

Antibiotics 201 for Laboratory Professionals



Erik Munson, Ph.D., D(ABMM)
Marquette University
Wisconsin Clinical Laboratory Network
Technical Advisory Group

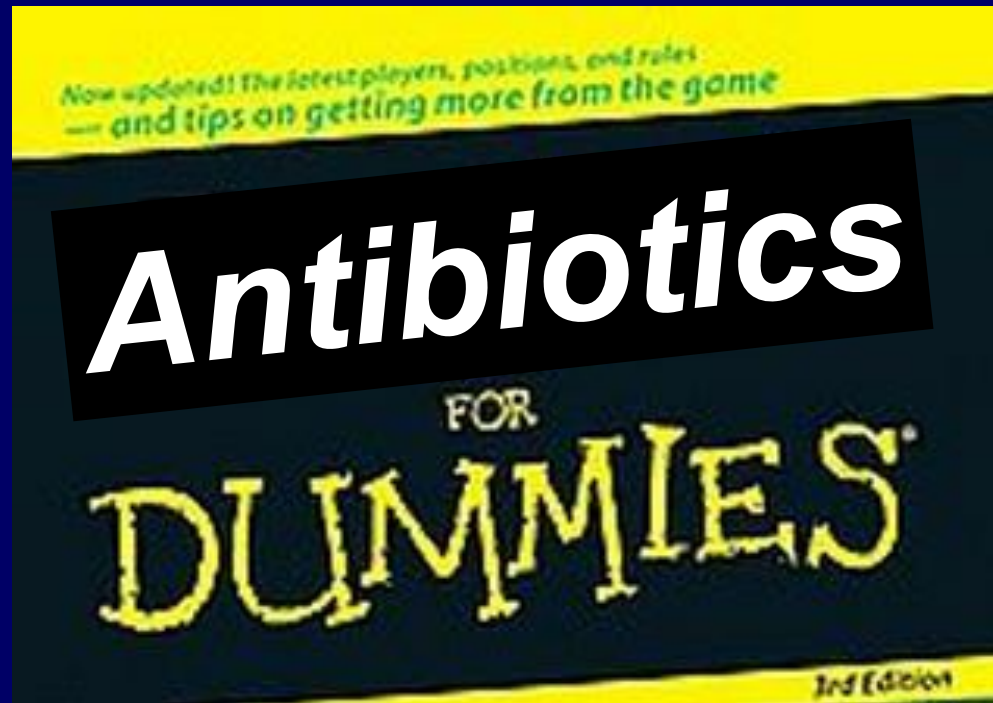
The presenter states no conflict of interest and has no financial relationship to disclose relevant to the content of this presentation.

OUTLINE

- I. Introductory comments
- II. Why you're really here with us today
 - A. List several newly-approved antibacterial agents and discuss their relevance to clinical practice
 - B. Describe modes of action and mechanisms of resistance that may be inherent to these agents
 - C. Ascertain the capability of performing antimicrobial susceptibility testing using these agents
- III. Examples of novel agents in the pipeline



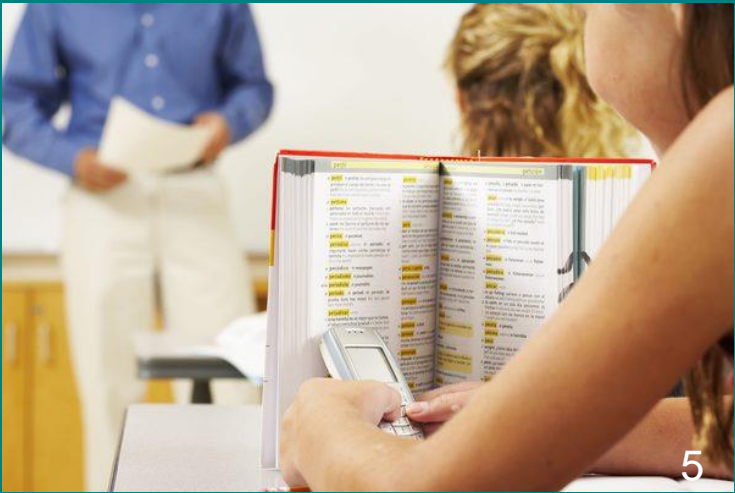
"D#*%it, Jim,
I'm not a physician."



...including myself



Introductory Comments



FACTORS TO CONSIDER

- Antimicrobial susceptibility testing (AST)
- Spectrum of therapy (empiric therapy)
- **Availability**

Cannot Enter Urinary Tract

macrolides

clindamycin

chloramphenicol

FACTORS TO CONSIDER

- Antimicrobial susceptibility testing (AST)
- Spectrum of therapy (empiric therapy)
- **Availability**

Cannot Enter Urinary Tract

macrolides

clindamycin

chloramphenicol

Cannot Enter CNS

fluoroquinolones

1st & 2nd generation cephems

clindamycin

macrolides

tetracycline

FACTORS TO CONSIDER

- Antimicrobial susceptibility testing (AST)
- Spectrum of therapy (empiric therapy)
- Availability
- Route of administration

Administration		Example
<i>Medical Lingo</i>	<i>Colloquial</i>	
IM	butt	ceftriaxone (also IV)
PO	oral	cephalexin
PO or parenteral	oral or IV	levofloxacin
parenteral	IV	vancomycin



FACTORS TO CONSIDER

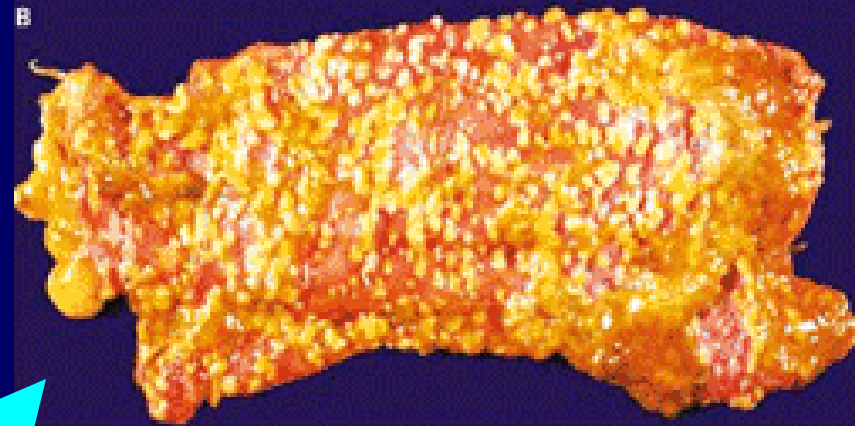
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parenteral	IV	vancomycin PO

FACTORS TO CONSIDER

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- Spectrum of therapy (empiric therapy)
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- **Route of administration**

Administration		Example
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IM	butt	ceftriaxone (also IV)
PO	oral	cephalexin
PO or parenteral	oral or IV	levofloxacin
parenteral	IV	vancomycin PO



Pseudomembranous colitis caused by *Clostridioides difficile*

FACTORS TO CONSIDER

- Antimicrobial susceptibility testing (AST)
- Spectrum of therapy (empiric therapy)
- Availability
- Route of administration
- Majority of excretion

Fluoroquinolone	Percentage Excretion	
	Renal	Biliary
levofloxacin	+++	-
ciprofloxacin	+++	+++++

FACTORS TO CONSIDER

- Antimicrobial susceptibility testing (AST)
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- Route of administration
- Majority of excretion

Fluoroquinolone	Percentage Excretion	
	Renal	Biliary
levofloxacin	+++	-
ciprofloxacin	+++	+++++

Shigella spp. report

ampicillin

trimethoprim-sulfa

ciprofloxacin

FACTORS TO CONSIDER

- Antimicrobial susceptibility testing (AST)
- Spectrum of therapy (empiric therapy)
- Availability
- Route of administration
- Majority of excretion
- Kinetics
- Dosing/half-life
- Co\$t
- Synergy
- Polymicrobial infections
- Side effects
- Cidal vs. static



ANTIBIOTIC RESISTANCE THREATS in the United States, 2013



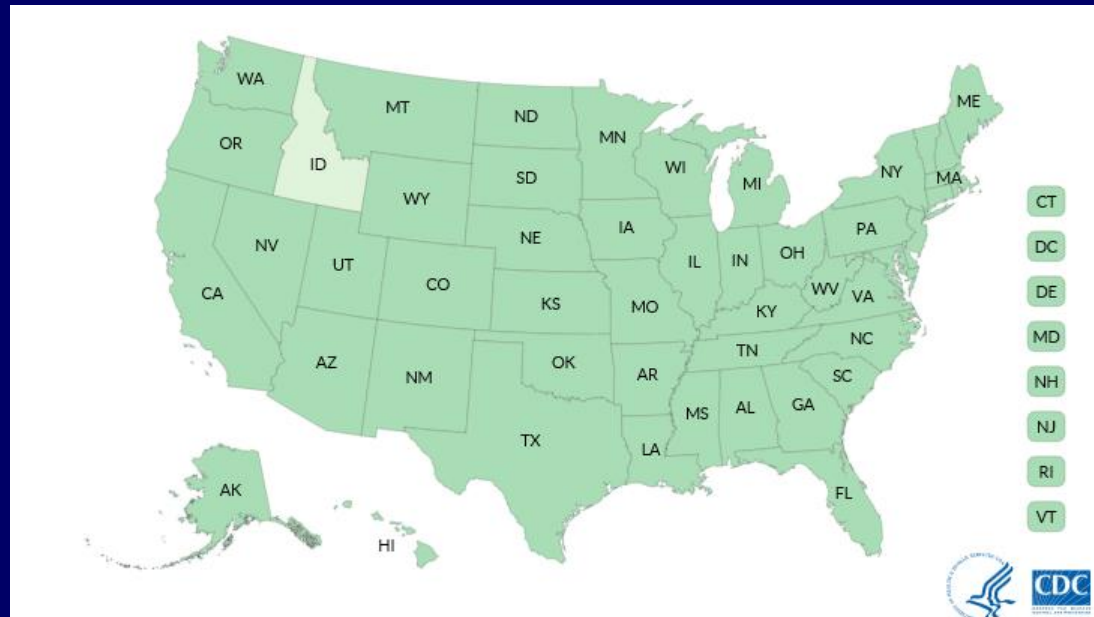
U.S. Department of
Health and Human Services
Centers for Disease
Control and Prevention

URGENT THREATS

C. difficile

Carbapenem-resistant *Enterobacteriaceae*

Drug-resistant *Neisseria gonorrhoeae*



Immediate public health threat that requires urgent and aggressive action

SERIOUS THREATS

Multidrug-resistant *Acinetobacter* spp.

Drug-resistant *Campylobacter* spp.

Fluconazole-resistant *Candida* spp.

ESBL-producing *Enterobacteriaceae*

Vancomycin-resistant *Enterococcus* spp.

Multidrug-resistant *Pseudomonas aeruginosa*

Drug-resistant non-typhoidal *Salmonella* spp.

Drug-resistant *Salmonella* Typhi

Drug-resistant *Shigella* spp.

Methicillin-resistant *Staphylococcus aureus*

Drug-resistant *Streptococcus pneumoniae*

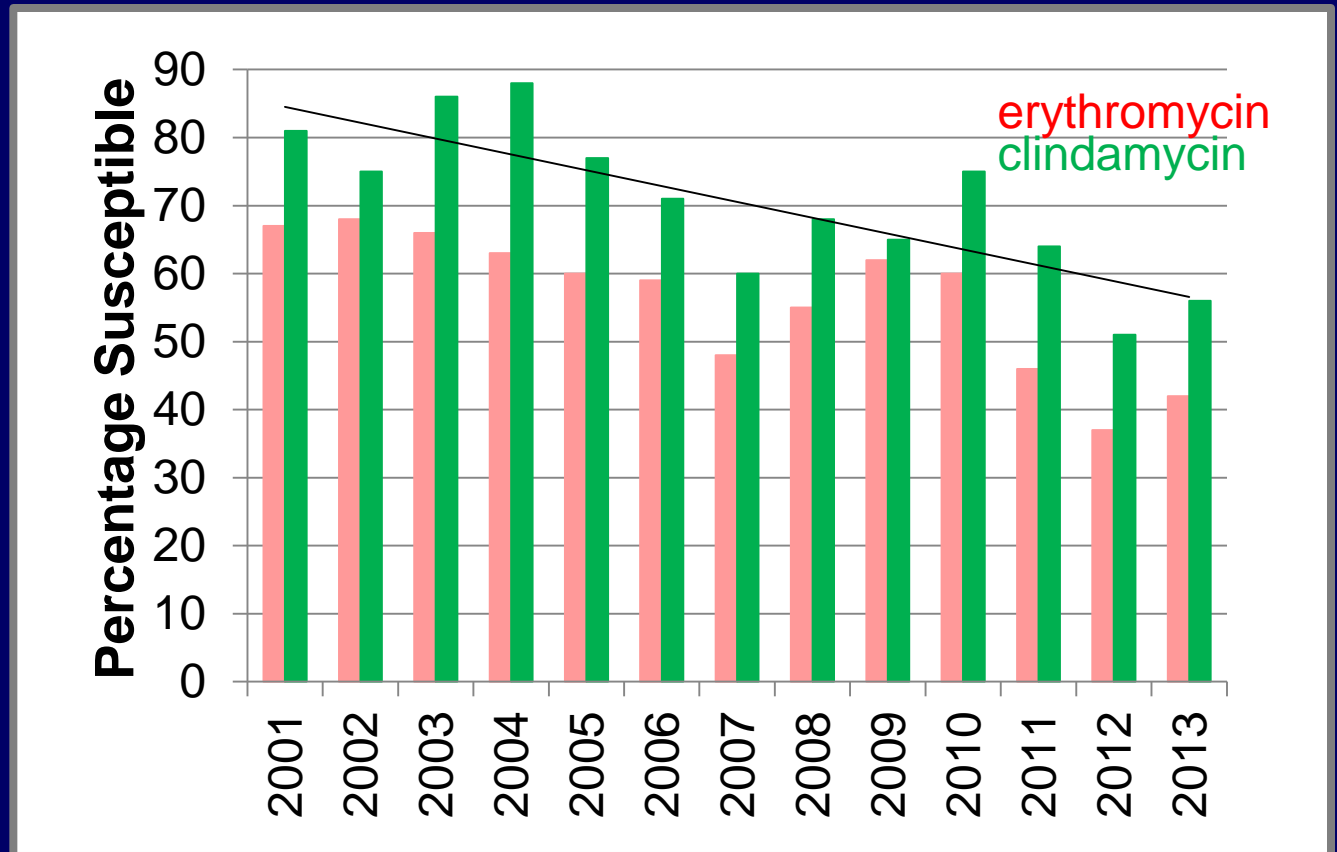
Drug-resistant tuberculosis

Requires prompt and sustained
action to ensure the problem
does not grow

CONCERNING THREATS

Vancomycin-resistant *Staphylococcus aureus*
Erythromycin-resistant group A *Streptococcus*
Clindamycin-resistant group B *Streptococcus*

Careful monitoring and preventive action are needed



OBLIGATORY SCARY STATS (G^RN^R)

Agent	Healthcare-associated Infections/year	Attributable Deaths
Carbapenem-resistant <i>Enterobacteriaceae</i>	9000	600
Drug-resistant <i>Acinetobacter</i> spp.	7300	500
ESBL-producing <i>Enterobacteriaceae</i>	26000	1700
Multidrug-resistant <i>Pseudomonas aeruginosa</i>	6700	440
Vancomycin-resistant <i>Enterococcus</i> spp.	20000	1300

