SEICAV
Sociedad Española de Infecciones Cardiovasculares

Infecciones Cardiovasculares Asociadas a Cuerpos Extraños y Biofilms

Santander, 30 de Octubre del 2015.

¿Tenemos cambios en el tratamiento médico empírico en endocarditis sobre válvula nativa y protésica?

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Potential conflict of interest

Dr. José M Miró has received honoraria for speaking or participating in Advisory Boards and/or research grants from the following Pharmaceutical Companies:

Abbott,
Boehringer-Ingelheim
Bristol-Myers Squibb
Chiron
Cubist
Merck
Novartis
Glaxo Smith Kline (GSK)
Gilead Sciences
Oxford Immunotec
Pfizer
Roche
Theravance

Do we have changes in the empirical antimicrobial treatment in NVE and PVE?

- Introduction
- 2015 Clinical Guidelines recommendations
- Staphylococci
- Viridans streptococci
- Enterococci
- Conclusions

Empirical Antimicrobial Therapy

Treatment of IE should be started promptly in acutely ill patients. Three sets of blood cultures should be drawn at 30-min intervals before initiation of antibiotics. The initial choice of empirical treatment depends on:

a) Whether the infection is acute (days) or subacute (weeks)
b) Whether the infection affects a native valve or a prosthesis [and if so, when surgery was performed (early vs. late PVE)].
c) The place of the infection (community, nosocomial, or non-nosocomial healthcare-associated IE) and knowledge of the local epidemiology, especially for antibiotic resistance and specific genuine culture-negative pathogens.

Once the pathogen is identified (usually in 24-48 h), the antibiotic treatment must be adapted to its antimicrobial susceptibility pattern.

Etiology of Endocarditis - ICE, N=2,781 (2000-05)

Murdoch DR et al. Arch Intern Med. 2009;169:463-473

*Staphylococcus aureus**	31%
Coag. Neg. staphylococci	11%
Viridans group streptococci	17%
Streptococcus bovis	6%
Other streptococci	6%
Enterococci	10%
HACEK**	2%
Fungi/Yeast	2%
Polymicrobial	1%
Culture negative	10%
Other	4%

81%

* 31% of isolates were MRSA; ** HACEK = *Haemophilus spp.*, *Aggregatibacter* (formerly *Actinobacillus*) *actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella* species

Etiology by Type of Endocarditis* ICE, N=2,781 (2000-2005)

	Native valve IE in IVDA (N=266)	Native valve IE in GP (N=1,843)	Prosthetic valve IE (N=556)	PM/ICD (N=175)	Health-care IE (N=557)
S. aureus	68%	27%	21%	41%	45%
MRSA	10%	13%	7%	15%	49%
C.N.S.	3%	8%	19%	16%	13%
VGS + *S. bovis*	11%	29%	20%	8%	10%
Enterococci	6%	12%	12%	6%	15%
HACEK	-	2%	1%	2%	-
Other	8%	15%	17%	18%	12%
No organism	4%	7%	10%	9%	5%

*Murdoch DR et al. Arch Intern Med. 2009;169:463-473

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AHA Scientific Statement

Infective Endocarditis in Adults: Diagnosis, Antimicrobial Therapy, and Management of Complications

A Scientific Statement for Healthcare Professionals From the American Heart Association

Endorsed by the Infectious Diseases Society of America

Larry M. Baddour, MD, FAHA, Chair; Walter R. Wilson, MD; Arnold S. Bayer, MD; Vance G. Fowler, Jr, MD, MHS; Imad M. Tleyjeh, MD, MSc; Michael J. Rybak, PharmD, MPH; Bruno Barsic, MD, PhD; Peter B. Lockhart, DDS; Michael H. Gewitz, MD, FAHA; Matthew E. Levison, MD; Ann F. Bolger, MD, FAHA; James M. Steckelberg, MD; Robert S. Baltimore, MD; Anne M. Fink, PhD, RN; Patrick O'Gara, MD, FAHA; Kathryn A. Taubert, PhD, FAHA; on behalf of the American Heart

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION
American Heart Association
Learn and Live

2015

Circulation. 2015; On line.

www.americanheart.org

European Society of Cardiology

European Heart Journal
doi:10.1093/eurheartj/ehv319

ESC GUIDELINES

2015 ESC Guidelines for the management of infective endocarditis

The Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC)

Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM)

EUROPEAN SOCIETY OF CARDIOLOGY

2015

Eur Heart J. 2015; On line.

www.secardiologia.es

2015 AHA Empiric Antibiotic Therapy of IE

Native valve IE

- **Acute** (days)* — **Vancomycin + cefepime**
- **Subacute** (weeks)** — **Vancomycin + ampicillin-sulbactam**

Prosthetic valve IE

- **Early PVE** (≤ 1 year)^ — **Vancomycin* + Gentamicin + Rifampin + Cefepime**
- **Late PVE** (>1 year)^^ — **Vancomycin + ceftriaxone**

* *S. aureus*, β-hemolytic streptococci and aerobic Gram-negative bacilli.
** *S. aureus*, VGS, S. bovis and Enterococci.
^ Staphylococci, enterococci and aerobic Gram-negative bacilli.
^^ Staphylococci, VGS and enterococi.

Proposed antibiotic regimens for initial empirical treatment of IE in acute severely ill patients by 2015 ESC Guidelines

Antibiotic	Dosage and route	Class[b]	Level[c]	Comments
Community-acquired native valves or late prosthetic valves (≥ 12 months post surgery) endocarditis				
Ampicillin with (Flu)cloxacillin or oxacillin with Gentamicin[d]	12 g/day i.v. in 4–6 doses 12 g/day i.v. in 4–6 doses 3 mg/kg/day i.v. or i.m. in 1 dose	IIa	C	Patients with BCNIE should be treated in consultation with an ID specialist.
Vancomycin[d] with Gentamicin[d]	30–60 mg/kg/day i.v. in 2–3 doses 3 mg/kg/day i.v. or i.m. in 1 dose	IIb	C	For penicillin-allergic patients
Early PVE (<12 months post surgery) or nosocomial and non-nosocomial healthcare associated endocarditis				
Vancomycin[d] with Gentamicin[d] with Rifampin	30 mg/kg/day i.v. in 2 doses 3 mg/kg/day i.v. or i.m. in 1 dose 900–1200 mg i.v. or orally in 2 or 3 divided doses	IIb	C	Rifampin is only recommended for PVE and it should be started 3–5 days later than vancomycin and gentamicin has been suggested by some experts. In healthcare associated native valve endocarditis, some experts recommend in settings with a prevalence of MRSA infections >5% the combination of cloxacillin plus vancomycin until they have the final S. aureus identification

BCNIE = blood culture-negative infective endocarditis; ID = infectious disease; i.m. intramuscular; i.v. intravenous; PVE prosthetic valve endocarditis.
If all initial blood cultures are negative and there is no clinical response, consider BCNIE etiology and maybe surgery for molecular diagnosis and treatment, and extension of the antibiotic spectrum to blood culture-negative pathogens (doxycycline, quinolones) must be considered.

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S. aureus IE Surgery & Mortality (1979-05)

	Surgery	Mortality
MSSA IE*		
- ICE-MD 1979-99 (N=248)*	25%&	23%
- ICE-PCS 2000-05 (N=283)**	37%&	23%
MRSA IE		
- ICE-MD 1979-99 (N=43)*	26%	37%
- ICE-PCS 2000-05 (N=141)**	39%	30%

*Miro JM, Anguera I et al. Clin Infect Dis. 2005.
**Fowler V, Miro JM et al. JAMA, 2005.

