Evaluation of doripenem *in vitro* activity in comparison with other carbapenems on carbapenem resistant clinical isolates of *Pseudomonas aeruginosa* from a French multicenter study

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Background

P. aeruginosa remains a serious challenge in intensive care units. Carbapenem resistance is increasing. Doripenem, a more recent carbapenem active against *P. aeruginosa* has been recently withdrawn from the European market. The objective of this study were to assess the *in vitro* activity of doripenem in comparison to other carbapenems on clinical strains of carbapenem-resistant *P.aeruginosa* collected in several French ICUs.

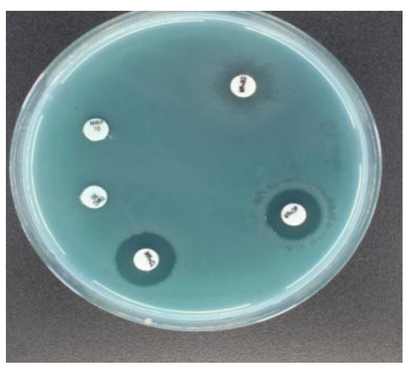
Material & methods

- Between February and October 2009, 326 *P. aeruginosa* strains were collected from a multicenter prospective cohort study of patients hospitalized in several French ICUs (Dynapyo Study[1]).
- Isolates resistant to at least one carbapenem were included. The identities of the strains were confirmed by API strips and their susceptibilities to antibiotics by Liofilchem® PATHOGENIC SYSTEM AST (Liofilchem, Italy).
- After genotyping the strains by PFGE, clonal strains were excluded to avoid strains acquired through cross transmission.
- Imipenem, meropenem and doripenem MICs were determined by the Agar dilution method and by E-tests.
- In 25 representative strains, the mechanisms responsible for carbapenem resistance were determined by the KPC & MBL disc kit (Liofilchem, Italy) and molecular approaches (PCR).

Interpretative Table. Synergy of meropenem with carbapenem inhibitors for confirmation of CRE.

Increase in inhibition zone of meropenem with the following inhibitor			Temocillin (TMO)*	β-lactamases
Phenylboronic acid (MR+BO)	Dipicolinic acid (MR+DP)	Cloxacillin (MR+CL)		
≥ 4 mm	< 5 mm	< 5 mm	---	KPC
< 4 mm	≥ 5 mm	< 5 mm	---	MBL
≥ 4 mm AND	< 5 mm	≥ 5 mm	---	AmpC + porin loss or efflux
< 4 mm	< 5 mm	< 5 mm	< 11 mm	OXA-48-like

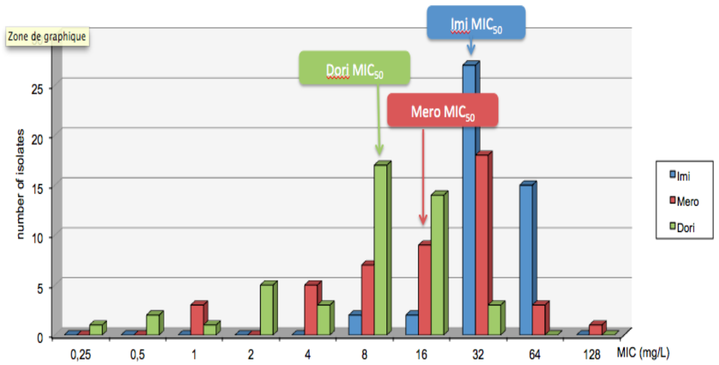
*Temocillin susceptibility test is recommended only in cases where no synergy is detected.



Agar plates of KPC and AmpC hyperproducer isolates

Results

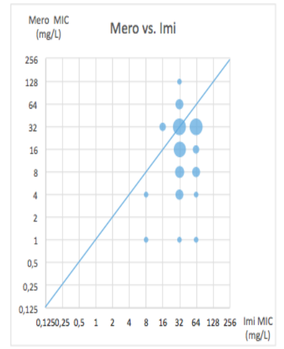
326 collected strains, 46 were resistant to carbapenem and included in the study (52%colonization/48% infection).

