Émergence de mutations dans le gène *ampC* chez *Pseudomonas aeruginosa* après traitement par ceftolozane-tazobactam

Deciphering the emergence of mutations in *Pseudomonas aeruginosa* after ceftolozane/tazobactam treatment and evaluating therapeutic alternatives

Léa Bientz[1,2], Hugo Boijout[1,2], Raoudha Grami[1], Ulysse Guyet[3], Marin Lahouati[4], Melissande Hertzmann[1], Antony Marques[1], Audrey Toirot[1,2], Sabine Aillerie[1], Laure Coulange-Mayonnove[1], Alexis Groppi[3], Macha Nikolski[3], Cécile Bébéar[1,2], Véronique Dubois[1,2*].

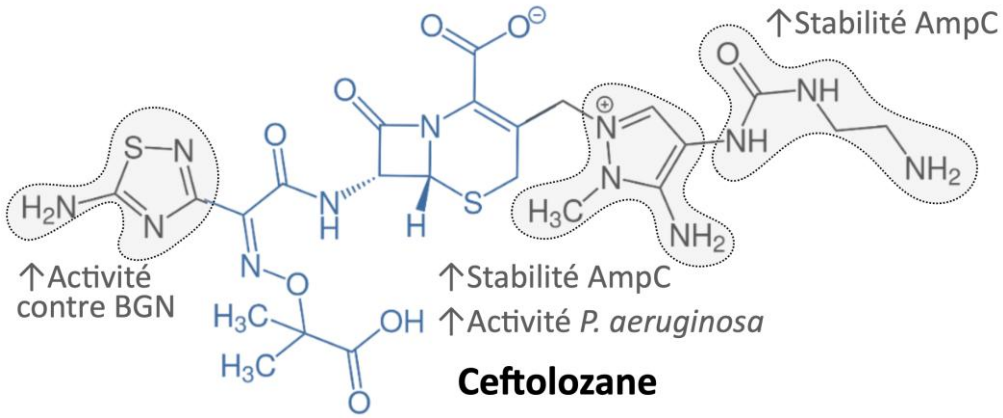
BMC Microbiol. 2025 Dec 9;26(1):22. doi: 10.1186/s12866-025-04517-z

Contexte

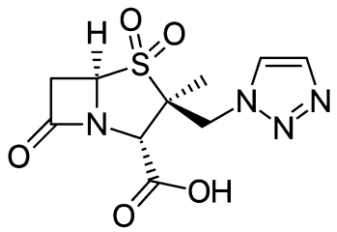
➔ **Traitement *P. aeruginosa* multi-résistants ?**

Hyperproduction céphalosporinase AmpC
Hyperproduction pompes d'efflux
Perte porine OprD

=> Ceftolozane-tazobactam (ZERBAXA®) (C/T)



Ceftolozane



Tazobactam

AMM (2015), 2022 : en **dernier recours**, si recours autres β-lactamines n'est pas envisageable en cas de résistance

➔ **Résistance au C/T**

/!\ Mutations dans gène *ampC*

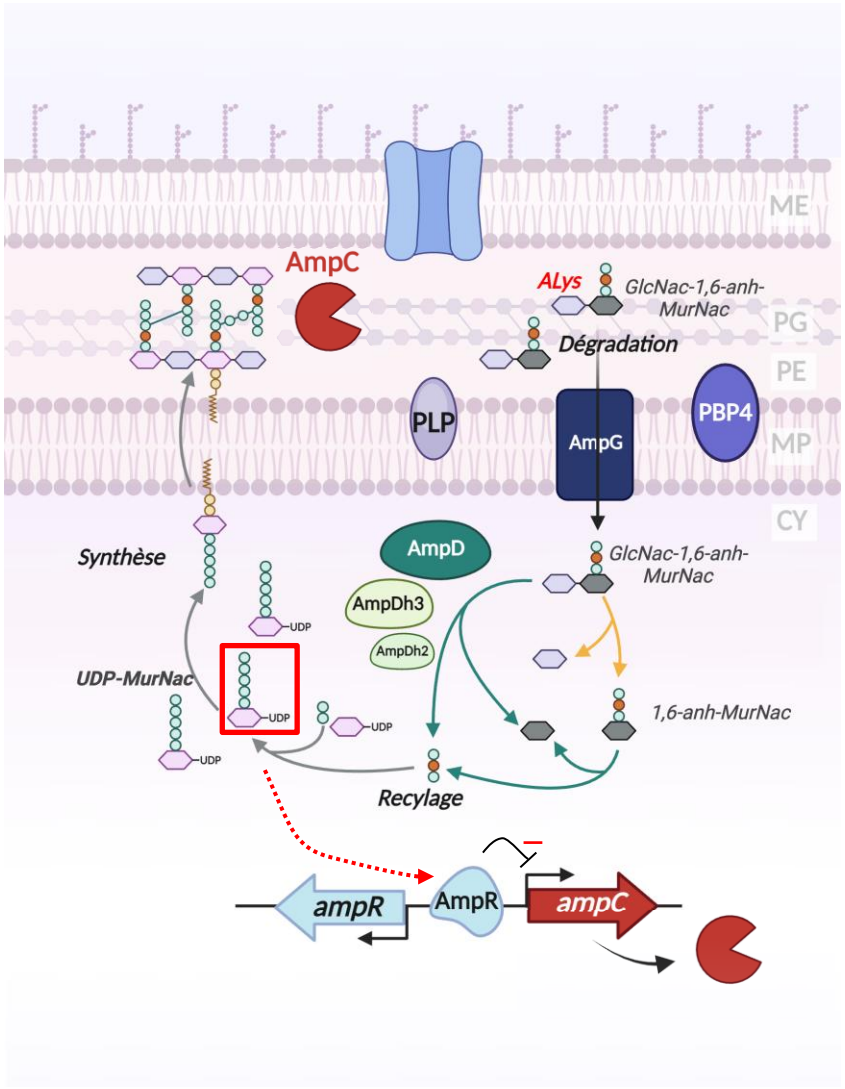
AAC Journals.ASM.org

Mutations in β-Lactamase AmpC Increase Resistance of *Pseudomonas aeruginosa* Isolates to Antipseudomonal Cephalosporins

M. Berrazeg,[a] K. Jeannot,[a] Véronique Yvette Ntsogo Enguéné,[b] I. Broutin,[b] S. Loeffert,[a] D. Fournier,[a] P. Plésiat[a]

