Drug Allergy: Antibiotics and Clinical Pathways

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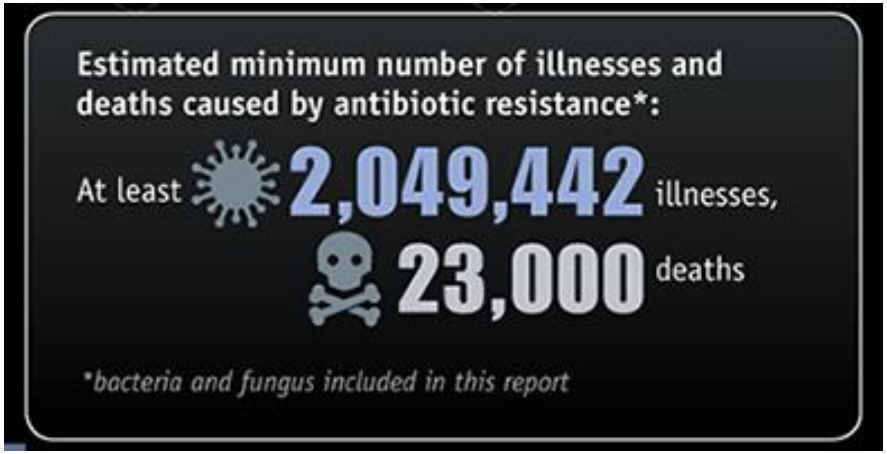
Disclosures

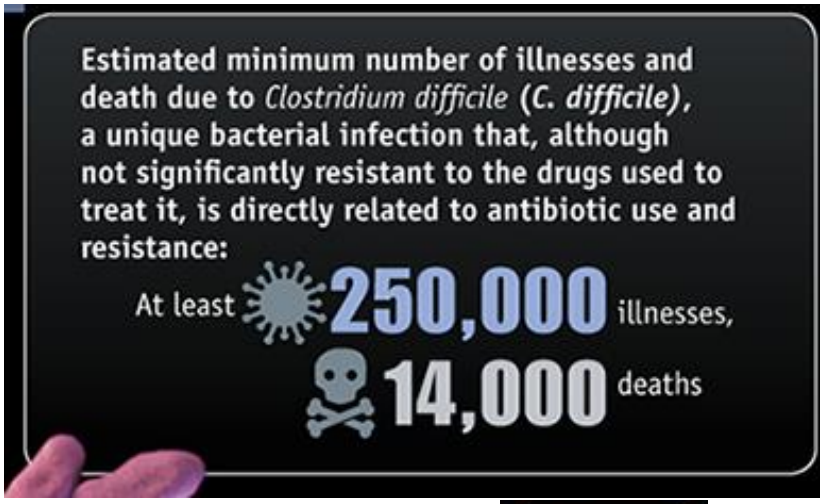
- None relevant to this talk

Objectives

- Improve knowledge of the role for skin testing and drug challenges in antibiotic allergy
- Incorporate antibiotic allergy clinical pathways into daily practice to optimize care

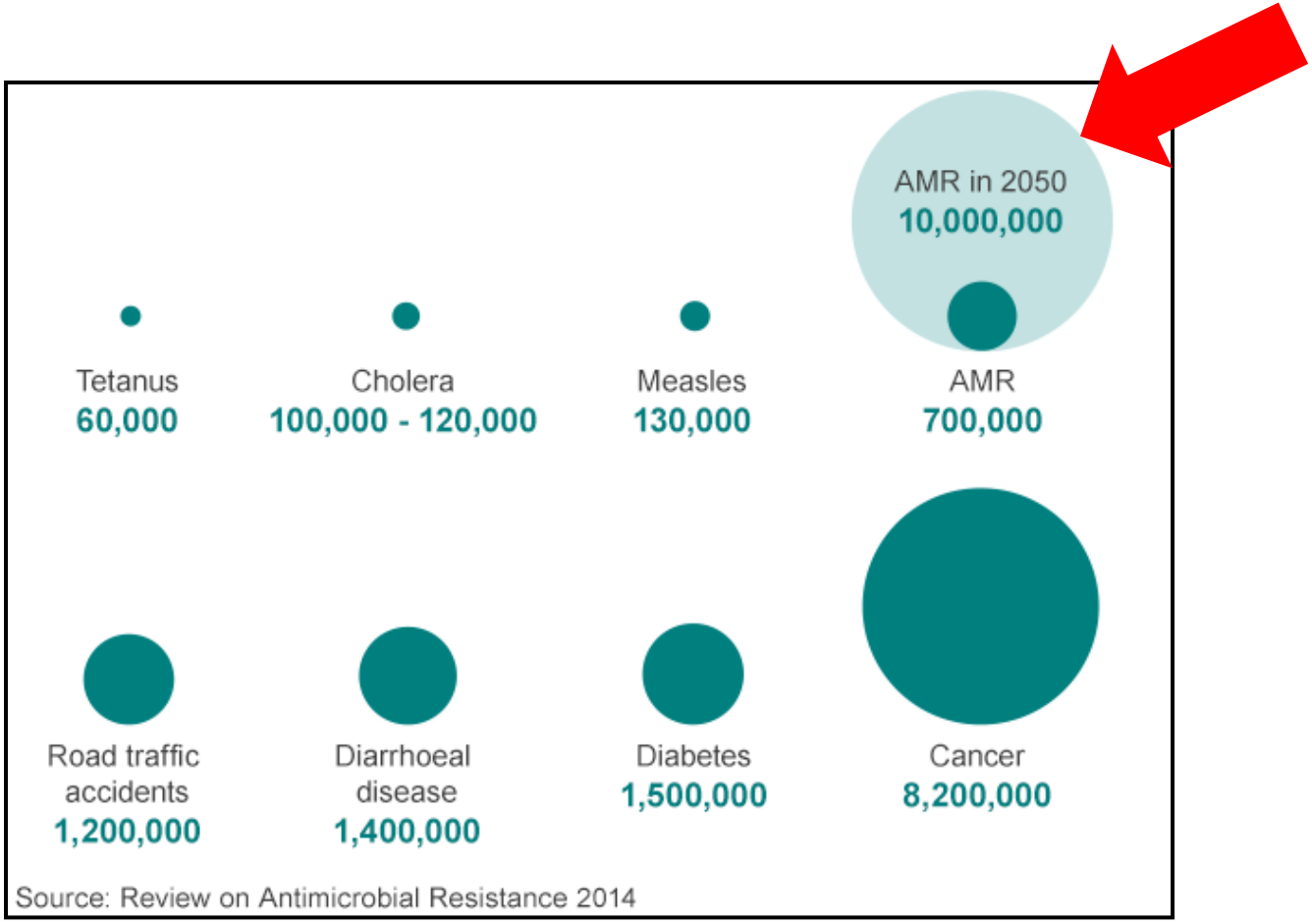
Antibiotic Resistance in the United States



