



Microbiology, Antibiograms and Anti-Infective Basics 101

Kimberly Claeys, PharmD Emily Heil, PharmD J. Kristie Johnson, PhD

Objectives

- Describe antibiotic spectrum of activity and clinical application of agents commonly used in long-term care
- Demonstrate an understanding of basic principles of microbiology with respect to organisms most commonly encountered in long-term care
- 3. Identify key elements and interpret antibiograms and microbiology lab reports

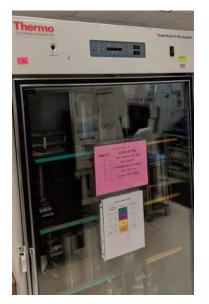
The Clinical Microbiology Laboratory: a Fundamental Resource



Urine samples are sent to the microbiology laboratory



Urine samples are plated onto media for bacterial pathogens in a biological safety hood



Plates are incubated overnight



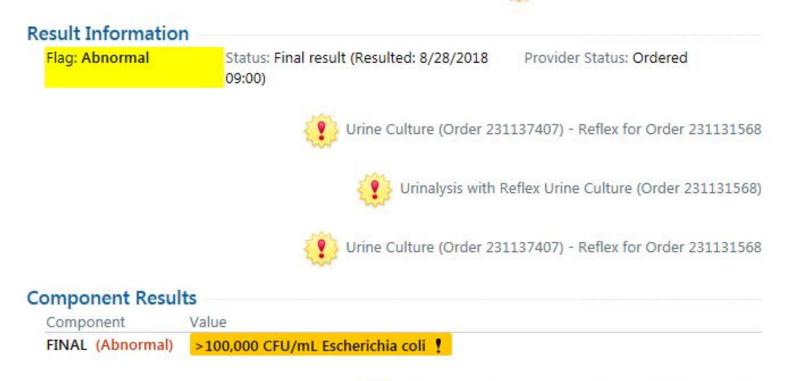


After incubation, plates are examined for bacterial pathogens





Report





Urinalysis with Reflex Urine Culture (Order 231131568)

Susceptibility Results

Escherichia coli	Results
Aztreonam	Resistant
Ceftriaxone	Resistant
Cefepime	Sensitive
Cefazolin	Resistant
Ciprofloxacin	Resistant
Nitrofurantoin	Resistant
Meropenem	Sensitive
Piperacillin-tazobactam	Resistant
Tetracycline	Resistant
Sulfamethoxazole/Trimethoprim	Resistant

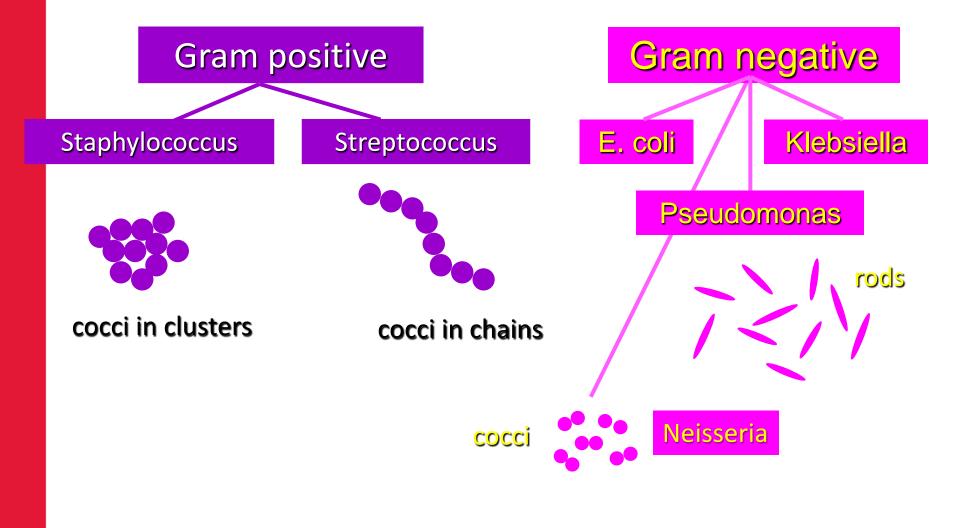
Old is New Again-Fosfomycin

- Breakpoints for 2 organisms only
- Agar dilution or disk diffusion only
- Agar media supplemented with 25 μg/ml of glucose-6-phosphate.

		MIC		DISK			
	S	I	R	S	I	R	
E. coli	≤64	128	≥256	≥16	13-15	≤12	
Enterococcus faecalis	≤64	128	≥256	≥16	13-15	≤12	

CLSI approved adding that *Enterobacteriaceae* other than *E. coli* should not be tested because the test is unreliable. FosA degradation of fosfomycin

