ß-lactam Antibiotic Allergy Management

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Disclaimer

- I have received honoraria from, have carried out clinical research with, and/or have served as a consultant for: AstraZeneca, Genentech, NIAID, WebMD.

Learning Objectives

- *After participation, the learner will be able to:*
  - Describe the approach to management of ß-lactam allergy in the context of antibiotic stewardship.
  - Relate the utility of direct oral challenge in patients with low or very low pre-test probability histories consistent with IgE mediated (allergic/anaphylactic) potential to penicillin.

What is the Most Important Medical Advance since 1840?

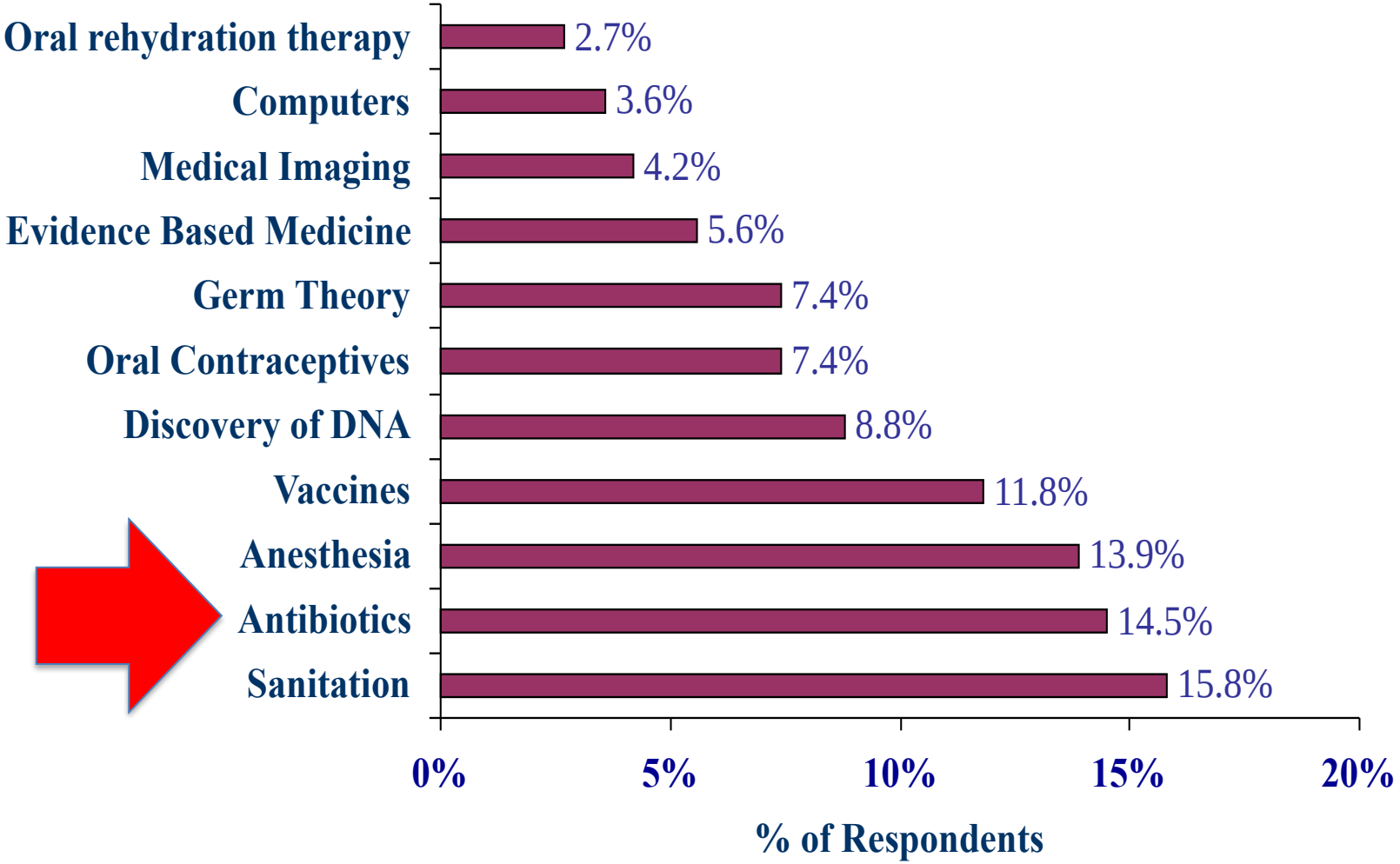
On Line Poll:
British Medical Journal

What is the Most Important Medical Advance since 1840?

BMJ 2007; 334: S2-S3

On Line Poll: BMJ

What is the Most Important Medical Advance since 1840?



BMJ 2007; 334: s2-s3

"A grand story." —The Wall Street Journal

THE DEMON UNDER THE MICROSCOPE

FROM BATTLEFIELD HOSPITALS TO NAZI LABS, ONE DOCTOR'S HEROIC SEARCH FOR THE WORLD'S FIRST MIRACLE DRUG

THOMAS HAGER

The Nobel Prize
Physiology/Medicine 1945

Sir Alexander Fleming
1881 - 1955

Sir Howard Walter Florey
1898 - 1968

Ernst Boris Chain
1906 - 1979

Alexander Fleming discovered the antimicrobial properties of penicillin in 1928. Twelve years later, Howard Florey and Ernst Chain developed the processes to produce penicillin in sufficient quantity for it to become widely available

Accessed November 1, 2018 at: http://ektalks.blogspot.com/2015/06/alexander-fleming-penicillin.html

Antibiotics Are Good For Us… But

- Antibiotics have changed the field of medicine
- We have been able to cure serious infections that previously were untreatable and fatal.
- Modern era -- the current challenge is overuse and misuse of antibiotics:
  - Use of antibiotics when not needed
  - Continued treatment when no longer necessary
  - Wrong dose
  - Broad- spectrum agents to treat susceptible organisms.

