J Infect Chemother (2007) 13:332–340
DOI 10.1007/s10156-007-0562-3

ORIGINAL ARTICLE

Akira Watanabe · Shigeru Fujimura · Toshiaki Kikuchi
Kazunori Gomi · Katsuhiro Fuse · Toshihiro Nukiwa

Evaluation of dosing designs of carbapenems for severe respiratory infection using Monte Carlo simulation

Received: January 31, 2007 / Accepted: June 25, 2007

Abstract Using the Monte Carlo simulation method, the influence of various doses and dosing frequencies of carbapenems on the antimicrobial activities against *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Pseudomonas aeruginosa*, which are the main causative organisms of respiratory infections, was studied with the aim of identifying optimized effectiveness. Based on pharmacokinetic (PK) parameters of individual carbapenems in healthy adults, data on changes in the respective blood concentrations in 2000 cases were simulated by applying a lognormal distribution to probability distributions of their volume of distributions and half-life periods. Based on minimum inhibitory concentration (MIC) distribution data of the individual carbapenems against these strains, MICs in the 2000 cases were also simulated. Using these data in blood concentrations and MICs, the probabilities of attaining various percentages of the dosing interval during which drug concentrations remain above MIC (T > MIC) were calculated at several dosing regimens. Considering the probabilities of attaining the bactericidal effect (50% T>MIC) and daily drug costs, imipenem (IPM) at 500 mg i.v. BID, panipenem (PAPM) at 500 mg i.v. BID, and biapenem (BIPM) at 300 mg i.v. BID against *Streptococcus pneumoniae*; meropenem (MEPM) at 500 mg i.v. BID or TID against *Haemophilus influenzae* infections; and MEPM at 500 or 1000 mg i.v. TID against *Pseudomonas aeruginosa*, each over 30 min, were determined as appropriate empirical treatments. Selecting carbapenems with superior antimicrobial activities and optimizing their dose regimens are important to improve the efficacy. Application of Monte Carlo simulation to MIC distributions allows determination of appropriate empiric therapy even if drug susceptibility of a causative organism in individual patients is unknown.

Key words Monte Carlo simulations · Carbapenem · Pharmacokinetics (PK)/pharmacodynamics (PD)

Introduction

Recently, proper use of antimicrobial agents for treatment of infections based on pharmacokinetics (PK)/pharmacodynamics (PD) has been recommended to save lives of patients and to prevent the emergence of resistant microorganisms. In clinical settings, several attempts have been made to select the PK/PD-based dosing regimens of antimicrobial agents more efficiently, including evaluation of the microbiological efficacy for severe infections in terms of PK/PD and simulating the blood concentrations[1] using Monte Carlo simulation.[2–5] With the aim of identifying optimal carbapenems and their dosing regimens for the treatment of severe respiratory infections caused by *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Pseudomonas aeruginosa*, we evaluated the influence of the dose, daily dosing frequency, and antimicrobial activity of each carbapenem on the therapeutic efficacy using Monte Carlo simulation.

Materials and methods

Dosing regimens of antimicrobial agents

Based on PK parameters of individual carbapenems in healthy adults (two-compartment model analysis)[6–13] (Table 1), the blood concentration–time profiles in 2000 cases from dosing regimens of each carbapenem were simulated. A lognormal distribution was applied to the probability distribution of the volume of distribution (V_d) and half-life ($T_{1/2}$) using the Monte Carlo simulation method. Total plasma

A. Watanabe (✉) · S. Fujimura
Research Division for Development of Anti-Infective Agents, Institute of Development, Aging and Cancer, Tohoku University, Seiryo-cho 4-1 Aoba-ku, Sendai 980-8575, Japan
Tel. +81-22-717-8540; Fax +81-22-717-8540
e-mail: akiwa@idac.tohoku.ac.jp

T. Kikuchi · K. Gomi · K. Fuse · T. Nukiwa
Department of Respiratory Oncology and Molecular Medicine, Institute of Development, Aging and Cancer, Tohoku University, Sendai, Japan

Table 1. Pharmacokinetic parameters of carbapenems

Carbapenem	V_d (l)	$T_{1/2}$
MEPM	22.00 ± 2.98	1.03 ± 0.13
IPM	16.3 ± 4.5	0.79 ± 0.04
PAPM	20.12 ± 3.51	1.07 ± 0.21
BIPM	15.4 ± 1.6	1.03 ± 0.1
DRPM	16.69 ± 1.67	0.94 ± 0.2

MEPM, Meropenem; IPM, imipenem; PAPM, panipenem; BIPM, biapenem; DRPM, doripenem

Table 2. Dosing regimens studied and daily cost of drug

Carbapenem	Dose (mg)	Daily dosing frequency	Daily cost of drug (Yen)[a]
MEPM	500	2	3490
	500	3	5235
	1000	2	6980
	1000	3	10470
IPM	500	2	3772
	500	3	5658
	1000	2	7544
	1000	3	11 316
PAPM	500	2	3592
	500	3	5388
	1000	2	7184
	1000	3	10776
BIPM	300	2	3726
	300	3	5589
	600	2	7452
	600	3	11178
DRPM	250	2	2394
	250	3	3591
	500	2	4788
	500	3	7182

[a] Drug price standard in Japan

concentrations of carbapenems were used for the simulation.

Dosing regimens of the carbapenems were as follows: meropenem (MEPM; Dainippon Sumitomo Pharma, Osaka, Japan), imipenem (IPM; Banyu Pharmaceutical, Tokyo, Japan), and panipenem (PAPM; Sankyo, Tokyo, Japan) at 500 mg BID, 500 mg TID, 1000 mg BID, or 1000 mg TID; biapenem (BIPM; Meiji Seika, Tokyo, Japan) at 300 mg BID, 300 mg TID, 600 mg BID, or 600 mg TID; and doripenem (DRPM; Shionogi, Osaka, Japan) at 250 mg BID, 500 mg BID, 250 mg TID, or 500 mg TID (Table 2).

In Japan, these drugs are generally used at the lower of the doses listed above twice daily.

