Cascading Antibiotic Reporting

Part 1: *Staphylococcus aureus*

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64 year old female with end stage renal disease on hemodialysis via a tunneled dialysis catheter presents after having fevers to 102 F during dialysis. She is well appearing but reports being more fatigued than normal. Blood cultures are sent from her dialysis line and patient is admitted to the hospital. Over the next 6 hours patient has turn for the worse with high fevers, tachycardia, sweats, and altered mental status. Patient is started on empiric antibiotics with vancomycin and piperacillin/tazobactam. Overnight the blood culture from earlier that day turns positive, with small Gram positive cocci in clusters. The GPCs are subsequently identified as *Staphyloccus aureus*.

MSSA

Aerobic and Anaerobic Broths: Staphylococcus aureus, coagulase positive : methicillin-susceptible (MSSA) (Methodology: Solid Phase Array) : Standard sensitivity replaced direct sensitivity on: 12/18/17. Cefazolin susceptibility inferred from oxacillin result.

Antibiotic	MICM Interp	Microtiter MIC (mcg/mL)
Cefazolin	S	
Ceftriaxone	-	<=8
Clindamycin	R[comment]	
Erythromycin	R	>4
Levofloxacin	S	<=0.25
Moxifloxacin	S	<=0.25
Oxacillin	S	<=0.25
Tetracycline	S	<=2
Trimeth_Sulfamethoxazole	S	<=2
Vancomycin	S	1

MRSA

Aerobic and Anaerobic Broths: Staphylococcus aureus, coagulase positive : methicillin-resistant (MRSA) (Methodology: Solid Phase Array) - For inpatients, isolate using contact precautions per institutional policy. Contact Infection Control if you have any questions.

Antibiotic	MICM Interp	Microtiter MIC (mcg/mL)
Clindamycin	R	>2
Daptomycin	S	<=0.5
Erythromycin	R	>4
Levofloxacin	R	4
Moxifloxacin	R	2
Oxacillin	R	>2
Tetracycline	S	<=2
Trimeth_Sulfamethoxazole	S	<=2
Vancomycin	S	

Antibiotic	Etest Interp	Etest MIC (mcg/mL)
Vancomycin	S	1.5

Sensitivity Code Descriptions

<< Back

Same MRSA in Urine

3+ Staphylococcus aureus, coagulase positive : Oxacillin (representing methicillin) resistance indicates resistance to cephalosporins, beta lactamase inhibitors, imipenem and all other beta lactams. - For inpatients, isolate using contact precautions per institutional policy. Contact Infection Control if you have any questions.

Antibiotic	MICM Interp	Microtiter MIC (mcg/mL)
Daptomycin	S	<=0.5
Levofloxacin	R	>4
Linezolid	S	2
Moxifloxacin	R	2
Nitrofurantoin	S	<=32
Oxacillin	R	
Tetracycline	S	<=2
Trimeth_Sulfamethoxazole	S	<=2
Vancomycin	S	1

hVISA

Aerobic Broth: Staphylococcus aureus, coagulase positive : methicillin-resistant (MRSA) (Methodology: Solid Phase Array) : Oxacillin (representing methicillin) resistance indicates resistance to cephalosporins, beta lactamase inhibitors, imipenem and all other beta lactams. Vancomycin Intermediate Staphylococcus aureus - For inpatients, isolate using contact precautions per institutional policy. Contact Infection Control if you have any questions.

Antibiotic	MICM Interp	Microtiter MIC (mcg/mL)
Ceftaroline	S	0.5
Clindamycin	R	>2
Daptomycin	NS	2
Erythromycin	R	>4
Levofloxacin	R	4
Linezolid	S	<=1
Moxifloxacin	R	2
Oxacillin	R	>2
Rifampin	S	<=1
Tetracycline	R	>8
Trimeth_Sulfamethoxazole	S	<=2

Antibiotic	Etest Interp	Etest MIC (mcg/mL)
Vancomycin	I	3

Antibiotic Cascade Reporting

The practice of selective release of antibiotic susceptibility information on a given clinical isolate with the intention of promoting the use of certain drugs/drug classes in certain situations

Considerations include:

- Known or inferred resistance
- Cost
- Drug availability (biologically, or otherwise)
- Stewardship priorities

Antibiotic Cascade Reporting

Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America Guidelines for Developing an Institutional Program to Enhance Antimicrobial Stewardship

Timothy H. Dellit,[1] Robert C. Owens,[2] John E. McGowan, Jr.,[3] Dale N. Gerding,[4] Robert A. Weinstein,[5] John P. Burke,[6] W. Charles Huskins,[7] David L. Paterson,[8] Neil O. Fishman,[9] Christopher F. Carpenter,[10] P. J. Brennan,[3] Marianne Billeter,[11] and Thomas M. Hooton[12]

- **"The clinical microbiology laboratory plays a critical role in antimicrobial stewardship by providing patient-specific culture and susceptibility data to optimize individual antimicrobial management and by assisting infection control efforts in the surveillance of resistant organisms and in the molecular epidemiologic investigation of outbreaks"**

PMID 17173212. Dellitt et al. IDSA and SHEA Guidelines for Developing an Institutional Program to Enhance Antimicrobial Stewarship. 2007.

