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The Practice of Prolonging Meropenem Infusion: A Narrative Review of Literatures Over the Last Decade

The Practice of Prolonging Meropenem Infusion: A Narrative Review of Literatures Over the Last Decade

Rifani Fauzi [1*]

Widyati [2]

Ika Puspita Sari [3]

[*1]Master of Clinical Pharmacy Program, Faculty of Pharmacy, Gadjah Mada University, Sleman, Yogyakarta, Indonesia

[2]Faculty of Military Pharmacy, Indonesia Defense University, Bogor, West Java, Indonesia

[3]Faculty of Pharmacy, Gadjah Mada University, Sleman, Yogyakarta, Indonesia

*email: rifani.fauzi@gmail.com

Abstrak

Background: The emergence of Antimicrobial Resistance (AMR) has forced clinicians and medical professionals to implement a strict Antimicrobial Stewardship policy. One of the pillar of Antimicrobial Stewardship is by optimizing the use of antibiotic agents. Beta-lactams demonstrate a time-dependent effect in combating bacteria. Since it is pharmacodynamically supported, a prolonged exposure via intravenous administration could be a feasible strategy to maximize the bactericidal effect. Meropenem, a beta-lactam antibiotic of carbapenems sub-class, also falls into the category above. However, there are questions to be answered regarding its stability, compatibility, safety, and clinical outcomes superiority compared to the standard intermittent infusion, before we can determine its effectiveness to be delivered as prolonged or extended infusion. Aims: This article would like to review literatures regarding the rationale behind the practice of prolonging meropenem infusion from the last decade. Method: For this narrative review we utilized articles extracted from Cochrane Library, ScienceDirect, and SageJournals databases from the last ten years. We also added complementary related articles from UpToDate®. Selected articles were limited to those published in english. Inclusion criteria specifically only including related articles to the practice of prolonging meropenem infusion on adult patients. A total of 18 articles were reviewed for the synthesis of this narrative review. Conclusion: Meropenem is eligible for prolonged infusion protocol since it is theoretically supported, adequate in stability, less concern for incompatibility, and potentially can provide better clinical outcomes compared to standard intermittent infusion.

Kata Kunci:
Meropenem
Prolonged infusion
Stability
Safety

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Abstract

Background: The emergence of Antimicrobial Resistance (AMR) has forced clinicians and medical professionals to implement a strict Antimicrobial Stewardship policy. One of the pillar of Antimicrobial Stewardship is by optimizing the use of antibiotic agents. Beta-lactams demonstrate a time-dependent effect in combating bacteria. Since it is pharmacodynamically supported, a prolonged exposure via intravenous administration could be a feasible strategy to maximize the bactericidal effect. Meropenem, a beta-lactam antibiotic of carbapenems sub-class, also falls into the category above. However, there are questions to be answered regarding its stability, compatibility, safety, and clinical outcomes superiority compared to the standard intermittent infusion, before we can determine its effectiveness to be delivered as prolonged or extended infusion. Aims: This article would like to review literatures regarding the rationale behind the practice of prolonging meropenem infusion from the last decade. Method: For this narrative review we utilized articles extracted from Cochrane Library, ScienceDirect, and SageJournals databases from the last ten years. We also added complementary related articles from UpToDate®. Selected articles were limited to those published in english. Inclusion criteria specifically only including related articles to the practice of prolonging meropenem infusion on adult patients. A total of 18 articles were reviewed for the synthesis of this narrative review. Conclusion: Meropenem is eligible for prolonged infusion protocol since it is theoretically supported, adequate in stability, less concern for incompatibility, and potentially can provide better clinical outcomes compared to standard intermittent infusion.

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INTRODUCTION

Beta Lactams is often regarded as the most extensively employed antibiotic class on a global scale. This deduction can be made based on the inclusion of various antibiotic sub-classes within the beta Lactams class, such as penicillins, cephalosporins, carbapenems, and monocyclic beta-lactamase. In the United States,

the utilization of Beta Lactams constitutes 65.24% of the total antibiotics prescribed over a period of ten years (Bush & Bradford, 2016). The over utilization of antibiotics is associated with a persistent challenge in the medical field, known as antimicrobial resistance. The available strategies for addressing antibiotic resistance are constrained. In the year 2019, the World Health Organization (WHO) recognized a total of 32 antibiotics that were in the process of clinical development. These antibiotics were specifically designed to target the priority diseases listed by the WHO. However, it is noteworthy that out of these 32 antibiotics, only six were categorized as novel (World Health Organization, 2019). We are depending on the implementation of Antimicrobial Stewardship Programs to resolve this critical problem.

