VISA infections

Jean-Ralph Zahar
Infection Control Unit
GH Paris Seine Saint Denis
jeanralph.zahar@aphp.fr

H-VISA and VISA infections

Jean-Ralph Zahar
Infection Control Unit
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jeanralph.zahar@aphp.fr

Disclosures

- Advisory board : MSD – Pfizer
- Financial support : MSD – Pfizer

- None for this presentation

What are we talking about?

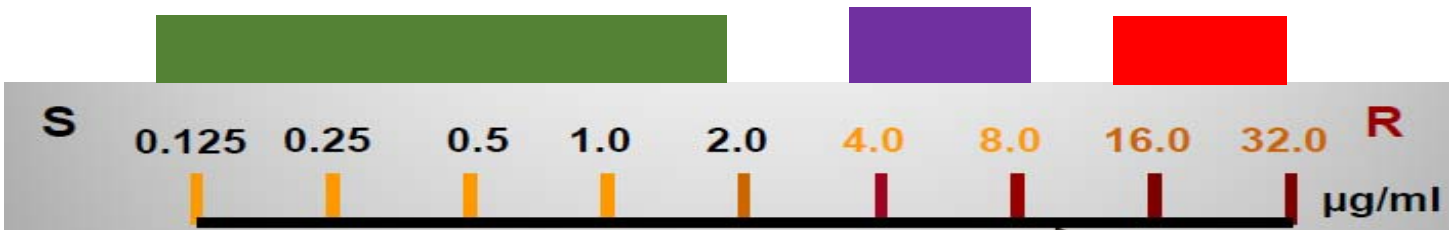
- *Staphylococcus aureus,* leading causative organism isolated from Bloodstream Infection (BSI)
- *Staphylococcus aureus* infections are associated with poorer clinical outcomes
- Isolates with a higher MIC to Glycopeptides but not considered as resistant
  - MIC $\geq$ 4 mg/l and < 16 mg/l
  - MIC > 2mg/l
- MIC should be determined by broth microdilution (Disk diffusion is unreliable)

Hassoun *et al,* Crit Care 2017

What are we talking about ?

- Described for the first time in 1996, in Japan
- The overall prevalence is low, estimated between 1% and 9% among MRSA isolates
- More frequent than Vancomycin Resistant *(vanA*) isolates
- Heterogeneous VISA and VISA are a continuum of strains with higher MIC to vancomycin

What we are we talking about ?



Several pheotypically and genotypically changes

VSSA

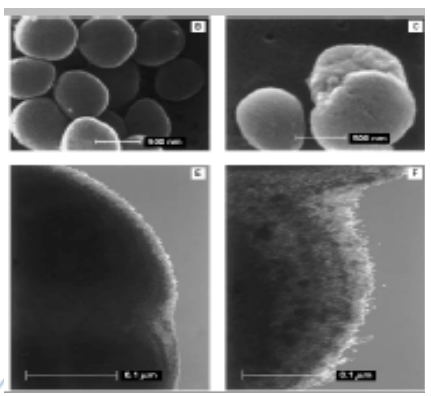
Cumulative mutation
regulatory loci

High Risk of
Clinical
failure with
vancomycin
treatment

H-VISA

Altered cellular architecture
Thickened PG
Increased capsule
Decrease protein A

VISA



inhibition of cell separation
accumulation of amorphous cell wall-like material at the bacterial surface

Gardete *et al,* J Clin Investigation 2014

Prevalence of h-Visa and Visa strains

Table 2. Prevalence of hVISA and VISA based on study period, origin of study, and isolate selection.[a]

	Category	Subcategory	No. Studies	No. Strains	Prevalence (%) (95% CI)
hVISA			76	99042	6.05 (4.78–7.48)
	Study period	Before 2006	42	40119	4.68 (3.19–6.41)
		2006–2009	10	6485	5.38 (2.40–9.48)
		2010–2014	5	680	7.01 (2.12–14.42)
	Continent	Asia	35	64692	6.81 (4.76–9.16)
		Europe-America	41	34350	5.60 (3.85–7.64)
	Clinical sample	Blood culture sample	21	5944	9.81 (6.71–13.42)
			55	93098	4.68 (3.51–6.00)
VISA			38	68792	3.01 (1.62–4.83)
	Study period	Before 2006	20	13394	2.05 (0.95–3.55)
		2006–2009	4	5630	2.63 (0.29–7.22)
		2010–2014	2	2090	7.93 (0.06–26.67)
	Continent	Asia	18	55362	3.42 (1.10–6.99)
		Europe-America	20	13430	2.75 (1.19–4.91)
	Clinical sample	Blood culture samples	7	2542	2.00 (0.03–6.88)
		All clinical samples	31	66250	3.24 (1.67–5.29)

6.05% - Blood samples

3.01%

Zhang *et al,* Plos One 2015

Why we are we talking about ?