Microbiology

This study was conducted using *Streptococcus pneumoniae* 20 strains; minimum inhibitory concentration (MIC) range 0.015–1.0 μg/ml), *Haemophilus influenzae* (25 strains; MIC range 8–32 μg/ml), and *Pseudomonas aeruginosa* (20 strains; MIC range 8–32 μg/ml), which are the main causative organisms of respiratory infections, and were selected from bacterial strains that had been isolated from respiratory specimens in 1999 to 2000.[14] MIC was measured using the broth microdilution method in accordance with the approved standard

Table 3. Minimum inhibitory concentration (MIC) distributions of carbapenems against 20 strains of *Streptococcus pneumoniae*

MIC (μg/ml)	Frequency of Isolates at Each MIC						MIC_{90} (μg/ml)
	0.03	0.06	0.12	0.25	0.5	1	
MEPM	11	2	2	3	1	1	0.25
IPM	16	2	2	–	–	–	0.06
PAPM	18	2	–	–	–	–	0.03
BIPM	16	–	2	2	–	–	0.12
DRPM	14	3	–	3	–	–	0.25

Table 4. MIC distributions of carbapenems against 20 strains of *Haemophilus influenzae*

MIC (μg/ml)	Frequency of Isolates at Each MIC									MIC_{90} (μg/ml)
	0.03	0.06	0.12	0.25	0.5	1	2	4	8	
MEPM	2	7	5	6	–	–	–	–	–	0.25
IPM	–	–	–	7	6	4	2	1	–	2
PAPM	–	–	1	11	2	3	3	–	–	2
BIPM	–	–	3	3	6	3	2	2	1	4
DRPM	–	5	6	3	4	1	1	–	–	0.5

Table 5. MIC distributions of carbapenems against 20 strains of *Pseudomonas aeruginosa*

MIC (μg/ml)	Frequency of Isolates at Each MIC									MIC_{90} (μg/ml)
	0.03	0.06	0.12	0.25	0.5	1	2	4	8	
MEPM	2	–	7	4	5	–	1	–	1	0.5
IPM	–	–	–	–	2	10	7	–	1	2
PAPM	–	–	–	–	–	1	1	7	11	8
BIPM	–	–	–	2	10	5	1	1	1	2
DRPM	–	5	6	4	2	1	1	1	–	1

of the Japanese Society of Chemotherapy.[15] Drug susceptibility results had been reported previously in part. Based on MIC distribution data (Table 3–5) of the individual carbapenems against these clinically isolated strains, the MICs in 2000 cases were simulated by the Monte Carlo simulation method.

Simulation method

Using the blood concentration–time profiles and MICs in 2000 cases, the probabilities of attaining percentages of the dosing interval during which drug concentrations remain above the MIC (T>MIC) of 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, and 100% were calculated at each dosing regimen in accordance with the equation of Kuti et al.:[16]

$$\%T>MIC = \ln(Dose/V_d \times MIC) \times (T_{1/2}/0.693) \times (100/DI)$$

where Dose is the amount of the drug given at each administration (mg), V_d is the volume of distribution (l), $T_{1/2}$ is the half-life (h), and DI is the dosing interval (h). Given the data by Walker et al.[17] indicating that bacterial responses (bactericidal effect) could be obtained at a T>MIC of greater than approximately 50%, the analysis[16] was conducted with a focus on the probability of attaining a T>MIC of 50% on the assumption that a T>MIC of greater than 50% would be required to cure severe infections. For the Monte Carlo

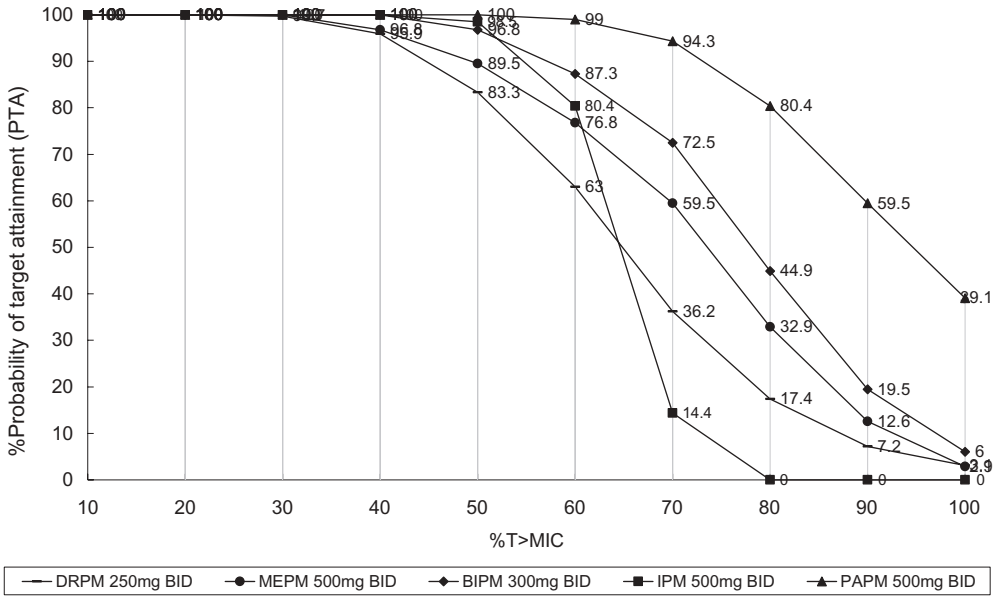

Fig. 1. Target attainment rates for meropenem (*MEPM*) at 500 mg BID, imipenem (*IPM*) at 500 mg BID, panipenem (*PAPM*) at 500 mg BID, biapenem (*BIPM*) at 300 mg BID, and doripenem (*DRPM*) at 250 mg BID against *Streptococcus pneumoniae*

