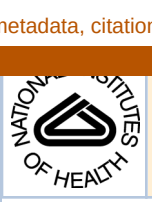

Published in final edited form as:

Pediatr Infect Dis J. 2013 July ; 32(7): 748–753. doi:10.1097/INF.0b013e31828be70b.

Adverse Events Associated with Meropenem versus Imipenem/Cilastatin Therapy in a Large Retrospective Cohort of Hospitalized Infants

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Abstract

Background—Carbapenems are commonly used in hospitalized infants despite a lack of complete safety data and associations with seizures in older children. We compared the incidence of adverse events in hospitalized infants receiving meropenem versus imipenem/cilastatin.

Methods—We conducted a retrospective cohort study of 5566 infants treated with meropenem or imipenem/cilastatin in neonatal intensive care units managed by the Pediatrix Medical Group between 1997 and 2010. Multivariable conditional logistic regression was performed to evaluate the association between carbapenem therapy and adverse events, controlling for infant factors and severity of illness.

Results—Adverse events were more common with use of meropenem compared with imipenem/cilastatin (62.8/1000 infant days vs. 40.7/1000 infant days, $P<0.001$). There was no difference in seizures with meropenem vs. imipenem/cilastatin (adjusted odds ratio [OR] 0.96; 95% confidence interval 0.68, 1.32). The incidence of death, as well as the combined outcome of death or seizure, was lower with meropenem use—OR 0.68 (0.50, 0.88) and OR 0.77 (0.62, 0.95), respectively.

Conclusion—In this cohort of infants, meropenem was associated with more frequent but less severe adverse events when compared with imipenem/cilastatin.

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Conflicts of interest

Christoph P. Hornik, Amy H. Herring, and Reese H. Clark have no relevant conflicts to disclose.

Keywords

meropenem; imipenem/cilastatin; adverse events; infant

Use of carbapenem antibiotics is increasing in hospitalized infants.[1] Meropenem and imipenem have broad-spectrum activity against multiple gram-positive and gram-negative, aerobic, facultative, and anaerobic bacteria.[2] Meropenem is Food and Drug Administration (FDA)-approved for use in children and infants >3 months of age, including those with bacterial meningitis, and imipenem combined with cilastatin is FDA-approved for use in children and infants <3 months of age.[3,4]

In adults, the safety profiles of both imipenem/cilastatin and meropenem are well-established and are similar for the most common clinical adverse events (AEs), including irritation at injection site, rash, diarrhea, nausea, vomiting, and pruritus, and for laboratory AEs, including elevation in hepatic transaminases, serum creatinine, and blood urea nitrogen levels.[5] The incidence of seizures, however, is considerably higher in adults treated with imipenem/cilastatin[6] when compared with those treated with meropenem.[7–9]

In pediatric patients, diarrhea and rash are among the most common clinical AEs and elevation in hepatic transaminases among the most common laboratory AEs reported with use of meropenem and imipenem/cilastatin.[3,4] Safety data for these 2 antibiotics in hospitalized infants are limited to single-center studies that have reported variable incidences of seizures.[10–14] No randomized studies comparing the safety of imipenem/cilastatin against meropenem have been conducted in any pediatric patient populations. We sought to compare the safety profile of imipenem/cilastatin versus meropenem in neonates and young infants using a large multicenter database.

METHODS

Study Cohort

This study used a retrospective cohort of all infants discharged from 322 neonatal intensive care units (NICUs) managed by the Pediatrix Medical Group from 1997–2010 who were treated with meropenem or imipenem/cilastatin during their first 120 days of life. The data were obtained from an administrative database that prospectively captures information from daily progress notes generated by clinicians on all neonates cared for by the Pediatrix Medical Group. Data on multiple aspects of care are entered into the system to generate admission notes, daily progress notes, procedure notes, and discharge summaries. Information is collected regarding maternal history and demographics, medications, laboratory results, culture results, and diagnoses. Medication dosing amounts and intervals are not recorded. The study was approved by the Duke University Institutional Review Board without the need for written informed consent as the data were collected without identifiers.

