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Assessment of imipenem-cilastatin 500mg q6h, meropenem 1g q8h and meropenem 500mg q6h following cefepime use in adult patients with neutropenic fever

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Abstract

Study objective—An alternative meropenem dosing strategy (500mg q6h) has been postulated to provide similar pharmacodynamics based on %T>MIC as traditional dosing with 1gm q8h while decreasing total daily dose. However, this dosing strategy has not been formally evaluated for empiric treatment of febrile neutropenic patients. The aim of this study was to compare clinical outcomes in patients treated with alternatively-dosed meropenem at 500mg q6h (Mero500q6), traditionally-dosed meropenem at 1gm q8h (Mero1q8), and imipenem-cilastatin at 500mg q6h (Imi500q6) following failure or intolerance of cefepime for febrile neutropenia.

Design—A retrospective, single-center, observational cohort study was performed.

Setting—Barnes-Jewish Hospital, a 1,250 bed urban academic medical center in St. Louis, MO.

Patients—Adult neutropenic fever patients admitted to either the Hematologic Malignancy or Hematopoietic Stem Cell Transplant service.

Intervention—A total of 127 patients were included: 40 patients treated with Imi500q6 from September 1, 2005, to August 31, 2006, and 87 patients treated with meropenem (Mero1q8=29, Mero500q6=58) from September 1, 2006, to August 31, 2007.

Measurements and main results—Primary outcomes including time to defervescence (median 3 vs. 2 vs. 3 days), need for additional antibiotics (20% vs. 17.2% vs. 13.8%), and time to additional antibiotics (median 5 vs. 2 vs. 1 days) were not statistically different between the Imi500q6, Mero1q8 and Mero500q6 groups, respectively. Differences in secondary outcomes including treatment duration (median 10 vs. 8 vs. 8 days), seizure incidence (0% vs. 0% vs. 0%), in-hospital mortality (5% vs. 6% vs. 7%), and 30-day mortality (12.5% vs. 6% vs. 14%) were not identified.

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Conclusion—Mero500q6h yielded similar patient outcomes, including time to defervescence, need for additional antibiotics, duration of therapy, and mortality as compared to traditional dosing of meropenem and imipenem-cilastatin in adult patients with febrile neutropenia and had no observed adverse impact on clinical outcomes.

Keywords

imipenem-cilastatin; meropenem; neutropenic fever

Introduction

Meropenem and imipenem-cilastatin are carbapenem antimicrobials recommended by the Infectious Diseases Society of America and the National Comprehensive Cancer Network for the empiric treatment of febrile neutropenia^{1,2}. While neither agent is FDA-approved for the empiric therapy of febrile neutropenia, imipenem-cilastatin at a dose of 500mg q6h holds FDA approval for endocarditis, bacteremia and osteomyelitis, as well as intrabdominal, lower respiratory tract, complicated urinary tract, skin, soft tissue and female genital infections. Meropenem is FDA-approved for intrabdominal infections at a dose of 1gm q8h and for complicated skin and skin structure infections at a dose of 500mg q8h. Meropenem 500mg q6h is currently not an FDA-approved dose, despite its similar pharmacokinetic profile to imipenem-cilastatin 500mg q6h^{3,4}.

Both imipenem-cilastatin and meropenem demonstrate concentration-independent activity, with successful bacterial killing associated with the percentage of time of the dosing interval that free drug concentrations remain above the minimum inhibitory concentration (MIC), (%T>MIC). Bacteriostatic and bactericidal effects of meropenem occur when concentrations are maintained above the MIC for 20% and 40% of the dosing period, respectively⁵. In terms of pharmacokinetics, meropenem possesses a short one hour half-life and linear dose-response relationship. Combined, these elements support the utilization of lower, more frequent doses to attain optimal %T>MIC. Using the meropenem Clinical and Laboratory Standards Institute (CLSI) susceptibility breakpoint of 4 mcg/mL, previous studies have estimated the %T>MIC to be similar when meropenem is dosed at 500mg q6h and 1gm q8h (43.9% and 45.8%, respectively.)^{4,6}

