Update on the Management and Prevention of MRSA

Louis D. Saravolatz, MD, MACP
St John Hospital and Medical Center
October 14, 2016

Disclosures
Louis Saravolatz, M.D. , MACP

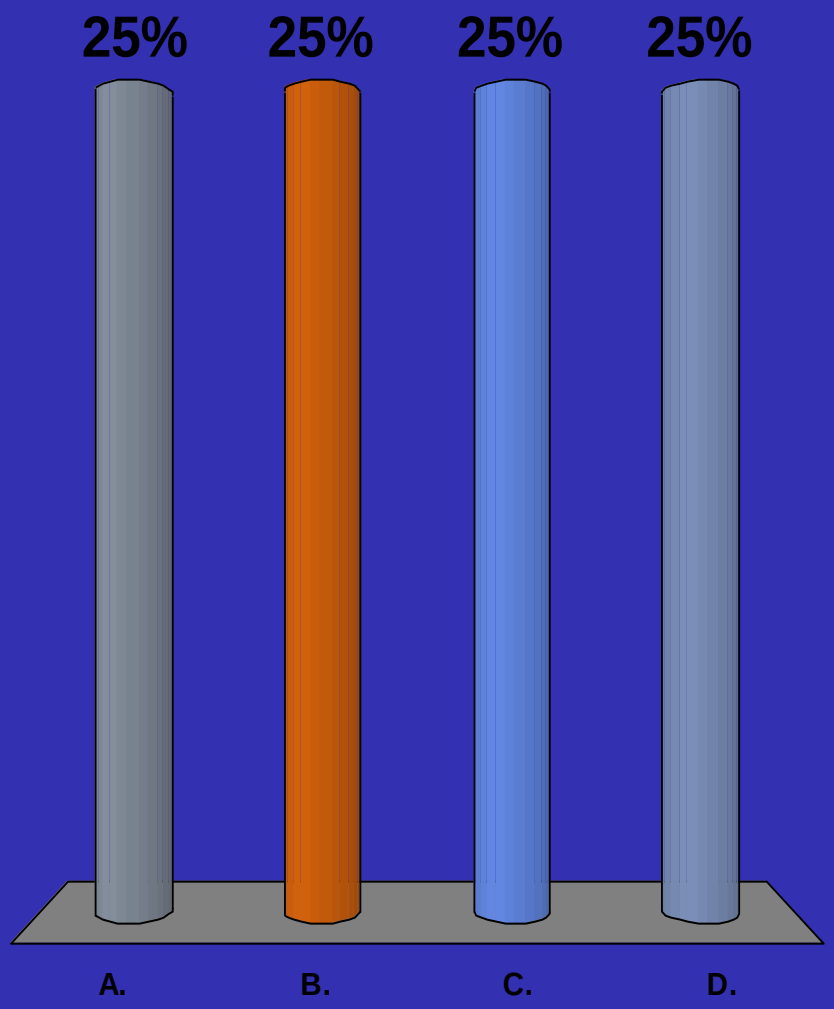
Research support: Lytix Laboratories, Cerexa, R-Pharm, Taxis, Theravance

Case Study Skin Infections

- 20-year-old wrestler presented to the ER with a “spider bite” on his arm. He developed a stinging feeling the previous day and now has pain in a golf ball-sized area
- Temperature, 38.7^{o} C
- Fluctuant area on arm that is warm, red, tender, and 5 $\times$ 7 cm
- WBC, 12,800/μL
- Gram stain of aspirate showed gram-positive cocci

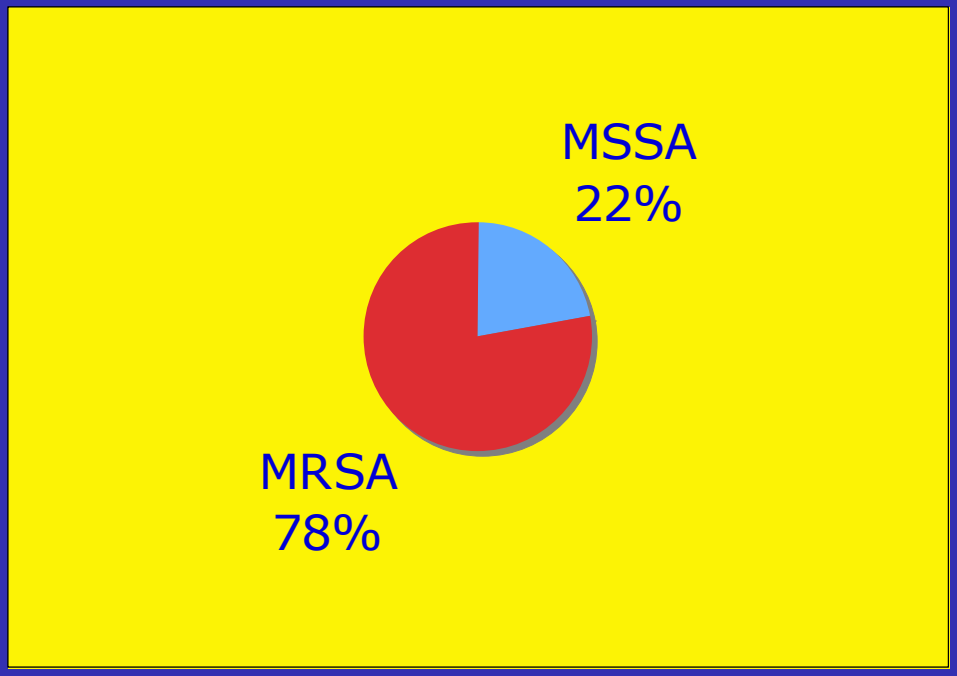
What is the most likely organism?

