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Hypersensitivity Reactions to Non-Betalactam Antibiotics in Children: An Extensive Review

2.AUTHORS:

Semanur Kuyucu

Francesca Mori

Marina Atanaskovic-Markovic

Jean-Christoph Caubet

Ingrid Terreehorst

Eva Gomes

Knut Brockow

3. AFFILIATIONS:

Prof Semanur Kuyucu,MD

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Department of Pediatric Allergy and Immunology, Mersin University, Sağlık Araştırma ve Uygulama Merkezi

Çiftlikköy kampüsü Yenişehir, 33343

Mersin, Turkey

semanurkuyucu@yahoo.com

Francesca Mori, MD, PhD
Allergy Unit, Department of Pediatric,
Anna Meyer Children's Hospital,
University of Florence,
Viale Pieraccini, 24
50139 Florence, Italy

f.mori@meyer.it

Marina Atanaskovic-Markovic, MD
Medical Faculty University of Belgrade
University Children's Hospital of Belgrade, Serbia
marinaa@EUnet.rs

Jean-Christoph Caubet, MD,
Pediatric Allergy Unit, Department of Child and Adolescent,
University Hospitals of Geneva, Geneva, Switzerland.
Jean-Christoph.Caubet@hcuge.ch

I. Terreehorst, MD, PhD
AMC, Dept ENT and Pediatrics
Meibergdreef 9
1105 AZ Amsterdam, the Netherlands
I.Terreehorst@amc.uva.nl

Eva Gomes MD,
Allergy Department,

Centro Hospitalar do Porto,
Porto, Portugal
evargomes@yahoo.com

Prof Knut Brockow, MD,
Department of Dermatology and Allergy Biederstein,
Technische Universität München,
Munich, Germany
knut.brockow@lrz.tu-muenchen.de

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5. Correspondent Author:

Semanur Kuyucu, MD

Department of Pediatric Allergy and Immunology, Mersin University,
Araştırma ve Uygulama Merkezi

Sağlık

Çiftlikköy kampüsü, Yenişehir ,33343

Mersin, Turkey

e-mail: semanurkuyucu@yahoo.com

ABSTRACTS PAGE

Authors:

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Abstract

In contrast to hypersensitivity reactions (HSR) to β -lactam antibiotics in children, studies about HSR to non- β -lactam antibiotics (NBLA) such as sulfonamides, macrolides, quinolones and anti-tuberculosis agents are scarce and information is generally limited to case reports. The aim of this extensive review was to summarize our present knowledge on clinical characteristics, evaluation and management of HSR to NBLAs in children based on the literature published between 1980 and 2013. NBLAs have been reported to induce a wide spectrum of HSRs from mild eruptions to severe, and sometimes fatal, systemic drug reactions, especially in some high-risk groups. The diagnosis relies upon history and remained unconfirmed by allergological tests in most of the cases. Obtaining a detailed history is valuable in the diagnosis of suspected reactions to NBLAs. Diagnostic in vivo and in vitro tests for NBLAs lack validation, which makes the diagnosis challenging. The definitive diagnosis of NBLA hypersensitivity frequently is confirmed by drug provocation test. Studies including children showed that only 7.8 % to 36 % of suspected immediate and delayed HSRs to NBLAs could be confirmed by skin tests and provocation tests. Therefore, a standardized diagnostic approach and management strategy should be developed and employed for pediatric patients in the evaluation of suspected HSRs to NBLAs, some of which may be critical and unreplacable in certain clinical situations.

Keywords:

Children, Drug Allergy, Drug Hypersensitivity, Non-beta(β)lactam antibiotics, Diagnosis

Correspondence:

Semanur Kuyucu, MD, Department of Pediatric Allergy and Immunology,
Department of Pediatric Allergy and Immunology, Mersin University,

Sağlık Araştırma ve Uygulama Merkezi

Çiftlikköy kampüsü, Yenişehir ,33343

Mersin, Turkey

e-mail: semanurkuyucu@yahoo.com

Introduction

Within the spectrum of adverse reactions to drugs (ADR), drug allergy is defined as a drug hypersensitivity reaction (HSR) that involve the immune system(1). While the clinical features can be comparable between children and adults, frequency and elicitors are quite different. Similar to adults, well-known elicitors of HSR are betalactam antibiotics, nonsteroidal antiinflammatory drugs and in perioperative reactions, neuromuscular blocking agents (1,2). A somewhat overlooked cause of HSR in children are the non- β -lactam antibiotics (NBLA). NBLAs can cause a wide spectrum of HSRs

from mild rashes to fatal systemic reactions by different mechanisms (1-3)(Table 1). In this article we discuss the epidemiology, clinical features and diagnostic procedures in children.

