Updates in Antimicrobial Stewardship

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Antimicrobial Stewardship Pharmacist
June 5th, 2019

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In sickness and in health®

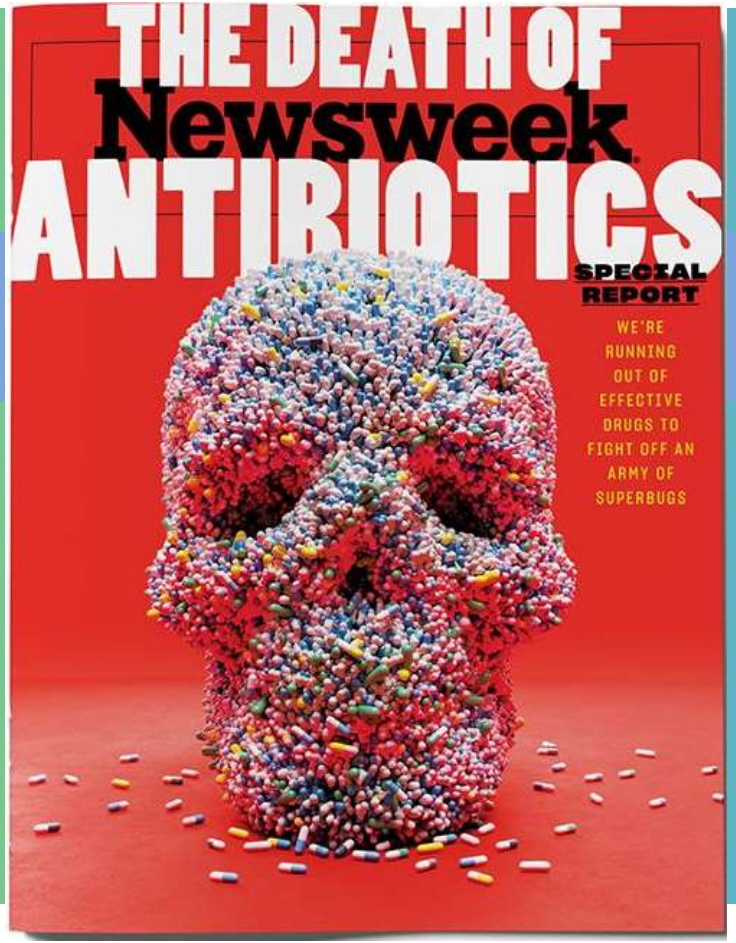
Disclosure

I have no conflicts of interest to disclose

Objectives

- Describe the national strategy for antimicrobial stewardship
- Identify recently approved/phase III antimicrobials and define their role in therapy
- Explain the role of diagnostic stewardship in the laboratory

The superbug that doctors have been dreading just reached the U.S.



The Golden Age of antibiotics comes to an end

Nightmare superbug cases rise in Illinois health-care facilities

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https://s.newsweek.com/sites/www.newsweek.com/files/styles/full/public/2019/05/10/fesuperbugscover.jpg

National Urgency for Optimal Antibiotic Use

- CDC estimates 2 million illnesses and 23,000 deaths as the result of antibiotic-resistant bacteria in the U.S
- Overuse of antimicrobials in healthcare and food production has led to an increase of bacterial drug resistance
- Studies show 30 – 50% of antibiotics prescribed are unnecessary or inappropriate
  - Avoidable costs for antibiotic misuse ranges from $27 – 42 billion in the U.S

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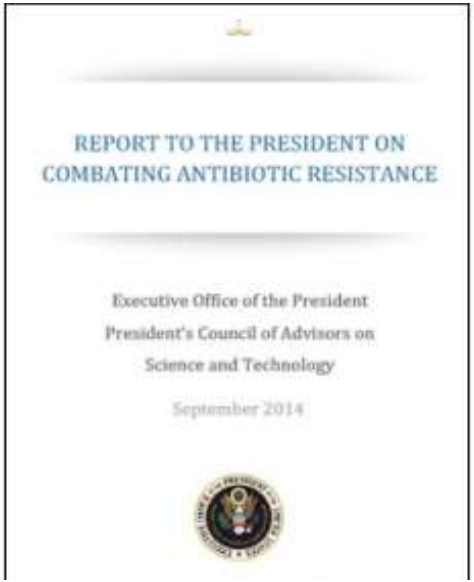
Mechanisms of Resistance

- Adaptive resistance:
  - Bacteria can adapt to their environment to survive: biofilms
- Acquired resistance:
  - Bacteria pass genetic material on plasmids
    - β-lactamases passed on plasmids – affects β-lactams
    - Bacteria have reduced permeability or can use efflux pumps to push antibiotic out of the cell: affects aminoglycosides, fluoroquinolones, macrolides, and tetracyclines
    - Alteration in drug-binding target – affects β-lactams, oxazolidinones, aminoglycosides, tetracyclines, glycopeptides
    - Alteration of the antibiotic – affects fluoroquinolones, aminoglycosides, lincosamides
    - Bypass the effect of the antibiotic – affects β-lactams, sulfamethoxazole/trimethoprim, glycopeptides

National Strategy for Antimicrobial Stewardship

Executive Order -- Combating Antibiotic-Resistant Bacteria

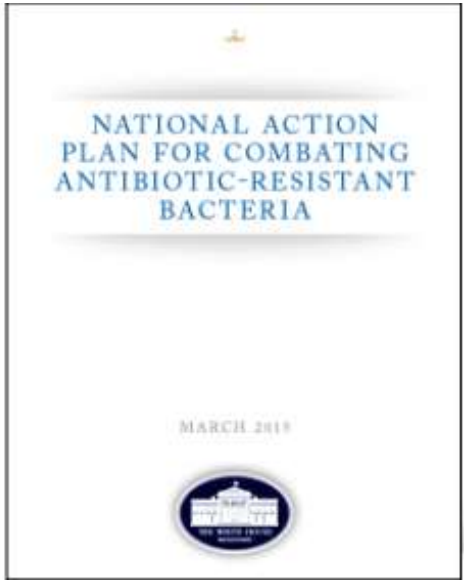


REPORT TO THE PRESIDENT ON COMBATING ANTIBIOTIC RESISTANCE

Executive Office of the President
President's Council of Advisors on Science and Technology

September 2014

NATIONAL STRATEGY FOR COMBATING ANTIBIOTIC-RESISTANT BACTERIA



NATIONAL ACTION PLAN FOR COMBATING ANTIBIOTIC-RESISTANT BACTERIA

MARCH 2015

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Active Legislation

- **Veterinary Feed Directive**
  - Effective October 2015
  - Requires a veterinary order/prescription for any medically important antimicrobials used in feed or water given to livestock
    - Previously over-the-counter
  - 2017: Outlawed antibiotics for purposes of growth promotion and feed efficiency
- **21st Century Cures Act**
  - December 2016
  - Monitoring AUR in federal facilities
  - FDA may approve antibiotic for a limited population if it is intended for a serious infection
  - New FDA website for susceptibility test interpretative criteria and devices: fda.gov/STIC

https://www.undispatch.com

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Antimicrobial Stewardship as a CMS Condition of Participation (CoP)

- Federal regulations (CoP) to be implanted that will require U.S. hospitals, critical access hospitals, and long-term care and nursing home facilities to have robust antibiotic stewardship programs that adhere to best practices, such as those contained in the CDC Core Elements for Hospital Antibiotic Stewardship Program recommendations.
  - Similar requirements should be phased in rapidly for other settings including long-term acute care hospitals, other post-acute facilities, ambulatory, surgery centers, and dialysis centers

