Preserving the Cure: Antimicrobial Stewardship Topics That Can Change Practice

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DISCLOSURE

Sadie Giuliani: no conflicts of interest to disclose

Topics

- Cephalosporins in patients with penicillin allergy
- Delabeling penicillin allergies
- 2025 IDSA Complicated UTI Guidelines
- Durations of therapy

The Problem

Susceptibility

	Escherichia coli, Carbapenem resistant (CRE)	
	LABMICSENS	Method Not Specified
Amikacin		8 ug/mL **Sensitive**
Amoxicillin + Clavulanate		>=32 ug/mL **Resistant** *
Ampicillin		>=32 ug/mL **Resistant** *
Ampicillin + Sulbactam		>=32 ug/mL **Resistant** *
Aztreonam		>=64 ug/mL **Resistant** *
Cefazolin		>=64 ug/mL **Resistant** *
Cefazolin (Urine)		>=64 ug/mL **Resistant** *
Cefepime		>=64 ug/mL **Resistant** *
Cefotaxime		>=64 ug/mL **Resistant** *
Cefotetan		16 ug/mL **Sensitive** *
Cefoxitin		>=64 ug/mL **Resistant** *
Cefpodoxime		>=8 ug/mL **Resistant** *
Ceftazidime		>=64 ug/mL **Resistant** *
Ceftazidime + Avibactam		0.5 ug/mL **Sensitive** [1]
Ceftolozane + Tazobactam		>=32 ug/mL **Resistant** *
Ceftriaxone		>=64 ug/mL **Resistant** *
Cefuroxime		>=64 ug/mL **Resistant** *
Cephalothin		>=64 ug/mL **Resistant** *
Ciprofloxacin		>=4 ug/mL **Resistant**
Doxycycline		
Ertapenem		>=8 ug/mL **Resistant** [1]
Erythromycin		
Extended Spectrum Beta Lactamase		Positive ug/mL **Positive** *
Gentamicin		<=1 ug/mL **Sensitive**
Gentamicin synergy		
Imipenem		1 ug/mL **Sensitive** *
Imipenem/Relebactam	0.50 ug/mL **Sensitive**	
Levofloxacin		>=8 ug/mL **Resistant**
Linezolid		
Meropenem		4 ug/mL **Resistant** [1]
Moxifloxacin		>=8 ug/mL **Resistant** *
Nalidixic Acid		>=32 ug/mL **Resistant** *
Nitrofurantoin		<=16 ug/mL **Sensitive** *
Piperacillin + Tazobactam		>=128 ug/mL **Resistant** *
Streptomycin synergy		
Tetracycline		2 ug/mL **Sensitive** *
Tigecycline		<=0.5 ug/mL **Sensitive** *
Tobramycin		>=16 ug/mL **Resistant**
Trimethoprim + Sulfamethoxazole		>=320 ug/mL **Resistant**

The Problem

GRAM NEGATIVE ORGANISMS	Number of isolates	NITROFURANTOIN§	CEFAZOLIN‖	AMPICILLIN	CEFTRIAXONE	AMPICILLIN/ SULBACTAM (UNASYN)	TRIMETHOPRIM/ SULFA (BACTRIM)	LEVOFLOXACIN	Pseudomonas and/or Multi-Drug Resistant Organisms Suspected: PIPERACILLIN/ TAZO	CEFTAZIDIME	CEFEPIME	MEROPENEM	GENTAMICIN	TOBRAMYCIN
Citrobacter freundii	33	96§	R	R	63	R	84	96	66	66	96	-	-	-
Enterobacter cloacae complex	65	45§	R	R	70	R	96	100	73	73	98	-	-	-
Escherichia coli	618	96§	90‖	65	92	74	86	88	-	-	-	-	-	-
*Haemophilus influenzae***	20	-	-	75	-	-	-	-	-	-	-	-	-	-
*Klebsiella (Enterobacter) aerogenes***	31**	25§	R	R	83	R	100	96	87	91	100	-	-	-
Klebsiella oxytoca	57	80§	75‖	R	100	87	89	98	-	-	-	-	-	-
Klebsiella pneumoniae complex	117	20§	96‖	R	96	87	91	93	-	-	-	-	-	-
*Morganella morganii***	24**,†	R	R	R	92	15	92	92	100	92	100	-	-	-
Proteus mirabilis	50	R	95‖	81	100	91	89	82	-	-	-	-	-	-
Pseudomonas aeruginosa	114	-	R	R	R	R	R	85	92	97	99	91	R	97
*Serratia marcescens***	48	R	R	R	100	R	97	97	-	-	-	-	-	-

#	ANTIBIOTICS ROUTINELY REPORTED [6] / ORGANISMS TESTED [2]	AMK % S	AMP % S	SAM % S	CEFAZ (Urine) % S	CEFP % S	CTT % S	TAZ % S	CRO % S	ERTA % S	GM % S	IMP % S	LEV % S	MER % S	MIN % S	TZP [5] % S	TET % S	TOB % S	TMP/ SMX % S	Urine Total # [3]	NFD % S
[15]	Acinetobacter baumanii [1]	71		63		44		47	12		60	56	47	53	81	47	56	60	50		
70	Enterobacter aerogenes							81	80		100		100	100		[5]			100	[39]	8
166	Enterobacter cloacae complex							83	82		99		98	99		[5]			95	83	49
2578	Escherichia coli **ALL**		48		83			91	85		88		70	100		[5]			71	2165	96
525	Escherichia coli **ESBL** [1, 4] 17 %	95	0		0	54	66	36	1	100	59	100	18	100	74	66	24	51	43	480	66
96	Klebsiella oxytoca				79			99	94		98		100	100		[5]			96	[44]	98
696	Klebsiella pneumoniae				97			98	98		98		96	99		[5]			92	497	38
61	Klebsiella pneumoniae **ESBL** [1, 4]				0	41	100	20	2	100	36	100	57	100		57	27	31	13	55	7
334	Proteus mirabilis		75		90			99	96		85		64	100		[5]			70	306	0
771	Pseudomonas aeruginosa							88			88		70	80		89					
83	Serratia marcescens							90	90		100		94	99		[5]			99	[19]	0

“Just one more day”

9%

Increase in *C. difficile* risk per day

Chalmers JD, et al. Risk factors for *Clostridium difficile* infection in hospitalized patients with community-acquired pneumonia. Journal of Infection 2006 Jul 1;73(1)45-53.

4%

Increase of penicillin-resistant *S. pneumoniae* per day

Nasrin D. Et al. Effect of beta-lactam antibiotic use in children on pneumococcal resistance to penicillin: prospective cohort study. BMJ. 2002 Jan 5;234(7328);28

4%

Increase in anti-pseudomonal resistance per day

Teshorne BF, et al. Duration of Exposure to Antipseudomonal beta-lactam Antibiotics in critically ill and development of new resistance. Pharmacotherapy. 2019 Mar;39(3):261-70.

