

Combined therapy of gram-positive infections

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ISCVID Dubrovnik 2013

Objective

Critically evaluate present state of combined treatment for Gram-positive infections

Treatment of Staphylococcal IE

Recommended combinations

- **MSSA NVIE, MRSA NVE**

- β -lactam (vancomycin) + Gentamicin 3 mg/kg 3-5 days in 2 or 3 doses (ECS, BSAC, AHA optional)

- **RSIE – IDUs**

- β -lactams 2 w (glycopeptides 4 w) (AHA gentamicin optional)
- Oral : ciprofloxacin+rifampin

- **MRSA NVE**

- add gentamicin + rifampin in patients who do not response on conventional therapy

- **PVE**

- β -lactam (vancomycin) + rifampin + gentamicin (2 w) (FQ)

Questions regarding gentamicin use in the treatment of staphylococcal IE

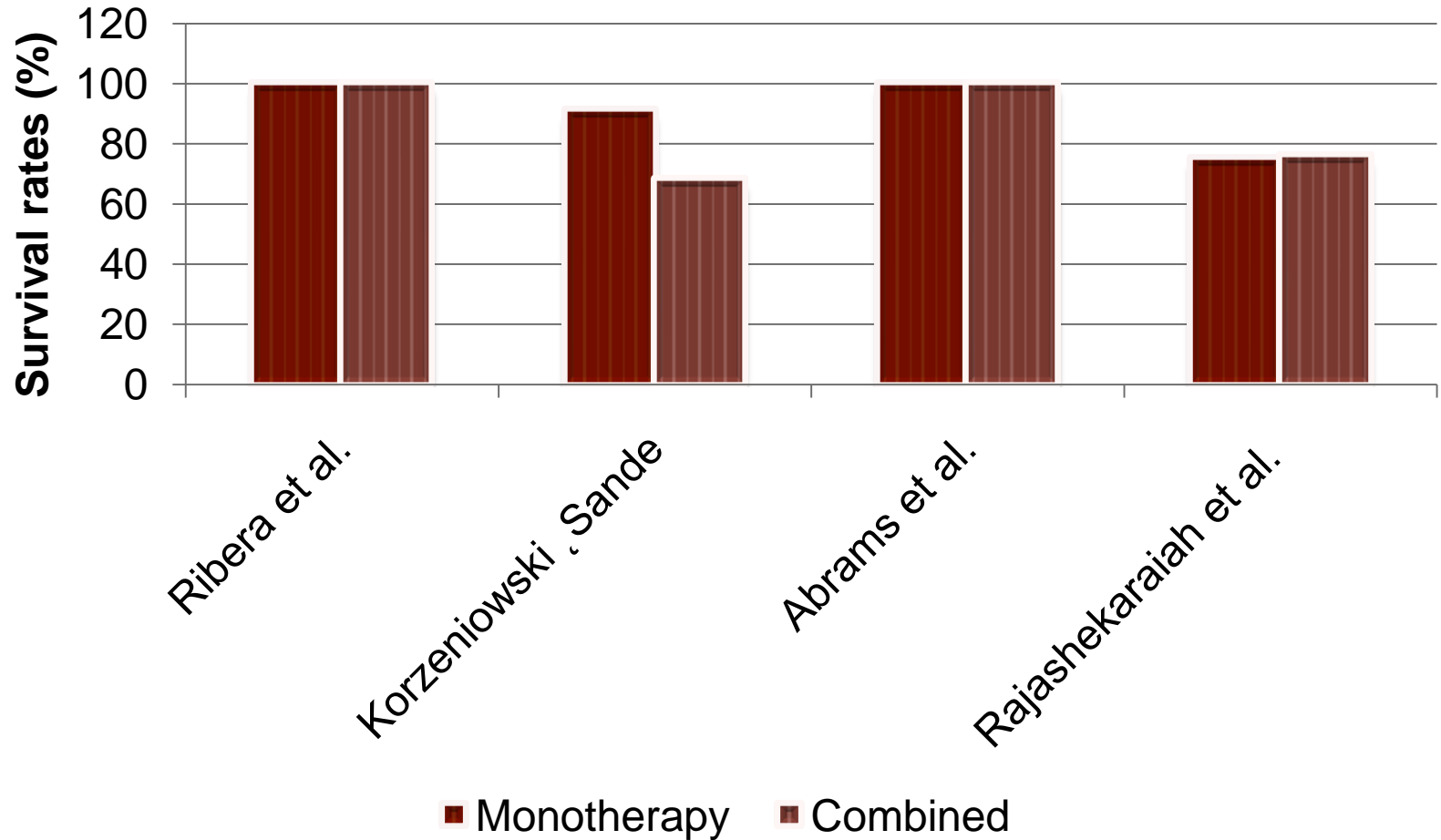
- Need? (effectiveness ?)
- Duration? (3 , 5, ≥ 14 days)
- Dose? (3 or 6 mg/kg?)
- Administration? (qd,bid,tid?)
- Longer persistence of bacteremia in addicts with RSIE in monotherapy group (13 vs 17 pts)
 - 3.6+-1.3 days vs. 2.6+-0.9 days
 - Negative BC on day 2: 1/13 vs 8/16 pts.

- Side effects are certain

- Nephrotoxicity
- Ototoxicity
- Obesity

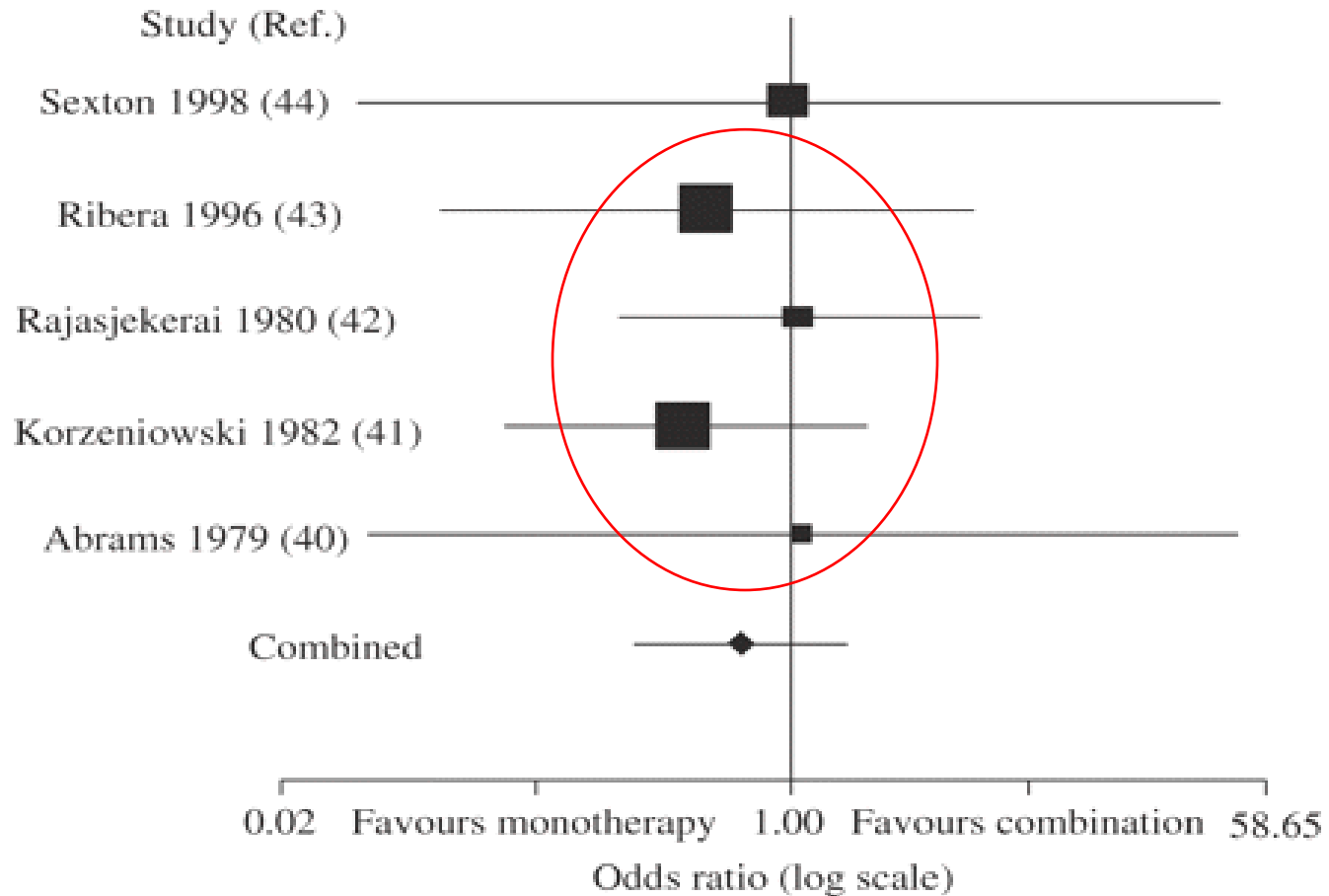
Korzenowsky et al. AIM,
1982

Survival rates in clinical trials comparing β -lactam monotherapy with combined gentamicin therapy



