Dropping the MIC or Dropping the Ball? New Antibiotic Approvals in the Post-Antibiotic Era

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Our Presenters

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Disclosures

- The presenters have no real or perceived conflicts of interest related to this presentation

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Learning Objectives

At the end of this session, participants should be able to:

1. Compare new and emerging antibiotics with existing antibiotics for bacterial infections
2. Assist antimicrobial stewardship programs in developing a treatment algorithm and determining place in therapy for recently approved antimicrobials
3. Select an optimal antibiotic regimen for a multidrug-resistant gram-negative bacterial infection

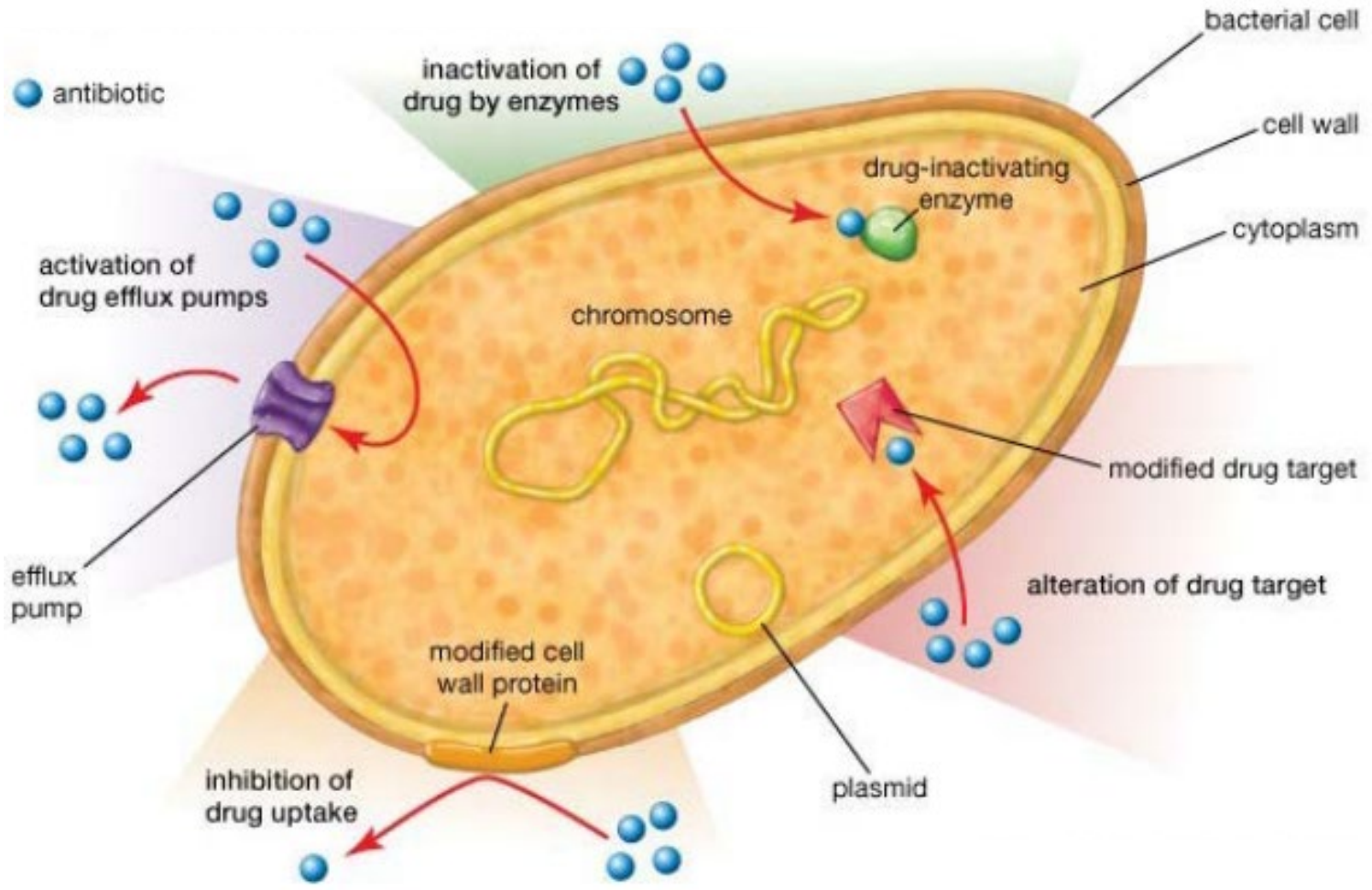
The Rise of Antibiotic Resistance

- The treatment of gram-negative bacteremia is increasingly complicated by the rising prevalence of multidrug-resistant strains of GNR
- The CDC illness and mortality estimates caused by antibiotic resistance
  - 2,868,700 illnesses
  - 35,900 deaths

Source: CDC. Antibiotic Resistance Threats in the United States, 2019. Atlanta, GA: U.S. Department of Health and Human Services, CDC; 2019.

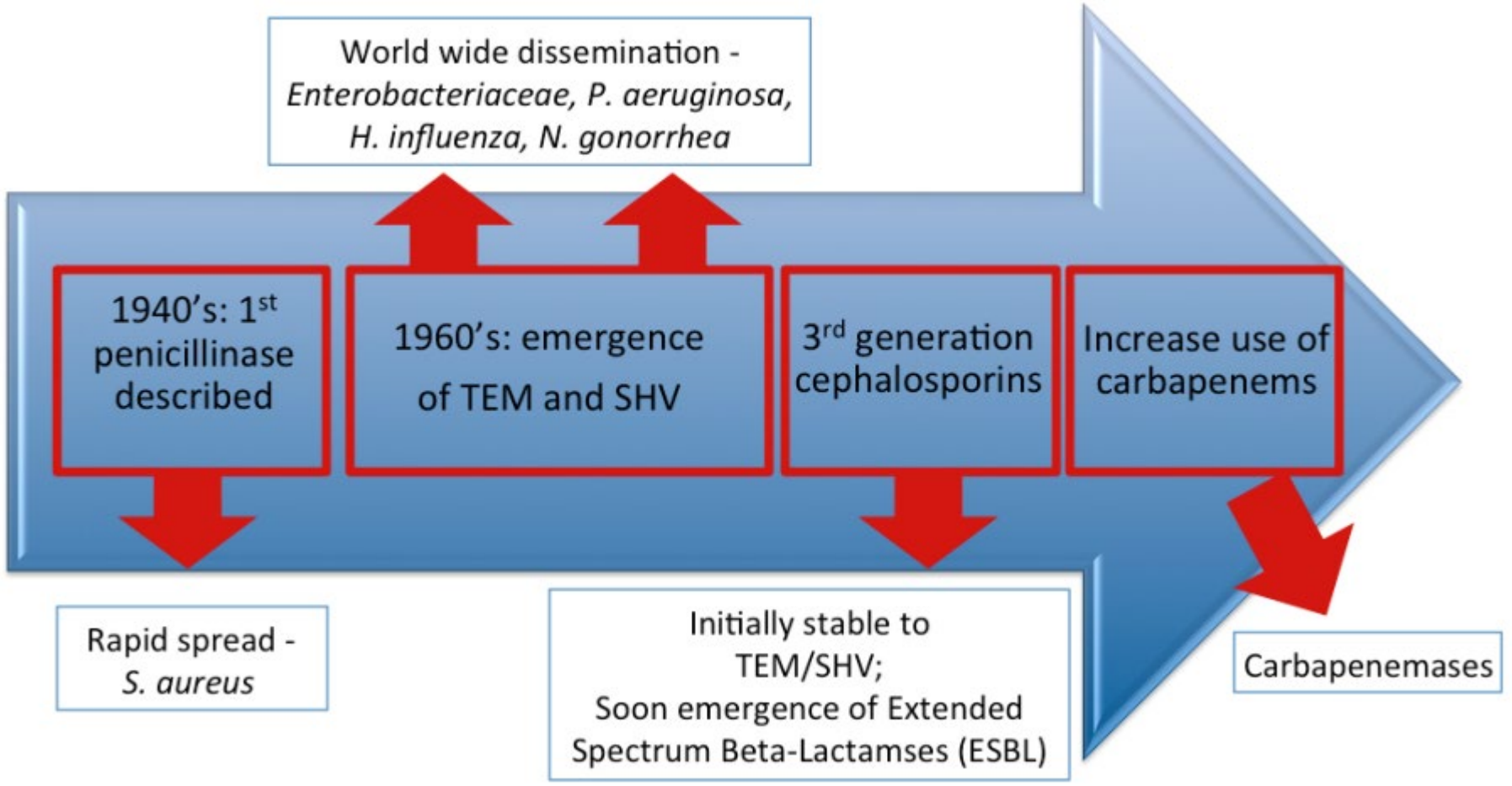
Mechanisms of Resistance

- Porin channels
- Efflux pumps
- Target modification
- Enzymatic



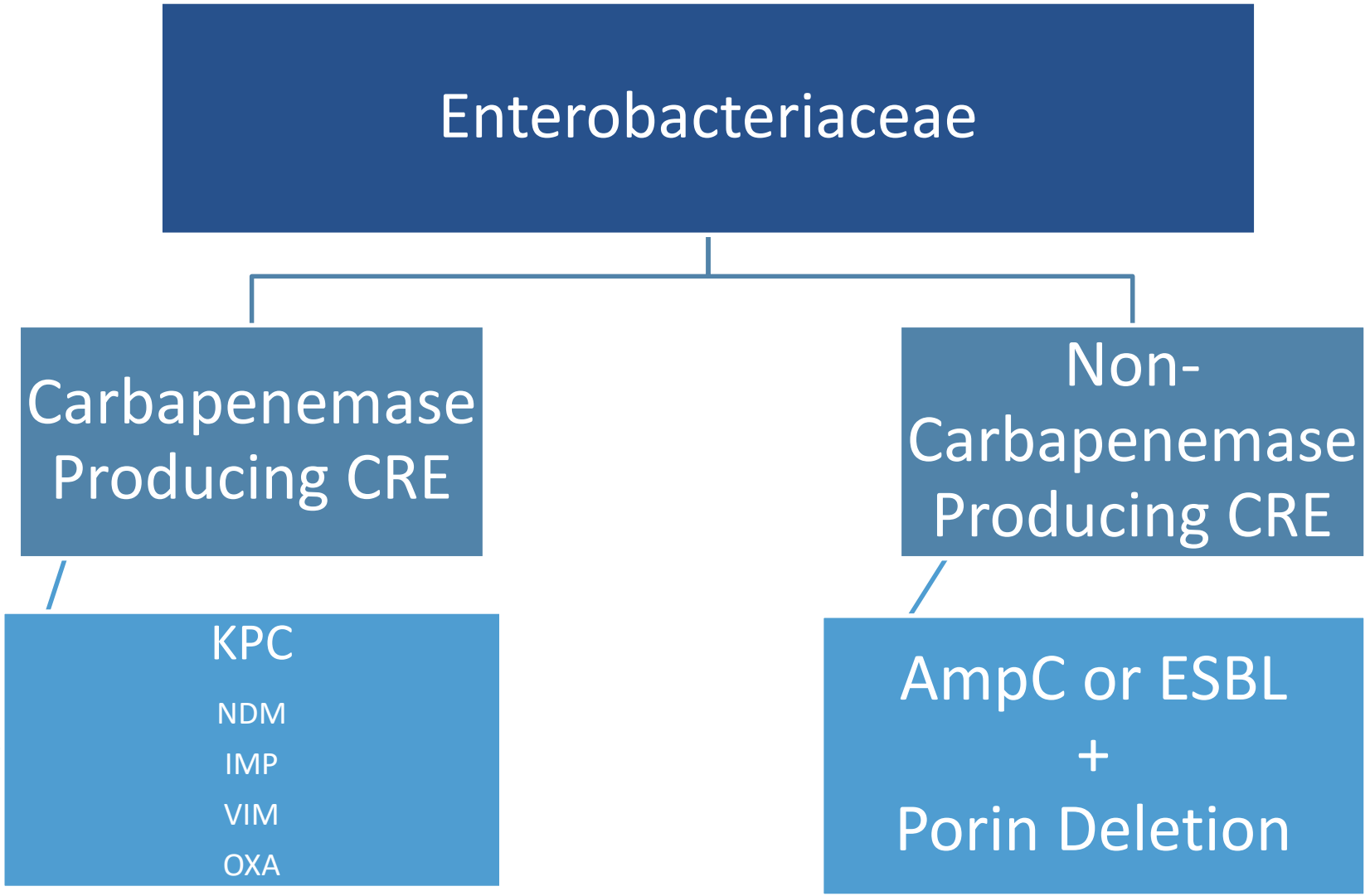
Source: Opal SM, Pop-Vicas A. Molecular Mechanisms of Antibiotic Resistance in Bacteria. Mandell GL, Douglas R, Bennett JE, eds. Principles and Practice of Infectious Diseases. 8th ed. Philadelphia, Pennsylvania: Churchill Livingstone; 2015:235-251.
Antibiotic resistance. (2015). In Encyclopedia Britannica. Retrieved from http://www.britannica.com/science/antibiotic-resistance.

