Bone and Joint Infections : synergistic antibiofilm effect of exebacase and antibiotics against *Staphylococcus epidermidis* strains

Aubin Souche, Camille Kolenda, Raymond Schuch, Tristan Ferry, Frédéric Laurent, Jérôme Josse

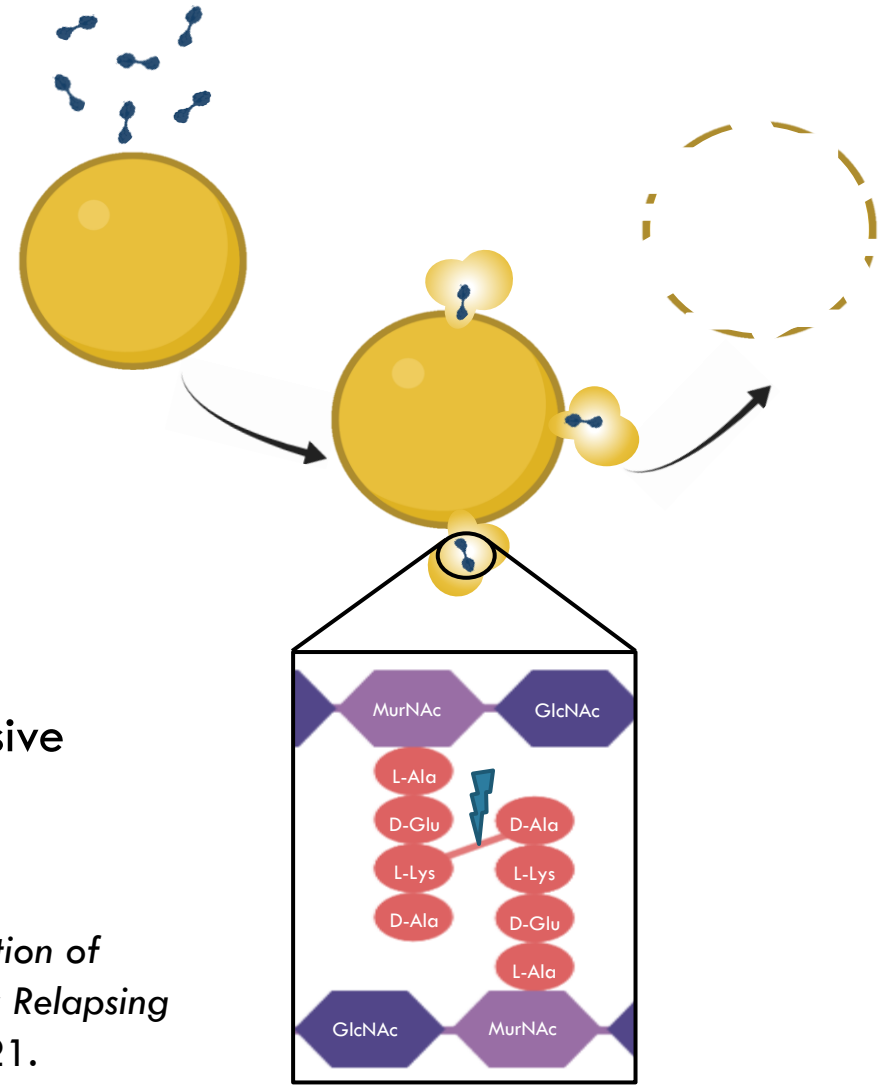
CIRI – Centre International de Recherche en Infectiologie
Equipe Pathogénie des Staphylocoques
INSERM U1111 – CNRS UMR5308 – ENS Lyon – Université de Lyon

Conflict of interest

- This study was funded by ContraFect Corporation

Exebacase – CF-301

- Phage lysins = peptidoglycan hydrolases
  - Innovative antimicrobial strategy
- Exebacase: antistaphylococcal lysin
  - On going clinical trial phase 3 : *Staphylococcus aureus* endocarditis/bacteriemia in addition to SOC
  - Phase 2 : improvements in clinical outcomes
- Compassionate use in PJI
  - Intraarticular use of Lysin-DAIR protocol followed by suppressive antimicrobial treatment
  - 10 patients in Lyon University Hospital

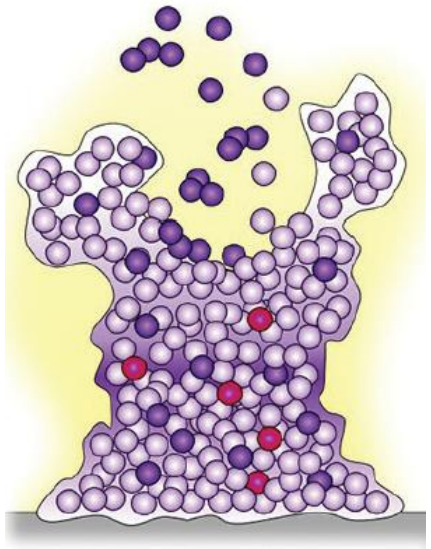


Ferry T *et al. Arthroscopic "Debridement and Implant Retention" With Local Administration of Exebacase Followed by Suppressive Tedizolid as Salvage Therapy in Elderly Patients for Relapsing Multidrug-Resistant S. epidermidis Prosthetic Knee Infection*. Frontiers in Medecine, 2021.

Aim of the study

Assessment of exebacse anti biofilm active to support its therapeutic potential in *S. epidermidis* PJI

Exebacase VS antibiotics
Compared anti-biofilm activity ?



