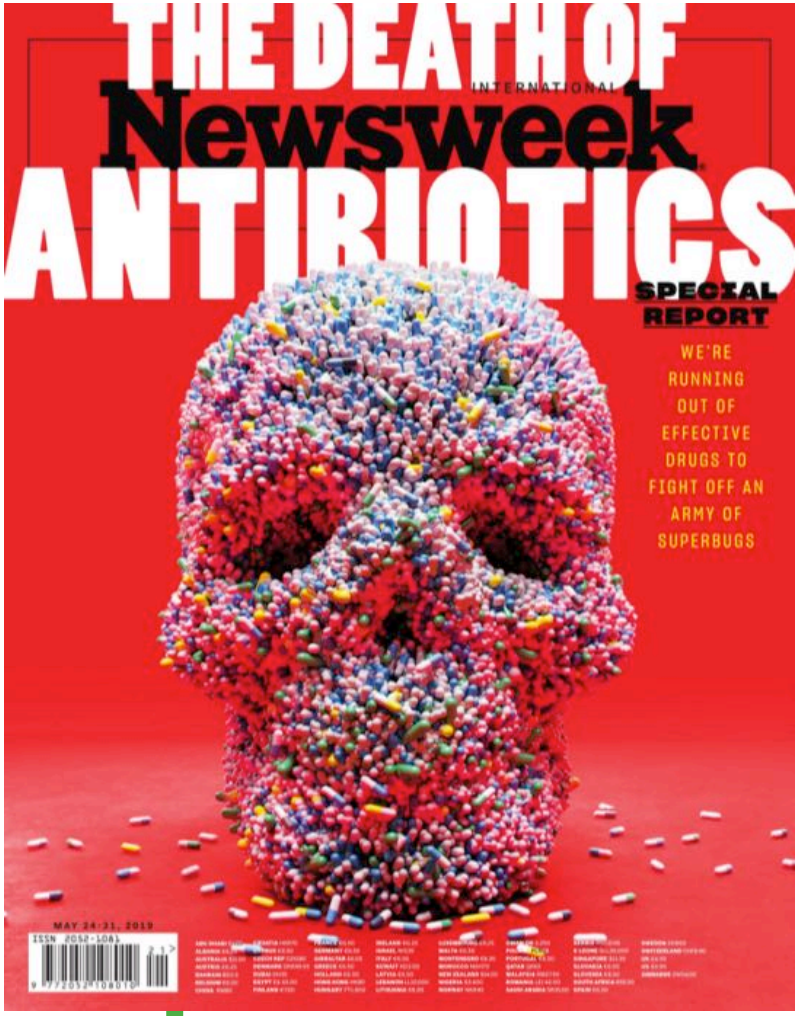


What's really new in antibiotic therapy?

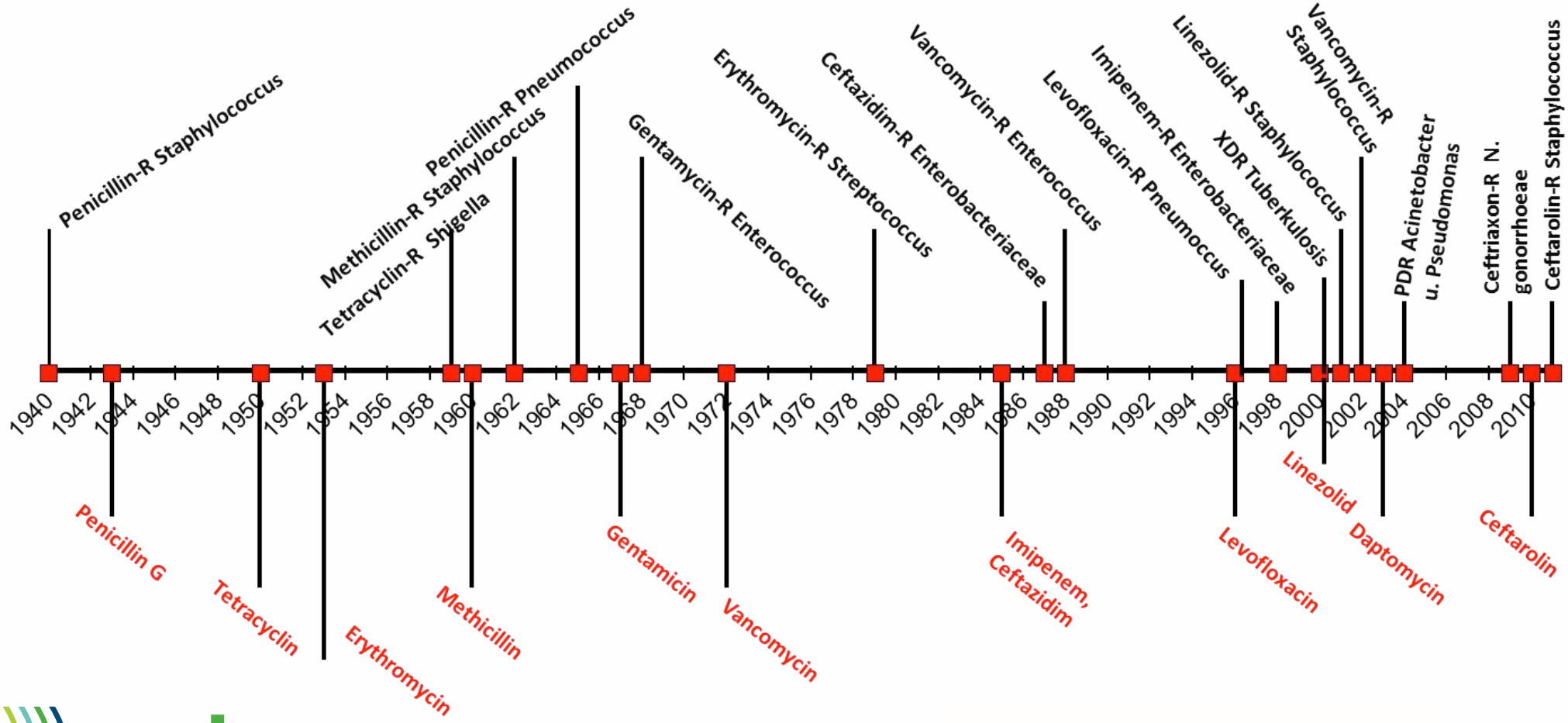
Martin J. Hug
Freiburg University Medical Center

Newsweek, May 24-31 2019

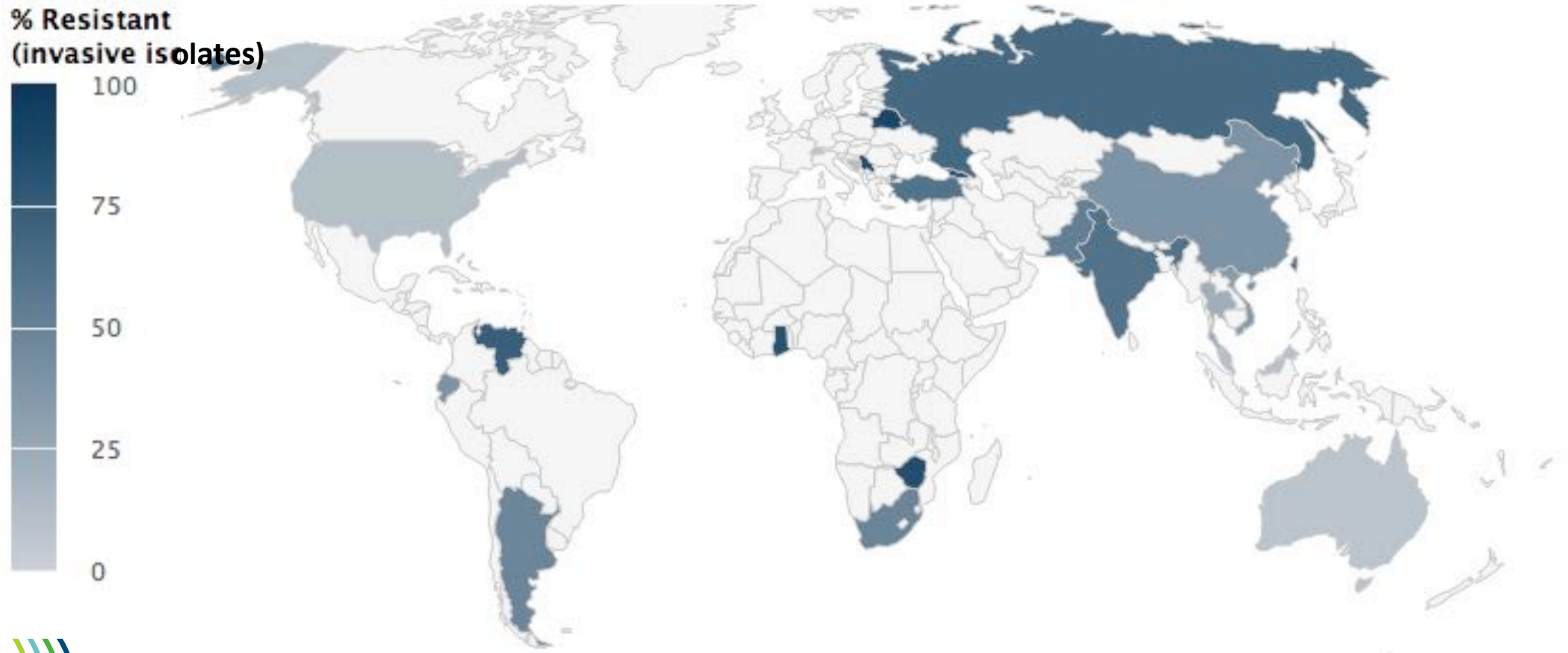
Disclosures

There are no conflicts of interest to declare

Antiinfectives and Resistance



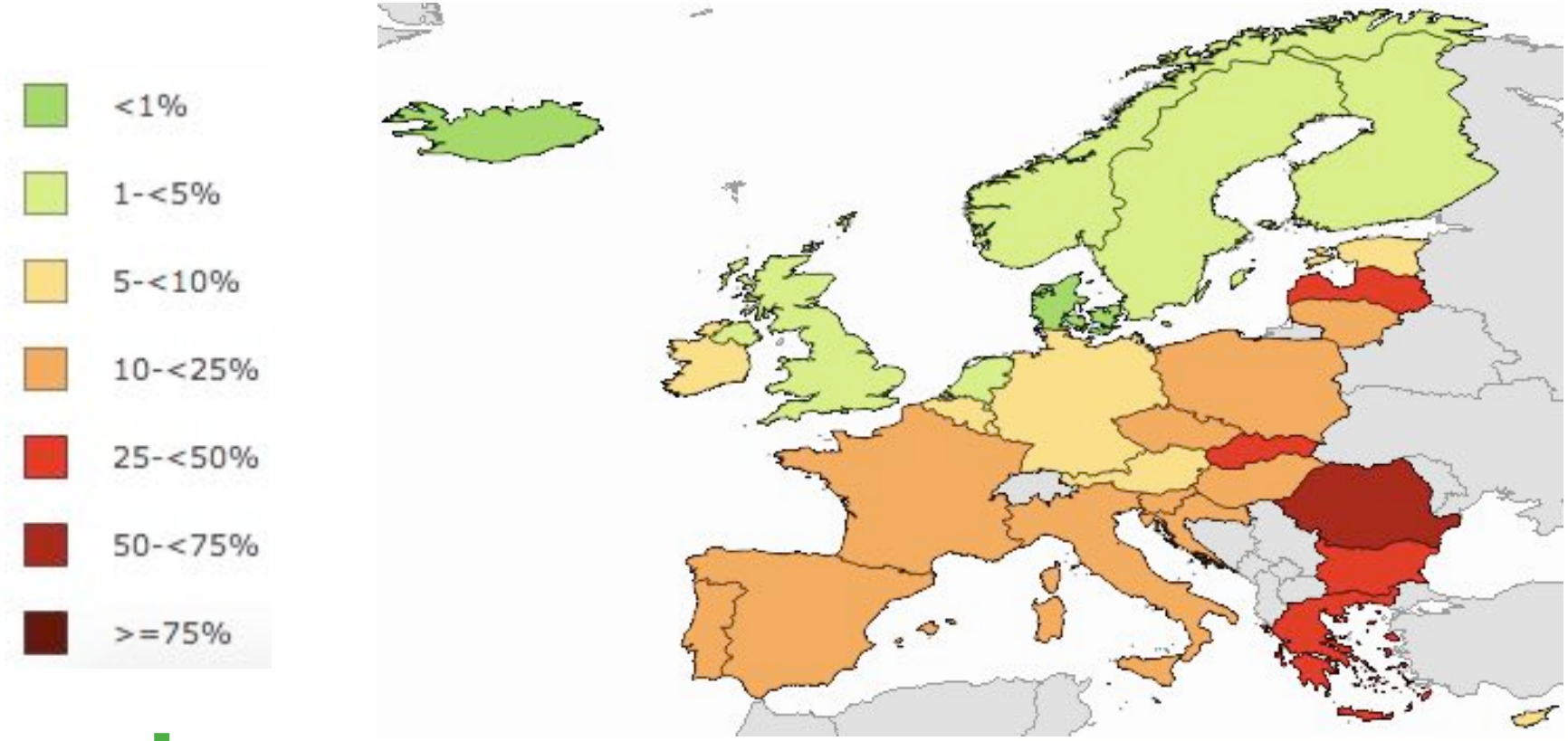
Resistance of *Klebsiella pneumoniae* to Pip.-Taz.



https://resistancemap.cddep.org/AntibioticResistance.php

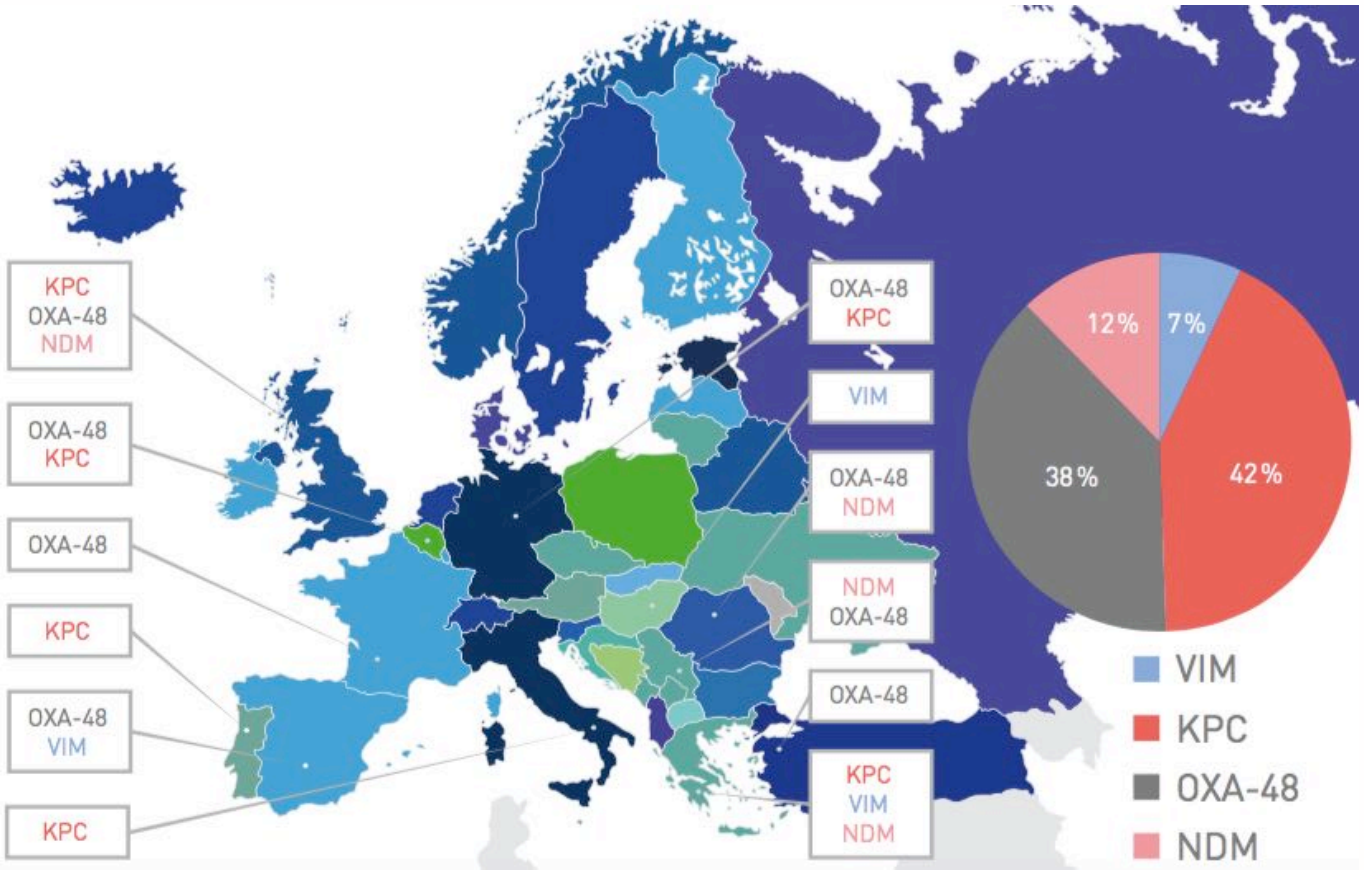
Multiresistant *Pseudomonas Aeruginosa*

Combined resistance against at least three different types of antibiotics, 2017



https://atlas.ecdc.europa.eu/public/index.aspx

Distribution of ESBL producing *Enterobacteriaceae*



Rossolini GM. Global threat of Gram-negative antimicrobial resistance. 27th ECCMID, Vienna, 2017, IS07

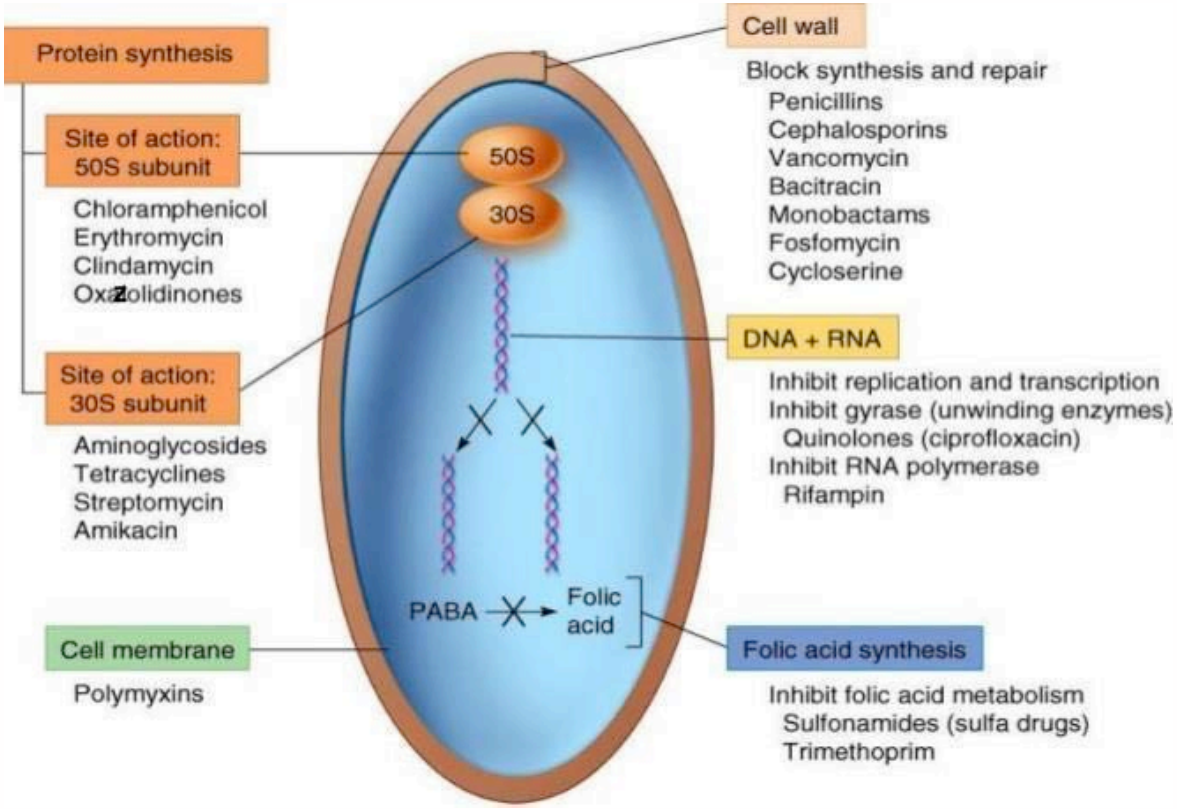
Priority Pathogens Defined by the World Health Organisation

