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Interprétation des tests de sensibilité aux carbapénèmes de *Pseudomonas aeruginosa*

Interpreting carbapenem susceptibility testing results for *Pseudomonas aeruginosa*

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Mots clés : tests de sensibilité aux antibiotiques, concentrations critiques, carbapénèmes, *Pseudomonas aeruginosa*

Keywords: antimicrobial susceptibility testing, breakpoints, carbapenems, *Pseudomonas aeruginosa*

Contribution of authors

Maïté Micaëlo performed the tests, interpreted the results, and wrote the article.

Florence Brossier contributed to result interpretation and to writing the article.

Nicolas Bréchot, Qin Lu, and Antoine Monsel took care of the patients' management.

Charles-Edouard Luyt took care of the patients' management and contributed to implementing the study protocol.

Vincent Jarlier reviewed the article.

Alexandra Aubry supervised the study (implementation, test performance, result interpretation) and reviewed the article.

Highlights

Few studies have been performed on antimicrobial susceptibility testing to carbapenems for *Pseudomonas aeruginosa* strains. The main strength of our work was the comparison of the two most widely used methods in laboratories: the disc diffusion method and the Etest method. On the basis of the former guidelines, poor correlation between both methods was observed for all carbapenems. These results highlight the need for applying the new EUCAST guidelines.

RÉSUMÉ

Objectifs. **-** Les bêtalactamines, dont les carbapénèmes, sont les antibiotiques les plus actifs contre *P. aeruginosa.* Peu d'études ont été réalisées sur les tests de sensibilité par diffusion et Etest du méropénème et du doripénème. L'objectif était de comparer l'activité *in vitro* de l'imipénème, du méropénème et du doripénème contre *P. aeruginosa*.

Méthodes. **-** Nous avons mesuré la sensibilité aux carbapénèmes (imipénème, méropénème et doripénème) de 311 souches de *P. aeruginosa*, responsables de pneumopathies acquises sous ventilation mécanique (PAVM), isolées sur une période de 31 mois dans deux unités de réanimation. La sensibilité de ces isolats a été déterminée par diffusion en milieu gélosé et par Etest.

Résultats. **-** L'interprétation des CMI a mis en évidence un pourcentage de souches sensibles plus important pour le doripénème que pour le méropénème et l'imipénème. La concordance complète entre la méthode de diffusion en milieu gélosé et par Etest était de 90,6 % et 89,7 % pour l'imipénème, 80,5 % et 82,6 % pour le méropénème et 80,5 % et 73,3 % pour le doripénème, pour les premiers isolats de PAVM et l'ensemble des isolats respectivement. La corrélation entre les deux méthodes est donc faible pour le méropénème et le doripénème, et ceci est principalement du fait d'erreurs mineures (17,7 % et 16,1 % pour le méropénème et 17,7 % et 25,7 % pour le doripénème pour les premiers isolats et l'ensemble des isolats respectivement).

Conclusions. - Ces résultats montrent l'importance de l'application des recommandations EUCAST pour *P. aeruginosa* et les carbapénèmes.

ABSTRACT

***Objectives*. -** Carbapenems are among the most powerful antipseudomonal agents. Limited data is available on drug susceptibility testing by routine methods (disc diffusion and Etest) for meropenem and doripenem. We aimed to compare the *in vitro* activity of imipenem, meropenem, and doripenem against *Pseudomonas aeruginosa*.

***Methods*. –** A total of 311 *P. aeruginosa* strains isolated from respiratory specimens in 170 patients who developed ventilator-associated pneumonia in two intensive care units were collected over a period of 31 months. The susceptibility of these isolates to imipenem, meropenem, and doripenem were determined by Etest and disc diffusion method.

***Results*. -** Considering either all isolates or only the first isolates recovered per patient (311 and 170 respectively) the susceptibility rate for doripenem was higher than that for meropenem and imipenem. When MICs determined by Etest were converted into interpretative categories (S, I, R) using French (CA-SFM) guidelines, a poor correlation was observed for meropenem and doripenem. The percentages of correlation with the disc diffusion method were 90.6% and 89.7% for imipenem, 80.5% and 82.6% for meropenem and 80.5% and 73.3% for doripenem, for the first isolates and all isolates, respectively. The rate of minor errors was as high as 17.7% and 16.1% for meropenem and 17.7% and 25.7% for doripenem for the first isolates and all isolates, respectively.

***Conclusion*. -** The accuracy of disc diffusion using CA-SFM guidelines appears unsatisfactory for all three carbapenems justifying guideline update for *P. aeruginosa* and carbapenems.

INTRODUCTION

Pseudomonas aeruginosa is one of the main organisms responsible for hospital-acquired infections, such as urinary tract infections and ventilator-associated pneumonia (VAP) [1,2]. Only a few antibiotics are available for the treatment of *P. aeruginosa* infections as this bacterium is naturally multidrug resistant due to the combination of impermeability, multiple efflux systems, and a chromosomal AmpC β-lactamase. *P. aeruginosa* can also develop acquired resistance to many antibiotics (cephalosporins, carbapenems, fluoroquinolones, aminoglycosides, etc.) [3,4]. Three of the four available carbapenems, i.e. imipenem, meropenem, and doripenem, are among the most powerful antipseudomonal agents. The spectrum of activity of these carbapenems differs; doripenem − a recently approved parenteral 1β-methylcarbapenem − being more active against Gram-positive bacteria than meropenem and more active against Gram-negative bacteria than imipenem [5,6]. Meropenem and doripenem have recently been marketed and limited data is available on the interpretation of susceptibility tests using EUCAST and CA-SFM (European Committee on Antimicrobial Susceptibility Testing and Antibiogram Committee of the French Society for Microbiology, respectively) breakpoints and the correlation of results yielded by the two methods widely used for *in vitro* susceptibility testing on agar, i.e. disc diffusion method and MIC determination by Etest. We aimed to compare the results obtained for imipenem, meropenem, and doripenem against *P. aeruginosa* using both methods.

