

Aspirin/NSAID Challenge Should Be Performed Routinely in Patients With Self-Reported Aspirin/NSAID Allergy



Andrew A. White, MD^a, and David M. Lang, MD^b La Jolla, Calif; and Cleveland, Ohio

Alert allergists may recognize the title of this Editorial as a familiar exhortation,¹ as it is very similar to the title of the only position statement from the American Academy of Allergy, Asthma, and Immunology published in more than 15 years.²

When patients with unverified penicillin allergy require antibiotic administration for infection or surgical prophylaxis, an alternative non-penicillin antibiotic (carbapenem, quinolone, macrolide, or vancomycin) is commonly prescribed; these alternative agents can be associated with greater cost, increased risk for untoward effects, and heightened rates of resistant nosocomial organisms, including methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococcus, as well as greater rates of *Clostridium difficile*. For these reasons, we have encouraged patients with self-reported penicillin allergy to undergo diagnostic evaluation to achieve delabeling.¹

In parallel with patients who are predisposed to untoward outcomes based on carrying the label of penicillin allergy, patients with self-reported “aspirin (ASA) allergy” also carry a burden that entails the need to avoid not only ASA but also nonsteroidal anti-inflammatory drugs (NSAIDs), which is also associated with suboptimal health care outcomes. In this issue of the journal, Li et al³ describe their experience carrying out an analogous delabeling of patients with unverified “ASA allergy.” Their data demonstrate, similar to the experience with self-reported penicillin allergy, that the overwhelming majority of patients reporting a history of past adverse reactions from ASA or NSAIDs consisting of a cutaneous eruption can successfully be delabeled via a direct oral challenge.

In addition to respiratory reactions in patients with ASA-exacerbated respiratory disease (AERD), ASA and NSAIDs may elicit cutaneous reactions in patients with NSAID-exacerbated cutaneous disease (NECD) and NSAID-induced urticaria angioedema (NIUA), each occurring via cyclooxygenase-1 inhibition, and may also provoke single-drug

NSAID-induced urticaria, angioedema, or anaphylaxis (SNIUAA).⁴ The characteristics of NECD, NIUA, and SNIUAA are displayed in Table 1. Tolerance can routinely be induced to ASA in AERD. Desensitization is less commonly performed in patients with NIUA, but tolerance can also likely be achieved in this condition. This is in distinction to NECD where attempted desensitization will likely lead to uncontrollable urticaria and to SNIUAA where desensitization would theoretically be possible but clinically unnecessary.

Although the diagnostic classification of ASA/NSAID hypersensitivity can sometimes seem daunting, the approach to diagnosis is straightforward—despite the lack of validated diagnostic skin or *in vitro* testing. The allergist is left with our 2 most powerful tools—a detailed clinical history and a diagnostic challenge. The ASA/NSAID challenge is likely an underused procedure. One year ago, this same group reported that patients with ASA/NSAID “allergy” on their medical record were more likely (odds ratio: 1.34) to end up with an opiate use disorder if treated for chronic back pain.⁵ It is important to note that this study focused on back pain; sadly, it would seem obvious that this same outcome would also apply to other chronic pain syndromes. Feng et al⁶ reported that in a large group of patients with coronary artery disease, 142 had “ASA allergy” listed and only 24% were on daily ASA prophylaxis. These studies demonstrate the risk to our patients by not having their ASA/NSAID hypersensitivity addressed. Ignoring the ASA/NSAID allergy during a routine outpatient visit can leave us in the difficult position of then needing to evaluate a cardiac patient in the hospital with an acute need for ASA. This would have been easier to address electively as an outpatient.

A uniform approach to ASA/NSAID hypersensitivity is lacking, although in many studies a 2-step challenge protocol is used in patients in whom AERD is not suspected.⁷ This is in contrast to multistep protocols that add time and complexity, creating various doses.⁸ AERD is readily identified via the clinical context (chronic rhinosinusitis with nasal polyposis, asthma, and respiratory ASA/NSAID reactions) and should be approached separately. In patients with a history of 1 or more respiratory reactions to ASA/NSAID or a need for emergency department/hospital utilization after an ASA/NSAID reaction, the diagnosis is nearly certain, thus obviating the need for a diagnostic challenge.⁹ Similarly, in patients with NECD and a convincing history of an ASA/NSAID-induced worsening of urticaria, a challenge would not be necessary until the urticaria is well controlled.¹⁰ However, all other patients with a label of “ASA/NSAID allergy” require a diagnostic challenge.

The current article by Li et al³ brings up several interesting observations that might be important to incorporate into a future standardized protocol. First, patients were more than 3

^aDepartment of Medicine, Division of Allergy, Asthma, and Immunology, Scripps Clinic and Research Foundation, La Jolla, Calif

^bDepartment of Allergy and Clinical Immunology, Respiratory Institute, Cleveland Clinic, Cleveland, Ohio

No funding was received for this work.

Conflicts of interest: The authors declare that they have no relevant conflicts of interest

Received for publication January 18, 2022; accepted for publication January 22, 2022.

Corresponding author: David M. Lang, MD, Cleveland Clinic, 9500 Euclid Ave, A90, Cleveland, OH 44195. E-mail: langd@ccf.org.

