Clinical pearls

Selection of patients for aspirin desensitization treatment

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Aspirin-exacerbated respiratory disease (AERD) is an acquired disease that consists of chronic hyperplastic eosinophilic sinusitis and nasal polyposis, asthma, and aspirin hypersensitivity.

Abbreviations used
AERD: Aspirin-exacerbated respiratory disease
GERD: Gastroesophageal reflux disease
5-LOINH: 5-Lipoxygenase inhibitor
LTR_1A: Leukotriene receptor 1 antagonist
NSAID: Nonsteroidal anti-inflammatory drug

ASPIRIN-EXACERBATED RESPIRATORY DISEASE AND CONCOMITANT PROVOKING FACTORS

There are very few patients with AERD who only have AERD and no other provoking factors. For example, in our series of 300 patients with AERD, two thirds had positive wheal-and-flare skin test responses that were frequently present since childhood.[1] Almost all patients with AERD have complications of infectious rhinitis and sinusitis (viral, bacterial, and fungal). Furthermore, all of the other myriad provoking factors for asthma, such as gastroesophageal reflux disease (GERD), irritant inhalation, and exercise, continue to be active provocateurs. Therefore clinicians need to identify other provoking factors and aggressively treat these non-AERD–provoking factors and mechanisms.

SEVERITY OF AERD

Although asthmatic patients with AERD tend to segregate in the severe persistent category, patients with AERD can have mild or moderate persistent asthma or even intermittent asthma. Furthermore, there is a subset of patients with AERD who have chronic hyperplastic eosinophilic sinusitis with nasal polyps but no asthma at all, including negative methacholine challenge results. As per the earlier points, the severity of asthma might be due to AERD itself or the addition of other provoking mechanisms. For example, we have seen patients with AERD who converted from severe asthma to mild intermittent asthma after a Nissan plication to correct their GERD (ie, severe GERD and mild AERD).

PHARMACOLOGIC TREATMENT OF AERD

We hope it is becoming clear that treatment of patients with AERD includes treatment of other provoking factors. If the patient has concomitant allergic rhinitis and asthma, particular attention should be paid to consideration of avoidance measures, antihistamines, and immunotherapy. Anti-IgE treatment for patients with both AERD and allergic asthma is currently under investigation.

Topical corticosteroids, leukotriene receptor antagonists (LTR_1A), and 5-lipoxygenase inhibitors (5-LOINHs) continue to be standard treatment for patients with AERD. These drugs are anti-inflammatory for AERD and effective for treatment of allergic respiratory diseases and exercise. Over the past 2 years, at the time of referral to us, 159 (86%) of 185 patients with AERD were taking montelukast, and 1 patient was taking zafirlukast. Although expensive, the use of both an LTR_1A and a 5-LOINH is a reasonable intervention in some patients with more severe disease. The use of systemic corticosteroids is common and necessary, particularly to control asthma, shrink nasal polyps, and provide drainage for infected sinuses. In a series of 300 patients with AERD, 45% used short courses of systemic corticosteroids, usually for infectious sinusitis episodes, and 32% used them

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on a daily or every-other-day basis.[1] Only 23% never required systemic corticosteroids.[1] The use of antibacterial and antifungal treatment is also frequently necessary but whenever possible should occur after sinus or sputum cultures.

ASPIRIN DESENSITIZATION TREATMENT

This intervention is both effective and underused. In a series of 172 patients with AERD treated with aspirin desensitization, significant reductions in infectious sinusitis episodes, symptom scores, and need for emergency department visits occurred. Improvement in olfactory scores and a decrease in need for systemic and nasal corticosteroids were observed.[2] There were no significant changes in the use of inhaled corticosteroids or LTR_1As, which were continued at the same doses. Because of side effects (epigastric pain being the most common), 14% discontinued aspirin during the first year. After eliminating patients who stopped aspirin because of side effects, the good to excellent improvement rate after 1 year of aspirin treatment was 115 (78%) of 148. Another 22 patients did not complete the first year of follow-up for a variety of reasons unrelated to side effects of aspirin. Of the remaining 126 patients, 110 (87%) enjoyed a good or excellent improvement in their clinical courses. In the 32% of patients taking prednisone daily or every other day, their average daily dose was 10.2 mg of prednisone at the beginning of aspirin treatment, 8.1 mg/d at 6 months, and 3.6 mg/d at 12 months ($P < .0001$). For the 45% of patients who were taking intermittent courses of systemic corticosteroids, courses decreased from 2.7 per year before aspirin desensitization treatment to 0.9 per year at 6 months and 0.5 per year at the 1 year ($P < .0001$). It is interesting and provocative that 14 of 16 patients who failed to respond to aspirin desensitization had concomitant IgE-mediated rhinitis and asthma: 14 of 14 to dust mites, 13 of 14 to animals (with animals remaining in the homes of 11), and 7 of 14 to molds.