MATERIALS AND METHODS

Bacterial strains

Consecutive isolates (n=311) of *P. aeruginosa* were prospectively collected by the laboratory of bacteriology at the Pitié-Salpêtrière Hospital (Paris, France) over a period of 31 months (January 2009 to July 2011). These isolates were obtained from the respiratory specimens of 170 patients who developed *P. aeruginosa* VAP in two intensive care units. Fifty-six (33%) patients had at least one VAP recurrence, defined as the persistence or reappearance of clinical and biological signs of infection and significant concentrations of *Pseudomonas aeruginosa* in lower respiratory tract specimens at least two days (but no more than 28 days) after completing antibiotic therapy for the first episode. A total of 311 isolates have been studied: 170 from the first episode of VAP and 141 from the subsequent episodes. After collection, the strains were frozen and stored for future analysis.

P. aeruginosa CIP 76110 (ATCC 27853) was used as control.

Antimicrobial susceptibility testing

The susceptibilities of the isolates to imipenem, meropenem, and doripenem were determined by disc diffusion method (Biorad®, Marnes-la-Coquette, France) according to the guidelines of the CA-SFM, as follows: overnight cultures on agar, suspension in distilled water to reach a turbidity equivalent to that of a 0.5 McFarland standard, then diluted to 1/10, inoculation of Mueller-Hinton agar plates (Biorad®) by swabbing, incubation for 18 hours at 37°C. The discs containing 10 µg doripenem, meropenem, and imipenem were supplied by Biorad®.

MICs of the carbapenems were determined by Etest (bioMérieux®, Marcy l'Étoile, France) on Mueller-Hinton agar using the manufacturer's instructions. Etest MIC values were rounded up to the nearest twofold dilution.

MIC results were also interpreted according to the 2013 guidelines of the CA-SFM (Table I). These guidelines recommend the same breakpoints as EUCAST for each of the three carbapenems (Table I).

Result analysis

The minimum concentrations of antibiotic required to inhibit the growth of 50% and 90% of the isolates tested (MIC_{50} and MIC_{90}, respectively) were calculated for each agent.

The correlation between interpretative categories based on disc diffusion method and Etest was evaluated for the isolates of the first episodes (n=170) and for all isolates (n'=311). MICs yielded by the latter were used as reference. A very major error (VME) was defined as susceptibility by agar diffusion method but resistance by Etest, a major error (ME) as resistance by agar diffusion method but susceptibility by Etest, and a minor error (mE) as intermediate susceptibility by one method and susceptibility or resistance by the other method (CLSI and FDA set standards).

The regression curve between the MIC values on the Y-axis and the inhibition diameters (arithmetic scale) on the x-axis was determined by the least squares method on 311 isolates, which distribution is depicted in Figure 1.

Software

All calculations were done using Microsoft Excel 2010 (Microsoft corporation Redmond, WA, USA) and BiostaTGV website [7]. Pearson's χ^2 test was used for testing categorization differences.

RESULTS

Activity of imipenem, meropenem, and doripenem against *P. aeruginosa* (Table II, Figure 2, Figure 3)

For the first isolates recovered per patient (n=170), MICs measured by Etest showed that doripenem displayed the most potent activity with MIC_{50} and MIC_{90} of 0.25 and 8 mg/L, respectively; meropenem and imipenem were less potent with MIC_{50}/MIC_{90} of 0.38/>32 and 2/>32 mg/L, respectively.

MICs measured by Etest for all isolates (n=311) showed that doripenem also displayed the most potent activity with MIC_{50} and MIC_{90} of 0.75 and 12 mg/L, respectively; meropenem and imipenem were less potent with MIC_{50}/MIC_{90} of 1/>32 and 4/>32 mg/L, respectively.

When MICs determined by Etest were converted into interpretative category breakpoints, the proportion of strains categorized as susceptible were 61% (n=104) for imipenem, 64% (n=111) for meropenem, and 69% (n=118) for doripenem considering the first isolates only (Table II).

Considering all isolates, the proportion of strains categorized as susceptible were 50% (n=157) for imipenem, 56% (n=175) for meropenem, and 59% (n=183) for doripenem (Table II). The assessed susceptibility rate was only significantly higher for doripenem as compared with imipenem (P=0.04), whereas no difference between the three carbapenems was observed when only considering the first isolates.

For imipenem, strains belonging to the wild-type population are classified as susceptible and are clearly different from the intermediate and resistant population; whereas for doripenem and meropenem less clear delineation between susceptible and intermediate and resistant population is observed (Figures 2 and 3). Indeed, the breakpoint defining a distinct population is ≥1.5 mg/L for meropenem and ≥0.5 mg/L for doripenem (i.e. slightly below susceptibility breakpoints).

The susceptibility rate assessed by disc diffusion method was significantly higher for doripenem than for meropenem and imipenem either for the first isolates or all isolates.

Comparing results obtained by disc diffusion method and by Etest using CA-SFM guidelines (Table II, Figure 1)

The percentage of correlation in terms of interpretative categories between the results obtained by the disc diffusion method following CA-SFM guidelines and the Etest method were 90.6% and 89.7% for imipenem, 80.5% and 82.6% for meropenem, and 80.5% and 73.3% for doripenem for the first isolates and all isolates, respectively. These differences in susceptibility rates (S versus I+R) between Etest and disc diffusion methods reached statistical significance for doripenem, whereas the differences were not statistically significant for meropenem and imipenem (Table II).

Errors were mostly minor errors (mE). The mE rates were 9.4% and 10.3% for imipenem, 17.7% and 16.1% for meropenem, and 17.7% and 25.7% for doripenem, only for the first isolates and for all isolates, respectively. No major error (ME) was observed for any carbapenem, and very major errors (VME) were rarely observed for meropenem (1.8% and 1.3%, only for the first isolates and for all isolates, respectively), and doripenem (1.8% and 1%, only for the first isolates and for all isolates, respectively), but not for imipenem.

DISCUSSION

Carbapenems are potent agents against *P. aeruginosa*. Unfortunately, limited data is available on the correlation of the two methods widely used for susceptibility testing in laboratories, whereas discrepancies in breakpoints are confusing [8]. Our study aimed to compare the results obtained for imipenem, meropenem, and doripenem against *P. aeruginosa* using both methods.

