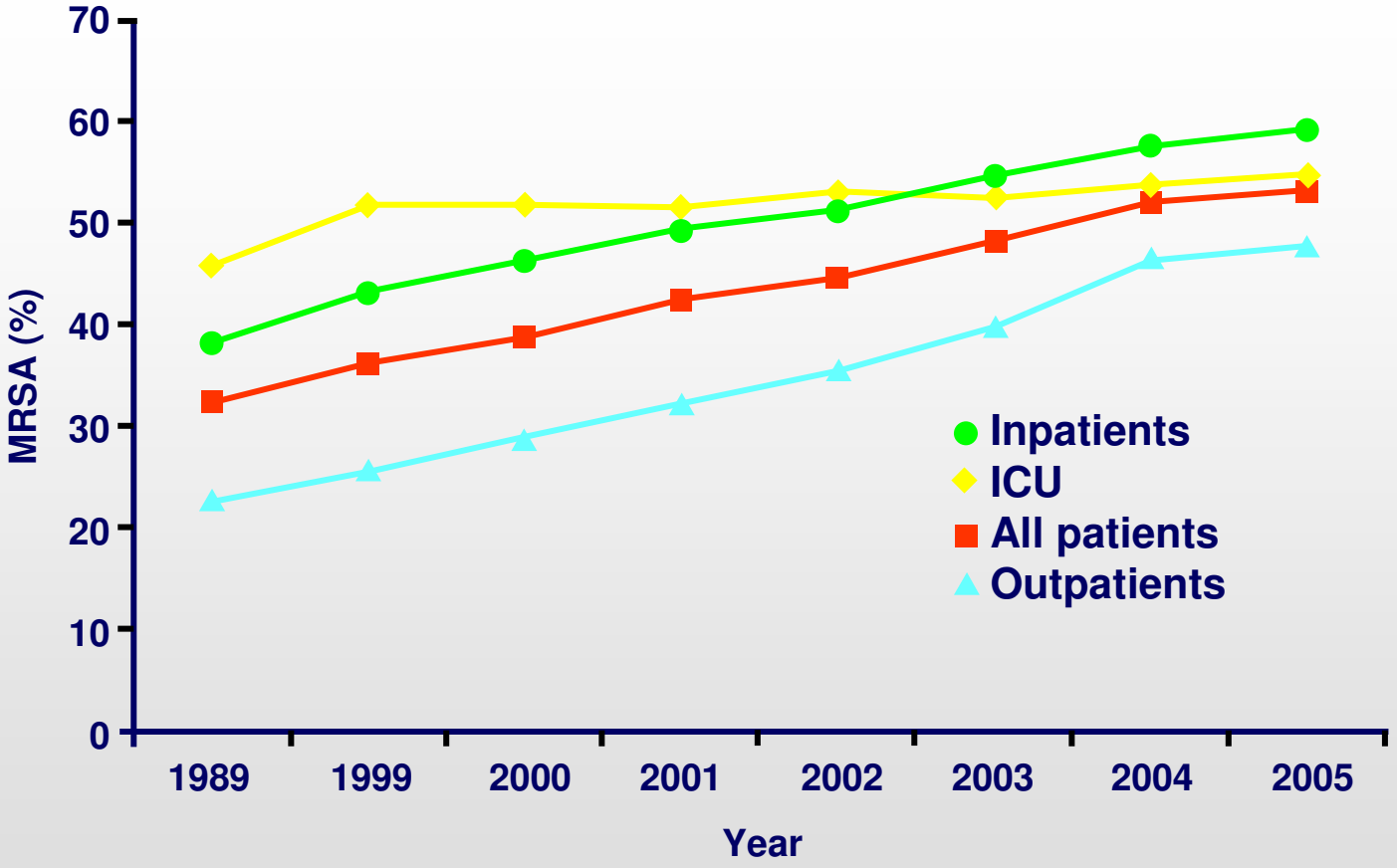
Treatment of MRSA SSTIs:
oral vs parenteral-
home vs hospital

Silvano Esposito MD
Department of Infectious Diseases
Medical School, University of Naples, Naples , Italy

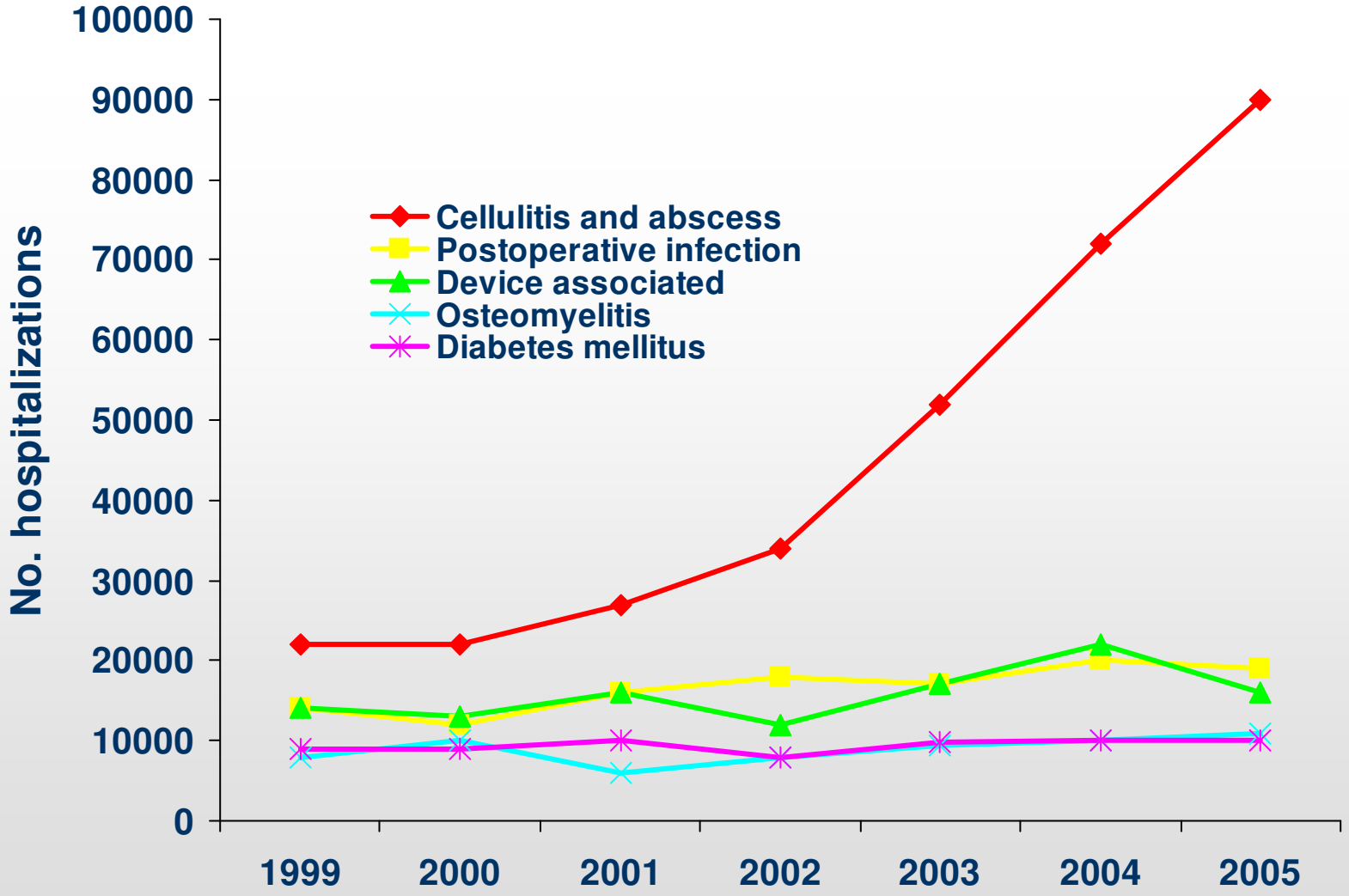
The rising prevalence of MRSA in the hospital and the community



S. aureus isolates from 300 clinical laboratories across the United States

(Styers D. *et al. Ann. Clin. Microbiol. Antimicrob.*, 2006)