Critical Priority	High Priority	Medium Priority
Acinetobacter baumanii carbapenem-resistant	***Enterococcus faecium*** vancomycin-resistant	***Streptococcus pneumoniae*** penicillin-non-susceptible
Pseudomonas aeruginosa carbapenem-resistant	***Helicobacter pylori*** clarithromycin-resistant	***Haemophilus influenzae*** ampicillin-resistant
Enterobacteriaceae carbapenem-resistant	***Salmonella species*** fluoroquinolone-resistant	***Shigella species*** fluoroquinolone-resistant
	Staphylococcus aureus vancomycin *or* methicillin -resistant	
	Campylobacter species fluoroquinolone-resistant	
	Neisseria gonorrhoae 3rd gen. cephalosporin-resistant fluoroquinolone-resistant	

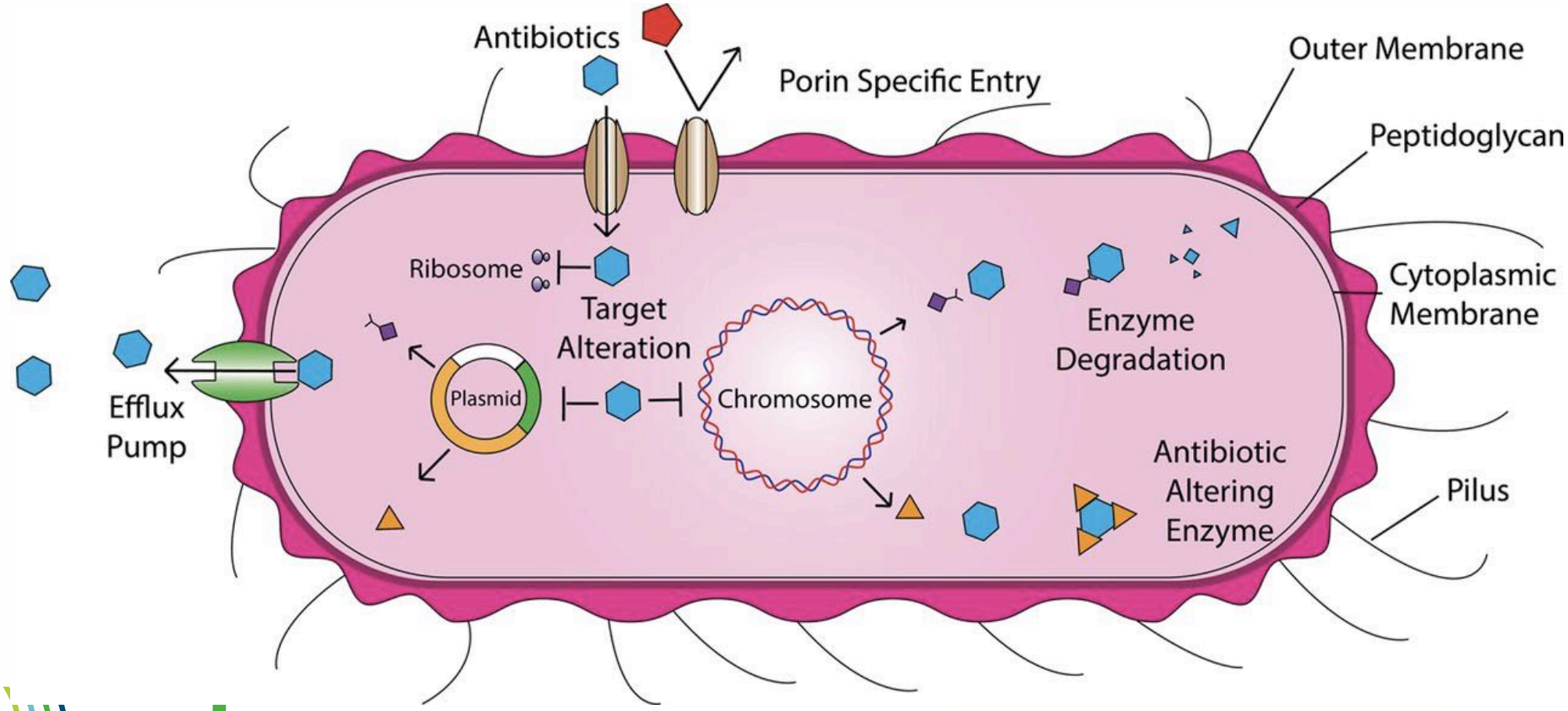
World Health Organization

Data taken from: https://www.who.int/foodsafety/publications/antimicrobials-sixth/en/

Antibacterial Targets



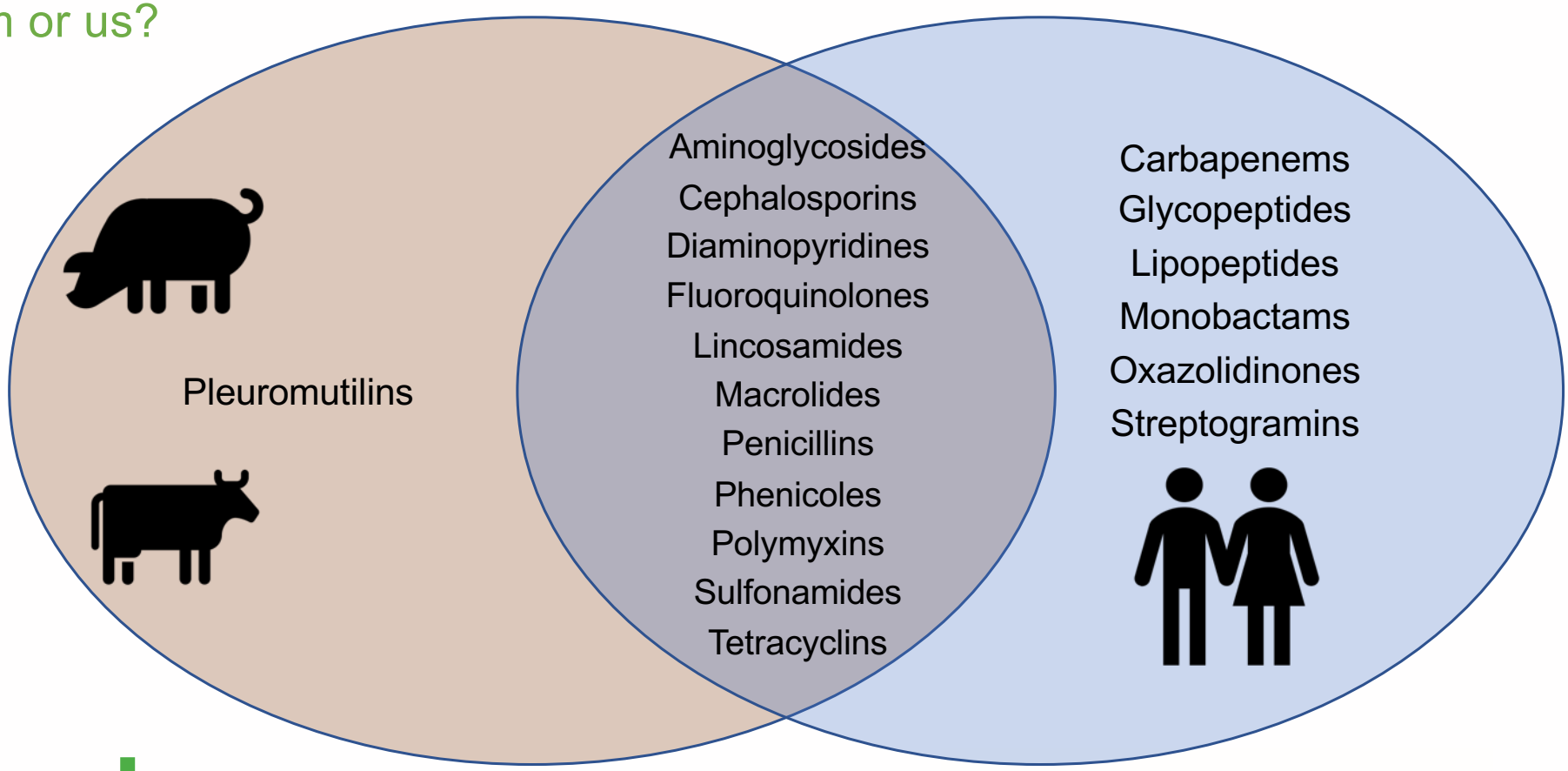
Resistance mechanisms



Mukerji S et al. Essays In Biochemistry 2017, 61(1) 23-35

Veterinary and Human use of Antibiotics

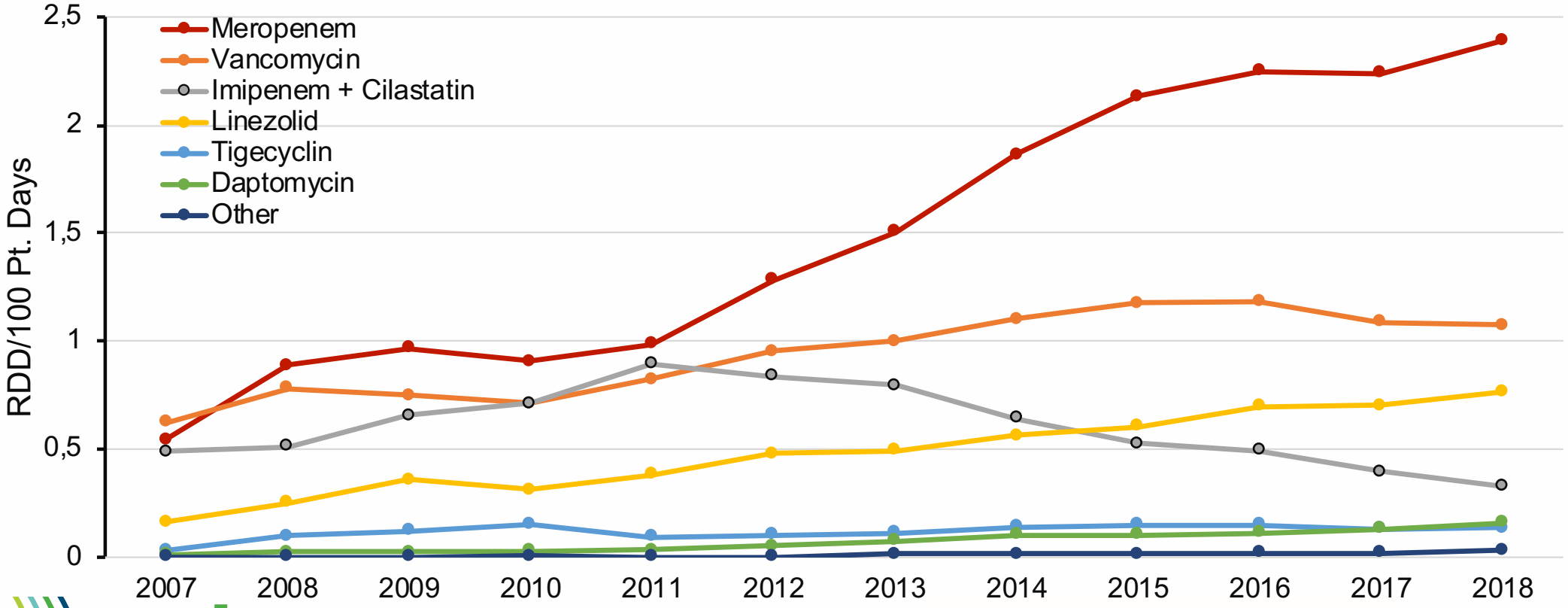
Them or us?



Data taken from: https://www.bvl.bund.de/SharedDocs/Downloads/07_Bundesamt/Veranstaltungen/Symposium2013/symposium2013_vortrag_wallmann.pdf

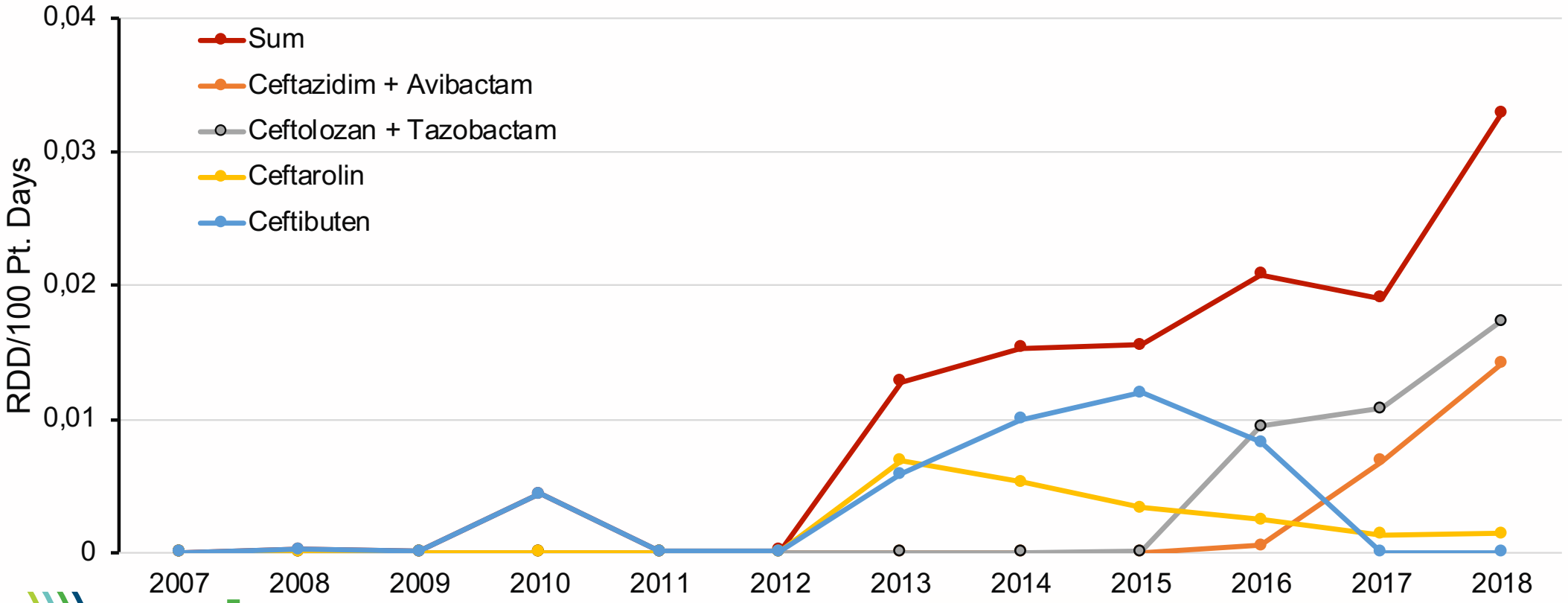
Use Density of Critically Important Antibiotics in German Hospitals

Data: ADKA if DGI antibiotic surveillance project

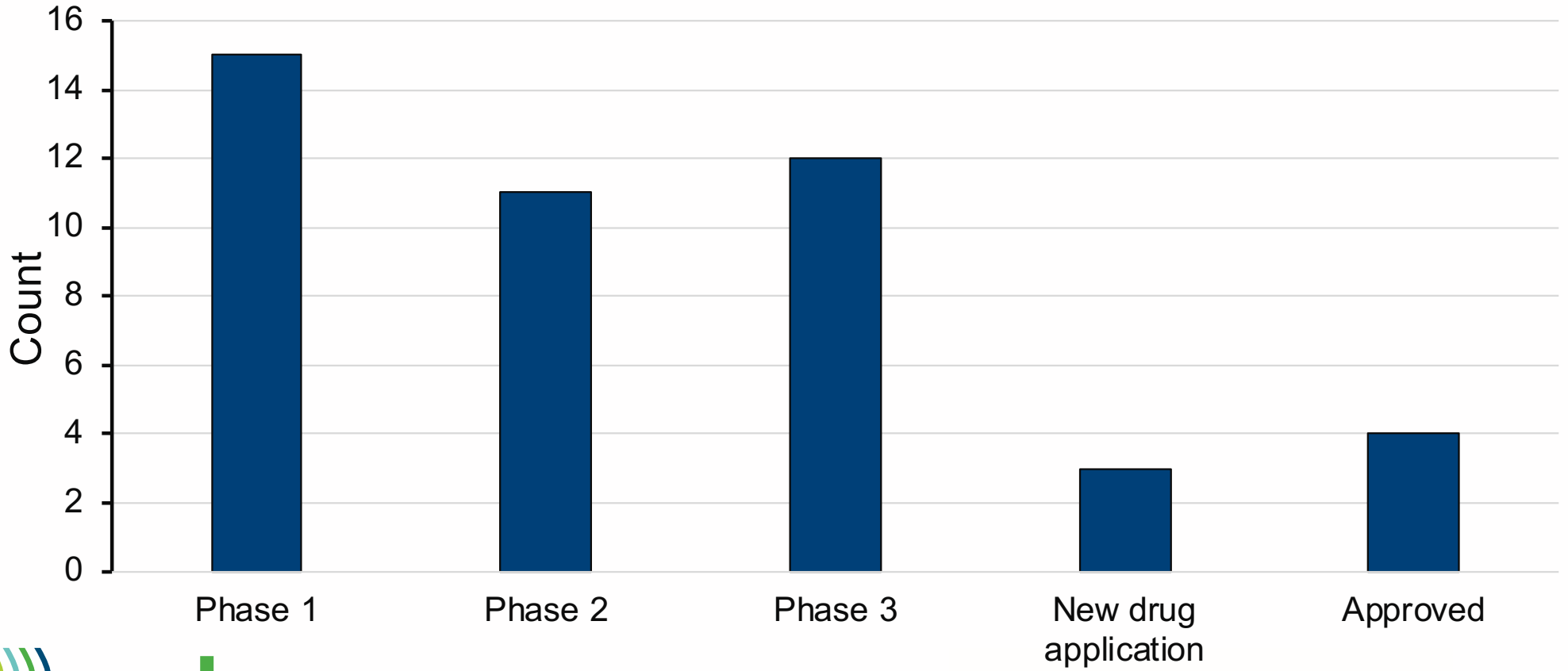


Use Density of Novel Cephalosporins in German Hospitals

Data: ADKA if DGI antibiotic surveillance project



Development Pipeline of Antibiotic Drugs

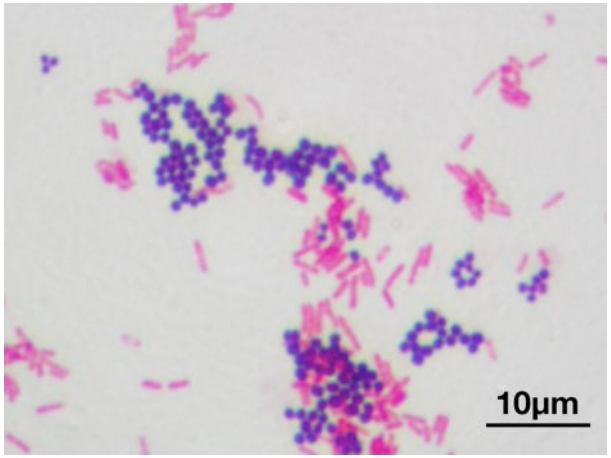


Data: https://www.pewtrusts.org/-/media/assets/2019/03/antibiotics-currently-in-global-clinical-development.pdf

