# 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.

1

## OUTLINE

I. Introductory comments

II. Why you're really here with us today

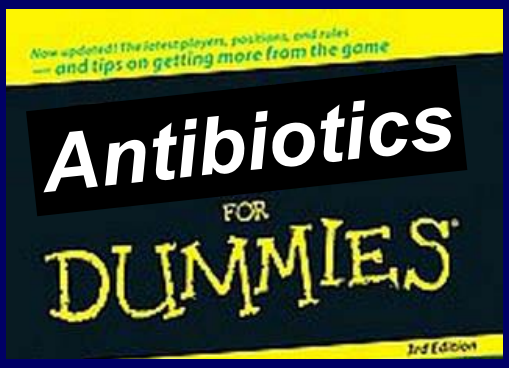
- A. List several newly-approved antibacterial agents and discuss their relevance to clinical practice
- B. Describe modes of action and mechanisms of resistance that may be inherent to these agents
- C. Ascertain the capability of performing antimicrobial susceptibility testing using these agents

III. Examples of novel agents in the pipeline

2

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

3




…including myself

4

## Introductory Comments

5

## FACTORS TO CONSIDER

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

Cannot Enter Urinary Tract

macrolides
clindamycin
chloramphenicol

6

# FACTORS TO CONSIDER

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

Cannot Enter Urinary Tract

macrolides
clindamycin
chloramphenicol

Cannot Enter CNS

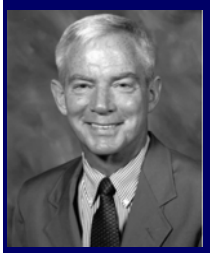
fluoroquinolones
1st & 2nd generation cephems
clindamycin
macrolides
tetracycline

7

# FACTORS TO CONSIDER

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

| Administration | | Example |
|---|---|---|
| *Medical Lingo* | *Colloquial* | |
| IM | butt | ceftriaxone (also IV) |
| PO | oral | cephalexin |
| PO or parenteral | oral or IV | levofloxacin |
| parenteral | IV | vancomycin |



8

# FACTORS TO CONSIDER

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

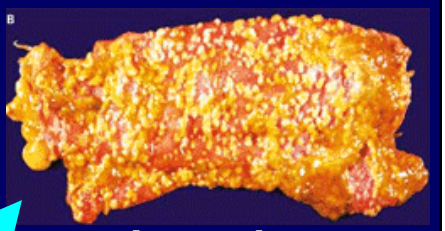
| Administration | | Example |
|---|---|---|
| *Medical Lingo* | *Colloquial* | |
| IM | butt | ceftriaxone (also IV) |
| PO | oral | cephalexin |
| PO or parenteral | oral or IV | levofloxacin |
| parenteral | IV | vancomycin PO |

9

# FACTORS TO CONSIDER

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

| Administration | | Example |
|---|---|---|
| *Medical Lingo* | *Colloquial* | |
| 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*[10]

# 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 | +++ | +++++ |

11

# 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 | +++ | +++++ |

*Shigella* spp. report
ampicillin
trimethoprim-sulfa
ciprofloxacin

12

# FACTORS TO CONSIDER

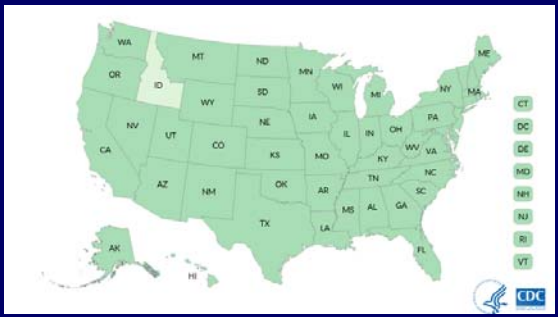
- Antimicrobial susceptibility testing (AST)
- Spectrum of therapy (empiric therapy)
- Availability
- Route of administration
- Majority of excretion
- Dosing/half-life
- Synergy
- Side effects
- Kinetics
- Co$t
- Polymicrobial infections
- Cidal vs. static

13


14

# URGENT THREATS

*C. difficile*
Carbapenem-resistant *Enterobacteriaceae*
Drug-resistant *Neisseria gonorrhoeae*




**Immediate public health threat that requires urgent and aggressive action**

15

# 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

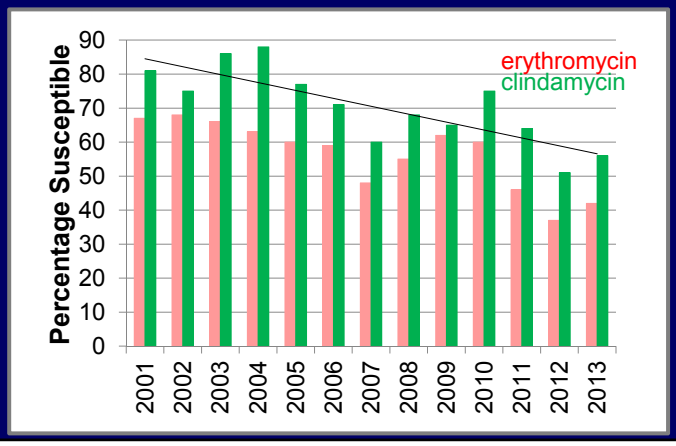
**Requires prompt and sustained action to ensure the problem does not grow**

