XI Congreso de la SEICAV 2022

Mesa 2: Aspectos Actuales de la Endocarditis Infecciosa

Sevilla, 11 de noviembre del 2022

Avances en el tratamiento antimicrobiano de la endocarditis infecciosa

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Transparency Declaration

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

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ViiV Healthcare

Advances in antimicrobial treatment of infective endocarditis

- **The paradigm shift is already here**
- How to finish the puzzle of the ideal antibiotic treatment: from bench to bedside
- Science fiction or reality: phages and lysins
- Some take home messages

Antibiotic treatment of infective endocarditis

0 1 2 ≥ 6 weeks

Early critical phase*

Continuation phase (resting bacteria)

Inpatient treatment
IV rapid bactericidal combinations
Cardiac surgery if indicated
+ Removal infected cardiac devices
+ Drain abscesses

Complicated cases: Continue inpatient IV treatment

From 10 days of treatment initiation and/or postsurgery consider home therapy (OPAT/oral antibiotic) in stable patients

*Planktonic bacteria

Perform TEE before therapy switch

Miro JM. SEICAV. Madrid. 2019; Cuervo G et al. Semin Respir Crit Care Med. 2022.

The NEW ENGLAND JOURNAL of MEDICINE

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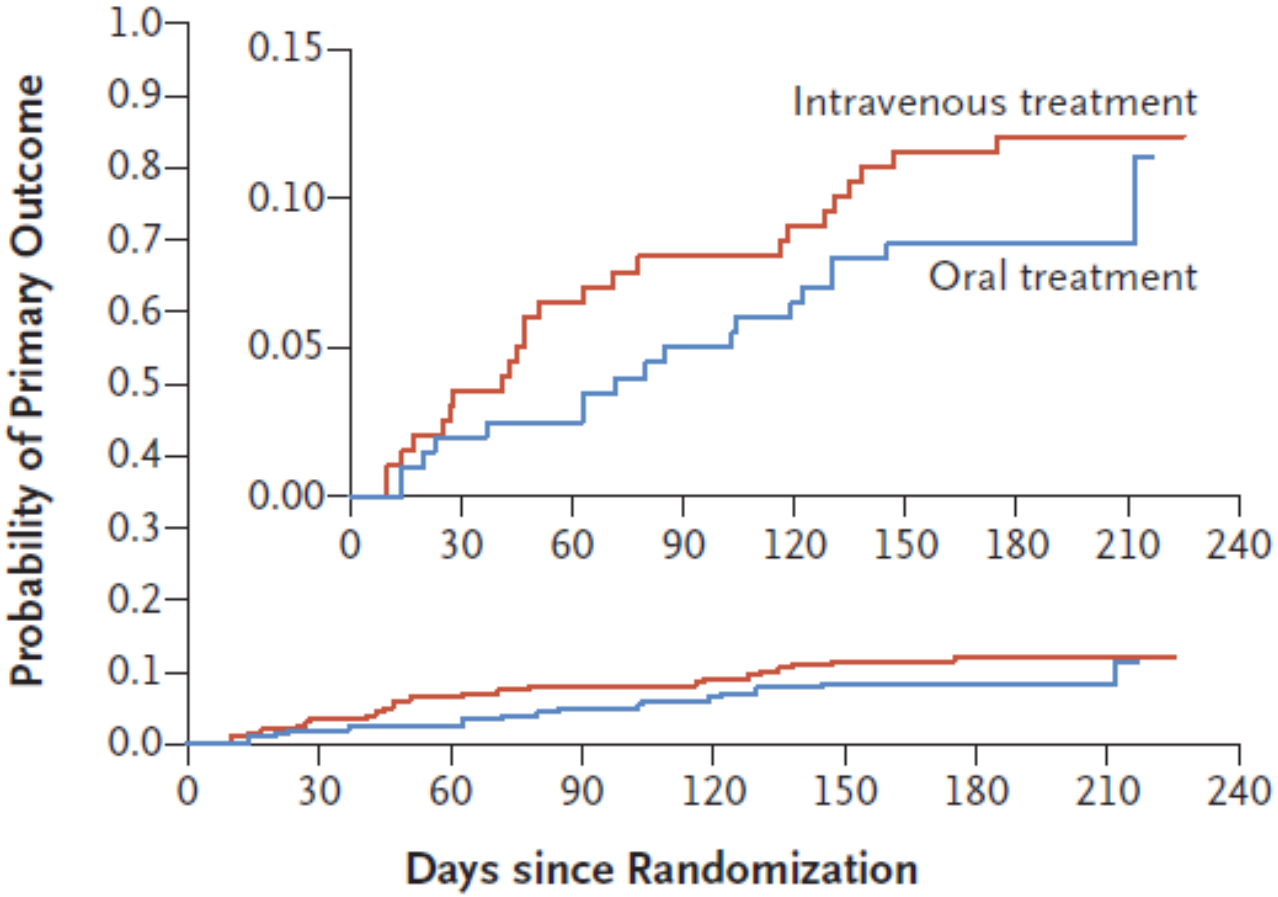
Partial Oral versus Intravenous Antibiotic Treatment of Endocarditis

Kasper Iversen, M.D., D.M.Sc., Nikolaj Ihlemann, M.D., Ph.D., Sabine U. Gill, M.D., Ph.D., Trine Madsen, M.D., Ph.D., Hanne Elming, M.D., Ph.D., Kaare T. Jensen, M.D., Ph.D., Niels E. Bruun, M.D., D.M.Sc., Dan E. Høfsten, M.D., Ph.D., Kurt Fursted, M.D., D.M.Sc., Jens J. Christensen, M.D., D.M.Sc., Martin Schultz, M.D., Christine F. Klein, M.D., Emil L. Fosbøll, M.D., Ph.D., Flemming Rosenvinge, M.D., Henrik C. Schønheyder, M.D., D.M.Sc., Lars Køber, M.D., D.M.Sc., Christian Torp-Pedersen, M.D., D.M.Sc., Jannik Helweg-Larsen, M.D., D.M.Sc., Niels Tønder, M.D., D.M.Sc., Claus Moser, M.D., Ph.D., and Henning Bundgaard, M.D., D.M.Sc.

Iversen K et al. N Engl J Med. 2019;380:415-24.

Partial Oral vs. IV Antibiotic Treatment of IE: The POET Trial



No. at Risk

Intravenous treatment	199	192	186	183	181	176	174	28	0
Oral treatment	201	197	196	191	188	184	183	36	0

IV Antibiotic Treatment at Hospital

No OPAT !!!

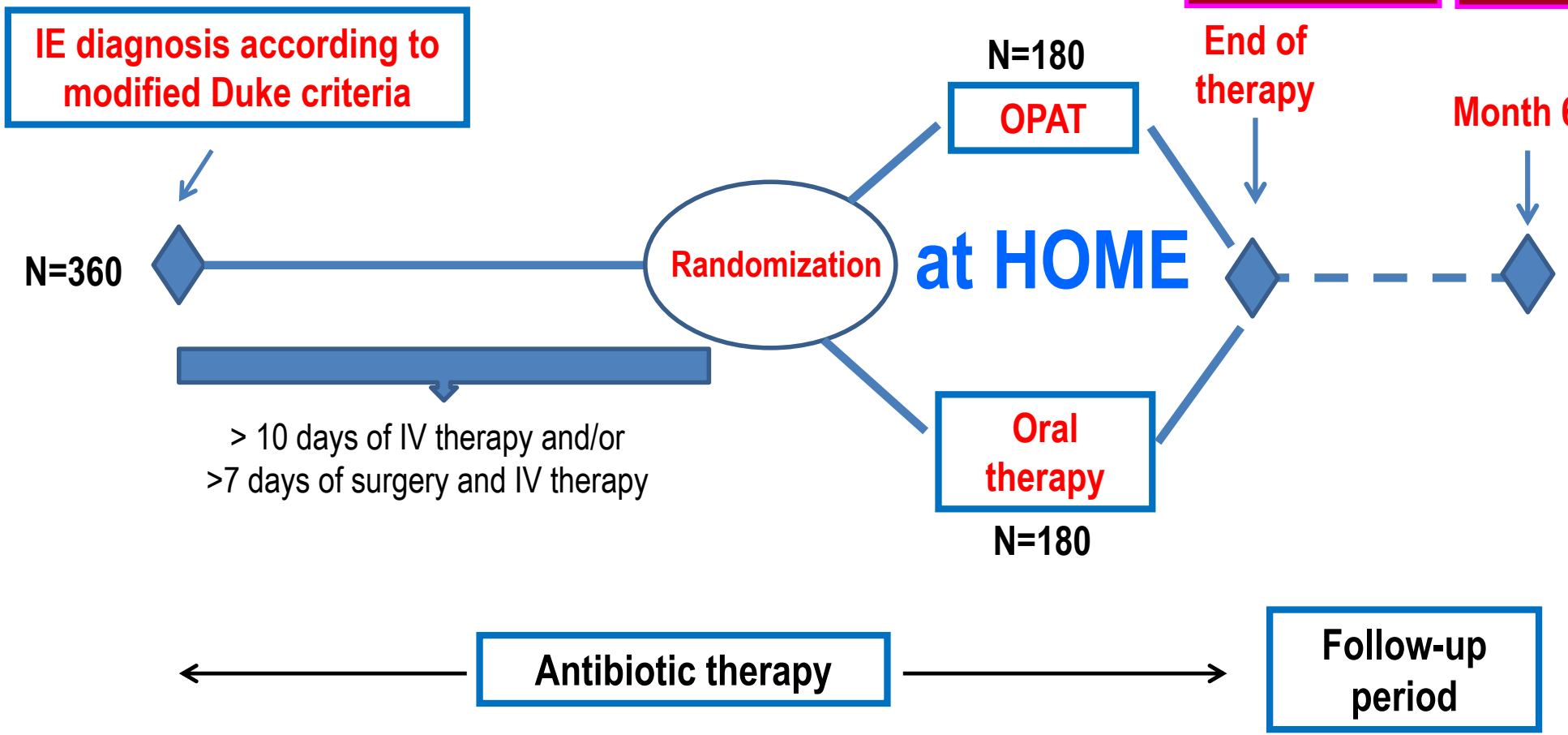
Iversen K et al. N Engl J Med. 2019;380:415-24.

Outpatient Oral *vs.* Parenteral Antimicrobial Therapy for IE trial (OraPAT-IE GAMES trial)

G. Cuervo

J. Ambrosioni

Investigator-driven, multicentre, open, non-inferiority RCT



The RODEO Trial: IV to Oral De-escalation Trial

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

Staphylococcal & Streptococcal IE (N=648)

→ **Full course of IV Therapy 6 weeks (2015 ESC)**

→ **IV (14 d.) to Oral Therapy LEV+RIF/AMX 4 weeks**

- Approved in October 2014.
- Recruitment started on March 2016.
- Only staphylococcal left sided NV/PV IE will be included. Susceptible to study drugs (MSSA, MSSE)
- The primary end point is a composition (M3) of all-cause mortality, unplanned cardiac surgery and relapse.

Dalbavancin for OPAT IE

	Spanish Study* N= 34	Austrian Study** N=27
Type of IE		
- NVE	32%	59%
- PVE		
- PCM/ICD		
Previous therapy		
- Days (median, IQR)		
OPAT, days (median)		
- Adverse events	6%	7%
- Failures	3%	7%
- Cure rate	**97%**	**93%**

EN-DALBACEN 2.0
Observational study (N=124)
Effectiveness: 91% (ITT)
Hidalgo-Tenorio C et al.
SEICAV 2022 - Oral Presentation

*Hidalgo-Tenorio C et al. Ann Clin Microbiol Antimicrob. 2019 Oct 19;18(1):30. doi: 10.1186/s12941-019-0329-6.; ** Tobudic S et al. Clin Infect Dis. 2018; 67:795-798; *** **1/3 received 500 mg once-weekly (LD 1000 mg) and 2/3 500 mg twice-weekly (LD 1500 mg)**

Advances in antimicrobial treatment of infective endocarditis

- The paradigm shift is already here
- **How to finish the puzzle of the ideal antibiotic treatment: from bench to bedside**
- Science fiction or reality: phages and lysins
- Some take home messages

Experimental Endocarditis Model

C. Garcia de la Maria

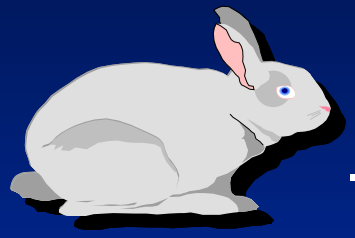
Day

0

1

2

5



- Aortic valve lesion - catheter (carotid artery)

⇦ ANTIBIOTIC PROPHYLAXIS

- I.V. microorganism challenge

⇦ PATHOGENESIS

⇦ ANTIBIOTIC TREATMENT
ANTIBIOTIC DIFUSSION INTO VEGETATIONS

- Animal sacrifice. Qualitative & quantitative culture of aortic valve vegetations

Garrison & Freedman, 1970; Durack & Benson, 1972; Sande & Irwin, 1974.

