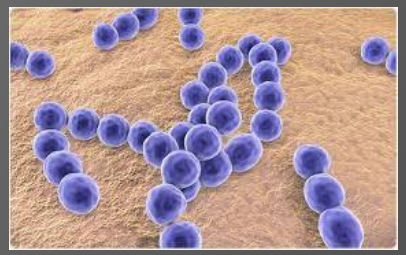
CENTRES DE RÉFÉRENCE POUR LES INFECTIONS OSTÉO-ARTICULAIRES COMPLEXES DU GRAND OUEST
CRIOGO

11ème réunion bibliographique du CRIOGO
Mardi 11 octobre 2022 - 18h45-19h15



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

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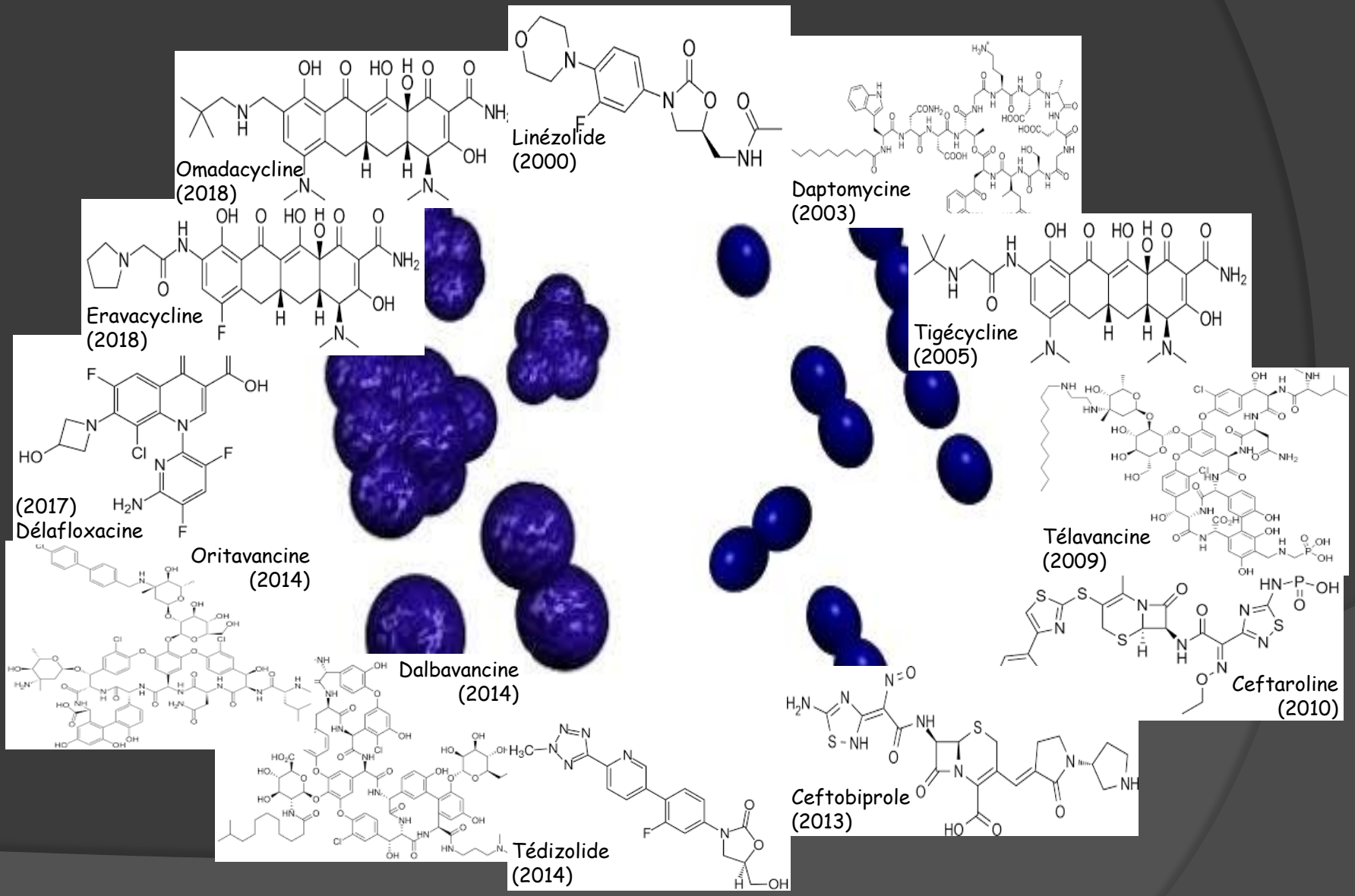
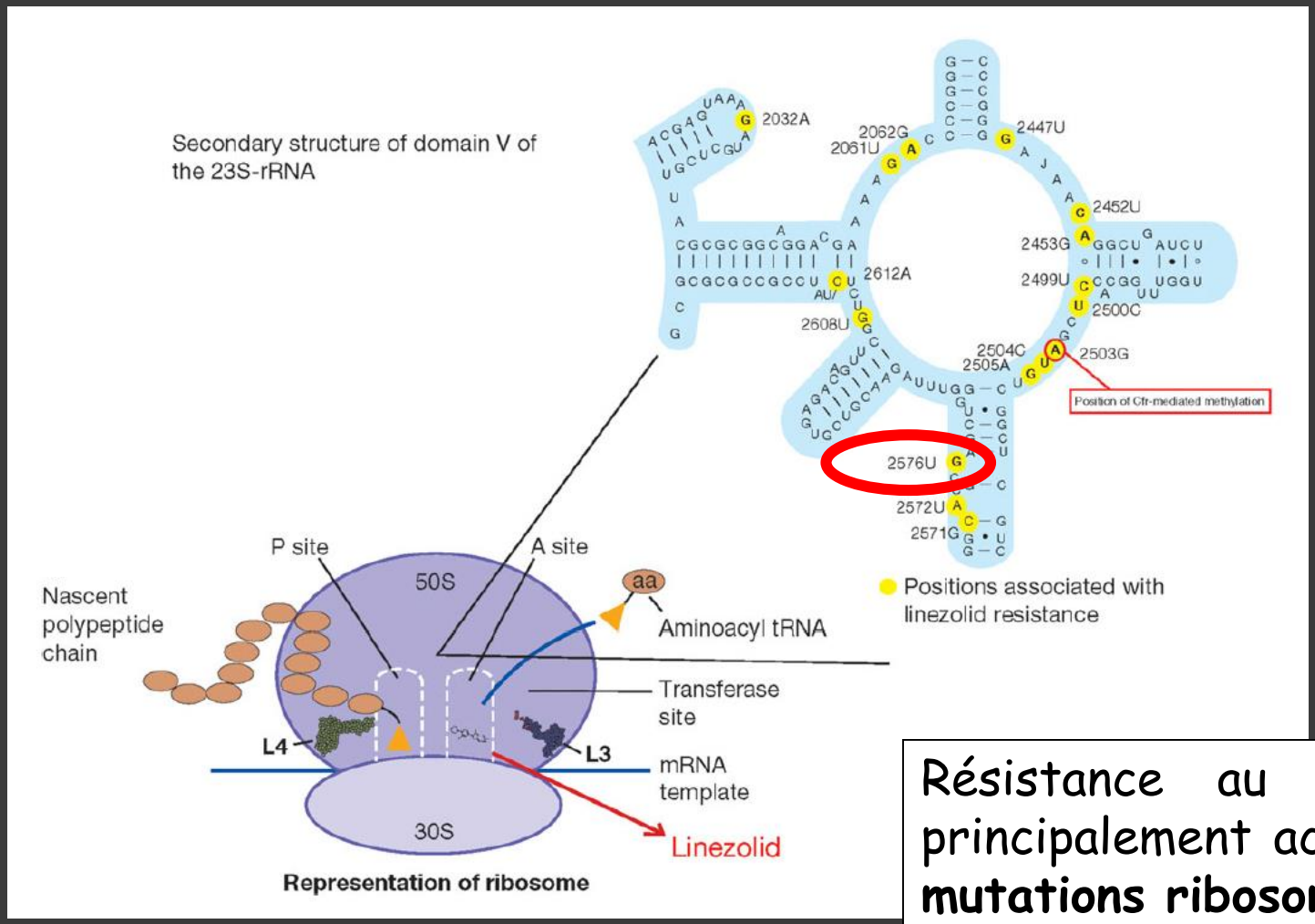
Quels antibiotiques ?



