Avui dia, tractar amb un sol fàrmac*, és "mala pràctica clínica"

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(Sense COIs)

* La bacterièmia per *S. aureus*

Combinar? Sí, sempre…

- Tractament empíric o orientat
- Situació clínica
- Presència de factors de risc per a bacterièmia complicada
- SASM/SARM
- Es coneix el focus? Quin és?
- Possibilitats de fer una ETE en <24h
- Possibilitats d'el·liminar el focus en un període de temps acceptable.
- És un tractament *de novo* o de rescat?
- Han aparegut resistències?
- Amb què combinar?
- Combinar durant tot el tractament?
- Com desescal·lar?
- CMI vanco? (hViSA/VISA; disfunció *agr*?)
- …

Hi ha prou evidència de qualitat per a recomanar la teràpia combinada com a 1ª línia en tots el casos?

Hi ha prou evidència de qualitat que apunta a uns resultats no satisfactoris amb la monoteràpia?

Bases del tractament combinat

- Agents sinèrgics
- Augmentar l'eficàcia (activitat bactericida)
- Evitar ("compensar"?) l'aparició de resistències
- Disminuir les dosis d'ambdós fàrmacs

Objectius del tractament combinat

- Escurçar el temps de bacterièmia
- Millorar ràpidament la situació clínica dels pacients greus
- Evitar complicacions i recidives
- Evitar la infecció de dispositius intravasculars i material protèssic.
- “Rescatar” casos amb fracassos previs a altres opcions

Quines combinacions ens podem plantejar ara per ara?

- Cloxacil·lina +: gentamicina, rifampicina, fosfomicina.
- Vancomicina +: cloxacil·lina, piper/tazo, rifampicina, gentamicina
- Daptomicina +: diferents betalactàmics (incloent ceftarolina), fosfomicina, cotrimoxazol, rifampicina, gentamicina, linezolid
- Linezolid+: carbapenems,…
- Fosfomicina + imipenem
- …

Cas 1

Dona de 85 anys amb TAVI col·locada 24h abans. Porta ingressada 48h. Presenta febre de 39ºC i un signes de flebitis al voltant d'un catèter venós perifèric.

1. Li treiem el catèter i prou
2. A més, dapto (6mg/kg o més?)
3. A més, vanco.
4. Dapto + cloxacil·lina
5. Vanco + piperacil·lina/tazobactam
6. Altres

Cas 1b

Mateixa pacient. Estem de guàrdia. Als HC creixen en 7h
EF. Segueix febril i amb més signes imflamatoris al braç.
No disposem de tests ràpids

1. Li treiem el catèter i prou
2. A més, dapto (6mg/kg o més?)
3. A més, vanco.
4. Dapto + cloxacil·lina
5. Vanco + piperacil·lina/tazobactam
6. Altres

Cas 1c

Mateixa pacient. A l'endemà. Els EF són SASM.

1. Li treiem el catèter i prou (nous HC)
2. A més, dapto (6mg/kg o més?)
3. A més, vanco.
4. Dapto + cloxacil·lina
5. Vanco + piperacil·lina/tazobactam
6. Altres

Cas 2

Home de 47 anys que consulta a urgències per febre, dispnea i tos amb expectoració purulenta. Fa dues setmanes diu que li van donar tamiflu a un altre centre per una suposada grip. Ha près 2 dies de levofloxací. Pneumònia bilobar a RxT. PA 130/80; FC 84; SpO2 (FiO2 31%): 93%. Als HC creixen EF en 16h.

1. Amoxi/clav
2. Ceftriaxona + azitro
3. Linezolid + dapto
4. Dapto + ceftarolina
5. Vanco + ceftriaxona
6. Altres

Cas 3

Home de 73 anys diabètic, en programa d'HD, que consulta a urgències per úlcera a un peu i febre. Rx osteomielitis calcani. Ha tingut tremolines clares durant la darrera sessió d'HD. No es coneixen col·lonitzacions prèvies. Aspecte sèptic.

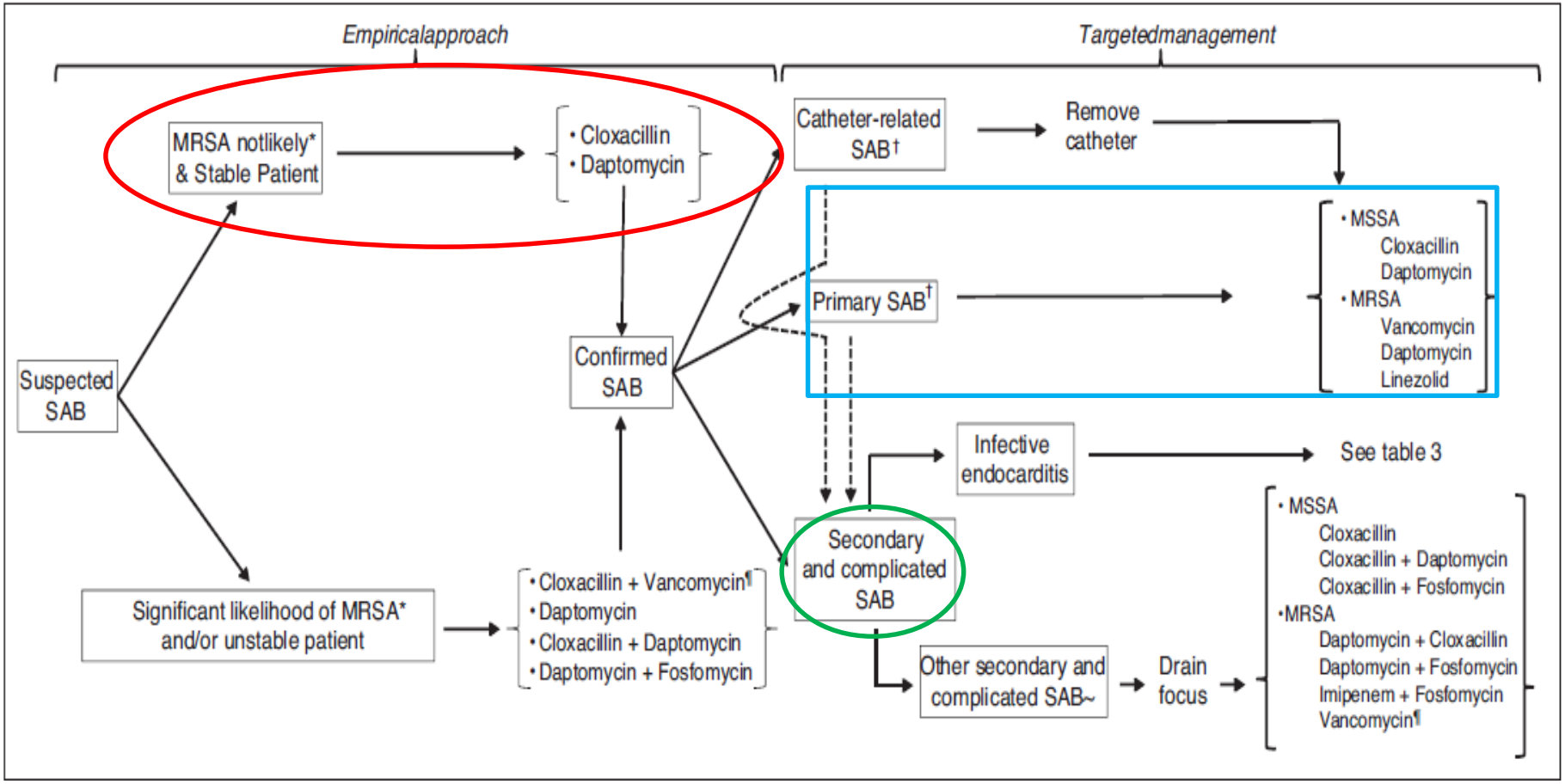
1. Linezolid
2. Dapto + ertapenem
3. Dapto + fosfomicina
4. Ceftriaxona + cloxacil·lina
5. Vanco + piperacil·lina/tazobactam
6. Altres

Consensus statement

Diagnosis and treatment of bacteremia and endocarditis due to *Staphylococcus aureus*. A clinical guideline from the Spanish Society of Clinical Microbiology and Infectious Diseases (SEIMC)

Francesc Gudiol[a], José María Aguado[b,*], Benito Almirante[c], Emilio Bouza[d], Emilia Cercenado[d], M. Ángeles Domínguez[e], Oriol Gasch[f], Jaime Lora-Tamayo[b], José M. Miró[g], Mercedes Palomar[h], Alvaro Pascual[i], Juan M. Pericas[g], Miquel Pujol[a], Jesús Rodríguez-Baño[i], Evelyn Shaw[a], Alex Soriano[j], Jordi Vallés[k]

Enferm Infecc Microbiol Clin. 2015,



Quan es recomana el ttx combinat en les guies de la SEIMC?

- Empíric:
  - Quan es sospita SARM (nosocomial, col·lonització prèvia, HD, residències, úlceres cutànies cròniques, CVC)
  - Vanco + cloxa
  - Dapto + BL si: sepsis greu/XS, ús de vanco en els 30 dies previs, IR, alta prevalència local de soques amb CMI vanco ≥1.5 mg/L
- Associada a catèter vascular
  - Quan la CMI de vancomicina és ≥1.5 mg/L per Etest si HC positius a les 72h o no milloria clínica (dapto + cloxa)
- Bacterièmia complicada:
  - Cloxa+dapto, cloxa+fosfo (SASM): persistència de febre o no milloria clínica, fracàs microbiològic, CMI vanco ≥1.5 mg/L
  - Dapto+fosfo, dapto+cloxa, fosfo+imipenem (SARM): sepsis greu/XS, bacterièmia persistent quan ja s'administren dosis de dapto 10mg/kg

Quan més?

- Quan el pacient sigui portador de DIC
- Sempre que estigui greu (encara que sigui una BAC, especialment a partir del 3r dia d'ingrés)
- Quan el focus sigui desconegut (bacterièmia primària)
- Pacient jove (amb EI dreta) per SAMS
- (No associar dapto + rifa/genta si infecció alt inòcul- bàsicament EI- per SARM)

Durant quant temps?

- SASM: 3-5 dies (fins a milloria clínica o HC negatius) si combinació amb penicilina antiestafilocòcica.
- SARM: 2 setmanes mínim (excepció: BAC no complicada)

Staphylococcus aureus bloodstream infection: A pooled analysis of five prospective, observational studies

Achim J. Kaasch [a,*], Gavin Barlow [b], Jonathan D. Edgeworth [c], Vance G. Fowler [d], Martin Hellmich [e], Susan Hopkins [f], Winfried V. Kern [g], Martin J. Llewelyn [h], Siegbert Rieg [g], Jesús Rodriguez-Baño [i,j], Matthew Scarborough [k], Harald Seifert [a], Alex Soriano [l], Robert Tilley [m], M. Estée Török [n], Verena Weiß [e], A.Peter R. Wilson [o], Guy E. Thwaites [c,p], on behalf of ISAC, INSTINCT, SABG, UKCIRG, and Colleagues[p]

Journal of Infection (2014) 68, 242–251

	Studies (for acronyms see Methods section)					Total (n = 3395)	p-Value
	INSTINCT (n = 912)	ES1 (n = 527)	ES2 (n = 168)	UKCIRG (n = 1459)	SABG (n = 329)		
Age at onset in years	66 (54–74)	64 (49–75)	67.5 (59–76)	64 (48–77)	59 (47–67)	64 (50–75)	<.0001
Male gender	606 (66.4)	351 (66.6)	102 (60.7)	928 (63.6)	180 (54.7)	2167 (63.8)	0.0019
MRSA	109 (12)	122 (23.1)	28 (16.7)	259 (17.8)	180 (54.7)	698 (20.6)	<.0001
Nosocomial SAB	443 (48.6)	270 (51.2)	95 (56.5)	508 (34.8)	67 (20.4)	1383 (40.7)	<.0001
Injection drug use	32 (3.5; 0)	14 (2.7; 0)	5 (3; 0)	125 (8.8; 2.3)	13 (4; 0)	189 (5.6; 1.0)	<.0001
Diabetes mellitus	226 (24.8; 0)	135 (25.6; 0)	65 (38.7; 0)	296 (20.7; 1.8)	134 (40.7; 0)	856 (25.4; 0.8)	<.0001
Dominant focus[a]							<.0001
Central venous catheter	172 (18.9)	106 (20.1)	27 (16.1)	266 (18.2)	66 (20.1)	637 (18.8)	
Peripheral venous catheter	78 (8.6)	94 (17.8)	39 (23.2)	85 (5.8)	9 (2.7)	305 (9.0)	
Skin and soft tissue infection	91 (10.0)	59 (11.2)	23 (13.7)	285 (19.5)	44 (13.4)	502 (14.8)	
Endocarditis	97 (10.6)	53 (10.1)	11 (6.5)	83 (5.7)	38 (11.6)	282 (8.3)	
Osteoarticular infection[b]	150 (16.4)	39 (7.4)	12 (7.1)	213 (14.6)	42 (12.8)	456 (13.4)	
Pneumonia	39 (4.3)	31 (5.9)	12 (7.1)	54 (3.7)	42 (12.8)	178 (5.2)	
Other focus[c]	105 (11.5)	39 (7.4)	15 (8.9)	199 (13.6)	36 (10.9)	394 (11.6)	
Focus not identified	180 (19.7)	106 (20.1)	29 (17.3)	274 (18.8)	52 (15.8)	641 (18.9)	
Echocardiography performed[d]	510 (55.9; 0)	228 (43.3; 0.2)	74 (44; 0)	822 (58.6; 3.8)	261 (79.3; 0)	1895 (56.8; 1.7)	<.0001
Outcome							
Length of hospital stay in days[e]	18 (10–31; 0)	15 (8–26; 0)	16 (9–25; 0)	17 (9–32; 2.9)	10 (6–18; 0)	16 (8–29; 1.2)	<.0001
Death within 7 days[f]	67 (7.3)	44 (8.4)	21 (12.5)	157 (10.8)	28 (8.5)	317 (9.4)	0.0312
Death within 14 days	102 (11.2)	68 (13)	34 (20.4)	238 (16.4)	50 (15.2)	492 (14.6)	0.0015
Death within 30 days	174 (19.2)	111 (21.2)	48 (29.4)	318 (22.2)	60 (18.3)	711 (21.2)	0.0418
Death within 90 days	276 (30.7)	128 (24.8)	62 (39.9)	425 (30.2)	72 (22.2)	963 (29.2)	0.0007

