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Yi-Ling Lai Date

Comparing Inpatient Mortality After a Switch
from Traditional to Alternative Dosing of Meropenem

By

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Master of Public Health

Epidemiology

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By

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Bachelor of Science
University of Washington
2012

Faculty Thesis Advisor: Jesse T. Jacob, M.D., M.Sc.

An abstract of
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Abstract

Comparing Inpatient Mortality After a Switch
from Traditional to Alternative Dosing of Meropenem
By Yi-Ling Lai

Meropenem is broad spectrum antibiotic used to treat a variety of serious and potentially life-threating infections. Based on pharmacologic modeling, smaller, more frequent dosing of this drug may provide a marginal benefit to patients by optimizing pharmacokinetics. Previous small-scale studies had not identified significant inferiority with the implementation of the alternative dosing method of meropenem. Therefore, this retrospective cohort study aimed to investigate whether the implementation of the alternative dosing method is deemed inferior to the traditional method in terms of inpatient mortality in a large scale academic facility which implemented alternative dosing. The inpatient mortality rate of patients who received meropenem with traditional dosing regimen during 2009 (n=572) in the hospital were compared to that of patients who received meropenem with alternative dosing regimen from February 2010 to January 2011 (n=684). Among the patients who received traditional dosing and alternative dosing, similar proportion of patients died in the hospital (17.5% vs. 15.8%, p=0.42). In multivariable analysis, controlling for age, intensive care unit drug administration, and Charlson comorbidity index, the odds ratio of having alternative dosing method vs. traditional dosing method among patients who died in the hospital is 0.78 (p=0.13), and is not statistically significant. Also, the results of the Kaplan-Meier survival analysis shows no significant difference in survival between patients who received traditional dosing and those who received alternative dosing (log-rank test p=0.80). The inpatient mortality change of patients before and after the implementation was assessed with interrupted time series analysis, and it shows similar, both decreasing, slopes of change in inpatient mortality before and after the implementation. This study also assessed the change in defined daily doses (DDD) to confirm the true implementation of the alternative method. The slopes individually show increase in DDD, with a dramatic downshift after time of implementation. The DDD data has an overall decreasing trend for the entire study course. While less amount of meropenem is administered the same results can be reached. Hospitals, especially those with low resources, can implement the alternative dosing method to treat infections with less amount of meropenem.

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Finally and most importantly, I would also like to thank my dearest parents, for their love throughout my life. They have showed me the expansion of knowledge is never ending. I am very appreciative for having such intelligent and open-minded parents.

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Introduction

The carbapenems, including meropenem, have a very broad spectrum of activity and are relatively safe, leading to their frequent use to treat a wide variety of serious and life-threatening infections. (2) Because of the increasing prevalence of resistant organisms, these β-lactams are also agents of last resort and there is an urgent need to use them optimally when there are used. Such dosing would both improve individual patient outcome and minimize the spread of resistance on a population level. (3) The therapeutic efficacy of an antibiotic depends on its ability to achieve specific pharmacokinetic (PK) and pharmacodynamics (PD) targets in relation to a pathogen's minimum inhibitory concentration (MIC). (3) (5) β-lactam antibiotics have the characteristic of being pharmacodynamically time dependent, and therefore the effectiveness of the drug depends on the dose, frequency, and length of time it has been infused. (3) (6) (7)

Alternative dosing strategies achieve similar pharmocodynamic targets compared with traditional dosing strategies, where alternative dosing methods includes administration by continuous or prolonged infusion or by smaller doses given more frequently to attain higher consistent drug levels compared with traditional dosing. (8) To compare dosage of traditional method and alternative method, a standardized value called the defined daily dose (DDD). It is defined by the World Health Organization as the assumed average maintenance dose per day for a drug used for its main indication in adults for a specific type of antibiotic. (9) With this value, institutions can benchmark their values against the standardized value, values from other institutions, or values from a dosing method under investigation. A previous study at a community hospital suggests that despite using a lower total daily dose of meropenem, the alternative dosing regimen

yield equivalent results, in terms of success rates, and duration of therapy compared with traditional dosing regimen. (10) From a pragmatic perspective, this dosing can improve pharmacodynamics while reducing DDD and therefore drug costs. Based on the existing data and these potential benefits, this study assesses the effect of this intervention on inpatient survival, the change of slope of inpatient mortality rate, and the change of slope of DDD of meropenem after the implementation of the alternative dosing method.

