Maintenance of Certification clinical management series

Series editor: James T. Li, MD, PhD

Evidence-based approach to aspirin desensitization in aspirin-exacerbated respiratory disease

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List of Design Committee Members: Katharine M. Woessner, MD, FAAAAI, and Andrew A. White, MD, FAAAAI (authors), and James T. Li, MD, PhD (series editor)

Activity Objectives

1. To understand the pathophysiology of aspirin-exacerbated respiratory disease (AERD) as it relates to oral aspirin challenge and desensitization.
2. To identify the steps necessary to perform a safe aspirin challenge in a patient with suspected AERD, including the role of leukotriene-modifying drugs.
3. To learn how to use intranasal ketorolac challenges for enhancing aspirin desensitization protocols.
4. To be able to identify the components of a positive provocative aspirin challenge result and know the appropriate treatments.

Recognition of Commercial Support: This CME activity has not received external commercial support.

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CLINICAL VIGNETTE

A 36-year-old graphic designer was referred for difficult-to-control asthma, chronic sinusitis, and a history of reacting to nonsteroidal anti-inflammatory drugs (NSAIDs). He had a past history of mild exercise-provoked bronchospasm in childhood that had resolved by his teenage years. His asthma recurred at about the age of 26 years, and since then, he has had ongoing difficulties with rhinitis, nasal polyposis, chronic sinusitis, and difficult-to-control asthma. Despite aggressive treatment of underlying allergic rhinitis with immunotherapy, high-dose inhaled corticosteroids, long-acting β-agonists, and montelukast, his clinical course has been marked by multiple hospital admissions for severe asthma exacerbations.

At the time of initial evaluation, the patient had undergone a total of 4 sinus surgeries for polyposis. He has persistent anosmia that temporarily improves with high-dose corticosteroids.

The patient's first reaction to an NSAID occurred in a postoperative setting at a hospital. He was given an NSAID and had a severe asthma exacerbation within a half hour of dosing that led to an 11-day stay in the intensive care unit. When he was discharged, it was recommended that he avoid all NSAIDs and consider undergoing aspirin desensitization.

A few months later, the patient inadvertently took Alka-Seltzer, not realizing it contained aspirin. He had a severe respiratory reaction, was rushed to the emergency department, and was admitted again to the intensive care unit. He did not require intubation. After that hospitalization, he was referred for aspirin desensitization. He underwent an aspirin desensitization attempt that he described as a rapid desensitization protocol with aspirin

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dosed every 15 minutes, with the intention of completing the procedure in 6 hours. Partway through the procedure, he experienced a severe reaction, the procedure was aborted, and he again required hospitalization.

The patient recently moved to San Diego, California, and after having a persistently difficult clinical course, he was referred by the pulmonary medicine department for aspirin desensitization.

The full version of this article, including a review of relevant issues to be considered, can be found online at www.jacionline.org. If you wish to receive CME or MOC credit for the article, please see the instructions above.

REVIEW

Aspirin-exacerbated respiratory disease (AERD) is characterized by a tetrad of chronic rhinosinusitis (CRS) with nasal polyposis, asthma, and sensitivity to all COX-1–inhibiting NSAIDs.[E1,E2] Although precipitation of acute reactions by ingestion of NSAIDs is the central characteristic of this disease, the underlying inflammatory disease process begins and continues independently of exposure to aspirin or other NSAIDs. AERD typically begins in the third or fourth decades of life, frequently after an upper respiratory tract infection, and is progressive, with aspirin sensitivity developing at any stage in the process (Table E1).[E3] Chronic sinusitis is a critical diagnostic criterion; in its absence, the diagnosis is unlikely.[E3,E4] Isolated cases have been reported in children and adolescents, but AERD is uncommon in those age groups.

Reactions to aspirin and other NSAIDs are a pseudoallergy because they are not IgE mediated but rather an abnormal biochemical response to COX-1 inhibition. Patients with AERD experience characteristic respiratory reactions to acetylsalicylic acid (ASA) and other COX-1–inhibiting NSAIDs. The reactions occur anywhere from 30 minutes to 3 hours after ingestion and include rhinorrhea, nasal congestion, ocular tearing and injection, periorbital swelling, and variable degrees of bronchoconstriction or laryngospasm. Additional symptoms can include severe abdominal cramping, epigastric pain, urticaria, and hypotension. The reactions are dose related in that small doses of NSAIDs can produce minimal symptoms (eg, nasal ocular reaction), with large doses precipitating life-threatening reactions that might require intubation or even be fatal.[E4]