Organism-specific Reporting Rules

S.aureus (urine)	S.aureus (non-urine)	SCNG (incl. S.lug) (urine)	SCNG (incl. S.lug) (non-urine)	Enterococcus (urine)	Enterococcus (non-urine)
Cefazolin [1](MSSA only)	Cefazolin[1] (MSSA only)	Cefox (hidden)	Cefox (hidden)	Ampicillin	Ampicillin
Cefox (hidden)	Cefox (hidden)	D-test (hidden)	Clindamycin [3]	Dapto (VRE only)	Dapto [7](VRE only)
Ceftriaxone [2]	Ceftriaxone [2]	Gentamicin (R only)	D-test (hidden)	Levofloxacin	Erythromycin [3]
Dapto (MRSA only)	Clindamycin [3]	Levofloxacin	Erythromycin[3]	Linezolid[10]	Gent synergy
D-test (hidden)	Dapto [7] (MRSA only)	Linezolid[10]	Gentamicin (R only)	Nitrofurantoin	Linez [3,9 ,10](VRE only)
Gentamicin (R only)	D-test (hidden)	Moxifloxacin	Levofloxacin [3]	Penicillin	Penicillin
Levofloxacin	Erythromycin [3]	Nitrofurantoin	Linezolid [3,9,10]	Tetracycline	Strep synergy
Linezolid[10]	Gentamicin (R only)	Oxacillin (R only) [4]	Moxifloxacin [3]	Vancomycin	Vancomycin
Moxifloxacin	Levofloxacin [3]	Tetracycline	Oxacillin [5]		
Nitrofurantoin	Linezolid [3,9,10]	Trimeth/sulfa	Rifampin (R only)		
Oxacillin [1,8]	Moxifloxacin [3]	Vancomycin	Tetracycline [3]		
Tetracycline	Oxacillin [1,8]		Trimeth/sulfa		
Trimeth/sulfa	Rifampin (R only)		Vancomycin		
Vancomycin[11]	Tetracycline [3]				
	Trimeth/sulfa Vancomycin [6, 11]				

- **Incorporate factors such as:**
  - **Intrinsic resistance**
  - **PK/PD**
  - **Overarching guidelines and local stewardship initiatives**

Intrinsic Resistance

Appendix B. (Continued)

B3. Staphylococci

Antimicrobial Agent / Organism	Novobiocin	Fosfomycin	Fusidic Acid
S. aureus/S. lugdunensis	There is no intrinsic resistance in these species.		
S. epidermidis			
S. haemolyticus			
S. saprophyticus	R	R	R
S. capitis		R	
S. cohnii	R		
S. xylosus	R		

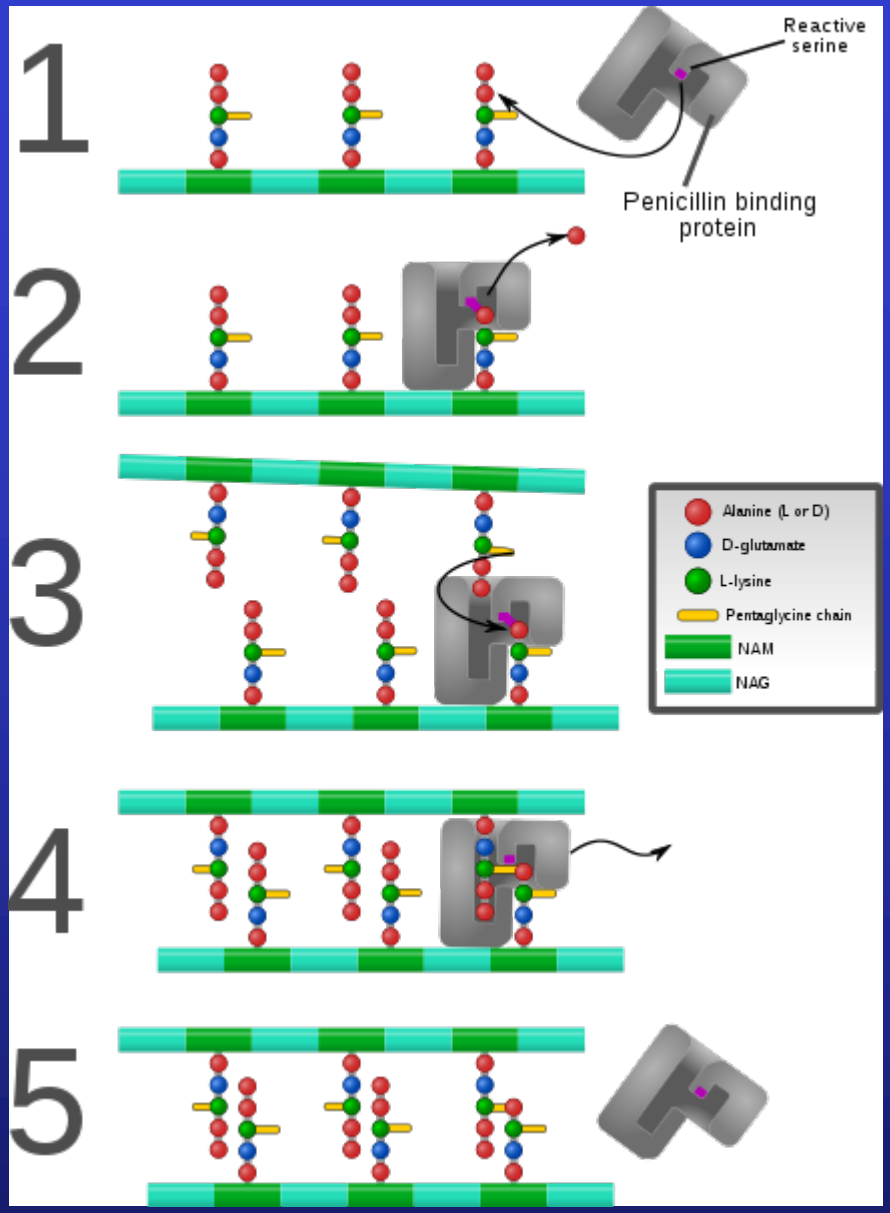
NOTE 1: These gram-positive bacteria are also intrinsically resistant to aztreonam, polymyxin B/colistin, and nalidixic acid.