At Barnes-Jewish Hospital, cefepime has traditionally been the first-line monotherapeutic option for the management of febrile neutropenia, with a carbapenem representing an acceptable second-line agent (Figure 1). This is in part due to the sensitivity of *P. aeruginosa* of 91 and 84%, respectively, to cefepime and meropenem at the institution. Imipenem-cilastatin was the preferred carbapenem at Barnes-Jewish Hospital until September 1, 2006, after which meropenem became the formulary carbapenem. Dosing of meropenem at 500mg q6h was allowed hospital-wide, including in the setting of febrile neutropenia. However, this meropenem dosing approach was not mandated, and prescribers were allowed to utilize a traditional dose of 1g q8h. This project aimed to compare clinical outcomes between neutropenic fever patients treated with imipenem-cilastatin 500mg q6h (Imi500q6), traditionally-dosed meropenem 1000mg q8h (Mero1q8) and alternatively-dosed

meropenem 500mg q6h (Mero500q6) following failure or intolerance of first-line cefepime therapy.

Methods

Study Location and Design

Barnes-Jewish Hospital is a 1,250 bed tertiary care center in St. Louis, Missouri. We performed a retrospective, single-center, observational cohort study evaluating patients treated with Imi500q6 infused over 60 minutes from September 1, 2005, to August 31, 2006, and meropenem infused over 30 minutes (Mero1q8 or Mero500q6) from September 1, 2006, to August 31, 2007, who were admitted to either the Hematopoietic Stem Cell Transplant (HSCT) or Hematologic Malignancy service.

The Washington University School of Medicine Human Research Protection Office and the Protocol Review and Monitoring Committee approved this study.

Study Subjects

Patients included in the study were diagnosed with a hematologic malignancy and neutropenic fever. Receipt of chemotherapy within 60 days prior to or during the study admission was required, as was receipt of the respective carbapenem for a minimum of 3 days. All enrolled patients were over 18 years of age.

Patients were excluded from the study if they received cefepime for less than 3 days prior to carbapenem initiation as institutional guidelines recommend cefepime as first-line therapy for neutropenic fever. This rule was also applied in keeping with the IDSA “2002 Guidelines for the Use of Antimicrobial Agents in Neutropenic Patients with Cancer” recommendation to reassess empiric therapy at 3–5 days.¹ Subjects were also excluded if they received an inappropriate carbapenem dose for their respective renal function for greater than 24 hours. In the event that patients were hospitalized multiple times during the study period, it was determined that the first hospitalization with eligibility would be used.

Data Collection

The Barnes-Jewish Hospital medical informatics system was queried to identify patients admitted to the Hematopoietic Stem Cell Transplant or Hematologic Malignancy unit in whom carbapenems were initiated between September 1, 2005, and August 31, 2007. Electronic and paper medical records were searched for the following demographic and baseline data: date of birth, sex, race, height, weight, Charlson comorbidity index score⁷, history of seizure disorder, primary oncologic diagnosis, history of hematopoietic stem cell transplant within the previous year, and date of death. In the event that a patient’s death was not documented in the database, a commercial version of the Social Security Death Master File was consulted to confirm date of death, if applicable.⁸ Other patient-specific data collected included degree of neutropenia severity and date of neutropenic resolution.

Duration of cefepime therapy as well as reason for drug discontinuation was documented. Data collected for carbapenem administration included dose, duration of therapy, early discontinuation of therapy, and creatinine clearance based on the last recorded serum

creatinine value drawn before carbapenem initiation. Creatinine clearance was calculated with ideal body weight using the Cockcroft-Gault equation⁹.

Microbiologic data included the dates and times of cultures, sources of specimens, culture and sensitivity results for all bacterial isolates, and positive *C. difficile* stool toxins collected after carbapenem initiation. Organism susceptibilities were determined by disk diffusion, therefore MICs were not available to use as data points.

Data collected for concurrent medications with the potential to affect fever status included: vancomycin, an aminoglycoside, or an antifungal at, or prior to, carbapenem initiation. Data regarding concurrent vancomycin therapy was collected to ascertain whether or not a variation in additional gram-positive agent prescribing patterns existed secondary to the slightly enhanced gram-positive coverage of imipenem beyond that of meropenem. With regard to agents that may have been selected for double gram-negative coverage, only aminoglycoside use was collected. Despite inclusion in the BJH neutropenic fever pathway, the addition of ciprofloxacin for double gram-negative coverage in this clinical scenario is exceedingly rare at our institution, secondary to a 30% *P. aeruginosa* resistance rate. Hence, this data was not collected. Finally, while data regarding appropriate dosing of vancomycin and aminoglycoside agents were not collected, full-time clinical pharmacists are employed on each study unit to enforce standard dosing protocols and provide therapeutic drug monitoring. In addition, the institution utilizes a pharmacy expert informatics system which flags patients with inappropriate drug dosing for renal function, sub- or supra-therapeutic drug concentrations, as well as drug interactions to further ensure appropriateness of therapy.