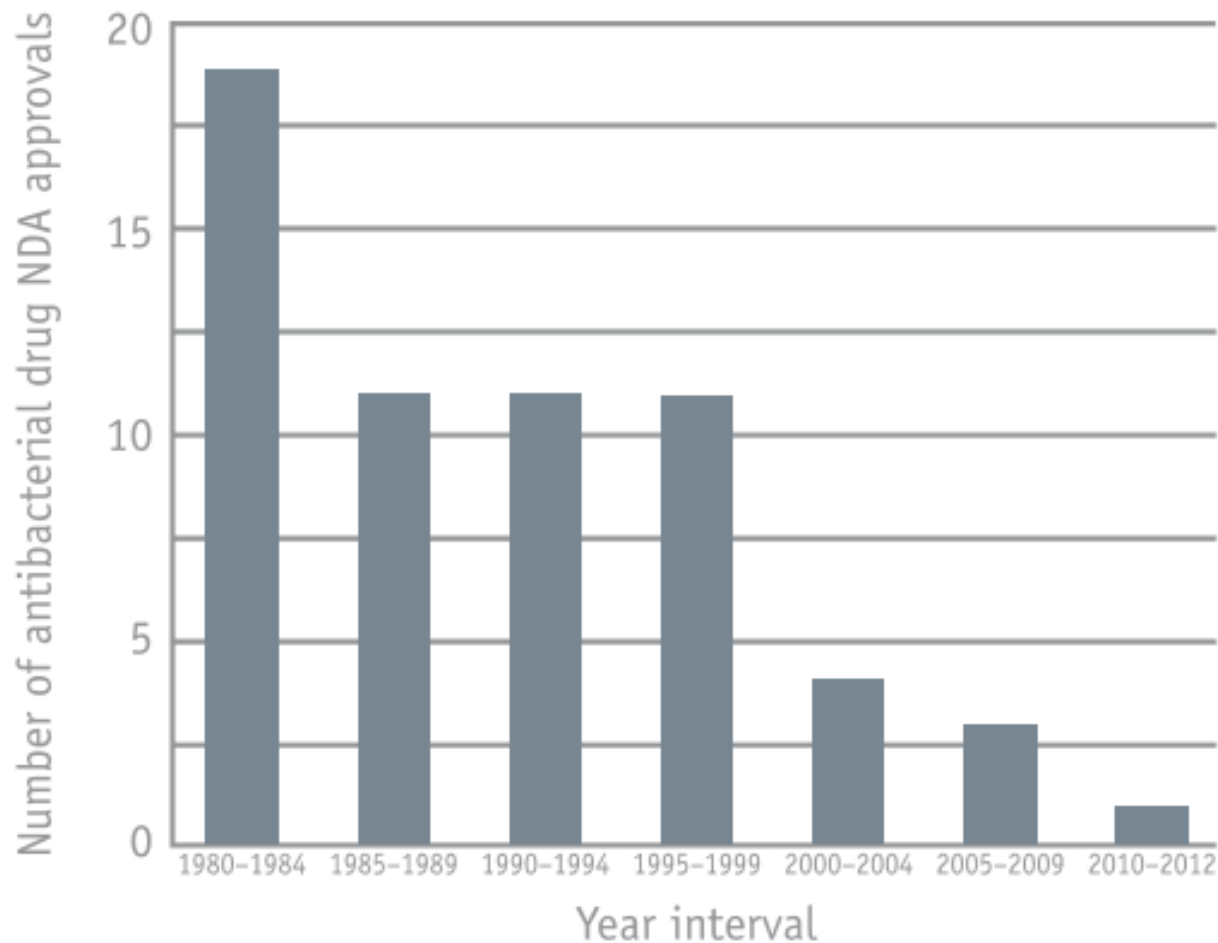
OBLIGATORY SCARY STATS (GPC)

Agent	Infections/year	Attributable Deaths
Methicillin-resistant <i>Staphylococcus aureus</i>	80000 severe infections	11000
Drug-resistant <i>Streptococcus pneumoniae</i>	1.2 million	7000
Erythromycin-resistant group A <i>Streptococcus</i>	1300	160
Clindamycin-resistant group B <i>Streptococcus</i>	7600	440

MORE OBLIGATORY SCARY STATS

Interval	% <i>Klebsiella</i> spp. possessing ESBL	% <i>E. coli</i> possessing ESBL	Reference
1997-2000	7.6	3.3	Clin. Infect. Dis. 32 : S94-102; 2001
2011-2013	16.3	12.0	Antimicrob. Agents Chemother. 59 : 3509-3517; 2015

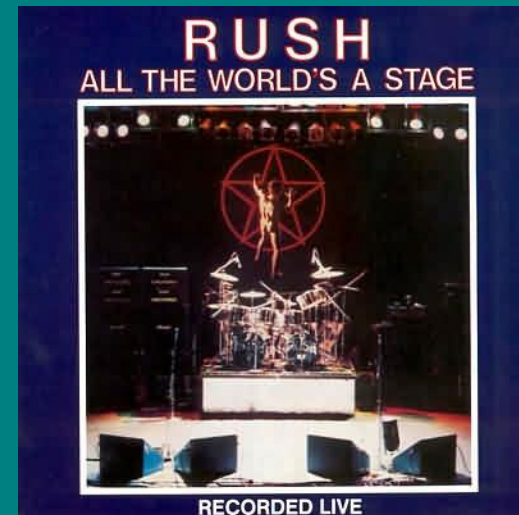
Number of Antibacterial New Drug Application (NDA) Approvals vs. Year Intervals*



*Intervals from 1980-2009 are 5-year intervals; 2010-2012 is a 3-year interval. Drugs are limited to systemic agents. Data courtesy of FDA's Center for Drug Evaluation and Research (CDER).

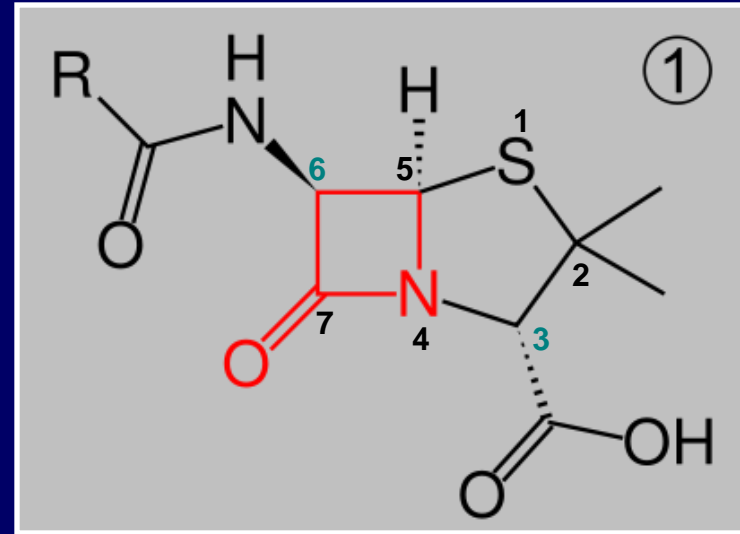


Setting the Stage



TWO BASIC SUBDIVISIONS

- β -lactam



- Non- β -lactam

TWO BASIC SUBDIVISIONS

- β -lactam

 - Penicillins

 - Cephems

 - Monobactams

 - Penems

- Non- β -lactam

ARBITRARY CLASSIFICATIONS

Activity

Generation

Narrow spectrum	First
Expanded spectrum	Second
Broad spectrum	Third
Extended spectrum	Fourth

ARBITRARY CLASSIFICATIONS

Activity

Narrow spectrum

Expanded spectrum

Broad spectrum

Extended spectrum



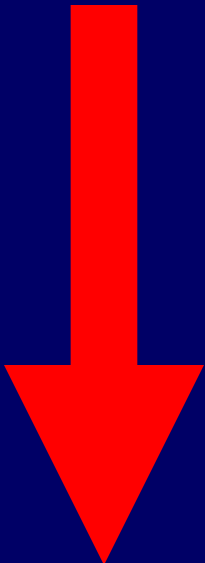
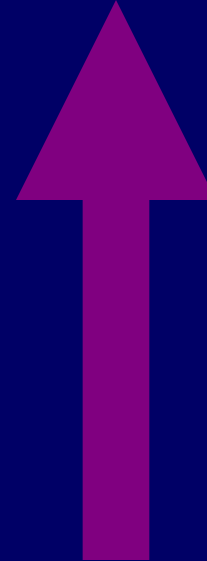
Generation

First

Second

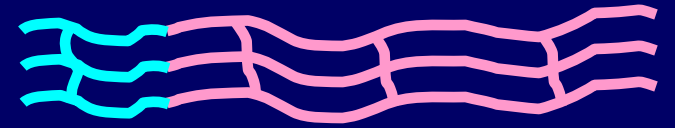
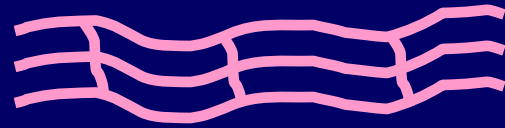
Third

Fourth

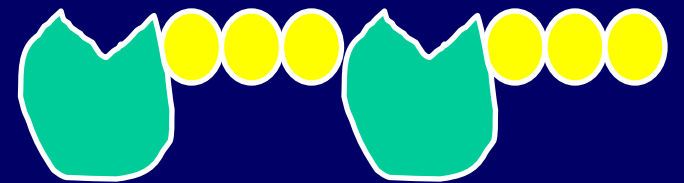
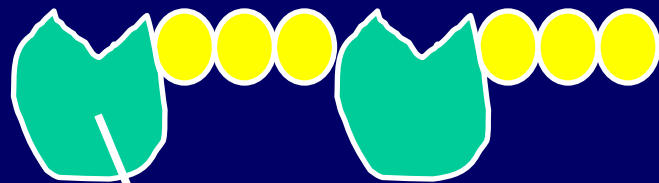


CELL WALL SYNTHESIS

cell wall
(peptidoglycan)

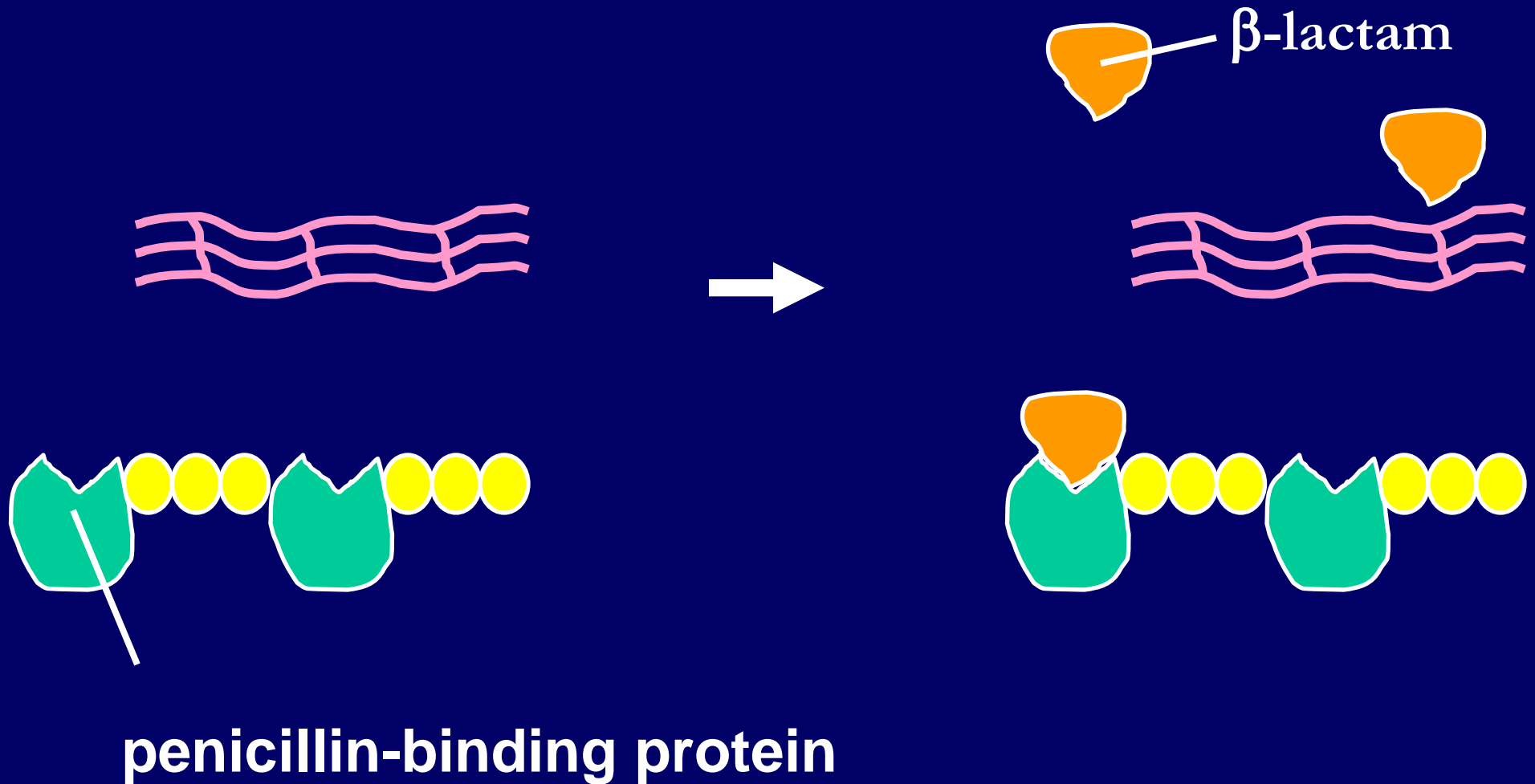


cell membrane



penicillin-binding protein

CELL WALL SYNTHESIS



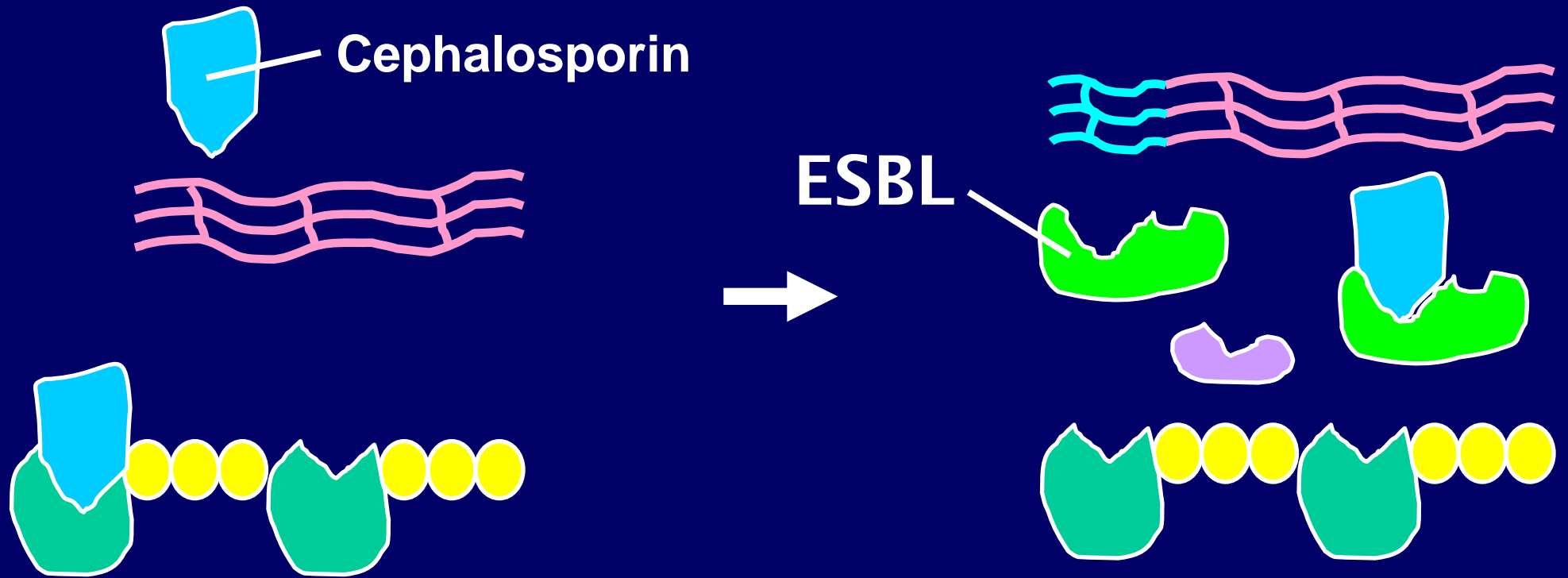
CEPHEM CLASS

Parameter	Description
Mechanism of action	<ol style="list-style-type: none">1. Bind to bacterial penicillin-binding proteins (PBP), interfering with cell wall synthesis2. Can trigger membrane-associated autolytic enzymes that destroy cell wall
Activity rendered	Cidal
Route of administration	PO or IV; e.g., cephalexin vs. cefazolin
Half-life	0.5 to 8 hours → q6h or q24h
Excretion	Mostly renal; cefoperazone with great biliary
Adverse effects	Allergic skin rash, drug fever, diarrhea; ↑creatinine, transaminases; leukopenia, thrombocytopenia

