TREATMENT OPTIONS FOR MRSA INFECTIONS

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A European survey of antibiotic management of methicillin-resistant *Staphylococcus aureus* infection: current clinical opinion and practice

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Abstract

Although the epidemiology of methicillin-resistant *Staphylococcus aureus* (MRSA) varies across Europe, healthcare-associated MRSA infections are common in many countries. Despite several national guidelines, the approach to treatment of MRSA infections varies across the continent, and there are multiple areas of management uncertainty for which there is little clinical evidence to guide practice. A faculty, convened to explore some of these areas, devised a survey that was used to compare the perspectives of infection specialists from across Europe on the management of MRSA infections with those of the faculty specialists. The survey instrument, a web-based questionnaire, was sent to 3840 registered delegates of the 19th European Congress of Clinical Microbiology and Infectious Diseases, held in April 2009. Of the 501 (13%) respondents to the survey, 84% were infection/microbiology specialists and 80% were from Europe. This article reports the survey results from European respondents, and shows a broad range of opinion and practice on a variety of issues pertaining to the management of minor and serious MRSA infections, such as pneumonia, bacteraemia, and skin and soft tissue infections. The issues include changing epidemiology, when and when not to treat, choice of treatment, and duration and route of treatment. The survey identified areas where practice can be improved and where further research is needed, and also identified areas of pan-European consensus of opinion that could be applied to European guidelines for the management of MRSA infection.

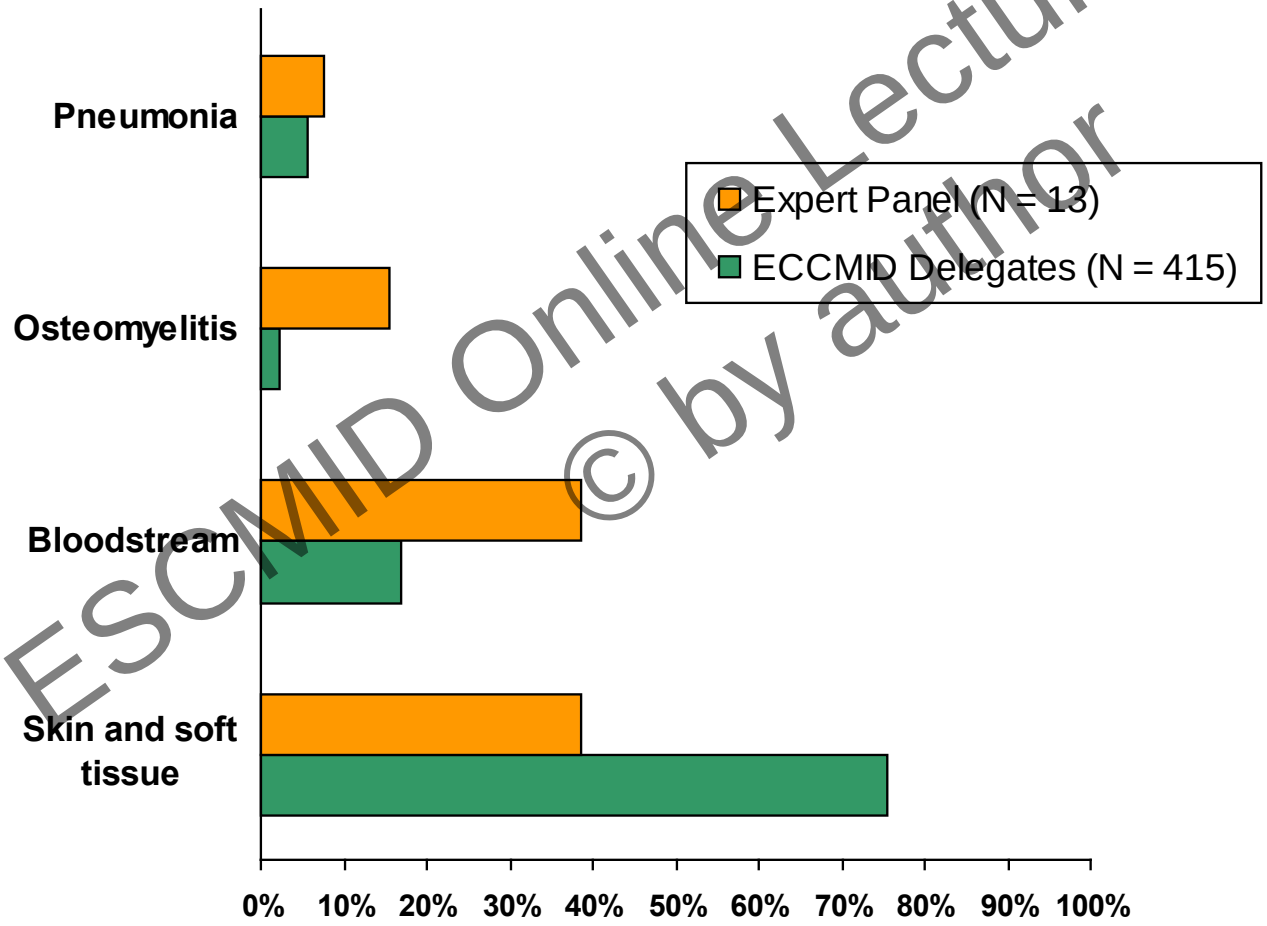
Keywords: antibiotic management, bacteraemia, healthcare-associated pneumonia, Methicillin-resistant *Staphylococcus aureus*, skin and soft tissue infection

Clin Microbiol Infect 2010; **16** (Suppl. 1), 3–30

Managing MRSA Infection in Europe – Opinions and Practice An Interactive Workshop

ECCMID, Helsinki
18 May, 2009

Which is the most frequent infection caused by MRSA in your practice?



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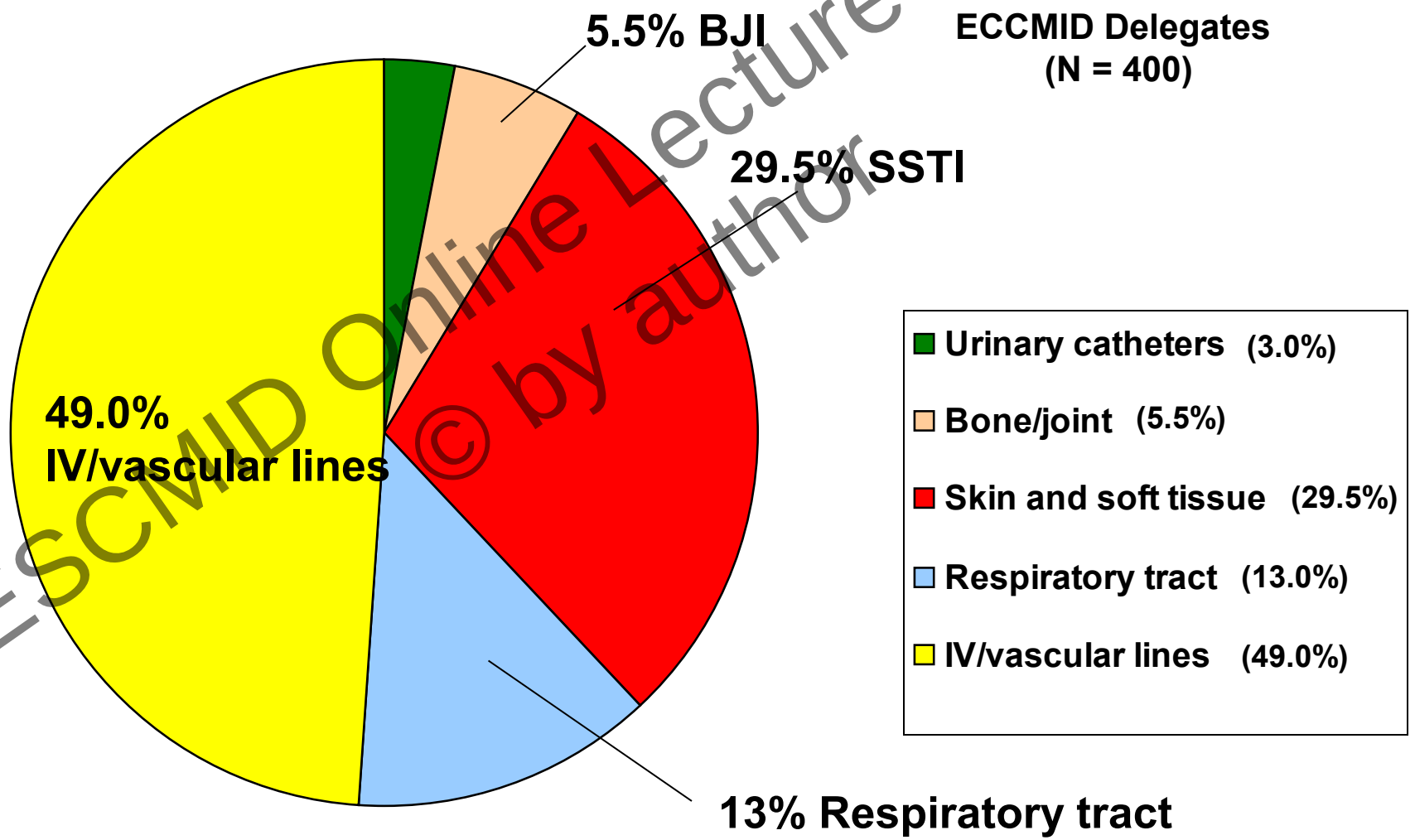
Which is the Most Common Focus of MRSA Bloodstream Infections in Your Practice?



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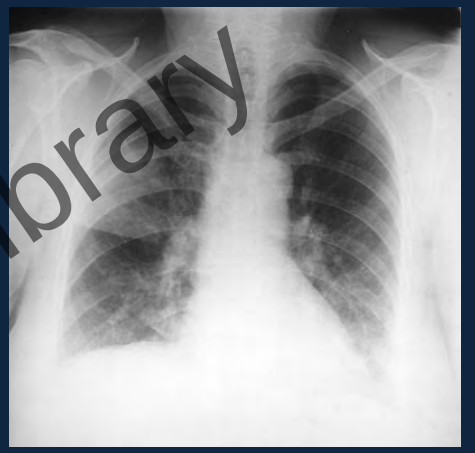
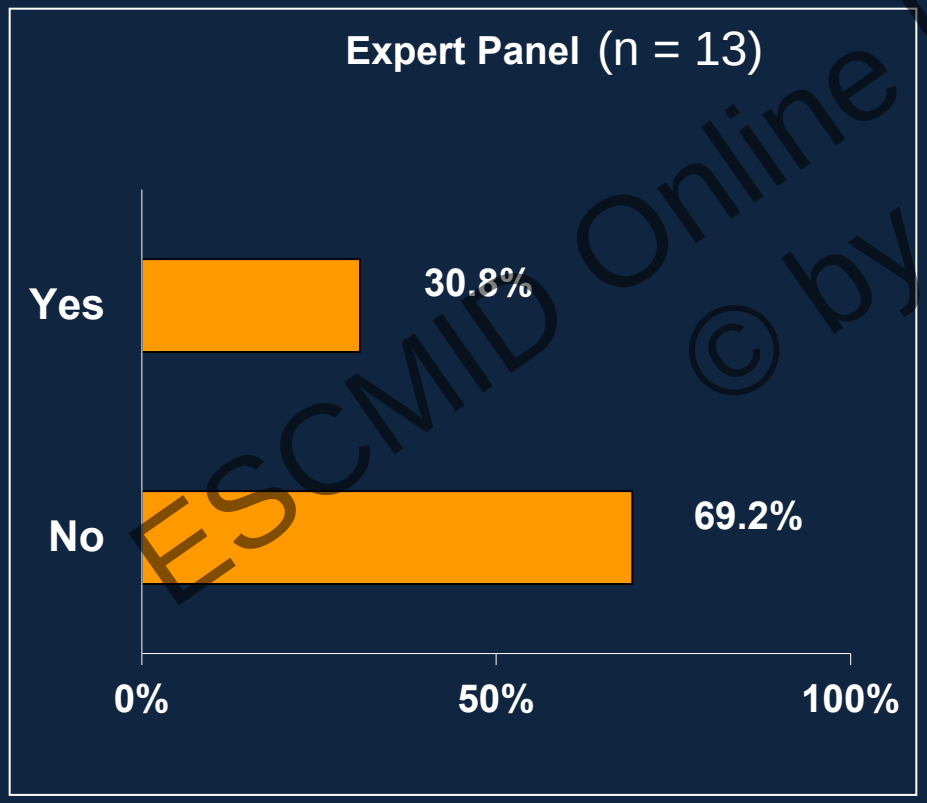
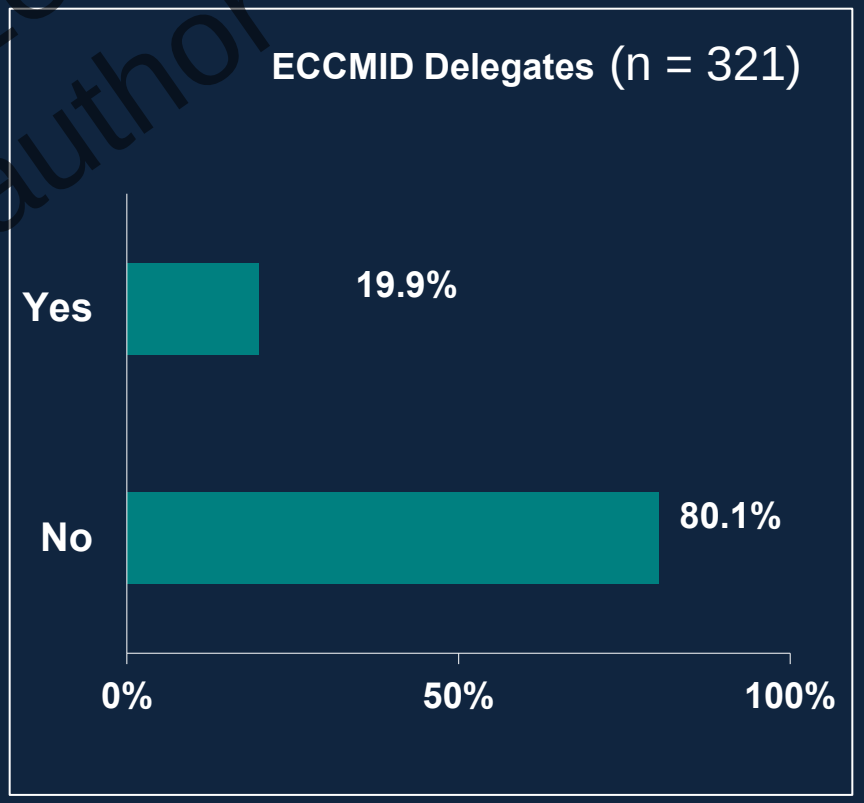
Should All Patients With a Clinical Suspicion of HCAP/HAP/VAP Be Treated With an Antimicrobial Agent Active Against MRSA?







