Original Article

Guiding Drug Provocation Testing for Ibuprofen Hypersensitivity in a Pediatric Population: Development of the I3A Risk-Stratification Tool

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What is already known about this topic? Ibuprofen is a main cause of drug hypersensitivity reactions in children. The gold standard for diagnosis is the drug provocation test, but there is no tool to guide this high-risk procedure.

What does this article add to our knowledge? We generated and validated in our cohort a risk-stratification tool to identify children at low risk of reacting to an ibuprofen provocation test, combining the items angioedema, anaphylaxis, and/or an age ≥10 years at index reaction.

How does this study impact current management guidelines? The I3A risk-stratification tool estimates the risk of performing an ibuprofen provocation test in children with suspected ibuprofen hypersensitivity. Notably, it highlights children at low risk of reaction for whom the test should be safe.

BACKGROUND: Ibuprofen is a main cause of drug hypersensitivity reactions in children. The gold standard for diagnosis is the drug provocation test (DPT).
OBJECTIVE: We aimed to create a clinical risk-stratification tool to guide this high-risk procedure.
METHODS: We prospectively recruited children with suspected ibuprofen hypersensitivity between January 2017 and March 2024. Using stepwise bidirectional multivariable logistic regression, we calculated a predictive score for a positive ibuprofen DPT.
RESULTS: Eighty-two patients with a median age of 5.9 years (interquartile range: 3.4-11.1 years) had an ibuprofen DPT. Eighteen (22.0%) patients had a positive challenge, with an anaphylactic reaction for 11 (61.1%). The I3A score (acronym for ibuprofen, 3As: angioedema, anaphylaxis, age, cutoff of 3) encompasses the following items: angioedema (2 points), anaphylaxis (1 point), and age at reaction ≥10 years old (1 point). The area under the curve of the I3A score was 0.84, and the optimal cutoff of <3 conferred a sensitivity of 84.4% (95% confidence interval [CI]: 66.7%-100.0%) and a specificity of 83.3% (95% CI: 75.0%-92.2%). The negative predictive value was estimated at 94.7% (95% CI: 90.0%-100.0%), and the positive predictive value at 60.0% (95% CI: 46.2%-76.2%). The relative risk of reacting to a challenge in the group I3A 3-4 compared with 0-2 was 11.4 (95% CI: 3.62%-35.7%, $P < .001$). Anaphylaxis after DPT was observed in 9 of 25 (36.0% [95% CI:

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Abbreviations used
aOR- Adjusted odds ratio
AUC- Area under the curve
CI- Confidence interval
COX- Cyclooxygenase
DPT- Drug provocation testing
HSR- Hypersensitivity reaction
IQR- Interquartile range
MCH- Montreal Children's Hospital
NECD- NSAID-exacerbated cutaneous disease
NERD- NSAID-exacerbated respiratory disease
NIAID/FAAN- National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network
NPV- Negative predictive value
NSAID- Nonsteroidal anti-inflammatory drug
OR- Odds ratio
PPV- Positive predictive value
ROC- Receiver operating characteristic curve
sNIDR- Selective NSAID-induced delayed reaction
(s)NIUAA- (Selective) NSAID-induced urticaria, angioedema, and/or anaphylaxis
WAO- World Allergy Organization

16.0%-56.0%]) in the high-risk group as compared with 2 of 57 (3.5% [95% CI: 0.0%-8.8%]) in the low-risk group (relative risk 10.3 [95% CI: 2.4%-43.5%]). CONCLUSIONS: We generated a risk-stratification tool to identify children at low risk of reacting to ibuprofen challenges. Further validation is required in external cohorts. **(J Allergy Clin Immunol Pract 2025;13:583-93)**

Key words: *Ibuprofen; Nonsteroidal anti-inflammatory drug; Drug challenge; Immediate hypersensitivity reaction; Risk-stratification score*

Nonsteroidal anti-inflammatory drugs (NSAIDs), commonly used as analgesics or antipyretics, are a main culprit of drug hypersensitivity reactions (HSRs) in the pediatric population.[1-4] Among NSAIDs, HSRs are mainly described with ibuprofen, as confirmed in different European cohorts,[5-9] accounting for 50% to 79% of NSAID HSRs.[5-7,9] These reactions can be selective allergies restricted to one molecule (and eventually structurally related drugs), or the cross-reactivity can be broader, based on cyclooxygenase (COX)-1 inhibition by the NSAIDs.[10-12] A proper diagnosis of an NSAID HSR is important in children, as their eligibility to selective COX-2 inhibitors, often offered to adults with NSAID allergy, is limited,[13] especially at younger age. Nonetheless, the history alone is not sufficient to diagnose NSAID hypersensitivity given that among patients reporting NSAID allergy, drug provocation testing (DPT) is positive in 14% to 68.2%.[6,9,10,12,14-16] Hence, the formal diagnosis relies mainly on DPT, which has proven reliable in predicting the risk of a subsequent reaction upon re-exposure.[17] However, DPT is resource-consuming, particularly in the case of a positive DPT, and places the patient at risk of reaction. Currently, no risk-stratification tool exists to increase the safety of these DPTs. Our study aims to bridge this knowledge gap by proposing and validating a clinical risk-stratification tool to predict the risk of a positive DPT in children with suspected ibuprofen HSR.

METHODS

Population selection

We prospectively recruited patients of pediatric age (between 0 and 18 years old) referred to the allergy division of the Montreal Children's Hospital (MCH) for suspected NSAID and acetaminophen HSRs between January 2017 and March 2024. Only patients with symptoms compatible with an ibuprofen HSR[18] were included. Patients with a reaction to an alternative NSAID, without a history of reaction to ibuprofen, were excluded from analysis, as well as patients who were not challenged with ibuprofen despite having a history consistent with an ibuprofen HSR. The study was approved by the local research ethics board (MUHC REB Number 12-084PED).

