INNOVATIONS in pharmacy

Volume 6 | Number 2 Article 204

2015

Pharmacokinetic Analysis of Meropenem and Piperacillin in Critically-Ill Patients Requiring Continuous Ven-Venous Hemodiafiltration

Brandon Ferlas

Kristina Nelson

Milind Junghare

Kimberly Boeser

Pharmacokinetic analysis of meropenem and piperacillin in critically-ill patients requiring continuous veno-venous hemodiafiltration

Brandon Ferlas[1], PharmD, MS; Kristina Nelson[1], PharmD; Milind Junghare[2], MD; Kimberly Boeser[1], PharmD, BCPS-AQID
[1] University of Minnesota Medical Center Department of Pharmacy
[2] University of Minnesota Physicians Division of Nephrology and Renal Diseases

Running Head: Meropenem and piperacillin in CVVHDF

This study was funded by the University of Minnesota Physicians Division of Nephrology and Renal Diseases and conducted in conjunction with the Department of Pharmacy.

Keywords: pharmacokinetics, critical care, dialysis, CRRT, CVVHDF, infectious disease

Abstract
Background: Literature has demonstrated proper antibiotic selection and prompt initiation of antibiotics are associated with lower morbidity and mortality. Septic patients have altered pharmacokinetics and often require continuous renal replacement therapy which contributes to altered drug clearance and metabolism. The current study evaluates the pharmacokinetics of meropenem and piperacillin/tazobactam in critically-ill patients requiring continuous veno-venous hemodiafiltration.
Purpose: This observational, prospective, single-center, nonrandomized study evaluated the pharmacokinetics of meropenem and piperacillin/tazobactam in critically-ill patients requiring continuous veno-venous hemodiafiltration.
Methods: Plasma drug concentrations were determined via high-performance liquid chromatography using three post-dose blood samples after steady-state antimicrobial agent administration.
Results: Meropenem peak drug concentrations ranged from 35.9 to 61 mcg/mL, while trough concentrations ranged from 3.9 to 16.7 mcg/mL. Piperacillin peak drug concentrations ranged from 240 to 331.8 mcg/mL, while trough concentrations ranged from 152.7 to 194.9 mcg/mL. Both drugs examined displayed peak concentrations relatively consistent with those expected from the literature, but observed trough concentrations for meropenem and piperacillin were uniformly high.
Conclusions: Intravenous doses of meropenem and piperacillin result in peak drug concentrations similar to those previously reported and trough concentrations significantly greater than those in the literature. While concentrations above an organism's MIC are desirable given the time-dependent nature of these beta-lactam antibiotics, decreased renal clearance of patients maintained on CVVHDF therapy while receiving higher doses of antimicrobials creates a situation in which drug accumulation and toxicity may occur. Given the complex nature of ICU patient care, increased pharmacovigilance and therapeutic drug monitoring are necessary in this unique population.

Introduction

Admissions to intensive care units (ICU) for sepsis have increased dramatically over the past 15 years[i]. Hall and colleagues demonstrated that a greater proportion of septicemia or sepsis hospitalizations end in death when compared with other hospitalized populations (17% versus 2%, respectively). Furthermore, a greater proportion of hospitalizations include sepsis or septicemia as a principal or secondary diagnosis. This figure increased from over 620,000 in 2000 to over 1.1 million in 2008. During this period, the overall number of hospitalizations did not change, but the rate of these hospitalizations increased by 70% between 2000 and 2008. Those who survive sepsis or septicemia may have permanent organ dysfunction or other irreversible manifestations.

Gaieske et al demonstrated that proper antibiotic selection and prompt initiation of antibiotics are associated with lower mortality[ii]. An analysis of patients with septic shock demonstrated that time to initiation of antimicrobial therapy was the strongest predictor of mortality. It was also demonstrated that inappropriate antibiotic selection was common, occurring in 32% of septic patients[2]. Mortality was nearly doubled in this group compared to those patients with appropriately selected antibiotics (34% versus 18%). Pathogen recovery is often limited, therefore, a broad-spectrum antimicrobial agent is often chosen for empiric treatment. Two such agents are meropenem and piperacillin/tazobactam[iii].

