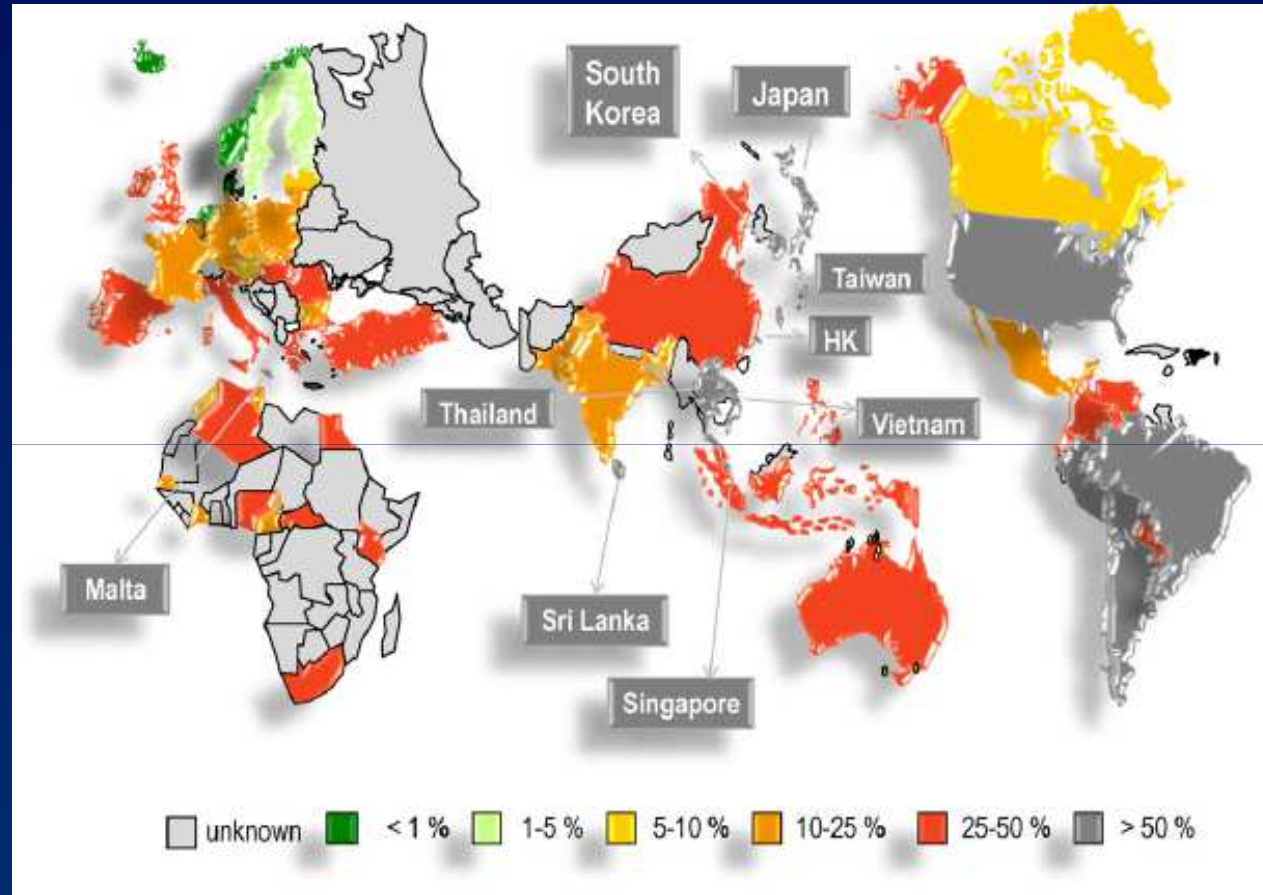# Methicillin-resistant *Staphylococcus aureus* (MRSA) and Vancomycin: Learning, Unlearning and Relearning

Sasheela Ponnampalavanar

Infectious Diseases Unit

Methicillin-Resistant *Staphylococcus aureus* is Highly Prevalent Worldwide

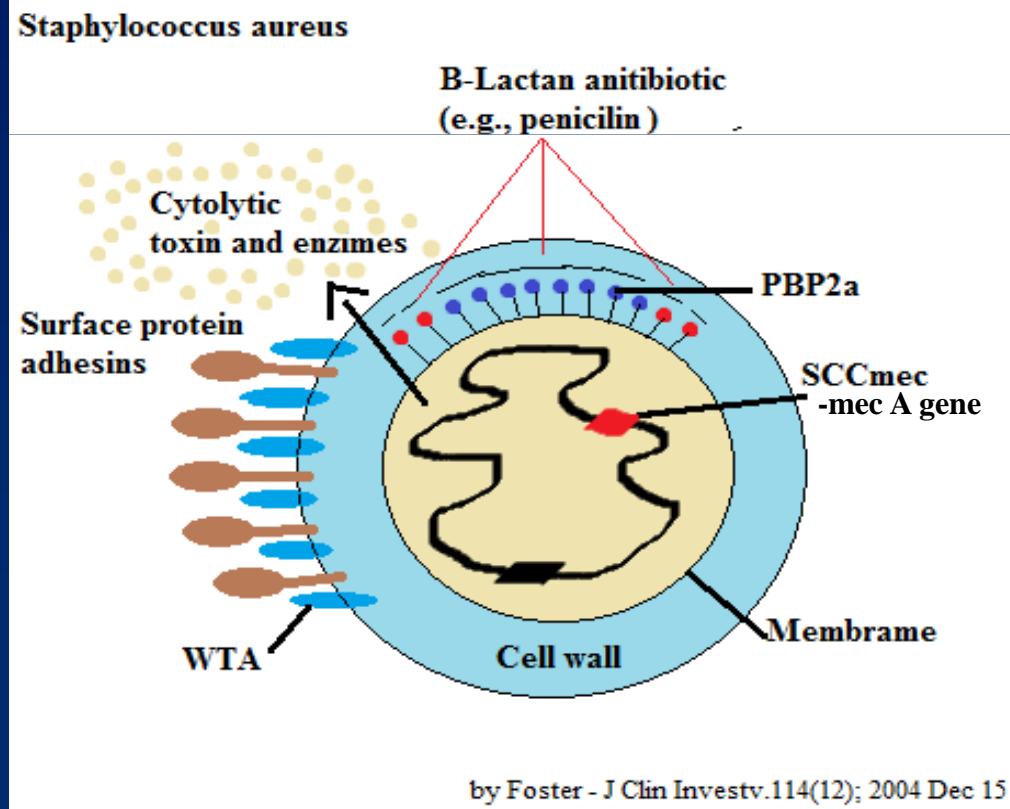Highest rates (>50%) are reported in North and South America, Asia and Malta

Stefania S, A et al. Int J Antimicrob Agent 2012;39:273–282.

