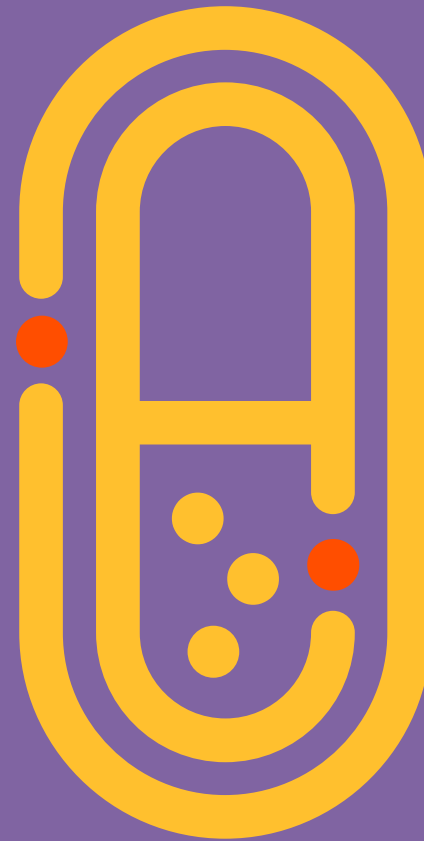


Antibiotic Stewardship is Here to Stay: Are You Ready?

DSHS Healthcare Safety Conference 2018
Kristi Kuper, PharmD, BCPS
Sr. Clinical Manager, ID
Vizient
July 23, 2018



Learning Objectives

- Describe factors that are driving antibiotic stewardship efforts
- Discuss best practices that can be implemented to improve antibiotic use
- Discuss how antibiotic stewardship can improve patient safety

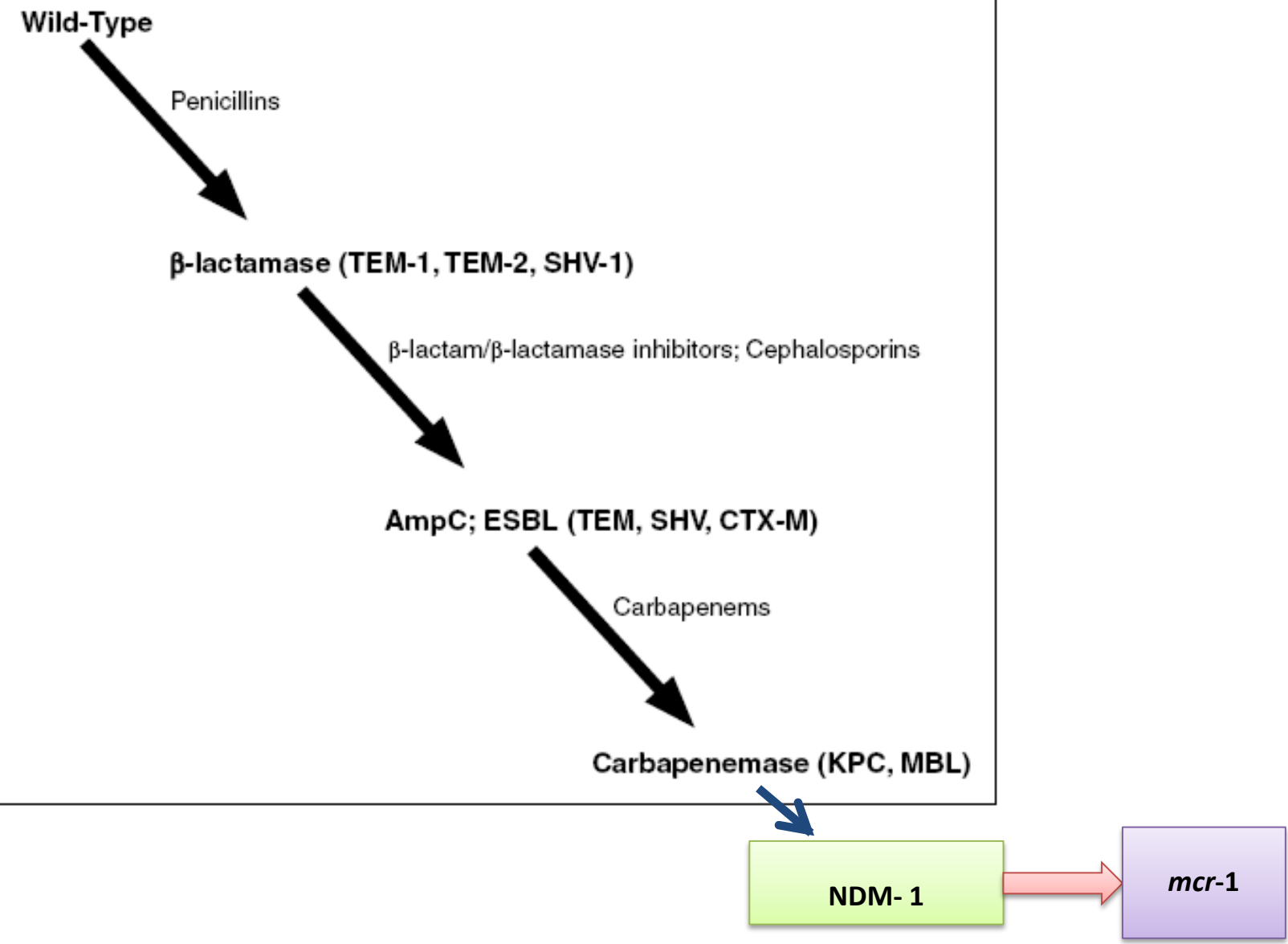
Disclosures

- I am an employee of Vizient which is a healthcare company

Why Do We Need Antibiotic Stewardship?