16

# CONCERNING THREATS

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

**Careful monitoring and preventive action are needed**




17

# OBLIGATORY SCARY STATS (GNR)

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

CDC; Antibiotic Resistance Threats in the United States, 2013

18

# OBLIGATORY SCARY STATS (GPC)

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

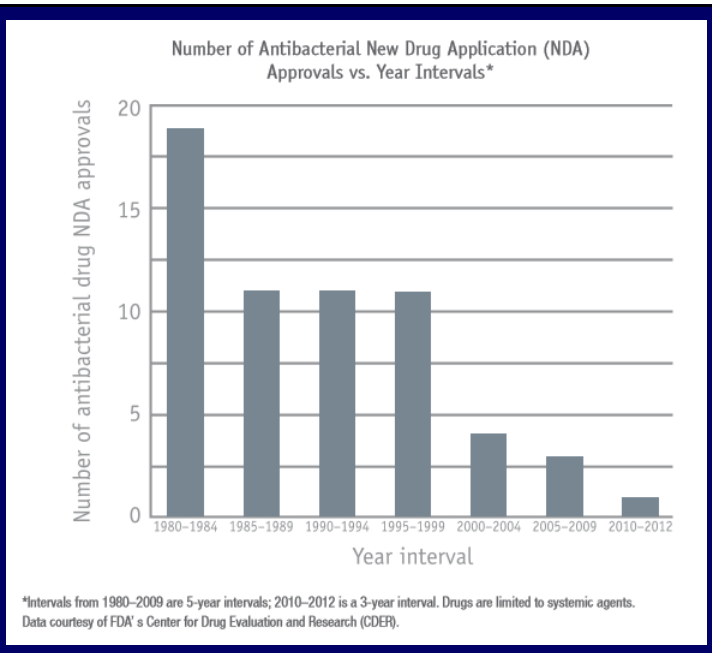
CDC; Antibiotic Resistance Threats in the United States, 2013

19

# MORE OBLIGATORY SCARY STATS

| Interval | % *Klebsiella* spp. possessing ESBL | % *E. coli* 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 |

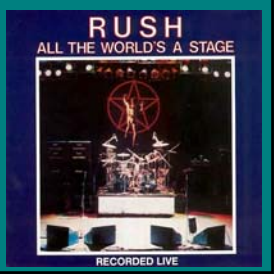
20




CDC; Antibiotic Resistance Threats in the United States, 2013

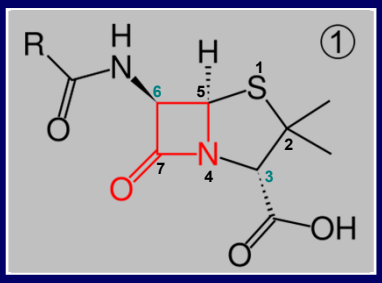
21

## Setting the Stage



# TWO BASIC SUBDIVISIONS

- β-lactam




- Non-β-lactam

23

# TWO BASIC SUBDIVISIONS

- β-lactam

  Penicillins
  Cephems
  Monobactams
  Penems

- Non-β-lactam

24

# ARBITRARY CLASSIFICATIONS

| Activity | Generation |
|---|---|
| Narrow spectrum | First |
| Expanded spectrum | Second |
| Broad spectrum | Third |
| Extended spectrum | Fourth |

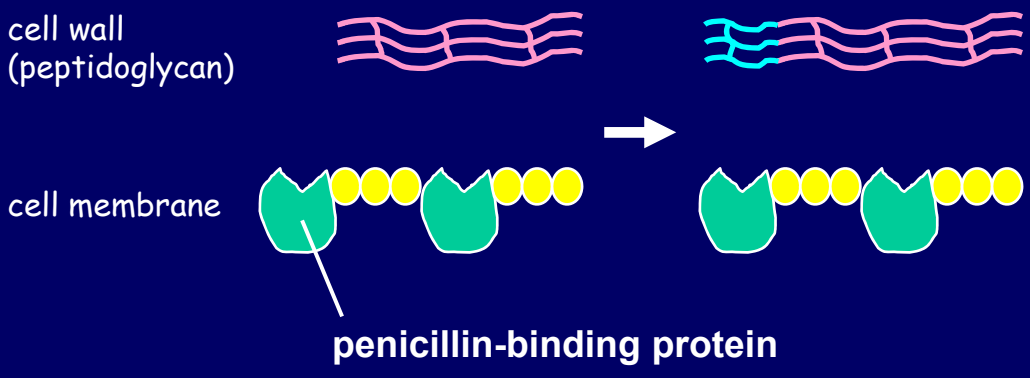
25

# ARBITRARY CLASSIFICATIONS

| Activity | Generation |
|---|---|
| Narrow spectrum | First |
| Expanded spectrum | Second |
| Broad spectrum | Third |
| Extended spectrum | Fourth |

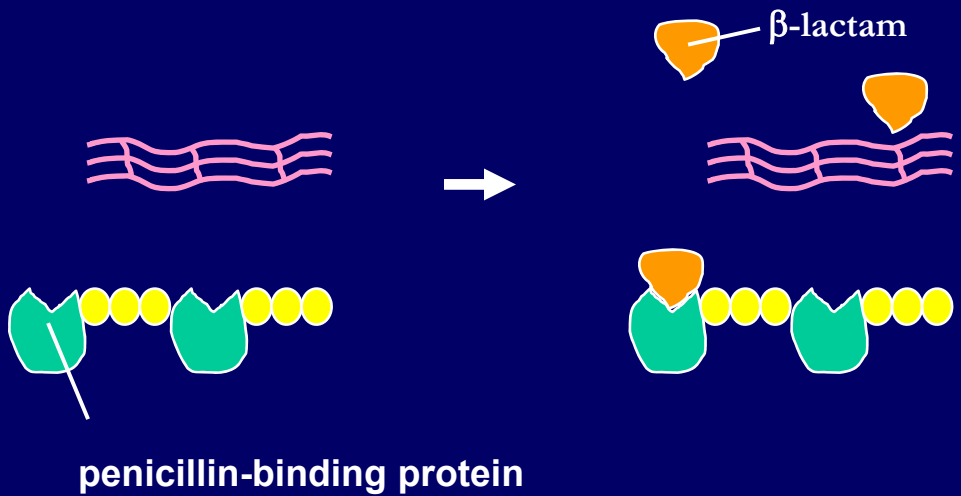
26

# CELL WALL SYNTHESIS




27

# CELL WALL SYNTHESIS




28

# CEPHEM CLASS

| Parameter | Description |
|---|---|
| Mechanism of action | 1. Bind to bacterial penicillin-binding proteins (PBP), interfering with cell wall synthesis<br>2. 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 |