- High rate of failure with vancomycin (it depends of PK/PD)
- a higher rate of mortality (63% vs 12%)
- Difficult to identify patients who are prone to be infected with these strains
  - Previous duration of vancomycin admistration (OR=13)

Fridkin *et al,* Clin Inf Dis 2002

The higher risk of failure/mortality still debated ?

- H-GISA and GISA seems to be less « virulent » compared to other VS-MRSA isolates
- H-GISA and GISA seems to have the same clinical outcome

TABLE 2. Rates of infection versus colonization for RVS-MRSA and VS-MRSA isolates

Site colonized or infected or type of infection	No. of patients with indicated type of isolate				*P* value
	RVS-MRSA (n = 58)		VS-MRSA (n = 59)		
	Infected[a]	Colonized[b]	Infected[a]	Colonized[b]	
Sites					
Total no.	29	29	46	13	0.003
Blood	3	—	20	—	
Sterile site[c]	5	—	10	—	
Urine	0	7	3	2	0.045
Sputum	7	14	5	4	0.69
Wound swab	14	8	8	7	0.73

TABLE 3. Response to treatment in patients with assessable clinical infection outcome

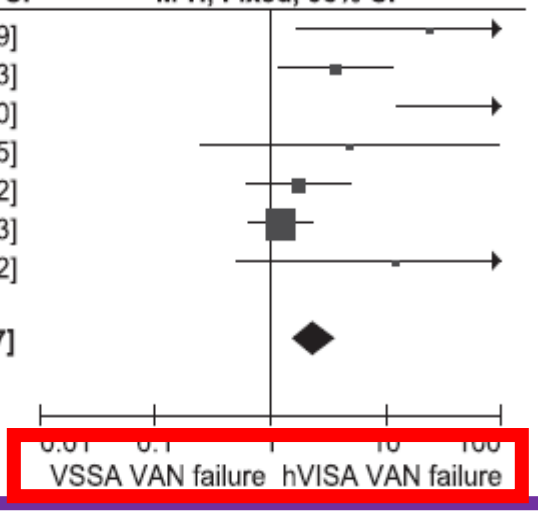
Treatment regimen	No. of patients with indicated type of isolate[a]				*P* value
	RVS-MRSA (n = 26)		VS-MRSA (n = 42)		
	Cure	Failure	Cure	Failure	
Glycopeptide alone[b]	8	6	21	5	0.22
Vancomycin in combination with additional agents	6[c]	4[d]	4[e]	1	0.60
No MRSA treatment[f]	2	0	6	5	0.49
Total	16	10	31	11	0.43

Horn *et al,* AAC 2009

Study or Subgroup	hVISA Events	hVISA Total	VSSA Events	VSSA Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Ariza (2)	12	14	1	5	0.8%	24.00 [1.69, 340.99]
Bae et al (4)	13	19	17	46	12.2%	3.70 [1.18, 11.53]
Charles et al (8)	5	5	1	48	0.1%	348.33 [12.59, 9636.20]
Fong et al (16)*	9	9	21	26	2.3%	4.86 [0.24, 97.05]
Horne et al (24)	10	26	11	42	20.2%	1.76 [0.62, 5.02]
Musta et al (41)	20	43	101	242	63.5%	1.21 [0.63, 2.33]
Neoh et al (42)	2	2	5	18	1.0%	12.27 [0.50, 299.32]
Total (95% CI)		**118**		**427**	**100.0%**	**2.37 [1.53, 3.67]**
Total events	71		157			

