MASSACHUSETTS GENERAL HOSPITAL
RHEUMATOLOGY, ALLERGY AND IMMUNOLOGY

Drug Hypersensitivity: Making Practical Use of Practice Parameters

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RACER

EAC Annual Conference 2024

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Learning Objectives

- Upon completion of this learning activity, participants should be able to identify key drug allergy practice parameter updates

- Upon completion of this learning activity, participants should be able to review drug challenge procedures in antibiotic allergy

Drug Allergy Workgroup

David Khan (Chair)

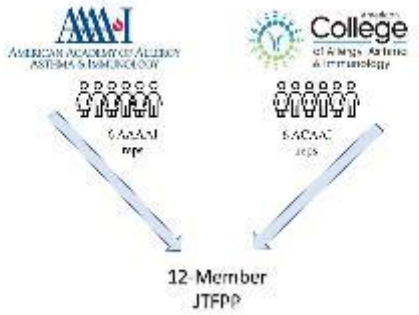
Aleena Banerji

Kim Blumenthal

Elizabeth Phillips

Roland Solensky

Drew White



David Golden
David Stukus

Drug Allergy Workgroup

Drug Allergy Parameter Update

- **Diagnostic Tests**
  - Drug challenge procedures
  - Delayed reaction testing
  - Pharmacogenomics

- **Antibiotic Updates**
  - Penicillins
  - Cephalosporins
  - Carbapenems
  - Monobactams
  - Sulfonamides
  - Fluoroquinolones
  - Macrolides

- **Other Updates**
  - NSAID Hypersensitivity
    - Aspirin challenge for acute cardiovascular disease
  - Chemotherapeutics
  - Biologics
  - Excipients

Drug Allergy Parameter Update

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Drug Challenge Procedures

Consensus-Based Statement	Strength of Recommendation	Certainty of Evidence
We suggest that when the clinical probability of a drug allergy is low, in patients without contraindications for a drug challenge, that it be performed with a 1- or 2-step drug challenge.	Conditional	Low

Khan *J Allergy Clin Immunol* 2022

Drug Challenge Procedures

- Patients deemed unlikely to be allergic to the drug
- Shared decision making may be used in patients with a higher pretest probability of true allergy or a history of more severe reactions when the benefit of drug therapy outweighs the risks
- For very low risk patients without significant comorbidities: Single full dose challenge (e.g., sulfonamide antibiotics & penicillins)
- Consider placebo-controlled challenges for possible or doubtful reactions to confirm or refute allergy

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Drug Challenge for Immediate Reactions

	Dose	Observation
1-Step	1 tab or Full PO/IV /IM/SC dose	30-60 min
2-Step	Step 1:¼ tab PO or 1/10th IV/IM/SC dose	30-60 min
	Step 2: 1 tab or Full PO/IV /IM/SC dose	30-60 min
Criteria for positive reaction	Urticaria, angioedema, exanthem, wheezing, hypoxia, hypotension, anaphylaxis	
Criteria for possible reaction	Flushing, vomiting, cough, abdominal cramping, persistent pruritus without rash, fever, mouth or eye soreness	
Doubtful reactions	Dizziness, tachycardia, subjective lip/tongue swelling, subjective throat tightness, lump in throat, dyspnea, transient pruritus without rash, headache	

USDAR grading scale for positive reactions

Drug Challenge Contraindications

Severe Cutaneous Adverse Drug Reactions	Severe Drug Anaphylaxis
SJS/TEN	
DRESS	**Organ Specific Drug Reactions**
AGEP	Cytopenias (anemia, neutropenia, leukopenia, thrombocytopenia)
	Drug induced liver injury
Drug-Induced Neutrophilic Dermatosis	Nephritis
Sweet's syndrome	Pneumonitis
	Meningitis
Drug-Induced Autoimmune Diseases	Pancreatitis
Bullous pemphigoid	
Pemphigus vulgaris	**Drug Induced Vasculitis**
Linear IgA bullous disease	Leukocytoclastic vasculitis
Drug induced lupus	Eosinophilic granulomatosis with polyangiitis
Other Cutaneous Drug Reactions	**ACE inhibitor angioedema**
Generalized bullous fixed drug eruption	
Exfoliative dermatitis	