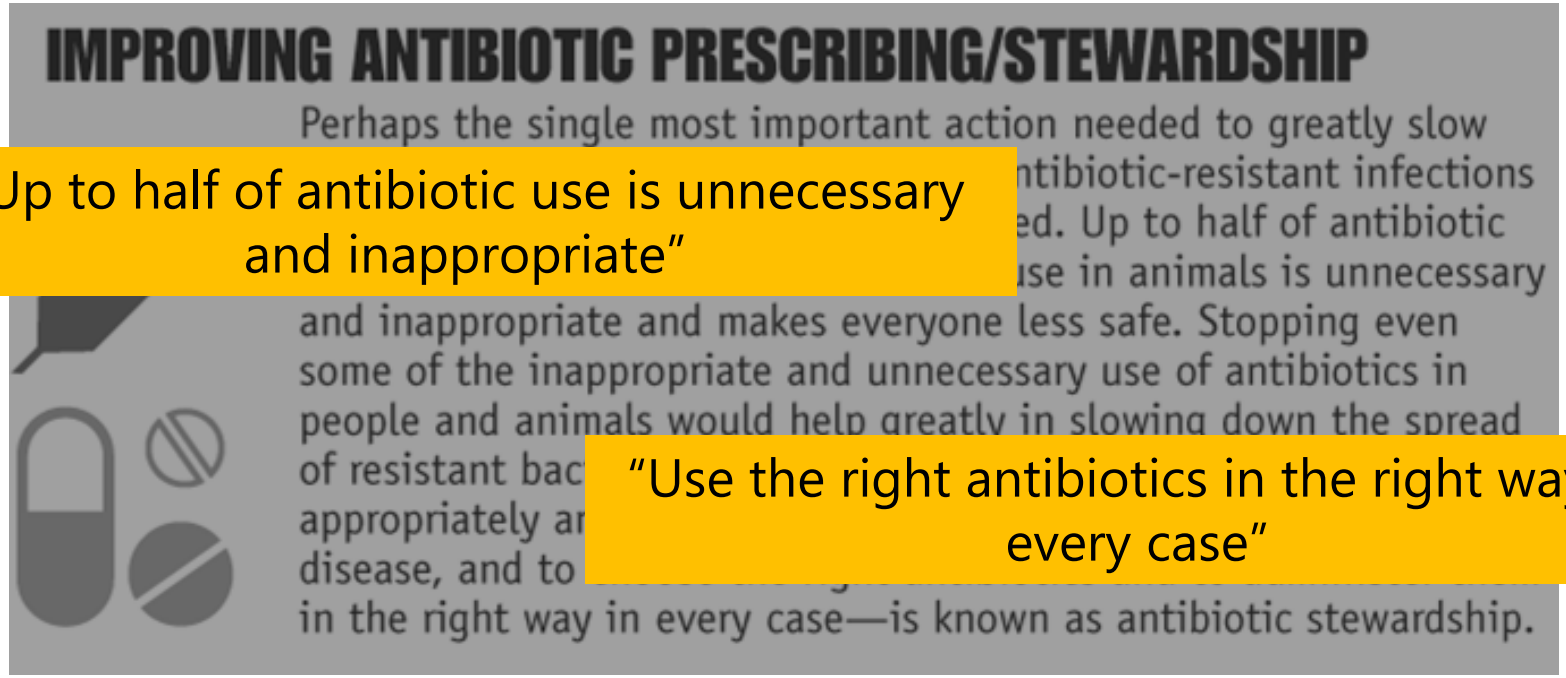


www.cdc.gov/drugresistance

Deaths Attributable to Antimicrobial Resistance



Critical Role of the Allergist



"Up to half of antibiotic use is unnecessary and inappropriate"

"Use the right antibiotics in the right way in every case"

www.cdc.gov/drugresistance

What Tools Do Allergists Have to Evaluate Patients with Drug Allergies?

- Proper Documentation of the Clinical History
- Skin Testing
- Drug Challenges and Desensitization
- Clinical Guidelines and Pathways

Evaluation of Drug Allergy is Difficult

- Clinical presentation is heterogeneous and can mimic many different pathophysiologic events
- Several drugs are often taken simultaneously
- Many factors besides the drugs can be involved
- History is often remote and poorly documented

JAMA Internal Medicine | Original Investigation

Development and Validation of a Penicillin Allergy Clinical Decision Rule

Jason A. Trubiano, MBBS, PhD; Sara Vogrin, MBBS, MBiostat; Kyra Y. L. Chua, MBBS, PhD; Jack Bourke, MBBS; James Yun, MBBS, PhD; Abby Douglas, MBBS; Cosby A. Stone, MD; Roger Yu, MD; Lauren Groenendijk, MD; Natasha E. Holmes, MBBS, PhD; Elizabeth J. Phillips, MD

- A validated point-of-care clinical decision rule
- Can be used by allergists and non-allergists to address the high burden of penicillin allergies, risk stratify and subsequently direct the appropriate de-labeling and prescribing strategies

JAMA Intern Med. 2020;180(5):745-752.

Methods

- A multicenter prospective antibiotic allergy-tested cohort of 622 patients was used for derivation and internal validation of a penicillin allergy rule
- Patients who reported a penicillin allergy underwent penicillin allergy testing
- Derived the model through backward stepwise logistic regression

PEN-FAST Clinical Decision Rule

Figure. PEN-FAST Penicillin Allergy Clinical Decision Rule

PEN	Penicillin allergy reported by patient	☐ *If yes, proceed with assessment*
F	Five years or less since reaction[a]	☐ **2 points**
A	Anaphylaxis or angioedema	
	OR	☐ **2 points**
S	Severe cutaneous adverse reaction[b]	
T	Treatment required for reaction[a]	☐ **1 point**
		☐ **Total points**

Interpretation

Points	
0	**Very low risk** of positive penicillin allergy test <1% (<1 in 100 patients reporting penicillin allergy)
1-2	**Low risk** of positive penicillin allergy test 5% (1 in 20 patients)
3	**Moderate risk** of positive penicillin allergy test 20% (1 in 5 patients)
4-5	**High risk** of positive penicillin allergy test 50% (1 in 2 patients)

The PEN-FAST clinical decision rule for patients reporting a penicillin allergy uses 3 clinical criteria of time from penicillin allergy episode, phenotype, and treatment required. A total score is calculated using PEN-FAST score in the upper panel, and interpretation for risk strategy is provided in the lower panel.

[a] Includes unknown.

[b] Forms of severe delayed reactions include potential Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms, and acute generalized exanthematous pustulosis. Patients with a severe delayed rash with mucosal involvement should be considered to have a severe cutaneous adverse reaction. Acute interstitial nephritis, drug induced liver injury, serum sickness and isolated drug fever were excluded phenotypes from the derivation and validation cohorts.

Validation of PEN-FAST

Table 4. Validation of PEN-FAST in Predicting a Positive Penicillin Allergy Test Result in All Derivation and Validation Cohorts

Cohort	No. of patients	No. (%) with positive finding[a]	Validation[b]				
			AUC (95% CI)	Sensitivity (95% CI), %	Specificity (95% CI), %	PPV (95% CI),%	NPV (95% CI), %
Melbourne, Australia	622	58 (9.3)	0.75 (0.68-0.81)	70.7 (57.3-81.9)	78.5 (74.9-81.9)	25.3 (18.8-32.7)	96.3 (94.1-97.8)
Perth, Australia	334	48 (14.4)	0.73 (0.66-0.81)	87.5 (74.8-95.3)	39.9 (34.1-45.8)	19.6 (14.5-25.6)	95.0 (89.4-98.1)
Sydney, Australia	80	27 (33.8)	0.78 (0.68-0.88)	70.4 (49.8-86.2)	84.9 (72.4-93.3)	70.4 (49.8-86.2)	84.9 (72.4-93.3)
Nashville, Tennessee	531	19 (3.6)	0.74 (0.62-0.86)	73.7 (4.8-90.9)	59.8 (55.4-64.0)	6.4 (3.5-10.4)	98.4 (96.3-99.5)

Abbreviations: AUC, area under the receiver operating characteristics curve; NPV, negative predictive value; PPV, positive predictive value.

[a] Indicates any penicillin allergy test with a positive finding.

[b] Based on a PEN-FAST score of at least 3.

PEN-FAST Summary

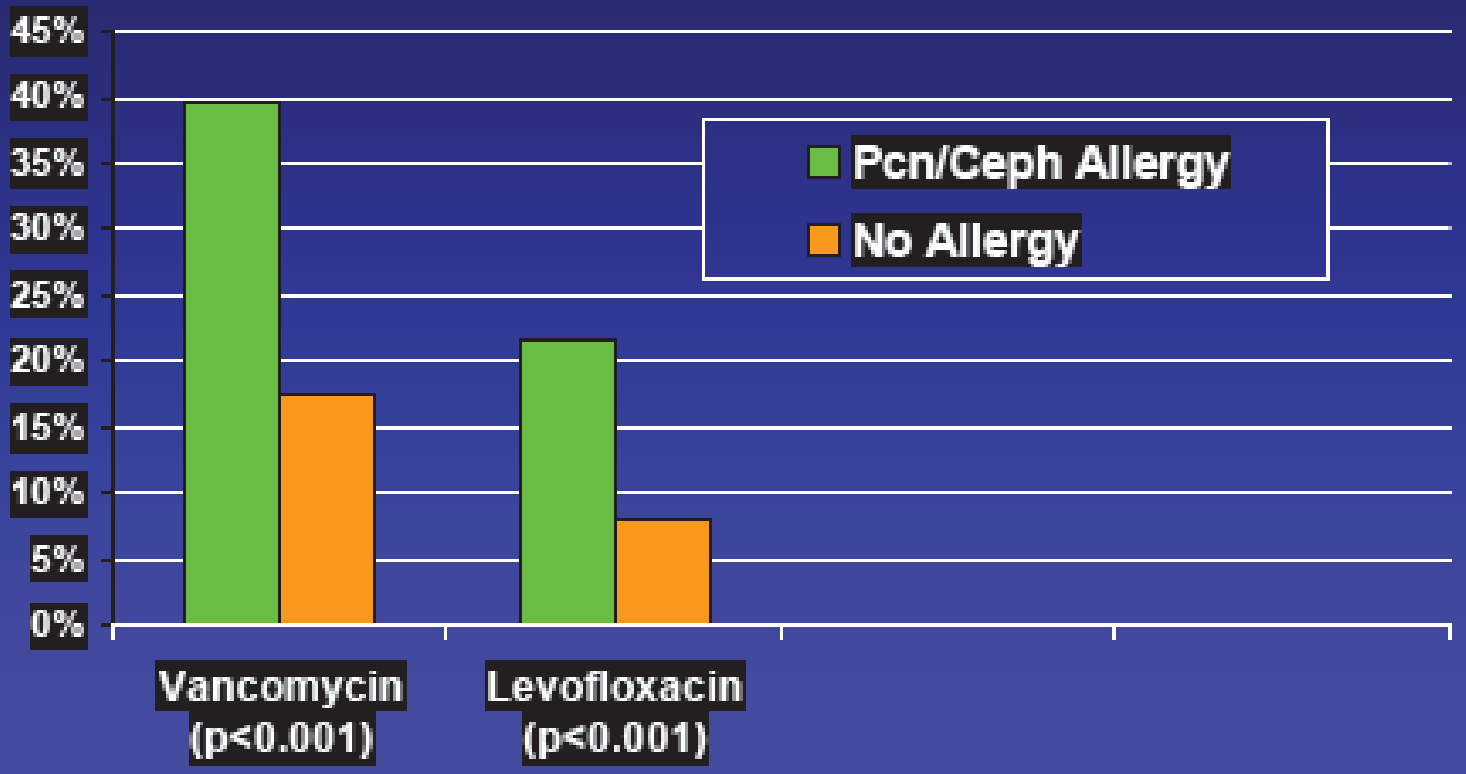
- PEN-FAST was found to be a practical tool with a high negative predictive value of 96%
  - uses penicillin allergy history to identify low-risk allergies in patients

