



# ANTIBIOTIC MYTHS: IV THERAPY IS BETTER THAN PO

David Quimby, MD

Assistant Professor, Infectious Diseases, Creighton University

# DISCLOSURES

- I have no financial or non-financial conflicts of interest to disclose
- There will be discussion of off-label use of medications. This is because most antibiotics are used for indications other than that for which initial FDA approval was granted.

# CASE PRESENTATION

- Patient is a 70 y/o man who presented with a several-week history of left ear pain that was progressive. He developed some drainage from his left ear.
- Past medical history of DM (Hba1c 7.2), HTN, bioprosthetic aortic valve
- Diagnosed with mastoiditis and MRI imaging suggested temporal bone osteomyelitis
- Ear culture grew *Streptococcus pneumoniae*, pan-susceptible. Blood cultures NG
- He was dismissed from the hospital on ceftriaxone 2g IV daily via PICC with plan for 42 days of therapy for osteomyelitis

# CASE PRESENTATION

- On day #35 of treatment, he developed malaise; fever developed on day #36.
- PICC line was removed on Day #37, blood cultures obtained. Antibiotic course for the temporal bone osteomyelitis was cut 5 days short
- Blood cultures turned positive 1/2 (line culture positive) for *Candida albicans*

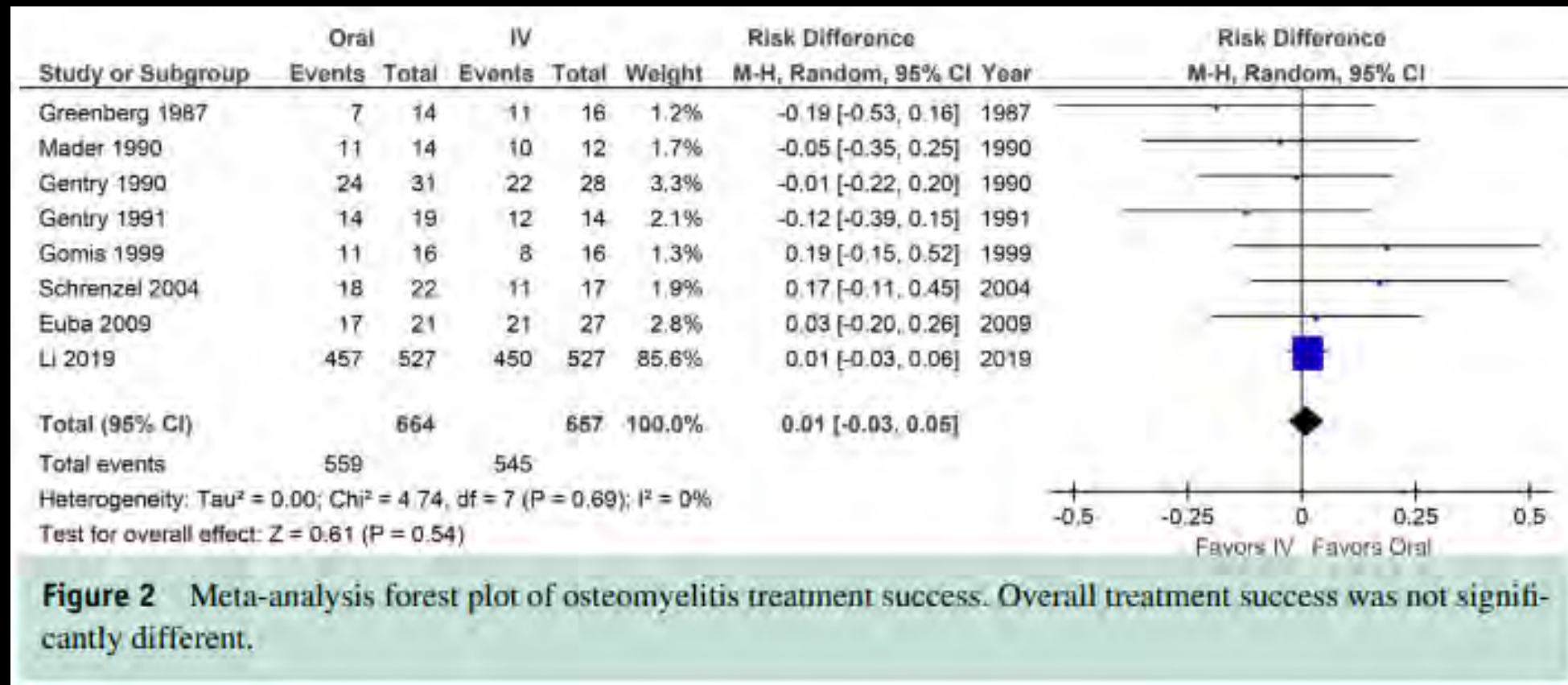
# LONG-TERM ANTIBIOTICS

- A variety of infections require long-term antibiotic therapy
- For some of these, oral therapy is generally felt to be appropriate by most
  - Lung abscess, liver abscess, intraabdominal abscesses
- For others of these, many providers prefer prolonged parenteral therapy
  - Bacteremia, endocarditis, osteomyelitis, joint infections, meningitis
- What are the actual data for these indications?

