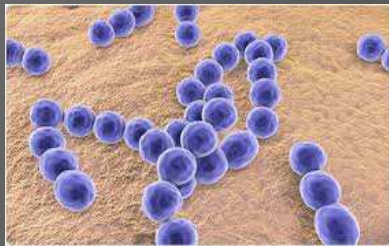


JEUDI 26 NOVEMBRE 2020
UFR Médecine Paris 7 Diderot,
site Xavier-Bichat - Paris 18^{ème}

63^{ème} journée Claude-Bernard



Communication AP-HP Nord Université de Paris - juillet 2020



Nouvelles résistances des bactéries à Gram positif

Pr. Vincent CATTOIR

Service de Bactériologie-Hygiène hospitalière, CHU de Rennes

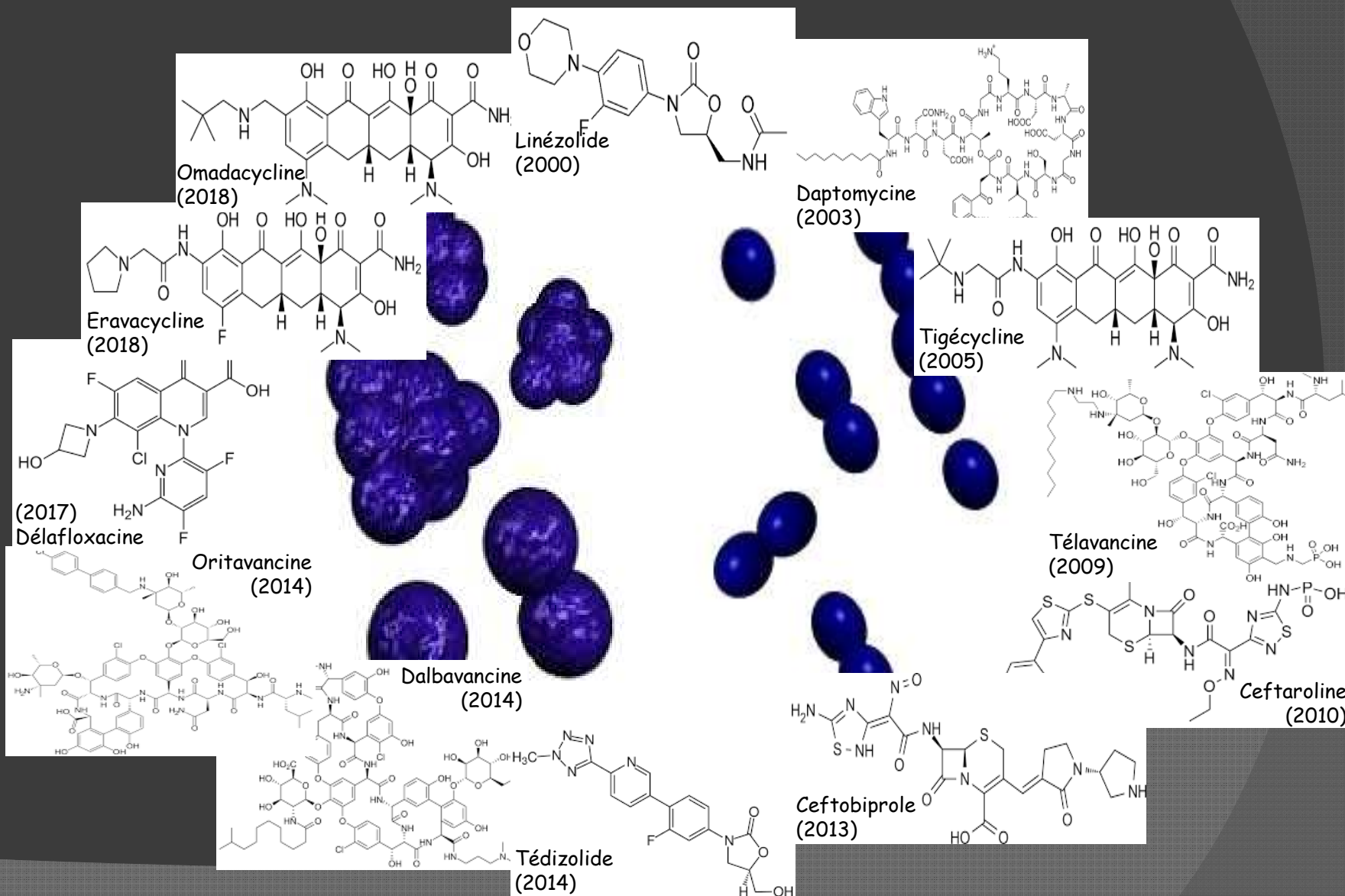
CNR de la Résistance aux Antibiotiques (laboratoire associé « Entérocoques »)

Faculté de Médecine & Unité Inserm U1230, Université de Rennes 1

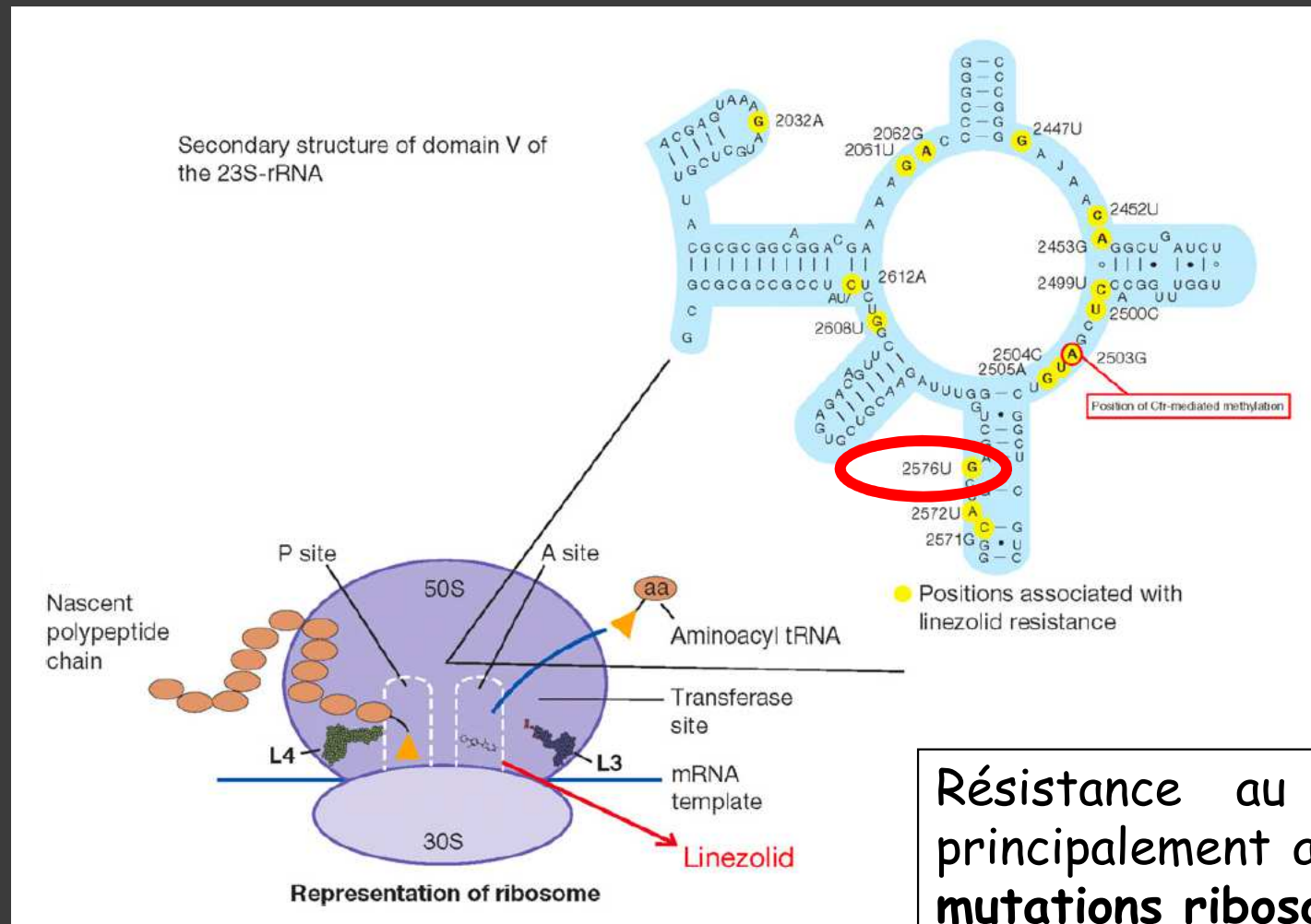
Section des Agents Anti-Infectieux et Comité de l'Antibiogramme de la SFM



Quels antibiotiques ?