- Up to 50% of antimicrobial use is inappropriate
- Antibiotics are unlike any other drug, in that the use of the agent in one patient can compromise its efficacy in another.
- Antibiotic overuse has negative consequences
- The antibiotic pipeline has improved but may not be sustained and is limited for highly resistant organisms.

Figure 1. The evolution of β -lactamases. ESBL = extended-spectrum β -lactamase; KPC = *Klebsiella pneumoniae* carbapenemase; MBL = metallo- β -lactamase; TEM-1, TEM-2, SHV-1, TEM, SHV, CTX-M= types of β -lactamases.



Superbugs Don't Respect Borders

How NDM-1 spread around the world



Year: 2006

Source: Pew Charitable Trust

Some Reasons Why We Have a Global Antibiotic Resistance Problem



Antibiotic Exposure Increases the Risks of Resistance

Pathogen and Antibiotic Exposure	Increased Risk
Carbapenem Resistant Enterobacteriaceae and Carbapenems	15 fold
ESBL producing organisms and cephalosporins	6- 29 fold

1. Patel G et al. Infect Control Hosp Epidemiol 2008;29:1099-1106/ Zaoutis TE et al. Pediatrics 2005;114:942-9. 3. Talon D et al. Clin Microbiol Infect 2000;6:376-84.

2. Slide credit A. Srinivasan, MD (CDC)

THE MODERN ERA OF ANTIBIOTIC STEWARDSHIP

CDC Report 2013



Estimated minimum number of illnesses and deaths caused annually by antibiotic resistance*:

At least  **2,049,442** illnesses,
 **23,000** deaths

**bacteria and fungus included in this report*

7 Core Elements of a Successful Antibiotic Stewardship Program

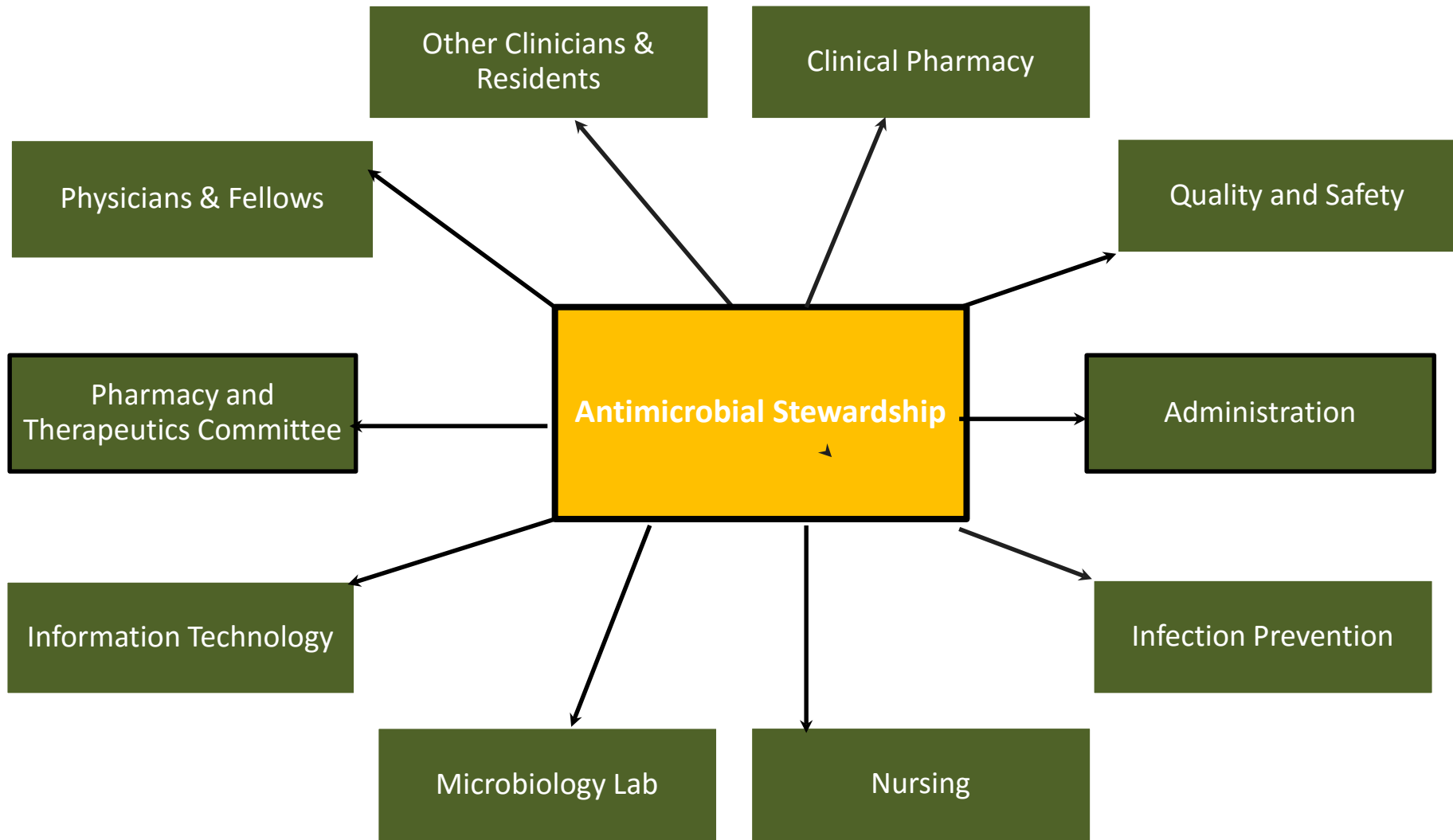
Antimicrobial stewardship is a coordinated program that promotes the appropriate use of antimicrobials (including antibiotics), improves patient outcomes, reduces microbial resistance, and decreases the spread of infections caused by multidrug-resistant organisms