NOTE 2: Oxacillin-resistant *S. aureus* and coagulase-negative staphylococci (methicillin-resistant staphylococci [MRS]) are considered resistant to other β-lactam agents, ie, penicillins, β-lactam/β-lactamase inhibitor combinations, cephems (with the exception of the cephalosporins with anti-MRSA [methicillin-resistant *S. aureus*] activity), and carbapenems. This is because most cases of documented MRS infections have responded poorly to β-lactam therapy, or because convincing clinical data that document clinical efficacy for those agents have not been presented.

Clinical Laboratory Standards Institute (CLSI) M100: Performance Standards for Antimicrobial Susceptiblity Testing. 27th Edition. 2017

Beta Lactam Antibiotics

Target

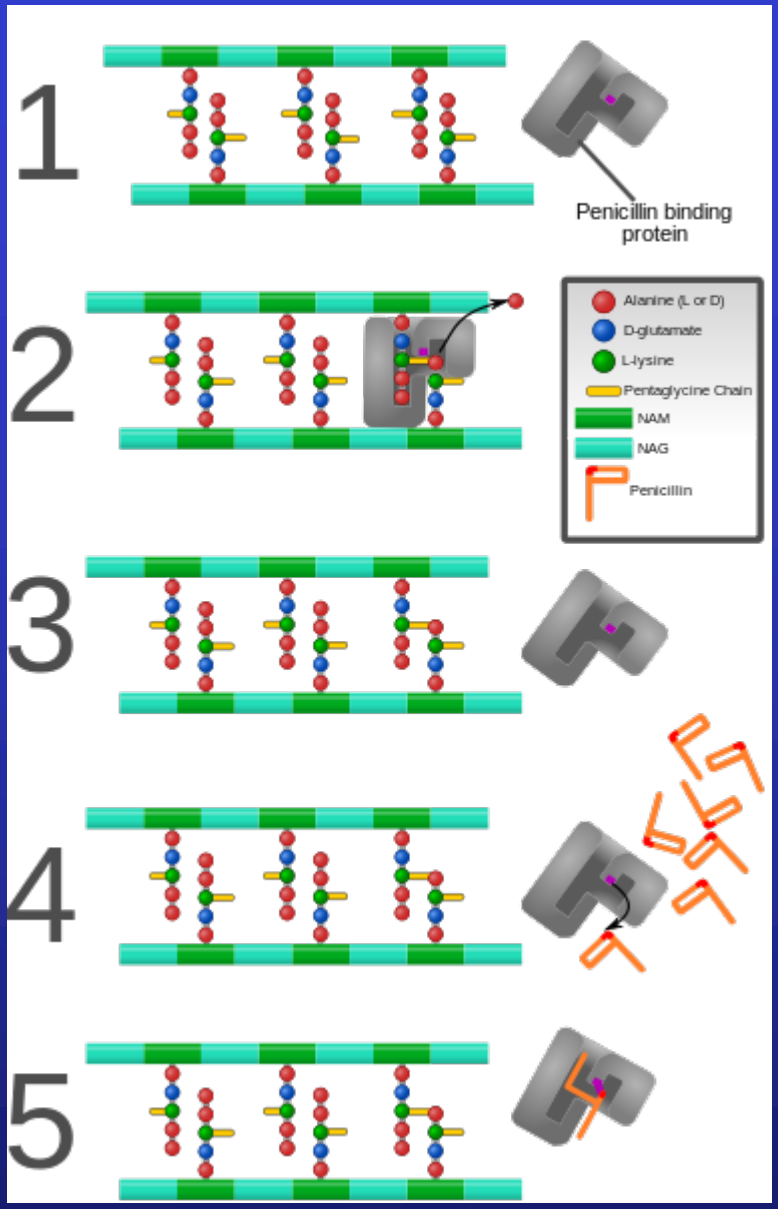


https:// https://en.wikipedia.org/wiki/B-lactam_antibiotic

- Actively-growing bacteria require continuous breaking, re-formation of peptidoglycan (PG) crosslinks in order to balance cell growth and stability
- Enzymes involved in transglycosylase and transpeptidase (necessary for PG elongation and crosslinking) are collectively referred to as Penicillin binding proteins (PBPs)

Beta Lactam Antibiotics

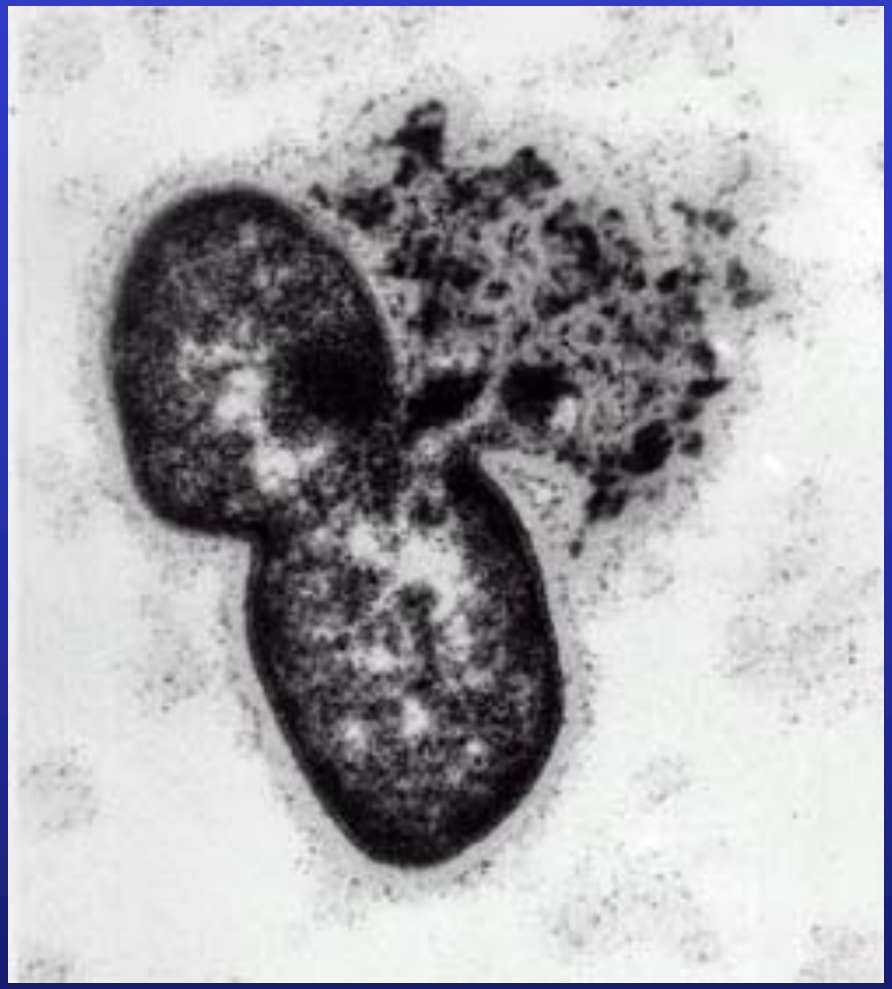
Mode of Action



- Beta lactam antibiotics bind PBPs, prevent transpeptidase activity, leading to cell death

