"Significado y Manejo de Infecciones Causadas por *Stafilococo aureus* Meticilino Resistente"

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Associate Chief for Clinical Affairs
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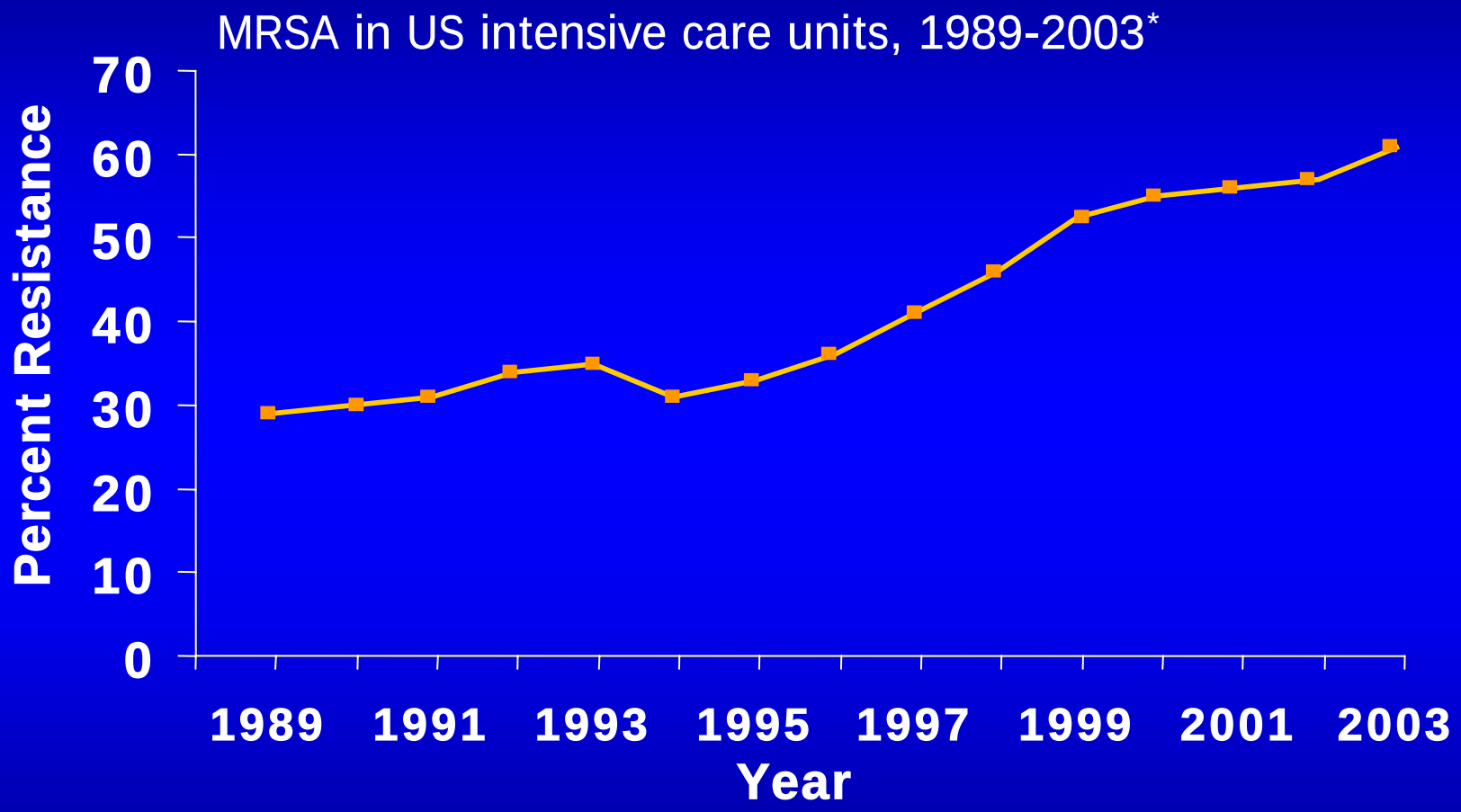
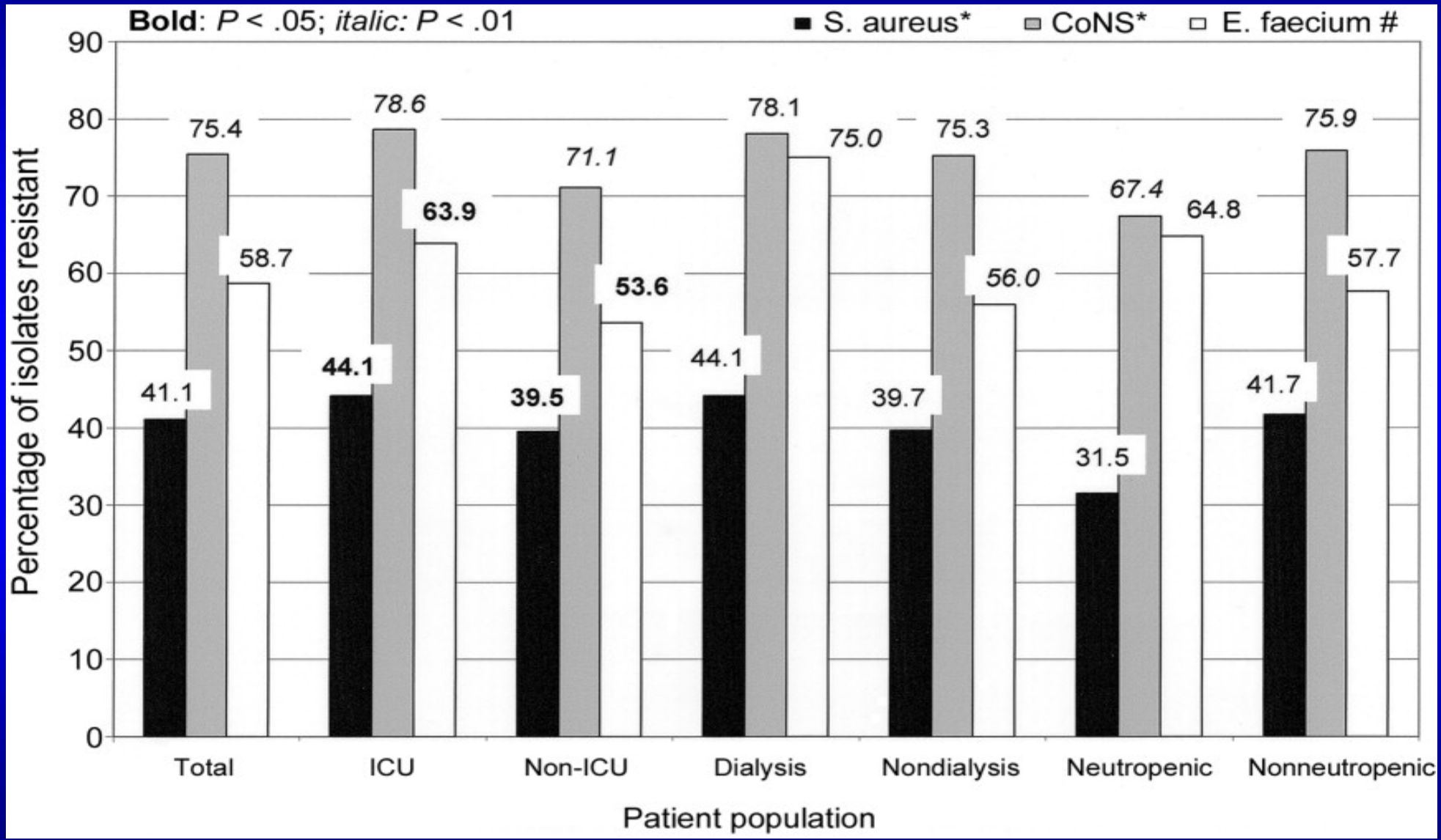
MRSA Is a Major Nosocomial Pathogen



*Based on data reported to the National Nosocomial Infections Surveillance (NNIS) System, 1989-2003, of nosocomial pneumonia infections among ICU patients (Partial data for 2003).
MRSA = methicillin-resistant *Staphylococcus aureus*.
Adapted from Division of Healthcare Quality Promotion. Centers for Disease Control and Prevention Web site. Accessed February 29, 2004.

Antimicrobial resistance among GP isolates (*n* = 13,665) isolated from patients with BSI



* % resist. to meth # % resist. to vanc

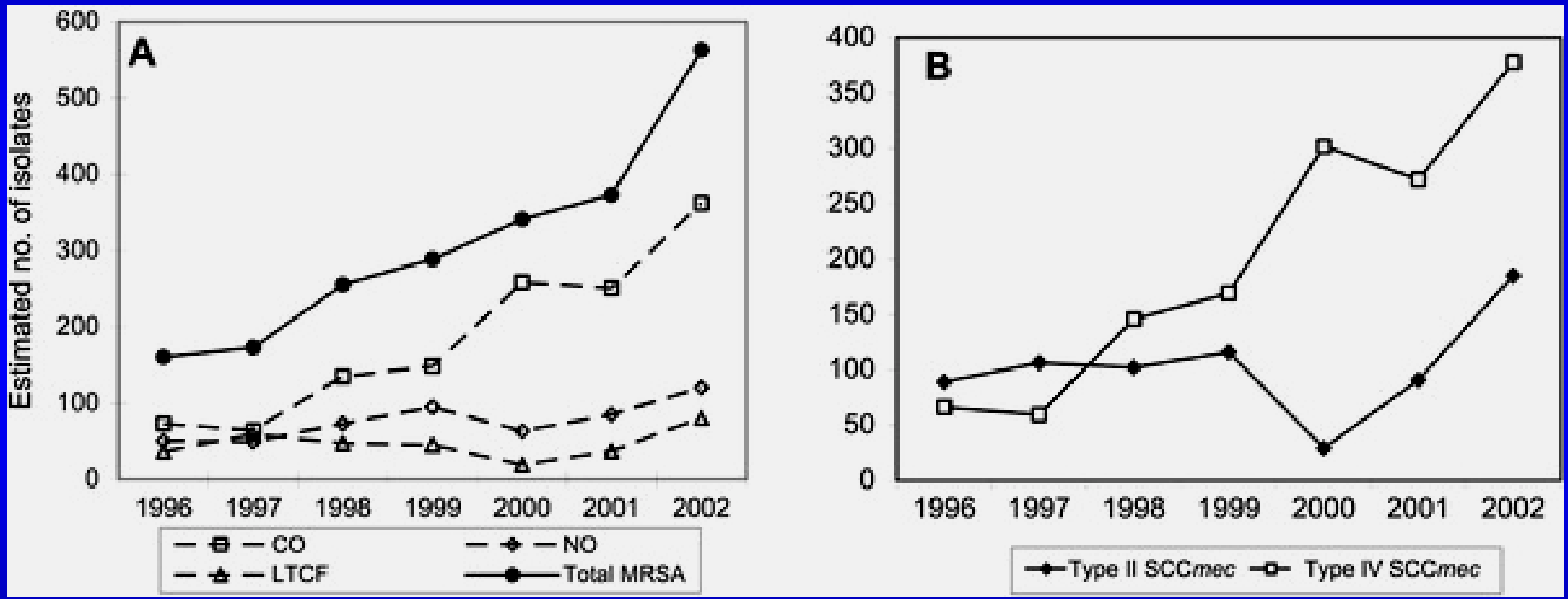
Wishplinghoff H et al. Clin Infect Dis. 2004 Aug 1;39(3):309-17