We observed that doripenem was the most active drug against *P. aeruginosa*, followed by meropenem and imipenem, as previously reported by several authors [5, 9-11]. On the basis of MIC results, the susceptibility rate did not exceed 70% (69% for the first isolates, 59% for

all isolates) for doripenem and was lower for imipenem (61% for the first isolates, 50% for all isolates), underlining the ability of *P. aeruginosa* to acquire resistance which phenotypic expression can differ according to the penem compound. The local origin of the clinical strains included in the study (resistance mechanisms not characterized) does not allow for reaching definite conclusions on the respective advantage of one penem over the others.

Disc diffusion method and Etest are two methods widely used for susceptibility testing in microbiological laboratories [12]. As the Etest method is the most convenient method used for MIC determination in routine clinical practice and was demonstrated to yield results with good correlation compared with the reference broth-microdilution method used in several studies [11, 13-17], we compared disc diffusion results with Etest MICs. Correlation between the disc diffusion method and the Etest method was limited, especially for doripenem (overestimation of susceptibility by 13% (P=0.01) or 17% (P<0.001) only for the first isolates and all isolates, respectively). For imipenem, the susceptibility rate was underestimated by 4% or 5% (despite a lack of statistical significance) only for the first isolates and all isolates, respectively. For meropenem, the rate was overestimated by 8% or 5% only for the first isolates and all isolates, respectively (Table II). Errors were almost exclusively minor errors, but the percentage was high particularly for meropenem and doripenem (≈17%-25%). The higher rate of errors observed when studying all isolates compared with the one observed when studying the first isolates only, could be due to the higher resistance rate observed among all strains. Indeed, as explained in a previous study, more than 50% of strains isolated from a second episode of VAP have a modified susceptibility to carbapenems [18]. Discrepancies for doripenem most often resulted from cases where the strain susceptibility pattern was intermediate by Etest method but was susceptible by disc diffusion method (64% irrespective of the isolates considered), which could lead to therapeutic hazard. Given the recommendation not to exceed ≥1.5% for very major errors, ≥3% for major errors, and 10%

for minor errors [19], the accuracy of the disc diffusion method using CA-SFM guidelines appears unsatisfactory for all three carbapenems. The strains for which a discrepancy was observed were retested and the same results were observed in each case (data not shown). Even if it is not adequate to interpret the inhibition zone diameter obtained with the CA-SFM methodology (lower inoculum) with EUCAST guidelines (Table I), attempts to do so suggest that the correlation could be better. Trends should however be confirmed by ad hoc studies.

Choosing a breakpoint able to discriminate between the wild-type and the non-wild-type population is challenging. Yet, breakpoint determinations are based on clinical data, pharmacokinetic–pharmacodynamic (PK-PD) properties, and MIC distributions [20-22]. EUCAST guidelines for penems and *P. aeruginosa* clearly differentiate the strains belonging to the major wild-type population and those with higher MICs and categorized as intermediate or resistant. The CA-SFM apply the EUCAST breakpoints and methods since June 2016 to homogenize the guidelines. In contrast, the CLSI guidelines are different and recommend similar breakpoints for the three carbapenems (2 and 8 mg/L). Some strains can therefore be categorized as susceptible, intermediate, or resistant, depending on the country where the patient is treated leading to a different therapeutic decision. These discrepancies between guidelines are surprising as doripenem, meropenem, and imipenem share similar pharmacokinetic–pharmacodynamic properties worldwide [6].

REFERENCES

[1] Chastre J, Fagon JY. Ventilator-associated pneumonia. Am J Respi Crit Care Med 2002; **165:** 867–903.

[2] Driscoll JA, Brody SL, Kollef MH. The epidemiology, pathogenesis and treatment of *Pseudomonas aeruginosa* infections. Drugs 2007; **67:** 351–68.

[3] Lister PD, Wolter DJ, Hanson ND. Antibacterial-resistant *Pseudomonas aeruginosa*: clinical impact and complex regulation of chromosomally encoded resistance mechanisms. Clin Microbiol Rev 2009; **22:** 582–610.

[4] Lambert PA. Mechanisms of antibiotic resistance in *Pseudomonas aeruginosa*. J R Soc Med 2002; **95** Suppl 41: 22–6.

[5] Jones RN, Huynh HK, Biedenbach DJ. Activities of doripenem (S-4661) against drug-resistant clinical pathogens. Antimicrob Agents Chemother 2004; **48:** 3136–40.

[6] Zhanel GG, Wiebe R, Dilay L, Thomson K, Rubinstein E, Hoban DJ, et al. Comparative review of the carbapenems. Drugs 2007; **67:** 1027–52.

[7] BiostaTGV website (http://marne.u707.jussieu.fr/biostatgv/). [Consulted 03/01/2018]

[8] Gómez-Garcés JL, López-Fabal F, Burillo A, Gil Y. *Pseudomonas aeruginosa* and carbapenems: the urgent need to harmonise disagreeing breakpoints. Int J Antimicrob Agents 2011;**38:** 452–53.

[9] Brown SD, Traczewski MM. Comparative in vitro antimicrobial activity of a new carbapenem, doripenem: tentative disc diffusion criteria and quality control. J Antimicrob Chemother 2005; **55:** 944–49.

[10] Pillar CM, Torres MK, Brown NP, Shah D, Sahm DF. In vitro activity of doripenem, a carbapenem for the treatment of challenging infections caused by gram-negative bacteria, against recent clinical isolates from the United States. Antimicrob Agents Chemother 2008; **52:** 4388–99.

[11] Nordmann P, Picazo JJ, Mutters R, Korten V, Quintana A, Laeuffer JM, et al. Comparative activity of carbapenem testing: the COMPACT study. J Antimicrob Chemother 2011; **66:** 1070–78.

[12] Jorgensen JH, Ferraro MJ. Antimicrobial susceptibility testing: a review of general principles and contemporary practices. Clin Infect Dis 2009; **49:** 1749–55.

[13] Amsler K, Santoro C, Foleno B, Bush K, Flamm R. Comparison of broth microdilution, agar dilution, and Etest for susceptibility testing of doripenem against gram-negative and gram-positive pathogens. J Clin Microbiol 2010; **48:** 3353–57.

