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About the Authors

David Fahmy, MD

Dr. David Fahmy is an Assistant Clinical Professor at McMaster University and the Program Director for its Adult and Pediatric Clinical Immunology & Allergy programs. He completed his medical school at the University of Western Ontario followed by a residency in internal medicine at the University of Toronto. He then completed his clinical immunology and allergy training at McMaster University, where he has stayed on in a clinical capacity with a focus on medical education. He has an academically focused practice in Hamilton and a community practice in Toronto.

Affiliations: Division of Clinical Immunology and Allergy, McMaster University, Hamilton, ON

Andrew Wong-Pack, MD

Dr. Andrew Wong-Pack is a clinical immunology and allergy fellow at McMaster University in Hamilton, Ontario. He completed his medical degree at Western University and completed his residency in Internal Medicine at the University of Toronto. His research interests include inborn errors of immunity, secondary immunodeficiency, drug allergy, and quality improvement in these areas.

Affiliations: Division of Clinical Immunology and Allergy, McMaster University, Hamilton, ON

A Practical Approach to NSAID Allergy

David Fahmy, MD
Andrew Wong-Pack, MD

Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely prescribed for pain management and inflammation.[1] Acetylsalicylic acid (ASA) is a commonly used treatment for cardiovascular diseases including acute coronary syndromes.[2] Reactions to NSAIDs can vary widely, ranging from exacerbation of underlying cutaneous and respiratory conditions to anaphylaxis and delayed hypersensitivity reactions (DHRs).[3,4] A thorough clinical history is essential for diagnosing NSAID hypersensitivity, with a focus on the systems involved, reaction timing, and the presence and control of comorbid allergic conditions. Although commonly referred to as an allergy, the mechanisms behind these reactions are not solely IgE-mediated. As such, the authors will primarily use the term "hypersensitivity reactions" in concordance with the latest American Academy of Allergy, Asthma and Immunology (AAAAI) drug allergy practice parameter.[5] While NSAID hypersensitivity reactions may cross-react among cyclooxygenase-1 (COX-1) inhibitors, reactions to selective cyclooxygenase-2 (COX-2) inhibitors are rare and they are typically well tolerated as alternative agents.[5]

Classification

NSAID hypersensitivity reactions can be classified into acute and delayed presentations. Acute hypersensitivity reactions can be further divided into four major phenotypes, while DHRs are often described as distinct entities **(Table 1)**.[6]

Phenotype	Symptoms	COX-1 Mediated	Comorbidities	Desensitization	Notes
Aspirin or NSAID-exacerbated respiratory disease (N-ERD or AERD)	Sneezing, congestion, bronchospasm, laryngospasm. Rare: gastrointestinal pain, flushing	Yes	Asthma, Chronic rhinosinusitis with nasal polyposis (CRSwNP)	Yes	After desensitization to 325 mg of ASA, tolerance is achieved to other COX-1 inhibitors
NSAID-exacerbated cutaneous disease	Urticaria, angioedema	Yes	Chronic Spontaneous Urticaria (CSU), 10-40% of patients	No, may exacerbate underlying CSU	COX-2 inhibitors are generally well tolerated. Single dose challenge can be considered once CSU is controlled.
NSAID-induced urticaria and angioedema	Urticaria, angioedema	Yes	None	Can be considered	8-11% may react to COX-2 inhibitors so in-office challenge can be considered.
Single NSAID-induced reactions	Urticaria, angioedema. Rare: anaphylaxis.	No	None	Typically not recommended but possible	Challenge to structurally dissimilar NSAID for diagnostic clarification.
Delayed hypersensitivity reactions	Meningitis, pneumonitis, nephritis, fixed drug eruption, DRESS, SJS, AGEP,	No	Varies	Not for severe reactions	Challenge not recommended for severe reactions

Table 1. Phenotypes of NSAID Hypersensitivity; *adapted from Table XVI. Khan DA, et al.*[5]
Abbreviations: AERD: Aspirin-exacerbated respiratory disease; **AGEP:** acute generalized exanthematous pustulosis; **ASA:** acetylsalicylic acid; **COX 1:** cyclooxygenase-1; **COX 2:** cyclooxygenase 2; **CRSwNP:** chronic rhinosinusitis with nasal polyps; **DRESS:** drug-related eosinophilia with systemic symptoms (DRESS); **CSU:** chronic spontaneous urticaria; **NSAID:** nonsteroidal anti-inflammatory drug; **SJS:** Steven Johnson Syndrome

Generic name	Brand names
Ibuprofen	Advil, Motrin
Naproxen	Aleve
Acetylsalicylic Acid	Aspirin

Table 2. Examples of commonly used oral COX-1 NSAIDs available over-the-counter in Canada; *courtesy of Andrew Wong-Pack, MD, David Fahmy, MD,*

Acute NSAID hypersensitivity

NSAID-exacerbated respiratory disease (N-ERD/AERD)