Résistance aux oxazolidinones



Résistance au linézolide
principalement acquise par
mutations ribosomales
(sélection *in vitro* = 10^{-9} - 10^{-11})

Résistance plasmidique : *cfr*

Gène codant pour une méthyltransférase ARNr 23S (A2503)

Oxazolidinones
(pas TZD)

Phénicolés

Streptogramines A

Pleuromutilines

Lincosamides

Antibiotic	MIC (µg/ml) ^a			
	<i>E. faecalis</i> 603-50427X	OG1RF	Tc6	Tc11
Linezolid	32	1	8	8
Linezolid ^b	24	2	8	6
Ampicillin	2	4	1	1
Vancomycin	1	2	2	2
Teicoplanin	≤1	≤1	≤1	≤1
Daptomycin	1	2	1	1
Ciprofloxacin	>4	2	1	1
Levofloxacin	>4	2	1	1
Chloramphenicol	64	4	64	64
Tigecycline	0.06	0.12	0.12	0.12
Quinupristin/dalfopristin	4	16	>16	>16
Tiamulin	64	>64	>64	>64
Clindamycin	>128	32	>128	>128
Fusidic acid	8	>128	>128	>128
Rifampin	0.25	>128	>128	>128

Phénotype PhLOPS_A

Autres variants : Cfr(B) à Cfr(E)

Résistance plasmidique : *optrA*

Gène pour une protéine de protection ribosomale

Bacterial isolate	MIC (mg/L)				
	CHL	FFC	LZD	TZD	VAN
Clinical <i>E. faecalis</i> E349 (with <i>optrA</i> -carrying pE349)	64	64	8	2	1
<i>E. faecalis</i> FA2-2	4	2	2	0.5	1
Transconjugant <i>E. faecalis</i> FA2-2-E349	32 x8	64 x32	8 x4	2 x4	1

→ Phénotype PhO

Résistance plasmidique : *poxtA*

Gène codant pour une protéine de protection ribosomale (id. 32 % Optra)

Antibiotic	MIC (mg/L)			
	<i>S. aureus</i> ^a		<i>E. faecalis</i> ^b	
	RN4220 (pMU- <i>poxtA</i>)	RN4220 (pMU-E)	JH2-2 (pMU- <i>poxtA</i>)	JH2-2 (pMU-E)
Linezolid	2	1	4	1
Tedizolid	0.5	0.25	0.5	0.25
Chloramphenicol	8	4	8	4
Florfenicol	16	2	16	2
Tigecycline	0.25	0.25	0.25	0.25
Tetracycline	0.25	0.125	0.25	0.125
Doxycycline	0.25	0.125	0.125	≤0.06

x2-4

x2

x2

x8

x2

→ Phénotype PhOT

Epidémiologie chez *S. aureus*

Programme **SENTRY** (427 centres, 45 pays, 1997-2016)

Antimicrobial Agent	No. of Isolates	MIC ₅₀	MIC ₉₀	MIC Range	CLSI ^a		
					%S	%I	%R
MSSA	114 300						
Ceftaroline	58 938	0.25	0.25	≤0.06–1	100.0	0.0	0.0
Dalbavancin	92 584	0.06	0.06	≤0.03–>0.25	>99.9		
Daptomycin	94 022	0.25	0.5	≤0.12–4	>99.9		
Delafloxacin	18 033	≤0.004	0.015	≤0.004–>1	98.1	0.9	0.9
Levofloxacin	102 405	≤0.5	≤0.5	≤0.5–>4	92.2	0.5	7.1
Linezolid	110 519	1	2	≤0.12–>8	>99.9		<0.1
Oritavancin	50 013	0.03	0.06	≤0.008–0.5	99.7		
Quinupristin-dalfopristin	68 250	≤0.5	≤0.5	≤0.5–>2	99.9	0.1	<0.1
Tedizolid	22 987	0.12	0.12	≤0.008–0.5	100.0	0.0	0.0
Teicoplanin	114 285	≤2	≤2	≤2–>8	>99.9		
Telavancin	46 041	0.03	0.06	≤0.015–0.25	>99.9		
Tigecycline	93 850	≤0.12	0.25	≤0.12–1	>99.9		
Vancomycin	114 297	1	1	≤0.12–4	>99.9	<0.1	0.0
MRSA	77 146						
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Delafloxacin	10 243	0.12	1	≤0.004–>1	74.3	12.3	13.4
Levofloxacin	72 075	>4	>4	>0.5–>4	22.4	1.7	75.0
Linezolid	75 780	1	2	≤0.25–>8	99.9		0.1
Oritavancin	35 262	0.03	0.06	≤0.008–0.5	99.6		
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Tigecycline	65 977	≤0.12	0.25	≤0.12–4	99.8		
Vancomycin	77 145	1	1	≤0.12–4	>99.9	<0.1	0.0

≤0,1 %

Epidémiologie chez *Enterococcus*

Programme **SENTRY** (298 centres, 1997-2016)

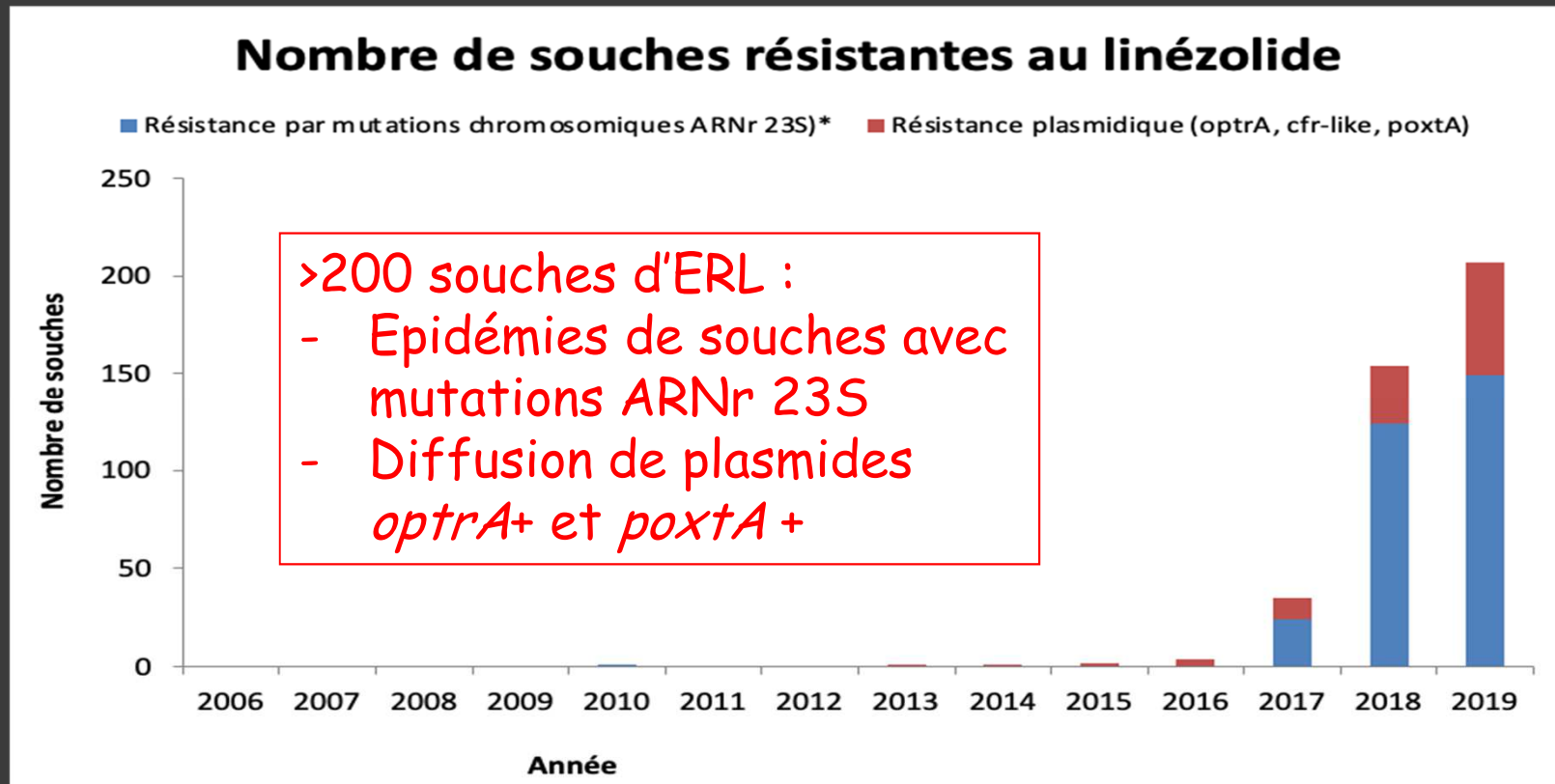
Activité sur 7 615 souches d'ERV (*vanA/ vanB*) :

Antimicrobial Agent	MIC _{50/90} (% of Tested Isolates Susceptible), mg/L ^a			
	NA (n = 5450)	EUR (n = 1374)	LATAM (n = 470)	APAC (n = 321)
Ampicillin ^b	>8/>8 (10.5)	>8/>8 (10.0)	>8/>8 (22.8)	>8/>8 (3.4)
Tetracycline ^c	>8/>8 (35.6)	≤4/>8 (57.5)	≤4/>8 (64.7)	≤4/>8 (62.3)
Tigecycline	≤0.12/≤0.12 (99.2)	≤0.12/≤0.12 (99.5)	≤0.12/≤0.12 (99.3)	0.12/0.25 (99.4)
Daptomycin	2/2 (99.6)	2/2 (100.0)	1/2 (100.0)	2/4 (99.7)
Oritavancin ^d	0.03/0.12 (92.3)	0.015/0.06 (95.7)	0.03/0.12 (92.2)	≤0.008/0.06 (98.3)
Linezolid	1/2 (98.0)	1/2 (99.2)	1/2 (99.6)	1/2 (99.4)
Tedizolid ^e	0.12/0.25 (99.5)	0.12/0.25 (99.5)	0.12/0.25 (100.0)	0.12/0.25 (100.0)
Quinupristin-dalfopristin ^f	≤0.5/>2 (95.9)	1/>2 (83.5)	1/>2 (84.9)	1/2 (92.4)

