Practical Approaches to NSAID/Aspirin Hypersensitivity

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Laidlaw Lab
RESPIRATORY INFLAMMATION
investigate . discover . treat

HARVARD MEDICAL SCHOOL

Learning Objectives

Upon completion of this learning activity, participants should be able to:

- Recognize the varying presentations of aspirin and NSAID hypersensitivity reactions.
- Use an Aspirin/NSAID Hypersensitivity pathway algorithm to help guide recommendations for further evaluation or drug challenge.
- Know how to perform a standard 2-dose aspirin/NSAID challenge in patients without AERD, but with a history of allergy to NSAIDs.

Adverse drug reaction ≠ Allergy

- Use of aspirin/NSAIDs precluded by reported adverse drug reactions
- Prevalence of reported NSAID allergy =1.5-3% in general population
- Clinical history → unreliable predictor of drug challenge outcome
  - Only 20% of patients with listed aspirin/NSAID allergy actually react to challenge
  - No skin testing available → drug challenge is gold standard for diagnosis

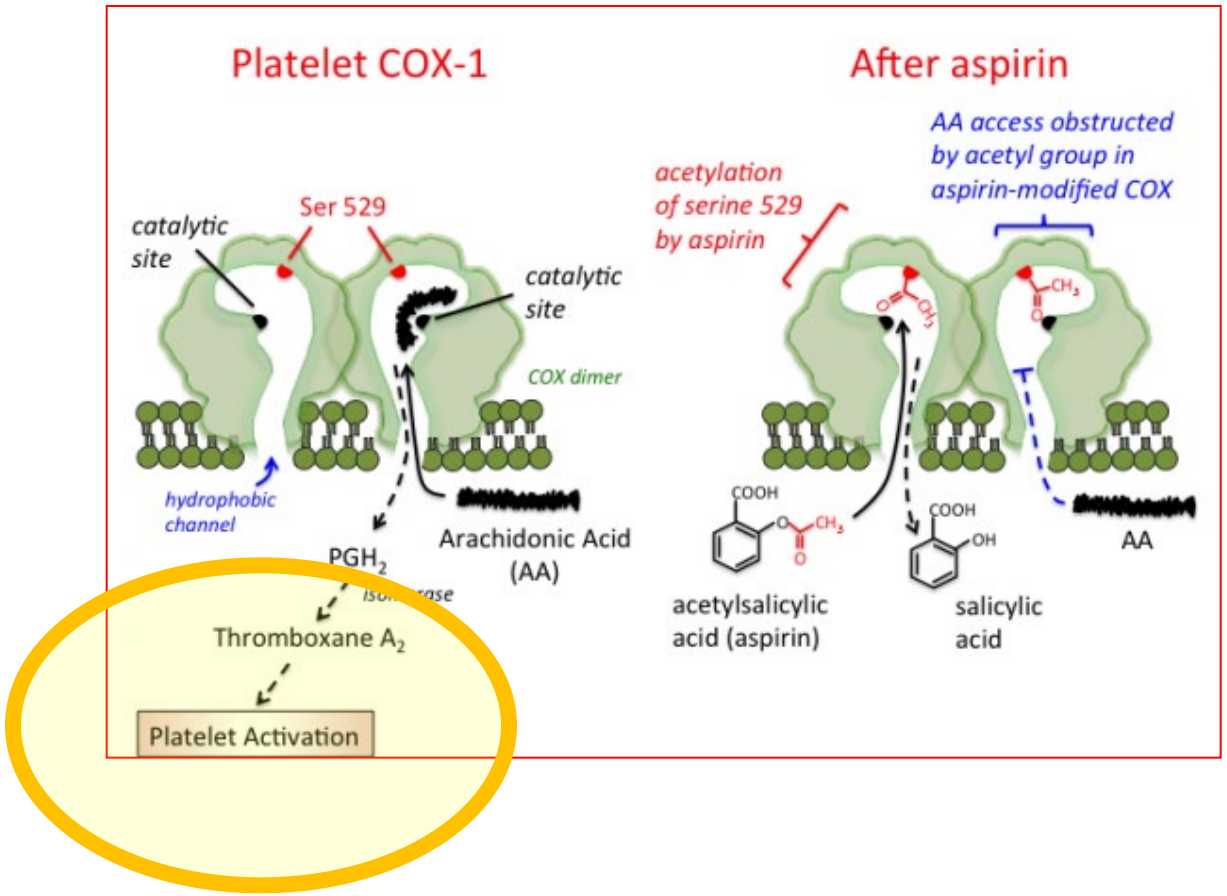
- Majority of hypersensitivity reactions to NSAIDs related to pharmacologic inhibition of COX-1
  - >95% of patients with true NSAID hypersensitivity can safely receive celecoxib (selective COX-2 inhibitor)