Definition of MRSA

oxacillin MIC $\geq$ 4 µg/mL
Resistant to penicillins & cephalosporins
mecA gene
Synthesis of PBP2a – loss target affinity

Staphylococcus aureus

B-Lactan anitibiotic
(e.g., penicilin)

Cytolytic
toxin and enzimes

Surface protein
adhesins

PBP2a

SCCmec
-mec A gene

WTA

Membrame

Cell wall

by Foster - J Clin Investv.114(12); 2004 Dec 15

Mechanism Of Resistance

Staphylococcus aureus evolution

Waness A. Revisiting Methicillin-Resistant Staphylococcus aureus Infections. *J Glob Infect Dis. 2010 Jan;2(1):49-56.*
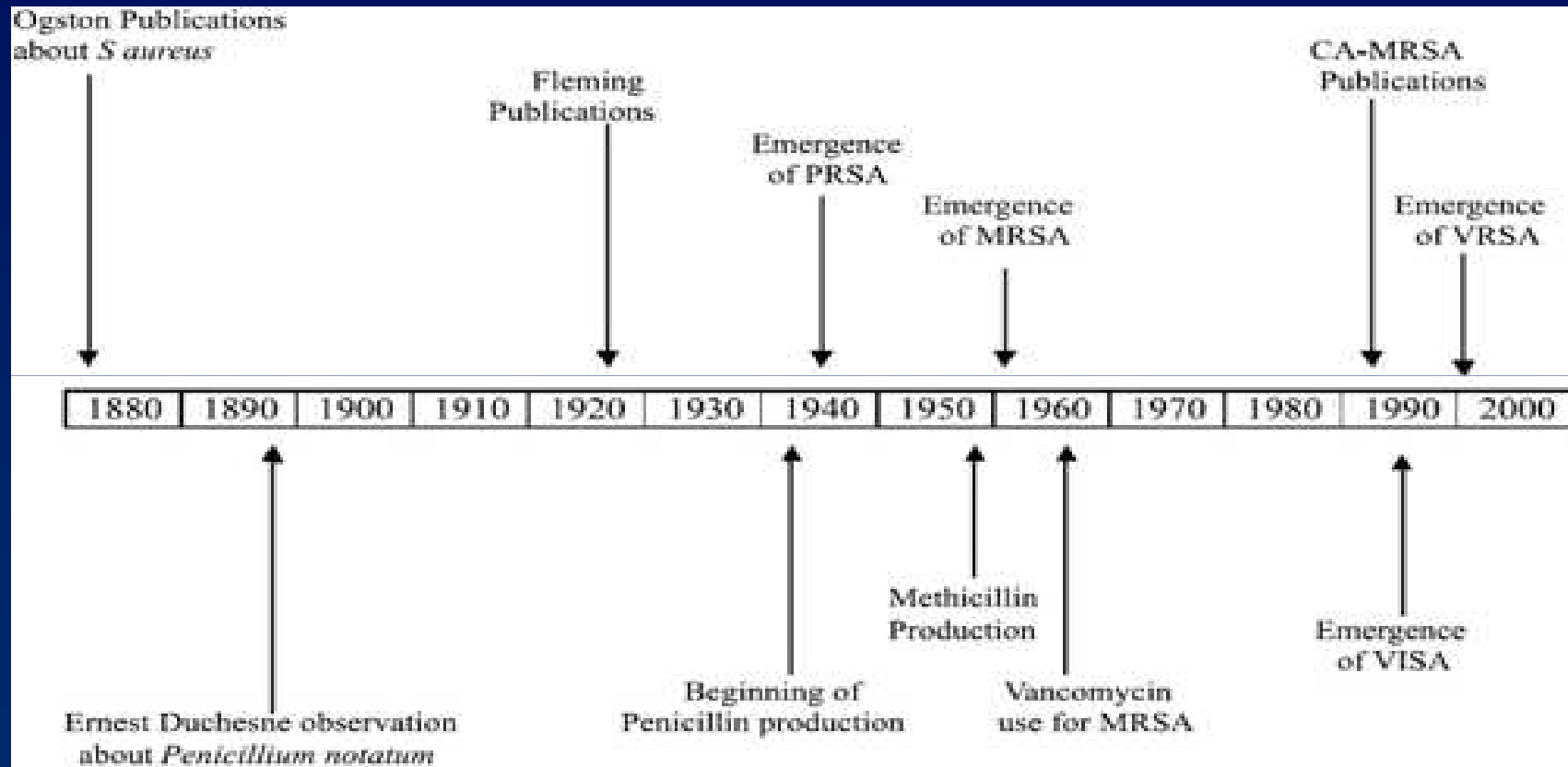
LA-MRSA

Netherlands (2004)

Asia

Canada

USA
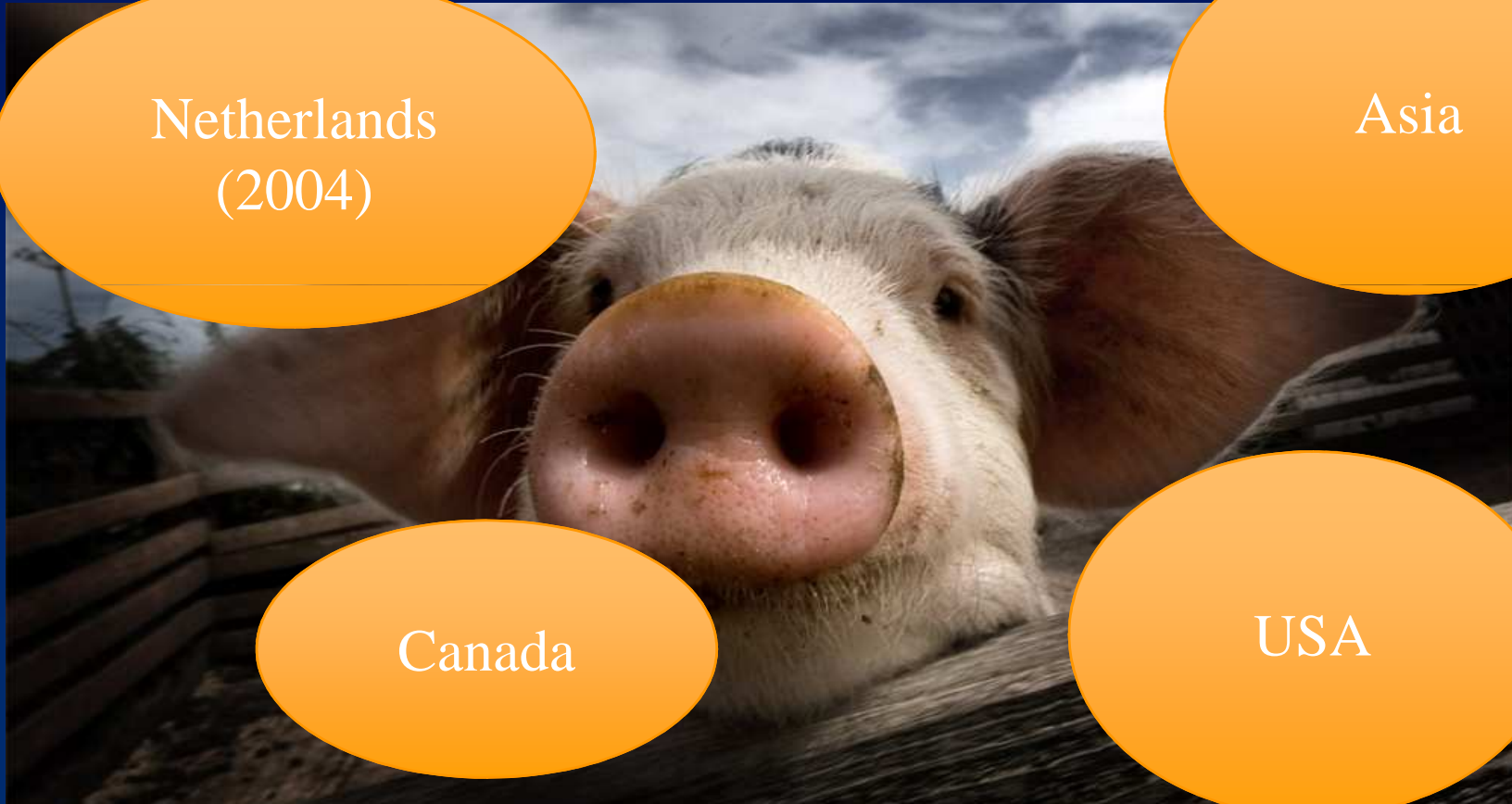
EPIDEMIOLOGY

	Hospital-acquired (HA)-MRSA	Community-acquired (CA)-MRSA
Description	Acquired in the hospital or healthcare setting Bacteria carry a relatively large SCC*mec* element, typically belonging to type I, II, or III	Acquired by persons who have not been recently hospitalised or had a medical procedure Bacteria carry smaller SCC*mec* elements, most commonly type IV or type V Different virulence factors may allow infection to spread more easily/cause more skin disease
Antibiotic resistance	Resistant to many non-beta-lactam antibiotics	Susceptible to many antibiotics (except beta-lactams)
Clinical presentation	Pneumonia, bacteraemia, and invasive infections	Mostly skin/soft tissue Rarely necrotising pneumonia and sepsis
Predominant groups at risk	Older age and those with comorbid conditions	Younger age — children, young adults

Differences between CA- and HA-MRSA are becoming less distinct

1. Moran Toro C et al. Can J Infect Dis Med Microbiol 2014;25(3):e76−e82; 2. Hidron A. Lancet 2009;9:384−92.
3. Lobo LJ, et al. CHEST 2010:130−6. 4. David MZ, et al. Clin Microbiol Rev 2010;23(3):616-87.