Against biofilm

Exebacase + antibiotics
Synergistic anti-biofilm activity ?

S. epidermidis PJI isolates

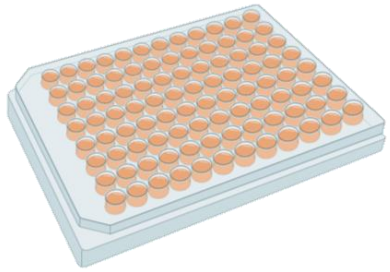
Strains	Biofilm production	Location	Antibiotic susceptibility				
			Oxacillin MICs (mg/L)	Rifampin MICs (mg/L)	Vancomycin MICs (mg/L)	Daptomycin MICs (mg/L)	Exebacase MICs (mg/L)
12	None	Knee	S	S	S	S	0,125
22	None	Knee	S	S	S	S	1
4	Low	Knee	R	S	S	S	1
10	Low	Hip	R	S	S	S	0,25
19	Low	Hip	S	S	S	S	1
24	Low	Knee	R	S	S	S	1
33	Low	Shoulder	R	S	S	S	0,125
34	Low	Knee	R	R	S	S	0,25
3	Moderate	Knee	R	S	S	S	2
7	Moderate	Knee	R	S	S	S	1
11	Moderate	Knee	S	R	S	S	0,125
13	Moderate	Knee	R	R	S	S	0,125
20	Moderate	Knee	R	R	S	S	0,25
25	Moderate	Hip	R	S	S	S	1
32	Strong	Knee	S	S	S	S	0,5
39	Strong	Shoulder	S	S	S	S	2
41	Strong	Knee	S	S	S	S	0,125
51	Strong	Hip	S	S	S	S	1
52	Strong	Knee	R	R	S	S	2

S Susceptible, R Resistant. Biofilm production evaluated according to Stepanović *et al.* 2000.

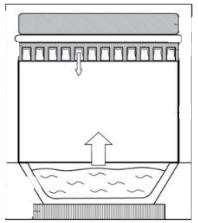
Exebacase MICs

- 0,125 – 2 mg/L

Exebacase and biofilm: synergies with antibiotics ?



Biofilm formation
37°C – 24h



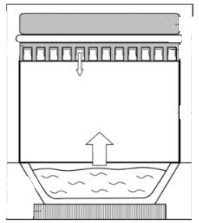
Steam wash
BiofilmCare®
(Tasse et al. 2018)
40 minutes

Treatement

24h

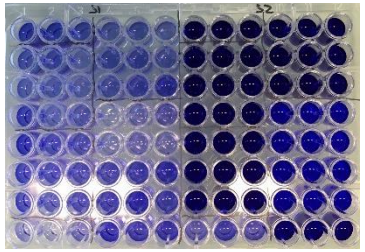
24h

+ 24h



Steam wash
BiofilmCare®
(Tasse et al. 2018)
40 minutes

Bactericidal effect
Bacterial inoculum



Anti-biomass effect
Crystal violet

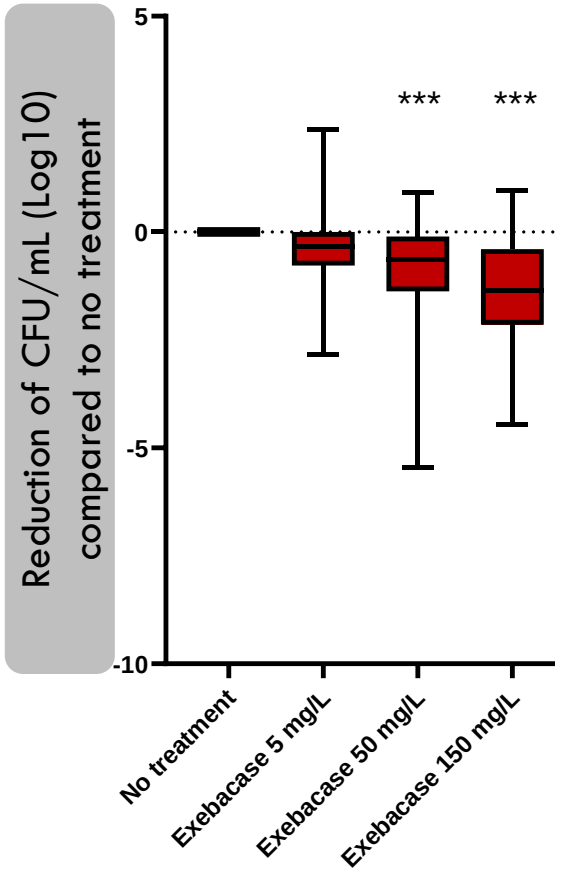
Exebacase
150, 50 or 5 mg/L

Antibiotics
Rifampin : 1 mg/L / Vancomycin : 10 mg/L / Daptomycin : 10 mg/L

Synergy: Effect AB > Effect A + Effect B

Bactericidal synergies on pre-formed biofilm ?

