Antibiotics: What you need to know in 2022

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Director, MGH Antimicrobial Stewardship Program
June 8, 2022

HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

MASSACHUSETTS GENERAL HOSPITAL
ANTIMICROBIAL STEWARDSHIP TEAM

Financial Disclosures

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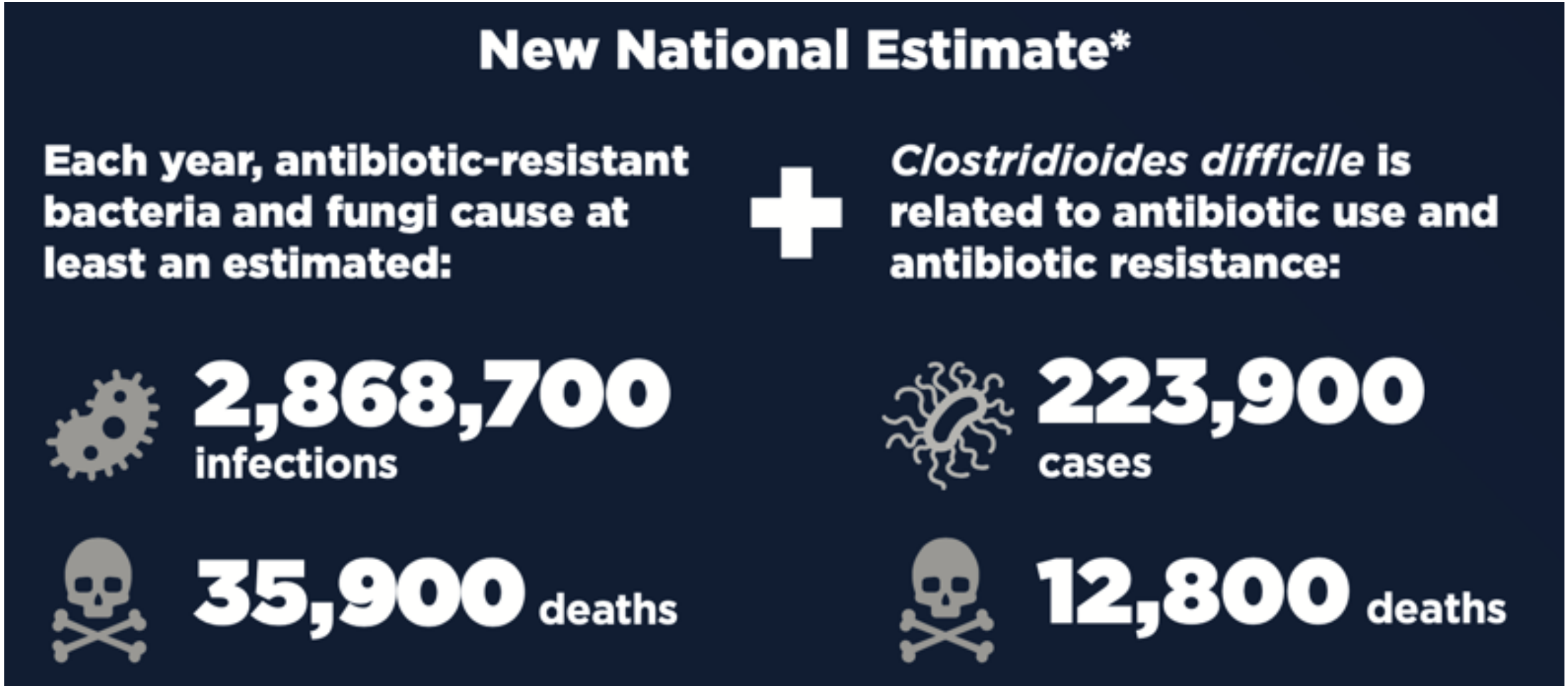
- World Health Information Science Consultants (WHISCON) – research support

Learning Objectives

- Provide a framework for antimicrobial therapy decisions
- Understand penicillin and cephalosporin allergy management
- Discuss the risks and benefits of fluoroquinolone therapy
- Review evidence for shorter courses of antibiotic therapy

Background – Multidrug-resistant organisms



Antibiotic Resistance Threats in the United States. CDC. 2019

Background – Multidrug-resistant organisms

- Antibiotic use is the most important risk factor leading to MDRO
- 13-40% of patients receive antibiotics inappropriately and/or for longer durations than necessary

Antibiotic Resistance Threats in the United States. CDC. 2019
CDC Vital Signs. March 2016
Cosgrove SE et al. Infect Control Hosp Epidemiol 2012;33:374

WHO sounds alarm on drug-resistant bacteria

Global health body warns none of antibiotics currently being developed are enough to tackle superbugs

Bacteria that cause pneumonia or sepsis are becoming more and more resistant to existing drugs, a process that has been accelerated by antibiotic misuse in humans and animals © Getty Images

The New York Times

Doctors Heavily Overprescribed Antibiotics Early in the Pandemic

Now they are using lessons from the experience to urge action on the growing problem of drug-resistant infections before it's too late.

To Combat Superbugs, All Animal Antibiotics Should Have Clear, Science-Based Durations of Use

Many antibiotics do not meet FDA's current definition of judicious use, which must be strengthened

ARTICLE May 6, 2021 By: David Hyun & Helene Sherburne Topics: Antibiotics & U.S. Policy Projects: Antibiotic Resistance Tags: Superbugs Read time: 5 min

