Aspirin-Exacerbated Respiratory Disease (AERD)

- Prior Terminology for AERD
  - aspirin-induced asthma
  - aspirin sensitive asthma
  - aspirin hypersensitivity
  - aspirin idiosyncrasy
  - aspirin intolerance
  - Samter’s triad
  - Aspirin triad
Objectives

We will discuss:

- Classification of ASA/NSAID hypersensitivity reactions
- AERD Characteristics
- Diagnosis of AERD
- ASA Desensitization

Case Example

- 39 y.o. female referred for treatment of chronic sinusitis.
- Bothered by right frontal and periorbital pain, long-term anosmia, nasal congestion, bilateral thick rhinorrhea.
- Diagnosed with asthma at age 22
- Diagnosed with CRS/NP at age 25
- Sinus surgery x 2 in 1990s
Case Example

- +Allergic rhinitis, currently treated with immunotherapy
- Undergoing treatment with omalizumab (anti-IgE) for asthma
- Treated almost continuously with systemic steroids for the last 17 years.

Case Example

- Now taking methylprednisolone 8 mg per day
- Requires steroid pulses every 5 weeks
- Has had spontaneous fractures
- On Reclast (bisphosphonate) for osteoporosis
Case Example

- In 1990s, had 2 episodes of severe asthma exacerbation after ingesting ibuprofen
  - Required ER visits
Questions for this Patient

- Can we significantly improve this patient’s sinus problems?
- How does this patient’s aspirin sensitivity alter the management of her sinus disease?
  - Indications for surgery
  - Surgical goals
  - Post-op medical management of sinusitis
- Is she a candidate for aspirin desensitization?

Aspirin-Exacerbated Respiratory Disease (AERD)

- Association of asthma, rhinosinusitis, nasal polyposis
- Symptoms with NSAID exposure (30-60 min)
  - Rhinorrhea, conjunctivitis, bronchospasm
    - Rarely flushing, urticaria, GI symptoms, laryngospasm, hypotension
- Dependent on COX-1 inhibition
- COX-2 inhibitors safe
Hypersensitivity reactions to aspirin and NSAIDs and cross-reactivity

<table>
<thead>
<tr>
<th>Type of reaction</th>
<th>Underlying disease</th>
<th>Cross-reactivity with COX-1 inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory (AERD)</td>
<td>Rhinitis, nasal polyps, sinusitis, asthma</td>
<td>Yes</td>
</tr>
<tr>
<td>Urticaria/AE</td>
<td>Chronic urticaria</td>
<td>Yes</td>
</tr>
<tr>
<td>Urticaria/AE</td>
<td>None</td>
<td>Yes or no</td>
</tr>
<tr>
<td>Anaphylaxis</td>
<td>None</td>
<td>No</td>
</tr>
</tbody>
</table>

The cross-reactivity patterns depicted in this table are generally true, but exceptions can occur.

AERD, angioedema.


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**TABLE I. Universal cross-reactions between aspirin and non-NSAIDs occur**

All of the following preferentially inhibit COX-1:

- Piroxicam (Feldene)
- Indomethacin (Indocin)
- Sulindac (Clinoril)
- Tolmetin (Tolectin)
- Ibuprofen (Motrin, Rufen, Advil)
- Naproxen (Naprosyn)
- Naproxen sodium (Anaprox, Aleve)
- Flurbiprofen (Nalfon)
- Meclofenamate (Medecmen)
- Mefenamic acid (Ponstel)
- Flurbiprofen (Ansaid)
- Diflunisal (Dolbid)
- Ketoprofen (Orudis, Oruvail)
- Diclofenac (Voltaren, Cataflam)
- Ketorolac (Toradol)
- Etodolac (Lodine)
- Nabumetone (Relafen)
- Oxaprozin (Daypro)

100% cross-reactivity in AERD with therapeutic dosage

Stevenson DD, Sczceklki A. JACI 2006;118:773-86
**COX-2 Inhibitors are Usually Tolerated in AERD**

