Clinica delle Malattie Infettive e Tropicali
Università degli Studi dell'Insubria –
Ospedale di Circolo e Fondazione Macchi, Varese
"Second Opinion" Infettivologica
Centro Nazionale Trapianti, ISS, Roma

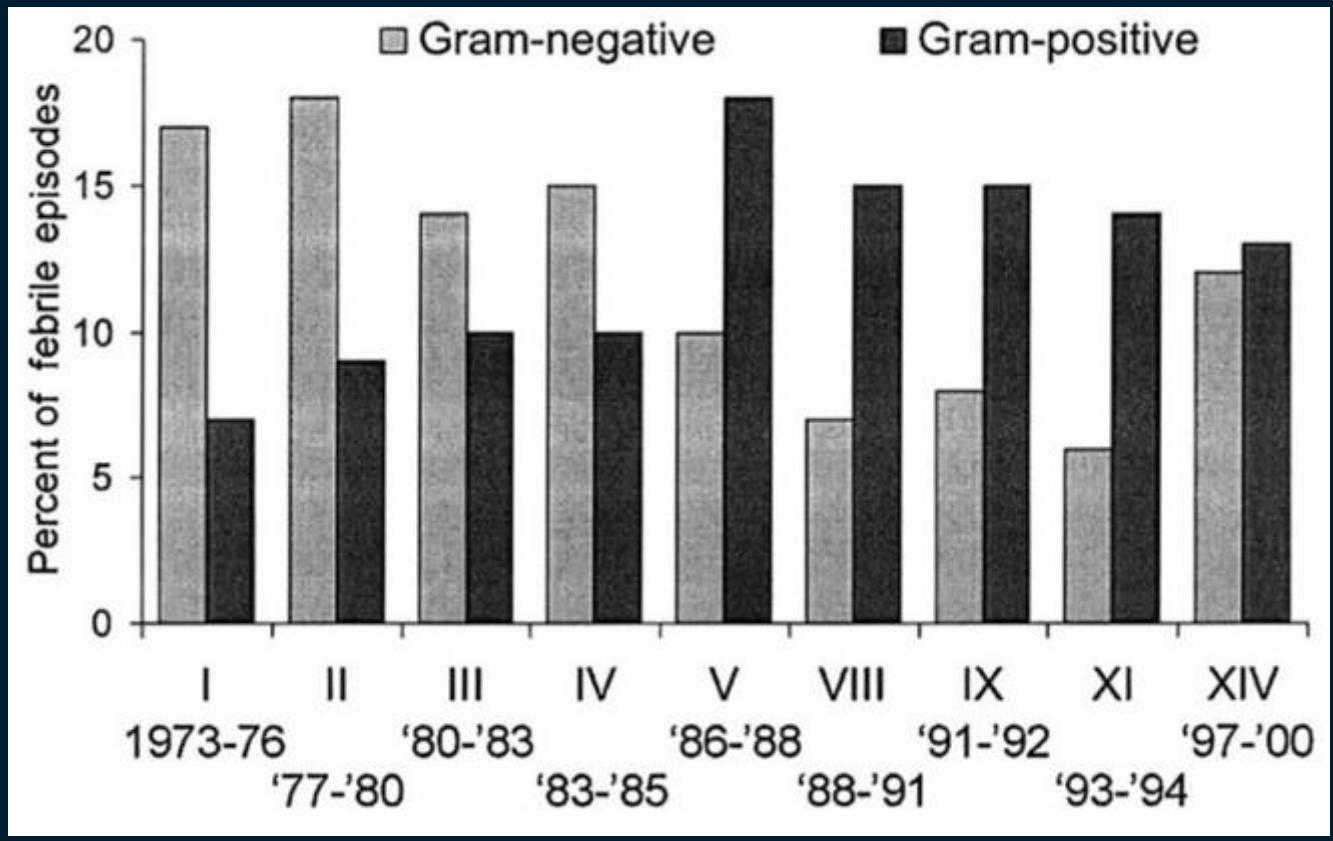
Daptomycin in Clinical Practice

Paolo Grossi

Turkish Febrile Neutropenia Congress
Ankara 25.02.2010

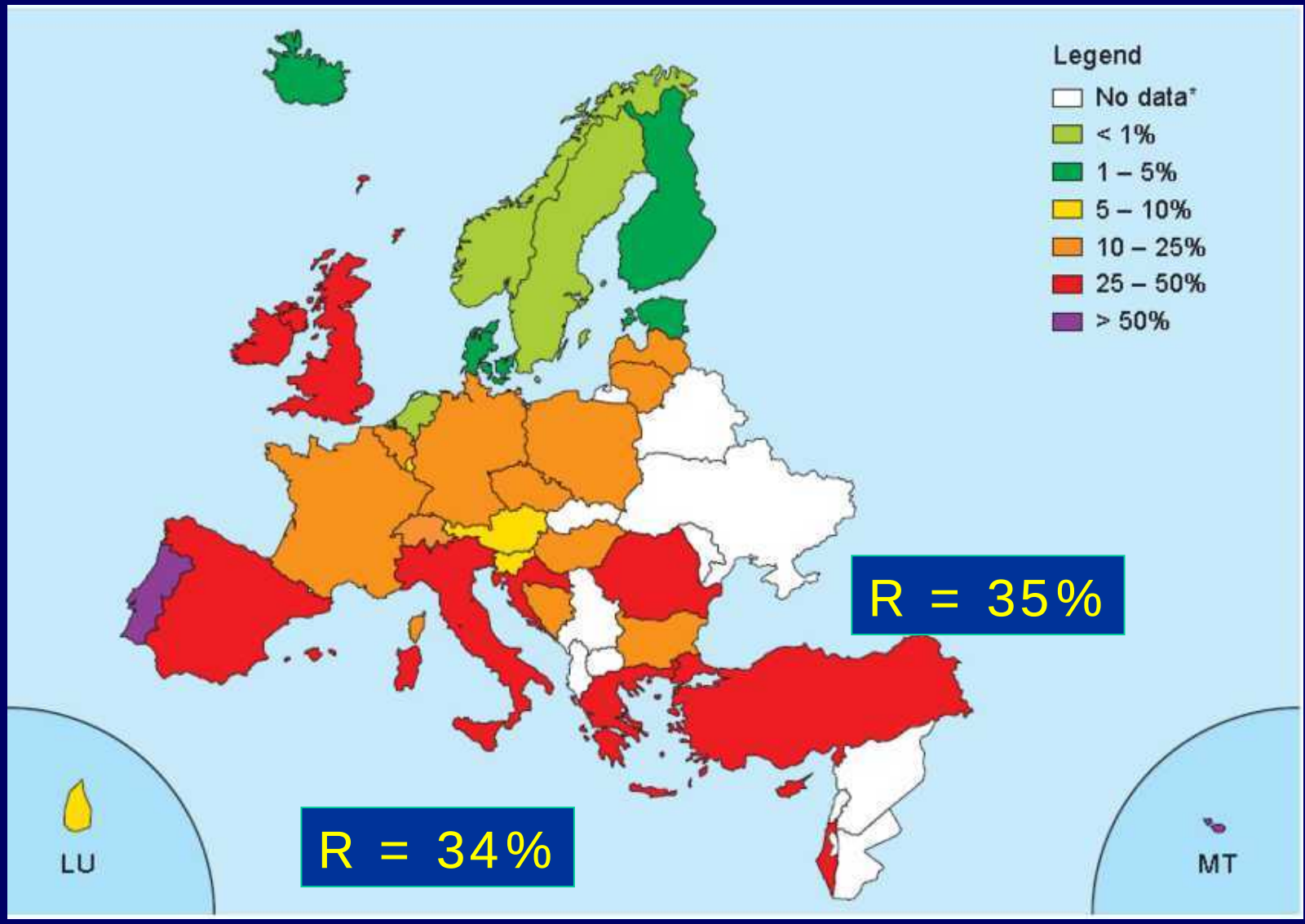
Shift from predominantly Gram-negative to predominantly Gram-positive pathogens

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



Viscoli C., et al. Clinical Infectious Diseases 2005; 40:S240-5

Staphylococcus aureus
Resistance to Oxacillin/Methicillin



EARSS Annual Report 2008

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)
Anti-MRSA not given first-line, %	**45**	**49**	**58**	**49**	**44**	**49**
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