Data collection

Once included, the patients and their parents completed a questionnaire on demographics, comorbidities, atopic status, parental atopic status, the reason for ibuprofen use, clinical characteristics of the index reaction, and its management. A posteriori, blinded for the challenge result, patients' phenotypes at index reaction were reviewed and classified as anaphylaxis if they met the National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network[19] or World Allergy Organization criteria.[20] Anaphylaxis severity was then further graded according to Muraro.[21] Index reactions were also classified as per European Academy of Allergy and Clinical Immunology guidelines into the different NSAID HSR classes, adapted to pediatric population:[11,13] (1) (s)NIUAA: (selective) NSAID-induced urticaria, angioedema, and/or anaphylaxis, (2) NECD: NSAID-exacerbated cutaneous disease, (3) NERD: NSAID-exacerbated respiratory disease, and (4) sNIDR: selective NSAID-induced delayed reaction. Of note, as cross-reactivity with other nonselective NSAIDs was not assessed for most patients, the patients with nonselective NIUAA (cross-intolerance for COX-1 inhibiting NSAIDs) and with selective NIUAA specific to ibuprofen or structurally related drugs were regrouped in the term (s)NIUAA.

The intake of food before the index reaction was not evaluated. Therefore, the presence of NSAID-induced or NSAID-exacerbated food allergy was not assessed.

Drug provocation test

DPT was performed at the MCH outpatient clinic and supervised by medical staff. A dose of 10 mg/kg body weight (maximum 400 mg) was targeted. Fasting was not required. The patient received 10% of that dose. If no reaction occurred in the subsequent 30 minutes, the remaining 90% of the dose was administered, which was followed by an additional 2 hours of surveillance. Emergency medications were ready in case of reaction (epinephrine, antihistamines, β_2-agonists, and corticosteroids). The presence of a reaction and the details of the latter were recorded. The challenge was considered positive if the phenotype was compatible with an HSR. In the absence of a reaction, the patient and parents were given the MCH's allergy division telephone contact. In case of any delayed reaction, notably skin or mucosal, occurring more than 2 hours after the last dose, they were given the instruction to call. In addition, patients with a negative challenge were contacted to assess subsequent use of NSAIDs. Patients with a positive DPT were proposed a DPT with an alternative NSAID or acetaminophen.

TABLE I. Characteristics of patients

Characteristics	Total (n = 82) n (%)	Challenge negative (n = 64) n (%)	Challenge positive (n = 18) n (%)	*P* value*
Demographics				
Male gender	42 (51.2)	33 (51.6)	9 (50.0)	1.000
Atopy†	39 (47.6)	30 (46.9)	9 (50.0)	1.000
Asthma	18 (22.0)	13 (20.3)	5 (27.8)	.527
Ethnicity				
White	53 (64.6)	42 (65.6)	11 (61.1)	.783
Chinese	7 (8.5)	5 (7.8)	2 (11.1)	.645
African	7 (8.5)	4 (6.3)	3 (16.7)	.175
Arab	7 (8.5)	6 (9.4)	1 (5.6)	1.000
Latin American	4 (4.9)	3 (4.7)	1 (5.6)	1.000
Indian	2 (2.4)	2 (3.1)	0 (0.0)	1.000
Southeast Asian	3 (3.7)	2 (3.1)	1 (5.6)	0.530
Aboriginal	1 (1.2)	1 (1.6)	0 (0.0)	1.000
Parent with allergies	30 (36.6)	23 (35.9)	7 (38.9)	1.000
Age at index reaction (y), median (IQR)	5.9 (3.4-11.1)	5.0 (3.0-9.0)	11.7 (6.7-14.7)	**.001**
Age at challenge (y), median (IQR)	8.2 (4.8-13.3)	7.2 (4.1-12.4)	12.2 (7.9-15.4)	**.024**
Interval between reaction and challenge (y), median (IQR)	0.7 (0.3-2.3)	1.0 (0.3-2.7)	0.4 (0.3-0.7)	**.001**
Age at reaction ≥10 years	23 (28.0)	12 (18.8)	11 (61.1)	**<.001**
Index reaction context				
First exposure to ibuprofen	29 (35.4)	26 (40.6)	3 (16.7)	.093
Location				
At home	73 (89.0)	56 (87.5)	17 (94.4)	.676
At school/daycare	2 (2.4)	1 (1.6)	1 (5.6)	.393
Unknown/other	7 (8.5)	7 (10.9)	0 (0.0)	.338
Cause for ibuprofen intake				
Infectious signs	60 (73.2)	48 (75.0)	12 (66.7)	.551
Isolated pain	9 (11.0)	7 (10.9)	2 (11.1)	1.000
Unknown/other cause	13 (15.9)	9 (14.1)	4 (22.2)	.468
Exposition route				
Oral	81 (98.8)	63 (98.4)	18 (100)	1.000
Parenteral	1 (1.2)	1 (1.6)	0 (0.0)	1.000
Timing after initiation of treatment				
Within first 3 days	71 (86.6)	54 (84.4)	17 (94.4)	.441
Unknown	11 (13.4)	10 (15.6)	1 (5.6)	.441
Timing after last dose				
Within 5 minutes	16 (19.5)	11 (17.2)	5 (27.8)	.327
Within 1 hour	43 (52.4)	35 (54.7)	8 (44.4)	.594
Within 8 hours	14 (17.1)	10 (15.6)	4 (22.2)	.495
Above 8 hours	4 (4.9)	4 (6.3)	0 (0.0)	.571
Unknown	5 (6.1)	4 (6.3)	1 (5.6)	1.000
Index reaction description				
Symptoms				
Skin rash	43 (52.4)	36 (56.3)	7 (38.9)	.285
Flushing	14 (17.1)	11 (17.2)	3 (16.7)	1.000
Pruritus	28 (34.1)	22 (34.4)	6 (33.3)	1.000
Angioedema	51 (62.2)	34 (53.1)	17 (94.4)	**<.001**
Rhinoconjunctivitis	11 (13.4)	7 (10.9)	4 (22.2)	.246
Throat tightness	10 (12.2)	5 (7.8)	5 (27.8)	**.037**
Diarrhea/vomiting	5 (6.1)	3 (4.7)	2 (11.1)	.301
Dyspnea	11 (13.4)	8 (12.5)	3 (16.7)	.699
Circulatory collapse	1 (1.2)	1 (1.6)	0 (0.0)	1.000
Phenotype classification				
(s)NIUAA	75 (91.5)	58 (90.6)	17 (94.4)	1.000
NECD	2 (2.4)	1 (1.6)	1 (5.6)	.393

