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**"Second Opinion" Infettivologica**  
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# **Daptomycin in Clinical Practice**

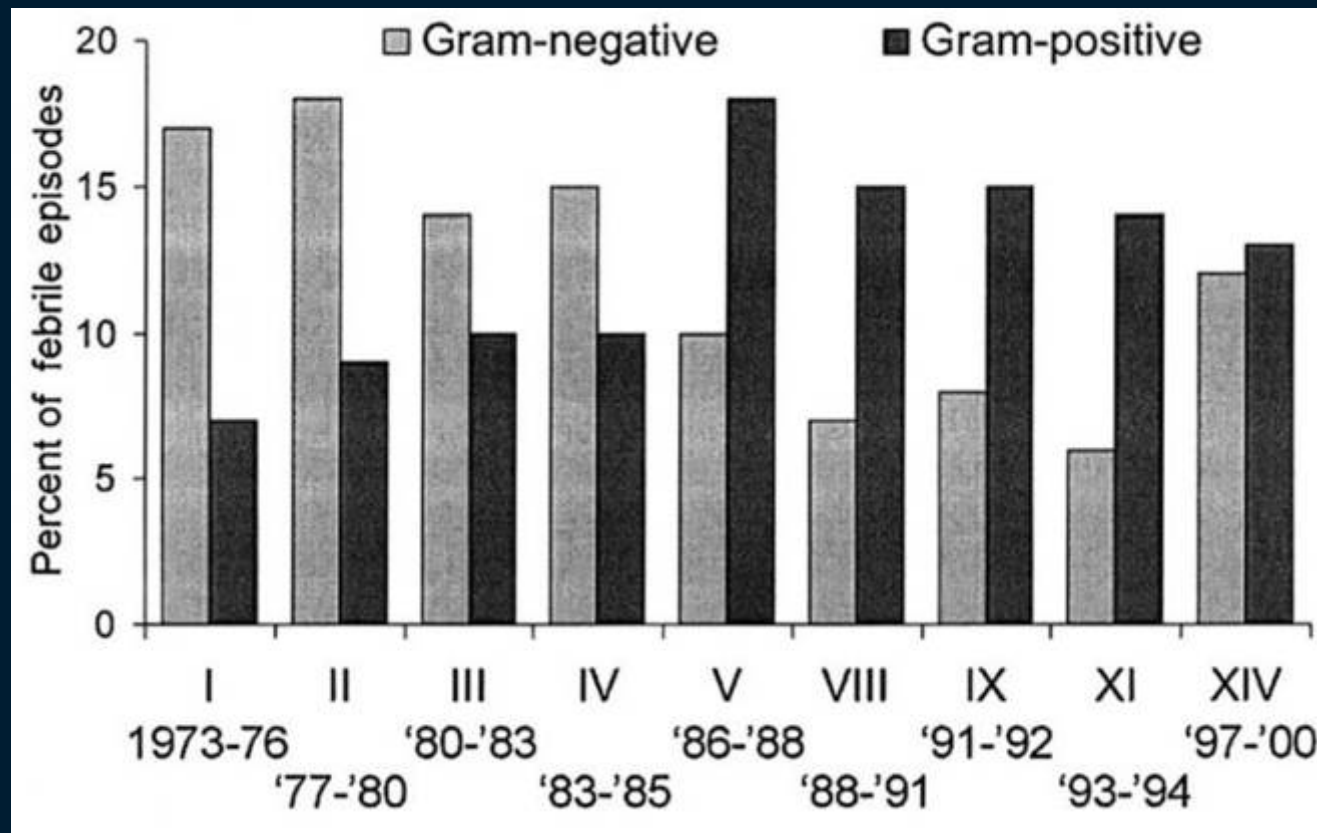
**Paolo Grossi**



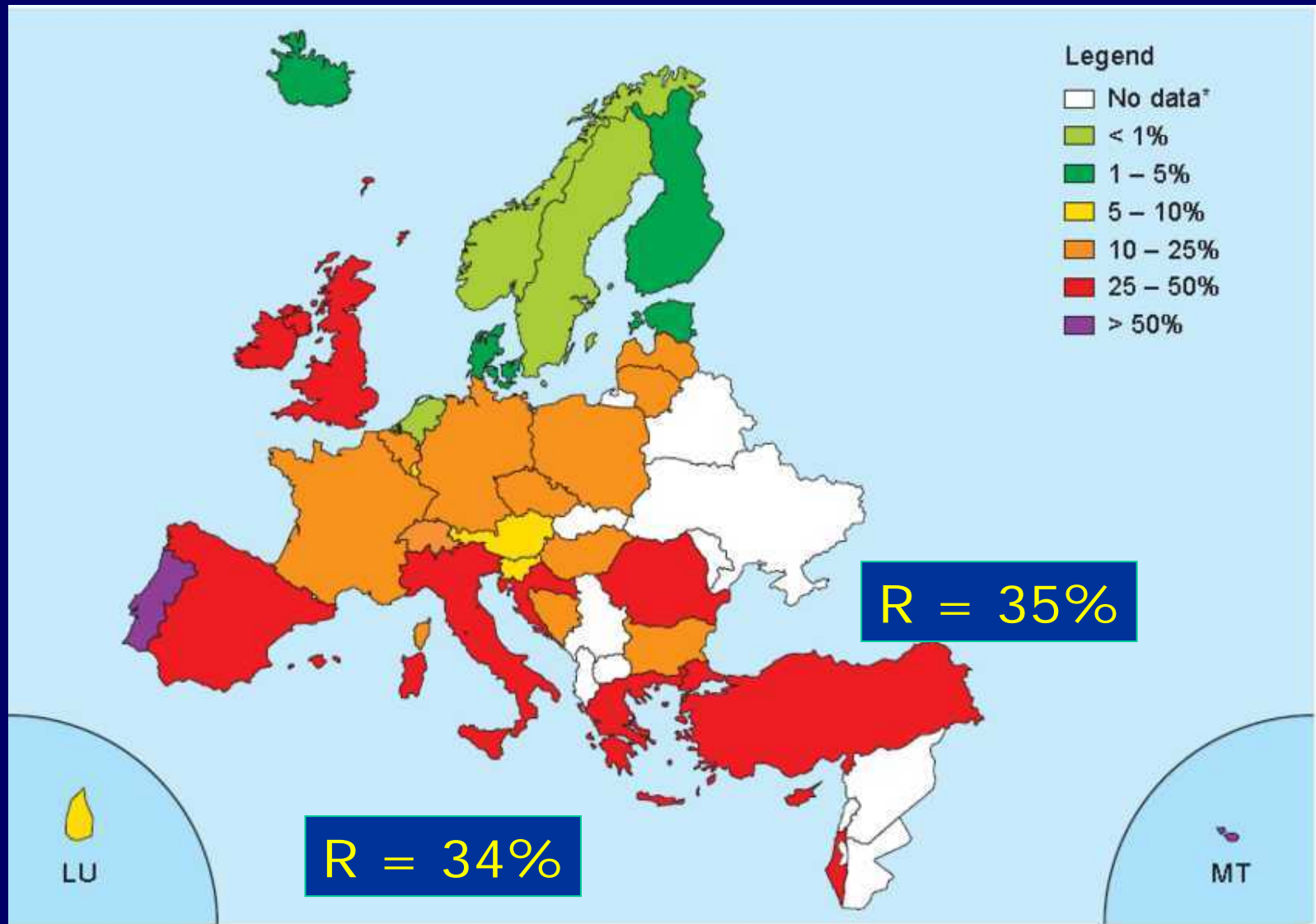
**Turkish Febrile Neutropenia Congress**  
**Ankara 25.02.2010**

# Shift from predominantly Gram-negative to predominantly Gram-positive pathogens

Single-organism bacteraemias in EORTC-IATG trials (1985–2000)



# *Staphylococcus aureus* Resistance to Oxacillin/Methicillin



# Study on European Practices of Infections (bacteraemia) with *Staphylococcus aureus* (SEPIA – study)

	Bacteraemia (n=152)	SSTI (n=132)	FN/FOU* (n=190)	Endocarditis (n=90)	i.v. catheter (n=31)	Total (n=605)
<b>Anti-MRSA not given first-line, %</b>	<b>45</b>	<b>49</b>	<b>58</b>	<b>49</b>	<b>44</b>	<b>49</b>
Mean time to anti-MRSA as second-line, days	6	10	13	5	5	6
Mean time to anti-MRSA as third-line, days	6	17	5	15	6	8