Barlam TF, et al Clin Inf Dis 2016; 62: e51-e77

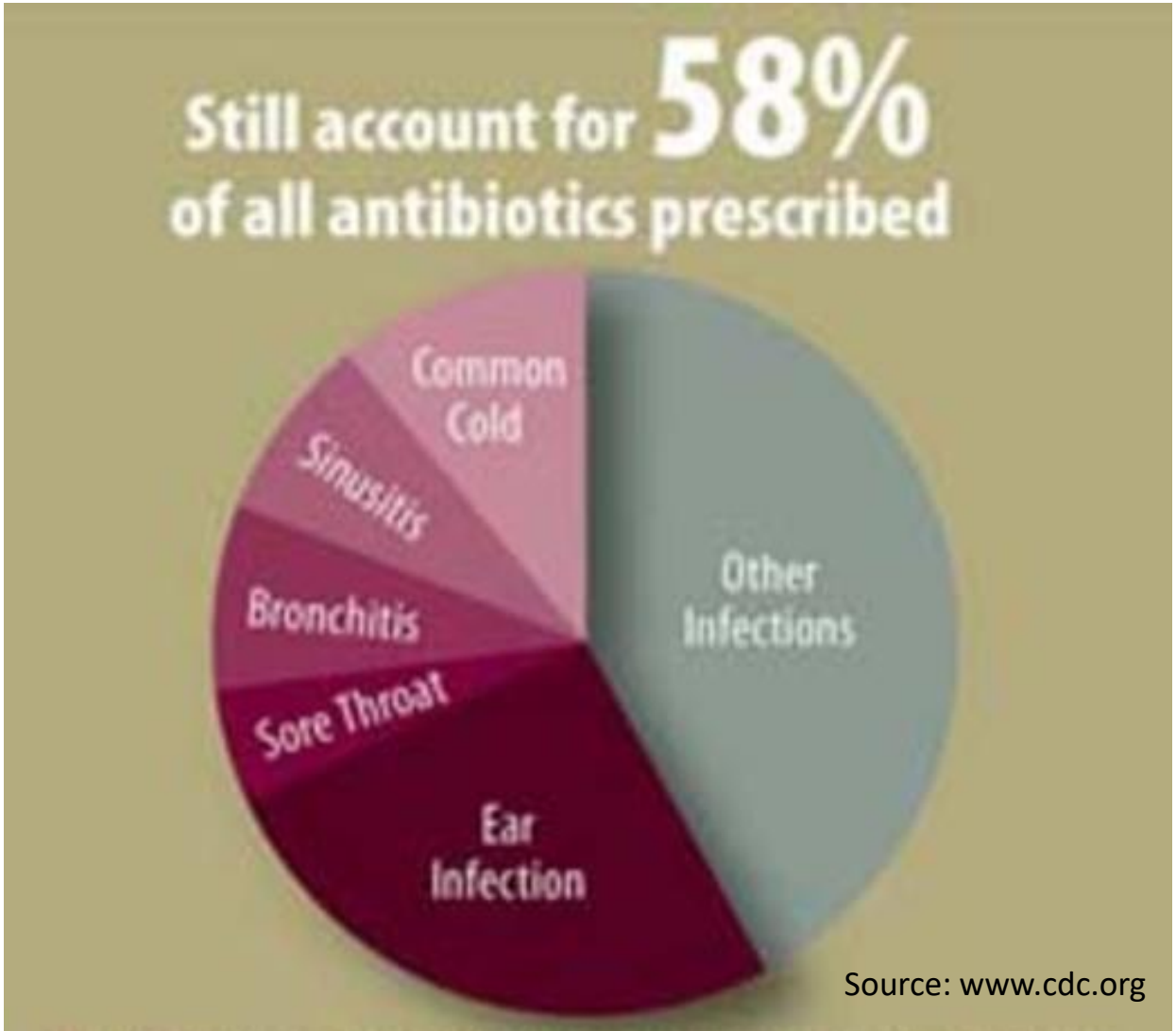
Antibiotics Are Good For Us… But

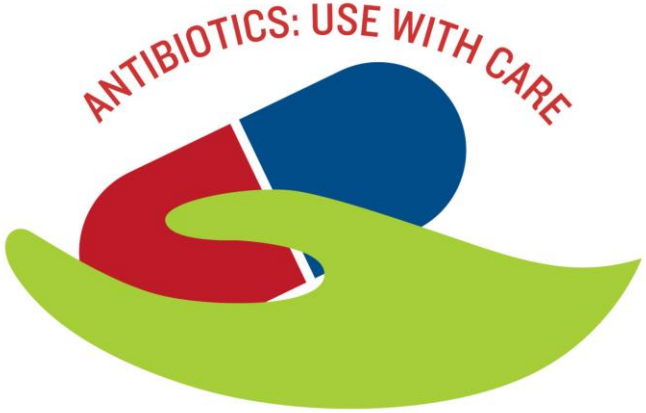
- Antibiotics have changed the field of medicine
- We have been able to cure serious infections that previously were untreatable and fatal.
- Modern era -- the current challenge is overuse and misuse of antibiotics:
  - overuse/misuse has led to increasing antibiotic resistance, and a surge in organisms resistant to antibiotics currently in our armamentarium
  - Slower pace of development of new antibiotics.
  - Need: Optimize use of existing antibiotics and newly developed antibiotics

