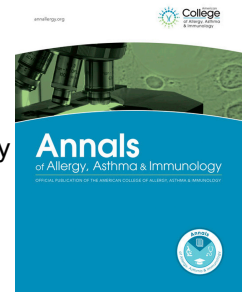


Accepted Manuscript

Two approaches for diagnosis of non-steroidal anti-inflammatory drug hypersensitivity in children

Isil Eser Simsek, M.D, Mujde Tuba Cogurlu, M.D., Metin Aydogan, M.D.



PII: S1081-1206(19)30505-8

DOI: <https://doi.org/10.1016/j.anai.2019.07.005>

Reference: ANAI 2951

To appear in: *Annals of Allergy, Asthma and Immunology*

Received Date: 22 January 2019

Revised Date: 1 July 2019

Accepted Date: 8 July 2019

Please cite this article as: Simsek IE, Cogurlu MT, Aydogan M, Two approaches for diagnosis of non-steroidal anti-inflammatory drug hypersensitivity in children, *Annals of Allergy, Asthma and Immunology* (2019), doi: <https://doi.org/10.1016/j.anai.2019.07.005>.

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Two approaches for diagnosis of non-steroidal anti-inflammatory drug hypersensitivity in children

Isil Eser Simsek, M.D., Mujde Tuba Cogurlu, M.D., Metin Aydogan, M.D.

Division of Pediatric Allergy and Immunology, Kocaeli University, Kocaeli, Turkey

Corresponding Author: to Isil Eser Simsek, M.D., Division of Pediatric Allergy and Immunology, Kocaeli University School of Medicine, 41380, Umuttepe, Kocaeli, Turkey.

Tel: +90 505 697 0848; Fax: +90 263 303 8003; E-mail address: dreserisil@hotmail.com

Conflict of interest : none

Funding source: none

The study was approved by the local ethics committee in Kocaeli University.

Keywords: non-steroidal anti-inflammatory drug, drug hypersensitivity, acetyl salicylic acid, children,, selective reaction, cross-intolerant.

Abbreviations: OPT: oral provocation test

NSAID-H: non-steroidal anti-inflammatory drug hypersensitivity

ASA: acetyl salicylic acid

SR: selective reaction

CI: cross intolerant

Word count: 2739 **Figures :** 1 **Tables:** 4

1 INTRODUCTION

2 Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used in the
3 treatment of fever and pain in children.¹ NSAID hypersensitivity (NSAID-H) is one of the
4 most common causes of drug-induced hypersensitivity reactions in child population.²

5 According to the timing of the reaction, NSAID-H is divided into two types: acute
6 reactions (immediate to several hours after exposure) and delayed reactions (more than 24 h
7 after exposure). Reactions to NSAIDs may be induced by a single drug (selective reactions
8 [SR]) via an immunologic mechanism (IgE-mediated or T cell-mediated), which is called an
9 allergic reaction, or may be induced by multiple NSAIDs via the cyclooxygenase enzyme
10 inhibition, which is responsible for cross-reactivity between NSAIDs with different chemical
11 structures and called a non-allergic reaction (cross-intolerant [CI]).^{3,4} The European Network
12 for Drug Allergy (ENDA) classification have identified two groups of SRs and three groups
13 of CIs (Table 2). These phenotypes are mainly based on authors' expertise and studies that
14 were conducted on adult populations.⁵⁻⁷ Although several studies have been published, the
15 classification according to the clinical phenotypes in children is still inadequate.⁸⁻¹²

16 Although skin prick/intradermal (ID) tests might be helpful for research purposes in IgE-
17 mediated reactions, the oral drug provocation test (OPT) with the culprit NSAID is the gold
18 standard in the diagnosis of NSAID-H.^{13,14} According to the recommendations that reporting
19 in previous studies, the OPT with aspirin to those report a reaction to multiple NSAIDs is
20 one possible approach to diagnose. Another approach for provocation is performing an
21 initial OPT with aspirin regardless of patients' reaction history and an additional OPT with
22 the culprit drug in the case of a negative OPT with ASA.^{15,16} Blanca-Lopez et al.¹⁶ reported
23 that the total number of OPTs required to diagnose NSAID-H was much lower with initial

24 ASA provocations , the authors suggest that initial ASA provocation is less time consuming
25 and additionally when a reaction occurs with the culprit NSAID that is used for the initial
26 OPT patients left the study, which is the reason of the non-completed studies.⁸

27 This retrospective analysis aims to identify (1) the frequency of confirmed NSAID-H
28 in children with a history of a reaction with NSAIDs, (2) the total number of OPTs required
29 to confirm NSAID-H according to the drug (ASA or culprit NSAID) used in the initial OPT,
30 (3) possible risk factors for an NSAID-related hypersensitivity reaction, (4) safe alternative
31 drugs for children with proven NSAID-H.

