Treat early, treat hard!
Role of new bactericidal antibiotic combinations

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Disclosures

Company / Name	Honoraria / Expense	Consulting / Advisory Board	Funded Research	Royalties / Patent	Stock Options	Ownership / Equity Position	Employee	Other (Please specify)
Roche		✓						
Genentech		✓						
Pfizer	✓	✓	✓					
Merck	✓		✓					
Angelini	✓	✓	✓					
Advanz pharma	✓	✓	✓					
Infectopharm			✓					
Menarini		✓						
Shionogi	✓	✓						

Outline

- Backbone agents MSSA vs MRSA
- What combination regimens add to the backbone
  - MSSA
  - MRSA
  - Strep / Enteroc
- Non-antibiotic combinations
- Tentative treatment algorithm

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Comparative Effectiveness of Beta-Lactams Versus Vancomycin for Treatment of Methicillin-Susceptible *Staphylococcus aureus* Bloodstream Infections Among 122 Hospitals

Jennifer S. McDanel,[1,2,3] Eli N. Perencevich,[1,2,3] Daniel J. Diekema,[2,4,5] Loreen A. Herwaldt,[1,2,5] Tara C. Smith,[1,a] Elizabeth A. Chrischilles,[1] Jeffrey D. Dawson,[6] Lan Jiang,[3] Michihiko Goto,[2,3] and Marin L. Schweizer[1,2,3]

N = 5633
definitive therapy

Yet, in the multivariable analysis, patients who were prescribed a beta-lactam for therapy of MSSA bloodstream infections had a 35% lower hazard of dying within 30 days compared with patients who received vancomycin after adjusting for severity of illness, aggregate comorbidities, osteomyelitis, beta-lactam allergy, facility type, age, and dialysis/ESRD (HR, 0.65; 95% CI, .52–.80).

β- lactam is the backbone for MSSA. Which is best ?

Clinical Infectious Diseases 2015; 61(3): 361–7

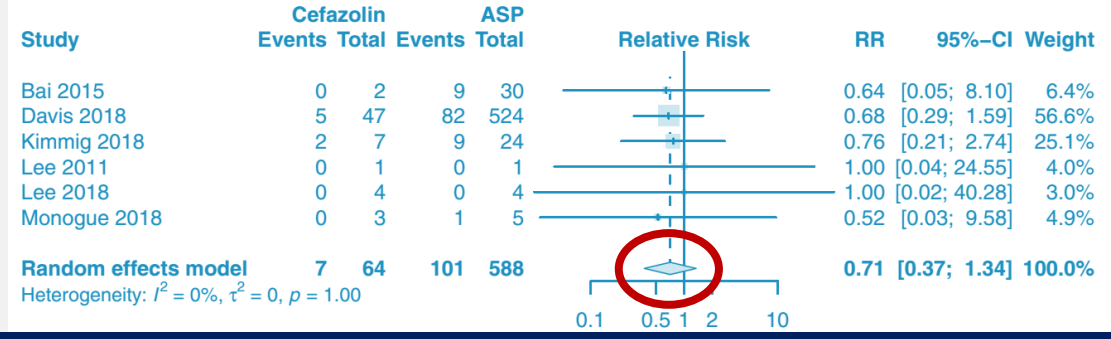
Systematic review

Cefazolin versus anti-staphylococcal penicillins for the treatment of patients with *Staphylococcus aureus* bacteraemia

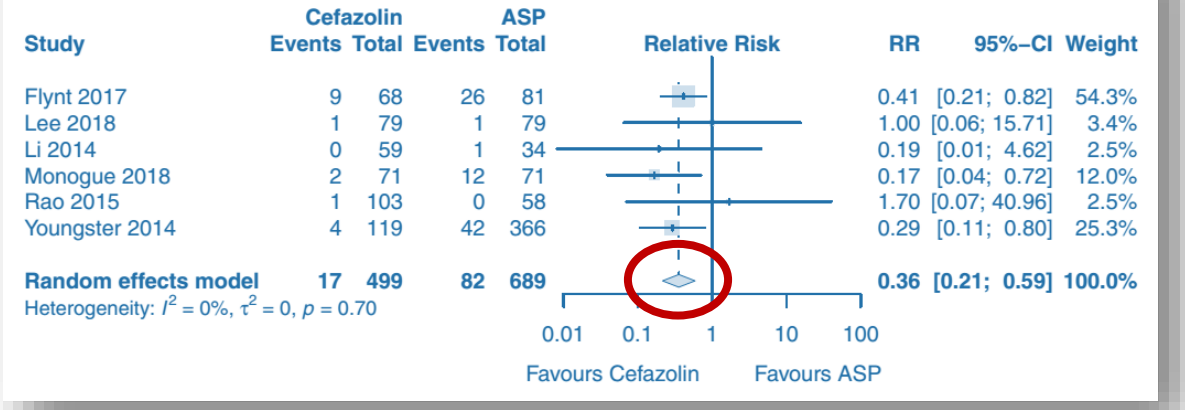
S. Weis [1,2,3,*], M. Kesselmeier [2,4], J.S. Davis [5,6], A.M. Morris [7], S. Lee [8], A. Scherag [2,4,9], S. Hagel [1,2,†], M.W. Pletz [1,†]

10451 pts data

30–day all–cause mortality in patients with endocarditis



Cefazolin may be the backbone for MSSA



Clinical Microbiology and Infection 25 (2019) 818–827

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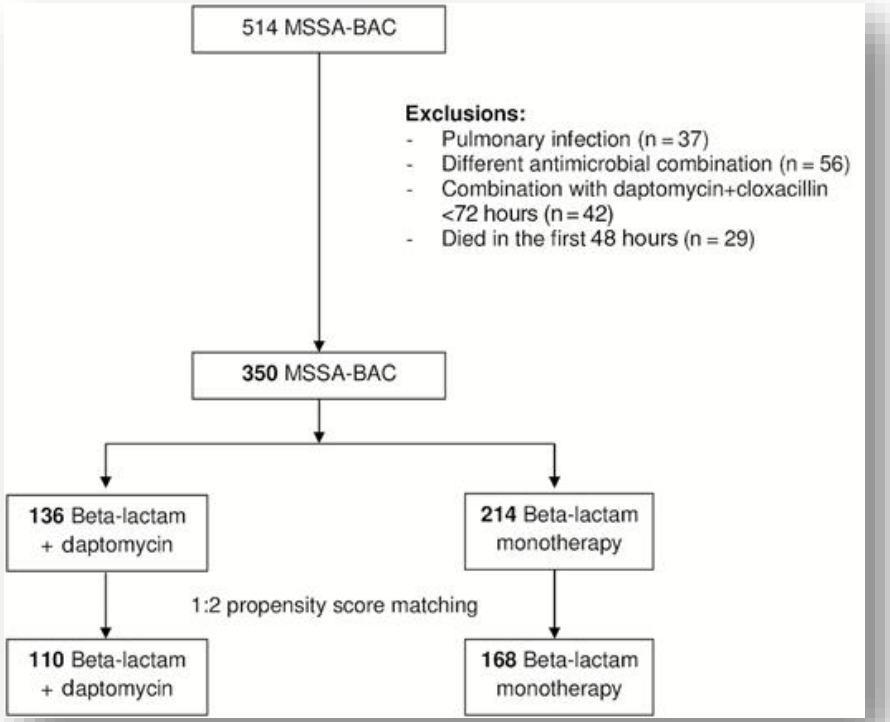
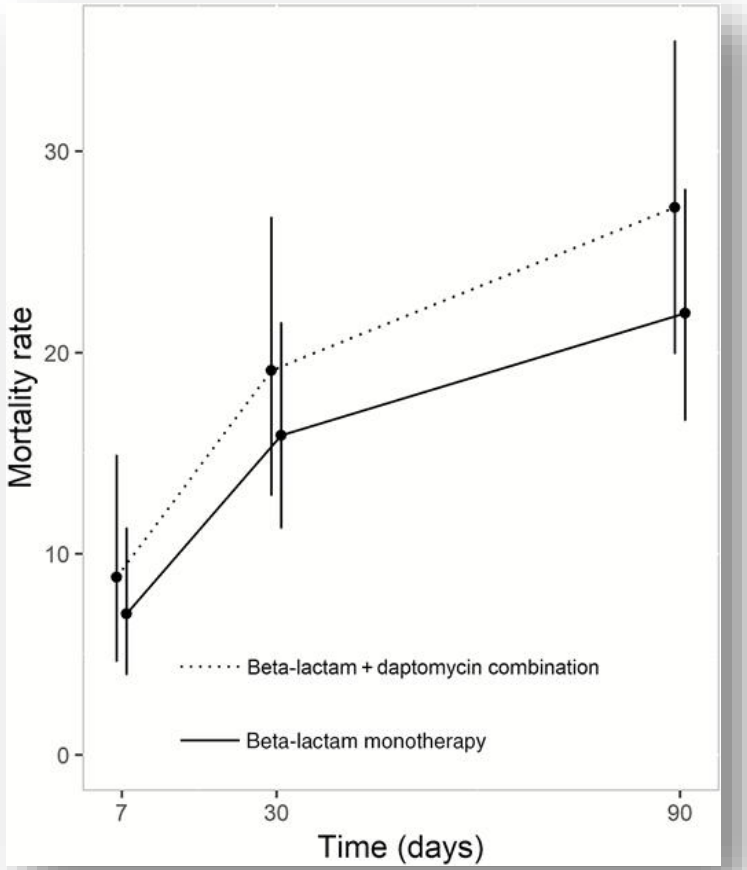
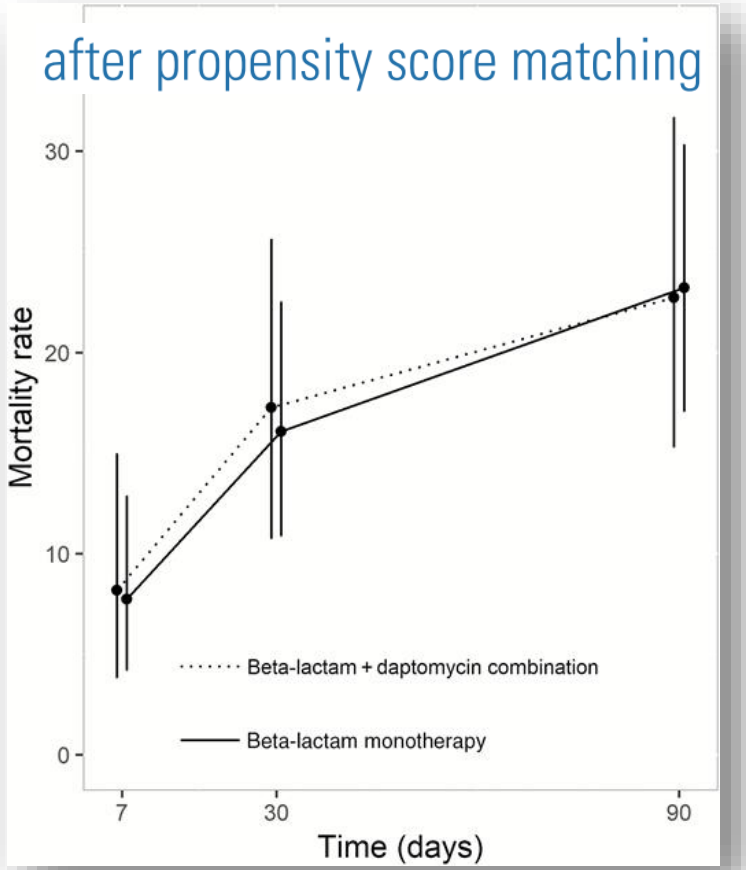
Impact of β-Lactam and Daptomycin Combination Therapy on Clinical Outcomes in Methicillin-susceptible *Staphylococcus aureus* Bacteremia: A Propensity Score–matched Analysis

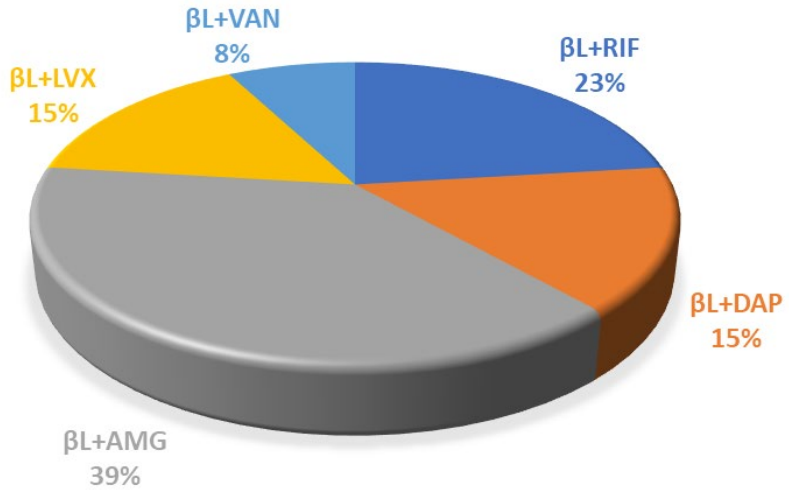
Sara Grillo,[1,2] Guillermo Cuervo,[1,2,3] Jordi Carratalà,[1,2,3,4] Immaculada Grau,[1,2,4,5] Natàlia Pallarès,[6,7] Cristian Tebé,[6,8] Lluisa Guillem Tió,[1] Oscar Murillo,[1,2,3,4] Carmen Ardanuy,[2,4,5,9] M. Angeles Domínguez,[2,3,4,9] Evelyn Shaw,[1,2,3] Carlota Gudiol[1,2,3,4] and Miquel Pujol[1,2,3]







