



# Non-steroidal Anti-inflammatory Drug Hypersensitivity in Children: From Urticaria to NSAID-Exacerbated Respiratory Disease

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## ABSTRACT

**Objective:** Non-steroidal anti-inflammatory drug (NSAID) hypersensitivity is one of the leading causes of drug hypersensitivity in children. However, data on phenotype distribution according to the 2025 World Allergy Organization (WAO) classification and on long-term outcomes remain limited. To describe the clinical characteristics, phenotype distribution, and long-term outcomes of children with NSAID hypersensitivity.

**Methods:** This retrospective, single-center study included 43 children (1-18 years) diagnosed with NSAID hypersensitivity between 2015 and 2020. Clinical characteristics, culprit drugs, atopic comorbidities, drug provocation test (DPT) results, and follow-up data were reviewed. Hypersensitivity reactions were classified according to the 2025 WAO classification.

**Results:** Urticaria and/or angioedema were the predominant clinical presentations (83.7%). The most frequently implicated drugs were ibuprofen (65.1%) and paracetamol (41.9%). According to the WAO classification, 46.5% of patients had single NSAID-induced urticaria/angioedema/anaphylaxis, 41.9% had NSAID-induced urticaria/angioedema/anaphylaxis, 7.0% had single NSAID-induced delayed hypersensitivity reactions, and 4.7% had probable NSAID-exacerbated respiratory disease (N-ERD). Nearly half (46.3%) reacted to NSAIDs from multiple chemical classes. DPT was performed in 16 patients (37.2%) either to evaluate the suspected culprit drug or to identify a safe alternative analgesic. During follow-up, 21.4% of patients who used NSAIDs after diagnosis reported tolerance upon culprit-drug re-exposure.

**Conclusion:** Pediatric NSAID hypersensitivity predominantly presents with cutaneous manifestations, although respiratory phenotypes such as N-ERD also occur. Careful clinical phenotyping, DPT, and identification of safe alternative analgesics are essential for optimal management. Prospective multicenter studies are needed to define the natural history of pediatric NSAID hypersensitivity and the predictors of the development of tolerance.

**Keywords:** Children, drug hypersensitivity, drug provocation test, nonsteroidal anti-inflammatory drug, NSAID-exacerbated respiratory disease, urticaria

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## INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used in children for fever, pain, and inflammation, and their effects depend largely on blockade of cyclooxygenase (COX). Hypersensitivity to this drug group was long regarded as an adult problem, yet reports in children and adolescents have grown steadily, and NSAIDs now rank alongside antibiotics as the drugs most often implicated in childhood hypersensitivity reactions.<sup>1,2</sup>

NSAIDs are classified into subgroups according to their pharmacological properties, particularly their degree of COX-

1 and COX-2 inhibition, and their chemical structures. Based on the underlying pathogenic mechanism, hypersensitivity reactions are broadly categorized as either cross-reactive reactions, which are non-immunological and associated with COX-1 inhibition, or selective reactions, which are immunologically mediated through IgE- or T-cell-dependent mechanisms. The World Allergy Organization (WAO) revised the phenotypic categories of this scheme in 2025 (Table 1).<sup>3,4</sup>

The revised phenotypes are based largely on adult data, and their manifestations in children are much less clear. In pediatric



series, skin findings predominate, whereas airway involvement is reported only rarely. Even so, NSAID-exacerbated respiratory disease (N-ERD) does occur before adulthood: a child with asthma, allergic rhinitis, or rhinosinusitis with polyps may respond to aspirin or another strong COX-1 inhibitor with rhinorrhea, sneezing, nasal blockage, ocular symptoms, cough, dyspnea, or marked bronchospasm, even when the complete Samter triad has not yet emerged.<sup>56</sup>

In addition, the accuracy of clinical history in suggesting NSAID hypersensitivity is relatively low in children. Only a third to a half of children labeled on clinical grounds are confirmed when challenged, so drug provocation testing (DPT) remains the reference method.<sup>79</sup> An incorrect label narrows the choice of analgesics and places an unnecessary burden on the family.