(continued)

TABLE I. *(Continued)*

Characteristics	Total (n = 82) n (%)	Challenge negative (n = 64) n (%)	Challenge positive (n = 18) n (%)	*P* value*
sNIDR	5 (6.1)	5 (7.8)	0 (0.0)	.581
Anaphylaxis‡	26 (31.7)	16 (25.0)	10 (55.6)	**.021**
Mild	12 (14.6)	6 (9.4)	6 (33.3)	**.02**
Moderate	13 (15.9)	9 (14.1)	4 (22.2)	.468
Severe	1 (1.2)	1 (1.6)	0 (0.0)	1.000
Evaluation by				
Emergency department	34 (41.5)	26 (40.6)	8 (44.4)	.792
Family doctor/clinic	20 (24.4)	16 (25.0)	4 (22.2)	1.000
No health care provider	28 (34.1)	22 (34.4)	6 (33.3)	1.000
Treatment				
Yes	57 (69.5)	45 (70.3)	12 (66.7)	.778
No	21 (25.6)	17 (26.6)	4 (22.2)	1.000
Unknown	4 (4.9)	2 (3.1)	2 (11.1)	.208
Type of treatment received				
Epinephrine IM	14 (17.1)	9 (14.1)	5 (27.8)	.177
H1 antihistamines	47 (57.3)	38 (59.4)	9 (50.0)	.592
Short-acting inhaled β_2-agonists	2 (2.4)	2 (3.1)	0 (0.0)	1.000
Corticosteroids	6 (7.3)	5 (7.8)	1 (5.6)	1.000
IV fluids	1 (1.2)	1 (1.6)	0 (0.0)	1.000
Duration of symptoms				
<3 days	70 (85.4)	55 (85.9)	15 (83.3)	.720
4-7 days	5 (6.1)	5 (7.8)	0 (0.0)	.581
Unknown	6 (7.3)	3 (4.7)	3 (16.7)	.116
I3A score§				<.001
0	18 (22.0)	17 (26.6)	1 (5.6)	
1	11 (13.4)	11 (17.2)	0 (0.0)	
2	28 (34.1)	26 (40.6)	2 (11.1)	
3	16 (19.5)	7 (10.9)	9 (50.0)	
4	9 (11.0)	3 (4.7)	6 (33.3)	

IM, Intramuscular; *IQR*, interquartile range; *IV*, intravenous; *NECD*, NSAID-exacerbated cutaneous disease; *NIAID/FAAN*, National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network; *sNIDR*, selective NSAID-induced delayed reaction; *(s)NIUAA*, (selective) NSAID-induced urticaria, angioedema, and/or anaphylaxis; *WAO*, World Allergy Organization.

Significant (<.05) *P* values are written in bold.

*P value calculated when comparing the patients who had a positive and negative challenge. P value calculated with the 2-sided Fisher exact test for categorical data and the Wilcoxon rank-sum test for continuous data.

†Atopy was defined by the presence of inhalant/food allergy, asthma, or atopic dermatitis.

‡According to the NIAID/FAAN and WAO criteria for classification, and Muraro[21] for grading.

§Items from the I3A score are underlined above.

Telephone follow-up

Telephone follow-ups were carried out for all patients with a negative DPT to assess the tolerance of re-exposure to ibuprofen using a standardized questionnaire. In case of a reaction, the same information as for the index reaction was gathered. Telephone follow-ups were carried out in June 2024, apart from 4 patients who already described re-exposure at a previous phone call in 2018/2019.

Descriptive statistical analysis

Descriptive analysis of the patients was conducted using SPSS software (version 29.0; IBM, Armonk, NY). Patients' characteristics were compared as a function of tolerance of the DPT using a 2-sided *P* value, and a significant difference was considered if the *P* value was strictly inferior to .05. Categorical variables and continuous variables were compared using the Fisher exact test and the Wilcoxon rank-sum test, respectively. When calculated, confidence intervals (CIs) were estimated by bootstrapping with 1000 iterations.

Analytical analysis: building of the clinical risk-stratification tool

Analytical statistics were performed in R Studio (version 4.3.2; R Foundation for Statistical Computing, Vienna, Austria). To determine the factors associated with a positive NSAID challenge, univariable logistic regression was performed for all continuous and dichotomous variables recorded. Variables with $P < .20$ and a prevalence $\geq$10.0% were retained.[22] Continuous variables were then recoded as dichotomous variables, and any variables that were deemed to be clinically implausibly related to a positive NSAID challenge were excluded (eg, location of reaction). A bidirectional stepwise logistic regression was performed on the remaining variables using the *leaps* package.[23] The optimal model was restricted to a maximum of 3 predictors for simplification of the subsequent scoring system and was selected by optimizing the adjusted R^2. To assess the resulting model's performance, the c-statistic, calibration slope, Hosmer-Lemeshow statistic, and Brier score were computed. The *rms* package[24] was used for the