≤2 %

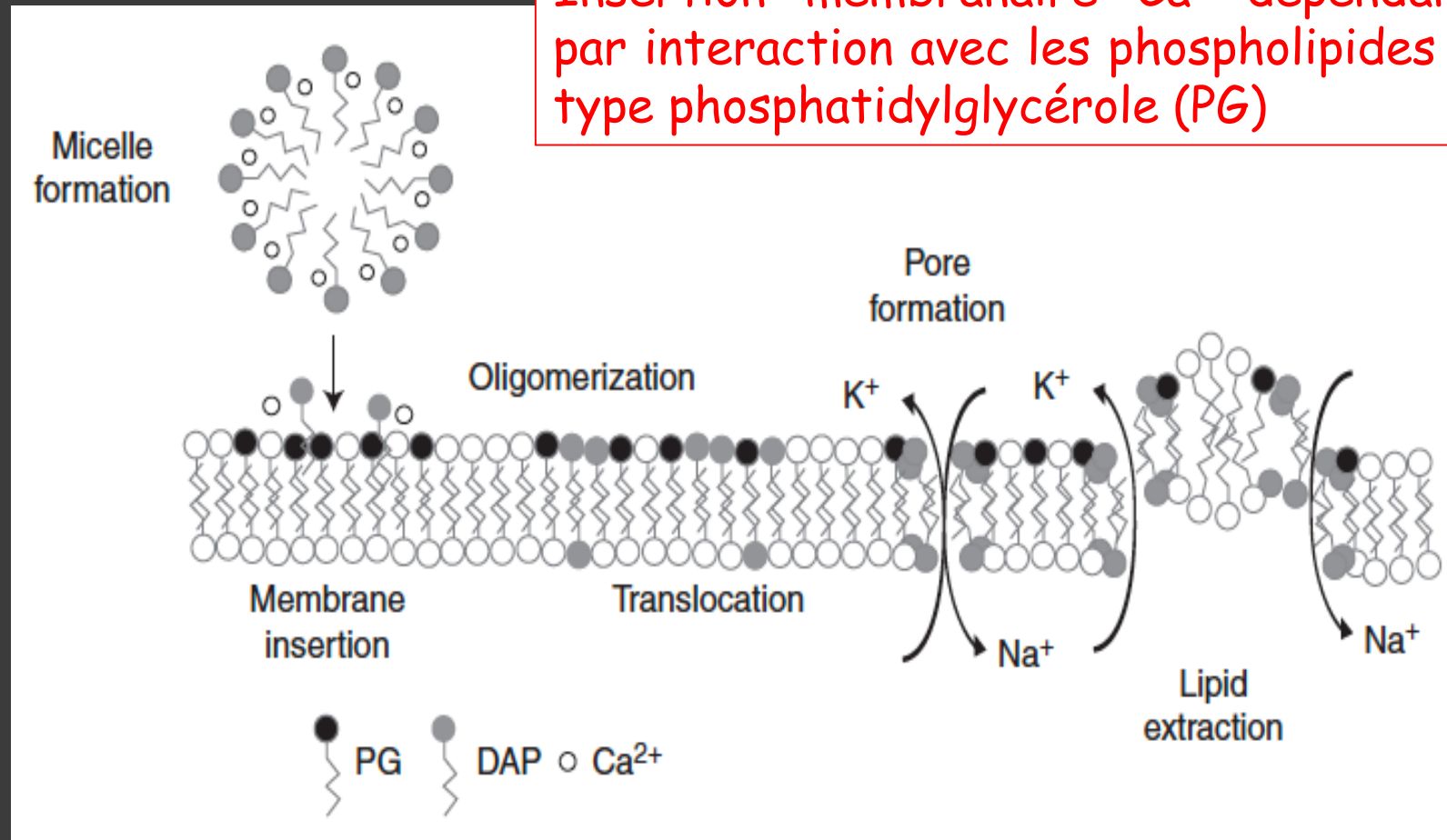
Emergence des ERL en France

Augmentation de la prévalence des Entérocoques Résistants au Linézolide (ERL), notamment depuis 2017



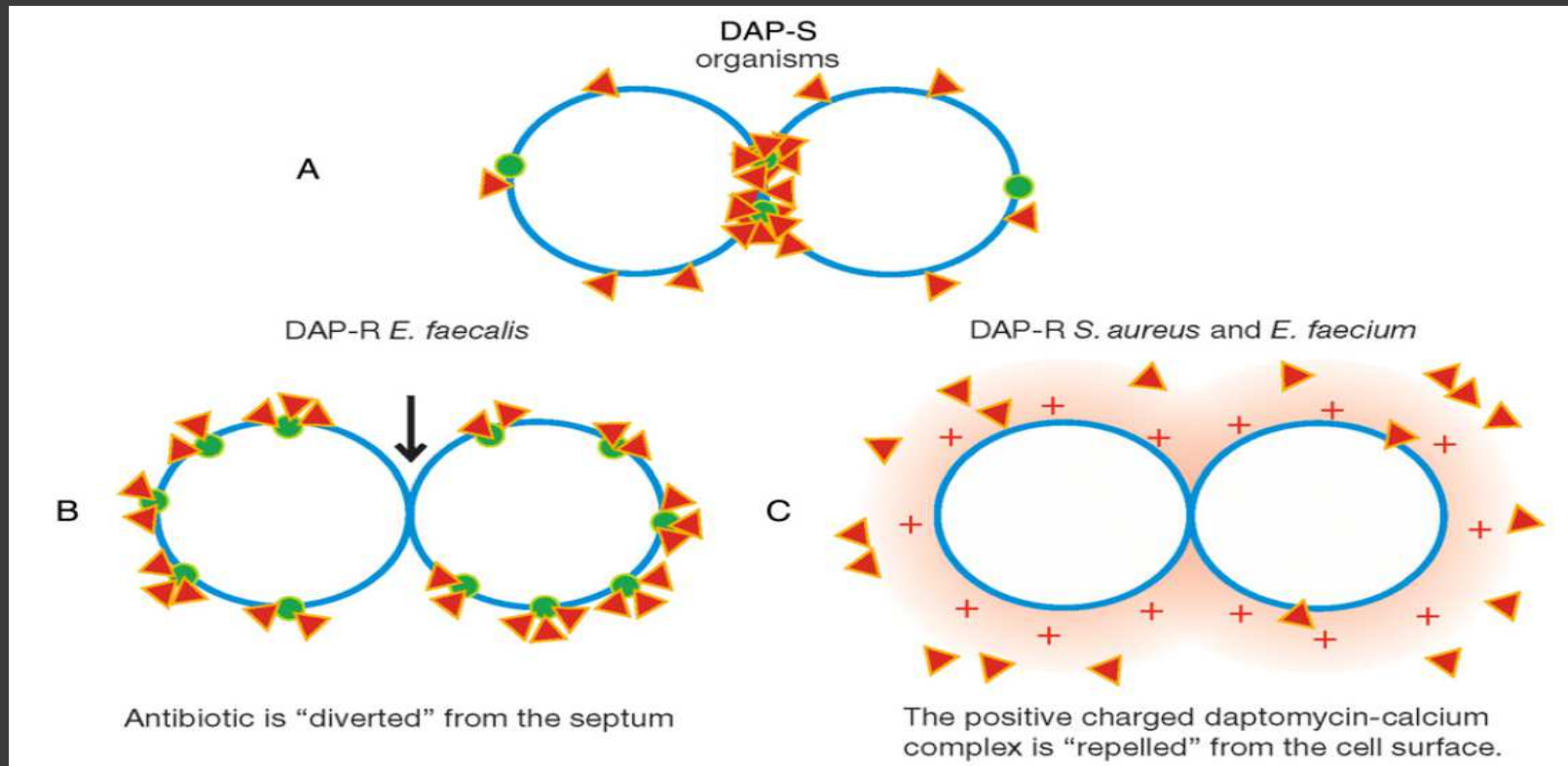
Mode d'action de la daptomycine

Insertion membranaire Ca^{2+} -dépendante
par interaction avec les phospholipides de
type phosphatidylglycérole (PG)



Résistance à la daptomycine

Résistance complexe due à de multiples mutations chromosomiques, notamment dans les gènes impliqués dans la réponse au stress d'enveloppe (ex. *vraSR*, *ycyFG*, *liaFSR*) ou le métabolisme des phospholipides (ex. *pgsA*, *mprF*, *gdpD*, *cls*)



Réversion de la résistance

Strain	MIC (mg/L) ^a				Changes in			
	DAP	VAN	TEC	TLV	Cls	LiaF	LiaS	LiaR
Aus0004	2	8	1	0.06	—	—	—	—
Mutants								
Mut4	4	8	0.5	0.12	—	—	—	—
Mut8	8	8	1	0.5	—	—	—	—
Mut16	16	8	1	1	—	—	Gly92Asp	—
Mut32	32	8	1	2	—	—	Gly92Asp	—
Mut64	64	8	1	2	Asn13Ser	—	Gly92Asp	—
Mut128	128	8	1	2	Asn13Ser	—	Gly92Asp	—
Revertants								
Rev4	2 (2)	4	1	0.06 (2)	—	—	—	—
Rev8	0.12 (64)	4	1	0.06 (8)	—	—	Val122Asp	—
Rev16	0.12 (128)	4	1	0.03 (32)	—	IS66 insertion ^{b,c}	Gly92Asp	—
Rev32	0.06 (512)	4	1	0.06 (32)	—	—	Gly92Asp	IS30 insertion ^b
Rev64	1 (64)	4	1	0.12 (16)	Asn13Ser	IS66 insertion ^{b,c}	Gly92Asp	—
Rev128	0.12 (1024)	4	1	0.12 (16)	Asn13Ser	IS982 insertion ^b	Gly92Asp	—

Résistance par étapes
et croisée avec TLV

Résistance instable
avec réversion
mais facilement re-
sélectionnable (10^{-6}
vs $<10^{-9}$)

Epidémiologie chez *S. aureus*

Programme SENTRY (427 centres, 45 pays, 1997-2016)

Antimicrobial Agent	No. of Isolates	MIC ₅₀	MIC ₉₀	MIC Range	CLSI ^a		
					%S	%I	%R
MSSA	114 300						
Ceftaroline	58 938	0.25	0.25	≤0.06–1	100.0	0.0	0.0
Delamanid	92 594	0.06	0.06	<0.03–>0.25	>99.9		
Daptomycin	94 022	0.25	0.5	≤0.12–4	>99.9		
Delatloxacin	18 033	≤0.004	0.015	≤0.004–>1	98.1	0.9	0.9
Levofloxacin	103 405	≤0.5	≤0.5	≤0.5–>4	92.3	0.5	7.1
Linezolid	110 519	1	2	≤0.12–>8	>99.9		<0.1
Oritavancin	50 013	0.03	0.06	≤0.008–0.5	99.7		
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Tedizolid	22 987	0.12	0.12	≤0.008–0.5	100.0	0.0	0.0
Teicoplanin	114 285	≤2	≤2	≤2–>8	>99.9		
Telavancin	46 041	0.03	0.06	≤0.015–0.25	>99.9		
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Delamanid	65 202	0.06	0.06	<0.03–>0.25	>99.9		
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≤0,1 %