CEPHEM CLASS

Parameter	Description
Spectrum of activity	<p>cefazolin: MSSA, streptococci</p> <p>cefuroxime: <i>Haemophilus</i>, <i>S. pneumoniae</i></p> <p>cefoxitin/cefotetan: Anaerobes</p> <p>ceftriaxone: Resistant enterics, <i>N. gonorrhoeae</i></p> <p>ceftazidime/cefepime: Resistant enterics, <i>Pseudo</i></p> <p>ceftobiprole: MRSA (not available in US)</p>
Interesting stuff	<p>Cross-reaction in 3-7% of penicillin-allergic patients</p> <p>Hypoprothrombinemia and bleeding tendencies associated with cefotetan, cefoperazone</p>

RESISTANCE VIA ESBL PRODUCTION



PENEM CLASS

Parameter	Description
Mechanism of action	Bind to penicillin-binding proteins 1 and 2, causing cell elongation and eventual lysis
Activity rendered	Cidal
Route of administration	IV
Half-life	1-4 hrs → q8h or q24h
Excretion	Renal
Adverse effects	Nausea, vomiting, diarrhea 5%; drug fever, rash, urticaria 3%; seizures 1%; other reversible effects

PENEM CLASS

Parameter	Description
Spectrum of activity	<p>Gram-positives (including penicillin-resist <i>S. pneumo</i>)</p> <p>Gram-negatives (including β-lactam- and aminoglycoside-resistant enterics, ESBL)</p> <p>Not effective versus MRSA, vancomycin-resistant <i>Enterococcus</i> spp., <i>Stenotrophomonas maltophilia</i></p> <p>Most potent β-lactam versus anaerobes</p>
Interesting stuff	<p>Widest spectrum of antibacterial activity of currently-available antimicrobials; imipenem administered with cilastatin (a dehydropeptidase I inhibitor)</p>

PENEM RESISTANCE

- Alteration of porin channels in bacterial cell wall, reducing permeability
- Carbapenemase production
 - Serine carbapenemases (class A β -lactamase)
 - Metallo- β -lactamase (class B β -lactamase)
 - OXA-type β -lactamase (class D β -lactamase)
- Plasmids carrying *bla*_{KPC} contain genes conferring resistance to aminoglycosides and fluoroquinolones

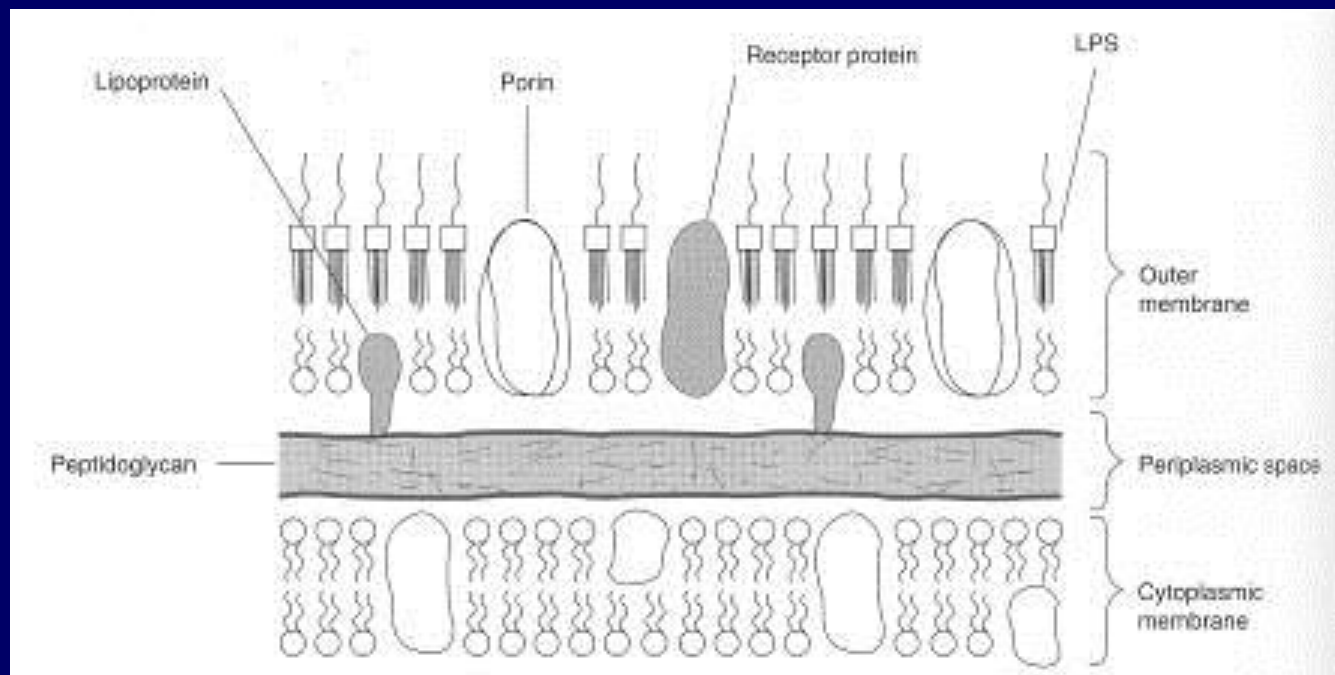


What Do We Do Next?



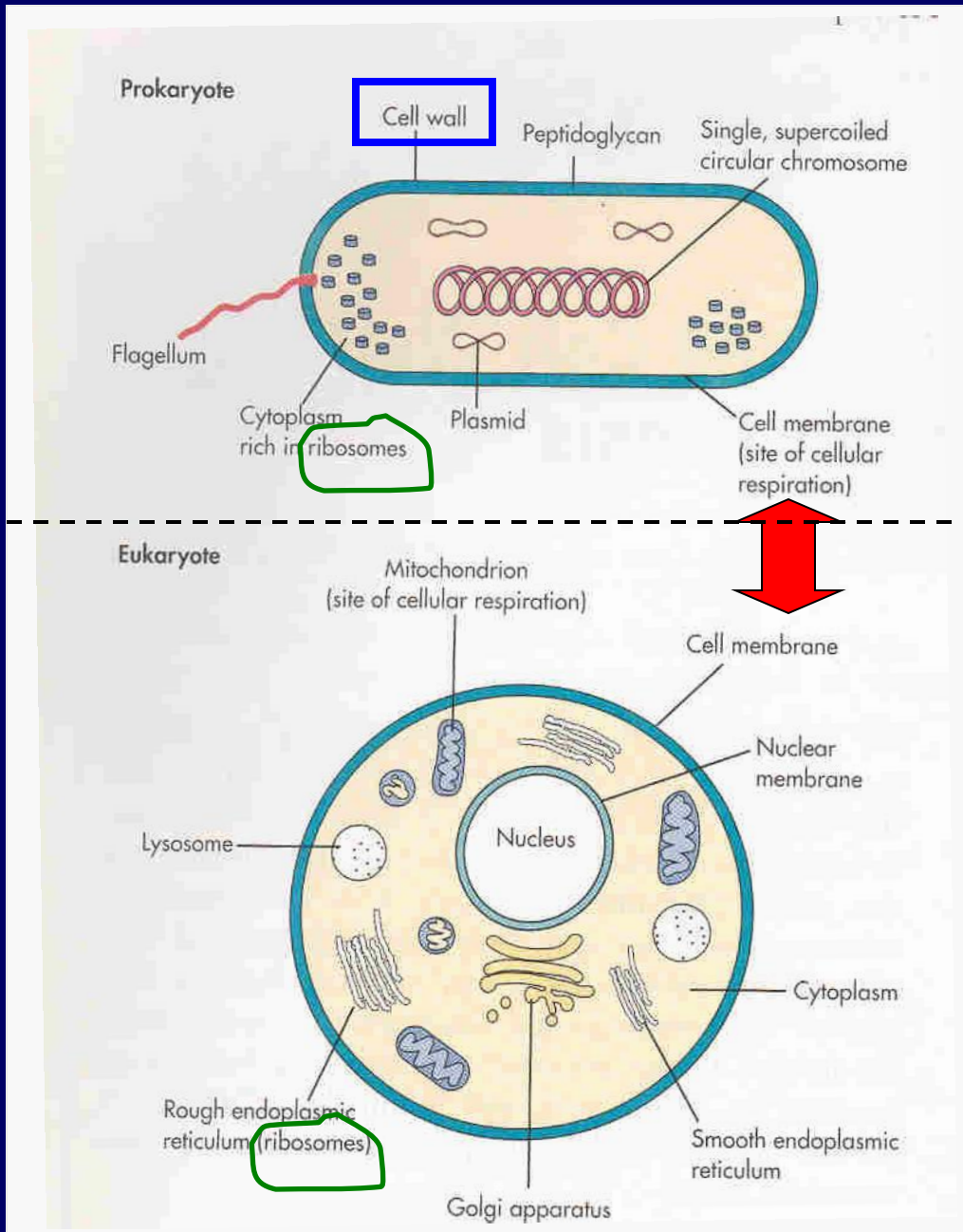
LIPOPEPTIDE CLASS

Subclass (if appropriate)	Agent(s)
polymyxin	polymyxin B
	polymyxin E (colistin)



POLYMYXIN SUBCLASS

Parameter	Description
Mechanism of action	1. Bind to phosphorylated head groups of lipid A, disrupting cell membranes and losing osmolarity 2. Disruption of biofilm formation
Activity rendered	Cidal
Route of administration	IV
Half-life	~3 hrs (colistin) ~7 hrs polymyxin B → q8h or q12h
Excretion	Renal
Adverse effects	Neurotoxicity (parasthesia, dizzy, vertigo, ataxia, slurred speech, confusion); nephrotoxicity (20%)



POLYMYXIN SUBCLASS

Parameter	Description
Spectrum of activity	<p>Only Gram-negative bacilli (especially <i>Pseudomonas aeruginosa</i>)</p> <p>Synergy with trimethoprim-sulfamethoxazole for serious infections caused by resistant <i>Serratia</i> spp., <i>P. aeruginosa</i>, <i>S. maltophilia</i>, <i>Burkholderia cepacia</i></p> <p>Pan-resistant Gram negative bacilli</p>
Interesting stuff	“We’re going back to 50 years ago!?!?”

POLYMYXIN RESISTANCE

- Decreased uptake

 - Efflux

 - Cell wall of some organisms prevents uptake

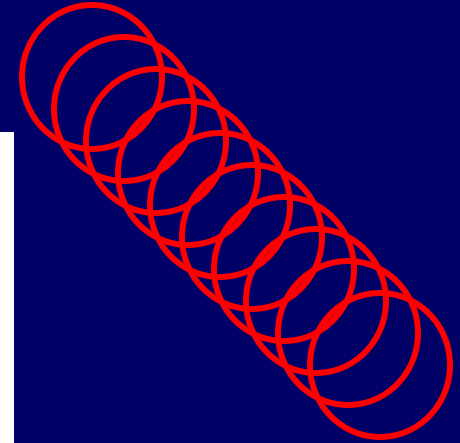
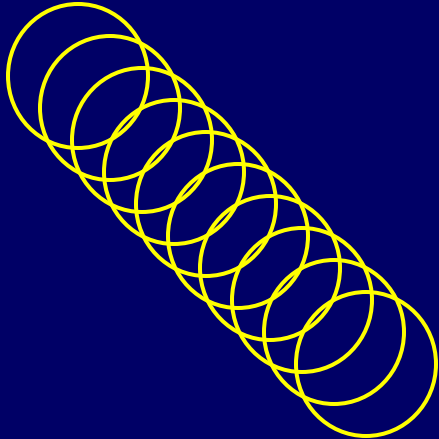
- Modification of phosphate groups of lipid A


- Lipopolysaccharide modifications

 - Alteration of fatty acid content of lipid A


 - Addition of amino, carboxyl groups

UH, OH




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Antimicrobial Agents and Chemotherapy


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LETTER TO THE EDITOR

Detection of *mcr-1* among *Escherichia coli* Clinical Isolates Collected Worldwide as Part of the SENTRY Antimicrobial Surveillance Program in 2014 and 2015

Mariana Castanheira, Michelle A. Griffin, Lalitagauri M. Deshpande, Rodrigo E. Mendes, Ronald N. Jones, Robert K. Flamm
 JMI Laboratories, North Liberty, Iowa, USA

TABLE 1 Occurrence of *mcr-1* among *E. coli* and *K. pneumoniae* clinical isolates collected worldwide during 2014 and 2015 as part of the SENTRY Antimicrobial Surveillance Program^a

Organism(s) and location where <i>mcr-1</i> -positive isolate(s) was observed	No. of <i>mcr-1</i> -positive isolates/ no. of colistin-resistant isolates (%)	No. of <i>mcr-1</i> -positive isolates with colistin MICs ($\mu\text{g/ml}$) of:		
		4	8	>8
All colistin-resistant organisms	19/390 (4.9)	10	8	1
<i>E. coli</i>	19/59 (32.2)	10	8	1
Belgium (Antwerp)	1/1	1		
Brazil (Florianopolis)	1/1	1		
Germany (Bonn and Kiel)	5/10	2	3	
Hong Kong	1/1	1		
Italy (Florence, Milan, and Rome)	4/9	3	1	
Malaysia (Kelantan)	1/1		1	
Poland (Warsaw)	1/2	1		
Russia (Yekaterinburg)	1/2	1		
Spain (Madrid)	3/3		2	1
USA (New York City)	1/15		1	

^a All *K. pneumoniae* isolates were negative for *mcr-1*.



