III Congresso TRIVENETO

Presidente Prof. Enzo Raise

ASPETTI DI FARMACOCINETICA E FARMACODINAMICA DEGLI ANTIBIOTICI NELLE INFEZIONI INVASIVE DA S. AUREUS

Prof. Ercole Concia

Università degli Studi di Verona

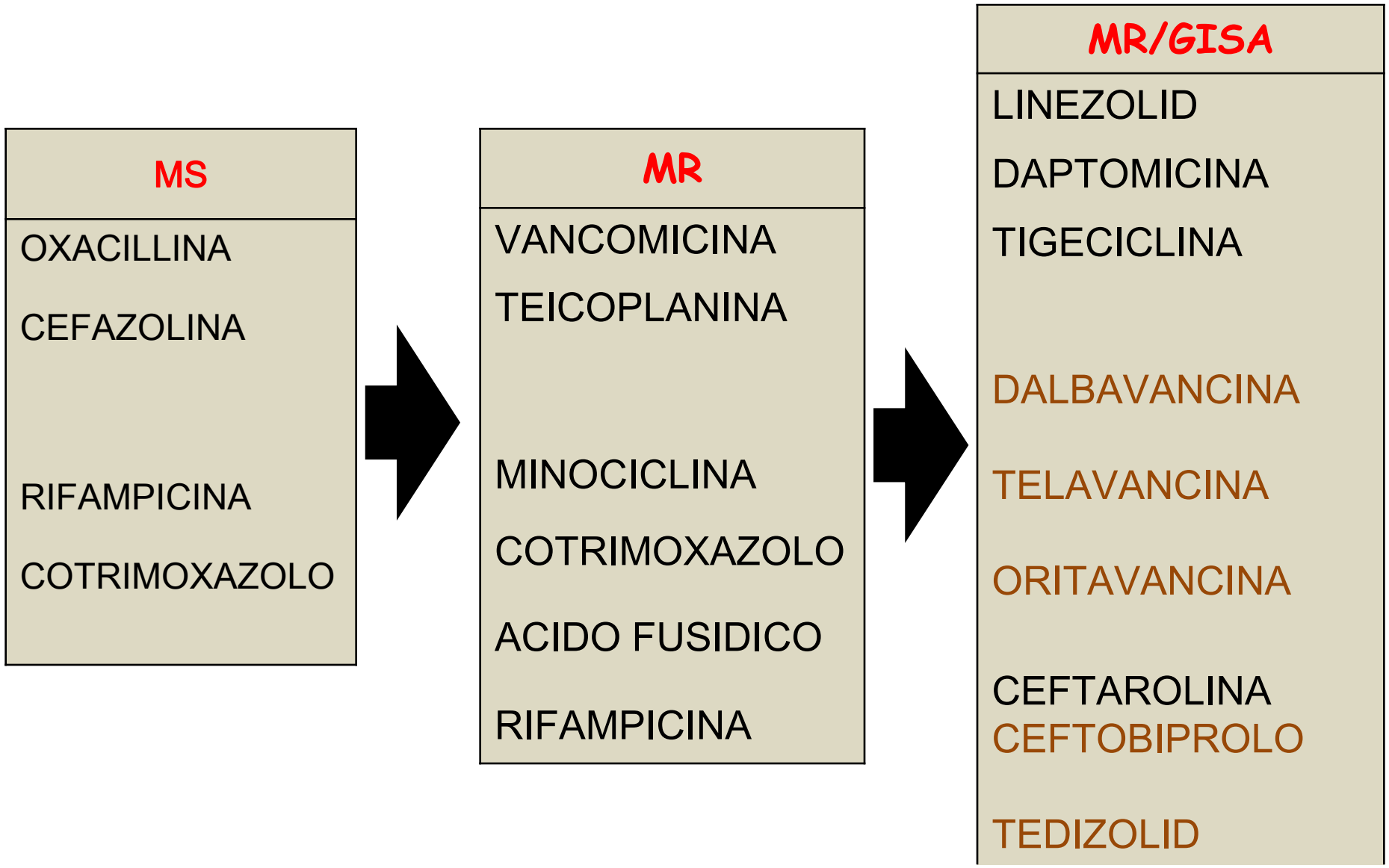
MRSA is a versatile, well equipped pathogen with the potential to evolve and adapt to its host as well as to the treatments developed to control its invasive damage.

US : MRSA causes approximately 95.000 invasive infections and 19.000 deaths per year.

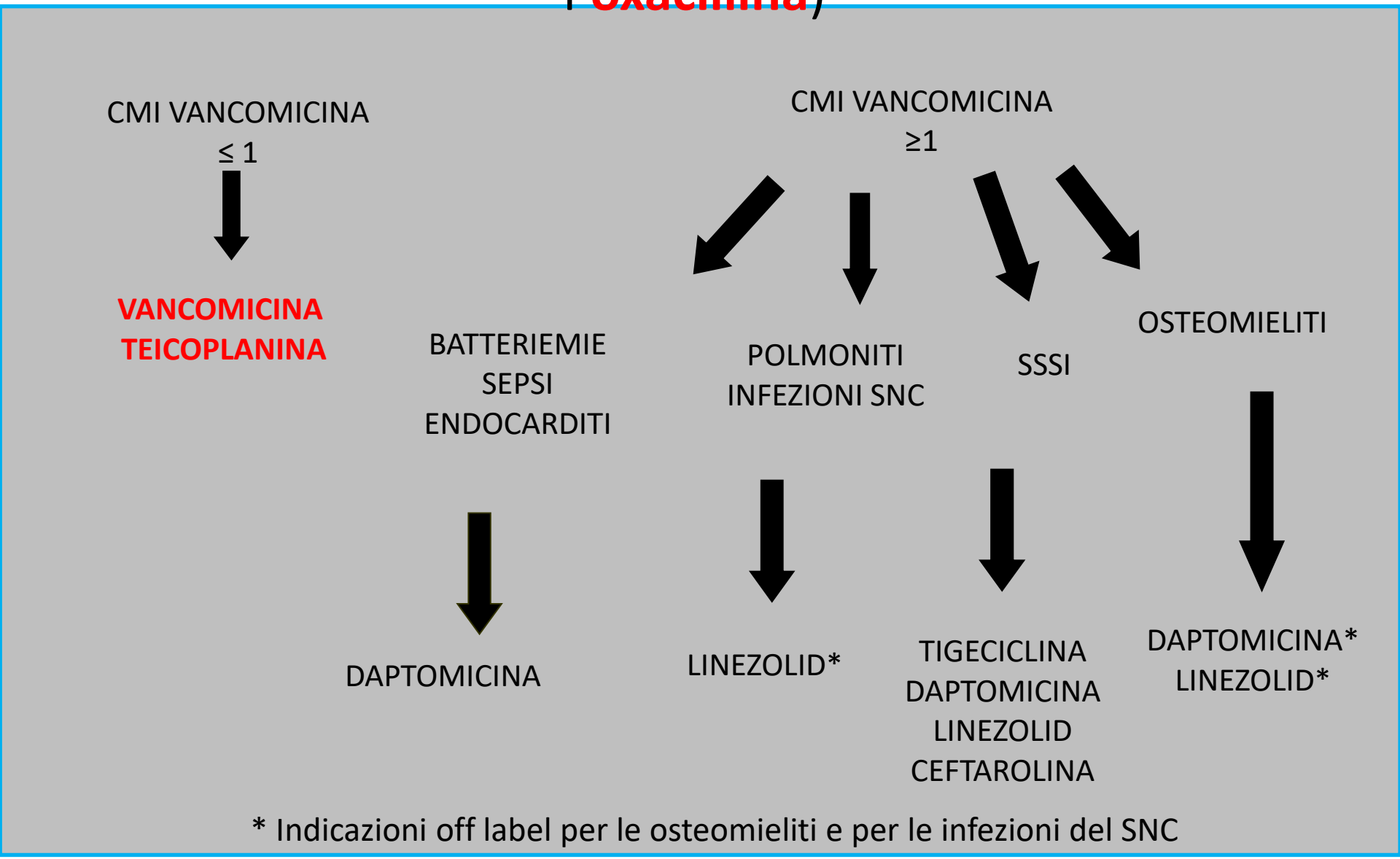
This mortality number is higher than the rates of deaths produced by HIV, viral hepatitis, Tbc and influenza combined.

M. Stryjewski CID 2014

ANTIBIOTICI AD ATTIVITA' ANTISTAFILOCOCCICA



TERAPIA DELLE INFEZIONI DA MRSA (nelle infezioni da MSSA la terapia d'elezione è l'**oxacillina**)



* Indicazioni off label per le osteomieliti e per le infezioni del SNC

TERAPIA DELLE INFEZIONI DA MSSA

VANCOMYCIN vs BETA-LACTAM

MSSA Bacteremia

Table 1. Summary of Published Studies Evaluating Empirical Therapy for Methicillin-Susceptible *Staphylococcus aureus* Bacteremia

Study	Year	Design	Study Size, No.	Outcome	Vancomycin vs β-Lactam	Result[a]
Vancomycin therapy vs β-lactam therapy[b]						
Chang et al [19]	2003	Prospective cohort	505	Bacteriologic failure[c]	19% vs 0%	OR, 6.5 (1.0–53)
Khatib et al [20]	2006	Prospective cohort	120	Overall mortality	27% vs 12%	HR, 2.3 (1.1–4.9)
Stryjewski et al [21][d]	2007	Prospective cohort	123	Treatment failure	31% vs 13%	OR, 3.5 (1.2–13)
Lodise et al [6][e]	2007	Retrospective cohort	84	Infection-related mortality	39% vs 11%	OR, 6.5 (1.4–29)
Kim et al [22]	2008	Retrospective case-control	27	Infection-related mortality	37% vs 11%	OR, 3.3 (1.2–9.5)
Schweizer et al [23]	2011	Retrospective	267	30-day in-hospital mortality	20% vs 3%	HR, 4.8 (2.1–11)[f]
Chan et al [24]	2012	Retrospective cohort	293 094	Hospitalization rate	12.5 vs 7.2[g]	HR, 1.6 (1.2–2.2)[f]
Vancomycin therapy vs vancomycin therapy de-escalated to β-lactam						
Lodise et al [6][e]	2007	Retrospective cohort	84	Infection-related mortality	33% vs 41%	NS
Schweizer et al [23]	2011	Retrospective cohort	267	30-day in-hospital mortality	20% vs 7%	HR, 3.2 (1–10)
Vancomycin therapy de-escalated to β-lactam therapy vs β-lactam therapy						
Khatib et al [25]	2006	Prospective cohort	168	Persistent bacteremia	56% vs 37%	$P = .03$
Lodise et al [6][e]	2007	Retrospective cohort	84	Infection-related mortality	41% vs 11%	Not reported

