Tübingen, 29.03.2014

THERAPIE MULTIRESISTENTER GRAMPOSITIVER ERREGER

Comprehensive
Infectious
Disease
Center

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Infektiologie
Innere Medizine I
Universitätsklinikum Tübingen

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Road map

- Which is the real impact on patients mortality of inappropriate empiric and targeted therapy for MDR gram-positive?
- How we can reduce related morbidity and mortality?
- Which the major limits and advantages of approved drugs?
- Which are, if any, new developments in the antibiotic pipeline?

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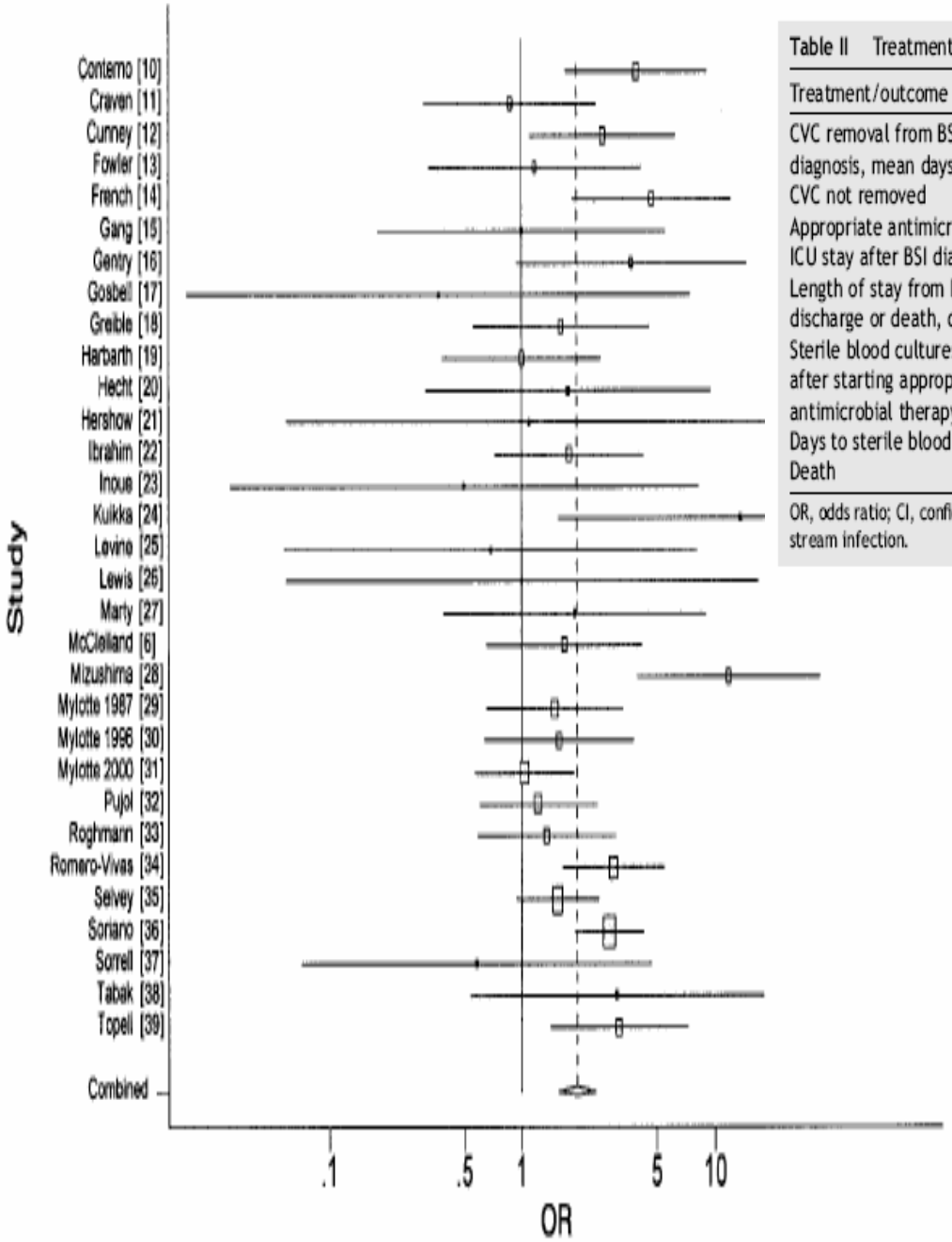

Table II Treatment and outcomes of meticillin-resistant *Staphylococcus aureus* bloodstream infections

Treatment/outcome	Cases ($N=50$)	Controls ($N=50$)	OR (95%CI)	P value
CVC removal from BSI diagnosis, mean days (±SD)	1.4 (0.2)	1.8 (0.3)	–	0.3
CVC not removed	8 (22%)	4 (10%)	2.2 (0.5–10.6)	0.2
Appropriate antimicrobial therapy	50	50	–	–
ICU stay after BSI diagnosis	20 (40)	15 (30)	1.6 (0.6–3.9)	0.3
Length of stay from BSI to discharge or death, days (±SD)	12 (1.9)	18 (1.8)	–	0.02
Sterile blood cultures within 72 h after starting appropriate antimicrobial therapy	21 (49)	22 (51)	0.9 (0.4–2.2)	1.0
Days to sterile blood cultures (±SD)	3.4 (2.5)	3.4 (2.6)	–	0.9
Death	18 (36)	6 (12)	4.1 (1.4–14)	0.005

OR, odds ratio; CI, confidence interval; CVC, central venous catheter; SD, standard deviation; ICU, intensive care unit; BSI, bloodstream infection.

Cosgrove,CID 2003;
Tacconelli, JHI 2006

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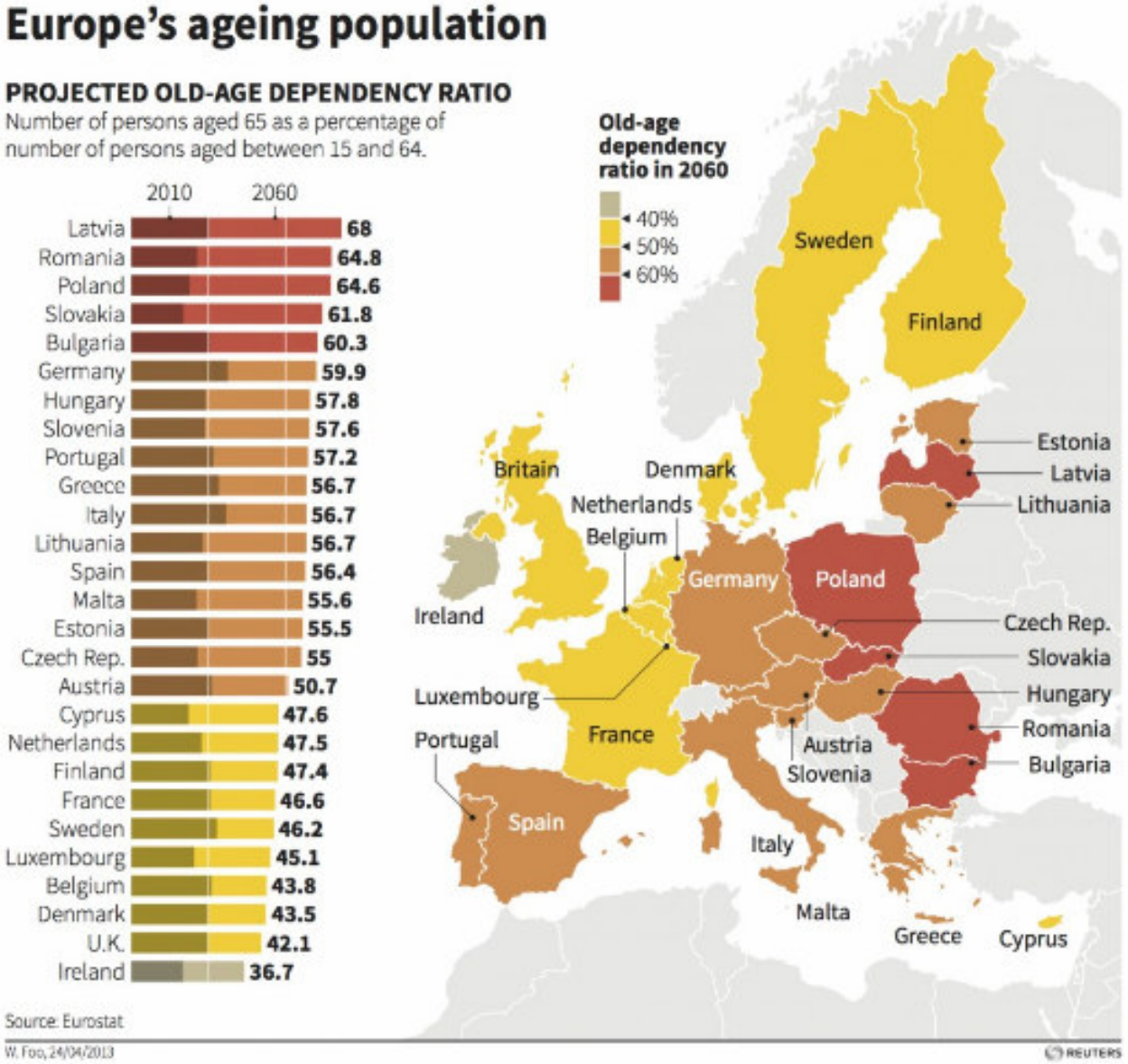
Europe's ageing population



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Mortality and length of hospitalization (LOS) TIMBER project

Exposure	Adjusted Mortality HR (95% confidence interval)	Excess LoS days (95% confidence interval)	Adjusted End-LoS HR (95% confidence interval)
MSSA BSI (n=898)	1.82 (1.50,2.21)	10.35 (9.44, 11.26)	0.54 (0.49, 0.60)
MRSA BSI (n=167)	2.38 (1.64,3.45)	12.22 (9.89, 14.55)	0.47 (0.37, 0.60)
3GCS-E BSI (n=2094)	1.16 (0.99, 1.36)	4.36 (3.91, 4.81)	0.80 (0.76, 0.85)
3GCR-E BSI (n=366)	1.79 (1.33, 2.41)	7.91 (6.66, 9.16)	0.58 (0.49, 0.67)

ECCMID 2014, oral presentation

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Mortality in Germany

Tab. 1 Hochrechnung zur Exzess-Letalität wegen Auftreten der jeweils multiresistenten Variante der Erreger statt der jeweils sensiblen Variante bei Blutstrominfektionen im Jahr 2010.