[14] Torres E, Villanueva R, Bou G. Comparison of different methods of determining beta-lactam susceptibility in clinical strains of *Pseudomonas aeruginosa*. J Med Microbiol 2009; **58:** 625–29.

[15] Markelz AE, Mende K, Murray CK, Yu X, Zera WC, Hospenthal DR, et al. Carbapenem susceptibility testing errors using three automated systems, disk diffusion, Etest, and broth microdilution and carbapenem resistance genes in isolates of *Acinetobacter baumannii-calcoaceticus* complex. Antimicrob Agents Chemother 2011; **55:** 4707–11

[16] Steward CD, Mohammed JM, Swenson JM,. Stocker SA, Williams PP, Gaynes RP, et al. Antimicrobial susceptibility testing of carbapenems: multicenter validity testing and accuracy levels of five antimicrobial test methods for detecting resistance in

Enterobacteriaceae and *Pseudomonas aeruginosa* isolates. J Clin Microbiol. 2003; **41**: 351-8.

[17] Burns JL, Saiman L, Whittier S, Larone D, Krzewinski J, Liu Z, et al. Comparison of agar diffusion methodologies for antimicrobial susceptibility testing of *Pseudomonas aeruginosa* isolates from cystic fibrosis patients. J Clin Microbiol. 2000; **38**: 1818-22.

[18] Luyt CE, Aubry A, Lu Q, Micaelo M, Bréchot N, Brossier F, et al. Imipenem, meropenem, or doripenem to treat patients with *Pseudomonas aeruginosa* ventilator-associated pneumonia. Antimicrob Agents Chemother. 2014;58(3):1372-80.

[19] National Committee for Clinical Laboratory Standards. Development of In Vitro Susceptibility Testing Criteria and Quality Control Parameters: Approved Standard M23-A2. NCCLS, Wayne, PA, USA, 2001.

[20] Comité de l'Antibiogramme de la Société Française de Microbiologie (CA-SFM) 2013. Société Française de Microbiologie. Home page at: http://www.sfm-microbiologie.org/UserFiles/files/casfm/CASFM2013vjuin.pdf. [Consulted 03/01/2018]

[21] European Committee on Antimicrobial Susceptibility Testing (EUCAST) 2013. Clinical breakpoints. Home page at: http://www.eucast.org/ast_of_bacteria/previous_versions_of_documents/ [Consulted 03/01/2018]

[22] Clinical and Laboratory Standards Institute. Performance Standards for Antimicrobial Susceptibility Testing: Twenty-Third Informational Supplement M100-S23. CLSI, Wayne, PA, USA, 2013.

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Tableau I. Concentrations et diamètres critiques établis par les comités de l'antibiogramme français (CA-SFM) et européen (EUCAST) pour *P. aeruginosa*

Table I. Carbapenem breakpoints (diameter by disc diffusion method and MICs) recommended by the European and French antibiotic susceptibility test committees for *P. aeruginosa*

Committee	**IMIPENEM**				**MEROPENEM**				**DORIPENEM**			
	Diameter (mm)		MIC (mg/L)		Diameter (mm)		MIC (mg/L)		Diameter (mm)		MIC (mg/L)	
	S	R	S	R	S	R	S	R	S	R	S	R
EUCAST	≥20	<17	≤4	>8	≥24	<15	≤2	>8	≥25	<19	≤1	>4
CA-SFM	≥22	<17	≤4	>8	≥22	<15	≤2	>8	≥24	<19	≤1	>4

S, susceptible; R, resistant

Tableau II. Catégorisation (S, I, R) des souches de *P. aeruginosa* selon la méthode de diffusion et la mesure des CMI par Etest d'après les recommandations françaises (CA-SFM)

Table II. Carbapenem susceptibility against *P. aeruginosa* isolates by Etest and by disc diffusion method interpreted using the CA-SFM guidelines

Carbapenem	**Type of isolates[b]**	**Etest**			**Disc diffusion**			***P* value[a]**
		S%	**I%**	**R%**	**S%**	**I%**	**R%**	
IMIPENEM	first	61	2	37	57	8	35	0.50
	all	50	3	47	45	10	45	0.20
MEROPENEM	first	64	13	23	72	18	10	0.24
	all	56	18	26	61	25	14	0.29
DORIPENEM	first	69	15	16	82	9	9	**0.01**
	all	59	23	18	76	13	11	**<0.001**

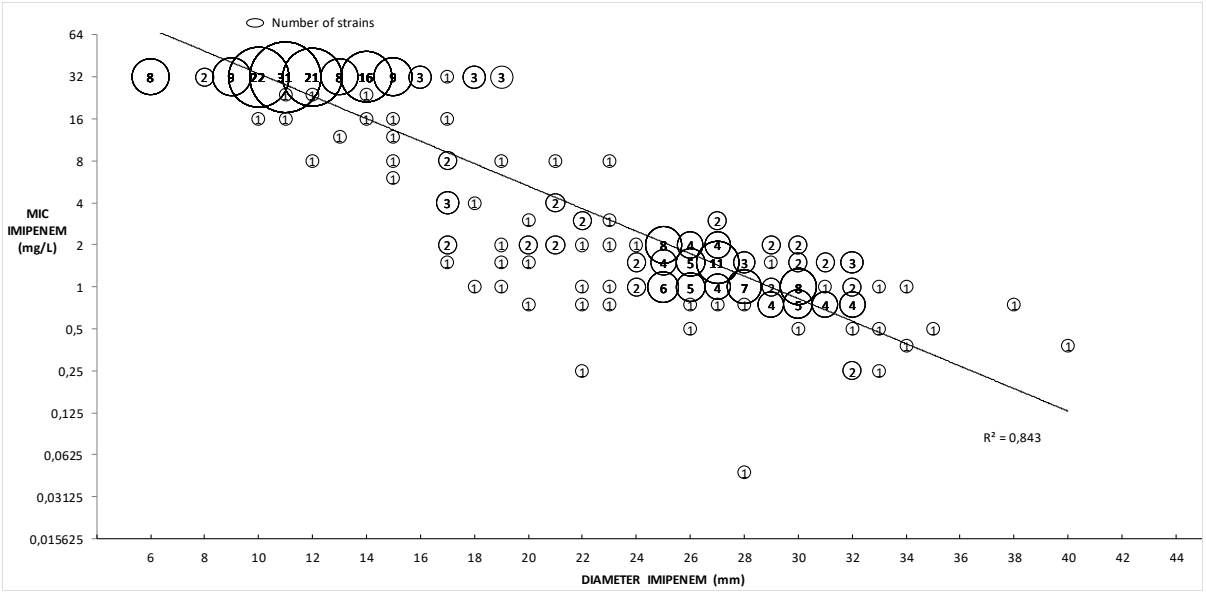
[a]Etest versus disc diffusion (S versus I+R), in bold: $P<0.05$