- Dedicating necessary human, financial and information technology resources
- Appointing a single leader responsible for program outcomes
- Appointing a single pharmacist leader responsible for working to improve antibiotic use
- Taking individual actions in a patient receiving antibiotics that are known to reduce antibiotic use
- Monitoring antibiotic prescribing and resistance patterns
- Regular reporting information on antibiotic use and resistance to doctors, nurses and relevant staff
- Educating clinicians about resistance and optimal prescribing (and educating patients about their medications)

Source: CDC Core Elements for Antibiotic Stewardship

Antimicrobial Stewardship Partners



The US response (2014-2015)

<p>The White House Office of the Press Secretary</p> <p>For Immediate Release September 18, 2014</p> <h2>Executive Order -- Combating Antibiotic-Resistant Bacteria</h2> <p>EXECUTIVE ORDER</p> <p>COMBATING ANTIBIOTIC-RESISTANT BACTERIA</p> <p>By the authority vested in me as President by the Constitution and the laws of the United States of America, I hereby order as follows:</p> <p>Section 1. Policy. The discovery of antibiotics in the early 20th century fundamentally transformed human and veterinary medicine. Antibiotics save millions of lives each year in the United States and around the world. The rise of antibiotic-resistant bacteria, however, represents a serious threat to public health and the economy. The Centers for Disease Control and Prevention (CDC) in the Department of Health and Human Services (HHS) estimates that annually at least two million illnesses and 23,000 deaths are caused by antibiotic-resistant bacteria in the United States alone.</p> <p>Detecting, preventing, and controlling antibiotic resistance requires a strategic, coordinated, and sustained effort. It also depends on the engagement of governments, academia, industry, healthcare providers, the general public, and the agricultural community, as well as international partners. Success in this effort will require significant efforts to: minimize the emergence of antibiotic-resistant bacteria; preserve the efficacy of new and existing antibacterial drugs; advance research to develop improved methods for combating antibiotic resistance and conducting antibiotic stewardship; strengthen surveillance efforts in public health and agriculture; develop and promote the use of new, rapid diagnostic technologies; accelerate scientific research and facilitate the development of new antibacterial drugs, vaccines, diagnostics, and other novel therapeutics; maximize the dissemination of the most up-to-date information on the appropriate and proper use of antibiotics to the general public and healthcare providers; work with the pharmaceutical industry to include information on the proper use of over-the-counter and prescription antibiotic medications for humans and animals; and improve international collaboration and capabilities for prevention, surveillance, stewardship, basic research, and drug and diagnostics development.</p> <p>The Federal Government will work domestically and internationally to detect, prevent, and control illness and death related to antibiotic-resistant infections by implementing measures that reduce the emergence and spread of antibiotic-resistant bacteria and help ensure the continued availability of effective therapeutics for the treatment of bacterial infections.</p> <p>Sec. 2. Oversight and Coordination. Combating antibiotic-resistant bacteria is a national security priority. The National Security Council staff, in collaboration with the Office of Science and Technology Policy, the Domestic Policy Council, and the Office of Management and Budget, shall coordinate the development and implementation</p>	 <h2>REPORT TO THE PRESIDENT ON COMBATING ANTIBIOTIC RESISTANCE</h2> <p>Executive Office of the President President's Council of Advisors on Science and Technology</p> <p>September 2014</p> 	 <h2>NATIONAL STRATEGY FOR COMBATING ANTIBIOTIC- RESISTANT BACTERIA</h2> <p><i>Vision: The United States will work domestically and internationally to prevent, detect, and control illness and death related to infections caused by antibiotic-resistant bacteria by implementing measures to mitigate the emergence and spread of antibiotic resistance and ensuring the continued availability of therapeutics for the treatment of bacterial infections.</i></p> <p>September 2014</p> 	 <h2>NATIONAL ACTION PLAN FOR COMBATING ANTIBIOTIC-RESISTANT BACTERIA</h2> <p>MARCH 2015</p> 
---	---	---	--

<https://obamawhitehouse.archives.gov/blog/2014/09/18/pcast-releases-new-report-combating-antibiotic-resistance;>
[https://obamawhitehouse.archives.gov/sites/default/files/docs/national action plan for combating antibiotic-resistant bacteria.pdf](https://obamawhitehouse.archives.gov/sites/default/files/docs/national_action_plan_for_combating_antibiotic-resistant_bacteria.pdf)

Antibiotic utilization reduction goals

- By 2020, the United States will
 - Reduce inappropriate antibiotic use for monitored conditions/agents by 20% from 2014 levels
 - Reduce inappropriate outpatient antibiotic use for monitored conditions/agents by 50% from 2010 levels
 - Eliminate the use of medically important antibiotics for growth promotion in animals

White House Antimicrobial Summit – June 2015

- Convened 150 key stakeholders across human and animal health sectors to discuss the increasing problem of antibiotic resistance

Human Health

Session 1: Improving Inpatient Prescribing; Focus on Patients

Session 2: Improving Outpatient Prescribing; Focus on Families

Session 3: Improving Long-term Care Prescribing; Focus on Aging Population

Session 4: Developing New Tools for Stewardship -- Better Therapies, Better Diagnostics