Epidémiologie chez *Enterococcus*

Programme **SENTRY** (298 centres, 1997-2016)

Activité sur **7 615 souches d'ERV** (*vanA* ou *vanB*) :

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	NA (n = 5450)	EUR (n = 1374)	LATAM (n = 470)	APAC (n = 321)
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Tetracycline ^c	>8/>8 (35.6)	≤4/>8 (57.5)	≤4/>8 (64.7)	≤4/>8 (62.3)
Tiacycline	≤0.12/≤0.12 (99.2)	≤0.12/≤0.12 (99.5)	≤0.12/≤0.12 (99.3)	0.12/0.25 (99.4)
Daptomycin	2/2 (99.6)	2/2 (100.0)	1/2 (100.0)	2/4 (99.7)
Oritavancin ^d	0.03/0.12 (92.3)	0.015/0.06 (95.7)	0.03/0.12 (92.2)	≤0.008/0.06 (98.3)
Linezolid	1/2 (98.0)	1/2 (99.2)	1/2 (99.6)	1/2 (99.4)
Tedizolid ^e	0.12/0.25 (99.5)	0.12/0.25 (99.5)	0.12/0.25 (100.0)	0.12/0.25 (100.0)
Quinupristin-dalfopristin ^f	≤0.5/>2 (95.9)	1/>2 (83.5)	1/>2 (84.9)	1/2 (92.4)

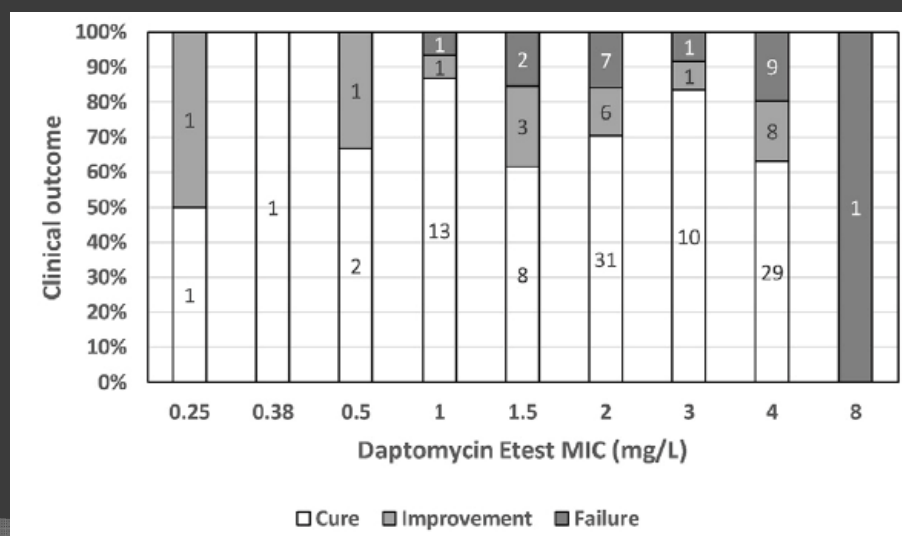
≤0,4 %

Concentrations critiques (EUCAST)

ECOFF *E. faecalis* (4 mg/l) ≠ ECOFF *E. faecium* (8 mg/L)

Probability of survival threshold (fAUC/MIC >27.43) attainment using Monte Carlo simulation [8]

Daptomycin MIC (mg/L)	Daptomycin dose			
	6 mg/kg/day	8 mg/kg/day	10 mg/kg/day	12 mg/kg/day
0.25	100	100	100	100
0.5	100	100	100	100
1	91.0, 97.9 ^a	98.7, 99.9 ^a	99.9, 100 ^a	100
2	32.4, 54.4 ^a	60.7, 80.4 ^a	80.4, 92.9 ^a	91.0, 97.9 ^a
4	1.5, 5.5 ^a	7.3, 18.1 ^a	18.1, 36.2 ^a	32.4, 54.4 ^a
8	0	0.0, 0.2 ^a	0.2, 2.0 ^a	1.5, 5.5 ^a
16	0	0	0	0



→ Pas de concentrations critiques EUCAST ("IE", insufficient evidence)
 → Nécessité d'études PK/PD et cliniques supplémentaires pour infections sévères traitées avec fortes posologies

Concentrations critiques (CLSI)

Reference	<i>Enterococcus faecium</i> , %	Dose: No. of Patients	Microbiologic Failure	Mortality
Gallagher, 2009 [29]	90	<6 mg/kg: 14 ≥6 mg/kg: 16	≥6 mg/kg with less microbiologic failure ($P = .04$) ^a	NR
Britt, 2017 [16]	88	6 mg/kg: 709 8 mg/kg: 142 ≥10 mg/kg: 60	8 and ≥10 mg/kg with less microbiologic failure than 6 mg/kg ($P = .01$)	Improved 30-day survival in multivariate analysis with ≥10 mg/kg compared to 6 mg/kg or 8 mg/kg ($P = .004$)
Chuang, 2017 [15]	All	<7 mg/kg: 36 7–9 mg/kg: 51 ≥9 mg/kg: 25	No difference ($P = .9$) ^b	Improved 14-day survival in multivariate analysis with ≥9 mg/kg compared to <7 mg/kg ($P = .003$)
Ye, 2018 ^c [30]	All	<10 mg/kg: 77 ≥10 mg/kg: 18	NR	Trend towards improved 28-day survival with ≥10 mg/kg daptomycin ($P = .15$)
King, 2011 [31]	91	≤6 mg/kg: 24 >6 mg/kg: 22	No difference ($P = 1.0$)	No difference ($P = 1.0$)
Hayakawa, 2014 [32]	86	6 mg/kg: 35 >6 mg/kg: 21	NR	No difference ($P = 1.0$)
Shukla, 2016 [14]	All	<8 mg/kg: 27 ≥8 mg/kg: 35	No difference ($P = .5$)	No difference ($P = .5$)

Version of Breakpoints	Susceptible (S), µg/mL	Susceptible Dose-Dependent (SDD), µg/mL	Intermediate (I), µg/mL	Resistant (R), µg/mL
M100, 28th ed. (previous)	≤4	...	...	...
M100, 29th ed. (revised 2019)	≤1 ^a	2–4 ^b	...	≥8
M100, 30th ed. (revised 2020— <i>Enterococcus faecium</i>)	...	≤4 ^b	...	≥8
M100, 30th ed. (revised 2020—other species)	≤2 ^a	...	4	≥8

^aThe breakpoint for susceptible is based on a dosage regimen of 6 mg/kg/day in adults.

^bThe breakpoint for S-DD is based on a dosage regimen of 8–12 mg/kg/day in adults and is intended for serious infections due to *Enterococcus* species. Consultation with an infectious diseases specialist is recommended.

Résistance à la tigécycline

- ❖ Mutations dans une courte région de la protéine ribosomale S10 (**RpsJ**) (positions 52-60)

Sample		MIC	Alignment
			42 47 52 57 62 67 72
<i>T. thermophilus</i>			LPTRVRRFTVIRGPFKHKDSREHFELRTHNR
<i>E. coli</i>			LPTRKECFTVLISPHVNKDARDQYEIRTHLR
This study	WT	0.125	LPTERSLYTIIIRATHKYKDSREQFEMRTHKR
	3I	0.5	LPTERSLYTIIIRETRKYKDSREQFEMRTHKR * *
	2R	8	LPTERSLYTII-----KYKDSREQFEMRTHKR *****
	1R	8	LPTERSLYTII--RATHKHKDSREQFEMRTHKR * *
Cattoir et al.	AusTig/HMtig1+2	0.25	LPTERSLYTIIIRATHKYKYSREQFEMRTHKR *
	EF16	0.5	LPTERSLYTIIIRATHEYKDSREQFEMRTHKR *

- ❖ Hyper-expression des gènes **plasmidiques** *tet(M)* et *tet(L)* et modification de **Tet(L)**

Epidémiologie chez *S. aureus*

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Tigecycline	≤0.12/≤0.12 (99.2)	≤0.12/≤0.12 (99.5)	≤0.12/≤0.12 (99.3)	0.12/0.25 (99.4)
Daptomycin	2/2 (99.6)	2/2 (100.0)	1/2 (100.0)	2/4 (99.7)
Oritavancin ^d	0.03/0.12 (92.3)	0.015/0.06 (95.7)	0.03/0.12 (92.2)	≤0.008/0.06 (98.3)
Linezolid	1/2 (98.0)	1/2 (99.2)	1/2 (99.6)	1/2 (99.4)
Tedizolid ^e	0.12/0.25 (99.5)	0.12/0.25 (99.5)	0.12/0.25 (100.0)	0.12/0.25 (100.0)
Quinupristin-dalfopristin ^f	≤0.5/>2 (95.9)	1/>2 (83.5)	1/>2 (84.9)	1/2 (92.4)