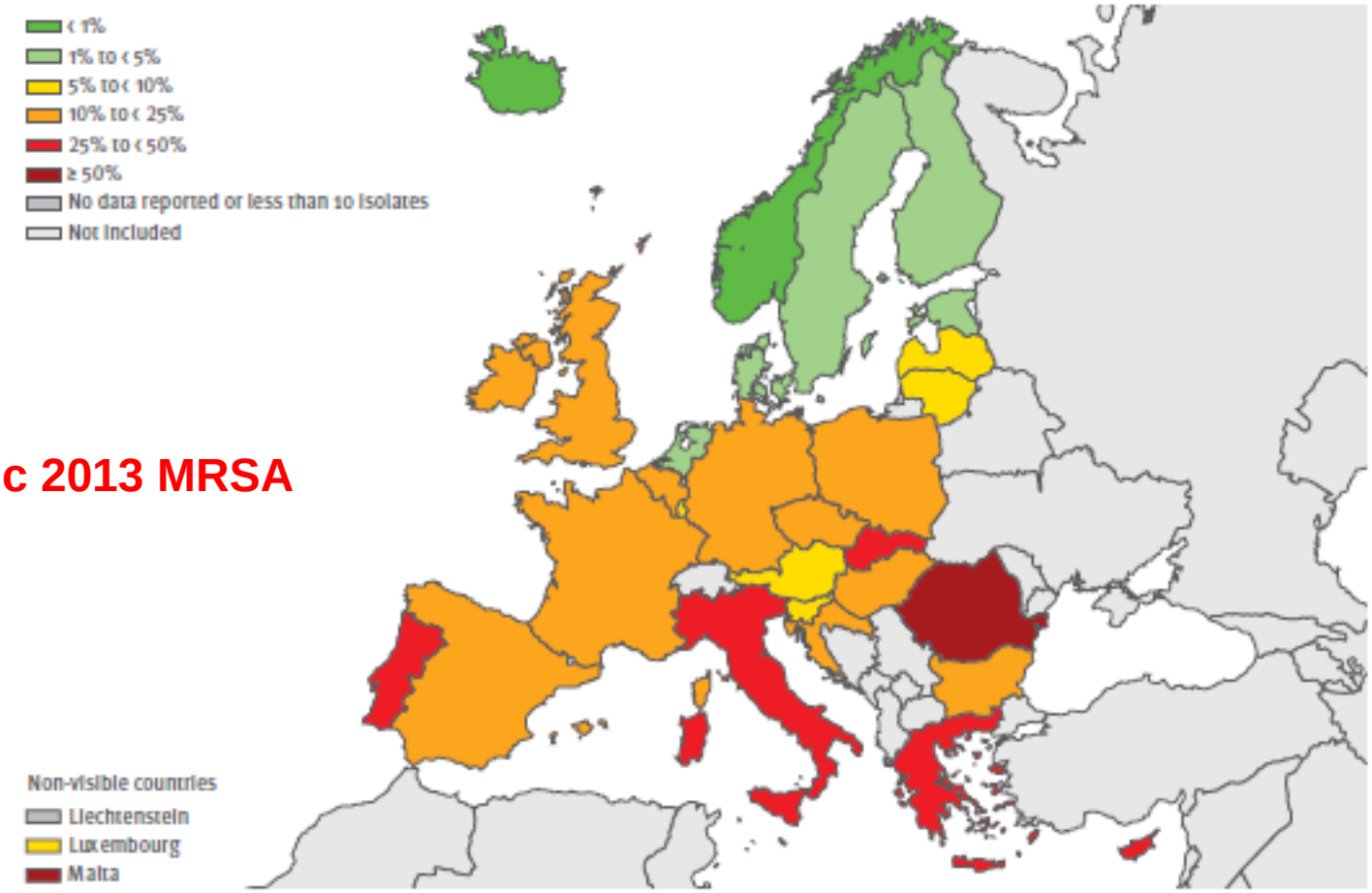
TERAPIA DELLE INFEZIONI DA MSSA

- OXACILLINA
- CEFAZOLINA
- CEFUROXIME
- CEFTRIAXONE

Stafilococco Aureo Meticillino Resistente

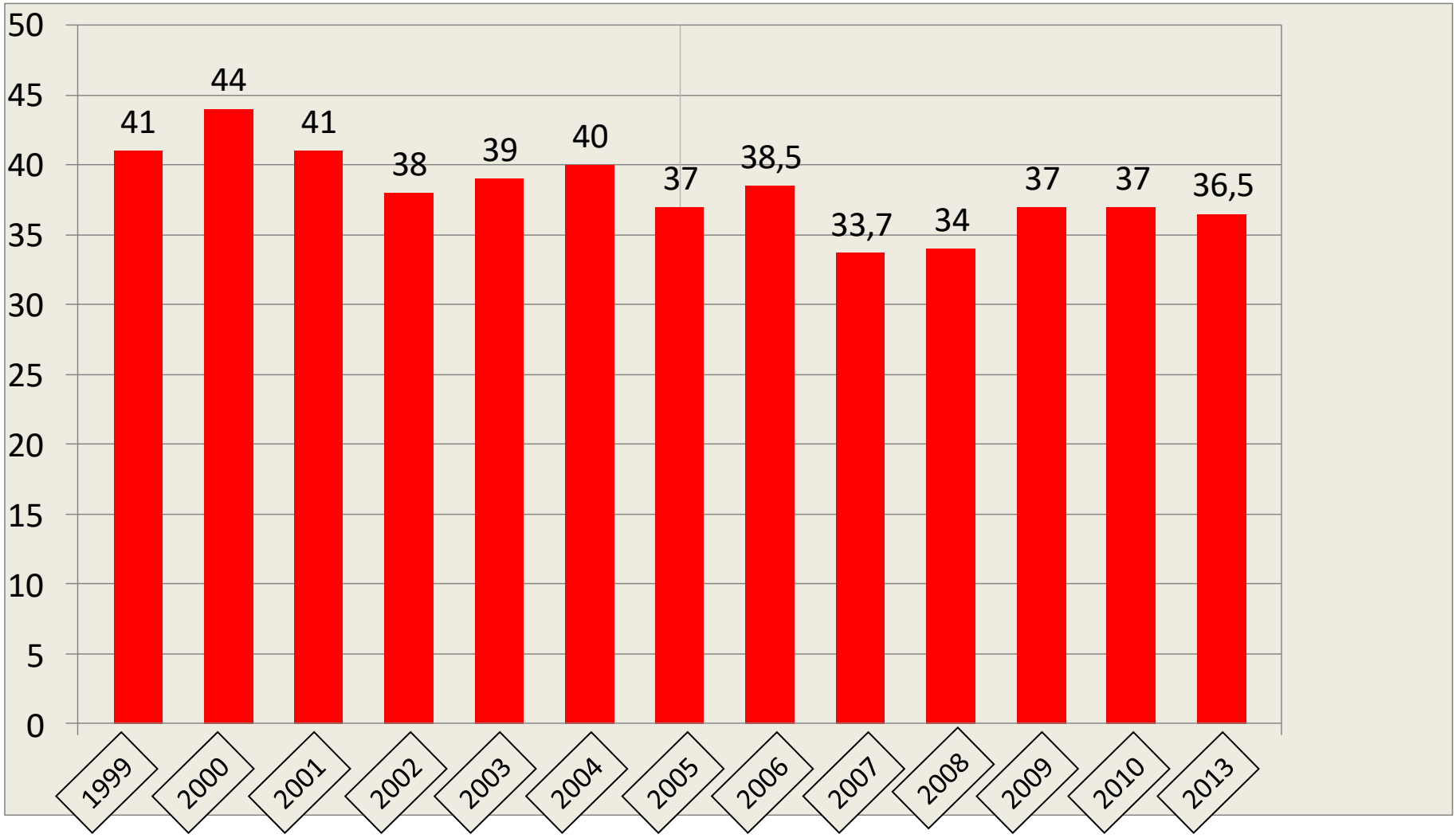
MRSA

Figure 3.23. *Staphylococcus aureus*. Percentage (%) of invasive isolates resistant to meticillin (MRSA), by country, EU/EEA countries, 2013