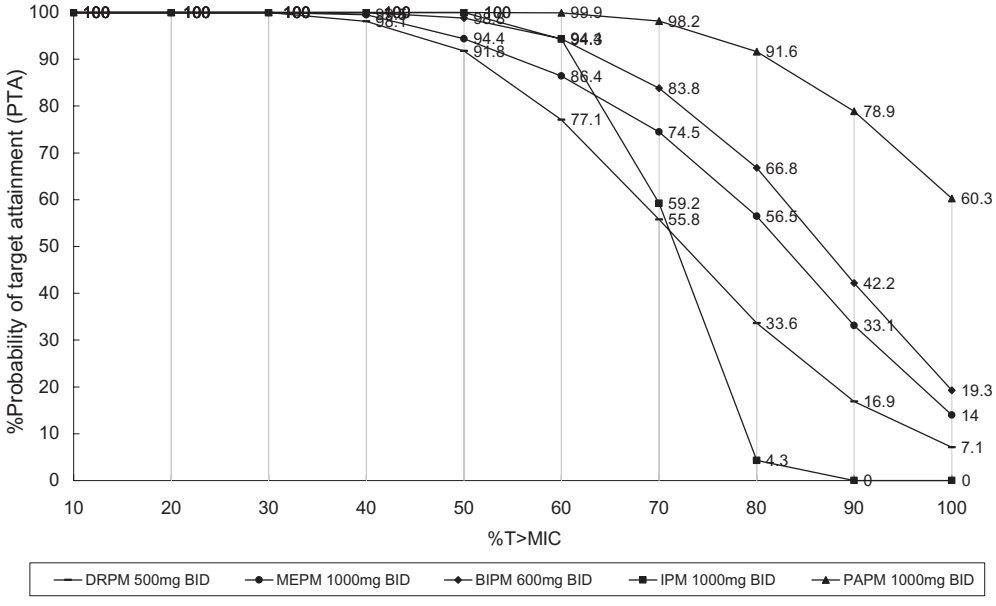

Fig. 2. Target attainment rates for MEPM at 1000 mg BID, IPM at 1000 mg BID, PAPM at 1000 mg BID, BIPM at 600 mg BID, and DRPM at 500 mg BID against *Streptococcus pneumoniae*

simulation, Crystal Ball 2000 (Kozo Keikaku Engineering, Tokyo, Japan) was used.

Results

Probabilities of attaining T>MIC targets for carbapenems against *Streptococcus pneumoniae* by individual dosing regimen

Lower doses, BID

The probabilities of attaining T>MIC targets for MEPM (500 mg BID), IPM (500 mg BID), PAPM (500 mg BID), BIPM (300 mg BID), and DRPM (250 mg BID) are shown in Fig. 1. The probabilities of attaining a T>MIC target of 50%, which is required for the treatment of severe infections, were as follows (in descending order): 100% for PAPM (500 mg BID), 98.5% for IPM (500 mg BID), 96.8% for BIPM (300 mg BID), 89.5% for MEPM (500 mg BID), and 83.3% for DRPM (250 mg BID).

Higher doses, BID

The probabilities of attaining T>MIC targets for MEPM (1000 mg BID), IPM (1000 mg BID), PAPM (1000 mg BID), BIPM (600 mg BID), and DRPM (500 mg BID) are shown in Fig. 2. The probabilities of attaining a T>MIC target of

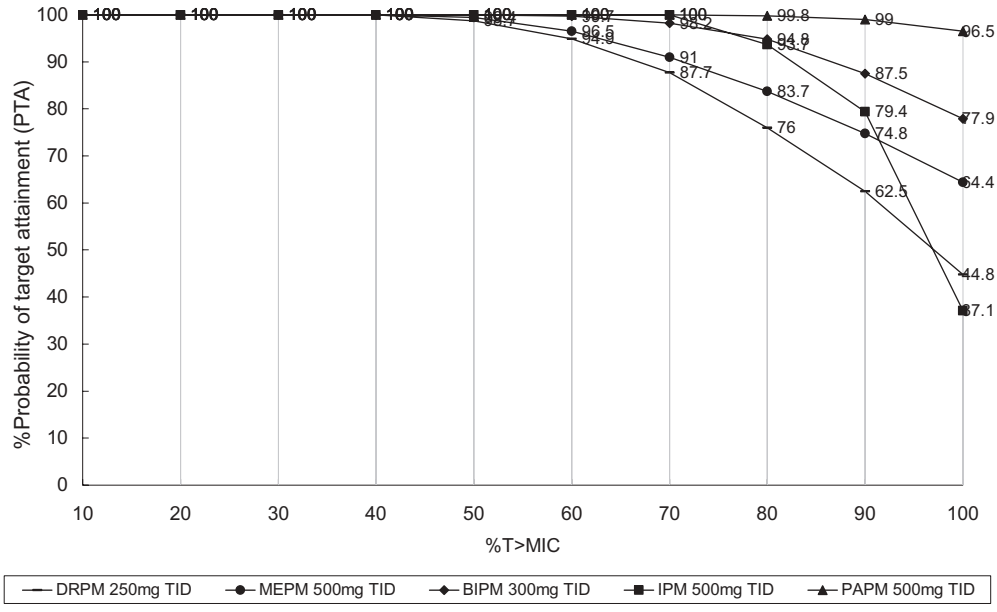

Fig. 3. Target attainment rates for MEPM at 500 mg TID, IPM at 500 mg TID, PAPM at 500 mg TID, BIPM at 300 mg TID, and DRPM at 250 mg TID against *Streptococcus pneumoniae*

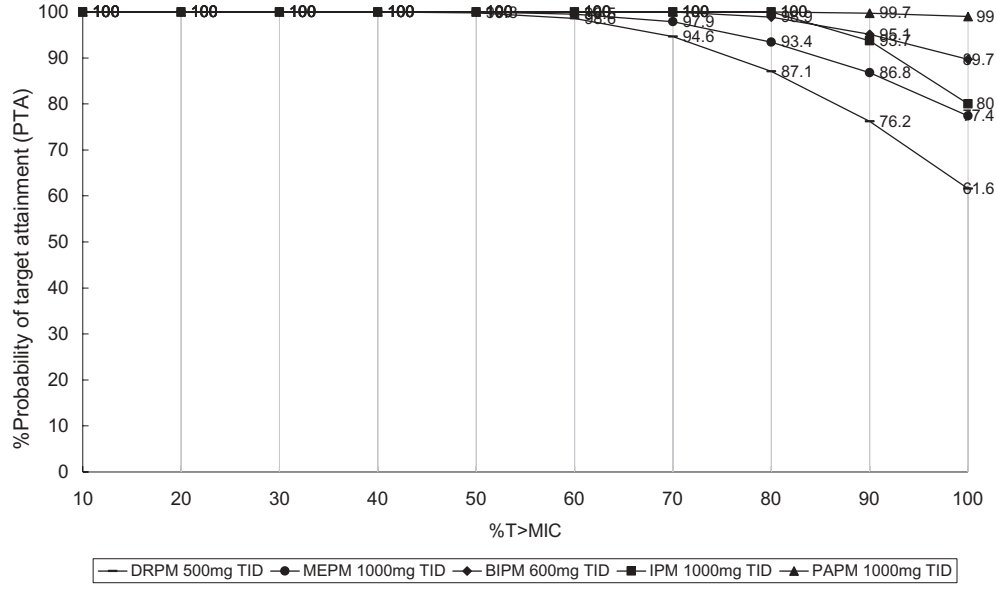

Fig. 4. Target attainment rates for MEPM at 1000 mg TID, IPM at 1000 mg TID, PAPM at 1000 mg TID, BIPM at 600 mg TID, and DRPM at 500 mg TID against *Streptococcus pneumoniae*

50%, which is required for the treatment of severe infections, were as follows (in descending order): 100% for PAPM (1000 mg BID), 100% for IPM (1000 mg BID), 98.8% for BIPM (600 mg BID), 94.4% for MEPM (1000 mg BID), and 91.8% for DRPM (500 mg BID).