Novel Antibiotics (a selection)

- Long acting Glycopeptides
- ß-lactams
- ß-lactams + ß-lactam inhibitors
- Pleuromutilines
- LpxC Inhibitors
- Bacteriophages
- ~~Fecal Microbiome Transfer~~ 

Antiinfective drugs – already FDA / EMA approved



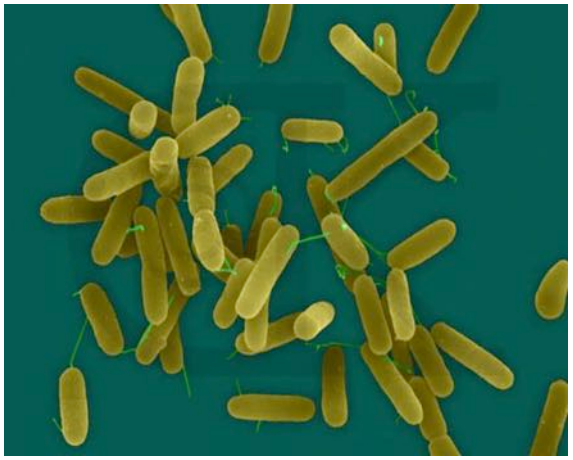
Gram-positive bacteria

DALBAVANCIN (Dalvance™/ Xydalba®)

ORITAVANCIN (Orbactiv™)

TEDIZOLID (Sivextro®)

CEFTOBIPROL (Zevtera®)



Gram-negative bacteria

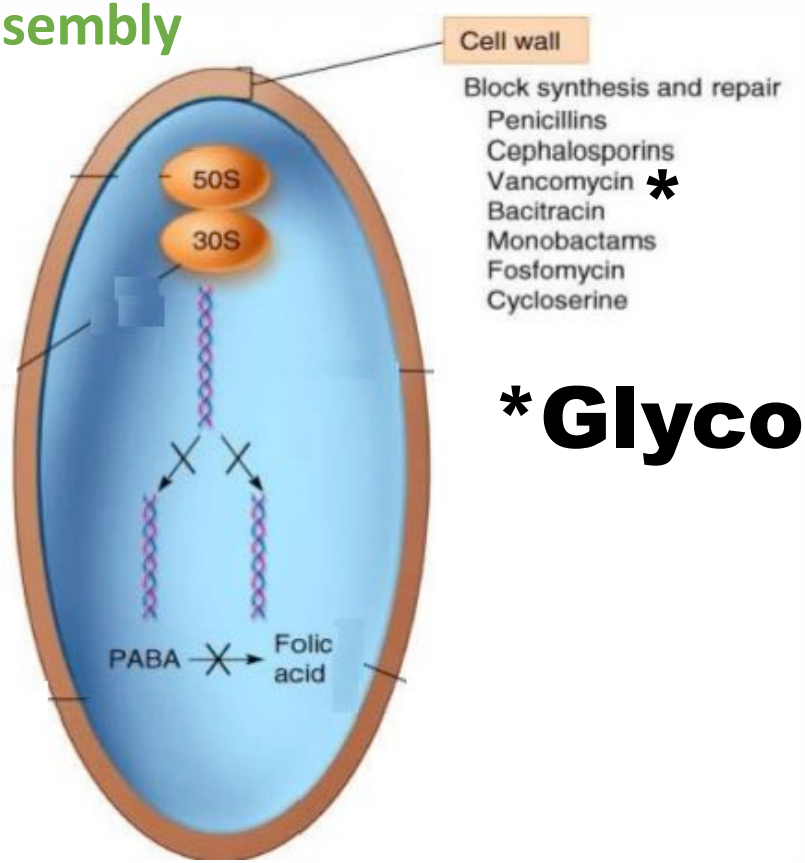
CEFTOBIPROL (Zevtera®)

CEFTOLOZAN-TAZOBACTAM (Zerbaxa™)

CEFTAZIDIM-AVIBACTAM (Avycaz™/ Zavicefta®)

Antibacterial Targets

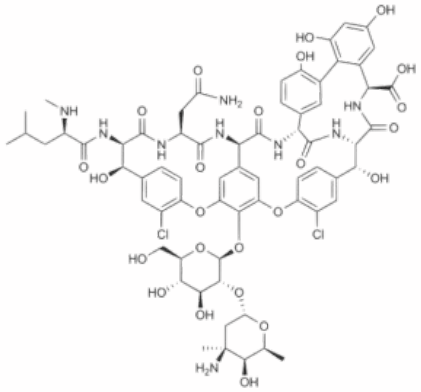
Inhibitors of cell wall assembly

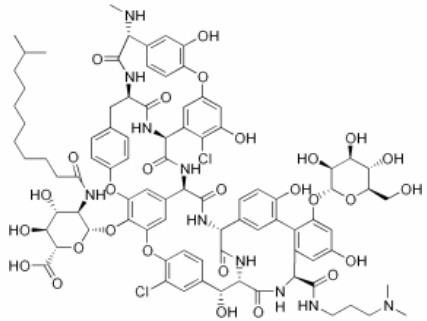


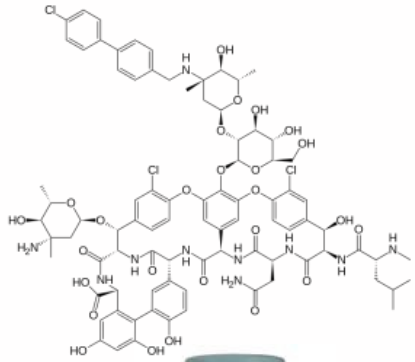
***Glycopeptides**

Novel Approved Antiinfectives: Glycopeptides

Vancomycin	Dalbavancin	Oritavancin

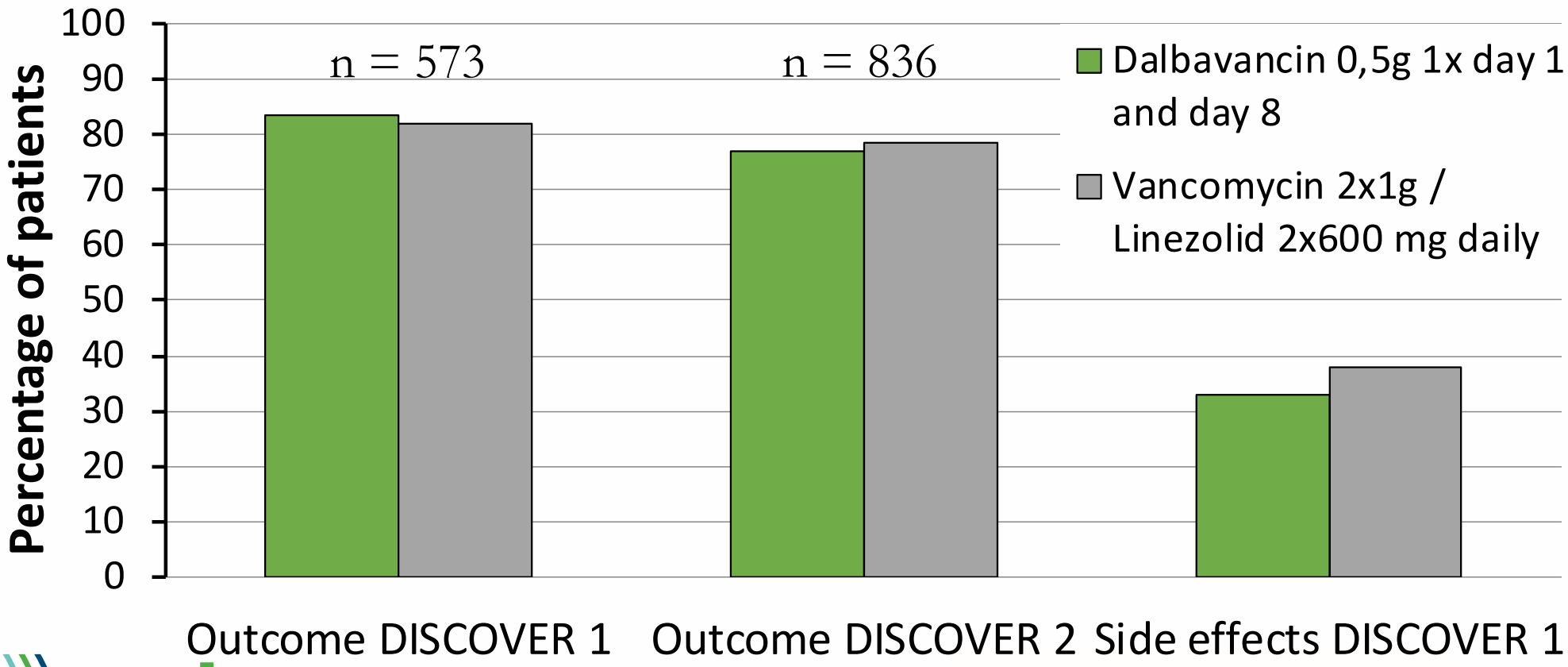






Clinical response to **Dalbavancin**

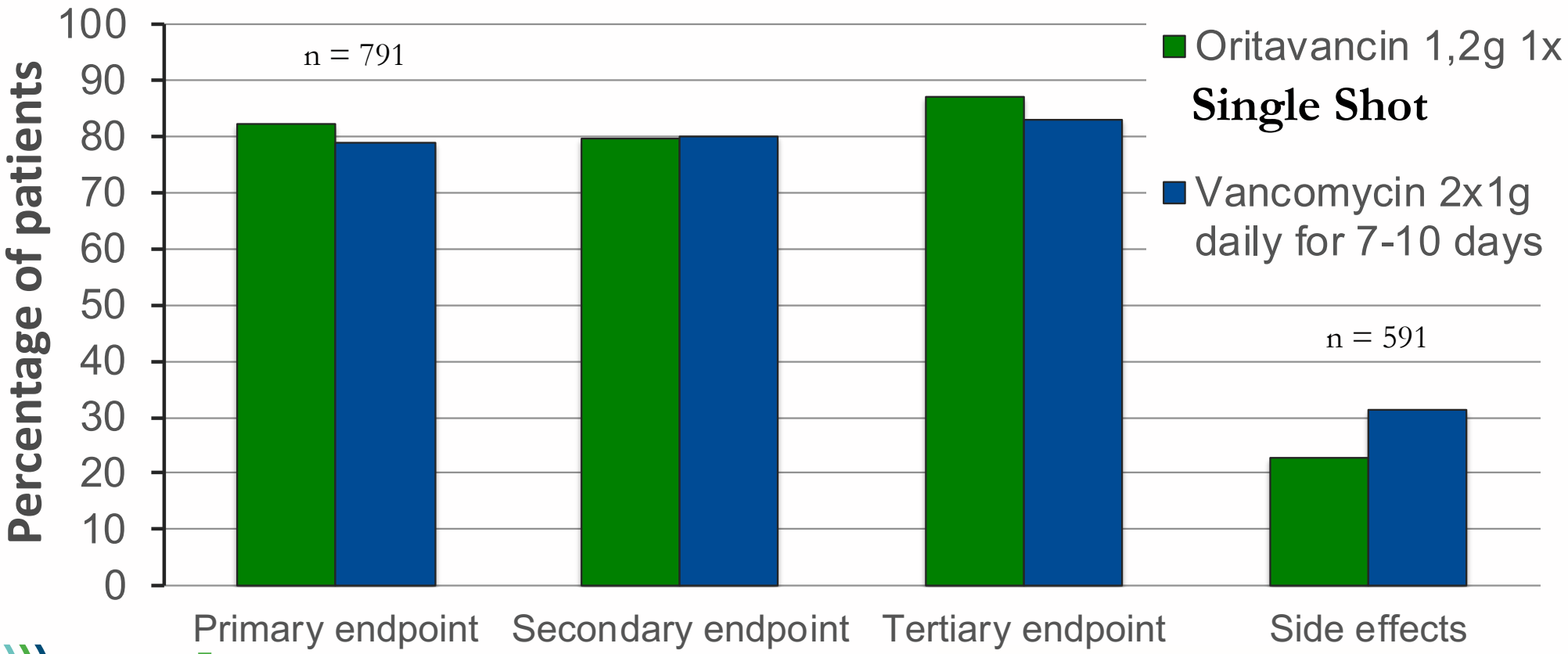
Acute bacterial skin and skin-structure infection



Data taken from: Boucher H et al. N Engl J Med 2014;370:2169-79

Clinical response to **Oritavancin**

Acute bacterial skin and skin-structure infection



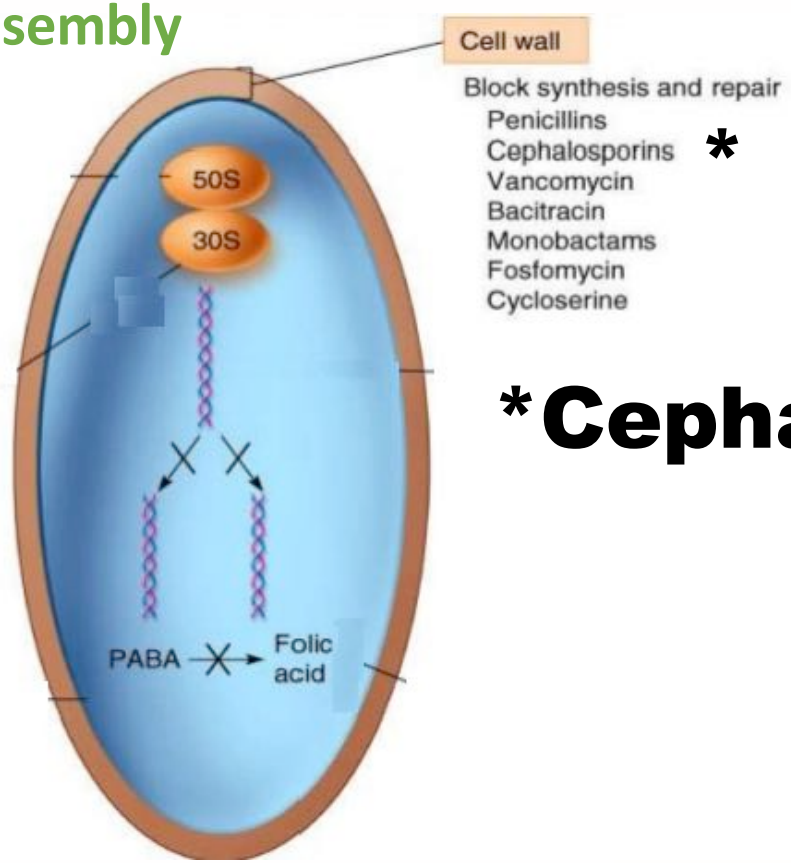
Data: Corey CG et al. N Engl J Med 2014;370:2180-90

Take Home Message

- Dalbavancin and Oritavancin are novel Glycopeptide antibiotics to treat infections caused by gram-positive bacteria.
- Oritavancin and Dalbavancin have an apparent half-life of 10 – 15 days respectively, which permits a single dosing regime.
- Both substances are aproved for the treatment of acute bacterial skin, skin-structure and soft tissue infections.
- To this end no data exist to demonstrate a clinical benefit compared to established Glycopeptides other than better treatment options in the outpatient sector.