Heterogeneity: Chi² = 17.79, df = 6 (P = 0.007); I² = 66%

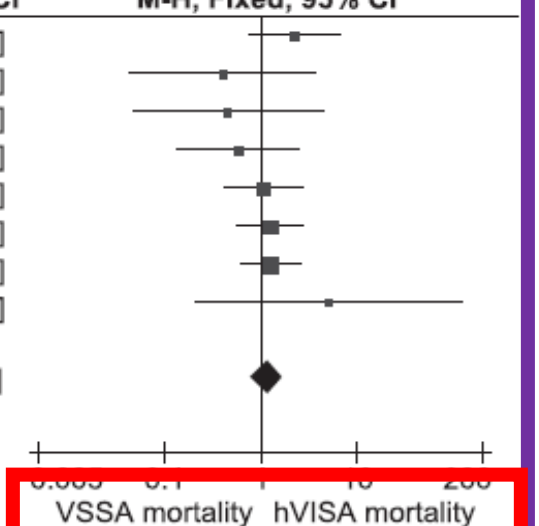
Test for overall effect: Z = 3.88 (P = 0.0001)



Study or Subgroup	hVISA Events	hVISA Total	VSSA Events	VSSA Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Bae et al (4)	8	19	16	65	8.7%	2.23 [0.76, 6.50]
Bert et al (5)	1	13	6	35	6.2%	0.40 [0.04, 3.71]
Charles et al (8)	1	5	17	48	5.3%	0.46 [0.05, 4.41]
Fong et al (16)	5	10	19	30	9.9%	0.58 [0.14, 2.46]
Horne et al (24)	12	58	11	56	18.4%	1.07 [0.43, 2.67]
Maor et al (37)	14	27	103	223	22.2%	1.25 [0.56, 2.79]
Musta et al (41)	14	43	67	242	28.3%	1.26 [0.63, 2.53]
Neoh et al (42)	2	2	8	16	0.9%	5.00 [0.21, 120.44]
Total (95% CI)		**177**		**715**	**100.0%**	**1.18 [0.80, 1.72]**
Total events	57		247			

Heterogeneity: Chi² = 4.75, df = 7 (P = 0.69); I² = 0%

Test for overall effect: Z = 0.84 (P = 0.40)

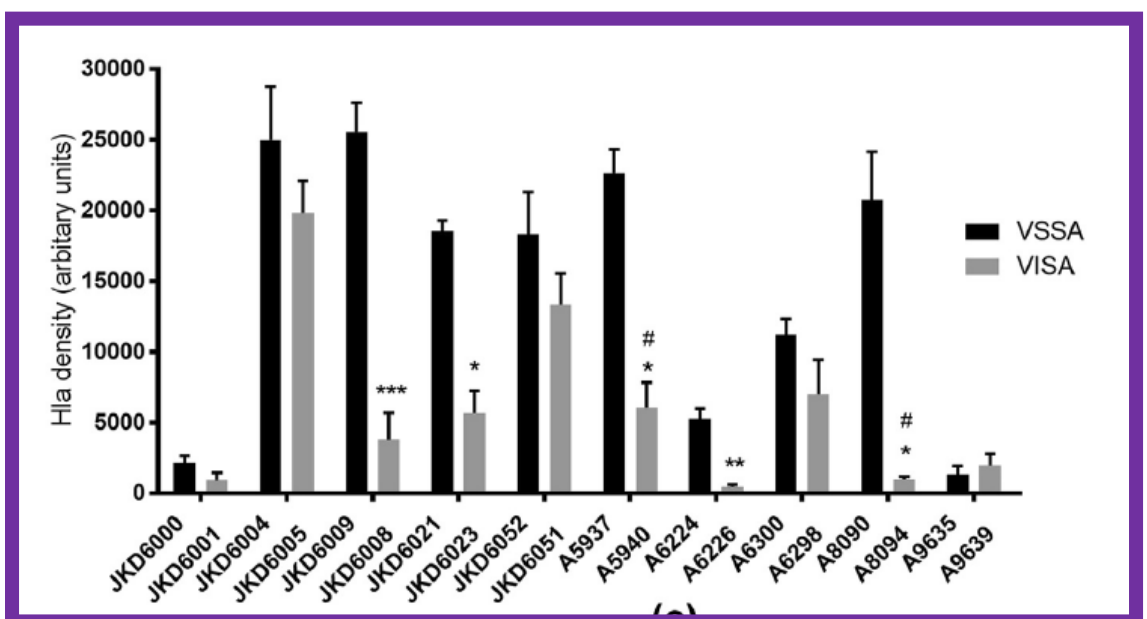


Hall *et al,* AAC 2011

Vancomycin-intermediate *Staphylococcus aureus* isolates are attenuated for virulence when compared with susceptible progenitors

