Drug Hypersensitivity Reactions: Tall Tales from Texas

David A. Khan, MD
Professor of Medicine and Pediatrics
Allergy & Immunology Program Director
UT Southwestern, Dallas, TX

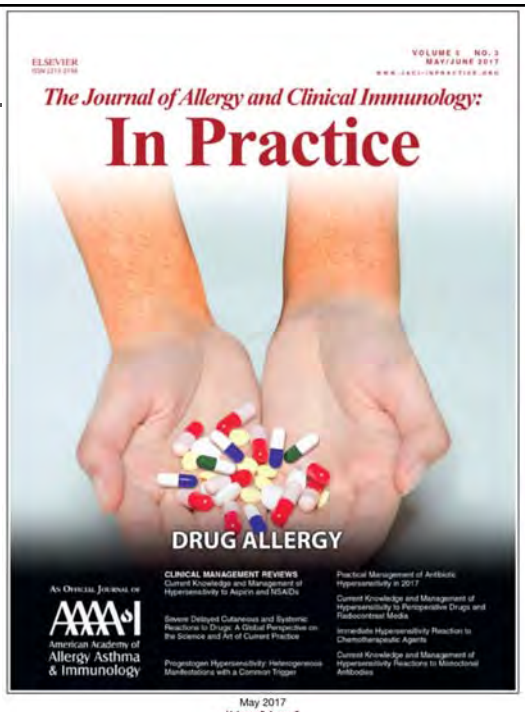
UT SOUTHWESTERN MEDICAL CENTER

Disclosures

- Research Grants
  - NIH
- Honoraria
  - UpToDate, Genentech
- Consulting
  - Aimmune (DSMB)
- Organizations:
  - Joint Task Force on Practice Parameters
  - AAAAI BOD

Objectives

- By attending this lecture the participant should be able to:
  - Gain an understanding of the benefits and limitations of pharmacogenetics in drug allergy
  - Gain an understanding of the spectrum of cutaneous drug reactions
  - Be able to recognize clinical features of specific drug hypersensitivity syndromes and mimics of drug allergy



Outline

- Drug Allergy Updates
  - Pharmacogenomics
  - AERD
  - Penicillin Allergy
- Drug Allergy Cases

Updates in Pharmacogenomics of Drug Allergy

Definitions

- Pharmacogenetics
  - Any influence that genetics may have on drug therapy
  - Usually deals with **single drug-gene** interactions
- Pharmacogenomics
  - Similar to pharmacogenetics but incorporates genomics and epigenetics to evaluate effect of **multiple genes** on drug responses

Clinical reviews in allergy and immunology

Pharmacogenomics and adverse drug reactions: Primetime and not ready for primetime tests

David A. Khan, MD *Dallas, Tex*

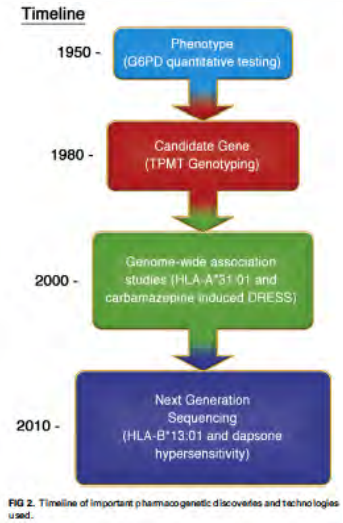


FIG 2. Timeline of important pharmacogenetic discoveries and technologies used.

Khan DA. J Allergy Clin Immunol 2016;138:943-55.

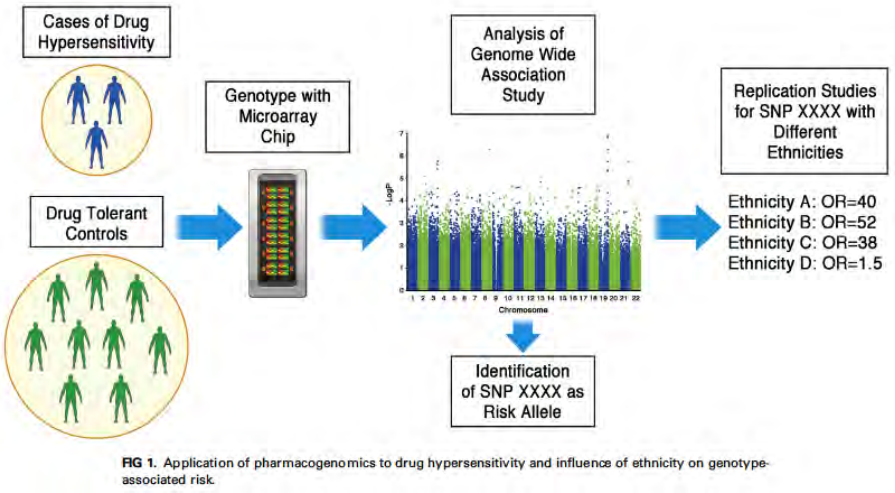


FIG 1. Application of pharmacogenomics to drug hypersensitivity and influence of ethnicity on genotype-associated risk.

Khan DA. J Allergy Clin Immunol 2016;138:943-55.

Pharmacogenetics in SJS

- Incidence of SJS is higher in Han Chinese with carbamazepine (CBZ) being the most common drug in Asians
- Pharmacogenetic study in a Han Chinese population including 44 CBZ-SJS patients and controls
- HLA-B*15:02 was found in 100% of CBZ-SJS pts and only 3% of CBZ-tolerant pts and 8.6% of general population
  - **OR**: CBZ-SJ/CBZ-tolerant: **2504** $p=3.13 \times 10^{-27}$

Chung WH et al. Nature 2004;428:486.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Carbamazepine-Induced Toxic Effects and HLA-B*1502 Screening in Taiwan

Pei Chen, Ph.D., Juei-Jueng Lin, M.D., Chin-Song Lu, M.D., Cheung-Ter Ong, M.D., Peiyuan F. Hsieh, M.D., Chih-Chao Yang, M.D., Chih-Ta Tai, M.D., Shey-Lin Wu, M.D., Cheng-Hsien Lu, M.D., Yung-Chu Hsu, M.D., Hsiang-Yu Yu, M.D., Long-Sun Ro, M.D., Chung-Ta Lu, M.D., Chun-Che Chu, M.D., Jing-Jane Tsai, M.D., Yu-Hsiang Su, M.D., Sheng-Hsing Lan, M.D., Sheng-Feng Sung, M.D., Shu-Yi Lin, M.S., Hui-Ping Chuang, B.S., Li-Chen Huang, B.S., Ying-Ju Chen, M.S., Pei-Joung Tsai, M.S., Hung-Ting Liao, M.S., Yu-Hsuan Lin, M.S., Chien-Hsiun Chen, Ph.D., Wen-Hung Chung, M.D., Ph.D., Shuen-Iu Hung, Ph.D., Jer-Yuarn Wu, Ph.D., Chi-Feng Chang, Ph.D., Luke Chen, Ph.D., Yuan-Tsong Chen, M.D., Ph.D., and Chen-Yang Shen, Ph.D., for the Taiwan SJS Consortium*

N Engl J Med 2011;364:1126-33.

No SJS in HLA-Screened Patients who Received Carbamazepine

Table 2. Adverse Events during the 2-Month Follow-up.

Adverse Event	HLA-B*1502–Positive with Alternative Medication (N=215)	HLA-B*1502–Negative with Carbamazepine (N=4120)	Total
	number of events		
Mild cutaneous events			
Rash and itching	5*	206	211
Rash, itching, and blisters	1†	20	21
Rash, itching, and oral ulcers	0	14	14
Rash, itching, blisters, and oral ulcers	0	7	7
Itching, blisters, and oral ulcers	0	2	2
Blisters and oral ulcers	0	3	3
Severe cutaneous events			
Maculopapular eruption	0	3	3
Hypersensitivity syndrome	0	2	2
Urticaria	1‡	1	2
Stevens–Johnson syndrome or toxic epidermal necrolysis	0	0	0

N Engl J Med 2011;364:1126-33.

Reduced Carbamazepine-Induced SJS Compared to Historical Incidence

Table 3. Historical Incidence of Carbamazepine-Induced SJS–TEN in 2002, 2003, and 2004, as Compared with the Incidence among Study Subjects.*

Variable	2002	2003	2004
New recipients of carbamazepine (no.)	50,917	48,522	49,670
Subjects with ICD-9-CM diagnostic code 695.1 (no.)	1441	1261	1354
Carbamazepine-induced SJS–TEN (no.)	123	108	116
Incidence of carbamazepine-induced SJS–TEN (%)	0.24	0.22	0.23
P value for comparison between historical incidence and incidence among study subjects†	<0.001	<0.001	<0.001

N Engl J Med 2011;364:1126-33.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

HLA-B*5701 Screening for Hypersensitivity to Abacavir

Simon Mallal, M.B., B.S., Elizabeth Phillips, M.D., Giampiero Carosi, M.D., Jean-Michel Molina, M.D., Cassy Workman, M.B., B.S., Janez Tomažič, M.D., Eva Jägel-Guedes, M.D., Sorin Rugina, M.D., Oleg Kozyrev, M.D., Juan Flores Cid, M.D., Phillip Hay, M.B., B.S., David Nolan, M.B., B.S., Sara Hughes, M.Sc., Arlene Hughes, Ph.D., Susanna Ryan, Ph.D., Nicholas Fitch, Ph.D., Daren Thorborn, Ph.D., and Alastair Benbow, M.B., B.S., for the PREDICT-1 Study Team*

Mallal S, et al. N Engl J Med. 2008 Feb 7;358(6):568-79.