The mechanism of action of beta lactam class antibiotics, which include meropenem, involves the inactivation of penicillin-binding proteins, which are crucial enzymes responsible for bacterial cell wall synthesis. This inactivation ultimately leads to the death of susceptible bacteria. Although individual beta lactam antibiotics exhibit varying half-lives, they are always classified as time-dependent antibiotics. This classification indicates the efficacy of these antibiotics in eradicating pathogens is not directly correlated with increasing drug concentrations within the target tissue (Lodise et al., 2006). Therefore, the main goal of the dosing regimen is to optimize the period of exposure of which the unbound drug remains in contact with the targeted tissue, while simultaneously ensuring that its concentration remains over the minimum inhibitory concentration (MIC) threshold. Pharmacodynamic expression of the proportion of the dosing period during which the concentration level of unbound drug remains above the MIC is represented as fT > MIC (Craig, 1998).

In order to enhance the probability of attaining the intended goal of fT > MIC for beta lactam antibiotics, adjustments can be made to the delivery method. This can involve increasing the dose, shortening the interval between doses, or prolonging the duration of drug infusion. Regarding the latter measure, the infusion may be prolonged for the entirety of the dosing duration (continuous infusion) or for around 40-50% of the dosing interval (approximately 3-4 hours of infusion) (Gillespie et al., 2005).

The 2016 guidelines from the Infectious Diseases Society of America (IDSA) made a weak recommendation regarding the implementation of antimicrobial stewardship programs. Specifically, they suggested considering the use of alternative dosing strategies for broad-spectrum beta-lactam antibiotics in hospitalized patients. The primary goal of this advice was to potentially mitigate costs associated with treatment (Barlam et al., 2016). Studies have been commenced to investigate clinical outcomes of prolonging beta-lactam infusion, showed varying degree of success (Aboulatta et al., 2020; Kondo et al., 2020; MacVane et al., 2014). To be more precise, the study of prolonging beta-lactams infusion should individually explored for each type of its antibiotics, this include meropenem.

METHODOLOGY

This review is intended to discuss relevant literature regarding the practice of prolonging meropenem infusion. The literature was searched from the Cochrane Library, ScienceDirect, and SageJournals, with supplementation articles from UpToDate®. The time span was narrowed to articles within the year 2013 up to 2023. The search keywords were "prolonged meropenem infusion, "extended meropenem infusion,", and "meropenem infusion safety". We limited study articles to focusing on adult patients only, with topics encompassing (1) stability of meropenem infusion, (2) compatibility of meropenem infusion, (3) safety profiles of prolonged meropenem

infusion, (4) Dosing of prolonged meropenem infusion, and (5) Comparison in pharmacodynamic and clinical outcomes between prolonged meropenem infusion and standard intermittent infusion. All the selected and reviewed articles were in english.

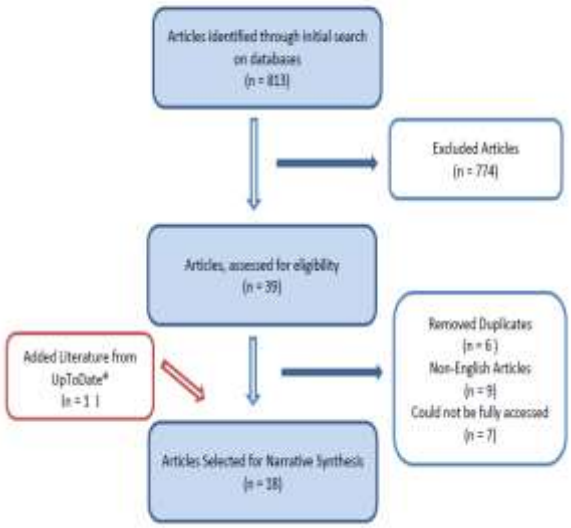

Figure 1. Flowchart of Search Strategy

FINDINGS

1. STABILITY

In order to be viable for prolonged infusion, meropenem, which is only available in parenteral form, must maintain its stability over the period of infusion. Merrem®, a meropenem product available in the US, is recommended for immediate use if reconstituted with Dextrose 5%. If reconstituted using normal saline, it can be stored up to 1 hour in room temperature, and maximum 15 hours if refrigerated (5^{O}C) (Merrem (Meropenem) IV Prescribing Information, 2013). However, multiple studies showed that reconstituted meropenem can maintain its stability over longer period of time in room temperature, further suggested its eligibility for prolonged infusion administration.