The prevalence of AERD is probably less than 5% in asthmatic patients, although higher rates have been reported.[E5-E8] Among asthmatic patients with CRS and nasal polyps, NSAID sensitivity might affect up to 20% to 40%.[E7,E8] Although the pathophysiology is incompletely understood, AERD is an acquired condition affecting the arachidonic acid metabolic pathway, with overproduction of the proinflammatory cysteinyl leukotriene and underproduction of prostaglandin E_2, an important regulator of the 5-lipooxygenase pathway (Fig E1).[E9-E14] This dysregulation is acutely worsened by COX-1 inhibition, which releases the "brake" on 5-lipooxygenase by further inhibiting prostaglandin E_2. Cells involved in these respiratory reactions include eosinophils, mast cells, and, as recently shown, platelets.[E15-E17]

The diagnosis of AERD depends on a provocative challenge with ASA, lysine-ASA (available outside of the United States), or another NSAID. A history of an asthma attack after ingestion of aspirin or another NSAID is suggestive; however, 16% of patients who believed they had AERD had negative oral ASA challenge results.[E18] Of patients with nasal polyps, chronic sinusitis, and asthma who were avoiding ASA/NSAIDs, only 43% had a positive oral aspirin challenge, with another 57% unnecessarily avoiding ASA.[E18] In rare instances "silent desensitization" to aspirin can occur with a false-negative provocative challenge/desensitization result (Fig E2).[E19]

Management of AERD

Once the diagnosis is confirmed, management involves treatment of the patient's asthma, medical and surgical management of CRS, and either complete avoidance of COX-1–inhibiting drugs or aspirin desensitization and continuous aspirin therapy.[E10,E20] The patient and treating physicians must be aware of all the COX-1–inhibiting NSAIDs that cross-react with aspirin so that they can be avoided (Table E2). Highly selective COX-2 inhibitors, such as celecoxib, have been shown to be safe and can be used in patients with AERD, although the first dose should be administered in the office.[E21-E24]

Indications for aspirin challenge and desensitization

Although most patients with AERD will benefit from continuous aspirin therapy, it is indicated for those with suboptimal control who are receiving currently available pharmacotherapy, those with inflammatory conditions requiring daily NSAID therapy, those with cardiovascular disease requiring antiplatelet therapy with ASA, or those with other indications for intermittent use of NSAIDs.[E24-E27]

The effectiveness of aspirin desensitization and continuous therapy in patients with AERD has been shown in multiple studies and includes significant improvement in overall symptoms and quality of life, decreased formation of nasal polyps and sinus infections, and reduced need for oral corticosteroids and sinus surgeries.[E28-E30] Early effects on nasal and asthma scores and sense of smell can be seen by 4 weeks.[E31] The mechanism of long-term aspirin therapy in patients with AERD is not known, but there is an immediate improvement in the baseline dysregulation of the arachidonic acid pathway with a decrease in levels of cysteinyl leukotrienes and their receptors, as well as a long-term decrease in IL-4–induced expression of leukotrienes by inhibition of the transcription factor signal transducer and activator of transcription 6.[E14,E32,E33]

Aspirin desensitization and aspirin therapy

Provocative oral aspirin challenge serves 2 purposes: confirmation of the AERD diagnosis based on the presence of typical respiratory symptoms and desensitization to aspirin and all COX-1–inhibiting NSAIDS. These protocols can be safely performed in specially equipped outpatient allergy clinics with continuous 1:1 monitoring along with the treating physician being directly available. It is critical that any concurrent cardiopulmonary conditions be under optimal control before challenge. The severity of the historical reaction does not predict outcomes in oral aspirin challenges; therefore a patient with a history of intubation caused by full-dose NSAID can safely undergo aspirin challenge and desensitization.[E34]

In preparation for oral aspirin challenge/desensitization, patients with suspected AERD are pretreated with leukotriene-modifying agents. Leukotriene-modifying agents are both used to treat AERD and reduce the severity of pulmonary reactions during provocative ASA challenges without blocking the nasoocular response.[E35-E38] Long-acting β-agonists and inhaled steroids are continued, but antihistamines are discontinued 1 week before the procedure because these medications might mask a response to aspirin challenge. The optimal timing of desensitization is 2 to 4 weeks after debulking sinus surgery because long-term aspirin therapy helps prevent regrowth of polyps. Baseline prebronchodilator FEV_1 of 70% or greater of the patient's best value and 1.5 L or greater are recommended.[E24] Contraindications to aspirin challenge include pregnancy, unstable asthma, gastric ulcers, or bleeding disorders. Informed consent should be obtained.