Increasing US Rates of Endocarditis With *Staphylococcus aureus*: 1999-2008

ARCH INTERN MED/VOL 172 (NO. 4), FEB 27, 2012

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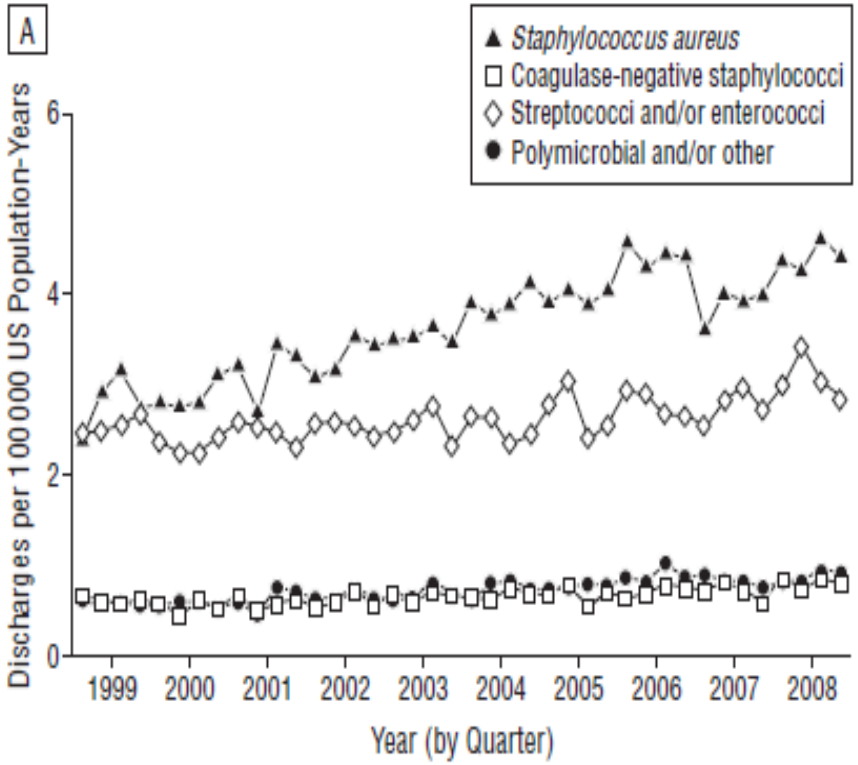
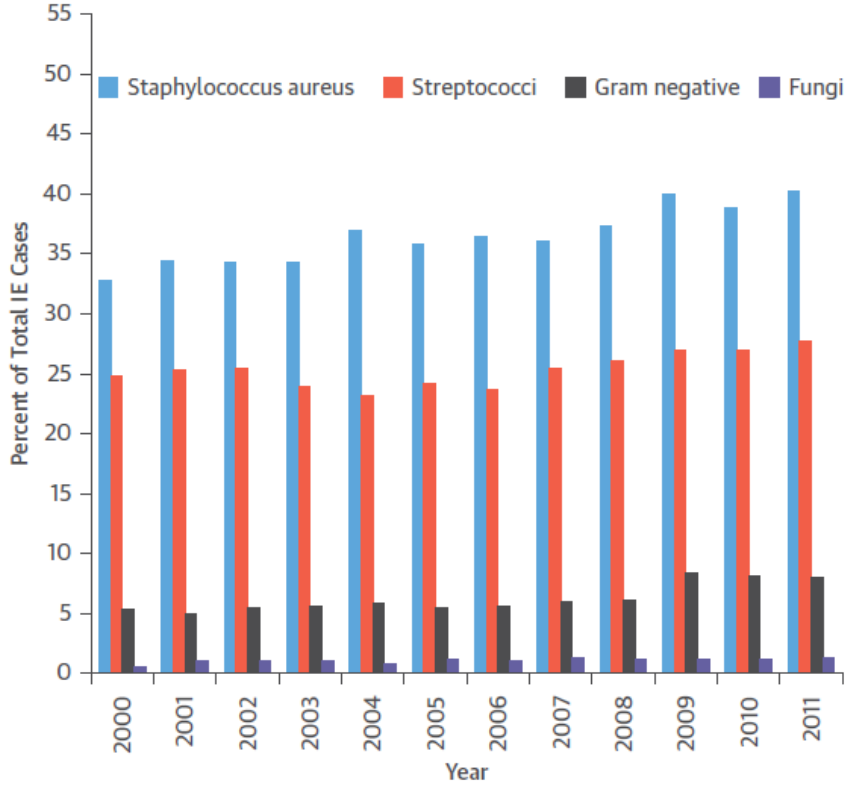


Trends in Infective Endocarditis Incidence, Microbiology, and Valve Replacement in the United States From 2000 to 2011

Sadip Pant, MD,* Nileshkumar J. Patel, MD,† Abhishek Deshmukh, MD,‡ Harsh Golwala, MD,* Nilay Patel, MD,§ Apurva Badheka, MD,‖ Glenn A. Hirsch, MD, MHS,* Jawahar L. Mehta, MD, PhD¶

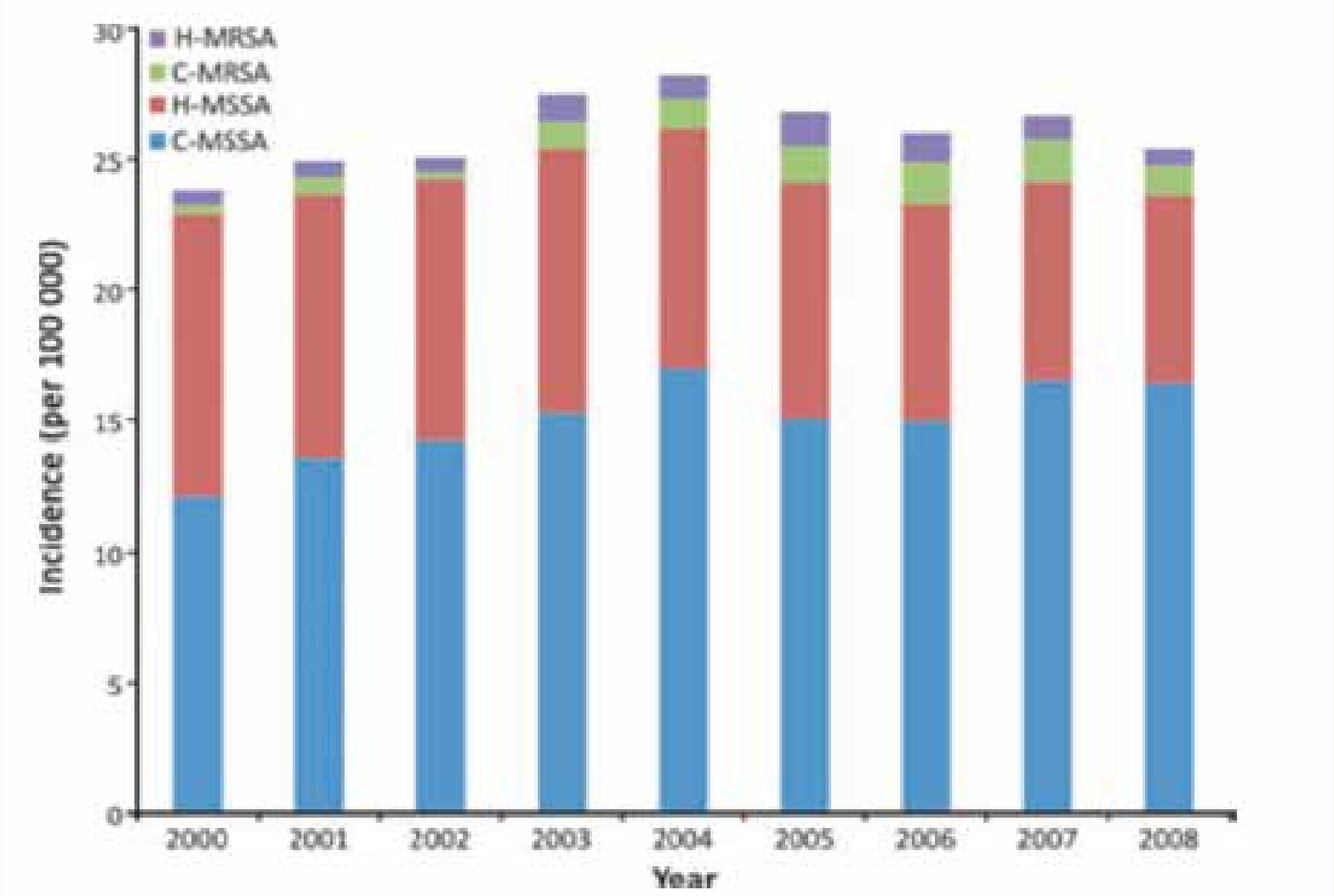
JACC VOL. 65, NO. 19, 2015



The changing epidemiology of *Staphylococcus aureus* bloodstream infection: a multinational population-based surveillance study

Clin Microbiol Infect 2013; **19**: 465–471

K. B. Laupland[1], O. Lyytikäinen[2], M. Søgaard[3], K. J. Kennedy[4], J. D. Knudsen[5], C. Ostergaard[6], J. C. Galbraith[7], L. Valiquette[8], G. Jacobsson[9], P. Collignon[4], and H. C. Schønheyder[3] for the International Bacteremia Surveillance Collaborative*



Worldwide decrease in methicillin-resistant *Staphylococcus aureus*: do we understand something?