TABLE II. Description of positive challenges

Patient	Gender	Age at reaction	Time between reaction and challenge	Initial reaction*	Cofactor at initial reaction	Challenge dose received before reaction (%)	Time between last dose and reaction	Symptoms of positive challenge*	Anaphylaxis criteria and severity†	Treatment	ED admission	Alternative challenges performed (with tolerance)	I3A score‡
1	M	6 y 1 mo	5 mo	(s)NIUAA: face angioedema	Fever	100	3 h	(s)NIUAA: face angioedema	No	AntiH1	No	No	2
2	M	3 y	5 y	(s)NIUAA: urticaria, angioedema, and rhinoconjunctivitis	Streptococcus angina	100	5 min	(s)NIUAA: face angioedema and urticaria	No	Epinephrin 0.3 mg IM (2 times)	No	Naproxen (tolerated)	3
3	M	18 mo	4 y 6 mo	(s)NIUAA: urticaria	URTI	100	40 min	(s)NIUAA: face angioedema, dyspnea, and wheezing	Yes, moderate	AntiH1 and Inh salbutamol	No	No	0
4	M	14 y	1 y 2 mo	(s)NIUAA: angioedema	No	100	80 min	(s)NIUAA: lip angioedema, abdominal pain, and itchy eyes	Yes, mild	AntiH1 and epinephrin 0.5 mg IM	No	Acetaminophen (tolerated)	3
5	F	12 y 3 mo	4 mo	(s)NIUAA: angioedema of face, throat, and dyspnea	URTI	100	40 min	(s)NIUAA: lip angioedema, dyspnea, throat tightness, conjunctivitis	Yes, moderate	AntiH1, Inh salbutamol, and epinephrin 0.5 mg IM	No	No	4
6	F	12 y 1 mo	4 mo	(s)NIUAA: angioedema of face, dyspnea, and cough	No	100	10 min	(s)NIUAA: itchy throat and neck, cough, and conjunctivitis	Yes, mild	AntiH1 and epinephrin 0.5 mg IM	No	No	4
7	M	16 y 6 mo	8 mo	(s)NIUAA: lip angioedema, urticaria, and dyspnea	Infectious signs	100	50 min	(s)NIUAA: face angioedema, dyspnea, itchy throat, and chest pressure	Yes, mild	AntiH1	No	Celecoxib (tolerated)	4
8	F	16 y 10 mo	7 mo	(s)NIUAA: lip angioedema and throat tightness	Infectious signs	100	40 min	(s)NIUAA: lip angioedema, rhinitis, cough, and throat itchiness	Yes, mild	AntiH1 and epinephrin 0.5 mg IM	No	Celecoxib (tolerated)	4
9	F	5 y 9 mo	3 mo	(s)NIUAA: face angioedema	Infectious signs	100	40 min	(s)NIUAA: face swelling, skin itchiness, and abdominal discomfort	Yes, mild	AntiH1 and epinephrin IM 0.27 mg	No	Naproxen (sNIUAA)	3
10	F	17 y 8 mo	3 mo	(s)NIUAA: oropharyngeal and ocular pruritus	No	10	5 min	(s)NIUAA: oropharyngeal pruritus. Placebo negative	No	No	No	Naproxen (sNIUAA)	3
11	F	9 y 2 mo	1 mo	(s)NIUAA: urticaria, wheezing, and throat tightness	Fever	100	45 min	(s)NIUAA: throat tightness, wheezing, and dyspnea	Yes, moderate	AntiH1, Inh salbutamol, and epinephrin 0.5 mg IM	No	Acetaminophen (tolerated)	3
12	M	13 y 7 mo	5 mo	(s)NIUAA: pruritus, angioedema, and rhinoconjunctivitis	COVID-19	Not documented	Not documented	(s)NIUAA: generalized pruritus, angioedema, and rhinoconjunctivitis	Yes, mild	Not documented	Not documented	No	4
13	F	7 y 1 mo	3 mo	(s)NIUAA: urticaria, flushing, face swelling, and vomiting	Fever	100	40 min	(s)NIUAA: urticaria and flushing	No	AntiH1	No	Celecoxib (tolerated)	3
14	F	15 y 6 mo	8 mo	(s)NIUAA: angioedema and urticaria	No	100	4 h	(s)NIUAA: angioedema, throat tightness, and wheezing	Yes, mild	AntiH1, Inh salbutamol, and epinephrin 0.3 mg IM	No	Celecoxib (tolerated)	3

(continued)

TABLE II. *(Continued)*

Patient	Gender	Age at reaction	Time between reaction and challenge	Initial reaction*	Cofactor at initial reaction	Challenge dose received before reaction (%)	Time between last dose and reaction	Symptoms of positive challenge*	Anaphylaxis criteria and severity†	Treatment	ED admission	Alternative challenges performed (with tolerance)	I3A score‡
15	M	11 y 4 mo	7 mo	(s)NIUAA: angioedema	No	100	1 hours	(s)NIUAA: angioedema and urticaria	No	AntiH1	No	Naproxen (sNIUAA) celecoxib (tolerated)	3
16	M	14 y 4 mo	5 mo	(s)NIUAA: angioedema and rhinoconjunctivitis	URTI	100	30 min	Rhinoconjunctivitis	No	AntiH1 and nasal decongestant	No	No	4
17	F	9 y 7 mo	6 mo	(s)NIUAA: face angioedema	Infectious signs	100	40 min	(s)NIUAA: urticaria, angioedema, dyspnea, and throat tightness	Yes, moderate	AntiH1 and epinephrin 0.3 mg IM	No	No	2
18	F	11 y 4 mo	2 mo	NECD: angioedema	Underlying chronic urticaria	100	4 h	NECD: lip/eye swelling	No	AntiH1 and prednisone	No	No	3

AntiH1, H1 antihistamine; *EAACI*, European Academy of Allergy and Clinical Immunology; *ED*, emergency department; *F*, female; *IM*, intramuscular; *Inh*, inhaled; *M*, male; *NECD*, NSAID-exacerbated cutaneous disease; *NIAID/FAAN*, National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network; *NSAID*, nonsteroidal anti-inflammatory drug; *(s)NIUAA*, (selective) NSAID-induced urticaria, angioedema, and/or anaphylaxis; *URTI*, upper respiratory tract infection; *WAO*, World Allergy Organization.

*NSAID phenotype according to the EAACI position paper.