Retrospective case analysis of patients with confirmed MRSA infections in the EU

\*FN febrile neutropenia; FOU fever of unknown origin

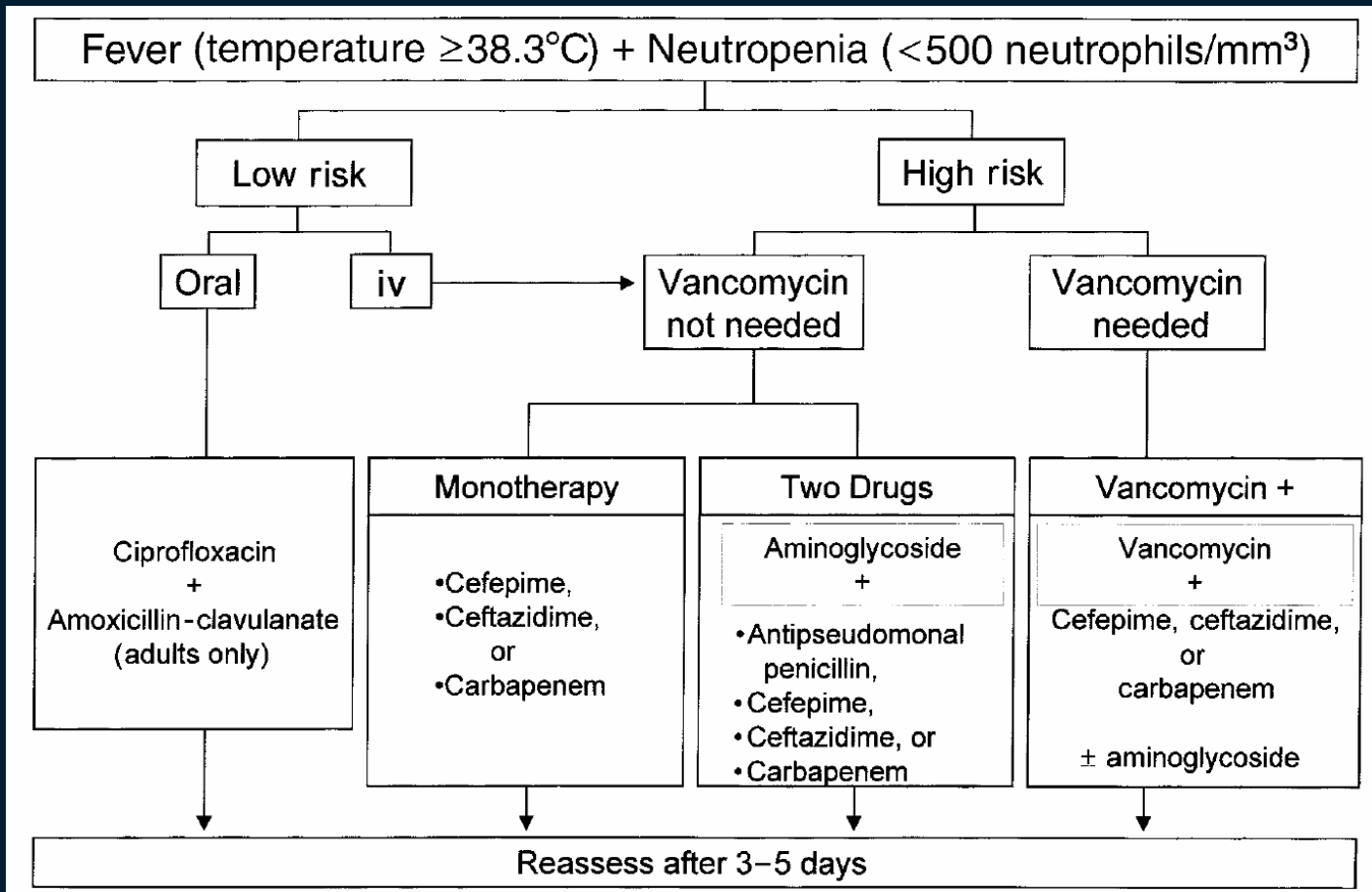
**Approximately 50% of MRSA patients receive inadequate first-line therapy**

# Glycopeptides in neutropenic patients

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- Should glycopeptides be given as upfront empiric therapy?
- Should glycopeptides be given in case of documented Gram-positive MDI?
- Should glycopeptides be given in cases of persistent fever after initial broad-spectrum empiric antibiotic therapy?