Susceptibility Testing for the Polymyxins: Two Steps Back, Three Steps Forward?

Shawn Vasoo

Department of Infectious Diseases and Infectious Diseases Research Laboratory, Institute of Infectious Diseases and Epidemiology, Tan Tock Seng Hospital, Singapore; Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore

J. Clin. Microbiol. **55**: 2573-2582; 2017



Colistin and Polymyxin B Susceptibility Testing for Carbapenem-Resistant and *mcr*-Positive *Enterobacteriaceae*: Comparison of Sensititre, MicroScan, Vitek 2, and Etest with Broth Microdilution

● Ka Lip Chew,^a My-Van La,^b Raymond T. P. Lin,^{a,c} ● Jeanette W. P. Teo^a

Department of Laboratory Medicine, Division of Microbiology, National University Hospital, Singapore, Republic of Singapore; Department of Laboratory Medicine, Changi General Hospital, Republic of Singapore; Ministry of Health, National Public Health Laboratory, Singapore, Republic of Singapore

J. Clin. Microbiol. **55**: 2609-2616; 2017

β -LACTAM/ β -LACTAMASE INHIBITORS

Subclass (if appropriate)	Agent(s)
NONE	amoxicillin-clavulanic acid
	ampicillin-sulbactam
	piperacillin-tazobactam
	ticarcillin-clavulanic acid

Clavulanic acid, sulbactam, tazobactam

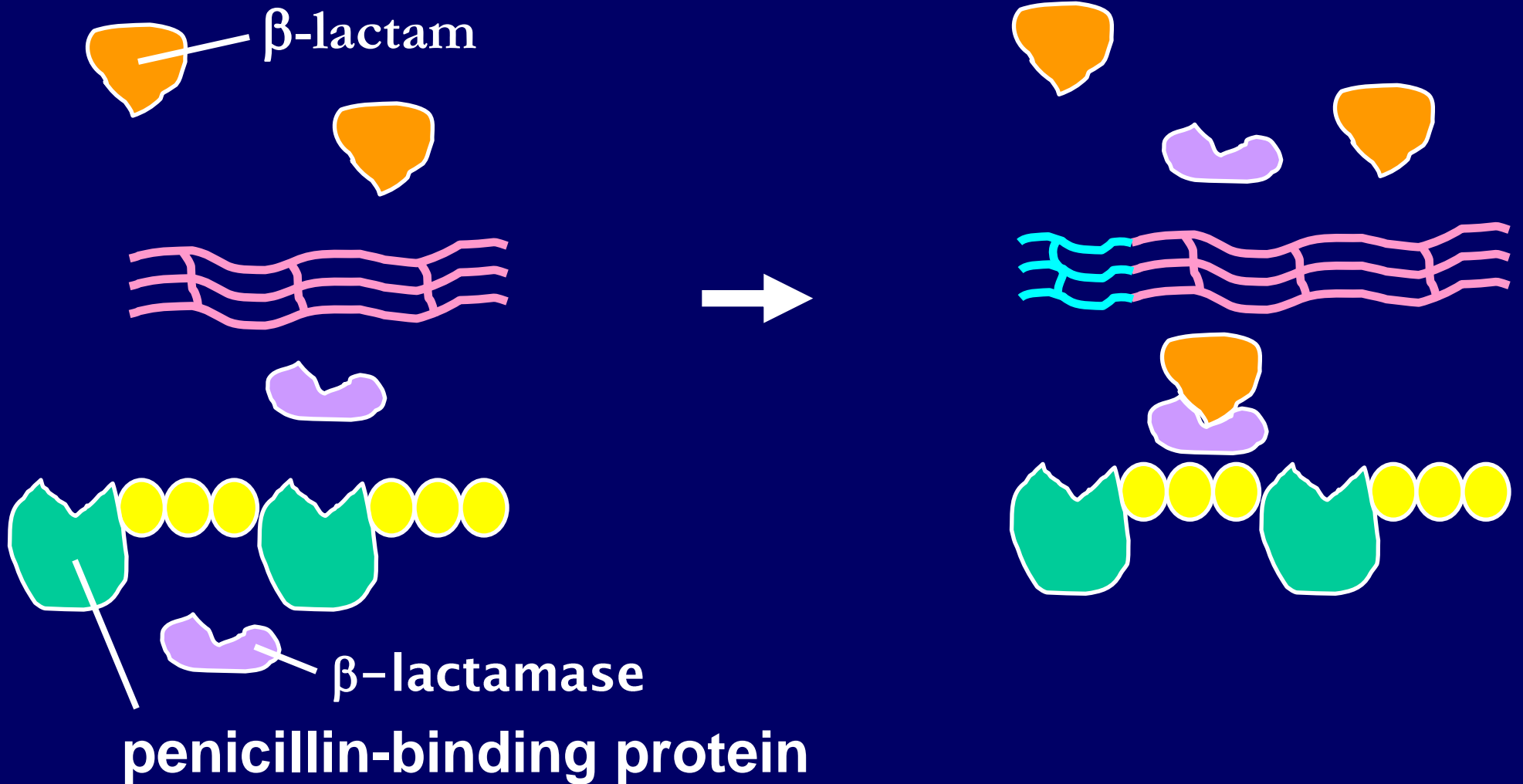
1. Alone have poor intrinsic antibacterial activity
2. Irreversibly complex with β -lactamase \rightarrow loss of enzyme activity
3. Can lower MIC up to 20-fold when combined with β -lactam agent

β -LACTAM/ β -LACTAMASE INHIBITORS

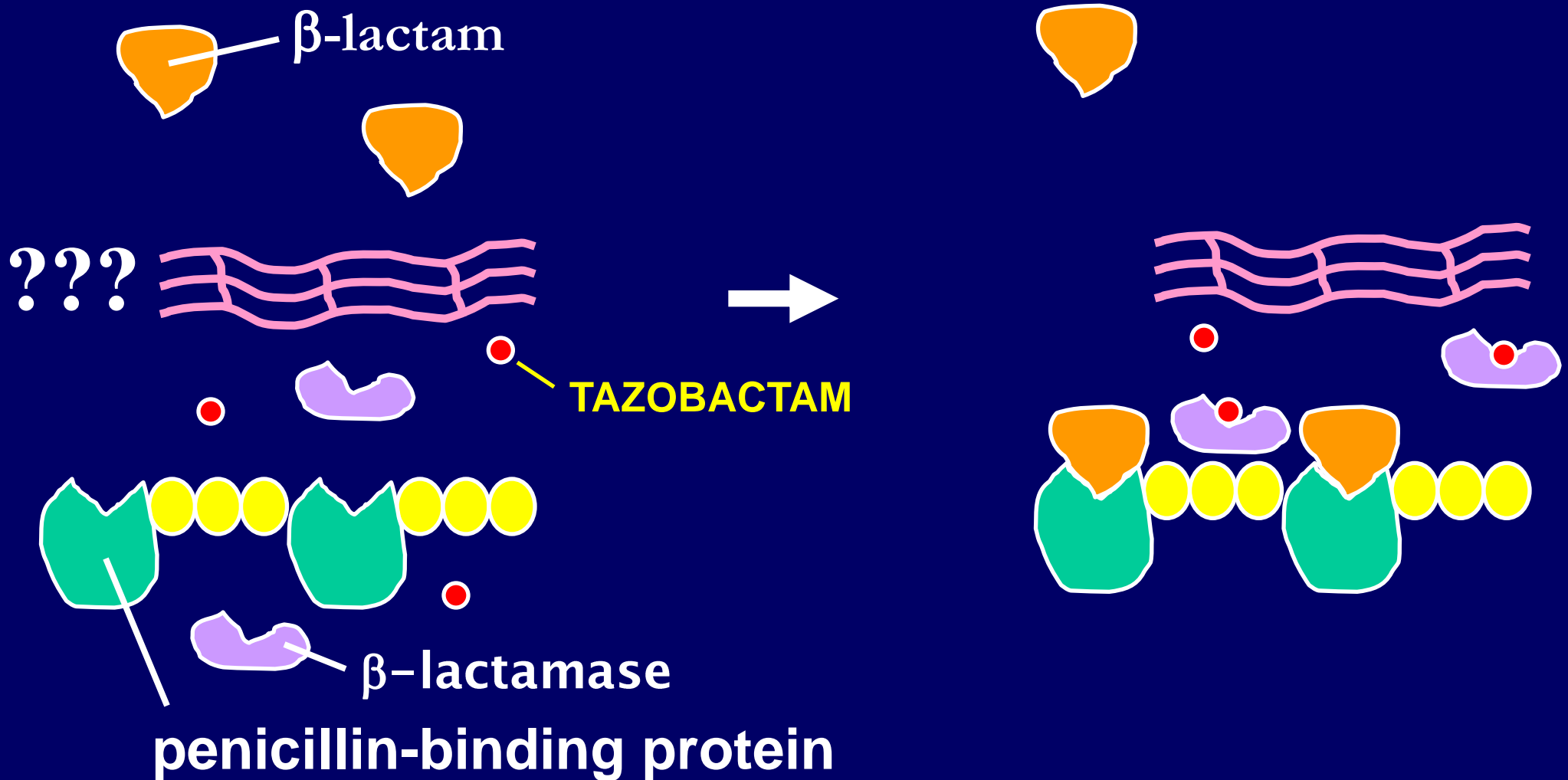
Subclass (if appropriate)	Agent(s)
NONE	amoxicillin-clavulanic acid
	ampicillin-sulbactam
	piperacillin-tazobactam
	ticarcillin-clavulanic acid
	ceftazidime-avibactam
	ceftolozane-tazobactam
	meropenem-vaborbactam
	aztreonam-avibactam
	cefepime-tazobactam
	cefepime-zidebactam

another inhibitor compound: relebactam

β -LACTAMASE



β -LACTAMASE INHIBITOR



CEFTAZIDIME-AVIBACTAM

Parameter	Description
a.k.a.	AVYCAZ
Indication	<ol style="list-style-type: none">1. Complicated intra-abdominal infections (in combination with metronidazole)2. Complicated urinary tract infections (including pyelonephritis)
Mechanism of action	<ol style="list-style-type: none">1. Inactivates β-lactamases2. Binds essential penicillin-binding proteins
Activity rendered	Cidal
Route of administration	IV
Half-life	2.76 h \rightarrow q8h
Excretion	Renal

CEFTAZIDIME-AVIBACTAM

Parameter	Description
Spectrum of activity	<p><i>Pseudomonas aeruginosa</i></p> <p><i>Enterobacteriaceae</i> (<i>E. coli</i>, <i>K. pneumoniae</i>, <i>E. cloacae</i>, <i>P. mirabilis</i>, <i>C. freundii</i>)</p> <p>Claims activity versus ESBL producers</p>
Adverse effects	<p>Hypersensitivity in penicillin-, cephem-, or penem-allergic patients</p> <p><i>C. difficile</i> infection</p> <p>CNS reactions, particularly in renal-impaired patients</p>

CEFTAZIDIME-AVIBACTAM

Organism	Method	Adopted	Testing/ Reporting	Breakpoint Range	Caveat(s)
<i>Enterobacteriaceae</i>	BMD, DD	2018	optional	full	
<i>P. aeruginosa</i>	BMD, DD	2018	optional	full	

Antimicrobial Activity of Ceftazidime-Avibactam Tested against Multidrug-Resistant *Enterobacteriaceae* and *Pseudomonas aeruginosa* Isolates from U.S. Medical Centers, 2013 to 2016

Helio S. Sader, Mariana Castanheira, Dee Shortridge, Rodrigo E. Mendes, Robert K. Flamm

JMI Laboratories, North Liberty, Iowa, USA

EPIDEMIOLOGY AND SURVEILLANCE

Organism category and antimicrobial agent (no. of isolates tested)	MIC (μg/ml)		CLSI ^b		EUCAST	
	MIC ₅₀	MIC ₉₀	%S	%R	%S	%R
XDR (448)^a						
Ceftazidime-avibactam →	0.5	2	97.8	2.2*	97.8	2.2
Ceftriaxone	>8	>8	2.0	97.3	2.0	97.3
Ceftazidime	>32	>32	5.4	91.5	2.9	94.6
Cefepime	>16	>16	10.5	79.9	6.4	85.8
Piperacillin-tazobactam	>64	>64	7.1	83.7	6.5	92.9
Meropenem	8	>8	21.2	72.5	27.5	48.2
Levofloxacin	>4	>4	8.7	84.8	2.2	96.4
Gentamicin	8	>8	27.0	50.0	23.4	73.0
Amikacin	16	32	60.2	9.6	46.5	39.8
Tigecycline	0.5	4	90.0	0.2*	81.0	10.0
Colistin	≤0.5	>8			61.3	38.7
CRE (513)^a						
Ceftazidime-avibactam →	0.5	2	97.5	2.5*	97.5	2.5
Ceftriaxone	>8	>8	2.1	97.5	2.1	97.5
Ceftazidime	>32	>32	4.3	93.0	2.3	95.7
Cefepime	>16	>16	8.4	77.9	3.2	87.1
Piperacillin-tazobactam	>64	>64	3.1	91.2	2.7	96.9
Meropenem	>8	>8	2.7	89.7	10.3	52.4
Levofloxacin	>4	>4	23.4	72.9	15.0	81.3
Gentamicin	8	>8	49.5	33.9	44.4	50.5
Amikacin	8	32	68.2	7.0	51.5	31.8
Tigecycline	0.5	1	98.8	0.0*	90.3	1.2
Colistin	≤0.5	>8			79.1	20.9
<i>P. aeruginosa</i>						
All isolates (7,868)						
Ceftazidime-avibactam →	2	4	97.1	2.9*	97.1	2.9
Ceftazidime	2	32	84.7	10.9	84.7	15.3
Cefepime	2	16	85.6	5.2	85.6	14.4
Piperacillin-tazobactam	4	64	81.0	9.4	81.0	19.0
Meropenem	0.5	8	81.3	12.8	81.3	6.8
Levofloxacin	0.5	>4	74.5	18.6	65.3	34.7
Gentamicin	2	8	87.0	8.4	87.0	13.0
Amikacin	4	8	96.5	1.9	91.8	3.5
Colistin	1	2	99.6	0.4	99.6	0.4

CEFTOLOZANE-TAZOBACTAM

Parameter	Description
a.k.a.	ZERBAXA
Indication	<ol style="list-style-type: none"> 1. Complicated intra-abdominal infections (in combination with metronidazole) 2. Complicated urinary tract infections (including pyelonephritis)
Mechanism of action	<ol style="list-style-type: none"> 1. Forms irreversible complex with β-lactamase 2. Binds PBP-1b, -1c, and -3 of <i>P. aeruginosa</i> Binds PBP-3 of <i>E. coli</i> to inhibit cell wall synthesis
Activity rendered	Cidal
Route of administration	IV
Half-life	3.12 h \rightarrow q8h
Excretion	Renal