Aspirin protocols

Table E3 and Fig E3 are 2 recommended protocols based on more than 1500 aspirin challenges in patients with AERD at the Scripps Clinic. The average time to reaction after the provoking dose of ASA is 102 minutes with the typical provoking dose being 45 to 100 mg of ASA hence the 3-hour dosing interval.[E39] The nasal ketorolac challenge followed by oral aspirin challenge shortens the procedure from 3 to 4 days to 1.5 days but cannot be used for patients with obstructing nasal polyps.[E40,E41] Naso-ocular reactions are the most common occurrence (90%), followed by bronchial and laryngeal symptoms (43%) with extrapulmonary reactions (gastrointestinal, 23%; cutaneous, 10%).[E34] If bronchial or laryngeal reactions occur, treat with albuterol or racemic epinephrine and repeat that dose of ASA. If a reaction is limited to the nasal membranes, use intranasal oxymetazoline, azelastine, or both and continue with the next dose of aspirin. In 1500 patients challenged at the Scripps Clinic, 3 (0.002%) experienced systemic symptoms and responded to intramuscular epinephrine with no hospitalizations.

Maintenance dose of aspirin

The optimal dose of aspirin is not known. The benefit of high-dose aspirin (650 mg twice a day) in controlling airways disease in patients with AERD is well established.[E28,E42] A study comparing twice-daily dosing of 325 versus 650 mg of ASA found that approximately half of the patients did well on the lower dose, whereas half required the 1300 mg/d dose. Our recommendations are to start at 650 mg twice a day for 1 month and titrate the dose down by 325 mg each month, as tolerated. A minimum dose of 325 mg of ASA is suggested for those patients who require cardioprotection because it also allows for cross-tolerance to all COX-1 NSAIDs but might not adequately treat the airways disease.[E42]

There is a refractory period of 48 to 72 hours after aspirin desensitization; this is maintained by continued aspirin therapy. If more than 96 hours passes between aspirin doses, we recommend repeat desensitization.[E43] If between 72 and 96 hours passes between aspiring doses, the patient should return to the office and receive 325 mg of ASA in a controlled setting.

Strong evidence supports the safety and clinical effectiveness of aspirin desensitization in the treatment of AERD.

THE CASE REVISITED

The patient's respiratory status was stabilized with a short course of high-dose corticosteroids, which also allowed for a medical polypectomy, optimizing the long-term outcomes of aspirin therapy. A recent evaluation by a head and neck surgeon found mild polyps, but the patient was not believed to be a surgical candidate. He was started on 10 mg/d montelukast 1 week before the ketorolac and oral aspirin challenges. Antihistamines were discontinued, and he maintained his combination formoterol and mometasone. A baseline pulmonary function test at the time of the procedure was notable for an FEV_1 of 3 L/s (or 67% of predicted value). After obtaining informed consent, the protocol was initiated. The patient had a naso-ocular reaction at the last step of the ketorolac challenge, which was treated with intranasal oxymetazoline. At 60 mg of aspirin, he had a 15% decrease in FEV_1, which was reversible with nebulized albuterol. He also experienced some mild urticaria that was responsive to the oral antihistamine cetirizine. Urticaria appearing during oral aspirin challenges can sometimes be quite dramatic, but typically, it resolves as the patient is desensitized to ASA and should not be an indication to discontinue the procedure. The 60-mg ASA dose was repeated with no further symptoms.

The patient was discharged from the clinic with stable pulmonary status. He returned the following day, at which point the oral challenge procedure was continued after confirming stable pulmonary function test results. He received the 150- and 325-mg doses of aspirin 3 hours apart with no further reaction. He was discharged home with instructions to start the 650-mg dosing that evening and continue 650 mg twice daily until follow-up in 1 month. At follow-up, he has been tolerating 650 mg of ASA with no reactions. He has had no asthma exacerbations or need for systemic steroids and has a sustained sense of smell.