Prospective Screening for HLA-B*5701 Reduces Hypersensitivity Reactions to Abacavir

Table 2. Incidence of Hypersensitivity Reaction to Abacavir.*

Hypersensitivity Reaction	Prospective Screening	Control	Odds Ratio (95% CI)*	P Value
	no. of patients/total no. (%)			
Clinically diagnosed				
Total population that could be evaluated	27/803 (3.4)	66/847 (7.8)	0.40 (0.25–0.62)	P<0.001
White subgroup	24/679 (3.5)	61/718 (8.5)	0.38 (0.23–0.62)	P<0.001
Immunologically confirmed				
Total population that could be evaluated	0/802	23/842 (2.7)	0.03 (0.00–0.18)	P<0.001
White subgroup	0/679	22/713 (3.1)	0.03 (0.00–0.19)	P<0.001

Immunologically confirmed via abacavir patch testing

Mallal S, et al. N Engl J Med. 2008 Feb 7;358(6):568-79.

Pharmacogenetic Associations and Severe Cutaneous Adverse Reactions

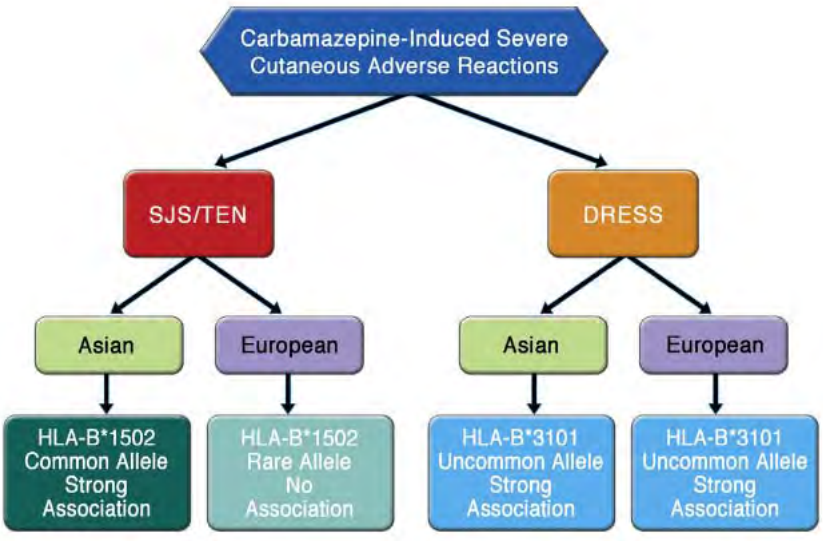
Drug-Reaction	Genotype	Ethnicity	No. Positive/ Total Cases vs. Controls	Odds Ratio	Type of Evidence	Screening Recommended by FDA
Carbamazepine-SJS	HLA-B*1502	Han Chinese	102/109 40/384	115.3	Meta-analysis (5 studies)	
		Thai	43/48 13/84	54.4	Meta-analysis (2 studies)	
		Malaysian	6/6 0/8	221	Single study	Yes
		Indian	6/8 0/10	70.4	Single study	
		Korean	1/7 0/50	23.3	Single study	
		Japanese	0/3 0/33	NA	Single study	No
Carbamazepine-DRESS	HLA-A*3101	European	18/39 22/579	24.1	Meta-analysis (3 studies)	No
		Asians	40/80 69/712	10.3	Meta-analysis (5 studies)	
Carbamazepine-SJS/TEN	HLA-A*3101	European	8/36 22/579	7.9	Meta-analysis (3 studies)	No

Khan DA. J Allergy Clin Immunol 2016;138:943-55.

Pharmacogenetic Associations and Severe Cutaneous Adverse Reactions

Drug-Reaction	Genotype	Ethnicity	No. Positive/ Total Cases vs. Controls	Odds Ratio	Type of Evidence	Screening Recommended by FDA
Abacavir hypersensitivity syndrome	HLA-B*5701	Multi-ethnic	484/1223 57/2869 (broad clinical criteria)	32.1	Meta-analysis (11 studies)	Yes
		Multi-ethnic	180/315 21/1168 (strict clinical criteria)	177.7	Meta-analysis (4 studies)	
		Multi-ethnic	81/81 38/1378 (patch test criteria)	859.1	Meta-analysis (4 studies)	
Allopurinol-SJS/TEN	HLA-B*5801	Asian	54/55 74/678 (matched controls)	96.6	Meta-analysis (4 studies)	No
		Asian & Mixed European	50/69 171/3378 (population controls)	79.3	Meta-analysis (5 studies)	
Dapsone hypersensitivity syndrome	HLA-B*1301	Han Chinese	65/76 148/1034	20.5	Single study	No

Khan DA. J Allergy Clin Immunol 2016;138:943-55.



Khan DA. J Allergy Clin Immunol 2016;138:943-55.

Issues with Genotype Screening

- Low positive predictive value for many genotypes
  - HLA-B*58:01 for allopurinol-induced SJS/TEN only 3%
- Screening based only on HLA genotyping will result in denial of therapies that would be beneficial and tolerated by many patients
- Data not always reproducible
  - HLA-A*31:01 and carbamazepine SJS/TEN in Europeans

White KD et al. J Allergy Clin Immunol 2015;136:219-34.

Updates in Aspirin Exacerbated Respiratory Disease (AERD)

Aspirin/NSAID Hypersensitivity Phenotypes

Hypersensitivity Reaction	Cross-Reactivity	Onset	Clinical Features	Underlying Disease	Mechanism
Aspirin Exacerbated Respiratory Disease (AERD)	Yes	Immediate	Naso-ocular Respiratory (GI, skin less often)	Asthma, nasal polyps	COX-1 Inhibition
Aspirin Exacerbated Cutaneous Disease	Yes	Immediate	Urticaria/Angioedema	Chronic urticaria	COX-1 Inhibition
Multiple NSAID-Induced Urticaria	Yes	Immediate	Urticaria/Angioedema	None	COX-1 Inhibition ?
Single NSAID Induced Urticaria/Anaphylaxis	No	Immediate	Urticaria/Angioedema Anaphylaxis	None	IgE mediated ?
Delayed Hypersensitivity	No	Delayed	Fixed drug eruption, SJS/TEN, MP exanthem, Hypersensitivity pneumonitis, aseptic meningitis	None	T cell mediated ?

New Theories in AERD

Mechanisms of allergy and clinical immunology

Prostaglandin E_2 resistance in granulocytes from patients with aspirin-exacerbated respiratory disease

Tanya M. Laidlaw, MD,[a,b] Anya J. Cutler,[b] Molly S. Kidder,[b] Tao Liu, PhD,[b] Juan Carlos Cardet, MD,[a,b] Heng Chhay,[b] Chunli Feng, MD,[b] and Joshua A. Boyce, MD[a,b,c] *Boston, Mass*

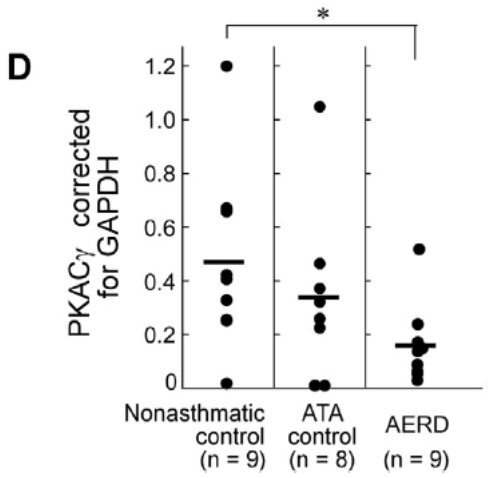
Neutrophils and Platelets are important in AERD

J Allergy Clin Immunol 2014;133:1692-01.

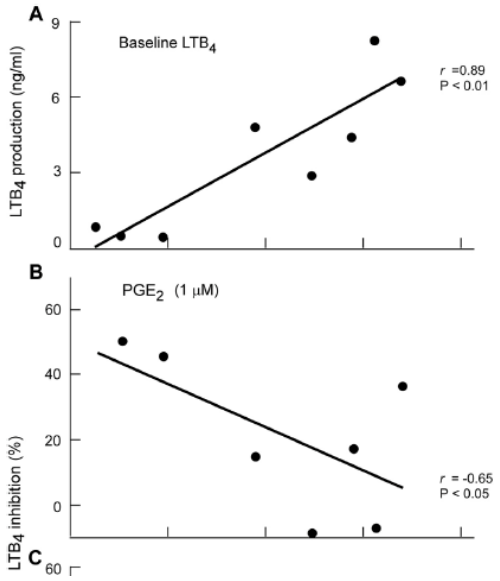
Role of PGE_2 in AERD

- Aspirin-exacerbated respiratory disease (AERD) is characterized by overproduction of leukotrienes
- Leukotriene production can be suppressed by PGE_2 and the cAMP dependent protein kinase A (PKA)
- PGE2 effects are mediated via EP receptors

Granulocyte PKACγ Activity is Reduced in AERD



Platelet-adherent Neutrophils Correlate with Increased LTB4 and Less LTB4 Inhibition