Lower doses, TID

The probabilities of attaining T>MIC targets for MEPM (500 mg TID), IPM (500 mg TID), PAPM (500 mg TID), BIPM (300 mg TID), and DRPM (250 mg TID) are shown in Fig. 3. The probabilities of attaining a T>MIC target of 50%, which is required for the treatment of severe infections, were 100% or near as follows: 100% for IPM (500 mg TID), 100% for PAPM (500 mg TID), 100% for BIPM (300 mg TID), 99.4% for MEPM (500 mg TID), and 98.7% for DRPM (250 mg TID).

Higher doses, TID

The probabilities of attaining T>MIC targets for MEPM (1000 mg TID), IPM (1000 mg TID), PAPM (1000 mg TID), BIPM (600 mg TID), and DRPM (500 mg TID) are shown in Fig. 4. The probabilities of attaining a T>MIC target of 50%, which is required for the treatment of severe infections, were 100% or near as follows: 100% for MEPM (1000 mg TID), 100% for IPM (1000 mg TID), 100% for PAPM (1000 mg TID), 100% for BIPM (600 mg TID), and 99.8% for DRPM (500 mg TID).

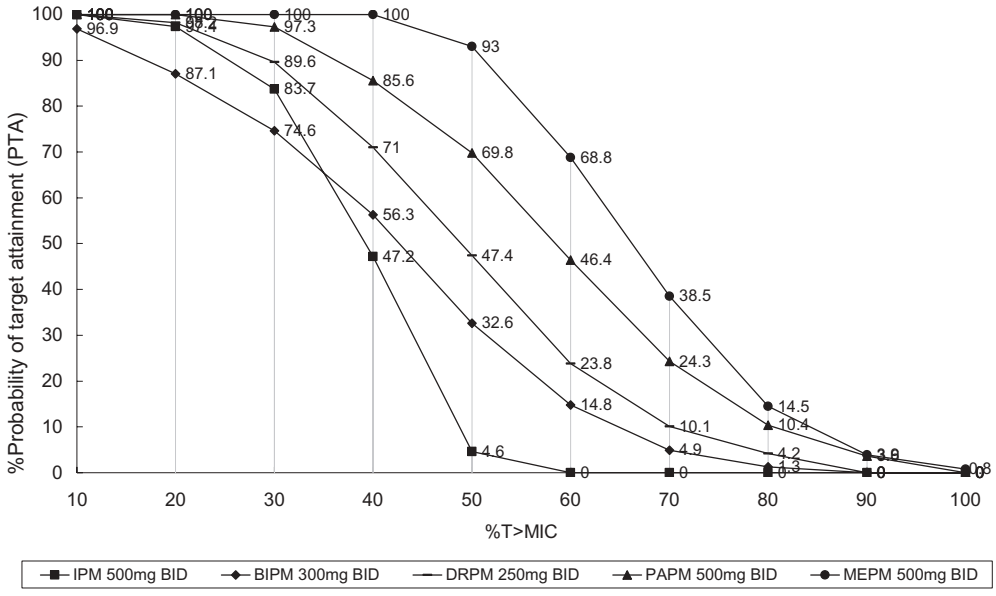

Fig. 5. Target attainment rates for MEPM at 500 mg BID, IPM at 500 mg BID, PAPM at 500 mg BID, BIPM at 300 mg BID, and DRPM at 250 mg BID against *Haemophilus influenzae*

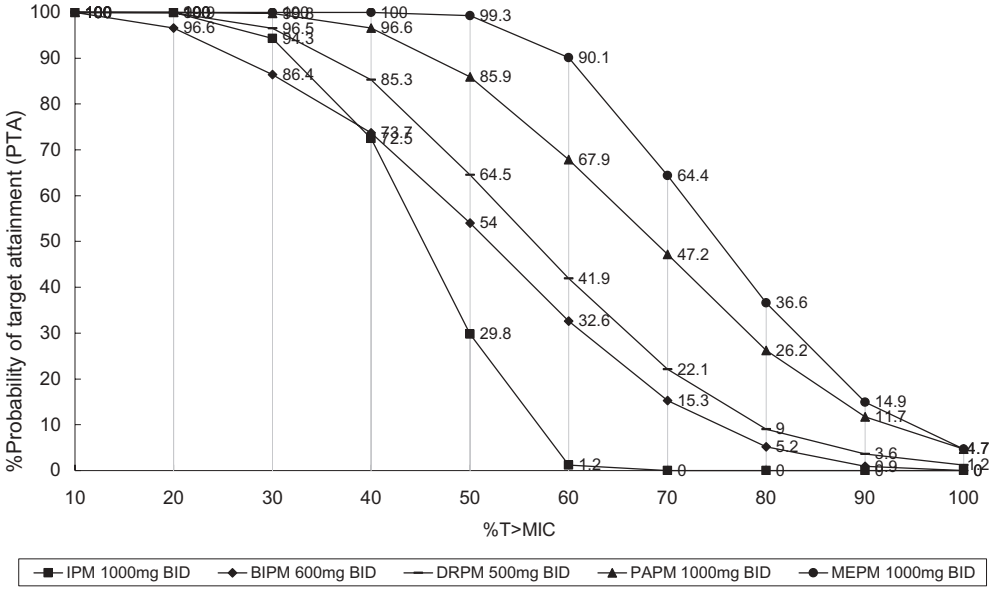

Fig. 6. Target attainment rates for MEPM at 1000 mg BID, IPM at 1000 mg BID, PAPM at 1000 mg BID, BIPM at 600 mg BID, and DRPM at 500 mg BID against *Haemophilus influenzae*

Probabilities of attaining T>MIC targets for carbapenems against *Haemophilus influenzae* by individual dosing regimen

Lower doses, BID

The probabilities of attaining T>MIC targets for MEPM (500 mg BID), IPM (500 mg BID), PAPM (500 mg BID), BIPM (300 mg BID), and DRPM (250 mg BID) are shown in Fig. 5. The probabilities of attaining a T>MIC target of 50%, which is required for the treatment of severe infections, were as follows (in descending order): 93% for MEPM (500 mg BID), 69.8% for PAPM (500 mg BID), 47.4% for DRPM (250 mg BID), 32.6% for BIPM (300 mg BID), and 4.6% for IPM (500 mg BID).

