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THERAPEUTIC DRUG MONITORING OF BETA-LACTAM ANTIBIOTICS IN CRITICALLY ILL PATIENTS WITH SEPSIS

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Digital Object Identifier: https://doi.org/10.13023/etd.2021.075

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THERAPEUTIC DRUG MONITORING OF BETA-LACTAM ANTIBIOTICS IN CRITICALLY ILL PATIENTS WITH SEPSIS

DISSERTATION

A dissertation submitted in partial fulfillment of the
requirements for the degree of Doctor of Philosophy in the
College of Medicine
at the University of Kentucky

By
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Lexington, Kentucky
Co-Director: Dr. Peter Morris, Professor of Medicine
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Lexington, Kentucky
2021

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ABSTRACT OF DISSERTATION

THERAPEUTIC DRUG MONITORING OF BETA-LACTAM ANTIBIOTICS IN CRITICALLY ILL PATIENTS WITH SEPSIS

Sepsis is a devastating diagnosis affecting over 750,000 patients a year, accounting for approximately 10% of all hospital admissions, costs more than $50,000 per patient, and exceeds $17 billion annual spending. The mortality rate for sepsis remains unacceptably high: one out of every three patients diagnosed with sepsis dies. Sepsis physiology induces physiologic changes to drug pharmacokinetic (PK) parameters that alter the ability to achieve the goal pharmacodynamic (PD) target for beta-lactams of >4-fold unbound concentration above the minimum inhibitory concentration for 100% of the dosing interval (100% *f*T >4x MIC). Sepsis treatment such as volume resuscitation and vasopressor agents increase cardiac output and circulating blood flow, resulting in increased glomerular filtration and enhanced elimination of antibiotics. The PK alterations observed in critically ill septic patients are strongly associated with sub-optimal beta-lactam concentrations. Sub-optimal beta-lactam dosing has resulted in higher rates of therapeutic failure and increased mortality in critically ill patients with sepsis. In addition to the risk of under-exposure, growing data suggest certain beta-lactam combinations are associated with increased nephrotoxicity. Therapeutic drug monitoring of beta-lactam antibiotics is a strategy to improve the outcomes of critically ill septic patients by maximizing efficacy and minimizing toxicity.

KEYWORDS: Sepsis, Therapeutic Drug Monitoring, Beta-lactam, Antibiotics, Personalized medicine

Melissa Lynn Thompson Bastin
4/9/2021
Date

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ACKNOWLEDGMENTS

The following dissertation, while an individual work, benefited from the insights and direction of several people. First, my Dissertation Chair, Dr. Peter Morris. Dr Morris exemplifies the high-quality scholarship and collaborative research practice, to which I aspire. I thank him for years of mentorship and sponsorship, and I truly would not be here today without him. In addition, Dr. Alison Woodworth and Dr. Erin Schuler have provided me with key experience in the development of my laboratory skills, that have expanded my skill set immensely. Dr. Neyra has been instrumental in helping me fine-tune my writing skills and grantsmanship. Dr. Aaron Cook has been my mentor, coach and sponsor over the years, and to whom I am deeply grateful for all the opportunities afforded to me. Without Dr. Cook's support of this project, we would not be here today. Next, I wish to thank the complete Dissertation Committee, and outside reader, respectively: Dr. Alison Woodworth, Dr. Jimmi Hatton, Dr. Mitzi Schumacher, and Dr. Chester D. Jennings. Each individual provided insights that guided and challenged my thinking, substantially improving the finished product.

In addition to the technical and instrumental assistance above, I received equally important assistance from family and friends. My husband, Adam Bastin, provided on-going support throughout the dissertation process, as well as technical assistance critical for completing the project in a timely manner. Finally, I wish to thank my collaborators on each project which has contributed to this dissertation, especially Dr. Erin Schuler.

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1.1.1 Sepsis overview and role of antibiotics

Sepsis is a medical emergency associated with 30% mortality rate and should be considered a public health crisis. Sepsis is a devastating diagnosis affecting over 750,000 patients a year, accounting for approximately 10% of all hospital admissions, costs more than $50,000 per patient, and exceeds $17 billion annual spending. (Lagu, Rothberg et al. 2012, Angus and van der Poll 2013) In 2017, 48.9 million cases of sepsis were recorded globally, causing 11 million deaths. (Rudd, Johnson et al. 2020)

Sepsis is characterized by a dysregulated host response to infection. There are various phenotypes described in the host sepsis response, ranging from hyper-immune to hypo-immune, which makes it challenging for clinicians to predict which patients will progress to the most severe form (sepsis with organ failure, or shock), and who will not. (Angus and van der Poll 2013) Despite advances in care over the last 2 decades, one out of every three patients diagnosed with sepsis dies. The mainstay for sepsis treatment resides in supportive care of injured systems, and supporting damaged organs. The organ failure associated with sepsis often affects the respiratory and cardiovascular systems, but also the kidneys. Multi-organ failure in sepsis is associated with the highest risk of death, which increases with each failed organ. (Lagu, Rothberg et al. 2012, Angus and van der Poll 2013, Rudd, Johnson et al. 2020) As there is not a drug available to treat sepsis directly, the treatment of sepsis focuses largely on supportive care, and treating the underlying infection. (Fink and Warren 2014) Thus, antibiotics are the only drug available to treat the underlying cause of sepsis. Therefore, appropriate antibiotic selection (agent, dose, route)

is of utmost importance when treating a septic patient. International sepsis guidelines recommend empiric anti-pseudomonas antibiotics for sepsis, such as cefepime, meropenem, aztreonam or piperacillin-tazobactam. (Rhodes, Evans et al. 2017)

As such, one of the most important predictors of mortality in sepsis is early administration of the above-mentioned appropriate antibiotics. (Liu, Fielding-Singh et al. 2017, Rhodes, Evans et al. 2017) Kumar and colleagues evaluated the timing of antibiotic administration in septic shock patients and found that a delay in antibiotic administration beyond the first hour of hypotension was associated with an increased risk in hospital mortality (odds ratio 1.67; 95% confidence interval, 1.12–2.48). (Kumar, Roberts et al. 2006) A confirmatory study from a large retrospective database of 35,000 inpatient cases of sepsis or septic shock found a 9% increased risk of death for each hour delay in administration; adjusted OR 1.09 (95% confidence interval [CI], 1.05-1.13)]. (Liu, Fielding-Singh et al. 2017) This study highlights the importance of early appropriate antibiotics across the spectrum of the disease severity, with signals of improved outcomes in patients with sepsis and septic shock. As the research evaluating impact of timing of antibiotic administration is mounting, an important theme is also emerging: the one-size-fits all dosing strategy of beta-lactam antibiotics is inadequate for critically ill patients. (Boucher, Wood et al. 2006, Roberts, Paul et al. 2014, Tsai, Lipman et al. 2015, Ehmann, Zoller et al. 2017, Rhodes, Evans et al. 2017)

1.1.2 Pharmacokinetic and Pharmacodynamics in critical illness Pharmacokinetic alterations

There are many changes which occur in critically injured sepsis patients that impact the way drugs are distributed into the body, metabolized, and eventually eliminated. This

is the science of pharmacokinetics, and the full understanding of these changes is paramount for optimizing antimicrobial therapy in sepsis. The changes specifically observed to be important for beta-lactam antibiotics are: 1) increased volume of distribution (Vd), which will decrease the initial concentration measured immediately following the dose, and 2) increased glomerular filtration, which will increase drug elimination. Changing either of these properties will alter the total body clearance of the drug. Plasma protein binding is also altered in sepsis, which can be significantly challenging with highly protein bound drugs, however the beta-lactam antibiotics in question (cefepime, meropenem and piperacillin-tazobactam) are not highly protein bound. The significance of alterations in plasma protein biding for these specific antibiotics has not been established. In summary, the pharmacokinetic alterations seen in critically ill patients with sepsis significantly alter the predicted concentrations, which have been established in young healthy volunteers following a standard dose. (Boucher, Wood et al. 2006, Tsai, Lipman et al. 2015)

The observed volume of distribution is often profoundly larger in critically ill patients, as compared to healthy controls. Intravascular volume expansion, which is a mainstay of the treatment of shock is recommended in international guidelines. Most septic patients will receive at least 30ml/kg as an initial crystalloid volume dose, and many patients receive much more. (Rhodes, Evans et al. 2017) Net increase interstitial fluid accumulation occurs due to this routine practice of volume resuscitation, and is enhanced by the underlying pathology of the disease state. Endothelial injury from sepsis and increased capillary permeability facilitate third spacing of intravascular fluid into non-vascular compartments, such as the tissues and lungs. The emptying of the vascular space precipitates shock, and the need for intravascular volume expansion. These mechanisms

independently and collectively increase the apparent Vd of hydrophilic drugs, such as: aminoglycosides, beta-lactam antibiotics, vancomycin, daptomycin. Simply stated, when the intravascular fluid moves into these extra-vascular spaces (the cell, muscle, lungs, skin)- the hydrophilic beta-lactam antibiotics follow. The large increase in the Vd has been observed in many patient phenotypes of sepsis, including those in the early stages of sepsis, or hyper-dynamic sepsis, and those receiving extra corporeal renal dialysis. In a study of surgical prophylaxis patients, gentamicin pharmacokinetic parameters were monitored. The septic patients vs. non-septic patients had an increased Vd from 0.29 L/kg to 0.48 L/kg. (Tang, Tang et al. 1999) In a different population of critically ill septic patients in acute renal failure requiring continuous renal replacement therapy (CRRT), the daptomycin pharmacokinetic parameters were measured. The typical range of Vd of daptomycin, as measured in healthy controls is 0.08-0.15 L/kg, which was increased to 0.23 L/kg in the critically ill patients in this study. (Khadzhynov, Slowinski et al. 2011, Vilay, Grio et al. 2011)

Another study in 80 patients with septic shock, acute renal failure (27%), and mechanical ventilation (71%) with a positive fluid balance at 24h (2.5L) measured beta-lactam serum concentrations. The measured volume of distributions of the beta-lactams in this study were approximately double that of healthy volunteers published in package inserts. Twenty-seven patients receiving piperacillin-tazobactam were observed to have a mean (range) Vd of 0.38L/kg (0.29-0.43); compared to healthy volunteers a Vd of 0.2L/kg. Sixteen patients receiving meropenem were observed to have a Vd of 0.43L/kg (0.31-0.77), as compared to 0.28L/kg in healthy volunteers. Cefepime was given to 19 patients, who displayed a mean (range) Vd of 0.36L/kg (0.33-0.44); which was substantially higher when compared to healthy volunteers (0.26L/kg). (Taccone, Laterre et al. 2010) These studies

highlight the important differences observed when pharmacokinetic parameters are directly measured in critically ill patients, as compared to healthy volunteers, or non-critically ill comparison groups. Based on the relationship between Vd and peak serum concentrations, one would need to double the dose in order to overcome the doubling of the Vd, in order to achieve the optimal post-infusion concentrations, in these patients-. However, this is not done routinely in clinical practice.

