

Current Review



Nonsteroidal anti-inflammatory drug hypersensitivity in the Asia-Pacific



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ABSTRACT

Nonsteroidal anti-inflammatory drug (NSAID) hypersensitivity reactions (HSRs) are often nonimmunologically mediated reactions which present with immediate HSR type manifestations. These are mediated by cyclooxygenase inhibition resulting in shunting towards the excessive production of leukotrienes. Important disease associations include asthma, nasal polyposis, and chronic spontaneous urticaria, especially among adults. The European Network on Drug Allergy/Global Allergy and Asthma European Network 2013 classification of NSAID HSR comprises nonselective HSR i.e., NSAID exacerbated respiratory disease (NERD), NSAIDs exacerbated cutaneous disease (NECD), NSAIDs induced urticarial-angioedema (NIUA); and selective (allergic) HSR i.e., single NSAID induced urticaria/angioedema or anaphylaxis, NSAIDs-induced delayed HSR. Much of the literature on genetic associations with NSAID HSR originate from Korea and Japan; where genetic polymorphisms have been described in genes involved in arachidonic acid metabolism, basophil/mast cell/eosinophil activation, various inflammatory mediators/cytokines, and different HLA genotypes. The Asian phenotype for NSAID HSR appears to be predominantly NIUA with overlapping features in some adults and children. NECD also appears to be more common than NERD, although both are not common in the Asian paediatric population. Between adults and children, children seem to be more atopic, although over time when these children grow up, it is likely that the prevalence of atopic adults with NSAID HSR will increase. Low-dose aspirin desensitization has been shown to be effective in the treatment of coronary artery disease, especially following percutaneous coronary intervention.

Keywords: Anaphylaxis; Asthma; Drugs; Hypersensitivity

INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) are a common cause of hypersensitivity reactions (HSRs) [1] in the Asia-Pacific region among adults [2] and children [3]. NSAIDs are commonly used as antipyretics or as analgesics in clinical practice. Certain NSAID like aspirin (acetylsalicylic acid [ASA]) is used for its antiplatelet action in the prevention or treatment of cardiovascular disease.

MECHANISM OF ACTION

The mechanism of action of NSAIDs is through the inhibition of cyclooxygenase (COX) enzyme of which there are 2 isoforms: COX-1 (constitutive) and COX-2 (inducible). COX-1 is found in platelets, gastric and renal epithelial cells. COX-1 inhibition may be associated with adverse effects e.g., bleeding diatheses; gastric perforations, ulcers and bleeds; or acute kidney injury. COX-inhibition leads to the excessive shunting towards leukotriene production in the arachidonic acid (AA) synthesis pathway in certain genetically predisposed individuals. These individuals develop leukotriene-mediated increase in capillary permeability, mucus hypersecretion, bronchoconstriction or increase in eosinophil chemotaxis. This results in the clinical manifestations of NSAID HSR i.e., urticaria, angioedema, rhinorrhoea/nasal congestion, wheeze, or syncope [1].

CLASSIFICATION OF NSAID HSR

NSAIDs may be classified according to their chemical properties or their relative potencies in inhibiting COX-1 or COX-2. The chemical classification of NSAIDs is shown in **Table 1** and the classification according to relative COX inhibition is shown in **Table 2**.

In 2013, the European Network on Drug Allergy/Global Allergy and Asthma European Network (ENDA/GA²LEN) classified NSAID HSRs as follows [4]:

Cross-reactive – nonallergic (nonimmunologically mediated reactions)

- Group 1: NSAIDs exacerbated respiratory disease (NERD) – patients with asthma, rhinosinusitis with/without nasal polyposis where respiratory symptoms are aggravated by NSAIDs;
- Group 2: NECD – patients with chronic spontaneous urticaria (CSU) where CSU is aggravated by NSAIDs;
- Group 3: NSAIDs induced urticaria-angioedema (NIUA) – where urticaria and/or angioedema is induced by 2 or more NSAIDs not belonging to the same chemical group.

