THE UPDATED ANTIBIOTIC ARMAMENTARIUM FOR WHEN BUGS GO BAD

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DISCLOSURE

- Nothing to disclose

OBJECTIVES

- Identify pathogens commonly associated with hospital-acquired infections
- Discuss antibiotics recently introduced to the market which are able to treat multidrug-resistant pathogens
- Determine potential applications of the newer antibiotics

CAUSATIVE PATHOGENS IN HEALTHCARE-ASSOCIATED INFECTIONS

Pathogen	All Health Care–Associated Infections (N=504)†		Pneumonia (N=110)	Surgical-Site Infections (N=110)	GI Infections (N=86)	UTIs (N=65)	Bloodstream Infections (N=50)
	no. (%)	*rank*			*number (percent)*		
Clostridium difficile	61 (12.1)	1	0	0	61 (70.9)	0	0
Staphylococcus aureus	54 (10.7)	2	18 (16.4)	17 (15.5)	1 (1.2)	2 (3.1)	7 (14.0)
Klebsiella pneumoniae or *K. oxytoca*	50 (9.9)	3	13 (11.8)	15 (13.6)	1 (1.2)	15 (23.1)	4 (8.0)
Escherichia coli	47 (9.3)	4	3 (2.7)	14 (12.7)	1 (1.2)	18 (27.7)	5 (10.0)
Enterococcus species‡	44 (8.7)	5	2 (1.8)	16 (14.5)	5 (5.8)	11 (16.9)	6 (12.0)
Pseudomonas aeruginosa	36 (7.1)	6	14 (12.7)	7 (6.4)	1 (1.2)	7 (10.8)	2 (4.0)
Candida species§	32 (6.3)	7	4 (3.6)	3 (2.7)	3 (3.5)	3 (4.6)	11 (22.0)
Streptococcus species¶	25 (5.0)	8	7 (6.4)	8 (7.3)	2 (2.3)	2 (3.1)	2 (4.0)
Coagulase-negative staphylococcus species	24 (4.8)	9	0	7 (6.4)	0	1 (1.5)	9 (18.0)
Enterobacter species	16 (3.2)	10	3 (2.7)	5 (4.5)	0	2 (3.1)	2 (4.0)
Acinetobacter baumannii	8 (1.6)	11, tie	4 (3.6)	2 (1.8)	0	0	0

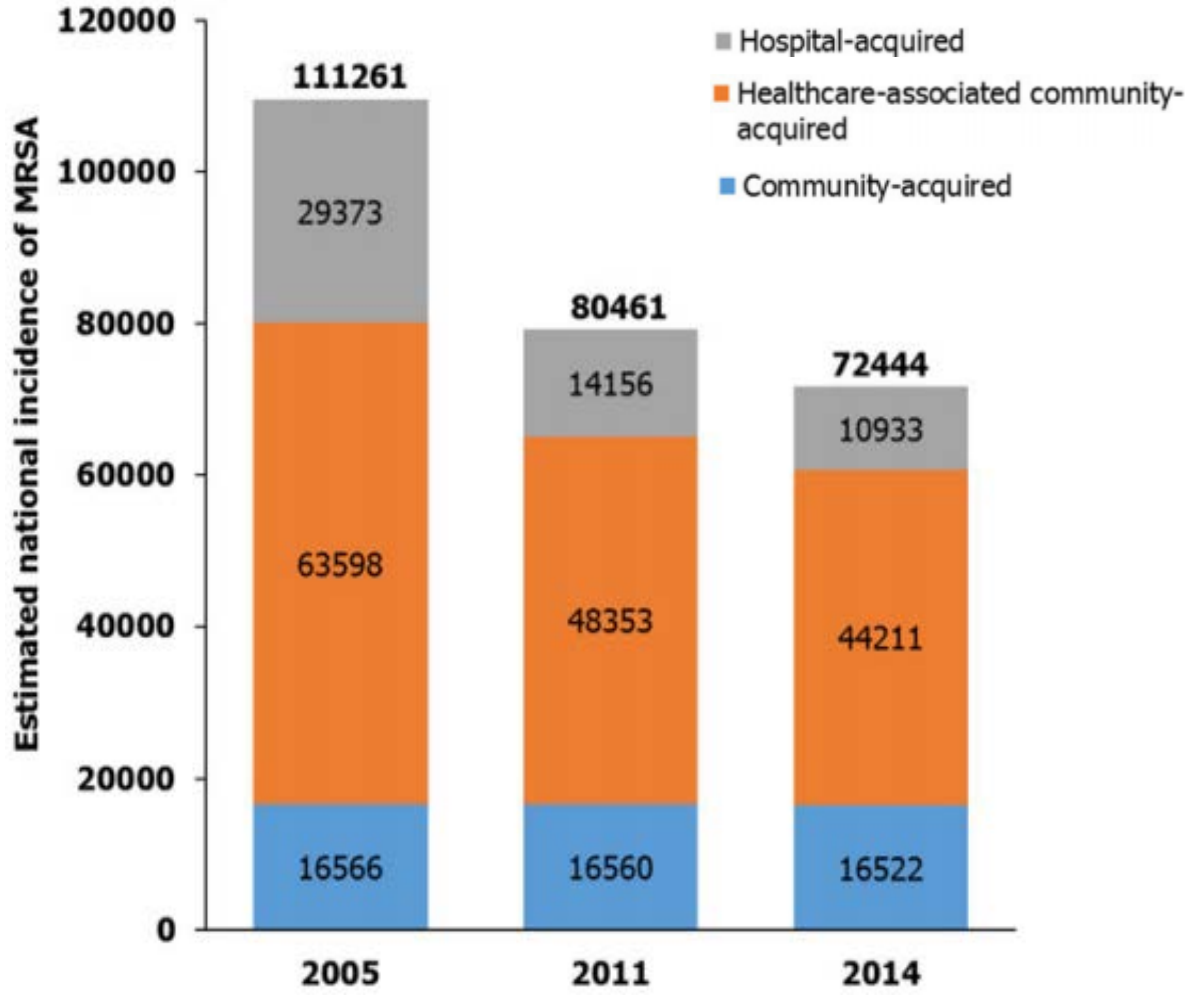
NEJM 2014;370:1198-208.

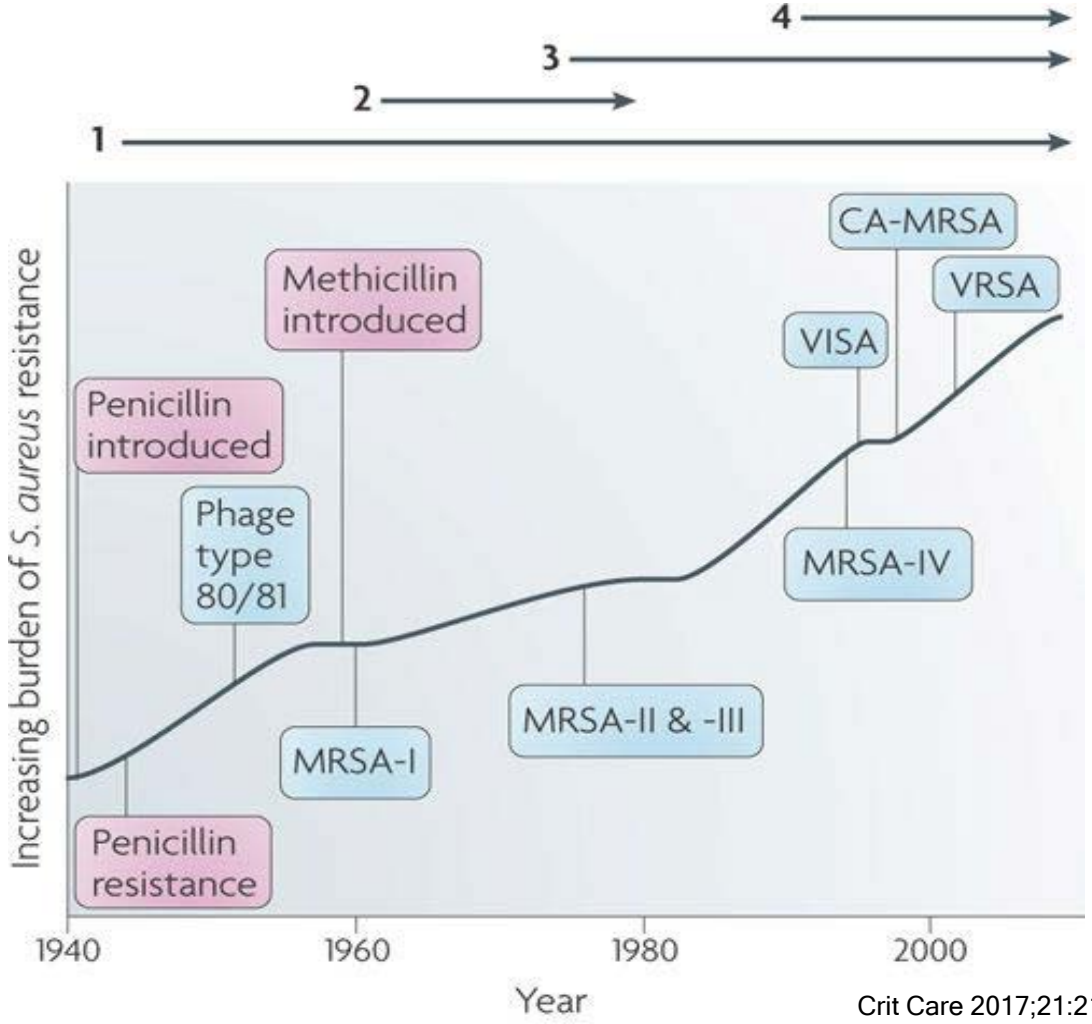
IMPACT OF ANTIBIOTIC RESISTANCE

Organism	Increased Risk of Death (OR)	Attributable Length of Stay (Days)	Attributable Cost
MRSA bacteremia	1.9	2.2	$6,916
MRSA surgical infection	3.4	2.6	$13,901
VRE infection	2.1	6.2	$12,766
Resistant *Pseudomonas* infection	3.0	5.7	$11,981
Resistant *Enterobacter* infection	5.0	9.0	$29,379
Carbapenem-resistant Enterobactereciae	1.12	5.0	$10,312

Clin Infect Dis 2006;42:S82-9.
Adapted from slide by George Nelson

PREVALENCE OF MRSA



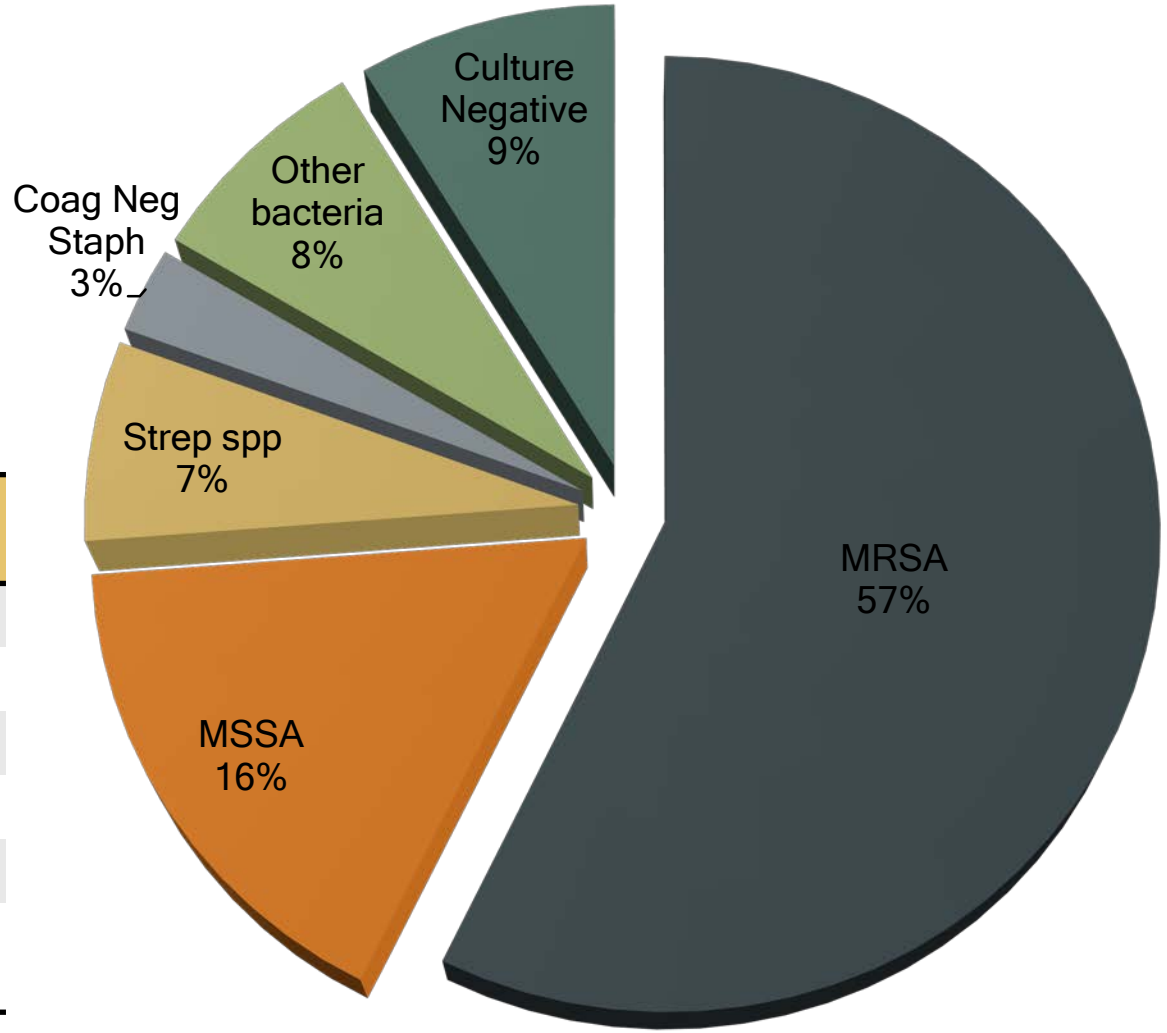


Crit Care 2017;21:211-21.
Nat Rev Microbiol. 2009;7:629-41.