Post 2015 Work

- Harmonizing antibiotic susceptibility testing between FDA approved breakpoints and other agencies (21st Century Cures Act)
- Developing incentives to encourage drug companies to develop antibiotics
 - Patent protection (5 additional years for Qualified Infectious Diseases Products)
 - Accelerated drug approval – less clinical trials required
- Veterinary Feed Directive Act
- FDA considering a “licensing fee” for antibiotics
- Presidential Advisory Council on Combating Antibiotic Resistant Bacteria (PAC CARB)
- National benchmark for antibiotic utilization known as the standardized antibiotic administration ratio (SAAR)
- Reporting through NHSN

Stewardship Seats At the Table

- Agency for Healthcare Research and Quality
- American Hospital Association
- American Society of Health Systems Pharmacists (ASHP)
- American Society of Consultant Pharmacists
- Association of State and Territorial Health Officials (ASTHO)
- Center for Disease Control and Prevention
- Center for Medicare and Medicaid Services (CMS)
- Federal Office of Rural Health Policy
- IDSA – Infectious Diseases Society of America
- The Joint Commission
- Leapfrog Group



- NQF – National Quality Forum
- QIO/QINs
- Pediatric Infectious Diseases Society (PIDS)
- PEW Charitable Trusts
- Society of Hospital Medicine (SHM)
- Society of Infectious Diseases Pharmacists
- Society for Healthcare Epidemiology of America (SHEA)
- The Joint Commission
- The White House
- U.S. News & World Report – Best Children’s Hospital Honor Roll

*Since 2014

The Joint Commission MM.09.01.01

EP	Description
1	Leaders establish antimicrobial stewardship as an organizational priority.
2	Educate staff and licensed independent practitioners involved in antimicrobial ordering, dispensing, administration, and monitoring about antimicrobial resistance and antimicrobial stewardship practices. Education occurs upon hire and annually thereafter.
3	Educate patients, and their families as needed, regarding the appropriate use of antimicrobial medications, including antibiotics. REMOVED FOR CAH and ACUTE CARE – 10/1/17 https://www.jointcommission.org/issues/article.aspx?Article=YorQ4E0NZh1SOmOxW2H%2FtFFcVyCrphOFImQsZM%2BlvPc%3D
4	The organization has an antimicrobial stewardship multidisciplinary team that includes the following members, when available in the setting: Pharmacist(s), infection disease physician, infection preventionists (part time/consultant staff acceptable)

The Joint Commission MM.09.01.01

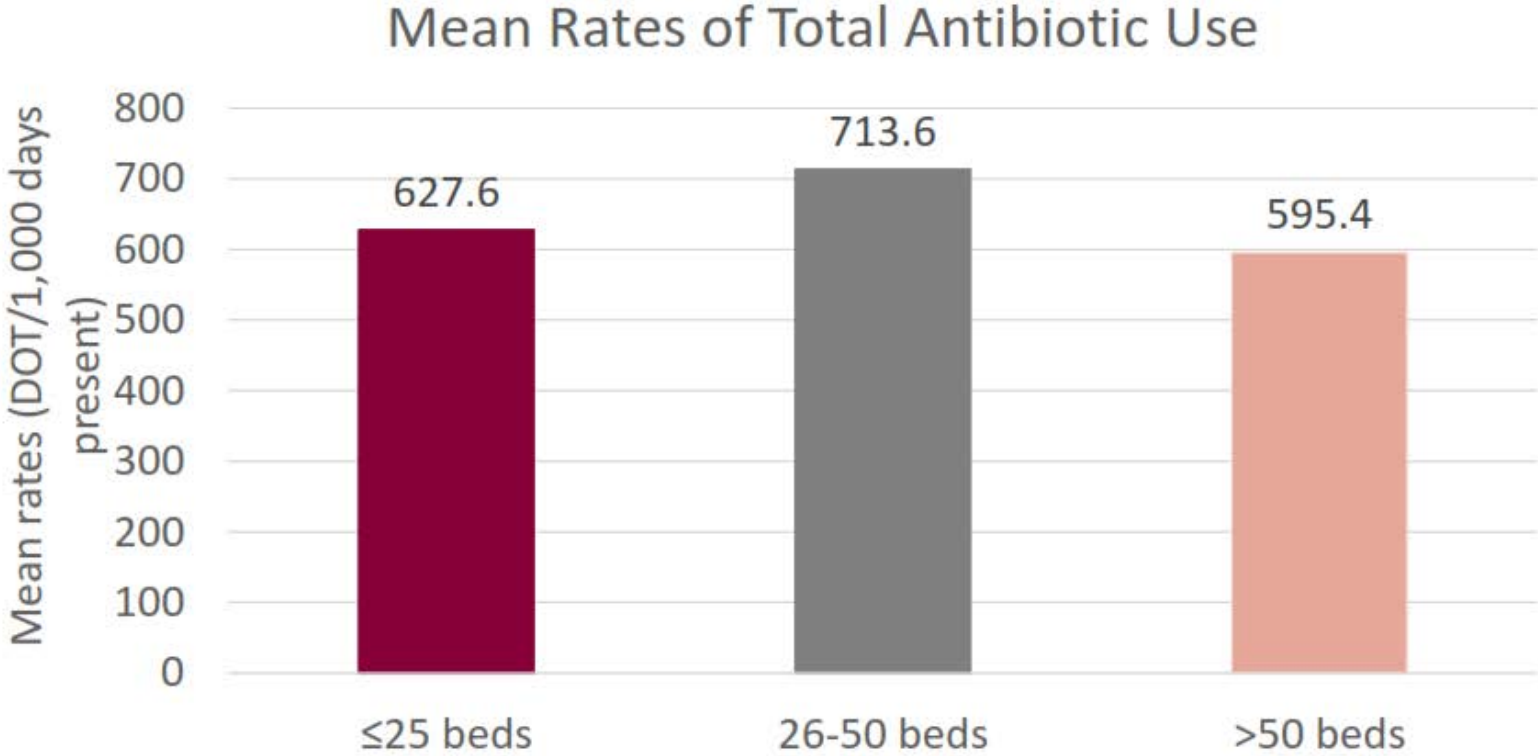
EP	Description
5	<p>The organization's antimicrobial stewardship program includes the following core elements:</p> <ul style="list-style-type: none">- Leadership commitment- Accountability- Tracking- Education- Action- Drug expertise- Reporting
6	<p>The organization's antimicrobial stewardship program uses organization-approved multidisciplinary protocols.</p>
7	<p>The organization collects and analyzes data on its antimicrobial stewardship program, including antimicrobial prescribing and resistance patterns</p>
8	<p>The organization takes action on improvement opportunities identified in its antimicrobial stewardship program</p>

