KAHOOT! ASP EDITION

AN INTERACTIVE GAME TO TEST YOUR KNOWLEDGE ON ANTIMICROBIAL STEWARDSHIP

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Both presenters have no conflicts of interest to report

At the completion of this activity, pharmacists will be able to:

1. Describe the Center of Disease Control and Prevention (CDC)'s core elements of antimicrobial stewardship
2. Identify antimicrobial stewardship strategies that will optimize and elevate clinical practice
3. Discuss new antimicrobial agents and their role in clinical practice

At the completion of this activity, pharmacy technicians will be able to:

1. Define The Joint Commission's mandates on antimicrobial stewardship
2. Describe different antimicrobial stewardship strategies used in clinical practice
3. Identify antimicrobial agents used in clinical practice

Question 1

The Joint Commission implemented an antimicrobial stewardship standard for which of the following settings:

A. Acute care hospital
B. Nursing home
C. Ambulatory care
D. All of the above

Medication Management Standard 09.01.01

- Effective January 1, 2017
- Applicable to hospitals, critical access hospitals, and nursing homes

Medication Management Standard 09.01.03

- Effective January 1, 2020
- Applicable to ambulatory care centers that routinely prescribe antibiotics

Question 2

Which of the following is **NOT** a CDC Core Element of Hospital Antibiotic Stewardship Programs?

A. Tracking and reporting
B. Hospital leadership commitment
C. Pharmacy expertise
D. Microbiology lab commitment

CDC Core Elements of Hospital Antibiotic Stewardship Programs

CDC. Core Elements of Hospital Antibiotic Stewardship Programs. Atlanta, GA: US Department of Health and Human Services, CDC; 2019.

Question 3

Which of the following is an example of prospective audit and feedback?

A. Calling a prescriber because they ordered a restricted antibiotic
B. A prescriber evaluating cefepime for appropriateness after 3 days of therapy
C. Reviewing a patient on piperacillin-tazobactam for sepsis after 72 hours
D. Renally adjusting ertapenem on a patient recovering from AKI

Prospective Audit and Feedback

- Reviewed at 48-72 hours by a member of the antimicrobial stewardship team and feedback is provided to the prescriber
  - Methods of delivery: phone, written chart notes, face-to-face ("hand-shake stewardship")

Benefits	Challenges
Prescriber autonomy is maintained	Adherence is voluntary
More clinical data is available for the stewardship team to make recommendations	Providers reluctant to change if a patient is improving on current therapy
Adresses de-escalation of broad spectrum antibiotics and duration of therapy	Identification of patients for interventions requires IT support

CDC. Core Elements of Hospital Antibiotic Stewardship Programs. Atlanta, GA: US Department of Health and Human Services, CDC; 2019.

Categories of Stewardship Interventions

Broad	Antibiotic time-out Prior authorization Prospective audit and feedback
Pharmacy-Driven	Automatic IV to PO conversion Dose adjustments Dose optimizations Duplication of therapy alerts Automatic stop dates Detection and prevention of antibiotic drug interactions
Infection and Syndrome Specific	Development of clinical pathways based on national guidelines and institution specific susceptibility patterns in the electronic medical record to guide empiric antibiotic selection (UTI, bloodstream infection, etc.)

CDC. Core Elements of Hospital Antibiotic Stewardship Programs. Atlanta, GA: US Department of Health and Human Services, CDC; 2014.

Question 4

Calculate the days of therapy (DOT) based on the following medication administration record:

A. 3
B. 5
C. 9
D. 15

March 18	March 19	March 20	March 21	March 22
Vancomycin 0600 1800	Vancomycin 0600 1800	Vancomycin 0600		
Cefepime 0600 1400 2000	Cefepime 0600 1400 2000	Cefepime 0600		
		Ceftriaxone 1000	Ceftriaxone 1000	Ceftriaxone 1000

Days of Therapy (DOT)

- Number of days that a patient receives an antibiotic
- Any dose of an antibiotic that is received on a calendar day represents 1 DOT
- If a patient is on multiple antibiotics the DOT will be the sum of DOT for each antibiotic
- DOT is standardized to 1000 patient days (DOT/1000 patient days) to allow comparison between hospitals of different sizes

CDC. Core Elements of Hospital Antibiotic Stewardship Programs. Atlanta, GA: US Department of Health and Human Services, CDC; 2019.

Days of Therapy (DOT)

March 18	March 19	March 20	March 21	March 22
Vancomycin 0600 1800	Vancomycin 0600 1800	Vancomycin 0600		
Cefepime 0600 1400 2000	Cefepime 0600 1400 2000	Cefepime 0600		
		Ceftriaxone 1000	Ceftriaxone 1000	Ceftriaxone 1000

3 Vancomycin DOT + 3 Cefepime DOT + 3 Ceftriaxone DOT = 9 DOT

Days of Therapy (DOT)

Advantages	Disadvantages
If normalized to patient days, can be used to compare antibiotic usage between institutions	Favors broad spectrum monotherapy over narrow spectrum combination therapy Example: Piperacillin-tazobactam x 7 days = 7 DOTs vs ceftriaxone + metronidazole x 7 days = 14 DOTs
Not affected by dosing	DOT for patients that receive a dosing interval > 24 hours are not accurately reported (antibiotic only counted on days it is administered)

CDC. Core Elements of Hospital Antibiotic Stewardship Programs. Atlanta, GA: US Department of Health and Human Services, CDC; 2019.

