Clinical Features of Aspirin Exacerbated Respiratory Disease (AERD)

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Objectives

• Describe the key clinical features that define the clinical triad of aspirin exacerbated respiratory disease, including those features that distinguish AERD from other endotypes of asthma and chronic sinusitis with nasal polyposis.

• Recognize the diagnostic challenges related to AERD and the importance of making an accurate diagnosis.

• Summarize key concepts in the management of AERD
• Samter’s triad
• Triad asthma
• Aspirin sensitive asthma
• Aspirin intolerant asthma
• Aspirin-induced asthma with nasal polyposis
• AERD (aspirin exacerbated respiratory disease)
• NERD (NSAID exacerbated respiratory disease)
AERD Overview

• NSAID Allergy / Pseudoallergy Classification
• Diagnosis
  • Epidemiology
  • Clinical features
  • Objective testing
• Natural history
• Management
## NSAID Reaction Classification

<table>
<thead>
<tr>
<th></th>
<th>Mechanism</th>
<th>Cross reaction</th>
<th>Potential to induced tolerance</th>
</tr>
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<tbody>
<tr>
<td>AERD</td>
<td>COX-1 inhibition</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Aspirin exacerbated cutaneous disease</td>
<td>CIU/AE COX-1 inhibition</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Multiple NSAID-induced U/AE</td>
<td>COX-1 inhibition</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Single NSAID-induced reactions</td>
<td>IgE</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>NSAID-induced delayed reactions</td>
<td>Multiple</td>
<td>No</td>
<td>Variable (depending on mechanism)</td>
</tr>
</tbody>
</table>

Kowalski et al. Immunol Allergy Clin N Amer 2013
Pathogenesis

- Dysregulated arachidonic acid metabolism

- Overproduction of cysteiny1 leukotrienes
  - Which further increase on exposure to cyclooxygenase-1 (COX-1) inhibitors

- Dysregulated prostaglandins
  - PGD2 is increased in AERD
  - PGE2 is decreased in AERD
  - These deviations are further deviated on exposure to COX-1 inhibitors
Arachidonic Acid Metabolism in AERD

Although CysLT\(_1\)R has trivial affinity for LTE\(_4\), patients with AERD show a selective hyperresponsiveness to bronchoconstriction induced by inhaled LTE\(_4\) compared with aspirin-tolerant asthmatic controls, suggesting that AERD involves additional upregulation of an unidentified LTE\(_4\)-specific receptor. Polypharmaceuticals in the CYSLTR2 gene encoding CysLT\(_2\)R, which negatively regulates the actions of CysLT\(_1\)R, are also associated with AERD, and certain alleles were associated with the magnitude in the decrement in FEV\(_1\) (forced expiratory volume in first second of expiration) measured during aspirin provocation. Collectively, these observations suggest that the end-organ reactivity to cysLTs that characterizes AERD may be partly caused by genetically determined patterns of CysLTR expression or function. Moreover, the selective LTE\(_4\) hyperresponsiveness in the face of high systemic levels is consistent with a potentially unique role for this stable end-metabolite of cysLTs in driving the disease.
Diagnosis of AERD

• Epidemiology

• Clinical features

• Objective testing → Graded challenge
Who Cares?

• Risk of future severe reactions to NSAIDs in AERD

• Specific treatments uniquely beneficial in this subgroup
  • Aspirin
  • Anti-leukotriene therapy
  • Biologic selection?

• Widespread lack of recognition of this subtype and implications for treatment within the wider medical community
Prevalence of AERD in ... 

- Asthma 7%
- Severe asthma 15%
- Asthma ICU admission 24%
- CRS w nasal polyps 10-16%
- CRSwNP and asthma 20-42%

Rajan et al. JACI 2014
Epidemiology of AERD

• 1.3 million in US with AERD

• Uncommon in children / adolescents

• AERD is more common in women 1.5-2.5x
Clinical Features of AERD

• Chronic disease manifestations

• Acute NSAID reactions
Clinical features of AERD

- Chronic rhinitis
- Progression to CRSwNP
- Asthma diagnosed within 1-5 years
  - Eosinophilic phenotype
  - Often rapidly progresses to moderate to severe asthma
- Around this time, first clinical reaction to NSAIDS
- Median age of onset = 30