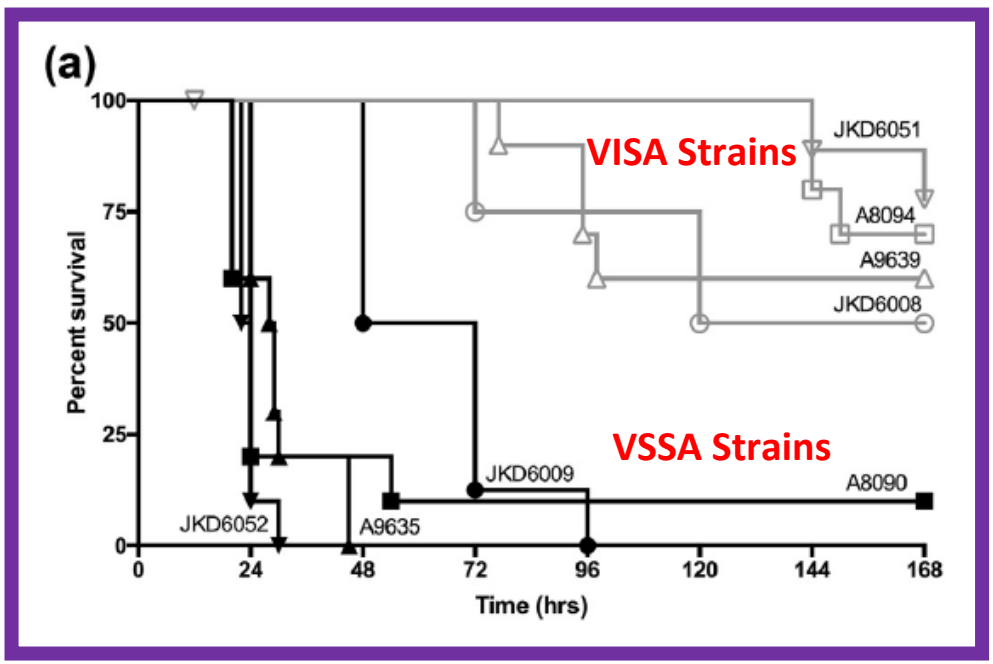
Assessing the production of virulent factors : Protein, α toxin
Correlate with agr activity
Evaluating host immune response in murine model

accessory gene regulator agr = virulence regulator gene



20 fold less α toxin, loss of agr activity

Animal models



Cameron *et al,* Clin Microb Inf 2017

The higher risk of failure/mortality still debated ?

- Why it could be difficult to highligth a difference in clinical practices ?
  - Testing methodologies
  - Confounding factors : severity at starting treatment, different populations of patients
  - PK/PD parameters and MIC are note taken into account
  - Non-antibiotic intervention : debridements/surgery

Lodise *et al,* AAC 2008
Soriano *et al,* Clin Inf Dis 2008

Who is prone to be infected ?

- Several publications with a little number of patients
- Case-control studies comparing VISA to MRSA infected patients
- Several risk factors identified
  - Underlying illness
  - Exposure ro intravascular garfts
  - Dialysis
  - Previous hospitalisation
  - Previous MRSA colonisation

Rueff, Infection 2004

Who is prone to be infected ?

Predictors of high vancomycin MIC values among patients with methicillin-resistant *Staphylococcus aureus* bacteraemia

Table 1. Bivariate comparison of clinical characteristics by high (
vancomycin MIC values

Demographic and clinical characteristics	High MIC ($n = 77$)		
Age (years), mean (SD)	58.8 (16.3)		
Sex (male), *n* (%)	56 (72.7)		
Weight (kg), mean (SD)	81.4 (24.9)		
Height (cm), mean (SD)	153.0 (9.7)		
Diabetes mellitus, *n* (%)	37 (48.1)		
Heart failure, *n* (%)	25 (32.5)		
Dialysis, *n* (%)	18 (23.4)		
History of hospitalization, *n* (%)	53 (68.8)	18 (64.3)	0.6
Recent antibiotics, *n* (%)	41 (53.2)	20 (71.4)	0.1
Recent vancomycin, *n* (%)	15 (19.5)	1 (3.6)	0.05
Recent non-vancomycin antibiotics, *n* (%)	25 (32.5)	17 (60.7)	0.009
Length of stay prior, median number of days (interquartile range)	2 (0–14)	0 (0–4.75)	0.1
Residence in an ICU at onset, *n* (%)	27 (35.1)	3 (10.7)	0.02
Baseline CL_{CR} (mL/min), mean (SD)	51.6 (32.4)	43 (33.4)	0.3
APACHE II score, mean (SD)	14.7 (6.8)	13.6 (5.8)	0.5
CDS-ID score, mean (SD)	3.7 (2.3)	3.6 (2.6)	0.9

