

GISA

mythe ou réalité ?

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Prevalence of GISA in France RICA I 2001

<u>abstract 106</u>	Monteil et al 38244 strains – 32 hospitals	0 %
<u>abstract 107</u>	Sanchez et al 13846 strains – 26 hospitals	0 %
<u>abstract 109</u>	Preney et al 301 strains – 12 hospitals	0,7 %
<u>abstract 112</u>	Reverdy et al 1351 strains – 108 hospitals	1,5 %
<u>abstract 110</u>	Burucoa et al 289 strains – 6 hospitals	21 %

**VANCOMYCIN-RESISTANT
STAPHYLOCOCCUS AUREUS :
APOCALYPSE NOW ?**

Tabaqchali S., 1997, Lancet 350 : 1644

**INTERMEDIATE VANCOMYCIN
RESISTANCE IN *STAPHYLOCOCCUS
AUREUS* : A MAJOR THREAT OR A
MINOR INCONVENIENCE ?**

Johnson AP, 1998, J.A.C. 42 : 289

**GLYCOPEPTIDE – INTERMEDIATE
STAPHYLOCOCCUS AUREUS :
REDISCOVERY OF AN OLD
PROBLEM ?**

Cercenado E, 2000, CMI 6 : 517

What happens after 1996 ?

- **Worldwide dissemination of a GISA clone ?**
- **Simultaneous emergence in many countries of different clones ?**
- **Other reasons ?**

GISA strains isolated in vivo before 1996

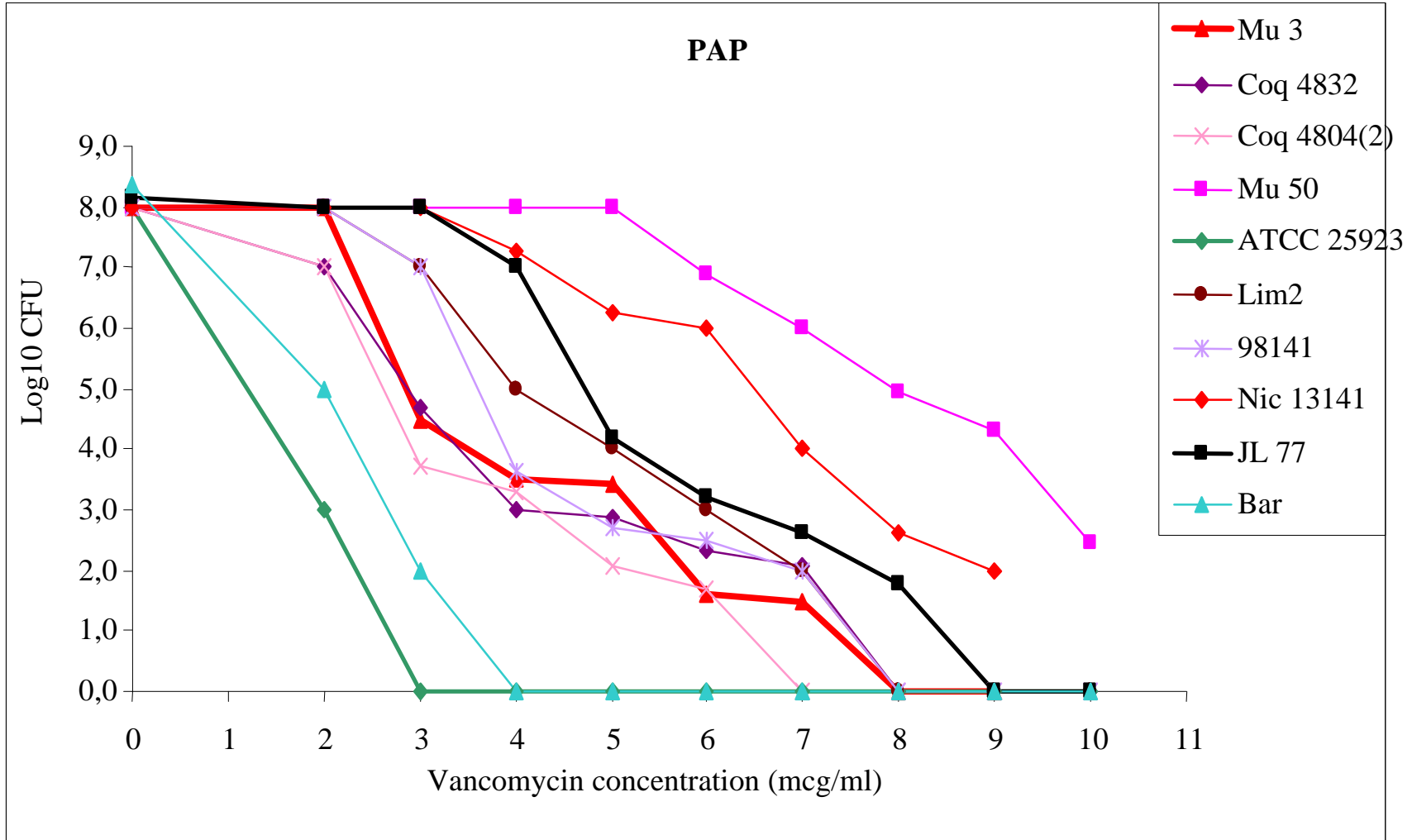
Kaatz	1990	Clinical failure	teicoplanin
Vedel	1990	Infection/colonisation	teicoplanin
Brunet	1990	Clinical failures	teicoplanin
Manquat	1992	Clinical failures	teicoplanin
Mainardi	1995	Clinical failures Nosocomial spread	vancomycin/teicoplanin
Quincampoix	1997	Clinical failures Nosocomial spread	vancomycin/teicoplanin