CMS CoP Update

- Status of CoPs for acute care and critical access hospitals unknown

- The NHSN Antimicrobial Use and Antimicrobial Resistance Module reporting has been identified as one option for eligible hospitals to meet stage 3 of the CMS Meaningful Use Program
  - Provides a mechanism for facilities to report and analyze antimicrobial usage as part of antimicrobial stewardship efforts at local facilities
  - Standardized Antimicrobial Administration Ratio (SAAR):
    - Provide a set of risk-adjusted AU summary statistics that hospitals can use to compare their AU data with nationally aggregated data
    - SAAR= $\frac{Observed\ Antimicrobial\ Days}{Predicted\ Antimicrobial\ Days}$

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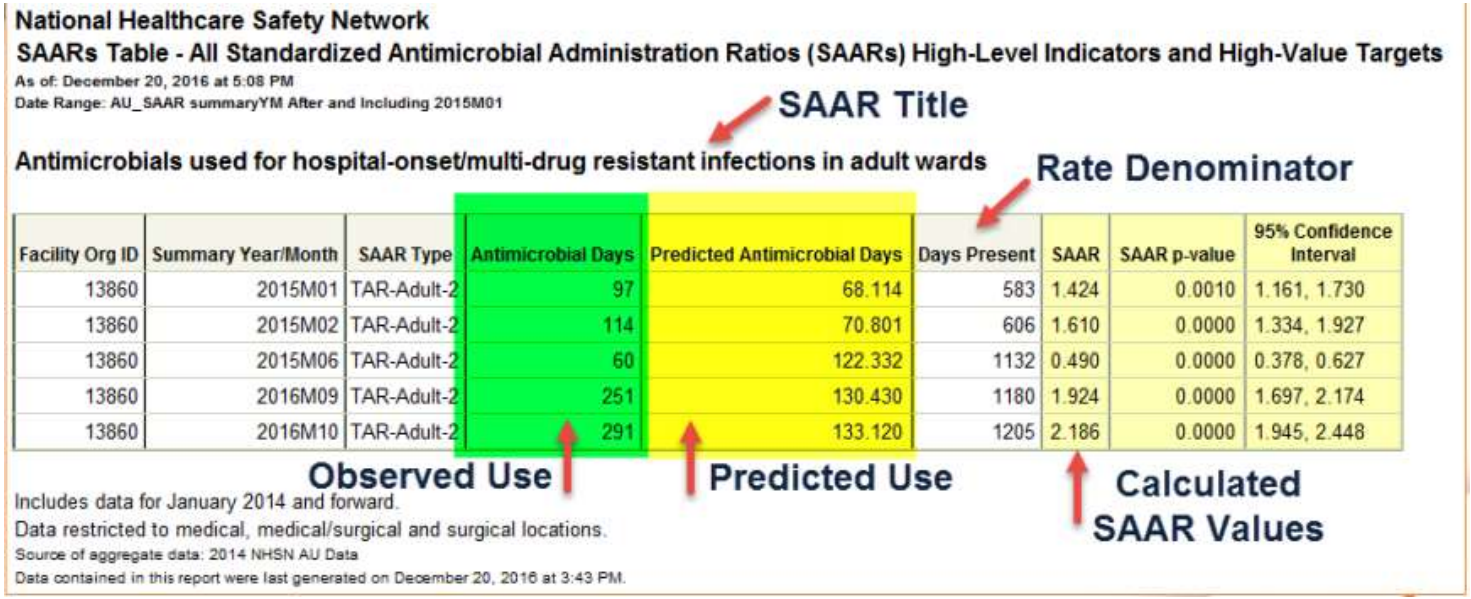
Example SAAR



National Healthcare Safety Network

SAARs Table - All Standardized Antimicrobial Administration Ratios (SAARs) High-Level Indicators and High-Value Targets

As of: December 20, 2016 at 5:08 PM

Date Range: AU_SAAR summaryYM After and Including 2015M01

SAAR Title

Antimicrobials used for hospital-onset/multi-drug resistant infections in adult wards

Rate Denominator

Facility Org ID	Summary Year/Month	SAAR Type	Antimicrobial Days	Predicted Antimicrobial Days	Days Present	SAAR	SAAR p-value	95% Confidence Interval
13860	2015M01	TAR-Adult-2	97	68.114	583	1.424	0.0010	1.161, 1.730
13860	2015M02	TAR-Adult-2	114	70.801	606	1.610	0.0000	1.334, 1.927
13860	2015M06	TAR-Adult-2	60	122.332	1132	0.490	0.0000	0.378, 0.627
13860	2016M09	TAR-Adult-2	251	130.430	1180	1.924	0.0000	1.697, 2.174
13860	2016M10	TAR-Adult-2	291	133.120	1205	2.186	0.0000	1.945, 2.448

Observed Use

Predicted Use

Calculated SAAR Values

Includes data for January 2014 and forward.

Data restricted to medical, medical/surgical and surgical locations.

Source of aggregate data: 2014 NHSN AU Data

Data contained in this report were last generated on December 20, 2016 at 3:43 PM.

The Joint Commission Antimicrobial Stewardship Standard

1. Leaders establish ASPs as an organizational priority
2. The hospital educates staff and licensed independent practitioners involved in antimicrobial ordering, dispensing, administration, and monitoring about antimicrobial resistance and antimicrobial stewardship practices
3. ~~The [critical access] hospital educates patients, and their families as needed, regarding the appropriate use of antimicrobial medications, including antibiotics~~
4. ASP Committee includes ID providers, IPs, pharmacists, and other practitioners

TJC Standard Continued

5. ASP includes leadership commitment, accountability, drug expertise, action (antibiotic time out), tracking, reporting, education
6. The hospital's antimicrobial stewardship program uses organization-approved multidisciplinary protocols: i.e. restrictions, guidelines for antibiotic use, prophylactic antibiotic guidelines
7. The hospital collects, analyzes, and reports data on its antimicrobial stewardship program
8. The hospital takes action on improvement opportunities identified in its antimicrobial stewardship program

Antimicrobial Stewardship

Goal:

- Optimize the treatment of infections and antibiotic use
  - Provide patient:
    - Right antimicrobial
    - Right time
    - Right dose
    - Right duration

Benefits:

- Reduce hospital-acquired infections
- Reduce inappropriate antibiotic use
- Improve patient outcomes and decrease adverse events

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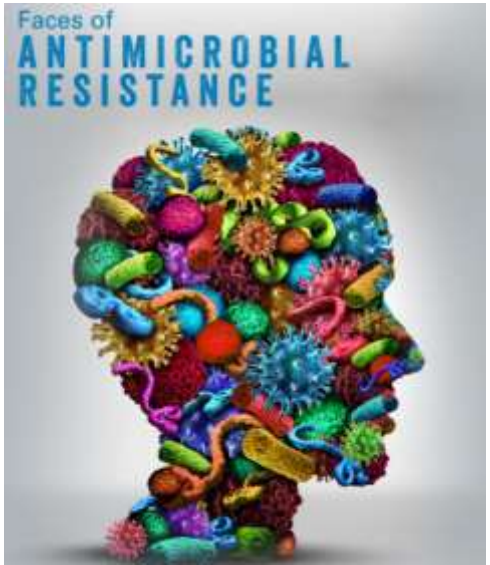
On Tuesday, April 13, my mom had a root canal, and the dentist prescribed the antibiotic clindamycin to treat an abscess. The next day, she felt fine. On Thursday, mom came home from work and said she didn't feel well. Thinking she caught a bug from one of her students, she still went to her class that night.