A study by Tomasello et al. on three products of meropenem manufactured by three different companies found that all three products could maintain their stability up to over 95% of their original concentration for 3 to 4 hours at room temperature. The stability only deteriorated at the sixth hour, with 8–10% decay (Tomasello et al., 2015). Even more compelling evidence was provided by a study in 2018. Venugopalan et al concluded that meropenem can be administered as continuous infusion (over 8 hours or 12 hours) since in 95% of cases studied on, the administration of meropenem via continuous infusion led to free drug concentrations that remained at or exceeded the minimum MIC of the pathogen throughout the whole dosing interval (Venugopalan et al., 2018).

Using High-Performance Liquid Chromatography (HPLC) assay, Fawaz et al concluded that meropenem can be continously given through intravenous infusion for at most 7 hours at 22^{O} C (average temperature at the setting) and for at most 5 hours at 33^{O} C (Fawaz et al., 2019). The methodology was developed, validated and verified in accordance to the guidelines set forth by the International Council for Harmonisation (ICH). More recent studies have also suggested that meropenem is eligible to be administered as a prolonged infusion, with factors like storage and temperature taken into consideration (Chen et al., 2020; Giménez-Giner et al., 2023).

2. COMPATIBILITY

Given the extended duration of a prolonged infusion procedure, it is more likely that it will be concomitantly administered with other medications through the same intravenous line. Problems of compatibility with other medications will arise and should be prevented if possible.

In 2019, a study with the objective of establishing the compatibility of injectable meropenem, tested meropenem compatibility with 101 different drugs

through Y-Site injection port. The compatibility was evaluated by a visual assessment and a particle count analysis by light obstruction immediately following mixing process. It was found that 83 of the 101 drugs were compatible in concomittant administration with meropenem both by visual assessment and using particle count analysis. Notable incompatibilty were observed in drugs like amiodarone, bupivacaine hydrochloride, calcium gluconate, ciprofloxacin lactate, dobutamine, diazepam, midazolam, ondansetron hydrochloride dihydrate, phenytoin sodium, vancomycin hydrochloride (Lessard et al., 2020). In literature, some of those incompatible drugs mentioned above were supposed to be compatible with meropenem (McEvoy & American Society of Health System Pharmacists, 2017). The authors concluded that the concentration of the drug solution played a major role, as was the case with dobutamine and vancomycin in the study.

3. SAFETY

Unfortunately, we could not find any related articles from the past 10 years regarding this topic. However, through supplementary article from UpToDate®, it is suggested that extended or continuous infusions of carbapenems present little difference in adverse events occurence compared to intermittent infusion administration (Moehring & Sarubbi, 2023). The sole exception applies to doripenem, as a clinical trial that involving patients with ventilator-associated pneumonia caused by gram-negative bacteria revealed that the administration of doripenem at a dosage of 1 gram over a 4-hour period every 8 hours for a duration of 7 days, when compared to the administration of Imipenem at a dosage of 1 gram over a 1-hour period every 8 hours for a duration of 10 days, was prematurely terminated due to the observation of higher mortality and clinical failure rates in the doripenem group (Kollef et al., 2012). There are several potential explanations for the findings. One possibility has to do with the shorter duration of doripenem therapy, particularly in patients with Pseudomonas aeruginosa infection, may have influenced the results. Another factor to consider is the absence of a loading dose in the extended infusion group, which could have had an impact. Additionally, the use of adjunctive antibiotics may have introduced confounding variables that need to be taken into account (Moehring & Sarubbi, 2023).