Erreger	MRSA	ESBL E.coli	Summe
Fälle pro Jahr in Deutschland	3 900	2097	5 997
Fälle zusätzlicher Letalität	421	256	677
MRSA = Methicillin-resistente S.aureus			
ESBL E. coli = Extended-Spectrum-Betalactamase- bildende E. coli			

Gastmeier, 2013 Dtsch Med Wochenschr

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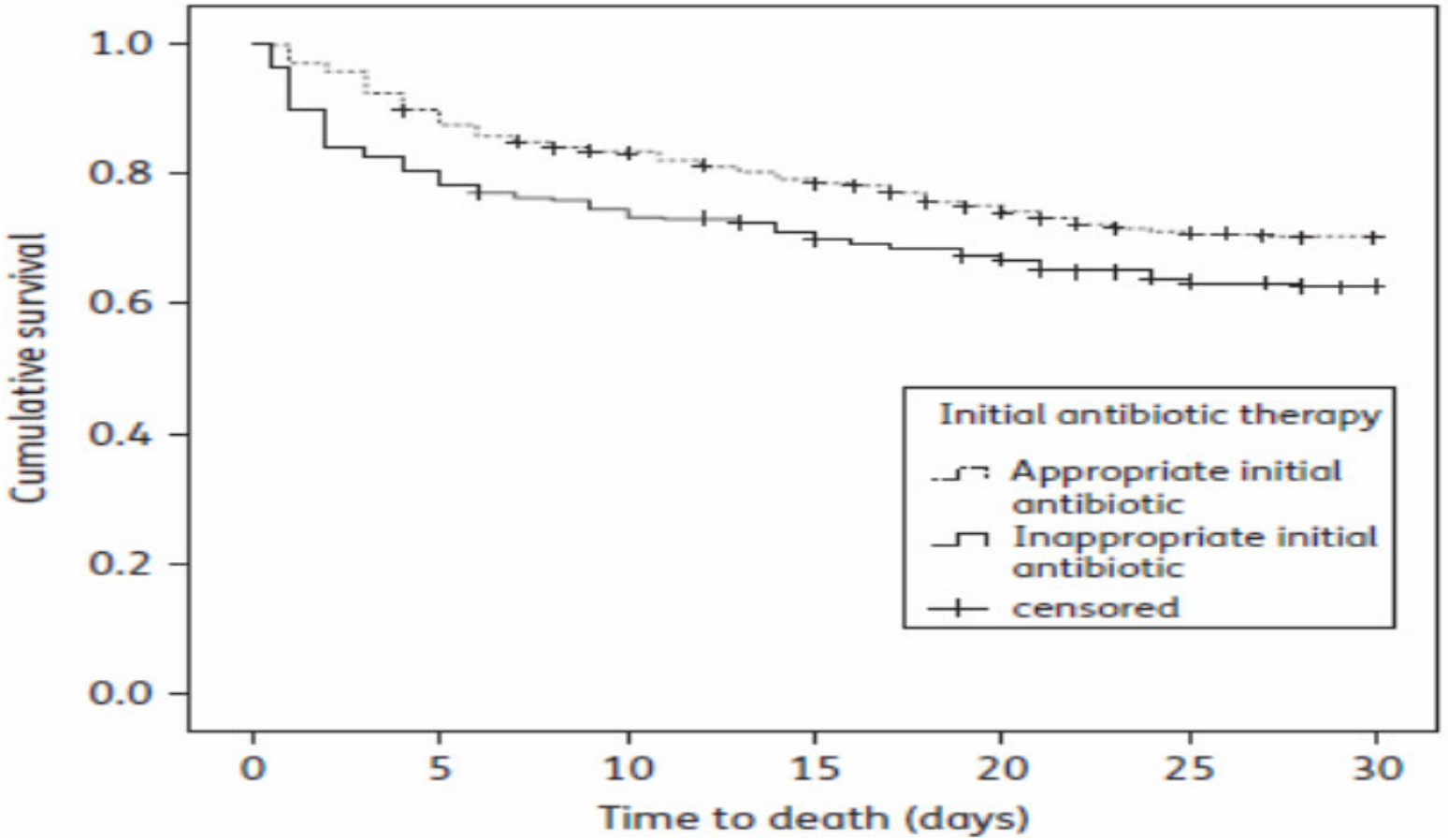
Predictive factors for early mortality among patients with methicillin-resistant Staphylococcus aureus bacteraemia



Gasch, JAC Feb 2013

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Impact of Routine Infectious Diseases Service Consultation on the Evaluation, Management, and Outcomes of *Staphylococcus aureus* Bacteremia

Table 4. Evaluation and classification of *Staphylococcus aureus* bacteremia by time period.

Variable	Before routine consultation ($n = 134$)	During routine consultation ($n = 100$)	P
Infectious diseases consultation	71 (53)	90 (90)	<.001
Time to consultation, median days (IQR)	3 (1–5)	2 (1–3)	.005
Duration of patient follow-up, median days (IQR)	60 (31–81)	54 (35–71)	.19[a]

Jenkins, CID 2008

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Rapid testing for methicillin-resistant Staphylococcus aureus: implications for antimicrobial stewardship

- 4 companies offer products for testing
  - sensitivity (91-100%)
  - specificity (95-100%)
- There is limited published evidence on the impact of any rapid MRSA assay on patient-level outcome and cost-effectiveness measures.
- Currently available rapid MRSA assays differ in specificity, sensitivity, cost, approved applications, and laboratory turnaround time, and published data are limited.

Geiger K, Am J Health Syst Pharm. 2013 Feb

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Invasive Methicillin-Resistant *Staphylococcus aureus* Infections in the United States

Table 5. Number and Percentage of Invasive Methicillin-Resistant *Staphylococcus aureus* Infections by Clinical Condition and Epidemiologic Classification, Active Bacterial Core Surveillance, United States, July 2004-December 2005[a]

Condition[b]	Community-Associated (n = 1226)	Health Care–Associated, No. (%)		Total, No. (N = 8792)[c]
		Community-Onset (n = 5191)	Hospital-Onset (n = 2375)	
Bacteremia	798 (65.1)	4019 (77.4)[e]	1794 (75.5)[e]	6611
Pneumonia	172 (14.0)	616 (11.9)[d]	383 (16.1)	1171
Cellulitis	278 (22.7)	456 (8.8)[e]	114 (4.8)[e]	848
Osteomyelitis	99 (8.1)	415 (8.0)	142 (6.0)[d]	656
Endocarditis	155 (12.6)	341 (6.6)[e]	60 (2.5)[d]	556
Septic shock	46 (3.8)	233 (4.5)	99 (4.2)	378

[a] Epidemiologic classification of disease consisted of health care–associated (either hospital-onset cases with a culture collected >48 h after hospital admission or community-onset cases with health care risk factors but a culture collected ≤48 h after hospital admission) and community-associated cases (those with no health care risk factors).
[b] Cases could have ≥1 clinical syndrome.
[c] Of 8987 observed cases with invasive methicillin-resistant *Staphylococcus aureus*, 114 (1.3%) could not be classified and 81 had missing condition.
[d] $P < .05$.
[e] $P < .01$; all comparisons use community-associated as the referent category.

Klevens, JAMA, 2007

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MRSA BSI at hospital admission

Table 3.. Two logistic regression analyses of risk factors associated with healthcare-associated MRSA bacteraemia within 24 h of hospitalization, including (first model) and excluding (second model) a history of previous MRSA infection or colonization

Variables	OR	95%CI	*P* value
First model			
previous MRSA infection or colonization	17.04	4.98–58.27	<0.001
cellulitis at hospital admission	4.27	1.52–11.94	0.006
presence of a central venous catheter	3.30	1.71–6.38	<0.001
skin ulcers at hospital admission	3.12	1.37–7.11	0.007
Second model			
presence of a central venous catheter	3.24	1.76–5.97	<0.001
hospitalization in the previous 6 months	2.01	1.11–3.65	0.02
quinolone therapy in the previous 30 days	1.99	1.07–3.69	0.02
diabetes mellitus	1.84	1.05–3.22	0.03

Tacconelli E, JAC, 2004

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VRE positive patients at hospital admission

Table 3. Risk index score for recovery of vancomycin-resistant enterococci at hospital admission, by associated risk factor.

Risk factor	Point value
Previous recovery of MRSA[a]	4
Long-term hemodialysis	3
Transfer from LTCF or hospital	3
Exposure to ⩾2 antibiotics[b]	3
Previous hospitalization[a]	3
Age >60 years	2

Tacconelli, CID 2004

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Risk factors for hospital-acquired MRSA infections

Table 2 Score for risk factors influencing antibiotic strategy according to the PEG recommendation

Risk factor	Points
Age >65 years	1
Preexisting structural lung disease	2
Recent antibiotic therapy	2
Late onset >4 days in hospital	3
Severe respiratory insufficiency with/without mechanical ventilation	3
Extrapulmonary organ failure	4

Abbreviation: PEG, Paul-Ehrlich-Gesellschaft.