Gram Reactions for Select Bacteria

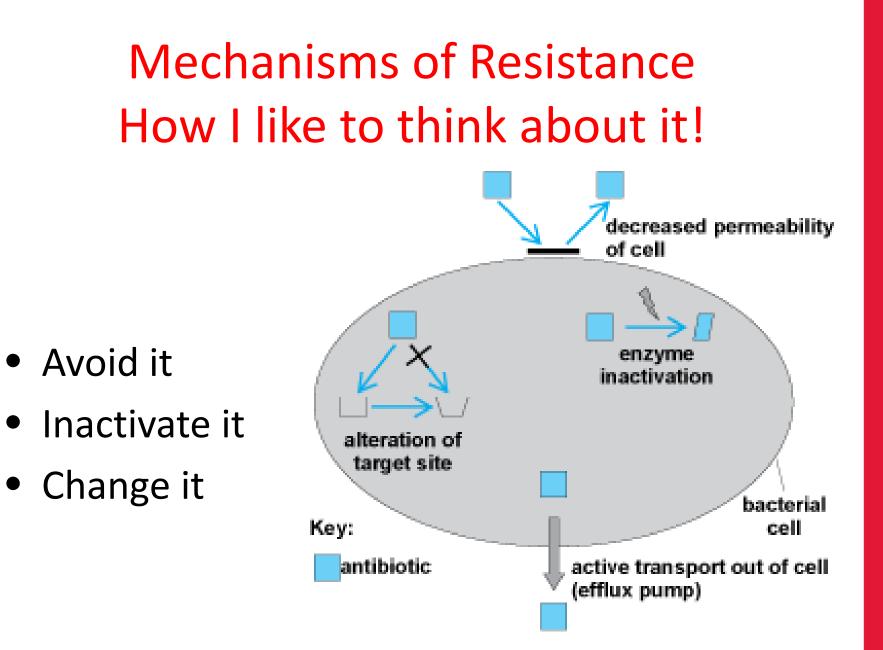


ESKAPE Bugs

<u>Enterococcus faecium (VRE)</u> <u>S</u>taphylococcus aureus (MRSA) <u>K</u>lebsiella pneumoniae <u>A</u>cinetobacter baumannii <u>P</u>seudomonas aeruginosa <u>E</u>nterobacter spp.

"...extraordinarily important, not only because they cause the lion's share of nosocomial infections but also because they represent paradigms of pathogenesis, transmission and resistance."

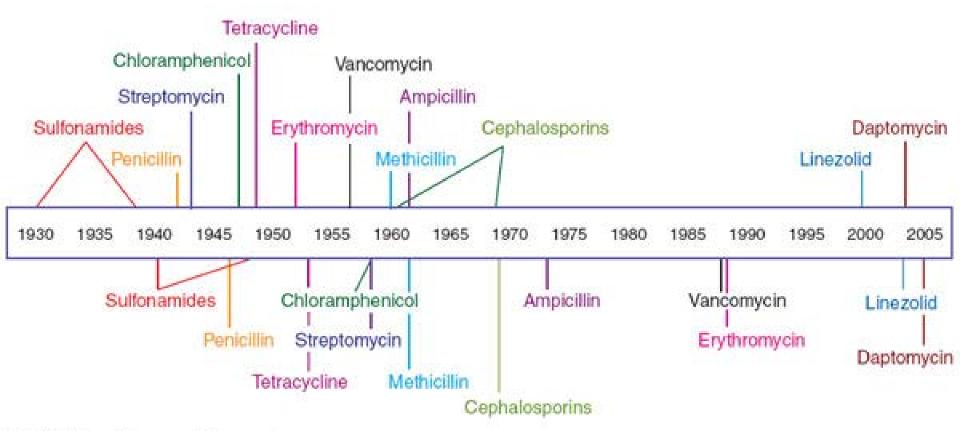
Cause majority of hospital infections Escape the effects of antibiotics Increase morbidity and mortality Increase LOS



McGraw-Hill Concise Encyclopedia of Bioscience. © 2002 by The McGraw-Hill Companies. Inc.

Rates of Antibiotic Resistance

Antibiotic deployment



Antibiotic resistance observed

Nature Chemical Biology 3:541, 2007

Resistant Gram-negative Bacteria: Importance of Long-term care facilities

INFECTION CONTROL AND HOSPITAL EPIDEMIOLOGY DECEMBER 2012, VOL. 33, NO. 12

ORIGINAL ARTICLE

Transfer from High-Acuity Long-Term Care Facilities Is Associated with Carriage of *Klebsiella pneumoniae* Carbapenemase–Producing *Enterobacteriaceae*: A Multihospital Study

Kavitha Prabaker, MD;^{1,2} Michael Y. Lin, MD, MPH;¹ Margaret McNally, RN, BSN, PCCN;³ Kartikeya Cherabuddi, MD;⁴
 Sana Ahmed, MD;⁵ Andrea Norris, DO;⁵ Karen Lolans, BS;¹ Ruba Odeh, DO;⁵ Vishnu Chundi, MD;⁶
 Robert A. Weinstein, MD;^{1,2} Mary K. Hayden, MD¹
 for the Centers for Disease Control and Prevention (CDC) Prevention Epicenters Program

MAJOR ARTICLE

The Importance of Long-term Acute Care Hospitals in the Regional Epidemiology of *Klebsiella pneumoniae* Carbapenemase– Producing Enterobacteriaceae

Michael Y. Lin,¹ Rosie D. Lyles-Banks,² Karen Lolans,³ David W. Hines,⁴ Joel B. Spear,⁵ Russell Petrak,⁴ William E. Trick,^{1,2} Robert A. Weinstein,^{1,2} and Mary K. Hayden;^{1,3} for the Centers for Disease Control and Prevention Epicenters Program

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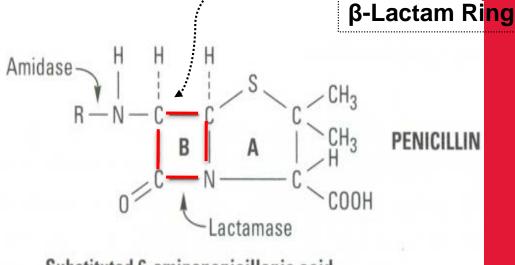
Mechanisms of β-lactam Resistance for Gram-Negative Bacteria

