

6. ¿Debemos seguir utilizando las pautas antibióticas recomendadas por los expertos (Guías SEC/AHA 2015) en endocarditis protésicas por *Staphylococcus aureus* o ECN?

Dr. José M. Miró
Hospital Clínic – IDIBAPS
Universidad de Barcelona
Barcelona

Correo electrónico: jmmiro@ub.edu



Therapy for Native Valve Endocarditis Due to *Staphylococcus aureus* or Coagulase Negative Staphylococci

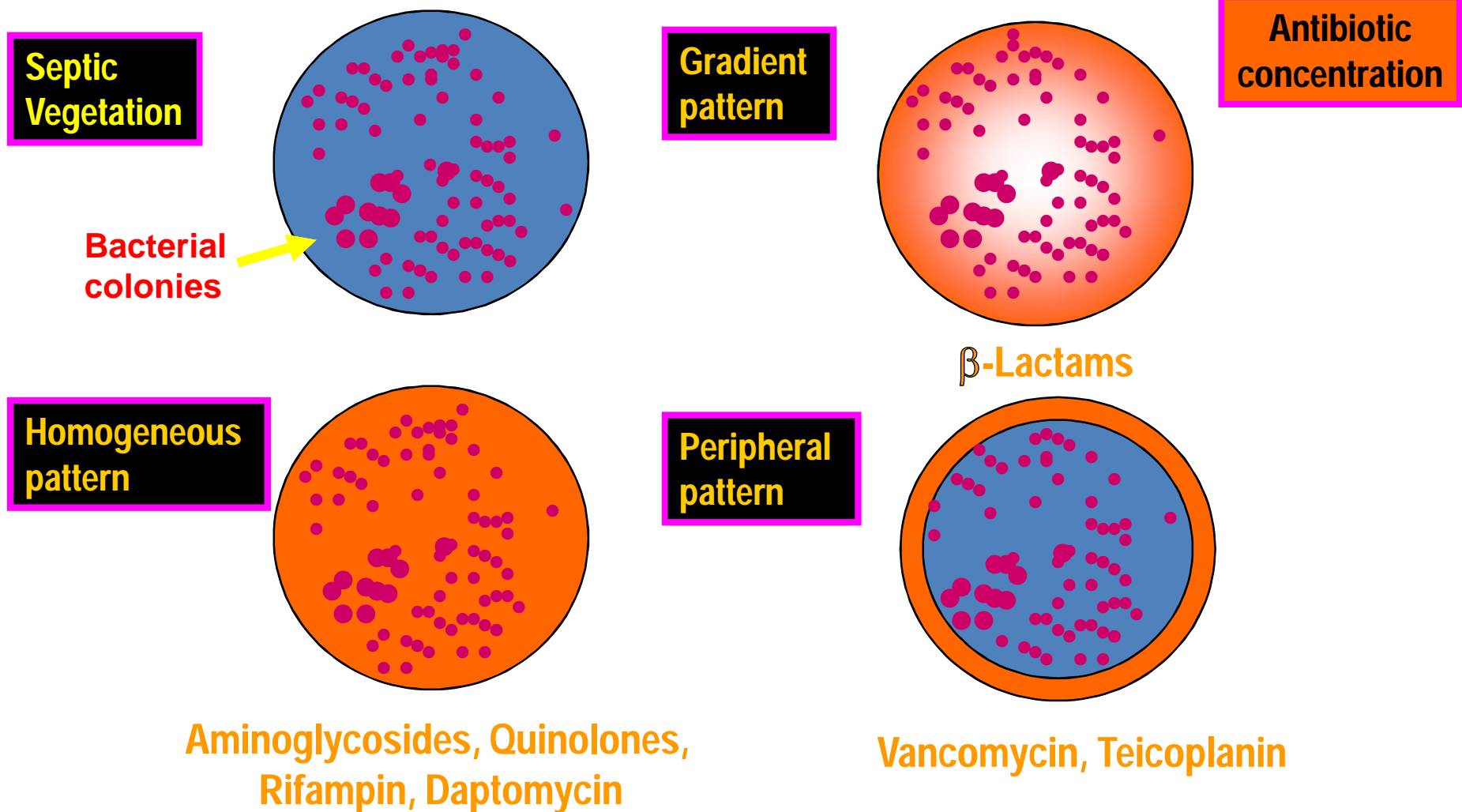
| Antibiotic | Dosage and Route | Duration |
|------------------------------|---|---------------|
| Nafcillin/Cloxacillin | 12 g/24 h in 6 divided doses IV | 4-6 wk |
| Cefazolin (AHA) | 6 g/24 h in 3 divided doses IV | 4-6 wk |
| Cotrimoxazole | 4800/960 mg/24 h in 4-6 doses IV/PO | 6 wk |
| + Clindamycin (ESC) | 1800 mg/24 h in 3 doses IV/PO | 1 wk |
| Vancomycin | 30-45 mg/kg/24 h. IV (in 2-3 doses)* | 4-6 wk |
| Daptomycin | ≥ 8 mg/kg/24 h | 4-6 wk |
| Cotrimoxazole | 4800/960 mg/24 h in 4-6 doses IV/PO | 6 wk |
| + Clindamycin (ESC) | 1800 mg/24 h in 3 doses IV/PO | 1 wk |