Resistance Through the Years



Source: C, Vernet T. Penicillin-binding proteins and β-lactam resistance. FEMS Microbiol Rev. 2008;32: 361-385

Mechanism of Carbapenem Resistance



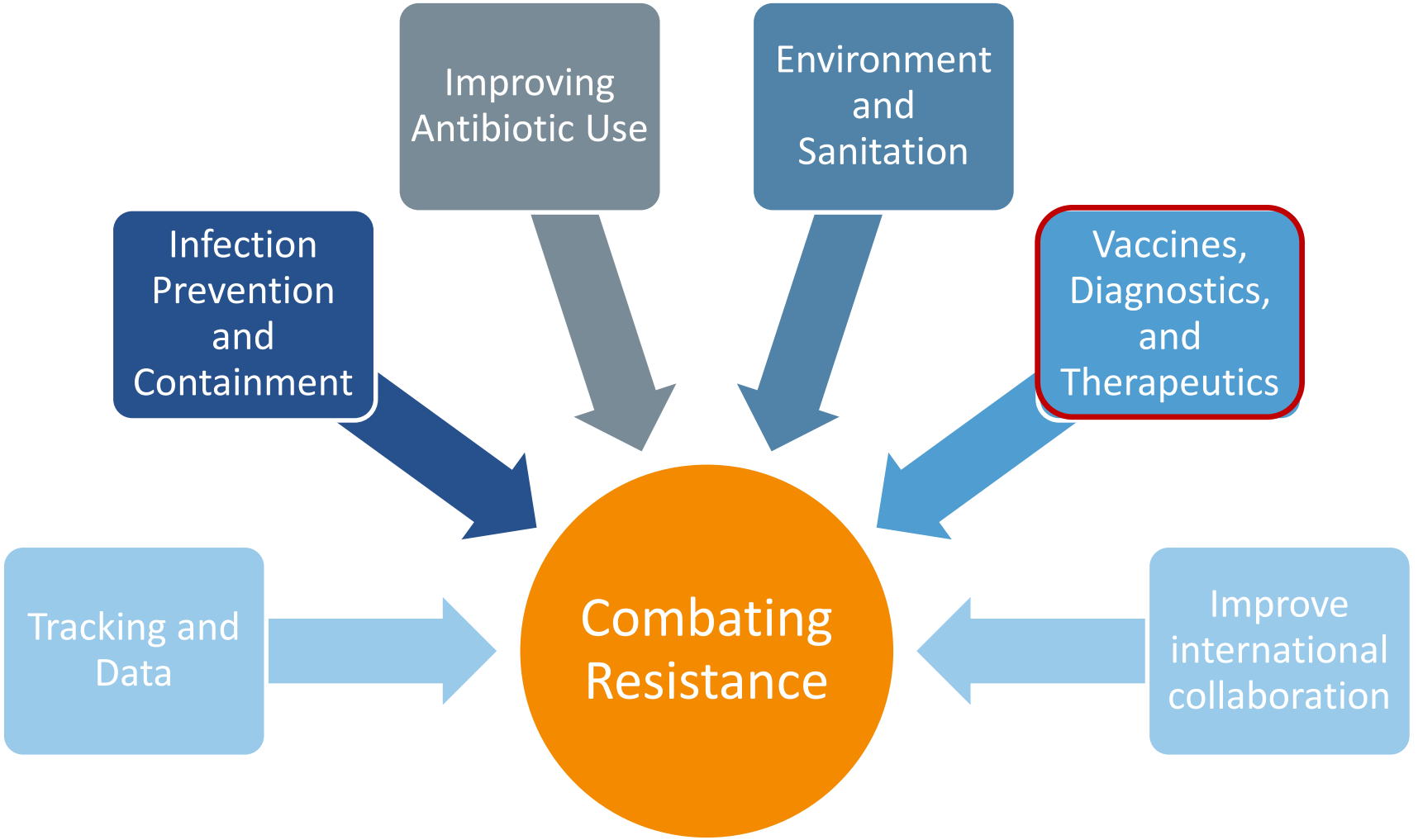
Global Spread of Resistance

A Closer Look at CRE

- Uncommon in the United State before 1992
- Rapidly increasing prevalence

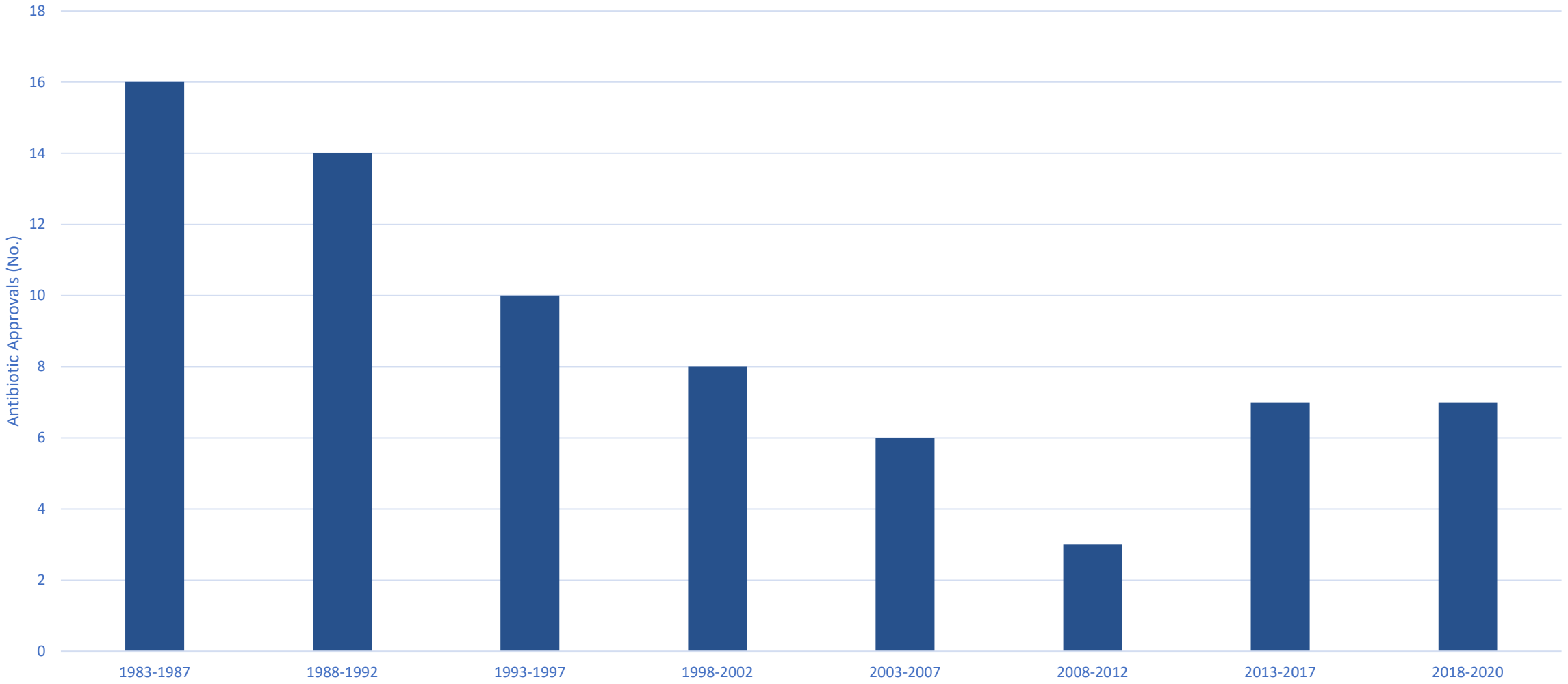
Source: Molton JS, Tambyah PA, Ang BS. The Global Spread of Healthcare-Associated Multidrug-Resistant Bacteria: A Perspective From Asia. Clin Infect Dis. 2013;56(9):1310-8.

Combating Antibiotic-Resistant Bacteria



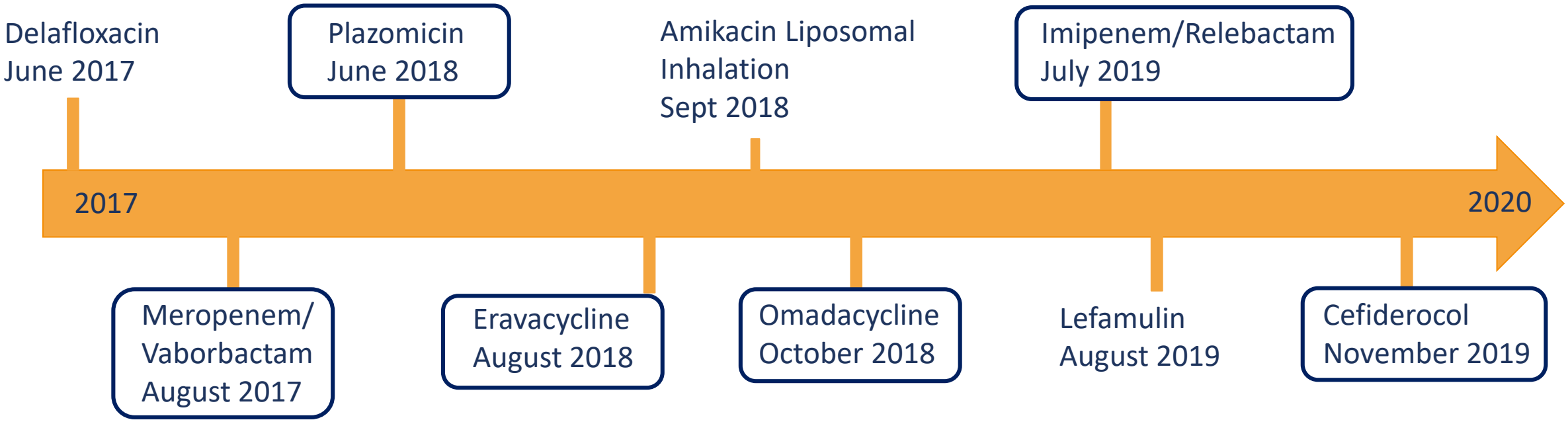
Source: CDC. Antibiotic Resistance Threats in the United States, 2019. Atlanta, GA: U.S. Department of Health and Human Services, CDC; 2019.

New Antibiotic Approvals



Source: U.S. Food and Drug Administration. Drug Approvals and Databases. Available at: https://www.fda.gov/drugs/development-approval-process-drugs/drug-approvals-and-databases. Accessed 24 June 2020.

New Antibiotic Approvals



Ceftolozane/tazobactam: December 2014
Ceftazidime/avibactam: February 2015

Source: U.S. Food and Drug Administration. Drug Approvals and Databases. Available at: https://www.fda.gov/drugs/development-approval-process-drugs/drug-approvals-and-databases. Accessed 24 June 2020.

Formulary Decisions and Stratification

- Value-based healthcare delivery requires a multi-disciplinary vision for innovation
- Leverage a Corporate structure with Division and Facility stakeholders to guide decision-making
- Traditionally assess efficacy, safety, and expense of new drugs against older drugs
- Incorporate more evidence-based decision-making
  - What is the quality of the clinical efficacy and safety evidence?
  - What are the associated risks?
  - How does the new drug compare to current therapeutic alternatives in terms of efficacy and safety?
  - What are the current gaps in the market? Societal benefits of the medication?
  - Operational considerations?
  - Susceptibility testing considerations? How do we position medications among users?
  - How does the product cost align with outcomes? Are there additional add-on payments?

Eravacycline

IGNITEing a new flame or up in smoke?

- Eravacycline is an IV fluorocycline antibiotic related to the tetracycline class
- Spectrum of activity
  - Gram-negatives: ESBL-positive Enterobacteriaceae, CRE, and multi-drug resistant Acinetobacter sp.
  - Gram-positives: MRSA, VRE
  - Overcomes common tetracycline resistance mechanisms, including efflux pumps and ribosomal protection, results in activity against several MDR pathogens.
  - Not active against Proteus sp., Providencia sp., Morganella sp., or P. aeruginosa.
- Approved in Adults with:
  - Complicated intra-abdominal infections (cIAI) – 1 mg/kg q12h
  - Should not be used for the treatment of urinary tract infections
- Niche in therapy
  - Treatment of cIAI due to MDROs when other treatment options are unavailable or are contraindicated
    - cIAI due to ESBL, AmpC, KPC, and some metallo-beta-lactamase (class B) enzymes, some MDR Acinetobacter sp., methicillin-resistant Staphylococcus aureus (MRSA), and vancomycin-resistant enterococci (VRE), polymyxin-resistance gene mcr-1
  - Similar to other tetracyclines, eravacycline may have a low risk of C. difficile infection.

