

Karbapenemler

In-vitro aktivite

Karbapenem sınıflaması

GRUP 1

Karbapenemler

(Nonfermentative gram-negative basillere karşı sınırlı aktivite, toplum kökenli infeksiyonlar için uygun)

GRUP 2

Karbapenemler

(Nonfermentative gram-negative basillere karşı da etkili - nosokomial infeksiyonlar için uygun)

GRUP 3

Karbapenemler

(Grup 2 ye ek olarak MRSA aktivitesi)

Ertapenem

Panipenem

Imipenem

Meropenem

Biapenem

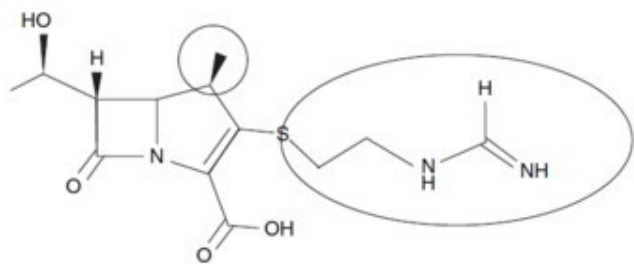
Doripenem

CS-023

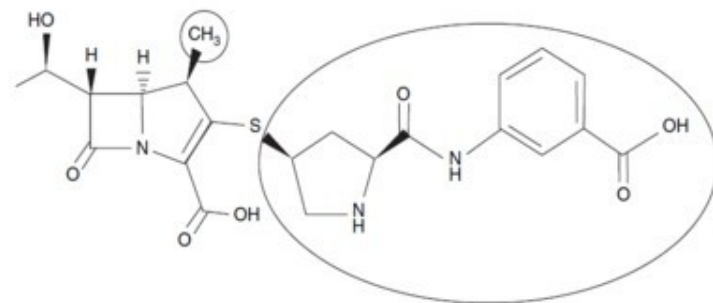
(araştırma aşamasında)

Carbapenem core

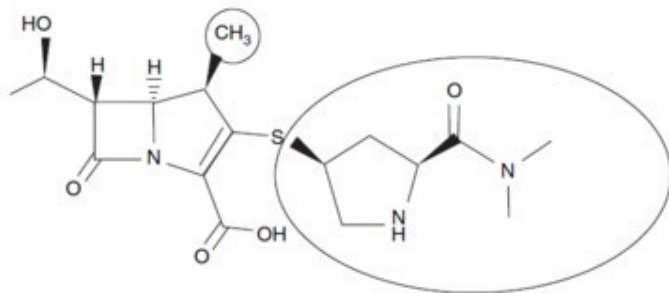
Side chain



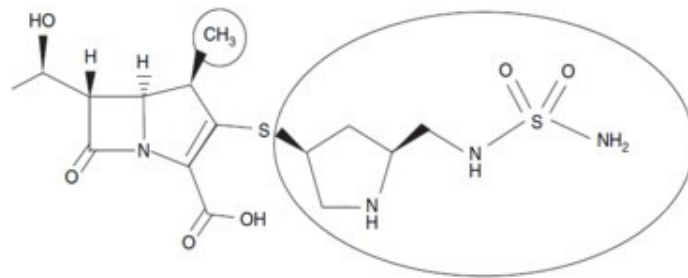
Imipenem



Ertapenem



Meropenem



Doripenem

Doripenem

- Gram-pozitiflere karşı meropeneme göre 2-4X düşük MİK
- *E.faecalis*'e karşı IMP'e benzer şekilde aktivite var, meropenemde yok
- Enterobacteriaceae'a karşı meropeneme çok benzer aktivite, imipenemden iyi
- *P.aeruginosa*'a karşı MİK değerleri meropenemden 1 dilüsyon daha düşük
- Anaeroblara karşı MİK₉₀ 1 µg/mL, *C.difficile* 2-4 µg/mL

Karbapenemler – in vitro aktivite

Gram pozitifler

Organism	No. of isolates ^b	Range of MIC ₉₀ values (mg/L) ^a		
		DOR	MEM	IPM
<i>Enterococcus</i> spp.	310	>32	>32	>8–>32
<i>E. faecalis</i>	141	4–16	8–16	2–4
<i>E. faecium</i>	21	>32	>32	>32
<i>Staphylococcus aureus</i> ^c	12 724	0.03–≤0.06	0.12–0.125	0.03–≤0.5
MRSA	1 391	8–32	8–>32	8–>32
<i>S. epidermidis</i>	15	2	4	0.5
methicillin or oxacillin susceptible	39	0.03	0.06	≤0.015
oxacillin resistant	17	4	8	2
<i>Streptococcus pneumoniae</i> ^c	8 514	≤0.008–1	≤0.008–1	≤0.008–1
penicillin intermediate or resistant	1 562	0.25–1	0.5–1	0.12–2

Karbapenem grup özelliği olarak

- *Stenotrophomonas maltophilia*,
- *Chryseobacterium indologenes*,
- *Elizabethkingia meningoseptica*
(*Chryseobacterium meningosepticum*),
- *Mycobacteria*
- *Enterococcus faecium*

dirençli

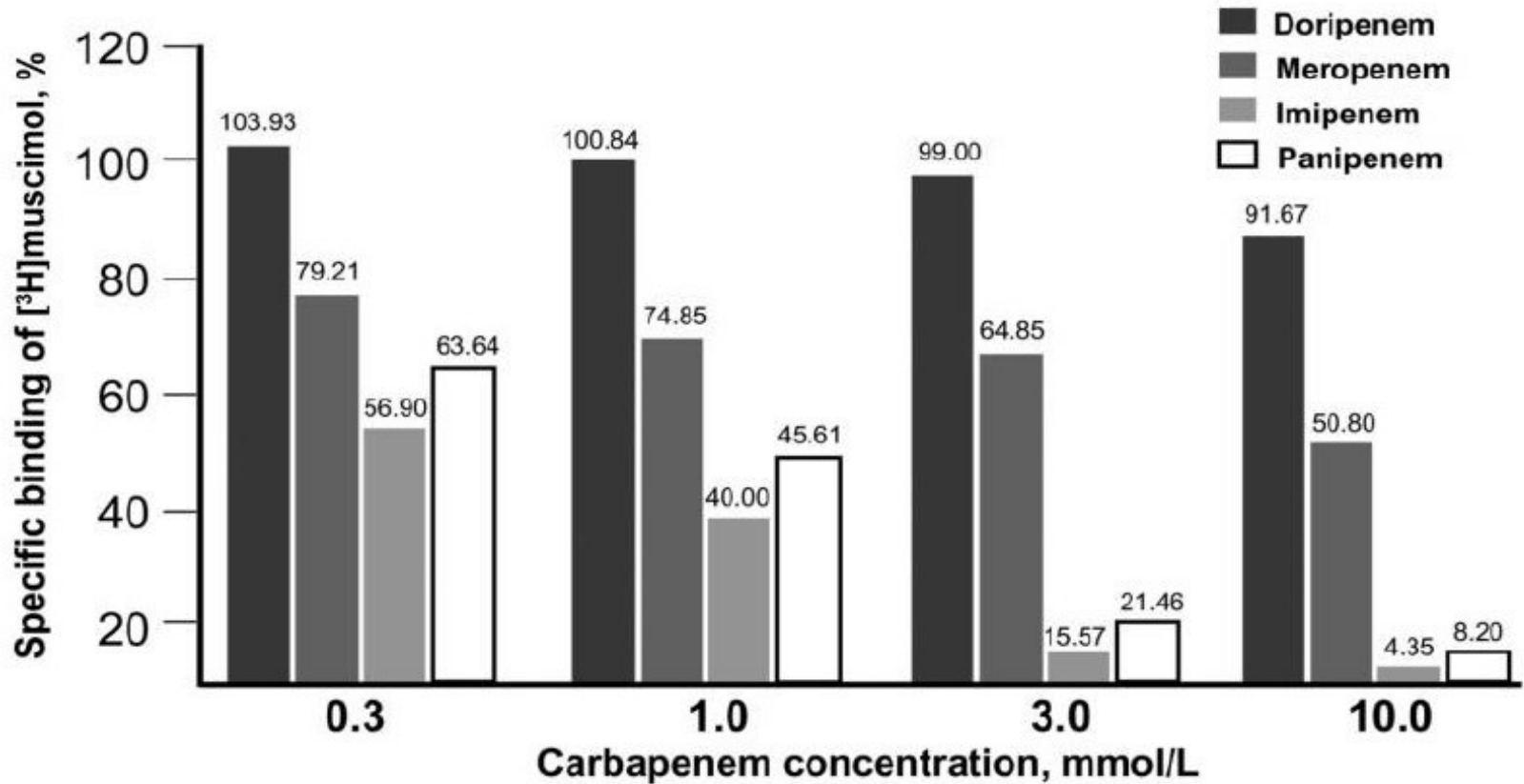
- İn-vitro olarak *P.aeruginosa*'da direnç oluşturma potansiyeli – meropeneme göre daha düşük

Antimicrob Agents Chemother 2004,;48:3086–3092.