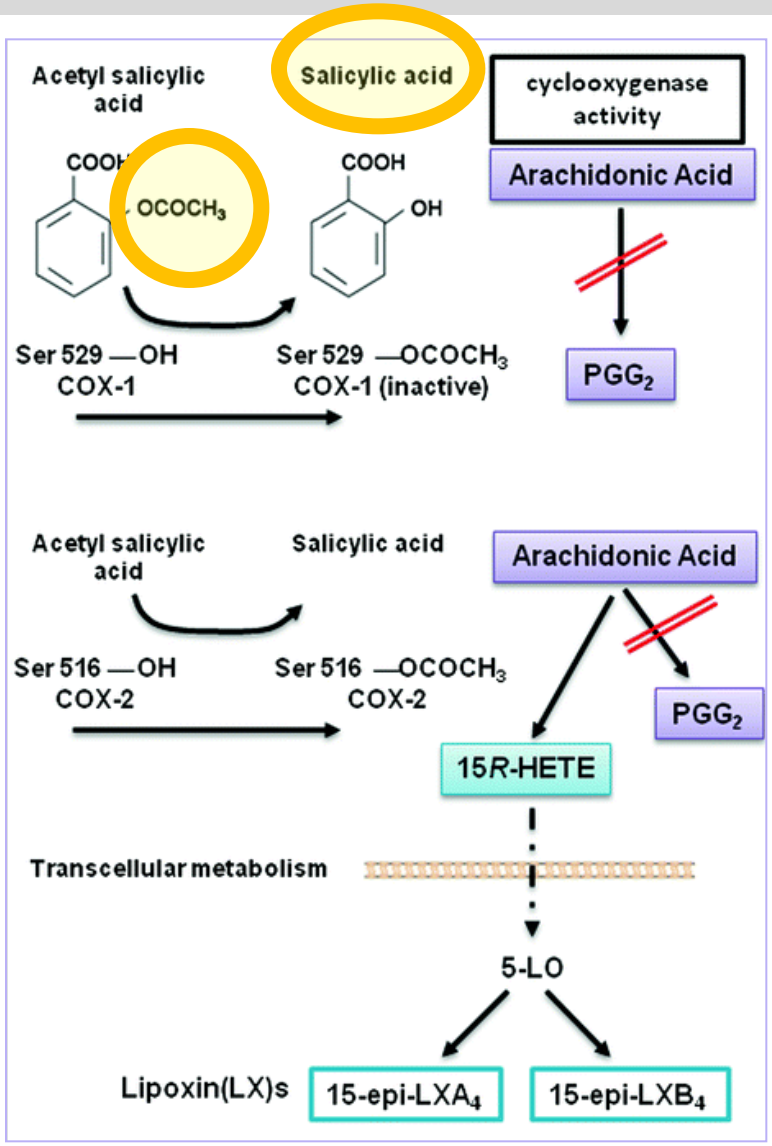
Gomes & Demoly, Curr Opin Allergy Clin Immunol, 2005
Blumenthal et al. JACI IP, 2017
Weberschock et al. Arch Dermatological Research, 2007

Classification of reactions

- **Allergic NSAID reactions** – presumed to be IgE mediated, elicited by a single NSAID
- **Pseudoallergic NSAID reactions** – Nonimmunologic, related to the cyclooxygenase (COX) 1-inhibiting properties of the drug, cross-reactive within class
  - Type 1 – NSAID-exacerbated asthma and rhinosinusitis (“AERD”)
  - Type 2 – NSAID-induced urticaria/angioedema in patients with chronic urticaria
  - Type 3 – NSAID-induced urticaria/angioedema in otherwise asymptomatic patient
  - Type 4 – Blended (mixed respiratory and/or skin) reactions in otherwise asymptomatic individuals (?)