French National Reference Center for Antibiotic Resistance, University Hospital of Besançon, Besançon, France[a]; Laboratoire de Cristallographie and RMN Biologiques, CNRS UMR8015 and Université Paris Descartes, Paris, France[b]

Contexte



N-acétylglucosamine

N-acétylmuramique

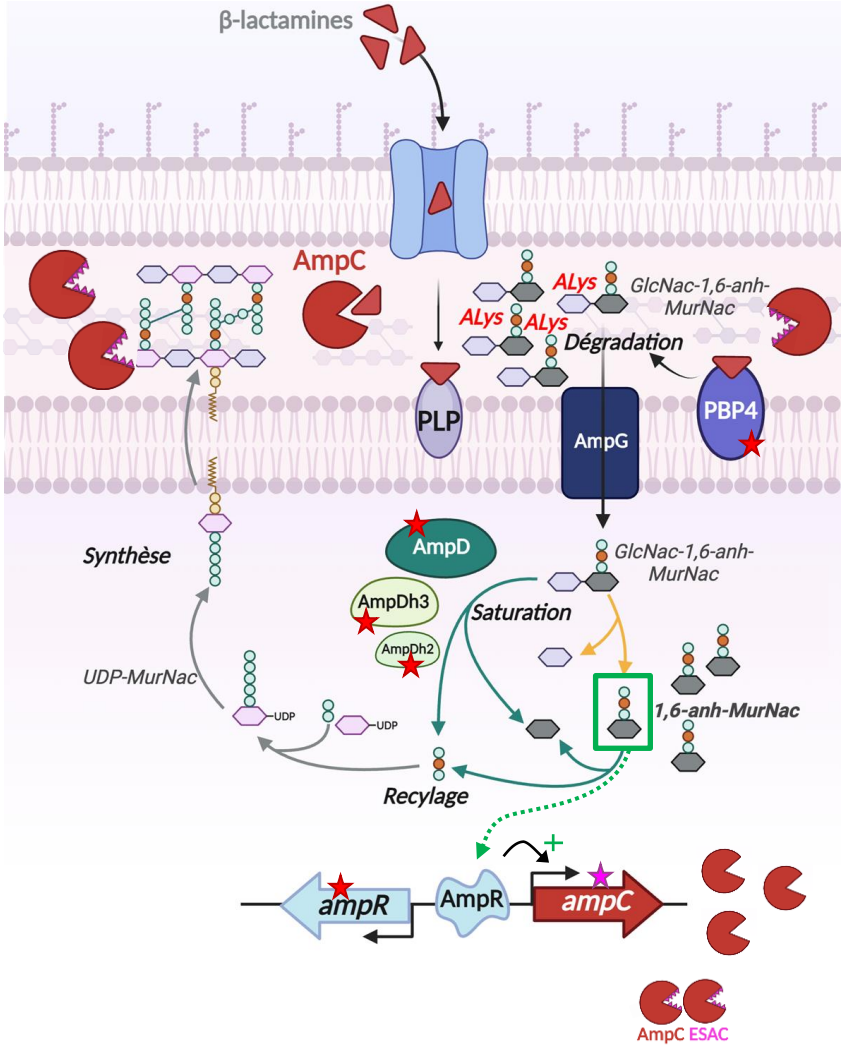
1,6 anhydro-N-acétylmuramique

amino-acides

TIC	TCC	PIP	PTZ	FEP	CAZ	ATM	IPM	MEM	C/T	CZA

ETAT BASAL

Contexte



Mutations inactivatrices

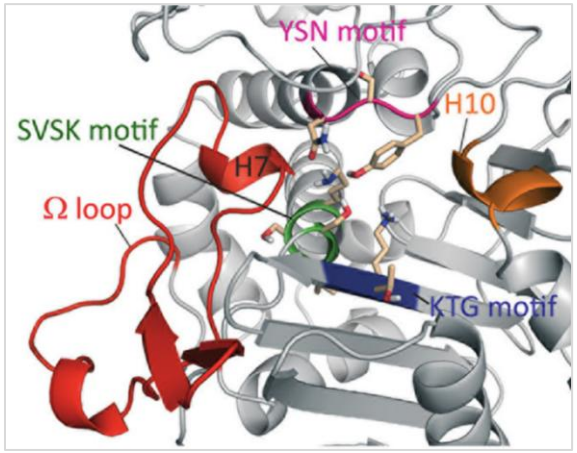
TIC	TCC	PIP	PTZ	FEP	CAZ	ATM	IPM	MEM	C/T	CZA

HYPERPRODUCTION REVERSIBLE

HYPERPRODUCTION IRREVERSIBLE

Mutations activatrices

TIC	TCC	PIP	PTZ	FEP	CAZ	ATM	IPM	MEM	C/T	CZA



ESAC
Extended-spectrum AmpC

Etude

Nov 2017
Janv 2019

50 patients traités par C/T



9 patients (18 %)
≥ 1 souches C/T-R

Patient	Sexe	Isolate	Isolation date	Unit	Sample	C/T treatment			Days of resistance emergence
						Initiation date	End date	Duration	
1	M	**24**	22/12/17	Thoracic ICU	Tracheal aspirate	22/11/17	15/12/17	23	26
		202	01/06/18	Cardiology	Tracheal aspirate	13/01/18	13/01/18	< 1	-
		201	01/06/18	Cardiology	Tracheal aspirate				≤ 138
2	M	**138**	14/03/18	ENT consultation	Pus	11/01/18	29/05/18	138	63
		194	31/05/18	Infectious disease	Pus				141
3	M	125	01/03/18	Thoracic ICU	BAL	28/02/18	06/04/18	37	-
		163	10/04/18	Thoracic ICU	Tracheal aspirate				41
4	M	**182**	09/05/18	Medicine	Sputum	24/04/18	07/05/18	14	16
		181	09/05/18	Medicine	Sputum				16
5	F	197	03/06/18	Burn ICU	Blood	05/06/18	19/06/18	14	-
		227	18/06/18	Burn ICU	Catheter				13
		229	18/06/18	Burn ICU	Superficial wound				13
		228	21/06/18	Burn ICU	Bone				16
6	M	275	09/08/18	Surgical ICU	Pus	09/08/18	26/08/18	17	-
		282	23/08/18	Surgical ICU	Pus				14
7	M	308	20/09/18	Burn ICU	Tracheal aspirate	10/10/18	25/10/18	15	-
		316	08/11/18	Geriatric medicine	Urine				29
8	M	314	09/10/18	Medical ICU	Tracheal aspirate	12/10/18	26/10/18	14	-
		319	26/10/18	Infectious disease	Sputum				14
9	M	325	20/12/18	Digestive ICU	Bile	21/12/18	15/01/19	25	-
		326	14/01/19	Digestive ICU	Sputum				24