ABSSSI MICROBIOLOGY AND TREATMENT OPTIONS

- Treatment options
  - Clindamycin
  - Trimethoprim-sulfamethoxazole
  - Doxycycline
  - Linezolid
  - Tedizolid

	Linezolid, N=102 N (%)	Tedizolid, N=25 N (%)
Adverse event	45 (45)	11 (44)
Peripheral neuropathy	24 (24)	5 (20)
Dsytonia-like reaction	0	3 (12)
Thrombocytopenia	6 (6)	1 (4)
Anemia	8 (8)	0
Gastrointestinal intolerance	9 (9)	5 (20)

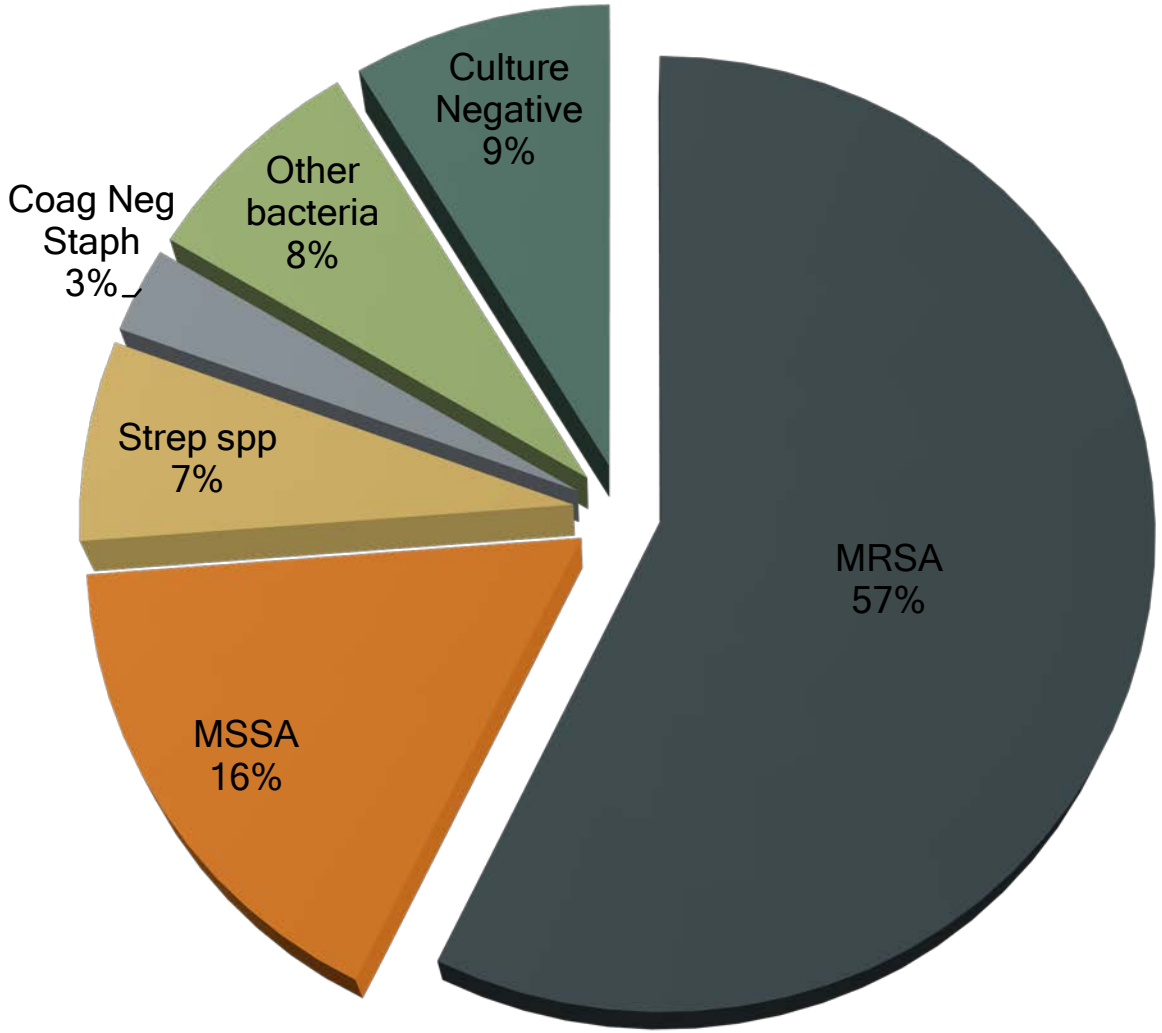


*ABSSSI = acute bacterial skin and skin structure infection

NEJM. 2006;355:666-74

SSTI MICROBIOLOGY AND TREATMENT OPTIONS

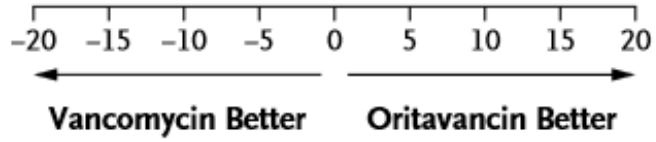
- Outpatient treatment options
  - Clindamycin
  - Trimethoprim-sulfamethoxazole
  - Doxycycline
  - Linezolid
  - Tedizolid
  - Telavancin
  - Oritavancin
  - Dalbavancin
  - Delafloxacin



NEJM. 2006;355:666-74

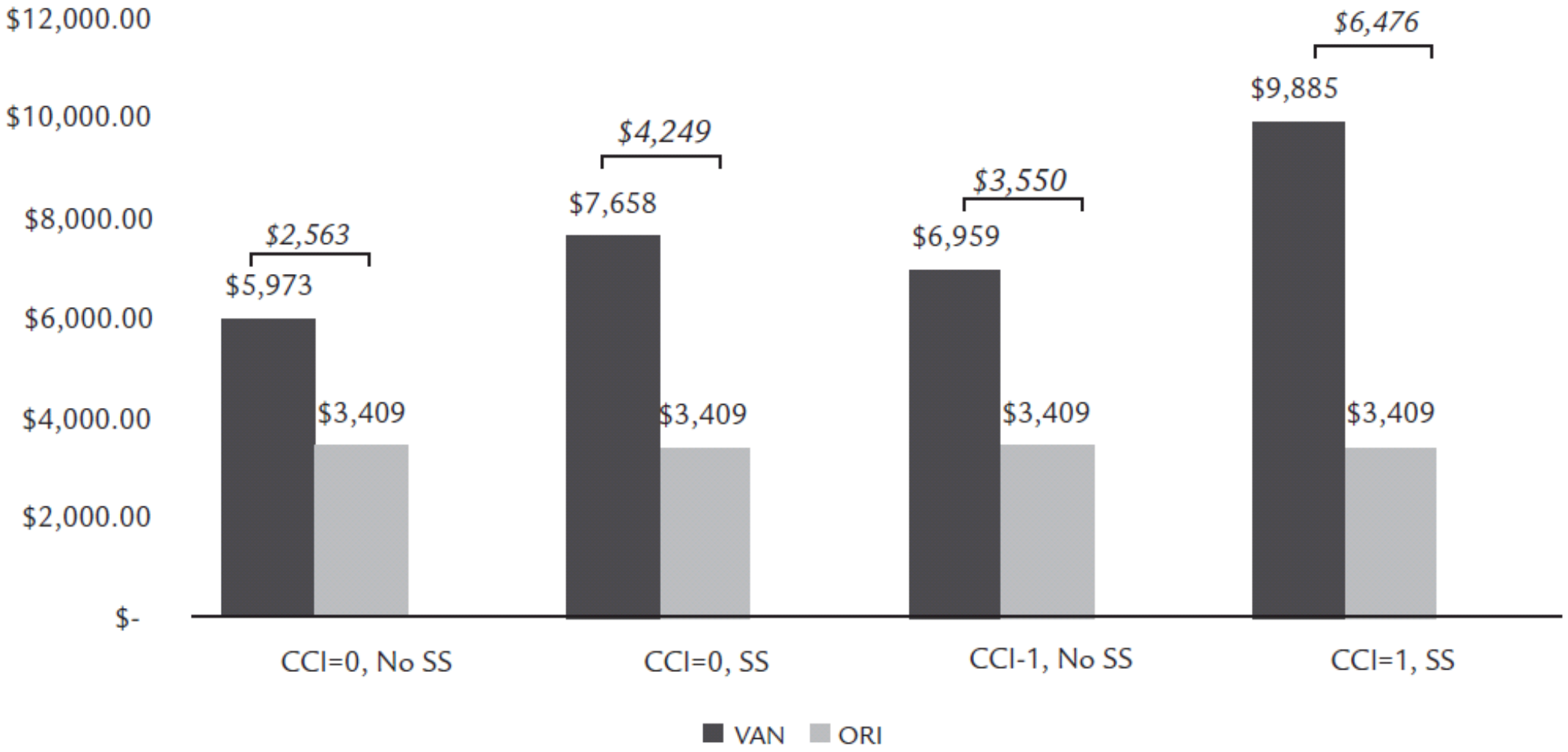
ORITAVANCIN - SOLO I

Subgroup	Oritavancin	Vancomycin	Percentage-Point Difference (95% CI)
	no. of events/total no. (%)		
Modified intention-to-treat population			
Primary efficacy outcome at ECE	391/475 (82.3)	378/479 (78.9)	3.4 (–1.6 to 8.4)
Investigator-assessed clinical cure at PTE	378/475 (79.6)	383/479 (80.0)	–0.4 (–5.5 to 4.7)
Lesion size reduction ≥20% at ECE	413/475 (86.9)	397/479 (82.9)	4.1 (–0.5 to 8.6)
CE population			
Primary efficacy outcome at ECE	344/394 (87.3)	342/397 (86.1)	1.2 (–3.6 to 5.9)
Investigator-assessed clinical cure at PTE	357/394 (90.6)	352/397 (88.7)	1.9 (–2.3 to 6.2)
Lesion size reduction ≥20% at ECE	362/394 (91.9)	370/397 (93.2)	–1.3 (–5.0 to 2.3)
Patients infected with MRSA in intention-to-treat population with microbiologic evaluation			
Primary efficacy outcome at ECE	84/104 (80.8)	80/100 (80.0)	0.8 (–10.1 to 11.7)
Investigator-assessed clinical cure at PTE	86/104 (82.7)	83/100 (83.0)	–0.3 (–10.7 to 10.0)
Lesion size reduction ≥20% at ECE	94/104 (90.4)	84/100 (84.0)	6.4 (–2.8 to 15.5)
Patients infected with MSSA in intention-to-treat population with microbiologic evaluation			
Primary efficacy outcome at ECE	96/116 (82.8)	92/110 (83.6)	–0.9 (–10.6 to 8.9)
Investigator-assessed clinical cure at PTE	89/116 (76.7)	88/110 (80.0)	–3.3 (–14.0 to 7.4)
Lesion size reduction ≥20% at ECE	98/116 (84.5)	94/110 (85.5)	–1.0 (–10.3 to 8.3)



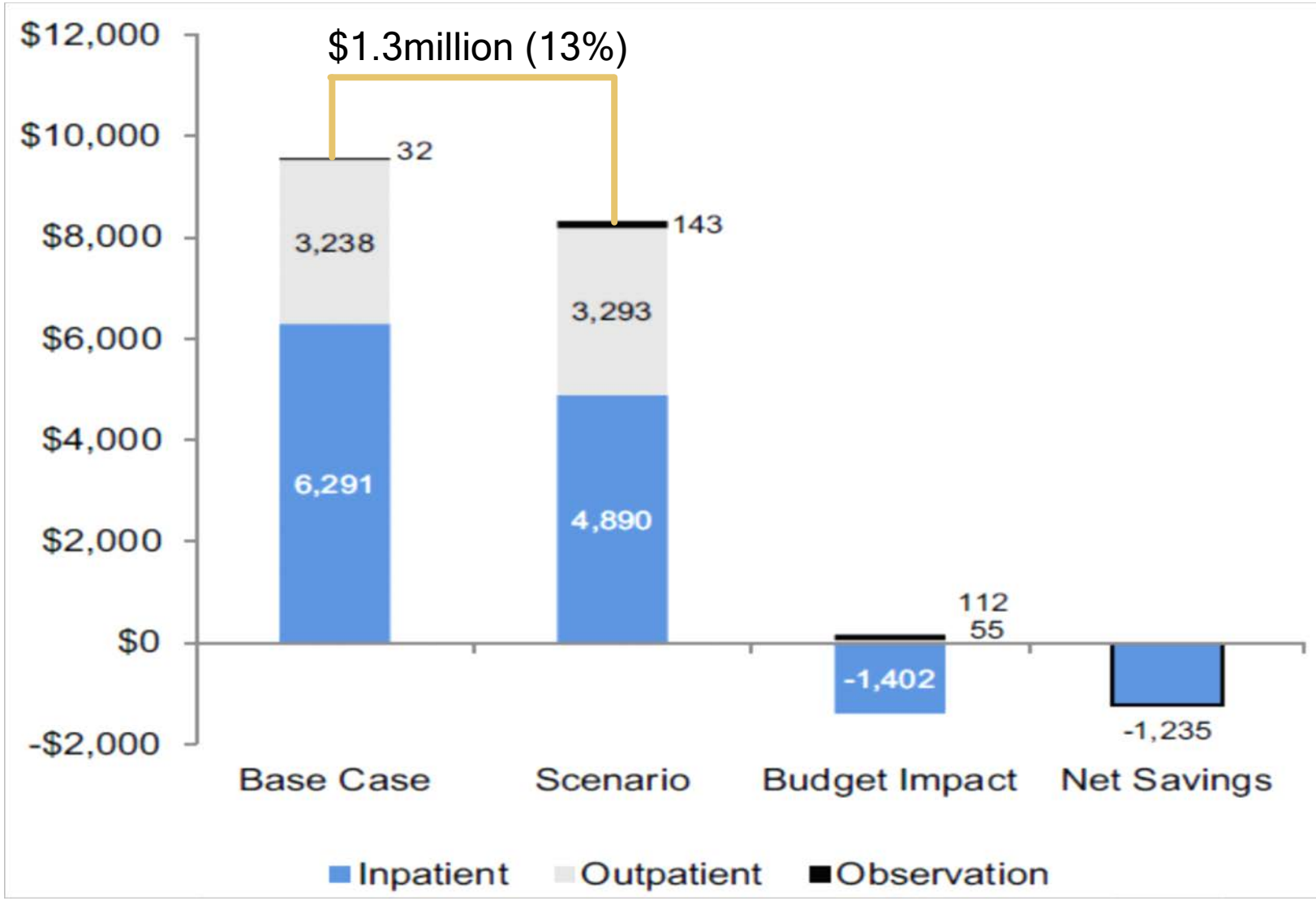
JAMA 2014;370:2180.

ECONOMIC IMPACT OF ORITAVANCIN FOR ABSSSI IN THE ED



Clin Ther 2016;38:136.