The following day, though, my mom stayed home from work, which is something she almost never did. She ended up in bed all weekend with what she thought was a stomach virus. On Saturday, she spoke to her doctor by phone. He prescribed, by phone, a prescription strength anti-diarrheal medicine and told her she should see a GI doctor on Monday. She began taking the medication later that day. We came to find out later that an anti-diarrheal medicine is one of the worst things you can take when you have *Clostridium difficile*, or *C. diff.*

PEGGY LILLIS

Brooklyn, NY



"...They would remove her colon 'in an attempt to save her life'."

At six o'clock the next morning, the doctor called Christian and told us to get to the hospital. My mom had not improved overnight and surgery was necessary. The doctor told us that she was so ill he was afraid she wouldn't survive surgery, but that she would very likely die from sepsis without it. We consented to the surgery, which my mom survived.

From late morning until the afternoon, it seemed that she was improving. But around 4 pm, her vital signs started to deteriorate. The doctors put her on 100% oxygen and provided additional drugs to support her blood pressure. She continued to decline throughout the afternoon.

At 7:20 pm, the ICU doctor informed us that my mom had passed. She had gone into cardiac arrest. They had tried to revive her several times to no avail.

WHAT'S NEW IN THE ANTIMICROBIAL PIPELINE

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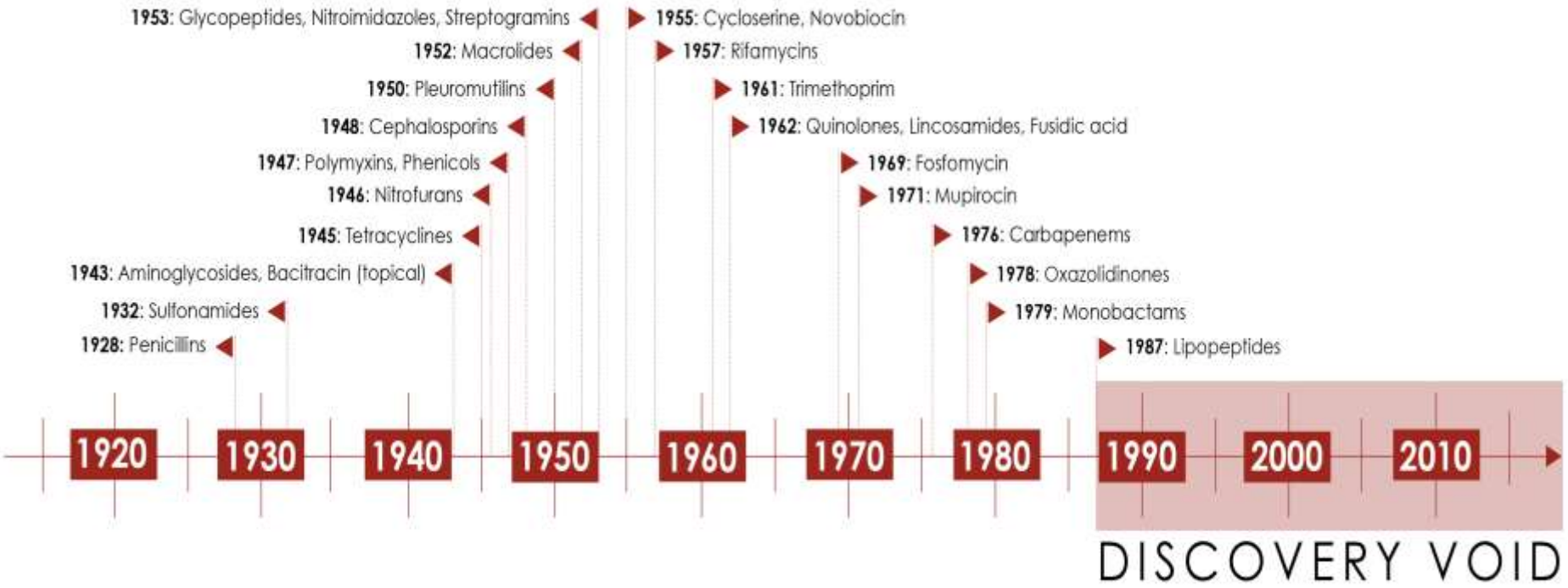
Antibiotics in the Pipeline



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Letter urges Congressional action to stimulate antibiotic development

Filed Under: Antimicrobial Stewardship

Chris Dall | News Reporter | CIDRAP News | Feb 06, 2019

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A coalition of drug makers, infectious disease experts, and public health advocates yesterday called on US lawmakers to pass measures that could "jumpstart" the development of critically needed antibiotics.

In a letter sent to lawmakers in the Senate and the House of Representatives, stakeholders from large and small pharmaceutical companies and organizations including the Infectious Diseases Society of America, the Pew Charitable Trusts, and Trust for America's Health asked Congress to "swiftly enact a package of incentives that would sustainably reinvigorate the pipeline of antibiotics while ensuring patient access and appropriate stewardship."

tupungato/ iStock

Incentives for New antibiotics

- GAIN Act
  - Generating Antibiotic Incentives Now
  - Signed into law 2012
  - Priority review of antimicrobial trials
  - Extra patent time: 5-7 years
  - Fast track for drugs against MRSA, VRSA, VRE, MDR Gram-negatives, and tuberculosis

Recently Approved Antimicrobials

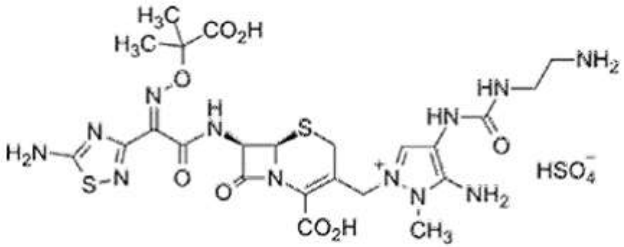
Drug	Brand Name	Class	Approval	Indication
Ceftolozane-Tazobactam	Zerbaxa®	Antipseudomonal cephalosporin + β-lactamase inhibitor	2014	cUTIs, cIAIs
Ceftazidime-avibactam	Avycaz®	Antipseudomonal cephalosporin+ Diazabicyclooctane inhibitor	2015	cUTIs, cIAIs, HAP/VAP
Meropenem-vaborbactam	Vabomere®	Carbapenem + Boronic acid based inhibitor	2017	cUTIs
Plazomicin	Zemdri®	Aminoglycoside stable against enzymatic destruction	2018	cUTIs
Eravacycline	Xerava®	Fluorocycline	2018	cIAIs
Omadacycline	Nuzyra®	Aminomethylcycline	2018	CAP, ABSSSI

Ceftolozane-Tazobactam

- Anti-pseudomonal cephalosporin + β-lactamase inhibitor
- Mechanism of Action:
  - Inhibits bacterial wall synthesis by binding to penicillin-binding proteins (PBPs)
  - Inhibition of β-lactamases
  - Tazobactam protects ceftolozane from ESBLs and cephalosporinases
- Place in therapy:
  - MDR *Pseudomonas aeruginosa*
    - Including carbapenem and ceftazidime-resistant strains
    - Expanding indications
  - Unreliable activity against ESBL and AmpCs
  - Not active against carbapenemases