Epidemiology of hypersensitivity reactions to non- β -lactam antibiotics

The overall incidence of HSRs to NBLAs has been estimated to be 1% to 3% in general population (1,2). Differences in prescription rates and genetic background are important factors influencing incidence and prevalence of drug reactions (3,4). Hence, the mostly implicated antibiotic groups, and incidence rates differ between countries. A recent study in the USA (25.3 % children), revealed that antibiotic classes with higher historical use, increasing decade of age and, for the first decade of life, male sex were associated with higher reported antibiotic HSR prevalence rates (3). Penicillins were most commonly reported to cause hypersensitivity in all age groups. Sulfonamides were on the second rank of HSR prevalence rates in pediatric age (0.5 % for 0-9 yrs and 2.2 % for 10-19 yrs, respectively), followed by macrolides (0.4 % for 0-9 yrs and 0.7 % for 10-19 yrs, respectively) and comparable to cephalosporins, while reactions to quinolone and tetracyclines were rare in children (3). Taking exposure to different antibiotics into account, reaction rates were highest to sulfonamides compared with other classes of antibiotics among adults and children (3,5).

Population-based questionnaire surveys among children in different countries revealed parent-reported drug HSR prevalence values from 2.8 % to 5.4 %, of which approximately 10 to 20 % was associated with NBLAs(6-9). Among NBLAs, agents mostly responsible for HSR were cotrimoxazole, macrolides and rifampicin(6-10).

Mechanisms and diagnosis of hypersensitivity reactions to non- β -lactam antibiotics

Different mechanisms including type I (IgE-mediated), type II (IgG or IgM-mediated), type III (immune complex-mediated) and type IV (T cell-mediated) HS reactions and non-immunologic reactions lead to different clinical manifestations of DHRs to NBLAs (1,2,11,12) (Table 1).

A detailed history is the most essential step towards an accurate diagnosis of a drug-induced reaction. In addition to the clinical history, a careful physical examination can help to better classify possible mechanisms underlying the reaction and to guide further investigations. A suspected IgE-mediated immediate reaction such as urticaria, angioedema, rhinitis, bronchospasm, and anaphylactic shock should be assessed by immediate-readings (15-20 min) of skin prick (SPT) and intradermal (IDT) tests, whereas serum-specific IgE assays to NBLA and flow cytometric basophil activation test (BAT) remain experimental (1,11).

When a T cell-mediated reaction such as maculopapular eruption (MPE), delayed-appearing urticaria, fixed drug eruption (FDE), acute generalized exanthematous pustulosis (AGEP), bullous exanthems such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS) is suspected, delayed-readings (24-72 hrs) of SPT and IDT and patch tests are indicated(1,12). For severe reactions, such as SJS,TEN and DRESS

skin tests, IDTs should be used with caution as they may reproduce DHRs (11,12). Skin tests are not helpful in type II or type III reactions (1,11).

Other tools, such as lymphocyte transformation test (LTT) and flow cytometric lymphocyte activation test (LAT) can be diagnostic aids in some T cell-mediated reactions (1,11). However, both skin tests and laboratory tests lack validation, which makes the diagnosis more challenging and uncertain than for β -lactam antibiotics. Skin tests are not standardized, have low sensitivity, and in higher concentrations can result in false positive reactions due to irritating properties of the drug. Nonirritating skin test concentrations have been proposed for some NBLAs, but have not yet been confirmed for children (1,16,17) (Table 2)(Table 5,online repository). If skin tests using established drug concentrations are positive, a drug hypersensitivity is likely. In this situation, the most cautious approach is to apply an alternative non-cross-reacting antibiotic or undergo a desensitization procedure (11,15). A negative skin test result does not exclude drug hypersensitivity. The definitive diagnosis of NBLA HSR frequently relies upon drug provocation tests (DPT) (11,13-15). In skin test-negative patients who have mild reaction histories, a DPT should be performed. DPT should not be performed in severe reactions e.g. SJS, TEN and DRESS, hematological manifestations, organ involvement or autoimmune diseases (1,11,15).

Detailed clinical evaluation studies including suggested diagnostic algorithms showed that only 10 to 40 % of suspected NBLA allergies could be confirmed among adults (13,18). Studies including only children for the evaluation of HSRs to NBLAs are scarce; they showed that approximately 7.8 % to 36 % of suspected reactions could be confirmed by skin tests and/or provocation tests (18-21).

SULFONAMIDES

Chemical structure and cross-reactivity

Currently, the most frequently encountered sulfonamide antibiotic is the combination of trimethoprim (TMP) and sulfamethoxazole (SMX). It is important for prophylaxis and eradication of opportunistic infections in serious diseases, such as AIDS or hematologic malignancies and is also commonly used for community infections in some regions of the world (1, 22).

A sulfonamide is any compound that contains a sulfonamide (SO_2NH_2) moiety and includes sulfanilamide and non-sulfanilamide drugs. Sulfonamide antibiotics are classified under sulfanilamide group and different from other sulfonamide-containing but non-sulfanilamide medications by the presence of an aromatic amine at the N4 position, and a substituted ring at the N1 position which are necessary for the development of hypersensitivity reactions (22,23)(Table 3, Online repository).