Table 1. Chemical classification of nonsteroidal anti-inflammatory drugs

Chemical group	Examples
Salicylic acid derivatives	Acetylsalicylic acid (aspirin) salsalate
Para-aminophenol	Acetaminophen (paracetamol)
Propionic acid derivatives	Ibuprofen, naproxen, ketoprofen
Acetic acid derivatives	Diclofenac, ketorolac, indometacin, sulindac
Enolic acid derivatives	Oxicams - piroxicam, meloxicam, tenoxicam Pyrazolones - phenylbutazone
Fenamic acid derivatives	Mefenamic acid
Selective cyclooxygenase-2 inhibitors	Celecoxib, etoricoxib, parecoxib

Table 2. Classification of NSAIDs according to COX inhibition

Relative COX-inhibition	COX-1 inhibition	COX-2 inhibition	Examples
Strong COX-1	+++	High dose	All nonselective NSAIDs
Poor COX-1	Partial (high dose)	Preferential (low dose)	Paracetamol, salsalate
Preferential COX-2	Partial (high dose)	+	Nimesulide, meloxicam
Selective COX-2	-	+++	Celecoxib, etoricoxib, parecoxib

NSAD, nonsteroidal anti-inflammatory drug; COX, cyclooxygenase.

Selective – allergic (immunologically mediated reactions)

- Group 4: Single NSAID-induced urticaria/angioedema or anaphylaxis – where urticaria, angioedema or anaphylaxis is induced by NSAIDs in the same chemical group; and where patients do not have underlying asthma or CSU;
- Group 5: NSAIDs-induced delayed HSRs e.g., maculopapular exanthema, Stevens Johnson syndrome/ toxic epidermal necrolysis.

COFACTORS, DISEASE ASSOCIATIONS, AND GENETIC POLYMORPHISMS

It remains unknown why individuals with NSAID HSR acquire this over time and what the triggers are. Among adults, chronic rhinosinusitis (CRS) with nasal polyposis (CRSwNP), chronic persistent asthma [5] and CSU are associated cofactors/comorbidities [6]. Mast cell activation syndromes may not be a significant risk factor as has commonly been perceived [7]. Although infections have been described as cofactors in follow-up studies on patients who had passed drug provocation tests [8], this has not been well-characterized in epidemiological/cohort studies. None of the other cofactors known to trigger anaphylaxis (including physical factors) have been described in association with NSAID HSR. However NSAIDs are a known cofactor in 1.2%–4.7% of cases of adult and paediatric anaphylaxis [9].

There are several genome-wide association and case-control studies on NSAID HSR which originate from this region, in particular from Korea and Japan [10, 11]. Genetic polymorphisms have been described mainly for NERD, with limited studies on NECD/ NIUA. Most studies focused on genes related to pathomechanisms including:

- AA metabolism pathways e.g., CysLT receptor 1 (CYSLTR1) [NERD], ALOX5 (5-lipoxygenase) [NECD/NIUA];
- Basophil/mast cell and eosinophil activation e.g., FCER1G (Fc epsilon receptor 1 gamma) [NERD], FCER1A (Fc epsilon receptor 1 alpha) [NECD], interleukin-4 (IL-4) and IL-13 [NERD];
- Other inflammatory mediators/cytokines e.g., IL-5R α [NERD], tumour necrosis factor-alpha (TNF- α) [NECD/NIUA], IL-17A [NERD in Japanese];
- HLA genotypes e.g., DPB1*0301 [NERD], DRB1*1302, DQB1*0609 [NECD]
- Other pathways e.g., CYP2C19 (Cytochrome P450) [NERD in Japanese], DPP10 (Dipeptidyl peptidase 10 gene) [NERD].

Well-characterised cases of familial NSAID HSR have been described [12]. Epigenetic modification e.g., DNA methylation may affect gene expression which then determine the phenotypic expression of the disease (NERD or aspirin-tolerant asthma), suggesting potential susceptibility genes and pathways involved in the pathogenesis of NERD [13].

EPIDEMIOLOGY OF ADULT NSAID HSR IN THE ASIA-PACIFIC

The worldwide prevalence of ASA hypersensitivity is reported to range from 0.5% to 1.9% of the general population, and comprise 25% among patients with asthma/ nasal polyposis,

and 27%–35% among patients with chronic urticaria. A meta-analysis on the prevalence of AERD based on different methodologies including questionnaire studies, medical records and oral challenges reported the prevalence of AERD in asthma as 7.15% (95% confidence interval [CI], 5.26%–9.03%), with the highest among patients with severe asthma comprising 14.89% (95% CI, 6.48%–23.29%). The prevalence of AERD in patients with nasal polyposis was reported as 9.69% (95% CI, 2.16%–17.22%); and in CRS 8.7% (95% CI, 1.02% to 18.34%) [14].