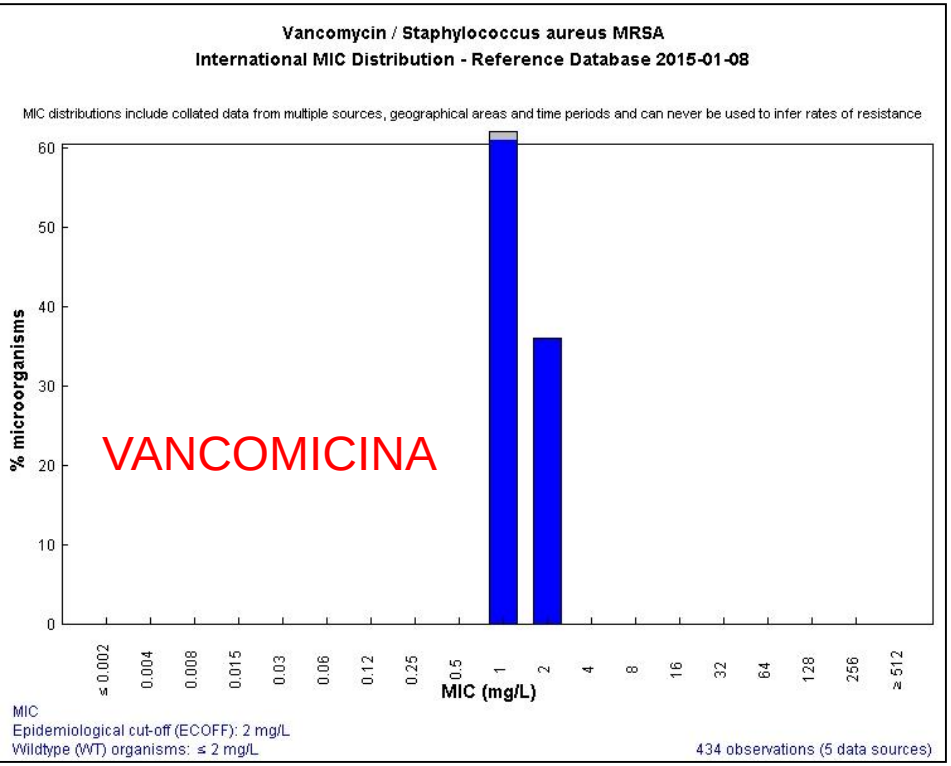


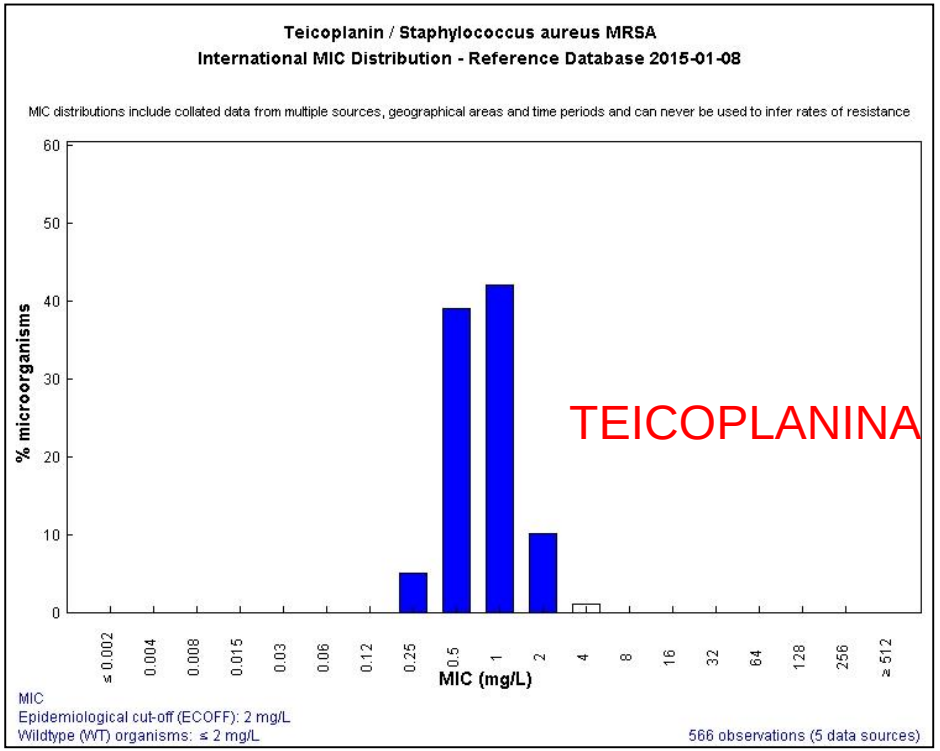
ecdc 2013 MRSA

Rate of invasive MRSA in Italy: 1999-2010



iCUS


Vancomycin / Staphylococcus aureus MRSA
International MIC Distribution - Reference Database 2015-01-08
MIC distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance
% microorganisms
60
50
40
30
20
10
0
VANCOMICINA
≤ 0.002
0.004
0.008
0.015
0.03
0.06
0.12
0.25
0.5
1
2
4
8
16
32
64
128
256
≥ 512
MIC (mg/L)
MIC
Epidemiological cut-off (ECOFF): 2 mg/L
Wildtype (WT) organisms: ≤ 2 mg/L
434 observations (5 data sources)


Teicoplanin / Staphylococcus aureus MRSA
International MIC Distribution - Reference Database 2015-01-08
MIC distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance
% microorganisms
60
50
40
30
20
10
0
TEICOPLANINA
≤ 0.002
0.004
0.008
0.015
0.03
0.06
0.12
0.25
0.5
1
2
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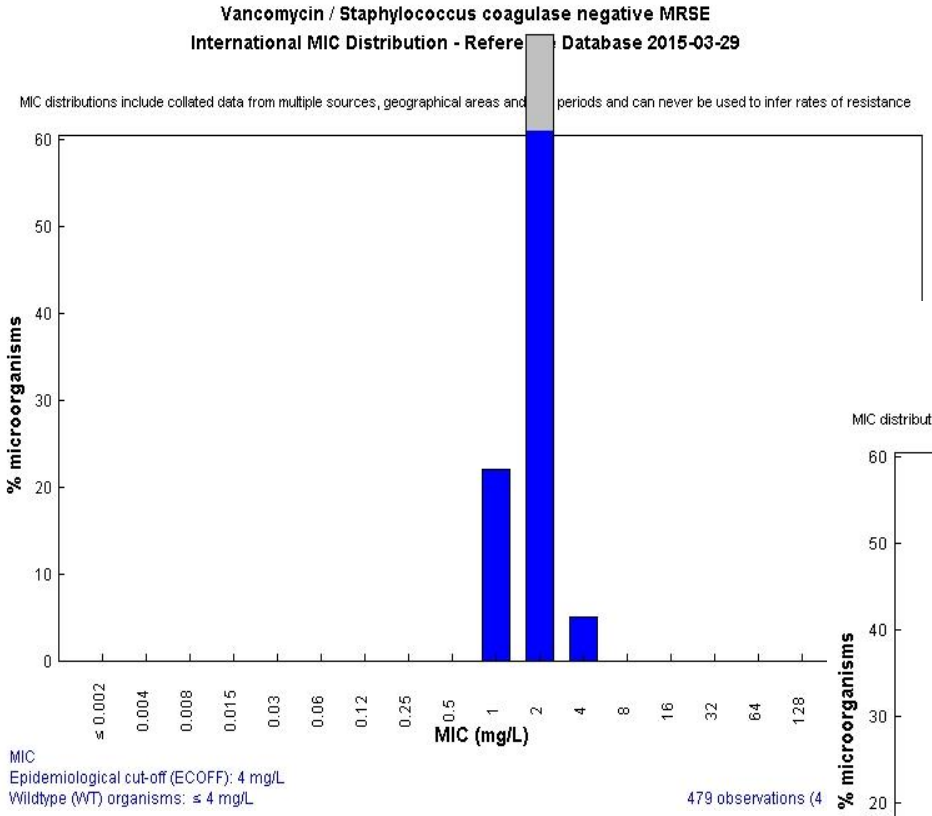
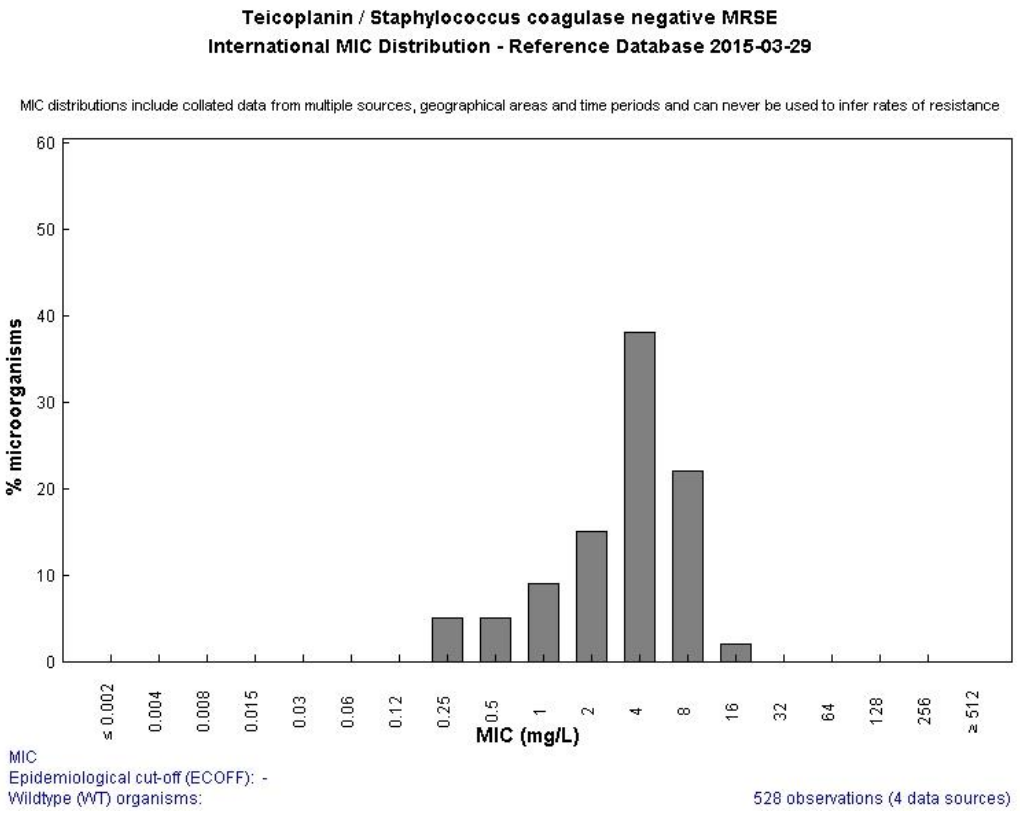
MIC (mg/L)
MIC
Epidemiological cut-off (ECOFF): 2 mg/L
Wildtype (WT) organisms: ≤ 2 mg/L
566 observations (5 data sources)

MRSA

MRSE



VANCOMICINA



TEICOPLANINA

Review

Clinical Management of *Staphylococcus aureus* Bacteremia
A Review

Thomas L. Holland, MD; Christopher Arnold, MD; Vance G. Fowler Jr, MD, MHS

IMPORTANCE Several management strategies may improve outcomes in patients with *Staphylococcus aureus* bacteremia.