Higher doses, BID

The probabilities of attaining T>MIC targets for MEPM (1000 mg BID), IPM (1000 mg BID), PAPM (1000 mg BID), BIPM (600 mg BID), and DRPM (500 mg BID) are shown in Fig. 6. The probabilities of attaining a T>MIC target of 50%, which is required for the treatment of severe infections, were as follows (in descending order): 99.3% for MEPM (1000 mg BID), 85.9% for PAPM (1000 mg BID), 64.5% for DRPM (500 mg BID), 54% for BIPM (600 mg BID), and 29.8% for IPM (1000 mg BID).

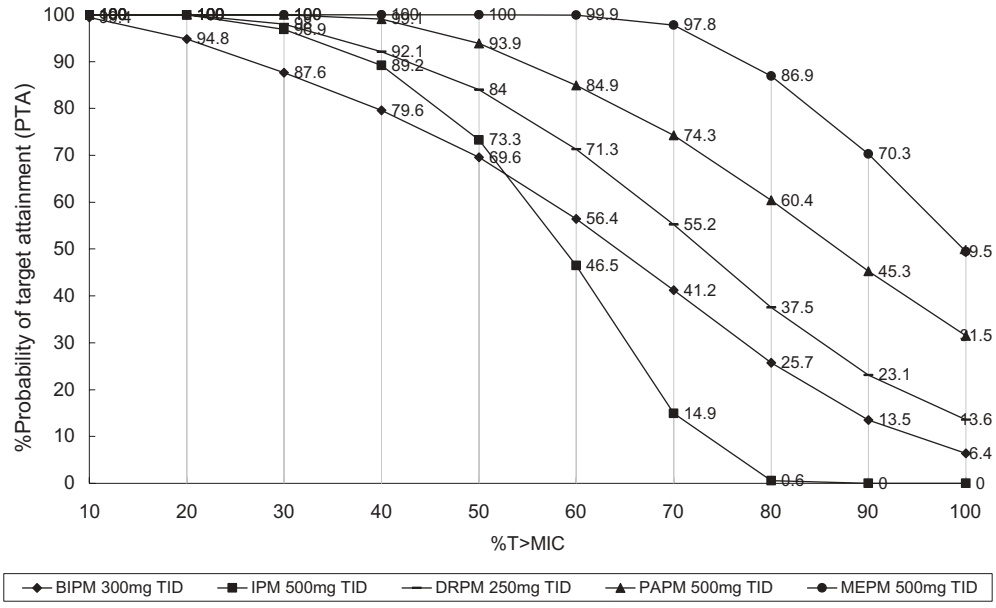

Fig. 7. Target attainment rates for MEPM at 500 mg TID, IPM at 500 mg TID, PAPM at 500 mg TID, BIPM at 300 mg TID, and DRPM at 250 mg TID against *Haemophilus influenzae*

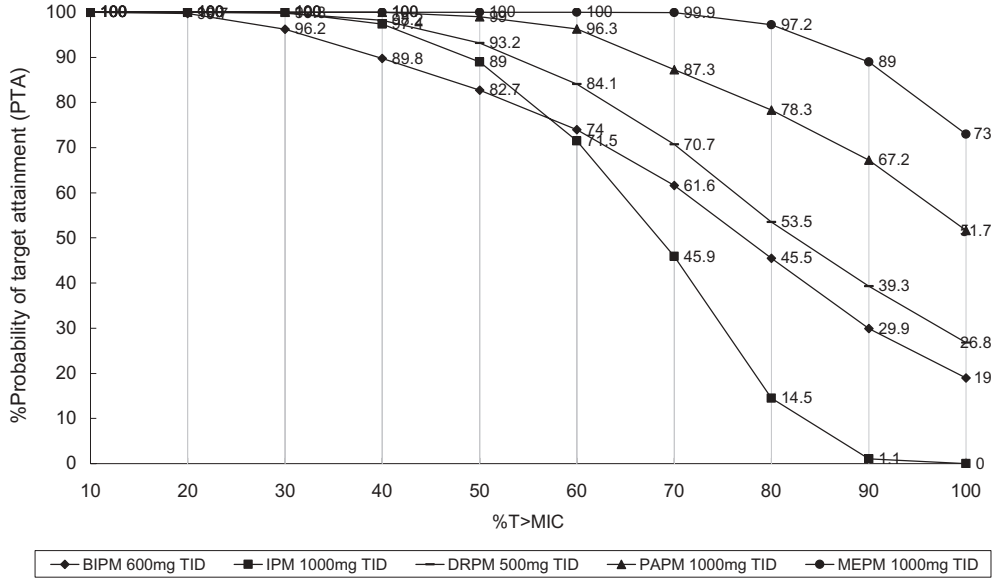

Fig. 8. Target attainment rates for MEPM at 1000 mg TID, IPM at 1000 mg TID, PAPM at 1000 mg TID, BIPM at 600 mg TID, and DRPM at 500 mg TID against *Haemophilus influenzae*

Lower doses, TID

The probabilities of attaining T>MIC targets for MEPM (500 mg TID), IPM (500 mg TID), PAPM (500 mg TID), BIPM (300 mg TID), and DRPM (250 mg TID) are shown in Fig. 7. The probabilities of attaining a T>MIC target of 50%, which is required for the treatment of severe infections, were as follows (in descending order): 100% for MEPM (500 mg TID), 93.9% for PAPM (500 mg TID), 84% for DRPM (250 mg TID), 73.3% for IPM (500 mg TID), and 69.6% for BIPM (300 mg TID).