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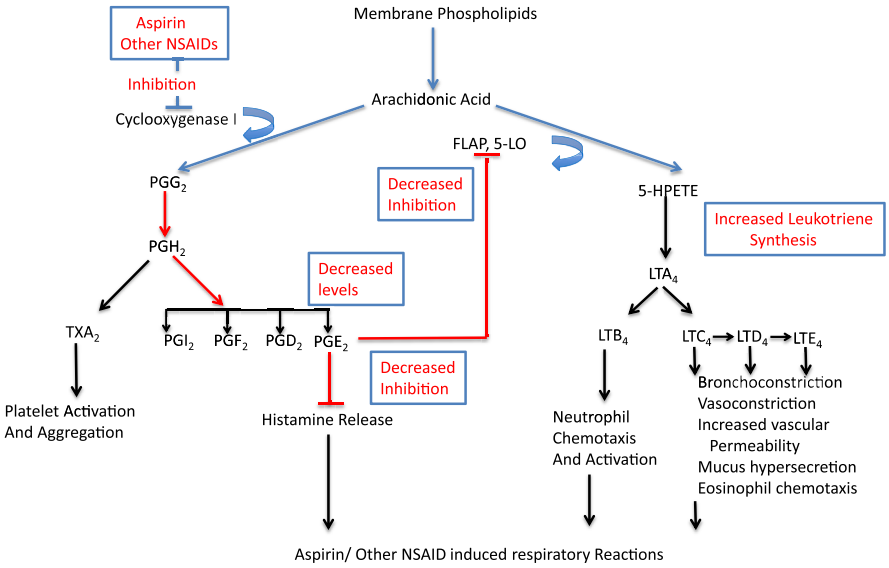

FIG E1. Schematic of the arachidonic acid pathway and associated findings in AERD pathophysiology, with increased levels of cysteinyl leukotrienes and their receptors, underproduction of prostaglandin E_2 *(PGE_2)*, and effect of aspirin/NSAID inhibition of COX-1 shown. *FLAP*, 5-lipoxygenase–activating protein; *5-LO*, 5-lipoxygeanse; *LT*, leukotriene; *TX*, thromboxane.

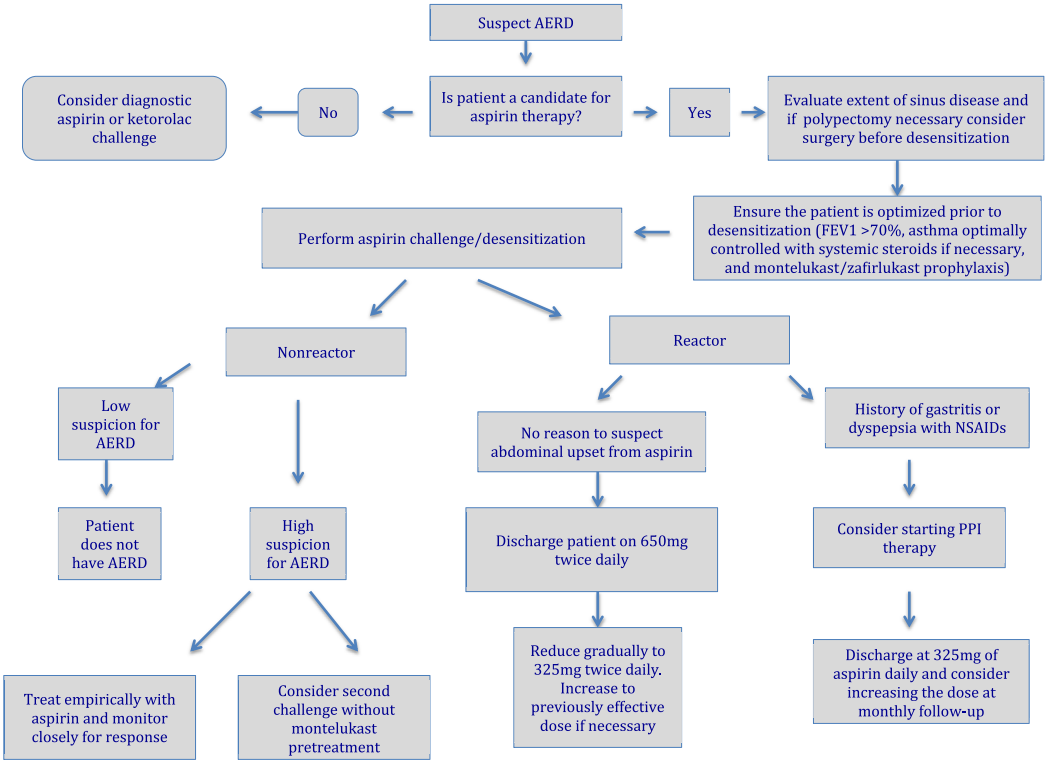

FIG E2. Workflow for a patient with AERD from diagnosis through desensitization. This algorithm outlines the various decision-making points that occur when a patient presents with a history suggestive of AERD. The issues of a negative challenge result, postdesensitization aspirin dosing, and gastrointestinal symptoms are highlighted.

