

EAACI/ENDA Position Paper: Diagnosis and management of hypersensitivity reactions to non-steroidal anti-inflammatory drugs (NSAIDs) in children and adolescents

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Abstract

Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used in the pediatric population as antipyretics/analgesics and anti-inflammatory medications. Hypersensitivity (HS) reactions to NSAID in this age group, while similar to adults, have unique diagnostic and management issues. Although slowly accumulating, published data in this age group are still relatively rare and lacking a unifying consensus. This work is a summary of current knowledge and consensus recommendations utilizing both published data and expert opinion from the European Network of Drug Allergy (ENDA) and the Drug Hypersensitivity interest group in the European Academy of Allergy and Clinical Immunology (EAACI). This position paper summarizes diagnostic and management guidelines for children and adolescents with NSAIDs hypersensitivity.

KEYWORDS

Adolescent, Child, EAACI, Drug Hypersensitivity, ENDA, Non Steroidal Anti Inflammatory Drugs, NSAIDs, Position Paper

1 | INTRODUCTION

Drug hypersensitivity reactions (DHR) are classified as type B adverse drug reactions (ADRs)—that is adverse effects of pharmaceutical formulations that clinically resemble allergy and are unpredictable, noxious, and unintended responses to a drug taken at a dose normally used in humans. These consist of many different clinical phenotypes with variable onset and severity.¹

Although some groups of drugs, such as beta-lactam antibiotics, induce hypersensitivity reactions via specific immunologic mechanisms in all age ranges,² others, for example contrast media, muscle relaxants, NSAIDs, and opioids, may induce reactions by different mechanisms, including non-immunologic.³ When reactions are mediated by specific immunologic mechanisms, they are also known as allergic reactions, and when non-immunologic mechanisms are proven or presumed, these are classified as non-allergic hypersensitivity.⁴

Non-steroidal anti-inflammatory drugs are extensively used by all age groups, from infants, to children and adults. Worldwide millions of people are exposed every day and many of these medications are freely available over the counter.⁵ As children grow older in addition to paracetamol and ibuprofen, they take other drugs that are usually prescribed for adults such as diclofenac, dipyrrone, oxicams, and acetyl-salicylic acid (ASA).^{6,7} Also in certain medical conditions, they may be exposed to indomethacin, weak cyclooxygenase (COX)-1 or selective COX-2 inhibitors, and others.

Non-steroidal anti-inflammatory drugs and antibiotics are by far the most frequent pharmaceutical preparations involved in hypersensitivity reactions. While in some studies, antibiotics are more common causes of DHRs in young children,⁸ other studies indicate that both in children and in adolescents, NSAIDs are the most frequent drug class involved, particularly in severe reactions.^{9,10} These differences can be explained by variations in the population studied, the patterns of consumption, the diagnostic criteria, and the time within which the study was performed.¹¹

There is an increasing demand for specialist evaluation of children with hypersensitivity reactions to NSAIDs. Although in many instances, reactions are mild and may not be life-threatening, they limit the future administration of these drugs to affected children. In many instances in the pediatric population, NSAIDs hypersensitivity is a class effect, and children will often develop reactions after taking alternative medications either as antipyretics or as anti-inflammatory drugs.

Although guidelines using mainly adult data are useful,^{12,13} they may not be optimal or sufficient. Data from published pediatric studies as well as expert opinion and experience are needed to address specific problems in children.

According to the World Health Organization (WHO) statements, the childhood range is up to 10 years old and the adolescence covers the ages from 10 to 19 years (http://www.who.int/topics/adolescent_health/en/). In the current manuscript, we will consider both childhood and adolescence as the *pediatric population*.

Recently, several reviews have been published on the subject, summarizing the available pediatric data;¹⁴⁻¹⁶ however, a unified approach in children as well as generally agreed upon guidelines is still lacking.

This manuscript represents a consensus document of the ENDA (European Network on Drug Allergy)/EAACI (European Academy of Allergy and Clinical Immunology) and focuses on hypersensitivity reactions to NSAIDs in children and adolescents. The aim is to provide a practical guideline for evaluating and managing children and adolescents with hypersensitivity reactions to NSAIDs.

2 | TERMINOLOGY AND DEFINITIONS

NSAID hypersensitivity reactions are defined as “conditions clinically resembling allergy that cause objectively reproducible symptoms or signs, initiated by exposure to this pharmacological group at a dose tolerated by normal subjects,” including both allergic and non-allergic hypersensitivity, and *NSAID allergic hypersensitivity* as “a NSAID-induced hypersensitivity reaction initiated by an immunologic mechanism” such as IgE or T-lymphocyte dependent.