- β-lactamases
 - Extended spectrum β-lactamases
 - Plasmid-mediated AmpC
 - Carbapenemases
- Efflux
- Porin



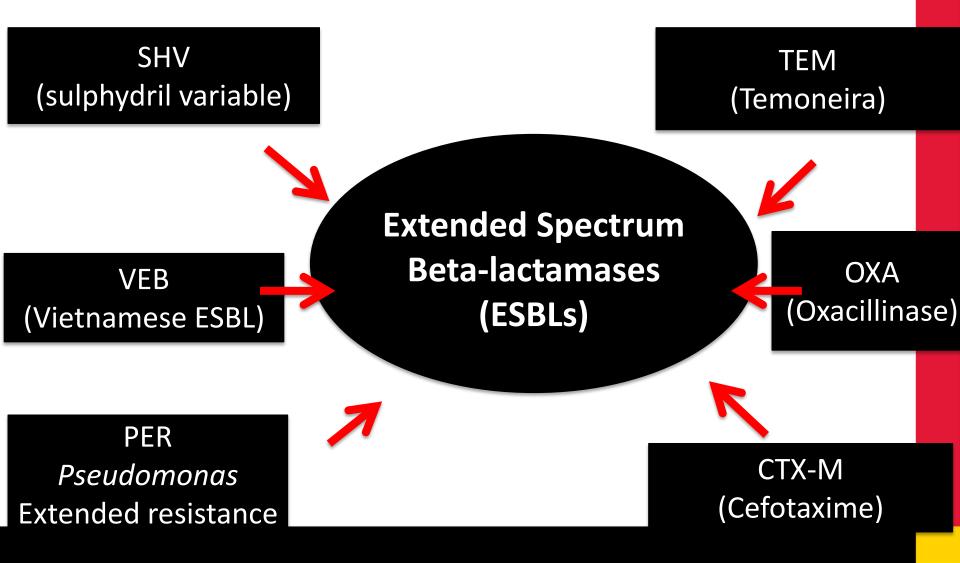
β-lactamase

- Enzyme produced that hydrolyzes the ßlactam ring
- Enzyme breaks the β-lactam ring open, deactivating the molecule's antibacterial properties.
- Differ based on antibiotic

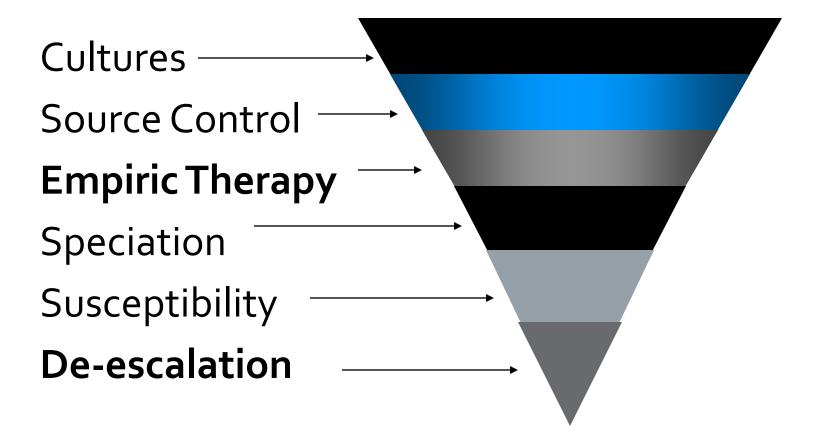


Substituted 6-aminopenicillanic acid

Extended Spectrum Cephalosporin-Resistant Gram-Negative Bacteria



Appropriate Antibiotic Management



Common Bacteria by Site of Infection

Mouth Peptococcus Peptostreptococcus Actinomyces	<u>Skin /Soft Tissue</u> <i>S aureus</i> <i>S pyogenes</i> <i>S epidermidis</i>	Abdomen E. coli Proteus Klebsiella Enterococcus Bacteroides
Urinary Tract E. coli Proteus Klebsiella Enterococcus Staph saprophyticus	Bone & Joint S. aureus S. epidermidis Streptococci N. gonorrhoeae Gram negative bacilli	Upper Respiratory S pneumoniae H influenza M catarrhalis S pyogenes
Meningitis S pneumoniae N meningitidis H influenza Group B strep E coli Listeria	Lower Respiratory (CAP) S pneumoniae H influenza K pneumoniae Legionella pneumophilia Mycoplasma Chlamydia	Lower Respiratory (HAP) <i>P aeruginosa</i> <i>Enterobacter</i> <i>Serratia</i> <i>S aureus</i> <i>Acinetobacter</i>

Oral Antibiotics That Cover Enteric GNRs

Guideline Recommended

Cystitis Only	Pyelonephritis/Complicated UTI
NitrofurantoinFosfomycin	 Sulfamethoxazole/Trimethoprim Fluoroquinolones (Cipro, Levo, NOT moxi)

Alternates

- Amoxicillin/Clavulanate
- 3rd Generation PO cephalosporins (e.g., cefpodoxime, cefdinir)