National Healthcare Safety Network (NHSN) Antimicrobial Use and Resistance (AUR) Module

- Managed by the Centers for Disease Control and Prevention
- Mechanism for facilities to report and analyze antimicrobial usage as part of antimicrobial stewardship efforts
- Provides facilities with data that can be used for inter-facility comparisons
- Evaluation of antimicrobial resistance

NHSN
NATIONAL HEALTHCARE SAFETY NETWORK

Antimicrobial Use and Resistance (AUR) Module.Updated: February 2021.

Question 5

Prolonged infusion effectively attain the pharmacodynamic efficacy target for which class of antibiotics:

A. Beta-lactams
B. Aminoglycosides
C. Fluoroquinolones
D. Glycopeptides

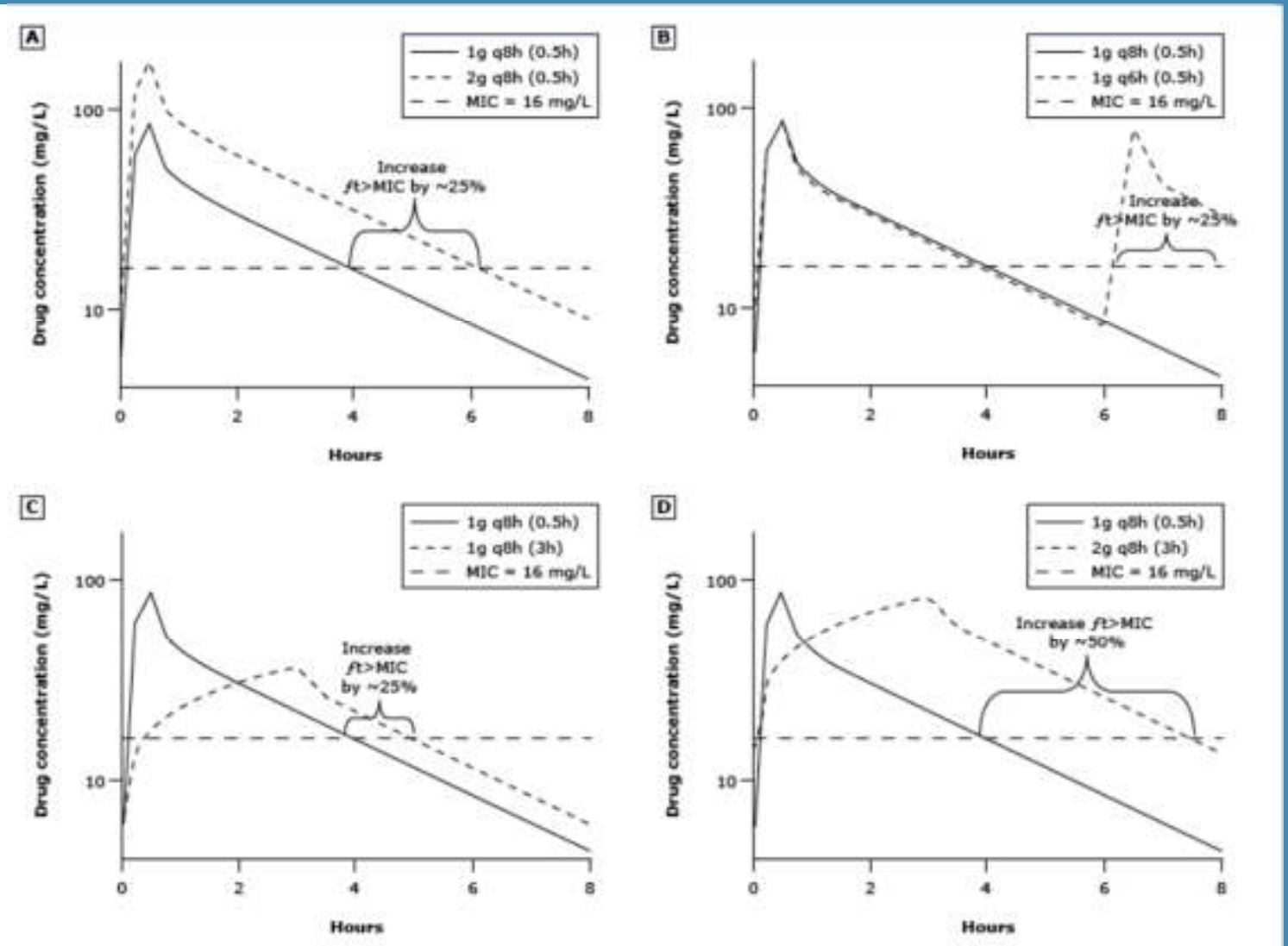
Prolonged Infusion of Beta-Lactams

- More effective than intermittent infusion in gram-negative infections
- Beneficial in infections due to pathogens with higher MICs
- Achieves adequate serum levels of antibiotics in critically ill or young patients altered pharmacokinetics
- Safe, reduced selection for drug resistance, cost benefit

Target attainments of %fT>MIC for beta-lactams and gram-negative pathogens	
Penicillins	50%
Cephalosporins	60-70%
Carbapenems	40%

%fT>MIC: % of the dosing interval that the concentration of free drug remains about the MIC of the pathogen.