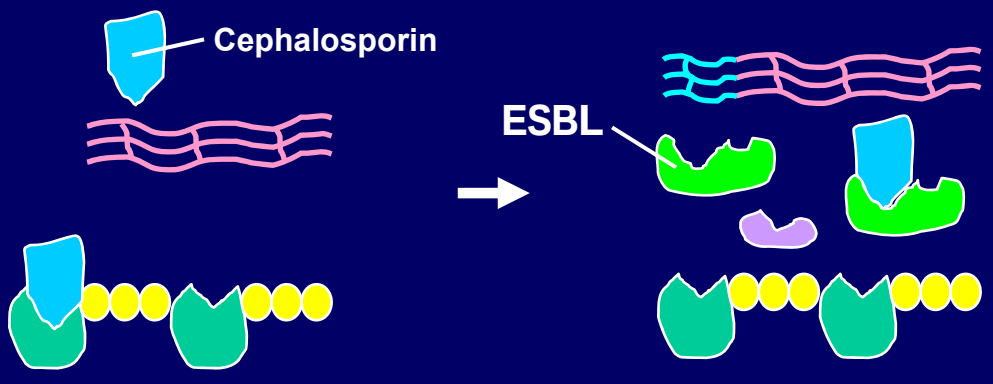
29

# CEPHEM CLASS

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

30

# RESISTANCE VIA ESBL PRODUCTION




31

# 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 |

32

# PENEM CLASS

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

33

# PENEM RESISTANCE

- Alteration of porin channels in bacterial cell wall, reducing permeability
- Carbapenemase production

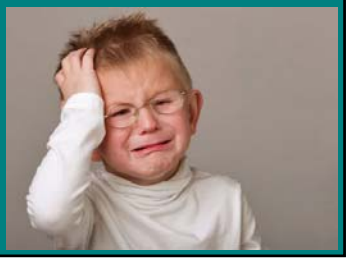
  Serine carbapenemases (class A β-lactamase)
  Metallo-β-lactamase (class B β-lactamase)
  OXA-type β-lactamase (class D β-lactamase)

- Plasmids carrying *bla*$_{KPC}$ contain genes conferring resistance to aminoglycosides and fluoroquinolones

Infect. Control Hosp. Epidemiol. **29:** 1107-1109; 2008

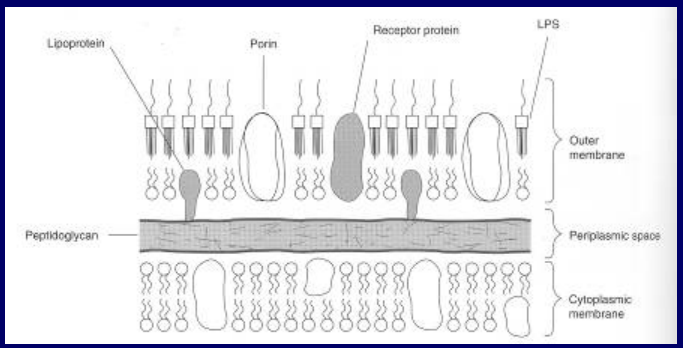
34

What Do We Do Next?



# LIPOPEPTIDE CLASS

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

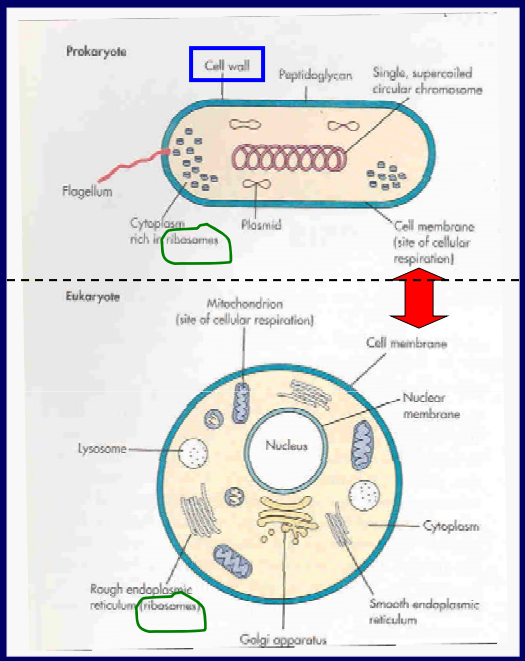



36

# POLYMYXIN SUBCLASS

| Parameter | Description |
|---|---|
| Mechanism of action | 1. Bind to phosphorylated head groups of lipid A, disrupting cell membranes and losing osmolarity<br>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%) |

37




38

# POLYMYXIN SUBCLASS

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

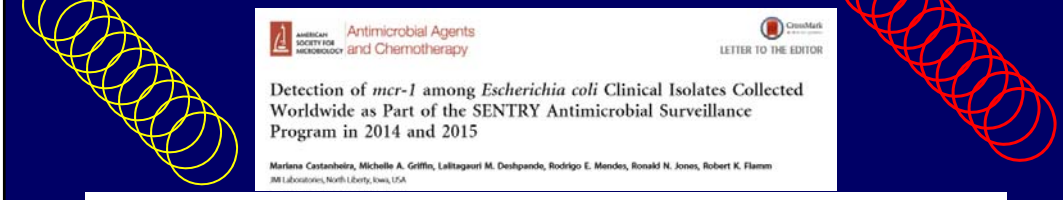
39

# 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

40

# UH, OH



Antimicrobial Agents and Chemotherapy

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 *mcr-1*-positive isolate(s) was observed | No. of *mcr-1*-positive isolates/ no. of colistin-resistant isolates (%) | No. of *mcr-1*-positive isolates with colistin MICs (μg/ml) of: | | |
|---|---|---|---|---|
| | | 4 | 8 | >8 |
| All colistin-resistant organisms | 19/390 (4.9) | 10 | 8 | 1 |
| *E. coli* | 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*.

Antimicrob. Agents Chemother. **60:** 5623-5624; 2016

41

Journal of Clinical Microbiology

COMMENTARY

## 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

Journal of Clinical Microbiology

BACTERIOLOGY

## 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[a]; Department of Laboratory Medicine, Changi General Hospital, Republic of Singapore[b]; Ministry of Health, National Public Health Laboratory, Singapore, Republic of Singapore[c]

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

42

# 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 → loss of enzyme activity
3. Can lower MIC up to 20-fold when combined with β-lactam agent