Clin Microbiol Infect 2015; **21**: 515–517

J.-M. Rolain, C. Abat, P. Brouqui and D. Raoult

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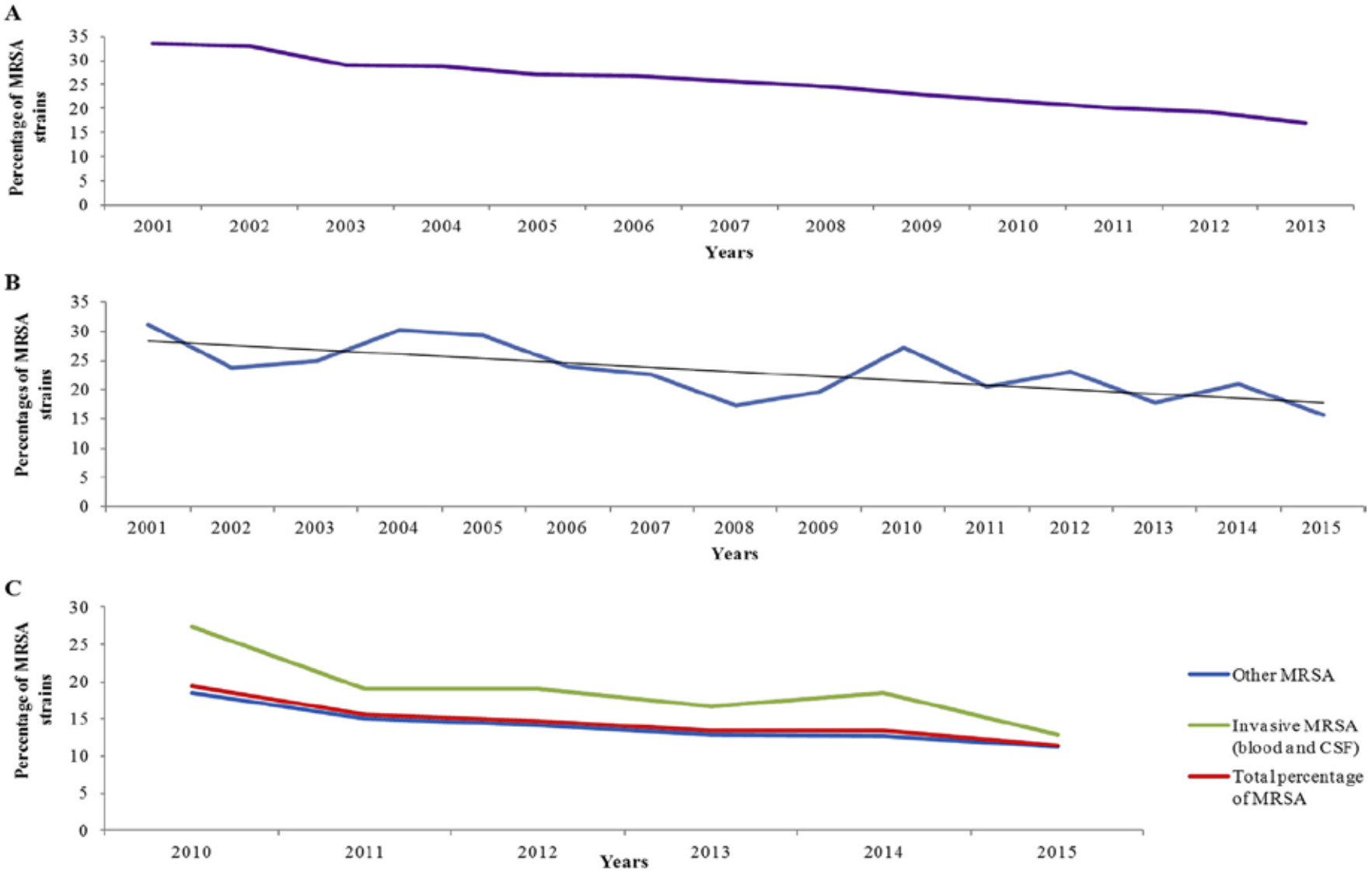
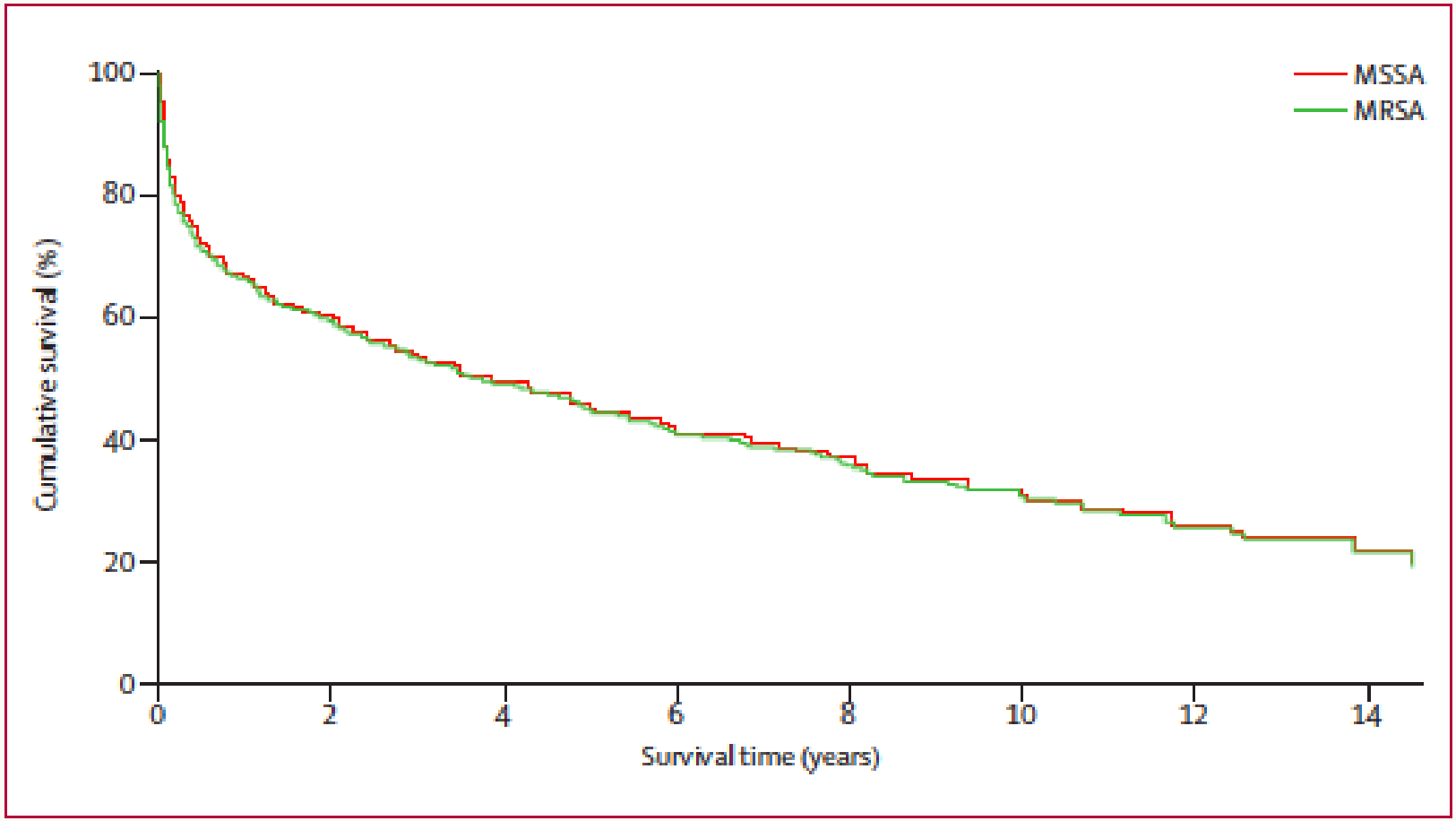


A comparison of long-term outcomes after meticillin-resistant and meticillin-sensitive *Staphylococcus aureus* bacteraemia: an observational cohort study

Lai Kin Yaw, James Owen Robinson, Kwok Ming Ho

Lancet Infect Dis 2014;
14: 967–75



Staphylococcus aureus bloodstream infection: A pooled analysis of five prospective, observational studies

Achim J. Kaasch [a,*], Gavin Barlow [b], Jonathan D. Edgeworth [c], Vance G. Fowler [d], Martin Hellmich [e], Susan Hopkins [f], Winfried V. Kern [g], Martin J. Llewelyn [h], Siegbert Rieg [g], Jesús Rodriguez-Baño [i,j], Matthew Scarborough [k], Harald Seifert [a], Alex Soriano [l], Robert Tilley [m], M. Estée Török [n], Verena Weiß [e], A.Peter R. Wilson [o], Guy E. Thwaites [c,p], on behalf of ISAC, INSTINCT, SABG, UKCIRG, and Colleagues[p]

Journal of Infection (2014) 68, 242–251

Patients with an unidentified infective focus were significantly older (median age 68 vs. 63 years, $p < 0.0001$), had less injection drug use (3% vs. 6.2%, $p = 0.002$), less diabetes mellitus (19.9% vs. 26.7%, $p = 0.0004$), and a significantly poorer outcome (45.9% vs. 25.3% crude 90-day mortality, $p < 0.0001$) than patients where a focus was assigned. Additionally, echocardiography was performed to a lesser extent (44.0% vs. 59.7%,

	7-day mortality		14-day mortality		30-day mortality		90-day mortality	
	Hazard ratio (95% CI)	p-Value	Hazard ratio (95% CI)	p-Value	Hazard ratio (95% CI)	p-Value	Hazard ratio (95% CI)	p-Value
Age at onset	1.03 (1.03–1.04)	<.0001	1.03 (1.03–1.04)	<.0001	1.03 (1.03–1.04)	<.0001	1.03 (1.03–1.04)	<.0001
Male gender	0.81 (0.65–1.02)	0.07	0.90 (0.75–1.08)	0.27	0.96 (0.83–1.12)	0.62	1.01 (0.88–1.15)	0.92
MRSA	1.59 (1.23–2.06)	0.0004	1.43 (1.16–1.76)	0.001	1.46 (1.22–1.74)	<.0001	1.61 (1.38–1.87)	<.0001
Nosocomial SAB	0.96 (0.76–1.21)	0.74	1.10 (0.92–1.33)	0.29	1.12 (0.97–1.31)	0.13	1.16 (1.02–1.32)	0.03
Injection drug use	0.72 (0.42–1.23)	0.23	0.52 (0.31–0.85)	0.009	0.55 (0.36–0.83)	0.004	0.53 (0.37–0.76)	0.0005
Diabetes mellitus	1.08 (0.84–1.39)	0.56	1.05 (0.86–1.29)	0.63	1.14 (0.97–1.35)	0.12	1.08 (0.94–1.25)	0.29
Dominant focus[a]								
Peripheral venous catheter	0.89 (0.45–1.76)	0.74	1.06 (0.62–1.83)	0.83	1.20 (0.81–1.78)	0.37	1.10 (0.80–1.52)	0.56
Skin and soft tissue infection	1.15 (0.68–1.96)	0.60	1.49 (0.97–2.27)	0.07	1.38 (0.99–1.93)	0.05	1.30 (0.99–1.70)	0.06
Endocarditis	2.25 (1.32–3.83)	0.003	3.11 (2.04–4.74)	<.0001	3.09 (2.24–4.27)	<.0001	2.70 (2.07–3.53)	<.0001
Osteoarticular infection	0.84 (0.46–1.54)	0.57	1.07 (0.67–1.73)	0.77	1.27 (0.90–1.80)	0.17	1.24 (0.94–1.64)	0.12
Pneumonia	6.51 (4.04–10.49)	<0.0001	7.08 (4.74–10.56)	<0.0001	5.38 (3.87–7.48)	<0.0001	4.66 (3.53–6.16)	<.0001
Other focus	1.75 (1.05–2.92)	0.03	2.23 (1.48–3.37)	0.0001	1.82 (1.30–2.53)	0.0004	1.68 (1.28–2.20)	0.0002
Focus not identified	5.17 (3.44–7.77)	<.0001	5.59 (3.96–7.89)	<.0001	4.27 (3.25–5.60)	<.0001	3.45 (2.76–4.31)	<.0001

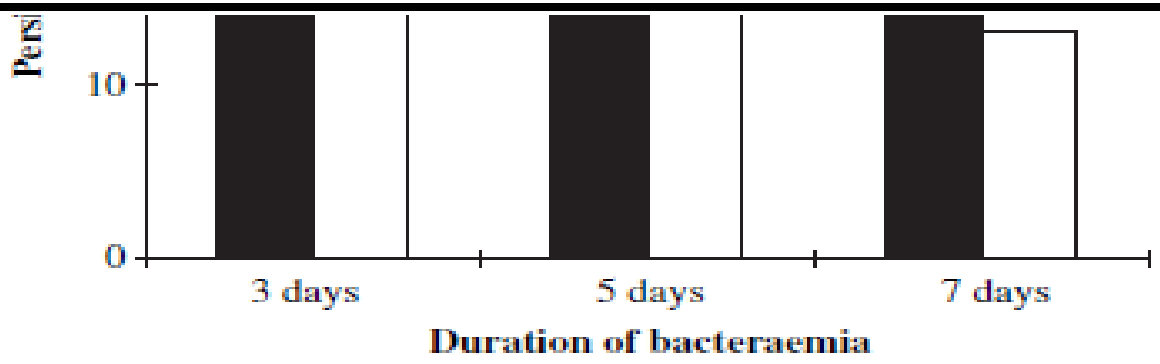
Follow-up in days

Outcome of inappropriate empirical antibiotic therapy in patients with *Staphylococcus aureus* bacteraemia: analytical strategy using propensity scores

S.-H. Kim,[1] W.-B. Park,[1] C.-S. Lee,[1] C.-I. Kang,[1] J.-W. Bang,[1] H.-B. Kim,[1] N.-J. Kim,[1] E.-C. Kim,[2,3] M. D. Oh[1,3] and K.-W. Choe[1,3]

Clin Microbiol Infect 2006; 12: 13–21

	Odds ratio (95% CI)	p
Methicillin resistance	21.8 (10.2–46.7)	< 0.001
Haematological malignancy	3.2 (1.4–7.5)	0.008
Long hospital stay before bactaeremia (≥ 2 weeks)	2.2 (1.1–4.3)	0.03
Previous MRSA colonisation	0.3 (0.1–0.7)	0.007



Predictive factors for early mortality among patients with methicillin-resistant *Staphylococcus aureus* bacteraemia