32 METHODS

33 This retrospective study was conducted in the Department of Pediatric Allergy and
34 Immunology at Kocaeli University, Turkey. All children who underwent an OPT with
35 NSAIDs in our outpatient clinic between January 2014 and December 2017 were included in
36 the study. Written informed consent was obtained from the parents, and the local ethics
37 committee approved the study at Kocaeli University.

38 OPTs were performed using two different approaches based on the drug used in the
39 initial OPT at different times in our department. One approach was an initial OPT with ASA.
40 In the case of a positive result with the ASA provocation , patients were defined as cross-
41 intolerant (CI) and additional OPTs were performed to find a safe alternative at least 4–6
42 weeks after the previous OPT. In the case of a negative result, an OPT with the culprit
43 NSAID was performed. Patients who had a positive OPT result with culprit NSAIDs were
44 defined as selective responders (SR). The second approach was an initial OPT with the
45 culprit NSAID. ASA provocation was performed to assess for CI if the initial OPT results
46 with the culprit NSAID was positive.

In all children with proven NSAID-H, an additional OPT with acetaminophen (also known as paracetamol) was performed to find a safe alternative; nimesulide was used in children >12 years old. Anti-histamines and all medications that might influence the outcome of the provocation tests were stopped at least one week before the test. Four or 5 increasing doses of NSAIDs, starting from low doses (1/10 of therapeutic doses) were given orally at intervals of 60 mins up to a single cumulative dose . The doses were administered according to the recommendations of ENDA.¹⁵ Maximum five doses were administered to prevent the possibility of desensitization. If no symptoms appeared during the OPT, the cumulative therapeutic dose appropriate for the patient's age and weight was reached. The outcome of the challenge was recorded as positive at any time during the challenge when symptoms appeared and the OPT was stopped and the reaction treated accordingly. Patients were monitored in the clinic for at least 2 hours after the last dose. If no symptoms appeared, the OPT was recorded as negative. Patients were asked to contact the clinic if there was a delayed reaction.

Data on the demographic and clinical features, coexisting chronic and/or allergic disease (such as chronic spontaneous urticaria, asthma, nasal polyps, chronic rhinosinusitis, allergic rhinitis), test results (complete blood cell count, total IgE, skin prick tests for aeroallergens) and standardized ENDA drug allergy questionnaires on drug allergy were collected from the medical records. The drug used for the initial OPT (ASA or culprit NSAID), results of the OPTs, the total number of OPTs (to diagnose and to find a safe alternative drug) were reviewed. Considering the OPT results, the estimated total number of OPTs for three approaches were calculated for patients with confirmed NSAID-H:

1. if an initial OPT with ASA was performed
2. if an initial OPT with culprit NSAID was performed

3. if an initial OPT with ASA in the case of suspected reaction to multiple NSAIDs and with culprit drug in those who had a suspected reaction to a single NSAID was performed.

Statistical Analysis

All statistical analyses were performed using IBM SPSS for Windows version 20.0 (IBM Corp., Armonk, NY, USA). Kolmogorov-Smirnov tests were used to test the normality of data distribution. Continuous variables were expressed as means $\pm$ standard deviation, medians (25th–75th percentiles), and categorical variables were expressed as counts (percentages). Comparisons of normally distributed continuous variables between the materials/groups were performed by using the Student's t test. Comparisons of non-normally distributed continuous variables between the groups were performed by using the Mann-Whitney U test. Comparisons of abnormally distributed continuous variables between the times were performed by using the Wilcoxon t test, Friedman analysis of variance by ranks and Tukey post hoc test. Comparisons of categorical variables between the groups were performed using the Fisher exact chi-squares test, Yates chi-squares test and Monte Carlo chi-squared test. A multiple logistic regression analysis was conducted to determine independent risk factors for NSAID-H by including all variables that identified with the univariate analysis.

