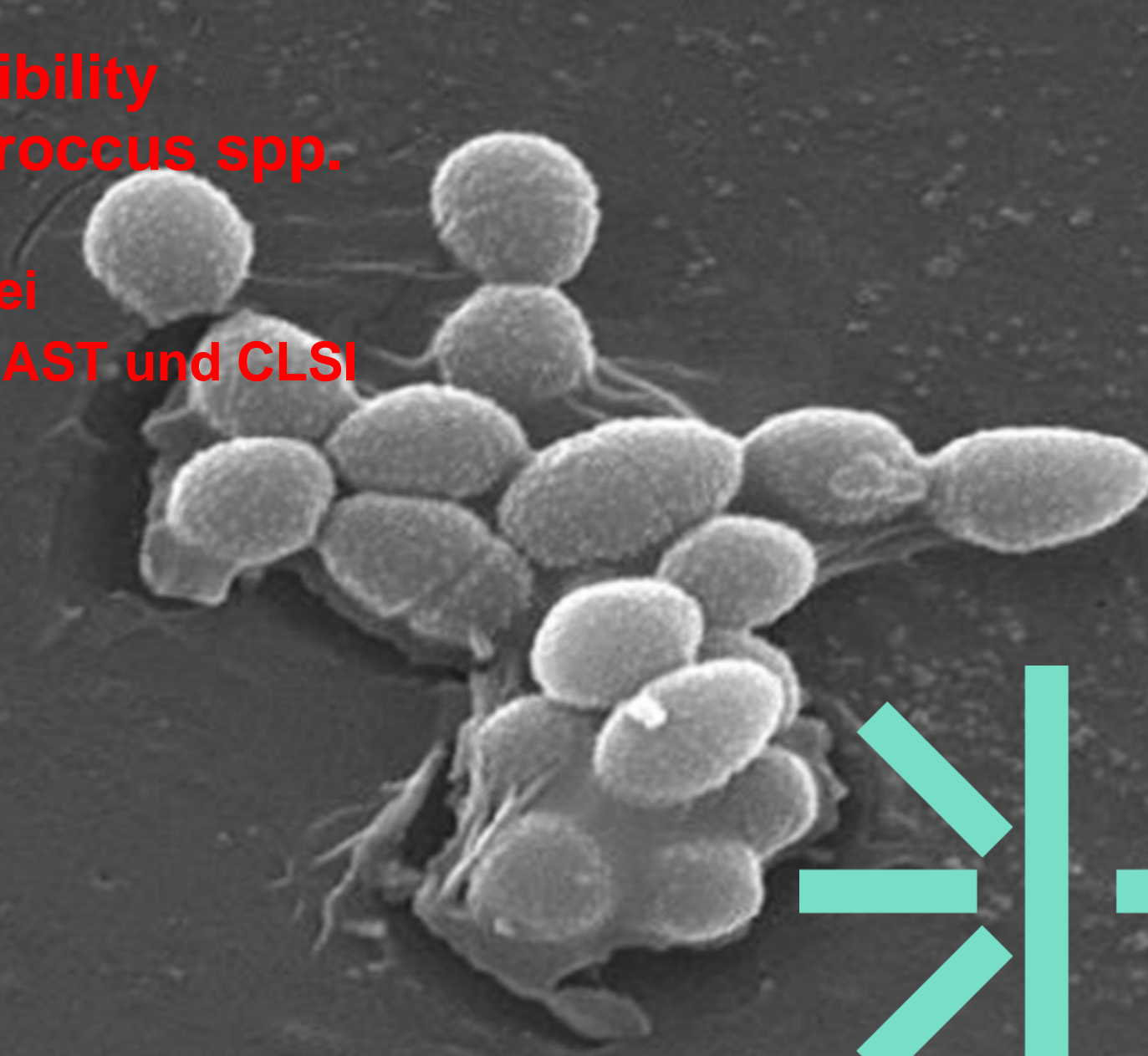


Daptomycin Susceptibility Breakpoints for Enterococcus spp.

