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In vivo efficacy of daptomycin in experimental endocarditis caused by vancomycin-resistant *Enterococcus faecium*

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Infectious endocarditis (IE) and *Enterococcus faecium*

Elderly patients with comorbidities (diabetes, hemodialysis)

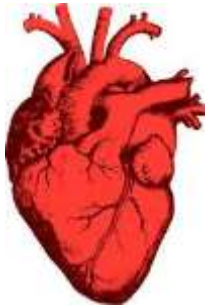
Native valve

1/3 healthcare associated

Sub acute and non-specific clinical presentation

1-year mortality = 30%

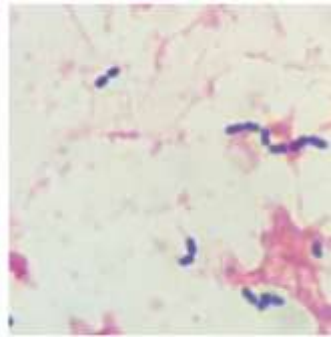
Treatment : glycopeptides



Vancomycin-resistant *Enterococcus faecium* (VRE)

80% *E. faecium* (USA)

➔ daptomycin



Cattoir et al. , Expert Review of Anti-infective Therapy 2014
Chirouze et al. Clinical Microbiology and Infection 2013
2015 ESC Guidelines

- Daptomycin susceptibility breakpoint= 4 mg/L
- Treatment failures and emergence of resistant mutants during daptomycin treatment of severe VRE infection
- Optimum posology according to MIC for VRE endocarditis : no in vivo study

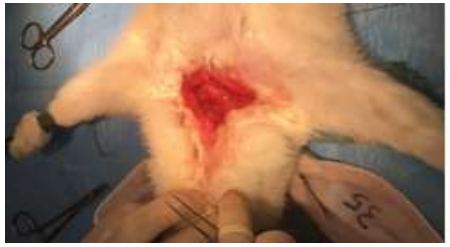
Objectives of the study

➔ **Determine *in vivo* the optimal dosage according to the MIC**

➔ **Evaluate the emergence of resistance**

Kelesidis et al. Journal of Antimicrobial Chemotherapy, 2013
Arias et al. Clinical Infectious Disease, 2007

Materiel & Methods




D0
- Cardiac catheterisation

D1
- Inoculation
- 10^8 CFU/mL

D3
- Blood culture
- Antibiotherapy (5 days)

D9
- Blood culture
- Sacrifice/dissection
- Quantitative cultures (cardiac vegetations / spleen)

Strains

- Aus0004 (MIC= 2 mg/L)
- Mut4 (MIC= 4 mg/L)

Daptomycin

- Control (*n*=12)
- 8 mg/kg (DAP8) (*n*=12)
- 12 mg/kg (DAP12) (*n*=12)

Resistant mutant analysis

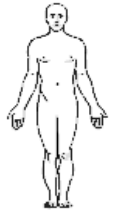
- Vegetations plated on agar supplemented with daptomycin (2x or 4x MIC)
- MIC (microdilution method)