Definitions

We identified each day that infants were exposed to either meropenem or imipenem/cilastatin. On the day that infants were transitioned from one carbapenem to another, we recorded only the initial carbapenem administered. We defined gram-negative infection as the presence of any gram-negative organism not considered to be a contaminant in a culture from blood, urine, or cerebrospinal (CSF) fluid while on carbapenem therapy or up to 7 days prior to initiation of carbapenem therapy. We defined seizure as either a seizure diagnosis or the initiation of 1 of the following antiepileptic drugs (AEDs): carbamazepine, fosphenytoin, pentobarbital, levetiracetam, or phenytoin. We did not include phenobarbital as an AED

because it is frequently used for other indications in this population (e.g., cholestasis). We defined a seizure, rash, or diarrhea as an AE only if the event started on the day that a carbapenem was administered, regardless of whether the infant had been diagnosed with a prior seizure, rash, or diarrhea episode. We defined death as an AE when the infant died on the day that a carbapenem was administered. The following were considered laboratory AEs: direct bilirubin >5 mg/dL, creatinine >1.7 mg/dL, aspartate aminotransferase (AST) >200 units/L, and alanine aminotransferase (ALT)>100 units/L on days that a carbapenem was administered. Each occurrence of a laboratory AE and seizure AE was counted.

Statistical Analysis

The unit of observation for this study was an infant day of exposure to meropenem or imipenem/cilastatin. We used standard summary statistics to describe the study variables. Infant-level continuous and categorical variables were compared between patients exposed to imipenem/cilastatin and meropenem using Student's t-test and chi-square tests, respectively. We used conditional univariable and multivariable logistic regression conditioned on postnatal age in days to examine the association between carbapenem treatment and outcomes controlling for gestational age (GA) in weeks, discharge year, highest daily fraction of supplemental oxygen (FiO_2), use of mechanical ventilation, use of inotropes (dopamine, dobutamine, epinephrine, norepinephrine, phenylephrine, or vasopressin), the presence of any positive culture from the CSF on the day of carbapenem treatment or up to 21 days prior to the start of therapy, a history of seizure diagnosis prior to the start of therapy, and the presence of grade III or IV intraventricular hemorrhage (IVH) prior to the start of therapy. Outcomes included laboratory AEs, death, seizures, and the combined outcomes of seizure or death or any AE as defined above. All analyses were performed using Stata 12 (College Station, TX) and assumed a significance limit of $\alpha = 0.05$.

RESULTS

Patient Characteristics and Drug Exposure

Our cohort consisted of 5566 infants with a mean GA of 29 weeks (5^{th}, 95^{th} percentile: 23, 38) and a mean birth weight of 1356 g (530, 3232). A total of 2087 (37.5%) infants received only imipenem/cilastatin, 3256 (58.5%) infants received only meropenem, and 223 (4.0%) infants received both carbapenems. Of the 223 infants who received both imipenem/cilastatin and meropenem, 28% received meropenem first, and 72% received imipenem/cilastatin first. Infants receiving imipenem/cilastatin were more mature compared with infants receiving meropenem—30 weeks GA (24, 38) vs. 29 weeks GA (23, 38), respectively; $P<0.001$ (see Table, SDC 1). Infants receiving imipenem/cilastatin had a higher birth weight compared with infants receiving meropenem—1424 g (554, 3164) vs. 1306 g (520, 3265), respectively; $P<0.001$. There was a higher proportion of Hispanic infants among those receiving imipenem/cilastatin compared with those receiving meropenem—63% vs. 38%; $P<0.001$.

Mean postnatal age of first exposure was slightly lower for imipenem/cilastatin compared with meropenem—22 days (3, 68) and 25 days (2, 74), respectively; $P=0.02$. The majority of infants were exposed to carbapenems for <14 days—79% for imipenem/cilastatin and 74% for meropenem. The proportion of patients exposed to carbapenems for >14 days decreased during our study period from 56% in 1997 to 24% in 2010 ($P=0.03$). Exposure to inotrope therapy and mechanical ventilation was lower while exposed to imipenem/cilastatin compared with meropenem (107.5/1000 infant days vs. 160.4/1000 infant days, $P<0.001$, and 516.0/1000 infant days vs. 600.9/1000 infant days, $P<0.001$), and exposure to an FiO_2>50% was higher while on imipenem/cilastatin compared with meropenem (200.3/1000

infant days vs. 167.2/1000 infant days, $P<0.001$). The proportion of infants with IVH or meningitis prior to the start of carbapenem therapy was higher in the meropenem group compared with the imipenem/cilastatin group (8% vs. 3%, $P<0.001$, and 1.5% vs. 0.5%, $P<0.001$).