Sources: Zhanel GG, Cheung D, Adam H, e al. Review of Eravacycline, a Novel Fluorocycline Antibacterial Agent. Drugs (2016) 76:567–588.
Solomkin J, Evans D, Slepavicius A, et al. Assessing the Efficacy and Safety of Eravacycline vs. Ertapenem in Complicated Intra-abdominal Infections in the Investigating Gram-Negative Infections Treated With Eravacycline (IGNITE 1) Trial. JAMA Surg . 2017 Mar 1;152(3):224-232.

Eravacycline - Activity against Carbapenem-Resistant *Enterobacteriaceae* and *Acinetobacter baumannii*

- Eravacycline MICs correlated closely with those of tigecycline, but mostly were around 2-fold lower;
- Both molecules retained full activity against isolates with high-level tetracycline and minocycline resistance.

Drug and Characteristic(s) (n)	≤0.06	0.13	0.25	0.5	1	2	4	8	≥16
Eravacycline									
KPC (45)		3	13	17	9	2	1		
VIM (44)			16	18	8	2			
IMP (15)		1	4	4	1	5			
NDM (42)		5	16	9	9	2	1		
Oxa-48 (44		2	18	15	5	2	2		
Porin loss + ESBL/AmpC (40)		1	13	10	8	5	3		

Source: Livermore DM, Mushtaq S, Warner M, et al. In Vitro Activity of Eravacycline Against Carbapenem-Resistant Enterobacteriaceae and Acinetobacter Baumannii. Antimicrob Agents Chemother . 2016 May 23;60(6):3840-4.

Eravacycline – Clinical Data

IGNITE Trial

- Eravacycline was evaluated for the treatment of cIAI in two Phase 3, randomized, double-blind, multi-center trials against ertapenem (IGNITE1, NCT01844856) and meropenem (IGNITE4, NCT 02784704).
  - Complicated intra-abdominal infections included appendicitis, cholecystitis, diverticulitis, gastric/duodenal perforation, intra-abdominal abscess, intestinal perforation, and peritonitis.
- The primary efficacy end point was clinical cure at TOC visit in the micro-ITT populations.
  - In both trials, eravacycline met the non-inferiority margin

Clinical Cure Rates at TOC in Phase 3 cIAI trials, micro-ITT population

	IGNITE1		IGNITE4	
	Eravacycline	Ertapenem	Eravacycline	Meropenem
Clinical cure, no/total (%)	191/220 (86.8%)	198/226 (87.6%)	177/195 (90.8%)	187/205 (91.2%)
Difference (95% CI)	-0.80 (-7.1 to 5.5)		-0.5 (-6.3 to 5.3)	

- Treatment of MDR Gram-negative organisms?
  - No data…

Sources: Solomkin J, Evans D, Slepavicius A, et al. Assessing the efficacy and safety of eravacycline vs. ertapenem in complicated intra-abdominal infections in the Investigating Gram-Negative Infections Treated with Eravacycline (IGNITE1) Trial. JAMA Surgery. 2017;152(3):224-232.
Tetraphase Pharmaceuticals, Inc. (2017, July 25). Tetraphase Announces Positive Top-Line Results from Phase 3 IGNITE4 Clinical Trial in Complicated Intra-Abdominal Infections [Press Release]. Retrieved from https://ir.tphase.com/news-releases/news-release-details/tetraphase-announces-positive-top-line-results-phase-3-ignite4

Eravacycline - Important Things to Know

- Approved for cIAIs
  - Failed non-inferiority trails for cUTI.
- Potential coverage for extensive resistant organisms
  - Lack of clinical efficacy data for infections caused by MDROs.
    - Phase 3 trials had very few patients with confirmed MDROs (i.e. ESBL-positive strains, CRE)
- Comparative data between other antibiotics for treatment of CRE and in general are lacking.
- Eravacycline does not have activity against *Pseudomonas aeruginosa* and should not be used for infections where this pathogen is suspected or confirmed.
- Only available in an intravenous formulation; the oral formulation is still in clinical development due to poor outcomes observed in the cUTI trials.
- Caution against use
  - Pregnancy, infancy, and childhood up to the age of 8 years
- Not included on *in vitro* automated susceptibility testing panels.

Omadacycline

A New Frontier for Tetracyclines or an OPTICal Illusion?

- Omadacycline is an aminomethylcycline, a semisynthetic derivative of tetracycline available in both IV and PO formulations
- Spectrum of activity
  - MRSA, penicillin-resistant and MDR *Streptococcus pneumoniae*, VRE, and many ESBL producers
    - Chemical structure allows it to overcome common resistance mechanisms seen with other tetracyclines, including efflux pumps and ribosomal protection, resulting in activity against several drug-resistant pathogens.
  - Approximately 50% of tetracycline-resistant A. baumannii are susceptible to omadacycline
  - Not active against *Proteus sp., Providencia sp., Morganella sp.,* or *P. aeruginosa*.
- Approved in Adults with:
  - Community-acquired bacterial pneumonia (CABP)
  - Acute bacterial skin and skin structure infections (ABSSSIs)
- Niche in therapy
  - Oral therapy with potential activity for ESBL producers
    - CAP, SSTIs, Osteo?

Source: Villano S, Steenbergen J, Loh E. Omadacycline: development of a novel aminomethylcycline antibiotic for treating drug-resistant bacterial infections. Future Microbiol. (2016) 11(11), 1421–1434.

Omadacycline - Activity Against Selected Gram-Negative Bacilli

Organism or group (n)	≤0.06	0.12	0.25	0.5	1	2	4	8	16	32	≥32
Imipenem-resistant Enterobacteriaceae (277)			0	9	42	50	45	45	39	36	11
Tetracycline-resistant Enterobacteriaceae (2,737)	0	2	55	320	527	574	436	272	278	203	70
Tigecycline-nonsusceptible Enterobacteriaceae (183)							0	3	34	94	52
Imipenem-resistant *E. coli* (4)		0	0	1	3						
Tetracycline-resistant *E. coli* (1,272)	0	2	54	310	448	312	111	28	4	3	
Imipenem-resistant *K. pneumoniae* (144)			0	3	26	44	36	25	5	5	
Tetracycline-resistant *K. pneumoniae* (430)			0	6	47	109	129	70	43	22	4
Tigecycline-nonsusceptible *K. pneumoniae* (22)								0	7	12	3

Source: Pfaller MA, Huband MD, Shortridge D, et al. Surveillance of Omadacycline Activity Tested Against Clinical Isolates From the United States and Europe as Part of the 2016 SENTRY Antimicrobial Surveillance Program. Antimicrob Agents Chemother . 2018 Mar 27;62(4):e02327-17.

Omadacycline – Clinical Data

OPTIC Trial

- Three Phase-3, non-inferiority trials comparing omadacycline to linezolid or moxifloxacin for the treatment of adult patients with either ABSSSI or CABP.

	OASIS-1 (ABSSSI)		OASIS-2 (ABSSSI)		OPTIC (CABP)	
	Omadacycline	Linezolid	Omadacycline	Linezolid	Omadacycline	Moxifloxacin
Clinical cure, no/total (%)	268/316 (84.8%)	266/311 (85.5%)	315/360 (87.5%)	297/360 (82.5%)	313/386 (81.1%)	321/388 (82.7%)
% Difference (95% CI)	-0.7 (-6.3 to 4.9)		5.0 (-0.2 to 10.3)		-1.6 (-7.1 to 3.8)	

- Treatment of MDR Gram-negative organisms?
  - No data…

Sources: O'Riordan W, Green, S, Overcash JS, et al. Omadacycline for Acute Bacterial Skin and Skin-Structure Infections. N Engl J Med 2019; 380:528-538.
O'Riordan W, Cardenas C, Shin E, et al. Once-daily Oral Omadacycline Versus Twice-Daily Oral Linezolid for Acute Bacterial Skin and Skin Structure Infections (OASIS-2): A Phase 3, Double-Blind, Multicentre, Randomised, Controlled, Non-Inferiority Trial. Lancet Infect Dis. 2019 Oct;19(10):1080-1090.
Stets R, Popescu M, Gonong JR, et al. Omadacycline for Community-Acquired Bacterial Pneumonia. N Engl J Med 2019; 380:517-527.

Omadacycline - Important Things to Know

- Approved for CABP and ABSSSIs
- Potential coverage for resistant organisms
  - Lack of clinical efficacy data for infections caused by MDROs.
    - Phase 3 trials had very few patients with confirmed MDROs (i.e. ESBL-positive strains, CRE)
  - Susceptibilities to doxycycline and/or minocycline should be checked prior to considering omadacycline since tetracyclines may retain activity against omadacycline susceptible isolates.
- Comparative data between other antibiotics for treatment of ESBLs and CRE are lacking.
- Omadacycline does not have activity against *Pseudomonas aeruginosa* and should not be used for infections where this pathogen is suspected or confirmed.
- Caution against use
  - Pregnancy, infancy, and childhood up to the age of 8 years
- Not included on *in vitro* automated susceptibility testing panels.

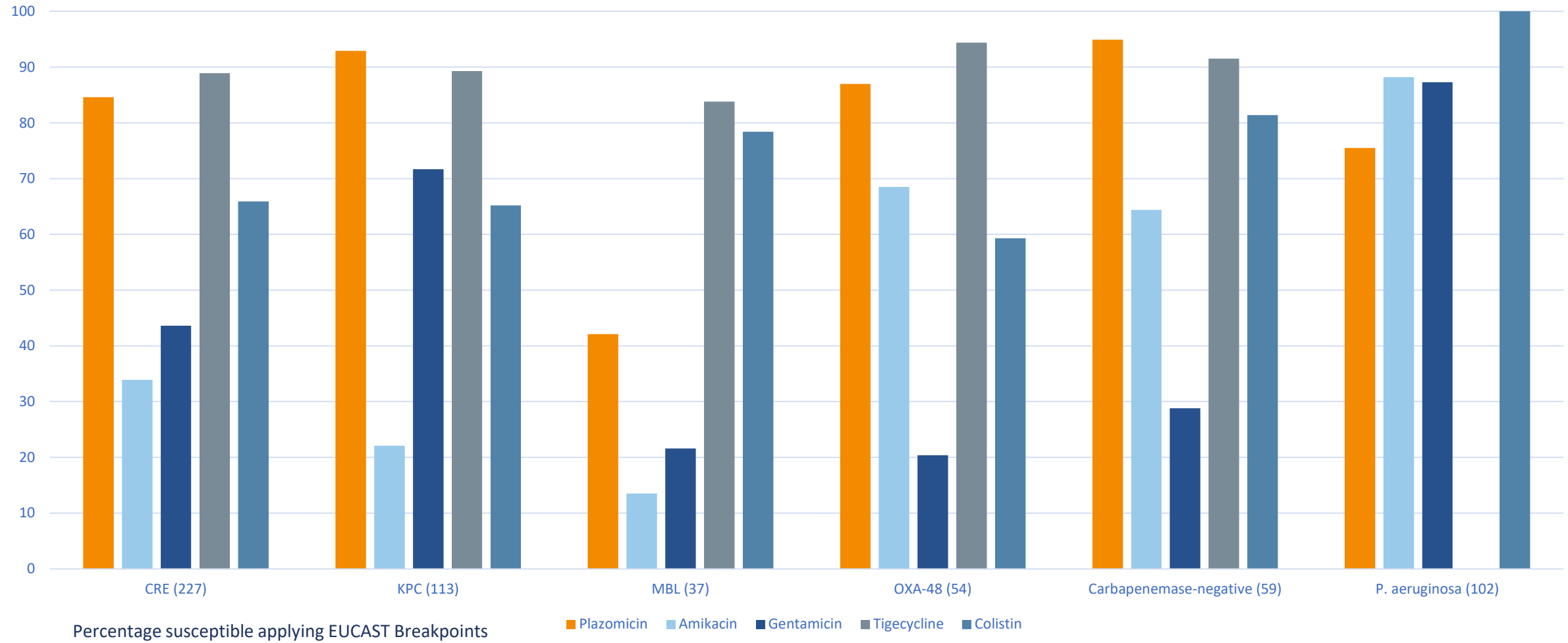
Plazomicin

CARE to Try an Aminoglycoside?