Another example of the variation of PK observed in critically ill patients is in a study by Lheureux et al. (Lheureux, Trepo et al. 2016) The aim of this study was to observe the impact of cirrhosis on pharmacokinetic measurements patients with sepsis. This study compared the pharmacokinetic profiles of septic critically ill patients with and without cirrhosis. Thirty-eight cirrhotic patients were matched to 38 non-cirrhotic pairs. All patients received 2 measured samples of their respective antibiotic (meropenem and piperacillin-tazobactam). Cirrhosis was defined as a Child-Pugh class B or C. Patients were matched on antibiotic (dose and type), 24- hour CrCl, CRRT intensity (for CRRT patients), SOFA score and total body weight. Each drug was compared to the PK/PD goal of 50%T> 4-8xMIC piperacillin and 40% meropenem. The EUCAST MIC thresholds for *P. aeruginosa* were ≤ 8 mg/L for piperacillin and ≤2 mg/L for meropenem. (Kahlmeter, Brown et al. 2006) Notable differences in pharmacokinetic profiles for the 2 drugs were observed. The cirrhotic patients had a lower meropenem Vd (0.43L/kg [0.37–0.80] vs 0.77 L/kg [0.47–1.12] 0.05) and a lower piperacillin CL, (24ml/min [16–41] vs. 39ml/min [28–62] p=0.009) than their matched controls. The cirrhotic patients were more likely to have excessive beta-lactam levels, and experienced more neurologic side effects. The expected pharmacokinetic alterations in cirrhosis (impact of impaired liver clearance, and reduced protein binding) is evident in this study. Non-renal clearance and protein binding is

considered negligible for most beta-lactam antibiotics, however the impact on overall pharmacokinetic profiles was significant in this study.

A systematic review of 57 studies summarized the impact of critical illness on pharmacokinetic parameters of beta-lactam antibiotics. This study measured the Vd, clearance, and tissue penetration of the beta-lactam antibiotics. (Goncalves-Pereira and Povoa 2011) The clearance of meropenem ranged from (4.7L/hr to 15.4L/hr) in the reviewed studies. Meropenem clearance closely correlated with CrCl in these patients, however the variability across patients and within the same patient, reached up to 20%. Tissue penetration was measured by microdialysis in several of the studies reviewed. Measuring tissue penetration provides insight into how much drug is being delivered into the site of infection. This concept has long been controversial, as assumptions are made about the relationship between the concentration of the antibiotic in the serum to the site of infection. Patients who are in shock, and on vasoactive agents to raise blood pressure have reduced peripheral circulation, and possibly reduced delivery of the antibiotic to the site of infection. For meropenem, the mean tissue: plasma ratio on day 1 of therapy was 0.44 for subcutaneous fat, and 0.74 in the peritoneum. The cumulative fraction of response was calculated for each antibiotic across all studies reviewed. This is the numeric product of multiplication of the percent target attainment for each MIC x the MIC distribution. This allows the viewer to understand how the meropenem dosing regimen performs against a variety of MICs encountered in the dataset. The cumulative fraction of response for meropenem was 100% against *Enterobacteriaceae* and 40.6% for *Pseudomonas* during intermittent bolus dosing. This increased to 100% for Pseudomonas when the dosing strategy was changed to continuous infusion. The directly calculated Vd was often much larger than expected from studies in healthy volunteers. For many beta-lactam antibiotics,

(meropenem, cefpirome, cefepime, piperacillin) the Vd determined from heathy volunteers fell outside of the range of measured volumes in this study. Piperacillin pharmacokinetic measurements were also widely variable from established normal ranges in healthy volunteers. Piperacillin clearance closely correlated to CrCl, yet many patients did not reach target attainment (<15%). Microdialysis assessment of tissue penetration was done, and revealed that the ratio of tissue: plasma was 0.1, correlating to 33% of the penetration seen in healthy adults. The cumulative fraction of response of piperacillin with a 30-minute infusion was found to be 53.4%, which increased to 92.3% with continuous infusion dosing. Cefepime demonstrated a nearly doubling of the expected Vd in the reviewed studies. At risk populations for altered cefepime pharmacokinetics included severe sepsis, septic shock, elderly with sepsis, burn patients and those diagnosed with nosocomial pneumonia. Cefepime clearance was found to correlate closely to CrCl (0.58- 0.77) in the reviewed studies. The cefepime cumulative fraction of response of a 2gram twice daily dose for Escherichia coli and Klebsiella pneumoniae was 78.9%, and for Pseudomonas aeruginosa 53.6%. However, when increasing the dose to 2 grams three times daily the cumulative fraction of response increased to 84.9%; a 4gm/day continuous infusion increased to 91.7%, and 6 g/day increased to 94.8%. The cumulative fraction of response for Acinetobacter baumanii with the maximum labeled dose in continuous infusion of 6 g/day, was only 75%. Microdialysis evaluation was done for cefepime in burned tissue and found to be widely variable ranging from 0.4 to 5.1. Sample concentrations from bronchial fluid in pneumonia patients were undetectable following an 89mg/kg/dose, however in a different study, concentrations were measured and increased with use of continuous infusion dosing strategy. Figure 1.1 below represent the various Vd observed in the studies, as compared to known values from healthy volunteers.

Figure 1.1 Volume of distribution of study patients vs. healthy volunteers

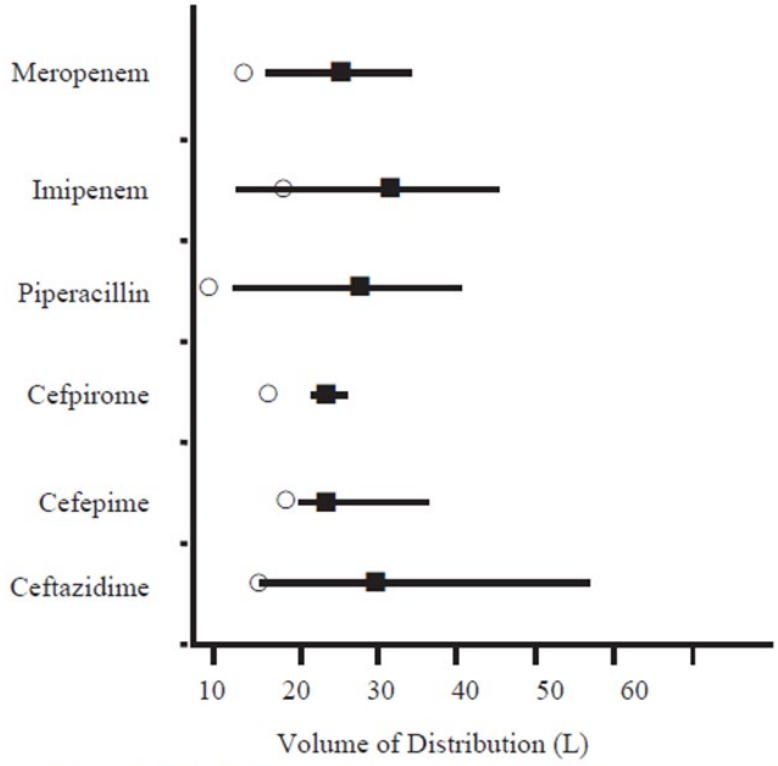
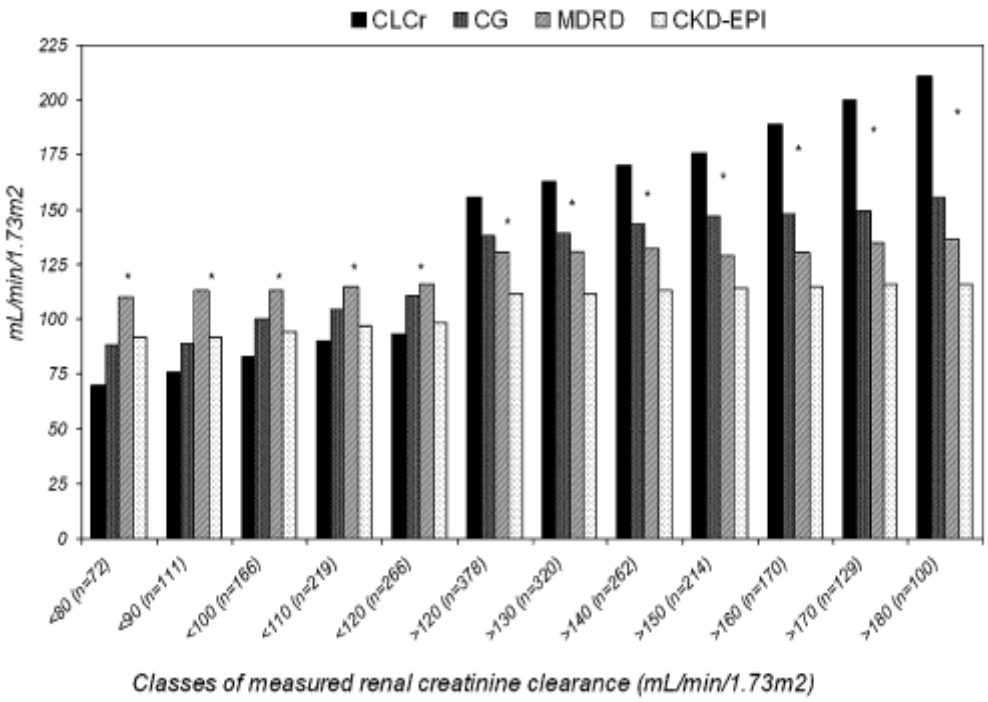


Figure 3 Heterogeneity of volume of distribution in litres of β-lactam antibiotics in ICU patients. Open circles: volume of distribution in healthy volunteers [44,51,89-92]; filled squares: weighted means of volume of distribution in the studies; straight lines: ranges of the means of volume of distribution in the studies.

In addition to the changes expected in volume of distribution and tissue penetration, clearance of medications is often altered in critical illness. Traditional glomerular filtration rate (GFR) equations that estimate a creatinine clearance based on serum creatinine can be inaccurate in critically ill patients. (Baptista, Neves et al. 2014) A prospective study done in 54 ICU patients (50% medical, 30% trauma) with a normal serum creatinine was done to compare the accuracy of 3 serum creatinine GFR equations as compared to the gold standard, an 8-hr urine creatinine collection test. The three methods tested were the Modified Diet in Renal disease, Cockroft-Gault, and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI). Data from 644 urine collection samples were matched to their respective equations. The three equations had an overall correlation coefficient of R = 0.2, suggesting poor agreement. In looking at sub-groups of patients with

various cut-off thresholds, the equations increasingly underestimated the GFR in patients measuring >120ml/min, and overestimated the GFR when CrCl was <120ml/min. (Figure 1.2) The correlation coefficient remains low (R<0.3) at the various cut-off points of GFR range.