- A. MRSA
- B. MSSA
- C. group A Streptococci
- D. group B Streptococci



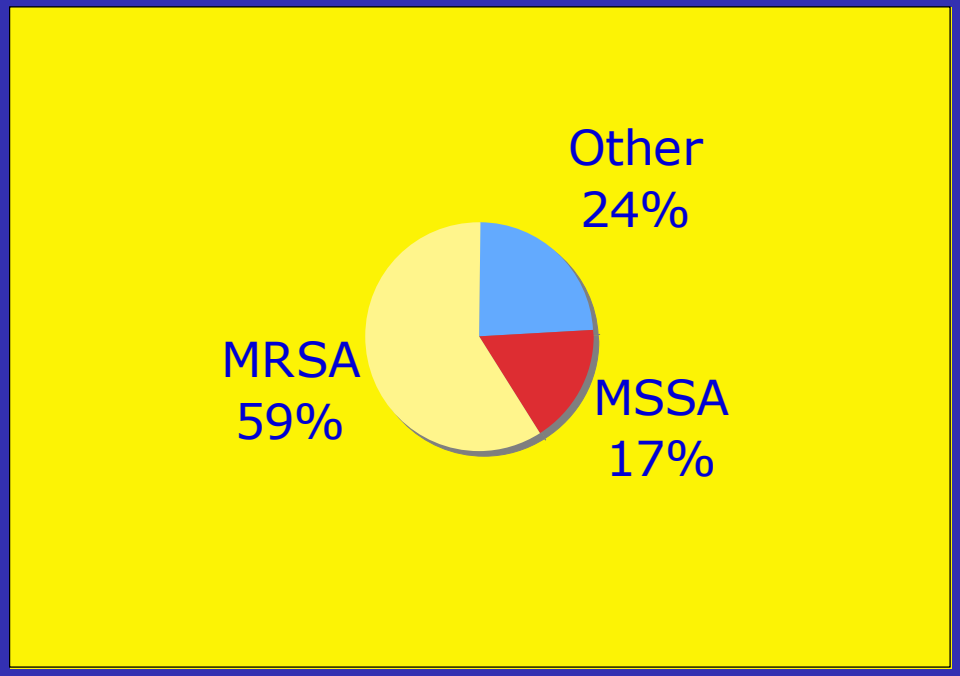
MRSA in U.S. EDs, August 2004

- 73% with MRSA had no risk factor for HCA infection



S. aureus

N=320



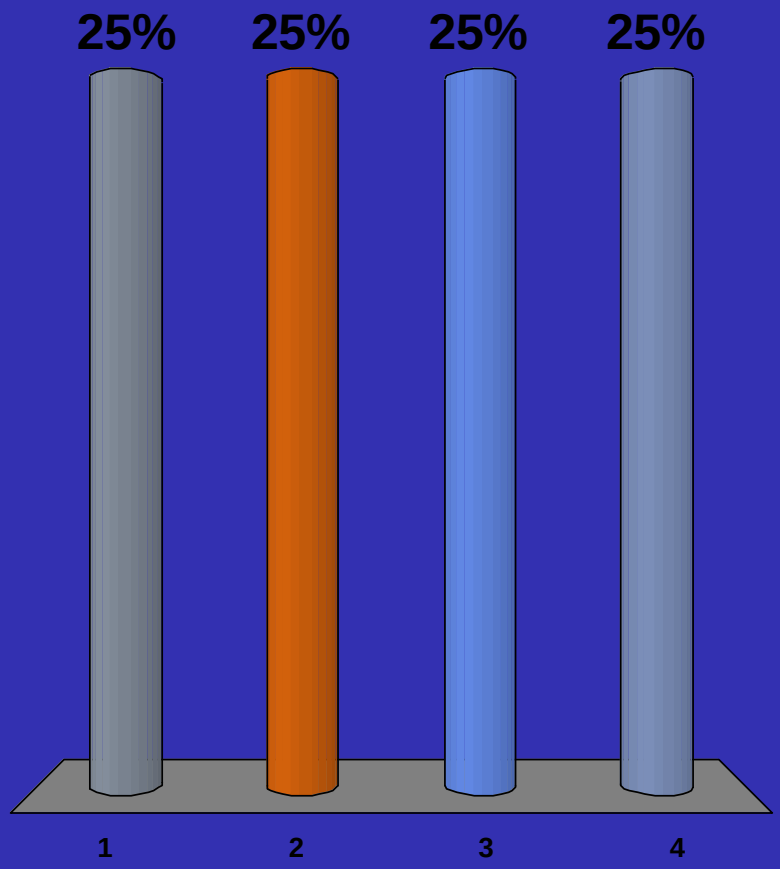
Total Isolates

N=422

NEJM 2006; 355:666-74.