Plasma daptomycin levels: dose equivalent human/rabbit

Time-kill curves: daptomycin bactericidal activity

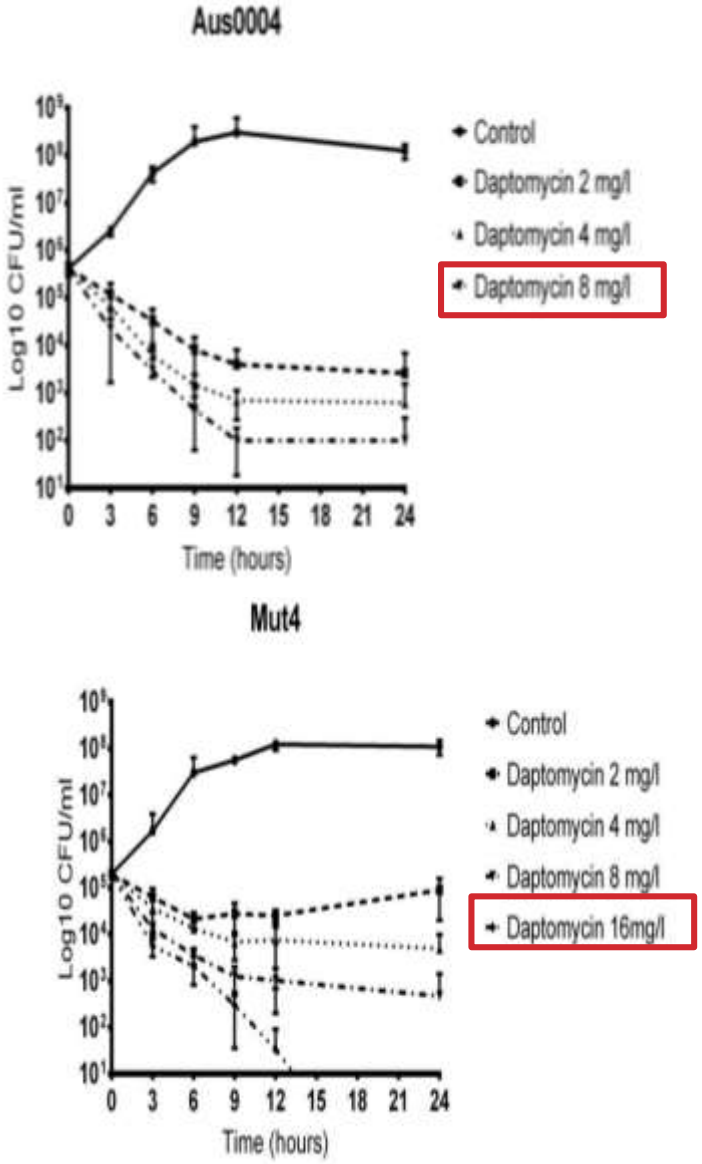
Results

Plasma concentrations

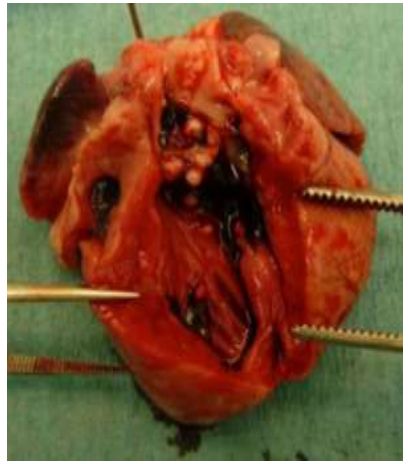
				
Dose (mg/kg)	8	12	22	30
AUC (mg.h/L)	858.2 ± 213	1277 ±253	987.8	1459