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IDSA Guidelines 2011
BSI

Bacteremia and infective endocarditis					
Bacteremia	Vancomycin	15–20 mg/kg/dose IV every 8–12 h	15 mg/kg/dose IV every 6 h	AII	The addition of gentamicin (AII) or rifampin (AI) to vancomycin is not routinely recommended.
	Daptomycin	6 mg/kg/dose IV QD	6–10 mg/kg/dose IV QD	AI/CIII	For adult patients, some experts recommend higher dosages of 8–10 mg/kg/dose IV QD (BIII). Pregnancy category B.

Liu, CID 2011

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The pharmacokinetics and pharmacodynamics of vancomycin in clinical practice: evidence and uncertainties

S. J. Vandecasteele[1], A. S. De Vriese[1] and E. Tacconelli[2]*

Table 1. Proposed vancomycin dose as a function of kidney function, administered as a continuous infusion or in an intermittent dosing regimen; the maximal infusion rate is 15 mg/min under all circumstances

Vancomycin continuous infusion schedule
Loading dose: 15 mg/kg in all patients
Maintenance dose:
infusion rate (mg/24 h) = 30 mg/kg/24 h
OR
infusion rate (mg/24 h) = [0.029 × CL_{CR} (mL/min) + 0.94] × target plateau level × 24 with target plateau level of 22.5 mg/L.
Vancomycin intermittent dosing schedule
Loading dose: 25 mg/kg in all patients
Maintenance dose [CKD stage, CL_{CR} (mL/min/1.73 m^2), vancomycin dose]:
0, >90, 15–20 mg/kg/12 h
2, 60–89, 20–30 mg/kg/24 h
3A, 45–59, 15–20 mg/kg/24 h
3B, 30–44, 10–15 mg/kg/24 h
4, 15–29, 7–10 mg/kg/24 h
5, <15, 10 mg/kg/48 h
Vancomycin haemodialysis schedule: http://www.azbrugge.be/VancomycinDoseCalculator.
CKD, chronic kidney disease.

JAC 2013

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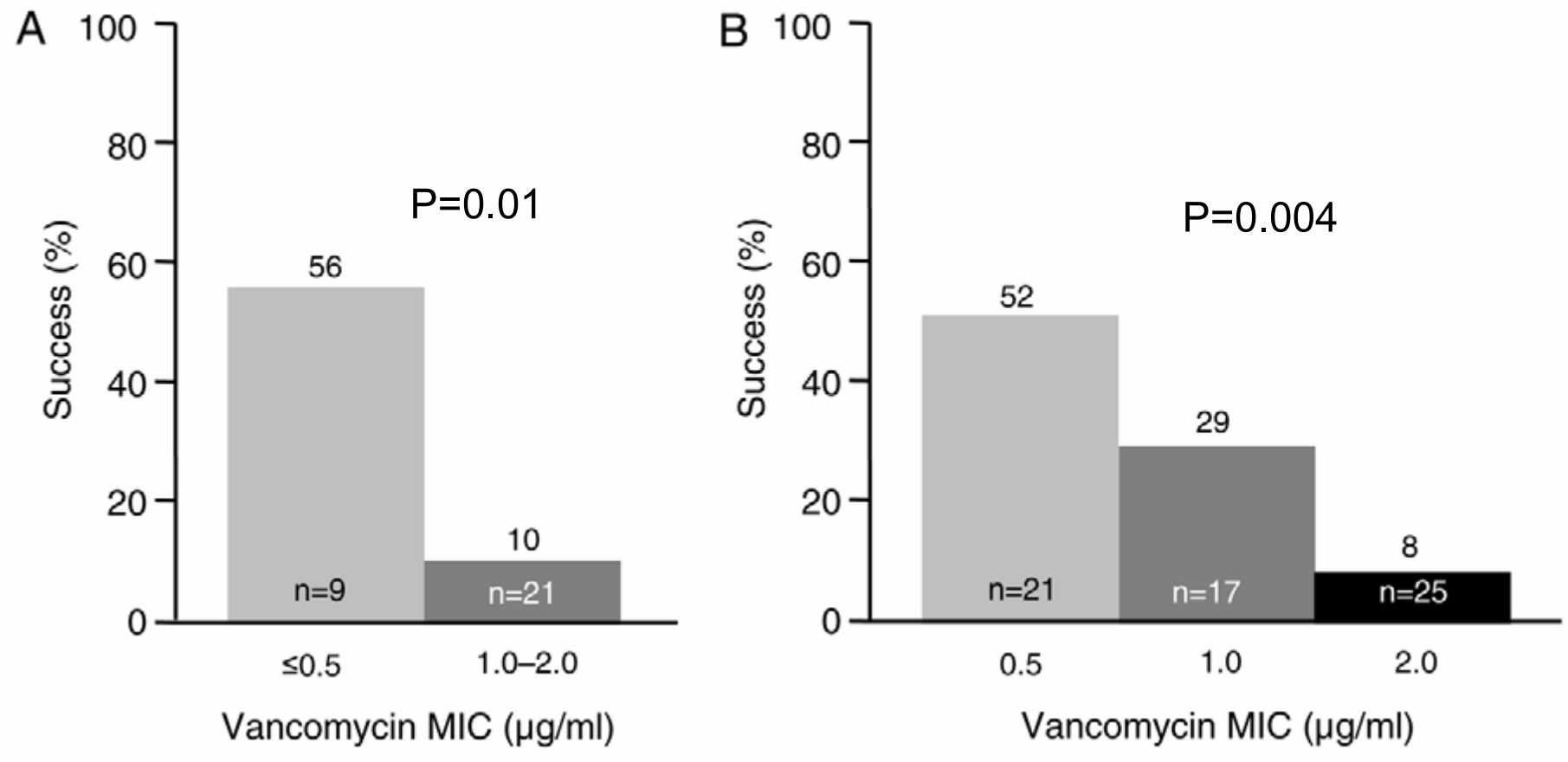
Vancomycin, MIC and mortality



Sakoulas et al. J Clin Microb 2004

Moise-Broder et al. CID 2004

Gould I. Int J Ant Ag 2008

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MRSA BSI
UK online survey

108 respondents

- 42% vancomycin alone (removable-focus infections)
- 49% plus RFD (cardiac / orthopaedic origin)
- 69% linezolid as a second line agent
- 19% daptomycin

Table 1. Percentage of positive responses to choice of antimicrobial based on vancomycin MIC (mg/L)

	MIC (mg/L)			
Action	1	2	4	>4
Continue unchanged	83.3	50	0	0
Add in rifampicin	88.9	61.1	25	2.8
Add in an aminoglycoside	50	66.7	33	16.7
Change to daptomycin	25	18.8	50	81.3
Change to linezolid	29	38.2	76.5	91.2
Change to tigecycline	75	25	25	50

Hussain JAC 2010

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Daptomycin vs vancomycin + gentamicin in MRSA bacteraemia and right-side endocarditis

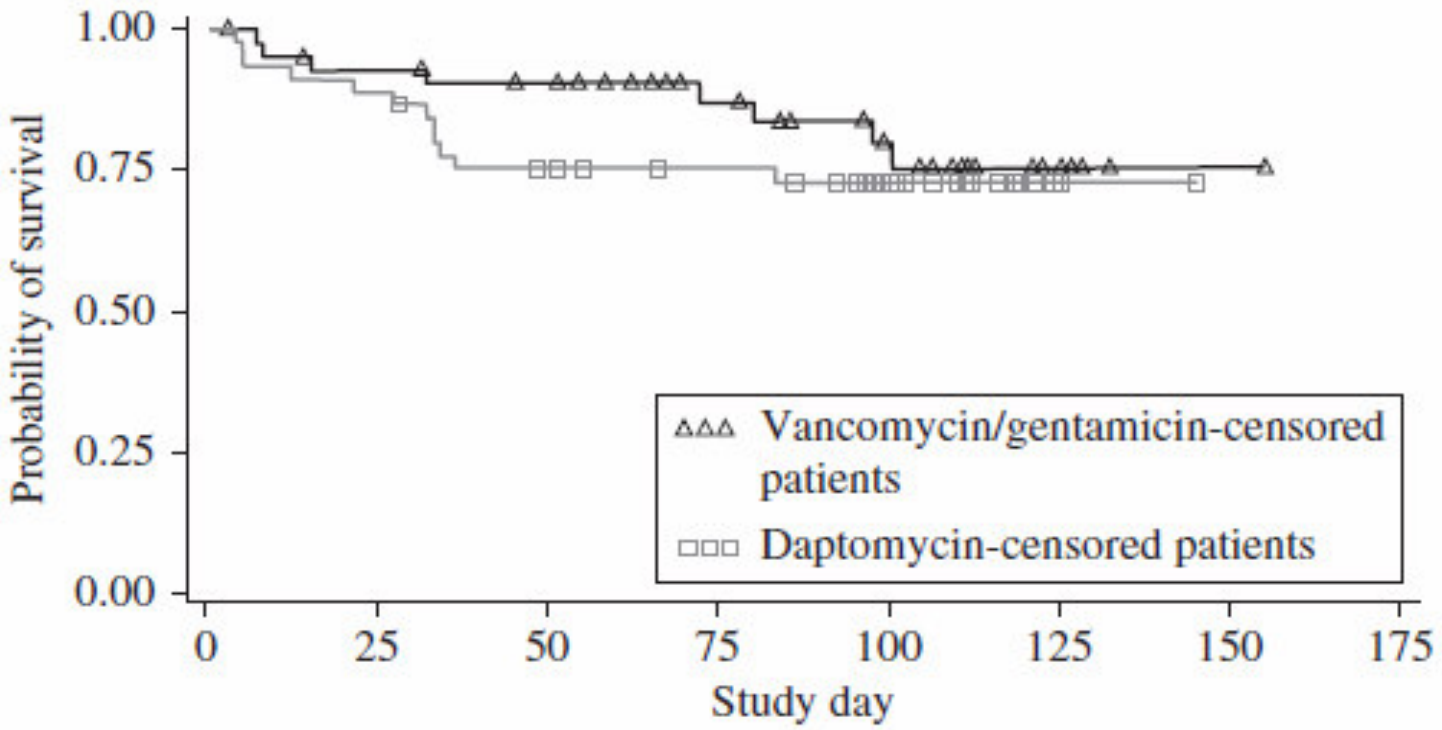

Figure 1. The Kaplan–Meier plot of overall survival. Wilcoxon $P = 0.25$, log-rank $P = 0.42$.