Data on NSAID hypersensitivity in children remain limited, and most published studies have primarily focused on the diagnostic accuracy of clinical history and on confirmation of suspected reactions by drug provocation testing. In contrast, information regarding long-term clinical outcomes and the distribution of respiratory phenotypes in the pediatric population is scarce. Therefore, the present study aimed to characterize the clinical features of children diagnosed with NSAID hypersensitivity at a single tertiary pediatric allergy center, determine the distribution of phenotypes according to the 2025 WAO classification, and assess the frequency of concomitant respiratory disease.

## METHODS

### Study Design and Patients

Children aged 1-18 years who were followed for NSAID hypersensitivity at the Pediatric Immunology and Allergy Clinic of University of Health Sciences Türkiye, İzmir Dr. Behçet Uz Child Disease and Pediatric Surgery Training and Research Hospital, Türkiye, between January 2015 and December 2020, were reviewed in this single-center, retrospective cross-sectional study. Eligibility required at least one reaction to NSAID intake. Children with an equivocal history and those whose families declined DPT were not included. The local ethics committee of University of Health Sciences Türkiye, Dr. Behçet Uz Child Disease and Pediatric Surgery Training and Research Hospital approved the protocol (June 3, 2021; approval no: 2021/10-05).

### Data Collection

Demographic, clinical, and laboratory data were retrieved from the hospital electronic medical records and outpatient charts. The collected variables included age, sex, age at diagnosis, duration of follow-up, interval between the index reaction and diagnosis, family history of atopy and drug allergy, personal history of atopic disease, concomitant diseases, culprit NSAIDs, clinical characteristics of the hypersensitivity reaction, potential cofactors (infection or food intake), hospitalization due to the reaction, and treatments administered.

Laboratory evaluations included a complete blood count, an absolute eosinophil count (AEC), total serum IgE, allergen-specific IgE levels, and skin prick test results. Asthma control, assessed by the asthma control test (ACT), and current controller therapy were recorded for each child with asthma, and each patient was asked about nasal polyposis and prior sinus surgery.

## Classification

Phenotypic classification was based primarily on a detailed clinical history and, when available, on DPT results, in accordance with the 2025 WAO classification; the defining features are summarized in Table 1. Because DPT was not performed in all patients, phenotypes assigned based clinical history were considered clinically probable rather than challenge-confirmed, unless hypersensitivity to the suspected culprit drug was demonstrated by a positive DPT. Urticaria, angioedema, or anaphylaxis after two or more chemically unrelated NSAIDs, without underlying chronic spontaneous urticaria, was recorded as NSAID-induced urticaria/angioedema/anaphylaxis (NIUAA); the same reactions confined to one drug or one chemical class, with other NSAIDs tolerated, were recorded as single NSAID-induced urticaria/angioedema/anaphylaxis (SNIUAA); symptoms arising only when a tolerated food was eaten together with an NSAID, were recorded as NSAID-exacerbated/induced food allergy (NEFA/NIFA); and delayed skin reactions after a single agent, were recorded as single NSAID-induced delayed hypersensitivity reactions (SNIDHR). Bronchospasm, cough, dyspnea, or a clear worsening of established airway symptoms after aspirin or a strong COX-1 inhibitor, once alternative causes had been excluded, define N-ERD, while exacerbation of pre-existing chronic spontaneous urticaria defines NSAID-exacerbated cutaneous disease (NECD).

NSAIDs were further categorized according to their chemical structure as propionic acid derivatives, salicylic acid derivatives, acetic acid derivatives, anthranilic acid derivatives (fenamates), pyrazolones, enolic acid derivatives (oxicams), para-aminophenol derivatives (paracetamol), sulfonanilide derivatives, and coxibs.