Résistance aux oxazolidinones



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

Munita et al., CIDS 2015

Résistance plasmidique : *cfr*

Gène codant pour une **méthyltransférase ARNr 23S** (A2503)

Oxazolidinones
(pas TZD)

Phénicolés

Streptogramines A
Pleuromutilines
Lincosamides

Antibiotic	MIC (µg/ml)[a] *E. faecalis* 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)

Diaz et al., AAC 2012; Schwarz et al., CMR 2020

Résistance plasmidique : *optrA*

Gène pour une **protéine de protection ribosomale**

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

➔ Phénotype PhO

Wang et al., JAC 2015

Résistance plasmidique : *poxtA*

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

	MIC (mg/L)				
	S. aureus[a]		*E. faecalis*[b]		
Antibiotic	RN4220 (pMU-*poxtA*)	RN4220 (pMU-E)	JH2-2 (pMU-*poxtA*)	JH2-2 (pMU-E)	
Linezolid	2	1	4	1	x2-4
Tedizolid	0.5	0.25	0.5	0.25	x2
Chloramphenicol	8	4	8	4	x2
Florfenicol	16	2	16	2	x8
Tigecycline	0.25	0.25	0.25	0.25	
Tetracycline	0.25	0.125	0.25	0.125	x2
Doxycycline	0.25	0.125	0.125	≤0.06	

➔ Phénotype PhOT

Antonelli et al., JAC 2018

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	CLSI[a] %I	CLSI[a] %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	92.2	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		
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Vancomycin	114 297	1	1	≤0.12–4	>99.9	<0.1	0.0
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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
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Vancomycin	77 145	1	1	≤0.12–4	>99.9	<0.1	0.0

≤0,1 %

Diekema et al., OFID 2019

Epidémiologie chez *Enterococcus*

Programme SENTRY (298 centres, 1997-2016)