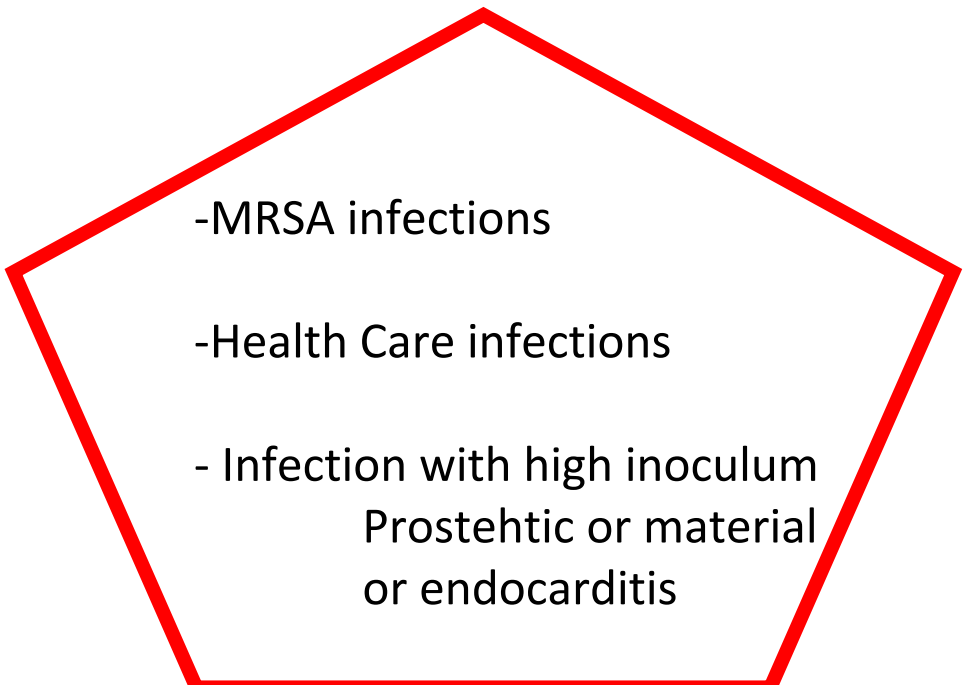
Table 4. Independent risk factors for infection due to *Staphylococcus aureus* with reduced susceptibility to vancomycin (MIC of vancomycin, ⩾4 μg/mL).

Risk factor	Adjusted OR (95% CI)
Vancomycin use (per week) in prior month	13.1 (1.8–100)
MRSA isolated from culture in prior second or third month	32.5 (1.1–947)
Vancomycin (per week) in prior 3–6 months	2.8 (1.1–7.0)

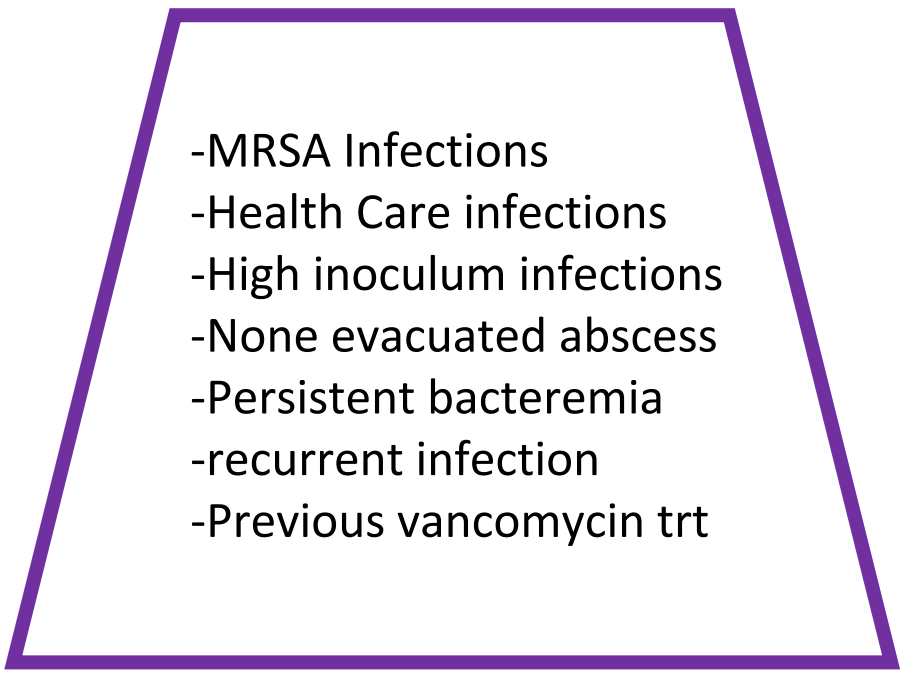
Fridkin *et al,* CID 2002

Lodise *et al,* JAC 2008

When should we evoke it ?