RESULTS

The study included 56 patients (28 females, 28 males) with suspected NSAID-H. Median age at the time of the OPT was 7.12 years (range, 1.25–18 years). The mean time interval ($\pm$ SD) between the last reported reaction to the drug and the OPT was (11.89 $\pm$ 16.07) months (range, 1.5–72 months) and median IQR was 4.6 months. The time interval between the drug intake and the occurrence of symptoms in clinic history was less than one

hr in 66.1% of the children. None of the patients had a delayed reaction (more than 24 h after exposure) . Thirty-five patients (62.5%) described a reaction to a single NSAID. According to the allergic reaction to other drug classes, parents reported a previous reaction in 13 (23.2%) of the children, but only one child had confirmed allergy against beta lactam antibiotics (we performed an allergy work-up for each patient in our center). Ibuprofen was the most commonly reported drug (76.8%) followed by acetaminophen (32%). The most common clinical manifestation was urticaria (53.5%). Other reported reactions were isolated angioedema (26.8%), urticaria-angioedema (12.5%), anaphylaxis (3.6%), respiratory manifestations with angioedema (1.8%) and isolated respiratory manifestations (1.8%). Fourteen children (25%) revealed atopy via skin prick testing and six patients (10.7%) had a parental history of NSAID-H.

Comparison of Initial OPTs with ASA and Culprit NSAID According to the Total Number of OPTs Required for Diagnosis and Safe Alternatives

We aimed to estimate the total number of OPTs for ASA and other drugs used in the initial OPT in patients with confirmed NSAID-H. We also calculated the total number of OPTs if an initial OPT was performed according to an algorithm (initial OPT with ASA in case of suspected reaction to multiple NSAIDs and with culprit drug in those who reaction to a single NSAID). When we compared the three approaches, there was a significant difference. In the case of an initial OPT with culprit NSAID, 85.7% of cases with NSAID-H would have required 3 or more OPTs. In the case of an initial OPT with ASA 3 or more OPTs would have been required in 14.3% of patients with NSAID-H, while with the algorithm the ratio would be 47.6% . The total number of OPTs for the three approaches is given in Table 1.

The Result of OPTs for Diagnostic Purposes and Safe Alternatives

We performed an initial OPT with culprit NSAID in 26 patients and with aspirin in 30 patients. Of the 56 patients, 21 (37.5%) were confirmed to have NSAID-H. Of the seven patients who had a positive initial OPT against culprit NSAID, two patients tolerated ASA, and five patients had a positive OPT result with ASA. Thirteen patients had a positive initial OPT result with ASA, and one patient who had a negative initial OPT with ASA tolerated the culprit drug. Of the 21 cases with NSAID-H, 18 patients (85.7%) were therefore classified as CI and three as SR (Fig. 1).

Twenty patients with NSAID-H were challenged to find a safe alternative (17 with acetaminophen, 3 with acetaminophen and nimesulide). One patient developed bronchospasm with nimesulide, and no reaction occurred when acetaminophen was given. None of the other patients developed reactions (Table 2).

Risk Factors Related to Confirmed NSAID-H

There were no significant differences regarding gender, history of clinical symptoms, the NSAID involved, previous reaction to another drug class, the time interval between last reported reaction to culprit drug and OPT, peripheral eosinophilia and the presence of NSAID-H in the family between the patients with NSAID-H and tolerant patients. The children with NSAID-H were older at the time of the first OPT (10.04 ± 5.33 years) than the tolerant patients (7.22 ± 4.52 years). Immediate reactions (≤ 1 h) after drug intake were more frequently reported in patients with proven NSAID-H compared to tolerant patients (86 vs. 54%, $p = 0.03$). Comparison of the clinical and laboratory profiles of the children with proven NSAID-H and tolerant children is given in Table 3. Of the 21 patients with NSAID-H, 10 (47.6%) had confirmed sensitization by skin prick testing; atopy in patients without NSAID-H was 11.4% ($p = 0.007$). Twenty three (65.7%) tolerant patients reported only one

previous reaction while patients with NSAID-H had more than one previous reaction to a NSAID with a statistically significant difference (76% , $p = 0.001$). If we consider the presence of a previous reaction to only unrelated NSAIDs, there was not significantly different between the patients with proven NSAID-H and tolerant patients (47.6 % vs. 34%, $p=0.32$).

