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

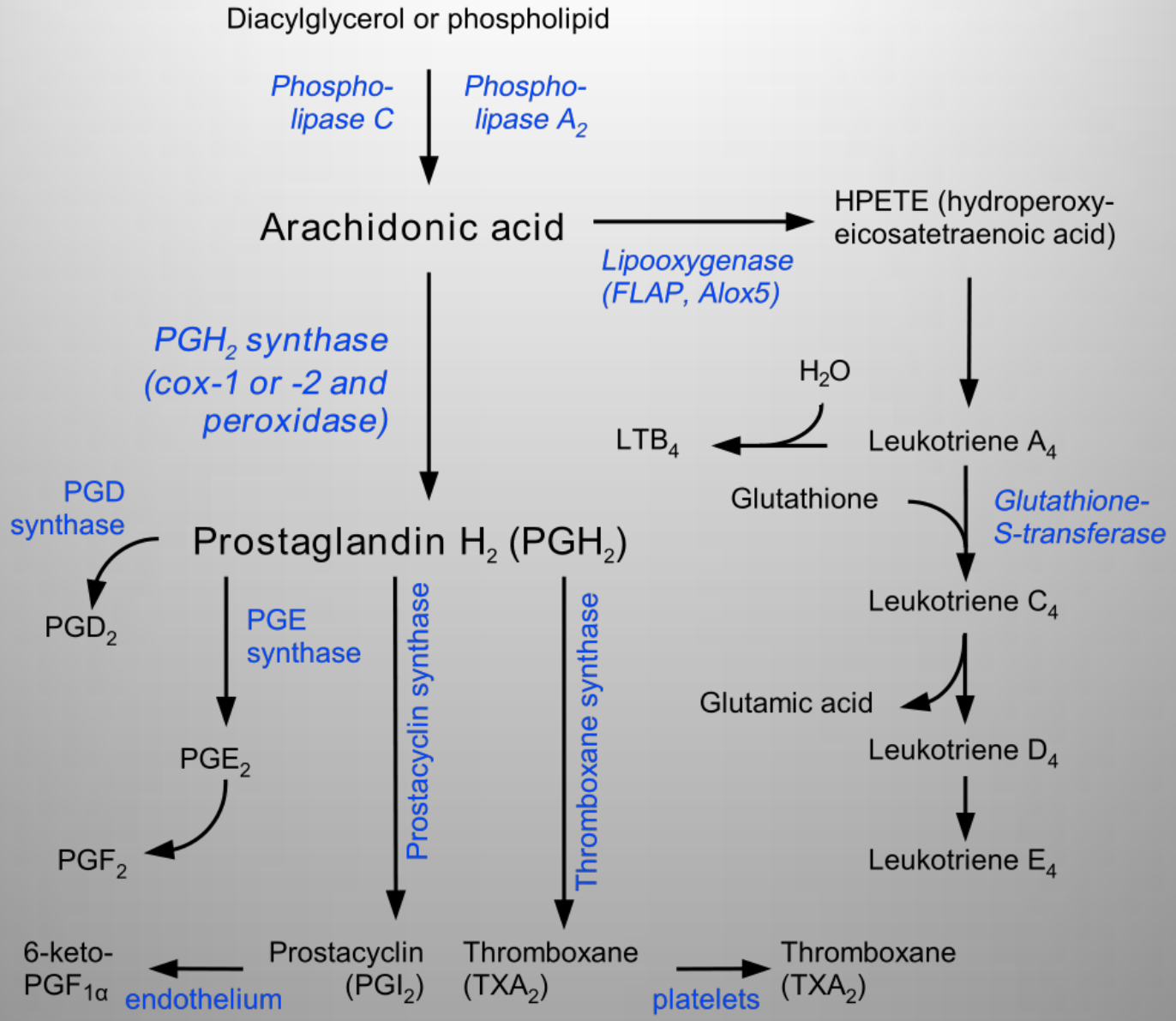
- CYSLTR2
- ALOX5
- LTC4S
- SLC6A12
- FILIP1
- IL17RA
- All effects are small