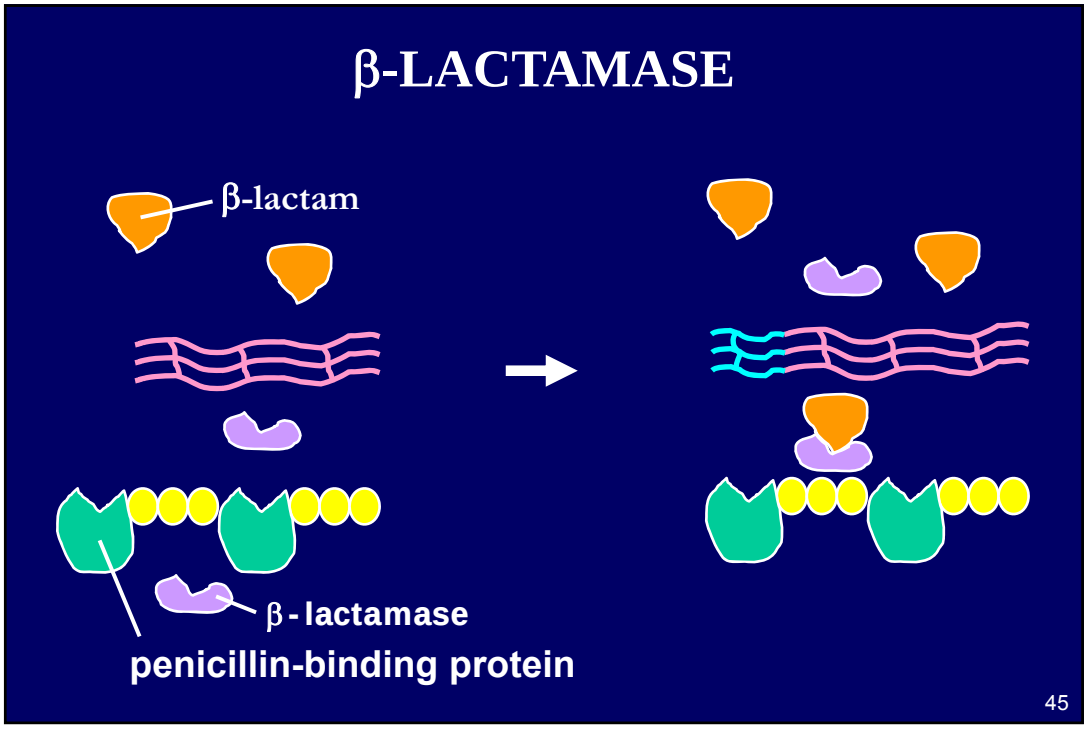
43

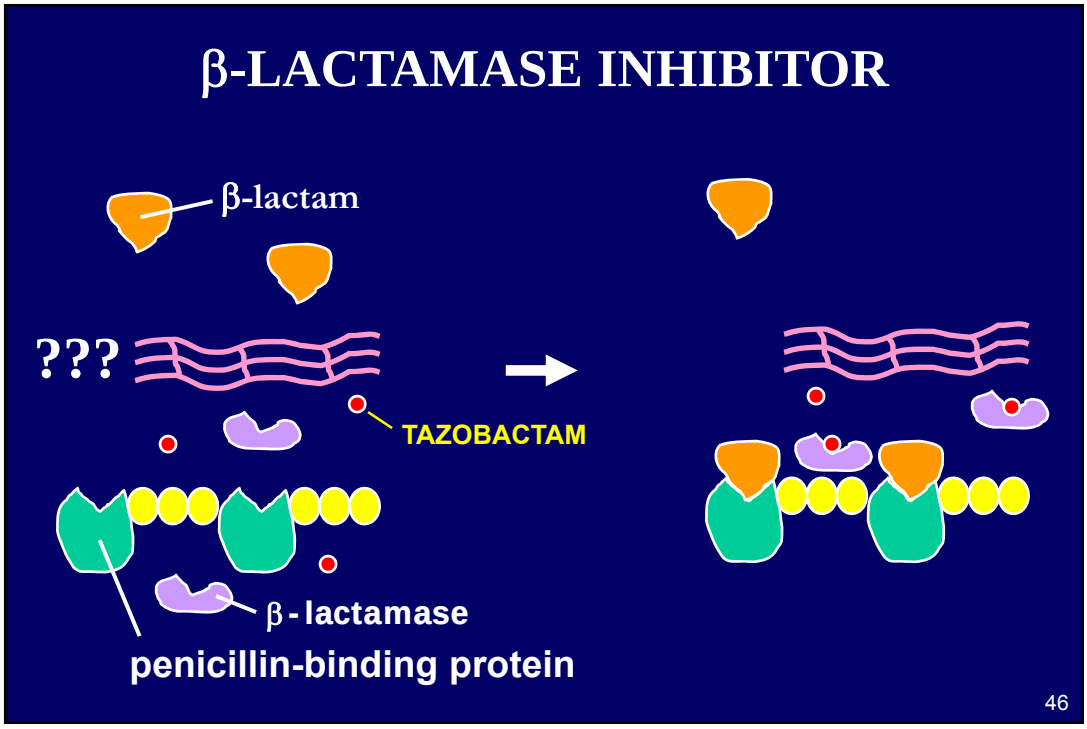
# β-LACTAM/β-LACTAMASE INHIBITORS

| 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

44


β-LACTAMASE
β-lactam
β - lactamase
penicillin-binding protein
45


β-LACTAMASE INHIBITOR
β-lactam
???
TAZOBACTAM
β - lactamase
penicillin-binding protein
46

# CEFTAZIDIME-AVIBACTAM

| Parameter | Description |
|---|---|
| a.k.a. | AVYCAZ |
| Indication | 1. Complicated intra-abdominal infections (in combination with metronidazole)<br>2. Complicated urinary tract infections (including pyelonephritis) |
| Mechanism of action | 1. Inactivates β-lactamases<br>2. Binds essential penicillin-binding proteins |
| Activity rendered | Cidal |
| Route of administration | IV |
| Half-life | 2.76 h → q8h |
| Excretion | Renal |

47

# CEFTAZIDIME-AVIBACTAM

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

48

# CEFTAZIDIME-AVIBACTAM

| Organism | Method | Adopted | Testing/ Reporting | Breakpoint Range | Caveat(s) |
|---|---|---|---|---|---|
| *Enterobacteriaceae* | BMD, DD | 2018 | optional | full | |
| *P. aeruginosa* | BMD, DD | 2018 | optional | full | |

CLSI M100; 28th ed.; 2018

49

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy®

**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 |
| ADR (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 |
| *P. aeruginosa* | | | | | | |
| 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 |