Effects of dose increase and prolonged infusion on beta-lactam exposure



MacVane SH, Kuti JL, Nicolau DP.
Int J Antimicrob Agents. 2014 Feb;43(2):105-13.

Question 6

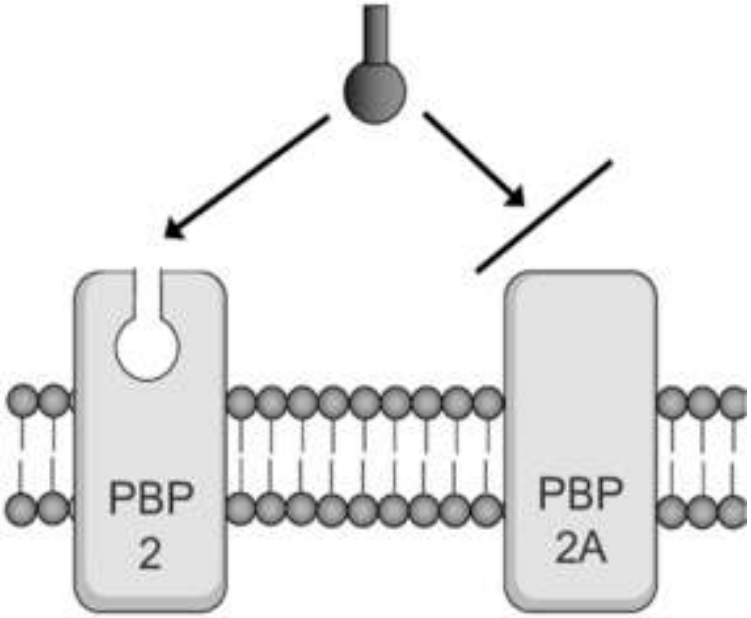
As the antimicrobial stewardship pharmacist, you receive a rapid diagnostic test alert from the microbiology laboratory for a positive blood culture. It is reported as *Staphylococcus aureus*, *mecA* gene not detected. The patient is on vancomycin and piperacillin-tazobactam.

Which of the following would be the most appropriate recommendation in this scenario?

A. Discontinue vancomycin, continue piperacillin-tazobactam
B. Discontinue vancomycin and piperacillin-tazobactam, start oxacillin
C. Discontinue piperacillin-tazobactam, continue vancomycin
D. Discontinue piperacillin-tazobactam, continue vancomycin, start oxacillin

*Staphylococcus aureus: mec*A gene

- Resistance mechanism: Target site modification
- *mec*A gene encodes penicillin-binding protein (PBP) 2 to become PBP2a so beta-lactams can no longer bind
  - Except ceftaroline



J Clin Microbiol. 2002 Nov; 40(11): 3970–3975.

Rapid Diagnostics Tests (RDT)

Timbrook, et al (2017)

- N = 5920 patients with bacteremia
- RDT vs Conventional Methods
  - Mortality benefit: OR 0.66 (95% CI: 0.54-0.80)
    - Number needed to treat: 20
  - **Presence of Antimicrobial Stewardship**
    - **Mortality benefit: OR 0.64 (95% CI: 0.51-0.79)**
  - Absence of Antimicrobial Stewardship
    - Mortality benefit: OR 0.72 (95% CI: 0.46-1.12)

Timbrook TT et al. Clin Infect Dis 2017;64:15–23.

Table 1. Antimicrobial stewardship considerations for optimal utility of FDA-approved RDTs for blood culture identification.

Technology type	Example systems (manufacturer)	Resistance detection	ASP considerations
PNA-FISH	Accelerate Pheno™ (Accelerate Diagnostics)	MRSA and macrolide-lincosamide-streptogramin B phenotypically reported	• First assay with rapid phenotypic AST® with potential utility among patients that would benefit from rapid PK/PD dose adjustments (e.g., critically ill with augmented renal clearance) • Unreliable when testing MIC of organism with multiple morphologies, or polymicrobial infections • Clinical outcomes studies limited
	PNA-FISH (AdvanDx)	None	• Combined with ASP, previously associated with reduction in LOS among CoNS-positive cultures, and reduced time to effective therapy with enterococcal bacteremia • May have limited utility because of limited target detection
PCR	Xpert MRSA/SA BC (Cepheid)	*SCCmec*, *mecA*	• Allows for prompt differentiation between MRSA and MSSA, expediting time to preferred treatment, and reducing mortality
	StaphSR (GeneOhm)	*mecA*	
mPCR	FilmArray® BCID (BioFire Diagnostics)	*mecA*, *vanA/B*, KPC	• Comprehensive number of targets detected (gram-positive, gram-negative, and yeast) • Multiple probes allow for identification of multiple organisms demonstrating utility in polymicrobial infections that may be missed by other technologies • Limited detection of genotypic resistance markers for gram-negative organisms
MALDI-TOF	MALDI-TOF (bioMérieux and Brucker)	None	• Ability to detect a vast array of bacterial and fungal microbes • May be useful in populations with high number of uncommon infections (e.g., facilities with large immunocompromised population, transplant centers) • Unable to detect resistance mechanisms or provide susceptibility reports
Nanoparticle probe technology	Verigene BC-GP (Nanosphere)	*mecA*, *vanA/B*	• Gram-negative panel has the most comprehensive genotypic resistance test capability commercially available, and can be used to streamline therapy for resistant (i.e., ESBL-producing) organisms faster
	Verigene BC-GN (Nanosphere)	KPC, NDM, CTX-M, VIM, IMP, OXA	• Unreliable for detection in polymicrobial bacteremia
NMR	T2Candida®, T2Bacteria®	None	• Can detect the presence of organisms from direct blood specimen without requiring prior isolation substantially expediting identification • Because of low limit of detection can detect positive blood cultures missed by standard testing; however, significant clinical threshold transient vs true bacteremia is unclear • De-escalation or discontinuation possible with negative result