Clinical Infectious Diseases® 2019;69(9):1480–8



The Effectiveness of Combination Therapy for Treating Methicillin-Susceptible *Staphylococcus aureus* Bacteremia: A Systematic Literature Review and a Meta-Analysis

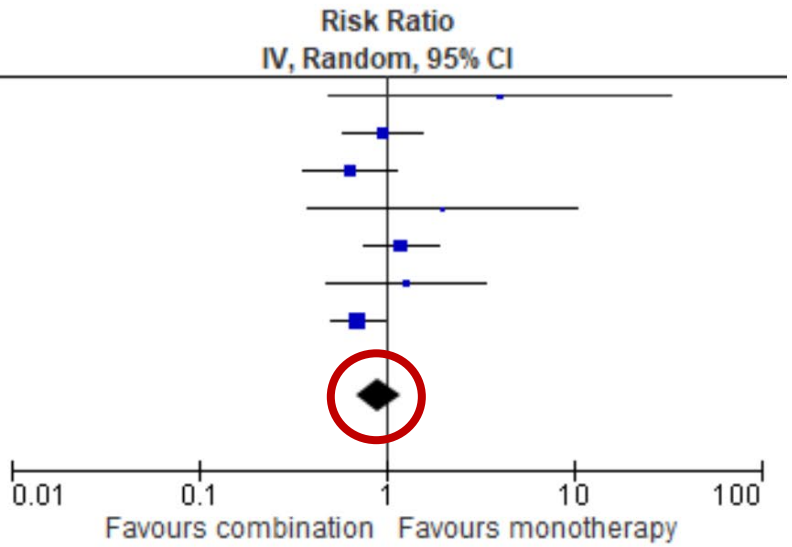
Sara Grillo [1,†], Mireia Puig-Asensio [1,2,3,*,†], Marin L. Schweizer [3,4], Guillermo Cuervo [1,2], Isabel Oriol [5], Miquel Pujol [1,2] and Jordi Carratalà [1,2,6]

30-day mortality

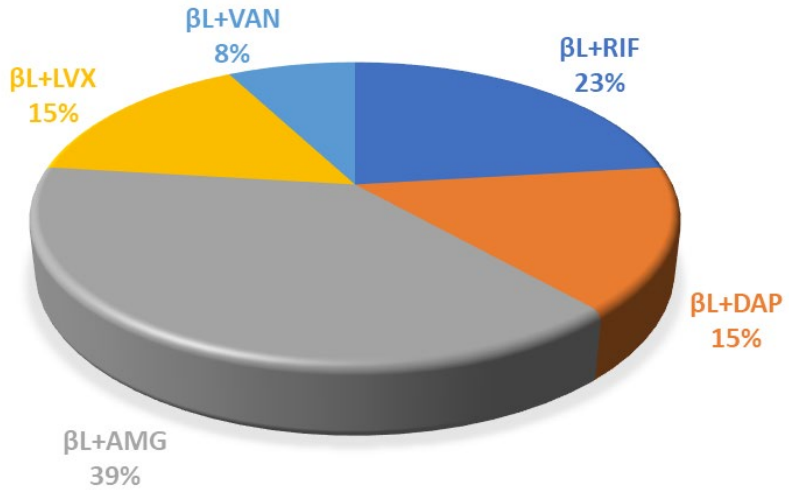
Study or Subgroup	Combination therapy Events	Total	Monotherapy Events	Total	Weight	Risk Ratio IV, Random, 95% CI	Year
Korzeniowski 1982	5	43	1	35	1.7%	4.07 [0.50, 33.24]	1982
Ruotsalainen 2006	26	191	27	190	19.8%	0.96 [0.58, 1.58]	2006
Forsblosom 2015	28	261	16	96	16.6%	0.64 [0.36, 1.14]	2015
Park 2017	4	46	2	46	2.6%	2.00 [0.39, 10.39]	2017
Grillo 2019	26	136	34	214	21.8%	1.20 [0.76, 1.91]	2019
Cheng 2020	8	53	6	51	6.8%	1.28 [0.48, 3.44]	2020
Rieg 2020	50	313	59	262	30.7%	0.71 [0.51, 1.00]	2020
Total (95% CI)		**1043**		**894**	**100.0%**	**0.92 [0.70, 1.20]**	
Total events	147		145				

Heterogeneity: Tau² = 0.03; Chi² = 8.14, df = 6 (P = 0.23); I² = 26%

Test for overall effect: Z = 0.63 (P = 0.53)



Microorganisms **2022**, *10*, 848. https://doi.org/10.3390/microorganisms10050848



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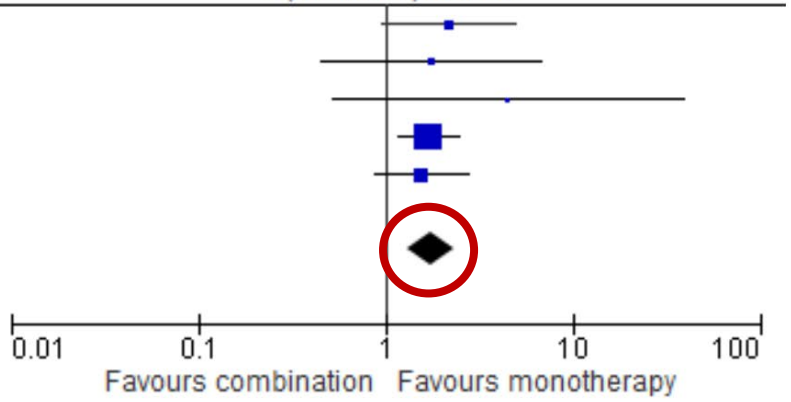
Drug-adverse events

Study or Subgroup	Combination therapy Events	Total	Monotherapy Events	Total	Weight	Risk Ratio IV, Random, 95% CI	Year
Korzeniowski 1982	16	43	6	35	11.8%	2.17 [0.95, 4.95]	1982
Ribera 1996	5	36	3	38	4.4%	1.76 [0.45, 6.83]	1996
Park 2017	4	37	1	42	1.7%	4.54 [0.53, 38.84]	2017
Thwaites 2018	63	370	39	388	57.8%	1.69 [1.17, 2.46]	2018
Cheng 2020	21	53	13	51	24.3%	1.55 [0.87, 2.76]	2020
Total (95% CI)		**539**		**554**	**100.0%**	**1.74 [1.31, 2.31]**	
Total events	109		62				

Heterogeneity: Tau² = 0.00; Chi² = 1.21, df = 4 (P = 0.88); I² = 0%

Test for overall effect: Z = 3.83 (P = 0.0001)



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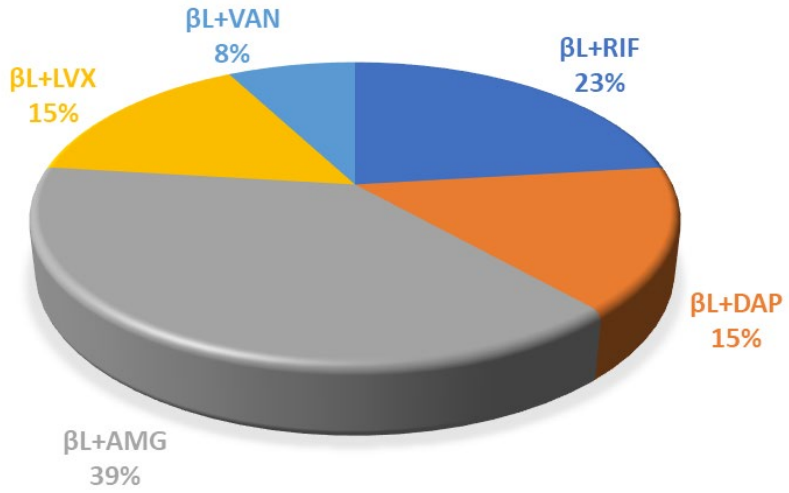

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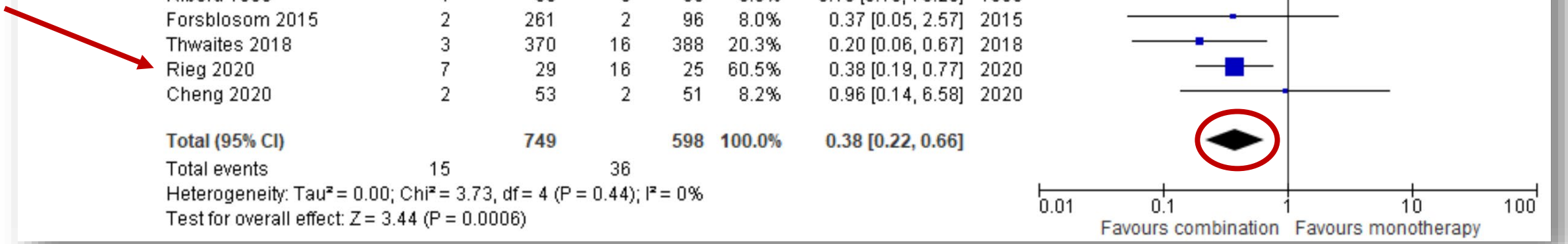
Sara Grillo [1,†], Mireia Puig-Asensio [1,2,3,*,†], Marin L. Schweizer [3,4], Guillermo Cuervo [1,2], Isabel Oriol [5], Miquel Pujol [1,2] and Jordi Carratalà [1,2,6]

Relapse or recurrence



Microorganisms **2022**, *10*, 848. https://doi.org/10.3390/microorganisms10050848

Combination antimicrobial therapy in patients with *Staphylococcus aureus* bacteraemia—a *post hoc* analysis in 964 prospectively evaluated patients

S. Rieg [1, *], I. Joost [1], V. Weiß [3], G. Peyerl-Hoffmann [1], C. Schneider [2], M. Hellmich [4], H. Seifert [5, 6], W.V. Kern [1], A. Kaasch [5]

MRSA 11.2%

Second agent	
Rifampicin	301 (58.8)
Fluoroquinolone	215 (42.0)
Aminoglycoside (gentamicin)	120 (23.4)
Fosfomycin	99 (19.3)

Patient characteristics and clinical data of 964 patients with SAB

Parameter	All patients	Monotherapy	Combination therapy	p[a]
No. of patients	964	452 (46.9%)	512 (53.1%)	
Age				0.23
Median (range)	66 (19–93)	65 (19–93)	66 (19–92)	
Interquartile range	53–74	54–72	53–75	
Sex				0.63
Percentage of female patients	321 (33.3)	147 (32.5)	174 (34.0)	
Study centre				0.0002
Percentage centre 1 patients (Freiburg)	500 (51.9)	263 (58.2)	237 (46.3)	
Charlson score				0.04
Median (range), mean	3 (0–12), 3.3	3 (0–12), 3.4	3 (0–11), 3.2	
Interquartile range	2–5	2–5	1–5	
Mode of acquisition				<0.0001
Community-acquired not healthcare-associated	165 (17.1)	45 (10.0)	120 (23.4)	
Community-onset healthcare-associated	290 (30.1)	114 (25.2)	176 (34.4)	
Hospital acquired	509 (52.8)	293 (64.8)	216 (42.2)	
14-day case fatality[c]	93/959 (9.7)	48/447 (10.7)	45/512 (8.8)	0.34
30-day case fatality[d]	175/952 (18.4)	82/443 (18.5)	93/509 (18.3)	1.0
90-day case fatality[e]	296/939 (31.5)	140/436 (32.1)	156/503 (31.0)	0.87
180-day case fatality[f]	344/918 (37.5)	167/428 (39.0)	177/490 (36.1)	0.44

Clinical Microbiology and Infection 2017; 23: 406.e1-e8

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impact of Combi-Rx on mortality after adjusting/controlling for survivor bias by including CoRx as a time-dependent covariable

Adjusted hazard ratios for all-cause 30- or 90-day mortality[a]

Parameter/variable	Day 30 mortality (*c* statistic 0.82, 95% CI 0.79–0.84)				Day 90 mortality (*c* statistic 0.77, 95% CI 0.74–0.79)			
	HR	95% CI		p	HR	95% CI		p
		Upper	Lower			Upper	Lower	
Age (per year)	1.014	1.002	1.026	0.017	1.020	1.011	1.029	<0.0001
Underlying disease (per point in Charlson comorbidity index)	1.249	1.168	1.335	<0.0001	1.212	1.150	1.277	<0.0001
Mode of acquisition (Ref.: community-acquired SAB)								
Community onset, healthcare associated	1.040	0.658	1.644	NS	1.380	0.944	2.019	NS
Hospital acquired	0.997	0.641	1.550	NS	1.317	0.909	1.908	NS
MRSA (Ref.: MSSA)	0.983	0.652	1.480	NS	1.149	0.841	1.569	NS
Dominant focus (Ref.: non-deep-seated foci)								
Endocarditis	1.344	0.780	2.318	NS	1.090	0.708	1.676	NS
Other deep-seated focus	1.194	0.759	1.877	NS	1.079	0.761	1.530	NS
Pneumonia	1.061	0.571	1.971	NS	0.992	0.614	1.603	NS
Unknown	1.222	0.780	1.914	NS	1.352	0.979	1.869	NS
Disseminated disease (Ref.: no)	0.846	0.548	1.308	NS	1.136	0.808	1.597	NS
Severity at presentation (Ref.: sepsis)								
Severe sepsis	3.421	2.118	5.527	<0.0001	1.910	1.380	2.642	<0.0001
Septic shock	10.651	6.898	16.445	<0.0001	5.882	4.387	7.885	<0.0001
ID specialist consultation (Ref.: no)	0.509	0.346	0.747	0.0006	0.685	0.499	0.939	0.0188
Combination therapy (Ref.: no)	0.953	0.679	1.338	NS	0.866	0.668	1.123	NS

Clinical Microbiology & Infection 2017; 23: 406.e1-e8

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subgroup of patients with implanted foreign bodies or devices

Should Rifampin be added to foreing body-related MSSA BSI upfront ?