Ceftolozane-Tazobactam

- ESBL activity
  - 58% ESBL K. pneumoniae from pneumonia patients
  - 78% ESBL from abdominal and urinary isolates
- Pseudomonal sensitivity
  - Ranges from 86-95%
  - 92% against meropenem resistant strains
- Weak activity against gram-positive organisms and anaerobes
- Decreased nephrotoxicity compared to aminoglycoside/polymyxin treated patients



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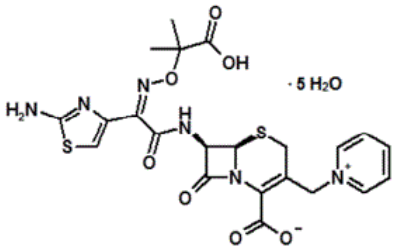
Ceftazidime-Avibactam

- 3rd generation anti-pseudomonal cephalosporin with novel β-lactamase inhibitor
- Mechanism of Action:
  - Inhibits bacterial wall synthesis by binding to penicillin-binding proteins (PBPs)
  - Inhibition of β-lactamases
  - Avibactam is active against ESBLs, KPC-type and OXA-48 carbapenemases
  - Not active against metallo- β-lactamases
- Place in therapy:
  - Enterobacteriaceae with KPC, ESBL, and OXA-48 resistance enzymes
  - Strong activity against *Pseudomonas aeruginosa*



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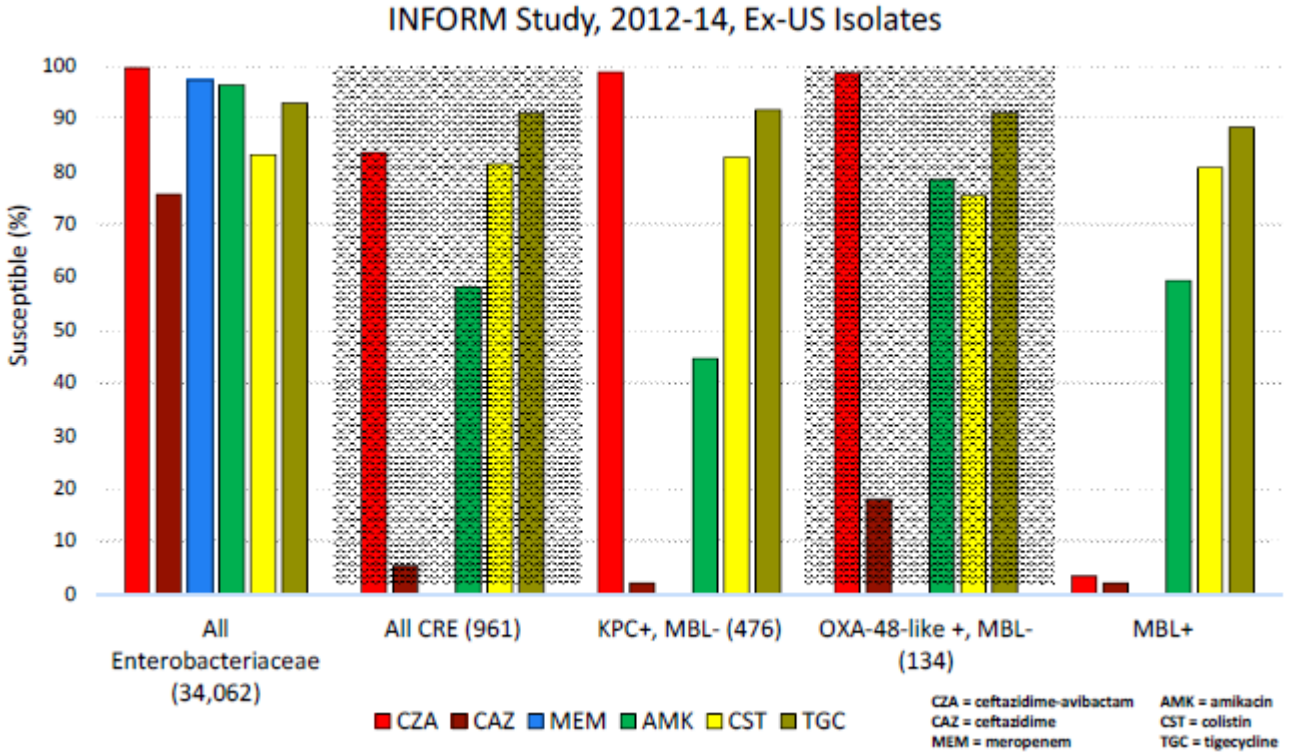
Ceftazidime-Avibactam



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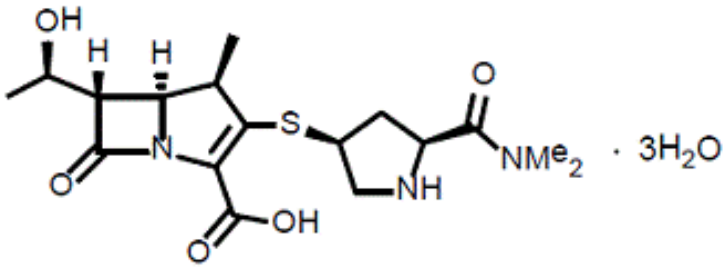
Slide from M. Rybak. The expanding pipeline. Presented May 10, 2019 at MAD-ID.

Meropenem-Vaborbactam

- Carbapenem with novel β-lactamase inhibitor
- Mechanism of Action:
  - Inhibits bacterial wall synthesis by binding to penicillin-binding proteins (PBPs)
  - Inhibition of β-lactamases
- Vaborbactam protects meropenem from degradation by certain serine β-lactamases
  - K. pneumoniae carbapenemases
  - ESBLs
  - It does not have antibacterial activity
  - Not active against metallo- β-lactamases or OXA-48 carbapenemases

Meropenem-Vaborbactam

- Place in Therapy:
  - Enterobacteriaceae producing KPC and class A and C β-lactamases
- Coverage Gaps
  - Not active against carbapenem-resistant *Pseudomonas* and *Acinetobacter,* metallo-β-lactamases or OXA-48 carbapenemases
- Off-label indications with increasing utilization
  - Bacteremia
  - Pneumonia



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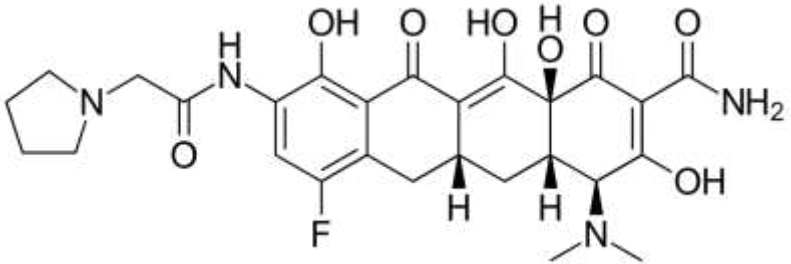
Eravacycline

- Fluorocycline
- Mechanism of Action:
  - Inhibits protein synthesis by binding to the 30S ribosomal subunit
- Eravacycline is bacteriostatic against gram-positive bacteria but showed bactericidal activity against strains of *E. coli* and *K. pneumoniae* in vitro
- Spectrum of Activity:
  - MRSA, VRE, *Enterobacteriaceae, Acinetobacter, Bacteroides, CRE, ESBL*