Figure 1.2 Comparison of GFR equations to 8-hour urine creatinine at various thresholds of GFR

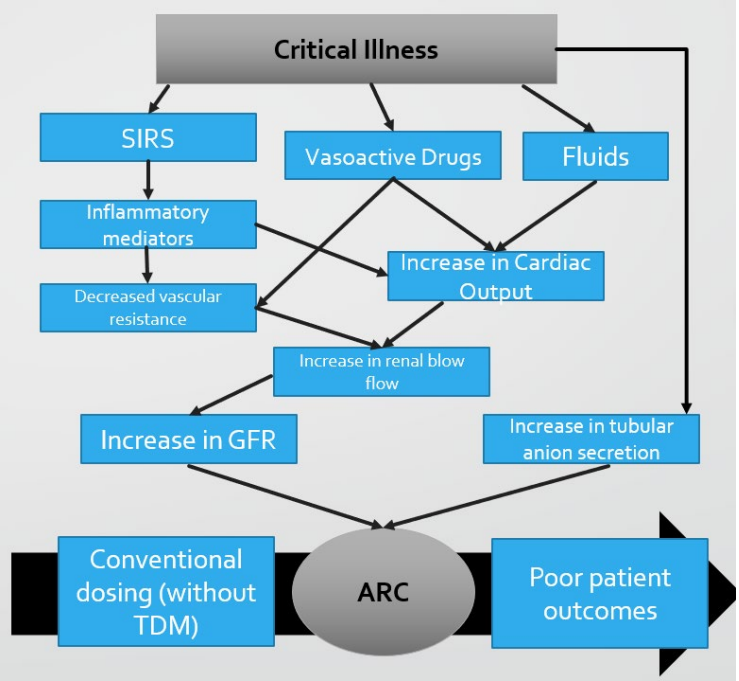


Serum creatinine based GFR equations were not developed, and have not been validated in critically injured patients. (Cockcroft and Gault 1976) The application of these equations to the ICU patient population deserves further study, and should be scrutinized when dosing medications. Determining medication dosing regimens based on flawed data can result in over or under dosing of key therapeutics. In the previous study, 55% of the patients exhibited augmented renal clearance (ARC). (Baptista, Neves et al. 2014) ARC is defined as a GFR of ≥130 ml/min. The hallmark of ARC is enhanced glomerular filtration, from which several factors and characteristics have been implicated in the causative

pathway, including increased renal blood flow, increased tubular anion secretion, renal tubular absorption, and heightened non-renal elimination. (Udy, Jarrett et al. 2014)

In septic patients, volume resuscitation and vasopressor agents to restore hypotension are the mainstay of initial hemodynamic management. Both interventions increase cardiac output and circulating blood flow, resulting in increased glomerular filtration and enhanced elimination of solute filtered through the kidney, leading to ARC. (Sime, Udy et al. 2015) Figure 1.3 highlights the intricate pathophysiology and additive effect of sepsis treatments on the risk of ARC.

Figure 1.3 Pathophysiology of augmented renal clearance



Although, only recently described in the medical literature, ARC has been identified in several critical care disease states. Patients who are younger in age, male, low serum creatinine at baseline, and a diagnosis of: sepsis, traumatic brain injury, subarachnoid hemorrhage, burn, or neutropenic fever are at highest risk of ARC. A risk stratification tool was developed, called the Augmented Renal Clearance in Trauma

Intensive Care scoring system (ARCTIC) score, to assist clinicians in the diagnosis of ARC for trauma patients. (Barletta, Mangram et al. 2017) In this landmark study from 2017, a retrospective evaluation of trauma patients determined predictors of ARC from weighted logistic regression and ROC analysis. Three independent variables emerged as key predictors for ARC in this population: age, serum creatinine, and gender. The weighted ARCTIC score is found in Table 1.1 and can assist clinicians in proactively identifying patients at high risk of ARC, and for whom may need more aggressive dosing regimens of renally eliminated medications. An ARCTIC score of 6 or higher had a sensitivity of 0.843, specificity of 0.682, positive predictive value of 0.842, and negative predictive value of 0.682, with an overall accuracy of 79%.

Table 1.1 ARCTIC Score

Variable	Points
Scr <0.7 mg/dl	3
Male sex	2
Age < 56 y	4
Age 56-75 y	3

ARC is difficult to predict and the effects on antimicrobial concentrations are challenging to measure without therapeutic drug monitoring. A prospective observational study done in Switzerland aimed to describe the prevalence of ARC, and describe any association between ARC, beta-lactam concentrations, and clinical outcomes of patients receiving beta-lactam antibiotics for sepsis. (Huttner, Von Dach et al. 2015) 100 Swiss patients diagnosed with sepsis, and exhibiting a CrCl ≥60 mL/min were enrolled. Patients

received beta-lactam TDM twice, once on days 1-3 and once again on day 5; 64/100 (64%) of patients exhibited ARC diagnosed as a CrCl ≥130ml/min as calculated by the Cockcroft-Gault creatinine clearance equation. (Cockcroft and Gault 1976) The beta-lactams measured in this study were imipenem 500mg q6h, meropenem, 2gm q8h, piperacillin 4.5g q8h, and cefepime 2gm q12g. The PK target for this study was T>100% 1x MIC, based on EUCAST breakpoints. (Kahlmeter, Brown et al. 2006) Imipenem was the most commonly encountered beta-lactam (54%), followed by piperacillin (33%), meropenem (11%) and cefepime (2%). Sixty-four patients exhibited ARC, with a median (IQR) CrCl 166 ml/min (145–200). ARC patients were younger, lower APACHE II scores and more likely to be admitted for trauma and neurological illness than non-ARC patients. In this cohort, ARC persisted at the 14-day point in 41/65 (76%) patients. Of all the trough concentrations drawn in this study, 20% were undetectable, and 71% were sub-therapeutic.

A prospective observational study done in 79 patients with augmented renal clearance, sepsis, shock (50%) and respiratory failure (20%) evaluated beta-lactam concentrations in patients receiving a continuous infusion. (Carrie, Petit et al. 2018) The beta-lactam doses were piperacillin 16gm or cefepime/ceftazidime/meropenem 6gm; all regimens were infused over 24 hours. Blood samples were collected at 24, 48 and 72 hours. ARC was diagnosed with a measured 24-h urine creatinine clearance within the first 72h of therapy. The primary study outcome was sub exposure, defined as a serum concentration < MIC of the bacteria, if the bacteria was not isolated, EUCAST breakpoints were used. (Kahlmeter, Brown et al. 2006) (EUCAST) An a priori subgroup was also analyzed, assessing the more aggressive PK/PD target of <4xMIC. All patients achieved a concentration above the MIC, however 20% (16/79) of patients had sub-optimal beta-lactam levels (<4x MIC), which was statistically significantly associated with CrCl (150

ml/min ± 66 vs 235 ± 58 ml/min, 246 ml/min $p < 0.0001$). The sub-optimal serum concentrations were associated with higher rates of therapeutic failure 16% (13/79), and development of resistant organisms 15% (2/13). (Carrie, Petit et al. 2018)

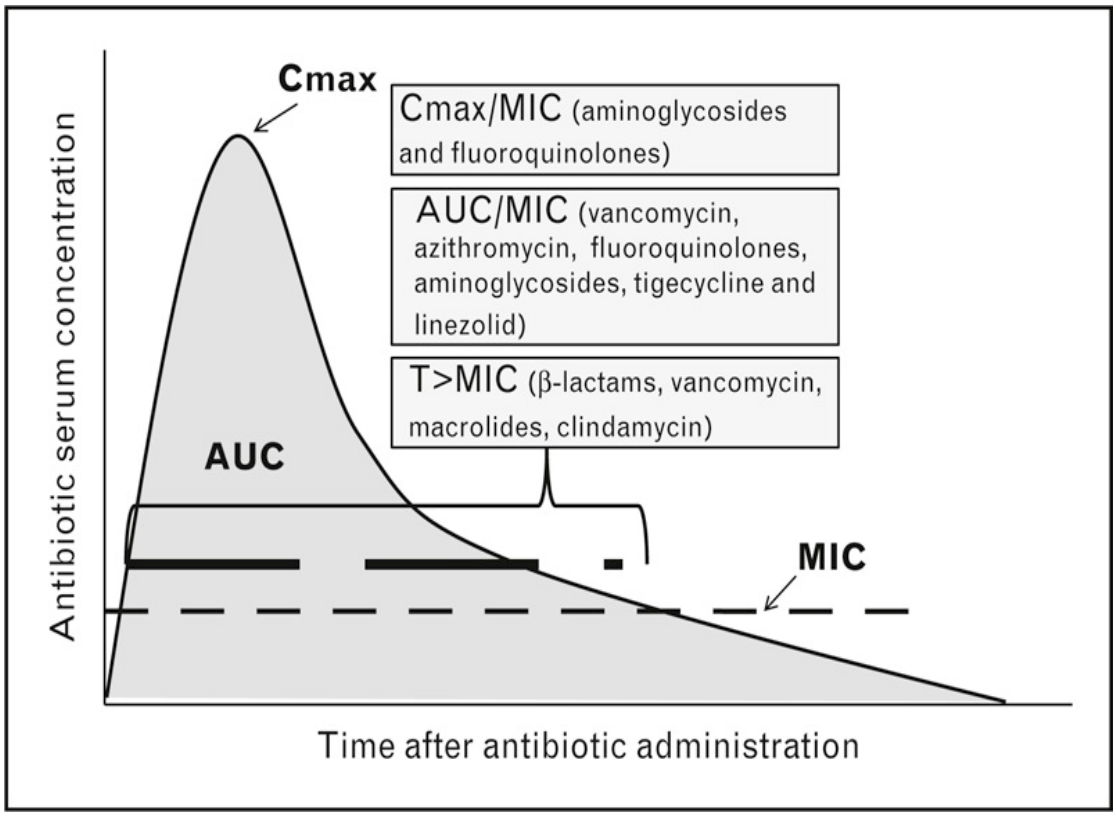
A sub-study by the same investigators sought to evaluate the impact of ARC on differing doses of piperacillin and the ability to achieve PK/PD target attainment in various scenarios of MIC breakpoints. (Carrie, Legeron et al. 2018) Monte Carlo simulation (n=5000) was done on 3 dosing regimens 12gm/day, 16gm/day, and 20gm/day. For the MIC of 16 (EUCAST breakpoint for *Pseudomonas*), the rate of underexposure was 19% (11/59), which associated with a higher CrCl in the underexposed: (219 ml/min ± 31 vs 131 ml/min ± 50, p= 0.0001). Underexposure was not statistically significantly associated with therapeutic failure (27.3% vs. 12.5%, p=0.22). A cut off of 170 ml/min predicted underexposure with a sensitivity of 1 (95% CI: 0.79–1), and specificity of 0.69 (95% CI: 0.61–0.76). Other variables, including weight, and BMI had no association with underexposure in this cohort. For patients with ARC and a CrCl of 170 ml/min, a daily dose of 20gm of piperacillin is needed to achieve adequate serum concentrations. This suggestion is above the currently labeled maximum dose of piperacillin, which is 16 gm a day.