Monotherapy vs. Combined gentamicin

All cause mortality



Questions regarding gentamicin use in the treatment of staphylococcal IE

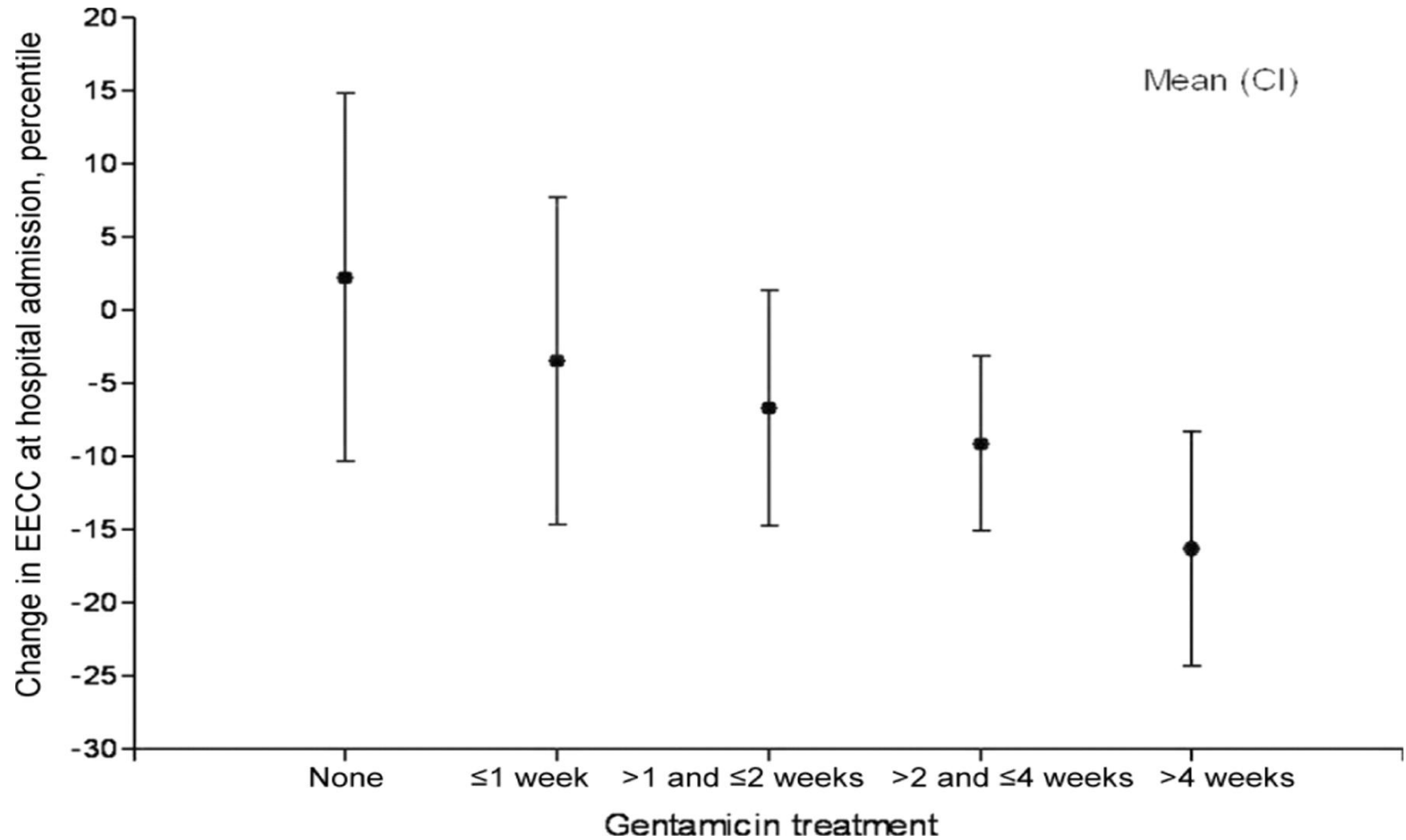
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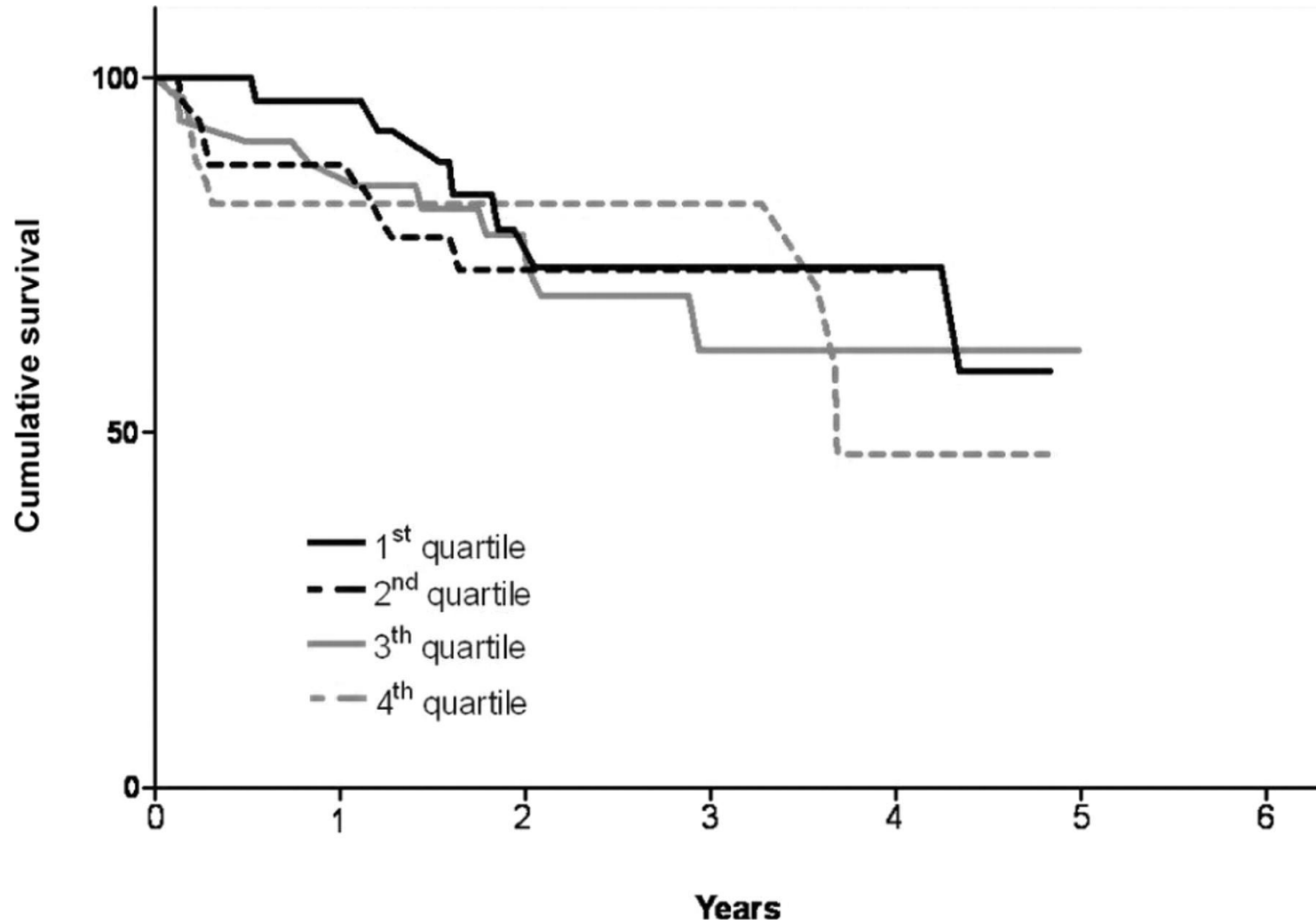
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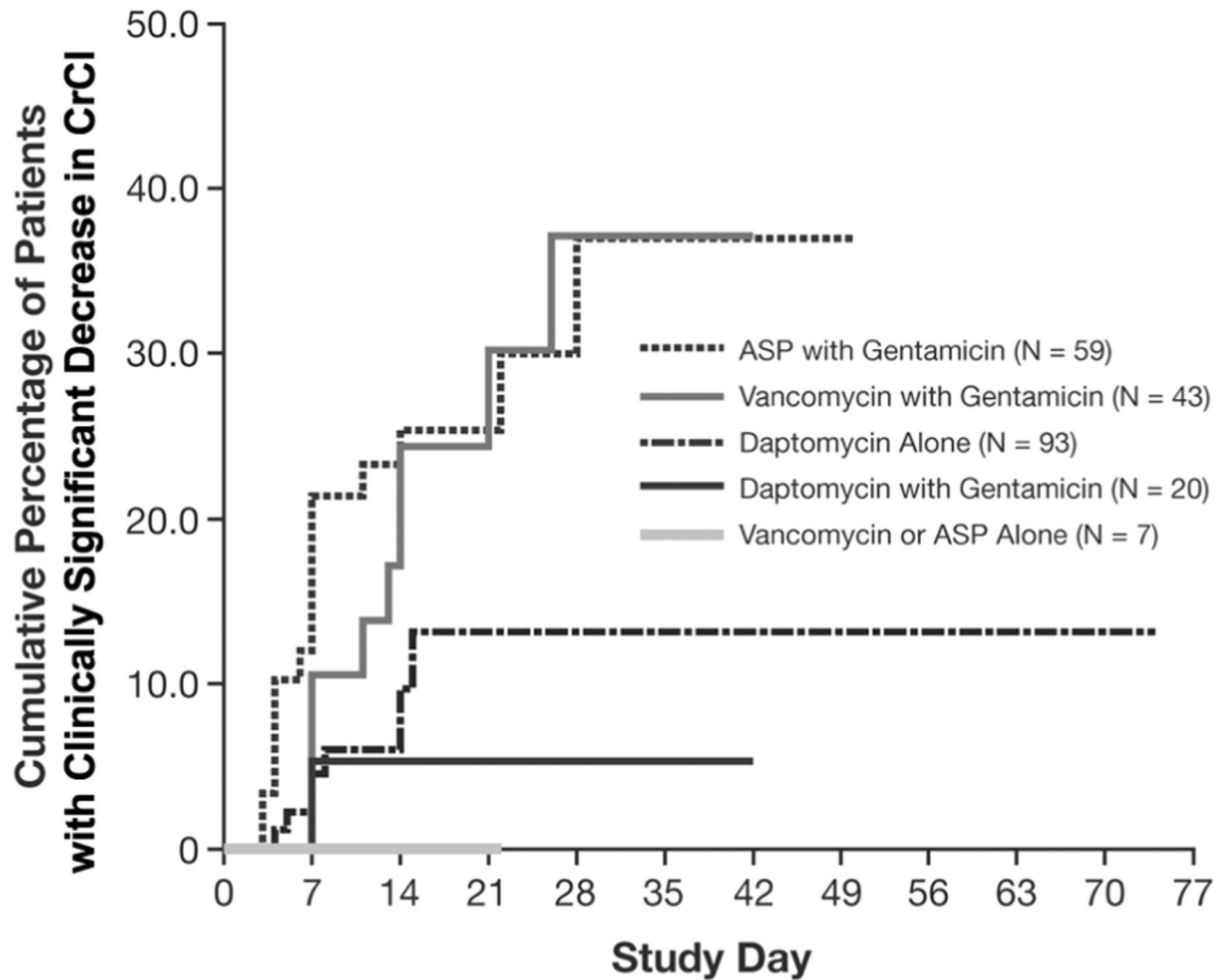
Mean percentile change in endogenous creatinine clearance (EECC) from diagnosis to hospital discharge in 286 patients with infective endocarditis, grouped by days of gentamicin treatment.