White and Stevenson. NEJM 2018
Kowalski et al. EAACI Position Paper. Allergy 2019
Chronic rhinosinusitis pattern

• Typical symptoms of CRSwNP
  • Nasal congestion / obstruction
  • Rhinorrhea
  • Facial pressure
  • Postnasal drip
  • Reduced or absent smell
    • ANOSMIA may be a clinical marker of AERD

• Generally more severe sinus disease than aspirin tolerant patients with CRSwNP
  • Recurrence after surgery is more common
  • 2x more sinus surgeries
  • younger age at time of first sinus surgery
  • more oral steroid dependent

ENFUMOSA Study Group. Eur Resp J 2003
Asthma pattern

• Eosinophilic asthma

• Asthma is 2x as likely to be severe asthma

• Medium to high dose inhaled steroids, usually in combination with LABAs

• Lower baseline lung function

• Less well controlled

• More hospitalizations (12% vs 2%)

White and Stevenson. NEJM 2018
Kowalski et al. EAACI Position Paper. Allergy 2019
Acute Reaction to NSAIDs

• 30-180 minutes
• usually starts with naso-ocular reaction
• bronchospasm of varying severity
• A subgroup will also develop other symptoms:
  • flushing
  • urticaria
  • nausea / vomiting
• rarely, hypotension and loss of consciousness, laryngospasm, laryngeal edema
• Reaction severity is DOSE DEPENDENT

White and Stevenson. NEJM 2018
Kowalski et al. EAACI Position Paper. Allergy 2019
Lack of history of NSAID reactions does not exclude AERD

- Accuracy of history is generally POOR
  - 15% not aware of NSAID sensitivity react at time of challenge
  - 10-15% with supposed NSAID sensitivity do not react at time of challenge
    - Some of these may be false negative challenges and truly have AERD

- Patients tolerating 81 mg daily may have AERD

- Predicting likelihood of reactions (asthma and CRS)
  - Severe asthma attacks after NSAID 100%
  - 2 or more episodes 89%
  - 1 mild or moderate episode 73-79%
  - Avoiding completely 43%

Kowalski et al. EAACI Position Paper. Allergy 2019
4 patient groups in whom a negative NSAID reaction history should not be trusted

• Adult onset asthma and severe polyps who have not been taking NSAIDs

• Adult onset asthma and severe polyps who are on biologic therapy and/or anti-leukotriene

• Patients with severe enough disease at baseline that worsening symptoms after NSAIDs may not be perceived

• Patients taking aspirin 81 mg chronically
  • Self desensitized and don’t know it
  • Started aspirin before onset of AERD
Likelihood of AERD ...

- Asthma but normal CT sinus: Extremely unlikely
- Nasal polyps and asthma onset childhood: Extremely unlikely
- Nasal polyps / pansinusitis but not asthma: Unlikely
- Rapid regrowth of polyps following surgery: Likely
- Complete anosmia with polyps: Likely

White and Stevenson. NEJM 2018
Objective Testing - ASPIRIN CHALLENGE

- Oral aspirin challenge remains gold standard for diagnosis of AERD

- Accuracy depends in part on setting
  - Recent sinus surgery
  - Anti-leukotriene therapy
  - Oral steroids

- Details covered in presentation on ASPIRIN DESENSITIZATION IN AERD
Indications
Aspirin Challenge vs. Desensitization

• Indications for challenge in AERD
  • suspected AERD but no clear history of prior NSAID reactions
  • as part of desensitization process for long-term therapy

• Indications for desensitization and long-term therapy in AERD
  • moderate or severe asthma
  • intractable nasal symptoms
  • aggressive polyps
  • Prevention of relapse of polyps following surgery
  • requirement for systemic steroids
  • indication for aspirin for CAD prevention or NSAIDs for other conditions

Bochenek et al. Immunol Allergy Clin N Am 2013
Objective Testing - Biomarkers

• None are superior to aspirin challenge for diagnosis of AERD

• Urinary leukotriene E4
  • Meta-analysis defined sensitivity, specificity, PPV, NPV for ULTE4 in AERD and specific thresholds