CEFTOLOZANE-TAZOBACTAM

Parameter	Description
Spectrum of activity	<p><i>Pseudomonas aeruginosa</i></p> <p><i>Enterobacteriaceae</i> (<i>E. coli</i>, <i>K. pneumoniae</i>, <i>K. oxytoca</i>, <i>E. cloacae</i>, <i>P. mirabilis</i>)</p> <p><i>Bacteroides fragilis</i></p> <p><i>Streptococcus anginosus</i> group</p> <p>Claims activity versus ESBL producers</p>
Adverse effects	<p>Hypersensitivity in penicillin-, cephem-, or penem-allergic patients</p> <p><i>C. difficile</i> infection</p>

CEFTOLOZANE-TAZOBACTAM

Organism	Method	Adopted	Testing/ Reporting	Breakpoint Range	Caveat(s)
<i>Enterobacteriaceae</i>	BMD	2016	optional	full	
<i>Enterobacteriaceae</i>	DD	2018	optional	full	
<i>P. aeruginosa</i>	BMD, DD	2016	optional	full	
Viridans <i>Strep.</i>	BMD	2016	supplemental	full	

Antimicrobial Activity of Ceftolozane-Tazobactam Tested against *Enterobacteriaceae* and *Pseudomonas aeruginosa* with Various Resistance Patterns Isolated in U.S. Hospitals (2011-2012)

David J. Farrell,^{a,b} Robert K. Flamm,^a Helio S. Sader,^{a,c} Ronald N. Jones^{a,d}

JMI Laboratories, North Liberty, Iowa, USA^a; Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, Ontario, Canada^b; Division of Infectious Diseases, Federal University of São Paulo, São Paulo, SP, Brazil^c; Tufts University School of Medicine, Boston, Massachusetts, USA^d

<i>P. aeruginosa</i> resistance status (no. of isolates tested) and antimicrobial agent ^a	MIC ₅₀	MIC ₉₀	% susceptible ^b	% resistant ^b
All isolates (1,971)				
Ceftolozane/tazobactam	0.5	2	— ^c	—
Ceftazidime	2	32	82.9	13.7
Cefepime	4	16	82.4	8.6
Meropenem	0.5	8	80.3	13.9
Piperacillin-tazobactam	8	>64	76.8	13.7
Aztreonam	8	>16	68.5	19.2
Levofloxacin	0.5	>4	74.9	19.1
Gentamicin	≤1	8	89.2	7.7
Colistin	1	2	99.1	0.2
MDR (310)				
Ceftolozane/tazobactam	2	8	—	—
Ceftazidime	32	>32	22.6	60.6
Cefepime	16	>16	22.5	38.7
Meropenem	8	>8	19.4	64.5
Piperacillin-tazobactam	>64	>64	11.0	60.0
Aztreonam	>16	>16	9.0	69.0
Levofloxacin	>4	>4	15.2	70.6
Gentamicin	4	>8	53.5	36.5
Colistin	1	2	98.4	0.3
XDR (175)				
Ceftolozane/tazobactam	4	16	—	—
Ceftazidime	32	>32	9.1	73.7
Cefepime	>16	>16	10.9	52.0
Meropenem	8	>8	7.4	76.0
Piperacillin-tazobactam	>64	>64	2.3	74.9
Aztreonam	>16	>16	4.6	72.6
Levofloxacin	>4	>4	2.9	88.0
Gentamicin	8	>8	38.9	49.7
Colistin	1	2	97.7	0.6

^a Abbreviations: MDR, multidrug resistant; XDR, extensively drug resistant (14).

^b According to CLSI interpretive criteria (13).

^c —, no published interpretive criteria.

TABLE 2 Antimicrobial activity of ceftolozane/tazobactam and various comparator agents against *Enterobacteriaceae* collected in the U.S. during 2011 to 2012

Organism(s) and antimicrobial agent ^a (no. tested)	MIC ₅₀	MIC ₉₀	% susceptible ^b	% resistant ^b
<i>Enterobacteriaceae</i> —all isolates (7,071)				
Ceftolozane/tazobactam	0.25	1	— ^c	—
Ceftazidime	0.12	16	88.1	10.5
Ceftriaxone	≤0.06	>8	85.2	13.8
Cefepime	≤0.5	1	94.0	5.0
Meropenem	≤0.06	≤0.06	98.0	1.8
Piperacillin-tazobactam	2	16	90.9	5.8
Aztreonam	≤0.12	16	88.0	10.5
Levofloxacin	≤0.12	>4	81.9	16.1
Gentamicin	≤1	4	90.7	8.2
Tigecycline ^d	0.25	1	98.2	0.1
Colistin	0.5	>4	—	—

Organism(s) and antimicrobial agent ^a (no. tested)	MIC ₅₀	MIC ₉₀	% susceptible ^b	% resistant ^b
<i>Enterobacteriaceae</i> —XDR (86)				
Ceftolozane/tazobactam	>32	>32	—	—
Ceftazidime	>32	>32	2.3	96.5
Ceftriaxone	>8	>8	0.0	100.0
Cefepime	>16	>16	15.1	73.3
Meropenem	>8	>8	22.1	70.9
Piperacillin-tazobactam	>64	>64	2.3	81.4
Aztreonam	>16	>16	3.5	93.0
Levofloxacin	>4	>4	0.0	93.0
Gentamicin	>8	>8	20.9	61.6
Tigecycline ^d	0.5	4	87.1	0.0
Colistin	>4	>4	—	—
<i>E. coli</i> , ESBL phenotype (327)				
Ceftolozane/tazobactam	0.5	4	—	—
Ceftazidime	16	>32	31.8	55.7
Ceftriaxone	>8	>8	8.3	90.2
Cefepime	16	>16	44.5	48.8
Meropenem	≤0.06	>8	97.6	1.5
Piperacillin-tazobactam	8	>64	77.4	13.5
Aztreonam	>16	>16	23.2	63.9
Levofloxacin	>4	>4	22.6	75.5
Gentamicin	2	>8	63.0	36.7
Tigecycline ^d	0.12	0.25	100.0	0.0
Colistin	≤0.25	0.5	—	—
<i>K. pneumoniae</i> , ESBL phenotype (244)				
Ceftolozane/tazobactam	32	>32	—	—
Ceftriaxone	>8	>8	5.3	93.4
Cefepime	>16	>16	27.9	60.7
Meropenem	≤0.06	>8	59.0	39.8
Piperacillin-tazobactam	>64	>64	25.4	65.2
Aztreonam	>16	>16	7.8	91.0
Levofloxacin	>4	>4	20.1	76.6
Gentamicin	4	>8	50.8	39.8
Tigecycline ^d	0.5	2	97.1	0.0
Colistin	0.5	>4	—	—

FOSFOMYCIN

Parameter	Description
a.k.a.	Monurol
Indication	Uncomplicated UTI in women caused by <i>Escherichia coli</i> and <i>Enterococcus faecalis</i>
Mechanism of action	<ol style="list-style-type: none">Inactivation of enolpyruval transferase, irreversibly blocking condensation of uridine diphosphate-N-acetylglucosamine with p-enolpyruvate (initial step in cell wall synthesis)Reduce adherence of bacteria to uroepithelial cells
Activity rendered	Cidal
Route of administration	PO (in US)
Distribution	Kidney, bladder wall, prostate, seminal vesicles
Half-life	5.7h (single 3 g packet)
Excretion	Renal > biliary

FOSFOMYCIN

Parameter	Description
Spectrum of activity	<p data-bbox="1037 472 1754 529"><i>Enterobacteriaceae (E. coli)</i></p> <p data-bbox="993 579 1798 636"><i>Enterococcus spp. (E. faecium)</i></p> <p data-bbox="907 686 1884 808">Claim activity versus ESBL-producing <i>Enterobacteriaceae</i></p> <p data-bbox="1058 865 1733 922">Claim activity versus CRE</p>
Adverse effects	Diarrhea

FOSFOMYCIN

Organism	Method	Adopted	Testing/ Reporting	Breakpoint Range	Caveat(s)
<i>E. coli</i>	agar diln	< 2010	supplemental	full	UTI only; DD needs glucose-6-phosphate
<i>E. coli</i>	DD	< 2010	supplemental	full	
<i>E. faecalis</i>	agar diln	< 2010	supplemental	full	UTI only; DD needs glucose-6-phosphate
<i>E. faecalis</i>	DD	< 2010	supplemental	full	

FOSFOMYCIN

Infect Dis Ther (2017) 6:233–243
DOI 10.1007/s40121-017-0150-5



ORIGINAL RESEARCH

Fosfomycin and Comparator Activity Against Select Enterobacteriaceae, *Pseudomonas*, and *Enterococcus* Urinary Tract Infection Isolates from the United States in 2012

Tiffany R. Keepers · Marcela Gomez · Chris Celeri · Kevin M. Krause · Donald Biek · Ian Critchley

CLSI *Enterobacteriaceae*
and *Enterococcus*

≤ 64 S

128 I

≥ 256 R

	MIC ₅₀	MIC ₉₀	Range	S (%)	I (%)	R (%)
<i>E. coli</i> ESBL-phenotype (<i>n</i> = 76)						
Fosfomycin	1	4	≤0.25 to >256	98.7	0.0	1.3
Ciprofloxacin	>32	>32	0.016 to >32	28.9	0.0	71.1
Levofloxacin	16	32	0.03 to >32	28.9	1.3	69.7
Nitrofurantoin	16	64	8 to 128	82.9	9.2	7.9
SXT	>32	>32	0.06 to >32	43.4	–	56.6
<i>Klebsiella</i> spp.: ESBL-phenotype (<i>n</i> = 65) ^c ← CAREFUL						
Fosfomycin	8	128	1 to >256	–	–	–
Ciprofloxacin	32	>32	0.016 to >32	21.5	4.6	73.8
Levofloxacin	16	>32	0.016 to >32	26.2	1.5	72.3
Nitrofurantoin	128	128	16 to >256	4.6	26.2	69.2

MIC range for five isolates of VRE (*E. faecalis*): 32-64

FOSFOMYCIN

Infection and Drug Resistance

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ORIGINAL RESEARCH

Frequency of colistin and fosfomycin resistance in carbapenem-resistant Enterobacteriaceae from a tertiary care hospital in Karachi

Location	n	% R	Reference
Greece	79	5.1	Int. J. Antimicrob. Agents 35 : 240-243; 2010
US	68	7.4	Antimicrob. Agents Chemother. 54 : 526-529; 2010
Germany	107	19.6	J. Clin. Microbiol. 52 : 1893-1897; 2014
Pakistan	251	12.3	Infect. Drug Resist. 10 : 231-236; 2017

FOSFOMYCIN RESISTANCE

- Mutations in transporter genes (decreased entry)
- Modification of MurA target (rare)

DISPATCHES

Emergence of Plasmid-Mediated Fosfomycin-Resistance Genes among *Escherichia coli* Isolates, France

Yahia Benzerara, Salah Gallah,
Baptiste Hommeril, Nathalie Genel,
Dominique Decré, Martin Rottman,
Guillaume Arlet

FosA, a glutathione *S*-transferase that inactivates fosfomycin, has been reported as the cause of enzymatic resistance to fosfomycin. We show that multiple lineages of FosA-producing extended spectrum β -lactamase *Escherichia coli* have circulated in France since 2012, potentially reducing the efficacy of fosfomycin in treating infections with antimicrobial drug-resistant gram-negative bacilli.

Addition of glutathione residue to fosfomycin (via glutathione *S*-transferase) inactivates fosfomycin; **plasmid-mediated**



Emerg. Infect. Dis. **23**: 1564-1567; 2017

CEFTAROLINE

Parameter	Description
a.k.a.	Teflaro
Indication	<ol style="list-style-type: none">1. Acute bacterial skin and skin structure infection2. Community-acquired bacterial pneumonia
Mechanism of action	<ol style="list-style-type: none">1. Bind to bacterial penicillin-binding proteins (PBP), interfering with cell wall synthesis2. Can bind PBP-2a of MRSA
Activity rendered	Cidal
Route of administration	IV
Half-life	2.66 h → q12h
Excretion	Renal

CEFTAROLINE

Parameter	Description
Spectrum of activity	<p><i>Staphylococcus aureus</i> (including MRSA)</p> <p>β-hemolytic streptococci groups A, B</p> <p><i>Streptococcus pneumoniae</i></p> <p><i>Haemophilus influenzae</i></p> <p><i>Enterobacteriaceae</i> (<i>E. coli</i>, <i>Klebsiella</i> spp.)</p> <p>NOT ESBL</p>
Adverse effects	<p>Hypersensitivity in cephem-allergic patients</p> <p><i>C. difficile</i> infection</p> <p>Direct Coomb's test seroconversion</p>

CEFTAROLINE

Organism	Method	Adopted	Testing/ Reporting	Breakpoint Range	Caveat(s)
<i>Enterobacteriaceae</i>	BMD, DD	2013	supplemental	full	
<i>Staphylococcus</i>	BMD, DD	2013	optional	full	only <i>S. aureus</i>
<i>Haemophilus</i>	BMD, DD	2013	supplemental	only suscept	only <i>H. influenzae</i>
<i>S. pneumoniae</i>	BMD, DD	2013	supplemental	only suscept	
β - <i>Streptococcus</i>	BMD, DD	2013	supplemental	only suscept	



Antimicrobial Susceptibility Trends among *Staphylococcus aureus* Isolates from U.S. Hospitals: Results from 7 Years of the Ceftaroline (AWARE) Surveillance Program, 2010 to 2016

Helio S. Sader, Rodrigo E. Mendes, Jennifer M. Streit, Robert K. Flamm
JMI Laboratories, North Liberty, Iowa, USA

TABLE 2 *Staphylococcus aureus* antimicrobial susceptibilities stratified by year (2010–2016)

Organism	Yr (no. isolates)	% Susceptible ^a						
		Ceftaroline	Oxacillin	Erythromycin	Clindamycin	Levofloxacin	Tetracycline	TMP-SMX ^b
<i>S. aureus</i>	2010 (1,364)	99.4	50.0	40.2	83.7	62.0	95.3	98.5
	2011 (1,370)	98.9	50.7	39.5	84.4	61.5	95.5	98.5
	2012 (4,131)	98.9	53.6	38.7	85.3	64.0	95.2	98.8
	2013 (4,123)	98.8	50.7	38.5	84.9	61.5	95.7	98.7
	2014 (3,026)	98.1	55.3	42.8	84.9	64.0	94.9	98.9
	2015 (3,506)	98.7	56.4	41.9	84.8	63.9	95.0	98.6
	2016 (3,536)	98.6	57.8	44.1	85.0	63.7	96.4	98.5
MSSA	2010 (682)	100.0	100.0	68.3	94.1	88.6	95.3	99.3
	2011 (695)	100.0	100.0	67.8	95.7	89.8	96.3	98.8
	2012 (2,214)	100.0	100.0	63.2	94.4	89.2	95.6	99.5
	2013 (2,092)	100.0	100.0	65.9	95.1	88.5	96.0	99.7
	2014 (1,673)	100.0	100.0	67.9	95.1	89.8	95.7	99.4
	2015 (1,978)	100.0	100.0	64.4	94.9	89.1	96.7	99.6
	2016 (2,043)	100.0	100.0	67.7	95.8	89.3	96.9	99.7
MRSA	2010 (682)	98.8	0.0	12.0	73.2	35.3	95.3	97.8
	2011 (675)	97.8	0.0	10.4	72.7	32.4	94.7	98.1
	2012 (1,917)	97.7	0.0	10.3	74.8	34.9	94.7	98.0
	2013 (2,031)	97.6	0.0	10.5	74.4	33.6	95.5	97.6
	2014 (1,353)	95.6	0.0	11.8	72.3	32.2	93.8	98.3
	2015 (1,528)	97.0	0.0	12.7	71.8	31.3	92.8	97.3
	2016 (1,493)	96.7	0.0	11.9	70.3	28.6	95.7	96.9

^aUsing breakpoints published by CLS (12).