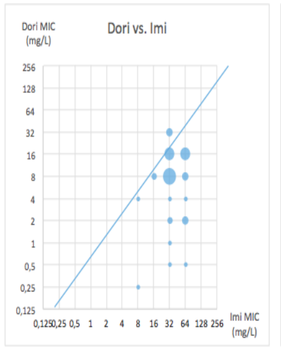


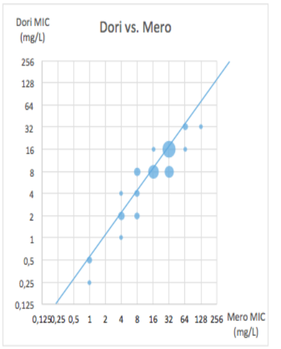
	MIC	n = 46 (%)		
	range	S	I	R
IMP	8 - 64	0	2 (4%)	44 (96%)
MRP	1 - 128	3 (7%)	12 (26%)	31 (67%)
DOR	0,25 - 32	4 (9%)	8 (17%)	34 (74%)

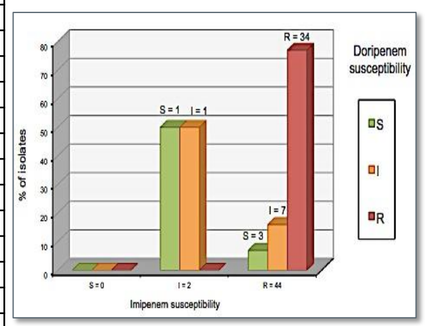
Strain	MRP10	MRP+DP	MRP+CL	MRP+BO	TMO	AC +/EFX/LP	KPC like	Multi-PCR Carba
1	8	13	8	15	6	-	-	-
2	8	13	9	18	6	-	-	-
3	15	19	15	20	6	-	KPC	KPC
4	10	12	12	15	6	-	KPC	NT
5	12	14	12	14	6	-	-	-
6	18	20	26	25	6	+	-	-
7	6	12	12	12	7	+	-	-
8	6	10	9	11	6	-	KPC	NT
9	6	10	6	10	6	-	KPC	
10	6	10	9	10	6	-	KPC	KPC
11	6	10	9	10	6	-	KPC	-
17	10	15	14	18	6	-	-	-
19	12	14	12	25	6	-	KPC	KPC
21	6	6	8	10	6	-	KPC	KPC
23	6	8	6	10	6	-	KPC	NT
25	9	12	10	14	6	-	KPC	KPC
27	7	11	8	16	6	-	KPC	KPC
30	8	12	10	12	6	-	KPC	NT
31	9	16	12	13	6	-	-	-
32	6	6	8	16	6	-	KPC	NT
35	6	14	14	12	6	+	-	-
39	18	21	19	18	7	-	-	-
42	6	9	13	15	6	+	-	-
45	6	7	12	10	6	+	-	-
46	6	6	6	10	6	-	KPC	NT
49	14	19	16	18	6	-	-	-
50	6	12	12	14	6	+	-	-

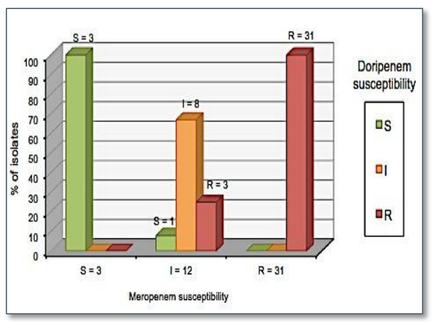
Liofilchem phnotypic test : MRP: Meropenem, DP: Dipicolinic acid; CL: Cloxacillin; BO: Boronic acid; TMO: Temocillin; AC+: AmpC hyperproduction; LP : Loss of porin, EFX : Efflux; NT: not yet tested.











Conclusion

The *in vitro* activities of doripenem and meropenem against carbapenem resistant *P. aeruginosa* were equivalent and better than imipenem activity. The genetic determinants responsible for resistance to carbapenems in the stains are multiple : hyper expression of AMPc, loss of porins and /efflux together with production of a KPC like carbapenemeses. The molecular characterization of the strains is still ongoing.