Before any treatment



During treatment

Hassoun *et al,* Crit Care 2017

Risk factors are mooving ?

Exposure of *Staphylococcus aureus* to Subinhibitory Concentrations of β-Lactam Antibiotics Induces Heterogeneous Vancomycin-Intermediate *Staphylococcus aureus*

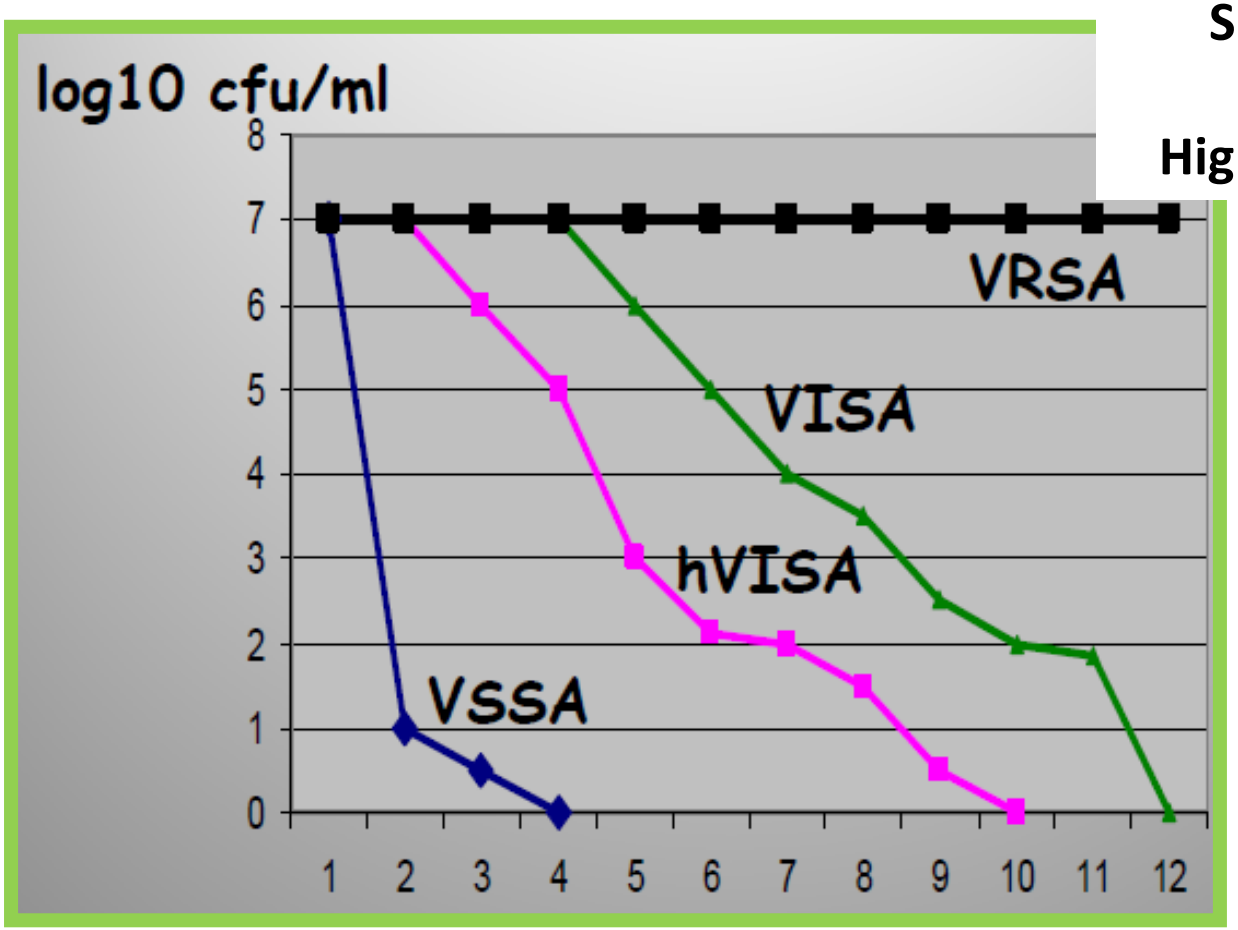
Roch *et al,* AAC 2014

Characterization of Vancomycin-Heteroresistant *Staphylococcus aureus* from the Metropolitan Area of Detroit, Michigan, over a 22-Year Period (1986 to 2007)[▽]

Ryback *et al,* JCM 2008

h-Visa identified from community acquired infections !