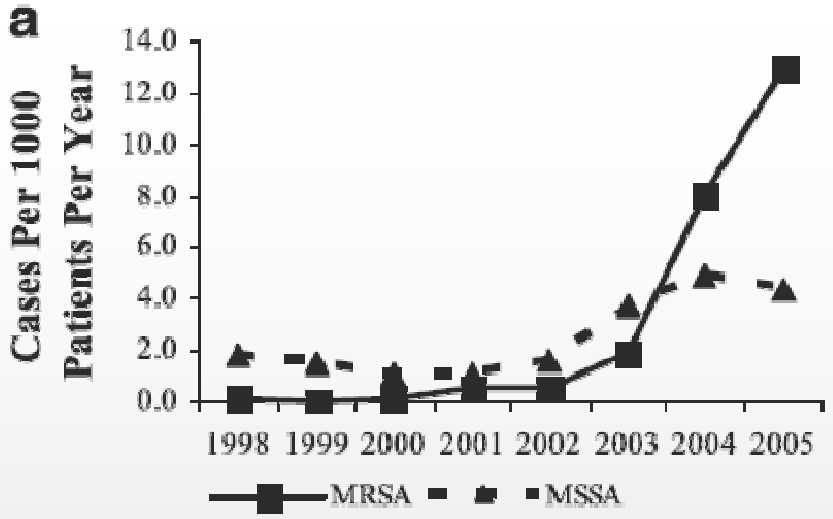
Primary diagnoses of *S. aureus*-related hospitalizations



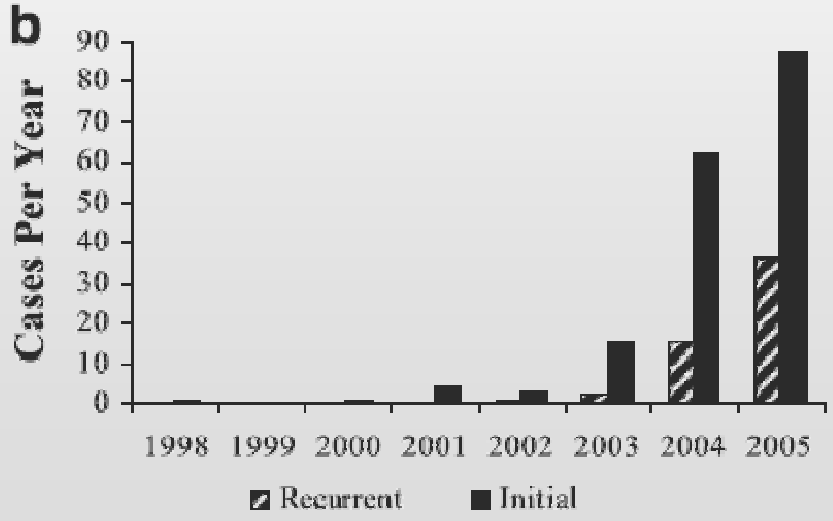
(Klein E., Smith D.L., Laxminarayan R., Emerg. Infect. Dis., 2007)

Treatment and Outcomes of Infections by MRSA at an Ambulatory Clinic

***(a) S. aureus* SSTI**



(b) Initial and recurrent MRSA SSTI



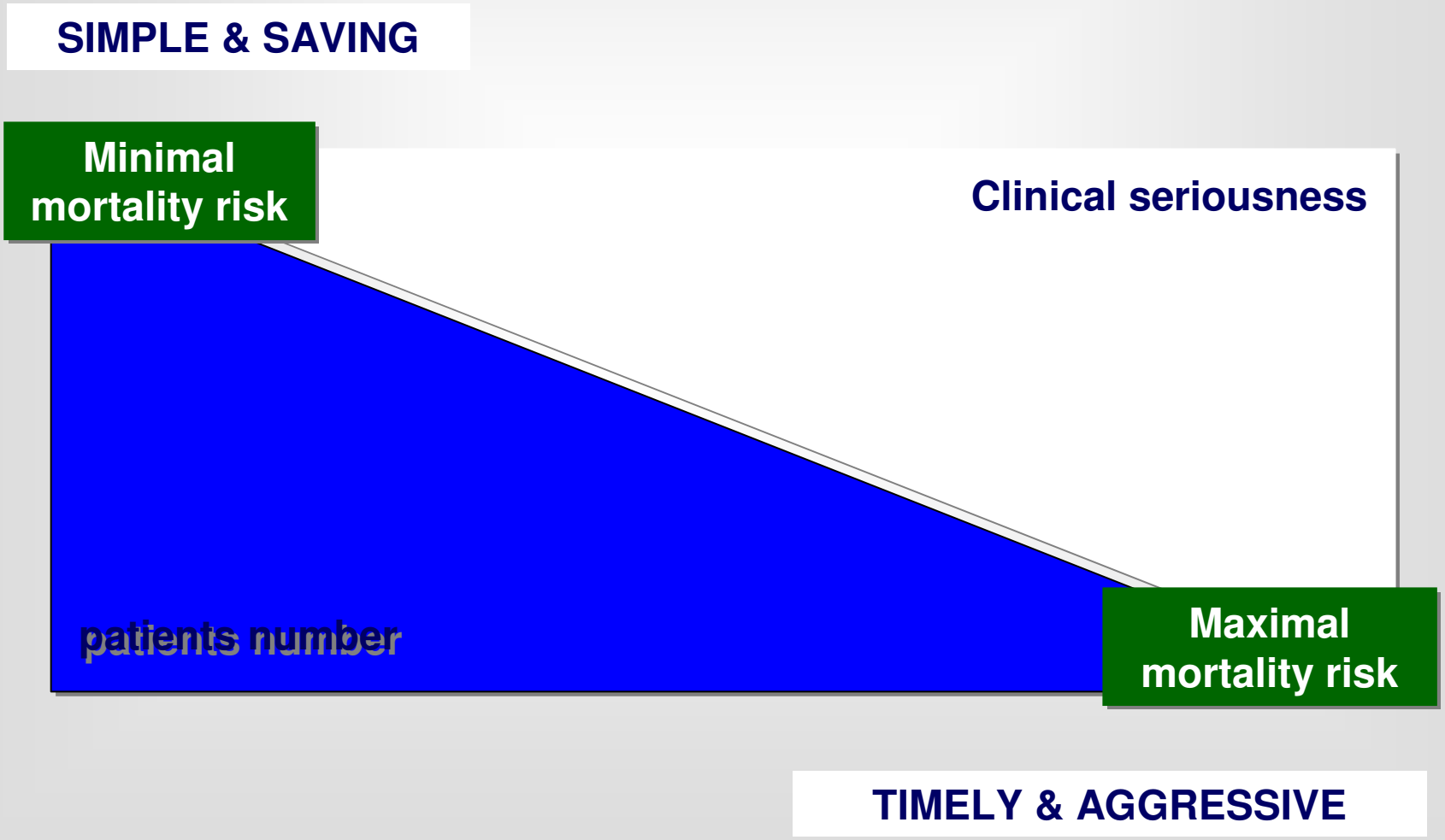
(Szumowski J.D., Antimicrob. Agents Chemother., 2007)

Factors to be considered for antibiotic therapy

- Patients selection
- Site of care
- Timing
- Route of administration
- Antibiotic choice
- Monotherapy or combination therapy
- Concomitant diseases
- Concomitant therapies
- Dosage
- Number of administrations
- Duration
- Cost