Time	Intranasal Ketorolac and oral aspirin Challenge
Day 1	
8:00 Am	1 spray* (1.26 mg)
8:30 AM	2 sprays* (1 each nostril)
9:00 AM	4 sprays* (2 each nostril)
9:30 AM	6 sprays* (3 each nostril)
10:30 AM	60 mg* ASA
12:00 PM	60 mg* ASA
3:00 PM	Discharge instructions
DAY 2	
8:00 AM	150* mg
11:00 AM	325* mg
2:00 PM	**Discharge instructions**

To prepare ketorolac:

- Ketorolac 60 mg/2 ml and mix with 2.75 ml preservative-free normal saline

- Use nasal spray bottle that delivers 100 microliters/actuation

- Prime 5 sprays before use, then each spray actuates 1.26 mg ketorolac solution

- Instruct patient to tilt head down while spraying and to sniff gently to avoid swallowing solution

Reaction Possibilities#

- Naso-ocular alone
- Naso-ocular + asthma
- Asthma only

Above may be accompanied by:

Laryngospasm, hives, flushing, gastric pain, hypotension

*Clinical and objective evaluation with spirometry performed before each dose

Challenge/Desensitization Outcomes:

- **Negative Challenge:** no reaction to any dose including 3 hours after 325mg aspirin

- **Aspirin Desensitization**: after a reaction has been treated and resolved, repeat provoking dose. If no reaction: continue to escalate the dose as above
- At 325 mg of Aspirin, desensitization is complete.
- Discharge patient home to take 650mg of aspirin that evening

FIG E3. Nasal ketorolac and oral aspirin challenge protocol. This table provides details for combining a nasal ketorolac challenge with an oral aspirin challenge for patients with suspected AERD. It is contraindicated in patients with obstructing nasal polyps. A potential advantage is a shift of the respiratory reaction from the lower to the upper respiratory tract, with shortening of the time involved.

TABLE E1. Features strongly associated with AERD

- Severe persistent asthma
- Complete anosmia
- Pansinusitis on imaging
- Nasal polyposis refractory to sinus surgery (multiple surgeries)
- Age of onset in fourth decade
- Incomplete response to antibiotics or corticosteroids
- Respiratory reaction to any NSAID or aspirin

TABLE E2. Cross-reacting and non–cross-reacting NSAIDs in patients with AERD

Cross-reacting NSAIDs in AERD, COX-1 inhibitors
• Aspirin
• Ibuprofen
• Nabumetone
• Diclofenac
• Indomethacin
• Naproxen
• Difunisal
• Ketoprofen
• Piroxicam
• Etodolac
• Ketorolac
• Sulindac
• Fenoprofen
• Meclofenamate
• Tometin
• Flurbiprofen
• Mefenamic acid
Drugs that do not cross-react with ASA in patients with AERD
• Sodium salicylate
• Salicylamide
• Choline magnesium
• Azapropazone
• Dextropropoxyphene
• Celecoxib
• Parecoxib
• Lumaricoxib
• Acetaminophen*
• Meloxicam*

Highly selective COX-2 inhibitors and non-COX inhibitors are generally well tolerated in patients with AERD.
*At higher doses (≥1000 mg of acetaminophen or 15 mg of meloxicam) these NSAIDs can inhibit COX-1 but are generally well tolerated.

TABLE E3. Oral aspirin challenge protocol

Oral aspirin challenge		
Time	**Day 1**	**Day 2**
8 AM	20-40 mg*	100-160 mg
11 AM	40-60 mg	160-325 mg
2 PM	60-100 mg	325 mg
• Confirm that the patient's baseline FEV_1 is the same as the prior best value and that they have not used their albuterol rescue inhaler in the past week. If not, consider 1-day placebo challenge to determine stability of airways.		
• *Choice of dosing: lower dose is chosen if the patient is not using a leukotriene-modifying drug, has a low baseline FEV_1, and has had a recent hospitalization or emergency department visit for asthma.		
• By using a pill cutter, an 81-mg ASA tablet can be cut into a half or a fourth.		
• Measure FEV_1 every hour and wait 3 hours between doses.		
• FEV_1 should be at $\geq$1.5 L and >60% of predicted value.		
• After a reaction has been treated and resolved, go to step "a."		
a. Repeat the ASA provoking dose.		
b. If no reaction, continue to escalate dose every 3 hours as above.		
c. At 325 mg of ASA, desensitization/tolerance is complete.		
d. Patient should be instructed to start 650 mg of ASA that night as their first dose and continue with 650 mg twice daily.		

This is one of many published protocols for aspirin desensitization. Lower starting doses of aspirin are provided for patients who are not pretreated with a leukotriene-modifying drug or have a low FEV_1. Otherwise, a higher starting dose can be chosen.