# Algorithm for initial management of febrile neutropenic patients



# Initial empiric glycopeptide in neutropenic patients (IDSA 2002)

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- Development of hypotension or shock
- Known colonisation with MRSA or penicillin-resistant pneumococcus
- Positive results for Gram-positive before identification
- Clinically suspected serious catheter-related infection (cellulitis)
- Institutions with high rate of infections due to MRSA or penicillin-resistant viridans streptococci

# ECIL recommendations for the use of glycopeptide antibiotic in neutropenic cancer patients

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Circumstances	Addition of glycopeptide	Quality of evidence and level of recommendation
Fever onset	Not recommended	I D
Persistent fever	Not recommended	I D
Predominance in the local epidemiology of resistant Gram-positive (e.g. MRSA, penicillin-R <i>S. pneumoniae</i> )	Recommended	III C
Severe sepsis and septic shock	Recommended	III C
Skin and soft tissue infections (including catheter-related infections)	Recommended	III C

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# Central venous catheter-related infections in hematology and oncology

Guidelines of the Infectious Diseases Working Party (AGIHO)  
of the German Society of Hematology and Oncology (DGHO)

Pathogen	Therapy	Duration <sup>a</sup>
<i>S. aureus</i> (methicillin-sensitive) <sup>b</sup>	Isoxazolylpenicillin (penicillinase-resistant penicillin) <sup>c</sup>	At least 2 weeks i.v. <sup>d</sup>
<i>S. aureus</i> (methicillin-resistant) <sup>b</sup>	Glycopeptide, linezolid, quinupristin + dalbapristin	At least 2 weeks i.v. <sup>d</sup>
Coagulase-negative staphylococci	According to susceptibility pattern; glycopeptide only in case of methicillin-resistance	For 5–7 days after defervescence (in patients with persistent neutropenia)
Enterococci	Aminopenicillin plus aminoglycoside glycopeptide plus aminoglycoside in case of ampicillin resistance Linezolid or quinupristin/dalbapristin in case of vancomycin-resistance	For 5–7 days after defervescence (in patients with persistent neutropenia)
<i>Candida albicans</i> <sup>b</sup>	Azole antifungal Alternative: amphotericin B lipid-based formulations or caspofungin	≥2 weeks
Nonalbicans <i>Candida</i> species <sup>b</sup>	Amphotericin B lipid-based formulations or caspofungin or voriconazole	≥2 weeks
All other pathogens	According to susceptibility pattern	Not defined

# Linezolid: Pros and Cons

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## ■ Pros

- I.V. and Oral formulation
- Pneumonia
- Novel mechanism

## ■ Cons

- FDA Black box warning for **increased mortality concerns in catheter-BSI trial\***
- **Myelosuppression** – duration dependent >2wks
- Serotonin syndrome esp with SSRI, MAO-inhibitors
- Optic neuritis
- Lactic acidosis

\*FDA. Available at: <http://www.fda.gov/cder/drug/infopage/linezolid/default.htm>.

# Catheter-related MRSA BSI

**Withdraw the catheter**

**A-II**

**Start empirically either:**

Vancomycin or teicoplanin

**A-I**

Daptomycin

**A-I**

**Definitive information – vancomycin MIC**

**Good clinical  
progress →  
continue  
with same drug**

**Vancomycin MIC  
≥ 1 ug/ml →  
daptomycin**

# Clinical Practice Guidelines for the Diagnosis and Management of Intravascular Catheter-Related Infection: 2009 Update by the Infectious Diseases Society of America