Some concern still exists about the use of other sulfonamide-containing drugs for patients who have a history of allergy to sulfonamide antibiotics. Theoretically, depending on the chemical structural differences, allergic cross-reactivity between sulfonamide antibiotics and non-sulfanilamide sulfonamides is not expected (23,24). Many adult studies supported an absence of clinical cross-reactivity (24,25). Hence, avoidance of non-sulfanilamide, sulfonamide containing drugs in patients sensitive to sulfonamide antibiotics is usually not recommended, although controversy exists in previously severe reactions (27).

On the other hand, a recent report employing LTT suggested that sulfasalazine represented an important exception and patients with hypersensitivity to sulfasalazine or sulfamethoxazole should be specifically advised to avoid both drugs (26). In addition, two sulfonamide drugs (amprenavir und fosamprenavir) which are used as protease inhibitors in HIV therapy should be regarded as another exception. Although, neither clinical nor in vitro data on immunologic crossreactivity with other sulfonamides are available, some authors still recommend to avoid such drugs if a previous severe allergy to a sulfonamide antibiotic is present(27).

Epidemiology

The antimicrobial sulfonamides are among the most common causes of drug allergy. The community-based prevalence of parent-,or self-reported HSR to sulfonamide antibiotics was found to range from 0.2 % to 2.2 % for different age groups in children (3,6-8). In a prospective study, the incidence of sulfonamide antibiotic-associated rash was 8.5 % in outpatient children prescribed sulfonamide antibiotics (5). Clinical studies including outpatient and inpatient children from Asian countries reported that cotrimoxazole was the most or secondmost common antibacterial responsible for drug eruptions, ranging from MPE to TEN (9,10). It has been estimated that reactions to TMP-SMX occur in approximately 3 % of the general population, 12-40 % of those with hematologic malignancies, and 30 to 70 % of patients with AIDS (2,28-30). A retrospective study between 2000 and 2010 from four sub-Saharan African countries including 177 adults and children, of which 54.8 % were HIV positive, revealed that antimicrobial sulfonamides were the most commonly (38.4%) associated drugs (31). This high risk is important, because almost all patients with HIV infection are at risk to develop *Pneumocystis carinii* (jiroveci) pneumonia and TMP-SMX is the principal agent used both for treatment and prophylaxis against this infection and also against malaria and toxoplasmosis (22,29). TMP-SMX reactions are also reported in HIV-infected infants and children (29,32,33). Chanock et al. reported that 15 % of 75 HIV-infected infants have developed TMP-SMX reactions, some of which were very severe (33).

Clinical features

Sulfonamide antibiotics rarely cause IgE-mediated reactions such as urticaria, angioedema and anaphylaxis and more commonly result in different types of delayed DHR mediated by T cells, immune complex diseases and immune-mediated hepatotoxicity in adults and children (1,9,10,22,28)(Table 1). In clinical studies of cutaneous drug eruptions, FDE and MPE were most common, and cotrimoxazole was the most common drug associated among adults and children in India (10,34). A pediatric study from West Africa, which included 35 children (4 HIV positive) with drug eruption showed that sulfonamides were the most frequently proven drug (11/21 proven cases) and that the main clinical patterns were FDE, maculopapular eruption, SJS/TEN, and urticaria (29).

Sulfonamides cause a disproportionate share of life-threatening ADRs, such as SJS, TEN and DRESS (35-37). A pooled analysis of two multicenter international case-control studies, the severe cutaneous adverse reaction (SCAR) study and the multinational severe cutaneous adverse reaction (EuroSCAR) study, showed that antimicrobial sulfonamides were identified as one of the four drugs

most strongly associated with SJS/TEN in subjects aged <15 years (36). A pediatric study, which evaluated antibiotic use and serum sickness demonstrated that TMP-SMX was among the most frequently associated antimicrobial agents with an incidence of 5 per 5,597 courses of treatment (39).

Diagnosis

Since in some populations sulfonamides are important antibiotics, it is necessary to establish the causal connection between sulfonamides and HSR. Skin prick test and early reading of IDT are employed for immediate reactions. Delayed (24,48,72 hrs) reading of IDT and patch tests might be helpful in nonimmediate reactions. A maximum concentration of 0.8 mg/ml for sulfomethoxazole has been described to be nonirritating for IDT (16). Different patch test concentrations and vehicles for cotrimoxazole (Table 5, Online repository) were recommended in adult studies (12,13,40). Patch tests should be applied to the site of the lesion in case of fixed drug eruption due to cotrimoxazole (12). The sensitivity of skin tests is not known. Probably, the sensitivity of skin tests is low, but the specificity is good which makes a positive result valuable (11,14,41). Lymphocyte transformation test and the lymphocyte toxicity assay (LTA) have been evaluated in patients with non-immediate reactions to sulfonamides. Some researchers found that the LTT was more sensitive; furthermore, the LTT can also test SMX compounds, which is not possible for in vivo tests (41). In patients with sulfonamide hypersensitivity, a recently described LTA reported a sensitivity and specificity of 98% and 89%, and positive and negative predictive values of 90% and 67%, respectively (42). However, these findings need to be confirmed by further studies. DPT remains the gold standard for the diagnosis of sulfonamide allergy both in adults and children (1,20,24). Provocation testing with the culprit sulfonamide should be performed in skin and in vitro test-negative patients who have mild reaction histories. In case of a severe reaction history, provocation testing is contraindicated (1,15).