In summary, the myriad of pharmacokinetic alterations in critical illness predispose patients receiving beta-lactams to under-exposure. These changes are not readily measurable; thus, any preemptive dosing adjustment would be considered a bit like shooting in the dark.

1.1.3 Target attainment

There is a known relationship between beta-lactam concentration and bactericidal activity. Beta lactam antibiotics exhibit time dependent killing. This simply means, optimizing the *time* the serum concentration is a threshold above the minimum inhibitory concentration (MIC) of the organism will optimize bactericidal effects and microbiologic outcomes. (Figure 1.4) This, time above the MIC (T>MIC), is the pharmacokinetic/pharmacodynamic (PK/PD) goal for beta-lactam antibiotics

Figure 1.4 Concentration time curve representation of optimal beta-lactam PK/PD target.



The MIC of an organism is the concentration at which, visible growth is inhibited on a microbiology plate. This threshold is determined for each antibiotic/ bacterium pair. The MIC represents the minimum serum concentration that must be achieve with an

antibiotic, in order to kill the bacteria. With increasing MIC levels, the effectiveness of the antibiotic is diminished. (Lodise, Lomaestro et al. 2006). Several limitations to the MIC thresholds exist. This is considered a snapshot in time, which does not reflect bacterial killing over the course of the entire dosing interval. It also does not provide information on the impact of higher doses on bacterial killing. Finally, the MIC does not take into consideration regrowth and killing of the organism, only the total net effect. Thus, while MIC remains the gold standard for assessing antibiotic activity, there are several caveats which must be taken into consideration when optimizing antibiotic dosing, and measuring microbiologic cure. (Lodise, Lomaestro et al. 2006) However, ultimately, the MIC is still the gold standard for assessing antibiotic susceptibility, and predicting therapeutic success.

The traditional PK/PD goal for beta-lactam antibiotics is based on the class of drug. To optimize the bactericidal killing of cephalosporins, the concentration should be above the MIC for 60-70% of the dosing interval; for penicillins 50%, and for carbapenems 40%. (Lodise, Lomaestro et al. 2006) These thresholds are considered the bare minimum targets. In recent years, a more aggressive target has been proposed for beta-lactams. The goal TDM target for beta-lactams of >4-fold unbound concentration above the minimum inhibitory concentration for 100% of the dosing interval (100% fT >4x MIC) has been suggested as the optimal target for beta-lactams in critically ill patients. (Roberts, Paul et al. 2014, Abdul-Aziz, Lipman et al. 2015) Achieving this TDM threshold has been associated with improved bacterial killing, reduced emergence of resistant isolates, increased microbiologic cure and improved clinical outcomes in critically ill patients. (Olofsson, Geli et al. 2005, Abdul-Aziz, Lipman et al. 2015, Abdul-Aziz, Lipman et al. 2017) (McKinnon, Paladino et al. 2008) Beta-lactam serum drug monitoring is the only way to monitor attainment of this TDM goal in critically ill patients with sepsis. (Boucher,

Wood et al. 2006) Sepsis, and the treatment of sepsis, induce pharmacokinetic changes to beta-lactam antibiotics, reducing the likelihood of achieving the TDM goal of (100% *f*T >4x MIC).

Not achieving the goal PK/PD goal for beta-lactam dosing in critically ill patients is associated with adverse patient outcomes. Inadequate beta-lactam levels in the early stages of sepsis have been associated with increased mortality in gram-negative bacterial infection. (Seyler, Cotton et al. 2011, Aitken, Altshuler et al. 2015, Carrie, Bentejac et al. 2018) Surviving Sepsis international guidelines recommends TDM-based optimization of all antimicrobials in sepsis, including beta-lactam antibiotics, (Rhodes, Evans et al. 2017) yet for various reasons, this recommendation is not implemented in every health system, including the University of Kentucky Medical Center. (Wong, Brinkman et al. 2014)

Kaska and et al performed a pharmacokinetic study in 18 critically ill patients admitted to a surgical ICU. (Kaska, Havel et al. 2018) The aims of this study were to identify patient characteristics associated with reduced target attainment. Meropenem dosed at 2 gm q8h over 3 hours, and piperacillin-tazobactam 4.5 gm q8h over 3 hours were given to patient's subject to TDM. The PK/PD goal of 100%fT>MIC was selected for this model. The free concentration was determined from the total plasma concentration, assuming the protein binding of piperacillin-tazobactam to be 22%, and assuming negligible meropenem protein binding. Of the 18 patients, eight displayed augmented renal clearance (44%) in this mixed trauma/surgical and septic population. TDM was performed between days 2-3 of therapy pending the patient's operation and procedures schedule. For meropenem, all patients (8/8) obtained 100%fT > 2 mg/L; 12.5% (1/8) reached the threshold of 100%fT>4-8 MIC, and 25% (2/8) who achieved the 100%fT>8 MIC. Overall,

for meropenem, only 12.5% reached the optimal target for critically ill patients. In the patients who received piperacillin-tazobactam, the goal 100%fT>16 mg/L was attained in 2/10 patients (20%). Seven patients with sub-therapeutic concentrations displayed ARC. In a mixed-liner model, the ability for piperacillin-tazobactam to reach the PK/PD goal was inversely related to cumulative fluid balance [β 1.2; (95% CI 0.55, 1.97) p=0.002]. Cumulative fluid balance was also positively associated with an increased Vd [β 0.02; (95% CI 0.00, 0.03) p=0.021]. Similar trends were seen with meropenem, yet no estimate reached statistical significance. This study has important limitations, the use of calculated free concentrations using population pharmacokinetic extrapolation is considered controversial, bearing in mind the wide variation seen in critically ill patients. This study used the European committee for antibiotic testing (EUCAST) breakpoints for *Pseudomonas* spp., a system not used in the United States, of which breakpoints can differ, however not for *Pseudomonas* currently. (Kahlmeter, Brown et al. 2006) All 18 patients did well clinically in this study, highlighting the need for larger clinical trials with more robust patient data. Doses were not adjusted in this study, therefore the impact of TDM optimization based on serum concentrations is unknown. There were no reports of toxicity in this trial.

When septic patients go into renal failure requiring continuous renal replacement therapy (CRRT), beta-lactam target-attainment and dosing is challenging, and standard doses are often associated with sub-therapeutic concentrations. (Seyler, Cotton et al. 2011) In a 53-patient study of septic patients with shock (23%) and mechanical ventilation (73%), who were receiving CRRT at standard guideline doses of 22ml/kg/hr had serum concentrations measured. The goal PK/PD parameter in this study was 4-5x>MIC for 40% of the dosing interval. In patients receiving meropenem 1gm every 12, 81% of patients

reached this threshold, zero cefepime (2gm q12h) patients reached the threshold, and only 71% of patients receiving piperacillin-tazobactam reached the goal at a dose of 4.5gm q6h. Meropenem was also associated with significant accumulation at 48 hours. (Seyler, Cotton et al. 2011). In another study conducted by Beumier et al, septic patients on CRRT (16-34ml/kg/hr) who were mechanically ventilated (72%) and had mean admission APACHE score of 21 received therapeutic drug monitoring of their beta-lactam antibiotic. (Beumier, Casu et al. 2014) The PK/PD goal in this study was 4-5x MIC (≥40% meropenem ≥70% cefepime and ≥50% piperacillin). Target attainment was defined as being able to achieve this PK/PD goal for 90% of the time. Of the whole cohort, 92% of patients met their respective target attainment. When TDM was performed early, 51% of patients exceeded target attainment, and 58% exceeded target attainment when TDM was performed again at 48h. (Beumier, Casu et al. 2014) Target attainment is challenging to reach in critically ill patients with sepsis, requiring CRRT, without therapeutic drug monitoring.

1.1.4 Antibiotic Dosing Controversies in Sepsis: Beta-lactam Toxicities

Considering the mounting data supporting under-dosing of beta-lactam antibiotics, one may conclude empiric or preemptive dose increases should circumvent this issue. However, toxicities have been reported with beta-lactams, many of which may exhibit a concentration dependent effect.

Certain beta-lactam combinations are increasingly associated with increased risk of acute kidney injury in sepsis. It is unknown at this time, if excessive piperacillin levels contribute to this phenomenon. An abundance of observational data support the additive toxicity of piperacillin/ vancomycin combinations over cephalosporin/ vancomycin

combinations. A recent meta-analysis evaluated 24,799 patients concluding the odds of developing acute kidney injury was 340% higher with vancomycin and piperacillin combinations, over other beta-lactams, with a number needed to harm of 11 patients [Odds ratio, 3.40; 95% CI, 2.57–4.50]. (Luther, Timbrook et al. 2018) The clinical impact and nephrotoxicity risk associated with piperacillin and vancomycin combinations has extensively evaluated. (Rutter, Burgess et al. 2017, Rutter and Burgess 2017, Rutter, Cox et al. 2017) One recent study found a 218% increased risk of nephrotoxicity with vancomycin and piperacillin over cefepime [OR 2.18;(95% CI, 1.64 to 2.94]. (Rutter, Cox et al. 2017) As piperacillin is the workhorse beta-lactam in many institutions based on bacteria susceptibility profiles, this growing body of literature is concerning for practitioners. There is a need to identify the mechanism of this interaction, and piperacillin therapeutic drug monitoring is the first step to solving this problem.

Many septic patients are at risk for under-dosing of beta-lactams; however, some patients may be at risk of over-dosing, possibly increasing the risk of acute kidney injury. TDM and personalization of dosing is the most precise way to select a dose for septic patients, maximizing efficacy, while minimizing toxicity. Acute kidney injury in sepsis doubles mortality and morbidity and can be prevented or attenuated with proper monitoring. (Chertow, Burdick et al. 2005) Acute kidney injury in hospitalized patients has been associated with significant increases in mortality, length of stay, and health care costs. (Chertow, Burdick et al. 2005) There is a need to identify acute kidney injury early in the patient course to prevent further damage and post- acute kidney injury complications.