Antibacterial Targets

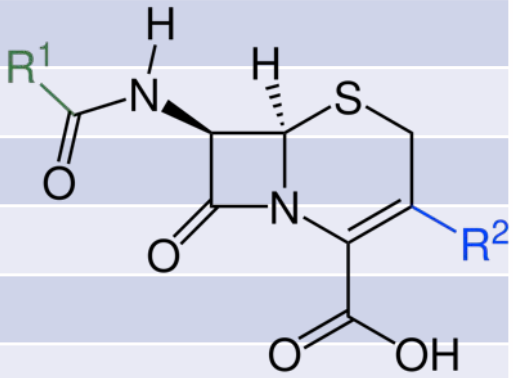
Inhibitors of cell wall assembly



***Cephalosporins**

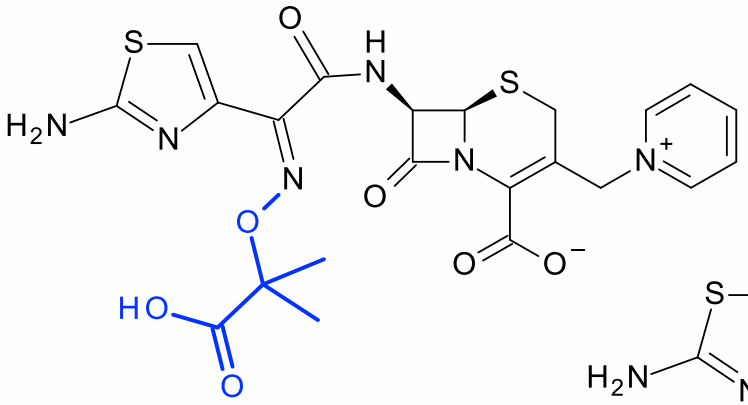
Novel Antiinfectives: Cephalosporins

(O) = oral use

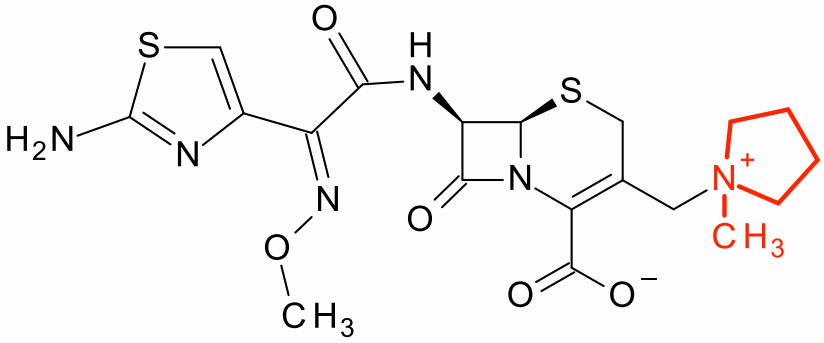
1st Generation	2nd Generation	3rd Generation	4th Generation
Cefazolin	Cefamandole	Cefoperazone	Cefepime
Cephalothin	Cefonicid	Cefotaxime	Cefpirome
Cefadroxil (O)	Cefuroxime (-axetil (O))	Ceftazidime	
Cephalexin (O)	Cefaclor (O)	Ceftizoxime	
Cephradine (O)	Cefprozil (O)	Ceftriaxone	
	Loracarbef (O)	Moxalactam	
		Cefdinir (O)	
	Cefmetazole	Cefditoren (O)	
	Cefotetan	Cefixime (O)	**5th Generation**
	Cefoxitin	Cefpodoxime (O)	Ceftarolin
		Ceftibuten (O)	Ceftobiprol

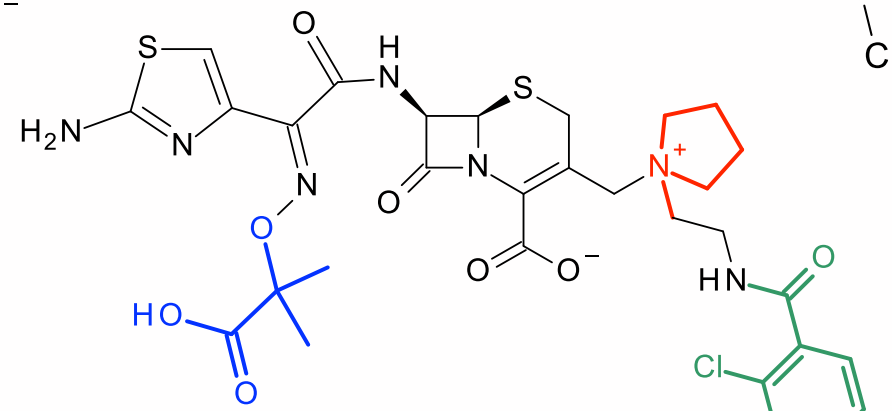
Cefiderocol – *same same* but different

Ceftazidime



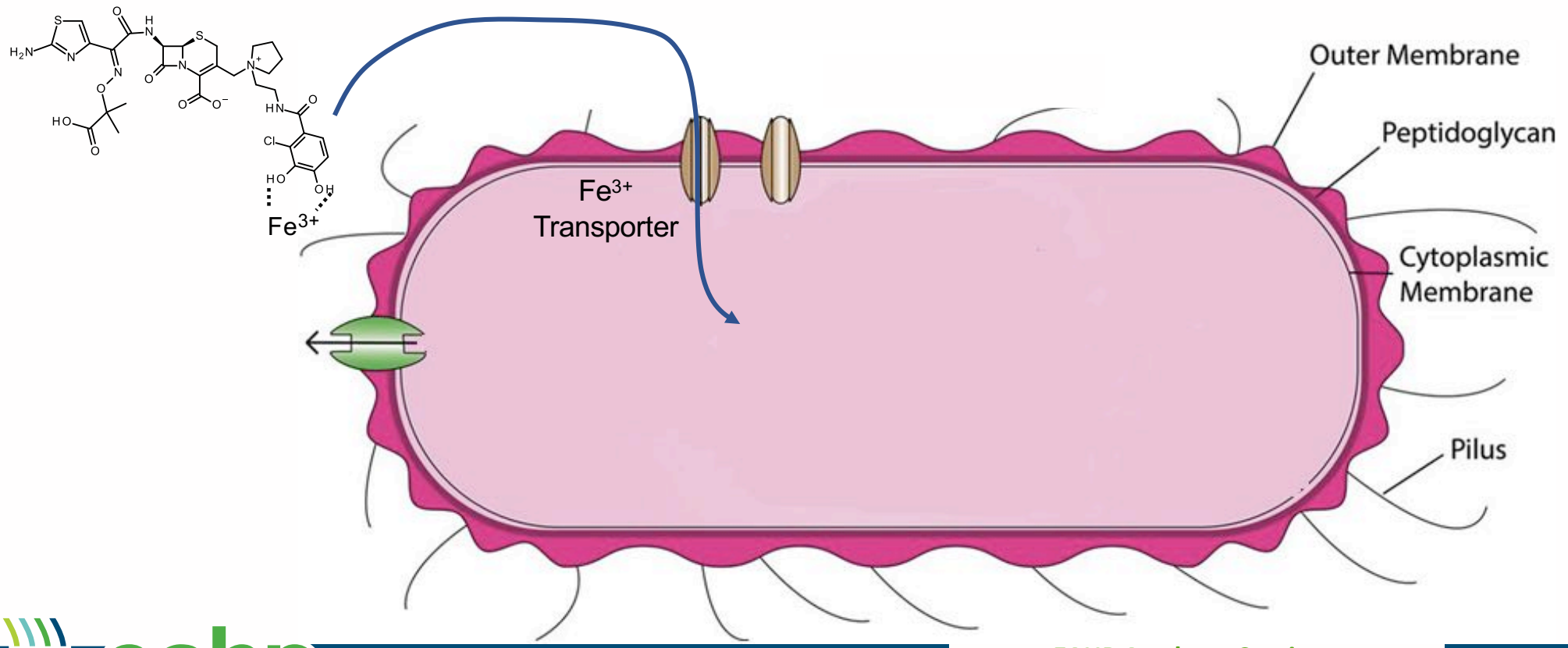
Cefepime





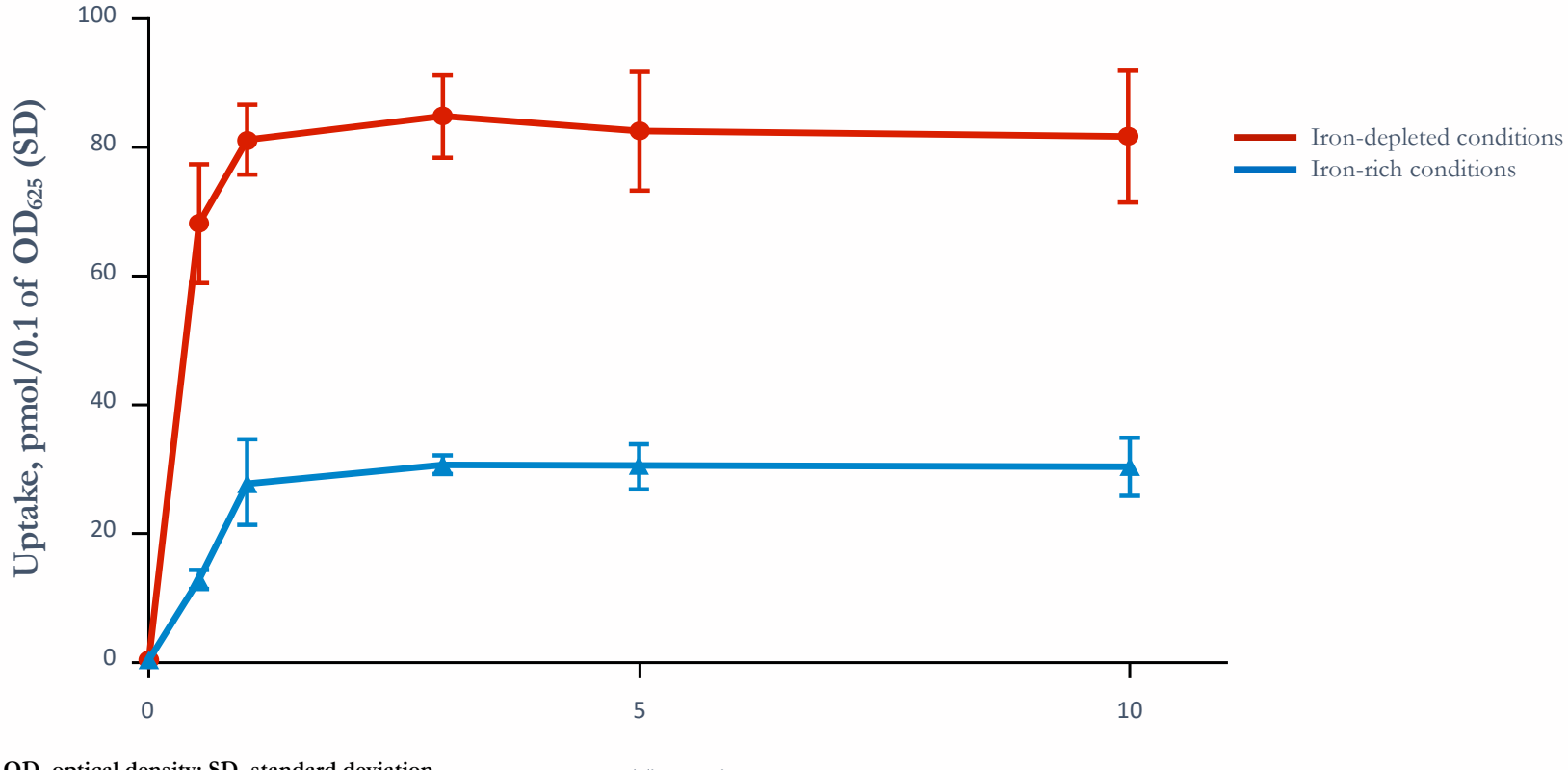
Cefiderocol

Porin Specific Entry of Cefiderocol



Uptake of Cefiderocol in Iron-depleted Conditions

Cefiderocol uptake into *P. aeruginosa* cells was >2 times higher under low iron conditions

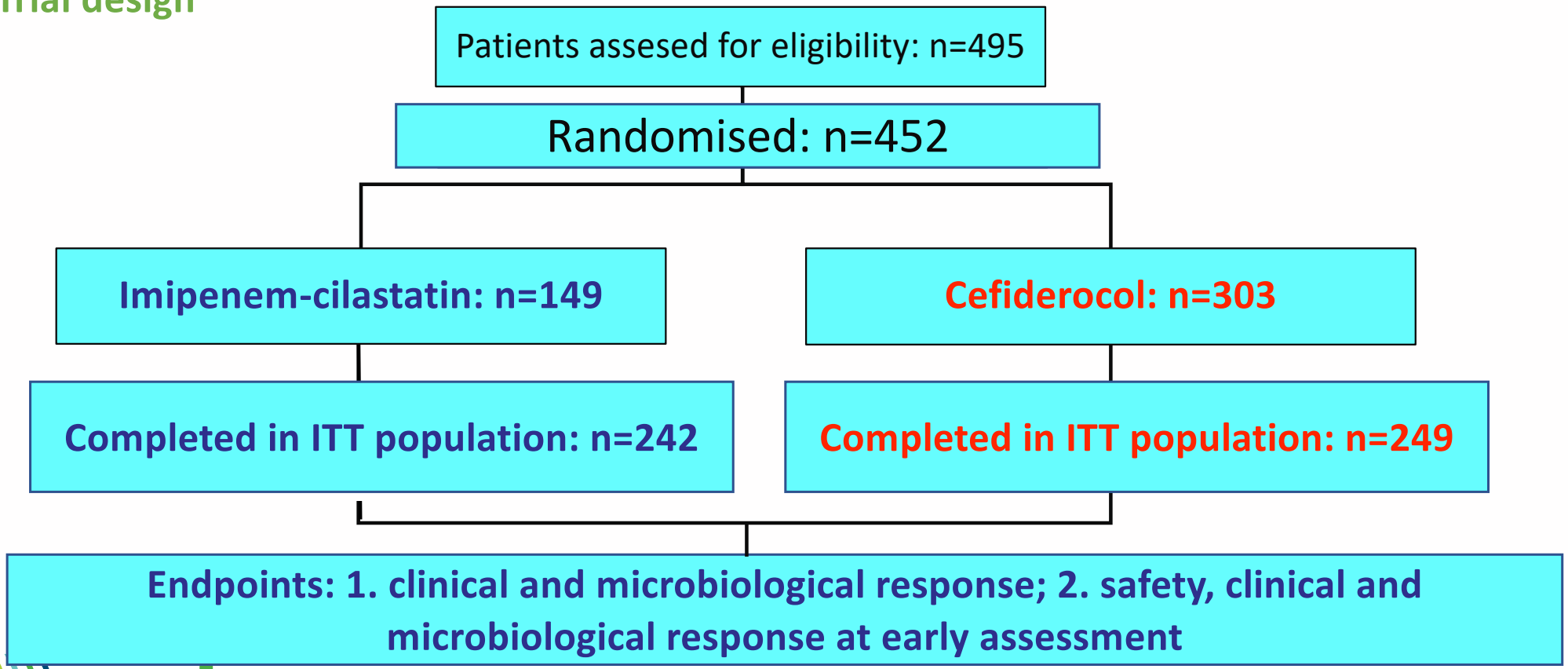


OD, optical density; SD, standard deviation

Ito A, et al. Antimicrob Agents Chemother 2016;60:7396–401

Cefiderocol in Complicated Urinary Tract Infections

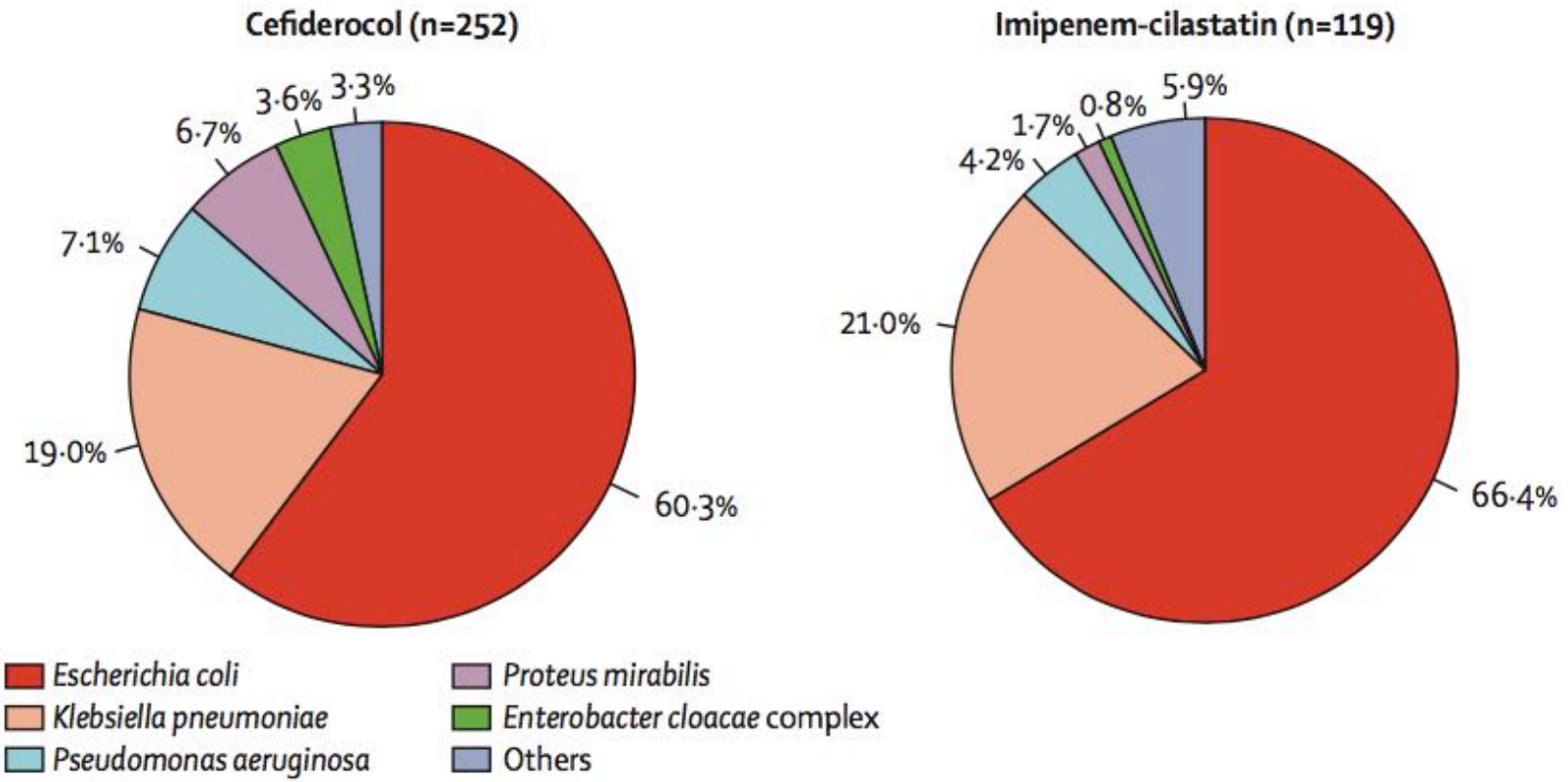
Trial design



Mod. from Portsmouth S et al. Lancet Infect Dis. 2018(12):1319-1328

Cefiderocol in Complicated Urinary Tract Infections

Distribution of pathogens isolated at baseline

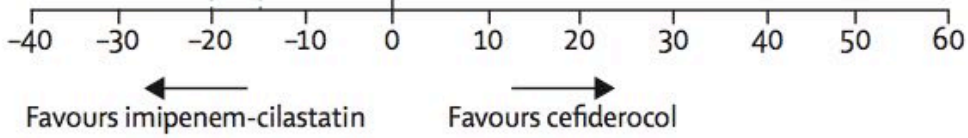


Mod. from Portsmouth S et al. Lancet Infect Dis. 2018(12):1319-1328

Cefiderocol in Complicated **U**rinary **T**ract **I**nfections

Results

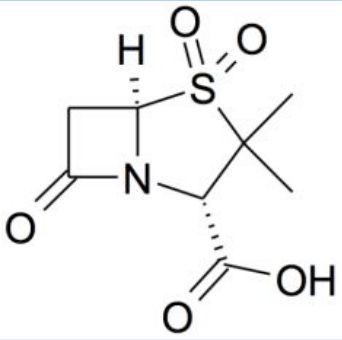
	n/N (%)		Treatment difference* (95% CI)
	Cefiderocol	Imipenem-cilastatin	
Analysis population			
mITT population	183/252 (73)	65/119 (55)	18·58 (8·23–28·92)
Microbiologically evaluable population	182/228 (80)	65/106 (61)	19·35 (8·87–29·82)
Age, years			
<65	87/113 (77)	32/54 (60)	17·73 (2·50–32·96)
≥65	96/139 (69)	33/65 (51)	18·30 (3·92–32·67)
Sex			
Men	84/119 (71)	25/48 (52)	18·50 (2·17–34·84)
Women	99/133 (74)	40/71 (56)	18·10 (4·38–31·81)
Clinical diagnosis			
cUTI with or without pyelonephritis	129/187 (69)	41/84 (49)	20·17 (7·60–32·75)
Acute uncomplicated pyelonephritis	54/65 (83)	24/35 (69)	14·51 (−3·37–32·38)



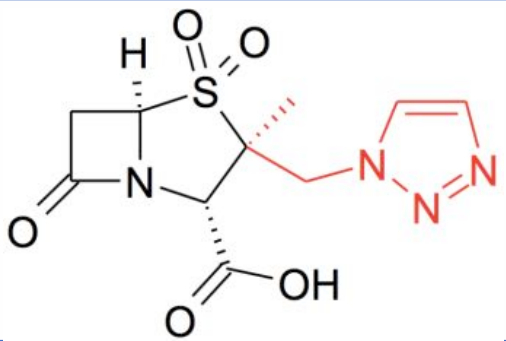
Mod. from Portsmouth S et al. Lancet Infect Dis. 2018(12):1319-1328

