

Cardiovascular Prophylaxis and Aspirin “Allergy”

Katharine M. Woessner, MD*, Ronald A. Simon, MD

KEYWORDS

- Coronary artery disease • Aspirin-exacerbated respiratory disease
- Cyclooxygenase • Acetylsalicylic acid • Nonsteroidal anti-inflammatory drug

KEY POINTS

- With rare exceptions, patients with a history of “aspirin/nonsteroidal anti-inflammatory allergy” will be able to safely take aspirin after either graded dose challenge or desensitization.
- Aspirin therapy should not be routinely denied to patients with history of aspirin sensitivity.
- Allergists should be proactive and consistent in their message that aspirin challenge/desensitization can be performed in the acute setting when clinically essential.

Aspirin (acetylsalicylic acid) is a potent antiplatelet therapy and is a cornerstone in the management of coronary artery disease (CAD) and other thrombotic diseases. Aspirin is an inhibitor of cyclooxygenase (COX). In the platelet, irreversible inhibition of COX leads to inhibition of thromboxane-mediated platelet aggregation (**Fig. 1**). A meta-analysis of multiple trials looking at patients at high risk for thrombotic events showed that aspirin is protective in most types of patients at increased risk of occlusive vascular events, including those with an acute myocardial infarction or ischemic stroke, unstable or stable angina, previous myocardial infarction, stroke or cerebral ischemia, peripheral arterial disease, or atrial fibrillation.¹ Despite extensive data supporting the role of aspirin in vascular disease, several at risk patients often fail to receive adequate antiplatelet therapy due to possible allergy to aspirin.

Aspirin therapy can result in a 33% event-reduction rate and is recommended for both primary prevention for at-risk patients and secondary prevention for those who already have cardiovascular disease.¹ Guidelines from the American College of Cardiology (ACC) and the American Heart Association (AHA) cite a class I indication for aspirin therapy unless a true sensitivity to aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs) exists, in which case thienopyridines (clopidogrel, ticagrelor, and

Disclosures: None.

Division of Allergy, Asthma and Immunology, Scripps Clinic, 3811 Valley Centre Drive, San Diego, CA 92130, USA

* Corresponding author.

E-mail address: Woessner.katharine@scrippshealth.org

Immunol Allergy Clin N Am 33 (2013) 263–274

<http://dx.doi.org/10.1016/j.iac.2012.11.004>

immunology.theclinics.com

0889-8561/13/\$ – see front matter © 2013 Elsevier Inc. All rights reserved.

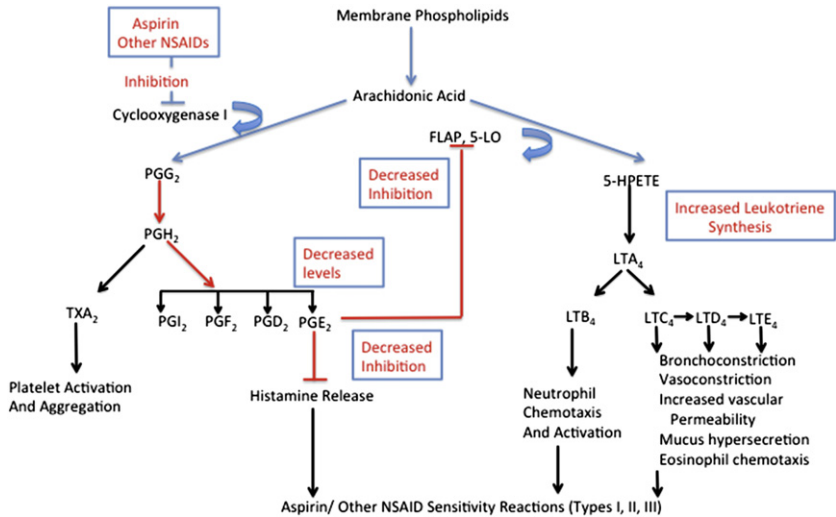


Fig. 1. Arachidonic acid is the substrate used to generate prostanoids and leukotrienes (LT). The cyclooxygenase-1 (COX-1) enzyme is the site of inhibition by aspirin and NSAIDs. Activation of COX-1 leads to synthesis of thromboxanes (TXA), a potent activation of platelets, and platelet aggregation, as well as the prostaglandins (PGI₂, PGF₂, PGD₂, and PGE₂). Inhibition of COX-1 leads to a rapid depletion of PGE₂. In the absence of the braking effect of PGE₂ on 5-lipoxygenase (5-LO) and 5-lipoxygenase-activating protein (FLAP), there is a dramatic increase in the synthesis of the cysteinyl leukotrienes. These arachidonic acid metabolites lead to the clinical manifestations of aspirin sensitivity including AERD, urticaria, and angioedema. 5-HPETE, 5-hydroxyperoxyeicosatetraenoic acid.