Rubio et al.
15 %

Díaz-Cañestro et al.
13,8 %

14 isolats R

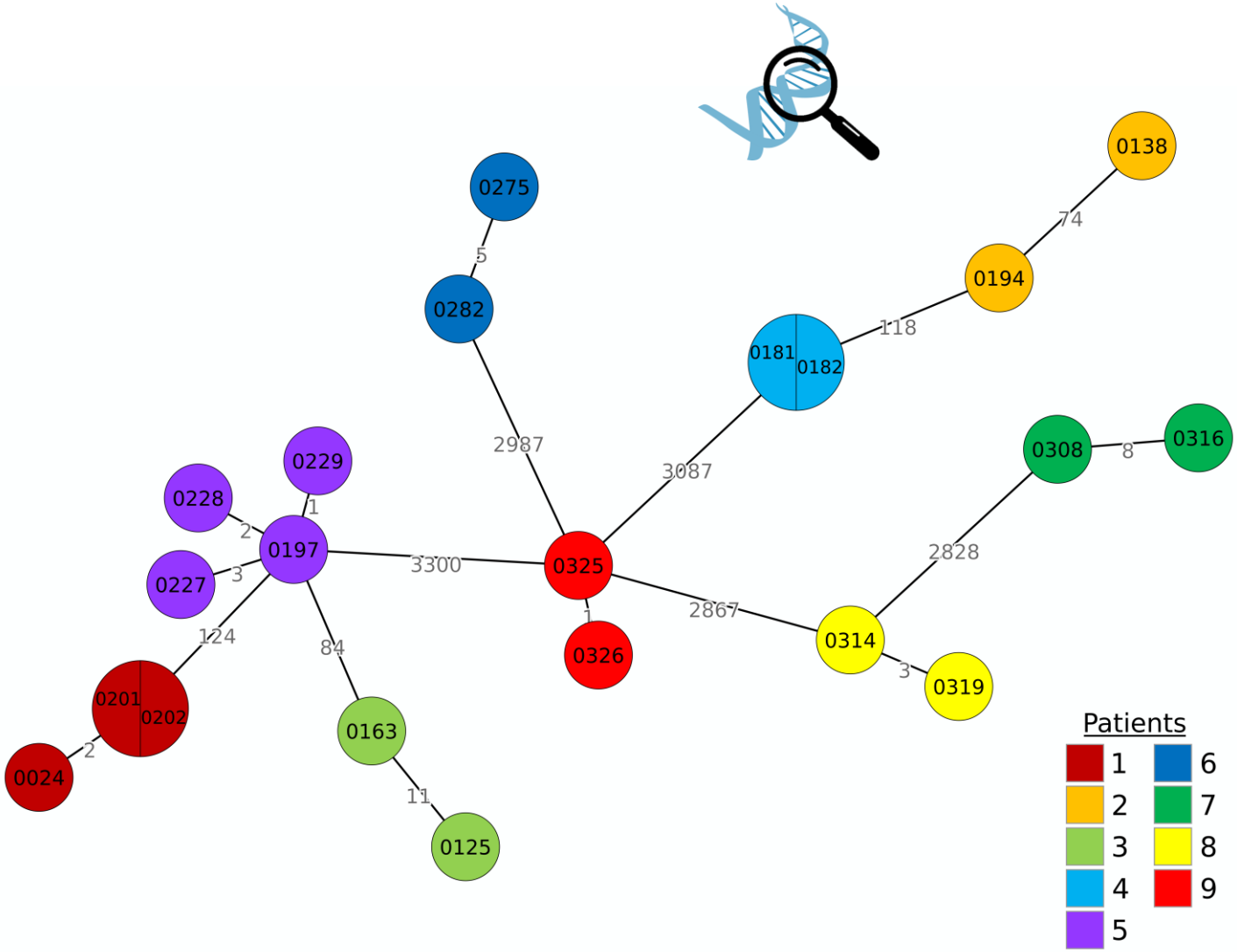
7 isolats S

Durée traitement
16 jours
[1-138 jours]

Apparition résistance
20 jours
[13-141 jours]

ST - cgMLST

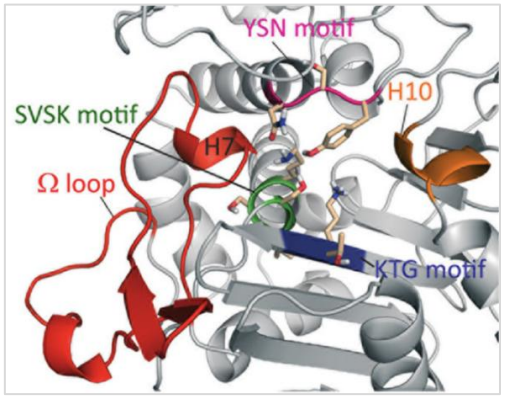
Patient	Isolate	ST
1	**24**	298
	202	298
	201	298
2	**138**	606
	194	606
3	125	446
	163	446
4	**182**	606
	181	606
5	197	446
	227	446
	229	446
	228	446
6	275	3268
	282	3268
7	308	27
	316	27
8	314	2465
	319	2465
9	325	483
	326	483



Gène *ampC*

Patient	Isolate	Variant	AmpC
1			
2			
3	125	PDC-16	G1D, T79A, V179L, G365A
	163	PDC-548	G1D, T79A, V179L, **P217Q**, G365A
4			
5	197	PDC-16	G1D, T79A, V179L, G365A
	227	PDC-552	G1D, **T70I**, T79A, V179L, G365A
	229	PDC-336	G1D, T79A, V179L, **E221K**, G365A
	228	PDC-326	G1D, T79A, V179L, **del210-216**, G365A
6	275	PDC-3	T79A
	282	PDC-392	T79A, **del210-216**
7	308	PDC-15	R53Q, T79A, P248L
	316	PDC-551	R53Q, T79A, **F121L**, P248L
8	314	PDC-5	R53Q, T79A
	319	PDC-446	R53Q, T79A, **E221K**
9	325	PDC-5	R53Q, T79A
	326	PDC-382	R53Q, **T70I**, T79A