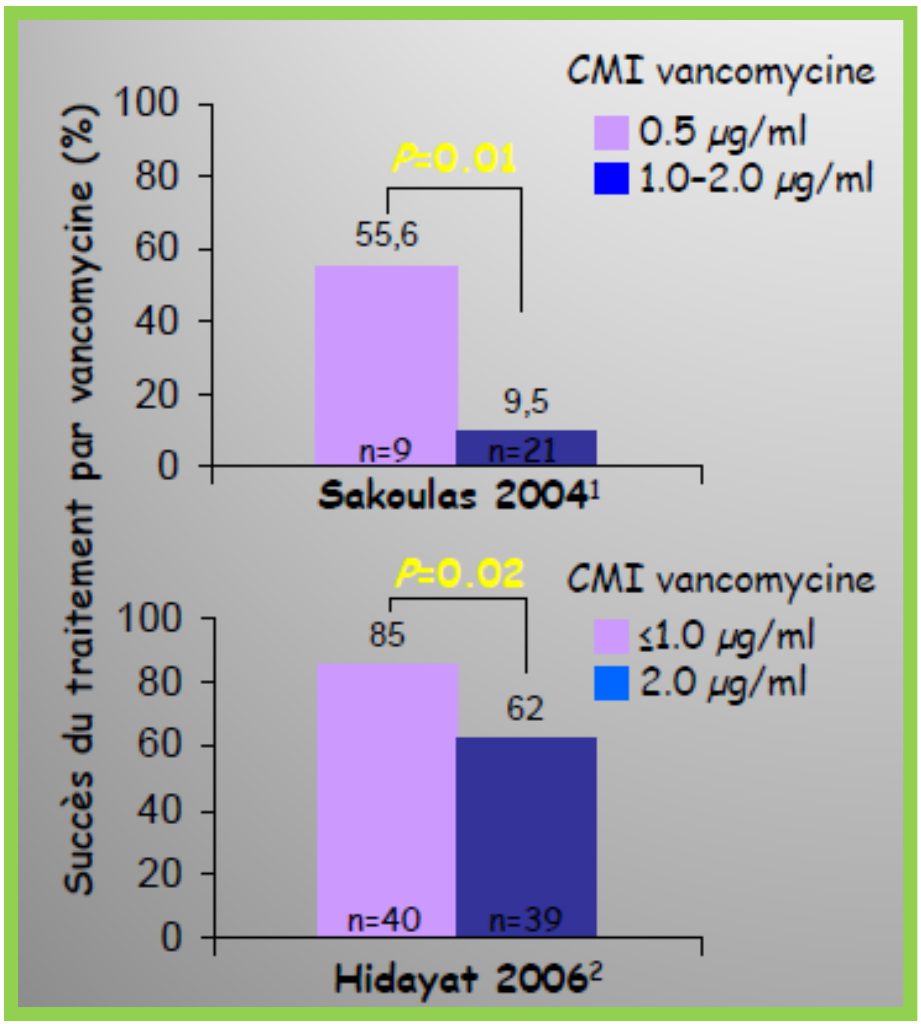
Is vancomycin still the reference treatment?