Time to reappraise the antibiotic treatment for MSSA IE: data from the experimental endocarditis model

Day

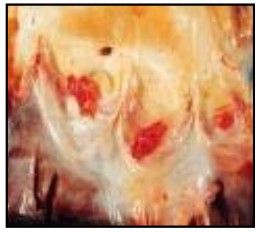
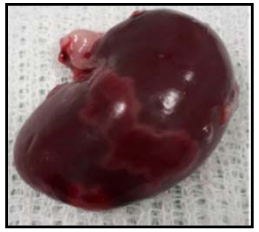
1 — Induction of nonbacterial thrombotic endocarditis of the aortic valve (the polyethylene catheter was left in place).

2 — Intravenous MSSA inoculum (5 x 10^5 CFU/mL).

3 — After 16 hours, blood cultures were taken from all animals, control animals were sacrificed and antibiotic treatment was started using the infusion pumps.

4 5 — Antibiotic treatment was maintained for 48h.
- Cloxacillin (2 g/4 h)
- Ceftaroline (600 mg/8h or 12h)
- Daptomycin (6 or 10 mg/Kg/day)
- Daptomycin + Cloxacillin
- Daptomycin + Ceftaroline

7 — Animals were sacrificed 6 half-lives after completing the antibiotic treatment.

Aortic valve vegetations, spleen and left kidney were quantitatively and qualitatively cultured.


Garcia de la Maria C et al. 15th ISCVID. Lausanne, Switzerland. June 2-4 2019 #O25

How to finish the puzzle of the ideal antibiotic treatment for IE

- *Staphylococcus aureus* **(MSSA)**

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

Garcia de la Maria C et al. 15th ISCVID. Lausanne, Switzerland. June 2-4 2019 #O25

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

Garcia de la Maria C et al. 15th ISCVID. Lausanne, Switzerland. June 2-4 2019 #O25

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)

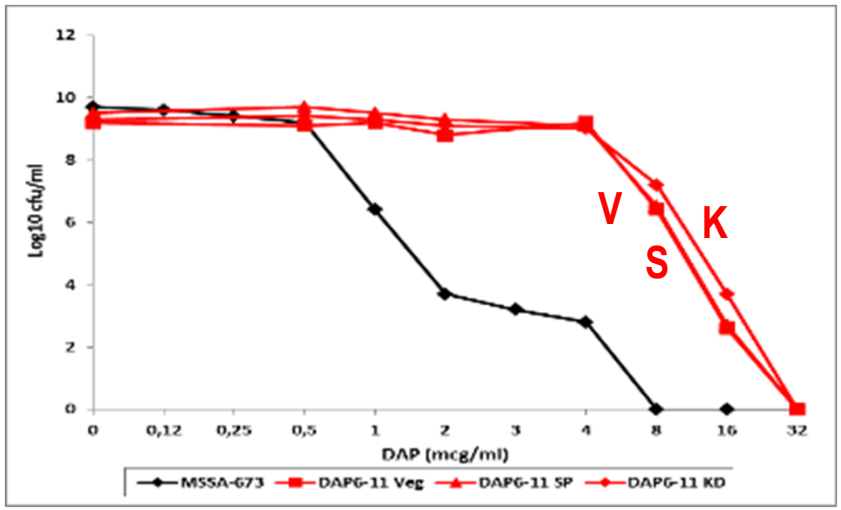
4/20 (20%) DNS isolates, **1/19 (5,3%) DNS isolates ; [a,b,c,d,e]$P < 0.05$ for all comparisons

Garcia de la Maria C et al. 15th ISCVID. Lausanne, Switzerland. June 2-4 2019 #O25

Results Populations analysis profile (PAP)

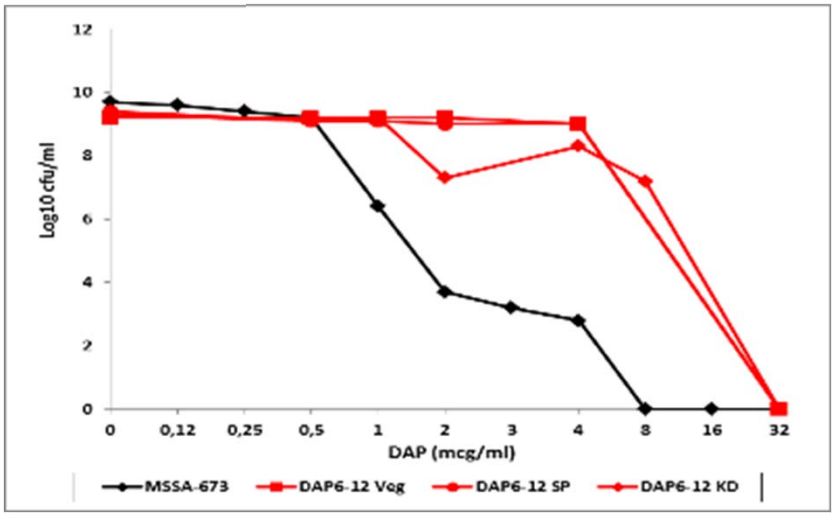
MSSA-673

DAP 6 mg/kg



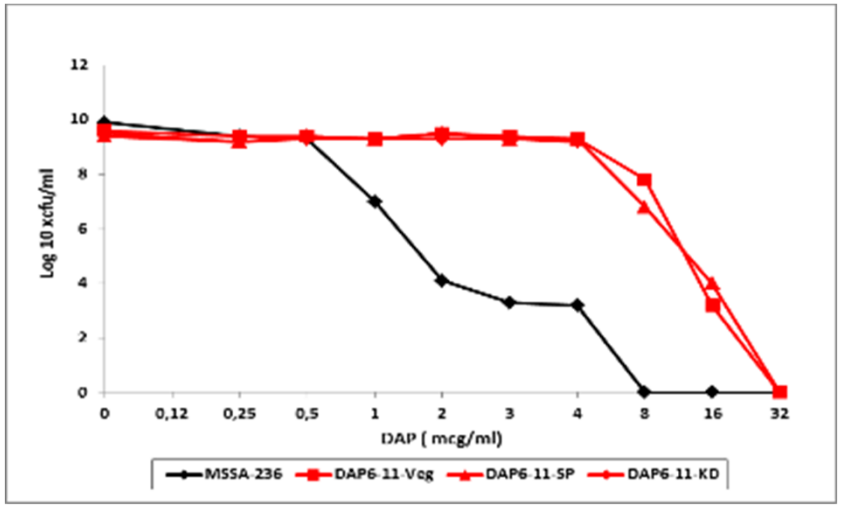
MSSA-673

DAP 6 mg/kg



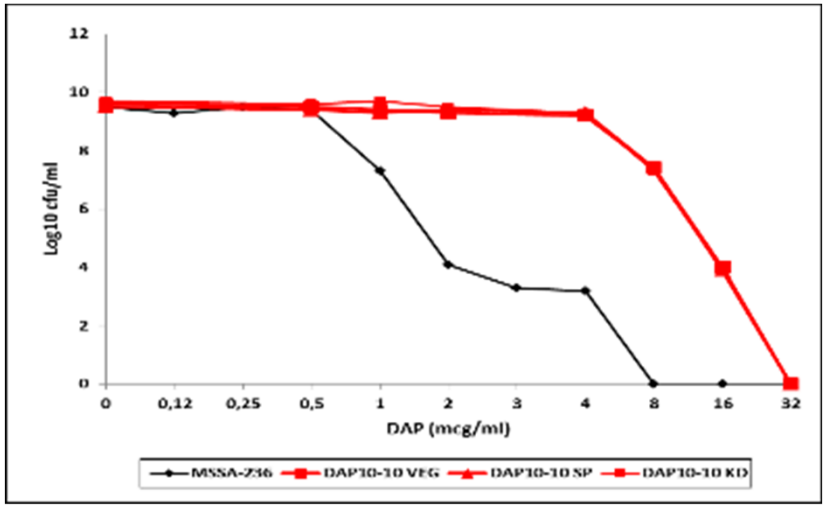
MSSA-236

DAP 6 mg/kg



MSSA-236

DAP 10 mg/kg



Garcia de la Maria C et al. 15th ISCVID. Lausanne, Switzerland. June 2-4 2019 #O25

Practical issues: How to improve the activity of daptomycin in MSSA infective endocarditis

- **Daptomycin must be given at high doses (10 mg/kg) and always combined with beta-lactams (cloxacillin, ceftaroline) or fosfomycin.**

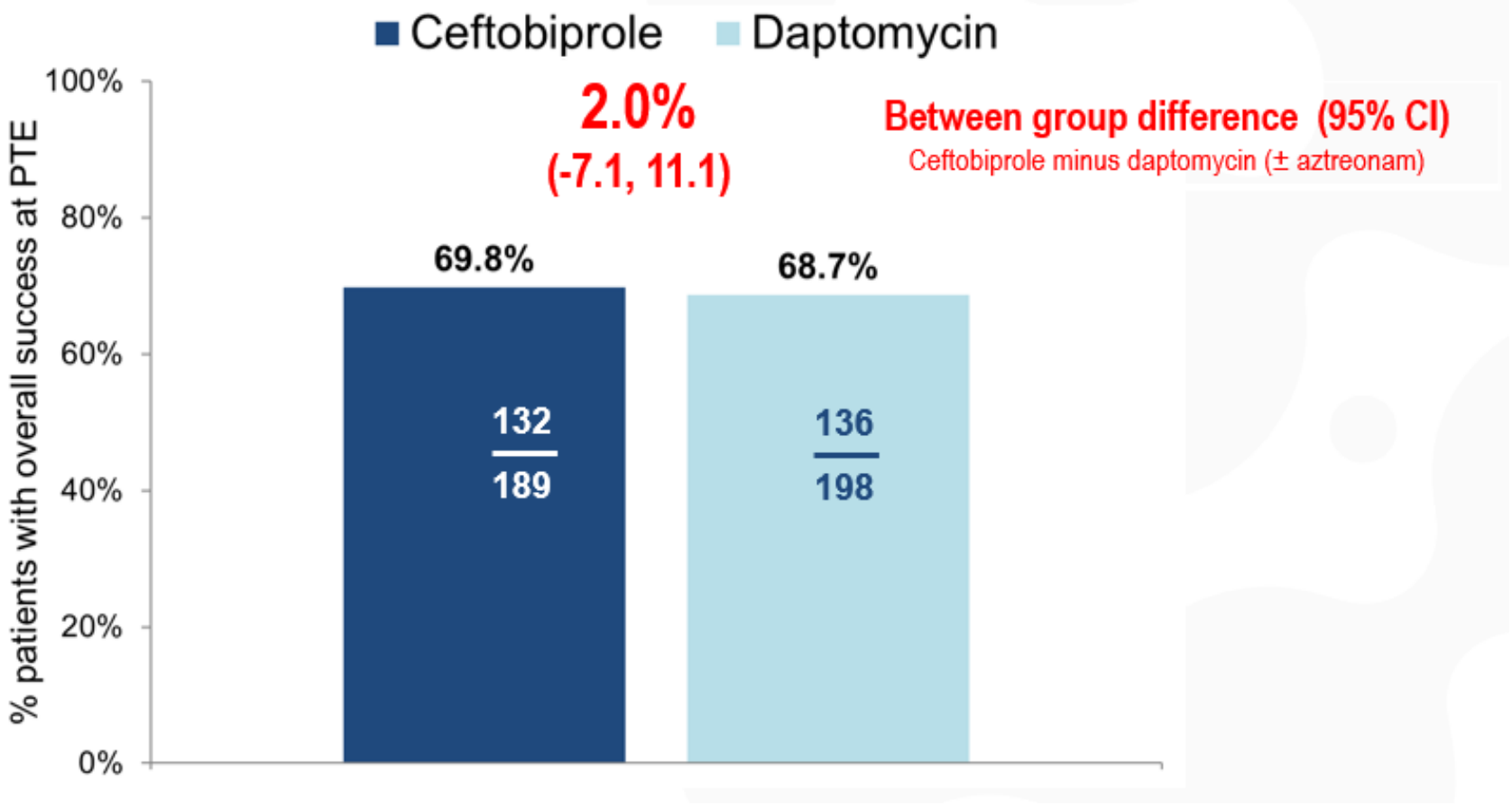
- In monotherapy there is a high risk of development of daptomycin resistance (DNS) and the activity in extracardiac metastasis (spleen, kidney) is lower than that of beta-lactams (cloxacillin, ceftaroline).