Antimicrob. Agents Chemother. **61:** e01045-17; 2017

50

# CEFTOLOZANE-TAZOBACTAM

| Parameter | Description |
|---|---|
| a.k.a. | ZERBAXA |
| Indication | 1. Complicated intra-abdominal infections (in combination with metronidazole)<br>2. Complicated urinary tract infections (including pyelonephritis) |
| Mechanism of action | 1. Forms irreversible complex with β-lactamase<br>2. Binds PBP-1b, -1c, and -3 of *P. aeruginosa*<br>Binds PBP-3 of *E. coli* to inhibit cell wall synthesis |
| Activity rendered | Cidal |
| Route of administration | IV |
| Half-life | 3.12 h → q8h |
| Excretion | Renal |

51

# CEFTOLOZANE-TAZOBACTAM

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

52

# CEFTOLOZANE-TAZOBACTAM

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

CLSI M100; 28th ed.; 2018

53

AAC Journals.ASM.org

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]

| *P. aeruginosa* 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.

Antimicrob. Agents Chemother. **57:** 6305-6310; 2013

54

**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] |
|---|---|---|---|---|
| *Enterobacteriaceae*—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] |
|---|---|---|---|---|
| *Enterobacteriaceae*—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 | — | — |
| *E. coli*, 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 | — | — |
| *K. pneumoniae*, 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 | — | — |

Antimicrob. Agents Chemother. **57:** 6305-6310; 2013

55

# FOSFOMYCIN

| Parameter | Description |
|---|---|
| a.k.a. | Monurol |
| Indication | Uncomplicated UTI in women caused by *Escherichia coli* and *Entercoccus faecalis* |
| Mechanism of action | 1. Inactivation of enolpyruval transferase, irreversibly blocking condensation of uridine diphosphate-N-acetylglucosamine with p-enolpyruvate (initial step in cell wall synthesis)<br>2. 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 |

56

# FOSFOMYCIN

| Parameter | Description |
|---|---|
| Spectrum of activity | *Enterobacteriaceae* (*E. coli*)<br>*Enterococcus* spp. (*E. faecium*)<br>Claim activity versus ESBL-producing *Enterobacteriaceae*<br>Claim activity versus CRE |
| Adverse effects | Diarrhea |

57

# FOSFOMYCIN

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

CLSI M100; 28th ed.; 2018

58

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

| | $MIC_{50}$ | $MIC_{90}$ | Range | *S* (%) | *I* (%) | *R* (%) |
|---|---|---|---|---|---|---|
| *E. coli* ESBL-phenotype (*n* = 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 |
| *Klebsiella* spp.: ESBL-phenotype (*n* = 65)[a] ← 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 |

59

# FOSFOMYCIN

Infection and Drug Resistance
Dovepress
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 |

60

# 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

61

# CEFTAROLINE

| Parameter | Description |
|---|---|
| a.k.a. | Teflaro |
| Indication | 1. Acute bacterial skin and skin structure infection<br>2. Community-acquired bacterial pneumonia |
| Mechanism of action | 1. Bind to bacterial penicillin-binding proteins (PBP), interfering with cell wall synthesis<br>2. Can bind PBP-2a of MRSA |
| Activity rendered | Cidal |
| Route of administration | IV |
| Half-life | 2.66 h → q12h |
| Excretion | Renal |

62

# CEFTAROLINE

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

63

# CEFTAROLINE

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

CLSI M100; 28th ed.; 2018

64

Antimicrobial Agents and Chemotherapy®

EPIDEMIOLOGY AND SURVEILLANCE

## 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)

| | | % Susceptible[a] | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Organism | Yr (no. isolates) | Ceftaroline | Oxacillin | Erythromycin | Clindamycin | Levofloxacin | Tetracycline | TMP-SMX[b] |
| *S. aureus* | 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 |

[a]Using breakpoints published by CLSI (12).
[b]TMP-SMX, trimethoprim-sulfamethoxazole.

Antimicrob. Agents Chemother. **61:** e01043-17; 2017

65

# TELAVANCIN

| Parameter | Description |
|---|---|
| a.k.a. | VIBATIV |
| Indication | 1. Complicated skin and skin structure infections<br>2. Hospital-acquired and ventilator-associated bacterial pneumonia caused by *S. aureus* |
| Mechanism of action | lipoglycopeptide (synthetic derivative of vancomycin)<br>Binds to late-stage peptidoglycan precursors (including lipid II)<br>Binds to bacterial membrane, disrupting membrane barrier function |
| Activity rendered | Cidal |
| Route of administration | IV infusion |
| Half-life | 8 hr → q24h |
| Excretion | Renal |