Vrais (et faux) problèmes posés par les GISA

- **méconnaissance des mécanismes de résistance.**
- **méconnaissance des exigences de ces souches.**
- **absence de consensus sur la définition et détection des GISA.**

- **CMI : inoculum et milieu dépendant.**
- **CMI : instabilité et induction de la résistance.**
- **CMI : différentiel faible ou nul entre S et R.**

- **Implications cliniques.**
 - **traitement : . vancomycine seule/en association ?**
 - . autres antibiotiques ?**
 - **sélection in vivo.**



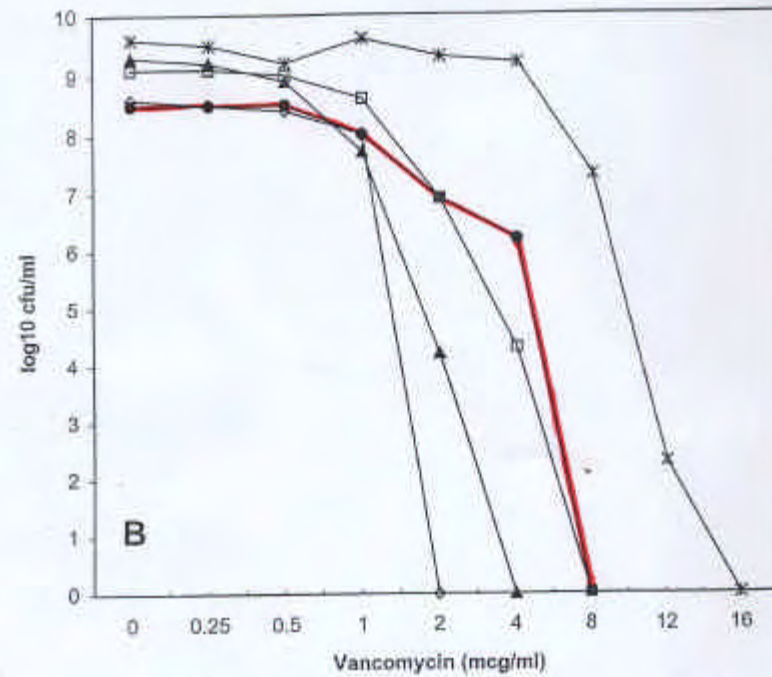


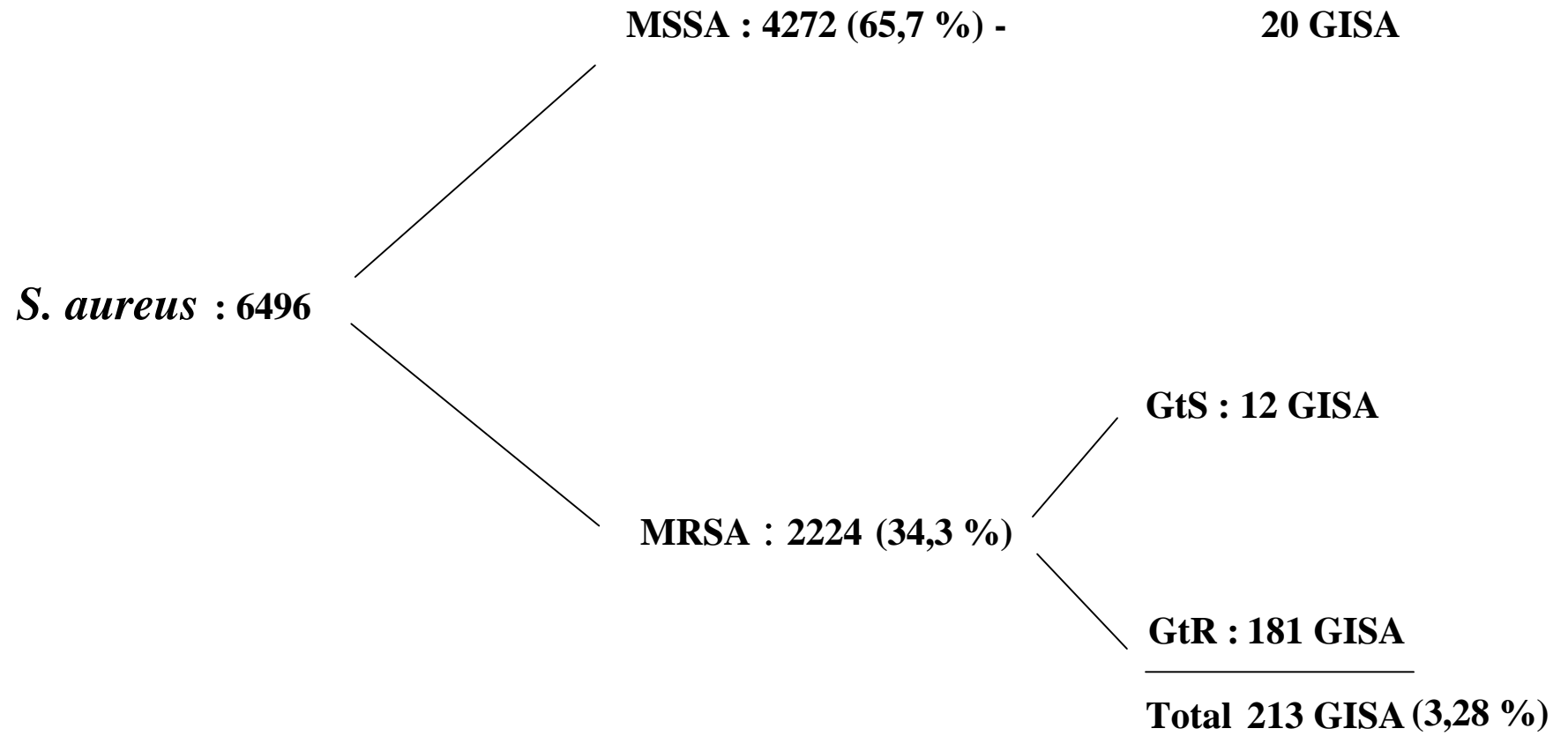
FIG. 1. Vancomycin population susceptibility profiles for HIP5836 (A), Mu50 (B), and 14379 (C). ●, first pass; □, second pass; ▲, fifth pass; ◇, tenth pass; ×, fifth pass on vancomycin agar for Mu50. mcg, micrograms.

VISA, VRSA, TISA, TRSA,
h-VISA, h-VRSA, h-TISA, h-TRSA
GISA, GRSA, h-GISA, h-GRSA



GISA

May 1999 → April 2005