Corresponding Author: Brandon Ferlas
2905 Inca St, Unit 3009, Denver, CO 80202
Email: ferla011@umn.edu

Renal injury requiring renal replacement therapy – including intermittent hemodialysis as well as various types of continuous renal replacement therapy – is estimated to occur in as many as 5% of ICU patients[4]. There is limited data supporting adequate dosing of medications for patients receiving renal replacement therapy. Estimating drug removal is complicated due to many factors including extracorporeal drug removal in addition to pharmacokinetic changes due to the underlying disease[iv,v]. Furthermore, these changes are not applicable to all patients receiving continuous renal replacement (CRRT) due to differences in techniques and instrumentation across institutions.

To estimate drug removal during CRRT many factors must be considered, including the pharmacokinetics and pharmacodynamics of the medication, interaction between the extracorporeal membrane and the medication, method of solute transport used for CRRT which may be by diffusion or convection and finally clinical significance of the medication clearance dependent on the extracorporeal circuit[4,5,vi,vii]. Many medications exhibit a multi-compartment distribution that is not affected largely by intermittent dialysis as the rate of removal exceeds the redistribution rate. CRRT affects the volume of distribution at a much slower rate, thus allowing for continuous redistribution to plasma and increasing the available drug for removal[4].

CRRT has several variants for the nephrologist to customize in order to provide individualized care. Continuous veno-venous hemofiltration (CVVH) which relies on convection for solute transport and thus is able to remove large particles (< 20kDa), continuous veno-venous hemodialysis (CVVHD) utilizes diffusive solute transport and thus limits extraction to smaller particles (< 300 Da), continuous veno-venous hemodiafiltration (CVVHDF) however incorporates both diffusion and convection to remove particles and thus has the capability to remove a broader range of particle sizes[5,7,viii,ix].

The current study is an institutional review board approved observational, prospective, single-center, nonrandomized study evaluating the pharmacokinetics of meropenem and piperacillin/tazobactam in critically ill patients requiring CVVHDF that took place from May 2013 to January 2014. The studied antimicrobials were selected due to their clinical significance. Meropenem and piperacillin/tazobactam are the two most commonly used broad spectrum, antimicrobial agents with activity against *Pseudomonas* sp. at our institution. Additionally, there is an absence of an established standard for routine therapeutic drug monitoring with these agents.

The primary objective of this study is to describe the clearance of meropenem and piperacillin/tazobactam to better understand the pharmacokinetics of two commonly used antibiotics used in the treatment of critically-ill patients simultaneously receiving CVVHDF therapy. A secondary objective was to evaluate the observed pharmacokinetics compared with previously published data for patients not requiring CVVHDF.

Methods

Study Design and Patient Population

Our institution has an adult critical care unit comprised of a 14-bed medical ICU, a 21-bed surgical ICU and a 16-bed cardiovascular ICU with medical ICU overflow. Patients included in this study were treated by the medical ICU team with either meropenem or piperacillin/tazobactam while simultaneously receiving CVVHDF for a minimum of 24 hours. Patients were excluded if they were under 18 years of age, over 75 years of age, prescribed custom dialysate solutions, experienced frequent CVVHDF interruptions[1], or had residual renal function (defined as urine output >400 mL in the 24 hour period preceding the post-dose lab draw window). Women who were pregnant or less than three months post-partum and patients with anticipated life expectancy of less than 24 hours were also excluded from the study. Eligible patients or their medical decision makers were approached by the primary investigator(s) to explain the study and obtain consent prior to study-specific lab draws taking place.