## Drug Provocation Testing

Families were informed about DPT, and their consent was documented prior to the procedure. Challenges followed an open, incremental-dose protocol in a day-care unit equipped for resuscitation, and a skin prick test with the suspected drug preceded the challenge when feasible. DPT served either to confirm reactivity to the suspected agent or to establish a tolerated alternative. Children remained under observation for at least two hours after receiving the full cumulative dose. The test was stopped if any objective sign—urticaria, angioedema, bronchospasm, or hypotension—occurred; it was then recorded as positive and treated accordingly. Successive challenges in the same child were separated by at least one week. No patient underwent drug desensitization.

| Table 1. WAO 2025 phenotypes of NSAID hypersensitivity <sup>3</sup> |                                                                                   |                  |                                                    |                                                       |                  |
|---------------------------------------------------------------------|-----------------------------------------------------------------------------------|------------------|----------------------------------------------------|-------------------------------------------------------|------------------|
| Phenotype                                                           | Clinical manifestations                                                           | Timing           | Underlying condition                               | Pathogenic mechanism                                  | Cross-reactivity |
| NSAID-exacerbated respiratory disease (N-ERD)                       | Nasal congestion, rhinorrhea, sneezing, nasal itch, ocular symptoms, bronchospasm | Immediate (≤6 h) | Asthma, chronic rhinosinusitis and/or nasal polyps | COX-1 inhibition                                      | Yes              |
| NSAID-exacerbated cutaneous disease (NECD)                          | Urticaria, angioedema                                                             | Immediate (≤6 h) | Chronic spontaneous or recurrent urticaria         | COX-1 inhibition                                      | Yes              |
| NSAID-induced urticaria/ angioedema/ anaphylaxis (NIUAA)            | Urticaria, angioedema, anaphylaxis                                                | Immediate (≤6 h) | None                                               | COX-1 inhibition                                      | Yes              |
| Single-NSAID-induced urticaria/ angioedema/ anaphylaxis (SNIUAA)    | Urticaria, angioedema, anaphylaxis                                                | Immediate (≤6 h) | None                                               | IgE-mediated                                          | No               |
| NSAID-exacerbated/induced food allergy (NEFA/NIFA)                  | Urticaria, angioedema, anaphylaxis                                                | Immediate (≤6 h) | Food hypersensitivity or sensitization             | NSAID as aggravating factor (NEFA) or cofactor (NIFA) | —                |
| Single-NSAID-induced delayed hypersensitivity reactions (SNIDHR)    | Contact dermatitis, FDE, MDE, SDRIFE, AGEP, DRESS, SJS, TEN, vasculitis           | Delayed (>6 h)   | None                                               | T-cell mediated                                       | No               |

NSAID: Non-steroidal anti-inflammatory drug, COX: Cyclooxygenase, FDE: Fixed drug eruption, MDE: Morbilliform drug eruption, SDRIFE: Symmetrical drug-related intertriginous and flexural exanthema, AGEP: Acute generalized exanthematous pustulosis, DRESS: Drug reaction with eosinophilia and systemic symptoms, SJS: Stevens-Johnson syndrome, TEN: Toxic epidermal necrolysis, WAO: World Allergy Organization

Follow-up and Clinical Outcomes

Parents or guardians were contacted by a structured telephone interview at the end of the study. Continued uneventful use of a previously documented alternative analgesic was recorded as safe alternative use, and uneventful re-exposure to the culprit drug was recorded as reported tolerance. Because these data were obtained by parental report, the dose administered, the number of subsequent exposures, and whether a full therapeutic dose was reached could not be verified; no confirmatory challenge was performed.

Statistical Analysis

SPSS 26.0 (IBM Corp., Armonk, NY, USA) was used for analysis. Continuous data are presented as median with range or interquartile range, and categorical data as counts and percentages. Groups were compared using the Mann-Whitney U test, the chi-square test, or the Fisher exact test, as required by the data, with significance set at a two-sided p below 0.05.

RESULTS

Demographic and Clinical Characteristics

Forty-three children were studied; 24 (55.8%) were boys. Median age at diagnosis was 7.8 years (range 1.3-17.5), median follow-up was 39 months (range 2-85), and median delay between the index reaction and diagnosis was 12 months (range 1-156). Diagnosis occurred between ages 2 and 5 years in 14 children (32.6%), between 6 and 11 years in 16 children (37.2%), and at 12 years or older in 12 children (27.9%); one child was diagnosed before the age of 2 years.