*Garcia de la Maria C et al. ECCMID. Amsterdam, NL, 2019 #00923; Garcia de la Maria C et al. 15th ISCVID. Lausanne, Switzerland. June 2-4 2019 #O25

Ceftobiprole = Daptomycin for the Treatment of Complicated SAB: Results ERADICATE Trial

Ceftobiprole met primary endpoint

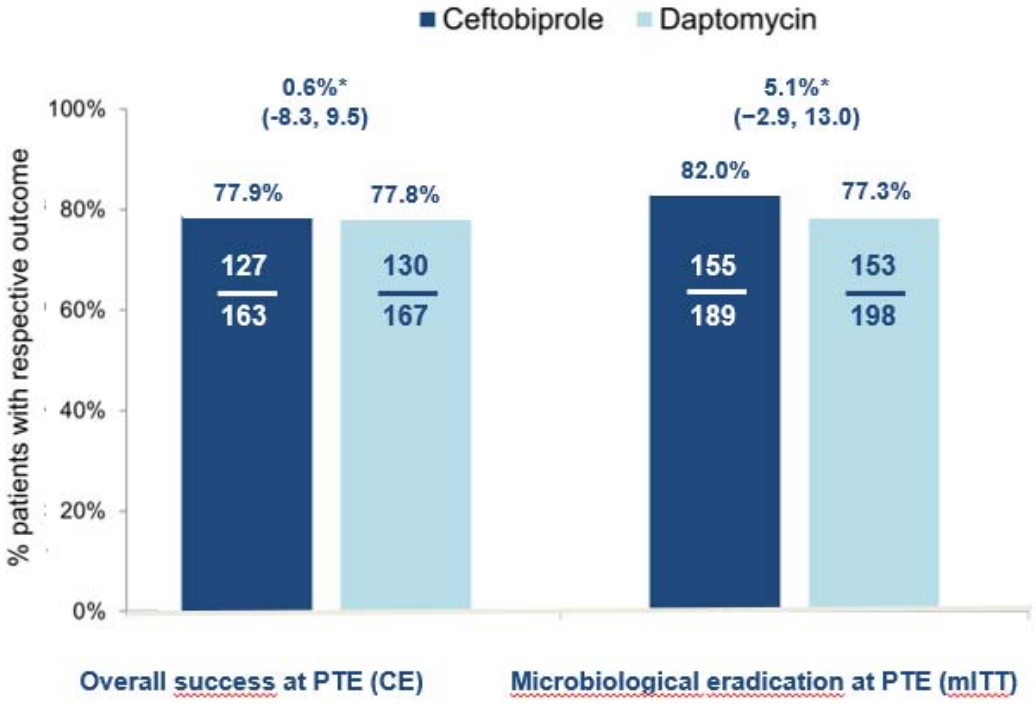
DRC assessed overall success at PTE in mITT population

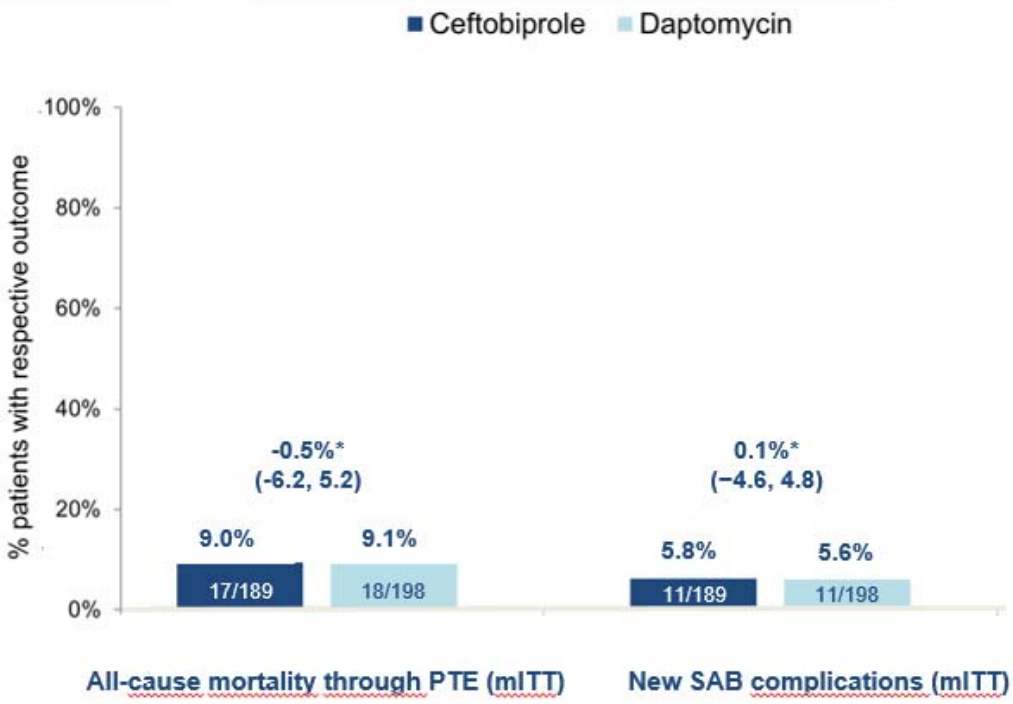


Holland T et al. IDWeek. Washington, D.C. Oct 13 2022; LB2302

Ceftobiprole = Daptomycin for the Treatment of Complicated SAB: Results ERADICATE Trial

Secondary efficacy outcomes were similar

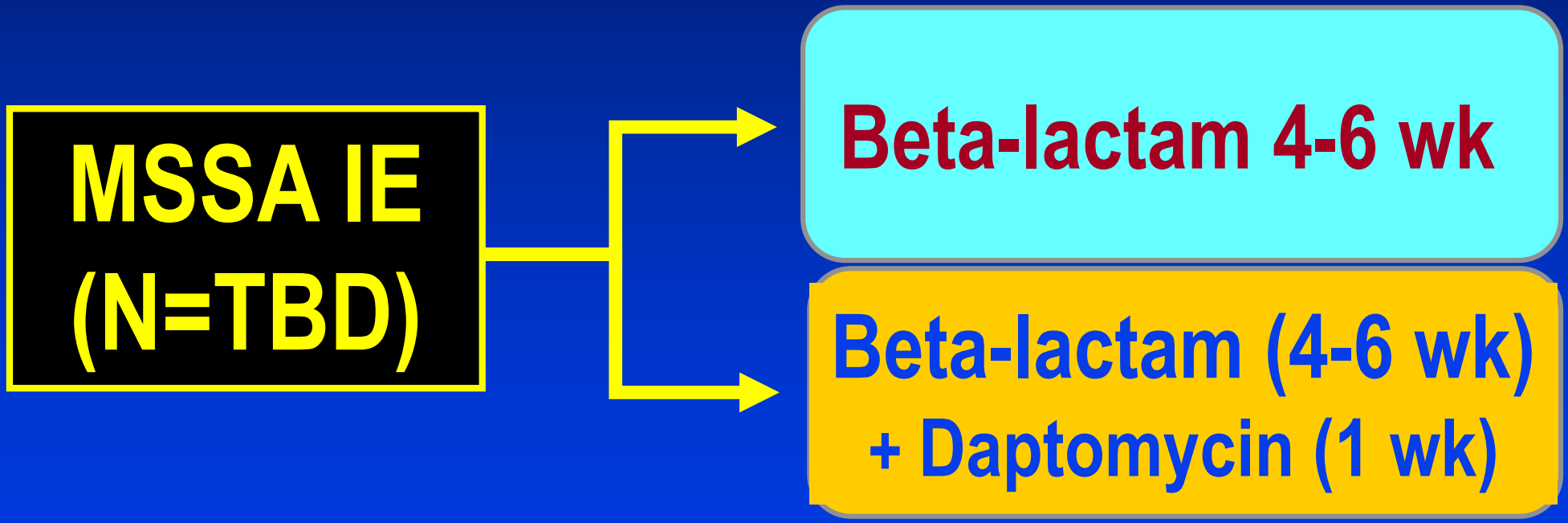




Holland T et al. IDWeek. Washington, D.C. Oct 13 2022; LB2302

RCT of the Efficacy and Safety of Beta-lactam *vs.* Beta-lactam plus Daptomycin for the Treatment of MSSA IE

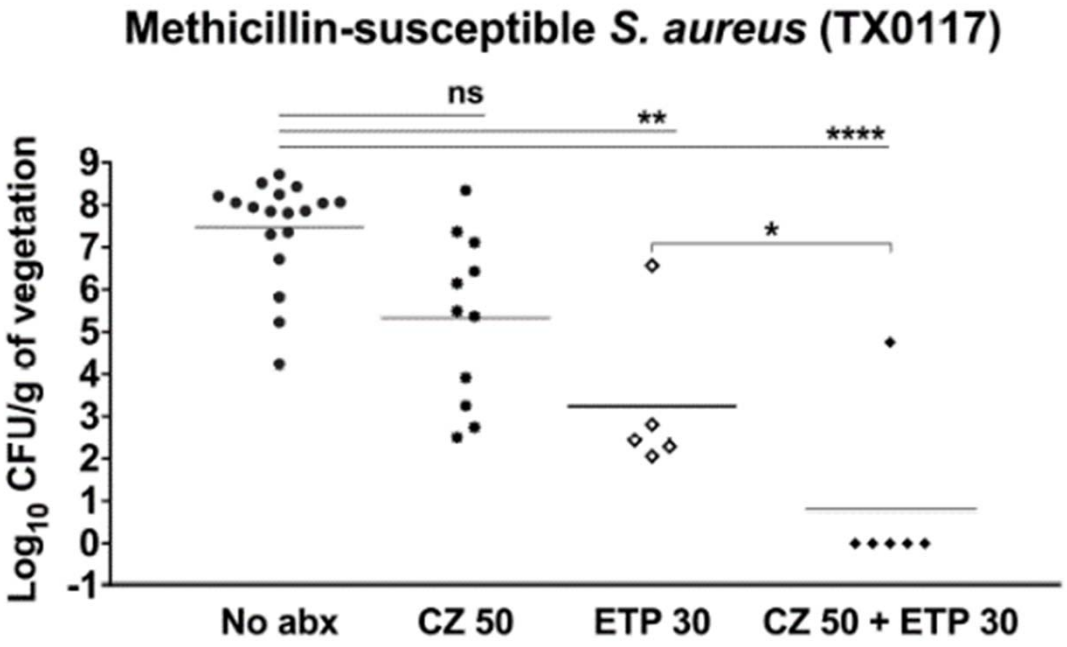
Multicenter, Randomized (1:1) Open-label Clinical Trial



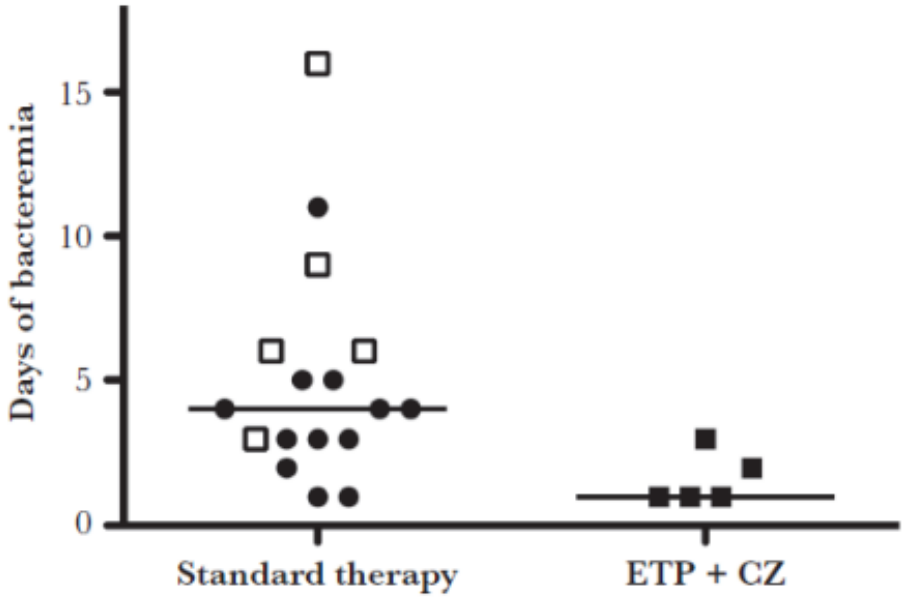
- Recruitment: 2 yr. Spain/Europe
- Only MSSA IE. Beta-lactam: cloxacillin or ceftaroline
- End points: TOC 12 weeks after finishing Rx, Toxicity, Relapses, Resistance, Surgery and Mortality.