Susan, JAC 2008

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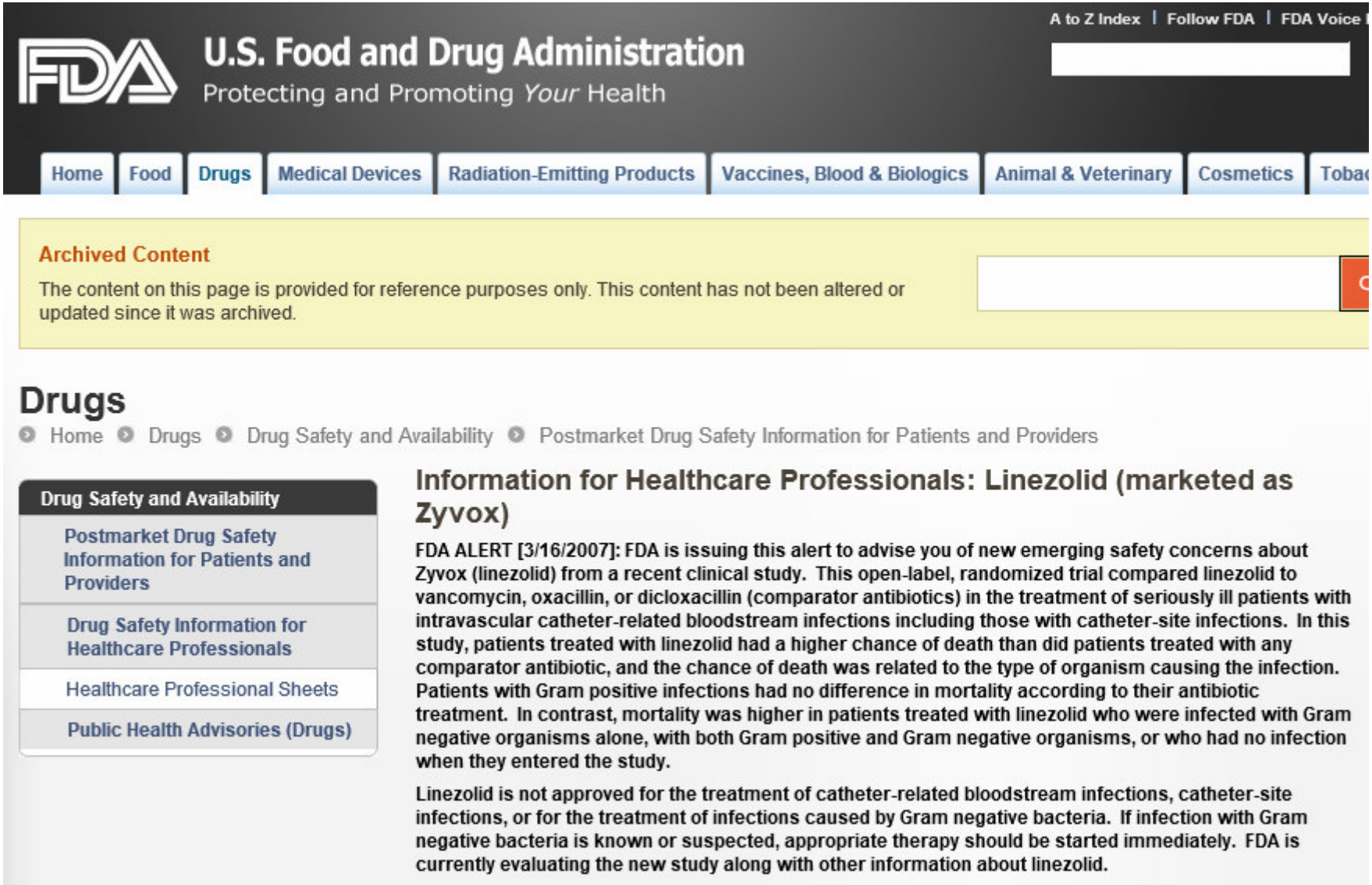
Criticisms

- Pre-specified subset analysis rather than a prospective, blinded study.
- Patients with renal failure and those with prosthetic devices or long-term indwelling venous catheters that could not be removed were to be excluded.
- Timing of surgical intervention that might have impacted outcomes was not standardized.
- The number of patients with left-sided endocarditis due to MRSA was small, and there were no treatment successes in this group.



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Drug Safety and Availability

- Postmarket Drug Safety Information for Patients and Providers
- Drug Safety Information for Healthcare Professionals
- Healthcare Professional Sheets
- Public Health Advisories (Drugs)

Information for Healthcare Professionals: Linezolid (marketed as Zyvox)

FDA ALERT [3/16/2007]: FDA is issuing this alert to advise you of new emerging safety concerns about Zyvox (linezolid) from a recent clinical study. This open-label, randomized trial compared linezolid to vancomycin, oxacillin, or dicloxacillin (comparator antibiotics) in the treatment of seriously ill patients with intravascular catheter-related bloodstream infections including those with catheter-site infections. In this study, patients treated with linezolid had a higher chance of death than did patients treated with any comparator antibiotic, and the chance of death was related to the type of organism causing the infection. Patients with Gram positive infections had no difference in mortality according to their antibiotic treatment. In contrast, mortality was higher in patients treated with linezolid who were infected with Gram negative organisms alone, with both Gram positive and Gram negative organisms, or who had no infection when they entered the study.

Linezolid is not approved for the treatment of catheter-related bloodstream infections, catheter-site infections, or for the treatment of infections caused by Gram negative bacteria. If infection with Gram negative bacteria is known or suspected, appropriate therapy should be started immediately. FDA is currently evaluating the new study along with other information about linezolid.

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CVC-related infections
Linezolid, phase 3

Table 3. Microbiologic outcome at test of cure 1–2 weeks after treatment.

Population	Linezolid group	Control group	95% CI	*P*
Modified intent-to-treat group	186/212 (87.7)	184/210 (87.6)	−6.2 to 6.4	
MME group				
Complicated SSSI (MME-1)	146/163 (89.6)	134/149 (89.9)	−7.1 to 6.4	.9161
Staphylococcus aureus	75/87 (86.2)	58/68 (85.3)	−10.2 to 12.0	
Methicillin-resistant *S. aureus*	42/48 (87.5)	34/39 (87.2)	−13.7 to 14.4	
Bloodstream infection (ME-2)	82/95 (86.3)	67/74 (90.5)	−13.8 to 5.4	.3989
S. aureus	46/56 (82.1)	35/42 (83.3)	−16.3 to 13.9	
Methicillin-resistant *S. aureus*	21/26 (80.8)	18/21 (85.7)	−26.2 to 16.4	

NOTE. Data are no. (%) of successes or no. (%) of patients assessed, unless otherwise indicated. Percentages were based on number of patients assessed and excluded patients with indeterminate or missing outcomes. ME, microbiologically evaluable; MME, modified microbiologically evaluable; SSSI, skin and skin-structure infection.

Wilcox, CID 2009

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IDSA Guidelines 2011
HAP

Antibiotic	Adult	Evidence Grade
Vancomycin	15-20 mg/kg IV Q8-12	AII
Linezolid	600 mg PO/ IV BID	AII
Clindamycin	600 mg PO/IV TID	BIII