Management

Although the best management strategy in a patient with sulfonamide hypersensitivity is to use a different drug, there are some clinical settings, especially in patients with HIV infection or hematologic malignancies, where no equally effective alternative exists. Continuing therapy despite adverse reactions (also known as treating-through) was shown to be effective in several case series, especially with the addition of antihistamines, antipyretics, prednisone, or therapeutic drug monitoring (41,43). Reintroducing cotrimoxazole after stopping treatment includes either desensitization or rechallenge at full dose. Several “desensitization” or “cautious graded challenge” protocols for immediate and delayed-type TMP-SMX reactions have been empirically developed and used for adult AIDS patients (41,44). Studies involving small numbers of pediatric patients, mostly with HIV, used different desensitization protocols with success rates from 70 to 100 % (Table 4, Online repository). A Cochrane metanalysis examining differences in patient outcomes between two different cotrimoxazole reintroduction strategies for prophylaxis in adults with HIV infection with previous mild or moderate adverse reaction found an advantage of using a desensitization protocol over a rechallenge protocol at six months of follow-up for both preventing discontinuation and a lower rate of overall DHRs (45). Nevertheless, desensitization

protocols should not be attempted in patients who have had severe drug-induced cutaneous reactions, such as SJS, TEN, DRESS, or systemic disease such as cytopenias and vasculitis (1,46)

MACROLIDES

Macrolides can be subdivided into 4 classes based on the number of atoms in the lactone ring: 12 (methymycin, picromycin), 14 (erythromycin, troleandomycin, roxitromycin, dirithromycin, clarithromycin), 15 (azithromycin) and 16 (spiramycin, josamycin, midecamycin) macrolides (47). Hypersensitivity reactions to macrolides are relatively uncommon when compared to betalactams and sulfonamides (2,6,7). In epidemiologic studies, the parent/self reported macrolide hypersensitivity prevalence ranged from 0.07 to 0.7 % in the pediatric population (3,6-8).

The clinical manifestations of HSRs to macrolides are generally mild, only seldomly severe reactions have been reported (Table 1) (1,47-50). The incidence of anaphylaxis with clarithromycin has been extremely low (1 per million) in pediatric patients (48). Nevertheless, because of their frequent use, a retrospective pediatric study from Spain reported that macrolides were among the most frequent causes of SJS/TEN (49).

Some allergological studies, mostly in adults, rarely including children, reported on results of skin tests and provocation tests (13,20,50-53). A problem for diagnosing macrolide hypersensitivity is that some macrolides are not available in injectable form and hence IDTs are not possible. Some authors have used sterile drug powder for IDTs (52). Maximum non-irritating intradermal concentrations are reported in Table 2. Rarely, patch tests are used in variable concentrations (Table 5, Online repository). Total skin test positivity rate in clinical studies has been from 28 to 43 % among adults with suspected macrolide hypersensitivity (47,50). In vitro testing has not been properly evaluated and provocation tests have been essential for accurate diagnosis of macrolide hypersensitivity in the majority of cases. In adult studies, macrolide hypersensitivity was confirmed by provocation tests in 2.7 to 17 % of patients (13,50,53). In children, there are few data on test results in suspected macrolide hypersensitivity. In a recent pediatric clinical study, out of 64 children who were referred with a history of a clarithromycin-associated HSR, nine (14 %) had positive IDTs at 0.5 mg/ml in the immediate reading and 6% showed a positive DPT (51). Sensitivity and specificity for this concentration in IDT has been reported as 75% and 90%, respectively. In a limited number of studies which included few children, all or most of children with suspected macrolide hypersensitivity tolerated oral provocation, and up to only 12 % of the reactions were confirmed (19,20,50-53).

Among patients with macrolide hypersensitivity, cross-reactivity have been reported in 5 of 20 cases (involving mostly spiramycin - erythromycin), while other 15 patients tolerated a different macrolide antibiotic (47). Recently, a child with anaphylaxis to both azithromycin and clarithromycin was reported (54). If macrolide antibiotics may rarely show cross-reactivity with non-antibiotic macrolides like tacrolimus remains unresolved, as one case has been reported, but not properly evaluated allergologically (55). In patients with HSR where a macrolide is urgently required,

desensitization may be necessary. Holmes et al reported a successful rapid oral desensitization to clarithromycin in an adult (56).