Barlam TF, et al Clin Inf Dis 2016; 62: e51-e77


1 in 2
More than half of all hospital patients receive an antibiotic.
CDC
Vitalsigns
www.cdc.gov/vitalsigns

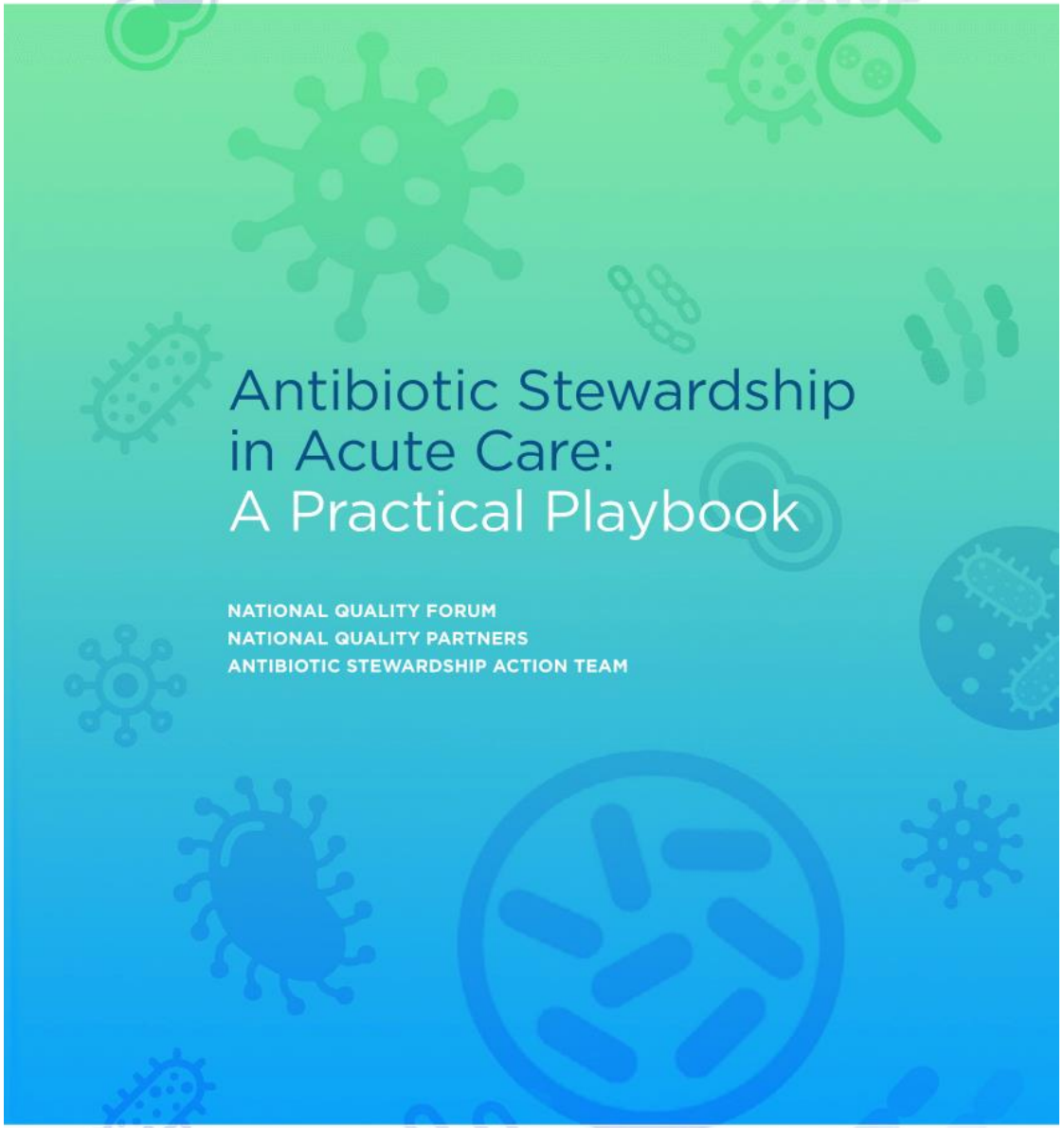
CDC Estimates 47 million Rx for Antibiotics Annually Are Unnecessary





ANTIBIOTIC STEWARDSHIP REFERS TO A SET OF COORDINATED STRATEGIES TO IMPROVE THE USE OF ANTIMICROBIAL MEDICATIONS WITH THE GOAL OF ENHANCING PATIENT HEALTH OUTCOMES, REDUCING RESISTANCE TO ANTIBIOTICS, AND DECREASING UNNECESSARY COSTS.

Accessed on November 1, 2018 at:https://www.shea-online.org/index.php/practice-resources/priority-topics/antimicrobial-stewardship



NATIONAL QUALITY FORUM

NATIONAL ACTION PLAN FOR COMBATING ANTIBIOTIC-RESISTANT BACTERIA

MARCH 2015

National Action Plan

- 50% reduction of *C. difficile* incidents
- 60% reduction in hospital-acquired CRE infections
- 35% reduction in hospital-acquired MDR Pseudomonas species infections
- 50% reduction in MRSA bloodstream infections
- 50% reduction in inappropriate antibiotic use in outpatient settings and a 20% reduction in inpatient settings

Accessed November 2 at: https://mms.mckesson.com/content/clinical-resources/laboratory-resources/antibiotic-stewardship/

Antibiotic Stewardship Strategies

IDSA/SHEA Guideline

- Suggest incorporation of clinical decision support via EMR at time of prescribing as a component of stewardship.
  - Provide clinicians with treatment recommendations
  - *weak recommendation, low quality evidence*
- Associated with reduced use of broad spectrum agents, improved dosing, fewer prescribing errors, lower cost, reduced LOS.