SELECTING AN ANTIMICROBIAL

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Name the Syndrome/Infection

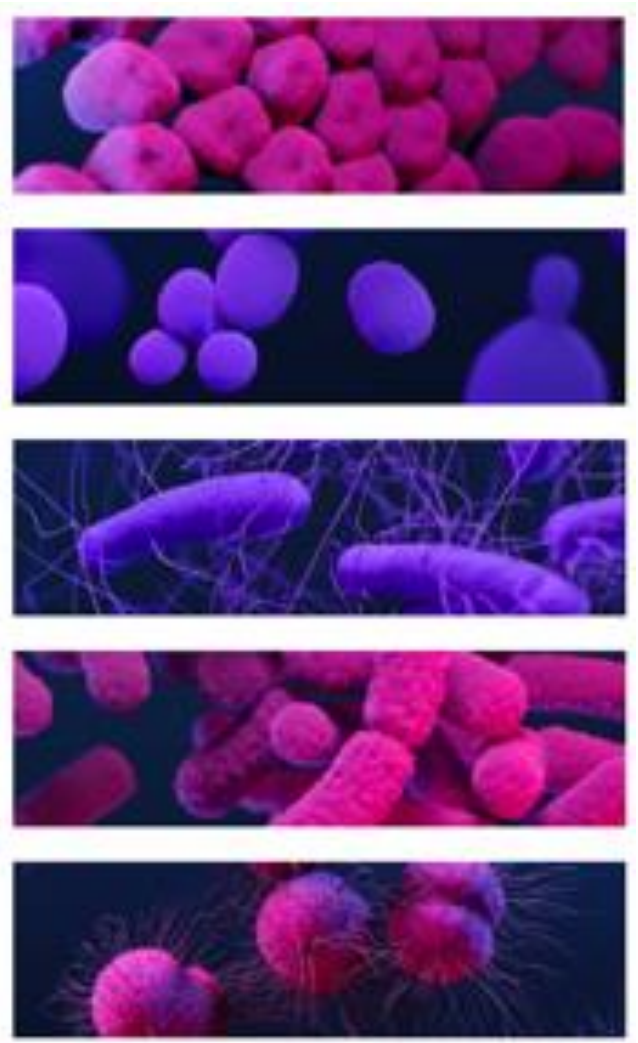
- **What am I treating?**
  - Sepsis / Fever Syndrome
  - Meningitis
  - Bacteremia
  - Pneumonia
  - Intra-abdominal infection
  - Skin & soft tissue infection (SSTI)
  - Urinary tract infection (UTI)

- **How broad or narrow do I need to be?**

What are the most likely pathogens?

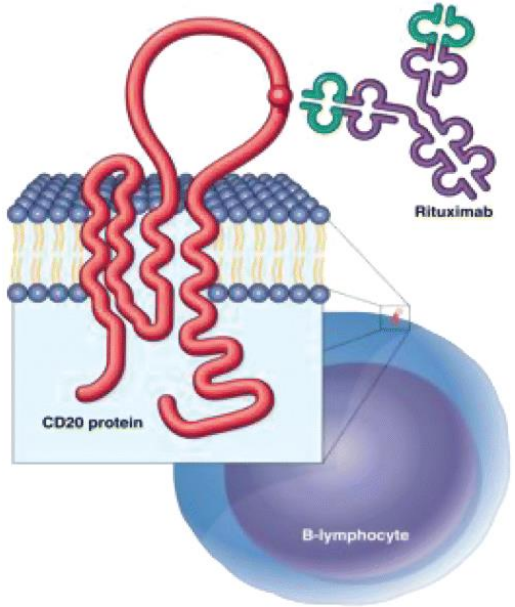
- What resistance may exist?

- ***Do*** I need to be worried about colonization?
  - Methicillin-resistant *Staphylococcus aureus*
  - Vancomycin-resistant *Enterococcus*
  - Multidrug-resistant gram-negatives



Who is the host?

- HIV/AIDS, immunodeficiency
- Chemotherapy, transplant recipient
- TNF alpha inhibitors, steroids



- Any exposures?
  - Sick contacts, children, animals
  - Any animal bites (or human)
  - Travel history, recent or remote

Where is the Infection?

Is the antimicrobial getting to the pathogen?

- Serum
- Cerebral spinal fluid
- Tissues
- Body fluid concentration

Dosing Appropriately

- Renal function
- Body weight
- Organism

Can I Give the Antimicrobial?

- Toxicity
  - Allergy
  - Renal failure
  - Mental status changes
  - *Clostridium difficile*

- Formulation/bioavailability
  - Intravenous
  - Oral
  - Inhaled
- Adherence/convenience
  - Daily
  - 3 times/day
  - 5 times/day

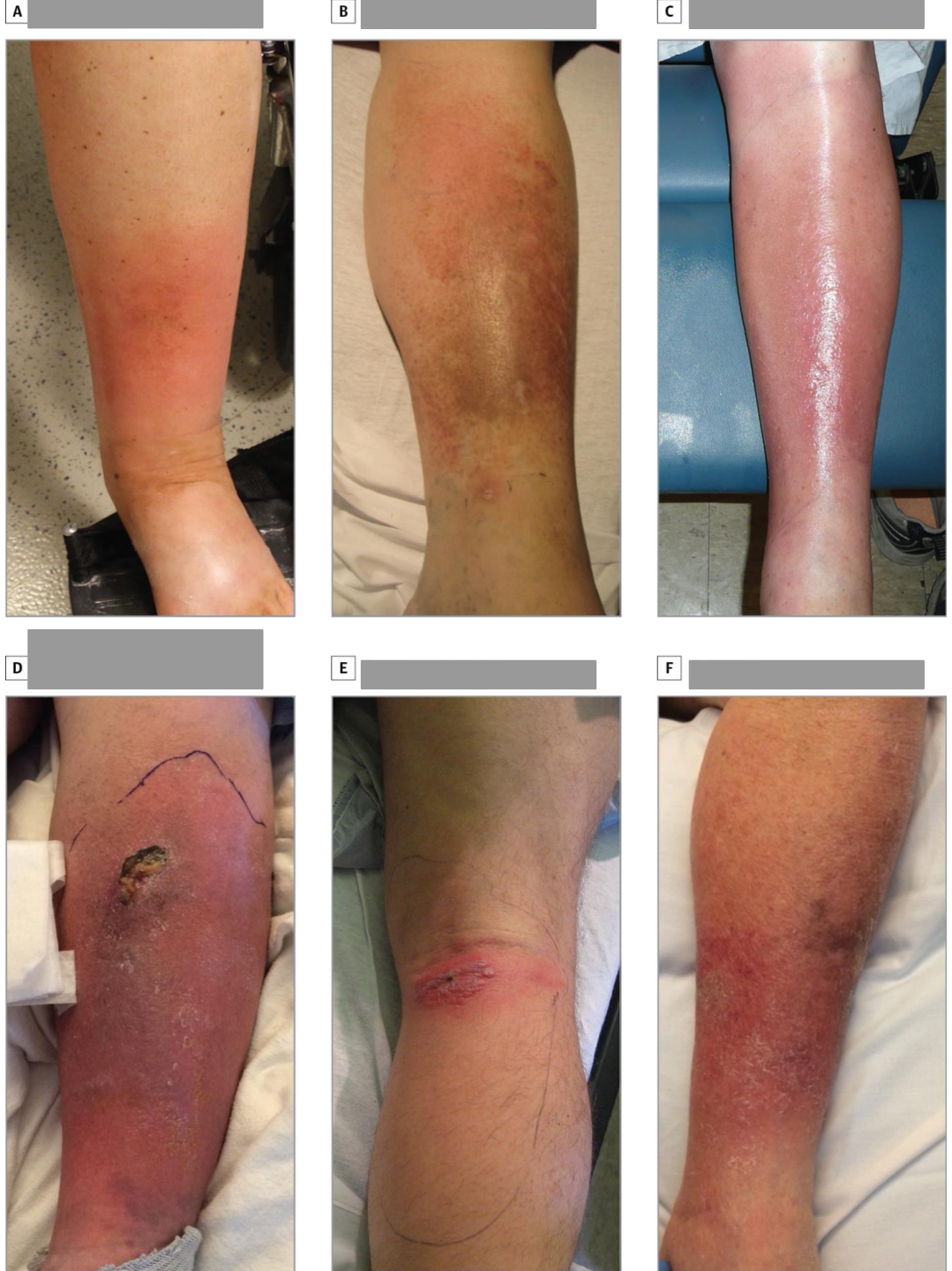
Duration / Cost / Availability

- Duration
  - Shortest duration with best therapeutic effect
- Cost/Availability
  - Formularies
  - Shortages