Kaplan-Meier plot of cumulative survival after hospital discharge for 136 patients with infective endocarditis by percentage change in endogenous creatinine clearance (EECC) from diagnosis to hospital discharge.

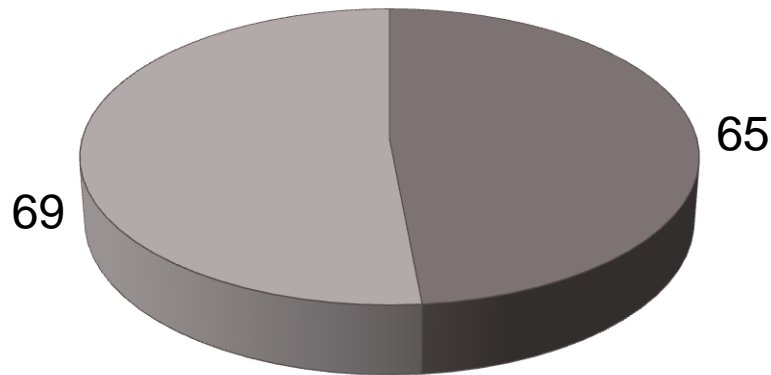


Time to a clinically significant decrease in creatinine clearance (CrCl).



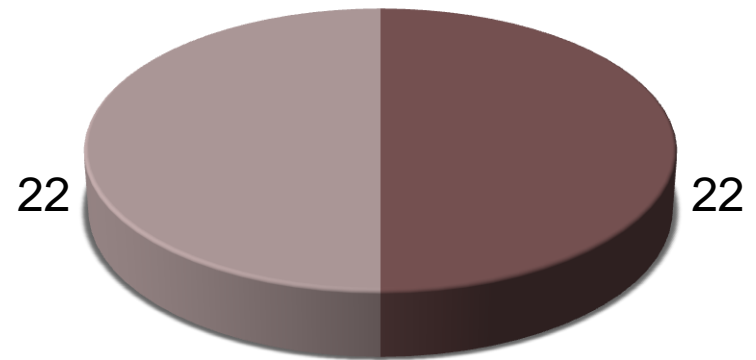
Use of gentamicin in the treatment of MSSA and MRSA IE – ICE PLUS STUDY