The need for and time to addition of intravenous vancomycin or an aminoglycoside following carbapenem initiation, scheduled steroids, and scheduled antipyretics were also collected. As needed antipyretic use was not captured. Patient receipt of concurrent medications with the capability to affect seizure threshold including scheduled anticonvulsants (benzodiazepines, fosphenytoin, gabapentin, levetiracetam, oxcarbazepine, phenytoin, pregabalin, primidone, topiramate, valproic acid and zonisamide) was captured. Finally, in response to a recently published meta-analysis describing the effect of hematopoietic colony stimulating factors on infection outcome and mortality, administration of growth factors was examined¹⁰. Administration of filgrastim, pegfilgrastim or sargramostim during or 30 days prior to hospitalization was documented.

Outcomes assessment

The following primary endpoints were assessed: 1) time to defervescence; 2) need for additional antibiotics [defined as the addition of intravenous vancomycin and/or an aminoglycoside]; and 3) time to first additional antibiotic [as in #2, defined in days].

Secondary outcomes included: 1) treatment duration [days of carbapenem therapy administered rounded to the nearest whole day]; 2) seizure incidence; 3) in-hospital mortality; and 4) 30-day mortality.

Definitions

Neutropenic fever was defined as a temperature of $\geq 38.3^{\circ}\text{C}$ or $\geq 38^{\circ}\text{C}$ for an hour or more in addition to an ANC $< 500/\text{mm}^3$. Fever resolution was defined as a temperature of $< 38^{\circ}\text{C}$ for 24 consecutive hours; neutrophil recovery was defined as an ANC $\geq 500/\text{mm}^3$ for 48 hours. Need for additional antibiotics was characterized as the addition of either intravenous vancomycin or an aminoglycoside after the study carbapenem had already been initiated. Receipt of oral vancomycin was not considered an additional antibiotic. In reference to a medication, the term “scheduled” was defined as administration of a drug around the clock for a minimum of 24 hours.

Appropriate carbapenem dosing in the setting of renal dysfunction was defined per the respective prescribing information for traditionally-dosed meropenem and imipenem-cilastatin^{3,4}. Appropriateness of alternatively-dosed meropenem based on renal function was defined as follows: 500mg every 6 hours for CrCl ≥ 50 ml/min; 500mg every 8 hours for CrCl 49-25 ml/min; 500mg every 12 hours for CrCl 24-10 ml/min; and 500mg every 24 hours for CrCl < 10 ml/min in accordance with institution suggested guidelines. However, realizing that creatinine clearance is not a precise measure of renal function, prescribers were given a 5mL/min interval in which to comply with adjusted dosing recommendations before the dose was deemed inappropriate. This rule was applied to all study arms.

Statistical Analysis

The ANOVA with Bonferroni correction was utilized for comparison of parametric continuous variables; Chi-squared or Fisher’s exact tests were used for categorical variables. Cox proportional hazard analysis was used for time-dependent variables. Statistical analysis was completed using the Statistical Package for the Social Sciences (SPSS®) version 16.0, Chicago, IL.

Results

Patient Characteristics

A total of 127 patients met study criteria and were included in the final analysis (40 in the Imi500q6 arm, 29 in the Mero1q8 arm and 58 in the Mero500q6 arm). The principal reason for exclusion in both the imipenem-cilastatin and meropenem groups was insufficient duration of cefepime therapy, followed by inappropriate renal dosing (Figure 2).

Baseline demographics were similar between groups and are summarized in Table 1. Study subjects were primarily middle-aged Caucasian men, with patients in the Mero500q6 arm statistically significantly older than those in the Imi500q6 arm ($p=0.03$). Comorbidity scoring assessed by the Charlson method was higher in the Mero500q6 arm than in the Imi500q6 arm ($p=0.02$). One patient in the Mero1q8 group had a history of seizure disorder; no patients in the Imi500q6 or Mero500q6 groups had any past history of seizures (Table 1).

