

Penicillin Allergy and *C. diff.* Infections

N. Franklin Adkinson, Jr., MD

Professor of Medicine, Johns Hopkins School of Medicine [1973]

VP for Medical Affairs, AllerQuest LLC [2005]

Penicillin Allergy Story

- Penicillin family of antibiotics – most common cause of drug allergy
- About 10% of US patients report having had penicillin allergy
- Most patients labeled with “penicillin allergy” never receive a penicillin-family antibiotic again
- Concern is risk of acute, potentially life-threatening *anaphylaxis*
 - Caused by allergic antibodies (IgE), diagnosed by skin testing
 - IgE disappears slowly over time (80% negative over 10 years)
 - Many penicillin reactions involve rashes not caused by IgE
- Bottom-line truth: when evaluated by skin testing, fewer than 1% of the population is truly allergic to penicillins (positive skin tests)

Medical Consequences of “Penicillin Allergy” Label

- Personal health consequences:
 - Higher healthcare costs with longer hospital stays
 - Suboptimal antibiotic therapy, with poorer outcomes
 - Increased antibiotic resistance
- Broad-spectrum antibiotics are often used as alternatives to the penicillin family
 - Leads to increased antibiotic-resistant infections, as shown in two large studies:

Population Studied	Study	<i>C. difficile</i> % Increase	MRSA % Increase	VRE % Increase
51,582 US inpatients	Macy and Contreras 2014 ¹	23%	14%	30%
301,399 UK outpatients	Blumenthal et al. 2019 ²	26%	69%	Not calculated

Abbreviations: MRSA, methicillin-resistant *Staphylococcus aureus*; VRE, vancomycin-resistant *Enterococcus*

1. Macy E, Contreras R. J Allergy Clin Immunol. 2014;133(3):790-6.
2. Blumenthal KG, et al. Br Med J. 2018;361:k2400.

A Simple Solution: Skin test and “delabel”

>95% pts now labeled with “penicillin allergy”

- **GOOD NEWS**

- Allergists know how to do this: skin test with “major determinant” (PRE-PEN) and the only available “minor determinant” (penicillin G), and then do an observed challenge with amoxicillin—about 97% accurate

- **BAD NEWS**

- Many (most) allergists don't do this because of difficulties:
 - Pen G not available in skin-testing concentrations
 - Oral challenge is time-consuming, and may be resisted by patients
 - 2-3 hour procedure unmanageable
 - Allergists awaiting “minor determinant mixture” to assure comprehensive testing

Response from AllerQuest LLC

- Formed by 3 allergists and a pharmacologist in 2005 to bring PRE-PEN back to market after a 5-year lapse (2003-2008)—SUCCESSFUL!
- Now our objective is to bring forward the “minor determinants” for comprehensive skin testing, without the need for an observed oral challenge—a kit, tentatively named “PRE-PEN Plus”
- Successful clinical trial in 455 history-positive patients soon to be published (JACI-IP 2019)—NPV >97%
- NDA application to FDA now under review

Other GOOD NEWS to look forward to:

- FDA approval for PRE-PEN Plus kit, which will allow efficient and comprehensive testing for penicillin allergy in hospitals and clinics across the US and elsewhere
- Increasing “delabeling” of the 30+ million Americans now falsely labeled as allergic to penicillin, facilitating
- Antimicrobial stewardship, with personal and public health benefits, including:
 - Slowing of spread of resistant organisms such as *C. difficile*,
 - Fewer constraints on appropriate antimicrobial treatments
 - Improved infectious outcomes for patients and the public health

Centers for Disease Control: “Is It Really a Penicillin Allergy?”

1. Approximately 10% of all U.S. patients report having an allergic reaction to a penicillin class antibiotic in their past.
2. However, many patients who report penicillin allergies do not have true IgE-mediated reactions. When evaluated, fewer than 1% of the population are truly allergic to penicillins.¹
3. Approximately 80% of patients with IgE-mediated penicillin allergy lose their sensitivity after 10 years.¹
4. Broad-spectrum antibiotics are often used as an alternative to penicillins. The use of broad-spectrum antibiotics in patients labeled “penicillin-allergic” is associated with higher healthcare costs, increased risk for antibiotic resistance, and suboptimal antibiotic therapy.¹
5. Correctly identifying those who are not actually penicillin-allergic can decrease unnecessary use of broad-spectrum antibiotics.¹

1. Joint Task Force on Practice Parameters; American Academy of Allergy, Asthma and Immunology; American College of Allergy, Asthma and Immunology; Joint Council of Allergy, Asthma and Immunology. *Ann Allergy Asthma Immunol.* 2010;105(4):259-73.

Availability of Penicillin Skin Test Reagents

Necessary Reagents	Available in USA?	Ready to Use for Penicillin Skin Testing?
PRE-PEN [®] (penicilloyl-polylysine)	Yes	Yes
Minor determinant mixture with:		
• Penicillin G potassium	Yes	No
• Penicilloate	No	No
• Penilloate	No	No
Amoxicillin sodium	No	No

“A major reason that penicillin skin testing is underutilized is that it requires the use of off-label, non-FDA-approved products. An easy-to-use penicillin skin testing kit that includes unit doses of not only benzylpenicilloyl-poly-lysine [PRE-PEN] but also a minor determinant mixture containing penicillin G, penicilloate, penilloate, and amoxicillin would be a great advance in the evaluation of penicillin allergy in the United States.”

“...the authors encourage the expedited approval by the FDA of a penicillin skin test kit that includes benzylpenicilloyl-poly-lysine, penicillin G, penilloate, penicilloate, and amoxicillin (PRE-PEN Plus), without the requirement to perform penicillin challenges in skin test–positive patients.”

**Endorsed by the Board of Directors,
American Academy of Allergy, Asthma & Immunology**

Source: Park MA et al. J Allergy Clin Immunol. 2015 March;135(3):816-7.

Why Do We Need All Five Reagents?

Results from AllerQuest Study in 455 Patients
with Label of Penicillin Allergy

Skin Test Reagent	Positive Test Result (N = 63) n (%)
Total who reacted to PRE-PEN®	22 (34.9%)
Reacted to PRE-PEN only	2 (3.1%)
Reacted to PRE-PEN + MDM only	5 (7.9%)
Reacted to PRE-PEN + amoxicillin only	0
Reacted to PRE-PEN + MDM + amoxicillin	15 (23.8%)
Reacted only to MDM and/or amoxicillin	41 (65.1%)
Reacted to MDM only	24 (38.1%)
Reacted to amoxicillin only	4 (6.3%)
Reacted to MDM + amoxicillin only	13 (20.6%)
Total who reacted to MDM	57 (90.5%)
Total who reacted to amoxicillin	32 (50.8%)
<ul style="list-style-type: none">• Only 35% reacted to the only reagent on the market (PRE-PEN).• Thus 65% would be at risk of severe allergic reaction.	

PRE-PEN Plus™

A comprehensive, convenient, stable, and easy-to-use penicillin skin test kit, containing:

- PRE-PEN® (penicilloyl-polysine, the “major determinant”)
- MDM for Injection (minor determinant mixture), including:
 - Penicillin G potassium
 - Penicilloate
 - Penilloate
- Amoxicillin Sodium for Injection
- Diluents, tools, negative and positive controls