Cefazolin plus Ertapenem as Salvage Therapy for MSSA IE

- **Cefazolin (CZ) plus ertapenem (ETP) combination therapy** was used successfully to salvage 11 cases (6 endocarditis) of persistent MSSA bacteremia, including immediate clearance (≤24 hours) in 8 cases.
- **In a second study**, MSSA IE cases treated with cefazolin (CZ) plus ertapenem (ETP) were compared with matched IE cases treated with standard beta-lactam monotherapy. The median duration of bacteremia experienced by patients (n = 12) while on CZ or NAF was 4 days (range 1–16 days) compared with 1 day (range 1–3 days) for patients (n = 5) treated with ETP + CZ (P = .01)



Efficacy of antibiotic therapy in the MSSA EE rat model



Total bacteremia days on standard *vs.* CZ + ETP therapy

Ulloa ER et al. Clin Infect Dis. 2020; 71:1413-1418; Gilbertie J et al. Open Forum Infect Dis. 2022 Mar 23;9(5):ofac159.

How to finish the puzzle of the ideal antibiotic treatment for IE

- *Staphylococcus aureus* (**MSSA**)
- *Staphylococcus epidermidis*
- **Viridans group streptococci**
- *Enterococcus faecium*

Vancomycin and Daptomycin combinations for the treatment of MRSE Experimental Endocarditis

TREATMENT GROUPS	Sterile Veg. no/total(%)	Median (IQR) (log_{10} UFC/g veg)
Control	0/15 (0)	7.4 (6 - 8.3)
SD-Vancomycin (VAN)	3/16 (19)[a,b]	2 (2 - 2)[d]
HD-VAN (AUC/MIC>400)	**5/15 (33)[c]**	2 (0 - 2,8)[e]

[a]*p*=0.002, [b]*p*=0.046, [c]*p*=0.03, [d]*p*=0.002, [e]*p*=0.015.

Garcia de la Maria C et al. SEICAV, Sevilla, 12 de Noviembre del 2022

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HD-VAN (AUC/MIC>400)	5/15 (33)[c]	2 (0 - 2,8)[e]
Daptomycin (DAP)-6 mg/kg	9/15 (60)[b]	0 (0 - 4.1)
DAP-10 mg/kg	11/15 (73%)[a,c]	0 (0-1)[d]

[a]p=0.002, [b]p=0.046, [c]p=0.03, [d]p=0.002, [e]p=0.015.

In none case were recovered isolates resistant to DAP or FOM.

Garcia de la Maria C et al. SEICAV, Sevilla, 12 de Noviembre del 2022

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HD-VAN (AUC/MIC>400)	5/15 (33)[c]	2 (0 - 2,8)[e]
Daptomycin (DAP)-6 mg/kg	9/15 (60)[b]	0 (0 - 4.1)
DAP-10 mg/kg	11/15 (73%)[a,c]	0 (0-1)[d]
Fosfomycin (FOM)	4/15 (27)	2 (1 - 2)
DAP-6 + Cloxacillin	11/15 (73)[ac]	0 (0 - 2)[d,e]
DAP-6 + FOM	4/10 (40)	2 (0 - 2)

[a]p=0.002, [b]p=0.046, [c]p=0.03, [d]p=0.002, [e]p=0.015.

In none case were recovered isolates resistant to DAP or FOM.

Garcia de la Maria C et al. SEICAV, Sevilla, 12 de Noviembre del 2022

Daptomycin (DAP) plus Ceftriaxone (CRO) for the treatment of Penicillin-resistant *Streptococcus mitis* EE

Treatment arms	Median (IQR) log_{10} CFU/g of vegetation	Median (IQR) log_{10} CFU/g of kidney
Untreated controls (7)	8.49 ± 0.65	5.27 ± 0.71
DAP 4 mg/kg iv once daily x 4 d (7)	7.66 ± 0.87	4.16 ± 0.78
DAP 6 mg/kg (7)	7.43 ± 1.06	3.90 ± 0.67
DAP 8 mg/kg (6)	8.24 ± 0.82	4.71 ± 0.91
DAP 10 mg/kg (6)	7.50 ± 1.08	4.18 ± 0.49
CRO 40 mg/kg iv once daily x 4 d (7)	7.81 ± 0.65	3.94 ± 0.51
DAP (4mg/kg) + CRO (6)	5.51 ± 1.18	1.93 ± 0.72
DAP (8mg/kg) + CRO (6)	0.62 ± 0.07[h]	0.69 ± 0.08[h]

[h]p<0.05 for all comparisons.

All DAP monotherapy arms developed HLDR.

Mishra NN et al. AAC. 2022; submitted

Daptomycin plus Fosfomycin for the treatment of Vancomycin-resistant *Enterococcus faecium* EE

Time-killing curves at inoculum 10^5				
Enterococcus faecium strains	Antibiotic combinations			
	DAP + AMP	DAP + CTL	DAP + ERT	DAP + FOM
EFAC-ERV1	Synergistic	Synergistic	Synergistic + Bactericidal	Synergistic
EFAC-ERV35	Synergistic	Synergistic	Synergistic + Bactericidal	Synergistic
EFAC-ERV98	Synergistic	Synergistic	Synergistic	Synergistic
EFAC-ERV99	Synergistic	Synergistic	Synergistic	Synergistic

DAP=Daptomycin; AMP=Ampicillin; CTL=Ceftaroline; FOM=Fosfomycin

Garcia-Gonzalez J et al. 2022. Manuscript in preparation

Daptomycin plus Fosfomycin for the treatment of Vancomycin-resistant *Enterococcus faecium* EE

In vivo results: Vegetations growth

Treatment group	Animals with sterile vegetations/total (%)	Median (IQR) log_{10} CFU/g of vegetation
Control (no treated)	0/10 (0%)	8,5 (7,8 - 9)[a]
Daptomycin (10 mg/kg/d)	0/10 (0%)	7,2 (5,6 - 7,7)[a,b]
Daptomycin + Fosfomycin (2 g/6h)	1/10 (10%)	2,9 (2 - 4,5)[b]

[a]*P*= 0.023 ; [b]*P*= 0.002

DAP monotherapy: **In 7 of the 10 strains (70%)** there was a MIC increase in the isolates recovered from the vegetations.

Garcia-Gonzalez J et al. 2022. Manuscript in preparation.

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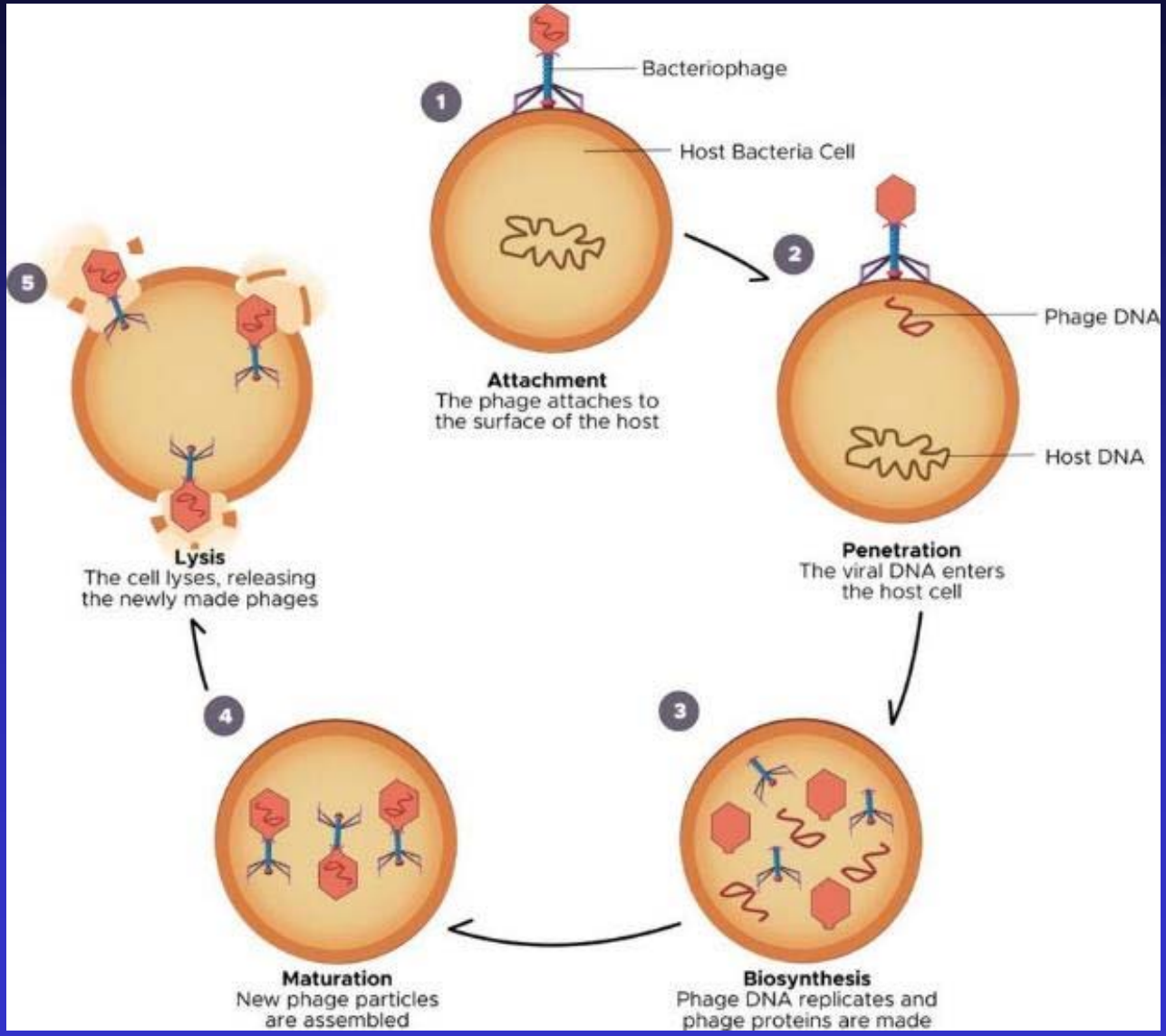
- The paradigm shift is already here
- How to finish the puzzle of the ideal antibiotic treatment: from bench to bedside
- **Science fiction or reality: phages and lysins**
- Some take home messages

Lysins and bacteriophages for SAB/IE

	ContraFect	lysovant	ARMATA PHARMACEUTICALS
Product	CF-301 (Exebacase)	LSVT-1701 (Tonabacase)	AP-SA02
MoA	Recombinant endolysin	Recombinant endolysin	Natural bacteriophage mix
Indication	M	M	SA bacteremia (TBD)
Stage	P		Phase 1b/2 ready
Position	P S c		First-in-class
RoA	2		IV infusion
Dosing	Single infusion Cannot be dosed twice	QD for 4-5 days Can likely be dosed multiple times	Single infusion (self replicating)
Dose adjustments	For renally impaired patients	None anticipated	TBD
Catalytic domains	1 (endopeptidase)	2 (endopeptidase, amidase)	TBD
Safety	AE profile similar to SOC	AE profile similar to SOC	Potential immune response

www.clinicaltrials.gov projects
Phages: 5
Lysins: 2
November 2022

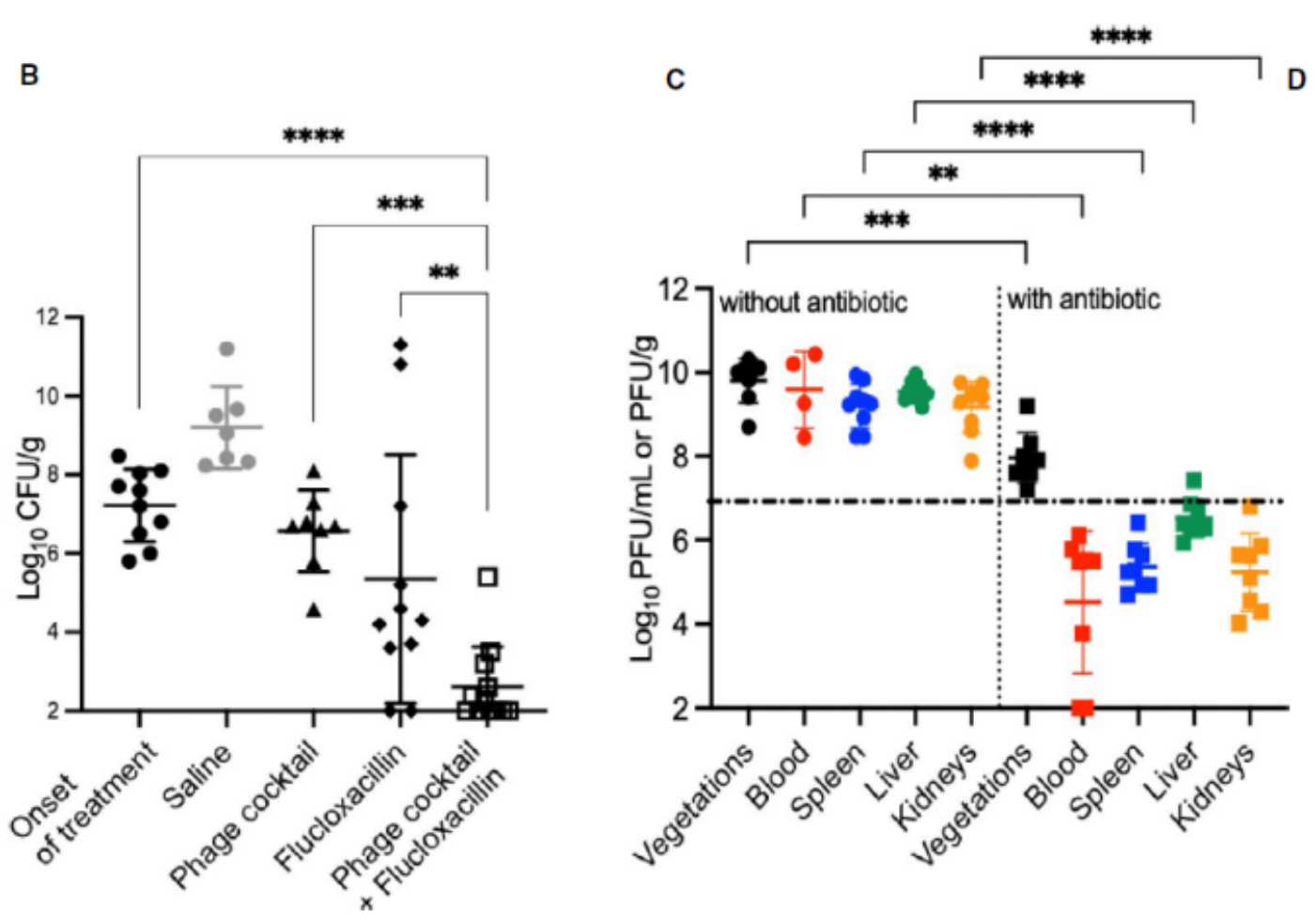
Life cycle of lytic phages "inside-out" bacterial killing



Bayer A. ISCVID. Barcelona. June 2022.