OBJECTIVES To review evidence of management strategies for *S aureus* bacteremia to determine whether transesophageal echocardiography is necessary in all adult cases and what is the optimal antibiotic therapy for methicillin-resistant *S aureus* (MRSA) bacteremia.

EVIDENCE REVIEW A PubMed search from inception through May 2014 was performed to identify studies addressing the role of transesophageal echocardiography in *S aureus* bacteremia. A second search of PubMed, EMBASE, and the Cochrane Library from January 1990 through May 2014 was performed to find studies addressing antibiotic treatment for MRSA bacteremia. Studies reporting outcomes from antibiotic therapy for MRSA bacteremia were included. All searches, which were limited to English and focused on adults, were augmented by review of bibliographic references from included studies. The quality of evidence was assessed using the Grades of Recommendation, Assessment, Development and Evaluation system with consensus of independent evaluations by at least 2 of the authors.

FINDINGS In 9 studies with a total of 4050 patients, use of transesophageal echocardiography was associated with higher rates of a diagnosis of endocarditis (14%-28%) compared with transthoracic echocardiography (2%-15%). In 4 studies, clinical or transthoracic echocardiography findings did not predict subsequent transesophageal echocardiography findings of endocarditis. Five studies identified clinical or transthoracic echocardiography characteristics associated with low risk of endocarditis (negative predictive values from 93% to 100%). Characteristics associated with a low risk of endocarditis include absence of a permanent intracardiac device, sterile follow-up blood cultures within 4 days after the initial set, no hemodialysis dependence, nosocomial acquisition of *S aureus* bacteremia, absence of secondary foci of infection, and no clinical signs of infective endocarditis. Of 81 studies of antibiotic therapy for MRSA bacteremia, only 1 high-quality trial was identified. In that study of 246 patients with *S aureus* bacteremia, daptomycin was not inferior to vancomycin or an antistaphylococcal penicillin, each in combination with low-dose, short-course gentamicin (clinical success rate, 44.2% [53/120] vs 41.7% [48/115]; absolute difference, 2.4% [95% CI, −10.2% to 15.1%]).

CONCLUSIONS AND RELEVANCE All adult patients with *S aureus* bacteremia should undergo echocardiography. Characteristics of low-risk patients with *S aureus* bacteremia for whom transesophageal echocardiography can be safely avoided have been identified. Vancomycin and daptomycin are the first-line antibiotic choices for MRSA bacteremia. Well-designed studies to address the management of *S aureus* bacteremia are needed.

Supplemental content at jama.com

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JAMA 2014

Optimal Antibiotic Therapy for MRSA Bacteremia

Vancomycin and daptomycin are the only FDA-approved agents for the treatment of MRSA bacteremia in the United States. Approval for vancomycin is based largely on historical precedent. Recently, concerns have emerged regarding clinical isolates of MRSA exhibiting increasing minimum inhibitory concentrations to vancomycin.[11] These concerns were underscored by the observation that patients with MRSA bacteremia due to isolates with higher (but still susceptible) vancomycin minimum inhibitory concentration had higher all-cause mortality than those infected with lower vancomycin minimum inhibitory concentration isolates.[74] The cause of this association is unknown.[75]

Vancomycin Dosing

- IV vancomycin 15-20 mg/kg (actual body weight) every 8-12 hrs, not to exceed 2 g per dose **(BIII).**
- In seriously ill patients with suspected MRSA infection, a loading dose of 25-30 mg/kg (actual body weight) may be considered **(CIII).**
  - Given risk of red man syndrome and possible anaphylaxis associated with large doses, consider prolonging infusion time 2 h and pre-medication with antihistamine .
- Continuous infusion vancomycin is unlikely to substantially improve patient outcome, compared with intermittent dosing **(AII).**

Vancomycin Therapeutic Drug Monitoring

- Obtain serum troughs at steady state (b/f 4th or 5th dose) **(BII).**
- Monitoring of peak vancomycin concentrations is not recommended **(BII).**
- For serious infections (e.g. bacteremia, endocarditis, osteomyelitis, pneumonia, severe SSTI [nec fasc]), target vancomycin trough concentrations of 15-20 μg/mL **(BII).**
- For most patients with SSTI with normal renal function and not obese, traditional doses of 1 g Q12 are adequate and trough monitoring is not required **(BII).**

Moise-Broder Clin Pharmacok 2004;43:925-42; Jeffres Chest 2006; 130:947-55; Arbeit R CID 2004;38:1673-81; Weigelt AAC 2005; 49:2260-6; Stryjewski CID 2008;46:1683-93; Lipsky JAC 2005;55:240-5; Breedt AAC 2005; 49:4658-66

Persistent MRSA Bacteremia/ Vancomycin Treatment Failures: Therapeutic Considerations

- In general, recommend a change in therapy rather than addition of other agents (e.g. rifampin/ gentamicin) to vanco
- High-dose daptomycin (10 mg/kg/day), if susceptible, in combination with another agent **(BIII):**
  - Gentamicin 1 mg/kg IV Q8
  - Rifampin 600 mg PO/ IV QD or 300-450 mg PO/ IV twice daily
  - Linezolid 600 mg PO/ IV BID
  - TMP-SMX 5 mg/kg IV BID
  - β-lactam antibiotic
- Note: prior vanco exposure and elevated vanco MICs associated with ↑ dapto MICs (> 1 μg/mL).

LaPlante K AAC 2004;48:4665-72;Tsuji BT AAC 2005;49:2735-45;Credito AAC 2007;51:1504-7; Baltch A AC 2008;52:1829-33;Rose W AAC 2008;52:831-6;Falagas ME JAC 2006;58:273-80;Steed AAC 2010;54:5187-92;Yang AAC 2010; 54:3161-9

- Addition of gentamicin to vancomycin is not recommended for bacteremia or native infective endocarditis (A II)

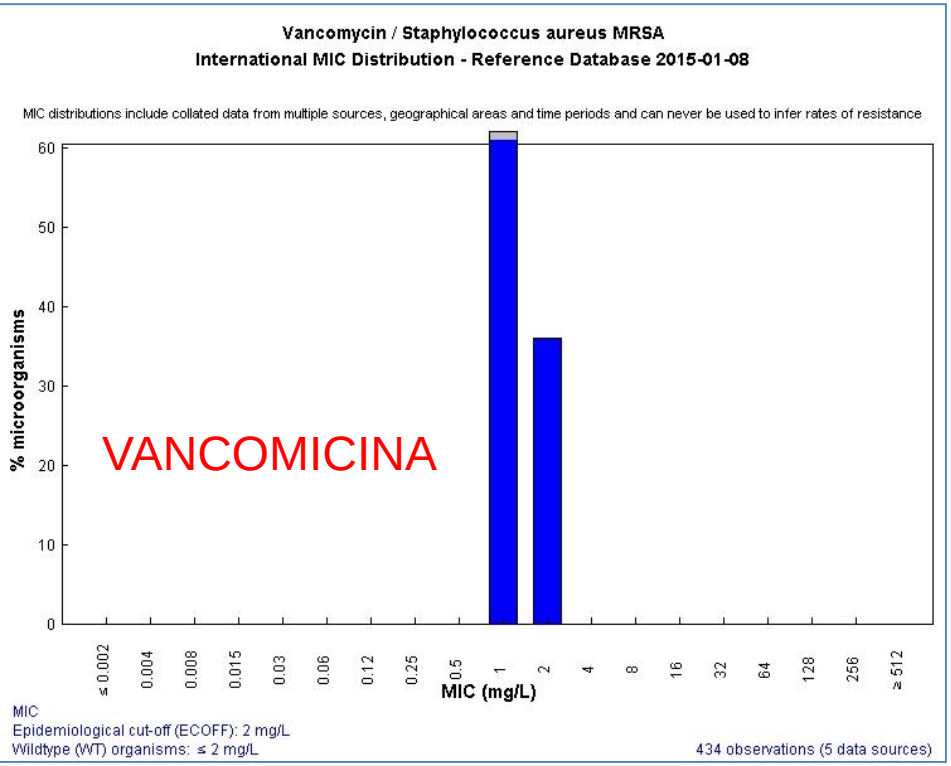
- Addition of rifampin to vancomycin is not reccommended for bacteremia or native infective endocarditis (A I)

- Additional blood cultures 2-4 days after initial positive cultures are reccommended to document clearance of bacteremia (A II)

IDSA 2011

Teicoplanin represents another potential alternative to vancomycin but is unavailable in the United States.[36,37] The addition of gentamicin, rifampin, or both to vancomycin for treating MRSA bacteremia and native valve infective endocarditis offers no meaningful benefit and may confer harm.[45,52] Adding a β-lactam antibiotic to vancomycin or daptomycin to treat MRSA bacteremia[56] is of unproven benefit. Low-quality evidence suggests that linezolid, trimethoprim-sulfamethoxazole, dalbavancin, ceftaroline, quinupristin-dalfopristin, and telavancin may be useful for patients who have not responded to first-line therapy. Tigecycline should be avoided. No data are yet available for tedizolid or oritavancin (both recently approved by the FDA for skin infections) or investigational compounds such as ceftobiprole to treat MRSA bacteremia.