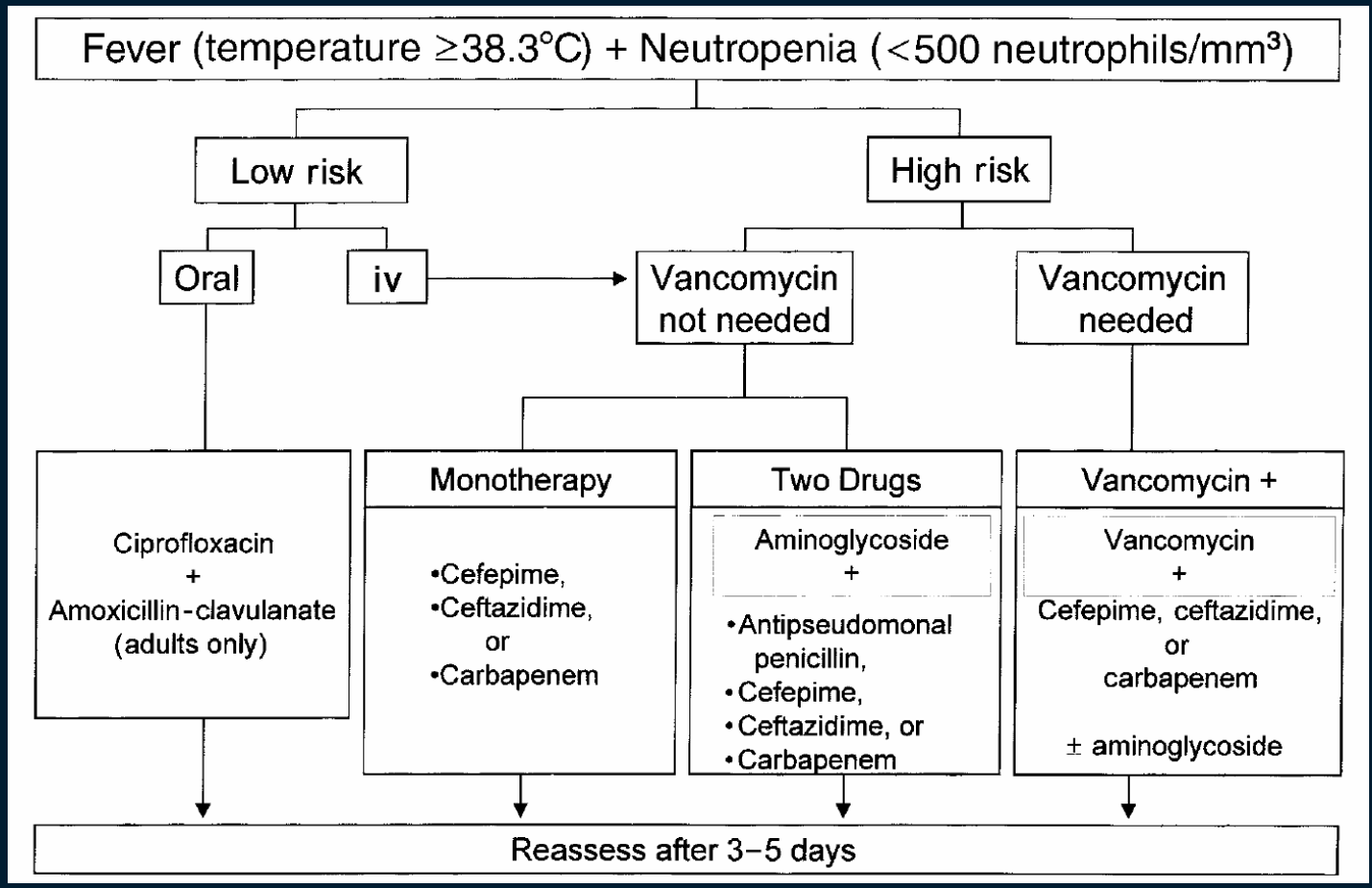
Approximately 50% of MRSA patients receive inadequate first-line therapy

Ammerlaan H et al. Clinical Infectious Diseases 2009; 49:997–1005

Glycopeptides in neutropenic patients

- 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



Hughes WT, et al. CID 2002;34:730-51

Initial empiric glycopeptide in neutropenic patients (IDSA 2002)

- 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)
- Insitutions 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