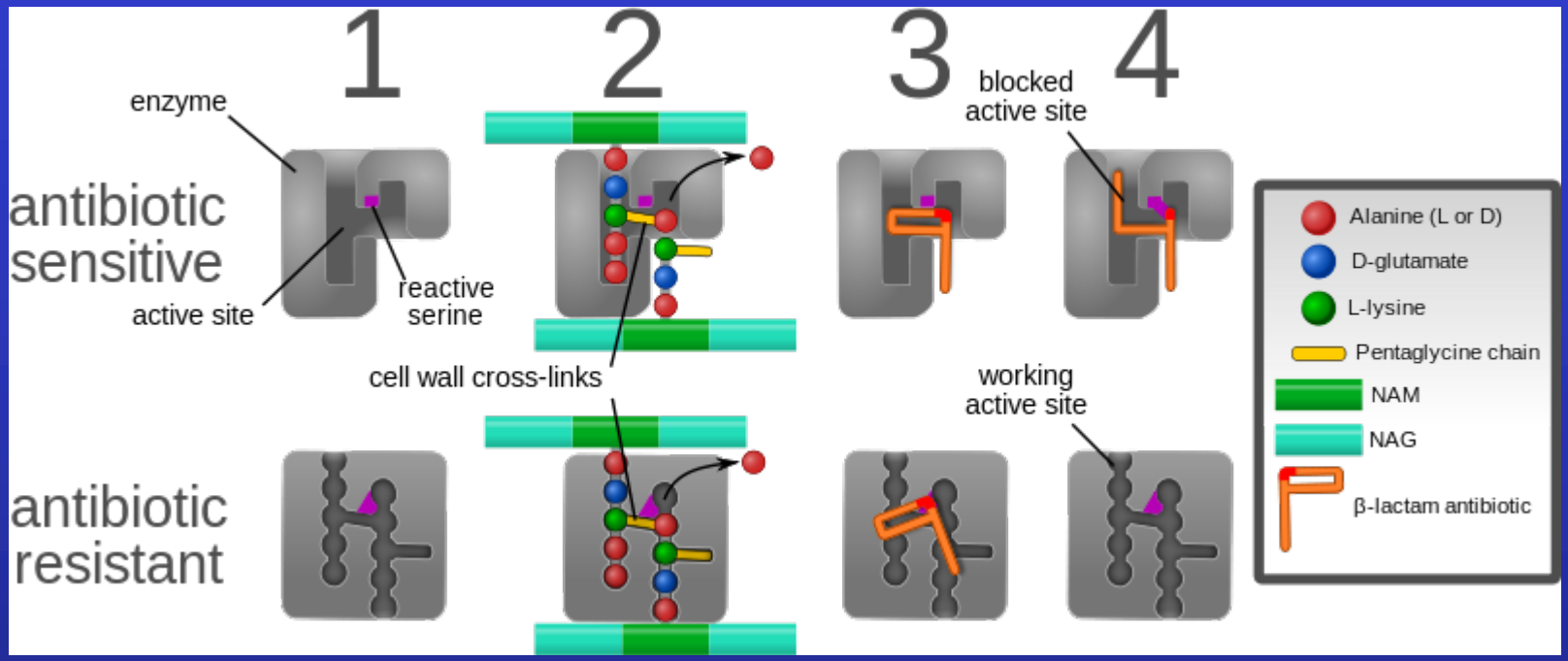
https:// https://en.wikipedia.org/wiki/B-lactam_antibiotic

Affect of Penicillin



Methicillin Resistant *S. aureus* (MRSA)

Resistance Mechanism



- Methicillin resistance results from production of PBP2a, an altered PBP that blocks antibiotic active site binding
- PBP2a is encoded for by the *mecA* gene
- Confers resistance to ALL BETA LACTAMS

https://en.wikipedia.org/wiki/Methicillin-resistant_Staphylococcus_aureus

CHROMagar

- Contains cefoxitin (methicillin analog) and chromogenic substrate

- Methicillin Resistant *Staphylococcus aureus* (MRSA)
  - Rose/mauve (cefoxitin resistant, hydrolyzes Staph specific substrate)
- Methicillin Susceptible *Staphylococcus aureus* (MSSA)
  - Inhibited (cefoxitin susceptible)
- Other bacteria
  - Blue (cefoxitin resistant, hydrolyzes non-Staph specific substrate)
  - Colourless (cefoxitin resistant, no hydrolysis)
  - Inhibited (cefoxitin susceptible)

S. aureus rapid testing

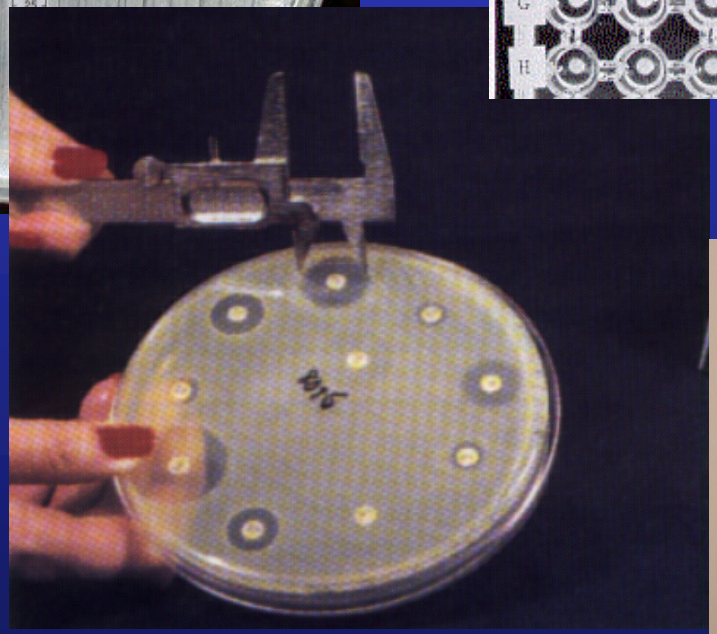
- GeneXpert, Cepheid
  - Automated PCR
  - MRSA surveillance
    - Direct sample: nares swab
    - ~5 min processing, 1 h PCR
  - MRSA, blood culture
- BD GeneOhm
  - *S. aureus*/MRSA
- BioFire FilmArray Blood Panel
- Etc.