The currently used classification was established by a panel of experts from the European Academy of Allergy and Clinical Immunology Task Force on NSAIDs.¹³

The term *selective reactor* (SR) has been applied for cases in which the clinical manifestation is due to a single drug or single subclass of NSAIDs with good tolerability to other subclasses. In general, this term includes NSAID allergic hypersensitivity reactions.

There are two well-defined phenotypes of selective HS reactions to NSAIDs:

1. Selective NSAID-induced urticaria, angioedema, and/or anaphylaxis (SNIUAA): These are immediate reactions, probably mediated by a specific IgE antibody.
2. Selective NSAID-induced delayed type HS reactions (SNIDR): These are reactions occurring within 24-48 hours after drug intake although the interval can be shorter. They are probably mediated by a specific T-cell response.

The term *cross-reactor* or according to the current classification, *cross-intolerance* (CI) reactions, is used in cases where the clinical manifestations are triggered by more than one subclass of NSAIDs, in which pharmacological mechanisms are the suspected pathophysiology. A combination of the inhibition of COX-1 in conjunction with an intrinsic regulatory defect in Arachidonic-acid metabolism triggers a biochemical cascade involving the generation of leukotrienes (LTs) and the release of mast-cell and eosinophil-derived mediators.

Currently, there are three well-defined phenotypes of cross-intolerant HS reactions to NSAIDs:

1. NSAIDs-exacerbated respiratory disease (NERD): manifesting primarily as bronchial obstruction, dyspnea, and/or nasal

congestion/rhinorrhea, occurring in patients with an underlying chronic airway respiratory disease.

2. NSAIDs-exacerbated cutaneous disease (NECD): urticaria and/or angioedema occurring in patients with a history of chronic spontaneous urticarial.
3. NSAIDs-induced urticaria/angioedema (NIUA): manifesting as wheals and/or angioedema occurring in otherwise healthy children.

The term *blended or mixed reaction* has been used for those cases of cross-intolerant HS with combined respiratory and cutaneous symptoms that can appear either simultaneously or in a timely evolutionary manner.¹⁴ As this type of reaction is observed in a significant proportion of children and adolescents, it could be included as a distinct phenotype in the clinical classification or more aptly as part of a multisystemic, anaphylactic type reaction, that is NSAIDs-induced urticaria/angioedema with/without respiratory and systemic symptoms of anaphylaxis (NIUAA).¹⁷

3 | CLASSIFICATION AND MECHANISMS OF NSAID HYPERSENSITIVITY IN PEDIATRIC PATIENTS

Classification of drug hypersensitivity is a critical step in managing these patients supporting the allergological work-up to be performed. However, establishing a diagnostic classification of NSAIDs hypersensitivity in the pediatric population is challenging due to (i) frequent presence of cofactors (eg, infections, exercise) and underlying conditions; (ii) lack of in vivo or in vitro reliable diagnostic methods; (iii) limited knowledge regarding the age-related drug metabolism and its influence on NSAIDs hypersensitivity; (iv) variability of clinical manifestations; (v) lack of worldwide comparable epidemiological data; and (vi) sparse data regarding the influence of age on the natural history of disease.

Recently, an increasing number of studies have been published, capturing validated clinical data, able to support a better classification for the pediatric population.¹⁸⁻²²

Based on the present data, we suggest applying a simplified classification shown in Table 1 to younger age, less than 10 years old children and the more detailed classification, adapted with small modifications from the adult recommendations, detailed in Table 2, to the older, adolescent age group. The rationale for this choice are (i) in young children, most reactions are non-immunologic, cross-intolerant, with a significant frequency of cofactors. (ii) The observed clinical patterns get similar to adults in older childhood and adolescence, but anaphylactic reactions (more than one organ involvement) are frequent enough to require a modification of the current classification.

We believe that the revised focused classification will support the appropriate management of children with NSAIDs hypersensitivity; however, the classification could change according to new data on the pathophysiology and the long-term natural history of the disease.

TABLE 1 Classification of non-steroidal anti-inflammatory hypersensitivity for the child aged (0-10 y) pediatric population

Cross-reactivity	Type of reaction	Clinical presentation	Chronology	Proposed mechanism	Influence of cofactors
Cross-intolerant reactions (Non-allergic)	Non-allergic NSAID hypersensitivity (NERD, NECD, NIUAA)	Urticaria, angioedema, dyspnea, rhinitis, conjunctivitis, anaphylaxis	Immediate (usually from minutes to several hours after exposure)	COX-1 inhibition	Possible
Non-cross-Intolerant reactions (Allergic)	Selective NSAID-induced urticaria/angioedema or anaphylaxis (SNIUAA)	Urticaria, angioedema, anaphylaxis	Immediate (<1 h)	IgE-mediated	Unknown
	Selective NSAID-induced delayed reactions (SNIDR)	Various symptoms and organs involved (eg, fixed drug eruption, SJS/TEN, nephritis)	Delayed onset (usually more than 24 h after exposure)	T-cell-mediated	Unknown

NSAIDs, non-steroidal anti-inflammatory drugs; COX-1, cyclooxygenase 1; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.