- PEN-FAST may aid the risk stratification of patients with penicillin allergy to facilitate implementation of de-labeling strategies and safe β-lactam prescribing

Role of Skin Testing in Drug Allergy

- Skin testing is the most rapid, sensitive, and cost-effective testing modality for the detection of IgE-mediated disease
- Results within 15-20 minutes
- Patients can see the reaction and this helps them understand that they are/are not allergic to a given substance

Penicillin Allergy & Use of Broad-Spectrum Antibiotics



Lee CE, et al. *Arch Intern Med* 2000; 160:2819-22.

PCN Skin Testing: Effect on Antibiotic Use

Study	% Pcn ST Negative	Effect on Broad Spectrum Antibiotic Use (% of Patients)
Harris AD (1999)	86%	Vancomycin 25% → 0% Quinolones 27% → 14%
Arroliga ME (2003)	89%	Vanco/Quinolones 100% → 58%
Nadarajah K (2005)	92%	Vancomycin 77% → 8% Quinolones 26% → 3%
Park M (2006)	96%	Vancomycin 30% → 16%
del Real GA (2007)	88%	Vancomycin 37% → 16% Quinolones 36% → 13%
Frigas E (2008)	?	Vancomycin 28% → 10%

Antibiotic Costs in "Penicillin Allergic" Patients

Study	Cost – Penicillin Allergic Patients	Cost – No Penicillin Allergy	P Value
Kraemer MJ (1987)[1]	$4.6	$1.75	<0.001
MacLaughlin EJ (2000)[2]	$28.6	$16.3	0.004
Sade K (2003)[3]	$81.7	$52.5	0.015
Sade K (2003)[4]	$43.0	$31.0	<0.0005

1. Average antibiotic costs per patient during 24 month period
2. Average antibiotic costs per patient (one course)
3. Average antibiotic costs per day during hospitalization
4. Average antibiotic costs per day – post-hospitalization treatment

Clinical Infectious Diseases

MAJOR ARTICLE

Penicillin Allergy Testing Is Cost-Saving: An Economic Evaluation Study

Bernardo Sousa-Pinto,[1,2,3] Kimberly G. Blumenthal,[4,5] Eric Macy,[6] Ana Margarida Pereira,[1,2] Luís Filipe Azevedo,[1,2] Luís Delgado,[2,3] and João Almeida Fonseca[1,2]

- Having a penicillin allergy label is associated with the use of less appropriate and more expensive antibiotics and increased healthcare utilization
- Penicillin allergy testing results in delabeling in most case and may be cost-saving

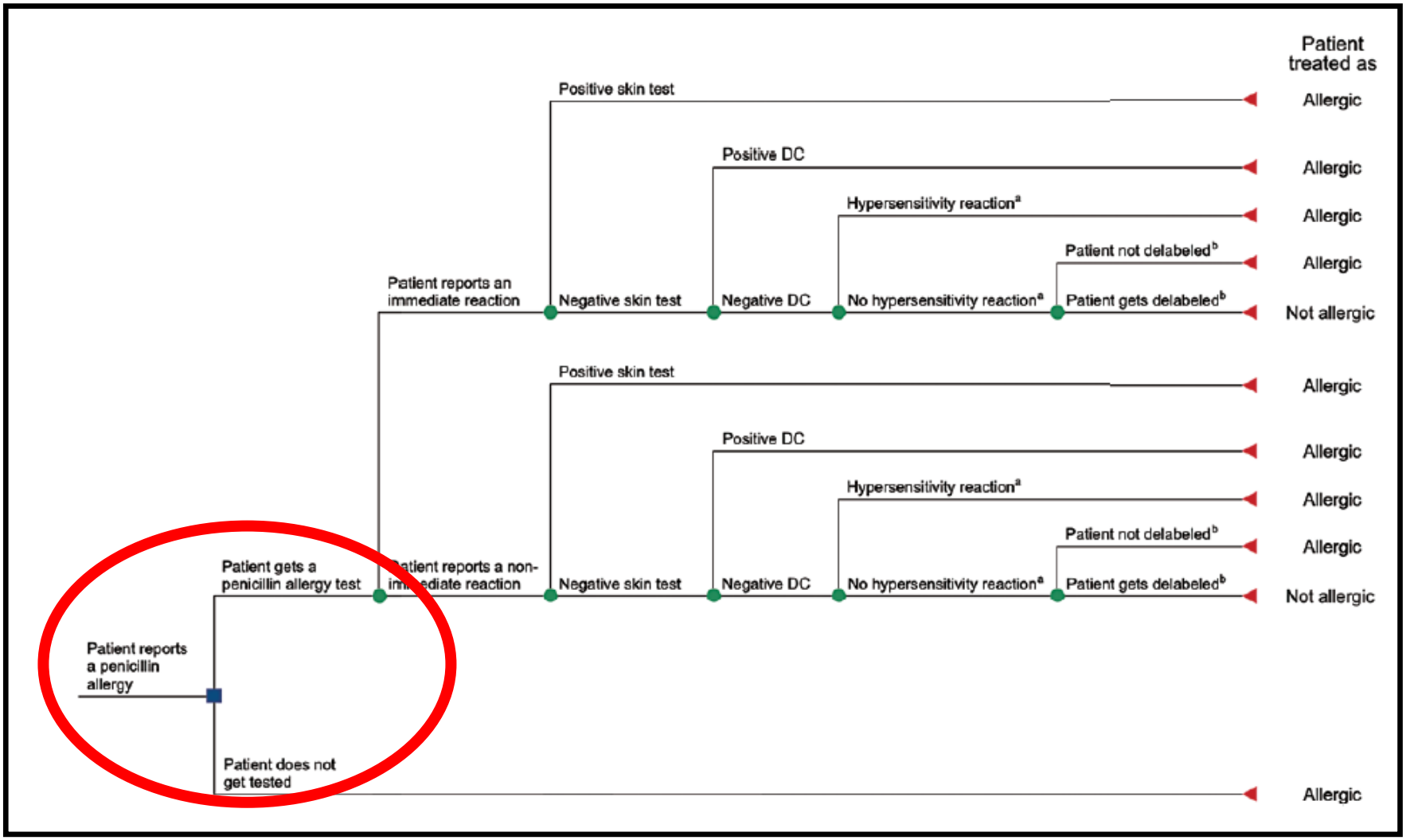
Methods

- Decision models to project the economic impact of two strategies for a patient with a penicillin allergy label:
  (1) diagnostic testing
  (2) no diagnostic testing

- Adopted health service perspective, considering costs with penicillin allergy tests, hospital bed-days/outpatient visits, antibiotic use, and diagnostic testing

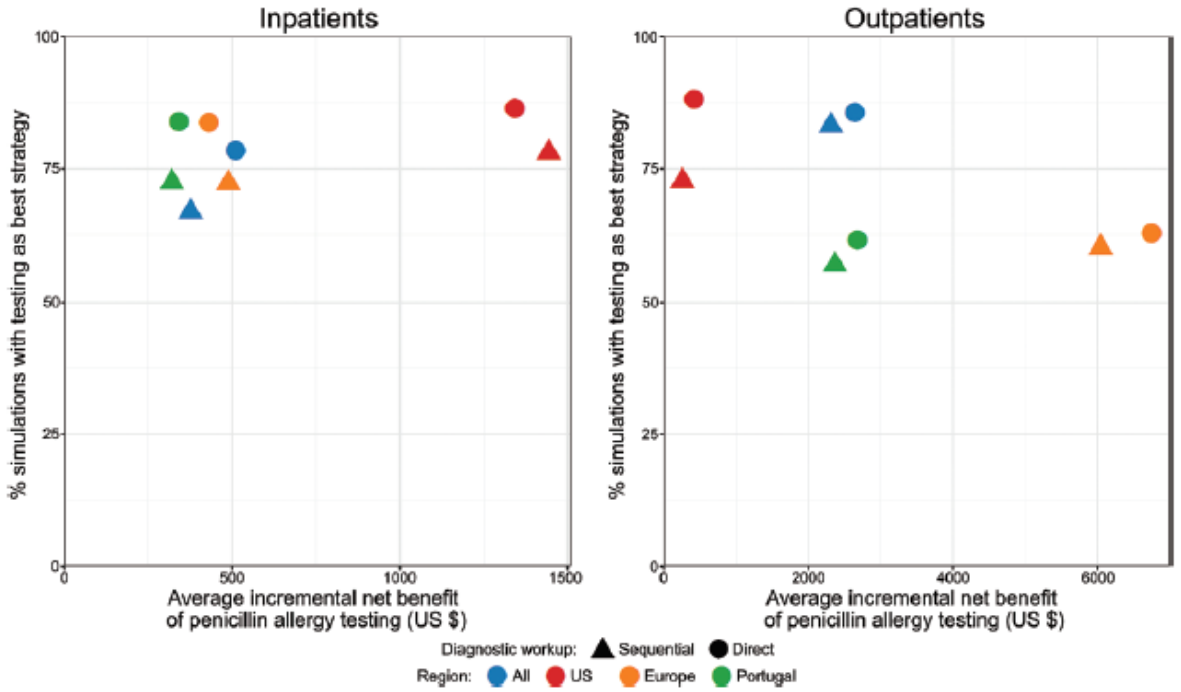
- Built and analyzed 24 base case decision models