Risk factors for MRSA

Health care-associated risk factors include:

Recent hospitalization (1 yr)[1]

Residence in a long-term care facility[11]

Recent surgery

Hemodialysis[10]

Community acquired risk factors include:

Incarceration

Military service

Sharing sports equipment

Sharing needles, razors, or other sharp objects

Additional risk factors for MRSA infection include:

HIV infection [2]

Injection drug use[2-5]

Prior antibiotic use- FQ and cephalosporins[6,7]

Colonization with MRSA[4,9]

Close contact with MRSA coloniser/infected[8]
    ~10% population colonized

Penetration trauma[11]

1. Trividic M, et al. Ann Dermatologie Venereologie 2002; 129(1 Pt 1): 27-9; 2. Vyas KJ, et al. J Int Assoc Prov AIDS Care 2014 3. Vayalumkal JV, et al. Cjem 2012; 14(6): 335-43; 4. Stenstrom R, et al. Cjem 2009; 11(5): 430-8; 5. Kuo DC, et al. J Emerg Med 2010; 39(1): 17-20; 6. MacDougall C, et al.CID 2005;41(4):435; 7. Tacconelli E et al. JAC (2008) 61, 26–38; 8. Weiss C, et al. BMC Res Notes 2011; 4: 33; 9. Davis KA et al. CID.2004;39(6):776;10. MMWR Morb Mortal Wkly Rep. 2007;56(9):197;11. Spindel SJ, et al. Infect Control Hosp Epidemiol. 1995;16(4):217;. 11. Stevens *et al*. Clin Infect Dis 2014; 59 (2): e10. 1. OTTER AND FRENCH. LANCET INFECT DIS 2010;10:227-39; 2. 2. POPOVICH AND WEINSTEIN. INFECT CONTROL HOSP EPIDEMIOL 2009;30:9-12

Poorer Outcomes: MRSA vs MSSA Infection

Those infected with MRSA have higher:

Mortality (BSI 1.5-2 folds)

higher healthcare and patients cost

acute renal failure,

hemodynamic instability

prolonged ventilator dependency

longer hospital stays

Inadequate initial abx treatment increases all-cause and infection-related mortality

Cosgrove SE, et al CID. 2003;36(1):53.;Blot SI, et al .Arch Intern Med. 2002;162(19):222Nickerson EK et al.PLoS ONE 4(8): e6512. 9.;3.; Cosgrove SE, et al.ICHE. 2005;26(2):166.; Kollef MH. Crit Care 2001;5:189−195; 5. Kollef MH et al. Chest 1999;115;462−474; 6. Ibrahim EH et al. Chest 2000;118:146−155…Marlieke E et.al, AAC 2011, 55; 1598- 1605 Stijn I et. al, Arch Intern Med 2002, 162 (19);2229-2235

Mainstay of parenteral therapy for
MRSA infections

Vancomycin

Missionary from Borneo sent a sample of dirt to a friend at Eli Lilly in 1953.

The compound isolated had activity against most gram positive organisms-'vanquish.' FDA-approved in 1958.[1]

Is still a powerful tool against gram positive organisms, BUT……

Levine DP. Vancomycin: A History. *Clin Infect Dis* 2006;42(Supplement 1):S5-S12.

Concerns about Vancomycin
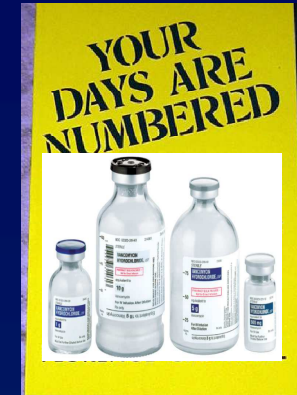
Slow bactericidal activity

   Kills Staphylococci more slowly than beta-lactams in vitro, particularly at higher inocula (10^7–10^9 colony-forming units)

Reducing susceptibility

Elevated vancomycin MIC within susceptibility range

Vanco MICs can vary based on testing method

Monitoring & Achieving the right levels

Toxicity – nephro & ototoxicity

Liu et al. Clinical Infectious Diseases 2011;52(3):e18–e55.; Goud I IJAA 2008 Apr; 31 suppl2:109

Reducing Vancomycin Susceptibility

60 % therapeutic failure with vancomycin MIC of 4 µg/mL
Lowering of breakpoint to 2 µg/mL (2007)

Pathogen	Susceptibility	MIC breakpoints (µg/ml)	Previous breakpoints
MRSA	Susceptible	≤ 2	≤4
VISA	Intermediate	4-8	8-16
VRSA	Resistant	≥ 16	64

Date of Publication: December 27, 2016

Elevated Vancomycin MIC Within Susceptibility Range

h VISA[1]

'MIC creep'

Inherent organism characteristics[3]:

resistance or virulence determinants,

accessory gene regulator (*agr*) type or function

1. Casapao AM et al. AAC 2013 Sep; 57(9): 4252–4259.; 3. Holems NE J Clin Microbiol. 2014 Sep; 52(9): 3384–3393
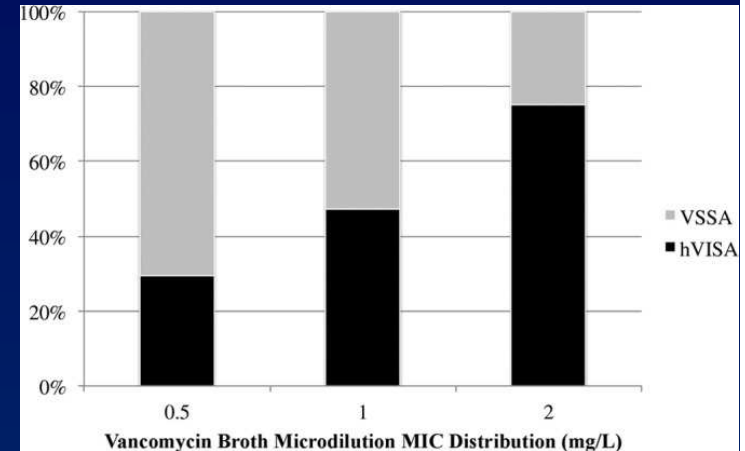
hVISA

Subpopulations of VISA within a population of MRSA (one organism per 10^5 to 10^6 organisms).

Using traditional testing methods, the vancomycin MIC for the entire population of the strain is within the susceptible range (≤ 2.0 µg/ml).

Vancomycin MIC distribution by the broth microdilution method and hVISA frequency for all MRSA isolates.

Due to:

Thickening of cell wall

altered penicillin biding protein and decrease call wall autolysis

MIC 2.