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

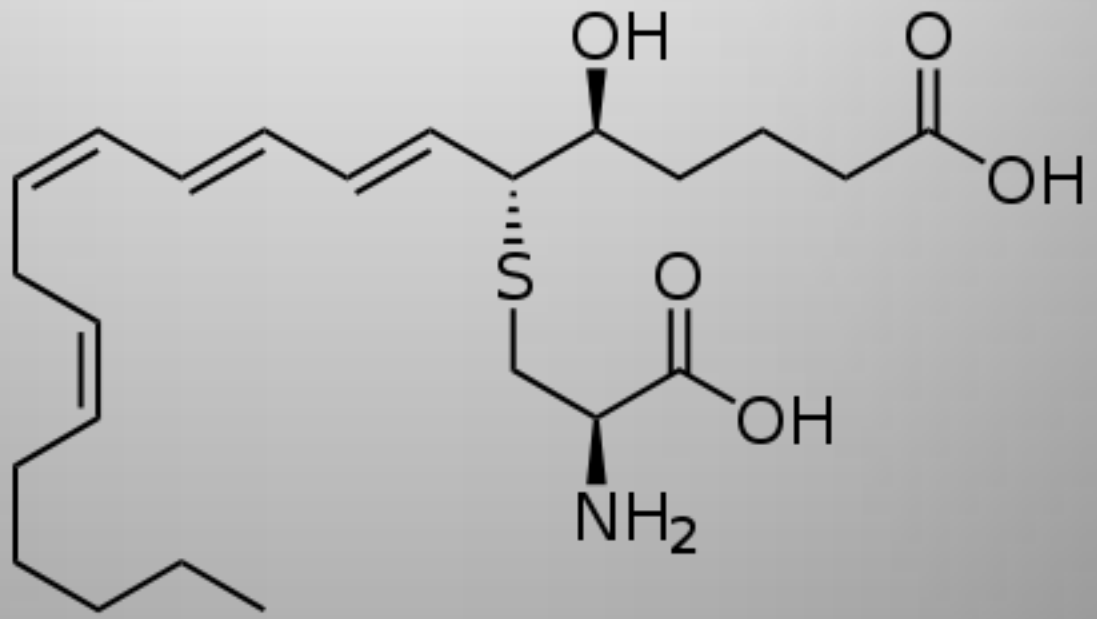
- Two pathways of metabolism to produce inflammatory mediators
  - Prostaglandins (COX-1 and COX-2)
  - Leukotrienes (5-LO)
- Inhibition of COX enzymes by aspirin provides more upstream metabolites for 5-LO
- 5-LO produces LTA4, LTB4, LTC4, LTE4
- LTC4 and LTE4 are cysteinyl leukotrienes


Diacylglycerol or phospholipid
Phospho-lipase C
Phospho-lipase A2
Arachidonic acid
HPETE (hydroperoxy-eicosatetraenoic acid)
Lipooxygenase (FLAP, Alox5)
PGH2 synthase (cox-1 or -2 and peroxidase)
H2O
LTB4
Leukotriene A4
Glutathione
Glutathione-S-transferase
PGD synthase
Prostaglandin H2 (PGH2)
Leukotriene C4
PGD2
PGE synthase
Prostacyclin synthase
Thromboxane synthase
Glutamic acid
Leukotriene D4
PGE2
PGF2
Leukotriene E4
6-keto-PGF1α
endothelium
Prostacyclin (PGI2)
Thromboxane (TXA2)
platelets
Thromboxane (TXA2)