Question 7

Which of the following dosing/monitoring methods is recommended for vancomycin?

A. Trough 15-20
B. Trough <2
C. AUC:MIC >800
D. AUC:MIC 400-600

Therapeutic monitoring of vancomycin for serious methicillin-resistant Staphylococcus aureus infections: A revised consensus guideline and review by the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the Society of Infectious Diseases Pharmacists

Published , 3/19/2020

American Journal of Health-System Pharmacy, zxaa036, https://doi.org/10.1093/ajhp/zxaa036
Published: 19 March 2020

To view the Executive Summary as published in *Clinical Infectious Diseases*, click here.

Michael J Rybak, Jennifer Le, Thomas P Lodise, Donald P Levine, John S Bradley, Catherine Liu, Bruce A Mueller, Manjunath P Pai, Annie Wong-Beringer, John C Rotschafer, Keith A Rodvold, Holly D Maples, Benjamin M Lomaestro

2020 Guideline Updates

- Target AUC:MIC 400-600
- Actual body weight
- Loading dose:
  - Non-obese: 20-35 mg/kg
  - Obese: 20-25 mg/kg
  - Max 3,000 mg
- Maintenance dose:
  - Non-obese: 15-20 mg/kg Q8-12H
  - Obese: use population kinetics (max 4,500 mg/day)
- Pediatric, neonate, and dialysis recommendations

Benefits of AUC:MIC Dosing Method

- Vancomycin troughs of 15-20 mg/mL associated with increased risk of nephrotoxicity
- AUC:MIC ratio ~400 related to increased survival rates in *S. aureus* bacteremia

Moise-Broder equation	● Daily dose of vancomycin divided by a CrCl-based estimate of vancomycin clearance ● Requires no serum concentrations ● Can underestimate AUC
Sawchuk-Zaske method (Trapezoidal rule)	● Uses 2-level PK (assumes 1 compartment model) ● Requires 2 steady state levels, collected during same interval ● Home-grown dosing calculators, EMR-based calculators, commercially available calculators
Bayesian model	● Uses population PK data ● Requires at least 1 serum concentration ● Most accurate AUC predictions ● Requires purchased software

Question 8

A 75-year-old male presents to the ED with complaints of left lower extremity pain and erythema. He has a chronic foley and the ED physician collects a urinalysis and urine culture. The urinalysis has 25 WBCs and 10 squamous cells. The urine culture grows *Proteus mirabilis* and *Enterococcus faecalis.*

Which of the following is the MOST appropriate recommendation?

A. Start antibiotics for both cellulitis and UTI
B. Start antibiotics for cellulitis but not UTI
C. Start antibiotics for UTI but not cellulitis
D. No antibiotics are indicated at this time

Asymptomatic Bacteriuria

- Pyuria may be present in asymptomatic bacteriuria
  - 50-100% patients with long term catheters
    - The longer the catheter is in situ, the higher likelihood of colonization
- Urinalysis and urine cultures **do not rule in** the diagnosis of a UTI, they can only **rule out** the diagnosis when negative
  - In patients age > 65 years:
    - Positive Predictive Value – 37%
    - Negative Predicted Value – 92% (100% in LTCF residents)
- Initiation of antibiotics based on a urinalysis, results in a misdiagnosis of a UTI in 20-40% of patients.

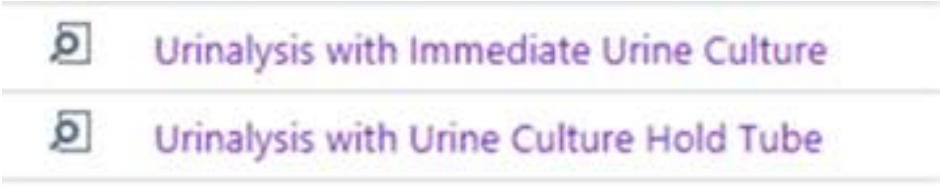
Remember: Always assess for urinary symptoms!

CID 2005;40:643-654;Juthani-Mehta, *Infect Control Hosp Epidemiology* 2007;28:889-891

Stewardship Initiative

- Elimination of reflex urine cultures for abnormal urinalysis
  - Allows for the physician to assess the patient for symptoms and request urine culture **only if indicated**

Date Range	Urine Cultures	Urine Cultures/Month
PRE: 1/1/2016 – 4/30/2016	3,613 (ED = 2,396)	903
POST: 1/1/2017 – 12/31/2017	7,032 (ED = 4,976)	586



Am J Infect Control. 2016 Dec 1;44(12):1750-1751. *J Clin Microbio.* 2016 Feb;54(2):254-8.