J Antibiot (Tokyo) 2006;59:220–228.

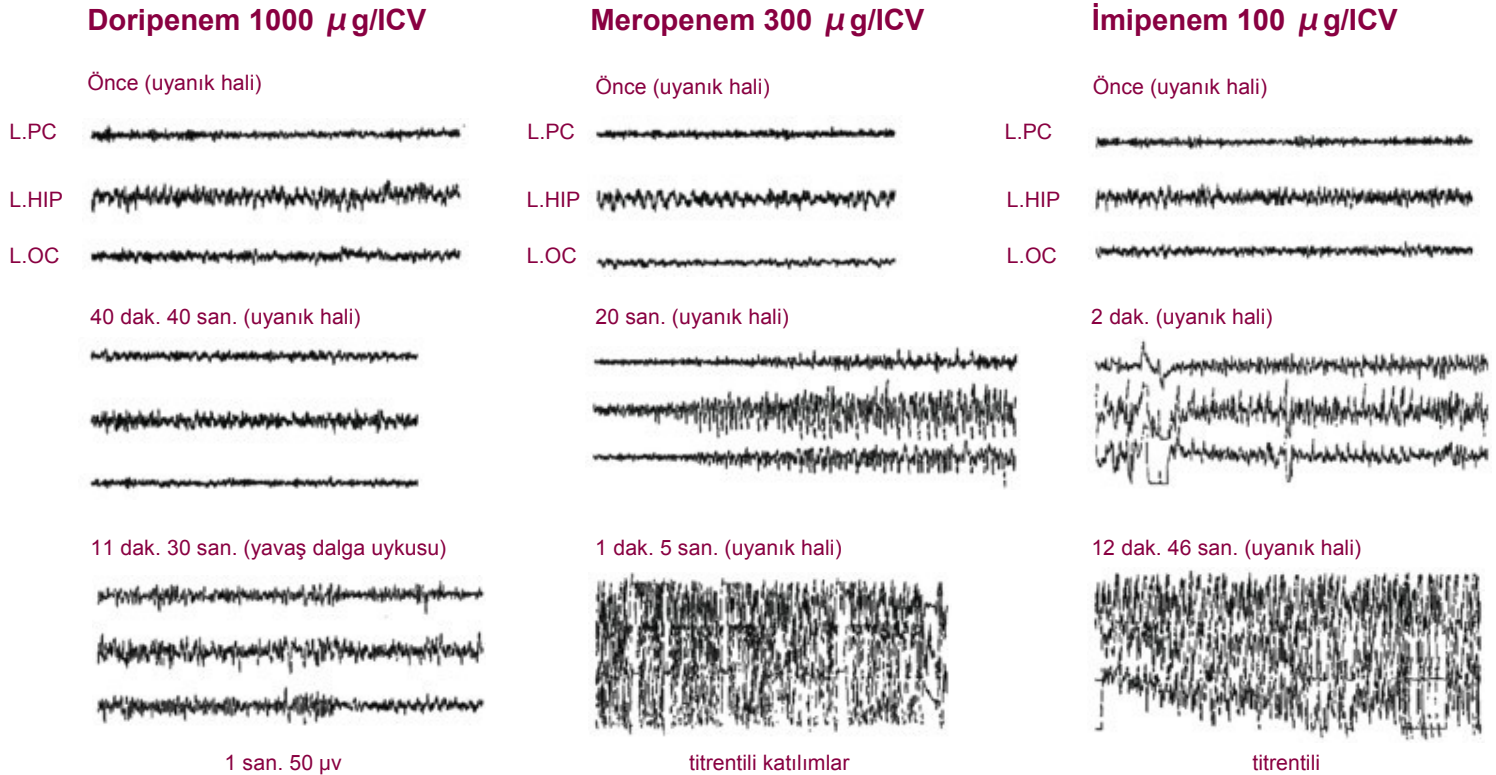
IMP ve MER'le karşılaştırıldığında daha düşük konvülsiyona yol açma potansiyeli

Horiuchi M, Toxicology 2006;222:114–124.



Doripenem İmipenem/Silastatine Göre SSS Yan Etkileri İle İlgili Olarak Daha İyi Bir Güvenlik Profiline Sahiptir.

Köpeklerde intraserebroventikular enjeksiyon sonrası EEG şablonu



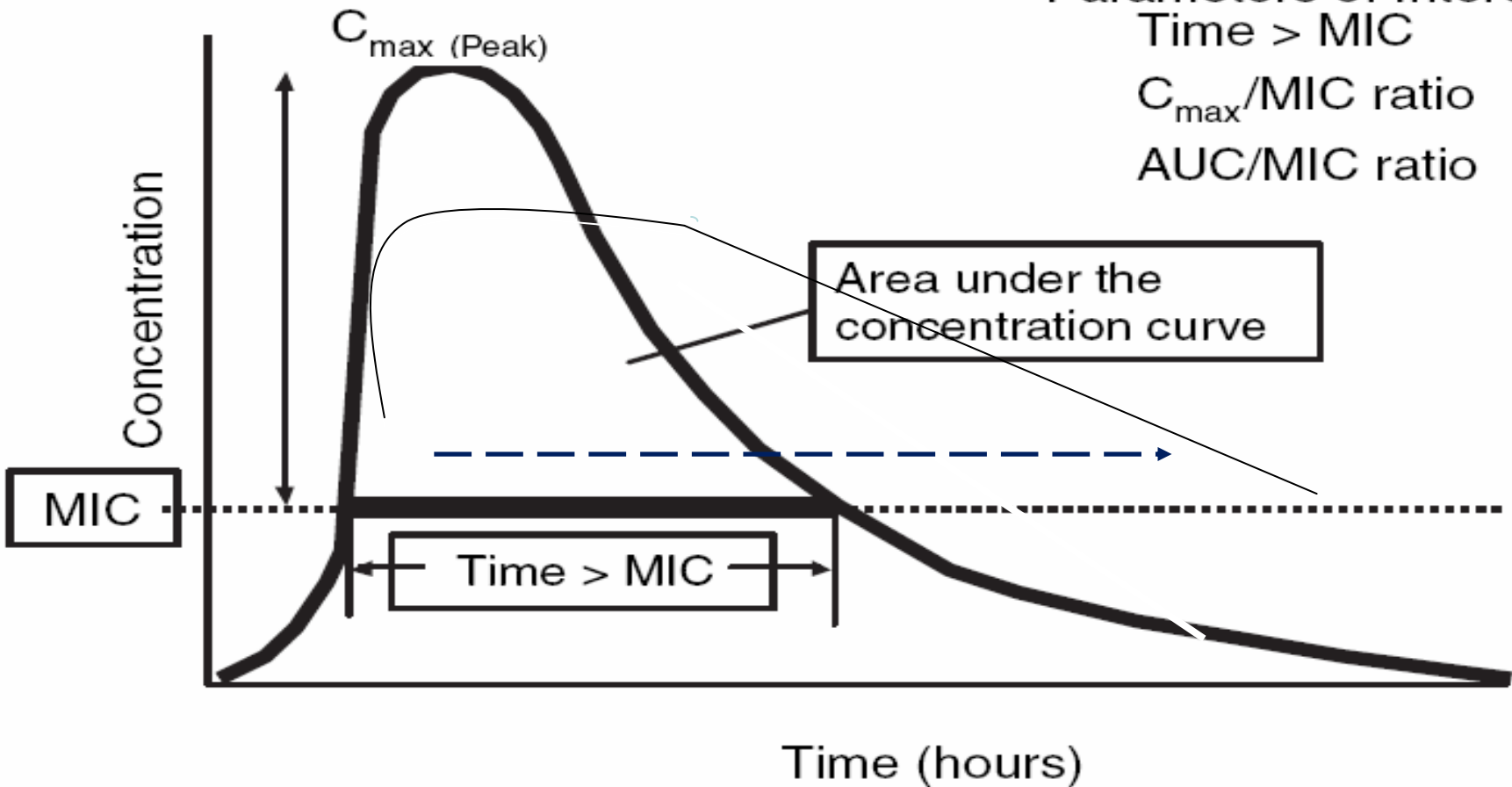
Karbapenem - Farmakoloji

Karakteristik	İmipenem	Meropenem	Ertapenem	Doripenem
Yarı ömür	1 saat	1 saat	4 saat	1 saat
Proteine bağlanma	% 20	% 2	% 85-95	% 9
Renal atılım	% 70	% 70	% 80	% 60-75
Oda ısısında sıvılarda stabilite	4 saat	6 saat	6 saat	12 saat

