

# NSAID Hypersensitivity in the Pediatric Population: Classification and Diagnostic Strategies

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**Abstract:** Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most frequently administered drugs, mainly for their antipyretic, but also for pain-relieving and anti-inflammatory effects in children. NSAIDs are composed of structurally divergent subgroups of drugs with similar pharmacological and adverse effects. Aspirin originates from salicin and was the first synthesized analgesic. As a prototype of NSAIDs; aspirin-induced hypersensitivity reactions were first reported, but subsequently, other phenotypes of hypersensitivity reactions were also described with aspirin and other NSAIDs. There are certain challenging aspects of NSAID-hypersensitivity in the pediatric population that need to be further investigated. These include the effect of age on drug metabolism and the natural history of the various phenotypes of NSAID-hypersensitivity, the effect of certain co-factors (infections, exercise) on NSAID-hypersensitivity, and diagnostic clinical and laboratory biomarkers clarifying the endotypes. In recent years, a non-negligible number of case series, studies and expert panel reports have been published in this field with some novel features and diagnostic modalities in the pediatric population. With the current review; the clinical phenotypes and diagnostic and management modalities of suspected NSAID-induced hypersensitivity reactions in childhood and adolescence were explained and updated by examining past and current publications.

**Keywords:** allergy, aspirin, child, drug, ibuprofen, paracetamol

## Introduction

Non-steroidal anti-inflammatory drugs (NSAID) are among the most frequently administered drugs, mainly for their antipyretic, but also for pain-relieving and anti-inflammatory effects in children.<sup>1</sup> Every child is exposed to a NSAID at least once, routinely without any alternative. NSAIDs provide relief while neither inducing sedation in the manner of narcotic analgesics nor causing systemic side effects as with steroids.<sup>2-4</sup> Thus, they can be considered as over-the-counter drugs used at much higher rates than based on prescriptions alone.<sup>1,2,5,6</sup>

The class of non-steroidal anti-inflammatory agents is comprised of structurally divergent subgroups of drugs with similar pharmacological and adverse effects (Table 1). Aspirin (acetylsalicylic acid) (ASA), the first synthesized analgesic, originates from salicin, which is the active ingredient of willow bark, and has been used since the time of the ancient Egyptians in traditional medicine.<sup>7</sup> The first clinical trial on the antipyretic and anti-inflammatory effects of salicylate was published by MacLagan in 1876 on patients with rheumatic fever.<sup>8</sup> An acetylated form of salicylate was available worldwide a few years later and was named as aspirin.<sup>7</sup> As a prototype NSAID, ASA-induced hypersensitivity reactions were reported soon after its first use.

NSAIDs-induced hypersensitivity reactions in adult and pediatric populations appear in an immediate or non-immediate manner with several distinct clinical phenotypes only in susceptible individuals.<sup>9,10</sup> An extensive series of patients older than 14 years of age was evaluated for actual drug hypersensitivity by diagnostic testing, and a majority of the culprit drugs responsible for actual drug hypersensitivity reactions (DHR) was confirmed as NSAIDs.<sup>11</sup> When the rates of confirmed mild and severe DHR in children and adults were compared, NSAIDs were found to have a greater impact on children than adults.<sup>12,13</sup> When only mild cutaneous reactions were considered, NSAIDs were also the drugs

**Table 1** Nonsteroidal Anti-Inflammatory Drugs According to Their Chemical Structures

Chemical Group & Drugs	Chemical Group & Drugs	Chemical Group & Drugs
<u><b>Propionic acid derivatives</b></u> Ibuprofen Naproxen Loxoprofen Flurbiprofen Ketoprofen Dexketoprofen Fenoprofen Indoprofen Oxaprozin Tiaprofenic acid	<u><b>Fenamic acid derivatives</b></u> Mefenamic acid Meclofenamic acid Flufenamic acid Tolfenamic acid  <u><b>Salicylic acid derivatives</b></u> Aspirin (Acetylsalicylic acid) Sodium Salicylate Salsalate Diflunisal Sulfasalazine	<u><b>Indol-acetic acid derivatives</b></u> Indomethacin Sulindac Tolmetin  <u><b>Naphthyl alkanone (non-acid derivative)</b></u> Nabumetone  <u><b>Pyridinic Sulfonamide derivatives</b></u> Nimesulide
<u><b>Phenyl-acetic acid derivatives</b></u> Diclofenac Etodolac Ketorolac Aceclofenac	<u><b>Enolic acid derivatives</b></u> Piroxicam Meloxicam Lornoxicam Tenoxicam Piroxicam	<u><b>Selective COX-II inhibitors (Diaryl heterocyclic acids)</b></u> Celecoxib Etoricoxib Rofecoxib Valdecoxib Paracoxib Lumiracoxib
<u><b>Pyrazolones</b></u> Phenylbutazone Dipyron (Metamizole) Propifenazone Oxyphenylbutazone Azapropazone	<u><b>Para-aminophenol</b></u> Paracetamol (acetaminophen)	<u><b>Benzethiazoline</b></u> Tiaramide

that resulted in the highest positivity rates during provocation tests in both groups.<sup>14</sup> NSAIDs were also reported as the primary elicitors of drug-induced anaphylaxis, not only in adults but also in children and adolescents, comprising more than 40% of all drug-induced anaphylactic reactions.<sup>15–18</sup>

There are certain challenging aspects of NSAID-hypersensitivity (NSAID-H) in the pediatric population that need to be further investigated. These include the effect of age on drug metabolism and the natural history of the different phenotypes of NSAID-H, the effect of certain co-factors (infections, exercise) on NSAID-H, and diagnostic, clinical and laboratory biomarkers clarifying the endotypes. In recent years, a non-negligible number of case series, studies and expert panel reports have been published in this field with some novel features and diagnostic modalities in the pediatric population.<sup>19</sup> The aim of the current review is to update the clinical phenotypes and diagnostic and management modalities of suspected NSAID-induced hypersensitivity reactions in childhood and adolescence by examining past and current publications.