Isolates : n=19
except for rifampin: n=14

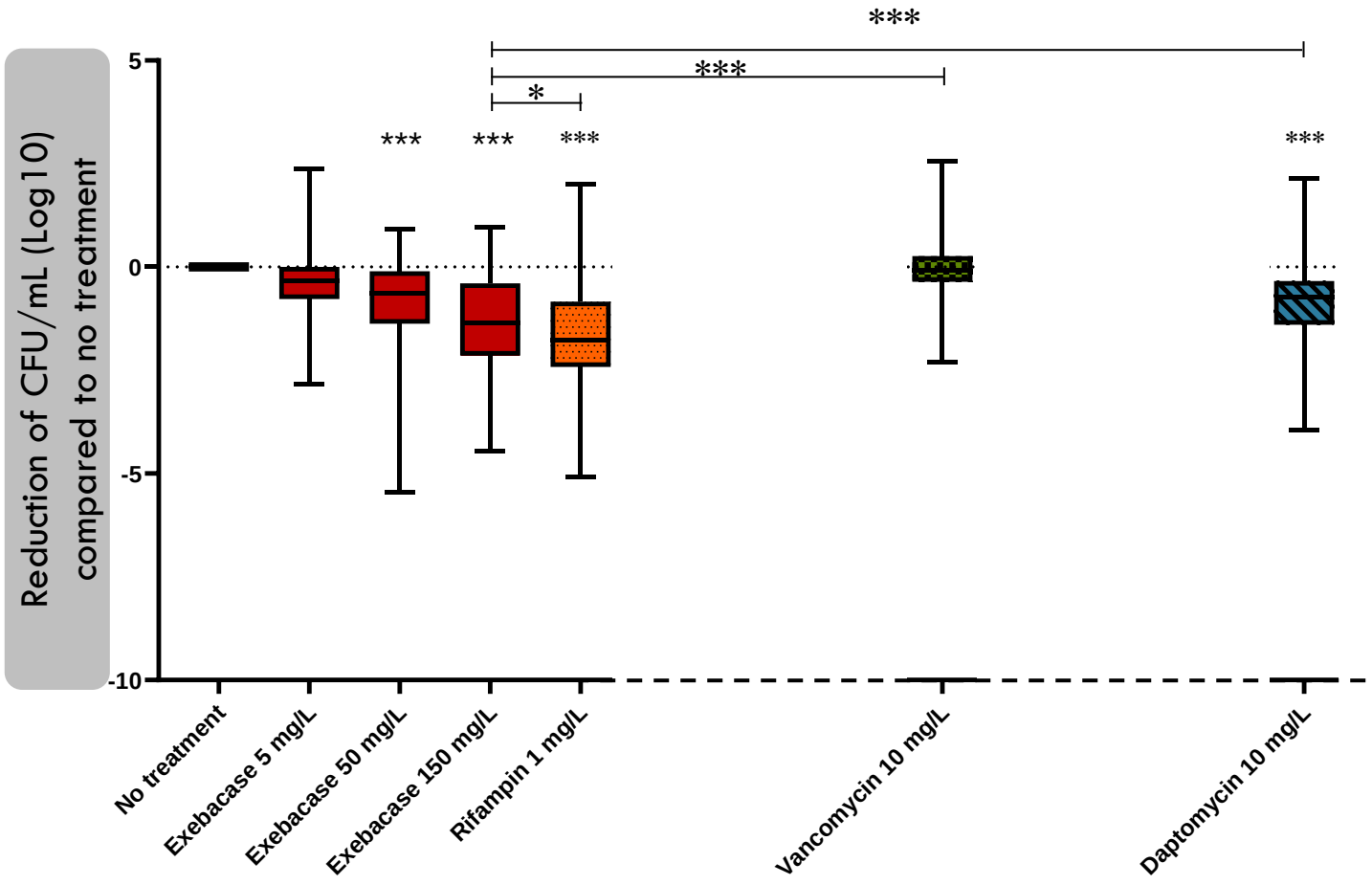


Exebacase

- Dose dependant
- Max effect: -1,7 log CFU

ANOVA + Dunnett post test, adjusted p-values * <0,05 / ** <0,01 / *** <0,001

Bactericidal synergies on pre-formed biofilm ?



Isolates : n=19
except for rifampin: n=14

Exebacase

- Dose dependant
- Max effect: -1,7 log CFU
- VS antibiotics
  - < Rifampin (p=0,0148)
  - > Vancomycin (p<0,001)
  - > Daptomycin (p<0,001)