5%

Increased odds of an adverse drug reaction (ADR) per day

Curran J, et al. Estimating daily antibiotic harms: an umbrella review with individual study meta-analysis. Clin Microbiol Infect. 2022 Apr;28(4):479-490. doi: 10.1016/j.cmi.2021.10.022.

What can we do about it?

TARGETED ANTIMICROBIALS

OPTIMIZED DURATIONS OF THERAPY

PATIENT EDUCATION WHEN ANTIBIOTICS ARE NOT THE ANSWER

Patient Case #1

45 year-old female is admitted with left lower extremity cellulitis. She complains of nausea and vomiting. SCr is 1.2 (baseline is 0.9). She is afebrile, wbc 12k, hemodynamically stable. She has a penicillin allergy. Which antibiotic is most appropriate?

1. PO sulfamethoxazole-trimethoprim
2. cefazolin
3. PO levofloxacin
4. vancomycin + aztreonam

Most cephalosporins are safe in the setting of penicillin allergy

Practice parameter

Drug allergy: A 2022 practice parameter update

Penicillin-Cephalosporin Cross-reactivity

Older data: 5-10%

Newer data: <2%

CBS 12	We suggest that for patients with a history of anaphylaxis to a penicillin, a structurally dissimilar R1 side chain cephalosporin can be administered without testing or additional precautions.	Conditional	Moderate
CBS 13	We suggest that for patients with a history of an unverified (not confirmed) nonanaphylactic penicillin allergy, a cephalosporin can be administered without testing or additional precautions.	Conditional	Moderate
CBS 14	We suggest that in patients with a history of an unverified nonanaphylactic cephalosporin allergy, a penicillin can be administered without testing or additional precautions.	Conditional	Low
CBS 15	We suggest that in patients with a history of anaphylaxis to cephalosporins, penicillin skin testing and drug challenge should be performed prior to administration of a penicillin therapy.	Conditional	Low

Caution in severe cutaneous reactions (SJS/TEN, DRESS, AGEP)

Khan DA, et al. J Allergy Clin Immunol. 2022 Dec;150(6):1333-1393.
Shenoy ES, et al. JAMA. 2019;321(2):188-199.

Structure: beta-lactam ring and side chains (R1 and R2)

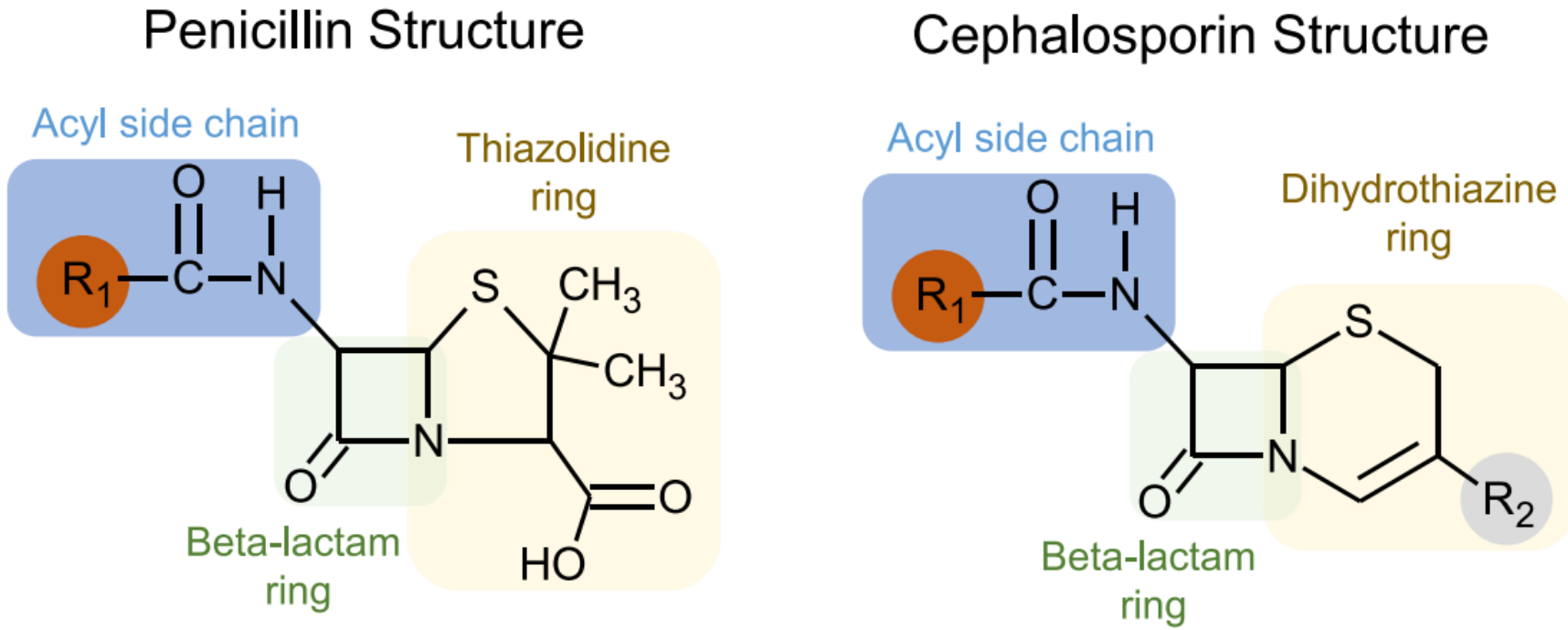


FIG 2. Penicillins and cephalosporins share common structures that are thought to be the source of cross-reactivity: (1) beta-lactam ring, shown in *green*; (2) side chain, or R group with R1 location shown in *red* and R2 location shown in *gray*. Cross-reactivity is largely based on R_1 side chains, with identical side chains in patients with IgE-mediated allergy posing the highest risk. Rarely, cross-reactivity has been demonstrated through R2 side chains and the beta-lactam ring (see Table XII).

Khan DA et al. J Allergy Clin Immunol. 2022 Dec;150(6):1333-1393.