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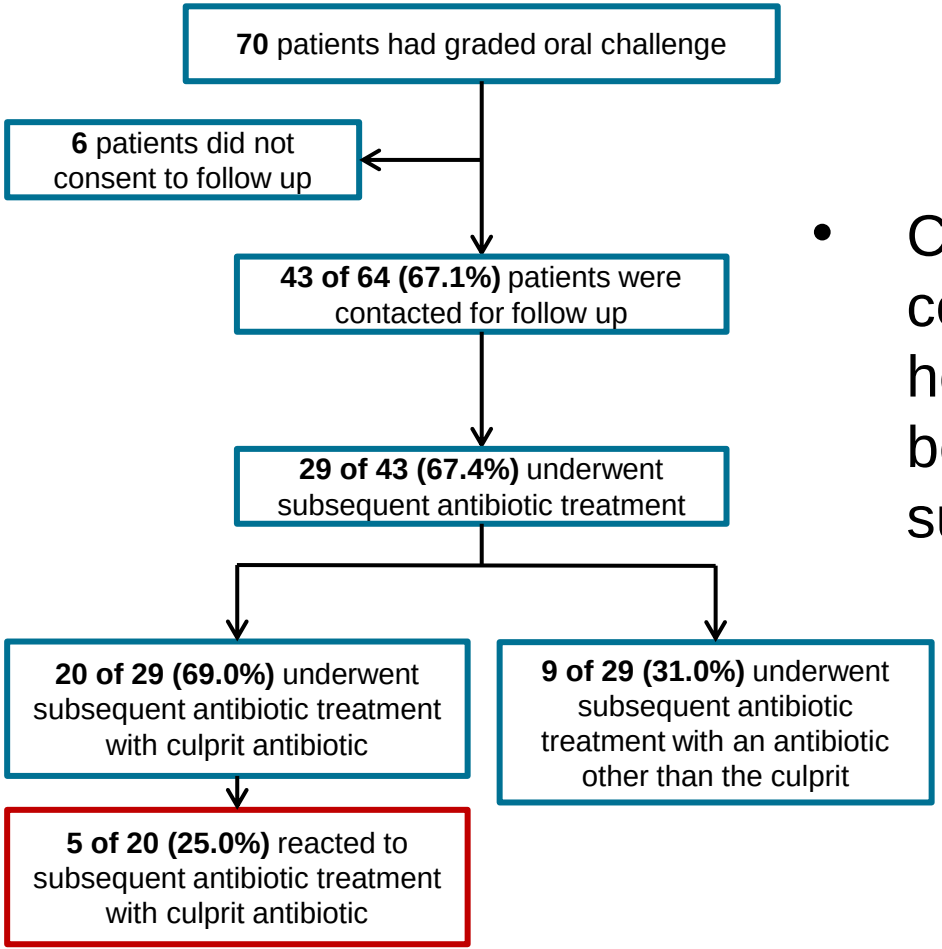
Original Article

Differentiating Between β-Lactam-Induced Serum Sickness–Like Reactions and Viral Exanthem in Children Using a Graded Oral Challenge

Variable	Patients (n = 75)
Age at index reaction, median (IQR)	2.00 (1.20, 4.00)
Sex, n (% males)	35 (46.7)
Symptoms of index reaction, n (%)	
Pruritus (generalized)	31 (41.3)
Urticaria	48 (65.3)
Angioedema	26 (34.7)
Macular/papular rash	33 (44.0)
Gastrointestinal	8 (10.7)
Throat tightness	2 (2.7)
Breathing difficulties	3 (4.0)
Arthritis/arthralgia	75 (100)
Fever	30 (40.0)
Antibiotic type, n (%)	
Amoxicillin	66 (88.0)
Clavulin	5 (6.7)
Cefprozil	2 (2.7)
Cephalexin	2 (2.7)

- Protocol: 10% dose then 20 min later 90% dose
- Immediate reactions: 2(2.7%)
- Nonimmediate reactions: 3(4.0%)
- All grade 1
- 70 (93.3%) negative

Colli *J Allergy Clin Immunol Pract* 2021



- Challenges may be considered for SSLR, however 25% may have benign symptoms with subsequent course

Colli *J Allergy Clin Immunol Pract* 2021

Placebo Challenges for Subjective Reactions or Multiple Drug Intolerance

Consensus-Based Statement	Strength of Recommendation	Certainty of Evidence
We suggest that placebo-controlled drug challenges be considered in patients with a history of primarily subjective symptoms and/or multiple reported drug allergies.	Conditional	Low

Khan *J Allergy Clin Immunol* 2022

Nocebo Effect

- The nocebo effect is the onset of untoward reactions following the administration of an indifferent substance.