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

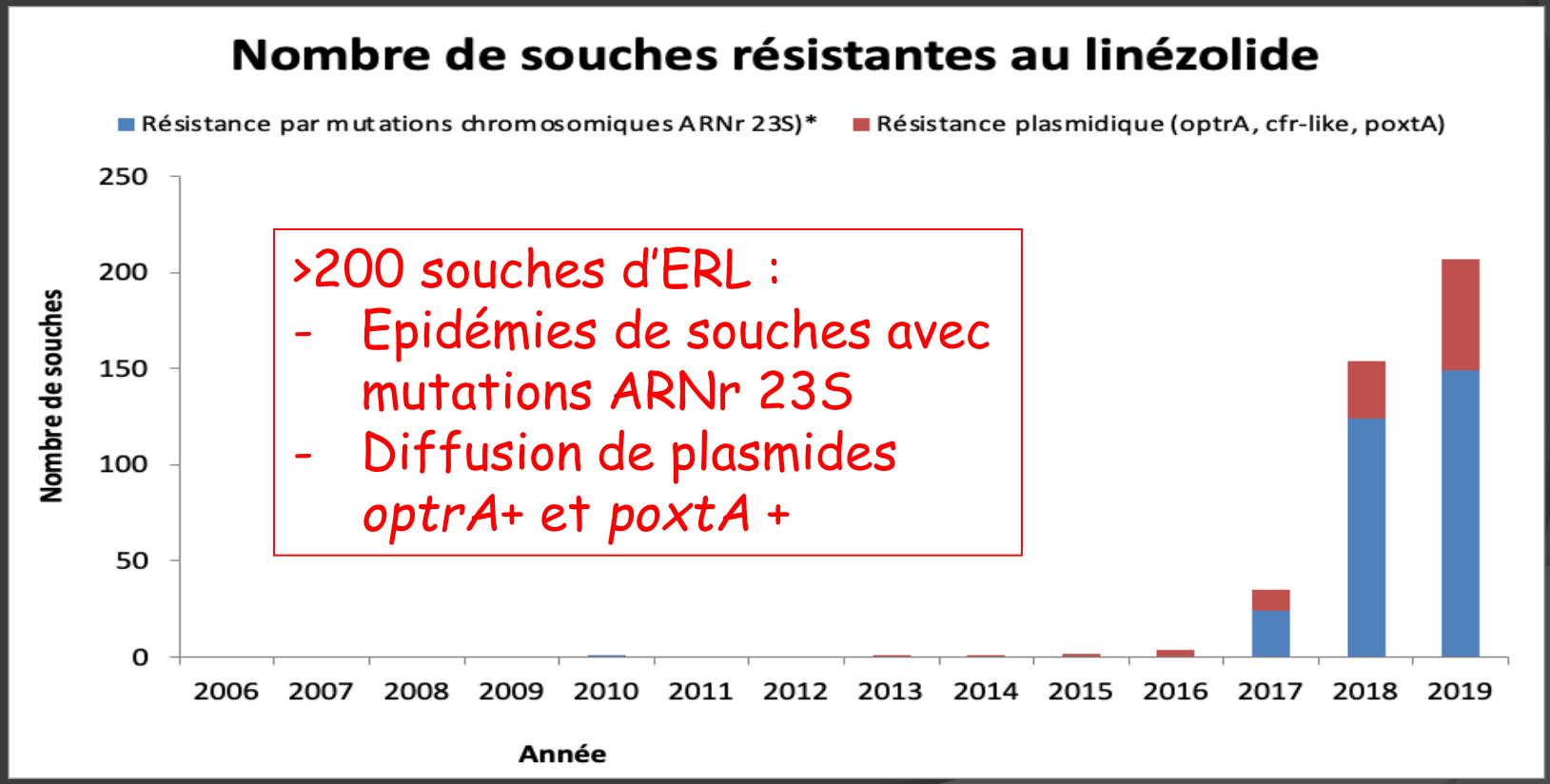
Antimicrobial Agent	$MIC_{50/90}$ (% of Tested Isolates Susceptible), mg/L[a] NA (n = 5450)	EUR (n = 1374)	LATAM (n = 470)	APAC (n = 321)
Ampicillin[b]	>8/>8 (10.5)	>8/>8 (10.0)	>8/>8 (22.8)	>8/>8 (3.4)
Tetracycline[c]	>8/>8 (35.6)	≤4/>8 (57.5)	≤4/>8 (64.7)	≤4/>8 (62.3)
Tigecycline	≤0.12/≤0.12 (99.2)	≤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 %

Pfaller et al., OFID 2019

Emergence des ERL en France

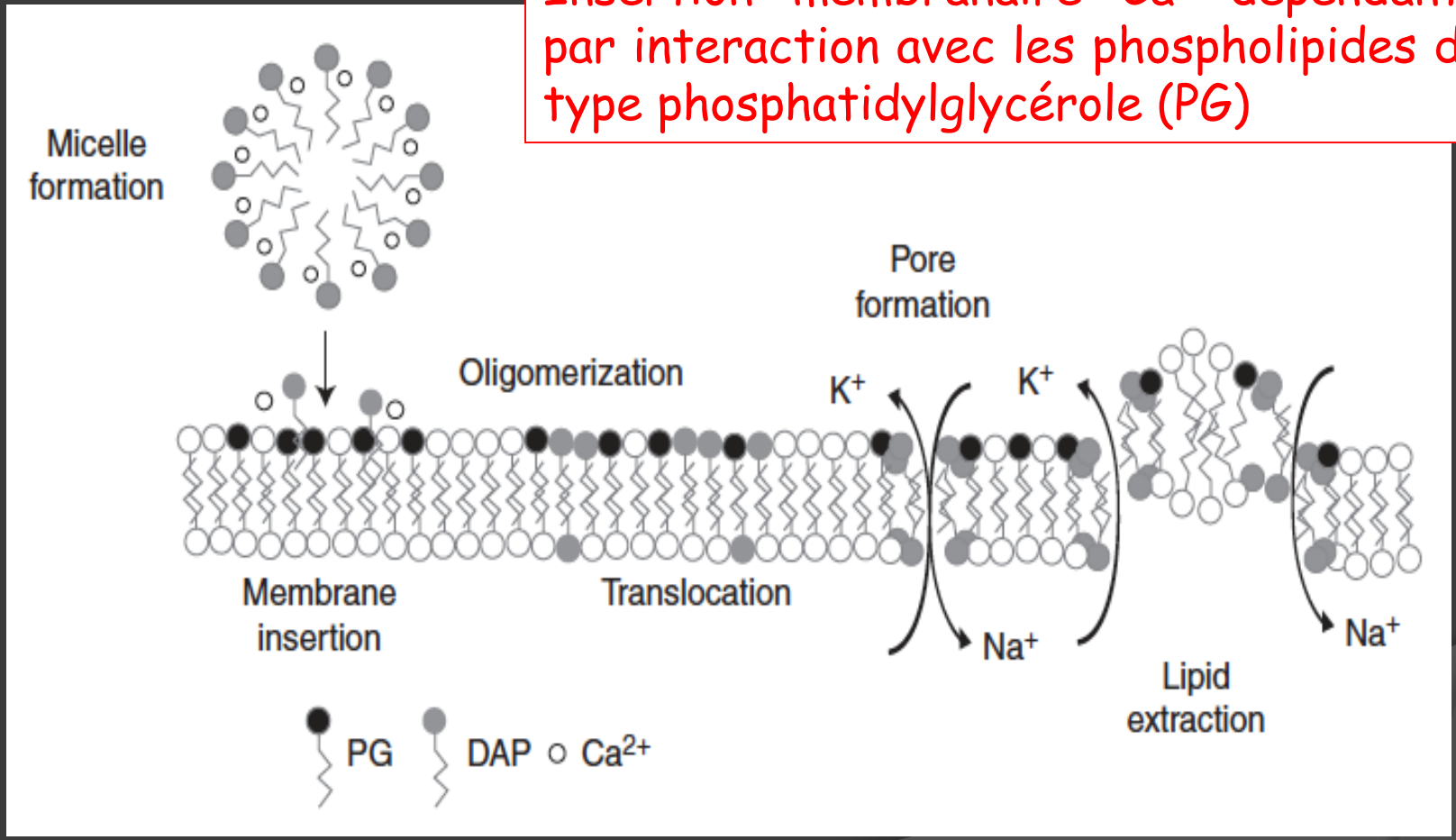
Augmentation de la prévalence des Entérocoques Résistants au Linézolide (ERL), notamment depuis 2017



