for non-β-lactam antibiotics they lack standardization. Therefore, the gold standard for the diagnosis of non-β-lactams hypersensitivity is a detailed clinical history and drug provocation tests (DPTs) where permitted.

According to the European Guidelines, DPTs are contraindicated in patients with history of anaphylaxis or potentially harmful skin reactions (SCARs).[3]

IRs can be investigated in vivo with immediate-reading skin tests and in selected cases, DPT and in vitro with serum specific IgE (sIgE) assays and flow cytometric

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basophil activation tests, ideally 2 months after the reaction.

In patients with a history of IRs, in the absence of subsequent exposure to the culprit antibiotic, hypersensitivity tends to decrease over time with reductions in serum sIgE and skin test reactions. It is estimated that 50% of patients with IgE-mediated penicillin allergy apparently lose their sensitivity 5 years after the skin eruption, rising to 80% after 10 years. For this reason, the European guidelines advise the retesting of patients who have experienced IRs to β-lactams and have negative DPTS. In general, the risk of resensitisation has been estimated to be very low (<1%), therefore it has been suggested that retesting in children only be performed in cases of severe reactions.[4]

The percentage of positive skin test results in patients with a clinical history of β-lactam allergic reactions varies between 7% and 76%, according to different studies. The ImmunoCAP system (Thermo Fisher, Uppsala, Sweden) to detect serum sIgE to β-lactams has a lower sensitivity than skin tests (from 12.5% to 25%) with a good specificity (from 83.3% to 100%).[5]

Multicenter studies have reported a basophil activation test sensitivity of 50% and specificity between 89% and 97%, suggesting the testing of more than one β-lactam.

Because of the limitations of in-vivo and in-vitro testing with β-lactams, recent European studies have reported that between 8.4% and 30.7% of patients with negative results reacted to drug challenge.

In any case, when combining SPT, IDTs and DPT, the possibility of removing the penicillin allergy label rises to 90%.[5]

There are only limited data regarding the predictive values of skin tests in amoxicillin allergy in children. Data from our group showed that[6] the sensitivity and specificity of SPTs and IDTs were 33% and 100%, respectively for IRs.

In case of NIRs, the diagnosis is based on in vivo tests [delayed-reading IDTs, patch tests and DPTs in selected cases] and in vitro tests such as lymphocyte transformation tests, lymphocyte activation tests and enzyme-linked immunospot (Millipore, Bedford, MA) assays for analysis of antigen-specific, cytokine-producing cells. Among the in vitro tests, lymphocyte transformation test has been used to investigate β-lactam allergy showing a variable sensitivity (ranging from 25% to 79%) for nonimmediate allergic reactions to penicillin. However, false-positive results have been reported in nonreactive patients who had recently been exposed to drugs.[5]

The sensitivity of skin tests in NIRs is lower than that of IRs. Moreover, the diagnosis of NIRs is difficult because the reactions may be favored by a concomitant viral infection, such as those caused by HIV, cytomegalovirus, human herpesvirus 6 or Epstein-Barr virus. For example, recent papers have demonstrated the possibility of a true and persistent sensitization to the culprit β-lactam during Epstein-Barr virus instead of a transitory loss of tolerance due to the infection.[7] MPE occurs in 1%–5% of rashes per β-lactam prescription. Most of the reactions are confirmed by DPTs,[8] and taking into account the difficulty of performing painful IDTs in children; recent papers suggest performing directly controlled DPTs in cases of benign rashes with β-lactams.[9] The sensitivity and specificity of amoxicillin SPTs and IDTs were 14% and 99%, respectively for NIRs in children.[6]

In cases of SCARS, the European guidelines recommend to first perform PTs and only in case of a negative response to perform IDTs.

IDTs with late reading may improve the diagnosis of NIRs to aminopenicillins by about 10%,[4] even though they can induce false-positive results due to the irritating concentrations tested and in some cases they have also provoked severe systemic reactions. In children, the risk of systemic reactions to skin testing is low, between 1% and 3%.[4]

Patch tests have demonstrated sensitivity (56.7%) in diagnosing severe NIRs to β-lactams, quinolones, vancomycin and amikacin.

Current guidelines recommend that in the context of NIRs to antibiotics, tests should be performed from 3 to 6 weeks up to 3–6 months after complete resolution of skin eruption.[10] In any case, peripheral blood T-lymphocytes may remain susceptible to specific activation when cultured with the culprit drug, suggesting a long-term memory even without further exposure.[9]

In the event of confirmed antibiotic hypersensitivity and the existence of effective antibiotics belonging to the same class, it is important to know the risks of any cross-reactivity.