GLYCOPEPTIDES

Glycopeptide antibiotics are important to treat patients with life-threatening gram-positive infections, have a demonstrated hypersensitivity to beta-lactams, or are infected with beta-lactam-resistant bacteria (57). A retrospective cohort study of pediatric patients in a 10 years (1995-2004) period showed that vancomycin was the drug most commonly associated with ADRs (58). Vancomycin is mainly associated with mild HSRs including the Red Man Syndrome (RMS), which is believed to be due to non-specific mast cell degranulation. Data on RMS in children are scarce. One retrospective study in 650 children who had been exposed to vancomycin found a low rate (1.6%) of RMS (59). More severe reactions to vancomycin were reported to occur in patients younger than 40 years, specifically in children (60). A recent study investigating clinical risk factors for RMS among children and young adults revealed that caucasian ethnicity, age ≥ 2 years, previous RMS history, vancomycin dose ≥ 10 mg/kg, vancomycin concentration ≥ 5 mg/ml, and previous anti-histamine use were significant risk factors, but not genetic variants in histamine metabolism or receptors (61).

Vancomycin may exceptionally cause immune-mediated anaphylaxis in adults and in children, but incidence is not known (62,63). The overall incidence of vancomycin-induced hypersensitivity has been reported as 5-14% of treated children (62,64). Suspected HSRs to vancomycin different from anaphylaxis, such as linear IgA bullous dermatosis (LABD), maculopapular exanthemas, AGEP, vasculitis, FDE, SJS/TEN, and DRESS have been mostly reported in adults (65-68).

In order to evaluate suspected vancomycin hypersensitivity, SPT, IDT, DPT, and BAT have been recommended. Non-irritant concentration for vancomycin SPT and IDT have been determined among adult volunteers (Table 2)(16), whereas the optimal patch test concentration of vancomycin has not been established (Table 5, Online repository). There are no validated *in vitro* tests. Recently, a T-cell mediated systemic HSR to vancomycin was confirmed by LTT in a child (69).

Whenever RMS occurs after infusion of vancomycin, instead of stopping the treatment, vancomycin administration practice should be adjusted to a lower infusion rate. Teicoplanin can be used in case of failure, although there is only limited evidence that switching to teicoplanin may be beneficial and safe in children (70). Possible allergic cross-reactivity between vancomycin and teicoplanin has been reported in adults (71,72).

Among glycopeptide antibiotics, most desensitization protocols are confined to vancomycin and are largely practised among adults. Only one report of successful desensitization has been described in an infant with vancomycin HSR (73).

AMINOGLYCOSIDES

Aminoglycosides are effective against aerobic, gram-negative bacteria and some mycobacteria, including mycobacterium tuberculosis. Aminoglycoside hypersensitivity is relatively uncommon, but important for some risk groups such as cystic fibrosis patients. Cases of adverse reactions to aminoglycosides in children after repeated administration have been reported (74).

Contact allergy to aminoglycosides, especially to neomycin, has been common and avoidance of prolonged topical aminoglycoside use is recommended. In 25 (11.5%) out of 218 asymptomatic schoolchildren, neomycin sensitisation was demonstrated in an European patch test series (25 allergens) (75). Contact allergy to aminoglycosides should be evaluated by patch test (Table 5, Online repository), although the specificity of the sensitization is usually weak.

Neomycin is also contained as traces in many vaccines, but only one single case of anaphylaxis has been linked to a neomycin-containing vaccine (76). Patients with anaphylaxis to topical or systemic neomycin should not be vaccinated with neomycin-containing vaccines, but they can be used in patients with delayed-type sensitization to neomycin, since the amount of neomycin found in vaccines is not believed to trigger delayed-type reactions (77).

Other aminoglycosides such as streptomycin, gentamicin and tobramycin have been reported to trigger HSRs by topical and/or systemic use mostly among adults, but also few pediatric patients (78-80, Online repository Table 5, ref 6). Immediate reactions to aminoglycosides have been evaluated by SPT and IDTs. Non-irritant concentrations for IDT for gentamicin and tobramycin are shown in Table 2 (16). Two cases of anaphylaxis to SPT with 1 mg/ml streptomycin concentration have been described. Thus, it has been suggested to start with concentrations of 0.1-1 ng/ml and gradually increase the concentration up to 20 mg/ml (81,82). However, the irritant properties of the highest concentrations have not been evaluated and it's not known whether a desensitization would occur with such a protocol. For delayed HSRs to aminoglycosides, patch tests have been performed (Table 5, Online repository). Cross-reactivity between aminoglycosides may occur (79). Desensitization protocols for aminoglycoside antibiotics have been proposed for children with cystic fibrosis (79,80).

TETRACYCLINES

Infrequent use of tetracyclines in young children results in very low HSR rates (83). Most frequently, tetracyclines are used for acne treatment in adolescents. They are a common cause of FDEs in adults and less often in children (84,85). Photosensitivity is a well-recognized other complication of tetracyclines (86). Photo-onycholysis can occur in association with a generalized phototoxic reaction, or even as an isolated event as reported in a 14-year-old girl (87). Minocycline is a quite common elicitor of DRESS (85). There is a limited experience on diagnostic procedures in HSRs to tetracyclines and beyond photopatch testing no specific procedures can be recommended.

QUINOLONES

Fluoroquinolones have a broad range of activity against both Gram-negative and Gram-positive bacteria (88) and can be classified into four groups, based on their chemical structure and their antibacterial activity (89). Nowadays the use and incidence of HSRs to quinolones are increasing (90).