## The Impact of NSAID-H in the Pediatric Population

Previous work concerning general NSAID-H in children and adolescents, mostly involved adults or individuals older than 14 years of age as children and adolescents composed less than 10% of the total study participants.<sup>11,20–24</sup> In addition, only compatible clinical history was considered in the diagnosis of actual NSAID-H in some of the prior studies.<sup>25–29</sup> In more recent studies of considerable interest, instances of actual NSAID-H in children and adolescents referred due to suspected NSAID-induced reactions, were thoroughly investigated through diagnostic tests. The rate of NSAID-H, as confirmed with oral provocation tests (OPT), was measured between 4% and 68% in various patient groups with histories of suspected reactions (Table 2).<sup>25,27,30–44</sup> Considering the general pediatric population, the rate of actual ASA-hypersensitivity (ASA-H) in 1632 control subjects was detected as 0.55% according to the OPT performed independent of suspected ASA-H history.<sup>45</sup> However, in a very recent study in which OPT with ASA was performed

**Table 2** Frequency of NSAID-H in Children

First Author/Date	N, Study Population	Age (Range or Mean (±SD))	Outcome of the Study	CI/ SR	Diagnostic Test	ASA/NSAID-H/ Paracetamol/ Ibuprofen
<b>Settipane, 1980<sup>26</sup></b>	638 healthy	2–16 y	ASA-H	NA	Hx	0.32%
<b>Ibero, 1982<sup>43</sup></b>	25 food allergic	25–153 mo	ASA-H	NA	OPT w ASA	7.8%
<b>Botey, 1984<sup>45</sup></b>	1632 healthy	infants, children	ASA-induced recurrent U/AO	NA	OPT w ASA	0.55%
<b>Bousetta, 2005<sup>44</sup></b>	25, Paracetamol-induced	8 mo–15 y	Paracetamol-H	1/0	OPT w Paracetamol and ASA	4%
<b>Hassani, 2008<sup>25</sup></b>	164, NSAID-induced	7 mo–17.3 y	NSAID-H	2.2	OPT w culprit drug and hx	49%
<b>Zambonino, 2013<sup>30</sup></b>	63, NSAID-induced	1–14 y	NSAID-H	1.4	OPT w culprit drug and ASA	68%
<b>Yilmaz, 2013<sup>34</sup></b>	58, NSAID-induced	4 mo–18 y	NSAID-H	1.7	OPT w culprit drug	29%
<b>Cavkaytar, 2015<sup>31</sup></b>	110, NSAID-induced	2–18 y	NSAID-H	1.1	OPT w culprit drug and ASA	27%
<b>Guvenir, 2015<sup>32</sup></b>	115, NSAID-induced	2 mo–17 y	NSAID-H	0.25	OPT w culprit drug and ASA	17%
<b>Ertay Karagol, 2013<sup>39</sup></b>	95, AO w/o U	8 mo–17 y	NSAID-H	NA	OPT w culprit drug	6%
<b>Cavkaytar, 2015<sup>40</sup></b>	68, CSU	2–18 y	ASA-H	NA	OPT w ASA	24%
<b>Cousin, 2016<sup>37</sup></b>	635, NSAID-induced	2–13 y	NSAID-H	4.3	OPT w culprit drug and ASA & other NSAIDs	16.9%
<b>Calvo Campoverde, 2016<sup>27</sup></b>	93, NSAID-induced	4–17 y	NSAID-H	1	OPT w culprit drug or hx in case of >1 rxn with the culprit NSAID & OPT w ASA	28%
<b>Alves, 2017<sup>35</sup></b>	119, NSAID-induced	5–14 y	NSAID-H	NA	OPT w culprit and alternative drug	7.6%
<b>Arikoglu, 2017<sup>36</sup></b>	106, NSAID-induced	1–18 y	NSAID-H	2	ST & OPT w culprit drug	29%
<b>Blanca-Lopez, 2018<sup>38</sup></b>	116, NSAID-induced	6 mo–14 y	NSAID-H	4.9	OPT w ASA & culprit drug	26%
<b>Guvenir, 2018<sup>46</sup></b>	2000 healthy	11.6 (3.5–14.5) y	NSAID-H	NA	OPT w culprit drug	0%
<b>Eser Simsek 2019<sup>41</sup></b>	56, NSAID-induced	7.1 (1.2–18) y	NSAID-H	6	OPT w ASA & culprit drug	37.5%
<b>Gaffar, 2020<sup>5</sup></b>	44, ibuprofen-induced	6.9 (±4.7) y	Ibuprofen-H	NA	OPT w ibuprofen	22.7%
<b>Yilmaz Topal, 2020<sup>33</sup></b>	243, NSAID-induced	84.3 (50.7–139.2) mo	NSAID-H	1.45	OPT w culprit drug	20.3%
<b>Sipahi Cimen, 2021<sup>42</sup></b>	60, Paracetamol-induced	2–18 y	Paracetamol-H	0.75	OPT w paracetamol and ibuprofen	13%

**Abbreviations:** AO, Angioedema; ASA, Aspirin (acetylsalicylic acid) ASA-H, Aspirin (acetylsalicylic acid) hypersensitivity; CSU, Chronic spontaneous urticaria; Hx, Clear-cut history; Ibuprofen-H, ibuprofen hypersensitivity; L-ASA, Lysine aspirin; Mo, months; NSAID, Nonsteroidal anti-inflammatory drug; NSAID-H, Nonsteroidal anti-inflammatory drug hypersensitivity; NA, Not applicable; OPT, Oral provocation test; Paracetamol-H, Paracetamol hypersensitivity; SD, Standard deviation; ST, Skin test; U, Urticaria; w, with; w/o, without; Y, years.

if there was a positive clinical history, only one participant had undergone OPT, and no ASA-H was detected in 2000 control subjects (Table 2).<sup>46</sup> In addition, NSAID-H was also examined in some other distinct patient clusters. As an example, NSAID-H was identified in 6% of children and adolescents referred to the allergy outpatient clinic with isolated angioedema, and ASA-H was detected with a rate of 24% in children and adolescents with chronic spontaneous urticaria.<sup>39,40</sup> ASA or other NSAID-H was determined in 0 to 33% of pediatric patients with asthma (Table 3).<sup>46–57</sup>

Aspirin was the most frequently used analgesic for children, until the marketing of the oral suspension form of ibuprofen and paracetamol.<sup>58,59</sup> Nowadays, ibuprofen and paracetamol are mostly used for young children, while naproxen, diclofenac, dexketoprofen, and dipyron are used frequently during adolescence.<sup>2,5</sup> An updated systematic review showed that in comparison to paracetamol, ibuprofen has a similar effect in fever control and recovery from the common cold in pediatric patients without a significant increase in gastrointestinal discomfort.<sup>60</sup> In a separate trial comprising 84,192 children, adverse events related to ibuprofen use at two differing doses were investigated and the risk of hospitalization for gastrointestinal bleeding or renal failure was found not to increase in comparison to the use of paracetamol.<sup>61</sup> However, although it is relatively safe in terms of other adverse events, ibuprofen is the most frequent cause of NSAID-induced hypersensitivity reactions in susceptible children.<sup>25,27,30–33,35,36,38,41,62,63</sup> It is a propionic acid derivative and a strong cyclo-oxygenase (COX) enzyme inhibitor like ASA. Gaffar et al reported actual ibuprofen hypersensitivity at a rate of 22.7% in children with a suspected history of ibuprofen-induced reactions, with half of the OPT resulting in anaphylactic reactions.<sup>5</sup> Increasing age was an independent risk factor for ibuprofen hypersensitivity.<sup>5</sup> The prevalence of ibuprofen hypersensitivity in children and adolescents with mild to moderate asthma was 2% with a 95% confidence interval of 0.2–7%.<sup>55</sup>