Antimicrobial Dosing and Serum Sample Collection

All patients within our institution receiving CVVHDF treatment and concomitant antimicrobial therapy with either meropenem or piperacillin/tazobactam, regardless of study eligibility, receive protocol-driven, renally-adjusted antimicrobial dosing (meropenem 1 gram intravenously every eight hours infused over 30 minutes or piperacillin/tazobactam 4.5 grams intravenously every six hours infused over 60 minutes). Both of these doses are greater than standard doses (500mg IV every six hours for meropenem, 3.375g IV every six hours for piperacillin/tazobactam) within our institution to account for increased clearance due to CVVHDF therapy.

[1] Frequent CVVHDF interruption was defined as two or more interruptions lasting less than four hours each within a 24 hour period. Prolonged CVVHDF interruption was defined as a cessation of CVVHDF for greater than four hours during the post dose lab window. Patients were re-considered for eligibility after a 24 hour period with no additional interruptions,

After at least 24 hours of continuous meropenem or piperacillin/tazobactam therapy with concurrent CVVHDF, three blood samples were collected by trained unit nursing staff via a pre-existing central venous catheter. Samples were drawn 0-30 minutes post-infusion (peak), 2.5-3 hours post-infusion (midpoint), and 0- 30 minutes prior to end of the dosing interval (trough). The time between infusion initiation through the end of the dosing interval was defined as the lab draw window. If CVVHDF encountered interruptions during the lab draw window, nursing staff were instructed to contact study personnel to determine if sampling could be continued. Blood samples were collected in 4 mL lavender-top tubes containing ethylenediaminetetraacetic acid (EDTA). Samples were placed on ice and delivered to the acute care laboratory immediately after collection.

Whole blood samples were processed to separate and isolate plasma following established laboratory protocol within two hours of collection. Isolated plasma was stored at -80 degrees Celsius until enrollment and sample collection was complete.

Dialysis Procedure and Drug Concentration Analysis

CRRT was performed using a PrismaFlex (Gambro) machine with M100 hemofilter and institution-standard solutions (PrismaSol BGK, Gambro, Lakewood, CO). CVVHDF was run via large bore vein access and settings were recorded for each patient during the lab draw period.

Meropenem and piperacillin concentrations were determined via high-performance liquid chromatography (HPLC) using cefuroxime as an internal standard.

Results

Five piperacillin/tazobactam and four meropenem subjects consented to the study and had at least one blood sample collected. Of these subjects, one in the meropenem group was excluded due nursing collection error, and two in the piperacillin/tazobactam group were excluded due to sample contamination (Figure 1). The three subjects that remained in each group are reported below as a case series. Relevant clinical, demographic, and treatment information for all patients was obtained from the electronic health record and is reported in Table 1.

Meropenem (Figure 2)

Case 1

A 52 year old male status post myeloablative allogeneic bone marrow transplant who was admitted for acute respiratory failure concerning for infection versus worsening graft-versus-host disease. Meropenem was initiated on admission, and CVVHDF was started on day one of admission. The evening prior to the lab draw window, the patient encountered a brief interruption in CVVHDF to allow for circuit change. The estimated down time was one hour. The patient's urine output during this time was decreasing, with an estimated output of 291 mL in the preceding 24 hours. Labs were significant for hypoalbuminemia. Sample collection occurred on day three of meropenem and the resulting concentrations were 61 mcg/mL, 39.4 mcg/mL and 16.7 mcg/mL for the peak, midpoint and trough concentrations, respectively. The calculated volume of distribution (Vd) for this patient was 17.1 L and estimated drug half-life was 3.6 hours.

Case 2

A 47 year old female who was admitted for pneumonia with worsening chest infiltrates. Meropenem initiated on day four of admission, and CVVHDF was started on day 12 of admission. During the lab draw window the patient encountered no interruptions in CVVHDF. Urine output during this time was increasing, with an estimated output of 262 mL in the preceding 24 hours. Labs were significant for hypoalbuminemia and a mild elevation in alkaline phosphatase. Sample collection occurred on day 17 of meropenem and the resulting concentrations were 47.3 mcg/mL, 13.6 mcg/mL and 3.9 mcg/mL for the peak, midpoint and trough concentrations, respectively. Calculated Vd for this patient was 15.4 L and estimated drug half-life was 1.9 hours.