# FIRST, SOME HISTORY

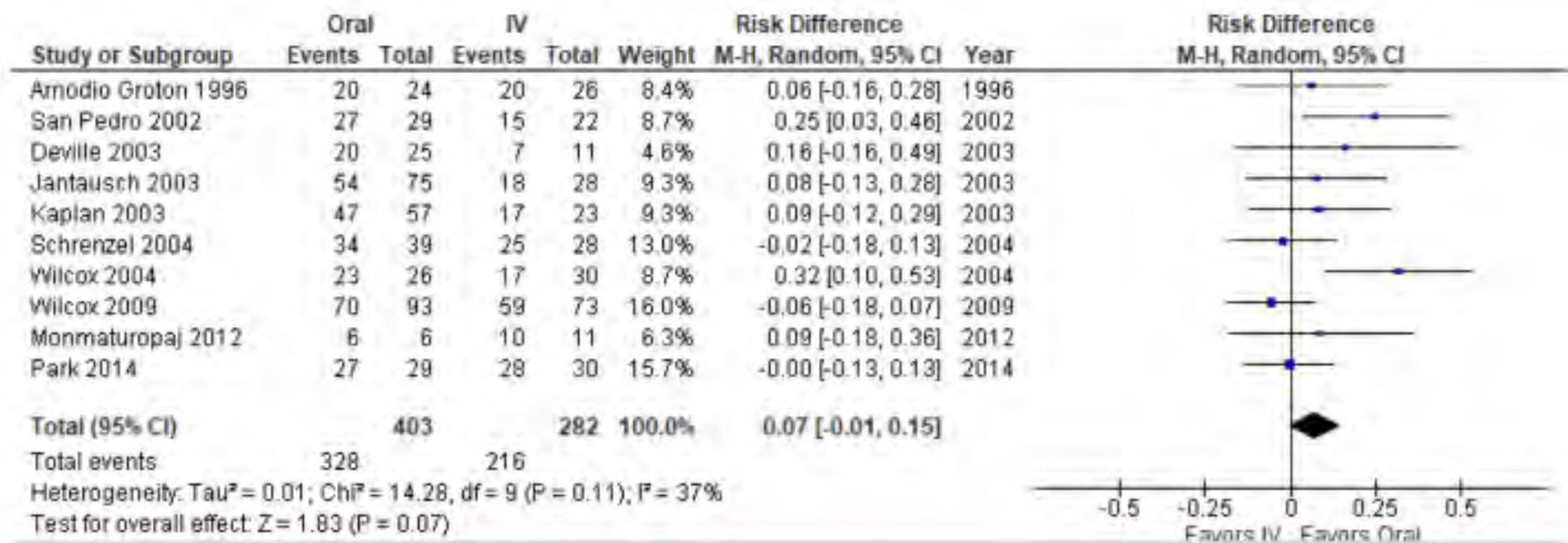
- Where did the “treat with 4-6 weeks of IV therapy” idea originate for osteomyelitis?
  - Uncontrolled case series on osteomyelitis published in 1970
  - Recipients received IV penicillin or aminoglycoside, no oral therapy attempted
  - Conclusion was “...osteomyelitis is rarely controlled without the combination of careful, complete surgical debridement and prolonged (4 to 6 weeks) parenteral antibiotic therapy at high dosage”
- Where did the “use parenteral therapy” for endocarditis originate?
  - Case series from 1940s and 1950s comparing IV penicillin to oral sulfanilamide, erythromycin or tetracycline

# OSTEOMYELITIS



**Figure 2** Meta-analysis forest plot of osteomyelitis treatment success. Overall treatment success was not significantly different.

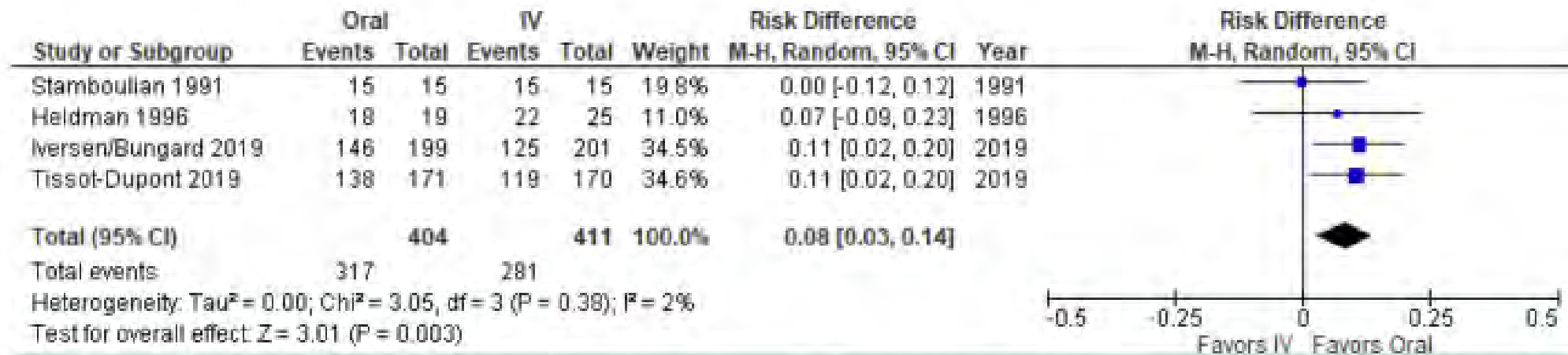
# BACTEREMIA



**Figure 3** Meta-analysis forest plot of bacteremia treatment success. Overall treatment success was not significantly different, although the confidence interval favored oral therapy.