Therapy for Prosthetic Valve Endocarditis Caused by *Staphylococcus aureus* or *S. epidermidis*

| Antibiotic | Dosage and Route | Duration |
|-------------------------------|---|------------|
| Vancomycin* | 30-45 mg/kg/24 h. IV (in 2-3 doses)* | ≥ 6 |
| + Rifampin | + 300 mg/8 h. IV/PO (after 3-5 days) | ≥ 6 |
| + Gentamicin | + 3 mg/kg/24h. IV/IM | 2 |
| Nafcillin/Cloxacillin* | 12 g/24 h in 6 divided doses IV | ≥ 6 |
| + Rifampin | + 300 mg/8 h. IV/PO (after 3-5 days) | ≥ 6 |
| + Gentamicin | + 3 mg/kg/24h. IV/IM | 2 |

*Vancomycin should be used in patients with immediate-type hypersensitivity reactions to β -lactam antibiotics. Cefazolin (6 g/24 h in 3 divided doses) may be substituted for nafcillin or cloxacillin in patients with non-immediate-type hypersensitivity reactions to penicillin.

Antibiotic Penetration into Vegetations

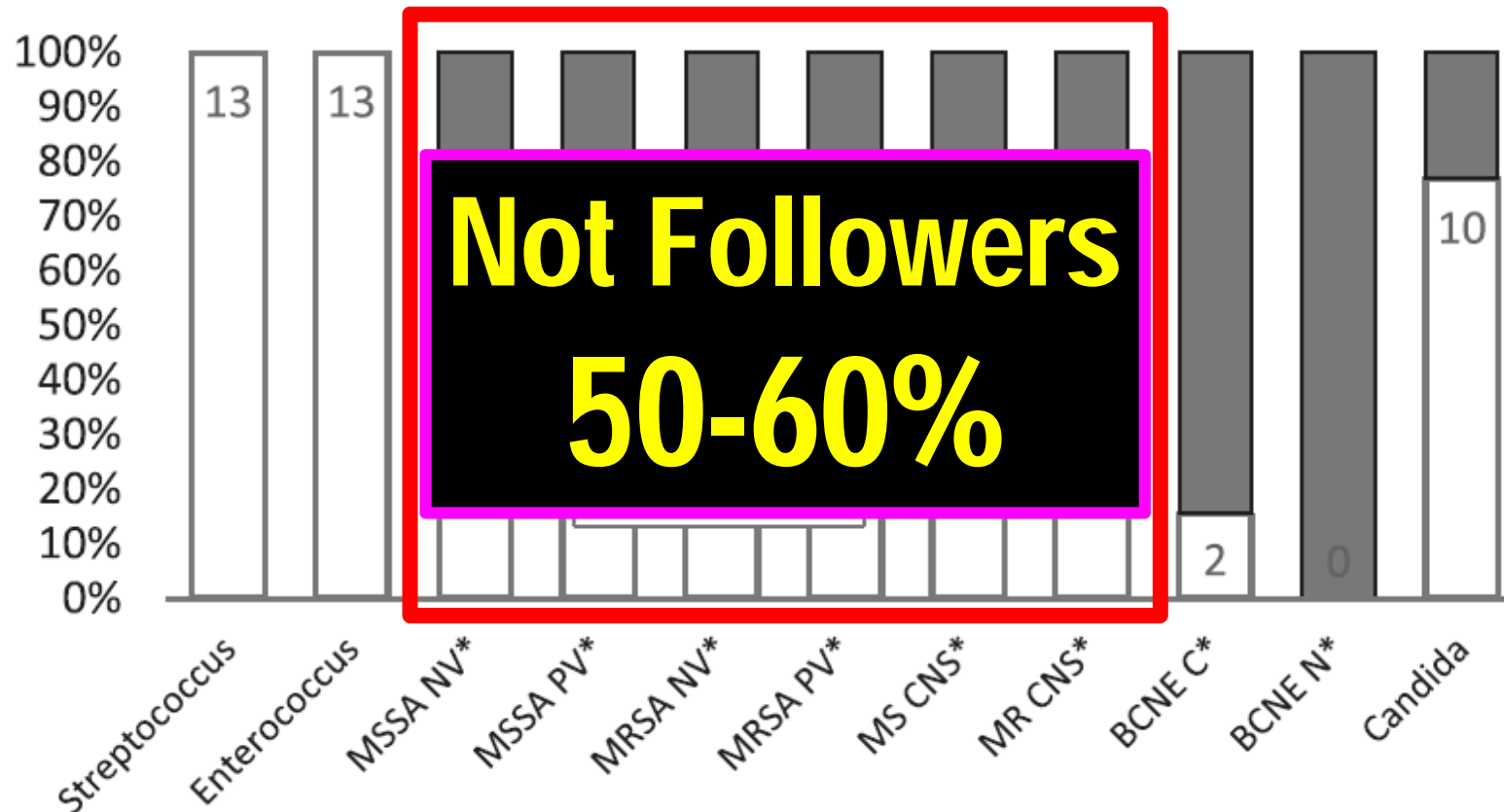


2015 AHA/ESC Guidelines for Antibiotic Treatment of Staphylococcal IE

**Change or not
Change
that is the question**

Hamlet, Act III, Scene I. Sir William Shakespeare, 1564 - 1616.

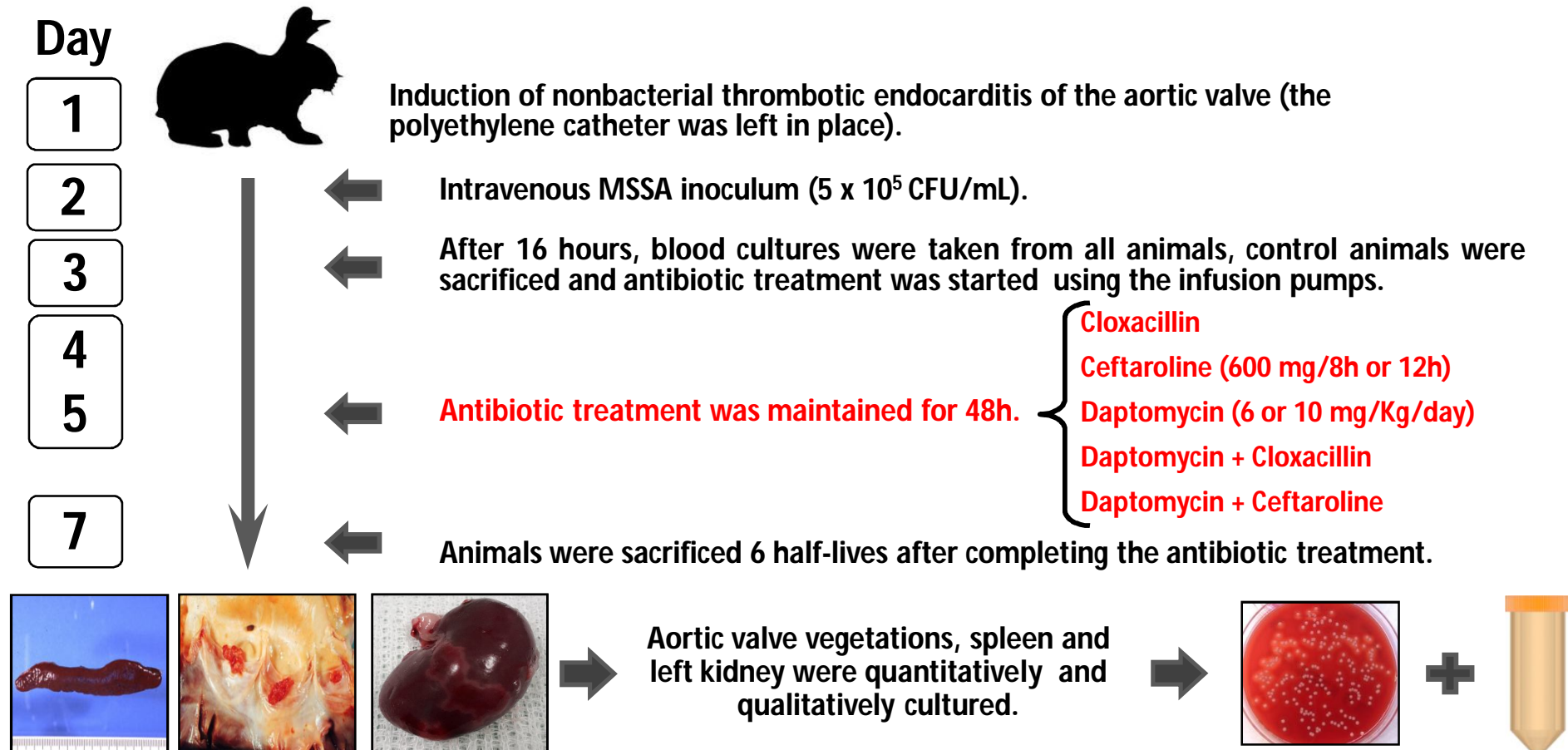
International experts in the antibiotic therapy of IE are not following the Guidelines for Staphylococcal IE