Eravacycline

- Place in Therapy:
  - Better side effect profile compared to tigecycline
  - Salvage therapy for CRE, ESBL, and *Acinetobacter*
- Limitations
  - High volume of distribution
    - Decreased bloodstream concentrations
  - 2 unsuccessful studies for cUTIs
  - No Pseudomonas coverage



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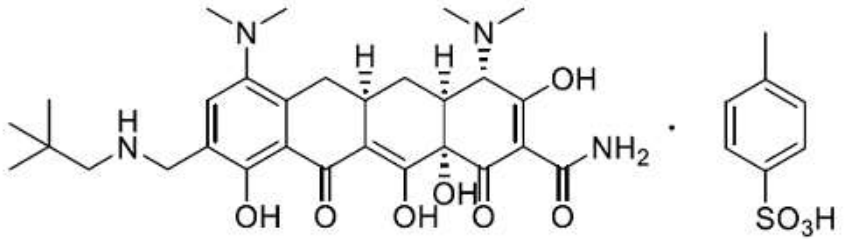
https://upload.wikimedia.org/wikipedia/commons/thumb/5/5b/Eravacycline_structure.svg/1200px-Eravacycline_structure.svg.png

Omadacycline

- Aminomethylcycline in the tetracycline class
- Mechanism of Action:
  - Inhibits protein synthesis by binding to the 30S ribosomal subunit
  - Has shown in vitro activity against tetracycline resistance mechanisms (tet M, tet K, tet L)
- FDA indications include:
  - Community acquired bacterial pneumonia
  - Acute bacterial skin and skin stricture infections
- Spectrum of Activity:
  - MRSA, VRE, *Enterobacteriaceae, Acinetobacter, Bacteroides, CRE, ESBL*

Omadacycline

- Activity against resistance:
  - Active against some strains of *S. aureus, S. pneumoniae*, and *H. influenzae* carrying macrolide resistance genes (erm A, B, and C) or
  - Ciprofloxacin resistance genes (gyrA and parC) and
  - β-lactamase positive *H. influenzae*
- Oral option available



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Plazomicin

- Aminoglycoside
- Mechanism of Action:
  - Interferes with bacterial protein synthesis by binding to 30S ribosomal subunit resulting in a defective bacterial cell membrane
- Spectrum of Activity:
  - Aminoglycoside-resistant enterobacteriaceae, ESBL, CRE
  - Weaker against Pseudomonas, Acinetobacter
- Boxed Warnings:
  - Nephrotoxicity
  - Ototoxicity
  - Neuromuscular blockade
  - Teratogenicity

Plazomicin

Table 3 Activity of plazomicin and comparator aminoglycosides against phenotypes and genotypes of *Enterobacteriaceae* isolates and other Gram-negative species

Organism phenotype/genotype	Breakpoint criteria for aminoglycoside-resistance (no. of isolates)	% of isolates inhibited by plazomicin at ≤4 μg/ml	MIC_{50}/MIC_{90} (μg/ml)			
			Plazomicin	Amikacin	Gentamicin	Tobramycin
Enterobacteriaceae	NA (4,362)	99.2	0.5 / 2	1 / 4	0.5 / 4	0.5 / 4
Amikacin-resistant	CLSI (14)	64.3	1 / >128	>32 / >32	>8 / >8	>8 / >8
	EUCAST (50)	90.0	0.5 / 4	32 / >32	2 / >8	>8 / >8
Gentamicin-resistant	CLSI (377)	96.6	0.5 / 2	2 / 8	>8 / >8	>8 / >8
	EUCAST (424)	95.5	0.5 / 2	2 / 8	>8 / >8	>8 / >8
Tobramycin-resistant	CLSI (292)	96.9	0.5 / 2	4 / 32	>8 / >8	>8 / >8
	EUCAST (423)	96.5	0.5 / 2	4 / 32	>8 / >8	>8 / >8
CRE	NA (97)	99.0	0.5 / 1	16 / 32	2 / >8	>8 / >8
CPE (all carrying *bla*$_{KPC}$)	NA (87)	98.9	0.25 / 1	16 / 32	4 / >8	>8 / >8
Carbapenemase-negative	NA (26)	100.0	0.5 / 1	4 / 16	1 / >8	2 / >8
Pseudomonas aeruginosa	NA (103)	71.8	4 / 16	2 / 8	2 / 8	0.5 / 1
Acinetobacter baumannii	NA (99)	65.2	2 / 32	4 / >32	1 / >8	1 / >8

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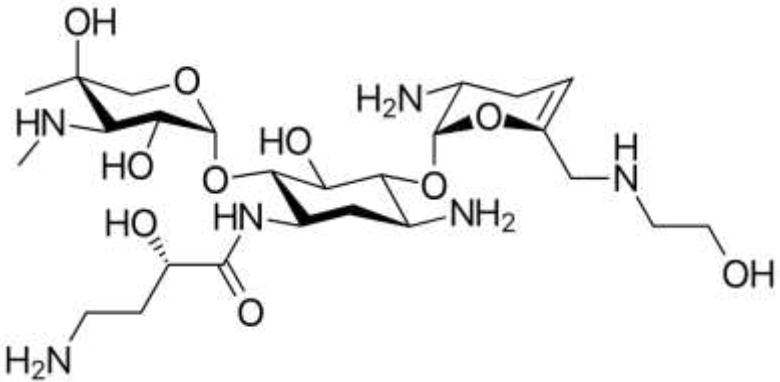
Castanheira M, Davis AP, Mendes RE, Serio AW, Krause KM, Flamm RK. Activity of Plazomicin against Gram-Negative and Gram-Positive Isolates Collected from U.S. Hospitals and Comparative Activities of Aminoglycosides against Carbapenem-Resistant Enterobacteriaceae and Isolates Carrying Carbapenemase Genes. Antimicrob Agents Chemother. 2018;62(8)

Plazomicin

- Place in Therapy:
  - MDR-Gram-negative cUTI/Pyelonephritis
- Limitations
  - Boxed warnings
  - Level monitoring



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Spectrum of Activity

Drug	ESBL	CRE (KPC)	CRE (MBL)	Carba-R Pseudomonas	MDR Acinetobacter
Ceftolozane-tazobactam					
Ceftazidime-avibactam					
Meropenem-vaborbactam					
Plazomicin					
Eravacycline					
Omadacycline					

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Slide derived from M Mahoney, PharmD. Presented at SHEA 2019 Meeting.

Question

A 75 year-old male is admitted to the hospital with fevers, chills, lower back pain, and complains of painful urination. His urine and blood cultures are positive for *Pseudomonas aeruginosa* with a meropenem MIC of 16. Which of the following medications should be tested for sensitivity for this patient?

A. Plazomicin

B. Eravacycline

C. Meropenem-vaborbactam

D. Ceftolozane-tazobactam

Question

A 75-year-old male is admitted to the hospital with fevers, chills, lower back pain, and complains of painful urination. His urine and blood cultures are positive for *Pseudomonas aeruginosa* with a meropenem MIC of 16. Which of the following medications should be tested for sensitivity for this patient?