Novel Antiinfectives: Combination of Cephalosporines with ß-Lactamase Inhibitors

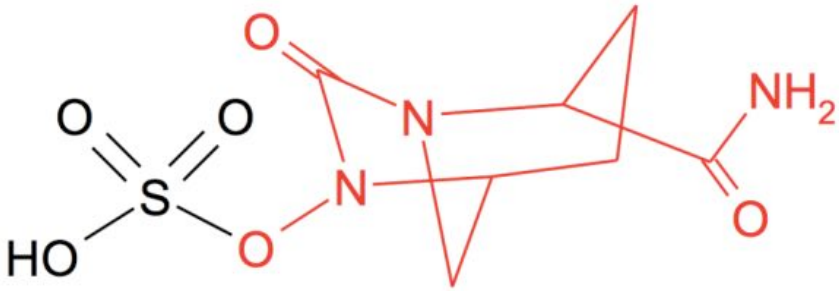
Sulbactam



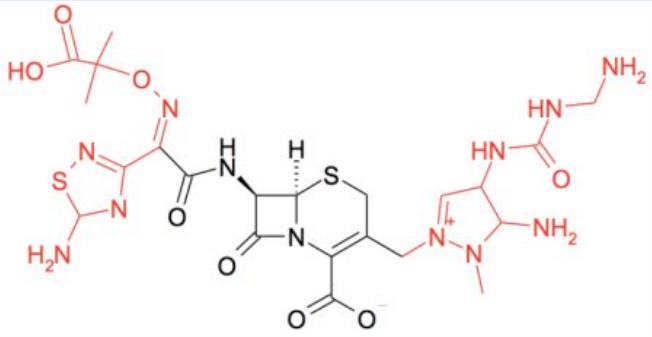
Tazobactam



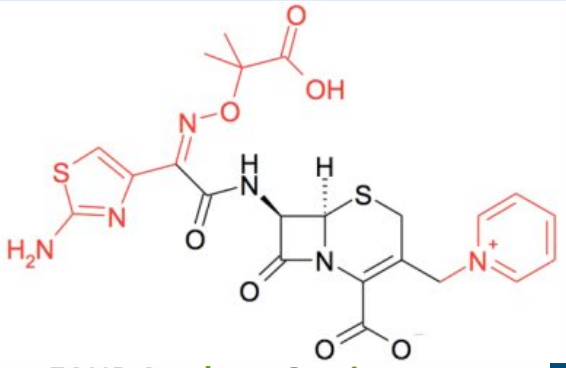
Avibactam



Ceftolozan

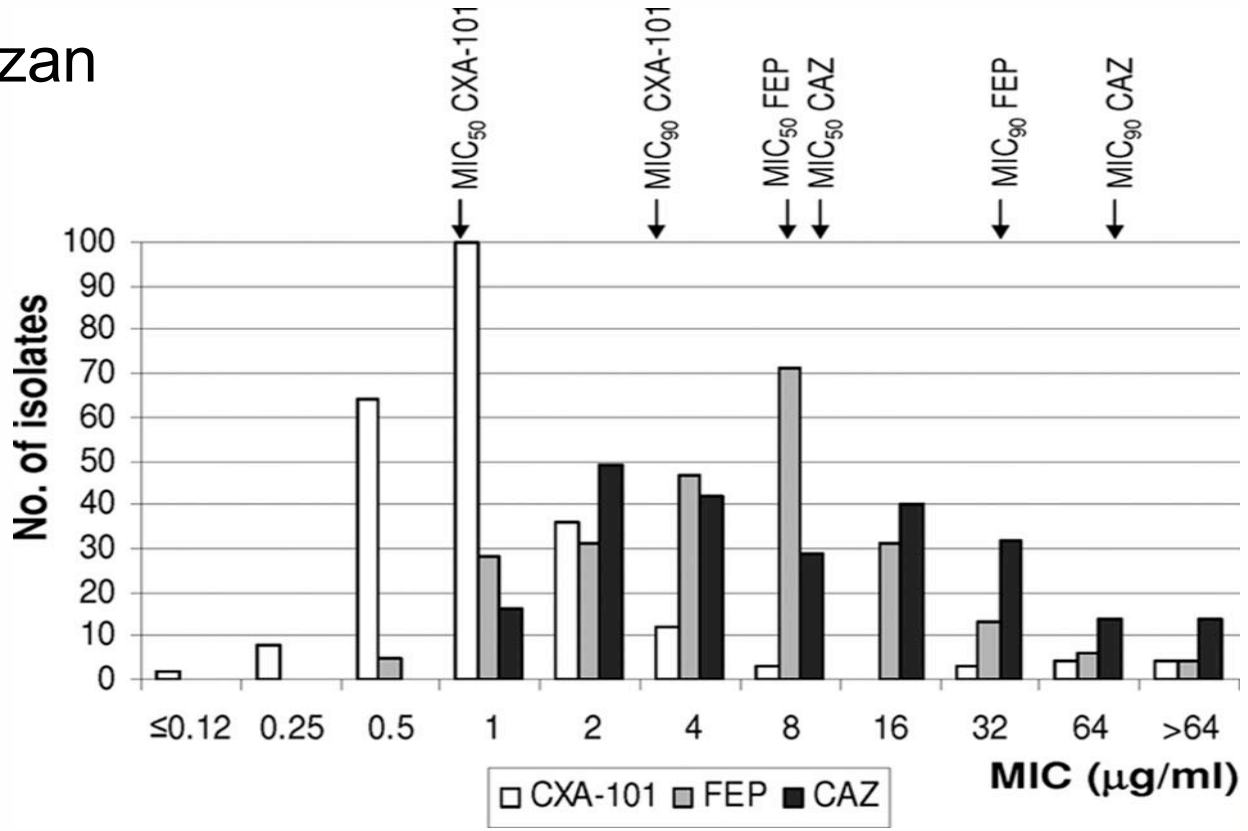


Ceftazidime



Susceptibility of Different Carbapenem-resistant Pseudomonas Strains in Spain

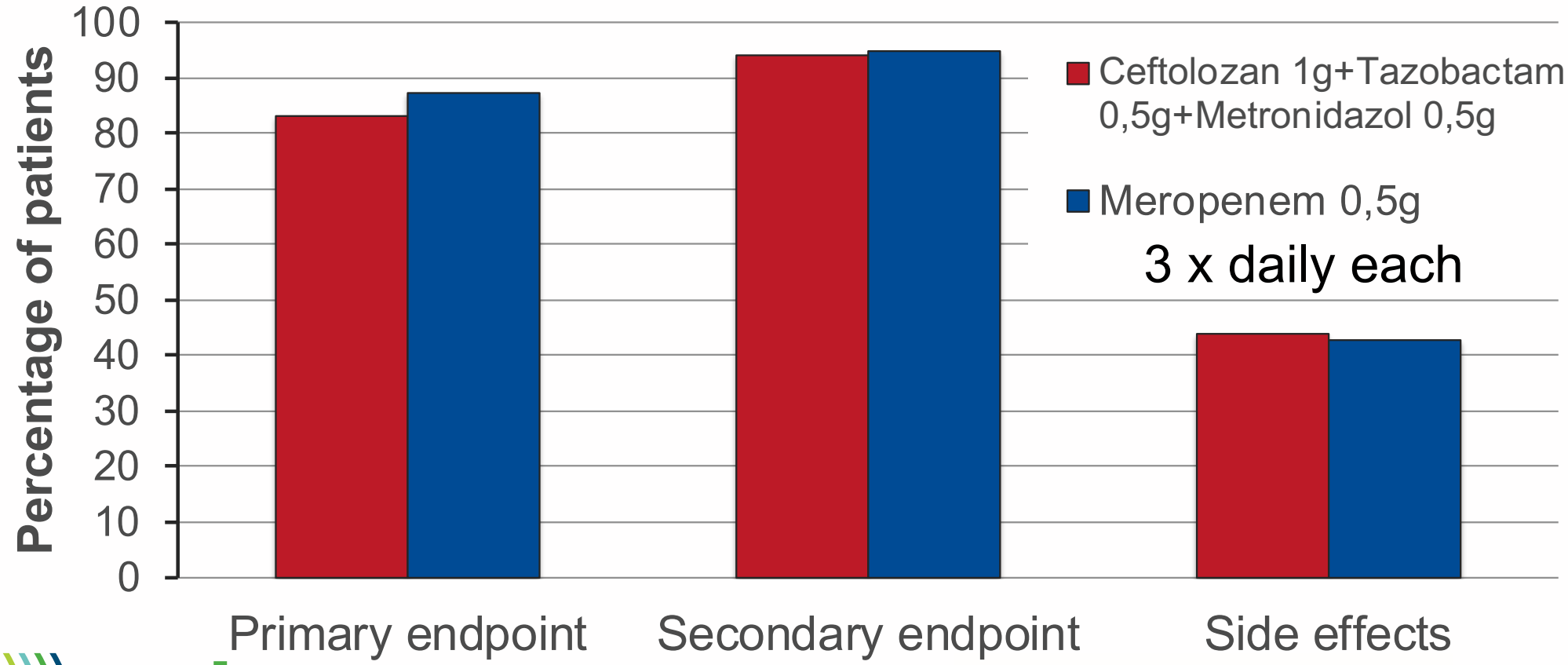
CXA-101 = Ceftolozan
CAZ = Ceftazidime
FEP = Cefepime



Juan C et al. Antimicrob. Agents Chemother. 2010;54:846-851

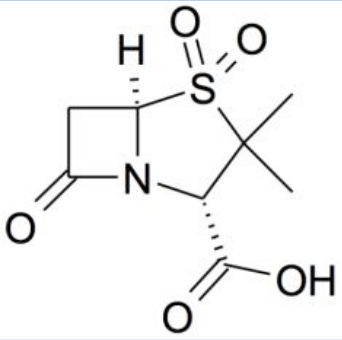
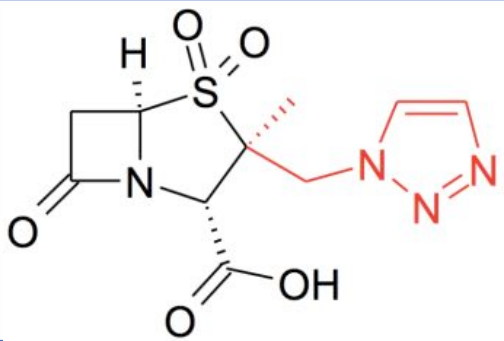
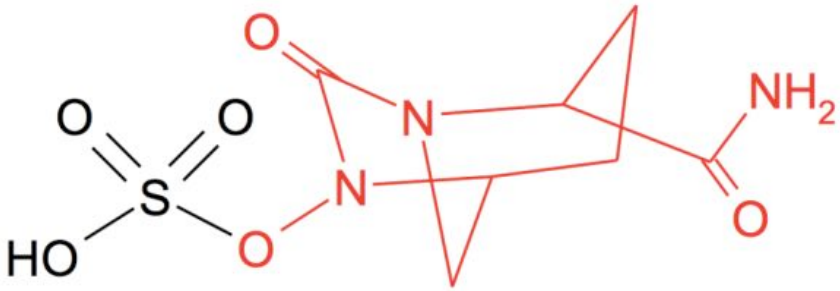
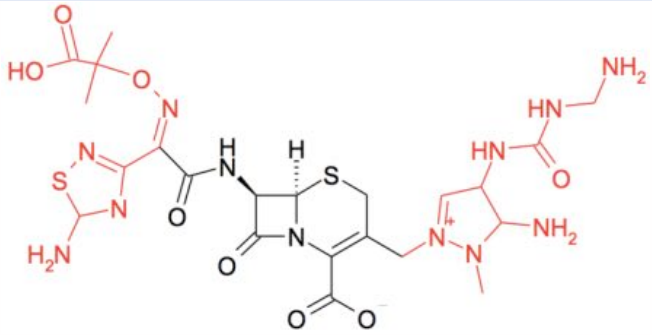
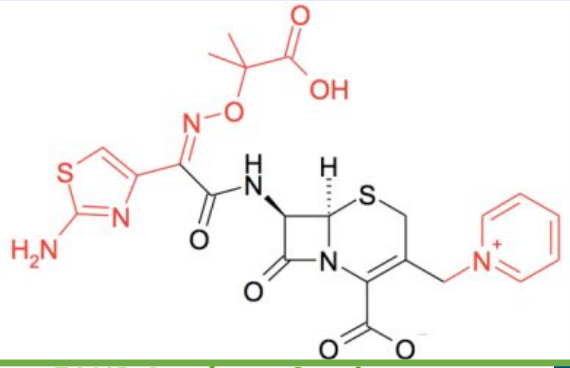
Clinical Response to Ceftolozan-Tazobactam

Acute abdominal infections



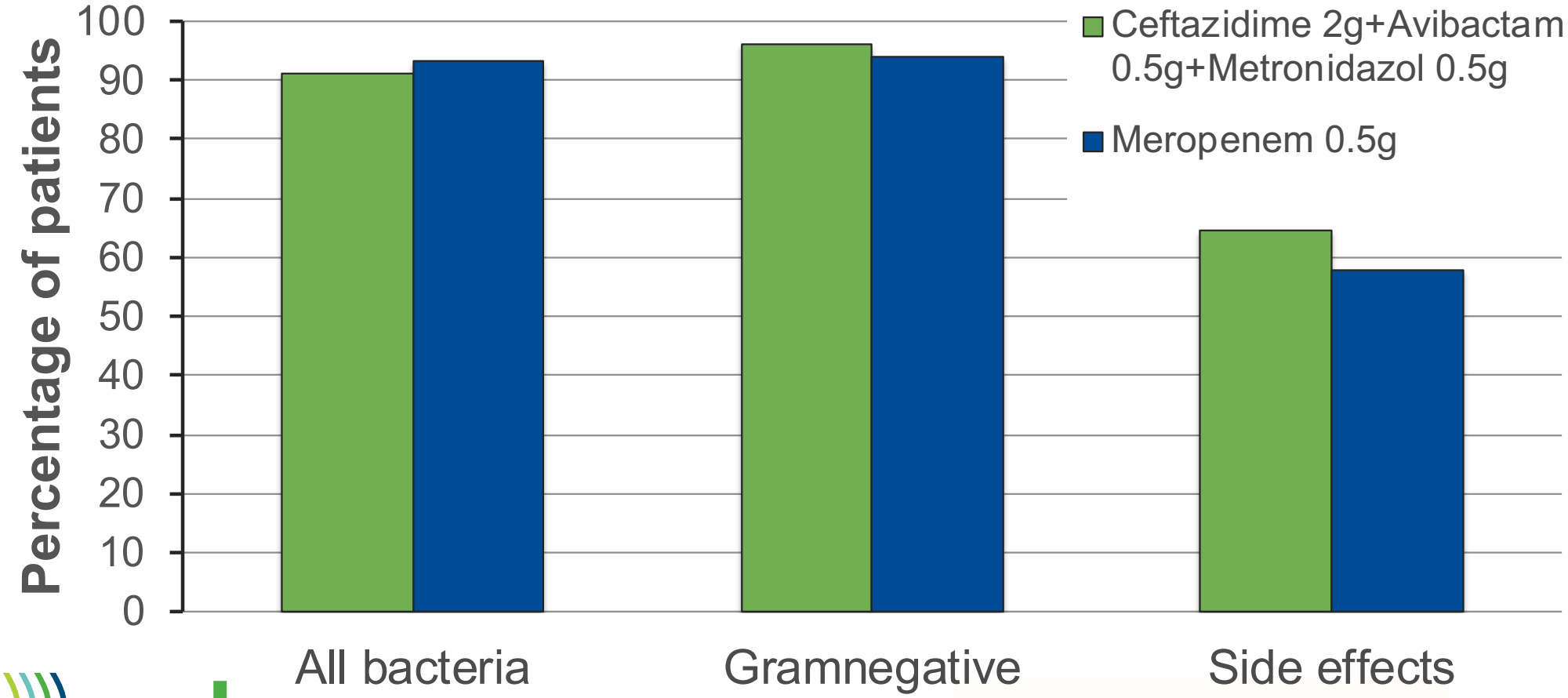
Data from: Solomkin J et al. Clin Infect Dis 2015;60(10):1462–71

Novel Antiinfectives: Combination of Cephalosporines with ß-Lactamase Inhibitors

Sulbactam	Tazobactam	Avibactam
		
	Ceftolozan	**Ceftazidime**
		

Clinical Response to Ceftazidime-Avibactam

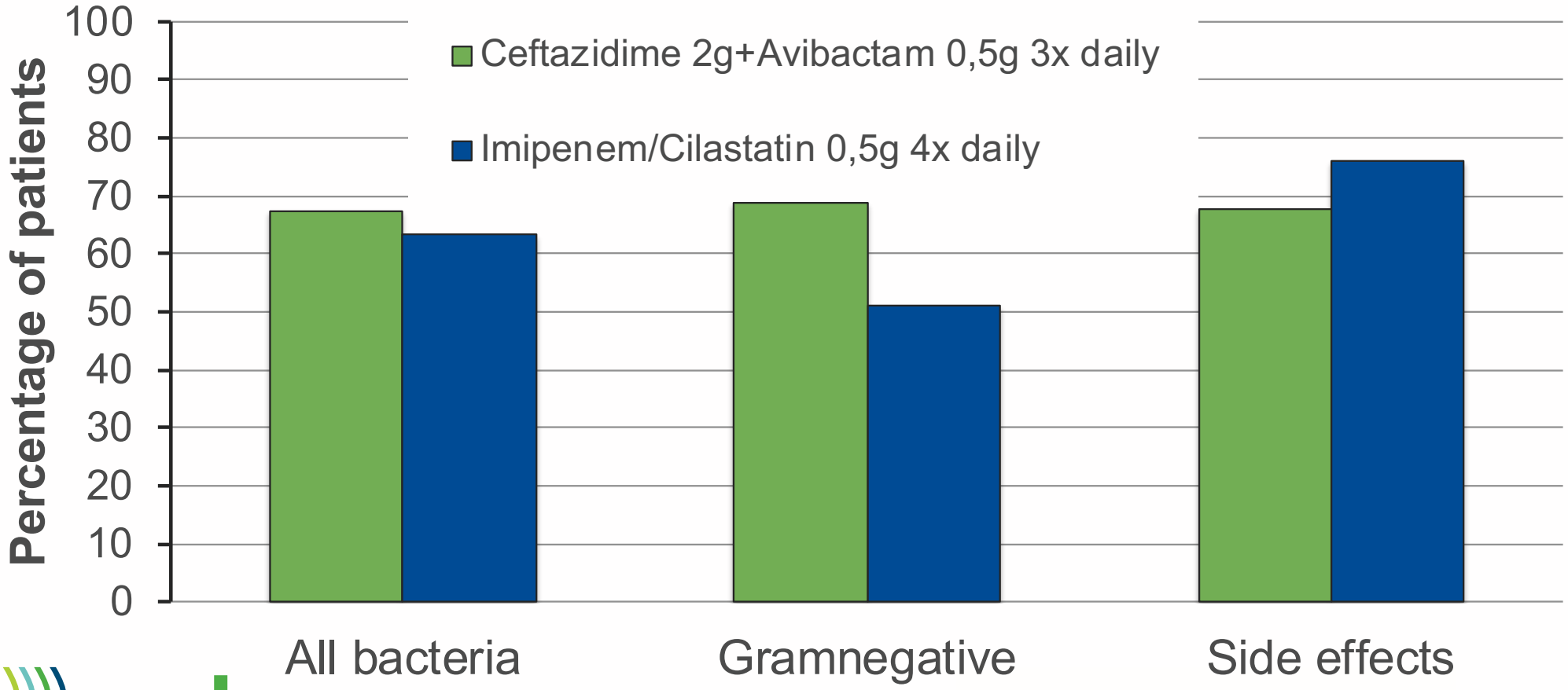
Acute abdominal infections



Data from: Lucasti C et al. J Antimicrob Chemother 2013; 68: 1183–1192

Clinical Response to Ceftazidime-Avibactam

Complicated urinary tract infections



Data from: Vasquez JA et al. Curr Med Res Opin. 2012;28(12):1921-31

Combinations of ß-lactams and BLI

Ongoing Clinical Trials

	Avibactam	Nacubactam	Relebactam	Vabor-bactam	Zidebactam
	Diazabi-cyclooctane	Diazabi-cyclooctane	Diazabi-cyclooctane	Cyclic boronate	Diazabi-cyclooctane
Aztreonam	**X***				
Cefepime					**X**
Imipenem-Cilastatin			**X**		
Meropenem		**X**		**X***	