Stewardship in Critical Access Hospitals

- Medicare Beneficiary Quality Improvement Project (MBQIP)
 - Listed under patient safety/inpatient core improvement initiative
- Required to fully implement an antibiotic stewardship program
 - Follow the CDC Core Elements by August 31, 2022 (4 year lead time)
 - Necessary to receive Flex grant funding
- Encourages to collaborate with health departments and QIO-QINs
- 2018 expectations
 - Enroll in National Healthcare Safety Network (NHSN)
 - Submit NHSN Annual Facility Survey
 - Become familiar with the CDC's 7 Core Elements

<https://www.ruralcenter.org/resource-library/mbqip-measures>

Critical Access Hospitals Use Antibiotics About As Much As Larger Hospitals



ANTIBIOTIC SAFETY

Antibiotics and the Patient Safety Impact

- What if something bad happens without an antibiotic? What is the number needed to treat?
 - Complications to common respiratory infections are very rare
 - Over 4400 patients with colds need to be treated to prevent 1 case of pneumonia
- What if something bad happens with an antibiotic? What is the number needed to harm?
 - Antibiotic adverse events can be severe
 - Life-threatening allergic reactions (e.g., anaphylaxis)
 - Antibiotic-associated diarrhea (e.g., *C. difficile* infection)
 - 1 in 1000 antibiotic prescriptions leads to an ER visit for an adverse event (~200,000 estimated ER visits/year in U.S.)
 - Antibiotic adverse events have long-term consequences for chronic disease: disruption of microbiota and microbiome linked to chronic disease

Petersen et al. *British Medical Journal*. 2007;335(7627): 982. Shehab, et al. *Clin Infect Dis*. 2008 Sep 15;47(6):735-43. 3. Shehab et al. *JAMA* 2016;316:2115-25. Bourgeois, et al. *Pediatrics*. 2009;124(4):e744-50. 5. Vangay, et al. *Cell host & microbe* 2015; 17(5): 553-564.

Adverse Events

- 1488 hospitalized patients were given antibiotics
- 20% experienced at least 1 antibiotic-associated adverse event
- 20% of non-indicated antibiotic regimens were associated with an adverse event, including 7 cases of *C. difficile*
- There was a 3% increased risk of an adverse event for every 10 days of antibiotics
- The most common (first 30 days)

Description	Incidence (%)
GI (diarrhea, vomiting, nausea)	42
Renal (> 1.5 times rise in creatinine)	24
Hematologic (anemia, leukopenia, thrombocytopenia)	15



[Home](#)

[Food](#)

[Drugs](#)

[Medical Devices](#)

[Radiation-Emitting Products](#)

[Vaccines, Blood & Biologics](#)

[Animal & Veterinary](#)

[Cosmetics](#)

[Tobacco Products](#)

News & Events

[Home](#) > [News & Events](#) > [Newsroom](#) > [Press Announcements](#)

FDA News Release

FDA updates warnings for fluoroquinolone antibiotics on risks of mental health and low blood sugar adverse reactions

[f SHARE](#) [TWEET](#) [LINKEDIN](#) [PIN IT](#) [EMAIL](#) [PRINT](#)

For Immediate Release

July 10, 2018

Release

The U.S. Food and Drug Administration today is requiring safety labeling changes for a class of antibiotics called fluoroquinolones to strengthen the warnings about the risks of mental health side effects and serious blood sugar disturbances, and make these warnings more consistent across the labeling for all fluoroquinolones taken by mouth or given by injection.

Inquiries

Media

[✉ Theresa Eisenman](#)
[☎ 301-796-2969](#)

Consumers

[☎ 888-INFO-FDA](#)

Related Information

- [Fluoroquinolone Antimicrobial Drugs Information](#)

Follow FDA

“Easy Wins” for Antibiotic Stewardship

- Avoiding overtreatment of asymptomatic bacteriuria
- Limiting duration of therapy
- Assessment of antibiotic use at transition of care
- Appropriate testing and treatment of *C. difficile*
- Avoiding duplicate anaerobic therapy

The 5 D's of Antibiotic Stewardship

- Goal: Ensure the 5 D's of optimal antimicrobial therapy

D agnosis	➡	Does the condition require antibiotic therapy?
D rug	➡	Is the bacteria susceptible?
D ose	➡	What is the recommended dose?
D uration	➡	What is the recommended duration?
D e-escalation	➡	Can the antibiotic be switched from IV to oral?