Biomarkers of tubular damage or dysfunction may be valuable in assessing and monitoring for clinical (and subclinical) acute kidney injury. Animal data suggests that antibiotic exposure is associated with increased levels of kidney injury molecule-1 (KIM-1) and neutrophil gelatinase-associated lipocalin (NGAL). (Luo, Chen et al. 2014, Rhodes, Prozialeck et al. 2016) Tubular injury markers (NGAL, KIM-1) and cystatin C can be used to detect sub-clinical acute kidney injury early, in order to adjust doses of nephrotoxic antibiotics. (Luo, Chen et al. 2014, Ostermann 2015)

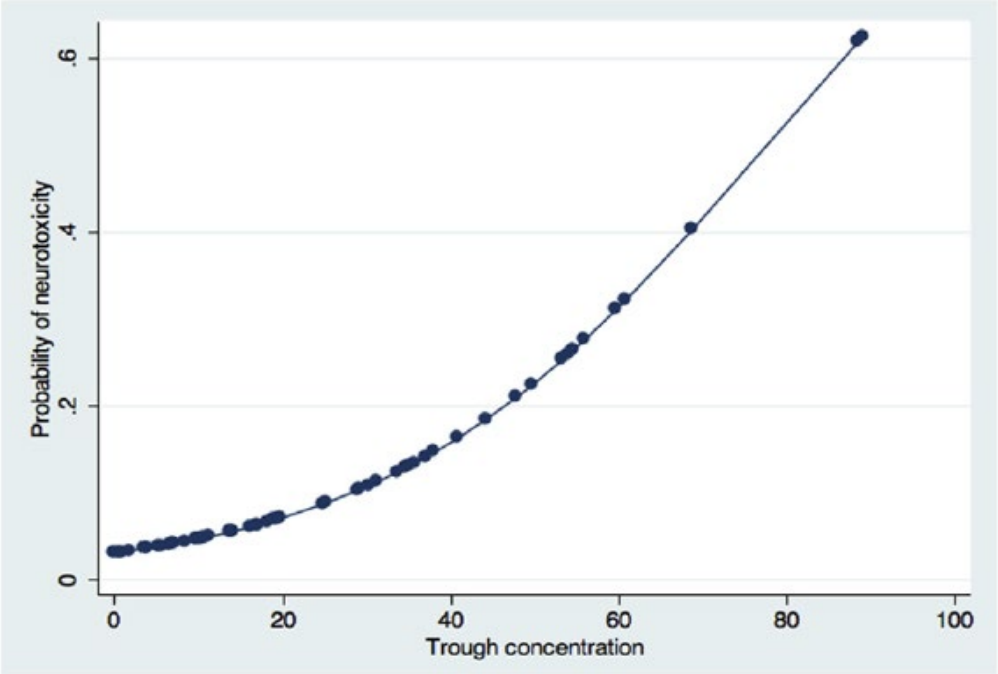
Cefepime is a popular option for the treatment of severe infections in hospitalized patients. (Harbarth, Pittet et al. 1998) It complements the broad-spectrum armamentarium with the ability to remain pharmacologically active against AmpC-producing organisms, and provide a carbapenem-free option. (D'Angelo, Johnson et al. 2016) Recently, the cephalosporins have gained favor over aminopenicillins (piperacillin-tazobactam) due to a possible safety benefit of less association with acute kidney injury. (Rutter and Burgess 2017) Cefepime, however, is not a magic bullet free of adverse side effects. Cefepime crosses the blood brain barrier, and can act as a competitive antagonist of gamma-amino butyric acid (GABA), thereby inhibiting this primary inhibitory neurotransmitter system. By way of inhibiting GABA transmission, cefepime exposure predisposes an environment for neuroexcitation, resulting in possible seizure activity. (Payne, Gagnon et al. 2017) Other mechanism for cefepime induced encephalopathy include the interaction with renal transporters responsible for carnitine transport elimination. (Fernandez-Fernandez and Ameneiros-Lago 2020) Cefepime, among other antibiotics, has been found to inhibit the organic cation transporter $OCTN_2$, resulting in increased excretion of carnitine in the urine, possibly resulting in a carnitine-deficient state. (Ganapathy, Huang et al. 2000) Hypo-

carnitine associated cephalosporin neurotoxicity has been reported previously with cefditoren. (Kim, Chu et al. 2012)

The use of therapeutic drug monitoring to identify patients at risk for cefepime neurotoxicity has gained attention in recent years. For centers that routinely perform these measurements, reporting a correlation with a therapeutic range would assist clinicians in dose adjusting to avoid this unwanted adverse effect. A Swiss study published the findings of cefepime TDM and association with neurotoxicity (Huwyler, Lenggenhager et al. 2017) in 2017. In this single-center retrospective study, 161 cefepime levels were drawn from 93 hospitalized patients. The hospital protocol includes a serum trough concentration to be drawn within 1 hour of the next dose. In this center, the creatinine clearance was estimated using the MDRD equation. The primary outcome was clinical toxicity, which was independently assessed by two investigators, a clinical pharmacologist and an infectious disease physician. Causality was assessed with the WHO-Uppsala Monitoring Centre system, a standardization assessment tool for causality of a medication side effect. Secondary study outcomes included cefepime failure, and over-dosing. The most commonly administered cefepime dose was 6 grams a day for patients with a CrCl >60ml/min. Renal dosing was not performed for 10% of these cases. The median trough concentration for those receiving 4 grams a day was 11.5 mg/L (IQR 5.6-22.3), and for those receiving 6 grams a day was 20.9 mg/L (IQR 12.4-43.5). Ten patients experienced a neurological event, and one patient experienced a rash attributed to cefepime therapy. Of the 10 patients with a neurological event, none fulfilled the formal assessment criteria as they all had other possible causes, including other neurotoxic drugs, or conditions. The most common event was confusion (n=5), altered cognition (n=4), followed by seizures (n=1). Neurotoxicity was associated with longer days of cefepime therapy (mean duration

8 ± 6.7) vs. 13 days (± 14.2), p =0.071; and higher serum trough levels 52.2 mg/L ± 8.4) vs. 21.3 mg/L± 19.2, p<0.001. For those receiving continuous infusions, the steady state concentration was higher in the neurotoxicity group, however did not reach statistical significance, likely due to lower sample size (n=4), mean steady state concentration 48.8 mg/L± 35.3 vs. 33.8 mg/L ± 24.6. There were no toxic events at a level of <35mg/mL. Overall, the probability of neurotoxicity increased with increasing serum trough concentrations. (Figure 1.5) Other characteristics associated with neurotoxicity were failure to adjust dosages for renal function, admission to an ICU, and febrile neutropenia treatment.

Figure 1.5 Probability of neurotoxicity with increasing cefepime trough concentrations



A retrospective study, conducted at a center which routinely performs beta-lactam TDM guided dosage optimization of meropenem and piperacillin, evaluated the impact of higher than labeled dosing of beta-lactam on the incidence of toxicity (McDonald, Cotta et

al. 2016). The TDM protocol calls for adjusting the total daily dose by decreasing the dosing interval, to achieve a PK/PD goal of unbound concentration above the MIC (*f*T>1xMIC) for 100% of the dosing interval. Thus, to achieve this goal, the dosing could have exceeded the package insert labeled maximum dose. In this study, high dose was defined as meropenem >6 grams a day for central nervous system infection, or >3 grams a day for routine infections. Piperacillin high dose was defined as >16 grams a day. Neurotoxicity, nephrotoxicity, hepatotoxicity, and hematological toxicity were assessed. Ninety-three patients were included in this study (meropenem= 47 and piperacillin = 46). The mean daily doses were 40% higher in the high dose group, as compared to the licensed-dose group. Both groups achieved the PK/PD target goal, and there were no differences in treatment course duration, or patient outcomes. There were no statistically different differences in the seizure, renal dysfunction, hepatotoxicity or neutropenia incidence between the two groups. This study has marked strengths and limitations. The pragmatic evaluation of an ICU protocol increases external validity. Targeting the same PK/PD parameter for all patients removed the confounding of excessive drug concentrations contributing to toxicity, although the PK/PD goal itself is debatable and will influence the resulting trough concentrations. This study is small, single center and retrospective. Further evaluation of these outcomes should be done in a prospective study design.

A systematic review of cefepime induced neurotoxicity was published in 2017. (Payne, Gagnon et al. 2017) Thirty-seven citations were included, representing data from 135 patients. One study was a prospective trial, and the rest were either retrospective cohort studies, or case reports. Patients were generally older (median 69 years old), in the ICU (81%), with renal dysfunction (80%), and received a cefepime regimen not adjusted for renal function (48%). Cefepime trough concentrations were reported for 13 patients

median 38 mg/L (range 15–224). Neurotoxicity developed at a median of 4 days (IRQ 2-6) after initiation of cefepime, with symptom resolution at a median of 2 days (IQR 1-3) after cefepime cessation. This review has key limitations, mainly the low-quality evidence summarized, only allows for descriptive statistics. While, identification of risk factors for cefepime neurotoxicity is an important step, these hypotheses should be tested in a prospective trial.

In a recent clinical evaluation of cefepime associated neurotoxicity, cefepime exposure within the first 48 hours was classified according to dose and renal dysfunction estimated by Cockcroft-gault equation. (Khan, DeMott et al. 2020) For those with moderate renal dysfunction (CrCl 30-60ml/min), a 48h dose of ≥ 8 g was considered high, and a 48h dose of <8g was considered low. For those with severe renal dysfunction (CrCl 11-29ml/min), high dose was defined as ≥ 4 g, and low dose was <4 grams. Cefepime associated neurotoxicity was defined as new-onset symptoms of signs of neurologic dysfunction "altered mental status, impaired consciousness, confusion, aphasia, agitation, myoclonus, tremor, EEG abnormalities, seizures, or nonconvulsive or myoclonus status epilepticus". (Khan, DeMott et al. 2020) Overall, many patients experienced a change in neurological status (42% vs 32% p=0.145) in the low and high exposure groups, respectively. However, when attributing the change in neurological status to cefepime, the incidence was lower (4% vs 10% p=0.093) in the low and high groups respectively. This was not associated with degree of renal dysfunction. Overall, the incidence of cefepime associated neurotoxicity was low in this study. Without the corresponding TDM measurements, it is difficult to understand the full spectrum of risk factors present in these toxic patients.

Piperacillin has also been implicated for causing neurotoxicity, as described in a retrospective cohort study of 53 ICU patients who were admitted to a center which performs TDM. (Quinton, Bodeau et al. 2017) The patients received a continuous infusion of piperacillin of 12 grams or 16 grams a day, according to renal function. Neurotoxicity was considered present if the patients received at least 48h of piperacillin, not on sedation, and the patient exhibited signs of neurologic dysfunction: confusion, coma, myoclonus, seizures or hallucinations. Patients with neurotoxicity had a statistically significant higher steady state concentration than those without: (159.9 mg/L versus 91.3 mg/L; P= 0.0016). A receiver operator curve analysis suggests that a cut-off level of 157.2 mg/L provides 96.7% specificity and 52.2% sensitivity for neurotoxicity (area under the concentration-time curve [AUC], 0.75; 95% confidence interval [CI], 0.61 to 0.89). After multivariate adjustment for CrCl <30ml/min, vasoactive medications, sepsis, hypocalcemia, only a piperacillin concentration (≥157.2 mg/L) remained a significant predictor of neurotoxicity, (Odds ratio 14.86, 95% CI (1.27–173.23), p= 0.0313.