NSAIDs act by competing with arachidonic acid to bind its site of action on a COX enzyme, leading to a reduction in the synthesis of prostaglandins and thromboxane in the arachidonic acid pathway. There are two well-known COX isoenzymes named as COX-I and COX-II. However, a splice variant of COX-I known as COX-III is assumed to be the site of action of paracetamol.<sup>19,64</sup> Paracetamol has relatively lower anti-inflammatory activity and results in actual hypersensitivity to a lesser extent than ibuprofen.<sup>25,31,38</sup> The rate of OPT-proven paracetamol hypersensitivity was 13% in children and adolescents with a suspected reaction in their history.<sup>42</sup> In a recent meta-analysis, the prevalence of OPT-proven paracetamol hypersensitivity was reported as 10.1%, with a 95% confidence interval of 4.5 to 15.5%.<sup>65</sup>

NSAID-H tends to persist for years. In a recent study, the rate of actual drug hypersensitivity was evaluated in both children and adults, with the analyses performed according to the time points of the index reaction and the diagnostic tests performed.<sup>12</sup> In this study, the investigators reported similar rates of confirmed NSAID-H in children with suspected NSAID-induced reaction history when diagnostic tests were performed in childhood or in adulthood.<sup>12</sup> Besides that, in

**Table 3** Frequency of NSAID-H in Asthmatic Children

First Author, Date	N, Study Population	Age (Range or Mean (±SD))	Outcome	Diagnostic Test	ASA/ NSAID-H
Falliers, 1973 <sup>57</sup>	1298, asthma	6–16 y	ASA-H	Hx & Medical records	1.9%
Rachelefsky, 1975 <sup>47</sup>	50, asthma	6–18 y	ASA-H	OPT w ASA	28%
Vedanthan, 1977 <sup>49</sup>	3, asthma	8–18 y	ASA-H	OPT w ASA	33%
Schuhl, 1979 <sup>48</sup>	32, asthma	6–11 y	ASA-H	OPT w ASA	0
Fischer, 1983 <sup>50</sup>	25, asthma	8–18 y	ASA-H	OPT w ASA	12%
Towns, 1984 <sup>51</sup>	29, asthma	5.5–14 y	ASA-H	OPT w ASA	21%
Hussein, 1989 <sup>52</sup>	70, asthma	6–17y	ASA-H	NPT w L-ASA	2.7%
Short, 2000 <sup>53</sup>	70, asthma	6–15 y	Diclofenac-H	OPT w Diclofenac	0
Capriles-Behrens, 2000 <sup>54</sup>	1007 asthma and rhinitis	0–21 y	NSAID-induced facial AO	History & confirmed with inadvertent re-exposure	4.1%
Debley, 2005 <sup>55</sup>	100, asthma	6–18 y	Ibuprofen-H	OPT w ibuprofen	2%
Soferman, 2013 <sup>56</sup>	42, asthma	12.4 ± 2.4	Paracetamol-H	OPT w Paracetamol	0%
Guenir, 2018 <sup>46</sup>	976 asthma	10.6 ± 4.2 y	NSAID-H	OPT w culprit drug and ASA	0.9%

**Abbreviations:** AO, Angioedema; AR, Allergic rhinitis; ASA-H, Aspirin (acetylsalicylic acid) hypersensitivity; L-ASA, Lysine-aspirin; H, Hypersensitivity; NSAID-H, Nonsteroidal anti-inflammatory drug hypersensitivity; OPT, Oral provocation test; SD, Standard deviation; W, With.

other studies, the interval between the index reaction and the diagnostic tests was not associated with the rates of actual NSAID-H in contrast to penicillin allergy, which would be expected to disappear over time.<sup>20,31</sup> Although these findings support the persistence of NSAID-H for years, more data are needed to determine the natural course of NSAID-H throughout childhood, adolescence and adulthood.

## The Clinical Features and Phenotypes of NSAID-Hypersensitivity Reactions

The clinical entities that emerge during NSAID-H are mainly cutaneous symptoms such as facial angioedema with or without urticaria.<sup>30,36–38,63</sup> Respiratory symptoms such as rhinoconjunctivitis and/or bronchospasm associated with cutaneous symptoms appear to a lesser extent.<sup>31,37</sup> Cutaneous and respiratory symptoms together are currently termed “blended reactions”.<sup>9</sup> It is important to note that the symptoms during OPT with the culprit drug or with ASA would be more severe and involve multiple organs compared to the index reaction, even requiring adrenaline to relieve the symptoms.<sup>30</sup> NSAID-induced hypersensitivity reactions were primarily described based on its pharmacological action on arachidonic acid metabolism and through immune-mediated pathways.<sup>66</sup> Pharmacologically, NSAIDs act by inhibiting COX-I and COX-II enzymes, blocking the production of prostaglandins, to relieve pain and inflammation.<sup>67</sup> Apart from other groups of drugs, NSAID-related hypersensitivity reactions emerge through selective-responsive (SR) or cross-intolerant (CI) pathways, necessitating a unique diagnostic approach in the pediatric population.<sup>19,68,69</sup> As a strong COX-I inhibitor, ASA has been widely used to discriminate cross-reactivity in pediatric studies.<sup>30–33,36–38</sup> The ratio of CI to SR phenotypes changes between 1.1 and 6 in pediatric patients with confirmed NSAID-H.<sup>30,31,33,34,36,37,41</sup> However, in only one study the number of CI patients was lower than the number of selective-responders with a ratio of 0.25.<sup>32</sup>

## Selective-Responsive Phenotypes

Initially, SR NSAID-H is grouped as selective-NSAID-induced-urticaria-angioedema or anaphylaxis (SNIUA/A) and selective-NSAID-induced-delayed-reactions (SNIDR), both implying DHR to only a single NSAID or one particular chemically related group of NSAIDs.<sup>19,70</sup> These reactions are immune-mediated, independent of COX inhibition. Drugs in this case act as haptens or prohaptens, binding to proteins, stimulating T and B cells and possibly cause reactions described by the Gell and Coombs classification.<sup>71</sup> Typically, immunoglobulin E (IgE) mediated type-1 reactions are responsible for SNIUA/A. IgE antibodies against dipyrone (metamizol) and propyphenazone were detected via skin prick tests (SPT) and intradermal tests (IDT) and with flow cytometric evaluation of basophil activation in patients with immediate-type DHR.<sup>72,73</sup> SPT responses with aspiryl-polylysine were found in patients with a history of anaphylactic shock history to ASA.<sup>74</sup> Specific IgE antibodies to ASA, ketorolac and paracetamol were also reported formerly as individual cases.<sup>75–77</sup> Taking into account the pediatric population, specific IgE has been detected via skin testing with metamizole and paracetamol in only a very small portion of SNIUA/A patients. In pediatric studies, SPT and IDT with diclofenac yielded negative results in all tested participants.<sup>31,34,36,42</sup> More recently, basophil activation to metabolites of metamizol was shown in patients with selective urticaria, angioedema and/or anaphylaxis to this NSAID.<sup>78</sup> Pyrazolones, propionic acid derivatives and diclofenac seem to induce IgE-mediated reactions in the majority of adult studies.<sup>79,80</sup>