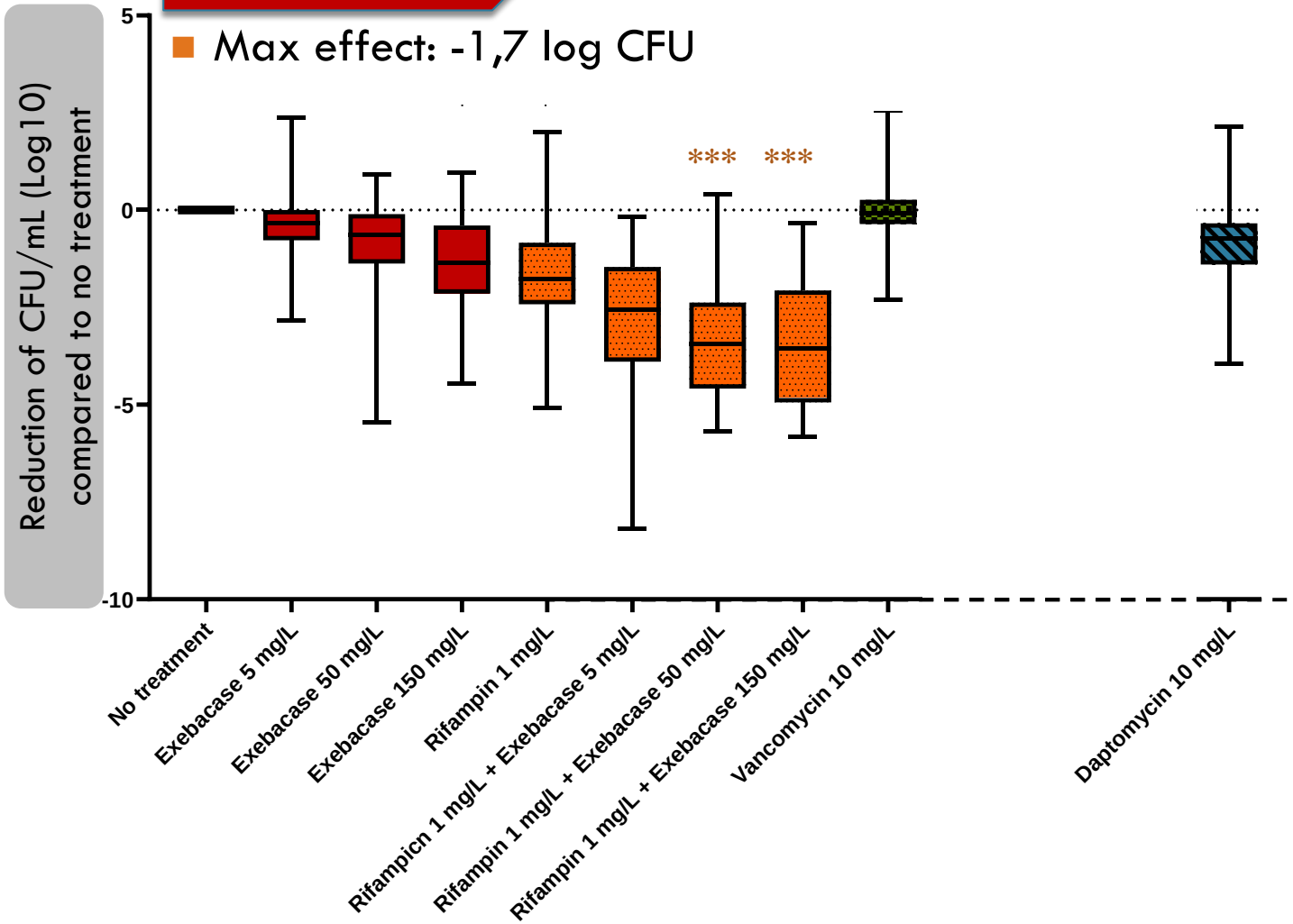
ANOVA + Dunnett post test, adjusted p-values * <0,05 / ** <0,01 / *** <0,001

Bactericidal synergies on pre-formed biofilm ?

Exebacase

Synergy

Isolates : n=19
except for rifampin: n=14



Synergies with rifampin

- Max effect: -3,5 log CFU

Paired t-test, Bonferroni adjusted p-values
* <0,05 / ** <0,01 / *** <0,001

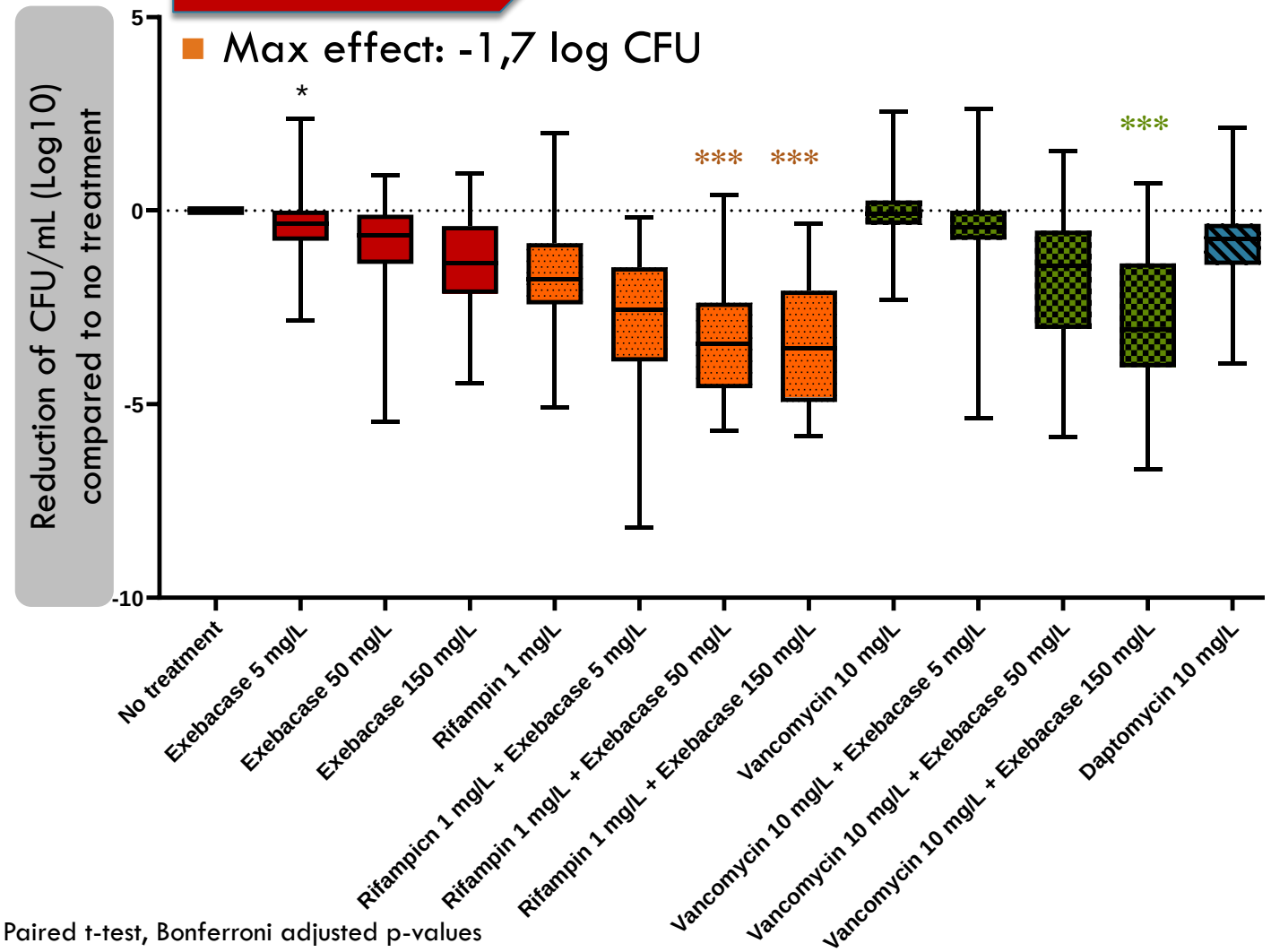
Bactericidal synergies on pre-formed biofilm ?