S. aureus rapid testing

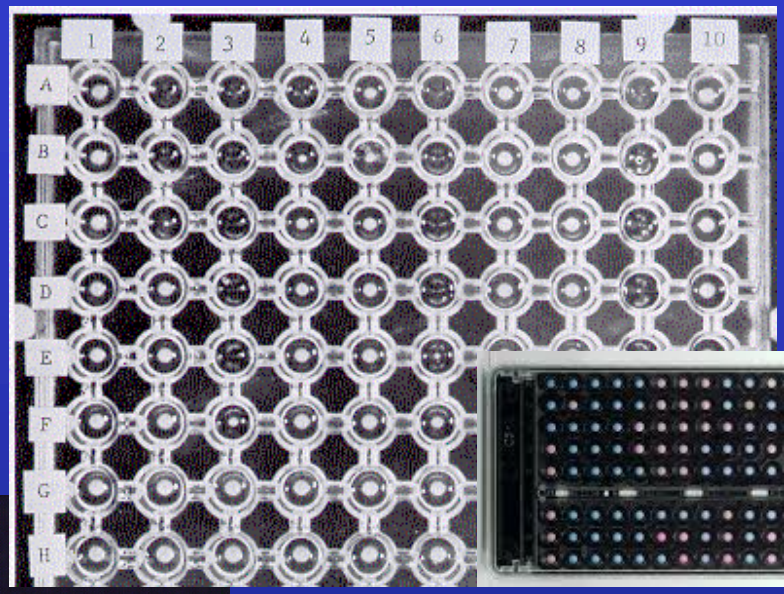
- PBP2a assays for MRSA
  - From pure colonies
  - Basis: antigen-based agglutination
  - Tests for presence of altered target
  - Performed on all *S.aureus* isolates cultured from sterile siteds/fluids

Antimicrobial Susceptibility Testing

Etest

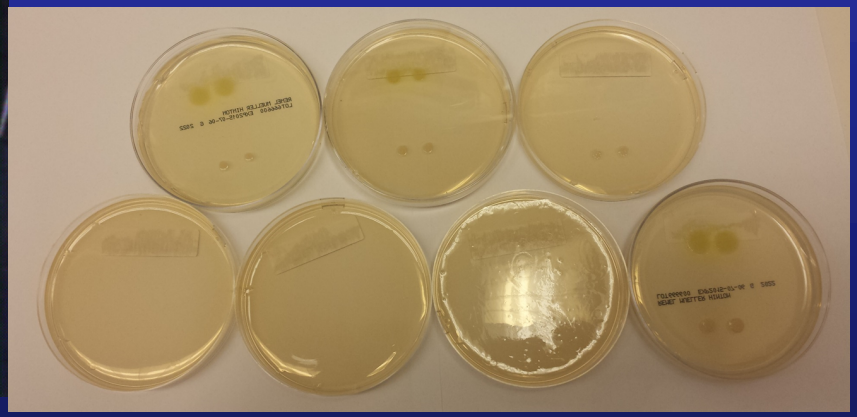


Kirby Bauer



Broth dilution

Agar dilution



(3) Historically, resistance to the penicillinase-stable penicillins (see Glossary I) has been referred to as "methicillin resistance" or "oxacillin resistance." MRSAs are those strains of *S. aureus* that express *mecA* or another mechanism of methicillin resistance, such as changes in affinity of penicillin-binding proteins for oxacillin (modified *S. aureus* strains).

(4) **Most** oxacillin resistance is mediated by *mecA*, encoding the PBP 2a (also called PBP2'). Isolates that test positive for *mecA* or PBP 2a should be reported as oxacillin resistant.

***S. aureus* and CoNS isolates that test resistant by cefoxitin MIC or cefoxitin disk or demonstrate oxacillin MICs ≥ 4 µg/mL should be reported as** oxacillin resistant. **For non-*S. epidermidis* CoNS with oxacillin MICs between 0.5 and 2 µg/mL, see comment (15).**

Mechanisms of oxacillin resistance other than *mecA* are rare and include a novel *mecA* homologue, *mecC*.[1] ***S. epidermidis* isolates with oxacillin MIC ≥ 0.5 µg/mL should be reported as oxacillin resistant.** MICs for strains with *mecC* are typically in the resistant range for cefoxitin and/or oxacillin; *mecC* resistance cannot be detected by tests directed at *mecA* or PBP 2a.

(5) Oxacillin-resistant *S. aureus* and CoNS (MRS), are considered resistant to other β-lactam agents, ie, penicillins, β-lactam/β-lactamase inhibitor combinations, cephems (with the exception of the cephalosporins with anti-MRSA activity), and carbapenems. This is because most cases of documented MRS infections have responded poorly to β-lactam therapy, or because convincing clinical data that document clinical efficacy for those agents have not been presented.

