Aspirin-Exacerbated Respiratory Disease (AERD)

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Disclosures for:

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I will be discussing products that are investigational or not labeled for use under discussion.
AERD is an acquired metabolic inflammatory disorder

- Ongoing airway inflammation
- Results from metabolic cause
- Exacerbated by aspirin or any NSAID use
- Acquired, never occurs prepubertally
Samter’s Triad

• Nasal polyposis
• Chronic sinusitis
• Asthma
• Aspirin sensitivity
Aspirin sensitivity is the hallmark of AERD

- Most sensitive and specific marker for AERD
- Not responsible for the pathogenesis of disease
- All NSAIDs that inhibit COX-1 exhibit the same reaction
  - Useful screen for other types of NSAID reaction
Aspirin worsens, but does not cause AERD

- Avoidance of NSAIDs and salicylate free diet do not prevent disease or prevent progression
- Many patients may never have taken aspirin, complicating diagnosis
A significant proportion of adult asthma is AERD

- 8.2% of U.S. adults are asthmatic
  - 9% of these have AERD
  - AERD is 30% of severe asthmatics

- 13% of U.S. adults have CRS
  - 15% of these have AERD
Asthma in AERD is severe, persistent and may be irreversible

- AERD has lower FEV1 following bronchodilator than ATA
- AERD more likely to be severe
- AERD more likely to require steroid therapy
- Likely to have remodeling of airways
### Tolerance of NSAIDs in AERD

**COX1 > COX2**
- Aspirin
- Bismuth (Pepto-Bismol)
- Ibuprofen (Motrin, Advil, Rufen)
- Naproxen (Naprosyn, Anaprox, Aleve)
- Ketoralac (Toradol)
- Indomethacin (Indocin)
- Nabumetone (Relafen)
- Tolmetic (Tolectin)
- Piroxicam (Feldene)
- Sulindac (Clinoril)
- Fenoprofen (Nalfon)
- Meclofenamate (Meclomen)
- Mefenamic Acid (Ponstel)
- Flurbiprofen (Ansaid)
- Diflunisal (Dolbid)
- Ketoprofen (Orudis, Oruval)
- Diclofenac (Voltaren, Cataflam)
- Etodolac (Lodine)
- Oxaprozin (Daypro)

**COX2 > COX1**
- Acetaminophen (Tyenol)
- Meloxicam (Mobic)
- Salsalate (Disalcid)
- Nimesulide (only available outside the United States, Mesulid, Redaflam, Severin, Biosal, Aulin)

**COX2 specific**
- Celecoxib (Celebrex)
Celecoxib tolerated by most patients with AERD

- 60 patients challenged with 200 mg celecoxib
- No reactions noted
- Occasional case reports of celecoxib intolerance in AERD patients in literature
- Intolerance appears to be rare
Some genetic markers may associate with AERD, but role is not known

- CYSLTR2
- ALOX5
- LTC4S
- SLC6A12
- FILIP1
- IL17RA
- All effects are small
Arachadonic acid metabolism is at the heart of the disease

- Early realization of role of PGE2 inhibition
- Multiple changes in AERD patients
  - Increased leukotriene production
  - Increased leukotriene receptor expression
  - Restoration of PGE2 prevents ASA response
AA metabolism

- Two pathways of metabolism to produce inflammatory mediators
  - Prostaglandins (COX-1 and COX-2)
  - Leukotrienes (5-LO)
- Inhibition of COX enzymes by aspirin provides more upstream metabolites for 5-LO
- 5-LO produces LTA4, LTB4, LTC4, LTE4
- LTC4 and LTE4 are cysteinyl leukotrienes
Diacylglycerol or phospholipid

**Phospholipase C**  **Phospholipase A₂**

Arachidonic acid

**Lipoxygenase (FLAP, Alox5)**

HPETE (hydroperoxy-eicosatetraenoic acid)

**PGH₂ synthase (cox-1 or -2 and peroxidase)**

**Prostaglandin H₂ (PGH₂)**

**PGD synthase**

PGD₂

**PGE synthase**

PGE₂

PGF₂

6-keto-PGF₁α

Prostacyclin (PGI₂)

Thromboxane (TXA₂)

Thromboxane (TXA₂)

Leukotriene A₄

H₂O

LTB₄

Leukotriene C₄

Leukotriene D₄

Leukotriene E₄

Glutathione

Glutathione-S-transferase

Glutamic acid

6-keto-PGF₁α

Prostacyclin (PGI₂)

Thromboxane (TXA₂)

Platelets
AERD patients produce increased leukotrienes

3-5 times baseline urinary LTE4 production

With NSAID exposure increases to 100-fold
ASA removes the brake on leukotriene production

- PGE2 is an inhibitor of 5-LO function
- Inhibition of COX-1 decreases PGE2 and removes this inhibition
- Also may shunt upstream precursors to 5-LO pathway
- This is true in both AERD and ATA patients
Inhaled PGE2 abolishes the response to ASA in AERD

Sestini, Am J Resp Crit Care Med 1996
Stickiness of platelets and neutrophils may result in AERD phenotype

Laidlaw, Blood 2012
Increased numbers of adherent platelets in AERD

\[ P < 0.01 \]

Laidlaw, Blood 2012
Is platelet adhesion a cause or effect?