Decision Tree Model



Results: Decision Model

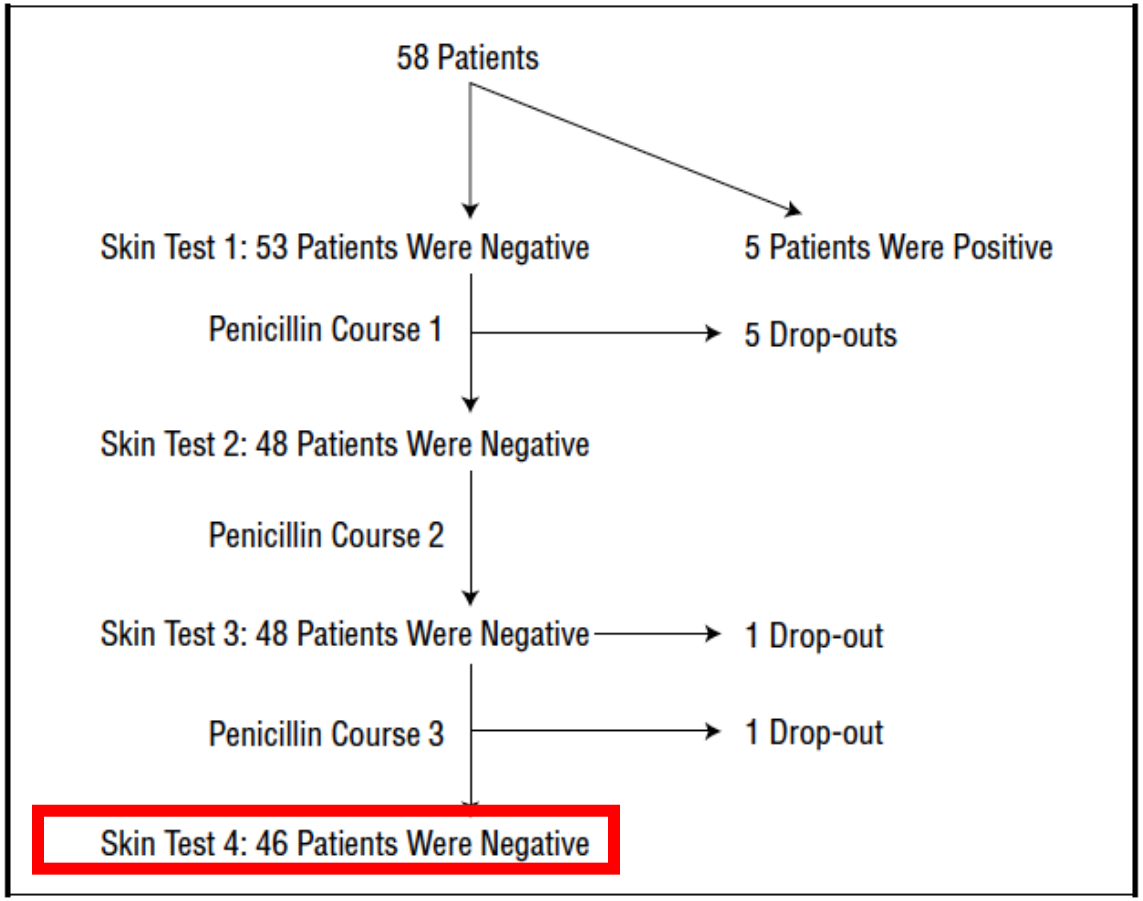
Allergy testing resulted in average savings of $657 for inpatients and $2746 for outpatients



- Penicillin allergy testing was cost-saving in all decision models built
- These results can inform guidelines, supporting the adoption of policies promoting widespread testing of patients with a penicillin allergy label

Lack of Resensitization with Oral Penicillins

Patients with a positive history but negative ST who tolerate a course of oral PCN are at minimally increased risk of PCN resensitization after multiple courses



MASSACHUSETTS GENERAL HOSPITAL

Solensky R, et al. Arch Intern Med 2002

Elective PCN Skin Tests

- Pros
  - No delay in initiating treatment because of wait for skin testing
  - May reduce use of other broad spectrum and more expensive antibiotics

- Cons
  - Resensitization (low risk)
  - Time/effort for clinic visit

Maintaining PCN Allergy Delabeling

- Penicillin skin testing and drug challenges are effective in removing penicillin allergy labels
- However, studies show that penicillin allergy labels persist in 9% to 51% of patients
  - Attributed to charting errors or limited understanding on the patient/providers' parts
- Effective counseling and post-discharge communication may be valuable interventions

Maintaining penicillin allergy delabeling: A quality improvement initiative

Shazia Lutfeali, MD[a], Felicia F. DiLoreto, PharmD[b], Kristin S. Alvarez, PharmD[b,c], Sheenal V. Patel, MD[d], Shyam R. Joshi, MD[e], Scott A. Tarver, PharmD[b], and David A. Khan, MD[a]

Implemented a large multidisciplinary inpatient penicillin allergy testing program

- Allergy-trained pharmacists performed testing
- Added interventions to improve communication and education about results of penicillin allergy testing

Interventions to Reduce Relabeling

November 2014—pharmacist counseling at the time of negative testing

June 2015—post procedure repeat pharmacist counseling scheduled within 7 to 10 days

November 2015—a best practice advisory alert was added to the EMR notifying providers of negative penicillin allergy testing results during attempts to add back allergy

April 2016—a wallet card documenting negative testing provided

Fifth intervention was manual chart review of all relabeled patients, performed by the pharmacist

Reported the effectiveness of these interventions in maintaining removal of the penicillin allergy label

TABLE II. Penicillin allergy relabel

Initial delabeled patients	N = 650
Patients with allergy relabel with QI interventions but before manual chart review (%)	84 (12.9)
Total number of relabels*	107
Time to first relabel (average days ± SD)	273.8 ± 301
Time to second delabel (average days ± SD)	19.8 ± 47.1
Person adding penicillin allergy label back (%)	
Registered nurse/LVN	63 (58.9)
Physicians/advanced practitioners	25 (23.6)
Pharmacist	7 (6.6)
Medical assistant	7 (6.6)
Unknown	5 (4.7)
Relabel due to merging of EMR data	4 (3.8)
Person removing allergy after relabel (%)	
Registered nurse/LVN	13 (14.3)
Physicians/advanced practitioners	17 (18.7)
Pharmacist	59 (64.8)
Medical assistant	1 (1.1)
Unknown	1 (1.1)
Patients with appropriate penicillin allergy relabel after QI interventions and manual chart review† (%)	16 (2.5)
Itching/irritation	8
Rash	7
Hives	1
Other	3

EMR, Electronic medical record; *LVN*, licensed vocational nurse; *QI*, quality improvement; *SD*, standard deviation.

*Patients may have had multiple relabels (N = 84).

†Patients may have had multiple symptoms.