Absence de carbapénémase

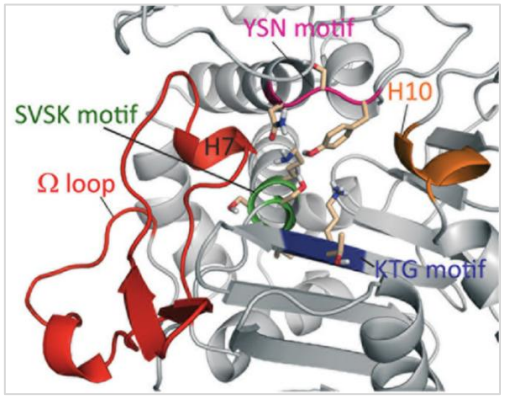


Gène *ampC*

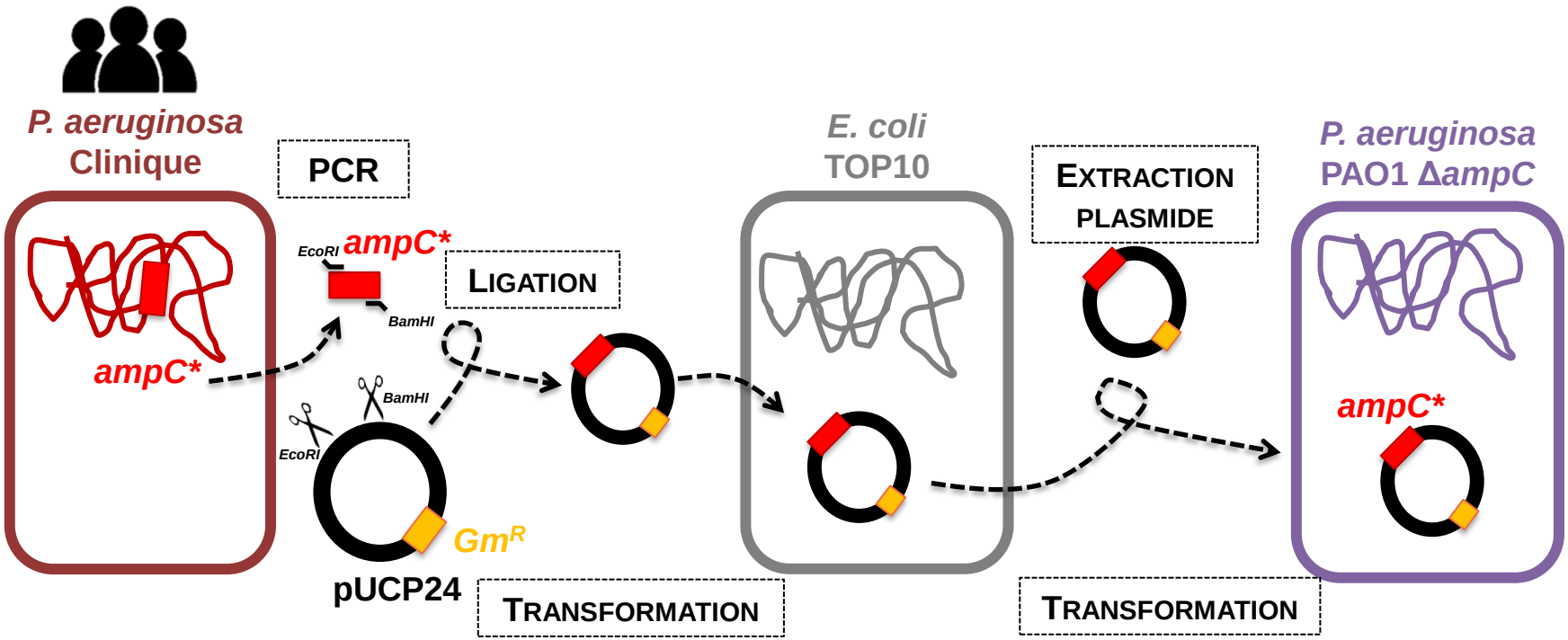
Patient	Isolate	Variant	AmpC
1	**24**	PDC-576	G1D, T79A, **F121L**, V179L, G365A
	202	PDC-96	G1D, T79A, **P154L**, V179L, G365A
	201	PDC-96	G1D, T79A, **P154L**, V179L, G365A
2	**138**	PDC-549	T79A, **F121L**, V179L, G365P
	194	PDC-550	T79A, **G157D**, V179L, G365P
3	125	PDC-16	G1D, T79A, V179L, G365A
	163	PDC-548	G1D, T79A, V179L, **P217Q**, G365A
4	**182**	PDC-550	T79A, **G157D**, V179L, G365P
	181	PDC-550	T79A, **G157D**, V179L, G365P
5	197	PDC-16	G1D, T79A, V179L, G365A
	227	PDC-552	G1D, **T70I**, T79A, V179L, G365A
	229	PDC-336	G1D, T79A, V179L, **E221K**, G365A
	228	PDC-326	G1D, T79A, V179L, **del210-216**, G365A
6	275	PDC-3	T79A
	282	PDC-392	T79A, **del210-216**
7	308	PDC-15	R53Q, T79A, P248L
	316	PDC-551	R53Q, T79A, **F121L**, P248L
8	314	PDC-5	R53Q, T79A
	319	PDC-446	R53Q, T79A, **E221K**
9	325	PDC-5	R53Q, T79A
	326	PDC-382	R53Q, **T70I**, T79A

Absence de carbapénémase

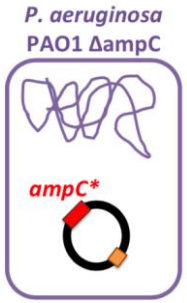
T70I (PDC-382, PDC-552)
F121L (PDC-549, PDC-551, PDC-576)
P154L (PDC-96)
G157D (PDC-550)
del210-216 (PDC-326, PDC-392)
P217Q (PDC-548)
E221K (PDC-336, PDC-446)