Question 9

A 55-year-old male is admitted with shortness of breath. He is requiring 4L O2 and is afebrile. While labs are pending, ceftriaxone, azithromycin and IV furosemide are initiated as both community acquired pneumonia (CAP) and acute exacerbation of heart failure are in the differential diagnosis. His labs return as follow:

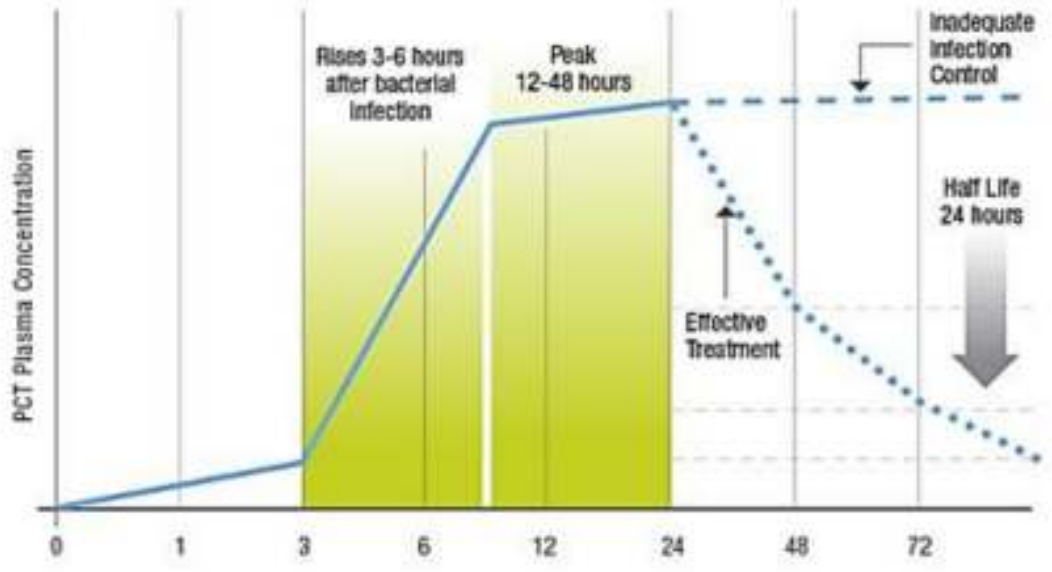
WBC = 10,000	BNP = 2750	Procalcitonin = 0.15

Which of the following is the MOST appropriate recommendation?

A. Continue antibiotics for CAP.
B. **Discontinue antibiotics. The patient does not have CAP.**
C. Discontinue azithromycin. The patient does not have atypical pneumonia.
D. Add vancomycin for MRSA coverage.

What is Procalcitonin?

- 116 amino acid precursor to calcitonin, produced in most cells and tissues
- Biomarker specific for systemic bacterial infections
- Rapidly released by parenchymal cells in response to bacterial toxins
- Undetectable in healthy persons