In the multiple logistic regression analysis, the only independent factor that showed significance was the number of episodes (odds ratio, 4.3; 95% confidence interval, 1.48–12.24; $p = 0.007$).

Classification of Patients with NSAID-H According to the ENDA

Classification

The patients with proven NSAID-H were further classified as NSAID-induced urticaria/angioedema ($n = 12$), NSAID-exacerbated cutaneous disease ($n = 1$), NSAID-exacerbated respiratory disease ($n = 2$), and single NSAID-induced urticaria/angioedema and/or anaphylaxis ($n = 3$). Three cases of CI could not be categorized according to the ENDA classification system because 2 of them had bronchospasm and facial angioedema, and one had respiratory symptoms without a previous history of asthma (Table 4).

DISCUSSION

In the present study, NSAID-H was confirmed by OPT in 21 (37.5%) patients. These findings are similar to previous studies that included children .^{10,16,17,19,20} Viola et al.²¹ found that 78.8% of patients with suspected NSAID-H tolerated the culprit drug in an OPT. In our study, 62.5% of children with a history compatible with hypersensitivity reactions after NSAID intake were confirmed as tolerant in OPT. In many children who develop urticaria

during acute infectious episodes, these reactions are often falsely attributed to the drug used, which demonstrates the significance of performing oral drug provocation tests.

As a result considering CI versus SR, most of our cases were CI, which is consistent with previous studies. The proportion of CI in children varies from 40% to 80%.^{9,11,16,17} The determination of cross-reactivity based on history in children with NSAID-H may be misleading. In our study, eight (50%) children with CI reacted to a single NSAID, and a patient who had suspected reactions to multiple NSAIDs was an SR. Children with CI could not be excluded in the study groups when only the culprit drug was given, which suggest the overestimation of SR. This situation demonstrates the significance of performing a provocation with ASA to determine CI.

After a confirmed diagnosis of NSAID-H, additional OPTs for the classification of the reaction and safe alternatives, especially in children with cross-intolerant reactions, should be performed. In the case of an initial OPT with a suspected drug, at least three visits should be planned for these purposes in many patients. According to a study by Blanca-Lopez et al.,¹⁶ who included an initial OPT with ASA, the total number of OPTs required to diagnose was much lower compared to the other studies. These authors also reported that the risk for non-completion of the study was the occurrence of a reaction in patients who were given the culprit drug in the initial OPT. The use of ASA in children is a concern due to the risk of Reye syndrome; therefore there is a limited number of studies on the use of ASA for evaluation of CI or in the diagnosis of the NSAID-H. ASA may cause cellular mitochondrial damage, which result with the inhibition of fatty acid metabolism in the setting of viral disease. Epidemiologic studies found that <0.1% of children who took ASA developed Reye syndrome; in conditions such as lack of viral infection, Reye syndrome is less likely.

In contrast to other centers, we did not follow the same diagnostic algorithm in all patients for reactions of suspected NSAID-H. OPTs were performed using two different approaches concerning the drug used in the initial OPT. One of the aim of this study was to retrospectively estimate the total number of OPTs for each drug (ASA and culprit NSAIDs) if they were used in an initial OPT. When we compared these approaches, there was a significant difference. In the case of an initial OPT with ASA, only 14.3% of patients with NSAID-H would have required 3 or more OPTs. We think that an initial OPT with ASA may be less time consuming and more comfortable, especially for patients who cannot attend additional visits and live in areas that are distant from clinics.

When SR and CI were further classified according to the ENDA/GA2LEN classification, three (14.3%) patients could not be categorized based on the underlying disease and clinical manifestations. Previous studies reported that some children with proven NSAID-H could not be classified according to the possible phenotypes described by the ENDA group.³ This classification was based on the authors' expertise in adolescents and adults in hypersensitivity reactions to NSAIDs.