66

# TELAVANCIN

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

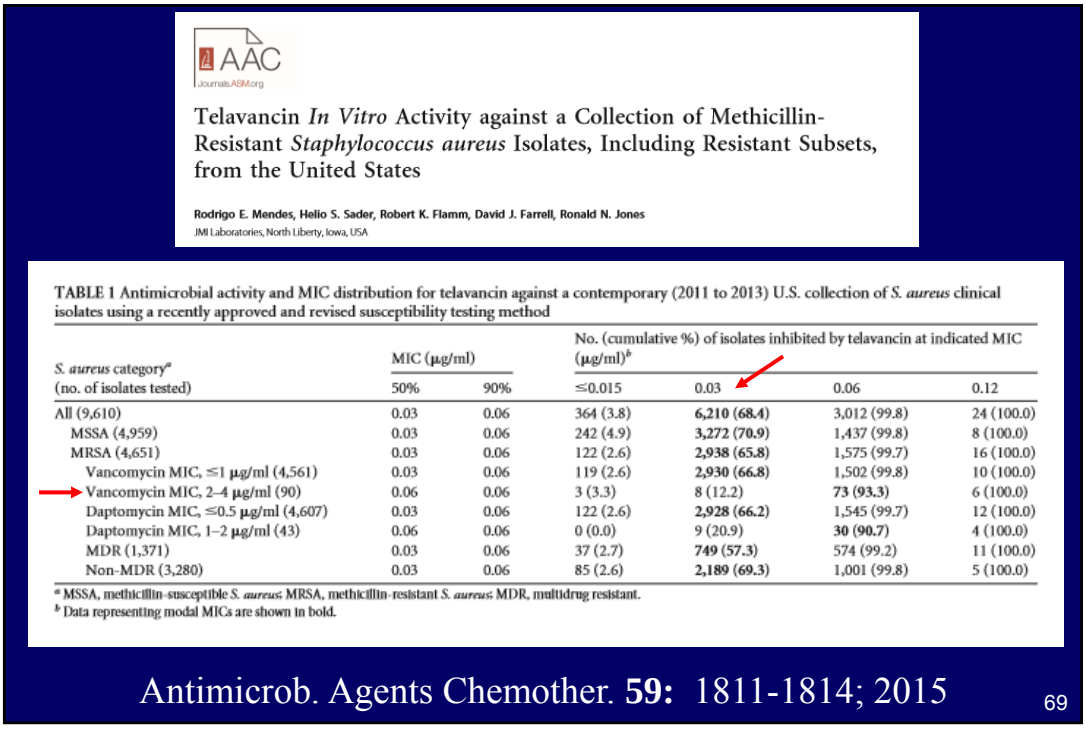
67

# TELAVANCIN

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

CLSI M100; 28th ed.; 2018

68



AAC
JournalsASM.org

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

| *S. aureus* category[a] (no. of isolates tested) | MIC (μg/ml) | | No. (cumulative %) of isolates inhibited by telavancin at indicated MIC (μg/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, ≤1 μg/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 μg/ml (90) | 0.06 | 0.06 | 3 (3.3) | 8 (12.2) | **73 (93.3)** | 6 (100.0) |
| Daptomycin MIC, ≤0.5 μg/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 μg/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.

Antimicrob. Agents Chemother. **59:** 1811-1814; 2015

69

# DALBAVANCIN

| Parameter | Description |
|---|---|
| a.k.a. | DALVANCE |
| Indication | natural lipoglycopeptide<br><br>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 |

70

# DALBAVANCIN

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

71

# DALBAVANCIN

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

CLSI M100; 28th ed.; 2018

72

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 (μg/ml) 50% | MIC (μg/ml) 90% | MIC (μg/ml) Range | % Susceptible[a] | % Resistant[b] |
|---|---|---|---|---|---|---|
| *S. aureus* | | | | | | |
| Oxacillin susceptible (27,052) | Dalbavancin | 0.06 | 0.06 | ≤0.03–0.25 | 100.0 | — |
| | Vancomycin | 1 | 1 | ≤0.12–4 | >99.9 | 0.0 |
| | Erythromycin | ≤0.25 | >2 | ≤0.25–>2 | 78.7 | 20.7 |
| | Clindamycin | ≤0.25 | ≤0.25 | ≤0.25–>2 | 95.8 | 4.0 |
| | Levofloxacin | ≤0.5 | ≤0.5 | ≤0.5–>4 | 92.8 | 6.7 |
| | Gentamicin | ≤2 | ≤2 | ≤2–>8 | 97.1 | 2.6 |
| | Tetracycline | ≤4 | ≤4 | ≤4–>8 | 93.7 | 5.8 |
| | Linezolid | 2 | 2 | 0.12–4 | 100.0 | — |
| Oxacillin resistant (19,721) | Dalbavancin | 0.06 | 0.06 | ≤0.03–0.5 | >99.9 | — |
| | Vancomycin | 1 | 1 | 0.25–4 | >99.9 | 0.0 |
| | Erythromycin | >2 | >2 | ≤0.25–>2 | 10.9 | 88.8 |
| | Clindamycin | >2 | >2 | ≤0.25–>2 | 47.8 | 52.1 |
| | Levofloxacin | >4 | >4 | ≤0.5–>4 | 18.3 | 80.1 |
| | Gentamicin | ≤2 | >8 | ≤2–>8 | 74.1 | 24.8 |
| | Tetracycline | ≤4 | >8 | ≤4–>8 | 81.1 | 18.4 |
| | Linezolid | 1 | 2 | ≤0.25–>8 | >99.9 | 0.04 |
| *E. faecalis* | | | | | | |
| Vancomycin susceptible (10,025) | Dalbavancin | ≤0.03 | 0.06 | ≤0.03–0.5 | >99.9 | — |
| | Ampicillin | ≤2 | ≤2 | ≤2–>16 | 99.6 | 0.2 |
| | Ciprofloxacin | 1 | >4 | 0.06–>4 | 62.2 | 33.6 |
| | Gentamicin (HL[c]) | ≤500 | >1000 | ≤500–>1000 | 68.5 | 31.5 |
| | Linezolid | 1 | 2 | ≤0.25–>8 | 99.8 | 0.1 |
| Vancomycin nonsusceptible (349) | Dalbavancin | >4 | >4 | ≤0.03–>4 | 27.8 | — |
| | Ampicillin | ≤2 | 4 | ≤2–>16 | 96.0 | 4.0 |
| | Ciprofloxacin | >4 | >4 | 0.5–>4 | 3.7 | 96.3 |
| | Gentamicin (HL) | >1000 | >1000 | ≤500–>1000 | 28.4 | 71.6 |
| | Linezolid | 1 | 2 | 0.25–>8 | 98.6 | 1.4 |
| *E. faecium* | | | | | | |
| Vancomycin susceptible (2,578) | Dalbavancin | 0.06 | 0.12 | ≤0.03–2 | 99.6 | — |
| | Ampicillin | >16 | >16 | ≤2–>16 | 15.6 | 84.4 |
| | Ciprofloxacin | >4 | >4 | 0.06–>4 | 8.1 | 83.7 |
| | Gentamicin (HL) | ≤500 | >1000 | ≤500–>1000 | 61.8 | 38.2 |
| | Linezolid | 1 | 2 | ≤0.25–>8 | 99.6 | 0.3 |
| Vancomycin nonsusceptible (2,176) | Dalbavancin | >4 | >4 | ≤0.03–>4 | 11.4 | — |
| | Ampicillin | >16 | >16 | ≤2–>16 | 0.8 | 99.2 |
| | Ciprofloxacin | >4 | >4 | ≤0.03–>4 | 0.7 | 98.3 |
| | Gentamicin (HL) | ≤500 | >1000 | ≤500–>1000 | 64.3 | 35.7 |
| | Linezolid | 1 | 2 | 0.5–>8 | 97.6 | 1.8 |