# ENDOCARDITIS



**Figure 4** Meta-analysis forest plot of endocarditis treatment success. Oral therapy was significantly more effective.

# SUMMARY OF THESE

- 21 published studies included in the meta-analyses
  - 20 were prospective randomized trials of IV vs PO for bacteremia, osteomyelitis, or endocarditis
  - One was a quasi-experimental pre/post study (endocarditis)
- Of these 21 studies
  - 21/21 showed oral therapy at least as effective as parenteral therapy
  - 0/21 showed parenteral therapy with better outcomes/superior to oral therapy

# COGNITIVE DISSONANCE?

- *“the state of having inconsistent thoughts, beliefs, or attitudes especially as relating to behavioral decisions and attitude changes”* –Oxford languages
- Frequently, for an MSSA prosthetic joint infection, therapy will consist of cefazolin and rifampin
  - The cefazolin is dosed 2g IV q8h
  - The rifampin is dosed 600mg PO daily or 300mg PO BID or 450mg PO BID
- Why are providers willing to trust the rifampin orally but not the other antibiotic?
  - If asked, the answer usually given is “bioavailability”

# BIOAVAILABILITY

| Antibiotic              | Bioavailability |
|-------------------------|-----------------|
| Amoxicillin             | 80% (74-92%)    |
| Cephalexin              | 90%             |
| Clindamycin             | 90%             |
| Doxycycline             | ~95% (90-100%)  |
| Levofloxacin            | 95%             |
| Linezolid               | ~100%           |
| Metronidazole           | 95%             |
| Rifampin                | 70-93%          |
| TMP-SMX (TMP component) | 90%             |

# CAVEATS

- Absorption not well-studied in patients with acute septic physiology
  - Clinical failures have been observed with transition to oral therapy prior to day 3 of treatment
- Patients need to have a functional GI tract
- There needs to be an effective oral agent that has been studied for the pathogen/infection in question
- Appropriate doses of medication need to be used
- Need to account for food (with/without)
- Patients still need to be monitored for ADR

## CASE #2

- Patient is a 72 y/o man (history of HTN and DVT) with right prosthetic knee joint. Increasing pain to the knee over a several week period. Knee was tapped twice in the outpatient setting; both cultures grew *Veillonella dispar*.
- Underwent a one-stage knee replacement surgery
- On POD#2, risk/benefit discussion with patient about IV vs PO antibiotic therapy
  - He opted for oral therapy. Started amoxicillin-clavulanate 875mg PO 4x/day
- Seen in clinic 3 weeks after discharge. Doing well. Amoxicillin-clavulanate changed to amoxicillin 875mg PO 4x/day as susceptibilities had returned
- Seen in clinic 12 weeks after surgery. Doing well.



# A Diagnostic Stewardship Initiative for Diagnosis of UTIs

Rudolf J. Kotula, MD, MBA, FACP, FIDSA

Nebraska Methodist Hospital

# Disclosures

- Consultant: GSK plc.

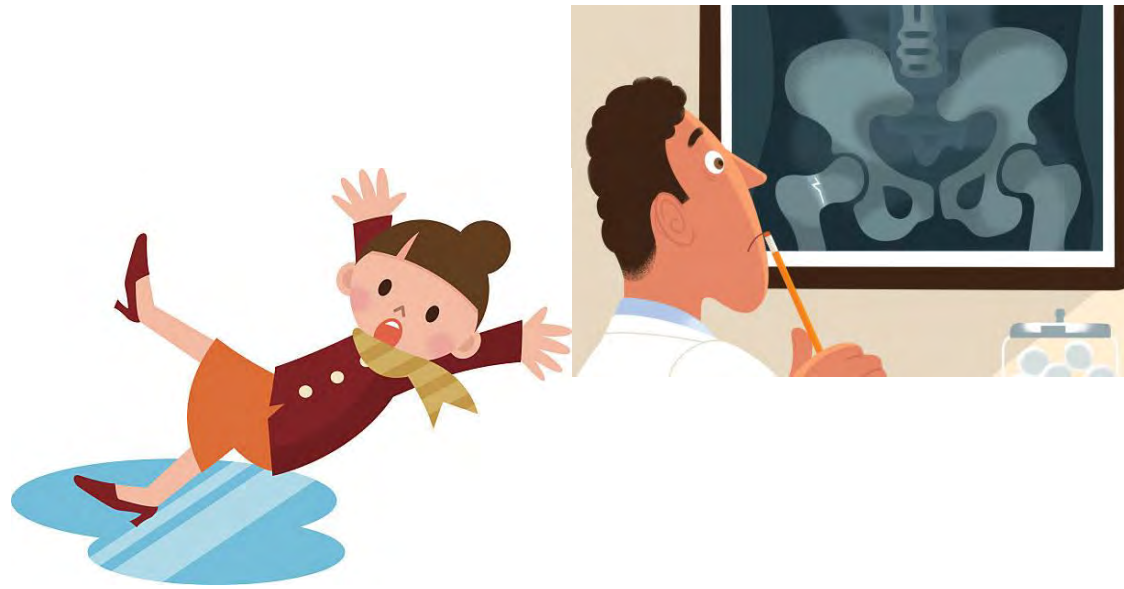




# **Does Bacteria In Urine Signifies a UTI?**

Yes or No?

# Case study



- Healthy, active female patient in 50s presented to ED after a fall at home
- Lives at home independently, takes no medications
- Normal state of health, fall due to ice on the sidewalk
- Exam and imaging showed a right closed hip fracture
- Admitted for closed reduction and nailing

# Case study continued



- Afebrile, no generalized symptoms of infection
- Reported no localized symptoms of urinary tract infection
- ROS genitourinary documented as “Negative”
- UA with reflex to culture was ordered in ED, despite absence of urinary symptoms