Prolonged infusions

$$T > \text{MIC} \uparrow$$

Parameters of Interest:
Time > MIC
 $C_{\text{max}}/\text{MIC}$ ratio
AUC/MIC ratio



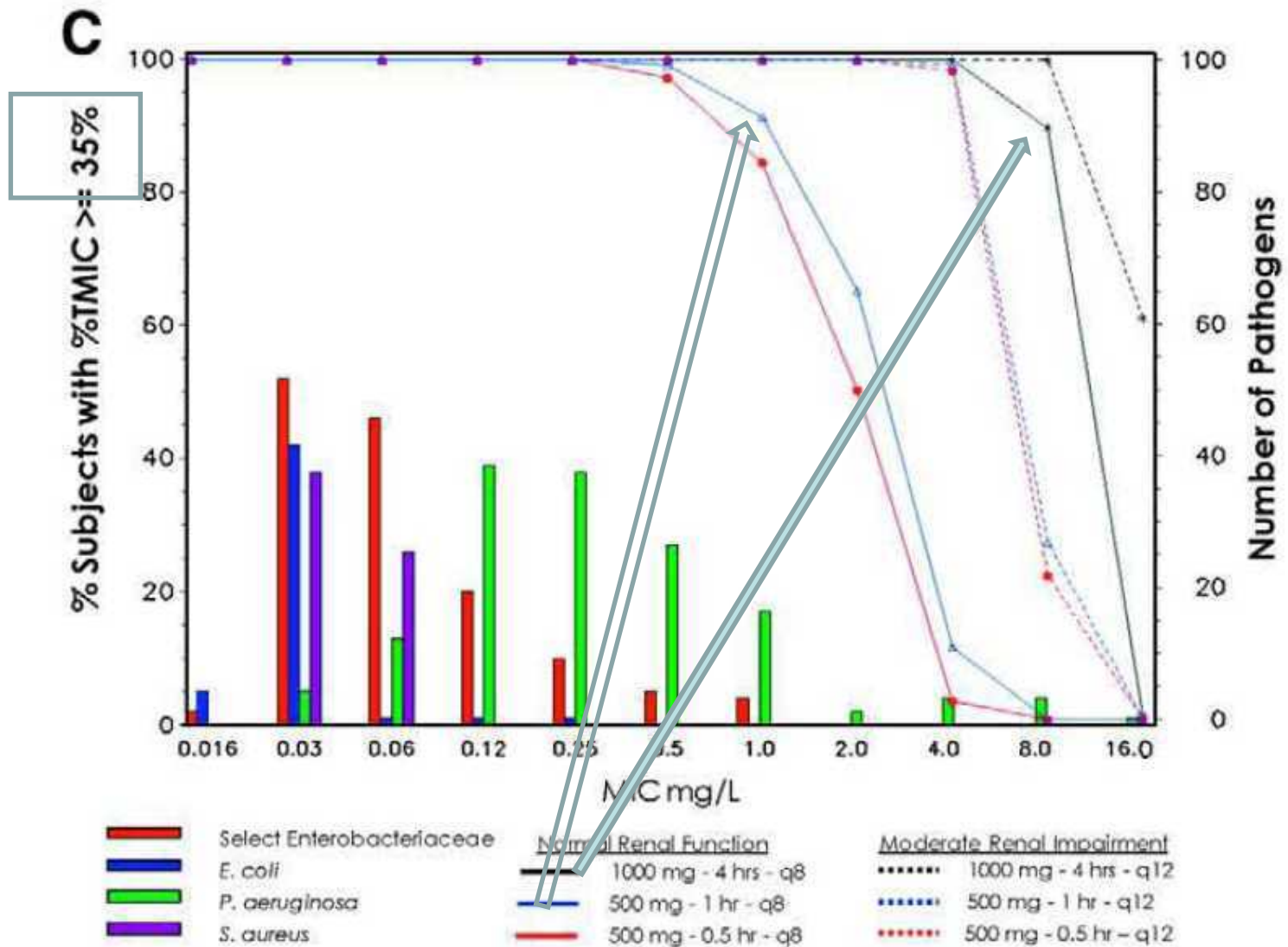
Doz
Renal fonksiyon bozukluđu olan hastalarda
(Bütün endikasyonlar)

Kreatinin klerensi	Doz	Sıklık	infüzyon süresi
> 50 mL/dk	Doz ayarlaması gerektirmez.		
30 - 50 mL/dk	250 mg	8 saatte bir	1 saat
> 10 - < 30 mL/dk	250 mg	12 saatte bir	1 saat

In-vitro duyarlık sınırları

	FDA	CLSI			EUCAST			
	Doripenem	Ertapenem	Imipenem	Meropenem	Doripenem	Ertapenem	Imipenem	Meropenem
Enterobacteriaceae	$S \leq 0.5$	$\leq 2 / > 4$	$\leq 4 / > 8$	$\leq 4 / > 8$	$\leq 1 / > 4$	$\leq 0.5 / > 1$	$\leq 2 / > 8$	$\leq 2 / > 8$
<i>Pseudomonas</i>	$S \leq 2$	Not active	$\leq 4 / > 8$	$\leq 4 / > 8$	$\leq 1 / > 4$	Not active	$\leq 4 / > 8$	$\leq 2 / > 8$
<i>Acinetobacter</i>	$S \leq 1$	Not active	$\leq 4 / > 8$	$\leq 4 / > 8$	$\leq 1 / > 4$	Not active	$\leq 2 / > 8$	$\leq 2 / > 8$
Enterococci	Not set				$\leq 1 / > 4^a$	Not active	$\leq 4 / > 8$	Not active
Staphylococci		$\leq 2 / > 4^b$	$\leq 4 / > 8^b$	$\leq 4 / > 8^b$	As oxacillin			
Streptococci	$S \leq 0.12^c$	Not set			$\leq 1 / > 1^d$	$\leq 0.5 / > 0.5$	$\leq 2 / > 2$	$< 2 / > 8$
Anaerobes	$S \leq 1$	$\leq 2 / > 4$	$\leq 4 / > 8$	$\leq 4 / > 8$	$\leq 1 / > 1$	$\leq 1 / > 1$	$< 2 / > 8$	$< 2 / > 8$

PD hedefler



Activity of doripenem and comparator antimicrobial agents tested against *E. coli*, *Klebsiella* spp. and *P. mirabilis* displaying positive criteria for an ESBL phenotype (i.e., MIC ≥ 2 $\mu\text{g/mL}$ for aztreonam or ceftazidime or ceftriaxone)

Organism (no. tested)/ antimicrobial agent	MIC ($\mu\text{g/mL}$)		Cumulative percentage inhibited at MIC					Percentage by category ^a
	50%	90%	≤ 0.5	1	2	4	8	Susceptible/resistant
<i>E. coli</i> (ESBL phenotype, 2363)								
Doripenem	≤ 0.06	≤ 0.06	99.0	99.3	99.5	99.8	99.9	99.0/–
Imipenem	≤ 0.5	≤ 0.5	97.1	99.1	99.5	99.6	99.8	99.6/0.2
Meropenem	≤ 0.12	≤ 0.12	98.9	99.1	99.3	99.5	99.8	99.5/0.2
Ertapenem	≤ 0.06	0.25	95.6	98.3	98.8	99.1	99.4	98.8/0.9
<i>E. coli</i> (non-ESBL phenotype, 15 478)								
Doripenem	≤ 0.06	≤ 0.06	>99.9	100.0	–	–	–	>99.9/–
Imipenem	≤ 0.5	≤ 0.5	99.6	>99.9	>99.9	100.0	–	100.0/0.0
Meropenem	≤ 0.12	≤ 0.12	>99.9	>99.9	100.0	–	–	100.0/0.0
Ertapenem	≤ 0.06	≤ 0.06	>99.9	>99.9	>99.9	100.0	–	>99.9/<0.1
<i>K. pneumoniae</i> (ESBL phenotype, 2444)								
Doripenem	≤ 0.06	1	89.6	91.5	92.8	94.9	97.2	89.6/–
Imipenem	≤ 0.5	1	84.9	90.4	92.5	93.9	95.4	93.9/4.6
Meropenem	≤ 0.12	1	89.3	90.7	92.7	93.7	95.4	93.7/4.6
Ertapenem	0.12	4	85.0	87.8	89.8	91.5	93.4	89.8/8.5
<i>K. pneumoniae</i> (non-ESBL phenotype, 5387)								
Doripenem	≤ 0.06	≤ 0.06	>99.9	>99.9	>99.9	>99.9	100.0	>99.9/–
Imipenem	≤ 0.5	≤ 0.5	97.4	99.7	100.0	–	–	100.0/0.0
Meropenem	≤ 0.12	≤ 0.12	>99.9	>99.9	>99.9	100.0	–	100.0/0.0
Ertapenem	≤ 0.06	≤ 0.06	99.8	>99.9	>99.9	>99.9	>99.9	>99.9/<0.1