prasugrel) are alternative antiplatelet agents that can be used.^{2,3} Combination therapy for aspirin with clopidogrel reduces adverse cardiovascular events in unstable angina, non-ST-segment elevation myocardial infarction, and ST-segment elevation myocardial infarction.^{4,5} It also improves survival and reduces adverse cardiac events in patients with acute coronary syndrome treated with either bare-metal stents (BMS) or drug-eluting stents (DES).^{3,5-7} The ACC, AHA, and the Society for Cardiovascular Angiography and Intervention (SCAI) recommend combination therapy for patients with acute coronary syndrome undergoing percutaneous intervention.^{3,8} According to the guidelines, therapy with aspirin should be life-long in these patients with CAD.

In the case of aspirin or NSAID hypersensitivity, monotherapy with a thienopyridine may be used as an alternative. However, this is not as cost-effective and carries a risk of hematologic complications including thrombotic thrombocytopenic purpura and neutropenia.⁹ An additional concern is the patient who needs to undergo coronary artery bypass grafting (CABG) surgery. Aspirin therapy can be continued through to surgery, whereas other antiplatelet therapies need to be stopped 5 to 7 days before CABG because their continued use is associated with increased CABG-related bleeding. Thus, patients relying on these alternative antiplatelet therapies are at risk of major cardiac events in the 5 to 7 days before surgery, owing to the lack of antiplatelet therapy.

For the physician, facing therapeutic decisions in a patient with cardiovascular disease and aspirin hypersensitivity is complicated, as aspirin/NSAID hypersensitivity can affect up to 0.5% to 1.9% of the general population and can be manifested by aspirin-exacerbated respiratory disease (AERD), urticaria/angioedema,

or anaphylaxis.^{10–12} The prevalence of AERD is estimated to be 4.3 % to 11% of asthmatics by history or review of medical records, and may be as high as 21% when aspirin challenges are used for diagnosis.^{13,14} For aspirin-induced urticarial/angioedema the prevalence upward of 0.3% in the general population.¹⁰ In patients with chronic urticaria, approximately one-third will experience an exacerbation with the use of COX-1-inhibiting NSAIDs and aspirin.¹⁵ Alternatively, the listed aspirin allergy on the medical record may be aspirin-induced gastritis, tinnitus, or misdiagnosis with aspirin as an innocent bystander.

Given the demonstrated efficacy of aspirin in cardiovascular disease, what should one do when faced with a patient who has an allergy to aspirin? Many patients erroneously believe they are allergic to aspirin and can be identified by taking a careful history to determine that their "allergy" was either a side effect or other misattribution to aspirin. Other patients who are allergic to a single NSAID have erroneously been counseled to avoid all NSAIDs including aspirin, whereas others are at risk of urticaria and/or angioedema with all COX-1-inhibiting NSAIDs including aspirin may not be aware of cross-sensitization. These clinical decisions are difficult for allergy specialists, and frequently even more daunting for practicing cardiology and neurology specialists. For those who report a prior reaction to aspirin, options such as aspirin challenge and desensitization are available and are recommended in the various cardiology guidelines.¹⁶ The focus of this article on providing a practical approach to the patient with a history of aspirin hypersensitivity who needs aspirin therapy.

The first issue to be addressed is identifying the type of reaction to aspirin the patient has previously experienced. This process is critical, as it will dictate subsequent intervention. The various types of reactions are listed here.

Type I: Aspirin-exacerbated respiratory disease. AERD is a unique disease whereby reactions to NSAIDs or aspirin occur in conjunction with sinus disease, nasal polyps, and asthma. Although asthma is not always present, nasal polyps and sinus disease exist in nearly all patients. These patients will typically experience worsening nasal and ocular symptoms as well as asthma symptoms within 1 to 2 hours of ingestion of any medication that blocks the COX-1 enzyme. Important historical clues in identifying these patients are the existence of sinus disease, loss of smell, the presence of reactions to more than one COX-1 inhibitor, and a typical reaction involving the airway.¹⁷ During NSAID-induced respiratory reactions, levels of prostaglandin E₂ are rapidly depleted. In the absence of the braking effect of prostaglandin E₂ on 5-lipoxygenase-activating protein and 5-lipoxygenase, there is a marked increase in cysteinyl leukotriene synthesis and release, along with release of histamine from mast cells (see [Fig. 1](#)). With few exceptions, all patients with AERD can undergo successful aspirin desensitization.