MIC 0.5

Sadar HS et al. JAC 2009;.Pillay SK et al. CID 2009, Charles PG CID 2004, Cazapao AM et al. AAC 2013, Holems NE et al J Clin Microbiol. 2014
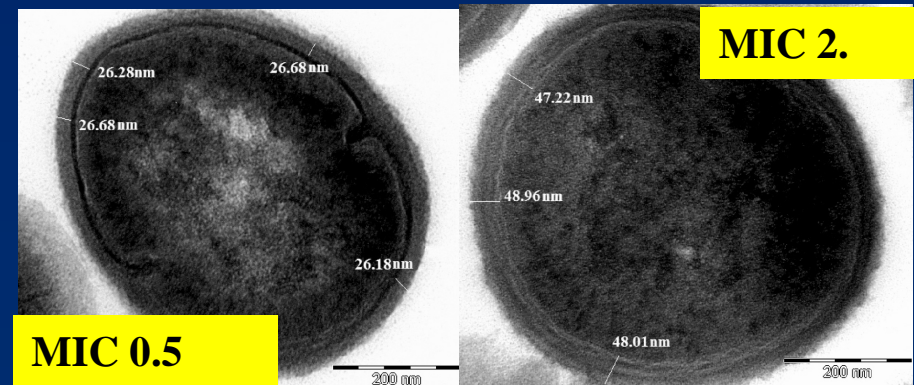
MIC Creep

Increasing Vancomycin MIC in MRSA isolates over time

"MIC creep"   observed in some centers but not others
Perhaps due to clonal dissemination or technical artifact
(storage, early vs late testing)
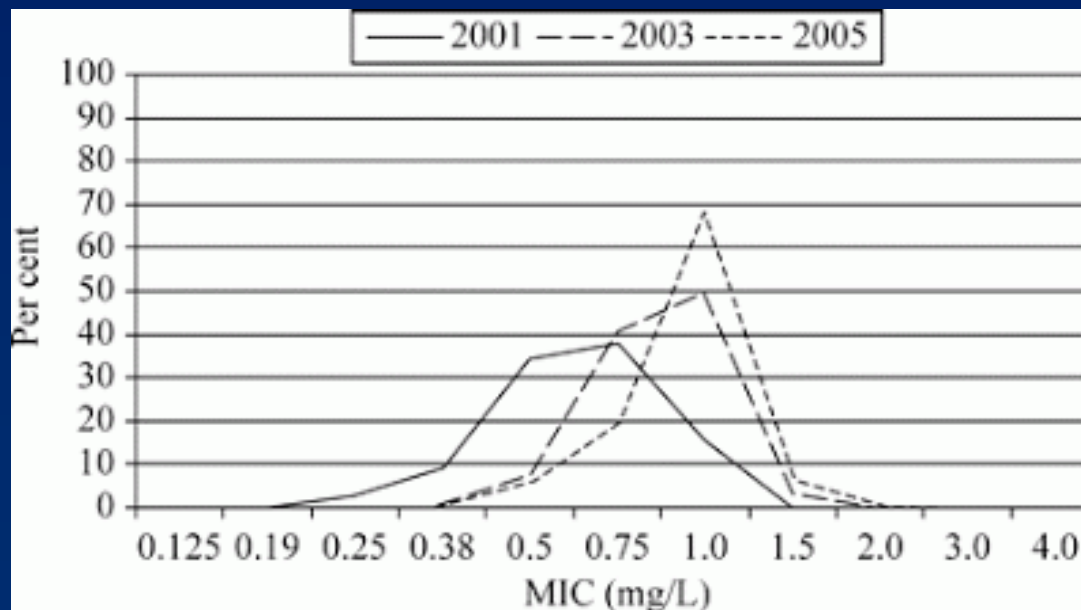
Steinkraus G, et al.J Antimicrob Chemother 2007;60(4):788-94

Inherent Organism Characteristic Associated With High Vanco MIC

Genetic and Molecular Predictors of High Vancomycin MIC in *Staphylococcus aureus* Bacteremia Isolates

An elevated vancomycin MIC is associated with poor outcomes in *Staphylococcus aureus* bacteremia (SAB) and is reported in patients with methicillin-susceptible *S. aureus* (MSSA) bacteremia in the absence of vancomycin treatment. Here, using DNA microarray and phenotype analysis, we investigated the genetic predictors and accessory gene regulator (*agr*) function and their relationship with elevated vancomycin MIC using blood culture isolates from a multicenter binational cohort of patients with SAB. Specific clonal complexes were associated with elevated (clonal complex 8 [CC8] [$P < 0.001$]) or low (CC22 [$P < 0.001$], CC88 [$P < 0.001$], and CC188 [$P = 0.002$]) vancomycin MIC. *agr* dysfunction ($P = 0.014$) or *agr* genotype II ($P = 0.043$) were also associated with an elevated vancomycin MIC. Specific resistance and virulence genes were also linked to an elevated vancomycin MIC, including *blaZ* ($P = 0.002$), *sea* ($P < 0.001$), *clfA* ($P < 0.001$), *splA* ($P = 0.001$), and the arginine catabolic mobile element (ACME) locus ($P = 0.02$). These data suggest that inherent organism characteristics may explain the link between elevated vancomycin MICs and poor outcomes in patients with SAB, regardless of the antibiotic treatment received. A consideration of clonal specificity should be included in future research when attempting to ascertain treatment effects or clinical outcomes.

Vancomycin Susceptibility Testing

Variability in Vancomycin MIC results:
BMD, Vitek 2 & E-test

N=1800
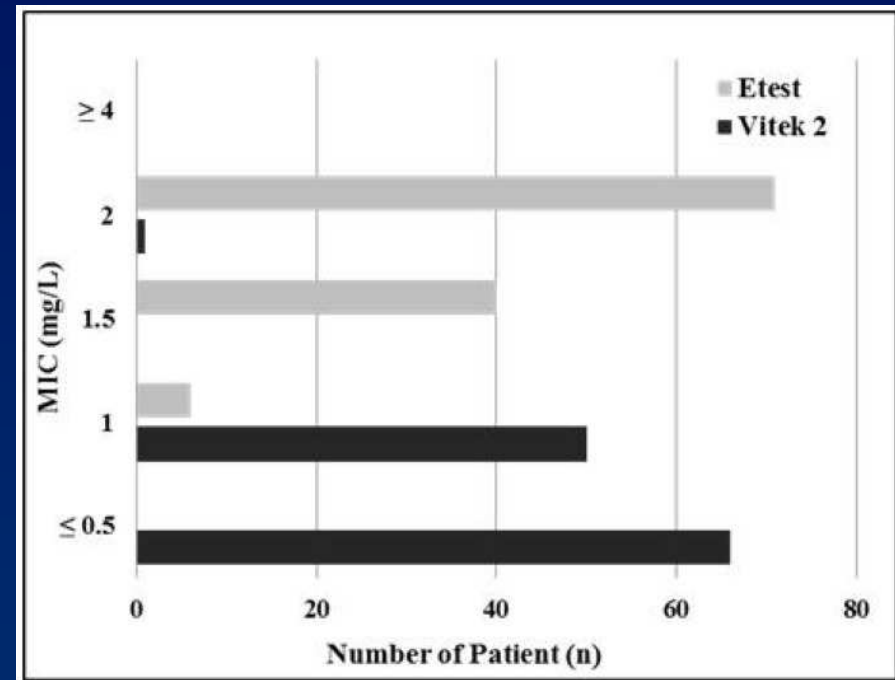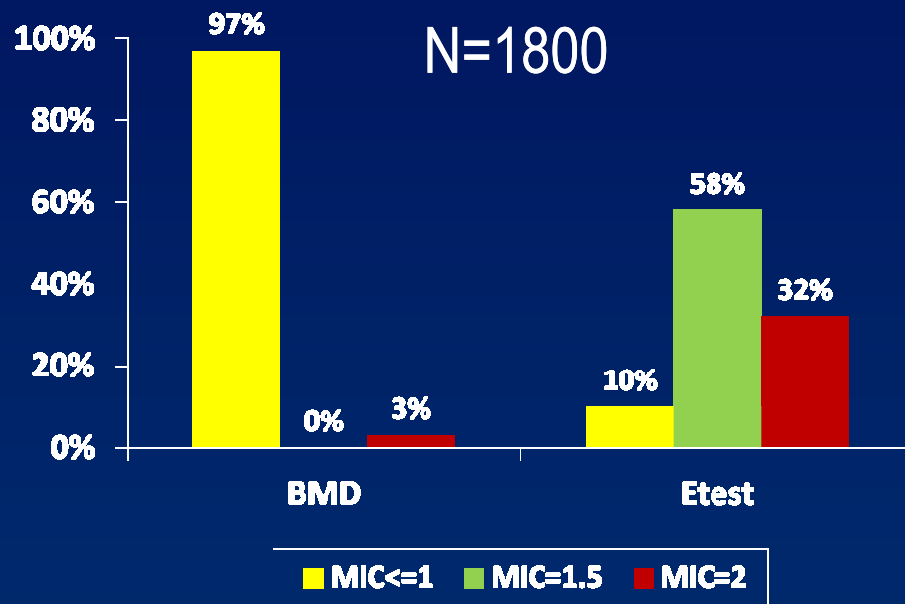
In general:

E test MIC results   0.5–1 dilution > BMD

Automated systems MIC generally produce MIC 1–2 dilutions <
BMD

Increased vanco MIC in *Staph aureus* isolates (pathogens) in Malaysia

Table 1. Vancomycin MIC of *S. aureus* isolates by the broth microdilution (BMD) method and Etest

Vancomycin MIC (µg ml^{-1})	MSSA [n (%)] 300		MRSA [n (%)] 300	
	BMD	Etest	BMD	Etest
0.25	1 (0.3)	0	7 (2.3)	0 (0)
0.5	261 (87)	0	171 (57)	6 (2)
0.75		2 (0.6)		9 (3)
1	38 (12.7)	101 (33.7)	122 (40.7)	40 (13.3)
1.5		149 (49.7)		154 (51.3)
2	0	48 (16)	0	91 (30.3)

6 major gov hospitals (2009- 5 months)
40% -blood, 12% - wound swabs, 6% -respiratory, 2.5% -urine, 25.5% - superficial &deep skin infection, 10.5% - tissue, 2% -CSF &peritoneal fluids, 1.5% -other samples.
This study did not look into clinical outcomes

Ahmad N, Nawi S, Rajasekaran G et al. J Med Microbiol. 2010 Dec;59(Pt 12):1530-2.

Does higher Vancomycin MIC lead to worse outcome in MRSA infection ?

Inconclusive

- Some studies suggest a worse outcome associated with vancomycin MIC $\leq$2 mcg/mL while others do not.

Sakoulas G, et al. J Clin Microbiol 2004
Lodise TP, et al. Antimicrob Agents Chemother 2008;.
Chang FY, et al. Medicine (Baltimore) 2003; 82:333.
Soriano A, et al. IClin Infect Dis 2008; 46:193.
van Hal SJ,et al . Clin Infect Dis 2012; 54:755.
Holmes NE, T et al. J Infect Dis 2011; 204:340.
Cervera C, et al. Clin Infect Dis 2014; 58:1668.

Kalil AC, et al.. JAMA 2014; 312:1552.
Lalueza A, et al. J Infect Dis 2010; 201:311.
Price J, et AL. J. Clin Infect Dis 2009; 48:997.
Baxi SM, et al. Antimicrob Agents Chemother 2016;

The Clinical Significance of Vancomycin Minimum Inhibitory Concentration in *Staphylococcus aureus* Infections: A Systematic Review and Meta-analysis

Clinical Infectious Diseases 2012;54(6):755–71

S. J. van Hal,[1,2] T. P. Lodise,[3] and D. L. Paterson[4]

[1]Department of Microbiology and Infectious Diseases, Sydney South West Pathology Services–Liverpool, South Western Sydney Local Health Network, New South Wales; [2]Antibiotic Resistance and Mobile Elements Group, Microbiology and Infectious Diseases Unit, School of Medicine, University of Western Sydney, Australia; [3]Albany College of Pharmacy and Health Sciences, New York; and [4]University of Queensland Centre for Clinical Research, Royal Brisbane and Womens Hospital Campus, Australia.

Study or Subgroup	High MIC ≥ 1.5µg/mL Events	Total	Low MIC < 1.5µg/mL Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Bae et al (12)	13	37	11	28	6.5%	0.84 [0.30, 2.31]
Choi et al (15)	4	34	6	36	4.6%	0.67 [0.17, 2.60]
Haque et al (19)	41	115	10	43	7.9%	1.83 [0.82, 4.08]
Hidayat et al (21)	12	51	4	44	5.3%	3.08 [0.91, 10.37]
Holmes et al (23)						
Lalueza et al (32)						
Liao et al (34)						
Lodise et al (36)						
Musta et al (43)						
Neuner et al (45)						
Schweizer et al (50)						
Soriano et al (52)						
Takesue et al (53)	33	97	62	662	10.4%	4.99 [3.04, 8.18]
van Hal et al (54)	38	117	73	236	10.6%	1.07 [0.67, 1.73]
Wang et al (55)	13	26	27	97	7.3%	2.59 [1.07, 6.30]
Total (95% CI)		**1553**		**1568**	**100.0%**	**1.64 [1.14, 2.37]**
Total events	391		289			

Odds Ratio
M-H, Random, 95% CI

Low MIC mortality   High MIC mortality

0.01   0.1   1   10   100

> Mortality association predominantly driven by:
> BSIs (OR, 1.58; 95% CI, 1.06-2.37; P = .03)
> Isolates with MIC of 2 µg/mL (Etest) (OR,1.72; 95% CI,1.34-2.21;P < .01).

> Mortality irrespective of the source of infection or MIC methodology

HOWEVER, ...

Association Between Vancomycin Minimum Inhibitory Concentration and Mortality Among Patients With *Staphylococcus aureus* Bloodstream Infections
A Systematic Review and Meta-analysis

38 studies ; 8291 episodes of SAB; 2006-2013,
MIC: High ≥1.5 mg/L & low <1.5mg/L

Overall mortality 26.1%.
26.8% high MIC vs 25.8% low (*P = .43*).
MRSA only *(n = 7232):* 27.6% high MIC vs 27.4% vs low MIC (*P = .41*).

No significant differences in risk of death between high vs low MIC:
   different study designs,
   microbiological susceptibility assays,MIC cutoffs,
   clinical outcomes, duration of bacteremia,
   previous vancomycin exposure, and
   treatment with vancomycin.