Sassi et al., JAC 2019 ; Rapport CNR Enc 2020

Mode d'action de la daptomycine

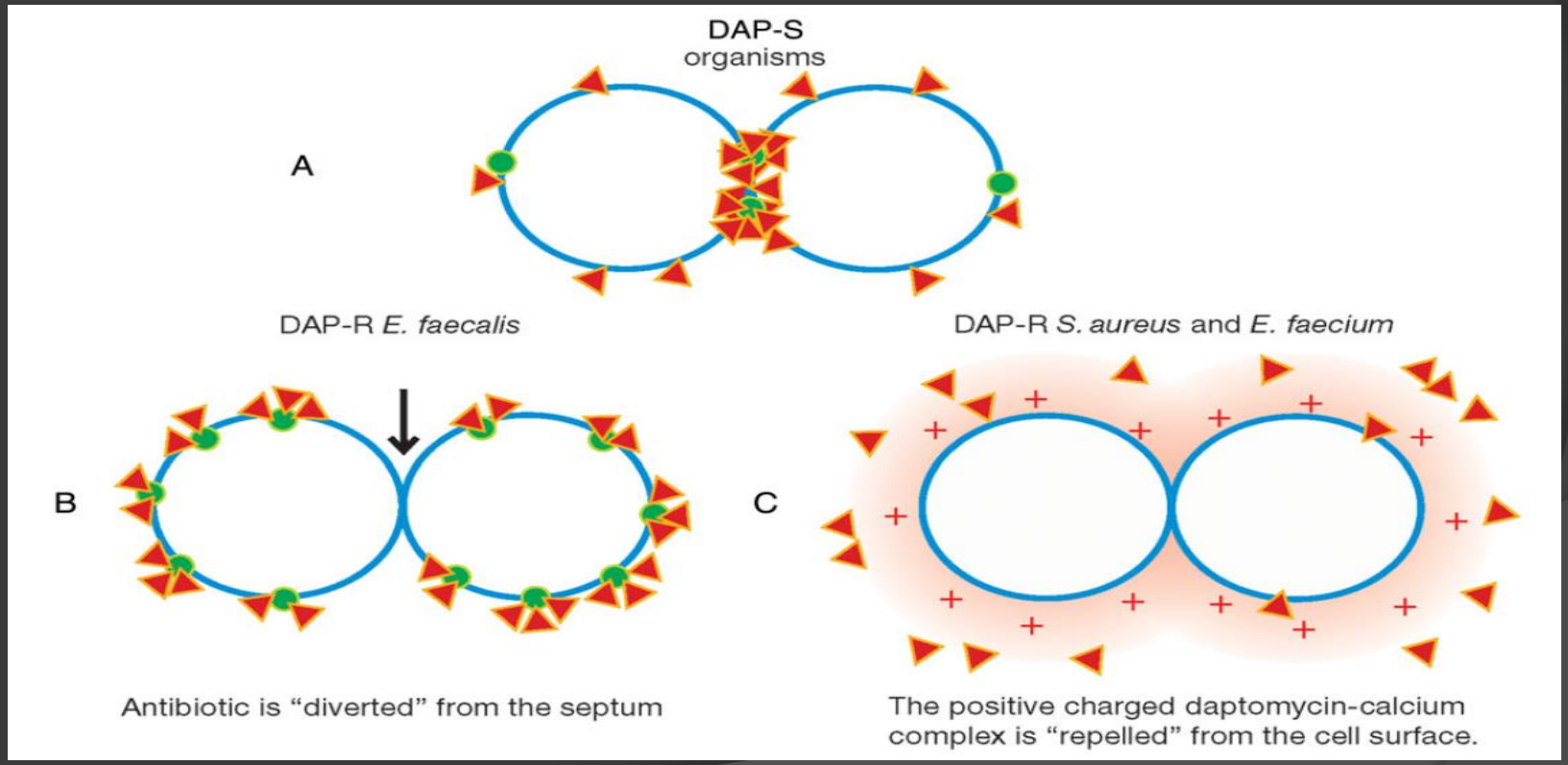
Insertion membranaire Ca^{2+}-dépendante par interaction avec les phospholipides de type phosphatidylglycérole (PG)



Miller et al., CHSPM 2016

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*, *yycFG*, *liaFSR*) ou le métabolisme des phospholipides (ex. *pgsA*, *mprF*, *gdpD*, *cls*)



Tran et al., ANYAS 2015 ; Munita et al., CID 2015

Réversion de la résistance

Strain	MIC (mg/L)[a] DAP	VAN	TEC	TLV	Changes in 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)	–	IS*66* insertion[b,c]	Gly92Asp	–
Rev32	0.06 (512)	4	1	0.06 (32)	–	–	Gly92Asp	IS*30* insertion[b]
Rev64	1 (64)	4	1	0.12 (16)	Asn13Ser	IS*66* insertion[b,c]	Gly92Asp	–
Rev128	0.12 (1024)	4	1	0.12 (16)	Asn13Ser	IS*982* insertion[b]	Gly92Asp	–