†Anaphylaxis diagnosis according to the NIAID/FAAN and WAO criteria, severity grading according to Muraro et al.[21]

‡I3A score: angioedema at index reaction = 2 points, anaphylaxis at index reaction = 1 point, and age of 10 years or above at index reaction = 1 point.

TABLE III. Development of the multivariate model

Variable	Univariable OR, 95% CI	Univariable *P* value	Multivariable OR, 95% CI	Multivariable *P* value	β-coefficient
Age at reaction ≥10 y	6.8, 2.2-21.2	<.001	5.3, 1.5-19.1	.010	1.7
Angioedema	15.0, 1.9-119.5	.011	14.8, 1.7-127.4	.014	2.7
Anaphylaxis	3.8, 1.3-11.1	.017	3.1, 0.87-11.4	.081	1.1
Previously exposed to NSAIDs	3.4, 0.90-13.0	.071			
Delay between index reaction and challenge ≤1 y	4.1, 1.1-15.7	.037			
Age at challenge ≥8 y	4.5, 1.3-15.2	.015			
Known food allergy	2.8, 0.69-11.1	.15			
Index reaction not a maculopapular rash	2.0, 0.69-5.9	.20			
Allergic rhinitis	2.4, 0.67-8.2	.18			
Epinephrin use	2.35, 0.67-8.2	.18			

CI, Confidence interval; *NSAID*, nonsteroidal anti-inflammatory drug; *OR*, odds ratio.

internal validation of the model using a 2000-iteration bootstrap to compute the optimism-adjusted area under the curve (AUC).

The resulting model was converted to a scoring system by assigning a score equivalent to the β-coefficients of each variable rounded to the nearest integer. For simplification, a maximum of 2 points were allocated if this did not significantly reduce the performance of the model. The optimal cutoff of the scoring system was determined using the Youden index. Sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV) were calculated for each potential cutoff. The pROC package was used to compute the scoring system's AUC and to plot a receiver operating characteristic curve.

RESULTS

Population description

Among the 111 patients referred for a history of HSR to NSAIDs or acetaminophen, 90 reported an index reaction to ibuprofen. Of these patients, an ibuprofen DPT was performed for 82 (91.1%) consenting families, and these patients were included in the analysis. Forty-two patients (51.2%) were male, 39 (47.6%) were atopic, among whom 18 (22.0%) were known for asthma. Ethnicity was predominantly White (53, 64.6%). The median age at the reaction and challenge was 5.9 years (interquartile range [IQR]: 3.4-11.1 years) and 8.2 years (IQR: 4.8-13.3 years), respectively (Table I and Figure E1, available in this article's Online Repository at www.jaci-inpractice.org).

Index reaction to ibuprofen

Most patients reported a previous exposure with tolerance to NSAIDs before the reaction to ibuprofen (53, 64.6%). In the majority of cases, the index reaction occurred at home (73, 89.0%), after taking the medication orally (82, 100.0%) in the context of an infection (60, 73.2%) or to treat pain (9, 11.0%). Most reactions occurred less than 8 hours after the last dose (73, 94.8%), with angioedema (51, 62.2%), rash (43, 52.4%), and pruritus (28, 34.1%) being the most common symptoms. Twenty-six patients (31.7%) fulfilled the anaphylaxis criteria (Table E1, available in this article's Online Repository at www.jaci-inpractice.org). While most patients had a phenotype of (s)NIUAA (75, 91.5%), 5 patients (6.1%) had delayed allergy (sNIDR), only 2 patients (2.4%) had underlying urticaria (with NECD), and no patients presented with NERD. Fifty-four patients (65.9%) requested medical assistance, and 57 (69.5%) required a treatment, which was mainly antihistamines (for 47 patients, 57.3%) and, less frequently, intramuscular epinephrine (for 14 patients, 17.1%, Table I).

Drug provocation testing

The median time between the index reaction and DPT was 0.7 years (IQR: 0.3-2.3 years). Sixty-four patients (78.0% [95% CI: 68.3%-86.6%]) had a negative challenge. Among the 18 (22.0%) patients with a positive challenge, 17 (94.4%) had (s)NIUAA at the index reaction and 1 (5.6%) had NECD (Table II). Of the children with a positive DPT, 12 (66.7%) had infectious symptoms at the time of the index reaction. For one patient, the timing of reaction to challenge and its treatment were not documented. Sixteen of 17 (94.1%) reacted after the second step, mainly within 1 hour (13 of 17, 76.5%). The types of reactions at DPT were comparable to the index reactions as the patient with NECD showed a recurrence of angioedema and all patients with (s)NIUAA at the index reaction presented with reactions compatible with (s)NIUAA except 1 patient with rhinoconjunctivitis only (symptom already present at the index reaction). Most patients (11 of 18, 61.1%) presented with anaphylaxis, 9 of 17 (52.9%) were treated with epinephrine, and no one required transfer to the emergency department. Finally, all patients then challenged to celecoxib or acetaminophen (5 and 2 patients, respectively) tolerated it, as compared with only 1 patient out of 4 (25%) who tolerated naproxen.

Initial development of the score

Following univariate logistic regression, 10 categorical variables were associated with the challenge result with a *P* value of <.20 and were integrated in the 2-sided stepwise approach to establish the predictive model. Six of them did not improve the model's adjusted R^2 and were removed from the final model: delay between reaction and challenge ≤1 year, age at challenge ≥ 8 years, known food allergy, no maculopapular rash at the index reaction, allergic rhinitis, and use of epinephrine to treat the index reaction. Because of the nonsignificant *P* value of the variable "antecedent of exposure to NSAIDs" upon multivariable analysis and the limited clinical value of the latter, it was not included in the final model. The 3 other variables had a positive impact on the performance of the model and had significant *P* values upon multivariable analysis: age at reaction ≥10 years (adjusted odds ratio [aOR] = 6.8, 95% CI: 2.2%-21.2%, β-coefficient: 1.7), the presence of angioedema (aOR = 15.0, 95% CI: 1.9%-119.5%, β-coefficient: 2.7), and the presence of anaphylaxis (aOR = 3.8, 95% CI: 1.3%-11.1%, β-coefficient: 1.1, Table III).