O. Gasch[1]*, M. Camoez[1], M. A. Domínguez[1], B. Padilla[2], V. Pintado[3], B. Almirante[4], J. A. Lepe[5], M. Lagarde[6], E. Ruiz de Gopegui[7], J. A. Martínez[8], M. Montejo[9], J. Torre-Cisneros[10], A. Arnáiz[11], M. A. Goenaga[12], N. Benito[13], J. Rodríguez-Baño[14] and M. Pujol[1] on behalf of the REIPI/GEIH Study Groups†

J Antimicrob Chemother 2013

Clinical characteristics			
age (years)	>70	0.01	2.77 (1.11–6.89)
gender	female	0.84	
Charlson score	>5	0.39	
McCabe scale	non-fatal		
	ultimately fatal	0.03	
	rapidly fatal	<0.01	10.38 (3.13–34.4)
Pitt score	>3	<0.01	13.36 (4.46–39.9)
acquisition	nosocomial		
	non-nosocomial[a]	0.031	
source	vascular catheter		
	skin and soft tissues	0.51	
	surgical site infection	0.46	
	endocarditis	0.40	
	lower respiratory tract	<0.01	
	unknown	<0.01	5.16 (1.67–15.9)
foreign body presence		0.03	
Microbiological studies			
agr type	I		
	II	0.11	
	III	0.76	
PFGE type	12		
	4	0.06	
	5	0.03	
	2	0.01	
clonal complex	5[b]		
	8	<0.01	
	22	0.17	
	other	0.08	
PVL		0.85	
vancomycin MIC	≥1.5 (mg/L)	0.08	
Initial treatment (<48 h)			
source drainage		<0.01	
inappropriate initial antibiotic		<0.01	3.88 (1.55–9.73)

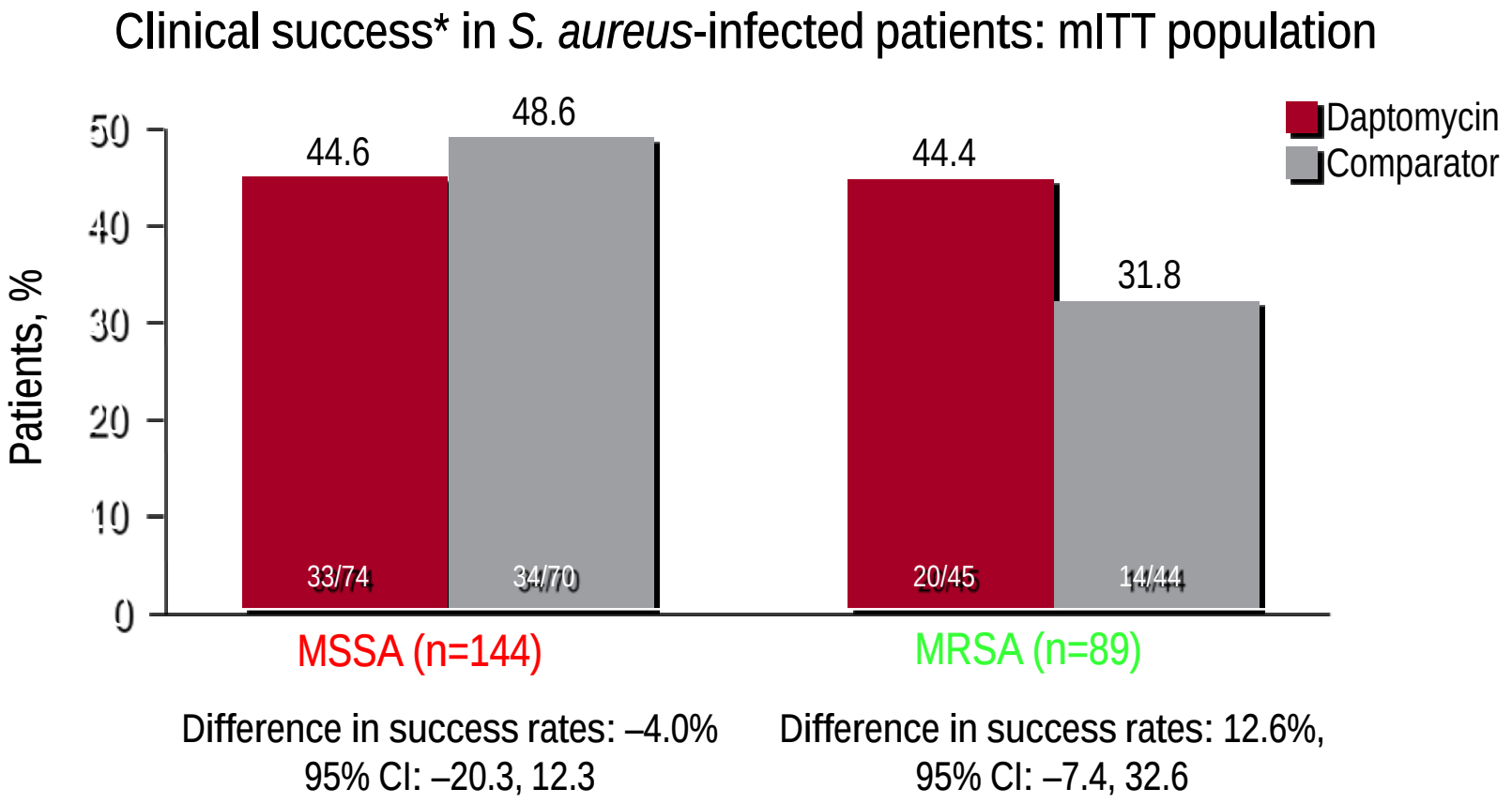
Predictive factors for mortality in patients with methicillin-resistant *Staphylococcus aureus* bloodstream infection: impact on outcome of host, microorganism and therapy

Clin Microbiol Infect 2013; 19: 1049–1057

O. Gasch[1], M. Camoez[1], M. A. Dominguez[1], B. Padilla[2], V. Pintado[3], B. Almirante[4], J. Molina[5], F. Lopez-Medrano[6], E. Ruiz[7], J. A. Martinez[8], E. Bereciartua[9], F. Rodriguez-Lopez[10], C. Fernandez-Mazarrasa[11], M. A.Goenaga[12], N. Benito[13], J. Rodriguez-Baño[14], E. Espejo[15], M. Pujol[1] and on behalf of REIPI/GEIH Study Groups*

				Univariate		Multivariate analysis with microdilution vancomycin MIC ≥ 1.5		Multivariate analysis with *E*-test vancomycin MIC ≥ 1.5
		Appropriate initial antibiotic *n* (%)	Inappropriate initial antibiotic *n* (%)	Univariate OR	Univariate p-Value			Multivariate OR (95% CI)
Age	>70	193 (52.3)	117 (58.2)	1.27	0.18			1.11 (0.76–1.63)
Gender	Female	126 (34.0)	65 (32.3)	0.93	0.65			1.01 (0.68–1.51)
Charlson score	>5	96 (26.1)	65 (32.3)	1.35	0.11			
McCabe	Non-fatal disease	183 (49.7)	94 (47.5)					
	Ultimately fatal	136 (37.0)	71 (35.9)	1.02	0.93			
	Rapidly fatal	49 (13.3)	33 (16.7)	1.31	0.29			
Pitt	≤3	287 (77.8)	166 (83.8)	0.68	0.09			1.68 (1.02–2.79)
Foreign body presence		187 (50.4)	80 (39.8)	0.65	0.015			1.27 (0.79–2.03)
Source								
	Skin and soft tissues	47 (12.7)	34 (16.9)	2.37	0.02			2.58 (1.35–4.90)
	Surgical site infection	24 (6.5)	12 (6.0)	1.64	0.2			
	Urinary tract	20 (5.4)	8 (4.0)	1.3	0.55			
	Lower respiratory tract	35 (9.4)	33 (16.4)	3.09	<0.001			3.55 (1.76–7.15)
	Unknown	41 (11.1)	49 (24.4)	3.91	<0.001			4.22 (2.25–7.93)
Distant secondary focus		76 (20.7)	25 (12.5)	0.65	0.015			0.64 (0.37–1.10)
Acquisition	Nosocomial	222 (60.0)	111 (55.8)					
	Non-nosocomial*	148 (40.0)	88 (44.2)	1.19	0.33			
	CC5 †	129(75.0)	271(77.7)	0.64	0.049	0.52 (0.33–0.83)		0.58 (0.36–0.94)
	CC22	12 (7.0)	37 (10.6)	0.50	0.032	0.45 (0.22–0.89)		0.46 (0.23–0.91)
	Other	12 (7.0)	21 (6.0)	0.75	0.40			
PVL		5 (2.9)	9 (2.5)	1.00	0.99			
Microdilution vancomycin MIC ≥ 1.5		7 (4.0)	11 (3.1)	1.56	0.13	1.71 (0.92–3.19)		
Microdilution vancomycin MIC ≥ 2		1 (0.6)	2 (0.6)	0.78	0.76			
E-test vancomycin MIC ≥ 1.5		69 (39.7)	160(44.9)	0.78	0.08			0.78 (0.58–1.05)
E-test vancomycin MIC ≥ 2		20 (11.5)	39 (11.0)	0.85	1.04			
Initial treatment (<48 hours)								
Source drainage or catheter withdrawal		49 (27.4)	153(40.5)	0.64	0.002	0.93 (0.63–1.36)		0.89 (0.61–1.29)
Inppropriate initial antibiotic		72 (41.1)	125(33.2)	1.39	0.014	1.39 (1.04–1.86)		1.37 (1.02–1.83)

Efficacy of daptomycin at 6 mg/kg for SAB/IE



*Clinical success at the visit 6 weeks after the end of therapy. Failure defined as clinical failure, microbiological failure, death, failure to obtain blood culture, receipt of potentially effective non-study antibiotics or premature discontinuation of the study medication

Fowler VG et al. *N Engl J Med* 2006;355:653–665

Vancomycin MICs ≥1 µg/ml: Outcomes against MRSA improved with Daptomycin in 2 cohort studies

- Patients with MRSA BSI with higher vancomycin MICs (>1 µg/ml) and failing on vancomycin have a higher probability of survival at 60 days when treated with daptomycin: *p*=0.022[1]

Outcomes with vancomycin MIC >1 µg/ml in patients with MRSAB[2]

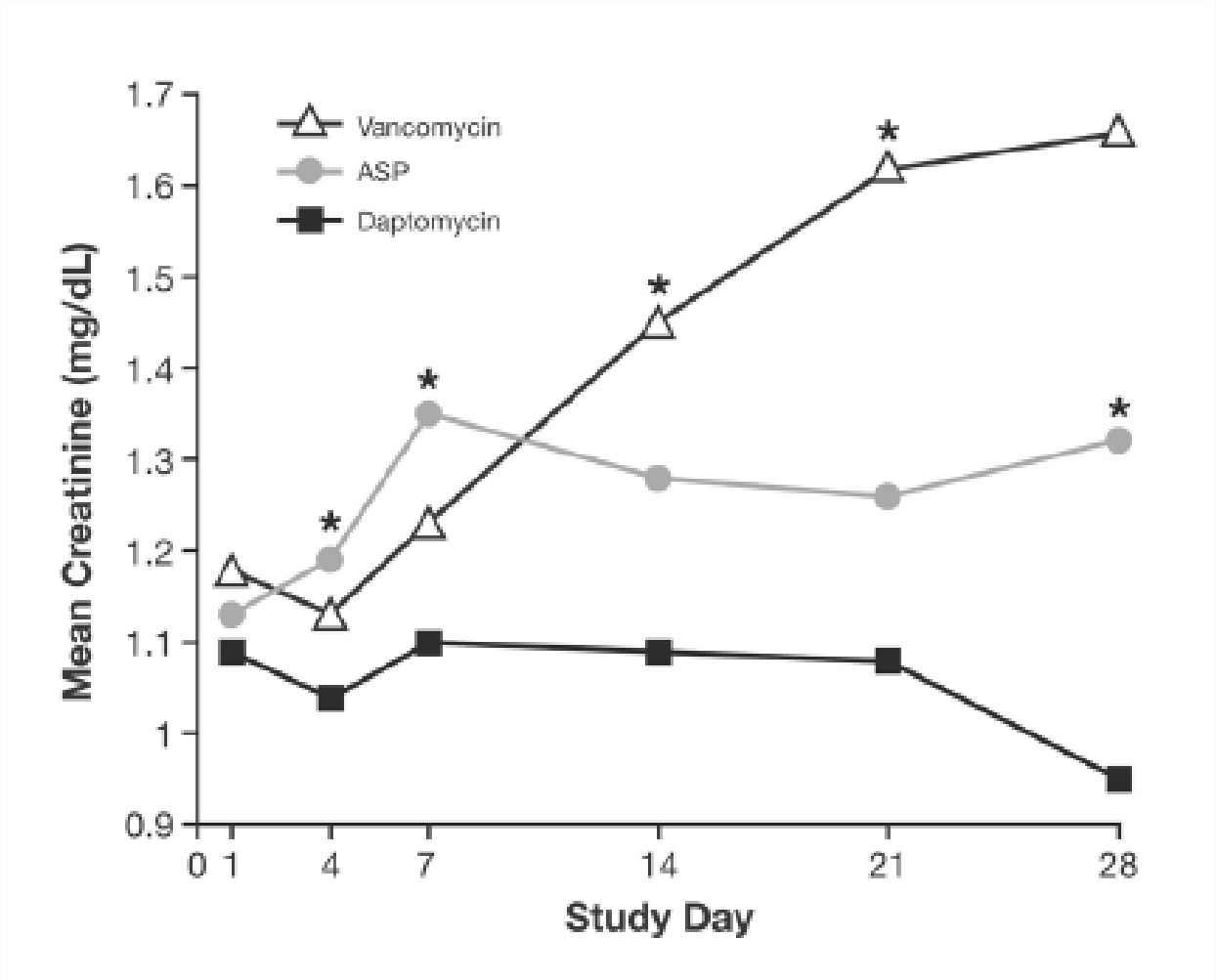
Factor	Daptomycin (N=85)	Vancomycin (N=85)	*P*-value
Clinical failure, n	17 (20.0)	41 (48.2)	<0.001
Mortality at 30 days, n	3 (3.5)	11 (12.9)	0.047
Persistent bacteraemia, n	16 (18.8)	36 (42.4)	0.001
Duration of bacteraemia, days	3 (2–5)	5 (3–8)	0.003
Length of stay, days	11 (8–18)	12 (8–17)	0.532
Duration of treatment, days	10 (8–17)	9 (6–16)	0.324
Recurrence of MRSAB within 30 days, n (%)	0 (0)	3 (4.1)	0.104