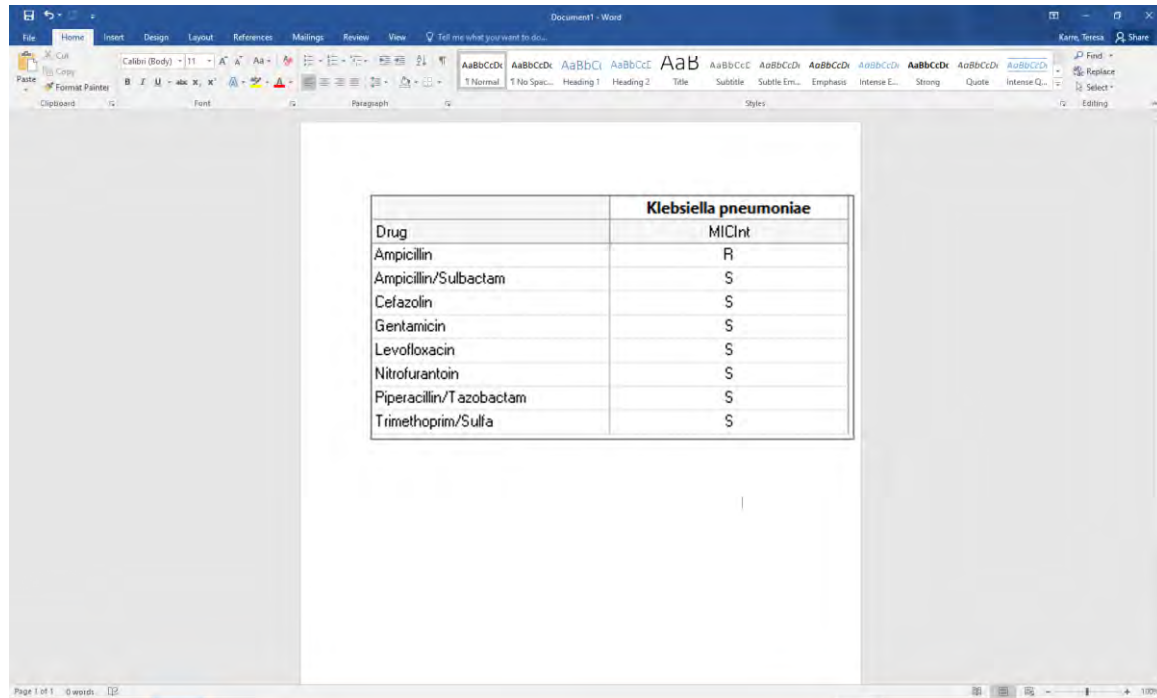
# Case study continued



| Urinalysis Results                          |               |
|---|---------------|
| Culture To Follow                           | * Yes         |
| Color Urine                                 | Yellow        |
| Appearance Urine                            | (A) Cloudy    |
| <input type="checkbox"/> Spec Gravity Urine | 1.011         |
| <input type="checkbox"/> pH Urine           | 6.0           |
| Leuk Ester Urine                            | (A) Large     |
| Nitrite Urine                               | (A) Positive  |
| Protein Urine                               | Negative      |
| Glucose Urine                               | Negative      |
| Ketone Urine                                | Negative      |
| Blood Urine                                 | Negative      |
| Rbc   | None Seen     |
| Wbc   | (A) 51-100    |
| Bacteria                                    | (A) 4+ / hpf  |
| Hyaline Cast                                | (A) 0-2 / lpf |
| Squam Epi Cells                             | None Seen     |

# Case study continued

Culture grew  $>100,000$  *Klebsiella pneumoniae*



| Drug                    | MIC <sub>int</sub> |
|-------------------------|--------------------|
| Ampicillin              | R                  |
| Ampicillin/Subactam     | S                  |
| Cefazolin               | S                  |
| Gentamicin              | S                  |
| Levofloxacin            | S                  |
| Nitrofurantoin          | S                  |
| Piperacillin/Tazobactam | S                  |
| Trimethopim/Sulfa       | S                  |

# Case study continued

- Diagnosed with “UTI” on the basis of the positive UA and culture
- While in hospital for treatment of her fracture, treated with Levofloxacin for her “UTI”



# Case study continued

- Following surgery, transferred to rehab unit, continued Levofloxacin
- Two weeks later, developed abdominal distention, nausea and leukocytosis with elevated lactate and procalcitonin
- CT scan showed severe, diffuse colitis
- Patient developed sepsis and acute kidney injury
- Transferred to ICU, required dialysis
- *C. difficile*: **POSITIVE**
- Patient started on therapy for *C. difficile* infection

# Case study continued



- Patient acutely decompensated
  - Increasing abdominal distension
  - Increasing respiratory requirements
  - Worsening leukocytosis
  - Worsening renal function
- Taken to surgery:
  - Bowel was ischemic, thickened, and injected- c/w toxic megacolon
  - Total abdominal colectomy, end ileostomy, mucus fistula



# Case study continued

- Subtotal colectomy specimen
  - Markedly edematous and acutely inflamed colonic mucosa and bowel wall
  - Superficial epithelial necrosis and crypt loss
  - “Volcano lesions” - dense neutrophilic inflammation extruding from the crypts
  - Pseudomembrane comprised of fibrin and inflammatory cells

# Case study discussion

- Could this outcome have been avoided?
- If so, how?
- Overutilization of urine cultures leads to real patient harm!

# Effects of inappropriate urine cultures

- Wasted lab testing -- ↑ costs
- A positive urine culture often encourages antimicrobial use, irrespective of symptoms.
- Thus, obtaining urine cultures when not clinically indicated, including for routine screening, promotes inappropriate antimicrobial use
- Inappropriate antibiotics
  - ↑ *C. diff* rates (8.5 fold increase in risk in pts. inappropriately tx with abx)
  - ↑ Resistance rates

## Did This Patient Have a UTI?

- Asymptomatic: Documented in her medical record that she had no dysuria, frequency, or other urinary complaints
- Presence of bacteria in the urine without symptoms = Asymptomatic bacteriuria (ASB), not UTI



# Symptoms of UTI

- Lower UTI

- Dysuria
- Frequency
- Urgency
- Suprapubic pain/tenderness
- Hematuria
- Generally GU specific

- Upper UTI

- Fever
- Nausea/vomiting
- CVA tenderness
- +/- lower tract symptoms
- Less specific than upper UTI, but still attributable to urinary tract