Kalil AC, et al.. JAMA 2014; 312:1552

Vancomycin MIC Does Not Predict 90-Day Mortality, Readmission, or Recurrence in a Prospective Cohort of Adults with *Staphylococcus aureus* Bacteremia

Sanjiv M. Baxi,[a,b] Angelo Clemenzi-Allen,[a] Alice Gahbauer,[c] Daniel Deck,[d] Brandon Imp,[a] Eric Vittinghoff,[f] Henry F. Chambers,[a] Sarah Doernberg[a]

TABLE 2 Presumed source of infection in 418 patients with *Staphylococcus aureus* bacteremia by vancomycin MIC status (MIC of <2 μg/ml versus MIC of 2 μg/ml)

Source	No. (%) of patients with source of infection	
	Vancomycin MIC < 2 μg/ml (n = 335)	Vancomycin MIC = 2 μg/ml (n = 83)
Community-acquired pneumonia	12 (3.6)	2 (2.4)
Hospital-acquired pneumonia	3 (0.9)	0 (0)
Ventilator-associated pneumonia	3 (0.9)	0 (0)
Implanted prosthetic material	14 (4.2)	3 (3.6)
Intravascular catheter	48 (14.3)	15 (18.1)
Abscess	43 (12.8)	8 (9.6)
Cellulitis	21 (6.3)	6 (7.2)
Musculoskeletal, bone	20 (6.0)	8 (9.6)
Musculoskeletal, joint	10 (3.0)	1 (1.2)
Surgical site infection	5 (1.5)	1 (1.2)
Urinary tract	8 (2.4)	2 (2.4)
Wound infection	9 (2.7)	0 (0)
Unknown	128 (38.2)	32 (38.6)
Other	11 (3.3)	5 (6.0)

418 BSI; 2008-2013; 83(19.9%) vancomycin MIC of 2 μg/ml.

Vancomycin MIC of 2 μg/ml vs <2 μg/ml was not associated with a greater hazard of mortality or composite outcome of mortality, readmission, and recurrence at either 30 days or 90 days after SAB diagnosis.

Baxi SM, et al. Antimicrob Agents Chemother 2016;22;60(9):5276-84.

Antimicrobial Agents and Chemotherapy®

Impact of Vancomycin MIC on Treatment Outcomes in Invasive *Staphylococcus aureus* Infections

TABLE 2 All-cause 30-day mortality rates of patients with invasive *Staphylococcus aureus* infections according to vancomycin MIC and patient subgroup[a]

MIC methodology subgroup	Mortality rate (no. of 30-day mortality cases/total no. of patients)	Etest			Broth microdilution		
		Low MIC	High MIC	P value	Low MIC	High MIC	P value
Total	27.4 (281/1,027)	26.7 (221/827)	30.0 (60/200)	0.351	26.7 (251/940)	34.5 (30/87)	0.119
MRSA infection	29.4 (198/673)	28.4 (143/503)	32.4 (55/170)	0.332	28.7 (173/603)	35.7 (25/70)	0.222
MSSA infection	23.4 (83/354)	24.1 (78/324)	16.7 (5/30)	0.360	23.1 (78/337)	29.4 (5/17)	0.561
Bloodstream infection	28.6 (272/950)	28.2 (216/766)	30.4 (56/184)	0.547	28.0 (244/870)	35.0 (28/80)	0.188
MRSA infection	30.7 (189/616)	30.1 (138/459)	32.5 (51/157)	0.571	30.1 (166/551)	35.4 (23/65)	0.385
MSSA infection	24.9 (83/334)	25.4 (78/307)	18.5 (5/27)	0.427	24.5 (78/319)	33.3 (5/15)	0.540

2-year, 1,027 patients , 10 hospitals South Korea,

673 (66%) patients with MRSA infections.
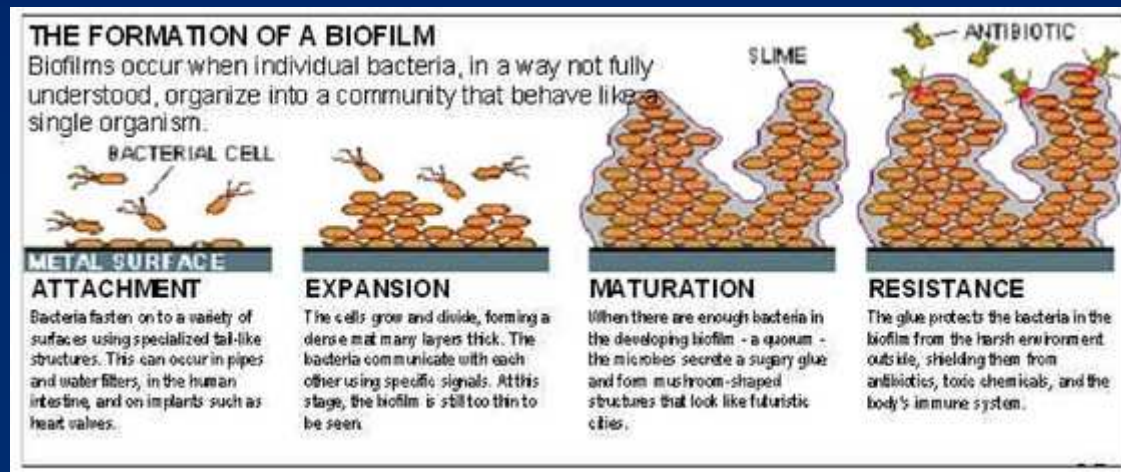
all-cause 30-day mortality -27.4%.

High MIC by either method was not associated with all-cause 30-day mortality, and this finding was consistent across MIC methodologies and methicillin susceptibilities.

Our data support the view that VAN-MIC alone is not sufficient evidence to change current clinical practice.

Song K-H, Kim M, et al AAC.01845-16.

Poor Biofilm Penetration

Staph Aureus- Capacity to form biofilm on invasive devices
Biofilm facilitates MRSA survival &multiplication on these
surfaces
prolonging the duration of organism exposure to antibiotic
promoting potential opportunity for transfer of antibiotic
resistance genes between organisms

THE FORMATION OF A BIOFILM

Biofilms occur when individual bacteria, in a way not fully understood, organize into a community that behave like a single organism.

SLIME — ANTIBIOTIC

BACTERIAL CELL

METAL SURFACE

ATTACHMENT
Bacteria fasten on to a variety of surfaces using specialized tail-like structures. This can occur in pipes and water filters, in the human intestine, and on implants such as heart valves.

EXPANSION
The cells grow and divide, forming a dense mat many layers thick. The bacteria communicate with each other using specific signals. At this stage, the biofilm is still too thin to be seen.

MATURATION
When there are enough bacteria in the developing biofilm - a quorum - the microbes secrete a sugary glue and form mushroom-shaped structures that look like futuristic cities.

RESISTANCE
The glue protects the bacteria in the biofilm from the harsh environment outside, shielding them from antibiotics, toxic chemicals, and the body's immune system.

Source of bacteremia associated with poorer outcome irrespective of MIC

TABLE 4 Factors associated with crude 30-day mortality by Cox proportional hazard regression with univariate and multivariate models[a]

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P
Source of bacteremia				
Low risk	1		1	
Intermediate risk	3.37 (0.93–12.2)	0.07	3.74 (1.01–13.79)	0.05
High risk	5.73 (1.55–21.18)	0.009	4.63 (1.24–17.33)	0.02
Previous MRSA	0.31 (0.07–1.34)	0.12		
Prior vancomycin therapy	1.44 (0.62–3.37)	0.40		
Receipt empirical vancomycin	0.49 (0.19–1.26)	0.14		
MIC of *S. aureus* bacteremia				
MIC = 2	1			
MIC ≤ 1.0	1.32 (0.52–3.38)	0.57		
SCC*mec* type				
II	1			
IV	0.82 (0.48–1.42)	0.49		
agr dysfunction	0.61 (0.23–1.65)	0.33		
Vancomycin trough level	1.01 (0.92–1.14)	0.69		
Bacterial eradication after treatment	0.06 (0.02–0.16)	<0.001	0.06 (0.02–0.17)	<0.001

[a] HR, hazard ratio; 95% CI, 95% confidence interval.

low-risk(10% mortality): intravenous catheter, UTI, gyne, ENT.
intermediate-risk source (10 -20%): SSTI, bone and unknown sources.
High-risk sources (20%)- endovascular sources, LRTI, abd, and CNS.