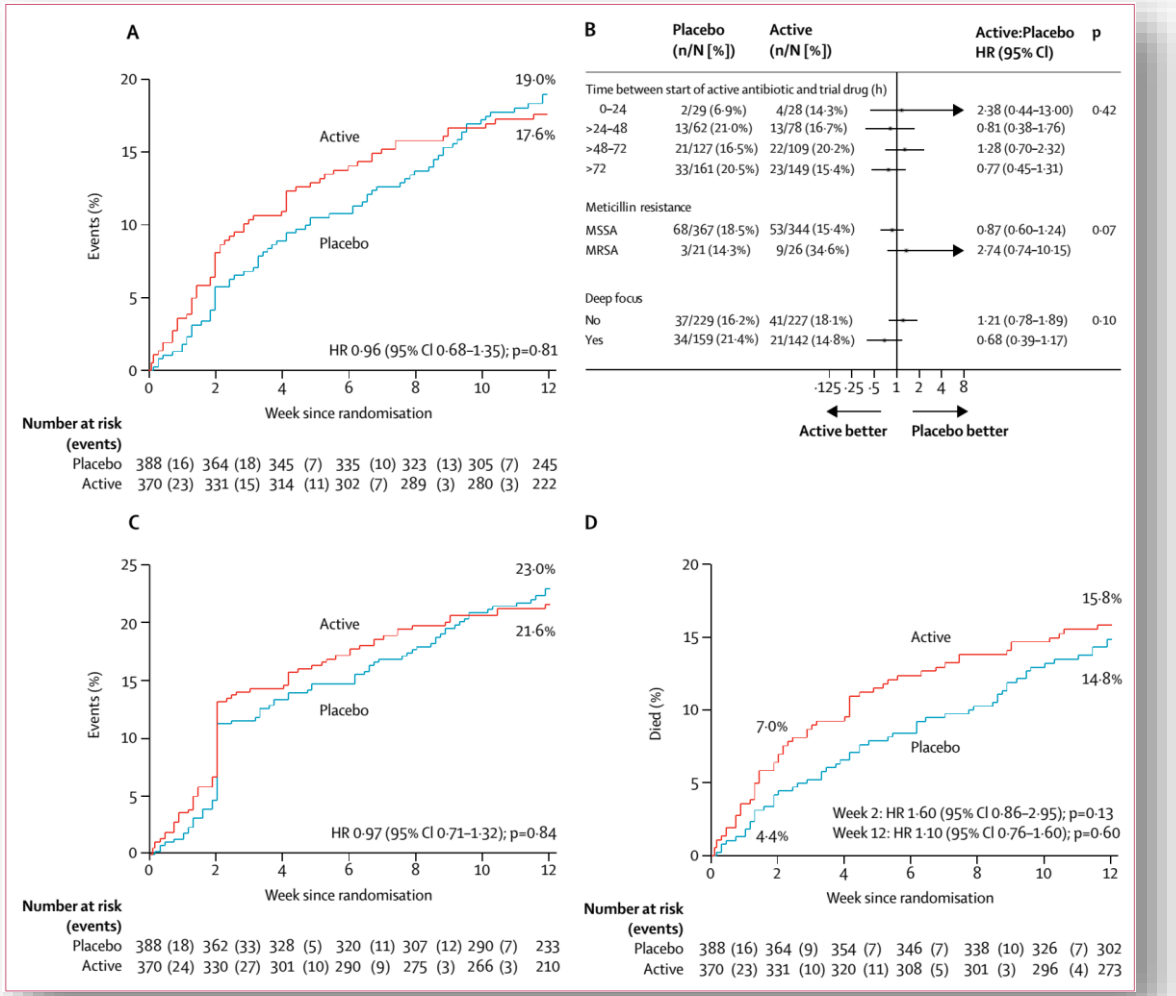
Age (per year)	1.021	1.000	1.043	0.0504	1.021	1.005	1.037	0.0100
Underlying disease (per point in Charlson comorbidity index)	1.267	1.130	1.421	<0.0001	1.196	1.100	1.301	<0.0001
Mode of acquisition (Ref.: community-acquired SAB)								
Community onset, healthcare associated	1.094	0.468	2.557	NS	1.358	0.687	2.684	NS
Hospital-acquired	0.736	0.314	1.722	NS	1.176	0.602	2.295	NS
MRSA (Ref.: MSSA)	0.612	0.286	1.310	NS	1.246	0.764	2.030	NS
Dominant focus (Ref.: non-deep-seated foci)								
Endocarditis	1.644	0.747	3.619	NS	1.144	0.622	2.105	NS
Other deep-seated focus	0.992	0.471	2.088	NS	1.079	0.614	1.895	NS
Pneumonia	0.591	0.165	2.123	NS	0.383	0.131	1.117	NS
Unknown	0.663	0.274	1.605	NS	1.192	0.671	2.120	NS
Disseminated disease (Ref.: no)	0.502	0.233	1.079	NS	1.201	0.723	1.995	NS
Severity at presentation (Ref.: sepsis)								
Severe Sepsis	2.814	1.208	6.555	0.0165	1.757	1.039	2.971	0.0355
Septic Shock	13.735	6.331	29.795	<0.0001	5.962	3.637	9.773	<0.0001
ID specialist consultation (Ref.: no)	0.547	0.283	1.056	NS	0.684	0.420	1.115	NS
Combination therapy (Ref.: no)	0.617	0.347	1.096	NS	0.605	0.398	0.919	0.0186

Clinical Microbiology & Infection 2017; 23: 406.e1-e8

Adjunctive rifampicin for *Staphylococcus aureus* bacteraemia (ARREST): a multicentre, randomised, double-blind, placebo-controlled trial

Guy E Thwaites, Matthew Scarborough, Alexander Szubert, Emmanuel Nsutebu, Robert Tilley, Julia Greig, Sarah A Wyllie, Peter Wilson,

758 pts
370 rifampicin - 388 placebo
6% MRSA
33 (4%) endocarditis



Treatment failure, disease recurrence, and death
from randomisation to 12 weeks

NO DIFFERENCE

More trial drug-modifying adverse events (p=0·004)

More drug interactions (p=0·0005)

Lancet 2018; 391: 668–78

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Comparative Effectiveness of Switching to Daptomycin Versus Remaining on Vancomycin Among Patients With Methicillin-resistant *Staphylococcus aureus* (MRSA) Bloodstream Infections

Marin L. Schweizer,[1,2] Kelly Richardson,[1] Mary S. Vaughan Sarrazin,[1,2] Michihiko Goto,[1,2] Daniel J. Livorsi,[1,2] Rajeshwari Nair,[1,2] Bruce Alexander,[1] Brice F. Beck,[1] Michael P. Jones,[1,3] Mireia Puig-Asensio,[2] Daniel Suh,[1] Madeline Ohl,[2] and Eli N. Perencevich[1,2]

Table 2. Analysis of 30-Day Mortality Among Patients Who Switch from Vancomycin to Daptomycin Compared With Patients Who Remain on Vancomycin

	Unadjusted Mortality Among Those Switched to Daptomycin (%)	Unadjusted Mortality Among Those Who Remained on Vancomycin (%)	Unadjusted χ^2 *P* value	Adjusted Association Using Cox Regression HR (95% CI)
Comparing patients who switched to daptomycin during the first hospitalization (606 patients) with patients who did not switch (6805 patients)	12.9	17.4	.004	.87 (.69, 1.09)
Comparing patients who switched to daptomycin within 3 days (108 patients) with patients who did not switch (6805 patients)	8.3	17.4	.013	.48 (.25–.92)

Daptomycin may be the backbone for MRSA

Clinical Infectious Diseases® 2021;72(S1):S68–73

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Vancomycin, Daptomycin, Antistaphylococcal β-Lactam, and Trimethoprim-Sulfamethoxazole Monotherapy and Combination Therapy in the Management of Methicillin-Resistant *Staphylococcus aureus*: A Network Meta-Analysis

Xiaonan Xu[1], Ni Lu[2†], Pan Song[3†], Mingzhen Zhou[2], Yuanxiao Li[1], Zirui Wang[2] and Xin Gao[2]*

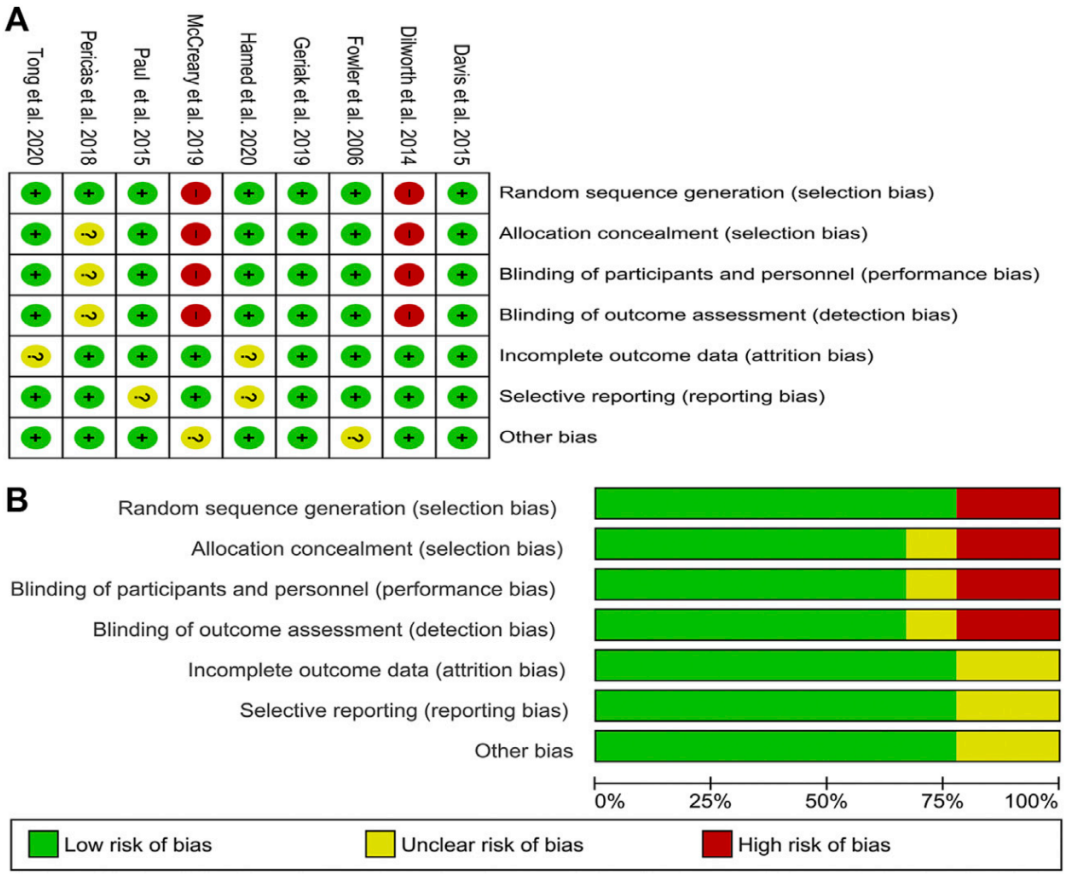

FIGURE 2 | Risk of bias graph and summary of the included studies **(A)** reviewers' judgments about each risk of bias item for eligible studies and **(B)** the judgments about each risk of bias item presented as percentages across all eligible studies.