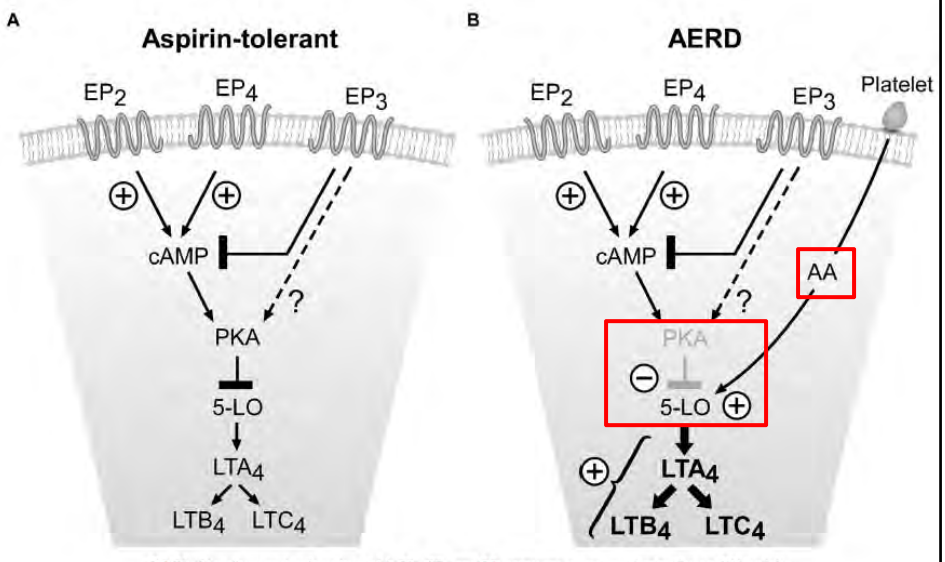
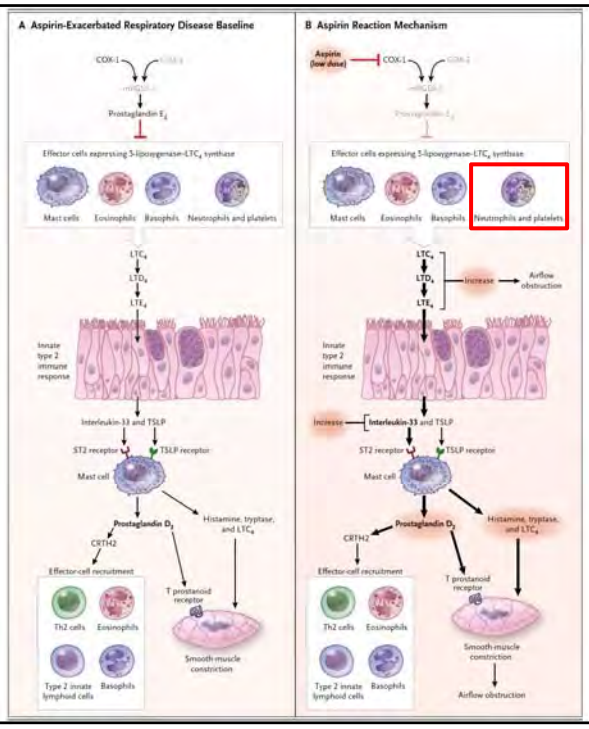


FIG E2. Signaling mechanisms by which EP_2, EP_3, and EP_4 receptors may control granulocyte PKA activity and LT production in controls (**A**) and patients with AERD (**B**).



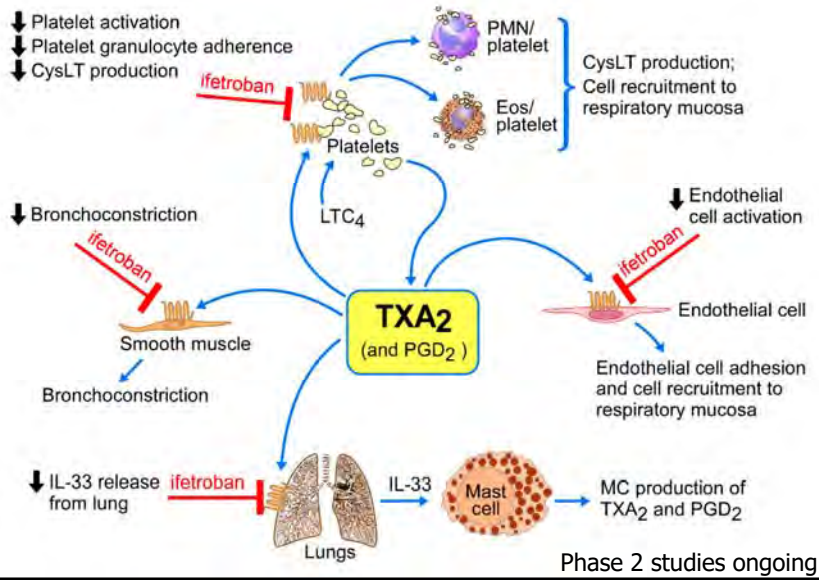
Laidlaw TM, Boyce JA. NEJM 2016;374:484-8.

Future Therapies in AERD

- Prasugrel
  - ADP receptor inhibitor
  - Reduces aggregation of platelets by binding to $P2Y_{12}$ receptors
- Study by Laidlaw et al. of 50 AERD patients treated with 4 weeks of prasugrel
  - Primary outcome was difference in provocative dose of aspirin
  - Overall no change in provocative dose, platelet activation, granulocyte adherence
  - 5 of 40 patients did not react on prasugrel

Laidlaw T et al. AAAAI 2017

Ifetroban (thromboxane receptor antagonist) in AERD



Phase 2 studies ongoing

Alcohol May Trigger AERD

Original Article

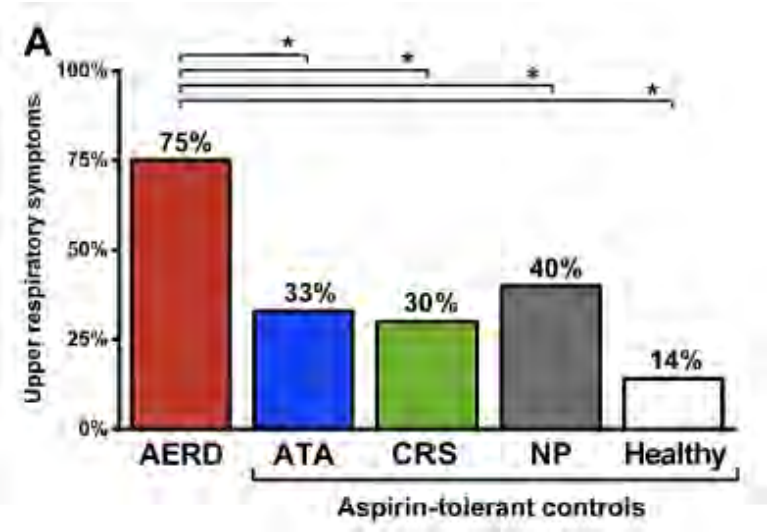
Alcohol-induced Respiratory Symptoms Are Common in Patients With Aspirin Exacerbated Respiratory Disease

Juan Carlos Cardet, MD[a], Andrew A. White, MD[b], Nora A. Barrett, MD[a,c], Anna M. Feldweg, MD[a,c], Paige G. Wickner, MD[a,c], Jessica Savage, MD, MHS[a,c], Neil Bhattacharyya, MD[d,e], and Tanya M. Laidlaw, MD[a,c]
Boston, Mass; and San Diego, Calif

Alcohol can inhibit catabolism of cys-leukotrienes

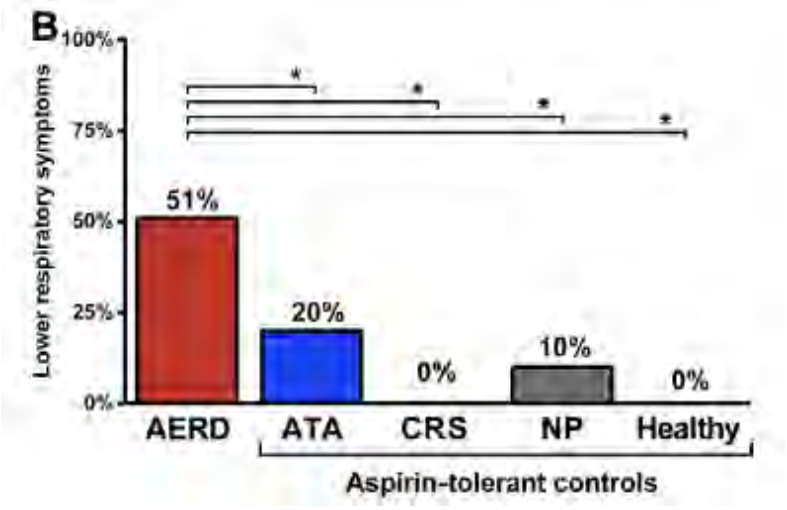
J Allergy Clin Immunol Pract 2014;2:208-13.

Reported Prevalence of Alcohol-Induced Rhinitis



J Allergy Clin Immunol Pract 2014;2:208-13.

Reported Prevalence of Alcohol-Induced Wheezing/Dyspnea



J Allergy Clin Immunol Pract 2014;2:208-13.

Aspirin Desensitization for AERD

Benefits of ASA Desensitization

- Long-term observational studies reveal
  - ↓ sinus infections
  - ↓ oral steroid bursts
  - ↓ anosmia
  - ↓ rhinitis
  - ↓ asthma symptoms
- After 1 yr therapy
  - Good-excellent improvement (78%) 115/148 pts
- Discontinuation due to side effects
  - 14% in 1st year (mostly epigastric pain)

Candidates for ASA Desensitization

- Patients with AERD who have moderate or severe asthma, intractable nasal congestion, or both on the basis of their AERD who have failed medical therapy
- Patients with AERD who are multiple nasal polyp formers
- Patients requiring systemic corticosteroids for control of AERD
- Patients with AERD who require aspirin for other diseases

Stevenson DD, Simon RA. J Allergy Clin Immunol 2006;118:801-4.