Case 3

A 33 year old male with a history of alcoholic cirrhosis, hepatitis and pancreatitis who was admitted for cholecystitis and *Enterococcus faecalis sepsis*. The patient received several courses of meropenem during prolonged hospital stay with restart two days prior to lab draw for healthcare associated pneumonia, CVVHDF was started six days prior to the lab draw window. Approximately 24 hours prior to the lab draw window the patient encountered a brief interruption in CVVHDF for a circuit change due to clotting. The estimated down time was one hour. The patient produced no urine output during the 24 hours prior to lab sampling. Labs were significant for severe hepatic impairment with hypoalbuminemia, moderately elevated alkaline phosphatase and AST, and significantly elevated total bilirubin. Sample collection occurred after the fifth dose of meropenem and the resulting concentrations were 35.9 mcg/mL, 20.5 mcg/mL and 14.1 mcg/mL for the peak, midpoint and trough concentrations, respectively. Calculated Vd for this patient was 34.4 L and estimated drug half-life was 4.6 hours.

Piperacillin/tazobactam (Figure 3)

Case 1

A 55 year old male with no remarkable past medical history was admitted for acute liver decompensation, acute kidney

injury and microscopic polyangiitis with diffuse alveolar hemorrhage. Piperacillin/tazobactam was initiated on the third day of admission, which was one day after CVVHDF initiation. No CVVHDF interruptions occurred within 24 hours prior to or during the lab draw window. The patient produced 37 mL of urine during the 24 hours prior to lab sampling. Labs were significant for hypoalbuminemia and significantly elevated total bilirubin, AST, and ALT. Sample collection occurred on the eighth day of admission, after 24 hours of concurrent piperacillin/tazobactam and CVVHDF therapy. The resulting piperacillin concentrations were 311.9 mcg/mL, 243.3 mcg/mL and 194.9 mcg/mL for the peak, midpoint and trough concentrations, respectively. Calculated Vd for this patient was 22.2 L and calculated piperacillin half-life was 5.8 hours.

Case 2

A 49 year old female with a history of scleroderma, pulmonary hypertension, pulmonary fibrosis, breast cancer status post mastectomy and reconstruction, chronic hepatitis C, and hypothyroidism who was admitted for acute hypoxic respiratory failure and septic shock requiring vasopressor support. Piperacillin/tazobactam and CVVHDF were initiated one day after admission, which was six days prior to the lab draw window. Approximately 1.5 hours prior to the lab draw window the patient encountered a brief interruption in CVVHDF for increased pressures. No urine output occurred during the 24 hours prior to lab sampling. Labs were significant for hypoalbuminemia and moderately elevated alkaline phosphatase and total bilirubin. Sample collection occurred on the seventh day of admission and the resulting piperacillin concentrations were 239.9 mcg/mL, 183.5 mcg/mL and 152.7 mcg/mL for the peak, midpoint and trough concentrations, respectively. Calculated Vd for this patient was 30.9 L and estimated half-life was 6.3 hours.

Case 3

A 35 year old male with a history of mechanical aortic and mitral valve replacements and severe pulmonic stenosis who was admitted for sepsis from an infected thrombus in an atriovenous fistula. Piperacillin/tazobactam was initiated on day six of admission, one day prior to CVVHDF. Approximately 14 hours prior to the lab draw window there was a brief machine malfunction resulting in CRRT interruption. Patient had no urine output during the 24 hours prior to lab sampling. Labs were significant for hypoalbuminemia, moderately elevated total bilirubin, and significantly elevated AST and ALT. Sample collection occurred on the eighth day of admission, after 24 hours of concurrent piperacillin/tazobactam and CVVHDF therapy. The resulting piperacillin concentrations were 331.8 mcg/mL, 276.1 mcg/mL and 182.5 mcg/mL for the peak, midpoint and trough concentrations, respectively. Calculated Vd for this patient was 18.5 L and calculated piperacillin half-life was 5.0 hours.