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published: 17 May 2022
doi: 10.3389/fphar.2022.805966

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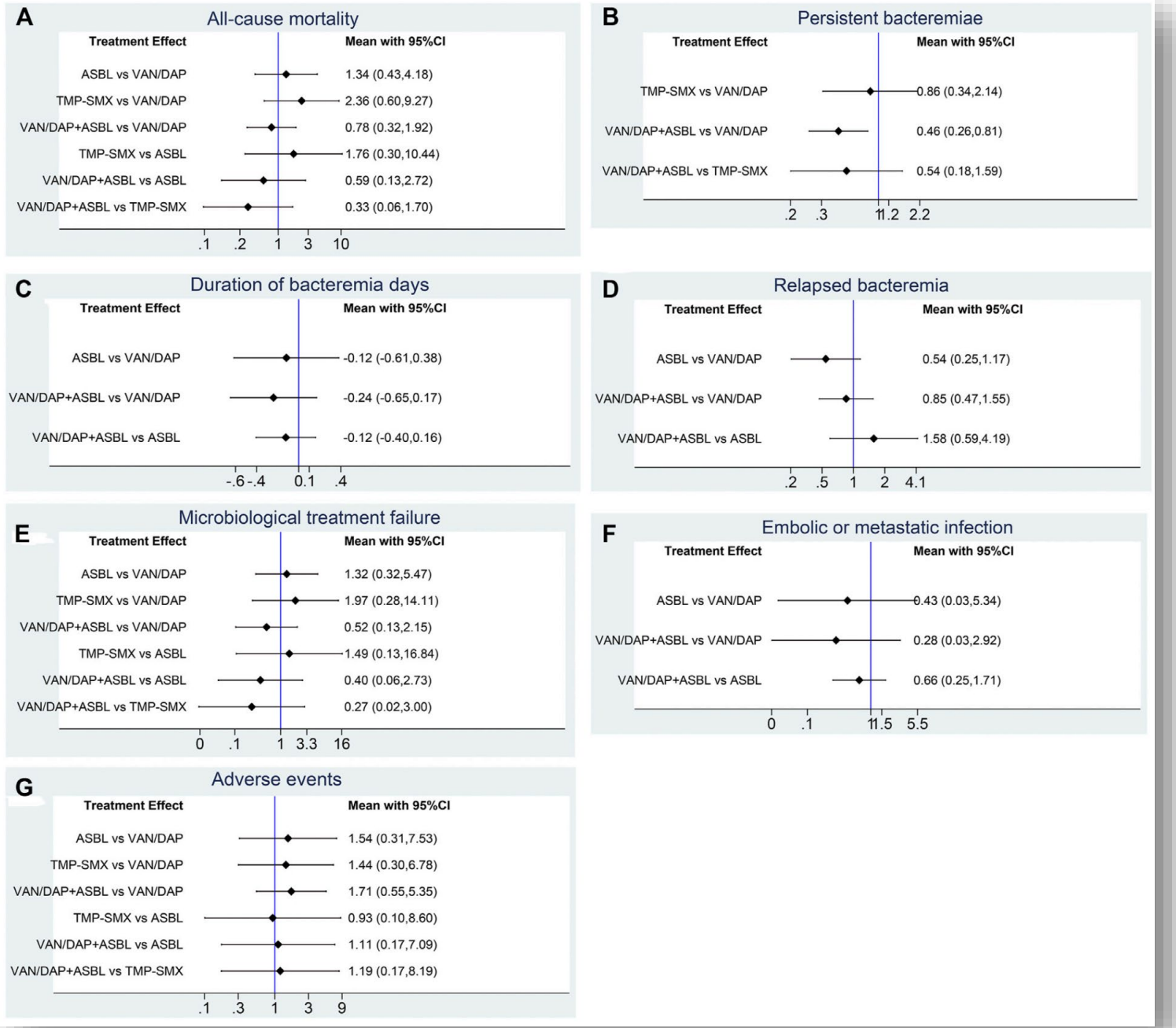

frontiers | Frontiers in Pharmacology

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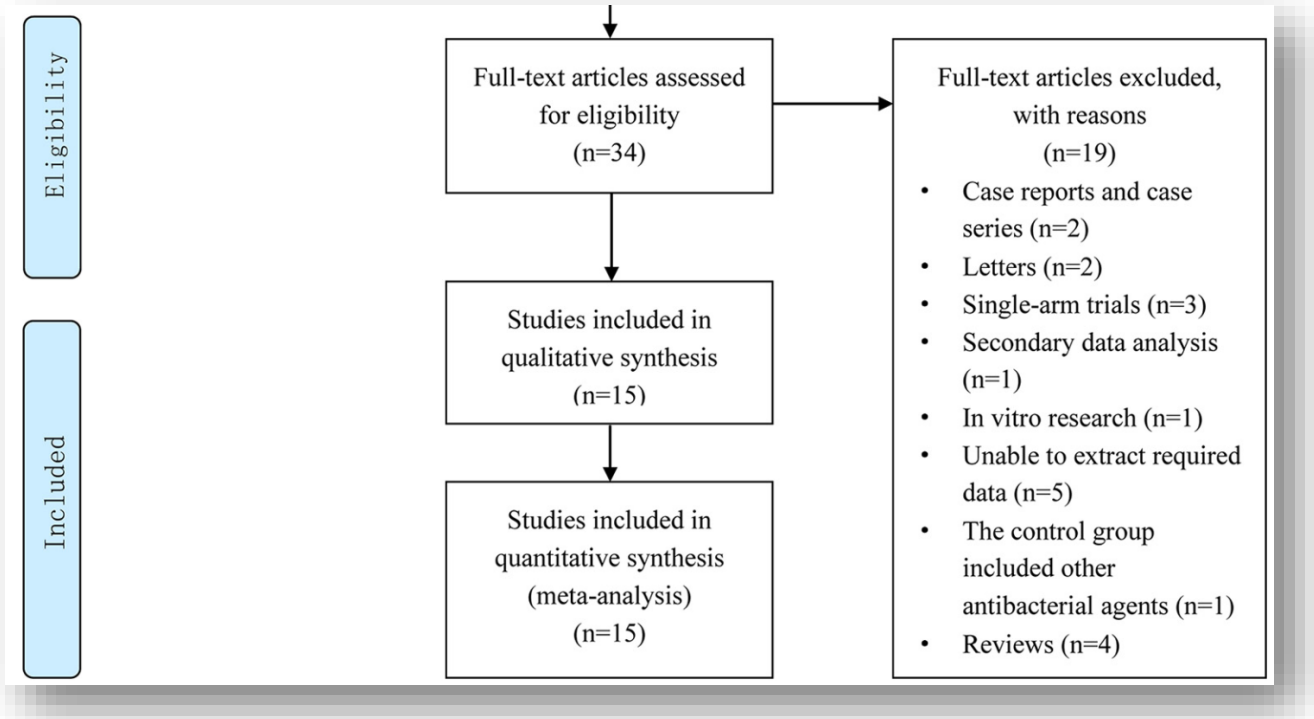
Adjuvant β-Lactam Therapy Combined with Vancomycin or Daptomycin for Methicillin-Resistant *Staphylococcus aureus* Bacteremia: a Systematic Review and Meta-analysis

Chunjiang Wang,[a] Chao Ye,[b] Linglong Liao,[c] Zhaohui Wang,[b] Ying Hu,[b] Chao Deng,[d] Liang Liu[e]



2,594 patients were included

1,189 [STAN]

1,405 [COMBO]

VAN	**7 studies**
DAP	**5 studies**
VAN/DAP	**3 studies**

b-lactam **ceftaroline in 4 studies**
cefazolin in 3 studies
flucloxacillin in 2 studies
cloxacillin in 1 study
cefepime in 1 study
mixed in 6 studies

3 RCTs
12 retrospective cohort studies
10 multicenter studies
4 single center

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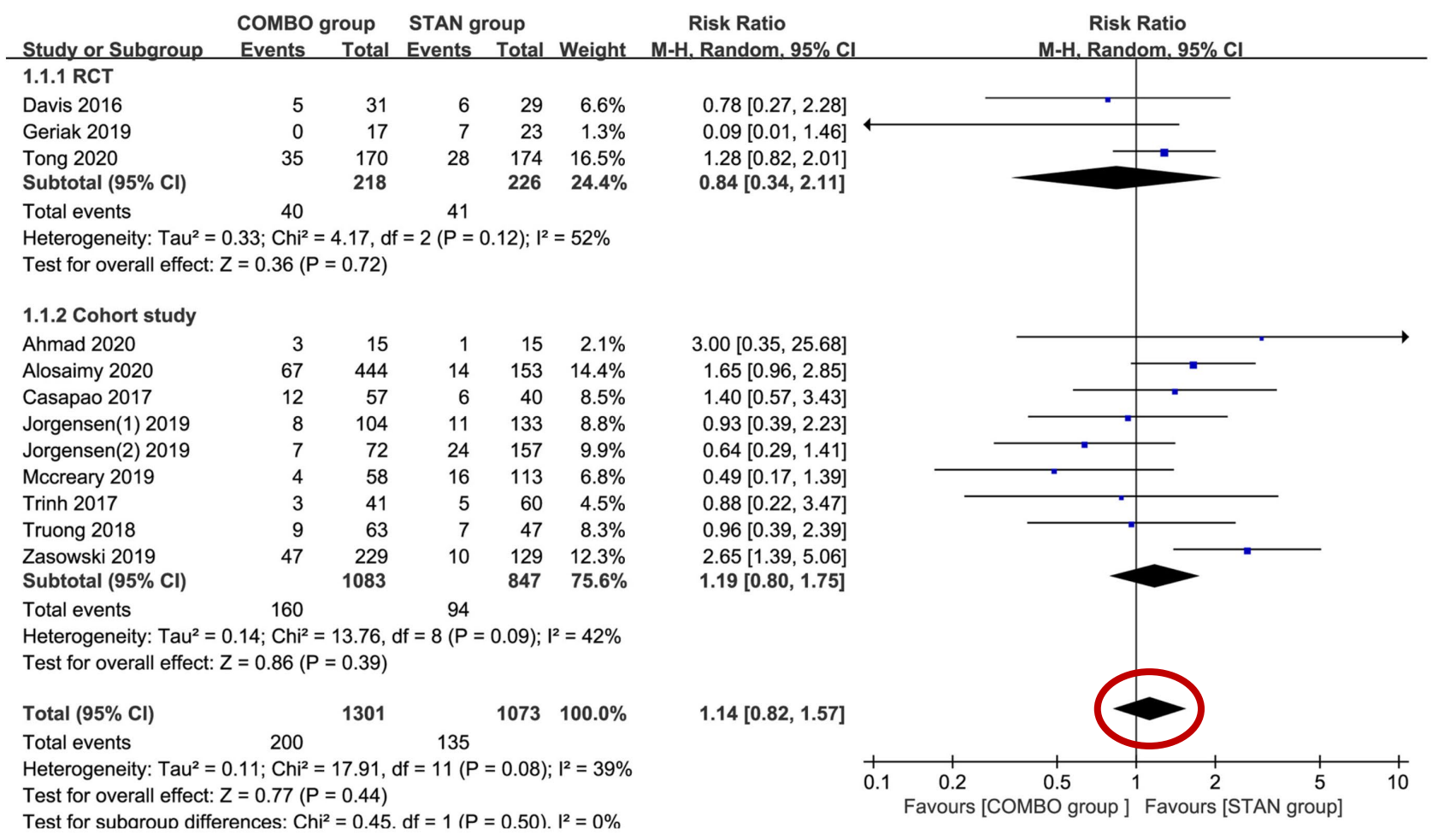
Forest plot of the risk ratio (RR) for crude mortality in patients with MRSA bacteremia



Adjuvant β-Lactam Therapy Combined with Vancomycin or Daptomycin for Methicillin-Resistant *Staphylococcus aureus* Bacteremia: a Systematic Review and Meta-analysis

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TABLE 2 Subgroup analysis results of different outcome indicators