# Asymptomatic Bacteriuria (ASB)

- **Presence of bacteria in the urine without GU symptoms**
- ASB in patients without indwelling catheters is  $\geq 10^5$  colony-forming units (CFU)/mL ( $\geq 10^8$  CFU/L) in a voided urine specimen without signs or symptoms attributable to UTI

# Clinical Practice Guideline for the Management of Asymptomatic Bacteriuria: 2019 Update by the Infectious Diseases Society of America<sup>a</sup>

Lindsay E. Nicolle,<sup>1</sup> Kalpana Gupta,<sup>2</sup> Suzanne F. Bradley,<sup>3</sup> Richard Colgan,<sup>4</sup> Gregory P. DeMuri,<sup>5</sup> Dimitri Drekonja,<sup>6</sup> Linda O. Eckert,<sup>7</sup> Suzanne E. Geerlings,<sup>8</sup> Béla Köves,<sup>9</sup> Thomas M. Hooton,<sup>10</sup> Manisha Juthani-Mehta,<sup>11</sup> Shandra L. Knight,<sup>12</sup> Sanjay Saint,<sup>13</sup> Anthony J. Schaeffer,<sup>14</sup> Barbara Trautner,<sup>15</sup> Bjorn Wullt,<sup>16</sup> and Reed Siemieniuk<sup>17</sup>

- 2005 IDSA guideline recommended that ASB should be screened for and treated only in:
  - Pregnant women
  - Pts. undergoing invasive urologic procedures
- Treatment not recommended for:
  - Healthy women
  - Older women or men
  - Diabetics
  - Pts. with indwelling catheters
  - Pts. with spinal cord injury
- The updated guideline includes new recommendations for populations not previously addressed

Addresses interpretation of nonlocalizing clinical symptoms in populations with a high prevalence of ASB.

# Can the UA Separate ASB from UTI?

- Pyuria
  - Leukocyte esterase on dipstick
  - WBCs on microscopic examination (>10/HPF)
  - Can be present due to other causes not specific to UTI
- Bacteriuria
  - Nitrite on dipstick
  - Bacteria present on microscopic examination
  - Can be present in the absence of UTI
- A positive result for either WBC or bacteria is not diagnostic of a UTI without symptoms
- **Absence of pyuria has strong negative predictive value for UTI**



# Can the UA Identify Contaminated Collections?

- Contaminated cultures can complicate the diagnosis of UTI
  - Often, but not always, grow **multiple organisms**
- Creates significant additional **workload for the lab**
- Can result in identification and reporting of organisms that are not responsible for the patient's symptoms
- Presence of squamous epithelial cells on UA microscopic in a clean catch indicate a contaminated collection
  - Not always present, but if present suggest that bacteria could be from skin/genital area rather than bladder
  - Can be useful to determine acceptability for culture
  - Cutoffs may vary from lab to lab- usually range of 5-10

# Can the Urine Culture Separate ASB from UTI? Yes or No?

- Most labs use a cutoff of  $10^2$ - $10^4$  for significant
- Most require two or fewer organism types (more suggests contamination or colonization)
- $>10^5$  of a single organism is very common in ASB- this does not indicate a UTI in the absence of symptoms!



# Goals for UTI diagnosis

- Strengthen the partnership between the laboratory and the clinician
- Limit urine culture ordering to patients in whom a UTI is likely throughout the hospital- not just emergency department
- Improve education throughout the hospital system re: the appropriate use of urine cultures
- Reduce treatment of asymptomatic bacteriuria



# Thank you !

- Any questions?

# Antibiotic Myth: History of Penicillin Allergy Means No Beta-Lactams

Erica Stohs, MD, MPH

Assistant Professor, Infectious Disease

University of Nebraska Medical Center

# Disclosures

- Investigator-Initiated Research: bioMerieux, Merck & Co., Inc.

# Case

62 yo F found found a lump in her right breast with subsequent mammogram demonstrating suspicion for breast cancer. A fine needle biopsy confirmed the diagnosis (DCIS) and she is about to undergo lumpectomy.

Surgical site infection prophylaxis is cefazolin.

She has a penicillin allergy from childhood. Reaction was a rash.

# Facts About Penicillin Allergy



Approx. 10% of patients report a history of penicillin allergy...**However**...Up to 90% of these individuals can tolerate penicillin

80% of patients with IgE-mediated penicillin allergy lose their sensitivity after 10 years

Family history of penicillin allergy does not mean that a patient is allergic to penicillin

Side effects are often confused with allergic reactions, leading to incorrect allergy labels