Skin and soft tissue infections Management

PREDICTION RULES AND RESOURCES INVESTMENT

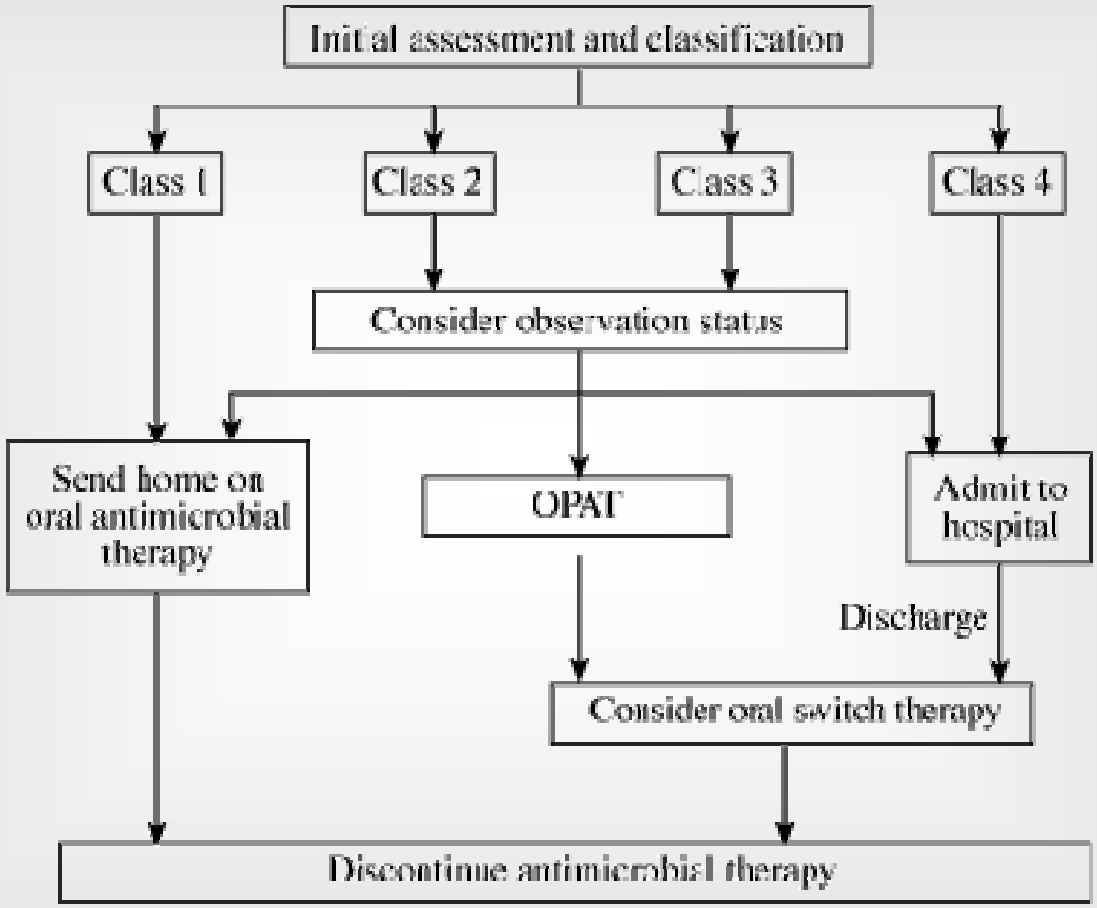


Classification of SSTIs by patient characteristics

Class	*Patient criteria*
1	Afebrile and healthy, other than cellulitis
2	Febrile and ill appearing, but no unstable comorbidities
3	Toxic appearance, or at least one unstable comorbidity, or a limb-threatening infection
4	Sepsis syndrome or life-threatening infection, e. g. necrotizing fasciitis

(Eron L. J., Antimicrob. Chemother., 2003)

Algorithm for managing SSTIs: site of care and route of therapy



(Eron L., J. Antimicrob. Chemother., 2003)

IDSA GUIDELINES

Practice Guidelines for the Diagnosis and management of Skin and Soft-Tissue Infections

Stevens D.L., Bisno A.L., Chambers H.F., Everett E. D., Dellinger P., Goldstein E.J., Gorbach S.L., Hirschmann J.V., Kaplan E.L., Montoya J.G., Wade J.C.

Clinical Infectious Diseases, 2005

Antimicrobial therapy for MRSA SSTI

Antibiotic therapy, by disease	*Adult dosage*	*Comment*
Vancomycin	30 mg/kg/day in 2 divided doses iv	For penicillin-allergic patients; parenteral drug of choice for treatment of infections caused by MRSA
Linezolid	600 mg every 12 h iv or 600 mg twice per day po	Bacteriostatic; limited clinical experience; no cross-resistance with other antibiotic classes; expensive; may eventually replace other second-line agents as a preferred agent for oral therapy of MRSA infections
Clindamycin	600/mgkg every 8 h iv or 300-450 mg 3 times per day po	Bacteriostatic; potential of cross-resistance and emergence of resistance in erythromycin-resistant strains; inducible resistance in MRSA
Daptomycin	4 mg/kg every 24 h iv	Bactericidal; possible myopathy
Doxicycline, minocycline	100 mg twice per day po	Bacteriostatic, limited recent clinical experience
TMP-SMZ	1 or 2 double-strength tablets twice per day po	Bactericidal; limited published efficacy data

Skin and soft-tissue infections caused by methicillin-resistant Staphylococcus aureus

Robert S. Daum

New England Journal Medicine, 2007

Oral agents for the outpatient treatment of putative community-associated MRSA infections

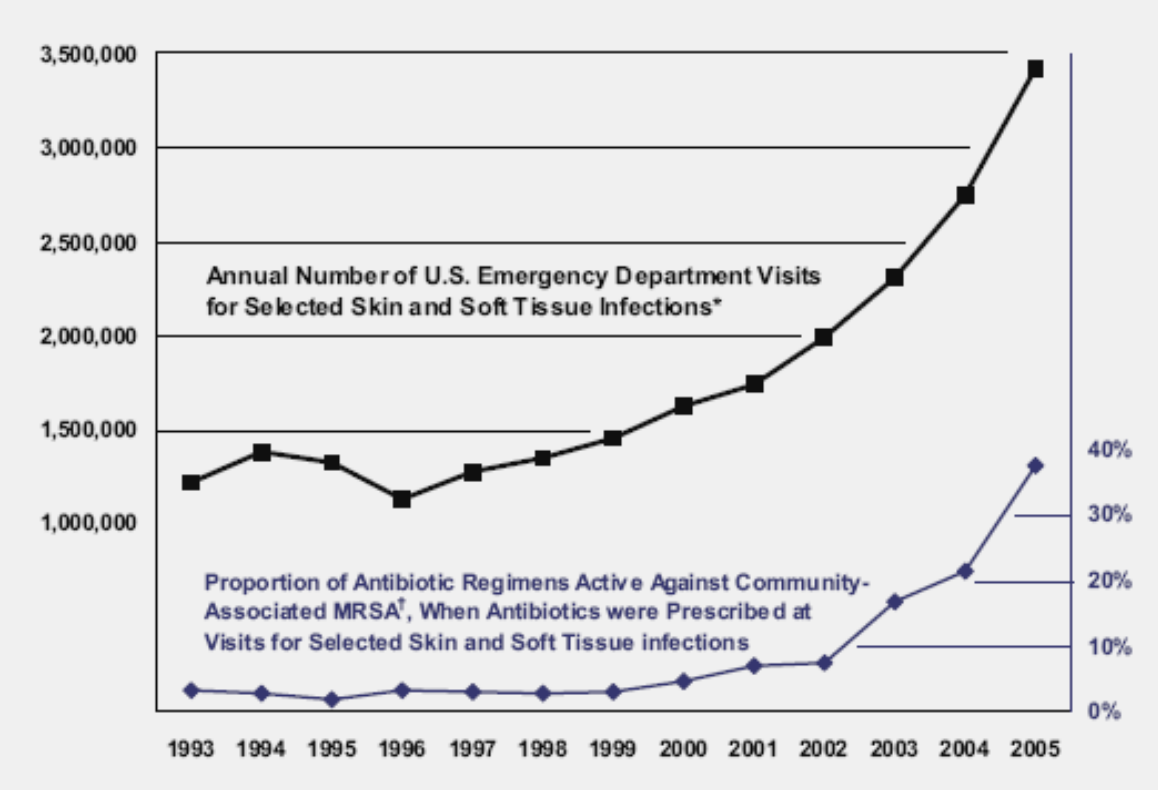
Medication	*Adult dosage*	*Comment*
Clindamycin	300 mg thrice daily	Many patients dislike the taste of the suspension
Trimethoprim-sulfamethoxazole	1 to 2 double-strength tablets twice daily (each tablet containing trimethoprim, 160 mg, and sulfamethoxazole, 800 mg)	…..
Doxycycline	100-200 mg/day, in one dose or two divided doses	…..
Minocycline	200 mg/day, in two divided doses	…..
Linezolid	600 mg twice daily	The cost is relatively high; oral suspension may not be immediately available at many pharmacies
Rifampin	20 mg/day, in one dose or two divided doses; maximum dose, 600 mg/day	No suspension is commercially available; capsule powder may be sprinkled on food such as applesauce

Oral antimicrobial agents for treatment of community-acquired MRSA infection

Agent	Adult dosage
Trimethoprim-sulfamethoxazole	1–2 double-strength tablets (160/800 mg) every 12 h
Doxycycline	100 mg every 12 h
Minocycline	100 mg every 12 h
Rifampin	600 mg every day
Clindamycin	300–600 mg every 6-8 h (pediatric dosage, 2–8 mg/kg every 6-8 h)
Linezolid	400–600 mg every 12 h
Fusidic acid (usually given in combination with rifampin)	500 mg every 8 h

(Moellering R.C., Clin. Infect. Dis., 2008)

Annual visits to US EDs for selected skin and soft tissue infections, during the emergence of community associated MRSA, 1993-2005



In the 2005, among such regimens, trimethoprim-sulfamethoxazole was prescribed at 51% (95% CI 41% to 62%) and clindamycin at 42% (95% CI 32% to 53%).