Penicillin allergy relabeling rate of 12.9% after negative testing

Multiple interventions to improve patient education and establish EMR checkpoints decreased relabeling rate to 2.5%

Multidisciplinary approach offers guidance to maintain drug allergy label removal

Graded Challenges for Drug Hypersensitivity

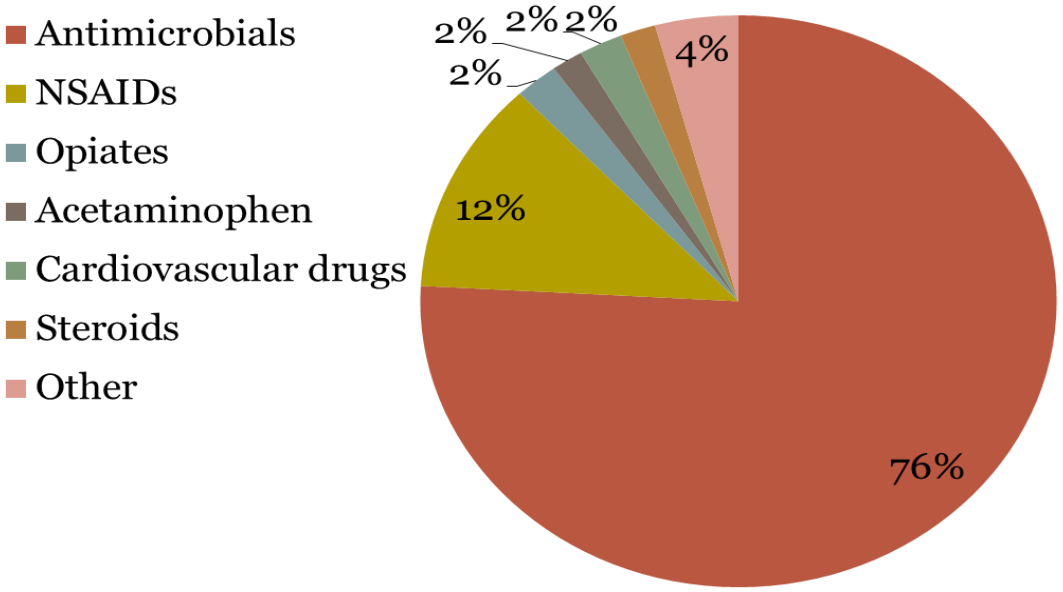
- Gold standard for evaluating drug hypersensitivity reactions
- Performed when low likelihood of allergy exists
- No evidence-based guidelines exist regarding the optimal number of steps
- Multi-step drug challenges may induce tolerance

Graded Challenge: 1-2 steps

- 5-year retrospective chart review of all test dose protocols
- Both initial HSR and adverse reactions during test dose protocols were independently classified and graded by severity
- Compared outcomes of 1-2 step protocols with multi-step protocols

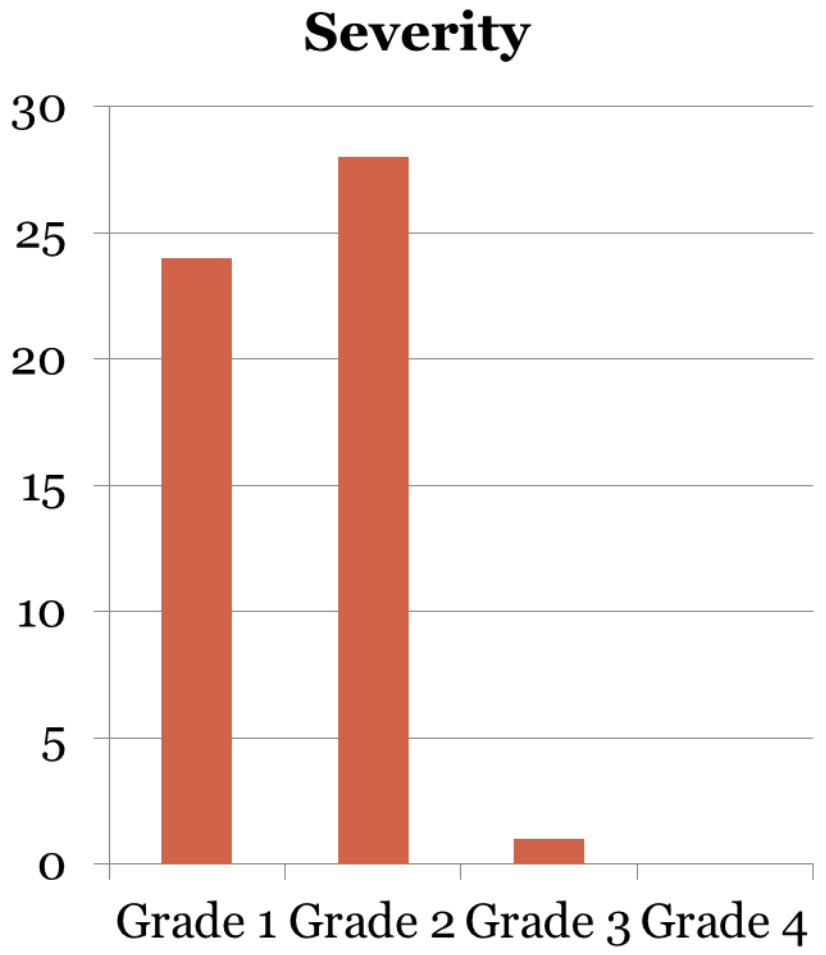
Drug Classes Prompting Test Doses

- Between 2008 and 2013, 456 patients underwent 497 test dose protocols with 1-2 steps



Reactions During Test Doses

- 53 test doses (11%) were associated with reactions during test dose protocols



Severity of Reactions During 1-2 Step Protocols vs. 3-4 Step Challenge Protocols

	1-2 Step (n=53) Reaction Rate	3-4 Step (n=10) Reaction Rate
Grade	11%	12%
1	24 (45.3%)	6 (60%)
2	28 (52.8%)	4 (40%)
3	1 (1.9%)	0 (0%)
4	0 (0%)	0 (0%)

- 1-2 step drug challenges are optimal to evaluate low-risk patients
- Safe and less resource intensive

- Multi-step drug challenges may be desensitizing the patient
- Confirm patient has a low-risk history

Drug Challenge (Test Dose) vs. Desensitization

- **Drug Challenge (Test Dose) is** utilized as a precautionary step in patients reported to have a history of a reaction to a necessary medication but in whom allergy has deemed the patient ***not allergic*** to the medication

- **Drug desensitization** is utilized when the a patient is allergic to a medication that is medically necessary

Drug Desensitization Principles

- Involves the introduction, usually within hours to days, of a temporary state of tolerance to a drug which the patient has a history of allergy
- Initial step involves administering an extremely minute amount (e.g., 1/10,000 of the usual dose) of the medication
- Gradually, the dose is increased and administered at fixed intervals (e.g., every 15 minutes) until the full dose is reached
- To maintain the temporary non-allergic state, the medication should be taken regularly
- Once the drug administration is interrupted or discontinued, the patient returns to being allergic to it

Indications for Drug Desensitization

(1) There are no alternatives to the drug of concern
- Penicillin in pregnant women with syphilis

(2) Drug of concern is more effective than the alternatives
- Cotrimoxazole for Pneumocystis in HIV-positive patient

(3) Drug of concern has a unique mechanism of action
- Aspirin in aspirin-exacerbated respiratory disease

Outcomes of a Guideline Implementation

Impact of a clinical guideline for prescribing antibiotics to inpatients reporting penicillin or cephalosporin allergy

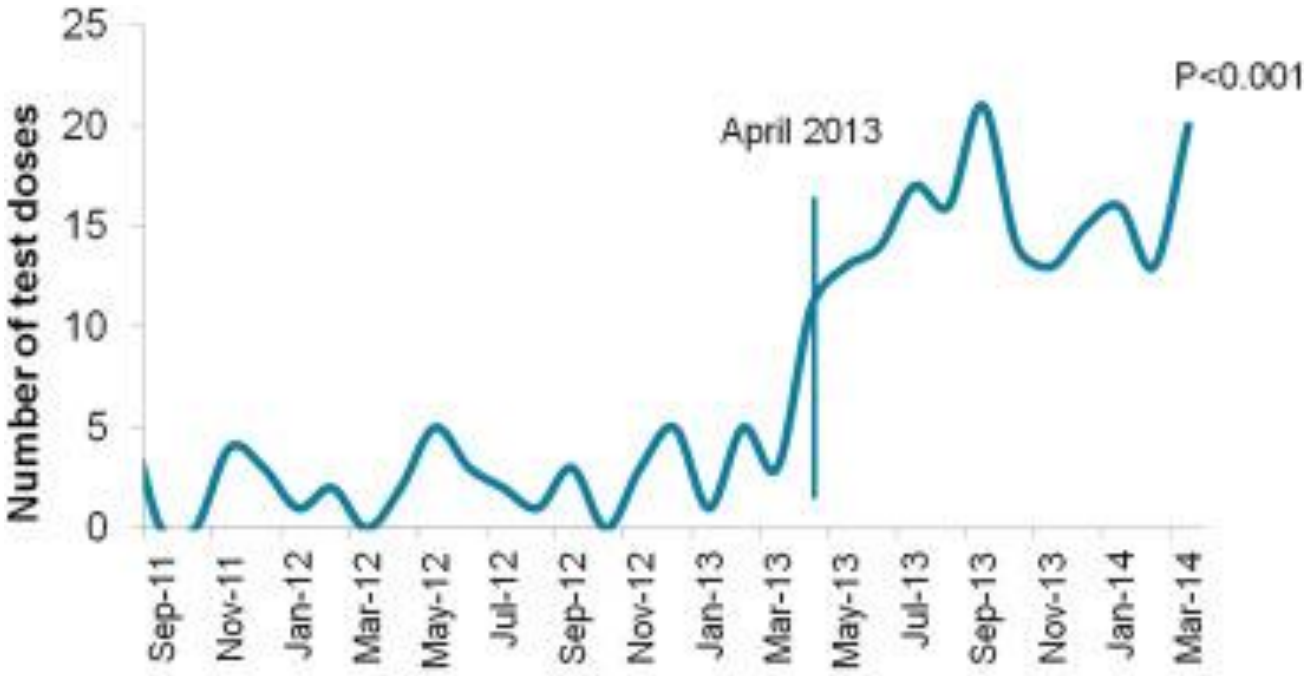
Kimberly G. Blumenthal, M.D.[1,2,3], Erica S. Shenoy, M.D., Ph.D.[2,3,4,5], Christy A. Varughese, Pharm. D.[4,7], Shelley Hurwitz, Ph.D.[3,6], David C. Hooper, M.D.[3,4,5], and Aleena Banerji, M.D.