1. Moore CL *et al. Clin Infect Dis* 2011;54:51
2. Murray KP *et al. Clin Infect Dis* 2013;56:1562

Initial Low-Dose Gentamicin for *Staphylococcus aureus* Bacteremia and Endocarditis Is Nephrotoxic

Clinical Infectious Diseases 2009; 48:713–21

Sara E. Cosgrove,[1] Gloria A. Vigliani,[2] Marilyn Campion,[a] Vance G. Fowler, Jr.,[5] Elias Abrutyn,[7,b] G. Ralph Corey,[5,6] Donald P. Levine,[8] Mark E. Rupp,[9] Henry F. Chambers,[10] Adolf W. Karchmer,[3] and Helen W. Boucher[4]

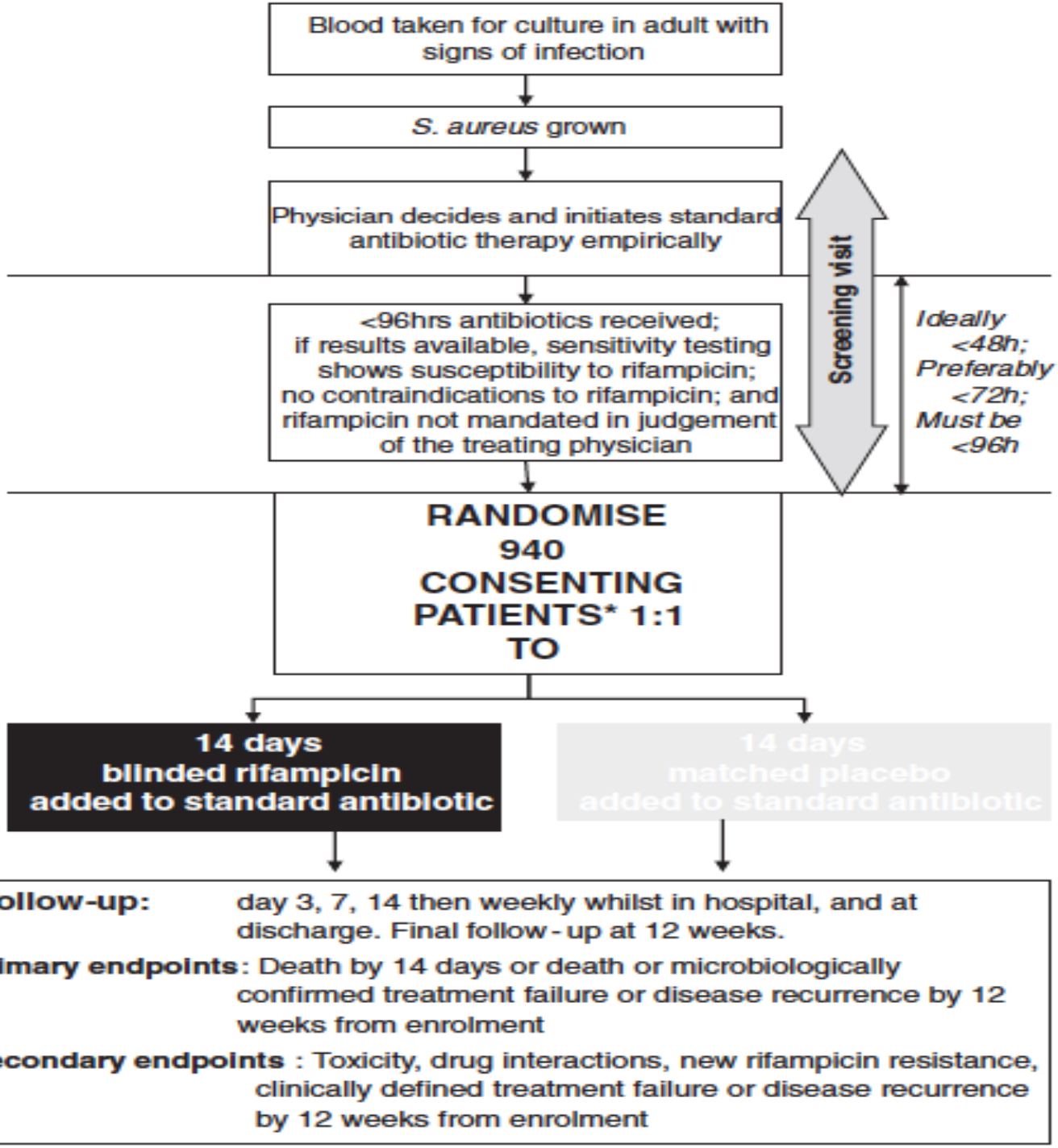


Addition of Gentamicin or Rifampin Does Not Enhance the Effectiveness of Daptomycin in Treatment of MRSA Experimental Endocarditis with a Vancomycin MIC of 2 µg/mL

Treatment group	No. of animals with sterile vegetation/ total (%)[b]	Median (range) IQR (log_{10} CFU/g of vegetation)[b]
Control[a]	0/15 (0)	10 (9.7–10)
Gentamicin	0/12 (0)	8.6 (8.1–9)
Rifampin	0/13 (0)	6.6 (5.2–10)
Daptomycin	10/15 (67)*†	0 (0–2)‡§
Daptomycin + gentamicin	9/15 (60)*¶	0 (0–2)‡‖
Daptomycin + rifampin	3/15 (20)†¶	3 (2–3.5)§‖

[a] The control animals were sacrificed 18 h after the infection was started.
[b] *, $P = 0.70$; †, $P = 0.01$; ‡, $P = 0.83$; §, $P = 0.02$; ¶, $P = 0.02$; ‖, $P = 0.04$. The symbols represent levels of statistical significance between two values with the same symbol.

Miró JM et al. *Antimicrob Agents Chemother*. 2009; 53:4172–4177


Blood taken for culture in adult with signs of infection
S. aureus grown
Physician decides and initiates standard antibiotic therapy empirically
<96hrs antibiotics received; if results available, sensitivity testing shows susceptibility to rifampicin; no contraindications to rifampicin; and rifampicin not mandated in judgement of the treating physician
Screening visit
Ideally <48h; Preferably <72h; Must be <96h
RANDOMISE 940 CONSENTING PATIENTS* 1:1 TO
14 days blinded rifampicin added to standard antibiotic
14 days matched placebo added to standard antibiotic
Follow-up: day 3, 7, 14 then weekly whilst in hospital, and at discharge. Final follow-up at 12 weeks.
Primary endpoints: Death by 14 days or death or microbiologically confirmed treatment failure or disease recurrence by 12 weeks from enrolment
Secondary endpoints : Toxicity, drug interactions, new rifampicin resistance, clinically defined treatment failure or disease recurrence by 12 weeks from enrolment

Improved Outcome with Early Rifampicin Combination Treatment in Methicillin-Sensitive *Staphylococcus aureus* Bacteraemia with a Deep Infection Focus – A Retrospective Cohort Study

Erik Forsblom*, Eeva Ruotsalainen, Asko Järvinen

PLOS ONE April 13, 2015

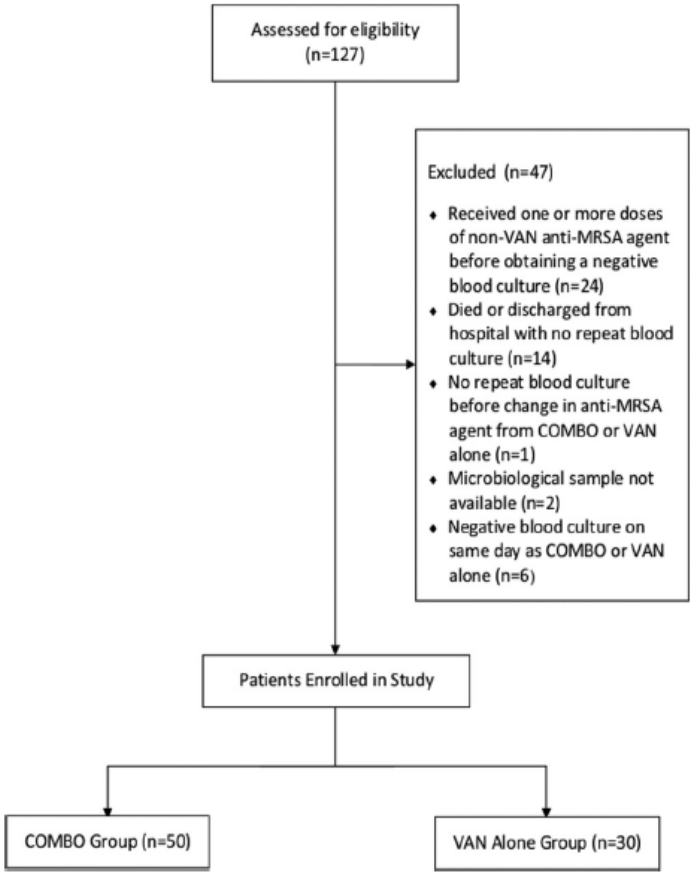
	Rifampicin therapy		Any length of rifampicin therapy vs. no rifampicin therapy	
Variables	No therapy n = 96 (27%)	Therapy of any length n = 261 (73%)	OR (95% CI)	p- value
SAB relapse [A]	2 (2)	2 (<1)	0.40 (0.06–2.89)	0.349
Mortality, at 28 days	16 (17)	28 (11)	0.60 (0.31–1.17)	0.130
Mortality, at 60 days	22 (23)	35 (13)	0.51 (0.28–0.93)	0.027
Mortality, at 90 days	25 (26)	41 (16)	0.53 (0.30–0.93)	0.026

AAC Journals.ASM.org

β-Lactams Enhance Vancomycin Activity against Methicillin-Resistant *Staphylococcus aureus* Bacteremia Compared to Vancomycin Alone

January 2014 Volume 58 Number 1

Thomas J. Dilworth,[a] Omar Ibrahim,[a] Pamela Hall,[b] Jora Sliwinski,[a] Carla Walraven,[c] Renée-Claude Mercier[a]