What is the rate of penicillin resistance for group A streptococci at your hospital?

1. 0%
2. 25%
3. 65%
4. 100%



Epidemiology of *S aureus* Infections

- Organism usually spread by direct person-to-person contact
- Spread from inanimate objects can occur and has been seen in outbreaks among football players, fencers, river raft guides, etc.
- Common denominators: Crowding, Contact, Cleanliness, Compromise of skin

Sheagren. *N Engl J Med.* 1984;310:1368-1373.
Rimland et al. *J Clin Microbiol*. 1986;24:137-138.
Centers for Disease Control (CDC). *MMWR Morb Mortal Wkly Rep*. 1982;31:605-607.

Epidemiology of *S aureus* Infections

- Predominant reservoir of organisms = human beings
- Approximately 15% – 35% of normal people harbor *S aureus* in nares or pharynx at a given point. Longitudinal view of carriage:
  - 30% prolonged, 50% intermittent, 20% never
  - Vaginal carriage in ~10% of premenopausal women
  - Rectal and perineal carriage also occur especially in CAMRSA
  - Oral pharyngeal colonization is higher for CAMRSA
- Patients with MRSA infections may have high prevalence (60%) of gastrointestinal colonization or carriage

Methicillin Resistant *S. aureus*

Healthcare and community associated

Invasive infections: 80,000 Deaths: 11,000

CA-MRSA Infections

Ocular, orbital infections

Ophthalmol 2006; 113:455-62.

SSTI

NEJM 2006; 355:666-74.

Hand infections

J Plast Reconst Surg 2006; 118:161-6.

Postpartum mastitis

CID 2003: 37:1313-9.

Endocarditis

Bacteremia

Clin Infect Dis 2006; 42:647-56

Pneumonia

EID 2006; 12:894-9.

Surgical site infections

Prosthetic joint infections

Am J Infect Cont 2005; 33:385-91.

Necrotizing fasciitis

NEJM 2005; 352:1445-53.

Pyomyositis

Clin Infect Dis 2006; 43:953-60.

Hematogenous osteoarticular infections

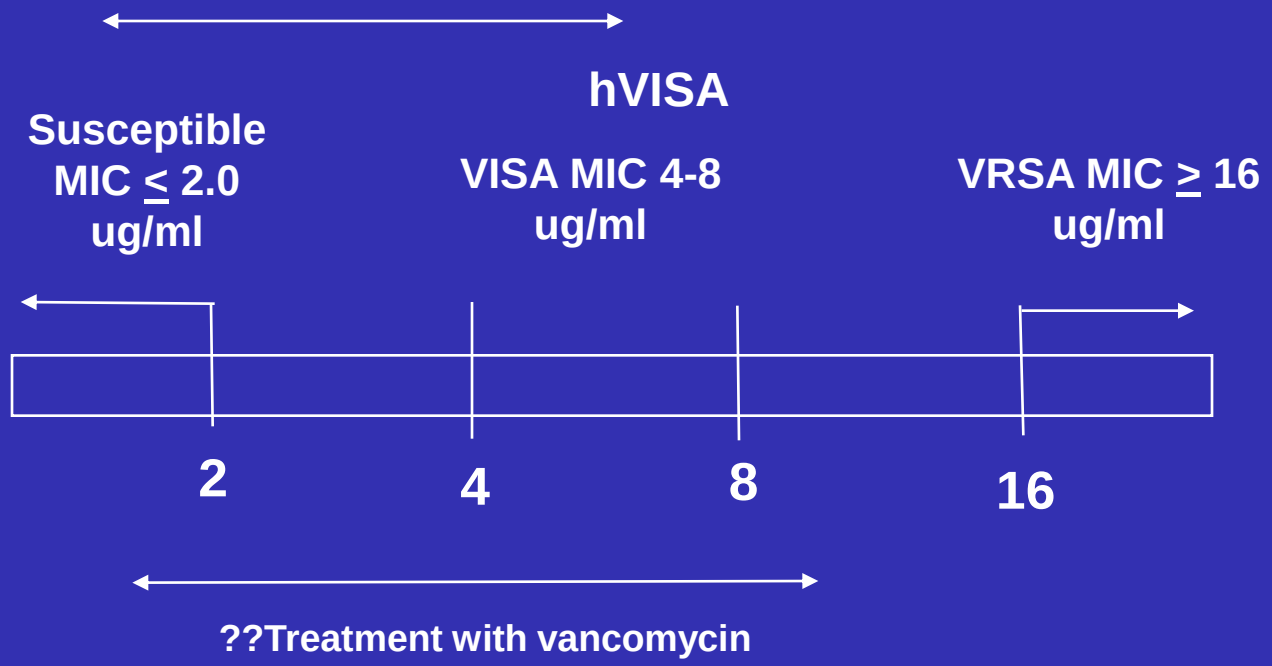
Pediatrics 2005; 115:642-8.