- Plazomicin is a next-generation IV aminoglycoside
- Spectrum of activity
  - Similar to the aminoglycoside class and includes Gram-negative organisms.
  - Expanded coverage against MDR Gram-negative organisms through its ability to block most AMEs that are often co-produced with other resistance mechanisms, including beta-lactamases and carbapenemases.
    - Activity against ESBLs and KPCs and some OXA-producing bacteria, polymyxin-resistance gene mcr-1.
  - Like other aminoglycosides, is inactive against isolates that produce 16S rRNA methyltransferases.
  - Unreliable option for infections caused by metallo-beta-lactamase producers and less potent against P. aeruginosa than other aminoglycosides
  - No demonstrable in vitro activity against Acinetobacter sp.
- Approved in adults with
  - cUTIs including pyelonephritis in adults with limited or no alternative treatment options.
  - Not approve a bacteremia indication based on data in a Phase 3 trial for serious infections caused by CRE.
- Niche in therapy
  - Treatment of cUTIs due to CRE
  - OPAT

Sources: Zemdri (plazomicin) [prescribing information]. South San Francisco, CA: Achaogen, Inc. June 2018.
Shaeer KM, Zmarlicka MT, Chahine EB, et al. Plazomicin: a next-generation aminoglycoside. *Pharmacotherapy* 2019; 39 (1): 77-93.

Comparative Plazomicin Activity Against Select Gram-Negative Bacilli



Percentage susceptible applying EUCAST Breakpoints

Source: Castanheira M, Deshpande LM , Woosley LN, et al. Activity of plazomicin compared with other aminoglycosides against isolates from European and adjacent countries, including Enterobacteriaceae molecularly characterized for aminoglycosidemodifying enzymes and other resistance mechanisms. J Antimicrob Chemother 2018; 73: 3346–3354.

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Plazomicin Outcomes Against CRE

- The CARE trail was a Phase 3, open-label study that evaluated plazomicin in two cohorts of patients with serious infections caused by CRE.
- The primary outcome was 28-day all-cause mortality or significant disease-related complications in the mMITT population.

		CARE		
		Plazomicin + Meropenem or Tigecycline	Colistin + Meropenem or Tigecycline	% Difference (95% CI)
Cohort 1	Primary Outcome (%)	4/17 (23.5%)	10/20 (50%)	-0.7 to 51.2
	28-day All-cause Mortality (%)	2/17 (11.8%)	8/20 (40%)	0.7-52.5
Cohort 2	BSI Primary Outcome (%)	5/14 (35.7%)	-	-
	BSI 28-day All-cause Mortality (%)	2/14 (14.3%)	-	-
	HABP/VABP 28-day All-cause Mortality (%)	4/9 (44.4%)	-	-
	cUTI 28-day All-cause Mortality (%)	0/4 (0%)	-	-

Source: McKinnell JA, Connolly LE, Pushkin R, et al. Poster #1853. Improved outcomes with plazomicin compared with colistin in patients with bloodstream infections caused by carbapenem-resistant Enterobacteriaceae (CRE): results from the CARE study. IDWeek; October 4-8, 2017; San Francisco, CA. Poster 1853.

Plazomicin – Important Things to Know

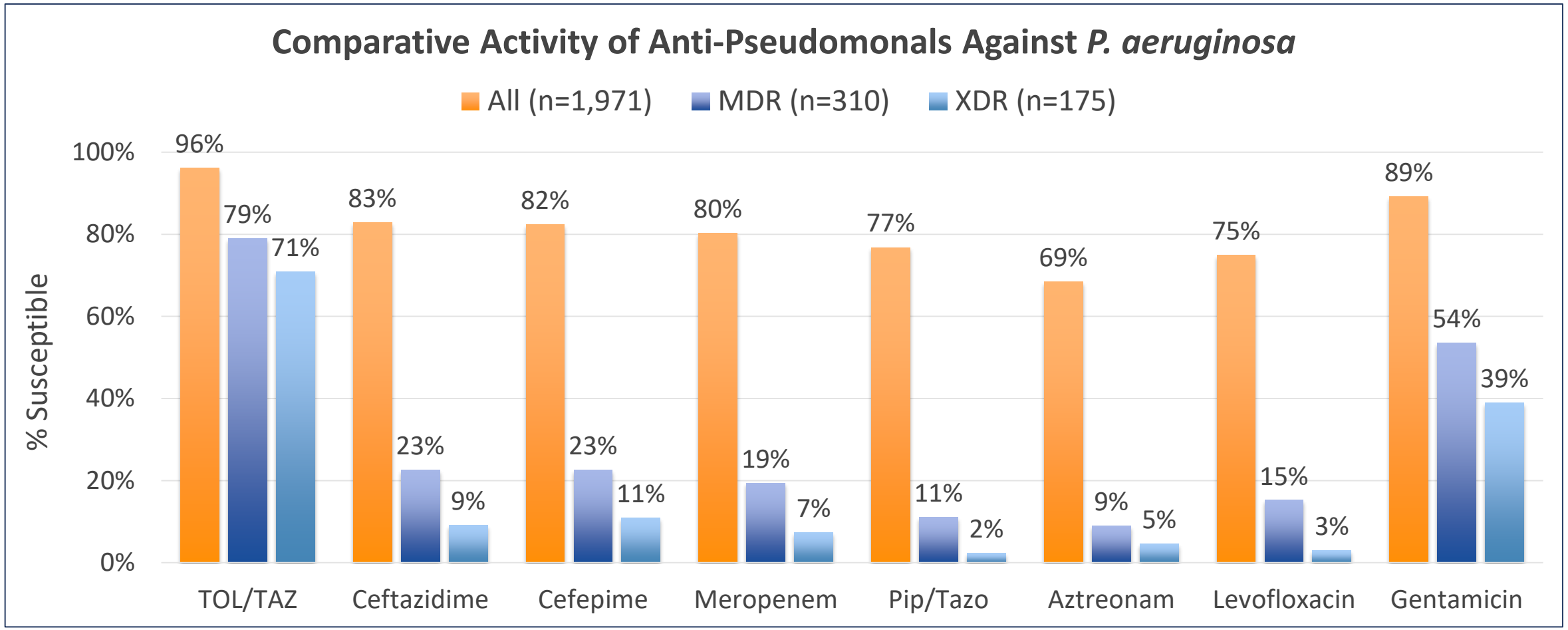
- Approved for cUTIs
- Potential coverage for CRE
  - Lack of clinical efficacy data comparing to newer beta-lactam/beta-lactamase combinations
  - No appreciable benefits for AG-resistant P. aeruginosa
- Potential in OPAT space
- Not included on in vitro automated susceptibility testing panels.
- Plazomicin carries black box warnings for nephrotoxicity, ototoxicity, neuromuscular blockade, and fetal harm in pregnant mothers.
- TDM required in most patients
  - Currently a send out lab

Ceftolozane/Tazobactam

An Old Beta-Lactamase Finds a New Partner

- Ceftolozane is a cephalosporin with potent anti-pseudomonal activity, similar to ceftazidime
- Tazobactam is a beta-lactamase inhibitor that protects ceftolozane from ESBLs and many cephalosporinases
- Spectrum of activity
  - Good activity: ESBL-producers and resistant *P. aeruginosa*, including carbapenem-resistant strains
  - Weak or no activity: ceftazidime-resistant *Enterobacter* spp, carbapenem-resistant Enterobacteriaceae (CRE), gram-positive organisms, and anaerobes
- Approved for adults with:
  - Complicated intra-abdominal infections (cIAI), in combination with metronidazole
  - Complicated urinary tract infections (cUTI), including pyelonephritis
  - Hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia (HABP/VABP)
- Niche in therapy
  - Severe beta-lactam-resistant/MDR *P. aeruginosa* infections

Ceftolozane/Tazobactam (TOL/TAZ) – MDR *P. aeruginosa* Activity



MDR, multidrug-resistant (nonsusceptible to ≥ 1 agent in ≥ 3 antimicrobial classes); XDR, extensively drug-resistant (nonsusceptible to ≥ 1 agent in all but ≤ 2 antimicrobial classes)

Source: Farrell DJ, et al. *Antimicrob Agents Chemother* 2013; 57: 6305-10.

Ceftolozane/Tazobactam (TOL/TAZ) – Outcomes in MDR *P. aeruginosa* Infections

- Initiation ≤ 4 days after culture improves survival and clinical cure

Mortality	aOR (95% CI)
TOL/TAZ > 4 days after culture	5.55 (2.14-14.4)
Age ≥ 60 years	0.2 (0.07-0.57)
Charlson comorbidity index	1.24 (1.01-1.52)
Vasopressor use	5.68 (2.15-14.98)
APACHE II	1.14 (1.08-1.22)

Clinical Success	aOR (95% CI)
TOL/TAZ ≤ 4 days after culture	5.55 (2.14-14.4)
Vasopressor use	0.16 (0.07-0.34)
APACHE II	0.95 (0.91-0.99)

- Improved clinical cure and less AKI versus aminoglycoside/polymyxin-based therapy

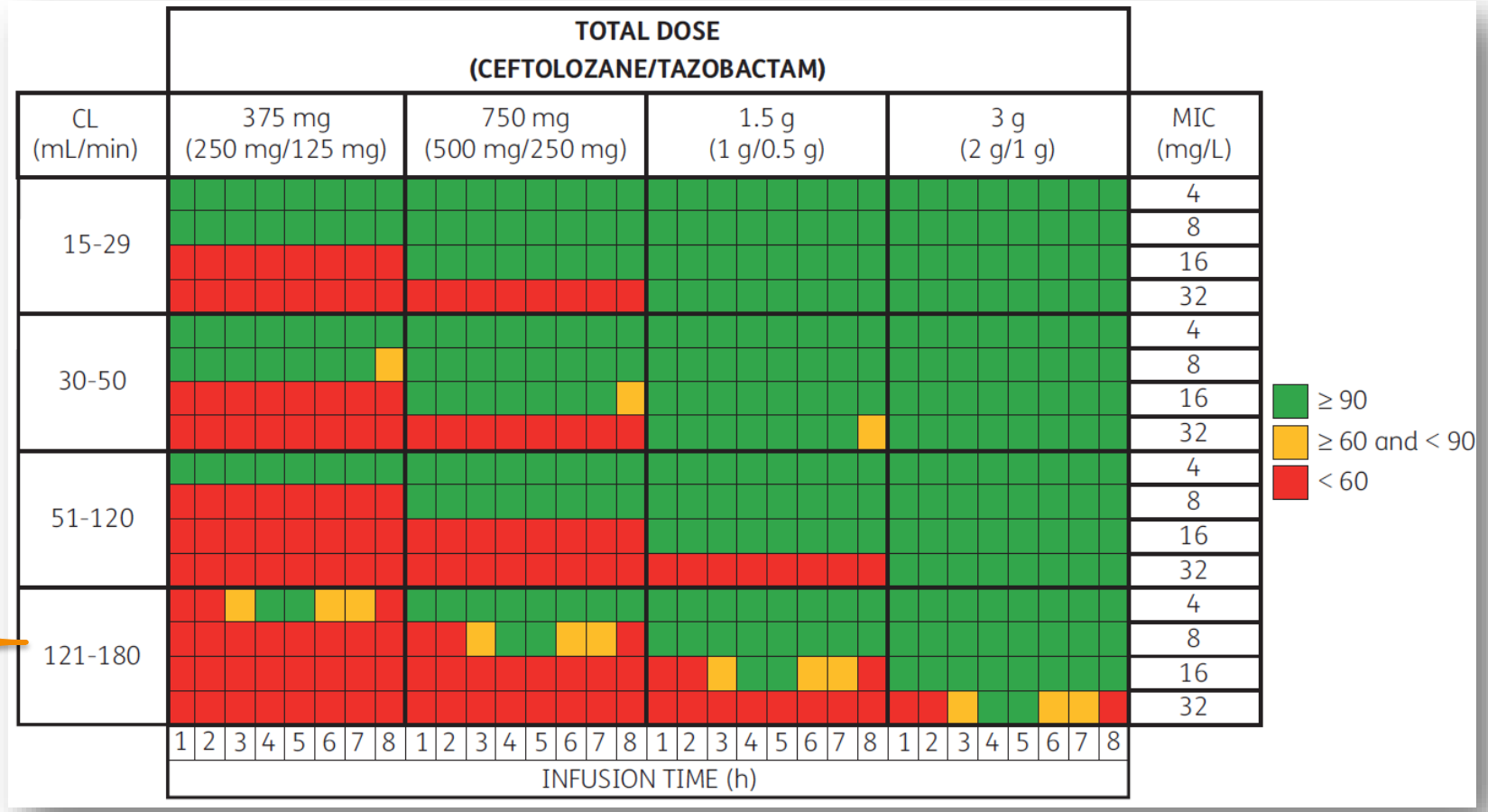
Outcome	TOL/TAZ (n=100)	AMG/Polymyxin (n=100)	aOR (95% CI)
Clinical cure	81 (81%)	61 (61%)	2.63 (1.31-5.3)
In-hospital mortality	20 (20%)	25 (25%)	0.62 (0.3-1.28)
Acute kidney injury	6 (6%)	34 (34%)	0.08 (0.03-0.22)

Concomitant antibiotics had no effect on clinical cure or mortality in these studies

Source:Gallagher JC, et al. *Open Forum Infect Dis* 2018; doi: 10.1093/ofid/ofy280; Pogue JM, et al. *Clin Infect Dis* 2019 Sep 23; ciz816. doi: 10.1093/cid/ciz816.