There is a small group of patients assumed to have selective hypersensitivity who react to more than one NSAID but tolerate aspirin and are named as “Multiple selective immediate reactors”. The clinical entity is named as “NSAID-Multiple Selective Immediate Reaction”.<sup>81</sup> Specific IgE antibodies against both paracetamol and dipyrone were shown in a 70-year-old woman who had an immediate urticaria history to both of these drugs and angioedema during OPT induced by celecoxib.<sup>82</sup> Interestingly, the patient had no reaction to aspirin and ibuprofen, which are strong COX-I inhibitors. Due to the fact that the patient had hypersensitivity first to dipyrone and began to react to paracetamol and celecoxib after multiple recurrent use, the patient was assumed to get IgE sensitized to multiple unrelated NSAIDs over time.<sup>83</sup> A pediatric patient tolerating aspirin with confirmed hypersensitivity to both ibuprofen and paracetamol was also reported.<sup>32</sup> In the study by Perez-Alzate et al an adolescent patient with immediate (in <1 h) urticaria and angioedema to both ibuprofen and dipyrone tolerating aspirin was also reported.<sup>80</sup> Further efforts are needed in the pediatric population to show specific IgE against specific NSAIDs and to elucidate its natural evolution over time.

NSAID-induced delayed reactions are mainly T-cell mediated type-4 severe cutaneous adverse drug reactions like Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic

symptoms (DRESS), but also organ-specific reactions such as hypersensitivity pneumonitis have also been reported.<sup>83–90</sup> Bronchiolitis obliterans may complicate SJS which was reported in a 5-year-old child with nimesulide use.<sup>91</sup> Delayed reactions emerge at least 24 hours after beginning NSAID treatment. These reactions appear less frequently compared to other types of SR or CI reactions and are reported as case series composing the minority of NSAID-induced reactions. Apart from SJS-TEN, NSAID use may also result in relatively less severe T-cell mediated delayed reactions such as maculopapular exanthema (MPE), fixed drug eruptions (FDE), linear IgA bullous dermatosis, acute generalized exanthematous pustulosis and erythema multiforme.<sup>32,92–94</sup> Even delayed contact hypersensitivity proven with patch tests was reported in adults with bufexamac, indomethacin, and etofenamate.<sup>95</sup> Taking the studies evaluating a pediatric population with a proven NSAID-H into consideration,<sup>5,25,27–38,62,63</sup> three patients with MPE induced by paracetamol and ibuprofen, two with FDE induced by paracetamol and another with erythema multiforme induced by ibuprofen were reported.<sup>5,32,33,42</sup>

## Cross-Intolerant Phenotypes

Cross-intolerant NSAID-H emerges from an aberrant response in the pharmacological activity of NSAIDs that is an excessive formation of leukotrienes and deprivation of prostaglandin E<sub>2</sub> and refers to three different phenotypes including NSAID-induced urticaria and/angioedema (NIUA), NSAID-exacerbated respiratory disease (NERD), and NSAID-exacerbated cutaneous disease (NECD) implying simultaneous hypersensitivity to strong COX-I inhibitors including aspirin and other chemically unrelated NSAIDs.<sup>70,96–100</sup> NIUA is attributed to otherwise healthy patients without an underlying allergic disease. Cross-intolerant NSAID-H seems to be more common than SR type and NIUA seems to appear more frequently than NECD and NERD in children and adolescents.<sup>31,32,36,37,41</sup> NSAID use may result in isolated facial angioedema in a considerably high rate of NIUA patients, both in adult and pediatric populations.<sup>11,30,31,36,39,101,102</sup> NECD has been defined in 24% and 10% of children and adolescents with chronic spontaneous urticaria and recurrent urticaria, respectively, but in only a minority of children and adolescents with confirmed NSAID-induced hypersensitivity reactions.<sup>31,33,40,41</sup> In this subtype, patients with active chronic urticaria develop exacerbations of urticaria and/or angioedema following exposure to the culprit NSAID. Similar rates of chronic urticaria development (6.15%) were detected in patients with NIUA, SNIUA/A and healthy controls at the end of 12 years of follow-up in an adult study.<sup>103</sup> There are indeterminate gaps regarding the beginning and course of NECD in childhood, and more data are needed.

NERD was previously known as “aspirin-exacerbated respiratory disease” and formerly described in adults with severe asthma and nasal polyposis composing Samter’s triad.<sup>104</sup> The frequency of aspirin-H in asthmatic children and adolescents was an object of interest beginning from the 1970s. Several studies done before the 1990s using OPT or nasal provocation test with aspirin revealed that it was between 0% and 33% (Table 3).<sup>46–57</sup> More recent data on pediatric patients with suspected NSAID-induced reactions showed that NERD has also been defined in children and adolescents with asthma and/or allergic rhinitis.<sup>31,96,105–110</sup> In the most recent study comparing a cohort of asthmatic patients (n=976) and controls (n=2000), the frequencies of confirmed NSAID-H and NERD were 0.9% and 0.3%, respectively, in the asthma group and there were no individuals with NSAID-H in the control group.<sup>46</sup> The children and adolescents in the NERD group may not have the typical features of Samter’s triad, which is characterized by severe asthma symptoms and recurrent nasal polyps in the existence of chronic eosinophilic airway inflammation as well as multiple NSAID-H.<sup>111</sup> The pediatric period would rather include the initial onset of a more severe type that will develop in adulthood. The genesis of nasal polyp is mentioned as a reliable marker of NERD onset and in their recent study, Bensko et al reported the pediatric period as the time for the disease onset in 6% of their adult NERD patients.<sup>112</sup>

Pediatric NERD patients have milder asthma and/or chronic rhinosinusitis with higher respiratory functions in comparison to adults.<sup>105,113,114</sup> Additionally, CI children and adolescents in this group (responding to aspirin with respiratory symptoms) have a lower rate of nasal polyposis.<sup>33,37,45,113</sup> Therefore, the typical patients exhibiting Samter’s triad in pediatric age are reported as a small case series.<sup>105–107</sup> Taking the pediatric patients with nasal polyposis into consideration, NSAID-H was detected in 3 of 28 patients attending pediatric otorhinolaryngology outpatient clinics during a 6-year period.<sup>105</sup> NERD and other phenotypes of NSAID-H prevalence are also variable within different

countries in Asia, which is attributed to the genotypical differences shown in genome-wide studies and case control studies from Malaysia and Japan.<sup>115</sup>