Diabetic foot infections

S.aureus Susceptibility– Detroit and Akron

	N	Oxa	Levo	CL	Vanc	T/S
St John	865	42	-	67	100	96
Det Rec	380	34	-	82	100	99
Summa	1594	53	68	67	100	98.1
Sinai-Grace	698	31	-	77	100	99

Definitions of VISA, hVISA and VRSA



CLSI M100-S16 16th suppl 2006;
Jones RN CID 2006;42:S13-24

Detection of Isolates with vanco MIC ≤ 2; Broth Microdilution vs E test

MIC	BMD	E Test
1	97%	10%
1.5	0	58%
2	3%	32%

Sader, AAC, 2009

Detection of VISA by different susceptibility testing methods

- Swenson, JCM 2008, compared to CLSI broth microdilution for detection of VISA
  - Phoenix, Microscan, E test overcalled some susceptible strains as VISA
  - Sensititre, Vitek 2 under called some VISA strains as susceptible
  - Vitek legacy, under called some VISA as susceptible, overcalled some VISA as resistant
- Acceptable variability for MIC methods is +/-1 doubling dilution

Vancomycin MIC's and Outcome

- Probability of achieving AUC/MIC $\geq$ 400 is 0% if MIC = 2
- Elevated MIC (1.5-2mcg/ml) is associated with vancomycin treatment failures
- The presence or absence of "MIC creep" is controversial
  - Observation in some centers but not others
  - ?technical artifact related to test method used.

MRSA:Treatment Options

- FDA-approved
  - Vancomycin
  - Linezolid
  - Daptomycin
  - Tigecycline
  - Telavancin
  - Ceftaroline
  - Dalbavancin
  - Oritavancin
  - Tedizolid
- Not FDA-approved, but frequently used
  - TMP-SMX
  - Clindamycin
  - Tetracyclines

- Investigational agents
  - PBP-2a–targeted β-lactams (eg, ceftobiprole)
  - Synthetic antimicrobial polypeptides (SAMPS)
  - FtsZ targets

Daptomycin

Microbiology: gram positive: MRSA, MSSA enterococci (VRE)
Action: cidal
Indications: Not pneumonia, bacteremia and right sided endocarditis, skin infections, prosthetic joint and septic arthritis
Dose: 4mg/kg IV q 24h soft tissue, 6mg/kg q 24h for bacteremia (8-10mg/kg q24h off label) osteomyelitis 6mg/kg q 24h (off label)
Adverse Events: diarrhea (5-12%), vomiting (3-12%) anemia (2-13%), elevated CPK (3-9%), renal failure (2-3%), pneumonia (3%)
Drug interactions: avoid with BCG, typhoid vaccine, caution with statins

Daptomycin vs Standard Therapy for Bacteremia and Endocarditis Caused by *S. aureus*

N=124

Daptomycin 6mg/kg

Outcome: 53/120 D vs 48/115

44.2% vs 41.7% (Delta=2.4, - 10.2 to 15.1%)

Microbiologic failure = 19 D vs 11

Reduced D susceptibility in 11/19

Renal dysfunction = 11% D vs 26.3%

Fowler et al, NEJM 2006; 355: 653-665

Telavancin

Microbiology: gram positive, MRSA, VISA, MSSA, enterococci ampicillin sensitive

Action: cidal, dual mechanism

Indications: skin, skin structure, pneumonia (MRSA) HAP, VAP

Dose: 10mg/kg IV q 24h (reduce in renal disease)

Adverse Events: metallic taste (33%), nausea (5-27%), vomiting (14%), serum creatinine rise (8%), fetal risk in animals, interferes with reagents for coagulation assays

Pregnancy category: C

Ceftaroline

Microbiology: gram positives, MRSA, MSSA,
not enterococci, gram negatives but less than 3rd generation cephalosporins

Action: cidal, cell wall PBP2A

Indication: skin, skin structure infections
pneumonia (not MRSA)

Dose: 600 mg q12h

Adverse events: (+) Coombs test without hemolysis (11%)
pruritus (4%), rash (3%), diarrhea (5%)
Increased transaminases (2%),
C. difficile (<2%), cross reactivity
with cephalosporins

Ceftaroline Heterorsistant *S. aureus*

Definition: subpopulations of lesser susceptibility within larger population of fully susceptible microorganisms

Isolates: N=57 MRSA(20), *h*VISA(4),VISA (20),DNSSA (7),LNSSA(6)

Methods: PAP (triplicate)