J Allergy Clin Immunol Pract 2022;10:1293-4.
2213-2198

© 2022 Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology

<https://doi.org/10.1016/j.jaip.2022.01.049>

TABLE I. Aspirin/NSAID sensitivity syndromes

Aspirin/NSAID sensitivity syndrome	Underlying condition	Cross-reaction with structurally unrelated COX-1 inhibitors	Induction of tolerance achievable
AERD	Chronic rhinosinusitis with nasal polyposis and asthma	Yes	Yes
NECD	Chronic urticaria	Yes	No
NIUA	N/A	Yes	Possibly
SNIUAA	N/A	No	Possibly

AERD, Aspirin-exacerbated respiratory disease; COX-1, cyclooxygenase-1; N/A, not applicable; NECD, nonsteroidal anti-inflammatory drug–exacerbated cutaneous disease; NIUA, nonsteroidal anti-inflammatory drug–induced urticaria/angioedema; NSAID, nonsteroidal anti-inflammatory drug; SNIUAA, single NSAID-induced urticaria, angioedema, and/or anaphylaxis.

Adapted from Shah et al.⁴ Reproduced with permission.

times likely to have a positive challenge if the reaction was in the prior 5 years. This would fit with a hypothesis that in some cases the potential for an ASA/NSAID reaction with re-exposure resolves spontaneously. Second, the vast majority (85%) of challenges were negative, signifying that for most of our patients with an “ASA/NSAID allergy” on the chart, it can likely be removed electively, via a direct challenge. Third, 36 subjects had “subjective only” symptoms on the first step of the challenge but went on to have a completely negative challenge. The number of patients with subjective symptoms and a negative challenge (36) was nearly the same as those with a positive challenge (48). Finally, there were differences in the provocative dose when evaluating 81 mg versus 325 mg of ASA where there are some patients for whom an 81 mg ASA goal yields a negative challenge but a higher dose might trigger reactivity. These observations can be directly translated into a protocol that considers a challenge in a reaction within 5 years to be higher risk, but that all patients should be offered a challenge. Challenges should proceed until objective signs or the final dose is reached because nearly 50% of symptomatic patients might have a negative challenge. Finally, diagnostic ASA challenges should not be considered negative unless a dose of 325 mg has been reached. An important therapeutic consideration for patients who require ASA for cardioprotection is that the target dose for a challenge procedure may be adjusted to 81 mg based on shared decision-making between the patient, allergist, and cardiologist.

Several practical measures can also be extracted from this study. A 2-step challenge is safe and efficient to answer the ASA/NSAID hypersensitivity question. For ASA, the doses can be easily generated in the clinic by cutting an 81 mg dose in half. Suspensions are readily available for ibuprofen to start at a 20 to 60 mg dose. Most patients reacted within 60 minutes of the provoking dose, but enough patients reacted between 60 and 120 minutes after the final dose to warrant consideration of a longer observation window after the final dose.

ASA/NSAID hypersensitivity continues to be one of the most common adverse drug reactions to pollute the medical charts of patients who could benefit from their use. In the past, strict avoidance of ASA/NSAID was recommended for such patients, and a drug challenge was “usually not advocated in most clinical

situations.”¹¹ It is now time for allergists to accept the challenge of removing the “allergy” label in the 85% of patients for whom it is unnecessary, and better characterizing and confirming the potential for an adverse reaction in the remaining 15%. This can be easily done in any allergy practice; it does not require specialized compounding of medication doses nor does it require specialized nursing or facilities. Similar to our experience with delabeling patients with a history of penicillin allergy, the evidence presented by Li et al³ provides support for the recommendation to extend this approach to patients with unverified “ASA/NSAID allergy” and to *routinely* perform ASA/NSAID challenges in these cases.

REFERENCES

- Lang D, Castells M, Khan DA, Macy E, Murphy A. Penicillin allergy testing should be performed routinely in patients with self-reported penicillin allergy. *J Allergy Clin Immunol Pract* 2017;5:333-4.
- Bush RK, Portnoy JM, Saxon A, Terr AI, Wood RA. The medical effects of mold exposure. *J Allergy Clin Immunol* 2006;117:326-33.
- Li L, Bensko J, Buchheit K, Saff RR, Laidlaw TM. Safety, outcomes, and recommendations for two-step outpatient nonsteroidal anti-inflammatory drug challenges. *J Allergy Clin Immunol Pract* 2022;10:1286-92.
- Shah RH, Kuder MM, Lang DM. Anaphylaxis to drugs, biological agents, and vaccines. *Immunol Allergy Clin North Am* 2022;42:121-44.
- Li L, Chang Y, Song S, Losina E, Costenbader KH, Laidlaw TM. Impact of reported NSAID “allergies” on opioid use disorder in back pain. *J Allergy Clin Immunol* 2021;147:1413-9.
- Feng CH, White AA, Stevenson DD. Characterization of aspirin allergies in patients with coronary artery disease. *Ann Allergy Asthma Immunol* 2013;110:92-5.
- Asero R. Oral aspirin challenges in patients with a history of intolerance to single non-steroidal anti-inflammatory drugs. *Clin Exp Allergy* 2005;35:713-6.
- Doña I, Blanca-López N, Cornejo-García JA, Torres MJ, Laguna JJ, Fernández J, et al. Characteristics of subjects experiencing hypersensitivity to non-steroidal anti-inflammatory drugs: patterns of response. *Clin Exp Allergy* 2011;41:86-95.
- Dursun AB, Woessner KA, Simon RA, Karasoy D, Stevenson DD. Predicting outcomes of oral aspirin challenges in patients with asthma, nasal polyps, and chronic sinusitis. *Ann Allergy Asthma Immunol* 2008;100:420-5.
- Sánchez J, Díez S, Cardona R. Clinical control of CSU with antihistamines allows for tolerance of NSAID-exacerbated cutaneous disease. *J Allergy Clin Immunol Pract* 2020;8:3577-35783.e1.
- Anderson J. Allergic and allergic-like reactions to drugs and other therapeutic agents. In: Lieberman P, Anderson J, editors. *Allergic Diseases: Diagnosis and Treatment*. Totowa, NJ: Humana Press, Inc; 2000. p. 320.