There were 24,539 imipenem/cilastatin infant days and 38,705 meropenem infant days. Duration of carbapenem therapy was slightly longer for infants exposed to meropenem alone (mean 11.1 days [range 1, 29 days]) compared with those exposed to imipenem/cilastatin alone (mean 10.6 days [1, 24]) ($P=0.03$). For infants exposed to imipenem/cilastatin, 18% had a documented gram-negative infection vs. 26% among infants exposed to meropenem ($P<0.001$), and 0.9% had a diagnosis of culture-positive meningitis vs. 2.2% among infants exposed to meropenem ($P<0.001$). Use of meropenem increased and use of imipenem/cilastatin decreased during our study period (Figure 1).

Clinical and Laboratory Events Associated with Carbapenem Therapy

Overall AEs were more common with meropenem compared with imipenem/cilastatin (62.8/1000 infant days vs. 40.7/1000 infant days; $P<0.001$). Infants exposed to imipenem/cilastatin and meropenem were more likely to have at least 1 AE compared with infants exposed to meropenem or imipenem/cilastatin alone (51.1% vs. 31.7% vs. 31.1%, respectively; $P<0.001$).

The most commonly observed laboratory AE was direct hyperbilirubinemia (25.7/1000 infant days). Overall laboratory AEs were more common while infants were exposed to meropenem compared with imipenem/cilastatin (56.1/1000 infant days vs. 31.3/1000 infant days; $P<0.001$), and all individual laboratory AEs evaluated were more common on meropenem (Table 1). The adjusted odds of a laboratory AE were higher while on meropenem compared with imipenem/cilastatin (odds ratio [OR] 1.41, 95% confidence interval 1.28, 1.55) (Table 2). Infants exposed to meropenem and imipenem/cilastatin were more likely to have at least 1 laboratory AE compared with infants exposed to meropenem or imipenem/cilastatin alone (39.9% vs. 25.6% vs. 19.7%; $P<0.001$).

Seizures were noted as a diagnosis for 336/5566 (6.0%) infants, and AEDs were started for 122/5566 (2.2%) infants while exposed to a carbapenem. There was a small but statistically significant difference in the proportion of infants diagnosed with a seizure while exposed to meropenem compared with imipenem/cilastatin—187/3479 (5.4%) vs. 180/2310 (7.8%); $P<0.001$. However, on multivariable analysis, there was no difference in the odds of seizures for infants on meropenem compared with imipenem/cilastatin—OR 0.96 (0.68, 1.32) (Table 2). This remained true in an analysis limited to infants without a prior history of seizures—OR 0.77 (0.54, 1.10).

Laboratory AEs were more common while exposed to imipenem/cilastatin before vs. after 2005 (27.1/1000 infant days vs. 35.7/1000 infant days, $P<0.001$), but there was no significant difference in the rates of seizures (3.4/1000 infant days vs. 2.7/1000 infant days, $P=0.31$) and overall AEs (38.5/1000 infant days vs. 42.6/1000 infant days, $P=0.10$). Seizures were more common while exposed to meropenem before vs. after 2005 (3.9/1000 infant days vs. 2.1/1000 infant days, $P=0.01$), but there was no significant difference in the rate of laboratory AEs (59.4/1000 infant days vs. 55.6/1000 infant days, $P=0.27$) and overall AEs (67.0/1000 infant days vs. 61.5/1000 infant days, $P=0.13$).

Mortality at any time during hospitalization was similar for infants exposed to meropenem vs. imipenem/cilastatin—611/3479 (17.6%) versus 419/2310 (18.1%), respectively; $P=0.57$. However, the adjusted odds of death or the combined outcome of death or seizure while exposed to carbapenem was significantly lower for infants exposed to meropenem compared

with imipenem/cilastatin—OR 0.68 (0.50, 0.88) and OR 0.77 (0.62, 0.95), respectively (Table 2). This remained true in an analysis limited to infants without a prior history of seizures—OR 0.65 (0.50, 0.85) and OR 0.73 (0.60, 0.90), respectively.