Aspirin-exacerbated respiratory disease (AERD) is specific to Aspirin and has been previously described as "Aspirin induced asthma" and "Aspirin sensitivity".[3] It is most famously described in the context of "Samter's Triad" as a combination of bronchial asthma, nasal polyposis, and life-threatening reactions to ASA.[7,8] These reactions occur in patients with underlying chronic rhinosinusitis and/or asthma. However, they are not unique to ASA, and cross-reactivity is common. Therefore, the term has been expanded to NSAID-*exacerbated respiratory disease* to highlight this.[5] Characteristic symptoms include an acute development of congestion, rhinorrhea, bronchospasm, and less commonly gastrointestinal and skin involvement, which can be clinically difficult to differentiate from anaphylaxis.[1] The onset is typically within 30-180 minutes after drug ingestion.[8]

The causative mechanism is thought to be secondary to the inhibition of COX-1, leading to a decrease of prostaglandin E2 and a shift toward leukotriene production.[3,10,11] Weak COX-1 inhibitors can cause reactions in particularly sensitive individuals, and, though rare, COX-2 inhibitors can cause reactions.[5] For a list of commonly used oral COX-1 NSAIDs availabe over-the-counter in Canada, please see **Table 2**.

NSAID-exacerbated cutaneous disease (NECD)

NSAID-exacerbated cutaneous disease (NECD) refers to patients with underlying chronic spontaneous urticaria (CSU) who experience worsening of their symptoms after exposure to an NSAID.[5] NSAIDs have been described as co-factors for the worsening of urticaria, which can affect approximately 10-40% of patients with an underlying CSU.[4,5] In addition, the initial presentation of cutaneous NSAID hypersensitivity has been described as a precursor to the development of CSU.[12] The mechanism is also thought to be secondary to COX-1 inhibition. Given the fluctuating nature of CSU, predicting who may react to NSAIDs is challenging.[12]

Multiple NSAID-induced urticaria and angioedema (NIUA)

Patients who develop isolated cutaneous manifestations without an underlying history or current diagnosis of CSU are thought to have multiple NSAID-induced urticaria and angioedema (NIUA), which is the most common type of NSAID hypersensitivity reaction.[5] The onset of symptoms varies and typically occurs 1-6 hours after drug ingestion.[13],These reactions are most commonly observed with potent COX-1 inhibitors, however, symptoms have also been reported with weak COX-1 inhibitors such as acetaminophen as well as with COX-2 inhibitors such as celecoxib.[3,5]

Single NSAID-induced urticaria/ angioedema or anaphylaxis (SNIUAA)

Cutaneous reactions to individual NSAIDs, including anaphylaxis, may involve an IgE-mediated mechanism, although the exact mechanism is not completely understood.[5] Patients can typically tolerate other NSAIDs without symptoms. However, when patients choose to avoid other NSAIDs prior to presentation, the diagnosis of a single NSAID-induced reaction can be challenging. There are few reports of anaphylaxis or isolated cutaneous symptoms with ASA, and reports of serum-specific IGE to NSAIDs are limited.[5]

Delayed NSAID hypersensitivity

NSAID-induced delayed hypersensitivity reactions

Delayed reactions typically occur >6 hours after drug ingestion. However, many delayed reactions may take days to weeks of exposure before clinical manifestations develop.

Fixed drug eruptions (FDE) are cutaneous reactions where lesions recur at the same anatomical region with each re-exposure. Contact and photocontact dermatitis have been reported with topical formulations of NSAIDs as well. In addition, maculopapular or morbilliform eruptions have been documented with various forms of NSAIDs.[14]

Severe cutaneous adverse reactions (SCARs) such as Steven Johnson Syndrome (SJS), Toxic-Epidermal Necrolysis (TEN), Acute Generalized Exanthematous Pustulosis (AGEP), and Drug related eosinophilia with systemic symptoms (DRESS) are rare but may occur with NSAIDs. The pathophysiology of these reactions is thought to be T-cell-mediated.[5,14]

Other uncommon manifestations of NSAID reactions include pneumonitis, meningitis, interstitial nephritis, and drug-induced liver injury,

which are considered other forms of type B reactions.[5,13]

Diagnosis and management of NSAID hypersensitivity

The recent publication of the 2022 AAAAI drug allergy practice parameter has revised and consolidated the approach to diagnosing and treating NSAID hypersensitivity.[9] Although the specific recommendations vary depending on the phenotype, a selective COX-2 inhibitor can generally be used for analgesia in any patient with acute NSAID hypersensitivity for intermittent use.[5] For multiple NIUA, an initial dose challenge in the clinic can be considered.[5] Immediate single NSAID-induced reactions are rarely caused by Aspirin. As a result, Aspirin becomes a useful diagnostic tool, as tolerance suggests that the culprit is a single non-ASA NSAID, whereas a reaction suggests that the patient is susceptible to the entire class of COX-1 inhibitors. The authors recommend a total challenge dose of 162mg of ASA as this would be the expected dose used acutely for cardiovascular emergencies. We recommend for COX-2 challenges, a total challenge dose of 200mg of celecoxib. We recommend challenges be completed in a two-step fashion with at least 30 minutes between doses and monitoring for at least two hours after the final dose. By removing the drug allergy labels to ASA and celecoxib, this opens therapeutic options for most patients. Subsequent challenges to alternatives would be up to the discretion of the allergist depending on the clinical history and patient preference or needs.