Expériences de clonage



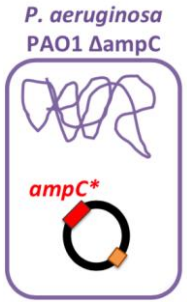
Clones C/T-S



	Variant	AmpC	MIC (mg/L)								
			PIP	TZP	CAZ	C/T	CZA	FEP	IPM	I/R	FDC
PAO1 Δ*ampC* + pUCP24-PDC-x											
6847	PDC-1	WT	128	64	8	1	1	4	0,5	0,5	0,5
6748	PDC-576	G1D, T79A, **F121L**, V179L, G365A	128	128	8	4	2	4	0,5	0,5	1
6844	PDC-549	T79A, **F121L**, V179L, G365P	128	64	16	2	2	4	0,5	0,5	1
6845	PDC-551	R53Q, T79A, **F121L**, P248L	256	64	32	4	2	8	0,5	0,5	1
6747	PDC-96	G1D, T79A, **P154L**, V179L, G365A	>256	128	32	4	1	4	0,5	0,5	1
6750	PDC-550	T79A, **G157D**, V179L, G365P	8	8	4	8	4	2	0,25	0,5	1
6751	PDC-548	G1D, T79A					4	2	0,25	0,25	1
6843	PDC-552	G1D, **T70I**,					8	8	0,25	0,5	2
6776	PDC-382	R53Q, **T70I**, T79A	8	8	16	32	4	4	0,25	0,5	1
6743	PDC-336	G1D, T79A, V179L, **E221K**, G365A	32	16	64	32	4	4	0,5	0,25	4
6842	PDC-446	R53Q, T79A, **E221K**	32	16	32	64	4	4	0,25	0,5	2
6827	PDC-326	G1D, T79A, V179L, **del210-216**, G365A	16	16	32	32	8	4	0,25	0,5	2
6846	PDC-392	T79A, **del210-216**	16	16	64	64	16	4	0,25	0,25	2
6893	PDC-16	G1D, T79A, V179L, G365A	64	64	8	1	1	4	1	1	1
6967	PDC-30	T79A, V179L, G365P	64	32	4	1	2	4	0,5	0,5	0,5
6948	PDC-15	R53Q, T79A, P248L	128	64	4	1	2	4	1	0,5	1
6894	PDC-5	R53Q, T79A	64	64	8	1	1	4	0,5	1	0,5
6920	PDC-3	T79A	64	32	8	0,5	1	4	1	0,5	0,5
Control strains											
6260	PDC-1	PAO1	4	4	0,5	1	1	1	1	0,5	0,5
6262	None	PAO1 Δ*ampC*	4	4	0,5	1	1	2	0,5	0,5	0,5
6861	None	PAO1 Δ*ampC* + pUCP24	2	2	1	1	1	1	0,5	0,5	0,5

Pas d'impact du polymorphisme

Clones C/T-R



	Variant	AmpC	MIC (mg/L) PIP	TZP	CAZ	C/T	CZA	FEP	IPM	I/R	FDC
PAO1 Δ*ampC* + pUCP24-PDC-x											
6847	PDC-1	WT	128	64	8	1	1	4	0,5	0,5	0,5
6748	PDC-576	G1D, T79A, **F121L**, V179L, G365A	128	128	8	4	2	4	0,5	0,5	1
6844	PDC-549	T79A, **F121L**, V179L, G365P	128	64	16	2	2	4	0,5	0,5	1
6845	PDC-551	R53Q, T79A, **F121L**, P248L	256	64	32	4	2	8	0,5	0,5	1
6747	PDC-96	G1D, T79A, **P154L**, V179L, G365A	>256	128	32	4	1	4	0,5	0,5	1
6750	PDC-550	T79A, **G157D**, V179L, G365P	8	8	4	8	4	2	0,25	0,5	1
6751	PDC-548	G1D, T79A, V179L, **P217Q**, G365A	16	16	16	32	4	2	0,25	0,25	1
6843	PDC-552	G1D, **T70I**, T79A, V179L, G365A	16	16	16	32	8	8	0,25	0,5	2
6776	PDC-382	R53Q, **T70I**, T79A	8	8	16	32	4	4	0,25	0,5	1
6743	PDC-336	G1D, T79A, V179L, **E221K**, G365A	32	16	64	32	4	4	0,5	0,25	4
6842	PDC-446	R53Q, T79A, **E221K**	32	16	32	64	4	4	0,25	0,5	2
6827	PDC-326	G1D, T79A, V179L, **del210-216**, G365A	16	16	32	32	8	4	0,25	0,5	2
6846	PDC-392	T79A, **del210-216**	16	16	64	64	16	4	0,25	0,25	2
6893	PDC-16	G1D, T79A, V179L, G365A	64	64	8	1	1	4	1	1	1
6967	PDC-30	T79A, V179L, G365P	64	32	4	1	2	4	0,5	0,5	0,5
6948	PDC-15	R53Q, T79A, P248L	128	64	4	1	2	4	1	0,5	1
6894	PDC-5	R53Q, T79A	64	64	8	1	1	4	0,5	1	0,5
6920					8						0,5
Cont											
6260									0,5		0,5
6262					0,5	1	1	2	0,5	0,5	0,5
6861	None	PAO1 Δ*ampC* + pUCP24	2	2	1	1	1	1	0,5	0,5	0,5

Différents niveaux de résistance

F121L, del210-216 première description expérimentale

P217Q première description

Pas d'impact du polymorphisme

Isolats cliniques

Patient	Isolate	MIC (mg/L)							*ampC* and regulation
		PIP	TZP	CAZ	C/T	CZA	FEP	IPM	AmpC
1	**24**	>256	>256	>256	32	16	32	32	G1D, T79A, **F121L**, V179L, G365A
	202	8	8	2	2	2	8	4	G1D, T79A, **P154L**, V179L, G365A
	201	>256	>256	>256	16	16	64	≥32	G1D, T79A, **P154L**, V179L, G365A
2	**138**	>256	>256	32	32	32	64	4	T79A, **F121L**, V179L, G365P
	194	64	64	>256	>256	>256	64	0.5	T79A, **G157D**, V179L, G365P
3	125	16	16	2	1	2	4	2	G1D, T79A, V179L, G365A
	163	32	32	128	32	32	16	0.5	G1D, T79A, V179L, **P217Q**, G365A
4	**182**	16	16	32	8	4	8	2	T79A, **G157D**, V179L, G365P
	181	16	16	32	32	64	4	2	T79A, **G157D**, V179L, G365P
5	197	256	128	8	1	2	8	≥32	G1D, T79A, V179L, G365A
	227	32	32	>256	>256	>256	32	2	G1D, **T70I**, T79A, V179L, G365A
	229	32	16	>256	32	4	8	4	G1D, T79A, V179L, **E221K**, G365A
	228	32	16	>256	>256	>256	16	2	G1D, T79A, V179L, **del210-216**, G365A
6	275	>256	>256	>256	4	8	256	≥32	T79A
	282	32	32	>256	>256	>256	32	2	T79A, **del210-216**
7	308	4	4	0.5	2	1	4	≥32	R53Q, T79A, P248L
	316	>256	>256	>256	>256	16	256	≥32	R53Q, T79A, **F121L**, P248L
8	314	128	128	8	2	4	32	2	R53Q, T79A
	319	32	32	>256	>256	>256	16	4	R53Q, T79A, **E221K**
9	325	256	128	16	4	4	16	≥32	R53Q, T79A
	326	32	32	>256	>256	64	32	2	R53Q, **T70I**, T79A