- Beta-lactam challenge, ~200 patients in US, **8%** reacted to placebo
- Placebo reactors commonly female and with more drug allergy labels

Iammatteo *J Allergy Clin Immunol Pract* 2019

Determinants of nocebo effect during oral drug provocation tests

S. Bavbek[a,*], Ö. Aydın[a], Z.Ç. Sözener[a], S. Yüksel[b]

137/228 (60%) had reactions to placebo

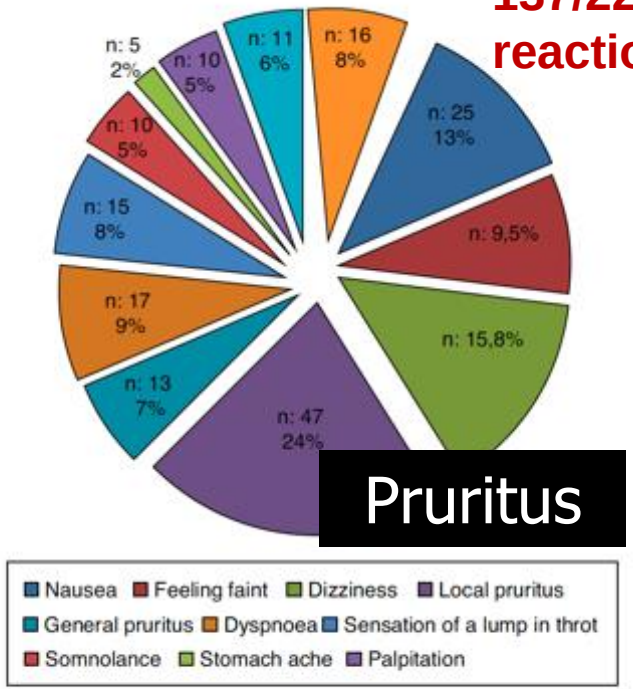


Figure 2 Subjective findings with placebo.

12% of nocebo reactions were objective

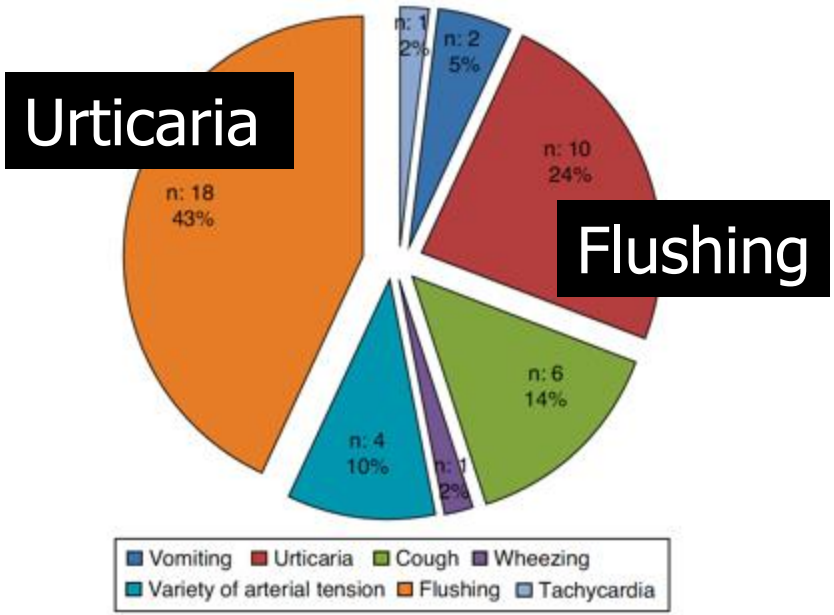


Figure 1 Objective findings with placebo.