Resistance stability testing performed

Results: 21% isolates were heteroresistant

Occurred among strains with reduced susceptibility to vanco, dapto, and linezolid

did not occur in USA 300

resistance was unstable

S. Saravolatz, H. Martin, J. Pawlak, L. Johnson, L. Saravolatz AAC 2014

TMP/SMX vs Vancomycin against S. aureus

N=101 IVDU's Hospitalized

Bacteremia (65) Endovascular (49)

No difference in defervescence, WBC drop, hospital stay

Overall cure 37/43 (TS) vs 57/58 (v) $P \leq 0.02$

Bacteremia duration

MSSA(N=54) 7.8d (TS) vs. 3.5d (V) P=0.05

MRSA(N=47) 5.2d (TS) vs. 5.6d (V) $P \geq 0.2$

Comparable rates for toxicities

Markowitz, Quinn, Saravolatz

Ann Intern Med 1992; 117; 390-398

TMP/SMX vs Vancomycin for MRSA

Objectives:	Non inferiority of TMP/SX vs Vancomycin for severe MRSA infections
Methods:	Open label, randomized controlled trial of TMP/SMX IV 320/1600 BID vs Vanco 1g q 12 h
	Primary outcome= death, treatment failure at 7 days, persistence of bacteremia, and persisting organ failure
Results:	N=252 (91 bacteremias- 36%)
	Failure: 38% (TMP/SMX) v 27%, (V),RR= 1.38,0.96, 1.99
	Non inferiority difference 10.4%
Conclusion:	High dose TMP/SMX did not achieve non inferiority compared to vancomycin

Paul et al, BMJ 2015; 350:2219

Clindamycin vs TMP-SMX for Uncomplicated Skin Infections

N= 524 patients with abscesses (30.5%), cellulitis (53.9%) and mixed infections (15.6%)

Clindamycin 300 mg T.I.D. vs SMX/TMP 2 SS B.I.D

Culture: N=296, *S. aureus* =41.4%, MRSA=77%

Clindamycin Resistant =12.4%,

SMX/TMP Resistant =0.5%

Cure rates = 89.5% (C) vs 88.2% (SMX/TMP)

Cure rates similar for abscesses and cellulitis

Miller etal, NEJM 2015:372

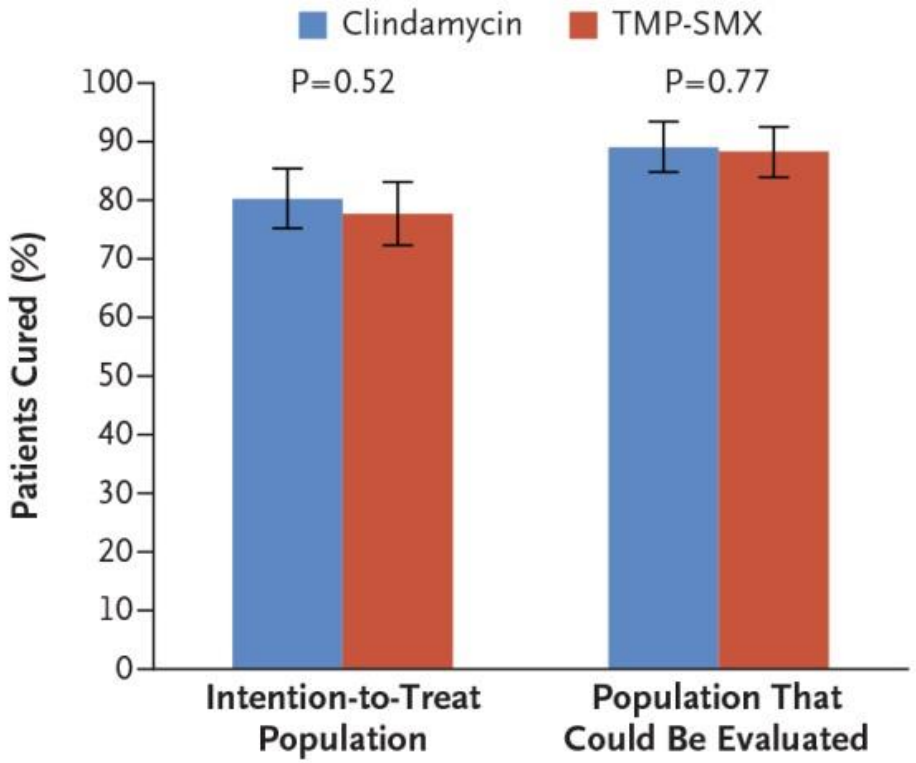


Figure 2. Comparison of the Efficacy of Clindamycin and TMP-SMX in Patients with Uncomplicated Skin Infection.

The graph shows the proportion of patients cured by the time of the test-of-cure visit in the intention-to-treat population and the population that could be evaluated. The actual confidence level was 95.60% after adjustment for interim analyses.