Benvenuto et al. Antimicrobial Agents and Chemotherapy, 2006

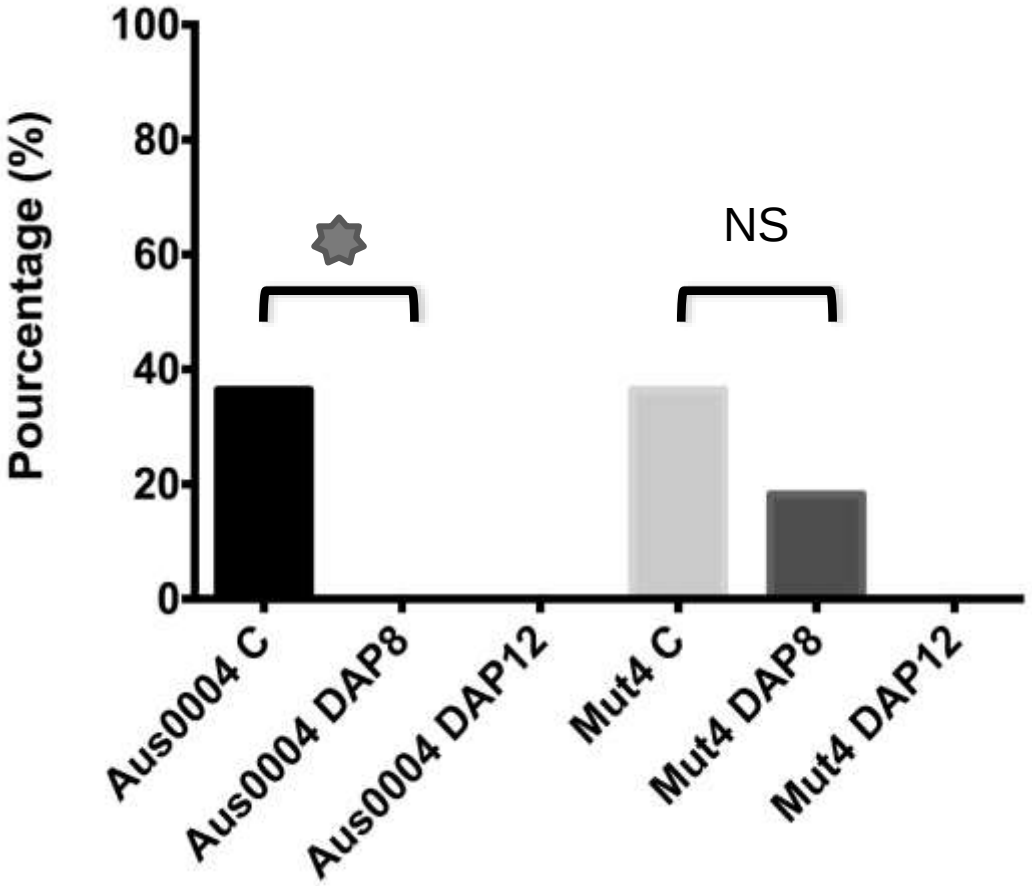
Time-kill curves



Experimental model (*n*= 65 rabbits)



Mortality



- Aus0004 (MIC= 2 mg/L)
  - Control: 4 (*n*=11)

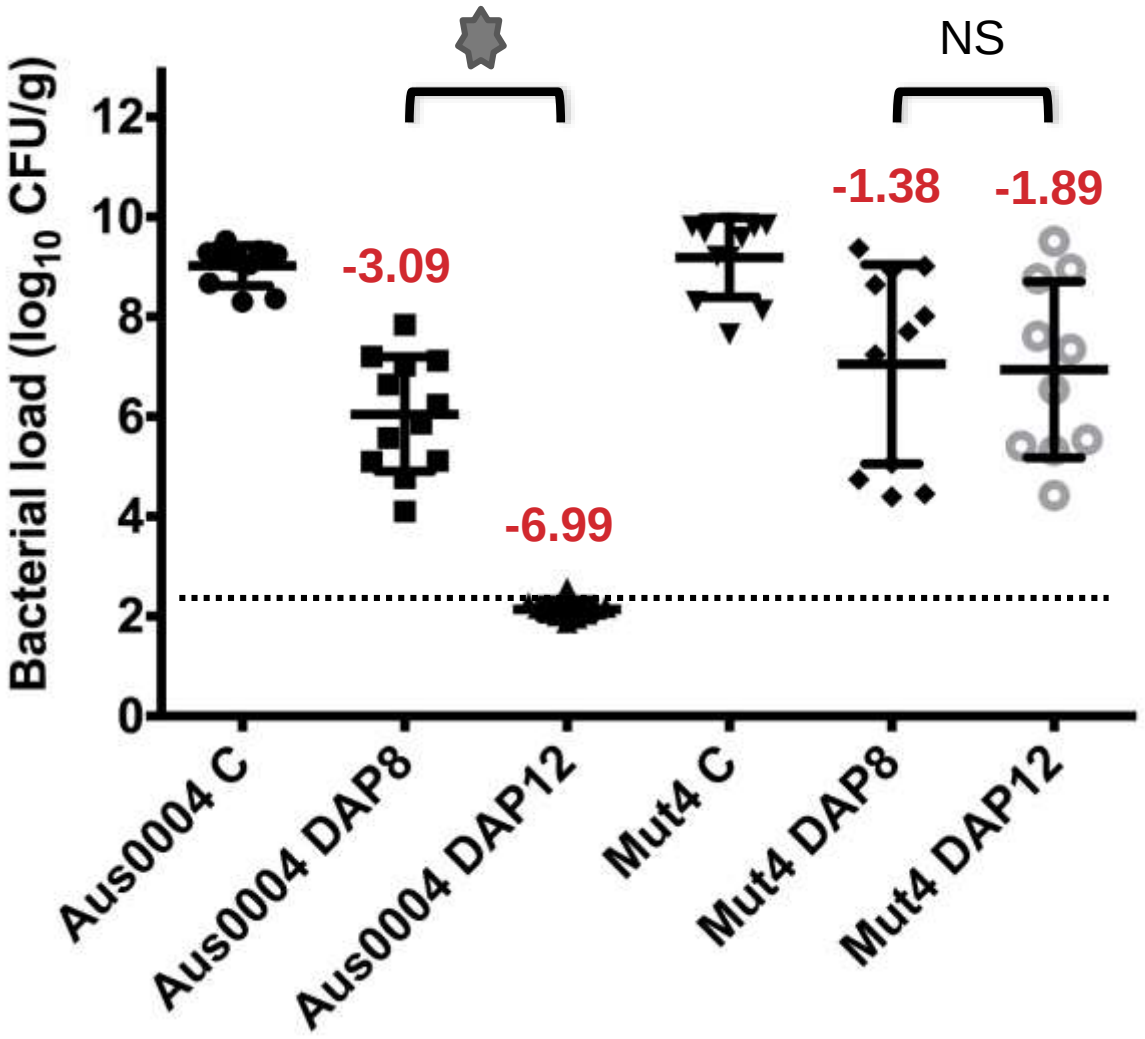
➔ Significant reduction with treatment (DAP8)