There was a trend ($p=0.06$) toward more cases of severe neutropenia in the meropenem arms as compared to the imipenem-cilastatin arm with similar rates of neutrophil recovery in all groups. Overall incidence of culture positive subjects was higher than previously described

in neutropenic fever patients in the primary literature.¹¹ Gram-positive pathogens predominated positive culture findings and similar rates of *C. difficile* superinfection were seen among all treatment arms (Table 2). The rates of positive bacterial cultures were comparable between groups and are summarized in Table 3. Susceptibility of isolated organisms with sensitivity to meropenem and imipenem-cilastatin routinely tested at Barnes-Jewish Hospital may be found in Table 4.

Concomitant medications

Few patients in any group received aminoglycoside therapy at the time of carbapenem initiation, but greater than 70% of patients received concurrent vancomycin in all treatment arms. A statistically higher incidence of antifungal therapy was seen in the meropenem arms, the majority of which was empiric in nature. Steroid and antipyretic utilization were similar between all 3 groups and no significant difference in scheduled anticonvulsant or hematopoietic colony stimulating factor usage was appreciated (Table 2).

Primary Outcomes

Time to defervescence, depicted by Figure 3, represents 36 Imi500q6, 22 Mero1q8 and 44 Mero500q6 patients. Twenty-five patients were afebrile before carbapenem initiation; these patients were excluded from this analysis. The median time to defervescence was similar between all groups; 3 days in the Imi500q6 and Mero500q6 arms, 2 days in the Mero1q8 arm. [Mero500q6 vs. Imi500q6, HR 0.912, 95% CI (0.574 – 1.451); Mero500q6 vs. Mero1q8, HR 0.881, 95% CI (0.511 – 1.519).] Data were censored at the time of additional antibiotics (Figure 2). Need for additional antibiotics was observed at similar proportions by all groups. A total of 20% in the Imi500q6 group, 17.2% in the Mero1q8 group and 13.8% in the Mero500q6 group required the addition of intravenous vancomycin or an aminoglycoside ($p=0.71$). Median time to addition of first antibiotic was 5 days in the Imi500q6 group (range 1–12), 2 days in the Mero1q8 group (range 1–22) and 1 day in the Mero500q6 group (range 1–6). [Mero500q6 vs. Imi500q6, HR 0.652, 95% CI (0.244 – 1.738); Mero500q6 vs. Mero1q8, HR 0.645, 95% CI (0.208 – 1.998).] Patients who received concomitant antibiotics were controlled for, as they were less likely to receive additional antibiotics later in their hospital course.

Secondary Outcomes

Median duration of treatment was 10 days in the Imi500q6 arm (range 10–32, SD $\pm$ 5.9) and 8 days in both meropenem arms [Mero1q8 (range 3–25, SD $\pm$ 6.5); Mero500q6 (range 3–35, SD $\pm$ 8.1)]. Data were adjusted for patients who expired while on the study drug. The trend toward shorter time to treatment discontinuation in the meropenem groups was not statistically significant [Mero500q6 vs. Imi500q6, HR 1.331, 95% CI (0.85–2.066); Mero500q6 vs. Mero1q8, HR 1.124, 95% CI (0.685–1.845).] Mortality was low throughout the study, with similar rates between treatment arms. In-hospital mortality in all groups was 5–7% ($p=0.92$), and 30-day mortality was 0 – 7% ($p=0.64$). No seizure activity was reported in any study patient (Table 5).

Discussion

This study revealed no difference in need for or time to additional antibiotics or time to defervescence in adult neutropenic fever patients treated with Imi500q6, Mero1q8 or Mero500q6. No differences in duration of treatment, incidence of seizure, in-hospital mortality or 30-day mortality were identified. Combined, this evidence suggests that alternatively-dosed meropenem at 500mg q6h may be as safe and efficacious as traditionally-dosed meropenem or imipenem-cilastatin for febrile neutropenia.

Utilization of alternative meropenem dosing in the treatment of neutropenic fever has been debated nationwide throughout both the infectious diseases and oncology communities, likely because limited evidence exists to support this alternative meropenem dosing strategy, especially in the setting of neutropenic fever. As described by Nyhlén and colleagues, febrile neutropenic patients demonstrate significantly increased volumes of distribution and nonrenal clearance as compared to healthy subjects. This alteration may suggest higher meropenem dosages would be required in this patient population to obtain adequate drug concentrations to reach required %T>MIC for bacterial killing. These authors concluded that meropenem dosed at 1g every 6 to 8 hours appeared to be suitable for the treatment of neutropenic fever, but hypothesized that a dose of 500mg every 6 hours may also be appropriate¹².