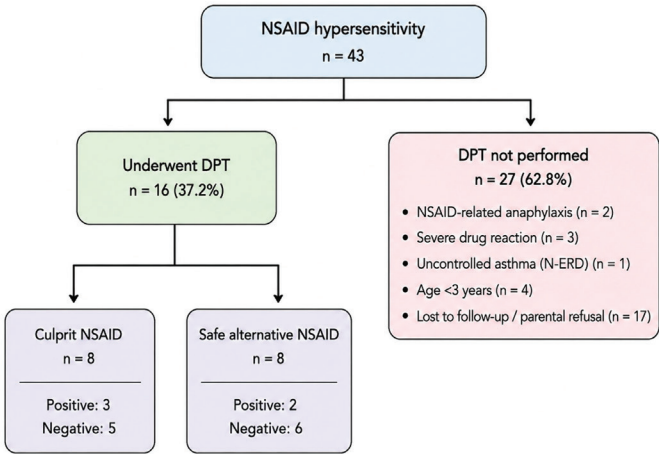


Figure 1. Flow diagram of drug provocation testing (DPT), showing eligibility, reasons for not testing, and the outcome of culprit and alternative NSAID challenges in 43 children with NSAID hypersensitivity.

NSAID: Non-steroidal anti-inflammatory drug

Twenty-one children (48.8%) had an atopic disorder; the most common were allergic rhinitis or rhinoconjunctivitis (n=10, 23.3%), followed by asthma (n=7), atopic dermatitis (n=2), and food allergy (n=2). Atopy in the family was recorded for 24 children (55.8%), and drug or NSAID hypersensitivity in a relative was recorded for 9 (20.9%). Infection accompanied the index reaction in six children (14.0%), and packaged food intake accompanied the index reaction in one child. Uneventful earlier use of the culprit

drug was reported in 38 of 41 children (92.7%), and 28 children (68.3%) had reacted on more than one occasion. Table 2 presents the full profile.

### Reaction Characteristics and Phenotype Distribution

Urticaria, angioedema, or both accounted for most presentations (36 patients, 83.7%). Two children (4.7%) had anaphylaxis with hypotension, generalized urticaria, and vomiting. Three (7.0%) patients had severe delayed skin reactions, with one case each of DRESS, SJS, and AGEP. In two children (4.7%), asthma worsened after NSAID intake. Four (9.8%) were admitted because of the index reaction; no fatalities occurred.

Under the 2025 WAO scheme, SNIUAA was the most common phenotype (20 patients, 46.5%), followed by NIUAA in 18 patients (41.9%), SNIDHR in 3 patients (7.0%), and probable N-ERD in 2 patients (4.7%) (Table 3). Chronic spontaneous urticaria was absent from the cohort; therefore, no child met the criteria for NECD, and no NEFA/NIFA cases were observed. The phenotype groups did not differ in age at diagnosis, sex, atopy, follow-up length, AEC, or total IgE ( $p>0.05$  throughout). Reactions to chemically unrelated NSAIDs were, predictably, far more common in NIUAA than in SNIUAA (94.4% vs. 5.0%,  $p<0.001$ ).

### Culprit Drugs

A specific agent was identified in 41 children (95.3%); the record read only "NSAID" for the other two. Ibuprofen was the most frequent, with 28 cases (65.1%), followed by paracetamol ( $n=18$ , 41.9%), metamizole ( $n=9$ , 20.9%), dextketoprofen ( $n=4$ , 9.3%), and acetylsalicylic acid ( $n=3$ , 7.0%). Culprit medications originated from a single chemical class in 22 children (53.7%) and from several classes in 19 children (46.3%). The most common pairing was paracetamol with ibuprofen, reported by 10 children.

### Laboratory Findings

Median AEC was 230 cells/mm<sup>3</sup> (range 10-817;  $n=27$ ), and median total IgE was 160 kU/L (range 3.9-456;  $n=21$ ). Skin prick testing was performed on 23 children, of whom 11 (47.8%) reacted to at least one aeroallergen or food, with molds, house dust mite, and pollens accounting for most sensitizations. Prick testing with the culprit NSAID was negative throughout.