Même mutation mais niveau de résistance au C/T différent

Isolats cliniques - Gènes régulateurs de *ampC*

Patient	Isolate	MIC (mg/L)							*ampC* and regulation	
		PIP	TZP	CAZ	C/T	CZA	FEP	IPM	AmpC	Modification in regulatory genes
1	**24**	>256	>256	>256	32	16	32	32	G1D, T79A, F121L, V179L, G365A	*ampR* **(D135N)**
	202	8	8	2	2	2	8	4	G1D, T79A, **P154L**, V179L, G365A	*ampR* (*T129P*, **D135N**)
	201	>256	>256	>256	16	16	64	≥32	G1D, T79A, **P154L**, V179L, G365A	*ampR* **(D135N)**
2	**138**	>256	>256	32	32	32	64	4	T79A, F121L, V179L, G365P	*ampD* **(ins 1b)**, ampDh3 **(A37*)**
	194	64	64	>256	>256	>256	64	0.5	T79A, G157D, V179L, G365P	*ampD* **(ins 1b)**
3	125	16	16	2	1	2	4	2	G1D, T79A, V179L, G365A	-
	163	32	32	128	32	32	16	0.5	G1D, T79A, V179L, **P217Q**, G365A	*ampD* **(IS)**
4	**182**	16	16	32	8	4	8	2	T79A, G157D, V179L, G365P	*ampD* **(IS)**
	181	16	16	32	32	64	4	2	T79A, G157D, V179L, G365P	*ampD* **(IS)**
5	197	256	128	8	1	2	8	≥32	G1D, T79A, V179L, G365A	*ampD* **(del 5b)**
	227	32	32	>256	>256	>256	32	2	G1D, **T70I**, T79A, V179L, G365A	*ampD* **(del 5b)**
	229	32	16	>256	32	4	8	4	G1D, T79A, V179L, E221K, G365A	*ampD* **(del 5b)**
	228	32	16	>256	>256	>256	16	2	G1D, T79A, V179L, **del210-216**, G365A	*ampD* **(del 5b)**
6	275	>256	>256	>256	4	8	256	≥32	T79A	*ampD* **(E125*)**
	282	32	32	>256	>256	>256	32	2	T79A, **del210-216**	*ampD* **(E125*)**
7	308	4	4	0.5	2	1	4	≥32	R53Q, T79A, P248L	-
	316	>256	>256	>256	>256	16	256	≥32	R53Q, T79A, F121L, P248L	*ampD* (V10G?), *dacB* (V138E?)
8	314	128	128	8	2	4	32	2	R53Q, T79A	*ampD* **(del 1b)**
	319	32	32	>256	>256	>256	16	4	R53Q, T79A, E221K	*ampD* **(del 1b)**, *ampDh3* (R134S?)
9	325	256	128	16	4	4	16	≥32	R53Q, T79A	*ampD* (G121E?)
	326	32	32	>256	>256	64	32	2	R53Q, **T70I**, T79A	*ampD* (G121E?), *ampDh3* (G158D?)

ESAC ⇔ Hyperproduction AmpC

Niveaux d'hyperproduction différents ⇔ Niveaux de résistance C/T différents ?

Isolats cliniques - Gènes régulateurs de *ampC*

Patient	Isolate	MIC (mg/L)							*ampC* and regulation	
		PIP	TZP	CAZ	C/T	CZA	FEP	IPM	AmpC	Modification in regulatory genes
1	**24**	>256	>256	>256	32	16	32	32	G1D, T79A, F121L, V179L, G365A	*ampR* **(D135N)**
	202	8	8	2	2	2	8	4	G1D, T79A, **P154L**, V179L, G365A	*ampR* (*T129P*, **D135N**)
	201	>256	>256	>256	16	16	64	≥32	G1D, T79A, **P154L**, V179L, G365A	*ampR* **(D135N)**
2	**138**	>256	>256	32						1b), ampDh3 **(A37*)**
	194	64	64	>25						1b)
3	125	16	16	2	1	2	4	2	G1D, T79A, V179L, G365A	-
	163	32	32	128	32	32	16	0.5	G1D, T79A, V179L, **P217Q**, G365A	*ampD* **(IS)**
4	**182**	16	16	32	8	4	8	2	T79A, G157D, V179L, G365P	*ampD* **(IS)**
	181	16	16	32	32	64	4	2	T79A, G157D, V179L, G365P	*ampD* **(IS)**
5	197	256	128	8	1	2	8	≥32	G1D, T79A, V179L, G365A	*ampD* **(del 5b)**
	227	32	32	>256	>256	>256	32	2	G1D, **T70I**, T79A, V179L, G365A	*ampD* **(del 5b)**
	229	32	16	>256	32					**(del 5b)**
	228	32	16	>256	>256					**(del 5b)**
6	275	>256	>256	>256	4					**(E125*)**
	282	32	32	>256	>256	>256	32	2	T79A, **del210-216**	*ampD* **(E125*)**
7	308	4	4	0.5	2	1	4	≥32	R53Q, T79A, P248L	-
	316	>256	>256	>256	>256	16	256	≥32	R53Q, T79A, F121L, P248L	*ampD* (V10G?), *dacB* (V138E?)
8	314	128	128	8	2	4	32	2	R53Q, T79A	*ampD* **(del 1b)**
	319	32	32	>256	>256	>256	16	4	R53Q, T79A, E221K	*ampD* **(del 1b)**, *ampDh3* (R134S?)
9	325	256	128	16	4	4	16	≥32	R53Q, T79A	*ampD* (G121E?)
	326	32	32	>256	>256	64	32	2	R53Q, **T70I**, T79A	*ampD* (G121E?), *ampDh3* (G158D?)

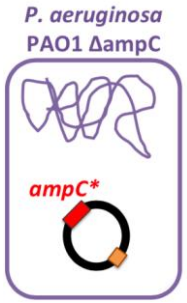
Absence d'hyperproduction AmpC => CMI C/T S

Autres mécanismes associés ?
Efflux, modification PLP, imperméabilité

ESAC ⇔ Hyperproduction AmpC

Niveaux d'hyperproduction différents ⇔ Niveaux de résistance C/T différents ?