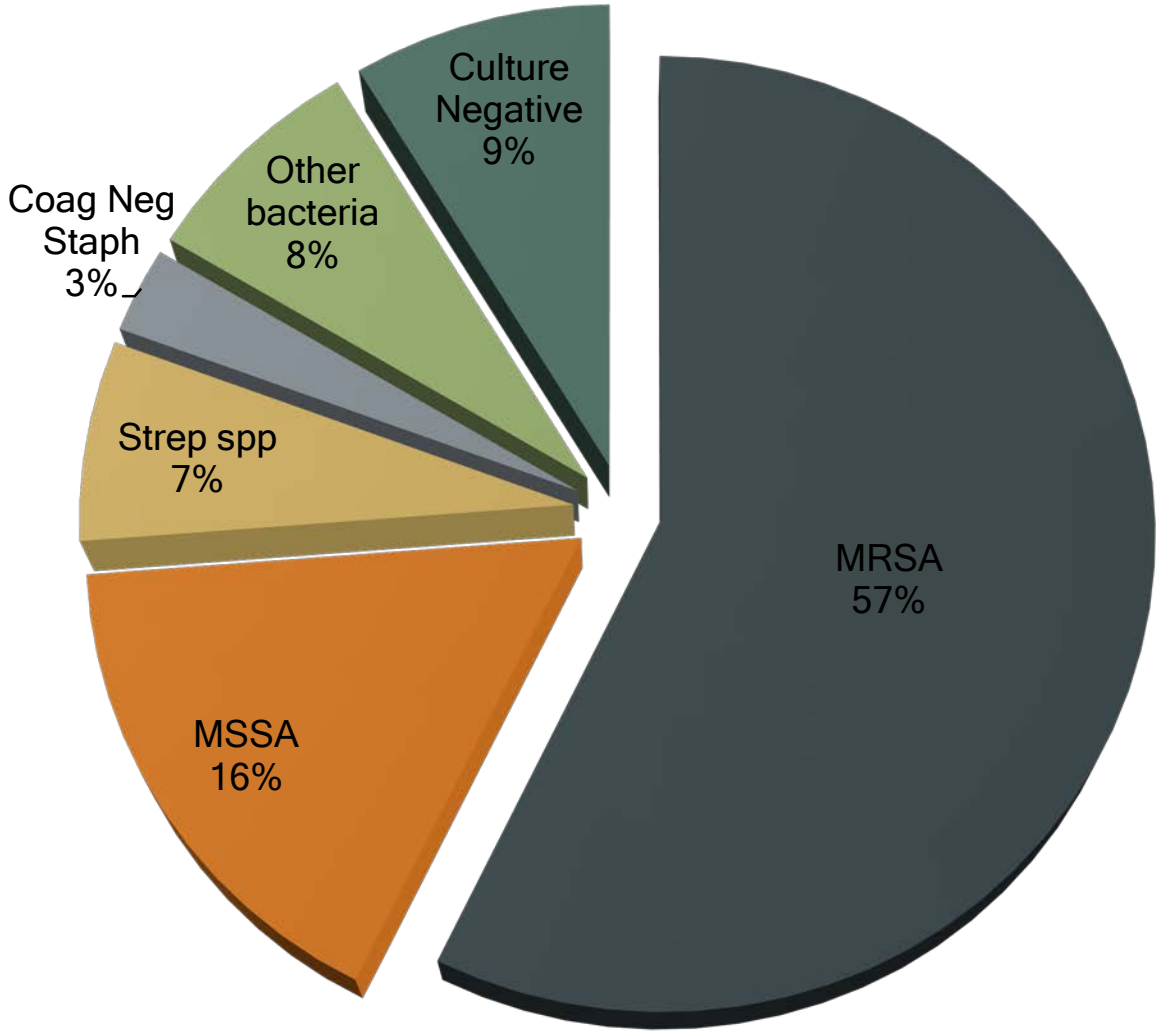
HOSPITAL BUDGET IMPACT ANALYSIS
HOSPITALS WITH AMBULATORY SERVICES



Clin Drug Investig 2016;36:157.

SSTI MICROBIOLOGY AND TREATMENT OPTIONS

- Outpatient treatment options
  - Clindamycin
  - Trimethoprim-sulfamethoxazole
  - Doxycycline
  - Linezolid
  - Tedizolid
  - Telavancin
  - Oritavancin
  - Dalbavancin
  - Delafloxacin



NEJM. 2006;355:666-74

DELAFLOXACIN VERSUS TIGECYCLINE FOR ABSSSI

	Delafloxacin 300 mg IV	Delafloxacin 450 mg IV	Tigecycline 50 mg IV
Staphylococcus aureus	*n* = 22	*n* = 27	*n* = 20
Cure, *n* (%)	21 (95.5)	25 (92.6)	18 (90.0)
Failure, *n* (%)	1 (4.5)	2 (7.4)	2 (10.0)
MRSA	*n* = 14	*n* = 20	*n* = 14
Cure, *n* (%)	13 (92.9)[a,b]	19 (95.0)[c]	12 (85.7)
Failure, *n* (%)	1 (7.1)	1 (5.0)	2 (14.3)
MSSA	*n* = 8	*n* = 7	*n* = 6
Cure, *n* (%)	8 (100.0)	6 (85.7)	6 (100.0)
Failure, *n* (%)	-	1 (14.3)	-

Int J Infect Dis 2015;3:67-73.

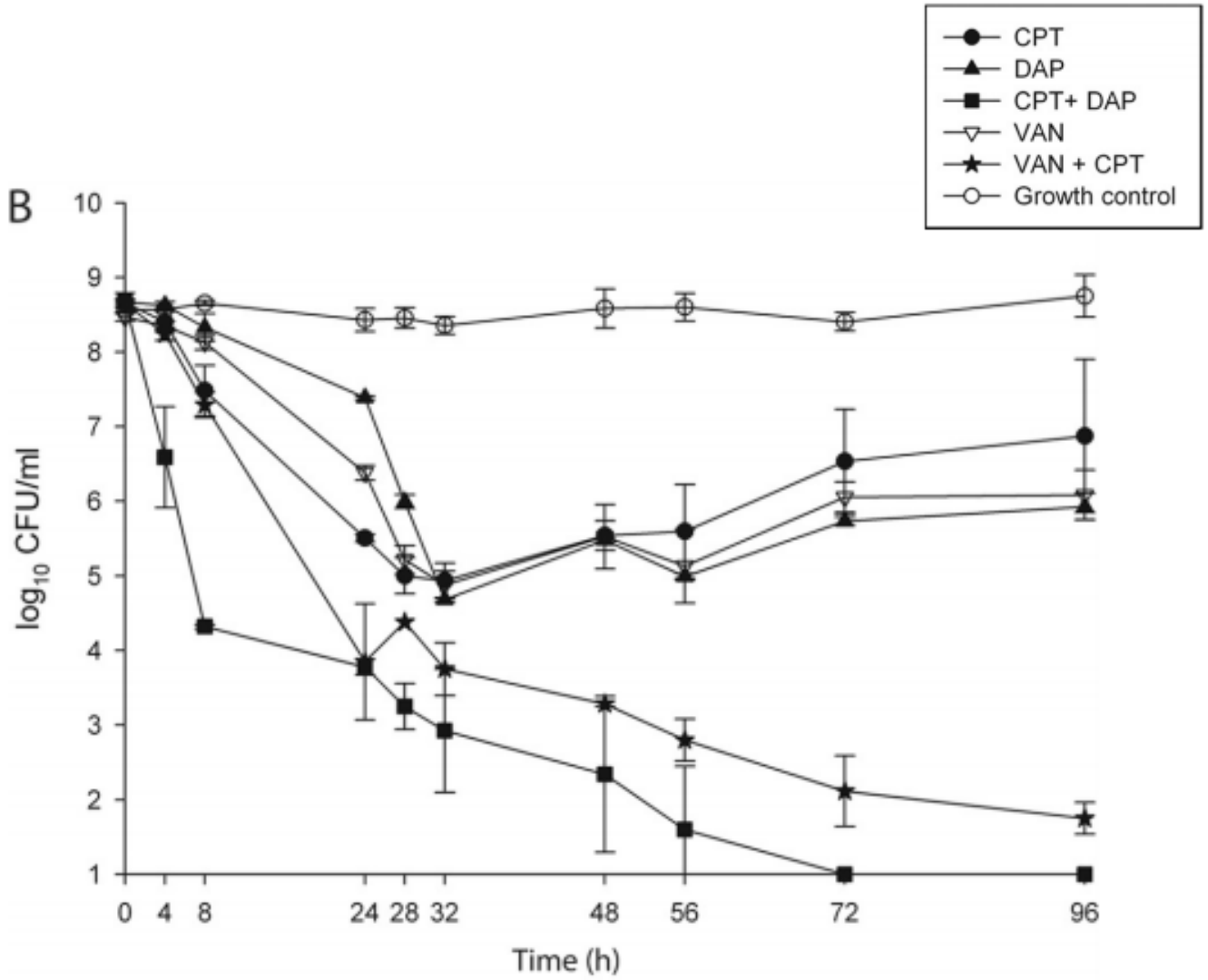
DELAFLOXACIN VERSUS VANCOMYCIN OR LINEZOLID FOR ABSSSI

	Delafloxacin	Linezolid	Vancomycin
Outcome/measurement technique			
erythema/digital measurement			
cessation of spread,[a] *n/N* (%)	61/78 (78.2)	56/75 (74.7)	69/95 (72.6)
20% reduction, *n/N* (%)	58/78 (74.4)	55/75 (73.3)	65/95 (68.4)
percentage change in area at follow-up, mean (SD)	−96.4 (13.96)	−87.7 (39.22)	−84.5 (35.73)[b]
Induration/digital measurement			
cessation of spread,[a] *n/N* (%)	54/78 (69.2)	47/75 (62.7)	72/95 (75.8)
20% reduction, *n/N* (%)	44/78 (56.4)	40/75 (53.3)	66/95 (69.5)
percentage change in area at follow-up, mean (SD)	−73.5 (48.56)	−77.1 (47.02)	−84.8 (30.05)
Body temperature (°C)[c]			
change from baseline to follow-up, mean (SD)	−0.2 (0.53)	−0.2 (0.59)	−0.2 (0.76)
Serum CRP (mg/L)[d]			
change from baseline to follow-up, mean (SD)	−37.4 (64.90)	−38.1 (54.51)	−43.2 (64.90)
Serum IL-6 (ng/L)[e]			
change from baseline to follow-up, mean (SD)	−7.9 (15.84)	−8.7 (19.11)	−9.7 (19.33)[b]

J Antimicrob Chemother 2016;71:821-29.

TREATMENT OF SYSTEMIC MRSA INFECTIONS

- Vancomycin
  - Dial-up internet bactericidal killing
- Linezolid
  - Static activity
- Daptomycin
- Ceftaroline
  - Synergistic combinations with daptomycin
- Oritavancin and dalbavancin



Antimicrob Agents Chemother 2013;57:66-73.

ORITAVANCIN FOR BACTEREMIA AND ENDOCARDITIS

Patient #	Indication	Reason for Use	Doses (#)	ADEs	Clinical Outcome	Comments
1	MSSA CLABSI	Refused OPAT	1	Nausea	Cure	PICC removed; Longer duration than recommended
2	MSSA bacteremia & wound infection	Refused OPAT	1	None	Cure	
3	MSSA bacteremia, iliopsoas abscess & sacral osteomyelitis	IVDU	1	None	Fail	Developed endocarditis likely due to persistent source
4	MSSA bacteremia & psoas abscess	IVDU	1	None	Lost to follow-up	
5	MSSA bacteremia	OPAT non-compliance	1	None	Cure	Source was cellulitis
6	MRSA bursitis	Refused OPAT	1	Nausea	Cure	Underwent 2 I&Ds prior to start of oritavancin
7	MSSA deep tissue infection	Allergies	3	Hearing Loss	Fail	Prior antibiotics included vancomycin x 6 weeks, clindamycin x 20 weeks

Failure rate between 28% - 40% (overall)

Infect Dis Ther 2017;6:277-89.
Open Forum Infect Dis 2015;2:1-5.

DALBAVANCIN AND INFECTIVE ENDOCARDITIS DUE TO *S. AUREUS*

Duration (weeks)	Type of IE	Prior Therapy (duration, week)	Failure	ADEs	Regimen
2	Native	Flucloxacillin & fosfomycin (2) Cefazoline & daptomycin (4)	No	None	Once
2	Native	Flucloxacillin & daptomycin (5)	No	None	Twice
2	Native	Cefuroxime & daptomycin (4)	No	None	Twice
4	Native	Vancomycin (1)	Yes	None	Twice
6	Prosthetic	Flucloxacillin & rifampin (2)	No	None	Once
6	Native	Flucloxacillin & daptomycin (1)	No	None	Twice
6	Native	Flucloxacillin & fosfomycin (1)	No	None	Twice
>6	CDE	Flucloxacillin (1)	Resistant	None	Once
>6	Native	Ceftriaxone (1) Daptomycin (1)	No	None	Twice
>6	Prosthetic	Flucloxacillin & rifampin (1)	No	None	Twice

J Clin Pharm Ther 2018;43:101-3.
Clin Infect Dis 2018;67:795-8.

ENTEROCOCCAL RESISTANCE

INTRINSIC

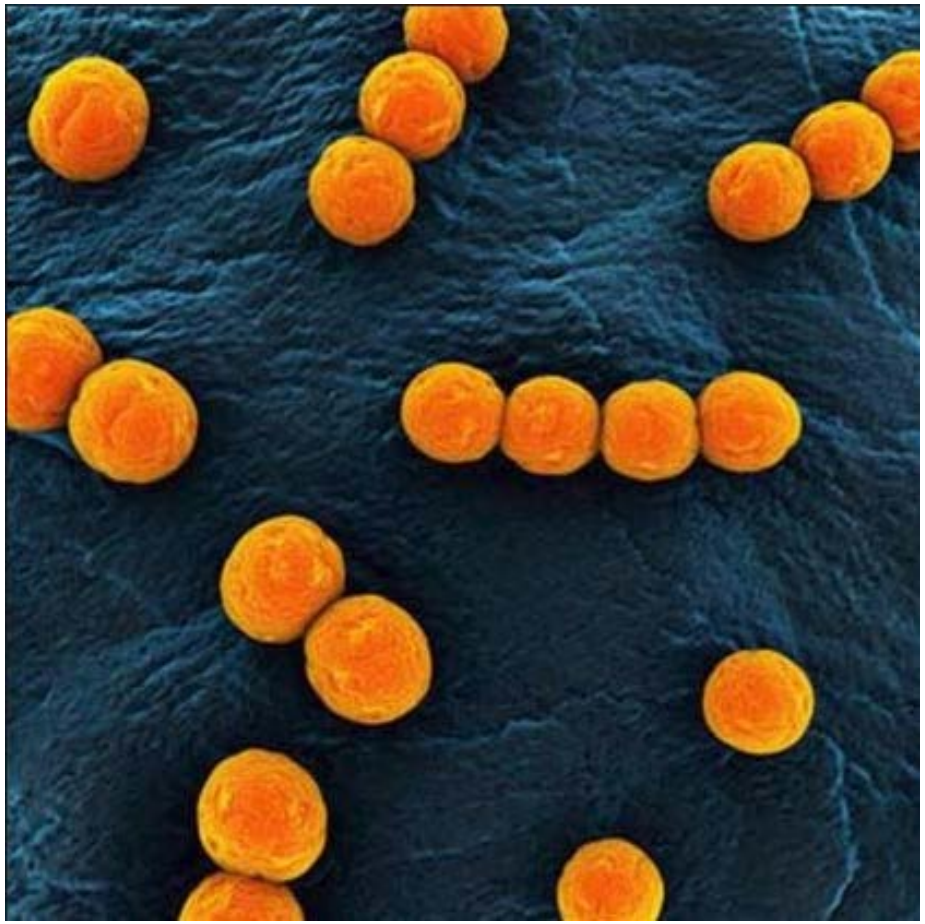
- Cephalosporins
- Penicillinase-resistant penicillins
- Aminoglycosides (excluding synergy)
- Clindamycin
- Fluoroquinolones
- Trimethoprim-sulfamethoxazole (in vivo)
- Vancomycin
  - *E. casseliflavus*
  - *E. gallinarium*

ACQUIRED

- Cephalosporins
- Penicillinase-resistant penicillins
- Aminoglycosides (excluding synergy)
- Tetracycline
- Erythromycin
- Fluoroquinolones
- Rifampin
- Nitrofurantoin
- Vancomycin

TREATMENT OF VANCOMYCIN-RESISTANT ENTEROCOCCUS

- Penicillin
- Ampicillin
  - Combination with ceftriaxone for endocarditis
- Daptomycin
  - Beta-lactam combinations
- Linezolid
- Tedizolid
  - Poor urine penetration
- Quinupristin-dalfopristin
  - *E. faecium* only
- Tigecycline
  - Not for bloodstream infections
- Oritavancin
  - Active against vanA
- Dalbavancin
  - Active against vanB



