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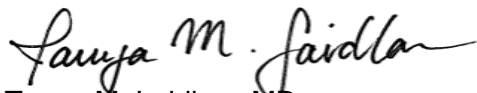
Dear Health Care Provider,

This patient is under specialized care with a condition known as “Aspirin-Exacerbated Respiratory Disease” or AERD, and previously known as Samter’s Triad. This is a unique condition in which patients usually suffer from asthma, sinus disease and nasal polyps, and develop hypersensitivity reactions to aspirin and other NSAIDs. It is further unusual because it is a condition in which, by definition, patients are allergic to aspirin but following an aspirin desensitization procedure, enjoy significant therapeutic benefit from taking aspirin every day. In AERD, patients have a significant burden of illness with high systemic corticosteroid requirements, high health care utilization for asthma exacerbations and sinusitis flares, and frequent sinus surgery. Many patients have a need for sinus surgery as frequently as every other year to control nasal polyp growth.

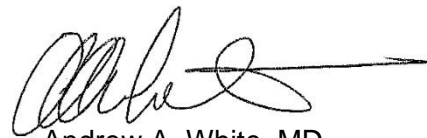
Daily aspirin therapy, at a dose of 650mg-1300mg per day, has been shown in four double-blind, randomized-controlled studies, to control polyp regrowth and sinus inflammation. Although there are certainly risks of being on long-term aspirin, these risks are reviewed in a balanced discussion with patients in consideration of the burden of their underlying illness. Longitudinal studies show that the vast majority of patients on long-term aspirin therapy do not have bleeding complications nor gastrointestinal ulceration.

We have heard from our patients that occasionally physicians have expressed concern over the high recommended dose of aspirin. Please be assured that the recommendation to place the patient on aspirin was done after a lengthy consultation and a shared-decision making process, and that an extensive risk/benefit discussion went into the decision. As with many other medications, aspirin therapy may have some safety concerns but also has a huge benefit on patient health outcomes.

Sincerely,



Tanya M. Laidlaw, MD
Director of Translational Research in Allergy
Director of AERD Center
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Andrew A. White, MD
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Summary of medications commonly used for patients with aspirin-exacerbated respiratory disease (AERD)

Inhaled corticosteroids or combination inhaled corticosteroid + long-acting bronchodilator

These medications are frequently used to treat asthma symptoms and are generally recommended to be taken every day, either once a day or twice a day. The inhaled corticosteroid component is intended to decrease the inflammation in the lungs, and the inhaled long-acting bronchodilator is intended to open up the lungs throughout the day and can be thought of as "long-acting albuterol". All medications in this class are prescription-only.

- Flovent® (fluticasone = steroid-only inhaler)
- QVAR® (beclomethasone = steroid-only inhaler)
- Pulmicort Flexhaler® (budesonide = steroid-only inhaler)
- Alvesco® (ciclesonide = steroid-only inhaler)
- Aerospir® (flunisolide = steroid-only inhaler)
- Asmanex® (mometasone = steroid-only inhaler)

- Advair® (fluticasone + salmeterol = combination inhaler)
- Wixela® (fluticasone + salmeterol = combination inhaler) (generic)
- Symbicort® (budesonide + formoterol = combination inhaler)
- Dulera® (mometasone + formoterol = combination inhaler)
- Breo Ellipta® (fluticasone + vilanterol = combination inhaler)

Intranasal corticosteroid sprays and rinses

These medications are frequently used to treat nasal congestion and nasal polyps, and are generally recommended to be taken every day, either once a day or twice a day. When the corticosteroid is sprayed or rinsed directly into the nose and sinuses, it can help to decrease the inflammation and swelling in those areas. Some medications in this class are available OTC.

- Flonase® (fluticasone spray) – available OTC
- Nasacort® (triamcinolone spray – available OTC)
- Rhinocort® (budesonide spray) – available OTC)
- Nasonex® (mometasone spray) – available only as a prescription
- Pulmicort Respules® (budesonide suspension liquid) – available only as a prescription, to be used either mixed in a saline sinus rinse solution, or instilled directly into the nostrils
- Xhance® – fluticasone spray in a new delivery mechanism – prescription only

Anti-leukotriene medications

Patients with AERD usually produce very high levels of inflammatory mediators called leukotrienes, and these contribute to a lot of the symptoms patients experience. All medications in this class are prescription-only.

- Singulair® (montelukast) ⇒ This is a pill taken once a day that blocks one of the receptors for leukotrienes. It is available by prescription-only and has an available generic form as well



- Accolate® (zafirlukast) → this is pill taken twice a day the blocks the same receptor as Singulair
- Zflo CR® (zileuton) ⇒ This is given as 2 pills taken twice a day and it blocks the enzyme that produces leukotrienes, so that leukotriene levels are lowered overall. The medication is quite expensive, though through the Zflo connect® program there are helpful discounts available.

Injections/Infusions

The following “biologic” medications are approved to treat moderate-to-severe eosinophilic or allergic asthma.

- Nucala® (mepolizumab) ⇒ This is an injection every 4 weeks that is approved for patients ages 12 and older. Mepolizumab works by decreasing inflammation caused by the signaling of the cytokine IL-5.
- Cinqair® (reslizumab) ⇒ This is an infusion every 4 weeks that is approved for adults (18 years and older). Reslizumab works by decreasing inflammation caused by the signaling of the cytokine IL-5.
- Fasenra® (benralizumab) ⇒ This is an injection once every 8 weeks after the first 2 months and is approved for patients ages 12 and older. Benralizumab works by decreasing inflammation caused by the signaling through the IL-5R α receptor.
- Xolair® (omalizumab) ⇒ This is an injection every 2 or 4 weeks approved to treat moderate-to-severe persistent allergic asthma in patients 6 years and older. It targets the IgE antibody to decrease inflammation and the allergic asthma response.
- Dupixent® (dupilumab) ⇒ This is an injection every two weeks that patients can learn to perform at home, approved to treat moderate-to-severe eosinophilic asthma or steroid-dependent asthma in patients ages 12 and older. It is approved to treat nasal polyps in adults 18 years and older. Dupilumab works by decreasing inflammation caused by the signaling of the cytokines IL-4 and IL-13.

Aspirin

Physician-supervised aspirin desensitization followed by daily high-dose aspirin is a widely used treatment for AERD. The doses that work best for most patients are either 650mg twice a day or 325mg twice a day. Taking high-dose aspirin often improves sinus and asthma symptoms and slows polyp regrowth after surgery in patients with AERD. Aspirin desensitization appears to have the best outcomes when it closely follows sinus surgery.



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-4Rα 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.

First Edition

Aspirin Exacerbated Respiratory Disease

A Guide for Patients

Andrew A. White, MD

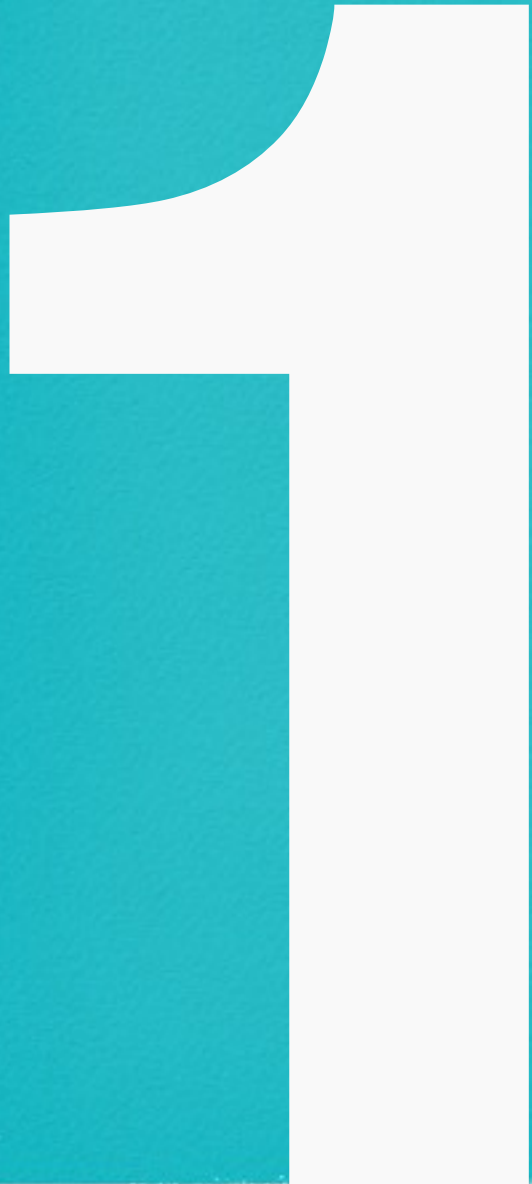
About the author:

Andrew White, MD, completed his initial medical training in Internal Medicine in the United States Navy before getting his Allergy and Immunology training at Scripps Clinic in San Diego. He joined the faculty and currently runs the Aspirin Exacerbated Respiratory Disease clinic there.

He is the recipient of the generous mentorship of Drs. Ron Simon, Katharine Woessner, David Mathison and Donald Stevenson who have done more than any group to further our understanding of AERD.

He is married with four children - two boys and two girls. When he isn't at work you will find him watching one of his kids' soccer games or out on the trails mountain biking.

Introduction



Introduction

Who am I?

So I am an allergist who specializes in Aspirin Exacerbated Respiratory Disease. Those of us who study this disease and take care of patients with it are constantly fascinated by it. It is a bizarre and intriguing illness. Much like the Rosetta Stone was the key to finally be able to decode an ancient language, AERD has the potential to decode and teach us a lot about asthma, allergies and sinus diseases.

I am one of the people who finds this disease fascinating and love taking care of patients with it. I have been doing research and along with others, am committed to finding out more about what is going on.

Who are you?

So you are probably a patient with AERD. Or at least you think you have AERD. Hopefully by the end of this book you will know how to get properly diagnosed. I also suspect that you are not quite as “fascinated” with this disease as I am. You are understandably probably much more interested in learning about why you got this disease in the first place - and how to make it go away. I will do my best to point towards how we ultimately hope to figure this out.

Names



Can we agree on a name?

The world of allergy still struggles to agree on a name for this condition. Many physicians, including myself, believe that Aspirin Exacerbated Respiratory Disease or AERD is the best name. I'm going to call it AERD for the duration of the book.

AERD was first described by M. Fernand Widal in 1922. It has at times been referred to as Widal's syndrome. Then in 1967 Dr. Max Samter published a paper describing the classic triad and for the next 25 years, the syndrome bore the name "Samter's Syndrome" In the early part of the 1900's through the 1980's many diseases were named after the discoverer. It makes sense, since a lot of things in science are named after the person who discovered them. The big problem in medicine is what if two different Dr. Jones discover completely different diseases at the same time and both decide to name it "Jones Syndrome?" You can see how that would get confusing. Or maybe you have similar sounding names like "Sail's disease" and "Sayle's syndrome." So there was a push to start naming diseases in a descriptive way. Unfortunately, that sometimes means long and somewhat clunky names like AERD. But to people who use it, there is no doubt what we mean.

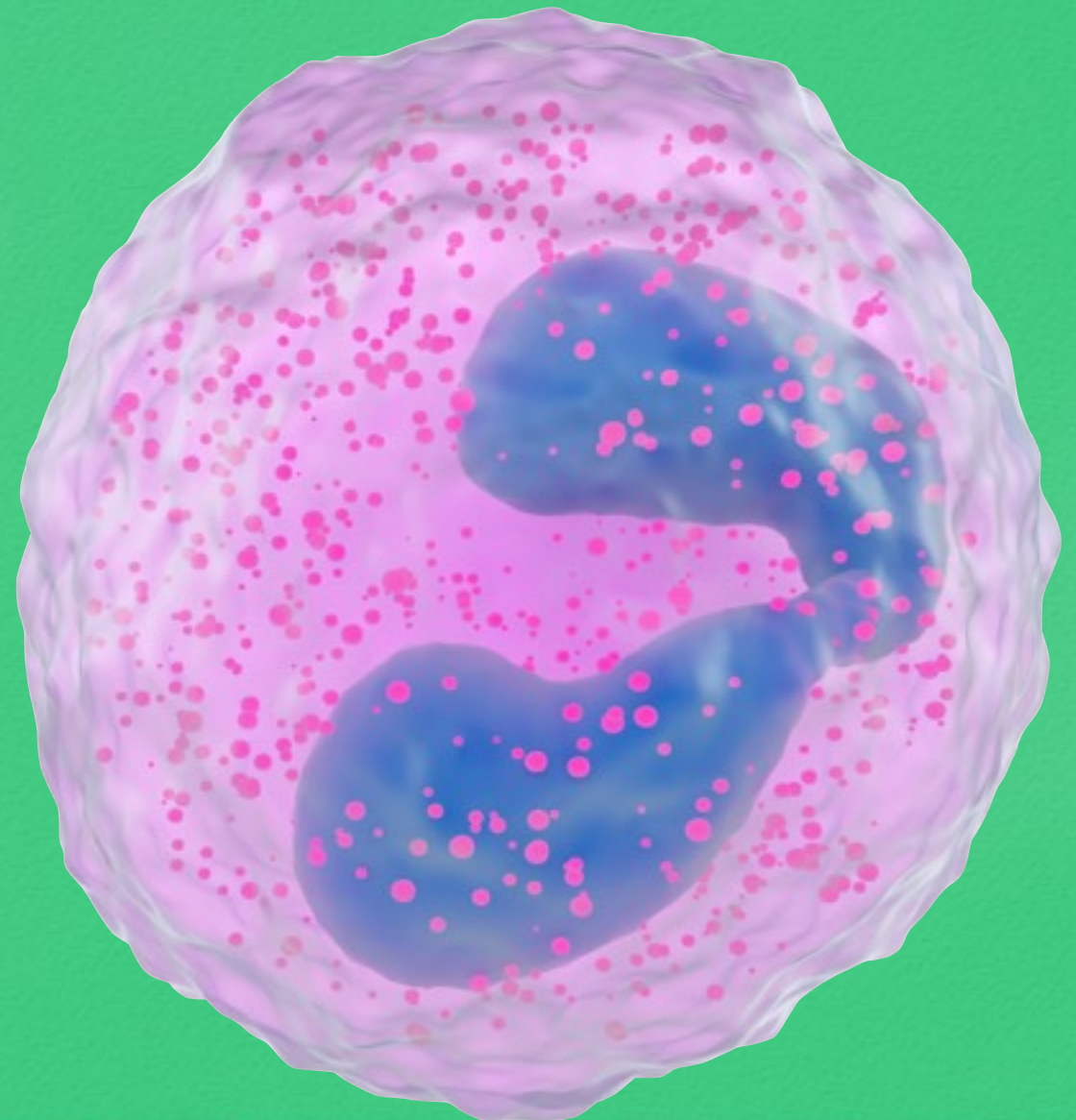
So as this shift in naming was taking place, in different places around the world, names like "Aspirin Induced Asthma" and "As-

pirin Intolerant Asthma" began to replace Samter Syndrome. The problem with "Aspirin induced Asthma" is that not all patients necessarily have asthma. So it was not completely accurate and could be confusing as to whether the sinus problems of AERD are actually a separate disease.