Urinary antibiotics

Nitrofurantoin	Fosfomycin
 Activity: S. saprophyticus, Enterococci, E.coli, Klebsiella, Proteus Duration 5-7 days Adverse Drug Effects GI: Take w/ food Pulmonary fibrosis (rare, with prolonged use) Peripheral neuropathy (rare) Contraindicated for use with CrCl <50 mL/min (inadequate urinary concentrations and/or increased ADRs although recently refuted) Beer's list avoid for long term prophylaxis use or in patients with reduced renal function 	 Activity: Enterococci (inc VRE), E.coli, Pseudomonas, Serratia, Citrobacter, Klebsiella, Proteus 3g PO x 1 (uncomplicated), 3g PO every 3 days x3 doses (complicated) Adverse Drug Effects Headache Diarrhea (Take w/ food) Hypokalemia Last choice of first line options \$\$\$ compared to other first line options

Fluoroquinolones

Agents	Spectrum of Activity	Comments
Ciprofloxacin	Cipro: Good enteric gram negatives,	Good bone penetration
(Cipro [®])	H. influenzae, moderate	Good bioavailability
	Pseudomonas, atypicals, poor S.	Chelate cations – bioavailability decreased when
Levofloxacin	pneumoniae, anaerobes, enterococci	administered with calcium, iron, antacids, milk,
(Levaquin [®])		multivitamins, magnesium
	Levo: Good enteric gram negatives, S.	Overprescribing has led to rising resistance
Naniflanasia	pneumoniae, H. influenzae, atypicals	CYP450 drug interactions possible (especially with
Moxifloxacin	Moderate Pseudomonas	cipro)
(Avelox®)	No anaerobes, enterococci, MRSA	Contraindicated in pregnancy
		Relatively contraindicated in children
Delafloxacin	Moxi – Similar to levo but with	All renally cleared except moxifloxacin
(Baxdela®)	improved anaerobic coverage, poor	(moxifloxacin achieves poor urinary penetration
	Pseudomonas coverage	and should not be used for UTI)
All PO and IV		Cipro is not a "respiratory fluoroquinolone"
	Dela: Similar to levo but with MRSA	
	coverage	

Trimethoprim/Sulfamethoxazole

Agents	Spectrum of Activity
Trimethoprim/Sulfamethoxazole	Good: S.aureus including MRSA,
IV and PO	H.influenzae, Stenotrophomonas
Bactrim DS [®] (or Septra DS)	maltophilia, Listeria, Pneumocystis jirovecii
800 mg SMX/160 mg TMP	Moderate: enteric Gram Negatives, S.
Bactrim SS [®] (or Septra SS)	pneumoniae, Salmonella, Shigella,
400 mg SMX/80 mg TMP	Nocardia
	No: Pseudomonas, S. pyogenes,
SMX:TMP is in a 5:1 ratio in all formulations	enterococci, anaerobes
Adverse Effects	Comments
Rash	Dose is based on trimethoprim component
Stevens-Johnson syndrome	Dose adjust for renal insufficiency
Bone marrow suppression	Interacts with warfarin
Crystalluria – recommended to take with a full	"Pseudo renal failure" – trimethoprim
glass of water	blocks creatinine secretion and can
Acute interstitial nephritis	increase the SCr without changing GFR
Trimethoprim causes hyperkalemia, especially at	
higher doses, elderly on ACEs/ARBs at higher risk	

Oral Beta-Lactams

Agents	Spectrum of Activity
 Cephalosporins (PO) Cefdinir Cefpodoxime Aminopenicillin/Beta-lactamase inhibitor Amoxicillin/Clavulanate 	Good: <i>Streptococci, Enterococci</i> (except the cephalosporins!), Enteric GNRs
Adverse Effects	Comments
Rash/Hypersensitivity Reactions GI Upset Neutropenia (rare) Interstitial nephritis (rare)	Less effective than FQs or SMX-TMP for UTIs, longer course required

Fluoroquinolones

- QT_c interval prolongation
 - **Risk increases with each** increasing offender
- Phototoxicity/ Photosensitivity
 - Not as common with FQs
- Seizures
- RISKS OUTWEIGH BENUTI Prim seizui
- nyperglycemia Hypoglyce
- Arthralgia, Achilles tendon rupture

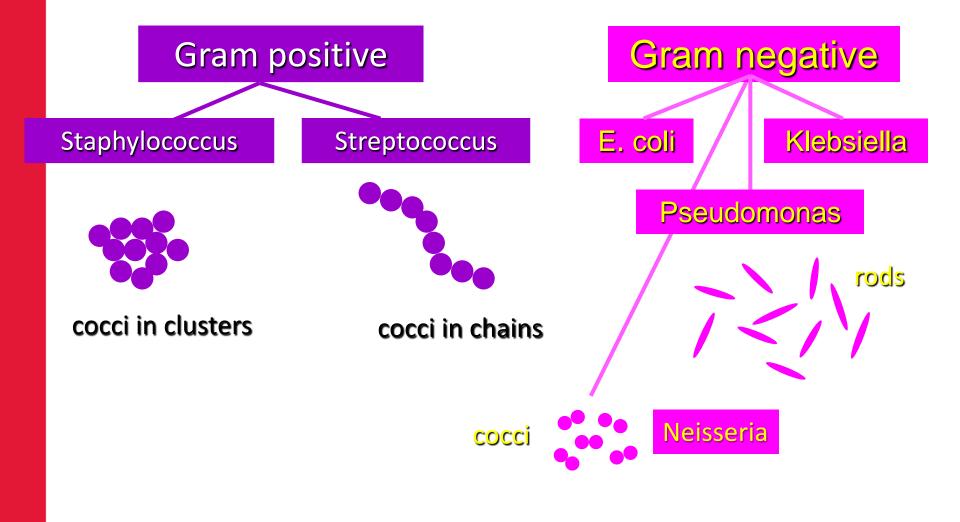
- GI 💵
 - difficile clated diarrhea
 - J: headache, dizziness, nsomnia, tremor, confusion, psychosis
- Hepatotoxicity
- Peripheral neuropathy
- May exacerbate weakness of myasthenia gravis
- **Cation interaction**