Methods

Design

This study follows a cohort of patients that received meropenem in the hospital retrospectively. In addition, it uses a quasi-experimental design to assess changes before and after the implementation of the intervention. Because the intervention is hypothesize to not have a major effect the primary outcome of inpatient morality, it is in effect a non-inferiority study.

Intervention

For patients with normal renal function, traditional dosing regimen of meropenem is defined as receiving 2000-mg intravenous injection over 30 minutes infusion every 8 hours for adult patients by the United States Food and Drug Administration (11) and the hospitals' antibiotic stewardship team, and alternative dosing regimen for this study is defined as receiving 500-mg intravenous injection over 30 minutes infusion every 6 hours.

Null Hypothesis

Alternative dosing regimen of meropenem is not inferior to the traditional dosing regimen in terms of inpatient mortality with a margin of 3% difference. The odds of having alternative meropenem dosing among patients who died in the hospitals after receiving meropenem treatment is not higher than those who survived in the hospital. The survival probability of patients on alternative dosing method is not inferior to that of those on traditional dosing method. The slope of inpatient mortality rate change before

the implementation of alternative meropenem dosing is not larger than that after the implementation.

Alternative Hypothesis

Alternative dosing regimen of meropenem is inferior to the traditional dosing regimen in terms of inpatient mortality with a margin of 3% difference. The odds of having alternative meropenem dosing among patients who died in the hospitals after receiving meropenem treatment is higher than those who survived in the hospital. The survival probability of patients on alternative dosing method is inferior to that of those on traditional dosing method. The slope of inpatient mortality rate change before the implementation of alternative meropenem dosing is larger than that after the implementation.

Study Population

All patients who received meropenem therapy at two 500-bed academic medical centers (Emory University Hospital and Emory University Hospital Midtown) in Atlanta, Georgia between January 1, 2009 and January 31, 2011 were considered for inclusion in the study cohort. January of 2010 is the month when alternative dosing protocol was implemented, and therefore no patients who received meropenem therapy during that month is included. Patients who were administered meropenem during January 1, 2009 to December 31, 2009 received the antibiotic in traditional dosing method, while patients who were administered meropenem during February 1, 2010 to January 31, 2011 received the antibiotic in alternative dosing method. Patients receiving <3 doses of meropenem (because the drug would not have had time to achieve steady state), or

standard dosing during the traditional therapy phase (for patients with cystic fibrosis or central nervous system infections as a specific exception to alternative dosing because these populations have different PD targets requiring standard dosing) were excluded. Only the first admission during the study period was included.

Baseline Characteristics

Baseline characteristics of all patients were obtained from the electronic medical records of the Emory University Hospital system. Demographic data included age at the time of service admission (in years), sex (male or female), and self-reported race (white, black, or other). The location of first dose of meropenem administered (intensive care unit (ICU) compared to non-ICU) and hospital were also captured from the electronic medical record. Charlson comorbidity index was included as an indication of the severity of comorbidities and was obtained from manual chart review.

Statistical Analysis

Means and standard deviations are used to measure central tendencies and spread for normally distributed variables. For the univariate analysis of categorical variables, counts and percentages are used to represent the characteristics of the cohort. Student's t-test (for continuous, normally distributed variables), and Chi-square test (for categorical variables) are used for assessing relationships between dosing regimen (traditional vs. alternative) and inpatient mortality status (mortality = yes vs. no), and patient characteristics. A variable is defined as normally distributed when the Shapiro-Wilk test for normality is statistically significant. Since all the continuous variables are normally distributed, only parametric tests are performed.