Most Allergy physicians in the United States now commonly use AERD when referring to this disease. Many Head and Neck Surgeons seem to still use "Samter Syndrome" or "Aspirin Intolerance." In Europe, the old name "Aspirin Induced Asthma" is still commonly used. In almost all cases, we are all talking about the same thing.

What

3



What is going on?

Once it is completely present, AERD is a disease that affects the airway. This includes the lungs, the nasal passages (your nose) and the sinuses. It almost always happens in people who have nasal polyps. It turns out that for most people, the polyps are the worst players.

What tends to happen for most folks is that the polyps and sinus problems start first. As the sinus problems worsen and the polyps grow, the asthma gets worse. Most people ride on a roller coaster of asthma that is dictated by what is going on in the sinuses. Sinus infection = asthma flare up. Polyps growing back = asthma getting worse.

I think the best way to think about this disease is kind of like how we think about an earthquake. Where I live in California, we occasionally will hear about an earthquake on the news, and even though a big part of the state may feel it, the real question is always “where is the epicenter?” Well, the sinuses are the epicenter for this disease. And I know that if you have this disease you probably already knew that.

Inflammation

If you are REALLY interested in what is going on, I will go over it in more and more detail. As much as I would like to keep it exciting and fascinating, it might quickly get dry and boring. Feel free to fast forward....

The first step is to understand the word ***inflammation***. It has a negative connotation, and most of us, if asked if we wanted to experience “inflammation,” would politely decline. But a life without inflammation would unfortunately be very, very short. We need inflammation to help our bodies fight infection. The only way that our bodies can know if we are infected is to send out signals. These signals draw more white blood cells to the area and rev up the production of chemicals that can fight bacteria, fungi and viruses. If we did not have this ability, we could die from something as simple as a common cold. In fact, babies who are born with a rare defective immune system known as Severe Combined Immune Deficiency (SCID) are born with critical pathways of the immune system missing that make it impossible for them to combat infection by triggering inflammation. For most of these babies the only effective treatment is a bone marrow transplantation to give them a new immune system.

So we definitely need inflammation. But too much of it can also be a bad thing. Autoimmune diseases like Rheumatoid Arthri-

tis, Crohn's Disease and Lupus are all diseases where the immune system causes inflammation to a completely normal part of the body - a part that does not have an infection. But our own body tries to fight it off like it is infected. This can be uncomfortable, come with a variety of other problems, and in time can permanently damage these tissues.

In AERD, you can think of it kind of like your body is trying to fight off a cold virus - from 10 years ago - and it is fighting it very, very hard, despite the fact that that cold virus was gone a long time ago. Whenever we get a cold our immune system simultaneously does two things: the first is to rev up inflammation to get things under control, but the second thing is to start sending signals out to dampen and turn off the inflammation as soon as it is no longer needed.

I think the best analogy would be in areas that are prone to wildfires and the fire department does a "controlled burn". They purposely set fire to a field in order to prevent the field from catching fire in the future. The purpose of the fire is for good, but could easily be dangerous, so as the firemen set the fire, they are ready with hoses and equipment to immediately put it out when it has served its purpose.

AERD has a more intense form of inflammation than all of the other common diseases that allergists take care of in the airways. Over and over again, studies have shown that patients with AERD have harder times with their asthma, have more diffi-

culty controlling their sinuses, and seem to need more medicine. This is all because the inflammation that is going on has gone completely out of control.

The two main allergy cell types in our bodies are known as **mast cells** and **eosinophils**. Both of these cells have many normal functions that keep us healthy. But they are both notorious for the allergy problems that they cause. Both of these cells are important in hay fever, eczema and asthma. And although both of them are important in AERD, the eosinophil is perhaps most prominent.

Eosinophils are beautiful pink cells under the microscope. They are actually named after "Eos" the goddess of the dawn in mythology. They contain a variety of packages in their cell called granules and these granules release a lot of things that cause inflammation. In AERD, your polyps are filled with eosinophils. Your lung lining is filled with eosinophils, and in many cases there are higher numbers of eosinophils in your bloodstream.

These eosinophils now are known in AERD to behave differently than eosinophils in other diseases. Something happens to the eosinophils to make them "angrier" in a way. Reminiscent of the Incredible Hulk - "you wouldn't like me when I'm angry."

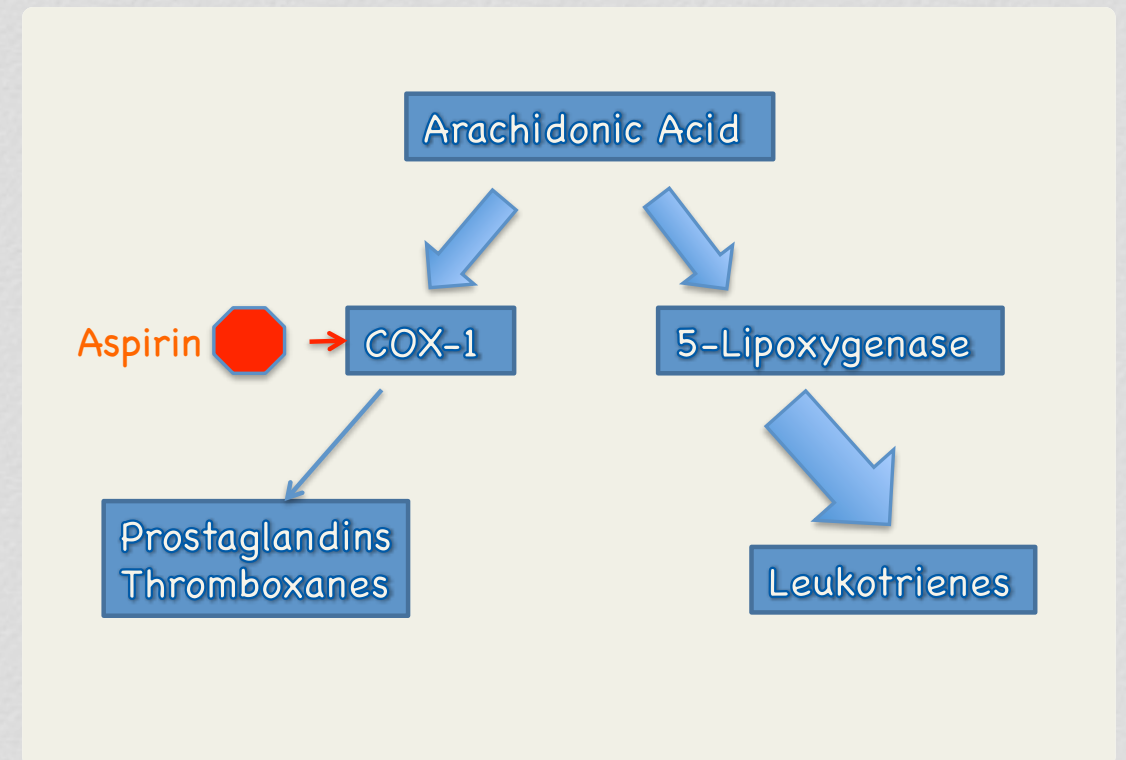
We also know that in AERD there are a group of chemicals known as eicosanoids that are abnormal. Eicosanoids are not

nearly as slickly named as eosinophils. They are named after the greek root eicos which stands for “twenty” because they have a structure containing 20 carbons. Not quite as poetic as the eosinophil name.

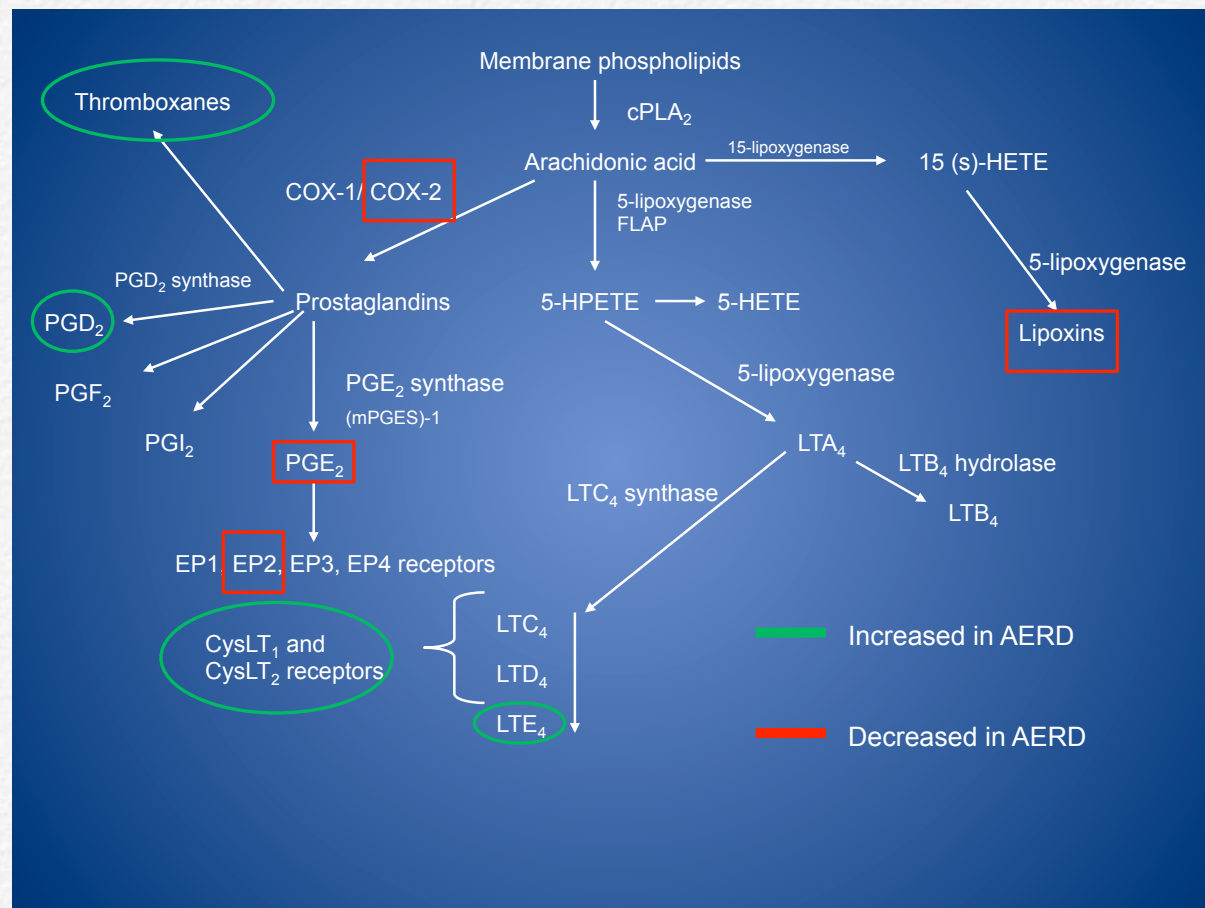
Eicosanoids come from a chemical called arachidonic acid. If you REALLY want to understand your disease, then you need to understand this pathway. It is painful for all physicians, trust me. Now that I am involved in researching this disease I have learned to LOVE this pathway. You should probably learn to hate it :(

In figure 1 you can see the general pathway that starts with arachidonic acid. It is a fascinating pathway where the arachidonic acid sits in the membrane of the cell. It waits until it gets a signal, and when that signal comes, it begins a process of conversion. Along the way there are many branch points but ultimately you end up with leukotrienes, prostaglandins and thromboxane. These chemicals have precise and critical functions in our immune system. We know that in AERD there are too many leukotrienes. There are too many receptors for leukotrienes so their effect is magnified. And probably most importantly, there is a low amount of prostaglandin E2. This brings us to the next chapter.....

Figure 1.



Arachidonic acid can be converted to leukotrienes or prostaglandins and thromboxanes through two different pathways. Aspirin blocks COX-1 which then decreases prostaglandins.



In AERD, there are a variety of abnormalities that have been discovered in this pathway. It is likely that the imbalance in these chemicals cause most of the problems patients with AERD experience

The Players

4



The organ systems

Sinuses

Humans have 4 different sinus cavities. The frontal sinuses are located in your forehead above your eyes. The maxillary sinuses are located on either side of your nose under your cheekbone. Your ethmoid sinuses are small air pockets between your eyes and at the very top of your nose. And the sphenoid sinuses are very deep in your head, between your eyes at the level of the top of your nose. Any and all of these can be affected in AERD. A significant number of people never had their frontal sinuses develop fully and they may not have them at all. This is just a normal variation and does not increase the likelihood of sinus problems in life.

The sinuses are important in the resonance of our voice and because they are filled with air, keep our skull from

being too heavy. They are prone to infection because they are located next to, and drain into the nose. They are lined with special hair cells called cilia which help keep the sinuses clear of mucus and infection. In AERD, or any sinus disease, the si-

nuses may no longer be able to drain properly. When this occurs, patients might start getting infected more often or have increasing problems with discomfort and fullness.

Lungs

Everyone pretty much knows that lungs are what bring oxygen into our tissues. They also get rid of carbon dioxide which is toxic to us. Air starts out in our mouth and travels down to the lungs through the trachea in our neck. From the trachea, the tube branches multiple times into bronchi and the smaller bronchioles.

These tubes bring the air from

Figure 2. Sinus Anatomy



Frontal sinus - in the forehead. Maxillary sinus - behind the cheek. Ethmoid sinuses - at the top of the nose extending back toward the brain. Sphenoid sinus - the sinus behind the ethmoid sinuses in the centermost part of the head.

the room to the alveoli. The alveoli are where the oxygen is brought to the bloodstream. The alveoli are not diseased in asthma. In asthma, the problem is with the bronchial tubes. These tubes can constrict, secrete mucus, or swell up from inflammation. When this occurs, we feel the urge to cough, sometimes producing mucus. When the constriction or swelling gets severe, we feel short of breath and have trouble getting rid of the carbon dioxide or getting enough oxygen into the system.