[b]The first isolates were recovered from the first VAP per patient (n=170), whereas "all" corresponds to all isolates included in the study irrespective of the number of VAP episodes

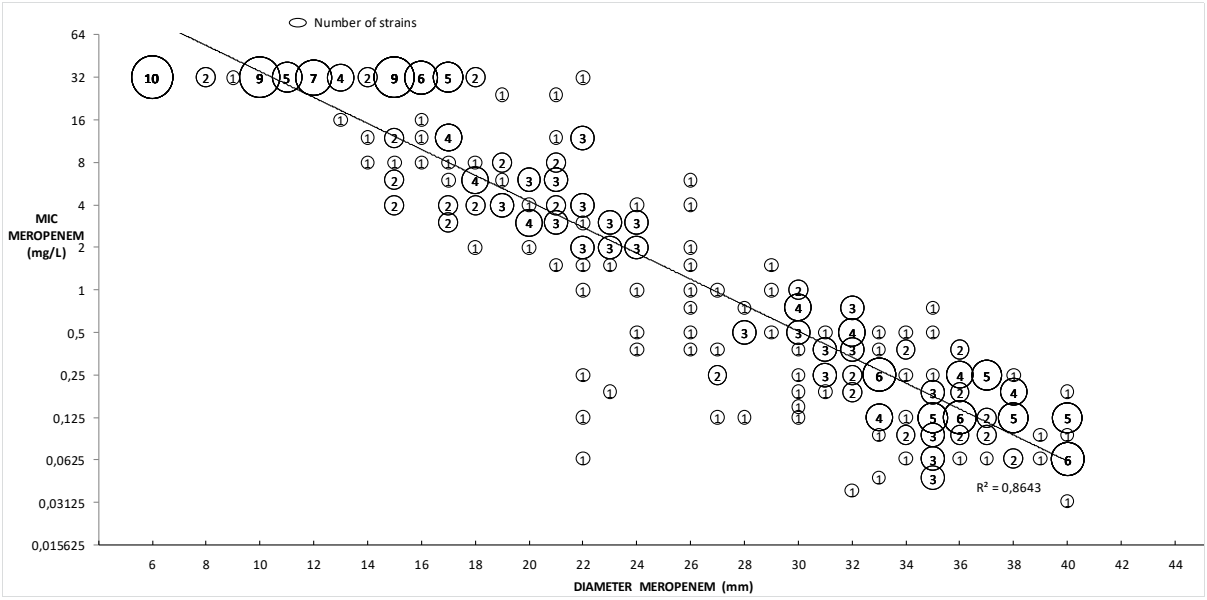
Figure 1. Corrélation entre les concentrations minimales inhibitrices et les diamètres d'inhibition pour l'imipénème (A), le méropénème (B) et le doripénème (C), selon les recommandations du CA-SFM pour l'ensemble des souches de *P. aeruginosa* étudiées (n=311). Les lignes en pointillé représentent les concentrations critiques selon le CA-SFM/EUCAST et celles constituées de traits et de points représentent les valeurs des diamètres critiques selon le CA-SFM. Le nombre de souches pour chaque valeur est noté dans un cercle.

Figure 1. Regression line and scattergram of (A) imipenem, (B) meropenem, and (C) doripenem minimum inhibitory concentrations (MICs) versus zone diameter breakpoints recommended by the CA-SFM for all isolates of *P. aeruginosa* included in the study (n=311). The broken lines represent the CA-SFM/EUCAST MIC breakpoint values and the dot lines represent the diameter breakpoint values recommended by the CA-SFM. The number of strains at each point is mentioned in a circle at scale.

A



B


Number of strains
MIC MEROPENEM (mg/L)
64
32
16
8
4
2
1
0,5
0,25
0,125
0,0625
0,03125
0,015625
6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40 42 44
DIAMETER MEROPENEM (mm)
R² = 0,8643