134 MSSA episodes
48,5 %



■ Yes ■ No

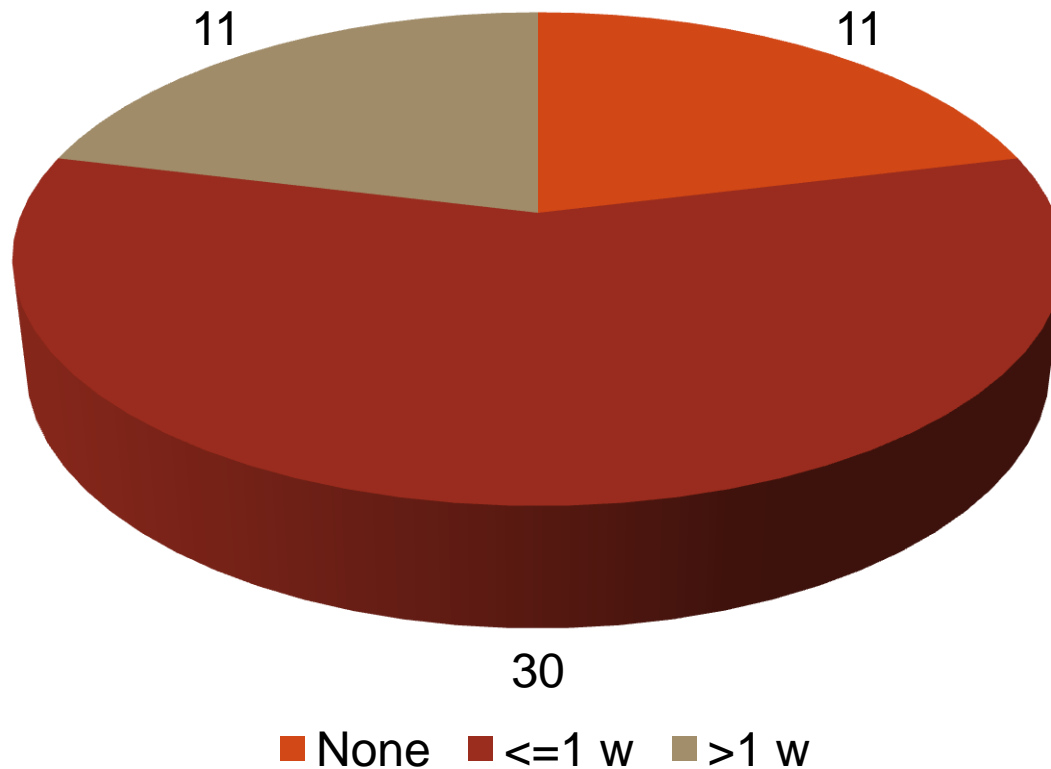
44 MRSA episodes
50.0 %



■ Yes ■ No

Use of gentamicin in the treatment of 52 episodes of *S.aureus* IE

No of patients



Use of gentamicin for *S. aureus* infections

Guidelines for the treatment of MRSA infections - (CID 2011; 52:285)

- Addition of gentamicin to vancomycin is not recommended for bacteremia or native valve infective endocarditis
- PVE ? (B-III)
- Vancomycin failure ? (B-III)

New combinations?

- Televancin + aminoglycosides¹
- Televancin + β -lactams (penems?¹)
- Tygecyclin + gentamicin²
- Daptomycin + β -lactams (gentamicin)³?

¹Leonard S, AAC, 2013; ² McConeghy KW, DMID, 2010; ³ Steenbergen JN, JAC 2009

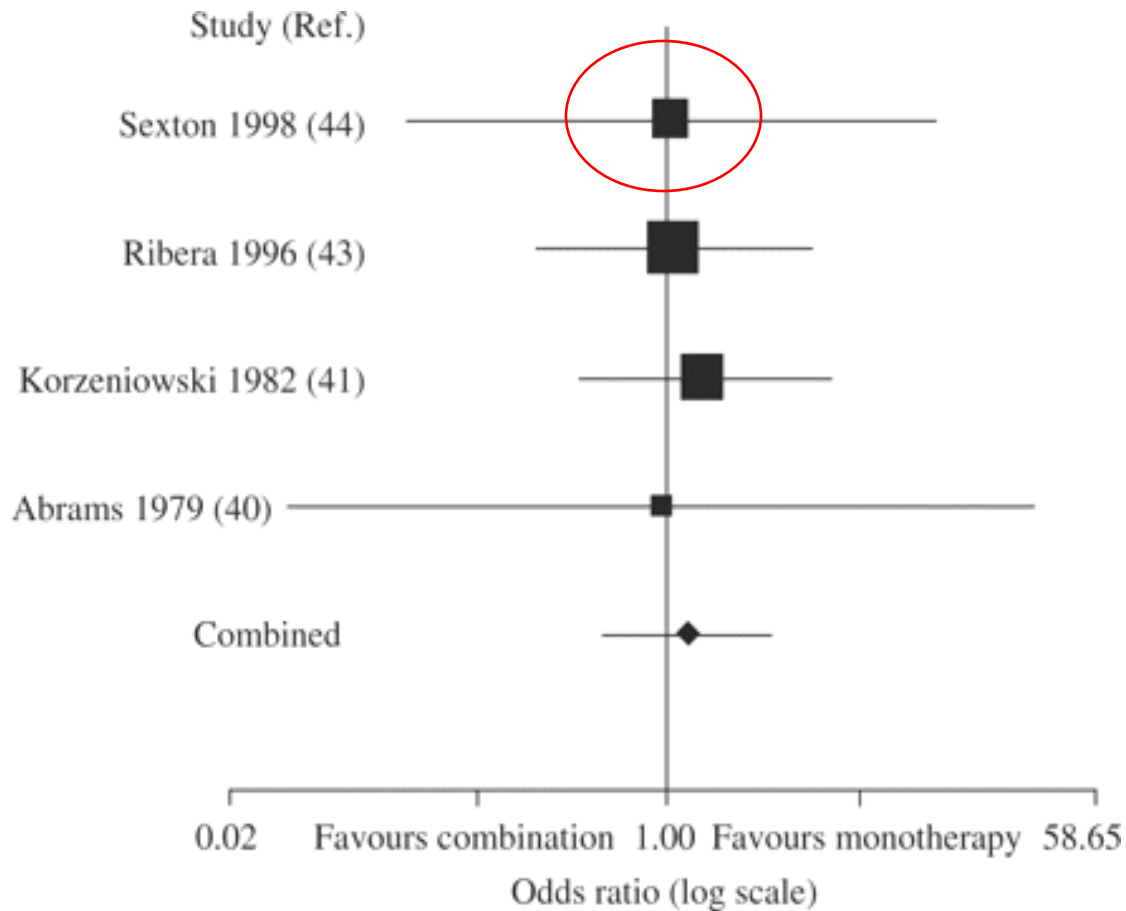
Treatment of *S.viridans* and *S.bovis* IE

Guidelines (AHA, ESC, BSAC)