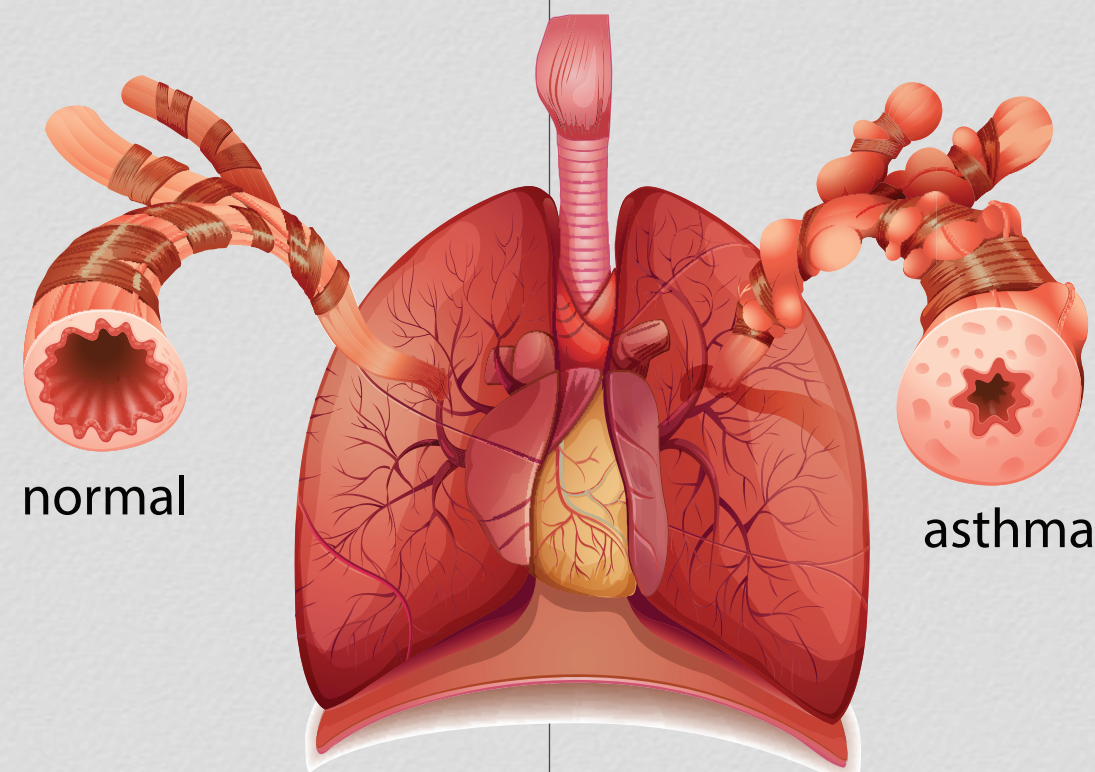
One Big Tube

There is an idea called the “Unified Airway” that most physicians who take care of AERD recognize as very important. This basically means that from the sinuses to the lungs, it is all variations on the same organ system. So, whatever affects the sinuses also can affect the lungs, and vice versa. There are some interesting science experiments that prove this can occur. I think that in AERD, the root of the prob-

lem for most patients is the sinuses. This means that for some patients with asthma, the asthma is being provoked or exacerbated from the sinus disease. It isn't unusual for us to hear from a patient that their asthma was out of control until they had their sinus surgery, after which their asthma improved without any other treatment. Similarly, a patient with an active sinus infection might note that their asthma got significantly worse and did not get better until the infection was appropriately treated.

In AERD, the sinuses are always affected and nearly every single patient has nasal polyps. This is usually the focal point of the disease. But because what is going on in the sinuses invariably affects the lungs (one big tube) asthma can also be a big problem in AERD. In fact, in medical studies that look at severe asthmatics, 1 in 8 of them have AERD.

Figure 2.1 Inflamed bronchiole in asthma



In asthma, the bronchi constrict, secrete mucus and are swollen. All of these activities can cause cough, wheeze and shortness of breath

Not everyone with AERD has problems with asthma. Some people may have very mild asthma. Although it is not common, some patients may not have asthma at all, and might only have nasal symptoms. That is one big reason why we have shifted away from calling AERD - “Aspirin Induced Asthma”.

Tests

There are several tests that doctors like to use to evaluate someone that we think is having sinus problems or asthma. The two easiest asthma tests are one called spirometry and the other is called exhaled nitric oxide.

Spirometry is a test where you must breathe very quickly and forcefully into a device attached to a computer. With a variety of measurements that are taken, we are able to tell whether you have “obstruction” or not. This means that the air is obstructed from getting OUT of your lungs - usually because of constriction or swelling in the bronchial tubes.

Exhaled nitric oxide or “FeNO” is a test that measures the amount of nitric oxide in your breath. It is an easy test to do and generally the higher the number, the more inflamed your bronchial tubes are. A high number usually means that your asthma is not completely controlled

We use these tests, in addition to symptoms, to guide whether to increase or lower medications, and also assess future risk of exacerbations.

Testing for sinus disease is not quite as easy. Most patients will become well acquainted with a nasopharyngoscope or nasal endoscopy. Usually the nasal passage is anesthetized and then a small scope is advanced in order to get a good look for polyps, infection, and blockage. We usually will also want to get a CAT scan of the sinuses. This gives a really good picture and is much better than an XRAY. We don’t have good measurements in sinus disease to gauge inflammation so, most decisions are made after discussing symptoms, and occasionally by repeating the CAT scan or endoscopy to see what those show.

There may be occasional patients who have hives, skin itching and even stomach symptoms that might be related to AERD. For most people, the problems in AERD are centered around the sinuses and the lungs.

React

5



As if having bad polyps growing out of your nose and having asthma that seems to get worse and worse is not bad enough....there is this bizarre drug allergy that happens too. AERD is defined by this reaction. That means that if you don't have a reaction to an NSAID then you don't have AERD. It is the only way that we really have to diagnose the condition. (This is a good time to remind you that if you don't know for sure what happens when you take an NSAID, challenging yourself at home is not the way to find out. You should talk with your doctor about the best way to prove whether you will react or not.)

At this point, you probably know what NSAIDs are. But to review it again for you, these are a group of medications that all essentially do the same thing. They block an important enzyme (chemical) in our body that happens to get activated when we get injured. The chemicals cause swelling and pain. So NSAIDs are great because they decrease the formation of these chemicals and make us feel better. Over the counter medications like aspirin, naproxen, and ibuprofen all work this way.

The enzyme that these medicines block is called cyclooxygenase 1 (COX-1). There are also a bunch of prescription NSAID's that block this enzyme as well. Most of these medicines are oral pills, but there are a few that now come as an in-

jection or as an eye drop. Exposure to this type of medication in any form will cause a reaction.

Aspirin has to be the most well known medicine associated with AERD (it has its name in the title after all). Aspirin is acetyl salicylic acid which is a salicylate. But it is not because it is a salicylate that it causes a reaction. Other salicylate drugs seem to be tolerated fine by patients with AERD. It all comes down to COX-1.

Celebrex (celecoxib) is another commonly used prescription pain medication. For a long time everyone including the FDA thought that it would cause a reaction if you had AERD. But those of us who study AERD thought that the only thing that could cause a reaction in AERD was a COX-1 blocker. Since Celebrex is a COX-2 inhibitor and does not affect COX-1 it turns out that it is safe in AERD. Although there are a few cases reported around the world of AERD patients who react to COX-2 inhibitors, these are very rare. At Scripps Clinic in San Diego, researchers gave dozens of AERD patients two different COX-2 inhibitors and not one patient reacted. To be on the safe side we still recommend that the first time you take it you do so in the doctor's office.

Why does this happen?

Well, this is currently the \$1,000,000.00 question. We kind of know what is happening when you take aspirin and in general the first steps that end up leading to the reaction. We definitely know what is happening DURING the reaction, but it is the very first “why” that is still a mystery.

If you remember in the last chapter, we left off discussing prostaglandin E2 (PGE2). If you have AERD you have less PGE2 around than I do. PGE2 does a lot of very different things in our bodies, but in AERD we are most interested in what it is doing in your nose, sinuses and lungs. In those parts, PGE2 has a zen-like calming effect on an enzyme called 5-lipoxygenase. 5-lipoxygenase is kind of like the very first domino in a long domino train you made when you were little. It is ready to tip over and set off a whole string of inflammation and PGE2 prevents that first domino (5-lipoxygenase) from falling over. We all have PGE2. But since you have AERD, you have less of it, and when you take an aspirin (or ibuprofen), you decrease the amount of PGE2 and now that domino (5-lipoxygenase) tumbles over. When this happens you start making industrial strength quantities of leukotrienes and histamine. And these things cause the really bad allergic reaction.

It is a nice tidy explanation. The problem is that we don’t understand why this doesn’t happen in someone with normal sinuses. In anyone who takes aspirin, they are going to lower their PGE2 level just as much as someone with AERD. It probably has

something to do with how much PGE2 is left over. If you have less to start with then you probably reduce it below a certain critical level.

WHY ME!!

This is all interesting, and will probably be helpful in the future for designing specific treatments. But it still doesn’t answer the question “Why did I get AERD?” I am struck by how similar the stories are that I hear from patients with AERD. Most of you were in really good health, many with no history of asthma or allergies. And then one day....

What makes it really hard for us researchers to figure this out, is we never know someone has AERD until at least a year, and more realistically, two-three years after it starts. No-one is going to assume you have AERD if you just start to have a mild sinus infection or a bit of asthma. It is only in retrospect after a sinus surgery, or severe asthma, or a bad reaction to an NSAID, that it all comes together.

AERD is not inherited the way that some classical genetic diseases are passed down. But there is definitely some risk that is inherited and transmitted in your genetic code. Researchers really have found several small changes in genes that do seem to increase the risk of AERD. But none of them are very strongly linked. To simplify it, you will probably pass on to your

children a small, but increased risk, of developing AERD. But your children also will probably need additional environmental triggers to develop full blown AERD.

One interesting observation is that in AERD, there are more people with a lot of childhood secondhand smoke exposure. It is possible that this early life exposure sort of “loaded the gun” and got a lot of the enzymes that are important in AERD slightly out of whack.

Then, it is possible that a virus or other more acute exposure triggers a more intense change to the immune system in your sinuses and lungs - and this change becomes irreversible. In fact, some patients with AERD describe getting a “cold” that never went away. It makes sense to the scientific community, but we don’t really have much proof that this is what is going on. And you can imagine that we can’t really do a scientific study on every person who gets a cold to see what percentage of them get AERD. It is certainly doable but would take a great deal of money.

Drugs

6



Drugs

If you are like most of the patients that I see, you probably are crestfallen when you go to see your doctor and he/she tells you to try ANOTHER medicine. And not just stop one medicine and substitute it with another, but add another pill to the pile you take everyday.

It has got to be really frustrating to have this disease. There are no ends to the ways and types of things we ask you to spray in your nose, and there is a laundry list of allergy medicines that might help.

But it is important for you to know what you are taking and why you should take these medicines.

So I will break these medicines (and other treatments) down for you:

Antihistamines - these are the allergy medicines that everyone knows. They are cheap, very safe, but unfortunately are very little help in AERD. They might help with some of the itching but won't help polyps or asthma.

Steroids - These come in several forms; oral, injected, nasal and inhaled. Oral and injected steroids work REALLY well, but the problem is the pesky side effects. They can and usually will

cause weight gain and mood changes. Long term they will make you more likely to have infection and bone problems like osteoporosis. They can also cause a rare but severe problem where the bone starts to die in one specific spot (avascular necrosis). So these medicines are good for a quick fix, but really aren't going to be a good long term option for most patients. The topical steroids in the nose and in the lungs are extremely safe. The main problem is that you can't deliver a spray to the sinuses very well; you only can really get it into the front part of your nose and that leaves a big part of your nose and sinuses that aren't treated completely. These topical steroids, though, are still probably the best medicines that we have right now.

Long acting beta agonists - These are usually referred to as LABAs. These are inhaled medications that help with asthma. They are rarely used alone, so you will usually take these in a combination with an inhaled steroid. The typical combination products in the United States are Dulera, Advair, and Symbicort. These are safe medications that usually can help get asthma under better control

Antileukotrienes - this primarily is montelukast (Singulair) in the United States. Other countries may use slightly different versions of this drug. It blocks the action of leukotrienes and can be really important in helping people with AERD. We definitely know that if or when you do aspirin desensitization, being on montelukast makes the desensitization much safer and easier.

5-lipoxygenase inhibitors - the only drug in this family is zileuton (Zyflo CR). If you go back a chapter, this drug blocks the enzyme 5-lipoxygenase which is the way that we form leukotrienes. It makes sense that this drug would work in AERD. There have not been a lot of good medical studies in patients with AERD on this drug, but it seems to have a positive effect. There are very low rates of liver inflammation on this drug so you need to get your labs checked occasionally. At least right now, this drug can also be fairly expensive.

Omalizumab (Xolair)- This is a type of medication known as a monoclonal antibody. These kinds of drugs are designed to be antibodies, just like the antibodies we use to fight infection. But these antibodies are designed to go to a specific chemical or part of your immune system, bind to it, and inactivate it. It is a very slick way of affecting the immune system. Omalizumab binds to an antibody known as IgE. This is the antibody that triggers an allergic response to cats, dog, peanuts, etc. It actually has nothing to do with the reaction to aspirin (remember that one is caused by COX-1). But omalizumab is a good drug for asthma, and also likely will help some of the sinus inflammation that is going on. It is not a drug that is specific for AERD and you might not be a good candidate for it for several reasons. It is included here to be thorough. It is only given as an injection in the doctor's office and can be expensive depending on insurance coverage.

Allergen Immunotherapy - This is what is usually termed "allergy shots". It is the series of weekly and/or monthly injections of substances that you are allergic to in order to desensitize you. This is given for airborne allergens like pollen, cat, dog, dust mite. New treatments with allergy pills under the tongue are also not available for certain allergen. This treatment is important for those with AERD who are ALSO allergic to these allergens. A significant minority of AERD patients have no identifiable allergies. In those patients, allergy shots will not serve any purpose. There are risks to doing allergy shots, and it doesn't always make sense to do this, so you should talk to your doctor have questions about this treatment.

Nasal irrigation - This is technically not a medicine. But, it is often an important part of treatment for sinus disease. There are several reasons it can be helpful. In some patient the thick secretions (mucus) that are formed can lead to problems and since there is so much of it, there isn't a good way to get it all out unless it is washed out. In patients with multiple surgeries, some of the normal sinus lining may have been removed or damaged. The sinus lining has little hairs called cilia that move in a rhythm to beat the mucus and bacteria out of the nose. After surgery sometimes these cilia do not work properly so sinus irrigation helps do what the body can't do for itself. Sinus irrigation is also a handy way to get other medicines deep in the nose. There aren't any medications that are FDA approved to be used this way, but most doctors who treat AERD will try

some combination of nasal medications with the nasal irrigation.