Table 2. Comparison of Standard Oral Aspirin and Modified Nasal Ketorolac Timeline[a]

Time	Oral aspirin challenge	Intranasal ketorolac and aspirin challenge
Day 1		
8 AM	20–40 mg	1 spray (1 in 1 nostril)
8:30 AM		2 sprays (1 in each nostril)
9 AM		4 sprays (2 in each nostril)
9:30 AM		6 sprays[b] (3 in each nostril)
10:30 AM		60 mg of aspirin
11 AM	40–60 mg	
12 noon		60 mg of aspirin
1:30 PM		Instructions and discharge
2 PM	60–100 mg	
5 PM	Instructions and discharge	
Day 2		
8 AM	100 mg	150 mg
11 AM	160 mg	325 mg
2 PM	325 mg	Instructions and discharge
5 PM	Instructions and discharge	

Lee RU et al. Ann Allergy Asthma Immunol. 2010;105:130 –135.

Original Article

An Hourly Dose-Escalation Desensitization Protocol for Aspirin Exacerbated Respiratory Disease

Justin R. Chen, MD, Brett L. Buchmiller, MD, and David A. Khan, MD *Dallas, Tex*

What is already known about this topic? Aspirin desensitization therapy using multiday protocols followed by maintenance dosing effectively treats upper and lower airway symptoms in patients with aspirin-exacerbated respiratory disease (AERD) who are inadequately controlled on inhaled glucocorticoids and leukotriene-modifying agents.

What does this article add to our knowledge? Patients reacting to aspirin or nonsteroidal anti-inflammatory drugs within 1 hour of ingestion can be safely desensitized using a protocol of hourly dose escalations that in many cases can be accomplished in a single day.

How does this study impact current management guidelines? Our findings support shortening the dosing intervals for patients without delayed reactions to aspirin, which applies to the majority of patients undergoing desensitization for AERD. This would reduce the need for prolonged observation and benefits both patients and practitioners.

Chen J, et al. J Allergy Clin Immunol Pract 2015;3:926-31.

UT Southwestern AERD Desensitization Protocol

TABLE I. Hourly dose-escalation aspirin desensitization protocol

Time	Dose
08:00	40 mg (20 mg if history of serious reaction)
09:00	81 mg
10:00	120 mg
11:00	162 mg
12:00	325 mg
13:30	Observation period

Chen J, et al. J Allergy Clin Immunol Pract 2015;3:926-31.

UT Southwestern Protocol

- Indicated for patients with a history of reactions to ASA or NSAIDs within 1 hour
- 57 hourly dose-escalation aspirin desensitizations performed in AERD subjects
- All but 1 patient successfully desensitized
  - 40% completed in 1 day
  - 60% in 2 days

Chen J, et al. J Allergy Clin Immunol Pract 2015;3:926-31.

Aspirin Therapy Post-Desensitization

- Typical initial dose of aspirin is 650 mg twice daily
- After 1-3 months, aspirin dose usually reduced to 325 mg twice a day
- Doses less than this rarely provide benefit for sinopulmonary disease
- Patients need to be maintained on aspirin therapy indefinitely

Urgent Need for Aspirin

- Many studies have performed "aspirin desensitizations" in patients with histories of both cutaneous and respiratory reactions to aspirin, all with similar high rate of success (>80%)
- Patients with chronic urticaria have higher failure rate
- Surprisingly good results in AERD patients
  - Likely due to lower doses used

Wong JT et al. J Allergy Clin Immunol 2000;105:997-1001.
Silberman S et al. Am J Cardiol 2005;95:509-10.
Rossini R et al. Am J Cardiol 2008;101:786-9.

Are These Really Desensitizations?

- Patients in these studies never had confirmatory challenges to determine if truly allergic to aspirin
- **Whether** these protocols truly **induce drug tolerance or are** simply a multi-stepped **graded challenge is unclear**

Rapid Aspirin "Desensitization" Protocol

Table 13. Rapid Aspirin Challenge/Desensitization Protocol for Patients With Coronary Artery Disease Requiring Aspirin[366]

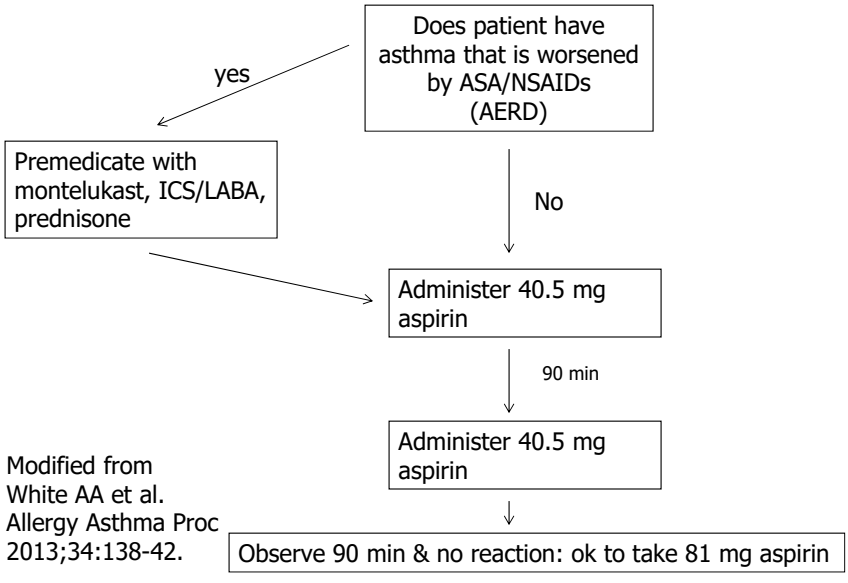
Time[a]	Aspirin dose, mg
0	0.1
15	0.3
30	1
45	3
60	10
75	20
90	40
105	81
120	162
135	325

[a] Dosing interval shown is 15 minutes but may also dose every 20 minutes with premedication with oral antihistamine.

Solensky R, Khan DA et al. Ann Allergy Asthma Immunol 2010;105:273e1-e78.

Adapted from: Wong JT et al. J Allergy Clin Immunol 2000;105:997-1001.

Aspirin Challenge for Acute Cardiac Needs



Modified from White AA et al. Allergy Asthma Proc 2013;34:138-42.

UT Southwestern Protocol for Urgent ASA Needs

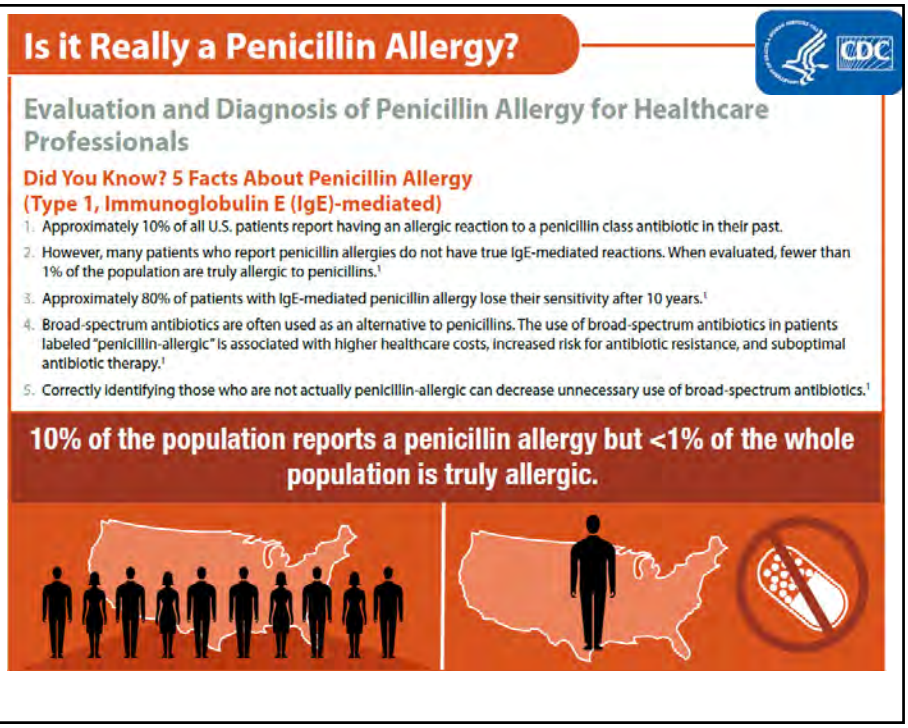
Historical Reaction to ASA/NSAID	Dosing strategy	Pretreatment
AERD	Split dosing, give 40.5 mg and wait 90 minutes then give another 40.5 mg	1 hr before: 40 mg prednisone, montelukast 10 mg, ICS/LABA
ASA-induced urticarial or angioedema	81 mg ASA	None
Vague	81 mg ASA	None
SJS or TEN to NSAID (not ASA)	81 mg ASA	None

Updates on Penicillin Allergy Disease

Why Testing for PCN Allergy Matters?

- PCN allergic patients receive higher rates of vancomycin, fluoroquinolones, clindamycin, and aztreonam
- β-lactams superior to vancomycin for MSSA
- β-lactams less failure for gram neg bacteremia
- PCN allergy labeled patients have longer hospital stays and are readmitted more frequently

Chen JR, Khan DA. Current Allergy Asthma Rep 20177:40.



AAAAI Position Statement

American Academy of Allergy Asthma & Immunology

Penicillin Allergy Testing Should Be Performed Routinely in Patients with Self-Reported Penicillin Allergy

Penicillin Allergy in Antibiotic Resistance Workgroup

Lang, DM, Castells MC, Khan DA, Macy EM, Murphy AW.

J Allergy Clin Immunol Pract 2017;5:333-4.