All MRSA bacteremia should be treated with intravenous antibiotics for a minimum of 14 days from the time of blood culture clearance. For those patients not meeting the definition of uncomplicated bacteremia, 4 to 6 weeks of therapy is recommended.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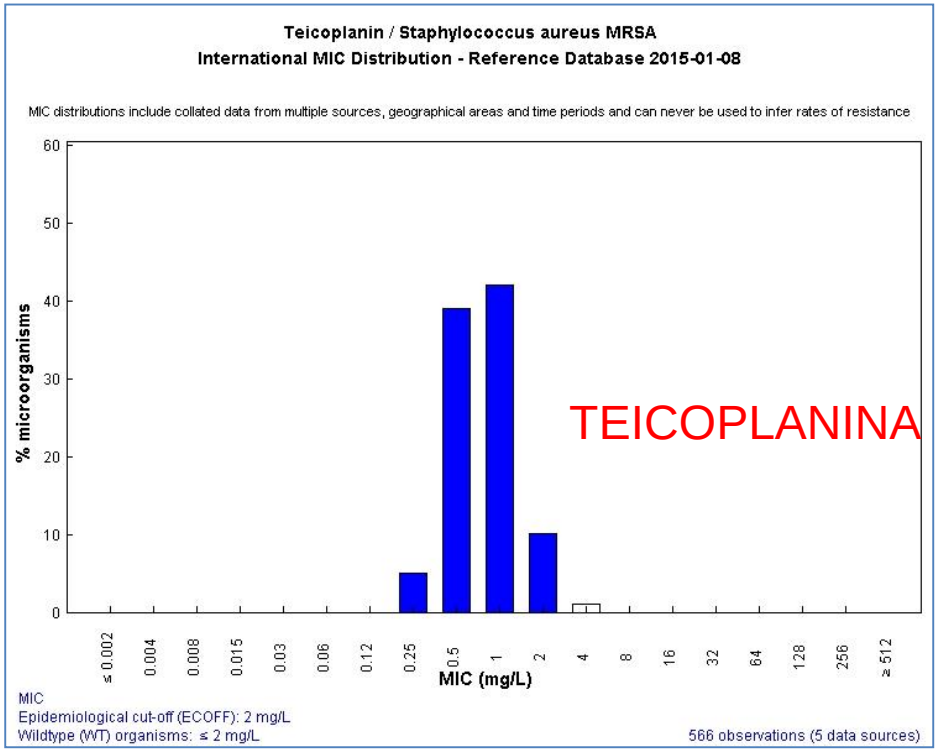
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MRSA

Contents lists available at ScienceDirect

Diagnostic Microbiology and Infectious Disease

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A 5-year survey of antimicrobial susceptibility profiles of methicillin-resistant *Staphylococcus aureus* (MRSA) isolated from patients with bloodstream infections in Northeast Italy

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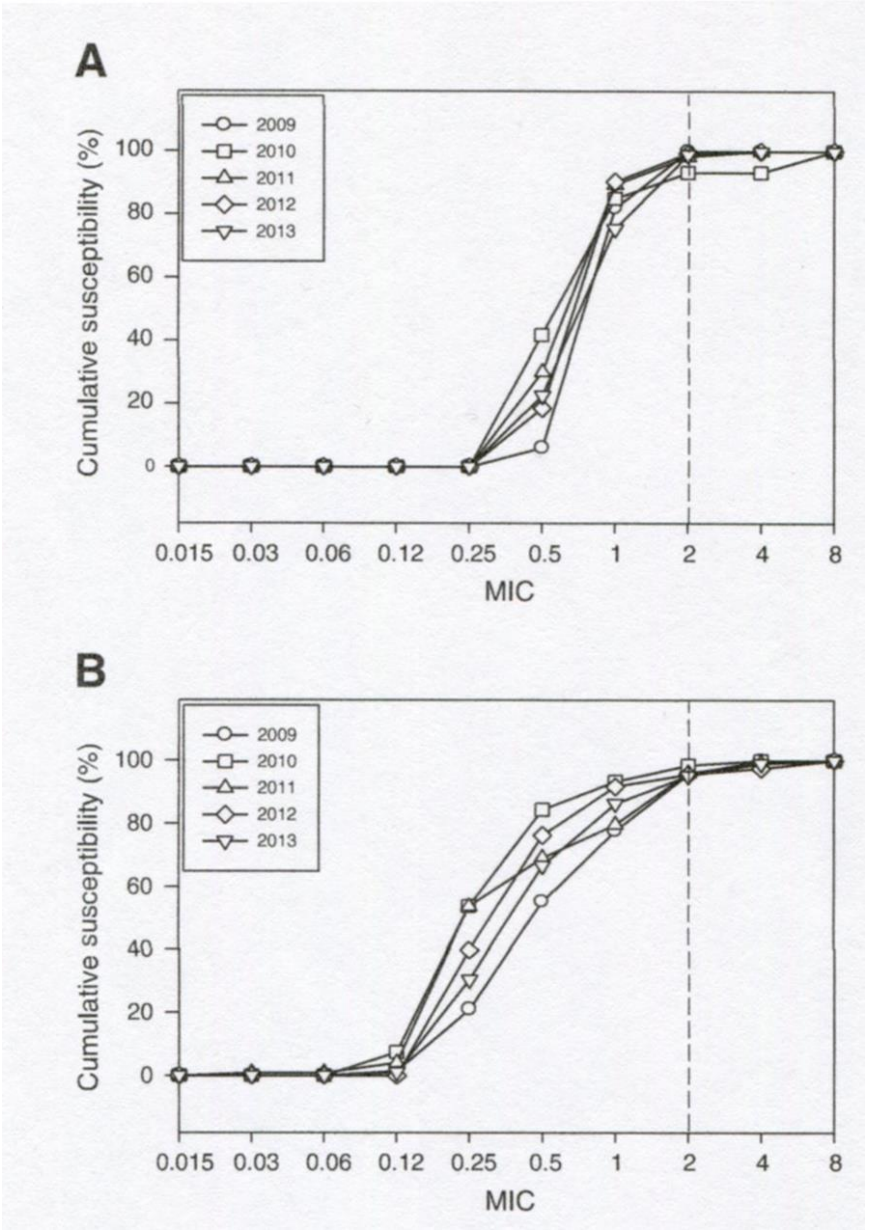
Bacteraemia

ABSTRACT

A 5-year survey (2009–2013) of antimicrobial susceptibility of methicillin-resistant *Staphylococcus aureus* (MRSA) isolated from patients with bloodstream infections was carried out in Northeast Italy. No upward creep of glycopeptides MICs was documented among 582 nonduplicate MRSA blood isolates, which were tested in accordance with broth microdilution and interpreted in accordance with EUCAST recommendations. Teicoplanin showed stably a lower MIC_{50} in comparison with vancomycin (0.25–0.5 versus 1 mg/L). The activities of newer anti-MRSA antibacterials stratified by glycopeptides MICs showed similar trends in MICs of either vancomycin or teicoplanin with those of daptomycin, linezolid, and tigecycline. We hypothesize that in centers with different distribution of glycopeptides MICs, downward for teicoplanin and upward for vancomycin, teicoplanin could be a more effective alternative to vancomycin for empirical treatment of MRSA-related bacteremia.



VANCOMYCIN

TEICOPLANIN

Fig. 1. Trend over time of antimicrobial susceptibility of MRSA isolates from blood cultures in 2009 (n = 67), in 2010 (n = 134), in 2011 (n = 123), in 2012 (n = 156), and in 2013 (n = 102) against vancomycin (panel A), teicoplanin (panel B), daptomycin (panel C), linezolid (panel D), and tigecycline (panel E). Dashed lines refer to the EUCAST clinical breakpoints of each antibiotic against MRSA ($^{**}P = 0.001$; $^{*}P < 0.05$).

Indicazioni	**Dose di carico**		**Dose di mantenimento**	
	Regime di dose di carico	**Concentrazioni minime sieriche da ottenere ai giorni 3 - 5**	**Dose di mantenimento**	**Concentrazioni minime sieriche da ottenere durante il mantenimento**
Infezioni complicate della cute e dei tessuti molli Polmonite Infezioni complicate del tratto urinario	400 mg per via endovenosa o intramuscolare (corrispondente a circa 6 mg/kg di peso corporeo) ogni 12 ore per 3 somministrazioni	>15 mg/L[1]	6 mg/kg di peso corporeo per via endovenosa o intramuscolare una volta al giorno	>15 mg/L[1] una volta la settimana
Infezioni delle ossa e delle articolazioni	800 mg per via endovenosa (corrispondente a circa 12 mg/kg di peso corporeo) ogni 12 ore per 3 – 5 somministrazioni	>20 mg/L[1]	12 mg/kg di peso corporeo per via endovenosa o intramuscolare una volta al giorno	>20 mg/L[1]

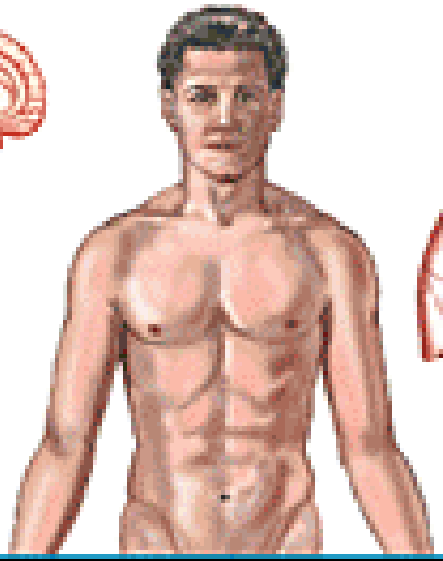
Indicazioni	**Dose di carico**		**Dose di mantenimento**	
	Regime di dose di carico	**Concentrazioni minime sieriche da ottenere ai giorni 3 - 5**	**Dose di mantenimento**	**Concentrazioni minime sieriche da ottenere durante il mantenimento**
Endocardite infettiva	800 mg per via endovenosa (corrispondente a circa 12 mg/kg di peso corporeo) ogni 12 ore per 3 – 5 somministrazioni	30-40 mg/L[1]	12 mg/kg di peso corporeo per via endovenosa o intramuscolare una volta al giorno	>30 mg/L[1]