Penicillin Allergies

- Approximately 1 in 10 people report a penicillin allergy, however <10% of these patients are actually allergic by penicillin skin testing
- Overall incidence of cross-reactivity with cephalosporins and carbapenems is low (<1% for later generation cephalosporins!)
- Beta-lactam ring + side chains contribute to cross-reactivity
- Beta-lactams with identical side chains should be avoided (e.g., avoid cephalexin in a patient with an amoxicillin allergy)

	Amoxicillin	Ampicillin	Cephalexin	Cefoxitin	Cefuroxime	Cefotaxime	Ceftazidime	Ceftriaxone	Cefepime
Amoxicillin		Х	Х						
Ampicillin	Х		Х						
Cephalexin	Х	Х							
Cefoxitin					Х				
Cefuroxime				Х					
Cefotaxime								Х	Х
Ceftazidime									
Ceftriaxone						Х			Х
Cefepime						Х		Х	

Gram Reactions for Select Bacteria



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Staphylococcus aureus

Is it MRSA or MSSA?

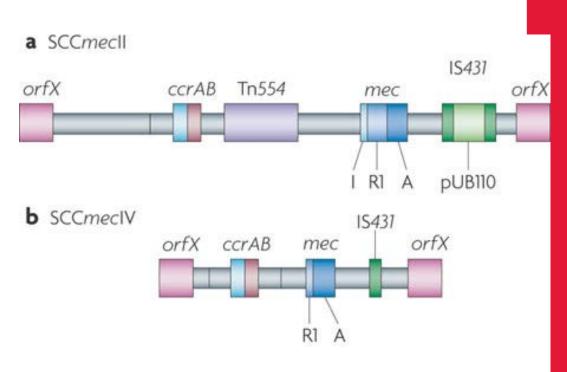


Mechanisms of MRSA

- Classic Resistance
 - mecA gene found in SCCmec
 - Chromosomally mediated
 - Altered PBP (penicillin binding protein) 2a
 - NOT due to β -lactamase inactivation

Staphylococcal Cassette Chromosomal (SCCmec)

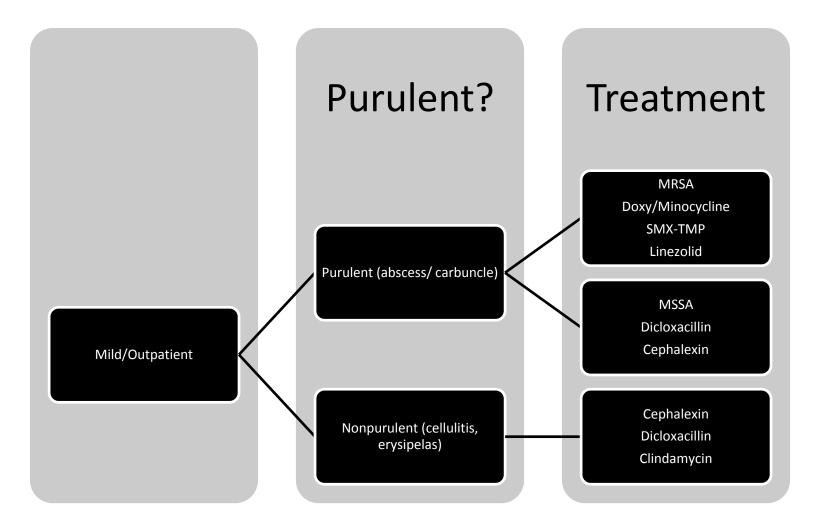
- To date there are 11
- Includes mecA
 mecA dropouts
- SCCmec typing



Susceptibility Results

Staphylococcus aureus	Results
Ampicillin	Resistant
Ciprofloxacin	Resistant
Clindamycin	Sensitive
Cefazolin	Resistant
Daptomycin	Sensitive
Doxycycline	Sensitive
Erythromycin	Sensitive
Gentamicin	Resistant
Linezolid	Sensitive
Oxacillin	Resistant
Rifampin	Resistant
Tigecycline	Sensitive
Vancomycin	Sensitive

Skin and Soft Tissue Infections



Oral Antibiotics for Gram Positives

Doxycycline/Minocycline	Cephalexin, Dicloxacillin
 Spectrum: Staphylococci (including MRSA), moderate Streptococci (increasing resistance), atypicals, rickettsial diseases ADEs: GI upset, photosensitivity, esophageal irritation, vertigo (mino) Administration: Take with food, separate from cations 	 Spectrum: <i>Streptococci</i>, MSSA Generally well tolerated ADEs: Hypersensitivity Frequent dosing (q8h for cephalexin, q6h for dicloxacillin)
Linezolid	Clindamycin
 Spectrum: MRSA/MSSA, Streptococci, VRE ADEs: bone marrow suppression, peripheral neuropathy (longer durations) MAOi – Interactions with serotonergic agents Generic but \$\$ compared to others 	 Spectrum: Streptococci, Staphylococci (increasing resistance with MRSA), GP anaerobes ADEs: Diarrhea, <i>C.difficile</i> infection Frequent dosing (q8h)



What tools are available for the selection of empiric therapy?