2003-2007

In vitro activities of β -lactam antimicrobials against *P. aeruginosa*, other nonfermentative bacilli, and *Aeromonas* spp. (14 979 isolates)

Organism (no. tested)/ antimicrobial agent	MIC ($\mu\text{g/mL}$)		Cumulative % inhibited at MIC ($\mu\text{g/mL}$) of:					% by category ^a
	50%	90%	≤ 0.5	1	2	4	8	Susceptible/resistant
<i>P. aeruginosa</i> (9256)								
Doripenem	0.5	8	54.8	69.2	77.2	85.9	93.3	77.2/- ^b
Meropenem	0.5	>8	51.2	65.9	73.3	80.0	87.6	80.0/12.4
Imipenem	2	>8	10.1	49.0	70.7	76.0	83.8	76.1/16.2
Ceftazidime	4	>16	- ^c	9.8	47.2	73.6	78.8	73.6/21.2
Cefepime	4	>16	1.6	14.2	43.8	61.4	75.9	75.9/12.6
Ceftriaxone	>32	>32	0.4	0.8	1.4	2.8	6.7	6.7/74.0
Piperacillin/tazobactam	8	>64	1.5	2.4	6.7	39.6	58.0	81.8/18.2
Aztreonam	8	>16	2.1	3.3	8.3	46.3	64.0	64.1/21.8

In vitro activity of doripenem tested against *P. aeruginosa* collected during 2003 to 2007, listed by source region

Region of isolation (no. tested)	Cumulative percentage inhibited at MIC ($\mu\text{g/mL}$) of				
	≤ 0.5	1	2	4	8
North America (2462)	62.8	77.7	84.9	93.4	98.1
Europe (3026)	55.3	69.1	77.2	86.2	93.4
Asia-Pacific (2121)	52.3	67.8	76.0	82.9	91.1
Latin America (1647)	45.7	58.4	67.2	78.2	88.5
All (9256)	54.8	69.2	77.2	85.9	93.3

64.0 Türkiye

In vitro Activity of Doripenem, Imipenem and Meropenem against Contemporary Gram-Negative Pathogens Circulating in Twelve Countries.

The Comparative Activity of Carbapenem Testing (COMPACT) Study

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Country	No. Centres	No. Isolates	Isolates resistant to at least one carbapenem*		
			No.	Mean %	% Range
Czech Rep	2	117	17	14.5	14.0 - 15.0
Egypt	1	46	13	28.3	-
Estonia	1	56	9	16.1	-
Greece	2	124	21	16.9	0 - 32.3
Italy	12	695	161	23.2	0 - 36.8
Latvia	1	43	6	14.0	-
Poland	1	59	7	11.9	-
Portugal	3	178	37	20.8	19.0 - 21.7
Russia	7	420	142	33.8	28.3 - 41.7
Slovak Rep	2	88	8	9.1	0 - 13.3
Spain	16	915	219	23.9	8.9 - 36.8
Turkey	10	596	182	30.5	21.7 - 40.7
Total	58	3337	822	24.6	0 - 41.7

* Based on the carbapenem Etest result reported by the centre. CLSI break points used for imipenem and meropenem, and FDA break points used for doripenem.

Table 3. Comparative activity of carbapenems

		MIC ₅₀	MIC ₉₀	Range
All Pathogens (n = 3,337)	Doripenem	0.12	16	0.004 - ≥64
	Imipenem	1	≥64	0.008 - ≥64
	Meropenem	0.25	≥64	0.004 - ≥64
<i>Pseudomonas spp.</i> (n = 1,632)	Doripenem	0.5	32	0.004 - ≥64
	Imipenem	2	≥64	0.015 - ≥64
	Meropenem	1	≥64	0.004 - ≥64
Enterobacteriaceae (n = 1,390)	Doripenem	0.03	0.12	0.004 - ≥64
	Imipenem	0.25	0.5	0.008 - ≥64
	Meropenem	0.03	0.12	0.004 - ≥64
Other Gram Negatives* (n = 315)	Doripenem	8	≥64	0.03 - ≥64
	Imipenem	32	≥64	0.06 - ≥64
	Meropenem	16	≥64	0.03 - ≥64
<i>Acintebacter spp.</i> (n = 257)	Doripenem	8	≥64	0.03 - ≥64
	Imipenem	32	≥64	0.06 - ≥64
	Meropenem	16	≥64	0.03 - ≥64

* Including *Acinetobacter spp.*

Pseudomonas (n:1632)

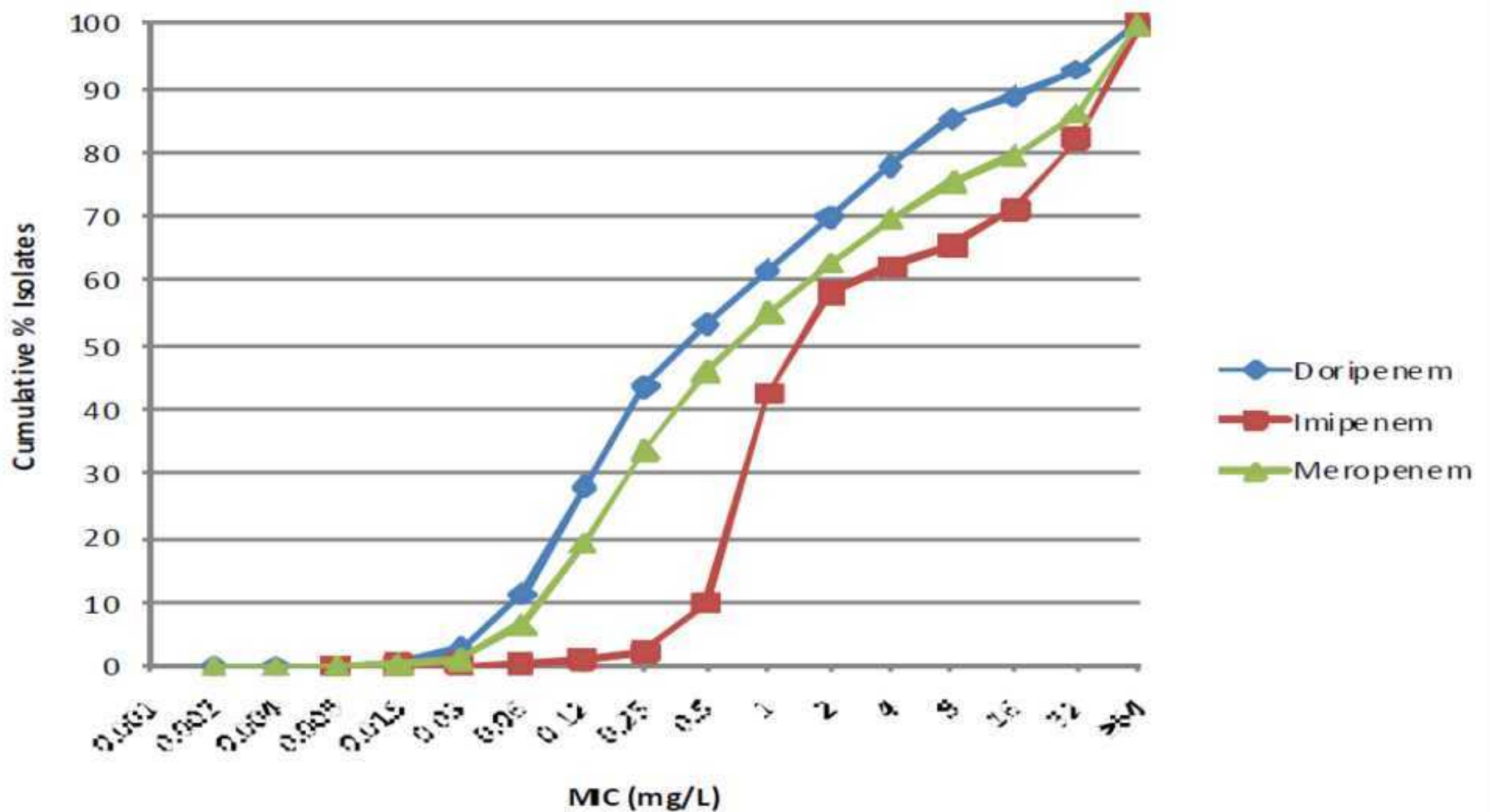


Figure 2. Enterobacteriaceae (n = 1,390)