In my experience, the first time that nasal irrigation is used it feels very awkward and most people probably wouldn't sign up for another round unless their doctor is recommending it. Yet, most patients end up finding it to be quite helpful if they stick with it.

Aspirin - it doesn't make any sense that it aspirin would work in this disease, but it plays an important part in treating the inflammation in AERD. It is a weird enough concept to use aspirin that we will give it its own chapter.

Sinus Surgery - The rate of sinus surgery in AERD is very high. That is because the polyps that occur are so aggressive, that even after extensive surgery they can return just as bad as they were before. So surgery by itself, is usually not an adequate treatment for AERD. But, surgery does play a significant role in the health of someone with AERD. Surgical techniques have improved considerably over the past decade. There are now subspecialists just in sinus surgery. For patients with AERD, seeing a sinus subspecialist is not a bad idea. Ideally, the decision to move forward with surgery should be made as a team with input from YOU, the allergist and the sinus surgeon.

Weird



This makes no sense

Aspirin treatment for AERD has been around since the late 1970's. Back then Dr. Donald Stevenson and his colleagues were studying what happened to individuals who took aspirin. They were very interested to learn what occurred during the reaction. How long after someone took aspirin would it take before the reaction started? Would it happen with ibuprofen and other similar pain medications? What dose of aspirin usually would cause the reaction? These were some of the questions that they were trying to get the answers to.

Surprisingly, several of the early patients described improved health in the days immediately following aspirin challenge. This led to the idea that aspirin could ultimately be a treatment for AERD. Sure enough, in the decades since that finding, a lot has been discovered about aspirin treatment in AERD.

Before going any further, there are some wording issues that need to be clarified. As allergists, the term desensitization refers to the procedure in which a drug is gradually introduced into the body so that it is ultimately tolerated. It generally occurs over hours to days, and as long as the drug is continued on a regular basis, the desensitized state is maintained.

In AERD, it is more complex than this. The term “desensitization” is usually used to describe the process of starting and continuing on aspirin therapy. Technically, “desensitization” occurs during the first 1-3 days of the process where the aspirin is started and the patient has a reaction. From that point on, desensitization is maintained by taking aspirin every day.

But after the initial desensitization, “aspirin treatment” might be a better term. The desensitization is now over and we are most interested in improving daily symptoms for the patient, not just by allowing them to safely take aspirin, but by seeing significant improvement in their symptoms and polyp growth by treatment doses of aspirin.

Another way to think about this is that “desensitization” is 99% successful. There are only a rare handful of patients who for various reasons either continue to react or have other unanticipated symptoms that do not allow them to get through the first days of desensitization. So almost every patient can be desensitized. But not every patient gets benefit from “aspirin treatment”.

Scripps Clinic has published its experience in treating patients with aspirin therapy. Several themes have emerged over the years and are now widely accepted among allergists.

-
- approximately 10-15% patients will have side effects or problems with aspirin that will make them stop it; stomach pain or, rarely, an ulcer, bleeding or pregnancy.
 - about 85% of patients will have improvement in their AERD. This means that they need less steroids, have fewer surgeries and slower polyp growth. Some may have improvement in their sense of smell.
 - Both of the above statistics need to be considered together in a patient considering aspirin therapy. They have an 85% chance of getting improvement while being on aspirin, but they also have a 10% chance of being unable to take the aspirin. That means that before starting aspirin treatment, there is about a 70% chance that any given patient will be able to tolerate aspirin AND benefit from it.
 - The dose of aspirin matters. Over the years several studies show that the dose of aspirin that needs to be taken to offer benefit is between 650mg and 1300mg per day. Some studies show benefit at a lower dose, as low as 325mg per day, but most patient seem to respond to higher doses.

Another way to think about this is that aspirin potentially does three things in our body. It interferes with making our blood clot. This is the reason that it is helpful in treating heart disease. Doses between 81 and 325mg once a day have this effect, so it is unlikely that it is this effect in AERD that is going

on. The second effect is by blocking COX-1 aspirin interferes with inflammation. At doses around 325mg - 650mg aspirin can help with sore ankles and back pain. When you take aspirin for pain relief, it is because of this effect.

But we think that there is a third option in AERD. We don't think it has anything to do with blood clotting, and doesn't have anything to do with blocking COX-1 either. There is a third way that aspirin uniquely helps you. We are fairly certain that it has to be aspirin (not ibuprofen) and it has to be a high dose. We unfortunately are not completely sure about this, but if we are right, this is a unique benefit of aspirin and could teach us a lot about asthma, nasal polyps and inflammation.

Aspirin seems to have a positive effect on a variety of symptoms that are important in AERD. It is hard to define exactly what makes it so frustrating to live with AERD. Some patients describe the frustration with always feeling "inflamed" with effects on mood, sleep, work performance and enjoyment of normal activities. If aspirin works, it seems to help with some of these symptoms. By turning down the inflammation, it decreases the speed that the polyps form, may lead to less need for other medications, and specifically may help the patient to feel BETTER. And that is what we are all really interested in right?

Another peculiar tidbit is that aspirin only seems to help you if you have AERD. You can have nasal polyps and asthma but

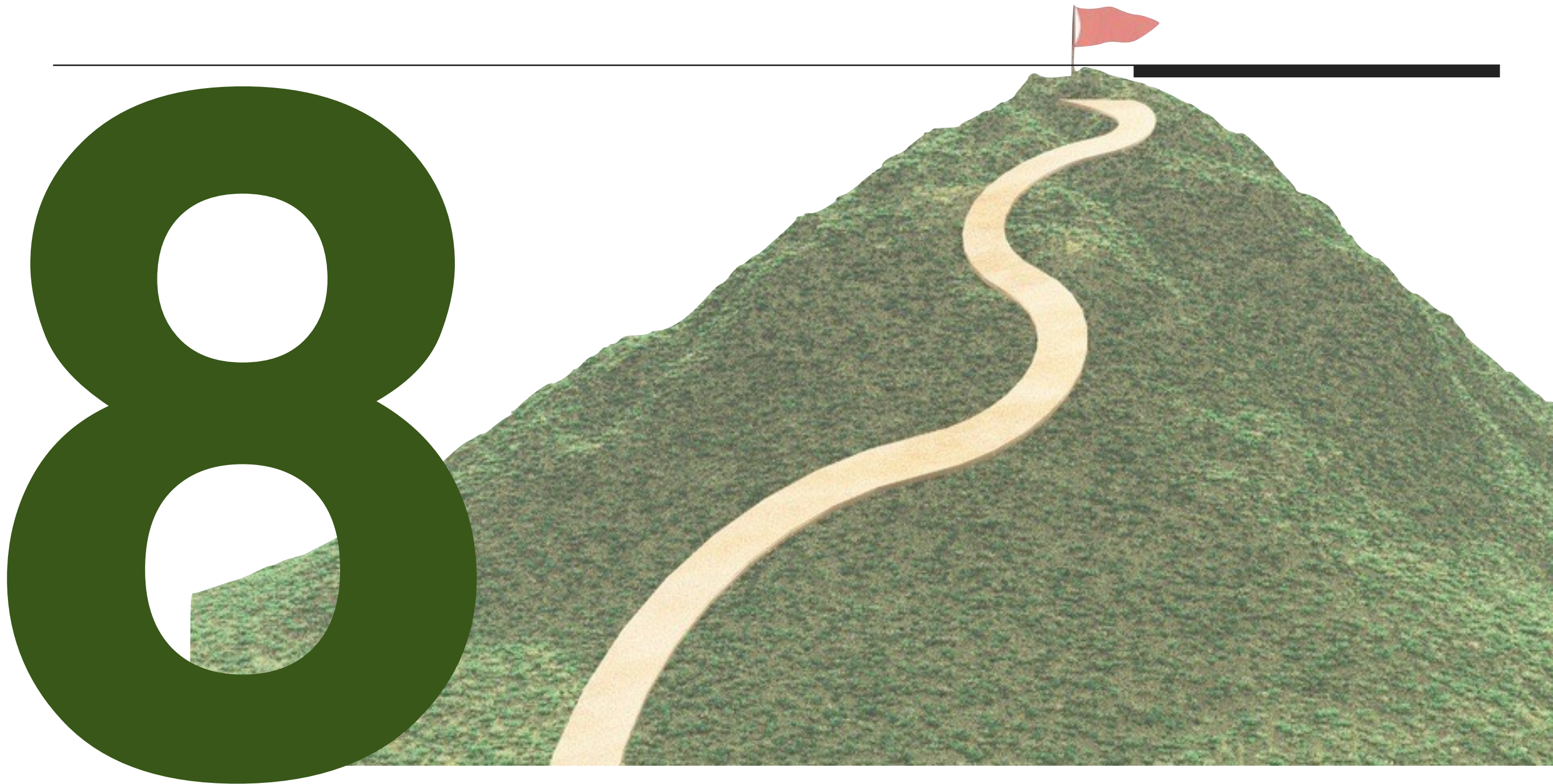
be tolerant of aspirin. Some patients can take aspirin but it does not seem to help them with symptoms, with polyp growth rate, or even affect some of the chemicals that we see change and improve with aspirin therapy in AERD.

One final note is in regards to “proof”. As patients, we all want a sure thing. And you have every right as a patient to understand how strong the science is behind a certain therapy. Aspirin treatment in AERD is unfortunately VERY difficult to study. For obvious reasons, any AERD patient must be desensitized first to be in a clinical trial studying aspirin desensitization. In a well designed medical study, there should always be a placebo group. In the placebo group, they get an empty pill that does nothing so the researchers can compare the “active” treatment (aspirin) to the placebo. Ideally, the patients and the researchers should not know who is getting which drug. But this creates a huge expense and a huge logistical problem because who wants to go through a desensitization and then go on placebo and then have to undergo another desensitization several months later? For these reasons, most studies have looked at patients self-comparisons. They will rate their symptoms over the past six months, and then rate their symptoms, medication use, need for surgery, emergency visits six months later. Researchers can then compare and see if the aspirin is helping.

These are the studies that provide us with a lot of statistics that I quoted earlier. Although they may not be the most scientifi-

cally rigorous studies, they are the best we have and mesh well with our clinical experience as doctors: that aspirin is a beneficial treatment -- not for everyone, but for a majority of patients.

Desensitize



How does one get desensitized?

A recent survey tells us that only about 1/2 of AERD patients are interested in getting desensitized to aspirin. There are a variety of reasons for this, some of which are perfectly understandable, but some which might be incorrect, and should be reconsidered.

We already talked about the benefits (and risks) of being on aspirin. It is meant to be a long term treatment, and obviously patients shouldn't consider doing a desensitization if for any reason they do not intend to stay on aspirin for a prolonged period of time.

But for any patient who is having problems with polyp growth, asthma, or quality of life because of AERD, and the other typical medications aren't working, then aspirin therapy is a good thing to consider.

And you can't go on aspirin unless you get desensitized.

Let's go through some of the reasons that you might be concerned or worried about getting desensitized.

1. Money

This is easily the biggest REAL problem in my experience. Aspirin desensitization is not a common procedure so many insurance plans might be unfamiliar with it. Usually approval from

the insurance company must be obtained first. Even with insurance, the cost can be significant. Without insurance it is out of reach of many patients. This is a serious shame, and hopefully the situation will change in the future. If you are worried about cost, your physician's office can give you the billing codes and you can contact your insurance to get an idea of the cost. If you are paying cash, many offices will give a significant discount or even consider payment plans to make it possible to consider this therapy.

2. Safety

This comes up over and over again. Most of you remember taking aspirin and then 30 minutes later found yourself in a car on the way to the hospital with a severe asthma attack. You are right to be concerned that a doctor wants to try to give you aspirin again. But there are two big reasons why it is MUCH safer in the setting of desensitization. First, we recommend that everyone take Singulair (montelukast) before and during the desensitization. It makes the asthma attacks much milder. Second, when you had your initial reaction you took a full dose for a headache or similar pain problem. We are giving a much lower dose, sometimes as low as 1/10th of the previous dose. Our studies have shown that even if you had a very severe reaction in the past, you aren't at a higher risk of having a severe reaction during a desensitization. There are always extenuating cir-

cumstances and you should discuss all of your concerns with your doctor.

3. Your doctor might not think it is worthwhile

Unfortunately, this continues to be a problem. Less so over the years, but it still is happening. I think that some doctors try this once or twice and the patient unfortunately doesn't get a lot better, so they think that it is all hype and not worth pursuing. Some doctors also might think that the risks are too high. My estimate is that they are unfamiliar with how to do the desensitization. If you think that you could benefit from being on aspirin and your doctor doesn't think it is worthwhile, consider getting a second opinion.

4. Logistics

At the absolute minimum, aspirin desensitization is going to take one FULL day in the clinic. That might be rushing it for most patients so we generally plan on two days. We also tell patients that they might need to be there for a 3rd day. The response to aspirin is somewhat unpredictable. You only compromise safety by going too fast. But if you have a busy job that you have a hard time being away from, the commitment to 2-3 days in the clinic might be hard. But there is no way around it.

Now is a good time to stress that there are a few patients with AERD who I know have tried to desensitize themselves at

home. That is a very bad idea. The responses we see in the clinic are unpredictable. We sometimes will have someone who we thought would probably be a pretty easy desensitization who has more problems than we anticipated. We have everything we need to treat them in the clinic, but there is no way that any patient has everything necessary at home. So please don't try it.

There are several places in the country that do a lot of aspirin desensitizations. If you aren't getting a lot of traction with your local doctor, consider a trip to one of these centers for a second opinion. At least you can get an idea of whether you are a good candidate and get all of your questions answered.

The other benefit of a trip like this is that the AERD expert can give you advice on all of your medications and perhaps suggest some changes that you have not yet tried.

Smell

9



Sense of Smell

The impairment in your sense of smell can be a frustrating part of this disease. When patients lose their sense of smell, the medical word for this is “anosmia”. Almost all patients with AERD have some degree of anosmia. Most patients have almost no sense of smell at all. This is specifically because of the polyps in the nose. Whether or not you have AERD, if you have nasal polyps, your sense of smell is likely affected.

Sense of taste is also affected because our sense of smell is so closely linked to our ability to taste. So of our five senses, two of them are significantly affected by AERD. Because it is not hearing or eyesight, the severity of these symptoms can be overlooked.