AERD patients produce increased leukotrienes

3-5 times baseline urinary LTE4 production

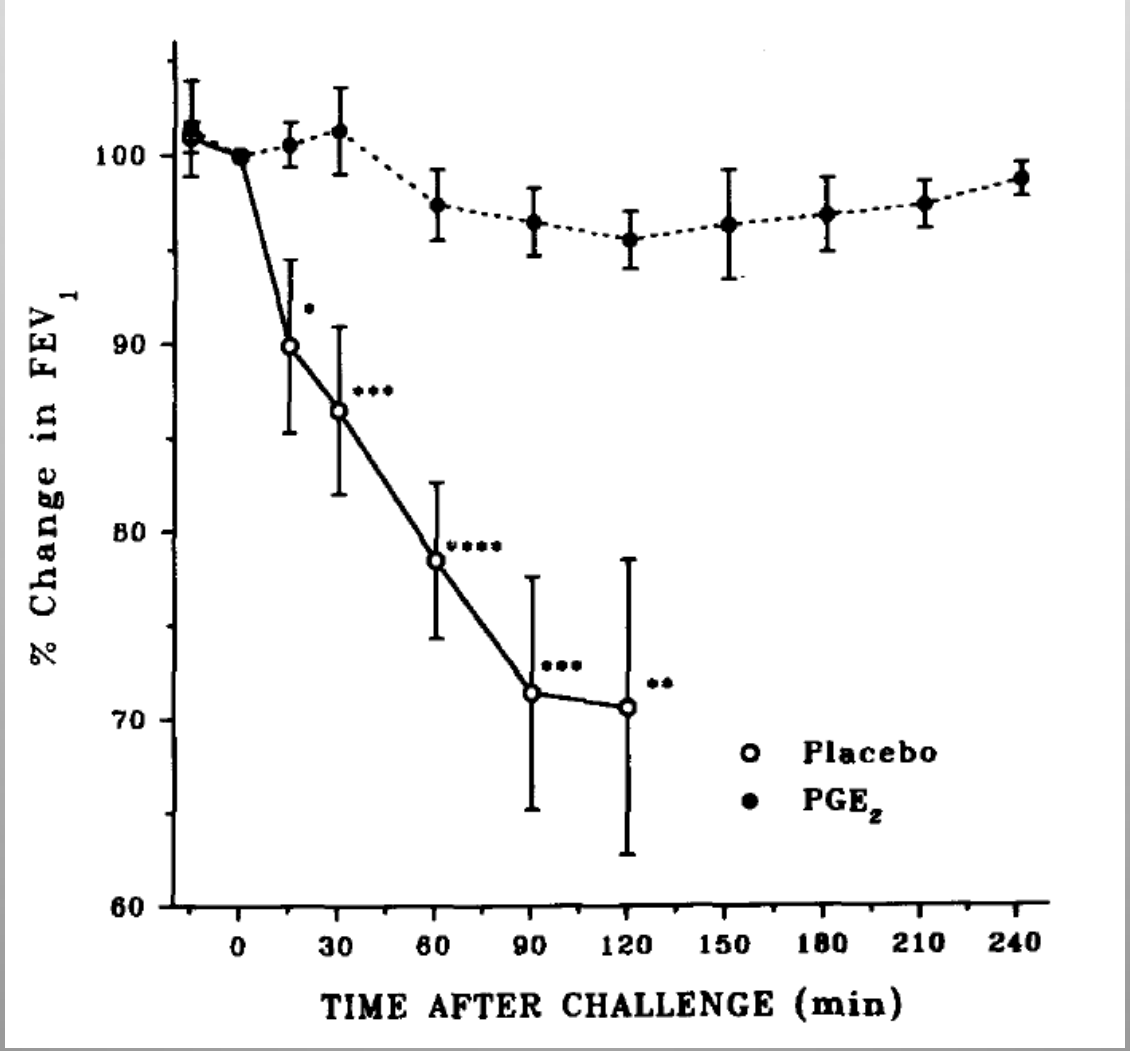
With NSAID exposure increases to 100-fold