Higher doses, TID

The probabilities of attaining T>MIC targets for MEPM (1000 mg TID), IPM (1000 mg TID), PAPM (1000 mg TID), BIPM (600 mg TID), and DRPM (500 mg TID) are shown in Fig. 8. The probabilities of attaining a T>MIC target of 50%, which is required for the treatment of severe infections, were as follows (in descending order): 100% for MEPM (1000 mg TID), 99% for PAPM (1000 mg TID), 93.2% for DRPM (500 mg TID), 89% for IPM (1000 mg TID), and 82.7% for BIPM (600 mg TID).

Probabilities of attaining T>MIC targets for carbapenems against *Pseudomonas aeruginosa* by individual dosing regimen

Lower doses, BID

The probabilities of attaining T>MIC targets for MEPM (500 mg BID), IPM (500 mg BID), PAPM (500 mg BID),

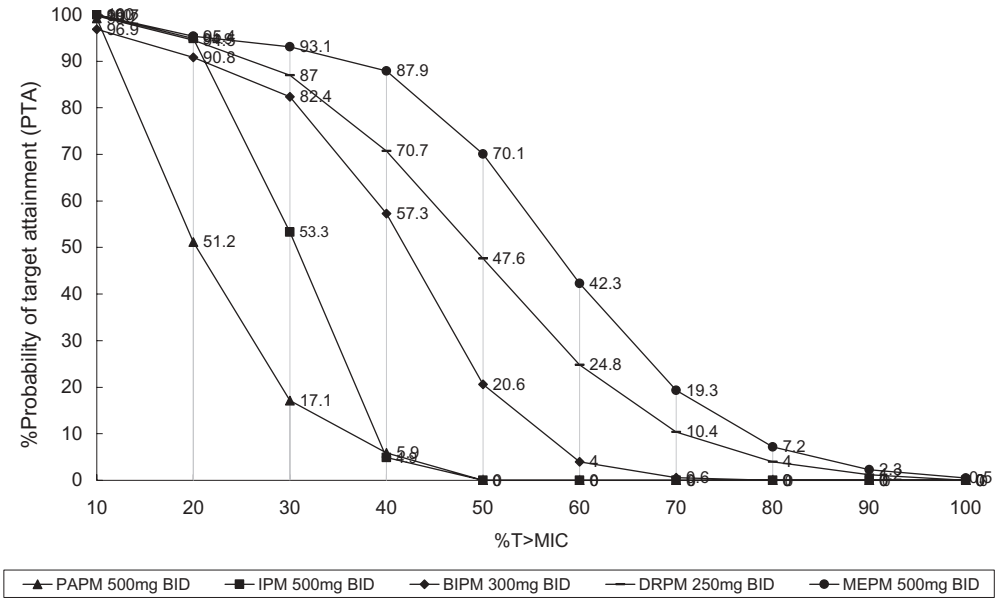

Fig. 9. Target attainment rates for MEPM at 500 mg BID, IPM at 500 mg BID, PAPM at 500 mg BID, BIPM at 300 mg BID, and DRPM at 250 mg BID against *Pseudomonas aeruginosa*

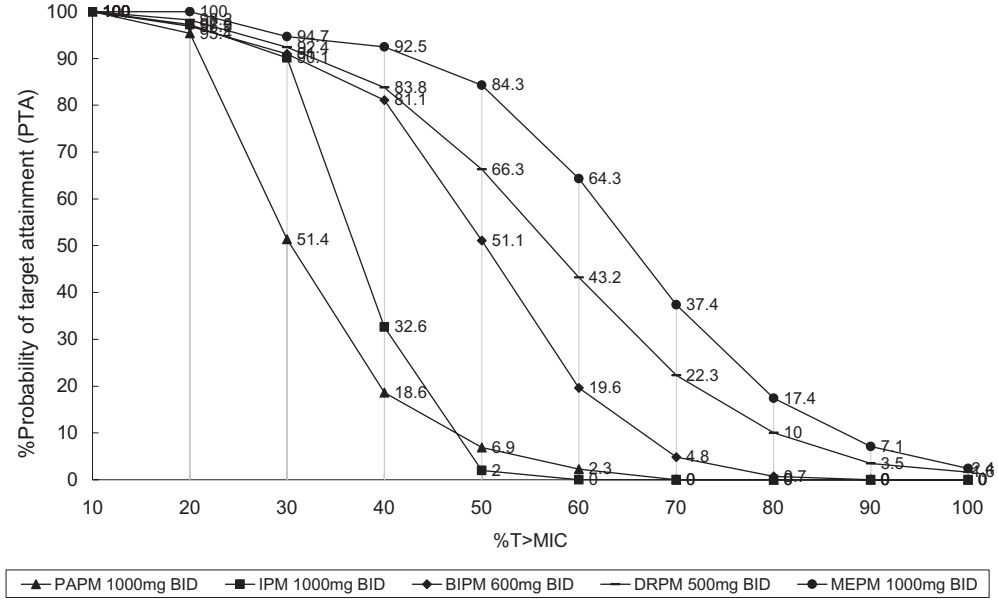

Fig. 10. Target attainment rates for MEPM at 1000 mg BID, IPM at 1000 mg BID, PAPM at 1000 mg BID, BIPM at 600 mg BID, and DRPM at 500 mg BID against *Pseudomonas aeruginosa*

BIPM (300 mg BID), and DRPM (250 mg BID) are shown in Fig. 9. The probabilities of attaining a T>MIC target of 50%, which is required for the treatment of severe infections, were as follows (in descending order): 70.1% for MEPM (500 mg BID), 47.6% for DRPM (250 mg BID), 20.6% for BIPM (300 mg BID), 0% for IPM (500 mg BID), and 0% for PAPM (500 mg BID).

Higher doses, BID

The probabilities of attaining T>MIC targets for MEPM (1000 mg BID), IPM (1000 mg BID), PAPM (1000 mg BID), BIPM (600 mg BID), and DRPM (500 mg BID) are shown in Fig. 10. The probabilities of attaining a T>MIC target of 50%, which is required for the treatment of severe infections, were as follows (in descending order): 84.3% for MEPM (1000 mg BID), 66.3% for DRPM (500 mg BID), 51.1% for BIPM (600 mg BID), 6.9% for PAPM (1000 mg BID), and 2.0% for IPM (1000 mg BID).