Exebacase

Synergy

Synergy

Isolates : n=19
except for rifampin: n=14



- Max effect: -1,7 log CFU

Paired t-test, Bonferroni adjusted p-values
* <0,05 / ** <0,01 / *** <0,001

Synergies with rifampin

- Max effect: -3,5 log CFU

Synergies with vancomycin

- Max effect: -2,82 log CFU

Bactericidal synergies on pre-formed biofilm ?

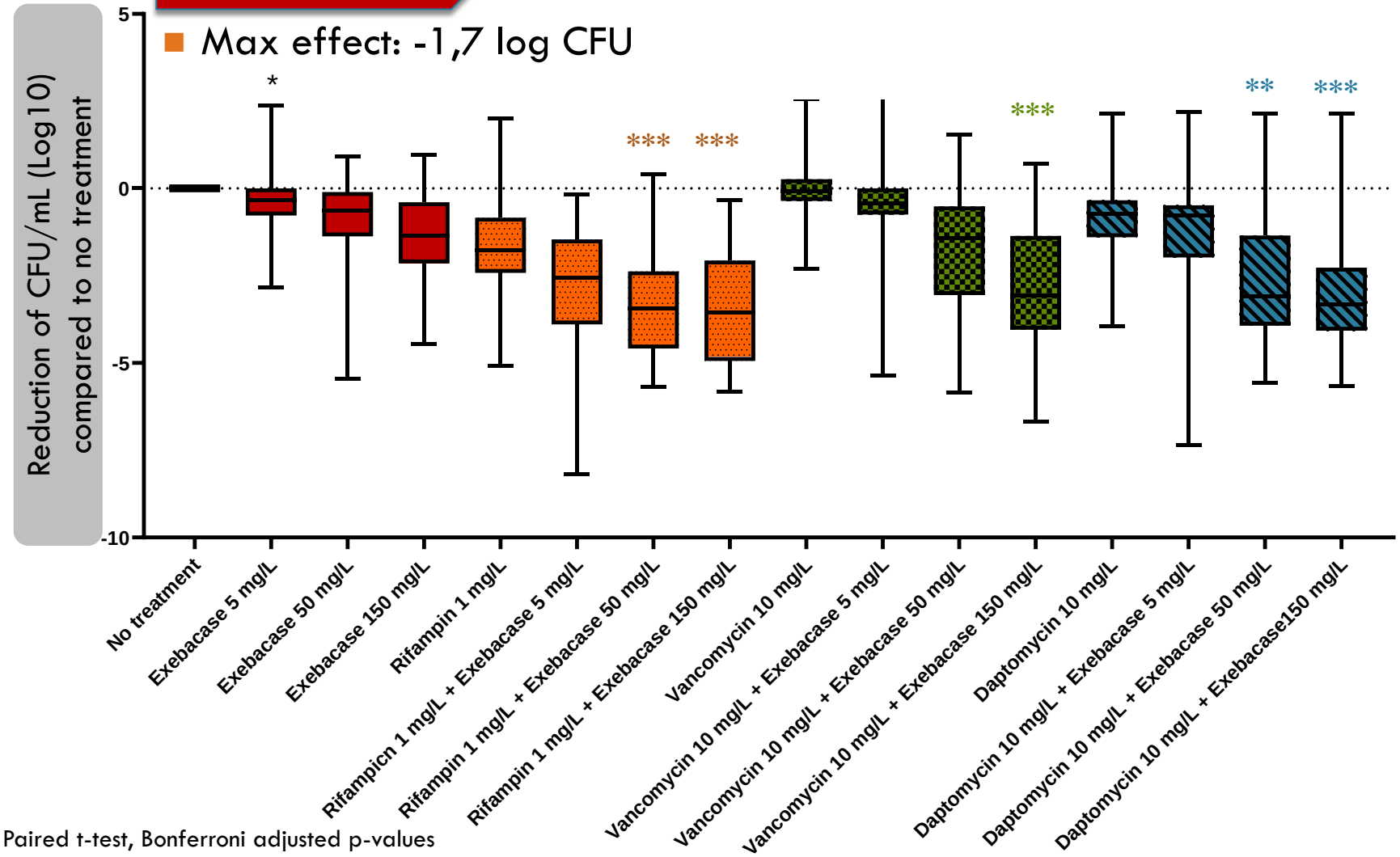
Exebacase

Synergy

Synergy

Synergy

Isolates : n=19