Community-MRSA

- Since late 1990's US and abroad
- Young individuals
  - Invasive infections (pneumonia, abscess)
    - (Panton-Valentine leukocidin, and others)
  - Outbreaks: sports teams, prisons, MSM
- Different from HA-MRSA
  - Genetic background
  - SCC*mec*

Herold et al. JAMA 1998; 279: 593-8
Dufour et al CID 2002; 35: 819-24
Daum et al. JID 2002; 186:1344-7
Deresinski S CID 2005; 40:562-73

Community-Adapted MRSA: Population Dynamics of an Expanding Community Reservoir of MRSA



Carleton HA et al. J Infect Dis. 2004 Nov 15;190(10):1730-8

Traditional Risk Factors for MRSA Infections

- Recent hospitalization [6, 12, 24 months?]
- Surgery
- Antimicrobial agents within the last 3 ,6,12 months?
- Presence of indwelling catheter
- Injection drug use
- Underlying Illness [Diabetes, Dialysis etc]
- Residence /Transfer in /from Nursing home

CA-MRSA case Definition

- Any Outpatient or Inpatient with culture confirmed MRSA infection within 48h of admission
- No history of hospitalization , surgery, renal dialysis, or residence in LTCF within a year
- No documented history of injection drug use
- No permanent indwelling catheter or percutaneous medical device present at time of culture
- No known MRSA infection before the study

Naimi et al, CID 2001:33

Pandemic Clones of MRSA

International Nomenclature	Sequence Type (ST-)	Staph. Chromosomal Cassette type(SCC*mec*)
Archaic Clone	**250**	**I**
Iberian Clone	**247**	**IA**
New York/Japan	**5**	**II**
Hungarian Clone	**239**	**III**
Brazilian Clone	**239**	**IIIA**
Pediatric Clone	**5**	**IV**

Pandemic clones of MRSA

- **Iberian clone**: *Spain, Portugal, Italy, United Kingdom, Germany, Switzerland, France, Czech Republic, Poland and US*
- **Brazilian clone**: *Brazil, Portugal, Argentina, Uruguay, Chile and Czech republic*
- **Hungarian clone**: *Hungary and Taiwan*
- **NewYork/Japan clone**: *Metropolitan NY, NewJersey, Pennsylvania, Connecticut and Tokyo:*
- **Pediatric clone**:*Portugal, Poland, US, Argentina and Colombia*

MRSA in Colombia

In Colombia, the first molecular epidemiological study of MRSA included isolates from Bogota city (1996–1998)

revealed the presence of a dominant clone that was a derivative of the 'Paediatric clone' (or PFGE pattern D)

This clone was initially recovered from paediatric patients in Portugal, Poland and Argentina

The Colombian isolates differed in that they were recovered from patients of all ages and were more resistant to antibiotics

Gomes AR, Sanches IS, Aires de Sousa M, Casta˜neda E, de Lencastre H. Molecular epidemiology of methicillin-resistant *Staphylococcus aureus* in Colombian hospitals: dominance of a single unique multidrug-resistant clone. Microb Drug Resist 2001;7:23–32

Dissemination of a Chilean clone in Colombian Hospitals

Tracking methicillin-resistant *Staphylococcus aureus* clones in Colombian hospitals over 7 years (1996–2003): emergence of a new dominant clone

César Cruz [a,b,c], Jaime Moreno [a], Adriana Renzoni [b], Marilyn Hidalgo [a], Jinnethe Reyes [c], Jacques Schrenzel [b], Daniel Lew [b], Elizabeth Castañeda [a], César A. Arias [c,d,*]

[a] *Microbiology Group, Instituto Nacional de Salud, Bogotá D.C., Colombia*
[b] *Genomic Research Laboratory, Division of Infectious Diseases, University Hospital of Geneva, Switzerland*
[c] *Bacterial Molecular Genetics Unit, Centro de Investigaciones, Universidad El Bosque, Bogotá D.C., Colombia*
[d] *Division of Infectious Diseases, University of Texas Medical School at Houston, Houston, TX, USA*

- 200 MRSA isolates from 17 Colombian hospitals collected 2001-2003
- 137 (68%) new dominant PFGE identical to MDR-MRSA clone identified in Chile between 1996 –1998

Dissemination of a Chilean clone in Colombian Hospitals

the majority of isolates (96%) exhibited multidrug resistance. They were all susceptible to vancomycin, teicoplanin and linezolid

a much higher percentage of isolates were resistant to ciprofloxacin and gentamicin

resistance to rifampicin has decreased overall

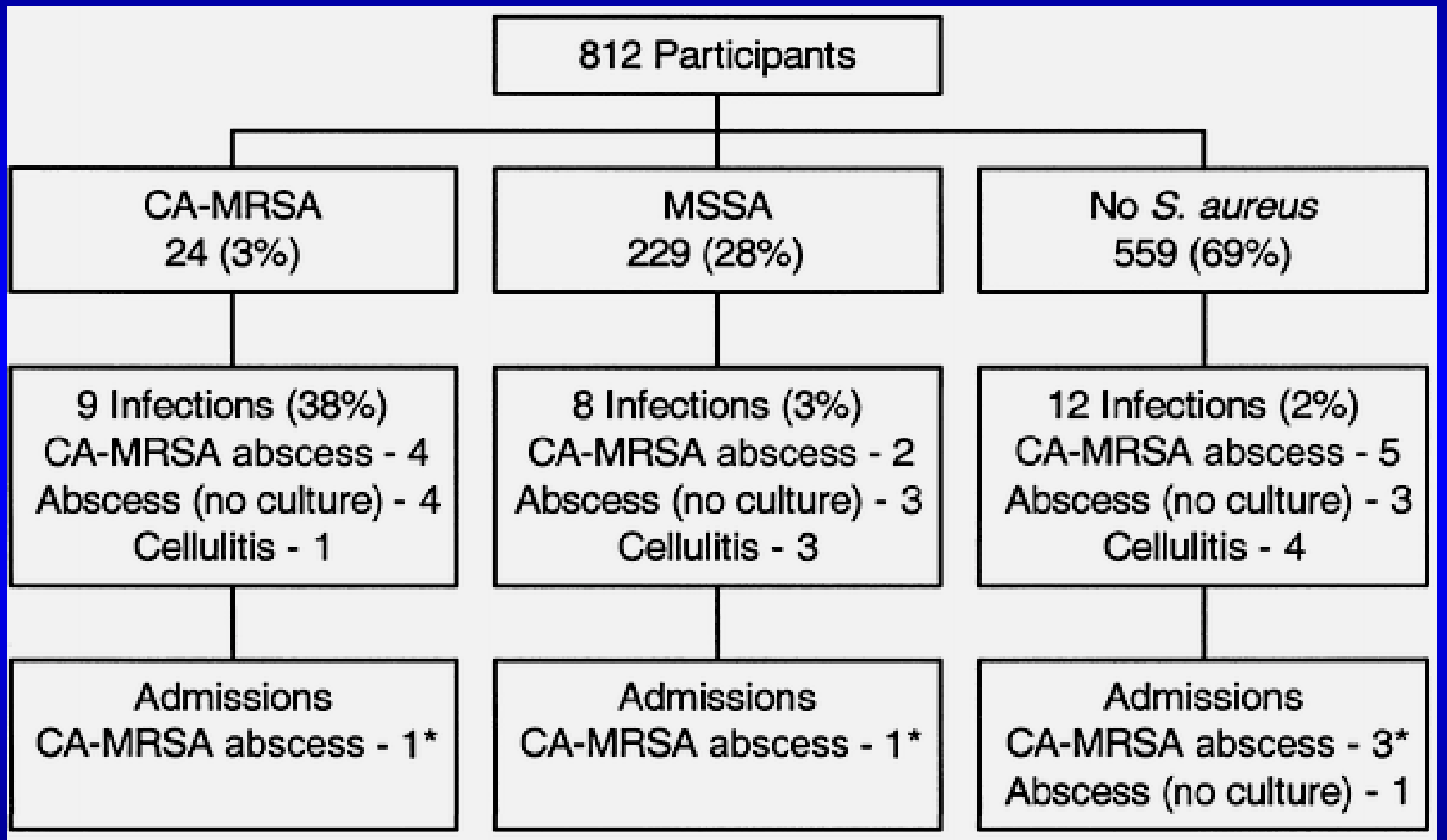
a high percentage of isolates remained resistant to macrolides and lincosamides (likely to represent MLSBtype resistance)

susceptibility to SXT continues to be high among Colombian MRSA isolates (more than 90%).