The response to acetaminophen in patients who are CI has been reported to be up to 25% in children.^{17,23,24} In this present study, we performed OPTs with acetaminophen as a safe alternative drug in all patients (except 1) with NSAID-H. None of the patients developed a reaction to high doses of acetaminophen, which is consistent with a previous study by Zambonino et al.¹⁰ We performed OPTs with nimesulide in only three children because we had a limited number of patients older than 12 years and some refused an OPT with this drug after they tolerated acetaminophen. One patient who tolerated acetaminophen reacted to nimesulide, and two other patients tolerated both drugs as safe alternatives.

211 In multivariate logistic regression analysis, only the number of episodes was
212 identified as a significant independent risk for proven NSAID-H. Although a positive
213 association with respiratory involvement, the number of drugs involved, a family history of
214 NSAID-H and gender have been reported in the literature, we did not find a significant
215 association between these factors and NSAID-H.^{17-19,25}

216 In conclusion, we show that the rate of CI reactions in children is much higher than
217 that of SRs and performing an initial OPT with ASA can improve patient compliance due to
218 a much smaller number of OPTs.

219

REFERENCES

1. Ortega N, Dona I, Moreno E, et al. Practical guidelines for diagnosing hypersensitivity reactions to nonsteroidal anti-inflammatory drugs. *J Investig Allergol Clin Immunol* 2014; 24:308–323.
2. Dona I, Blanca-Lopez N, Torres MJ, et al. Drug hypersensitivity reactions: patterns of responses, drug involved and temporal variation in a large series of patients evaluates. *J Investig Allergol Clin Immunol* 2012; 22:363–371.
3. Kowalski ML, Asero R, Bavbek S, et al. Classification and practical approach to the diagnosis and management of hypersensitivity to nonsteroidal anti-inflammatory drugs. *Allergy* 2013; 68:1219–1232.
4. Ayuso P, Blanca-Lopez N, Dona I, et al. Advanced phenotyping in hypersensitivity drug reactions to NSAIDs. *Clin Exp Allergy* 2013; 43:1097–1109.
5. Dona I, Blanca-Lopez N, Cornejo-Garcia JA, et al. Characteristics of subjects experiencing hypersensitivity to non-steroidal anti-inflammatory drugs: patterns of response. *Clin Exp Allergy* 2011; 41:86–95.
6. Caimmi S, Caimmi D, Bousquet PJ, Demoly P. How can we better classify NSAID hypersensitivity reactions? – Validation from a large database. *Int Arch Allergy Immunol* 2012; 159:306–312.
7. Quiralte J, Blanco C, Delgado J, et al. Challenge-based clinical patterns of 223 Spanish patients with nonsteroidal anti-inflammatory-drug-induced reactions. *J Investig Allergol Clin Immunol* 2007; 17:182–188.

8. Cousin M, Chiriac A, Molinari N, Demoly P, Caimmi D. Phenotypical characterization of children with hypersensitivity reactions to NSAIDs. *Pediatr Allergy Immunol* 2016; 27:743–748.
9. Zambonino MA, Torres MJ, Muñoz C, et al. Drug provocation tests in the diagnosis of hypersensitivity reactions to non-steroidal anti-inflammatory drugs in children. *Pediatr Allergy Immunol* 2013; 24:151–159.
10. Cavkaytar O, Arik Yilmaz E, Karaatmaca B, et al. Different phenotypes of non-steroidal anti-inflammatory drug hypersensitivity during childhood. *Int Arch Allergy Immunol* 2015; 167:211–221.
11. Arikoglu T, Aslan G, Yildirim DD, Batmaz SB, Kuyucu S. Discrepancies in the diagnosis and classification of nonsteroidal anti-inflammatory drug hypersensitivity reactions in children. *Allergol Int* 2017; 66:418–424.
12. Guvenir H, Dibek Misirlioglu E, Vezir E, et al. Nonsteroidal anti-inflammatory drug hypersensitivity among children. *Allergy Asthma Proc* 2015; 36:386–393.
13. Kidon M, Blanca-Lopez N, Gomes E, et al. EAACI/ENDA position paper: diagnosis and management of hypersensitivity reactions to non-steroidal anti-inflammatory drugs (NSAIDs) in children and adolescents. *Pediatr Allergy Immunol* 2018; 29:469–480.
14. Cavkaytar O, du Toit G, Caimmi D. Characteristics of NSAID-induced hypersensitivity reactions in childhood. *Pediatr Allergy Immunol* 2018. doi:10.1111/pai.12980.
15. Kowalski ML, Makowska JS. Seven steps to the diagnosis of NSAIDs hypersensitivity: how to apply a new classification in real practice? *Allergy Asthma Immunol Res* 2015; 7:312–320.