Pharmacokinetic modeling has been proposed to assist in identification of therapeutic thresholds of cefepime concentrations to predict neurotoxicity. (Rhodes, Kuti et al. 2016) A pharmacokinetic/toxicodynamic model was created from published cases of cefepime neurotoxic (n=32) patients and cefepime non-toxic patients (n=22). Serum concentrations, along with covariates including age, diagnosis, CrCl, were fit in the simulation model. A threshold of trough 22mg/L was used a prior in the model, as it has been previously associated with neurotoxicity. Weight was not available for all patients, therefore when unavailable, was fixed at the median of 72 kg. Overall, the mean probability of neurotoxicity at a trough of 22mg/L was 51.4% (95% CI 16.4- 85). Sensitivity was 16.7%, and specificity was 100% at this threshold, and the overall incidence of

neurotoxicity was only 21.6%. Simulation results displayed a dose of 2 grams every 8 hours had the highest probability of exceeding a trough concentration >22mg/L within the first 24h of dosing (26-56%). Classification and regression (CART) modeling was attempted to determine if a different threshold would better predict the event of neurotoxicity; however, due to low sample size, the investigators were unable to complete this analysis. Overall, the threshold of 22mg/L performed with low precision to predict the incidence of neurotoxicity in this simulated experiment. Other pharmacokinetic exposures such as total exposure and peak concentrations should be explored as predictors for cefepime neurotoxicity.

The exact mechanism, risk factors and concentration thresholds for development of neurotoxicity beta-lactam treated patients are unknown. Diligent dosing according to pathogen, MIC and organ function can help reduce excessive drug exposure and possible toxicities. Therapeutic monitoring of beta-lactam concentrations appears to be an ideal method of avoiding toxic drug concentrations, while optimizing bactericidal killing.

1.1.5 Therapeutic Drug Monitoring Overview: TDM of Anti-infective

Therapeutic drug monitoring is a fundamental pharmacist activity in relation to anti-infective agents. Decades of research and experience have highlighted the importance of serum concentration monitoring in an effort to optimize efficacy and safety of agents such as vancomycin and aminoglycosides. The strategy by which these agents are monitored and adjusted continues to evolve. In addition, novel agents and new knowledge about older anti-infectives have created clinical scenarios for which TDM is necessary. This section explores contemporary strategies for TDM of anti-infectives, with common abbreviations found in Table 1.2.

Table 1.2 Common abbreviations in this chapter

AUC0-24	Area under the concentration-time curve over a 24-hour period
Cmax	Maximum concentration
Cpeak	Serum concentration at the end of distribution phase
fT>MIC	Free concentration time above minimum inhibitory concentration
HDEI	High-dose extended interval
MIC	Minimum inhibitory concentration
PD	Pharmacodynamic
PK	Pharmacokinetic
TDM	Therapeutic drug monitoring
T>MIC	Time above minimum inhibitory concentration
Vd	Volume of distribution

Therapeutic drug monitoring is often necessary for anti-infectives with a narrow therapeutic index or with substantial interpatient variability displayed with standard dosing. Clinicians need to identify specific guidelines and thresholds to serve as boundaries or goals of therapy to optimize safety and efficacy. Many of the agents for which TDM is routinely used may be harmful if not carefully monitored. Therefore, clinicians should understand the relationship between serum concentrations and adverse effects. For example, aminoglycosides are known to cause nephrotoxicity in patients with prolonged exposure to high serum concentrations; however, toxicity may occur in patients who have concentrations in therapeutic range. (Barclay and Begg 1994) Adjustment of the dose based on serum concentrations and clinical PK assessment permits a more personalized dose that should lead to safer drug exposure.

Pharmacodynamic variables that are associated with bacterial killing and clinical efficacy can also be targets for TDM. Dosing strategies to optimize bactericidal activity by

targeting a specific peak to MIC ratio (Cpeak: MIC) or T>MIC can be developed by first monitoring serum concentrations and adjusting therapy to meet these goals. (Craig 1998) Some anti-infectives exhibit marked variability between individuals. This leads clinicians to personalize the dose considering variables such as weight, renal or hepatic function. Classic examples of these considerations are the variability of vancomycin clearance in relation to renal function or voriconazole as a result of hepatic function and/or pharmacogenetic factors. Reliance on standard adjustments for these variables is not entirely accurate and some anti-infectives do not have predictable PK for reasons other than weight and renal function. (Udy, Varghese et al. 2012) Overall, if the serum concentrations of an agent have good association with safety and efficacy and/or exhibit marked and clinically relevant variability with standard dosing, the agent is likely a viable option for TDM.

Pharmacokinetic variables can be thought of in two different ways: population-specific or patient-specific. Population -specific PK assumes the patient is reflective of the typical patient with regard to drug disposition, metabolism, and/or elimination. Equations for population-specific PK variables are usually derived from PK studies of the drug. Clinicians should be mindful of the source of these equations and whether their specific patient would fit the population from which the equations were derived. For example, a commonly used population elimination rate constant (Ke) for aminoglycosides was developed using an undefined population including patients and healthy volunteers. (Bechtol and Black 1975) It may be inappropriate for a clinician to estimate the clearance of a patient with cystic fibrosis using this equation because patients with cystic fibrosis are known to have different aminoglycoside clearance and were not represented in this study. A common pitfall of the use of online calculators for aminoglycoside or vancomycin dosing

is that the source of their calculations is often not evident (or is not sought out by the user). This situation may lead the clinician to use population guidelines and equations that are not appropriate for the specific patient. Practically, population-specific guidelines can be a helpful start for clinicians when deciding on an individualized dose for a patient. However, given the narrow therapeutic index for agents that typically require TDM, going beyond population-specific variables is usually advisable.

Patient-specific PK guidelines can be generated by sampling serum concentrations around a given dose. Such sampling can provide clinicians with various PK guidelines that describe the nature of the disposition and elimination of the drug, as well as reflect the effect of various physiologic processes on the PK of the agent. For example, evaluation of vancomycin peak and trough concentrations not only permits the clinician to calculate the elimination rate constant and Vd, but also to assess these values in the context of fluid resuscitation, diuresis, acutely changing renal function, and other clinical characteristics that may affect vancomycin PK, rendering the population-specific PK equations unusable. Important assumptions should be acknowledged when using samples to generate patient-specific PK guidelines. Intravascular volume status, protein binding, tissue penetration, and elimination are all assumed to be relatively constant during the sampling period (although, in reality, fluctuation in these variables is common in acutely ill patients). Similarly, consistency of dosing to permit a steady-state, superimposable concentration-time curve is also assumed. Clinicians should be mindful of these assumptions when interpreting serum concentrations and calculating PK variables. When possible, precise evaluation of organ function and protein binding should be performed. In addition, alterations in volume of distribution, clearance, and other PK variables may occur in critically ill patients, those at

extremes of body weight, and other patients for whom end-organ function may be abnormal.

The development of TDM services has provided many benefits related to cost and patient outcomes. Numerous studies have described reductions in toxicity related to pharmacist-directed TDM and dose individualization for various anti-infective agents, including aminoglycosides and antifungal agents such as voriconazole. (Bechtol and Black 1975, Streetman, Nafziger et al. 2001, Touw, Neef et al. 2005, Park, Kim et al. 2012) Early studies of TDM for aminoglycosides suggested that overall costs were lower with a TDM approach and mortality was also reduced. (Touw, Neef et al. 2005) Similarly, TDM of vancomycin is proven to be cost effective in oncology or intensive care patients and can reduce the incidence of nephrotoxicity. (Bond and Raehl 2005, Touw, Neef et al. 2005) More recently, TDM has improved the therapeutic response and reduce the occurrence of central nervous system or hematologic toxicity of antifungal agents such as voriconazole and flucytosine. (Pasqualotto, Howard et al. 2007, Park, Kim et al. 2012)

Creation of a standardized approach to PK monitoring and documentation is a necessity for establishing an institution-wide TDM program. Practitioners should agree regarding the preferred PK and PD targets. Clinical pharmacists should be involved with creation of TDM protocols, as well as educated on protocol implementation and other institutional standards such as extent and frequency of documentation. Education of nurses and prescribers on proper ordering and collection of serum samples for TDM should mitigate the occurrence of sample waste and spurious results. Collaboration with other ancillary services such as the clinical laboratory is also necessary to validate reliable assays

and establish policies on how supratherapeutic concentrations will be handled, such as notifying pharmacists.

Figure 1.6. General calculations for one-compartment, first-order elimination (eg. aminoglycosides, vancomycin at steady state)

Patients with First-Dose Kinetics

1. Calculate patient-specific elimination rate (k):

$$k = \frac{Ln\,(C1_{random}/C2_{random})}{T'}$$ T' = Time between C1 and C2

2. Calculate the Cmax:

$$C_{max} = C1/e^{-kt'}$$ t' = time between C1 and end of the infusion

3. Calculate the volume of distribution (Vd):

$$Vd = \frac{\frac{LD}{t}(1-e^{-kt})}{k(C_{max})}$$ LD = loading dose (mg)
t = Infusion time

4. Calculate the estimated steady-state peak and trough concentrations:

$$\text{Peak} = \frac{(\text{dose}/t')(1-e^{-ke\,(t')})}{Vd\,(ke)(1-e^{-ke\,(T)})}$$

$$\text{Trough} = C_{peak}\,(e^{-ke\,(T-t')})$$

(where T is the interval and t' is the infusion time)

5. Determine if trough meets goal concentration (from protocol). If trough (calculated above) > goal concentration, time above the MIC is 100%. If trough is less than this concentration, calculate the time at which it fell below this concentration, and thus the new dosing interval.

t' = ln(Cpeak/goal conc.)/k (t'= new dosing interval rounded to the nearest hour)

6. Follow dosing protocol for goal assessment, and dose adjustments

Patients with Steady State Kinetics

1. Follow step 1 as above.
2. Calculate the steady state C_{peak} and C_{trough} from C1 and C2, respectively:

$$C_{max} = \frac{C1}{e^{-kt'}}$$ t' = Time between C1 as drawn and end of infusion

$$C_{tr} = C2 \times e^{-kt'}$$ t' = Time between C2 as drawn and C_{tr}

3. Calculate volume of distribution (Vd):

$$V_d = \frac{\left(\frac{MD}{t}\right)x\,(1-e^{-kt})\,x\,e^{-kT}}{C_{pk}^{ss}\,x\,k\,x\,(1-e^{-k\tau})}$$ t= infusion time in hours; T= time between end of infusion and Cpk (steady state)