Genotypic and Phenotypic differences attributed to HA and CA-MRSA

	HA-MRSA	CA-MRSA
mec A located on	SCC*mec* I, II, III	SCCmec IV, V
Growth rate in culture media	slower	faster
Antimicrobial resistance	multiresistance	Beta-lactam only/ + Ery
Panton Valentine Leucocidin genes	negative	majority +

Natural History of Community-Acquired MRSA Colonization and Infection in 812 Soldiers



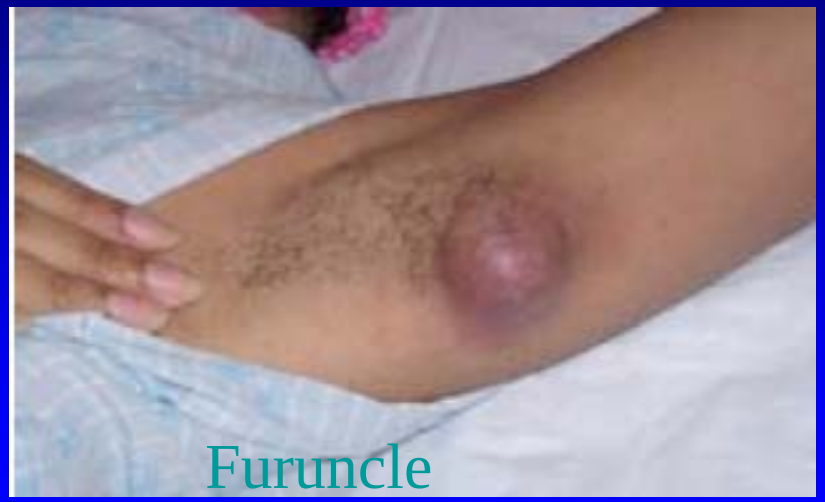
Ellis MW et al. Clin Infect Dis. 2004 Oct 1;39(7):971-9

MRSA and VRE Infections Associated With Higher Attributable Mortality

- Attributable mortality was 21% in MRSA vs 8% in MSSA
- Attributable mortality was 37% in VRE patients
- Total mortality was 67% in patients with VRE bacteremia compared with 30% in control patients

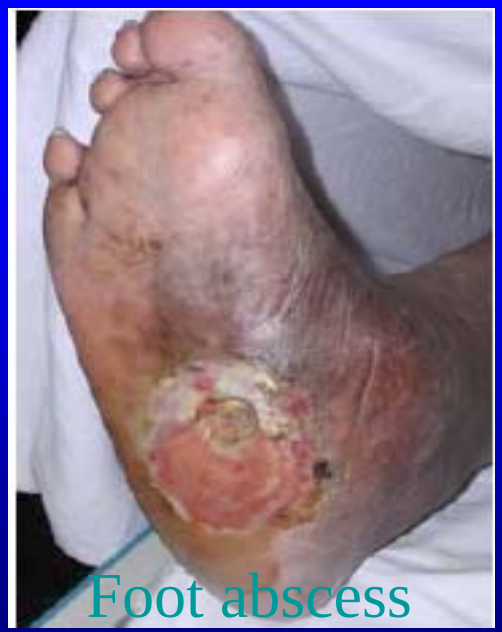
Rubin RJ, et al. *Emerging Infect Dis*. 1999;5:9-17.
Edmond MB, et al. *Clin Infect Dis*. 1996;23:1234-1239.