B-LACTAMS AND CROSS-REACTIVITY

Patients selectively react to different β-lactams sharing an identical side chain or to the nuclear region of the antibiotic, resulting in cross-reactivity among different β-lactams.[4]

The β-lactam ring is less likely to cause cross-reactivity. Patients with positive penicillin skin tests have a risk of about 2% of reacting to cephalosporins. When patients with a history of penicillin allergy are directly administered a cephalosporin without skin testing, the chance of reacting to the cephalosporin is approximately 1%.[4] When a penicillin-allergic patient is administered a cephalosporin with identical R1 side chains, the risk of an allergic reaction increases by 30%.

Cephalosporins should be administered by means of graded challenge in patients with suspected penicillin or cephalosporin allergy. A desensitization protocol should be performed in patients with positive skin tests to the required β-lactams or a history of β-lactam anaphylaxis. The exact allergenic determinants of cephalosporins have not yet been identified; however, cross-reactivity among cephalosporins is largely based on the similarity of the chemical structure of the R1 side chain.

Carbapenems

Cross-reactivity between penicillins or cephalosporins and carbapenems is rare (1%). In NIRs the frequency of cross-reactivity ranges from 0% to 5% according to different studies.[4] Cross-reactivity among carbapenems is not known, but in a few cases there have been reports of tolerance to a different carbapenem.[4]

Monobactams

Aztreonam and ceftazidime share the same R1 chain. As regards the cephalosporins, up to 3% of patients have positive skin-test results for aztreonam.[4]

NON-B-LACTAMS AND CROSS-REACTIVITY

Non-β-lactam antibiotics consist of quinolones, macrolides, sulphonamides, aminoglycosides, rifamycin, glycopeptides and clindamycin, all of which have very different chemical structures, antimicrobial spectra and immunogenic properties.

Quinolones

Cross-reactivity among quinolones is common between first and second generation quinolones and to a lesser extent, between the third and fourth generation.

Macrolides

Cross-reactivity is rare in this class of antibiotic so if one macrolide is not tolerated; it is recommended to select another if indicated.[11]

Sulfonamide Antibiotics

There is no cross-reactivity among sulphonamides and nonantibiotic sulphonamides. Cross-reactivity among sulphonamide antibiotics has been reported.[11]

Sulfasalazine represents an important exception, and patients with hypersensitivity to sulfasalazine or sulfamethoxazole should be specifically advised to avoid both drugs.

Aminoglycosides

Cross-reactivity among aminoglycosides is common, reaching 50% or higher among those belonging to the deoxystreptamine group. Streptomycin does not share common antigenic structures with other aminoglycosides that belong to the deoxystreptamine group and cross-reactivity to the latter has not been reported.[11]

Glycopeptides

Vancomycin can directly activate mast cells and is associated with a "red man syndrome." Premedication with antihistamines, slowing the infusion rate and avoidance of concomitant mast cell secretagogues (eg, opiates) are helpful in patients with red man syndrome. Teicoplanin can be used in case of failure, although there is only limited evidence in children.[11]

In short, various diagnostic algorithms have been proposed for the evaluation of IRs and NIRs that will differ also depending on the antibiotic class involved (Fig. 1).[12] When a clear time interval between the last drug intake and the hypersensitivity reaction is missing; patients should be investigated for both IRs and NIRs.