Trough Vancomycin serum levels after 2-4 administrations

or continuous infusion (CI)

N = 1737 patients*

	< 5	5-10	10-15	15-20	20-25	25-30	30-35	35-40	> 40 mg/L	TOTAL
bid	148	204	160	103	70	35	22	12	26	780
	19,0 %	68,8 %				12,2 %				
CI	15	60	212	173	176	121	74	59	67	957
	7,9 %	71,2 %				20,9 %				

1st assay only

dialyzed patients excluded

Expected vancomycin failures

N = 44

Author	Ploy	Fridkin	Charles	Rotun	Kim	Wong	Hiramatsu	Andrade-Baiochi	Smith	MMWR	Trakulsomboon	Ward	Sugino	Ariza	Hassan	Howe	Moore	Bert	Haraga	Lutz
N° patients	1	4	5	1	1	4	2	1	2	1	2	1	1	12	1	1	1	1	1	1
low serum levels*	?	?	+	+	?	?	?	?	OK	+	?	+	OK	?	?	+	?	+	OK	+
teicoplanin	+				+						+	+			+					
antagonistic combinations	+	+		+			+		+			+	+					+	+	
foreign devices	+	+	+	+		+		+	+	+				+		+				
undrained abscesses	+	+		+	+		+				+		+							
endocarditis			+							+								+		
end-stage patients		+		+	+	+		+	+											
total risk factors	5	4			3			2			1									