Type II: Urticaria/angioedema in the setting of chronic urticaria (CIU). NSAIDs can cause worsening urticaria and angioedema in patients who have active CIU. These patients likely have a history of tolerating NSAIDs or aspirin, but in the midst of their chronic urticaria have worsening of urticaria from the mast cell-destabilizing properties of NSAIDs. These patients will have a history of persistent urticaria made worse by NSAIDs and likely have a history of tolerance of NSAIDs during remission of their underlying urticaria. The proposed pathophysiology, similar to that of AERD, is related to COX-1 inhibition leading to excessive leukotriene production by 5-lipoxygenase activity, and thus to increased vascular permeability and subsequent urticaria.¹⁸ The Scripps experience has been that these patients cannot be desensitized to aspirin during

the active phase of their chronic urticaria. This COX-1-mediated effect will occur with any NSAID or aspirin. The prevalence of NSAID-induced urticarial in patients with chronic urticaria is between 20% and 30%.^{19,20} Therefore, it is worth challenging a patient with chronic urticaria because up to two-thirds will tolerate aspirin.

Type III: Urticaria and angioedema induced by multiple NSAIDs mediated through COX-1 inhibition. These patients do not have preexisting urticaria and also have no evidence of nasal polyps or asthma. As expected by the mechanism, they may have experienced urticaria or angioedema from several members of the NSAID family. Unlike the patient with underlying chronic urticaria, these patients generally can undergo successful aspirin desensitization.

Type IV: Single NSAID-induced reactions. NSAIDs can cause isolated, immunologically mediated urticaria and angioedema and/or anaphylaxis. The presumed mechanism is formation of immunoglobulin E (IgE) antibodies against specific epitopes in specific NSAIDs. These patients will have reactions related to one specific NSAID. These reactions are poorly understood, but the specificity of the reaction to one NSAID suggests that a specific IgE mechanism is involved, possibly attributable to drug haptenization. A history of tolerance of other NSAIDs should highlight this type of reaction as most likely. These reactions are limited to a specific NSAID but, because of structural similarity among a family of NSAIDs, cross-reactions may exist (see the article by Woessner and colleagues elsewhere in this issue on classification of NSAID reactions). Patients with an IgE-mediated reaction to any other NSAID should not have difficulty taking aspirin, whose chemical structure eliminates cross-recognition by specific IgE antibodies.

Aspirin has been reported in the literature as a historical cause of anaphylaxis by patients seen in emergency rooms.²¹ There is one report of positive skin tests to lysyl aspirin in patients with aspirin-induced urticaria.^{22,23} These observations suggest that aspirin-induced anaphylaxis is a possibility. Nevertheless, despite an extensive literature search and careful review, peer consultation throughout multiple medical systems, and an exhaustive review of the cases of aspirin reactions in the Scripps Medical System, the authors are unable to find even one convincing case of an anaphylactic reaction to aspirin.

DIAGNOSIS OF ASPIRIN/NSAID HYPERSENSITIVITY

There are no established tests on skin or blood that can reliably diagnose hypersensitivity to aspirin/NSAIDs. As such, provocative challenge tests are the only available modalities in the United States.

REVIEW OF THE LITERATURE

Because of the often emergent need of aspirin for cardiovascular disease, there is a paucity of literature on well-controlled aspirin challenges/desensitizations in this patient population. Thus, before performing desensitization it is almost always unknown whether the patient even has hypersensitivity to aspirin. The latest study by De Luca and colleagues²⁴ involved 43 patients with a history suggesting aspirin hypersensitivity who needed cardiac stenting, more than 50% of whom had acute coronary syndrome. The patients underwent a rapid intravenous aspirin challenge/desensitization protocol either before the catheterization, in the catheterization laboratory, or following the procedure. A success rate of 97.6% was reported. One patient with chronic urticaria did not tolerate aspirin therapy. McMullan and Wedner²⁵ have

recently published a retrospective study looking at 81 patients with reported aspirin allergy and cardiovascular disease who underwent aspirin desensitization, including 22 treated as outpatients. The investigators noted that 19.7% of the desensitizations were associated with reactions, with 5 patients unable to complete the aspirin desensitization. Risk factors for reactions during desensitization included history of aspirin-induced angioedema and historical reaction to aspirin within the previous year.