### Drug Provocation Testing

Twenty-seven children were not challenged for the following reasons: previous NSAID anaphylaxis ( $n=2$ ), severe drug reactions ( $n=3$ ), poorly controlled asthma with N-ERD ( $n=1$ ), age below 3 years ( $n=4$ ), and loss to follow-up or withheld parental consent ( $n=17$ ) (Figure 1).

Drug provocation tests were performed on 16 patients. Five of the eight children challenged with the suspected culprit tolerated it. All five had reported reactions to two or more chemically unrelated NSAIDs and had been assigned to the NIUAA phenotype on the basis of history. In each case, the negative challenge allowed removal of the label for the tested agent alone. Because the remaining implicated NSAIDs were not challenged, the NIUAA phenotype was retained and avoidance of the untested drugs continued. No phenotype was revised after DPT. Among

**Table 2. Demographic and clinical characteristics of the study population ( $n=43$ )**

| Variable                                              | n (%) or median (range) |
|-------------------------------------------------------|-------------------------|
| Sex, male                                             | 24 (55.8)               |
| Age at diagnosis, years                               | 7.8 (1.3-17.5)          |
| Follow-up duration, months                            | 39 (2-85)               |
| Interval between index reaction and diagnosis, months | 12 (1-156)              |
| <b>Personal history of atopy</b>                      | 21 (48.8)               |
| Allergic rhinitis/rhinoconjunctivitis                 | 10 (23.3)               |
| Asthma (with or without allergic rhinitis)            | 7 (16.3)                |
| Atopic dermatitis                                     | 2 (4.7)                 |
| Food allergy                                          | 2 (4.7)                 |
| Family history of atopy                               | 24 (55.8)               |
| Family history of drug allergy                        | 9 (20.9)                |
| <b>Asthma</b>                                         | 7 (16.3)                |
| Well controlled/partly controlled/uncontrolled        | 3/2/2                   |
| Nasal polyposis                                       | 0 (0)                   |
| Hospitalization due to the index reaction             | 4/41(9.8)*              |
| *Data were available for 41 patients                  |                         |

**Table 3. Phenotype distribution and baseline characteristics according to the 2025 WAO classification**

| Characteristic                                                                                                                                                                                                                                                       | SNIUAA ( $n=20$ ) | NIUAA ( $n=18$ ) | SNIDHR ( $n=3$ ) | Probable N-ERD ( $n=2$ ) |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|------------------|------------------|--------------------------|
| Male sex, n (%)                                                                                                                                                                                                                                                      | 10 (50.0)         | 10 (55.6)        | 2 (66.7)         | 2 (100)                  |
| Age at diagnosis, years, median                                                                                                                                                                                                                                      | 7.9               | 7.8              | 6.3              | 13.5                     |
| Follow-up duration, months, median                                                                                                                                                                                                                                   | 40.5              | 27.5             | 76.0             | 39.0                     |
| Personal history of atopy, n (%)                                                                                                                                                                                                                                     | 13 (65.0)         | 6 (33.3)         | 0 (0)            | 2 (100)                  |
| Asthma, n (%)                                                                                                                                                                                                                                                        | 3 (15.0)          | 2 (11.1)         | 0 (0)            | 2 (100)                  |
| SNIUAA: Single-NSAID-induced urticaria/angioedema/anaphylaxis, NIUAA: NSAID-induced urticaria/angioedema/anaphylaxis, SNIDHR: Single-NSAID-induced delayed hypersensitivity reactions, N-ERD: NSAID-exacerbated respiratory disease, WAO: World Allergy Organization |                   |                  |                  |                          |

the eight patients challenged with a presumed safe alternative, six tolerated the tested drug, whereas two developed urticaria (Table 4). Thus, five patients were shown to tolerate a suspected culprit drug, whereas six were shown to tolerate an alternative NSAID; these outcomes were considered separately.