Many patients that I treat are very bothered by their inability to enjoy a meal, or the fact that they might not smell smoke or a

burning dinner in the oven. Even though you can go through life without anyone being aware that you are missing this

sense, I have no doubt that it significantly impacts your life.

Our sense of smell is different in terms of the nerves that control it. We generally have one large nerve that goes to the ears to control hearing, and similarly with the eyes, there is the large optic nerve that connects the brain to the eye. The sense of smell is different. A large number of microscopic nerves come directly from the brain and travel through the bone between your eyes down into the roof of your nose. We smell things because the small, microscopic chemicals coming from the smelly socks are airborne and end up being sucked up into your nose. These chemicals

come into contact with the nerves and depending on what the chemical is, and how it interacts with the nerves your brain receives a signal: “smelly socks”.

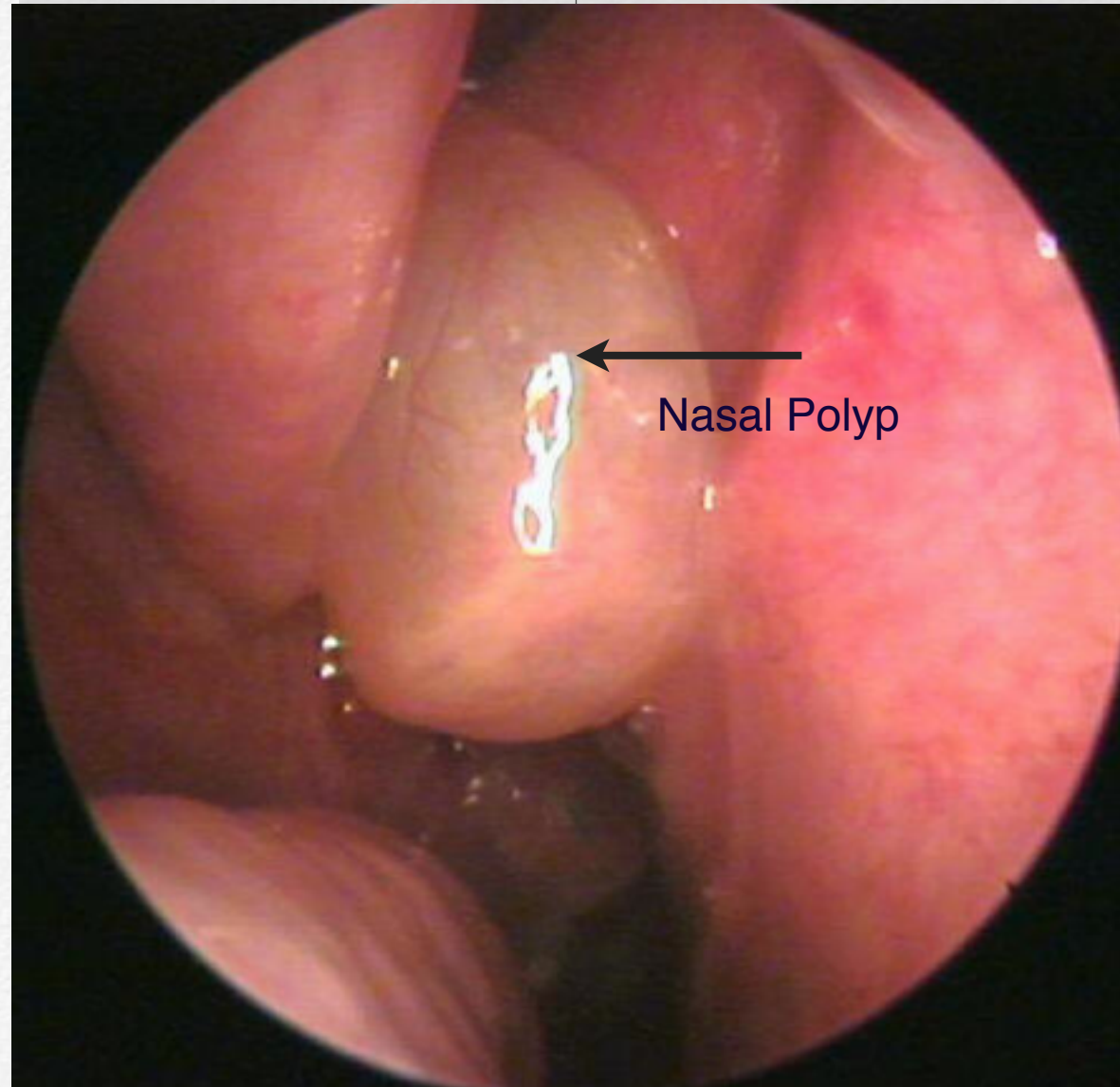
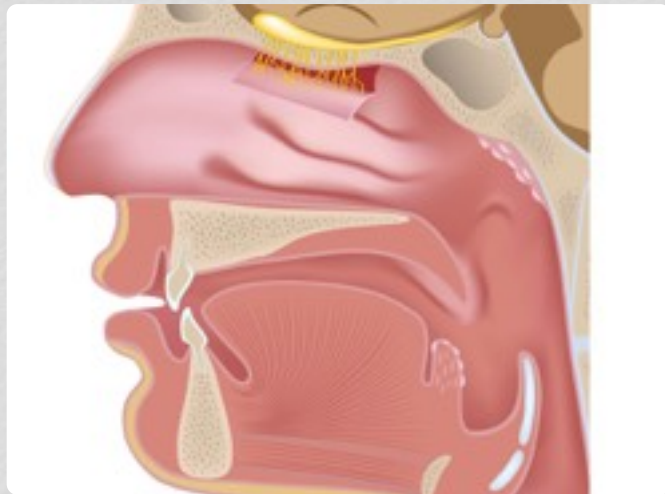


Figure 3 Olfactory nerves

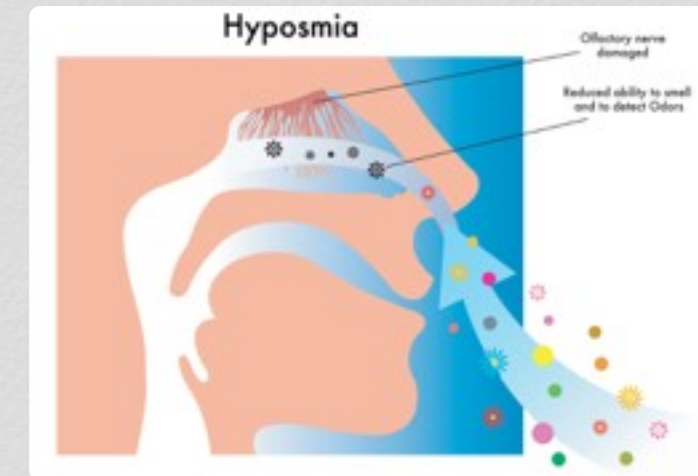


Your sense of smell comes through a bony plate between your brain and your skull

A common symptom of nasal polyps is anosmia. This is probably because the polyps grow densely right in the area where the nerves are coming out of the brain. The nerves are probably compressed and blocked so that nothing airborne can touch them. There also is the possibility that all of the inflammation in the sinuses damages this area. We know unfortunately that some pa-

tients never get their sense of smell back in AERD. Some patients may get it back briefly after surgery or after a burst of steroids. Some of you are lucky and may get significant and permanent improvement with nasal sprays or other medicines like zileuton or montelukast.

Figure 3.1 Sense of smell



When chemicals in the air can no longer get to your olfactory nerves, you lose your sense of smell. This can happen because polyps block this area

Myth

10

Salicylates

I've treated AERD long enough to hear many patients tell me how they have been on a "low salicylate diet". Let me tell you what that means and why I don't think it makes any sense if you have AERD.

Probably the best known salicylate is Acetyl Salicylic Acid also known as "aspirin". You may know that aspirin was discovered from the bark of a tree and found to have medicinal qualities. It was ultimately purified and now most of the world has access to this drug.

We know that in AERD, you react to aspirin because it blocks the enzyme COX-1. That is why you also will react to ibuprofen, naproxen, ketorolac, etc. But these last three NSAIDS are NOT salicylates. Furthermore, there are several medications that exist that are salicylates that DO NOT block COX-1. These are commonly used in Gastroenterology or Rheumatology to treat autoimmune diseases. These medications have been studied in AERD and you will not react to them. This is not surprising, because we know that they do not block COX-1.

Somewhere along the line, someone got the idea that if acetyl salicylic acid (aspirin) is bad, then maybe there are aspirin-like products in the diet (salicylates) that should be avoided. I think

that the implication is that if you are eating salicylates in your diet you are keeping your sinuses inflamed.

But this does not make as much sense now that we know a lot about desensitization. We know that if we desensitize you to aspirin, you will stay desensitized for 48 hours before you start to react again. And as discussed in a previous chapter, being on aspirin DAILY actually is beneficial for a majority of patients. So if being on aspirin daily is helpful for you, then why would dietary salicylates daily be harmful and you would continue to react to them?

To me, the argument to be on a low salicylate diet comes out something like this: "Aspirin is a salicylate and salicylates start with the letter 'S,' so you should avoid all foods that start with the letter S."

Diet

This topic opens the question of diet in the treatment of AERD. I certainly don't think that a low salicylate diet has any specific role in the treatment of AERD. But I also have no doubt that in certain ways our diet might be quite important.

We have recently learned that in AERD, most patients do not tolerate alcohol. This is perhaps more likely with red wine, but most patients can't tolerate any alcohol. It usually causes intense nose stuffiness and maybe mild asthma. But it isn't the

same reaction that is happening with aspirin. We truthfully don't know exactly how to explain this, but have no doubt that in most patients if you drink alcohol you are going to feel worse.

What about other foods? We really don't know. At all. Many patients will tell me that they have cycled through a gluten free or milk free diet. Many have been on much more intensive and restrictive diets. Some feel they have helped. Many feel that they do not. None of the diets that seem to be effective have a common theme.

It is likely that the combination of diet changes with exercise leads to some weight loss and overall sense of well being. If the diet is not overly restrictive and as a patient you feel significantly better, I usually encourage you to continue it. But I more likely am counseling patients that their diet does not seem to be offering them benefit, and just because they read on the internet that a XYZ diet will work wonders, doesn't make it true. If I can improve their quality of life a bit by allowing them to eat pizza again, then I think of that as a small victory.

Although there are no specific diets that are known to help AERD, here are a few of my own suggestions:

1. Lose weight - obesity contributes to inflammation and the severity of asthma. The closer you can get to your ideal body weight the better you will feel.

2. Vitamin D - This is an important vitamin for respiratory health. There is a lot of debate about how important it is, but many patients have low levels of vitamin D and might feel better if the levels are normal.
3. Healthy Diet - Although a healthy diet can be more expensive and more work, a lot of fresh fruits and vegetables, fish that are high in omega 3 fatty acids, and avoidance of heavily processed foods make a lot of sense.

A piece of brown, textured paper is shown with a large, irregular tear. The tear reveals a white background underneath. The phrase "UNCOVER THE FACTS" is printed in bold, black, sans-serif capital letters across the white area. To the left of the main tear, there is a smaller, partially torn section of the brown paper, creating a layered effect.

UNCOVER THE FACTS

Forward



Where We Are Now

I have no doubt that many of you are not satisfied with where we are at in our current treatment of AERD. Let me explain some of the difficulties that complicate our ability to move forward and some ways that I think you can help.

First, the big question of “why did I get this disease” should get answered. But honestly, right now, that is too difficult. There does not appear to be a genetic or inherited component so it is likely something environmental or an infection that may be a trigger. Since most people are sick for quite some time before the diagnosis is considered it is frequently difficult if not impossible to go back in time one, two or five years to try to reconstruct what may have been going on when the illness started. We have identified more childhood second-hand cigarette exposure in AERD patients as a possible environmental factor. Perhaps with less childhood second-hand smoke exposure now we will see less AERD in future generations.

I think, though, that there is more promise right now going forward with a treatment more tailored and specific for AERD. We now know SO MUCH about the inflammation that is going on, that we can identify several pathways that might work very well. There are currently drugs that have been created that would be

worth testing in AERD. The main problem is money. Clinical trials cost money and AERD is not a highly visible disease.

But it should be.

At least seven to nine percent of asthmatics have AERD, and up to 15% of severe asthmatics have it. It is much more common than allergists, pulmonologists and head and neck surgeons think. Mostly because we don't ask the right questions.

So there are a lot of you out there, but you don't know it and the medical community does not know it. And this is an area that could easily be remedied by a patient advocacy group. The generation of a website and interest both on the patient side and the physician side would go a long way toward convincing pharmaceutical companies to invest in this disease.

There are several locations in the US and also in Europe that actively engage in research trials in AERD. Obviously, to uncover new treatments for this condition we need willing patients with AERD to consider participating in these trials. Many trials can be identified by a fairly simple search on www.clinicaltrials.gov. Also, most allergists would know of AERD specialty centers that you could travel to in order to discuss these treatments further.

How To Get Where We Want To Be

Despite these limitations, there is one advantage that AERD has. It is a very homogenous disease. This means that every AERD patient is extremely similar to the next one. Asthma is the opposite. When you look at 100 asthmatics, some of them are very allergic, some of them are not. Some have nasal polyps, some don't. Some respond really well to inhaled steroids, some don't. These differences make it very difficult when a drug company studies their drug because maybe they just didn't have the right kind of asthmatics in their failed trial.

AERD is attractive to study because every patient is so SIMILAR. Not just the stories about how they have reacted, and how many sinus surgeries they have. But, on the tissue that goes to the lab from the surgeries and on blood testing. You are all pretty similar. So instead of studying ALL asthmatics, companies would have an advantage (I think) by studying an appropriate drug to treat AERD. I'd like to see that happen.

Finally, I encourage you to be your own advocate. I know that many of you figured out that you had AERD before your doctor did. Unfortunately some of you probably had to write the name down for a doctor who never heard of it before. I bet some of you know more about AERD than your own doctor does. So if you think you have a question that is not being answered ade-

quately, or you want more information about a treatment that might be an option for you, you should pursue it.



REVIEW ARTICLE

Dan L. Longo, M.D., *Editor*

Aspirin-Exacerbated Respiratory Disease

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N Engl J Med 2018;379:1060-70.