*FDA approved

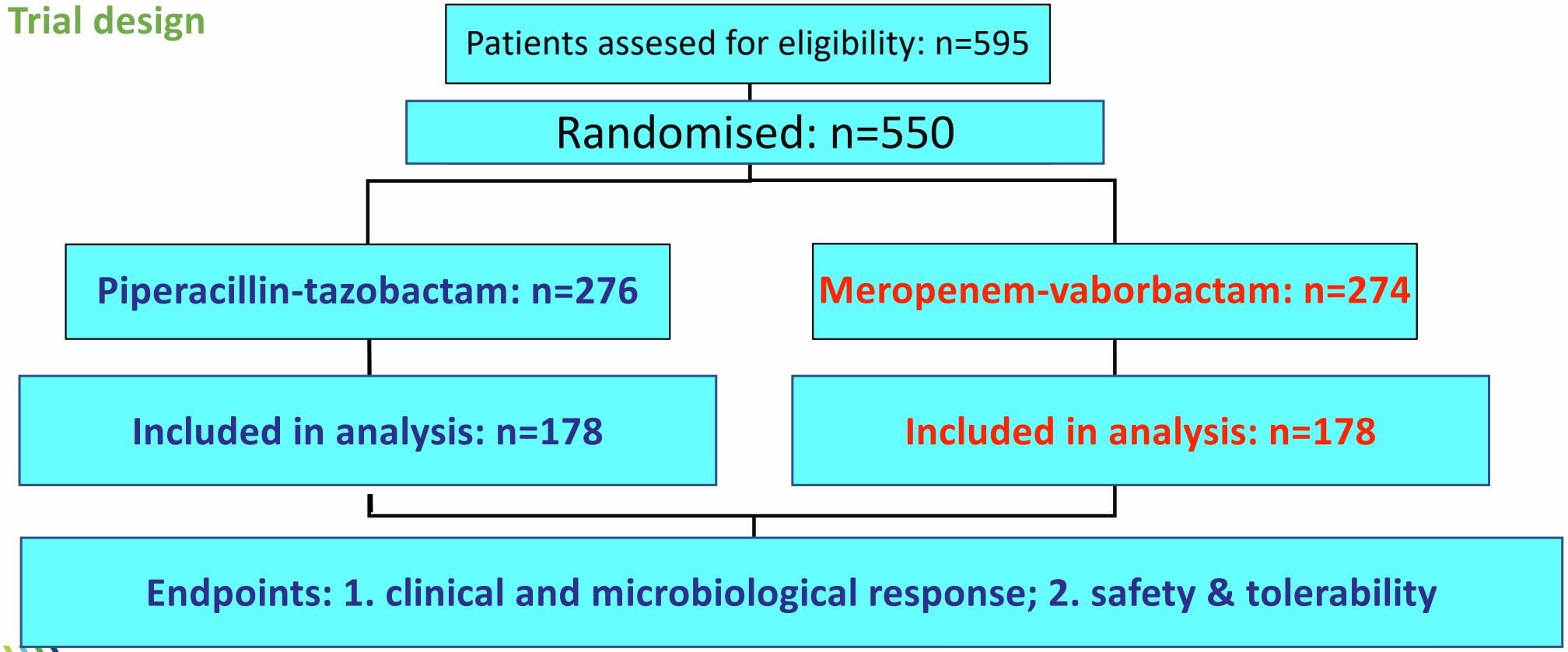
Combinations of ß-lactams and BLI

Ongoing Clinical Trials – early development

	AAI-101	ETX0282	ETX2514	VNRX-5133
	ß-lactame	Diazabicyclo-octane	Diazabicyclo-octane	Cyclic boronate
Cefepime	X			X
Cefpodoxime-proxetil		X		
Imipenem-Cilastatin			X	
Sulbactam			X	

Targeting **A**ntibiotic **N**on-susceptible **G**ram-negative **O**rganisms (TANGO) Trial – Meropenem+*Vaborbactam*

Trial design



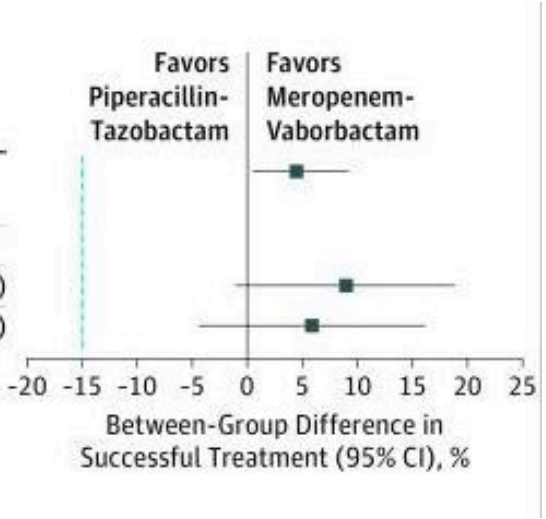
Mod. From: Kaye KS et al. JAMA. 2018 ;319(8):788-799

Targeting **A**ntibiotic **N**on-susceptible **G**ram-negative **O**rganisms (TANGO) Trial – Meropenem+*Vaborbactam*

TANGO I: Complicated Urinary Tract Infection

A Primary end points

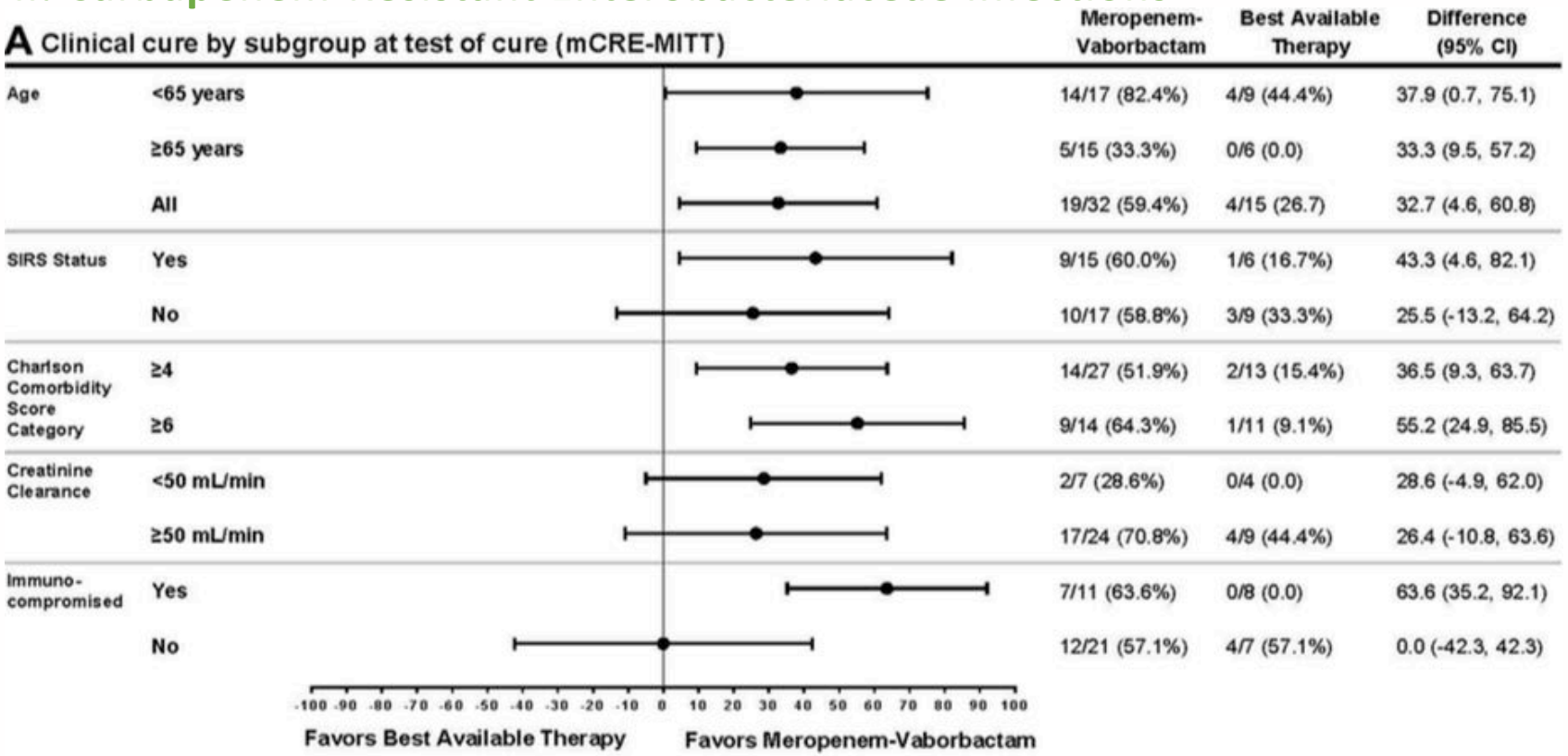
	No. of Patients Successfully Treated/Total No. (%)		Between-Group Difference (95% CI), %
	Meropenem-Vaborbactam	Piperacillin-Tazobactam	
FDA primary: overall success at end of intravenous treatment (microbiologic MITT analysis)[a,b]	189/192 (98.4)	171/182 (94.0)	4.5 (0.7 to 9.1)
EMA primary: microbial eradication at test of cure			
Microbiologic MITT analysis[b]	128/192 (66.7)	105/182 (57.7)	9.0 (-0.9 to 18.7)
Microbiologic evaluable analysis	118/178 (66.3)	102/169 (60.4)	5.9 (-4.2 to 16.0)



Kaye KS et al. JAMA 2018;319(8):788-799

Targeting **A**ntibiotic **N**on-susceptible **G**ram-negative **O**rganisms (TANGO) Trial – Meropenem+*Vaborbactam*

TANGO II: Carbapenem-Resistant Enterobacteriaceae Infections



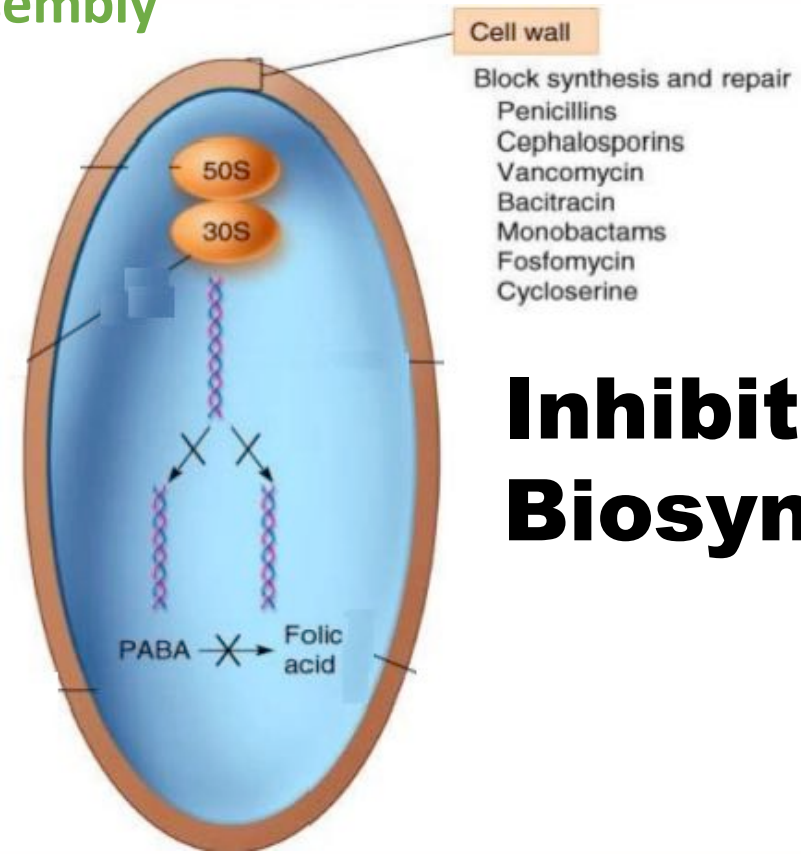
Wunderink RG et al. Infect Dis Ther 2018;7:439–455

Take Home Message

- Cefiderocol is a novel substance related to the 3rd and 4rth generation cephalosporins ceftazidime and cefepime but has an additional residue that binds to iron.
- The unique structure of cefiderocol results in an increased concentration of the antibiotic in the bacterium thus bypassing some but not all resistance mechanisms.
- Several combinations of cephalosporins and carbapenems with beta-lactamase inhibitors result in an increased activity against multiresistant gram-negative bacteria.
- To this end none of the novel compounds demonstrates to be vastly superior to existing ß-lactam antibiotics but some may be effective against otherwise resistant bugs.

Antibacterial Targets

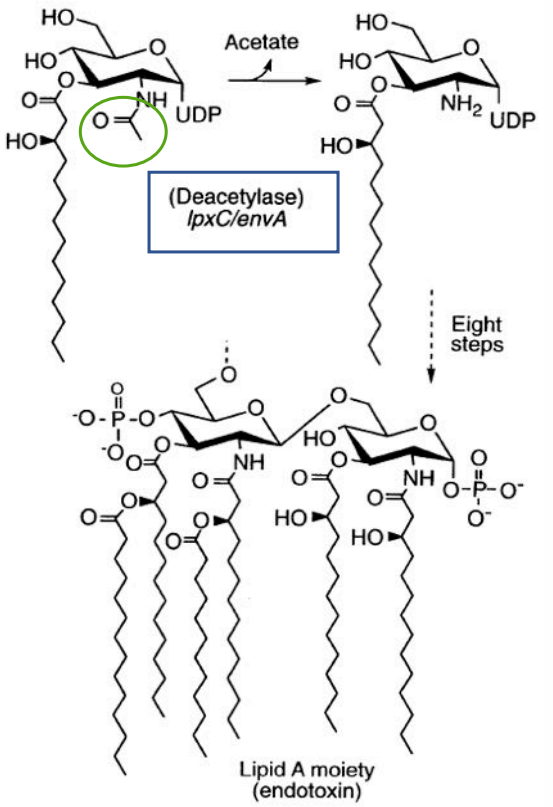
Inhibitors of cell wall assembly



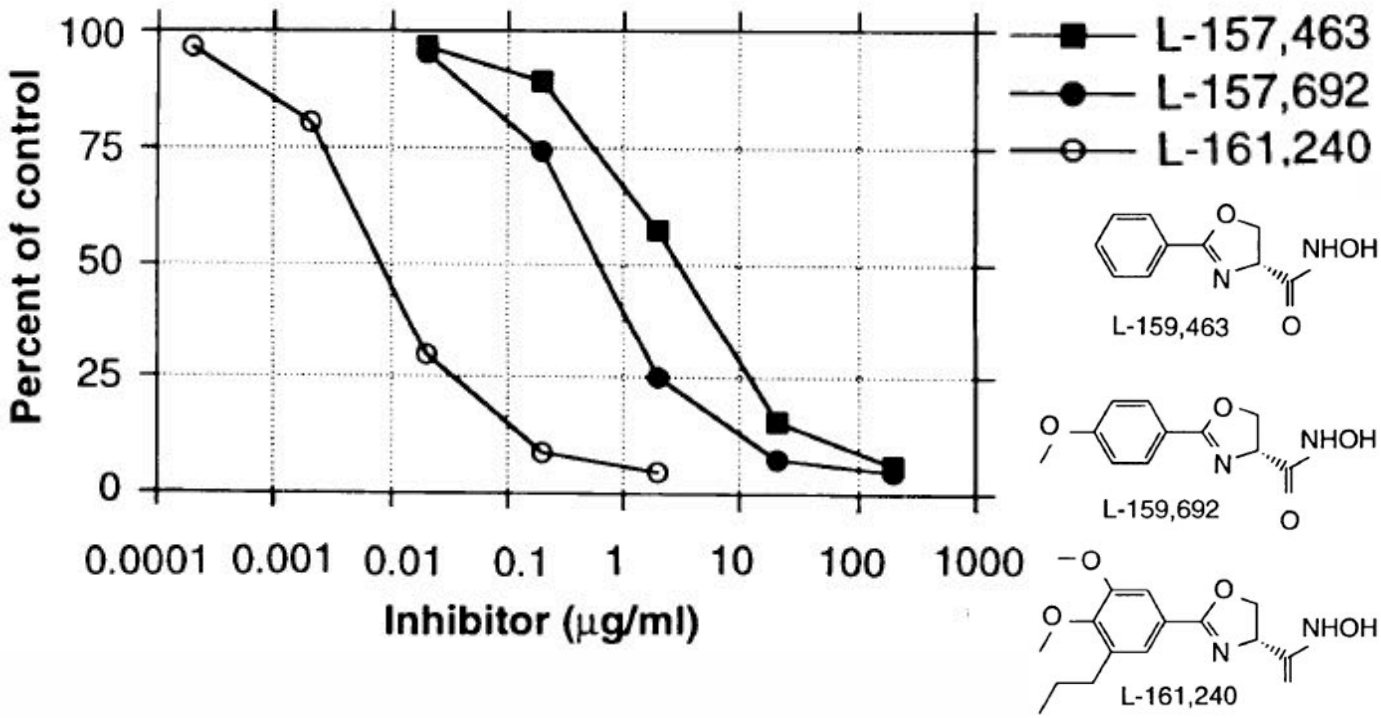
Inhibitors of Lipid A Biosynthesis

UDP-3-O-acyl-N-acetylglucosamine deacetylase (LpxC)