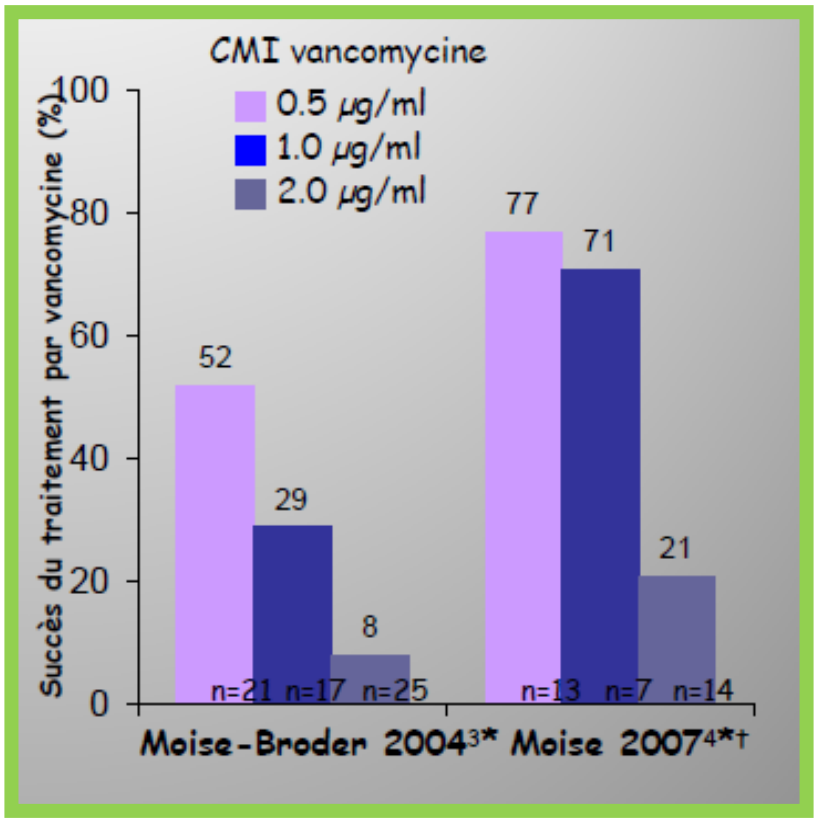


Slow bactericidal activity
Need higher dose
Higher risk of nephro toxicicy

Slides : R Leclercq CHU Caen

The risk failure for MRSA with MIC >1 mg/l to vancomycin





Moise-broder *et al,* Clin Inf Dis 2004
Moise Broder *et al,* AAC 2007
Hidayat *et al,* Arch int Med 2006
Sakoulas *et al,* JCM 2004

How can we treat these isolates ?

Table 1. In Vitro Activity of 11 Antimicrobial Agents Against 33 Vancomycin-Intermediate *Staphylococcus aureus* Isolates

Antimicrobial Agent	VISA MIC Range	VISA (% Susceptible)	VISA MIC_{50}	VISA MIC_{90}
Linezolid	0.5–4	100	2	4
Telavancin	0.25–1	100	0.5	0.75
Tigecycline	0.03–1	97	0.12	0.25
Minocycline	0.03–16	94	0.12	4
Ceftaroline	0.25–2	85	0.5	2
Trimethoprim/sulfamethoxazole	0.06/1.2–>4/76	70	0.25/4.8	>4/76
Rifampin	<0.004–>4	51	1	>4
Clindamycin	0.06–>64	30	>64	>64
Daptomycin	1–8	30	2	4
Moxifloxacin	0.25–16	6	2	8
Vancomycin	4–8	0	4	8

Saravolatz *et al,* Clin Inf Dis 2012

Other antibiotic choices

- Daptomycin :
  - 4 to 8 times more active than vancomycin
  - Cross resistance between daptomycin and vancomycin (Patel, CID 2006)
  - Exposure to vancomycin induce h-resistance to daptomycin (Sakoulas – AAC 2006)
  - One study suggested a high rate of resistance for H-Visa and VISA (Kelley, JAC 2011)
    - 15% for h-VISA and 38% for VISA

- **Linezolid**
  - Non- bactericidal antibiotic
  - Several case reports – but frequently used in combination
  - Excellent pulmonary diffusion

Gomes *et al,* Phramacotherapy 2015

Other antibiotic choices

- Ceftaroline
  - Broad range of activity
  - Supported by in vivo and in vitro data (Saravolatz, CID 2010), (Steed, AAC 2011)
  - Utility is well demonstrated for MRSA Infections (Cosimi *et al,* Open forum Inf Dis 2017)
  - Little clinical experience for VISA strains

- Combination : beta lactams and vancomycin or daptomycin
  - Beta lactams seems to have a synergistic activity
  - VISA may be inhibited at lower vancomycin concentration when exposed to beta lactams

Gomes *et al,* Phramacotherapy 2015

Take home message

- H-VISA are the great majority of VISA strains
- H-VISA and VISA emerged in patients with vancomycin treatment
- Consider the risk if MIC > 2mg/l
- Less virulent strains (compared to MRSA and MSSA)
- Need to use higher dose of Vancomycin or novel antibiotics for Gram positive bacteria