Dalbavancin – Therapy for SSTI

Dalbavancin – a lipoglycopeptide, half life=2 weeks, 53% protein bound,

Microbiology: MIC 90 =0.06 mcg/ml

Action: cidal

FDA approval: SSTI only

Clinical trial: Dalbavancin day 1(1500mg) vs 1 (1000mg)& 8(500mg)
Clinical outcomes on day 14 were 84% v 84.8% (n=698)

Adverse events: SAE D=2.6%, V-L= 4.0% NS
Any events D 1 dose=20.1%, 2 dose=19.9%
Headache, nausea ,vomiting, diarrhea <3%
Drug discontinuation 1.7% vs 1.4%

Dunne et al, CID: 2016

Boucher et al NEJM, 2014 Showed non inferiority to Vancomycin

Oritavancin- Therapy for SSTI

Oritavancin – Lipoglycopeptide, prolonged half life 2 weeks

FDA approval: SSTI

Clinical Trial: Oritavancin 1200 mgx1(3h) vs Vanco 7-10d

Cure 0=79.6% vs. V= 80.0%

Adverse events: SAE 0=7.4% vs. V= 7.3%
Drug discontinuation 0=2.3% vs V=2.7%

Corey, NEJM, 2014

	DRTX Estimates			MD estimates		Saravolatz
Drug	Dalbavacin	Vancomycin	Daptomycin	Oritavancin	Vancomycin	SMX/TMP
Inpatient days	NA	5d	5d	NA	4d	NA
Outpatient days	1,8	9d	9d	1d	6d	10d
$ Drug inpatient	NA	100	1400	NA	180	NA
$ Drug outpatient	3,000	200	2500	2900	270	18
Inpatient Medical	NA	9700	9700	NA	6173	NA
Outpatient Med	900	3000	2500	415	**1128**	**120**
Total Costs	$3,896	$13,022	$16,083	$3,315	$7,751	$138
Equity Research, Credit Suisse, January 2014						

Prolonged Half Life Drugs

PRO	Con
Administration frequency	Limited clinical experience/indications
Fewer compliance issues	Allergy/adverse event exposure time
Adverse events	Infusion time (0), 2 doses (D)
No long term access	Less closely monitored
May be helpful in chronic	Most patients in trial were not MRSA
Infections (osteomyelitis)	Drug cost
	Resistance with overuse

Efficacy of Chlorhexidine on Hospital-Acquired Infections

Background: Chlorhexidine baths have been shown to reduce hospital-acquired infection and acquisition of multidrug resistant organisms

Methods: A multicenter, cluster–randomized, non-blinded crossover trial (9ICUs, 6 BMT programs) chlorhexidine wash cloths versus non-antimicrobial washcloths for 6 months followed by a crossover for 6 months

Results: N=7727 patients; MDRO= 5.10(C) vs. 6.6/1000 patient days, p=0.03, Hospital acquired bacteria= 4.78 (C) vs 6.6/1000 patient days, p=0.007.

Conclusions: Chlorhexidine washcloths reduced the rate of acquisition of MDR O's and reduced the rate of hospital-acquired bacteremias.

Climo et al, NEJM, Feb, 2013

Retapamulin and Mupirocin Resistance

Isolates: 155 MRSA

Results: Retapamulin 2.6%,
Mupirocin 10.3%
Mupirocin High level ,10/155,6.5%
Low level 6/155, 3.9%

Saravolatz et al AAC 2013

Decreased Susceptibility – Retapamulin, Mupirocin and Chlorhexidine

Isolates: 200 (I-SSTI), 200 (≤ 3 SSTI) *S. aureus*

Results: Retapamulin resistance 38/400(9.5%)

Mupirocin resistance 39/400 (9.8%)

Chlorhexidine resistance 14%

McNeil et al AAC 2014

LTX – 109 against *S. aureus*

LTX -109 SAMP – cidal via cell membrane disruption

Isolates: MRSA (96), VISA (33), VRSA (13), LNSSA (6), DNSSA (7)

Results:

MIC range = 2-4 mcg/ml

MBC range 2-8 mcg/ml

Not influenced by resistance to other agents

Formulation concentration =20,000 mcg/ml

Rapidly kills *S.aureus* in < 1 hour

Post antibiotic effect may be up to 8 hours.