Penicillin – Cephalosporin structural similarity

		Penicillins							1st								2nd			
		Nafcillin	Oxacillin	Dicloxacillin	Penicillin G / V	Piperacillin	Ampicillin	Amoxicillin	Cefadroxil	Cefatrizine	Cephalexin	Cefazolin	Ceftezole	Cephalothin	Cephapirin	Cefoxitin	Cefuroxime	Cefotetan	Cefprozil	Cefaclor	Cefonicid	Cefamandole
PCN	Nafcillin																					
	Oxacillin			r1																		
	Dicloxacillin		r1																			
	Penicillin G / V					r1'	r1'	r1'	r1	r1	r1								r1	r1	r1	r1
	Piperacillin				r1'		R1'	r1'	r1'	r1'	R1'								r1'	R1'	r1'	r1'
	Ampicillin				r1'	R1'		r1'	r1	r1	**R1**								r1	**R1**	r1	r1
	Amoxicillin				r1'	r1'	r1'		**R1**	**R1**	r1'								**R1**	r1	r1	r1

		3rd										4th		5th			Mono
		Cefoperazone	Ceftibuten	Cefdinir	Cefixime	Ceftriaxone	Cefditoren	Cefodizime	Cefotaxime	Cefpodoxime	Ceftazidime	Cefepime	Cefpirome	Ceftaroline fosamil	Ceftolozane	Cefiderocol	Aztreonam
PCN	Nafcillin																
	Oxacillin																
	Dicloxacillin																
	Penicillin G / V	r1'															
	Piperacillin	R1"															
	Ampicillin	r1'															
	Amoxicillin	R1'															

R1 (red cell) - *identical* R1 structure

R1’ or R1’’ - only the ring or branch chain moiety of the R1 structure is identical, respectively.

r1 or r2 - *similar* R1 or R2 structures

R1’ or r1’’ - only the ring or branch chain moiety of the R1 structure is similar, respectively

Blank cells – no R1 or R2 structural similarities

Zagursky RJ, et al. J Allergy Clin Immunol Pract 2018;6:72-81

Penicillin – Cephalosporin cross-reactivity with IDENTICAL R1 side chain structure

40% Type I hypersensitivity (immediate, anaphylaxis)

20% Type IV hypersensitivity (delayed, dermatologic)

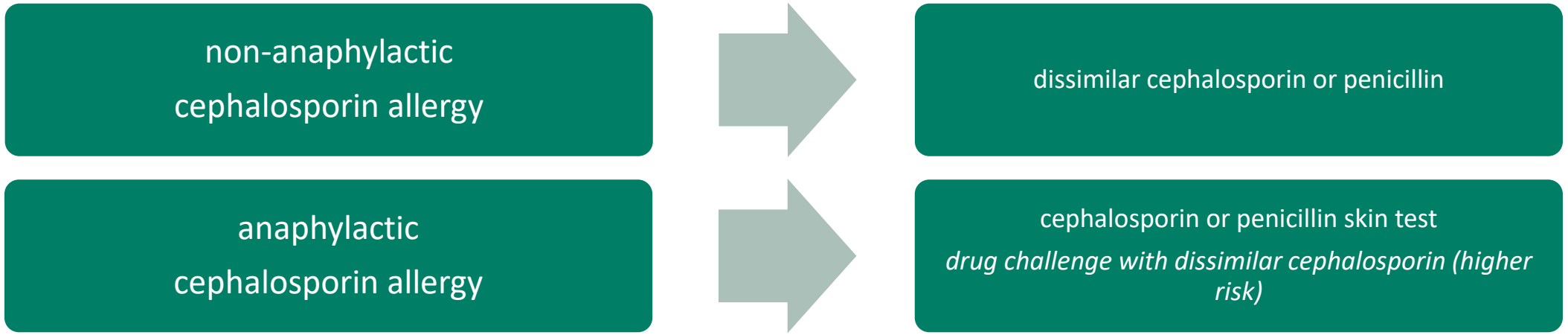
ampicillin – cephalexin
amoxicillin – cefadroxil
ceftriaxone – cefepime
aztreonam – ceftazidime?

- Aminopenicillin/aminocephalosporin: One large population-based study (over 1.1M antibiotic courses) found similar rates of allergic reaction to ampicillin, cephalexin, and cefaclor (AAC) in patients with a preexisting ACC allergy compared to patients with a preexisting sulfonamide allergy used as the control (0.87% vs 0.7%, p=0.11). The rate was 0.41% in patients with no preexisting AAC/sulfa allergy.
- The R2 side chain and beta-lactam ring appear to be unimportant for cross-reactivity.

Romano A, et al. J Allergy Clin Immunol Pract 2018; 6(5): 1662-72.
Romano A, et al. J Allergy Clin Immunol 2016; 138(1): 179-86.
Macy E, et al. J Allergy Clin Immunol Practice. 2022 Feb;10(2):550-555.

Cephalosporin – Cephalosporin Cross-reactivity

CBS 10	We suggest that for patients with a history of nonanaphylactic cephalosporin allergy, direct challenges (without prior skin test) to cephalosporins with dissimilar side chains be performed to determine tolerance.	Conditional	Moderate
CBS 11	We suggest that for patients with a history of anaphylaxis to a cephalosporin, a negative cephalosporin skin test should be confirmed prior to administration of a parenteral cephalosporin with a nonidentical R1 side chain.	Conditional	Low



- The R2 side chain seems to be less important than the R1 side chain

Khan DA, et al. J Allergy Clin Immunol. 2022 Dec;150(6):1333-1393.

Non-anaphylactic reactions can be challenged directly with structurally unrelated cephalosporins

- Cefazolin shares no side chain similarity with any other beta-lactam!
- Side-chain-based cross-reactivity charts are widely available online

(+) Known cross-reactive (X) Same side chain	Penicillin	Amoxicillin	Ampicillin	Cephalexin	Cefadroxil	Cefazolin	Cefuroxime	Cefoxitin	Cefotaxime	Cefixime	Cefpodoxime	Ceftriaxone	Ceftazidime	Cefepime	Cefiderocol	Ceftolozane	Ceftaroline	Ceftobiprole	Aztreonam
Penicillin		+	+	+															
Amoxicillin	+		+	+	X														
Ampicillin	+	+		X															
1st Generation Cephalosporins																			
Cephalexin	+	+	X																
Cefadroxil		X																	
Cefazolin																			
2nd Generation Cephalosporins																			
Cefuroxime																			
Cefoxitin																			
3rd Generation Cephalosporins																			
Cefotaxime											X	X		X					
Cefixime																			
Cefpodoxime									X			X		X					
Ceftriaxone									X		X			X					
Ceftazidime															X				X
Later Generation Cephalosporins																			
Cefepime									X		X	X							
Cefiderocol													X						X
Ceftolozane																			
Ceftaroline																		X	
Ceftobiprole																	X		
Monobactam																			
Aztreonam													X		X				

Jeffres M. Cross-Reactivity Between Cephalosporins and Penicillins: How Beta-Lactam Side Chain Grids Are (Probably) Saving Lives. IDStewardship.com. Accessed 8/30/2025. https://www.idstewardship.com/cross-reactivity-cephalosporins-penicillins-story-side-chains/