16. Blanca-Lopez N, Haroun-Diaz E, Ruano FJ, et al. Acetyl salicylic acid challenge in children with hypersensitivity reactions to nonsteroidal anti-inflammatory drugs differentiates between cross-intolerant and selective responders. *J Allergy Clin Immunol Pract* 2018; 6:1226–1235.
17. Hassani A, Ponvert C, Karila C, Le Bourgeois M, De Blic J, Scheinmann P. Hypersensitivity to cyclooxygenase inhibitory drugs in children: a study of 164 cases. *Eur J Dermatol* 2008; 18:561–565.
18. Yilmaz O, Ertoy Karagol IH, Bakirtas A, et al. Challenge-proven nonsteroidal anti-inflammatory drug hypersensitivity in children. *Allergy* 2013; 68:1555–1561.
19. Topal E, Celiksoy MH, Catal F, Sayan GY, Sancak R. The value of the clinical history for the diagnosis of immediate nonsteroidal anti-inflammatory drug hypersensitivity and safe alternative drugs in children. *Allergy Asthma Proc* 2016; 37:57–63.
20. Alves C, Romeira AM, Abreu C, Carreiro -Martins P, Gomes E, Leiria-Pinto P. Non-steroidal anti-inflammatory drug hypersensitivity in children. *Allergol Immunopathol* 2017; 45:40–47.
21. Viola M, Rumi G, Valluzzi RL, Gaeta F, Caruso C, Romano A. Assessing potential determinants of positive provocation tests in subjects with NSAID hypersensitivity. *Clin Exp Allergy* 2011; 41:96–103.
22. Blanca-López N, Cornejo-García JA, Plaza Serón MC, et al. Hypersensitivity to nonsteroidal anti-inflammatory drugs in children and adolescents: cross-intolerance reactions. *J Investig Allergol Clin Immunol* 2015; 25:259–269.
23. Asero R. Risk factors for acetaminophen and nimesulide intolerance in patients with NSAID-induced skin disorders. *Ann Allergy Asthma Immunol* 1999; 82:554–558.

24. Boussetta K, Ponvert C, Karila C, Bourgeois ML, Blic J, Scheinmann P. Hypersensitivity reactions to paracetamol in children: a study of 25 cases. *Allergy* 2005; 60:1174–1177.
25. Blanca-López N, Torres MJ, Doña I, et al. Value of the clinical history in the diagnosis of urticaria/angioedema induced by NSAIDs with cross intolerance. *Clin Exp Allergy* 2013; 43:85–91.

Table 1. The estimated number of OPT according the initial OPT

	Initial OPT with culprit NSAID	Initial OPT with ASA	Initial OPT with algorithm	p
Mean±SD	3,28±0.71	2,14±0.35	2,57±0.67	<0.001
The total number of OPT,n (%)				
1	0	0	0	
2	3(14.4%)	18(85.7%)	11(52.4%)	
3	9(42.8%)	3(14.3%)	8(38.1%)	
4	9(42.8%)	0	2(9.5%)	