- Mut4 (MIC= 4 mg/L)
  - Control: 4 (*n*=11)
  - DAP8: 2 (*n*=11)

➔ No significant reduction

P<0.05

Vegetations bacterial count



P<0.05

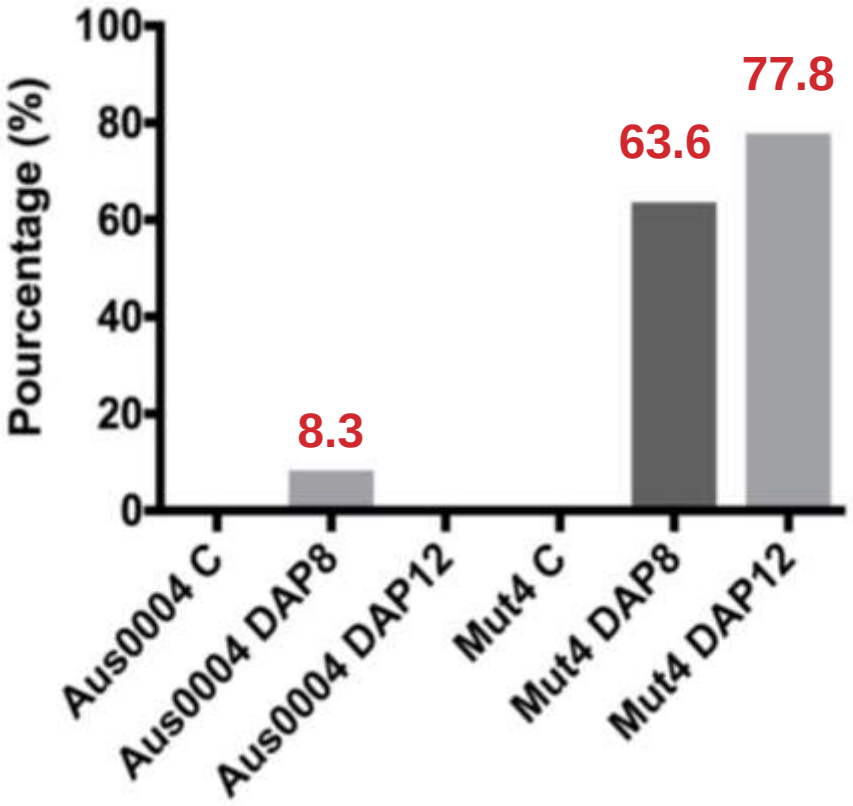
- Aus0004 (MIC= 2 mg/L)
  - Significant reduction with both doses

➔ DAP12 > DAP 8

- Mut 4 (MIC= 4 mg/L)
  - Significant reduction with both doses

➔ DAP8 = DAP12

Resistant mutant



- Aus0004 (MIC= 2mg/L)
  - DAP8: 8,3%

  ➔ MIC= 4 mg/L

- Mut4 (MIC= 2mg/L)
  - DAP8: 63,6%

  ➔ MIC= 8 – 32mg/L

  - DAP12: 77,8%

  ➔ MIC= 8 – 16mg/L

Discussion

VRE – MIC= 2 mg/L

The two dosages were efficient, but 12 mg/kg seems more efficient than 8 mg/kg

- ➔ % sterilized vegetations
- ➔ No resistance

- **Hall *et al.*** Antimicrobial Agents and Chemotherapy, 2012

Evaluation of standard and high dose daptomycin versus linezolid against vancomycin-resistant Enterococcus isolates in an in vitro pharmacokinetic/pharmacodynamiq model with stimulated endocardial vegetations.