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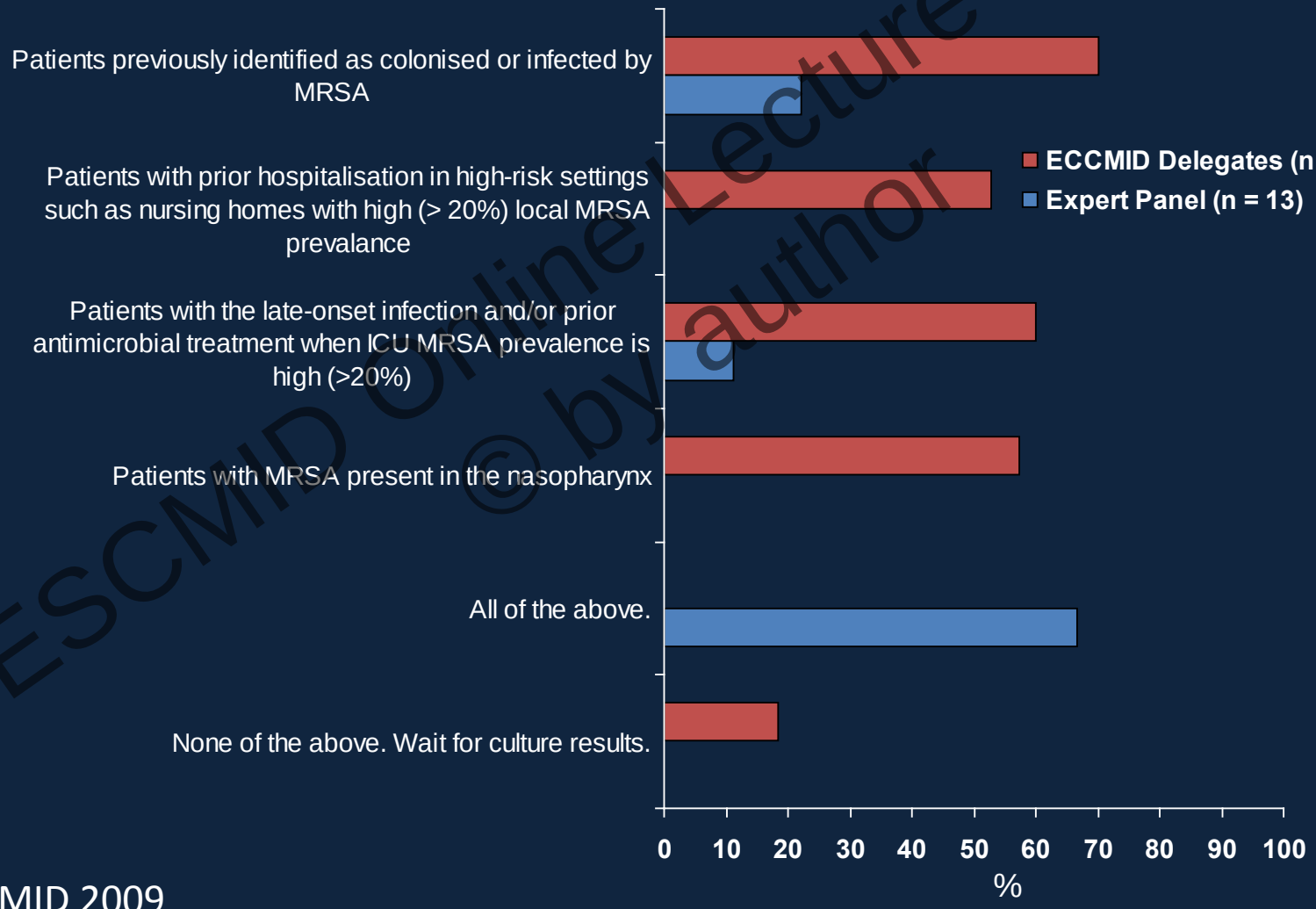
If the Answer to the Previous Question is NO, Then Which Categories of Patients With a Clinical Suspicion of HCAP/HAP/VAP Should Be Treated With an Antimicrobial Agent Active Against MRSA? (choose all that apply)



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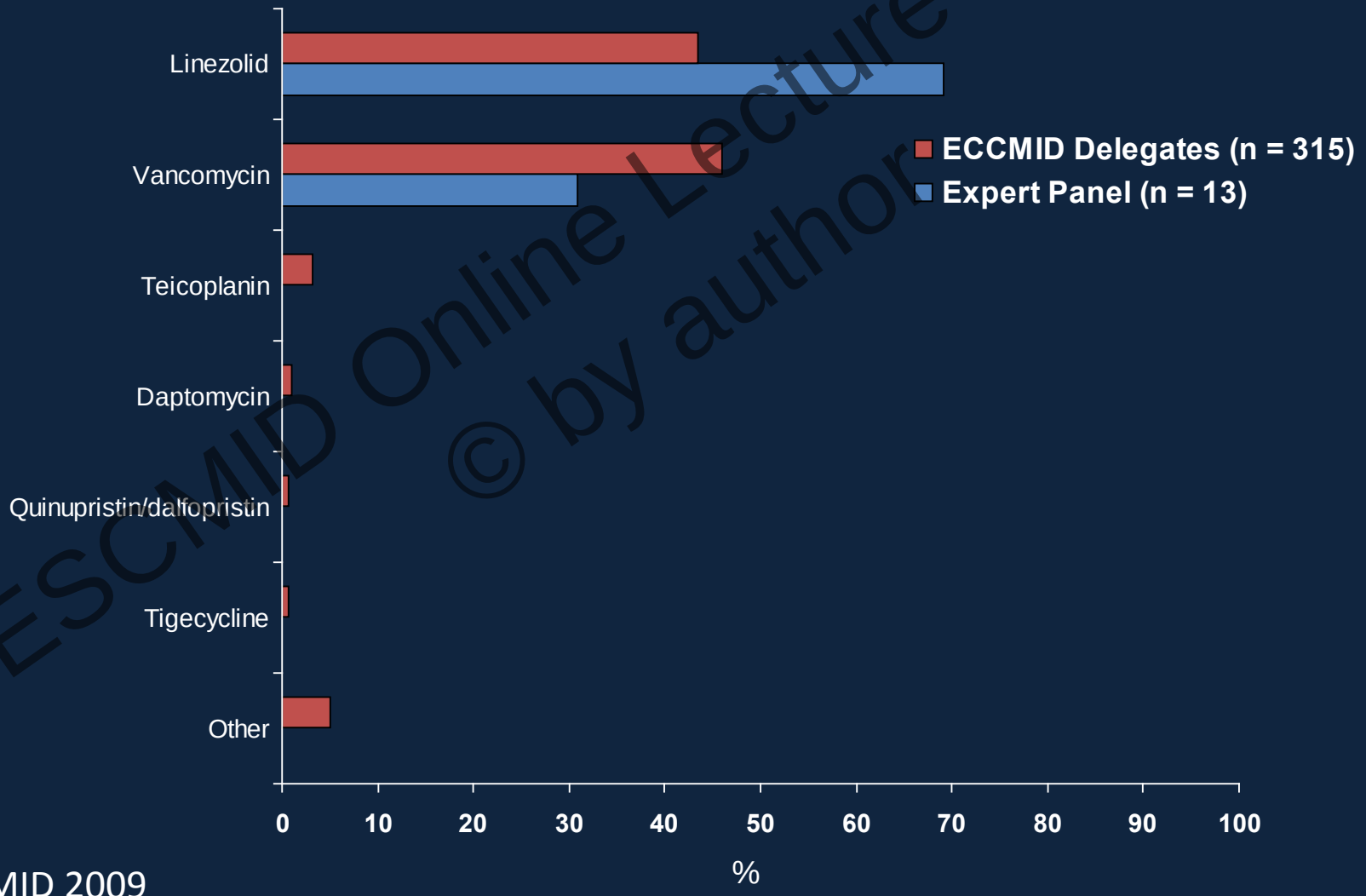
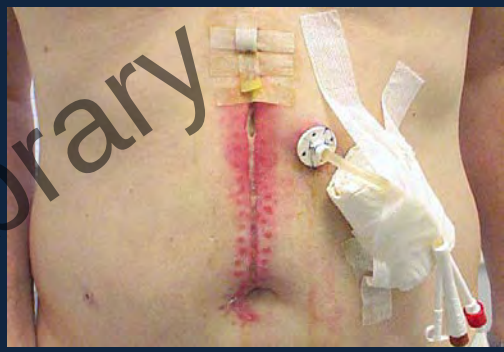
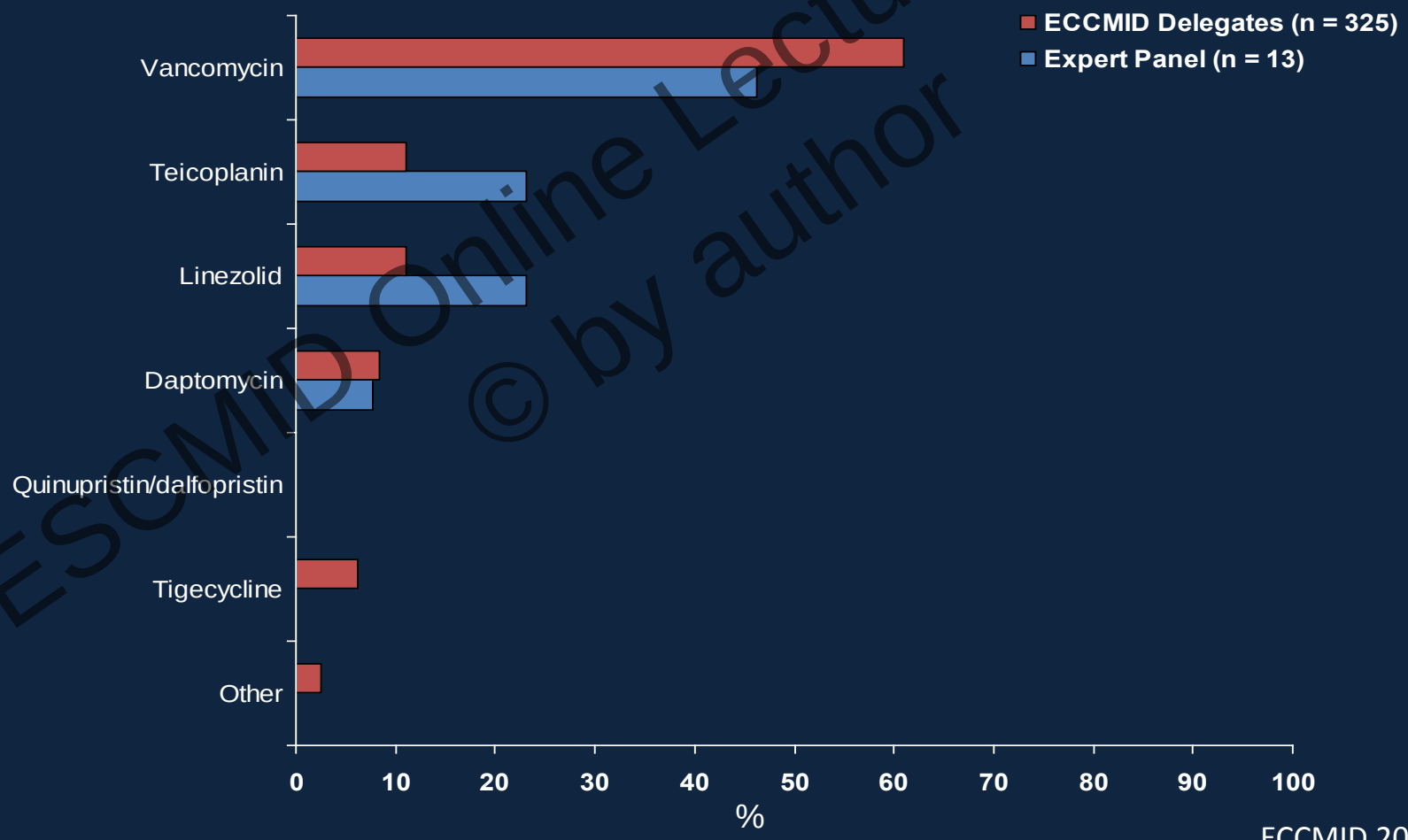
When MRSA Pneumonia (HCAP/HAP/VAP) is Confirmed, What Do You Regard as the Most Appropriate Treatment Regimen?