NSAID-exacerbated respiratory disease (N-ERD/AERD)

For patients with a clinical history strongly suggestive of N-ERD such as experiencing two or more respiratory reactions to different NSAIDs, or a respiratory reaction requiring hospitalization, an oral challenge is not recommended. Instead, Aspirin desensitization can be considered if indicated.[5] Skin testing to ASA or in vitro tests are not recommended for diagnosis.[15] When there is diagnostic uncertainty, such as in the setting of atypical or minor symptoms or to only a single NSAID, an oral challenge to Aspirin is suggested for diagnosis.[5]

Desensitization is recommended for patients who require daily therapy, such as for secondary cardiovascular prevention or to reduce polyp regrowth.[16] Protocols can vary, including multi-day protocols, and the AAAAI practice parameter can be referenced for these.[5] Should a patient develop a reaction during desensitization, this serves as a positive challenge. Doses should be repeated and increased until the patient tolerates a minimum daily dose of either 81 mg or 325 mg of ASA.[5,16] Higher doses, such as 650 mg twice daily, may be needed for polyp control.[16] After 5 days without therapy, repeat desensitization is required for all patients and sometimes if >48 hours occur between doses.[5]

Desensitization therapy has been shown to be cost effective.[16,17] However, with the increasing use of dupilumab for chronic rhinosinusitis with nasal polyposis (CRSwNP), using desensitization for N-ERD may be shifting.[5]

NSAID-exacerbated cutaneous disease (NECD)

The diagnosis of NSAID-exacerbated cutaneous disease (NECD) relies on the presence of active CSU combined with the worsening of cutaneous symptoms.[12] The mainstay of treatment is to control the underlying urticaria, and a single-dose challenge can be considered once control is achieved.[18] Desensitization is not typically recommended as this may trigger a flare of the urticaria.[5]

Multiple NSAID-induced urticaria and angioedema (NIUA)

Diagnosing NIUA can be challenging in patients who avoid all NSAIDs after a reaction to a single NSAID. As such, a challenge with a structurally dissimilar NSAID, typically Aspirin as the initial choice, is recommended.[5] Although COX-2 inhibitors are generally well tolerated in all NSAID hypersensitivity cases, an in clinic challenge can be considered given the low rate of reactions in this phenotype (8-11%).[19] Patients who pre-medicate with high dose non-sedating antihistamines may be able to tolerate occasional NSAIDs.[5]

Single NSAID-induced urticaria/ angioedema or anaphylaxis (SNIUAA)

After identifying the culprit NSAID, it is recommended to challenge with a structurally dissimilar NSAID for the initial evaluation, preferentially with Aspirin when possible. Single NSAID-induced reactions to Aspirin are rare, and most challenges to Aspirin in this setting are negative, allowing future use. While desensitization is theoretically possible given the concerns about an IgE-mediated mechanism, it is typically not

recommended given the high rate of negative challenges to Aspirin.[5]

NSAID-induced delayed hypersensitivity reactions

In the setting of severe cutaneous reactions or other severe idiosyncratic NSAID reactions, challenging the culprit NSAID or its class is not recommended. Patch testing has been evaluated for FDE, and patients may tolerate a structurally dissimilar NSAID. Additional diagnostic tools are needed in this phenotype.[5]

Acute desensitization for acute coronary syndromes

For all non-AERD NSAID immediate hypersensitivity reactions, a modified rapid two-step protocol has been reported. This consists of an initial dose of 40.5 mg of Aspirin and a second dose of 40.5 mg 90 minutes later.[20] The dose can be repeated as a single dose or a dose of 325 mg later for further clarification. The benefit of successfully tolerating a challenge rather than desensitization is the removal of the Aspirin allergy label and eliminating the need for desensitization if doses are missed.[20] Desensitization remains a safe option for unstable patients or those with AERD.[5]

Summary

NSAIDs are widely used medications with multiple indications and are common triggers of hypersensitivity reactions. A thorough clinical history and a systematic approach to diagnostic evaluation and management is essential for distinguishing between the various phenotypes of NSAID hypersensitivity. Proactive evaluation of individuals labelled with an NSAID allergy is recommended due to their role of these drugs in cardiovascular diseases and non-opioid analgesia.

Correspondence

Andrew Wong-Pack , MD
Email: andrew.wong-pack@medportal.ca

Financial Disclosures

None declared.

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