Predictors with a $p<0.20$ and biologic plausibility were eligible for inclusion in modeling. Logistic regression, using the outcome of inpatient morality is performed to control for interactive variables such as age, ICU drug administration, and Charlson comorbidity index (dichotomized to >2 vs. ≤2). It is also used to calculate the odds ratio for inpatient mortality. When calculating the odds ratio, interactions between each variables in the final models are assessed with chunk interaction test. Models were created using all potential variables including backward selection. Several models were considered, and the final model was chosen based on goodness of fit and biologic plausibility.

Survival analysis with the LIFETEST procedure in SAS is used to generate a graphical representation of inpatient survival probability with a Kaplan-Meier curve. The two groups (traditional and alternative dosing) were compared up to 90 days after the first dose of meropenem was administered, and the log-rank test was used to assess for differences in survival during the period between the two groups. The change in the slope of the inpatient mortality rate is assessed with an interrupted time series analysis.

With the AUTOREG procedure in SAS, we correct for the autocorrelation and the homoscedasticity that associates with interrupted time series analyses. (15) The inpatient mortality rate for each month is calculated by dividing the total number of deaths per month by the total number of admissions receiving at least three days of meropenem in that month. Statistical significance is assessed at alpha=0.05 for all statistical tests. All statistical analyses were conducted using SAS software, versions 9.3 and 9.4 (SAS Institute, Inc., Cary, NC).

Outcomes

The primary outcome of the study is inpatient mortality. Inpatient mortality is defined as patient death that occurred in patients who received meropenem treatment at least once during the study period (January 1, 2009 to January 31, 2011). Secondary outcomes include DDD/1000 patient days, and the change in slopes of the mortality rate before and after the intervention.

Results

Study Population

A total of 33,683 doses of meropenem were given in 1579 admissions. Among 1315 unique patients, those receiving <3 days of meropenem t (n= 4, 0.3%), who received standard dosing during the traditional therapy phase (n= 34, 2.6%) or were treated for cystic fibrosis patients (n= 21, 1.6%) central nervous system infections were excluded, resulting in a final cohort of 1256 patients with 572 patients (45.5%) receiving traditional dosing and 684 patients received alternative dosing.

Total Inpatient Mortality Counts

From January 1, 2009 to January 31, 2011, excluding January 2010, there were a total of 208 patients who died in the two hospitals of this study among the 1256 patients who met the inclusion criteria (overall mortality rate=0.166). [Table 3] The patients who died in the hospital tended to be older, male, non-white, received meropenem in the ICU, had Charlson comorbidity index that was higher than 2, and stayed at Clifton facility.

Univariate Analysis

All of the continuous variables we assess are normally distributed with statistical significance under the Shapiro-Wilk test (age, p=<0.0001). Therefore, only parametric tests are performed. The average age of the patients who died in the hospital was 62.5 (± 16.6), which was 5.7 years older than those who did not die in the hospital. The sex of the patients who died were quite evenly distributed between male and female, but like the total study population sex distribution, slightly more males (59.1%) experienced the outcome. There were no significant differences between the distribution of patients who

died and those who did not for patient's sex, and race. Of the patients who died, less than half were white (42.3%). Over 50 percent of the patients who died were administered meropenem in the ICU (81.7%), had a Charlson comorbidity index that was greater than 2 (76.9%), and hospitalized in Clifton facility (64.4%). The Charlson comorbidity index ranged from 0 to 14 among the final study cohort, with a median of 3. The complete summary results of univariate analysis of outcomes by patient characteristics are displayed fully in Table 3.

Multivariate Analysis

A multivariable model is selected by stepwise selection. A model was considered initially including dosing method and patient characteristics including age, male sex, white race, and facility, with an odds ratio of 0.83 (confidence interval: 0.61, 1.13) which was not statistically significant (p=0.23), and a c score of 0.63. The white race variable had a p-value for effect estimate that was not significant, and was dropped out of the model. The variable male sex had a borderline significance (p=0.06), and was kept in the model for next round of analysis.

With the addition of ICU status, the model now contained the variables dosing method, age, male sex, Midtown facility, and ICU status. The odds ratio estimate of the alternative dosing method with this model was 0.77 (confidence interval: 0.56, 1.05). The model fit was also better than the one described in the previous paragraph, with a c score of 0.74. The variables male sex and Midtown facility became non-significant after the addition of ICU status, and was then dropped out of the model.