Résistance par étapes et croisée avec TLV

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

Sinel et al., JAC 2016

Epidémiologie chez *S. aureus*

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

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Diekema et al., OFID 2019

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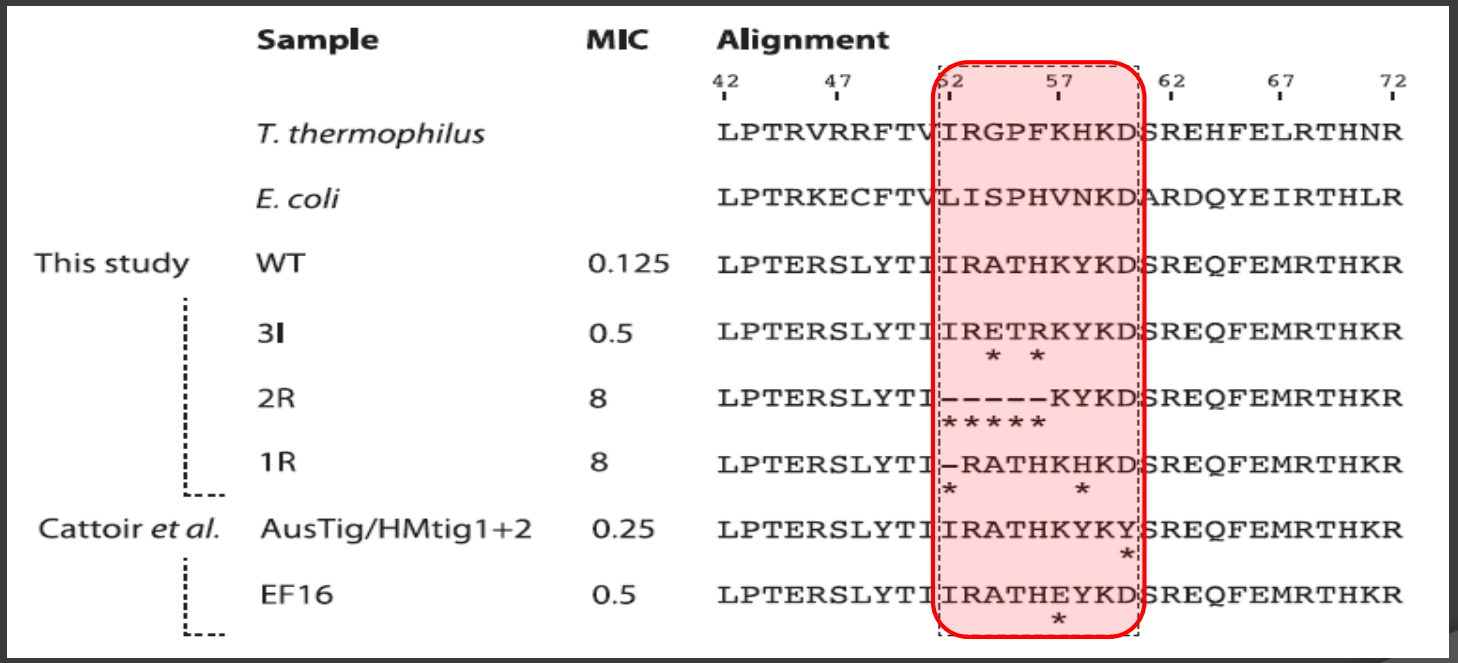
≤0,4 %

Pfaller et al., OFID 2019

Résistance à la tigécycline

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



	Sample	MIC	Alignment (positions 42 47 52 57 62 67 72)
	T. thermophilus		LPTRVRRFTVIRGPFKHKDSREHFELRTHNR
	E. coli		LPTRKECFTVLISPHVNKDARDQYEIRTHLR
This study	WT	0.125	LPTERSLYTIIRATHKYKDSREQFEMRTHKR
	3I	0.5	LPTERSLYTIIRETRKYKDSREQFEMRTHKR
	2R	8	LPTERSLYTI-----KYKDSREQFEMRTHKR
	1R	8	LPTERSLYTI-RATHKHKDSREQFEMRTHKR
Cattoir *et al.*	AusTig/HMtig1+2	0.25	LPTERSLYTIIRATHKYKYSREQFEMRTHKR
	EF16	0.5	LPTERSLYTIIRATHEYKDSREQFEMRTHKR

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

Cattoir et al., AAC 2015 ; Niebel et al., IJAA 2015 ; Fiedler et al., JAC 2015

Epidémiologie chez *S. aureus*

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Diekema et al., OFID 2019

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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 %

Pfaller et al., OFID 2019

Activité de l'éravacycline

Souches isolées entre 2013 et 2017 dans 37 pays

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

Morrissey et al., AAC 2020

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
S. aureus	0.12/0.25	0.12/0.25
Methicillin-susceptible *S. aureus*	0.12/0.25	0.12/0.25
Methicillin-resistant *S. aureus*	0.12/0.25	0.12/0.25
S. lugdunensis	0.06/0.12	0.06/0.12
S. pneumoniae	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
S. pyogenes	0.06/0.12	0.06/0.12
S. pyogenes macrolide resistant	0.12/0.12	0.12/0.12
Viridans group streptococci	0.06/0.12	0.06/0.12
S. anginosus group	0.03/0.12	0.06/0.06
Enterococcus faecalis	0.12/0.25	0.12/0.25
Enterococcus faecium	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)