except for rifampin: n=14



Paired t-test, Bonferroni adjusted p-values
* <0,05 / ** <0,01 / *** <0,001

Synergies with rifampin

- Max effect: -3,5 log CFU

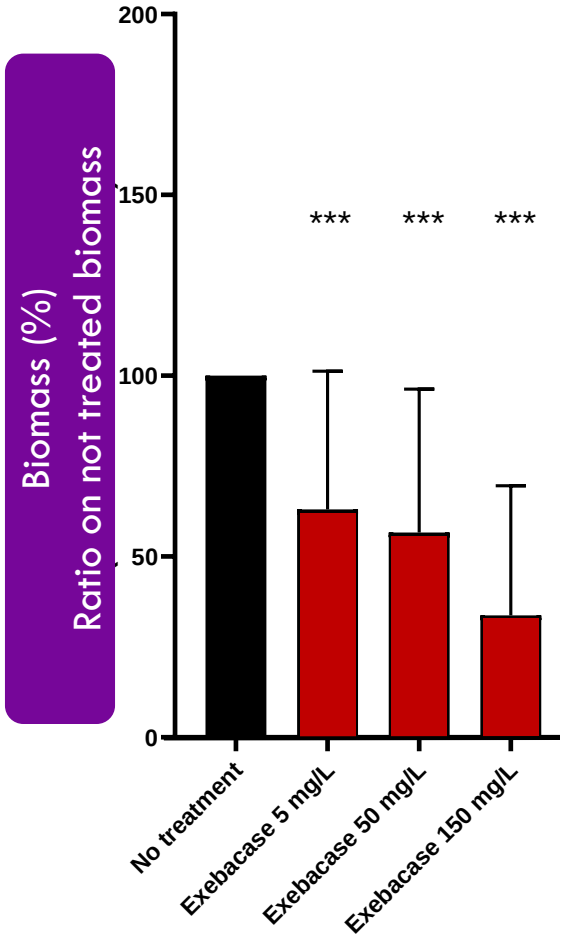
Synergies with vancomycin

- Max effect: -2,82 log CFU

Synergies with daptomycin

- Max effect: -3,1 log CFU

Anti-biomass synergies on pre-formed biofilm ?



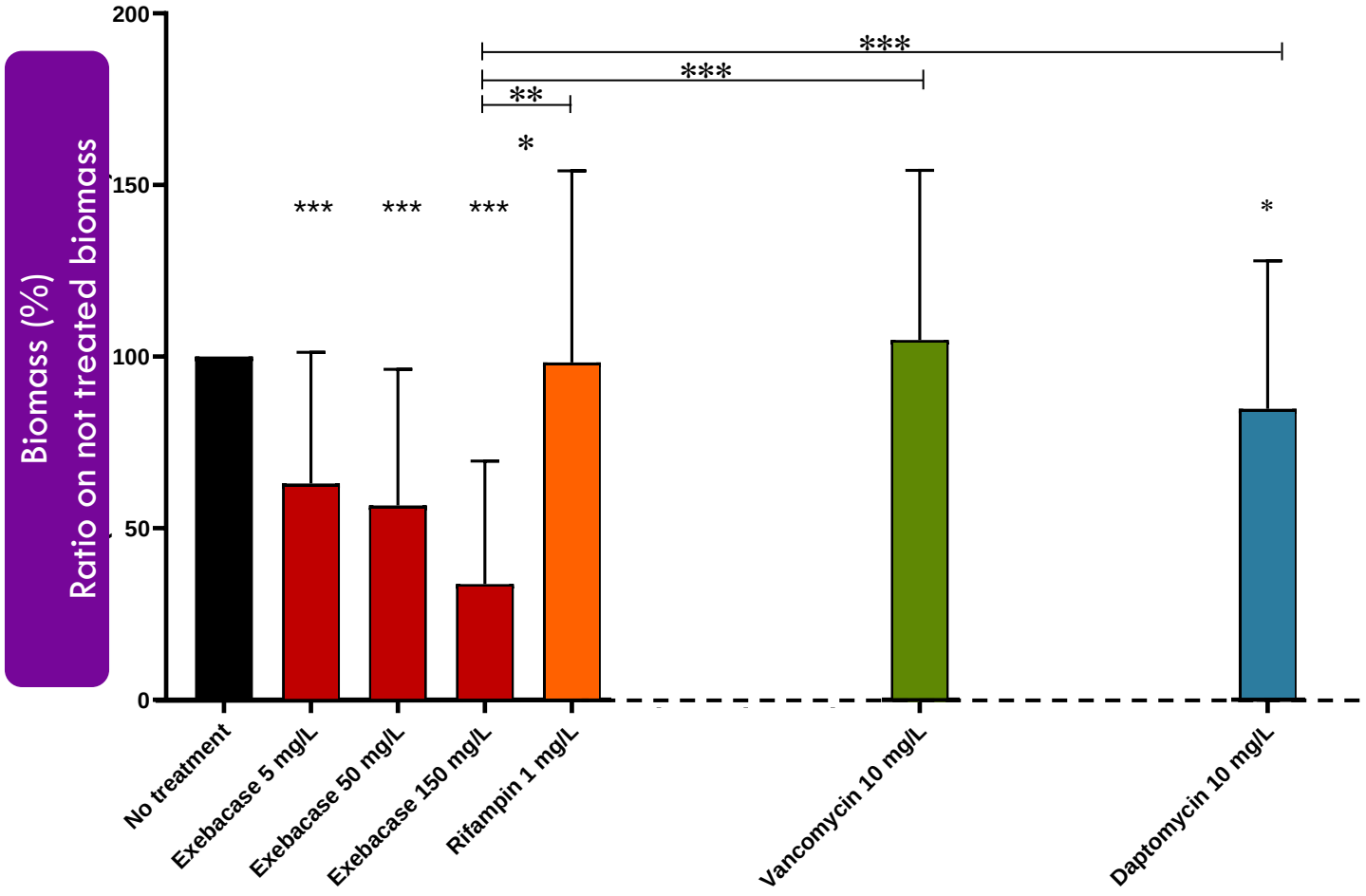
Isolates : n=19
except for rifampin: n=14