Cefoxitin / oxacillin phenotypes for the staphylococci, and how to report them!

	Cefoxitin MIC	Oxacillin MIC	Report Oxacillin	Notes
S. aureus / S. lugdunensis	R	R	R	Common phenotype
	S	R	R	Rare phenotype Hyperexpressed *blaZ* or other PBPs (not *mecA*/PBP2a)
	R	S	R	Rare phenotype Low expression of *mecA* or possibly *mecC*
	S	S	S	Common phenotype
S. epidermidis	Do not test	S	S	
	Do not test	R	R	Common phenotype
S. pseudintermedius	Do not test	R	R	
	Do not test	S	S	Common phenotype
Other spp.	Do not test	S	S	
	Do not test	R, MIC 0.5-2.0	R	If cefoxitin disk is "R"
	Do not test	R (0.5 – 2.0)	S	If cefoxitin disk is "S"
	Do not test	R (>2.0)	R	Common phenotype

https://www.asm.org/index.php/clinmicro-blog/item/6241-testing-staphylococci-for-oxacillin-resistance-why-is-it-so-complicated

Overarching Guidelines

Adapted from CLSI M100, Table 1A

A. Primary	B. Optional/ Report Selectively	C. Supplemental	D. Urine Only
Erythromycin, Azithromycin or Clarithromycin	Ceftaroline	Ciprofloxacin or Levofloxacin	Nitrofurantoin
Clindamycin	Daptomycin	Moxifloxacin	Sulfisoxazole
Oxacillin	Linezolid and/or Tedizolid	Gentamicin	Trimethoprim
Penicillin	Doxycycline and/or Tetracycline and/or Minocycline	Chloramphenicol	
Trimethoprim/ Sulfamethoxazole	Vancomycin	Oritavancin	
	Rifampin	Televancin	

Local Guidelines

Excerpted from UW Medicine Sepsis Guidelines

PNEUMONIA

A. Community-acquired pneumonia [non-aspiration risk] (*S. pneumoniae, atypicals*)
Diagnosis: Send sputum gram stain & culture, CXR, and blood cultures.

- Ceftriaxone 1 gm IV q24 hours **PLUS**
- Azithromycin 500 mg PO/IV q24 hours
- If previous MRSA colonization or infection, **CONSIDER ADDING:** Vancomycin loading dose IV x1 (2 gm if ≥70 kg, 1.5 gm if <70kg), then 15 mg/kg IV q12 hours

Typical Duration: 7 days

B. CAP with cavitary lesion(s) (*Oral anaerobes and MRSA*)

- Ampicillin/Sulbactam 3 gm IV q6 hours **PLUS**
- Azithromycin 500 mg PO/IV q24 hours **PLUS**
- Vancomycin loading dose IV x1 (2 gm if ≥70 kg, 1.5 gm if <70kg), then 15 mg/kg IV q12 hours

Typical Duration: 10-21 days

CF or Lung transplant patients: Call Pulmonary Transplant and Transplant Infectious Diseases Consult.

C. High-risk for MDRO pneumonia [i.e.from skilled nursing facility, etc](MRSA, resistant Gram-negative rods including *Acinetobacter, Pseudomonas*, ESBL)

- Cefepime 2g IV q8 hours +/- Vancomycin loading dose IV x1 (2 gm if ≥70 kg, 1.5 gm if <70kg), then 15 mg/kg IV q12 hours if h/o MRSA infection/colonization

Typical Duration: 7 days

D. UWMC only: Ventilator-associated Pneumonia (VAP) regardless of hospitalization day

- Treat as **High-risk for MDROs (see section C)**

E. HMC only:

- **Early onset VAP (i.e. ≤ 4 days of hospitalization or ventilation) or aspiration:** Ceftriaxone 1g IV daily **OR** Ampicillin-sulbactam 3g IV q6h
- **Late-onset [> 4 days inpatient],** Treat as **High-risk for MDROs (see section C)**

F. For all Pneumonia pts:

⇒ **During flu seasons, send Flu testing and then give oseltamivir 75mg - 150mg PO/NGT q12.**

⇒ **Yeast in the sputum rarely represents true infection.**

BLOODSTREAM

A. Suspected Line infection (MRSA, Gram-negative rods)
*Diagnosis: Order antibiotics immediately and draw paired, simultaneous, **quantitative** blood cultures from all central line lumens AND one peripheral site. Central line CFU x2 more than peripheral site CFU strongly suggests line infection.*

- Vancomycin loading dose IV x1 (2 gm if ≥70 kg, 1.5 gm if <70kg), then 15 mg/kg IV q12 hours **PLUS**
- Cefepime 2gm IV q8 hours
- Please consult Infectious Diseases if considering line salvage

B. Suspected endocarditis, hemodynamically stable, no valve insufficiency:
Diagnosis: Draw 3 sets of blood cultures prior to antibiotics and consult Infectious Diseases.