Original Article

A Proactive Approach to Penicillin Allergy Testing in Hospitalized Patients

Justin R. Chen, MD[a], Scott A. Tarver, PharmD[b], Kristin S. Alvarez, PharmD[b], Trang Tran, PharmD[b], and David A. Khan, MD[a] *Dallas, Tex*

J Allergy Clin Immunol Pract 2017 (in press).

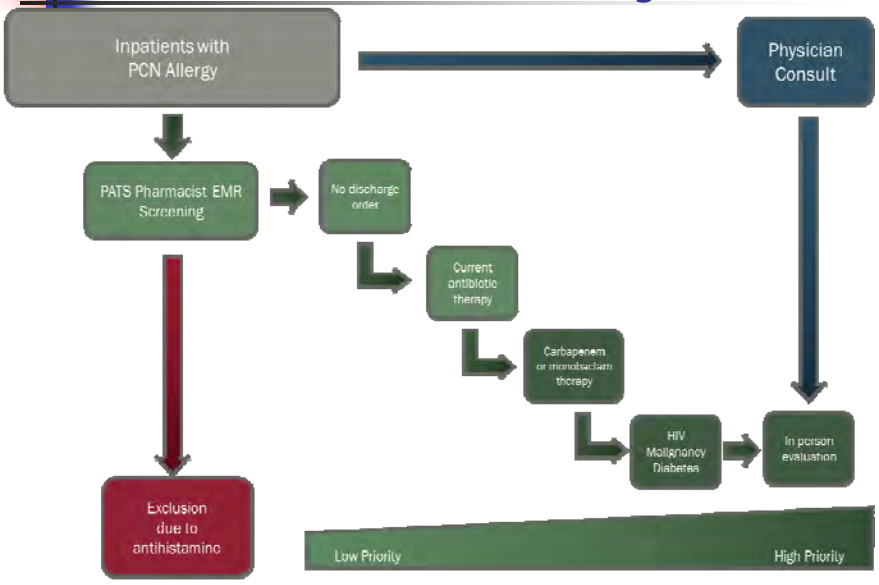
Penicillin Allergy Testing Service (PATS)

- Established November 2014
- Collaboration between the UT Southwestern Division of Allergy & Immunology and Pharmacy Services at Parkland
- Utilizes a dedicated allergy pharmacist trained by A&I physicians
- Patients seen by referral from the primary team or through a selection process to be discussed in this presentation

Why a Pharmacist?

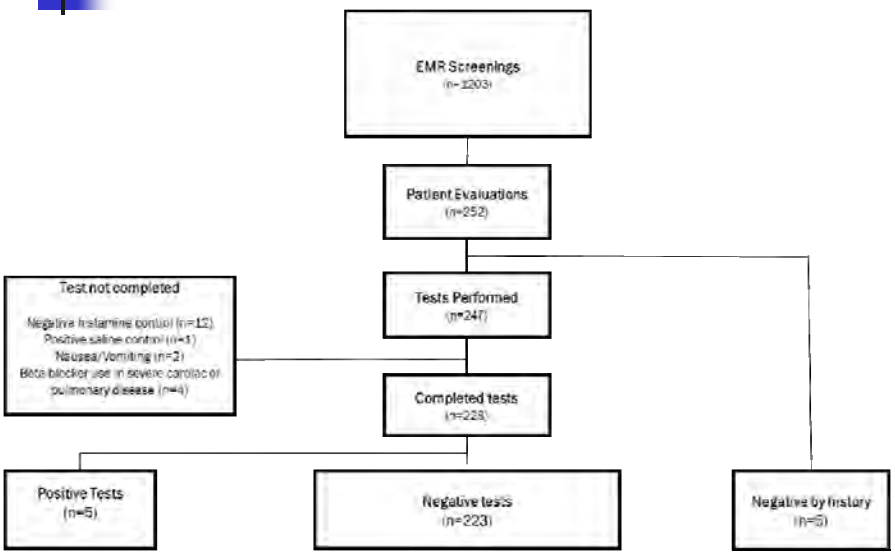
- Parkland Pharmacy Dept received funding from Medicaid 1115 waiver
- **Other Reasons**
  - highly educated/trained med professionals
  - greater understanding of drugs/names/adverse effects
  - used to protocols
  - accustomed to reviewing medications in detail
  - well equipped to educate patients after completion of testing
  - may also advise physicians on optimal posttest antibiotics

Selection of Inpatients to Undergo Penicillin Testing



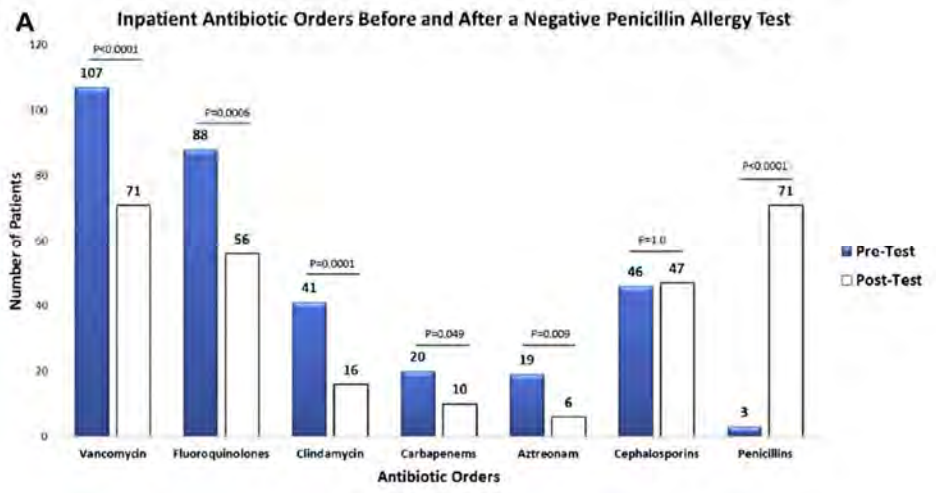
Chen J et al. J Allergy Clin Immunol Pract 2017 (in press).

Outcomes of Proactive In Patient Penicillin Testing



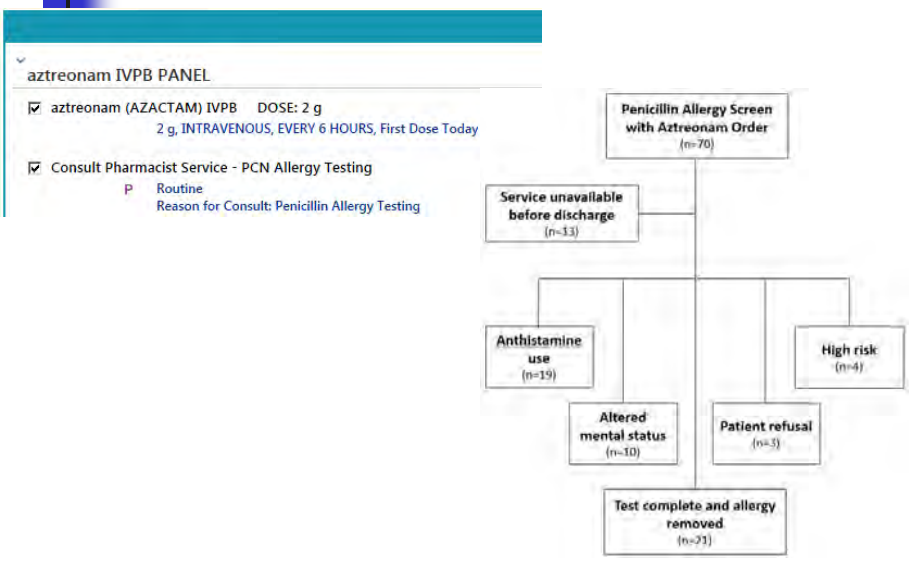
Chen J et al. J Allergy Clin Immunol Pract 2017 (in press).

Changes in Antibiotics Due to Penicillin Allergy Testing



Chen J et al. J Allergy Clin Immunol Pract 2017 (in press).

Reflexive Penicillin Allergy Testing with In-Hospital Aztreonam Use



Chen J et al. Abstract AAAAI 2017

Reflexive Penicillin Allergy Testing with In-Hospital Aztreonam Use

- Patients tested negative accumulated 46.8 inpatient days of penicillin and 25 days of cephalosporins
  - Direct cost $326.47
- Projected cost savings compared with use of aztreonam: 82-92%
- To show cost savings, targeting expensive antibiotics like aztreonam is a reasonable strategy

Are Penicillin Skin Tests Needed in Children?

Research

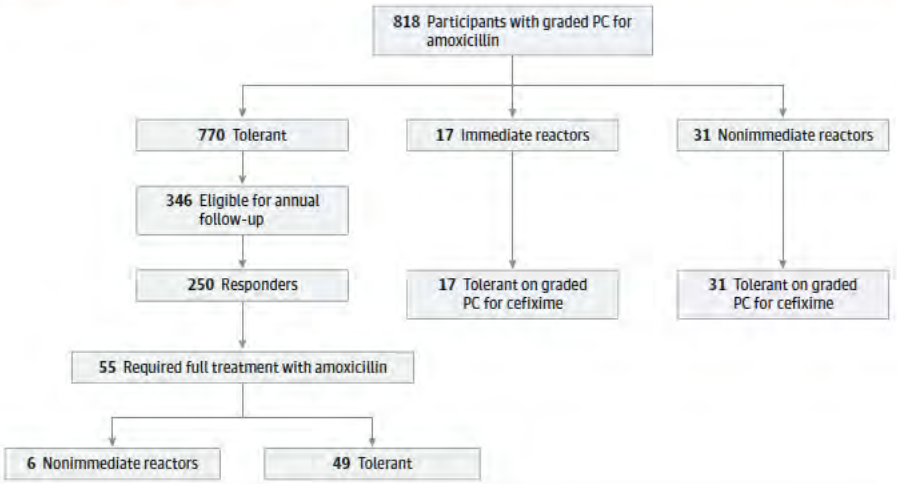
Original Investigation

Assessing the Diagnostic Properties of a Graded Oral Provocation Challenge for the Diagnosis of Immediate and Nonimmediate Reactions to Amoxicillin in Children

Christopher Mill, MPH; Marie-Noël Primeau, MD; Elaine Medoff, MD; Christine Lejtenyi, MD; Andrew O'Keefe, MD; Elena Netchiporouk, MD; Alizee Dery, BSc; Moshe Ben-Shoshan, MD, MSc

Mill C, et al. JAMA Pediatr. 2016;170(6):e160033.