^bTMP-SMX, trimethoprim-sulfamethoxazole.

TELAVANCIN

Parameter	Description
a.k.a.	VIBATIV
Indication	<ol style="list-style-type: none">1. Complicated skin and skin structure infections2. Hospital-acquired and ventilator-associated bacterial pneumonia caused by <i>S. aureus</i>
Mechanism of action	lipoglycopeptide (synthetic derivative of vancomycin) Binds to late-stage peptidoglycan precursors (including lipid II) Binds to bacterial membrane, disrupting membrane barrier function
Activity rendered	Cidal
Route of administration	IV infusion
Half-life	8 hr → q24h
Excretion	Renal

TELAVANCIN

Parameter	Description
Spectrum of activity	<p><i>Staphylococcus aureus</i> (MRSA and MSSA)</p> <p><i>Streptococcus pyogenes</i></p> <p><i>Streptococcus agalactiae</i></p> <p><i>Streptococcus anginosus</i> group</p> <p><i>Enterococcus faecalis</i> (vancomycin-susceptible)</p>
Adverse effects	<p>Hypersensitivity</p> <p>Diarrhea</p> <p>Interferes with laboratory coagulation testing</p>

TELAVANCIN

Organism	Method	Adopted	Testing/ Reporting	Breakpoint Range	Caveat(s)
<i>Staphylococcus</i>	BMD	2016	supplemental	only suscept	only <i>S. aureus</i>
<i>Enterococcus</i>	BMD	2016	supplemental	only suscept	only vancomycin susceptible <i>E. faecalis</i>
β - <i>Streptococcus</i>	BMD	2016	supplemental	only suscept	all β - <i>Streptococcus</i>
Viridans <i>Strep.</i>	BMD	2016	supplemental	only suscept	all viridans group <i>Streptococcus</i>

Telavancin *In Vitro* Activity against a Collection of Methicillin-Resistant *Staphylococcus aureus* Isolates, Including Resistant Subsets, from the United States

Rodrigo E. Mendes, Helio S. Sader, Robert K. Flamm, David J. Farrell, Ronald N. Jones
JMI Laboratories, North Liberty, Iowa, USA

TABLE 1 Antimicrobial activity and MIC distribution for telavancin against a contemporary (2011 to 2013) U.S. collection of *S. aureus* clinical isolates using a recently approved and revised susceptibility testing method

<i>S. aureus</i> category ^a (no. of isolates tested)	MIC ($\mu\text{g/ml}$)		No. (cumulative %) of isolates inhibited by telavancin at indicated MIC ($\mu\text{g/ml}$) ^b			
	50%	90%	≤ 0.015	0.03	0.06	0.12
All (9,610)	0.03	0.06	364 (3.8)	6,210 (68.4)	3,012 (99.8)	24 (100.0)
MSSA (4,959)	0.03	0.06	242 (4.9)	3,272 (70.9)	1,437 (99.8)	8 (100.0)
MRSA (4,651)	0.03	0.06	122 (2.6)	2,938 (65.8)	1,575 (99.7)	16 (100.0)
Vancomycin MIC, $\leq 1 \mu\text{g/ml}$ (4,561)	0.03	0.06	119 (2.6)	2,930 (66.8)	1,502 (99.8)	10 (100.0)
→ Vancomycin MIC, 2–4 $\mu\text{g/ml}$ (90)	0.06	0.06	3 (3.3)	8 (12.2)	73 (93.3)	6 (100.0)
Daptomycin MIC, $\leq 0.5 \mu\text{g/ml}$ (4,607)	0.03	0.06	122 (2.6)	2,928 (66.2)	1,545 (99.7)	12 (100.0)
Daptomycin MIC, 1–2 $\mu\text{g/ml}$ (43)	0.06	0.06	0 (0.0)	9 (20.9)	30 (90.7)	4 (100.0)
MDR (1,371)	0.03	0.06	37 (2.7)	749 (57.3)	574 (99.2)	11 (100.0)
Non-MDR (3,280)	0.03	0.06	85 (2.6)	2,189 (69.3)	1,001 (99.8)	5 (100.0)

^a MSSA, methicillin-susceptible *S. aureus*; MRSA, methicillin-resistant *S. aureus*; MDR, multidrug resistant.

^b Data representing modal MICs are shown in bold.

DALBAVANCIN

Parameter	Description
a.k.a.	DALVANCE
Indication	natural lipoglycopeptide Bacterial skin and skin structure infections caused by designated Gram-positive organisms
Mechanism of action	binds to D-alanyl-D-alanine terminus of stem pentapeptide in nascent cell wall peptidoglycan, preventing cross-linking of cell wall
Activity rendered	Cidal
Route of administration	IV infusion
Half-life	346 h → single dose (or two doses over 7d)
Excretion	Renal and biliary

DALBAVANCIN

Parameter	Description
Spectrum of activity	<p><i>Staphylococcus aureus</i> (MRSA and MSSA)</p> <p><i>Streptococcus pyogenes</i></p> <p><i>Streptococcus agalactiae</i></p> <p><i>Streptococcus dysgalactiae</i></p> <p><i>Streptococcus anginosus</i> group</p> <p><i>Enterococcus faecalis</i> (vancomycin-susceptible)</p>
Adverse effects	<p>Elevated serum transaminase levels</p> <p>Hypersensitivity reactions</p> <p>Nausea</p> <p><i>C. difficile</i> diarrhea</p>

DALBAVANCIN

Organism	Method	Adopted	Testing/ Reporting	Breakpoint Range	Caveat(s)
<i>Staphylococcus</i>	BMD	2018	supplemental	only suscept	only <i>S. aureus</i>
<i>Enterococcus</i>	BMD	2018	supplemental	only suscept	only vancomycin susceptible <i>E. faecalis</i>
β - <i>Streptococcus</i>	BMD	2018	supplemental	only suscept	only <i>S. pyogenes</i> , <i>S. agalactiae</i> , <i>S. dysgalactiae</i>
Viridans <i>Strep.</i>	BMD	2018	supplemental	only suscept	only <i>S. anginosus</i> group

TABLE 1. Activities of dalbavancin and comparator agents against 81,673 gram-positive cocci isolated from 33 countries worldwide

Organism or group and susceptibility subset (no. tested)	Antimicrobial agent	MIC ($\mu\text{g/ml}$)			% Susceptible ^a	% Resistant ^b
		50%	90%	Range		
<i>S. aureus</i>						
Oxacillin susceptible (27,052)	Dalbavancin	0.06	0.06	$\leq 0.03-0.25$	100.0	—
	Vancomycin	1	1	$\leq 0.12-4$	>99.9	0.0
	Erythromycin	≤ 0.25	>2	$\leq 0.25->2$	78.7	20.7
	Clindamycin	≤ 0.25	≤ 0.25	$\leq 0.25->2$	95.8	4.0
	Levofloxacin	≤ 0.5	≤ 0.5	$\leq 0.5->4$	92.8	6.7
	Gentamicin	≤ 2	≤ 2	$\leq 2->8$	97.1	2.6
	Tetracycline	≤ 4	≤ 4	$\leq 4->8$	93.7	5.8
	Linezolid	2	2	0.12-4	100.0	—
Oxacillin resistant (19,721)	Dalbavancin	0.06	0.06	$\leq 0.03-0.5$	>99.9	—
	Vancomycin	1	1	0.25-4	>99.9	0.0
	Erythromycin	>2	>2	$\leq 0.25->2$	10.9	88.8
	Clindamycin	>2	>2	$\leq 0.25->2$	47.8	52.1
	Levofloxacin	>4	>4	$\leq 0.5->4$	18.3	80.1
	Gentamicin	≤ 2	>8	$\leq 2->8$	74.1	24.8
	Tetracycline	≤ 4	>8	$\leq 4->8$	81.1	18.4
	Linezolid	1	2	$\leq 0.25->8$	>99.9	0.04
<i>E. faecalis</i>						
Vancomycin susceptible (10,025)	Dalbavancin	≤ 0.03	0.06	$\leq 0.03-0.5$	>99.9	—
	Ampicillin	≤ 2	≤ 2	$\leq 2->16$	99.6	0.2
	Ciprofloxacin	1	>4	0.06->4	62.2	33.6
	Gentamicin (HL) ^c	≤ 500	>1000	$\leq 500->1000$	68.5	31.5
	Linezolid	1	2	$\leq 0.25->8$	99.8	0.1
Vancomycin nonsusceptible (349)	Dalbavancin	>4	>4	$\leq 0.03->4$	27.8	—
	Ampicillin	≤ 2	4	$\leq 2->16$	96.0	4.0
	Ciprofloxacin	>4	>4	0.5->4	3.7	96.3
	Gentamicin (HL)	>1000	>1000	$\leq 500->1000$	28.4	71.6
	Linezolid	1	2	0.25->8	98.6	1.4
<i>E. faecium</i>						
Vancomycin susceptible (2,578)	Dalbavancin	0.06	0.12	$\leq 0.03-2$	99.6	—
	Ampicillin	>16	>16	$\leq 2->16$	15.6	84.4
	Ciprofloxacin	>4	>4	0.06->4	8.1	83.7
	Gentamicin (HL)	≤ 500	>1000	$\leq 500->1000$	61.8	38.2
	Linezolid	1	2	$\leq 0.25->8$	99.6	0.3
Vancomycin nonsusceptible (2,176)	Dalbavancin	>4	>4	$\leq 0.03->4$	11.4	—
	Ampicillin	>16	>16	$\leq 2->16$	0.8	99.2
	Ciprofloxacin	>4	>4	$\leq 0.03->4$	0.7	98.3
	Gentamicin (HL)	≤ 500	>1000	$\leq 500->1000$	64.3	35.7
	Linezolid	1	2	0.5->8	97.6	1.8

In Vitro Activity of Dalbavancin against Drug-Resistant *Staphylococcus aureus* Isolates from a Global Surveillance Program

Sandra P. McCurdy,^a Ronald N. Jones,^b Rodrigo E. Mendes,^b Sallaja Puttagunta,^a Michael W. Dunne^a
 Durata Therapeutics, Branford, Connecticut, USA^a; JMI Laboratories, North Liberty, Iowa, USA^b

TABLE 1 Activity of dalbavancin and selected Gram-positive focused agents when tested against resistance phenotypes of *S. aureus* from a worldwide surveillance program, 2002 to 2012

Organism/subset (no. tested) ^a	Antimicrobial agent	MIC (μg/ml)			% susceptible ^b
		50%	90%	Range	
All <i>S. aureus</i> (62,195) MRSA (26,975)	Dalbavancin	0.06	0.06	≤0.008 to 0.5	99.7
	Dalbavancin	0.06	0.06	≤0.008 to 0.5	99.6
	Daptomycin	0.25	0.5	≤0.06 to 4	99.9
	Vancomycin	1	1	≤0.12 to 4	99.9
	Linezolid	1	2	≤0.12 to 16	99.9
	Tigecycline ^c	0.12	0.5	≤0.015 to 1	99.9
	Clindamycin	≤0.06	>2	≤0.06 to >8	60.3
Daptomycin NS (37)	Dalbavancin	0.06	0.12	≤0.03 to 0.5	91.9
	Vancomycin	2	2	1 to 4	94.6
	Linezolid	1	2	0.5 to 4	100.0
	Tigecycline	0.12	0.25	≤0.03 to 0.25	100.0
	Clindamycin	>2	>2	≤0.06 to >2	43.2
Linezolid R (19)	Dalbavancin	0.06	0.12	≤0.03 to 0.12	100.0
	Vancomycin	1	2	0.5 to 2	100.0
	Daptomycin	0.5	0.5	0.25 to 0.5	100.0
	Tigecycline	0.12	0.5	0.06 to 0.5	100.0
	Clindamycin	>2	>2	≤0.25 to >2	42.1
Tigecycline NS (38)	Dalbavancin	0.06	0.06	≤0.03 to 0.12	100.0
	Vancomycin	1	2	0.5 to 2	100.0
	Daptomycin	0.25	0.5	0.25 to 0.5	100.0
	Linezolid	2	2	1 to 2	100.0
	Clindamycin	>2	>2	≤0.06 to >2	26.3

TEDIZOLID

Parameter	Description
a.k.a.	SIVEXTRO
Indication	Acute bacterial skin and skin structure infections caused by designated susceptible organisms
Mechanism of action	oxazolidinone binds 50S ribosome subunit, inhibiting protein synthesis
Activity rendered	Static
Route of administration	IV, PO
Half-life	12h → q24
Excretion	Mostly biliary

TEDIZOLID

Parameter	Description
Spectrum of activity	<i>Staphylococcus aureus</i> (MRSA and MSSA) <i>Streptococcus pyogenes</i> <i>Streptococcus agalactiae</i> <i>Streptococcus anginosus</i> group <i>Enterococcus faecalis</i>
Adverse effects	Safety and efficacy has not been adequately established in neutropenic patients

TEDIZOLID

Organism	Method	Adopted	Testing/ Reporting	Breakpoint Range	Caveat(s)
<i>Staphylococcus</i>	BMD	2016	optional	full	only <i>S. aureus</i>
<i>Enterococcus</i>	BMD	2016	optional	only suscept	only <i>E. faecalis</i>
β - <i>Streptococcus</i>	BMD	2016	supplemental	only suscept	only <i>S. pyogenes</i> , <i>S. agalactiae</i>
Viridans <i>Strep.</i>	BMD	2016	supplemental	only suscept	only <i>S. anginosus</i> group

TABLE 2 Summary of tedizolid and linezolid activity tested against five pathogen groups (3,032 isolates) included in this study