Patient Case #1

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1. PO sulfamethoxazole-trimethoprim
2. **cefazolin**
3. PO levofloxacin
4. vancomycin + aztreonam

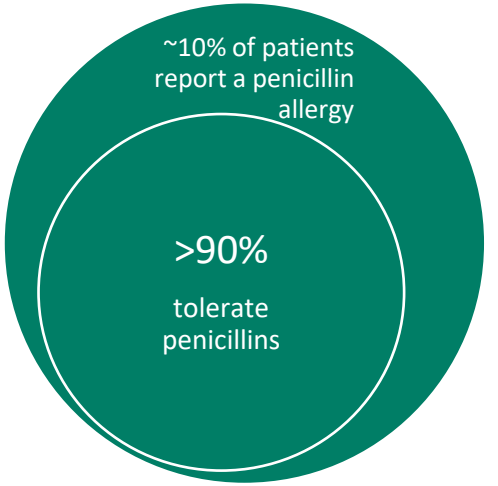
Patient Case #2

A 60-year-old male states he has a penicillin allergy. His reaction was a rash/hives as a child (his mother told him). He does not know if treatment was required. You talk to him about the importance of assessing if he is still allergic to penicillin. You calculate his PEN-FAST score as 1. What is the next step?

1. Refer him to an allergist for skin testing
2. Offer him an oral amoxicillin challenge
3. Delete his allergy because he no longer has an allergy
4. Tell him he is still very likely allergic to penicillins and no further follow-up is needed

Is it a true penicillin allergy? Making a case to delabel

Beta-lactams			
CBS 4	We recommend that a proactive effort should be made to delabel patients with reported penicillin allergy, if appropriate.	Strong	Moderate
CBS 5	We recommend against any testing in patients with a history inconsistent with penicillin allergy (such as headache, family history of penicillin allergy, or diarrhea), but a 1-step amoxicillin challenge may be offered to patients who are anxious or request additional reassurance to accept the removal of a penicillin allergy label.	Strong	Low
CBS 6	We suggest penicillin skin testing for patients with a history of anaphylaxis or a recent reaction suspected to be IgE-mediated.	Conditional	Low
CBS 7	We recommend against the routine use of multiple-day challenges in the evaluation of penicillin allergy.	Strong	Low
CBS 8	We recommend against penicillin skin testing prior to direct amoxicillin challenge in pediatric patients with a history of benign cutaneous reaction (such as MDE and urticaria).	Strong	Moderate
CBS 9	We suggest that direct amoxicillin challenge be considered in adults with a history of distant (ie, >5 years ago) and benign cutaneous reactions (such as MDE and urticaria).	Conditional	Low



Khan DA, et al. J Allergy Clin Immunol. 2022 Dec;150(6):1333-1393.

What has changed?

Rate of IgE-mediated penicillin allergies is decreasing

- Decreased use of parenteral penicillins, anaphylactic reactions to oral amoxicillin are rare

Penicillin-specific IgE wanes with time

- 80% of people are no longer allergic after 10 years

Some cutaneous reactions are a result of underlying infection or interaction between the infectious agent and the antibiotic

- viral exanthems in childhood, Epstein-Barr virus and aminopenicillin

Assumption penicillin allergies run in families

- independent risk factor for self-reported penicillin allergy, account for 16% of reported allergies in one study

Mislabeling predictable nonimmunologic symptoms as allergic

- intolerances or side effects

Shenoy ES, et al. JAMA. 2019;321(2):188-199.
Apter AJ, et al. J Allergy Clin Immunol. 2008 Jul;122(1):152-158.

Consequences of a Penicillin Allergy

increased risk of **mortality** with the use of **less effective antibiotics**

50% increased odds of **surgical site infection**

increased rates of infection with methicillin-resistant *Staphylococcus aureus* (**MRSA**) and vancomycin-resistant *Enterococcus* (**VRE**)

higher health care **costs** (including more hospital days and readmissions)

Increased risk of **adverse effects** including ***C. difficile***

Castells M, et al. NEJM. N Engl J Med. 2019;381:2338-51.

PEN-FAST Tool

- Helpful for identifying low risk allergies (score <3)
- Adults only, should not be used in children <12 years old

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)

Trubiano JA, et al. JAMA Intern Med. 2020;180;(5):745-752.
Copaescu AM, et al. JAMA Netw Open. 2022;5;(9):e2233703.

PALACE study: Direct oral challenge for PEN-FAST score <3

JAMA Internal Medicine

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

POPULATION

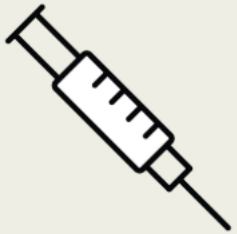
130 Men, 247 Women

Adults ≥18 y old with a low-risk penicillin allergy

Median age, 51 y

INTERVENTION

377 Participants analyzed



190 Control

Skin prick and intradermal penicillin testing, followed by oral challenge if skin testing results are negative

187 Intervention

Direct oral penicillin drug challenge

SETTINGS / LOCATIONS

6 Hospitals in North America and Australia

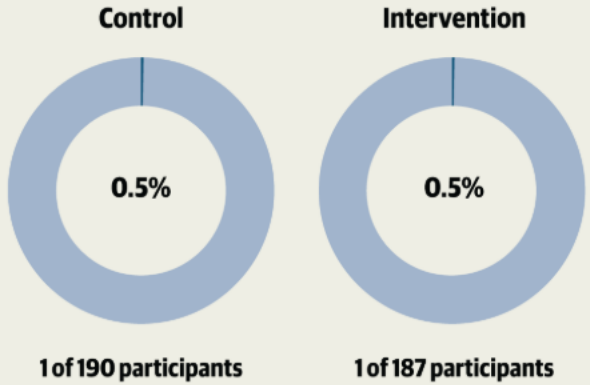
PRIMARY OUTCOME

Between-group difference in the proportion of participants with a physician-verified immune-mediated positive oral penicillin challenge (percentage points); noninferiority margin was set at 5 percentage points

