

State of the Art: Medical treatment of aspirin exacerbated respiratory disease (AERD)

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ABSTRACT

Aspirin exacerbated respiratory disease (AERD) is characterized as adult onset asthma, nasal polyps, chronic rhinosinusitis, and hypersensitivity to a cyclooxygenase-1 (COX-1) inhibitor, viz aspirin or nonsteroidal antiinflammatory drugs (NSAIDs). The method for diagnosing AERD is with aspirin challenge, and treatment includes aspirin desensitization followed by continued daily aspirin. Although oral challenge has been the mainstay in the United States, lysyl-aspirin has been validated as a diagnostic tool for aspirin-sensitive asthma and will be discussed further in this article. The challenges with aspirin therapy surrounding endoscopy and perioperative aspirin therapy will be discussed. Additionally, daily aspirin therapy is not for everyone. Aspirin is relatively contraindicated in those with a history of gastrointestinal bleed and an absolute contraindication in pregnancy. Aspirin desensitization and subsequent treatment has been shown to be highly effective for AERD.

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This “State of the Art” article will emphasize certain aspects of the treatment of aspirin exacerbated respiratory disease (AERD) that are important but less well known and not necessarily easily found in other sources related to this topic. Briefly, the typical history of a patient with AERD includes previous tolerance of cyclooxygenase-1 (COX-1) inhibitors, including aspirin and nonsteroidal antiinflammatory drugs (NSAIDs). Many patients with AERD report that the disease initially develops with symptoms of an acute upper respiratory tract infection that evolves into clinical features of nasal congestion with anosmia and progression to chronic pansinusitis and nasal polyps. Asthma can precede the upper airway disease or develop later.¹ A minority may not even have asthma or bronchial hyperreactivity as defined by a methacholine challenge. The sections covered in this article will include the following: treatment, aspirin desensitization, colonoscopy and aspirin, approach to surgery in AERD, AERD patients who are candidates for aspirin desensitization and treatment, and AERD patients who are not candidates for aspirin desensitization and treatment.

Treatment

The treatment of AERD includes complete avoidance of COX-1 inhibiting drugs or aspirin desensitization with continuous aspirin therapy.² Surgery may also be necessary to remove obstructing tissues preventing appropriate topical therapy, drain blocked sinuses, and remove inflammatory mediators in trapped mucin. Surgery can also allow for intraoperative therapy in the form of steroid-impregnated nasal packing.³ Medications are also helpful. For instance, topical and systemic corticosteroids help to block eosinophilic infiltration. Leukotriene modifiers and 5-lipoxygenase inhibitors, specifically montelukast, decreases lower respiratory reactions without significantly masking upper respiratory symptoms.^{4,5}

Aspirin Desensitization

Oral Aspirin Treatment. The goal of aspirin desensitization in patients with AERD is to decrease nasal congestion, decrease the need for additional sinus and polyp surgeries, decrease the frequency of infectious sinusitis per year, improve the sense of smell, and improve asthma

control.⁶ The improvement in asthma control maybe both a direct effect of the aspirin as well as an indirect effect improving the rhinosinusitis. Aspirin treatment in AERD patients also reduces the need for systemic corticosteroid bursts.⁷ In the Berges-Gimeno study, the average daily dose of systemic corticosteroids in those patients taking daily and alternate-day prednisone decreased from 10.7 to 3.8 mg per day.⁶

The aspirin dose used to treat AERD patients is variable depending upon the goal. If a patient has well-controlled AERD and the goal is to take aspirin for cardiovascular disease prevention, then challenge and desensitization to 81 mg is sufficient.⁸ Patients remain indefinitely desensitized to 81 mg by taking this dose on a daily basis. However, this dose is not sufficient to allow patients to safely consume any other dose of NSAIDs.⁷ A dose of 325 mg per day is needed to remain desensitized to other COX-1 inhibitors.

Lee *et al.*⁹ showed that 325 mg twice daily was equally efficacious as 650 mg twice daily to prevent recurrence of symptoms. In this study, 137 subjects who had undergone successful aspirin desensitization were randomized into two groups, 650 mg twice daily versus 325 mg twice daily. After a month of randomization, the subjects either decreased or increased their dosage based on their symptoms and continued the same dose for 12 months. 48% of subjects on 325 mg twice daily did not require a dosage increase, whereas 52% of subjects required an increase in dosage to 650 mg twice daily because of inadequate symptom control. Subjects that were taking either 325 mg twice daily or 650 mg twice daily showed reduced number of sinus infections, hospitalization for asthma, and sinus operations. Subjects also reported improvement in anosmia, asthma symptoms, and less need for systemic corticosteroids. Based on these results, it was recommended that patients begin on 650 mg twice daily and subsequently reduce their dose to 325 mg twice daily as tolerated.⁹

Some studies in the literature have shown clinical efficacy at lower doses of daily aspirin therapy in AERD patients. Rozsasi *et al.* found that 100 mg per day was not effective treatment for either the upper or the lower respiratory tract in any subject.¹⁰ Polyps returned in all seven patients, and these patients required surgery at the one-year follow-up. There was no change in asthma symptoms, pulmonary function, or medication use. However, all seven subjects treated with 300 mg per day had no polyp regrowth and surgery was not required. In addition, they had no symptom change, decreased medication use, and improved pulmonary function testing.¹⁰

Other studies have demonstrated benefit from doses between 100 and 300 mg per day.^{10–12} The most recent of these studies was demonstrated by Comert *et al.*,¹¹ who included 40 patients treated with aspirin 300 mg per day and followed at one and three years. There was a statistically significant improvement in sense of smell, reduced sinus surgeries, and reduced need for systemic steroids.