Ceftolozane/Tazobactam – Alternative Dosing using PK/PD Strategies

- Higher MICs
  - Good renal function + high MIC → lower probability of adequate exposure
  - Extended infusion allows for less drug/day while achieving ≥ 90% probability of adequate exposure
  - MIC=4: 375mg q8h (4h inf)
  - MIC=8: 750mg q8h (4h inf)
  - MIC=16: 1.5g q8h (4h inf)
  - MIC=32: 3g q8h (4h inf)



- Outpatient infusion
  - Stable for up to 24 hours at room temperature
  - Case series of 7 patients given continuous infusion for MDR *P. aeruginosa* infection – most received 4.5 grams/day
  - 6/7 achieved symptom resolution and 3/3 had microbiologic success

Source: Natesan S, et al. *J Antimicrob Chemother* 2017; 72: 2813-6; Jones BM, et al. *Open Forum Infect Dis* 2020; doi: 10.1093/ofid/ofaa014.

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Ceftolozane/Tazobactam – Important Things to Know

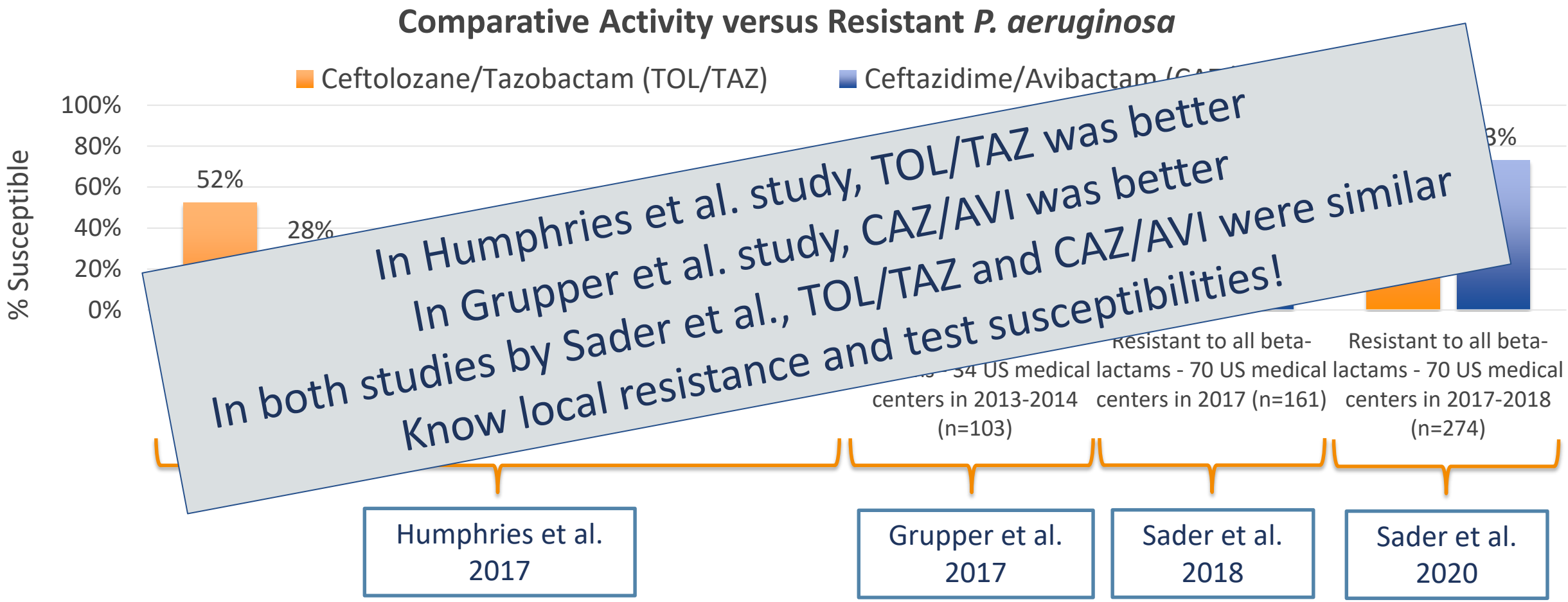
- Place in therapy → beta-lactam-resistant *P. aeruginosa* infections
- Improved outcomes seen in MDR *P. aeruginosa* infections compared to aminoglycoside/polymyxin-based therapy
  - Earlier initiation improves outcomes
  - Monotherapy is perfectly adequate
- Warning in package insert on decreased efficacy in cIAI patients with CrCl of 30 to 50 mL/min
- Recommended dose is higher in HABP/VABP (3 g q8h) versus cIAI or cUTI (1.5 g q8h)
  - Infusion time is 1 h
- Prolonged infusions can be used to overcome higher MICs in resistant isolates
  - Evaluate patient's renal function and MIC to develop individualized dosing regimen based on PK/PD data

Ceftazidime/Avibactam

CRACKing Down on CRE

- Ceftazidime is a 3rd generation cephalosporin
- Avibactam is a beta-lactamase inhibitor that expands ceftazidime's coverage to include ESBLs and some carbapenemases (KPC- and OXA-producers)
- Spectrum of activity
  - Good activity: ESBL-producers and most carbapenem-resistant Enterobacteriaceae (CRE)
  - Variable to good activity: resistant *P. aeruginosa*
  - No activity: metallo-beta-lactamase-producing Enterobacteriaceae (MBLs), gram-positive organisms, and anaerobes
- Approved for:
  - Complicated intra-abdominal infections (cIAI), in combination with metronidazole, in patients ≥ 3 months
  - Complicated urinary tract infections (cUTI), including pyelonephritis, in patients ≥ 3 months
  - Hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia (HABP/VABP) in adults
- Niche in therapy
  - Severe CRE infections
  - Polymicrobial infection involving CRE and carbapenem-resistant/MDR *P. aeruginosa*

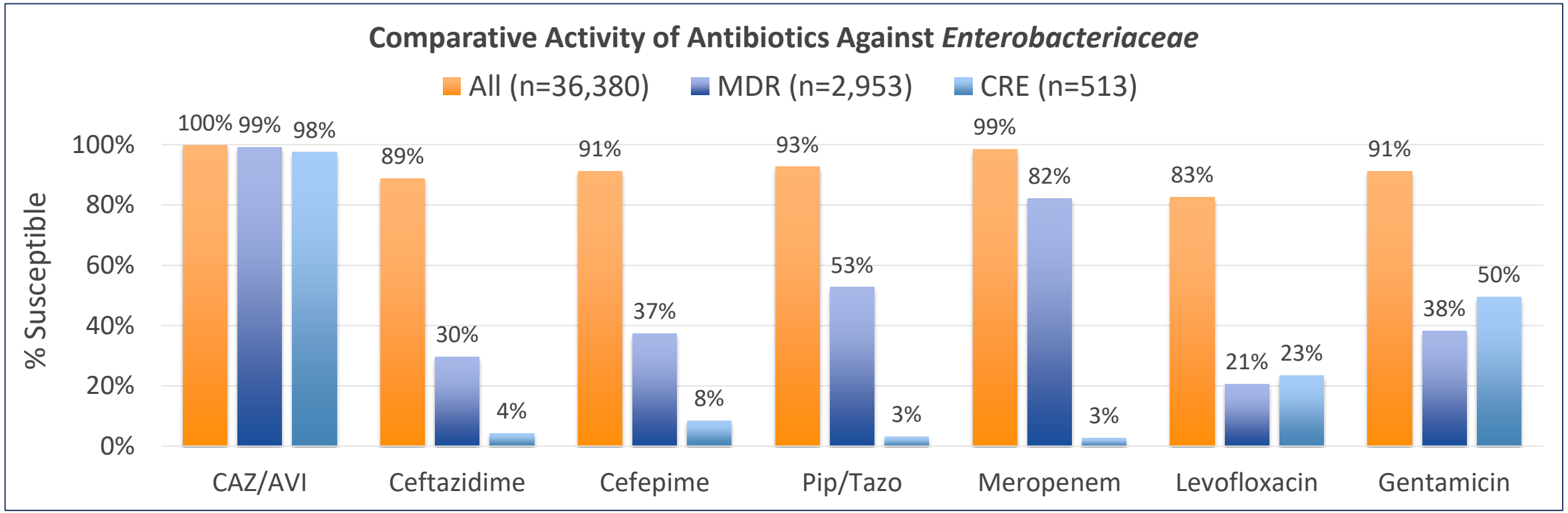
Ceftazidime/Avibactam vs. Ceftolozane/Tazobactam *P. aeruginosa* Activity



In Humphries et al. study, TOL/TAZ was better
In Grupper et al. study, CAZ/AVI was better
In both studies by Sader et al., TOL/TAZ and CAZ/AVI were similar
Know local resistance and test susceptibilities!

Sources: Humphries RM, et al. *Antimicrob Agents Chemother* 2017; 61: e01858-17; Grupper M, et al. *Antimicrob Agents Chemother* 2017; 61: e00875-17; Sader HS, et al. *Antimicrob Agents Chemother* 2018; 62: e01587-18; Sader HS, et al. *Diagn Microbiol Infect Dis* 2020; 96: 114833.

Ceftazidime/Avibactam (CAZ/AVI) – CRE Activity



CRE, carbapenem-resistant Enterobacteriaceae; MDR, multidrug-resistant (nonsusceptible to ≥ 1 agent in ≥ 3 antimicrobial classes)

- Resistance to CAZ/AVI
  - Resistance emergence has been reported in 3 of 37 treated patients with KPC infections
  - No activity versus MBL-producing Enterobacteriaceae

Source: Sader HS, et al. *Antimicrob Agents Chemother* 2017; 61: e01045-17; Shields RK, et al. *Clin Infect Dis* 2016; 63: 1615-8.

Ceftazidime/Avibactam (CAZ/AVI) – Outcomes in CRE Infections

- Improved survival and clinical cure and lower AKI versus alternative regimens in CRE bacteremia

Outcome	CAZ/AVI (n=13)	Alternatives (n=96)	aOR (95% CI)
Clinical success	11 (85%)	39 (41%)	8.64 (1.61-46.39)
30-day mortality	1 (8%)	30 (31%)	NR
Acute kidney injury	2 (18%)	27 (28%)	NR

- CRACKLE study: improved benefit-risk outcomes versus colistin in CRE infections, majority of whom received another anti-CRE antibiotic or carbapenem (CAZ/AVI 47%; colistin 74%)

Outcome	CAZ/AVI (n=38)	Colistin (n=99)	P-value
IPTW-mortality	9%	32%	0.001

- No difference in outcomes when comparing mono- versus combination therapy for CRE infections
  - Exception: CRE that produce metallo-beta-lactamases (MBLs) → CAZ/AVI + aztreonam associated with decreased mortality, clinical failure, and LOS versus other active agents in MBL bacteremia
    - *Why*? aztreonam has MBL activity; CAZ/AVI has ESBL activity

Source: Shields RK, et al. *Antimicrob Agents Chemother* 2017; 61: e00883-17; van Duin D, et al. *Clin Infect Dis* 2018; 66: 163-71; Onorato L, et al. *Int J Antimicrob Agents* 2019; 54: 735-40.