In the Asia-Pacific region, the prevalence of NSAID HSR among adults in CRS cohorts from China (based on history and not on the ENDA/GA²LEN 2013 classification and evaluation) was reported to be low (0.28%–1.46%) [15]. A prospective cohort study from Guangdong, China reported AERD/NERD prevalence of 2 of 351 (0.57%) among the CRS population of whom the majority 319 of 351 had CRSwNP [16]. The authors retrospectively found 346 cases over 30 years (1979–2010) reported in the China Academic Journal Network Publishing Database. It has been postulated that the lower prevalence of tissue and blood eosinophilia in Chinese CRS in contrast to western studies may be a possible explanation for the low prevalence of NSAID HSR among Asian CRS. In the endotypic classification of CRS [17], CRSwNP is associated with Th2 high eosinophilic inflammation and the Th2 high asthma endotype/ phenotype.

The Cohort for Reality and Evolution of Adult Asthma in Korea is a 9-year (2005–2013), prospective cohort study of patients aged 19 years or older with asthma involving 11 centres in Korea [18]. In this questionnaire study, aspirin-intolerant asthma (AIA) comprised 68 of 1,173 (5.8%) adult asthmatics. AIA was associated with younger age, higher prevalence of rhinosinusitis and atopic dermatitis, and more frequent exacerbations. There were no significant differences in lung function, asthma severity or the use of asthma controllers. In another study from Korea [19], using 2-step cluster analysis using urticaria, CRS, and atopy, in a Korean NERD cohort (n = 302), 4 subtypes of NSAID HSR were defined comprising:

- Subtype 1 (NERD with CRS/atopy and no urticaria)
- Subtype 2 (NERD with CRS and no urticaria/atopy)
- Subtype 3 (NERD without CRS/urticaria)
- Subtype 4 (NERD with urticaria).

Subtypes 1 and 3 were found to be associated with higher urinary leukotriene E₄(LTE₄), and subtype 1 with the most asthma exacerbations. This is consistent with the existence of the 2 predominant endotypes of severe asthma [20] where eosinophilic inflammation-predominant Th2 (high) inflammation asthma, is characterized by late-onset disease, rhinosinusitis, ASA hypersensitivity, blood and sputum eosinophilia, elevated fractional exhaled nitric oxide and periostin. Humanized antibodies against Th2 targets, such as anti-IgE (Omalizumab), anti-IL4R α (Dupilumab), anti-IL-5 (Mepolizumab), and anti-IL-13 antibodies are effective in Th2 high asthma. In contrast, neutrophilic inflammation-predominant Th2 (low) severe asthma is associated with Th17 mediated inflammation and steroid resistance in general.

In Singapore, NSAID HSR comprise 8.4% of 227 referrals from public healthcare institutions and 20.7% of 247 referrals from military servicemen (unpublished). Majority of adult patients in Singapore present with NIUA (periorbital and facial edema being the most common), with majority (95%) able to tolerate up to 120-mg Etoricoxib during drug provocation test [21].

A recent study of 62 Malays from Malaysia showed that the most common phenotypes were NIUA (63.9%) and NECD (9.8%). NERD comprised only 1.6%. There was a significant proportion (19.7%) who had overlapping manifestations that were not classifiable using the 2013 ENDA/GA²LEN classification. The most common causative NSAIDs were diclofenac, mefenamic acid or paracetamol in all groups [22]. An association with HLA-A*11:01 and A*24:02 was also observed [23].

EPIDEMIOLOGY OF PAEDIATRIC NSAID HSR IN ASIA-PACIFIC

The most common manifestations among children are cutaneous and respiratory reactions [24]. Older questionnaire-based studies report the prevalence as 0.2% (2 of 618) children, and the estimated rate in atopic children as 4% [25]. Challenge-confirmed ASA hypersensitivity has been reported as 5% in asthmatic children (0%–14%) in contrast to 21% (14%–29%) in asthmatic adults. There is a fairly limited range of NSAIDs used in children, e.g. ibuprofen and paracetamol.

Recent studies have shown that it is difficult to classify children using the ENDA/GA²LEN 2013 Classification. A study from Montpellier, France [26] of 107 children found that 43 of 107 (40.2%) could not be classified. This was because in contrast to adults, clinical manifestations and underlying diseases were different i.e., CRSwNP is uncommon in children and adolescents, risk factors like chronic urticaria, allergic rhinoconjunctivitis were more common in adults. In another Turkish study of 106 patients where 27 of 31 patients (87%) were confirmed by drug provocation test (DPT), 24% were not classifiable. It was suggested that for children, 3 groups may suffice:

- Group I: nonallergic NSAID hypersensitivity – ENDA 1 [NERD], 2 [NECD], 3 [NIUA]
- Group II: single NSAID induced urticaria, angioedema or anaphylaxis (ENDA 4)
- Group III: single NSAID induced delayed reactions (ENDA 5).