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Topical Aspirin Treatment. In Europe, lysyl-aspirin is available for the diagnosis and treatment of AERD. Several studies have been published using different protocols and doses of lysyl-aspirin in the treatment of AERD. There were also conflicting conclusions and decreasing effectiveness over time. Patriarca *et al.* concluded that topical lysyl-aspirin is effective in preventing the recurrence of nasal polyps after polypectomy.¹³

Similarly, Nucera *et al.* looked at patients who underwent surgical polypectomy and were given lysyl-aspirin; these patients were followed for one, three, and six years.¹⁴ Of the surgical polypectomy and lysyl-aspirin treated patients, 93% were relapse free at one year, 55% were relapse free at three years, and 35% were relapse free at six years.¹⁴ In contrast, the controls (surgical polypectomy without medical treatment) were 49% relapse free at one year, 15% relapse free after three years, and 6.5% relapse free six years after surgery.¹⁴ A highly significant statistical difference was seen between the relapse rates of lysyl-aspirin-treated subjects and controls ($p < 0.001$). In contrast, Parikh *et al.* evaluated 11 AERD patients and treated them with 16 mg of topical lysyl-aspirin every other day for six months. They found no statistically significant clinical difference between the active versus placebo treatments.¹⁵

Colonoscopy and Aspirin

Colonoscopies present another dilemma for the aspirin desensitized patient. The average age of an AERD patient's onset of disease is 34 years.¹⁶ By the time patients with AERD are diagnosed, desensitized, and treated with aspirin, they are not far from 50 years old when they will likely undergo a screening colonoscopy. Although some gastroenterologists prefer holding aspirin before a colonoscopy, there is now data showing no increased risk of bleeding when performing colonoscopies with biopsies in patients on aspirin and NSAIDs compared with those who were not.¹⁷ The most recent study looked at patients on acetylsalicylic acid/NSAIDs and saw no significant difference between postpolypectomy bleeding compared with similar patients not taking such medications. The authors concluded that holding acetylsalicylic acid/NSAIDs before a colonoscopy or polypectomy was unnecessary.¹⁷

Approach to Surgery in AERD

When an AERD patient on aspirin has surgery, there is a potential risk of increased bleeding. However, several procedures and surgeries can be performed on aspirin without this increased risk. These procedures and surgeries include colonoscopy with biopsy (as discussed above), carotid endarterectomy, neuraxial blocks, cataract surgery, coronary artery bypass grafting, laparoscopic cholecystectomy, and colorectal cancer resection.¹⁷⁻²³ Although it is generally recommended that patient having sinus surgeries (including functional endoscopic sinus surgery) hold aspirin anywhere from 5 to 14 days, there is no scientific data supporting this.²⁴⁻²⁶ One should at least weigh the risk of stopping aspirin with the risk associated with its continuation in AERD patients on aspirin. Discontinuing aspirin is ultimately the decision left to the surgeon, but if aspirin is held for longer than three days, then repeat desensitization is required before the patient can safely resume aspirin again.²⁷

AERD Patients Who Are Candidates for Aspirin Desensitization and Treatment

Candidates for aspirin desensitization and treatment include AERD patients who require aspirin or NSAIDs for treatment of other diseases, regularly take or require frequent bursts of systemic corticosteroids, or have had multiple polypectomies or sinus surgeries. There is another group of patients (or physicians) who opt for treatment, because they are not satisfied with their clinical state. It is also not uncommon for an AERD patient to seek desensitization because of frustration with anosmia.

Which AERD Patients Are Not Candidates for Aspirin Desensitization and Treatment?

Although most practitioners consider a gastrointestinal bleed to be a contraindication for aspirin desensitization, this is only a relative contraindication. Studies have shown a decreased rate of bleeding in patients on NSAIDs who take proton pump inhibitors.²⁸ Additionally, one could use agents such as misoprostol to replace prostaglandin E₂, which is decreased in AERD patients and is further reduced with aspirin treatment.²⁹ Prostaglandin E₂ is also cytoprotective to the gastric mucosa.³⁰ Cotherapy with these medications can reduce gastrointestinal complications associated with aspirin therapy.

Pregnant AERD patients are not candidates for aspirin desensitization and treatment because aspirin is an absolute contraindication during the third trimester of pregnancy. Aspirin use during pregnancy is associated with premature closure of the ductus arteriosus and neonatal primary pulmonary hypertension.³¹

CONCLUSION

The approach to treating these patients with AERD involves addressing nasal and sinus pathology, reducing exposure to aeroallergens, asthma control, and aspirin desensitization with daily aspirin. Strong evidence supports the clinical effectiveness of aspirin desensitization in the treatment of AERD. AERD desensitization improves respiratory symptoms and reduces polyp formation, nasal congestion, and need for surgery. Continued research efforts in understanding the pathophysiology and possible prevention of AERD are needed to manage this condition more effectively.

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