Antimicrobial Timeout

- Obtain cultures before starting antimicrobials
- Use rapid diagnostics
- Reassess at 48-72 hours

- “Response to therapy” should not be the only guide for therapeutic decisions
- Have the courage to make a diagnosis
- Follow recommended guidelines



Where is the infection?

Raff AB and Kroshinsky D. JAMA 2016;316:325

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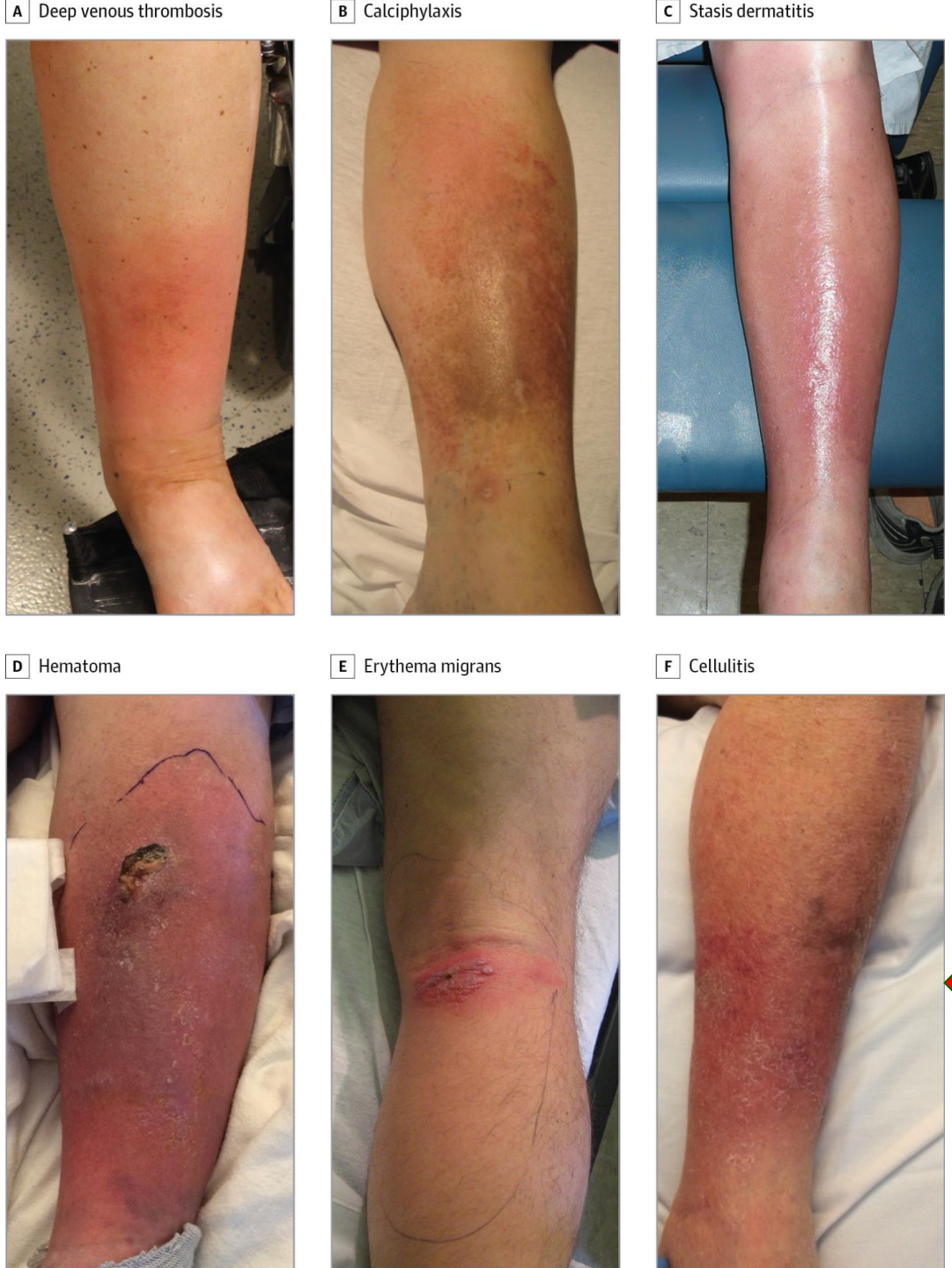

Where is the infection?

Raff AB and Kroshinsky D. JAMA 2016;316:325

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Failure to Respond

- Presence of a nonbacterial infection or a non-infectious process mimicking infection
- Inadequate dosing of antimicrobials
- Incorrect drug for site of infection
- Antimicrobial resistance
- Failure of source control
  - Drain an abscess, relieve an obstruction, remove a foreign body
- Superinfection
- Adverse drug reaction
- Impairment of host defense – local or systemic

Case 1

- 60 yo woman with ceftriaxone-susceptible *Streptococcus pneumoniae* meningitis
- She developed anaphylaxis to penicillin when she had amoxicillin as a 20 year old

What antibiotic would you give her?

A. Vancomycin
B. Ceftriaxone by test dose procedure
C. Chloramphenicol
D. Moxifloxacin

Case 1 – Answer

- 60 yo woman with ceftriaxone-susceptible *Streptococcus pneumoniae* meningitis
- She developed anaphylaxis to penicillin when she had amoxicillin as a 20 year old

What antibiotic would you give her?