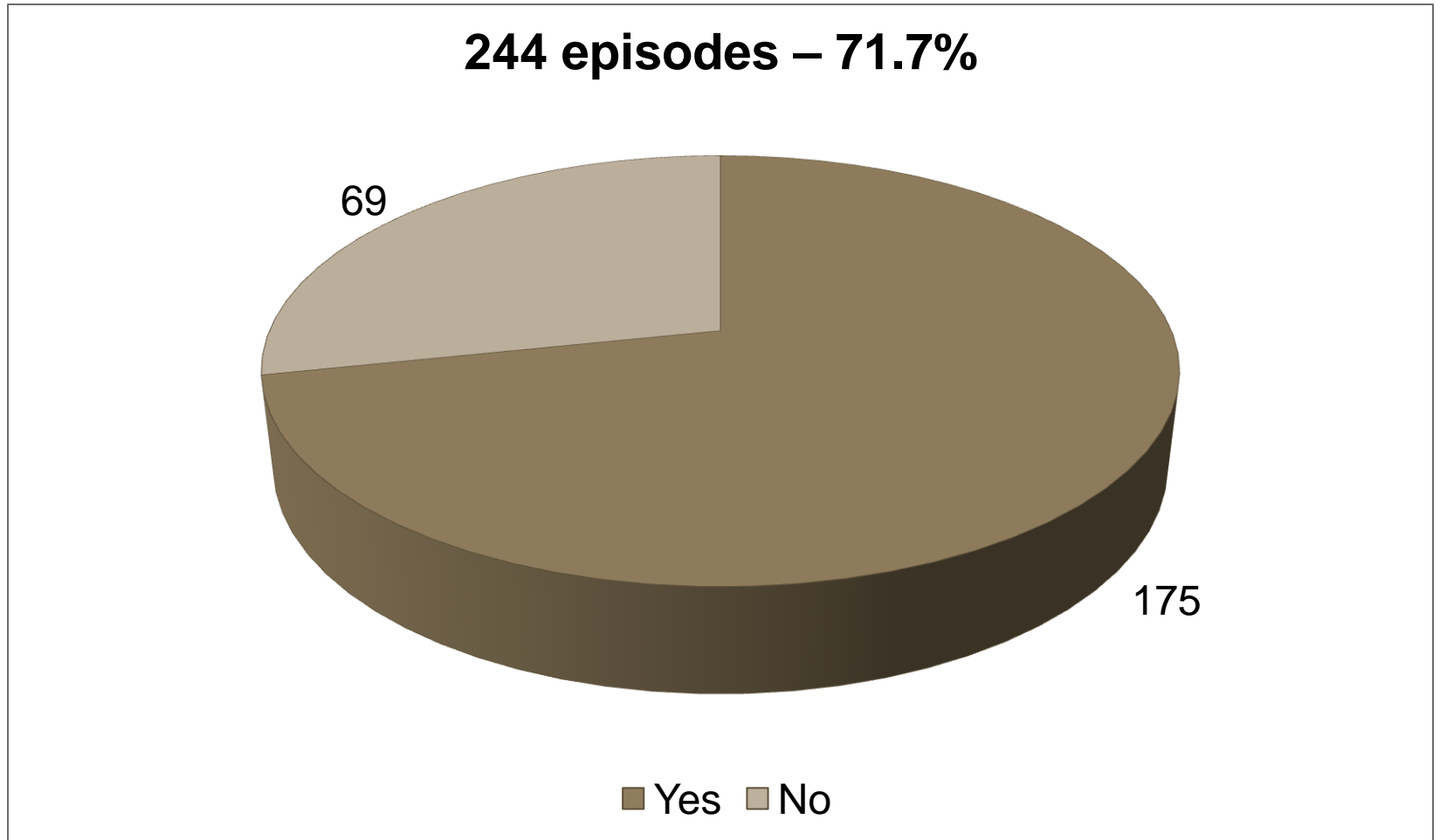
Position of gentamicin

- Two-weeks treatment
- Infection caused by a strain which penicillin MIC >0.12 and ≤ 0.5 mg/L (2 weeks, once daily)
- PVE
 - 2 weeks if MIC <0.12 mg/L
 - 6 weeks if MIC >0.12 mg/L

The role of aminoglycosides for the treatment of IE caused by Gram-positive bacteria

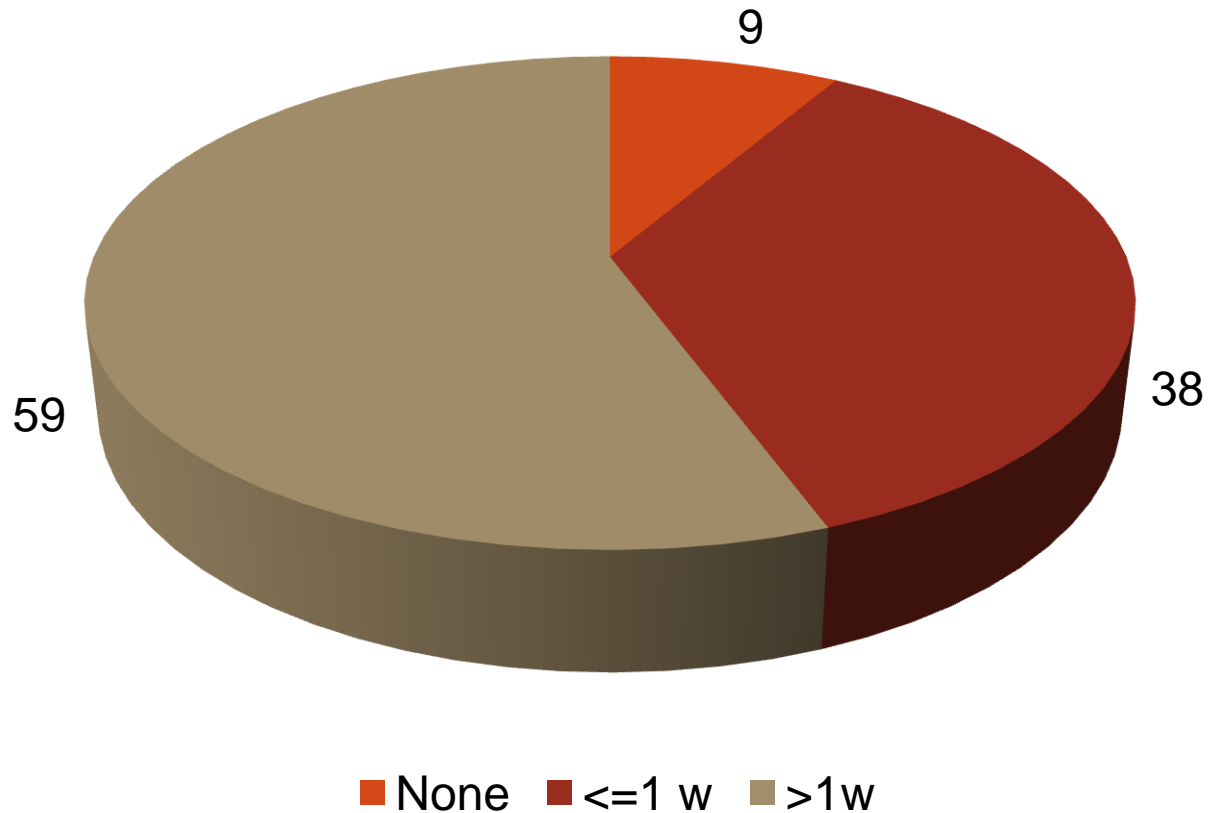


Use of gentamicin in the treatment of *S. viridans* IE – ICE PLUS STUDY



Use of gentamicin in the treatment of 106 episodes of streptococcal IE

No of patients



Treatment of Enterococcal IE

Current Guidelines (AHA, ESC, BSAC)

- **Penicillin S**

- ampicillin or penicillin
(*vancomycin*)

+

gentamicin (1 mg/kg
tid)

(*streptomycin for
gentamicin R*)

- **Gentamicin R**

- *E. faecalis*

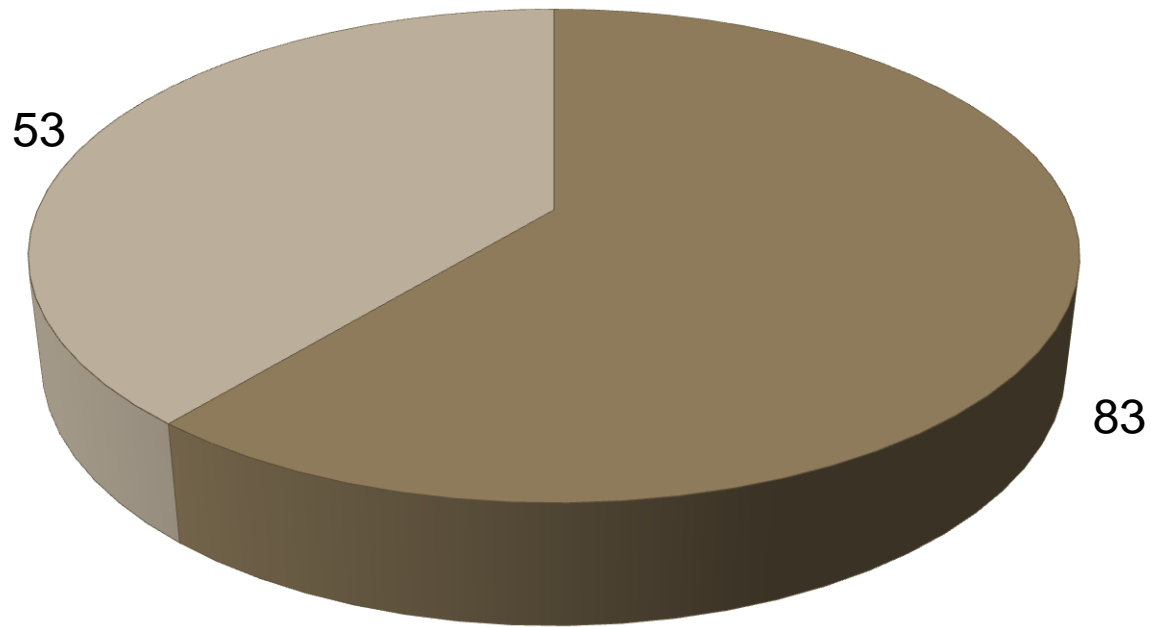
- ampicillin+ceftriaxone
- imipenem+ampicillin
- ampicillin
 - (*BSAC guidelines*)