Finally, the variable indicating high Charlson comorbidity index (>2) was included in the model in addition to the significant variables that resulted from the last analysis. Since the distribution of Charlson comorbidity index among patients was not normally distributed, and since a Charlson comorbidity index of greater than 2 is considered more ill, the variable was dichotomized into two groups: >2 and ≤2 for meaningful statistical and clinical inferences. The final multivariate model chosen includes variables that are statistically significant for the alternative hypothesis that the variable coefficient does not equal to 0, and the exposure variable – alternative dosing. The final model is composed of the following variables: alternate dosing, age, ICU administered meropenem, Charlson comorbidity index greater than 2. The summary results of the odds ratio estimate from the multivariate model are shown in Table 2. The final model has a good fit with the c score of 0.76.

After a chunk interaction test, no interaction is detected among the variables that are included in the final model.

Survival Analysis

The Kaplan-Meier survival curves of the study population [Figure 1] shows a visual divergence until 30 days, but over the entire period assessed (90 days), there log-rank test demonstrates no difference between the survival probabilities of the patients on traditional meropenem dosing vs. patients on alternative meropenem dosing.

Interrupted Time Series Analysis

Defined Daily Dose

In the AUTOREG model for interrupted time series analysis, time variable is one that increases throughout the course of the study, with 1 increase by each month. The method variable is set to 0 for alternative dosing method, and 1 for alternative dosing method. The time-after-implementation variable is one that was held at 0 before the implementation of the alternative dosing method, and increased by 1 by each month after the implementation. All of these variables have significance with p-value <0.0001. In Figure 2, the blue hollow circles represent the data point of the inpatient mortality of each month, and the black solid circles represent the regression lines that are fitted for each dosing methods. The black solid circle line before January 2010 represents the regression line of the traditional dosing method, and the one after January 2010 represents that of the alternative dosing. The grey solid line represents the regression line for the entire study period. Figure 2 shows the effect of implementation of the alternative dosing. The rate of DDDs of meropenem per 1000 patient-days are steadily rising until the end of 2009. (slope = 0.50) Beginning in February of 2010, the absolute DDD/10000 patient days dropped dramatically, congruent with the timing of the implementation of the alternative dosing method. Subsequently, the slope of meropenem consumption appears to continue to increase after the intervention. (slope = 1.53)

Inpatient Mortality

The variables included in the AUTOREG model is the same as that of the DDD model. All of them have significance (p <0.0001) except for the time-after-

implementation variable (p=0.72). Overall inpatient mortality decreased over the study period from January 2009 to January 2011. The legend of the shapes are as described for the DDD in Figure 3. From Figure 3, we can see that all the trends for inpatient mortalities are decreasing. The overall regression line (grey solid line) has an overall negative slope (-0.18). The slopes (changes of change) of inpatient mortality for alternative vs. traditional dosing methods do not seem to differ, while both have negative slopes (traditional: -0.39, alternative: -0.41).

Discussion

Based on the findings that consumption decreased appropriately when alternative dosing was implemented and that mortality appeared to decrease linearly during the entire study period, the null hypothesis cannot be rejected and that the alternative dosing method of meropenem is not inferior to the traditional dosing method of meropenem using inpatient mortality as an outcome. With the univariate [Table 1, Table 3], multivariate logistic regression [Table 2], survival [Figure 1], and interrupted time series analyses [Figure 2, Figure 3], we cannot observe statistically significant difference between the two meropenem dosing methods. With an overall decrease of the define daily dose and the benefits of using fewer amounts of meropenem to treat infections mentioned in the introduction section, the inpatient mortality rate also has an overall decrease after the implementation of the alternative dosing method, although the rates of the decrease do not seem to differ.

Our findings that inpatient mortality rates were actually lower in the alternative dosing period after controlling for confounding factors is reassuring. This is also supported by the slopes of the mortality rates being similar before and after implementation of alternative dosing. Though there was visual evidence that 30-day survival was improved in alternative dosing, over the entire 90 day period of survival analysis there was no difference. Together these findings uphold the theoretical findings that improving PK and PD characteristics improve patient care and suggest that alternative dosing may not simply be non-inferior but superior to traditional dosing the patient population we studied.