- Adhesion is driven by lipid mediators
- Could be a result of excess leukotriene production
- Could also be a self-sustaining feedback loop
- Effects of aspirin desensitization not yet known
Aspirin challenge vs. aspirin desensitization

• Not all asthmatics will have taken NSAIDs
• Challenge (historical or clinical) is the only reliable way to diagnose AERD
• Procedure is similar for both, mostly the intent differs
Mechanism of aspirin desensitization is unknown

- Reduction in CysLT production
- Reduction of CysLT1R expression
- Effect is rapid (within days)
Aspirin desensitization protocol

• Two day procedure at a minimum
• Starting dose of 20.25 mg aspirin
• Double dose every 3 hours
• If reaction, treat and wait to return to baseline or at least 3 hours
• Repeat last dose and advance to 325 mg
Final dose and follow-up

- 650 mg BID as target dose
- After 325 mg increase to 650 mg can happen at home
- Return to clinic in one month
- Reduce dose to lowest tolerated (no less than 325 mg daily)
Desensitization on non-consecutive days can be done safely

- Standard protocol assumes consecutive days
- Approximately 100 desensitizations over 2 years with non-consecutive desensitization days
- Similar outcomes to those reported
- Occasional mild worsening of asthma in between days
Choosing the starting dose of aspirin

- Need to start below triggering dose
- Most reactions occur at 60-80 mg
- A small percentage will react at 40.5 mg
- 20.25 mg only rarely associated with reactions
Aspirin desensitization results in rapid improvement in AERD symptoms

- Relief of congestion often almost immediate
- Improvement in asthma control within one month
- Improvement is long-lasting so long as aspirin is continued
Handling silent desensitizations

• When challenged with aspirin by protocol may occasionally have silent desensitizations
• If suspected, continue aspirin for one month after challenge and assess improvement
• Lack of significant improvement in symptoms suggests negative challenge and aspirin should be discontinued
Nasal congestion is the most useful marker in aspirin challenge

- During challenge, monitor physical exam, peak flow/FEV1, nasal congestion if possible
- Nasal congestion is most sensitive and specific marker
- Changes in FEV1 or mild nasal congestion may be only signs of reaction
Pretreatment with leukotriene modifiers reduces severity of reactions

- Montelukast or zileuton blunts but does not eliminate reaction
- Prednisone generally not required
- Preparation to manage anaphylaxis is essential
- IV access is generally maintained through procedure
Nasal ketorolac may be used for ASA desensitization

• Rapidly absorbed solution
• Commercially available solution is too concentrated for this use
• Dose is systemically absorbed and systemically active
• Enables more rapid (but not one day) desensitization
Other NSAIDs are not effective for ASA desensitization

- Other NSAIDs provide reversible inhibition of COX
- ASA binding is irreversible
- Irreversibility appears to be required for adequate desensitization
Desensitization results in decreased IL-4 and CysLT1R expression

- Reduction in the TH2 bias associated with disease
- Diminished CysLT1R expression results in lower sensitivity to leukotriene mediators
- Does this occur rapidly enough to explain the success of desensitization?
Associated diseases in AERD must also be managed separately

- Prevalence of atopy is increased in AERD
- Desensitization does not improve atopy
- Allergic fungal sinusitis and chronic rhinosinusitis should also be considered and will not improve without specific therapy
ASA desensitization is effective for at least 5 years (and probably longer)

- 14% discontinue aspirin
- Almost all due to side effect
  - Dyspepsia
- 80% note improvement
  - Need for polypectomy decreases to 14%
  - May continue to improve up to one year on aspirin therapy
Complications of aspirin desensitization and long term use

• Dyspepsia most common
• GI bleed in 4/172
• 6/172 had NSAID induced urticaria
• Macular degeneration?
• Beneficial effects also exist
  – Coronary artery disease
  – Decreased incidence of metastatic disease
Alternative diagnostic strategies other than aspirin challenge

- Measurement of urinary LTE4
- Statistically different, but inadequate performance as a clinical test
- Challenge with low dose aspirin may improve sensitivity and specificity
- Still has risk of challenge
Alternative therapies other than desensitization for AERD

- Leukotriene modifier drugs
  - Zileuton, montelukast, zafirlukast
- Omalizumab
  - Case report using high dose with aspirin tolerance
- Lebrikizumab?
  - Periostin levels are elevated in AERD, but no specific reports of use