Long-term Follow-up and Clinical Outcomes

Six of the 28 children who had taken an NSAID since diagnosis (21.4%) had retaken the culprit drug without reporting a reaction and were recorded as having reported tolerance upon culprit-drug re-exposure. The dose taken, the number of subsequent exposures, and whether a full therapeutic dose was reached could not be verified, and no subjects underwent supervised re-challenge. Among the six children, four with SNIUAA and two with NIUAA, the median age at diagnosis was 6.3 years and the median follow-up was 51 months; neither age at diagnosis (p=0.575) nor follow-up duration (p=0.801) distinguished them from the rest of the cohort. The remaining 22 (78.6%), two of them with SNIDHR, had used a previously tolerated alternative without trouble. A further 15 children had avoided NSAIDs entirely and, therefore, could not be evaluated for subsequent tolerance to NSAIDs. This proportion therefore represents reported re-exposure outcomes in a selected subgroup and should not be interpreted as a remission or tolerance rate for the entire cohort.

Patients with NSAID-Exacerbated Respiratory Disease

Both children with N-ERD (4.7%) were boys, diagnosed at 11 and 16 years of age. Each was atopic and was taking an inhaled

corticosteroid with a long-acting  $\beta_2$ -agonist; asthma was partly controlled in one and uncontrolled in the other. They had neither nasal polyps nor earlier sinus surgery.

The first patient developed a cough, dyspnea, and an asthma exacerbation approximately 3 hours after ibuprofen intake. At hospital presentation, cough and wheezing were documented, and spirometry showed an FEV<sub>1</sub> of 71% predicted. He reported one previous episode of similar respiratory symptoms following exposure to ibuprofen. His ACT score was 12. There were no clinical or laboratory findings suggestive of a concomitant infection, and no evidence of chronic rhinosinusitis. DPT was not performed, and the patient was subsequently lost to clinical follow-up. During the final telephone interview, he reported subsequent use of paracetamol without a reaction, and reported continued treatment with inhaled corticosteroid/long-acting  $\beta_2$ -agonist therapy.

The second patient developed a cough and dyspnea approximately 2 hours after exposure to both paracetamol and dextetoprofen. During evaluation in the emergency department, the patient's oxygen saturation was 92%, rhonchi were noted on auscultation, and the respiratory symptoms improved following salbutamol administration. Spirometry showed an FEV<sub>1</sub> of 75% predicted. He reported two previous episodes with similar respiratory symptoms following NSAID exposure. There was no clinical evidence of concomitant infection or chronic rhinosinusitis. A DPT with nimesulide was subsequently performed to identify a safe alternative and yielded a negative result.

| Table 4. Drug provocation tests: tested drug, role, outcome and diagnosis after testing                                                                                                                                                      |                      |             |             |                      |                                             |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------|-------------|-------------|----------------------|---------------------------------------------|
| #                                                                                                                                                                                                                                            | Phenotype before DPT | Drug tested | Role        | Result               | Diagnosis after DPT                         |
| 1                                                                                                                                                                                                                                            | NIUAA                | Paracetamol | Alternative | Positive (urticaria) | NIUAA                                       |
| 2                                                                                                                                                                                                                                            | NIUAA                | Metamizole  | Culprit     | Positive (urticaria) | NIUAA                                       |
| 3                                                                                                                                                                                                                                            | NIUAA                | Paracetamol | Culprit     | Negative             | NIUAA; paracetamol delabeled                |
| 4                                                                                                                                                                                                                                            | SNIUAA               | Paracetamol | Alternative | Negative             | SNIUAA; safe alternative documented         |
| 5                                                                                                                                                                                                                                            | NIUAA                | Metamizole  | Alternative | Positive (urticaria) | NIUAA                                       |
| 6                                                                                                                                                                                                                                            | SNIUAA               | Paracetamol | Alternative | Negative             | SNIUAA; safe alternative documented         |
| 7                                                                                                                                                                                                                                            | NIUAA                | Paracetamol | Culprit     | Positive (urticaria) | NIUAA                                       |
| 8                                                                                                                                                                                                                                            | SNIUAA               | Paracetamol | Alternative | Negative             | SNIUAA; safe alternative documented         |
| 9                                                                                                                                                                                                                                            | NIUAA                | Paracetamol | Alternative | Negative             | NIUAA; safe alternative documented          |
| 10                                                                                                                                                                                                                                           | NIUAA                | Ibuprofen   | Alternative | Negative             | NIUAA; safe alternative documented          |
| 11                                                                                                                                                                                                                                           | NIUAA                | Paracetamol | Culprit     | Negative             | NIUAA; paracetamol delabeled                |
| 12                                                                                                                                                                                                                                           | NIUAA                | Paracetamol | Culprit     | Negative             | NIUAA; paracetamol delabeled                |
| 13                                                                                                                                                                                                                                           | NIUAA                | Paracetamol | Culprit     | Negative             | NIUAA; paracetamol delabeled                |
| 14                                                                                                                                                                                                                                           | NIUAA                | Ibuprofen   | Culprit     | Positive (urticaria) | NIUAA                                       |
| 15                                                                                                                                                                                                                                           | NIUAA                | Paracetamol | Culprit     | Negative             | NIUAA; paracetamol delabeled                |
| 16                                                                                                                                                                                                                                           | Probable N-ERD       | Nimesulide  | Alternative | Negative             | Probable N-ERD; safe alternative documented |
| DPT: Drug provocation test, NSAID: Non-steroidal anti-inflammatory drug, SNIUAA: Single-NSAID-induced urticaria/angioedema/anaphylaxis, NIUAA: NSAID-induced urticaria/angioedema/anaphylaxis, N-ERD: NSAID-exacerbated respiratory disease, |                      |             |             |                      |                                             |