(Pallin D.J., Ann. Emerg. Med., 2008)

Prospective Randomized Trial of Empiric Therapy with Trimethoprim-Sulfamethoxazole or Doxicycline for Outpatient SSTIs in an Area of High Prevalence of MRSA

- ✓ To evaluate empirical therapy with TMP-SMZ or doxycycline for outpatient SSTIs in an area of high prevalence of MRSA , a randomized, prospective, open-label investigation was performed.

- ✓Of the 34 subjects included in the study, 14 received TMP-SMZ (8 with MRSA) and 20 received doxycycline (15 with MRSA).

- ✓ The overall clinical failure rate was 9%, with all failures occurring in the TMP-SMZ group. However, there was no significant difference between the clinical failure rate of empirical TMP-SMZ therapy and that of doxycycline therapy.

(Cenizal M.J., Antimicrob. Agents. Chemother., 2007)

Tetracyclines as an oral treatment option for patients with community onset SSTIs caused by MRSA

Setting. A retrospective cohort study of all patients who received monotherapy with either an expanded-spectrum tetracycline (doxycycline and minocycline) or a beta-lactam (cefazolin, piperacillin-tazobactam, cephalexin, dicloxacillin, amoxicillin-clavulanate) for the treatment of CO-MRSA SSTI was conducted at the University of Arkansas between October 2002 and February 2007.

Characteristic	Value for group treated with[b]:		OR (95% CI)	*P*
	Tetracycline (90 episodes)	β-Lactam (192 episodes)		
Type of infection			1.12 (0.63–1.99)	>0.2[c]
Abscess	66 (73)	145 (76)		
Cellulitis	9 (10)	26 (14)		
Furuncle/carbuncle	15 (17)	21 (11)		
Lesion size, cm [median (interquartile range)] (n = 206)[d]	4 (3–6)	4 (3–5)		>0.2
SIRS (n = 249)	13 (17)	28 (16)	0.98 (0.48–2.01)	>0.2
Incision and drainage performed at time zero	69 (77)	156 (81)	1.32 (0.72–2.42)	>0.2
Incision and drainage performed by a surgical service (n = 225)	31 (45)	100 (64)	2.19 (1.23–3.90)	0.01
Site of infection:				
Head and neck	8 (9)	13 (7)	0.74 (0.30–1.87)	>0.2
Upper extremity[e]	19 (21)	40 (21)	0.98 (0.53–1.82)	>0.2
Trunk	13 (14)	21 (11)	0.73 (0.35–1.53)	>0.2
Genitoperineal/perirectal	9 (10)	12 (6)	0.60 (0.24–1.48)	>0.2
Lower extremity[f]	33 (37)	78 (41)	1.18 (0.71–1.98)	>0.2
Hand or foot	8 (9)	28 (15)	1.75 (0.76–4.01)	0.18
Treatment failure	4 (4)	24 (13)	3.07 (1.03–9.14)	0.035
Repeat incision and drainage performed[g]	4 (100)	19 (79)		
Subsequent hospital admission		16 (67)		
Median no. of follow-up visits (range)	1 (1–4)	1 (1–5)		0.18

[a] The SSTI was considered to have a community onset if the organism was isolated from a culture specimen obtained in an outpatient setting or within 48 h after admission.
[b] Data are numbers (percentages) of patients exhibiting the characteristic, unless otherwise indicated.
[c] For abscess versus nonabscess.
[d] Maximum diameters of abscesses, furuncles, and carbuncles.
[e] Including the axilla but not including the hand.
[f] Including buttocks but not including feet.
[g] Refers to the subset of patients whose sites of SSTI were incised and drained (n = 225).

(Ruhe J.J., Antimicrob. Agents Chemother., 2007)

Fusidic acid and rifampicin

- ✓ Fusidic acid and rifampicin are useful agents with excellent antistaphylococcal activity.
- ✓ Resistance develops rapidly if either is used as monotherapy.
- ✓ There are few data regarding the combination of fusidic acid and rifampicin for the treatment of MRSA.
- ✓ Jensen et al. published a case series reported MRSA elimination in 33 of 38 (86.8%) clinical episodes following treatment with rifampicin and fusidic acid. Rifampicin resistance developed in two cases and three cases died still harbouring MRSA.
- ✓ Cox et al. used the combination of rifampicin 0.6 g/day and fusidic acid 1.5 g/day was in an outbreak that occurred in 3 hospitals and 15 care homes. Eight patients with SSTI were successfully treated.

(Moellering R.C., Clin. Infect. Dis. 2008; Jensen K. Lancet 1968; Cox R.A., J. Hosp. Infect. 1995; Gemmell C.G., J. Antimicrob. Chemother 2006; Enocha D.A., Inter. J. Antimicrob. Agent 2008)

Guidelines for UK practice for the diagnosis and management of MRSA infections presenting in the community

"If the patient is known to be MRSA-positive OR lesion cultures yield MRSA alone, then community treatment should be either oral doxycycline (contra-indicated in children <12 years) 100 mg 12 hourly, or fusidic acid 500 mg 8 hourly, or trimethoprim 200 mg 12 hourly, each combined with rifampicin 300 mg 12 hourly. Fusidic acid and rifampicin should NOT be used as monotherapy because of the danger of resistance emergence. All these agents can be used in penicillin allergic patients".

(Nathwani D., J. Antimicrob. Chemother. 2008)

Clindamycin

- ✓ At present, in the US, TMP-SMX and clindamycin are the most commonly used antimicrobial drugs for the outpatient treatment of CA MRSA infections.
- ✓ It appears that TMP-SMX is the agent primarily preferred for the therapy of adults in the US, and clindamycin is favored by many pediatricians.
- ✓ Although there are no RCT of the use of clindamycin therapy for CA MRSA infections, available anecdotal experience suggests that it is likely to be effective, provided that the organism is susceptible in vitro.
- ✓ A potential advantage of clindamycin is that it suppresses production of PVL and other virulence factors in MRSA.
- ✓ Organisms that exhibit resistance to erythromycin and susceptibility to clindamycin may exhibit resistance either because of efflux or via the inducible expression of the MLS_B gene (these organisms will be found to be susceptible by clinical microbiology laboratory testing).

(Moellering R.C., Clin. Infect. Dis. 2008; Enocha D.A., Inter. J. Antimicrob. Agent 2008; Nathwani D., J. Antimicrob. Chemother 2008; Siberry G.K., Clin. Infect. Dis., 2003)

Linezolid compared with teicoplanin for the treatment of suspected or proven Gram +ve infections

Aim: The efficacy, safety and tolerability of linezolid was compared with teicoplanin in a RCT on patients with suspected or proven Gram +ve infection. Patients received intravenous (iv) ± oral linezolid 600 mg every 12 h (n = 215) or iv or intramuscular teicoplanin (n = 215) for up to 28 days.