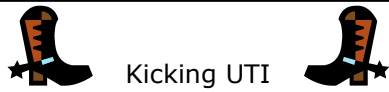
Asymptomatic Bacteriuria is Common

Population	% ASB
Healthy pre-menopausal women	<5%
Women 65-90 years old	6-16%
Women ≥90 years old	22-43%
Female long-term care residents	25-50%
Men >65 years old	5-21%
Male long-term care residents	15-35%
Indwelling urinary catheters	100%

Nicolle. Infect Dis Clin North Am. 1997; 11:647. Nicolle. Infect Control Hosp Epidemiol. 2001; 22:167. Warren, et al. J Infect Dis. 1982; 146:719. Saint, et al. H Am Geriatr Soc. 2006; 54:1055.

Urine culture on admission increases antibiotic use and length of stay

- Retrospective cohort study of a national dataset from 2009 to 2014 (230 hospitals)
- Total of 88,841 patients included
 - No urine culture (n=47,411) vs urine culture (n=41,070) on admission
- Evaluated admissions based on MS-DRG. Patients were case matched by facility, age, gender, and 3 measures of disease severity
- Obtaining a urine culture on admission led to an increase in days of inpatient antibiotic use (incidence rate ratio, 1.26, $p < 0.001$) and resulted in an additional 36,607 days of inpatient antibiotic treatment
- 2.1% increase in LOS ($p = 0.004$) equaling 6,071 additional bed days

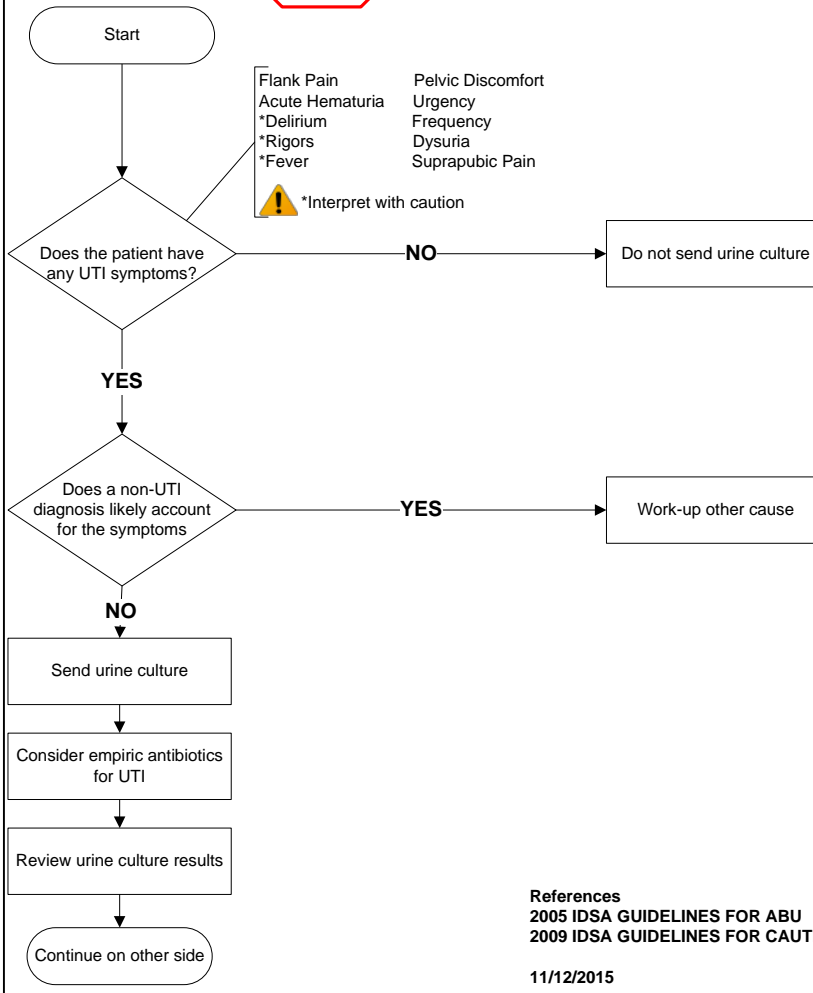


Kicking UTI The No Knee-Jerk Antibiotics Campaign

Symptomatic UTI versus Asymptomatic Bacteriuria



PYURIA, cloudy urine, foul smell or positive urinalysis are not symptoms of UTI and are not indications for antibiotics