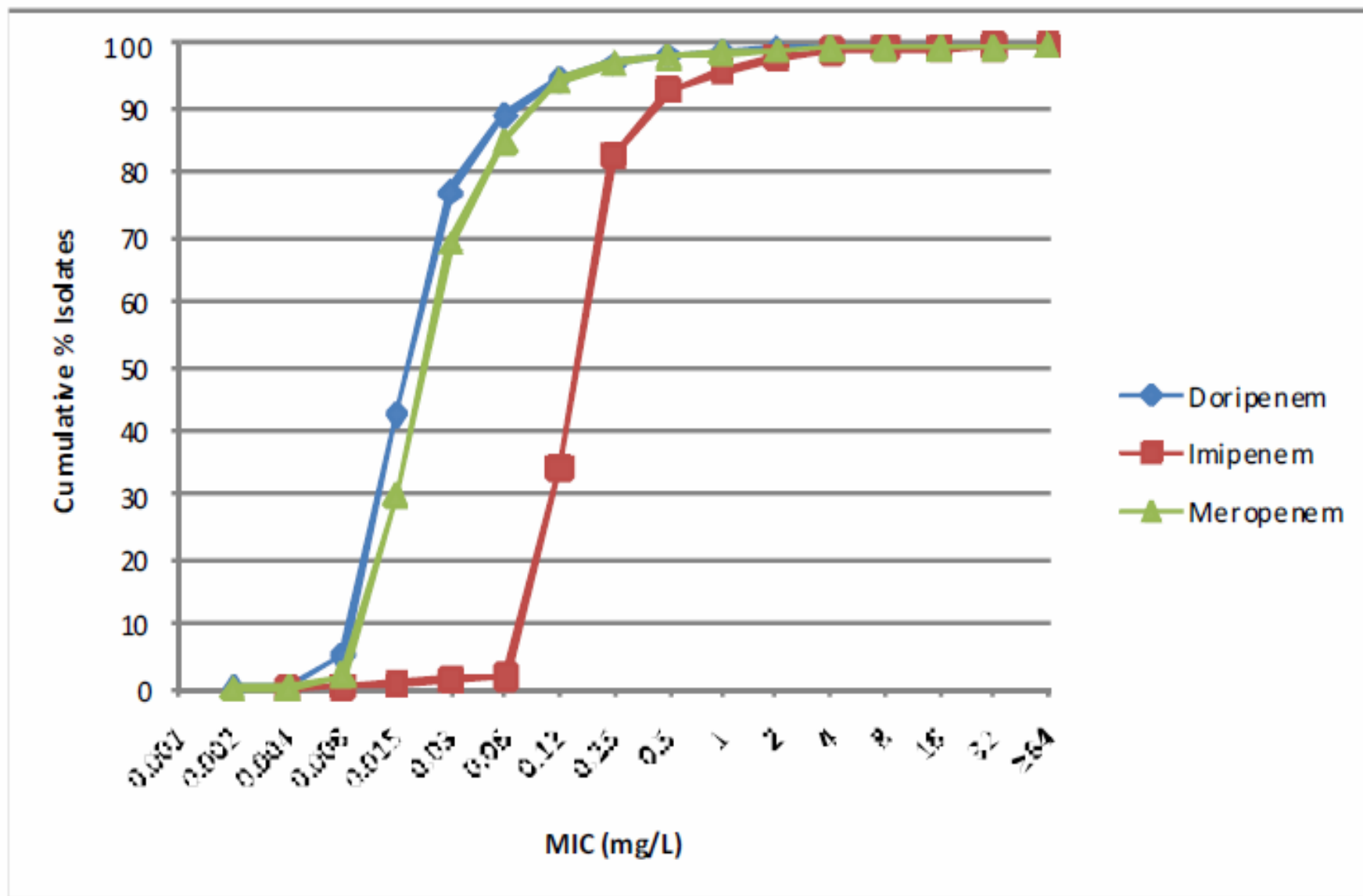


Table 4. Comparative activity of carbapenems by patient type

	ICU				Non-ICU					
	n	MIC (mg/L)			n	MIC (mg/L)				
		MIN	MAX	50%	90%		MIN	MAX	50%	90%
All Pathogens	1,534					1,802				
Doripenem		0.008	0.25	32	≥64		0.004	0.12	8	≥64
Imipenem		0.015	1	≥64	≥64		0.008	0.5	≥64	≥64
Meropenem		0.008	0.5	≥64	≥64		0.004	0.12	32	≥64
<i>Pseudomonas</i> spp.	759					872				
Doripenem		0.015	1	32	≥64		0.004	0.25	16	≥64
Imipenem		0.12	4	≥64	≥64		0.015	2	≥64	≥64
Meropenem		0.03	2	≥64	≥64		0.004	0.5	≥64	≥64
Enterobacteriaceae	570					820				
Doripenem		0.008	0.03	0.12	≥64		0.004	0.03	0.06	16
Imipenem		0.015	0.25	0.5	≥64		0.008	0.25	0.5	≥64
Meropenem		0.008	0.03	0.12	≥64		0.004	0.03	0.12	≥64
Other Gram negatives	205					110				
Doripenem		0.03	8	≥64	≥64		0.03	8	≥64	≥64
Imipenem		0.06	32	≥64	≥64		0.06	32	≥64	≥64
Meropenem		0.06	16	≥64	≥64		0.03	32	≥64	≥64

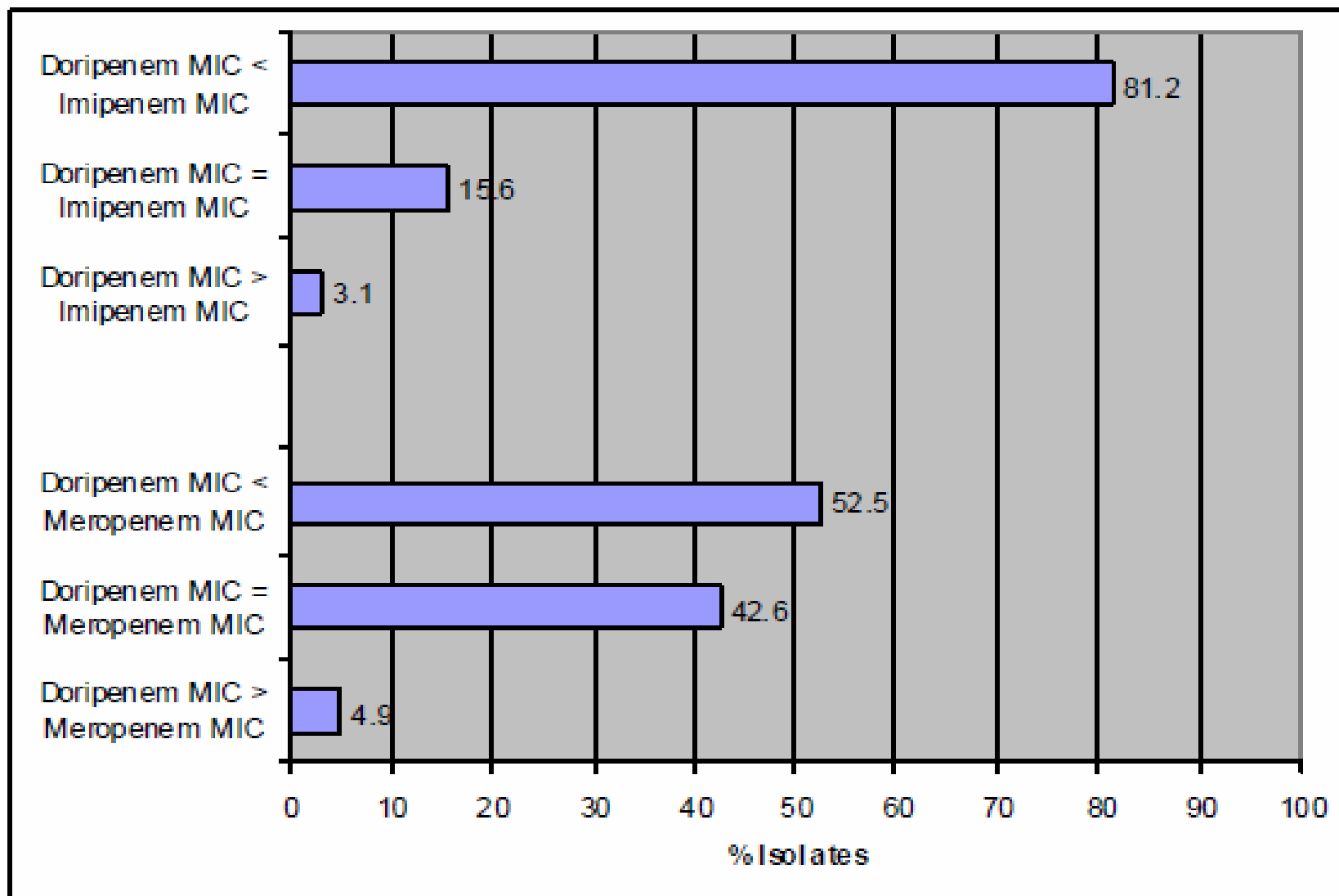
Table 5: Activity of doripenem by infection type