≤0,7 %

Activité de l'éravacycline

Souches isolées entre 2013 et 2017 dans 37 pays

Organism ^a	No. of isolates	Cumulative % of isolates inhibited by the following eravacycline MIC ($\mu\text{g/ml}$) ^a :											
		≤ 0.001	0.002	0.004	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2
<i>S. aureus</i> ^b	2,588				0.4	3.8	33.4	84.5	94.8	97.6	99.4	100	
<i>S. aureus</i> , MR ^b	1,304				0.2	4.1	32.8	80.8	91.6	95.5	98.8	100	
<i>S. aureus</i> , MS ^b	1,284				0.5	3.5	34.0	88.3	98.0	99.8	100		
<i>S. epidermidis</i> ^b	1,012				1.4	11.5	28.2	45.7	63.4	84.6	97.1	99.8	100
<i>S. epidermidis</i> , MR ^{b,c}	480				1.9	10.8	30.8	43.8	66.7	90.4	97.9	99.8	100
<i>S. epidermidis</i> , MS ^{b,c}	255				2.0	24.3	47.8	59.6	75.7	96.9	99.6	99.6	100
<i>S. haemolyticus</i> ^b	731				1.2	13.5	34.6	45.6	64.8	89.9	96.0	98.8	100
<i>S. haemolyticus</i> , MR ^{b,c}	440				0.5	11.4	30.9	36.8	60.2	90.0	95.2	98.0	100
<i>S. haemolyticus</i> , MS ^{b,c}	134				5.2	35.8	76.9	85.8	94.8	97.8	99.3	100	
<i>E. faecalis</i>	1,586				0.2	2.6	28.9	94.5	99.4	99.7	100		
<i>E. faecalis</i> , VR ^d	59						23.7	89.8	98.3	100			
<i>E. faecalis</i> , VS	1,505				0.2	2.7	29.4	94.8	99.5	99.7	100		
<i>E. faecium</i>	1,221				0.6	4.3	60.2	95.0	97.7	99.1	99.8	100	
<i>E. faecium</i> , VR ^d	510				0.6	3.7	54.9	93.1	96.1	98.0	99.6	100	
<i>E. faecium</i> , VS	702				0.6	4.6	63.8	96.3	98.9	99.9	100		
<i>S. pneumoniae</i> ^e	596	0.8	2.0	14.8	73.0	97.8	100						
<i>S. agalactiae</i>	1,239				0.7	13.4	70.5	98.0	99.8	100			
<i>S. pyogenes</i>	1,192			0.2	3.6	47.8	96.0	100					
<i>S. anginosus</i> group ^f	346	5.2	5.5	8.7	19.9	46.5	86.4	99.1	100				

→ Excellente activité sur les cocci à Gram + (y compris sur les souches multi-résistantes)

Activité de l'omadacycline

Programme de surveillance **SENTRY 2016-2018** (73 centres, 19 pays, 49 000 souches cliniques)

Organism	MIC _{50/90} (mg/liter)	
	United States	Europe
<i>S. aureus</i>	0.12/0.25	0.12/0.25
Methicillin-susceptible <i>S. aureus</i>	0.12/0.25	0.12/0.25
Methicillin-resistant <i>S. aureus</i>	0.12/0.25	0.12/0.25
<i>S. lugdunensis</i>	0.06/0.12	0.06/0.12
<i>S. pneumoniae</i>	0.06/0.12	0.06/0.12
Penicillin resistant	0.06/0.12	0.06/0.12
Tetracycline resistant	0.06/0.12	0.06/0.12
Beta-hemolytic streptococci	0.12/0.25	0.12/0.25
<i>S. pyogenes</i>	0.06/0.12	0.06/0.12
<i>S. pyogenes</i> macrolide resistant	0.12/0.12	0.12/0.12
Viridans group streptococci	0.06/0.12	0.06/0.12
<i>S. anginosus</i> group	0.03/0.12	0.06/0.06
<i>Enterococcus faecalis</i>	0.12/0.25	0.12/0.25
<i>Enterococcus faecium</i>	0.06/0.12	0.06/0.12
Vancomycin nonsusceptible (MIC, ≥ 8 mg/liter)	0.12/0.12	0.06/0.12

→ Excellente activité sur les cocci à Gram + (y compris sur les souches multi-résistantes)

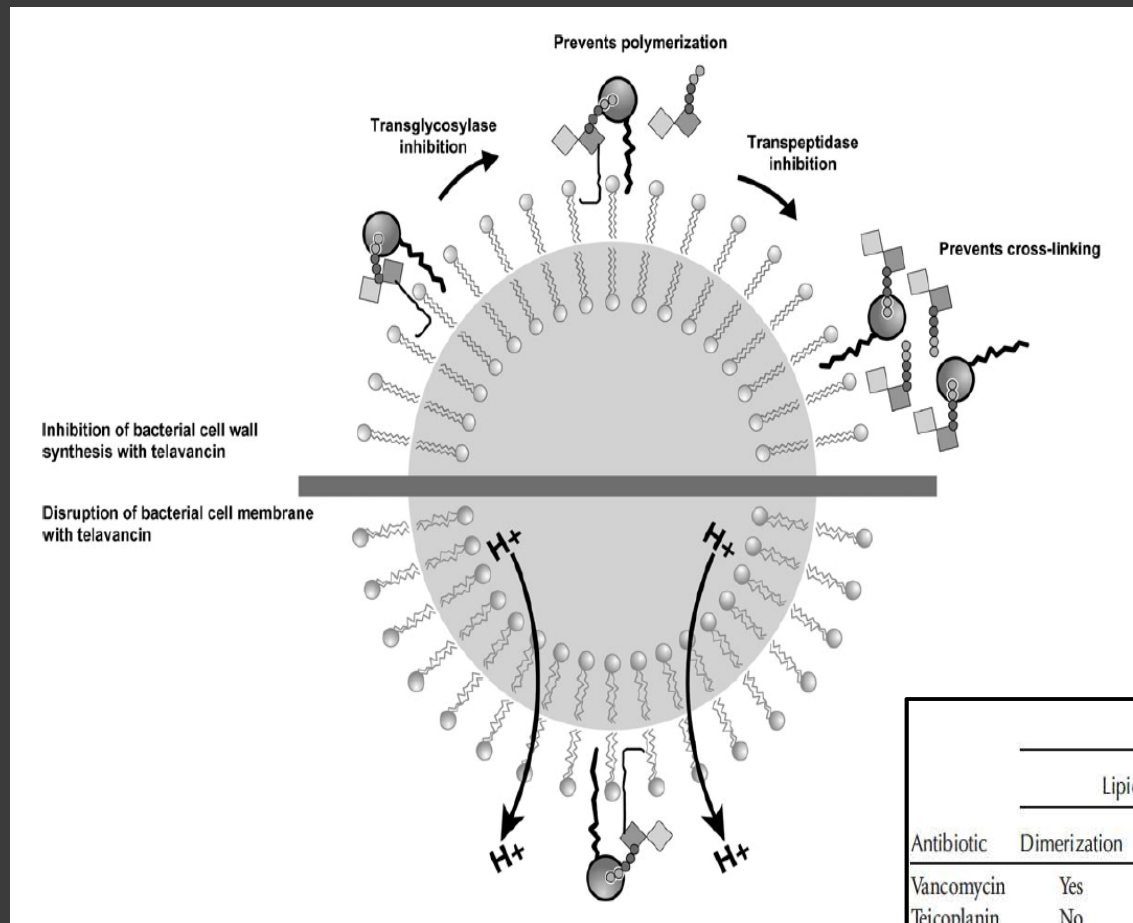
Résistance à l'éravacycline

Collection de 60 souches isolées en France → 4 souches R :

Isolate	MIC (mg/L) ^a					Detection of tet genes				RpsJ alterations ^b							
	ERC	TGC	DOX	MIN	TET	tet(M)	tet(L)	tet(O)	tet(S)	42+44+46+48+50+52+54+56+58+60+62+64+66+68+70+72	42+44+46+48+50+52+54+56+58+60+62+64+66+68+70+72	42+44+46+48+50+52+54+56+58+60+62+64+66+68+70+72	42+44+46+48+50+52+54+56+58+60+62+64+66+68+70+72	42+44+46+48+50+52+54+56+58+60+62+64+66+68+70+72	42+44+46+48+50+52+54+56+58+60+62+64+66+68+70+72	42+44+46+48+50+52+54+56+58+60+62+64+66+68+70+72	42+44+46+48+50+52+54+56+58+60+62+64+66+68+70+72
<i>E. faecium</i> DO						-	-	-	-	LPTERSLYTIIRATHKYKDSREQFEMRTHKRL							
<i>E. faecium</i> 17-477	1.5	8	16	16	>32	+	+	-	-	*****;*****							
<i>E. faecium</i> 18-481	0.19	1	16	32	>32	+	-	-	+	*****;*****							
<i>E. faecium</i> 18-626	0.19	1	8	32	>32	+	-	-	+	*****;*****							
<i>E. faecium</i> 18-785	0.25	2	>32	32	>32	+	+	-	-	*****;*****							
<i>E. faecium</i> 18-394.1	0.047	0.5	>32	32	>32	-	+	-	-	*****;*****							
<i>E. faecium</i> AusTig	0.023	0.5	1	0.5	0.5	+	-	-	-	*****;*****							
<i>E. faecium</i> HMTig1	0.023	0.5	2	0.5	0.5	-	-	-	-	*****;*****							
<i>E. faecium</i> EF16	0.047	0.5	16	16	>32	+	-	-	-	*****;*****							
<i>E. faecium</i> HMTig2	0.094	0.25 ^d	2	0.25	2	-	-	-	-	*****;*****							
<i>E. faecium</i> EF22	0.064	0.25 ^d	4	0.5	16	+	+	-	-	*****;*****							
<i>E. faecalis</i> V583						-	-	-	-	LPTERSLYTVIRATHKYKDSREQFEMRTHKRL							
<i>E. faecalis</i> 18-106	0.023	0.5	0.06	≤0.03	≤0.03	-	-	-	-	*****							

Selon EUCAST : sensible si ≤0,125 mg/L ; résistant si >0,125 mg/L)

Mode d'action des lipoglycopeptides



2 cibles moléculaires :

- Peptidoglycane
- Membrane cellulaire

Antibiotic	Mechanism			
	Lipid II-binding		Transpeptidation (enzymatic)	Membrane (permeabilization-depolarization)
	Dimerization	Membrane anchoring		
Vancomycin	Yes	No	No	No
Teicoplanin	No	Yes	No	No
Dalbavancin	No	Yes	No	No
Oritavancin	Yes	Yes	Yes	Yes
Telavancin	Yes	Yes	Unknown	Yes