Additional analyses

Given the high incidence of AEs in infants exposed to both imipenem/cilastatin and meropenem, we repeated a subset of our analysis excluding those 223 infants. There was no significant difference in the rates of seizures while exposed to meropenem compared with imipenem/cilastatin (2.3/1000 infant days vs. 2.8/1000 infant days, P=0.23). These results are similar to those of the entire cohort described above (Table 1). Lastly, to account for the potential confounding of renal insufficiency at the time of carbapenem initiation on drug choice, we repeated our multivariable regression model including an indicator variable of a creatinine >1.7 mg/dl on the first day of each carbapenem course. There was again no statistical difference in the odds of seizures for infants exposed to meropenem compared with imipenem/cilastatin—OR 0.79 (0.54, 1.15)

DISCUSSION

We present the largest retrospective safety study of carbapenem therapy conducted in infants. Overall AEs measured in this study were more common in infants exposed to meropenem compared with imipenem/cilastatin. This difference was due to a higher incidence of laboratory AEs. Clinical AEs, including seizures or death, were less common in infants exposed to meropenem. This association remained true in multivariable analysis adjusted for gestational and postnatal age and surrogates of severity of illness.

Imipenem/cilastatin was the first carbapenem to receive FDA approval in 1985 and is labeled for infants but not recommended for central nervous system (CNS) infections due to an increased seizure risk in children.[4] In a previous study, seizures were reported in 7/21 (33%) children aged 3–48 months treated with imipenem/cilastatin for bacterial meningitis.[15] This study was terminated early as a result, and the authors concluded that the use of imipenem/cilastatin for the treatment of bacterial meningitis in children may be limited by a possible increased incidence of drug-related seizure activity. A seizure incidence of 2.5% was reported in a series of 80 infants 24–41-weeks gestational age treated with imipenem/cilastatin during an outbreak of multidrug resistant *Klebsiella pneumoniae* from 1994–1995 in a single NICU.[10] In this study, the mean daily dose of imipenem/cilastatin was 25 mg/kg, though 1 infant suffered a seizure at a dose of only 20 mg/kg/day. Another single-center study of 104 infants 25–41-weeks gestational age treated with imipenem/cilastatin reported a seizure incidence of 8.9%.[11] Infants in this study were all treated with a daily dose of 50 mg/kg. This incidence is comparable to the 7.8% incidence of seizure observed in infants treated with imipenem/cilastatin in our cohort. Unfortunately, we did not have information on imipenem/cilastatin dosing to evaluate the association between drug dosing and seizure incidence.

A recent review of carbapenem drugs highlighted that, of the 32 studies with at least 1 seizure episode related to imipenem/cilastatin, 12 reported 1 or more identifiable risk factors for seizures and that most of the seizures were observed in patients with existing CNS disorders.[16] In our cohort, only 8/180 (4.4%) infants who had a seizure while exposed to imipenem/cilastatin had a documented CSF infection or IVH grade III or IV. This difference may be related to other CNS conditions for which we were unable to control, as well as undocumented CSF infections due to the difficulty in obtaining CSF for culture from the most seriously ill infants.[17]

Meropenem was the second carbapenem approved by the FDA for use against multidrug-resistant infections and is currently approved for complicated skin and skin structure infections, intra-abdominal infections, and bacterial meningitis. However, meropenem is currently not labeled for use in infants <3 months old.[3] Molecular modification of the C2 side chain of meropenem compared with imipenem is believed to contribute to its lower potential for neurotoxicity.[18] A recent safety review of 6154 patients treated in 54 efficacy studies reported no seizures in the subpopulation of 1148 children, 383 of whom were treated for meningitis.[19] In a prospective randomized trial of 258 children aged 2 months to 12 years, 15/79 (19%) evaluable children in the meropenem group suffered a seizure.[20] However, none of these seizures were attributed to meropenem. Similarly, a retrospective review of 53 patients aged 4 days to 20 years treated with meropenem for various infections including meningitis reported 3 cases of seizures that were not considered to be drug-related.[21] Several smaller single-center pharmacokinetic studies of meropenem in infants, including premature infants, have not reported seizures during treatment.[12–14] In a recent multicenter clinical trial of 200 term and preterm infants ≤90 days of age treated with meropenem for intra-abdominal infections, 10 seizures (5%) were reported, but none were felt to be probably or definitely related to meropenem therapy.[22] This incidence is similar to the incidence of seizures observed in our cohort that was exposed to meropenem (5.4%). In multivariable analysis, we did not find a statistically significant difference in the odds of seizures between infants exposed to imipenem/cilastatin versus meropenem. This is despite the fact that our sample size gave us >90% power to detect an at least 3% difference in the incidence of seizures between infants exposed to imipenem/cilastatin versus meropenem.