DOI: 10.1056/NEJMr1712125

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SALICYLIC ACID IS FOUND IN AN EXTRACT PREPARED FROM THE BARK OF white willow trees and has been used for thousands of years for the relief of fever and pain.¹ In 1897, Felix Hoffmann, a young chemist employed by Friedrich Bayer and Company, acetylated salicylic acid to produce acetylsalicylic acid. By 1899, Bayer had patented the drug, named it “aspirin,” and begun selling it around the world. Consumption skyrocketed, with aspirin then used for controlling pain, fever, headache, arthritis, and other diseases.¹ It was not until 1922, in a case report by Widal et al., that respiratory disease exacerbated by aspirin was first described.² After an oral challenge with aspirin, a female volunteer with all the hallmarks of underlying respiratory disease had an asthma attack, profuse rhinorrhea, and urticaria. The same reactions occurred after oral challenges with antipyrine, which had been synthesized in 1883 and was the only other available nonsteroidal antiinflammatory drug (NSAID) at that time.

In 1967, Max Samter, an immunologist in the United States who was unaware of the 1922 French report, believed that he had discovered this disease and named it “Samter’s Triad” (nasal polyps, asthma, and sensitivity to aspirin).³ Since then, a number of descriptors of the disease have appeared (e.g., aspirin intolerance, aspirin idiosyncrasy, and aspirin-induced asthma). Aspirin-exacerbated respiratory disease (AERD) became the preferred term in the United States, reflecting a shift away from the implication that the disease occurs only in the lower airways. Although AERD is the preferred term in the United States and other countries around the world, many parts of Europe and the Middle East prefer NSAID-exacerbated respiratory disease.

CLINICAL DESCRIPTIONS AND HALLMARKS OF THE DISEASE

AERD is characterized by mucosal swelling of the sinuses and nasal membranes, formation of polyps, and asthma. But unlike most patients with identical clinical features, patients with AERD also have respiratory reactions after ingesting aspirin and other NSAIDs. These reactions typically involve the upper airways (nasal congestion, rhinorrhea, and sneezing) and lower airways (laryngospasm, cough, and wheeze). Less commonly, gastrointestinal symptoms (abdominal pain and nausea) and cutaneous symptoms (flushing and urticaria) occur but are almost always accompanied by some degree of respiratory involvement. AERD is acquired, appearing any time from late childhood to adulthood; the median age at onset is around 30 years.^{4,5} On the basis of patients’ recollections, about 50% of AERD cases appear after a viral respiratory infection.⁶ Ongoing symptoms of AERD are perennial rhinorrhea, nasal congestion, and anosmia, almost always with the addition of asthma. Once the disease has become established, and usually by the time medical evaluation is sought, patients with AERD have nasal polyps and pansinusitis on imaging studies. Most patients with AERD are unable to drink alcoholic beverages without having upper- or lower-airway hypersensitivity reactions; the underlying mechanism is un-

clear.⁷ Although some patients report reactivity to any alcoholic beverage, red wine and beer cause reactions in the vast majority of patients, suggesting additional contributions beyond the ethanol component.

AERD does not preclude other provoking mechanisms. These include exacerbations of asthma and rhinitis during viral infections, gastroesophageal reflux, irritant provocations, exercise-induced exacerbations, and IgE-mediated reactions to pollen, dust, animals, and foods.

Patients with AERD are usually referred initially to a head and neck surgeon. In contrast to the outcome after routine sinus surgery in patients without AERD, in most patients with AERD, surgery is followed by rapid and aggressive recurrence of nasal polyps, as early as a few weeks postoperatively.⁸

The severity and progression of AERD vary markedly.⁹ At one end of the spectrum, AERD involves only the upper airways¹⁰; at the other end, AERD causes severe asthma and rhinosinusitis, with remodeling of the upper and lower airways.¹¹ Among patients with asthma or chronic sinusitis, those with AERD are the most likely to have severe disease that is difficult to manage.^{8,11-14}

AERD is never present at birth and rarely clusters in families.^{4,5} It is only slightly more common in females than in males^{4,5} and is found in all countries except China, where the occurrence is rare.¹⁵ Attempts to find a single AERD gene have failed, and all efforts to find combinations of genetic variations or single-nucleotide polymorphisms have pointed to only partial associations.^{16,17} The combination of genetic susceptibility and external respiratory assaults such as virus infections and air pollution continues to be a viable hypothesis for the genesis of AERD.

ATOPIC DISEASES

Among the patients in whom AERD develops in the third decade of life, two thirds have a history of atopy and the other third are free from any allergies.⁴ Most investigators accept the view that underlying allergic disease is separate from AERD and not the cause of it. AERD is best classified as a coexisting condition.

REACTIONS TO CYCLOOXYGENASE 1 INHIBITORS

At therapeutic doses, all cyclooxygenase 1 (COX-1) inhibitors, including aspirin, initiate respiratory

reactions in patients with AERD (Table 1). As shown in Figure 1, even low doses of aspirin acetylate COX-1, permanently inhibiting function until new enzyme is generated (>48 hours). All other NSAIDs are competitive inhibitors of the COX-1 enzyme channel, with much shorter blockades of COX-1 functions (<12 hours). The larger the doses of COX-1-inhibiting NSAIDs, including aspirin, the larger the ensuing respiratory reactions. The mechanisms by which NSAIDs cause respiratory reactions in patients with AERD were reviewed in detail by Laidlaw and Boyce in 2016.¹⁸ Figures 1 and 2 show the precarious homeostasis of mast cells at baseline and the critical depletion of prostaglandin E₂ (PGE₂) when COX-1 is inhibited. In AERD, PGE₂ scarcely inhibits the inflammatory cascades at baseline, and when PGE₂ is depleted, nothing is available to stop mast-cell discharge and synthesis of additional mediators.¹⁹

Ibuprofen and indomethacin were introduced into the market in 1962 and 1963, respectively. Both these drugs are potent inhibitors of COX-1. Confirming the observation of Widal et al.,² Vanselow and Smith reported in 1967 that oral challenges with aspirin and indomethacin induced respiratory reactions in a patient with AERD.²⁰ Shortly thereafter, Samter and Beers reported that ibuprofen cross-reacted with aspirin and that the chemical configurations of ibuprofen and aspirin were so different that immune recognition of both drugs was improbable.^{3,21}

Table 1 lists NSAIDs that cause respiratory reactions on first exposure in patients with AERD. Most COX-1 inhibitors are sold as tablets or capsules, which take 30 to 90 minutes after ingestion to be absorbed and to circulate and initiate respiratory reactions in patients with AERD. Ketorolac is available in tablet form and in solution for intravenous, intranasal, and intramuscular administration. In patients with AERD, the time from intravenous administration of ketorolac to a reaction is about 15 minutes.²² At high doses, weak inhibitors of COX-1, such as acetaminophen²³ and salsalate,^{24,25} barely induce mild respiratory reactions and only in a minority of patients with AERD (Table 1).

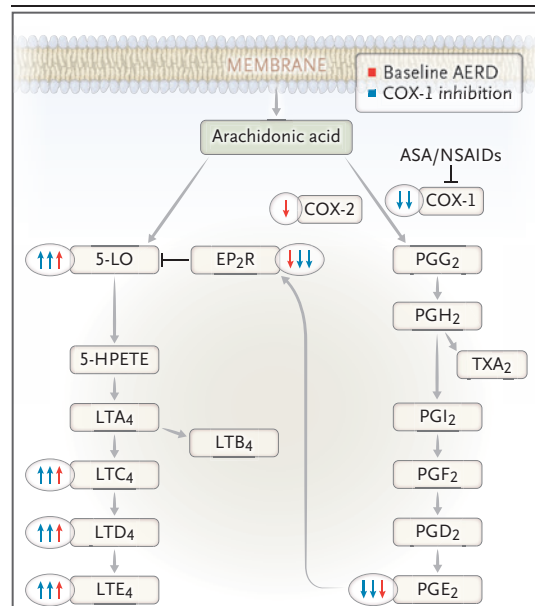
Specific cyclooxygenase 2 (COX-2) inhibitors do not cause respiratory reactions in patients with AERD (Table 1).²⁶ These larger molecules cannot access the smaller COX-1 channel and can fit only into the wider COX-2 enzymes as competitive inhibitors. Therefore, they cannot interfere with constitutive activity of the COX-1 enzymes in mast

Table 1. Cyclooxygenase 1 (COX-1) and Cyclooxygenase 2 (COX-2) Inhibitors That Trigger Respiratory Reactions in Patients with Aspirin-Exacerbated Respiratory Disease (AERD).*

Medication	Route of Administration
Highly selective COX-1 inhibitors	
Acetylsalicylic acid	Oral (OTC)
Antipyrine–benzocaine	Otic only (OTC)
Benoxaprofen	Oral
Diclofenac	Oral, topical
Etodolac	Oral
Fenoprofen	Oral
Flurbiprofen	Oral
Ibuprofen	Oral (OTC)
Indomethacin	Oral
Ketoprofen	Oral, topical
Ketorolac	Oral, IM, IV, nasal
Meclofenamate	Oral
Dipyrene	Oral
Mefenamic acid	Oral
Naproxen	Oral (OTC)
Oxaprozin	Oral
Piroxicam	Oral
Tolmetin	Oral
Weakly selective COX-1 inhibitors	
Acetaminophen	Oral (OTC)
Choline magnesium trisalicylate	Oral
Diflunisal	Oral
Salsalate	Oral
Highly selective COX-2 inhibitors	
Celecoxib	Oral
Etoricoxib†	Oral
Lumiracoxib†	Oral
Parecoxib†	IV, IM
Preferentially selective COX-2 inhibitors (COX-1 inhibition at high doses)	
Meloxicam	Oral
Nabumetone†	Oral
Nimesulide†	Oral, topical

* In patients with AERD, respiratory reactions are triggered by first exposure to any nonsteroidal antiinflammatory drug (NSAID), except COX-2 inhibitors. Prior drug sensitization is unnecessary for this competitive inhibition reaction of COX-1 and then COX-2 enzymes. Listed drugs are available by prescription only unless designated as available over the counter (OTC). IM denotes intramuscular, and IV intravenous.

† This drug is not available in the United States.

**Figure 1. Mechanisms Underlying Respiratory Reactions to Cyclooxygenase 1 (COX-1) Inhibitors.**

At baseline, inflammation of the respiratory tract is already ongoing in patients with aspirin-exacerbated respiratory disease (AERD). With COX-1 inhibition by any nonsteroidal antiinflammatory drug (NSAID), the loss of prostaglandin E₂ (PGE₂) inhibitory control leads to massive release of histamine and generation of cysteinyl leukotrienes by mast cells, an event that is unique to AERD. (Prostaglandin D₂ [PGD₂] is pharmacologically inhibited with COX-1 inhibition, but the level greatly increases during reactions through mast-cell and eosinophil activation.) COX-1 inhibition does not block this alternative pathway, which continues unchecked. Red arrows represent abnormal baseline conditions in patients with AERD, and blue arrows indicate changes after COX-1 inhibition. The number of arrows indicates the magnitude of change. ASA denotes acetylsalicylic acid, EP₂R prostaglandin E₂ receptor, 5-HPETE 5-hydroperoxyeicosatetraenoic acid, LT leukotriene (types A₄, C₄, D₄, and E₄), 5-LO 5-lipoxygenase, PG prostaglandin (types G₂, H₂, I₂, and F₂), and TXA₂ thromboxane A₂.

cells, basophils, eosinophils, and platelets, including critical synthesis of PGE₂. Only two COX-2 inhibitors are available in the United States: celecoxib and the 7.5-mg dose of meloxicam. The 15-mg dose of meloxicam causes mild respiratory reactions in patients with AERD, functioning as a partial COX-1 inhibitor (Table 1).²⁷ Substitution of COX-2 inhibitors for COX-1 inhibitors is a useful strategy in patients with known AERD or

those with unphenotyped asthma in whom AERD has not been ruled out. Unfortunately, COX-2 inhibitors can be obtained only by prescription, which often causes patients with AERD to unknowingly rely on readily available over-the-counter COX-1 inhibitors.

DIAGNOSTIC ROLE OF THE MEDICAL HISTORY

Table 2 lists the types of histories that can be elicited from patients with asthma or nasal polyposis. Obtaining this information is essential because it provides the best clues in determining whether AERD is present. Although 24-hour urinary leukotriene E_4 (LTE_4) measurements may prove useful diagnostically, an observed aspirin challenge, which definitively induces recognizable symptoms and changes in lung function, is currently required to make the diagnosis of AERD.³⁰ Oral aspirin is commonly used for diagnostic challenges, but experience with nasal and inhaled lysine–aspirin challenges in Europe led to the use of nasal ketorolac as a substitute in the United States.^{31–33} More than 80% of patients reporting any history of mild respiratory symptoms after NSAID ingestion will have positive oral aspirin challenges (Table 2).³⁴ Unfortunately, with the diagnosis based on the patient's history, both underdiagnosis and overdiagnosis of AERD are inevitable. Despite this shortcoming, linking NSAID ingestion to respiratory symptoms is the most important step in identifying patients who should undergo a diagnostic challenge. The second most important step is computed tomographic sinus imaging. A normal sinus study essentially rules out AERD (Table 2).

PREVALENCE

There are no accurate data on the prevalence of AERD in the general population or among patients with asthma, nasal polyposis, or both. A heavy diagnostic burden is placed on the only distinguishing event found exclusively in cases of AERD — namely, a history of a respiratory reaction to aspirin or other COX-1-inhibiting NSAIDs. We performed a meta-analysis to estimate the prevalence of AERD, stratifying potential bias by looking at study types separately and in the aggregate.

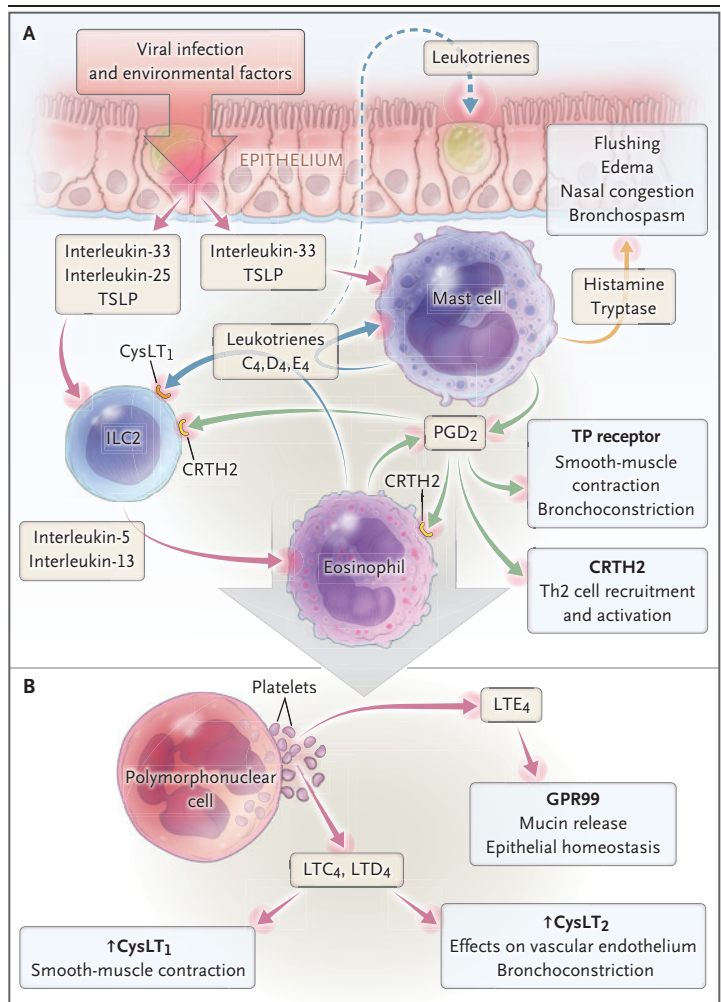


Figure 2. Inflammatory Pathways in AERD.