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 *S. pneumoniae*)	Recommended	III C
Severe sepsis and septic shock	Recommended	III C
Skin and soft tissue infections (including catheter-related infections)	Recommended	III C

Cometta A, et al. EJC 2007;S5:23–31

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[a]
S. aureus (methicillin-sensitive)[b]	Isoxazolylpenicillin (penicillinase-resistant penicillin)[c]	At least 2 weeks i.v.![d]
S. aureus (methicillin-resistant)[b]	Glycopeptide, linezolid, quinupristin + dalfopristin	At least 2 weeks i.v.![d]
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/dalfopristin in case of vancomycin-resistance	For 5–7 days after defervescence (in patients with persistent neutropenia)
Candida albicans[b]	Azole antifungal Alternative: amphotericin B lipid-based formulations or caspofungin	≥2 weeks
Nonalbicans *Candida* species[b]	Amphotericin B lipid-based formulations or caspofungin or voriconazole	≥2 weeks
All other pathogens	According to susceptibility pattern	Not defined

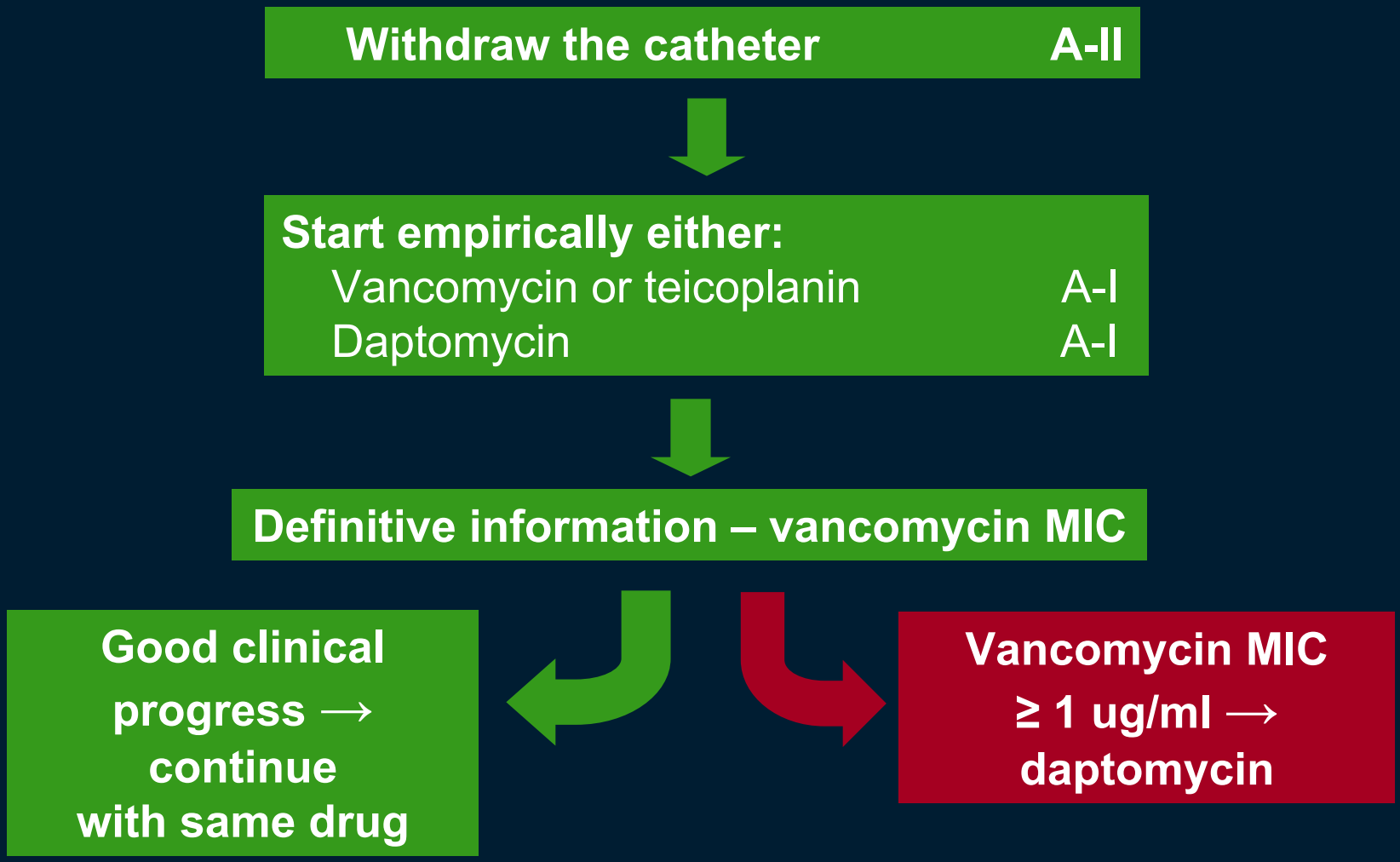
Hans-Heinrich Wolf, et al. Ann Hematol 2008;87:863–876