Eine Darstellung von zwei
Positionpapers von EUCAST und CLSI

Journal Club 09.11.2019

Seraina Bally



Background

- Mangels Alternativen wird Daptomycin zunehmend für Infekte mit *Enterokokken spp.* eingesetzt (Speziell für VRE)
- Die von der EMA und FDA bewilligte Dosierung -> 4-6mg/kg/d:
 - Ausgerichtet auf *S. aureus* Infektionen
- **EUCAST**: Breakpoints für *Staphylokokken* und *Streptokokken* **S <1 mcg/ml** und **R >1 mcg/ml**, jedoch ungenügende Evidenz für *Enterokokken spp.*
- **CLSI**: Breakpoint für alle *Enterokokken spp.* **S < 4 mcg/ml**, **R >= 8 mcg/ml**

Wie kann ein Breakpoint festgelegt werden

- Dosisfindung (PK-PD Studien)
- Klinische Outcomestudien
- Sicherheitsstudien für eine bestimmte Dosis
- Informationen zur Resistenzentwicklung
- Empfindlichkeitstestungen zur Unterstützung der Pharmakotherapie

Dosisfindung

- Pharmakokinetik-Pharmakodynamik Untersuchungen:
- Bestimmender Faktor der Wirksamkeit für Daptomycin fAUC/MIC

Table 1

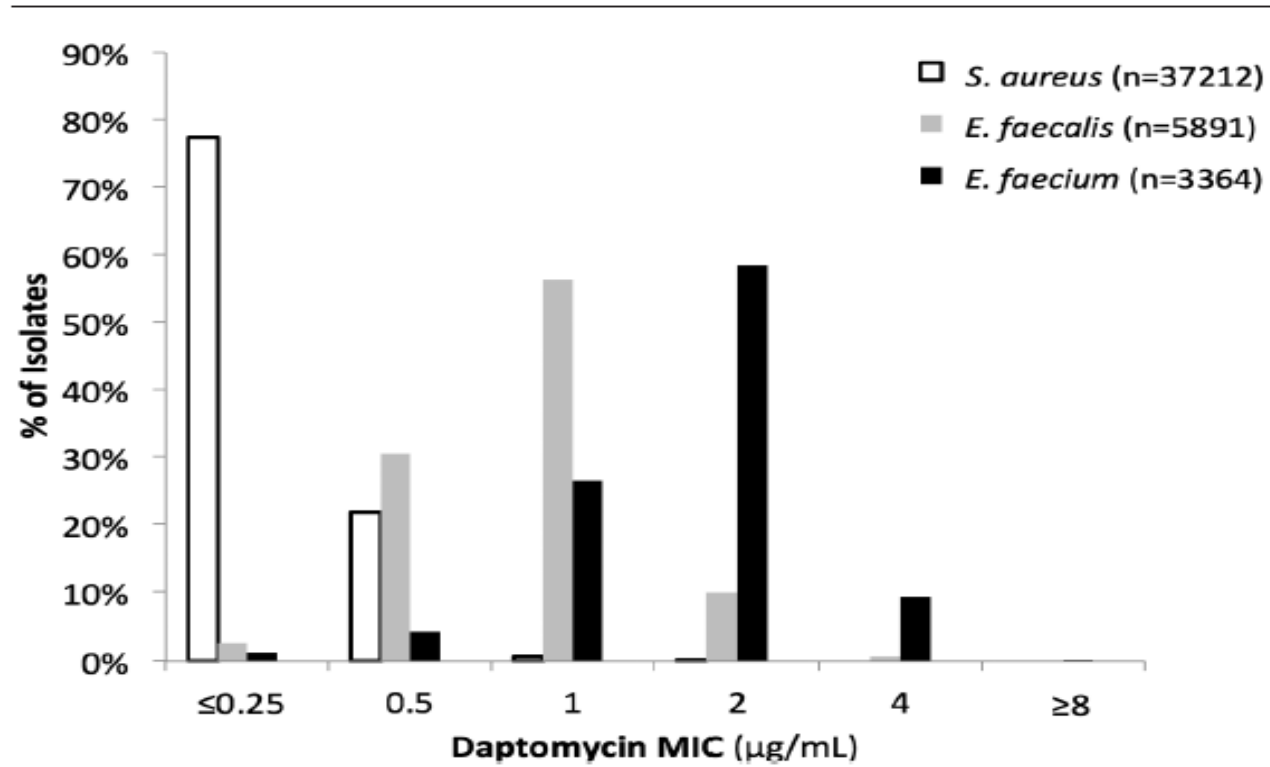
Probability of survival threshold (fAUC/MIC >27.43) attainment using Monte Carlo simulation [8]