Bavbek *Allergol Immunopathol (Madr)* 2015

Placebos in Practice

- 3 Step Drug Challenge Protocols
  - Placebo, drug (test dose), drug (full dose)
  - Placebo, placebo, drug (full dose)

- Options for Placebo
  1. Opaque capsules using inert filler (e.g., microcrystalline cellulose)
  2. Flavored syrup vehicle
  3. Flavored yogurt with flavored compounding syrup as masking agent

Delayed Reaction Testing

Consensus-Based Statement	Strength of Recommendation	Certainty of Evidence
We suggest that for specific phenotypes of delayed drug HSRs where the pretest probability is high (eg, DRESS), but the implicated agent is uncertain, that dIDT and/or PT may be useful as adjunctive tests to support drug causality.	Conditional	Very Low

Khan *J Allergy Clin Immunol* 2022

Delayed Reaction Testing: Patch

Clinical Scenario	Sensitivity of Patch Testing
AGEP	58-64%
DRESS	32-80%
SJS/TEN	9-24%

Placement

48hr Reading

- Sensitivity varies based causal drug and drug concentrations used
- A negative test does not exclude causality
- Timing: > 6 weeks after reaction and > 4 weeks after discontinuation of systemic steroids

Instructional video: https://www.youtube.com/watch?v=-KmMF_X5g4g

Khan *J Allergy Clin Immunol* 2022

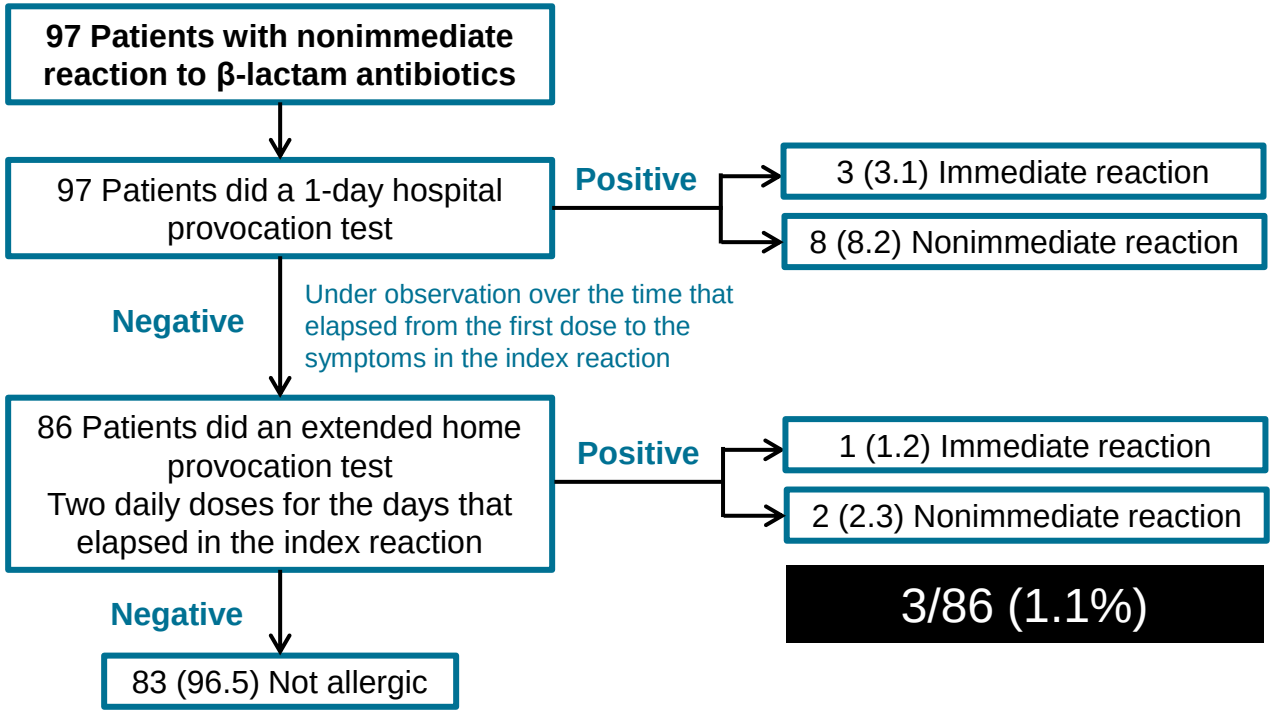
No Prolonged Drug Challenges

Consensus-Based Statement	Strength of Recommendation	Certainty of Evidence
We recommend against the routine use of prolonged (multi-day) challenges in the evaluation of penicillin allergy.	Strong	Low