Exebacase

- Dose dependant
- Max effect: -66%

ANOVA + Dunnett post test, adjusted p-values * <0,05 / ** <0,01 / *** <0,001

Anti-biomass synergies on pre-formed biofilm ?



Isolates : n=19
except for rifampin: n=14

Exebacase

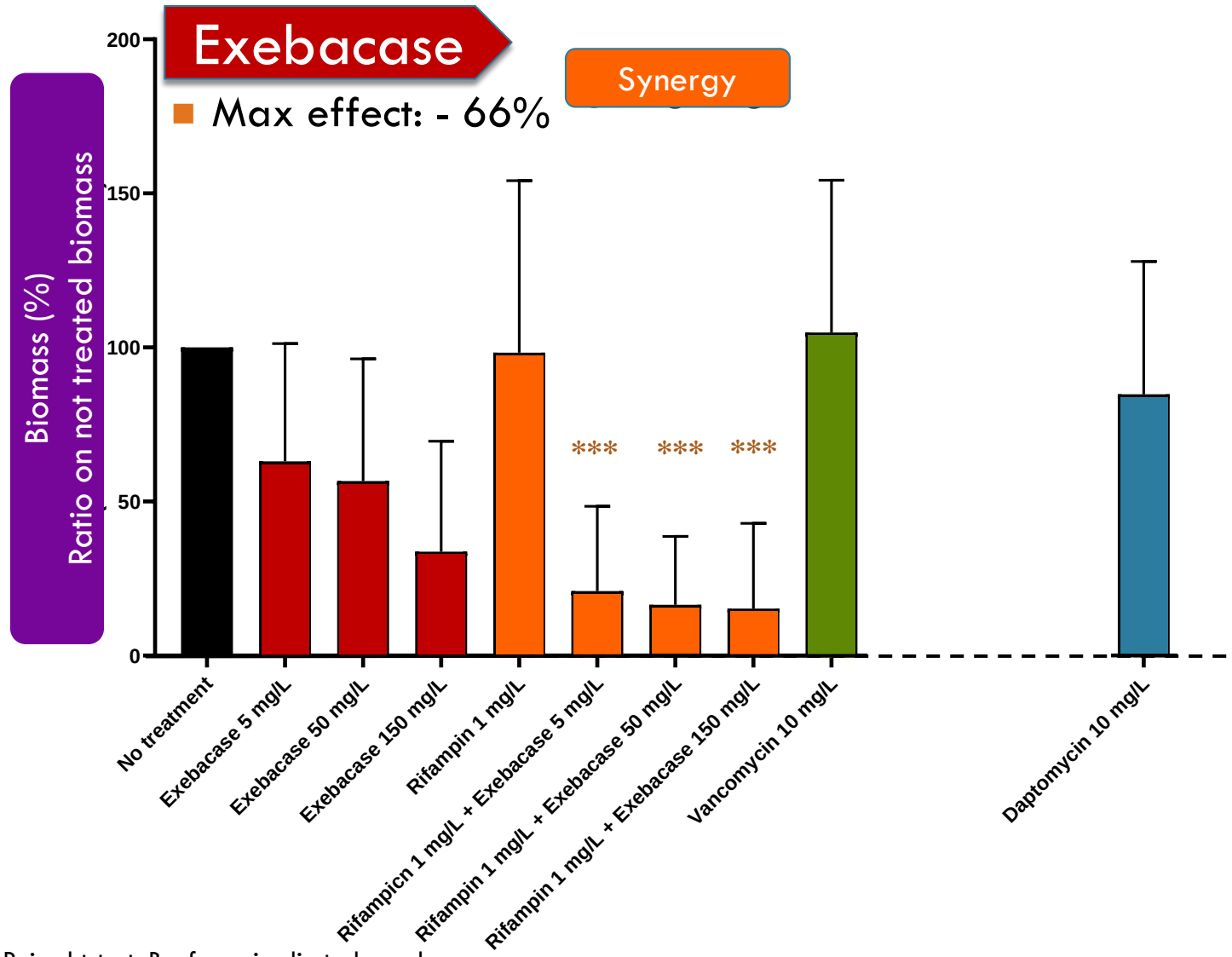
- Dose dependant
- Max effect: -66%

- > rifampin ($p<0,001$)
- > vancomycin ($p<0,001$)
- > daptomycin ($p<0,001$)

ANOVA + Dunnett post test, adjusted p-values * <0,05 / ** <0,01 / *** <0,001

Anti-biomass synergies on pre-formed biofilm ?