Figure 1. Flow Diagram of 818 Patients With a Graded Oral Provocation Challenge (PC) for Amoxicillin

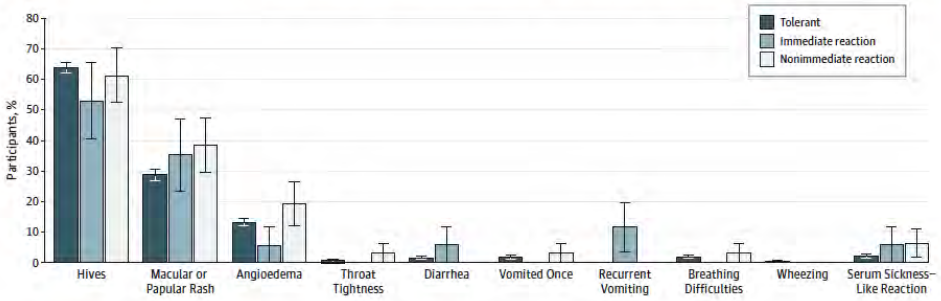


Challenge Protocol: 10% dose then 20 min later 90% dose amoxicillin

All immediate and delayed reactions were mild (few cases of SSL reactions)

59

Figure 2. Clinical Characteristics of Participants According to Results on a Graded Oral Provocation Challenge for Amoxicillin



The 3 groups were comparable regarding most clinical characteristics of the suspected reactions. Error bars indicate standard error.

No features predicted immediate reactions to challenge.

Children with histories of rashes persisting > 7 days (OR=4.8) and those with a parental history (OR=3.0) were more likely to have a delayed reaction

60

Other Studies of Challenge Only Penicillin Testing

The role of penicillin in benign skin rashes in childhood: A prospective study based on drug rechallenge

Jean-Christoph Caubet, MD,[a] Laurent Kaiser, MD,[b] Barbara Lemaitre, MS,[b] Benoit Fellay, PhD,[c] Alain Gervaix, MD,[a] and Philippe A. Eigenmann, MD[a] *Geneva and Fribourg, Switzerland*

J Allergy Clin Immunol 2011;127:218-22.

Original Article

Oral Challenge without Skin Testing Safely Excludes Clinically Significant Delayed-Onset Penicillin Hypersensitivity

Ronit Confino-Cohen, MD, Yossi Rosman, MD, Keren Meir-Shafrir, MD, Tali Stauber, MD, Idit Lachover-Roth, MD, Alon Hershko, MD, and Amon Goldberg, MD *Kfar Saba and Tel-Aviv, Israel*

J Allergy Clin Immunol Pract 2017;5:669-75

Amoxicillin challenge without penicillin skin testing in evaluation of penicillin allergy in a cohort of Marine recruits

Mark H. Tucker, MD, Chad M. Lomas, MD, Nanda Ramchandar, MD, and Jeremy D. Waldram, MD

J Allergy Clin Immunol Pract 2017;5:813-4.

When to Skip Penicillin Skin Tests

- Histories not consistent with hypersensitivity (e.g. headache, GI upset)
- Children with amoxicillin reactions
- Benign rashes?
  - Only Australia has penicillin challenge without skin testing as part of a guideline
  - Reasonable but is it medicolegally sound?

Persistence of Penicillin Allergy in the Medical Record

- While penicillin allergy testing/challenge is an effective tool for proving tolerance to penicillin, the drug allergy listed in the medical record determines whether patients receive penicillins in the future
- Multiple studies have shown that penicillin allergy labeling may persist in 36-49% of patients with negative penicillin allergy tests

Warrington RJ, et al. *Allergy Asthma Proc.* 2000;21(5):297-9.
Gerace KS, Phillips E. *J Allergy Clin Immunol Pract.* 2015;3(5):815-816.
Rimawi RH, Shah KB, Cook PP. *Journal of Hospital Medicine.* 2013;8:615–618.

Parkland

UTSouthwestern Medical Center

Effectiveness of Interventions to Maintain Penicillin Allergy Label Removal as Part of an Inpatient Penicillin Allergy Testing Protocol

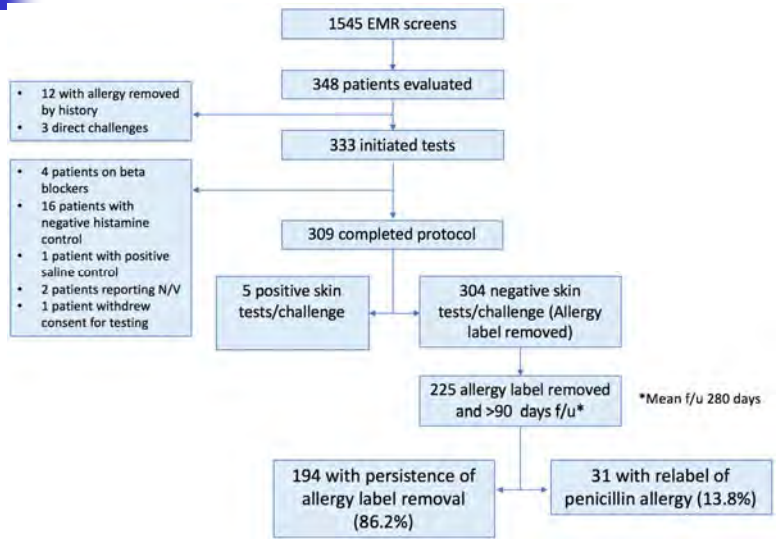
Sheenal V. Patel, MD, Scott A. Tarver, PharmD, Kristin S. Alvarez, PharmD, Kristin Lutek, PharmD, James Schlebus, David A. Khan, MD

Oral Abstract AAAAI 2017

Interventions to Maintain Penicillin Allergy Label Removal

1. Pharmacist counseling at the time of negative test, active removal of allergy, procedure note documentation (began November 2014)
2. Pharmacist counseling at post-discharge visit (telephone call or face to face visit) (began June 2015)
3. Best practice advisory (pop-up alerts) in the electronic medical record alerting providers to negative penicillin allergy test result on attempt to add back allergy (began November 2015)
4. Wallet card given to patient at time of negative test documenting negative penicillin allergy testing (began April 2016)

Results



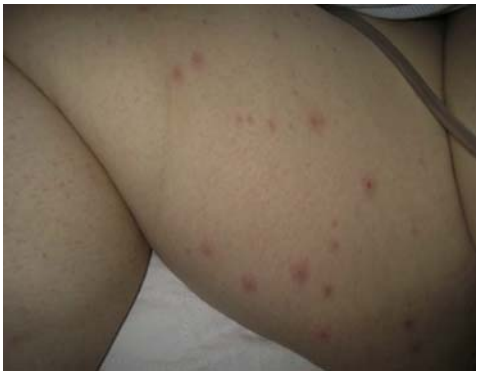
Lessons Learned

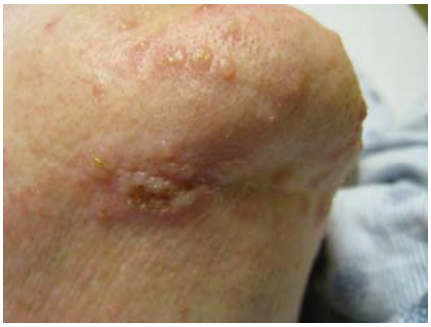
- Partnering with hospital-based employees in leadership positions makes things happen quicker
  - Pharmacy partnership was key to our success
- Promoting penicillin allergy as part of antibiotic stewardship is important
  - Helps administrators choose good medical care without need to focus on $$
- Proving cost savings requires longer follow up or cherry-picking patients
- Allergists can be integral to an inpatient testing protocol without actually being in the hospital

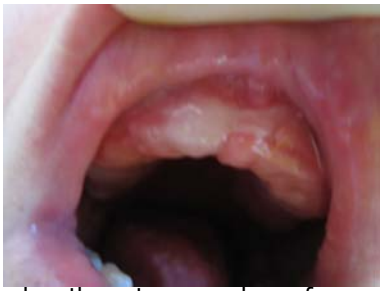
Tales from the Great State of Texas

"Fluconazole Allergy"

- A 49-year-old woman with diabetes admitted due to a wound infection after inguinal hernia repair. She received a dose of **cefazolin** intraoperatively followed by **ticarcillin/clavulanate** and **vancomycin**. In addition she was started on **fluoxetine** for depression and **hydrocodone** as needed for pain. Three days later, cultures obtained at surgery revealed methicillin resistant *Staphylococcus aureus* and the ticarcillin/clavulanate was discontinued and she remained on vancomycin. On post-operative day nine, she received a dose of **fluconazole** for oral thrush and 30 minutes later she noted diffuse itching. Within hours she developed a diffuse, painful vesicular eruption. The Allergy & Immunology service was consulted for evaluation of fluconazole allergy.







Physical examination was notable for scattered erythematous papules, a few targetoid lesions , and tense blisters involving the arms, legs, palms, labia, and tongue with a few erosions on the gingiva.