Reasons for Changing the Antibiotic Treatment of Staphylococcal Endocarditis

- The current recommendations are based on non-randomized clinical studies performed 40 years ago
- The combination of vancomycin and gentamicin is very nephrotoxic
- It has not been possible to reduce mortality in recent decades
- There are new antibiotics that are very effective and safer to be evaluated.
- There are new antibiotic strategies (antibiotic stewardship, OPAT) that will optimize the treatment of staphylococcal endocarditis

MSSA Experimental Endocarditis Model



Results

In vivo results: Vegetations growth

| Treatment group | Animals with sterile vegetations/total (%) | Median (IQR) log ₁₀ CFU/g of vegetation |
|-------------------------------------|--|--|
| Control (no treated) | 0 / 20 (0) | 9.6 (8.8 - 10.1) |
| CLO (2g/4h) | 5 / 20 (25) ^a | 2 (1.5 – 5.7) |
| CTL (600 mg/12h) | 9 / 19 (47) ^b | 2 (0 – 5.7) |
| CTL (600 mg/8h) | 10 / 21 (48) ^c | 2 (0 – 4.5) |
| DAP (6 mg/kg/24h) [*] | 10 / 20 (50) ^d | 1 (2 - 3.7) |
| DAP (10 mg/kg/24h) ^{**} | 10 / 19 (53) ^e | 0 (0 - 2) |
| DAP (6 mg/kg/24h) + CLO (2g/4h) | 18 / 20 (90) ^{a,b,c,d,e} | 0 (0 - 0) |
| DAP (6 mg/kg/24h) + CTL (600 mg/8h) | 19 / 20 (95) ^{a,b,c,d,e} | 0 (0 - 0) |

4/20 (20%) DNS isolates, **1/19 (5,3%) DNS isolates (DAP MIC = 2 mcg/ml); ^{a,b,c,d,e}*P* < 0.05 for all comparisons

Results *In vivo* results: Spleen growth

| Treatment group | Animals with sterile spleen/total (%) | Median (IQR) log ₁₀ CFU/g of spleen |
|-------------------------------------|---------------------------------------|--|
| Control (no treated) | 0 / 20 (0) | 5.7 (5.1 - 6) |
| CLO (2g/4h) | 19 / 20 (95) ^a | 0 (0 - 0) |
| CTL (600 mg/12h) | 16 / 19 (84) ^b | 0 (0 - 0) |
| CTL (600 mg/8h) | 21 / 21 (100) ^c | 0 (0 - 0) |
| DAP (6 mg/kg/24h)* | 9 / 20 (45) ^{a,b,c,d,e} | 2 (0 - 2.2) |
| DAP (10 mg/kg/24h)** | 14 / 19 (74) ^{c,d} | 0 (0 - 1) |
| DAP (6 mg/kg/24h) + CLO (2g/4h) | 20 / 20 (100) ^d | 0 (0 - 0) |
| DAP (6 mg/kg/24h) + CTL (600 mg/8h) | 20 / 20 (100) ^{a,b,c,d,e} | 0 (0 - 0) |