<table>
<thead>
<tr>
<th>Assay</th>
<th>Threshold</th>
<th>Sens</th>
<th>Spec</th>
<th>PPV</th>
<th>NPV</th>
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<tr>
<td>EIA-Am</td>
<td>192</td>
<td>0.55</td>
<td>0.82</td>
<td>0.75</td>
<td>0.66</td>
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<td>EIA-Cay</td>
<td>510</td>
<td>0.76</td>
<td>0.77</td>
<td>0.70</td>
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<td>Mass spec</td>
<td>167-173</td>
<td>0.70</td>
<td>0.81</td>
<td>0.86</td>
<td>0.79</td>
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<tr>
<td>RIA</td>
<td>66-69</td>
<td>0.81</td>
<td>0.79</td>
<td>0.65</td>
<td>0.88</td>
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</tbody>
</table>

• Depends on type of assay studied (EIA, RIA, Mass spec)
• Not predictive enough to be used diagnostically

• FENO, eosinophils, urinary 3-bromotyrosine, periostin have not distinguished AERD from ATA

Hagan et al. J Allergy Clin Immunol Pract 2017
Medical Management of AERD

- Lifestyle measures
- Saline irrigation
- Nasal Steroids
- Anti-leukotriene therapy
- Asthma therapy
- Aspirin
- Sinus surgery
- Biologic therapy
- Oral Steroids
Dietary Measures and NSAID avoidance

• "low salicylate" diet is controversial

• High omega-3 / low omega 6 diet is interesting but unproven

• Tartrazine / Yellow No. 5 is not associated with reactions or worsening disease

• Advise patients that alcohol consumption can result in respiratory reactions

• Avoid inhibitors of COX-1
  • unless desensitized and taking aspirin therapeutically

Kowalski et al. EAACI Position Paper. Allergy 2019
Schneider et al. J Allergy Clin Immunol Pract 2018
Hierarchy of risk of reactions to COX inhibition

Bochenek et al. Immunol Allergy Clin N Am 2013
Saline irrigation
Nasal Steroids

• Very important for control of sinus disease in AERD

• 4 options
  • Standard dose nasal steroid sprays
    • e.g. Fluticasone 2 sprays per nostril once daily
  • High dose nasal steroid sprays
    • Nasonex is only product FDA approved for treatment of nasal polyps
    • Approved dose is 2 sprays per nostril BID
    • Other NCS products widely used at this dose
  • Xhance
    • Fluticasone administered via Optinose Exhalation Delivery System
  • Intranasal application of other products
    • Budesonide respules
    • Steroid eye drops
Anti-leukotriene therapy

• AERD patients have higher leukotriene levels

• Accumulating evidence that leukotriene blockade is beneficial in AERD

• 3 options in US
  • 2 CysLT1 Receptor blockers
    • Montelukast (Singulair)
    • Accolate
  • 5-lipoxyegenase inhibitor
    • Zileuton (Zyflo)

• Zileuton likely more effective than CysLT receptor blockers
  • CysLT receptor blockade is weak and does not block LTE4
  • Proven effectiveness in AERD
  • Retrospective sub-analysis in AERD patients in original asthma studies showed dramatic (20%) improvement in FEV1

Laidlaw et al. J Allergy Clin Immunol 2017
Asthma Management
Adults & adolescents 12+ years

**PREFERRED CONTROLLER**
to prevent exacerbations and control symptoms

**PREFERRED RELIEVER**
Other reliever option

**STEP 1**
As-needed low dose ICS-formoterol *
Low dose ICS taken whenever SABA is taken †

**STEP 2**
Daily low dose inhaled corticosteroid (ICS), or as-needed low dose ICS-formoterol *
Leukotriene receptor antagonist (LTRA), or low dose ICS taken whenever SABA taken †

**STEP 3**
Low dose ICS-LABA

**STEP 4**
Medium dose ICS, or low dose ICS+LTRA #
High dose ICS, add-on tiotropium, or add-on LTRA #
Add low dose OCS, but consider side-effects

**STEP 5**
High dose ICS-LABA
Refer for phenotypic assessment ± add-on therapy, e.g. tiotropium, anti-IgE, anti-IL5/5R, anti-IL4R

1 © Global Initiative for Asthma, www.ginasthma.org
Aspirin Desensitization and Long-term Treatment
Clinical Effectiveness