CANDIDATES FOR ASPIRIN DESENSITIZATION TREATMENT

Some patients with AERD have mild upper airway disease, with asthma attacks occurring rarely (after ingesting aspirin/nonsteroidal anti-inflammatory drugs [NSAIDs] and perhaps with one viral respiratory infection per year). These patients are largely asymptomatic while taking topical corticosteroids, sometimes an LTR_1A, and an occasional burst of prednisone and avoiding aspirin and NSAIDs. Other than the cost of the above medications versus the cost of aspirin, there is no particular reason to add aspirin desensitization to their regimen. On the other hand, the following categories of patients with AERD are candidates for aspirin desensitization treatment:

1. Patients with AERD who have no concomitant respiratory diseases but who have moderate or severe asthma, intractable nasal congestion, or both on the basis of their AERD should be considered for aspirin desensitization if they have failed to respond to topical corticosteroids, LTR_1As, and a 5-LOINH. Comment: This is an ideal group to treat with aspirin because they have severe disease, and yet the results of treatment will not be affected by a lack of response to treatment of a concomitant disease, such as allergic rhinitis and asthma. After aspirin treatment, many of these patients can reduce or discontinue other anti-inflammatory medications.
2. Patients with AERD whose concomitant respiratory diseases are also under aggressive therapy but have failed to respond to treatment, including topical corticosteroids, LTR_1As, and a 5-LOINH. Comment: This is a large and significant group of patients, but an impediment to a successful change in course, despite the addition of aspirin desensitization treatment, is lack of simultaneous treatment and modification of concomitant diseases. After daily treatment with aspirin, continuation of other treatments is likely to be required.
3. Patients with AERD who are multiple nasal polyp formers. Comment: Virtually all patients with AERD form nasal polyps, but some form and reform nasal polyps with greater frequency. It is routine for otolaryngologists to carry out extensive and careful endoscopic surgery on patients with AERD, only to be faced with new nasal polyps a few months later. Aspirin desensitization and daily aspirin treatment shifts the need for reoperation from an average of 1 every 3 years to 1 every 10 years.
4. Patients requiring systemic corticosteroids for control of AERD. Comment: Patients taking prednisone daily or every other day or taking frequent bursts are all candidates for aspirin desensitization treatment. The side effects of corticosteroids can be worse than AERD.
5. Patients with AERD who require aspirin for other diseases. Comment: The standard protocol for patients after receiving a coronary stent is a combination of aspirin, 325 mg every day, and clopidogrel (Plavix), 75 mg every day, for 3 to 6 months. This treatment significantly prevents thrombosis within the stent. Also, millions of individuals are taking 81 mg/d aspirin to prevent cardiovascular disease. Although this dose is high enough to maintain the aspirin-desensitized state, it is usually insufficient to treat AERD.

WHY IS ASPIRIN DESENSITIZATION TREATMENT UNDERUSED?

First and foremost, it might be difficult to know whether the patient has AERD. The condition is both underdiagnosed (patient not taking aspirin or NSAIDs for whatever reason) and overdiagnosed (patient has an unrelated asthma attack or exacerbation within 3 hours of ingesting aspirin or an NSAID). Second, the process of making the diagnosis with provocative aspirin challenges and of then proceeding to aspirin desensitization presents its own challenges. The first is the potential danger from

TABLE I. Outpatient aspirin desensitization for AERD: suggestions from the Allergy Division, Scripps Clinic

Rationale:

1. Aspirin-induced reactions are dose dependent. Aspirin given in small enough doses will usually induce smaller reactions than the historical reaction (650 mg of aspirin).
2. For many patients, historical aspirin reactions occurred before the use of controller therapies: ICSs, LABs, LTMDs, and SCSs. Pretreatment with these medications usually provides stability to the lower airways during aspirin challenge.

Patient selection:

1. Suspected AERD with mild-to-moderate prior historical reactions.
2. Unresponsive to ICSs, LABs, and LTMDs.
3. Aggressive nasal polyp formers.
4. Unable to discontinue SCSs or many bursts of SCSs.
5. In need of daily aspirin because of coronary artery disease.