**TABLE III.** Selective COX-2 inhibitors preferentially inhibit COX-2

<table>
<thead>
<tr>
<th>Inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celecoxib (Celebrex)*</td>
</tr>
<tr>
<td>Rofecoxib (Vioxx)†</td>
</tr>
<tr>
<td>Valdecoxib (Bextra)†</td>
</tr>
<tr>
<td>Etoricoxib (Arcoxia)‡</td>
</tr>
<tr>
<td>Parecoxib (Dynasiat)‡</td>
</tr>
<tr>
<td>Lumiracoxib (Provigo)‡</td>
</tr>
</tbody>
</table>

Rare reports of patients with AERD who react to COX-2 inhibitors

Stevenson DD, Szczeklik A. JACI 2006;118:773-86

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**Anaphylaxis from ASA/NSAIDs**

- Anaphylactic reactions can occur after exposure to specific NSAIDs
- No underlying respiratory disease
- Reactions are drug-specific
  - Potential for structurally related NSAID reaction
- May be IgE-mediated
Prevalence of AERD

Unselected populations
- 1-4%

Asthmatics undergoing ASA challenge
- 10-20%

Asthmatics with nasal polyps and sinusitis
- 30-40%

Asthmatics with history of NSAID reactions
- 66-97%

Demographics of AERD

Patients
- Age at onset
  - 29-34 yrs
- 3:2 female:male in U.S.
- Family history rare
  - 1% in U.S.
- Aeroallergen sensitivity common
  - 34% prick testing
  - 64% prick & ID testing

Stevenson DD, Sczceklak A. JACI 2006;118:773-86
Development of AERD

- Chronic Rhinitis usually develops first
  - Progresses to hyperplastic sinusitis with nasal polyposis
  - most have opacification of sinuses
  - Multiple sinus surgeries
  - Hyposmia/anosmia very common

- Asthma
  - Present early in life
  - *De novo* 2 years on average after polyposis

Stevenson DD, Sczceklk A. JACI 2006;118:773-86

Pathophysiology of AERD
AERD: Key Points

- NSAID exposure does not cause the disease
- NSAID exposure does not sustain the disease

Pathophysiology of AERD

- An abnormal metabolism of arachidonic acid involving both the lipoxygenase (LO) and the cyclooxygenase (COX) pathways.
- This deviation results in an imbalance of the synthesis of eicosanoids, leukotrienes, and prostaglandins.
- Anti-inflammatory prostaglandins, especially E2, decrease; and the synthesis of leukotrienes (A4,B4,C4,D4,E4) is increased.
- Mast cells and eosinophils promote airway inflammation.

Pathophysiology of AERD

Leukotriene forming enzymes are increased in AERD Polyps
Cysteinyl leukotrienes are overproduced in AERD polyps

Perez-Novó. JACI 2005;115:1189-96

AERD patients excrete high levels of LTE4 in urine

Higashi et al. JACI Feb 2004
**Sinus Surgery reduces LTE4 in urine**

Higashi et al. JACI Feb 2004

**Long term asthma outcomes in AERD patients appear to improve after ESS**

<table>
<thead>
<tr>
<th></th>
<th>12 Months postoperative</th>
<th>Mean 10 years follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Asthma attack frequency</strong> (n = 27)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased</td>
<td>17 (44.4)</td>
<td>24 (88.9)</td>
</tr>
<tr>
<td><strong>Asthma-related physician visits</strong> (n = 29)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased</td>
<td>18 (62.1)</td>
<td>27 (93.1)</td>
</tr>
<tr>
<td><strong>Asthma-related emergency room visits</strong> (n = 18)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased</td>
<td>17 (94.4)</td>
<td>16 (88.9)</td>
</tr>
<tr>
<td><strong>Asthma-related hospitalizations</strong> (n = 11)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased</td>
<td>10 (90.9)</td>
<td>10 (90.9)</td>
</tr>
<tr>
<td><strong>Oral steroid use</strong> (n = 25)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No change</td>
<td>7 (28.0)</td>
<td>1 (4.0)</td>
</tr>
<tr>
<td>Decreased/stopped</td>
<td>18 (72.0)/8 (32.0)</td>
<td>22 (81.5)/11 (44.0)</td>
</tr>
<tr>
<td>Increased</td>
<td>0 (0.0)</td>
<td>2 (8.0)</td>
</tr>
<tr>
<td><strong>Inhaled steroid use</strong> (n = 28)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No change</td>
<td>18 (64.3)</td>
<td>14 (50.0)</td>
</tr>
<tr>
<td>Decreased/stopped</td>
<td>9 (32.1)/1 (3.6)</td>
<td>9 (32.1)/1 (3.6)</td>
</tr>
<tr>
<td>Increased</td>
<td>1 (3.6)</td>
<td>5 (17.9)</td>
</tr>
</tbody>
</table>

Values are given as n (%).