Linezolid: Pros and Cons

- 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



Gudiol F *et al.* *Enferm Infecc Microbiol Clin* 2009;27:105–115

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?

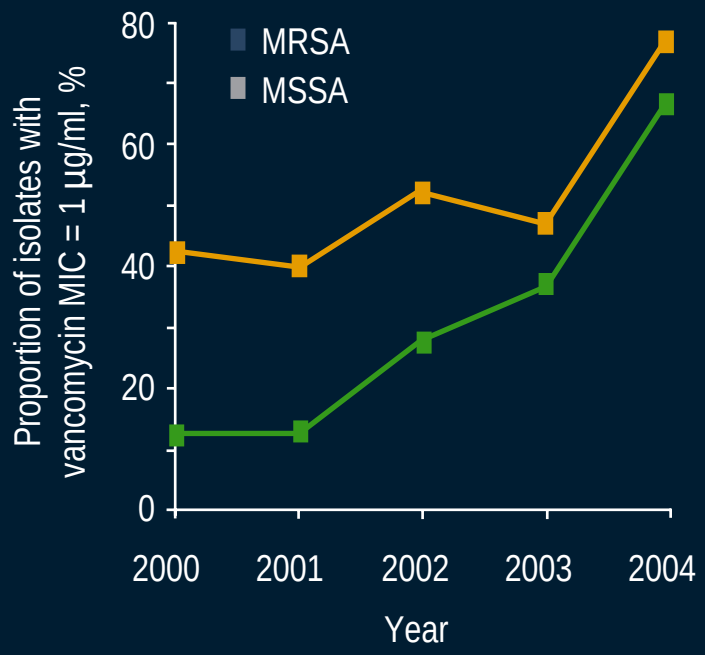
Recommendation	Strength or quality of recommendation
For uncomplicated Coagulase negative staphylococcal CRBSI, treat with Nafcillin or Oxacillin, 2 g q4h for 5–7 days if the catheter is removed and for 10–14 days, in combination with antibiotic lock therapy, if the catheter is retained	B-III
Vancomycin is recommended for empirical therapy in heath care settings with an elevated prevalence of MRSA/MRSE; for institutions in which the preponderance of MRSA isolates have **vancomycin minimum inhibitory concentration (MIC) values >2 µg/mL**, **alternative agents, such as daptomycin, should be used**	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:[1]
  - 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[2–7]

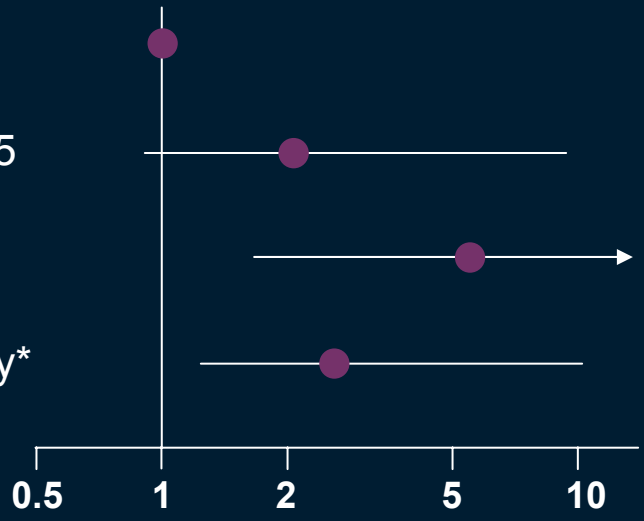
Increased vancomycin MICs for *S. aureus* over a 5-year period