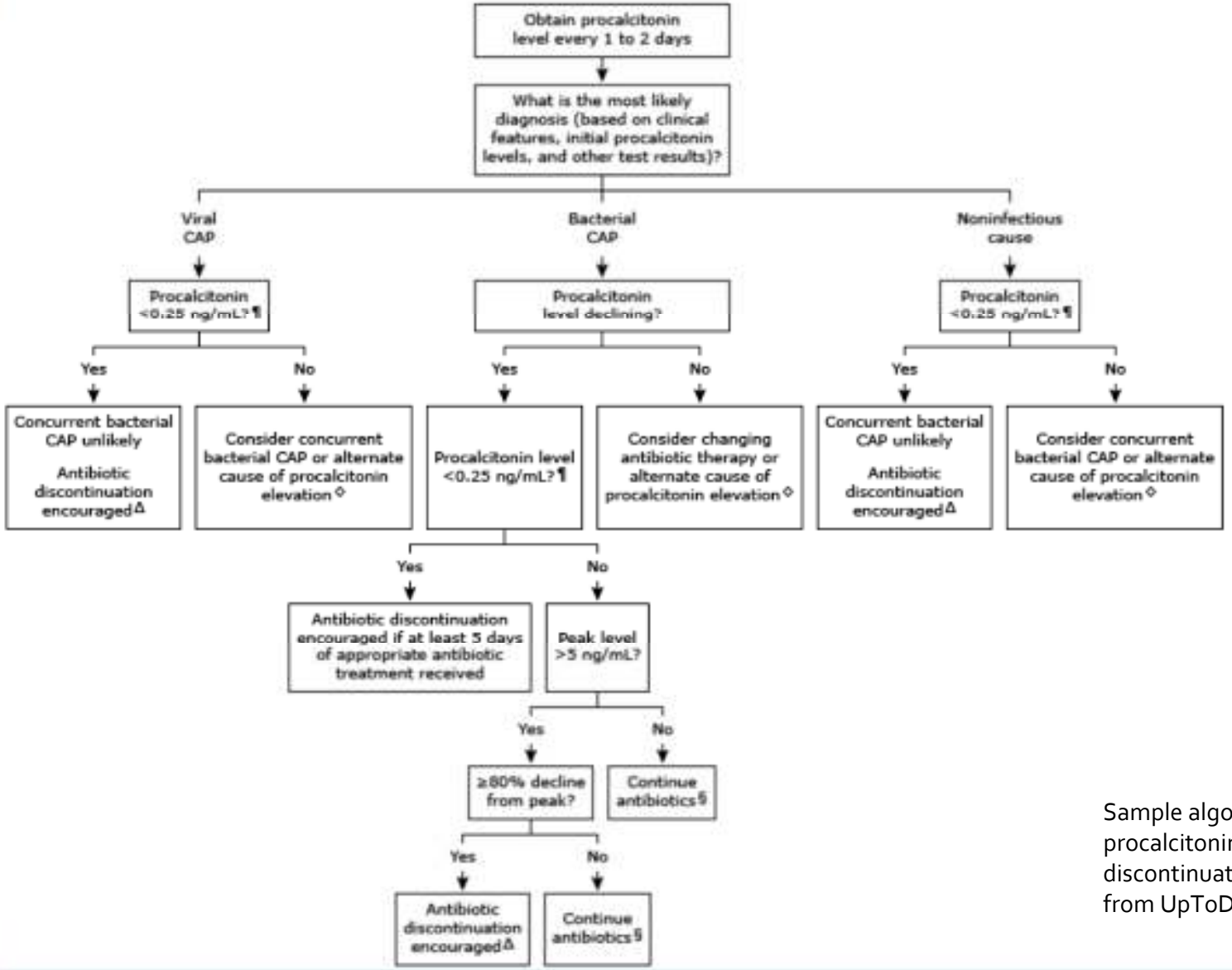


Brunkhorst FM, et, al. Intensive Care Med. 1998 Aug;24(8):888-9.

Procalcitonin in Antimicrobial Stewardship

- Guides early discontinuation of antibiotics
- Monitor response to antibiotic therapy
- Differentiation of bacterial and viral infections
- Diagnosis, risk stratification, and monitoring of sepsis and septic shock
- Not to be used as sole marker for antibiotic initiation

Conditions that may falsely elevate procalcitonin levels	- Major stressors: severe trauma, cardiac arrest or circulatory shock, surgery, burns, pancreatitis, and intracranial hemorrhage - Immediate postnatal period - After receipt of immunomodulatory agents (T-cell antibodies, alemtuzumab, IL-2) - Certain neoplasms - Newborns <48-72 hours - Malaria and some fungal infections - Significantly compromised renal function (ESRD, hemodialysis)



Sample algorithm for procalcitonin guided antibiotic discontinuation CAP patients from UpToDate

Question 10

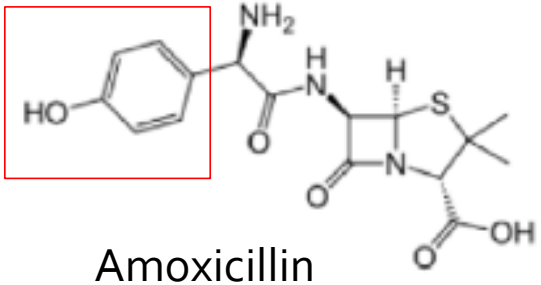
A 45-year-old female patient presents from her outpatient orthopedic office due to concern of a septic knee joint. An aspiration was performed and the culture is positive for methicillin-susceptible *Staphylococcus aureus*. The patient has a documented penicillin allergy of hives which occurred 5 years ago. Which of the following antibiotics is MOST appropriate to recommend at this point in time?

A. Vancomycin
B. Oxacillin
C. Cefazolin
D. Tigecycline

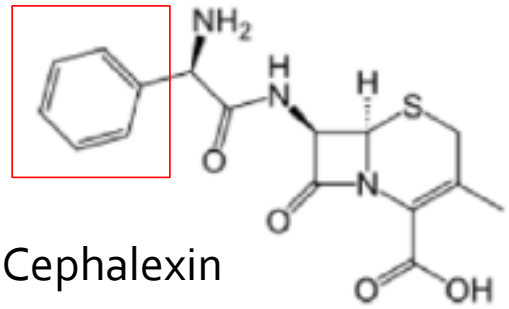
Cross-Reactivity of Penicillins to Cephalosporins

Picard M, et al (2019)

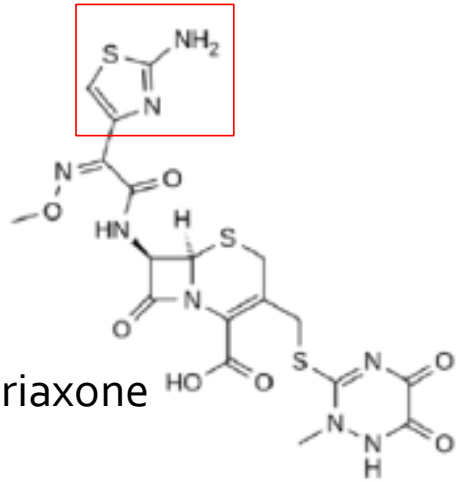
- N = 1269 patients with proven IgE- or T-cell–mediated penicillin allergy
- Conclusion: R1 side chain similarity correlates most with cross-reactivity