Type 2 inflammation has a circular path in patients with AERD (Panel A). Allergens, viral infection, and environmental factors are all capable of initiating epithelial injury and release of alarmins, interleukin-33, thymic stromal lymphopoietin (TSLP), and interleukin-25. These upstream cytokines have multiple effects focusing on type 2 inflammatory responses. Type 2 innate lymphoid cells (ILC2) and mast cells in AERD both amplify the responses, leading to eosinophilia and potential feed-forward mechanisms. Leukotrienes enhance these pathways and can control ILC2 responses. Platelet-adherent neutrophils (Panel B) further increase the leukotriene burden in AERD. Despite COX-1 inhibition of prostaglandins, a paradoxical oversynthesis of prostaglandin D_2 (PGD_2) occurs as a result of mast-cell and eosinophil activation through thromboxane (TP) receptors. PGD_2 receptors stimulate the recruitment of type 2 helper T (Th2) cells. Cysteinyl leukotrienes C_4 (LTC_4) and D_4 (LTD_4) act on both cysteinyl leukotriene receptor 1 (CysLT₁) and cysteinyl leukotriene receptor 2 (CysLT₂). Leukotriene E_4 (LTE_4) has minimal function at CysLT₁ and CysLT₂ but binds G protein-coupled receptor 99 (GPR99), leading to mucin release and submucosal swelling. CRTH2 denotes chemoattractant receptor-homologous molecule expressed on Th2 cells.

Table 2. Likelihood of AERD on the Basis of Historical Information.*

Historical Information	Likelihood of Positive OAC†
In patients with asthma and opacified sinuses on imaging	
Respiratory symptoms within 90 min after ingestion of an NSAID on one occasion	80%
Respiratory symptoms within 90 min after ingestion of 1 or 2 NSAIDs on ≥ 2 occasions	89%
Mild respiratory symptoms (treated by patient with antihistamines or nebulizer)	80%
Moderate respiratory symptoms (treated in medical office or emergency department)	84%
Severe respiratory symptoms (requiring hospitalization)	100%
Asthma and sinus disease in the absence of exposure to NSAIDs	42%
Daily aspirin therapy (81 mg) for cardiovascular prophylaxis; desensitization with first exposure‡	Unlikely
Additional baseline disease characteristics	
Asthma but normal sinus on CT scans§	Extremely unlikely
Nasal polyps and pansinusitis on imaging, without asthma (upper-airway AERD)	Unlikely
Asthma attacks after ingestion of any alcoholic beverages	Highly likely
Complete anosmia associated with nasal polyps	Highly likely
Rapid regrowth of nasal polyps after first sinus or polyp resection	Highly likely
Nasal polyps and asthma in childhood	Extremely unlikely

* Data are from Cardet et al.,⁷ Kim and Kountakis,⁸ Mascia et al.,¹² Dursun et al.,²⁸ and Lee-Sarwar et al.²⁹ Respiratory symptoms comprise the following, alone or in any combination: rhinorrhea, nasal congestion, sneezing, chest tightness, wheezing, shortness of breath, and need for an albuterol nebulizer. Tolerance of COX-2 inhibitors is expected in AERD, and COX-2 inhibitor use should not influence the diagnostic assessment.

† A positive oral aspirin challenge (OAC) is the definitive diagnostic test for AERD.

‡ Daily aspirin therapy does not preclude a diagnosis of AERD. Patients may accidentally desensitize themselves or start taking aspirin before the development of AERD. Stopping aspirin therapy or extending the interval between doses to more than 72 hours unmasks the hypersensitivity, and positive challenges may be seen. Exposure to acetaminophen at a dose of 1000 mg or higher results in modest COX-1 inhibition and triggers mild reactions in 33% of patients with AERD.

§ AERD is an acquired disease and ultimately involves mucosal swelling of the entire respiratory tract. A reaction to an NSAID can occur early in the development of the disease, before sinus opacification is identified on computed tomographic (CT) scans but after the onset of asthma. AERD is usually diagnosed at a later stage of the disease.

gate.³⁴ Oral aspirin challenges are the accepted standard for diagnosing AERD but are not performed in most prevalence studies. In fact, reaction information reported by patients is used in most studies. In our meta-analysis, the prevalence of AERD was 7.2% in the general population of patients with asthma, 14.9% among patients with severe asthma, 9.7% among patients with nasal polyps, and 8.7% among those with chronic sinusitis.³⁴ Furthermore, oral aspirin challenges were positive in 20 to 42% of patients with nasal polyps, asthma, and chronic rhinosinusitis but no known exposure to COX-1-inhibiting NSAIDs.^{28,35,36} AERD is not rare. On the basis of a disease prevalence of 7.2% and 19 million patients in the United States who have asthma, a total of 1,368,000 patients have AERD.

Using a computerized search strategy for a large electronic health system database, Cahill and colleagues found that 12.4% of patients who fulfilled the critical components of the AERD diagnosis (nasal polyps, asthma, and respiratory reactions to NSAIDs) did not have that diagnosis in their medical records and had not been referred for oral aspirin challenges or desensitization.³⁷

NON-AERD HYPERSENSITIVITY TO NSAIDS

Hypersensitivity reactions to individual NSAIDs through immune recognition may trigger anaphylaxis. Hives after ingestion of a specific NSAID or flares of chronic urticaria after exposure to any COX-1 inhibitor have nothing to do with AERD.

PATHOLOGICAL AND PHARMACOPATHOLOGICAL FEATURES OF AERD

In 1971, Vane published his explanation for why aspirin and other COX-1 inhibitors cross-react in patients with AERD.³⁸ Inhibition of COX-1 deprives inflammatory cells of the internal synthesis of prostaglandins (Fig. 1), particularly the protective PGE₂. In 1975, Szczeklik and colleagues definitively showed that inhibition of prostaglandins through increased doses of NSAIDs correlated perfectly with the same drug's ability to induce asthma reactions in patients with known AERD.³⁹

These findings provided a mechanism to explain hypersensitivity reactions in patients with AERD; however, much more about AERD remains confounding. Although AERD is characterized by high eosinophil levels with increased numbers and activity of mast cells, no evidence suggests that the disease is the consequence of antigen-specific IgE mechanisms. Several lines of evidence now point toward the role of innate mucosal immune responsiveness in directing a potent type 2 immune response (Fig. 2). Still unanswered are questions about whether the inciting event is virus-induced or toxin-induced injury and why the inflammatory responses fail to resolve spontaneously.

Specifically, the innate cytokines thymic stromal lymphopoietin (TSLP), interleukin-25, and interleukin-33, released from epithelia, are critical in the early steps of this innate type 2 inflammatory response.⁴⁰ Buchheit et al.⁴¹ showed that TSLP is directly involved in the synthesis of PGD₂ in mast cells. Liu et al.⁴² subsequently identified interleukin-33 as a central hub directing mast-cell activation and eosinophil recruitment after epithelial injury (Fig. 2).

Although innate, epithelia-derived signals might be critical upstream mediators in AERD, a central component of the disease is up-regulated cysteinyl leukotriene. Central observations in AERD are the enhanced response to cysteinyl leukotrienes^{43,44} and elevated cysteinyl LTE₄ levels both at baseline and during acute reactions.⁴⁵ LTE₄ is capable of driving pulmonary eosinophilia.^{46,47} As the stable end-product of leukotriene metabolism, LTE₄ plays a critical and probably underappreciated role. Lee et al. initially described

LTE₄-induced enhancement of airway responsiveness to histamine, an effect not seen with leukotriene C₄ (LTC₄) and leukotriene D₄ (LTD₄), suggesting the presence of a unique LTE₄ receptor.⁴⁸ After aspirin desensitization, LTE₄-induced bronchospasm is markedly diminished in patients with AERD, a response that does not occur in patients with aspirin-treated asthma who do not have AERD.⁴³ G protein-coupled receptor 99 (GPR99), a specific LTE₄ receptor, might transduce the biologic effects previously described.^{49,50}

Patients with AERD have diminished effects of PGE₂, a key stabilizer of cyclooxygenase that also has an antiproliferative effect. Mediated through altered expression of the EP₂ receptor, this effect was shown to be under epigenetic control, potentially influenced by infectious or inhaled environmental toxins.⁵¹ Impairment in appropriate COX-2 up-regulation might further diminish the production of PGE₂, exacerbating the imbalance.⁵² The observations that eosinophils in AERD may have unique interferon gamma production and responsiveness,⁵³ that platelets adherent to leukocytes can markedly augment cysteinyl leukotriene production in AERD,⁵⁴ and that a subgroup of difficult-to-desensitize patients with AERD have poor suppression of PGD₂ after aspirin administration⁵⁵ all point to AERD as a unique inflammatory airway disease.

MEDICAL TREATMENT

AERD is treated medically in a stepwise fashion according to established guidelines for the management of asthma and chronic sinusitis. Management usually progresses through the use of controller inhaler medications and leukotriene-modifier drugs, with the possible use of biologic agents as indicated for asthma. The upper airways are similarly treated with topical glucocorticoids, and if this treatment fails, it is necessary to add antihistamines, leukotriene modifiers, and systemic glucocorticoids. Zileuton, an inhibitor of 5-lipoxygenase, merits attention, since it partially blocks the formation of all cysteinyl leukotrienes, including LTE₄, and has proved to be effective in the treatment of AERD.⁵⁶ LTE₄ would not be markedly affected by the CysLT₁ receptor antagonists montelukast, zafirlukast, and pranlukast. Most patients with AERD have difficulty

managing airway inflammation and are therefore candidates for aspirin desensitization and daily aspirin therapy. In fact, the only unique treatment for AERD that is currently available is aspirin desensitization.

SURGICAL TREATMENT

By the time they consult a physician, many patients with AERD have severe nasal polyposis. At this stage, the only available medical intervention is systemic glucocorticoid therapy, which eventually fails or has unacceptable side effects. Surgical debulking of nasal polyps and functional endoscopic sinus surgery provide ventilation of the sinuses and facilitate the delivery of topical medications as well as removal of an inflammatory nidus (eosinophilic polyps).⁵⁷⁻⁵⁹ Since polyps recur rapidly, it is recommended that aspirin desensitization be performed shortly after sinus surgery.^{60,61} Although preventing further surgical intervention is a cardinal goal of medical therapy, repeat polypectomies are common despite medical management.

ASPIRIN DESENSITIZATION AND TREATMENT WITH ASPIRIN

Drug desensitization, also called induction of drug tolerance, can be used for selected medications. Aspirin desensitization is achieved by starting at low oral doses of aspirin (approximately 40.5 mg) and gradually increasing the dose over a period of 1 to 3 days, during which drug-induced reactions become milder and shorter and then disappear. When the target dose of 325 mg is achieved, any additional doses of aspirin or other COX-1-inhibiting NSAIDs do not induce hypersensitivity reactions.

Desensitization to aspirin was first performed by Widal and associates in 1922.² In 1976, Zeiss and Lockey reported a 72-hour refractory period after a positive oral challenge with indomethacin.⁶² Also in 1976, Bianco and colleagues⁶³ induced asthma with inhaled aspirin-lysine in a patient with AERD. For the next 72 hours, inhalation of the same provoking doses of aspirin-lysine did not induce any asthmatic response (refractory period).

In 1980, during a study of mediator release after aspirin-induced asthma in a patient with

AERD, we used aspirin at a dose of 325 mg to induce a large respiratory reaction.⁶⁴ The next day, a 325-mg dose of aspirin was again administered, and no respiratory reaction occurred. The patient reported to us that she could breathe through her nose and smell for the first time in years. This result led to our first treatment trial with daily aspirin in the desensitized state, which decreased nasal mucosal swelling but did not change the presence of asthma; a methacholine inhalation challenge still induced bronchospasm.⁶⁴ During the next year, systemic glucocorticoids were discontinued in the first patient and reduced by 50% in another patient, with continued patency of the nasal passages in both patients. This study was followed by confirmatory studies in other centers⁶⁵⁻⁷⁰ and at the Scripps Clinic,⁷¹⁻⁷³ all of which showed significant improvement in rhinosinusitis outcomes. Improvement in asthma outcomes was seen in some patients but was not consistently observed in all the studies. Table 3 summarizes the therapeutic benefits of aspirin desensitization in patients with AERD.

The mechanisms behind effectiveness in the treatment of AERD have been only partly untangled. It is not simply achieving a state of tolerance to aspirin that has a therapeutic benefit, since the dose necessary to improve airway inflammation is generally much higher than that needed to start a respiratory reaction or maintain desensitization. Of the many observations noted, down-regulation of the LTC₄ receptors,⁷⁴ decreases in inflammatory PGD₂,⁵⁵ decreased effects of LTE₄,⁷⁵ and effects on interleukin-4 expression through STAT6 down-regulation^{76,77} provide opportunities to understand the mechanism underlying this benefit (Table 3).

Aspirin desensitization, followed by aspirin treatment at a dose of 325 to 650 mg twice daily, is now the standard of care for patients with AERD after debulking of nasal polyps and sinuses has been performed (within 3 to 4 weeks after the first sinus polyp operation).⁷⁸ Aspirin desensitization is performed in the clinic under medical supervision, followed by institution of daily aspirin treatment in the desensitized state. Aspirin can be discontinued for 48 hours without loss of desensitization. While taking daily aspirin, patients are also protected from inadvertent exposure to COX-1 NSAIDs, since cross-desensitization to all NSAIDs is universal. Outpatient aspirin

Table 3. Consequences of Aspirin Desensitization, Followed by Daily Aspirin Treatment, in Patients with AERD.