&$P<0.005$

What is the best empiric antibiotic therapy against MSSA and MRSA Bacteremia/IE?

- ß-Lactam [e.g. cloxacillin] (MSSA)
- Vancomycin (MSSA/MRSA)
- Vancomycin plus ß-Lactams (MRSA/MSSA)
- Daptomycin alone (MSSA/MRSA)
- Daptomycin plus ß-Lactam/Fosfomycin (MRSA/MSSA)

What is the best empiric antibiotic therapy against MSSA and MRSA Endocarditis?

- ß-Lactam [e.g. cloxacillin] (MSSA)
- Vancomycin (MSSA/MRSA)
- Vancomycin plus ß-Lactams (MRSA/MSSA)
- Daptomycin alone (MSSA/MRSA)
- Daptomycin plus ß-Lactam/Fosfomycin (MRSA/MSSA)

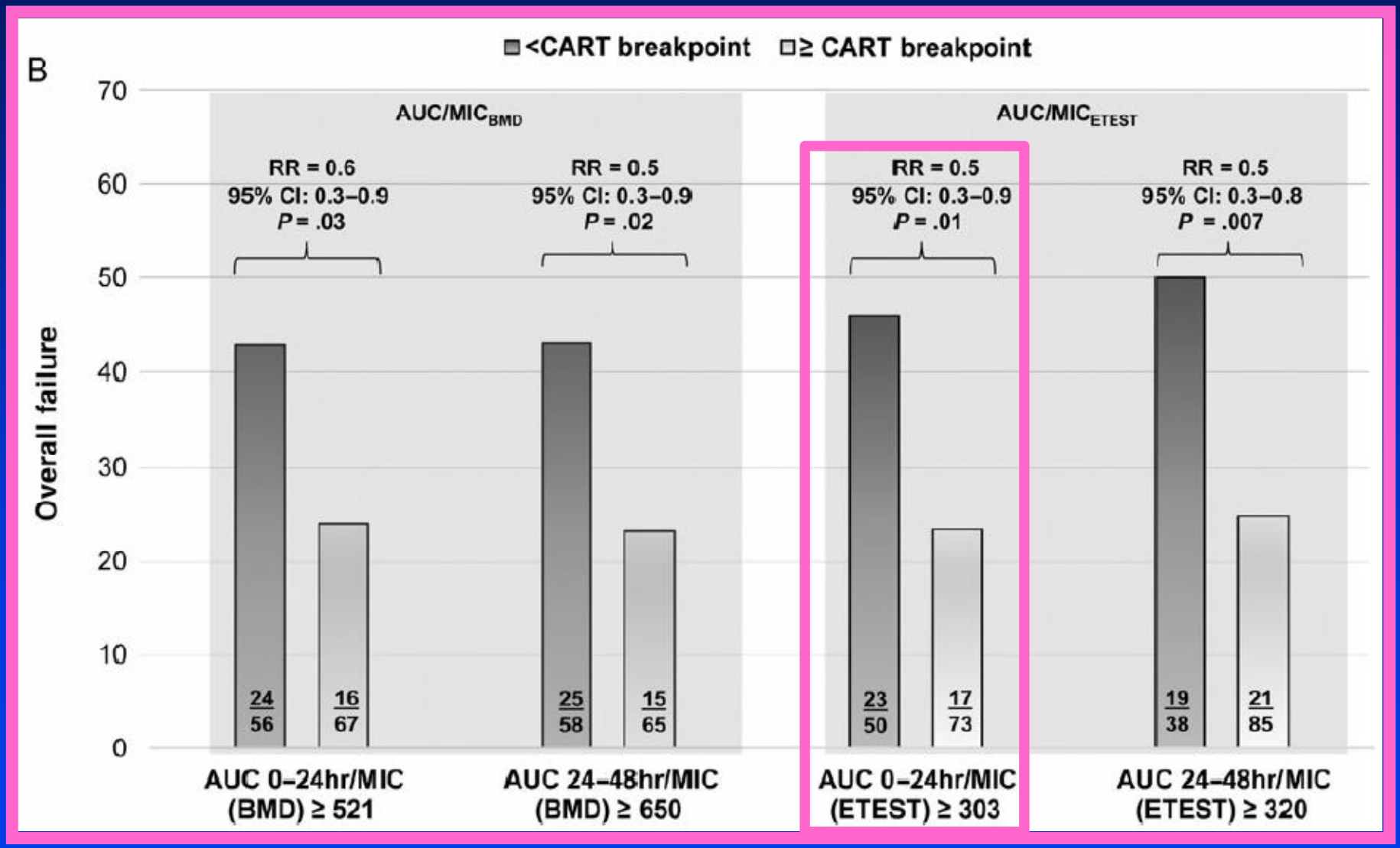
What are the problems when we are treating MRSA IE with Vancomycin?

- Poor bactericidal activity
- Poor diffusion within the vegetations
- Vancomycin MIC (AUC/MIC PD target)
- hVISA strains
- Tolerance

→ High rate of failures

Vancomycin Exposure (AUC) in Patients With MRSA BSI

Lodise TP et al. Clin Infect Dis 2014;59:666–75.



AIM OF THE STUDY

To compare the activity of CLO, VAN, DAP, and the combination CLO+VAN against MSSA and MRSA EE

Castañeda X et al. 52nd ICAAC, San Francisco, USA, 2012. Abstract B-648.

Activity of Cloxacillin (CLO) plus Vancomycin (VAN) against MRSA-277 EE

Strain	Sterile veg/Total (%)	Median(IQR) Log_{10} CFU/g veg
Control	0/15(0)	9 (8.6-9.5)
VAN (1 g/6h)	8/16 (50)[a,b]	1 (0-2.2)[d]
DAP (6 mg/Kg/d)	13/18 (72)[b,c]	0 (0-1.5)
CLO+VAN	**13/15 (87)[a,c]**	**0 (0-0)[d]**