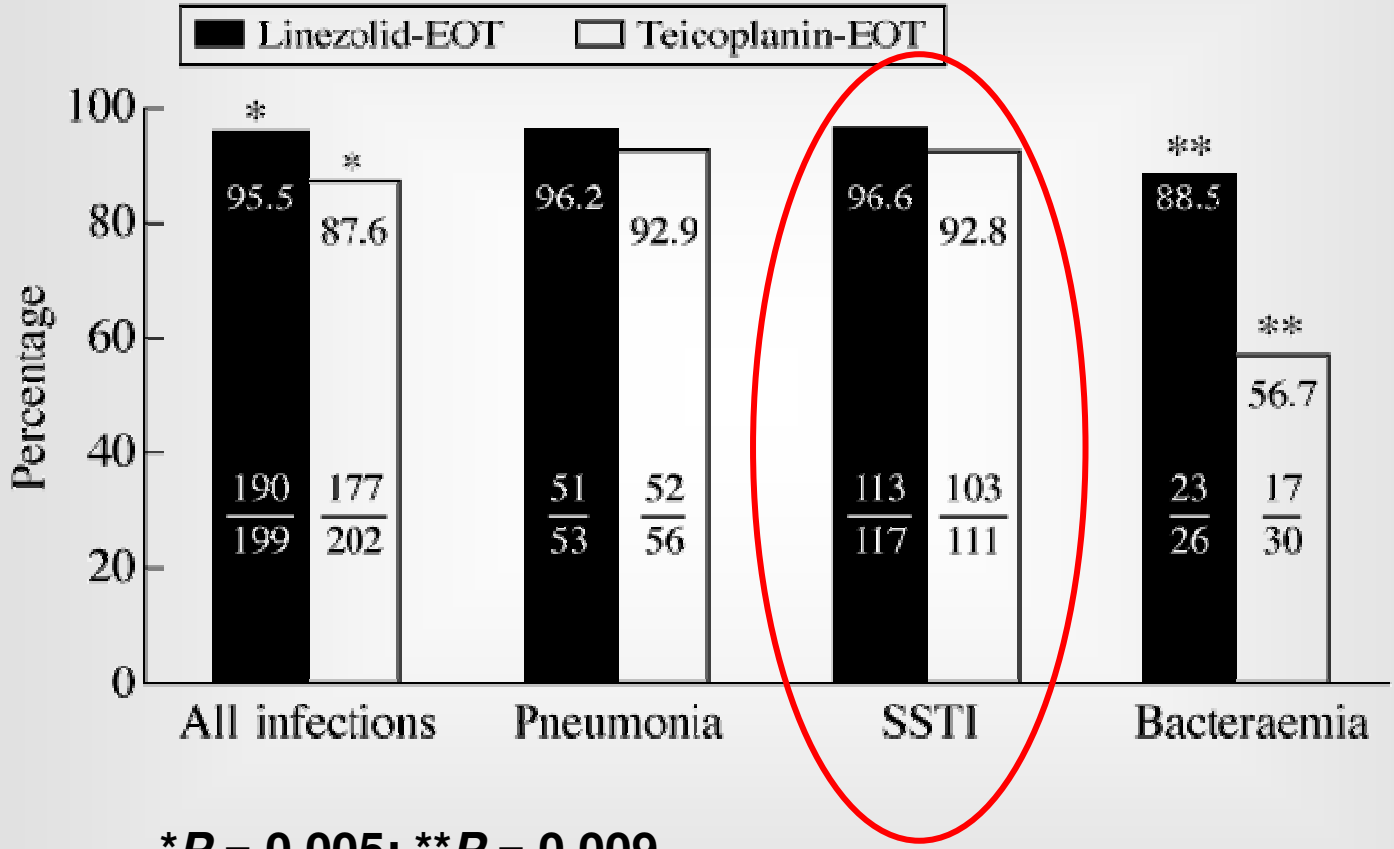
Summary of antibiotic treatment durations

	Average iv treatment duration (days)		Average non-iv treatment duration (days)		Average total treatment duration (days)	
Site of infection	linezolid	teicoplanin	oral linezolid	teicoplanin (im)	linezolid	teicoplanin
All infections	6.2	9.4	9.4	8.0	13.3	11.9
Pneumonia	6.1	8.8	7.6	5.3	12.1	10.2
SSTI	5.8	8.8	10.1	8.5	14.3	12.5
Bacteraemia	7.5	12.0	10.9	NA	12.1	12.1

Abbreviations: SSTI, skin/soft tissue infections; NA, not applicable—all bacteraemia patients in the teicoplanin group received only iv doses.

(Wilcox M., J. Antimicrob. Chemother., 2004)

Rates of clinical success with linezolid and teicoplanin by site of infection at end-of-treatment visit: ITT population



*P = 0.005; **P = 0.009

(Wilcox M., J. Antimicrob. Chemother., 2004)

Linezolid versus vancomycin in treatment of complicated skin and soft tissue infections

Patients were randomized (1:1) to receive linezolid (600 mg) every 12 h either intravenously (i.v.) or orally or vancomycin (1 g) every 12 h i.v.

Clinical success at TOC visit of CE and ME patients

Diagnosis and patient type	% of patients (no. cured/total) after treatment with:		95% CI	*P* value
	Linezolid	Vancomycin[b]		
Major skin abscess				
CE patients	98.3 (116/118)	91.1 (92/101)	1.19, 13.24	0.026
ME patients	98.0 (97/99)	90.1 (82/91)	1.14, 14.6	0.028
Cellulitis				
CE patients	91.5 (205/224)	91.5 (184/201)	−5.33, 5.28	0.993
ME patients	91.6 (120/131)	91.7 (99/108)	−7.12, 6.99	>0.999
Infected surgical incision				
CE patients	98.0 (50/51)	88.2 (45/51)	0.18, 19.43	0.112
ME patients	97.7 (43/44)	88.1 (37/42)	−1.11, 20.37	0.106

[a] Results do not include indeterminate outcomes. TOC visits occured 7 days after the end of treatment. CI, confidence interval.

[b] Patients could be switched to nafcillin, oxacillin, dicloxacillin, or flucloxacillin based on culture results.

(Weigelt J., Antimicrob. Agents Chemother., 2005)

Recommended parenteral therapy for class 2 and 3 SSTIs caused by MRSA

Recommended antimicrobial agent	Alternative antimicrobial agents	Comments
Clindamycin		suitable for certain community-acquired MRSA strains
Daptomycin		once daily; iv only; highly bactericidal
Linezolid		suitable for hospital- or nursing-home-acquired MRSA; oral bioavailability almost 100%
Teicoplanin		once-daily iv or im administration; loading doses may be necessary for severe infections
Vancomycin		appropriate for hospital- or nursing home-acquired MRSA
	quinupristin + dalfopristin	must be administered with a peripherally inserted central catheter line, twice daily
	fusidic acid + rifampicin	for class 1 patients
	minocycline	paucity of data and experience; for class 1 patients
	rifampicin + …	only used in combination with other drugs

(Eron L., J. Antimicrob. Chemother., 2003)