Blumenthal et al., Ann Allergy Asthma Immunol 2015

Guideline Based Evaluation of PCN Allergy History

Blumenthal et al., Ann Allergy Asthma Immunol 2015

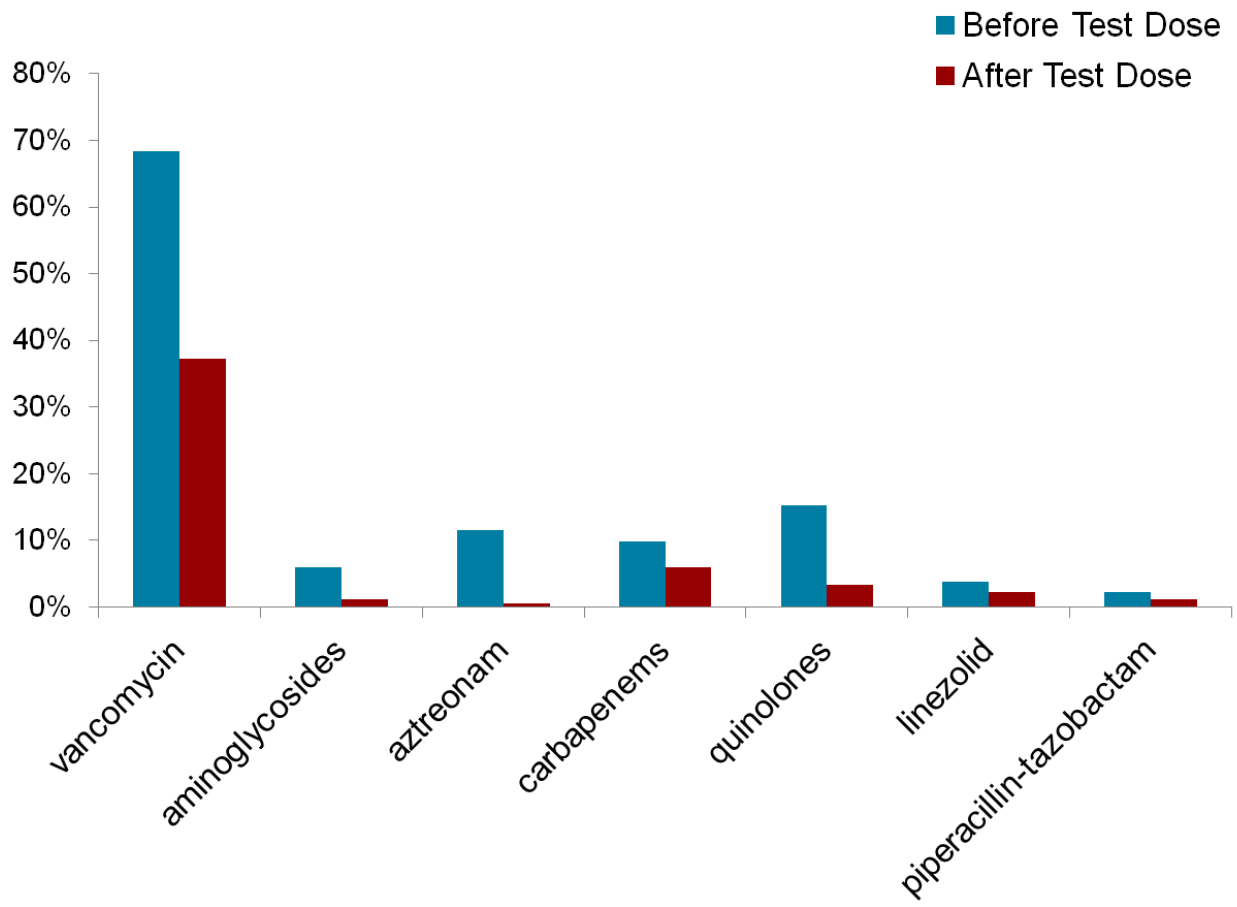
Outcomes: Increase in Number of Test Doses



	Pre-guideline	Post-guideline	P Value
ADRs N (%)	3 (6)%	7 (4%)	0.44

Blumenthal et al., Ann Allergy Asthma Immunol 2015

Outcomes: Decrease in Broad Spectrum Antibiotics



Blumenthal et al., Ann Allergy Asthma Immunol 2015

Clinical Infectious Diseases
MAJOR ARTICLE

The Penicillin Allergy Delabeling Program: A Multicenter Whole-of-Hospital Health Services Intervention and Comparative Effectiveness Study

Kyra Y. L. Chua,[1] Sara Vogrin,[2] Susan Bury,[1,3] Abby Douglas,[4] Natasha E. Holmes,[1] Nixon Tan,[1] Natasha K. Brusco,[5,6] Rebecca Hall,[1] Belinda Lambros,[4] Jacinta Lean,[4] Wendy Stevenson,[1] Misha Devchand,[1,3] Kent Garrett,[3] Karin Thursky,[4,7,8] M. Lindsay Grayson,[1,9] Monica A. Slavin,[4,8] Elizabeth J. Phillips,[10,11] and Jason A. Trubiano[1,4,9]

- Penicillin allergies are associated with inferior patient and antimicrobial stewardship outcomes
- Implemented a whole-of-hospital program to assess the efficacy of *inpatient* delabeling for low-risk penicillin allergies in hospitalized inpatients

Chua et al. Clin Infect Dis. 2021 Aug.

Methods

- Patients ≥ 18 years of age with a low-risk penicillin allergy were offered a *single-dose oral penicillin challenge or direct label removal based on history (direct delabeling)*

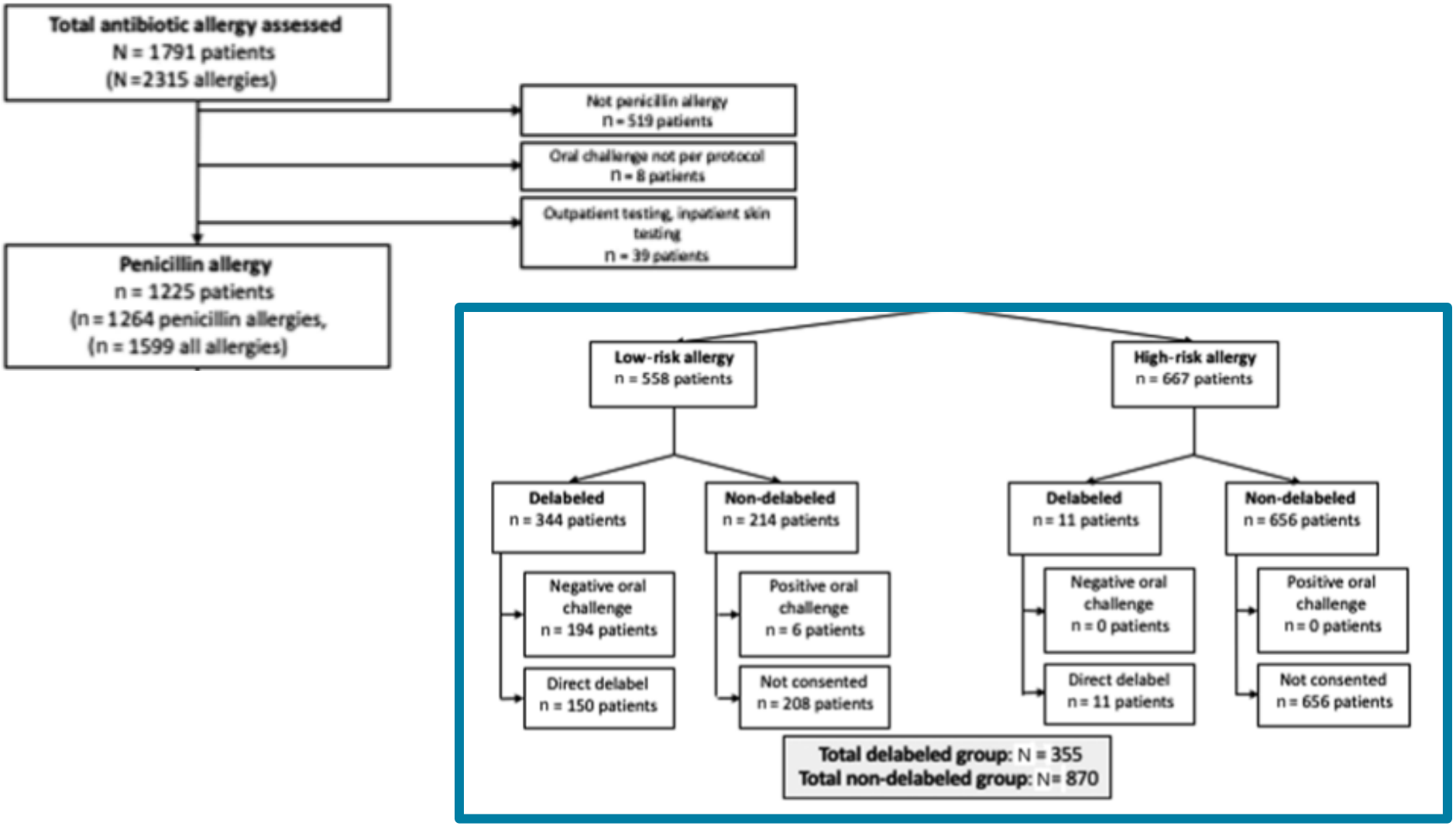
- Studied the proportion of patients delabeled, antibiotic utilization pre-(index admission) and post-delabeling