Daptomycin MIC (mg/L)	Daptomycin dose			
	6 mg/kg/day	8 mg/kg/day	10 mg/kg/day	12 mg/kg/day
0.25	100	100	100	100
0.5	100	100	100	100
1	91.0, 97.9 ^a	98.7, 99.9 ^a	99.9, 100 ^a	100
2	32.4, 54.4 ^a	60.7, 80.4 ^a	80.4, 92.9 ^a	91.0, 97.9 ^a
4	1.5, 5.5 ^a	7.3, 18.1 ^a	18.1, 36.2 ^a	32.4, 54.4 ^a
8	0	0.0, 0.2 ^a	0.2, 2.0 ^a	1.5, 5.5 ^a
16	0	0	0	0

^a Males and females were simulated separately. Values are presented as 'male, female' for MICs at which the probability differs.

Dosisfindung

- MIC-Distributions:



Klinische Daten bei Bakteriämie

Table 3. Comparison of Outcomes in Daptomycin-treated Patients With Daptomycin-susceptible Enterococcal Bacteremia, Stratified by Daptomycin Dose

Reference	<i>Enterococcus faecium</i> , %	Dose: No. of Patients	Microbiologic Failure	Mortality
Gallagher, 2009 [29]	90	<ul style="list-style-type: none"> <6 mg/kg: 14 ≥6 mg/kg: 16 	≥6 mg/kg with less microbiologic failure ($P = .04$) ^a	NR
Britt, 2017 [16]	88	<ul style="list-style-type: none"> 6 mg/kg: 709 8 mg/kg: 142 ≥10 mg/kg: 60 	8 and ≥10 mg/kg with less microbiologic failure than 6 mg/kg ($P = .01$)	Improved 30-day survival in multivariate analysis with ≥10 mg/kg compared to 6 mg/kg or 8 mg/kg ($P = .004$)
Chuang, 2017 [15]	All	<ul style="list-style-type: none"> <7 mg/kg: 36 7–9 mg/kg: 51 ≥9 mg/kg: 25 	No difference ($P = .9$) ^b	Improved 14-day survival in multivariate analysis with ≥9 mg/kg compared to <7 mg/kg ($P = .003$)
Ye, 2018 ^c [30]	All	<ul style="list-style-type: none"> <10 mg/kg: 77 ≥10 mg/kg: 18 	NR	Trend towards improved 28-day survival with ≥10 mg/kg daptomycin ($P = .15$)
King, 2011 [31]	91	<ul style="list-style-type: none"> ≤6 mg/kg: 24 >6 mg/kg: 22 	No difference ($P = 1.0$)	No difference ($P = 1.0$)
Hayakawa, 2014 [32]	86	<ul style="list-style-type: none"> 6 mg/kg: 35 >6 mg/kg: 21 	NR	No difference ($P = 1.0$)
Shukla, 2016 [14]	All	<ul style="list-style-type: none"> <8 mg/kg: 27 ≥8 mg/kg: 35 	No difference ($P = .5$)	No difference ($P = .5$)

Abbreviation: NR, not reported.