Table 2. The characteristics of patients who were diagnosed NSAID-H

Patient	Age	Atopy / allergic disease	Culprit drugs	Initial OPT (cumulative dose,%)	Reaction during OPT	Safe alternatives	Class
1	5.2	- /-	Ibuprofen Metamizol	Aspirin (23)	Urticaria-angioedema	Acetaminophen	CI
2	5.3	HDM/-	Ibuprofen	Aspirin (30)	Urticaria-angioedema	Acetaminophen	CI
3	3.8	-/-	Ibuprofen	Ibuprofen (100)	Urticaria	Not performed	SR
4	7.5	-/Drug allergy	Ibuprofen Metamizole	Ibuprofen (100) Metamizole (60)	Urticaria Urticaria-angioedema	Acetaminophen	CI
5	13	HDM /asthma	Ibuprofen	Ibuprofen(100)	Anaphylaxis	Acetaminophen	CI
6	14	HDM/Rhinitis	Diclofenac Metamizole Acetaminophen	Aspirin (25)	Anaphylaxis	Acetaminophen	CI
7	2	-/CU	Ibuprofen Acetaminophen	Ibuprofen (100) Acetaminophen	Urticaria Not reaction	Acetaminophen	SR
8	3.8	-/-	Ibuprofen	Aspirin (10)	Urticaria	Acetaminophen	CI
9	5.3	Alternaria/Asthma	Ibuprofen	Aspirin (10)	Asthma	Acetaminophen	CI
10	18	Pollen/Asthma	Ibuprofen	Aspirin (10)	Angioedema	Acetaminophen	CI
11	15.2	HDM /Asthma	Ibuprofen	Aspirin (100)	Urticaria	Acetaminophen	CI
12	15	Pollen/Asthma	Ibuprofen	Aspirin(25)	Asthma	Acetaminophen (Nimesulide not tolerated)	CI
13	6.5	-/CU	Ibuprofen	Aspirin (10)	Urticaria	Acetaminophen	CI
14	16.3	-/-	Unknow	Aspirin (10)	Urticaria	Acetaminophen	CI
15	15	-/-	Flurbiprofen	Aspirin	Tolerated (Urticaria with Flurbiprofen)	Acetaminophen	SR
16	3.3	-/-	Ibuprofen Aspirin	Aspirin (33)	Urticaria	Acetaminophen	CI
17	17	HDM/Asthma	Flurbiprofen	Aspirin (15)	Angioedema	Acetaminophen Nimesulide	CI

18	7	-/-	Ibuprofen	Ibuprofen (100)	Urticaria	Acetaminophen	CI
19	15.7	-/-	Ibuprofen Flurbiprofen	Ibuprofen(30) Flurbiprofen (100)	Urticaria Urticaria	Acetaminophen	CI
20	12	HDM,pollen/Rhinitis	Ibuprofen Acetaminophen	Aspirin (30)	Angioedema	Acetaminophen Nimesulid	CI
21	10	HDM/Asthma	Ibuprofen	Aspirin (10)	Urticaria	Acetaminophen	CI

TABLE 3 Characteristics of the proven NSAID-H patients and the NSAID-tolerant patients

	Proven NSAID-H (n=21)	NSAID-Tolerant (n=35)	p
Age at OPT time (years) (mean $\pm$ s.d.)	10.04 $\pm$ 5.33	7.22 $\pm$ 4.52	0.04
Sex(male)	12 /21(57%)	16/35 (45.8%)	NS
Drug involved(%)			
Ibuprofen	17/21 (81%)	27/35 (75%)	
Acetaminophen	4/21	14/35	
Flurbiprofen	3/21	2/35	
Metamizole	4/21	0/35	
Naproxen	0/21	2/35	
Diclofenac	1/21	1/35	
Aspirin	1/21	1/35	
Reaction interval after drug intake, <1 hr	18/21(86%)	19/35(54%)	0.03
Symptoms on admission			
Urticaria(with/without angioedema)	11/21 (52.4%)	26/35 (74.2%)	NS
Angioedema	7/21 (33.3%)	8/35 (22.8%)	NS
Anaphylaxis	2/21 (9.5%)	1/35 (2.8%)	NS
Respiratory manifestation	1/21 (4.7%)	0/35 (0%)	NS
The time interval between last reported reaction and OPT, months (mean $\pm$ s.d.)	14.27 $\pm$ 15.50	10.47 $\pm$ 16.34	NS
Atopic sensitization	10/21(47.6%)	4/35(11.4%)	0.007
Family history of NSAID-H	3/21(14.3%)	3/35(8.6%)	NS
The number of episode, mean $\pm$ s.d.)	2.14 $\pm$ 0.96	1.37 $\pm$ 0.54	0.001
Serum total IgE(IU/mL), (mean $\pm$ s.d.)	210.2 $\pm$ 155.1	136.4 $\pm$ 238.4	0.008
Serum eosinophilia,, (mean $\pm$ s.d.)	203.3 $\pm$ 184.3	211.5 $\pm$ 186	NS