4. Follow steps 5,6 as above.

Figure 1.7. Example Beta-lactam dosing protocol

Drug ***(3hr infusion)***	**Initial dose regimen**	**Goal empiric trough concentration (5x MIC)**	**Dose adjustments <100% *f*T>4 MIC**	**Dose adjustments for elevated levels >100% *f*T>10× MIC**
Piperacillin	4 gram q6	≥80 mcg/ml	Step 1. Calculate new dosing interval required to obtain goal trough (with equations above) Step 2: Increase total daily dose by decreasing dosing interval. Step 3: Maximum doses defined as a total daily dose 2x higher than standard labeled doses (piperacillin 32 gram, cefepime 12 gram, meropenem 12 gram, aztreonam 12 gram) Step 4: If maximum dose exceeded, consider dual therapy Step 5: Consider dual therapy against resistant isolates	Step 1. Calculate new dose/interval based on patient specific PK parameters to target goal range.
Cefepime	2 gram q8	≥40 mcg/ml		
Meropenem	2 gram q8	≥10 mcg/ml		
Aztreonam	2 gram q8	≥40 mcg/ml		

β-Lactams

The β-lactam class of antibiotics has widely been used as the backbone for empiric and definitive coverage of a variety of severe infections, including sepsis. (Rhodes, Evans et al. 2017) The TDM target for β-lactams of more than 4-fold unbound concentration above the MIC for 100% of the dosing interval (100% f >T greater than 4 times the MIC) has been suggested in critically ill patients. (Roberts, Paul et al. 2014, Abdul-Aziz, Lipman et al. 2015) However, less aggressive goals for bacteriostatic activity include a T>MIC of more than 50% of the dosing interval. (Craig 1998) Achieving the more aggressive TDM goal has been associated with improved bacterial killing, reduced emergence of resistant isolates, increased microbiologic cure, and improved clinical outcomes in critically ill

patients. However, the optimal goals for therapy have not been established and should be individualized to the patient situation. (Olofsson, Geli et al. 2005, McKinnon, Paladino et al. 2008, Abdul-Aziz, Lipman et al. 2015, Abdul-Aziz, Lipman et al. 2017)

The largest β-lactam monitoring study to date found only 35% of ICU patients met the TDM goal of 100% f T greater than 4 times MIC, and achieving this PK/PD goal was associated with a 2% increase in the odds of a positive clinical out- come (OR 1.02; 95% CI, 1.01–1.05). (Roberts, Paul et al. 2014) A recent study evaluated β-lactam concentrations in septic patients with augmented renal clearance and found 20% (16 of 79) of patients had suboptimal β-lactam concentrations (less than 4 times MIC). The suboptimal serum concentrations were associated with higher rates of therapeutic failure (16% [13 of 79]) and development of resistant organisms (15% [2 of 13]). (Carrie, Bentejac et al. 2018) Inadequate β-lactam concentrations in the early stages of sepsis have been associated with increased mortality in gram-negative bacterial infection. (Seyler, Cotton et al. 2011, Aitken, Altshuler et al. 2015, Carrie, Legeron et al. 2018) The Surviving Sepsis International Guideline recommends TDM-based optimization of all anti-infectives in sepsis, including β-lactam antibiotics, although this recommendation is not implemented in every health system. (Rhodes, Evans et al. 2017) (Wong, Brinkman et al. 2014)

Therapeutic drug monitoring of β-lactam antibiotics can range in intensity from first-dose sampling—similar to first- dose sampling for vancomycin using two measurements— to steady-state sampling (peak and trough) or using a single trough concentration. The target concentration will depend on the β-lactam selected as well as the MIC of the likely pathogen, if known. Available dosing protocols are limited in the literature; however, a reasonable approach for sampling tends to be a serum trough for

intermittent infusions or a steady-state random sample for continuous infusion dosing regimens. Calculations for PK will be similar to other anti-infectives, such as elimination constant, the lowest concentration, which is the trough or nadir before next dose, termed Ctrough, and Cmax, from which the T>MIC can be established. (Figure 1.6 and Figure 1.7) Adjusting the dosing interval is a strategy that has been suggested to achieve PD goals in patients who are not in the target range. (Roberts, Ulldemolins et al. 2010) More data are needed to guide best practices with TDM and dose optimization in this setting because toxicities, such as neurotoxicity, are also evident with higher concentrations of these agents.(Durand-Maugard, Lemaire-Hurtel et al. 2012, Quinton, Bodeau et al. 2017)

The use of a continuous infusion or prolonged infusion will optimize the f T>MIC variable. However, without increasing the total daily dose, the more aggressive PD target of f T > than 4 times MIC is difficult to achieve. (Carrie, Legeron et al. 2018) A study in 59 critically ill patients evaluated continuous infusion piperacillin/tazobactam on target attainment at varying MICs. Doses of 22.5 g/24 hours were required to achieve target attainment with high MICs and when the glomerular filtration rate was greater than 170 mL/minute. (Carrie, Legeron et al. 2018) Considering these factors, critically ill patients, who are more likely to benefit from aggressive β-lactam dosing, are also most likely to display altered PK/PD profiles. Dose optimization on the basis of TDM is a strategy to overcome challenges with variable dose responses in select populations.

Therapeutic drug monitoring is squarely within the pharmacist's domain in patient care. Use of TDM can optimize safety and efficacy for potentially toxic anti-infectives with a narrow therapeutic index, particularly in patients at risk of toxicity or therapeutic failure, such as those on concomitant nephrotoxins, critically ill and immunosuppressed patients,

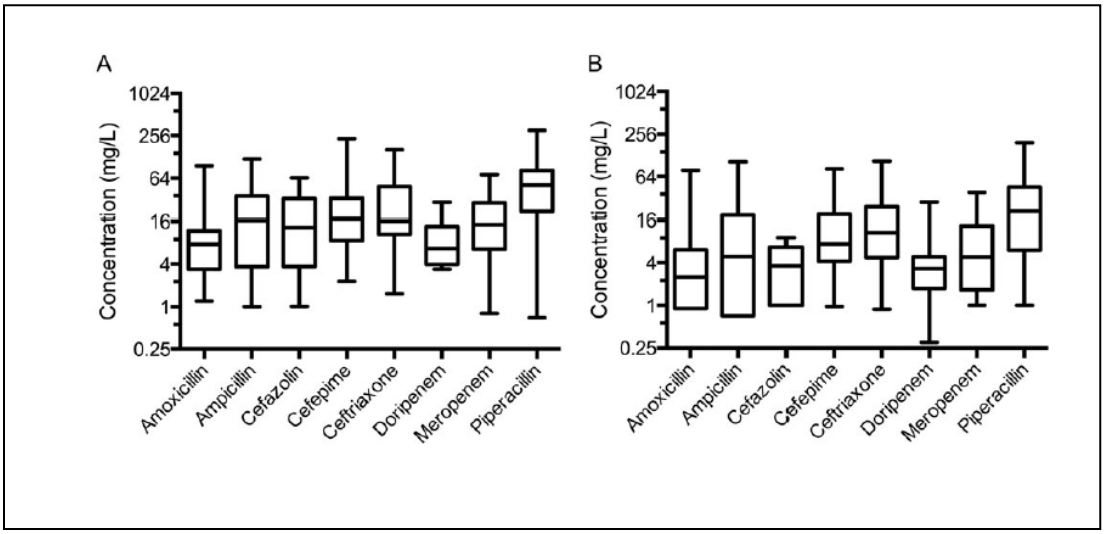
and patients requiring prolonged durations of therapy. The art and science of TDM requires practice with the PK equations and careful attention to the assumptions and pitfalls of the commonly used strategies for monitoring. Individualization of therapies beyond the classic anti-infectives (vancomycin and aminoglycosides) associated with TDM is broadening as assay availability becomes more prevalent and the under- standing of inter- and intra-patient variability grows. Pharmacists must be attentive to these developments and remain at the forefront of ensuring personalized, safe, and effective pharmacotherapy by using TDM when possible.

1.1.6 Evidence for Beta-lactam Therapeutic Drug Monitoring in Critically Ill Patients

The largest beta-lactam monitoring study to date is the DALI study "DALI: Defining Antibiotic Levels in Intensive Care Unit Patients: Are Current β-Lactam Antibiotic Doses Sufficient for Critically Ill Patients?", from an Australian group which leads the globe in beta-lactam research. (Roberts, Paul et al. 2014) This was a multi-national, multi-center prospective point prevalence study. Included patients were admitted to an enrolling ICU who received a target beta-lactam antibiotic (amoxicillin/clavulanate, ampicillin, cefazolin, ceftriaxone, doripenem, meropenem, and piperacillin/tazobactam. Patients consented into the study, and enrollment took place on Mondays throughout the study period. Each patient received 2 blood draws 1) mid-way though the dosing interval and 2) a trough prior to a dose. The unbound concentration of the beta-lactam, was measured for the highly protein-bound molecules: cefazolin and ceftriaxone, otherwise total concentrations were measured. The PK/PD targets and study outcomes for this study were 4-fold. 1) 50% f T>MIC 2) 50% f T>4×MIC 3) 100% f T>MIC and 4) 100% f T>4×MIC. The PK/PD goal was adjusted to the isolated bacteria/MIC for each patient. If the MIC was unknown, the standard EUCAS

breakpoint for Pseudomonas was used. The primary clinical outcome was a positive microbiologic outcome- defined as completion of the antibiotic course without need for re-escalation to a broader or different antibiotic within 48h of cessation. A total of 384 patients were enrolled into this study. The median (IQR) APACHE II score was 18 (13-24), and CrCl 80ml/min (42-125). The antibiotic concentrations were calculated at 50% and 100% of the dosing interval, and are represented by the boxplot and whisker graph in Figure 1.8.

Figure 1.8. Box and whisker plot of antibiotic concentrations at 50% (A) and 100%(B) of the dosing interval



There was an over 500-fold concentration difference in the concentrations seen at 50% and 100% of the dosing interval. The primary outcome, (100% fT >4x MIC) was met by 35% of patients. Achieving this PK/PD parameter was associated with a 2% increase in the odds of a positive clinical outcome (OR 1.02, [95% CI 1.01–1.05]). (Roberts, Paul et al. 2014)

Table 1.3. Multivariate Logistic regression models for a positive clinical outcome at 50%>MIC and 100%>MIC

	50% $fT_{>MIC}$			100% $fT_{>MIC}$		
Model Parameters	OR	95% CI	*P* Value	OR	95% CI	*P* Value
APACHE II score	0.94	.92–.96	<.001	0.94	.92–.96	.97
SOFA score	0.97	.94–1.00	.053	0.97	.94–1.01	.13
50% $fT_{>MIC}$	1.03	1.01–1.04	.001	. . .		
100% $fT_{>MIC}$	. . .			1.02	1.01–1.05	.040
AIC	1758.60					
BIC	1785.07					

Data are presented as estimates of odds ratios (95% CI) and *P* values. Abbreviations: AIC, Akaike information criteria; APACHE, Acute Physiology and Chronic Health Evaluation II; BIC, Bayesian information criteria; CI, confidence interval; $fT_{>MIC}$, time the free (unbound) antibiotic concentration was maintained above the minimum inhibitory concentration; OR, odds ratio; SOFA, Sequential Organ Failure Assessment.