Treating rhinosinusitis may improve asthma in AERD

![Chart showing pre- and postoperative predicted FEV1 values for A-S and A-T patients.](chart)

Fig. 3. Pre- and postoperative predicted FEV1 values. A-S = aspirin sensitive; A-T = aspirin tolerant.


Treating rhinosinusitis with surgery can improve asthma control in AERD patients
Sinus disease in AERD and the benefits of surgery

In general, AERD patients have worse sinus disease

- Patients with AERD have significantly worse preoperative CT scores and worse endoscopy scores both preoperatively and postoperatively.

- AERD patients showed a similar degree of improvement after surgery although patients with AERD had final scores that were significantly worse.

Laryngoscope, 115:2199–2205, 2005
Endoscopy scores are worse in AERD patients, both before and after surgery

Fig. 1. Aspirin (ASA)-intolerant patients had worse preoperative, intermediate postoperative and long-term postoperative endoscopy scores than ASA-tolerant patients.

Quality of life scores improve after ESS, but worsen over time

Fig. 3. Both aspirin (ASA)-tolerant and ASA-intolerant patients' RSDI scores improved after endoscopic sinus surgery.
Medication requirements may not change after ESS in AERD

Indications for Sinus Surgery in AERD

- Large symptomatic polyp burden
- Mucoceles
- Excessive systemic steroid requirements for sinonasal disease → need access for topical intranasal steroid therapy
- Poorly controlled asthma
How is AERD diagnosed?

Diagnosis of AERD begins with the history

How Good is the History?

100% of patients with reactions to ASA/NSAID that had a poor response to albuterol and required medical intervention or hospitalization had positive ASA challenges.

88% of patients with 2 or more historical reactions to ASA/NSAID had positive ASA challenges.

Diagnosis of AERD

- No reliable in vitro test
- **Challenge tests are the gold standard**
- Types of challenges
  - Oral
  - Bronchial inhalation
    - L-lysine aspirin
  - Nasal inhalation
    - ketorolac

Drugs are often withdrawn prior to aspirin challenge

**Drug withdrawal before oral aspirin challenge procedures:**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short-acting β₂-agonists</td>
<td>6 h (8 h, if possible)</td>
</tr>
<tr>
<td>Ipratropium bromide</td>
<td>6 h (8 h, if possible)</td>
</tr>
<tr>
<td>Long-acting β₂-agonists</td>
<td>24 h (48 h, if possible)</td>
</tr>
<tr>
<td>Long-acting theophylline</td>
<td>24 h (48 h, if possible)</td>
</tr>
<tr>
<td>Tiotropium bromide</td>
<td>24 h (48 h, if possible)</td>
</tr>
<tr>
<td>Short-acting antihistaminics</td>
<td>3 days</td>
</tr>
<tr>
<td>Cromolyn sodium</td>
<td>8 h</td>
</tr>
<tr>
<td>Nedocromil sodium</td>
<td>24 h</td>
</tr>
<tr>
<td>Leukotriene modifiers</td>
<td>At least 1 week</td>
</tr>
</tbody>
</table>

*Allergy 2007: 62: 1111–1118*
Placebo Challenge: Day 1

- Start challenge if FEV1 > 70% predicted
- Administer 1 capsule of placebo (saccharin lactate in gelatin capsules) every 1.5-2 hrs (3-4 doses)
- Measure FEV1 every 30 minutes
- If variation of FEV1 < 15%, may proceed to challenge next day
  - If FEV1 variation > 15%, asthma unstable and cannot challenge

European ASA Challenge Example

Table 1. The consecutive and cumulative doses of aspirin used in oral aspirin challenge