Pfaller et al., AAC 2020

Résistance à l'éravacycline

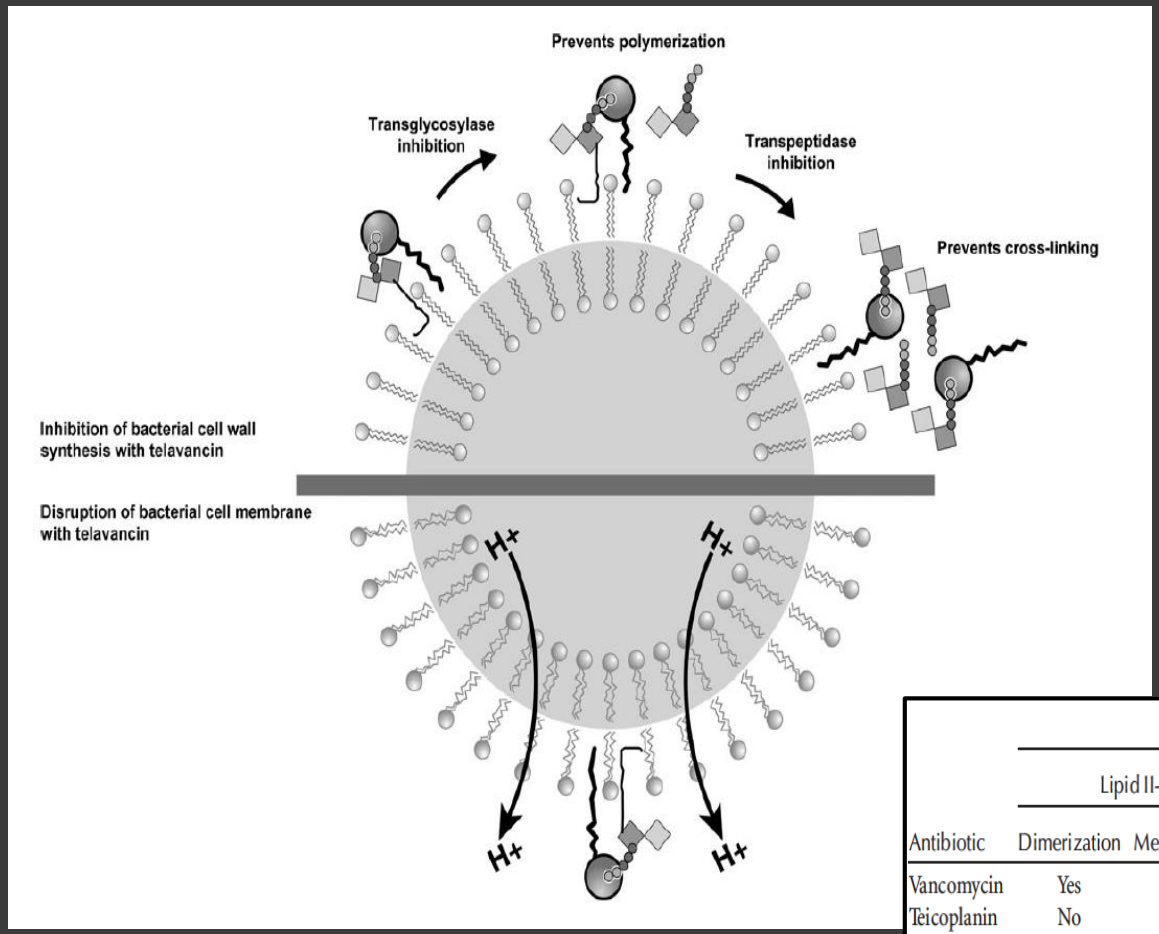
60 souches d'entérocoques isolées en France → 4 souches R :

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••••47••••52••••57••••62••••67••••72
E. faecium DO						–	–	–	–	LPTERSLYTIIRATHKYKDSREQFEMRTHKRL
E. faecium 17-477	**1.5**	**8**	16	16	>32	+	+	–	–	••••••••••:•••••••••••••••••••
E. faecium 18-481	**0.19**	**1**	16	32	>32	+	–	–	+	•••••••••••:••••••••••••••••••
E. faecium 18-626	**0.19**	**1**	8	32	>32	+	–	–	+	•••••••••••:••••••••••••••••••
E. faecium 18-785	**0.25**	**2**	>32	32	>32	+	+	–	–	••••••••••••••:••••••••••••••••
E. faecium 18-394.1	0.047	**0.5**	>32	32	>32	–	+	–	–	••••••••••••••••••:••••••••••••
E. faecium AusTig	0.023	**0.5**	1	0.5	0.5	+ [c]	–	–	–	••••••••••••••••••:••••••••••••
E. faecium HMtig1	0.023	**0.5**	2	0.5	0.5	–	–	–	–	••••••••••••••••••:••••••••••••
E. faecium EF16	0.047	**0.5**	16	16	>32	+	–	–	–	••••••••••••••:••••••••••••••••
E. faecium HMtig2	0.094	0.25 [d]	2	0.25	2	–	–	–	–	••••••••••••••••••:••••••••••••
E. faecium EF22	0.064	0.25 [d]	4	0.5	16	+	+	–	–	•••••••••••••••••••••••••••••••••
E. faecalis V583						–	–	–	–	LPTERSLYTVIRATHKYKDSREQFEMRTHKRL
E. faecalis 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)

Boukthir et al., IJAA 2020

Mode d'action des lipoglycopeptides



2 cibles moléculaires :
- Peptidoglycane
- Membrane cellulaire

	Mechanism			
	Lipid II-binding			
Antibiotic	Dimerization	Membrane anchoring	Transpeptidation (enzymatic)	Membrane (permeabilization–depolarization)
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

Zeng et al., CHSPM 2016

Activité des lipoglycopeptides

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

Activité x 8-32

Zeng et al., CHSPM 2016

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	CLSI[a] %I	CLSI[a] %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 %

Diekema et al., OFID 2019

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*)

Pfaller et al., OFID 2019

Résistance à la dalbavancine

Antimicrobial	S72982 (blood)	F34968 (urine)	S7-D2(*in vitro*)
	MIC (µg/mL)	MIC (µg/mL)	MIC (µg/mL)
Dalbavancin	0.015	0.5 x32	1
Daptomycin	0.25	1 x4	0.5
Levofloxacin	>4	>4	>4
Moxifloxacin	2	2	2
Nafcillin	16	128 x8	16
Telavancin	0.064	0.25	0.38
Trimethoprim/sulfamethoxazole	>2/38	>2/38	>2/38
Vancomycin	1	4 x4	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