Barlam TF, et al Clin Inf Dis 2016; 62: e51-e77

Antibiotic Stewardship Strategies
IDSA/SHEA Guideline

- Suggest use of antibiotic "time outs" or "stop orders" (e.g., 48 or 72 hours).
  - Encourage providers to perform routine review of antibiotic regimens to improve antibiotic prescribing
  - *weak recommendation, low quality evidence*
- Associated with reduced duration of antibiotic administration in patients receiving empiric therapy

Barlam TF, et al Clin Inf Dis 2016; 62: e51-e77

NQF Measure #2720

- Compares antibiotic use with nationally aggregated data standards, using a set of Ratios (SAAR: Standardized Antimicrobial Administration Ratios), observed-predicted antibiotic use for each of 16 antibacterial agent patient care location combinations

Numerator Statement:

- Days of antimicrobial therapy for antibacterial agents administered to adult and pediatric patients in medical, medical/surgical, and surgical wards and medical, medical/surgical, and surgical intensive care units.

Denominator Statement:

- Days present for each patient care location—adult and pediatric medical, medical/surgical, and surgical wards and adult and pediatric medical, medical/surgical, and surgical intensive care units—is defined as the number of patients who were present for any portion of each day of a calendar month for each location…

Antimicrobial Stewardship Programs Big Rocks

- **Broad spectrum agents predominantly used for hospital-onset/multi-drug resistant bacteria** – semi-synthetic penicillins, cephalosporins, aminoglycosides, and other agents.
- **Broad spectrum agents predominantly used for community-acquired infection** – carbapenems, cephalosporins, fluroquinolones.
- **Anti-MRSA agents** – ceftaroline, dalbavancin, daptomycin, linezolid, oritavancin, quinupristin/dalfopristin, tedizolid, telavancin, and vancomycin.
- **Agents predominantly used for surgical site infection prophylaxis** – cefazolin, cefotetan, cefoxitin, cefuroxime.

SAAR is an Observed-to-Predicted (O-to-E) ratio

- **Observed antibiotic use**–Days of therapy reported by a health care facility for a specified category of antimicrobial agents in a specified patient care location or group of locations
- **Predicted antibiotic use** – Days of therapy predicted for a healthcare facility's use of a specified category of antimicrobial agents in a specified category patient care location or group of locations on the basis negative binomial regression modeling applied to nationally aggregated AU data

The calculated SAAR value is always greater than or equal to 0, and a value of 1.0 implies equivalency between observed and predicted antimicrobial use.

 A SAAR less than 1 may indicate antibiotic under use

 A SAAR of 1 indicates that antibiotic use is equivalent to the referent population's antibiotic use

 A SAAR greater than 1 may indicate excessive antibiotic use

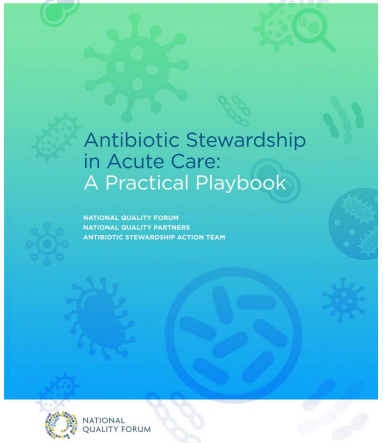
More Efficient
Health Care Delivery

- Reduced Cost
- Improved Quality
- Improved Outcomes

→ **Improved Value**

Accessed Nov 1, 2020, at: https://www.123rf.com/photo_36650944_a-doctor-showing-a-signboard-with-the-word-allergy-written-in-it.html

NQF Playbook: Practical Approach to Antibiotic Stewardship -- Interventions



- Establish guidance for antibiotic allergy assessment (e.g., penicillin allergy assessment protocol) – including recommendations on which patients might benefit from skin testing.

PENICILLIN AS A CHEMOTHERAPEUTIC AGENT

BY

E. CHAIN, PH.D. CAMB.
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A. D. GARDNER, D.M. OXFD, F.R.C.S.
N. G. HEATLEY, PH.D. CAMB.
M. A. JENNINGS, B.M. OXFD,
J. ORR-EWING, B.M. OXFD,
A. G. SANDERS, M.B. LOND.

(From the Sir William Dunn School of Pathology, Oxford)

IN recent years interest in chemotherapeutic effects has been almost exclusively focused on the sulphonamides and their derivatives. There are, however, other possibilities, notably those connected with naturally occurring substances. It has been known for a long time that a number of bacteria and moulds inhibit the growth of pathogenic micro-organisms. Little, however, has been done to purify or to determine the properties of any of these substances. The antibacterial substances produced by *Pseudomonas pyocyanea* have been investigated in some detail, but without the isolation of any purified product of therapeutic value.

Recently, Dubos and collaborators (1939, 1940) have published interesting studies on the acquired bacterial antagonism of a soil bacterium which have led to the isolation from its culture medium of bactericidal substances active against a number of gram-positive micro-organisms.[1] Pneumococcal infections in mice were successfully treated with one of these substances, which, however, proved to be highly toxic to mice (Hotchkiss and Dubos 1940) and dogs (McLeod et al. 1940).