# Facts About Penicillin Allergy



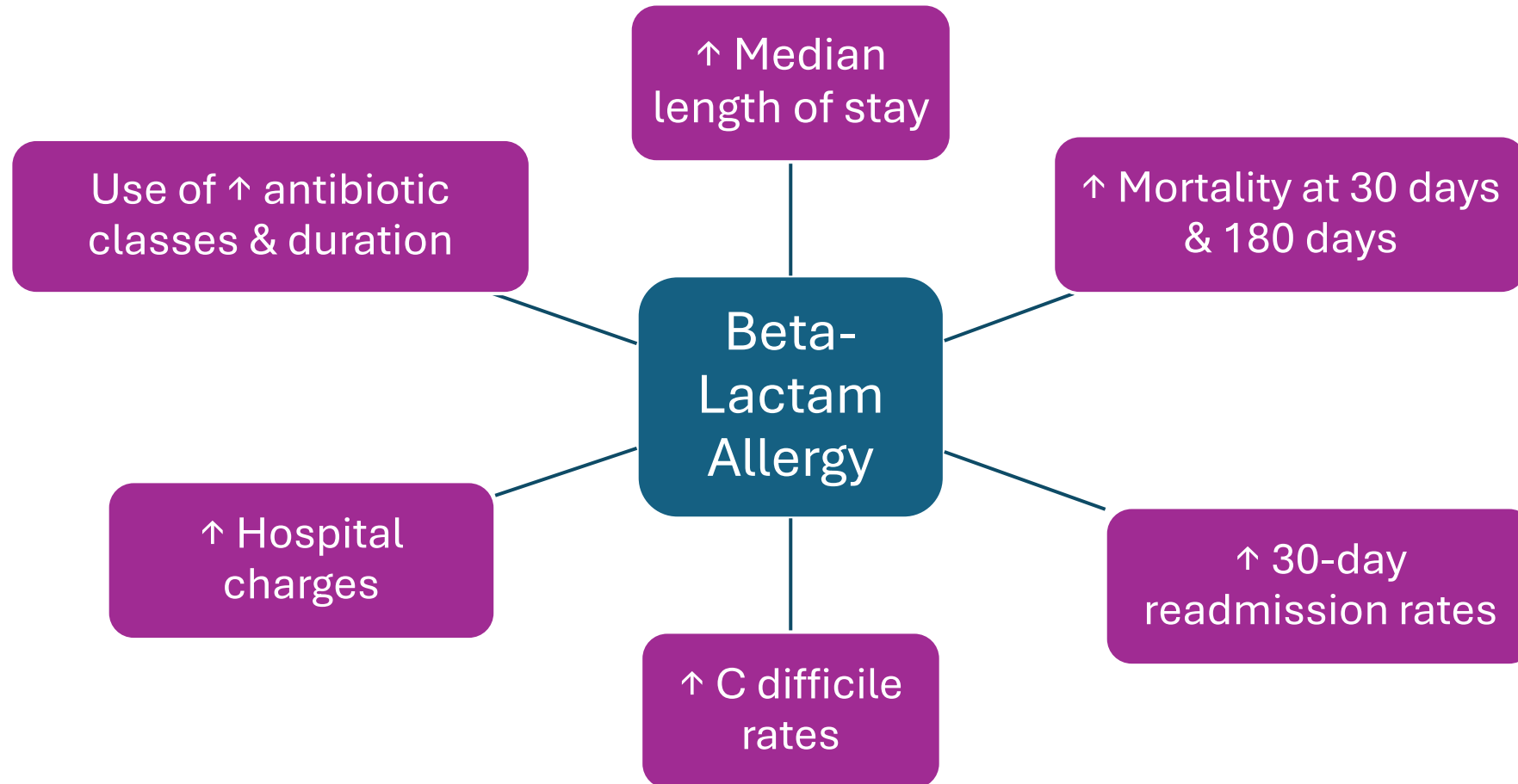
Some very minor risk reactions can be delabeled by taking a detailed history

Severe reactions following penicillin allergy testing in eligible patients are rare, estimated at a frequency of 0.06%

Negative penicillin skin testing results carry a predictive value for anaphylaxis >95% and approaches 100% when combined with oral amoxicillin challenge

PO amoxicillin challenges are safe and effective for delabeling low-risk patients

# Harms of Beta-Lactam Allergies



# Delabeling Interventions

- 3 intervention types that address different reaction risk levels



## History

- Asking questions to assess and clarify the penicillin allergy



## PO drug challenge

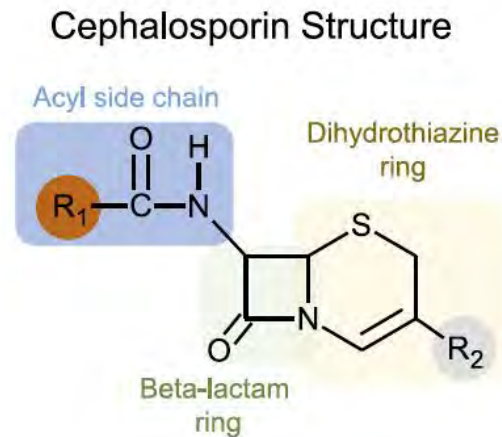
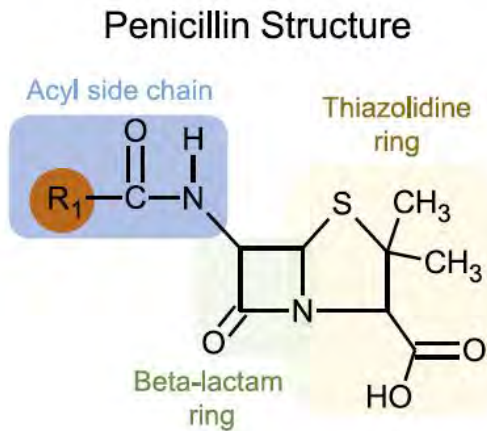
- Small, PO test dose(s) of amoxicillin



## Skin testing

- Scratch testing
- Intradermal testing

# Antibiotic Side Chains Matter



Khan et al. J Allergy Clin Immunol 2022;150(6).