Activité des lipoglycopeptides

Species	MIC ₅₀ /MIC ₉₀ (μg/mL), ECOFF, or breakpoint				
	Vancomycin	Teicoplanin	Telavancin	Oritavancin	Dalbavancin
<i>Staphylococcus aureus</i>	1/1 ^a	0.5/1 ^b	0.06/0.06 ^c	0.03/0.06 ^d	0.06/0.06 ^e
<i>S. aureus</i> (MRSA)	1/2 ^a	1/2 ^b	0.06/0.06 ^c	0.03/0.06 ^d	0.06/0.06 ^e
<i>S. aureus</i> (VISA)	4–8 ^f	2 ^g	0.12/0.25 ^c	–/1 ^h	0.5/– ^e
<i>Streptococcus pneumoniae</i>	0.25/0.5 ^a	0.12/0.12 ^b	0.008/0.015 ^c	0.002/0.004 ^a	0.015/0.03 ^a
<i>Streptococcus pyogenes</i>	0.5/1 ^a	0.5 ^g	0.03/0.03 ^c	0.03/0.25 ^d	≤0.03/≤0.03 ^e
<i>Streptococcus agalactiae</i>	0.25/0.5 ^a	0.12/0.12 ^b	0.03/0.06 ^c	0.03/0.12 ^d	≤0.03/0.12 ^e
<i>Streptococcus anginosus</i>		0.12/0.12 ^b		≤0.008/0.015 ^d	≤0.03/≤0.03 ^e
<i>Enterococcus faecium</i> VSE	0.5/1 ^a	0.25/1 ^b	≤0.015/0.03 ^c	≤0.008/0.015 ^d	0.06/0.12 ^e
<i>E. faecium</i> VRE	512/512 ^a	64/>64 ⁱ	1/>1 ^c	0.008/0.06 ^d	>4/>4 ^e

Activité x 8-32

Epidémiologie chez *S. aureus*

Programme SENTRY (427 centres, 45 pays, 1997-2016)

Antimicrobial Agent	No. of Isolates	MIC ₅₀	MIC ₉₀	MIC Range	CLSI ^a		
					%S	%I	%R
MSSA	114 300						
Ceftaroline	58 938	0.25	0.25	<0.06-1	100.0	0.0	0.0
Dalbavancin	92 584	0.06	0.06	≤0.03->0.25	>99.9		
Daptomycin	94 022	0.25	0.5	≤0.12-4	>99.9		
Delafloxacin	18 033	≤0.004	0.015	≤0.004->1	98.1	0.9	0.9
Levofloxacin	103 405	≤0.5	≤0.5	≤0.5->4	92.3	0.5	7.1
Linezolid	110 519	1	2	≤0.12->8	>99.9		<0.1
Oritavancin	50 013	0.03	0.06	≤0.008-0.5	99.7		
Quinupristin-dalfopristin	68 250	≤0.5	≤0.5	≤0.5->2	99.9	0.1	<0.1
Tedizolid	22 987	0.12	0.12	≤0.008-0.5	100.0	0.0	0.0
Teicoplanin	114 285	<2	<2	<2->8	>99.9		
Telavancin	46 041	0.03	0.06	≤0.015-0.25	>99.9		
Tigecycline	93 850	≤0.12	0.25	≤0.12-1	>99.9		
Vancomycin	114 297	1	1	≤0.12-4	>99.9	<0.1	0.0
MRSA	77 146						
Ceftaroline	40 731	1	1	0.015->8	91.6	8.2	0.2
Dalbavancin	65 302	0.06	0.06	≤0.03->0.25	>99.9		
Daptomycin	66 380	0.25	0.5	≤0.12-4	99.9		
Delafloxacin	10 243	0.12	1	≤0.004->1	74.3	12.3	13.4
Levofloxacin	72 075	>4	>4	≤0.5->4	23.4	1.7	75.0
Linezolid	75 780	1	2	≤0.25->8	99.9		0.1
Oritavancin	35 262	0.03	0.06	≤0.008-0.5	99.6		
Quinupristin-dalfopristin	46 141	≤0.5	1	≤0.5->2	99.5	0.3	0.2
Tedizolid	13 828	0.12	0.12	0.015->1	>99.9	0.0	<0.1
Teicoplanin	77 120	<2	<2	<2->16	>99.9	<0.1	<0.1
Telavancin	31 000	0.03	0.06	≤0.015-0.25	>99.9		
Tigecycline	65 977	≤0.12	0.25	≤0.12-4	99.8		
Vancomycin	77 145	1	1	≤0.12-4	>99.9	<0.1	0.0

≤0,1 %

Epidémiologie chez *Enterococcus*

Programme **SENTRY** (298 centres, 1997-2016)

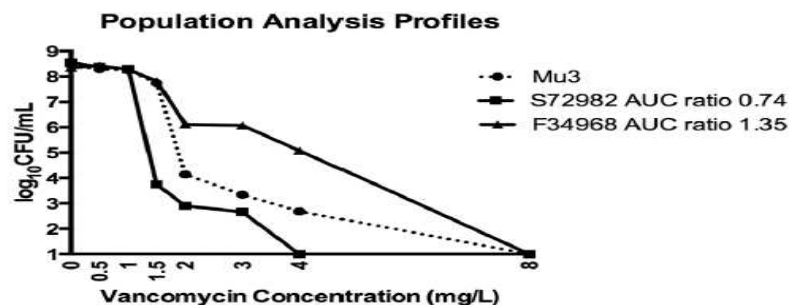
Activité sur **7 615 souches d'ERV** (*vanA* ou *vanB*) :

Antimicrobial Agent	MIC _{50/90} (% of Tested Isolates Susceptible), mg/L ^a			
	NA (n = 5450)	EUR (n = 1374)	LATAM (n = 470)	APAC (n = 321)
Ampicillin ^b	>8/>8 (10.5)	>8/>8 (10.0)	>8/>8 (22.8)	>8/>8 (3.4)
Tetracycline ^c	>8/>8 (35.6)	≤4/>8 (57.5)	≤4/>8 (64.7)	≤4/>8 (62.3)
Tigecycline	≤0.12/≤0.12 (99.2)	≤0.12/≤0.12 (99.5)	≤0.12/≤0.12 (99.3)	0.12/0.25 (99.4)
Daptomycin	2/2 (99.6)	2/2 (100.0)	1/2 (100.0)	2/4 (99.7)
Oritavancin ^d	0.03/0.12 (92.3)	0.015/0.06 (95.7)	0.03/0.12 (92.2)	≤0.008/0.06 (98.3)
Linezolid	1/2 (98.0)	1/2 (99.2)	1/2 (99.6)	1/2 (99.4)
Tedizolid ^e	0.12/0.25 (99.5)	0.12/0.25 (99.5)	0.12/0.25 (100.0)	0.12/0.25 (100.0)
Quinupristin-dalfopristin ^f	≤0.5/>2 (95.9)	1/>2 (83.5)	1/>2 (84.9)	1/2 (92.4)

1,7-7,8 %
(*vanA*)

Résistance à la dalbavancine

Antimicrobial	S72982 (blood)	F34968 (urine)	S7-D2(<i>in vitro</i>)
	MIC (µg/mL)	MIC (µg/mL)	MIC (µg/mL)
Dalbavancin	0.015	0.5	1
Daptomycin	0.25	1	0.5
Levofloxacin	>4	>4	>4
Moxifloxacin	2	2	2
Nafcillin	16	128	16
Telavancin	0.064	0.25	0.38
Trimethoprim/sulfamethoxazole	>2/38	>2/38	>2/38
Vancomycin	1	4	4



✓ **Sélection *in vivo*** d'une souche urinaire de SARM après TTT séquentiel par VAN et DAL d'une bactériémie sur KT

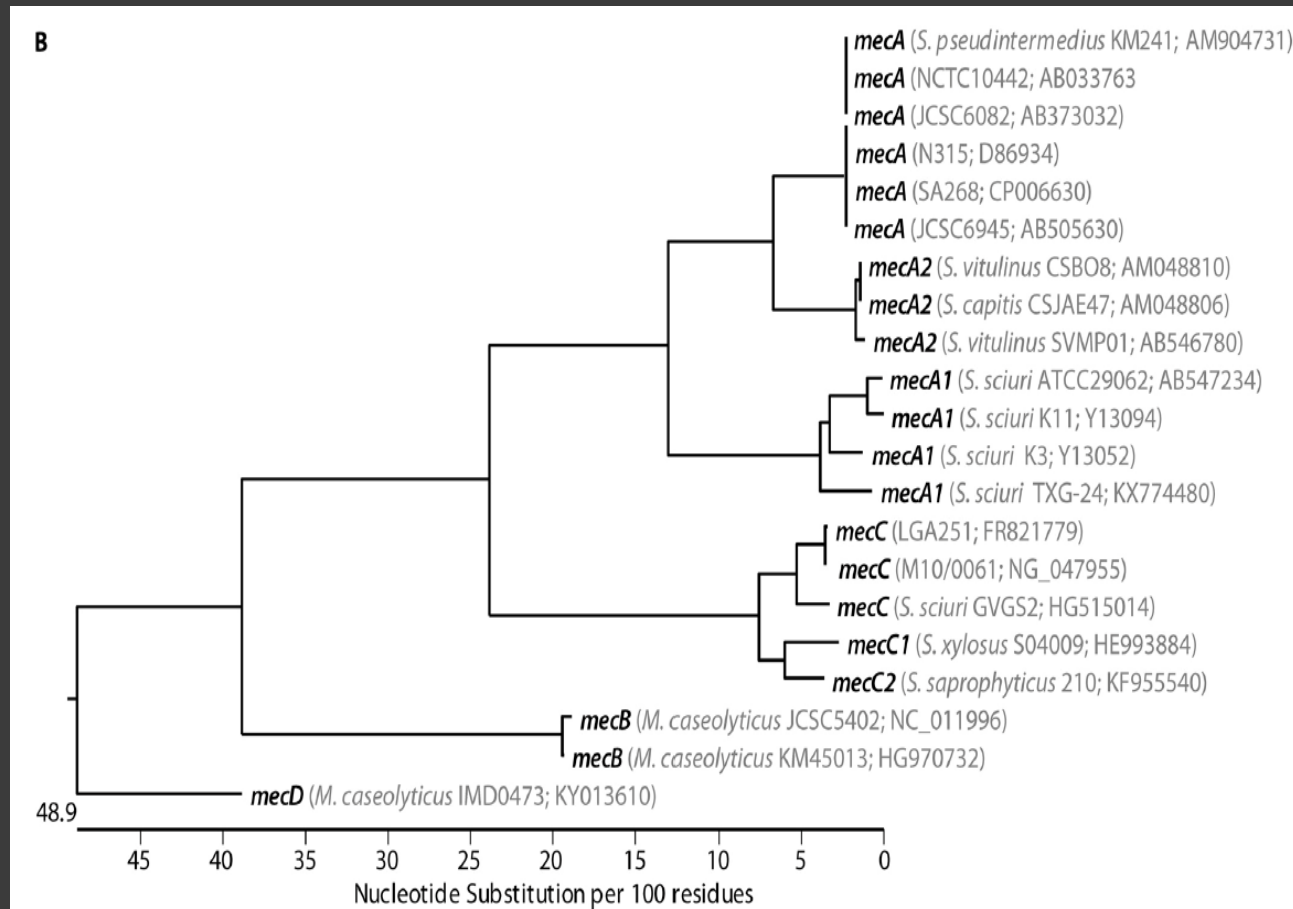
✓ **Sélection *in vitro*** d'un mutant à partir de la souche de bactériémie