TABLE 2 Classification of non-steroidal anti-inflammatory hypersensitivity for the older pediatric population and adolescents (10-19 y.o.)

Cross-reactivity	Type of reaction	Clinical presentation	Chronology	Proposed mechanism	Influence of cofactors and/or underlying conditions)
Cross-Intolerant reactions (Non-allergic)	NSAIDs-exacerbated respiratory disease (NERD)	Bronchial obstruction, dyspnea and/or nasal congestion, rhinorrhea	Immediate (usually form minutes to several hours after exposure)	COX1-inhibition	Strong (Asthma, Rhinosinusitis)
	NSAIDs-exacerbated cutaneous disease (NECD)	Wheals and/or angioedema		COX1-inhibition	Strong (Chronic urticaria)
	NSAIDs-induced urticaria/angioedema/anaphylaxis (NIUAA)	Wheals and/or angioedema with/without respiratory symptoms		Unknown, probably COX-1 inhibition	Unknown
Non-cross-Intolerant reactions (Allergic)	Selective NSAID-induced urticaria/angioedema or anaphylaxis (SNIUAA)	Wheals, angioedema, anaphylaxis		IgE-mediated	Unknown
	Selective NSAID-induced delayed reactions (SNIDR)	Cutaneous and mucous reactions (eg, maculopapular exanthema, fixed drug eruption) Complex hypersensitivity conditions (eg, Acute generalized exanthematous pustulosis, Drug Reaction with Eosinophilia and Systemic Symptoms, SJS/TEN) Organ-specific disorders (eg, nephritis, hepatitis)	Delayed onset (usually more than 24 h after exposure)	T-cell mediated	Unknown

NSAIDs, non-steroidal anti-inflammatory drugs; COX-1, cyclooxygenase 1; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.

4 | CLINICAL ENTITIES AND NATURAL HISTORY OF NSAIDS HYPERSENSITIVITY IN PEDIATRIC PATIENTS

Hypersensitivity reactions to NSAIDs may involve the skin, the respiratory system, or both and may also cause other organ-specific diseases. Reactions can be mediated by specific immunologic mechanisms, or mediators can be released in the absence of any specific immunologic recognition.¹³ These patterns of reactions, although documented to occur at any age, seem to have well differentiated age-related clinical characteristics.^{14,15}

Most of the published data in children come from case reports and small series and are therefore subjected to biases, with only few studies verified by challenge. For the adolescent age group, most of the data available on hypersensitivity reactions to NSAIDs come from studies where they are part of a series where adults are also included. In most instances, less than 20% of the patients included are younger than 20 years old.¹⁰ The second major difficulty is that in some studies, only specific drugs^{23,24} or entities are considered, such as asthma or urticaria/angioedema while others are global evaluation of how the different entities occur in specific age groups.^{25,26}

However, based on the information provided by these studies, we can extrapolate that the occurrence and relative frequency of the major clinical entities in the adolescent age group that include cross-intolerant (non-allergic hypersensitivity) and selective responders (allergic reactions) are similar to those occurring in adults.^{14,15}

Thus, cross-intolerant urticaria with or without angioedema (NIUA) is the most common clinical entity, followed by those cases with airways involvement. Of particular relevance in this age group is the combination of cutaneous and respiratory symptoms. When patients with cross-intolerance reactions develop preferentially cutaneous involvement and then respiratory symptoms follow in a timely manner, they are frequently called mixed reactions, here included in the modified NIUAA classification. Alternatively, both types of reactions can occur in the context of anaphylaxis in a patient with a selective, immune (IgE)-mediated reaction with varying severity.²⁵

Aspirin hypersensitivity in adult patients with chronic urticaria (CU) is seen in 10%-40% of CU patients^{27,28} and classified as NECD. The reported incidence of aspirin hypersensitivity in children and adolescents with chronic urticarial is 24%.²⁹

It is very uncommon in the pediatric age group to encounter the classical Sumter's triad.³⁰ In this age group, rhinitis may be more frequent than asthma as an associated factor and indirect evidence support that they are more atopic than adults with NERD.²²

The factors that determine the type and presentation of an NSAID hypersensitivity reaction in children are largely unknown. The relative proportion of CI vs selective responders in series carried out in children varies from 25% to 70%.^{17,20,21,26,31,32} Recent data comparing clinical entities, urticaria and/or angioedema, anaphylaxis, and respiratory, between a group of

children aged 2-14 years old vs one of adolescents and young adults aged 15-20,³³ showed significantly more angioedema with or without urticarial in the younger group and more anaphylaxis in the adolescent group. Also there was a significant difference in the predominance of males over females in the children's group.