* **OK** : adequate serum levels

+ : low serum levels

? : no data

Evidence Based Medicine

Adequate serum levels demonstrated

In 3/44 = 6,8 % of patients only !

sig B

Controls the expression of 251 genes

198 genes up-regulated

- cell-wall synthesis → MICs
- biofilm production
- fibronectin binding proteins
- pigment production
- stress-proteins (> 40)

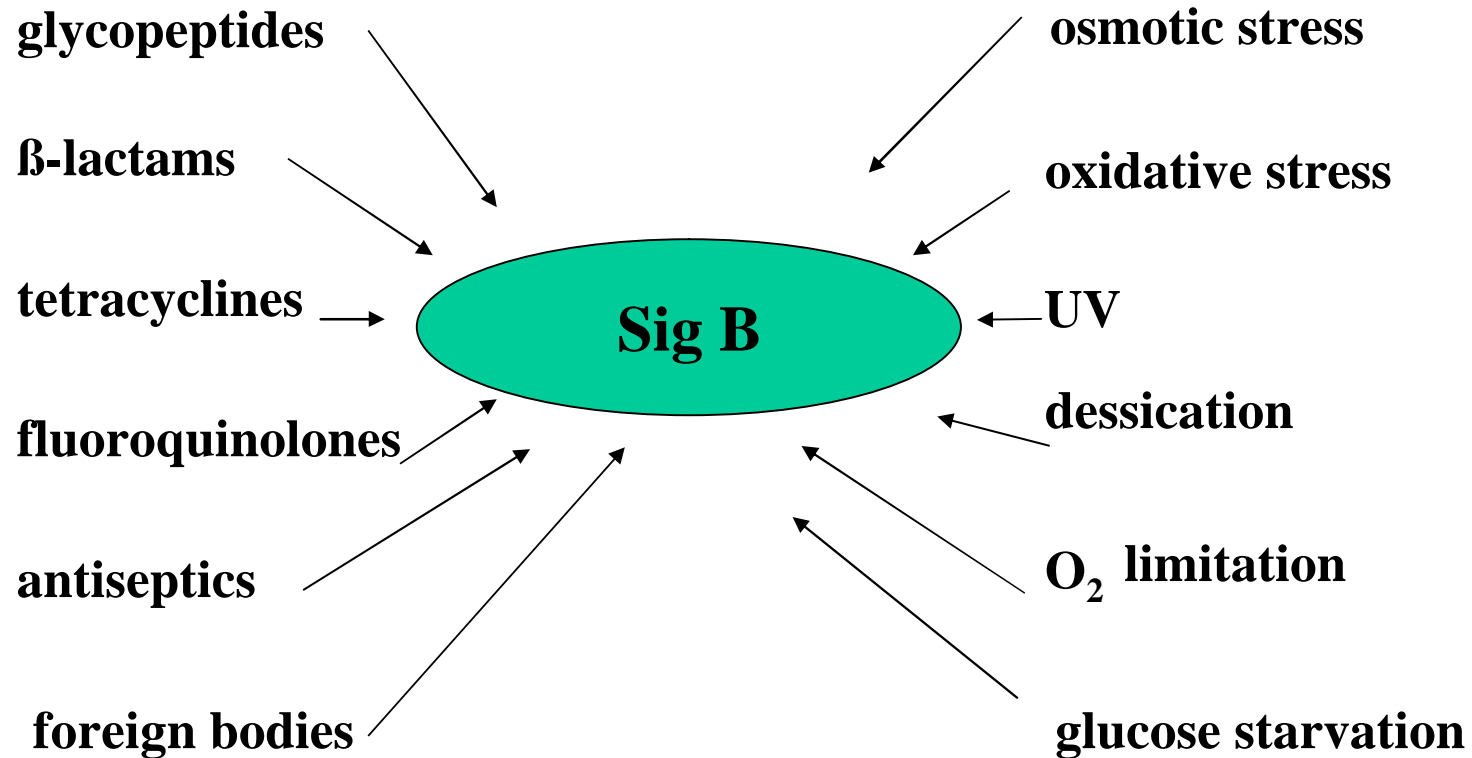
glycopeptides

β -lactams

53 genes down-regulated

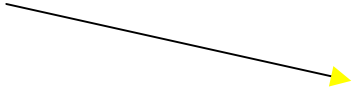
Exotoxins : coagulase, clumping factor,
thermonuclease, proteases, lipases,
hemolysin

Induction of sigB activity

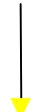


foreign body

S. aureus



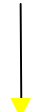
selection clone producing fibronectin, biofilm.