Antimicrob. Agents Chemother. **53:** 1260-1263; 2009

73

AAC Journals.ASM.org

*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] Sailaja 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) 50% | MIC (μg/ml) 90% | MIC (μg/ml) Range | % susceptible[b] |
|---|---|---|---|---|---|
| All *S. aureus* (62,195) | Dalbavancin | 0.06 | 0.06 | ≤0.008 to 0.5 | 99.7 |
| MRSA (26,975) | 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 |

Antimicrob. Agents Chemother. **59:** 5007-5009; 2015

74

# TEDIZOLID

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

75

# TEDIZOLID

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

76

# TEDIZOLID

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

CLSI M100; 28th ed.; 2018

77

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 (μg/ml): ≤0.008 | 0.015 | 0.03 | 0.06 | 0.12 | 0.25 | 0.5 | 1 | 2 | 4 | $MIC_{50}$ (μg/ml) | $MIC_{90}$ (μg/ml) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *S. aureus* (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 (98.8) | 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 |
| *S. pyogenes* (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 |
| *S. agalactiae* (145) | Linezolid 80 | | | | | | | 36 (24.8) | 109 (100.0) | | | 1 | 1 |
| | Linezolid 100 | | | | | | | 2 (1.4) | 136 (93.2) | 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 |
| *S. anginosus* 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 |
| *E. faecalis* (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 |

Antimicrob. Agents Chemother. **60:** 5393-5399; 2016

78

# Some Future Prospects

79

Antimicrobial Agents and Chemotherapy

*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 (μg/ml) Range | $MIC_{50}$ | $MIC_{90}$ | R%[b] |
|---|---|---|---|---|---|
| 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 |

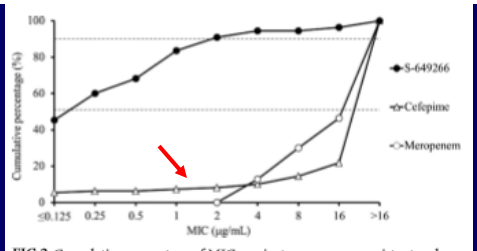



FIG 2 Cumulative percentage of MICs against meropenem-resistant carbapenemase-producing *Enterobacteriaceae*. The test strains were 110 *E. coli*, *K.*

Antimicrob. Agents Chemother. **60:** 729-734; 2016

80

J Antimicrob Chemother 2016; **71**: 670 - 677
doi:10.1093/jac/dkv402 Advance Access publication 7 December 2015

Journal of Antimicrobial Chemotherapy

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

**Akinobu Ito[1]*, Naoki Kohira[1], Samuel K. Bouchillon[2], Joshua West[3], Stephen Rittenhouse[3], Helio S. Sader[4], Paul R. Rhomberg[4], Ronald N. Jones[4], Hidenori Yoshizawa[1], Rio Nakamura[1], Masakatsu Tsuji[1] and Yoshinori Yamano[1]**

[1]*Discovery Research Laboratory for Core Therapeutic Areas, Shionogi & Co., Ltd, Toyonaka, Osaka, Japan;* [2]*International Health Management Associates, Inc., Schaumberg, IL 60173, USA;* [3]*GlaxoSmithKline, Collegeville, PA 19426, USA;* [4]*JMI 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

*Received 15 July 2015; returned 8 September 2015; revised 7 October 2015; accepted 29 October 2015*

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

| Species (no. of strains) | Compound | MIC (mg/L) range | $MIC_{50}$ | $MIC_{90}$ |
|---|---|---|---|---|
| *A. baumannii* (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 |
| *P. aeruginosa* (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 |
| *S. maltophilia* (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 |

[a]ISB supplemented with 20 μmol/L apo-transferrin was used.
[b]CAMHB supplemented with 20 μmol/L apo-transferrin was used.

J. Antimicrob. Chemother. **71:** 670-677; 2016

81

*A. baumannii*

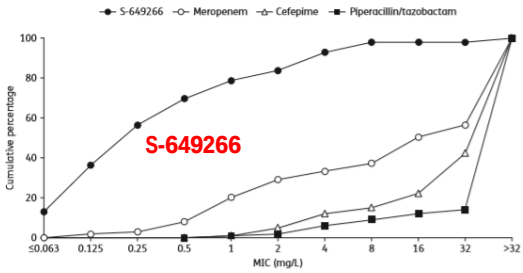



**Figure 2.** Cumulative MIC distribution of S-649266 for drug-resistant *A. baumannii* determined in ISB supplemented with apo-T. MICs of meropenem, cefepime and piperacillin/tazobactam were determined in CAMHB.

*P. aeruginosa*

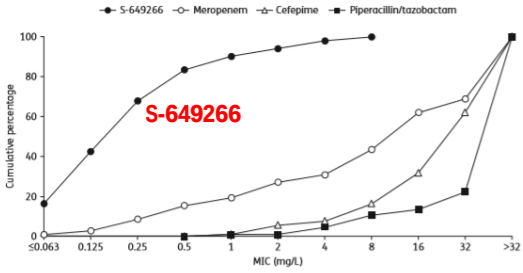



**Figure 3.** Cumulative MIC distribution of S-649266 for drug-resistant *P. aeruginosa* determined in CAMHB supplemented with apo-T. MICs of meropenem, cefepime and piperacillin/tazobactam were determined in CAMHB.

J. Antimicrob. Chemother. **71:** 670-677; 2016

82

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy®

SUSCEPTIBILITY

## *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. Sahm[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*

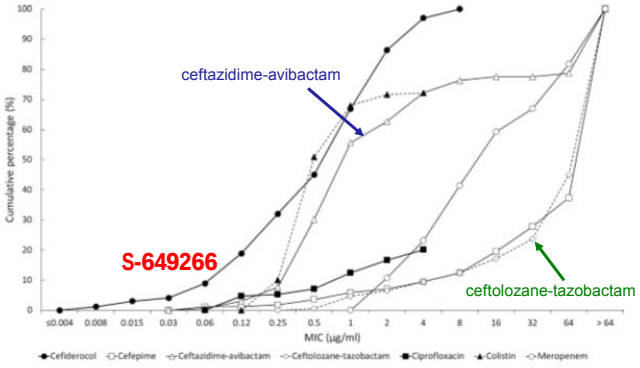



FIG 3 Cumulative MIC susceptibility curves for cefiderocol and comparators against 169 meropenem nonsusceptible *Enterobacteriaceae* from North American and European medical center laboratories. For colistin and ciprofloxacin, the endpoint of their respective cumulative MIC susceptibility curves represents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