[a]$p=0.05$, [b]$p=0.29$, [c]$p=0.6$ [d]$p=0.09$

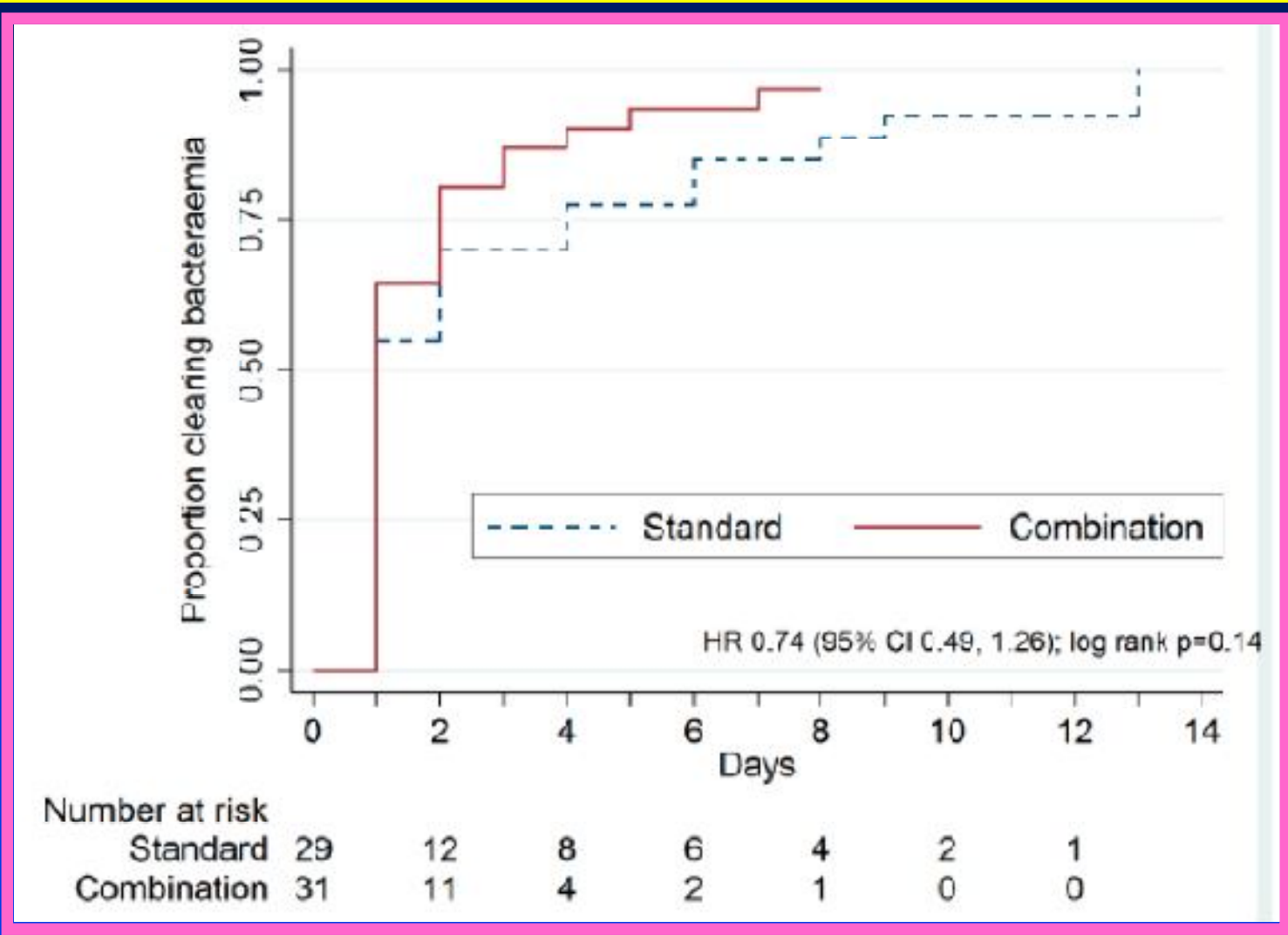
Castañeda X et al. 52nd ICAAC, San Francisco, USA, 2012. Abstract B-648.

Combination of Vancomycin and β-lactam therapy for MRSA Bacteremia (CAMERA): A pilot RCT

	Standard therapy	Combination therapy	Relative Risk (95% CI)	P value
Intention to treat population	***N=29***	***N=31***		
Hospital mortality	5 (17%)	5 (16%)	0.96 (0.48,1.90)	0.91
28 day mortality	5 (17%)	5 (16%)	0.96 (0.48,1.90)	0.91
90 day mortality	6 (21%)	5 (16%)	0.86 (0.46,1.59)	0.65
Duration of bacteremia >3 days	8 (28%)	4 (13%)	0.47 (0.16,1.39)	0.16
Duration of bacteremia >7 days	4 (14%)	1 (3%)	0.23 (0.03,1.97)	0.14
Relapsed bacteremia	1 (3%)	0 (0%)	0	0.30

Davis JS et al. CID 2015, on line.

Combination of vancomycin and β-lactam therapy for MRSAB (CAMERA): A pilot RCT



Davis JS et al. CID 2015, on line.

Activity of Cloxacillin (CLO) plus Vancomycin (VAN) against MSSA-678 EE

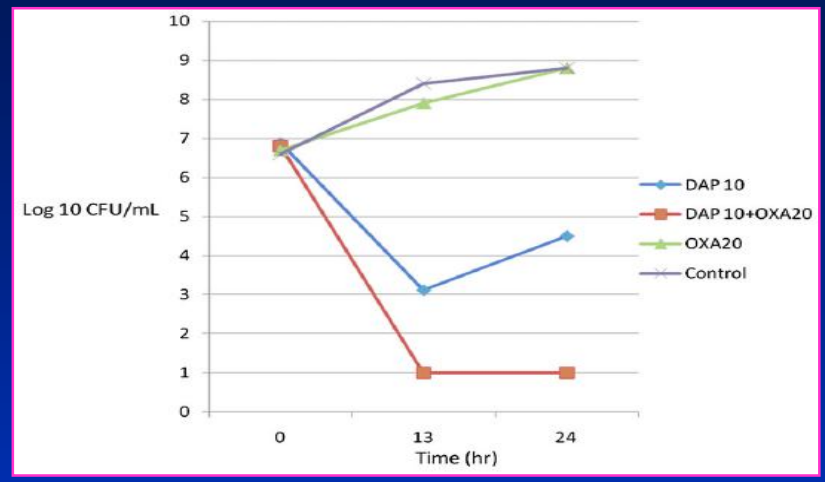
Strain	Sterile veg/Total (%)	Median (IQR) Log_{10} CFU/g veg
Control	0/15(0)	9 (8-9.2)
CLO (2 g/4h)	9/15 (60)[a,b]	0 (0-2)
VAN (1.25 g/8h)	10/14 (71)[c]	0 (1-1.5)
DAP (6 mg/Kg/d)	13/13 (100)[a,c,d]	0 (0-0)
CLO+VAN	**10/14 (71)[b,d]**	**0 (0-1.5)**

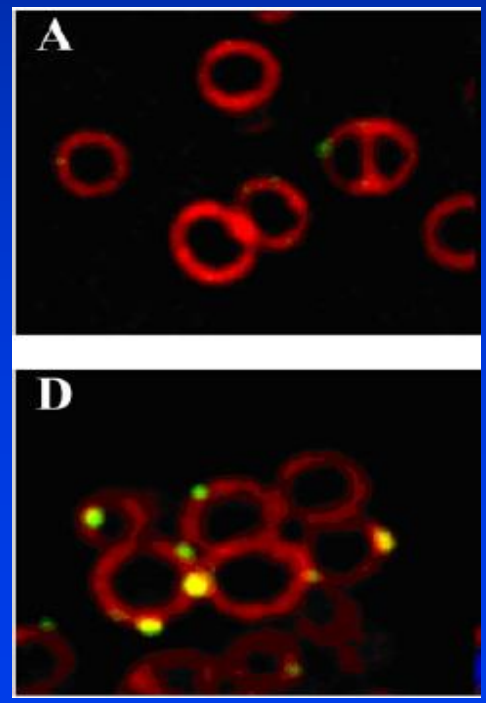
[a]$p=0.02$; [b]$p=0.7$; [c]$p=0.09$; [d]$p=0.09$

Castañeda X et al. 52nd ICAAC, San Francisco, USA, 2012. Abstract B-648.

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.