C

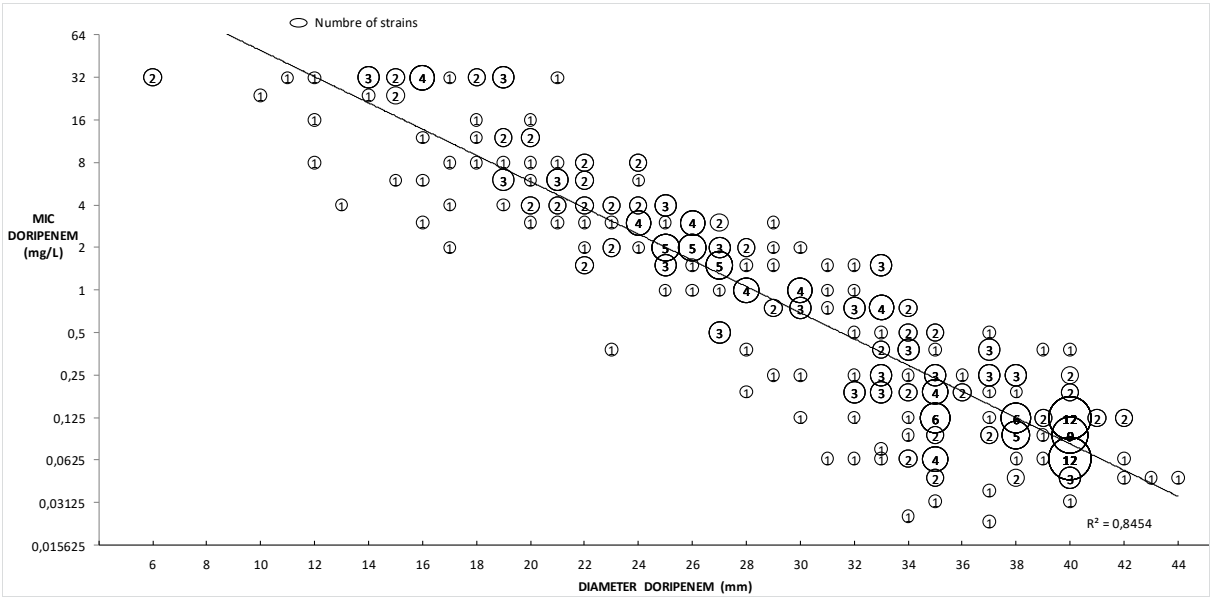
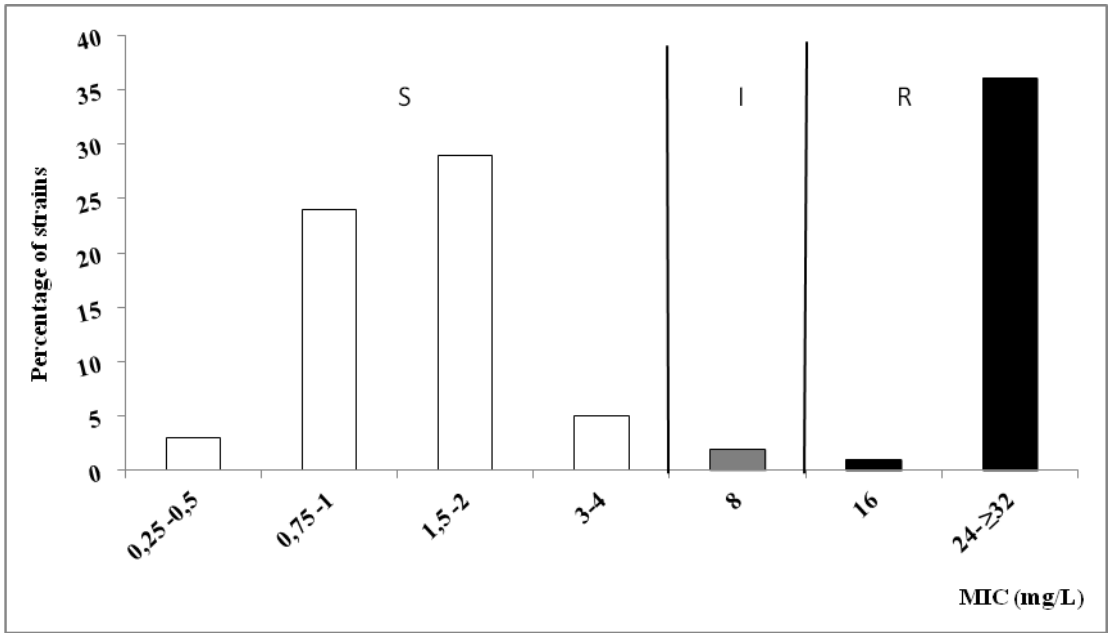

Numbre of strains
MIC DORIPENEM (mg/L)
64
32
16
8
4
2
1
0,5
0,25
0,125
0,0625
0,03125
0,015625
6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40 42 44
DIAMETER DORIPENEM (mm)
R² = 0,8454

Figure 2. Histogrammes de répartition (%) des CMI de l'imipénème (A), du méropénème (B) et du doripénème (C) vis-à-vis des souches de *P. aeruginosa* isolées lors des premiers épisodes de PAVM chez les 170 patients.

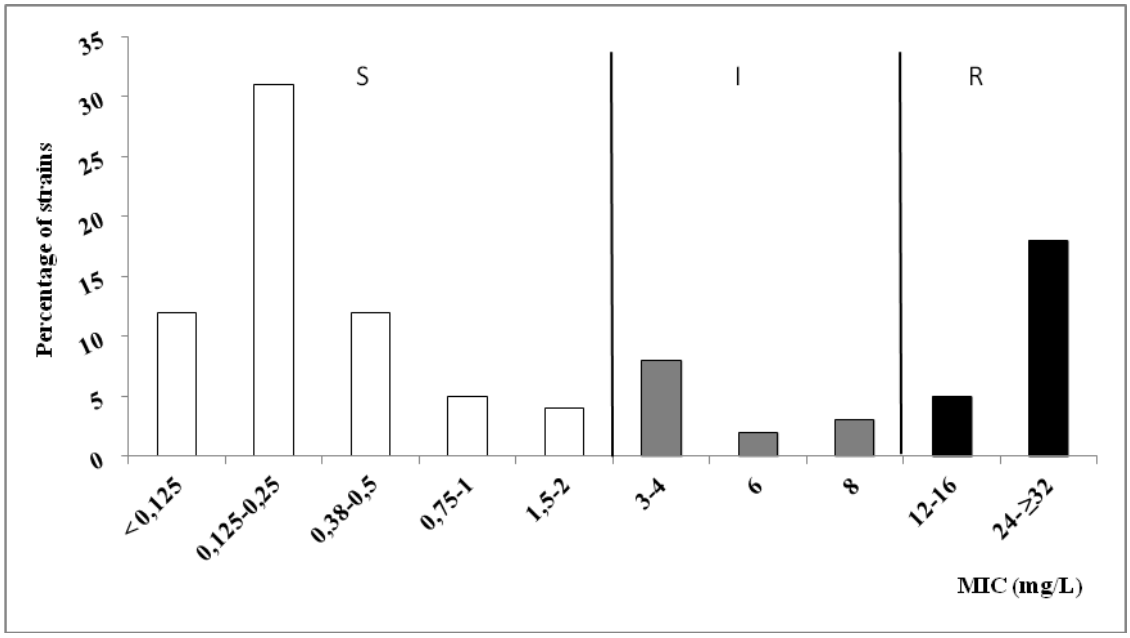
Les souches sensibles sont représentées en blanc, les souches intermédiaires en gris et les souches résistantes en noir selon les concentrations critiques du CA-SFM/EUCAST (représentées par des lignes).