A. Vancomycin

B. Ceftriaxone by test dose procedure

C. Chloramphenicol

D. Moxifloxacin

PENICILLIN ALLERGY MANAGEMENT

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Background – Penicillin Allergy

- Penicillin allergy (10-15% of hospitalized patients)
  - Poor clinical outcomes
  - Longer length of stay
  - Increased readmissions
  - Increased rates of *Clostridioides difficile* (C. diff)
  - Increased methicillin-resistant *Staphylococcus aureus* (MRSA)
  - Increased vancomycin-resistant *Enterococcus* (VRE)

- Beta-lactam allergy
  - Inappropriate antibiotics for Gram-negative bacteremia

Macy E and Contreras R. *J Allergy Clin Immunolo* 2014;133(3):790-6
MacFadden DR et al. *Clin Infect Dis* 2016;63(7):904-10
Jeffres MN et al. *J Allerg Clin Immunol* 2016;137(4):1148-53
Blumenthal KG et al. *Ann Allergy Asthma Immunol* 2015:115;294

Clarify Antibiotic Allergies

- Take a history!
  - 60-year-old woman with penicillin allergy in her 20s
  - Likely to tolerate penicillin or, at minimum, a higher generation cephalosporin

- 90-99% with reported allergy will tolerate PCNs

Blumenthal et al. *Ann Allergy Asthma Immunol* 2015;115(4):294

Mass General Brigham

GUIDELINE FOR: PENICILLIN AND CEPHALOSPORIN HYPERSENSITIVITY PATHWAY

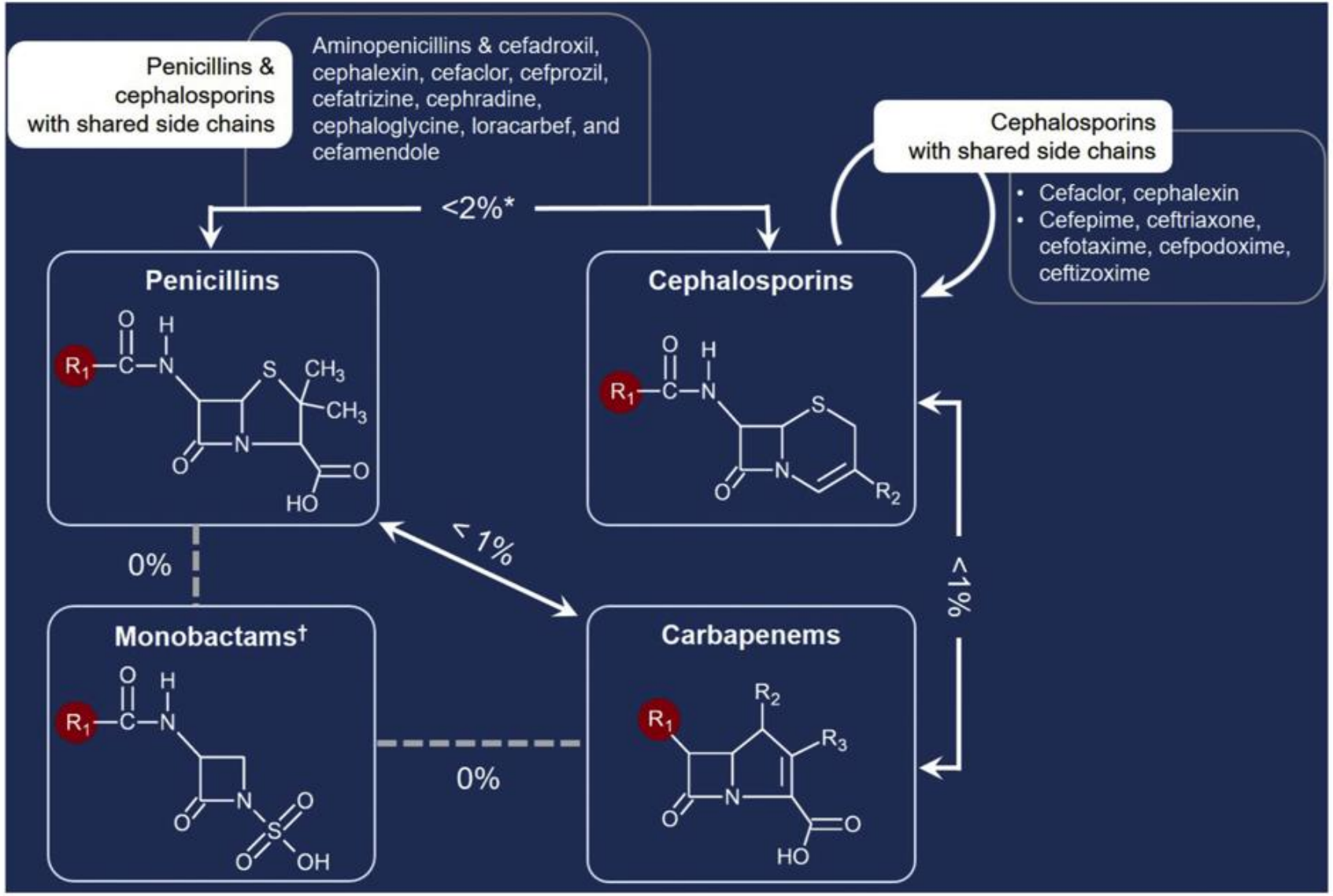
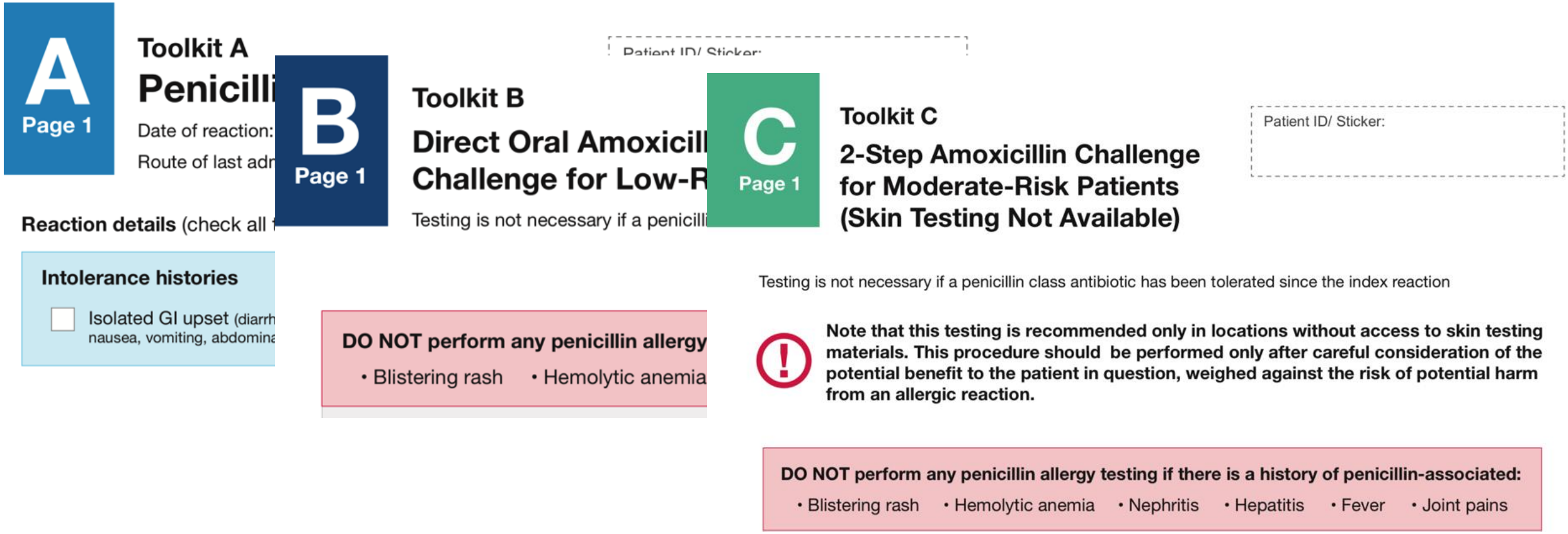