SY Park et al AAC 2013

Timely Effective Antibiotic Rx & Source Control Improves Outcome

A prospective, observational study ,1 year period, 270 patients, Invasive SA
A provincial hospital, Thailand
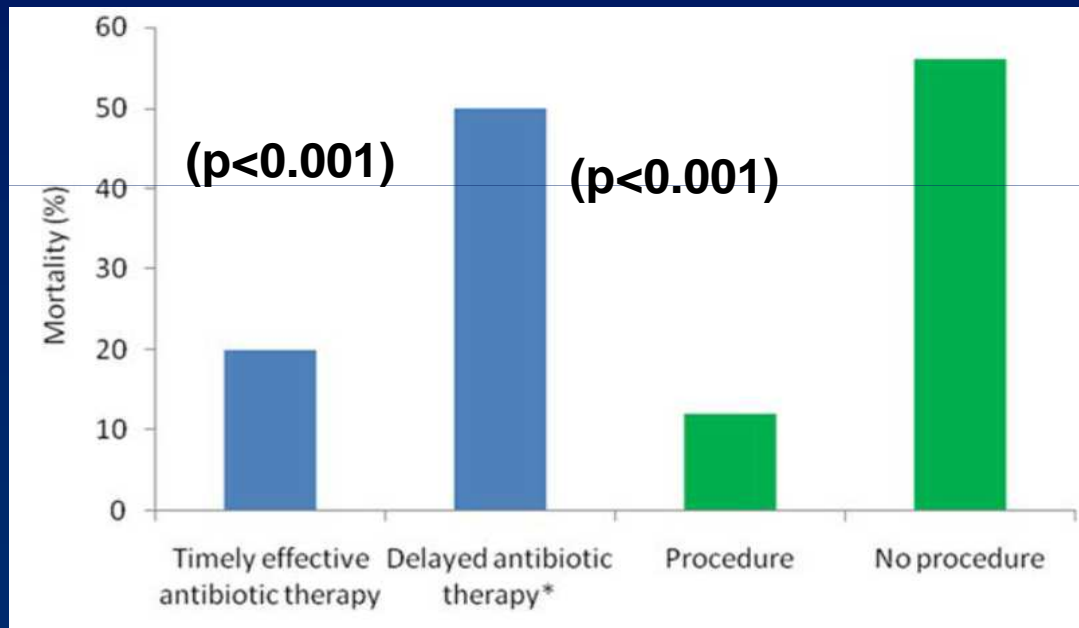
Reduced all cause mortality:
- Source control
- Effective abx on the same day as the positive culture.
- PVL negative

"KNIFE-AMYCIN"

Nickerson et al. 2009: PLoS ONE 4(8): e6512.

Vancomycin dosing

- based on the type and severity of infection, patient weight, and renal function
  - High risk or intermediate risk
    - loading dose (25 to 30 mg/kg)
  - Low risk : loading dose not necessary.
- Dose and interval based on actual BW and GFR (do not exceed 2gm)
- Extremely obese (BMI$\geq$40 kg/m2)- use adjusted BW

Rybak M et al. Am J Health Syst Pharm. 2009;66(1):82. ; Liu C, et al. (IDSA) Clin Infect Dis. 2011;52(3):e18.

Continuous versus intermittent infusion of vancomycin for the treatment of Gram-positive infections: systematic review and meta-analysis
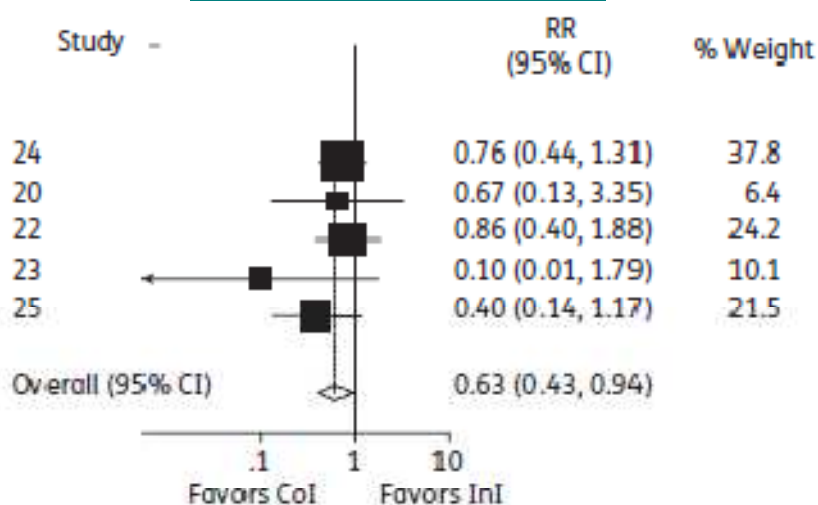
nephrotoxicity

mortality

Figure 2. Forest plot summary (fixed effect) of the unadjusted RR of the studies included in the meta-analysis comparing nephrotoxicity rates in patients treated with CoI versus InI of vancomycin.
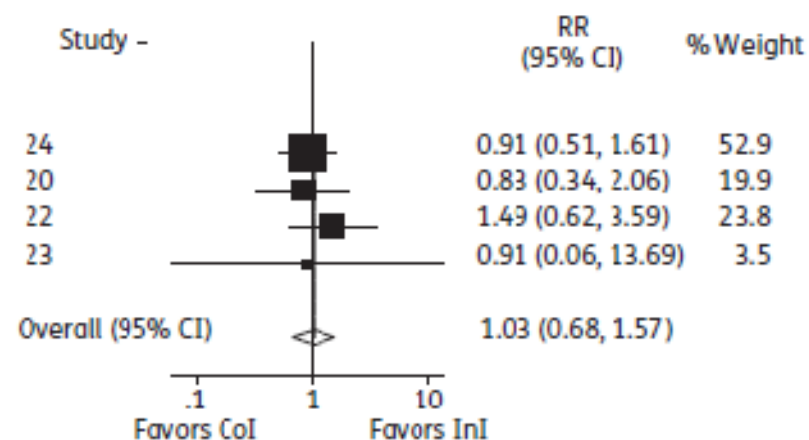
Figure 3. Forest plot summary (fixed effect) of the unadjusted RR of the studies included in the meta-analysis comparing overall mortality rates in patients treated with CoI versus InI of vancomycin.

One RCT and five observational studies
Less nephrotoxicity but no difference in mortality

Continuous vs Standard dosing?

- No difference in microbiological and clinical clearance.

- concentrations above 10 μg/mL were reached more than 30 hours faster with continuous infusions

- No difference in pharmacodynamics variables including the AUC-MIC ratio.

IDSA

Continuous infusion vancomycin regimens are **NOT** recommended (A-II)

Wysocki M,et al. AAC 2001; 45:2460–2467.; James JK, et al . AAC 1996; 40:696–700.; Rybak M, et al. Am J Health Syst Pharm 2009; 66:82–98.

Achieving the Right levels
What should we monitor?
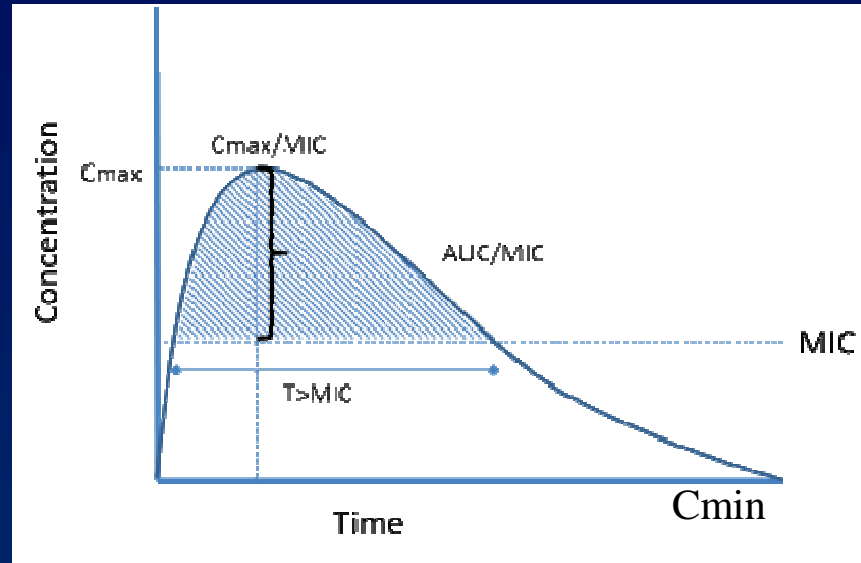
AUC/MIC best predictor for vanco efficacy

AUC/MIC $> 400^{\#}$ for clinical & micro response

Troughs used as surrogate marker for AUC for monitoring efficacy since more practical method

Troughs should be maintained **> 10 mg/L or 15-20 mg/L** for complicated infections

Some evidence for AUC/MIC > 578 in critically ill pts

However…..