Discussion

This observational, prospective, single-center, nonrandomized study evaluating the pharmacokinetics of meropenem and piperacillin-tazobactam in critically ill patients requiring CVVHDF provided insight about the plasma concentrations of two antimicrobial agents commonly used in critically ill patients requiring CVVHDF at our institution.

Previous studies have reported pharmacokinetics of meropenem and piperacillin in renal replacement therapy patients, but variations in study design and methods have prevented clear conclusions from being drawn about drug elimination in this subset of patients[6].

Antimicrobial treatment of critically ill patients in the ICU is complex due to factors such as resistant organisms, immunosuppression, and concomitant medical diagnoses and interventions. The time-dependent, bactericidal nature of beta-lactam antibiotics necessitates antimicrobial concentrations above the minimum inhibitory concentration (MIC) for 40-50% of the dosing interval for optimal bactericidal activity[x]. The two antimicrobial agents studied are frequently used to treat potential *Pseudomonas aeruginosa* infections. *Pseudomonas aeruginosa* is a common pathogen that has demonstrated increasing resistance and is frequently isolated from critically ill patients at our institution. For this reason, comparison of observed drug concentrations to MIC breakpoints for this organism will be made.

Meropenem peak drug concentrations ranged from 35.9 to 61 mcg/mL, while trough concentrations ranged from 3.9 to 16.7 mcg/mL. Compared to reported values for healthy volunteers[xi], the observed concentrations tended to be higher, especially at the end of the dosing interval. Meropenem peak concentrations were not well correlated with literature values, while trough concentrations were uniformly higher than expected values, revealing a potentially decreased rate of elimination.

Using a *Pseudomonas aeruginosa* MIC breakpoint of 4 mcg/mL[xii], only one concentration was observed below the MIC, indicating that meropenem concentrations above the MIC were achieved for an adequate period throughout the lab draw window in all three patients. From an antimicrobial efficacy perspective, these drug concentrations would be expected to contribute to optimal antibacterial efficacy against pathogens susceptible to this agent.

While no specific reports of adverse events relating to meropenem were recorded in these patients, the risk for drug accumulation and subsequent toxicity increases with increasing drug concentrations. Trough concentrations observed in this study were several-fold higher than those observed in healthy volunteers, which could prompt the need for increased pharmacovigilance and adverse event monitoring. Common side effects of meropenem injection include headache, nausea, diarrhea, pain, and anemia[11].

Piperacillin peak drug concentrations ranged from 240 to 331.8 mcg/mL, while trough concentrations ranged from 152.7 to 194.9 mcg/mL. Compared to reported values for healthy volunteers[xiii] , piperacillin peak concentrations are somewhat similar to the literature, but midpoint and trough concentrations are significantly higher than literature values. The pharmacokinetic profiles including therapeutic peaks and elevated troughs observed for all three patients are similar, suggesting a decreased rate of elimination for patients on CVVHDF therapy.

No concentrations were observed below the *Pseudomonas aeruginosa* MIC breakpoint of 32 mcg/mL[11]. In fact, the lowest observed concentration was about five times greater than this breakpoint. As observed in the meropenem group, these high drug concentrations would be expected to contribute to optimal antibacterial efficacy against pathogens susceptible to this agent.

Similar to the meropenem group, no reports of adverse events relating to piperacillin/tazobactam administration or accumulation were recorded in these patients, although greatly elevated trough concentrations observed in this study should prompt the need for increased pharmacovigilance and adverse event monitoring. Common side effects of piperacillin/tazobactam injection include headache, nausea, diarrhea, constipation, insomnia, and pruritis[13].