The most common laboratory AEs included in the FDA-approved product label for infants <3 months of age treated with imipenem/cilastatin include elevated AST (6%), creatinine (5%), and bilirubin (3%).[4] In a multicenter study from Japan, a laboratory abnormality was reported in 18% of 160 preterm or term infants treated with imipenem/cilastatin.[23] This is comparable to our cohort, where 19.7% of 2310 infants had a laboratory AE while exposed to imipenem/cilastatin. Laboratory AEs were more common in a pharmacokinetic and safety study of 61 infants, where 31% of infants had changes in their complete blood cell count, liver, or renal function tests after initiation of imipenem/cilastatin.[24] However, the AEs were considered serious in only 2 infants (3%). Laboratory AEs most frequently observed in a retrospective study of 53 patients aged 4 days to 20 years receiving meropenem included low platelet counts in 3.8% and elevated liver function tests in 7.5%.[21] These findings are similar to our cohort, where 6.9% of the 3479 infants exposed to meropenem had an elevation of their AST or ALT. The specific mechanism of meropenem-associated hepatotoxicity is unclear, though rare cases of vanishing bile duct syndrome in adults have been attributed to meropenem and reversed with discontinuation of the drug.[25]

There are no randomized controlled trials comparing meropenem with imipenem/cilastatin in the pediatric population. The only pediatric study comparing meropenem with imipenem/cilastatin was performed in a single bone marrow transplant unit on 16 patients with a mean age of 9.7 years who were prospectively evaluated while receiving empiric meropenem therapy and compared to a historical matched control cohort treated with imipenem/cilastatin in the same unit.[26] The authors reported a statistically significant decrease in the number of vomiting episodes, as well as lower cost of therapy for those patients receiving meropenem. Other AEs occurring in both cohorts were not reported. Studies in the adult population have generally reported fewer adverse events in patients treated with meropenem compared with imipenem/cilastatin.[8,27] We found that, in our cohort of infants, overall AEs were more common with meropenem compared with imipenem/cilastatin when examined as a function of relative treatment duration (62.3/1000 infant days for meropenem vs. 40.5/1000 infant days for imipenem/cilastatin). However, when reporting adverse events occurring at a patient level, our findings were similar to those in adults: 31.7% of

meropenem-only exposed infants experienced at least 1 adverse event versus 31.1% of imipenem/cilastatin-only exposed infants. Adverse events were most frequently seen in infants exposed to both meropenem and imipenem/cilastatin (51.1%). This may be related to a higher severity of illness and/or longer overall duration of carbapenem treatment in infants exposed to both drugs compared with meropenem or imipenem/cilastatin exposure alone.

The duration of carbapenem treatment courses decreased over the study period. Our data do not allow us to clearly identify the reasons for this change. However, clinicians' greater attention to avoid antibiotic exposure may be related to antibiotic stewardship programs and other quality improvement initiatives. The proportion of overall AEs observed while on imipenem/cilastatin or meropenem remained stable when compared between the 1997–2004 and 2005–2010 time periods: 38.5/1000 infant days vs. 42.6/1000 infant days (P=0.10) on imipenem/cilastatin and 67.0/1000 infant days vs. 61.5/1000 infant days (P=0.13) on meropenem.

The strengths of our study include a large, diverse, multicenter cohort of infants <3 months of age. We were further able to report the first comparison of AEs in meropenem versus imipenem/cilastatin from the same infant cohort. Our study is limited by the retrospective nature of the analysis. These data are not from a prospective clinical trial that has undergone the scrutiny of independent monitoring, but rather are derived from electronic documentation. Advantages of a prospective randomized controlled clinical trial include: 1) randomization to protect from unmeasured confounders; 2) standardized drug dosing; and 3) less heterogeneous patient populations determined by inclusion/exclusion criteria. Specifically, certain infants have been exposed to both imipenem/cilastatin and meropenem, and we do not know the indication for carbapenem administration or the reasoning for switching the infant from one carbapenem to the other. Information about dosing amount and interval is not available, which limits our ability to evaluate its association, in particular with seizures. For example, if meropenem was used at relatively higher doses to treat instances of meningitis or presumed meningitis, this may have biased our results in finding towards an increase in AEs in infants treated with meropenem. The addition of sites to the database over time likely shifted the distribution of demographic variables. This is reflected in the increased proportion of Hispanic infants exposed to imipenem/cilastatin, which was used more frequently during the early part of our study. In our regression models, we controlled for those demographic variables that we felt were likely to affect the outcome, such as gestational and postnatal age and discharge year. We also attempted to control for severity of illness by including surrogate markers such as inotrope and ventilator use and supplement oxygen administration. However, differences in frequency of AEs could be related to other comorbidities, use of additional therapies such as total parenteral nutrition or other medications that cannot all be controlled for in a non-randomized study. Laboratory AEs may be affected by the frequency of laboratory draws, which occurred at the discretion of the treating clinician. Imipenem is further administered together with cilastatin, a renal dihydropeptidase I inhibitor, and observed AEs could be due to the cilastatin rather than the imipenem molecule. Finally, we are only able to describe association between adverse events and drug exposure, rather than infer causality.