4. DOSING, PHARMACODYNAMIC PROFILES, AND CLINICAL OUTCAME

Theoretically, the success of meropenem therapy depends on how long the free drug concentration stays above the targeted MIC level in the intended human tissues. This is why dosing, prolonged administration, and pharmacodynamics all play important roles in determining how optimal an antibiotic therapy is and ultimately influence clinical outcomes (Kuti, 2016).

A pharmacodynamic profiling application had been studied by Koomanachai et al. in 2016. The aim was to determine optimal beta-lactam regimens in a prominent university hospital in Thailand. The MIC data of *Escherichia coli*, *Klebsiella Pneumoniae*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii* were taken from clinical specimens. Subsequently, the pharmacodynamic profiling was performed using Monte Carlo simulation, employing various beta-lactams with meropenem included, administered at standard, high dosage, and prolonged infusion. The result on meropenem showed that both dosing regimens of Meropenem whether in intermittent infusion or prolonged infusion were optimal against Escherichia coli and Klebsiella Pneumoniae, defined by cumulative fraction of response (CFR) equal to or greater than 90% (Koomanachai et al., 2016).

Another pharmacodynamic profiling using Monte Carlo simulation also done under the study by

Kiratisin et al., focusing solely on carbapenems with larger data pool from Asia-Pacific region. The result was almost identical with the more recent study by Koomanachai et al., with the exception of meropenem with dosing regimen 2g every 8 hours administered as 3 hours extended infusion could achieved optimal exposure against *P. aeruginosa* (CFR 89.5% for ICU patients and 92.5% for non ICU patients) (Kiratisin et al., 2013). There were relatively numerous studies on prolonging Meropenem infusion for critically ill populations. Critically ill patients face an increased likelihood of experiencing subtherapeutic concentrations, which consequently elevates their chance of treatment failure, thus bring forth more challenge in achieving optimal Meropenem therapy.

A study in 2013 provided an insight of how effective prolonged beta-lactams infusion protocol against gram-negative bacteria infections in the ICU compared to intermittent infusion, designed as before-after study. Focusing on Meropenem, the results showed that more patient in the intermittent infusion administration group received Meropenem (35.5% vs 24.5%, p = 0.007), but in general there was no discernible benefit in employing prolonged infusion (PI) protocol for gram-negative bacteria infections as an empiric treatment over intermittent infusion (II). In terms of treatment efficacy (PI 51.0% vs II 56.6%, p = 0.204), mortality (PI 23.0% vs II 19.4%, p = 0.329), and hospital length of stay (PI median 10.8 vs II median 9.3, p = 0.138), also showed that prolonged infusion protocol was not cliniczlly superior than intermittent infusion (Arnold et al., 2013).

Focusing on the emergence of antimicrobial resistance, a restrospective cohort study by Dhaese et al. concluded that the emergence of antimicrobial resistance among its population was not related to the mode of infusion (Dhaese et al., 2018).

There were three studies focusing on the pharmacokinetic and pharmacodynamic (PK/PD). Two out of three of those studies were simulated on patients with severe respiratory infection. Kong et al. found that usual dosing regimen of Meropenem (2 hours infusion of 1g every 8 hours) could provide good coverage for pathogens with MICs of ≤ 4µg/mL, but to achieve fT > MIC of 80% or 100%, increased doses, more prolonged infusion, shorter intervals, or combinations of those methods might be required (Kong et al., 2017). That result also coherent with the more recent findings from the study in 2021, also focusing on population with severe respiratory infection (Lan et al., 2022). Those result further confirmed by Alsultan et al.,that concluded that extended infusion or continuous infusion might be the better dosing strategies of meropenem in critically ill patients (Alsultan et al., 2021).

Further clinical outcomes comparison between prolonged infusion (PI) and intermittent infusion (II) protocol also explored by a restrospective study in 2020. The study found that the mortality was lower (PI 19% vs II 37%, p = 0.01) and the clinical response was higher (PI 83% vs II 46%, p = 0.038) in the prolonged infusion group compared the intermittent infusion group (Ahmed et al., 2020).

There were few studies on more specific population, as presented by Corcione et al., focusing on gram-negative bacteria infections in burn patients. They suggested that a combination of 2 hours infusion with a higher dose of meropenem, including loading dose, might be a preferred strategy in achieving effective PK parameters (Corcione et al., 2020).