FIGURE 3. Beta-lactam structure and cross-reactivity examples. Beta-lactam antibiotics include the penicillins, cephalosporins, carbapenems, and monobactams. This figure demonstrates the overall cross-reactivity between classes sharing the core beta-lactam ring. Current data support that cross-reactivity between penicillins and cephalosporins is higher for those that share common R1 side chains and in patients with severe reactions histories. This figure demonstrates a few examples of side chains where there has been clinical cross-reactivity observed. More comprehensive side chain cross-reactivity has been discussed elsewhere.[33,61,62] *Except for shared side chains.[33,61,62] †Monobactams have no shared cross-reactivity, except for aztreonam and ceftazidime.

Chiriac AM et al. J Allergy Clin Immunol Pract 2019;7(1):46-60

Toolkit for Evaluation and Management of Penicillin Allergy

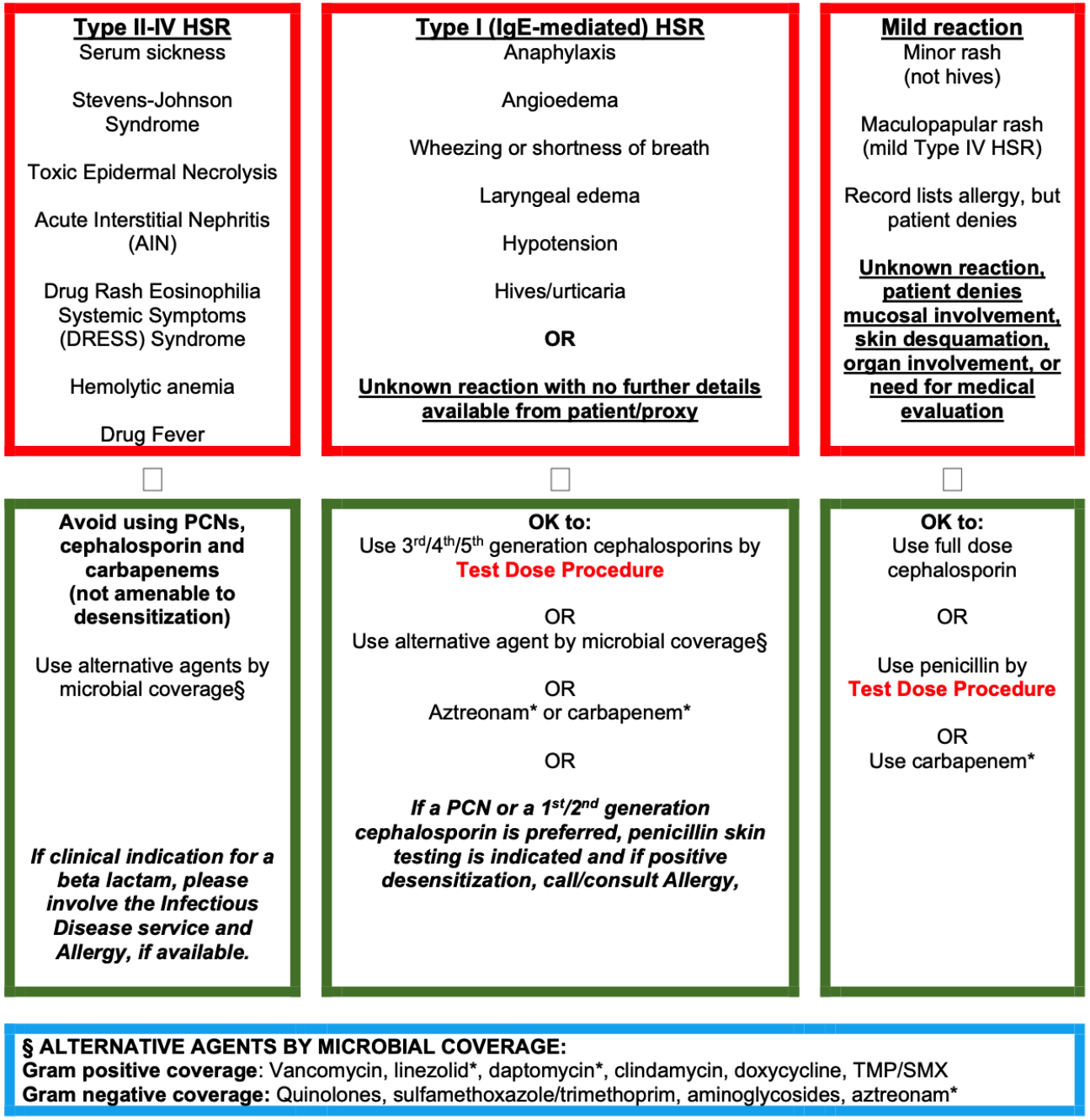
January 2019 Journal of the American Medical Association



Shenoy ES et al. JAMA 2019/321(2):188-199.