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

Treatment group	Risk of mortality (OR [95% CI])	*P*-value
Vancomycin MIC=1		
Vancomycin MIC=1.5		
Vancomycin MIC=2		
Inappropriate therapy*		



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

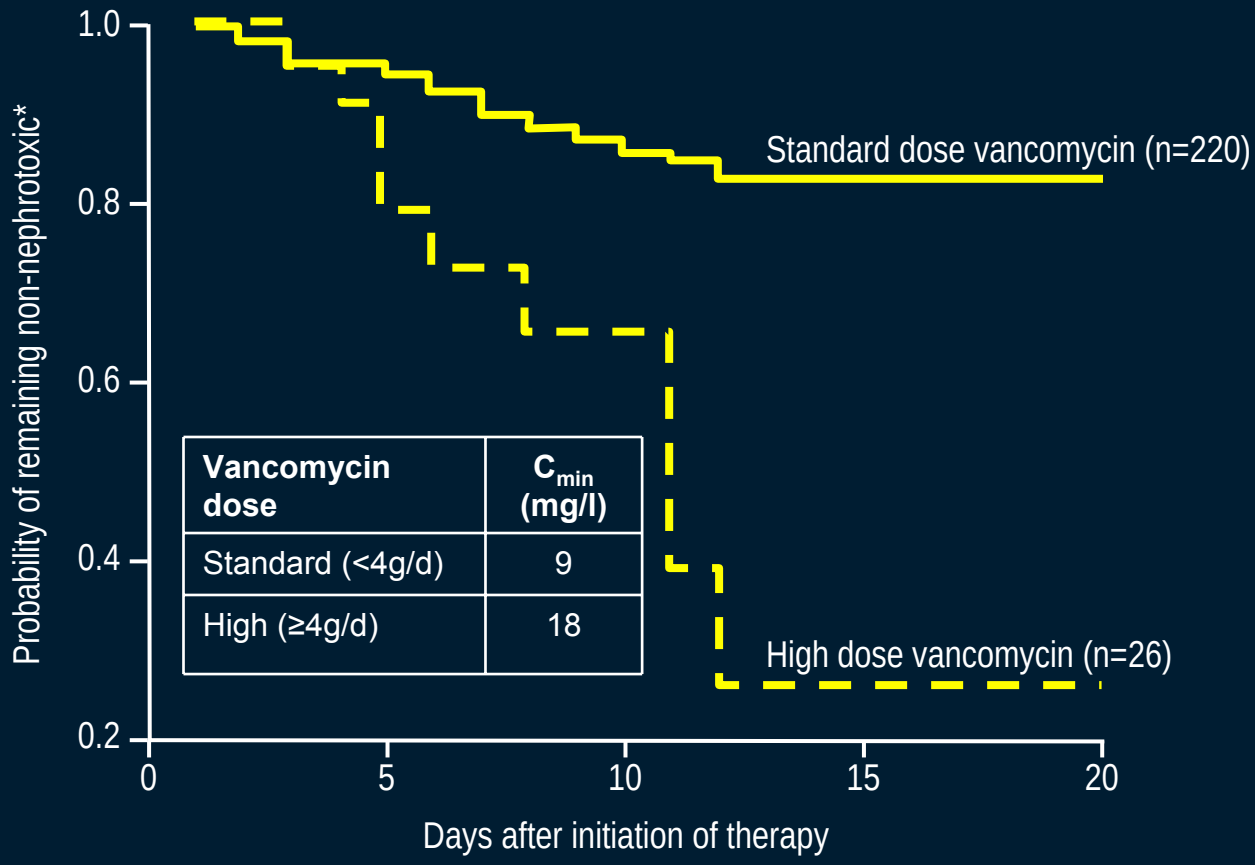
Soriano A *et al. Clin Infect Dis* 2008;46:193–200

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 ≥0.5 mg/dl

Lodise T *et al. Antimicrob Agents Chemother* 2008;52:1330–1336

Marketed alternatives to vancomycin

	Daptomycin[1]	Linezolid[2]	Tigecycline[1]
First in class	✓	✓	✖
Spectrum: MRSA=MSSA	✓	✓	✓
VRE=VSE	✓	✓	✓
Gram-negative	✖	✖	✓
B. fragilis	✖	✖	✓
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?

- 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

IDSA Draft Guidelines for the Treatment of MRSA

CUBIST

Daptomycin Development History