A study investigating penetration ratio of meropenem in epithelial lining fluid (ELF), showed that prolonged infusion protocol proven statistically could achieve higher ELF/plasma ratio

of AUCs compared to intermittent infusion (mean ± SEM : 0.02 ± 0.033 vs 0.20 ± 0.033, p = 0.047) (Frippiat et al., 2015).

Lastly, a study comparing two empirical prolonged infusion regimens of meropenem, one regimen was 2 g meropenem every 8 hours in 24 hours for two days, followed by 1 g meropenem every 8 hours in 24 hours; the other regimen was 1 g meropenem every 6 hours in 24 hours. Both regimens were found to be sufficient in achieving elevated level of fT > MIC for pathogens with MICs < 4 mg/L. However, when higher MICs were targeted, the fT > MIC in the 1 g meropenem every 6 hours in 24 hours group decreased in faster rate than the other group (Eisert et al., 2021).

CONCLUSION

The practice of prolonged infusion can be applied to Meropenem therapy since it is theoretically supported and Meropenem has adequate stability profile. Compatibility issues should be taken into consideration in accordance to the literatures with more precautions on high concentration drug solution.

While the clinical outcomes superiority over the standard intermittent infusion can not be definitively acquired, we encourage the practice of prolonging Meropenem infusion since it has the potential, especially among critically ill populations. Preferred methods of administration that may yield better outcomes are longer infusion period, increased doses, shorter interval between doses, or combinations of those methods.

Articles related to the topic in this narrative review are compiled into **Table 1** below.

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Table 1. Articles Related to Topics for Narrative Synthesis

Author(s)	Design	Population	Sample Size	Outcome(s) / Conclusion
Tomasello et al.	In vitro experiment	Meropenem products from three different manufactures	6	At the 3 to 4 hour mark, all three drugs maintained more than 95% of their initial concentration. However, by the sixth hour, there was a deterioration of 8% to 10%.
Venugopalan et al.	retrospective, observational study	Adult, meropenem-naive patients	22	The median daily dose of meropenem was 6 g/day, with a range of 2-6 g/day. This dose led to a median serum concentration of 17.8 mg/L, with an interquartile range of 9.3-27.8 mg/L. Meropenem administered as a continuous infusion achieved free drug concentrations equal to or higher than the MIC of the pathogen during the whole dosing period in 95% of cases. 80% of patients achieved clinical cure. The stability trial demonstrated minimal drug degradation after the 12-hour dosing interval.
Fawaz et al.	In vitro experiment	Meropenem product from generic brand and AstraZeneca®	2 groups, divided by temperature setting	Meropenem should not be administered via continuous infusion for a duration of 24 hours. However, it is feasible to administer meropenem via continuous infusion for at least 7 hours if the temperature remains

				below 22°C, and for 5 hours if the temperature remains below 33°C.
Chen et al.	In vitro experiment	Meropenem and Vaborbactam products	5 replicates for each group of 4, 8, and 16 mg/mL concentrations	All replicates at room temperature maintained meropenem and vaborbactam stability for 12 hours, with concentration-dependent degradation. Refrigerated experiments showed stability at all doses for 120 hours.
Giménez-Giner et al.	In vitro experiment	Admixtures of Meropenem	2 groups of meropenem admixtures : (i) in infusor, (ii) in infusion bag, with various concentration and temperatures setting	At 4.5° C, meropenem 6 g in a 24-hour infusion in 240 mL of 0.9% NaCl can be infused at 10 mL/h. Meropenem 1 or 2 g in 0.9% NaCl in a 250-mL infusion bag can be infused for 3–4 h. Admixtures can be prepared in the infusion bag with 24 h stability.
Lessard et al.	In vitro experiment	Meropenem combination with other drugs through Y-Site injection	Meropenem with 101 types of drug	Out of the 101 drugs that were examined, 83 were determined to be compatible, while the remaining 17 were deemed incompatible.
Moehring & Sarubbi	UpToDate article	Beta-lactams antibiotic	-	Safety : Meropenem is relatively safe to be administered as prolonged infusion.
Koomanachai et al.	Randomized Controlled Trial	Clinical specimens of 4 bacteria isolates : - *Eschirichia coli* (EC) - *Klebsiella pneumoniae* (KP) - *Pseudomonas aeruginosa* (PA) - *Acinetobacter baumannii* (AB)	250 sample each. 1000 in totals	- When evaluating the Enterobacteriaceae, the percentage of susceptibility to cephalosporins varied from 60% for ceftriaxone to 86% for cefepime. - All carbapenems demonstrated a susceptibility rate of 90% and CFR of 90% for both (EC) and (KP). - Cefepime and ceftazidime shown a greater percentage of susceptibility (82-83%) towards (PA) compared to the carbapenems (61-69%). The only treatment that produced an optimum CFR (92%) against this organism was doripenem administered at a dose of 2 grams every 8 hours as 4-hours prolonged infusion.
Kiratisin et al.	Comparative Activity of Carbapenem Testing (COMPACT) surveillance study	Doripenem, imipenem, and meropenem regimens againts various gram negative organism isolates from Asia-Pacific region	5000 patients Monte Carlo Simulation for each regimen	Standard regimens of carbapenems are expected to be highly effective in the Asia-Pacific region. But, to handle resistant non-fermenting gram-negative bacteria such as Pseudomonas aeruginosa and Acinetobacter baumannii, it will be necessary to employ higher dose combined with prolonged infusion protocol regimen.
Arnold et al.	Single-center, before-after, comparative effectiveness trial	ICU patients at Barnes-Jewish Hospital	503 patients	Regular utilization of extended infusion of time-dependent antibiotics for empirical treatment of gram-negative bacterial infections does not provide any benefits compared to intermittent administration of antibiotics in terms