Blumenthal KG et al. Ann Allergy Asthma Immunol 2015:115;294 – algorithm updated 2022

Figure 1. Penicillin Hypersensitivity Pathway.[2-5]



Blumenthal KG et al. Ann Allergy Asthma Immunol 2015:115;294 – algorithm updated 2022

Figure 2. Cephalosporin Hypersensitivity Pathway

Type II-IV HSR
Serum sickness

Stevens-Johnson Syndrome

Toxic Epidermal Necrolysis

Acute Interstitial Nephritis (AIN)

Drug Rash Eosinophilia

Systemic Symptoms (DRESS) Syndrome

Hemolytic anemia

Drug Fever

Type I (IgE-mediated) HSR
Anaphylaxis

Angioedema

Wheezing or shortness of breath

Laryngeal edema

Hypotension

Hives/urticaria

OR

Unknown reaction with no further details available from patient/proxy

Mild reaction
Minor rash (not hives)

Maculopapular rash (mild Type IV HSR)

Record lists allergy, but patient denies

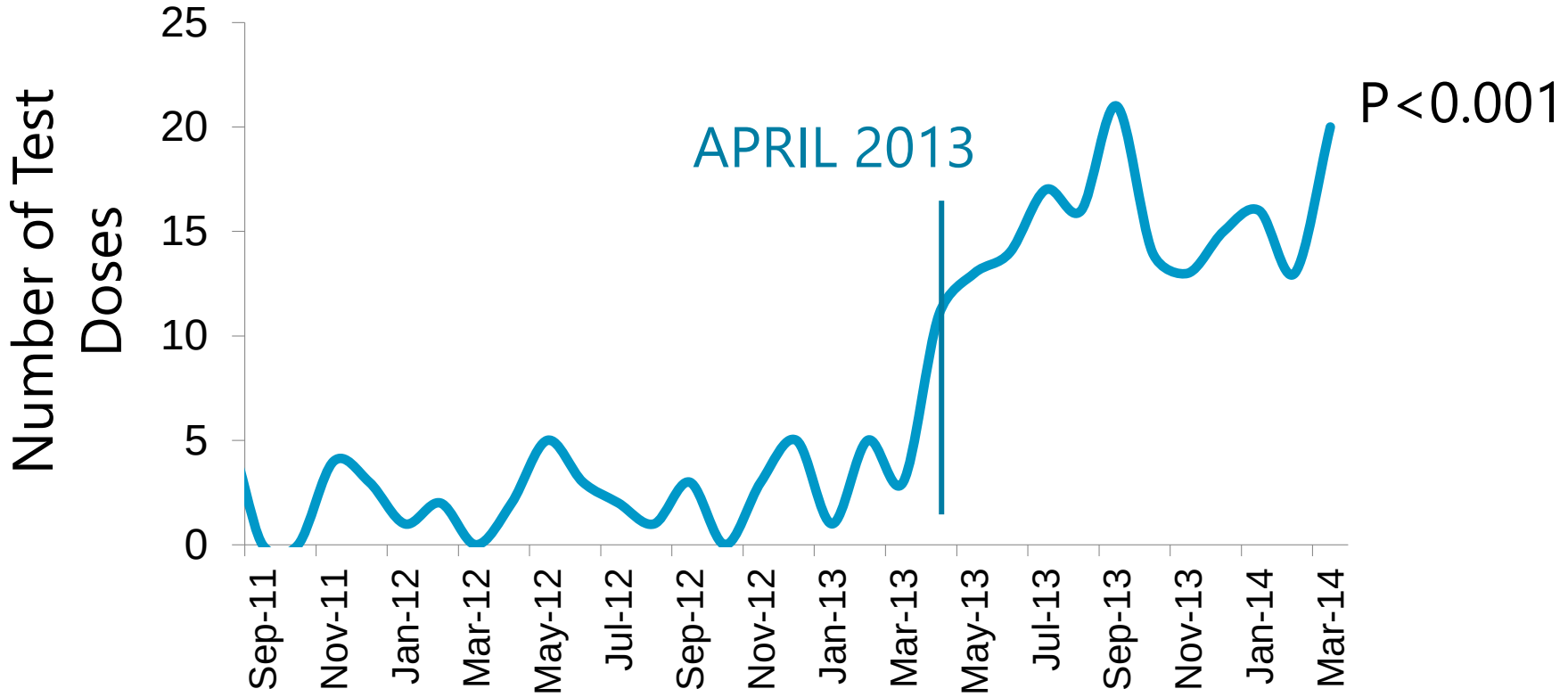
Unknown reaction, patient denies mucosal involvement, skin desquamation, organ involvement, or need for medical evaluation

Reaction to:

	1st/ 2nd Generation	3rd/4th Generation	
☐	☐	☐	☐
Avoid using PCNs, cephalosporins and carbapenems (not amenable to desensitization) Use alternative agents by microbial coverage§ ***If clinical indication for a beta lactam, please involve the Infectious Disease service and Allergy, if available.***	**OK to:** Administer 3rd/4th/5th generation cephalosporin if dissimilar side chains† by **Test Dose Procedure** **OR** Use carbapenem* **OR** Use alternative agents by microbial coverage§ **OR** ***If a PCN or a 1st/2nd generation cephalosporin is preferred, penicillin skin testing is indicated and if positive desensitization, call/consult Allergy***	**OK to:** Administer PCN or cephalosporin if dissimilar side chains† by **Test Dose Procedure** **OR** Use carbapenem* **OR** Use alternative agents by microbial coverage§	**OK to:** Use a different generation cephalosporin and cephalosporin with dissimilar side chains† **OR** Use PCN by **Test Dose Procedure** **OR** Use carbapenem* **OR** Use alternative agents by microbial coverage§

§ ALTERNATIVE AGENTS BY MICROBIAL COVERAGE (see Table 1 for additional details):
Gram positive coverage: Vancomycin, linezolid*, daptomycin*, clindamycin, doxycycline, TMP/SMX
Gram negative coverage: Quinolones, sulfamethoxazole/ trimethoprim, aminoglycosides, aztreonam*

Safe Increase in Monthly Test Doses



	Pre-Period	Post Period	P Value
ADRs N (%)	3(6.1)%	7 (3.8%)	0.44

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Blumenthal *Ann Allergy Asthma Immunol* 2015