Following the work on lysozyme in this laboratory it occurred to two of us (E. C. and H. W. F.) that it would be profitable to conduct a systematic investigation of the chemical and biological properties of the antibacterial

1. See *Lancet*, 1940, 1, 1172.

Features of Penicillin Allergy

- Observed consistently in minority receiving penicillin.
- Occurred in individuals who previously received penicillin without adverse reaction
- If no previous exposure to penicillin, adverse reaction appeared only after several treatment days
- Reaction reproduced by challenge with small amount of drug.

Prevalence of Penicillin Allergy

- Varies based on population studied.
- History of "allergy" to penicillin
  - claimed by approximately 10% of general population.
- Results of Allergy/Immunology evaluation with skin testing and oral challenge
  - **True prevalence of allergy to penicillin**
    - **A. 50%**
    - **B. 30%**
    - C. **15%** **1980s**
    - D. **1-10 %** **NOW**

"Is It Really a Penicillin Allergy?"

The CDC has released a new fact sheet recommending testing patients for a true penicillin allergy before prescribing broad spectrum antibiotics.

Less than 1% of the population is truly penicillin allergic! [1]

Broad-spectrum antibiotics are often used as an alternative to penicillins. The use of these antibiotics for patients labeled "penicillin allergic" is associated with:

- Increased Risk for Antibiotic Resistance[1]
- Suboptimal Antibiotic Therapy[1]
- Higher Healthcare Costs[1]

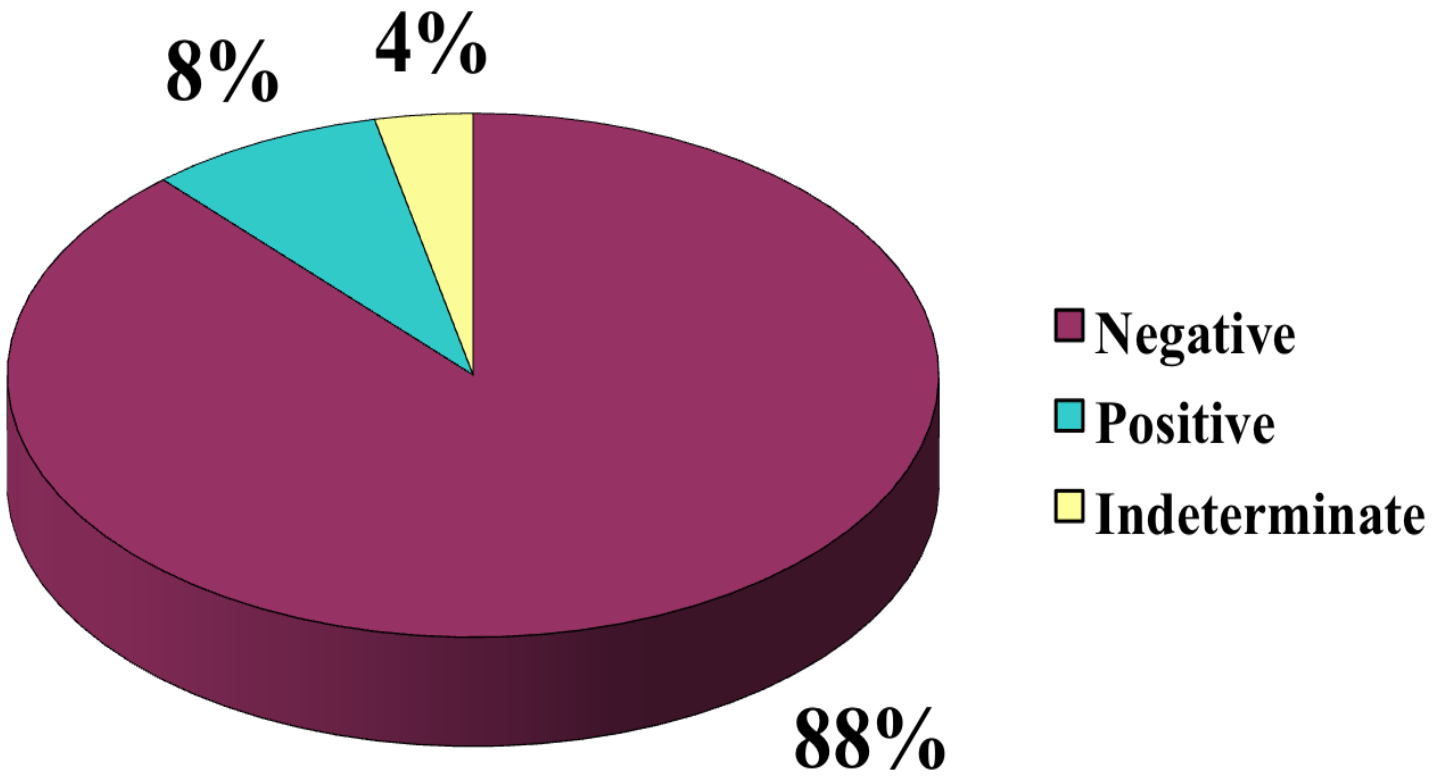
1. Joint Task Force on Practice Parameters representing the American Academy of Allergy, Asthma and Immunology; American College of Allergy, Asthma and Immunology; Joint Council of Allergy, Asthma and Immunology. Drug allergy: an updated practice parameter. Ann Allergy Asthma Immunol. 2010 Oct;105(4):259-273.