A history of recurrent episodes of adverse reactions in the young age group does not necessarily correlate with a challenge proven diagnosis. Patients with a challenge proven diagnosis were more likely in the older age group.^{33,34}

A rarely described entity in adults, NSAIDs-induced delayed type maculopapular exanthema in the context of infection in children, is ubiquitous and second only to that reported following the use of amino penicillin antibiotics.^{35,36}

Non-steroidal anti-inflammatory drugs can be significant cofactors, particularly in adolescents, in the development of food- and drug-induced and also food-associated exercise-induced urticarial/anaphylaxis.³⁷⁻³⁹ The possible mechanisms involved are also pending further elucidation as are those related to the interactions of NSAID hypersensitivity reactions and autoimmune and inflammatory diseases in children.⁴⁰

Key notes:

Non-steroidal anti-inflammatory hypersensitivity in the pediatric population

- Classical NSAID Exacerbated Respiratory Disease (NERD) is less frequent in childhood, may be presenting with Rhinitis rather than Asthma

- Increased frequency of Cross Intolerant reactions, Lower frequency of allergic reactions (SRs) in pediatric population than in adults although regional variations may apply.

- NSAIDs isolated periorbital angioedema is particularly frequent among school children, teenagers and young adults.

- Anaphylactic reactions have been described in 9%-40% of NSAIDs-induced reactions in children, with an increased frequency compared to adults.

5 | EPIDEMIOLOGY, RISK FACTORS, AND DRUGS INVOLVED IN PEDIATRIC PATIENTS

Although prescribed less frequently in this age group, NSAIDs are considered in tandem with beta-lactam antibiotics, the most common cause of hypersensitivity drug reactions.^{9,14,41-45} Approximately 12.5% of pooled reported adverse drug reactions in infants and children under the age of 2 years, suspected of causing serious or fatal outcomes, are caused by indomethacin, paracetamol, or ibuprofen, although no clear classification of reactions was provided.⁴⁶

In general, NSAIDs are well tolerated in children. In a large study carried out by Lesko et al⁴⁷ in more than 55 000 children treated with ibuprofen during an acute febrile illness, asthma was reported in 0.08% of the cases and erythema multiforme in 0.005%. Most of the occurrence of even these rare adverse reactions may be attributed to the infectious disease causing the febrile illness. More recently, in a retrospective study published in Asia, use of NSAIDs has been directly correlated with asthma

exacerbations in children, specifically short-term consumption of aspirin, ibuprofen, and diclofenac.⁴⁸

As ASA is generally not prescribed for children, the involvement of this drug in eliciting reactions in this age group is extremely minor and largely unknown, whereas in adults, it is a major contributor to patient-reported and physician-diagnosed NSAIDs reactions.¹³ In the past, where aspirin was still a commonly used antipyretic in children, the prevalence of children with HS to ASA was about 0.3%, similar to that seen in the same study in adults.⁴⁹

About a quarter of patients with a diagnosed hypersensitivity reaction to NSAIDs present to medical attention, before 18 years of age.²² In a large questionnaire survey in Europe, prevalence of NSAID intolerance in subjects between 10 and 20 years was estimated at about 10%, and it was significantly lower in children under the age of 10 years.⁵⁰ However, there is significant variability between published studies, probably due to geographic differences,²² population and subpopulations (ethnic groups) studied,⁵¹ the case definition used as well as other less well-defined factors.

In a study carried out in an Asian population, about a third of children developing acute NSAID hypersensitivity reactions in a medical setting were 6 years old or younger.⁴² When compared with the group of children with later onset of NSAID hypersensitivity, children with onset before 6 years had a significantly increased probability of reactions to paracetamol (83% in children with early onset vs 46% in >6 years old) and a low incidence of respiratory symptoms.⁵² However, as these children presented to a tertiary medical centre's allergy department, a selection bias can be assumed usually toward more severe reactions.

In contrast to data published in adults with NSAID hypersensitivity reactions, in children, especially in the younger age group, males are as frequently if not more frequently involved than females.^{11,18,33}

In the pediatric population, the most common implicated medications inducing in NSAIDs hypersensitivity reactions are ibuprofen and paracetamol.^{16,17}

A fair number of children with NSAIDs-induced skin reaction are seen by dermatologists. Maculopapular exanthema and urticaria/angioedema are the most common clinical presentation of NSAIDs hypersensitivity in the pediatric dermatologist's office.³⁶

At all ages, drug allergy including NSAIDs hypersensitivity is more likely to be confirmed in adults than in children. Children have less exposure to drugs, and maculopapular exanthems due to acute infections are more common.⁵³ However, rashes associated or induced by ibuprofen and paracetamol specifically were the 4th and 5th causes of all adverse drug reactions including both children and adults in the summary of drug reactions reported to the European medicine agency.⁵⁴

5.1 | Diagnosis of NSAID hypersensitivity in children

The diagnostic protocol for the investigation of an NSAIDs hypersensitivity reaction in children and adolescents is highly dependent on the presumed mechanism of reaction and the likelihood of reproducible persistent symptoms. For example, with a young, usually healthy child, who has experienced a maculopapular rash in the context of a febrile illness 24 hours after receiving a dose of paracetamol, where the likelihood of a viral exanthem is significantly higher than that of an allergic reaction, a short, drug provocation test, whereby a full dose of the age and weight appropriate formulation can be given in a single day while the patient is under observation, may be the only appropriate evaluation, if any is indicated.