Cumulative Antimicrobial Susceptibility Test data (AKA: Antibiogram)

- A report generated by analysis of results on isolates that reflects the percentage of the first isolate per patient of a given species that is susceptible to each antimicrobial agent routinely tested
- Primary aim of guiding clinicians in the selection of initial empirical antimicrobial therapy for infections
- Guidelines for creating an antibiogram



M39-A4

Analysis and Presentation of Cumulative Antimicrobial Susceptibility Test Data; Approved Guideline—Fourth Edition

This document describes methods for recording and analysis of antimicrobial susceptibility hest data, consisting of cumulative and origoing summaries of susceptibility patterns of clinically significant microorganisms.

Recommendations Preparation of Cumulative Antibiogram

- Analyze/present data at least annually
- Include only species with ≥ 30 isolates of each species
- Include diagnostic (not surveillance) isolates
- Include the 1st isolate/patient; no duplicate patient isolates



Often difficult to get 30 isolates in LTCFs

Antibiograms

- Who makes them?
 - Microbiologist
 - Pharmacist
 - Infection control practitioner
- Who uses them?
 - Clinician
 - Pharmacist
 - Infection control practitioner

Appendix E1. Cumulative Antimicrobial Susceptibility Report Example - Antimicrobial Agents Listed Alphabetically (Hypothetical Data)

														_
Gram-Negative Organisms	No. Strains	Amikacin	Ampicillin	Cefazolin	Cefotaxime	Ceftazidime	Ciprofloxacin	Nitrofurantoin [†]	Gentamicin	Meropenem	Piperacillin- tazobactam	Trimethoprim- sulfamethoxazole	Tobramycin	
Acinetobacter baumannii	32	80	R	R	34	52	51	_1	60	80	46	58	59	
Citrobacter freundii	49	100	R	R	72	67	90	78	100	99	67	67	100	
Enterobacter aerogenes	31	100	R	R	68	69	92	85	91	99	74	95	91	
Enterobacter cloacae	76	99	R	R	61	62	92	81	90	99	77	84	90	
Escherichia coli	1433	99	36	68	96	94	72	98	91	99	51	65	92	
Klebsiella pneumoniae	543	99	R	72	91	92	84	74	94	95	86	81	94	
Morganella morganii	44	100	R	R	85	81	99	R	100	99	64	75	100	
Proteus mirabilis	88	100	87	80	99	99	89	R	90	100	70	73	93	
Pseudomonas aeruginosa	397	97	6	'D o	utir	۰ ۰		mu	lati		or	tih	ind	ra
Salmonella spp.	32	-					Cu							
Serratia marcescens	50	10	Ge	ner	ally		all is	sola	ate	s f	ron	na	fac	
Shigella spp.	33	_	04		100	100	25			100	04	02		
Stenotrophomonas maltophilia	72	R	R	R	R	63	6	R	R	R	-	98	R	

Memorial Medical Center 1 January – 31 December 2012 Cumulative Antimicrobial Susceptibility Report*

* The percent susceptible for each organism/antimicrobial combination was generated by including the first isolate of that organism encountered on a given patient. † Nitrofurantoin data from testing urine isolates only. * (-) drug not tested or drug not indicated.

Abbreviations: No., number; R, intrinsic resistance.

Antibiogram Challenges in Long-Term Care

- Long-term care facilities have unique challenges when developing antibiograms
 - Facility with small number of patients
 - Limited number of diagnostic isolates
 - Working with multiple laboratories
 - Lack of electronic medical records

Antibiogram Challenges in Long-Term Care

- 1. Extending antibiogram beyond one year
- 2. Creating regional antibiogram
- 3. Using antibiogram from nearby hospital
- 4. Collapse antibiogram information

Extending Antibiogram Beyond One Year

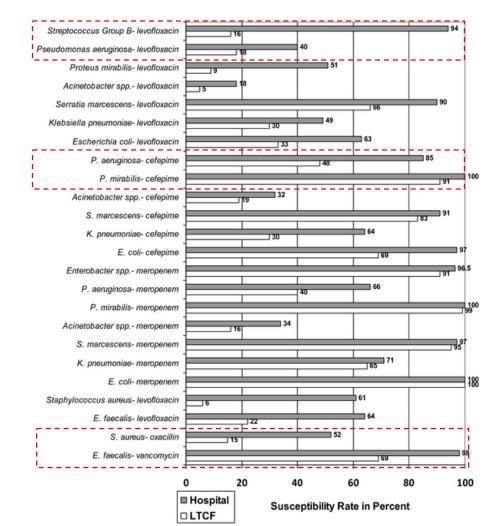
- CLSI M39 promote approach of extending data longer than 1 year to overcome low numbers of isolates
 - Technically easiest to operationalize
- More accurate susceptibility of extended time period
- May not capture changes in resistance patterns over time

Creating Regional Antibiogram

- Antibiogram data from 13 hospitals combined
 - 12 community hospitals; 1 central tertiary care referral hospital
- Overall, similar rates of resistance among common organisms
 - Oxacillin resistant *S. aureus*: 51% to 58%
 - Vancomycin resistant *E. faecium*: 75%
 - Ampicillin/sulbactam resistant *E. coli*: 48% to 56%
- Significant differences in methodology, interpretation and antibiotic panels used by area laboratories

Using Antibiogram from Nearby Hospital

- Antibiogram of isolates from LTCF residents generated
- Compare susceptibilities to local acute care
- Resistance more
 common on LTCF
- Widest disparities
 - Levofloxacin
 - Meropenem
 - Cefepime



Kindschuh W et al. J AM Geriatr Soc 2012 Apr;60(4):798-800.