| Beta-Lactam Cross Reactivity |                | PCNs           |           |             |            | 1st Gen CPNs |            | 2nd Gen CPNs |           |          | 3rd Gen CPNs |           |            |          | 4th Gen CPN | Advanced CPNs |             | CARB        |             | MONO      |           |           |
|------------------------------|----------------|----------------|-----------|-------------|------------|--------------|------------|--------------|-----------|----------|--------------|-----------|------------|----------|-------------|---------------|-------------|-------------|-------------|-----------|-----------|-----------|
|                              |                | Penicillin G/V | Oxacillin | Amoxicillin | Ampicillin | Piperacillin | Cefadroxil | Cephalexin   | Cefazolin | Cefaclor | Cefoxitin    | Cefprozil | Cefuroxime | Cefdinir | Cefotaxime  | Cefepime      | Ceftaroline | Ceftolazone | Cefiderocol | Ertapenem | Meropenem | Aztreonam |
| PCNs                         | Penicillin G/V | Black          |           |             |            |              |            |              |           |          |              |           |            |          |             |               |             |             |             |           |           |           |
|                              | Oxacillin      | Black          | Black     |             |            |              |            |              |           |          |              |           |            |          |             |               |             |             |             |           |           |           |
|                              | Amoxicillin    |                | Black     | Black       |            |              |            |              |           |          |              |           |            |          |             |               |             |             |             |           |           |           |
|                              | Ampicillin     |                |           | Black       | Black      |              |            |              |           |          |              |           |            |          |             |               |             |             |             |           |           |           |
|                              | Piperacillin   |                |           |             | Black      | Black        |            |              |           |          |              |           |            |          |             |               |             |             |             |           |           |           |
| 1st Gen CPNs                 | Cefadroxil     |                |           |             |            | Black        |            |              |           |          |              |           |            |          |             |               |             |             |             |           |           |           |
|                              | Cephalexin     |                |           |             |            | Black        | Black      |              |           |          |              |           |            |          |             |               |             |             |             |           |           |           |
|                              | Cefazolin      |                |           |             |            |              | Black      | Black        |           |          |              |           |            |          |             |               |             |             |             |           |           |           |
|                              | Cefaclor       |                |           |             |            |              |            | Black        | Black     |          |              |           |            |          |             |               |             |             |             |           |           |           |
| 2nd Gen CPNs                 | Cefoxitin      |                |           |             |            |              |            |              | Black     |          |              |           |            |          |             |               |             |             |             |           |           |           |
|                              | Cefprozil      |                |           |             |            |              |            |              | Black     | Black    |              |           |            |          |             |               |             |             |             |           |           |           |
|                              | Cefuroxime     |                |           |             |            |              |            |              |           | Black    | Black        |           |            |          |             |               |             |             |             |           |           |           |
|                              | Cefdinir       |                |           |             |            |              |            |              |           |          | Black        | Black     |            |          |             |               |             |             |             |           |           |           |
| 3rd Gen CPNs                 | Cefotaxime     |                |           |             |            |              |            |              |           |          | Black        | Black     |            |          |             |               |             |             |             |           |           |           |
|                              | Cefepime       |                |           |             |            |              |            |              |           |          |              | Black     | Black      |          |             |               |             |             |             |           |           |           |
|                              | Ceftaroline    |                |           |             |            |              |            |              |           |          |              |           | Black      | Black    |             |               |             |             |             |           |           |           |
|                              | Ceftolazone    |                |           |             |            |              |            |              |           |          |              |           |            | Black    | Black       |               |             |             |             |           |           |           |
| Advanced CPNs                | Cefiderocol    |                |           |             |            |              |            |              |           |          |              |           |            |          |             |               | Black       | Black       |             |           |           |           |
|                              | Ertapenem      |                |           |             |            |              |            |              |           |          |              |           |            |          |             |               |             |             | Black       | Black     |           |           |
|                              | Meropenem      |                |           |             |            |              |            |              |           |          |              |           |            |          |             |               |             |             |             | Black     | Black     |           |
| MONO                         | Aztreonam      |                |           |             |            |              |            |              |           |          |              |           |            |          |             |               |             |             |             |           | Black     | Black     |