- *E. faecium*

- Linezolid
- Quinupristin-dalfopristin

Use of gentamicin in the treatment of enterococcal IE – ICE PLUS STUDY

136 episodes – 61.0%



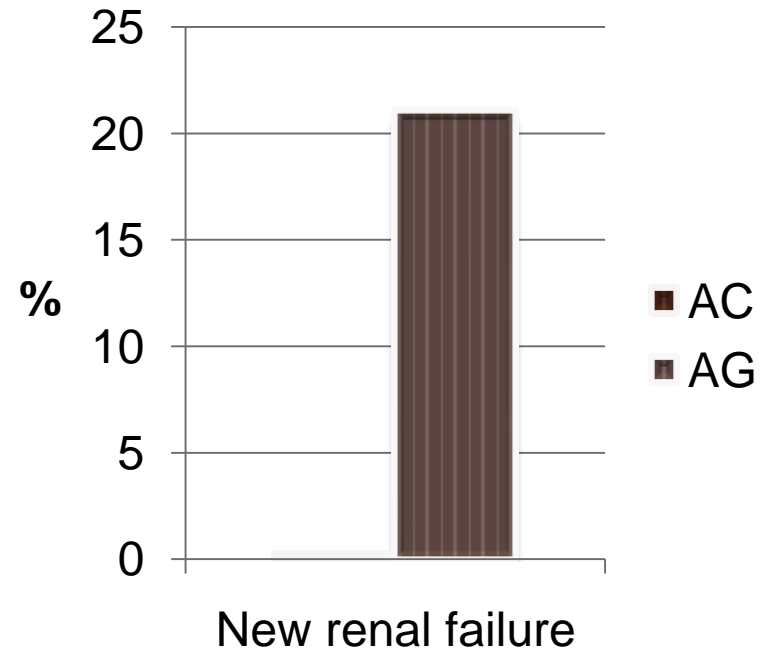
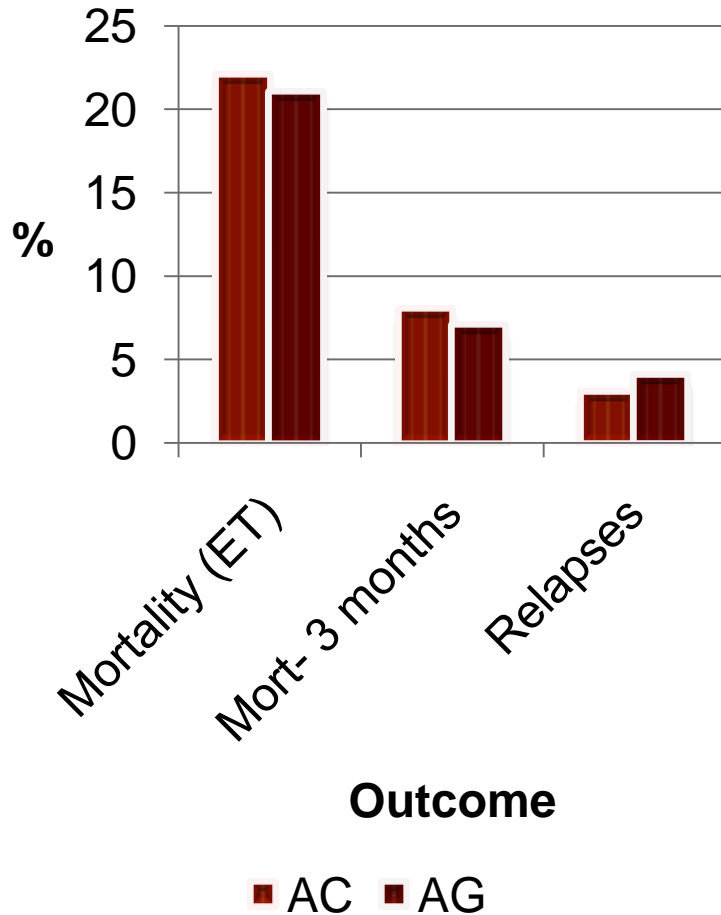
■ Yes ■ No

Other combinations for enterococcal infections

- Ampicillin + ceftriaxone¹
- Daptomycin+gentamycin
- Tigecycline+rifampicin

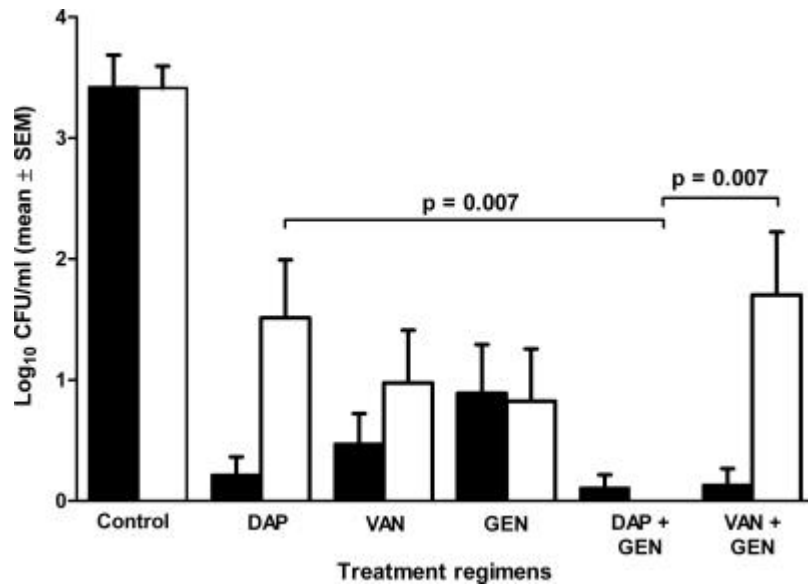
¹Fernandez-Hidalgo, N. CID; 2013

Ampicillin Plus Ceftriaxone Is as Effective as Ampicillin Plus Gentamicin for Treating Enterococcus faecalis Infective Endocarditis

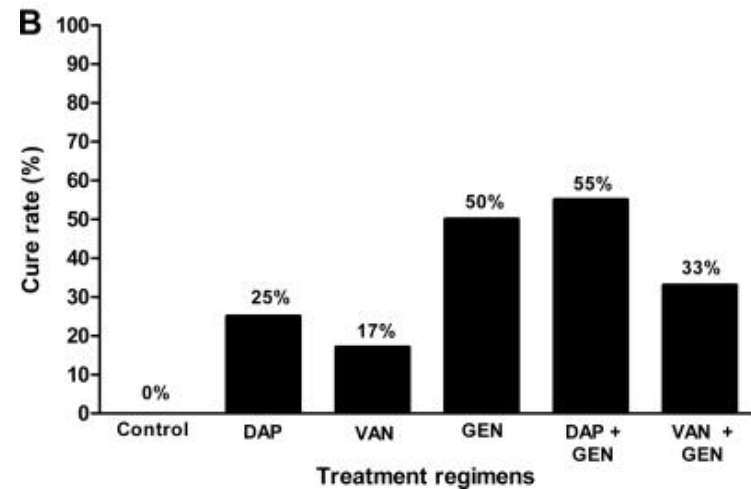
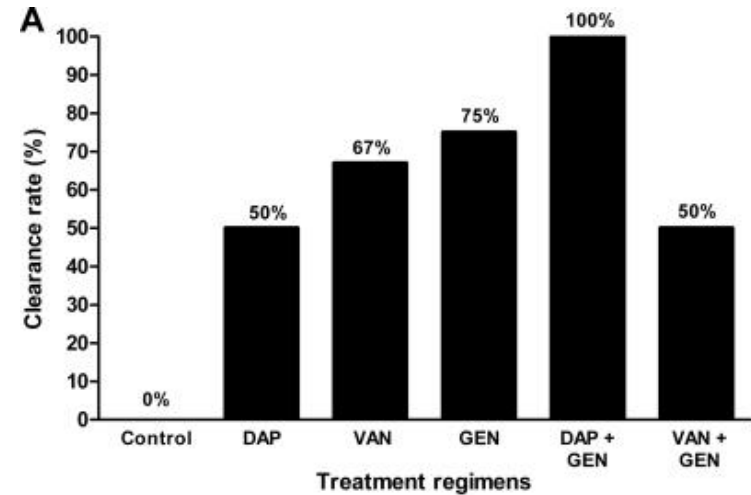


Fernandez-Hidalgo, N.
CID; 2013

Gentamicin Improves the Activities of Daptomycin and Vancomycin against *Enterococcus faecalis* *In Vitro* and in an Experimental Foreign-Body Infection Model



Bacterial load of planktonic bacteria in cage fluid during treatment (black bars) and 5 days after treatment (white bars). Values are means ± standard errors of the means (SEM). DAP, daptomycin; VAN, vancomycin; GEN, gentamicin



Is it time to change guidelines?