Kuti and colleagues first described the alternative meropenem dosing scheme utilizing Monte Carlo simulation in a general patient population in 2003. The authors performed a 5,000 subject simulation to evaluate the percentage of time that meropenem drug concentrations remained above the CLSI-susceptibility breakpoint of 4mcg/mL obtained with a 500mg q6h regimen as opposed to that of a conventional 1g q8h dose. They reported a mean %T>MIC for 500mg q6h to be 43.91% (95% CI 36.77–51.46%) as compared to 45.77% (95% CI 40.06–50.69%) with the higher dose. The authors concluded that the pharmacodynamically-inspired 500mg q6h meropenem dosing scheme resulted in a %T>MIC similar to that seen with traditional regimens⁶. Ariano and colleagues corroborated these findings 2 years later in a retrospective analysis of 60 patients with neutropenic fever and confirmed bacteremia. These authors reported a %T>MIC of 75% and 68% for patients treated with meropenem 500mg q6h versus meropenem 1g q8h, respectively¹³.

In 2004 Kotapati and colleagues evaluated the effect of meropenem 500mg q6h on clinical outcomes. The authors assessed 85 patients by means of a retrospective review, 45 of whom received meropenem 500mg q6h and 40 of whom received meropenem 1g q8h. Primary diagnoses included pneumonia, intrabdominal infection, bacteremia and skin or soft tissue infection. The authors disclosed that a small portion of enrolled subjects were diagnosed with neutropenic fever, but the 'other' category encompassing patients diagnosed with either sepsis or neutropenic fever consisted of only 3 patients, implying that only 1–2 subjects of their total study sample were in fact diagnosed with febrile neutropenia. However, in the overall patient population, time to temperature normalization occurred on day 3 in both the alternative and traditional meropenem arms which was similar to our study where

defervescence was observed on day 3 in the Imi500q6 and Mero500q6 groups, and on day 2 in the Mero1q8 group¹⁴.

In December of 2007 Patel and colleagues published a comparison of clinical and pharmacoeconomic outcomes between a control group of 100 patients dosed with meropenem 1g q8h and a study group of 192 patients dosed with meropenem 500mg q6h. Primary infection sites included the abdomen, lungs, genitourinary tract and skin; unfortunately, neutropenic patients were excluded from the analysis. Similar to our findings, the study authors found no statistically significant difference between groups with regard to duration of treatment or hospital mortality. Finally, the authors commented on a statistically significant cost savings with the alternative meropenem strategy given one third less total drug was used per treatment course with 500mg q6h versus 1g q8h¹⁵.

Limitations

This analysis has some limitations. First, it is a retrospective investigation. To help control for this factor, objective study endpoints such as time to defervescence and addition of antibiotics were selected to minimize bias during the data collection process. However, while patient groups demonstrated an equivalent incidence of comorbid conditions and a repeat review of the database revealed no systematic variance, due to the retrospective nature of the study, prescriber preference for one meropenem dosage strategy over the other cannot be ruled out as a source of potential bias. Second, the sample size is small which limits the power of the analysis. Several patients were excluded for failure to receive 3 days of cefepime therapy; the nationwide cefepime shortage during the study period likely contributed to the subsequent exclusion of additional subjects. The limited enrollment also reflects the single center study design as well as our sample size of convenience, in that we included only patients treated with these agents during a predetermined study period. The small sample size may also be a consequence of carbapenems serving as second-line, not first-line, agents of choice for febrile neutropenia at the institution. Unfortunately, we also experienced high exclusion rates secondary to stringent inclusion and exclusion criteria utilized in part as an attempt to maintain similar gram-negative antimicrobial exposure between study subjects. Finally, enrolled subjects received concurrent medications that may have obscured the study findings. Additionally, data regarding only scheduled antipyretics was collected; therefore, effects of one-time or as-needed antipyretic doses cannot be ruled out as a source of confounding.

Conclusions

Despite the limitations of the study, this paper adds to the scarce body of literature describing the successful use of alternatively-dosed meropenem. To our knowledge, this is the first investigation to address clinical outcomes in patients receiving pharmacodynamically-inspired meropenem dosing at 500mg q6h for neutropenic fever. Although the safety and efficacy of this strategy cannot be confirmed by this study, we did not observe any evidence suggesting an apparent adverse impact of this novel dosing scheme and believe the data support continuation of this dosing strategy for febrile neutropenia at our institution.