Table 4. Classification of NSAID hypersensitivity according to the **ENDA classification**

	n (%)
1. NSAID-exacerbated respiratory disease (NERD)	2 (9)
2. NSAID-exacerbated cutaneous disease (NECD)	1(4,5)
3. NSAID-induced urticaria/angioedema (NIUA)	12(59,1)
4. Single NSAID-induced urticaria/angioedema and/or anaphylaxis (SNIUAA)	3(13,6)
5. Single NSAID-induced delayed reactions (SNIDR)	0
unclassified	3(13,6)

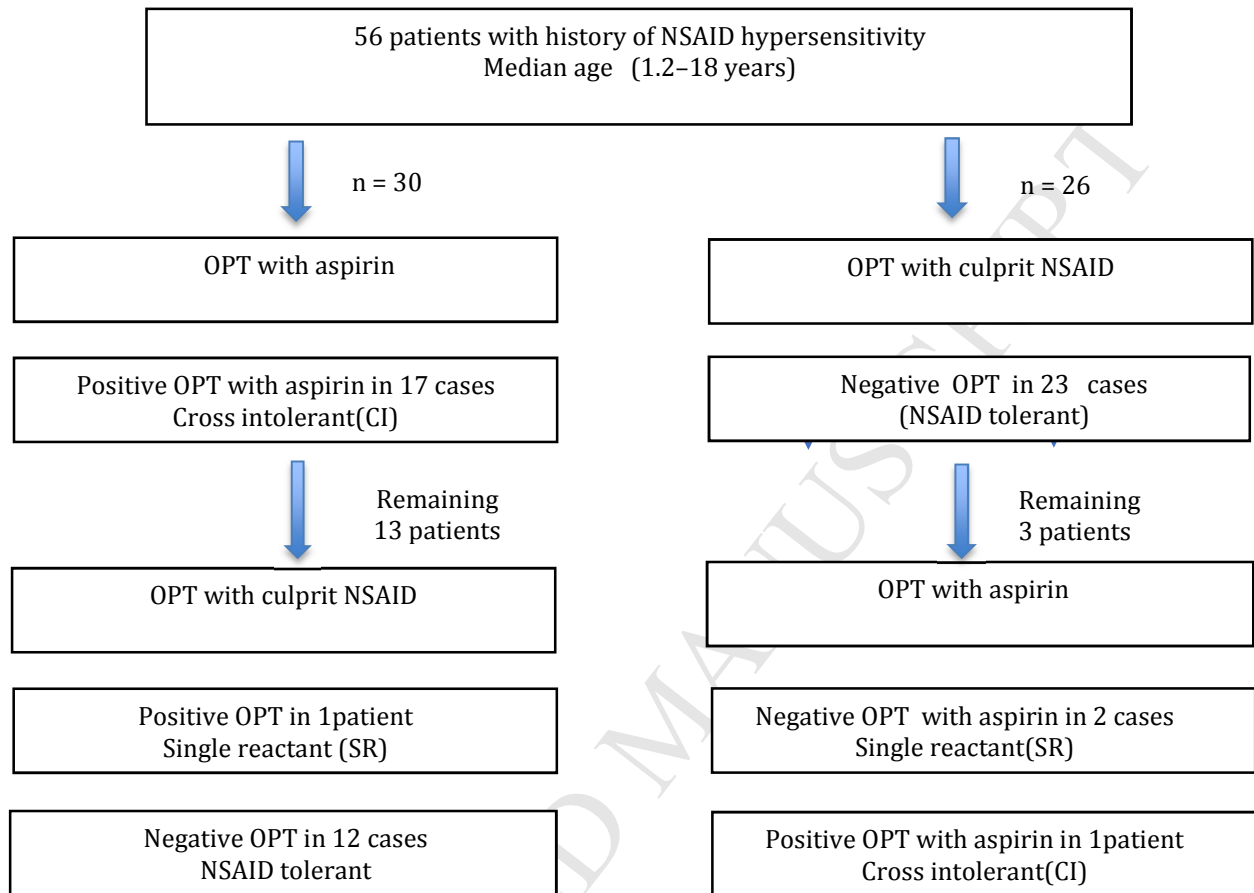


Figure1. Diagnostic flow chart