In Spain, quinolones are the third leading cause of confirmed hypersensitivity to drugs, after anti-inflammatory drugs and beta-lactams, having an increase in incidence from 0.53% in 2005 to 5.96% in 2009 (91). Anaphylaxis incidence has been 1/1.000.000 with levofloxacin among treated adult patients and much higher with a rate of about 1:1000 with ciprofloxacin among 3200 schoolchildren (92,93). A pediatric safety study of ciprofloxacin involving data of 16,184 patients ≤ 17 years gave an estimated risk of 0.046 suspected HSRs in every 100 patients (94). In a review, all quinolones had been implicated with HSRs, with highest reaction rates for ciprofloxacin, moxifloxacin and levofloxacin among adults (91).

Immediate hypersensitivity reactions to quinolones have a similar rate of allergic and nonallergic anaphylaxis among different quinolones (95). Since 2000, there has been an increase in the number of cases of anaphylaxis, mainly from moxifloxacin. In studies in adults from Spain (96) and Germany (97), moxifloxacin was involved in 63.2 and 54 %, levofloxacin in 7.9 and 15 %, ciprofloxacin in 28.9 and 13% and ofloxacin in 10% of anaphylactic reactions caused by quinolones. Reactions induced by moxifloxacin were more severe, with 75% of reactions comprising anaphylaxis or anaphylactic shock, versus 54% in those induced by ciprofloxacin (96). Most nonimmediate reactions to quinolones are maculopapular rashes. The estimated incidence varies between different quinolones, with ranges from 1% to 7%, gemifloxacin being associated with a higher incidence of skin rashes (particularly in female patients younger than 40 years) (89,98). FDE, AGEP, SJS, TEN and linear immunoglobulin A disease are less frequent. Bullous quinolone HR have been mostly seen among adults, only seldomly among children (91,99,100, Online repository Table 5 ref 7). HIV-infected adults have an increased frequency of ciprofloxacin reactions including anaphylaxis (101).

Non-irritating concentrations for IDTs with levofloxacin in adults have recently been published (Table 2) (16,17). The BAT has been reported to be useful for immediate reactions in adults (specificity 100%, sensitivity from 28.9 to 71.1%) (96,102). These data need to be confirmed. In nonimmediate reactions to quinolones, PTs have been used (Table 5, Online repository). Positive LTTs have been described in nonimmediate reactions (Online repository Table 5 ref 7). DPT is the gold standard to establish or exclude a diagnosis in skin-test-negative cases. Recent studies showed that only 11.8 to 32 % of adult patients with a history of HSRs to quinolones were positive on DPT (55, 103, Online repository Table 5 ref 8). Only 5% of adult patients with negative skin tests had a positive DPT (NPV:95 %), whereas 50% of the adults with positive skin tests had a positive DPT (PPV:50%)(104). It has been described that previous hypersensitivity to beta-lactams (OR: 4.571), immediate-type reactions (OR: 17.33) and reactions induced by moxifloxacin (OR: 3.091) were significantly associated with confirmed diagnosis of fluoroquinolone hypersensitivity in adults (103).

Quinolone cross-reactivity studies in adults concluded that the level of cross-reactivity among this group of antibiotics is important (95, 97, 98, 99-106, Online repository Table 5 ref 7,8). Cross-

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reactivity among those molecules could not be predicted by any test, seems not to be a bilateral phenomenon and is higher between first and second generation quinolones. Some authors have found a lower degree of cross-reactivity among newer quinolones (107). According to Lobera et al. levofloxacin may be a safer alternative in cases of reaction to first, second, or fourth generation quinolones (108).

ANTI-TUBERCULOSIS DRUGS

Tuberculosis (tbc) is a worldwide prevalent and potentially fatal disease. Currently, therapeutic regimens include isoniazid (INH), rifampicin (RIF), pyrazinamide (PZA), ethambutol (EMB) and streptomycin, all associated with a high rate of ADRs, which can lead to treatment failure (109). Most ADRs associated with anti-tuberculosis drugs are predictable. Drug HSR, hepatitis, influenza-like illness and arthralgia have been reported to be more rare (15-20%) in both children and adults (109,110). Pediatric studies revealed ADR rates ranging from 1.1 to 65.7 % among different populations (110-112). The frequency of drug reactions increased with age from 2.3% at age 0-19 years to 8.4% for those $\geq$ 60 years. Females and caucasians had higher reaction rates than their counterparts (112).

Adverse drug reactions with cutaneous manifestations due to antituberculosis drugs raise the suspicion of hypersensitivity and can be confined to the skin only or be part of a multisystem reaction. While maculopapular eruptions are the most common reactions, FDE, lichenoid drug eruption, urticaria, photodermatitis, DRESS, SJS/TEN, AGEP and vasculitis have been reported, mostly in adults (109,113-116). The incidence of anti-tuberculosis ADRs varied from 0.1 to 20 % in pediatric and adult patients in different studies (114, 116-118).