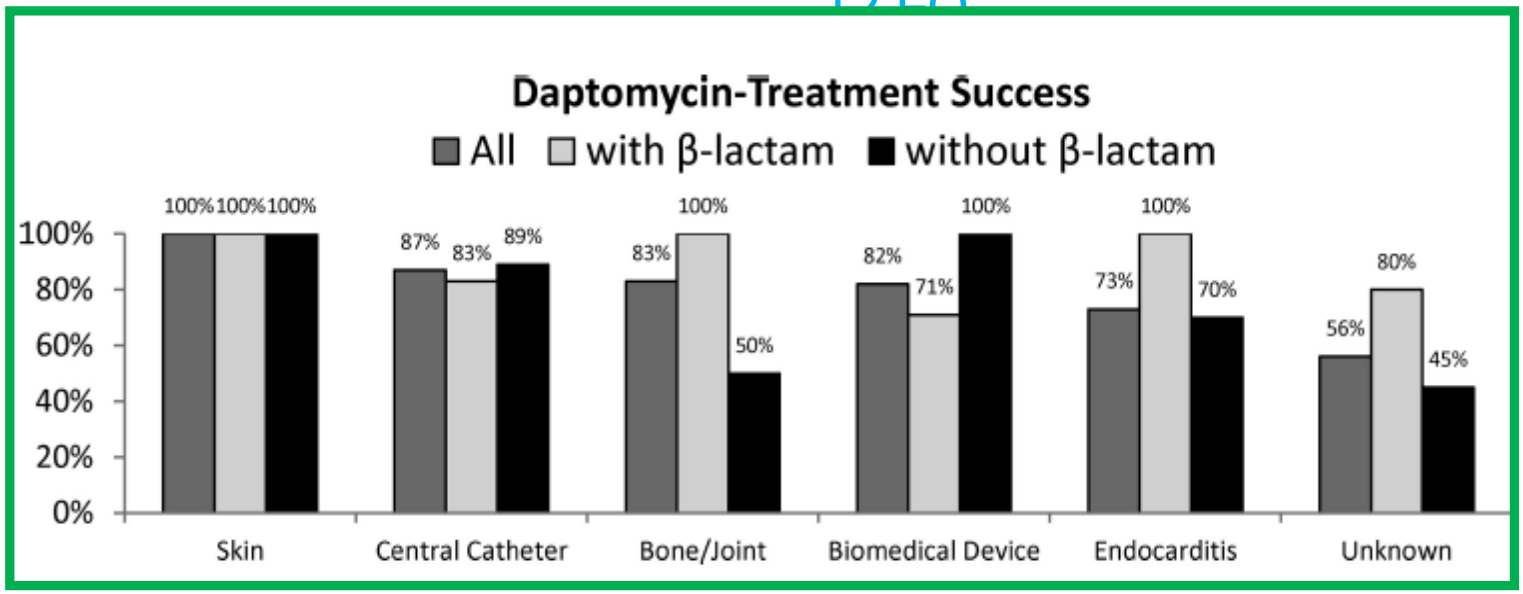
Variable[b]	Value for the variable[a] OR	95% CI	*P* value
Treatment group (Combo vs VAN alone)	5.15	1.21–29.7	0.026
Age (yr)	0.99	0.95–1.04	0.719
LOS (days)	1.04	0.99–1.14	0.101
Vancomycin serum level (mg/liter)[c]	0.97	0.93–1.01	0.136
Cancer	1.24	0.24–12.41	0.816
Hemodialysis	0.07	0.01–0.33	<0.001
Immunosuppression	3.51	0.39–465.03	0.317
Injection drug use	4.96	0.56–654.41	0.178
MRSA colonization	0.76	0.17–4.44	0.733
Endocarditis	1.02	0.24–5.88	0.985
Osteomyelitis	4.58	0.52–604.59	0.206
ICU admission	0.79	0.19–3.67	0.753
Ventilator use	1.46	0.29–14.56	0.676
Pitt bacteremia score of ≥4	1.07	0.82–1.69	0.653
MRSA strain (USA300 vs USA100)	2.52	0.62–11.67	0.197
agr functionality	1.08	0.18–4.77	0.920

Variable	Value for the variable[a] AOR	95% CI	*P* value
Treatment group (Combo vs VAN alone)	11.24	1.72–144.34	0.010
Vancomycin serum level (mg/liter)[b]	0.93	0.86–0.98	0.006
Hemodialysis	0.042	0.01–0.25	<0.001

Outcomes of Daptomycin alone or with Concomitant Beta-Lactams for SAB in Patients with mild or Moderate Renal Impairment

NO DIFFERENCES WERE FOUND REGARDING OUTCOMES BETWEEN MSSA AND MRSA

Factor	OR (95% CI)	*P* value
Unknown source of bacteremia	7.59 (1.55–37.2)	0.012
Moderate renal insufficiency (vs mild insufficiency)	9.11 (1.45–56.8)	0.018
Prior vancomycin treatment failure	11.2 (1.95–64.5)	0.007



Moise et al, AAC 2013

Reasons for Microbiological Failure in Patients with SAB/IE Treated with Daptomycin at 6 mg/kg

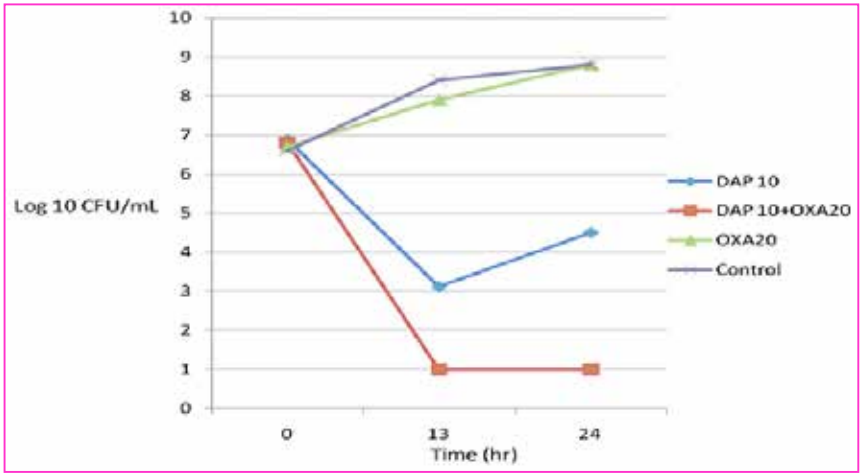
Fowler VG et al. N Engl J Med 2006;355:653–665

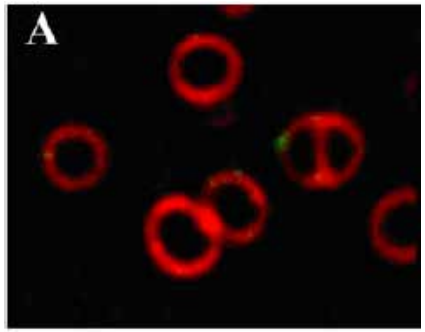
- 19 patients (16%) had microbiological failure.
  - Complications of endocarditis, 7 cases
  - Intravascular infections, 6 cases
  - Osteomyelitis or septic arthritis, 4 cases
  - Undrained abscesses, 2 cases

Þ Daptomycin MIC increased on therapy from 0.25 (5 isolates) or 0.5 (1) to 2.0 (5) and 4.0 (1) µg/mL.

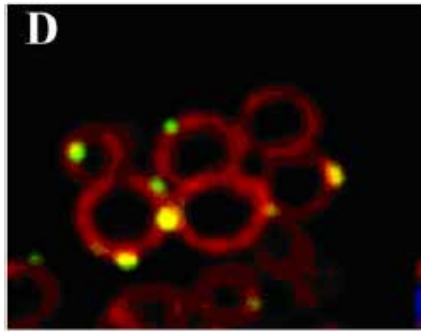
Daptomycin and β-lactams (Nafcillin)

- DAP + NAF as salvage regimen
  - 7 cases with persistent MRSA bacteremia (7-22 days)
  - DAP used as 2nd line agent in all
  - Only one case with DAP non-susceptibility
  - Bacteremia cleared with nafcillin (NAF)
- Why?
  - Increased daptomycin membrane binding with addition of NAF.
  - Nafcillin led to a reduction in the net positive surface charge.





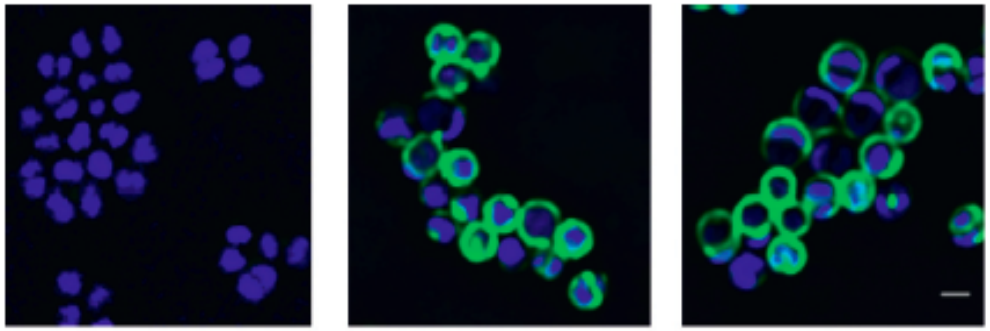
DAP (green) binding with & without NAF (yellow)

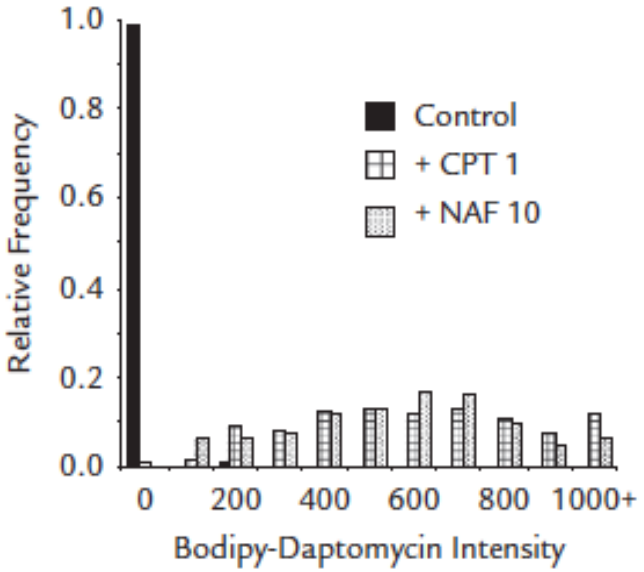


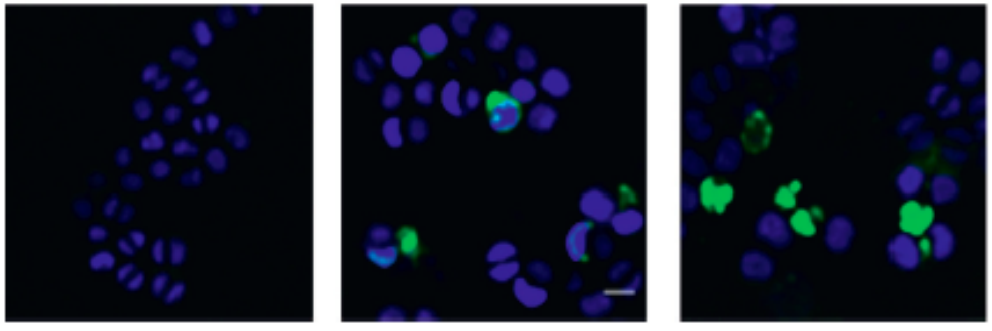
Dhand A et al. Clin Infect Dis. 2011;53:158-163.

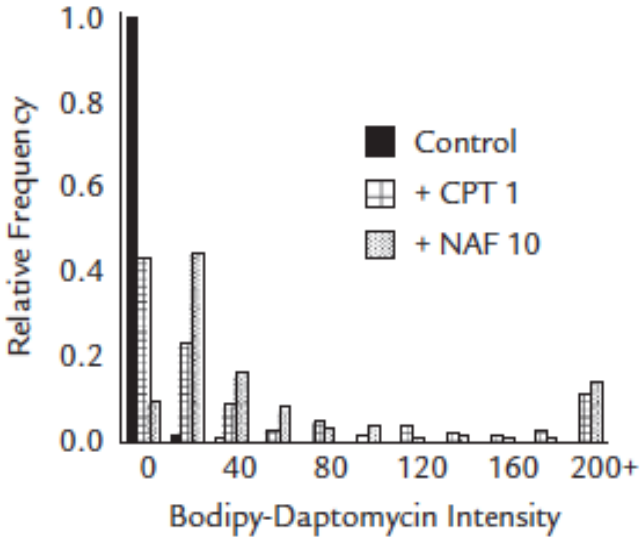
Antimicrobial Salvage Therapy for Persistent Staphylococcal Bacteremia Using Daptomycin Plus Ceftaroline