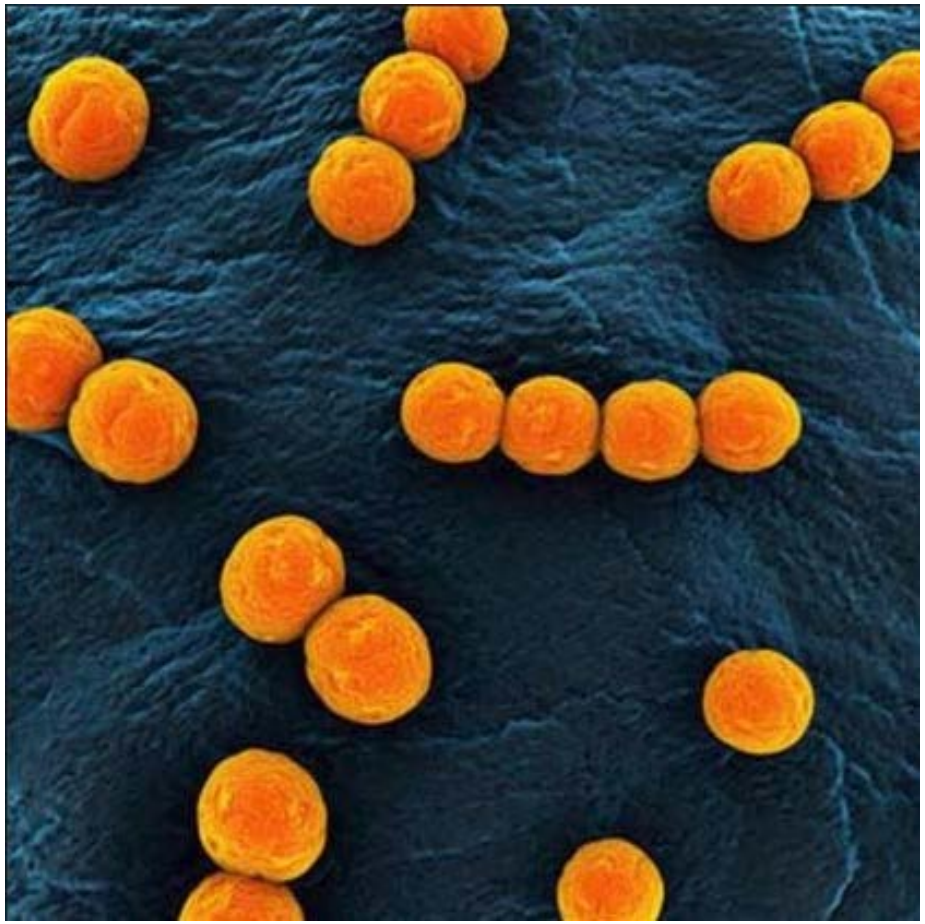
ORITAVANCIN AND DALBAVANCIN FOR ENTEROCOCCAL BACTEREMIA

Antibiotic	Type of IE, if present	Prior Therapy (duration, week)	Failure	ADEs	Notes
Oritavancin	Bacteremia	Ampicillin (4)	No	None	
Oritavancin	Prosthetic	Daptomycin & tigecycline (4) Linezolid (4)	Yes	Nausea, LFT increase	16 weeks of once or twice weekly dosing
Dalbavancin	Prosthetic	Vancomycin (3)	Death	No	
Dalbavancin	Native	Ceftriaxone & ampicillin (2)	No	None	
Dalbavancin	Native	Ceftriaxone & ampicillin (1)	No	None	

Clin Infect Dis 2018;67:795-8.
Infect Dis Ther 2017;6:277-89.
Open Forum Infect Dis 2015;2:1-5.

TREATMENT OF VANCOMYCIN-RESISTANT ENTEROCOCCUS

- Penicillin
- Ampicillin
  - Combination with ceftriaxone for endocarditis
- Daptomycin
  - Beta-lactam combinations
- Linezolid
- Tedizolid
  - Poor urine penetration
- Quinupristin-dalfopristin
  - *E. faecium* only
- Tigecycline
  - Not for bloodstream infections
- Oritavancin
  - Active against vanA
- Dalbavancin
  - Active against vanB
- Fosfomycin IV
  - Oral only indicated for uncomplicated cystitis



FOSFOMYCIN IV

- Not available in US
  - Pending approval
  - Available in Europe
- Phosphoenolpyruvate analog
  - Bacterial cell wall inhibition by binding to and inactivating enolpyruvate transferase
- Broad spectrum activity, including VRE
  - Except many *Pseudomonas* and *Acinetobacter* species
- Clinical uses
  - Urinary tract infections, intra-abdominal infections, pulmonary infections, osteomyelitis, bacteremias

THE RISE OF MDR PSEUDOMONAS

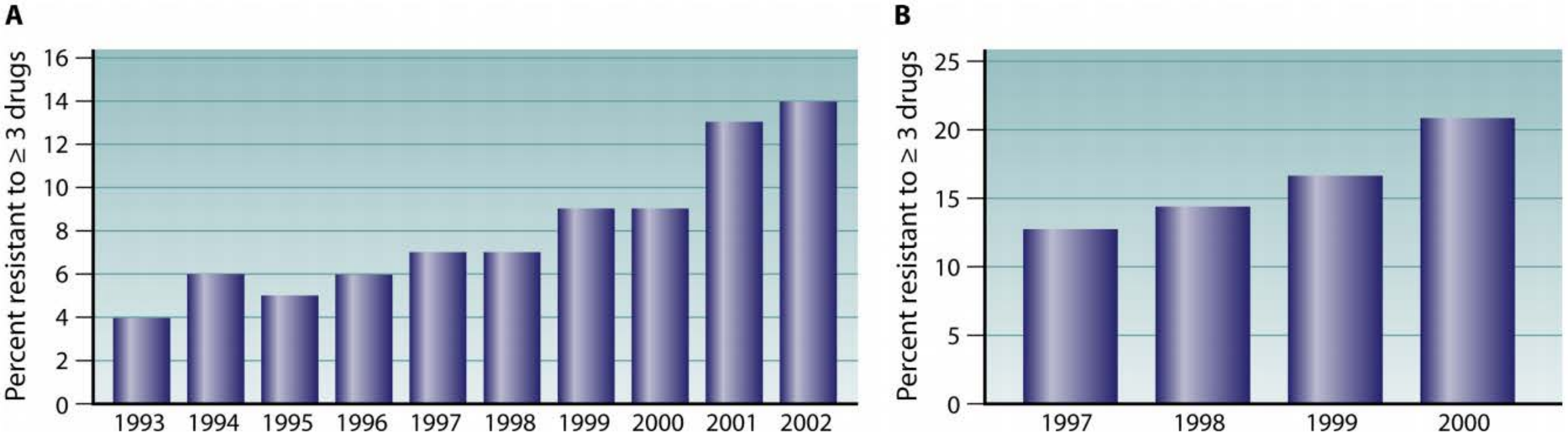


FIG. 1. Increasing prevalence of multidrug resistance among *P. aeruginosa* isolates from ICU patients in the United States. (A) Data for 13,999 nonduplicate isolates collected from 1993 to 2002 (178); (B) data for 37,390 isolates collected from 1997 to 2000 (132). Data represent the percentage of *P. aeruginosa* isolates that expressed a phenotype of multidrug resistance (resistance to three or more drug classes) during each year of the studies. (Panel A is adapted from reference 178 with permission; panel B is based on data from reference 132.)

Clin Microbiol Rev. 2009 Oct; 22(4): 582-610.

CEFTOLOZANE-TAZOBACTAM

TABLE 2. IC_{50} of CXA-101, ceftazidime, and imipenem for *P. aeruginosa* PAO1 PBPs

PBP	Mean IC_{50} (μg/ml) ± SD[a]		
	CAZ	CXA	IMP
1b	0.12 ± 0.03	0.07 ± 0.01	0.13 ± 0.01
1c	>2	0.64 ± 0.17	0.08 ± 0.005
2	>2	1.36 ± 0.56	0.08 ± 0.01
3	0.04 ± 0.01	0.02 ± 0.007	0.12 ± 0.2
4	1.23 ± 0.49	0.29 ± 0.05	0.02 ± 0.01
5/6	>2	>2	0.2 ± 0.09

[a] IC_{50}, 50% inhibitory concentration; CXA, CXA-101; CAZ, ceftazidime; IMP, imipenem.

Antimicrob Agents Chemother. 2010 Sep;54(9):3933-7

Antimicrob Agents Chemother. 2007 Mar;51(3):826-30

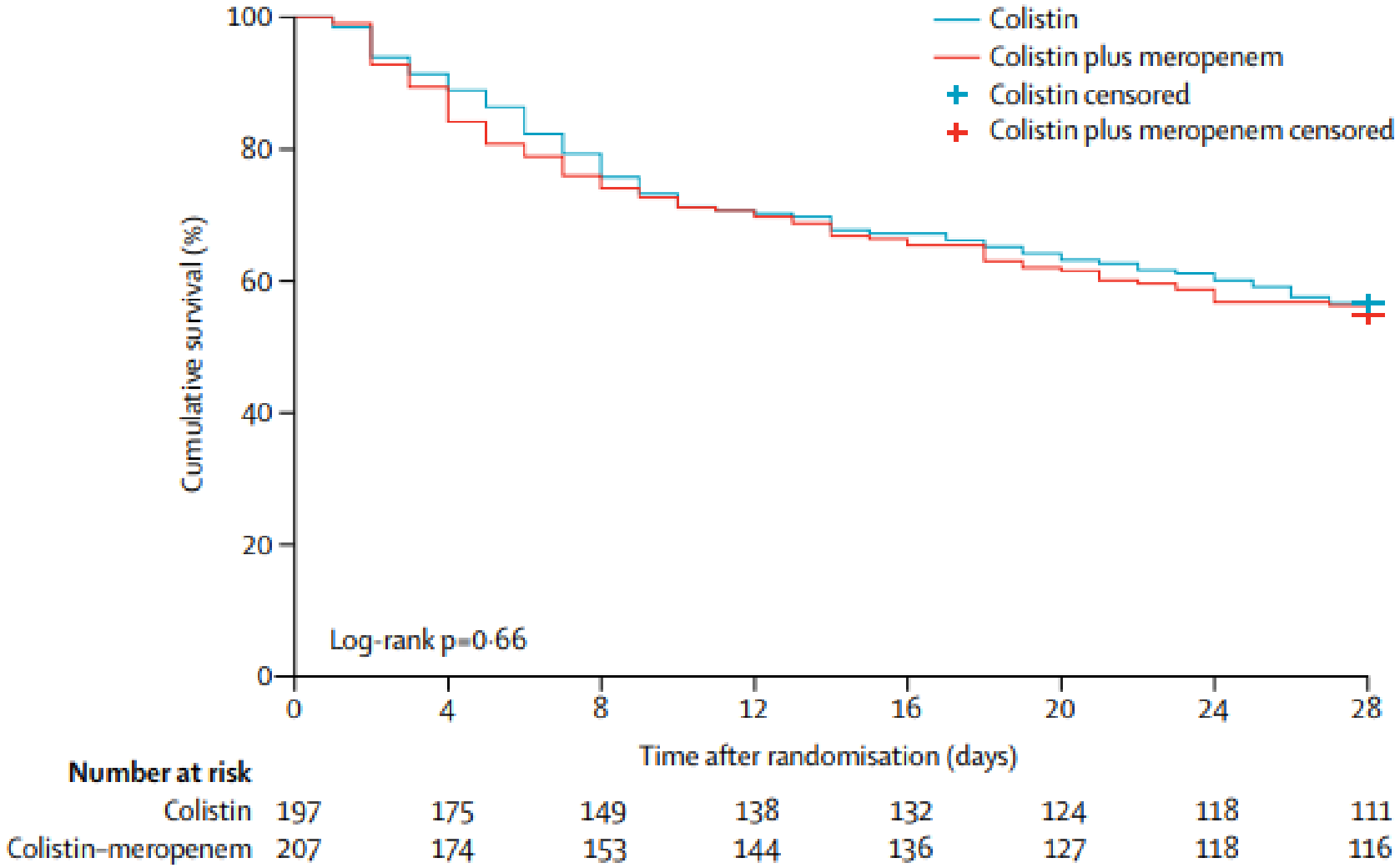
SUSCEPTIBILITY RATES OF CEFTOLOZANE-TAZOBACTAM AND CEFTAZIDIME-AVIBACTAM

β-lactam agent/s to which isolates were NS (no. of isolates/total, %)	S to CZA (no. of isolates, %)	S to C/T (no. of isolates, %)	P value[a]
FEP (168/290, 58%)	114, 68%	142, 85%	0.0003
CAZ (157/290, 54%)	105, 67%	132, 84%	0.0006
TZP (185/290, 64%)	133, 72%	159, 86%	0.0013
ATM (183/290, 63%)	132, 72%	159, 87%	0.0007
FEP\ CAZ (133/290, 46%)	82, 62%	108, 81%	0.0006
FEP\ TZP (147/290, 51%)	97, 66%	122, 83%	0.0012
FEP\ATM (131/290, 45%)	82, 63%	108, 82%	0.0005
CAZ\ TZP (145/290, 50%)	95, 66%	121, 83%	0.0007
CAZ\ATM (121/290, 42%)	73, 60%	99, 82%	0.0004
TZP\ATM (148/290, 51%)	99, 67%	125, 85%	0.0006
FEP\CAZ\TZP (127/290, 44%)	78/127, 61%	103/127, 81%	0.0008
FEP\CAZ\ATM (106/290, 37%)	59/106, 56%	84/106, 79%	0.0004
FEP\TZP\ATM (121/290, 42%)	73/121, 60%	98/121, 81%	0.0006
CAZ\TZP\ATM (118/290, 41%)	70/118, 59%	96/118, 81%	0.0003
4- β-lactam agents (103/290, 36%)	56/103, 54%	81/103, 79%	0.0004

- Meropenem non-susceptible *Pseudomonas* isolates
- Resistance to ≥ 1 beta-lactam
  - Ceftazidime-avibactam inhibitory activity was significantly lower than ceftolozane-tazobactam

Antimicrob Agents Chemother. 2017;61:e00875-17.