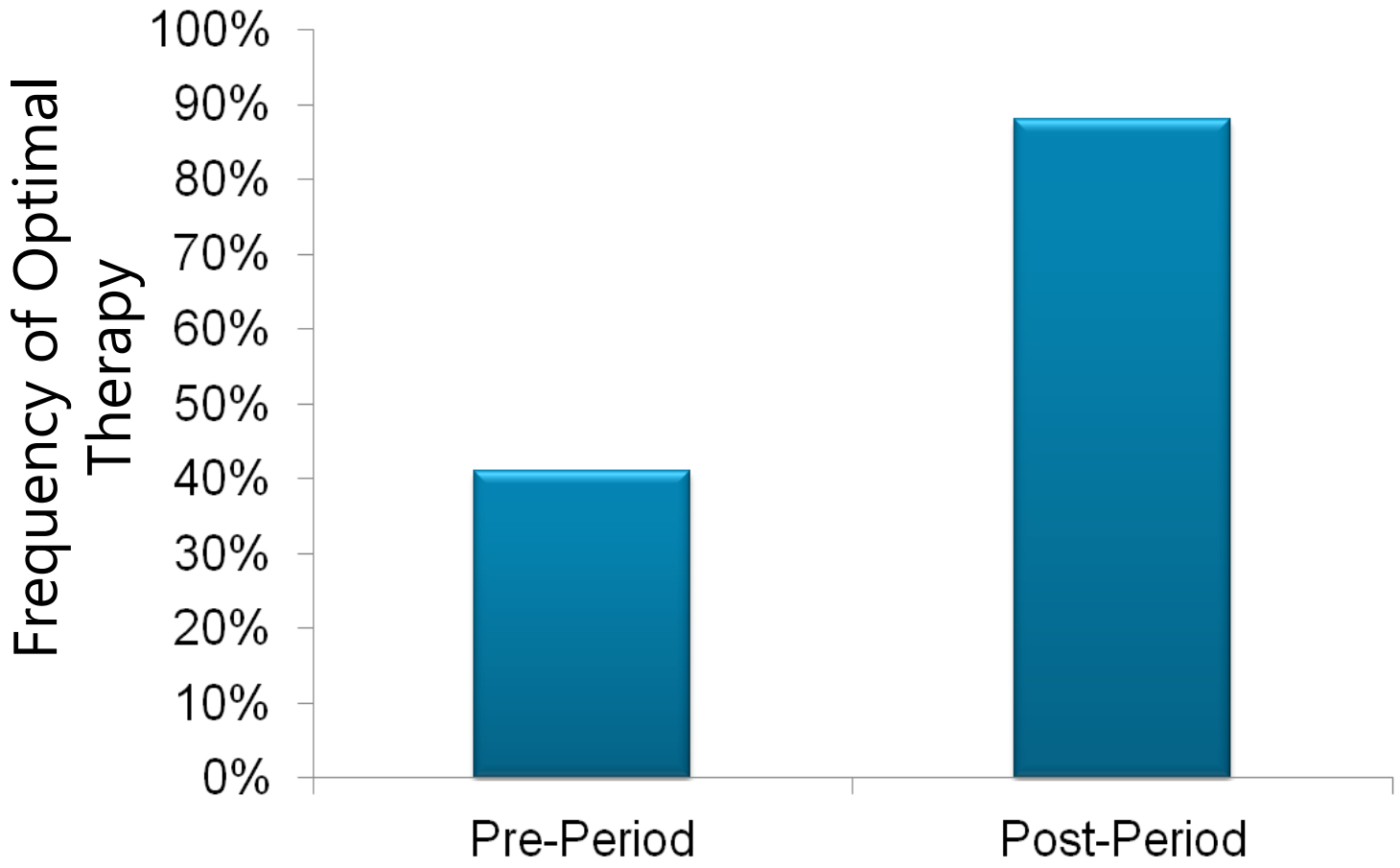
Test Doses Decreased Alternative Antibiotic Use

Patients on therapy before vs after the test dose:

- Vancomycin (68% vs 37%, p<0.001)
- Aztreonam (12% vs 0.5%, p<0.001)
- Aminoglycosides (6% vs 1%, p=0.004)
- Quinolones (15% vs 3%, p<0.001)

Blumenthal *Ann Allergy Asthma Immunol* 2015

Increased First Line Therapy in methicillin-susceptible *Staph aureus* Bacteremia



Blumenthal *PLoS ONE* 2016

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Penicillin as Drug of Choice

- *Streptococcus* infection (Group A Strep pharyngitis)
- Endocarditis
  - *Streptococcus viridans* and *gallolyticus (bovis)*
  - Often in combination with gentamicin
- *Actinomyces* species
  - Often 6 – 12 months of therapy
- *Cutibacterium (Propionibacterium) acnes*
  - Native and prosthetic shoulder infections
- Syphilis

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Penicillin to Prevent Recurrent Leg Cellulitis

Kim S. Thomas, Ph.D., Angela M. Crook, Ph.D., Andrew J. Nunn, M.Sc., Katharine A. Foster, Ph.D., James M. Mason, D.Phil., Joanne R. Chalmers, Ph.D., Ibrahim S. Nasr, M.Sc., Richard J. Brindle, D.M., John English, M.B., B.S., Sarah K. Meredith, F.F.P.H., Nicholas J. Reynolds, M.D., F.R.C.P., David de Berker, M.D., F.R.C.P., Peter S. Mortimer, M.D., F.R.C.P., and Hywel C. Williams, Ph.D., F.R.C.P., for the U.K. Dermatology Clinical Trials Network's PATCH I Trial Team*

N Engl J Med 2013;368:1695-703.
DOI: 10.1056/NEJMoa1206300

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Case 1 – Revisit

- 60 yo woman with ceftriaxone-susceptible *Streptococcus pneumoniae* meningitis
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FLUOROQUINOLONES

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Fluoroquinolones – Should we even bother?

- Multiple F

FDA Dr
warnin
antibio

FDA Drug Safety Communication: FDA advises restricting fluoroquinolone antibiotic use for certain uncomplicated infections; warns about disabling side effects that can occur together

FDA News Release

FDA warns about increased risk of ruptures or tears in the aorta blood vessel with fluoroquinolone antibiotics in certain patients

Fluoroquinolones – Should we even bother?

- July 2008 – tendinitis and tendon rupture
- August 2013 – Peripheral neuropathy
- May 2016 - restrict use for certain uncomplicated infections
- July 2016 – disabling side effects of the tendons, muscles, joints, nerves, and central nervous system
- July 2018 – significant decreases in blood sugar and certain mental health side effects
- December 2018 – avoid in patients with aortic aneurysm or are at risk for an aortic aneurysm (h/o blood vessel blockages or aneurysms, high blood pressure, certain genetic conditions such as Marfan syndrome and Ehlers-Danlos syndrome, and elderly patients.

Fluoroquinolones – Should we even bother?

- FDA - Should be reserved to treat life-threatening bacterial infections
- Pyelonephritis (short course)
- Community-acquired pneumonia (IDSA guidelines)
- Osteomyelitis (intravenous-sparing therapy)
- Fever & neutropenia (treatment in low-risk, prophylaxis in others)

DURATION OF THERAPY

EDITORIAL

The New Antibiotic Mantra—"Shorter Is Better"

Brad Spellberg, MD

Table. Infections for Which Short-Course Therapy Has Been Shown to Be Equivalent in Efficacy to Longer Therapy

	Treatment, Days	
Disease	Short	Long
Community-acquired pneumonia[1-3]	3-5	7-10
Nosocomial pneumonia[6,7]	≤8	10-15
Pyelonephritis[10]	5-7	10-14
Intraabdominal infection[11]	4	10
Acute exacerbation of chronic bronchitis and COPD[12]	≤5	≥7
Acute bacterial sinusitis[13]	5	10
Cellulitis[14]	5-6	10
Chronic osteomyelitis[15]	42	84

Abbreviation: COPD, chronic obstructive pulmonary disease.