Mechanism of action of acetyl salicylic acid (“aspirin”)





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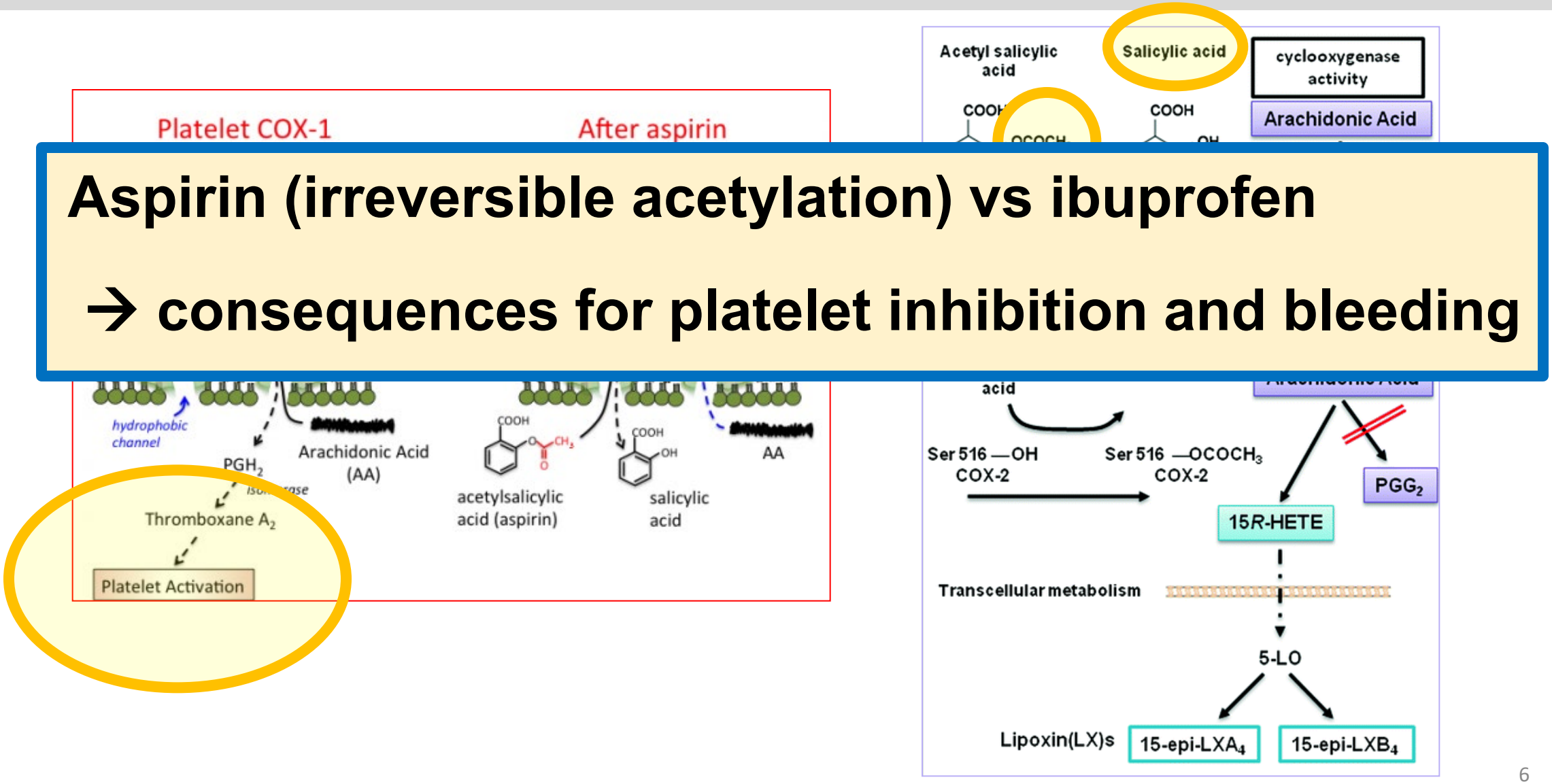