Protocol:

One to 7 days before challenge, determine airway stability.

1. FEV_1 >60% of predicted value (>1.5 L absolute).
2. FEV_1 every hour × 3 hours—<10% variability.
3. Start or continue montelukast, 10 mg every day.
4. Start or continue ICSs/LABs.
5. Start SCS burst for low FEV_1 or any bronchial instability.
6. Discontinue antihistamines 48 hours before challenge.

Oral aspirin challenge

1. Day 1: start intravenous line at 7-8 AM with heparin lock (keep in for 3 days).
2. At Scripps, we use gelatin capsules with 30, 45, 60, 100, 150, or 325 mg of aspirin powder. You can use a pill cutter and 81-mg aspirin tablets. Use a first dose of 20.25 or 40.5 mg of aspirin followed by 60.75, 81, and 101.25 mg; then half a 325-mg aspirin tablet; and then a full 325-mg aspirin tablet. Increase every 3 hours.
3. FEV_1 and clinical assessment every hour or with any symptoms.
4. Reaction will likely occur with doses between 20 and 101 mg. When it occurs, treat with the medications described below. This is called the provoking dose.
5. After the patient is completely stabilized, the provoking dose can be repeated on day 1 (assuming another 3 hours before 5 or 6 PM). Otherwise, symptoms should be treated, the patient should be sent home, and the provoking dose should be repeated the next morning. Day 2: start with repeating provoking dose (if not given on day 1). Otherwise, physician can begin increasing the dose every 3 hours (101.25, 162, 325, and 650 mg).
6. If nasal, gastrointestinal, or cutaneous reactions occur on day 1, pretreat with H_1 and H_2 blocker for the remainder of the challenge sequence.
7. Chance of reaction to repeated threshold dose is small, but if it occurs, repeat that dose until reactions cease and then proceed to the next highest dose of aspirin.

Treatment of the aspirin-induced reactions

1. Ocular: topical antihistamine.
2. Nasal: antihistamine (oral) or diphenhydramine, 50 mg administered intravenously, topical decongestant.
3. Laryngeal: racemic epinephrine nebulization (2.5 mg/2 mL), 5 inhalations and pause.
4. Bronchial: 5 inhalations of β-agonist every 5 minutes until comfortable.
5. Gastrointestinal cramping: intravenous ranitidine, 50 mg.
6. Urticaria/angioedema: intravenous diphenhydramine, 50 mg.
7. Hypotension: epinephrine 1:1000 0.3 mL administered intramuscularly (occurred in 1 in 300 of our patients).

ICS, Inhaled corticosteroid; *LAB*, long-acting bronchodilator; *LTMD*, leukotriene modifier drug; *SCS*, systemic corticosteroid.

giving a dose of aspirin and having the patient experience a severe asthma attack or a systemic reaction caused by release of histamine into the circulation. Second, acquiring the knowledge of how to conduct these challenges requires special efforts. Third, challenges are space and time consuming and require constant nursing supervision and intervention. Comment: Fortunately, several events have occurred in the past few years that are helpful. First, pretreatment with a cysteinyl LT_1RA (montelukast or zafirlukast), zileuton, or both significantly reduces the incidence of any aspirin-induced bronchospastic responses and modifies those that occur.[3] Second, because of the above, expensive inpatient aspirin desensitization has largely been replaced with treatment in outpatient aspirin desensitization centers. After proper training, nurses have become very skilled at conducting oral aspirin challenges, with a responsible physician on site, selecting each advancing dose of aspirin. Not every community in the United States has one of these centers, but cooperation to develop one per community or region allows a 1-time referral to a place where maximization of resources, personnel, and expertise can be focused. See Table I for a suggested protocol for outpatient aspirin desensitization.

WHAT IS THE PROPER DOSE OF ASPIRIN AFTER ASPIRIN DESENSITIZATION HAS BEEN COMPLETED?

After aspirin desensitization, start aspirin, 650 mg twice daily, for the first month and reduce the dosage to

325 mg twice daily if the patient is doing well (nasal congestion is gone and sense of smell has returned). If the patient is taking systemic corticosteroids daily or every other day, reduce and discontinue corticosteroids before reducing aspirin. After reducing the dose, if there is a return of nasal congestion, increase aspirin doses to prior levels.

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