Lower doses, TID

The probabilities of attaining T>MIC targets for MEPM (500 mg TID), IPM (500 mg TID), PAPM (500 mg TID), BIPM (300 mg TID), and DRPM (250 mg TID) are shown in Fig. 11. The probabilities of attaining a T>MIC target of

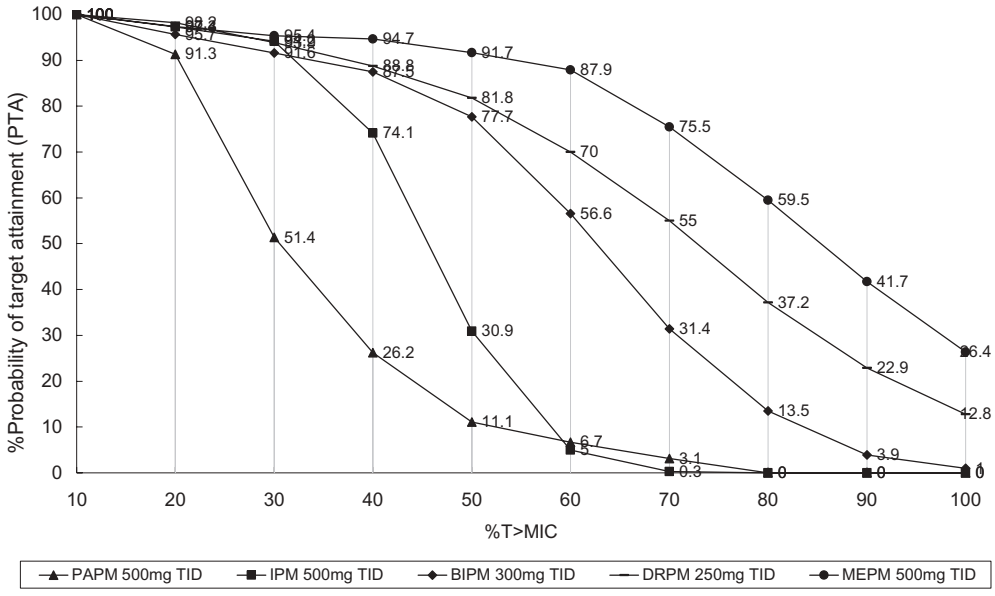

Fig. 11. Target attainment rates for MEPM at 500 mg TID, IPM at 500 mg TID, PAPM at 500 mg TID, BIPM at 300 mg TID, and DRPM at 250 mg TID against *Pseudomonas aeruginosa*

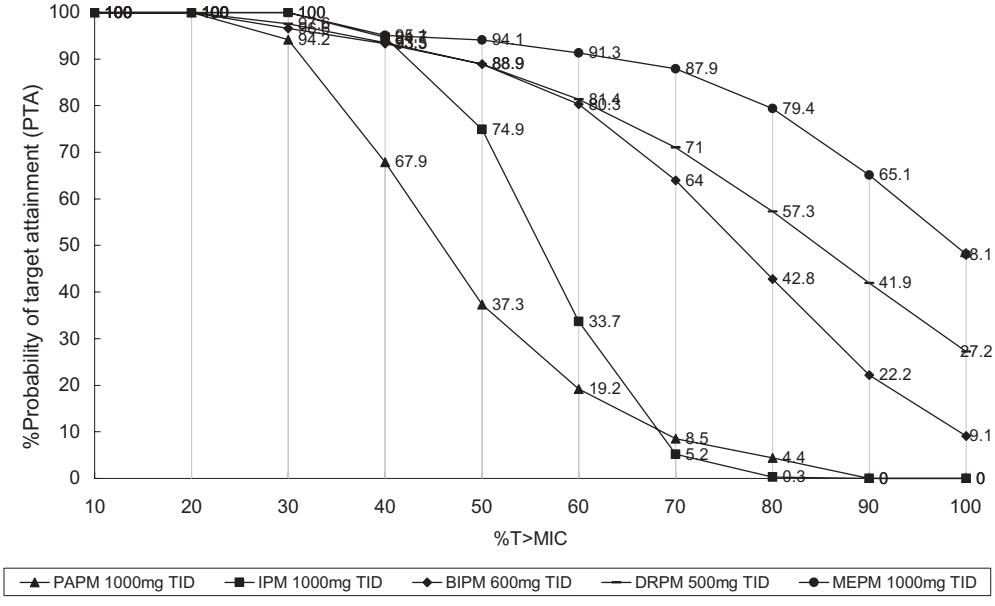

Fig. 12. Target attainment rates for MEPM at 1000 mg TID, IPM at 1000 mg TID, PAPM at 1000 mg TID, BIPM at 600 mg TID, and DRPM at 500 mg TID against *Pseudomonas aeruginosa*

50%, which is required for the treatment of severe infections, were as follows (in descending order): 91.7% for MEPM (500 mg TID), 81.8% for DRPM (250 mg TID), 77.7% for BIPM (300 mg TID), 30.9% for IPM (500 mg TID), and 11.1% for PAPM (500 mg TID).

Higher doses, TID

The probabilities of attaining T>MIC targets for MEPM (1000 mg TID), IPM (1000 mg TID), PAPM (1000 mg TID), BIPM (600 mg TID), and DRPM (500 mg TID) are shown in Fig. 12. The probabilities of attaining a T>MIC target of 50%, which is required for the treatment of severe infections, were as follows (in descending order): 94.1% for MEPM (1000 mg TID), 88.9% for DRPM (500 mg TID), 88.9% for BIPM (600 mg TID), 74.9% for IPM (1000 mg TID), and 37.3% for PAPM (1000 mg TID).

Discussion

In this study, we evaluated optimal carbapenems and their dosing regimens for the treatment of severe infections envisioned to be caused by *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Pseudomonas aeruginosa*, which are the main causative organisms of respiratory infections. This work used Monte Carlo simulation in order to determine appropriate empiric therapy for severe respiratory infections. Behind this study is our intention to theoretically correct the current situation in Japan, in which it is difficult

to efficiently conduct high-dose or divided-dose therapy of antimicrobial drugs without the occurrence of resistant organisms.

The results of this study suggest that IPM at 500 mg BID, PAPM at 500 mg BID, and BIPM at 300 mg BID can be expected to be very effective in the treatment of severe respiratory infections thought to be caused by *Streptococcus pneumoniae*. MEPM and DRPM are expected to be more effective at doses increased to 1000 mg BID and 500 mg BID, respectively, but much more effective with TID dosing frequency increased without doubling the dose (500 mg and 250 mg, respectively).