## How should catheter-related infections generally be managed?

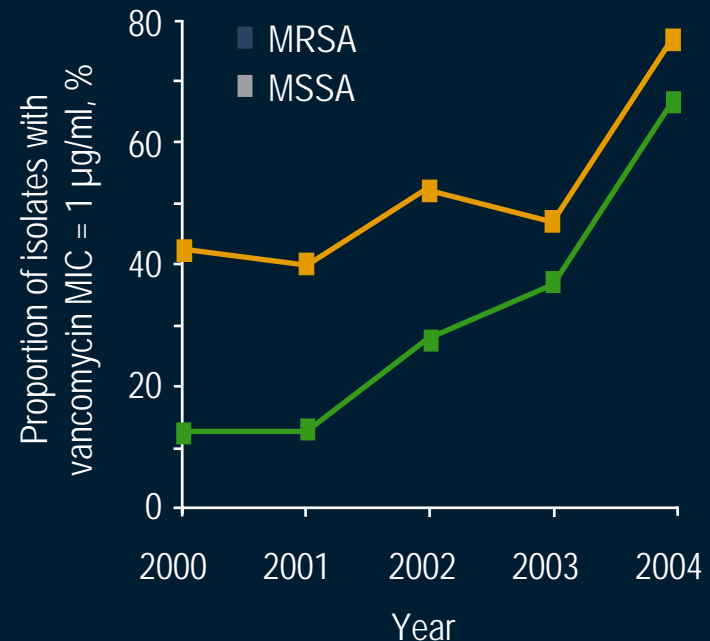
Recommendation	Strength or quality of recommendation
For uncomplicated Coagulase negative staphylococcal CRBSI, treat with Nafcillin or Oxacillin, 2 g q4h for 5–7 days if the catheter is removed and for 10–14 days, in combination with antibiotic lock therapy, if the catheter is retained	B-III
Vancomycin is recommended for empirical therapy in health care settings with an elevated prevalence of MRSA/MRSE; for institutions in which the preponderance of MRSA isolates have <b>vancomycin minimum inhibitory concentration (MIC) values &gt;2 µg/mL, alternative agents, such as daptomycin, should be used</b>	A-II
Linezolid should not be used for empirical therapy (i.e., for patients suspected but not proven to have CRBSI)	A-I

Modified from Mermel LA, et al. *Clinical Infectious Diseases* 2009;49:1–45

# Growing evidence for vancomycin MRSA MIC creep

- According to a study at a US medical centre for the period 2000–2004:<sup>1</sup>
  - Over 90% of *S. aureus* isolates had vancomycin MICs <2 µg/ml
  - The proportion of MSSA and MRSA isolates with vancomycin MIC of 1 µg/ml increased
  - The proportion of MSSA and MRSA isolates with vancomycin MIC ≤0.5 µg/ml decreased
- Several other studies have demonstrated vancomycin MIC creep in MRSA<sup>2–7</sup>