Some risk groups may have a higher incidence of ADRs to anti-tuberculosis drugs. Cytochrome P450 drug-metabolizing enzyme polymorphisms (CYP2C19 and CYP2C9) have been recently implicated with a higher risk of developing tbc-associated MPE (119). Also, HIV infection is an important risk factor among adults and children (120). A retrospective study in children and adults with SJS/TEN in four sub-Saharan African countries from 2000 to 2010 showed that HIV serology was positive in 69 (54.8%) of 126 patients tested with anti-tuberculosis drugs, which made them the third cause after sulfonamides (38.4%) and nevirapine (19.8%) (31).

So far, there is no agreement on which of the currently used drugs are most frequently implicated in ADRs. Some authors suggest that PZA is the most frequent offender, others suggest streptomycin or RIF (116,121). Regarding EMB, its most frequent ADR is ocular toxicity. However, HSRs such as MPE, TEN and other organ specific reactions may also occur (113,122). In children, EMB is mainly included in an antituberculosis regimen when the bacteria are likely to be resistant to INH. Current guidelines recommend that EMB should only be given with caution to children aged < 5 years (122).

Diagnosis of HSRs to antituberculosis agents is difficult, as the mechanisms are still largely unknown and immunological diagnostic tests have been rarely evaluated. Recently, non-irritating IDT concentrations for RIF have been recommended (Table 2)(17). Rodrigues Carvalho S et al. tested INH

at the same concentration used for RIF: undiluted for SPT and 1:10 dilution for IDT (123). In case of delayed reactions, SPTs and late-reading of IDTs have been employed, for RIF, EMB or INH, PTs have been also used (Table 5, Online repository). Among in vitro tests, the sensitivity of drug lymphocyte stimulation test was only 14.9% for all drugs (INH 14.3%, RIF 13.6%, EMB 14.3%, PZA 0%)(124).

In case of severe ADRs to antituberculosis drugs, withdrawal of the offending drug is mandatory and improves outcome (113). Whether and how to rechallenge is still a matter of debate. Desensitization has been used successfully in antituberculosis drug-associated HSR in adults(123,125,126). The experience is limited in pediatric age and there are only few reports in particular with rifampicin(46,127,128).

CONCLUSION

In conclusion, population-based parental-reported questionnaire surveys among children revealed drug HSR prevalence rates from 2.8 % to 5.4 % in a limited number of studies from different countries. Non-betalactam antibiotics, mostly co-trimoxazole and macrolides, comprised approximately 10 to 20% of all HSRs to drugs. However, differences in prescription rates of drugs, and genetic background of different populations influence the incidence and prevalence of these reactions in a given population. In some developing countries, and some high risk groups, HSRs to cotrimoxazole and antituberculosis drugs may be more prevalent and important than betalactam reactions. On the other hand, a very limited number of studies report on the value of diagnostic procedures. Extrapolated data from adults suggest that only 10 to 30 % of suspected HSRs can be confirmed in children. Hence, a standardized diagnostic approach and management protocols should urgently be developed and employed for pediatric patients in the evaluation of suspected HSRs to NBLAs, some of which may be critical and unreplacable in particular clinical circumstances.

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Table 1 . Clinical Spectrum of Non- β -lactam Antibiotic Induced Hypersensitivity Reactions

Antibiotic Group	Hypersensitivity Reaction
Sulfonamides ^{2,5,9,10,22,24,29,31,34-37,,38,39}	Maculopapular eruption, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, fixed drug eruption, drug fever, urticaria, angioedema, anaphylaxis, acute generalized exanthematous pustulosis, serum sickness-like reactions, exfoliative dermatitis, blood dyscrasias, allergic myocarditis, periarteritis nodosa like vasculitis, photosensitivity reactions, drug reaction with eosinophilia and systemic symptoms (DRESS)
Macrolides ^{1,2,20,47-49,52, 55}	Urticaria, angioedema, maculopapular eruption, fixed drug eruption, contact dermatitis, photosensitivity reactions, Stevens-Johnson syndrome, toxic epidermal necrolysis,

	anaphylaxis, acute generalized exanthematous pustulosis, hepatitis, vasculitis, DRESS
Fluoroquinolones ^{89,91, 98-100, Online repository Table 5 ref 4}	Urticaria, angioedema, anaphylaxis, flushing, fever, photosensitivity reactions, erythema nodosum
Vancomycin ^{62, 63, 65-68}	Anaphylaxis, skin eruption, exfoliative dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis, drug fever, vasculitis
Aminoglycosides ^{79, 80-82 Online repository Table 5 ref 2}	Contact dermatitis, anaphylaxis, urticaria, maculopapular eruption, exfoliative dermatitis, DRESS
Tetracyclines ⁸⁵⁻⁸⁸	Fixed drug eruption, urticaria, angioedema, anaphylaxis, DRESS
Anti-tuberculosis drugs ^{109, 113-116}	Maculopapular eruption, fixed drug eruption, photosensitivity reactions, urticaria, photodermatitis, DRESS, acute generalized exanthematous pustulosis, Stevens-Johnson syndrome, toxic epidermal necrolysis