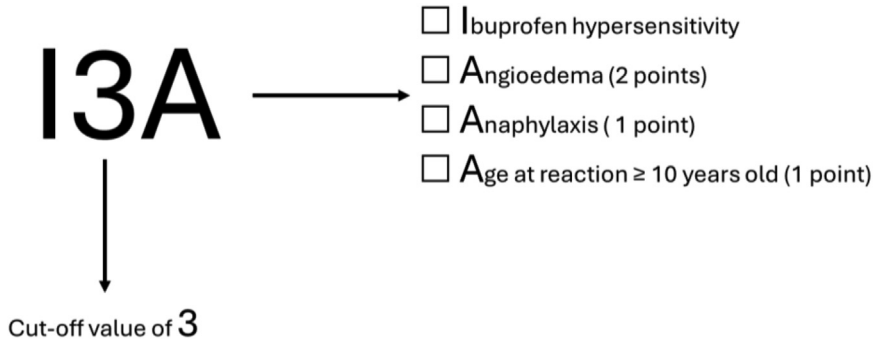


FIGURE 1. The I3A score for ibuprofen hypersensitivity in a pediatric population.

Simplification of the initial score

Points of the score were allocated by rounding the β-coefficient. This gave the following score: angioedema (3 points), anaphylaxis (1 point), and age at reaction ≥10 years (2 points). The AUC was 0.86. To simplify the model, its performance was assessed when the β-coefficient was rounded to the lower value, that is angioedema (2 points), anaphylaxis (1 point), and age at reaction ≥10 years (1 point, Figure 1). The AUC was 0.853. The internal validation revealed an optimism of 0.02; thus, the optimism-adjusted AUC was 0.84 (Figure 2, *A-C*).

Cut-off of the score

The difference in sensitivity, specificity, NPV, and PPV according to the score cut-off is detailed in Figure 2, *D*. According to the Youden index, the optimal cut-off value was <3. A minority of patients had a score of ≥3 (25 patients, 30.5%). At this cut-off, the sensitivity was 84.4% (95% CI: 66.7%-100.0%) and the specificity 83.3% (95% CI: 75.0%-92.2%). The NPV was 94.7% (95% CI: 90.0%-100.0%) with a PPV of 60.0% (95% CI: 46.2%-76.2%). Lower cut-offs were associated with a low PPV below 50.0%, with more than 50% of patients being above the cut-off. The cut-off of 4 had a significantly decreased NPV with no significant difference in PPV. The evolution of NPV and PPV according to the prevalence is described in Figure E2 (available in this article's Online Repository at www.jaci-inpractice.org). The relative risk of reacting to a challenge in the group I3A 3-4 as compared with 0-2 was 11.4 (95% CI: 3.6%-35.7%, $P < .001$). Anaphylaxis after DPT was observed in 9 of 25 (36.0% [95% CI: 16.0%-56.0%]) in the high-risk group as compared with 2 of 57 (3.5% [95% CI: 0.0%-8.8%]) in the low-risk group (risk ratio 10.3 [95% CI: 2.4%-43.5%]).

Follow-up of patients

After a median time of 4.5 years (IQR: 1.54-6.29 years), telephone follow-ups were conducted (mainly in June 2024) to assess the tolerance of the intercurrent ibuprofen treatments for the 64 patients with negative challenges. We established contact with 58 (90.6%) of them, and 37 (63.8%) were re-exposed to ibuprofen. Thirty-six (97.3% [95% CI: 91.9%-100.0%]) tolerated it. One patient (initial I3A score of 2 with angioedema at the index reaction) had a reaction after subsequent use that consisted in angioedema and chest pain resolving with antihistamines.

DISCUSSION

We have conducted, to our knowledge, the first study to establish a valid clinical risk-stratification tool to predict ibuprofen allergy in children.

After analyzing the factors influencing the ibuprofen DPT outcome, we were able to build a risk-stratification tool that we named I3A: I for ibuprofen, 3 for a cutoff score of 3, and for the 3 As related to the 3 factors identified, namely, angioedema, anaphylaxis, and age. Based on the presence of angioedema (2 points), anaphylaxis (1 point), and the age at index reaction (1 point if ≥10 years old) and using this cutoff <3 for a low-risk population, the score had an NPV over 90%, which was significantly higher than the challenge tolerance rate without previous stratification. The patients with a score of 3 or 4 were significantly more prone to react and to have anaphylaxis upon DPT with risk ratios over 10.

Besides, an important strength of our study is the longitudinal follow-up after a median time of 4.5 years reassuring the safe use of ibuprofen for patients with negative challenges. Indeed, our study also highlighted the high NPV over 90% of a negative ibuprofen DPT regarding the risk of reaction upon further ibuprofen re-exposures, as already suggested in another paper by Topal et al.[17] Hence, the I3A score demonstrated its ability to identify a population at lower risk of reaction to an ibuprofen DPT, with safe further re-exposure in case of a negative DPT.

The added value of a clinical assessment tool before DPT has already been shown in drug allergy with the PEN-FAST score, which facilitates safer challenges to penicillin in adult patients without skin testing.[22,25] In the field of NSAID allergy, this need for a clinical risk-stratification tool is particularly important in the absence of a reliable skin test.[11] On top of that, the risk of a reaction to NSAID DPT is not negligible, ranging from 14.0% to 68.2% according to studies, the larger published European retrospective cohort by Mori et al with 526 children finding a rate of positive challenges of 19.6%.[6,9,10,12,14-16] Among these positive DPTs, severe reactions are not uncommon. The risk of anaphylaxis to NSAID DPT ranged between 6.0% and 24.0% of patients with confirmed HSR in different studies,[9,10,12,14-16] with 7.0% of systemic reaction in the cohort described by Mori et al.[6] In our cohort, the rate of anaphylaxis upon DPT was even higher, with over 50.0% of reactions manifesting as anaphylaxis. This could be explained by the fact that DPT was performed even for anaphylaxis at the index reaction. The protocol used with a direct increase from 10.0% to 100.0% of the regular ibuprofen dose in 30 minutes as compared with more progressive protocols over 3 to 5 steps every 30 to 60 minutes[8,9,15] or even over several days[10,12] could also be a factor in the number of anaphylaxis reactions.