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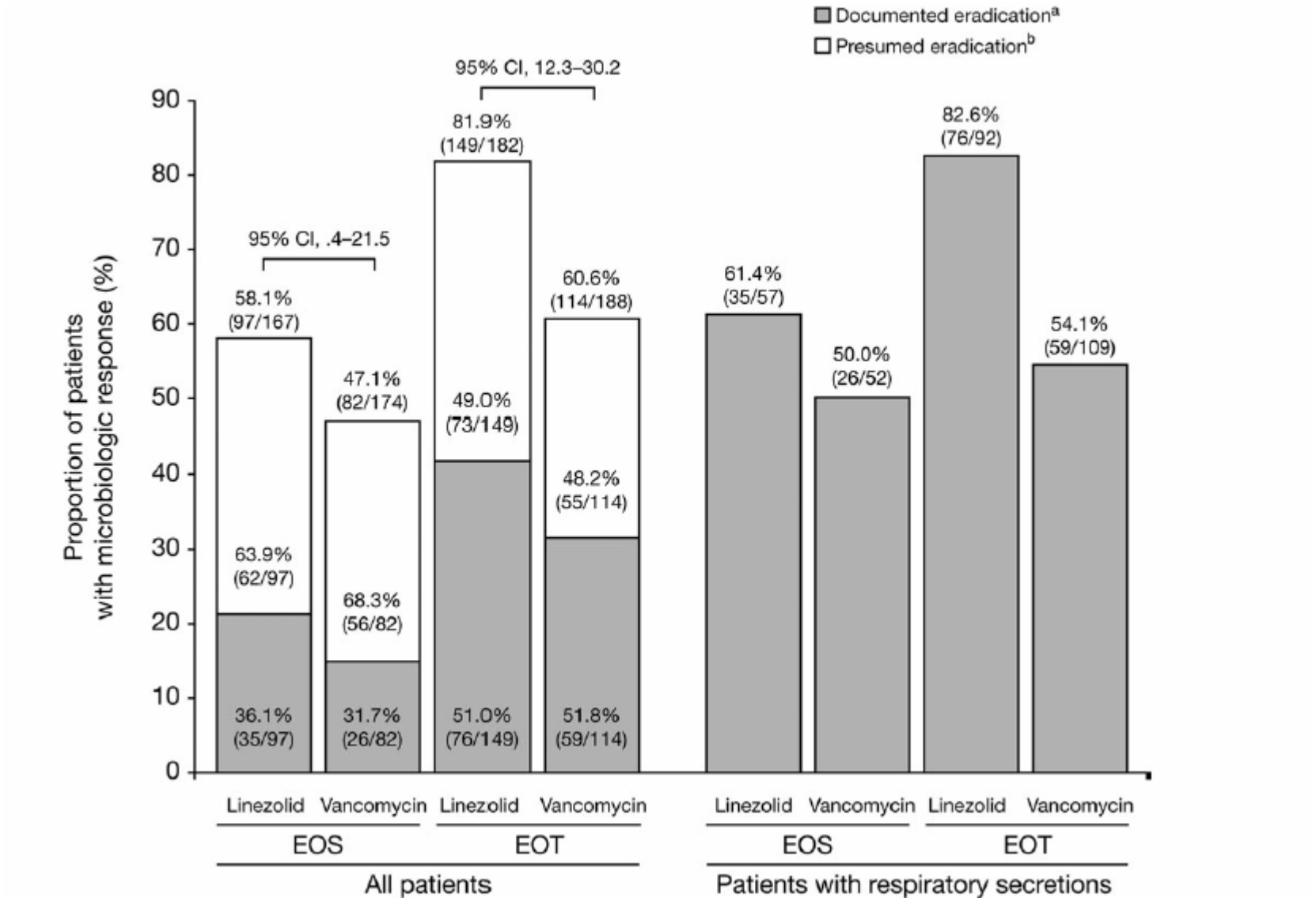

Wunderink, CID 2012

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Criticisms

- Unequal distribution of medical comorbidities
- Clinical cure was a subjective outcome ("resolution of clinical signs and symptoms of pneumonia compared with baseline, improvement or lack of progression in chest imaging, and no requirement for additional antibacterial treatment")
- Majority of HAP are not diagnosed
- Lack of loading dose for vancomycin

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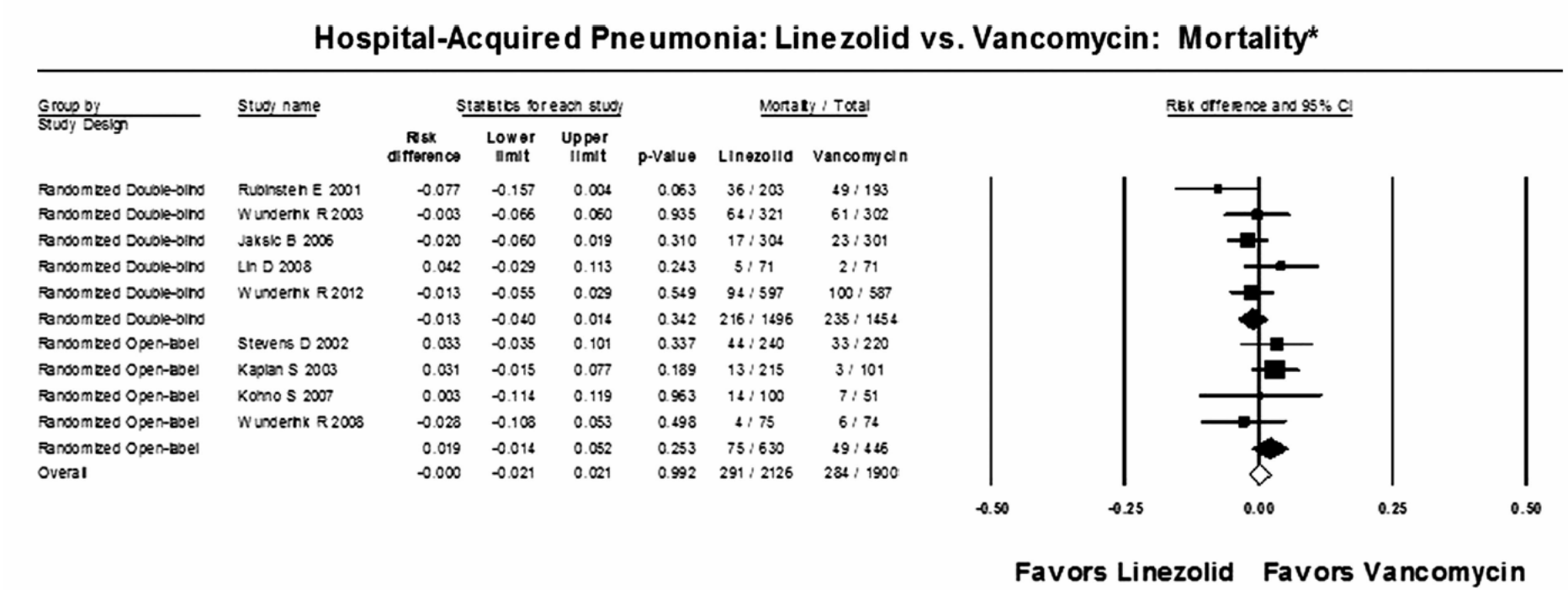
HAP
Linezolid versus Vancomycin



Kalil, BMJ 2013

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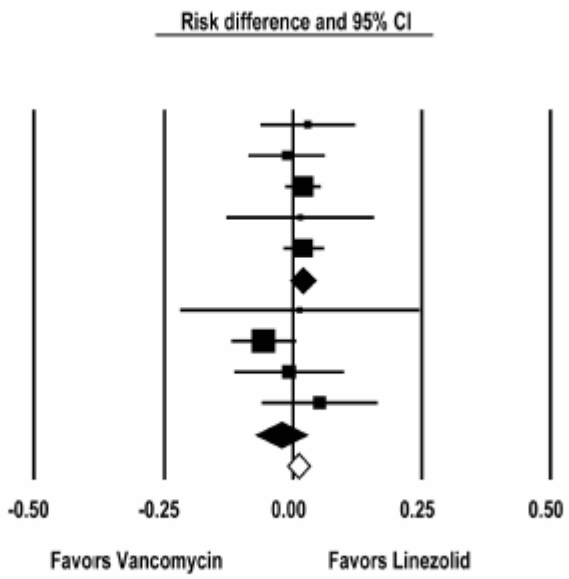
HAP
Linezolid versus Vancomycin

(a) **Hospital-Acquired Pneumonia: Linezolid vs. Vancomycin: Clinical Response***

Group by Study Design	Study name	Risk difference	Lower limit	Upper limit	p-Value	Mortality / Total Linezolid	Mortality / Total Vancomycin
Randomized Double-blind	Rubinstein E 2001	0.029	-0.064	0.121	0.548	71 / 203	62 / 193
Randomized Double-blind	Wunderink R 2003	-0.012	-0.088	0.063	0.747	114 / 321	111 / 302
Randomized Double-blind	Jaksic B 2006	0.019	-0.016	0.055	0.288	19 / 304	13 / 301
Randomized Double-blind	Lin D 2008	0.014	-0.130	0.158	0.848	19 / 71	18 / 71
Randomized Double-blind	Wunderink R 2012	0.021	-0.019	0.062	0.306	95 / 597	81 / 587
Randomized Double-blind		0.017	-0.007	0.041	0.159	318 / 1496	285 / 1454
Randomized Open-label	Stevens D 2002	0.013	-0.221	0.247	0.914	20 / 39	16 / 32
Randomized Open-label	Kaplan S 2003	-0.057	-0.121	0.007	0.081	9 / 215	10 / 101
Randomized Open-label	Kohno S 2007	-0.008	-0.115	0.100	0.889	11 / 100	6 / 51
Randomized Open-label	Wunderink R 2008	0.052	-0.062	0.165	0.372	13 / 75	9 / 74
Randomized Open-label		-0.024	-0.073	0.024	0.327	53 / 429	41 / 258
Overall		0.009	-0.012	0.031	0.409	371 / 1925	326 / 1712



*Intention-to-Treat Population. Z=0.826; P=0.409; Heterogeneity: Q=5.878; P=0.661; I2=0%

Kalil, BMJ 2013

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HAP
Linezolid versus Vancomycin

(b) **Hospital-Acquired Pneumonia: Linezolid vs. Vancomycin: MRSA* Eradication**

Group by Study Design

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renal failure, thrombocytopenia and drug discontinuation due to adverse events. Our sample size provided 99.9% statistical power to detect differences between drugs regarding clinical response and mortality.

Conclusions: Linezolid and vancomycin have similar efficacy and safety profiles. The high statistical power and the near-zero efficacy difference between both antibiotics demonstrates that no drug is superior for the treatment of hospital-acquired pneumonia.