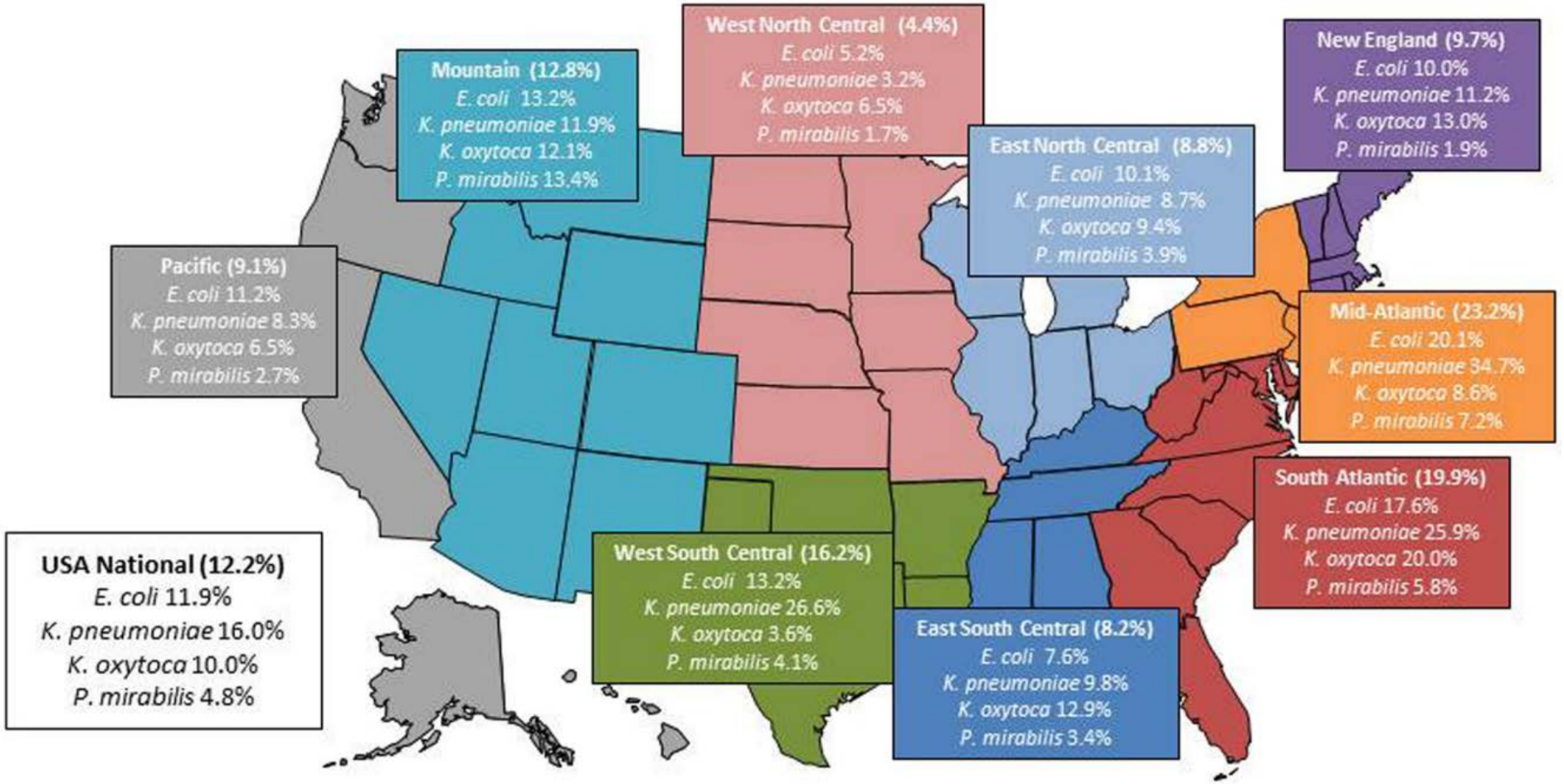
COLISTIN: TO COMBINE OR NOT TO COMBINE



Number at risk								
Colistin	197	175	149	138	132	124	118	111
Colistin–meropenem	207	174	153	144	136	127	118	116

Lancet Infect Dis 2018;18:391-400.

ESBL GEOGRAPHIC VARIATION



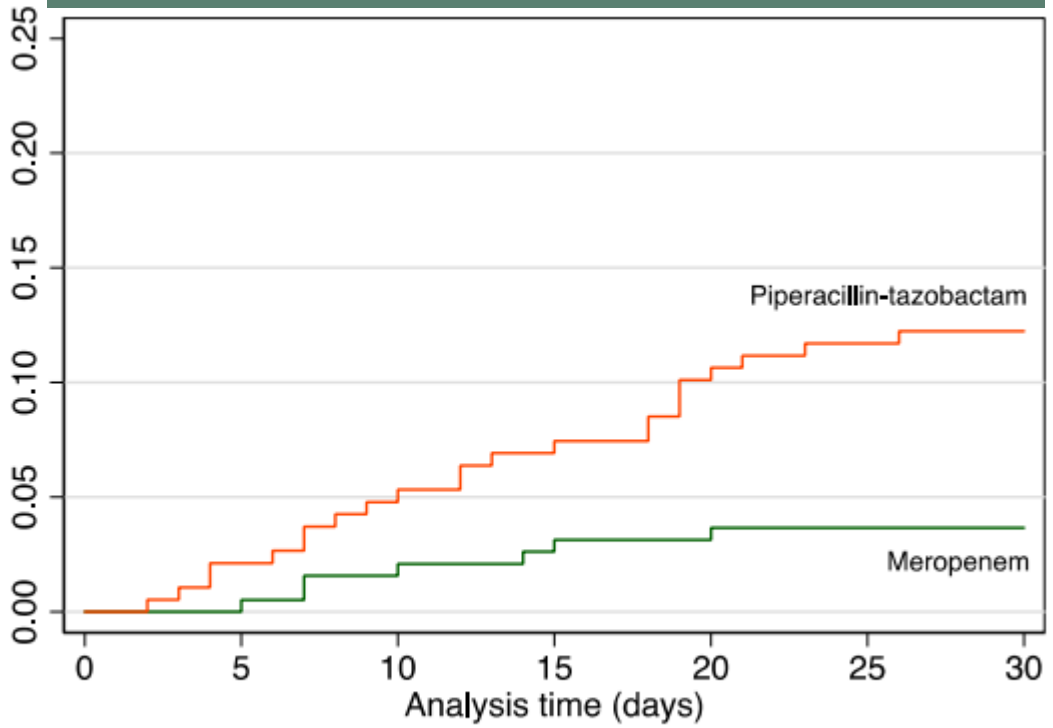
Antimicrob Agents Chemother. 2014;58(2):833-8

TREATMENT OF ESBL-PRODUCING GRAM-NEGATIVES

- Fluoroquinolones
- Carbapenems
  - Ertapenem
  - Meropenem
  - Imipenem-cilastatin
- Colistin
- Ceftazidime-avibactam
- Tigecycline
  - Should not be used for bacteremia
  - Higher mortality in VAP
- Fosfomycin (IV or PO)
- Piperacillin – tazobactam
  - MERINO Trial

PIPERACILLIN-TAZOBACTAM VERSUS MEROPENEM

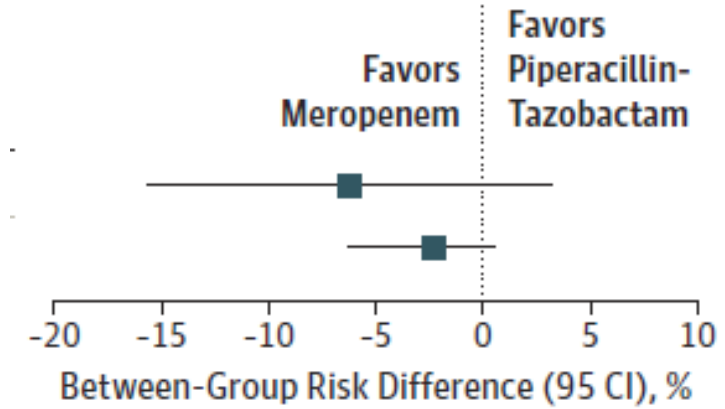
Primary Outcome: All-cause mortality at 30 days



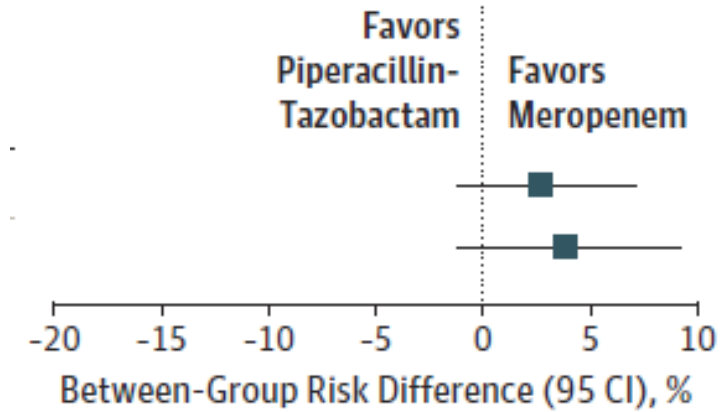
Number at risk

intervention = PTZ	188	184	179	175	169	166	165
intervention = MER	191	191	188	186	185	184	184

Clinical and Microbiological Success at Day 4



Microbiological Relapse

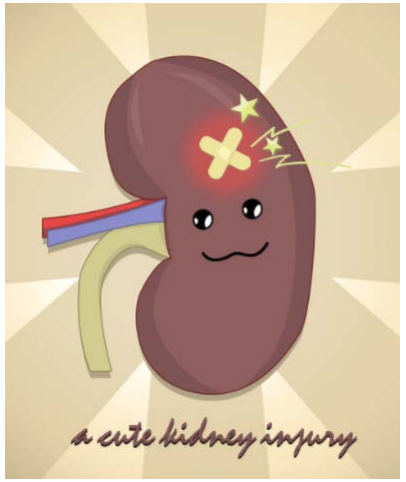


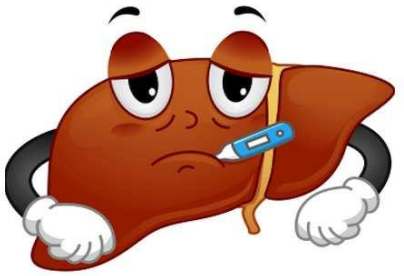
JAMA 2018;320:984-94.

CDC THREAT REPORT

HISTORY OF CRE TREATMENT

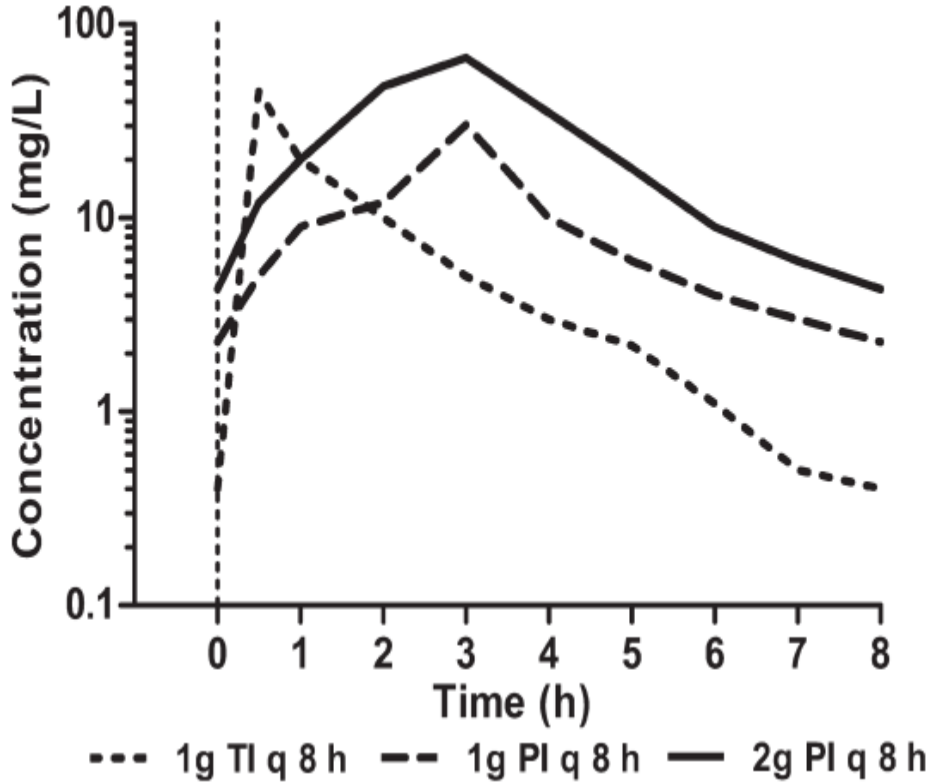
- Polymixins (colistimethate, polymixin B)
  - Nephrotoxicity, neurotoxicity, hepatotoxicity
  - Multiple formulations → dose confusion/potential for error
- Aminoglycosides
  - Bactericidal
  - Nephrotoxicity, ototoxicity
  - Worse outcomes with monotherapy
- Tigecycline
  - Bacteriostatic
  - Poor option for bacteremia and pneumonia
- Fosfomycin (IV or PO)
- **Combination therapy with polymixin + carbapenem**

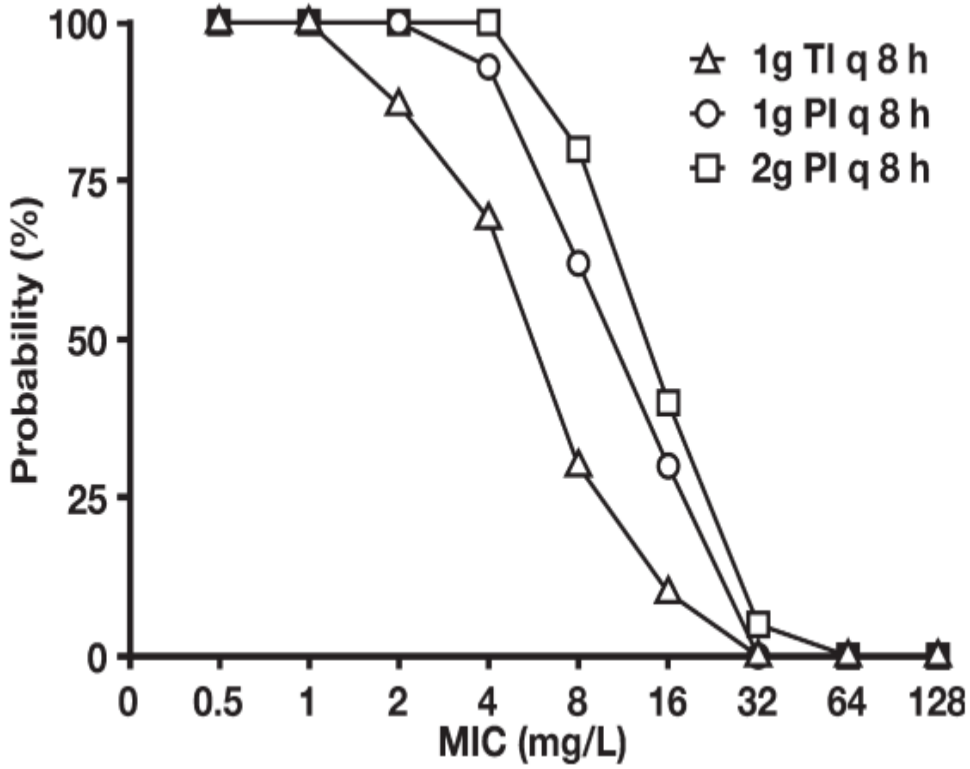




Diagn Microbiol Infect Dis. 2013 February;75(2): 115-120.

CRE - MEROPENEM DOSING STRATEGIES





Clin Microbiol Infect 2011;17:1135-1141.