Collapse Antibiogram Information

- Grouping similar organisms
- Consider grouping by specimen site (i.e. urine)
- Limitation that some bacteria in similar groups may have intrinsic resistance

Organism	# isolates	Amox/Clav	Cefazolin	Ceftriaxone	Ciprofloxacin	TMP/SMX	Nitrofurantoin
Urinary Gram-negatives	127	84	74	82	67	85	99

Escherichia coli, Klebsiella pneumoniae, and Proteus mirabilis

Antibiogram Challenges in Long-Term Care

Approach	Advantages/Disadvantages		
Extending the antibiogram data beyond 1 year	 Technically simple/easy to crate Resistance patterns may change from year to year 		
Creating a regional antibiogram	 Helpful if residents access facilities throughout the region Requires coordination between multiple laboratories and facilities 		
Using antibiograms of nearby hospitals	 Antibiograms already annually made by hospitals Bacteria that infect LTCF residents may not have similar antimicrobial susceptibilities to those of the hospital population 		
Collapsed antibiograms	 Help guide infection-specific antibiotic choices Intrinsic resistance of some bacteria to specific antibiotics would not be listed 		

M.-S.A. Tolg et al. / JAMDA xxx (2018) 1e4

- Antibiograms help guide antibiotic choices before patient specific culture/susceptibility information is available
- Guide initial *empiric* therapy recommendations

INFECTION CONTROL AND HOSPITAL EPIDEMIOLOGY OCTOBER 2014, VOL. 35, NO. S3

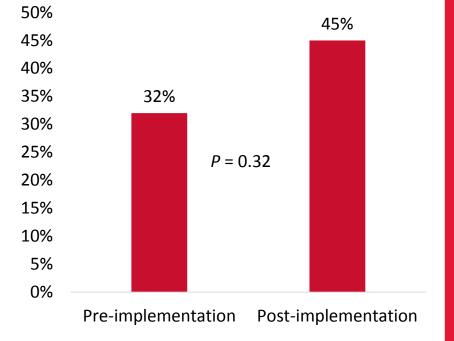
ORIGINAL ARTICLE

Using Antibiograms to Improve Antibiotic Prescribing in Skilled Nursing Facilities

Jon P. Furuno, PhD;¹ Angela C. Comer, MPH;^{2,3} J. Kristie Johnson, PhD, D(ABMM);^{2,4} Joseph H. Rosenberg, BS;² Susan L. Moore, PhD, MSPH;⁵ Thomas D. MacKenzie, MD, MSPH;⁵ Kendall K. Hall, MD, MS;⁶ Jon Mark Hirshon, MD, MPH, PhD^{2,3,7}

Using Antibiograms to Improve Antibiotic Prescribing in Skilled Nursing Facilities

- Quasi-experimental study of implementation of SNFspecific antibiograms at three facilities in Maryland
- Evaluate effectiveness through assessment of changes in empiric antibiotic prescribing (SNF 1, 118 beds)



Empiric Antibiotic Appropriateness

Validated antibiogram available

Policy & procedure for antibiogram

Educate nursing and prescribers

Disseminate antibiogram

- AHRQ Toolkit Phase 3: Implementation
 - Provides sample policies and procedures
 - Educational materials
 - Draft emails and communications
- <u>https://www.ahrq.gov/nhguide/toolkits/help-</u> <u>clinicians-choose-the-right-antibiotic/toolkit3-</u> <u>develop-implement-antibiogram-program.html</u>

Comprehensive Antibiogram Toolkit: Phase 3 Sample Policy

[NAME OF NURSING HOME]

RE: Antibiogram Program

[DATE]

Antibiotics are among the most commonly prescribed pharmaceuticals in long-term care settings, yet reports indicate that a high proportion of antibiotic prescriptions are inappropriate. The adverse consequences of inappropriate prescribing practices—including drug reactions/interactions, secondary complications, and the emergence of multidrug-resistant organisms—have become more common. Inappropriate prescribing practices by primary care clinicians and overuse of newer, broad-spectrum antibiotics when either no antibiotic or an older narrow-spectrum drug would suffice are believed to be the primary contributors to this problem. As a result of the above complexities, nursing homes increasingly are recognized as reservoirs of antibiotic-resistant bacteria.

Antibiograms aggregate information for an entire institution over a period of several months or a year. They display the organisms present in clinical specimens sent for laboratory testing and the susceptibility of each organism to an array of antibiotics. Use of antibiograms helps reduce reliance on broad-spectrum antibiotics as initial therapy and leads to fewer clinical failures of antibiotics that are first prescribed.

To improve appropriate antibiotic use for the residents at [NAME OF NURSING HOME], the antibiogram program will be implemented on [DATE]. A facility-specific antibiogram will be made available to all prescribing clinicians on [DATE], prior to implementation.

[NAME AND TITLE OF AUTHORIZING OFFICER]

[DATE]

Comprehensive Antibiogram Toolkit: Phase 3 Sample Procedures'

[NURSING HOME NAME]

[DATE]

Purpose and Scope

This procedure covers the use of an antibiogram at [NURSING HOME NAME]. Antibiotics are among the most commonly prescribed pharmaceuticals in long-term-care settings, yet reports indicate that a high proportion of antibiotic prescriptions are inappropriate. The use of antibiograms can help reduce inappropriate prescribing and lead to fewer clinical failures of antibiotics that are first prescribed.