A. Plazomicin

B. Eravacycline

C. Meropenem-vaborbactam

D. Ceftolozane-tazobactam

Phase III Antibiotics in the Pipeline

Drug	Class	Indication
Cefiderocol	Cephalosporin	MDR Gram-negative infections Carbapenem-resistant(CR) *Acinetobacter baumannii,* CR *P. aeruginosa, CRE*
Iclaprim	2,4-diaminopyrimidine	Acute bacterial skin and skin stricture infections, hospital-acquired pneumonia, Gram-positive infections (MRSA included)
Lefamulin	Pleuromutulin	Community-acquired pneumonia, complicated UTI, skin and skin stricture infections *CR A. baumannii, CR P. aeruginosa, CRE*
Pretomanid	Nitroimidazole analog	MDR-TB
Ibrexafungerp	Antifungal	*Candidiasis* (including *C. auris*), *Aspergillosis*, vulvovaginal candidiasis, *Pneumocystis* pneumonia

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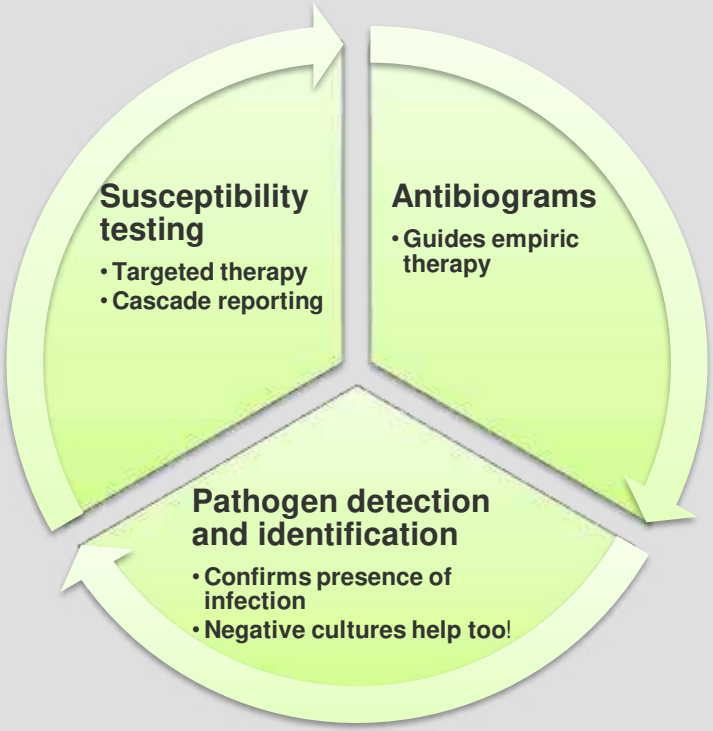
The Microbiology Lab & Antimicrobial Stewardship



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Diagnostic Stewardship

- Right Test → Right Patient → Right Time
- Over-Testing → Over-Diagnosis → Over-Treatment
  - *Clostridioides difficile*
  - Urinary Tract Infections
- Evaluate patient for symptoms
  - Risk factors
- Active infection versus colonization
- Optimize antimicrobial treatment

Clostridioides difficile

- New Infectious Disease Society of America Guidelines
  - What is the best-performing method for detecting patients at increased risk for clinically significant *C. difficile* infection?
    - Use a stool toxin test as part of a multistep algorithm rather than a NAAT alone for all specimens received in the clinical laboratory when there are no pre-agreed institutional criteria for patient stool submission

      -Glutamate dehydrogenase (GDH) + toxin

      -GDH + toxin, arbitrated by NAAT

      -NAAT + toxin

Test	Sensitivity	Specificity
GDH	High	Low
EIA	Low	Moderate
NAAT	High	Low/Moderate

Clostridioides difficile

- Glutamate Dehydrogenase (GDH) EIAs
  - Enzyme produced by both toxigenic **AND** **non-toxin producing C. difficile**
  - May require toxin identification by another test
- Toxin Enzyme-linked immunosorbent assay (EIAs)
  - Utilized antibodies against C. difficile antigens (i.e. proteins) to detect toxins
    - Toxin A and B
- Nucleic Acid Amplification Techniques (NAAT/PCR)
  - Detects gene for toxin A and/or toxin B
    - Does **NOT** detect toxin production

Fecal Studies	
C Difficile Toxins A and B	See C diff NAAT
C difficile Ag	See C diff NAAT
C difficile NAAT	* C Positive
Fecal Description	Liquid; Liquid

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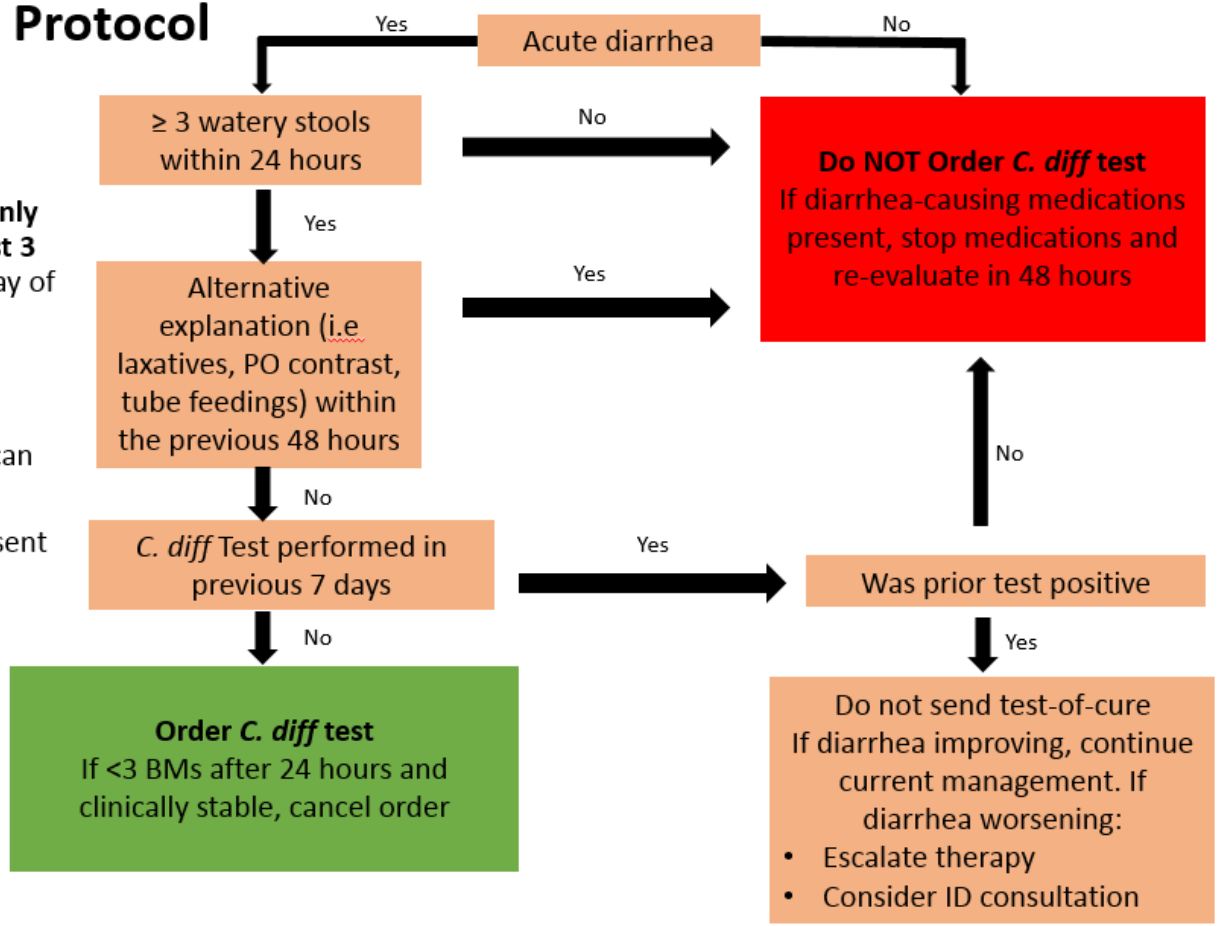
C. difficile Testing Protocol

Key Points:

- **Nursing driven protocol can only be only be ordered on the first 3 days of hospital admission** (day of admission is hospital day 1)
- Confirm clinical diagnosis (≥ 3 watery stools/24 hours)
- Confirm no medications that can cause diarrhea
- Confirm no recent *C. diff* test sent



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Clostridium difficile Ticket to Lab

OpID_____ Date_____/_____/_____

Patient Label

This form must be included with all samples sent to the lab for *C. diff* testing.