????

- What kind of drug reaction is this?
  - SJS?
- What drug was the culprit?
  - Fluconazole?

Potential Culprits

- Onset of pruritus within 30 minutes of fluconazole may have been due to an IgE-mediated reaction, however the appearance of vesicular reactions within hours would make it highly unlikely that the fluconazole was the culprit drug
- beta-lactams were considered unlikely due to their discontinuation 6-9 days prior
- Hydrocodone is a common cause of pruritus from pseudoallergic reactions but vesicular eruptions would be rare
- Fluoxetine is also rarely the cause of vesicular drug eruptions
- Vancomycin is the most common cause of linear IgA bullous disease which may also affect mucosal surfaces and may also cause DRESS

Case Epilogue

- Stevens Johnson syndrome was also a consideration due to the targetoid lesions and involvement of 2 mucosal sites.
- We recommended discontinuation of vancomycin.
- CBC with differential and comprehensive metabolic panel were normal
- Skin biopsy was performed with immunofluorescence and was consistent with a diagnosis of **linear IgA bullous dermatitis**
- She was started on systemic steroids due to worsening of the eruptions and painful lesions and had rapid improvement and eventual resolution of her symptoms

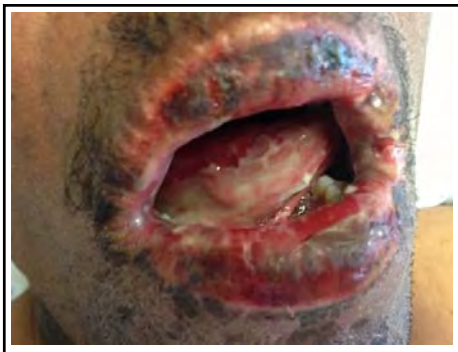
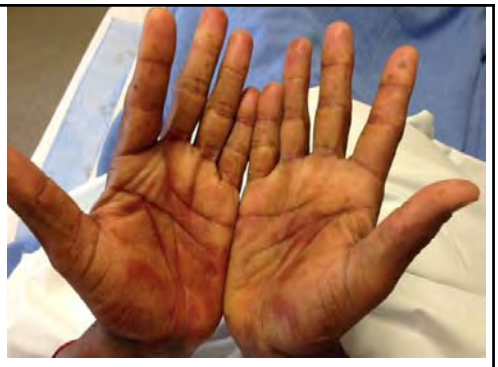
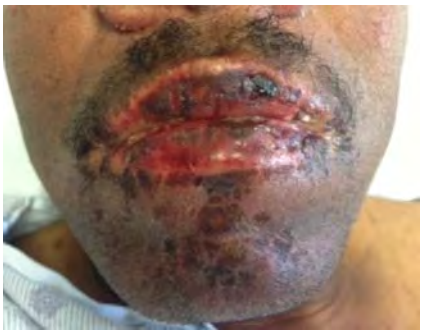
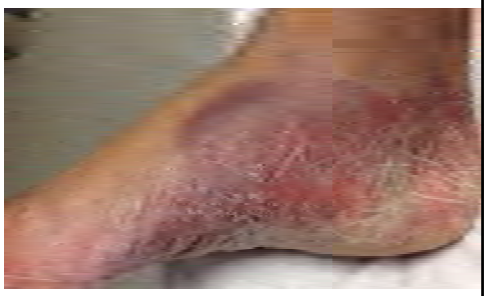
Linear IgA Bullous Dermatosis

- Most commonly with vancomycin
- Other medications
  - Captopril, furosemide, lithium, TMP/SMX
- Tense blisters that mimic bullous pemphigoid
- Generally occurs within 24 hours to 15 days following administration of the offending drug
- Vancomycin-induced LAD is not dose dependent and the severity of the reaction does not correlate with serum vancomycin levels

Navi D, et al. Dermatol Online J 2006;12:12.

"Happy 40th Birthday!"

- A man who just turned 40 wanted to make a change in his life and decided to take an antibiotic to "clean me out".
- He acquired some penicillin from a local street vendor of drugs
- A few days after taking his penicillin he developed a diffuse rash

?????

- What kind of Reaction is This?
  - SJS?
- What was the cause?
  - Penicillin

Case Epilogue

- Patient reported a history of Bactrim allergy resulting in hyperpigmented patches on hands and penis
- This reaction started at same places but became more widespread
- Skin biopsy consistent with fixed drug eruption
- "Penicillin" was likely sulfamethoxazole

Fixed Drug Eruptions

- Common type of drug eruption but often unrecognized as such
  - Considered a T-cell mediated reaction
- Typically develops 1-2 weeks for initial reaction but sooner with later exposures
- Occur in same location with each subsequent exposure to drug
- Pleomorphic
  - eczema
  - erythematous papules
  - hyperpigmented areas
  - bullous
  - Urticarial
- May be diffuse with mucosal involvement
- Examples
  - Tetracycline, NSAIDs, carbamazepime

A Case of Chronic Hives

- A 25 yo F notes a > 2 yr history of daily urticaria and episodic angioedema, no physical triggers
- Prior laboratories have been unrevealing
- She has failed high doses of antihistamines including doxepin, hydroxyzine, cetirizine, fexofenadine as well as ranitidine, montelukast and alternative agents including dapsone and hydroxychloroquine
- She does feel that her urticaria flares in her premenstrual phase and will actually improve or go away several days after her period

????

- Could her CU be related to her hormones?
- How to test?
- How to treat?

Progestogen Hypersensitivity in 24 Cases: Diagnosis, Management, and Proposed Renaming and Classification

Dinah Foer, MD[b,*], Kathleen M. Buchheit, MD[b,*], Antonio Rosario Gargiulo, MD[c], Donna Marie Lynch, BSN, RN[b], Mariana Castells, MD, PhD[b,*], and Paige G. Wickner, MD, MPH[b,*] *Boston, Mass*

TABLE I. Characteristics of patients with PH (N = 24)

	Value
Medical history	
Age of onset (y), mean (range)	29.7 (13-48)
Endogenous progesterone trigger, %	42
Exogenous progestogen trigger, %	58
	25 OCP
	25 IVF
	4 Emergency contraception
	4 IUD
Relation to menses, %	75% within week before menses
Atopy*	46%
Symptoms, %	
Dermatologic†	54 Dermatitis‡
	54 Urticaria/angioedema
Asthma	13
Anaphylaxis	8
Positive skin testing, %	50

Diagnostic modality	Concentration progesterone (mg/mL)
Skin test	50
Intradermal	0.005
	0.05
	0.5

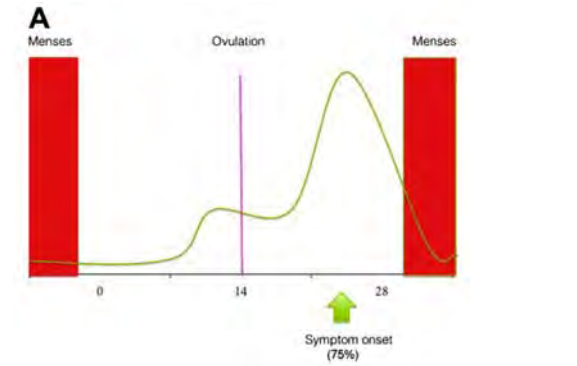
TABLE IV. Classification of PH presentation

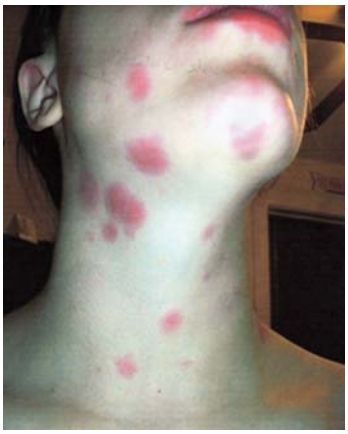
Classification	Triggers	Manifestation
Endogenous		
Primary	Menses	Perimenstrual symptoms
	Pregnancy	Monthly symptoms after completion of non-IVF pregnancy
Exogenous		
Secondary	Supplemental progestogen*	Symptoms only during supplemental progestogen administration
Mixed†	Supplemental progestogen*	Took supplemental progestogen, then develops perimenstrual symptoms in future

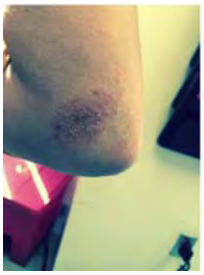
J Allergy Clin Immunol Pract 2016;4:723-9.

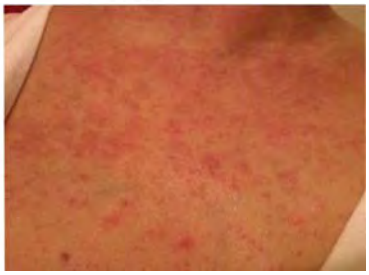
Progesterone skin testing

- Skin prick
  - 50 mg/ml
- Intradermal
  - 0.005, 0.05, 0.5 mg/ml diluted in benzyl alcohol or olive oil
- Irritant reactions can be seen with both diluents









Prieto-Garcia A et al. Fertil Steril. 2011 Mar 1;95(3):1121
Foer D et al. J Allergy Clin Immunol Pract 2016;4:723-9.