Figure 2. Distribution (%) of the MICs of imipenem (A), meropenem (B) and doripenem (C) against the *P. aeruginosa* strains recovered from the first VAP per patient (n=170). Susceptible strains are represented in white, intermediate strains in grey and resistant strains in black according to the CA-SFM/ EUCAST breakpoints (represented by the lines).

A. Imipenem



B. Meropenem


Percentage of strains
35
30
25
20
15
10
5
0
S
I
R
<0,125
0,125-0,25
0,38-0,5
0,75-1
1,5-2
3-4
6
8
12-16
24-≥32
MIC (mg/L)

C. Doripenem

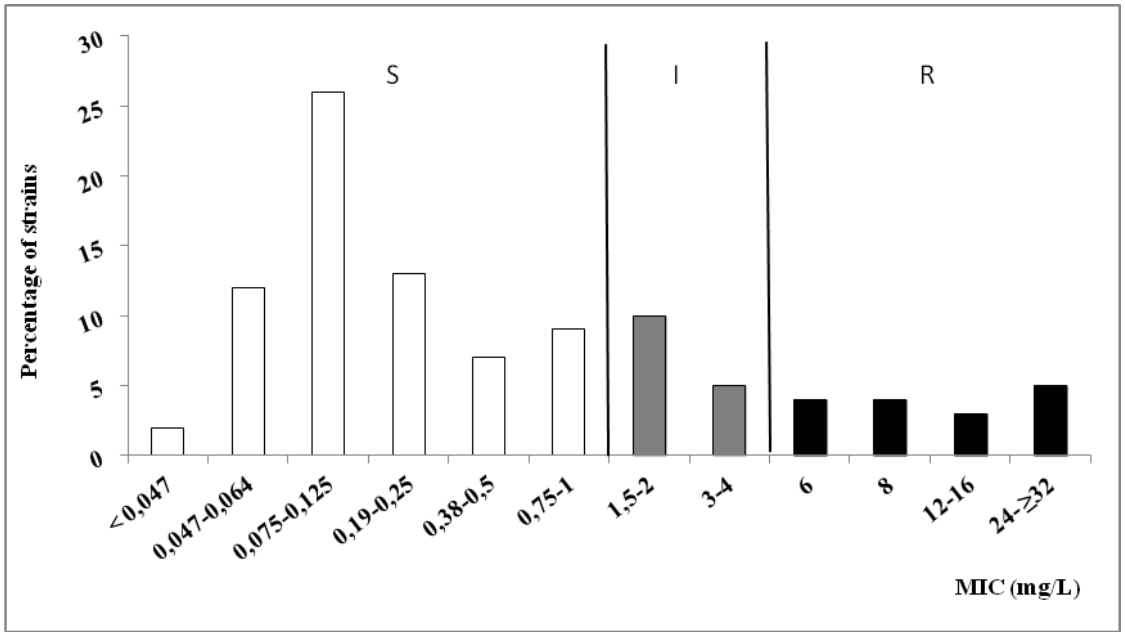
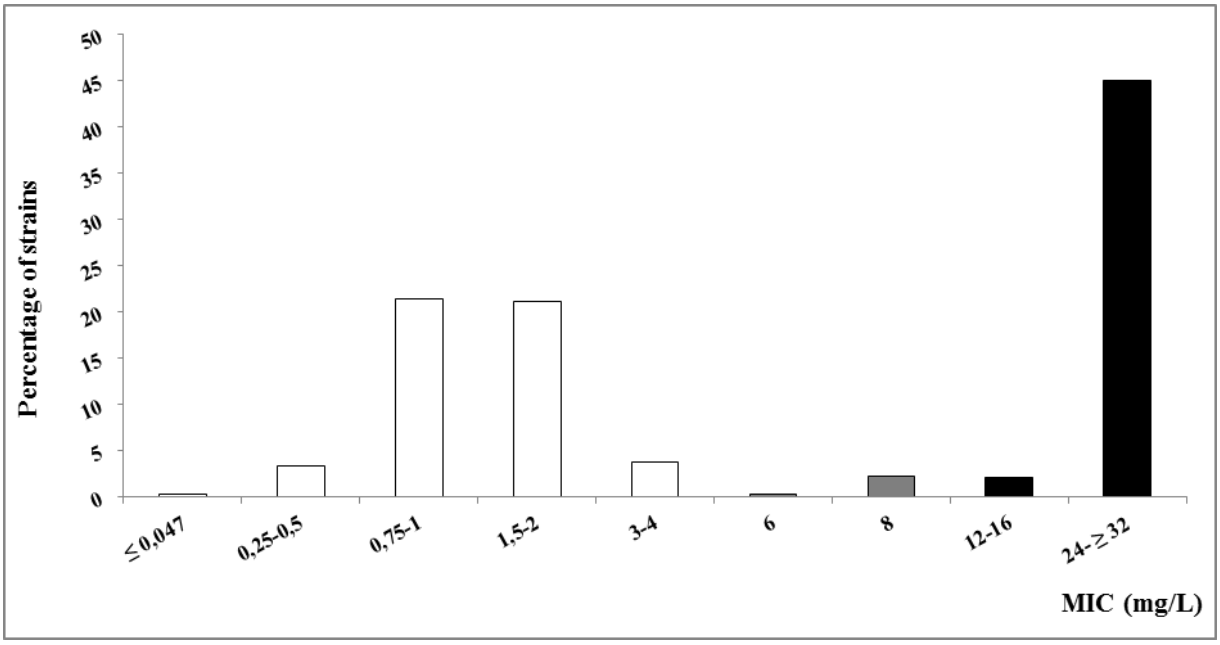

Percentage of strains
30
25
20
15
10
5
0
S
I
R
<0,047
0,047-0,064
0,075-0,125
0,19-0,25
0,38-0,5
0,75-1
1,5-2
3-4
6
8
12-16
24-≥32
MIC (mg/L)