Aspirin (irreversible acetylation) vs ibuprofen

→ consequences for platelet inhibition and bleeding

Important uses for aspirin and NSAIDs

1. Cardiovascular protection (aspirin)
2. Prevention of preeclampsia in pregnancy (aspirin)
3. Pain control (NSAIDs)

Cardiovascular protection – consequences for "NSAID-allergic" patients

- **Aspirin** is first-line for acute coronary syndromes → dual anti-platelet therapy indicated following stent placement
  - Retrospective cohort study at Brigham and Women's Hospital for patients admitted with MI and stent placement.
  - Aspirin recommended "as soon as possible" upon presentation with non-STEMI
  - Aspirin helps to stabilize coronary plaque and buy time for definitive treatment like stent placement.
- **For non-STEMI, NSAID "allergy" patients had ~158 minutes longer median door-to-procedure time compared to non-allergic patients**
  - (Goal door-to-procedure time is 90 minutes)

Li et al. AAAAI Poster 2025

Aspirin for pre-eclampsia prevention → no good alternative

- Women at increased risk for preeclampsia who received low-dose aspirin (60-150mg/d) have reduced risk for:
  - preeclampsia by 24% (NNT 42)
  - preterm birth by 14% (NNT 65)
  - intrauterine growth restriction by 20% (NNT 71)
  - no increased risk for perinatal mortality, placental abruption, post-partum hemorrhage, fetal intracranial bleeding

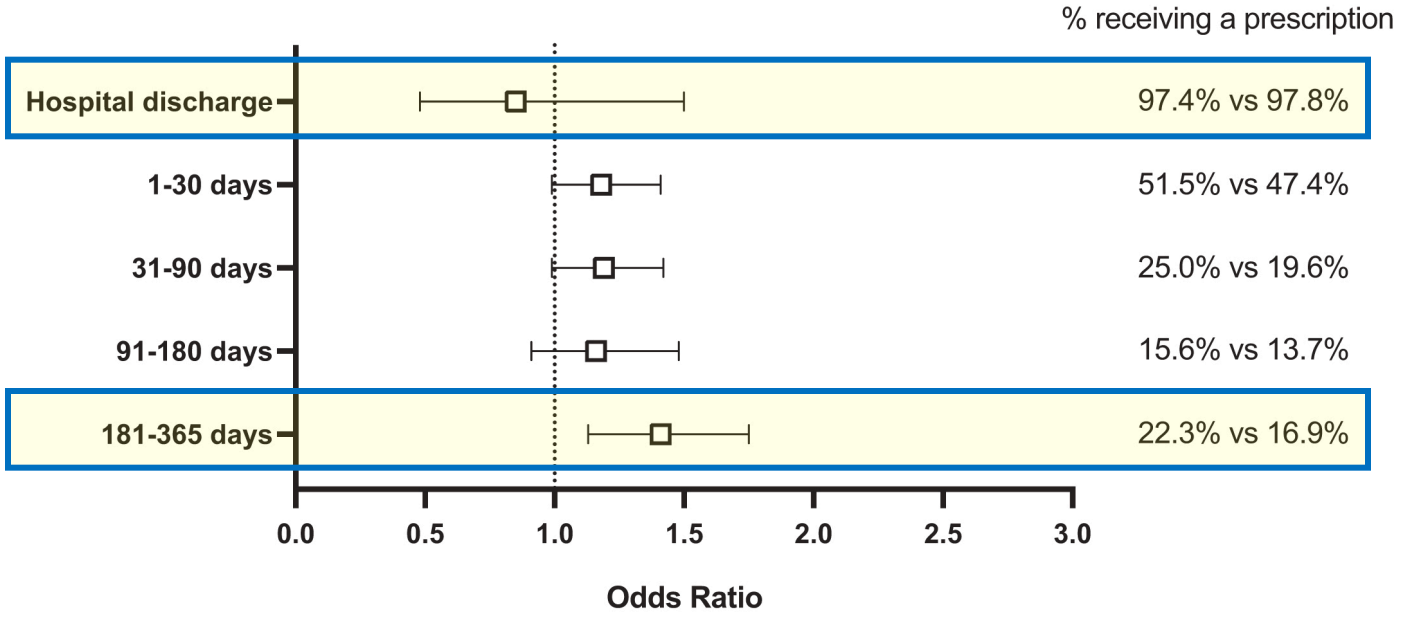
- **ACOG:** Low-dose aspirin (81 mg/day) prophylaxis is recommended in women at high risk of preeclampsia → should be initiated between 12-28 weeks of gestation (optimally before 16 weeks) and continued daily until delivery