Penicillin Allergy –Morbidity

- Among patients with “penicillin allergy”
  - 39.7% received vancomycin
  - 21.5% received levofloxacin
- No antibiotic allergy
  - 17.4% received vancomycin
  - 8.0% received levofloxacin
- Large morbidity (unrecognized) from withholding penicillin because of “allergy”

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

Cleveland Clinic Experience



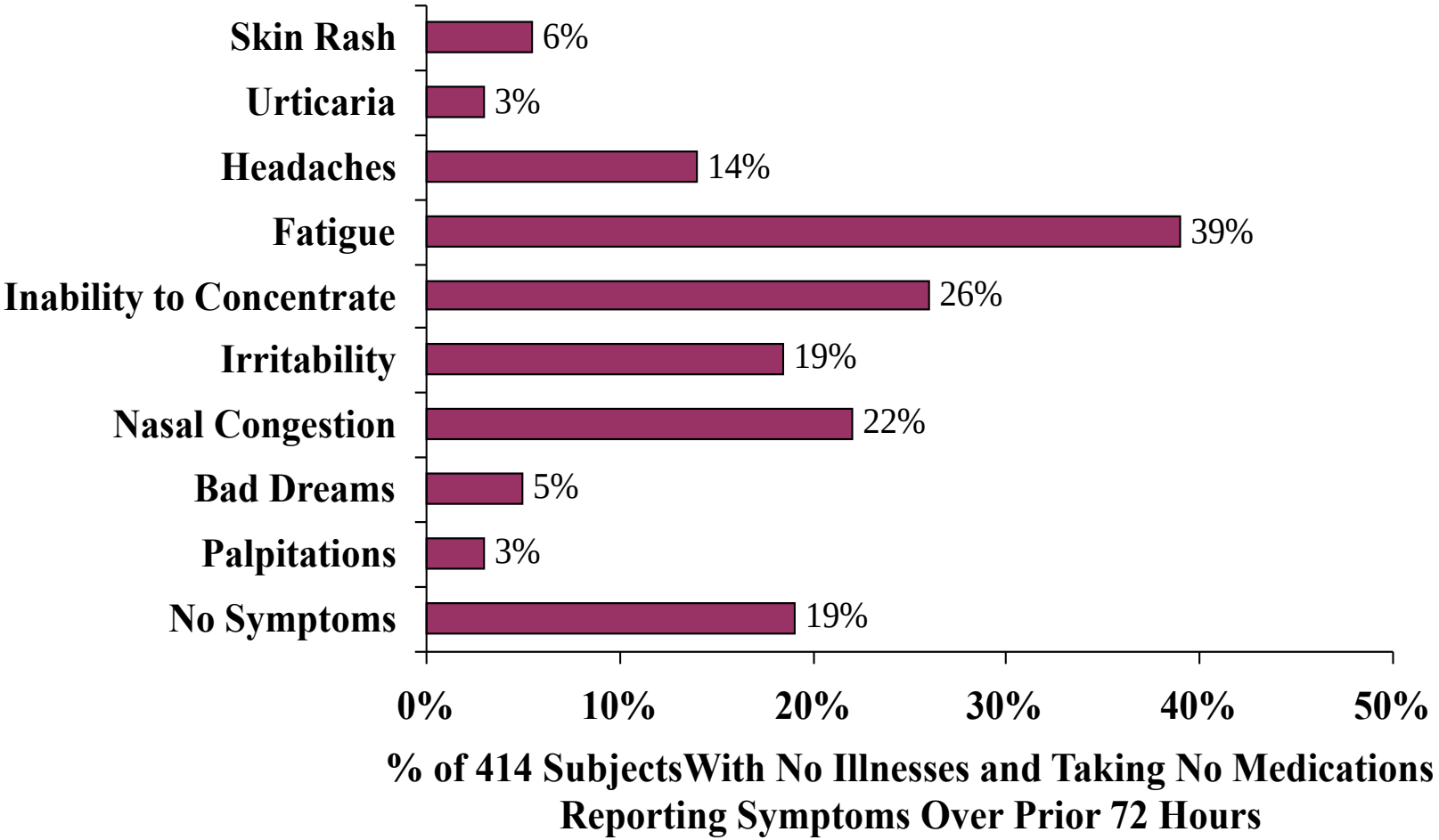
Negative Predictive Value = 99.3%

Alvarez del Real G, et al Ann Allergy Asthma Immunol 2007; 98: 355-9.


WHY?

Symptoms of Adverse Drug Reaction:

Baseline Frequency



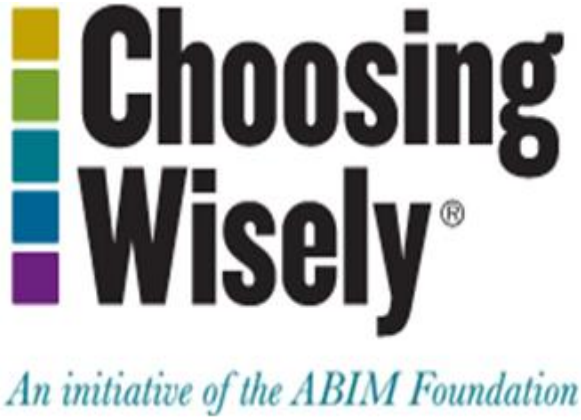
Reidenberg M, Lowenthal D. N Engl J Med 1968; 279: 678-9.

https://www.universalmedicalid.co.uk/prod_uk/allergic-to-penicillin-stickers-217

Why Skin Test to Penicillin?