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



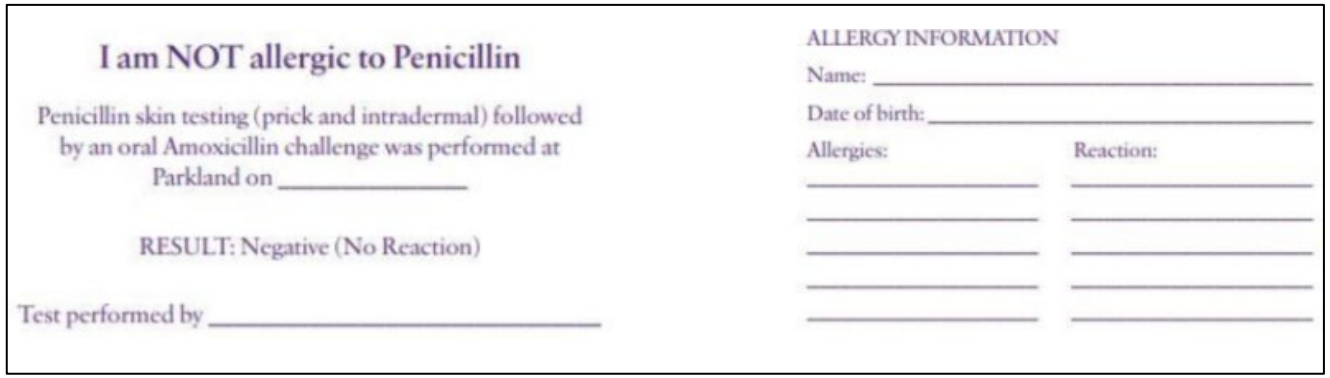
Risk difference, 0.0084 (90% CI, -1.22 to 1.24) percentage points, which is less than the noninferiority margin

Copaescu AM, Vogrin S, James F, et al. Efficacy of a clinical decision rule to enable direct oral challenge in patients with low-risk penicillin allergy: the PALACE randomized clinical trial. *JAMA Intern Med*. Published online July 17, 2023. doi:10.1001/jamainternmed.2023.2986

Practical Tips for Oral Challenges

- Inpatient
  - Engage multidisciplinary team
    - Nursing, pharmacy, LIPs
  - Create order panel with reaction medications and instructions for nursing
- Outpatient
  - Reimbursable procedure
  - Coding and procedure guidance on AAAAI website

Consider a statement of tolerance in their after-visit summary or a wallet card



I am NOT allergic to Penicillin

Penicillin skin testing (prick and intradermal) followed by an oral Amoxicillin challenge was performed at Parkland on _____

RESULT: Negative (No Reaction)

Test performed by _____

ALLERGY INFORMATION

Name: _____

Date of birth: _____

Allergies: Reaction:

https://college.acaai.org/coding-for-penicillin-allergy-testing-everything-you-need-to-know/
https://education.aaaai.org/penicillin-allergy-center/penicillin

Copaescu AM, et al. JAMA Intern Med. 2023;183;(9):944-952.
Staicu ML, et al. J Allergy Clin Immunol Pract. 2020 Oct;8(9):2858–2868.e16.
Kufel WD, et al. Pharmacy (Basel). 2019 Sep 197(3):136.
Lutfeali S, et al. J Allergy Clin Immunol Pract. 2021.

Patient Case #2

A 60-year-old male states he has a penicillin allergy. His reaction was a rash/hives as a child (his mother told him). He does not know if treatment was required. You talk to him about the importance of assessing if he is still allergic to penicillin. You calculate his PEN-FAST score as 1. What is the next step?

1. Refer him to an allergist for skin testing
2. **Offer him an oral amoxicillin challenge**
3. Delete his allergy because he no longer has an allergy
4. Tell him he is still very likely allergic to penicillins and no further follow-up is needed

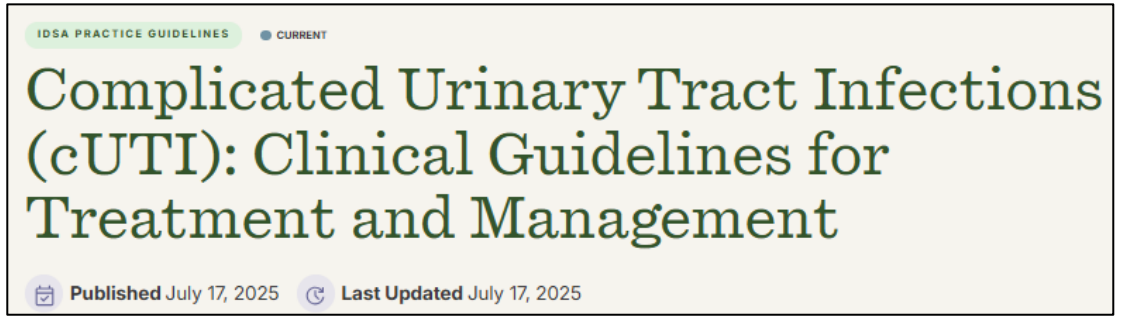
Patient Case #3

A patient receives empiric therapy with ceftriaxone 2g IV daily for complicated UTI. Urine culture grows >100k CFU/ml of *K. pneumoniae* resistant to fluroquinolones but susceptible to all other tested antibiotics. Blood cultures also grow the same organism. On hospital day 3 she is afebrile, vital signs are normal as well as labs and mentation. Which duration and route of antibiotic therapy should the patient receive?

1. Ceftriaxone for 11 more days (14 days total)
2. Ceftriaxone for 4 more days (7 days total)
3. PO trimethoprim-sulfamethoxazole for 11 more days (14 days total)
4. PO trimethoprim-sulfamethoxazole for 4 more days (7 days total)