Antimicrob. Agents Chemother. **61:** e00093-17; 2017

83

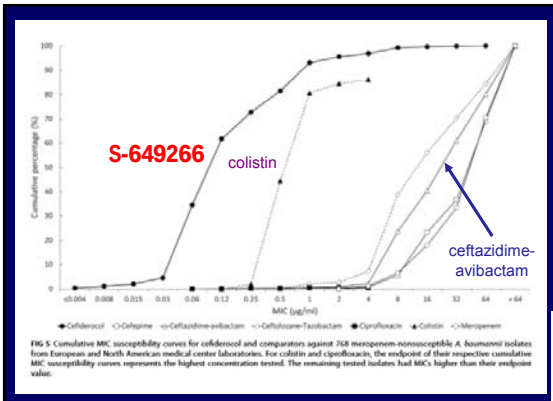



FIG 5 Cumulative MIC susceptibility curves for cefiderocol and comparators against 768 meropenem-nonsusceptible *A. baumannii* isolates from European and North American medical center laboratories. For colistin and ciprofloxacin, the endpoint of their respective cumulative MIC susceptibility curves represents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

*A. baumannii*

*P. aeruginosa*

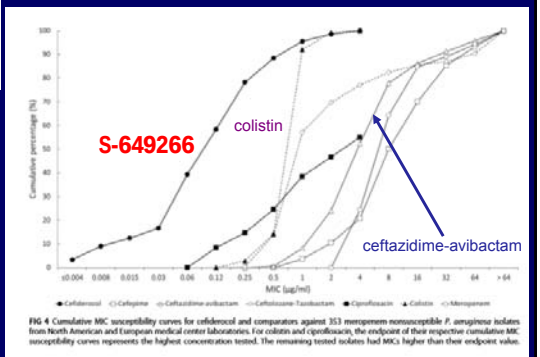



FIG 4 Cumulative MIC susceptibility curves for cefiderocol and comparators against 353 meropenem nonsusceptible *P. aeruginosa* isolates from North American and European medical center laboratories. For colistin and ciprofloxacin, the endpoint of their respective cumulative MIC susceptibility curves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

Antimicrob. Agents Chemother. **61:** e00093-17; 2017

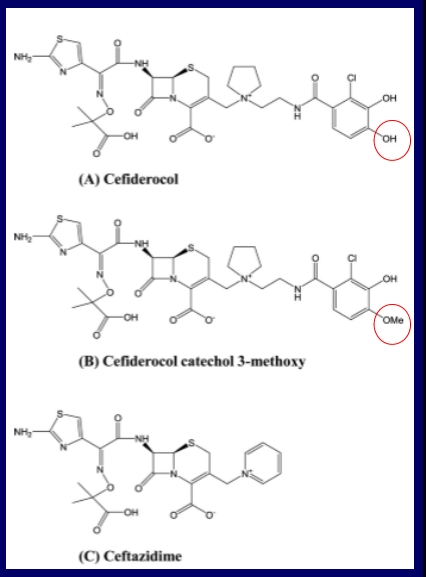
84

Antimicrobial Agents and Chemotherapy

## 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



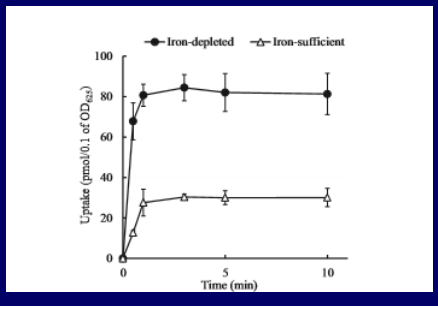

Antimicrob. Agents Chemother. **60:** 7396-7401; 2016

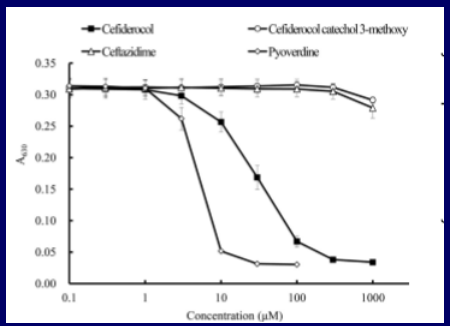
85

**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 (μg/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.




Antimicrob. Agents Chemother. **60:** 7396-7401; 2016

86

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy®

SUSCEPTIBILITY

## *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. Sahm[a]**

[a]International Health Management Associates, Inc., Schaumburg, Illinois, USA
[b]The Medicines Company, San Diego, California, USA
[c]Department 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*

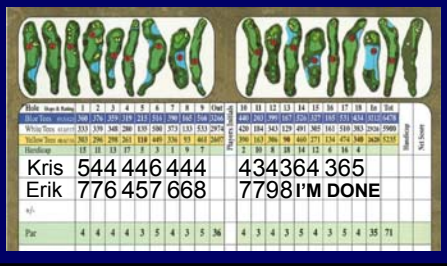
| Family, genus, or species[a] (no. of isolates) | Antimicrobial agent(s) | MIC[b] (μg/ml) | | | % of isolates with the following MIC interpretation[c]: | | |
|---|---|---|---|---|---|---|---|
| | | Range | 50% | 90% | Susceptible | Intermediate | Resistant |
| All *Enterobacteriaceae*[d] (991) | Meropenem-vaborbactam | ≤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 |

Antimicrob. Agents Chemother. **62:** e01904-17; 2018

87

# ONE PERSON'S SCORECARD

| Agent | ESBL | CRE | *Pseudomonas* | MRSA | VRE |
|---|---|---|---|---|---|
| polymyxins | watch out | | ✓ | - | - |
| ceftazidime-avibactam | ✓ | ✓ | ✓ | - | - |
| ceftolozane-tazobactam | ✓ | - | ✓ | - | - |
| fosfomycin | ✓ | careful | careful | - | careful |
| ceftaroline | - | - | - | ✓ | - |
| telavancin | - | - | - | ✓ | - |
| dalbavancin | - | - | - | ✓ | - |
| tedizolid | - | - | - | ✓ | hedging |




88