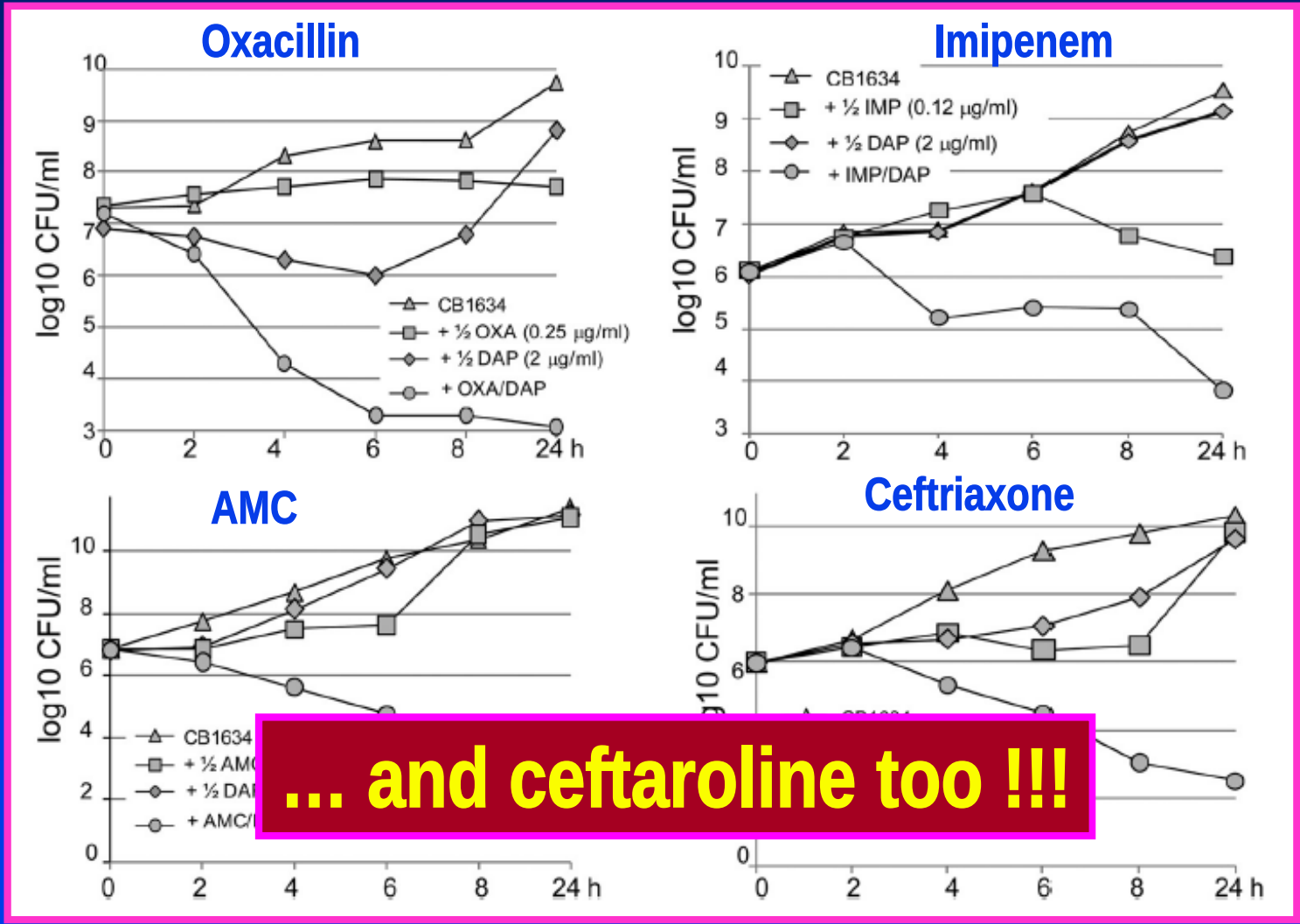


DAP (green) binding with & without NAF (yellow)

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

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(12):6192.

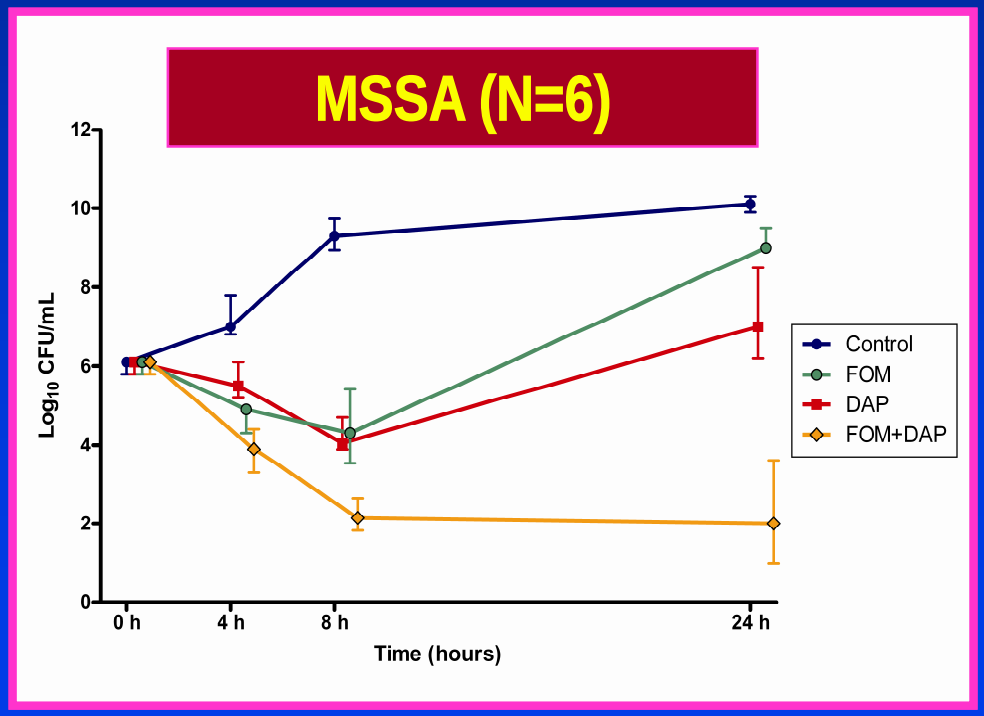


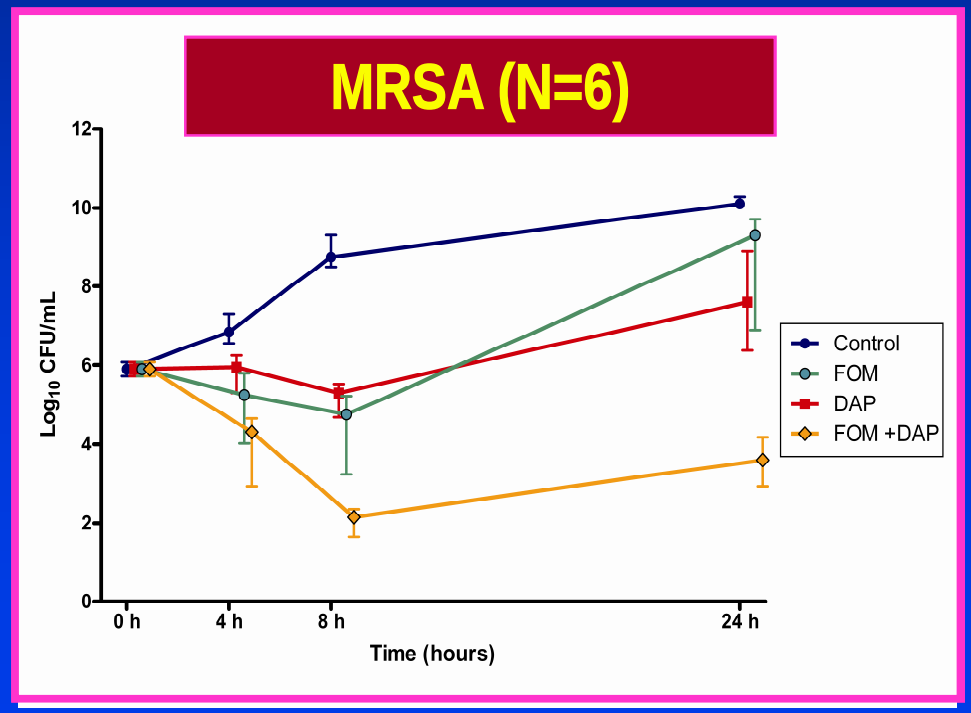
... and ceftaroline too !!!