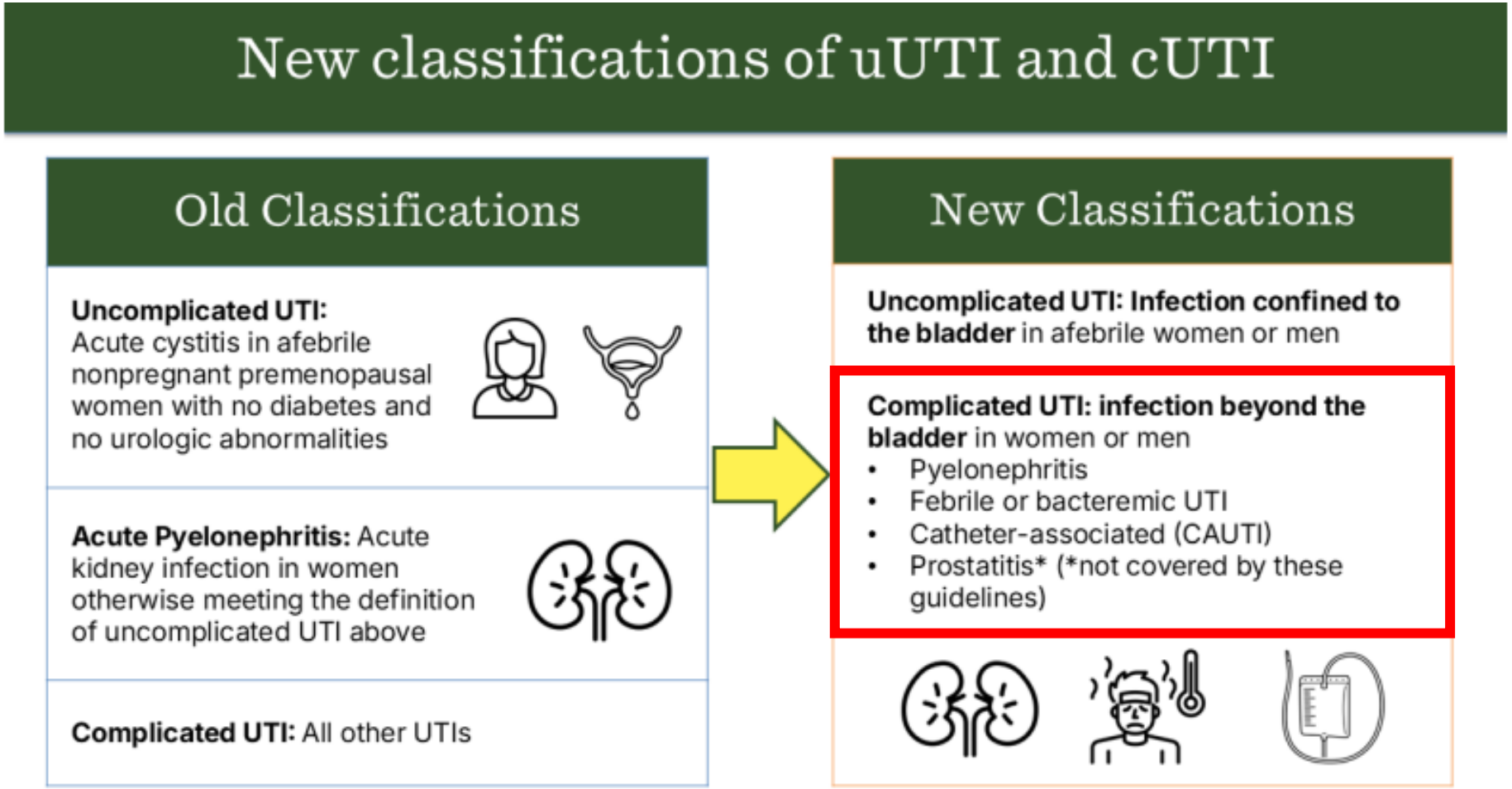
2025 IDSA Complicated UTI Guidelines

- Most important outcome: mortality (rarely identified in clinical trials though)
- Other critical outcomes
  - Clinical cure at test-of-cure (TOC)
  - Recurrence of infection at late follow-up
- Important but not critical
  - Microbiologic eradication
- Clinical decision threshold = ≥10% increase in clinical failure and microbiologic cure
  - If antibiotic A leads to increase in clinical failure of >10% compared to antibiotic B, difference was clinically unacceptable



Trautner BW, et al. IDSA. July 17, 2025. https://www.idsociety.org/practice-guideline/complicated-urinary-tract-infections/

cUTI = infection extending beyond the bladder



Trautner BW, et al. IDSA. July 17, 2025. https://www.idsociety.org/practice-guideline/complicated-urinary-tract-infections/

Who do these guidelines not apply to?

- Uncomplicated UTI = bladder only
  - Dysuria, urgency, frequency, suprapubic pain
  - No systemic signs or symptoms
  - Can include:
    - Men
    - Recurrences
    - Underlying urologic abnormalities
    - Immunocompromise
    - Diabetes
  - Updated IDSA guidelines in progress!
  - See WikiGuidelines Group Consensus Statement in interim
- Asymptomatic bacteriuria
  - see IDSA ASB guidelines

- Generally excluded from clinical trials
  - Renal transplant
  - Pregnant, lactating
  - Neutropenia and other immunocompromise
  - Pediatrics
  - Transgender or gender diverse persons
  - Lack of source control (urinary obstruction)
  - Urinary stones
  - Catheterized patients
  - Abscesses of the urinary tract
  - Prostatitis
  - Renal failure
  - Nephrostomy tubes or urinary stents

Trautner BW, et al. IDSA. July 17, 2025. https://www.idsociety.org/practice-guideline/complicated-urinary-tract-infections/
Nelson Z, et al. JAMA Netw Open. 2024;7(11):e2444495

Preferred Drugs

Condition of the Patient	Preferred	Alternative
Sepsis with or without shock**	Third or fourth generation cephalosporins,* carbapenems,# piperacillin-tazobactam, fluoroquinolones&	Novel beta lactam-beta lactamase inhibitors,+ cefiderocol, plazomicin, or older aminoglycosides%
Without sepsis, IV route of therapy	Third or fourth generation cephalosporins,* piperacillin-tazobactam, or fluoroquinolones&	Carbapenems,# newer agents (novel beta lactams-beta lactamase inhibitors,+ cefiderocol, plazomicin), or older aminoglycosides%
Without sepsis, oral route of therapy	Fluoroquinolones& or trimethoprim-sulfamethoxazole	Amoxicillin-clavulanate or oral cephalosporins (see **Table 3.1**)

Trautner BW, et al. IDSA. July 17, 2025. https://www.idsociety.org/practice-guideline/complicated-urinary-tract-infections/