The gold standard for the diagnosis of NSAIDs hypersensitivity in children is the drug provocation test.⁸ In a clinical setting, at this juncture, there may be a very limited value for the performance of either skin tests or laboratory tests in most children.

5.1.1 | In vivo testing— skin tests

As the proposed mechanism of CI NSAID hypersensitivity reactions is not immune mediated, there is no indication for performing allergy skin tests in the investigation of this type of reactions.

Skin tests in the diagnosis of selective NSAID-induced urticaria/angioedema or anaphylaxis (SNIUAA): Skin testing has been used for the diagnosis of immediate reactions to metamizole, dipyrone, and paracetamol in children. As with other drug allergy testing, intradermal test may be more sensitive, however, a negative skin test does not exclude the diagnosis and all results need to be confirmed by challenge. Drug formulations and concentration for skin tests in children need to be further validated. The standard use of skin testing in the diagnosis of these patients cannot be recommended at present.^{20,26} See Table 3 for proposed concentrations and formulations of metamizole/dipyrone, and paracetamol for skin and intradermal testing.

Skin tests in the diagnosis of Selective NSAID-induced delayed reactions (SNIDR): Data focusing on the use of skin tests in children with SNIDR are not available at this time.

5.1.2 | Laboratory testing

A limited number of in vitro tests are available; however, their clinical validity including sensitivity, specificity as well as positive and negative predictive values is not well established in children.⁵⁵

The cellular allergen stimulation test, which quantitates basophil leukotriene (LT) release, has been proposed for the diagnosis

	Formulation	Skin test	Intradermal test
Acetaminophen	Perfalgan®	10 mg/mL	1 mg/mL
Metamizole sodium	Novalgine®	40-400 mg/mL 400 mg/mL	0.4-4 mg/mL 40 mg/mL

TABLE 3 Test concentrations and formulations of metamizole and paracetamol for skin and intradermal testing

of Aspirin Exacerbated Respiratory Disease (AERD) and can be extended to the other NERD entities (rhinitis and nasal polyposis) although the diagnostic yield widely differs in different studies.⁵⁶⁻⁵⁸ In vitro assays for NECD and NIUAA are similar to those described for NERD but more difficult to apply and interpret in children.

The basophil activation test has been used in the evaluation of SNIUAA in adults, but data in children are sparse and the test's specificity and predictive values in this population are unknown.⁵⁹⁻⁶²

Overall, The EAACI and other expert societies do not recommend these techniques for the diagnosis of NSAID hypersensitivity at this time.¹³

5.1.3 | Drug provocation tests (DPT)

In addition to the classical protocols established in adults, there are several well-published, diagnostic protocols for evaluating hypersensitivity reactions to NSAIDs in children.^{16-18,21,22,26,63} The pediatric protocols differ in their details, however, several principles are common to all and are summarized below as a consensus:

1. The drug provocation test (DPT) is the gold standard for the diagnosis of NSAIDs hypersensitivity in children. In most cases, an open or single blinded procedure is sufficient to establish the diagnosis.
2. Management decisions may require more than one, sometimes several provocation procedures in each patient.
3. Challenge/DPT testing with the culprit drug is not recommended in patients with a history of severe reactions such as grade IV-V anaphylaxis or SJS/TEN, DRESS, or severe organ-specific reactions such as allergic hepatitis. In these cases, the diagnosis should be based on the clinical history and histopathology data.¹⁵
4. All DPTs in children should be performed by experienced teams in an appropriate setting that can ensure the safety of young patients re-exposed to a potentially deleterious drug.⁸ Pediatric resuscitation expertise and facilities should be available and continuously maintained.
5. There is a relative contraindication of performing drug provocation tests in patients with active disease such as uncontrolled asthma, flaring urticaria, or an underlying disease limiting the use of rescue medications such as adrenaline.
6. Medications such as antihistamines, systemic corticosteroids, and antileukotrienes should be discontinued prior to performing DPT according to current recommendations.⁶⁴
7. Consider performing lung function tests prior to the DPT in all patients when possible, particularly in patients with a clinical history of asthma, wheezing, and respiratory reactions.
8. The initial challenge dose should be low. In most settings, between 1/10 and 1/4 of the age and weight adjusted therapeutic dose of the drug would be appropriate. However, lower initial

doses may be indicated if an IgE-mediated mechanism is suspected or in patients with a severe prior reaction.