In a Spanish cohort [27] of children (2–14 years) and adolescents/ young adults (15–25 years) where NSAID HSR was diagnosed based on history and oral provocation test with ASA, there were significantly more males among children and females among the adolescents and young adults. NSAID use was more commonly for infection among children and for pain relief among adolescents/ young adults. A further case-control study by the same group showed that cross intolerance was more common than selective reactors, and that subjects were more likely to be atopic and develop respiratory or anaphylaxis manifestations.

In Singapore, a retrospective case series [28] showed that young, Asian, atopic children with mean age 7.4 years (range, 1.4–14.4 years), predominantly Chinese males tended to develop NIUA with isolated facial and periorbital edema. The reactions occurred in a dose- and potency-dependent manner with cross-reactive reactions to NSAIDs (most commonly ibuprofen and paracetamol). Children with onset before 6 years of age had an increased likelihood of reacting to paracetamol (odds ratio, 9.6; 95% CI, 1.6–58.0; $p < 0.05$) over time [29]. Etoricoxib 90 mg (body weight > 50 kg) was tolerated in majority of children (>95% DPTs) who underwent DPTs as they were unable to take both paracetamol and ibuprofen. At present the only approved indication for the use of celecoxib is in children 2 years old and above with juvenile idiopathic arthritis, and etoricoxib is only registered for use in those aged 16 years old and above.

CLINICAL APPROACH TO THE DIAGNOSIS OF NSAID HSR

Patients should be clinically phenotyped through careful history of the index reaction which should include skin and all other organ-systems manifestations. The drug history should clearly elucidate if the patient had reacted to a single or multiple NSAIDs, including the route of administration (oral, intramuscular, intravenous, suppository, or topical). The history of associated cofactors during the index reaction should also be sought e.g. febrile illness/infection. This will require sufficient health literacy on the part of the patient [30] and/or carefully curated drug allergy information from the patient, electronic medical records (EMRs) or drug allergy/adverse drug reaction notification systems linked to EMRs [31].

A detailed history of associated comorbidities should include atopy (allergic rhinitis, asthma, atopic dermatitis) among children and adolescents; and asthma, CRS with/without nasal polyposis, and CSU among adults.

As NSAID HSR are nonimmune mediated, the use of skin tests and *in vitro* tests for specific IgE are limited. Basophil activation tests are not widely available in most centres, and there remain issues with the sensitivity and specificity of these tests for NSAID HSR [32]. Thus, drug provocation tests often need to be done [33] using:

- The culprit drug (where the history of the index reaction is equivocal)
- ASA (to exclude cross-reactivity in single reactors) [33]
 - ASA nasal or bronchial provocation test (NERD)
 - ASA oral challenge (all other types of NSAID HSR)
- With selective COX-2 inhibitor (for cross-reactors to offer patients an alternative drug to use).

A careful risk-benefit assessment for DPT with informed consent needs to be undertaken before any DPT is carried out [34, 35].

ASPIRIN DESENSITIZATION IN CORONARY ARTERY DISEASE

Desensitization is a therapeutic procedure where within hours to days, induction of temporary tolerance to medication to which the patient had developed an adverse reaction to occurs. The indications for desensitization are where no alternative medications are available for treatment of that condition; and where benefits of desensitization outweigh the risks. There are internationally accepted guidelines on the contraindications and safety measures for desensitization [36]. ASA desensitization was originally used at high dose (325–650 mg/day) to treat CRSwNP. This was subsequently adapted in the form of low-dose (100 mg/day) to treat coronary artery disease (CAD) especially before/after percutaneous coronary intervention (PCI). Various protocols have been described in the literature with up to 10-step rapid dose escalations.

Although the exact mechanisms remain unclear, ASA desensitization in AERD (NERD) has demonstrated a reduction in peripheral monocyte synthesis of LTB₄, down-regulation of cysteinyl leukotriene receptors [37], inhibition of STAT-6 (signal transducers and activators of transcription 6 signaling) in CD4 cells and IL-4 production [38], and increase in CD4+

IL-10 and CD4+ γ interferon [39]. In aspirin-intolerant urticaria, desensitization has been shown to lead to absence of mast cell degranulation, and reduction in urinary LTE₄ inversely proportional to that of thromboxane B₂ [40, 41].