COMBINATION THERAPY FOR CRE

- 125 patients with KPC bloodstream infections
- 89% isolates resistant to meropenem with MIC ≥ 4
- 30 day mortality 41.6%
  - Monotherapy 54.3%

    combination 34.1%

    p=0.02

Table 1. Univariate Analysis of Factors Associated With Death Among Patients With Bloodstream Infections Due to *Klebsiella pneumoniae* Carbapenemase–Producing *K. pneumoniae*

Variable	No. (%) of Patients		*P* Value	OR (95% CI)
	Nonsurvivors (n = 52)	Survivors (n = 73)		
Postantibiogram antimicrobial regimens				
Monotherapy	25 (48.1)	21 (28.7)	.02	1.59 (1.06–2.38)
Tigecycline	10 (19.2)	9 (12.3)	.28	1.32 (.81–2.16)
Colistin	11 (21.5)	11 (15.1)	.37	1.25 (.77–2.03)
Gentamicin	4 (7.6)	1 (1.3)	.09	1.98 (1.21–3.23)
Combination therapy	27 (51.9)	52 (71.2)	.02	0.62 (.41–.94)
2-drug combinations	23 (44.2)	33 (45.2)	.91	0.97 (.64–1.48)
Tigecycline + colistin	7 (13.4)	16 (21.9)	.22	0.68 (.35–1.32)
Tigecycline + gentamicin	6 (11.5)	6 (8.2)	.53	1.22 (.66–2.25)
Other 2-drug combinations[e]	10 (19.2)	11 (15.1)	.54	1.17 (.71–1.95)
3-drug combinations	4 (7.7)	19 (26.1)	.009	0.36 (.15–.92)
Tigecycline + colistin + meropenem	2 (3.8)	14 (19.2)	.009	0.27 (.07–1.01)
Other 3-drug combinations[f]	2 (3.8)	5 (6.8)	.47	0.67 (.21–2.21)
Inadequate initial antimicrobial treatment	39 (75)	36 (49.3)	.003	2.00 (1.19–3.34)
Presentation with septic shock	13 (25)	4 (5.5)	.002	2.11 (1.47–3.04)
APACHE III score (mean ± SD)	40 ± 22	24 ± 15	<.001	…

Clin Infect Dis 2012;55:943-50.

COMBINATION REGIMENS FOR CRE TREATMENT

TABLE 3 Definitive antimicrobial therapy and mortality in 17 patients who received combination therapy and 19 patients who received monotherapy

Definitive treatment	*n* (%)	Mortality *n* (%)
Combination therapy	15 (44)	2 (13.3)
Colistin-polymyxin B combined with:		
Carbapenem	5 (33)	1 (20)
Tigecycline	1 (7)	0
Fluoroquinolone	1 (7)	0
Tigecycline combined with:		
Carbapenem	3 (20)	0
Aminoglycoside	2 (12)	0
Carbapenem-fluoroquinolone	1 (7)	1 (100)
Aztreonam-fluoroquinolone	1 (7)	0
Cefepime-gentamicin	1 (7)	0
Monotherapy	19 (46)	11 (57.8)
Colistin-polymyxin B	7 (36.8)	4 (57.1)
Tigecycline	5 (26.3)	4 (80)
Carbapenem	4 (21)	2 (50)
Gentamicin	1 5.2)	0
Ampicillin-sulbactam	1 (5.2)	0
Piperacillin-tazobactam	1 (5.2)	1 (100)
Total	34 (83)	13 (38.2)

- Multicenter CRE treatment study
  - 256 patients received 69 unique regimens
    - 1-4 drugs in combination

Anti Microb Agents Chemother 2012;56:2108-13.
Open Forum Infect Dis 2017;4:2:ofx063

CEFTAZIDIME + AVIBACTAM

- Avibactam reduces MIC against Enterobacteriaceae 4-1024 fold
  - 4 fold against Pseudomonas
- Enzyme inhibition
  - Ambler class A and C enzymes
    - CTX-M, SHV, TEM, KPC, AmpC, etc.
  - Some Ambler D class enzymes
    - OXA enzymes

	β-lactamase enzyme[a]	MIC		MIC reduction (fold)
		Ceftazidime	Ceftazidime-avibactam[b]	
Escherichia coli				
Extended-spectrum β-lactamases	CTX-M-9	2	0.25	8
	CTX-M-14	2	0.06	32
	CTX-M-15[c]	32	0.12	256
	PER-1	256	1	256
	SHV-3	32	0.06	512
	SHV-4	128	0.25	512
	SHV-5	64	0.25	256
	TEM-3	64	0.25	256
	TEM-5	32	0.06	512
	TEM-6	>128	0.5	>256
	TEM-7	16	1	16
	TEM-8	256	0.25	1024
	TEM-9	>128	0.5	>256
	TEM-10	128	0.5	256
	TEM-12	16	0.25	64
	TEM-16	256	0.5	512
	TEM-24	>64	4	>16
	TEM-43	4	0.25	16
	OXA-2	0.25	0.12	2
	OXA-48	4	≤0.008	≥512
	CTX-M-2, TEM-1	32	0.5	64
	CTX-M-15, TEM-1[c]	32	0.12	256
	CTX-M-15, OXA-1[c]	16	0.25	64
	CTX-M-16, TEM-1[c]	>128	1	>128
	SHV-12, TEM-1	16	0.06	256
	CTX-M-15, TEM-1, OXA-1[c]	128	0.25	512

Drugs 2013; 73:159-177

CEFTAZIDIME + AVIBACTAM

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  - 4 fold against Pseudomonas
- Enzyme inhibition
  - Ambler class A and C enzymes
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	β-lactamase enzyme[a]	MIC		MIC reduction (fold)
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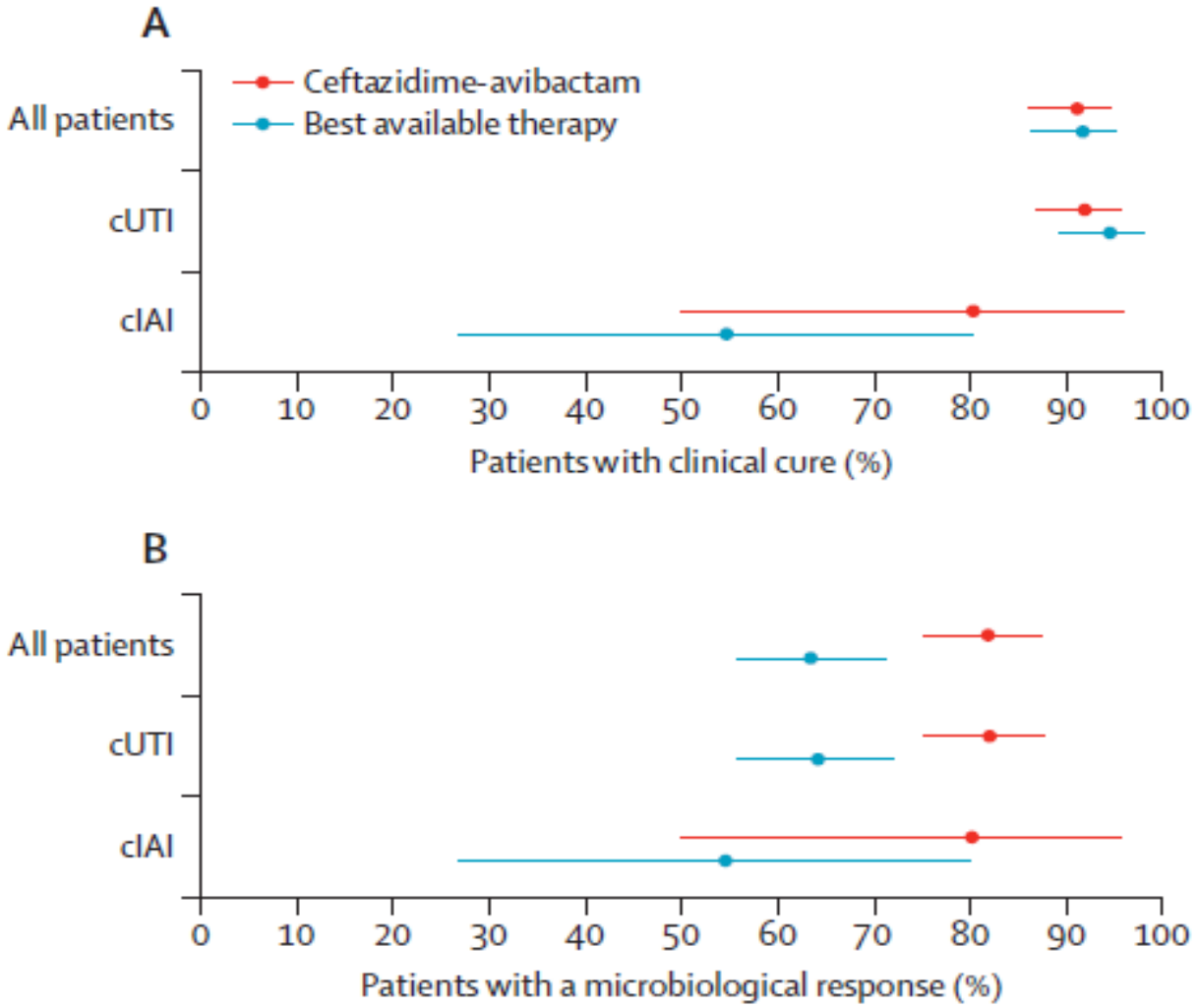
	CTX-M-15[c]	32	0.12	256
	PER-1	256	1	256
	SHV-3	32	0.06	512
	SHV-4	128	0.25	512
	SHV-5	64	0.25	256
	TEM-3	64	0.25	256
Carbapenemases	KPC-2	64	0.25	256
	KPC-2, TEM-1	128	0.5	256
	KPC-3	64	2	32
	GES-3	128	0.25	512
	GES-4	128	1	128
Metallo-β-lactamases	NMC-A	0.25	≤0.015	≥16
	PER-1	>64	4	>16
	VEB-1	2	0.5	4
	IMP-1	256	64	4
	NDM	>256	>256	>1
	VIM-1	>512	512	>1
Ambler class C β-lactamases	AmpC	16	1	16
	AmpC, CTX-M-15	>32	0.12	>56
	AmpC, CTX-M-15, OXA-1, TEM-1	>32	0.25	>128
	ACC-1	>64	4	>16
	CMY-2, VEB-2	256	128	2
	CMY-2, CTX-M-14, TEM-1	128	1	128
	CMY-2, CTX-M-15, OXA-1	32	0.06	512
	FOX-1	32	4	8

Drugs 2013; 73:159-177

CEFTAZIDIME-AVIBACTAM VERSUS BEST AVAILABLE THERAPY (BAT) FOR CEFTAZIDIME-RESISTANT ENTEROBACTERIACEAE



Lancet Infect Dis 2016;16:661-73.

CEFTAZIDIME-AVIBACTAM SUPERIORITY AGAINST CRE K. PNEUMONIAE BACTEREMIA

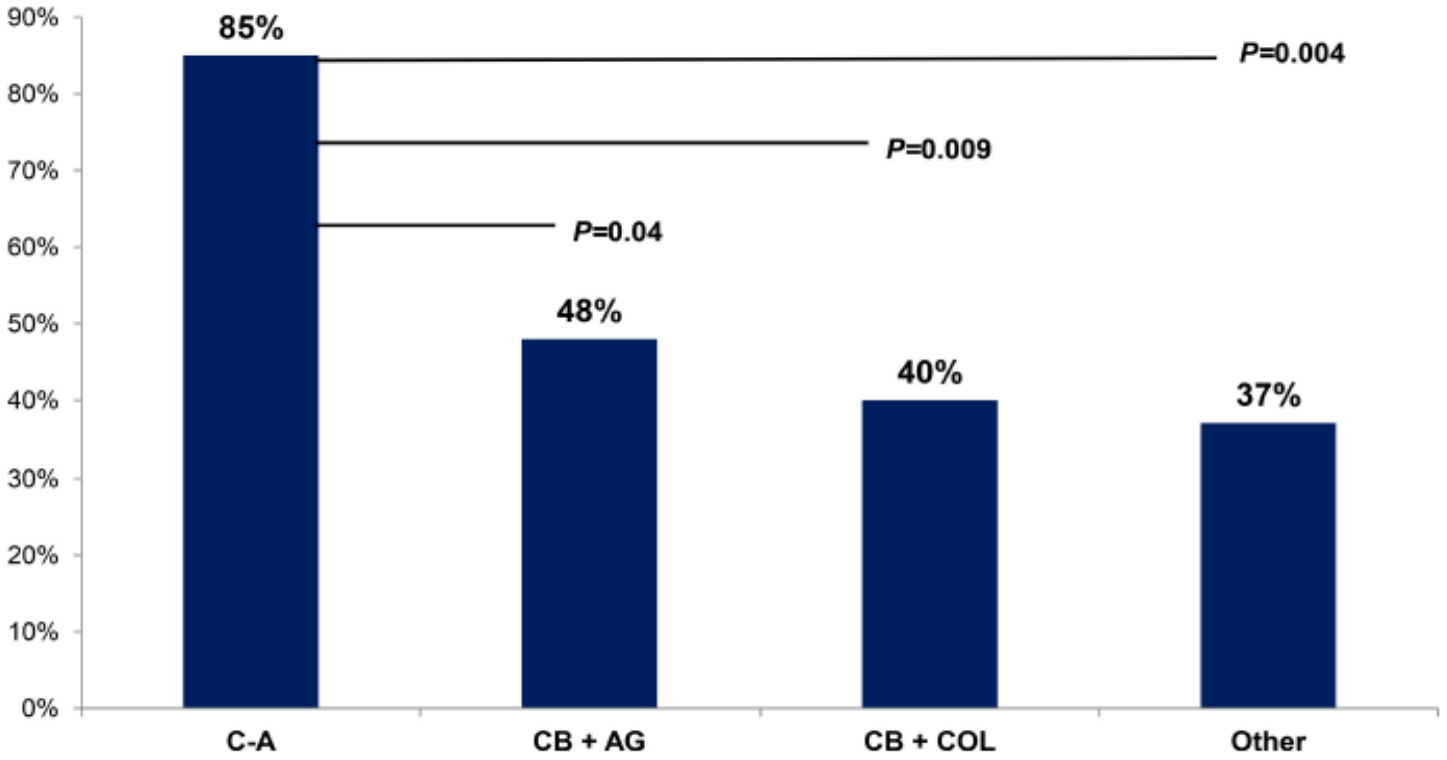
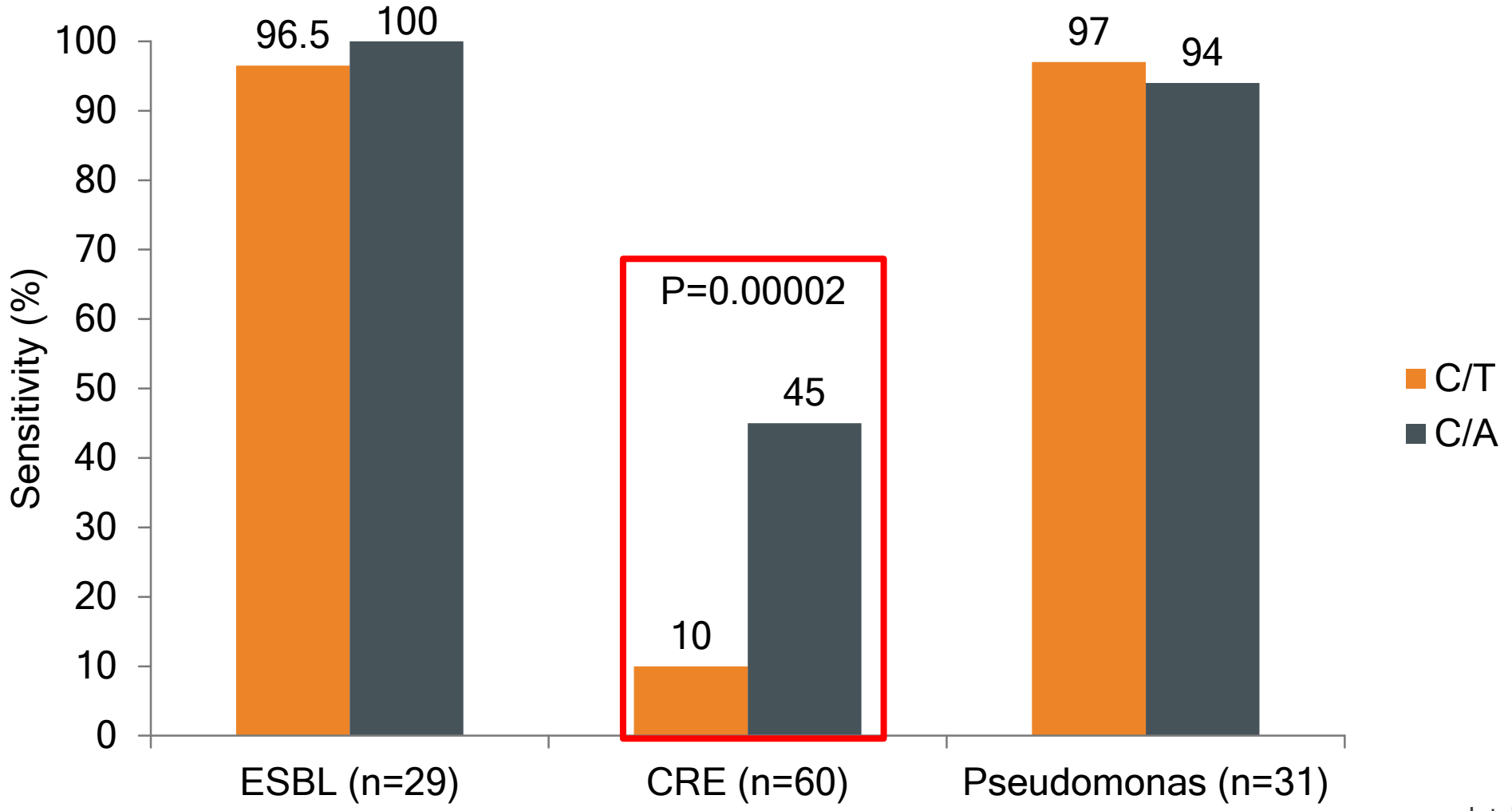