9. Subsequent doses of the drug should be given at 60 minutes intervals. However, shorter or longer periods of observation between doses should be considered depending on timing and severity of the reported reactions.⁶⁵
10. The doses may be rapidly incremental where a low suspicion of hypersensitivity exists, that is with a paracetamol challenge in a patient with a prior maculopapular exanthema in the context of an acute febrile illness or a DPT with COX-2-specific inhibitors in a patient with a prior non-severe reaction to a non-selective NSAIDs.
11. A DPT should be stopped and treatment initiated immediately with the diagnosis of an allergic response. In cases with a positive DPT, children should be observed for 2-4 hours after the last challenge dose or until patient is stabilized. In most cases of non-IgE-mediated NSAIDs-induced hypersensitivity, the main stay of treatment is rapidly absorbed systemic corticosteroids such as 1-2 mg/kg methyl-prednisolone, 0.1 mg/kg betamethasone or region-specific equivalent medications, antihistamines and treatment of bronchospasm if present. Intramuscular adrenaline is indicated in cases of anaphylaxis.
12. To establish a negative challenge, the total cumulative dose (TCD) of the drug given should be at least paracetamol 15-20 mg/kg/dose, ibuprofen 10 mg/kg/dose, ASA 15-20 mg/kg/dose, with the maximal dose established at adult therapeutic doses.
13. An observation period of at least 1.5-2 hours is recommended at the end of a negative, well tolerated DPT.
14. In some cases, additional doses of the drug can be necessary, after a negative observed challenge, and may be given at home in the following days. Documented instances with an apparently negative challenge have occurred in cases where only small incremental doses were given without a full challenge dose as described above.
15. In patients with NERD, particularly in adolescents, a nasal provocation test with Lysine-ASA can be considered as a substitute to the oral provocation test with better safety and good sensitivity.⁶⁶⁻⁶⁸
16. All observed DPT protocols are designed to rule out an immediate reaction. In established delayed, non-immediate reactions (SNIDRs), some of these general rules may not be applicable.

6 | NSAIDS HS IN CHILDREN—MANAGEMENT

After a confirmed diagnosis of NSAID hypersensitivity, the classification of the reaction should be established, as selective reactors may have better options for alternative medications, compared to children with cross-intolerant reactions.

In both selective and CI reactors, oral and written information on the drugs to avoid and alternatives that are safe and can be used, including the formulation and dosage, should be given to patients,

family, and primary physicians, to facilitate future treatment decisions.

In those patients with a cross-intolerant type of HS, in whom no safe, alternative NSAIDs could be ascertained, the main indications for the use of these drugs, namely inflammation, hyperthermia, and pain, need be addressed and instructions about the optimal management of each situation should be given.

A general algorithm on management of children with NSAID HS is proposed below and alternative medications and procedures for these children are also suggested.

The EAACI IG on drug allergy has recently released a document “drug allergy pass” that can be used as an informative tool for drug-allergic patients.⁶⁹ Desensitization can be tried in case of need for particular conditions, although specific protocols for pediatric patients are lacking.

6.1 | Alternative medications

The use of alternative, safe medication, mainly for patients with the CI type of NSAID hypersensitivity, if no tolerated formulations have been identified, has to cover three major functions:

1. Alternative treatment of fever

The majority of children with CI NSAIDs HS can tolerate at least low (antipyretic) doses of paracetamol without eliciting an allergic reaction.⁵² For those who cannot, physical means of temperature lowering, such as bathing in tepid water, lowering environmental temperatures, and maintaining good hydration with cooled liquids, may be at least partially effective. The use of specific COX2 inhibitors has been evaluated in these patients and found to be safe for most.⁷⁰ However, the general use of COX II-specific inhibitors in young children is not approved and few countries have age appropriate formulations for this age group. In a prospective observational study in Singapore, the use of a patented Traditional Chinese formulation Yin Qiao San, as a temperature lowering agent in a small group of young children with HS to ibuprofen and paracetamol, was found to be both safe and effective.⁷¹

2. Alternative treatment for inflammation

Corticoids are effective and potent anti-inflammatory drugs that can be used in children along with complementary therapies such as physiotherapy and acupuncture. In 80%-85% of children with CI NSAIDs HS, one or more COX2-specific or COX2 preferential medication may be safe for use, after an appropriate DPT has been performed.⁷²⁻⁷⁴ Although no specific COX2 inhibitors are currently approved for use in patients less than 12 years of age, the off-label use of these medications is quite common and seems to be safe in pediatric rheumatology patients.⁷⁵ Extensive evidence-based use of these drugs, along with documented challenge protocols aimed at establishing their safety for NSAIDs HS children, makes these the alternative of choice for both anti-inflammatory

and analgesic indications. The main obstacle to their use in young children is the lack of appropriate pediatric formulations in most areas of the world.