Outcome (subjects)	Subgroup[a]	No. of studies	RR[b] (95% CI)	*P* value	I^2 (%)
Crude mortality	VAN+BL	6	1.28 (0.83–1.99)	0.26	27
	DAP+BL	3	0.53 (0.28–0.98)	0.04	0
	BL (ceftaroline)	3	0.58 (0.12–2.83)	0.5	52
	RCTs	3	0.84 (0.34–2.11)	0.72	52
	Cohort studies	9	1.19 (0.80–1.75)	0.39	42
Clinical failure	VAN+BL	6	0.79 (0.59–1.06)	0.11	55
	DAP+BL	4	0.75 (0.46–1.22)	0.25	23
	BL (ceftaroline)	1	0.93 (0.52–1.68)	0.82	NA[c]
	RCT	1	0.89 (0.68–1.18)	0.43	NA
	Cohort studies	9	0.77 (0.62–0.97)	0.02	44
Bacteremia recurrence	VAN+BL	6	0.61 (0.39–0.96)	0.03	0
	DAP+BL	2	0.72 (0.39–1.35)	0.31	0
	BL=Ceftaroline	2	0.81 (0.31–2.11)	0.66	0
	RCTs	2	0.77 (0.40–1.48)	0.44	0
	Cohort studies	9	0.63 (0.47–0.85)	0.002	0
Persistent bacteremia	VAN+BL	6	0.61 (0.47–0.79)	0.0002	0
	DAP+BL	1	0.74 (0.43–1.28)	0.28	NA
	RCTs	2	0.54 (0.32–0.88)	0.01	0
	Cohort studies	7	0.66 (0.56–0.79)	<0.00001	0
Nephrotoxicity	VAN+BL	4	0.93 (0.55–1.59)	0.8	18
	DAP+BL	2	2.11 (0.33–13.47)	0.43	34
	BL (ceftaroline)	1	0.44 (0.02–10.29)	0.61	NA
	RCTs	2	2.29 (0.39–13.53)	0.36	41
	Cohort studies	7	1.08 (0.75–1.54)	0.68	21

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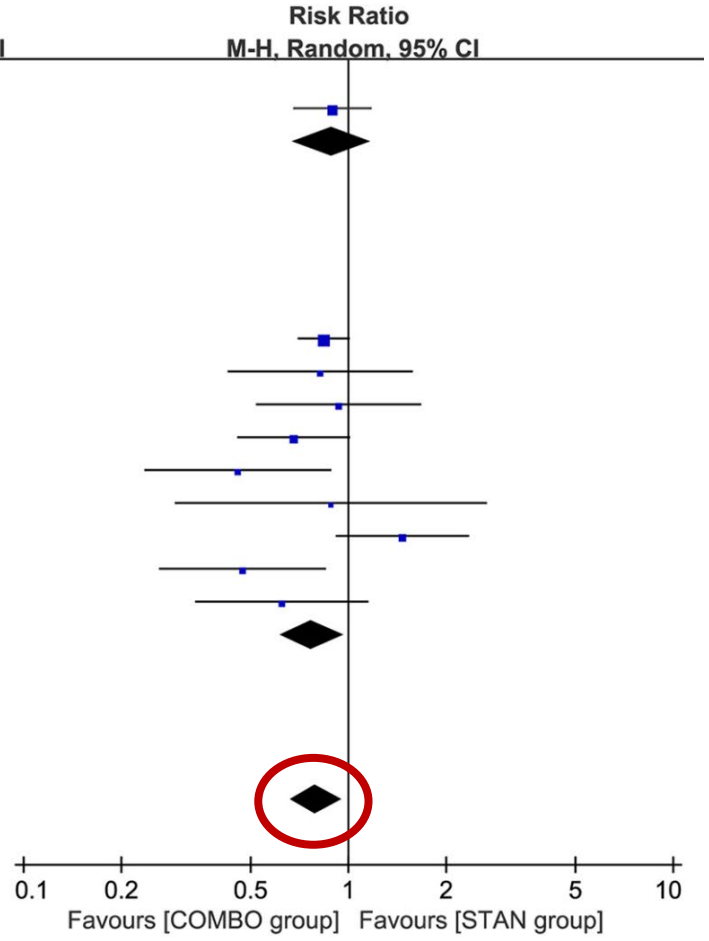
Forest plot of the risk ratio (RR) for clinical failure in patients with MRSA bacteremia

Study or Subgroup	COMBO group Events	Total	STAN group Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
2.1.1 RCT						
Tong 2020	59	170	68	175	17.8%	0.89 [0.68, 1.18]
Subtotal (95% CI)		**170**		**175**	**17.8%**	**0.89 [0.68, 1.18]**
Total events	59		68			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.80 (P = 0.43)						
2.1.2 Cohort Study						
Alosaimy 2020	195	444	80	153	23.0%	0.84 [0.70, 1.01]
Casapao 2017	14	57	12	40	6.2%	0.82 [0.42, 1.58]
Fox 2018	14	41	15	41	7.4%	0.93 [0.52, 1.68]
Jorgensen(1) 2019	26	104	49	133	12.4%	0.68 [0.45, 1.01]
Jorgensen(2) 2019	9	72	43	157	6.2%	0.46 [0.24, 0.88]
Moise 2013	4	22	7	34	2.5%	0.88 [0.29, 2.67]
Taylor 2019	22	37	15	37	10.1%	1.47 [0.91, 2.35]
Trinh 2017	10	41	31	60	7.3%	0.47 [0.26, 0.85]
Truong 2018	13	56	16	43	6.9%	0.62 [0.34, 1.15]
Subtotal (95% CI)		**874**		**698**	**82.2%**	**0.77 [0.62, 0.97]**
Total events	307		268			
Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 14.37$, df = 8 (P = 0.07); $I^2 = 44\%$						
Test for overall effect: Z = 2.26 (P = 0.02)						
Total (95% CI)		**1044**		**873**	**100.0%**	**0.80 [0.66, 0.96]**
Total events	366		336			
Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 14.71$, df = 9 (P = 0.10); $I^2 = 39\%$						
Test for overall effect: Z = 2.41 (P = 0.02)						
Test for subgroup differences: $Chi^2 = 0.64$, df = 1 (P = 0.43), $I^2 = 0\%$						



Adjuvant β-Lactam Therapy Combined with Vancomycin or Daptomycin for Methicillin-Resistant *Staphylococcus aureus* Bacteremia: a Systematic Review and Meta-analysis

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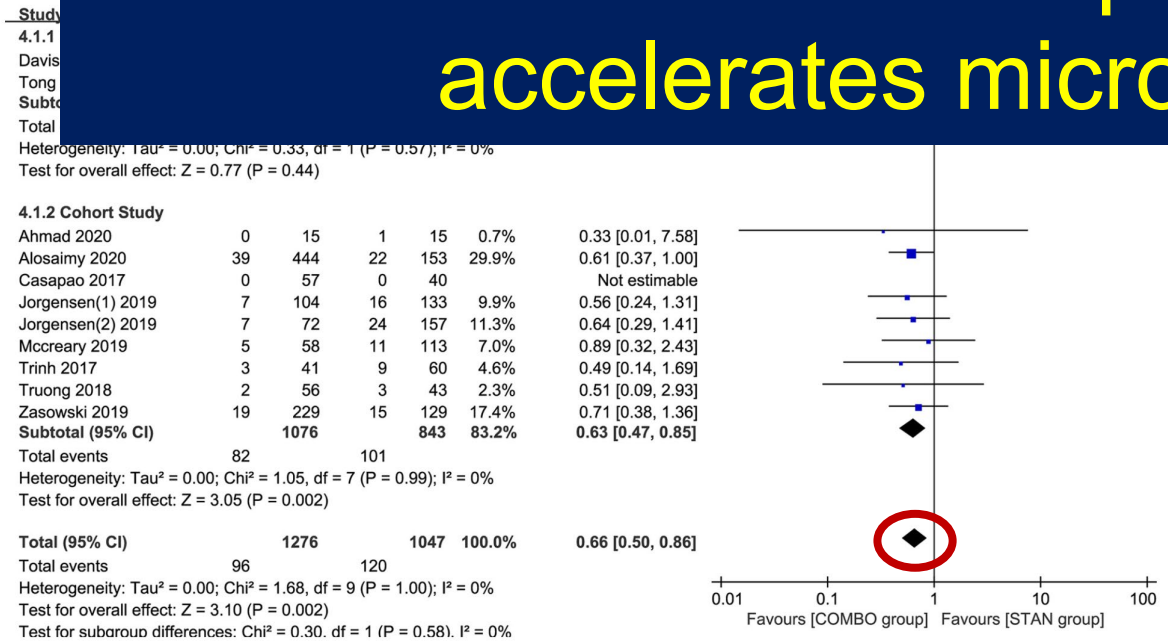
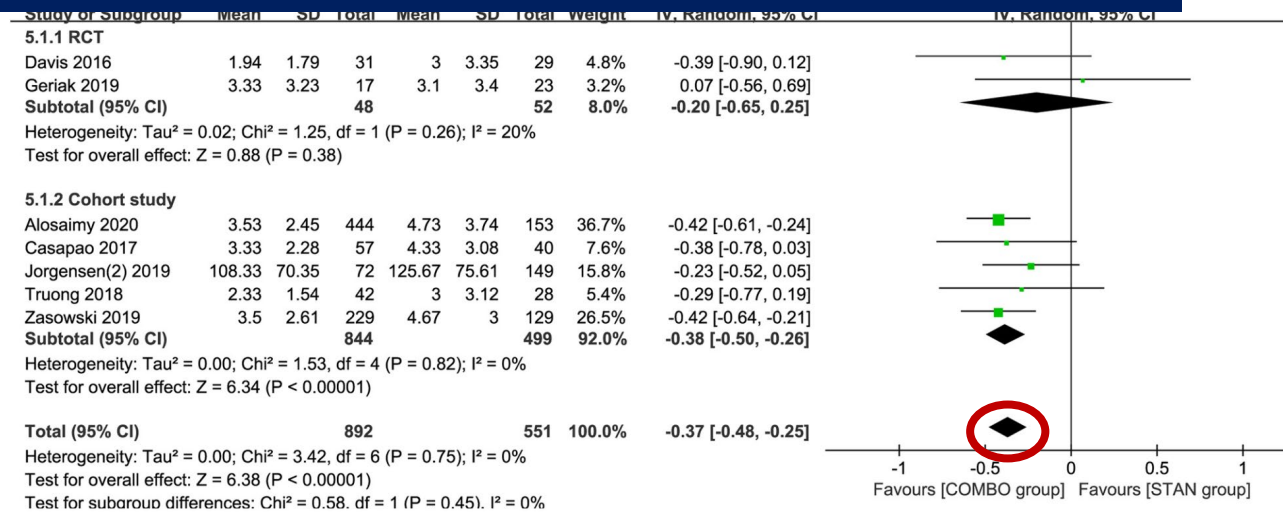
Adding a beta-lactam to VAN / DAP does not improve survival but accelerates microbiological response





Clinical Data on Daptomycin plus Ceftaroline versus Standard of Care Monotherapy in the Treatment of Methicillin-Resistant *Staphylococcus aureus* Bacteremia

Matthew Geriak,[a] Fadi Haddad,[b] Khulood Rizvi,[c] Warren Rose,[d] Ravina Kullar,[e] Kerry LaPlante,[f] Marie Yu,[b] Logan Vasina,[a] Krista Ouellette,[a] Marcus Zervos,[c] Victor Nizet,[f] George Sakoulas[a,g]

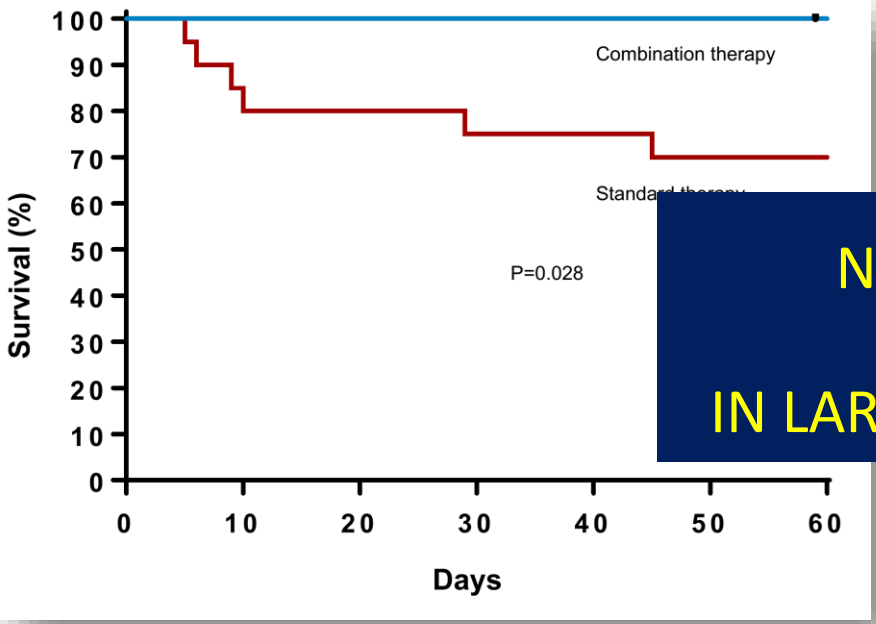


TABLE 4 Study outcomes

Outcome	Values by treatment type: Combination therapy	Monotherapy	*P* value
Mortality, *n* (%)			
In hospital	0 (0)	6 (26)	0.02
30 day	0 (0)	6 (26)	0.02
	0 (0)	7 (30)	0.03
QR) days	3 (1.5, 5.5)	3 (1, 5.3)	0.56
ays	11 (6, 14)	12 (8, 23)	0.24

NEEDS CONFIRMATION

IN LARGER AND RIGOROUS R.C.T.