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*Methicillin-Resistant Staphylococcus aureus Microbiological Evaluable/Per-Protocol Population. Z=1.199; P=0.230; Heterogeneity: Q=4.146; P=0.657; I2=0%

Kalil, BMJ 2013

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IDSA Guidelines 2011
SSI

Antibiotic	Adult	Evidence Grade
Vancomycin	15-20 mg/kg IV Q8-12	AI
Linezolid	600 mg PO/ IV BID	AI
Daptomycin	4 mg/kg IV QD	AI
Telavancin	10 mg/kg IV QD	AI
Clindamycin	600 mg PO/IV Q8	AIII
Doxicline Cotrimoxazole		

Tacconelli CID 2013

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Tygecicline

- Approved for SSI and abdominal infections
- Advantage of coverage of gram negative
- Clinical failures and development of resistance under therapy have been reported
- Superinfections with pathogen inherently resistant to tygecicline are a matter of great concern
- **Primary BSI, UTI and VAP present a challenge for the use of tigecycline**

Hirsch, JAC 2010; Anthony, CID 2008

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Tygecicline

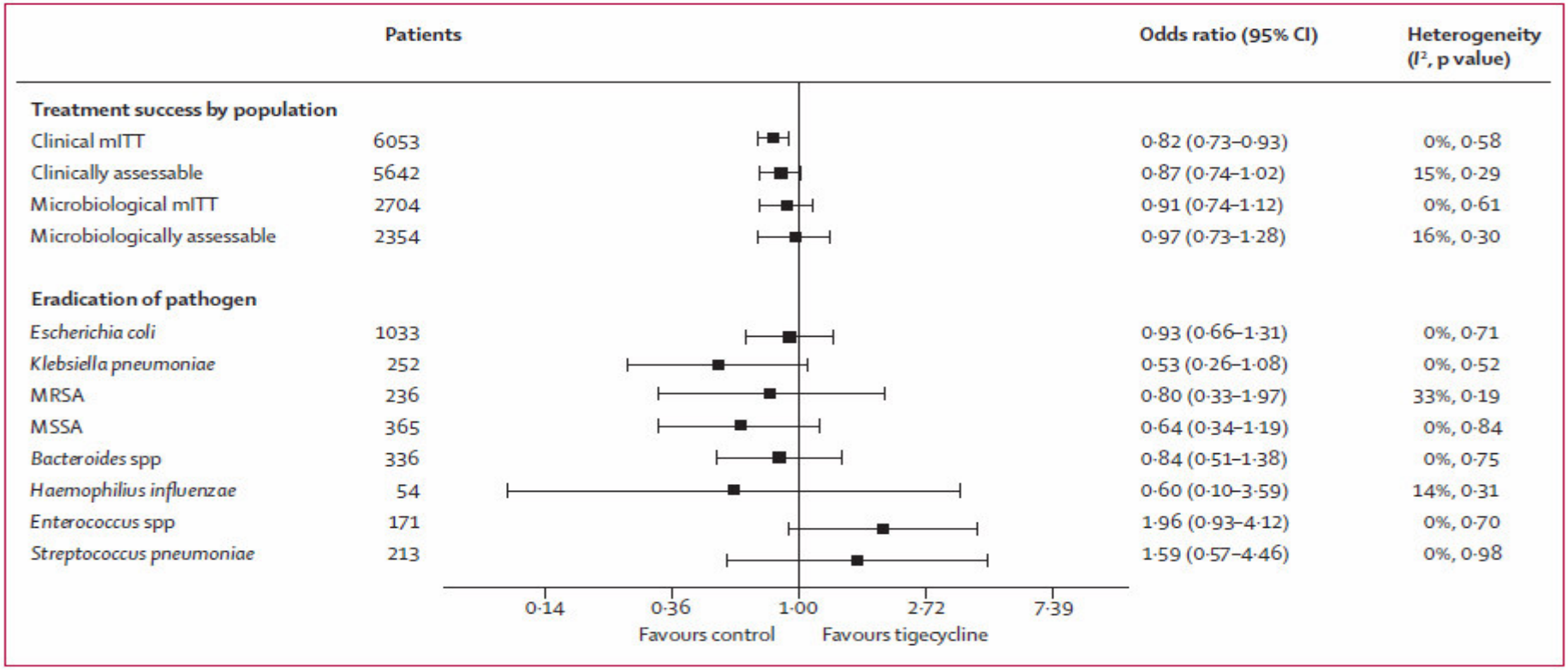

Figure 4: **Comparative effectiveness of tigecycline versus comparator antibiotics**
Vertical line indicates no difference between the two treatment groups. Pooled odds ratios were calculated from random-effects models with the Mantel-Haenszel method. mITT=modified intention to treat. MRSA=meticillin-resistant *Staphylococcus aureus*. MSSA=meticillin-sensitive *Staphylococcus aureus*.

All cause mortality was higher in the tygecicline group than in the comparator, but the difference was not statistically significant (1.28, 0.97 – 1,69)

Tasina, LID 2013

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Telavancin vs vancomycin

Table 7. Microbiologic eradication at test of cure, by gram-positive pathogens: pooled analysis (studies 0017 and 0018).

Microbiologic eradication	Proportion of patients (%)	
	Telavancin treatment arm	Vancomycin treatment arm
Total	473/527 (89.8)	468/536 (87.3)
Staphylococcus aureus		
MRSA	250/278 (89.9)	257/301 (85.4)
MSSA	161/181 (89.0)	157/176 (89.2)
Enterococcus faecalis	25/27 (92.6)	31/34 (91.2)
Streptococcus species		
Streptococcus pyogenes	21/23 (91.3)	23/25 (92.0)
Streptococcus agalactiae	17/19 (89.5)	18/19 (94.7)
Streptococcus anginosus	11/11 (100.0)	8/8 (100.0)

NOTE. MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*.

Table 5. Patients cured at test of cure in studies 0017 and 0018: pooled analysis.

Population	Proportion of patients (%)		Difference in cure rates (95% CI for the difference)[a]
	Telavancin treatment arm	Vancomycin treatment arm	
Study 0017			
Clinically evaluable	304/346 (87.9)	302/349 (86.5)	1.3 (−3.6 to 6.3)
All treated	323/426 (75.8)	321/429 (74.8)	1.0 (−4.8 to 6.8)
Study 0018			
Clinically evaluable	354/399 (88.7)	346/395 (87.6)	1.1 (−3.4 to 5.6)
All treated	387/502 (77.1)	376/510 (73.7)	3.4 (−1.9 to 8.7)
Pooled analysis (studies 0017 and 0018)			
Clinically evaluable	658/745 (88.3)	648/744 (87.1)	1.2 (−2.1 to 4.6)
All treated	710/928 (76.5)	697/939 (74.2)	2.3 (−1.6 to 6.2)

NOTE. All percentages were calculated relative to the number of nonmissing observations.

[a] For the difference between the telavancin treatment arm and the vancomycin treatment arm for the proportion of patients who were cured.

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The high affinity of ceftaroline for penicillin-binding proteins is responsible for the potent activity observed against clinically relevant pathogens. With respect to the treatment of CABP, the activity of ceftaroline against pathogens such as S. pneumoniae, S. aureus, Haemophilus influenzae and Moraxella catarrhalis demonstrates coverage across a broad range of pathogens typically encountered in clinical practice. Ceftaroline is also very active against common pathogens seen in ABSSSIs such as S. aureus (methicillin-susceptible S. aureus and methicillin-resistant S. aureus) and Streptococcus pyogenes.

Abstract

Data regarding ceftaroline use for meticillin-resistant Staphylococcus aureus bacteraemia (MRSAB) are lacking. Here we review the outcomes of 31 patients with MRSAB treated with ceftaroline, including 9 patients with endocarditis. Clinical success was observed in 23 patients (74.2%). Adverse events associated with prolonged therapy were rare and included eosinophilic pneumonia, rash and diarrhoea. We conclude that ceftaroline can be used for MRSAB.

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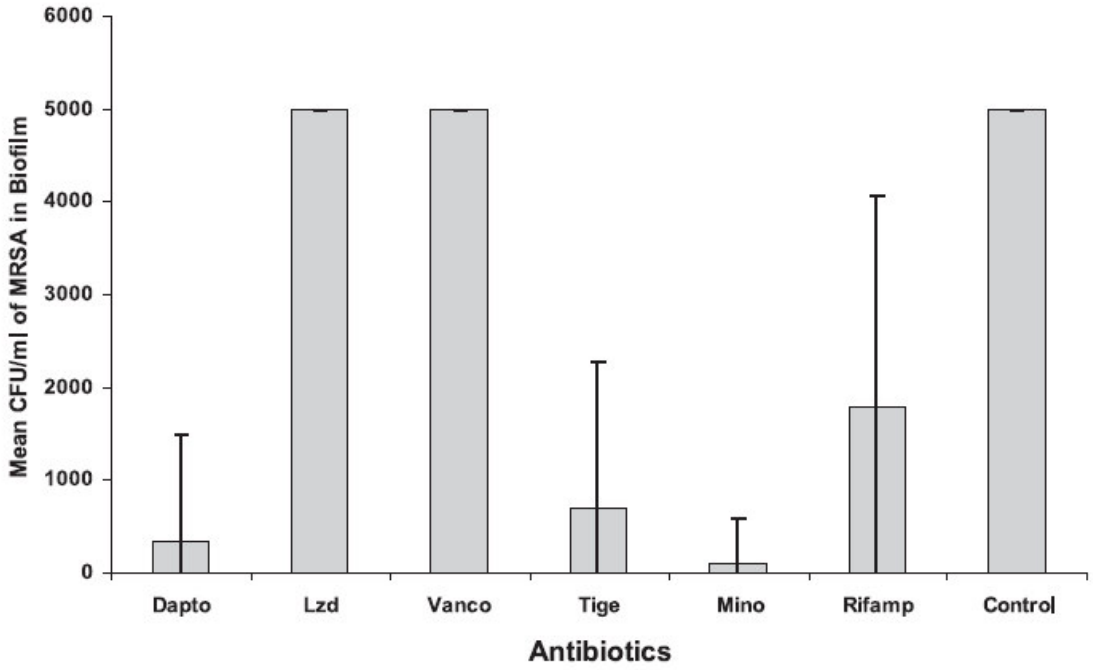
Daptomycin, Linezolid, and Tigecycline against Catheter-Related MRSA Bacteremic Isolates Embedded in Biofilm



Raad , AAC, 2007

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Addition of Rifampin to Vancomycin for Methicillin-Resistant *Staphylococcus aureus* Infections: What Is the Evidence?