Pathogen	Infection type	n	MIC ₅₀	MIC ₉₀	Range
<i>Pseudomonas spp.</i>	BSI	474	0.25	32	0.03 - ≥64
	cIAI	339	0.5	32	0.015 - ≥64
	NP	819	1	32	0.004 - ≥64
Enterobacteriaceae	BSI	682	0.03	0.06	0.004 - 32
	cIAI	366	0.03	0.12	0.004 - 2
	NP	342	0.03	0.12	0.004 - ≥64**
Other Gram negatives*	BSI	103	8	≥64	0.03 - ≥64
	cIAI	45	8	≥64	0.03 - ≥64
	NP	167	8	≥64	0.03 - ≥64
<i>Acinetobacter spp.</i>	BSI	95	8	≥64	0.06 - ≥64
	cIAI	41	8	≥64	0.03 - ≥64
	NP	121	4	≥64	0.03 - ≥64

* Including *Acinetobacter spp.*

** One *K. pneumoniae* isolate with an MIC of ≥ 64 mg/L to all three carbapenems

Figure 5: Relative activity* of Doripenem vs. imipenem and meropenem against *P. aeruginosa* (n = 1,621)



COMPACT Merkezler – Türkiye

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Dr. Melda Sınırtaş		Dr. Harika Esener	

Metod

Eylül-Aralık 2008 tarihleri arasında izole edilen 60 klinik izolat

Tür	Her Merkez
<i>Pseudomonas aeruginosa</i>	30
Enterobacteriaceae	24
<i>Acinetobacter</i> spp. ve diğer Gram-negatif bakteriler	6
Toplam	60

Çalışmaya alınma kriterleri

İzolatlar komplike intra-abdominal enfeksiyonları, bakteriyemi ya da nozokomiyal pnömonisi (VAP dahil) olan YBÜ hastaları ve YBÜ dışı hastalardan alındı .

Metod

Her merkez E-test kullanarak tüm izolatlar için doripenem, imipenem ve meropenem MİK değerlerini belirledi

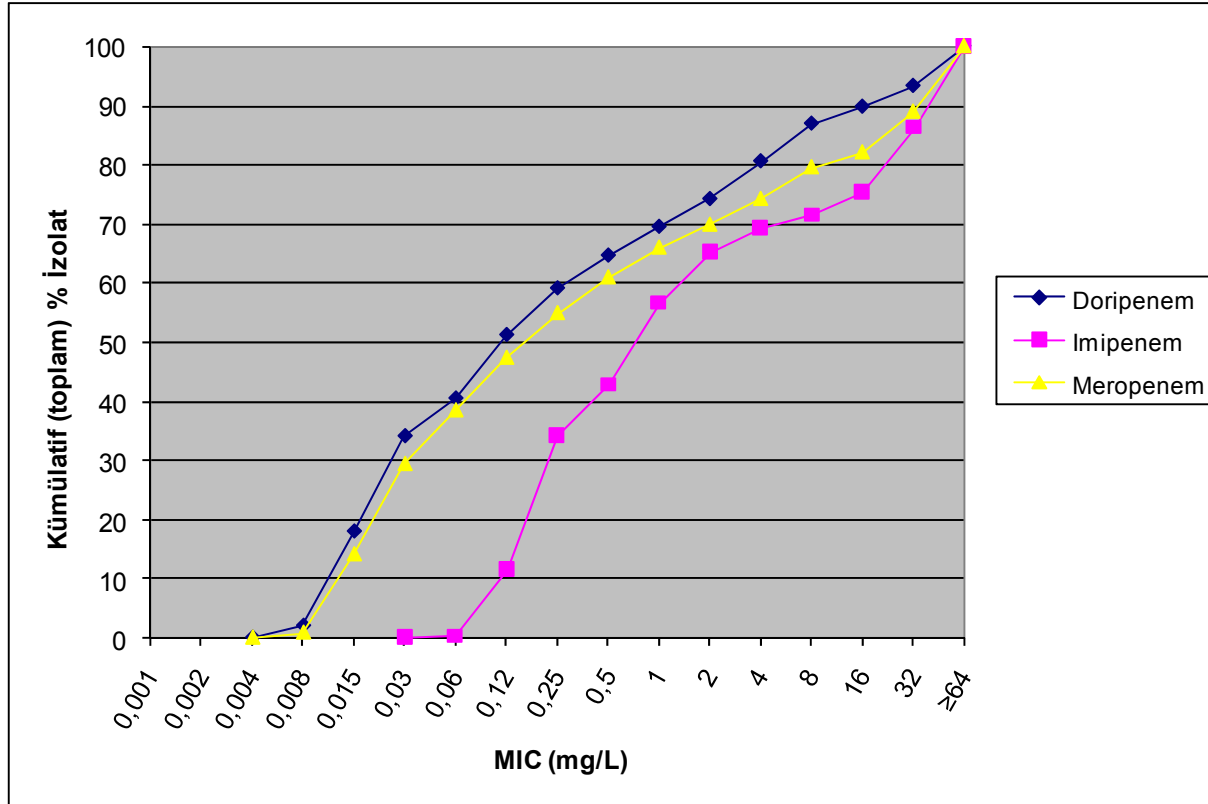
Tüm izolatlar Quotient Bioresearch Ltd'e Ocak 2009 da iletildi.

Karbapenem dirençli izolatların hepsi – diğerlerinin %10 u rastgele seçildi ve MİK değerleri CLSI broth mikrodilüsyon yöntemi ve E-test ile değerlendirildi.