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

Miro JM et al. Antimicrob Agents Chemother. 2012; 56:4511-5

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





Evaluation of the efficacy and safety of Daptomycin ± Fosfomycin for the treatment of MRSA BSI in Spain

PI 12/01907 (231,715 €) - Dr. Miquel Pujol (H. Bellvitge)

Multicenter, Randomized (1:1) Open-label Clinical Trial

MRSA BSI (N=240)

→ **Daptomycin (DAP) 10 mg/kg/d**

→ **DAP (10 mg/kg/d) + Fosfomycin (2 g/6h)**

- Recruitment: 2014-15; 12 weeks of F/U.
- Drugs adjusted to renal failure
- Susceptible to study drugs
- End points: TOC 12 weeks after finishing Rx, Toxicity, Resistance and Mortality.

Daptomycin plus Fosfomycin *vs.* Daptomycin plus Cloxacillin for the Treatment of MRSA EE with a Van MIC of 2 mg/L

Miro JM et al. ECCMID, Barcelona May 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] $P = .025$

Daptomycin plus Fosfomycin *vs.* Daptomycin plus Cloxacillin for the Treatment of MSSA EE – 24 h Results

Garcia de la Maria C et al. ICAAC, San Diego, CA, 2015 Abs. B-063

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]

[a]$P = .001$; [b]$P < .001$; [c]$P = .59$; [d]$P = .001$; [e]$P < .001$

What would be the antibiotic combinations to treat MSSA / MRSA / DNS *S. aureus* Endocarditis?

- **Daptomycin + Beta-lactams***

- **Daptomycin + Fosfomycin**
- Fosfomycin + Imipenem
- Daptomycin + Trimethoprim-Sulfamethoxazole**
- Other antibiotic combinations***

* Ceftaroline, cloxacillin/nafcillin.

*** Trimethoprim-Sulfamethoxazole + Clindamycin; Linezolid + Carbapenems.

** Steed ME et al. AAC. 2010; 54:5187–5192; Claeys KC et al. AAC. 2015 59: 1969-1976.

Surgery and Mortality Rates of 103 CoNS IE H. Clínic, Barcelona, Spain

	Surgery	Mortality
IE in general population (N=36)	31%	44%
PV IE (N=31)	71%	45%
Pacemaker/ICD IE (N=36)	92%	6%
Overall	**≈64%**	**≈31%**

Garcia-de-la-Maria C et al. PLoS One. 2015.

Daptomycin in the treatment of experimental endocarditis due to methicillin-resistant *Staphylococcus epidermidis* (MRSE)

García-de-la-Maria C *et al. Antimicrob Agents Chemother* 2010; 54:2781-6.

Treatment groups	Doses	Sterile vegetations/ #total (%)	Median (IQR) log10 cfu/g veg
Control	-/-	0/15 (0)	7.4 (6; 8.3)
Vancomycin-SD	1 g/12 h	3/16 (19) [a]	2 (2; 2)
Vancomycin-HD	1 g/6 h	5/15 (33) [b]	2 (0; 2)
Daptomycin - 6	6 mg/kg 24 h	9/15 (60) [a]	0 (0; 4)
Daptomycin - 10	10 mg/kg 24 h	11/15 (73) [b]	0 (0; 1)

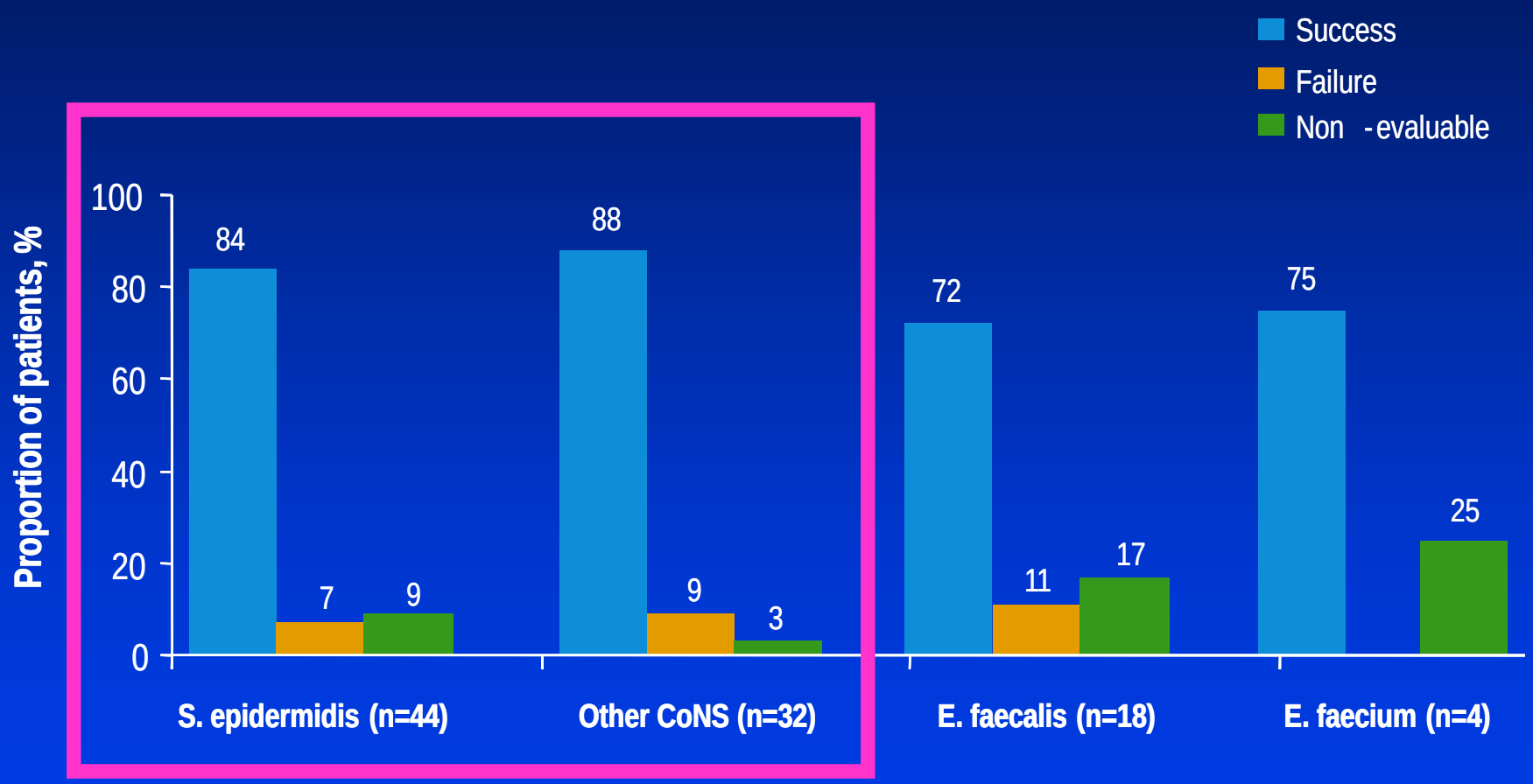
[a]*P*=0.02; [b]*P*=0.03.