References

1. Hughes WT, Armstrong D, Bodey GP, Bow EJ, Brown AE, Calandra T, Feld R, et al. 2002 Guidelines for the use of antimicrobial agents in neutropenic patients with cancer. *Clin Infect Dis*. 2002; 34:730–51. [PubMed: 11850858]
2. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: prevention and treatment of cancer related infections. V.1. 2008. Available at http://www.nccn.org/professionals/physician_gls/PDF/infections.pdf
3. Merck and Co., Inc. Primaxin (imipenem-cilastatin) package insert. Whitehouse Station, NJ: 2007.
4. Astra Zeneca. Merrem (meropenem) package insert. Wilmington, DE: 2007.
5. Drusano GL. Prevention of resistance: a goal for dose selection of antimicrobial agents. *Clin Infect Dis*. 2003; 36(Suppl 1):S42–50. [PubMed: 12516029]
6. Kuti JL, Maglio D, Nightingale CH, Nicolau DP. Economic Benefit of a Meropenem dosage strategy based on pharmacodynamic concepts. *Am J Health-Syst Pharm*. 2003; 60:565–8. [PubMed: 12659058]
7. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987; 40:373–83. [PubMed: 3558716]
8. Social Security Death Index. <http://ssdi.rootsweb.com>
9. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron*. 1976; 16:31–41. [PubMed: 1244564]
10. Sung L, Nathan PC, Alibhai SMH, Tomlinson GA, Beyene J. Meta-analysis: effect of prophylactic hematopoietic colony-stimulating factors on mortality and outcomes of infection. *Ann Intern Med*. 2007; 147:400–11. [PubMed: 17876022]
11. Serody JS, Berrey MM, Albritton K, O'Brien SM, O'Brien SM, Capel EP, et al. Utility of obtaining blood cultures in febrile neutropenic patients undergoing bone marrow transplantation. *Bone Marrow Transplant*. 2000; 26:533–8. [PubMed: 11019843]
12. Nyhlén A, Ljungberg B, Nilsson-Ehle I. a Swedish Study Group. Pharmacokinetics of meropenem in febrile neutropenic patients. *Eur J Clin Microbiol Infect Dis*. 1997; 16:797–802. [PubMed: 9447900]
13. Ariano RE, Nyhlén A, Donnelly JP, Sitar DS, Harding G, Zelenitsky SA. Pharmacokinetics and pharmacodynamics of meropenem in febrile neutropenic patients with bacteremia. *Ann Pharmacother*. 2005; 39:32–8. [PubMed: 15598967]
14. Kotapati S, Nicolau DP, Nightingale CH, Kuti JL. Clinical and economic benefits of a meropenem dosage strategy based on pharmacodynamic concepts. *Am J Health-Syst Pharm*. 2004; 61:1264–70. [PubMed: 15259757]
15. Patel GW, Duquaine SM, McKinnon PS. Clinical outcomes and cost minimization with an alternative dosing regimen for meropenem in a community hospital. *Pharmacotherapy*. 2007; 27(12):1637–43. [PubMed: 18041884]

Figure 1.

Abbreviated Barnes-Jewish Hospital Febrile Neutropenia Treatment Pathway ANC –
Absolute neutrophil count

^aVancomycin is added if patient specific-indications are present including: severe mucositis, clinical evidence of catheter-related infection, known colonization with resistant streptococci or staphylococci, sudden temperature spike >40°C, hypotension or sepsis.

^bMetronidazole is added if there is a suspected oropharyngeal or intra-abdominal source of infection.

^cGentamicin is added for double gram-negative coverage for 72 hours if patient is clinically unstable.

Figure 2.

Explanation of subject exclusions

^aPatients excluded under the “other” category received meningitis dosing, did not carry a hematologic malignancy diagnosis or were enrolled into the study during a prior admission.