Isolates : n=19
except for rifampin: n=14

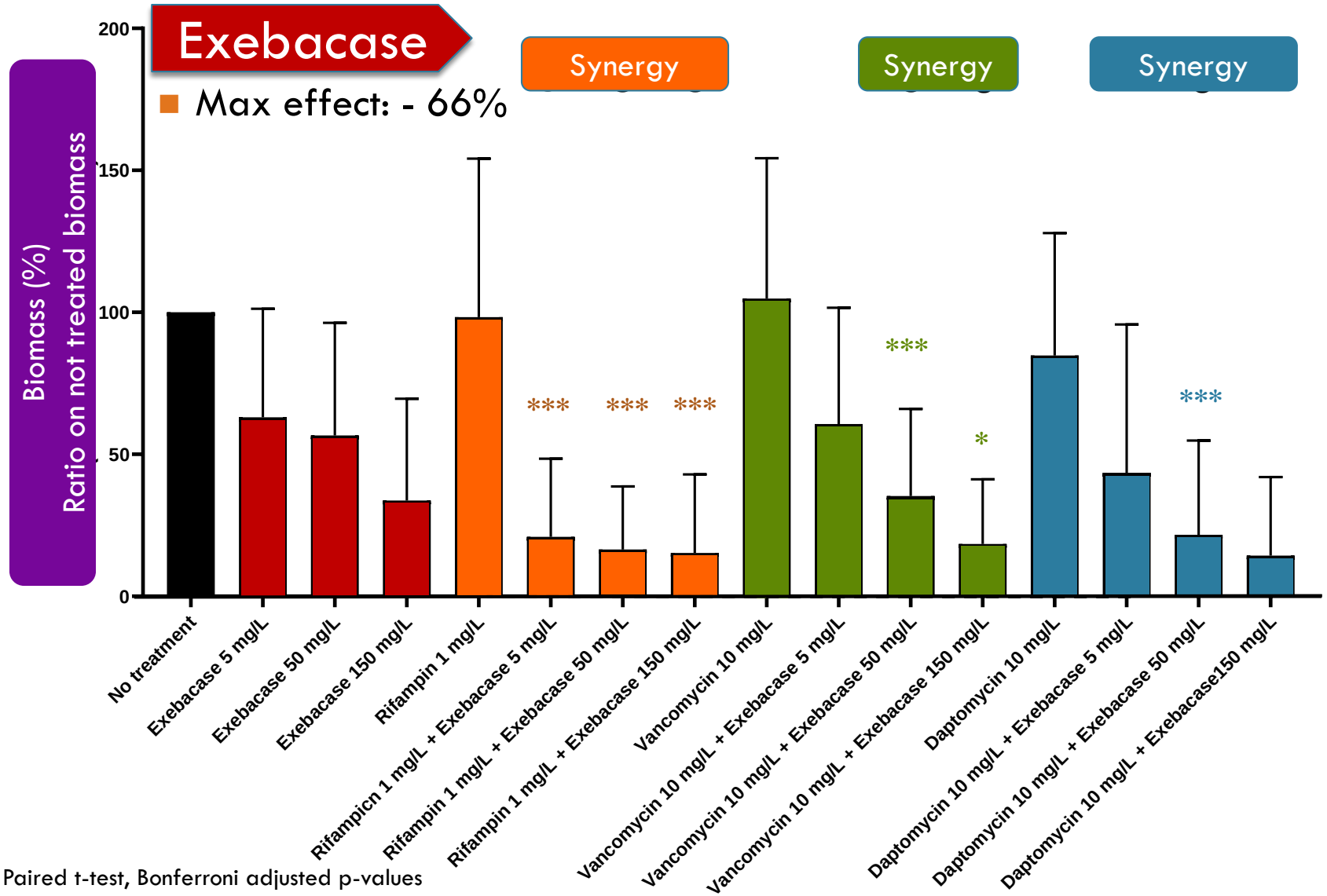


Synergies with rifampin

- Max effect: -84%

Paired t-test, Bonferroni adjusted p-values
* <0,05 / ** <0,01 / *** <0,001

Anti-biomass synergies on pre-formed biofilm ?



Paired t-test, Bonferroni adjusted p-values
* <0,05 / ** <0,01 / *** <0,001

Isolates : n=19
except for rifampin: n=14

Synergies with rifampin

- Max effect: -84%

Synergies with vancomycin

- Dose dependant
- Max effect: -81%

Synergies with daptomycin

- Dose dependant
- Max effect: -85%

Conclusion

- **Dose dependant** effects of exebacase against *S. epidermidis* biofilm: Bactericidal and antibiomass effects

- **Synergistic effects with antibiotics** frequently used to treat PJI : Exebacase likely degrades biofilm matrix facilitating action of antibiotics

- Need for **high local exebacase concentrations** (50-150 mg/L)

Thank you for your attention

Team Staphylococcal pathogenesis

Centre International de Recherche en Infectiologie

Contrafect Corporation

ContraFect
MOLECULAR TREATMENTS FOR INFECTIOUS DISEASE