Strengths and Limitations

This is the largest study to our knowledge that investigates the outcomes of implementing alternative meropenem dosing method in a hospital setting, and involves two hospitals. It is also one of the first studies to utilize interrupted time series analysis to detect changes in slope of inpatient mortality while correcting for error term autocorrelation and heteroscedasticity in addition to analysis with logistic regression models. (12) (15) Furthermore, the data of this study is very complete with no missing values, which makes inferences drawn from the results more valid. This study corroborates previous smaller clinical studies as well as PK/PD modeling studies, re-enforcing its external validity.

This study also has some limitations. The quasi-experimental study design (interrupted time series) uses an error term not independent through time, and the study population is not randomized to either exposure status. We corrected for this by using the AUTOREG procedure with SAS. (15) The AUTOREG procedure corrects for autocorrelation, and the heteroscedasticity. We did exclude some patients based on pre-specified clinical criteria as a part of the alternative dosing strategy, which can limit the application of this approach. However, these patients collectively only make up 4.5% of the original study population, and have little effect on the results.

A post-hoc power calculation (using ClinCalc (16)) found a calculated power of 12.5% if the true difference in mortality was our finding of 1.7% decrease with alternative dosing. To reach the 80% power to detect 3% change in inpatient mortality, this study will need to have a population of 4686 with 2343 patients on each dosing

method. (17) However, our intention was not to prove a morality difference, and we suggest that we have adequately show non-inferiority.

Lastly, this study did not account for empiric (no clear microbiology) compared to directed (where there is a confirmed organism) antimicrobial therapy. Resistance could not be taken into account, and there is a possibility that these and unmeasured confounder could bias the results of the study. However, we have approached mortality from different approaches and controlled for the more important measurable confounders.

Future Directions

From the strengths and limitations of this study, a design of an improved future studies can be proposed. For instance, a larger study population can be recruited, or a dataset pooled from multiple institutions can be used to draw results, as a larger population can provide a study with more statistical power. Also, data from a low resource institution can be utilized to draw inferences for global application. Future studies can also incorporate microbiology culture of patients to more accurately assess the efficiency and results of the implementation of alternative dosing method, and compare it to the traditional dosing method.

Public Health Implications

Since decreasing defined daily dose by the implementation of alternative dosing regimen of meropenem does not affect inpatient mortality rate significantly, physicians may be able to prescribe fewer grams of meropenem, but achieve better PD targets without increasing mortality. For high resource hospitals, this would mean that budget for drug purchasing can be decreased due to the lowered amount of meropenem prescribed.

Furthermore, this is especially important for places with fewer health care resources or access to health care.

Globally, many places have limited resources, including antibiotics, and with fewer defined daily doses administered, there can be equal number deaths prevented and improved drug accessibility, which results in more efficient drug use. Limited resources also result in lowered community resistance theoretically.

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Tables and Figures

Table 1. Demographic Information of the Study Population by Dosing Method

Variables (mean ± SD , n (%) or median [IQR])	Patients Met Inclusion Criteria (N=1256)	Traditional Dosing (n=572)	Alternative Dosing (n=684)	P-Value
Age	57.8±16.5	57.0±17.1	58.4±16.0	0.16
Male Sex (vs. Female Sex)	668 (53.2)	287 (50.2)	381 (55.7)	0.05
White Race (vs. Non-White Race)	572 (45.5)	239 (41.8)	333 (48.7)	0.01
ICU (=Yes)	617 (49.1)	268 (46.9)	349 (51.0)	0.14
Charlson comorbidity index >2 vs. ≤2	700 (55.7)	309 (54.0)	391 (57.2)	0.26
Clifton vs. Midtown	931 (74.1)	438 (76.6)	493 (72.1)	0.07
Inpatient Mortality=Yes	208 (16.6)	100 (17.5)	108 (15.8)	0.42