In summary, in this retrospective cohort study of hospitalized infants, we observed fewer seizures and deaths in infants exposed to meropenem compared with imipenem/cilastatin. Laboratory AEs were more commonly observed in patients reeceiving meropenem. Overall the lower incidence of seizures and death supports the use of meropenem over imipenem/cilastatin in infants <3 months of age; however, this may come at the expense of more frequent laboratory abnormalities including elevated creatinine and liver function tests.

Acknowledgments

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The EMMES Corporation (Data Coordinating Center): Ravinder Anand, Traci Clemons, Gina Simone

Funding

This work was performed under the Best Pharmaceuticals for Children Act Pediatric Trials Network (Contract No. HHSN275201000003I). This study used Clinical and Translational Science Award biostatistical services through the Division of Pediatric Quantitative Sciences (NIH-5UL-1RR024128-01).

Dr. Benjamin receives support from the United States government for his work in pediatric and neonatal clinical pharmacology (1R01HD057956-02, 1R01FD003519-01, 1U10-HD45962-06, 1K24HD058735-01, and Government Contract HHSN267200700051C) and the nonprofit organization Thrasher Research Foundation for his work in neonatal candidiasis (www.thrasherresearch.org); he also receives research support from Astellas Pharma US, AstraZeneca, Johnson & Johnson, Pfizer, Biosynexus, and UCB Pharma; consulting fees from Cerexa and Astellas Pharma US.; and other support from industry for neonatal and pediatric drug development (www.dcri.duke.edu/research/coi.jsp). Dr. Cohen-Wolkowiez received support from the National Institute of Child and Human Development (1K23HD064814-01). Dr. Van Den Anker receives support from the United States government for his work in pediatric and neonatal clinical pharmacology (5R01HD060543; 5K24DA027992; 5R01HD048689; 5U54HD071601); he also receives research support from the European Union FP7 grants TINN (223614);TINN2 (260908); NEUROSIS (223060); and GRIP (261060). Dr. Capparelli receives salary support from the United States government (U54 HD071600-01) and research support from Trius and Cerexa Pharmaceuticals. Dr. Smith received receives salary support for research from the National Institutes of Health and the U.S. Department of Health and Human Services (NICHD 1K23HD060040-01 and DHHS-1R18AE000028-01).