Clinical Therapeutics/Volume 36, Number 10, 2014

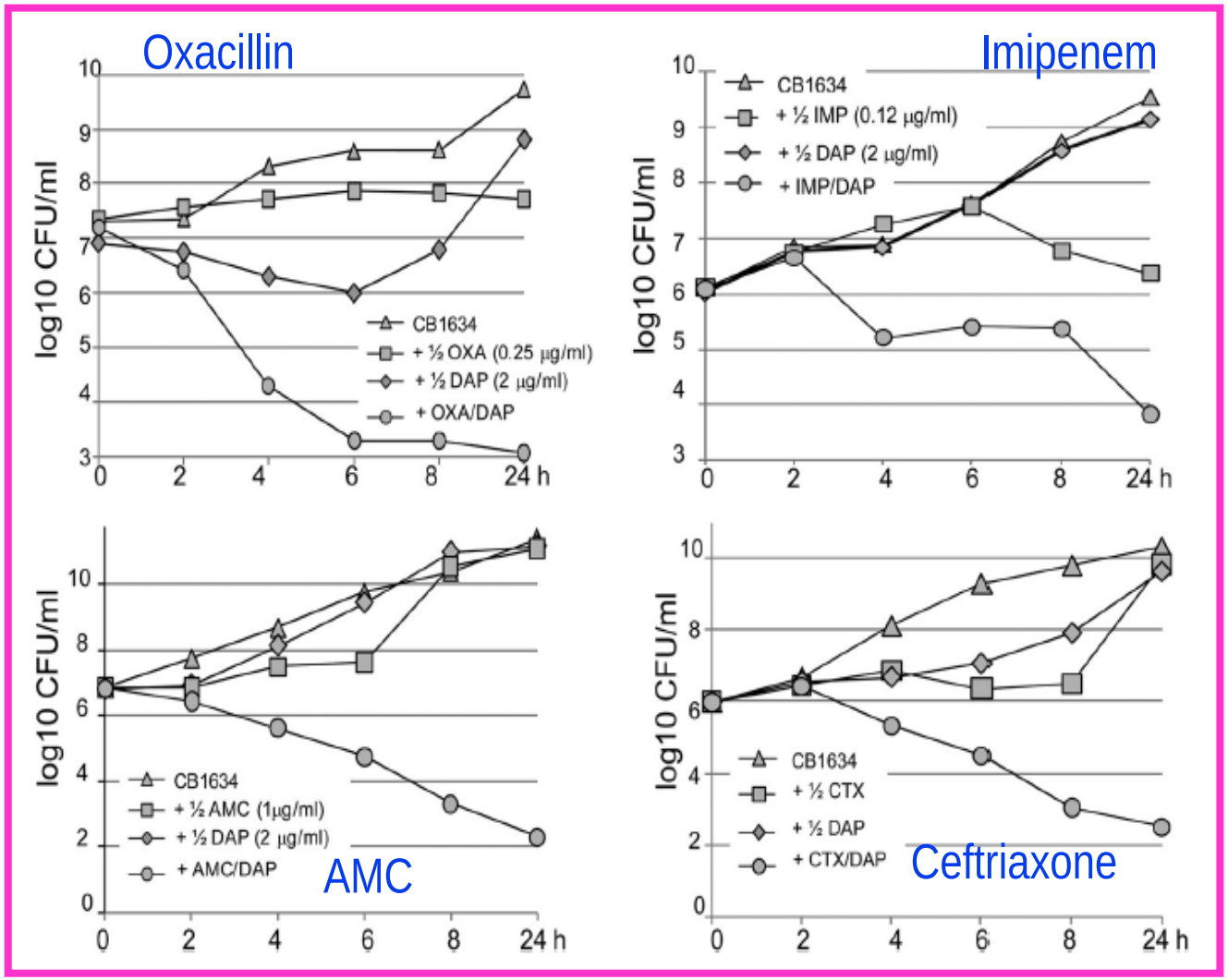








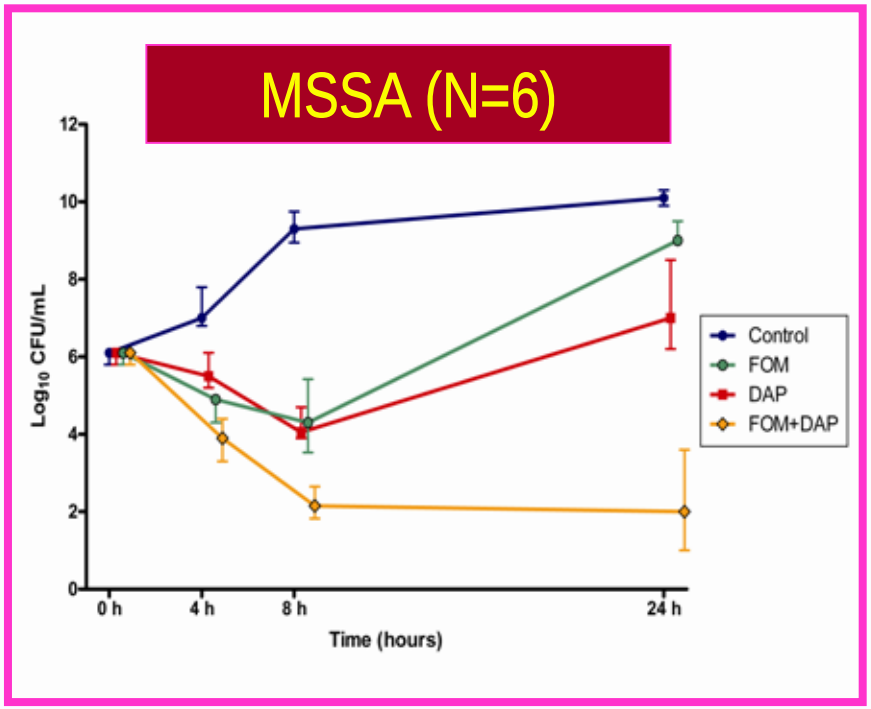
β-Lactams Increase the Antibacterial Activity of Daptomycin against Clinical MRSA Strains and Prevent Selection of Daptomycin-Resistance

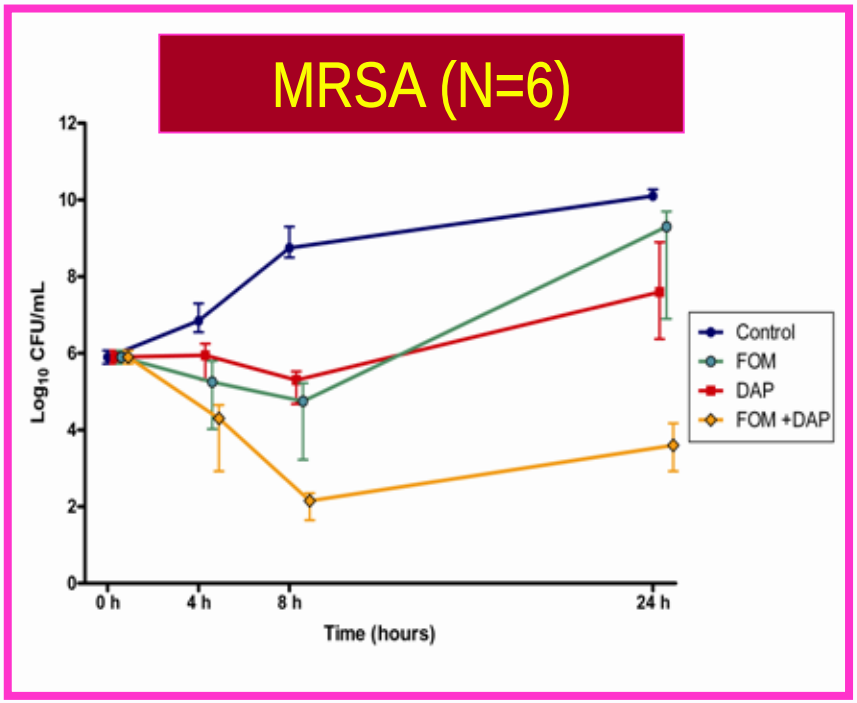


Mehta S et al. AAC. 2012; 56:6192.

Daptomycin plus Fosfomycin is Synergistic against Methicillin-susceptible (MSSA) and Methicillin-resistant *Staphylococcus aureus* (MRSA) Strains

Two patients with complicated MRSA NV IE and one patient with MSSA PVE were succesfully treated with the combination of daptomycin plus fosfomycin.





Miró JM et al. AAC. 2012; 56:4511-5

The Combination of Daptomycin plus Fosfomycin has Synergistic, Potent, and Rapid Bactericidal Activity against MRSA in a Rabbit Model of EE

Miró JM et al. 53rd ECCMID, Barcelona 2014

Treatment group	Animals with sterile vegetations/total (%)	Median log_{10} cfu/g of vegetation (IQR)
Control	0/12 (0)	10 (9.8–10)
Daptomycin (6 mg/kg/24 h)	13/18 (72)[a]	0 (0–1.5)[b]
Daptomycin (6 mg/kg/24 h) + cloxacillin (2 g/4 h)	14/16 (88)	0 (0–0)
Daptomycin (6 mg/kg/24 h) + fosfomycin (2 g/6 h)	16/16 (100)[a]	0 (0–0)[b]
Daptomycin (10 mg/kg/24 h)	14/15 (93)	0 (0–0)

[a] $P = .046$
[b] $P = .025$

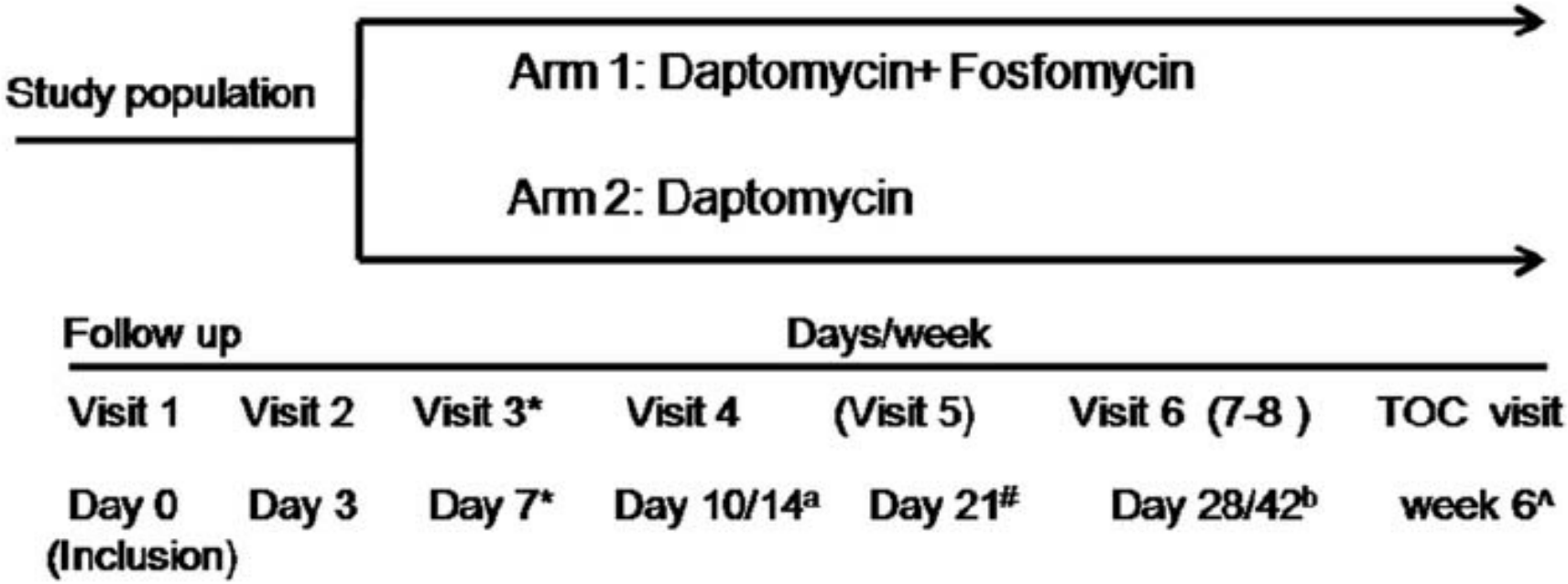
MIC MRSA STRAIN=2 µg/mL

BMJ Open

Daptomycin plus fosfomycin versus daptomycin monotherapy in treating MRSA: protocol of a multicentre, randomised, phase III trial

E Shaw,[1] J M Miró,[2] M Puig-Asensio,[3] C Pigrau,[3] F Barcenilla,[4] J Murillas,[5] G Garcia-Pardo,[6] E Espejo,[7] B Padilla,[8] A Garcia-Reyne,[9] J Pasquau,[10] J Rodriguez-Baño,[11] J López-Contreras,[12] M Montero,[13] C de la Calle,[2] V Pintado,[14] E Calbo,[15] O Gasch,[16] M Montejo,[17] M Salavert,[18] M J Garcia-Pais,[19] J Carratalà,[1] M Pujol,[1] on behalf of the Spanish Network for Research in Infectious Diseases (REIPI RD12/0015), Instituto de Salud Carlos III, Madrid, Spain, and GEIH (Hospital Infection Study Group)

N=240



Poster: B-063

Daptomycin (DAP) plus Fosfomycin are Synergistic and Bactericidal against Methicillin-Susceptible *Staphylococcus aureus* (MSSA) Experimental Endocarditis (EE).

C. García de la Mária, J.M. Pericás, J. Garcia Gonzalez, Y. Armero, A. Tellez, S. Ninot, M. Almela, E. Quintana, C. Falces, F. Marco, J. Llopis, D. Fuster, A. Moreno, J.M. Miró* and the Hospital Clínic Endocarditis Study Group#, Hospital Clínic-IDIBAPS, University of Barcelona, Barcelona, Spain.