Grade A recommendation
• Improved nasal symptom scores
• Reduced nasal corticosteroid dose
• Reduced sinus infection
• Reduced sinus operations
• Reduced systemic corticosteroid use
• Improved asthma symptom scores
• Reduced inhaled corticosteroid use
• Reduced urgent and ER visits and hospitalizations

Improves clinical course of 67-78% of patients with AERD

1Sinusitis Practice Parameter, J Allergy Clin Immunol 2005
2Stevenson et al. J Allergy Clin Immunol 1984
3Sweet et al. J Allergy Clin Immunol 1990
4Stevenson et al. J Allergy Clin Immunol 1996
5Berges-Gimeno et al. J Allergy Clin Immunol 2003
6Lee et al. J Allergy Clin immunol 2007
7Hope et al. J Allergy Clin Immunol 2009
Aspirin

• For treatment of AERD: 325-650 mg BID
  • Start aspirin 650 mg BID for first month
  • If nasal passages are patent, taper to 325 mg BID
  • If symptoms recur, increase back to 650 mg BID

• Lower doses probably not effective for mgmt of sinus disease or asthma

• Other dosing may be appropriate for other indications
  • Maintain desensitization: 81-325 mg daily
  • CAD/stroke prevention: 81 mg daily
    • this may NOT protect against NSAID reactions or higher aspirin dosing PRN

• Beneficial effect as early as 1 month

• Best outcomes if started shortly after sinus surgery

White et al. Immunol Allergy Clin N Amer 2013
How long can aspirin be discontinued and restarted safely?

• Aspirin must be taken daily to maintain tolerance

• If aspirin is discontinued for > 48 hours, likely to become sensitive again
  • <2 days → restart at home
  • 2-5 days → in office challenge 325 mg
  • >5 days → repeat desensitization

• Peri-operative aspirin management can be challenging

White et al. Immunol Allergy Clin N Amer 2013
Long-term aspirin and GI adverse effects

• High rate of discontinuation of aspirin at 12 months
  13-25%

• 14-18% discontinue aspirin therapy due to GI adverse effects
  • dyspepsia
  • abdominal pain
  • gastritis
  • intestinal bleeding

Baker et al. Allergy Asthma Proc 2011
Lee et al. J Allergy Clin Immunol 2007
Adappa et al. Int Forum Allergy Rhinol 2018
GI adverse effects and aspirin

What is the risk? 2 meta-analyses

- low dose (75-325 mg/d)
  - >57,000 subjects in 14 RDBPCT for CAD prevention
  - RR of 2.07 vs. placebo

- high dose (900-1500 gm/d)
  - >66,000 subjects in 24 RCTs (12 studies of high dose aspirin) vs. placebo
  - 2.47% vs. 1.42%; OR 1.68
  - Did not appear to be dose response relationship

Baker et al. Allergy Asthma Proc 2011
Derry et al. BMJ 2000
Lanza et al. Am J Gastroenterol 2009
GI adverse effects and aspirin

What to do about it?

- PPIs are highly effective at reducing GI complications of NSAIDs and aspirin
- Misoprostol works as well but less well tolerated
- Moderate risk patients should be treated with PPI or misoprostol

### Table 1

**High risk**

1. History of a previously complicated ulcer, especially recent
2. Multiple (>2) risk factors

**Moderate risk (1–2 risk factors)**

1. Age >65 years
2. High dose NSAID therapy
3. A previous history of uncomplicated ulcer
4. Concurrent use of aspirin (including low dose) corticosteroids or anticoagulants

**Low risk**

1. No risk factors

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Baker et al. Allergy Asthma Proc 2011
Derry et al. BMJ 2000
Lanza et al. Am J Gastroenterol 2009
Sinus surgery in AERD

• Benefits of sinus surgery
  • improved sinus scores
  • improved asthma control
  • Facilitates delivery of topical corticosteroids

• But early relapse in AERD is common

• Ideal approach is aspirin desensitization post-operatively as close as possible to reduce polyp recurrence

• Best post-operative medical regimen for reducing relapse rate
  • Aspirin
  • LT blockade
  • Nasal steroids
  • Biologics?