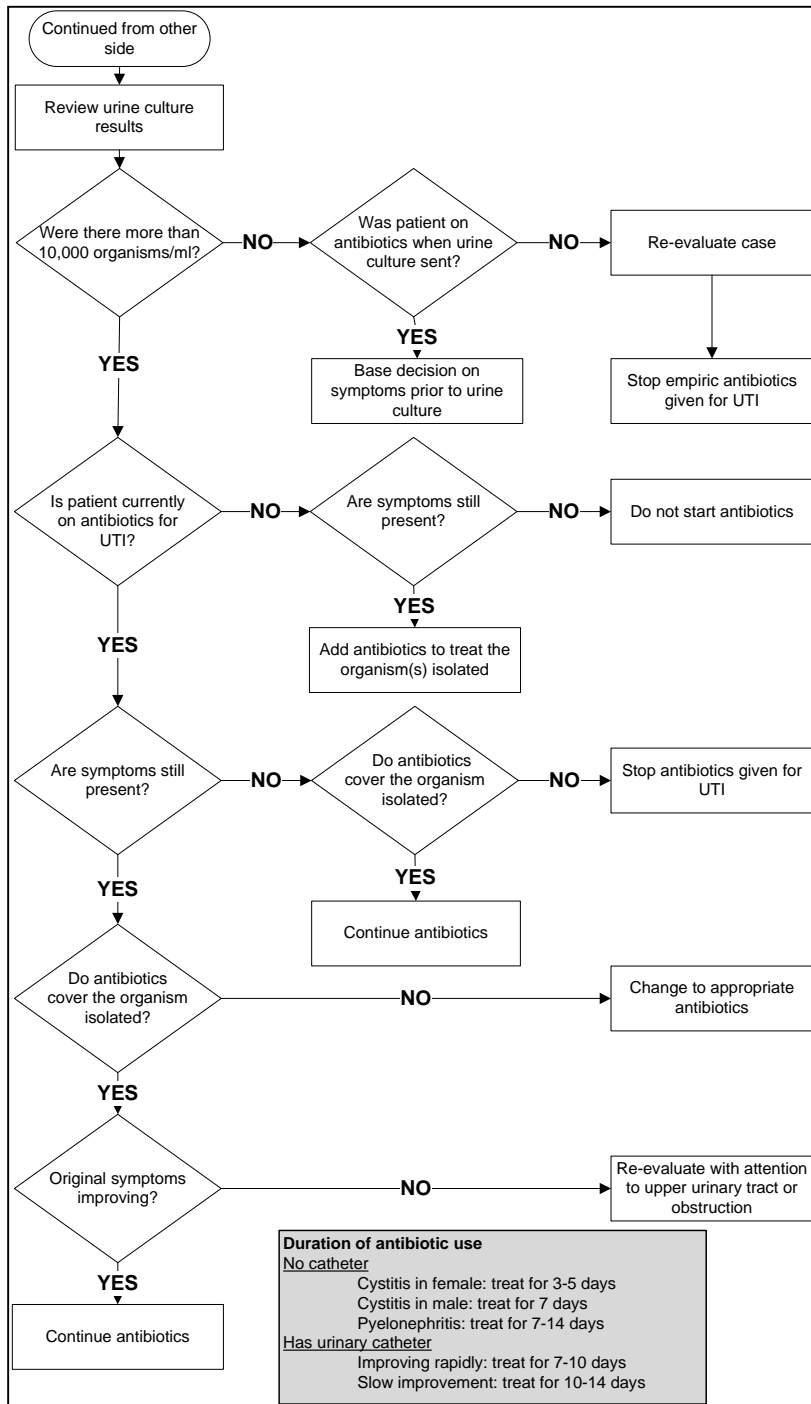
What is missing?

- Cloudy urine
- Foul-smelling urine

Citation: Trautner, B, et al. Infect Dis Clin North Am. 2014 March ; 28(1): 15–31. doi:10.1016/j.idc.2013.09.005

References
2005 IDSA GUIDELINES FOR ABU
2009 IDSA GUIDELINES FOR CAUTI

11/12/2015



Citation: Trautner, B, et al. Infect Dis Clin North Am. 2014 March ; 28(1): 15–31. doi:10.1016/j.idc.2013.09.005

Mental status changes & UTIs

- Bacteriuria and delirium are both independently common in the elderly
- Although patients with symptomatic UTIs may present with delirium, no evidence that delirium, falls, or confusion are symptoms of a UTI in the absence of urinary symptoms
 - 72 elderly residents without traditional UTI symptoms with and without bacteriuria were evaluated: no differences in insomnia, malaise, fatigue, anorexia between the two groups
- If a patient has signs of systemic infection and delirium, empiric antibiotic therapy may be warranted

McKenzie, et al. Am J Med. 2014;127:255-7. Boscia, et al. Am J Med 1986;81:979-82. Nicolle, et al. Infect Control Hosp Epidemiol. 2000;21:537-45.

Summary: Asymptomatic bacteriuria

- Treatment of asymptomatic bacteriuria is common
- Educate both nurses and prescribers
 - Foul-smelling urine, cloudy urine, pyuria, or mental status changes alone \neq urinary tract infection
- Keep algorithms simple and available at point of care
- If education not enough, consider discontinuing reflex urine culture results reporting

Example from a large health system (2018)

Current:

Greater or equal to 5 WBC, any nitrites, any leukocyte esterase

Changing to:

Greater or equal to 10WBC with symptoms of a UTI

- Nitrites and leukocyte esterase not used

Antibiotic Stewardship and Duration

- The right drug at the right dose for the right duration
- Objectives:
 - Optimize patient safety –
 - Right duration maximizes cure and minimizes antibiotic exposure thus reducing adverse drug events such as CDI and other toxicities
 - Facilitates earlier removal of invasive devices
 - Improves drug compliance
 - Reduce resistance – shortest duration needed for cure reduces selection of resistance
 - Decrease costs – optimizing duration can save money

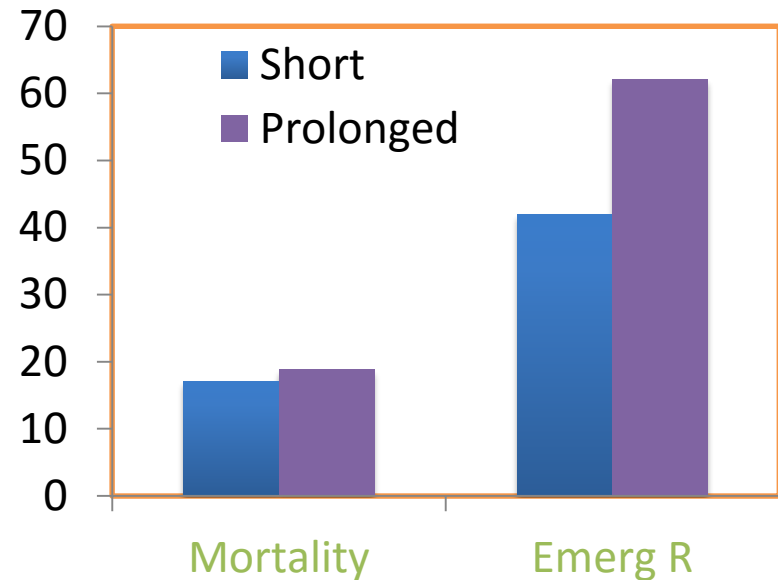
Historical Perspective on Duration

- Staphylococcal sepsis treated in 1941 with PCN over 4 days with clinical improvement but when drug ran out, succumbed to infection – prolonged treatment need to avoid failure?
- Meads et al. administered PCN for PNA until definite clinical improvement and Temp < 100°F x 12 hours, then another 2-3 days of treatment
 - Need to treat beyond resolution of symptoms driven by desire to prevent relapse; however in further case series analysis, not relapses but reinfections with distinct bacterial serotypes
- Unclear how desire to prevent reinfection transformed into dogma that antibiotic resistance can be prevented by continuing therapy beyond resolution of sx