Amoxicillin



Cephalexin

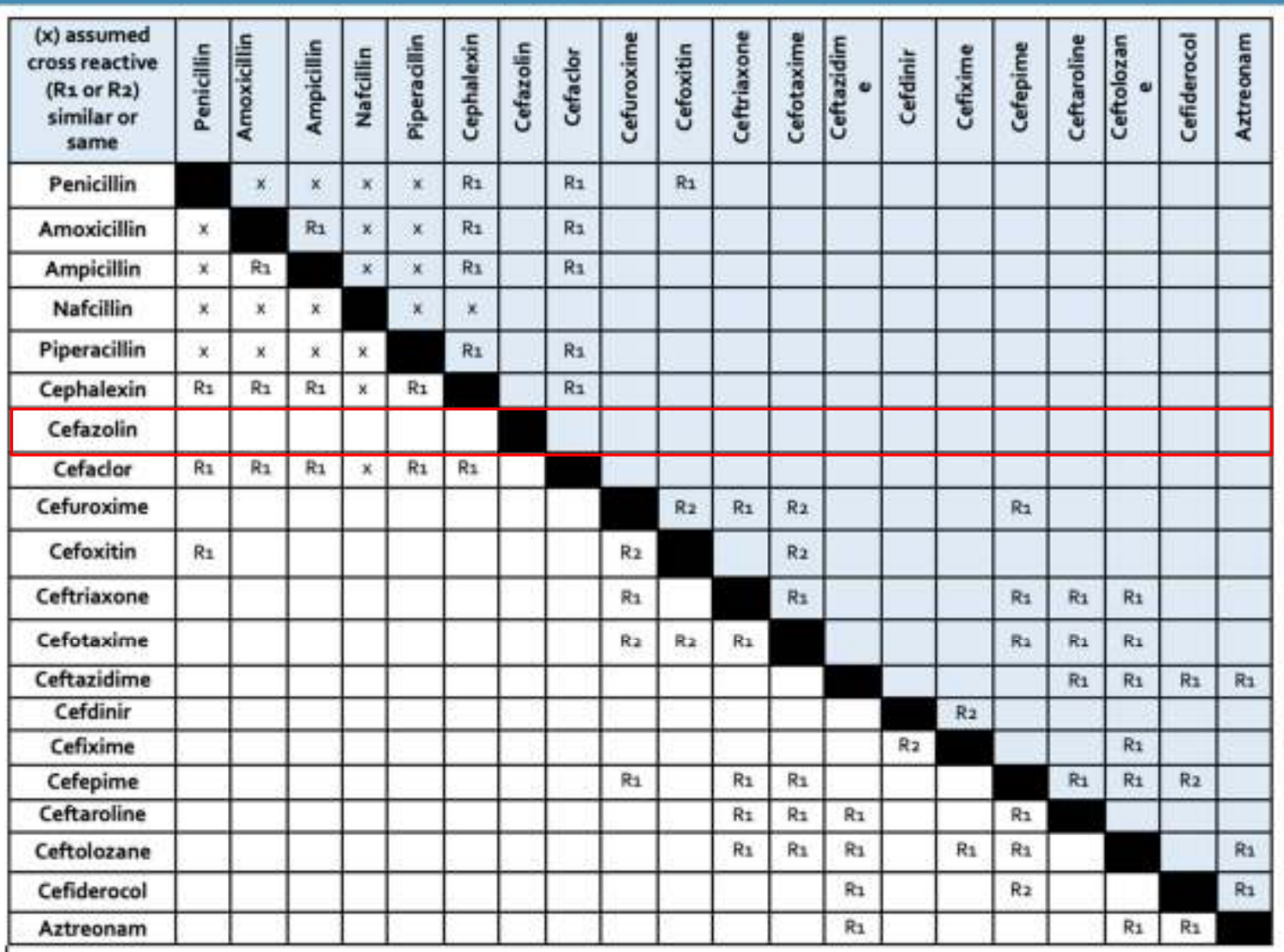


Ceftriaxone

16% cross-reactivity

2% cross-reactivity

Picard M, Robitaille G, Karam F, et al. Cross-Reactivity to Cephalosporins and Carbapenems in Penicillin-Allergic Patients: Two Systematic Reviews and Meta-Analyses. *J Allergy Clin Immunol Pract*. 2019 Nov - Dec;7(8):2722-2738.



(x) assumed cross reactive (R1 or R2) similar or same	Penicillin	Amoxicillin	Ampicillin	Nafcillin	Piperacillin	Cephalexin	Cefazolin	Cefaclor	Cefuroxime	Cefoxitin	Ceftriaxone	Cefotaxime	Ceftazidime	Cefdinir	Cefixime	Cefepime	Ceftaroline	Ceftolozane	Cefiderocol	Aztreonam
Penicillin		x	x	x	x	R1		R1		R1										
Amoxicillin	x		R1	x	x	R1		R1												
Ampicillin	x	R1		x	x	R1		R1												
Nafcillin	x	x	x		x	x														
Piperacillin	x	x	x	x		R1		R1												
Cephalexin	R1	R1	R1	x	R1			R1												
Cefazolin																				
Cefaclor	R1	R1	R1	x	R1	R1														
Cefuroxime										R2	R1	R2				R1				
Cefoxitin	R1								R2			R2								
Ceftriaxone									R1			R1				R1	R1	R1		
Cefotaxime									R2	R2	R1					R1	R1	R1		
Ceftazidime																	R1	R1	R1	R1
Cefdinir															R2					
Cefixime														R2				R1		
Cefepime									R1		R1	R1					R1	R1	R2	
Ceftaroline											R1	R1	R1			R1				
Ceftolozane											R1	R1	R1		R1	R1				R1
Cefiderocol													R1			R2				R1
Aztreonam													R1					R1	R1	