Drug Concentration Implications

While both drugs examined displayed peak concentrations consistent with those expected from the literature, observed trough concentrations for meropenem and piperacillin were uniformly high. While concentrations above an organism's MIC are desirable given the time dependent nature of these beta-lactam antibiotics, the decreased renal clearance of patients maintained on CVVHDF therapy while receiving higher doses of antimicrobials creates a situation in which drug accumulation and potential toxicity may occur.

While patients enrolled in this study had CRRT interruptions monitored closely and were excluded if interruptions were frequent or prolonged, CRRT is often interrupted for planned or unplanned reasons. During this time, antimicrobial medication doses may still be given, despite CRRT clearance being temporarily absent. This may lead to drug concentrations even higher than those observed in this study and a presumably higher risk of adverse events due to prolonged elevation in drug concentrations.

Potential mechanisms by which elevated troughs and associated toxicity may be avoided include dose reduction and dosing interval extension. As peak concentrations were relatively consistent with therapeutic literature values, dosing interval extension is likely the most effective method by which lower troughs could be attained while maintaining therapeutic peaks. For example, increasing the interval of piperacillin/tazobactam from six hours to eight hours or 12 hours would still achieve the peak concentrations desired for therapeutic efficacy, but would also give patients a longer period to clear the drug, thereby reducing their plasma drug concentrations and decreasing the risk of associated toxicity. Further study in this area is warranted to fully assess the potential for toxicity of these agents and investigate mechanisms and dosing strategies to avoid these adverse events.

Strengths

The present study examined the pharmacokinetics of two commonly used antimicrobial medications in critically ill patients requiring CVVHDF therapy. Patients in this study were treated for multiple indications and had varied demographic and clinical parameters. Samples were collected after steady-state would have been expected to occur, and interruptions in CVVHDF therapy were controlled for.

Additionally, the study was observational in nature and provided results based on actual clinical care without changing existing practices. As a result, interruptions in CVVHDF, slight variations in dose administration, performance of diagnostic tests and other aspects of routine patient care are incorporated into our results and reflect actual clinical practice when compared to well-controlled studies.

Limitations

The small number of patients enrolled from a single-center decrease the widespread applicability of the presented information. A majority of the patients treated with CVVHDF at our institution suffer from concomitant hepatic impairment, which may not represent the patient characteristics of other centers, further limiting the applicability of results.

Conclusions

Critically ill patients requiring CVVHDF have altered pharmacokinetics of antimicrobial agents. Intravenous doses of meropenem 1 gram every eight hours and piperacillin/tazobactam 4 grams/0.5 grams every six hours result in peak drug concentrations similar to those previously reported and trough concentrations significantly greater than those in the literature. Given the complex nature of ICU patient care, increased pharmacovigilance and therapeutic drug monitoring are warranted in this unique population. Further study of pharmacokinetics in CVVHDF patients is necessary to achieve greater understanding of drug elimination and metabolism in the setting of continuous renal replacement.

Acknowledgements: The authors recognize the contributions of Rory Remmel, PhD; Anja Rubenstein, PhD; and Ryan Harding for technical assistance and design of the drug concentration assays.

References

[1] Margaret Jean Hall, Ph.D.; Sonja N. Williams, M.P.H.; Carol J. DeFrances, Ph.D.; and Aleksandr Golosinskiy, M.S. Inpatient Care for Septicemia or Sepsis: A Challenge for Patients and Hospitals.
NCHS Data Brief No. 62 June 2011.

[2] Gaieski DF, Mikkelsen ME, Band RA, Pines JM, Massone R, Furia FF, Shofer FS, Goyal M. Impact of time to antibiotics on survival in patients with severe sepsis or septic shock in whom early goal-directed therapy was initiated in the emergency department. Crit Care Med. 2010;38(4):1045.

[3] Schmidt, GA, Mandel, J. Evaluation and management of severe sepsis and septic shock in adults. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. Accessed on November 25, 2013.

[4] Schetz M. Drug dosing in continuous renal replacement therapy: general rules. Curr Opin Crit Care. 2007 Dec;13(6):645-51.