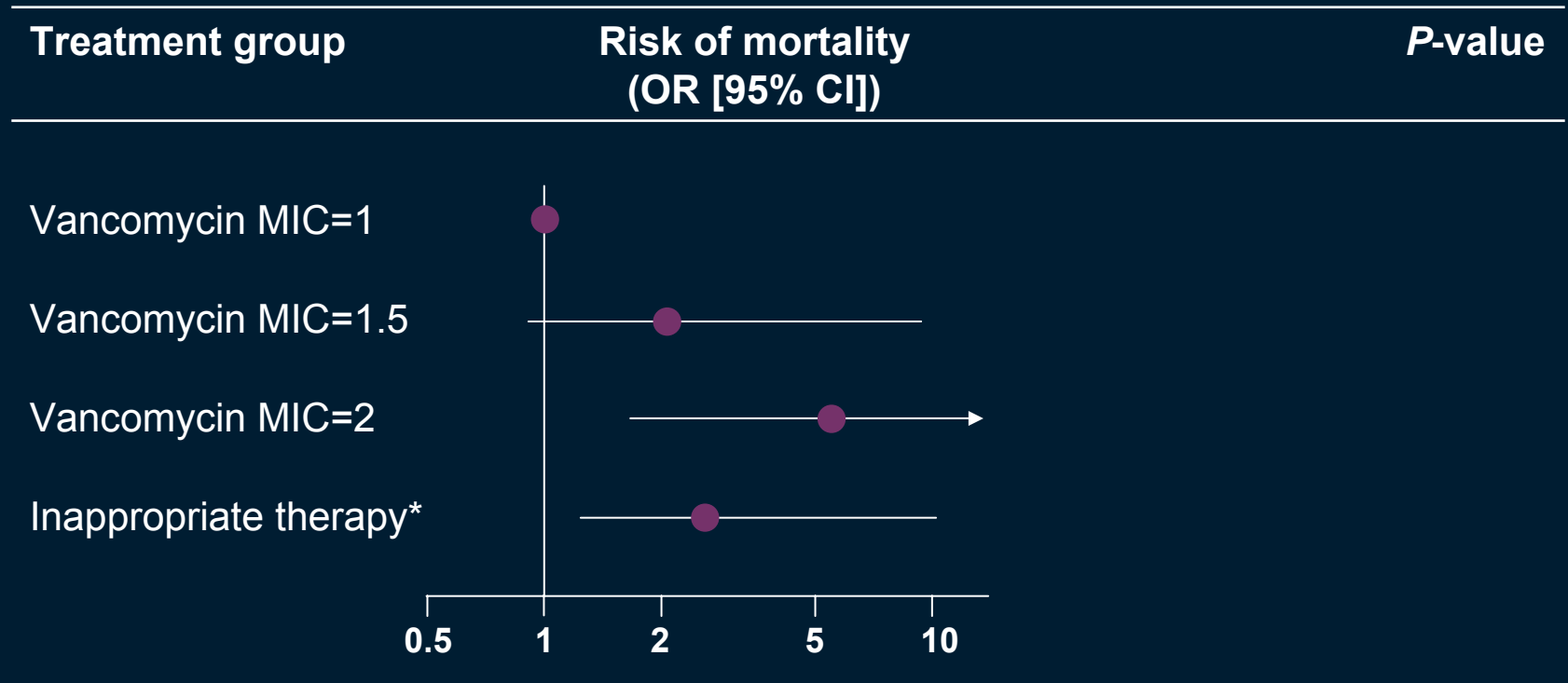
Increased vancomycin MICs for *S. aureus* over a 5-year period



1. Wang G *et al.* *J Clin Microbiol* 2006;44:3883–3886  
2. Delgado A *et al.* *J Clin Microbiol* 2007;45:1325–1329  
3. Rodriguez-Morales AJ *et al.* *Int J Antimicrob Agents* 2007;29:607–609

4. Karpadia M *et al.* *ICAAC* 2005; Abstract E-807  
5. Golan Y *et al.* *IDSA* 2006; Abstract LB-11  
6. Zaragoza R *et al.* *ICAAC* 2007; Abstract K-724  
7. De Sanctis J *et al.* *ICAAC* 2007; Abstract D-882