In the ADAPTED (aspirin desensitization in patients with coronary artery disease) Registry, a prospective, multicenter, observational study from 7 Italian centers (n = 330), ASA desensitization was found to be successful in 315 patients (95.4%), of whom 253 (80.3%) continued ASA \geq 12 months. Among the 15 patients (4.6%) where desensitization was unsuccessful, adverse reactions were minor [42]. In the European Academy of Allergy and Clinical Immunology Drug Interest Group on Challenge and Desensitization Procedures in CAD study comprising 10 Allergy centres (n = 310), where 70% of the patients had NIUA as the index reaction, desensitization was successful in 145 of 147 subjects (98.6%) [43].

In a retrospective case series from Hong Kong (n = 24), where mean age was 64 \pm 13 years, male (67%), index reaction was NIUA in 92%, and comprised 54% of acute coronary syndrome, 83% were successfully desensitised at the initial attempt. This was using a 5-step protocol up to ASA 155-mg cumulative dose. Among the 8 (33%) who developed a HSR during desensitisation, 4 of 8 (50%) limited cutaneous reactions and completed desensitisation [44].

In Singapore, our group has a collaborative service with our cardiologists using a 7-step ASA desensitization protocol up to cumulative 100-mg ASA. This is used for inpatients admitted for acute coronary syndromes requiring emergency PCI, and for elective outpatient coronary angiograms/interventions. Among patients where desensitization is unsuccessful at the initial attempt, we have attempted maintaining them at 50 mg twice daily with good effect without severe systemic reactions occurring. Six to 8 weeks later, we again attempt to change the dose frequency back to 100 mg once daily to see if tolerance can be maintained.

CONCLUSION

The Asian phenotype for NSAID HSR appears to be predominantly NIUA with overlapping features in some adults and children. NECD also appears to be more common than NERD, although both are not common in the Asian paediatric population. Between adults and children, children seem to be more atopic, although over time when these children grow up, it is likely that the prevalence of atopic adults with NSAID HSR will increase over time. There are also differences in single nucleotide polymorphisms between Asians and Caucasians. Low-dose Aspirin desensitization has been shown to be effective in CAD. This is particularly pertinent in the Asia-Pacific region with ageing populations and the increasing incidence of type 2 diabetes mellitus/metabolic syndrome.

REFERENCES

1. Kowalski ML, Asero R, Bavbek S, Blanca M, Blanca-Lopez N, Bochenek G, Brockow K, Campo P, Celik G, Cernadas J, Cortellini G, Gomes E, Nizankowska-Mogilnicka E, Romano A, Szczeklik A, Testi S, Torres MJ, Wöhrl S, Makowska J. Classification and practical approach to the diagnosis and management of hypersensitivity to nonsteroidal anti-inflammatory drugs. *Allergy* 2013;68:1219-32.

[PUBMED](#) | [CROSSREF](#)