Vancomycin and Daptomycin MIC/MBCs were 2/4 and 0.5/1 mg/L respectively.

Daptomycin, simulating 6 mg/kg and 10 q 24 h i.v.; Vancomycin, simulating 30 mg/kg/24 h. divided in 2 doses i.v. and 60 mg/kg/24 h divided in 4 doses achieving AUC/MIC = 400.

Daptomycin for CoNS Endocarditis – EU-CORE

Dohmen P et al. 20th *ECCMID*, Vienna (Austria), 2010 Poster O 511



Clinical success was defined as the sum of cured and improved patients

New Therapies for Prosthetic Valve Endocarditis Caused by Methicillin-Resistant CoNS

Regimen	Dosage and route	Duration (weeks)*
Daptomycin*	10 mg/kg/24 h. IV	≥ 6
+ Rifampin (PVE)	+ 300 mg/8 h. PO/IV	≥ 6
+ Gentamicin (PVE)	+ 3 mg/kg/24h. IV/IM (in 2-3 doses)	2
Alternatives		
- Ceftaroline	600 mg/kg/8h IV	≥6
- Linezolid	600 mg/12 h. PO/IV	≥6
- Other antibiotics*		

***MRSA NV IE** = Daptomycin plus Beta-lactams or Fosfomycin; Fosfomycin plus Imipenem; Televancin, Dalbavancin; Oritavancin, Tedizolid and other active antibiotics against MRSA

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Rates of Selection of Resistance and High-Level Resistance after Exposure to Daptomycin among VGS and *S. bovis* isolates from IE

Microorganism(s)	No. strai	No. (%) that were[b]:		HLDR (MIC, ≥256 mg/liter)
Mitis group	92			25 (27)
S. mitis	51			14 (27)
S. oralis	19			9 (47)
S. sanguis	15			2 (13)
S. gordonii	4			0 (0)
S. parasanguis	3			0 (0)
Bovis group	54	2 (4)	0	0
Anginosus group	10	5 (50)	5 (50)	0
Mutans group	8	0	0	0
Salivarius group	4	0	0	0

[a] Screening was considered positive if the microorganism grew in the presence of 0.5 mg or 1 mg/liter daptomycin.

[b] DNS, daptomycin nonsusceptible; HLDR, high-level daptomycin resistance.

Mitis Group

DNS 67-100%

HLDR 0-47%

Garcia de la Maria C et al. AAC; 2013, 57:2319-2325.

High-Level Daptomycin Resistance (HLDR) in VGS Developed upon *In Vitro* Exposure to Daptomycin

Dapto MIC
>256 mg/L

Akins RS et al. AAC; 2015, 59:2102-12.

Treatment of EE caused by Penicillin-Resistant *S. mitis* with Daptomycin and Vancomycin Alone or Combined with Gentamicin

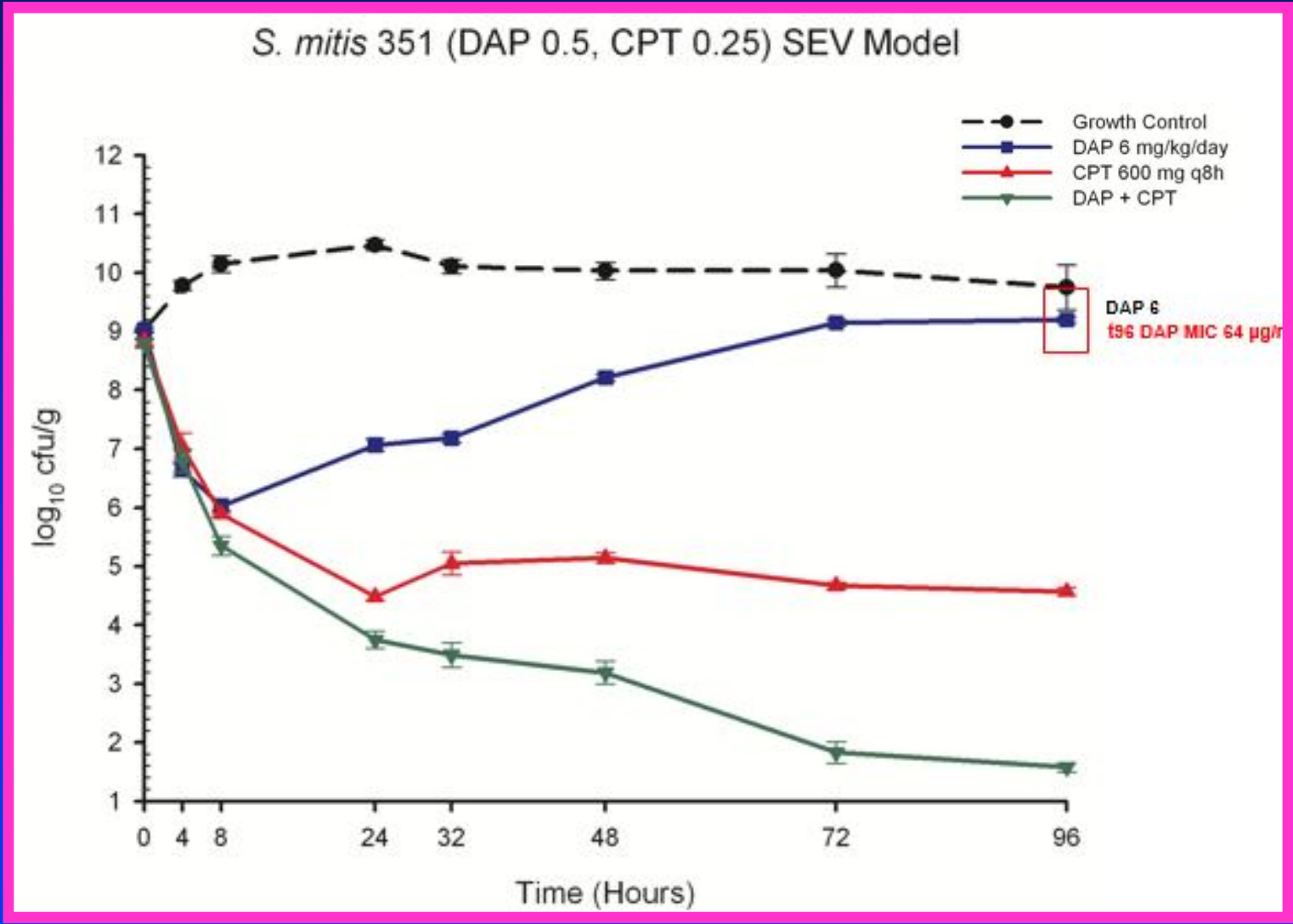
Garcia-de-la-Maria C et al. Antimicrob Agents Chemother. 2013, 57:2319-2325.