[5] Heintz BH, Matzke GR, Dager WE. Antimicrobial dosing concepts and recommendations for critically ill adult patients receiving continuous renal replacement therapy or intermittent hemodialysis. Pharmacotherapy. 2009 May;29(5):562-77.

[6] Li AM, Gomersall CD, et al. A systematic review of antibiotic dosing regimens for septic patients receiving continuous renal replacement therapy: do current studies supply sufficient data? J Antimicrob Chemother. 2009 Nov;64(5):929-37.

[7] Joy MS, Matzke GR, et al. A primer on continuous renal replacement therapy for critically ill patients. Ann Pharmacother. 1998 Mar;32(3):362-75.

[8] Liu F, Mehta R. Chapter 52. Continuous renal replacement therapy. In: Lerma EV, Berns JS, Nissenson AR, eds. CURRENT Diagnosis & Treatment: Nephrology & Hypertension. New York: McGraw-Hill; 2009.

[9] Forni LG, Hilton PJ. Continuous hemofiltration in the treatment of acute renal failure. N Engl J Med 1997 May;336(18):1303-9.

[10] Drusano GL. Pharmacokinetic optimisation of β-lactams for the treatment of ventilator-associated pneumonia. Eur Respir Rev. 2007 Aug; 16(103) 45-49.

[11] Product Information: MERREM(R) intravenous injection, meropenem intravenous injection. AstraZeneca Pharmaceuticals LP (per FDA), Wilmington, DE, 2013.

[12] CLSI. *Performance Standards for Antimicrobial Susceptibility Testing; Twenty-Second Informational Supplement.* CLSI Document M100-S22. Wayne, PA: Clinical and Laboratory Standards Institute; 2012.

[13] Product Information: ZOSYN(R) IV injection, piperacillin and tazobactam IV injection. Wyeth Pharmaceuticals Inc., Philadelphia, PA, 2007.

Table 1: Patient Clinical and Demographic Information

	Meropenem			Piperacillin		
	Patient 1	Patient 2	Patient 3	Patient 1	Patient 2	Patient 3
Gender	Male	Female	Male	Male	Female	Male
Age	52	48	33	55	49	35
Weight (kg)	154.2	67.2	113	68.2	78.8	69.3
Height (m)	1.8	1.57	1.85	1.67	1.6	1.6
BSA (m2)	2.78	1.71	2.41	1.78	1.87	1.75
Antimicrobial Indication	HCAP	HCAP	Sepsis	UTI, Possible sepsis	Septic shock	Sepsis
Antimicrobial (mg/kg) per Dose	6.5	14.9	8.8	14.7	12.7	14.4
AST/ALT	34/66	102/49	128/40	172/111	37/55	2133/114
Total bilirubin	0.4	0.5	23.2	23.1	4.4	4.7
Albumin	2.3	1.9	2.6	2	2.1	2.7
Urine Output (mL) (Preceding 24 hr)	291	262	0	37	0	0
Vd (L)	17.1	15.4	34.4	22.2	30.9	18.5
t1/2 (hours)	3.6	1.9	4.6	5.8	6.3	5
Circuit Type	CVVHDF	CVVHDF	CVVHDF	CVVHDF	CVVHDF	CVVHDF
Filter	M100	M100	M100	M100	M100	M100
Blood Flow Rate (mL/min)	200	140	200	180	200	180
Ultrafiltrate rate (mL/hr)	1800	900	1700	1000	1200	700
Dialysate rate (mL/hr)	1800	800	1700	1000	1000	1000
Patient Survival	No	No	No	No	Yes	No

All data obtained from electronic medical record. Values reported were most recent available prior to lab draw window.