Chromosomal base position	S72982 sequence	F34968 sequence	S7-D2 sequence	Gene ID	Gene name	Gene function	Mutation type	Amino acid change
25206	A	T	A	CH51_00100	OmpR	DNA-binding	NA	p.Glu85Asp
707079	C	T	C	Intergenic	NA	NA	NA	A
837096	A	T	A	CH51_00100	OmpR	DNA-binding	NA	p.Asn35Ile
1025246	A	T	A	CH51_00100	OmpR	DNA-binding	Missense variant	p.Asn71Tyr
2039377	A	T	A	CH51_00100	OmpR	DNA-binding	NA	NA
2108957	A	T	A	CH51_00100	OmpR	DNA-binding	Missense variant	p.Pro126Leu
2109093	A	T	A	CH51_10280	yvqF	Membrane protein	In-frame deletion	p.Ile78del
2214235	A	T	A	Intergenic	NA	NA	NA	NA

Résistance complexe avec multiples mutations chromosomiques

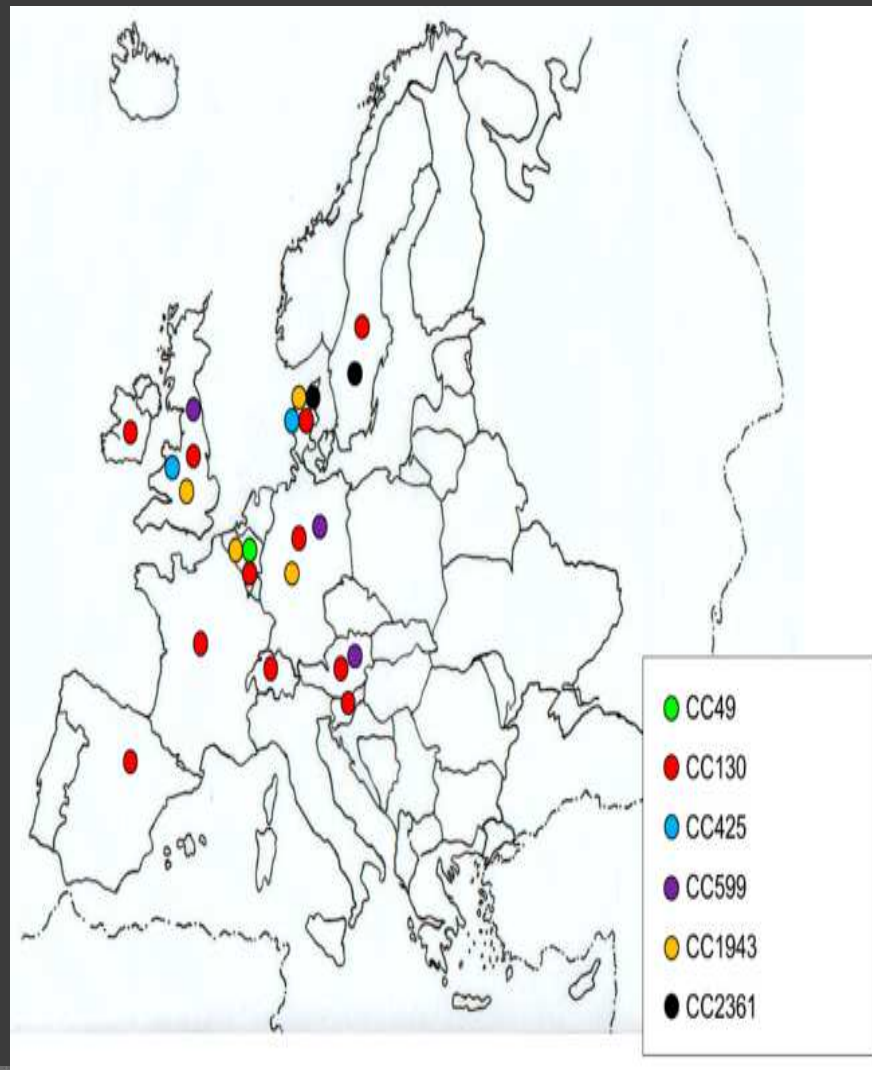
Nouveau variant *mecC+*

Décrit en 2011 dans des souches animales de SARM (*mecA*-)



} 70 % id. *mecA*

Souches humaines de SARM *mecC*⁺

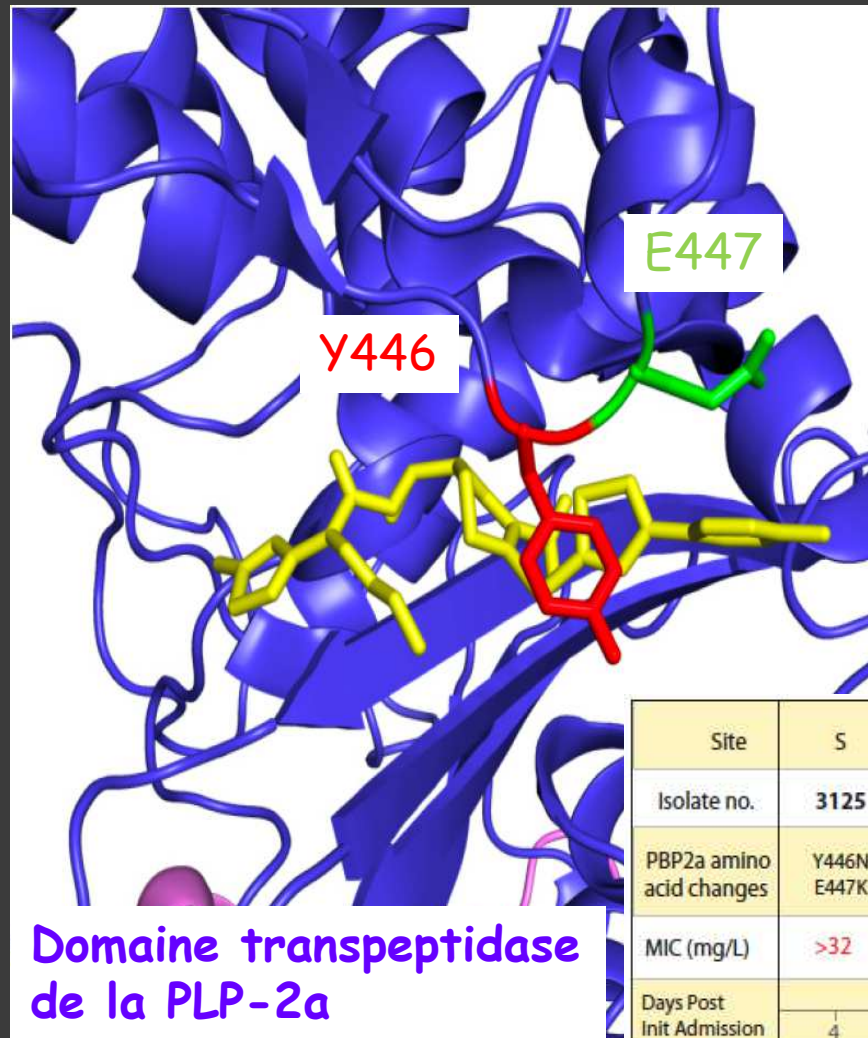


-Souches **rarement isolées chez l'homme** :

Type of Sample/Infection	Number of Isolates ²
Screen swab ¹	54
Skin lesion/dermatitis/impetigo wound/post-operative wound/skin and soft tissue infections	158
Blood	16
Urine	7
Nosocomial pneumonia/sputum/ Tracheal aspirate	7
Nose	5
Eye/ear	3
Fluid of heel/joint fluid	3
Mouth/Nose	2
Ear	1
Finger	1
Fluid	1
Hand	1
Percutaneous endoscopic gastrostomy site	1
Retrosternal abscess	1
Toe	1
Unknown	34

-Souches principalement animales
-SARM généralement multi-S

Résistance à la ceftaroline



6 souches isogéniques de SARM isolées chez un patient atteint de mucoviscidose :

Strain	Collection date (day/mo/yr)	Source	Resistance (M)
			Ceftaroline
TMHS-3125	1/21/2013	Sputum	R (>32)
TMHS-3957	3/21/2013	Sputum	S (1)
TMHS-4147	3/28/2013	Sputum	S (1)
TMHS-4519	5/9/2013	Sputum	I (1.5)
TMHS-5006	6/19/2013	Blood	R (>32)
TMHS-5007	6/20/2013	Sputum	R (>32)

Site	S	S	S	S	B	S	Mutation(s) ^a
Isolate no.	3125	3957	4147	4519	5006	5007	Asn104Lys Val117Ile Met122Ile Asp139Trp Asn146Lys Glu150Lys Glu170Lys Val117Ile Asn204Lys Asn206Lys Asp208Glu Ser225Arg Ala228Val Thr235Ile Asn236Lys Glu239Lys Gly246Glu Lys281Arg His351Asn, H351Gln*
PBP2a amino acid changes	Y446N E447K			Y446N	Y446N E447K	E239K Y446N E447K	
MIC (mg/L)	>32	1	1	1.5	>32	>32	Leu357Ile* Tyr446Asn* Glu447Lys* Ile563Thr* Ser649Ala*
Days Post Init Admission	4	63	70	112	153	154	

^a*, in the penicillin-binding domain.