A variety of other experiences with desensitization for an acute need for aspirin have been published, all with similar rates of success, and all limited in their interpretation by the lack of aspirin challenge to confirm that indeed the patients had aspirin sensitivity in the first place.²⁶⁻³¹ The salient point here is that a patient who is not allergic to aspirin can go through a "desensitization protocol" without "any reaction" and end up taking aspirin in the alleged "desensitized state." For example, Wong and colleagues²⁷ evaluated 11 patients who required aspirin in the acute setting. The patients mostly had aspirin-associated cutaneous symptoms, although one patient may have had AERD based on the history provided. Rossini and colleagues²⁸ evaluated 26 patients with acute coronary disease and a history of aspirin allergy. Twenty-three of these patients underwent successful desensitization, but very little of their history of a prior reaction is reported in the article, and no patients had previously undergone a blinded aspirin challenge to confirm they were allergic to aspirin. Two of the 3 patients in whom desensitization was unsuccessful had chronic urticaria worsened by the ingestion of an NSAID. In total, the literature reports 214 patients who underwent aspirin desensitization in an acute setting.⁶⁻¹⁴ Desensitization was judged to be "successful" in 203 patients. However, the authors' interpretation is that most of these patients actually underwent negative challenges, and therefore may not have been aspirin sensitive. Five of the 11 failures were in patients with preexisting chronic urticaria. Very importantly, there were no significant complications or morbidity associated with any of the desensitization failures despite the variety of protocols used.

SCRIPPS CLINIC EXPERIENCE WITH ASPIRIN CHALLENGES AND DESENSITIZATION FOR CAD

Given the lack of compelling data that true IgE-mediated/anaphylactic reactions to aspirin occur, it is likely that prolonged desensitization protocols starting at extremely low doses of aspirin are unnecessary. This notion is in line with the authors' clinical experience at Scripps Clinic over the past 15 years. In an initial evaluation of 30 patients with "aspirin allergy," 24 had a history of urticaria and 6 had a history of anaphylaxis to one NSAID (patients with AERD are not included in this analysis). In the urticaria group, urticaria was due to NSAIDs in 15 patients and due to aspirin in 6. All 6 cases of reported anaphylaxis events were associated with NSAIDs. None were attributed to aspirin. All patients underwent an aspirin challenge starting at 30 mg or 60 mg, based on the preference of the treating physician. None of the 15 patients with NSAID-associated anaphylaxis were challenged with the suspect NSAID. Doses of aspirin were doubled every 30 to 90 minutes until a full 325 mg of aspirin was administered. Twenty-eight patients had a negative challenge, including all 15 patients with prior reactions to other NSAIDs. Of the 6 cases with a prior history of urticaria, after ingesting aspirin 2 patients experienced mild urticaria. Both progressed with successful desensitization to aspirin and continued taking aspirin on a daily basis. There were no cases of anaphylaxis. All were successfully treated with aspirin.

In a more recent case series, 11 patients referred to the authors for "aspirin allergy" and the need for aspirin treatment were evaluated. All underwent aspirin challenge with a starting aspirin dose of either 30 or 40 mg, and the dose was doubled in

90 minutes. One patient had itching, rhinorrhea, and tearing after the second dose was given. This reaction was easily treated with antihistamines, and the final dose of 325 mg was given to ensure that desensitization was complete. One patient developed 2 small hives after the last dose. No patients reacted to the first dose, and in 9 patients there were no objective signs of a reaction. In all patients, a 325-mg dose concluded the challenge, but patients may have been subsequently treated with lower doses of aspirin at the discretion of their other health care providers.

A PRACTICAL APPROACH TO PATIENTS WITH A HISTORY SUGGESTING ASPIRIN HYPERSENSITIVITY

A practical approach to the urgent need for aspirin administration in the patient with a history of an adverse reaction to aspirin or another NSAID is presented. These recommendations are guided both by an exhaustive review of the literature, and the authors' clinical experience framed by an understanding of the mechanisms of the various aspirin/NSAID reactions.

The Goal of Aspirin Challenge/Desensitization

In almost all settings, the urgent need for aspirin is necessitated by its well-known antiplatelet effect. Because a significant antiplatelet effect is seen at 81 mg of aspirin, the initial goal of reaching this dose is reasonable for most patients. As seen in the CURRENT-OASIS 7 trial, there was no significant difference in end points between the low dose (75–100 mg aspirin dose) and high dose (300–325 mg daily aspirin) on cardiovascular death, myocardial infarction, and stroke at 30 days.³² Thus, the goal of the allergist should be to achieve a dose of 81 mg aspirin as quickly and safely as possible. In combination with new potent platelet inhibitors such as prasugrel and clopidogrel, there are no data to suggest that 325 mg of aspirin is more efficacious than 81 mg at preventing restenosis in the first 24 to 48 hours.