Meropenem/Vaborbactam

It Takes Two to TANGO

- Meropenem is a carbapenem with broad-spectrum activity
- Vaborbactam is a boronic acid beta-lactamase inhibitor active against KPC-producing CRE
- Spectrum of activity
  - Good activity: KPC-producers, most CRE
  - Weak or no activity: carbapenem-resistant Pseudomonas and gram-negative organisms producing metallo-beta-lactamases (MBLs) or OXA-enzymes
- Dose is higher than standard meropenem dosing → 4 g q8h (3h infusion) = 2 grams of meropenem
- Approved for adults with:
  - Complicated urinary tract infections (cUTI), including pyelonephritis
- Niche in therapy
  - Severe CRE infections

Meropenem/Vaborbactam – KPC-Producing CRE Activity

- Great activity vs. CRE that produce KPC; no advantage against CRE with other mechanisms of resistance:

Antibiotic	MIC_{90} (mg/L)				
	CRE (n=265)	KPC-producers (n=135)	OXA-48-producers (n=25)	MBL-producers (n=41)	CP-negative CRE (n=63)
Meropenem/Vaborbactam	32	0.50	> 32	> 32	4
Meropenem	> 32	> 32	> 32	> 32	16

- Comparable activity to ceftazidime/avibactam against CRE that produce KPC:

Antibiotic	Susceptible Breakpoint (mg/L)	MIC_{50} (mg/L)	MIC_{90} (mg/L)	% Susceptible
Meropenem/Vaborbactam	4	0.06	1	99
Ceftazidime/Avibactam	8	1	4	98.2

MIC_{50}, concentration inhibiting 50% of isolates; MIC_{90}, concentration inhibiting 90% of isolates

Source: Kazmierczak KM, et al. *Int J Antimicrob Agents* 2019; 53: 177-84; Hackel MA, et al. *Antimicrob Agents Chemother* 2018; 62: e01968-17.

Meropenem/Vaborbactam (MVB) – Outcomes in CRE Infections

- In cohort of patients with gram-negative infection treated with meropenem/vaborbactam:
  - Clinical success: 28/40 (70%)
  - 30-day mortality: 3 (7.5%)
  - 30-day recurrence: 5 (12.5%)
- TANGO-II Study: improved survival and clinical cure and lower AKI versus “best available therapy” (BAT) in serious CRE infections

Outcome	MVB (n=32)	BAT (n=15)	Difference (95% CI)
Clinical cure	21 (65.6%)	5 (33.3%)	32.3 (3.3 to 61.3)
Microbiologic cure	21 (65.6%)	6 (40%)	25.6 (-4.1 to 55.4)
28-day mortality	5 (15.6%)	5 (33.3%)	-17.7 (-44.7 to 9.3)
Renal-related adverse effects	2 (4%)	6 (24%)	-20 (NR)

Source: Alosaimy S, et al. *Open Forum Infect Dis* 2020; doi: 10.1093/ofid/ofaa051; Wunderink RG, et al. *Infect Dis Ther* 2018; 7: 439-55..

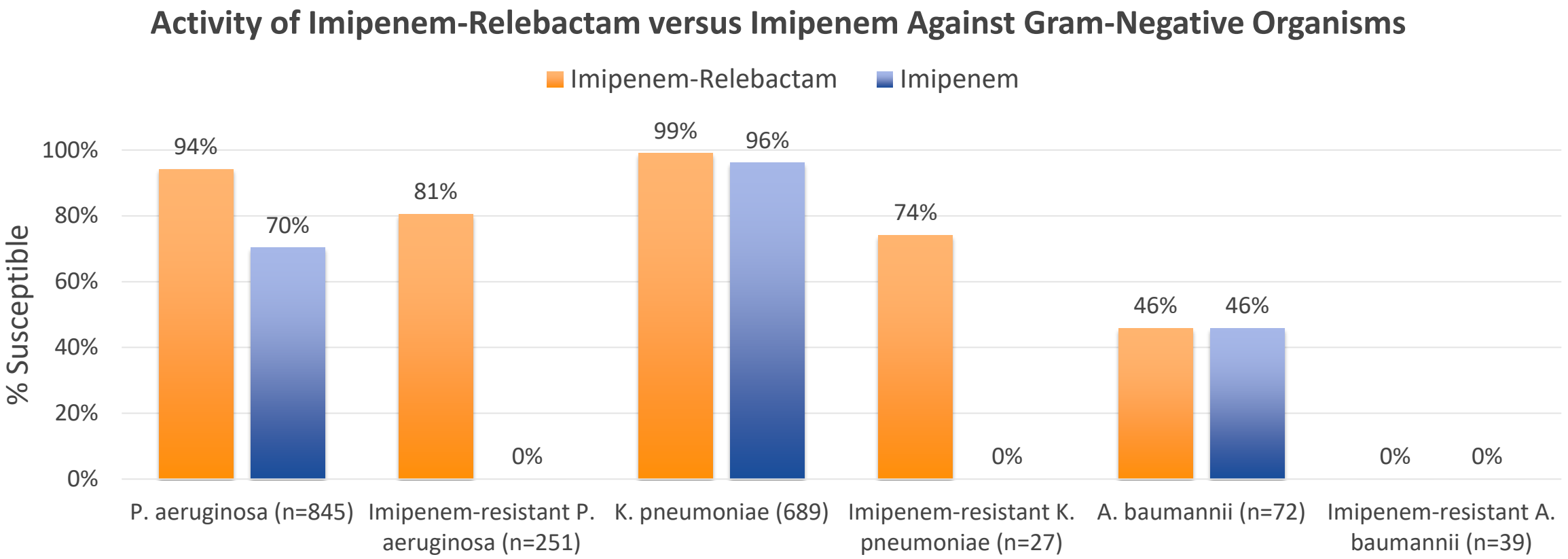
Imipenem-Cilastatin/Relebactam

Relebactam RESTOREs MDR Activity for Imipenem

- Imipenem-cilastatin is a carbapenem
- Relebactam is a beta-lactamase inhibitor, which broadens imipenem's activity to KPC-producing CRE and some MDR *P. aeruginosa* that produce beta-lactamases in concert with other resistance mechanisms
- Spectrum of activity
  - Good activity: KPC-producers, most CRE, carbapenem-resistant Pseudomonas
  - Weak or no activity: gram-negative organisms producing metallo-beta-lactamases (MBLs) or OXA-enzymes
- Approved for adults with:
  - Complicated intra-abdominal infections (cIAI), in combination with metronidazole
  - Complicated urinary tract infections (cUTI), including pyelonephritis
  - Hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia (HABP/VABP)
- Niche in therapy
  - Severe CRE infections
  - Polymicrobial infection involving CRE and carbapenem-resistant/MDR *P. aeruginosa*

Imipenem-Cilastatin/Relebactam – MDR Gram-Negative Activity

- Improved activity against *P. aeruginosa* and CRE; no advantage against carbapenem-susceptible *Enterobacteriaceae* or *Acinetobacter baumannii*



Source: Lob SH, et al. *Antimicrob Agents Chemother* 2017; 61: e02209-16.

HEALTHTRUST UNIVERSITY CONFERENCE

Imipenem-Cilastatin/Relebactam – Outcomes in MDR Infections

- RESTORE-IMI 1 Study: similar efficacy but less nephrotoxicity and fewer deaths compared to imipenem + colistin in carbapenem-resistant gram-negative infections

Outcome	Imipenem-cilastatin/ Relebactam	Imipenem + Colistin	Adjusted Difference (90% CI)
Favorable overall response	15/21 (71.4%)	7/10 (70%)	-7.3 (-27.5 to 21.4)
HABP/VABP favorable response	7/8 (87.5%)	2/3 (66.7%)	20.8 (NR)
cIAI favorable response	0/2 (0%)	0/2 (0%)	0
cUTI favorable response	8/11 (72.7%)	5/5 (100%)	-27.3 (-52.8 to 12.8)
28-day mortality	2/21 (9.5%)	3/10 (30%)	-17.3 (-46.4 to 6.7)
Nephrotoxicity	3/29 (10.3%)	9/16 (56.3%)	-45.9 (-69.1 to -18.4)

Source: Motsch J, et al. *Clin Infect Dis* 2019; 70: 1799-1808.

Comparative Activity of CRE Beta-Lactams

- Susceptibility by beta-lactamase:

	% of Susceptible Isolates				
	All CRE (n=62)	Non-CP-CRE (n=38)	KPC (n=5)	OXA-48 (n=6)	NDM (n=5)
Ceftazidime/Avibactam	87.1	100	100	100	0
Meropenem/Vaborbactam	79	92.1	100	66.7	0
Imipenem/Relebactam	71	89.5	100	50	0

CP, carbapenemase; CRE, carbapenem-resistant Enterobacteriaceae

- CRE beta-lactam/beta-lactamase inhibitors are not interchangeable
- Important to know local resistance patterns and test susceptibility to CRE agents being considered
- In a multicenter, retrospective cohort study, no differences in clinical success, mortality, or adverse events were seen in patients with CRE infections treated with ceftazidime/avibactam versus meropenem/vaborbactam

Source: Senchyna F, et al. *Diagn Microbiol Infect Dis* 2019; 93: 250-7; Ackley R, et al. *Antimicrob Agents Chemother* 2020; 64: e02313-19.

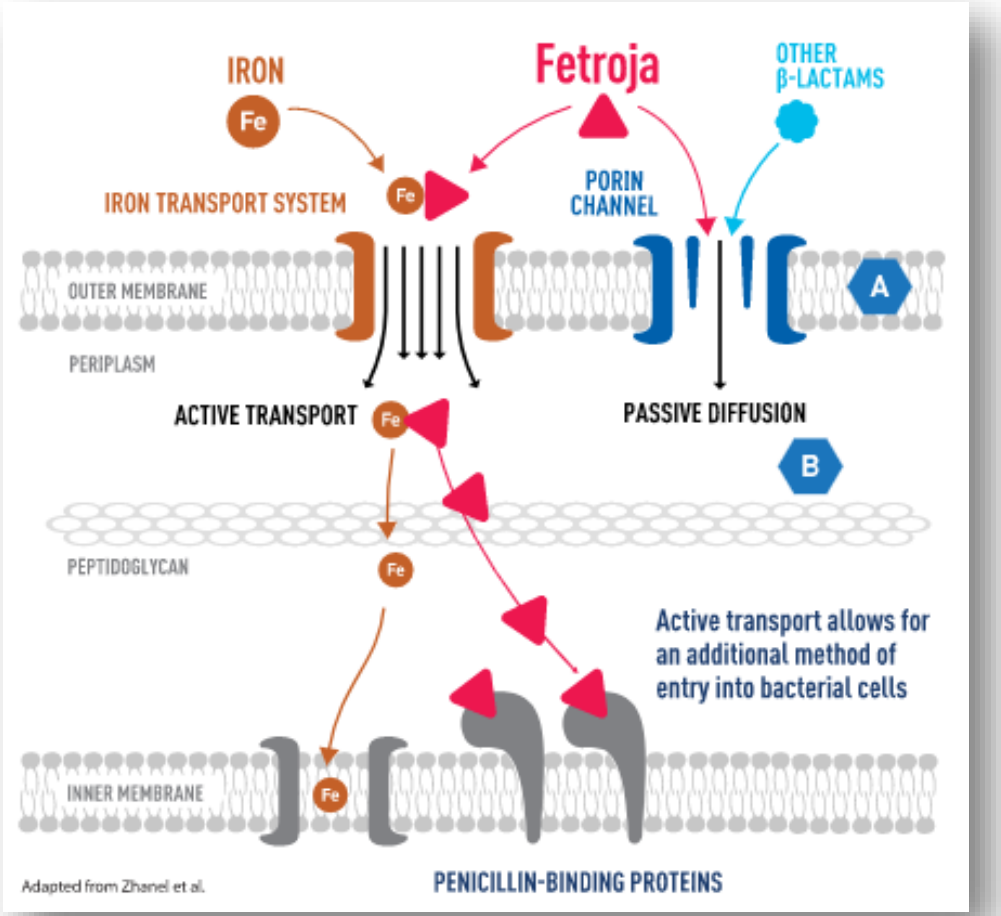
Key Differences Between CRE Beta-Lactams

	Ceftazidime/Avibactam	Meropenem/Vaborbactam	Imipenem-cilastatin/Relebactam
Notable activity	KPC-producing CRE OXA-48 producers Some carbapenem-resistant *P. aeruginosa*	KPC-producing CRE	KPC-producing CRE Carbapenem-resistant *P. aeruginosa*
Notable gaps in coverage	MBL producers *A. baumannii* Ceftazidime-resistant *S. maltophilia*	MBL producers OXA-48 producers Carbapenem-resistant *P. aeruginosa* *A. baumannii* *S. maltophilia*	MBL producers OXA-48 producers *A. baumannii* *S. maltophilia*
Approved indications	Adults and pediatrics: cUTI cIAI HABP/VABP	Adults only: cUTI	Adults only: cUTI cIAI HABP/VABP
Infusion time	2 h	3 h	30 min
Stability of diluted solution	12 h (room temp) 24 h (refrigeration)	4 h (room temp) 22 h (refrigeration)	2 h (room temp) 24 h (refrigeration)
Notable warnings	Decreased efficacy in cIAI patients with CrCl 30-50 mL/min	Decreases valproic acid concentrations	Decreases valproic acid concentrations