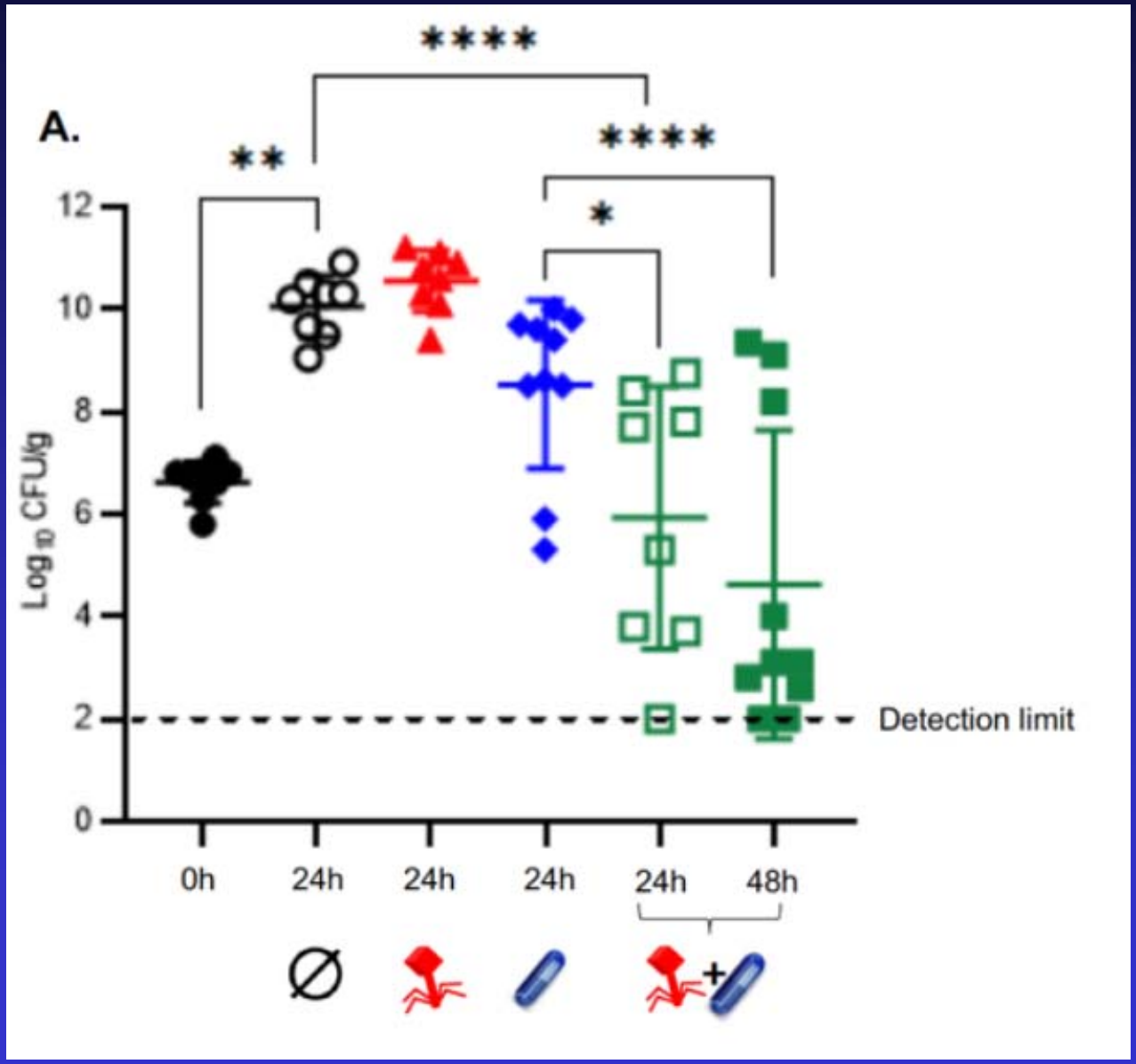
Subtherapeutic Doses of Flucoxacillin Synergize with Bacteriophages for Treatment of MSSA EE

- The efficacy of a phage cocktail combining **Herelleviridae phage vB_SauH_2002 and Podoviriae phage 66** was evaluated against a MSSA strain in vitro and in vivo in a rodent model of EE.



Save J, et al. J Am Heart Assoc. 2022;11:e023080. DOI: 10.1161/JAHA.121.023080 1.

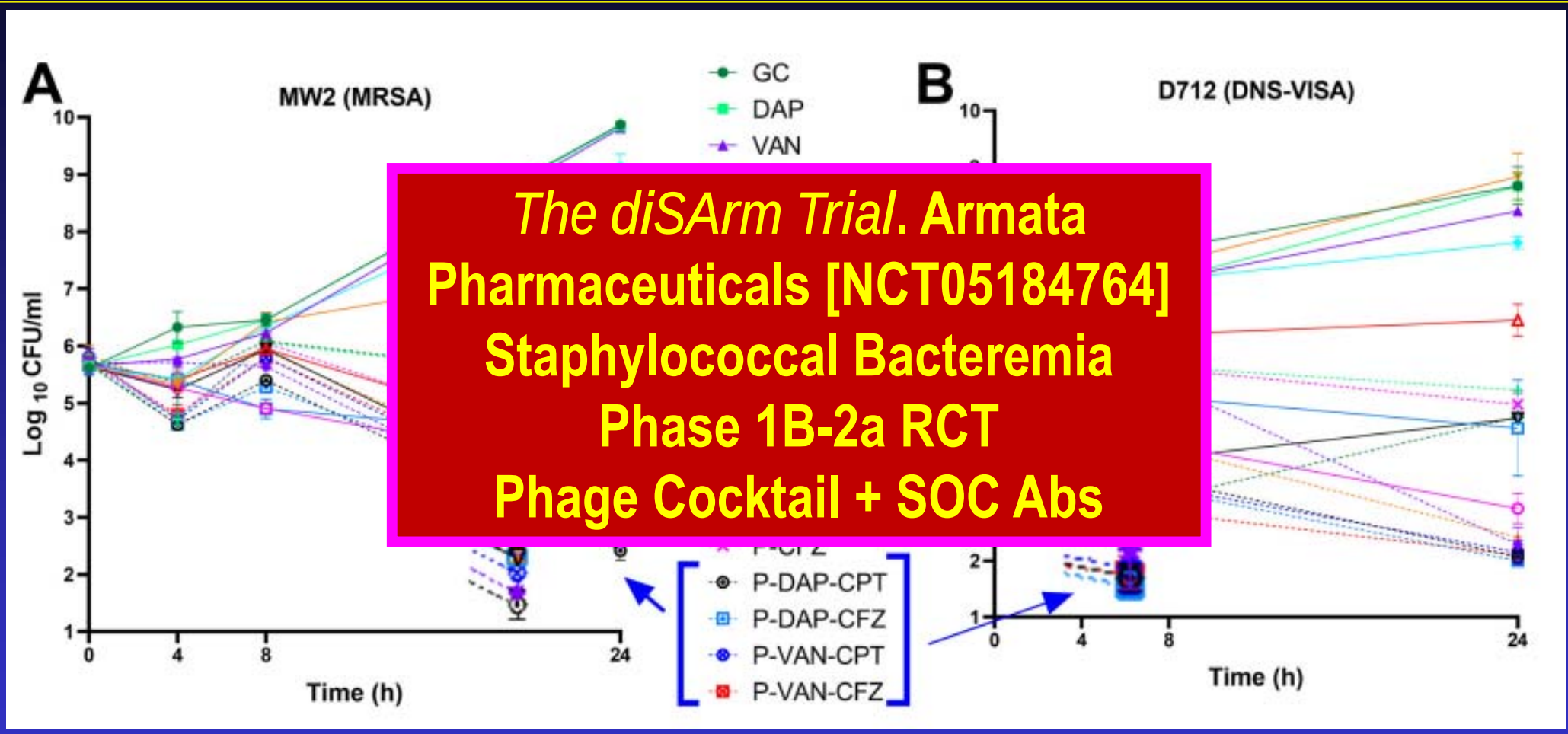
Subtherapeutic Doses of Vancomycin Synergize with Bacteriophages for Treatment of MRSA EE



Bacterial loads in cardiac vegetations measured at 6 h post infection (i.e., 0 h or onset of treatment) in the control rats (closed black circles, n = 8) and 24 h after the onset of treatment in rats given a mock therapy (saline, open black circles, n = 8), **the Phage Cocktail (Herelleviridae vB_SauH_2002 and Routreeviridae 66)** alone for 24 h (closed red triangles, n = 8), a low dose of vancomycin alone for 24 h (closed blue diamonds, n = 10), or the **Phage Cocktail in combination with vancomycin** for 24 h (open green squares, n = 8) and 48 h (closed green squares, n = 10).

Save J, et al. Viruses. 2022 Aug 16;14(8):1792.

Bacteriophage-Antibiotic Combination Strategy against MRSA



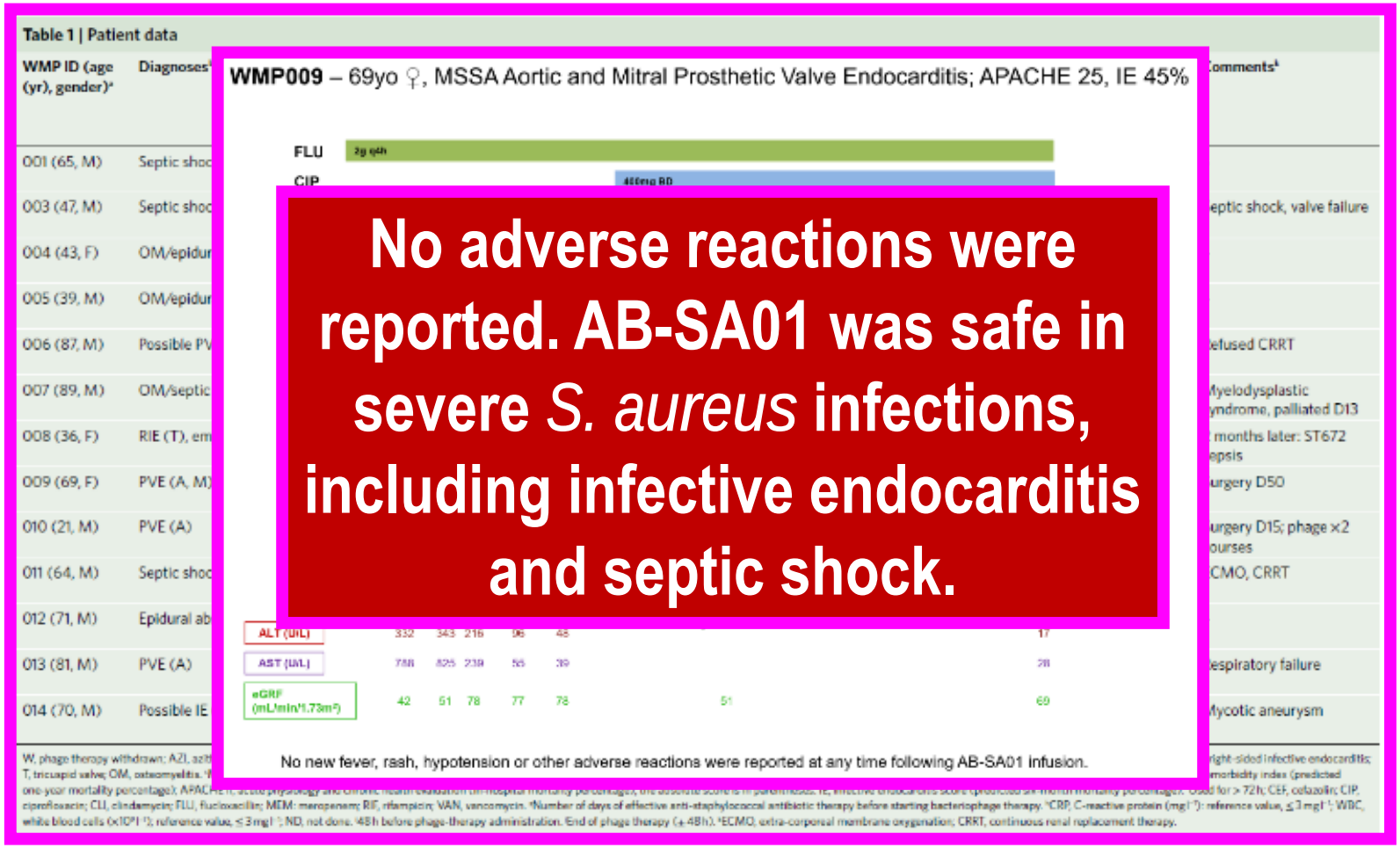
The diSArm Trial. **Armata Pharmaceuticals [NCT05184764] Staphylococcal Bacteremia Phase 1B-2a RCT Phage Cocktail + SOC Abs**