doi:10.1001/jamainternmed.2016.3646

Comparing the Outcomes of Adults With Enterobacteriaceae Bacteremia Receiving Short-Course Versus Prolonged-Course Antibiotic Therapy in a Multicenter, Propensity Score–Matched Cohort

Darunee Chotiprasitsakul,[1] Jennifer H. Han,[2] Sara E. Cosgrove,[3] Anthony D. Harris,[4] Ebbing Lautenbach,[2] Anna T. Conley,[5] Pam Tolomeo,[2] Jacqueleen Wise,[2] and Pranita D. Tamma[6]; for the Antibacterial Resistance Leadership Group

- 385 matched pairs, median duration 8 d vs 15 d
- No difference in mortality
- Odds of recurrence bacteremia and *C. difficile* were similar
- Trend towards decreased emergence of MDRO Gram-negative bacteria

Chotiprasitsakul et al. *CID* 2018;66(2):172–7

Clinical Infectious Diseases

MAJOR ARTICLE

Seven Versus 14 Days of Antibiotic Therapy for Uncomplicated Gram-negative Bacteremia: A Noninferiority Randomized Controlled Trial

Dafna Yahav,[1,2] Erica Franceschini,[3] Fidi Koppel,[4] Adi Turjeman,[2,5] Tanya Babich,[2,5] Roni Bitterman,[4] Ami Neuberger,[4,6] Nesrin Ghanem-Zoubi,[4] Antonella Santoro,[3] Noa Eliakim-Raz,[1,2] Barak Pertzov,[5] Tali Steinmetz,[5] Anat Stern,[4] Yaakov Dickstein,[4] Elias Maroun,[4] Hiba Zayyad,[4] Jihad Bishara,[1,2] Danny Alon,[7] Yonatan Edel,[2,8] Elad Goldberg,[9] Claudia Venturelli,[3] Cristina Mussini,[3] Leonard Leibovici,[2,5] Mical Paul[4,6]; for the Bacteremia Duration Study Group[a]

- Randomized, multi-center, open-label, non-inferiority trial, ~600 patients
- Stable at 48 hours randomized to 7 vs 14 days
- 90-day composite of all-cause mortality, relapse, complications, readmission, extended hospitalization
- 68% with urinary source, similar outcomes in both groups including adverse events

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ORIGINAL ARTICLE

Shortened Antimicrobial Treatment for Acute Otitis Media in Young Children

Alejandro Hoberman, M.D., Jack L. Paradise, M.D., Howard E. Rockette, Ph.D., Diana H. Kearney, R.N., C.C.R.C., Sonika Bhatnagar, M.D., M.P.H., Timothy R. Shope, M.D., M.P.H., Judith M. Martin, M.D., Marcia Kurs-Lasky, M.S., Susan J. Copelli, B.S., D. Kathleen Colborn, B.S., Stan L. Block, M.D., John J. Labella, M.D., et al.

- 520 children 6-23 months with AOM
- Amox-clav 10 d vs 5 d noninferiority study
- Measured clinical response, recurrence, NP colonization
- More clinical failure with 5 d 77/229 (34%) vs 39/238 (16%)
- No difference in rates of recurrence, AEs, or NP colonization of PCN-NS organisms

N Engl J Med 2016; 375:2446-2456
DOI: 10.1056/NEJMoa1606043

Shorter Is Better

Diagnosis	Short (d)	Long (d)	Result	#RCT
CAP	3-5	5-14	Equal	15
Atypical CAP	1	3	Equal	1
VAP	8	15	Equal	2
cUTI/Pyelonephritis	5 or 7	10 or 14	Equal	9*
Intra-abdominal Infection	4	10	Equal	2
GNB Bacteremia	7	14	Equal	3**
Cellulitis/Wound/Abscess	5-6	10	Equal	4†
Osteomyelitis	42	84	Equal	2
Osteo with Removed Implant	28	42	Equal	1
Debrided Diabetic Osteo	10-21	42-90	Equal	2‡
Septic Arthritis	14	28	Equal	1
AECB & Sinusitis	≤5	≥7	Equal	>25
Neutropenic Fever	AFx72 h	+ANC>500	Equal	1
Post Op Prophylaxis	0-1	1-5	Equal	55Ψ
P. vivax Malaria	7	14	Equal	1

Total: 15 Conditions 121 RCTs

*2 RCT included males, the smaller one found lower 10-18 d f/up cure in males with 7 days of therapy but no difference at longer follow-up, larger exclusive male study found no diff in cure; **GNB bacteremia also in UTI/cIAI RCTs; †3 RCTs equal, 1 (low dose oral flucox) ↑relapses 2° endpoint; ‡all patients debrided, in 1 study total bone resection (clean margins); ΨIncludes meta-analysis of 52 RCTs; refs at https://www.bradspellberg.com/shorter-is-better

- CAP = community-acquired pneumonia
- VAP = ventilator-associated pneumonia
- GNB = Gram negative bacilli
- AECB = acute exacerbation of chronic bronchitis

https://www.bradspellberg.com/shorter-is-better

Shorter Is Better Exceptions

Diagnosis	Short (d)	Long (d)	Result	#RCT
Prosthetic Joint Infection	6 wk	12 wk	Inferior	1*
Early Pros. Joint Infect.	8 wk	12-26 wk	Equal	1*
Otitis Media < 2 yr old	5	10	Inferior	1
Otitis Media >2 yr old	<10	10	Equal	49**
Strep Throat: Nml PCN	3-5	7-10	Inferior	5†
Strep Throat: Other Abx	3-5	7-10	Equal	>20†
Strep Throat: QID PCN	5	10	Equal	1
Chronic Pulm Aspergillus	6 mo	12 mo	Inferior	1
Total: 4 Diseases				>25 RCTs

* 6 vs. 12 week inferior for all-comers in largest trial, driven primarily but not entirely by DAIR cohort, but other RCT from Shorter Is Better table demonstrated 4-6 weeks may be non inferior, and small RCT of PJI within 1 month of implant showed non-inferiority of 8 vs. 12-26 wks;
**meta-analysis of 49 trials; 3% increased short term failure, but by 1 month of follow up, no difference;
†meta-analysis of >25 trials.
refs at https://www.bradspellberg.com/shorter-is-better

https://www.bradspellberg.com/shorter-is-better

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Take Home Points

- All antibiotic use can lead to resistance
- Penicillin-allergic patients can often tolerate other beta-lactams
- Consider oral antibiotics (non-fluoroquinolone based) in uncomplicated Gram-negative rod bacteremia
- Shorter courses of antibiotics likely as effective as longer courses in the right patient populations

Thank you!

Follow me and my team on Twitter

@ARLetourneau
@mgh_ast

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