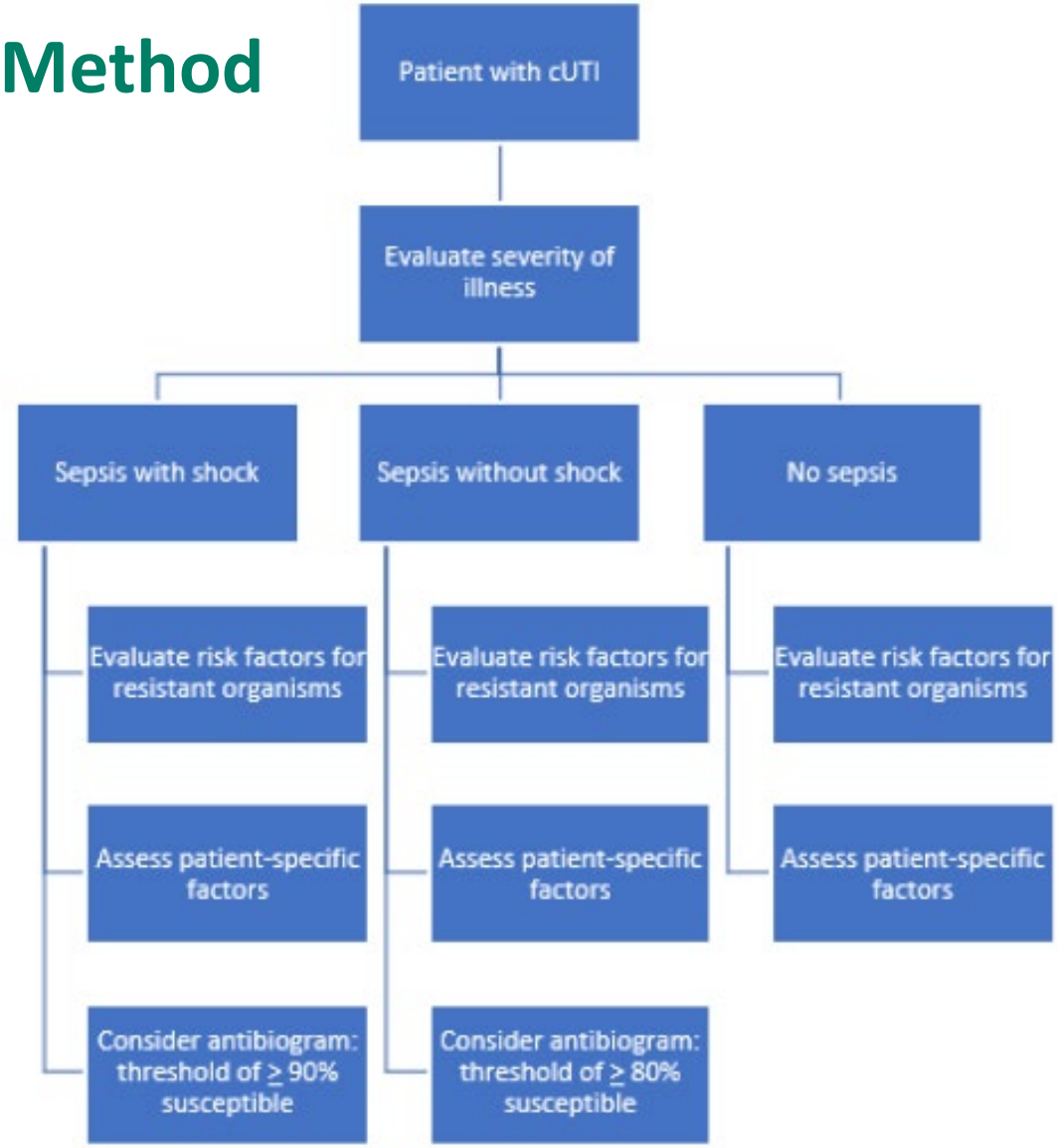
Empiric Selection using the Four Step Method

1. **Severity of illness**
   - ≥2 SOFA score increase, qSOFA or SIRS
   - Without sepsis, inappropriate empiric antibiotic treatment (IEAT) unlikely to impact mortality (<5%)

2. **Risk factors for resistance**
   - Recent > distant urine cultures and antibiotics
   - 3-6 month look back
   - Avoid fluoroquinolones if used in last 12 months

3. **Patient-specific considerations**
   - Allergies, contraindications, drug-drug interactions

4. **If septic, consider the antibiogram**
   - Use data from the last 12 months
   - Based on modeling of increased mortality risk associated with IEAT in sepsis/shock
   - Use prior cultured organism, or if none, use *E coli*



Trautner BW, et al. IDSA. July 17, 2025. https://www.idsociety.org/practice-guideline/complicated-urinary-tract-infections/

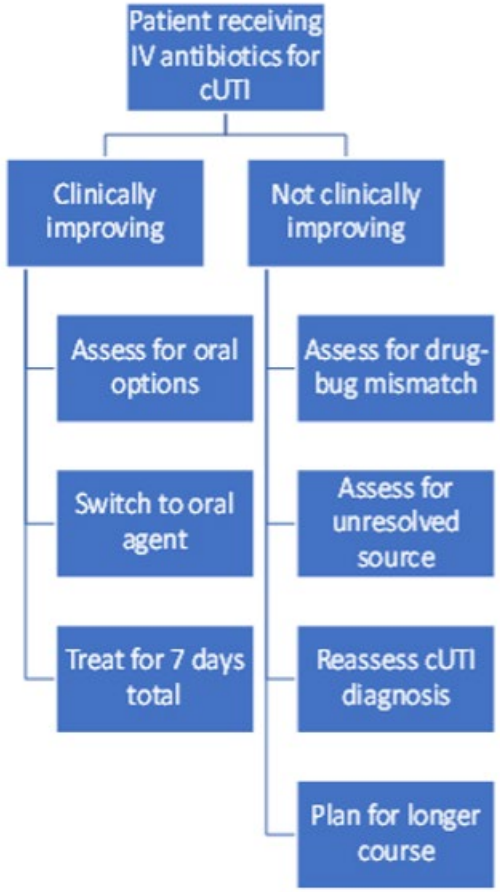
Definitive Antibiotic Therapy

- Suggest targeted spectrum instead of continuing empiric broad-spectrum antibiotics
- May be less practical in the outpatient setting
- Places high value on stewardship
  - Unclear resistance prevention benefits

Timing of IV to PO

- Some patients can be managed entirely with PO antibiotics in the outpatient setting
- Transition to PO antibiotics when:
  - Clinically improving
  - Able to take PO medication
  - There is an effective PO option
- Includes Gram negative bacteremia
  - Afebrile, hemodynamically stable, source control (obstruction relief)
- Trials mostly excluded catheters, sepsis or septic shock, immunocompromise, severe renal insufficiency, functional/structural abnormalities

Figure 1.2: Stepwise assessment of IV to oral switch and duration of antibiotic therapy



Abbreviations: IV=intravenous, cUTI=complicated UTI. Drug-bug mismatch means that the causative organism is not susceptible to the antibiotic prescribed.

Trautner BW et al. IDSA. July 17, 2025. https://www.idsociety.org/practice-guideline/complicated-urinary-tract-infections/

PO options: The bug doesn't care how the drug got there

✓ **Preferred**:
- third generation cephalosporins (cefpodoxime)
- sulfamethoxazole/trimethoprim (SXT)
- fluoroquinolones (FQ)
- most data with FQ, female, no catheter, no abscess

❓ **Conflicting evidence:**
- earlier generation cephalosporins
  - cefuroxime, ?understudied
  - cephalexin, ?suboptimal dosing
- amoxicillin +/- clavulanate
  - ?suboptimal dosing
- low bioavailability third generation cephalosporins (cefdinir)
  - More readmissions than FQ/SXT

❌ Nitrofurantoin and oral fosfomycin have inadequate blood/tissue penetration

Table 1.2: Dosing of oral antibiotics for complicated UTI (in alphabetical order)