- **Contraindications to use:**
  - Absolute: aspirin or NSAID hypersensitivity
  - Relative: history of GI bleed, active PUD, severe hepatic dysfunction

Henderson et al. Ann Intern Med, 2014
Duley et al. Cochrane Database Syst Rev, 2007
ACOG Committee Opinion, Low dose aspirin use during pregnancy, 2016

Pain control – NSAID “allergy” increases post-op opioid use and hospital length of stay in orthopedics

Proportion receiving outpatient opioid scripts following total joint replacement



But NSAID allergy pts received higher doses

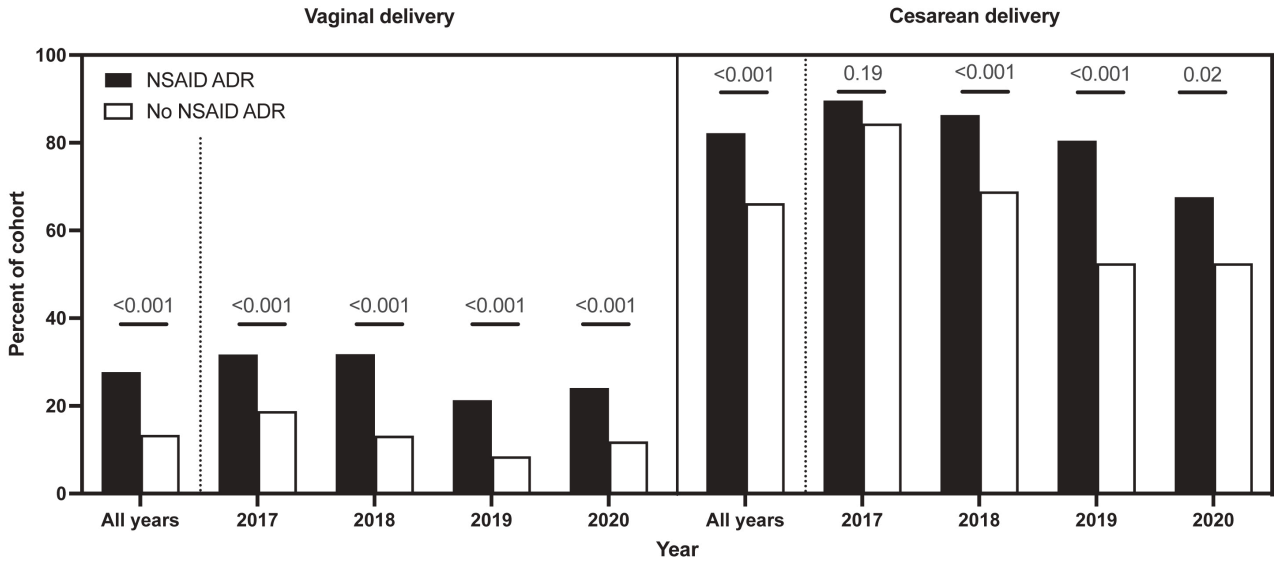
41% higher odds of opioid script 6-12mo later

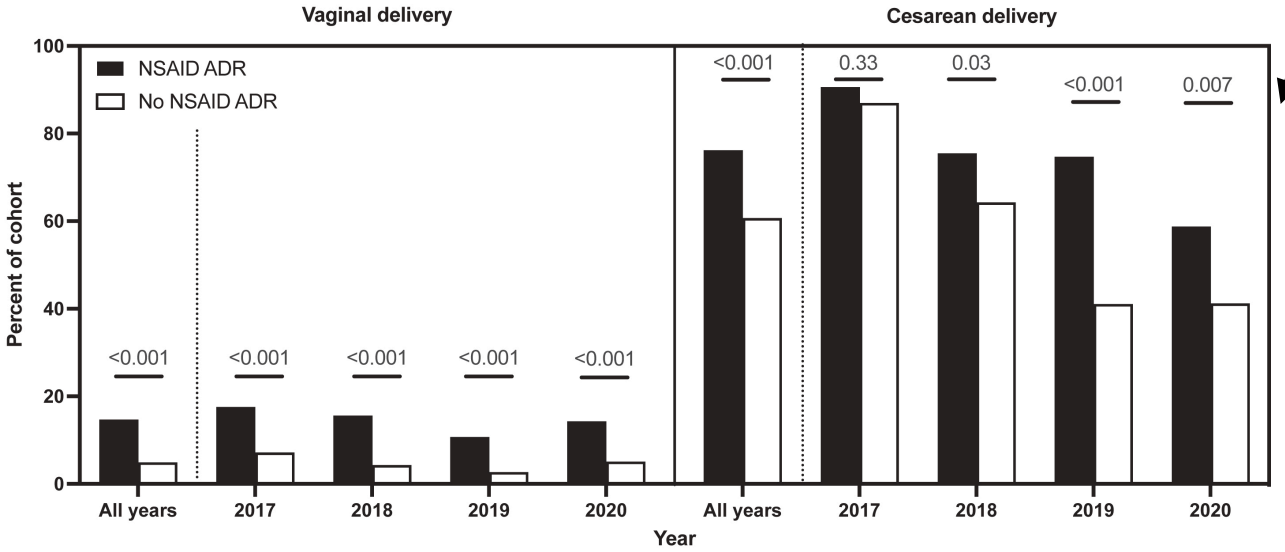
Median hospital stay for total joint replacement (hip/knee)