The first step in evaluating these patients is to determine whether there is a likelihood of a real aspirin allergy or if they merely have intolerance. Many patients experience side effects such as tinnitus, easy bruisability, or gastrointestinal symptoms, which they attribute to an aspirin allergy. Such patients can be given aspirin without any special protocol.

Once it has been determined that the historical reaction may represent an aspirin allergy, the next step is to characterize the type of reaction (mucocutaneous vs AERD). Every attempt should be made to identify AERD and to obtain historical evidence as to whether a history of reactions or tolerance to any other NSAID exists.

Location and Timing

The authors believe that for all patients with an unstable arterial lesion (evolving myocardial infarction, evolving transient ischemic attack or cerebrovascular accident, and so forth), the intravascular intervention should occur first and considerations for challenge/desensitization should be secondary. This approach is predicated by the concern that in any patient, there is a real possibility of causing asthma or histamine-mediated coronary vasospasm, which in an already unstable patient could be catastrophic.

The location of the aspirin challenge/desensitization will vary depending on the nursing and monitoring resources available to the allergist. A one-to-one, constant nursing attendance is required, with the supervising physician immediately available. Modalities to treat potentially severe asthmatic and urticarial reactions must be available, including epinephrine. In the authors' institution almost all desensitization/oral

challenge procedures occur in the outpatient clinic. Patients discharged soon after cardiac stenting are sent directly to the Allergy outpatient clinic for aspirin challenge and desensitization to aspirin if required. Nevertheless, it is recognized that in other clinics/practices this same approach to aspirin challenge/desensitization will be undertaken in a monitored hospital bed.

In a patient unstable enough that continued hospitalization is necessary for management of the underlying medical condition, the goal of successful aspirin administration is paramount and takes precedence over obtaining an accurate diagnostic aspirin challenge. For this reason, pretreatment with steroids, antihistamines, and montelukast should be considered in all such patients, with the caveat that in a heavily premedicated patient, the lack of any symptoms during the challenge/desensitization procedure cannot be interpreted as a true "negative challenge" but could also represent a "silent desensitization/challenge." This aspect has implications for future aspirin use if there is a lapse in aspirin administration.

The authors believe that the converse situation is true in patients who are stable for discharge from the hospital before aspirin challenge/desensitization. Nearly all of these patients referred to the clinic after hospitalizations can be desensitized in the outpatient setting. In this setting, obtaining an accurate diagnosis is important and can safely be obtained by withholding steroid and antihistamine pretreatment, and by only using these as treatment modalities for patients who react.

Aspirin Challenge/Desensitization Protocol

Two very similar protocols can be considered, depending on the suspicion of the type of previous reaction (**Fig. 2**).

AERD

Patients who are asthmatic should be screened for the likelihood of AERD. Many times the patient's history and reported recent tolerance of another NSAID can eliminate the possibility of AERD. With an equivocal history or uncertainty about the diagnosis, further evaluation for AERD should take place. This assessment can be done by performing a nasal examination for polyps and obtaining a Waters view sinus radiograph or computed tomography of the sinuses. If the sinuses are clear or a unilateral opacified sinus is identified, the patient does not have AERD. With pansinusitis, even without prior exposure to aspirin, approximately one-third will have a respiratory reaction to aspirin, signaling the final quatrad of AERD (pansinusitis, nasal polyps, asthma, and aspirin-induced respiratory reaction).

For unstable patients that likely have AERD, the approach is as follows. Pretreatment with oral montelukast 10 mg, inhaled corticosteroid/long-acting β -agonist, systemic corticosteroids (usually intravenous), and antihistamines should be given to everyone. Then, using a pill cutter, give one-half of an 81-mg aspirin tablet. This dose is generally lower than the provoking dose of 60 to 90 mg that causes reactions in most AERD patients. This dose can then be repeated in 90 minutes. At this point the patient will have 81 mg of aspirin in the system, and this 81-mg dose can be repeated daily. In AERD patients, it is likely that they will react to the second dose of 40.5 mg of aspirin. Symptoms will generally be mild to moderate, but should be anticipated and promptly treated with nebulized β -agonists, oral or intravenous antihistamines, or other medications. A thorough review of the treatment of AERD reactions has been published.³³ If a reaction occurs after the first or second dose of aspirin, further dosing the following day should lead to minimal or no further symptoms. At a dose of 81 mg per day some patients may not be completely desensitized, and care should be taken with higher doses of aspirin or other full-strength NSAIDs. In a stable outpatient AERD