4/20 (20%) DNS isolates, **1/19 (5,3%) DNS isolates ; ^{a,b,c,d,e}*P* < 0.05 for all comparisons

Results

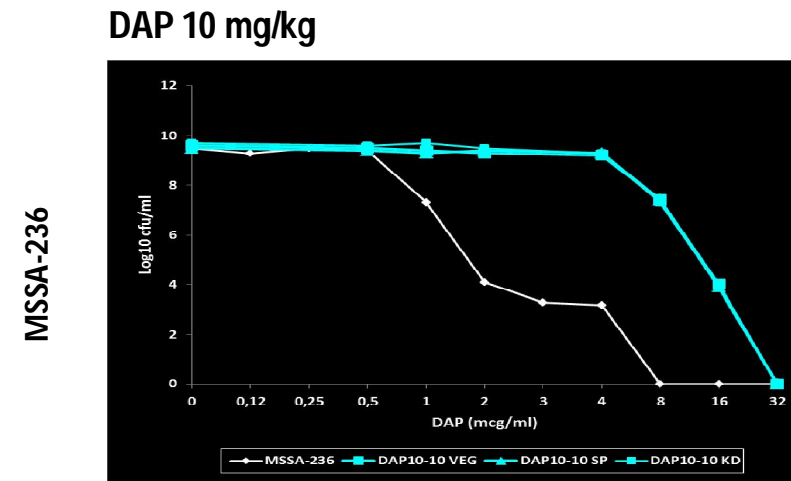
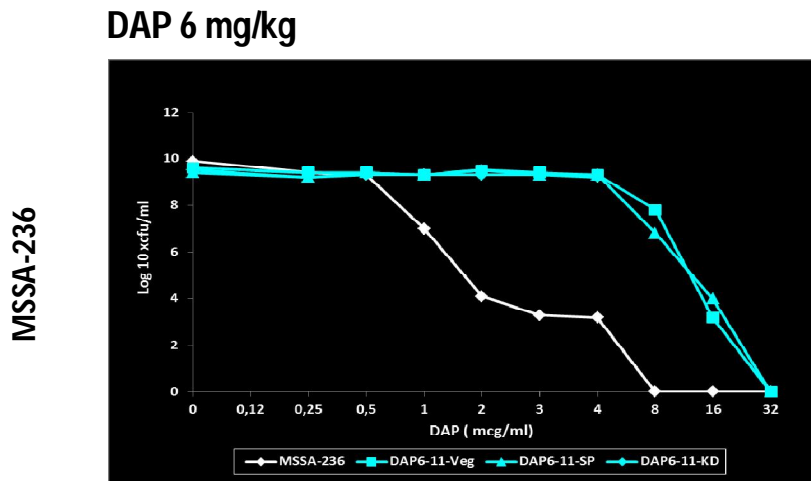
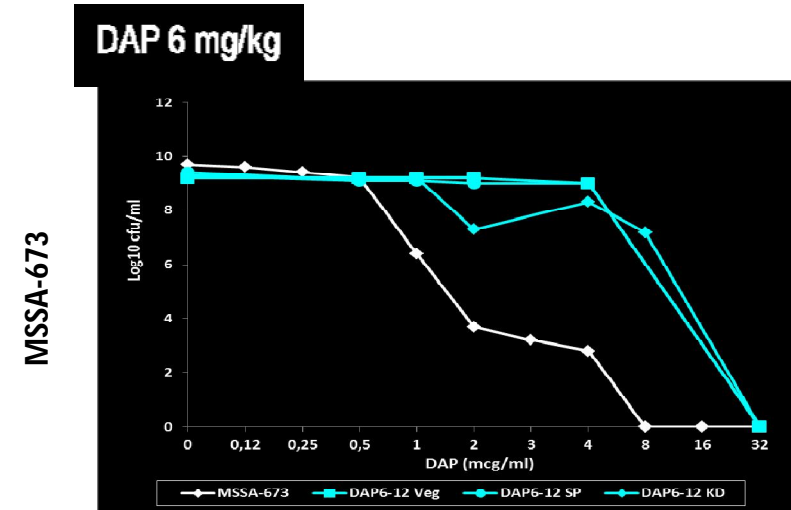
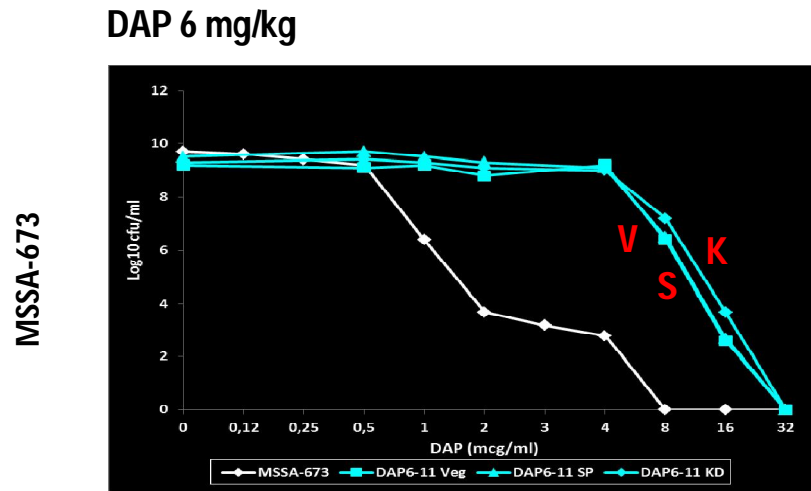
In vivo results. Kidney growth