ELSEVIER

International Journal of Antimicrobial Agents 30 (2007) 1–3

INTERNATIONAL JOURNAL OF
Antimicrobial
Agents

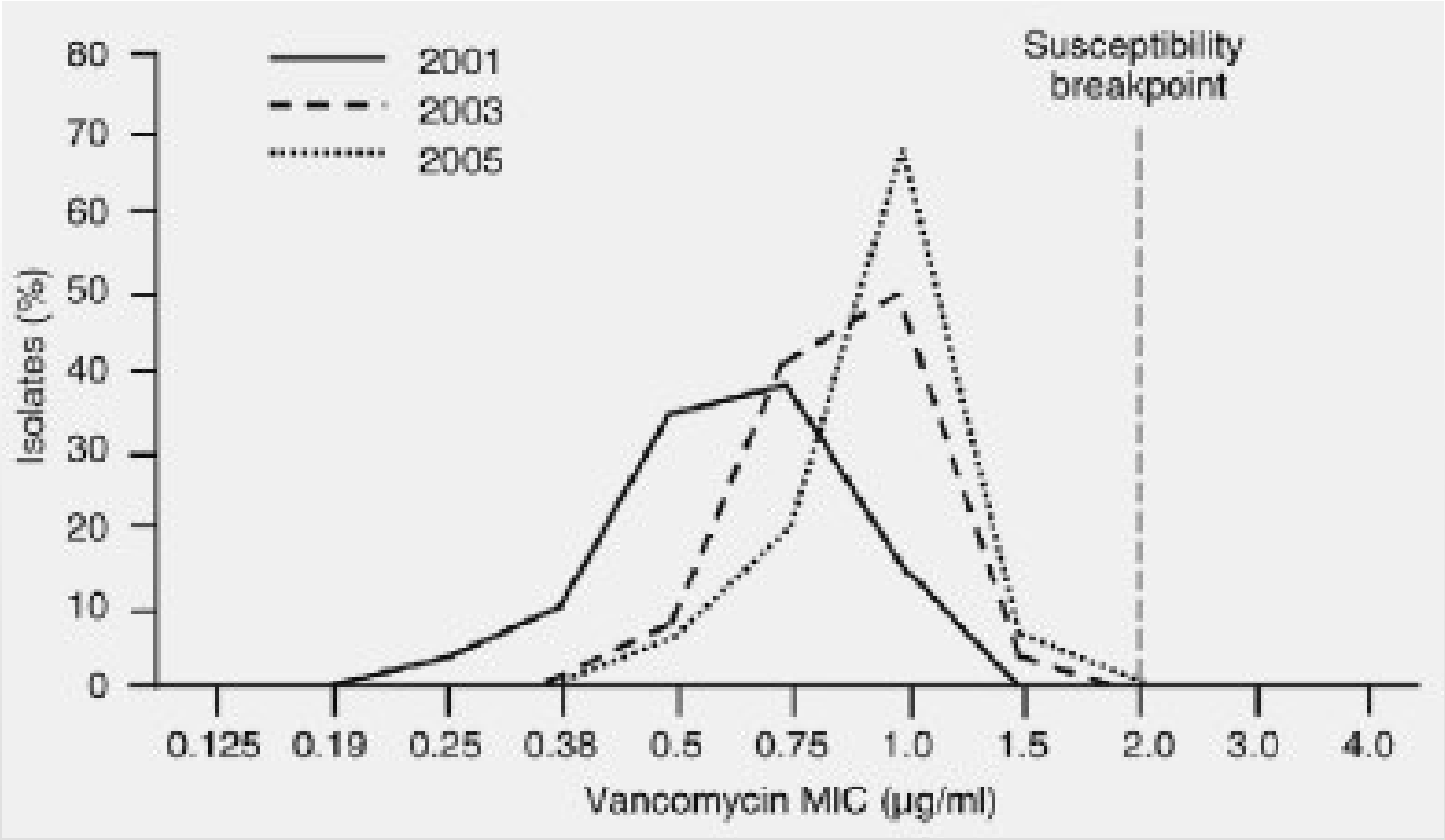
www.ischemo.org

Editorial

The problem with glycopeptides

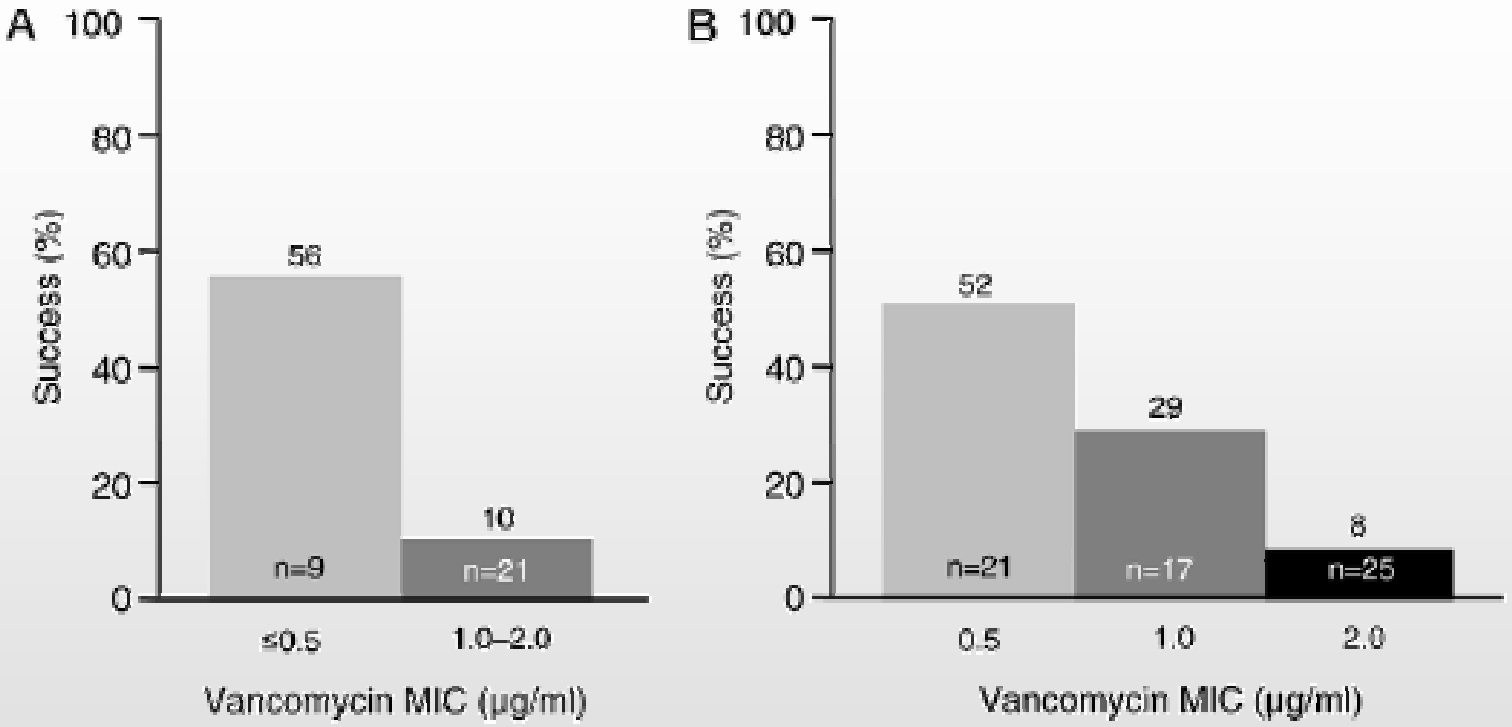
I.M. Gould *
Department of Medical Microbiology, Aberdeen Royal Infirmary, Foresterhill, Aberdeen AB25 2ZN, UK

Vancomycin 'MIC creep' over 5 years in the New Hanover Regional Medical Center, NC, USA



(Steinkraus G., J. Antimicrob. Chemother. 2007)

Vancomycin success by MIC



(Gould I.M., Inter. J. Antimicrob. Agent., 2008; Sakoulas G., J. Clin. Microbiol., 2004; Moise-Broder P.A., Clin. Infect. Dis., 2004)

The Efficacy and Safety of Tigecycline in the Treatment of SSSIs: Results of 2 Double-Blind Phase 3 Comparison Studies with Vancomycin-Aztreonam

Clinical cure rates by study population at the test-of-cure visit.

Population, type of infection	Tigecycline		Vancomycin-aztreonam		Difference (tigecycline − vancomycin-aztreonam), % (95% CI)	Test for noninferiority, *P*	Test for differences
	No. of patients/total	Percentage of patients (95% CI)	No. of patients/total	Percentage of patients (95% CI)			
Clinically evaluable	365/422	86.5 (82.9–89.6)	364/411	88.6 (85.1–91.5)	−2.1 (−6.8 to 2.7)	<.001	.4233
c-mITT	429/538	79.7 (76.1–83.1)	425/519	81.9 (78.3–85.1)	−2.1 (−7.1 to 2.8)	<.001	.4183
Microbiologically evaluable	241/279	86.4 (81.8–90.2)	231/261	88.5 (84.0–92.1)	−2.1 (−8.1 to 3.8)	<.001	.5378
Monomicrobial	139/161	86.3 (80.0–91.2)	133/150	88.7 (82.5–93.3)	−2.3 (−10.2 to 5.7)		
Polymicrobial	102/118	86.4 (78.9–92.0)	98/111	88.3 (80.8–93.6)	−1.8 (−11.2 to 7.6)		−2.1 (7.7 to 3.5)[a]
m-mITT	318/377	84.4 (80.3–87.9)	304/360	84.4 (80.3–88.0)	−0.1 (−5.6 to 54.)	<.001	1.0000
Monomicrobial	185/217	85.3 (79.8–89.7)	183/214	85.5 (80.1–89.9)	−0.3 (−7.3 to 6.8)		
Polymicrobial	133/160	83.1 (76.4–88.6)	121/146	82.9 (75.8–88.6)	0.2 (−8.6 to 9.3)		−0.1 (−5.3 to 5.2)

NOTE. c-mITT, clinical modified intent-to-treat population; m-mITT, microbiological modified intent-to-treat population.