For a cSSTI Caused by MRSA, What Would Be Your Initial IV Treatment?





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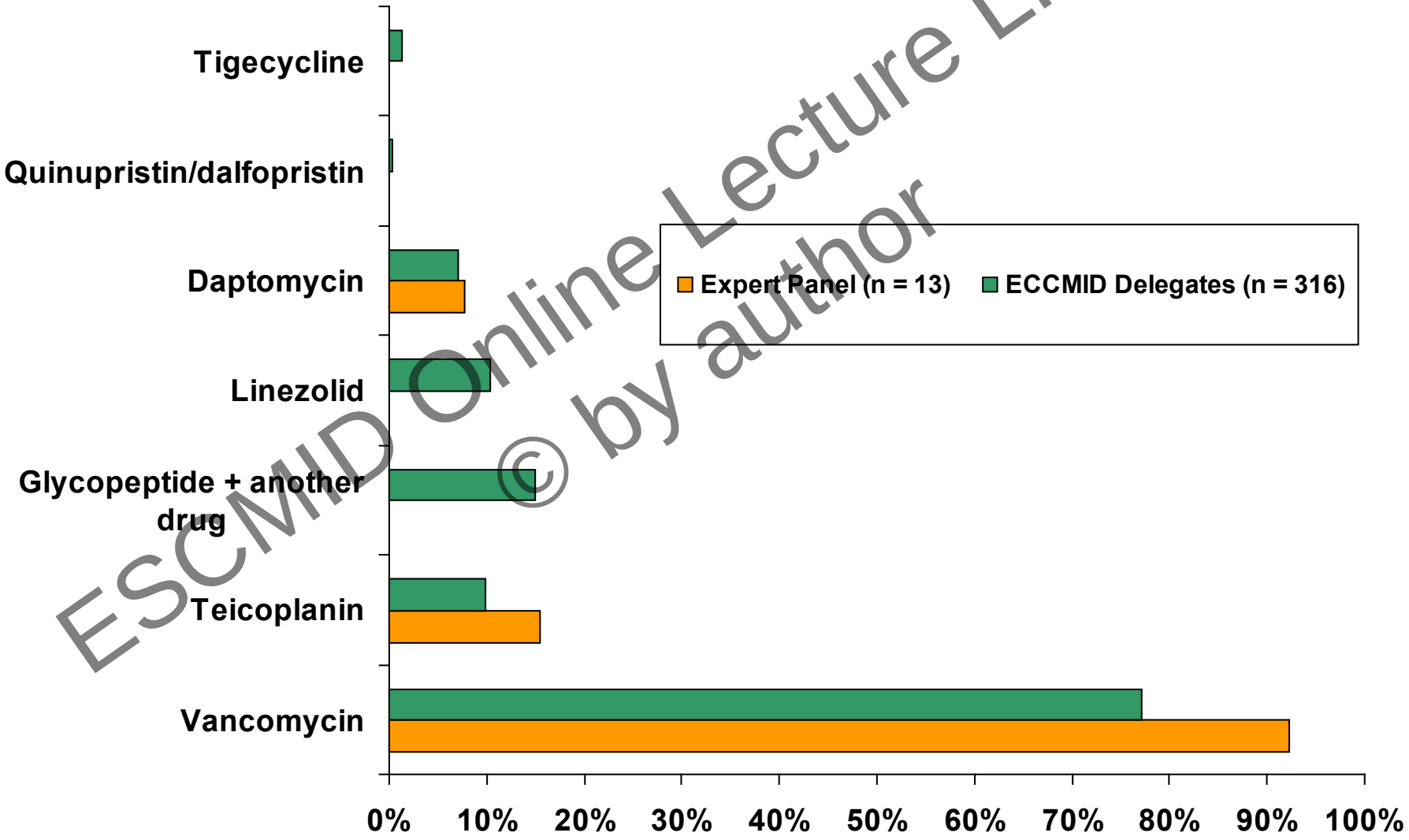
For a Confirmed MRSA Bacteraemia, What is Your First-Line Treatment?

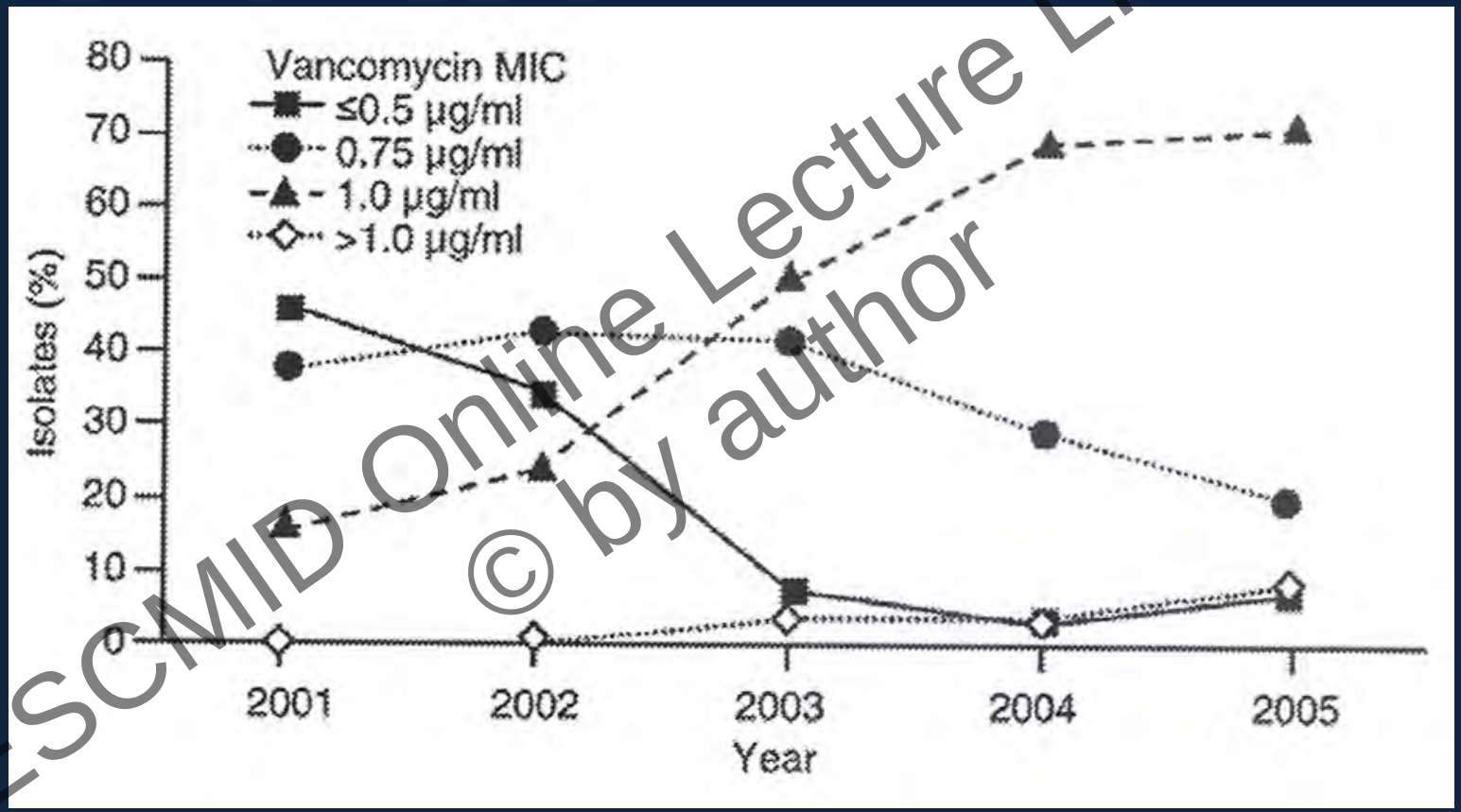


Vancomycin

- Vancomycin is the standard of care for treating MRSA[1]
- Limitations[1,2]
  - Slow bactericidal activity
  - Inconsistencies in tissue distribution based on the degree of tissue inflammation
  - Variable tissue penetration
  - Toxicity
  - Complicated dosing and blood level monitoring required
    - Recommend vancomycin trough levels
      - CNS infection: 15-20 mg/L
      - MRSA bacteraemia and endocarditis: 10-15 mg/L
      - MRSA pneumonia: 15-20 mg/L
  - MIC creep

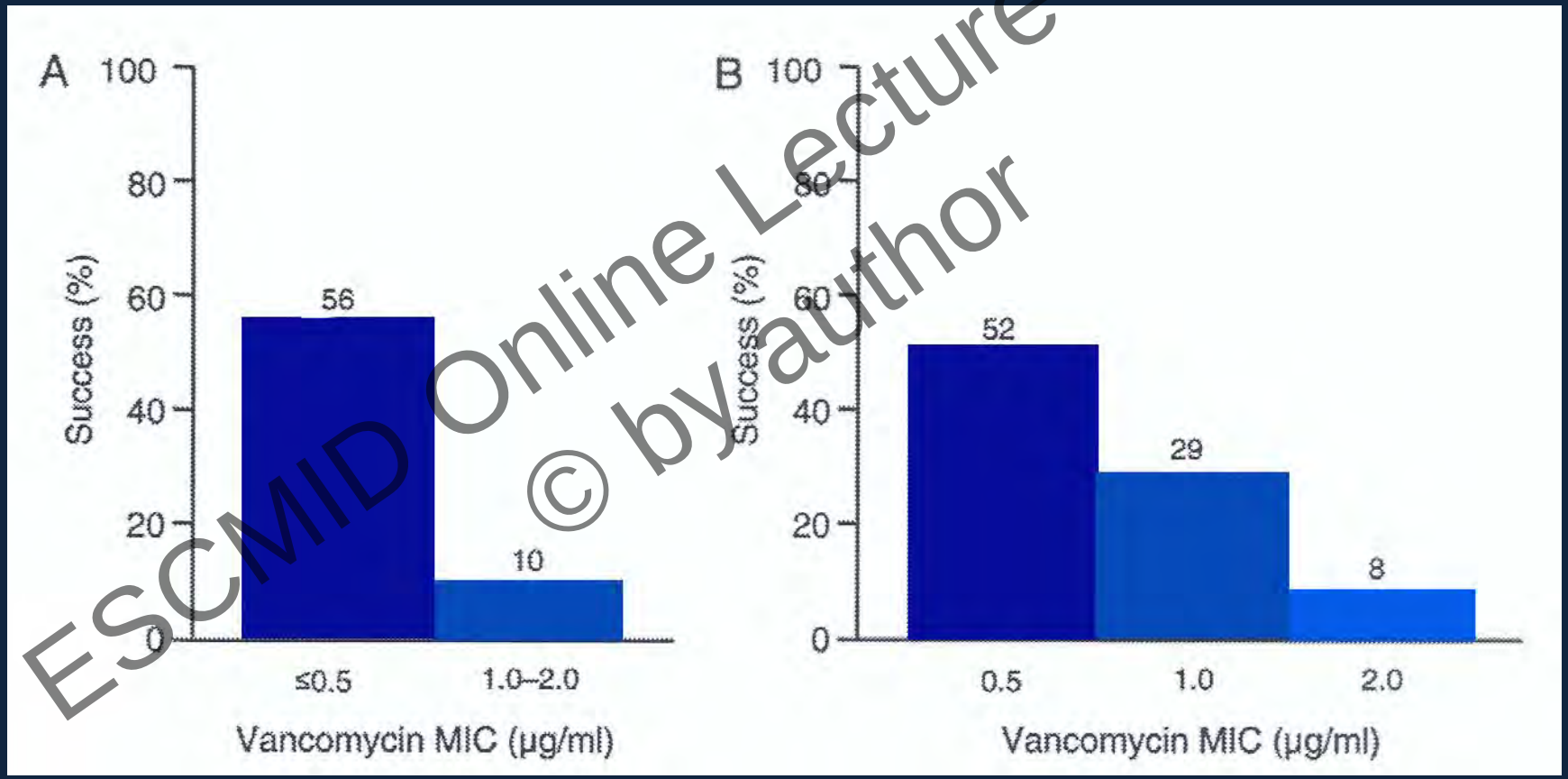
1. Sakoulas G, et al. *J Clin Microbiol*. 2004;42:2398-2402. 2. Rybak M. *Clin Infect Dis*. 2006;42:S35-S39.

