



## **Aspirin-Exacerbated Respiratory Disease: Guide for Physicians**

### **TERMINOLOGY**

- Aspirin-exacerbated respiratory disease (AERD) = triad of **asthma**, chronic rhinosinusitis with **nasal polyposis**, and acute upper and lower **respiratory reactions to nonsteroidal anti-inflammatory drugs (NSAIDs)** that inhibit cyclooxygenase-1 (COX-1).
- Also known as Samter's triad, aspirin-sensitive or aspirin-intolerant asthma.

### **CLINICAL PRESENTATION**

AERD is typically diagnosed in adulthood. For most patients, refractory rhinitis develops first and evolves into chronic eosinophilic rhinosinusitis, anosmia, and nasal polyps. It is common for patients to require multiple sinus surgeries and/or polypectomies. As the rhinosinusitis becomes more severe, most develop asthma. Within this timeframe, patients also become NSAID sensitive. The asthma and nasal symptoms of AERD continue over time, despite with NSAID avoidance. Rarely, patients develop NSAID sensitivity prior to the other components of the triad.

### **DIAGNOSIS**

Therapies to target AERD inflammation are necessary for optimal outcomes, therefore making the diagnosis is paramount. In patients who present with asthma, nasal polyposis, and respiratory reaction(s) to NSAIDs, a diagnosis of AERD can often be made clinically. The following additional features are common in AERD:

- 1) Rapid recurrence of nasal polyps after surgery
- 2) Respiratory reactions with alcohol consumption (in 80% of patients with AERD)
- 3) Peripheral blood and nasal polyp tissue eosinophilia

History alone may be inadequate to accurately diagnose AERD because 15% of patients with AERD do not become aware of their NSAID hypersensitivity until they undergo a physician-monitored aspirin challenge. These patients tend to fall into one of the following groups:

1. They have not used NSAIDs since developing the other symptoms of AERD.
2. Leukotriene modifiers (e.g. montelukast, zileuton) can block NSAID-induced symptoms such that the patient is unaware of any reaction to these medications.
3. They are already using 81mg aspirin daily for cardiac protection. These patients might still be aspirin sensitive at higher doses.



## MANAGEMENT

### 1. NSAID avoidance –

- Avoid all COX-1-inhibiting NSAIDs, which are frequently found in over-the-counter (OTC) preparations
- Acetaminophen is safe although mild reactions can occur at 1000mg doses
- Celecoxib is the only available selective COX-2 inhibitor in the United States and is, except in rare cases, well-tolerated in patients with AERD.

### 2. Aspirin desensitization and high-dose aspirin therapy –

- Aspirin desensitization and initiation of daily high-dose aspirin therapy is considered the gold standard of treatment in AERD.
- Aspirin treatment improves sinus and asthma outcomes in most AERD patients
- Aspirin therapy started shortly after a debulking polypectomy may be the most effective sequence for controlling polyp regrowth.
- The optimal daily dose of aspirin is usually 325mg twice a day or 650mg twice a day.

### 3. Leukotriene-modifying drugs –

- Montelukast and zileuton have been shown to improve asthma control and lung function in AERD.
- Montelukast reduces bronchoconstrictive response during aspirin desensitization; thus, pretreatment with montelukast is recommended for patients undergoing aspirin desensitization.

### 4. Biologics –

- Several reports indicate that **omalizumab** may decrease aspirin-induced symptoms and improve the symptoms of AERD.
- **Mepolizumab** is a humanized anti-IL-5 monoclonal antibody that is approved to treat severe eosinophilic asthma, and **dupilumab** is a humanized anti-IL-4R $\alpha$  antibody that will be approved to treat moderate-to-severe asthma by the end of 2018. Both mepolizumab and dupilumab decrease total nasal polyp score in patients with nasal polyposis (including AERD).

### 5. Dietary interventions - Central to AERD pathogenesis is dysregulated metabolism of the omega-6 arachidonic acid resulting in the overproduction of cysteinyl leukotrienes and other proinflammatory lipids.

- A diet that decreases omega-6 fatty acid consumption to below 4g per day and increases omega-3 to above 4g is a helpful therapeutic adjunct in many patients with AERD.