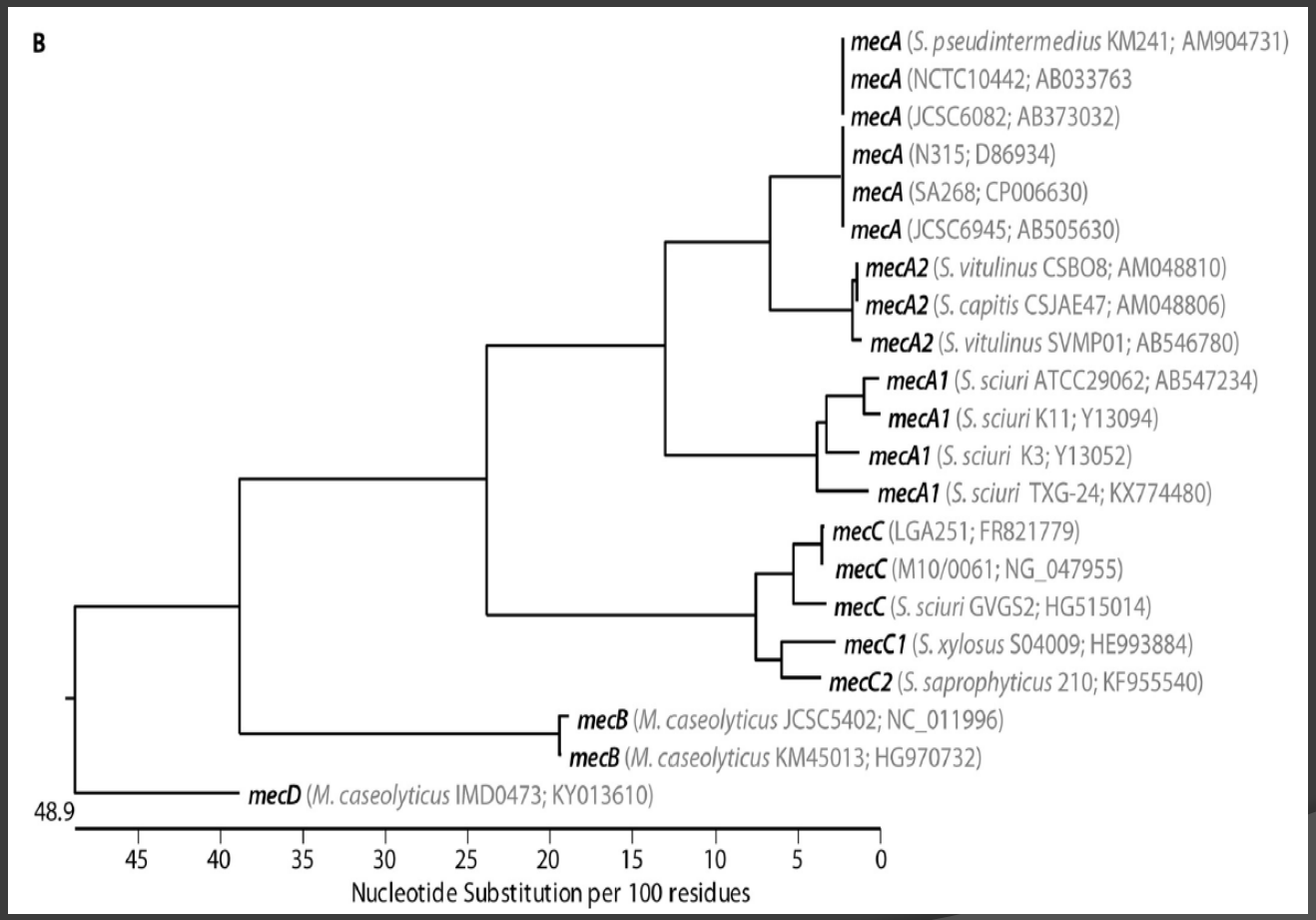
Chromosomal base position	S72982 sequence	F34968 sequence	S7-D2 sequence	Gene ID	Gene name	Gene function	Mutation type		Amino acid change
25206	A	T	A	CH51_00100	*OmpR*	DNA-bind			.Glu85Asp
707079	C	T	C	Intergenic					A
837096	A	T	A						p.Asn35Ile
1025246						porter MgtE	Missense variant	c.211A>T	p.Asn71Tyr
2039377							NA	NA	NA
2108957					*yvqF*	Membrane protein	Missense variant	c.377C>T	p.Pro126Leu
2109093				CH51_10280	*yvqF*	Membrane protein	In-frame deletion	c.232_234delATC	p.Ile78del
2214235			A	Intergenic	NA	NA	NA	NA	NA

Résistance complexe avec multiples mutations chromosomiques

Werth et al., CMI 2018

Nouveau variant *mecC+*

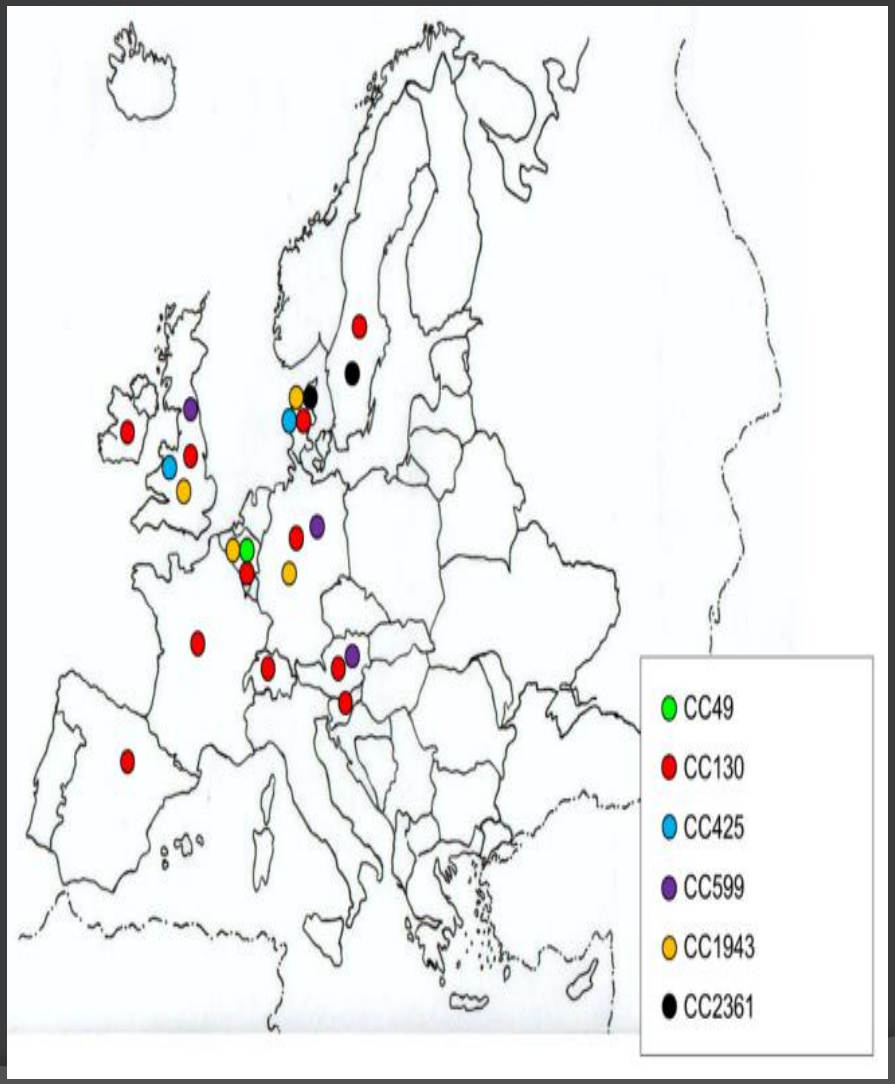
Décrit en 2011 dans des souches animales de SARM (*mecA-*)