Time-kill experiments versus MRSA strain MW2 and DNS VISA strain D712. **Triple combinations are highlighted as they demonstrated bactericidal activity compared with single antibiotics at the end of 24 h exposure**. VAN, vancomycin; DAP, D, daptomycin; CPT, ceftaroline; CFZ, cefazolin; Phage, P, bacteriophage Sb-1

Kebriaei R et al. AAC. 2020 Jun 23;64(7):e00461-20.

Safety of bacteriophage therapy in severe *Staphylococcus aureus* infections including IE

- In this single-arm non-comparative trial, 13 patients with severe S. aureus infections were IV administered three Myoviridae bacteriophages (AB-SA01) as adjunctive therapy twice daily for 14 d.
- Primary endpoint was safety and tolerability (90 d.)



Petrovic-Fabijan Al et al. Nat Microbiol. 2020 Mar;5(3):465-472.

Lysins and bacteriophages for SAB/IE

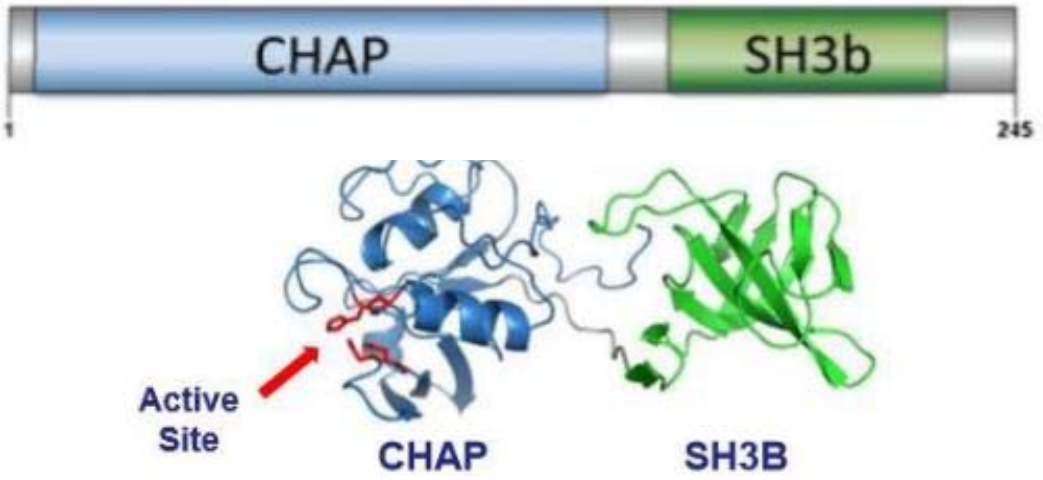
	ContraFect	lysovant	ARMATA PHARMACEUTICALS
Product	**CF-301 (Exebacase)**	**LSVT-1701 (Tonabacase)**	**AP-SA02**
MoA	**Recombinant endolysin**	**Recombinant endolysin**	**Natural bacteriophage mix**
Indication	MRSA bacteremia incl. RSIE	MSSA/MRSA bacteremia incl. IE	SA bacteremia (TBD)
Stage	Ph 3 initiated Jan 2020	Ph 2b ready	Phase 1b/2 ready
Position	First-in-class Significantly ahead of competition	Best-in-class Efficacy, Coverage, Safety	First-in-class
RoA	2-hour IV infusion	1-hour IV infusion	IV infusion
Dosing	Single infusion Cannot be dosed twice	QD for 4-5 days Can likely be dosed multiple times	Single infusion (self replicating)
Dose adjustments	For renally impaired patients	None anticipated	TBD
Catalytic domains	1 (endopeptidase)	2 (endopeptidase, amidase)	TBD
Safety	AE profile similar to SOC	AE profile similar to SOC	Potential immune response

CF-301 *vs.* LSVT-1701 structure

CF-301 (Exebacase)

- Molecular mass: 26 kDa
- Two functional domains:
- One catalytic domain
  - CHAP endopeptidase
- C-terminal cell binding domain (SH3B)

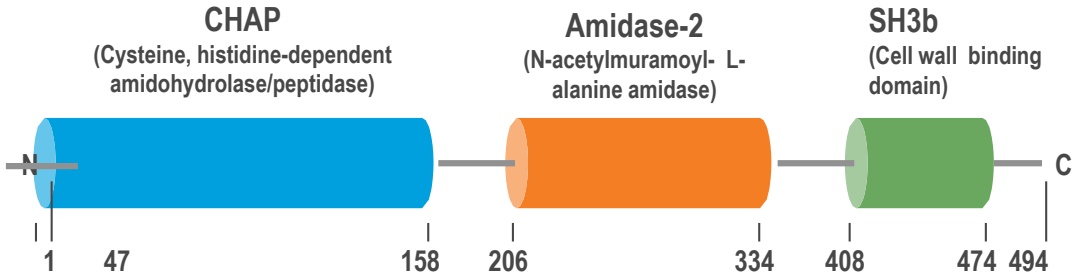
CF-301 endolysin domain structure



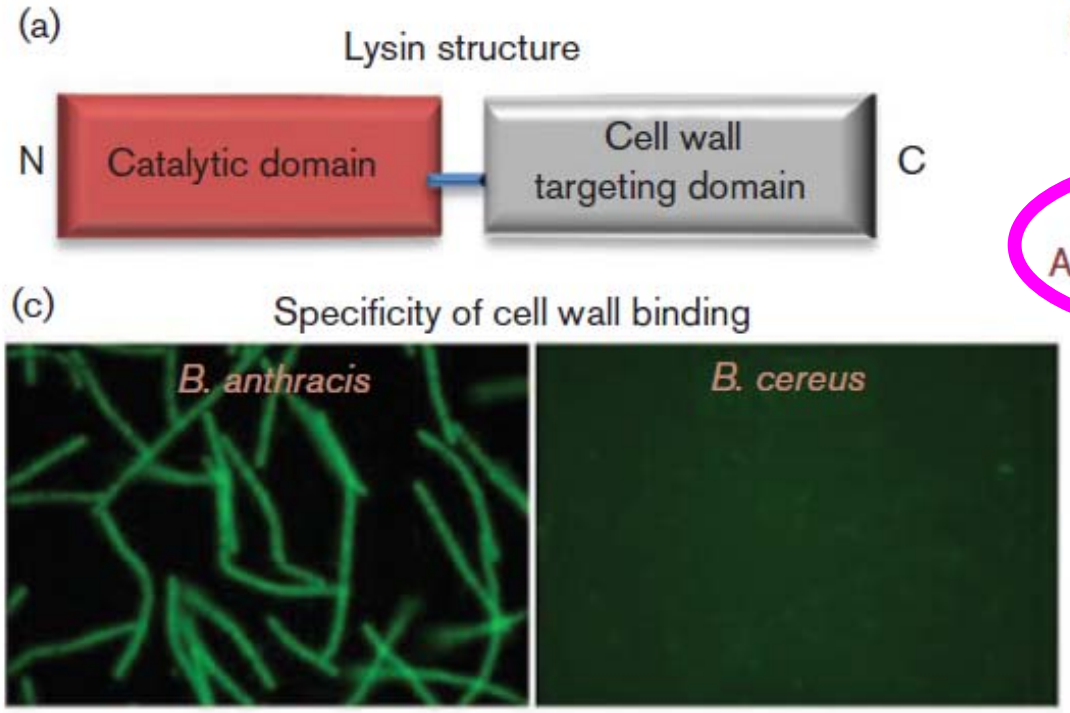
LSVT-1701 (Tonabacase)

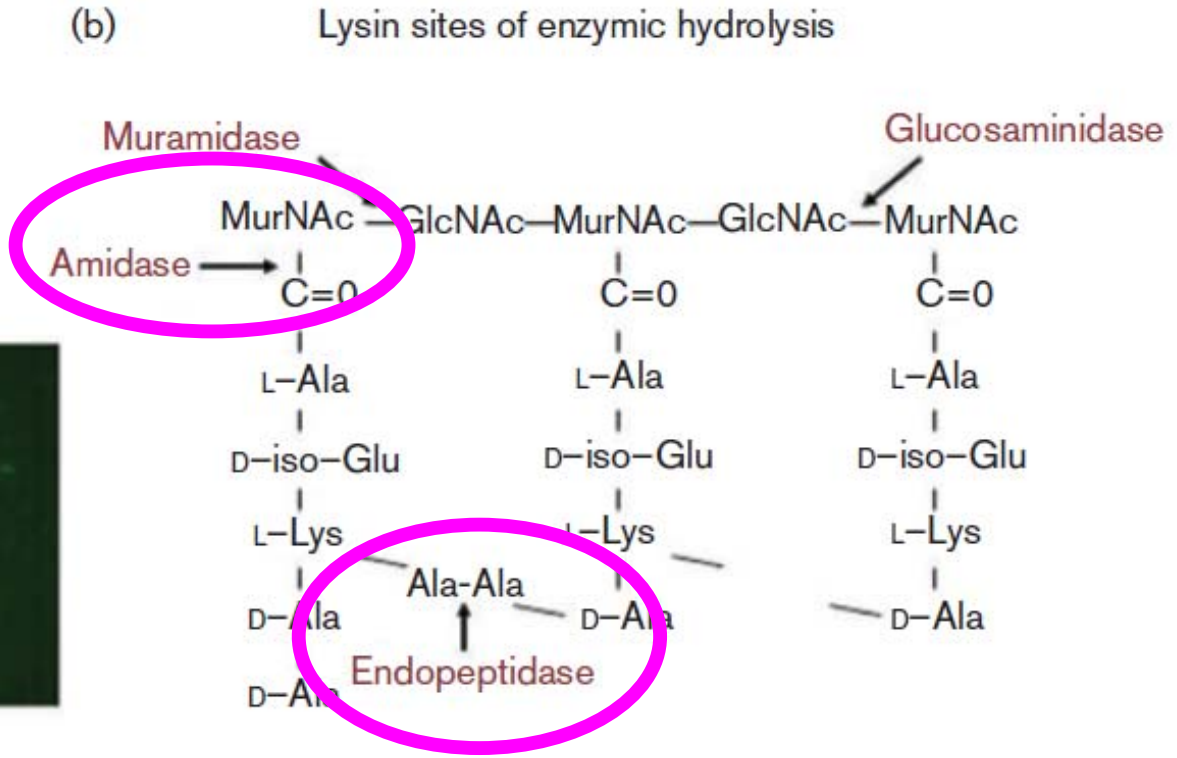
- Molecular mass: 54.6 kDa
- Three functional domains:
- Two catalytic domains
  - CHAP endopeptidase
  - Amidase
- SH3b cell wall targeting domain