^aHigh-dose daptomycin was also associated with a positive clinical outcome ($P < .01$).

^bOnly 55% of the patients in the study were able to be evaluated for microbiologic failure.

^cDaptomycin susceptibility testing was not performed in this study.

Klinische Daten bei Endokarditis

- In wenigen kleinen Studien (N 5-9) konnte dargelegt werden dass eine Dosis von 6-10mg/kg/d (*Enterococcus faecalis* und *faecium*) wirksam waren

Sicherheit einer Hochdosistherapie

- Haupttoxizität -> Anstieg der CK

Table 4. Rates of Creatine Kinase Elevation in Observational Studies of High-dose Daptomycin

Reference	Indication for Treatment	CK Elevation Definition	≤6 mg/kg, % (n)	8 mg/kg, % (n)	10 mg/kg, % (n)
Casapao, 2013 [27]	Enterococcal infection	≥3 times ULN or ≥5 times ULN if CK elevated at baseline	...	3.1 (220) ^a	...
Seaton, 2015 [40]	Any infection	Not specified	1.0 (4892)	2.8 (645)	...
Roux, 2016 [41]	Bone and joint infections	Any elevation >ULN	...	7.0 (43) ^a	...
Durante-Mangoni, 2016 [42]	Endocarditis	Any elevation >ULN or doubling of CK if elevated at baseline	...	14.7 (102) ^b	...
Chuang, 2017 ^c [15]	VRE bacteremia	Any elevation >ULN	5.6 (36)	7.8 (51)	4.0 (25)
Britt, 2017 [16]	VRE bacteremia	≥3 times ULN or ≥5 times ULN if CK elevated at baseline	1.4 (441)	1.0 (103)	0 (51)

Values represent the percentage of patients who developed CK elevations and the total number of patients evaluated. Abbreviations: CK, creatine kinase; ULN, upper limit of normal; VRE, vancomycin-resistant *Enterococcus*.

^aAll patients with CK elevations were asymptomatic.

^bCK elevations occurred a median of 15 days after initiation of therapy and required discontinuation of therapy in only 4 of the 15 patients with CK elevations.

^cOnly 1 patient had a CK elevation ≥10 times the ULN.