Typical MRSA Disease @ the Emergency Room Frazee et al, 2005

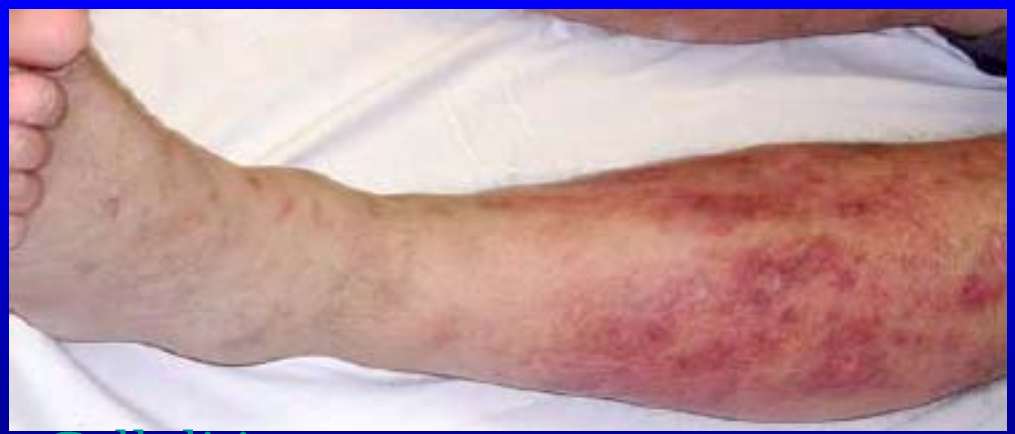


Furuncle

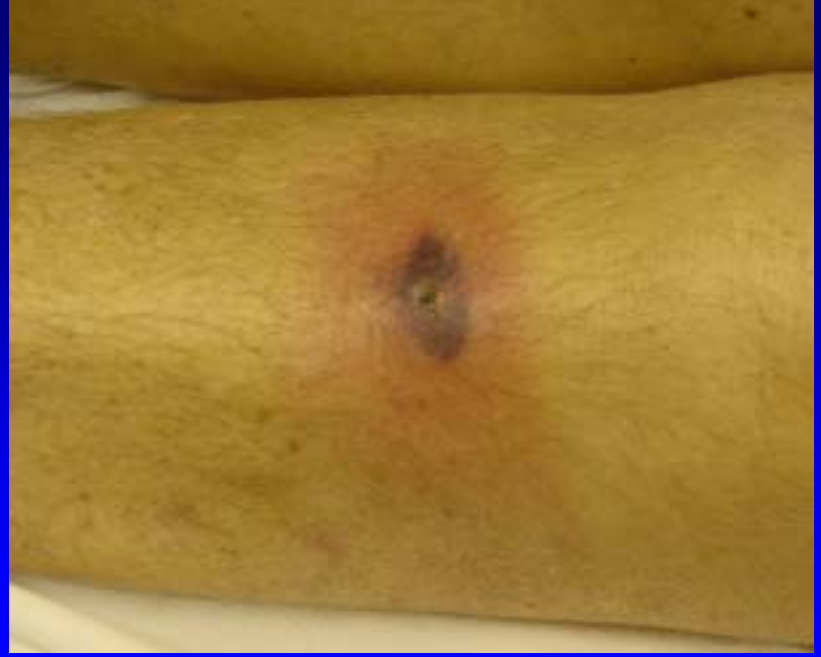
Deep Abscess

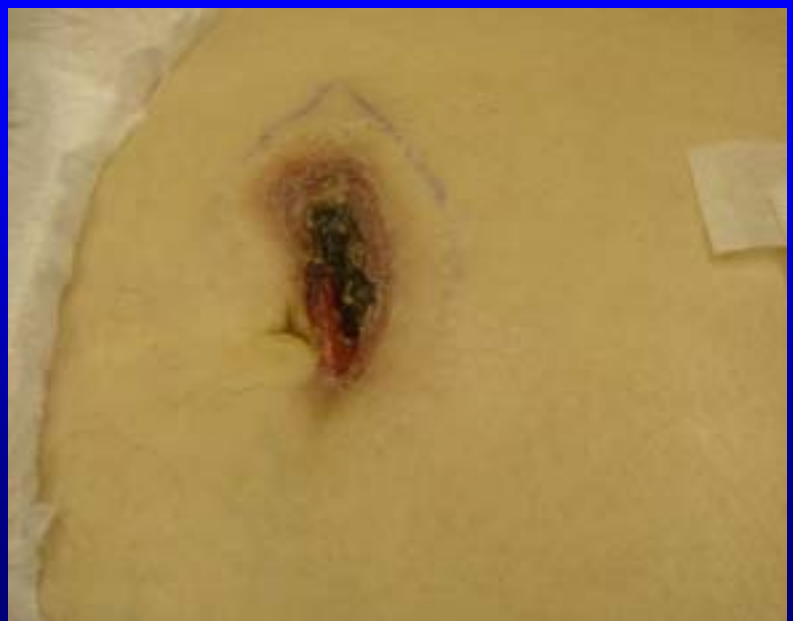


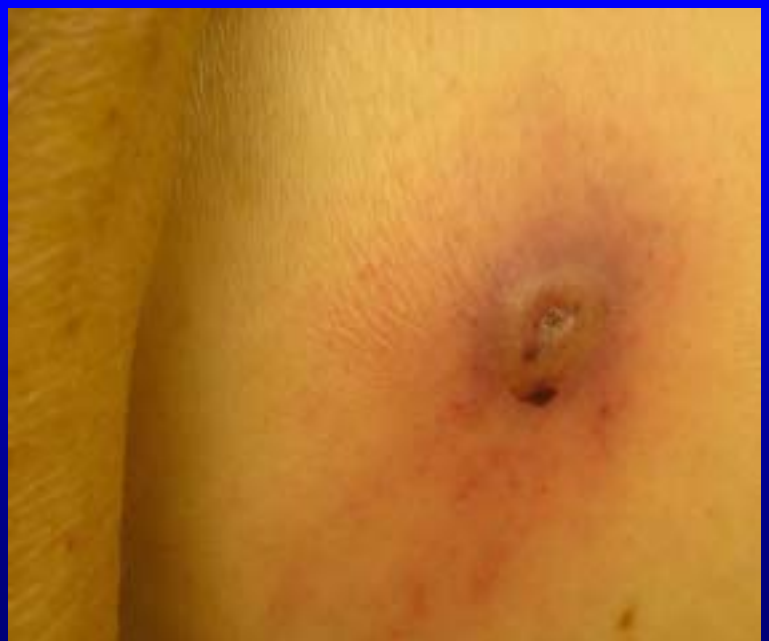
Foot abscess



Cellulitis

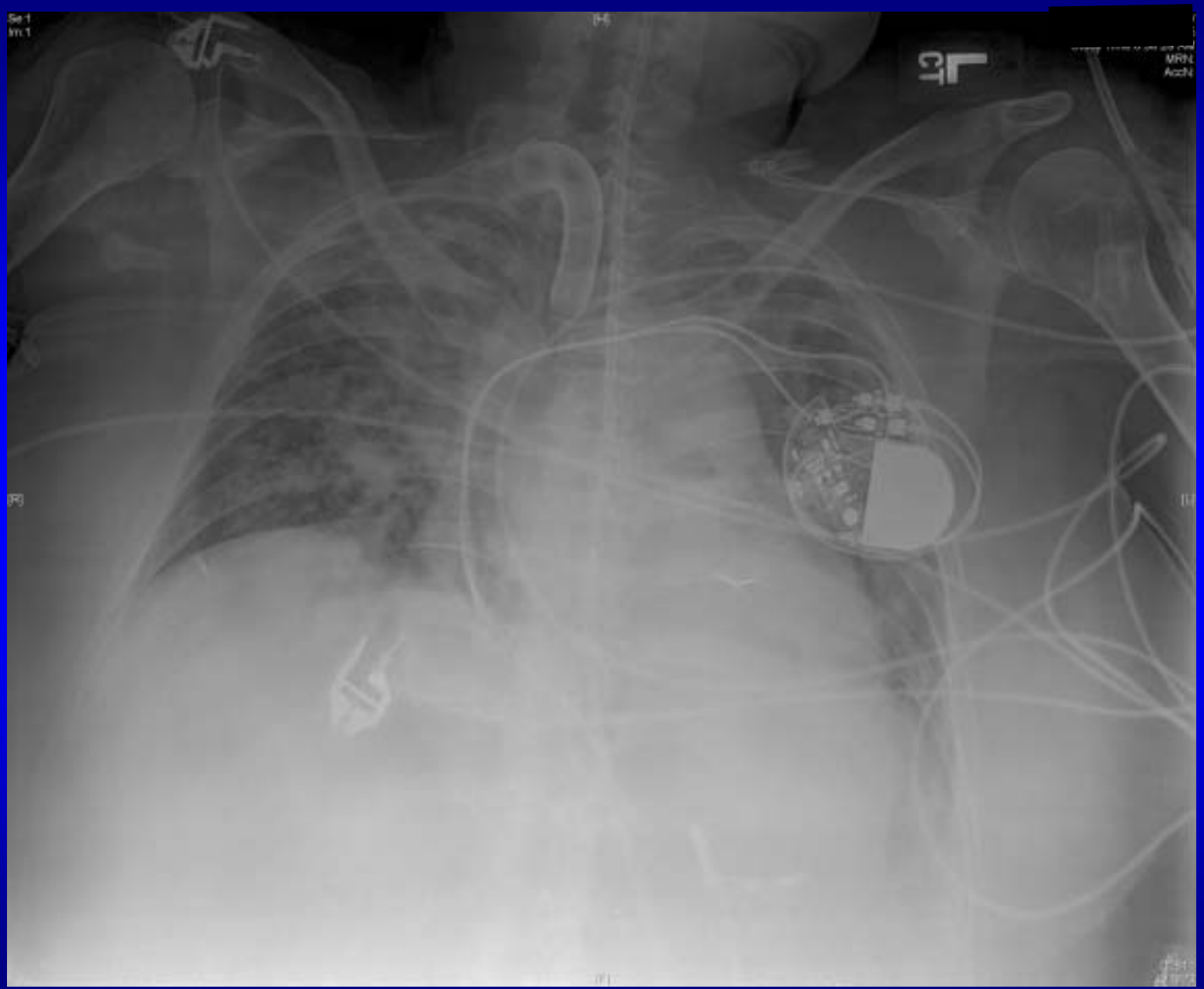






Cellulitis in Immunocompetent Patients Without an Unusual Epidemiological Exposure

- Streptococci, ß-hemolytic groups A, B, C,G
  - *macrolide-resistant?
- *Staphylococcus aureus*
  - *methicillin-resistant ?



Etiologic Agents of Nosocomial Pneumonia

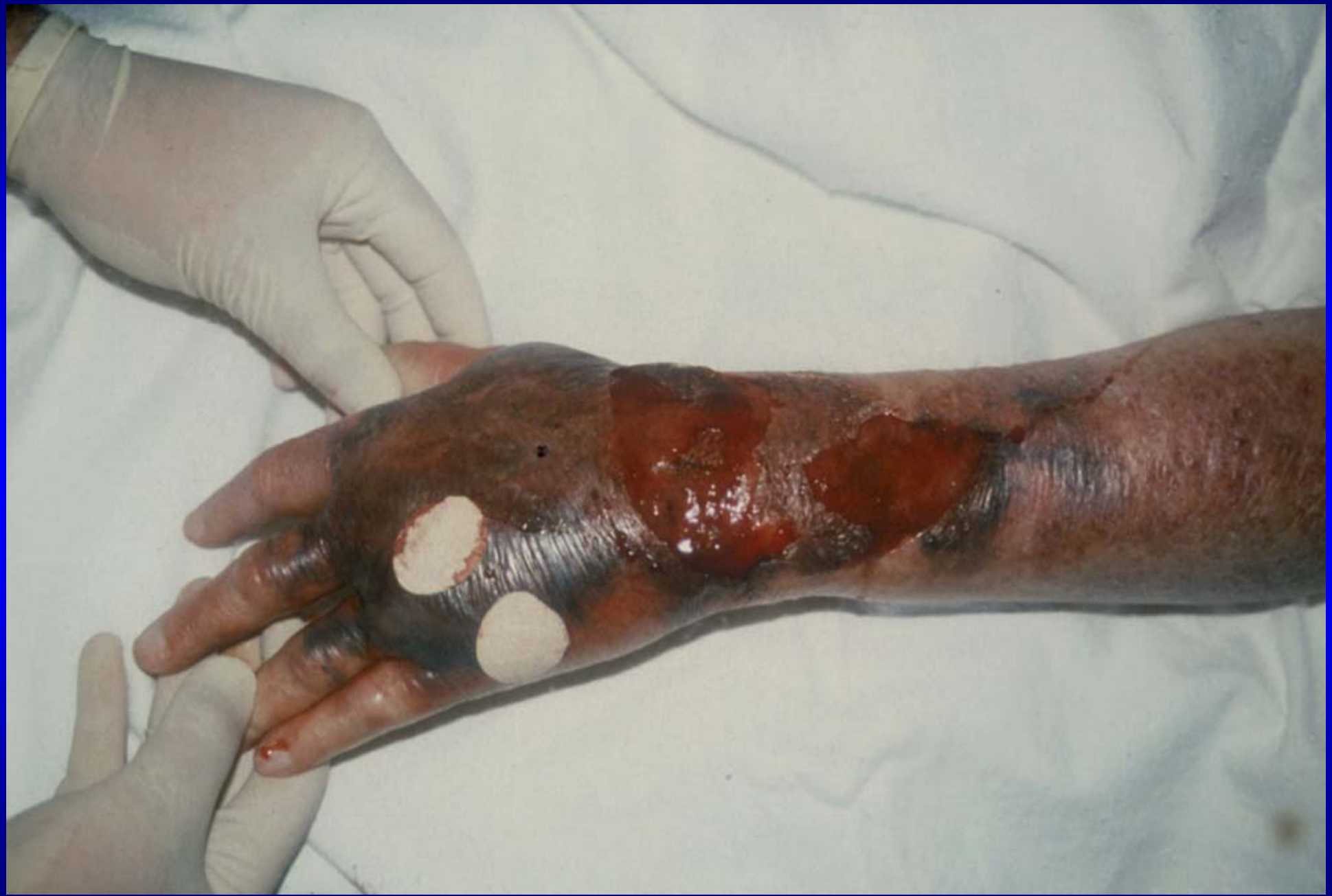
- no risk factors
- severe, late onset NP (≥ 5 days)
  - "SPICE A" organisms:
  - MRSA

6 cases of Vancomycin-resistant *S. aureus* (VRSA) since 2002

- 4 unrelated cases in Michigan,1 in Pennsylvania , 1 in New York
- MIC between 32ug and 1024ug/ml
- All patients had underlying infections with MRSA
- All colonized with Vancomycin resistant *Enterococcus faecalis/ faecium*

Mechanism of resistance *:Van A* from enterococci

VRSA, MIC ≥ 32 µg/mL
VISA, MIC = 8 - 16 µg/mL



Necrotizing Fasciitis Caused by Community-Associated Methicillin-Resistant Staphylococcus aureus in Los Angeles

Loren G. Miller, M.D., M.P.H., Francoise Perdreau-Remington, Ph.D., Gunter Rieg, M.D., Sheherbano Mehdi, M.D., Josh Perlroth, M.D., Arnold S. Bayer, M.D., Angela W. Tang, M.D., Tieu O. Phung, M.D. and Brad Spellberg, M.D.