Organism (no.)	Agent and read ^a	No. (cumulative percentage) of isolates inhibited at MIC ($\mu\text{g/ml}$):										MIC ₅₀ ($\mu\text{g/ml}$)	MIC ₉₀ ($\mu\text{g/ml}$)	
		≤ 0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4			
<i>S. aureus</i> (2,382)	Linezolid 80					2 (0.1)	17 (0.8)	668 (28.8)	1661 (98.6)	34 (100.0)			1	1
	Linezolid 100						3 (0.1)	51 (2.3)	1128 (49.6)	1166 (98.6)	34 (100.0)	2	2	
	Tedizolid 80			8 (0.3)	445 (19.0)	1807 (94.9)	122 (100.0)						0.12	0.12
	Tedizolid 100			2 (0.1)	24 (1.1)	875 (37.8)	1427 (97.7)	54 (100.0)					0.25	0.25
MSSA (1,681)	Linezolid 80						5 (0.3)	429 (25.8)	1218 (98.3)	29 (100.0)			1	1
	Linezolid 100							24 (1.4)	760 (46.6)	869 (98.3)	28 (100.0)	2	2	
	Tedizolid 80			3 (0.2)	300 (18.0)	1294 (95.0)	84 (100.0)						0.12	0.12
	Tedizolid 100				15 (0.9)	605 (36.9)	1023 (97.7)	38 (100.0)					0.25	0.25
MRSA (701)	Linezolid 80					2 (0.3)	12 (2.0)	239 (36.1)	443 (99.3)	5 (100.0)			1	1
	Linezolid 100						3 (0.4)	27 (4.3)	368 (56.8)	297 (99.1)	6 (100.0)	1	2	
	Tedizolid 80			5 (0.7)	145 (21.4)	513 (94.6)	38 (100.0)						0.12	0.12
	Tedizolid 100			2 (0.3)	9 (1.6)	270 (40.1)	404 (97.7)	16 (100.0)					0.25	0.25
<i>S. pyogenes</i> (258)	Linezolid 80							103 (39.9)	155 (100.0)				1	1
	Linezolid 100							3 (1.2)	233 (91.5)	22 (100.0)			1	1
	Tedizolid 80				52 (20.2)	203 (98.8)	3 (100.0)						0.12	0.12
	Tedizolid 100				7 (2.7)	150 (60.9)	101 (100.0)						0.12	0.25
<i>S. agalactiae</i> (145)	Linezolid 80							36 (24.8)	109 (100.0)				1	1
	Linezolid 100							2 (1.4)	136 (95.2)	7 (100.0)			1	1
	Tedizolid 80				9 (6.2)	126 (93.1)	10 (100.0)						0.12	0.12
	Tedizolid 100				1 (0.7)	69 (48.3)	74 (99.3)	1 (100.0)					0.25	0.25
<i>S. anginosus</i> group (54)	Linezolid 80					1 (1.9)	7 (14.8)	29 (68.5)	16 (98.1)	1 (100.0)			0.5	1
	Linezolid 100					1 (1.9)	4 (9.3)	10 (27.8)	35 (92.6)	4 (100.0)			1	1
	Tedizolid 80	1 (1.9)	0 (1.9)	5 (11.1)	26 (59.3)	22 (100.0)							0.06	0.12
	Tedizolid 100	1 (1.9)	0 (1.9)	2 (5.6)	12 (27.8)	30 (83.3)	9 (100.0)						0.12	0.25
<i>E. faecalis</i> (193)	Linezolid 80						1 (0.5)	31 (16.6)	140 (89.1)	20 (99.5)	1 (100.0)		1	2
	Linezolid 100						1 (0.5)	0 (0.5)	71 (37.3)	112 (95.3)	9 (100.0)		2	2
	Tedizolid 80			1 (0.5)	3 (2.1)	80 (43.5)	108 (99.5)	1 (100.0)					0.25	0.25
	Tedizolid 100				1 (0.5)	14 (17.8)	130 (75.1)	42 (96.9)	6 (100.0)				0.25	0.5



Some Future Prospects



In Vitro Antimicrobial Activity of a Siderophore Cephalosporin, S-649266, against *Enterobacteriaceae* Clinical Isolates, Including Carbapenem-Resistant Strains

Naoki Kohira,^a Joshua West,^b Akinobu Ito,^a Tsukasa Ito-Horiyama,^a Rio Nakamura,^a Takafumi Sato,^a Stephen Rittenhouse,^b Masakatsu Tsuji,^a Yoshinori Yamano^a

Discovery Research Laboratory for Core Therapeutic Areas, Shionogi & Co., Ltd., Toyonaka, Osaka, Japan^a; GlaxoSmithKline, Collegeville, Pennsylvania, USA^b

TABLE 1 MICs and resistance rates of S-649266 and other antimicrobial agents against 617 clinical isolates of *Enterobacteriaceae*^a

Species (no. of isolates)	Test compound	MIC ($\mu\text{g/ml}$)			R% ^b
		Range	MIC ₅₀	MIC ₉₀	
Total, 6 species (617)	S-649266	≤ 0.063 to >64	≤ 0.063	0.5	
	Cefepime	≤ 0.125 to >32	≤ 0.125	8	9.2
	Ceftazidime	≤ 0.125 to >32	0.25	>32	24.5
	Meropenem	≤ 0.063 to >16	≤ 0.063	0.125	2.6
	Levofloxacin	≤ 0.031 to >8	0.125	>8	13.3

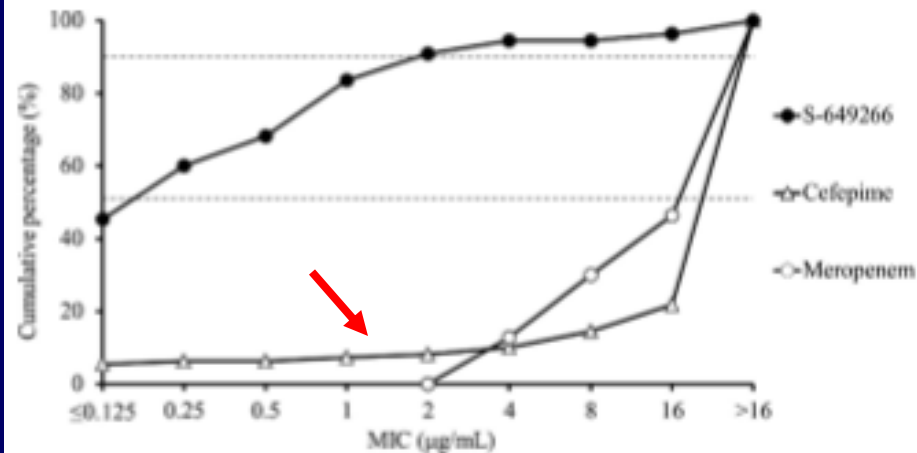


FIG 2 Cumulative percentage of MICs against meropenem-resistant carbapenemase-producing *Enterobacteriaceae*. The test strains were 110 *E. coli*, *K.*

In vitro antimicrobial activity of S-649266, a catechol-substituted siderophore cephalosporin, when tested against non-fermenting Gram-negative bacteria

Akinobu Ito^{1*}, Naoki Kohira¹, Samuel K. Bouchillon², Joshua West³, Stephen Rittenhouse³, Helio S. Sader⁴, Paul R. Rhomberg⁴, Ronald N. Jones⁴, Hidenori Yoshizawa¹, Rio Nakamura¹, Masakatsu Tsuji¹ and Yoshinori Yamano¹

¹Discovery Research Laboratory for Core Therapeutic Areas, Shionogi & Co., Ltd, Toyonaka, Osaka, Japan; ²International Health Management Associates, Inc., Schaumburg, IL 60173, USA; ³GlaxoSmithKline, Collegeville, PA 19426, USA; ⁴JMI Laboratories, North Liberty, IA 52317, USA

*Corresponding author. Tel: +81-6-6331-7144; Fax: +81-6-6331-8612; E-mail: akinobu.ito@shionogi.co.jp

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Table 1. *In vitro* activities of S-649266 against non-fermenting Gram-negative bacteria

Species (no. of strains)	Compound	MIC (mg/L)		
		range	MIC ₅₀	MIC ₉₀
<i>A. baumannii</i> (104)	S-649266 ^a	≤0.063–4	0.125	2
	ceftazidime	2 to >32	>32	>32
	meropenem	≤0.063 to >16	>16	>16
	levofloxacin	≤0.031 to >8	>8	>8
	cefepime	≤0.125 to >32	32	>32
<i>P. aeruginosa</i> (104)	S-649266 ^b	≤0.063–4	≤0.063	1
	ceftazidime	0.25 to >32	4	>32
	meropenem	≤0.063 to >16	0.5	>16
	levofloxacin	0.063 to >8	1	>8
	cefepime	≤0.125 to >32	4	32
<i>S. maltophilia</i> (108)	S-649266 ^b	≤0.063–4	0.125	0.5
	ceftazidime	0.5 to >32	32	>32
	meropenem	1 to >16	>16	>16
	levofloxacin	0.125 to >8	1	8
	cefepime	0.5 to >32	32	>32

^aISB supplemented with 20 μmol/L apo-transferrin was used.

^bCAMHB supplemented with 20 μmol/L apo-transferrin was used.

A. baumannii

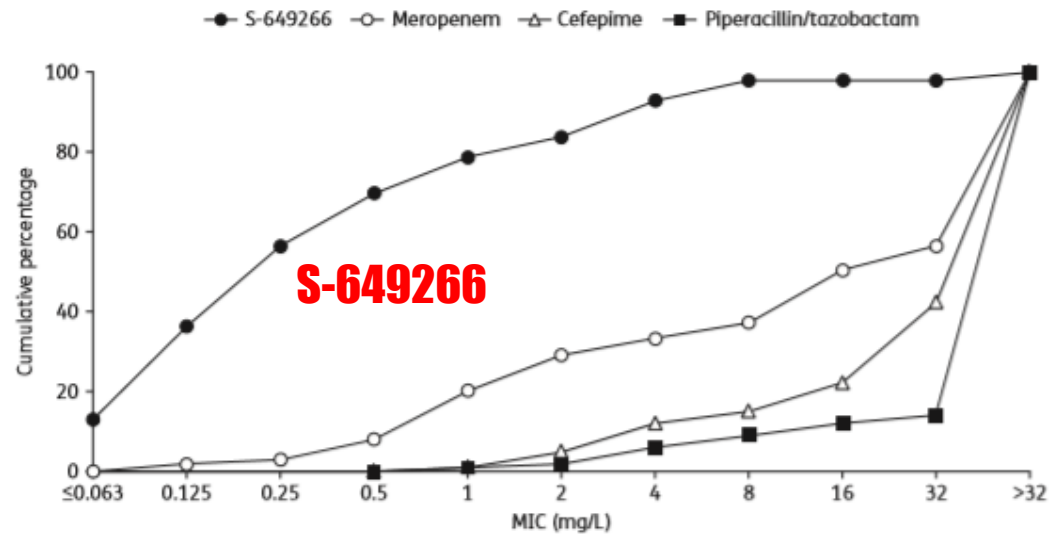


Figure 2. Cumulative MIC distribution of S-649266 for drug-resistant *A. baumannii* determined in ISB supplemented with apo-T. MICs of meropenem, cefepime and piperacillin/tazobactam were determined in CAMHB.

P. aeruginosa

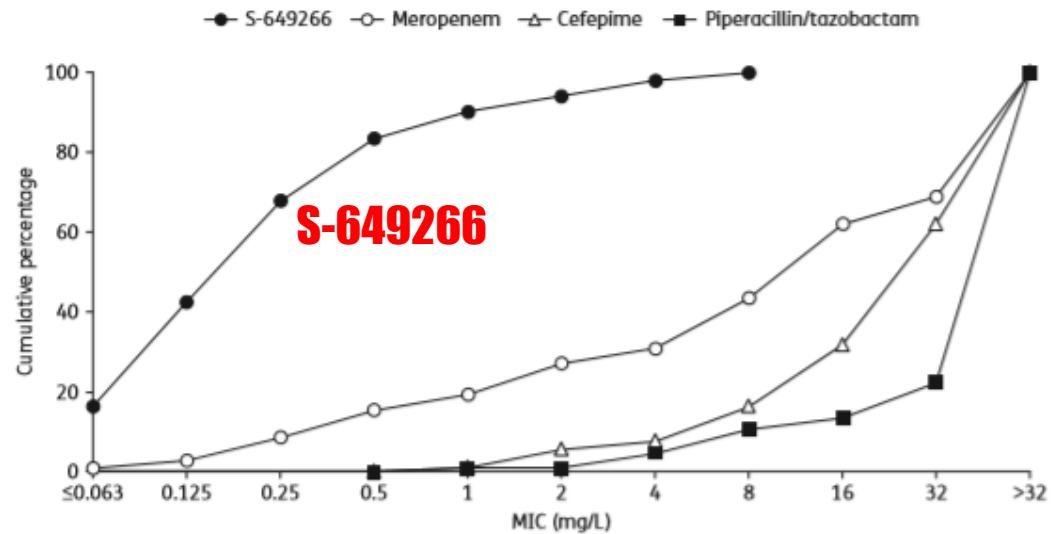


Figure 3. Cumulative MIC distribution of S-649266 for drug-resistant *P. aeruginosa* determined in CAMHB supplemented with apo-T. MICs of meropenem, cefepime and piperacillin/tazobactam were determined in CAMHB.



In Vitro Activity of the Siderophore Cephalosporin, Cefiderocol, against a Recent Collection of Clinically Relevant Gram-Negative Bacilli from North America and Europe, Including Carbapenem-Nonsusceptible Isolates (SIDERO-WT-2014 Study)

Meredith A. Hackel,^a Masakatsu Tsuji,^b Yoshinori Yamano,^c Roger Echols,^d James A. Karlowsky,^e Daniel F. Sahn^a

International Health Management Associates, Inc., Schaumburg, Illinois, USA^a; Drug Discovery & Disease Research Laboratory, Shionogi & Co., Ltd., Osaka, Japan^b; Pharmaceutical Research Division, Shionogi & Co., Ltd., Osaka, Japan^c; Clinical Development and Medical Affairs, ID3C, LLC, Easton, Connecticut, USA^d; Department of Medical Microbiology, College of Medicine, University of Manitoba, Winnipeg, Manitoba, Canada^e

carbapenem-NS *Enterobacteriaceae*

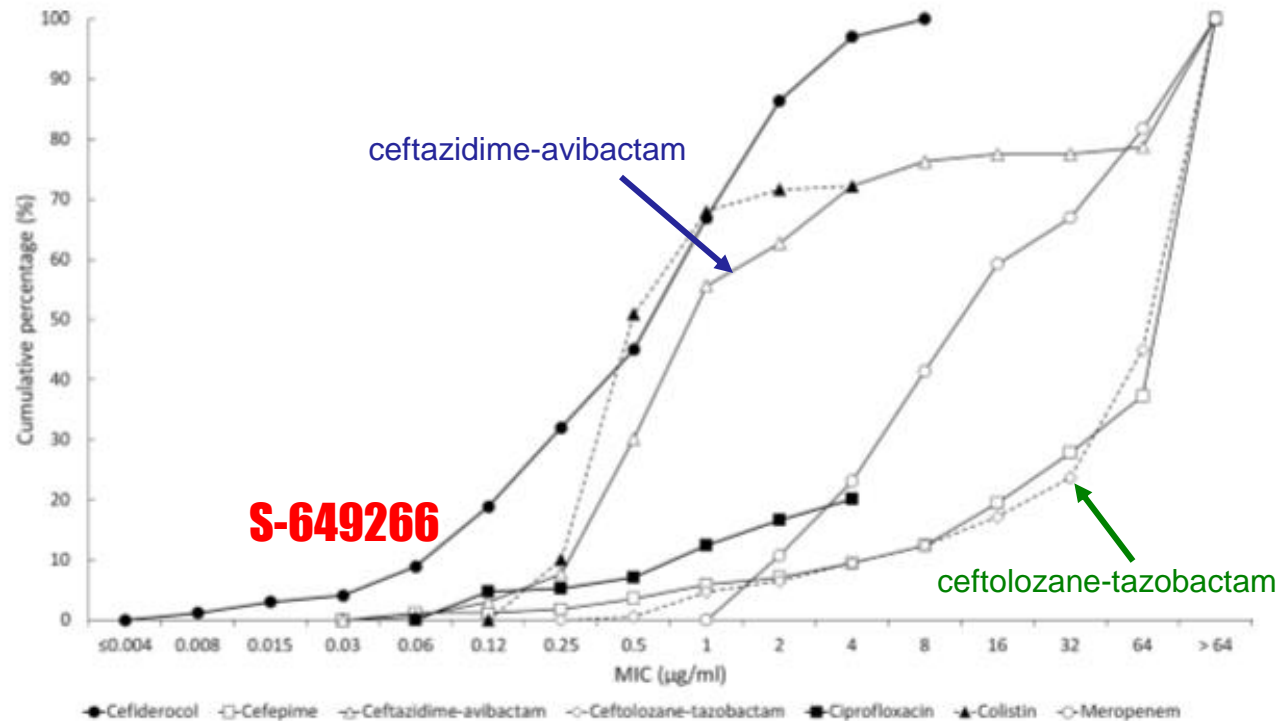


FIG 3 Cumulative MIC susceptibility curves for cefiderocol and comparators against 169 meropenem nonsusceptible *Enterobacteriaceae* from North American and European medical center laboratories. For colistin and ciprofloxacin, the endpoint of their respective cumulative MIC susceptibility curves represents the highest concentration tested. The remaining tested isolates had MICs higher than their endpoint value.