2. Blumenthal KG, Lai KH, Huang M, Wallace ZS, Wickner PG, Zhou L. Adverse and hypersensitivity reactions to prescription nonsteroidal anti-inflammatory agents in a large health care system. *J Allergy Clin Immunol Pract* 2017;5:737-43.
[PUBMED](#) | [CROSSREF](#)
3. Cavkaytar O, du Toit G, Caimmi D. Characteristics of NSAID-induced Hypersensitivity Reactions in Childhood. *Pediatr Allergy Immunol* 2018 Sep 8 [Epub]. <https://doi.org/10.1111/pai.12980>.
[PUBMED](#) | [CROSSREF](#)
4. Kowalski ML, Makowska JS, Blanca M, Bavbek S, Bochenek G, Bousquet J, Bousquet P, Celik G, Demoly P, Gomes ER, Nizankowska-Mogilnicka E, Romano A, Sanchez-Borges M, Sanz M, Torres MJ, De Weck A, Szczeklik A, Brockow K. Hypersensitivity to nonsteroidal anti-inflammatory drugs (NSAIDs) - classification, diagnosis and management: review of the EAACI/ENDA(#) and GA2LEN/HANNA*. *Allergy* 2011;66:818-29.
[PUBMED](#) | [CROSSREF](#)
5. White AA, Stevenson DD. Aspirin-exacerbated respiratory disease. *N Engl J Med* 2018;379:1060-70.
[PUBMED](#) | [CROSSREF](#)
6. Sánchez-Borges M, Caballero-Fonseca F, Capriles-Hulett A. Cofactors and comorbidities in patients with aspirin/NSAID hypersensitivity. *Allergol Immunopathol (Madr)* 2017;45:573-8.
[PUBMED](#) | [CROSSREF](#)
7. Hermans MAW, van der Vet SQA, van Hagen PM, van Wijk RG, van Daele PL. Low frequency of acetyl salicylic acid hypersensitivity in mastocytosis: the results of a double-blind, placebo-controlled challenge study. *Allergy* 2018 Mar 22 [Epub]. <https://doi.org/10.1111/all.13445>.
[PUBMED](#) | [CROSSREF](#)
8. Loh W, Lim HH, Rao R, Goh A, Ong LX, Chiang WC. Tolerance to etoricoxib in children with nonsteroidal anti-inflammatory drug hypersensitivity. *Asia Pac Allergy* 2015;5:40-6.
[PUBMED](#) | [CROSSREF](#)
9. Wölbling F, Fischer J, Köberle M, Kaesler S, Biedermann T. About the role and underlying mechanisms of cofactors in anaphylaxis. *Allergy* 2013;68:1085-92.
[PUBMED](#)
10. Pham DL, Kim JH, Trinh TH, Park HS. What we know about nonsteroidal anti-inflammatory drug hypersensitivity. *Korean J Intern Med* 2016;31:417-32.
[PUBMED](#) | [CROSSREF](#)
11. Jurado-Escobar R, Perkins JR, García-Martín E, Isidoro-García M, Doña I, Torres MJ, Cornejo-García JA. Update on the genetic basis of drug hypersensitivity reactions. *J Investig Allergol Clin Immunol* 2017;27:336-45.
[PUBMED](#) | [CROSSREF](#)
12. Mastalerz L, Setkowicz M, Sanak M, Rybarczyk H, Szczeklik A. Familial aggregation of aspirin-induced urticaria and leukotriene C synthase allelic variant. *Br J Dermatol* 2006;154:256-60.
[PUBMED](#) | [CROSSREF](#)
13. Cheong HS, Park SM, Kim MO, Park JS, Lee JY, Byun JY, Park BL, Shin HD, Park CS. Genome-wide methylation profile of nasal polyps: relation to aspirin hypersensitivity in asthmatics. *Allergy* 2011;66:637-44.
[PUBMED](#) | [CROSSREF](#)
14. Rajan JP, Wineinger NE, Stevenson DD, White AA. Prevalence of aspirin-exacerbated respiratory disease among asthmatic patients: A meta-analysis of the literature. *J Allergy Clin Immunol* 2015;135:676-81.
[PUBMED](#) | [CROSSREF](#)
15. Lu Y, Li S, Song L, Jin H, Li Y, Zhong N, Zhang X. Low prevalence of hypersensitivity to nonsteroidal anti-inflammatory drugs in Chinese patients with chronic rhinosinusitis. *Eur Arch Otorhinolaryngol* 2014;271:2711-5.
[PUBMED](#) | [CROSSREF](#)
16. Fan Y, Chen S, Qu X, Zuo K, Li X, Huang J, Xu G, Mi J, Li H. A lower prevalence of asthma among patients with chronic rhinosinusitis in southern China. *J Allergy Clin Immunol* 2011;127:520-2.
[PUBMED](#) | [CROSSREF](#)
17. Kim DW, Cho SH. Emerging endotypes of chronic rhinosinusitis and its application to precision medicine. *Allergy Asthma Immunol Res* 2017;9:299-306.
[PUBMED](#) | [CROSSREF](#)
18. Moon JY, Kim SH, Kim TB, Kim SH, Chang YS, Lee JH, Cho YS, Park JW, Jang AS, Park CS, Nahm DH, Cho YJ, Cho SH, Choi BW, Moon HB, Yoon HJ; COREA study group. Aspirin-intolerant asthma in the Korean population: prevalence and characteristics based on a questionnaire survey. *Respir Med* 2013;107:202-8.
[PUBMED](#) | [CROSSREF](#)