- Vancomycin loading dose IV x1 (2 gm if ≥70 kg, 1.5 gm if <70kg), then 15 mg/kg IV q12 hours **PLUS**
- Ceftriaxone 2gm IV q24 hours
- Consult Infectious Diseases

CELLULITIS

Not-applicable to device-related infections (eg ICD, pacemakers,VADs, etc): Consult Infectious Diseases

A. Non-purulent skin/soft tissue infection:
(Streptococcus species)

- Cefazolin 2g IV q8h
- PO option for Strep/MSSA: Cephalexin 500mg QID

B. Purulent/abscess forming skin/soft tissue infection:
(*S.aureus:* MSSA or MRSA)
Diagnosis: I&D abscess; send pus (not wound swab) for gram stain and culture.

- Vancomycin loading dose IV x1 (2 gm if ≥70 kg, 1.5 gm if <70kg), then 15 mg/kg IV q12 hrs
- De-escalate when culture data available
- PO options for MRSA: Bactrim or Doxycycline

Typical Duration: 5-7 days; Consult Infectious Diseases for PO step-down options

Organism-specific Reporting Rules

S.aureus (urine)	S.aureus (non-urine)	SCNG (incl. S.lug) (urine)	SCNG (incl. S.lug) (non-urine)
Cefazolin [1](MSSA only)	Cefazolin[1] (MSSA only)	Cefox (hidden)	Cefox (hidden)
Cefox (hidden)	Cefox (hidden)	D-test (hidden)	Clindamycin [3]
Ceftriaxone [2]	Ceftriaxone [2]	Gentamicin (R only)	D-test (hidden)
Dapto (MRSA only)	Clindamycin [3]	Levofloxacin	Erythromycin[3]
D-test (hidden)	Dapto [7] (MRSA only)	Linezolid[10]	Gentamicin (R only)
Gentamicin (R only)	D-test (hidden)	Moxifloxacin	Levofloxacin [3]
Levofloxacin	Erythromycin [3]	Nitrofurantoin	Linezolid [3,9,10]
Linezolid[10]	Gentamicin (R only)	Oxacillin (R only) [4]	Moxifloxacin [3]
Moxifloxacin	Levofloxacin [3]	Tetracycline	Oxacillin [5]
Nitrofurantoin	Linezolid [3,9,10]	Trimeth/sulfa	Rifampin (R only)
Oxacillin [1,8]	Moxifloxacin [3]	Vancomycin	Tetracycline [3]
Tetracycline	Oxacillin [1,8]		Trimeth/sulfa
Trimeth/sulfa	Rifampin (R only)		Vancomycin
Vancomycin[11]	Tetracycline [3]		
	Trimeth/sulfa Vancomycin [6, 11]		

Eur J Clin Microbiol Infect Dis (2016) 35:1151–1157
DOI 10.1007/s10096-016-2645-5

ORIGINAL ARTICLE

Impact of microbiology cascade reporting on antibiotic de-escalation in cefazolin-susceptible Gram-negative bacteremia

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Received: 9 February 2016 / Accepted: 5 April 2016 / Published online: 29 April 2016

Abstract Cascade reporting (CR) involves reporting the susceptibilities of broad-spectrum agents only when the organism is resistant to more narrow-spectrum agents. The purpose of this study is to evaluate the impact of CR on antibiotic de-escalation practices and to characterize the impact of CR on clinical outcomes. CR rules were implemented in the microbiology laboratory at Atlantic Health System (AHS) in June 2013. A retrospective chart review was conducted at two community teaching hospitals in adult patients who had a blood culture positive for a Gram-negative organism susceptible to cefazolin and who were empirically treated with broad-spectrum beta-lactam (BSBL) antibiotics. De-escalation practices were compared in the pre-CR (July 2012–December 2012) and post-CR (July 2013–December 2013) periods. The primary endpoint was the percentage of patients whose BSBL agent was de-escalated to agents listed on the post-CR antibiotic susceptibility report within 48 h of the final report. Secondary endpoints include the difference in pre-CR and post-CR periods in terms of hospital length of stay, in-hospital mortality, 30-day readmission, *Clostridium difficile* infections, and re-initiation of a BSBL agent within 7 days. A total of 73 patients were included; 31 in the pre-CR and 42 in the post-CR period. Patients had similar baseline characteristics. Therapy was de-escalated in 48 % of pre-CR vs 71 % of post-CR patients ($p=0.043$). No significant differences were observed in secondary endpoints between patients in the pre-CR and post-CR periods. CR resulted in significant improvements in de-escalation practices without affecting safety outcomes.

Introduction

Broad-spectrum antibiotics revolutionized medicine by allowing for the treatment of infections caused by organisms that had developed resistance to older, narrower-spectrum agents. Unfortunately, the widespread use of these newer agents has led to a corresponding increase in drug-resistant bacteria. Furthermore, the number of newly approved antimi-

Thank You