N Engl J Med
Volume 352;14:1445-1453
April 7, 2005

The NEW ENGLAND JOURNAL of MEDICINE

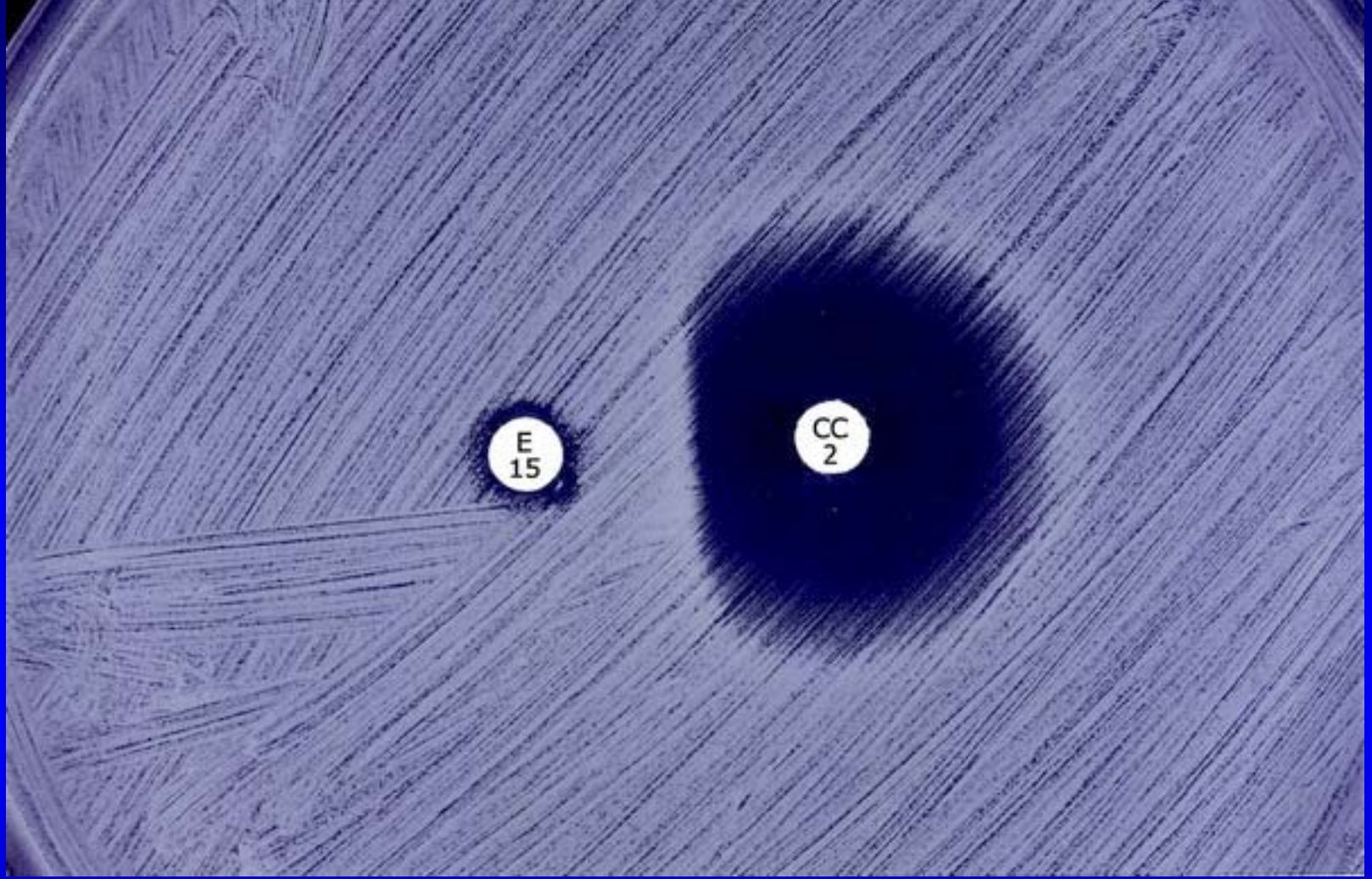
Select Antibiotic Options for Methicillin-Susceptible *S. aureus* (MSSA)

Predictable activity against MSSA

- dicloxacillin/nafcillin
- cephalexin/cefazolin
- amoxicillin/clav. acid
- ampicillin/sulbactam
- ertapenem/imipemen
- vancomycin
- linezolid
- dalfo/quinupristin
- daptomycin
- tigecycline

Need antibiogram

- TMP/SMZ
- moxi/levo 750
- macrolides (clarithro, etc)
- clindamycin
- tetracyclines
- telithromycin
- (gentamicin)
- (rifampin)



Example of a positive D-zone test result for detection of inducible clindamycin resistance. The organism shown is *S. aureus* ATCC BAA 977 that contains *erm*(C) and demonstrates the induced macrolide, lincosamide, and group B streptogramin resistance (MLSBi) phenotype

Lewis JS and Jorgensen JH Clin Infect Dis. 2005 Jan 15;40(2):280-5

Select Antibiotic Options for Methicillin-Resistant *S. aureus* (MRSA)

Predictable activity against MRSA

- vancomycin
- linezolid
- quinupristin/ dalfopristin
- daptomycin
- tigecycline

Need antibiogram

- TMP/SMZ
- macrolides (i.e clarithro)
- clindamycin
- tetracycline
- moxi/levo 750
- (rifampin)
- (gentamicin)

Antibiotic Options for MRSA Approved within the Past 7 Years

- quinupristin/ dalfopristin
- linezolid
- daptomycin
- tigecycline

Quinupristin/dalfopristin

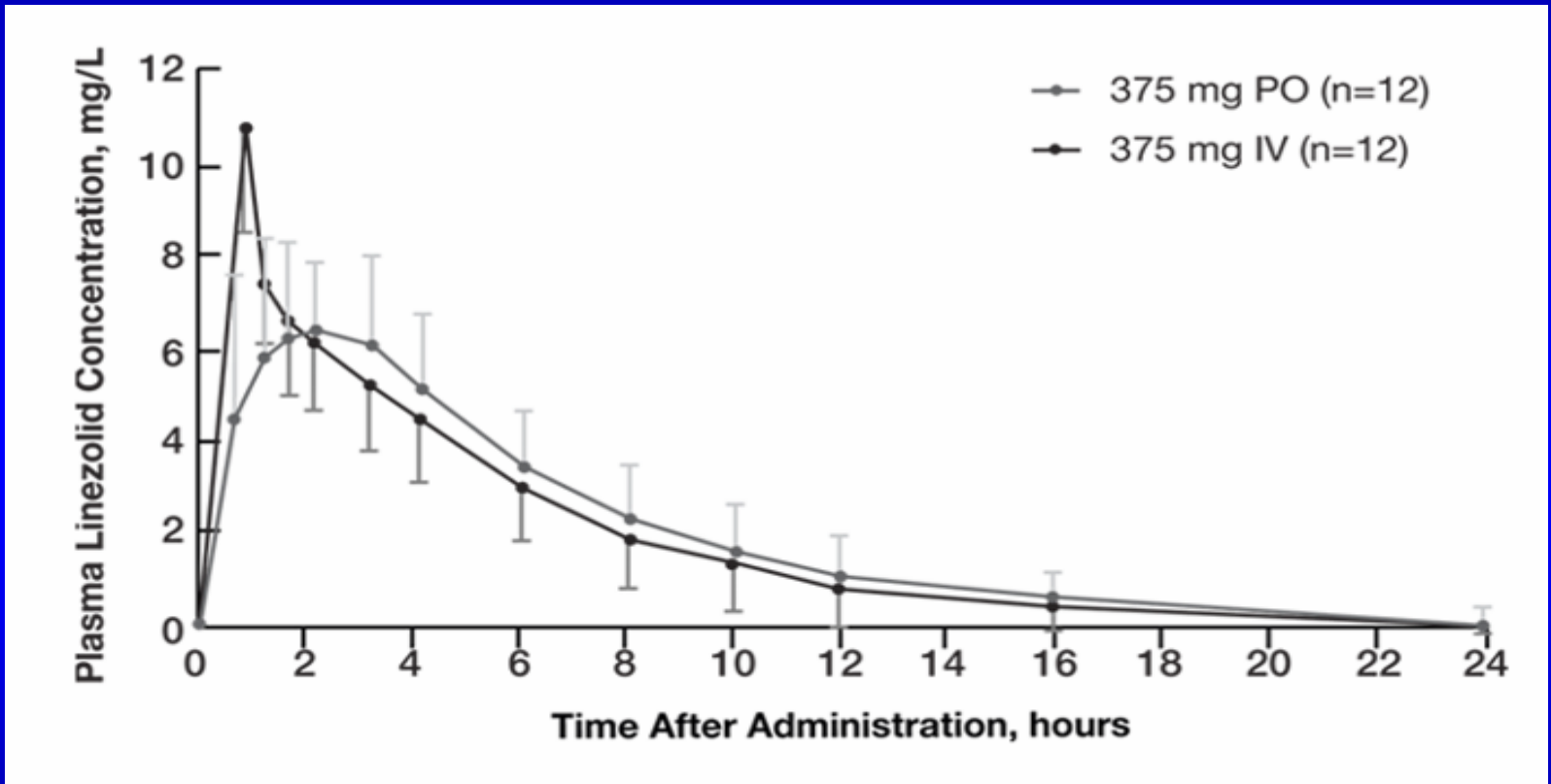
- active against aerobic GPC including *E. faecium* (including VRE), *S. aureus* and *epidermidis* (including MRSA and MRSE), *S. pyogenes* and *S. pneumoniae* (including DRSP)

- Adverse events may include: phlebitis (can be severe) with peripheral IV administration), arthralgia and myalgia, hyperbilirubinemia and elevated LFT's, emergence of resistance during therapy, drug-drug interactions

Linezolid

- active against aerobic GPC including *E. faecium* and *faecalis* (including VRE), *S. aureus* and *epidermidis* (including MRSA and MRSE), *S. pyogenes* and *S. pneumoniae* (plus PRSP)
- available IV and PO (oral bioavailability is 100%)
- no dose adjustment is recommended for patients with renal insufficiency or mild-to-moderate hepatic insufficiency
- adverse events may include: headache, nausea, diarrhea, thrombocytopenia, anemia, peripheral neuropathy, lactic acidosis, optic disk pathology
- should not be used in endocarditis

Linezolid Mean Serum Concentrations After PO and IV Doses Are Almost Identical in Adults