<table>
<thead>
<tr>
<th>Consecutive doses of aspirin (mg)</th>
<th>Cumulative doses of aspirin (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10*</td>
<td>10</td>
</tr>
<tr>
<td>27</td>
<td>27</td>
</tr>
<tr>
<td>44</td>
<td>71</td>
</tr>
<tr>
<td>117</td>
<td>188</td>
</tr>
<tr>
<td>312</td>
<td>500</td>
</tr>
<tr>
<td>500*</td>
<td>1000</td>
</tr>
</tbody>
</table>

Allergy 2007: 62: 1111–1118
Aspirin Desensitization for AERD
Biochemical Changes with ASA Desensitization

- AERD Pathophysiology
  - ↑ urinary LTE$_4$
  - ↑ LTE$_4$ and TXB$_2$ in BAL
  - ↑ cysLT1 receptor expression
  - ↑ response to inhaled LTD$_4$

- After ASA desensitization
  - ↓ uLTE$4$, ↓ BHR to LTE$4$
  - ↓ LTC$4$ and histamine in nasal secretions
  - ↓ expression of cysLT1 receptor

Stevenson DD, Sczceklik A. JACI 2006;118:773-86

Clinical Benefits of ASA Desensitization

- Long-term observational studies suggest:
  - ↓ ‘sinus infections’
  - ↓ oral steroid bursts
  - ↓ anosmia
  - ↓ rhinosinusitis symptoms
  - ↓ asthma symptoms

Stevenson DD, Sczceklik A. JACI 2006;118:773-86
**Changes in Disease after ASA Desensitization**

**TABLE II.** Analysis of changes in markers of clinical disease after greater than 1 year of treatment with aspirin desensitization (n = 128)

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>24 y after therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median</td>
<td>Range</td>
</tr>
<tr>
<td>No. of sinus infections</td>
<td>5.0</td>
<td>0-12</td>
</tr>
<tr>
<td>Sniff scores</td>
<td>0.0</td>
<td>0-3</td>
</tr>
<tr>
<td>Nasal symptom scores</td>
<td>2.0</td>
<td>0-4</td>
</tr>
<tr>
<td>Asthma symptom scores</td>
<td>3.0</td>
<td>0-4</td>
</tr>
<tr>
<td>Sinos operatively</td>
<td>0.2</td>
<td>0-3</td>
</tr>
<tr>
<td>Hospitalizations for asthma</td>
<td>0.0</td>
<td>0-5</td>
</tr>
<tr>
<td>Emergency department visits for asthma</td>
<td>0.15</td>
<td>0-15</td>
</tr>
</tbody>
</table>

Values were determined with the Wilcoxon signed-rank statistic. Two-tailed P values were reported.


**Changes in Therapy after ASA Desensitization**

**TABLE III.** Analysis of treatment with corticosteroids before, at 6 months after, and greater than 1 year after starting aspirin desensitization therapy

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Aspirin treatment at 6 mo</th>
<th>Aspirin treatment at &gt;1 y</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SEM</td>
<td>Mean</td>
</tr>
<tr>
<td>Nasal corticosteroids (mg/d)</td>
<td>271.4</td>
<td>10.3</td>
<td>252.2</td>
</tr>
<tr>
<td>Inhaled corticosteroids (mg/d)</td>
<td>867.3</td>
<td>52.1</td>
<td>829.9</td>
</tr>
<tr>
<td>Daily corticosteroids (mg/d)</td>
<td>108.1</td>
<td>1.8</td>
<td>81.1</td>
</tr>
<tr>
<td>Short courses of corticosteroids</td>
<td>5.7</td>
<td>0.7</td>
<td>5.8</td>
</tr>
</tbody>
</table>

Values were determined with the paired t test.
*Comparisons were made between baseline and 6 months and baseline and greater than 1 year.