**NO STRUCTURAL SIMILARITY** Cross reaction unlikely, no R1 or R2 side chain similarity

**LOW STRUCTURAL SIMILARITY** Cross reaction less likely, similar R1 or R2 side chain

**HIGH STRUCTURAL SIMILARITY** Cross reaction likely, identical R1 or R2 side chain

PCNs = penicillins  
CPNs = cephalosporins

CARB = carbapenems  
MONO = monobactams

# PEN-FAST

Externally validated tool, including immunocompromised patients

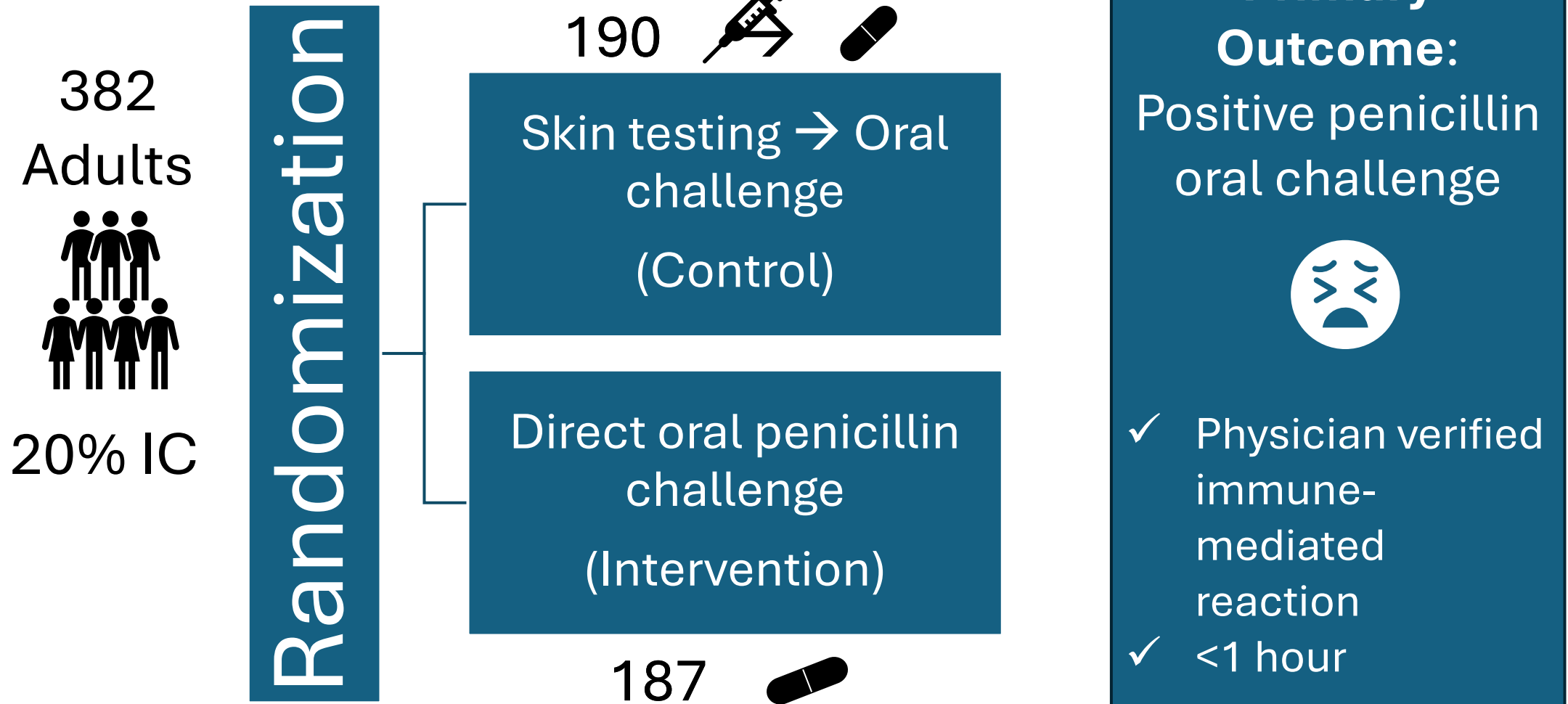


Trubiano JA et al. JAMA Int Med 2020;180(5):745-52.

|  |  |   |
|--|--|---|
| <b>PEN</b>                             | Penicillin allergy reported by patient   | <input type="checkbox"/> <i>If yes, proceed with assessment</i> |
| <b>F</b>                               | Five years or less since reaction <sup>a</sup>   | <input type="checkbox"/> <b>2 points</b>                        |
| <b>A</b>                               | Anaphylaxis or angioedema  | <input type="checkbox"/> <b>2 points</b>                        |
|  | OR   |   |
| <b>S</b>                               | Severe cutaneous adverse reaction <sup>b</sup>   |   |
| <b>T</b>                               | Treatment required for reaction <sup>a</sup>   | <input type="checkbox"/> <b>1 point</b>                         |
|  |  | <hr/>   |
|  |  | <input type="checkbox"/> <b>Total points</b>                    |
| <b>Interpretation</b>                  |  |   |
| <input type="checkbox"/> <b>Points</b> |  |   |
| <input type="checkbox"/> <b>0</b>      | <b>Very low risk</b> of positive penicillin allergy test <1% (<1 in 100 patients reporting penicillin allergy) |   |
| <input type="checkbox"/> <b>1-2</b>    | <b>Low risk</b> of positive penicillin allergy test 5% (1 in 20 patients)                                      |   |
| <input type="checkbox"/> <b>3</b>      | <b>Moderate risk</b> of positive penicillin allergy test 20% (1 in 5 patients)                                 |   |
| <input type="checkbox"/> <b>4-5</b>    | <b>High risk</b> of positive penicillin allergy test 50% (1 in 2 patients)                                     |   |

# Efficacy of a Clinical Decision Rule to Enable Direct Oral Challenge in Patients With Low-Risk Penicillin Allergy

## The PALACE Randomized Clinical Trial



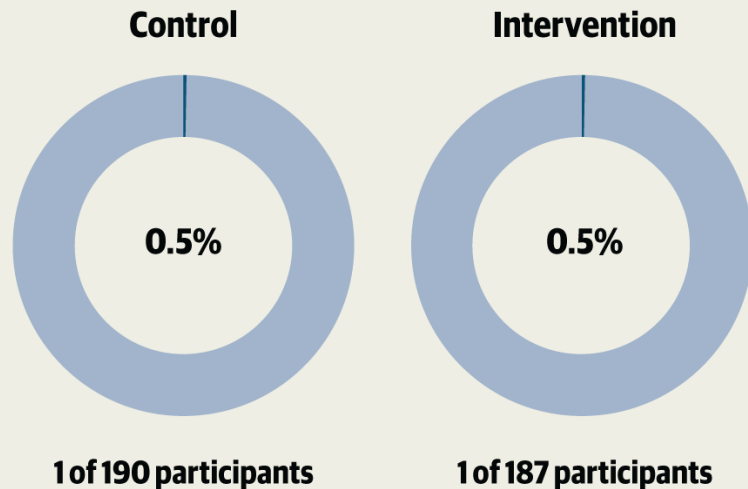
# Efficacy of a Clinical Decision Rule to Enable Direct Oral Challenge in Patients With Low-Risk Penicillin Allergy

## The PALACE Randomized Clinical Trial

### FINDINGS

The intervention was found to be noninferior to the control for the primary outcome in adults with low-risk penicillin allergy

#### Proportion of participants with a positive oral penicillin challenge



**Risk difference**, 0.0084 (90% CI, -1.22 to 1.24) percentage points, which is less than the noninferiority margin

### Other Findings:

- No difference in delayed immune reactions up to 5 days
- Penicillin allergy was removed in 186/190 of the control and 186/187 of the intervention group.
- 94% of participants had a PEN-FAST score <2.

### Take-Aways:

- For patients with PEN-FAST score of 0-1 → Direct oral challenge
- Shorter time in clinic
- Less expensive
- Less labor-intensive
- Adaptable to inpatient and outpatient settings

# Antibiotic Allergy- Takeaways

## De-label

- Address antibiotic allergies

## Optimize

- SSI prophylaxis

## Oral Challenge

- Penicillin using PEN-FAST tool