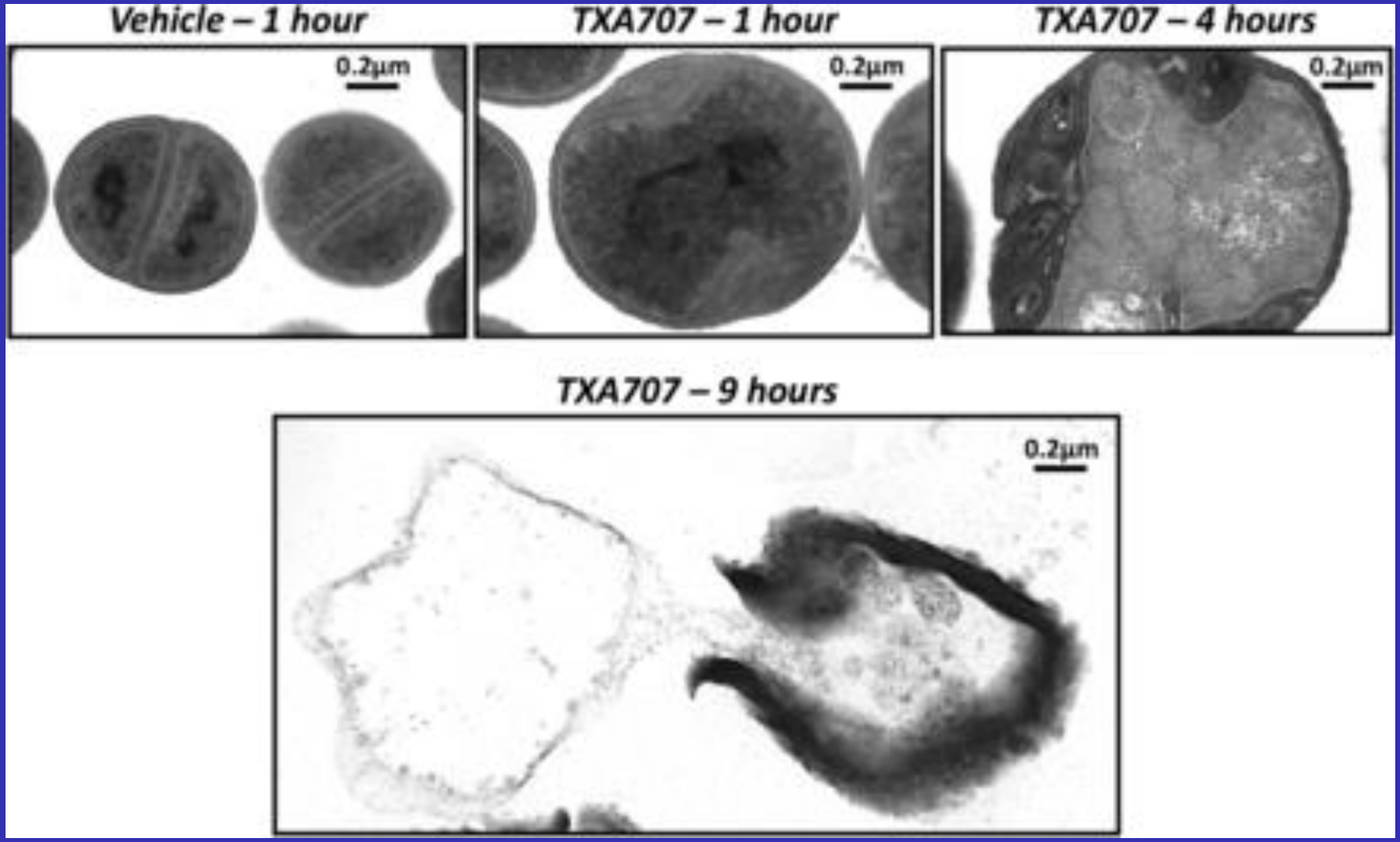
Saravolatz et al AAC, 2012, ICAAC, 2014

FtsZ Targets

- Bacterial cell division protein FtsZ- a new drug target.
- Critical role in cell division. If disrupted leads to cell death
- Active against *S. aureus* resistant to various antimicrobial agents.

Kaul et al, AAC 2013

FtsZ Targeting Drugs inhibiting Bacterial Replicase



Recurrent MRSA SSTI: Decolonization Regiments

- Mupirocin twice daily x 5-10 days (CIII)
  - Raz – Arch Int Med 1996, RCT of pts with recurrent MSSA furunculosis: mup vs placebo: decrease nasal colonization ($P<0.001$), decrease recurrent SST ($P<0.002$)
  - Ellis AAC 2007, Cluster RCT decrease nasal colonization but not 1st time SSTI
- Mupirocin twice daily x 5-10 days AND topical skin antiseptic (e.g.chlorhexidine or dilute bleach baths) x 5-14 days (CIII)
  - Whitman ICAAC 2008, cluster RCT:CHG wipes no decrease in SSTI's
  - Bode NEJM 2010 RCT combo decreased surgical site infection rates by 60%
  - Kaplan – bleach baths: (¼ cup, ¼ tub water or1 tsp per gallon for 15 min, 2x/week x 3M

Recurrent MRSA SSTI: Decolonization Regiments

- Oral antimicrobials not routinely recommended (A III) Consider oral agent in combination with rifampin only if other measures fail (CIII)
  - Cochran Review 2003, No benefit in HA-MRSA eradication or reduction in infection rates
  - Falagas AJIC 2007, systematic review of rifampin – based combination regimens vs monotherapy with other antibiotics improved eradication of *S.aureus*, no assessment of infection rates
  - Watch for rifampin resistance, drug interactions, side effects

Bleach Baths

Study Design: Randomized, single-blinded controlled trial of bleach baths BIWx3 months + routine hygienic measures (RHM) vs RHM alone. 5ml bleach/ 1 gallon H_2O

Patients: 3 m-18 years treated for suspected *S. aureus* STI

Outcome: nurse blinded to group contacted families at 2 W, 3,6 and 12m

Bleach Baths (continued)

Results: RHM&B RHM alone

MA-STI (1y) 84/495(17%) 103/492 (20.9%) P=0.15

Conclusion: Most infections were MRSA (138/182)

60% colonized at ≥ 1 site.