Epidémiologie chez *S. aureus*

Programme **SENTRY** (427 centres, 45 pays, 1997-2016)

Antimicrobial Agent	No. of Isolates	MIC ₅₀	MIC ₉₀	MIC Range	CLSI ^a		
					%S	%I	%R
MSSA							
Ceftaroline	58 938	0.25	0.25	≤0.06–1	100.0	0.0	0.0
Daibavancin	92 584	0.06	0.06	≤0.03→0.25	>99.9		
Daptomycin	94 022	0.25	0.5	≤0.12–4	>99.9		
Delafloxacin	18 033	≤0.004	0.015	≤0.004→1	98.1	0.9	0.9
Levofloxacin	103 405	≤0.5	≤0.5	≤0.5→4	92.3	0.5	7.1
Linezolid	110 519	1	2	≤0.12→8	>99.9		<0.1
Oritavancin	50 013	0.03	0.06	≤0.008–0.5	99.7		
Quinupristin-dalfopristin	68 250	≤0.5	≤0.5	≤0.5→2	99.9	0.1	<0.1
Tedizolid	22 987	0.12	0.12	≤0.008–0.5	100.0	0.0	0.0
Teicoplanin	114 285	≤2	≤2	≤2→8	>99.9		
Telavancin	46 041	0.03	0.06	≤0.015–0.25	>99.9		
Tigecycline	93 850	≤0.12	0.25	≤0.12–1	>99.9		
Vancomycin	114 297	1	1	≤0.12–4	>99.9	<0.1	0.0
MRSA							
Ceftaroline	40 731	1	1	0.015→8	91.6	8.2	0.2
Daibavancin	65 302	0.06	0.06	≤0.03→0.25	>99.9		
Daptomycin	66 380	0.25	0.5	≤0.12–4	99.9		
Delafloxacin	10 243	0.12	1	≤0.004→1	74.3	12.3	13.4
Levofloxacin	72 075	>4	>4	≤0.5→4	23.4	1.7	75.0
Linezolid	75 780	1	2	≤0.25→8	99.9		0.1
Oritavancin	35 262	0.03	0.06	≤0.008–0.5	99.6		
Quinupristin-dalfopristin	46 141	≤0.5	1	≤0.5→2	99.5	0.3	0.2
Tedizolid	13 828	0.12	0.12	0.015→1	>99.9	0.0	<0.1
Teicoplanin	77 130	≤2	≤2	≤2→16	>99.9	<0.1	<0.1
Telavancin	31 000	0.03	0.06	≤0.015–0.25	>99.9		
Tigecycline	65 977	≤0.12	0.25	≤0.12–4	99.8		
Vancomycin	77 145	1	1	≤0.12–4	>99.9	<0.1	0.0

0 %

8,4 %

Activité de la délafloxacine

Table 1 In vitro activity of delafloxacin against selected clinical isolates

Pathogen	Total no of isolates	MIC ₉₀ (µg/mL; range across studies) [% susceptible; CLSI/EUCAST]		
		Delafloxacin	Levofloxacin	Vancomycin
Gram-positive isolates				
<i>Enterococcus faecalis</i> [15]	450	1	> 4 [70.7/70.7]	2 [97.8/97.8]
<i>Staphylococcus aureus</i> [15, 17]	2035	0.25	> 4 [64.4/64.4]	1 [100/100]
MRSA [15, 17]	867	0.25–0.5	> 4 [30/30]	1 [100/100]
MRSA LEV-R [17]	195	0.25	NR	NR
MRSA LEV-S [17]	101	0.008	NR	NR
MSSA [15, 17]	1172	0.008–0.03	2 [89.8/89.8]	1 [100/100]
MSSA LEV-R [17]	39	0.25	NR	NR
MSSA LEV-S [17]	358	0.008	NR	NR
<i>S. aureus</i> LEV-R [17]	232	0.25	NR	NR
<i>S. aureus</i> LEV-S [17]	455	0.008	NR	NR
MR CoNS [15]	125	0.5	> 4 [38.4/38.4]	2 [100/100]
MS CoNS [15]	75	0.06	4 [88/88]	2 [100/100]

NB : Paramètres PK :

- $C_{\max}$ moyenne = 9 mg/L
- $AUC_{0-\infty}$ = 21 mg.h/L

Activité x 16-64

Résistance à la délafloxacine

Bacterial strains					MIC (mg/L)			
	original designation	plasmid	mutations in QRDR	Origin	DFX	CIP	LVX	MXF
MSSA	ISP794	—	none	MGH	0.002	0.125	0.125	0.03
	MT5224c4	—	gyrA (Ser84Leu)	MGH	0.016	0.125	0.125	0.125
	SS1	—	grlA (Ser80Phe)	MGH	0.016	1	0.5	0.25
	EN1252A	—	gyrA (Ser84Leu) grlA (Ser80Phe)	MGH	0.5	32	8	4
MRSA	2926		none	HMS	0.03	1	0.25	0.125
	14990		gyrA (Ser84Val) grlA (Ser80Phe)	HMS	0.25	128	16	8
	14490		gyrA (Ser84Leu, Glu409Lys) grlA (Ser80Phe)	HMS	1	128	32	8
	700699		gyrA (Ser84Leu) grlA (Ser80Tyr, Glu84Gly)	ATCC	1	>256	64	8

Strain	Mutant no.	DFX MIC (mg/L) ^a	Mutations in QRDR			
			gyrA	gyrB	grlA	grlB
2926	parent	0.03	—	—	—	—
14990	parent	0.5	Ser84Val	—	Ser80Phe	—
	990.1	4	Ser84Val	—	Ser80Phe	—
	990.2	4	Ser84Val	—	Ser80Phe	—
	990.3	32	Ser84Val	Asp437Asn	Ser80Phe	—
	990.4	16	Ser84Val	Arg458Leu	Ser80Phe	—
700699	parent	1	Ser84Leu, Glu409Lys	—	Ser80Phe	—
14490	parent	1	Ser84Leu	—	Ser80Tyr, Glu84Gly	—
	490.1	8	Ser84Leu, Ser85Pro	—	Ser80Tyr, Glu84Gly	—
	490.2	32	Ser84Leu, Glu88Lys	—	Ser80Tyr, Glu84Gly	—
	490.3	64	Ser84Leu	Asp437Asn	Ser80Tyr, Glu84Gly	—
	490.4	32	Ser84Leu	Asp437Ala	Ser80Tyr, Glu84Gly	—

Fréquence de sélection *in vitro* de mutants R = 10^{-9} – 10^{-11}

Anti-Gram+ en développement

Drug Name	Phase	Company	Drug Class	Spectrum Against Gram-Positive Bacteria	Potential Indication
Iclaprim	NDA filed	Roche	dihydrofolate reductase inhibitor	MRSA, vancomycin-intermediate and vancomycin-resistant, and macrolide-, quinolone- and trimethoprim-resistant strains	ABSSSI
Cethromycin	NDA filed	Abbott Laboratories (acquired by Advanced Life Sciences Inc.)	ketolide	telithromycin-resistant <i>S. pneumoniae</i>	CABP
Solithromycin	Phase III	Cempra Pharmaceuticals	fluoroketolide	MRSA and macrolide-resistant <i>M. pneumoniae</i>	CABP
Contezolid (MRX-1)	Phase III	MicuRx Pharmaceuticals, Inc.	oxazolidinone	MRSA, penicillin-resistant and penicillin-intermediate <i>S. pneumoniae</i> , and VRE	ABSSSI
Contezolid Acefisamil (MRX-4)	Phase III	MicuRx Pharmaceuticals, Inc.	oxazolidinone	MRSA, VRE	MRSA & VRE infections in hospital setting
Lascufloxacin	NDA filed	Kyorin Pharmaceutical Co., Ltd.	fluoroquinolone	MRSA, <i>S. epidermidis</i> , <i>E. faecalis</i> , <i>S. pyogenes</i> , <i>S. agalactiae</i> , and penicillin-resistant <i>S. pneumoniae</i>	CABP; URTI
Nemonoxacin (Taigexyn) ¹	Phase III	TaiGen Biotechnology Co., Ltd.	non-fluorinated quinolone	MRSA, multidrug-resistant <i>S. pneumoniae</i> and vancomycin-resistant pathogens	CABP; ABSSSI
Levonadifloxacin (WCK771)	Phase III	Wockhardt Ltd.	fluoroquinolone	MRSA and staphylococci resistant to levofloxacin and moxifloxacin	ABSSSI; HAP
Zabofloxacin (DW-224a) ²	Phase III	Dong Wha Pharmaceutical Industry Ltd.	fluoroquinolone	MRSA, methicillin-resistant coagulase-negative staphylococci, <i>S. pyogenes</i> , <i>E. faecalis</i> and <i>S. pneumoniae</i>	CABP
Brilacidin (PMX30063)	Phase III	Innovation Pharmaceuticals Inc.	defensin mimetic	<i>S. aureus</i> and <i>S. epidermidis</i>	ABSSSI

Conclusion



- Faible prévalence de la résistance aux nouveaux ATB (sauf pour oxazolidinones)
- Mécanismes moins variés par rapport aux BGN
- 10 molécules en développement clinique de phase III



- Emergence de la résistance aux oxazolidinones (ERL)
- Résistance décrite *in vivo* pour tous les ATB
- Absence de consensus sur les concentrations critiques pour la daptomycine et entérocoques