[1] Misurata con FPIA

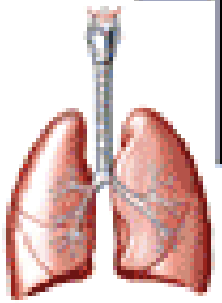
SCHEDA TECNICA TEICOPLANINA ottobre 2014

Vancomycin Penetration

CNS: <10%

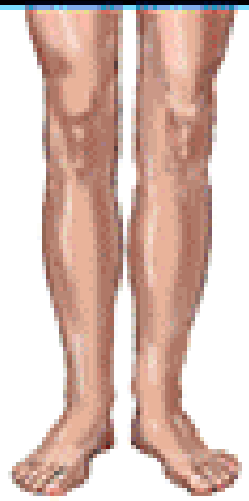


Epithelial lining fluid[3]: 18%

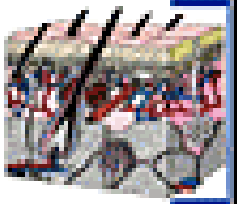


Lung tissue[2]: 17%–24%

Sternal bone[1]: 57%
Heart valve[4]: 12%



Bone[5]: 7%–13%



Fat[4]: 14%
Muscle[4]: 9%

1. Massias L et al. *Antimicrob Agents Chemother.* 1992;36:2539-2541. 2. Cruciani M et al. *J Antimicrob Chemother.* 1996;38:865-869. 3. Lamer C et al. *Antimicrob Agents Chemother.* 1993;37:281-286. 4. Daschner FD et al. *J Antimicrob Chemother.* 1987;19:359-362. 5. Graziani AL et al. *Antimicrob Agents Chemother.* 1988;32:1320-1322.

CINETICA DI ALCUNI ANTIBIOTICI NELL'ELF

ANTIBIOTICO	RAPPORTO ELF/PLASMA %
Piperaciilina/Tazobactam	PIP: 56 TAZ: 90
Ceftazidime	20
Cefepime	100
Ceftriaxone	30 (lung)
Meropenem	30-50
Ertapenem	30
Ciprofloxacina	100
Levofloxacina	150-200
Gentamicina	30-100
Vancomicina	**20**
Teicoplanina	**30**
Linezolid	**300-400**
Tigeciclina	50-100 (0,06-0,19)

Intensive Care Med (2006) 32:775–779
DOI 10.1007/s00134-006-0136-3

BRIEF REPORT

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Michèle Adoun
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Steady-state trough serum and epithelial lining fluid concentrations of teicoplanin 12 mg/kg per day in patients with ventilator-associated pneumonia

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Abstract *Objective:* To determine the steady-state trough serum and epithelial lining fluid (ELF) concentrations of teicoplanin 12 mg/kg per day in critically ill patients with ventilator associated pneumonia. *Design and setting:* Prospective, pharmacokinetic study in the surgical intensive care unit in a university hospital. *Patients:* Thirteen adult patients with nosocomial bacterial pneumonia on mechanical ventilation were enrolled. *Interventions:* All subjects received a 30-min intravenous infusion of 12 mg/kg teicoplanin every 12 h for 2 consecutive days followed by 12 mg/kg once daily. Teicoplanin concentrations in serum and ELF were determined simultaneously 4–6 days after antibiotic administration started. *Measurements and results:* The median total and free concentrations of teicoplanin in serum at trough were 15.9 μg/ml (range 8.8–29.9) and 3.7 (2.0–5.4), respectively. The concentration in ELF was 4.9 (2.0–11.8). *Conclusions:* In critically ill patients with ventilator-associated pneumonia the administration of high teicoplanin doses is required to reach sufficient trough antibiotic concentrations in lung tissues at steady state. At that time trough-free concentrations of teicoplanin in serum and ELF are comparable.

Keywords Teicoplanin · Lung diffusion · Epithelial lining fluid · Intensive care unit · Human

Table 2 Individual steady-state serum and epithelial lining fluid (ELF) concentrations at trough and percentage penetration of 12 mg/kg teicoplanin once daily administered to 13 critically ill patients with ventilator-associated pneumonia (*FU* fraction of teicoplanin not bound to plasma proteins)

Patient no.	Serum (μg/ml)			ELF (μg/ml)	Percentage penetration[a]
	Total	Free	FU (%)		
1	20.1	4.1	20	3.6	88
2	10.1	3.4	34	11.3	332
3	8.8	3.7	42	10.9	294
4	13.8	2.8	20	3.6	128
5	15.0	4.6	31	11.8	256
6	13.5	3.0	22	2.0	66
7	15.9	4.5	28	10.8	240
8	16.2	5.4	33	2.6	48
9	21.0	4.6	22	5.4	117
10	18.1	4.3	24	5.6	130
11	23.8	2.0	8	4.9	245
12	29.9	2.6	9	3.8	146
13	14.2	2.4	17	3.5	146
Median	15.9	3.7	22	4.9	146
Range	8.8–29.9	2.0–5.4	8–42	2.0–11.8	48–332

[a] ELF to free serum concentration ratio values

O. Mimoz Int. Care Med. 2006

TERAPIA DELLE BATTERIEMIE ED ENDOCARDITI (valvola nativa) DA MRSA

DAPTOMICINA	**6 mg/Kg/dose (8-10 mg/Kg/dose)**
VANCOMICINA	15-20 mg/Kg/dose ogni 8-12 h

ENDOCARDITI VALVOLA PROTESICA: VANCOMICINA+GENTAMICINA+RIFAMPICINA

IDSA Guidelines 2011

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, May 2011, p. 2160–2165 Vol. 55, No. 5
0066-4804/11/$12.00 doi:10.1128/AAC.01291-10

Impact of Dose De-Escalation and Escalation on Daptomycin's Pharmacodynamics against Clinical Methicillin-Resistant *Staphylococcus aureus* Isolates in an *In Vitro* Model[▽]

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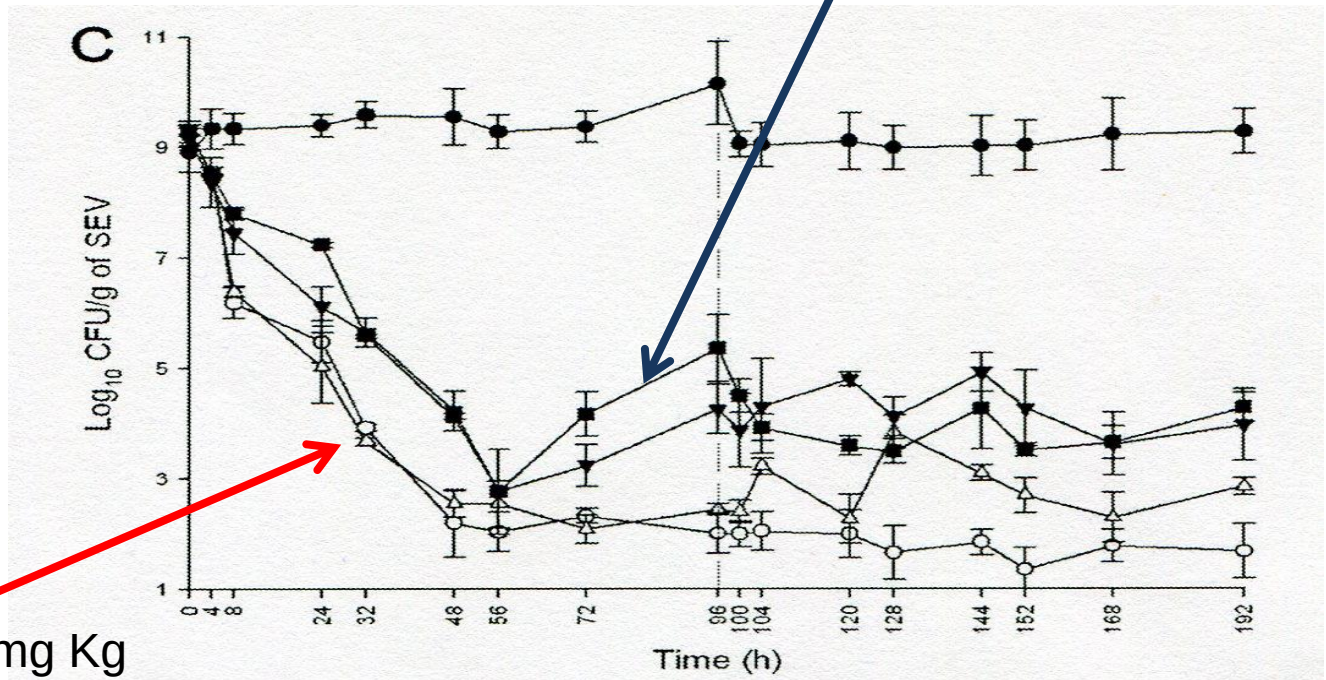
De-escalation and escalation therapeutic strategies are commonly employed by clinicians on the basis of susceptibility results and patient response. Since no *in vitro* or *in vivo* data are currently available to support one strategy over the other for daptomycin, we attempted to evaluate the effects of dose escalation and de-escalation on daptomycin activity against methicillin-resistant *Staphylococcus aureus* (MRSA) isolates using an *in vitro* pharmacokinetic/pharmacodynamic (PK/PD) model with simulated endocardial vegetations. Three clinical MRSA isolates, including one heterogeneous vancomycin-intermediate *S. aureus* (hVISA) isolate and one vancomycin-intermediate *S. aureus* (VISA) isolate, were exposed to daptomycin at 10 or 6 mg/kg of body weight/day for 8 days using a starting inoculum of $\sim 10^9$ CFU/g of vegetations, with dose escalation and de-escalation initiated on the fourth day. Daptomycin MIC values ranged from 0.5 to 1 μg/ml. In the PK/PD model, high-dose daptomycin (10 mg/kg/day) and de-escalation simulation (10 to 6 mg/kg/day) appeared to be the most efficient regimens against the three tested isolates, exhibiting the fastest bactericidal activity (4 to 8 h) compared to that of the standard regimen of 6 mg/kg/day and the escalation therapy of 6 to 10 mg/kg/day. The differences in the numbers of CFU/g observed between dose escalation and de-escalation were significant for the hVISA strain, with the de-escalation simulation exhibiting a better killing effect than the escalation simulation ($P < 0.024$). Although our results need to be carefully considered, the use of high-dose daptomycin up front demonstrated the most efficient activity against the tested isolates. Different therapeutic scenarios including isolates with higher MICs and prolonged drug exposures are warranted to better understand the outcomes of escalation and de-escalation strategies.