SAL-1 endolysin domain structure



Lysin structure, cleavage sites, and specificity

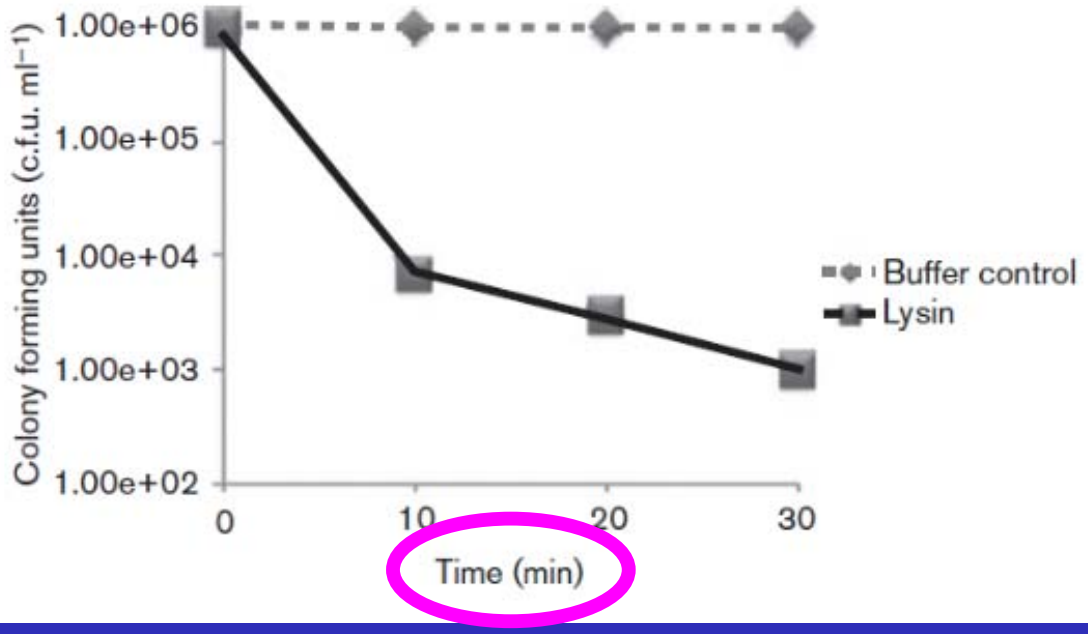


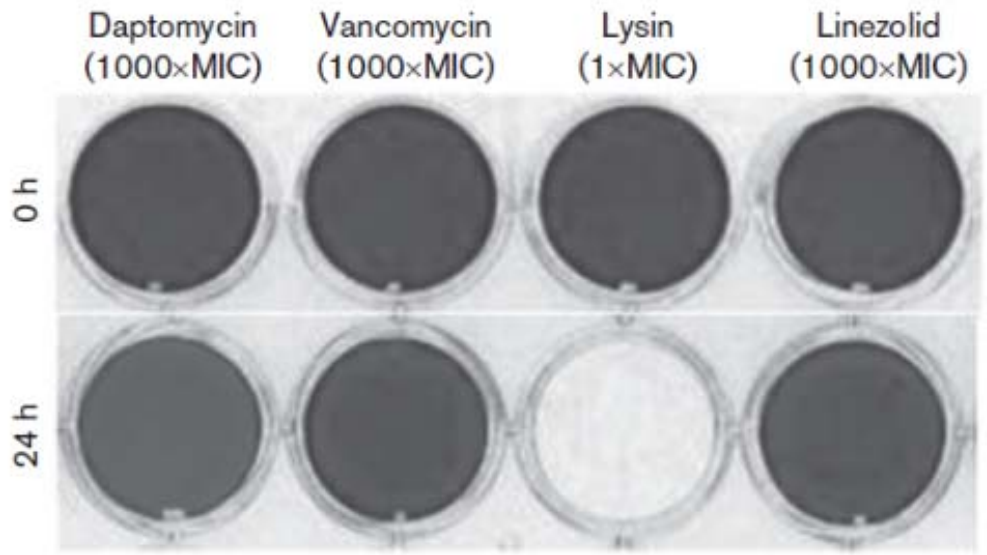


(a) Two-domain structure of phage lytic enzymes, ranging in size from 25 kDa; **(b)** Peptidoglycan bonds sensitive to cleavage by lysins. **(c)** The C-terminal cell-wall targeting (CWT) domain of the PlyG lysin directs species-specific binding to B. anthracis. Fluorescence micrographs depict the specific binding of PlyG (fused to green fluorescent protein) to the surface of B. anthracis, and not to the surface of a very closely related organism (B. cereus).

Pastagia M et al. J Med Microbiol. 2013; 62, 1506–16

Rapid killing ability of lysins (minutes)

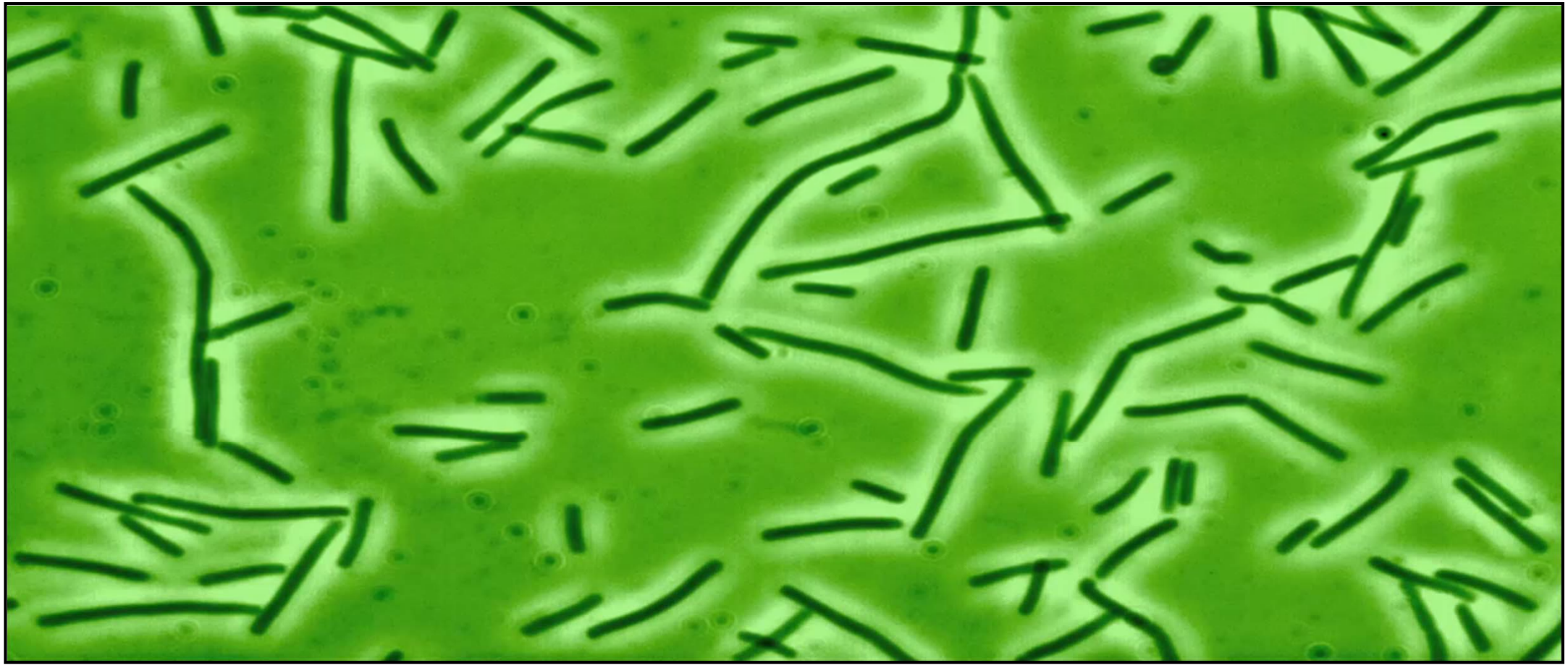




Time-kill experiments using the staphylococcal-specific lysin ClyS (MIC90 32 mg/mL) against MRSA reveal a 3 log c.f.u. mL **reduction of bacteria within 30 min**. **Biofilm assays** with *Staphylococcus aureus* demonstrate **clearance within 24 h** at MIC of ClyS and minimal clearance with antibiotics at 1000 MIC.

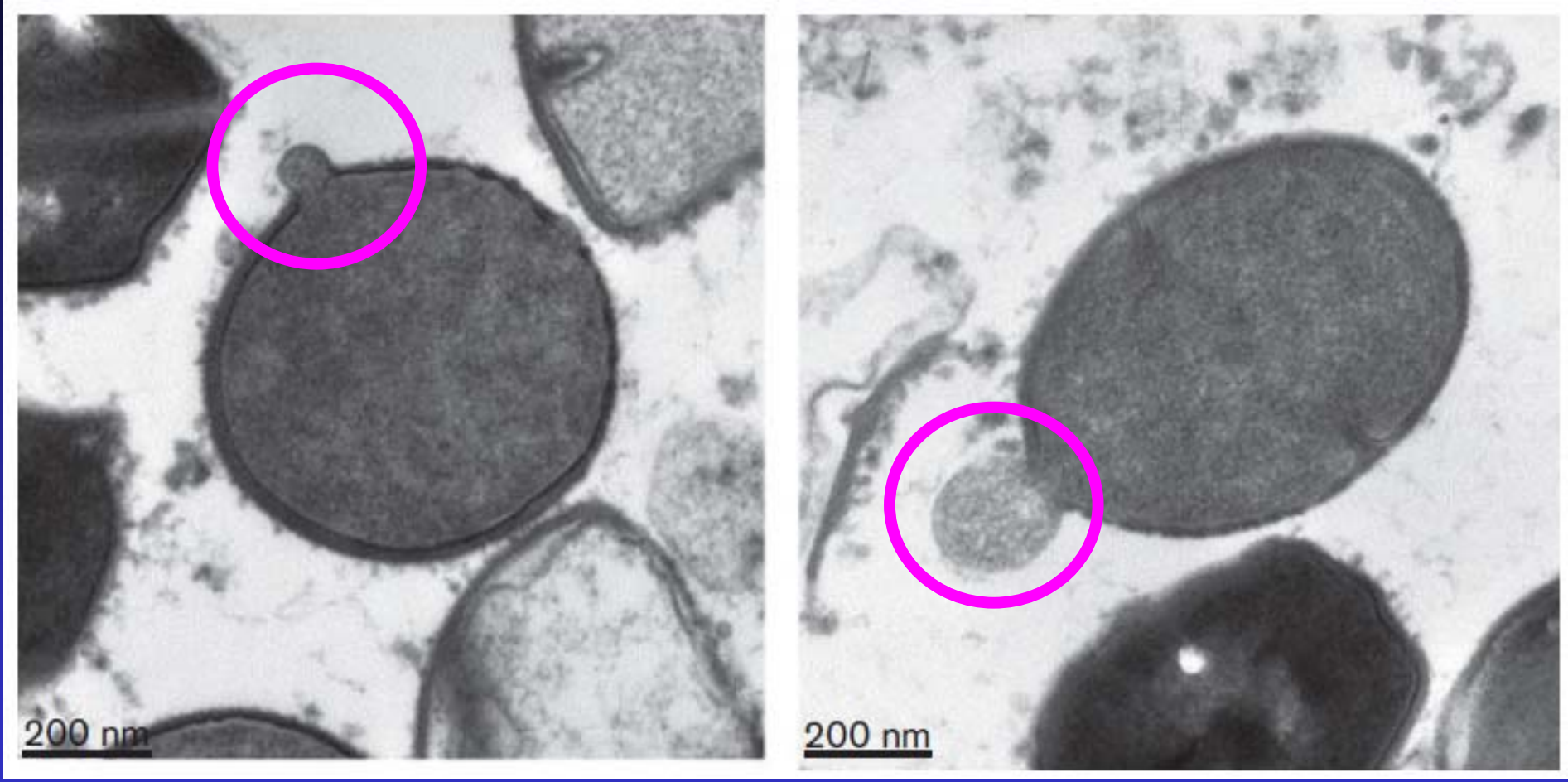
Pastagia M et al. J Med Microbiol. 2013; 62, 1506–16

Lysins have rapid, targeted bactericidal action



From Contrafect Inc.