# Vancomycin MIC significantly predicts for mortality in MRSA

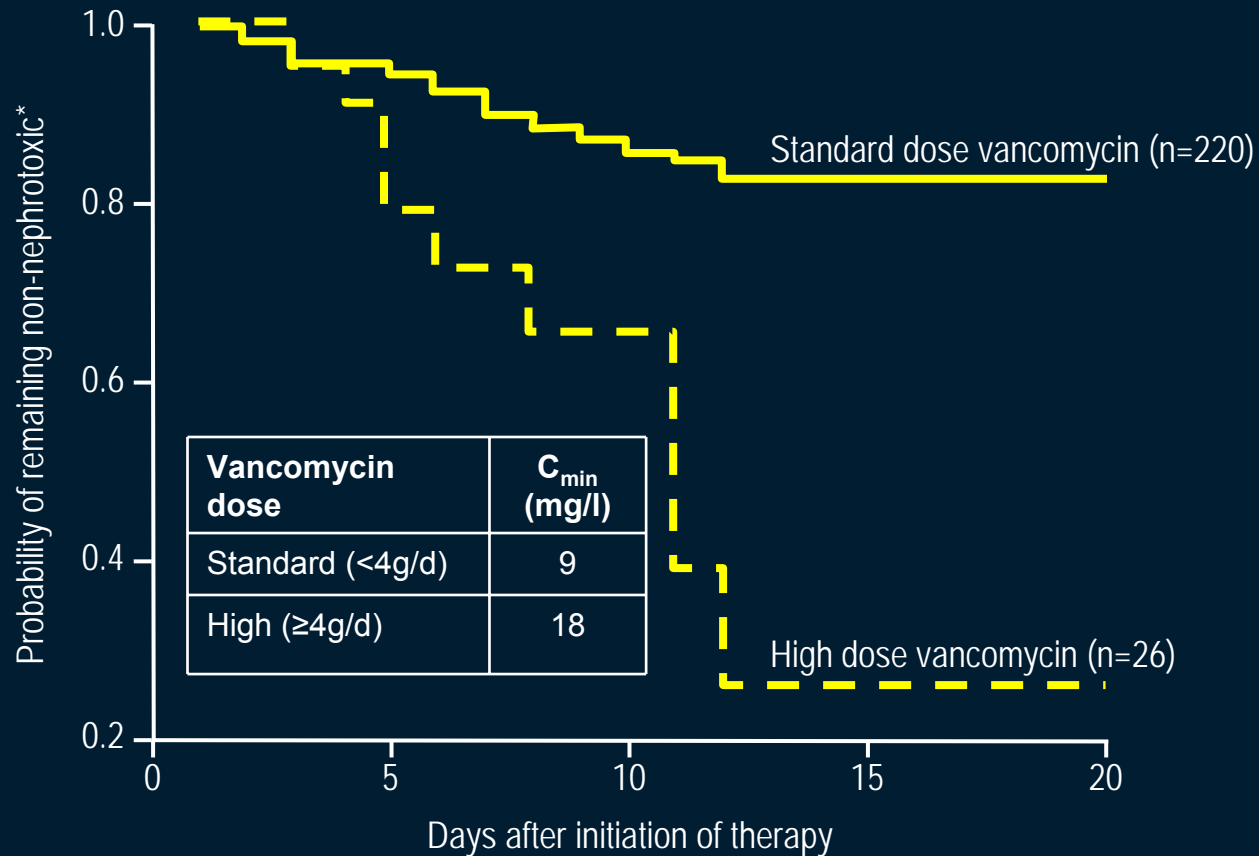


\*Inappropriate therapy defined as empirical therapy to which the MRSA strain was resistant

# In adults, what are the recommendations for vancomycin dosing?

- Vancomycin **15-20 mg/kg** (actual body weight) every 8-12 hours in patients with normal renal function is recommended (AIII).
- For seriously ill patients (sepsis, meningitis, pneumonia, or endocarditis) suspected to have MRSA, a **vancomycin loading dose of 25-30 mg/kg** (actual body weight) may be considered (CIII).

# Higher vancomycin doses associated with increased incidence of nephrotoxicity



\*Nephrotoxicity: increase in Cr  $\geq$ 0.5 mg/dl

# Marketed alternatives to vancomycin

	Daptomycin <sup>1</sup>	Linezolid <sup>2</sup>	Tigecycline <sup>1</sup>
First in class	✓	✓	✗
Spectrum: MRSA=MSSA	✓	✓	✓
VRE=VSE	✓	✓	✓
Gram-negative	✗	✗	✓
<i>B. fragilis</i>	✗	✗	✓
Cidality	+++	+/-	+/-
Dosing interval	OD	BID	BID
Formulations	i.v.	i.v./po	i.v.
Potential uses: Skin	✓	✓	✓
Pneumonia	✗	✓	(CAP*)
BSI	✓	✗	✗
Suitable for outpatient use	✓	✓	✗

\*United States only

1. Ziglam H. *Expert Opin Pharmacother* 2007;8:2279–2292

2. Vardakas KZ, et al. *Expert Opin Pharmacother* 2007;8:2381–2400



# What are the recommendations for managing MRSA bacteraemia and endocarditis?

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- Vancomycin or daptomycin 6 mg/kg i.v. once daily (AII)
- Some experts recommend daptomycin 8–10 mg/kg i.v. once daily (BIII)
- Doses of up to 12 mg/kg for 2 weeks safe in healthy volunteers
- Clinical trial underway to further evaluate safety and efficacy
- There are limited data regarding the use of daptomycin in children

# Daptomycin Development History