Llewelyn MJ et al. The antibiotic course has had its day. *BMJ* 2017; 358:j3418; Spellberg B. The New Antibiotic Mantra—“Shorter Is Better.” *JAMA Internal Medicine*. 2016;176(9):1254-1255.

Prolonged Antibiotic Course Increases Resistance

- Prospective, randomized double-blind clinical trial in 51 French ICUs of adults with VAP (n=401)
- Randomized to 8 days vs. 15 days of therapy
- No difference in mortality or recurrent infections
 - More recurrences in 8-day arm for NLFGN
- MDROs emerged less frequently in patients receiving 8 days



Chastre J, et al. JAMA 2003;290:2588.

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

Disease	Treatment, Days	
	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.

Spellberg B. The New Antibiotic Mantra—“Shorter Is Better.” *JAMA Internal Medicine*. 2016;176(9):1254-1255.

Transitions of Care – Denver Health

- 53% of discharge antibiotic prescriptions were inappropriate
 - UTI, CAP, SSTI accounted for 67% of inappropriate prescriptions
- Excessive duration of therapy 33%
- Suboptimal antibiotic selection 17%

Transitions of Care – Hospital of University of Pennsylvania

- 70% of discharge antibiotic prescriptions were inappropriate
- 76% of those inappropriate were due to absence of an acceptable indication and inappropriate duration

CLOSTRIDIUM DIFFICILE
ASSOCIATED DISEASE

Antibiotics and Risk For *C. difficile*








Very Commonly Related to CDI	Less Commonly Related to CDI	Uncommonly Related to CDI
Clindamycin Ampicillin Amoxicillin Cephalosporins (3 rd and 4 th generation higher risk) Fluoroquinolones	Other penicillins Sulfonamides Trimethoprim Trimethoprim- Sulfamethoxazole Macrolides Carbapenems	Aminoglycosides Metronidazole Rifampin Chloramphenicol Tetracyclines Daptomycin Tigecycline Vancomycin

N Engl J Med 2015;372:1539-48. Beauduy C, MacDougall C. *Hospital Pharm* – 2013;48(2 Suppl 1): S7-S13. Vardakas KZ, et al. *International Journal of Antimicrobial Agents* 2016; 48: 1-10.

Diagnostic testing stewardship

1. Only test symptomatic patients (3 or more unformed stools within the last 24 hrs)
2. Evaluate the consistency of the stool. Only test diarrheal stools
3. Do not test stools of patients who have been on laxatives
4. Do not retest for at least 7 days during the same episode of diarrhea
5. Cancel order if > 24 hours old
6. Do not test stool from asymptomatic patients
7. Empower nursing to obtain order
8. Empower laboratory to discontinue order

Bristol Stool Chart

Type 1		Separate hard lumps, like nuts (hard to pass)
Type 2		Sausage-shaped but lumpy
Type 3		Like a sausage but with cracks on its surface
Type 4		Like a sausage or snake, smooth and soft
Type 5		Soft blobs with clear-cut edges (passed easily)
Type 6		Fluffy pieces with ragged edges, a mushy stool
Type 7		Watery, no solid pieces. Entirely Liquid

Duplicate Anaerobe Therapy

- Anaerobes are normal flora of the intestinal tract
 - Most intestinal anaerobes are gram-negative organisms (e.g., *Bacteroides* spp., *Prevotella* spp., etc.)
- Routine double coverage of β L- β LI or carbapenems with metronidazole is not recommended given the excellent anaerobic activity of these agents

Exceptions for Duplicate Coverage

- *C. difficile* infections
 - Addition of metronidazole to clindamycin, β L- β LI, or carbapenems in patients who cannot receive oral vancomycin or fidaxomicin based on 2017 guidelines
- Necrotizing fasciitis
 - Addition of clindamycin to β L- β LI
- Parasitic infections
 - Addition of metronidazole for *Trichomonas*, *Giardia*, *Entamoeba histolytica* to clindamycin, β L- β LI, or carbapenems

What's The Harm?

- Resistance is rare and not a major clinical concern
- Metronidazole is relatively inexpensive (<10 USD/day)
- Can have side effects: Generally not serious but still cause discomfort
 - Peripheral neuropathy when administered in high doses and over prolonged periods of time
 - Headache (18%)
 - Metallic taste (9%)
 - Nausea (10%)
 - Disulfiram-reaction
 - Abdominal cramps, nausea, emesis, headaches, flushing

How Can You Change This Practice?

- Likely a knowledge gap
 - Educate clinicians that use of multiple drugs active against anaerobes is not necessary and puts patients at risk for additional drug toxicities
- When conducting post-prescription review on piperacillin-tazobactam or carbapenems, look out for metronidazole!
- Consider educating nurses on surgical wards
- Engage staff pharmacists and clinical pharmacists

QUESTIONS