FIG 1 Rates of 30-day clinical success across treatment regimens. Among patients with carbapenem-resistant *Klebsiella pneumoniae* bacteremia, rates of clinical success were significantly higher among patients receiving ceftazidime-avibactam than among those who received a carbapenem plus aminoglycoside ($P = 0.04$) or colistin ($P = 0.009$) or other regimens ($P = 0.004$). Other regimens included aminoglycoside ($n = 11$), carbapenem ($n = 8$), colistin ($n = 4$), tigecycline ($n = 4$), and ciprofloxacin ($n = 2$) monotherapy, as well as combination regimens of colistin plus tigecycline ($n = 3$), aminoglycoside plus tigecycline ($n = 2$), and 1 each of aminoglycoside plus cefepime, aminoglycoside plus colistin plus tigecycline, colistin plus aztreonam, colistin plus cefepime, colistin plus ciprofloxacin, carbapenem plus doxycycline, and carbapenem plus tigecycline.

Antimicrob Agents Chemother 2017;61:e00883-17.

CEFTOLOZANE-TAZOBACTAM VERSUS CEFTAZIDIME-AVIBACTAM FOR MULTIDRUG-RESISTANT GRAM-NEGATIVES

- Comparison of activity against 120 MDR bacterial strains



Int J Infect Dis. 2017; 62: 39-43

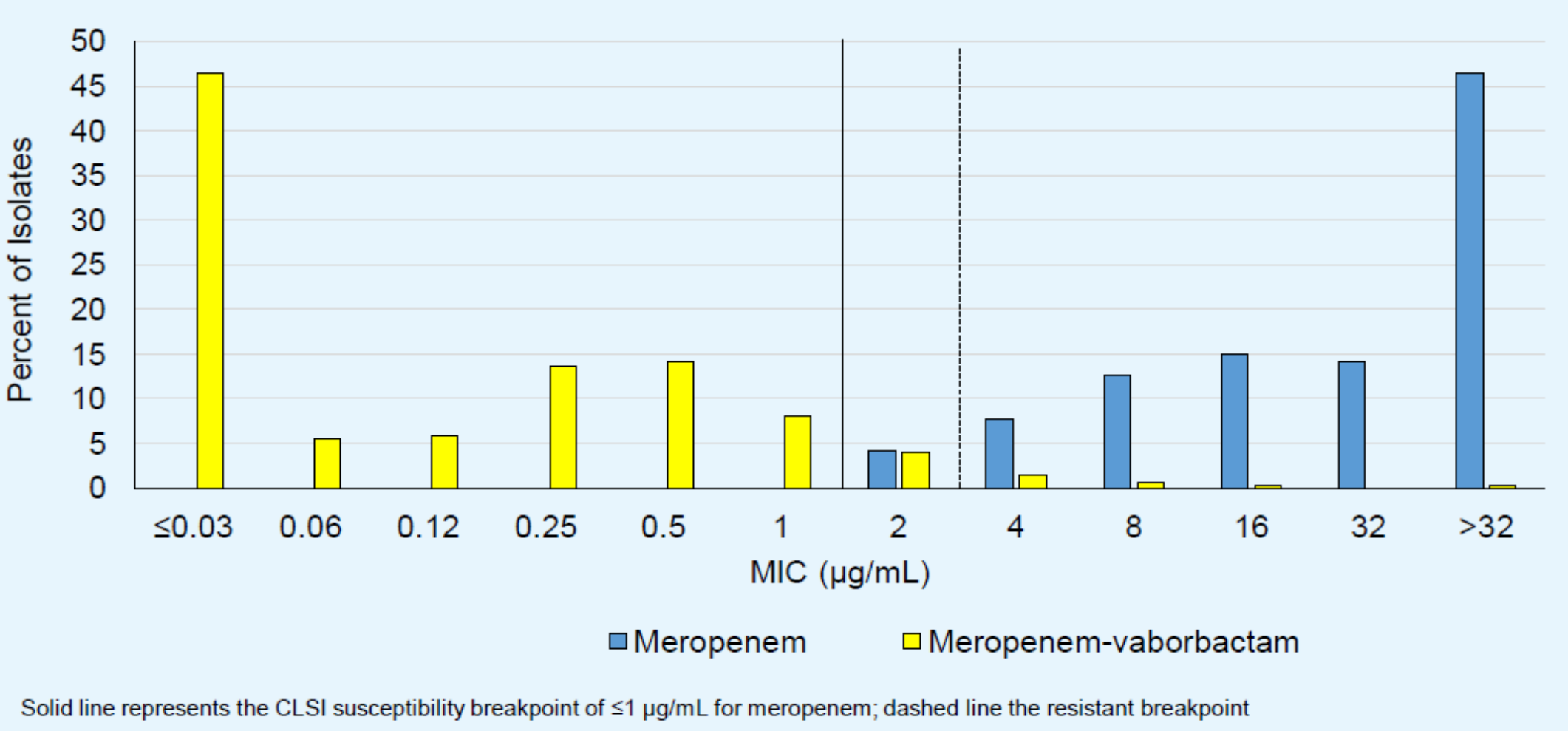
MEROPENEM - VABORBACTAM

- Well known carbapenem + novel beta-lactamase inhibitor
- Vaborbactam
  - Cyclic boronic acid beta-lactamase inhibitor
  - Lacks in vitro antibacterial activity
  - Potent inhibitor of
    - Class A (KPC, CTX-M, SHV, TEM)
    - Class C (P99, MIR, FOX)
- Most effective in inhibiting KPC when combined with meropenem versus other beta-lactams
- Slowly reversible binding, residence time ~16 hours

Antimicrob Agents Chemother. 1989 Apr;33(4):562-5

Antimicrob Agents Chemother. 1989 Jul;33(7):1009-18.

MIC DISTRIBUTIONS FOR KPC-PRODUCING ENTEROBACTERIACEAE



Antimicrob Agents Chemother. 2016 Aug 22;60(9):5454-8

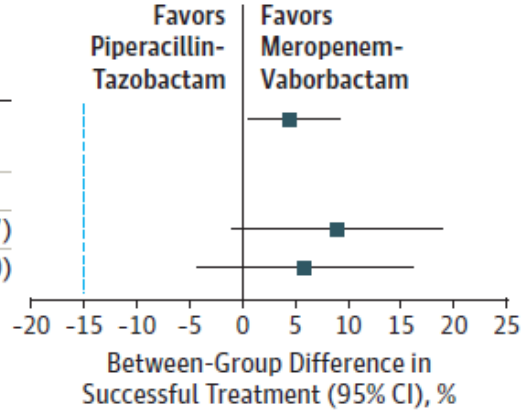
Antimicrob Agents Chemother. 2017 Dec 21;62(1)

MEROPENEM-VABORBACTAM

TANGO I

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)



TANGO II

Table 2. Sensitivity Analysis – Clinical Outcomes by Visit Across All Indications (mCRE-MITT Population)[1,2]

	Outcomes Across All Indications		Sensitivity Analysis	
	VABOMERE N = 28 n (%)	BAT N = 15 n (%)	VABOMERE N = 19 n (%)	BAT N = 15 n (%)
Clinical Cure at EOT	18 (64.3)	5 (33.3)	16 (84.2)	5 (33.3)
Clinical Cure at TOC	16 (57.1)	4 (26.7)	13 (68.4)	4 (26.7)
Microbiologic Cure* at EOT	18 (64.3)	6 (40.0)	-	-
Microbiologic Cure* at TOC	14 (50.0)	5 (33.3)	-	-
Day-28 Mortality	5 (17.9)	5 (33.3)	1 (5.3)	5 (33.3)

BAT = best available therapy; mCRE-MITT = microbiological carbapenem-resistant Enterobacteriaceae Modified Intent to Treat; EOT = end of therapy; TOC = test of cure

* Microbiologic eradication of baseline pathogen at respective visit or absence of culture result at respective visit

JAMA. 2018 Feb 27;319(8):788-799.

WHICH ONE TO CHOOSE?

Comparison of Novel MDR GNR Antimicrobials			
	Ceftazidime-avibactam	Ceftolozane-tazobactam	Meropenem-vaborbactam
FDA-approval	Feb 2015	Jan 2016	Aug 2017
Manufacturer	Allergan	Merck	Melinta
Novel agent	Avibactam	Ceftolozane	Vaborbactam
PK/PD	T>MIC	T>MIC	Mero: T>MIC Vaborbactam: AUC/MIC
FDA for cIAI	Yes (+metro)	Yes (+metro)	No
FDA for cUTI	Yes	Yes	Yes
Pseudomonas?	+	++	++
CRE enterics?	++	+	++
Dose	2.5g q8hrs	1.5g q8hrs	4g q8hrs

Clin Infect Dis. 2016;63(2):234-41
Clin Infect Dis 2018 [Epub ahead of print].

WHICH ONE TO CHOOSE?

Comparison of Novel MDR GNR Antimicrobials			
	Ceftazidime-avibactam	Ceftolozane-tazobactam	Meropenem-vaborbactam
FDA-approval	Feb 2015	Jan 2016	Aug 2017
Manufacturer	Allergan	Merck	Melinta
Novel agent	Avibactam	Ceftolozane	Vaborbactam
PK/PD			Mero: T>MIC bactam: AUC/MIC
FDA for cIAI			No
FDA for cUTI			Yes
Pseudomonas?			++
CRE enterics?			++
Dose			4g q8hrs

Organism	Resistance Present	Ceftazidime/ Avibactam	Meropenem/ Vaborbactam
Enterobacteriaceae			
	ESBL	+++	+++
	AmpC	+++	+++
	KPC	+++	+++
	MBL	–	*
	OXA-48–like	+++	*
Acinetobacter baumannii			
	Carbapenem- resistant	–	–
Pseudomonas aeruginosa			
	Carbapenem-resistant	++	–
	Pan-β-lactam resistant	+	–
Stenotrophomonas maltophilia			
	Ceftazidime-resistant	–	–

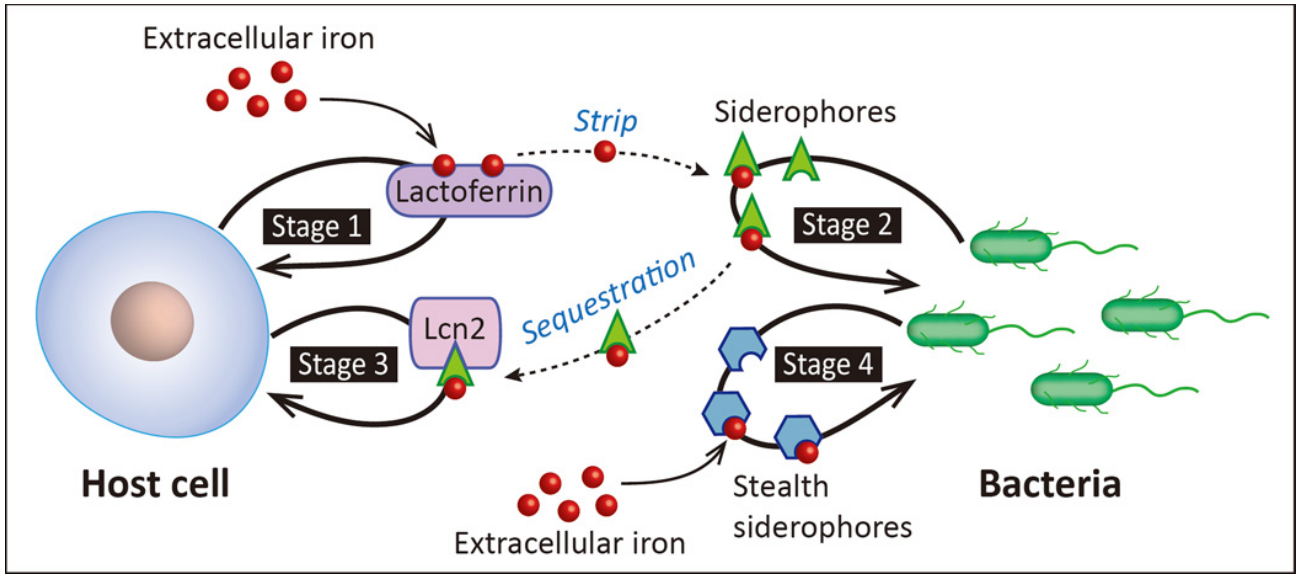
Clin Infect Dis. 2016;63(2):234-41
Clin Infect Dis 2018 [Epub ahead of print].