Modified from Zagursy RJ et al J Allergy Clin Immunol Pract 2018;6(1):72-81

Pharmacist Lead Allergy Assessment

Study	Results
Tripp et al; 1993	**28% (169/606)** of documented drug allergies were removed after a pharmacist-conducted patient allergy history
Sigona et al; 2016	**34.3% (11/32)** patients had discrepancy between EMR and reported allergy and history obtained after interview
Harig et al; 2018	**61%** (**123/202)** patients required a change in allergy history after questionnaire and interview.

Tripp et al *Am J Hosp Pharm* 1993;50;95-98 ; Sigona et al A *Am Pharm Assoc* 2016;56(6)665-669; Harig A *P&T* 2018;43(11):676

Question 11

An 80- year-old female is started on ceftriaxone, vancomycin, and doxycycline for severe community acquired pneumonia. Her MRSA nasal screen result is negative. Which of the following is the MOST appropriate recommendation?

A. Discontinue vancomycin and doxycycline

B. Discontinue vancomycin

C. Continue ceftriaxone, vancomycin, and doxycycline

D. Discontinue all antibiotics

Clinical Infectious Diseases

MAJOR ARTICLE

The Clinical Utility of Methicillin-Resistant *Staphylococcus aureus* (MRSA) Nasal Screening to Rule Out MRSA Pneumonia: A Diagnostic Meta-analysis With Antimicrobial Stewardship Implications

Diane M. Parente,[1] Cheston B. Cunha,[2,3] Eleftherios Mylonakis,[2,3] and Tristan T. Timbrook[4]

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- Included 22 studies (n=5,163)
- 10% prevalence

	Pooled	CAP/HCAP	VAP
Sensitivity	70.9%	85%	40.3%
Specificity	90.3%	92.1%	93.7%
PPV	44.8%	56.8%	35.7%
NPV	96.5%	98.1%	94.8%

Parente DM et al. CID 2018;67:1-7

Question 12

Cefiderocol is a novel antibiotic used to treat:

A. Multidrug-resistant *Pseudomonas aeruginosa*

B. Methicillin-resistant *Staphylococcus aureus*

C. Non-tuberculosis mycobacterium

D. Vancomycin-resistant *Enterococcus faecium*

Cefiderocol (Fetroja)

Mechanism of action	Inhibits bacterial cell wall synthesis
Dose	2g IV Q8H administered over 3 hours (renal dose adjustment required)
Spectrum of activity	Ambler class A, B, C, or D beta-lactamases producing bacteria *Acinetobacter baumannii* *Pseudomonas aeruginosa* *Stenotrophomonas maltophilia*
Adverse effects	N/V/D, increased AST/ALT

Zhanel GG, et al. *Drugs.* 2019. Feb;79(3):271-289; Wu JY, et al. *Infec Dis Ther.* 2020 Mar;9(1):17-40.

Question 13

Meropenem-vaborbactam has activity against which of the following bacteria:

A. Carbapenem-resistant *Pseudomonas aeruginosa*
B. Carbapenem-resistant *Acinetobacter baumannii*
C. Stenotrophomonas maltophilia
D. Carbapenem-resistant Enterobacterales

Meropenem-vaborbactam (Vabomere)

Mechanism of action	Inhibits bacterial cell wall synthesis
Dose	4g IV Q8H administered over 3 hours (renal dose adjustment required)
Spectrum of activity	Ambler class A and C beta-lactamases producing bacteria - Lower MICs have been observed compared to ceftazidime-avibactam against carbapenem-resistant Enterobacterales *Pseudomonas aeruginosa* - No enhanced activity against meropenem-resistant strains
Adverse effects	N/V/D, CNS effects

Petty LA , et al. *Infect Drug Resist.* 2018 Sep 12;11:1461-1472.;Novelli A, et al. *Expert Rev Anti Infect Ther.* 2020 May 3:1-13

Question 14

Which of the following antibiotic is MOST likely to have activity against carbapenem-resistant *Acinetobacter baumannii*:

A. Ceftazidime-avibactam
B. Ceftolozane-tazobactam
C. Eravacycline
D. Imipenem-cilastatin-relebactam

Eravacycline (Xerava)

Mechanism of action	Inhibits protein synthesis
Dose	1mg/kg IV Q12H administered over 60 minutes
Spectrum of activity	Methicillin-resistant *staphylococcus aureus* Vancomycin-resistant *Enterococcus* species Ambler class A, B, C, or D beta-lactamases producing bacteria *Acinetobacter baumannii* *Stenotrophomonas maltophilia*
Adverse effects	N/V (less than tigecycline), infusion site reactions

Alosaimy S. *Pharmacotherapy.* 2020 Mar;40(3):221-238; Zhanel GG, et al. *Drugs.* 2016 Apr;76(5):567-88.

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NYSCHP Virtual Annual Assembly 2021