- Direct Delabeling

- Mild non-immune-mediated adverse drug reaction or where subsequent tolerance to the implicated penicillin was ascertained

- Oral Challenge

- Unknown reaction > 10 years ago
- Type A adverse drug reaction where direct delabeling was not accepted by the patient
- History of achildhood rash or MPE


Total antibiotic allergy assessed
N = 1791 patients
(N =2315 allergies)
Not penicillin allergy
n = 519 patients
Oral challenge not per protocol
n = 8 patients
Outpatient testing, inpatient skin testing
n = 39 patients
Penicillin allergy
n = 1225 patients
(n = 1264 penicillin allergies,
(n = 1599 all allergies)
Low-risk allergy
n = 558 patients
High-risk allergy
n = 667 patients
Delabeled
n = 344 patients
Non-delabeled
n = 214 patients
Delabeled
n = 11 patients
Non-delabeled
n = 656 patients
Negative oral challenge
n = 194 patients
Direct delabel
n = 150 patients
Positive oral challenge
n = 6 patients
Not consented
n = 208 patients
Negative oral challenge
n = 0 patients
Direct delabel
n = 11 patients
Positive oral challenge
n = 0 patients
Not consented
n = 656 patients
Total delabeled group: N = 355
Total non-delabeled group: N= 870

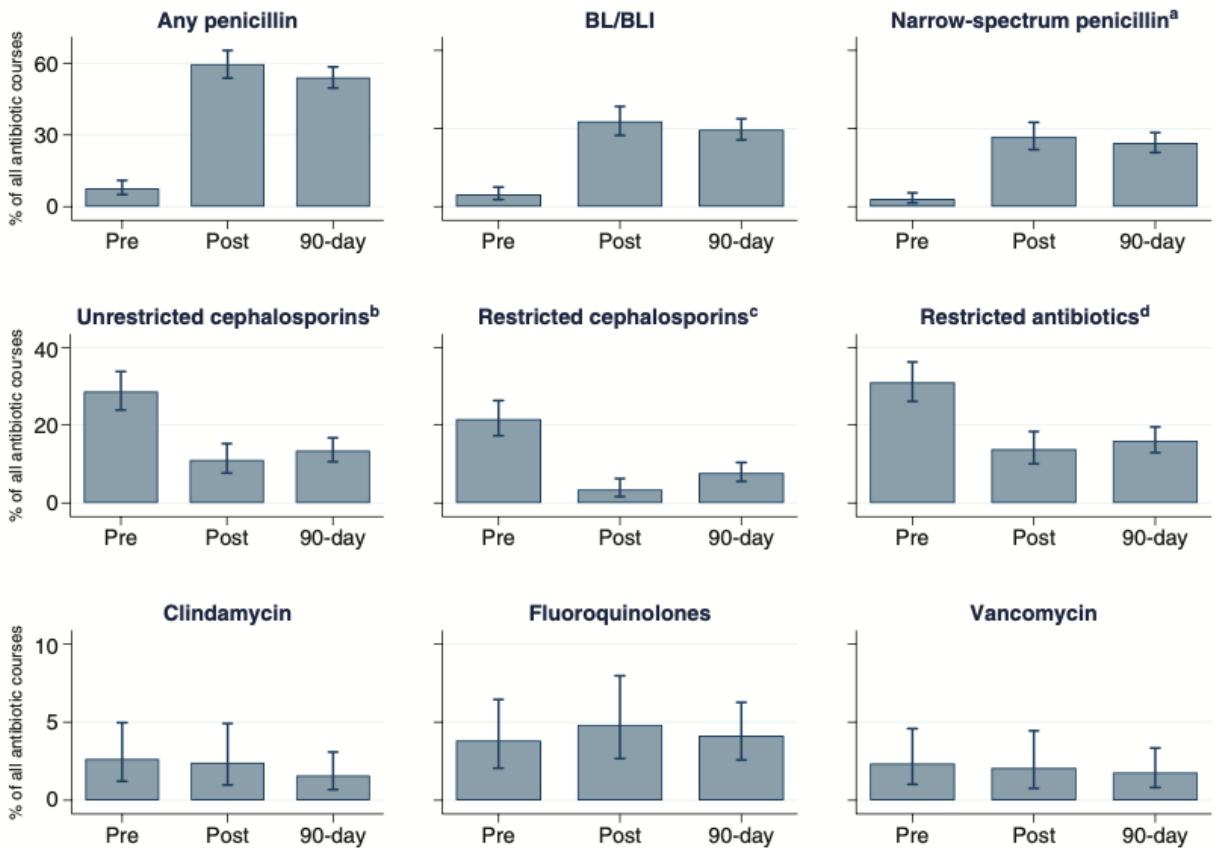


Figure 2. Antibiotic utilization in the delabeled cohort (n = 355). Errors bars represent 95% confidence intervals. [a]A narrow-spectrum penicillin was defined as 1 of penicillin VK, penicillin G, flucloxacillin, dicloxacillin, ampicillin, or amoxicillin. [b]An unrestricted cephalosporin included first- or second-generation cephalosporins. [c]A restricted cephalosporin included third-generation or later cephalosporins. [d]A restricted antibiotic included lincosamides (ie, clindamycin, lincomycin), fluoroquinolones (ie, norfloxacin, ciprofloxacin, moxifloxacin), vancomycin, carbapenems (ie, ertapenem, meropenem), and third-generation or later cephalosporins (ie, cefepime, ceftazidime, ceftriaxone). Abbreviations: 90-day, 90-day posttesting admission; BL/BLI, β-lactam/β-lactamase inhibitor; pre, pretesting index admission; post, posttesting index admission.

Inpatient Clinical Pathway: Successful

- Health services inpatient program used risk stratification with a combination of direct delabeling or oral penicillin challenge

- Led to positive impact on use of preferred antibiotics and appropriate antibiotic prescribing

Original Research

Outpatient penicillin allergy evaluation during pregnancy and associated clinical outcomes

Jason H. Kwah, MD, MSCI; Martina S. Burn, MD; Jane Liao, MD; Jennifer Cate, MD; Moeun Son, MD, MSCI

- Beta-lactam antibiotics are often clinically indicated in the peripartum period, posing a challenge for pregnant women who report a penicillin allergy
- Antibiotic allergy testing is rarely performed during pregnancy, even though most have a low risk history