- Treatment of patients assumed to be“allergic” to penicillin with broad spectrum antibiotics associated with suboptimal care outcomes:
  - Drug-resistant organisms
  - Higher cost
  - Increased risk for adverse effects
  - Greater rates of *C difficile,* MRSA & VRE
- Can be done safely even in young children, pregnant women, critically ill patients, and in pre-organ transplant patients.

Philipson E, et al. J Reprod Med 2007; 52: 480-4
Solensky R, et al. Ann Allergy Asthma Immunol 2010; 105:259-273
Macy E, Contreras R. J Allergy Clin Immunol 2014;133:790-6.



Don't overuse non-beta lactam antibiotics in patients with a history of penicillin allergy, without an appropriate evaluation.

http://www.choosingwisely.org/clinician-lists/american-academy-allergy-asthma-immunlogy-non-beta-lactam-antibiotics-penicillin-allergy/

AAAAI Position Statement

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

Approved by the AAAAI Board of Directors, July 2016

J Allergy Clin Immunol Pract 2017;5: 333-334.

Antibiotic Stewardship Strategies

IDSA/SHEA Guideline

- Suggest antibiotic stewardship programs promote allergy assessment and penicillin skin testing when appropriate in patients with a history of ß-lactam allergy.
  - Encourage mechanisms that ensure allergy assessments are performed.
  - *weak recommendation, low quality evidence*
- Associated with improved antibiotic selection, reduced use of alternative antibiotics, decreased LOS and cost.

Barlam TF, et al Clin Inf Dis 2016; 62: e51-e77

Antibiotic Stewardship Strategies

IDSA/SHEA Guideline

- **Recommend** antibiotic stewardship programs promote allergy assessment and penicillin skin testing when appropriate in patients with a history of ß-lactam allergy.
  - Encourage mechanisms that ensure allergy assessments are performed.
  - ***STRONG*** *recommendation, low quality evidence*
- Associated with improved antibiotic selection, reduced use of alternative antibiotics, decreased LOS and cost.

Macy E, Khan D, Castells M, Lang D. Clin Inf Dis 2017; 64; 531-533.

Strategies for Antibiotic Stewardship

- Sequential study assessing 3 strategies:
  - **Standard of Care**
    - June-Nov 2014
    - Allergy/Immunology consults (referral by primary team)
  - **History-appropriate penicillin skin testing**
    - Nov 2014 – June 2015
    - Tracker identified skin test eligible patients identified, diagnostic evaluation performed if ok'd by primary team
  - **Computerized guideline application with decision support**
    - Nov 2015-June 2016
    - Clinical pathway implemented.
    - Primary teams empowered to stratify patients according to history
      - Very low-pretest probability: one-step beta-lactam challenge without prior skin testing
      - Low-pretest probability: two-step beta-lactam challenge without prior skin testing
      - Moderate-high pretest probability: Allergy/Immunology consultation

Blumenthal K, et al J Allergy Clin Immunol 2017; 140: 154-161.

Strategies for Antibiotic Stewardship

- Primary Outcome
  - Use of formulary unrestricted penicillins and cephalosporin antibiotics
- Secondary Outcomes
  - Proportion of patients discharged on penicillin or cephalosporin.
  - Adverse drug reactions
  - Inpatient use of alternative antibiotics
    - Vancomycin
    - Clindamycin
    - Daptomycin
    - Linezolid
    - Carbapenems
    - Aztreonam
    - Aminoglycosides

Blumenthal K, et al J Allergy Clin Immunol 2017; 140: 154-161.

1000 Inpatients Receiving ≥ 1 Dose of Antibiotic

Exclusions – re-hospitalization, admission not due to infection, etc.

SOC	PST	CDS
[N = 148]	[N = 278]	[N = 199]

Blumenthal K, et al J Allergy Clin Immunol 2017; 140: 154-161.

1000 Inpatients Receiving ≥ 1 Dose of Antibiotic

Exclusions – re-hospitalization, admission not due to infection, etc.

PST

[N = 278]

- Skin test eligible = 179
- Skin tested = 43
- OR = 5.7 (95% CI = 2.6 – 12.5)

Reasons:

- testing not coordinated prior to discharge
- Patient refused testing
- Primary team refused testing
- Patient left AMA

Blumenthal K, et al J Allergy Clin Immunol 2017; 140: 154-161.

1000 Inpatients Receiving ≥ 1 Dose of Antibiotic

Exclusions – re-hospitalization, admission not due to infection, etc.

SOC	PST	CDS
[N = 148]	[N = 278]	50% [N = 199] **OR= 1.8** **(95%CI = 1.1-2.9)**

Blumenthal K, et al J Allergy Clin Immunol 2017; 140: 154-161.

Table 3. Risk Stratification for Penicillin Allergy Evaluation

	Low Risk	Medium Risk	High Risk
History[a]	Isolated reactions that are unlikely allergic (eg, gastrointestinal symptoms, headaches) Pruritus without rash Remote (>10 y) unknown reactions without features of IgE[b] Family history of penicillin allergy	Urticaria or other pruritic rashes Reactions with features of IgE but not anaphylaxis[b]	Anaphylactic symptoms[c] Positive skin testing Recurrent reactions Reactions to multiple β-lactam antibiotics
Action	Prescribe amoxicillin course or perform a direct amoxicillin challenge under observation.[d]	Skin test followed by amoxicillin challenge under observation if the skin test is negative.[e] Consider allergy/immunology referral.	Allergy/immunology referral or desensitization.

Shenoy ES, et al JAMA 2019; 321-188-199.