6 mg/Kg



10 e poi 6mg Kg

FIG. 1. *In vitro* activity of daptomycin. (A) B010-01; (B) hVISA R3099; (C) VISA NRS-118. Filled circles, growth control; open circles, daptomycin at 10 mg/kg/day; open triangles, daptomycin at 10 to 6 mg/kg/day; filled inverted triangles, daptomycin at 6 mg/kg/day; filled squares, daptomycin at 6 to 10 mg/kg/day. The vertical dashed line represents the time for de-escalation or escalation therapy, if it was performed.

DAPTOMYCIN NON SUSCEPTIBLE DNS

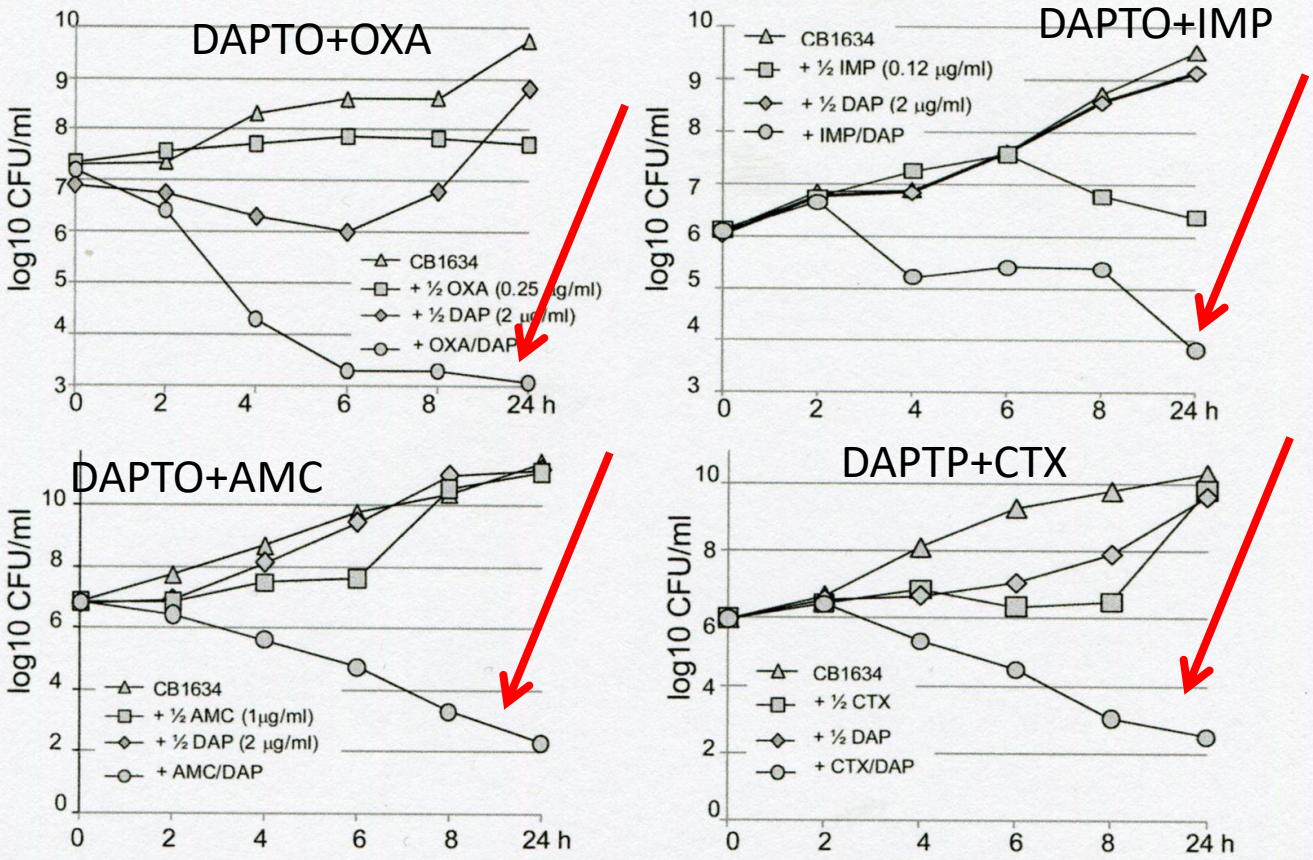


FIG 1 Analysis of antibacterial efficacy of DAP–β-lactams against DAP^r MRSA strain CB1634. Synergy time-kill analyses were performed using MH broth with a 10^6-CFU/ml inoculum at 0, 2, 4, 6, 8, and 24 h and the specified concentrations of antibiotics: DAP, 2 µg/ml; OXA, 0.25 µg/ml; IMP, 0.12 µg/ml; AMC, 1 µg/ml; CTX, 1 µg/ml. A minimum of three independent experimental runs were performed for each DAP–β-lactam combination.

AAC 2012

In summary our data show that the DAP- betalactam combination may significantly enhance both the in vitro and in vivo efficacy of anti-MRSA therapeutic options against DAPr MRSA infections and represent an option in preventing DAPr selection in persistent or refractory MRSA infection.

S. Metha AAC 2012

ELSEVIER

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www.ischemo.org

Linezolid pharmacokinetic/pharmacodynamic profile in critically ill septic patients: intermittent versus continuous infusion☆

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Abstract

Pharmacokinetics and pharmacodynamics are significantly altered in critically ill septic patients and the risk of prolonged periods with concentrations below the minimum inhibitory concentration (MIC) and of low area under the serum concentration–time curve/MIC (AUC/MIC) ratios is of concern. We compared the pharmacokinetic/pharmacodynamic (PK/PD) profile of linezolid administered by intermittent or continuous infusion in critically ill septic patients. Patients were divided into two groups: intermittent infusion (Group I) (600 mg/12 h); or continuous infusion (Group C) (300 mg intravenous loading dose +900 mg continuous infusion on Day 1, followed by 1200 mg/daily from Day 2). Linezolid serum levels were monitored for 72 h and microbiological data were collected. The clinical outcome was monitored. Sixteen patients completed the study. MICs of susceptible pathogens were 2 mg/L for 80% of the isolates. In Group I, linezolid trough serum levels (C_{min}) varied widely and were below the susceptibility breakpoint (4 mg/L) during the study period; in 50% of patients C_{min} was <1 mg/L. In Group C, mean linezolid serum levels were more stable and, starting from 6 h, were significantly higher than C_{min} levels observed in Group I and were always above the susceptibility breakpoint. Time that the free drug concentration was above the MIC (T_{free} > MIC) of > 85% was more frequent in Group C than in Group I ($P < 0.05$). Finally, with continuous infusion it was possible to achieve AUC/MIC values of 80–120 more frequently than with intermittent infusion ($P < 0.05$). According to PK/PD parameters, continuous infusion has theoretical advantages over intermittent infusion in this population of patients.

Keywords: Linezolid; Pharmacokinetics; Pharmacodynamics; Sepsis; Critically ill patients; Continuous infusion

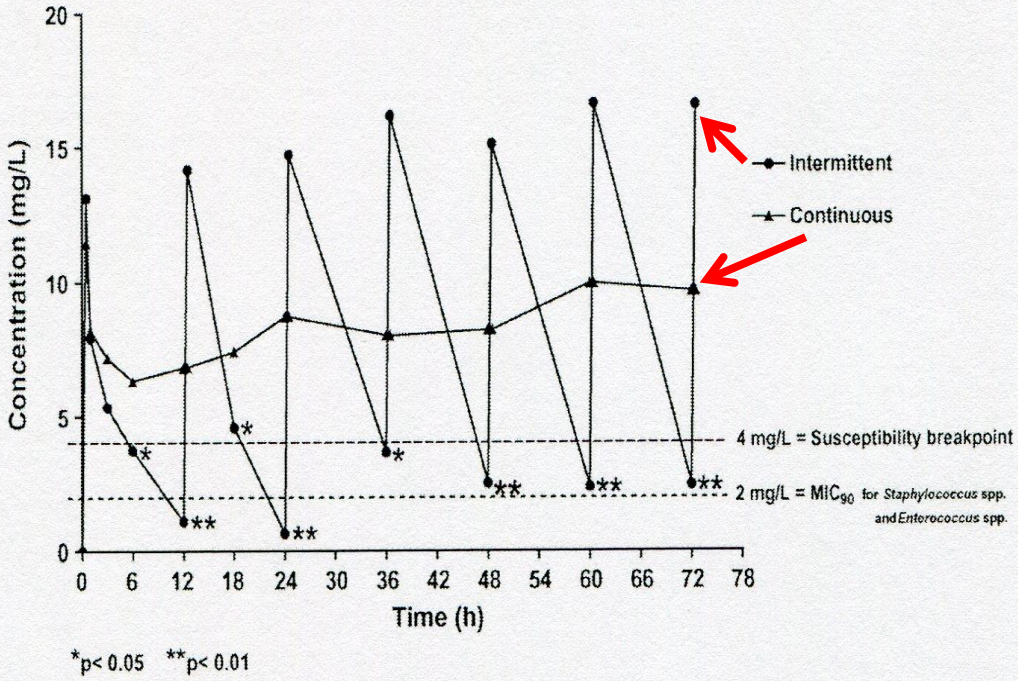


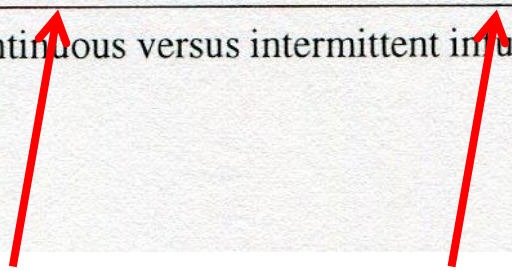
Fig. 1. Mean serum concentrations of linezolid in critically ill septic patients after intravenous administration of 1200 mg daily: intermittent versus continuous infusion ($n = 8$ patients each group).