## Changes in Classification for Children and Adolescents

The clinical phenotypes of NSAID-H in children and adolescents were originally presumed to be based on the phenotypes of adults.<sup>34,70</sup> The most widely accepted classification was proposed by experts of the European Academy of Allergy and Clinical Immunology (EAACI) and European Network of Drug Allergy (ENDA), including the five previously mentioned phenotypes based on the timing of the reaction, clinical symptoms, number of culprit NSAIDs, the existence of cross-reactivity, and the existence of underlying disease like asthma or chronic urticaria.<sup>70,104</sup> However, with an increasing number of publications, it was apparent that the phenotypes of NSAID-H in pediatric populations would not fit those of adults.<sup>31,33,37</sup> An example of this circumstance was the appearance of both respiratory (laryngospasm and/or bronchospasm) and cutaneous symptoms (angioedema and/or urticaria) in cross-intolerant patients with no underlying disease.<sup>116</sup> In fact, these reactions were initially described by Stevenson et al a long time ago and described as a non-IgE mediated cross-intolerant phenotype.<sup>117</sup> But, it was not included in the original EAACI-ENDA classification of NSAID-H and multisystemic anaphylactic reactions were only described for selective responders in that classification.<sup>70,104</sup> During the following years, Cousin et al reported that 40% of children and adolescents with respiratory and cutaneous manifestations induced by NSAIDs could not be classified according to original EAACI-ENDA classification.<sup>37</sup> The unclassified patients with blended reactions also existed in different studies in pediatric age.<sup>31,33,36,37</sup> Blended reactions are considered and named as NIUAA in the latest position EAACI paper on pediatric NSAID-H.<sup>19</sup>

According to the published data, the association of CI blended reactions with a particular systemic disease is obscure.<sup>37</sup> In some studies, pediatric patients with blended reactions and asthma as an underlying disease are reported.<sup>31,33,37</sup> Since children have an evolving immune system and the systemic diseases would emerge later in adulthood, it might be improper to categorize them according to their underlying disease. The proposed classification of phenotypes of pediatric NSAID-induced hypersensitivity reactions according to recently published data is presented in Table 4.

NSAIDs may act as a co-factor inducing or aggravating food-dependent exercise-induced urticaria/angioedema or anaphylaxis, and the related phenotype is now defined as food-dependent NSAID-induced hypersensitivity (FDNIH) and

**Table 4** Proposed Classification of Phenotypes of Pediatric NSAID-Hypersensitivity According to Recent Data\*

Type of the Reaction	Phenotype	Timing of the Reaction	Underlying Disease	Clinical Manifestation
Selective responder	<b>SNIUA/A</b> <b>MSIR</b> <b>SNIDR</b>	Usually immediate (within minutes up to 1 hour) Usually more than 24 hours after exposure	None None	Urticaria/angioedema and/or anaphylaxis Fixed drug eruption Maculopapular exanthema Severe bullous reactions Contact/photocontact dermatitis Pneumonitis, Nephritis Aseptic meningitis
Cross- intolerant	<b>NIUA</b> <b>Blended (NIUAA)</b> <b>NECD</b> <b>NERD</b>	Within one hour up to several hours	None ± AR and/or Asthma Chronic urticaria Asthma/rhinosinusitis nasal polyposis	Urticaria/angioedema Angioedema + Asthma/Stridor/rhinosinusitis Urticaria/angioedema Asthma/rhinosinusitis

**Notes:** \*Food Dependent NSAID-induced Hypersensitivity (FDNIH) is not included yet but would be with the emergence of further descriptive data.

**Abbreviations:** AR, Allergic rhinitis; MSIR, Multiple selective immediate reactor; NECD, NSAID-exacerbated cutaneous disease; NERD, NSAID-exacerbated respiratory disease; NIUA, NSAID-induced urticaria and/or angioedema; NIUAA, NSAID-induced urticaria and/or angioedema and/or anaphylaxis; NSAID, Nonsteroidal anti-inflammatory drug; SNIDR, Selective NSAID-induced delayed reaction; SNIUA/A, Selective NSAID-induced urticaria angioedema or anaphylaxis.

classified as a subgroup of NSAID-H for adults.<sup>81,118</sup> In this case, food or an NSAID does not induce a reaction exclusively; however, exercise 4 to 6 hours preceded by simultaneous ingestion of the specific food and the NSAID induces the reaction. In some cases, solitary food ingestion would result in a mild reaction such as oral allergy syndrome or contact urticaria.<sup>118,119</sup> Motomura et al excluded those patients who showed reaction to causal food without exercise and investigated the effect of aspirin on NSAID-tolerant children with a suspected history of food-dependent exercise induced anaphylaxis (FDEIA).<sup>120</sup> They performed a food challenge test on 3 separate days with exercise, with aspirin, and exercise together with aspirin, respectively. Exercise alone induced immediate reactions in 54%, aspirin alone induced reactions in 14%, aspirin and exercise together induced immediate reactions in half of the children tested during FCTs.<sup>120</sup> It is important to note that 77% of children who showed a reaction (including wheezing and hypotension) to the food, exercise and aspirin challenge on the third day, had no reaction neither to aspirin nor to exercise on the first and second days. Furthermore, aspirin also acted as an enhancer during the food challenge test without exercise in 2 patients. Aspirin administration was even used as a consequential step of provocation methodology in children and adolescents with a suspected history of FDEIA.<sup>121,122</sup> In the pediatric population, the most frequent causal foods are wheat, peach, apple and shrimp<sup>120,122</sup> The clinical entity discussed here would be affected by the environmental temperature, the amount of humidity, and the dose of the NSAID. The ingestion of aspirin or other COX-I inhibitors as well as other co-factors should be kept in mind in children and adolescents with an history of idiopathic anaphylaxis or suspected unexplained allergic reactions.

According to the recent EAACI position paper for pediatric patients, the classification of the clinical phenotypes differs based on the patients' age. As an example, for patients between 0 and 10 years; CI reactions comprise a unique group which would present with cutaneous and/or respiratory symptoms emerging from minutes to several hours after taking the culprit NSAID, while SR reactions are classified into two as the original classification.<sup>19</sup> For pediatric patients older than 10 years of age CI patients are classified into three as NIUA/anaphylaxis (NIUAA), NECD and NERD. NECD and NERD are strongly associated with underlying chronic urticaria and asthma and/or rhinosinusitis while the association of NIUA/A with an underlying disease is unknown.<sup>19</sup>