The main limitation of our study is that the patients were evaluated in only one center, the MCH, and the I3A score was not validated on an external cohort. In our cohort, the phenotypes of

A

Model performance.

Characteristic	Value
C-statistic/AUC	0.86
Hosmer-Lemeshow statistic	$\chi 2 = 6.8$, P =0.34
Calibration slope	1.04
Brier score	0.11

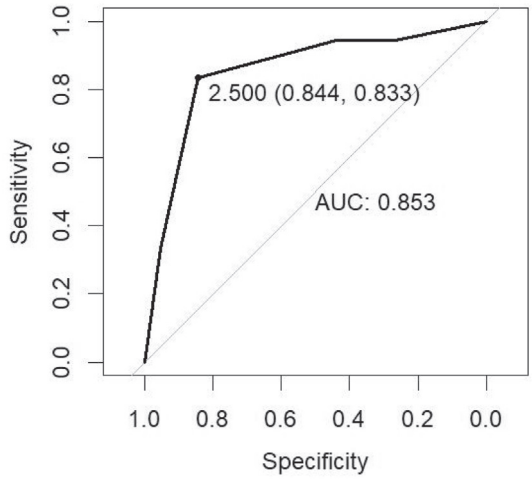
B

Internal validation.

Factor	Value
Optimism	0.02
Optimism-corrected AUC	0.84

C

ROC curve of the predictive model



Legend: optimal cut-off by Youden's index is ≥3 with a sensitivity of 83.3% and specificity of 84.4% and an AUC of 0.85, 95%CI=0.74-0.95.

D

I3A score performance according to the cut-off

Cut-Off	Patients above the Cut-off	Sensitivity, 95%CI	Specificity, 95%CI	NPV, 95%CI	PPV, 95%CI
≥1	64 (78.0%)	94.4, 83.3-100.0	26.6, 15.6-37.5	94.4, 82.3-100.0	26.6, 23.1-30.5
≥2	53 (64.6%)	94.4, 83.3-100.0	43.8, 31.3-56.3	96.6, 88.5-100.0	32.1, 26.9-38.3
≥3	**25 (30.5%)**	**84.4, 66.7-100.0**	**83.3, 75.0-92.2**	**94.7, 90.0-100.0**	**60.0, 46.2-76.2**
≥4	9 (11.0%)	33.3, 16.7-55.6	95.3, 89.1-100.0	83.6, 79.7-88.4	66.7, 37.5-100.0

FIGURE 2. I3A score performance and validation: (A) model performance, (B) internal validation, (C) ROC curve of the predictive model, (D) score performance according to the cut-off. Bold denotes cutoff value deemed optimal by the Youden index. *AUC*, Area under the curve; *CI*, confidence interval; *NPV*, negative predictive value; *PPV*, positive predictive value; *ROC*, receiver operating characteristic curve.

the reactions were comparable to other studies with high rates of angioedema,[8,26-31] skin manifestation,[9,26] and (s)NIUAA reactions.[11] Therefore, we still believe that the I3A score will be applicable to other centers. More studies will be needed to confirm this assumption. Another limitation of our study is the PPV of the score, evaluated at 60.0% (95% CI: 46.2%-76.2%). Indeed, despite a score of 3 to 4, still 10 of 25 patients (40.0%) were able to tolerate challenges. This PPV is comparable to other risk-stratification tools like PEN-FAST[22,25] for penicillin. Nonetheless, in case of a high PEN-FAST score, skin testing can be offered

to further risk-stratify patients. There is no such tool for NSAIDs. This raises the question of the clinical impact of our score for this high-risk population, and more studies will be needed to assess it further. As mentioned above, the rate of anaphylaxis in our cohort was particularly high as compared with literature, and the protocol used could be an explanation. It is possible that in case of the I3A score of 3 to 4, a more gradual challenge should be used to hamper the risk of a more severe reaction. The choice to challenge to an alternative like acetaminophen or celecoxib according to the age is also possible, but would only allow the use of that specific alternative until further testing is performed. In our cohort, no patient reacted to these alternatives, and rates of cross-reactivity are low in the literature.[14,26,31,32] Given reports on decreased NSAID sensitivity over time in cases of NIUA[33] among adults (not demonstrated in children yet), another alternative could be to delay challenges to at least 5 years after the index reaction, but this would require more studies. Another limitation is the absence of specific assessment of food intake before the index reaction. Hence, cases of NSAID-induced or NSAID-exacerbated food allergy could have been missed. Besides, in our study, we focused our work on ibuprofen in children owing to the sensitization profile in our center, and further validation is required in external cohorts. Being a potent COX-1 inhibitor[34] and the main culprit in NSAID HSRs in children,[5-9] this drug is representative of NSAID HSRs. Nonetheless, further research is needed to confirm whether the same factors are determinants in other nonselective NSAID HSRs and in older patients. Finally, we focused our work on risk stratification before an ibuprofen challenge, despite a history of HSR to the latter. Our study was not built to compare the safety and efficacy of this procedure against performing challenges to alternatives (eg, acetaminophen and coxibs), which are theoretically at lower risk of reaction.

In conclusion, we generated the score I3A, a risk-stratification tool with high sensitivity to identify patients at low risk of reacting to ibuprofen challenges in children. More research is needed on the way to manage patients evaluated at higher risk, as well as to validate the score with other NSAIDs and on different cohorts.