İzolatların Toplanması

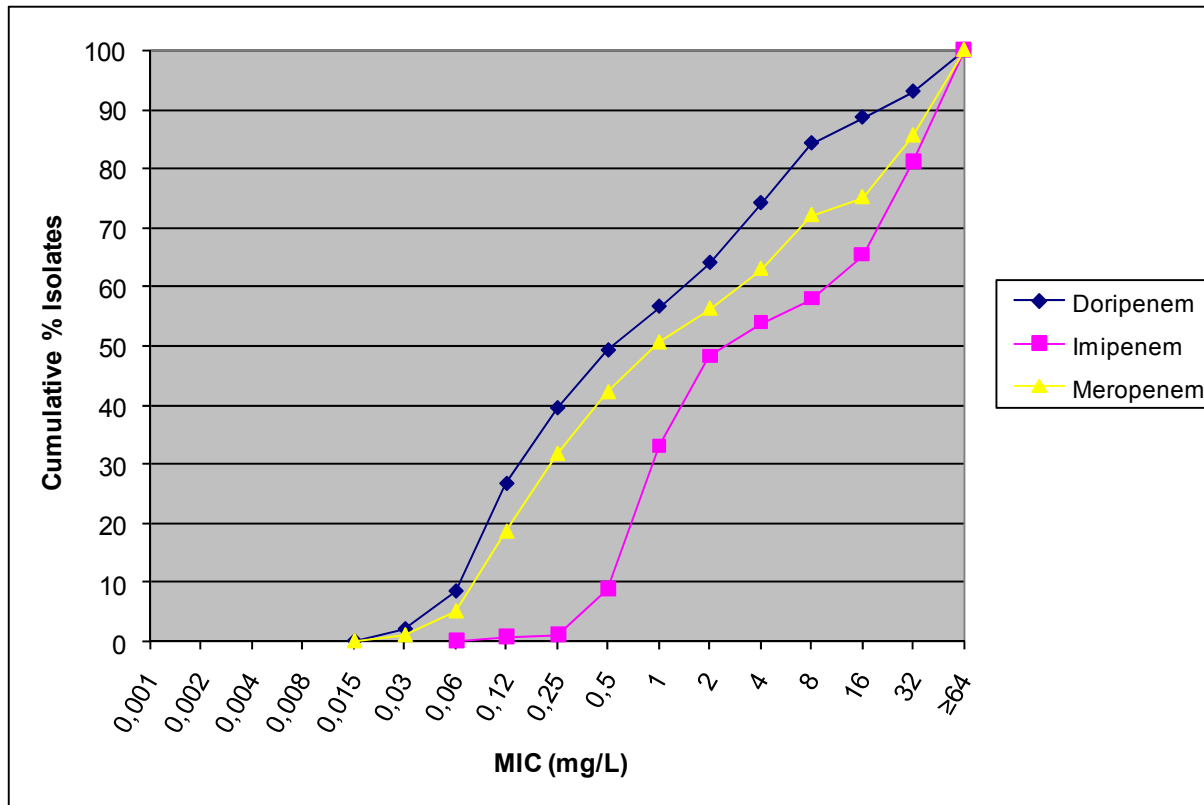
- 10 merkez (toplam 80 merkez)
- 596 adet toplanan uygun izolat (Toplam miktarın % 13.3'ü)
 - % 42.4 Nozokomiyal pnömoni
 - % 40.4 Kan dolaşımı enfeksiyonları
 - %17.1 kCYDI
 - % 51.8 Yoğun bakım ünitesi hastaları
 - % 48.2 Yoğun bakım ünitesi dışı hastalar
- 297 (% 49.8) *Pseudomonas* spp.
 - 293 (% 98.7) *P. aeruginosa*
- 240 (% 40.3) Enterobacteriaceae
 - 115 (% 47.9) *E. coli*
 - 84 (% 35.0) *K. pneumoniae*
- 59 (% 9.9) Diğer gram-negatifler
 - 52 (% 88.1) *A. baumannii*

Tüm Patojenler (n = 596)



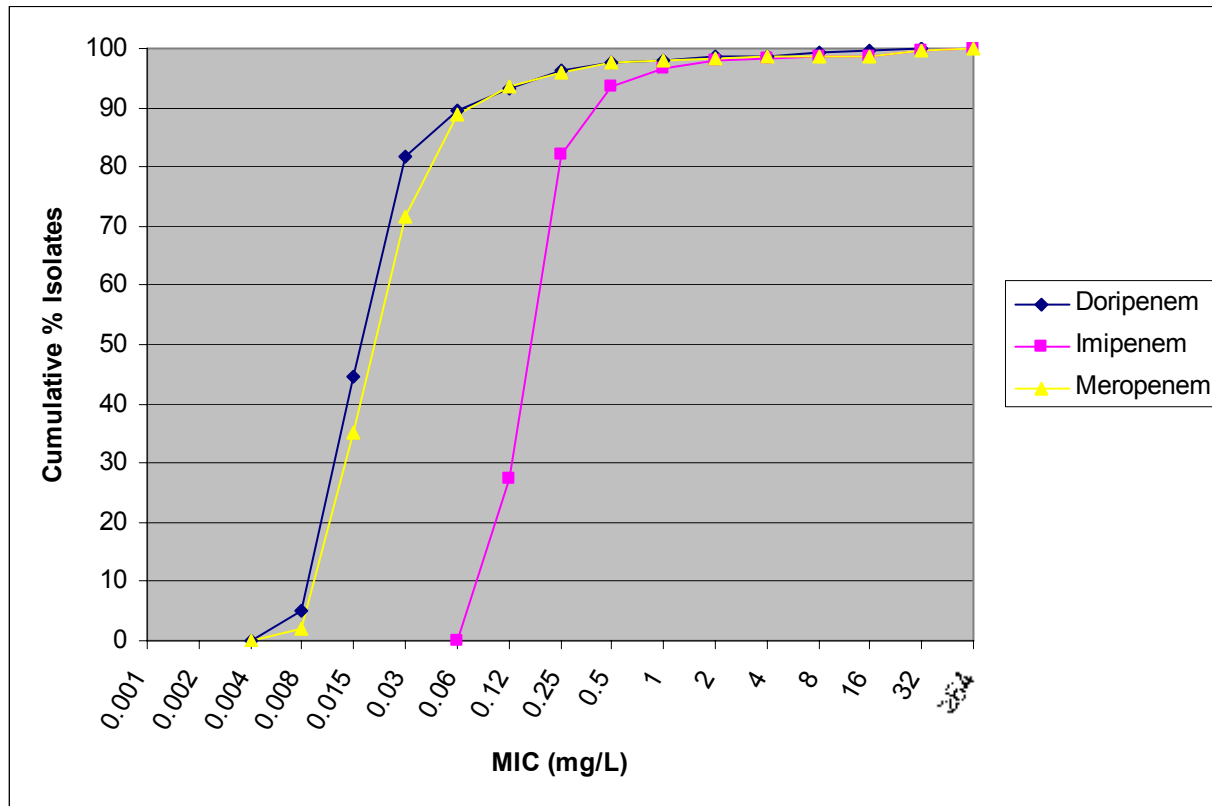
	MIC (mg/L)			
	Min	50%	90%	Max
Doripenem	0.008	0.12	32	≥64
Imipenem	0.06	1	≥64	≥64
Meropenem	0.008	0.25	≥64	≥64

Pseudomonas spp. (n = 297)



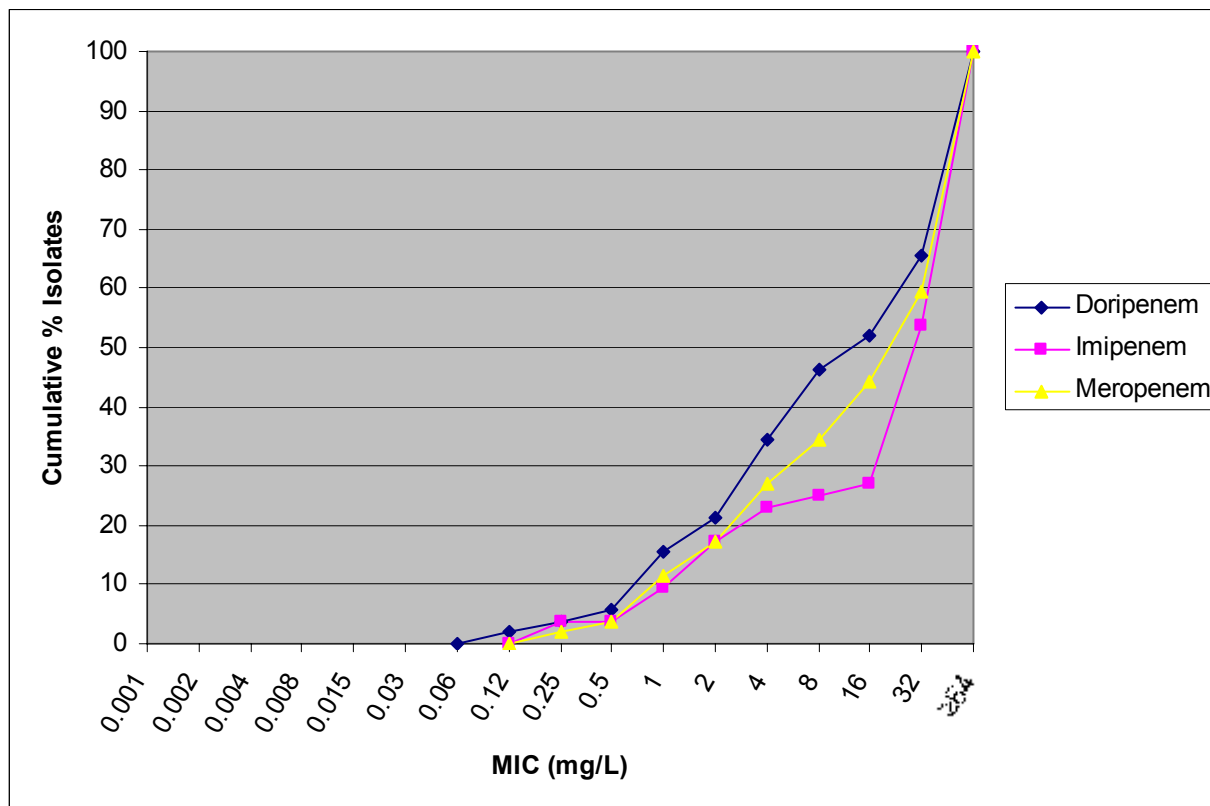
	MIC (mg/L)			
	Min	50%	90%	Max
Doripenem	0.03	1	32	≥64
Imipenem	0.12	4	≥64	≥64
Meropenem	0.03	1	≥64	≥64