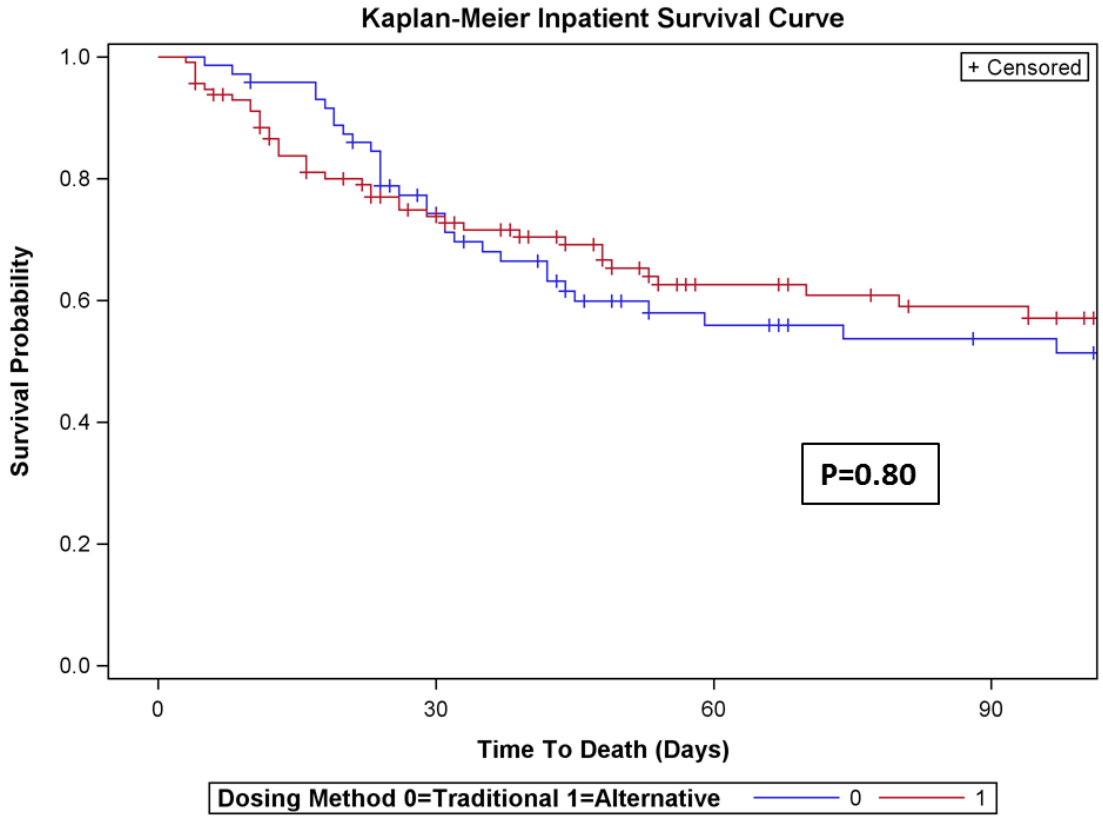
Table 2. Table of Odds Ratios Calculated with Multivariable Logistic Regression

Effect	**Odds Ratio Estimate**	**95% Confidence Limits**		**P-Value**
Alternative Dosing vs. Traditional	0.781	0.568	1.075	0.13
Age	1.015	1.004	1.026	0.01
ICU= Yes	5.182	3.548	7.567	<0.01
Charlson comorbidity index >2 vs. ≤2	2.327	1.622	3.339	<0.01

Table 3. Demographic Information of the Study Population by Inpatient Mortality

Variables (mean ± SD , n (%) or median [IQR])	**Inpatient Mortality = No (n=1048)**	**Inpatient Mortality =Yes (n=208)**	**P-Value**
Age	56.8±16.3	62.5±16.6	<0.01
Male Sex (vs. Female Sex)	545 (52.0)	123 (59.1)	0.06
White Race (vs. Non-White Race)	484 (46.2)	88 (42.3)	0.31
ICU (=Yes)	447 (42.7)	170 (81.7)	<0.01
Charlson comorbidity index >2 vs. ≤2	540 (51.5)	160 (76.9)	<0.01
Clifton vs. Midtown	797 (76.1)	134 (64.4)	<0.01