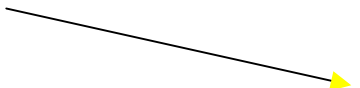
selection activated sig B



selection low-prevalence hGISA



Glycopeptide/ β -lactam



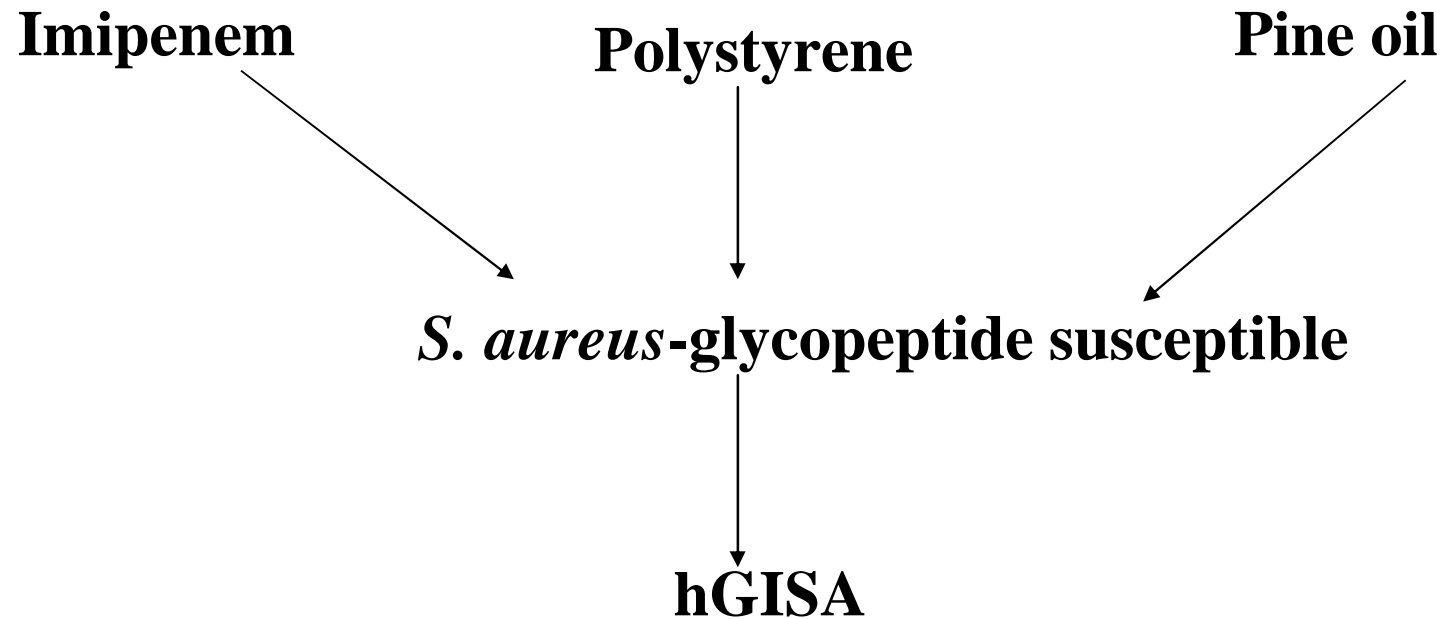
predominance hGISA

Vancomycin versus β -lactams

	<u>Patients</u>	<u>Failure rate</u>
vancomycin	19	52,6 %
β -lactams	13	7,7 %

Bishop M et al 2004
42nd IDSA abst. 513

Selection of hGISA strains



Historique

Problèmes posés par les GISA.

Mécanismes de résistance.

Implications cliniques.

Sélection in vivo.

Vancomycin induces the transcription of 139 genes ...

**The following genes regulate the activity of glycopeptides
AND β -lactams**

sig B

pbp 2

vra SR

tca A

mur Z

prs A

msr A

lyt A

sgt B

mgr A