→ NSAID allergy patients = **4.0 days**
→ Non-allergic patients = **3.0 days** ($p<0.001$)

Li et al. JACI 2023

Pain control – NSAID “allergy” increases postpartum opioid use

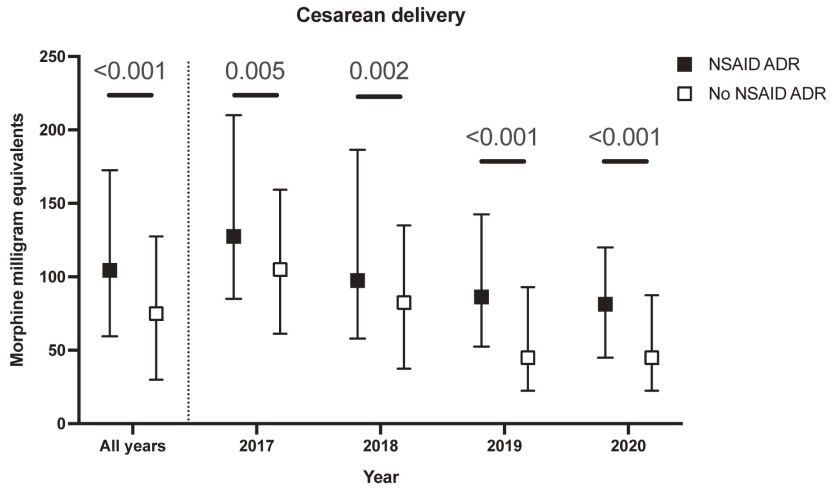




Proportion of patients receiving:

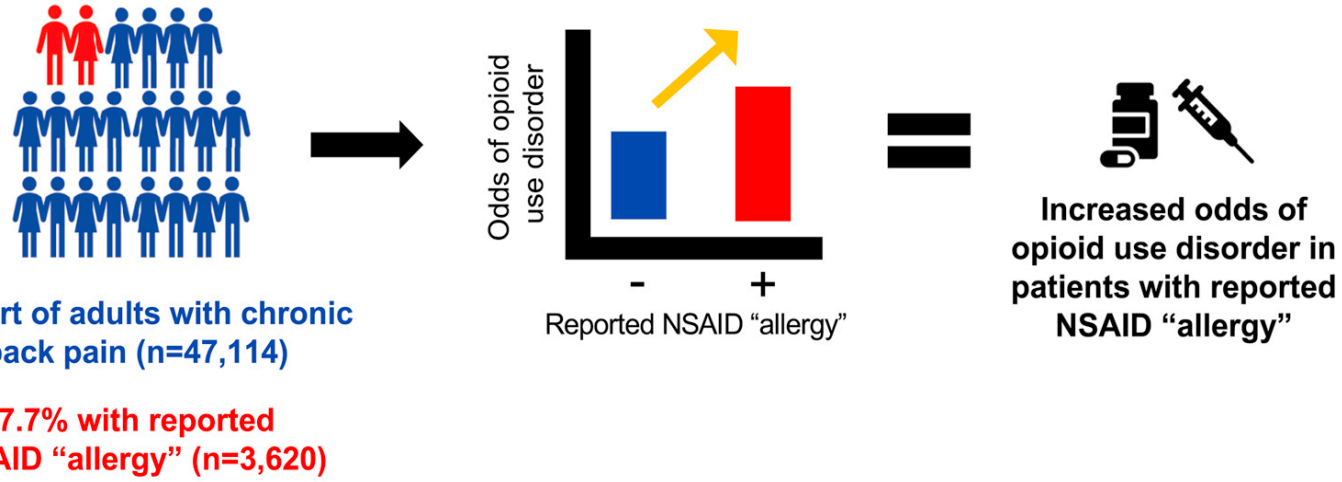
- **inpatient** postpartum opioids
- **outpatient** opioid script at discharge