## Risk Factors of NSAID-Hypersensitivity in Childhood

There exists a tremendous amount of epidemiological data on predictive factors for actual NSAID-H in pediatric patients. Common findings show that emergence of the reaction in one hour after the NSAID intake, older age, facial angioedema without urticaria and emergence of respiratory symptoms, together with cutaneous symptoms, are closely associated with actual NSAID-H.<sup>25,31,36–38,63</sup> Facial angioedema was reported in all patients with confirmed NSAID-H in an Asian cohort.<sup>28</sup> Personal and familial history of atopy and atopic diseases were thoroughly investigated in various studies.<sup>25,30,31,34,36–38,123</sup> Data from Spanish, French and Asian children revealed that inhalant aeroallergen sensitization increased the risk for actual NSAID-H,<sup>25,30,37</sup> even allergic rhinoconjunctivitis was associated with NSAID-H.<sup>37</sup> Cross-intolerant NSAID-H was more frequently associated with aeroallergen sensitization compared to SR NSAID-H.<sup>30</sup> The results of one of the studies indicated that family history of NSAID-H increased the risk of actual NSAID-H five times,<sup>34</sup> but in other studies, there was no association of either atopy or familial drug allergy history.<sup>31,36,38,63</sup> The history of multiple suspected reactions induced by different NSAIDs would also increase the risk for actual NSAID-H;<sup>20,36,63</sup> however, the details (eg, the severity of reactions) should be evaluated individually because the history alone would not be reliable especially in younger children.<sup>9</sup>

## NSAID-Induced Anaphylaxis

NSAIDs are the most frequently implicated group of drugs inducing anaphylactic reactions both in adults and children.<sup>18,124–127</sup> Drug-induced anaphylaxis (DIA) may occur even at younger ages in childhood. In a recent study, the database of the German Federal Institute for drugs was analyzed through validation of the reports of patients aged 0 to 17 years during the period between 2000 and 2016. In this study, 29% and 18% of patients with DIA were between 3–6 and 16–17 years of age, respectively, and a total of 22% of all DIA cases were induced by analgesics/antipyretics.<sup>128</sup> Ibuprofen ranked first with a frequency of 19% among all drugs, while NSAID-induced anaphylactic



reactions were more frequently seen in atopic children and adolescents in comparison with antibiotics and other groups of drugs.<sup>128</sup>

Drug-induced anaphylaxis was confirmed in 8% of pediatric anaphylaxis cases during a one-year period in an allergy outpatient department, constituting a minority compared to food-induced anaphylaxis. It is important to note that NSAIDs were responsible for the 80% of the drug-induced cases.<sup>129</sup> When pediatric patients with DHR referred to an allergy outpatient department in Brazil during a two-year period were evaluated, DIA was recorded in a quarter and NSAIDs were responsible for 70% of the reactions.<sup>130</sup> Anaphylaxis was reported with a rate between 9% and 32% in children and adolescents with proven NSAID-H.<sup>31–34,36,38,62</sup> In patients with confirmed drug-induced anaphylaxis after antibiotics, NSAIDs were responsible for the second highest DHR referral rate.<sup>131</sup>

According to a recent survey including 62,737 adult and pediatric participants from 13 different countries all over Europe, dyspnea prevalence was reported as 1.9% after NSAID ingestion, revealing significant variation between different countries in Europe.<sup>21</sup> Predominantly cutaneous and respiratory symptoms emerge during NSAID-induced anaphylactic reactions.<sup>18</sup> In any case, evaluation of the patient according to selectivity or cross-reactivity and finding a safe alternative NSAID is important during the follow-up of the patient.

## Diagnostic Approach and Drug Provocation Tests in the Evaluation of NSAID-H

Taking a detailed clinical history of the suspected reaction including the description of cutaneous symptoms induced by the culprit NSAID, is the key for the accurate guidance of the patients.<sup>19</sup> The interval between the NSAID intake and the onset of each symptom, other drugs involved, cofactors and the course of events during the following hours, requirement for a treatment during the recovery of the patient and response of the patient to the treatment of the hypersensitivity reaction are all important parameters in decision of the diagnostic tests. If the patient is admitted to a health-care center, medical records from the responsible physician should be sought. The dose, type and group of NSAIDs that can be used by the patient, particularly after the index reaction, would aid the determination of the NSAID-H phenotype for the individual patient. Additionally, the personal history of atopy, allergic rhinitis, asthma and urticaria should be evaluated for each patient.

Diagnostic tests should be performed at least four to six weeks after the index reaction for an appropriate individual response.<sup>83</sup> Diagnostic tests are composed of OPT in the majority of the cases but skin tests (ST) may also be helpful in cases of suspected IgE-mediated selective-reactions with metamizole and paracetamol. Sipahi Çimen et al reported that paracetamol ST was positive in only one of 45 patients with a suspected paracetamol induced reaction and OPT confirmed that this patient could safely be administered paracetamol.<sup>42</sup> However, OPT was positive in three of 44 ST negative patients yielding a negative predictive value of 93% for paracetamol ST.<sup>42</sup> The value of STs with other NSAIDs is limited because there is a scarcity of data on nonirritating concentrations of different NSAIDs and parenteral forms of some of the NSAIDs are not widely available. Due to the infrequency of SNIDR in childhood, the sensitivity and specificity of late reading of IDT and patch tests with NSAIDs are not known. There is a distinct lack of information about the predictive value of STs not only in children but also in adults, such as the late reading of intradermal tests and patch tests with differing NSAIDs.<sup>81</sup> Additionally, as in-vitro tests such as basophil activation with NSAIDs are not commonly used for diagnosis of actual NSAID-H, their diagnostic validity needs to be established in large scale studies.

Performing a drug provocation test (DPT) with the culprit NSAID, is essential for accurate diagnosis of NSAID-H, particularly in the pediatric population due to the insufficiency of other in-vivo and in-vitro diagnostic tests.<sup>31,33,37,132</sup> DPT is the gold standard, and in the event of an actual diagnosis, another DPT with a strong COX-I inhibitor is mandatory to assess cross-reactivity.<sup>19,62,133</sup> In adults, clinical history would be more reliable, especially in cases of multiple episodes with different NSAIDs.<sup>134</sup> For adults, in CI NSAID-H, DPT is recommended for patients with less than three episodes of reactions in their history except for those in the NERD group.<sup>134</sup> According to EAACI guidelines on NERD, if an adult with asthma and/or chronic rhinosinusitis with nasal polyposis has experienced at least two episodes of immediate respiratory symptoms induced by different NSAIDs during the last five years, there is no need for a DPT, the history alone being sufficient for an accurate diagnosis.<sup>96</sup> However, it is important to note that in children, the existence of multiple clinical histories with different types of NSAIDs would not always indicate an actual diagnosis of NSAID-H and cross-reactivity.<sup>9,31</sup> Taking the less frequent existence of NERD and NECD into account in the pediatric

population,<sup>31,32,36</sup> the reliability of clinical history according to various age groups and phenotypes warrants further investigation in future studies.