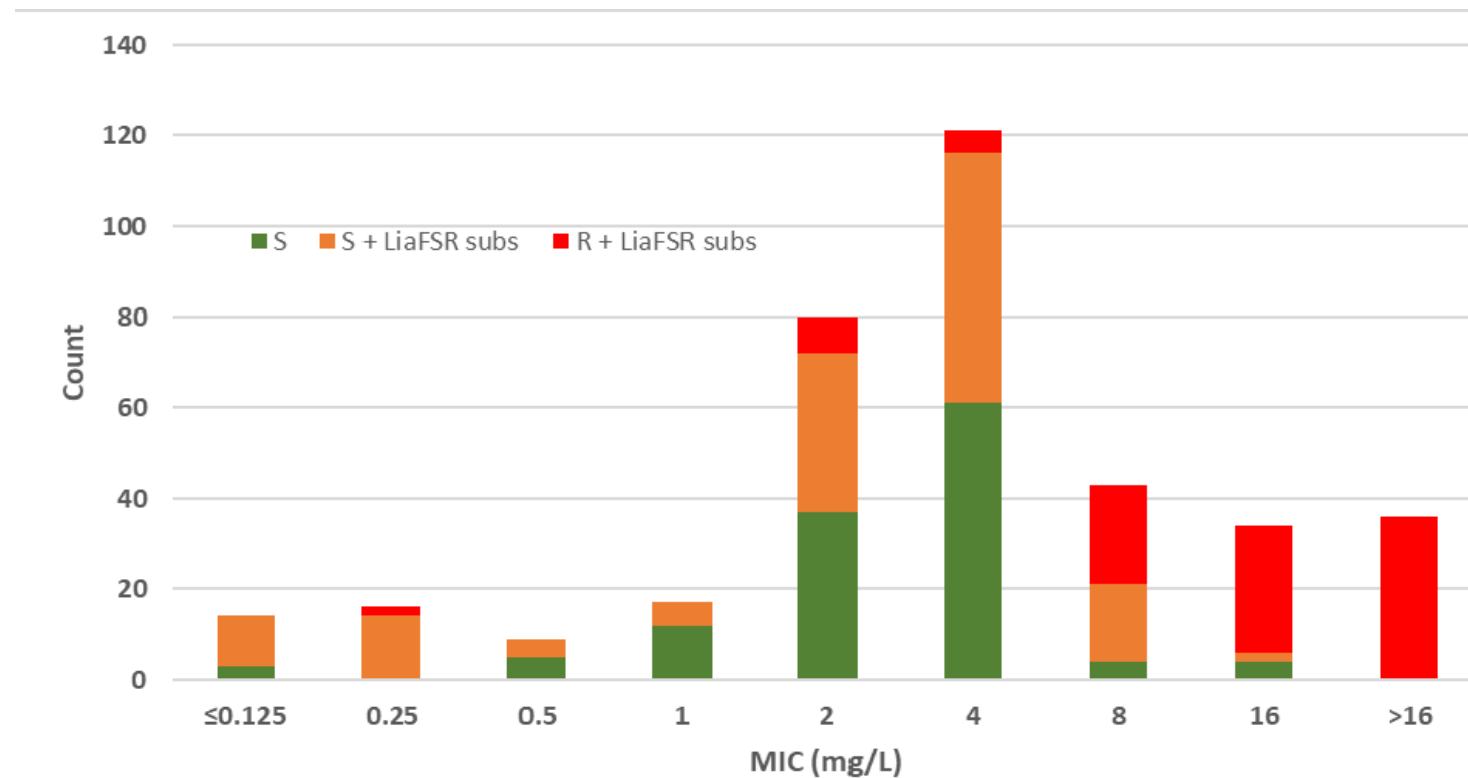
Daptomycin in the treatment of enterococcal bloodstream infections
And endocarditis: a EUCAST position paper
J. Turnidge et al

Informationen zur Resistenzentwicklung

- Unter Therapie kann eine Resistenz entwickelt werden, hauptsächlich basierend auf der Mutation LiaFSR
- In Vitro Daten lassen vermuten, dass es zur Verhinderung einer solchen Resistenz eine Dosis von 10-12 mg/kg/d braucht

Empfindlichkeitstestungen zur Unterstützung der Pharmakotherapie

- Grosse Variabilität der MIC zwischen den Laboren und den Herstellern der entsprechenden Test-KIDs



Casapao AM1, Kullar R, Davis SL, Levine DP, Zhao JJ, Potoski BA, Goff DA, Crank CW, Segreti J, Sakoulas G, Cosgrove SE, Rybak MJ. Multicenter study of high-dose daptomycin for treatment of enterococcal infections. *Antimicrob Agents Chemother.* 2013;57(9):4190-6.

Vergleich

EUCAST

- Kein klinischer Breakpoint:
 - Unsicherheit der Wirksamkeit in entsprechen hoher Dosis in allen Wildtypisolaten von *E. faecalis* und *E. Faecium*
 - Fehlende Bewilligung der hohen Dosis durch EMA
 - Weitere prospektive Studien

CLSI

- Festlegung Breakpoint:
 - *Enterococcus faecalis* S $\leq 2\text{mg/l}$; I 4mcg/ml , R $\geq 8\text{mcg/ml}$
 - *Enterococcus Faecium* SDD (Dosis 8 – 12 mg/kg/d) $\leq 4\text{mcg/ml}$; R $\geq 8\text{mcg/ml}$