ASA removes the brake on leukotriene production

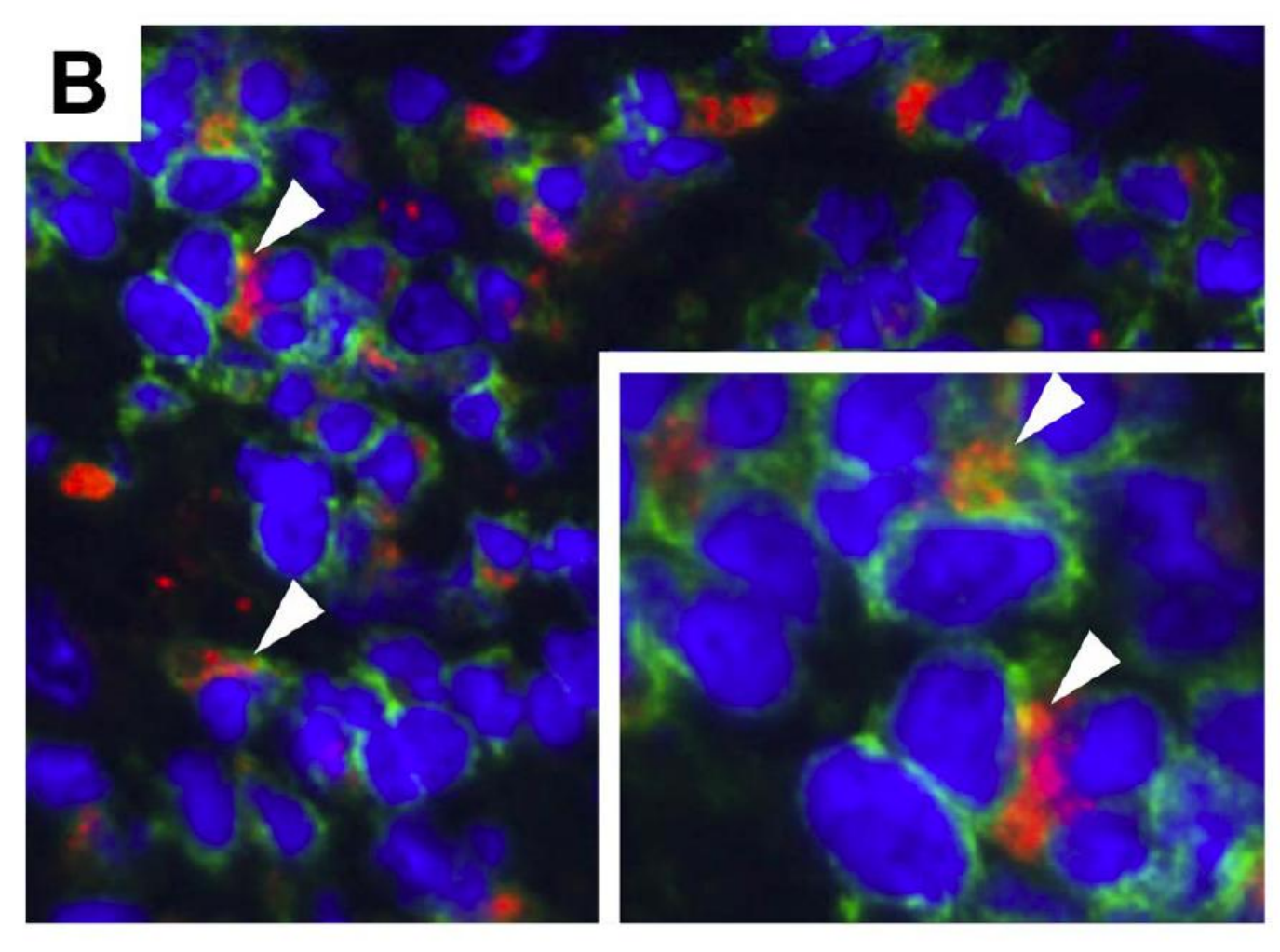
- PGE2 is an inhibitor of 5-LO function
- Inhibition of COX-1 decreases PGE2 and removes this inhibition
- Also may shunt upstream precursors to 5-LO pathway
- This is true in both AERD and ATA patients