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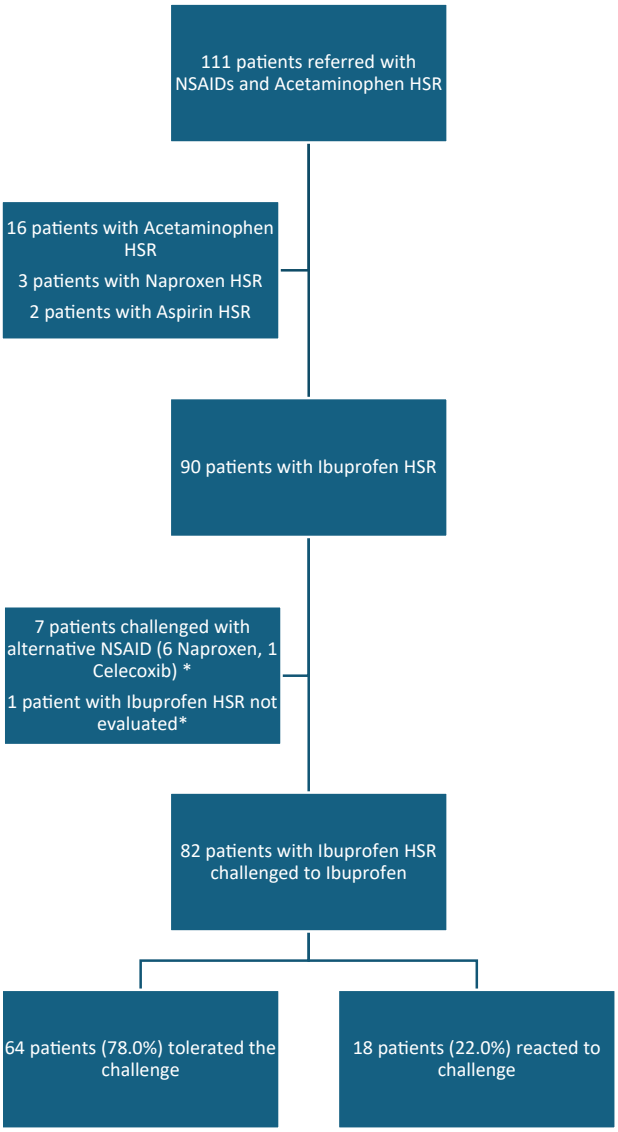

FIGURE E1. Flowchart of the population. *Patients not rechallenged to ibuprofen as per clinician discretion: 2 patients had anaphylaxis and 6 patients had mucocutaneous signs (among whom 4 with angioedema). *HSR*, Hypersensitivity reaction; *NSAID*, nonsteroidal anti-inflammatory drug.

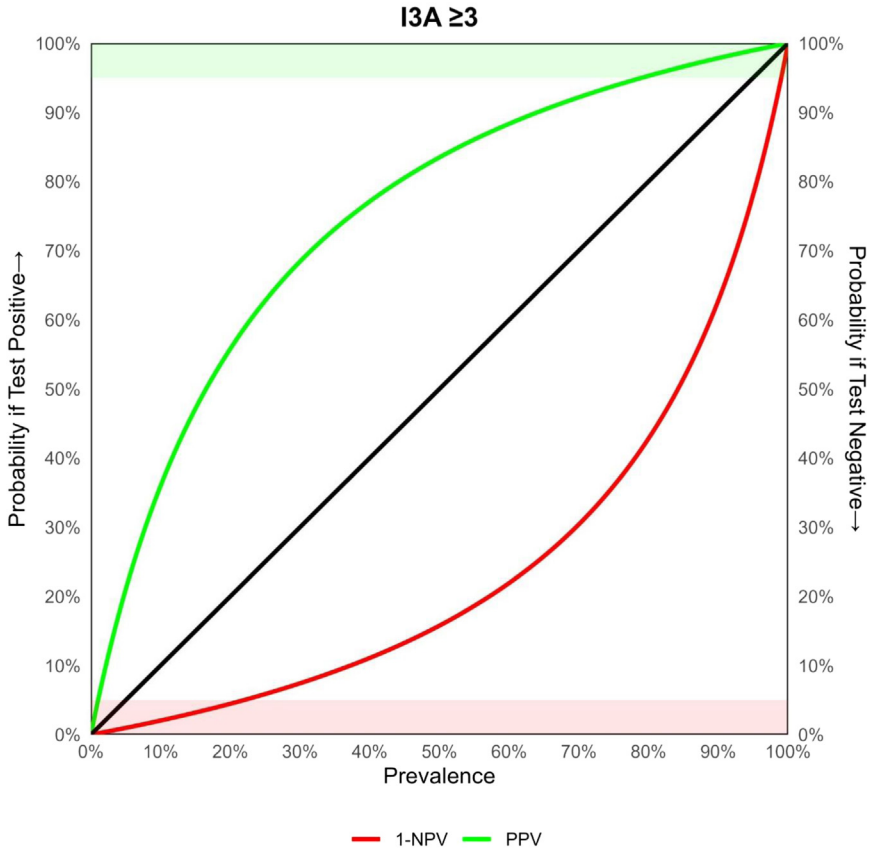

FIGURE E2. Evolution of negative and positive predictive values according to the prevalence. *NPV,* Negative predictive value; *PPV,* positive predictive value.

TABLE E1. Systems involved in patients with anaphylaxis* at index reaction

Patient	Cutaneous symptoms	Cardiovascular symptoms	Respiratory symptoms	Digestive symptoms
1	X		X	
2	X		X	
3	X		X	
4	X		X	
5	X		X	
6	X		X	
7	X		X	X
8	X		X	
9	X		X	
10	X		X	
11	X		X	
12	X		X	
13	X		X	
14	X		X	
15	X		X	
16	X		X	
17	X		X	
18	X		X	
19	X		X	
20	X			X
21	X		X	
22	X		X	
23	X		X	
24	X		X	
25	X	X		X
26	X		X	

NIAID/FAAN, National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network; *WAO*, World Allergy Organization.
*According to the NIAID/FAAN and WAO criteria.