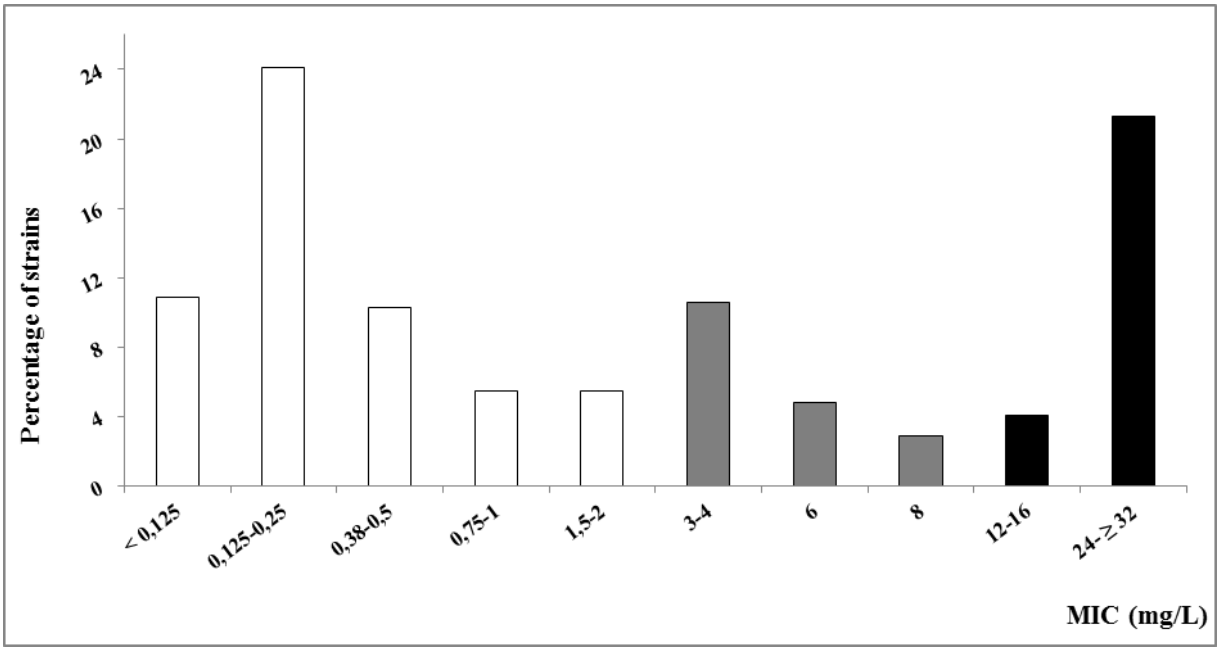
Figure 3. Histogrammes de répartition (%) des CMI de l'imipénème (A), du méropénème (B) et du doripénème (C) vis-à-vis des 311 souches de *P. aeruginosa* incluses dans cette étude.
Les souches sensibles sont représentées en blanc, les souches intermédiaires en gris et les souches résistantes en noir selon les concentrations critiques du CA-SFM/EUCAST (représentées par des lignes).

Figure 3. Distribution (%) of the MICs of imipenem (A), meropenem (B) and doripenem (C) against all *P. aeruginosa* strains included in the study (n=311). Susceptible strains are represented in white, intermediate strains in grey and resistant strains in black according to the CA-SFM/ EUCAST breakpoints (represented by the lines).

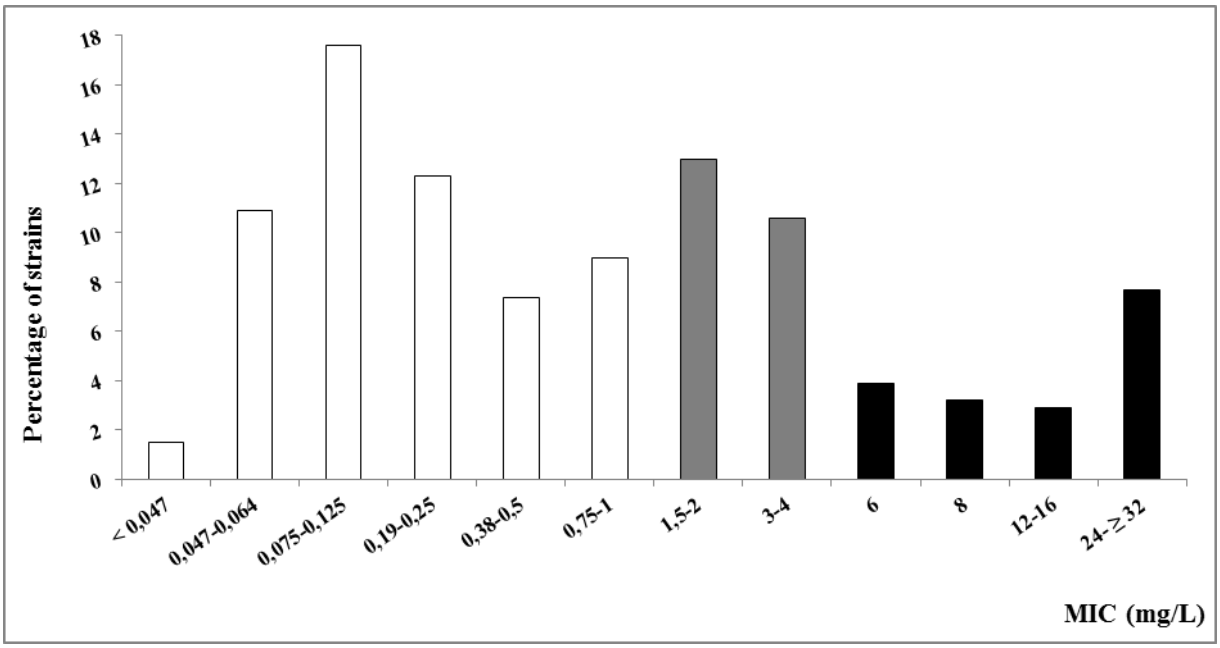
A. Imipenem



B. Meropenem


Percentage of strains
0
4
8
12
16
20
24
< 0,125
0,125-0,25
0,38-0,5
0,75-1
1,5-2
3-4
6
8
12-16
24-≥32
MIC (mg/L)

C. Doripenem


Percentage of strains
0
2
4
6
8
10
12
14
16
18
< 0,047
0,047-0,064
0,075-0,125
0,19-0,25
0,38-0,5
0,75-1
1,5-2
3-4
6
8
12-16
24-≥32
MIC (mg/L)