Treatment groups	# Sterile veg./ # total (%)	Median (IQR) log10 cfu/g veg	HLDR MIC≥256 mg/L
Control	0/15 (0)	9.1 (9–9.6)	0%
Vancomycin-SD (1 g q12h iv)	0/12 (0)	3.4 (2–4)	-
Daptomycin-SD (6 mg/kg q24h iv)	1/11 (9)	6.7 (5.9–7.8)	63%*
Daptomycin-HD (10 mg/kg q24h iv)	1/12 (8)	6.1 (5.2–7.2)	67%*
Daptomycin + Gentamicin	18/23 (78)	0 (0-2)	9%*
Vancomycin + Gentamicin	6/12 (50)	1 (0-2.2)	-

*P=0.004.

Ceftaroline (CPT) and daptomycin (DAP) are synergistic against *Streptococcus mitis* in a SEV model

Smith JR et al. ICAAC, San Diego, CA. 2015, Poster # A-494.



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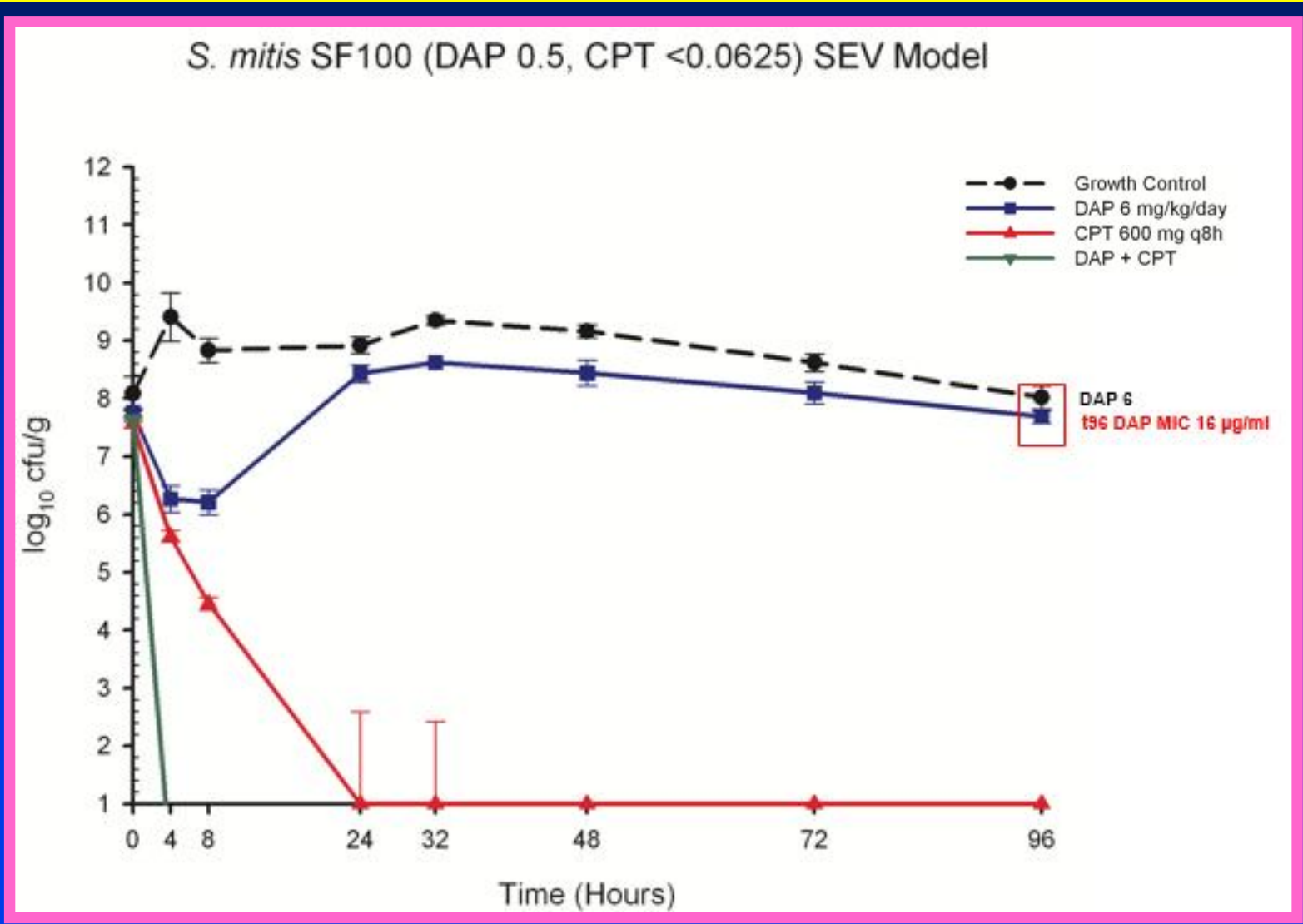

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Enterococcal IE: Species and Resistance

	HCB 1997-2011	ICE 2000-06
No. of episodes	80	500
Species		
- *E. faecalis*	97%	91%
- *E. faecium*	3%	4%
- Other/NIS	-	5%*
Resistance patterns		
- HLAR	39%	38%
- VRE	0%	3%

Pericas JM, CMI; 2014; 20:O1075-83; Chiruze C et. CMI, 2013;19:1140-7.

**E. durans*, 6; *E. casseliflavus*, 2; *E. gallinarum*, 1; NIS, 19.

AHA Scientific Statement

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION
American Heart Association
Learn and Live

Infective Endocarditis in Adults: Diagnosis, Antimicrobial

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Table 18 Antibiotic treatment of infective endocarditis due to *Enterococcus* spp.

Antibiotic	Dosage and route	Duration, weeks	Class[g]	Level[h]	Ref.[i]	Comments
Beta-lactam and gentamicin-susceptible strains (for resistant isolates see [a,b,c])						
Amoxicillin* with	200 mg/kg/day i.v. in 4–6 doses	4–6	I	B	6,8, 129, 135, 136, 186	6-week therapy recommended for patients with >3 months symptoms or PVE
Gentamicin[d]	3 mg/kg/day i.v. or i.m. in 1 dose	2–6**	I	B		
	Paediatric doses:[e] Ampicillin 300 mg/kg/day i.v. in 4–6 equally divided doses Gentamicin 3 mg/kg/day i.v. or i.m. in 3 equally divided doses					
Ampicillin with Ceftriaxone	200 mg/kg/day i.v. in 4–6 doses	6	I	B	183–185	This combination is active against *Enterococcus faecalis* strains with and without HLAR, being the combination of choice in patients with HLAR *E. faecalis* endocarditis.
	4 g/day i.v. or i.m. in 2 doses	6	I	B		
	Paediatric doses:[e] Amoxicillin as above Ceftriaxone 100 mg/kg/12 h i.v. or i.m.					This combination is not active against *E. faecium*

Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM)

Eur Heart J. 2015; On line.

www.secardiologia.es

Ampicillin + Daptomycin for HLAR EF EE

EFAE-DS: Strain that does not present the ability to develop daptomycin resistance after exposure to subinhibitory daptomycin concentrations.