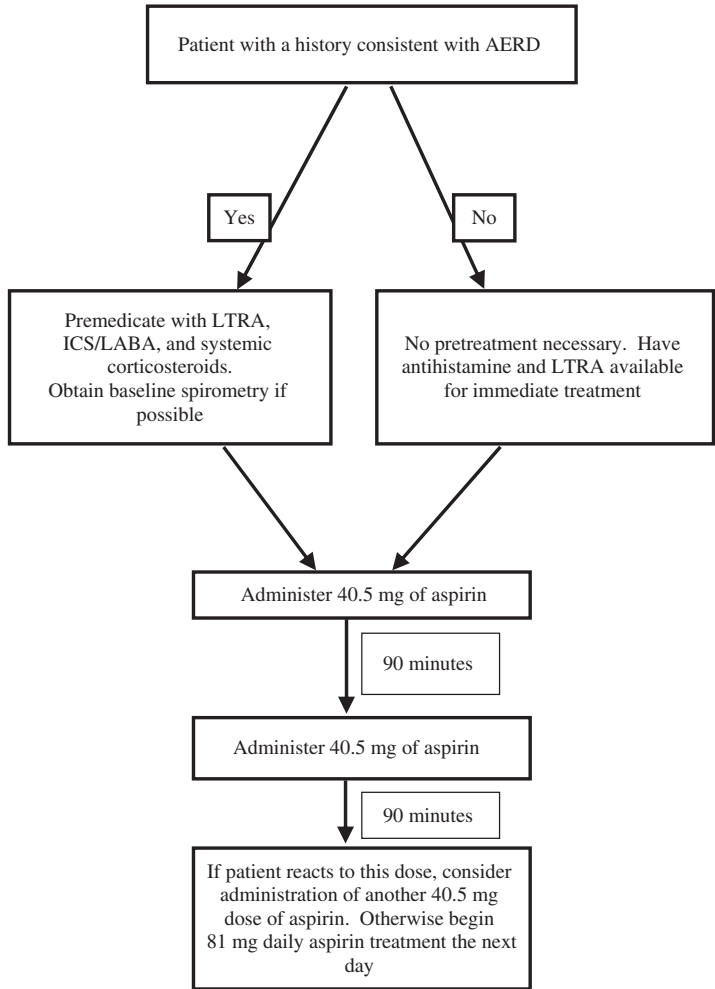


Fig. 2. Oral aspirin challenge/desensitization algorithm and protocol. AERD, aspirin-exacerbated respiratory disease; ICS, inhaled corticosteroids; LABA, long-acting β 2-antagonists; LTRA, leukotriene receptor antagonists.

desensitization, systemic corticosteroids may not be necessary, and antihistamine use as pretreatment may mask symptoms of a reaction and create confusion over whether the patient truly has AERD. It should be noted that at 81 mg a day, the underlying AERD is not going to be treated.

Cutaneous reactions

Challenge or desensitization can be started at the same doses (40.5 mg aspirin). Pretreatment with an antihistamine and/or leukotriene receptor antagonist is likely to confuse negative versus positive reactions, but these should be added as soon as a cutaneous reaction occurs. A 40.5-mg dose of aspirin is appropriate, and as per the aforementioned protocol can be repeated in 90 minutes to reach the 81-mg target dose. This recommended challenge/desensitization protocol is predicated on the following premise. Conclusive evidence that aspirin can induce IgE-mediated

anaphylaxis remains elusive and may not even exist. However, if the presenting patient gives a history of, or emergency-room records document a particularly severe prior aspirin reaction, starting with 20.25 mg of aspirin or less can be considered. Starting with an 81-mg aspirin tablet, a pill cutter can be used to obtain the 20.25-mg dose. In those patients with a severe historical reaction to aspirin, evaluation for AERD is warranted.

With oral desensitizations that involve the hospital pharmacy, there can be a considerable delay in obtaining the required dilutions. In the authors' experience, the majority of patients with a prior cutaneous reaction to another NSAID or a rash occurring more than 10 years previously and associated with ingesting aspirin will not react to 81 mg of aspirin. Conversely, as published recently by McMullan and Wedner,²⁵ historical reactions to aspirin within the past year are likely to be associated with a reaction during the procedure.

In summary, the approach to the patient with a previous aspirin reaction is to administer half of a baby aspirin (40.5 mg) and repeat the dose in 90 minutes. Only differences in the character of the reaction need to be considered by the ordering physician.