All *C. diff* samples must first be verified for the following criteria:

☐ Patient has had 3 or more watery stools in 24 hours (stool takes the shape of the container).

☐ No *C. diff* tests resulted "positive/detected" in the last 2 weeks.

☐ Patient has not been given stool softeners, laxatives, or bowel preps given in the hospital in the last 48 hours.

If a sample does not meet all above criteria:

☐ Ordered "by policy" by nursing ***(to be used for hospital day 1-3 ONLY)***.

STOP, discard sample and cancel order for testing. The criteria was not met and therefore is not covered by existing policy.

☐ Ordered by physician. **STOP**, prior to sending sample to lab, contact physician and discuss appropriateness of test.

- If physician still wants testing to be performed:
  - Send sample along with this form to the lab.
  - Physician's name:_____
  - Submit an event report

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Asymptomatic Bacteriuria

- Definition:
  - Isolation of significant colony counts of bacteria in the urine from a person WITHOUT symptoms of a UTI
- UTI
  - Common symptoms of cystitis are dysuria, frequency, urgency and suprapubic pain.
  - Common symptoms of pyelonephritis are fever and flank pain.
  - Common symptoms of catheter-associated UTI are fever and suprapubic tenderness.
  - Mental status changes alone do not indicate a UTI.
  - Foul smelling or cloudy urine does not indicate a UTI.

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Cosgrove. Best Practices in the Diagnosis and Treatment of Asymptomatic Bacteriuria and Urinary Tract Infections. AHRQ Lecture Series presented March 2018.

Asymptomatic Bacteriuria is Common

Population	Prevalence
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%
Male long-term care residents	15-35%
Diabetic women	9-27%
People receiving hemodialysis	28%
People with indwelling urinary catheters	100%

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Cosgrove. Best Practices in the Diagnosis and Treatment of Asymptomatic Bacteriuria and Urinary Tract Infections. AHRQ Lecture Series presented March 2018.

Asymptomatic Bacteriuria

- Treating asymptomatic bacteriuria is not beneficial for patients
  - Numerous studies have demonstrated a lack of benefit
- Treatment may cause harm!
  - Increased risk of subsequent UTIs
  - Adverse events
  - Resistance!
- Only pregnant women and patients with impending urologic procedure should receive treatment for ASB
- Urinalysis and reflex culture should only be performed when patients have symptoms

Molecular Rapid Diagnostic Testing in Bloodstream Infections

Meta-analysis showed reduction in mortality when RDTs were combined with ASPs

The reduction in mortality was not statistically significant in studies without ASPs

↓ mortality in Gram-positive and Gram-negative bacteremias

↓ length of stay

↓ time to effective therapy

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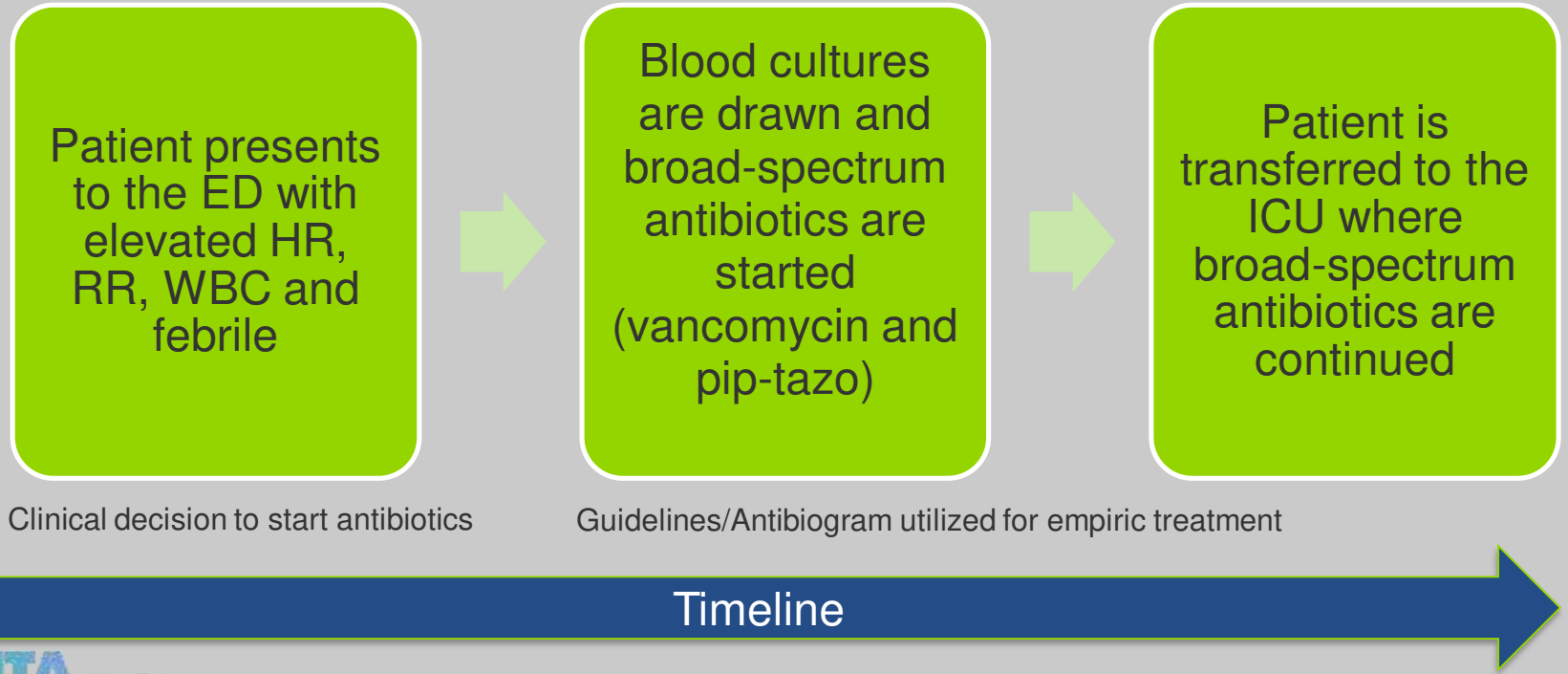
Molecular Rapid Diagnostic Testing in Bloodstream Infections