DPT with NSAIDs should be performed in a clinical setting equipped with emergency medications and experienced staff under medical supervision at least four weeks after the index reaction. Antihistamines or other drugs that would affect the outcome should be stopped for a certain period, and patients undergoing beta-blocker treatment should ask their physician to stop the drug before DPT.<sup>135</sup> Eligible patients, should perform a respiratory function test before starting and during DPT, and their asthma and/or allergic rhinitis should be under control as well as any other systemic diseases. The total dose and dose scheme administered for frequently consumed drugs in related studies including children and adolescents is shown in Table 5. The challenge usually starts with 1/4 to 1/20 of the total single dose appropriate for the age and weight of the patient, and the total dose is given in 4 to 5 doses in an escalating manner generally at one to 1.5-hour intervals.<sup>31–34,63,136</sup> An interval of 20 to 30 minutes has also been preferred in some studies based on the index reaction history.<sup>25,32,36,42</sup> There is no consensus in regards to DPT protocol worldwide. A multicenter retrospective study including centers from Italy, Spain, Switzerland, Portugal and Serbia revealed that during DPT, either 1/100 or 1/10 or 1/4 of the single therapeutic dose was used as the initial dose and the total number of steps were either 2, 3 or 4 at different centers.<sup>62</sup> Additionally, apart from the one-day protocol performed in the majority of the studies,<sup>28,31–33,37,113</sup> a 2-day and 3-day DPT protocol was implemented in Spain and Serbia, respectively, and DPT with aspirin was commonly performed only in Spain.<sup>62</sup> The authors remarked that 30% and 20% of the NSAID hypersensitive patients in the Serbian center reacted during the second and the third day, respectively.<sup>62</sup>

The observation period after the last dose intake is based on the history of index reaction. However, a hospital observation period of 3 to 6 hours is generally enough in one-day protocols. It is important to note that the patient would need to contact the physician afterwards because CI cutaneous reactions would appear several hours after exposure.<sup>19,34,38,78</sup>

**Table 5** Examples of NSAID Doses Utilized During Oral Provocation Tests in children<sup>29–31,39,62,146,147</sup>

Drug	Dose (mg/kg)	Dose (mg)	Interval btw. Doses	Additional Doses at Home
<b>ASA</b>	10 mg/kg	10, 17, 44, 117, 312 mg	1.5h	–
<b>ASA</b>	20 mg/kg	1st day: ¼, ¼, ¼ of TCD 2nd day: ½, ½ of TCD	1h	+ (2 days)
<b>Ibuprofen</b>	10 mg/kg	¼, ¼, ½ of TCD	1h	+ (2 days)
	10 mg/kg	10, 30, 50, 100, 200 mg	1.5h	–
<b>Diclofenac</b>	25 mg/dose	1, 5, 25 mg	1.5h	–
<b>Flurbiprofen</b>	100 mg/dose	5, 15, 30, 50 mg	1.5h	–
<b>Ketoprofen</b>	0.5 mg/kg	1, 5, 20.80 mg	1.5h	–
<b>Dexketoprofen</b>	25 mg	1, 3, 7, 14 mg	1.5h	–
<b>Paracetamol</b>	15 mg/kg	¼, ¼, ¼ and ¼ of TCD	1h	–
	15 mg/kg	Single dose	1h	+ (2 days)
	20 mg/kg	Single dose	1h	–
<b>Metamizol</b>	20 mg/kg	¼, ¼, ½ of TCD	1h	+ (2 days)
	20 mg/kg	10, 50, 125, 250	1.5h	–
<b>Meloxicam</b>	7.5 mg/dose	¼, ½, ½ of TCD	1h	+ (2 days)
	15 mg/dose	2.5–5–7.5 mg	1h	–
<b>Tolmetin</b>	160 mg/dose	10–50–100 mg	–	–
<b>Etoricoxib</b>	60 mg/dose	¼, ¼, ½ of TCD	1h	+ (2 days)
	60 mg (<60kg)	Single dose	–	–
	90 mg (>60 kg)	–	–	–
<b>Nimesulide</b>	100 mg/dose	25–75–100 mg	1h	–
<b>Culprit NSAID<sup>a</sup></b>	–	1/10, 2/10, 7/10 of TCD	30–90 min	1 or 2 or 3 days
	–	¼, ¾ of TCD	30–90 min	1 day

**Notes:** <sup>a</sup>In case of anaphylaxis in the history; 1/100, 1/10 and full dose are given. In 2 or 3 day OPT performing centers, the NSAID is given as single dose on days following the first day.

**Abbreviations:** ASA, Aspirin (acetylsalicylic acid); min, minute; NSAID, Nonsteroidal anti-inflammatory drug; TCD, total cumulative dose.

DPT with the culprit NSAID is contraindicated in the case of severe anaphylaxis, NSAID-induced autoimmune disease, severe cutaneous adverse reactions such as SJS, TEN and severe specific organ involvements such as cytopenia, hepatitis or drug reaction with eosinophilia and systemic symptoms.<sup>19</sup> It is important to note that being on the safe side is crucial while performing DPTs, especially in patients who have experienced anaphylaxis in the past. The patient should be evaluated carefully in terms of the need for a DPT with the culprit drug, and in these cases, lower initial doses (ie, 1% or less of the reactive dose) should be preferred.<sup>36</sup> As a new approach, Nohra et al suggested taking into account the pharmacodynamics and pharmacokinetic properties of NSAIDs while deciding on the initial dose, following doses, and the time interval implemented between doses during OPT. In their study, they classified NSAIDs into rapid (ASA, ketoprofen, ibuprofen and tiaprofenic acid), moderate (diclofenac and celecoxib) and slow absorption (piroxicam) groups. Based on the reactive threshold time and doses in their results, they suggested implementing 20–30–50% of the daily total therapeutic dose (TTD) every 30 minutes for the rapid absorption group, 5–15–30–50% of TTD every 30 minutes for diclofenac, 20–80% of the TTD every 30 minutes for etoricoxib, and 25–75% of the TTD every 3 hours for piroxicam, and a surveillance period of 3 hours after the last dose of OPT for all patients.<sup>137</sup> However, the authors insisted on compulsory lower initial doses in case of an anaphylactic index reaction with the offending NSAID in order to ensure safety.<sup>137</sup>

During DPT, positive results might be urticaria and/or angioedema, maculopapular exanthema, rhinitis, cough, wheezing with or without dyspnea, hoarseness and anaphylaxis based on the index reaction. If the result of a DPT with the culprit NSAID is negative, it is highly significant; as the negative predictive value of DPT was reported as 100% and 96.3% in the pediatric population (100% for paracetamol, 94% for ibuprofen), whereas it was reported as 96.4% in adults.<sup>136,138,139</sup>

Aspirin is a strong COX-I inhibitor and has been frequently used in current studies to assess cross-intolerance among children and adolescents with actual NSAID-H. Performing the DPT with aspirin initially before the culprit drug would be an option that determines the CI patients at the first step.<sup>38,41</sup> A positive DPT with aspirin lowers the number of diagnostic DPT for the patient. In case of a negative one, the patient undergoes another DPT with the culprit NSAID in order to assess actual selective-reactivity.<sup>38,41</sup> DPT with aspirin has been performed orally in the majority of pediatric studies in a single blinded pattern with a total of 10 mg/kg/dose in 4 to 5 steps.<sup>31,32,40</sup> However, there are also studies in the pediatric population utilizing doses of aspirin as high as 15 to 20 mg/kg in which the authors performed the DPT on two consecutive days.<sup>30,38</sup> During the first day, three incremental doses were given, reaching half of the therapeutic dose, and on the second day, two doses were administered up to the full dose.<sup>38</sup> Nevertheless, it should be kept in mind that DPT with aspirin might result in more severe reactions involving the respiratory tract than the index reaction.<sup>30</sup>