Inhaled PGE2 abolishes the response to ASA in AERD



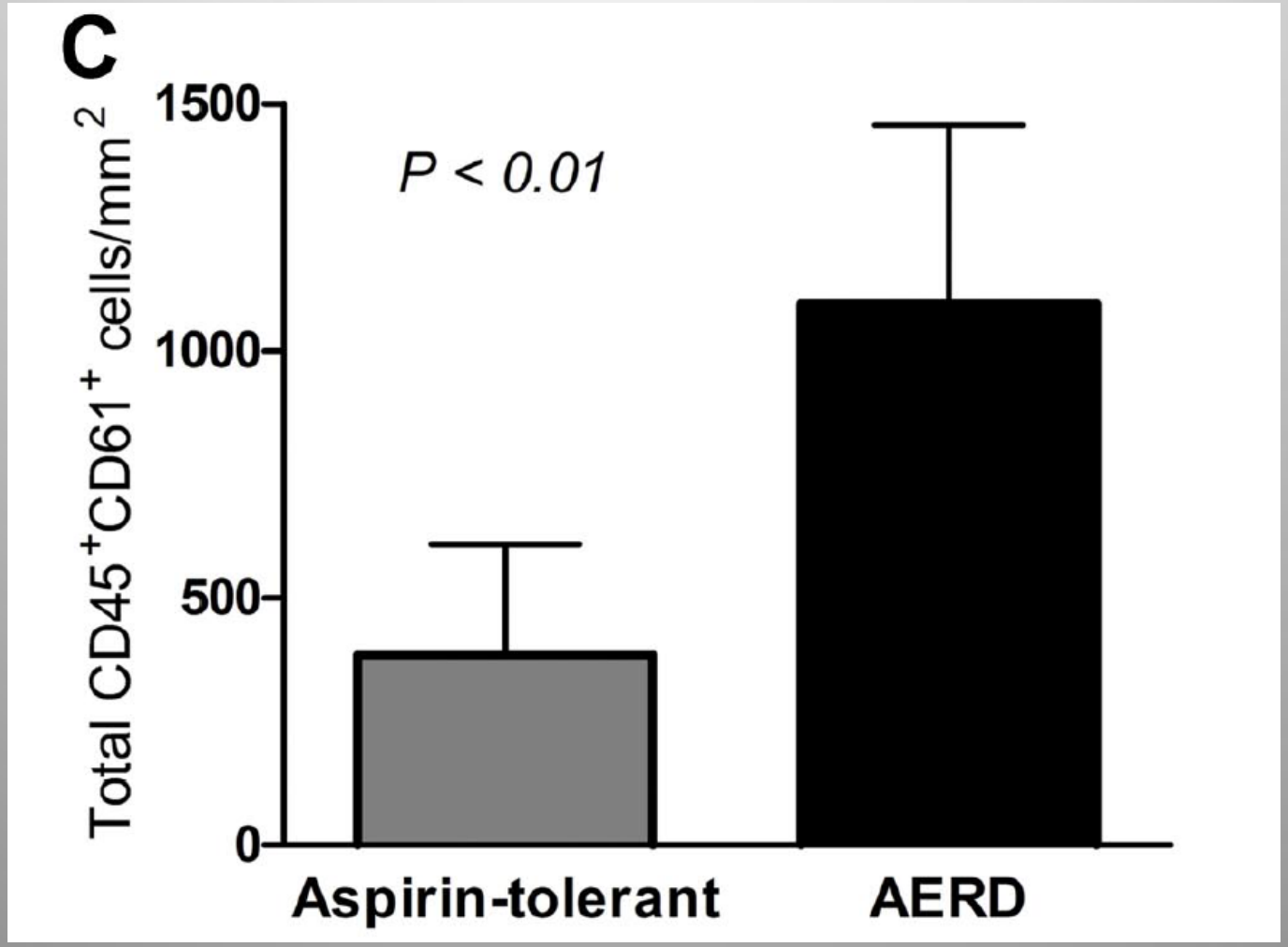
Sestini, Am J Resp Crit Care Med 1996

Stickiness of platelets and neutrophils may result in AERD phenotype



Laidlaw, Blood 2012

Increased numbers of adherent platelets in AERD



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