19. Lee HY, Ye YM, Kim SH, Ban GY, Kim SC, Kim JH, Shin YS, Park HS. Identification of phenotypic clusters of nonsteroidal anti-inflammatory drugs exacerbated respiratory disease. *Allergy* 2017;72:616-26.
[PUBMED](#) | [CROSSREF](#)
20. Braido F, Tiotiu A, Kowal K, Mihaicuta S, Novakova P, Oguzulgen IK. Phenotypes/endotypes-driven treatment in asthma. *Curr Opin Allergy Clin Immunol* 2018;18:184-9.
[PUBMED](#)
21. Llanora GV, Loo EX, Gerez IF, Cheng YK, Shek LP. Etoricoxib: a safe alternative for NSAID intolerance in Asian patients. *Asian Pac J Allergy Immunol* 2013;31:330-3.
[PUBMED](#) | [CROSSREF](#)
22. Bakhtiar MF, Too CL, Tang MM, Tan LK, Sulaiman S, Fauzi NA, Nagum AR, Rayappa GC. Non-steroidal anti-inflammatory drugs (NSAIDs) hypersensitivity phenotypes and their common triggering medications. *Clin Transl Allergy* 2018;8(Suppl 3):P130.
23. Bakhtiar MF, Too CL, Tang MM, Tan LK, Sulaiman S, Fauzi NA, Nagum AR, Rayappa GC. HLA-A*11:01 and A*24:02 are risk factors for Malay patients with urticaria/angioedema induced by non-steroidal anti-inflammatory drugs. *Clin Transl Allergy* 2018;8(Suppl 3):P93.
24. Kidon M, Blanca-Lopez N, Gomes E, Terreehorst I, Tanno L, Ponvert C, Chin CW, Caubet JC, Soyer O, Mori F, Blanca M, Atanaskovic-Markovic M. 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;29:469-80.
[PUBMED](#) | [CROSSREF](#)
25. Settignano RA, Constantine HP, Settignano GA. Aspirin intolerance and recurrent urticaria in normal adults and children. *Epidemiology and review. Allergy* 1980;35:149-54.
[PUBMED](#) | [CROSSREF](#)
26. Cousin M, Chiriac A, Molinari N, Demoly P, Caimmi D. Phenotypical characterization of children with hypersensitivity reactions to NSAIDs. *Pediatr Allergy Immunol* 2016;27:743-8.
[PUBMED](#) | [CROSSREF](#)
27. 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;66:418-24.
[PUBMED](#) | [CROSSREF](#)
28. Kidon MI, Kang LW, Chin CW, Hoon LS, See Y, Goh A, Lin JT, Chay OM. Early presentation with angioedema and urticaria in cross-reactive hypersensitivity to nonsteroidal antiinflammatory drugs among young, Asian, atopic children. *Pediatrics* 2005;116:e675-80.
[PUBMED](#) | [CROSSREF](#)
29. Kidon MI, Liew WK, Chiang WC, Lim SH, Goh A, Tang JP, Chay OM. Hypersensitivity to paracetamol in Asian children with early onset of nonsteroidal anti-inflammatory drug allergy. *Int Arch Allergy Immunol* 2007;144:51-6.
[PUBMED](#) | [CROSSREF](#)
30. Jarernsripornkul N, Chaipichit N, Chumworathayi P, Krska J. Management for improving patients' knowledge and understanding about drug allergy. *Pharm Pract (Granada)* 2015;13:513.
[PUBMED](#) | [CROSSREF](#)
31. Blumenthal KG, Park MA, Macy EM. Redesigning the allergy module of the electronic health record. *Ann Allergy Asthma Immunol* 2016;117:126-31.
[PUBMED](#) | [CROSSREF](#)
32. Ariza A, Fernandez TD, Doña I, Aranda A, Blanca-Lopez N, Melendez L, Canto G, Blanca M, Torres MJ, Mayorga C. Basophil activation after nonsteroidal anti-inflammatory drugs stimulation in patients with immediate hypersensitivity reactions to these drugs. *Cytometry A* 2014;85:400-7.
[PUBMED](#) | [CROSSREF](#)
33. Nizankowska-Mogilnicka E, Bochenek G, Mastalerz L, Swierczyńska M, Picado C, Scadding G, Kowalski ML, Setkowicz M, Ring J, Brockow K, Bachert C, Wöhrl S, Dahlén B, Szczeklik A. EAACI/GA2LEN guideline: aspirin provocation tests for diagnosis of aspirin hypersensitivity. *Allergy* 2007;62:1111-8.
[PUBMED](#) | [CROSSREF](#)
34. Aberer W, Bircher A, Romano A, Blanca M, Campi P, Fernandez J, Brockow K, Pichler WJ, Demoly P; European Network for Drug Allergy (ENDA); EAACI interest group on drug hypersensitivity. Drug provocation testing in the diagnosis of drug hypersensitivity reactions: general considerations. *Allergy* 2003;58:854-63.
[PUBMED](#) | [CROSSREF](#)
35. Kowalski ML, Ansotegui I, Aberer W, Al-Ahmad M, Akdis M, Ballmer-Weber BK, Beyer K, Blanca M, Brown S, Bunnag C, Hulett AC, Castells M, Chng HH, De Blay F, Ebisawa M, Fineman S, Golden DB, Haahtela T, Kaliner M, Katelaris C, Lee BW, Makowska J, Muller U, Mullol J, Oppenheimer J, Park HS, Parkerson J, Passalacqua G, Pawankar R, Renz H, Rueff F, Sanchez-Borges M, Sastre J, Scadding G,