Khan *J Allergy Clin Immunol* 2022

Original Article

Provocation Tests in Nonimmediate Hypersensitivity Reactions to β-Lactam Antibiotics in Children: Are Extended Challenges Needed?



Delayed reactions occurred **6 hrs to 7 days** from initial challenge

García Rodríguez *JACI In Practice* 2019

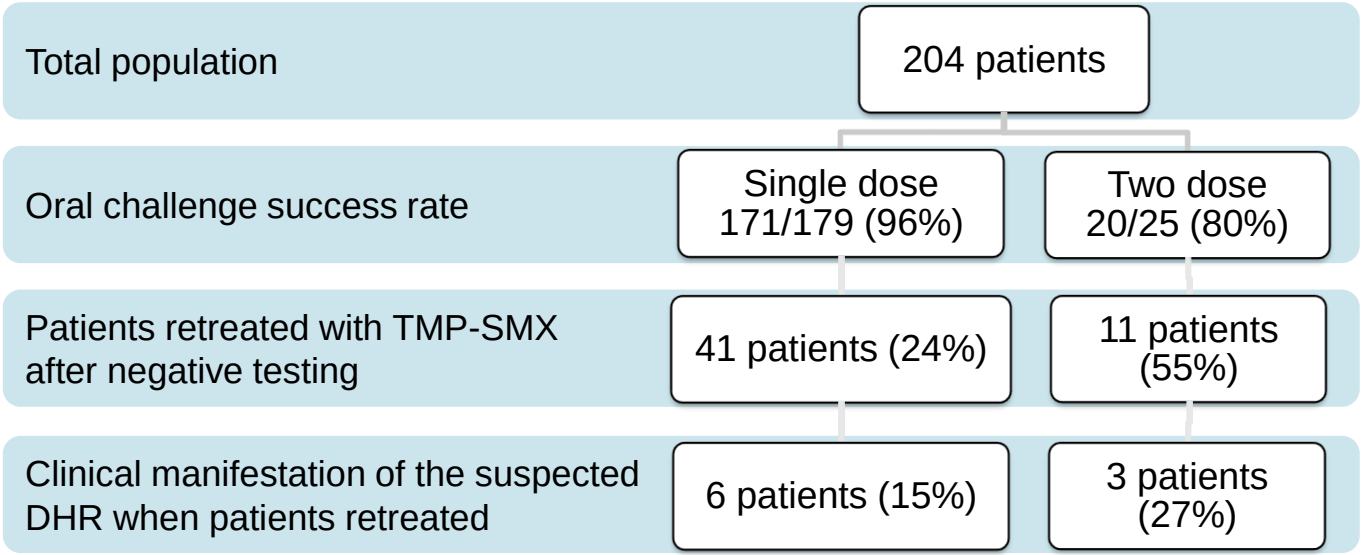
Diagnosis of Sulfonamide Allergy

Consensus-Based Statement	Strength of Recommendation	Certainty of Evidence
We suggest that for patients with histories of benign cutaneous reactions (e.g., maculopapular exanthem, urticaria) to sulfonamide antibiotics that occurred > 5 years ago, a full dose challenge with trimethoprim-sulfamethoxazole be performed when there is a need to de-label a sulfonamide antibiotic allergy.	Conditional	Low

Khan *J Allergy Clin Immunol* 2022

Clinical Communications

Oral challenge with trimethoprim-sulfamethoxazole in patients with "sulfa" antibiotic allergy



- Time since index reaction associated with reduced risk of challenge failure (aOR 0.88 [95% CI 0.80, 0.96])
- Nonimmediate history associated with reduced risk of challenge failure (aOR 0.26; 95% CI 0.06, 1.10; p=0.05) **aOR 8.45 for immediate hx**