Clones – Autres antibiotiques



	Variant	AmpC	MIC (mg/L)								
			PIP	TZP	CAZ	C/T	CZA	FEP	IPM	I/R	FDC
PAO1 Δ*ampC* + pUCP24-PDC-x											
6847	PDC-1	WT	128	64	8	1	1	4	0,5	0,5	0,5
6748	PDC-576	G1D, T79A, **F121L**, V179L, G365A	128	128	8	4	2	4	0,5	0,5	1
6844	PDC-549	T79A, **F121L**, V179L, G365P	128	64	16	2	2	4	0,5	0,5	1
6845	PDC-551	R53Q, T79A, **F121L**, P248L	256	64	32	4	2	8	0,5	0,5	1
6747	PDC-96	G1D, T79A, **P154L**, V179L, G365A	>256	128	32	4	1	4	0,5	0,5	1
6750	PDC-550	T79A, **G157D**, V179L, G365P	8	8	4	8	4	2	0,25	0,5	1
6751	PDC-548	G1D, T79A, V179L, **P217Q**, G365A	16	16	16	32	4	2	0,25	0,25	1
6843	PDC-552	G1D, **T70I**, T79A, V179L, G365A	16	16	16	32	8	8	0,25	0,5	2
6776	PDC-382	R53Q, **T70I**, T79A	8	8	16	32	4	4	0,25	0,5	1
6743	PDC-336	G1D, T79A, V179L, **E221K**, G3	32	16	64	32	4	4	0,5	0,25	4
6842	PDC-446	R53Q, T79A, **E221K**	32	16	32	64	4	4	0,25	0,5	2
6827	PDC-326	G1D, T79A, V179L, **del210-216**, G365A	16	16	32	32	8	4	0,25	0,5	2
6846	PDC-392	T79A, **del210-216**	16	16	64	64	16	4	0,25	0,25	2
6893	PDC-16	G1D, T79A, V179L, G365A	64	64	8	1	1	4	1	1	1
6967	PDC-30	T79A, V179L, G365P	64	32	4	1	2	4	0,5	0,5	0,5
6948	PDC-15	R53Q, T79A, P248L	128	64	4	1	2	4	1	0,5	1
6894	PDC-5	R53Q, T79A	64	64	8	1	1	4	0,5	1	0,5
6920	PDC-3	T79A	64	32	8	0,5	1	4	1	0,5	0,5
Control strains											
6260	PDC-1	PAO1	4	4	0,5	1	1	1	1	0,5	0,5
6262	None	PAO1 Δ*ampC*	4	4	0,5	1	1	2	0,5	0,5	0,5
6861	None	PAO1 Δ*ampC* + pUCP24	2	2	1	1	1	1	0,5	0,5	0,5

↓ PIP, TZP

Isolats cliniques – Autres antibiotiques

Patient	Isolate	MIC (mg/L)							*ampC* and regulation	
		PIP	TZP	CAZ	C/T	CZA	FEP	IPM	AmpC	Modification in regulatory genes
1	**24**	>256	>256	>256	32	16	32	32	G1D, T79A, **F121L**, V179L, G365A	*ampR* **(D135N)**
	202	8	8	2	2	2	8	4	G1D, T79A, **P154L**, V179L, G365A	*ampR* (*T129P*, **D135N)**
	201	>256	>256	>256	16	16	64	≥32	G1D, T79A, **P154L**, V179L, G365A	*ampR* **(D135N)**
2	**138**	>256	>256	32	32	32	64	4	T79A, **F121L**, V179L, G365P	*ampD* **(ins 1b)**, ampDh3 **(A37*)**
	194	64	64	>256	>256	>256	64	0.5	T79A, **G157D**, V179L, G365P	*ampD* **(ins 1b)**
3	125	16	16	2	1	2	4	2	G1D, T79A, V179L, G365A	-
	163	32	32	128	32	32	16	0.5	G1D, T79A, V179L, **P217Q**, G365A	*ampD* (IS)
4	**182**	16	16	32	8	4	8	2	T79A, **G157D**, V179L, G365P	*ampD* (IS)
	181	16	16	32	32	64	4	2	T79A, **G157D**, V179L, G365P	*ampD* (IS)
5	197	256	128	8	1	2	8	≥32	G1D, T79A, V179L, G365A	*ampD* **(del 5b)**
	227	32	32	>256	>256	>256	32	2	G1D, **T70I**, T79A, V179L, G365A	*ampD* **(del 5b)**
	229	32	16	>256	32	4	8	4	G1D, T79A, V179L, **E221K**, G365A	*ampD* **(del 5b)**
	228	32	16	>256	>256	>256	16	2	G1D, T79A, V179L, **del210-216**, G365A	*ampD* **(del 5b)**
6	275	>256	>256	>256	4	8	256	≥32	T79A	*ampD* **(E125*)**
	282	32	32	>256	>256	>256	32	2	T79A, **del210-216**	*ampD* **(E125*)**
7	308	4	4	0.5	2	1	4	≥32	R53Q, T79A, P248L	-
	316	>256	>256	>256	>256	16	256	≥32	R53Q, T79A, **F121L**, P248L	*ampD* (V10G?), *dacB* (V138E?)
8	314	128	128	8	2	4	32	2	R53Q, T79A	*ampD* **(del 1b)**
	319	32	32	>256	>256	>256	16	4	R53Q, T79A, **E221K**	*ampD* **(del 1b)**, *ampDh3* (R134S?)
9	325	256	128	16	4	4	16	≥32	R53Q, T79A	*ampD* (G121E?)
	326	32	32	>256	>256	64	32	2	R53Q, **T70I**, T79A	*ampD* (G121E?), *ampDh3* (G158D?)