- individual variability between a measured trough concentration and the actual AUC value

- Lack of correlation between trough concentrations and AUC has been observed in some studies

- Inconsistent data on the correlation between high trough level and better outcome .

- Dosing should instead focus on AUC:MIC values, which have strong evidence of benefit BUT tedious

Steinmetz Tet al. Clin Microbiol Infect. 2015 Jul;21(7):665-73. ; UPrybylski JP SOPharmacotherapy. 2015 Oct;35(10):889-98.

Systematic Review and Meta-Analysis of Vancomycin-Induced Nephrotoxicity Associated with Dosing Schedules That Maintain Troughs between 15 and 20 Milligrams per Liter

Nephrotoxicity occurred between 4.3 and 17 days after initiation of vancomycin

Higher troughs (>15 mg/liter) were associated with increased nephrotoxicity. Also if in ICU or on concomitant nephrotoxic drugs

Study or Subgroup	High troughs ≥15mg/L Events	Total	Low trough <15mg/L Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Bosso et al. (21)	42	142	13	146	17.6%	4.30 [2.19, 8.43]
Cano et al. (22)	22	89	7	99	14.4%	4.32 [1.74, 10.69]
Chung et al. (23)	12	25	16	48	13.4%	1.85 [0.69, 4.96]
Jeffres et al. (15)	27	49	13	45	15.1%	3.02 [1.28, 7.11]
Kullar et al. (32)	8	116	1	84	5.2%	6.15 [0.75, 50.13]
Kullar et al. (8)	27	139	23	141	18.4%	1.24 [0.67, 2.28]
Lodise et al. (36)	7	27	14	139	13.0%	3.13 [1.12, 8.69]
Zimmermann et al. (51)	8	12	0	33	2.9%	126.56 [6.19, 2585.90]
Total (95% CI)		599		735	100.0%	3.12 [1.81, 5.37]
Total events	153		87			

Heterogeneity: Tau² = 0.32; Chi² = 16.80, df = 7 (P = 0.02); I² = 58%
Test for overall effect: Z = 4.10 (P < 0.0001)

Odds Ratio M-H, Random, 95% CI — 0.01 0.1 1 10 100 — Low troughs <15mg/L High troughs ≥15mg/L
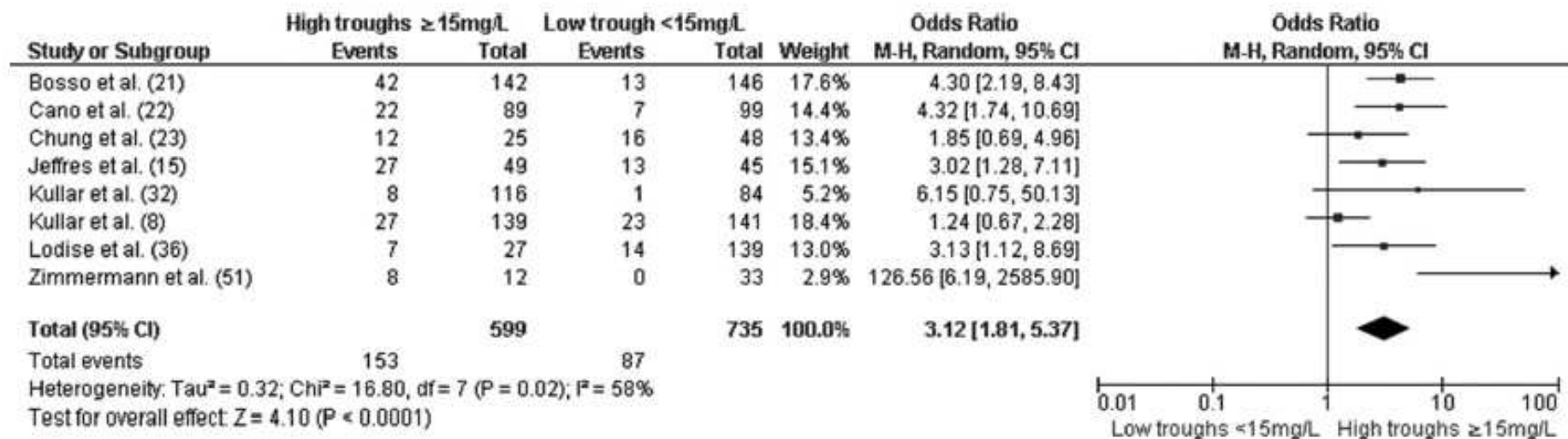
FIG 2 Forest plot (using Mantel-Haenszel [M-H] analysis) of events denoting nephrotoxicity associated with vancomycin, comparing rates for initial trough levels of ≥15 mg/dl and <15 mg/dl. Squares indicate point estimates, and the size of the square indicates the weight of each study. All initial trough levels were obtained at the time or shortly after steady state was achieved (i.e.. after the 3rd dose) and not greater than 4 days into therapy (see Table 2 for more details).

Risk Factors for Mortality

Age

underlying cardiac disease

respiratory infection

poor source control

unknown source of infection

dementia

hVISA: 2.37-fold-increased risk of failure (95% CI, 1.53 to 3.67) compared to. *aureus* VSSA

higher Charlson score
shock at onset
arrival to hospitalization from an institution

Nickerson EK et al.PLoS ONE 2009 4(8): e6512. Yahav D et al.European Journal of Clinical Microbiology & Infectious Diseases May 2016,35(5,) 785-790

UNLEARN AND RELEARN
Is high MIC the only reason for worse outcome in MRSA?

The relationship between worse outcomes and elevated vancomycin MICs is inconclusive

Reasons are multifactorial and incompletely understood.

Vancomycin susceptibility may vary dependent on testing methodologies, evolving MRSA epidemiology, pathogen specific characteristics .

Patients' comorbidities, source control, severity of infection, biofilm formation, delay effective treatment

Dosing & Monitoring method may not be precise

An elevated MIC by itself should not lead clinicians to rush to switch therapies in patients with SAB

- Decision should be based on **clinical response** esp if vancomycin MIC approaches the limit of the susceptible range (2 mcg/mL)
  - Consider discontinue and switch to
    - daptomycin * (8 to 10 mg/kg IV OD)
    - Combination
      - Daptomycin plus ceftaroline / other beta-lactams (BL)
      - Vancomycin plus ceftaroline or other BL
      - Daptomycin plus trimethoprim-sulfamethoxazole
      - Ceftaroline plus trimethoprim-sulfamethoxazole
    - Monotherapy: telavancin, ceftaroline, and linezolid

How can we improve MRSA treatment outcomes with Vancomycin

Prompt identification and early treatment based on patients
risk factors

Prompt and aggressive source control

Adequate dosing- avoid suboptimal treatment (leads to reduce susceptibility)

MRSA is evolving-Surveillance

"You must unlearn what you have learned."

— Yoda
The Empire Strikes Back