Proceeding to 325 mg Aspirin

Depending on the intervention, aspirin doses as high as 325 mg may be recommended by the referring cardiologist for optimum antiplatelet effect.⁸ This dose can be achieved by continuing the aspirin dosing. Conversely, the patient may be discharged from the acute hospitalization on 81 mg of aspirin, and a follow-up visit may be made to increase the dose to 325 mg. For all patients who have been taking 81 mg aspirin uneventfully, they can undergo the rest of the challenge/desensitization in one visit to the outpatient clinic (see [Fig. 2](#)).

Patients Who Should Not be Desensitized to Aspirin

Nearly all patients with a history of a reaction to aspirin will be able to be properly evaluated and treated with aspirin following an oral challenge or desensitization. In a few circumstances the challenge/desensitization or challenge is contraindicated. If there is a history of aspirin-associated Stevens-Johnson syndrome, toxic epidermal necrolysis, hypersensitivity pneumonitis, or drug rash with eosinophilia and systemic symptoms (DRESS) syndrome, rechallenge can be dangerous and desensitization would be unsuccessful. Aspirin is an unlikely candidate for these reactions under any circumstances. In a patient who develops one of these conditions and who has been on a stable dose of aspirin 81 mg a day for years, the culprit drug is more likely to be the newly introduced drug (anticonvulsant, sulfonamide, certain NSAIDs). The problem is that there is a tendency for physicians to stop all medications, even the innocent bystanders. Rechallenge with aspirin, after informed consent, can be considered in this latter circumstance.

Assuming linkage with aspirin, allergic interstitial nephritis and serum sickness will not be amenable to desensitization.¹² Patients with chronic urticarial and historical reactions to aspirin and NSAIDs represent a unique situation. Although desensitization can be safely attempted, in the authors' experience persistent recalcitrant urticaria and angioedema make long-term use of aspirin or NSAIDs very difficult. There is a report of one successful desensitization protocol used for a patient with chronic urticaria requiring aspirin, but this case study cannot be extrapolated to all patients with chronic hives.³⁴ For patients with chronic urticaria/angioedema with no historical reaction to aspirin, about two-thirds will tolerate aspirin, and it would be appropriate to give them the full dose of 81 mg or 325 mg.

SUMMARY

With rare exceptions, patients with a history of “aspirin/NSAID allergy” will be able to safely take aspirin after either graded dose challenge or desensitization. Such an inexpensive and effective medication should not be withheld from most patients. A variety of protocols has been described, and although the exact mechanism of desensitization and patient characterization remains somewhat obscure, the take-home message is that in nearly all patients, negative challenge or desensitization was successful. Allergists should be proactive and consistent in their message that aspirin challenge/desensitization can be performed in the acute setting when clinically essential.

REFERENCES

1. Antithrombotic Trialists Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002;324:71–86.
2. Ryan TJ, Antman EM, Brooks NH, et al. 1999 update: ACC/AHA Guidelines for the Management of Patients With Acute Myocardial Infarction: Executive Summary and Recommendations: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Acute Myocardial Infarction). *Circulation* 1999;100:1016–30.
3. Braunwald E, Antman EM, Beasley JW, et al. ACC/AHA guidelines for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction: executive summary and recommendations. A report of the American College of Cardiology/American Heart Association task force on practice guidelines (committee on the management of patients with unstable angina). *Circulation* 2000;102:1193–209.
4. Sabatine MS, Cannon CP, Gibson CM, et al. Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. *N Engl J Med* 2005;352:1179–89.
5. Yusuf S, Zhao F, Mehta SR, et al. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 2001;345:494–502.
6. Mehta SR, Yusuf S, Peters RJ, et al. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. *Lancet* 2001;358:527–33.
7. Steinhubl SR, Berger PB, Mann JT 3rd, et al. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. *JAMA* 2002;288:2411–20.
8. Smith SC Jr, Feldman TE, Hirshfeld JW Jr, et al. ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/SCAI Writing Committee to Update 2001 Guidelines for Percutaneous Coronary Intervention). *Circulation* 2006;113:e166–286.
9. Gaspoz JM, Coxson PG, Goldman PA, et al. Cost effectiveness of aspirin, clopidogrel, or both for secondary prevention of coronary heart disease. *N Engl J Med* 2002;346:1800–6.
10. Settiple RA, Constantine HP, Settiple GA. Aspirin intolerance and recurrent urticaria in normal adults and children. *Epidemiology and review. Allergy* 1980; 35:149–54.
11. Gomes E, Cardoso MF, Praca F, et al. Self-reported drug allergy in a general adult Portuguese population. *Clin Exp Allergy* 2004;34:1597–601.