- Sicherer S, Tantilipikorn P, Tracy J, van Kempen V, Bohle B, Canonica GW, Caraballo L, Gomez M, Ito K, Jensen-Jarolim E, Larche M, Melioli G, Poulsen LK, Valenta R, Zuberbier T. Risk and safety requirements for diagnostic and therapeutic procedures in allergology: World Allergy Organization Statement. *World Allergy Organ J* 2016;9:33.
[PUBMED](#) | [CROSSREF](#)
36. Cernadas JR, Brockow K, Romano A, Aberer W, Torres MJ, Bircher A, Campi P, Sanz ML, Castells M, Demoly P, Pichler WJ; European Network of Drug Allergy and the EAACI interest group on drug hypersensitivity. General considerations on rapid desensitization for drug hypersensitivity - a consensus statement. *Allergy* 2010;65:1357-66.
[PUBMED](#) | [CROSSREF](#)
37. Juergens UR, Christiansen SC, Stevenson DD, Zuraw BL. Inhibition of monocyte leukotriene B4 production after aspirin desensitization. *J Allergy Clin Immunol* 1995;96:148-56.
[PUBMED](#) | [CROSSREF](#)
38. Katial RK, Martucci M, Burnett T, Faino A, Finkas L, Liu S, Alam R. Nonsteroidal anti-inflammatory-induced inhibition of signal transducer and activator of transcription 6 (STAT-6) phosphorylation in aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol* 2016;138:579-85.
[PUBMED](#) | [CROSSREF](#)
39. Aksu K, Kurt E, Alatas Ö, Gülbas Z. Effect of aspirin desensitization on T-cell cytokines and plasma lipoxins in aspirin-exacerbated respiratory disease. *Allergy Asthma Proc* 2014;35:148-55.
[PUBMED](#) | [CROSSREF](#)
40. Arm JP, O'Hickey SP, Spur BW, Lee TH. Airway responsiveness to histamine and leukotriene E4 in subjects with aspirin-induced asthma. *Am Rev Respir Dis* 1989;140:148-53.
[PUBMED](#) | [CROSSREF](#)
41. Grzelewska-Rzymowska I, Szmidt M, Rozniecki J, Grzegorzczak J. Aspirin-induced neutrophil chemotactic activity (NCA) in patients with aspirin-sensitive urticaria after desensitization to the drug. *J Investig Allergol Clin Immunol* 1994;4:28-31.
[PUBMED](#)
42. Rossini R, Iorio A, Pozzi R, Bianco M, Musumeci G, Leonardi S, Lettieri C, Bossi I, Colombo P, Rigattieri S, Dossena C, Anzuini A, Capodanno D, Senni M, Angiolillo DJ. Aspirin desensitization in patients with coronary artery disease: results of the multicenter ADAPTED registry (Aspirin Desensitization in Patients With Coronary Artery Disease). *Circ Cardiovasc Interv* 2017;10.
[PUBMED](#) | [CROSSREF](#)
43. Cortellini G, Romano A, Santucci A, Barbaud A, Bavbek S, Bignardi D, Blanca M, Bonadonna P, Costantino MT, Laguna JJ, Lombardo C, Losappio LM, Makowska J, Nakonechna A, Quercia O, Pastorello EA, Patella V, Terreehorst I, Testi S, Cernadas JR; EAACI Drug Interest Group on Challenge and Desensitization Procedures with Aspirin in CAD, Dionicio Elera J, Lippolis D, Voltolini S, Grosseto D. Clinical approach on challenge and desensitization procedures with aspirin in patients with ischemic heart disease and nonsteroidal anti-inflammatory drug hypersensitivity. *Allergy* 2017;72:498-506.
[PUBMED](#) | [CROSSREF](#)
44. Lee JK, Tsui KL, Cheung CY, Chau CH, Chan HL, Wu KL, Cheung GS, Choi MC, Chan KK, Li SK. Aspirin desensitisation for Chinese patients with coronary artery disease. *Hong Kong Med J* 2013;19:207-13.
[PUBMED](#)