Vancomycin "MIC creep"



I. Gould et al. Int J Antimicrob Agents 2008;31:1-9.

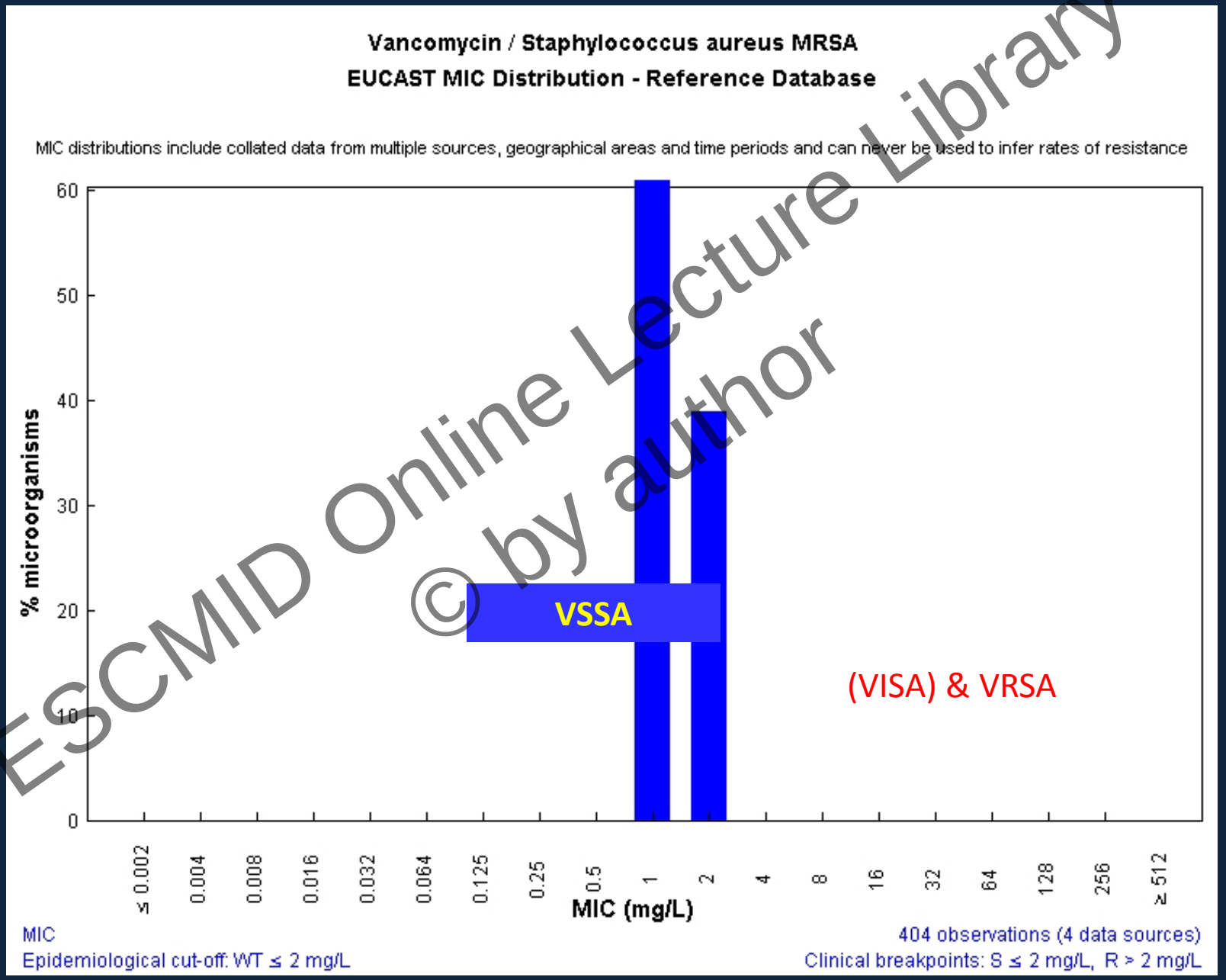
Vancomycin: Minimal inhibitory concentrations (MICs) and clinical success



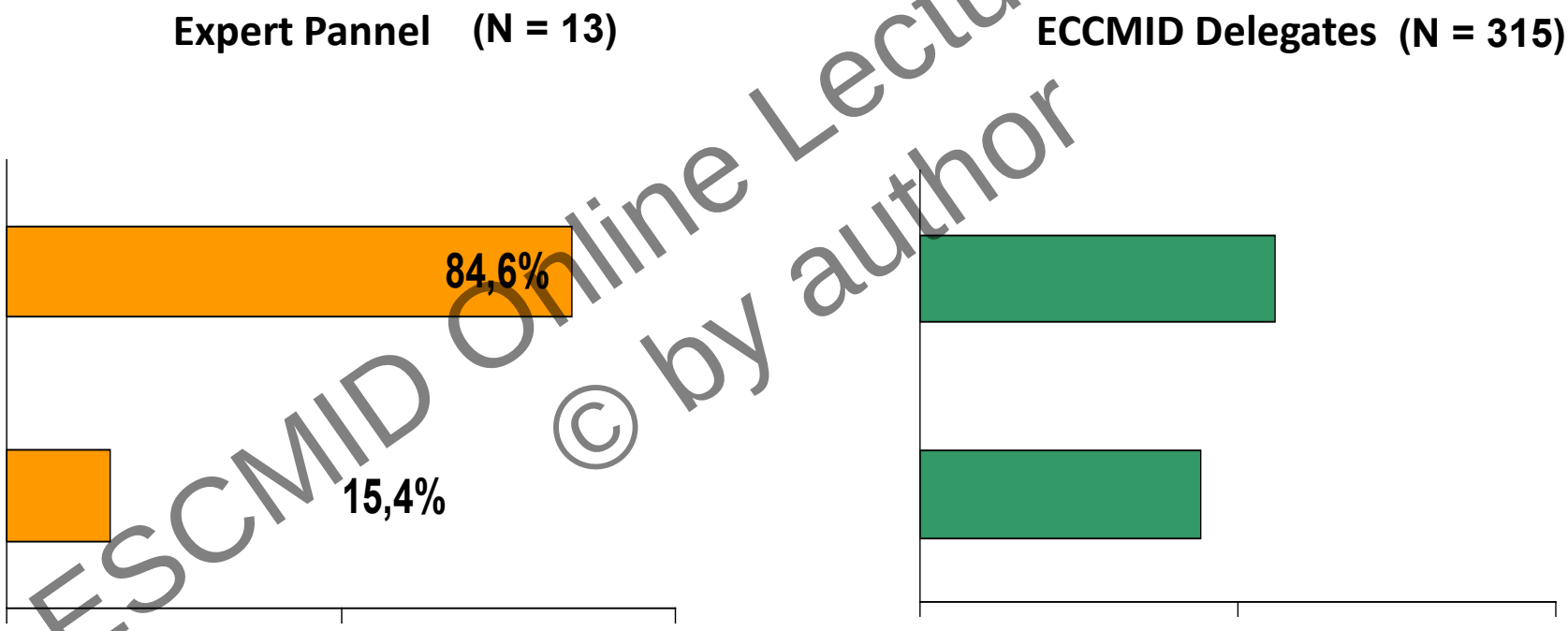
I. Gould et al. Int J Antimicrob Agents 2008;31:1-9.

Vancomycin Break-Point Concentrations

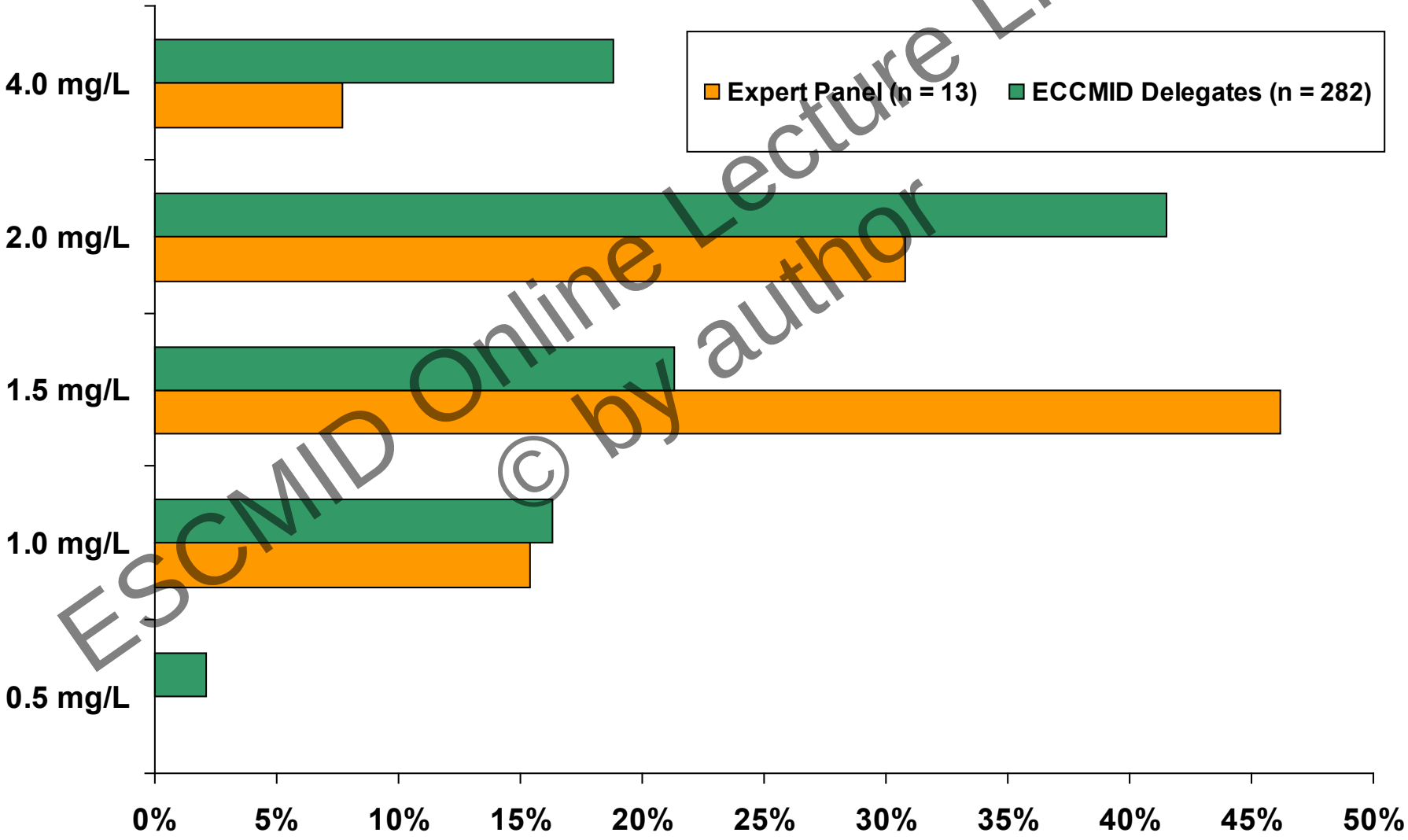
	Vancomycin (mg/L)					
	1	2	4	8	16	32
CLSI, (old)	VSSA			VISA		VRSA
CLSI, 2006	VSSA		VISA		VRSA	
EUCAST	VSSA		VRSA			