Simon Tremblay, Tim TY Lau, Mary HH Ensom

CONCLUSIONS: Limited evidence exists to support the adjunctive use of rifampin to treat MRSA infections. The combination may increase drug interactions, adverse effects, and rifampin resistance. Further studies are needed to define the role of rifampin adjunct therapy.

Ann Pharmacother 2013;47:1045-54.

Published Online, 28 May 2013, *theannals.com*, doi: 10.1345/aph.1R726

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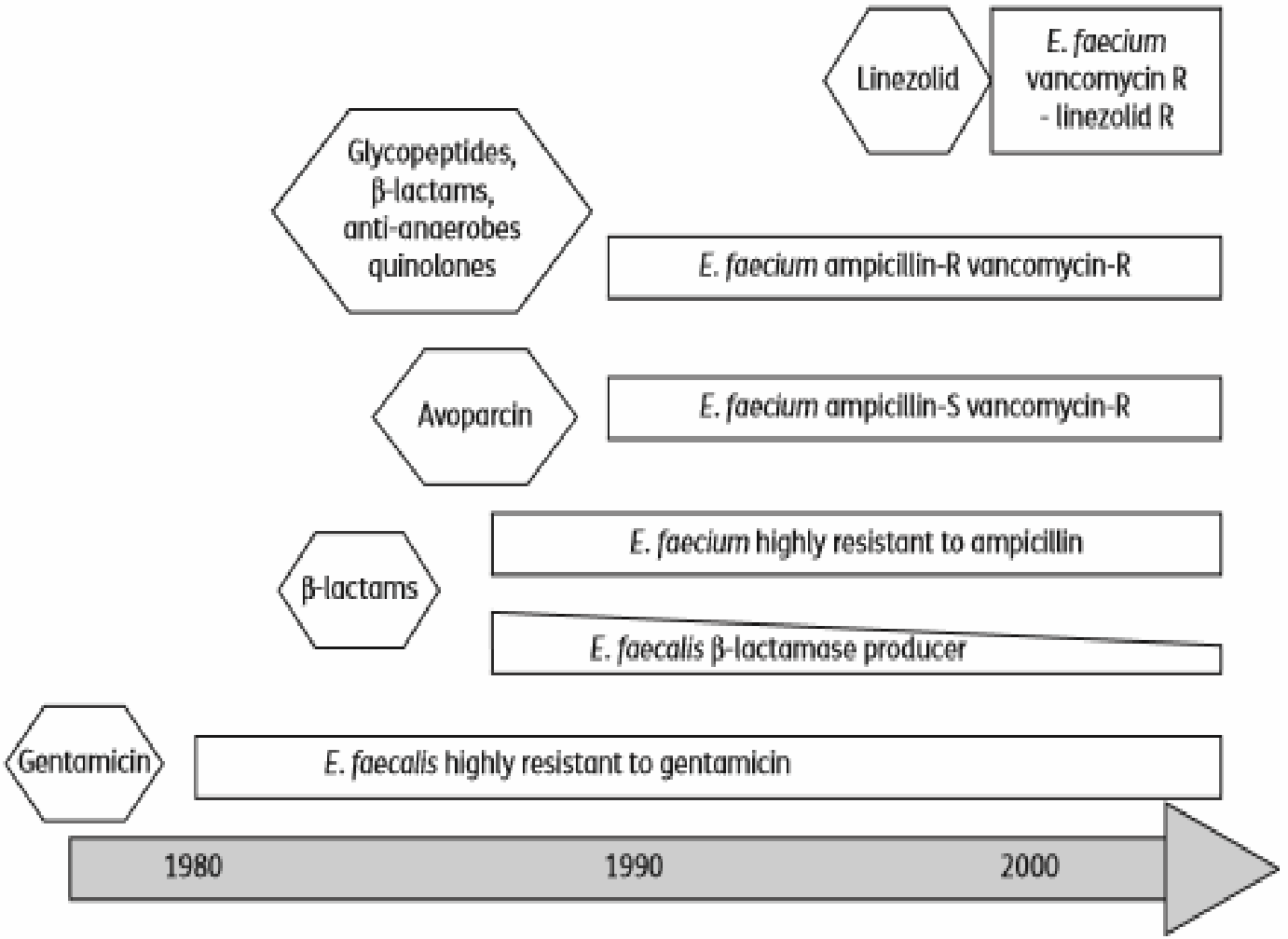

Figure 3. The walk of enterococci towards multiple antibiotic resistance. Selector antibiotics are shown in the lozenges.

Cattair, JAC 2013

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New drugs for MRSA

Name	Mode of Action	Conditions	Route(s)	Status
		exposed to inhalation anthrax and in May 2007)		
EDP-420	Inhibition of bacterial protein synthesis by targeting 50S ribosomal subunit	CA-pneumonia	Oral	Phase II
NXL 103 (XRP 2868)	Inhibition of bacterial protein synthesis by targeting ribosomal subunits (synergistic effect)	Acute bacterial skin and skin structure infections, CA- pneumonia	Oral	Phase II
Delafloxacin	Inhibition of bacterial Gyrase	Acute bacterial skin and skin structure infections, Complicated skin and skin structure infections	Oral, IV	Phase II
LBM-415	Inhibition of bacterial protein synthesis by inhibiting peptide deformylase	CA-respiratory tract infections	Oral	Phase I (development terminated)
GSK1322322	Inhibition of bacterial protein synthesis by inhibiting peptide deformylase	Bacterial skin and skin structure infections and hospitalized CA- pneumonia	Oral	Phase II
Locilex™ (MSI-78 topical cream)	Formation of an amphipathic α-helical peptide on membranes that induces pore or changes membrane permeability	Diabetic foot infections caused by drug-sensitive and –resistant bacteria including MRSA, VRE, extended-spectrum β-lactamase producing bacteria	Topical	Phase III
OligoG CF-5/20	Immunomodulating activity	Lung infections in cystic fibrosis	Inhalation	Phase I
F598	Inhibition of virulence by targeting the PNAG carbohydrate of the bacterial capsule	*S. aureus* and other clinically relevant bacteria	IV	Phase I

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Long-Term Risk for Readmission in MRSA+

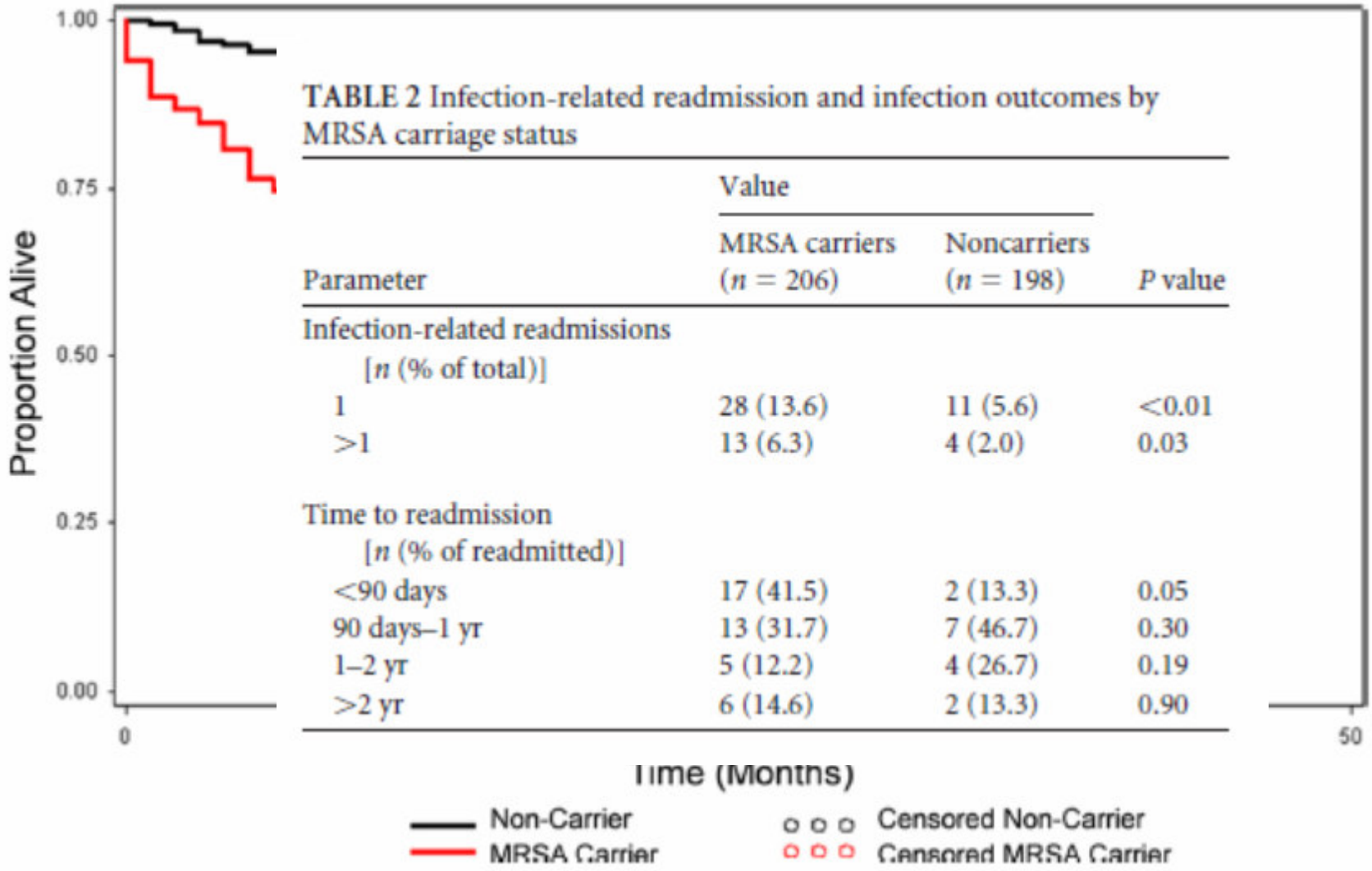

TABLE 2 Infection-related readmission and infection outcomes by MRSA carriage status

Parameter	Value: MRSA carriers (n = 206)	Value: Noncarriers (n = 198)	P value
Infection-related readmissions [n (% of total)]			
1	28 (13.6)	11 (5.6)	<0.01
>1	13 (6.3)	4 (2.0)	0.03
Time to readmission [n (% of readmitted)]			
<90 days	17 (41.5)	2 (13.3)	0.05
90 days–1 yr	13 (31.7)	7 (46.7)	0.30
1–2 yr	5 (12.2)	4 (26.7)	0.19
>2 yr	6 (14.6)	2 (13.3)	0.90

FIG 1 Kaplan-Meier survival plot for MRSA carriers and noncarriers.