- **Werth *et al*.** Antimicrobial Agents and Chemotherapy, 2014

Defining daptomycin resistance prevention exposures in vancomycin-resistant Enterococcus faecium and Enterococcus faecalis

- **Senneville *et al.*** International Journal of Antimicrobial Agents, 2016

Toward a definition of daptomycin optimal dose : lessons from experimental and clinical data.

VRE – MIC= 4 mg/L

The two dosages were moderatly efficient

- ➔ Bacterial load diminution
- ➔ No sterilization of vegetations
- ➔ Mortality rate similar to control
- ➔ Many resistant mutants

- **Shukla *et al.***, Clinical Infectious Disease, 2016

Influence of minimal inhibitory concentration in clinical outcomes of Enterococcus faecium bacteremia treated with daptomycin: is it time to change the breakpoint?

Reassessment of the daptomycin susceptibility breakpoint for enterococci (2 mg/L?)

Acknowledgment

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Backup slides

Limits

- Monotherapy
- Risks of recurrence/mid term mortality?

Perspectives

- Mechanism of resistance
- Daptomycin in association

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 Gentamicin[d]	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
	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. This combination is not active against *E. faecium*
	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.					
Vancomycin[f] with Gentamicin[d]	30 mg/kg/day i.v. in 2 doses	6	I	C		
	3 mg/kg/day i.v. or i.m. in 1 dose	6	I	C		
	Paediatric doses:[e] Vancomycin 40 mg/kg/day i.v. in 2–3 equally divided doses. Gentamicin as above					

HLAR: high-level aminoglycoside resistance; IE: infective endocarditis; MIC: minimum inhibitory concentration; PBP: penicillin binding protein; PVE: prosthetic valve endocarditis.
[a]High-level resistance to gentamicin (MIC >500 mg/L): if susceptible to streptomycin, replace gentamicin with streptomycin 15 mg/kg/day in two equally divided doses.
[b]Beta-lactam resistance: (i) if due to beta-lactamase production, replace ampicillin with ampicillin–sulbactam or amoxicillin with amoxicillin–clavulanate; (ii) if due to PBP5 alteration, use vancomycin-based regimens.
[c]Multiresistance to aminoglycosides, beta-lactams and vancomycin: suggested alternatives are (i) daptomycin 10 mg/kg/day plus ampicillin 200 mg/kg/day i.v. in four to six doses; (ii) linezolid 2 × 600 mg/day i.v. or orally for ≥8 weeks (IIa, C) (monitor haematological toxicity); (iii) quinupristin–dalfopristin 3 × 7.5 mg/kg/day for ≥8 weeks. Quinupristin–dalfopristin is not active against *E. faecalis*; (iv) for other combinations (daptomycin plus ertapenem or ceftaroline), consult infectious diseases specialists.

- **Shukla *et al.***, Clinical Infectious Disease, 2016

Influence of minimal inhibitory concentration in clinical outcomes of Enterococcus faecium bacteremia treated with daptomycin: is it time to change the breakpoint?

➔ Retrospective study

➔ 62 patients – E. faecium bacteremia

➔ MIC= 3-4 mg/L

➔ Strains with MICs= 3-4 mg/L : microbiological failures

- **Hall *et al.*** Antimicrobial Agents and Chemotherapy, 2012

Evaluation of standard and high dose daptomycin versus linezolid against vancomycin-resistant Enterococcus isolates in an in vitro pharmacokinetic/pharmacodynamiq model with stimulated endocardial vegetations.

➔ Simulated vegetations

➔ MIC= 2 – 4 mg/L

➔ Bactericial acyivity maintained at 96h only with 10 and 12 mg/kg

➔ Daptomycin doses of > 10 mg/kg may be necessary to treat high inoculum VRE infections.

- **Werth et al.** Antimicrobial Agents and Chemotherapy, 2014

Defining daptomycin resistance prevention exposures in vancomycin-resistant Enterococcus faecium and Enterococcus faecalis

➔ Simulated vegetations

➔ MIC= 2 mg/L

➔ 4, 6 and 8 mg/kg: resistant mutants

➔ Doses of >10 mg/kg may be required to prevent reistance in serious enterococcal infections.