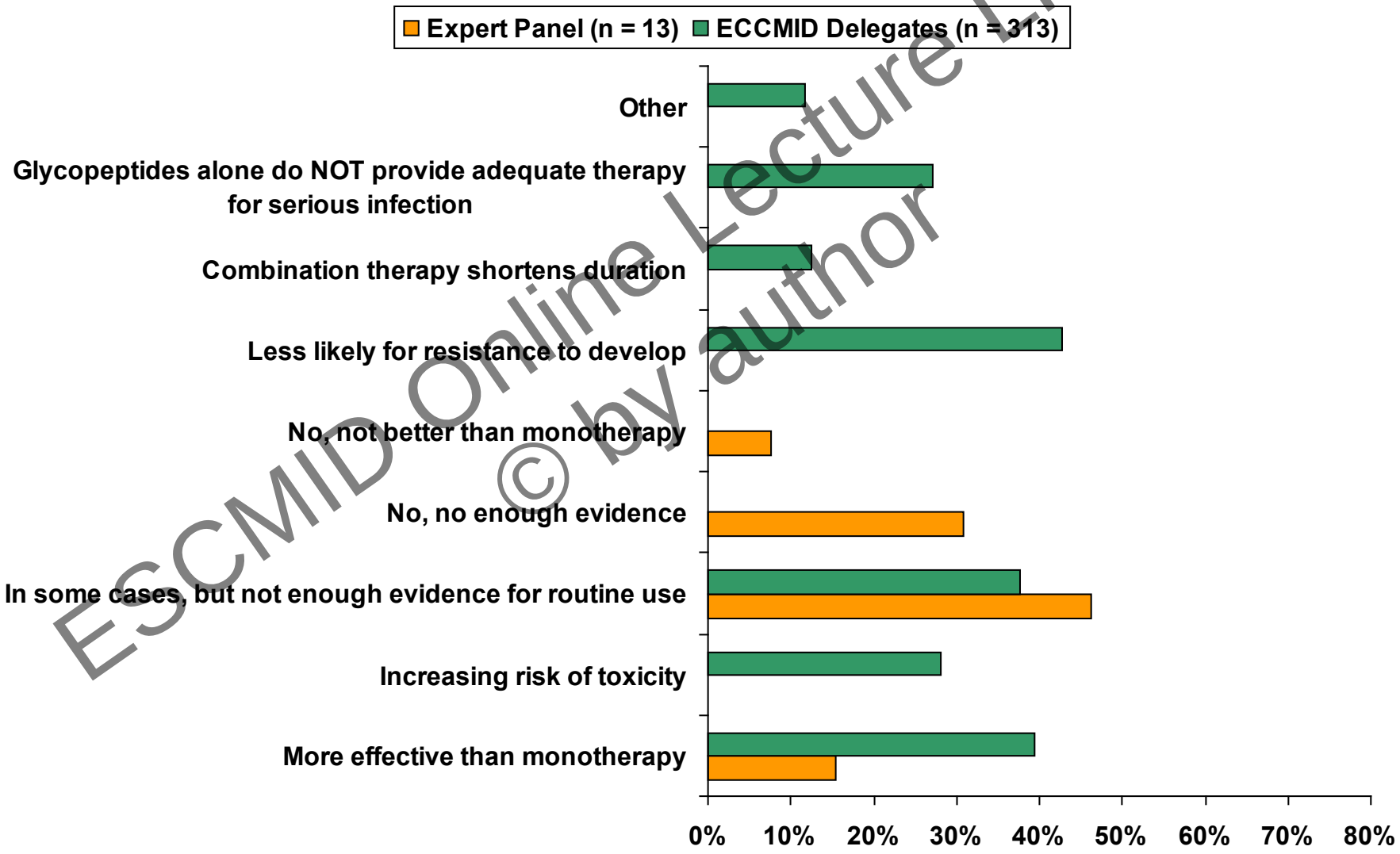
Do You Use the Glycopeptide MIC Routinely to Guide Your Choice of Treatment?



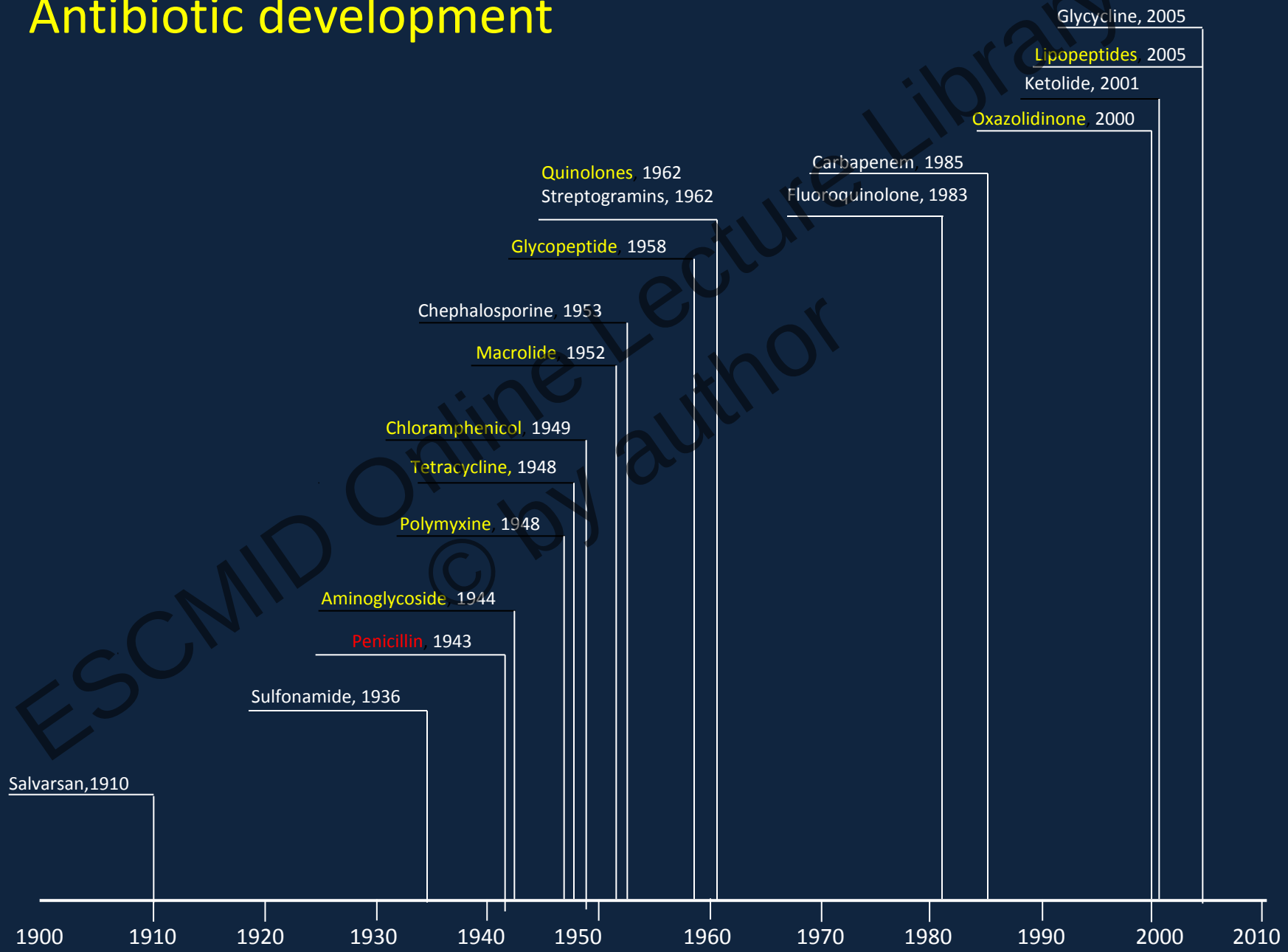
At which Vancomycin MIC Level for MRSA (by E Test) Would You Replace Vancomycin With An Alternative Antibiotic?



In Your Opinion, How Does Combination Therapy Compare with Monotherapy to Treat Serious MRSA Infection? (choose all that apply)



Antibiotic development



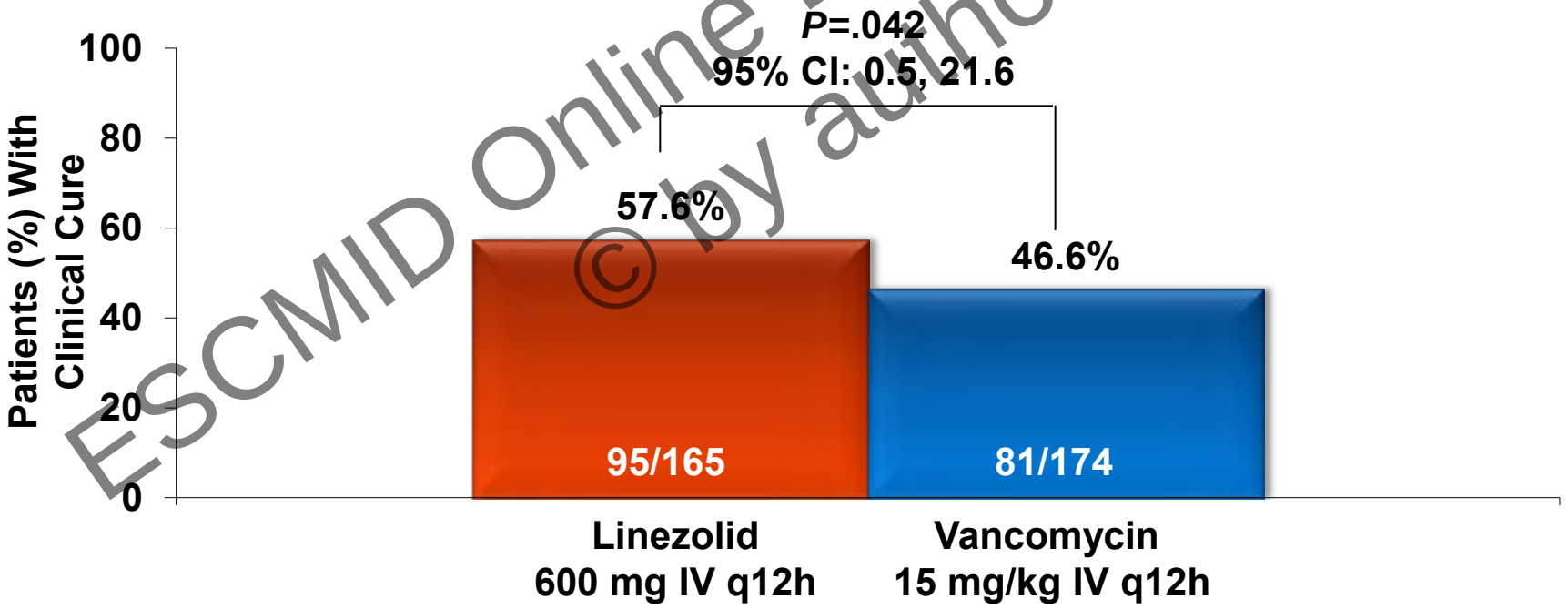
Linezolid

- Oxazolidinone (inhibitor of bacterial protein synthesis)
- Spectrum: G+ bacteria including MRSA, VRE
- Linezolid resistance rare in MSSA and MRSA
- Excellent oral bioavailability
- EMEA approved for the treatment of
  - Complicated SSTIs due to MRSA
  - Nosocomial pneumonia

ZEPHyR study

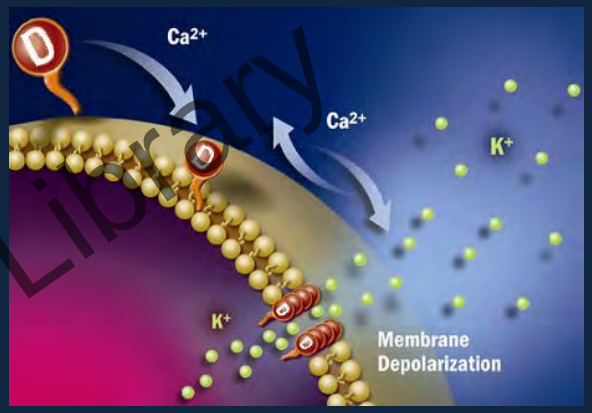
linezolid *vs* **vancomycin** in the treatment of nosocomial pneumonia caused by MRSA

- a double-blind, randomized, non-inferiority with a nested superiority hypothesis study, n=1225, n=448 culture +MRSA, n=348 evaluable EOS
- superiority of linezolid in primary end point: clinical success rate



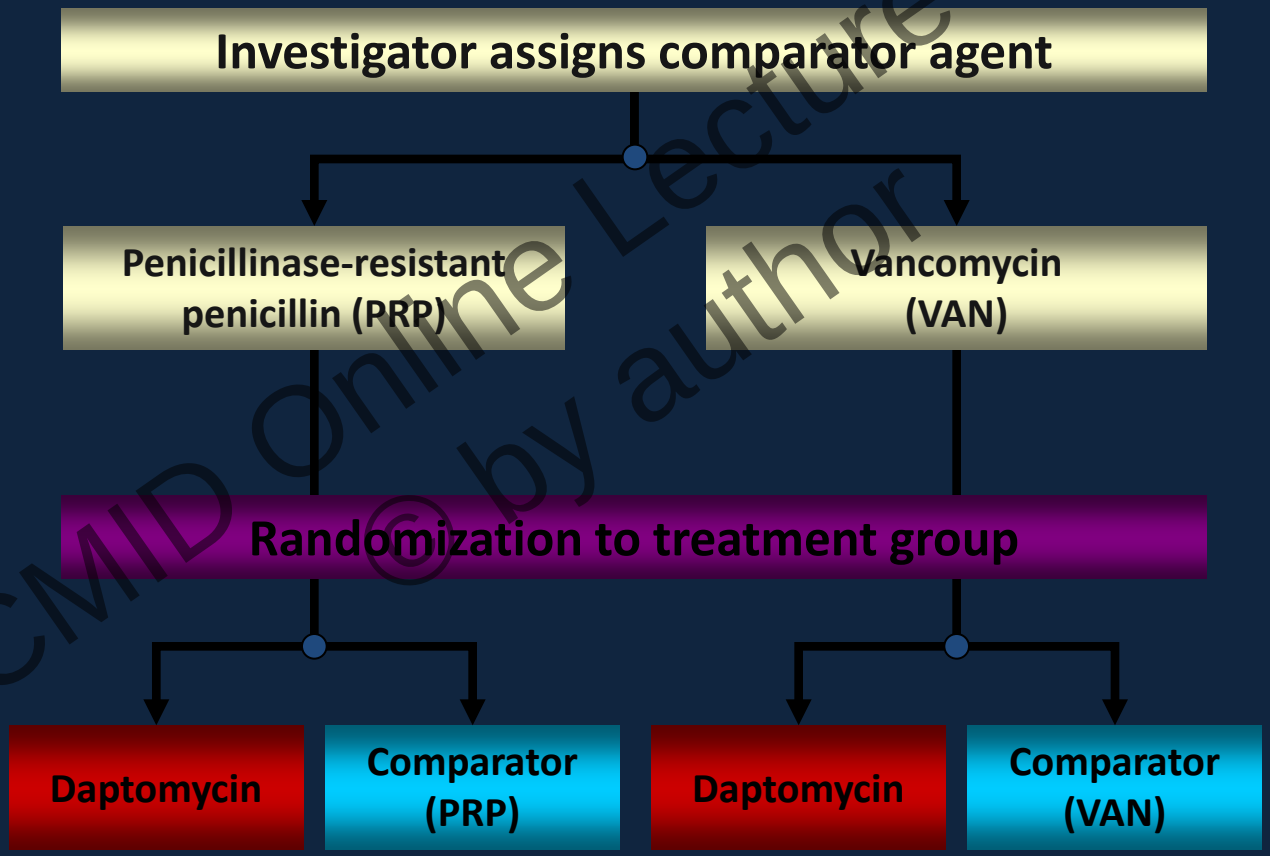
Wunderink et al. Clinical Infectious Diseases 2012;54(5):621–9