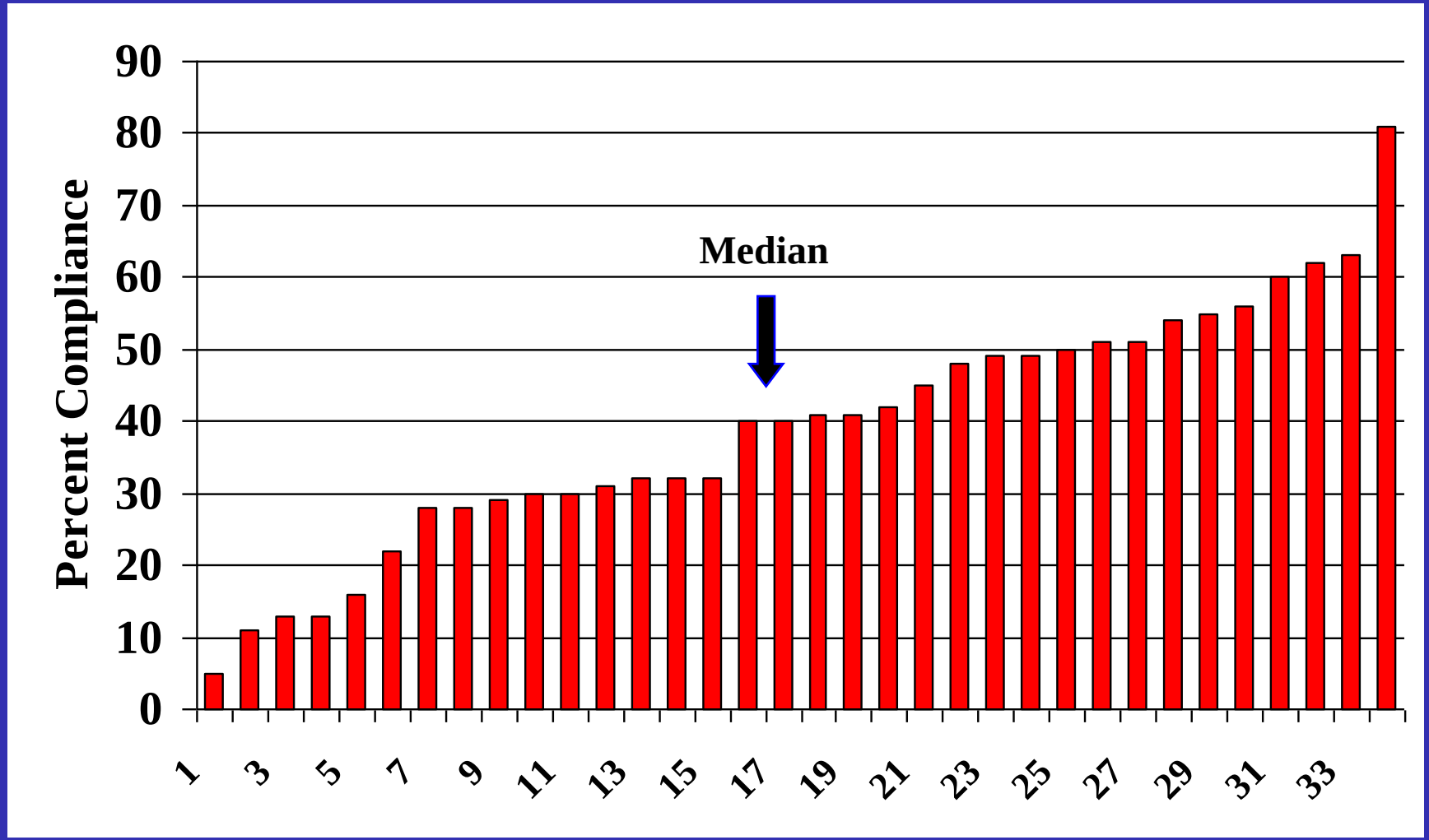
Colonization sites groin (38%) > nares (22%) > throat (17%)

Colonization decreased with age (6y), 46% v 27% P<0.001

Bleach baths decreased recurrence MA-STI by 20% but this was not statistically significant

Kaplan et al CID 2014

Percent Hand Washing Compliance among HCWs in 34 Observational Studies, 1981-2000



Summary of Take Home Points

- MRSA is the major *S. aureus* pathogen in the hospital and the community
- Treatments in the hospital still favor vancomycin but other options include daptomycin, telavancin, and linezolid
- Oral therapies include SMX/TMP, doxycycline, clindamycin, and linezolid
- Prevention remains a challenge, but handwashing, chlorhexidine, and mupirocin currently should be used.


It's no mystery you feel a song coming on... you have a staff infection.
Reynolds