DPTOR DESENSITIZATION

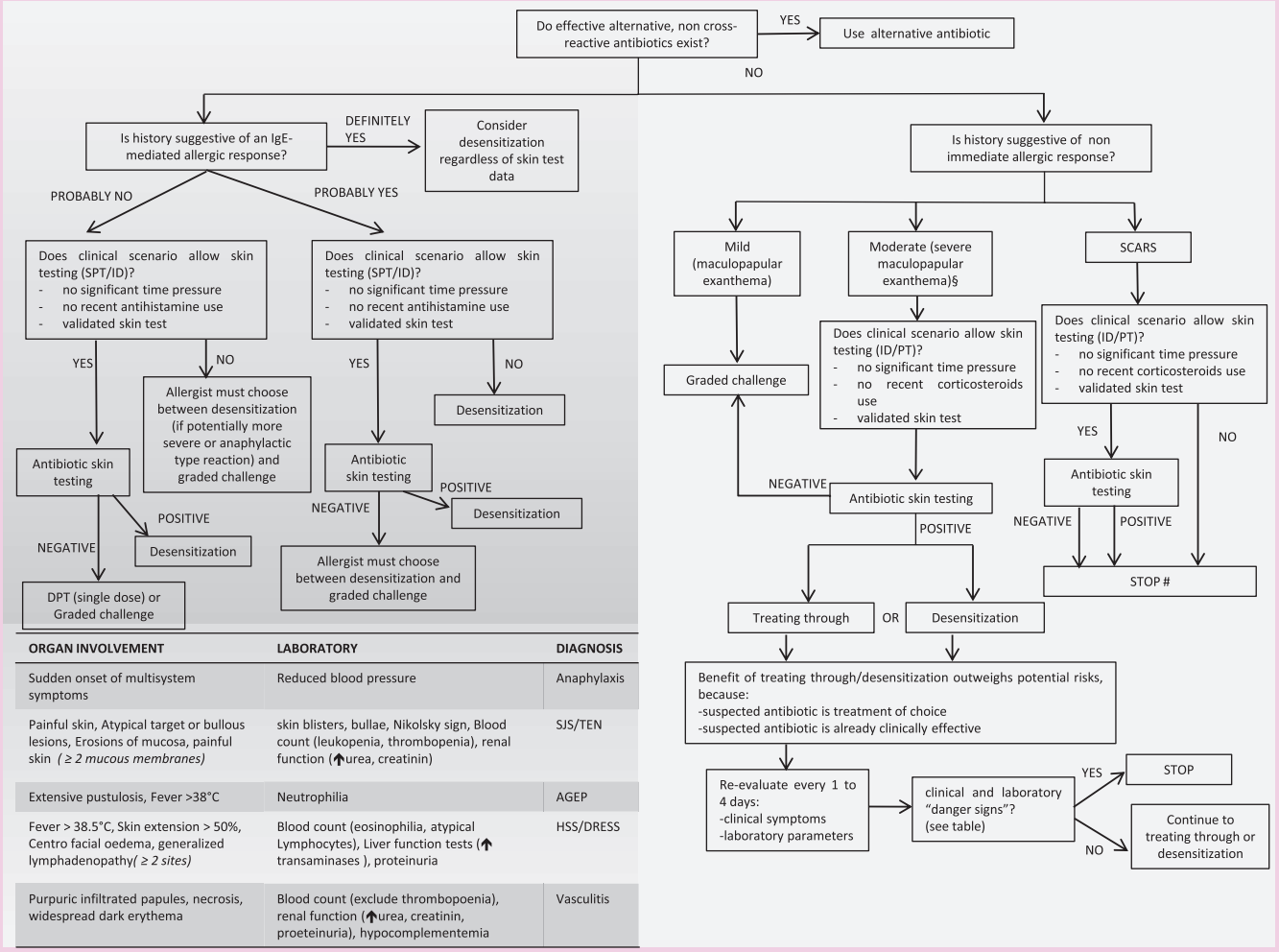
The gold standard for diagnosis of drug allergy is DPT in the form of single-dose challenge or graded challenge (no more than 4 steps). DPT is a diagnostic measure and de-labeling strategy as opposed to desensitization, which is a therapeutic measure for inducing tolerance to a drug in highly sensitized children. Both DPT and desensitization should be carried out in an appropriate medical setting with continuous monitoring and personnel trained to treat anaphylaxis.

"TREATING THROUGH"

In patients with antibiotic-associated MPE, the physician needs to identify the offending agent and make the decision to either suspend or continue the antibiotic therapy. Several factors should be taken into account because "treating through" is a risky procedure: ie, has the antibiotic been clinically effective in treating a serious bacterial infection? Are non-cross-reactive antibiotics associated with a suboptimal antimicrobial activity or unfavorable side effects? Is close patient monitoring applicable, and last but not least, has a diagnosis of complicated MPE been unequivocally made. Every effort should be made to differentiate MPEs from more serious cutaneous reactions (Fig. 1).[13,14] In any case, severe cutaneous skin reactions may also resemble MPEs in the very early stages.

CONCLUSION

Management of drug allergy in children depends on an accurate clinical history that can be conducive for appropriate testing



ORGAN INVOLVEMENT	LABORATORY	DIAGNOSIS
Sudden onset of multisystem symptoms	Reduced blood pressure	Anaphylaxis
Painful skin, Atypical target or bullous lesions, Erosions of mucosa, painful skin *(≥ 2 mucous membranes)*	skin blisters, bullae, Nikolsky sign, Blood count (leukopenia, thrombopenia), renal function (↑urea, creatinin)	SJS/TEN
Extensive pustulosis, Fever >38°C	Neutrophilia	AGEP
Fever > 38.5°C, Skin extension > 50%, Centro facial oedema, generalized lymphadenopathy*(≥ 2 sites)*	Blood count (eosinophilia, atypical Lymphocytes), Liver function tests (↑ transaminases), proteinuria	HSS/DRESS
Purpuric infiltrated papules, necrosis, widespread dark erythema	Blood count (exclude thrombopoenia), renal function (↑urea, creatinin, proeteinuria), hypocomplementemia	Vasculitis

FIGURE 1. Management of suspected antibiotic reactions in children: operative flowchart adapted from Gomes et al,[9] Turvey et al,[12] Trautmann et al[13] and Demoly et al.[14] §More severe exanthemas, such as those with high extent and density of skin lesions and long duration, complications or danger signs.

and identification of the underlying immunopathologic mechanisms. New classifications based on phenotypes and endotypes may give rise to more individualized treatments for drug allergy in the future.[15]

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