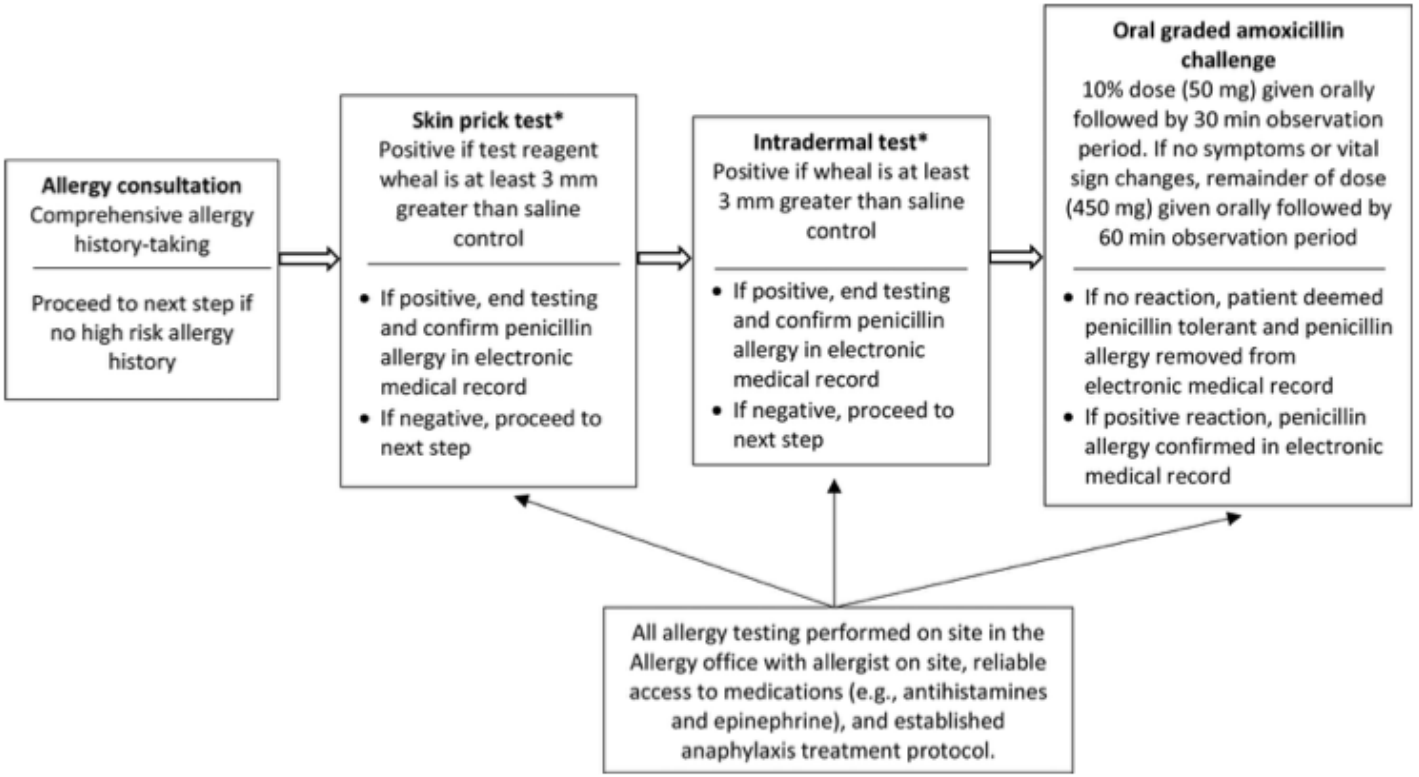
Kwah et al. Am J Obstet Gynecol MFM. 2022 Jun.

Methods

- A retrospective cohort study of all pregnant women with a penicillin allergy documented in the EMR who delivered from Sept 2020 to Oct 2021
- Assessed a hospital-wide multidisciplinary program to identify, refer, evaluate, and test pregnant women with unverified penicillin allergies

FIGURE 1

Schema of the penicillin allergy verification testing protocol and interpretation of results



Asterisk denotes that skin testing was performed using 3 test reagents (benzylpenicilloyl polylysine [Pre-Pen], penicillin G, and ampicillin) and 2 controls (histamine as a positive control and saline solution as a negative control).

TABLE 2

Mother-infant dyad outcomes among pregnant women referred and not referred for penicillin allergy evaluation

Outcome	Referred for penicillin allergy evaluation (n=232)	Not referred for penicillin allergy evaluation (n=457)	OR (95% CI)	Adjusted OR (95% CI)[a]	Difference in medians (95% CI)
Maternal outcomes					
Alternative antibiotic use[b]	20/129 (15.5)	85/257 (33.1)	0.38 (0.22–0.65)	0.49 (0.27–0.89)	NA
Postpartum infection	9 (3.9)	20 (4.4)	0.88 (0.40–1.99)	NA[c]	NA
Maternal length of postpartum hospital stay (h)	46.8 (38.4–58.3)	46.6 (37.6–61.4)	NA	NA	0.2 (−2.9 to 3.2)
Neonatal outcomes[d]					
NICU admission	34 (14.7)	79 (17.4)	0.81 (0.53–1.26)	0.64 (0.40–1.04)	NA
Neonatal laboratory draw[e]	25 (10.8)	58 (12.7)	0.83 (0.50–1.37)	0.68 (0.40–1.17)	NA
Neonatal antibiotic treatment	13 (5.6)	37 (8.1)	0.67 (0.35–1.28)	NA[c]	NA
Neonatal length of birth hospitalization stay (h)	47.4 (38.4–66.2)	48.1 (37.9–71.1)	NA	NA	−0.7 (−4.2 to 2.8)

CI, confidence interval; *NA*, not applicable; *NICU*, neonatal intensive care unit; *OR*, odds ratio.

Data are presented as number/total number (percentage), number (percentage), or median (interquartile range), unless otherwise specified.

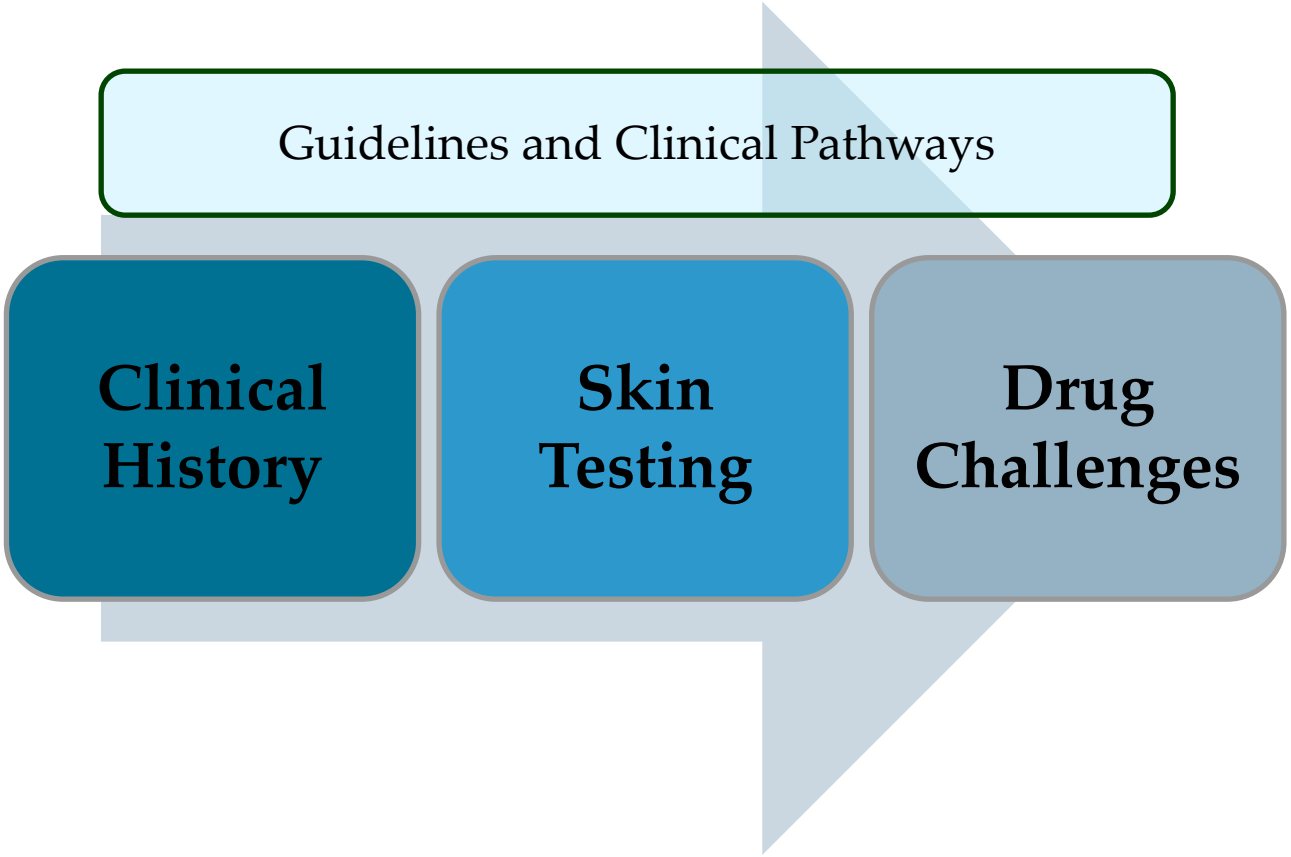
[a] Model adjusted for maternal body mass index at delivery, history of other allergies, type of index reaction, years since index reaction (as a categorical variable), and nulliparity; [b] Alternative antibiotic use was defined as the use of clindamycin or vancomycin for clinical indications in which a beta-lactam antibiotic would be considered first-line treatment; [c] Because of the small numbers, models were not adjusted because of overfitting the models; [d] Of note, 3 cases in the nonreferred group did not have neonatal data as 2 cases were third-trimester intrauterine fetal demises and 1 case was a previable second-trimester pregnancy loss; [e] Neonatal laboratory draw for complete blood count, C-reactive protein, and/or blood culture.

Kwah. Penicillin allergy evaluation during pregnancy. Am J Obstet Gynecol MFM 2022.

PCN Allergy Pregnancy Clinical Pathway

- Documented the feasibility, safety, and clinical benefit of an outpatient penicillin allergy evaluation program for pregnant women
  - 99% of women tested were found to be penicillin tolerant
- Referred patients were significantly less likely to receive alternative antibiotics
- More pregnant patient evaluations needed to assess whether there are additional clinical benefits

Drug Allergy Delabeling by the Allergist



Summary

- Evaluation and diagnosis of drug allergy remains difficult
- Skin testing has significant utility but need to understand how to interpret the results
- Treatment is avoidance, skin testing, test dose or desensitization
- Emerging guidelines and clinical pathways offer novel approaches to care