[a] Adjusted difference and its 95% CI are calculated from a generalized linear model with a binomial probability function and an identity link.

(Ellis-Grosse E.J., Clin. Infect. Dis., 2005)

The Safety and Efficacy of Daptomycin for the Treatment of Complicated Skin and Skin-Structure Infections

Clinical success rates, by study population

Population	Daptomycin group		Comparator group[a]		95% CI[b]
	No. of patients	Success rate, %	No. of patients	Success rate, %	
Intent-to-treat	534	71.5	558	71.1	−5.8 to 5.0
Modified intent-to-treat	428	74.5	471	74.7	−5.5 to 5.9
Clinically evaluable	446	83.4	456	84.2	−4.0 to 5.6
Microbiologically evaluable	365	84.7	396	85.9	−3.8 to 6.3

[a] Cloxacillin, flucloxacillin, nafcillin, oxacillin, or vancomycin.
[b] The 95% CI around the difference in success rate (the rate in the comparator group minus that for the daptomycin group).

(Arbeit R.D. et al., Clin. Infect. Dis., 2004)

The Safety and Efficacy of Daptomycin for the Treatment of Complicated Skin and Skin-Structure Infections

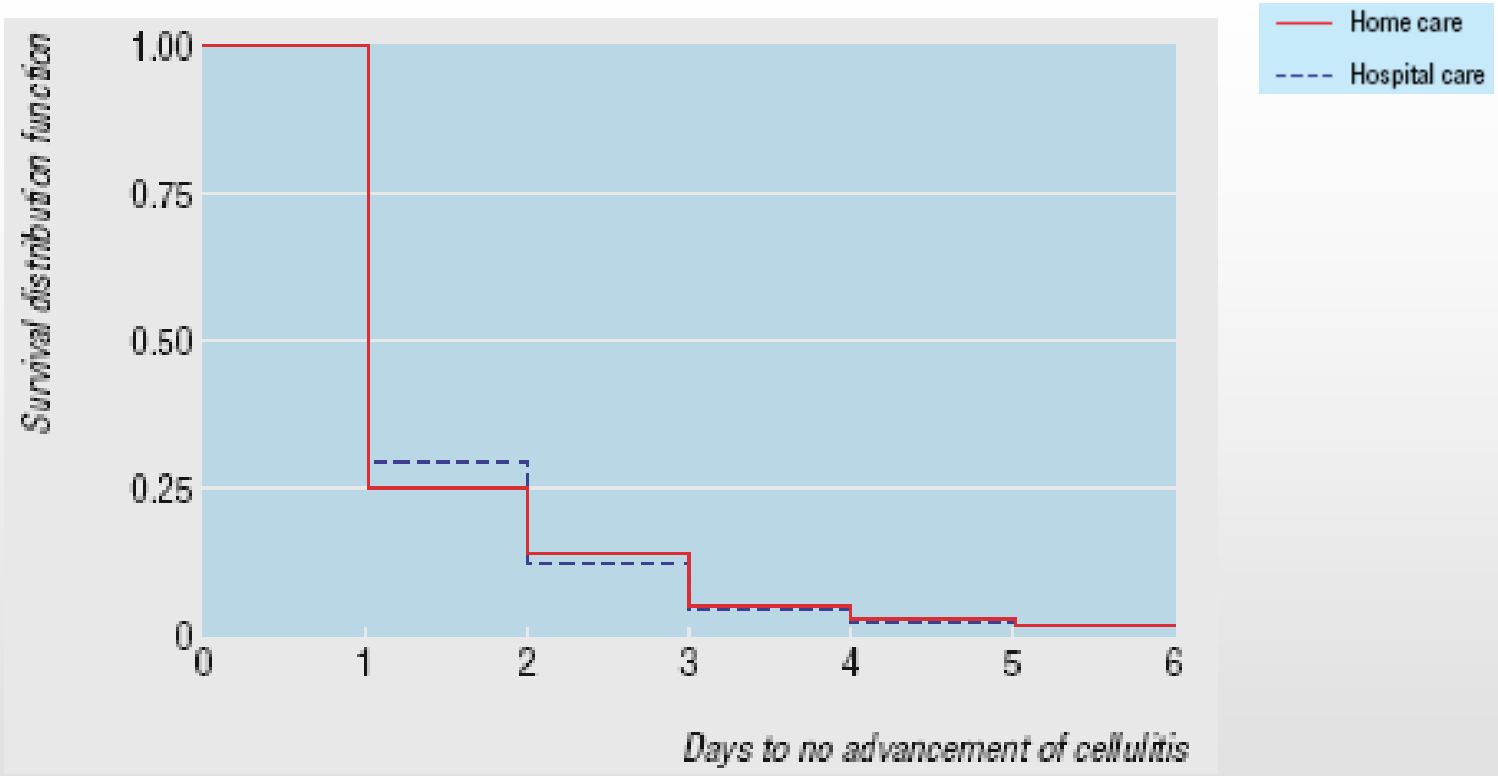
Clinical success rates, by investigator baseline diagnosis

	Daptomycin group		Comparator group[a]		
Investigator diagnosis	No. of patients	Success rate, %	No. of patients	Success rate, %	95% CI[b]
Wound infection	169	84	180	87	−4.8 to 10.1
Major abscess	102	92	92	88	−12.6 to 4.3
Infected ulcer, diabetic	47	66	56	70	−14.4 to 21.8
Infected ulcer, nondiabetic	47	79	58	83	−11.2 to 19.3

[a] Cloxacillin, flucloxacillin, nafcillin, oxacillin, or vancomycin.
[b] The 95% CI around the difference in success rate (the rate in the comparator group minus that for the daptomycin group).

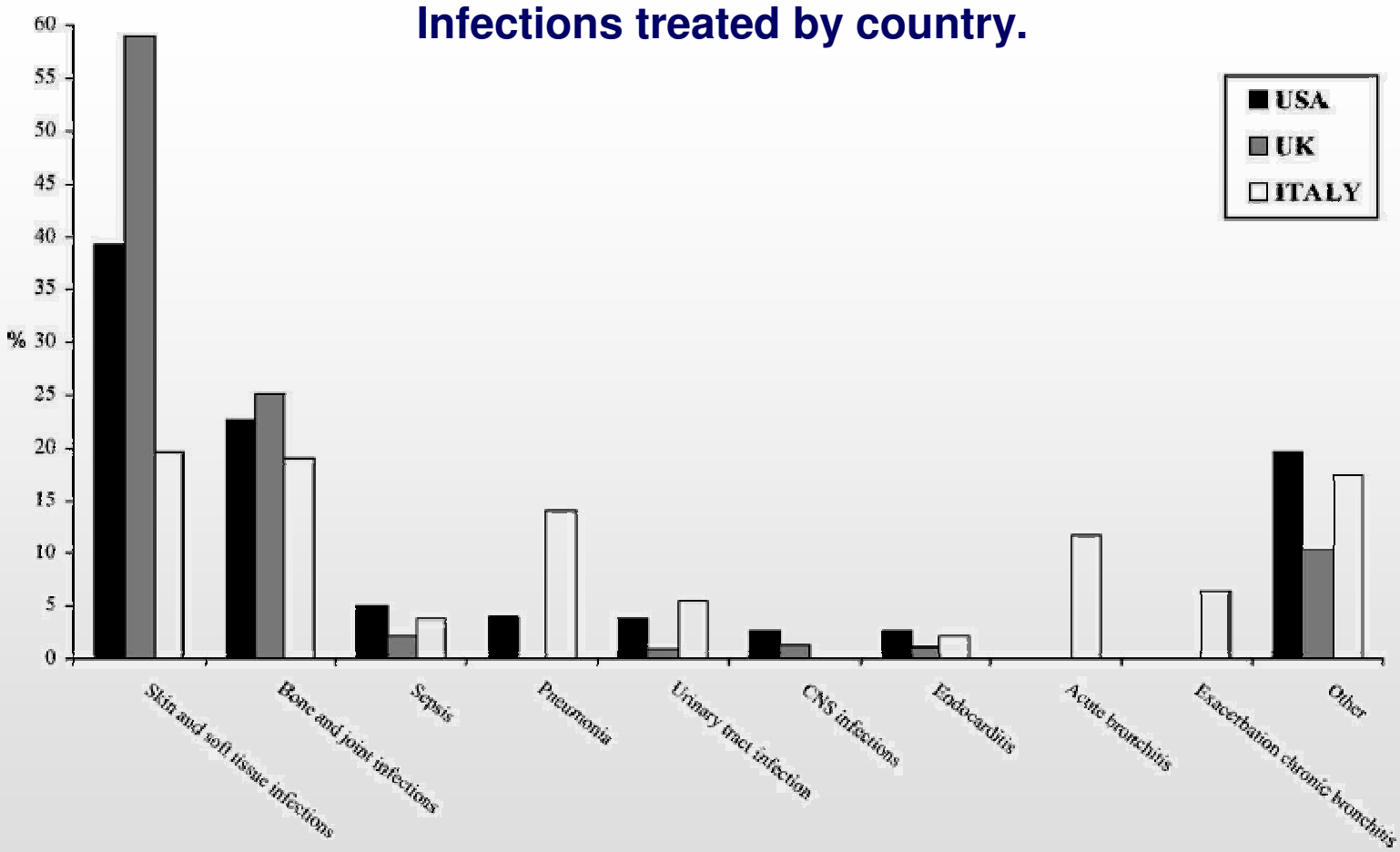
(Arbeit R.D. et al., Clin. Infect. Dis., 2004)