Treatment groups (72 hours)	Sterile veg/ Total veg	Median log cfu/g veg. (IQR_{25}-IQR_{75})	Detection of resistant subpopulations (PAP)
Control	0/10	8.5 (8 - 9)[a]	ND
Daptomycin (10 mg/Kg/day)	0/10	7.1 (6.2 - 8.3)[a,b,c]	0/10
Daptomycin (10 mg/Kg/day) + Ampicillin (2g/4h)	0/10	2.9 (2 - 4.1)[b,d]	0/10
Ampicillin (2g/4h) + Ceftriaxone (2g/12h)	0/10	4.1 (3.3 - 4.3)[c,d]	ND

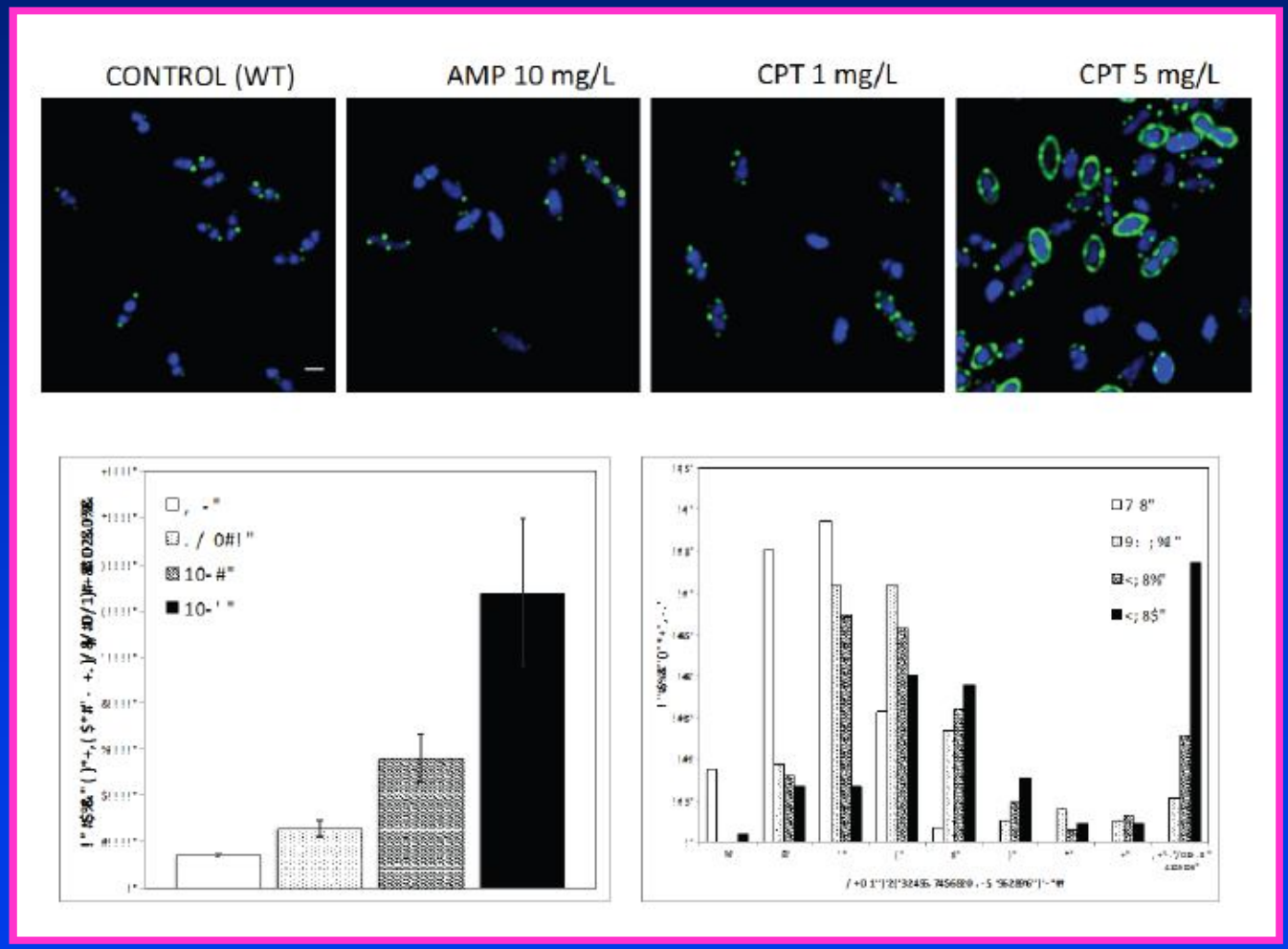
[a]P=0.39; [b]P<0.001; [c]P<0.001; [d]P=0.67

Pericas et al. ICAAC. 2014; Abs. E-320.

Treatment of HLAR *Enterococcus faecalis* Endocarditis with Daptomycin Plus Ceftaroline

Sakoulas G et al. AAC 2013 May 20. [Epub ahead of print]

A recurrent case of left-sided endocarditis caused by high-level aminoglycoside resistant (HLAR) *Enterococcus faecalis* was successfully treated with ceftaroline and daptomycin.



β-Lactams Enhance Daptomycin Activity against Vancomycin-Resistant *Enterococcus faecalis and E. faecium*

Smith JT et al. AAC. 2015; 59:2842-48

	Log_{10} CFU/ml ± SD at 96 h		
Regimen	R6981 *E. faecalis*	R6370 *E. faecium*	8019 *E. faecium*
DAP	6.43 ± 0.26	6.65 ± 0.21	7.75 ± 0.52
CPT	8.58 ± 0.05	8.02 ± 0.05	7.38 ± 0.28
ERT	9.42 ± 0.47	8.15 ± 0.07	8.18 ± 0.14
AMP	7.53 ± 0.11	7.60 ± 0.14	7.63 ± 0.15
DAP-CPT	2.00 ± 0.00[a,b]	2.25 ± 0.35[a,b]	2.00 ± 0.00[a,b]
DAP-ERT	2.34 ± 0.26[a,b]	2.00 ± 0.00[a,b]	2.14 ± 0.08[a,b]
DAP-AMP	4.75 ± 0.21[a]	4.63 ± 0.01[a,b]	2.09 ± 0.10[a,b]
Growth control	8.94 ± 0.13	8.50 ± 0.14	8.42 ± 0.08

[a] Significantly different from any single-agent regimen.

[b] Enhancement from any single-agent regimen.

What would be the antibiotic combinations to treat Vancomycin-Resistant *E. faecium* (VRE) IE?

- **Daptomycin + Beta-lactams***
- Daptomycin + Tigecycline (+ Gentamicin)
- Daptomycin + Fosfomycin
- Oritavancin (+Gentamicin)
- Tigecycline + Gentamicin

* Ceftaroline, ertapenem or ampicillin.
Smith JR et al. JAC 2015; on line.

Munita JM et al. Curr Infect Dis Rep (2012) 14:339–349
Pericas JM et al. Future Microbiol. 2015.

Do we have changes in the empirical antimicrobial treatment in NVE and PVE?

- Introduction
- 2015 Clinical Guidelines recommendations
- Staphylococci
- Viridans streptococci
- Enterococci
- Conclusions

Take home messages

- The 2015 ESC IE guidelines recommended ampicillin plus cloxacillin plus gentamicin as empiric therapy for NVE and late PVE; vancomycin plus gentamicin plus rifampin for early PVE and cloxacillin plus vancomycin for HCA NVE.
- The 2015 AHA IE guidelines recommended vancomycin-based regimens for all types of NVE and PVE.
- My personal opinion is to recommend as empiric therapy the combination of daptomycin plus ceftaroline for acute NVE and PVE.
- Once the pathogen is identified (usually in 24-48 h), the antibiotic treatment must be adapted to its antimicrobial susceptibility pattern.

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