TABLE 5 Treatment-related adverse events

Event	No. of patients: Combination therapy	Monotherapy
Treatment failure	1[a]	3[b]
Acute kidney injury	0	1
Asymptomatic elevated CPK[c]	0	1
Eosinophilic pneumonia	1[d]	0

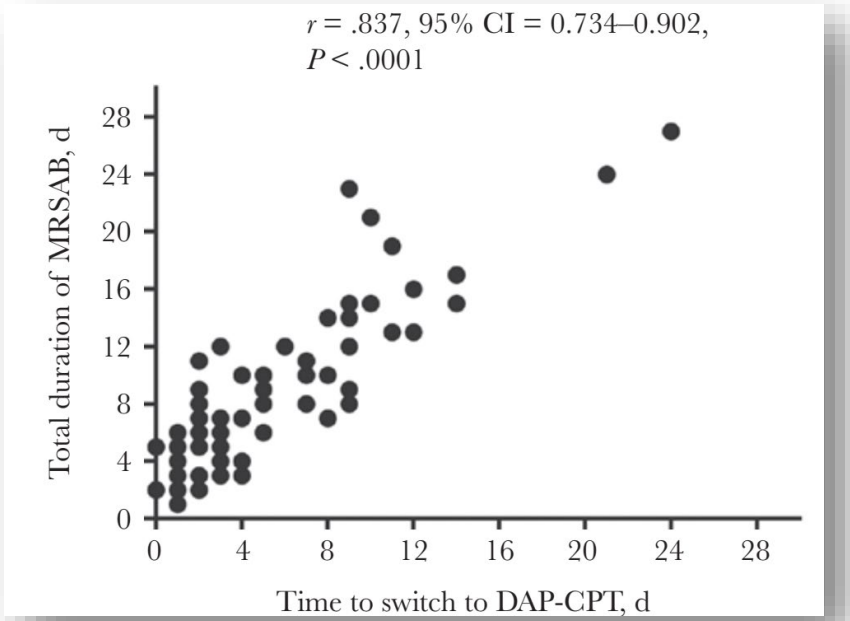
Vancomycin trough (initial, mg/liter) 16.2 (10.7, 19.8)

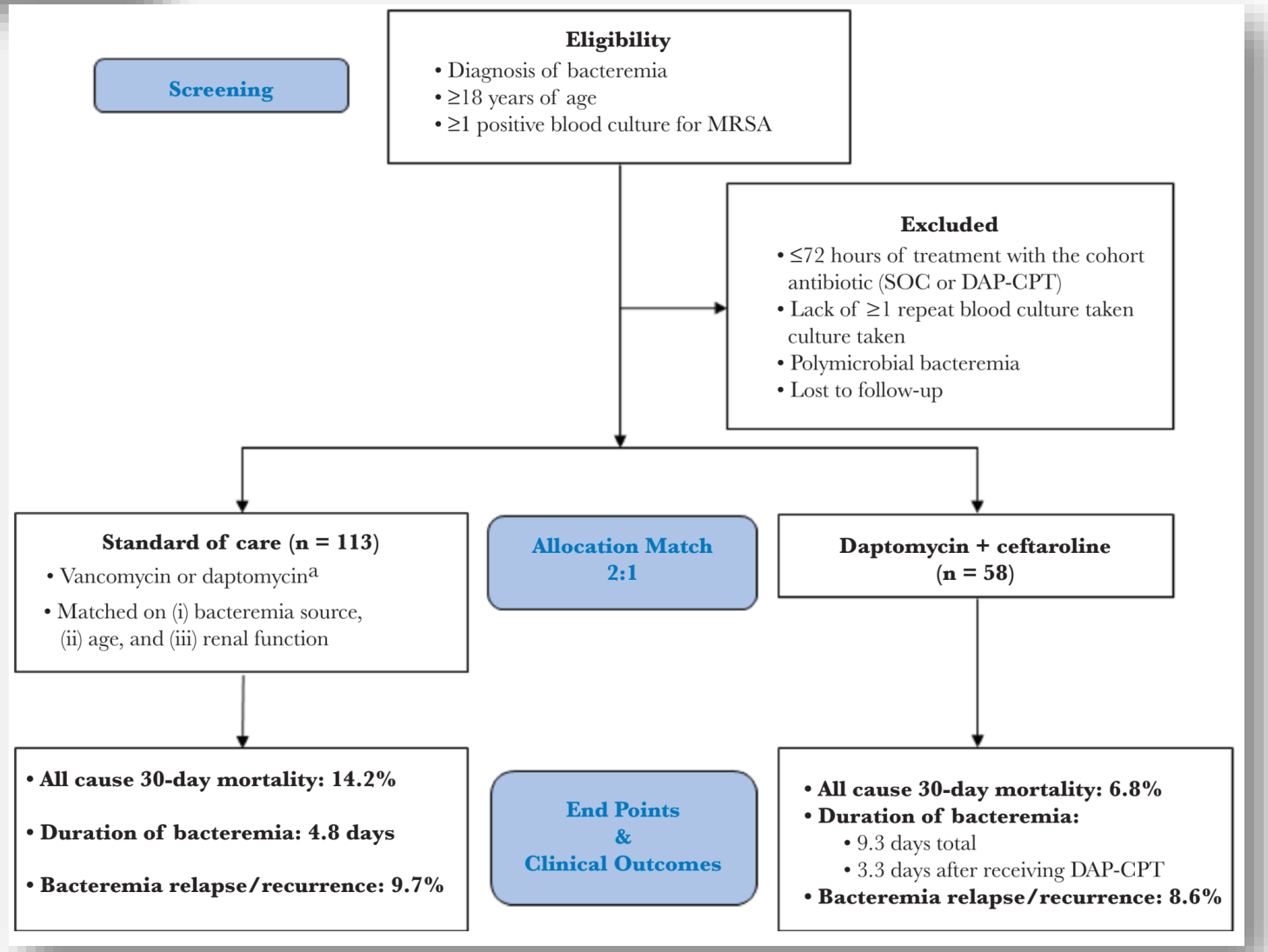
Daptomycin dose (median, mg/kg) 8.3

Antimicrob Agents Chemother. 2019; 63 (5): e02483-e18
see also AAC 2019; 63 (11): e00900-19

Multicenter Cohort of Patients With Methicillin-Resistant *Staphylococcus aureus* Bacteremia Receiving Daptomycin Plus Ceftaroline Compared With Other MRSA Treatments

Erin K. McCreary,[1,a] Ravina Kullar,[2] Matthew Geriak,[3] Evan J. Zasowski,[4] Khulood Rizvi,[6] Lucas T. Schulz,[1] Krista Ouellette,[3] Logan Vasina,[3] Fadi Haddad,[4] Michael J. Rybak,[5,6] Marcus J. Zervos,[6,7] George Sakoulas,[4,8] and Warren E. Rose[1,9]





Open Forum Infectious Diseases® DOI: 10.1093/ofid/ofz538

Daptomycin Plus Fosfomycin Versus Daptomycin Alone for Methicillin-resistant *Staphylococcus aureus* Bacteremia and Endocarditis: A Randomized Clinical Trial

Miquel Pujol,[1,a] José-María Miró,[2,a] Evelyn Shaw,[1] Jose-María Aguado,[3] Rafael San-Juan,[3] Mireia Puig-Asensio,[4] Carles Pigrau,[4] Esther Calbo,[5]

Table 2. Primary and Secondary Outcomes

Outcome	Daptomycin Plus Fosfomycin, No. of Patients/Total (%)	Daptomycin Alone, No. of Patients/Total (%)	Relative Risk (95% CI)
Primary endpoint			
Treatment success at TOC	40/74 (54.1)	34/81 (42.0)	1.29 (.93–1.8)
Secondary endpoints			
Positive blood cultures at day 3	2/74 (2.7)	15/81 (18.5)	0.15 (.04–.63)
Positive blood cultures at day 7	0/74 (0.0)	5/81 (6.2)	−6.2 (−11.4 to −.9)[a]
Positive blood cultures at TOC	0/74 (0.0)	4/81 (4.9)	−4.9 (−9.7 to −.2)[a]
Microbiological failure at TOC	0/74 (0.0)	9/81 (11.1)	−11.1 (−18.0 to −4.3)[a]
No. of episodes of complicated bacteremia at TOC	12/74 (16.2)	26/81 (32.1)	0.51 (.28–.94)
Any AE leading to treatment discontinuation	13/74 (17.6)	4/81 (4.9)	3.56 (1.21–10.44)
Overall mortality at day 7	3/74 (4.1)	6/81 (7.4)	0.55 (.14–2.12)
Overall mortality at TOC	18/74 (24.3)	22/81 (27.2)	0.9 (.53–1.54)

Open Forum Infect Dis. 2019; 7(1): ofz538

7 DAYS OF COMBO

170 Included in primary analysis
6 Excluded
4 Lost to follow-up
2 Randomized in error
144 Included in per-protocol analysis
26 Excluded (received <75% of study β-lactam doses)

99% VANCO

175 Included in primary analysis
5 Excluded
3 Lost to follow-up
2 Randomized in error
175 Included in per-protocol analysis

JAMA | Original Investigation

Effect of Vancomycin or Daptomycin With vs Without an Antistaphylococcal β-Lactam on Mortality, Bacteremia, Relapse, or Treatment Failure in Patients With MRSA Bacteremia

A Randomized Clinical Trial

Steven Y. C. Tong, MBBS, PhD; David C. Lye, MBBS; Dafna Yahav, MD; Archana Sud, MD; J. Owen Robinson, MD; Jane Nelson, BN; Sophia Archuleta, MD;

Should we limit combination rx to the early phase ?

Outcomes	Combination Therapy	Standard Therapy	Risk Difference, % (95% CI)	*P* Value
Primary Outcome[a,b]				
Primary analysis population	59/170 (35)	68/175 (39)	−4.2 (−14.3 to 6.0)	.42
Per protocol	47/144 (33)	68/175 (39)	−6.2 (−16.7 to 4.3)	.25
Secondary Outcomes[c]				
All-cause mortality[d]				
Day 14	13/170 (8)	13/174 (7)	0.2 (−5.4 to 5.8)	.95
Day 42	25/170 (15)	19/174 (11)	3.8 (−3.3 to 10.8)	.29
Day 90	35/170 (21)	28/174 (16)	4.5 (−3.7 to 12.7)	.28
Persistent bacteremia[e]				
Day 2	50/167 (30)	61/173 (35)	−5.3 (−15.3 to 4.6)	.29
Day 5	19/166 (11)	35/172 (20)	−8.9 (−16.6 to −1.2)	.02
Microbiological relapse[a]	14/169 (8)	18/175 (10)	−2.0 (−8.1 to 4.1)	.52
Microbiological treatment failure[a]	16/170 (9)	17/175 (10)	−0.3 (−6.5 to 5.9)	.92
Acute kidney injury[f]	34/145 (23)	9/145 (6)	17.2 (9.3 to 25.2)	<.001
Duration of intravenous antibiotics, mean (SD), d	29.3 (19.5)	28.1 (17.4)		.72

JAMA. 2020; 323(6): 527-537

Clinical Outcomes With Definitive Treatment of Methicillin-Resistant *Staphylococcus aureus* Bacteremia With Retained Daptomycin and Ceftaroline Combination Therapy vs De-escalation to Monotherapy With Vancomycin, Daptomycin, or Ceftaroline

Courtney N. Nichols,[1] Lynn C. Wardlow,[2] Kelci E. Coe,[1] and Mohammad Mahdee E. Sobhanie[1]