3. Alternative treatment for pain— Analgesia

Opiates are approved for the use of pain control in post-surgical situations at very young ages, but very similar to their use as antipyretics and anti-inflammatory agents, COX2-specific drugs are the alternative of choice in our evaluation, after an appropriate DPT has been performed.^{76,77}

6.1.1 | Desensitization

Although well-documented HS to NSAID exists in the pediatric age group and cross-reactive HS predominates over SR, we could not find any publication or case reports specifically concerning desensitization to aspirin, ibuprofen, paracetamol, or any other NSAIDs medication in children. Moreover, in a questionnaire sent to this task force participants and ENDA members, none reported experience with desensitization procedures in this age group.

Theoretically, desensitization, at least to aspirin, can have indications in children as in adults. However, we must keep in mind that NERD and nasal polyposis which are classical indications for desensitization are both rare among children. Also the need of aspirin for prophylaxis or treatment of cardiovascular diseases including congenital defects is unusual, so the sum of two uncommon pediatric diseases, that is both NSAID HS and cardiovascular disease, would be exceptional. The most recognized cardiac condition requiring aspirin therapy for longer periods in children is Kawasaki disease,⁷⁸ which has a higher incidence before the age of 2 years. The incidence of NSAID HS increases with age being very, very rare before age 2 years, explaining the lack of experience and publications on this subject.

In face of the complete lack of evidence to support any recommendation, the panel would advise in case of need, to use an age/weight/disease adjusted established adult protocol under the same safety and surveillance requirements (Figure 1).^{13,79}

7 | SUMMARY, RECOMMENDATIONS, AND UNMET NEEDS

Utilizing both published data and expert opinion from the ENDA and members of the Drug Hypersensitivity interest group in the European Academy of Allergy and Clinical Immunology, we have summarized diagnostic and management guidelines for children and adolescents with NSAIDs hypersensitivity.

Hypersensitivity reactions (HS) to NSAIDs in children are more common than previously appreciated. In part, this may be due to the rising prevalence of allergic disease, a cofactor and/or frequent underlying condition in the most common phenotype of NSAIDs HS in children—the cross-intolerant (CI) type. The

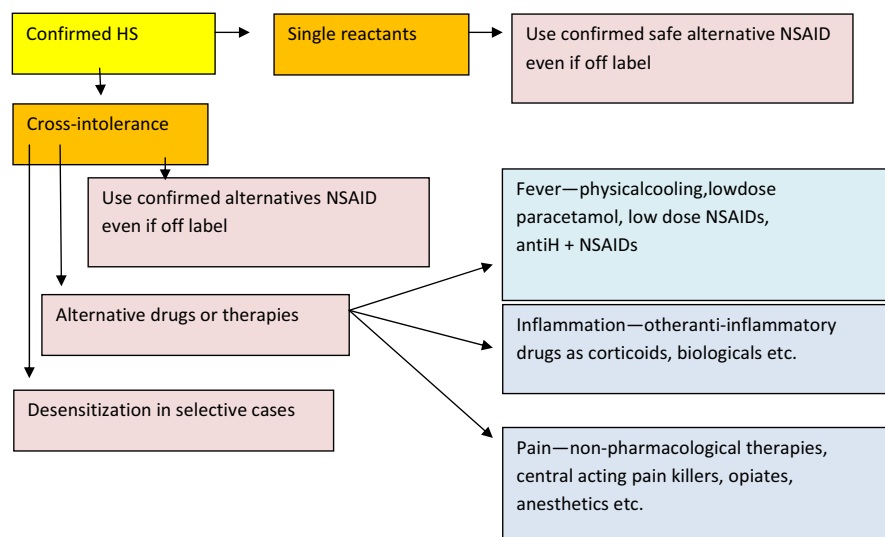


FIGURE 1 Algorithm for the management of children with non-steroidal anti-inflammatory drugs hypersensitivity reactions [Colour figure can be viewed at wileyonlinelibrary.com]

increased prevalence of reactions in children may be also due to some increased awareness and prompt recognition and referral by primary physicians.

Unique clinical and epidemiological features, especially in children under 10y old, warrant special consideration. An overwhelming majority of these young patients have the CI form, including in some cases, intolerance to paracetamol, a weak COX3 inhibitor, and the most common medication used for fever and pain in children worldwide. The pathophysiology of these reactions, especially in this young age, is not well defined, as is the role of exacerbating cofactors such as viruses, exercise, and food.