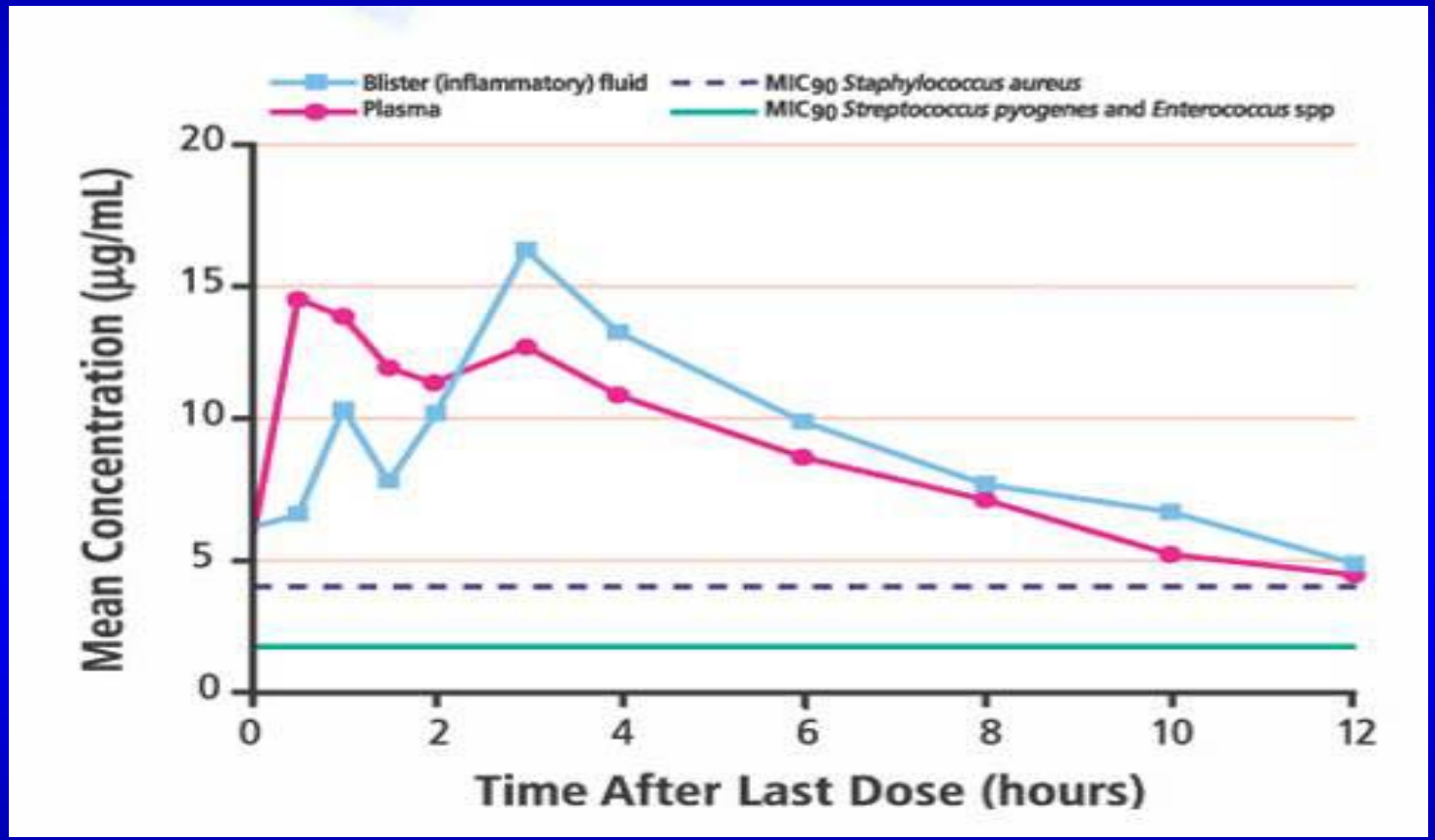


Mean (± SD) plasma linezolid concentration in healthy subjects after single PO / IV dose of 375 mg

Adapted from French G. *Int J Clin Pract*. 2001;55:61.

Skin Blister Fluid Penetration in Adults

Concentration vs MIC_{90} of Linezolid Against Gram-Positive Organisms

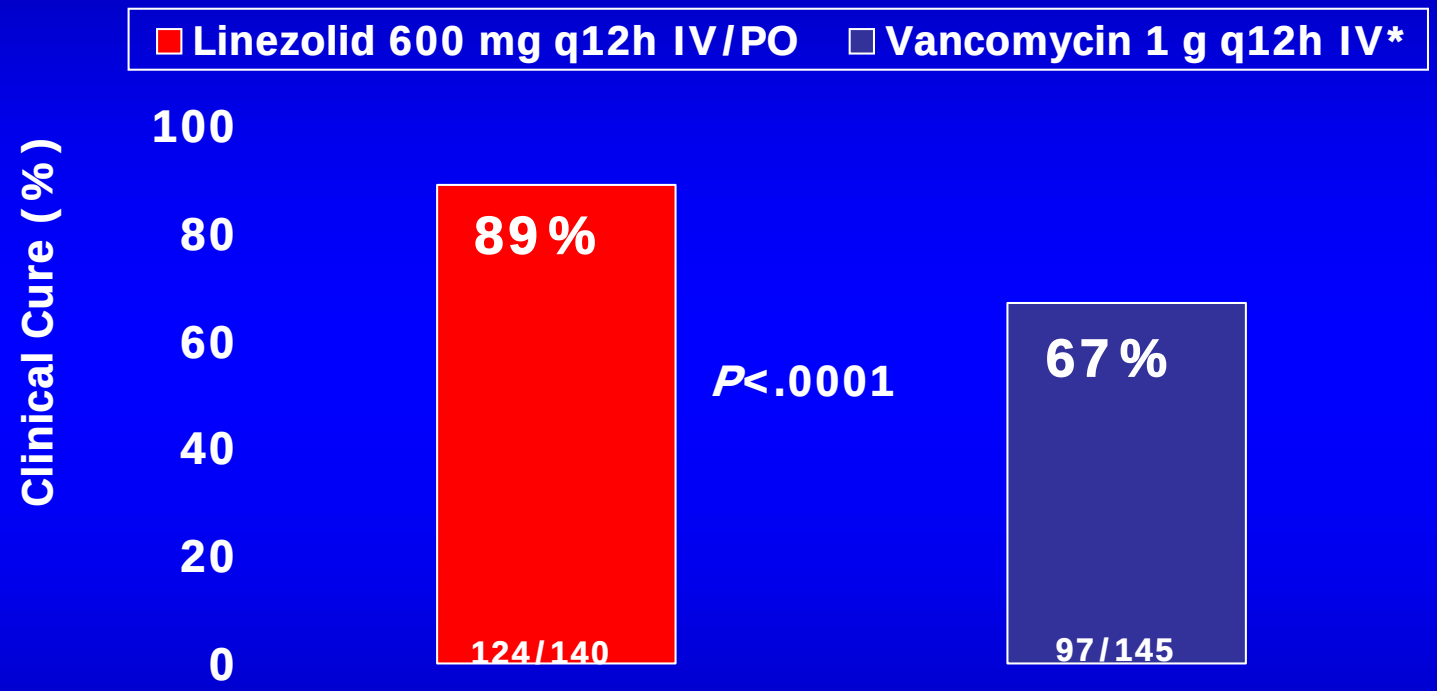


Pharmacokinetics in healthy volunteers and in vitro activity do not necessarily imply a correlation with clinical effectiveness.

MIC_{90} = minimum concentration needed to inhibit 90% of organisms.

Adapted from Gee T et al. *Antimicrob Agents Chemother*. 2001;45:1843-1846.

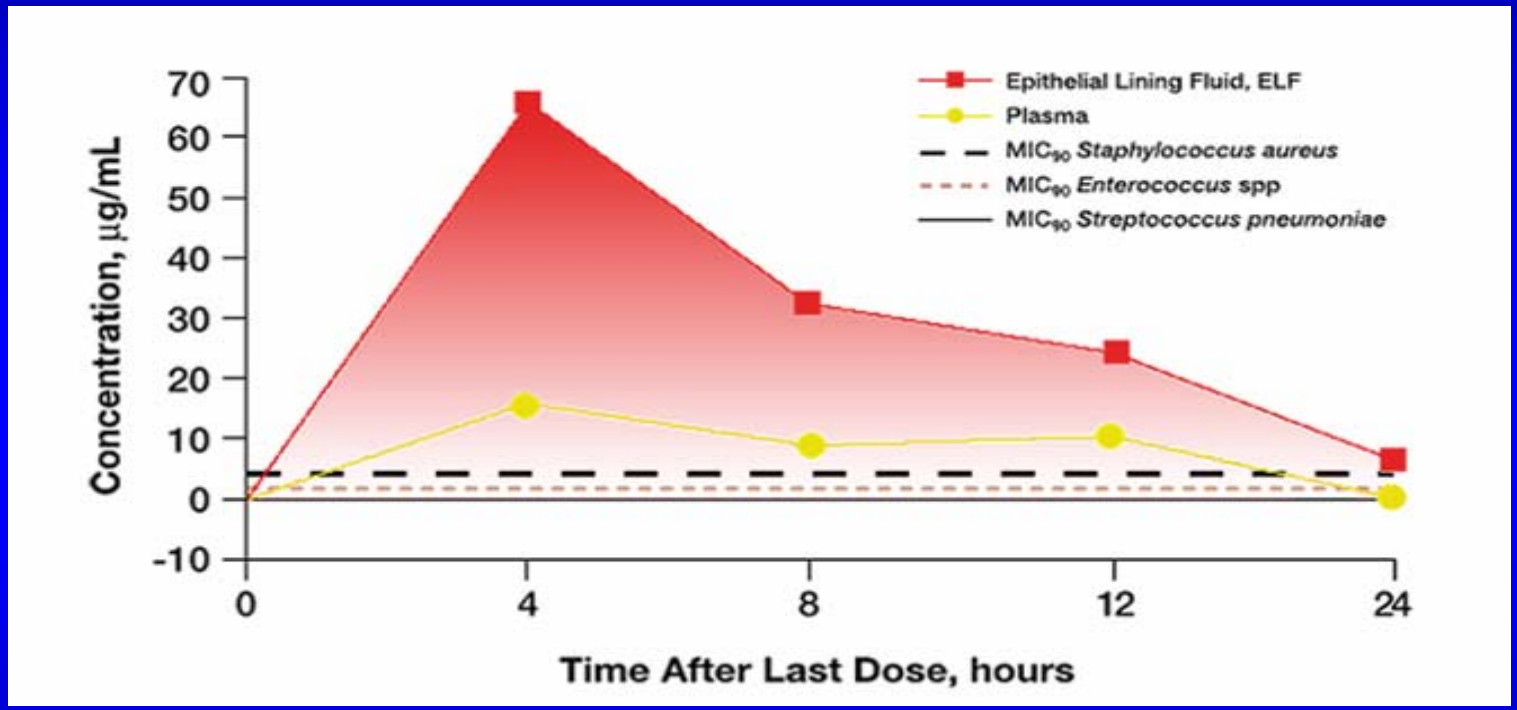
Linezolid Versus Vancomycin* for cSSSIs
Microbiological Efficacy in MRSA cSSSIs



*Vancomycin changed to oxacillin/nafcillin/flucoxacillin/dicloxacillin if MSSA was identified.
cSSSIs = complicated skin and skin structure infections.
MRSA = methicillin-resistant *Staphylococcus aureus.*

Adapted from Data on file. Pfizer Inc., New York, NY.