Drugs	Oral absorption (%)	Urinary excretion (%)	Dose for patients with normal renal function
Amoxicillin-clavulanate	80 (amoxicillin)[22] variable (clavulanate)[23]	50-70 (amoxicillin)[22] 25-40% (clavulanate)[22]	875mg-125mg every 8 to 12 hours[24-32] Other regimens may be more effective[a]
Cefixime	50[33]	50[33]	400mg once daily[34]
Cefpodoxime	50[33]	80[33]	200mg to 400mg every 12 hours[31,35,36]
Ceftibuten	75-90[33]	73[33]	9mg/kg daily (children)[b] 400mg daily or 200mg every 12 hours (adults)[37,38]
Cefuroxime	52[33,39]	90[33,39]	500mg every 12 hours[31,40]
Cephalexin	90[33]	90[33]	500mg to 1000mg every 6 hours[24-29,32,41,42] Other regimens may be more effective[a]
Ciprofloxacin	70[43]	40-50[43]	500mg to 750mg every 12 hours [28,31,41,44,45]
Levofloxacin	99[46]	64-100[46]	500mg to 750mg daily[19,36,41,45]
Other oral beta-lactams (e.g. amoxicillin, cefadroxil, cefaclor, cefdinir)	Comparative clinical outcomes data vs highly bioavailable oral alternatives are more limited and/or discouraging; consider use with infectious disease pharmacist consultation if alternatives are not available.		
Trimethoprim-sulfamethoxazole	70-90[47]	84 (sulfamethoxazole), 66 (trimethoprim)[47]	800mg-160mg every 12 hours[31,44]

Trautner BW et al. IDSA. July 17, 2025. https://www.idsociety.org/practice-guideline/complicated-urinary-tract-infections/

Duration of Therapy

- Trials excluded catheters, severe sepsis, immunocompromising conditions, abscesses, CKD, prostatitis, complete urinary obstruction, undergoing urologic surgical procedures

- Important to diagnose prostatitis: 10-14 days
  - Two trials in men with febrile UTI showed decreased clinical cure but did not clearly exclude prostatitis

- Beta-lactams may require higher doses

Fluroquinolones: 5-7 days

Non-fluoroquinolones: 7 days

Bacteremia: 7 days

Trautner BW, et al. IDSA. July 17, 2025. https://www.idsociety.org/practice-guideline/complicated-urinary-tract-infections/
Heil EL, et al. Open Forum Infect Dis. 2021 Oct 11;8(10):ofab434

Patient Case #3

A patient receives empiric therapy with ceftriaxone 2g IV daily for complicated UTI. Urine culture grows >100k CFU/ml of *K. pneumoniae* resistant to fluroquinolones but susceptible to all other tested antibiotics. Blood cultures also grow the same organism. On hospital day 3 she is afebrile, vital signs are normal as well as labs and mentation. Which duration and route of antibiotic therapy should the patient receive?

1. Ceftriaxone for 11 more days (14 days total)
2. Ceftriaxone for 4 more days (7 days total)
3. PO trimethoprim-sulfamethoxazole for 11 more days (14 days total)
4. ***PO trimethoprim-sulfamethoxazole for 4 more days (7 days total)***

Patient Case #4

You are seeing a patient in clinic with community-acquired pneumonia. What is the shortest duration of therapy to consider for this patient?

1. 3 days
2. 5 days
3. 7 days
4. 10 days

2025 ATS Community Acquired Pneumonia (CAP) Guidelines

3-5 days	• Outpatient CAP
3-5 days	• Inpatient, non-severe CAP
≥5 days	• Inpatient, severe CAP

Jones BE, et al. Am J Respir Crit Care Med. 2025 Jul 18. doi: 10.1164/rccm.202507-1692ST. Online ahead of print.

Shorter Is Better

Diagnosis	Short (d)	Long (d)	Result	#RCT
CAP	3-5	5-14	Equal	14
Atypical CAP	1	3	Equal	1
Possible PNA in ICU	3	14-21	Equal	1*
VAP	5-8	10-15	Equal	3
Empyema	14-21	21-42	Equal	2
Cystic Fibrosis Exacerbation	10-14	14-21	Equal	1
Bronchiectasis Exacerbation	8	14	Equal	1
cUTI/Pyelonephritis	5 or 7	10 or 14	Equal	13**
Intra-abd Infection	4	8-10	Equal	3
Complex Appendicitis	1-2	5-6	Equal	2
Bacteremia (non *S. aureus*)	7	14	Equal	4†
Cellulitis/Wound/Abscess	5-6	10	Equal	4‡
Osteomyelitis	42	84	Equal	2
Osteo Removed Implant	28	42	Equal	1
Debrided Diabetic Osteo	10-21	42-90	Equal	2Φ
Septic Arthritis	14	28	Equal	1
Bacterial Meningitis (peds)	4-7	7-14	Equal	6
AECB & Sinusitis	≤5	≥7	Equal	>25
Variceal Bleeding	2-3	5-7	Equal	2
Neutropenic Fever	AFx72h/3 d	+ANC>500/9 d	Equal	2
Post Op Prophylaxis	0-1	1-5	Equal	57Ψ
Erythema Migrans (Lyme)	7-10	14-20	Equal	3
P. vivax Malaria	7	14	Equal	1
Early Syphilis	1 IM	3 IM in 3 wks	Equal	2

Total: 24 Conditions >150 RCTs

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

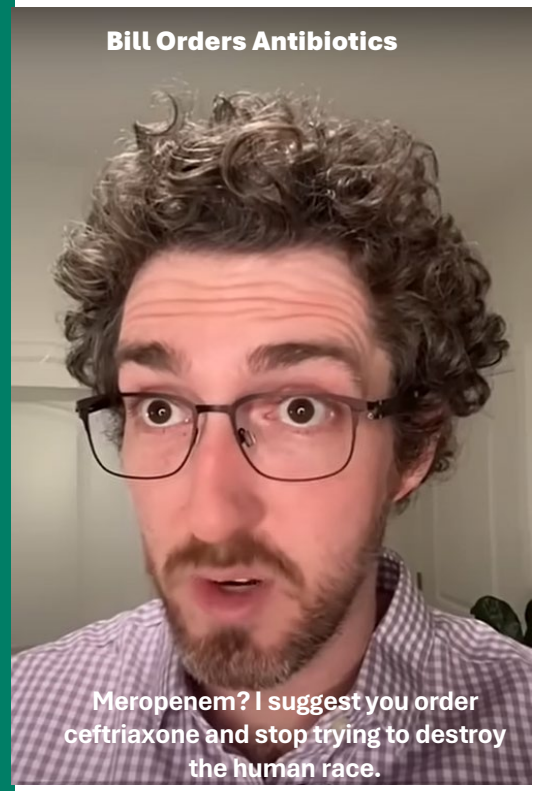
Patient Case #4

You are seeing a patient in clinic with community-acquired pneumonia. What is the shortest duration of therapy to consider for this patient?

1. ***3 days***
2. 5 days
3. 7 days
4. 10 days

SEPT. 28

NATIONAL PENICILLIN ALLERGY DAY



Questions?

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