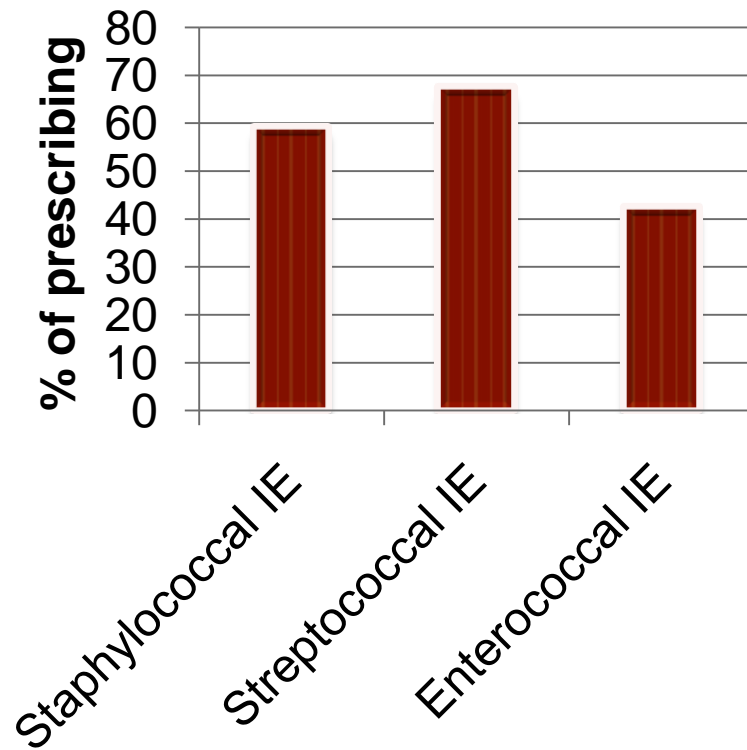
Daily routine doesn't follow guidelines!

Median time of gentamicin treatment and the incidence of premature withdrawal

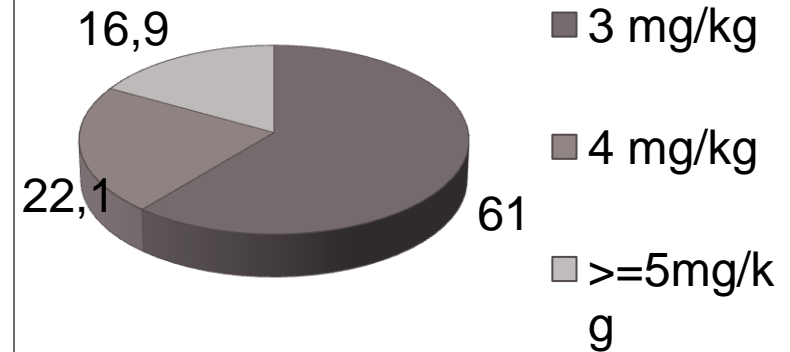
- Olaison et al. CID 2002
- median 15 days
- premature withdrawal 65/75 (**86.7%**) (before 36 weeks)
- Fernandez-Hidalgo N, CID 2013
- median 23 days (IQR, 14–34 days) if no adverse event; 14 days [IQR, 12–20 days] if AE)
- premature withdrawal 56/87 (**64.1%**)

Gentamicin use in IE

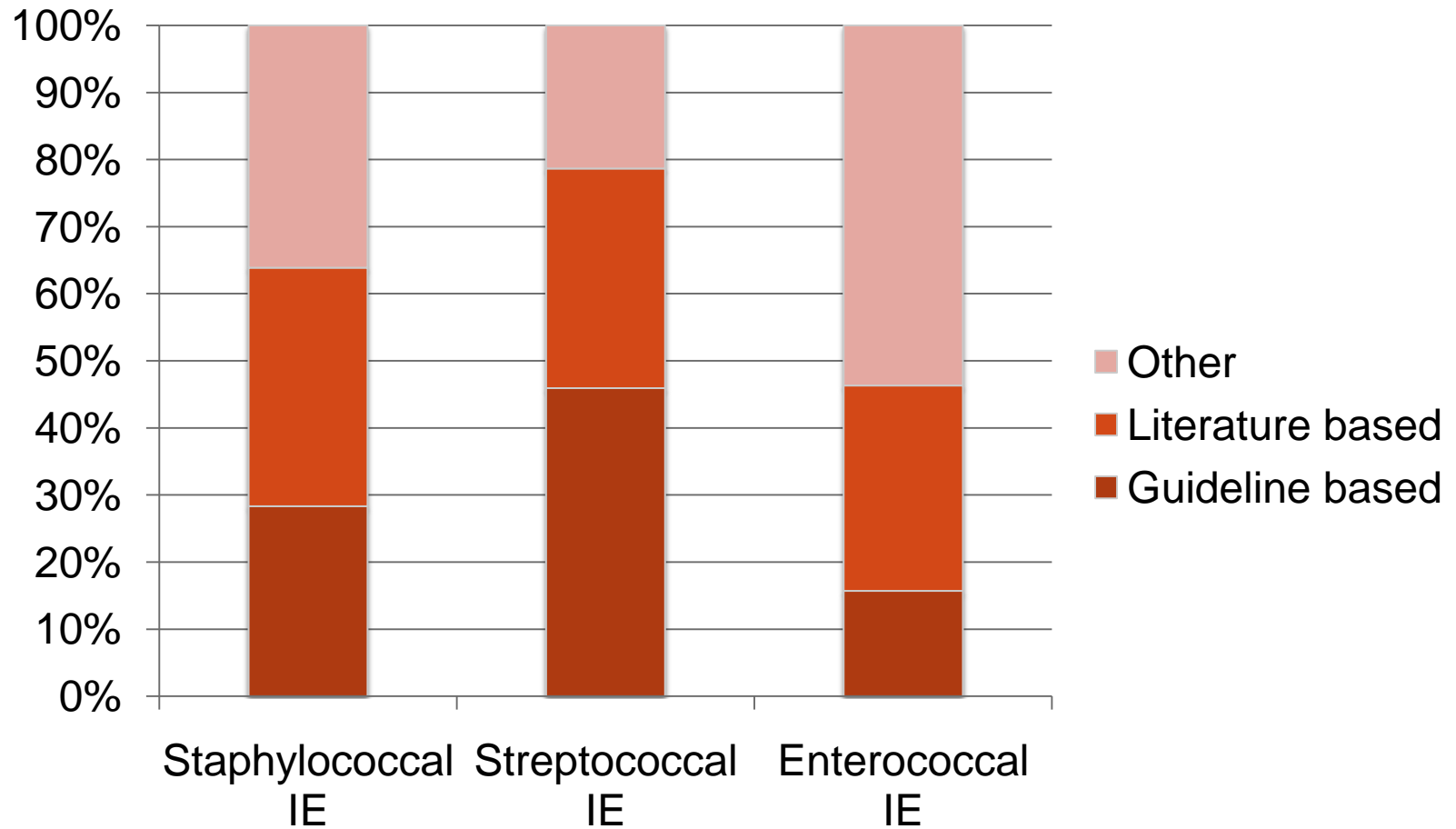
Administration once-daily



Gentamicin dose used by physicians (%)