Krantz *J Allergy Clin Immunol Pract* 2019

Quinolone and Macrolide Allergy

Consensus-Based Statement	Strength of Recommendation	Certainty of Evidence
We suggest using a 1- or 2-step drug challenge without preceding skin testing to confirm tolerance in patients with a history of non-anaphylactic reactions to fluoroquinolones or macrolides.	**Conditional**	**Low**

Khan *J Allergy Clin Immunol* 2022

Quinolones

- Incidence of immediate onset quinolone allergy is increasing
- First dose reactions due to MRGPRX2
- Delayed reactions to quinolones occur in 2-3%
- Skin testing not reliable due to high irritant potential of quinolones
- No clear patterns of cross-reactivity
- Drug challenges recommended for diagnosis

Khan *J Allergy Clin Immunol* 2022

Original Article

Clinical Characterization and Diagnostic Approaches for Patients Reporting Hypersensitivity Reactions to Quinolones

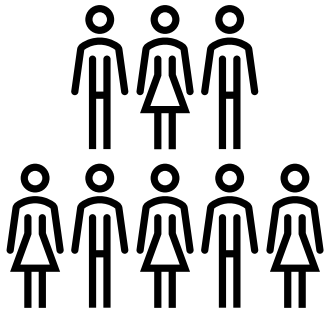
- Full diagnosis not possible in 442/612, but remaining 170 patients:
  - 128 were confirmed as having HSRs to quinolones
  - 42 as nonallergic (tolerant) to quinolones

- Confirmed hypersensitivity associated with:
  - History of anaphylaxis to moxifloxacin, OR=96
  - Reporting immediate reaction, OR 19
  - Ciprofloxacin is culprit, OR=0.11
  - Symptoms were MPE, FDE, urticaria or angioedema, OR=0.05

- Tolerance to alternative:
  - 2/5 ciprofloxacin HSR tolerated levofloxacin
  - 3/5 levofloxacin HSR tolerated ciprofloxacin
  - 3/8 moxifloxacin HSR tolerated ciprofloxacin and 2/2 tolerated levofloxacin

Doña *J Allergy Clin Immunol Pract* 2020

NSAID Allergy Labels



0.5-5%
General population

2-2.3%
People of childbearing age

Up to 20%
Patients with asthma and nasal polyps

2.5%
Patients with cardiac disease

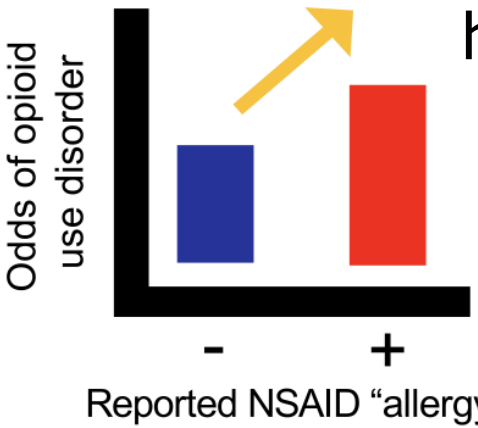
Up to 30%
Patients with chronic spontaneous urticaria

7-9%
Patients with chronic back pain or undergoing orthopedic surgery

Dona *Allergy* 2020; Li *J Allergy Clin Immunol* 2020; Laidlaw & Cahill. *J Allergy Clin Immunol Pract* 2017