Concentration Versus MIC_{90} of Linezolid Against Gram-Positive Organisms



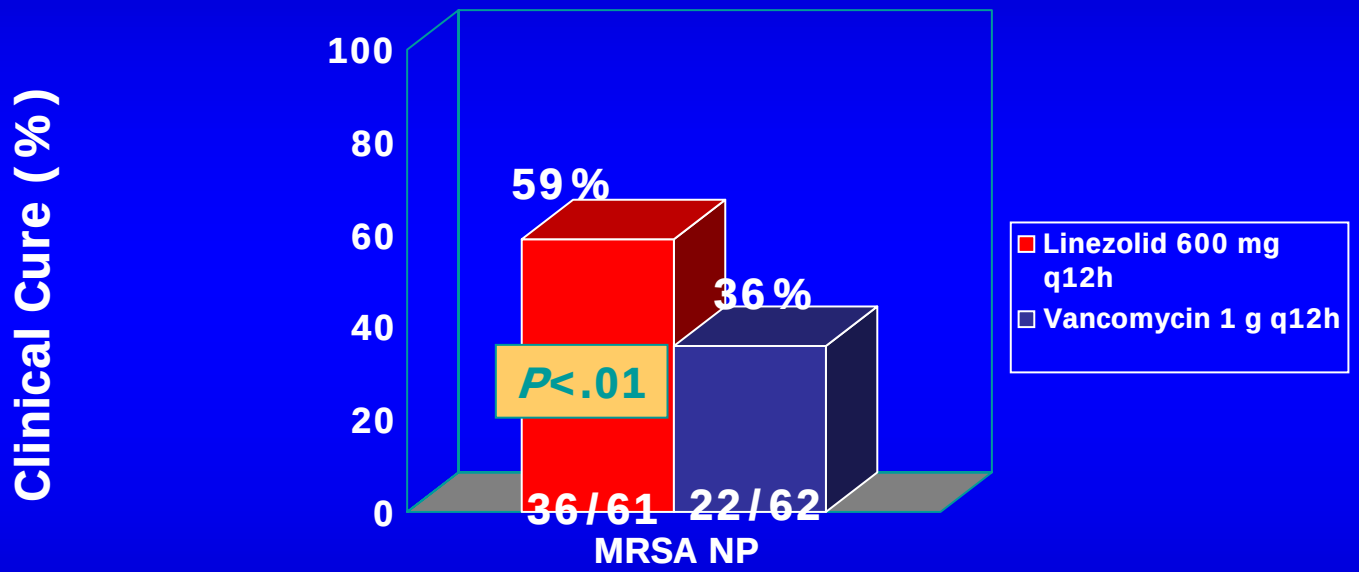
Pharmacokinetics in healthy adult volunteers and in vitro activity do not necessarily imply a correlation with clinical effectiveness.

MIC_{90} = minimum concentration needed to inhibit 90% of organisms.

Adapted from Conte JE Jr et al. *Antimicrob Agents Chemother*. 2002;46:1477.

Linezolid Delivers Excellent Efficacy in Patients With NP Caused by MRSA

Clinical cure rates in NP patients with MRSA



A post hoc analysis of 2 identical, randomized, double-blind, multicenter, multinational, comparator-controlled trials that compared the safety and efficacy of linezolid IV and vancomycin IV for 7 to 21 days in 1019 patients with nosocomial pneumonia, including ventilator-associated pneumonia. Patients were treated for 7 to 21 days with optional aztreonam 1 g to 2 g q12h.
Excludes missing and indeterminate.
NP = nosocomial pneumonia; MRSA = methicillin-resistant *Staphylococcus aureus.*

Adapted from Wunderink RG et al. *Chest.* 2003;124:1789-1797.

Daptomycin

- daptomycin is active against aerobic Gram-positive cocci including *E. faecium* and *faecalis* (including VRE), *S. aureus* and *epidermidis* (including MRSA and MRSE), and *S. pyogenes*
- rapid, concentration-dependent, bactericidal action *in vitro*
- distinct mechanism – low resistance potential
- monitor CK
- daptomycin is not indicated for the treatment of pneumonia
- bacteremia and endocarditis

Tigecycline

- indicated for intraabdominal and skin soft tissue infections
- mixed infections (MRSA plus Enterobacteriaceae)
- ESBL producers
- pan-resistant Acinetobacter spp.
- multi-resistant GPC (MRSA, VRE)
- Monitor for development of resistance during therapy
- should not be used for UTI
- nausea and voming frequent side effects
- avoid in children and pregnancy

Livermore D J Antimicrob Chemother. 2005 Aug 24; [Epub ahead of print]
Zinner S. CID 2005;41:S289-S292

Empirical Therapy for SSTI in Immunocompetent Patients

- MRSA is less likely and patient not severely ill
  - dicloxacillin, cephalexin, amoxicillin/clav. acid*
  - nafcillin, cefazolin, ampicillin/sulbactam*, ertapenem*,
  - vancomcyn, linezolid, tigecycline*
  - TMP/SMX
  - clindamycin
  - tetracycline
  - moxifloxacin/levofloxacin 750
  - macrolides

anaphylaxis to PCN

*when GPC , GNR, and anerobes are a consideration in mixed infections, i.e. diabetic foot, animal bites

Empirical Therapy for SSTI in Immunocompetent Patients

- MRSA is more likely and patient is not severely ill
  - linezolid
  - TMP/SMX
  - clindamycin
  - tetracycline

*when GPC , GNR, and anerobes are a consideration in mixed infections, i.e. diabetic foot, animal bites

Empirical Therapy for SSTI in Immunocompetent Patients

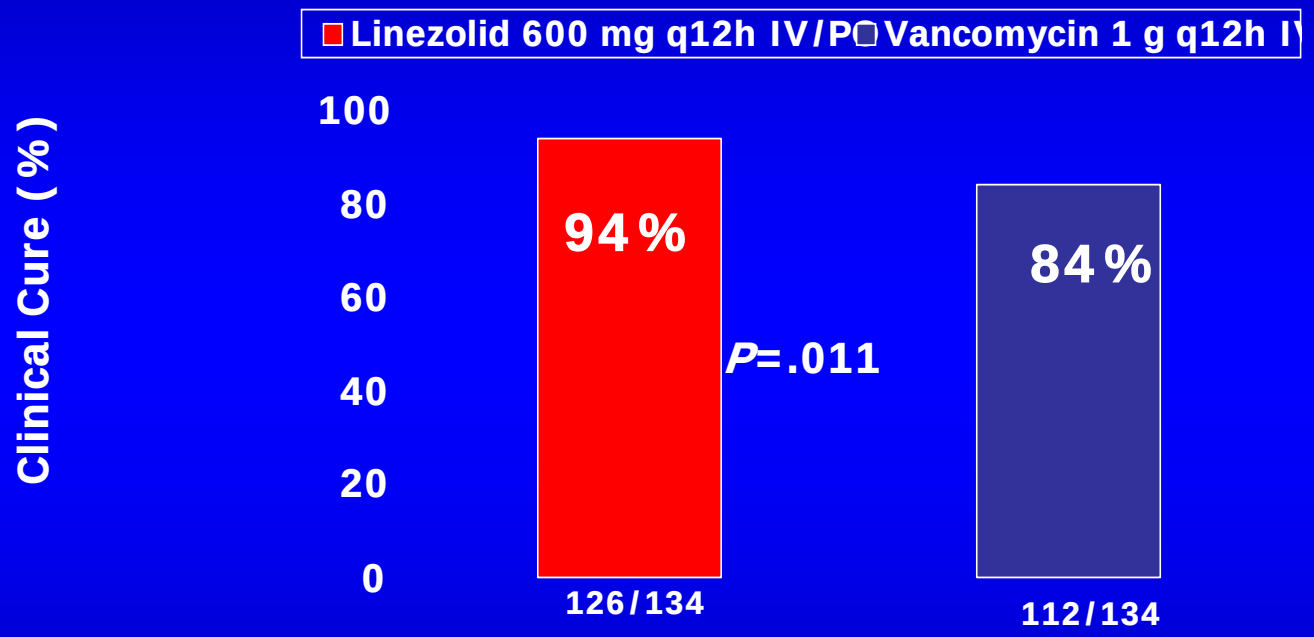
- MRSA is more likely and patient severely ill
  - vancomycin
  - linezolid
  - daptomycin
  - dalfopristin/quinupristin
  - tigecycline*

*when GPC , GNR, and anerobes are a consideration in mixed infections, i.e. diabetic foot, animal bites

Stevens DL, Bisno AL, Chambers HF, Everett ED, Dellinger P, Goldstein EJ, Gorbach SL, Hirschmann JV, Kaplan EL, Montoya JG, Wade JC.

Practice guidelines for the diagnosis and management of skin and soft-tissue infections.
Clin Infect Dis. 2005 Nov 15;41(10):1373-406.