Figure 3.
Time to deference

Table 1

Baseline Characteristics

	Imi500q6 N=40	Mero1q8 N=29	Mero500q6 N=58	P
Age, yrs, mean ($\pm$ SD)	46.7 ($\pm$ 13.5)	53.0 ($\pm$ 12.8)	54.0 ($\pm$ 14.0)	0.03 ^a
Male	27 (68%)	14 (48%)	40 (69%)	0.14
Caucasian	36 (90%)	28 (97%)	46 (79%)	0.41
History of seizure disorder	0 (0%)	1 (3.4%)	0 (0%)	0.18
Charlson Comorbidity Index median (range)	3 (2–7)	3 (2–8)	3.5 (2–9)	0.02 ^b
Primary diagnosis				0.78
AML	23 (57.5%)	11 (37.9%)	32 (55.2%)	
ALL	2 (5%)	2 (6.9%)	2 (3.4%)	
CML	1 (2.5%)	1 (3.4%)	1 (1.7%)	
CLL	2 (5%)	1 (3.4%)	1 (1.7%)	
MM	2 (5%)	4 (13.8%)	9 (15.5%)	
NHL	5 (12.5%)	6 (20.7%)	5 (8.6%)	
HL	1 (2.5%)	1 (3.4%)	3 (5.2%)	
MDS	4 (10%)	3 (10.3%)	3 (5.2%)	
Other ^c	0 (0%)	0 (0%)	2 (3.4%)	
HSCT in previous year	19 (47.5%)	18 (62.1%)	28 (48.3%)	0.41
Obese (BMI $\geq$ 30)	18 (45%)	15 (51%)	16 (27.6%)	0.30
BMI 30–34.9	12 (30%)	11 (37.9%)	12 (20.7%)	
BMI 35–39.9	3 (7.5%)	3 (10.3%)	3 (5.2%)	
BMI $\geq$ 40	3 (7.5%)	1 (3.4%)	1 (1.7%)	

ANC- Absolute Neutrophil Count; AML- Acute Myeloid Leukemia; ALL- Acute Lymphoblastic Leukemia; CML- Chronic Myeloid Leukemia; CLL- Chronic Lymphocytic Leukemia; MM- Multiple Myeloma; NHL- Non-Hodgkin's Lymphoma; HL- Hodgkin's Lymphoma; MDS- Myelodysplastic Syndrome; HSCT- Hematopoietic Stem Cell Transplant; BMI- Body Mass Index

^a Mero500q6 vs. Imi500q6, $p=0.03$; Mero500q6 vs. Mero1q8, $p=0.18$.

^b Mero500q6 vs. Imi500q6, $p=0.02$; Mero500q6 vs. Mero1q8, $p=0.12$.

^c 1 patient with Mantle Cell Lymphoma; 1 patient with Richter transformation from CLL to immunoblastic B-cell high grade NHL

Table 2

Patient characteristics at time of carbapenem initiation

	Imi500q6 N=40	Mero1q8 N=29	Mero500q6 N=58	P
ANC 100/mm ³	35 (88%)	28 (96.6%)	57 (98%)	0.06
Culture positive	8 (20%)	9 (31%)	19 (32.83%)	0.82
Gram (+)	6/8 (75%)	6/9 (66.7%)	12/19 (63%)	
Gram (–)	1/8 (12.5%)	1/9 (11%)	4/19 (21%)	
Polymicrobial ^a	1/8 (12.5%)	2/9 (22%)	3/19 (16%)	
Medications begun prior to or at the time of carbapenem initiation				
Aminoglycoside	1 (3%)	2 (6.9%)	6 (10%)	0.33
Vancomycin	31 (78%)	24 (82.8%)	41 (71%)	0.44
Antifungal	16 (40%)	22 (75.9%)	37 (63.8%)	0.04
Steroid	17 (43%)	13 (44.8%)	28 (48%)	0.85
Anticonvulsant	7 (17.5%)	3 (10.3%)	14 (24%)	0.29
Antipyretic	2 (5%)	2 (6.9%)	2 (3.4%)	0.77
Growth factor	28 (29.8%)	24 (25.5%)	42 (44.7%)	0.46

^aOrganisms involved in polymicrobial cases included coagulase-negative staphylococci, *P. aeruginosa*, *K. pneumoniae*, *E. faecalis*, *E. cloacae*, *Leuconostoc*, *Granulicatella* and *E. casseliflavus*.