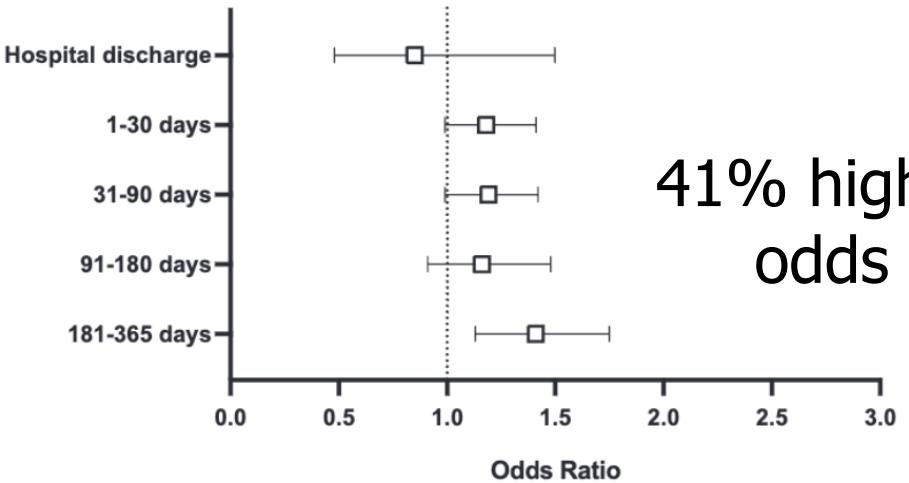
NSAID Allergy Labels: Opioid Use Risks

Chronic back pain



34% higher odds

Arthroplasty



41% higher odds

Li *J Allergy Clin Immunol* 2020; Li *J Allergy Clin Immunol Pract* 2023

	Classification of NSAID-induced hypersensitivity reactions			
	Clinical phenotype	**Clinical symptoms**	**Cross-reactivity**	**Putative mechanism**
Acute	Aspirin-exacerbated respiratory disease (AERD/N-ERD)	Nasal congestion, rhinitis, bronchoconstriction, asthma exacerbation, rash (mixed)	Cross-reactive reactions within NSAID class	COX-1 inhibition
Acute	NSAID-exacerbated cutaneous disease (NECD)	Urticaria and/or angioedema, respiratory (mixed)	Cross-reactive reactions within NSAID class	COX-1 inhibition
Acute	NSAID-induced urticaria / angioedema / anaphylaxis in patients without underlying cutaneous disease (NIUAA)	Urticaria and/or angioedema, anaphylaxis, upper respiratory, GI (mixed)	Cross-reactive reactions within NSAID class	Likely COX-1 inhibition
Acute	Single NSAID-induced urticaria / angioedema / anaphylaxis (SNIUAA)	Urticaria and/or angioedema, anaphylaxis	Single drug-induced	Likely IgE mediated
Delayed	Delayed reactions to NSAIDs	Varies: fixed drug eruption, maculopapular rash, severe cutaneous drug reaction	Single drug-induced or cross-reactive	Varies: T cell-mediated, ?other

NSAID-induced food allergy (NIFA) / NSAID-exacerbated food allergy (NEFA)

AERD: Challenge or Desensitization?

Drug allergy: A 2022 practice parameter update

	Strength of recommendation	Certainty of evidence
We recommend against an oral aspirin challenge to confirm the diagnosis of AERD in cases of high diagnostic certainty based on clinical history; however, aspirin desensitization remains a therapeutic option when indicated.	Strong	Low
We suggest an oral aspirin challenge to confirm the diagnosis of AERD in cases of diagnostic uncertainty.	Conditional	Moderate
We suggest that a challenge procedure be used to diagnose AERD when there is diagnostic uncertainty and that a desensitization protocol be used when the intention is to place a patient on a daily therapeutic aspirin dose for cardioprotection, pain relief, or to control nasal polyp regrowth.	Conditional	Moderate

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AERD: Challenge or Desensitization?

TABLE XIX. Clinical characteristics determining the need for challenge versus desensitization in patients with AERD *

Consider diagnostic aspirin challenge	Consider aspirin desensitization
Single reaction to an NSAID	Reaction to ≥2 different NSAIDs
Minor symptoms	Reaction requires hospitalization
Atypical symptoms (lightheadedness, cutaneous only, prolonged symptoms for >24 h)	Typical upper or lower airway symptoms lasting <6 h
Minor nasal polyp burden	Severe recurrent nasal polyposis

*Individual patients may exhibit some criteria from each column. The clinician will need to determine based on an aggregate assessment of these factors whether to offer a challenge or consider aspirin desensitization.