Isolats cliniques – Autres antibiotiques

Patient	Isolate	MIC (mg/L)							*ampC* and regula	
		PIP	TZP	CAZ	C/T	CZA	FEP	IPM	AmpC	OprD
1	**24**	>256	>256	>256	32	16	32	32	G1D, T79A, **F121L**, V179L, G365A	*oprD*_2 **(IS256)**
	202	8	8	2	2	2	8	4	G1D, T79A, **P154L**, V179L, G365A	*oprD*_2 **(IS256)**
	201	>256	>256	>256	16	16	64	≥32	G1D, T79A, **P154L**, V179L, G365A	*oprD*_2 **(IS256)**
2	**138**	>256	>256	32	32	32	64	4	T79A, **F121L**, V179L, G365P	*oprD*_1 **(K133R)**
	194	64	64	>256	>256	>256	64	0.5	T79A, **G157D**, V179L, G365P	*oprD*_1
3	125	16	16	2	1	2	4	2	G1D, T79A, V179L, G365A	*oprD*_2
	163	32	32	128	32	32	16	0.5	G1D, T79A, V179L, **P217Q**, G365A	*oprD*_2
4	**182**	16	16	32	8	4	8	2	T79A, **G157D**, V179L, G365P	*oprD*_1 **(ins 1b)**
	181	16	16	32	32	64	4	2	T79A, **G157D**, V179L, G365P	*oprD*_1 **(ins 1b)**
5	197	256	128	8	1	2	8	≥32	G1D, T79A, V179L, G365A	*oprD*_2 **(IS3)**
	227	32	32	>256	>256	>256	32	2	G1D, **T70I**, T79A, V179L, G365A	*oprD*_2 **(IS3)**
	229	32	16	>256	32	4	8	4	G1D, T79A, V179L, **E221K**, G365A	*oprD*_2 **(IS3)**
	228	32	16	>256	>256	>256	16	2	G1D, T79A, V179L, **del210-216**, G365A	*oprD*_2 **(IS3)**
6	275	>256	>256	>256	4	8	256	≥32	T79A	*oprD*_1 **(E176*)**
	282	32	32	>256	>256	>256	32	2	T79A, **del210-216**	*oprD*_1 **(E176*)**
7	308	4	4	0.5	2	1	4	≥32	R53Q, T79A, P248L	*oprD*_1 **(W339*)**
	316	>256	>256	>256	>256	16	256	≥32	R53Q, T79A, **F121L**, P248L	*oprD*_1 **(W339*)**
8	314	128	128	8	2	4	32	2	R53Q, T79A	*oprD*_4
	319	32	32	>256	>256	>256	16	4	R53Q, T79A, **E221K**	*oprD*_4 **(IS5_pro)**
9	325	256	128	16	4	4	16	≥32	R53Q, T79A	*oprD*_1 **(del 14b)**
	326	32	32	>256	>256	64	32	2	R53Q, **T70I**, T79A	*oprD*_1 **(del 14b)**

OprD_1 (LESB58), OprD_2 (PA14), OprD_4 (PAO1)

Alternatives thérapeutiques

Patient	Isolate	MIC (mg/L)										*ampC* and regulati
		CAZ	C/T	CZA	FEP	IPM	I/R	FDC	AMK	CIP	CST	AmpC
1	**24** 🔴	>256	32	16	32	32	1	1	8	0.5	1	G1D, T79A, **F121L**, V179L, G365A
	202 🟢	2	2	2	8	4	2	0.25	8	0.5	0.5	G1D, T79A, **P154L**, V179L, G365A
	201 🔴	>256	16	16	64	≥32	2	0.5	4	0.5	1	G1D, T79A, **P154L**, V179L, G365A
2	**138** 🔴	32	32	32	64	4	1	2	16	2	1	T79A, **F121L**, V179L, G365P
	194 🔴	>256	>256	>256	64	0.5	0.5	8	32	1	1	T79A, **G157D**, V179L, G365P
3	125 🟢	2	1	2	4	2	1	2	4	0.25	0.5	G1D, T79A, V179L, G365A
	163 🔴	128	32	32	16	0.5	0.5	1	8	0.5	1	G1D, T79A, V179L, **P217Q**, G365A
4	**182** 🔴	32	8	4	8	2	2	1	1	0.5	0.5	T79A, **G157D**, V179L, G365P
	181 🔴	32	32	64	4	2	2	1	2	0.5	1	T79A, **G157D**, V179L, G365P
5	197 🟢	8	1	2	8	≥32	4	1	8	32	1	G1D, T79A, V179L, G365A
	227 🔴	>256	>256	>256	32	2	2	1	16	32	1	G1D, **T70I**, T79A, V179L, G365A
	229 🔴	>256	32	4	8	4	2	4	4	32	1	G1D, T79A, V179L, **E221K**, G365A
	228 🔴	>256	>256	>256	16	2	1	2	16	32	1	G1D, T79A, V179L, **del210-216**, G365A
6	275 🟢	>256	4	8	256	≥32	4	0.5	8	0.25	1	T79A
	282 🔴	>256	>256	>256	32	2	1	2	8	0.25	1	T79A, **del210-216**
7	308 🟢	0.5	2	1	4	≥32	2	0.5	4	0.125	0.5	R53Q, T79A, P248L
	316 🔴	>256	>256	16	256	≥32	2	2	4	0.25	0.5	R53Q, T79A, **F121L**, P248L
8	314 🟢	8	2	4	32	2	1	1	4	0.5	1	R53Q, T79A
	319 🔴	>256	>256	>256	16	4	2	2	4	1	0.5	R53Q, T79A, **E221K**
9	325 🟢	16	4	4	16	≥32	2	0.25	4	0.25	1	R53Q, T79A
	326 🔴	>256	>256	64	32	2	1	1	4	0.25	1	R53Q, **T70I**, T79A
	🔴 **Isolats C/T-R**					%	100 I/R	85,7 FDC	92,9 AMK	57,1 CIP	100 CST	

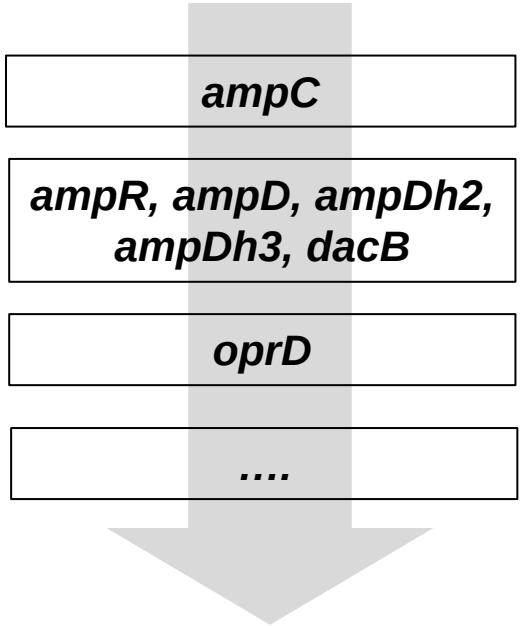
Conclusion - Discussion

Emergence resistance sous traitement C/T : 18%

Impacts des mutations dans AmpC

Mutations	Niveau R C/T	CMI PIP PTZ IPM
F121L P154L	Faible (2-4xCMI)	Inchangée
G157D	Moyen (8xCMI)	↓
T70I del210-216 **P217Q** E221K	Elevé (32-64xCMI)	↓

Analyse globale



Alternatives thérapeutiques

Imipénème/relebactam
Colistine
Céfidérocol
Amikacine
Ciprofloxacine