*e-mail:

Treatment group	Animals with sterile vegetations/total (%)	Median log_{10} CFU/g of vegetation (IQR)
Control	0 / 10 (0)	9 (8.1 – 9.3)
Daptomycin 6mg/kg/24h	0 / 11 (0)[a,b]	2 (2 – 3.3)[d,e]
Daptomycin 6mg/kg/24h + Fosfomycin 2g/6h	8 / 11 (73)[a,c]	0 (0 – 0)[d]
Daptomycin 6mg/kg/24h + Cloxacillin 2g/4h	10 / 11 (91)[b,c]	0 (0 – 0)[e]

Ø **Introduction:**

- Ø Methicillin-suscept… infective endocardi… decades (*Tong et a…*
- Ø New antimicrobial … infections
- Ø Sakoulas et al ha… staphylococcal β-l… refractory MRSA ba…

Ø **Objective**:

- Ø Our group has sho… *vitro* against severa… patients with MRSA…

The aim of this study was to know the activity … cloxacillin (CLO) in the treatment of the experimental …

1. *IN VITRO* studies

1.1. Microorganisms:

For this study, a MSSA isolate (MSSA-678) was … isolated from infective endocarditis diagnosed pa…

1.2 MIC/MBC : Oxacillin (OXA), fosfomycin (FOM… microdilution and E-test methods according to th… DAP susceptibility testing was performed in Muell… methodology. FOM test broth medium (MHB) wa… methodology. *S. aureus* ATCC 29213 was used …

1.3 Time-killing curves (TKC) assay: TKC were… described criteria (*Isenberg, 2004*). An inoculum … tested were: 0.5 x MIC and 1 x MIC. - Synergy … the test tube with the combination and the test tu… organisms in the presence of the combination h… the drugs had to be present in a concentration … when used alone. Bactericidal activity was defin… the initial inoculum.

All the strains recovered from the TKC assay and… detect decreased susceptibility to daptomycin.

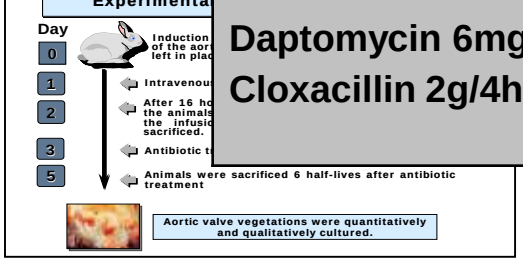
2. *IN VIVO* studies

2.1. Human-like pharmacokinetics studies

Antibiotics, simulating CLO 2 g/4h, FOM 2g/6h … controlled infusion pump in order to reproduce th…

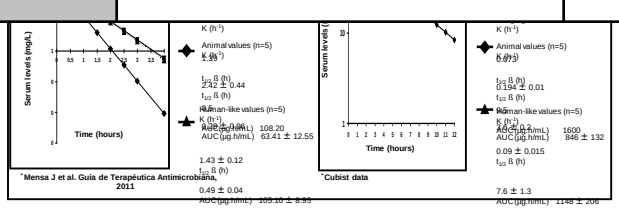
2.2. Induction of endocarditis and installation …

Experimental aortic valve IE was induced accor… *Med. 1970;42: 394-410*). At baseline, another ca… the jugular vein and tunnelled subcutaneously t… was connected to a swivel and then to a compute…



3. Treatment groups:

- DAP (simulating 6 mg/Kg/d iv)
- DAP+CLO (simulating 6 mg/Kg/d iv + simulating 2 g/4h iv)
- DAP+FOM (simulating 6 mg/Kg/d iv + simulating 2 g/6h iv)



Research in Infectious Diseases [REIPI RD06/0008])

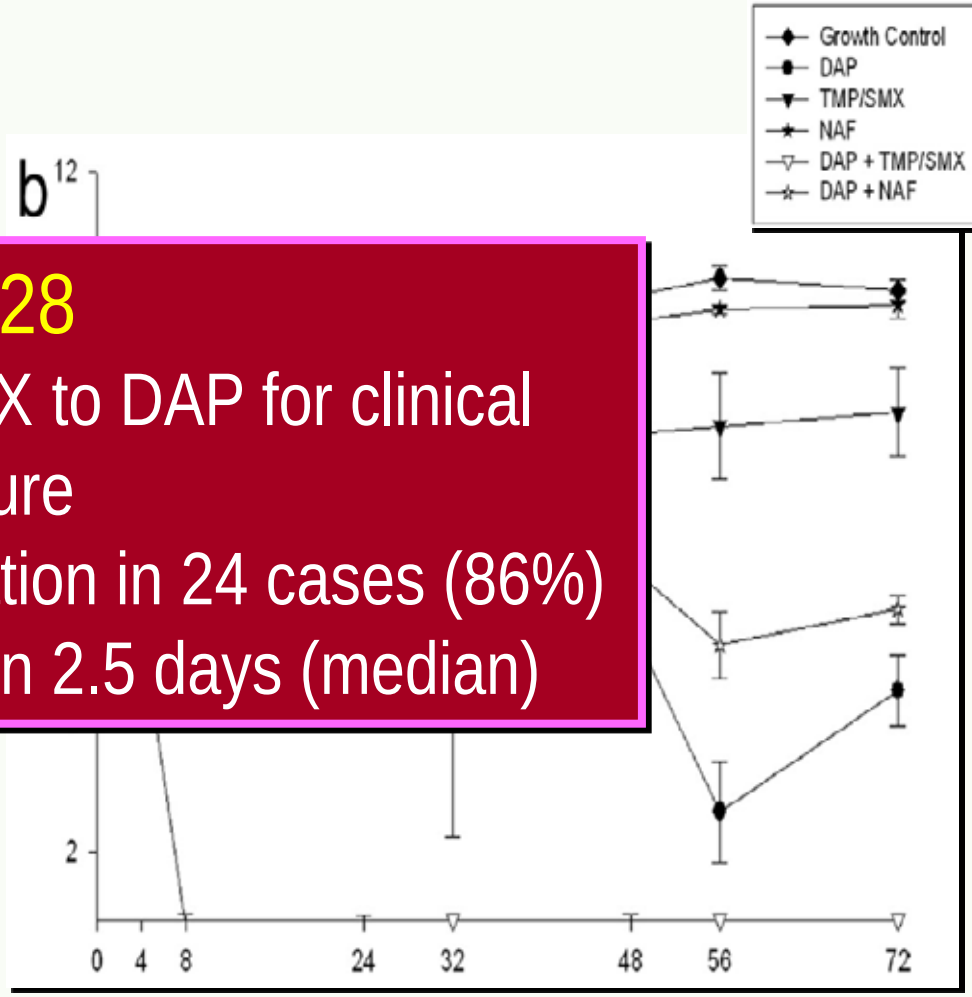
- Ø Fundació Clínic per a la Recerca Biomèdica, Barcelona.
- Ø Fundación Máximo Soriano, Barcelona.
- Ø Cubist provided the daptomycin powder.

#The members of the **Hospital Clinic Endocarditis Study Group**, Hospital Clínic-IDIBAPS, University of Barcelona School of Medicine, Barcelona, Spain, are: J. M. Miró, J.M Pericás, A. Moreno, C. García-de-la-Mària, Y. Armero, A. Téllez and J. M. Gatell (Infectious Diseases Service); F. Marco, M. Almela, and J. Vila (Microbiology Service); E. Quintana, D. Pereda, M. Castellà, S. Ninot and C. A. Mestres (Cardiac Surgery Service); C. Falces, J. C. Paré, M. Azqueta, M. Sitges (Cardiology Service); D. Fuster and U. Granados (Nuclear Medicine Service); J. Ramírez and T. Ribalta (Pathology Department); M. Brunet (Toxicology Service); D. Soy (Pharmacy Service); and J. Llopis (Statistics).

Impact of the Combination of Daptomycin and Trimethoprim-Sulfamethoxazole on Clinical Outcomes in Methicillin-Resistant *Staphylococcus aureus* Infections

Antimicrobial Agents and Chemotherapy
April 2015 Volume 59 Number 4

Kimberly C. Claeys,[a,b] Jordan R. Smith,[a,b] Anthony M. Casapao,[a,b]* Ryan P. Mynatt,[c] Lisa Avery,[d] Anjali Shroff,[e] Deborah Yamamura,[e] Susan L. Davis,[b,f] Michael J. Rybak[a,b]



N=28

Addition of TMP/SMX to DAP for clinical failure

Microbiological eradication in 24 cases (86%)

Bacteremia cleared in 2.5 days (median)

Salvage Treatment for Persistent Methicillin-Resistant *Staphylococcus aureus* Bacteremia: Efficacy of Linezolid With or Without Carbapenem

Clinical Infectious Diseases 2009; 49:395–401

Hee-Chang Jang,[1] Sung-Han Kim,[1,a] Kye Hyoung Kim,[1] Choong Jong Kim,[1] Shinwon Lee,[1] Kyoung-Ho Song,[1] Jae Hyun Jeon,[1] Wan Beom Park,[1] Hong Bin Kim,[1] Sang-Won Park,[1] Nam Joong Kim,[1] Eui-Chong Kim,[2] Myoung-don Oh,[1] and Kang Won Choe[1]

Patient group	No. of patients	*S. aureus*–related mortality,[a] no. (%) of patients	30-day mortality,[b] no. (%) of patients
Vancomycin-continue group	19	10 (53)	10 (53)
Vancomycin	14	6 (43)	6 (43)
Vancomycin and aminoglycosides or rifampicin	5	4 (80)	4 (80)
Linezolid salvage group	16	2 (13)	4 (25)
Linezolid	7	0 (0)	2 (29)
Linezolid and carbapenem	9	2 (22)	2 (22)

Efficacy and Safety of Fosfomycin Plus Imipenem as Res mia and E ant *Staphy* cal Trial

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N = 16 cases (12 with IE)

Patients with VAN or DAP microbiological failure

Microbiological eradication in all cases (100%)

Bacteremia cleared in <3 days

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Efficacy and Safety of Fosfomycin (FOS) plus Imipenem (IMI) vs. Vancomycin (VAN) for Complicated Bacteremia (CB) and Endocarditis (IE) due to Methicillin-Resistant *Staphylococcus aureus* (MRSA): A Randomized Clinical Trial

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ICAAC ICC2015

	FOS+IMI (N=8)	VAN (N=7)	p
Type of Bacteremia, %:			
▪ Infective endocarditis	4 (50%)	4 (57%)	1.000
▪ Complicated bacteremia	4 (50%)	3 (43%)	
Age, median (IQR)	83.5 (67-86)	76.0 (71-80)	0.565
Female sex, %	4 (50%)	2 (29%)	0.608
Predisposing conditions and underlying diseases, %:			
▪ Diabetes Mellitus	3 (38%)	3 (43%)	1.000
▪ Chronic lung disease	5 (63%)	0	0.026
▪ Ischemic heart disease	1 (12%)	3 (43%)	0.282
▪ Chronic renal failure	1 (12%)	1 (14%)	1.000
▪ Chronic liver disease	1 (12%)	0	0.533
▪ History of cancer	4 (50%)	1 (14%)	0.282
▪ HIV infection	0	1 (14%)	0.467
▪ Previous intravenous drug use	0	0	1.000
▪ Congenital heart disease, history of infective endocarditis	0	1 (14%)	0.467
▪ Pacemaker/cardiac defibrillator	0	3 (43%)	0.553
▪ Valve prosthesis	2 (25%)	2 (29%)	1.000
▪ Age-adjusted Charlson score, median (IQR)	8.0 (8-12)	6.0 (4-8)	0.256
Pressumed mode of acquisition, %:			
▪ Nosocomial	4 (50%)	4 (57%)	0.576
▪ Nonnosocomial health care associated	3 (38%)	3 (43%)	
▪ Community acquired	1 (12%)	0	
Type of endocarditis, %:			
▪ Native valve	2 (25%)	1 (14%)	0.122
▪ Prosthetic valve	2 (25%)	2 (29%)	
▪ Pacemaker lead/intracardiac device	0	1 (14%)	
Outcomes, %:			
▪ Positive blood cultures at fourth day of study treatment	0	1 (14%)	1.000
▪ Switch of treatment arm at day 7	0	2 (29%)	0.462
▪ Secondary effects related to study drug	1(12%)	3 (42%)	0.132
▪ Gram negative rods superinfection	0	4 (57%)	0.026
▪ In-hospital mortality	4 (50%)	0	0.051
▪ Mortality at 12 weeks after study drug completion	4 (50%)	1 (14%)	0.282
▪ Relapse at 12 weeks	0	1 (14%)	0.467
▪ Curation at end of study	4 (50%)	3 (42%)	0.763

Conclusions

1. Malgrat que l'evidència per a tractar en combinació encara és escasa, sí tenim prou evidència per a dir que els resultats obtinguts fins ara es poden millorar.
2. El criteri clínic i el context manen a l'hora de decidir tractar en combinació de forma empírica.
3. La nostra principal preocupació és sospitar i tractar a temps la bacterièmia nosocomial per SASM
4. Una bacterièmia primària també pot ser motiu per a tractar en combinació.
5. Encara no podem acomiadar-nos definitivament de la gentamicina i la rifampicina (alt inòcul per SARM: no els primers 3-5d)
6. Per a SARM, les combinacions més potents són les de dapto amb fosfomicina, ceftarolina o cotrimoxazol
7. Per a SASM, daptomicina amb betalactàmics.