In addition, IPM at 1000 mg TID, PAPM at 1000 mg TID, MEPM at 1000 mg TID, BIPM at 600 mg TID, and DRPM at 500 mg TID, which are the dosing regimens with the highest dose and daily dosing frequency, are expected to be the most effective. From the viewpoint of cost efficiency, however, IPM at 500 mg BID, PAPM at 500 mg BID, and BIPM at 300 mg BID are recommended for the treatment of severe respiratory infections thought to be caused by *Streptococcus pneumoniae*, based on the daily cost of each drug (Table 2).

In the treatment of severe respiratory infections envisioned to be caused by *Haemophilus influenzae*, on the other hand, MEPM at 500 mg BID is expected to be effective. However, none of the other carbapenems studied are expected to be sufficiently effective even at twice-daily treatment at double the dose or thrice-daily treatment at the unchanged dose.

To enhance the therapeutic efficacy of the carbapenems other than MEPM, it may be necessary to maximize the dose and daily dosing frequency, exemplified by IPM at 1000 mg TID, PAPM at 1000 mg TID, BIPM at 600 mg TID, and DRPM at 500 mg TID. From the viewpoint of cost efficiency, MEPM at 500 mg BID or TID is recommended for the treatment of severe respiratory infections thought to be caused by *Haemophilus influenzae*.

In the treatment of severe respiratory infections envisioned to be caused by *Pseudomonas aeruginosa*, none of the carbapenems are expected to be very effective at twice-daily treatment at a lower dose. MEPM at 500 or 1000 mg TID may be necessary. However, a dosing regimen of MEPM at 1000 mg TID has not been approved in Japan. To improve the survival rate in patients with severe respiratory infections thought to be caused by *Pseudomonas aeruginosa*, it may be essential to approve this dosing regimen in Japan, as in European countries and the United States.

The above results demonstrated that in the treatment of severe respiratory infections caused by *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Pseudomonas aeruginosa*, the carbapenem and dosing regimen to be selected depends on the causative organism. To improve the therapeutic efficacy, it may be important to increase the dose and/or daily dosing frequency of carbapenems, because they are reported to be associated with few adverse effects such as nephrotoxicity or central toxicity,[18,19] and to select antimicrobial carbapenems because the therapeutic efficacy is affected by the antimicrobial activity.

In conclusion, to determine appropriate empiric therapy, the Monte Carlo simulation method can be applied to MIC distributions in the regions or institutions themselves even if the antimicrobial activity (based on MIC) of antimicrobial agents to be selected is unknown. In the future, it may be necessary to clinically verify the findings from this study and identify the T>MIC required to cure severe infections.

References

1. Mikamo H. Optimizing meropenem therapy based on pharmacokinetics/pharmacodynamics (PK/PD) for severe infectious disease. Antibiot Chemother 2005;21:105–13.
2. Kuti JL, Dandekar PD, Nightingale CH. Use of Monte Carlo simulation to design an optimized pharmacodynamic dosing strategy for meropenem. J Clin Pharmacol 2003;43:1116–23.
3. Lomaestro BM, Drusano GL. Pharmacodynamic evaluation of extending the administration time of meropenem using a Monte Carlo simulation. Antimicrob Agents Chemother 2005;49:461–3.
4. Kuti JL, Nightingale CH, Nicolau DP. Optimizing pharmacodynamic target attainment using the MYSTIC antibiogram: data collected in North America in 2002. Antimicrob Agents Chemother 2004;48:2464–70.
5. Sun HK, Kuti JL, Nicolau DP. Pharmacodynamics of antimicrobials for the empirical treatment of nosocomial pneumonia: a report from the OPTAMA program. Crit Care Med 2005;33:2222–7.
6. Nakashima M, Uematsuu T, Kanamaru M. Phase-I clinical study of meropenem. Chemotherapy 1992;40 Suppl 1:258–75.
7. Wiseman LR, Wagstaff AJ, Brogden RN, Bryson HM. Meropenem: a review of its antibacterial activity, pharmacokinetic properties, and clinical efficiency. Drugs 1995;50:73–101.
8. Saito A, Kato Y, Ishikawa K, Odagaki E, Shinohara M, Fukuhara I, et al. Study of imipenem/cilastatin sodium (MK-0787/MK-0791). Chemotherapy 1985;33 Suppl 4:379–91.
9. Clissold SP, Todd PA, Campoli-Richards DM. Imipenem/Cilastatin: a review of its anti-bacterial activity, pharmacokinetic properties, and therapeutic efficacy. Drugs 1987;33:183–241.
10. Nakashima M, Uematsu T, Kamakura M, Tajima M, Naganuma H, Hisaoka M, et al. Phase-I clinical study of panipenem/betamipron. Chemotherapy 1991;39 Suppl 3:242–64.
11. Goa KL, Noble S. Panipenum/betamipron. Drugs 2003;63:913–25.
12. Saito R, Miura T, Tarao F. Study of disposition of biapenem. Chemotherapy 1994;42 Suppl 4:277–84.
13. Nakashima M, Oguma T. Phase-I study of doripenem in healthy adults. Chemotherapy 2005;53 Suppl 1:104–23.
14. Watanabe A, Tokue Y, Takahashi H, Kikuchi T, Kobayashi T, Gomi K, et al. Comparative in vitro activity of carbapenem antibiotics against respiratory pathogens isolated between 1999 and 2000. J Infect Chemother 2001;7:267–71.
15. Committee for Revision of MIC Determination Method. Revision of minimal inhibitory concentration (MIC) determination method (in Japanese). Chemotherapy (Tokyo) 1990;38:102–5.
16. Kuti JL, Dandekar PK, Nightingale CH, Nicolau DP. Use of Monte Carlo simulation to design an optimized pharmacodynamic dosing strategy for meropenem. J Clin Pharmacol 2003;43:1116–23.
17. Walker MR, Andes D, Conklin R, Ebert S, Craig WA. Pharmacodynamic activities of meropenem in animal infection model. ICAAC 1994: Proceedings of 35th Interscience Conference on Antimicrobial Agents and Chemotherapy; 1994 September 17–20; San Francisco. Abstr A-91.
18. Norrby SR, Newell PA, Faulkner KL, Lesky W. Safety profile of meropenem: international clinical based on the first 3125 patients treated with meropenem. J Antimicrob Chemother 1995;36 Suppl A:207–23.
19. Favero AD. Clinically important aspects of carbapenem safety. Curr Opin Infect Dis 1994;7 Suppl 1:S38–S42.