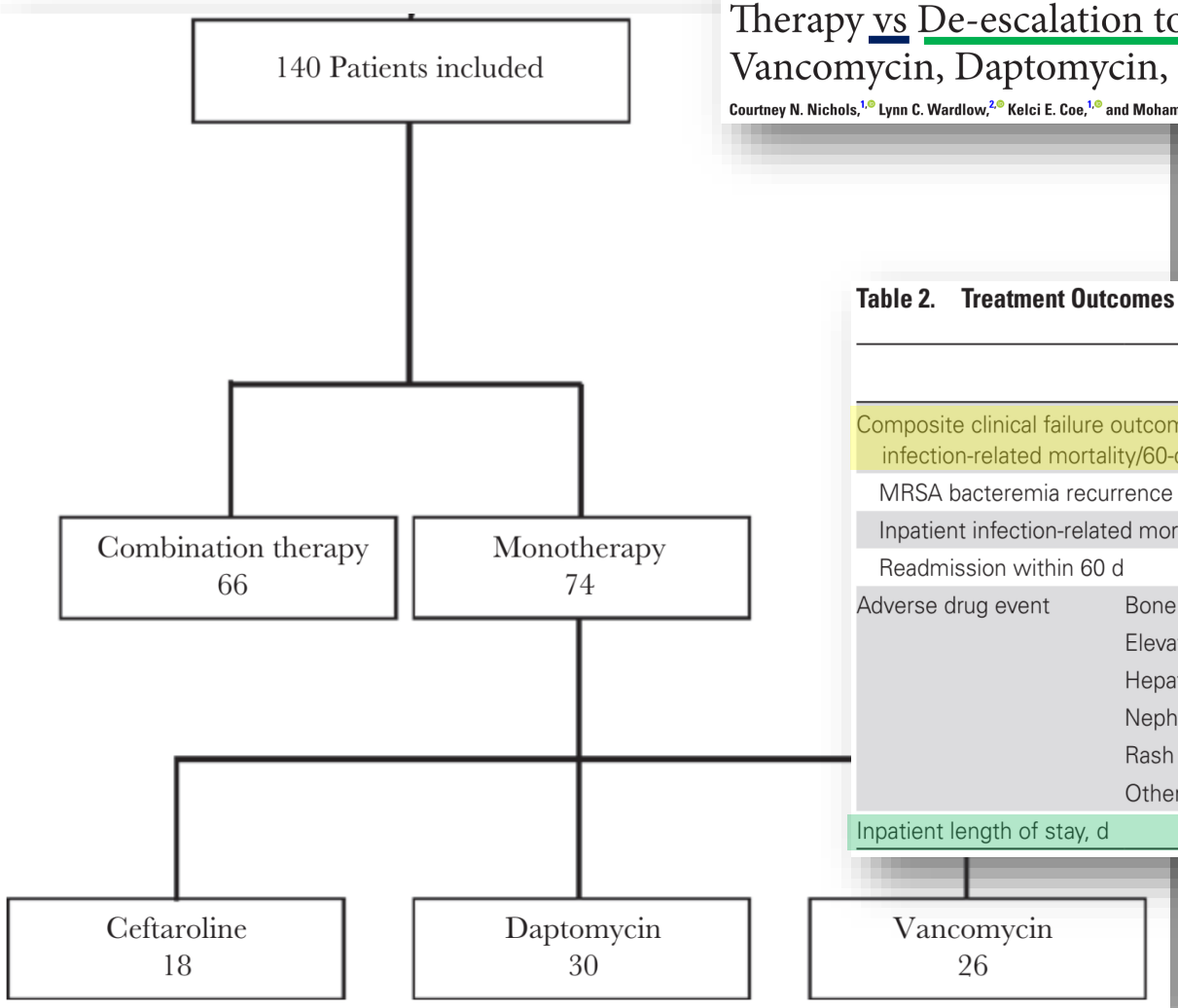


Table 2. Treatment Outcomes

		Combination Therapy (n = 66)	Monotherapy (n = 74)	*P* Value (CT vs MT)
Composite clinical failure outcome: 60-d recurrence/inpatient infection-related mortality/60-d readmission		14 (21)	18 (24)	.66
MRSA bacteremia recurrence within 60 d		2 (3)	5 (7)	.45
Inpatient infection-related mortality		1 (2)	4 (5)	1
Readmission within 60 d		13 (20)	13 (18)	.75
Adverse drug event	Bone marrow suppression	1 (2)	0	.47
	Elevated creatine kinase	0	0	
	Hepatotoxicity	0	0	
	Nephrotoxicity	0	0	
	Rash	0	0	
	Other[a]	1 (2)	1 (1)	1
Inpatient length of stay, d		26 [20–41]	24.5 [16–33]	.08

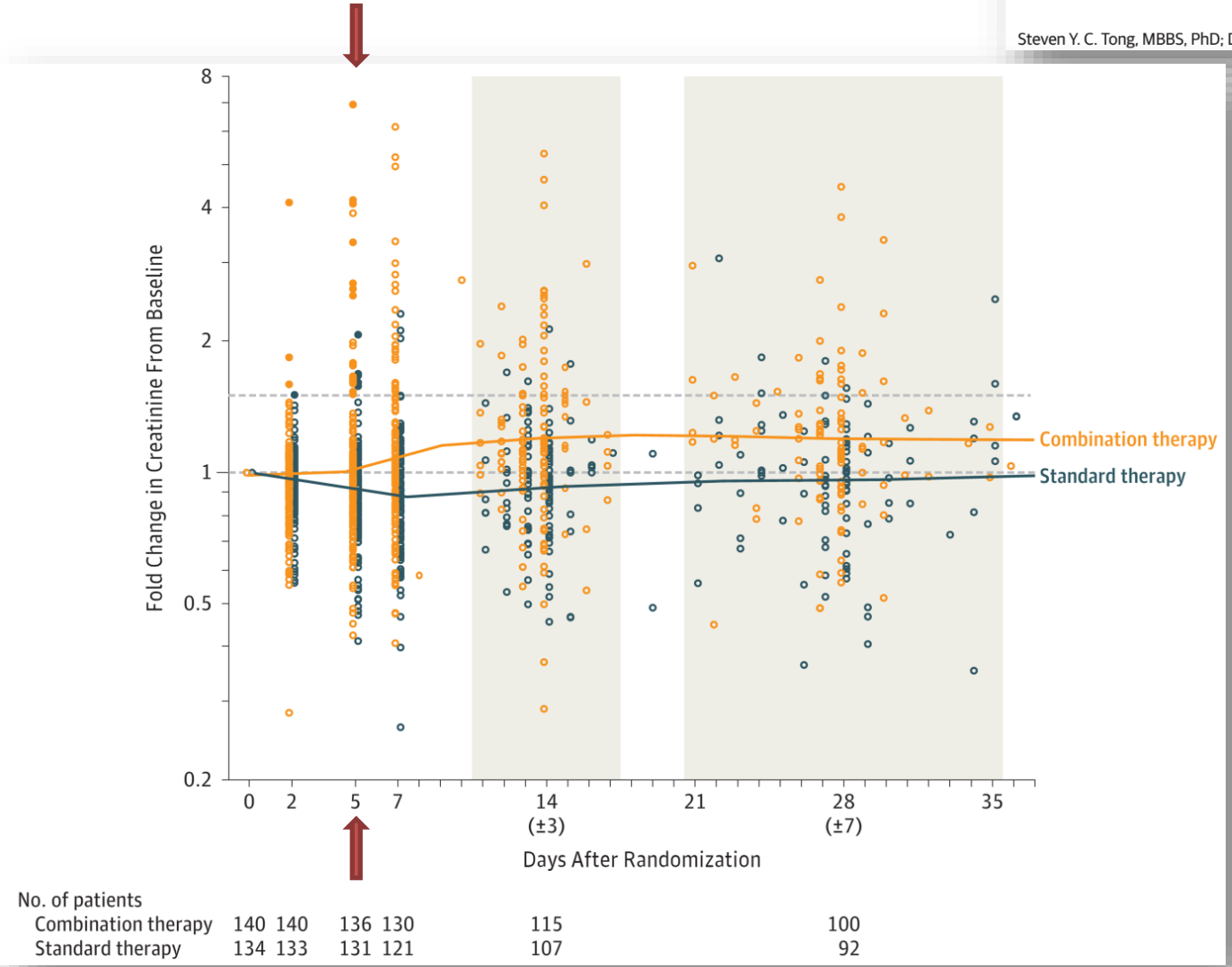
Open Forum Infectious Diseases®2021 https://doi.org/10.1093/ofid/ofab327

99% VANCO

JAMA | Original Investigation

Effect of Vancomycin or Daptomycin With vs Without an Antistaphylococcal β-Lactam on Mortality, Bacteremia, Relapse, or Treatment Failure in Patients With MRSA Bacteremia
A Randomized Clinical Trial

Steven Y. C. Tong, MBBS, PhD; David C. Lye, MBBS; Dafna Yahav, MD; Archana Sud, MD; J. Owen Robinson, MD; Jane Nelson, BN; Sophia Archuleta, MD;



Characteristics	Combination Therapy (n = 174)	Standard Therapy (n = 178)
Trough vancomycin level, mean (SD), μg/mL		
Day 1	15.1 (8.1)	14.7 (7.3)
Day 2	17.9 (9.1)	17.2 (8.0)
Day 3	20.1 (7.6)	19.2 (7.5)

JAMA. 2020; 323(6): 527-537

Treat early, treat hard MRSA
Role of new bactericidal antibiotic combinations

Combine early, to hit harder

HOW LONG?

AFTER 3-5 DAYS?

Switch to monotherapy

Reduce ADR

Reduce MDR-selection

Reduce costs

Outline

- Backbone agents MSSA vs MRSA
- **What combination regimens add to the backbone**
  - MSSA
  - MRSA
  - **Strep / Enteroc**
- Non-antibiotic combinations
- Tentative treatment algorithm

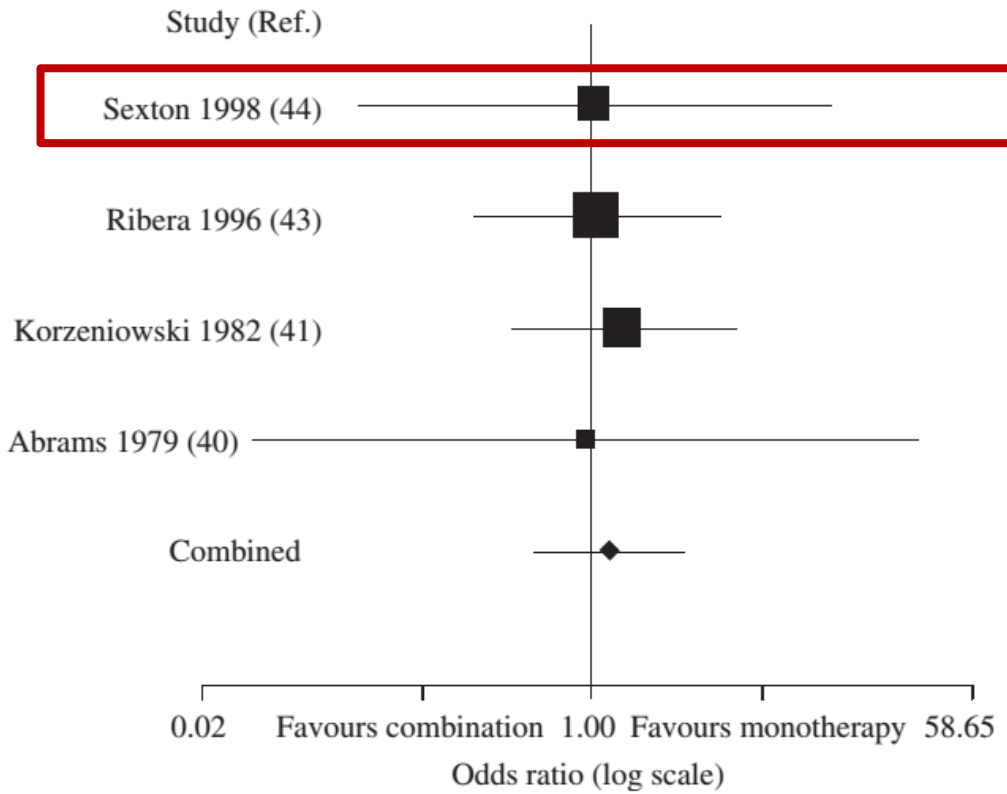
Journal of Antimicrobial Chemotherapy (2006) **57**, 639–647
doi:10.1093/jac/dkl044
Advance Access publication 24 February 2006