				of treatment effectiveness, mortality rate, or duration of hospitalization.
Dhaese et al	Restrospective cohort study	Patient of the ICU of the Ghent University Hospital	205 patients	The development of antimicrobial resistance to piperacillin/tazobactam or meropenem was not influenced by the method of infusion.
Kong et al	Prospective study	Intracerebral hemorrhage patients with nosocomial pneumonia	11 Patients	When aiming for a target of 40% time above the minimum inhibitory concentration (T>MIC), the typical dosing regimens can effectively combat infections with MICs of 4 μg/mL or lower. However, in cases when an increasingly resistant infection or when targeting higher MIC (80-100%), it may be necessary to administer larger doses of drugs, prolonging infusion time, reduce the interval between doses, and/or employ a combination of different therapies.
Lan J et al	Prospective study	ICU patients	236 total blood samples from 48 patients	In order to attain the most favorable pharmacokinetic/pharmacodynamic target attainment (PTA), meropenem should be delivered either through frequent dosing or via continuous intravenous infusion.
Alsultan et al	Prospective observational study	ICU patients at King Khalid University Hospital	83 samples from 43 critically ill patients	Over 50% of the patients failed to achieve PKPD target, therefore better dosing strategies were required, such as utilizing extended or prolonged infusion administration.
Ahmed et al	Retrospective cohort study	Medical Intensive Care Unit (MICU) patients at urban tertiary academic medical center in New York City	148 patients in total	The mortality was lower (PI 19% vs II 37%, p = 0.01) and the clinical response was higher (PI 83% vs II 46%, p = 0.038) in the prolonged infusion group compared the intermittent infusion group.
Corcione et al	Prospective cohort study	Patients at the Burn Center of CTO Hospital, Città della Salute e della Scienza (Turin, Italy)	17 burn patients	The data indicated that administering a 2-hour infusion of meropenem at a higher dosage, which includes a loading dose, may lead to the attainment of beneficial pharmacokinetic characteristics.
Frippiat et al	single-centre, open-label, prospective comparative study	Patients from five ICUs, with a total of 42 medical and surgical beds, at the Centre Hospitalier Universitaire du Sart Tilman, Liege, Belgium	55 patients in total	The recommended treatment for severe nosocomial pneumonia was administration of 2 g meropenem intravenously over a period of 3 hours, every 8 hours. This treatment protocol successfully reached the maximum desired pharmacodynamic goals in both plasma and epithelial lining fluid (ELF).
Eisert et al	The DOMESEP (Dosing of Meropenem in Septic Shock) study is a prospective	ICU patients at the University Hospital Aachen (UHA) and University	32 patients in total	Both dosing regimens in the study were adequate in treating pathogens with low MIC (<4 mg/L), but more resistant strains require higher doses of meropenem.

observational study	Hospital Muenster (UHM)

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