Role in bacterial wall formation

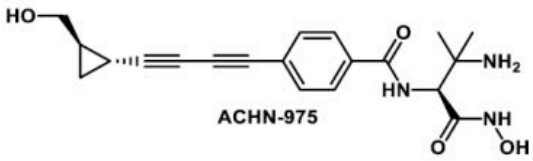
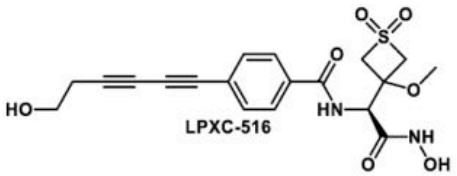
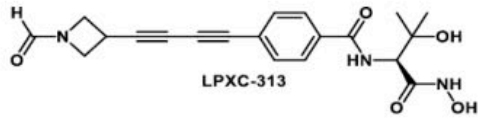
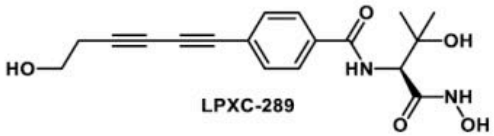


Effect of lpxC inhibition on e.coli growth



Onishi HR et al. Science 1996;274(5289):980-982

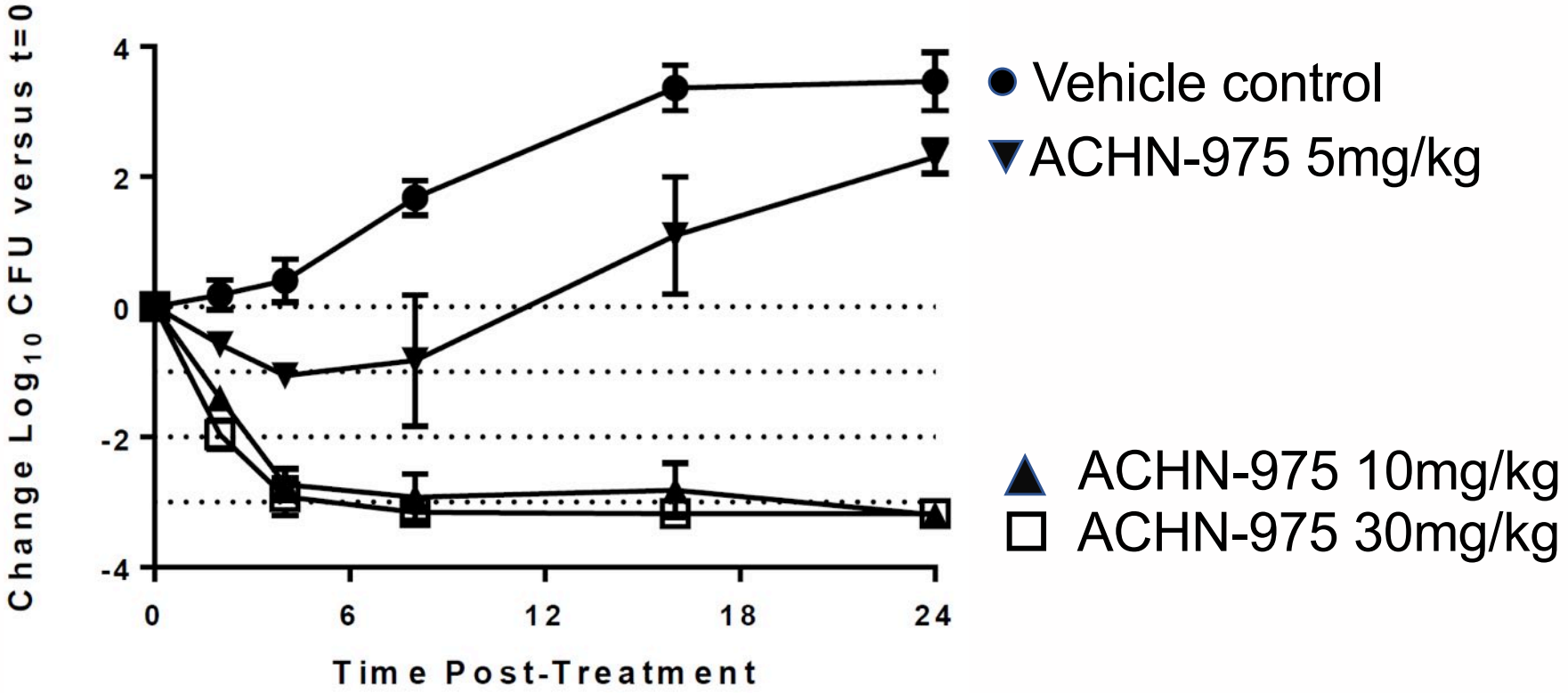
In Vitro Activity of LpxC Inhibitors

Compound	Molecular Weight	*P. aeruginosa* LpxC IC_{50} (nM)	MIC_5 (μg/mL)[a]	Rat Clp (L/hr/kg)[b]
 ACHN-975	369.4	0.68	0.38	0.83
 LPXC-516	420.4	0.71	2.3	1.1
 LPXC-313	383.4	4.8	2.4	1.3
 LPXC-289	344.4	13	1.8	1.9

Krause KM et al. Antimicrob Agents Chemother doi:10.1128/AAC.00977-19

In Vivo Bactericidal Activity of ACHN-975

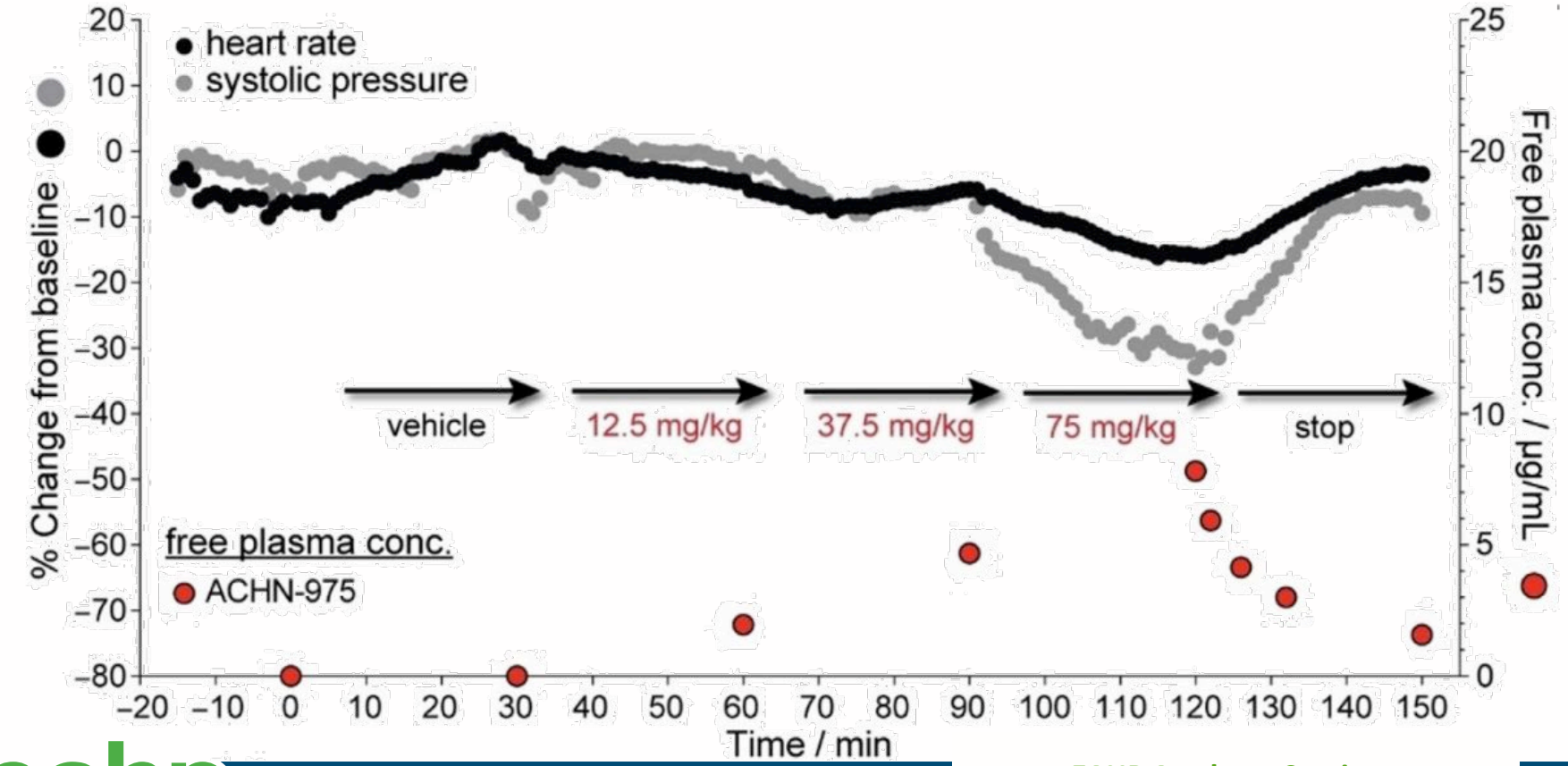
Neutropenic Mouse Thigh Model, Multiresistant *Pseudomonas aeruginosa*



Krause KM et al. Antimicrob Agents Chemother 2019 doi:10.1128/AAC.00977-19

ACHN-975 seems to be an ideal compound but…

Effect of ACHN-975 on heart rate and systolic pressure of male Sprague–Dawley rats



Mod. from Cohen F et al. ChemMedChem. 2019;14(16):1560-1572

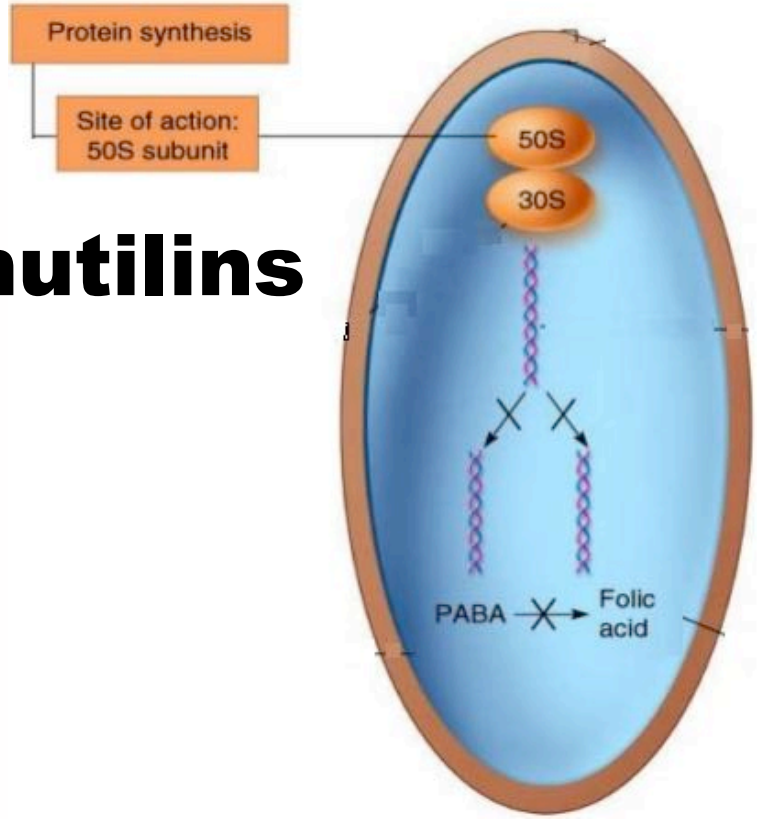
Take Home Message

- Inhibitors of the UDP-3-O-acyl-N-acetylglucosamine deacetylase (LpxC) have bactericidal activity against gramnegative bacteria.
- The most potent candidate is ACHN-975 with nanomolar affinity to LpxC.
- Unfortunately ACHN-975 and related compounds have negative effects on the cardiovascular system.
- To this end no clinical trials are performed with any LpxC inhibitor.

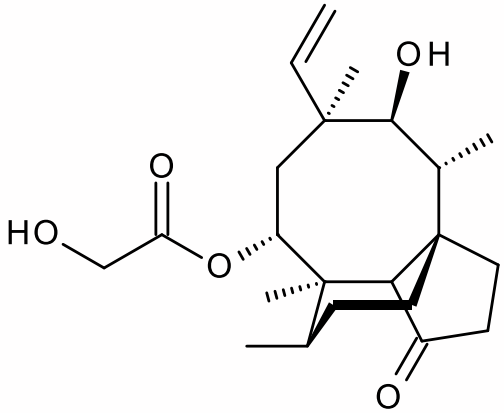
Antibacterial Targets

Inhibitors of protein synthesis

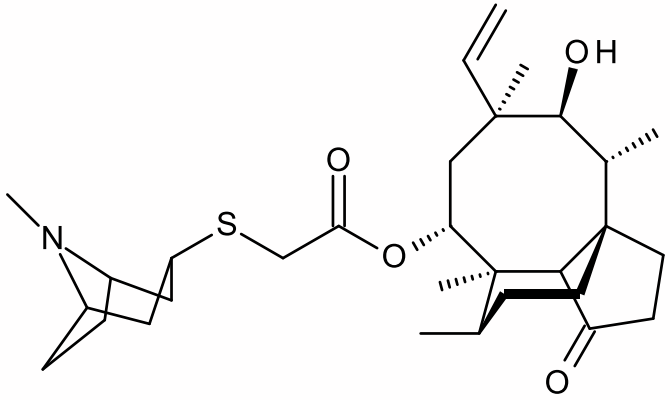
Pleuromutilins



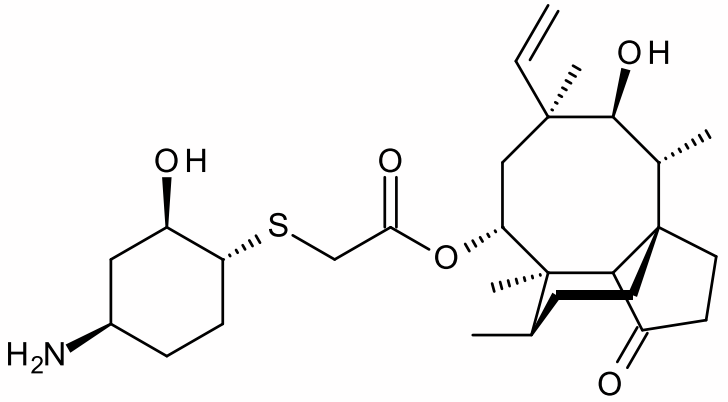
Pleuromutilins



Pleuromutilin



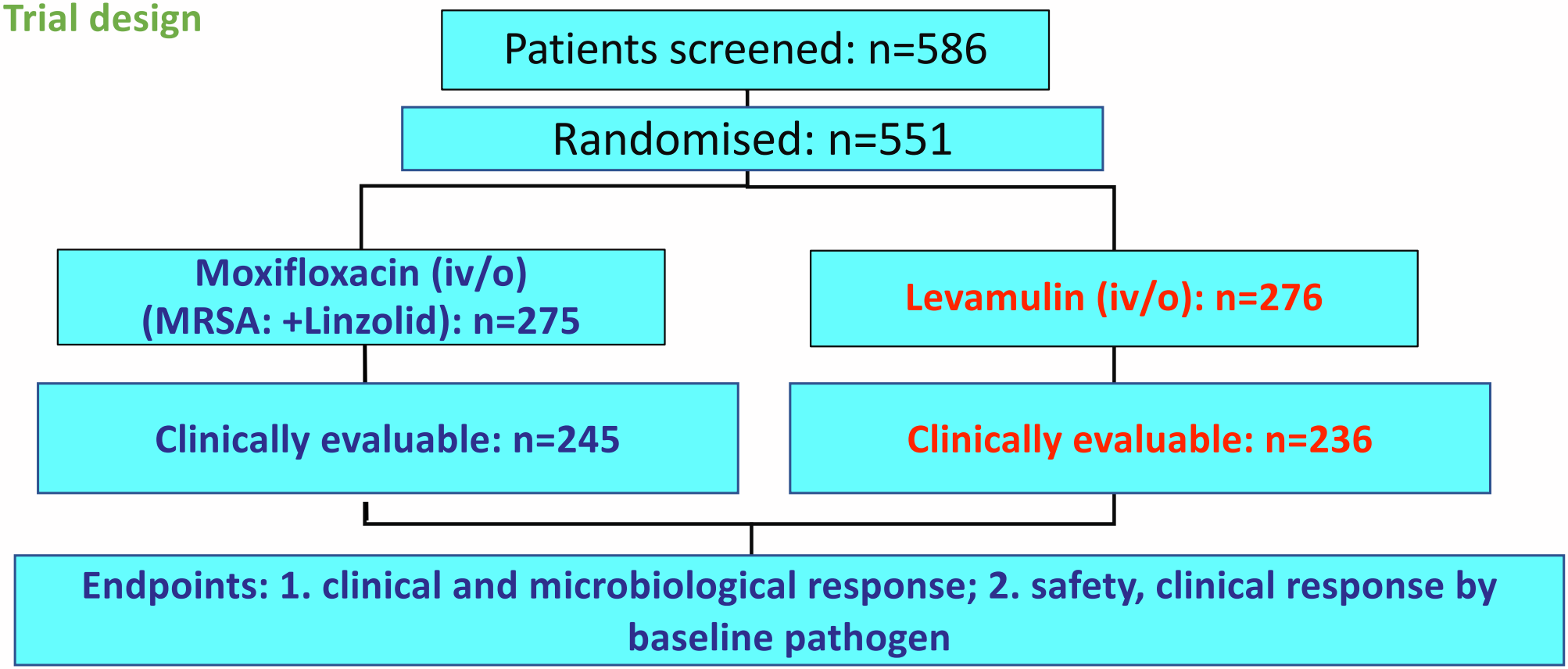
Retapamulin
(Altargo®, topical cream)



Levamulin
(Xenleta™, oral, i.v.)