Timing of desensitization

- If indicated, proceed with ESS
- Perform desensitization 4-6 weeks later
- If desensitized patient again needs surgery, can reduce dose briefly, only hold ASA for a day

Long-term ASA Desensitization

- Aspirin therapy is continued indefinitely
- Even brief discontinuation requires repeat of desensitization procedure
- Discontinuation usually due to GI side effects
  - e.g. gastritis
Candidates for ASA Desensitization

- Patients with AERD who have moderate or severe asthma, intractable nasal symptoms who have failed medical therapy
- Patients with AERD who require multiple sinus surgeries
- Patients requiring systemic corticosteroids for control of AERD
- Patients with AERD who require aspirin for other diseases


Why Aspirin Desensitization is Underutilized

- Fear of severe reactions
- Perceived need for inpatient or ICU setting
- Evidence of efficacy is primarily observational
- Time-consuming
Aspirin Desensitization for AERD

Protocols

Aspirin Desensitization Joint Task Force Protocol

- Use 81 mg aspirin tablets and cut with pill cutter

- Start with 20.25 mg ASA (1/4 of 81 mg) followed by 40.5, 81, 162.5, 325 mg at 90 minute intervals

Scripps ASA Desensitization Protocol

- Start with 30 mg aspirin followed by 60, 100, 150, 325 and 650 mg every 3 hrs

Desensitization Dosing After Reactions

- Treat symptoms and after return to baseline, repeat dose that caused reaction
  - For naso-ocular symptoms, do not need to wait for full recovery
  - For significant bronchospasm (>25% ↓ FEV1), lung function typically improves over hours and usually desensitization is halted and resumed following day (typically without event)

- Most patients become refractory after 1st bronchial reaction
Does Historical Severity of Reaction Predict Reaction to ASA Challenge?

- Do historical aspirin- or NSAID–induced reactions predict the severity of reactions in oral aspirin challenge (OAC)?

- Williams, et al. assessed the relationship between historical aspirin- or NSAID-induced bronchial reactions and the severity of bronchial reactions during OAC in patients with AERD at Scripps

Williams AN et al. JACI 2007;120:273-7.

There is no Correlation between Severity of Historical aspirin/NSAID reaction with Desensitization Reaction

<table>
<thead>
<tr>
<th>OAC bronchial reaction severity</th>
<th>Historical reaction treatment location</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Home (n = 68), n (%)</td>
</tr>
<tr>
<td>&lt;20% decrease in FEV₁</td>
<td>53 (84)</td>
</tr>
<tr>
<td>20% to 29% decrease in FEV₁</td>
<td>5 (8)</td>
</tr>
<tr>
<td>≥30% decrease in FEV₁</td>
<td>5 (8)</td>
</tr>
</tbody>
</table>

Dose for historical reaction (550 mg) was ~ 9 times provoking dose during challenge (62 mg) (P < .0001)
Pretreatment for ASA Desensitization

- “The ideal pre-aspirin challenge controller regimen appears to be LTMDs (currently a leukotriene receptor antagonist), long-acting beta 2-agonists, and inhaled corticosteroids”

- “Systemic corticosteroids should be added whenever hyperirritable airways fail to abate with this program”


Leukotriene Modifiers Reduce Frequency and Severity of Bronchospasm during ASA desensitization

![Graph](image)

Figure 1. Comparison of forced expiratory volume in 1 second (FEV₁) change in all patients taking leukotriene modifier drugs (LTMDs) (n = 260) with all patients not taking LTMDs (n = 417) (χ² P < .001).

Safety of Using Leukotriene Modifiers in ASA Challenges

- Only 2 of 96 asthmatic reactions in patients on leukotriene modifiers had FEV1 decline > 40%
  - Both responded to routine management
  - 1 received IM epinephrine
  - No ICU transfers
- 6 pts treated with LTRA and zileuton
  - 1 (17%) had an asthmatic response


ASA Dosing Recommendations

- After completing aspirin desensitization, patients should be started on 650 mg of aspirin twice daily
- After 1 month, if improvement in symptoms, may attempt to decrease dosage of aspirin gradually to the lowest effective dosage (usually 325 mg twice daily) to minimize any potential complications of aspirin

Medical Therapy for AERD
Rhinosinusitis

- Most patients require daily medications and intermittent systemic steroid ‘bursts’ to keep rhinosinusitis controlled

- Options:
  - Topical Steroids
  - Systemic Steroids
  - Anti-leukotrienes (montelukast, zileuton)
  - Macrolides or other Antibiotics

Conclusions

- AERD is common in patients with CRS/NP
- Rhinosinusitis appears to be more severe in AERD patients
- Treatment of sinus disease may improve asthma control
- Aspirin desensitization therapy appears to be an effective treatment for AERD
- ASA desensitization can be done safely in the office setting with appropriate premedication and protocols