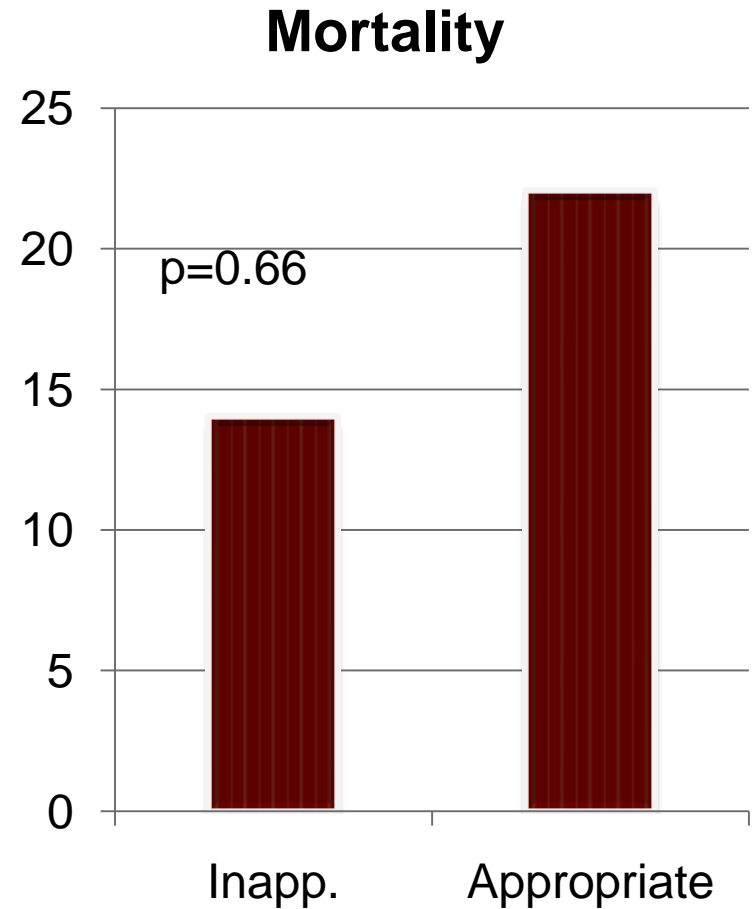
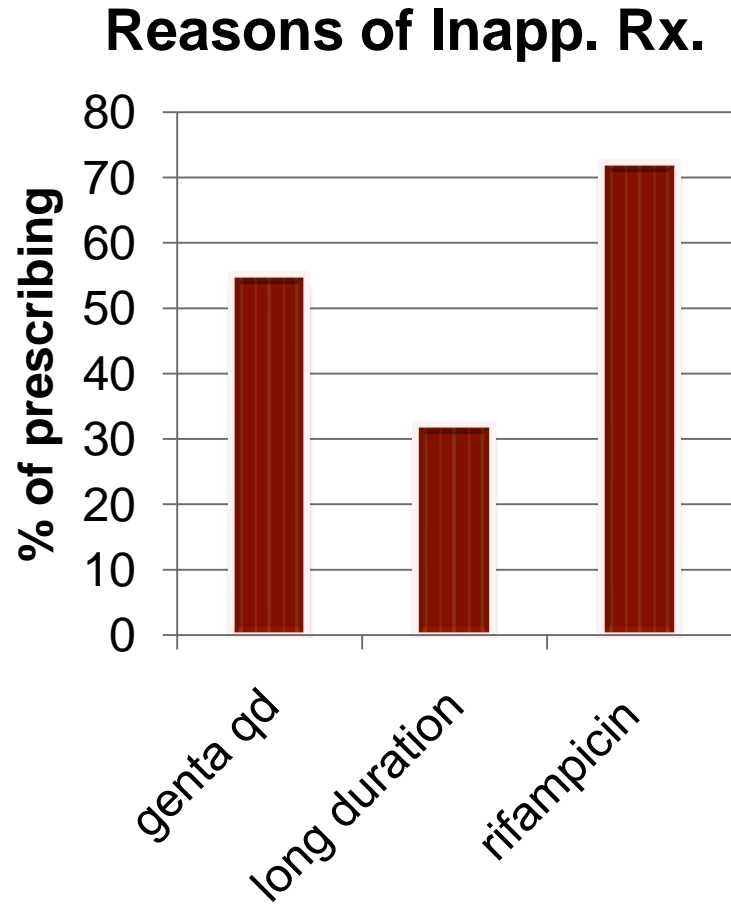


Prescription patterns in the treatment of IE

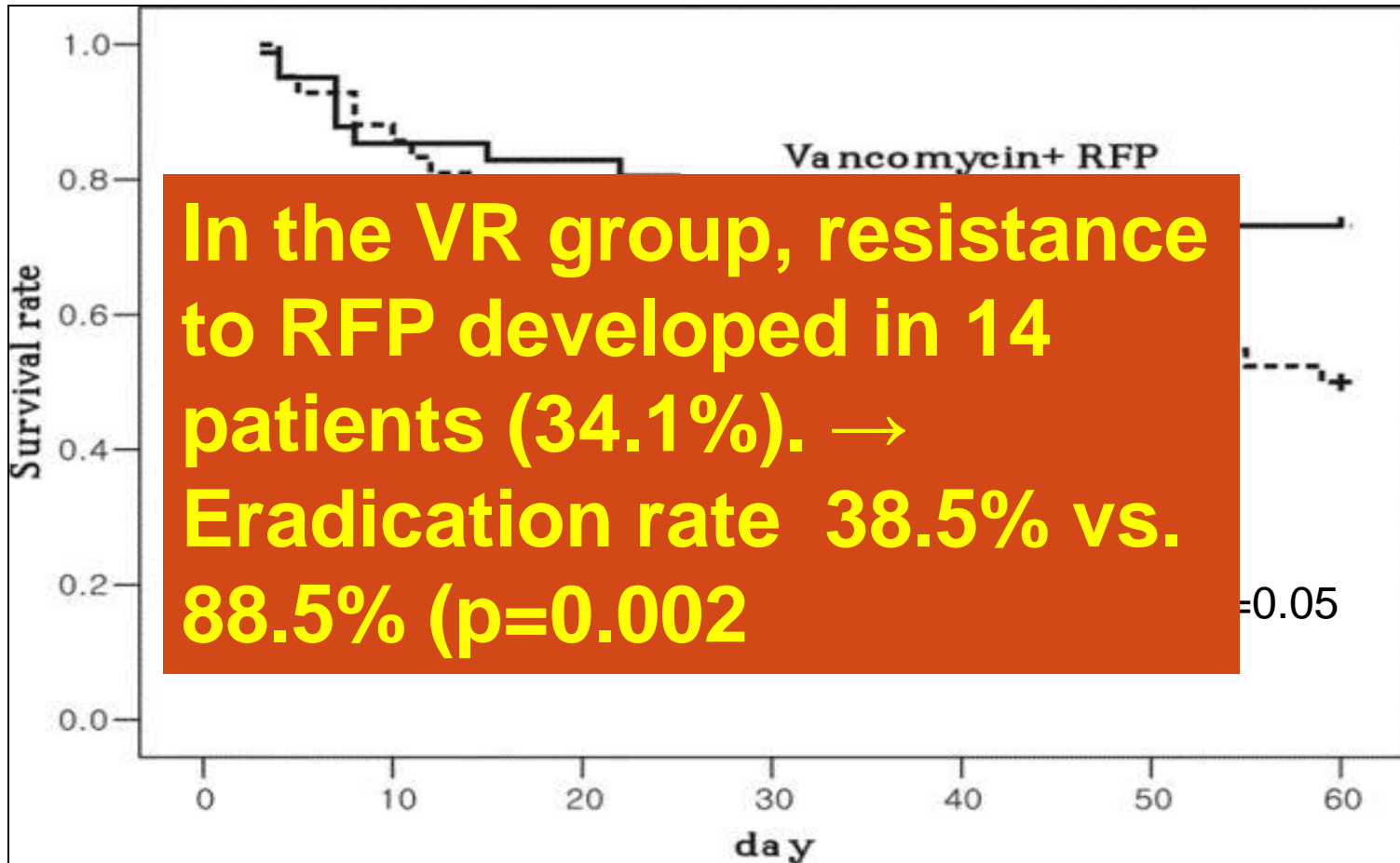


Gentamicin use in IE

Deviation from guidelines



Effect of vancomycin plus rifampicin in the treatment of nosocomial methicillin-resistant *Staphylococcus aureus* pneumonia



Conclusions

- Effectiveness of gentamicin use for some G+ve infections is dubious
- Harms of gentamicin use are well evidenced
- Different physicians' attitudes to use combined treatment
- Use of rifampicin associated with increase in resistance
- New combinations emerging – clinical data still missing