Levamulin **E**valuation **A**gainst **P**neumonia (LEAP 1) Trial

Trial design



Mod. from File TM S et al. Clin Inf Dis. 2019;XX:1-9 DOI: 10.1093/cid/ciz090

Levamulin Evaluation Against Pneumonia (LEAP 1) Trial

Results 1

	ECR				IACR at TOC			
	microITT		microITT-2		microITT		microITT-2	
Baseline pathogen, rate[a] (n/N)	Lefamulin	Moxifloxacin ± Linezolid	Lefamulin	Moxifloxacin ± Linezolid	Lefamulin	Moxifloxacin ± Linezolid	Lefamulin	Moxifloxacin ± Linezolid
Streptococcus pneumoniae	88.2% (82/93)	93.8% (91/97)	85.7% (36/42)	88.6% (39/44)	84.9% (79/93)	87.6% (85/97)	81.0% (34/42)	86.4% (38/44)
MDR	… (6/6)	… (5/6)	… (6/6)	… (5/6)	… (6/6)	… (4/6)	… (6/6)	… (4/6)
Staphylococcus aureus[b]	100.0% (10/10)	… (4/4)	… (7/7)	… (3/3)	80.0% (8/10)	… (4/4)	… (6/7)	… (3/3)
Haemophilus influenzae	92.2% (47/51)	94.7% (54/57)	… (6/6)	… (5/6)	84.3% (43/51)	84.2% (48/57)	… (5/6)	… (6/6)
Moraxella catarrhalis	92.0% (23/25)	100.0% (11/11)	… (0/1)	… (1/1)	80.0% (20/25)	100.0% (11/11)	… (0/1)	… (1/1)
Mycoplasma pneumoniae	84.2% (16/19)	90.0% (18/20)	92.9% (13/14)	91.7% (11/12)	84.2% (16/19)	95.0% (19/20)	85.7% (12/14)	91.7% (11/12)
Legionella pneumophila	88.9% (16/18)	85.7% (12/14)	88.2% (15/17)	85.7% (12/14)	77.8% (14/18)	78.6% (11/14)	82.4% (14/17)	78.6% (11/14)
Chlamydophila pneumoniae	90.9% (10/11)	94.7% (18/19)	… (8/9)	93.3% (14/15)	72.7% (8/11)	68.4% (13/19)	… (7/9)	73.3% (11/15)

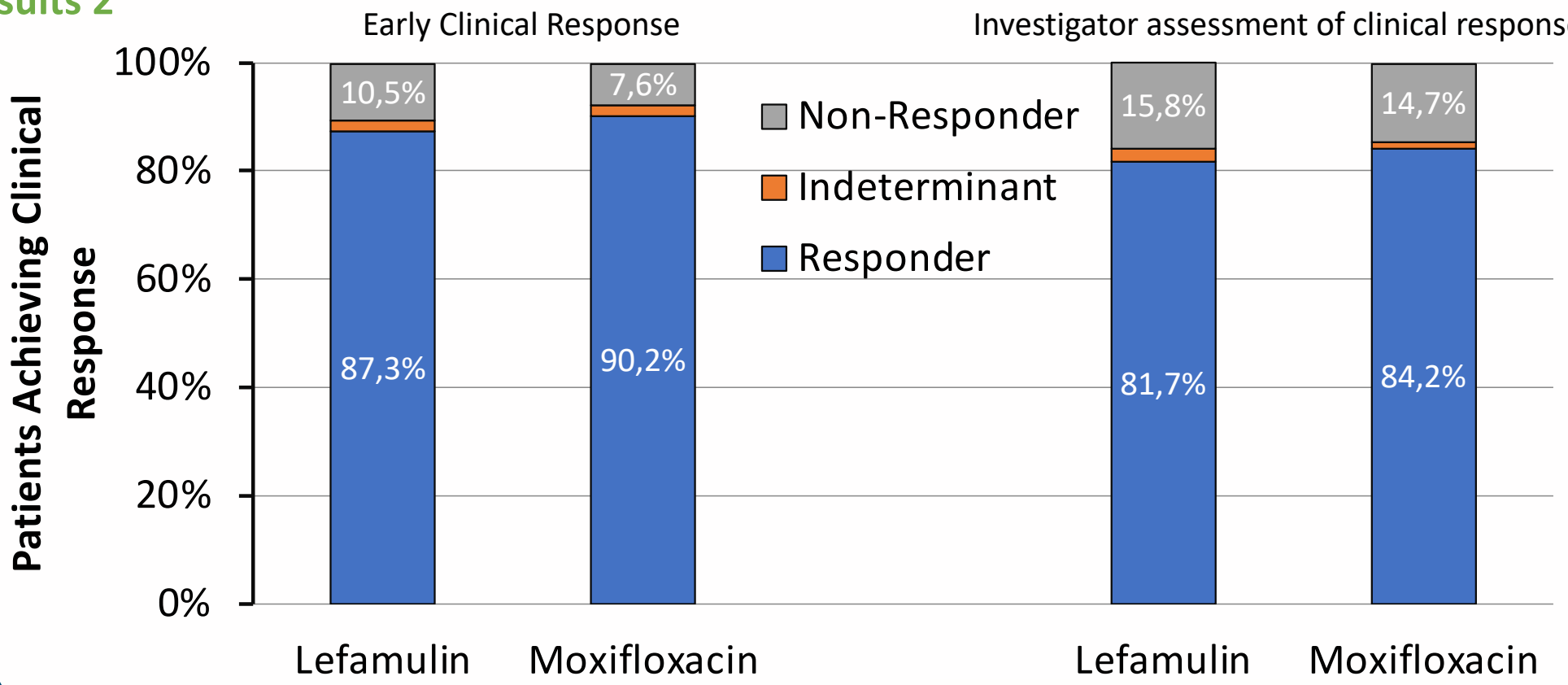
MDR isolates were defined as isolates displaying resistance phenotype to ≥2 of the following: oral penicillin, moxifloxacin, ceftriaxone, clindamycin, azithromycin or erythromycin, doxycycline, or trimethoprim/sulfamethoxazole. The microITT group consisted of all patients in the ITT analysis set who had ≥1 baseline pathogen detected. The microITT-2 group consisted of all patients in the ITT analysis set who had ≥1 baseline pathogen detected by diagnostic means other than polymerase chain reaction. Percentages are not included for numbers <10.

Abbreviations: ECR, early clinical response; IACR, investigator assessment of clinical response; ITT, intent-to-treat; MDR, multidrug-resistant; microITT, microbiological ITT; microITT-2, microbiological ITT-2; TOC, test of cure.

Mod. from File TM S et al. Clin Inf Dis. 2019;XX:1-9 DOI: 10.1093/cid/ciz090

Levamulin Evaluation Against Pneumona (LEAP 1) Trial

Results 2

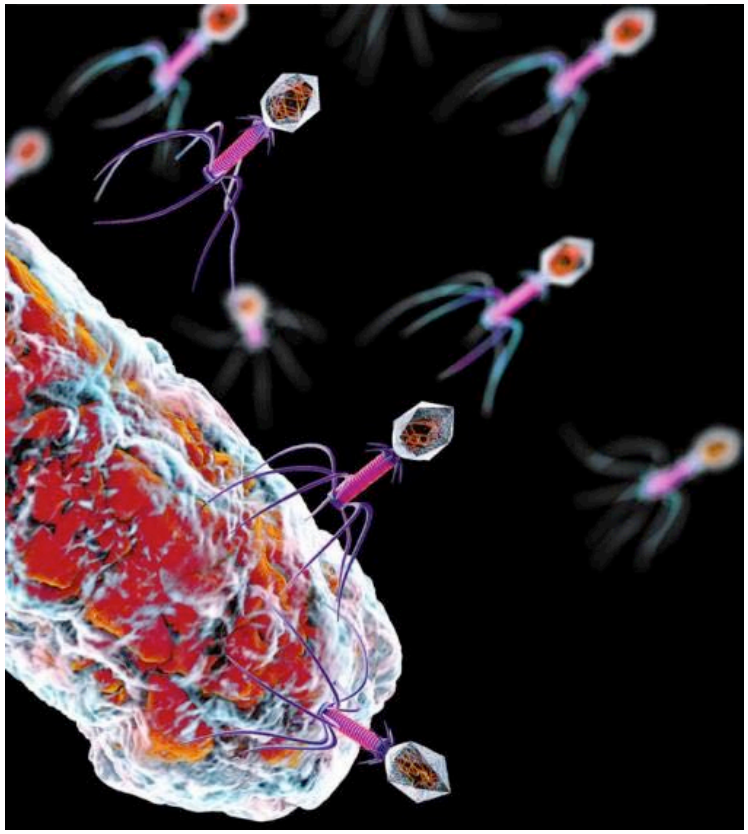


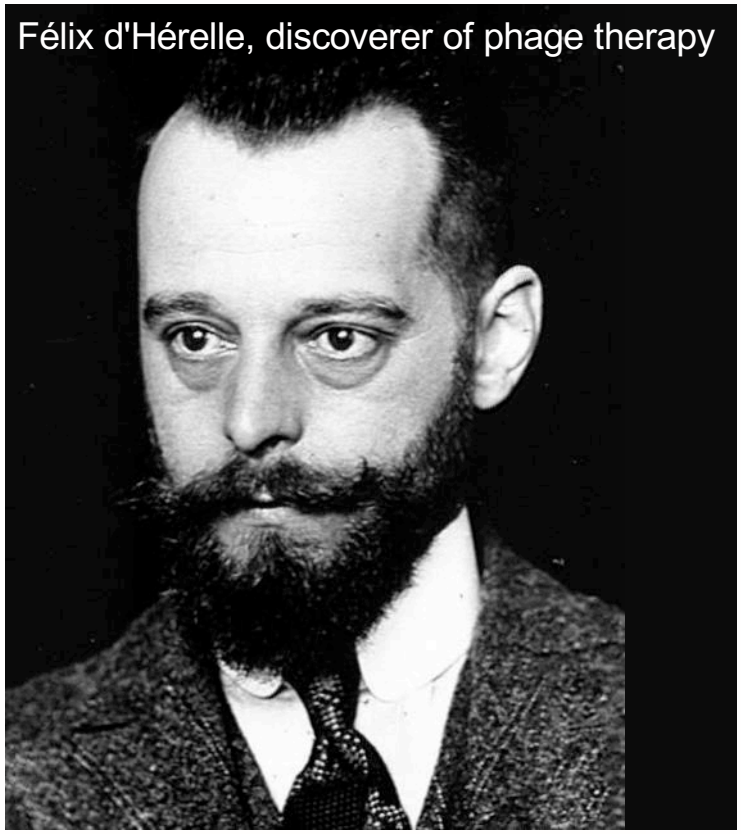
Mod. from File TM S et al. Clin Inf Dis. 2019;XX:1-9 DOI: 10.1093/cid/ciz090

Take Home Message

- Pleuromutilins selectively inhibit bacterial translation through binding to the 50s ribosomal subunit.
- Tiamulin and valnemulin are two established pleuromutilins in veterinary medicine.
- Levamulin is the first candidate for systemic use and exhibits activity against a number of resistant bacteria.
- The LEAP trial demonstrates non-inferiority of Levamulin against Moxifloxacin alone or in combination with Linezolid.
- To this end resistance patterns caused by the use of pleuromutilins in veterinary medicine cannot be anticipated.

Bacteriophages – Friend of Foe?





Newsweek, May 24-31 2019

http://gallica.bnf.fr/ark:/12148/btv1b32000224/f64.item

Bacteriophage preparation targeting antibiotic-resistant Pseudomonas aeruginosa in chronic otitis

Trial design

Patients screened: n=44

Randomised: n=24

Placebo (200 µL saline): n=12

Bacteriophages (200µL=100,000pfu BC-BP 01-06): n=12

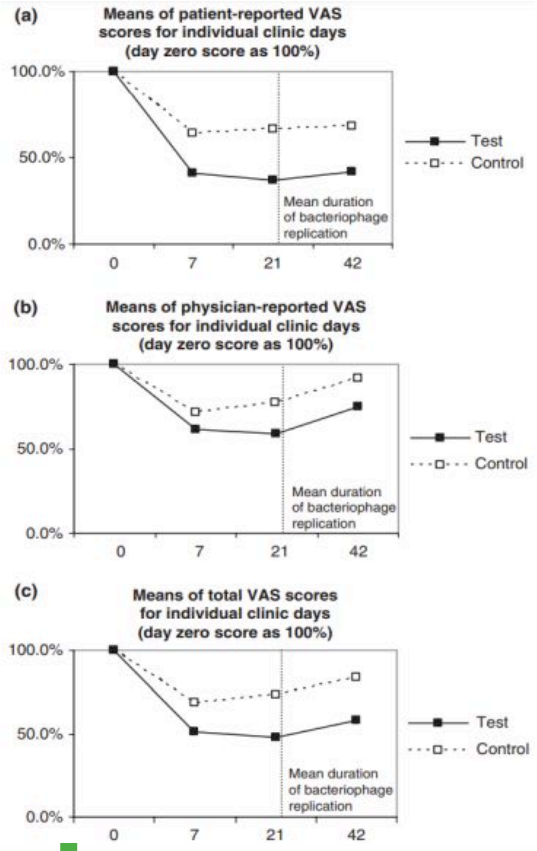
Clinically evaluable: n=12

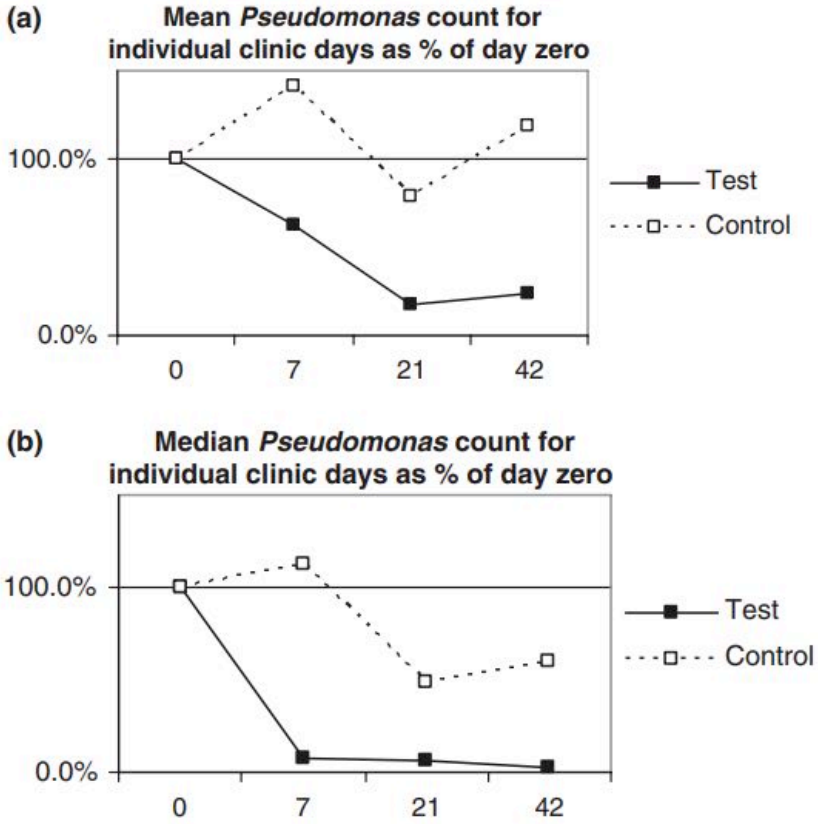
Clinically evaluable: n=12

Endpoints: 1. Patient reported and Physician assessed appearance;
2. Bacterial levels of P.a.

Mod. from: Wright A et al. Clin. Otolaryngol. 2009, 34, 349–357

Bacteriophage preparation targeting antibiotic-resistant *Pseudomonas aeruginosa* in chronic otitis





Mod. from: Wright A et al. Clin. Otolaryngol. 2009, 34, 349–357

Bacteriophage therapy of ventilator-associated pneumonia and empyema caused by *Pseudomonas aeruginosa*

Case Report

- 77 year old female post thoracotomy after adenocarcinoma of the right lower lobe
- On the second day increased white blood cell count and CRP
- After two weeks of intravenous antibiotic treatment detection of multiresistant Pseudomonas aeruginosa in BAL
- On day 23 AB-PA01 (AmpliPhi Biosciences Corporation) a phage product of four obligately lytic bacteriophages (two Myoviridae and two Podoviridae, each at ~1 × 10^9 plaque-forming units (PFU)/mL) was administered intravenously and via nebuliser

Maddocs S et al AJRCCM Articles in Press. 2019 10.1164/rccm.201904-0839LE

Case Report: Successful Treatment of Pneumonia

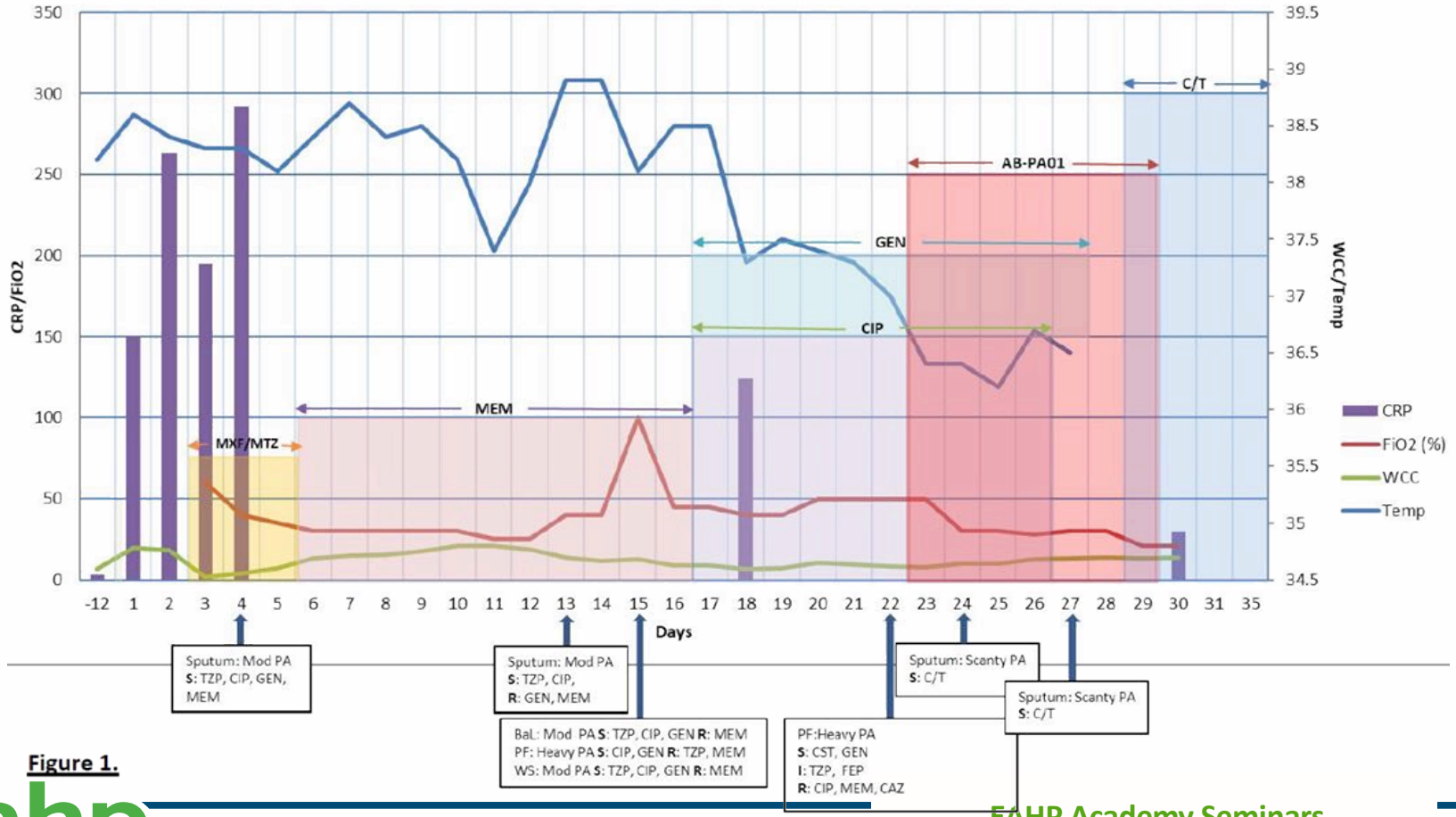


Figure 1.

Maddocs S et al AJRCCM Articles in Press. 2019 10.1164/rccm.201904-0839LE

Take Home Message

- Bacteriophages have been used for more than a century to treat bacterial infections but sound scientific results are scarce.
- Case studies and small size clinical trials have demonstrated that bacteriophages seem to be effective against multiresistant bacteria with reasonable safety and tolerability.
- Development, production and administration of bacteriophages is dependent of the respective microbial pattern and therefore hard to be upscaled. It is unlikely that bacteriophages will become a household *off the shelf* therapy any time soon.

Freiburg University – Medical Center - Pharmacy

Hugstetter Str. 55

D-79106 Freiburg

GERMANY

+49 761-270-54510

martin.hug@uniklinik-freiburg.de