The aspirin challenge may also be performed by inhalation of lysine aspirin or by its nasal application in patients with a history of NSAID-induced respiratory symptoms.<sup>140,141</sup> Oral provocation tests with aspirin were introduced into medical practice in the 1970s but during the 1980s bronchial and nasal inhalation methods became known and were put into practice.<sup>142</sup> These two methods have been widely used in studies involving adults with aspirin-induced asthma, and the nasal method was found safer and faster with a lower negative predictive value.<sup>141</sup> However, validation of its diagnostic utility remains to be elucidated in the pediatric population, particularly in patients with a history of NSAID-induced respiratory symptoms.

## Finding Safe Alternatives: What are the Options?

For patients with CI NSAID-H determination of a safe alternative NSAID is essential. Cross-intolerant reactions are dependent to the strength of COX-I inhibition.<sup>69</sup> For this purpose, NSAIDs partially or preferentially inhibiting COX-I or selectively inhibiting COX-II enzymes are preferred (Table 6). Etodolac, nabumeton, tolmetin, nimesulide and meloxicam are preferential inhibitors of COX-II and partial inhibitors of COX-I, paracetamol is a weak inhibitor of COX enzymes while “coxibs” are selective COX-II inhibitors.<sup>9</sup> However, even the degree of cross-reactivity between different “coxibs” and strong COX-I inhibitors might differ for an individual.<sup>143</sup> In a study including both adult and pediatric CI patients, the reaction rates for nimesulide, rofecoxib, celecoxib and meloxicam were 21.3%, 3%, 33.3% and 17.3%, respectively.<sup>144</sup> In a case series of adolescents with NERD, 80% of patients tolerated nimesulide and 20% tolerated meloxicam.<sup>113</sup> Sanchez-Borges et al confirmed a 100% tolerance to valdecoxib and rofecoxib through OPT in 7 CI adolescents.<sup>145</sup> They also confirmed 90% tolerance to celecoxib in 11 CI NSAID-hypersensitive children.<sup>101</sup> Etoricoxib

**Table 6** NSAID Classes According to Their Potency on COX Enzyme Inhibition

<b>Strong COX-I inhibitors</b>
Aspirin, ibuprofen, ketoprofen, flurbiprofen, ketorolac, diclofenac, sulindac, fenoprofen, piroxicam, indomethacin, naproxen, oxazoprin, mefenamic acid, diflunisal
<b>Preferential COX-I inhibitors at low dose and weak COX-I inhibitors at high dose</b>
Nimesulid, meloxicam, tolmetin, etodolac, nabumeton
<b>Weak COX-I inhibitors</b>
Paracetamol and salsalate
<b>Selective COX-II inhibitors</b>
Celecoxib, etoricoxib and parecoxib

**Abbreviations:** COX, Cyclo-oxygenase; NSAID, Nonsteroidal anti-inflammatory drug.

has frequently been evaluated for tolerance in pediatric populations with CI NSAID-H. In 24 CI Asian children aged 8 to 18 years from Singapore, the tolerance rate of etoricoxib tolerance was 96%.<sup>146</sup> Paracetamol and etoricoxib were tolerated in all of the 41 patients between 9 and 14 years of age with challenge proven angioedema induced by aspirin and ibuprofen, however, only one patient reacted to meloxicam.<sup>147</sup> In a very recent study involving 217 pediatric and adult cases with NSAID-H from Spain, OPT with etoricoxib was negative in all of the cases and only 5.5% of the participants reacted to meloxicam.<sup>14</sup>

Paracetamol has lesser adverse reactions and fewer cross-reactions with NSAIDs than other COX-I inhibitors,<sup>36,117</sup> but still might cross-react with COX-I inhibitors at high doses of 15 mg/kg.<sup>148</sup> Topal et al reported two children who reacted to high-dose paracetamol out of eight CI children tolerating low-dose paracetamol.<sup>63</sup> Arikoglu et al reported that low-dose tolerance was 44% in children with paracetamol hypersensitivity.<sup>36</sup> It is important to note that in particular, young children hypersensitive to both ibuprofen and low-dose paracetamol have limited choice for the treatment of fever. In that case, some other physical methods of external or internal cooling must be applied.

The most important factor affecting the decision of the alternative NSAID is the age of the patient and the availability of the alternative drug.<sup>19</sup> Generally, selective COX-II inhibitors are not approved for patients below 12 years of age, even not approved for those up to 18 years of age in some countries. Etoricoxib is only registered for use in those aged 16 years old and above, and nimesulid is available for patients 12 years and above.<sup>149</sup> Tolmetin can be safely used in patients older than 2 years of age but is not available worldwide.<sup>150</sup> However, even off-label EAACI suggests the use of alternative NSAID in the management of CI NSAID-hypersensitive children due to the data for their safe use in the pediatric age group.<sup>19,151,152</sup> In any case, confirmation of the safe use of the alternative NSAID via OPT is necessary.

Due to availability alternative medication desensitization protocols with the culprit NSAID are not prevalent in the literature. Only in case of no alternative medication in patients with a particular disease would desensitization be an option. For example, Heath et al reported a successful 3-day mesalamine desensitization protocol in a patient with ulcerative colitis unresponsive to other immunosuppressive treatments and with severe anaphylaxis history to multiple NSAIDs.<sup>153</sup> On the other hand, with a particular therapeutic purpose, desensitization to aspirin would be an optional treatment method for patients with NERD phenotype and might improve both asthma and rhinosinusitis symptoms.<sup>107,113,154</sup>

## Conclusion

In summary, current studies indicate that NSAID-H is frequently seen in children and adolescents and warrants a detailed diagnostic approach, mainly with DPT in the appropriate individuals. Diagnostic approach also includes the determination of alternative medication. Not only mild cutaneous reactions but also respiratory symptoms and severe anaphylaxis could occur with NSAID use. Recent investigations reveal different phenotypes of NSAID-H in childhood. There might still be unknown pathways beyond NSAID-H in children due to different pharmacokinetics and pharmacodynamics.

Children are not small adults, and the endotypes of selective-responsive and CI NSAID-H is yet to be evaluated in this particular age group. It is important to note that CI NSAID-H predominates SR NSAID-H and history with multiple NSAIDs alone is not directed for an accurate diagnosis in children. The influence of skin tests on the diagnosis of NSAID-H, the natural course of NSAID-H beginning from childhood into adulthood and its impact on different phenotypes are additional subjects for further clinical investigations.

## Disclosure

The authors report no conflicts of interest in this work.

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