Table 3Positive culture data collected prior to carbapenem initiation^b

	Imi500q6 N=40	Mero1q8 N=29	Mero500q6 N=58
Gram Positive			
OSSA	0/16 (0%)	1/9 (11%)	1/33 (3%)
ORSA	3/16 (19%)	0/9 (0%)	0/33 (0%)
Coag-negative staph	6/16 (37.5%)	6/9 (67%)	12/33 (36%)
<i>E. faecium</i>	3/16 (19%)	0/9 (0%)	5/33 (15%)
<i>E. faecalis</i>	0/16 (0%)	0/9 (0%)	3/33 (9%)
Other ^a	2/16 (12.5%)	0/9 (0%)	5/33 (15%)
Gram Negative			
<i>P. aeruginosa</i>	1/16 (6.3%)	1/9 (11%)	1/33 (3%)
<i>Klebsiella</i>	1/16 (6.3%)	0/9 (0%)	2/33 (6%)
<i>Enterobacter</i>	0/16 (0%)	1/9 (11%)	4/33 (12%)
Source of infection			
Blood	12/16 (75%)	6/9 (67%)	27/33 (82%)
Lung	1/16 (6.3%)	1/9 (11%)	0/33 (0%)
Tissue	2/16 (12.5%)	2/9 (22%)	3/33 (9%)
Urine	1/16 (6.3%)	0/9 (0%)	3/33 (9%)

^a Other refers to 1 each of *Bacillus* and *E. casseliflavus* in the Imi500q6 group, 1 each of *S. salivarius*, *Bacillus*, *Leuconostoc*, *Granulicatella*, and Group B streptococcus in the Mero500q6 group.

^b Data reflect several subjects with positive culture findings from multiple sites. For example, if *ORSA*, *E. faecium*, and Coagulase-negative staphylococci were isolated from separate sites on a single patient, the data was categorized as gram positive, culture positive episode.

OSSA- Oxacillin-sensitive *Staphylococcus aureus*; ORSA- Oxacillin-resistant *Staphylococcus aureus*

Table 4

Susceptibility patterns of isolated organisms with sensitivity to meropenem and imipenem-cilastatin routinely tested at Barnes-Jewish Hospital.

	P. aeruginosa	Klebsiella	Enterobacter
Meropenem/Imipenem	2/3 (67%)	3/3 (100%)	5/5 (100%)
Gentamicin	3/3 (100%)	3/3 (100%)	5/5 (100%)
Ciprofloxacin	2/3 (67%)	3/3 (100%)	5/5 (100%)
Piperacillin-tazobactam	3/3 (100%)	3/3 (100%)	1/5 (20%)
Ceftazidime/Cefepime	3/3 (100%)	3/3 (100%)	5/5 (100%)
Ceftriaxone	0/3 (0%)	3/3 (100%)	1/5 (20%)
Cefazolin	0/3 (0%)	3/3 (100%)	1/5 (20%)

Table 5

Outcomes following carbapenem initiation

	Imi500q6 N=40	Mero1q8 N=29	Mero500q6 N=58	P
Reason for carbapenem start				0.4
Rash/allergy to cefepime	4 (10%)	2 (6.9%)	6 (10.3%)	
Fever 3 days on cefepime	13 (32.5%)	7 (24.1%)	15 (25.9%)	
New fever not on antibiotics	0 (0%)	0 (0%)	2 (3.4%)	
New fever on cefepime	15 (37.5%)	14 (48.3%)	25 (43.1%)	
Documented breakthrough infection	1 (2.5%)	0 (0%)	0 (0%)	
Desire for enhanced anaerobic coverage	1 (2.5%)	0 (0%)	5 (8.6%)	
Unknown	6 (15%)	6 (20.6%)	7 (8.6%)	
Need for renal dosing	2 (5%)	0 (0%)	4 (6.9%)	0.36
Need for additional antibiotics ^a	8 (20%)	5 (17.2%)	8 (13.8%)	0.71
Vancomycin	5 (12.5%)	2 (6.9%)	5 (8.6%)	0.70
Aminoglycoside	4 (10%)	3 (10.3%)	6 (10.3%)	0.99
Neutropenia resolution	28 (70%)	21 (72.4%)	45 (78%)	0.68
<i>C. difficile</i> infection	4 (10%)	1 (3.4%)	7 (12%)	0.43
Mortality				
In-hospital mortality	2 (5%)	2 (6.2%)	4 (6.9%)	0.82
30-day mortality	5 (12.5%)	2 (6.2%)	8 (13.8%)	0.64
Need to change therapy	4 (10%)	5 (17.2%)	5 (8.6%)	0.47
Rash	4 (10%)	3 (10.3%)	2 (3.4%)	
New Fever	0 (0%)	2 (6.9%)	2 (3.4%)	
Sepsis	0 (0%)	0 (0%)	1 (1.7%)	

^a 1 patient in the Imi500q6 arm and 3 patients in the Mero500q6 arm were initiated on both vancomycin and an aminoglycoside during their carbapenem course.