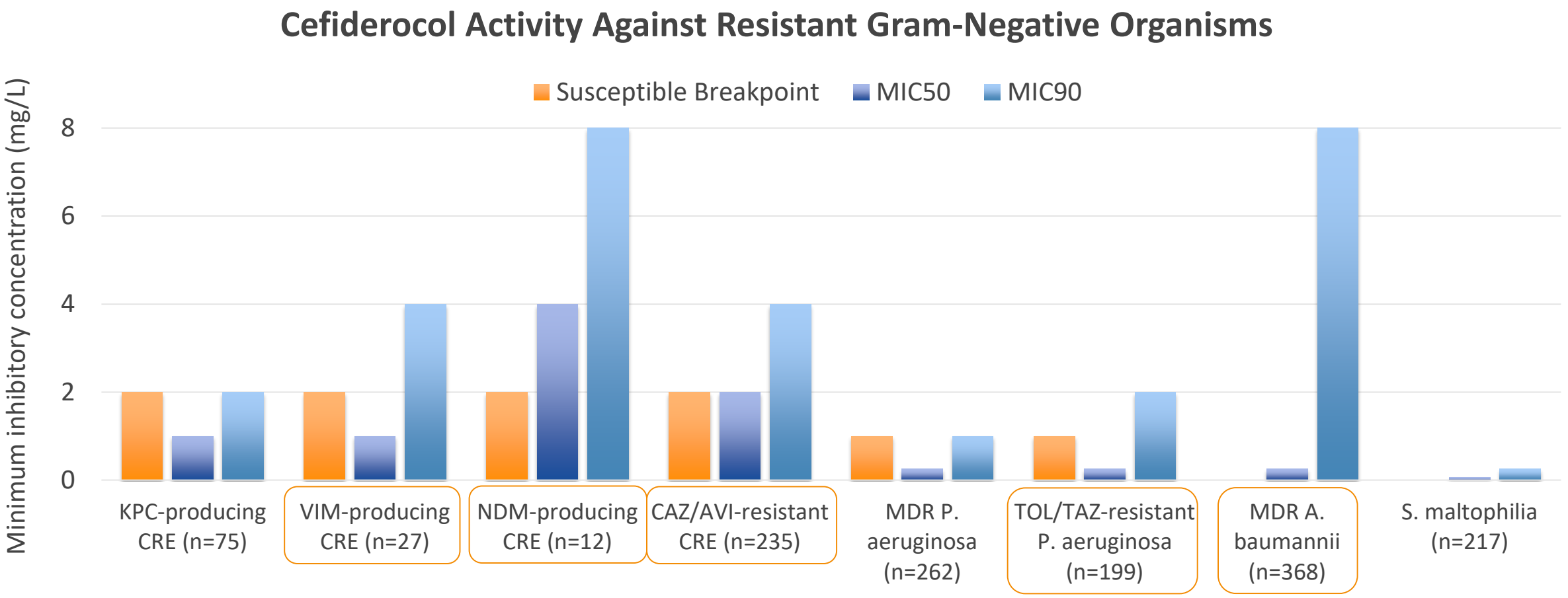
Cefiderocol

InCREDIBLE or Irrelevant?

- Cefiderocol is a novel cephalosporin that works by chelating ferric ions and using the bacterial iron transport system to cross the outer membrane of Gram-negative bacteria into the periplasmic space
- Spectrum of activity
  - Good activity: gram-negative organisms that produce any beta-lactamase, including CRE, MBL-producers, *P. aeruginosa*, *A. baumannii*, *S. maltophilia*
  - No activity: gram-positive organisms and anaerobes
- Approved for:
  - Complicated urinary tract infections (cUTI), including pyelonephritis in adults who have limited or no alternative treatment options
- Niche in therapy
  - Severe infections caused by gram-negative organisms resistant to all other treatment options



Cefiderocol – MDR Gram-Negative Activity



MIC50, concentration inhibiting 50% of isolates; MIC90, concentration inhibiting 90% of isolates

MIC_{90} higher than susceptible breakpoint → unreliable activity which necessitates susceptibility testing

Source: Kazmierczak KM, et al. *Int J Antimicrob Agents* 2019; 53: 177-84; Hackel MA, et al. *Antimicrob Agents Chemother* 2018; 62: e01968-17.

Cefiderocol – Outcomes in MDR Gram-Negative Infections

- Compassionate use data in carbapenem-resistant infections revealed some successful outcomes
  - 49/74 survived (66%), 3 of whom subsequently died due to other causes
  - 17/74 died due to infection (23%); 6 died due to other reasons (8%)
- CREDIBLE-CR: open-label randomized study of carbapenem-resistant infections showed similar clinical and microbiological outcomes versus "best available therapy" (BAT) but higher all-cause mortality with cefiderocol

Outcome	Cefiderocol	BAT	Difference (95% CI)
Clinical cure	42/80 (52.5%)	19/38 (50%)	2.5 (-16.8 to 21.8)
Microbiological eradication	25/80 (31.3%)	9/38 (23.7%)	7.6 (-9.3 to 24.5)
Day 14 all-cause mortality	19/101 (18.8%)	4/49 (12.2%)	6.6 (-5.4 to 18.5)

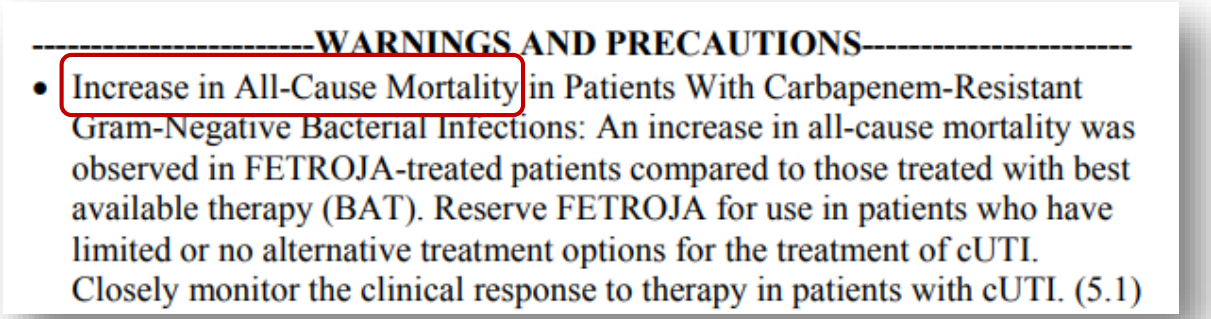
  - Adjudication committee assessed death related to infection and failure of antibiotic in 15.8% of cefiderocol- and 8.2% of BAT-treated patients
  - Higher mortality driven by an increase in deaths among cefiderocol patients with HAP/VAP/HCAP and BSI/sepsis

Source: U.S. Food and Drug Administration. FDA Briefing Document: Cefiderocol Briefing Document for the Antimicrobial Drugs Advisory Committee (AMDAC). October 16, 2019. Accessed from: https://www.fda.gov/advisory-committees/advisory-committee-calendar/october-16-2019-antimicrobial-drugs-advisory-committee-meeting-announcement-10162019-10162019. Accessed June 2020.

Cefiderocol – Important Things to Know

- Major advantage is activity versus MBL producers and non-lactose fermenting gram-negative rods (*P. aeruginosa*, *A. baumannii*, *S. maltophilia*)
  - Frequency of MBL enzyme is currently low in the US
  - Hospitals should evaluate local resistance in gram-negative organisms to determine formulary status and restrictions
- Doses are recommended to be adjusted in patients with *augmented* renal function
- Each dose needs to be infused over 3 hours
  - Diluted solution stable for 4 hours at room temp
- Approved duration is 7-14 days, which is longer than what is recommended for other effective agents for cUTI (ie, 5-7 days for fluoroquinolones)
- Increased mortality added as warning in package insert

Creatinine clearance (mL/min)	Dose
≥ 120 (augmented renal function)	2 g q6h
60 to 119	2 g q8h
30 to 59	1.5 g q8h
15 to 29	1 g q8h
< 15	0.75 g q12h
Hemodialysis	0.75 g q12h; give dose post-HD on dialysis days
CVVH	1 g q12h
CVVHD or CVVHDF	1.5 g q12h



----------WARNINGS AND PRECAUTIONS----------

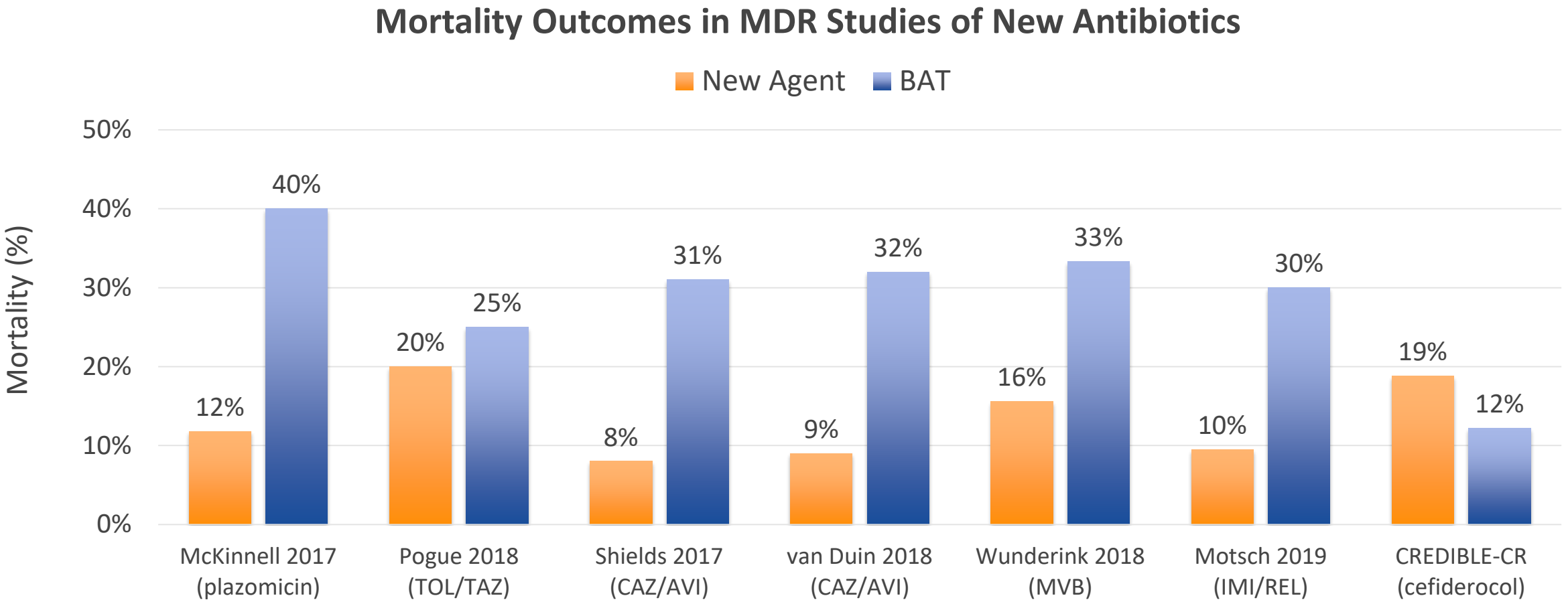
- Increase in All-Cause Mortality in Patients With Carbapenem-Resistant Gram-Negative Bacterial Infections: An increase in all-cause mortality was observed in FETROJA-treated patients compared to those treated with best available therapy (BAT). Reserve FETROJA for use in patients who have limited or no alternative treatment options for the treatment of cUTI. Closely monitor the clinical response to therapy in patients with cUTI. (5.1)

Summary of Activity of Newer Antibiotics

Antibiotic	Organism or Beta-Lactamase						
	ESBL	KPC	MBL	OXA-48	Beta-lactam-resistant *P. aeruginosa*	MDR *A. baumannii*	*S. maltophilia*
Omadacycline	+	-	-	ND	-	+/-	+/-
Eravacycline	+	+/-	+/-	+	-	+/-	+/-
Plazomicin	+	+	+/-	+	-	+/-	-
Ceftolozane/Tazobactam	+	-	-	-	+	-	-
Ceftazidime/Avibactam	+	+	-	+	+/-	-	-
Meropenem/Vaborbactam	+	+	-	-	-	-	-
Imipenem/Relebactam	+	+	-	-	+	-	-
Cefiderocol	+	+	+	+	+	+	+

+, reliable in vitro activity; +/-, may retain some in vitro activity; -, not reliably active
ESBL, extended-spectrum beta-lactamase; KPC, *K. pneumoniae* carbapenemase; MBL, metallo-beta-lactamase; MDR – multidrug-resistant; ND, no data

New CRE Agents Improve Mortality (*for the most part*)



CAZ/AVI, ceftazidime/avibactam; IMI/REL, imipenem-cilastatin/relebactam; MVB, meropenem/vaborbactam; TOL/TAZ, ceftolozane/tazobactam

Source: Shields RK, et al. *Antimicrob Agents Chemother* 2017; 61 (8): e00883; van Duin D, et al. *Clin Infect Dis* 2018; 66 (2): 163-71; Wunderink RG, et al. *Infect Dis Ther* 2018; 7: 439-55.