## DISCUSSION

We reviewed 43 children with NSAID hypersensitivity, assigned them to the 2025 WAO phenotypes, and followed their course. Cutaneous phenotypes predominated; N-ERD, although rare, was present in the cohort.

Skin involvement in 83.7% of our patients is consistent with earlier pediatric work. Podlecka et al.<sup>10</sup> found urticaria, angioedema, or both in 84.9% of confirmed cases, and Kidon et al.<sup>5,11</sup> described the same pattern as the usual presentation of cross-reactive hypersensitivity in younger children. Culprit distribution also agreed with published series: ibuprofen (65.1%) and paracetamol (41.9%) headed our list, which most likely reflects how often the two are given as antipyretics rather than any greater intrinsic risk.<sup>7,12</sup>

SNIUAA (46.5%) were more prevalent than NIUAA (41.9%) in this study. Arikoglu et al.<sup>8</sup> reported a similar ranking among 31 confirmed children—SNIUAA 11, NIUA 8, NECD 6, and N-ERD 1. Chronic spontaneous urticaria was absent from our cohort, so NECD did not appear; the disorder is less frequent in children than in adults, among whom Koh et al.<sup>13</sup> classified 11.6% of cross-reactive cases as NECD. NEFA/NIFA, which was added to the classification in 2025, was likewise unrepresented.

N-ERD cases accounted for 4.7% of our cohort; they were followed up as probable cases of N-ERD because DPT testing for the offending drug was not possible. Pediatric figures are sparse: roughly 0.9% of asthmatic children have confirmed NSAID hypersensitivity and about 0.3% have N-ERD.<sup>6</sup> The condition usually declares itself in the third or fourth decade, with reported onsets spanning puberty to the eighth decade.<sup>14</sup> Among adults with asthma it affects 5.5-12.4%, rising toward 20% where aspirin challenge is applied.<sup>15,16</sup> Diagnosis rests chiefly on a characteristic history and physical examination rather than on laboratory testing. Neither of our two patients had nasal polyps, in keeping with earlier behavior pediatric reports, which suggests early disease in which the Samter triad is not yet complete.<sup>6,17</sup> Asthma and upper airway symptoms, therefore, should be systematically assessed in any child suspected of NSAID hypersensitivity; prescribing NSAIDs to asthmatic children warrants caution.

Only 37.2% of our patients were challenged, which is the principal limitation of the study. Parental refusal and loss to follow-up limit confirmation in everyday practice, and other series from Türkiye report the same difficulty.<sup>9</sup> Nonetheless, the reference standard remains a challenge, since history alone misleads. Yilmaz et al.<sup>7</sup> confirmed just 14% of children reporting reactions to one NSAID and 44% of those reporting reactions to several. A recent prospective study of 336 children confirmed roughly one in three; febrile infection explained a large share of the remainder, and NEFA/NIFA accounted for 14%.<sup>18</sup> We identified no NEFA/NIFA cases. Infection coincided with the index reaction in 14.0% of our patients; therefore, some episodes may have been infection-

related exanthems rather than true drug hypersensitivity. Labeling a child as NSAID-allergic without confirmation risks lifelong avoidance for no reason.<sup>4,19</sup>