Responsibility for Implementing the Antibiogram

[IDENTIFY WHO WILL IMPLEMENT THE PROCEDURE]

Procedures [ADD DETAILS SPECFIC TO FACILITY]

- 1. Development of the initial and subsequent antibiograms
- 2. Initial and ongoing training for nurses
- 3. Introduction and ongoing communication with prescribers
- 4. Monitoring the use of the antibiogram

Documentation

[List any documents that will be used. Attach the antibiogram, training materials, and quality-improvement tracking documents.]

Records

[List any records that will be kept in conjunction with the program (for example, the infection-control log).]

[NAME AND TITLE OF AUTHORIZING OFFICER] [DATE]

Ways to Integrate Antibiogram Information

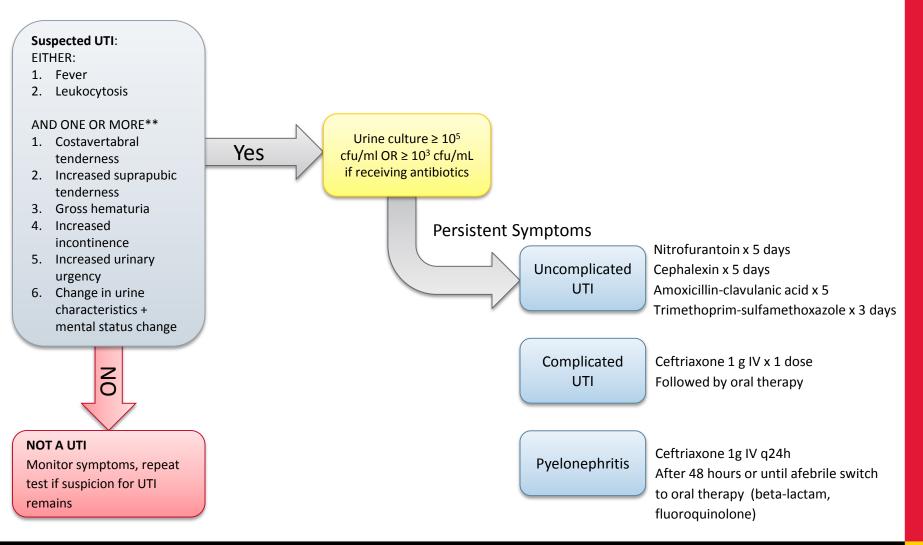
- 1. Development of facility-specific policies, procedures, and pathways
- 2. Changes in order-sets and/or clinical decision support services
- 3. Decisions regarding changes in formulary
- 4. Assessing resistance trends

Arizona Department of Health Services Antibiogram Toolkit. https://www.azdhs.gov/documents/preparedness/epidemiology-disease-control/healthcare-associatedinfection/advisory-committee/antimicrobial-stewardship/antibiogram-toolkit.pdf

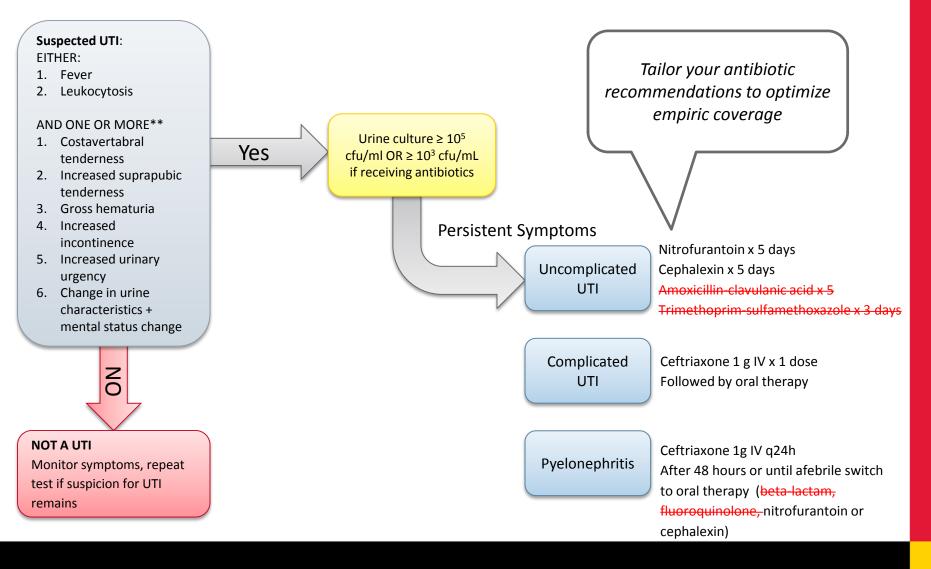
Ways to Integrate Antibiogram Information

- Important to incorporate local susceptibility information in facility policies/procedures
- Compare national guideline recs to antibiogram information
- Change recommended antibiotics in facility pathway based on antibiogram

Ways to Integrate Antibiogram Information



Ways to Integrate Antibiogram Information



- Once antibiogram information incorporated, continuous quality improvement important
- CMS State Operations Manual
 - Tracking of *C. difficile*, MRSA, CRE
 - Monitoring of antibiotic use
- More to come!!





Microbiology, Antibiograms and Anti-Infective Basics 101

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