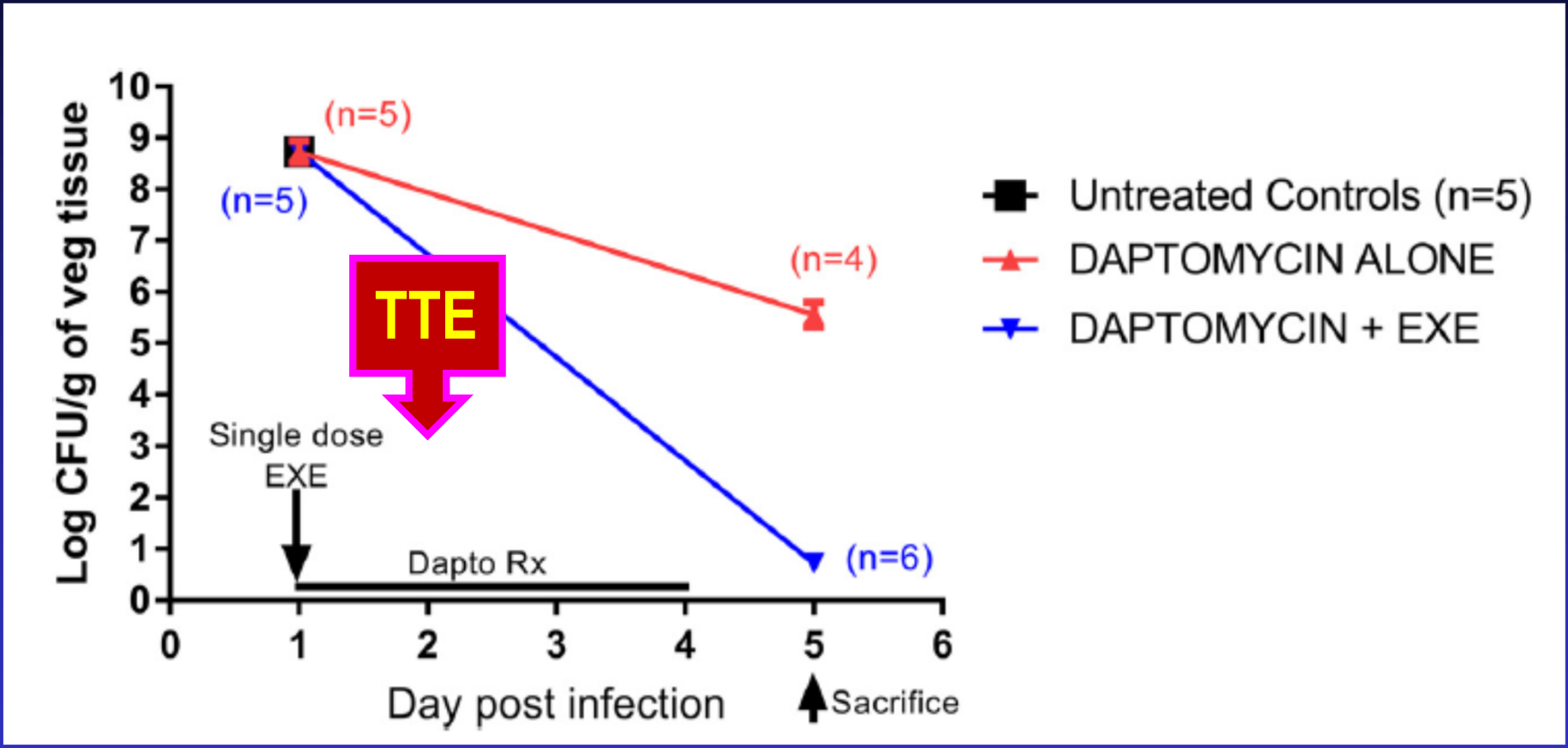
Lysin activity against MRSA



Exogenous application of the Staphylococcus aureus lysin, ClyS, causes **peptidoglycan disruption** and hypotonic **lysis within 60 seconds.**
The **cytoplasmic membrane is shown extruding** through regions of the cell wall weakened by ClyS.

Pastagia M et al. J Med Microbiol. 2013; 62, 1506–16

Lysin Exebacase (CF-301) in MRSA EE & TTE



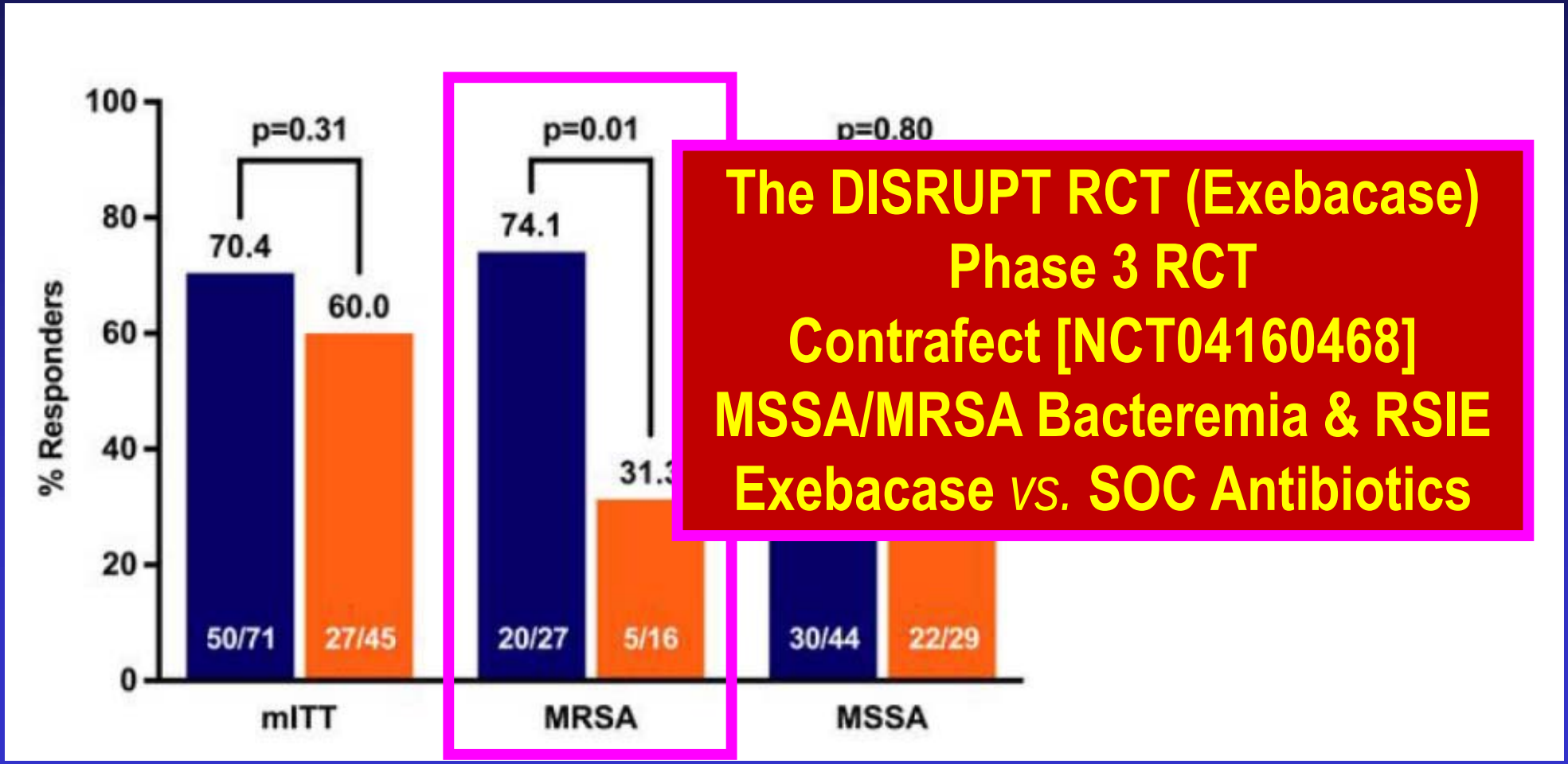
There was a statistical trend toward reduced maximum vegetation size in the exebacase (EXE) plus daptomycin *vs.* the daptomycin alone therapy groups (P=0.07)

TTE = Transthoracic echocardiography

Shah SU et al. AAC. 2020 Jun 23;64(7):e00482-20.

Exebacase for SAB and IE – Phase 2 RCT

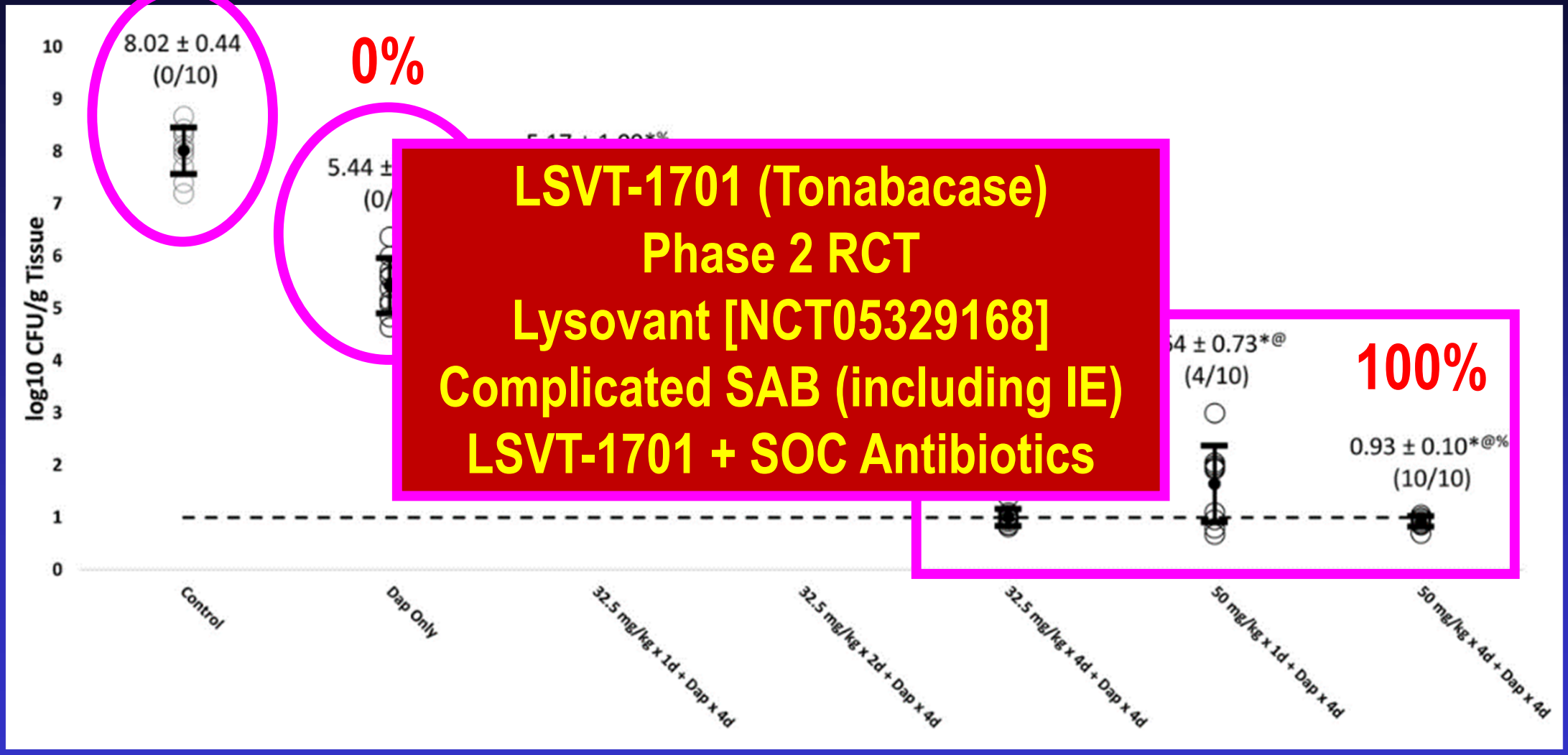
- Phase 2 RCT including 121 patients with SAB/IE to receive a single dose of exebacase or placebo.
- All patients received standard-of-care antibiotics.
- The primary efficacy endpoint was clinical outcome (responder rate) at Day 14



mITT= microbiological intent-to-treat; MRSA=methicillin-resistant S. aureus; MSSA=methicillin-sensitive; S. aureus. Note: The p-values for the MRSA and MSSA subgroups are ad-hoc p-values.

Fowler VG Jr. et al. J Clin Invest. 2020; 130:3750-60.

Lysin LSVT-1701 plus Daptomycin in MRSA EE



Reduction of MRSA bioburden in cardiac vegetations with LSVT-1701 in combination with daptomycin (Dap). Open circles, individual bioburdens; filled circles, mean bioburdens; error bars, standard deviations; dashed line, limit of experimental sterility

Huang DB et al. AAC. 2021; 65(8):e0050821.

Advances in antimicrobial treatment of infective endocarditis

- The paradigm shift is already here
- How to finish the puzzle of the ideal antibiotic treatment: from bench to bedside
- Science fiction or reality: phages and lysins
- Some take home messages

Future take home messages

- **There is no doubt that the antibiotic treatment of endocarditis is changing**: IV antibiotic induction followed by oral consolidation.
- The experimental endocarditis model can help us to find effective antibiotic combinations for the treatment of endocarditis. But, for its inclusion in clinical practice guidelines, **we need to carry out clinical trials in IE!**
- **Phage and lysine adjuvant treatment of endocarditis is not science fiction, it's here**. Clinical trials with lysins are very advanced and will allow to know its positioning in the treatment armamentarium of SAB/IE.
- We must use **platforms** as well structured as **GAMES** to be able to carry out clinical trials to improve the management and prognosis of this disease.

2022 Members of the Hosp. Clinic Cardiovascular Infections &

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