Quezada AAC 2012

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Studies by intervention	Pooled relative risk (95% CI)					
	All studies	Cardiac studies	Total joint arthroplasty or orthopedic studies	Peer reviewed publications*	Randomized controlled trials	Observational studies
Decolonization studies:						
Gram positive SSIs	0.41 (0.30 to 0.55)†	0.46 (0.32 to 0.67)†	0.32 (0.22 to 0.47)	0.41 (0.30 to 0.55)†	0.63 (0.36 to 1.13)†	0.35 (0.27 to 0.46)
Staphylococcus aureus SSIs	0.39 (0.31 to 0.50)	0.45 (0.34 to 0.58)	0.32 (0.21 to 0.47)	0.39 (0.31 to 0.50)	0.46 (0.29 to 0.73)	0.37 (0.28 to 0.49)
MRSA SSIs	0.30 (0.15 to 0.62)†	0.69 (0.36 to 1.31)	0.16 (0.09 to 0.28)	0.30 (0.15 to 0.62)†	NA†	0.28 (0.12 to 0.62)
MSSA SSIs	0.50 (0.37 to 0.69)	0.46 (0.29 to 0.72)†	0.56 (0.31 to 1.01)	0.50 (0.37 to 0.69)	0.61 (0.30 to 1.25)†	0.43 (0.29 to 0.62)†
Glycopeptide prophylaxis studies:						
Gram positive SSIs	0.70 (0.47 to 1.04)†	0.76 (0.49 to 1.18)†	0.69 (0.37 to 1.30)	0.62 (0.39 to 0.98)†	1.13 (0.90 to 1.42)	0.35 (0.12 to 1.03)†
S aureus SSIs	0.53 (0.24 to 1.16)†	0.52 (0.17 to 1.56)†	0.92 (0.59 to 1.44)	0.41 (0.20 to 0.84)	0.73 (0.33 to 1.63)	0.41 (0.10 to 1.64)†
MRSA SSIs	0.40 (0.20 to 0.80)	0.39 (0.15 to 1.03)	0.46 (0.13 to 1.63)†	0.32 (0.14 to 0.73)	0.65 (0.23 to 1.82)	0.22 (0.06 to 0.81)†
MSSA SSIs	1.47 (0.91 to 2.38)	1.32 (0.82 to 2.12)	1.18 (0.65 to 2.13)	0.81 (0.38 to 1.73)	1.01 (0.23 to 4.54)	1.48 (0.84 to 2.60)
Bundle studies:						
Gram positive SSIs	0.41 (0.30 to 0.56)	NA‡	0.44 (0.31 to 0.65)	0.36 (0.24 to 0.53)	NA§	0.41 (0.30 to 0.56)
S aureus SSIs	0.29 (0.19 to 0.42)	NA‡	0.33 (0.21 to 0.52)	0.27 (0.15 to 0.47)	NA§	0.29 (0.19 to 0.42)
MRSA SSIs	0.22 (0.12 to 0.38)	NA‡	0.27 (0.14 to 0.53)	0.19 (0.10 to 0.38)	NA§	0.22 (0.12 to 0.38)
MSSA SSIs	0.45 (0.26 to 0.78)	NA‡	0.42 (0.23 to 0.77)	0.52 (0.27 to 1.01)	NA§	0.45 (0.26 to 0.78)

Shweizer, BMJ 2013

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What is already known on this topic

Surgical site infections (SSIs) are potentially preventable adverse events of cardiac and orthopedic operations

SSIs significantly increase hospital length of stay, readmission rates, healthcare costs, and mortality rates

Clinicians and researchers have debated whether nasal decolonization or glycopeptide antibiotic prophylaxis reduce SSIs caused by Gram positive bacteria

What this study adds

Among patients undergoing cardiac or orthopedic surgery:
Nasal decolonization with mupirocin ointment was protective against Gram positive SSIs

Preoperative prophylaxis with anti-methicillin (meticillin) resistant *Staphylococcus aureus* (MRSA) antibiotics when given to all patients was not protective against Gram positive SSIs

A bundle that included nasal decolonization and anti-MRSA prophylaxis for MRSA carriers was significantly protective against Gram positive SSIs

Decolonisation and glycopeptide prophylaxis and SA SSI

Shweizer, BMJ 2013

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Household transmission prevention

Table 2. Prevention Strategies for Patients with Recurrent MRSA Skin and Soft-Tissue Infections and for Their Household Members.*

Avoid sharing personal hygiene items (e.g., razors, brushes, and towels)
Apply 2% mupirocin ointment to the anterior nares with a sterile cotton applicator twice a day for 5 days
Apply 4% chlorhexidine gluconate solution with the hands or with a clean washcloth to all body parts, excluding the face, open wounds, and mucous membranes, followed by a thorough rinse with water daily for 5 days†

Singer, NEJM 2013 Mar

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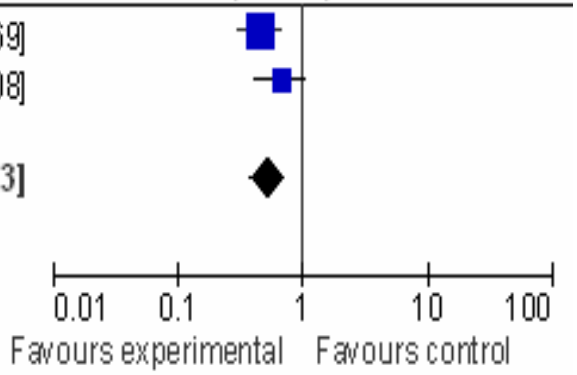
Hand hygiene measures and contact precautions to reduce VRE
A systematic review and meta-analysis

Study or Subgroup	Intervention group Events	Total	Control group Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bradley 1999	25	131	43	102	62.7%	0.45 [0.30, 0.69]
Lai 2006	19	79	29	80	37.3%	0.66 [0.41, 1.08]
Total (95% CI)		**210**		**182**	**100.0%**	**0.53 [0.39, 0.73]**
Total events	44		72			

Heterogeneity: Chi² = 1.36, df = 1 (P = 0.24); I² = 26%

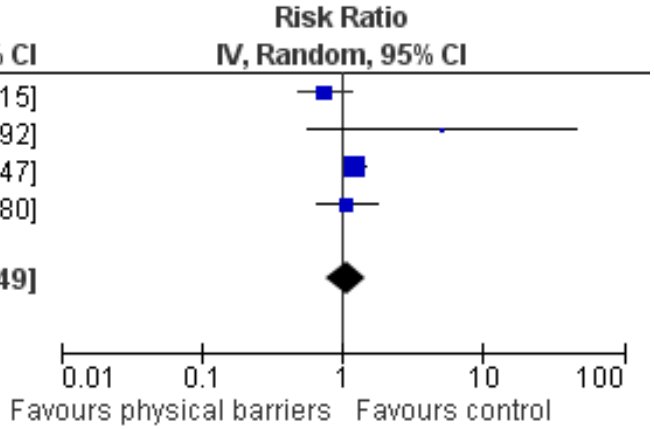
Test for overall effect: Z = 3.91 (P < 0.0001)



Study or Subgroup	Physical barriers Events	Total	Control group Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Bearman 2007	35	257	35	192	28.1%	0.75 [0.49, 1.15]
Bearman 2010	4	192	1	243	2.2%	5.06 [0.57, 44.92]
Huskins 2011	316	5434	175	3705	46.0%	1.23 [1.03, 1.47]
Slaughter 1996	24	93	21	88	23.7%	1.08 [0.65, 1.80]
Total (95% CI)		**5976**		**4228**	**100.0%**	**1.07 [0.77, 1.49]**
Total events	379		232			

Heterogeneity: Tau² = 0.05; Chi² = 6.25, df = 3 (P = 0.10); I² = 52%

Test for overall effect: Z = 0.40 (P = 0.69)



Tacconelli E, JAC 2014

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Conclusions

- Vancomycin is the preferred agent to treat MRSA.
- S.aureus with reduced susceptibility to vancomycin have been reported
- Linezolid and daptomycin has been demonstrated as effective although type of diseases, risk for potential development of resistance, toxicities, and costs must be taken into consideration before its use.
- Tigecycline, telavancin, and ceftaroline are well tolerated but lack the clinical data to support a superior place in treatment over vancomycin.
- Several new agents in various stages of development have also demonstrated MRSA activity.
- **Currently, vancomycin remains the gold-standard treatment option for MRSA infections.**

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