Before Aspirin Desensitization	Aspirin Desensitization and Daily Aspirin Therapy
Nasal congestion	Nasal decongestion, with improved patency
Anosmia	Improvement in sense of smell
Mean no. of viral rhinosinusitis episodes, 6 per yr	Mean no. of viral rhinosinusitis episodes, 1–2 per yr
Aggressive formation of nasal polyps	Reduction in nasal polyp formation
Disturbed sleep due to nasal obstruction	Restorative sleep on clinical observation
Mean interval between sinus or polyp surgeries, 3 yr	Mean interval between sinus or polyp surgeries, 9 yr
Uncontrolled asthma	Improved asthma control
Need for systemic glucocorticoids	Decreased need for systemic glucocorticoids
Marked impairment in quality of life	Quality-of-life scores significantly improved
High costs of medical and surgical care	Low costs of desensitization and daily aspirin
Ongoing reactivity to COX-1–inhibiting NSAIDs	Protection from NSAID reactions

desensitization, followed by daily aspirin therapy, reduces health care expenditures for the management of AERD, since the costs of this approach are much lower than the costs of additional sinus surgery and outpatient and emergency department visits.⁷⁹ In a large study involving patients with AERD, revision sinus surgery was needed every 3 years, on average, before aspirin desensitization; after desensitization and daily treatment with aspirin, the mean interval for sinus revision surgery was 9 years.⁸⁰ Some patients had no recurrence of nasal polyposis.

Not surprisingly, there are two complications of long-term aspirin desensitization treatment. The first is gastric pain or ulcer caused by diminished synthesis of gastric prostaglandin (PGI₂) formation and inadequate repopulation of gastric mucosal cells (occurring in <15% of patients).^{72,73,81} The second complication is bleeding, usually in the skin (ecchymosis) but occasionally in the nose, bronchi, bladder, or gastrointestinal tract.

Physicians caring for patients with AERD should not attempt aspirin desensitization without special training and appropriate nursing supervision.⁸² The procedure is not for the novice and should be conducted in a dedicated diagnostic and treatment center where severe reactions can largely be prevented and those that occur can be promptly identified and treated. Aspirin desensitization centers are scattered throughout the United States and the world, particularly in large group practices, academic centers, and large allergy groups, where aspirin desensitization pro-

cedures are routinely performed in the presence of leukotriene-modifier blockade to mitigate lower respiratory tract symptoms.⁸³ Aspirin desensitization protocols focus on safety, speed of completion, and comfort. Differences in protocols are debated,^{78,84–86} but all procedures accomplish the same end result — namely, administration of a full 325-mg aspirin tablet without any respiratory signs. One of two results occurs during aspirin challenges. If the challenge is negative, the patient continues to use NSAIDs as needed. If the challenge is positive, incremental increases in the aspirin dose are continued until desensitization is achieved. Thus, during diagnostic aspirin challenges, an accurate diagnosis of AERD is established, and aspirin desensitization treatment is initiated.

Awareness of AERD continues to be overshadowed by the false assumption that it is a rare, esoteric disease. This misperception is combined with unfounded safety concerns about diagnostic oral aspirin challenges. Clinicians should realize that aspirin desensitization, followed by daily aspirin therapy, is a disease-specific treatment that offers a benefit for the majority of patients with AERD. Now that phenotyping in asthma and sinus disease can guide treatment decisions, AERD is a diagnosis worth considering.

Dr. White reports receiving fees for serving on a speakers' bureau from AstraZeneca. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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Aspirin Exacerbated Respiratory Disease (AERD)



Overview

- Aspirin-exacerbated respiratory disease (AERD), also known as Samter's Triad.
- Chronic medical condition that consists of three clinical features: asthma, sinus disease with recurrent nasal polyps, and sensitivity to aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) that inhibit an enzyme called cyclooxygenase-1.
- This sensitivity usually manifests as respiratory reactions occur upon ingesting, inhaling or topical use of an NSAID.
- The exact cause of the reactions is not known.
- Approximately 7% of all adults with asthma and 14% of all adults with severe asthma have AERD. And 30% of adults with asthma and nasal polyps have AERD which is around 1.2 million to 1.6 million people in the United States with AERD.
- AERD can develop quite suddenly in adulthood, usually between the ages of 20 and 50, and there is no clearly-understood trigger that causes the disease.

Symptoms

- People with AERD usually have asthma, nasal congestion and recurrent nasal polyps.
- Symptoms often do not respond sufficiently to conventional treatments.
- Many people experience chronic sinus infections and a loss of sense of smell is common.
- A characteristic feature of AERD is that people develop respiratory reactions to aspirin and other NSAIDs.
- These reactions classically involve both upper respiratory symptoms (increased nasal congestion, frontal headache or sinus pain, and sneezing) as well as lower respiratory symptoms (cough, wheezing, chest tightness), but they can also induce skin flushing, rash, abdominal pain and occasionally vomiting.
- It has been noted that about 75% of all people with AERD develop mild-to-moderate respiratory reactions when they drink alcohol. These reactions are not always specific to just one type of alcohol and often occur after consuming less than one glass of alcohol.

Diagnosis

- The diagnosis of AERD is a clinical one.
- There is no one specific test or blood result that alone can be used to diagnose the disease.
- The symptom triad of asthma plus nasal polyps plus respiratory reactions to NSAIDs is considered diagnostic for AERD.



Aspirin Exacerbated Respiratory Disease (AERD)



- However, for people whose history of possible reaction to an NSAID is not clear, it is often helpful to do a formal aspirin challenge to confirm the diagnosis. This can be done either as an oral challenge, or as a combination of an intranasal and oral challenge, and the procedure is done in a hospital or clinic with an experienced doctor and medical team.
- People with AERD have high numbers of eosinophils, a type of immune cell that is involved in inflammation, in their nasal polyps.
- They often have elevated levels of eosinophils in their blood.
- Though the presence of an elevated eosinophil level is not required as part of the diagnosis, it can be a helpful additional insight.



Treatment

- People with AERD who have not been desensitized to aspirin should avoid all NSAIDs in order to prevent reactions.
- Even with the complete avoidance of NSAIDs, people will continue to have symptoms of asthma, nasal congestion and recurrent polyps.
- Acetaminophen is usually safely tolerated at low doses (up to 500mg at a time or below 1000 mg).
- Most people with AERD will need to use daily medications to control their symptoms: inhaled corticosteroids for asthma, intranasal steroid sprays or steroid sinus rinses can help to control the nasal symptoms, and nasal polyps can also be treated with steroids injected directly into the polyps.
- Biologic medications such as mepolizumab and omalizumab may also be of benefit.
- Several non-steroid medications are also available, specifically medications that inhibit the production of leukotrienes (zileuton) or block the function of leukotrienes (Montelukast and Zafirlukast) and can help to treat some of the symptoms.
- Despite intensive medical therapy, the need for surgical removal of nasal polyps in AERD is very common, though unfortunately the rate of recurrence of nasal polyps after surgery is high.
- Aspirin desensitization in order to initiate daily high-dose aspirin therapy can also be used as a steroid-sparing treatment in some patients.
- In people with AERD, an aspirin desensitization procedure can be performed by administering gradually increasing doses of aspirin in a hospital or clinic that specializes in such treatment.
- The goal of aspirin desensitization is to have the person begin long-term daily aspirin therapy, which in many people can decrease the regrowth of nasal polyps and reduce the need for corticosteroid medications.



LIST OF COMMONLY AVAILABLE NSAIDS AND COX-1 INHIBITORS TO AVOID

Patients with Aspirin Exacerbated Respiratory Disease (AERD), also known as Samter's Triad or Aspirin Sensitive Asthma, should completely avoid all non-steroidal anti-inflammatory drugs (NSAIDs) that inhibit the COX-1 enzyme.

The list below details most commonly available COX-1 inhibitors in the United States – the generic drug name in **bold**, followed by most of the brand names in *italics*. All of these medications should be avoided. Please read all medication labels, and check with your healthcare providers to ensure that you are not mistakenly given a prescription for a medication listed below.

Aspirin or salicylate-containing medications

Exedrine
Pepto- Bismol
Alka-Seltzer
Aggrenox
Anacin
Arthropan
Ascriptin
Asperbuf
Aspergum
Aspermin
Aspir-Mox
Aspirtab

Ibuprofen

Motrin
Advil

Naproxen

Aleve
Anaprox

Salsalate

Amigesic
Salflex
Argesic

Flurbiprofen

Ansaid

Ketorolac

Toradol

Diclofenac

Arthrotec

Note: this list may be incomplete – contact your doctor if you have questions about the safety of medications not listed above.

If you have been desensitized to aspirin and are on aspirin therapy, you may also be able to safely take other NSAIDs, but check with your allergist if you are unsure.



Instructions for decreasing dose of daily aspirin prior to a surgical procedure for patients with AERD who are on high-dose daily aspirin therapy

These instructions are a way to help you to (A) decrease your daily aspirin at home prior to surgery, in order to safely undergo surgery and lower your risk of blood loss during the surgical procedure, and (B) maintain the aspirin desensitization so that you can safely re-start your daily aspirin without developing a reaction.

1. Prior to initiating any change in your daily aspirin dose, please contact your primary AERD specialist at the BWH AERD Center.
2. Prior to surgery, discuss your aspirin treatment with your surgical team and review these instructions with your surgeon to confirm that they are comfortable with this aspirin plan.
 - 14 days before the procedure, decrease aspirin to only 81mg per day.
 - The day before the procedure, do not take any aspirin.
 - The morning of the procedure, do not take any aspirin.
 - After the procedure is over, take 81mg of aspirin in the evening.
 - The day after the procedure, take 81mg aspirin twice a day.
 - The next day, take 162mg twice a day.
 - The following day, take 325mg twice a day.
 - The next day go back up to 650mg aspirin twice a day if that is the dose you are regularly on (or stay at 325mg twice a day if that is the dose you are regularly on).



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Budesonide (Pulmicort) + Saline Irrigation/Rinse

Peter Hwang, MD

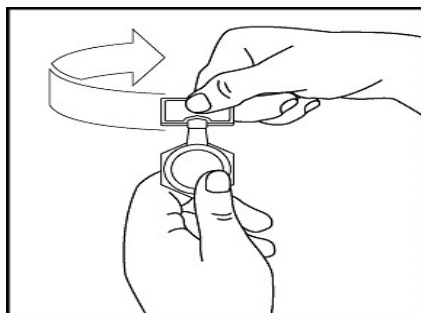
Jayakar Nayak, MD, PhD

Jane Wang, RN, MSN, FNP

Budesonide (Pulmicort) is an anti-inflammatory steroid medication used to decrease nasal and sinus inflammation. It is dispensed in liquid form in a vial. Although it is manufactured for use with a nebulizer, we intend for you to use it with the NeilMed Sinus Rinse bottle (preferred) or a Neti pot.

Instructions:

1. Make 240cc of saline in the NeilMed bottle using the salt packets or your own saline recipe (see separate handout).
2. Add the entire 2cc vial of liquid Budesonide (Pulmicort) to the rinse bottle and mix together.
3. While in the shower or over the sink, tilt your head forward to a comfortable level. Put the tip of the sinus rinse bottle in your nostril and aim it towards the crown or top of your head. Gently squeeze the bottle to flush out your nose. The fluid will circulate in and out of your sinus cavities, coming back out from either nostril or through your mouth. Try not to swallow large quantities and spit it out instead.
4. Perform Budesonide (Pulmicort) + Saline irrigations 2 times daily.



Budesonide (Pulmicort) vial to be twist opened before emptying into NeilMed Sinus Rinse bottle or a Neti pot.





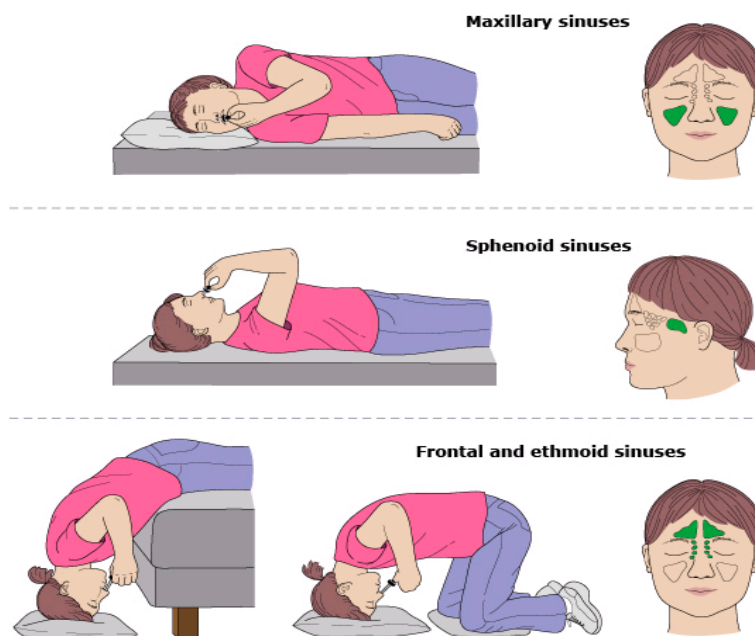
Pulmicort (budesonide) Respule Instructions for Nasal Irrigation

This medication is not FDA approved for this exact use, and for this technique it should not be used in a nebulizer, but instilled into the nose as described below. The irrigations are easy to use but take a little getting used to.

Sinus irrigation technique of the right nostril:

1. Instill half of the solution in the respule into your right nostril and pinch your nose closed.
2. Lie face down across a bed with your head hanging over the side (see 3rd position shown in drawings) and stay face down for 60 seconds – this will irrigate the right frontal and ethmoid sinuses.
3. Move to lie on the bed with the right side of your face resting on the bed (see 1st position shown in drawings) for 60 seconds – this will irrigate the right maxillary sinus.
4. Move to lie flat on your back (see 2nd position shown in drawings) for 60 seconds – this will irrigate the right sphenoid sinus.
5. Gently blow out into a sink to expel the remaining solution from your right sinus
6. Repeat for the left side.

Positions for administering sinus medications



This position is the most important, as you can turn your head from side to side a bit and get the maxillary and sphenoid sinuses too, with just this one position.

These positions allow nasal medications to penetrate into the sinuses, highlighted in green in the right-hand column. To give the medications, get into the position shown and give the medication into the nose. Stay in the position for the amount of time specified by your healthcare provider. For the maxillary sinuses (first position), the medication must be given on each side separately. For the other two positions, medications can be given to both sides of the nose at the same time.

Courtesy of Daniel L. Hamilos, MD.

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