Khan *J Allergy Clin Immunol* 2022

NSAID Challenge in ACS

Consensus-Based Statement	Strength of Recommendation	Certainty of Evidence
We suggest a 2-step aspirin challenge for patients with a history of aspirin allergy to aid in the management of acute cardiovascular disease.	**Conditional**	**Very Low**

Khan *J Allergy Clin Immunol* 2022

NSAID Challenge

AAAAI Drug Allergy Practice Parameter Recommends

2-step aspirin 81 mg challenge for cardiovascular emergencies:

- Dose #1 = **40.5 mg** → 90 min. observation
- Dose #2 = **40.5 mg** → 90 min. Observation
- Continue **Aspirin 81 mg daily**

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Summary of Important Changes

1. Recommendation to define a positive skin test as a wheal that is ≥ 3 mm than the negative control for prick/puncture or intradermal tests accompanied by a ≥ 5 mm flare
2. *Suggestion to use of 1- or 2-step drug challenges for low-risk patients*
3. *Suggestion to use placebo challenges in patients with subjective symptoms or multiple reported drug allergies*
4. *Suggestion to consider dIDT and/or patch tests (PT) to identify culprit drugs for specific phenotypes of delayed drug reactions where the implicated agent is uncertain*
5. Recognition that most pharmacogenetic associations identified to date are currently unlikely to translate into clinical practice
6. *Recommendation for proactive penicillin allergy de-labeling*
7. *Recommendation against multiple day challenges in evaluation of penicillin allergy*
8. *Recommendation against penicillin skin testing prior to direct amoxicillin challenge in low-risk pediatric patients*
9. *Consideration for direct amoxicillin challenge in adults with low-risk penicillin allergy histories*
10. Recognition that patients with selective allergic reactions to piperacillin-tazobactam may be identified with skin tests to piperacillin-tazobactam and may tolerate other penicillins
11. *Suggestion to perform direct challenge to cephalosporins with dissimilar side chains in patients with non-anaphylactic cephalosporin allergy*
12. *Suggestion to perform skin tests to parenteral cephalosporins (prior to challenge) with non-identical R1 side chains in patients with anaphylactic cephalosporin allergy*
13. *Specific guidance on administration of cephalosporins to patients with various phenotypes of penicillin allergy*
14. *Specific guidance on administration of penicillins to patients with various phenotypes of cephalosporin allergy*
15. *Suggestion to administer carbapenems without prior testing in patients with other beta-lactam allergies*
16. *Recommendation that allergists collaborate with hospitals and healthcare systems to implement beta-lactam allergy pathways to improve antibiotic stewardship outcomes*

Summary of Important Changes

17. *Suggestion to use a 1-step trimethoprim-sulfamethoxazole challenge rather than desensitization for low-risk patients where there is a need to de-label sulfonamide allergy*
18. *Suggestion to use 1- or 2-step drug challenge for non-anaphylactic reactions to fluoroquinolones or macrolides without preceding skin testing*
19. Recommendation against aspirin challenge to confirm a diagnosis of aspirin exacerbated respiratory disease (AERD) in cases of high diagnostic certainty based on history but that aspirin desensitization remains a therapeutic option when indicated
20. Suggestion for oral aspirin challenge only in patients where there is diagnostic uncertainty of AERD
21. Suggestion that cyclooxygenase 2 (COX-2) inhibitors may be used in any non-steroidal anti-inflammatory drug (NSAID) hypersensitivity phenotype when an NSAID is needed
22. Suggestion to use oral aspirin challenge in patients with NSAID-induced urticaria/angioedema to determine tolerance to other NSAIDs
23. *Suggestion for 2-step aspirin challenge (not desensitization) for patients with a history of aspirin allergy in acute need of aspirin for cardiovascular disease*
24. Suggestion that patients with non-immediate chemotherapy or biologic reactions be treated with slowed infusion rate, graded dose scalation, and/or pre-medications without desensitization
25. Suggestion that for patients with immediate reactions to taxanes, the severity of the initial reaction may assist in risk stratification and management
26. Suggestion that patients with non-immediate reactions to monoclonal antibodies (mAb) may be treated with a slowed infusion, graded dose escalation, and/or premedication without desensitization
27. Recognition that excipient allergy is very rare but may be considered in patients with anaphylaxis to ≥2 structurally unrelated products that share a common excipient

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Contribute to the COVID-19 Vaccine Allergy Registry!
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