CEFIDEROCOL

- Not yet FDA-approved

- Siderophore cephalosporin
  - Catechol siderophore side chain

- Utilizes iron as “Trojan Horse”
  - Cefiderocol and iron ions are transported into bacterial cell
  - Accelerated influx
  - Catechol siderophore carries cephalosporin (Greek soldiers) into the cell (city of Troy)

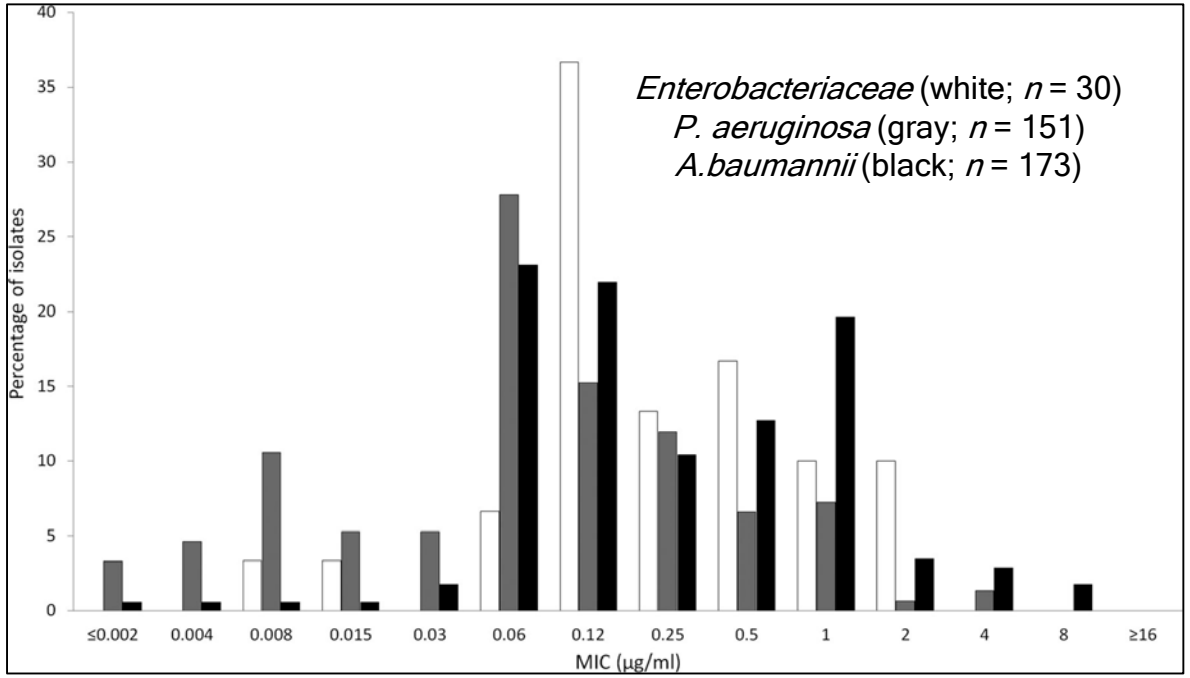


Trends Mol Med.2016. 22(12):1077-90.
Oral 859. Cefiderocol. IDWeek 2017.

CEFIDEROCOL GRAM-NEGATIVE ACTIVITY

- 99.6% of 9205 gram-negative rods inhibited by cefiderocol
  - Enterobacteriaceae, *Pseudomonas*, *Acinetobacter*, *Stenotrophomonas*
- 98.3% of meropenem-resistant gram-negative strains inhibited
- *In vitro* activity against CRE, including KPC or metallo-beta-lactamases (eg. NDM-1)

Cefiderocol MIC distributions meropenem-resistant isolates



Antimicrob Agents Chemother. 2017. 61 no. 9e00093-17

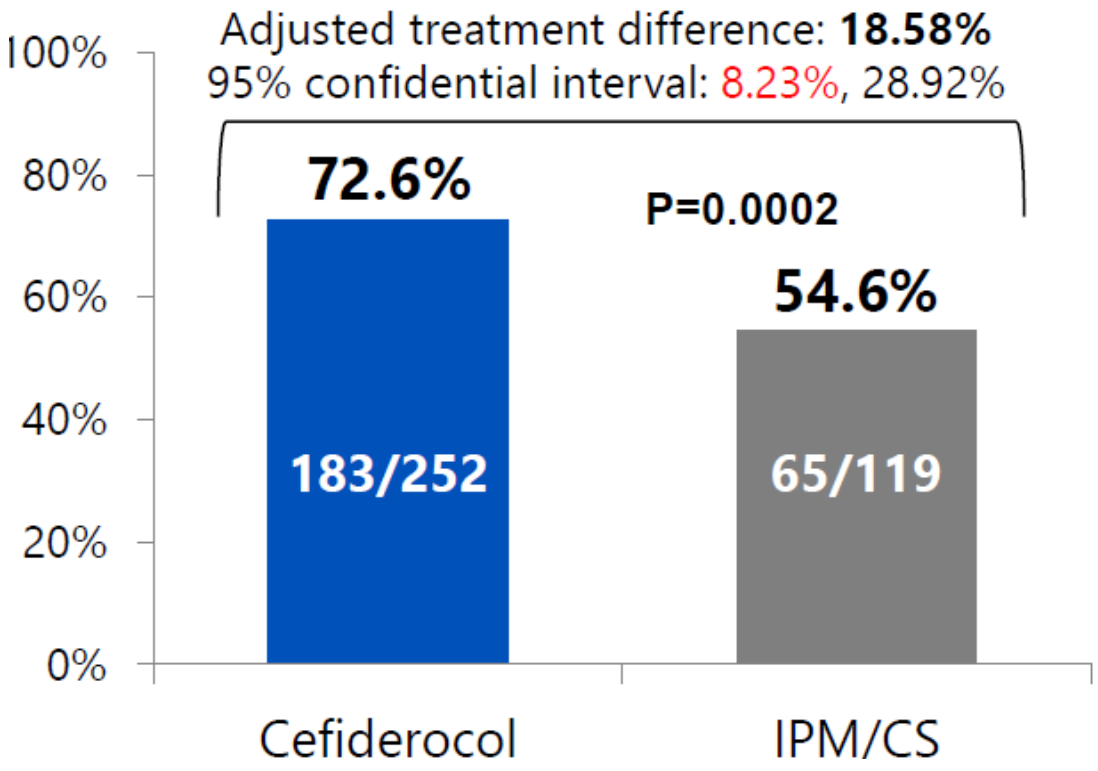
DEVELOPMENT PROGRAM

	APEKS*-cUTI	APEKS-NP	CREDIBLE-CR
Feature	Site/indication focus US Pivotal	Site/indication focus	Pathogen focus Europe Pivotal
Population	cUTI/AUP	HAP/VAP/HCAP	cUTI, HAP/VAP/HCAP, BSI, sepsis 2/2 CR GNR
Design	Double blind RCT 2:1	Double blind RCT 1:1	Open lable RCT 2:1
Comparator	Imipenem	Meropenem	BAT**
Status	Completed NCT02321800	On-going NCT0303280	On-going NCT02714595

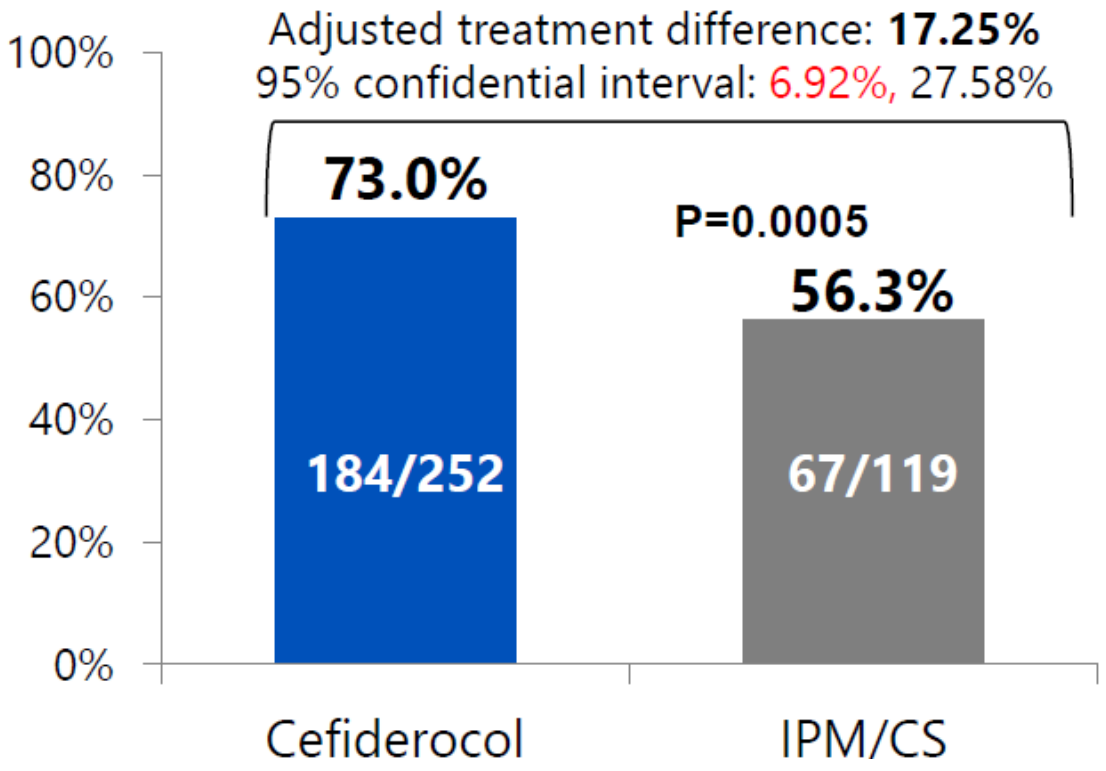
*APEKS = Acinetobacter, Pseudomonas, E. coli, Klebsiella, Stenotrophomonas
**BAT= Best Available Therapy

APEKS-CUTI

Primary Endpoint
Composite Outcome at TOC
(Clinical Response and Microbiological Response)

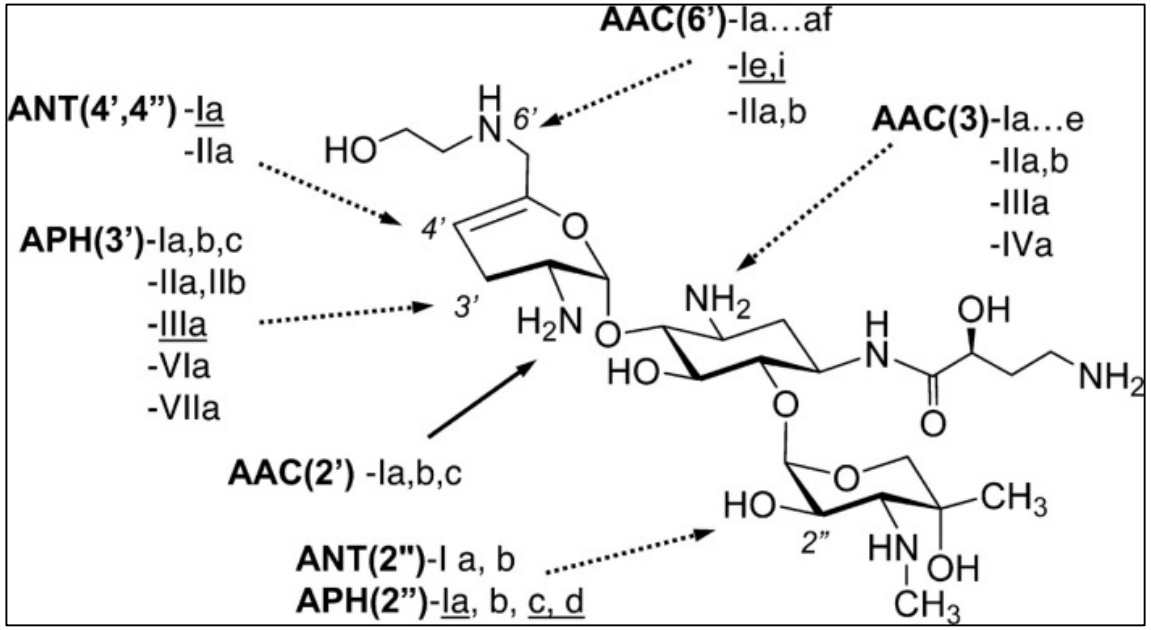


Secondary Endpoint
Microbiological Response at TOC



PLAZOMICIN

- Not yet FDA-approved
- Next generation aminoglycoside
- Unique structure protects against resistance
- Spectrum of activity
  - CRE Enterobacteriaceae
  - ESBL *Klebsiella*
  - ESBL *E.coli*
  - *S. aureus*

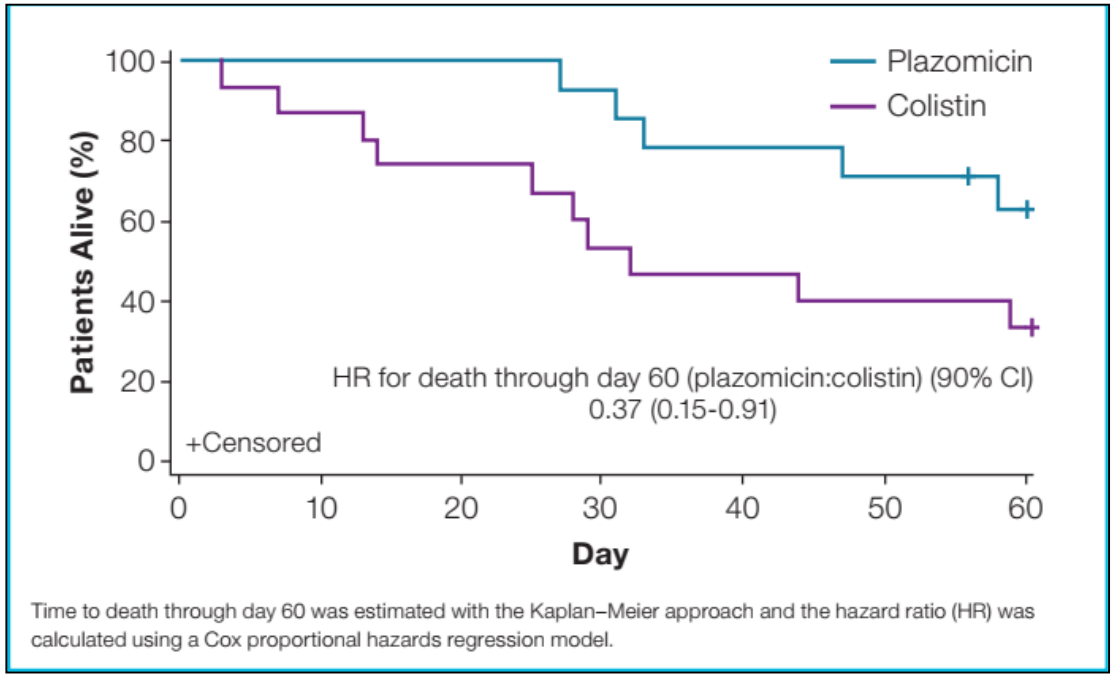


Antimicrob Agents Chemother. 2010. 54; 11: 114636-42
Expert Rev Anti Infect Ther. 2012. 10(4):459-73.

PHASE 3 DEVELOPMENT PLAN

- EPIC → cUTI vs meropenem
  - Met non-inferiority FDA 1º endpoints
  - Superiority for EMA 1 º endpoints

- CARE→ CRE vs colistin (both +/- meropenem or tigecycline)
  - 69 patients
  - Top-line CARE data: lower mortality rate compared to colistin



Golan et al. Poster 1859, IDWeek 2017
Friedland. Oral 860. Plazomicin. IDWeek 2017.

CONCLUSIONS

- Multidrug-resistant bacteria are an ever increasing problem within institutions and the community
- Mindful use of antibiotics if of imperative importance
  - Optimal dosing strategies
  - Combination therapy versus monotherapy
- Not a single “right” answer to treat these pathogens
  - Increasing information to guide appropriateness

THE UPDATED ANTIBIOTIC ARMAMENTARIUM FOR WHEN BUGS GO BAD

WHITNEY J. NESBITT, PHARMD, BCPS

ANTIMICROBIAL STEWARDSHIP PHARMACIST

VANDERBILT UNIVERSITY MEDICAL CENTER