12. Kowalski ML, Makowska JS, Blanca M, et al. Hypersensitivity to nonsteroidal anti-inflammatory drugs (NSAIDs)—classification, diagnosis and management: review of the EAACI/ENDA(®) and GA2LEN/HANNA*. *Allergy* 2011;66:818–29.
13. Hedman J, Kaprio J, Poussa T, et al. Prevalence of asthma, aspirin intolerance, nasal polyposis and chronic obstructive pulmonary disease in a population-based study. *Int J Epidemiol* 1999;28:717–22.
14. Jenkins C, Costello J, Hodge L. Systematic review of prevalence of aspirin induced asthma and its implications for clinical practice. *BMJ* 2004;328:434.
15. Moore-Robinson M, Warin RP. Effect of salicylates in urticaria. *Br Med J* 1967;4: 262–4.
16. Solensky R. Drug allergy: desensitization and treatment of reactions to antibiotics and aspirin. In: Lockey P, editor. *Allergens and allergen immunotherapy*. New York: Marcel Dekker; 2004. p. 585–606.
17. Szczeklik A, Nizankowska-Mogilnicka E, Sanak M. Hypersensitivity to aspirin and non-steroidal anti-inflammatory drugs. In: Adkinson NF, Bochner BS, Busse WW, et al, editors. *Middleton's allergy: principles and practice*. Philadelphia: Mosby; 2008. p. 1227–39.
18. Grattan CE. Aspirin sensitivity and urticaria. *Clin Exp Dermatol* 2003;28:123–7.
19. Mathison DA, Lumry WR, Stevenson DD. Aspirin in chronic urticaria and/or angioedema: studies of sensitivity and desensitization. *J Allergy Clin Immunol* 1982;69:135.
20. Doeglas HM. Reactions to aspirin and food additives in patients with chronic urticaria, including the physical urticarias. *Br J Dermatol* 1975;93:135–44.
21. Kemp SF, Lockey RF, Wolf BL, et al. Anaphylaxis. A review of 266 cases. *Arch Intern Med* 1995;155:1749–54.
22. Phills JA, Perelmutter L. IgE mediated and non-IgE mediated allergic-type reactions to aspirin. *Acta Allergol* 1974;29:474–90.
23. Blanca M, Perez E, Garcia JJ, et al. Angioedema and IgE antibodies to aspirin: a case report. *Ann Allergy* 1989;62:295–8.
24. De Luca G, Verdoia M, Binda G, et al. Aspirin desensitization in patients undergoing planned or urgent coronary stent implantation. A single-center experience. *Int J Cardiol* 2012. [Epub ahead of print].
25. McMullan KL, Wedner HJ. Safety of aspirin desensitization in patients with reported aspirin allergy and cardiovascular disease. *Clin Cardiol* 2012. [Epub ahead of print].
26. Fajt ML, Petrov AA. Outpatient aspirin desensitization for patients with aspirin hypersensitivity and cardiac disease. *Crit Pathw Cardiol* 2011;10:17–21.
27. Wong JT, Nagy CS, Krinzman SJ, et al. Rapid oral challenge-desensitization for patients with aspirin-related urticaria-angioedema. *J Allergy Clin Immunol* 2000; 105:997–1001.
28. Rossini R, Angiolillo DJ, Musumeci G, et al. Aspirin desensitization in patients undergoing percutaneous coronary interventions with stent implantation. *Am J Cardiol* 2008;101:786–9.
29. Dalmau G, Gaig P, Gazquez V, et al. Rapid desensitization to acetylsalicylic acid in acute coronary syndrome patients with NSAID intolerance. *Rev Esp Cardiol* 2009;62:224–5.
30. Silberman S, Neukirch-Stoop C, Steg PG. Rapid desensitization procedure for patients with aspirin hypersensitivity undergoing coronary stenting. *Am J Cardiol* 2005;95:509–10.
31. Ortega-Loayza AG, Raza S, Minisi AJ, et al. Aspirin desensitization/challenge in 3 patients with unstable angina. *Am J Med Sci* 2010;340:418–20.

32. Mehta SR, Tanguay JF, Eikelboom JW, et al. Double-dose versus standard-dose clopidogrel and high-dose versus low-dose aspirin in individuals undergoing percutaneous coronary intervention for acute coronary syndromes (CURRENT-OASIS 7): a randomised factorial trial. *Lancet* 2010;376:1233–43.
33. Stevenson DD, Simon RA. Selection of patients for aspirin desensitization treatment. *J Allergy Clin Immunol* 2006;118:801–4.
34. Slowik SM, Slavin RG. Aspirin desensitization in a patient with aspirin sensitivity and chronic idiopathic urticaria. *Ann Allergy Asthma Immunol* 2009;102:171–2.