Table 2 .Nonirritating Skin Test Concentrations of Non-Betalactam Antibiotics

Antibiotic	Full-strength concentration	Maximum skin prick test concentration*	Maximum intradermal test concentration*
Tobramycin ¹⁶	40 mg/ml	Full-strength	4 mg/ml (1/10 dilution)
Gentamycin ¹⁶	40 mg/ml	Full-strength	4 mg/ml (1/10 dilution)
Clindamycin ¹⁶	150 mg/ml	Full-strength	15 mg/ml (1/10 dilution)
Levofloxacin** ¹⁶	25 mg/ml	5 mg/ml	0.025 mg/ml (1/1000 dilution)
Ciprofloxacin ¹⁷	2 mg/ml	NA	0.006 mg/ml (1/300 dilution)
Erythromycin** ¹⁶	10-50 mg/ml	Full-strength	0.01-0.05 mg/ml (1/1000 dilution)
Clarithromycin ^{17,51}	50 mg/ml	Full-strength	0.05 mg/ml ¹⁷ (1/1000 dilution)

			0.5 mg/ml ⁵¹ (1/100 dilution)
Azithromycin** ¹⁶	100 mg/ml	Full-strength	0.01 mg/ml (1/10,000 dilution)
Vancomycin ¹⁶	50 mg/ml	Full-strength	0.005 mg/ml (1/10,000 dilution)
Co-trimoxazole ¹⁶	80 mg/ml	Full-strength	0.8 mg/ml (1/100 dilution)
Nafcillin ¹⁶	250 mg/ml	Full-strength	0,0025 mg/ml (1/10000 dilution)
Rifampicin ¹⁷	60 mg/ml	NA	0.002 mg/ml (1/30.000 dilution)

*These are maximum non-irritant concentrations. The starting concentrations should be 10 to 1000 times more diluted, according to the severity of index reaction

**Drugs with high non-specific irritation potential.

NA: not applicable

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Table 3. Classification of sulfonamide drugs

Sulfanilamides	
Antibiotics	Sulfamethoxazole
	Sulfadiazine
	Sulfisoxazole
	Sulfapyridine(in sulfosalazine)
	sulfacetamide
Protease inhibitors	Amprenavir
	Fosamprenavir
Non-sulfanilamides	
Diuretics	Acetazolamide, Bumetanide, Chlorthalidone, Clopamide, Dorzolamide, Furosemide, Diazoxide, Chlorothiazide, Hydrochlorthiazide, Indapamide, Mefruside, Metozalone, Xipamide, Torasemide
Carbonic anhydrase inhibitors:	Acetazolamide Brinzolamide Dorzolamide Methazolamide
COX2 inhibitors	Celecoxib Etoricoxib
Sulfonylureas	Carbutamide, Acetohexamide Chlorpropamide, Tolbutazide, Tolazamide, Tolbutamide, Glipizide, Gliclazide, Glibenclamide, Glibornuride, Glipiride, Glisoxepide, Glycophamide, Glimepiride
Others	Probenecid, Sotalol, Sumatripan, Delavirdine, Tamsulosin, Topiramate Mefenide, Sulfasalazine

Table 4. Oral TMP-SMX desensitization studies in children

Study authors	No of cases	Ages (months, years)	Length of Protocol	% completed and success rate	Mean Follow-up (months)
Palusci et al. ¹	5	7.5 mo-12 y	4 hours	80	17 mo
Kletzel et al. ²	7	7-21 yr	3 days	72	5.7 mo
Kreuz et al. ³	4	4-13 yr	3-4 week	100	Not specified
Nagaraian et al. ⁴	5	7-17 yr	7 hour	80	10 mo
Yango et al. ⁵	3	6 mo-13 yr	4-5 days	75	2-3 mo

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Table 5. Patch test concentrations for non-betalactam antibiotics

Family	Antibiotic	Concentrations	References
Sulfonamides	Co-trimoxazole	5-30 % dilution(pet), 80 mg/mL dilution(aq), 10-50 % dilution(DMSO: dimethyl sulfoxide)	Romano A,et al ¹ Lammintausta K,et al ² Barbaud A. ³
Macrolides	Erythromycin	1-30 % dilution(pet) Pure in powder	Romano A,et al ¹ Lammintausta K,et al ² Barbaud A. ³
Glycopeptides	Vancomycin	10% dilution (aq)	Kwon HS et al. ⁴
Aminoglycosides	Neomycin	20% dilution (pet)	Morris SD et al. ⁵ Paniagua MJ et al. ⁶
	Gentamycin,amikacin, tobramycin	20% dilution (pet)	
	Streptomycin	1% dilution (aq)	
Quinolones		10-25% dilution (pet)	Schmid DA et al. ⁷ Seitz Cs et al. ⁸
Antituberculosis drugs	Rifampicin, ethambutol, isoniazid	Up to 50% dilution (aq or pet)	Strauss RM. ⁹ Bakkum RS. ¹⁰

*aq=aqueous

**pet=petrolatum

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