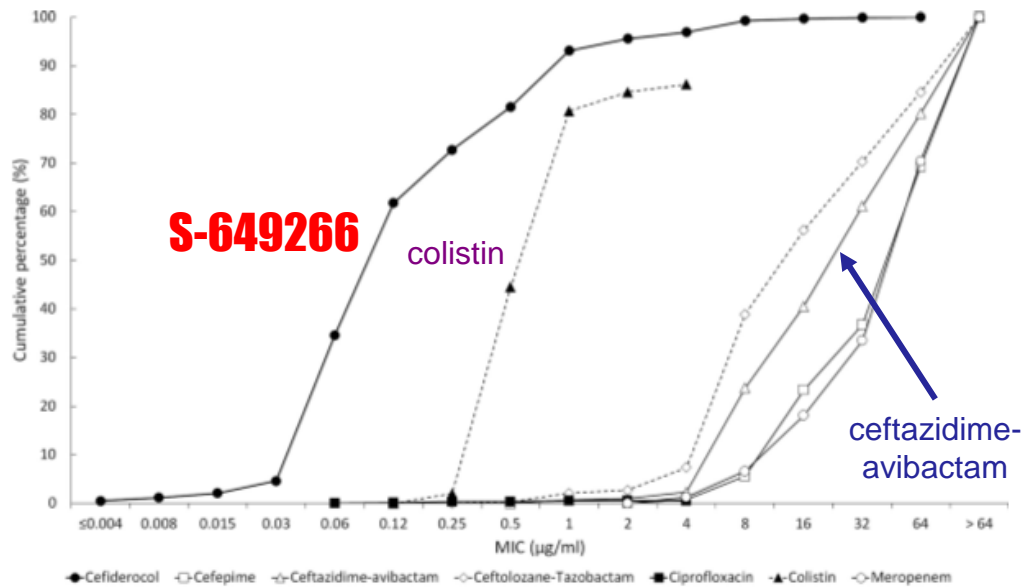


FIG 5 Cumulative MIC susceptibility curves for cefiderocol and comparators against 768 meropenem-nonsusceptible *A. baumannii* isolates from European and North American medical center laboratories. For colistin and ciprofloxacin, the endpoint of their respective cumulative MIC susceptibility curves represents the highest concentration tested. The remaining tested isolates had MICs higher than their endpoint value.

A. baumannii

P. aeruginosa

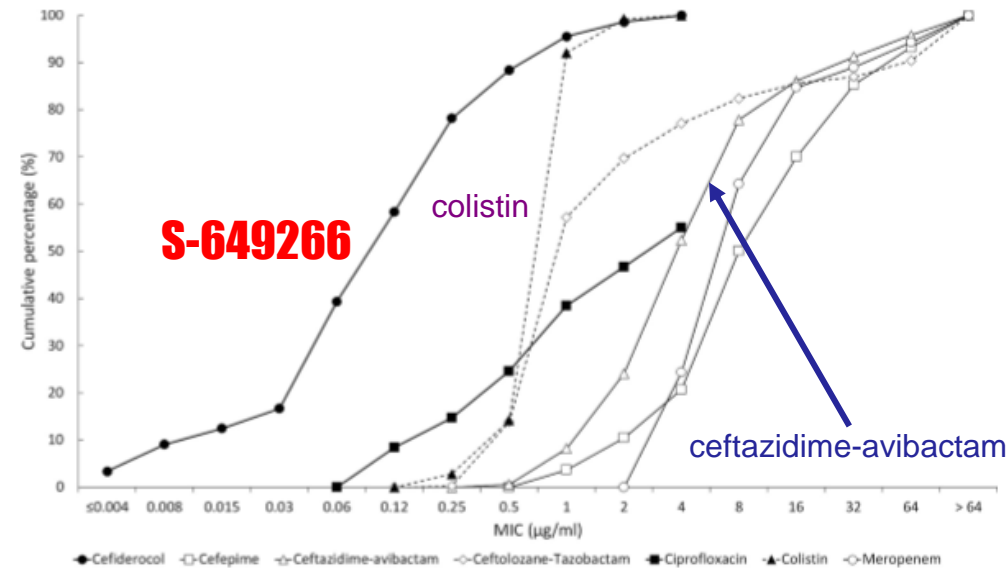


FIG 4 Cumulative MIC susceptibility curves for cefiderocol and comparators against 353 meropenem-nonsusceptible *P. aeruginosa* isolates from North American and European medical center laboratories. For colistin and ciprofloxacin, the endpoint of their respective cumulative MIC susceptibility curves represents the highest concentration tested. The remaining tested isolates had MICs higher than their endpoint value.



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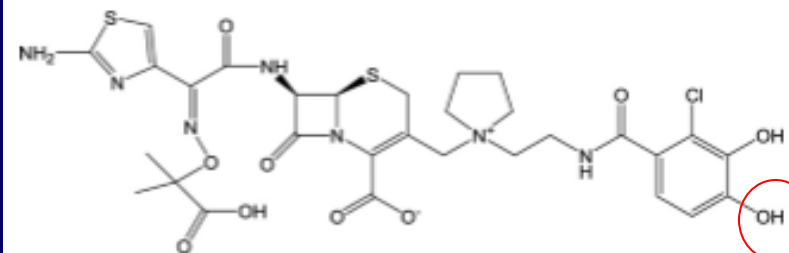


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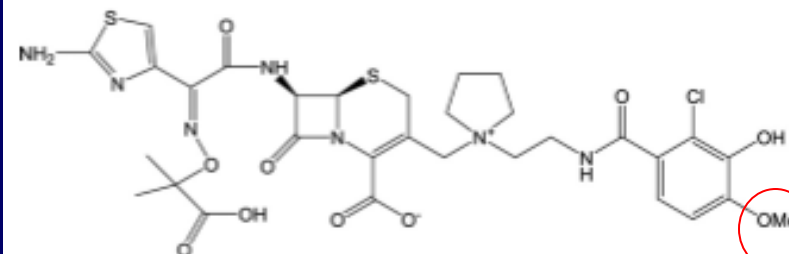
Siderophore Cephalosporin Cefiderocol Utilizes Ferric Iron Transporter Systems for Antibacterial Activity against *Pseudomonas aeruginosa*

Akinobu Ito, Toru Nishikawa,  Shuhei Matsumoto, Hidenori Yoshizawa, Takafumi Sato, Rio Nakamura, Masakatsu Tsuji, Yoshinori Yamano

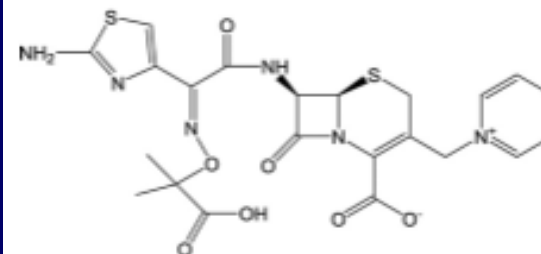
Drug Discovery and Disease Research Laboratory, Shionogi & Co., Ltd., Osaka, Japan



(A) Cefiderocol



(B) Cefiderocol catechol 3-methoxy

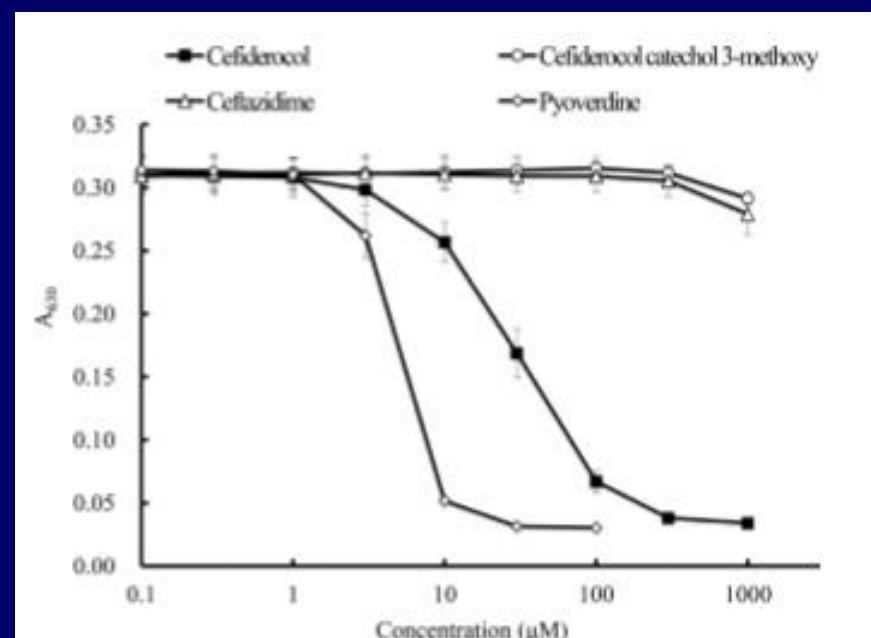
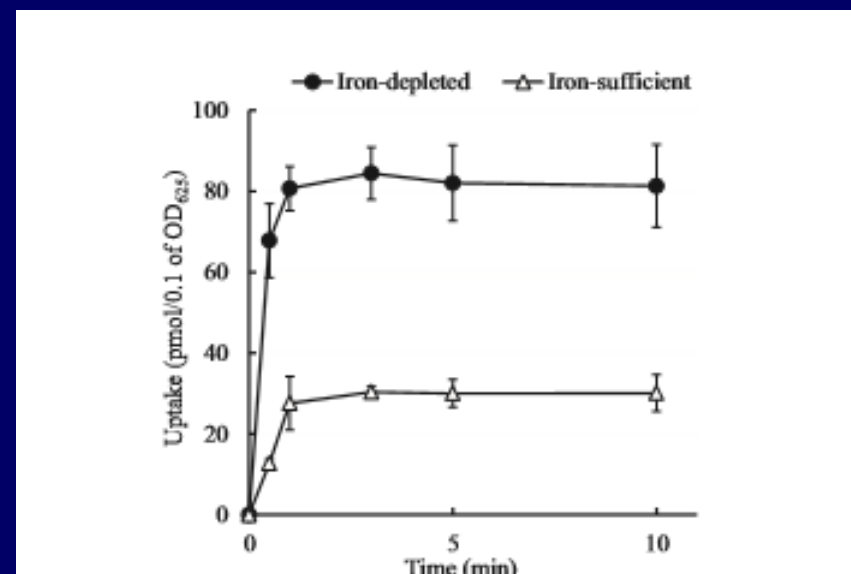


(C) Ceftazidime

TABLE 1 MICs of cefiderocol, cefiderocol catechol 3-methoxy, and ceftazidime against *P. aeruginosa* PAO1 in CAMHB and ID-CAMHB supplemented with a range of ferric iron concentrations

Medium and iron addition (mg/liter) ^a	Total iron (mg/liter)	MIC ($\mu\text{g/ml}$)		
		Cefiderocol	Cefiderocol catechol 3-methoxy	Ceftazidime
CAMHB				
0	0.2	0.125	8	0.5
ID-CAMHB				
0	0.02	0.031	8	0.5
0.01	0.03	0.063	4	0.5
0.03	0.05	0.063	8	0.5
0.05	0.07	0.063	8	1
0.1	0.12	0.125	8	1
0.3	0.32	0.25	8	1
0.5	0.52	0.5	8	1
1	1.02	0.5	8	1
10	10.02	1	8	1

^a CAMHB, cation-adjusted Mueller-Hinton broth; ID-CAMHB, iron-depleted CAMHB.





In Vitro Activity of Meropenem-Vaborbactam against Clinical Isolates of KPC-Positive *Enterobacteriaceae*

Meredith A. Hackel,^a Olga Lomovskaya,^b Michael N. Dudley,^b James A. Karlowsky,^c Daniel F. Sahn^a

^aInternational Health Management Associates, Inc., Schaumburg, Illinois, USA

^bThe Medicines Company, San Diego, California, USA


^cDepartment of Medical Microbiology and Infectious Diseases, College of Medicine, University of Manitoba, Winnipeg, Manitoba, Canada

TABLE 1 *In vitro* activities of meropenem-vaborbactam and comparator agents against 991 clinical isolates of KPC-positive *Enterobacteriaceae*

Family, genus, or species ^a (no. of isolates)	Antimicrobial agent(s)	MIC ^b (μg/ml)			% of isolates with the following MIC Interpretation ^c :		
		Range	50%	90%	Susceptible	Intermediate	Resistant
All <i>Enterobacteriaceae</i> ^d (991)	Meropenem-vaborbactam	≤0.03 to >32	0.06	1	99.0	0.6	0.4
	Meropenem	2 to >32	32	>32	0	4.1	95.9
	Ceftazidime-avibactam	≤0.06 to >64	1	4	98.2		1.8
	Ceftazidime	1 to >64	>64	>64	3.0	2.5	94.5
	Tigecycline	≤0.06 to 8	1	2	95.8	3.6	0.6
	Minocycline	0.5 to >64	8	32	44.5	30.4	25.1
	Gentamicin	≤0.06 to >64	1	>64	63.4	6.3	30.4
	Polymyxin B	0.25 to >16	0.5	16	NA	NA	NA

ONE PERSON'S SCORECARD

Agent	ESBL	CRE	<i>Pseudomonas</i>	MRSA	VRE
polymyxins	watch out		✓	-	-
ceftazidime-avibactam	✓	✓	✓	-	-
ceftolozane-tazobactam	✓	-	✓	-	-
fosfomicin	✓	careful	careful	-	careful
ceftaroline	-	-	-	✓	-
telavancin	-	-	-	✓	-
dalbavancin	-	-	-	✓	-
tedizolid	-	-	-	✓	hedging



Hole	Slope & Rating	1	2	3	4	5	6	7	8	9	Out	10	11	12	13	14	15	16	17	18	In	Tot	Handicap	Net Score
Blue Tees 69.5/123		360	376	359	319	215	516	390	165	566	3260	440	203	399	167	526	327	185	531	434	3212	6478		
White Tees 67.0/117		333	339	348	280	135	500	373	133	533	2974	420	184	343	129	491	305	161	510	383	2926	5900		
Yellow Tees 68.6/116		303	296	298	261	110	449	336	93	461	2607	390	163	306	90	460	271	134	474	340	2628	5235		
Handicap		15	11	13	17	5	3	1	9	7		2	10	8	18	14	12	6	16	4				
Players Initials																								
Kris		5	4	4	4	6	4	4	4	4		4	3	4	3	6	4	3	6	5				
Erik		7	7	6	4	5	7	6	6	8		7	7	9	8	I	M	D	O	N	E			
+/-																								
Par		4	4	4	4	3	5	4	3	5	36	4	3	4	3	5	4	3	5	4	3	5	71	