White and Stevenson. NEJM 2018.
Adappa et al. Int Forum Allergy Rhinol 2018
Biologic Therapy in AERD

• AERD is a sub-endotype of type 2, eosinophilic asthma
• Biologics in this asthma endotype seem to work as in the aspirin tolerant endotype
• Limited studies starting to emerge in applications of biologics in treatment of AERD

Omalizumab (Xolair)
Reslizumab (Cinquair)
Mepolizumab (Nucala)
Benralizumab (Fasenra) - No data
Dupilumab (Dupixent) - No data
Omalizumab (Xolair) in AERD

- Anti-IGE monoclonal antibody
- Most reports are case reports and small case series suggesting beneficial effect in AERD endotype
- Mechanism of effect in AERD not known
  - AERD is not considered a form of allergic asthma
- 1 case series of 7 patients, compared effect of omalizumab after 6 months of therapy to before treatment
  - Improved asthma exacerbation rate (0 vs 2.14 before treatment, p = 0.026)
  - Improved AQLQ score (6.36 vs 5.76 before treatment, p = 0.18)
  - No change in FEV1

Reslizumab (Cinquair)

• Anti IL5 monoclonal antibody administered IV (3 mg/kg) q 4 weeks
• post hoc analysis of 2 pivotal trials
• Compared outcomes between AERD and aspirin tolerant patients with asthma with CRSwNP
• Similar improvements in exacerbation rates, FEV1, asthma symptom scores

<table>
<thead>
<tr>
<th></th>
<th>AERD</th>
<th>CRSwNP</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exacerbation rate reduction</td>
<td>79%</td>
<td>85%</td>
<td>44%</td>
</tr>
</tbody>
</table>

Mepolizumab (Nucala)

- Anti-IL5 monoclonal antibody
- Results in reduction in tissue and peripheral eosinophils
- FDA approved for severe asthma
- AERD associated with high levels of tissue and peripheral eosinophilia and IL-5
- 2 clinical trials showed mepolizumab (750 mg IV q4 weeks x 6 doses) was highly effective in treatment of nasal polyps
- 14 AERD patients who received mepolizumab for severe asthma
  - 100 mg SC q 4wks for at least 3 doses
- Improvement in
  - SNOT-22 sino-nasal symptom scores
  - ACT asthma symptom scores
  - Reduced oral steroid use

Tuttle et al. J Allergy Clin Immunol Pract 2018
Benralizumab (Fasenra)

- Monoclonal antibody that targets IL-5 receptor α subunit leading to depletion of eosinophils
- FDA approved for add-on maintenance therapy in severe asthma with eosinophilic phenotype
- Subanalysis of phase III pivotal trial showed better response in primary endpoint of nasal polyposis
Nasal polyposis predicts better response to Benralizumab for severe asthma

% reduction in annual exacerbation rate vs placebo

- NP
- No NP
- NP eos >300
- No NP eos >300
- NP eos < 300
- No NP eos < 300

Bleeker et al. Eur Resp J 2018
Nasal polyposis predicts better response to Benralizumab for severe asthma

- Presence of nasal polyps also associated with better outcomes in other secondary outcomes
  - FEV1 improvement from baseline compared to placebo
  - Total asthma symptoms score
  - ACQ-6

Bleeker et al. Eur Resp J 2018
Dupilumab (Dupixent)

- Anti-IL4 and anti-IL-13 receptor monoclonal antibody
- FDA approved for asthma and CRSwNP
- 19 patients with AERD in the phase II trial showed clear and dramatic benefit in the upper respiratory manifestations of AERD
  - improved total polyp score
  - Improved SNOT-22 symptom score
  - Improved UPSIT smell score
Future Directions

• Biomarkers
  • Urinary LTE4?
  • Nasal lavage fluid?
  • Others

• Biologic therapy – Need more data in AERD

• Mechanistic studies ongoing
Summary

• Making diagnosis of AERD is VERY important
• Diagnosis can be challenging from history alone
• Aspirin challenge is only currently available objective test for confirming AERD
• Anti-leukotriene therapy is uniquely suited to the problem of excessive leukotrienes involved in pathophysiology of AERD
  • CysLT receptor antagonists
  • 5-lipoxygenase inhibition likely even more effective
• Long term aspirin therapy is highly effective
• Biologic therapies targeting Th2 pathways in AERD clearly have a role and generally highly beneficial but exact role remains unknown