| Treatment group | Animals with sterile kidney/total (%) | Median (IQR) log ₁₀ CFU/g of kidney |
|-------------------------------------|---------------------------------------|--|
| Control (no treated) | 0 / 20 (0) | 4.6 (3.9 - 10.1) |
| CLO (2g/4h) | 16 / 20 (80) ^a | 0 (0 - 0) |
| CTL (600 mg/12h) | 17 / 19 (89) ^b | 0 (0 - 0) |
| CTL (600 mg/8h) | 20 / 21 (95) ^c | 0 (0 - 0) |
| DAP (6 mg/kg/24h) [*] | 8 / 20 (40) ^{a,b,c,d} | 2.4 (0 - 4.6) |
| DAP (10 mg/kg/24h) ^{**} | 12 / 19 (63) ^{c,d} | 0 (0 - 2) |
| DAP (6 mg/kg/24h) + CLO (2g/4h) | 20 / 20 (100) ^d | 0 (0 - 0) |
| DAP (6 mg/kg/24h) + CTL (600 mg/8h) | 20 / 20 (100) ^{a,b,c,d,e} | 0 (0 - 0) |

4/20 (20%) DNS isolates, **1/19 (5,3%) DNS isolates ; ^{a,b,c,d,e} $P < 0.05$ for all comparisons

Results

Populations analysis profile (PAP)



Efficacy of Daptomycin plus Fosfomycin against Methicillin-Resistant Staphylococci

- Synergistic and rapidly bactericidal against MRSA EE
- At least as effective as Daptomycin plus Cloxacillin against MRSA EE
- More effective than vancomycin against MRSA EE
- Less effective than Daptomycin plus Cloxacillin against MRSE EE

Garcia de la María C. AAC. 2018 May 25;62(6). pii: e02633-17;
Garcia de la Maria C et al. SEIMC 2017. Manuscript in preparation

SEICAV Proposal for the Antibiotic Treatment of Staphylococcal Endocarditis



IV Rapid Bactericidal Combinations*
+ Drain abscesses
+ Removal foreign body devices

Adding Rifampin in PVE, TAVI-IE, CIED-IE

Outpatient antibiotic therapy: Oral vs. IV

***Daptomycin plus BL or Fosfomycin in allergic patients**

Guidelines vs. New Proposal

2015 ESC/AHA IE

SEICAV Proposal

Prop

- S
- M
- S
- A

RCT in IE (Resting bacteria)

- POET Trial (Denmark, NEJM, 2019)
- RODEO Trial (France)
- OroPAT-IE GAMES Trial (FIS, Spain)

Con

- S
- T
- N
- No RCT SA PVE

RCT in BAC/IE (Planktonic bacteria)

- BACSARM (FIS, Spain)
- SAFO Trial (FIS, Spain)

tro

erapy
untries