Figure 1: Patient enrollment and inclusion summary for meropenem and piperacillin/tazobactam groups

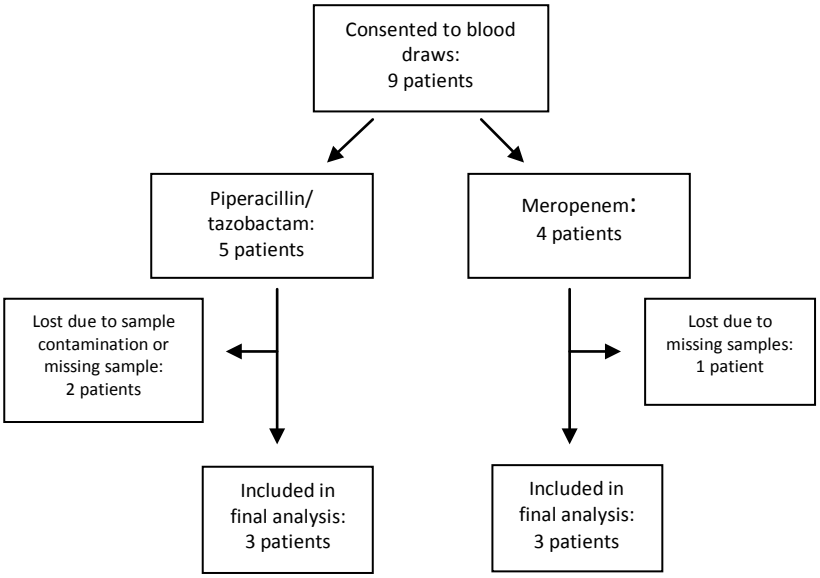

Figure 2: Meropenem plasma concentrations over time in study subjects during lab draw window (compared with literature values extrapolated from healthy volunteers given 1 gram meropenem dose)

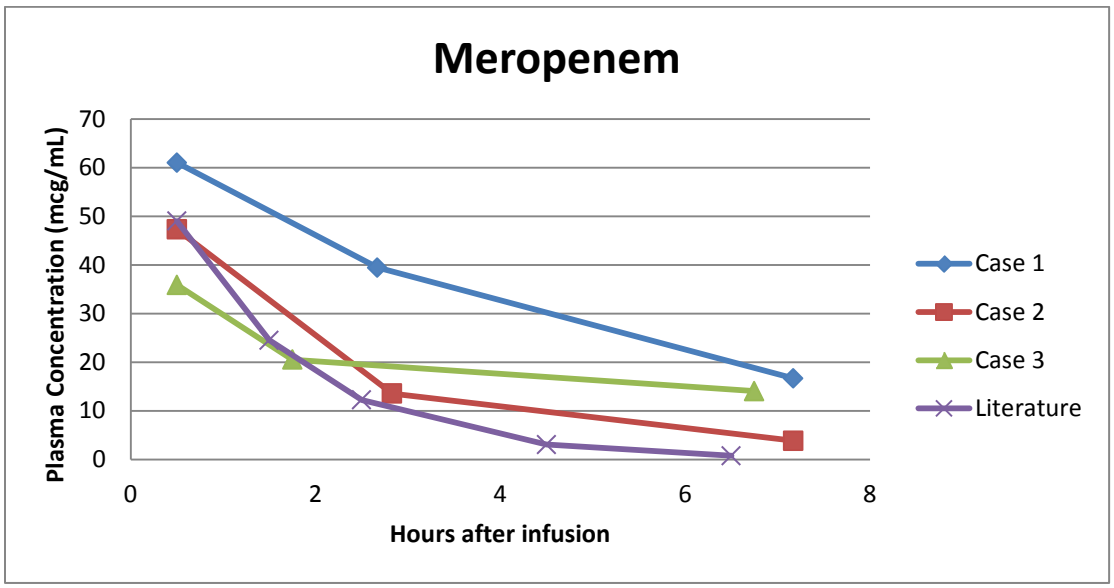

Figure 3: Piperacillin plasma concentrations over time in study subjects during lab draw window (compared with literature values reported for healthy volunteers given 4 gram piperacillin dose)