Clinical Action

ESBL

Severe infection
Meropenem

UTIs
Trim/sulfa
Nitrofurantoin
Levofloxacin
Aminoglycosides
Fosfomycin
Pip/Tazo or Cefepime (?)

CRE

Severe infection
MVB
CAZ/AVI
IMI/REL

Alternatives
Plazomicin combination therapy
Tigecycline
Eravacycline
Polymyxin combination therapy

UTIs
Aminoglycosides, plazomicin
Colistin
Fosfomycin
Trim/sulfa
Nitrofurantoin

Beta-lactam-resistant *P. aeruginosa*

Severe infection
TOL/TAZ

Alternatives
CAZ/AVI
IMI/REL
Polymyxin combination therapy

UTIs
Aminoglycosides
Colistin
Fosfomycin

Carbapenem-resistant *A. baumannii*

Severe infection
Ampicillin/sulbactam
Levofloxacin
Trim/sulfa
Doxycycline/minocycline
Tigecycline
Eravacycline
Cefiderocol

Alternatives
Polymyxin + another susceptible agent

UTIs
Aminoglycosides
Colistin
Nitrofurantoin

S. maltophilia

Severe infection
Trim/sulfa

Alternatives
Levofloxacin
Ceftazidime
If resistant to all above options:
Minocycline
Tigecycline
Eravacycline
Cefiderocol

CAZ/AVI, ceftazidime/avibactam; CRE, carbapenem-resistant Enterobacteriaceae; ESBL, extended-spectrum beta-lactamase; IMI/REL, imipenem-cilastatin/relebactam; MVB, meropenem/vaborbactam; TOL/TAZ, ceftolozane/tazobactam

Cascade Susceptibility Testing

- Can take at least a couple of years after drug approval to be included on standard in vitro susceptibility panels
- Gaps in spectrum of activity among all new antibiotics
- Susceptibility testing of new antibiotics needs to be done through other means (ie, Etest, disk diffusion, send to outside lab)
- Some providers may request susceptibility testing to several new agents without consideration of typical coverage of each drug or place in therapy → increases costs without added benefit
- Facilities should consider creating cascade testing based on documented resistance and preferred therapy options

MDRO Cascade Susceptibility Testing

Organism	Criteria	Additional Testing
Enterobacteriaceae	For isolates I/R to all of the following: cefepime, piperacillin/tazobactam, **and** meropenem from sterile sites, including bronchial washes and BALs	• Set up: ceftazidime/avibactam, meropenem/vaborbactam, minocycline, tigecycline, colistin/polymyxin • Set up aztreonam if not on automated panel • Do not test minocycline, tigecycline, eravacycline, or colistin/polymyxin on Proteus, Morganella, Providencia (intrinsically resistant) • Do not test colistin/polymyxin on *Serratia marcescens* (intrinsically resistant)
	Urine - for isolates I/R to all of the following: cefepime, piperacillin/tazobactam, **and** meropenem	• Set up: ceftazidime/avibactam, meropenem/vaborbactam, colistin/polymyxin, fosfomycin* • Set up aztreonam if not on automated panel • Do not test colistin/polymyxin on *Serratia marcescens* (intrinsically resistant) *Fosfomycin should not be used for pyelonephritis
Acinetobacter spp.	For isolates I/R to all of the following: ampicillin/sulbactam, meropenem, **and** trimethoprim/sulfamethoxazole from sterile sites, including bronchial washes and BALs	• Set-up: colistin/polymyxin, tigecycline, minocycline* • Set up trimethoprim/sulfamethoxazole if not on automated panel *Consider testing doxycycline as some isolates may retain susceptibility
	Urine - for isolates I/R to all of the following: ampicillin/sulbactam, meropenem, **and** trimethoprim/sulfamethoxazole	• Set-up: colistin/polymyxin • Set up trimethoprim/sulfamethoxazole if not on automated panel
Pseudomonas aeruginosa	For isolates I/R to all of the following: cefepime, piperacillin/tazobactam, **and** meropenem from sterile sites, including bronchial washes and BALs	• Set up colistin/polymyxin, ceftolozane/tazobactam, ceftazidime/avibactam • Set up aztreonam if not on automated panel • Do not test meropenem/vaborbactam (no activity versus isolates not susceptible to meropenem) • Do not test tigecycline and minocycline (intrinsically resistant)
	Urine - for isolates I/R to all of the following: cefepime, piperacillin/tazobactam, **and** meropenem	• Set-up: ceftolozane/tazobactam, ceftazidime/avibactam, colistin/polymyxin, fosfomycin • Set up aztreonam if not on automated panel

Note: if cefiderocol is requested, it must be requested from Infectious Diseases; it is recommended that antimicrobial stewardship assess criteria for use due to increased mortality risk.

Future Direction and Challenges

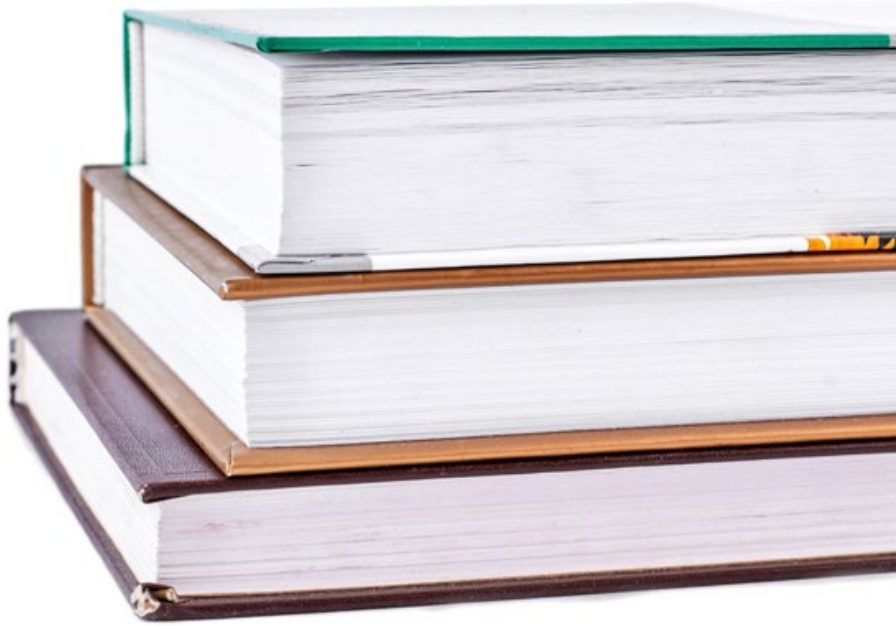
- Products on the Horizon → continued demand for innovation
  - IV fosfomycin was expected Q2 2020
    - Recently rejected by FDA due to inability to conduct on-site inspections in Europe due to COVID-19 travel restrictions
    - Nabriva plans to meet with FDA to discuss next steps
  - Aztreonam/avibactam in Phase 3 trials
- Costs vs. Market Need
  - Considerable costs and high failure risk with antibacterial drug discovery and development
  - Low profit margin for manufactures
    - Short courses of therapy versus drugs for chronic conditions
    - Effective generic drugs for most infections
  - Limited lifespan of antibacterials due to drug resistance
  - Antimicrobial stewardship programs limiting antibacterial use
- Alternative Payment Systems
  - 2020 CMS rule changes eliminated some criteria for NTAP and increased payment from 50% to 75% for QIDPs

Source: http://investors.nabriva.com/news-releases/news-release-details/nabriva-therapeutics-receives-complete-response-letter-fda-nda-0; https://www.pfizer.com/science/find-a-trial/nct03329092; https://www.cidrap.umn.edu/news-perspective/2019/08/medicare-payment-changes-aim-boost-antibiotic-development#:~:text=To%20make%20NTAP%20more%20useful,(QIDPs)%20by%20the%20FDA.

Assessment Question 1

Which of the following new antibiotics has demonstrated safety and efficacy in the treatment of complicated urinary tract infections in adults but was also associated with an increase in all-cause mortality in carbapenem-resistant infections?

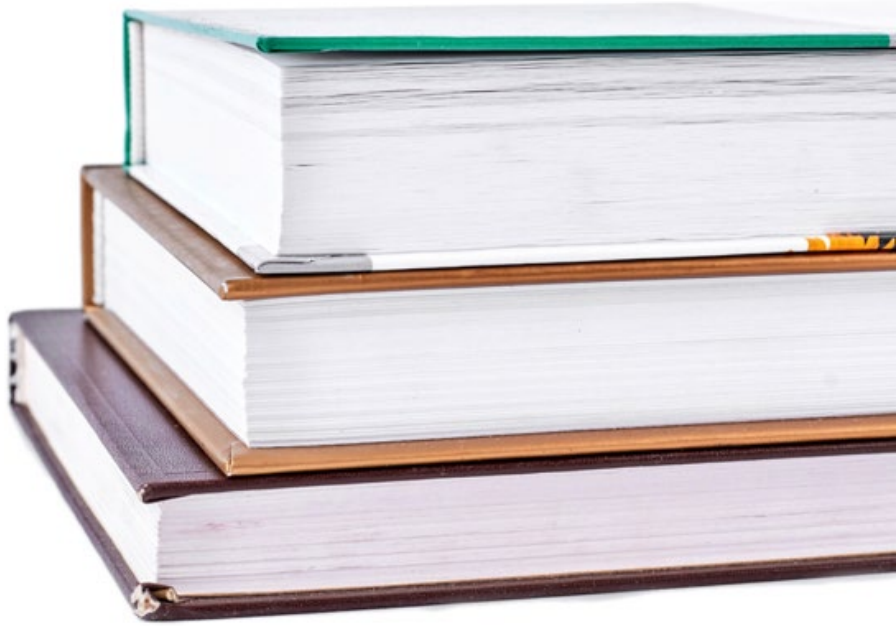
a. Plazomicin
b. Eravacycline
c. Omadacycline
d. Cefiderocol



Assessment Question 2

When developing a treatment algorithm, which of the following strategies can be used to determine a place in therapy for recently approved antimicrobials?

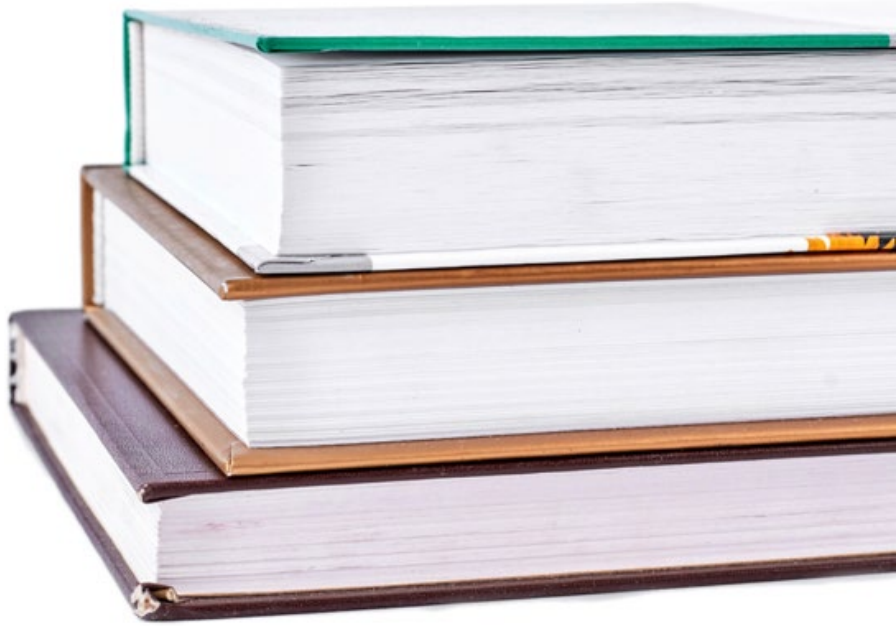
a. Assess the efficacy, safety, and expense of new drugs against older drugs
b. Availability of susceptibility testing
c. Local resistance data
d. All of the above



Assessment Question 3

Which of the following drug regimens from the list below has demonstrated reliable in vitro activity against carbapenem-resistant *P. aeruginosa?*

a. Eravacycline
b. Meropenem/Vaborbactam
c. Ceftolozane/Tazobactam
d. Plazomicin



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Thank you…

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