Enterobacteriaceae (n = 240)



	MIC (mg/L)			
	Min	50%	90%	Max
Doripenem	0.008	0.03	0.12	32
Imipenem	0.12	0.25	0.5	≥64
Meropenem	0.008	0.03	0.12	≥64

A. baumannii. (n = 52)



	MIC (mg/L)			
	Min	50%	90%	Max
Doripenem	0.12	16	≥64	≥64
Imipenem	0.25	32	≥64	≥64
Meropenem	0.25	32	≥64	≥64

YBÜ vs. YBÜ-dışı

	MIC (mg/L)							
	ICU				Non-ICU			
	MIN	50%	90%	MAX	MIN	50%	90%	MAX
All (n = 309/287)								
Doripenem	0.008	0.5	32	≥64	0.008	0.12	8	≥64
Imipenem	0.06	2	≥64	≥64	0.12	0.5	≥64	≥64
Meropenem	0.008	1	≥64	≥64	0.008	0.12	32	≥64
<i>Pseudomonas</i> spp. (n = 160/137)								
Doripenem	0.03	2	32	≥64	0.03	0.25	16	≥64
Imipenem	0.12	16	≥64	≥64	0.12	2	≥64	≥64
Meropenem	0.03	4	≥64	≥64	0.03	0.5	≥64	≥64
Enterobacteriaceae (n = 105/135)								
Doripenem	0.008	0.03	0.12	32	0.008	0.03	0.06	16
Imipenem	0.12	0.25	0.5	32	0.12	0.25	0.5	≥64
Meropenem	0.008	0.03	0.12	32	0.008	0.03	0.06	≥64
Other Gram-negatives (n = 44/15)								
Doripenem	0.03	8	≥64	≥64	0.25	8	≥64	≥64
Imipenem	0.06	32	≥64	≥64	0.25	≥64	≥64	≥64
Meropenem	0.06	16	≥64	≥64	0.12	≥64	≥64	≥64

Referans Laboratuvarı ile karşılaştırmalı olarak merkezlerin Doripenem Etest MİK değeri

	Merkez Etest MİK (mg/L)													
	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	≥64
0.008														
0.015	3	6	3											
0.03		2	7	1										
0.06					2	1								
0.12				3	6	2			1					
0.25		2	1		3	3	1		1	1				
0.5						4	4	3		1				
1						2		1	4		1		1	
2							1	6	5	3				
4								1	12	9	6	1	3	1
8								1	1	19	13	2	7	4
16							1		1	3	8	6	2	9
32									1	1	8	5	4	4
≥64									2	1	2	3	4	22

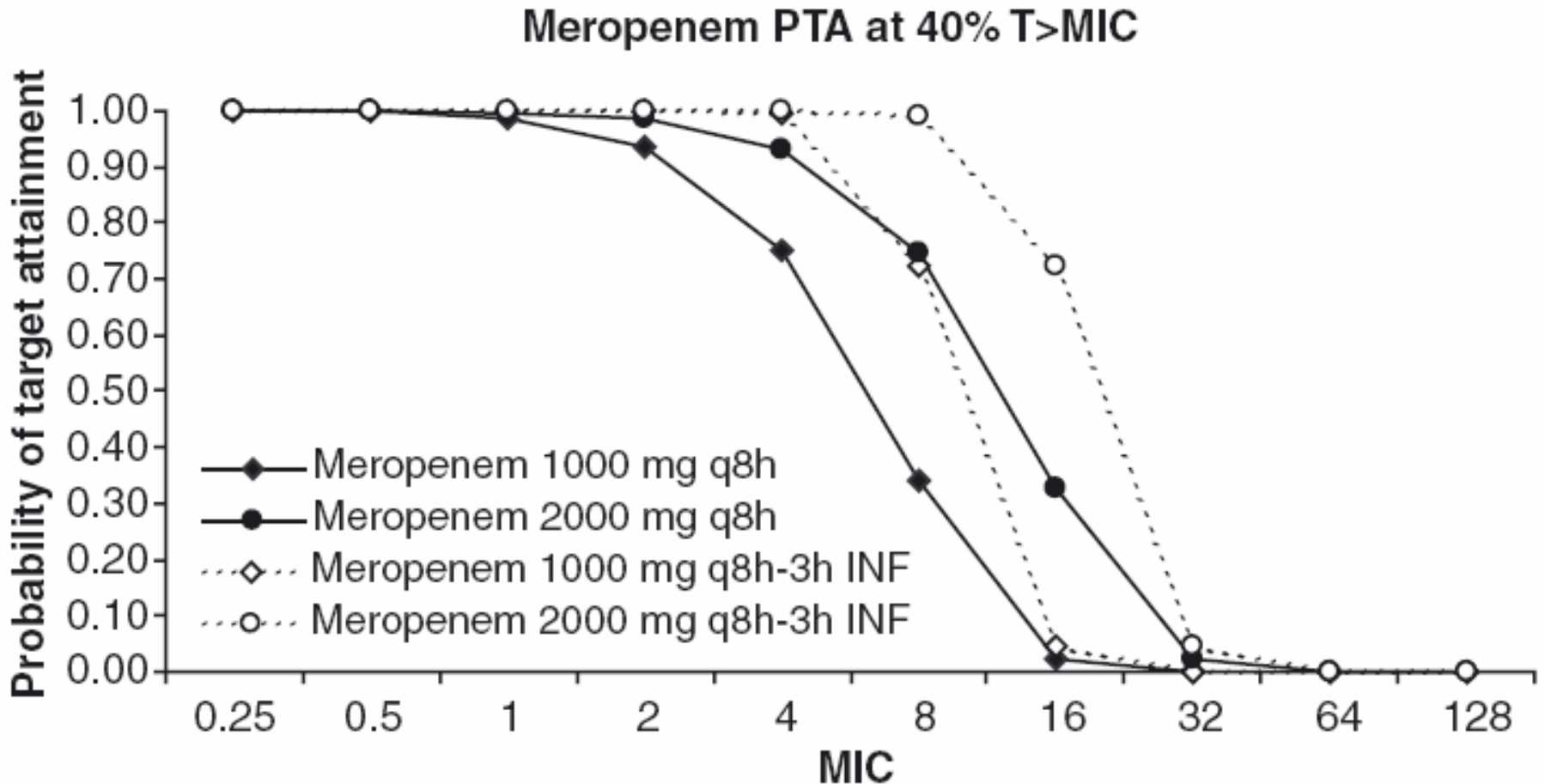
 MİK

 Bir kat dilüsyon MİK değeri

DOR	IMP	MEM	n
S	R	R	4
S	R	I	4
S	R	S	16
S	I	R	2
S	I	I	3
S	I	S	2
S	S	S	60

DOR	IMP	MEM	n
NS	R	R	113
NS	R	I	22
NS	R	S	9
NS	I	R	1
NS	I	I	2
NS	I	S	1
NS	S	R	2
NS	S	I	1
NS	S	S	10

Meropenem PD modelling – *P.aeruginosa*



	MIC (mg/L)					
	0.5	1	2	4	8	16
Pseudomonas spp.						
Doripenem	49.2	56.6	64.0	74.1	84.2	88.6
Imipenem	8.8	33.0	48.2	53.9	57.9	65.3
Meropenem	42.1	50.5	56.2	63.0	72.1	75.1

penetration of doripenem into inflamed meninges was 14.8% and 7% into noninflamed meninges.

Successful treatment with doripenem and tobramycin of ventriculitis due to imipenem- and meropenem-resistant *Pseudomonas aeruginosa*

Michael S. Gelfand, Kerry O. Cleveland* and Shirin A. Mazumder

Journal of Antimicrobial Chemotherapy 2009 63(6):1297-1299

- meropenem MIC: 8 mg/L
- doripenem MIC: 1.5 mg/L
- doripenem (1 g iv infused over 60 min every 8 h) and tobramycin (10 mg it daily)

Doripenem'in *A.baumannii*'ye etkinliđi

İzolat	Antibiyotik	% MİK>8 ug/ml	MİK ₉₀
OXA-58	Doripenem	% 33	4
	İmipenem	% 100	16
	Meropenem	% 100	16

► Doripenem, *Acinetobacter baumannii*'nin blaOXA-58 geni eksprese edilen suşlarında imipenem ve meropeneme göre belirgin bir üstünlüđe sahiptir .