Finding a well-tolerated analgesic is as important as identifying the cause. Paracetamol was tolerated in 9 of 11 challenges (81.8%), and nimesulide was tolerated in the one child tested. Yilmaz et al.<sup>7</sup> reported tolerance to paracetamol in 60% and to nimesulide in 88.8% of children, and adult data give tolerance rates of 90% for paracetamol 1,300 mg, 96% for meloxicam 15 mg, and 98% for celecoxib 200 mg in cross-reactive disease.<sup>13</sup> Agents with weak COX-1 activity and preferential or selective COX-2 inhibitors are thus reasonable choices for cross-reactive phenotypes, once the challenge has proved negative. Metamizole behaved differently; both challenges were positive; therefore, pyrazolones warrant caution as substitutes.

Tolerance upon re-exposure to the culprit drug was reported in 21.4% of children who had used an NSAID during follow-up. This finding should be interpreted differently from the 52.1% tolerance rate reported by Uluc et al.,<sup>20</sup> who established tolerance by supervised re-challenge after at least three years and reported a median time to tolerance of 6.16 years, with an initial reaction age of  $\leq 11.75$  years associated with tolerance development. In our study, tolerance was assessed using parental reports for children who were re-exposed, whereas those who continued to avoid NSAIDs could not be evaluated for subsequent tolerance. Therefore, our findings cannot be interpreted as an estimate of the spontaneous resolution rate of NSAID hypersensitivity. Supervised re-challenge, when clinically appropriate, may be valuable several years after diagnosis to identify children who have developed tolerance and to potentially avoid unnecessary long-term drug restriction.

## Study Limitations

The main limitations of this study include its retrospective, single-center design, small sample size, and inability to perform DPT in all patients. An important consideration when interpreting our findings is that phenotype assignment was predominantly based on clinical history, because DPT could not be performed in all patients. Therefore, the reported phenotype distribution primarily reflects clinically assigned WAO phenotypes rather than challenge-confirmed NSAID hypersensitivity. In particular, the two respiratory cases were classified as probable N-ERD because culprit-drug DPTs were not performed, despite recurrent temporally related reactions and documented objective respiratory findings. Furthermore, long-term outcome data were obtained through telephone interviews and are therefore susceptible to recall bias. Despite these limitations, the relatively long median follow-up period of 39 months and the application of the 2025 WAO classification represent important strengths of the study.

## CONCLUSION

Urticaria and angioedema characterize most pediatric NSAID hypersensitivity, with ibuprofen and paracetamol the most commonly reported culprits. Selective and cross-reactive patterns occurred at broadly similar frequencies, and although uncommon, airway involvement compatible with N-ERD was present in childhood and should be sought. Because phenotypes were assigned predominantly on clinical grounds, these proportions are provisional. Careful airway assessment, confirmation by challenge, wherever feasible, and documentation of a tolerated analgesic form the core of management. Prospective multicenter studies are needed to characterize the natural history and predictors of tolerance.

## Ethics

**Ethics Committee Approval:** The local ethics committee of University of Health Sciences Türkiye, Dr. Behçet Uz Child Disease and Pediatric Surgery Training and Research Hospital approved the protocol (June 3, 2021; approval no: 2021/10-05).

**Informed Consent:** Written consent was obtained from parents or legal guardians before drug provocation testing. For the retrospective record review, the requirement for written consent was waived by the ethics committee, and verbal consent was obtained prior to the follow-up telephone interviews.

## Footnotes

### Authorship Contributions

Surgical and Medical Practices: Ö.S., Concept: Ö.S., F.Ç.Ç., Design: C.Ş.K., Ö.S., D.C., Data Collection or Processing: Ö.S., F.Ç.Ç., S.Ö.B., İ.T., M.Ş.K., İ.A.H., Analysis or Interpretation: Ö.S., Literature Search: Ö.S., Writing: Ö.S., F.Ç.Ç., C.Ş.K.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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