Cumulative inpatient opioid dose



Li et al. JACI 2024

NSAID “allergy” increases opioid use disorder



Odds Ratio of opioid use disorder (≥2 ICD codes) =

1.34 - 1.60 (p<0.0001) for NSAID “allergy” patients

- Only 35.8% of NSAID “allergy” patients had seen an allergist (vs 25.8% of non-allergy)
- >1/2 of NSAID “allergy” patients had side effect (eg, GI upset) as reason for allergy

Li et al. JACI 2021

So what can we do about it?

Aspirin/NSAID Hypersensitivity Pathway

Side Effect

Gastrointestinal upset

Bleed

Dizziness

Headache

Altered mental status

Elevated creatinine

Hepatotoxicity

Consider aspirin or NSAID use (e.g. dose reduction or with PPI) if benefits outweigh the risks and with appropriate monitoring, at the discretion of the treating provider

E-consult to Allergy if additional assistance is required.

History of aspirin/NSAID-induced respiratory reaction

Wheezing

Rhinitis

Nasal congestion

Cough

Shortness of breath

Asthma exacerbation

For patients with:

- Aspirin-Exacerbated Respiratory Disease (AERD)
- Aspirin-Induced Asthma (AIA)
- Isolated respiratory reaction to aspirin or NSAIDs

Okay to use:
Selective COX-2 Inhibitor

If aspirin or a non-selective NSAID is preferred, please refer to Allergy for formal evaluation and possible drug challenge/desensitization.

Other Hypersensitivities

Immediate Reaction
Anaphylaxis
Hypotension
Angioedema
Laryngeal edema
Hives / Urticaria
Flushing
Wheezing (+other symptoms)

Delayed Reaction
Delayed maculopapular rash
Stevens-Johnson Syndrome
Toxic Epidermal Necrolysis
DRESS Syndrome
Serum Sickness
Acute Interstitial Nephritis
Cytopenia
Drug Fever
Fixed Drug Eruption

OR

unknown reaction WITHOUT mucosal involvement, skin desquamation, or organ involvement

Avoid using aspirin or NSAIDs (non-selective or selective); use alternative agents

If aspirin or a specific NSAID is preferred, please refer to Allergy for formal evaluation and possible drug challenge/desensitization.

Common NSAIDs by pharmacologic inhibition of COX enzymes:
Nonselective: aspirin, ibuprofen, ketorolac, naproxen, indomethacin, diclofenac, meloxicam
Selective COX-2: celecoxib (only one available in the United States)

Aspirin/NSAID Challenge/Desensitization Protocols

Non-AERD ASA/NSAID Hypersensitivity Protocols

Outpatient Aspirin/NSAID Challenge
Step 1. 1/10-1/4 dose – 60-min observation
Step 2. Full dose – 120-min observation

Aspirin – 40.5mg, 325mg
Naproxen – 50mg, 500mg
Ibuprofen – 60mg, 600mg

Li L et al, J Allergy Clin Immunol Pract 2021.

History of Urticaria/Angioedema with Aspirin

Time	Dose of aspirin
0	5 mg
½ hr	10 mg
1 hr	20 mg
1½ hr	40 mg
2 hr	81 mg
2½ hr	162 mg
3 hr	325 mg

No premedication recommended

Safety of Outpatient Aspirin/NSAID Challenges

	No Reaction	Immediate Reaction	Delayed Reaction	Total
Aspirin	114	15	3	132
Ibuprofen	52	6	2	60
Naproxen	8	1	1	10
Other NSAID*	2	1	0	3
Total	176 (85.9%)	23 (11.2%)	6 (2.9%)	205 (100%)

>85% with no reaction and allergy removed
Of those that reacted, 62.5% occurred at >60 minutes

Li L et al, J Allergy Clin Immunol Pract 2021.