Figure 1. Kaplan-Meier Survival Analysis of Traditional vs. Alternative Dosing of Meropenem (P-value of Log Rank Test Displayed)



	0 Days		30 Days		60 Days		90 Days	
Dosing Method	**N at Risk**	**Survival in % (95% CI)**	**N at Risk**	**Survival in % (95% CI)**	**N at Risk**	**Survival in % (95% CI)**	**N at Risk**	**Survival in % (95% CI)**
Traditional	72	100 (-, -)	49	74.3 (63.4, 83.8)	28	55.9 (43.6, 67.9)	23	53.7 (41.2, 66.0)
Alternative	114	100 (-, -)	69	73.8 (65.1, 81.7)	39	62.6 (52.5, 72.1)	31	59.0 (48.4, 69.2)

Figure 2. Time Interrupted Series Analysis of the Change of Slope of Defined Daily Dose Before and After the Implementation of Alternative Dosing of Meropenem

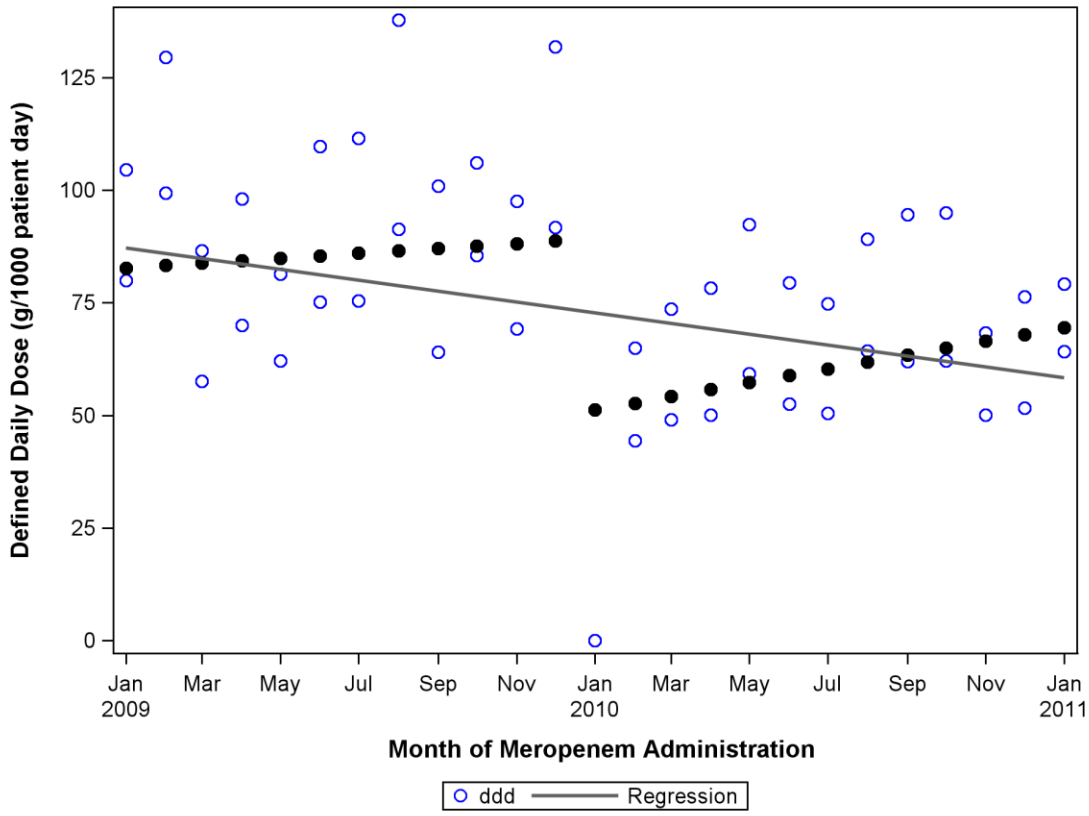


Figure 3. Time Interrupted Series Analysis of the Change of Slope of Inpatient Mortality Rate per 100 Patients Who Received Meropenem Before and After the Implementation of Alternative Dosing of Meropenem