Linezolid Versus Vancomycin* for cSSSIs
Clinical Cure Rates in MRSA cSSSIs



*Vancomycin changed to oxacillin/nafcillin/flucoxacillin/dicloxacillin if MSSA was identified.
cSSSIs = complicated skin and skin structure infections.
MRSA = methicillin-resistant *Staphylococcus aureus.*

Adapted from Data on file. Pfizer Inc., New York, NY.

Linezolid vs Vancomycin for surgical-site infections

Clinical Success (%)	Linezolid % (n = 66)	Vancomycin % (n = 69)	*p* value	95% CI
ITT	93 (53/57)	87 (48/55)	0.3563	-5.32 to 16.73
MITT	96 (45/47)	87 (40/46)	0.1582	-2.53 to 20.10
CE	98 (52/53)	87 (47/54)	0.0602	1.40 to 20.75

Weigelt J et al. Am J Surg 2004; 188: 760-766

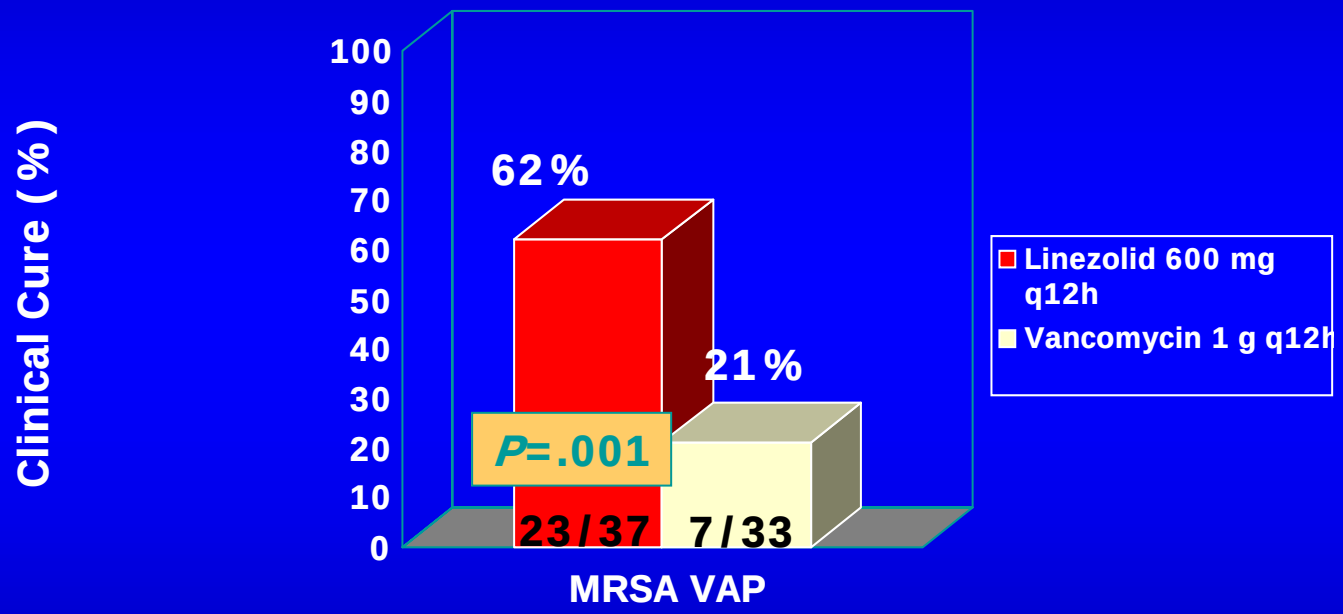
Linezolid vs Vancomycin for surgical-site infections

Microbiological Success Rate %	Linezolid %	Vancomycin %	*p* value	95 % CI
ME	84 (41/49)	58 (28/49)	0.0073	7.97 to 42.71
MRSA	87 (26/30)	48 (14/29)	0.0022	16.51 to 60.27
MSSA	89 (8/9)	56 (5/9)	0.2941	-5.08 to 71.75

Weigelt J et al. Am J Surg 2004; 188: 760-766

Linezolid Delivers Excellent Efficacy in Patients With VAP Caused by MRSA

Clinical cure rates in VAP patients with MRSA

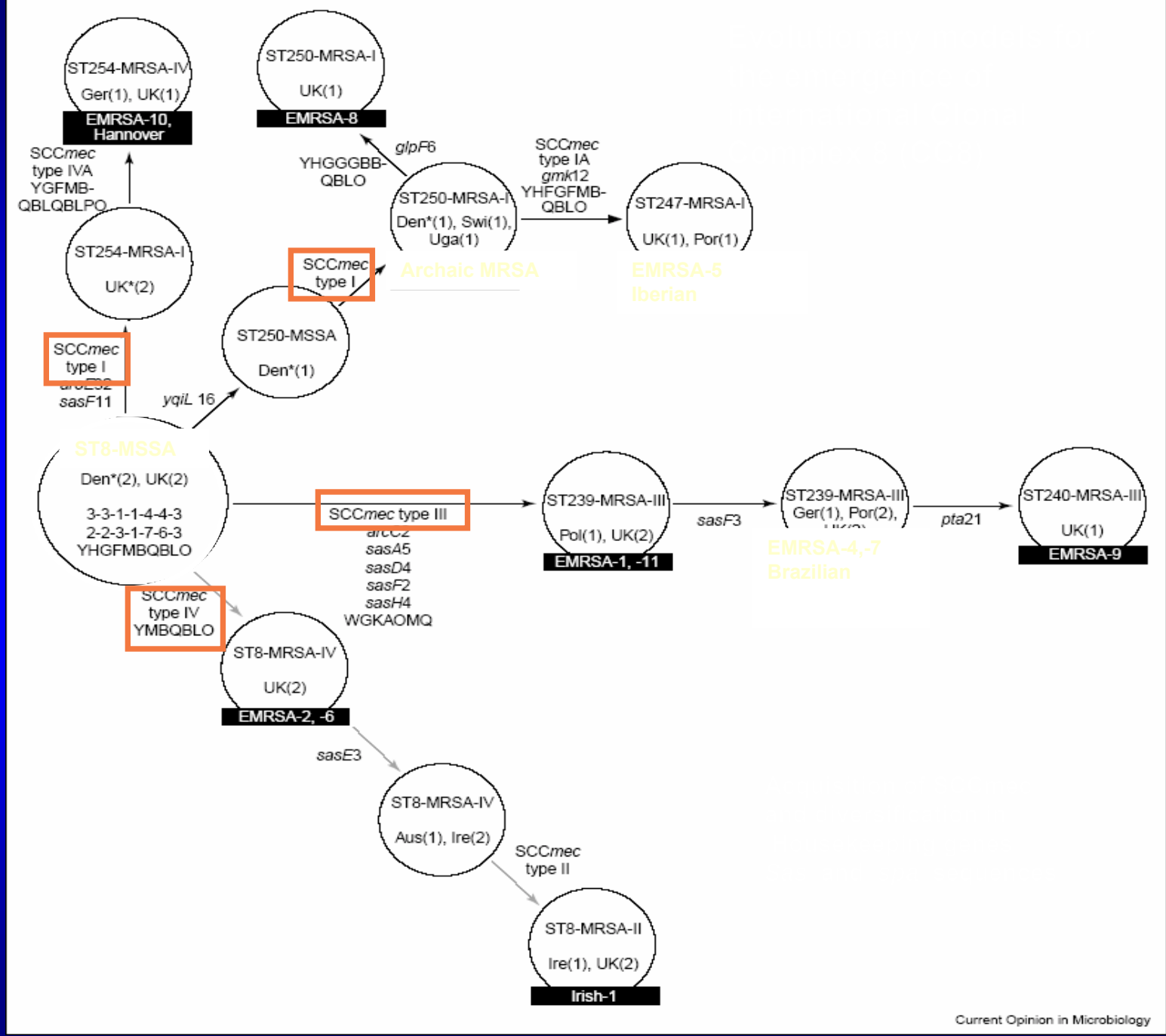


A post hoc analysis of 2 identical, randomized, double-blind, multicenter, multinational, comparator-controlled trials that compared the safety and efficacy of linezolid IV and vancomycin IV for 7 to 21 days in 1019 patients with nosocomial pneumonia, including VAP. Patients were treated for 7 to 21 days with optional aztreonam 1 g to 2 g q12h.

VAP = ventilator-associated pneumonia; MRSA = methicillin-resistant *Staphylococcus aureus.*

Adapted from Kollef MH et al. *Intensive Care Med.* 2004;30:388-394.

Please see full prescribing information available in this kit.


ST254-MRSA-IV
Ger(1), UK(1)
EMRSA-10, Hannover
SCCmec type IVA YGFMB-QBLQBLPQ
ST254-MRSA-I
UK*(2)
SCCmec type I
sasF11
ST250-MRSA-I
UK(1)
EMRSA-8
YHGGGBB-QBLO
glpF6
ST250-MRSA-I
Den*(1), Swi(1), Uga(1)
SCCmec type IA gmk12 YHFGFMB-QBLO
ST247-MRSA-I
UK(1), Por(1)
Archaic MRSA
EMRSA-5
Iberian
SCCmec type I
ST250-MSSA
Den*(1)
yqiL 16
ST8-MSSA
Den*(2), UK(2)
3-3-1-1-4-4-3
2-2-3-1-7-6-3
YHGFMBQBLO
SCCmec type III
arcC2
sasA5
sasD4
sasF2
sasH4
WGKAOMQ
ST239-MRSA-III
Pol(1), UK(2)
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sasF3
ST239-MRSA-III
Ger(1), Por(2),
EMRSA-4,-7
Brazilian
pta21
ST240-MRSA-III
UK(1)
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SCCmec type IV YMBQBLO
ST8-MRSA-IV
UK(2)
EMRSA-2, -6
sasE3
ST8-MRSA-IV
Aus(1), Ire(2)
SCCmec type II
ST8-MRSA-II
Ire(1), UK(2)
Irish-1
Current Opinion in Microbiology