If desensitization needed:

1. Urgent need for NSAID as inpatient, can't do challenge
2. or… Did challenge previously and had positive reaction

Case #1 – cardiac cath lab calls

Cardiac cath lab calls → a 61yo M with listed aspirin allergy needs a cath in the next 3 weeks and cardiology team wants him to get 325mg dose of aspirin the day before cath, and then go home on 81mg aspirin QD after that.

They want you to admit him to the cardiac ICU for aspirin desensitization.

You call patient and learn he has no atopy, no asthma, no sinus disease, and no history of urticaria; aside from cardiovascular disease and overweight, he is in good health.
His mom told him when he was in elementary school he took **aspirin** for a headache and developed eye swelling for 1-2 days afterwards and the doctors told him he should never take aspirin again.
He has avoided aspirin for the last 50 years, and for pain or headaches
he now takes either acetaminophen or ibuprofen without reaction.

What are the best options for his care going forward?

Case #1 – cardiac cath lab calls

2-dose challenge to aspirin (final of 325mg dose) as outpatient or inpatient

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What are the best options for his care going forward?

Case #2 – lots of hives (and ibuprofen)

New 33yo F in your clinic explains that in her 20s she used to get hives “all the time”, sometimes daily for weeks, occasionally with mild lip swelling. When she took **ibuprofen** for cramps the hives would start up again or get worse. Happened several times.

PMH: No asthma, no sinus disease, no environmental allergies. Diagnosed with hypothyroidism at age 26yo, now on thyroid hormone replacement.

She has avoided ibuprofen, naproxen, and aspirin for last 10 years; for pain or headaches she only takes acetaminophen. Hasn’t had any hives or swelling in 7-8 years. She would like to be able to take **ibuprofen** for her menstrual cramps and occasional muscle aches.

What are the best options for her care going forward?

2-dose challenge to **ibuprofen** (final of 600mg or 800mg dose) as outpatient

Case #2B – lots of hives (but after naproxen)

New 33yo F in your clinic explains that in her 20s she used to get hives “all the time”, sometimes daily for weeks, occasionally with mild lip swelling. When she took **naproxen** for cramps the hives would start up again or get worse. Happened several times.

PMH: No asthma, no sinus disease, no environmental allergies. Diagnosed with hypothyroidism at age 26yo, now on thyroid hormone replacement.

She has avoided ibuprofen, naproxen, and aspirin for last 10 years; for pain or headaches she only takes acetaminophen. Hasn’t had any hives or swelling in 7-8 years. She would like to be able to take **ibuprofen** for her menstrual cramps and occasional muscle aches.

What are the best options for her care going forward?

2-dose challenge to **naproxen** (final of 500mg or 1000mg dose) as outpatient

Case #3 – second pregnancy

Maternal-Fetal Medicine colleague asks you to evaluate a 34yo F who is 14 weeks pregnant. She developed early-onset preeclampsia during her 1st pregnancy, complicated by preterm delivery at 33 1/7 weeks of gestation.

– ACOG recommends initiating low-dose **aspirin** (81mg/day) between 12-28wks (optimally before 16 weeks) for preeclampsia prevention.

PMH: The patient tells you that when she was a teenager there were two instances when she took **ibuprofen** and she felt itchy for a few hours afterwards and had some red rash too. She has never taken aspirin.
No hives, asthma, no sinus disease, no environmental allergies. Otherwise healthy.

She has avoided ibuprofen, naproxen, and aspirin for last 15 years; for pain or headaches she only takes acetaminophen.

What are the best options for her care going forward?

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What are the best options for her care going forward?

2-dose challenge to **aspirin** (final of 81mg dose) as outpatient while pregnant

And then 2-dose challenge to **ibuprofen** as outpatient after pregnancy

Take-home summary

- **>80% (false)** — Over 80% with a reported aspirin/NSAID allergy do not have a reaction upon challenge
- **Cross-reactive** — Most reactions due to inhibition of COX-1 (cross-reactive among NSAIDs)
- **Side effect** — Side effects common (headache, dizzy, GI upset) or adverse rxn (GI bleed, tinnitus)