Daptomycin



- Unique mechanism of action
  - Disruption of bacterial membrane potential (G+ bacteria)
  - Bactericidal effect
  - No cross resistance with other antibiotic classes
- Revival of an old drug: PK/PD→ less side effects with 1x daily dosing
- Clinical indications
  - Complicated skin & soft tissue infections (cSSTI)
  - Right-sided endocarditis
  - Bacteraemia related to cSSTI and endocarditis
  - NOT suitable for pneumonia

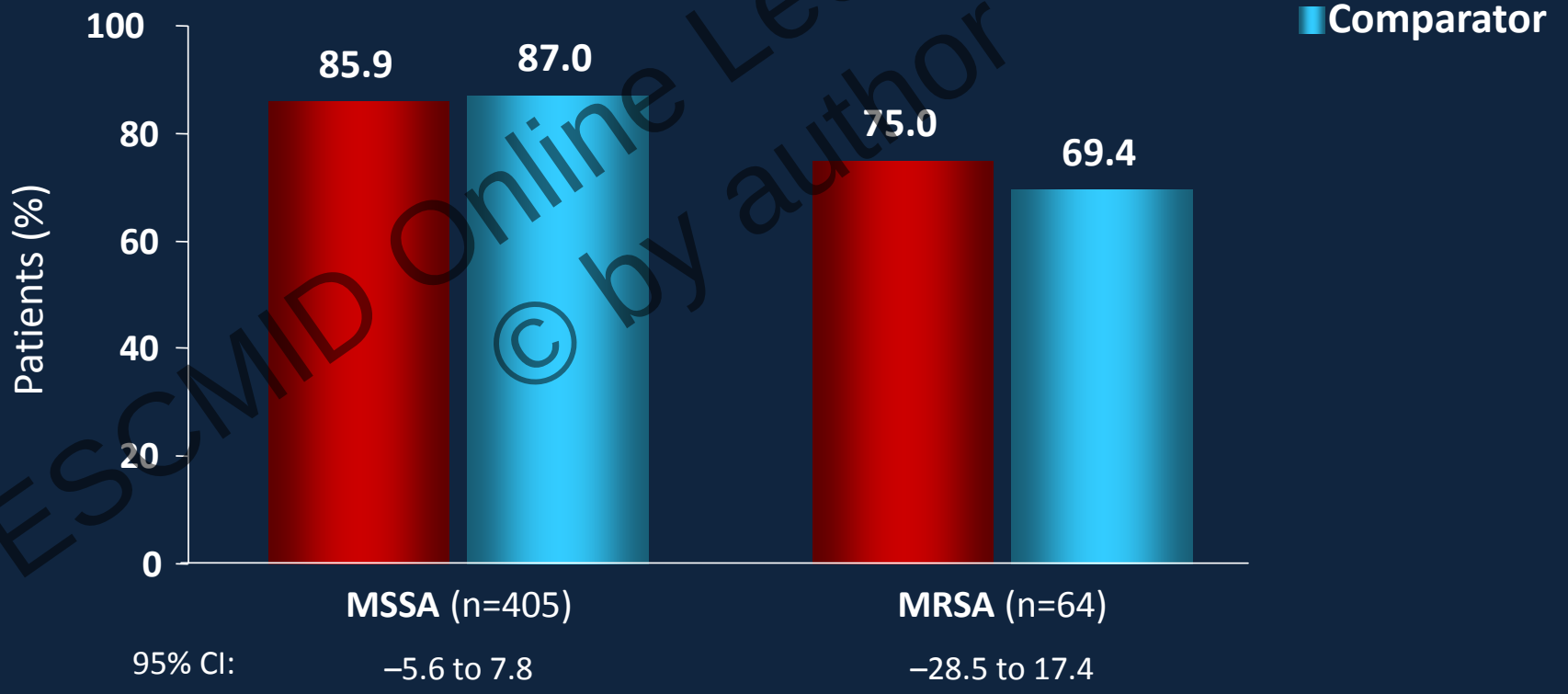
Phase III clinical trials of daptomycin in cSSTIs: study design



Arbeit *et al. Clin Infect Dis* 2004;38:1673–1681

Phase III clinical trials of daptomycin in cSSTIs

Clinical success* in *S. aureus* infected patients: ME population



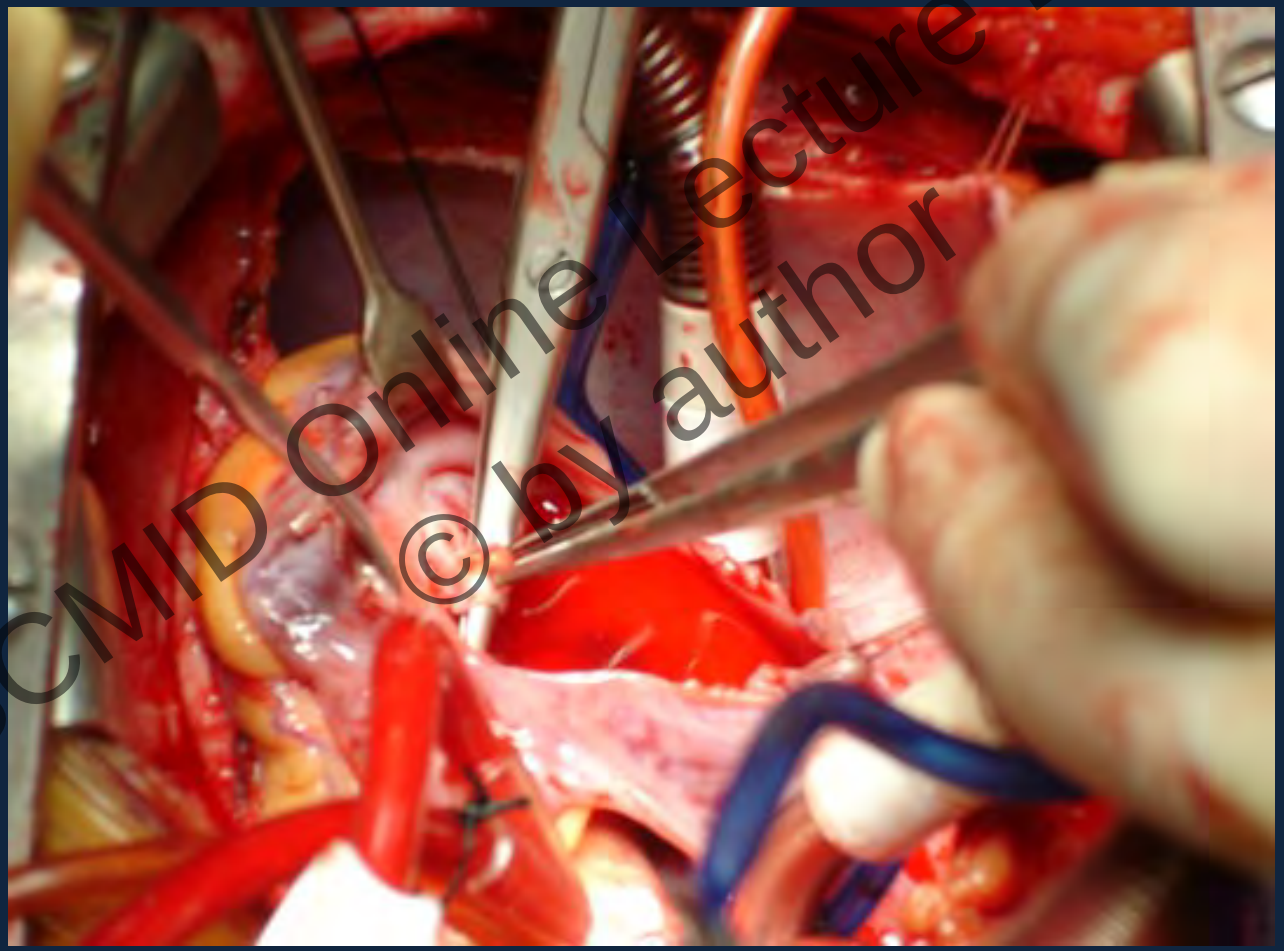
*Cure or improvement sufficient to stop antibiotic treatment

ME, microbiologically evaluable

Arbeit *et al. Clin Infect Dis* 2004;38:1673–1681

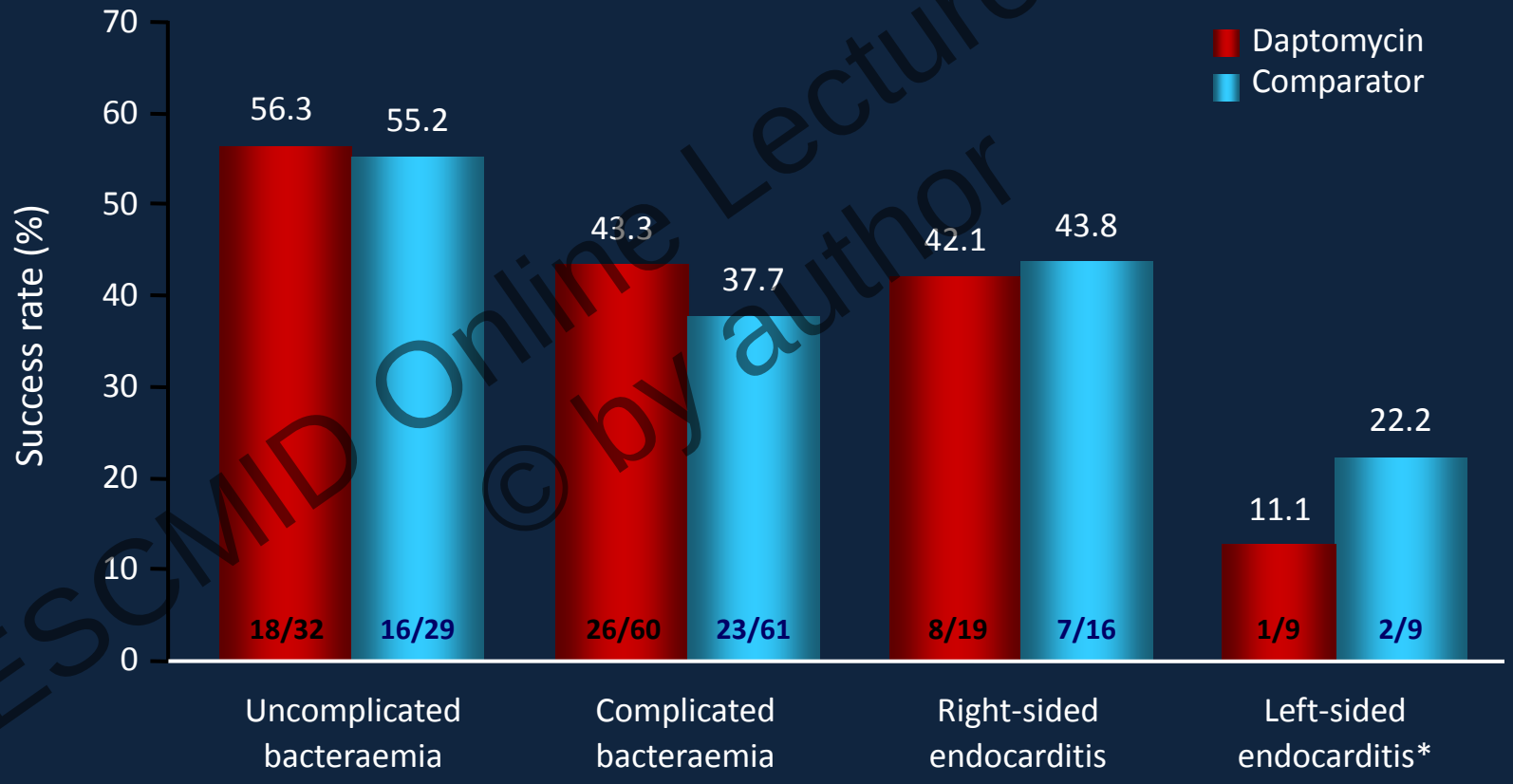
endocarditis

daptomycin: **6 mg/kg**; 1x daily



Phase III *S. aureus* bacteraemia and infective endocarditis study:

Success rates at 6-week test of cure by final diagnosis

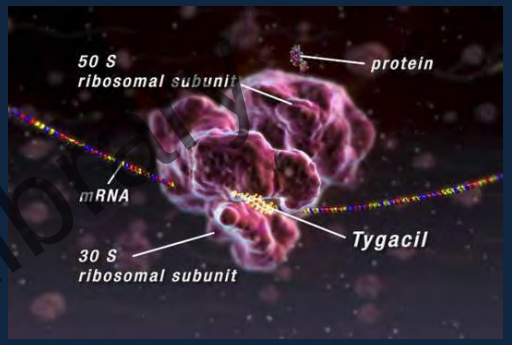


mITT population

*Limited data in LIE preclude determination of efficacy

Fowler *et al*. *NEJM* 2006;355:653–665

Tigecycline



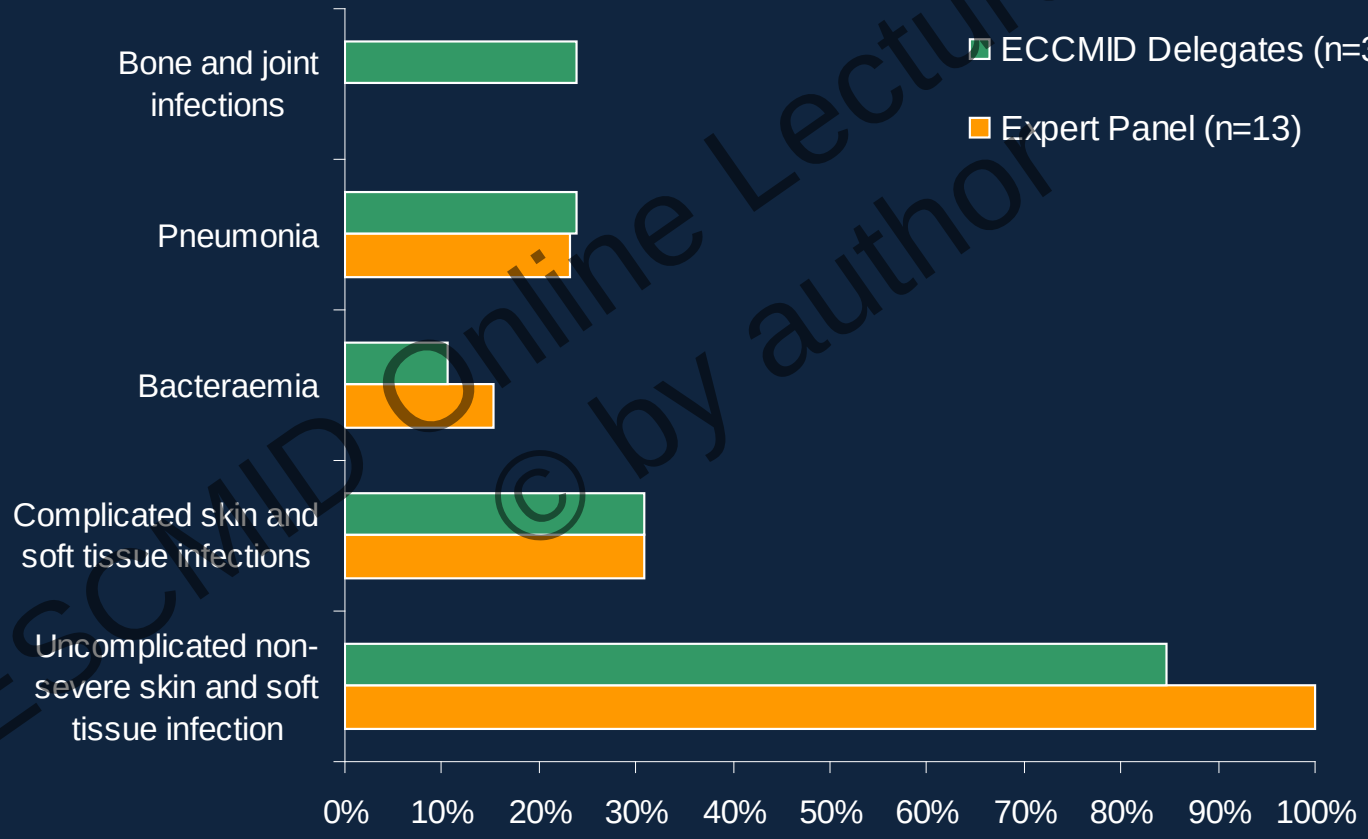
- Glycylcycline class
  - semisynthetic derivatives of tetracycline antibiotics with the maintained antibacterial effect but greater stability against mechanisms of tetracycline resistance
- Broad spectrum of activity:
  - Gram-positive pathogens, including MRSA and VRE
  - Gram-negative pathogens, including ESBL producers (intrinsic resistance in P.aeruginosa, Proteeae
  - Anaerobic pathogens
- Tigecycline monotherapy cure rates non-inferior to vancomycin plus aztreonam
- Clinical indications
  - Complicated skin & soft tissue infections (cellulitis, wound infection, abscesses,ulcers, and burns)
  - Complicated abdominal infections

MRSA Oral Treatment

- MRSA infections that are treated ambulatory
  - Mild infections (skin infections, UTIs)
  - Infections that need long-term therapy (osteomyelitis)

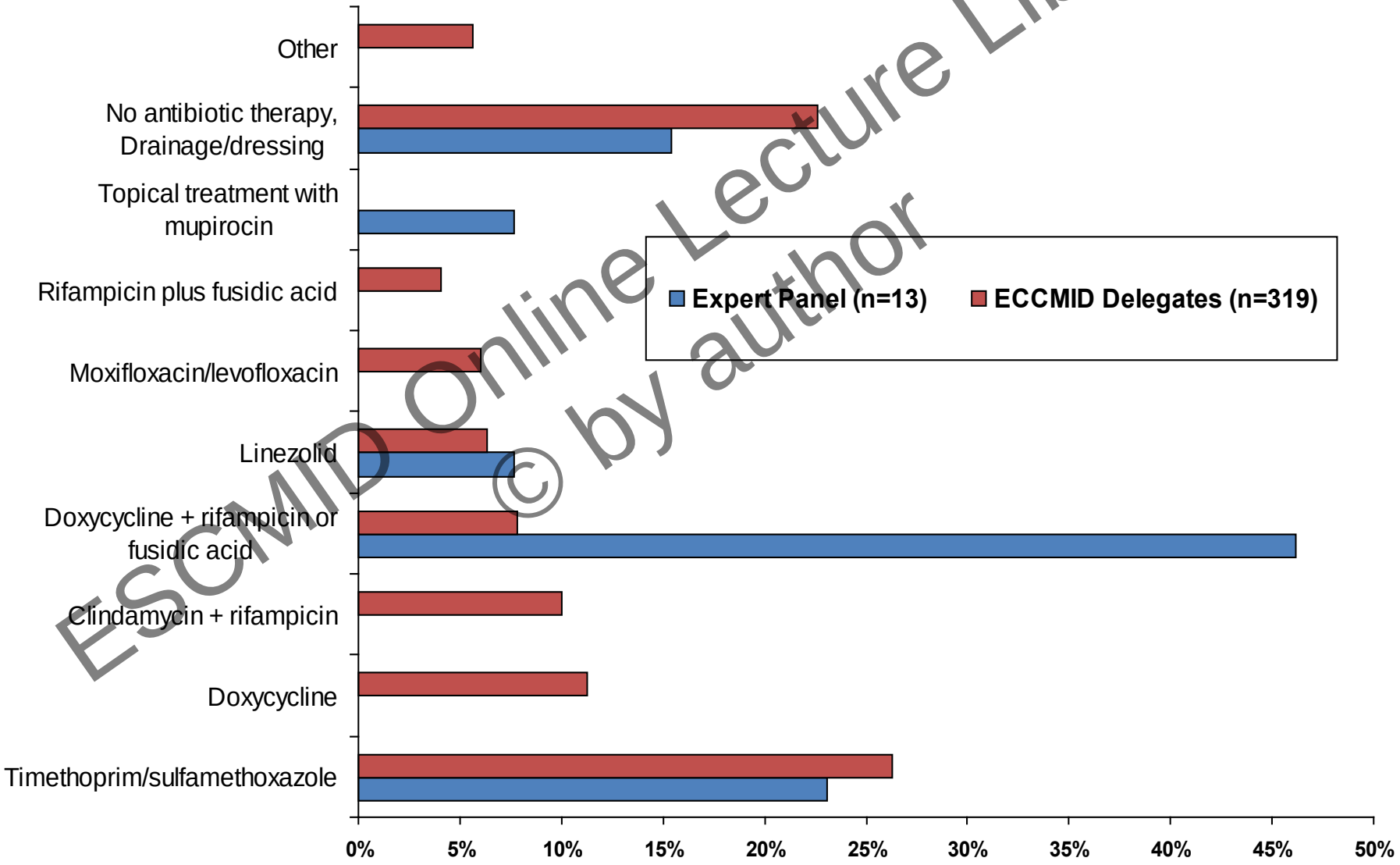
- MRSA infections in hospitalised patients – switch to oral therapy

Are oral antibiotics ever justified for the initial treatment of proven MRSA infection in the following? (choose all that apply)



ECCMID 2009

For minor infections of soft tissue caused by MRSA and not requiring hospitalisation, which antibiotic would you choose?



Skin and Soft-Tissue Infections

Effect of Initial Therapy on Selected Outcomes among 453 Patients with Confirmed Skin or Soft-Tissue Infections Due to Community-Associated MRSA, 2001–2002.*

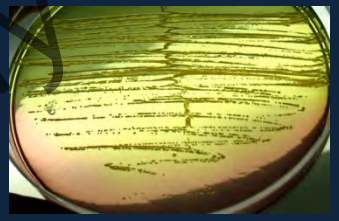
Initial Therapy	No. of Patients	Follow-up Visit to Health Care Provider		Incision and Drainage on Follow-up Visit	New Anti-microbial Agent Prescribed on Follow-up Visit
		≥1 Times	≥2 Times		
Incision and drainage					
Yes — no. (%)	196	54 (28)	30 (15)	19 (10)	45 (23)
No — no. (%)	257	69 (27)	43 (17)	14 (5)	66 (26)
Rate ratio (95% CI)	—	1.01 (0.80–1.29)	0.94 (0.70–1.27)	1.37 (1.00–1.87)	0.92 (0.71–1.18)
Inactive therapy					
Yes — no. (%)	254	59 (23)	35 (14)	15 (6)	55 (22)
No — no. (%)	199	64 (32)	38 (19)	18 (9)	56 (28)
Rate ratio (95% CI)	—	0.81 (0.66–1.00)	0.83 (0.65–1.07)	0.80 (0.54–1.17)	0.85 (0.69–1.05)
Incision and drainage					
Inactive therapy — no. (%)	108	20 (19)	11 (10)	8 (7)	16 (15)
Active therapy — no. (%)	88	34 (39)	19 (22)	11 (12)	29 (33)
Rate ratio (95% CI)	—	0.60 (0.41–0.87)	0.63 (0.39–1.02)	0.75 (0.43–1.28)	0.58 (0.39–0.88)
No incision and drainage					
Inactive therapy — no. (%)	146	39 (27)	24 (16)	7 (5)	39 (27)
Active therapy — no. (%)	111	30 (27)	19 (17)	7 (6)	27 (24)
Rate ratio (95% CI)	—	0.99 (0.78–1.26)	0.98 (0.73–1.31)	0.87 (0.51–1.49)	1.05 (0.83–1.34)

Fridkin SK, et al. *NEJM*. 2005.

Skin and Soft-Tissue Infections

- **Incision and drainage + oral antibiotics**
  - Systemic signs of infection
  - Large lesions (> 5 cm in diameter)
  - Failure of I&D alone
  - Nose or face involved

Skin and Soft-Tissue Infections

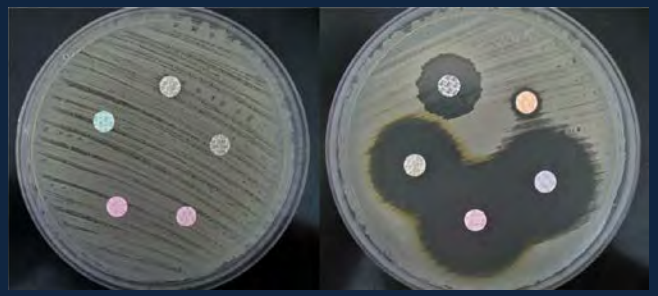


- **Incision and drainage + oral antibiotic active against MSSA**
  - Most uncomplicated SSTIs caused by GAS and MSSA
  - Oral antistaphylococcal penicillin or cephalexin
  - Culture and susceptibility testing
- **Incision and drainage + oral antibiotic active against MRSA**
  - CA-MRSA increasing in frequency
  - CA-MRSA more virulent
  - Use of antibiotics will prevent recurrent infections and the spread of CA-MRSA
  - Culture and susceptibility testing

Clinical Decisions, www.NEJM.org, 2008.