Randomised controlled trial of intravenous antibiotic treatment for cellulitis at home compared with hospital



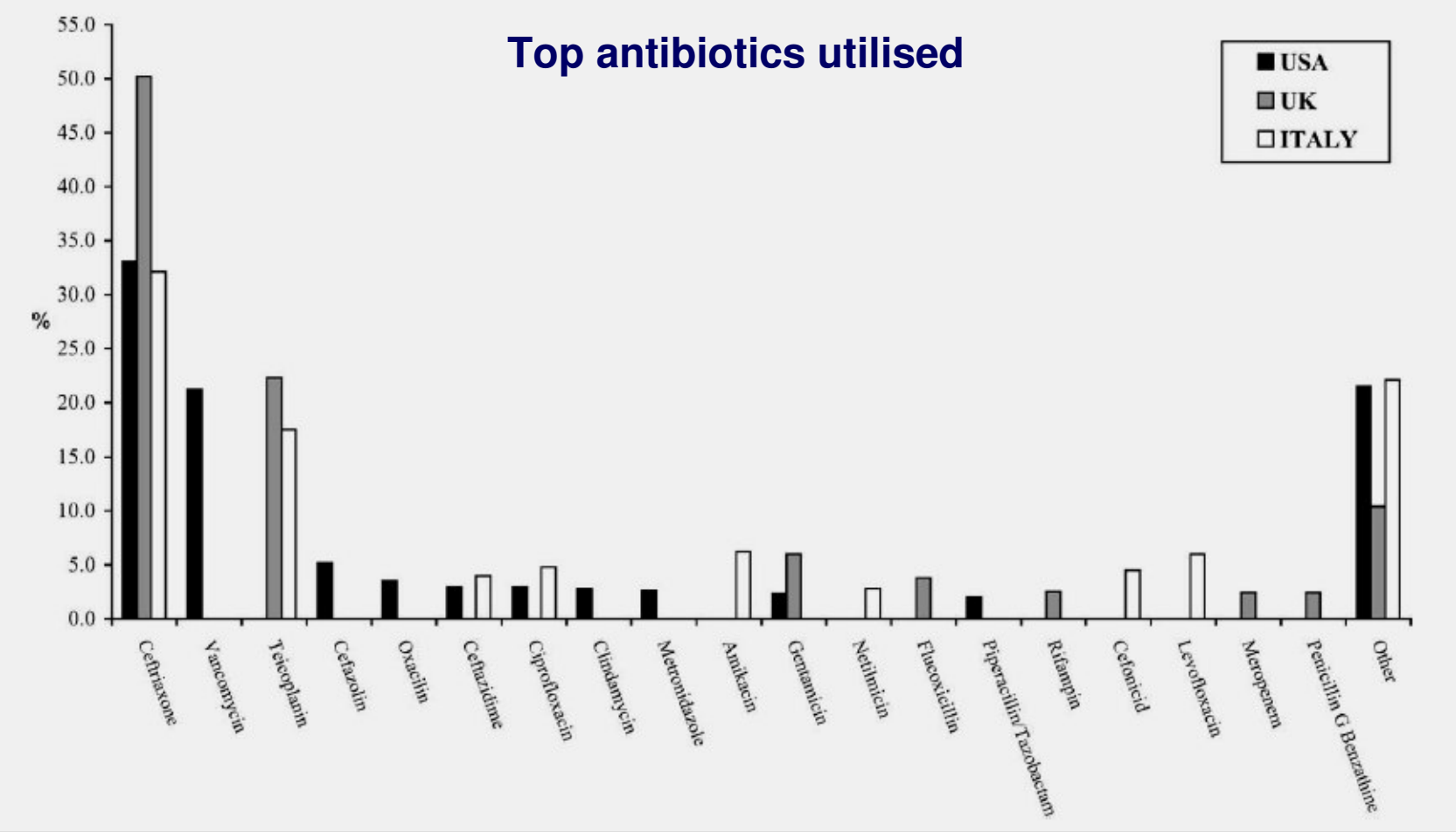
(Corwin P., B.M.J., 2005)

Outpatient parenteral antibiotic therapy (OPAT) in different countries: a comparison



(Esposito S., Inter. J. Antimicrob. Agent, 2004)

Outpatient parenteral antibiotic therapy (OPAT) in different countries: a comparison



(Esposito S., Inter. J. Antimicrob. Agent, 2004)

Outpatient parenteral antibiotic therapy with daptomycin: insights from a patient registry

Infection type by location of daptomycin therapy

Type of infection	OPAT patients, no. (% of OPAT patients)	IPAT patients, no. (% of IPAT patients)	Total no. (% of total infections)	p-value*
Endocarditis	14 (2.6%)	15 (3.6%)	29 (3.1%)	0.349†
Bacteremia	73 (13.5%)	143 (34.8%)	216 (22.8%)	< 0.001
Osteomyelitis	98 (18.2%)	18 (4.4%)	116 (12.2%)	< 0.001†
Other	78 (14.5%)	75 (18.3%)	153 (16.1%)	0.113
cSSSI	177 (32.8%)	123 (30.0%)	300 (31.6%)	0.351
ucSSSI	99 (18.4%)	36 (8.8%)	135 (14.2%)	< 0.001
Total	539 (56.8%)‡	410 (43.2%)‡	949 (100%)	< 0.001

*Differences in proportion of infection type for OPAT patients vs. IPAT patients. Chi-square test unless otherwise indicated. Overall table chi-square $p < 0.001$. †Fisher's exact test. ‡no. (% of total infections). OPAT, outpatient parenteral antibiotic therapy; IPAT, inpatient parenteral antibiotic therapy; cSSSI, complicated skin and skin structure infections; ucSSSI, uncomplicated skin and skin structure infections.

(Martone W.J., Int. J. Clin. Pract., 2008)

Conclusions

- **The prevalence of MRSA is rising in the hospital and the community**
- **SSTIs as primary diagnosis of *S. aureus*-related hospitalizations is dramatically rising as well**
- **Site of care and route of administration are important factors to be considered for antibiotic therapy according to the clinical severity of the infection**
- **Several old drugs (rifampin, clindamycin, doxicycline, cotrimoxazole) can be effective as oral agents**
- **Few new agents (daptomycin, tigecycline, linezolid) are available as parenteral agents**
- **Linezolid is the only agent available as oral and parenteral formulation. This makes easier a possible sequential therapy and an early discharge**