C. Adembri

Table 4
Trough serum concentrations of linezolid in Group I patients (intermittent infusion of 600 mg every 12 h) compared with serum levels in Group C patients (1200 mg daily as continuous infusion) measured at the same time points (mean ± standard deviation)

Time (h)	Serum concentration (mg/L)	
	Group I	Group C
12	1.1 ± 1.5	7.3 ± 4.3**
24	0.65 ± 0.6	9.1 ± 5.5**
36	3.7 ± 4.8	8.1 ± 2.9*
48	2.5 ± 3.7	8.2 ± 2.7**
60	2.4 ± 3.9	9.9 ± 4.8**
72	2.5 ± 3.1	10.6 ± 4.5**

*$P < 0.05$ and **$P < 0.01$, continuous versus intermittent infusion (two-way ANOVA).



INFUSIONE INTERMITTENTE

INFUSIONE CONTINUA

C. Adembri

NUOVI ANTIBIOTICI

NUOVI ANTIBIOTICI IN STUDIO

TETRACICLINE
Eravaciclina
Omadaciclina

KETOLIDI
Cetromicina
Solitromicina

CHINOLONI
Nemonoxacina
Delafloxacina
Finafloxacina
Zobofloxacina
Chinafloxacina
Ozenoxacina
JNJ-Q2
DS-8587
KPI-10
GSK2140944
ACH-702

MONOBATTAMI
BAL30072

OXAZOLIDINONI
Tedizolid
Radezolid
Posizolid
MRX-1
LCB01-0371

INIBITORI ENZIMATICI COMBINAZIONI
Ceftolozane-Tazobactam
Ceftazidime-Avibactam
Ceftarolina-Avibactam
Aztreonam-Avibactam
Imipenem-MK-7655
Biapenem-RPX7009

AMINOGLICOSIDI
Plazomicina

POLIMIXINE
CB-182,804

CARBAPENEMI
Panipenem
Biapenem
Razupenem

LIPOGLICOPEPTIDI
Telavancina
Dalbavancina
Oritavancina

AGENTI ATTIVI SULLE MEMBRANE
Brilacidina
POL7080
ACHN-975

COMPOSTI ANTI C. difficile
Surotomicina
Cadazolid
LFF571
NVB302

REVIEW ARTICLE

Drugs 2010; 70 (7): 859-886
0012-6667/10/0007-0859/$55.55/0

New Lipoglycopeptides

A Comparative Review of Dalbavancin, Oritavancin and Telavancin

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Table I. *In vitro* activity of dalbavancin, oritavancin, telavancin and vancomycin against Gram-positive organisms[2,24,28-48]

Bacteria	Dalbavancin			Oritavancin			Telavancin			Vancomycin		
	MIC_{50}	MIC_{90}	range	MIC_{50}	MIC_{90}	range	MIC_{50}	MIC_{90}	range	MIC_{50}	MIC_{90}	range
Staphylococcus aureus (MS)	0.06	0.06	≤0.008–0.5	0.06	0.12	≤0.004–2	0.25	0.5	≤0.015–2	1	1	0.25–2
S. aureus (MR)	0.06	0.06	≤0.008–0.5	0.06	0.25	≤0.004–4	0.25	0.5	≤0.06–2	1	2	0.25–2
Staphylococcus epidermidis (MS)	≤0.03	0.06	0.015–0.25	0.25	0.5	0.008–1	0.25	1	0.12–1	2	2	1–2
S. epidermidis (MR)	0.06	0.06	0.015–1	0.5	0.5	≤0.004–4	0.5	1	0.25–2	2	4	1–4
Streptococcus pyogenes (group A)	0.015	0.03	≤0.002–0.06	0.12	0.25	0.008–0.5	0.03	0.06	0.03–0.12	0.5	1	0.5–1
Streptococcus agalactiae (group B)	0.06	0.12	0.008–0.25	N/A	0.12	0.03–0.5	0.06	0.06	0.002–0.25	0.25	0.5	0.25–0.5
Other β-haemolytic *Streptococcus* spp.	≤0.008	0.06	≤0.002–0.25	N/A	0.5	0.001–1	0.03	0.06	0.002–0.25	0.25	0.5	0.25–1
Streptococcus pneumoniae (PS)	0.015	0.03	≤0.008–0.06	0.002	0.004	≤0.0005–0.25	0.015	0.03	0.008–0.06	0.25	0.5	0.06–1
S. pneumoniae (PI)	0.015	0.03	≤0.008–0.06	0.004	0.008	≤0.0005–0.5	0.015	0.03	0.008–0.12	0.5	1	0.25–1
S. pneumoniae (PR)	0.015	0.03	≤0.008–0.25	0.004	0.008	≤0.0005–0.015	0.015	0.03	0.008–0.12	0.25	0.5	0.06–2

G.G. Zhanel Drugs 2010

DALBAVANCIN

Dalbavancin

- Activity versus most Gram +
- Bactericidal
- Good PK profile (concentrations, long half-life, low potential for interaction
- Good safety proflie

DOSE DALBAVANCINA:
1 g giorno 1 poi 500 mg giorno 8

Revolutionary drugs

DALBAVANCIN

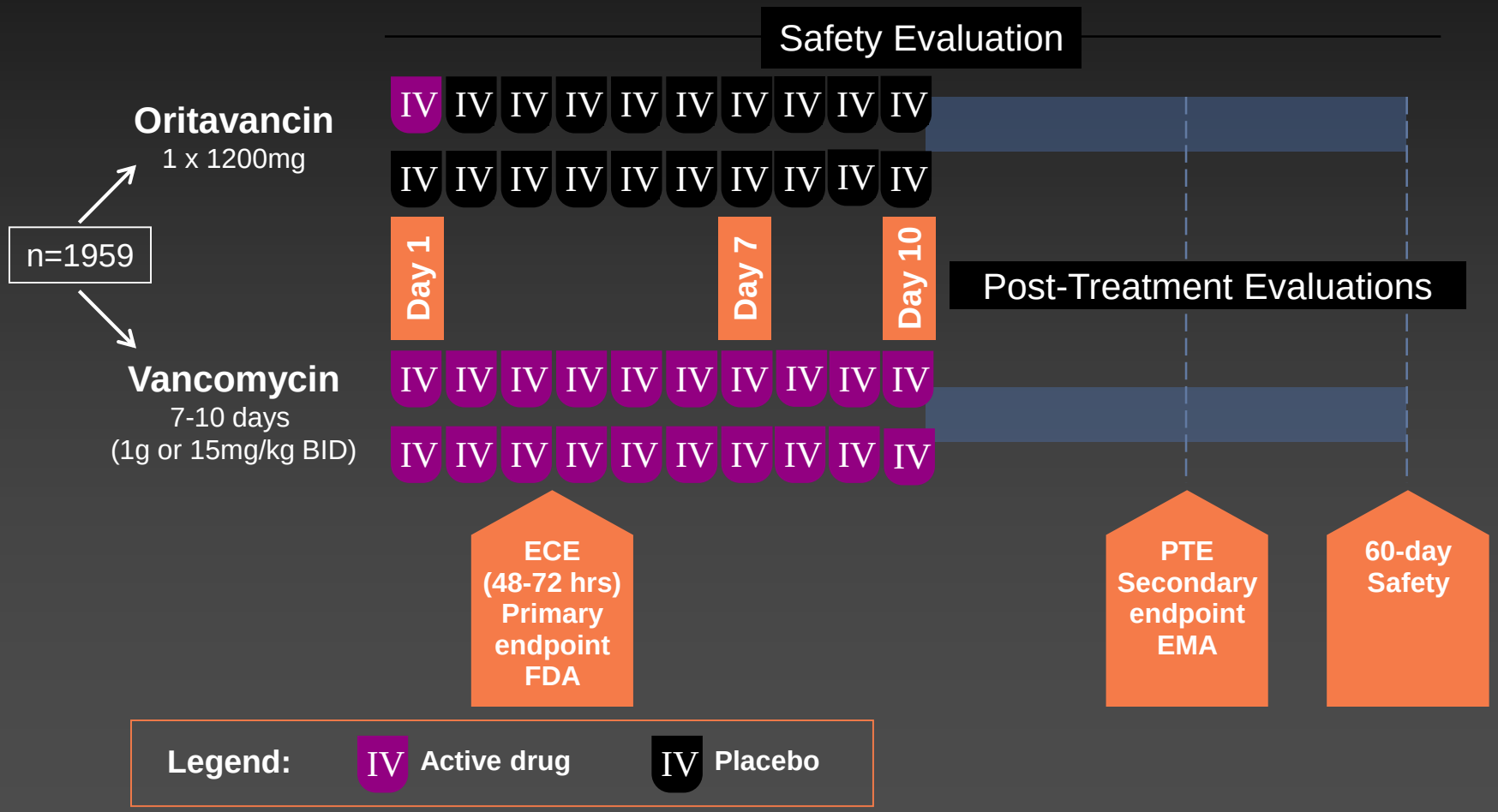
- Long half life (5-7 days)
- Weekly drug
- Protein binding (93%)
- Only IV
- Potential for OPAT
- Well tolerated
- Potential for many indications
- Cost

DOSE DALBAVANCINA:
1 g giorno 1 poi 500 mg giorno 8

ORITAVANCIN

Oritavancin Phase III Clinical Studies

- Randomized double blind trial design with 60 day safety follow up



Note: Infusions on days 7-10 were administered at the investigators' discretion