JAC

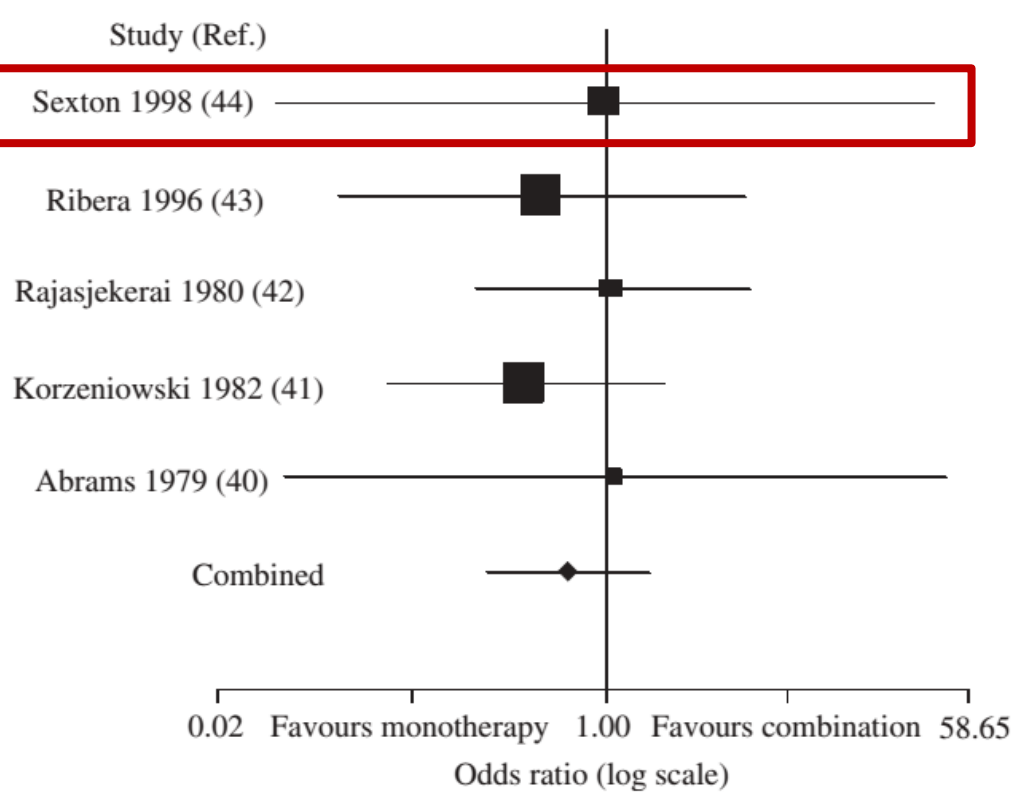
The role of aminoglycosides in combination with a β-lactam for the treatment of bacterial endocarditis: a meta-analysis of comparative trials

Matthew E. Falagas[1,2]*, Dimitrios K. Matthaiou[1] and Ioannis A. Bliziotis[1]

clinical cure (treatment success)



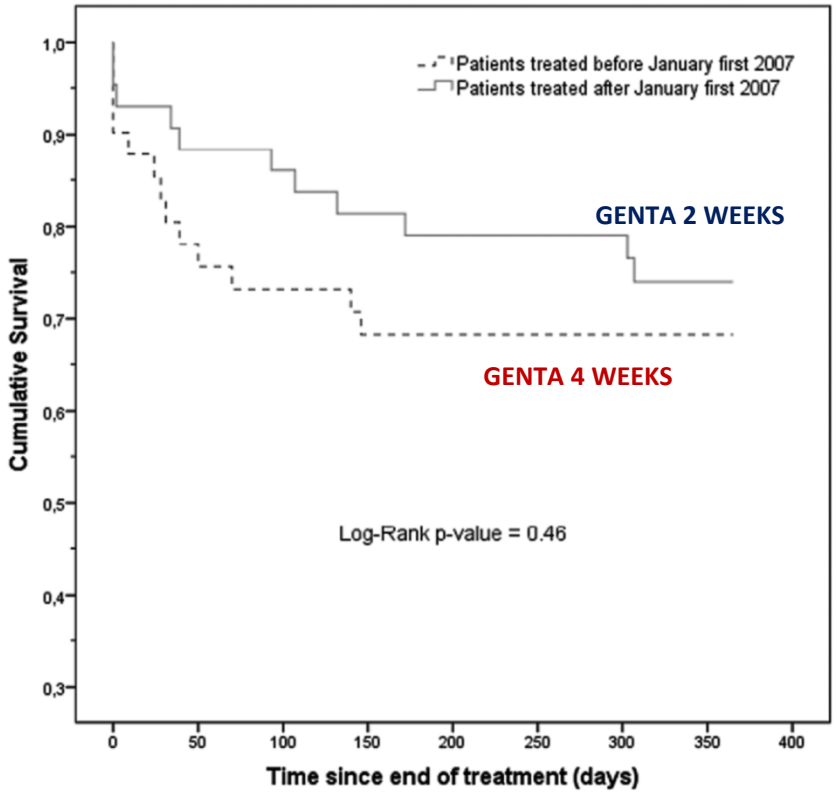
all-cause mortality



Enterococcus faecalis Infective Endocarditis

A Pilot Study of the Relationship Between Duration of Gentamicin Treatment and Outcome

Anders Dahl, MD; Rasmus V. Rasmussen, MD, PhD; Henning Bundgaard, MD, DMSc;



Variable	Before 2007 (n=41)	After January 1, 2007 (n=43)	*P* Value
Gentamicin treatment, median (IQR), d	28 (18 to 42)	14 (7 to 15)	<0.001
eGFR admittance, median (IQR), mL/min	66 (41 to 95)	75 (52 to 99)	0.22
eGFR at 14 days, median (IQR), mL/min	57 (40 to 90)	67 (38 to 95)	0.65
eGFR discharge, median (IQR), mL/min	45 (32 to 75)	66 (50 to 93)	0.008
eGFR change, median (IQR), mL/min	–11(–25 to–3)	–1 (–13 to 4)	0.009

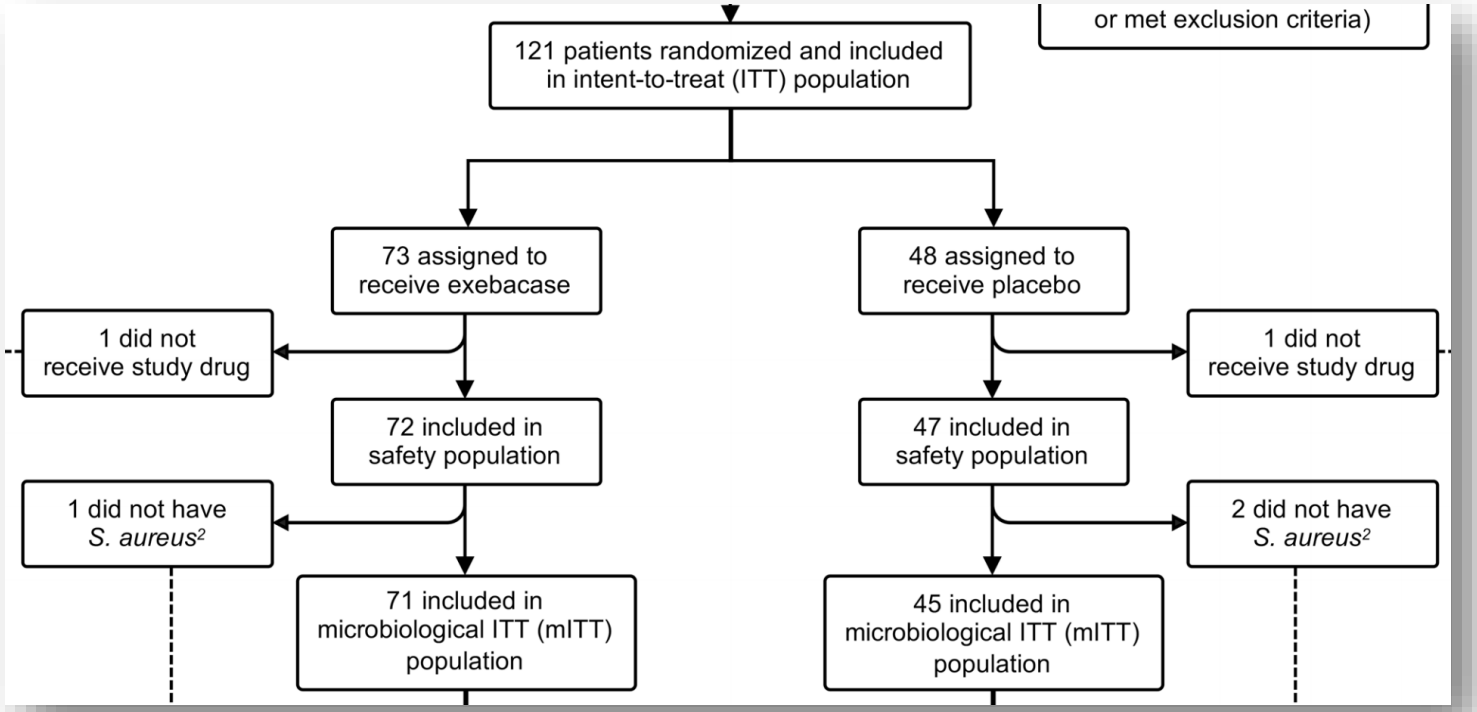
Circulation. 2013;127:1810-1817

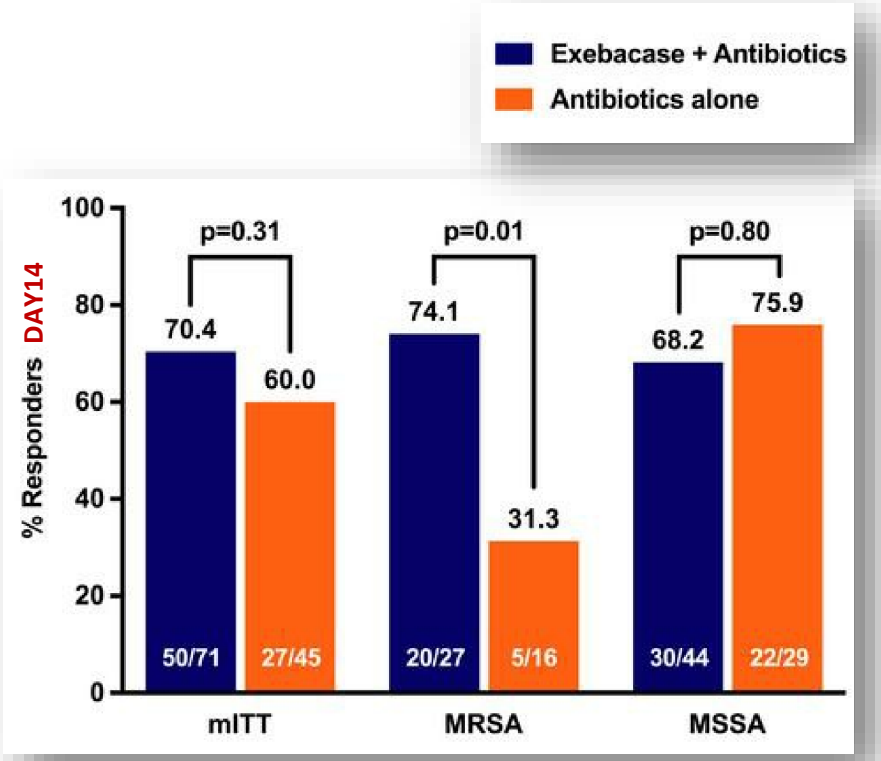
Outline

- Backbone agents MSSA vs MRSA
- What combination regimens add to the backbone
  - MSSA
  - MRSA
  - Strep / Enteroc
- **Non-antibiotic combinations**
- Tentative treatment algorithm

Exebacase for patients with *Staphylococcus aureus* bloodstream infection and endocarditis

Vance G. Fowler Jr.,[1,2] Anita F. Das,[3] Joy Lipka-Diamond,[4] Raymond Schuch,[5] Roger Pomerantz,[5] Luis Jáuregui-Peredo,[6] Adam Bressler,[7] David Evans,[8] Gregory J. Moran,[9] Mark E. Rupp,[10] Robert Wise,[11] G. Ralph Corey,[1] Marcus Zervos,[12] Pamela S. Douglas,[1,2] and Cara Cassino[5]





Once again: no survival advantage with combination

The Journal of Clinical Investigation Volume 130 Number 7 July 2020

Summary

- An overwhelming wealth of low quality data consistently suggests that combination therapy is not more effective than monotherapy in IE
- Prolonged combination therapy is associated with more toxicity
- Early, upfront, high dose combination of 2 bactericidal agents (including a beta-lactam and daptomycin) consistently clears BC in MRSA, MSSA BSI/IE
- The limited available evidence suggests cBSI/IE might benefit from an initial, short-phase of aggressive combination therapy, followed by a step down to an *in vitro* active monotherapy

Outline

- Backbone agents MSSA vs MRSA
- What combination regimens add to the backbone
  - MSSA
  - MRSA
  - Strep / Enteroc
- Non-antibiotic combinations
- **Tentative treatment algorithm**

Suspected Infective Endocarditis: obtain blood cultures and start treatment

DAPTOMYCIN ≥8 mg/kg
AMOXI-CLAV 2.2 gr q4h

CULTURE RESULTS

MET-SUSC STAPH
ENTERO
STREPTO

SWITCH TO:
CEFAZOLIN / ASP
AMPICILLIN + CEFTRIAX
AMPICILLIN ± GENTA 2wks

NEGATIVE
PAT. IMPROVING

CONTINUE
DAPTOMYCIN ≥8 mg/kg
AMOXI-CLAV 2.2 gr q4h

MET-RES STAPH

NVE → ↑ DAPTO 10 mg/kg + CEFTAROLINE 3-5 days

PVE

↑ DAPTO 10 mg/kg + FOSFOMYCIN 24 gr/d 3-5 days → DAPTO 10 mg/kg + RIFAMPIN 0.9-1.2 gr/d

EDM 2022, based on personal interpretation of the available evidence