RCT: Skin Testing vs. Direct Challenge

- Patients ≥ 5 years old with cutaneous-only or unknown history, seen over 5 month period.
  - Skin testing (50.3%)
  - 2-step amoxicillin challenge (49.7%)
- Penicillin allergy present in 363/2465 (14.7%)
  - 67.8% female
  - Mean age = 35.3 (+/- 25.3) years

Mustafa SS, et al J Allergy Clin Immunol Pract 2019; 7: 2163-70.

RCT: Skin Testing vs. Direct Challenge

TABLE III. Outcomes of randomized penicillin allergy evaluations

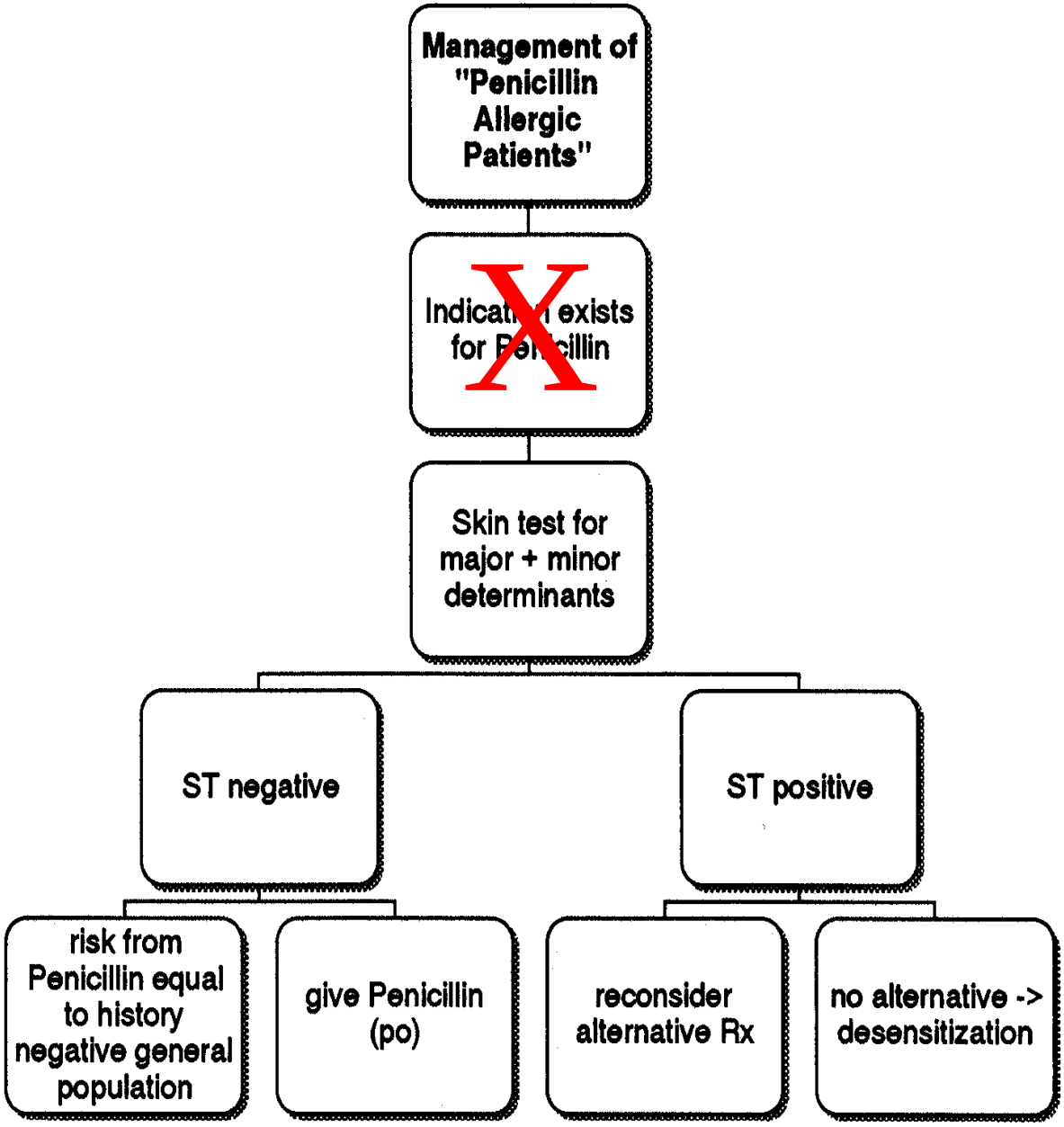
Outcome	Penicillin SPT	DC	Difference
Patients	80	79	
PST Positive/DC fail, n (%)	10 (12.5)	3 (3.8)	8.7% ($P = .079$)
PST Negative/DC pass	70 (87.5)	76 (96.2)	

"… Of the 3 failed direct challenges, each resulted in cutaneous only manifestations and all were successfully treated with oral antihistamines."

Mustafa SS, et al J Allergy Clin Immunol Pract 2019; 7: 2163-70.

Direct Challenge

Citation	Positive / Total Challenged	% Positive DC
Mustafa JACI Pract 2019	3/79	3.8
Iammatteo JACI Pract 2019	4/155	2.6
Confino-Cohen JACI Pract 2017	9/617	1.5
Trubiano Open Forum Inf Dis 2018	0/46	0
Chua Clin Inf Dis 2020	6/200	3
Krusenstjerna-Hafstrøm BMC Pediatr 2020	4/141	2.6
	26/1238	**2.1%**



Solensky R, et al. Ann Allergy Asthma Immunol 2010; 105(4):259-273

ROCK AND ROLL
HALL OF FAME + MUSEUM