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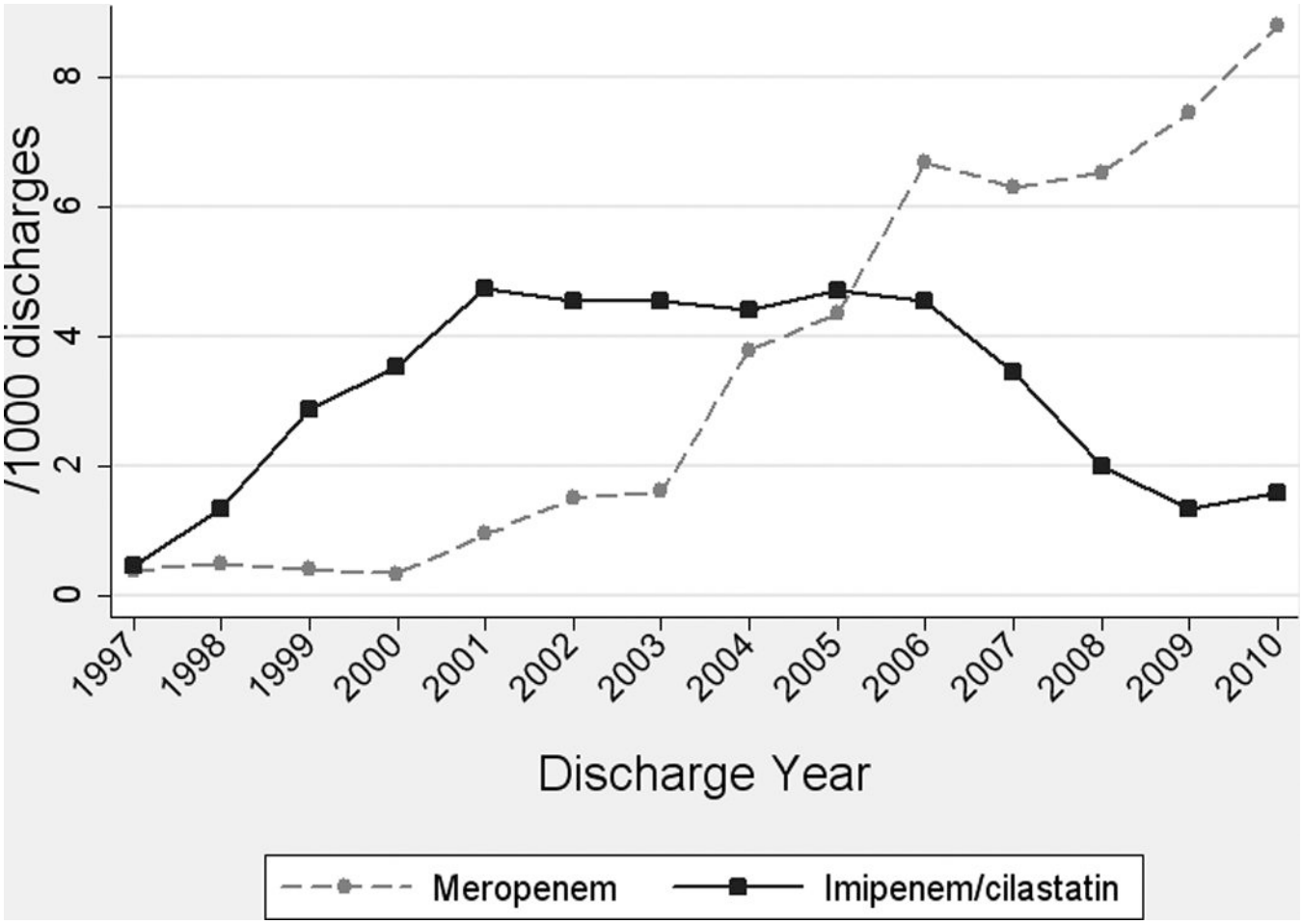

FIGURE 1.
Meropenem and imipenem/cilastatin use over time.

TABLE 1

Diagnostic and Laboratory Adverse Events Associated with Carbapenem Therapy (/1000 days)

	Imipenem/cilastatin (N=24,539 days)	Meropenem (N=38,705 days)	*P*
Diagnostic AE			
Seizure diagnosis	3.0	2.3	0.09
Antiepileptic drug	0.9	1.2	0.24
Seizure diagnosis or antiepileptic drug	3.7	3.3	0.57
Seizure diagnosis and antiepileptic drug	0.2	0.2	0.65
Rash	0.2	0.4	0.15
Diarrhea	0.1	0.2	0.42
Death	6.6	3.8	<0.001
Death or seizure	10.2	7.1	<0.001
Laboratory AE			
Creatinine >1.7 mg/dL	12.2	24.0	<0.001
Direct bilirubin >5 mg/dL	18.7	30.2	<0.001
AST >200 U/L	1.7	4.3	<0.001
ALT >100 U/L	2.0	7.0	<0.001

Results are displayed as occurrences per 1000 infant days.

TABLE 2

Diagnostic and Laboratory Adverse Events (Meropenem Relative to Imipenem/Cilastatin), Odds Ratios and 95% Confidence Intervals

	Univariable analysis	Multivariable analysis*
Any AE	1.56 (1.45, 1.69)	1.29 (1.18, 1.42)
Laboratory AE	1.80 (1.66, 1.96)	1.41 (1.28, 1.55)
Seizure	0.93 (0.71, 1.23)	0.96 (0.68, 1.32)
Death	0.61 (0.49, 0.77)	0.68 (0.50, 0.88)
Death or seizure	0.73 (0.61, 0.87)	0.77 (0.62, 0.95)

*Adjusted for GA, discharge year, inotropic support, FiO2, ventilator support, positive CSF culture, postnatal age, history of seizure prior to carbapenem, and IVH grade III or IV.