70 % id. *mecA*

Garcia-alvarez et al., LID 2011 ; Lakhundi & Zhang et al., CMR 2018

Souches humaines de SARM mecC+



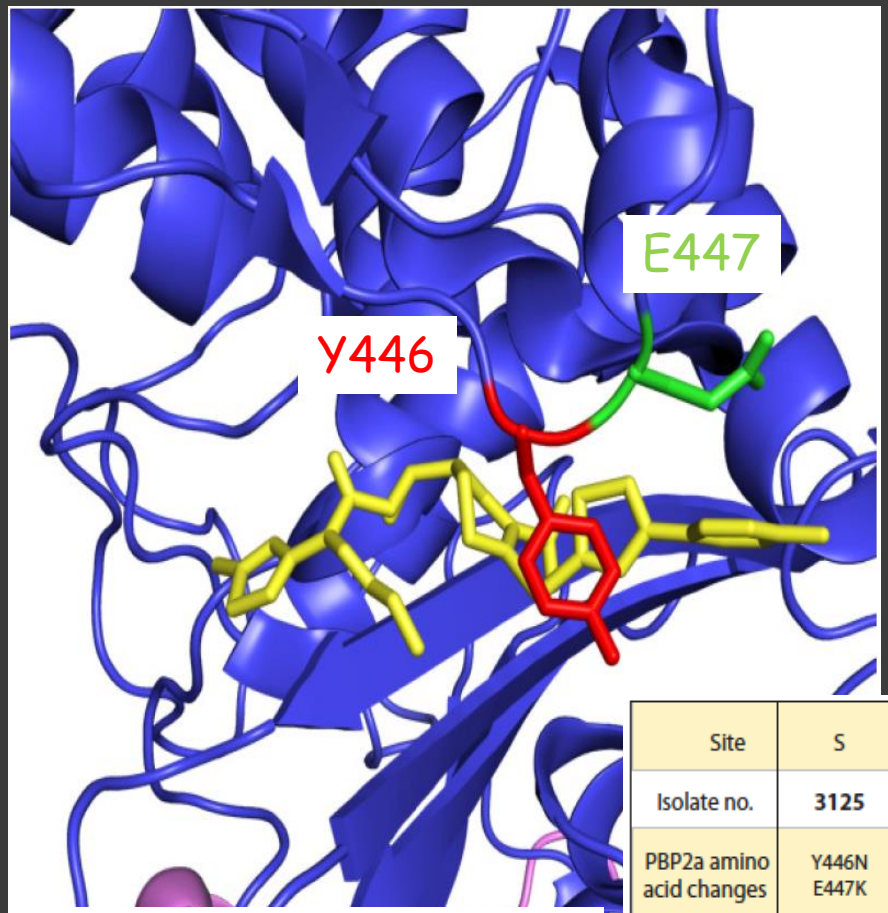
-Souches **rarement isolées chez l'homme** :

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

Lozano et al., MO 2020

Résistance à la ceftaroline



Domaine transpeptidase de la PLP-2a

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

Strain	Collection date (day/mo/yr)	Source	Resistance (N 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* Leu357Ile* Tyr446Asn* Glu447Lys* Ile563Thr* Ser649Ala*
PBP2a amino acid changes	Y446N E447K			Y446N	Y446N E447K	E239K Y446N E447K	
MIC (mg/L)	>32	1	1	1.5	>32	>32	
Days Post Init Admission	4	63	70	112	153	154	

[a]*, in the penicillin-binding domain.

Wesley Long et al., AAC 2014 ; Watkins et al., AAC 2019

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	CLSI[a] %I	CLSI[a] %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	77 130	≤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 %

Diekema et al., OFID 2019

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				
Enterococcus faecalis [15]	450	1	>4 [70.7/70.7]	2 [97.8/97.8]
Staphylococcus aureus [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
S. aureus LEV-R [17]	232	0.25	NR	NR
S. aureus 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]

FDA breakpoints

≤0,12 mg/L

≤0,25 mg/L

Activité x 16-64

Scott, Drugs 2020

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}

Remy et al., JAC 2012

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 *S. pneumoniae*	CABP
Solithromycin	Phase III	Cempra Pharmaceuticals	fluoroketolide	MRSA and macrolide-resistant *M. pneumoniae*	CABP
Contezolid (MRX-1)	Phase III	MicuRx Pharmaceuticals, Inc.	oxazolidinone	MRSA, penicillin-resistant and penicillin-intermediate *S. pneumoniae*, 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, *S. epidermidis*, *E. faecalis*, *S. pyogenes*, *S. agalactiae*, and penicillin-resistant *S. pneumoniae*	CABP; URTI
Nemonoxacin (Taigexyn) [1]	Phase III	TaiGen Biotechnology Co., Ltd.	non-fluorinated quinolone	MRSA, multidrug-resistant *S. pneumoniae* 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, *S. pyogenes*, *E. faecalis* and *S. pneumoniae*	CABP
Brilacidin (PMX30063)	Phase III	Innovation Pharmaceuticals Inc.	defensin mimetic	*S. aureus* and *S. epidermidis*	ABSSSI

Koulenti et al., Microorganisms 2020

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+++) à surveiller

-Résistance décrite *in vivo* pour tous les ATB

-Peu de nouvelles stratégies antibactériennes innovantes