The absence of laboratory, in vivo or in vitro tests with good diagnostic and predictive value, leaves the drug provocation test as the sole means for the diagnosis of both HS and tolerated drugs. In general, more than one, usually 3-4, DPTs are needed in the management of each patient. Each DPT procedure is time-consuming and resource consuming as well as placing the child at risk of reactions. There is an urgent need for the development of better diagnostic tools.

The long-term natural history of NSAIDs HS in children is unknown, may be different from adults and across different age groups, so periodical re-evaluation may be warranted. In particular, chronic urticaria in children is usually a short, self-limited disease but we have no data at present on the evolution of NECD in adolescents after the resolution of their urticaria. In a similar vein, asthma in children and adolescents may take an intermittent form with long periods without any disease activity. Data suggest that children and adolescents with NERD do not have as yet the severe form of inflammation associated with nasal polyposis and uncontrolled asthma and so may be more amenable to long-term intervention.

Key notes:

NSAIDs hypersensitivity in the pediatric population Management

Drug Provocation tests are useful both for the confirmation of hypersensitivity and the election of safe alternative medications

COX2 specific preparations although not approved in children have been prescribed and are useful as alternative medications

The natural history of NSAIDs HS in children is unknown, so periodical re-evaluation may be warranted

8 | BOUNDARY OF MEANING (BOM)

BOM for NSAIDs hypersensitivity in children: A position paper of the European network of drug allergy (ENDA)

The reproducibility of research results in medicine has become a subject of intense scrutiny, in particular the process of conclusion and generalizability of acquired data from clinical studies.

The outcome of a review or a research paper should clarify to the reader what are the claims presented in the paper that are candidates for reproducibility studies.⁸⁰

To provide a formalized generalizability of findings for this work, we refer to generalizability as one of the eight dimensions of information quality.⁸¹ We present a methodology developed in the context of formative assessment in educational programs.⁸² Specifically, applying Meaning Equivalence Reusable Learning Objects (MERLO) statements to define a boundary of meaning (BOM) representing a generalizability of findings. This represents what can and what cannot be inferred from the study and enables researchers to design studies that are capable of challenging or reproducing the published results. MERLO statements are derived from alternative representations of a

conceptual target statement, where one group of statements is legitimate conclusion of the study or a generalized inference in the opinion of the authors (included statements). Not included statements

are similarly sounding affirmations but their meaning is not supported by the conclusions of the study and is outside the boundaries of meaning that are generalizable and/or reproducible.

NSAIDs hypersensitivity in the Pediatric Population—Generalizability Boundary of Meaning (BOM)

Target statement	Meaning equivalence (MEF) Included	Surface similarity (SSF) Not included
The diagnosis and management of NSAIDs hypersensitivity in children and adolescents should be performed in specialized centers by experienced medical personnel	In children, a clinical history of an adverse reaction to a drug is not a reliable indicator for the presence of a hypersensitivity reactions Although the most common manifestation of a hypersensitivity reaction to NSAIDs in children is angioedema/urticaria, anaphylactic reactions are not rare	Ibuprofen is a safe alternative antipyretic, in children with a history of reactions to paracetamol as the molecular structure is quite dissimilar In contrast to hypersensitivity reactions to antibiotics, the incidence of NSAID hypersensitivity in children is quite low
There are unique features in all aspects of the diagnosis and management of NSAIDs hypersensitivity in children	Compared to adults, children with NSAIDs hypersensitivity show an increased frequency of cross-intolerant reactions and a lower frequency of allergic, single/specific reactions Classical NSAID Exacerbated Respiratory Disease (NERD) is less frequent in childhood and may present with rhinitis rather than asthma	The perceived differences between children and adults in the field of NSAIDs hypersensitivity are a consequence of different pathogenetic mechanisms
Drug provocation tests are useful for both the diagnosis of hypersensitivity and the election of safe alternative medications	The diagnosis of NSAIDs hypersensitivity in children and adolescents is largely dependent on the performance of one or more drug provocation tests The ascertainment of safe alternative medication through drug provocation tests is critical in the pediatric age group when most reactions to NSAIDs are of the cross-intolerant (CI) type	All children with a suspected NSAIDs hypersensitivity reaction should be challenged Provocation tests for NSAIDs in children and adolescents are identical to those performed in adults
COX2-specific medications, although generally not approved in children, have been prescribed and are useful as alternative medications	Many published studies have shown the safety of COX2-specific medications in the pediatric age group	COX2-specific medications are the best option for all NSAID hypersensitive children In children with NSAIDs hypersensitivity, a COX2-specific medication can be prescribed without a prior drug provocation test
The natural history of NSAIDs hypersensitivity is unknown, so periodical re-evaluation may be warranted	Children with NSAIDs hypersensitivity require long-term follow-up as individuals and as a group	All children with NSAIDs hypersensitivity should be re-challenged periodically

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