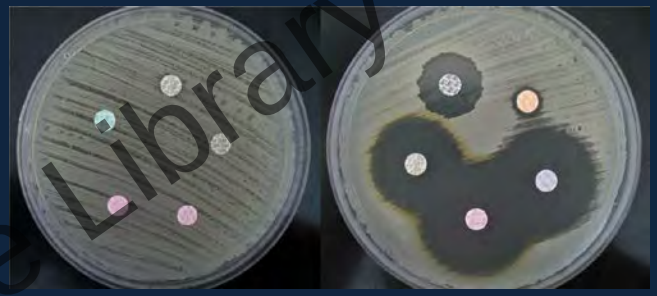
Skin and Soft-Tissue Infections

- **Oral antibiotic treatment for known MRSA infections**
  - To treat MRSA infections, clinicians should select an MRSA drug with proven in vivo effectiveness, ie, daptomycin, linezolid, quinupristin/dalfopristin, minocycline, or vancomycin, and not rely on in vitro susceptibility data. Linezolid and minocycline are available for oral administration...



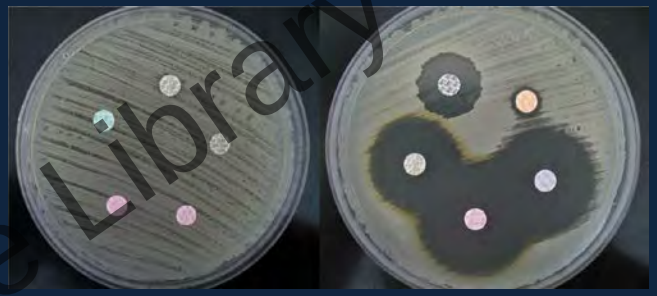
Cunha BA. *CMI*. 2005.

Skin and Soft-Tissue Infections



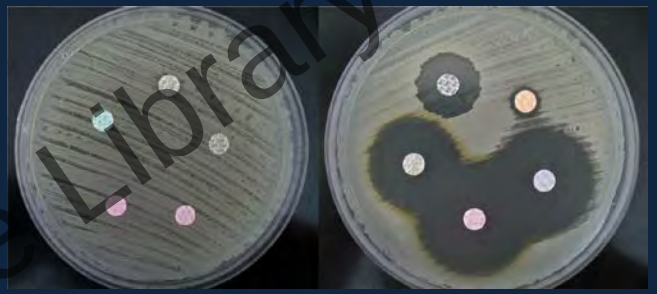
- **Co-trimoxazole**
  - Advantages of the use of oral co-trimoxazole
    - Convenient dosing (twice/day)
    - Low cost
    - Good oral bioavailability
  - Bactericidal effect in staphylococcal infections (MRSA)
  - TMP-SMX is synergistic in vivo
  - Geographical variations in sensitivity to co-trimoxazole
    - Brazilian clone more often resistant to TMP-SMX than the Iberian clone
  - High-dose therapy in HIV patients/well-defined AE profile
  - For decades used for UTI, RTI, GI infections
  - Not FDA-approved to treat any staphylococcal infection
  - Not effective for the treatment of GAS infections

Skin and Soft-Tissue Infections



- **Tetracyclines (doxycycline, minocycline)**
  - Advantages of the use of tetracyclines
    - Convenient dosing (twice/day)
    - Low cost
    - High skin concentration
  - Geographical variations in sensitivity to tetracyclines
    - UK MRSA guidelines
    - Doxycycline and minocycline active against some tetracycline-resistant isolates
  - Not effective for the treatment of GAS infections
  - Not recommended in pregnant women and children < 8 years

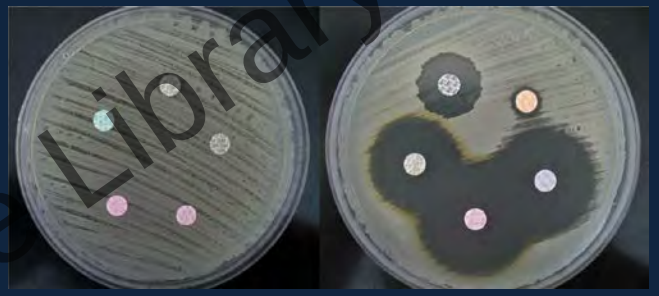
Skin and Soft-Tissue Infections



- **Rifampicin**
  - Excellent in vitro activity
  - Excellent oral bioavailability
  - High mutation rate/never used as a single agent
  - High concentrations in mucosa – eradication of MRSA carriage
  - Favourable activity against biofilm

- **Fusidic acid**
  - Oral/topical treatment
  - High mutation rate/never used as a single agent

Skin and Soft-Tissue Infections



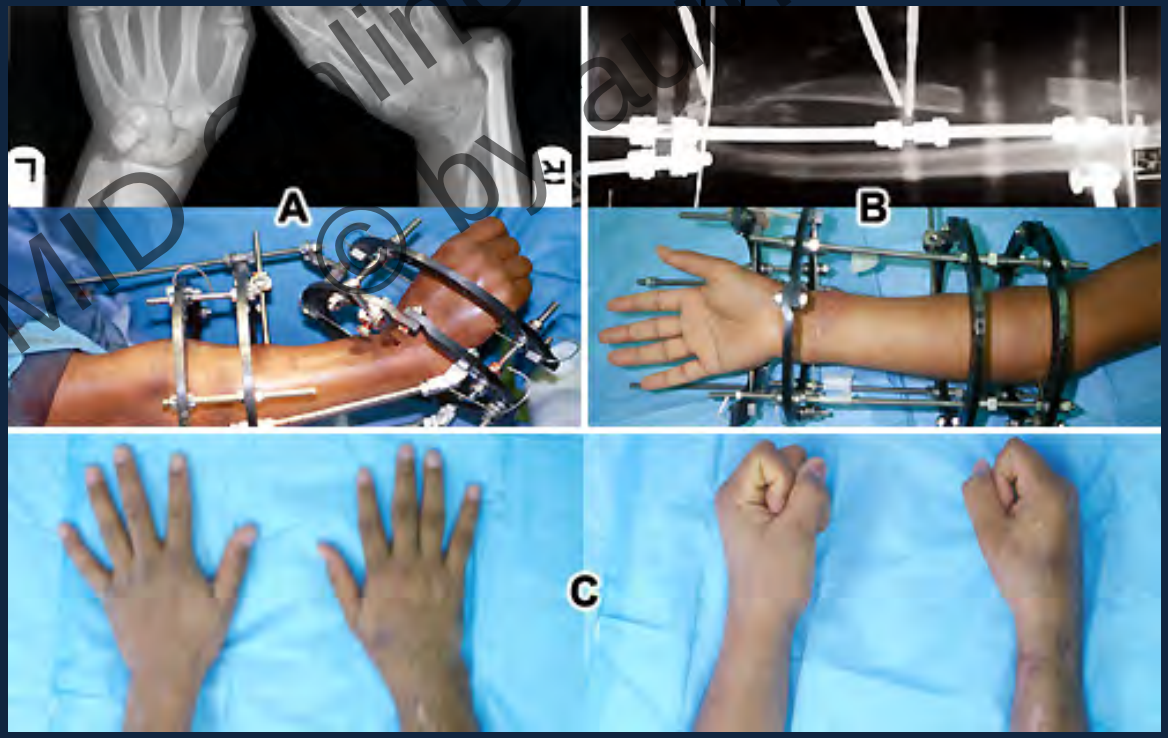
- **Fluoroquinolones (moxifloxacin, levofloxacin)**
  - Newer fluoroquinolones have better AUC/MIC ratio for staphylococcal infections than ciprofloxacin
  - FDA-approved for uncomplicated SSTIs caused by *S. aureus*
  - High rates of resistance among MRSA isolates
  - High potential for development of resistance during therapy
  - The use of fluoroquinolones is promoting MRSA spread

Skin and Soft-Tissue Infections

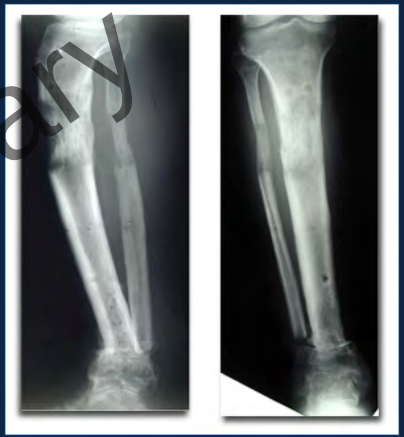
- **Clindamycin**
  - Advantages of the use of oral clindamycin
    - High skin and bone concentration
    - Low cost
  - Geographical variations in sensitivity to clindamycin
    - Resistance rates high in HA-MRSA, variable in CA-MRSA
    - Inducible clindamycin resistance should be reported
  - Most published experience with SSTIs
  - Recommended for SSTIs, bone and joint infections
  - *Clostridium difficile*-associated disease may occur more frequently in association with clindamycin compared with other antibiotics

Bone and Joint Infection

- Osteomyelitis management: More art than science? (Johnston BL, et al. *Can J Infect Dis Med Microbiol*. 2007)
  - Lack of well-designed, prospective, randomised, controlled studies with sufficient follow-up period

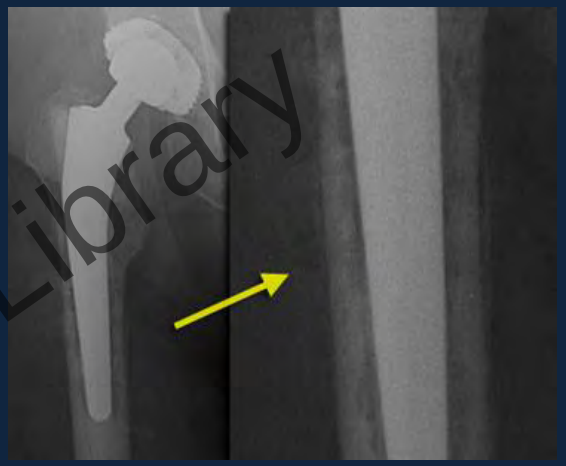


Bone and Joint Infection



- Chronic osteomyelitis and prosthetic joint infection
  - Critical duration of therapy?
  - Relative efficacy of various antibiotic classes?
    - Good bone penetration (animal models)
    - In vivo/in vitro results
    - Choice of oral antibiotics
  - Development of resistance
  - Implant removal or retention

Can Implant Removal be Avoided in MRSA Prosthetic Joint Infection?



- As MRSA is a typical difficult-to-treat organism, a **two-stage exchange arthroplasty** with a 6-to-8-week interval of systemic antibiotic therapy should be the therapy of choice. Explantation is followed by further long-term systemic antibiotic therapy
- However, in the presence of severe co-existing illness (patient inoperable), long-term suppressive antibiotic treatment may also be an option

What are the Antibiotic Treatment Options for Long-Term Oral Therapy of MRSA Osteomyelitis and Prosthetic Joint Infection?

- Rifampicin, clindamycin and fluoroquinolones have good bioavailability and bone penetration...

.....but rifampicin should never be given alone and most MRSA strains are resistant to clindamycin and fluoroquinolones….

- Oral therapy should include a combination of rifampicin plus co-trimoxazole or fusidic acid if the MRSA strain is susceptible to both agents

Long-Term Oral Therapy of MRSA Osteomyelitis and Prosthetic Joint Infection

- High-dose oral co-trimoxazole is effective in ambulatory treatment of MRSA-infected orthopaedic implants (Stein A. *AAC*. 2008)
  - Prospective but not randomized controlled study
  - 39 patients with orthopaedic implant infection were treated with high-dose co-trimoxazole (20 mg/kg TMP + 100 mg/kg SMX)
  - Duration of treatment: 6 months for hip infections, 9 months for knee infections, 6 months for osteosynthetic device infections
  - Follow-up: at least 24 months (up to 72 months)
  - 20% patients discontinued therapy because of AEs (skin allergy, GI symptoms) + 5 patients developed megaloblastic anaemia without the need for discontinuation of antibiotic therapy
  - Cure rate: 66.7% ITT, 86.7% in those who completed treatment, 60.7% without implant removal, 81.8% with implant removal
  - In 3 out of 4 patients who did not respond to therapy, a co-trimoxazole-resistant MRSA strain was isolated

Osteomyelitis and Prosthetic Joint

- Oral co-trimoxazole 3 × 960 mg after 2 weeks of parenteral therapy (vancomycin 2 × 1 g IV + rifampicin 2 × 450 mg IV/PO) (Barberan J. *CMI*. 2006; Trampuz A. *Swiss Med Wkly*. 2005)

- Vancomycin or trimethoprim/sulfamethoxazole for MRSA osteomyelitis (VOTSMO) (University of Washington)
  - Study design: treatment, randomized, open-label, active-control, parallel assignment, efficacy study
  - May 2006–May 2011, estimated enrollment: 300 patients
  - Co-trimoxazole 320/1600 mg PO bid # vancomycin 1 g bid

"Relax – MRSA will get you before the Pig Flu"