TABLE II. Slow oral desensitization protocol for a progestin

Day	Dose (based on progestin component)	Number of capsules × capsule dose per day	Total daily dose
Day 1	1.25 μg in AM, 2.5 μg in PM	1 × 1.25 μg; 2 × 1.25 μg	3.75 μg
Day 2	2.5 μg in AM, 12.5 μg in PM	2 × 1.25 μg; 1 × 12.5 μg	15 μg
Day 3	12.5 μg in AM, 25 μg in PM	1 × 12.5 μg; 2 × 12.5 μg	37.5 μg
Day 4	37.5 μg in AM, 37.5 μg in PM	3 × 12.5 μg; 3 × 12.5 μg	75 μg
Day 5	50 μg in AM, 75 μg in PM	1 × 50 μg; 1 × 50 μg + 2 × 12.5 μg	125 μg
Day 6	250 μg	2 × 125 μg	250 μg
Day 7	500 μg	4 × 125 μg	500 μg
Day 8	500 μg	4 × 125 μg	500 μg
Day 9	1 mg	1 × 1 mg	1 mg

Target dose for this protocol: Norethindrone 1 mg/ethinyl estradiol 0.02 mg.

TABLE III. IM progesterone desensitization protocol for IVF

Time	Dose (IM progesterone 50 mg/mL)
0 min	1 mg
30 min	2 mg
60 min	4 mg
90 min	8 mg
120 min	16 mg
150 min	18.5 mg
Total dose	50 mg
Target daily dose	Intravaginal progesterone 90-180 mg (ie, 8% gel once or twice daily) or IM progesterone 50-75 mg daily, depending on IVF protocol

Patients were premedicated with H1 and H2 blockers, completed in outpatient infusion center with registered nurse trained in desensitization.

85

TABLE V. Summary of patient management and outcomes

Strategy	Medical management (N = 13)	Desensitization (N = 11)
Method	Hormone-based therapies (54%)	Oral protocol (73%)
	Nonhormonal therapies* (62%)	IM protocol (27%)
Outcome	Symptom improvement (92%)	Symptom improvement: dermatologic (88%); asthma/anaphylaxis (100%)
		Tolerating IVF (3 of 3)
		Pregnancy (2 of 3)

*Includes patients comanaged on OCPs.

The 2 anaphylaxis pts tolerated the slow 9 day oral protocol?!

Foer D et al. J Allergy Clin Immunol Pract 2016;4:723-9.

86

Progestogen Hypersensitivity

- Autoimmune Progesterone Dermatitis is old term
- New term: Progestogen
  - Not all are due to progesterone
  - Some from synthetic derivatives
- Hypersensitivity
  - Not all dermatitis
  - Not all autoimmune

Case Epilogue

- Sera sent to University of Cincinnati with elevation of progesterone-specific IgE
- Referred to gynecology for treatment with GnRH agonist
- She received a dose of 11.25 mg of leuprolide (Lupron) but within a week was found to be pregnant
- Managed CU with antihistamines during pregnancy
- Started on omalizumab 300 mg every month in March 2016 with near complete control of hives
- Treated through a second pregnancy with omlaizumab

Aspirin Allergy?

- 39 yo F has a recent history of aspirin ingestion and within 20 minutes developed tongue numbness, tingling in her arms, chest pressure, and lightheadedness. She went to ED and was given another dose of aspirin and had worsening of her symptoms which resolved in 12-24 hrs
- Past history notable for latex allergy with contact urticaria, and rhinitis symptoms when exposed to powdered gloves
- Family history of CAD, HTN

Case Continued

- In light of subjective symptoms with aspirin (tongue numbness and lightheadedness) and low likelihood of true allergy a placebo controlled challenge was performed

Placebo Challenge Results

- 1 capsule (placebo) administered
  - 30 minutes later complained of tongue numbness
  - Physical exam normal
- 2 capsules (placebo administered) 15 minutes later
  - Tongue numbness increased and complained of lightheadedness (BP unchanged)
  - All symptoms spontaneously resolved after another 90 minutes

Aspirin Challenge

- Discussed results of placebo challenge and reassured her that her symptoms were not medication-induced and no sign of an allergic reaction
- Proceeded to open challenge with 325 mg aspirin
- Observed for an hour with no symptoms

Placebo Controlled Drug Challenges

- The choice of performing an open vs. a placebo controlled challenge is based on reaction type and patient characteristics
- Clinical features suggestive of needing a placebo challenge
  - Subjective symptoms of drug allergy (e.g. pruritus)
  - Anxiety level of patient regarding challenge to particular drug
  - Multiple drug allergy patients

Placebo Controlled Drug Challenges

- Techniques
  - Opaque capsules
  - Inert filler
  - Multiple placebos in highly anxious patients
  - For history of delayed reactions, consider full day of placebo followed by active drug on separate day

Placebo Tools

Fagron

Symptoms with Placebo

- UT Southwestern study of drug challenges
- 19 patients underwent 21 placebo controlled challenges as an outpatient
- 57% of placebo challenges resulted in symptoms
- Signs/symptoms
  - Flushing
  - Pruritus
  - Tongue numbness
  - Throat tightness

Kao L et al. Ann Allergy Asthma Immunol 110 (2013) 86e91

Reactions to Placebo

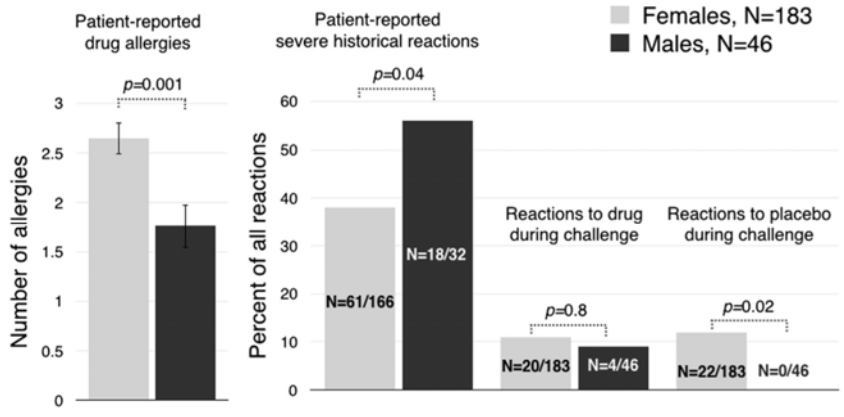


FIGURE 1. Analysis of patients' characteristics by sex.

Iammatteo M et al. J Allergy Clin Immunol Pract 2017;5:711-7.

Tips for the "Placebo Talk"

- Validate their reactions are legitimate
- Reassure them that anxiety is normal with drug challenges
- Inform them that anxiety reactions can mimic drug allergy and make it hard for you to discern
- Discuss that placebo challenges help you determine if reaction is anxiety or allergy
- Indicate that this is a routine practice

Tips for Management of Placebo/Subjective Reactions

- Examine the patient
- Take photos of "swelling"
- Reassure that reaction does not appear to be severe
- Delay next dose of challenge until symptoms resolved or nearly resolved
- Avoid medications
- Oxygen may be used if needed as a soothing measure

Multiple Drug Anaphylaxis Case

- 71 yo woman with *E. coli* UTI and bacteremia developed throat itching, swelling and dysphonia after 4th dose of ciprofloxacin
- Changed to meropenem and had similar reaction to 3rd dose
- History of multiple drug-induced anaphylaxis with throat closure and dysphonia including penicillin, cephalexin, sulfonamides, tetracycline and clarithromycin

Khan DA. Ann Allergy Asthma Immunol 110 (2013) 2e6.

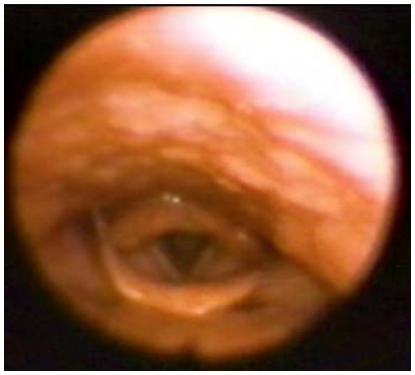
Case

- Further questioning
  - No other symptoms with reactions
  - All symptoms localized to throat
  - No witnessed orofacial swelling

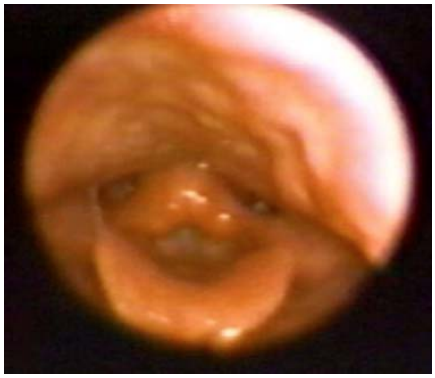
Case

- After baseline laryngoscopy, open ciprofloxacin IV challenge performed
- 15 minutes later developed throat itching, tightness and dysphonia
  - Symptoms identical to prior reactions
- Laryngoscopy showed paradoxical adduction of vocal cords with inspiration
- Patient informed about findings, taught throat relaxation methods and "anaphylactic" symptoms aborted in 5 minutes

Vocal Cord Dysfunction (VCD)



Normal glottis



Adduction of vocal cords during VCD attack

Drug-Induced Vocal Cord Dysfunction

- Histories usually described as “anaphylaxis”
- Symptoms localized to throat
- May have subjective swelling of lips/tongue but **lack objective evidence of orofacial swelling**
- May have multiple drugs involved
- Fiberoptic laryngoscopy is another useful tool in evaluating “drug allergy” patients

Khan DA. Ann Allergy Asthma Immunol 110 (2013) 2e6.

Conclusions

- Pharmacogenomics is still evolving in drug allergy
- Approach to aspirin allergy varies by urgency and nature of reaction but both ASA challenges and desensitizations can be done in the office
- Allergists are important to stamp out "Penicillin Allergy Disease"
- Ability to recognize patterns of cutaneous drug reactions will aid in timely and correct diagnosis and management of drug allergic reactions
- Placebo challenges are very helpful for subjective drug reactions