Assay	Pathogens	Turn-around Time	Resistance Markers
Biofire FilmArray Blood Culture Identification	*Enterococcus, L. monocytogenes, Staphylococcus, S. aureus, Streptococcus, S. agalactiae, S. pneumoniae, S pyogenes, A. baumannii, H. influenza, N. meningitides, P. aeruginosa, Enterobacteriaceae, Enterobacter cloacae, E. coli, K. oxytoca, K. pneumoniae, Proteus, Serratia marcescens, Candida spp.*	1hr	mecA, vanA/B, KPC
Gene Xpert MRSA/SA	*S. aureus*	<1hr	mecA
PNA-FISH	*S. aureus, CoNS, Enterococcus, E. coli, K. pneumoniae, P. aeruginosa, Candida spp*	~1.5hr	None
QuickFISH	*S. aureus, CoNS, enterococci, E. coli, K. pneumoniae, P. aeruginosa*	<30min	None
MALDI-TOF	Gram-positive, Gram-negative bacteria, yeasts, filamentous fungi, mycobacteria	1-2hrs or less	None

Molecular Rapid Diagnostic Testing in Bloodstream Infections

Assay	Pathogens	Turn-around Time	Resistance Markers
Verigene Gram-positive (BC-GP)	*S. aureus, S. epi, S. lugdunensis, S anginosus, S. agalactiae, S. pneumoniae, S. pyogenes, E. faecalis, E. faecium, Staph spp., Strep spp., Listeria spp.*	2.5hr	mecA, vanA/B
Verigene Gram-negative (BC-GN)	*E. coli, Shigella spp., K. pneumoniae, K. oxytoca, P. aeruginosa, S. marcescens, Acinetobacter spp., Proteus spp., Citrobacter spp., Enterobacter spp.*	2hr	KPC, NDM, CTX-M, VIM, IMP, OXA
Accelerate Pheno	*S. aureus, S. lugdunensis, CoNS, E. faecalis, E. faecium, Streptococcus spp., E. coli, Klebsiella spp., Enterobacter spp., Proteus spp., Citrobacter spp., S. marcescens, P. aeruginosa, A. baumannii, C. albicans, and C. glabrata.*	ID: 1.5hr AST: 7hr	Susceptibility performed
T2 Candida Panel	*Candida* spp.: *C. albicans*, *C. tropicalis*, *C. parapsilosis*, *C. krusei*, and *C. glabrata*	~6hrs	None

Rapid Diagnostics with an ASP



Molecular Rapid Diagnostic Testing in Bloodstream Infections

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Molecular Rapid Diagnostic Testing in Bloodstream Infections

Example Guidelines

Pathogen Detected	Preferred Therapy	Comments
Staphylococcus aureus mecA negative = MSSA mecA positive = MRSA	Cefazolin Vancomycin	Nafcillin is an alternative to cefazolin
***Staphylococcus* genus** with negative *S. aureus* PCR <u>Blood Culture result:</u> 1 of 2 BCX positive 2 of 2 BCX positive *mecA* negative *mecA* positive	Consider with-holding or discontinuing therapy as likely contaminant nafcillin Vancomycin	In severely ill patients consider starting/continuing therapy until more definitive results return
E. coli no resistance markers CTX-M Gene	Ceftriaxone Meropenem	99% susceptible
Klebsiella pneumoniae no resistance markers CTX-M Gene	Ceftriaxone Meropenem	99% susceptible

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Molecular Rapid Diagnostic Testing in Bloodstream Infections

- Over-use of broad-spectrum agents
  - Side effects
    - Nephrotoxicity
    - Allergic reactions
  - *C. difficile*
- Increase the risk of poor outcomes
- Increase length of stay
- **Promote Resistance**

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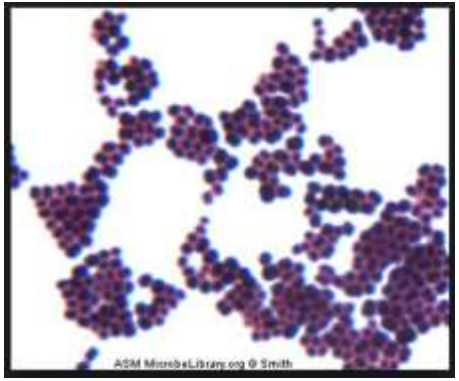
MRSA PCR for De-escalation

- MRSA Pneumonia associated with poor outcomes
  - Among 2,259 adults hospitalized with community-acquired pneumonia, 0.7% has MRSA pneumonia
- **Results of Over-Utilization of Vancomycin:**
  - Increase in the prevalence of vancomycin-resistant *Enterococci* (VRE)
  - "MIC Creep"
    - Leads to an increase in vancomycin-intermediately-sensitive S. aureus (VISA – MIC >2) and vancomycin resistant S. aureus (VRSA – MIC > 8)
  - For *Staphylococcus aureus* MIC ≥ 2, vancomycin is likely ineffective
  - Nephrotoxicity



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Self W et al. CID 2016;63(3):300-309.

Staphylococcus aureus

- *Staphylococcus aureus*
  - Principal reservoir is the nares

- MRSA PCR nasal swab may be useful diagnostic test to rule out MRSA pneumonia

- MRSA PCR assays are commercially available rapid molecular surveillance technologies with the ability to detect MRSA nares colonization
  - These assays offer high sensitivity and specificity- both greater than 90%

Dangerfield and Colleagues

- Retrospective cohort study in a tertiary care center

- All patients with confirmed PNA who had both a nasal swab MRSA PCR test and bacterial culture within predefined time intervals were included
  - 2740 patients had a nasal swab MRSA PCR and of those 696 had a bacterial culture performed
  - MRSA PCR had 88% sensitivity, 90.1% specificity, 35.4% PPV, and 99.2% NPV

Harris and Colleagues

- Prospective cohort study in non-ICU adults
  - 29,978 patients screened of which 12,080 had suspected infection
  - 5609 patients (46.4%) were deemed “high MRSA risk”
  - Among the “high risk” patients, 11.1% tested positive on MRSA nares screening. Of the positive screened, 23.8% had a sample positive for MRSA on clinical culture
  - Only 2.4% of “high risk” patients that screened negative had a sample positive for MRSA on clinical culture
  - Cultures: 58.5% wound, 10.6% sputum, 9.3% blood,1.3% bronch
  - The NPV=98% in the high risk subgroup for any site

Baby and Colleagues

- Retrospective analysis of patients who received anti-MRSA therapy for suspected pneumonia before and after implementation of a pharmacist driven protocol for nasal MRSA PCR testing
- Decreased anti-MRSA therapy by 2 days
- No significant difference in clinical improvement
- Non-significant difference in LOS although favored the protocol group (11.04 days vs 7.8 days P=0.41)
- Significantly less AKI in protocol group (26% vs 3.3% P=0.02)
- Less vancomycin troughs ordered in protocol group (48.1% vs 16.7%)

Follow-up Nasal PCR Results

- If nasal PCR yields a negative result, and no exclusion criteria are met, contact provider to consider discontinuation of anti-MRSA therapy
  - NPV > 98%
- If nasal PCR yields a positive result, this demonstrates colonization, but there is no evidence to use this result to inform antimicrobial therapy decisions (PPV < 38%)

Conclusion

- Antimicrobial Stewardship is multi-disciplinary
  - We all need to work harder to fight resistance!
- Rapid Diagnostic Tests are changing the game
- Antibiotic stewardship = patient safety
- New antimicrobials are great but not a substitution for stewardship!

https://imgur.com/gallery/ZwiU4ZL

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THANK YOU

Updates in Antimicrobial Stewardship
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