Table 1.3 displays the result of the multivariate regression models built for a positive outcome at 50%*f*T>MIC and 100%*f*T>MIC. Hitting either target, while controlling for other variables in the model, was associated with an increased odd of a positive clinical outcome.

This study is the largest of its kind to demonstrate the relationship between achieving a PK/PD target and a positive clinical outcome in an ICU patient. Many limitations exist in this study, the lack of randomized design, the lack of intervention arm, and the broad inclusion criteria (including medical prophylaxis patients). This study builds the argument to embracing of TDM in the ICU.

Another large study of beta-lactam TDM was published recently by the same lead author. (Roberts, Joynt et al. 2020) The SMARRT study was a multi-national, multi-center study of patients requiring CRRT and beta-lactam therapy. Septic patients who require CRRT are among the sickest in the hospital, with mortality rates over 50%. (Bagshaw, Uchino et al. 2007) Volume overload is a commonly occurring complication, which has negative associations with mortality in septic CRRT patients. (Woodward, Lambert et al. 2019) Volume overload, along with variations in CRRT prescribing and delivery are

associated with variable antibiotic concentrations, and difficult to predict pharmacokinetic response. (Seyler, Cotton et al. 2011) Patients from 29 centers had beta-lactam trough concentrations drawn while on CRRT. The estimated GFR was calculated from the CRRT prescription, and intrinsic clearance from urine creatinine collection tests. Clinical improvement was determines by the treating physician, and MIC breakpoints were determined from EUCAST published breakpoints. (EUCAST) Two PK/PD goals were determined: 100%T>MIC, and 100%4x>MIC. Toxic concentrations were prespecified as: piperacillin >150mg/L and meropenem >50mg/L.

The most common CRRT modality was CVVHDF (14.7%), followed by CVVHD (36.8%), PIRRT (27.4%) and then CVVH (14.7%). The estimated GFR from the CRRT and measured clearance was 50ml/min (range 35- 66). For the meropenem patients (187), a trough concentration <1xMIC was associated with a 2.55-fold increase in mortality (HR 2.55, 95% CI: 1.33-4.90). Of the 160 patients who received piperacillin trough concentrations, were not associated with mortality. Table 1.4 shows the result of the Cox survival analysis, of antibiotic concentration, type and mortality. (Roberts, Joynt et al. 2020)

Table 1.4 Association of trough concentrations with adjusted and unadjusted 28-d mortality

Antibiotic	Mortality (n, %)	HR (95% CI)	P value	Adjusted HR (95% CI)*	P value
Meropenem (n=187)					
2-8 mg/L	14 (34.1)	1.00		1.00	
<2 mg/L	4 (57.1)	2.02 (1.10-3.72)	0.011	2.55 (1.33-4.90)	0.012
>8 mg/L	71 (51.1)	1.55 (1.05-2.29)		1.39 (0.89-2.15)	
Piperacillin (n=160)					
16-64 mg/L	25 (49.0)	1.00		1.00	
<16 mg/L	3 (50.0)	1.06 (0.38-2.99)	0.605	1.41 (0.77-2.58)**	0.317
>64 mg/L	62 (60.2)	1.26 (0.80-2.00)		1.19 (0.92-1.53)**	
β-lactam (n=347)					
Meropenem or Piperacillin 1xMIC-4xMIC	39 (42.4)	1.00		1.00	
Meropenem or Piperacillin <1xMIC	7 (53.8)	1.41 (0.73-2.76)	0.212	1.54 (1.03-2.30)**	0.053
Meropenem or Piperacillin >4xMIC	133 (55.0)	1.33 (0.95-1.87)		1.23 (0.99-1.51)**	
Tazobactam (n=101)					
≤5 mg/L	12 (63.2)	1.00		1.00	
>5 mg/L	40 (48.8)	0.66 (0.39-1.13)	0.127	0.74 (0.58-0.94)**	0.014
Vancomycin (n=60)					
≤15 mg/L	20 (60.6)	1.00		1.00	
>15 mg/L	9 (33.3)	0.44 (0.14-1.43)	0.175	0.45 (0.14-1.51)	0.197

*adjusted for centre-effects, age, APACHE II score and total modified SOFA score at sampling

**values are relative risk (RR) and 95% confidence intervals from generalized estimating equation models as the proportional hazards assumption was not met in cox regression model

A prospective trial of TDM dosage adjustments of beta-lactam antibiotics was done in febrile neutropenic patients receiving piperacillin/tazobactam. (Sime, Roberts et al. 2015) 32 patients were enrolled in this trial, and were randomized to traditional dosing, or TDM dosage optimization for a 100%T>MIC PK/PD goal. Febrile neutropenia was defined as an oral temperature ≥38.38C (101.8F), or ≥38.08C (100.48F) for <1 hour, in the presence of a neutrophil count <500 cells/mm3. Patients were sampled at steady state (3rd or 4th dose), and then again immediately after any TDM changed were made. Unbound piperacillin concentrations were calculated from the total concentration measured, assuming a 30% protein binding. MIC specific targets were calculated, and when unavailable, EUCAST breakpoints were used. Dosing adjustments were done by decreasing the dosing interval by 25%-50% at the same dose. If the concentration exceeded 100%T>10xMIC, a dosage adjustment downward was done. The patients enrolled into this study were mostly male, median age 60 (52-64), and commonly had ARC 10 (30%). The primary outcome was reached in 25% of control patients, and 10% intervention patients at

first TDM, p=1. At the second TDM, this increased to 19% in control, and 69% of intervention patients, p=0.012. At the third sampling, the intervention patients continued to meet the primary outcome goal 70% vs. 7% control, p=0.004. Limitations of this study were the long return time on beta-lactam levels (12h), and a relatively low starting dose of piperacillin (4.5g every 8h over 30 minutes). Even with TDM based dosage optimization, almost 30% of patients still did not meet the primary PK/PD goal. However, this is the first randomized trial to demonstrate TDM based dosage adjustments can increase target attainment in critically ill patients. Validation on a larger scale, which includes evaluation of patient outcomes is warranted.

1.1.7 Analytic Methods

There are no FDA approved tests for beta-lactam measurements. The available methods of measuring beta-lactam concentrations in human fluids are limited to lab-developed tests, of which the availability, analytic method and reporting range greatly among centers. (Carlier, Stove et al. 2015) An international survey conducted in 2013 sought to determine how many centers perform beta-lactam measurements, and use them to improve patient care. Nine ICU centers were included in the survey result. TDM services were managed by physicians and pharmacists alike, and were available for approximately 5 days each week. Only 1 center from the United States responded to survey, the majority of centers performing these measurements are in Europe and Australia. Piperacillin-tazobactam and meropenem were the most commonly monitored drugs (100%) of units surveyed.

The analytic methods utilized by respondents included: bioactivity assay, HPLC/UV, HPLC, UPLC-MS/MS, and LC-MS/MS. For the LC-MS/MS method, the accuracy reported was 86.8%-101.5%; precision: CV was <14.6% and the accuracy reported was 86.4%-112.3%. All labs reported to meet the regulatory requirements for precision and accuracy. Most protocols had the measurement available within the same day, and the patients were sampled at steady-state (day 2-3 of therapy), and contained a dose adjusting algorithm for sub-therapeutic and supra-therapeutic concentrations.

Chromatography techniques such as LC-MS/MS are associated with high equipment cost, and require highly trained personnel, thus possibly limiting the cost-effectiveness of this method. The bioactivity assay, is another method which is faster and easier to set up, yet is associated with less accuracy in the presence of concomitant antibiotics. (Carlier, Stove et al. 2015)

A 2015 review of the literature by Carlier et al identified 15 studies of published methods of beta-lactam measurement in the literature. (Carlier, Stove et al. 2015) Of the 15 methods that used chromatographic assays: 14 used reverse phase separation, either coupled to UV light (9/15), or mass spectrometry (6/15). Meropenem was the most commonly measured agent (14/15), followed by piperacillin (11/15). The calibration range varied among methods. For piperacillin, the upper limit of quantification ranged from 5 mg/L to ≥100 mg/L, and six of the methods were <100mg/L. For cefepime the limit of quantification ranged 50-250 mg/L, and meropenem 9-200mg/L. For a drug like piperacillin, the ideal limit of quantification is above 100mg/L, as large doses of 12-16 grams are commonly given to ICU patients. If the limit of quantification is below the measured concentration, a dilution must be performed for quantification, which will delay the result reaching the bedside providers. The lower limit of quantification of an assay is

ideally below the MIC of the organism. Of these published reports, the lower limit of quantification varied: cefepime 0.01mg/L – 2; meropenem 0.04mg/L – 2mg/L; and piperacillin 0.005mg/L – 10mg/L. Ohmori and colleagues presented their development of a beta-lactam method using LC-tandem MS. (Ohmori, Suzuki et al. 2011)

1.1.8 Dissertation Hypothesis and Specific Aims

Dissertation hypothesis: A major class of antibiotics used in the treatment of severe infections which causes sepsis and septic shock are the beta-lactams antibiotics. The underlying pathophysiology and treatments for patients with sepsis induce inter-patient variability in the pharmacokinetic profile of beta-lactam antibiotics, which alters the ability to achieve the goal PK/PD target attainment for severe infections. Therapeutic drug monitoring is a strategy to overcome the variability of the current dosing approach by personalizing doses according to patient parameters. There are no currently FDA approved tests to measure beta-lactam antibiotic concentrations for therapeutic drug monitoring. Our hypothesis is that therapeutic drug monitoring for beta lactam antibiotics will overcome the pharmacokinetic variation in patients with severe sepsis, in order to achieve the optimal PK/PD target for severe infections.

Aim 1: To determine the impact of routine currently recommended renal dosage adjustments in patients with septic shock due to gram negative bacteremia on patient outcomes

Aim 1 Hypothesis: The currently recommended renal function guided dosage regimens of beta-lactam antibiotics in septic shock patients with acute kidney injury is associated with fewer vasopressor-free days alive in the ICU, when compared to those who receive unadjusted beta-lactam regimens

Aim 2: To examine the relationship of beta-lactam PK/PD target attainment achievement, as measured by therapeutic drug monitoring, with clinical outcomes in patients admitted to the ICU for sepsis

Aim 2 Hypothesis: Achieving the beta-lactam PK/PD target attainment (100%T>4xMIC) is associated with improved clinical outcomes in ICU patients with sepsis as compared to those who fail to achieve the PK/PD target

Aim 3: To develop a Laboratory Developed Test using LC-MS to measure beta-lactam concentrations in hospitalized patients

Aim 3 Hypothesis: A Laboratory Developed Test utilizing LC-MS technology will improve beta-lactam concentration accuracy over available detection methods, and facilitate personalized dosing of beta-lactam antibiotics for hospitalized patients with sepsis

CHAPTER 2. AIM 1: TO DETERMINE THE IMPACT OF ROUTINE CURRENTLY RECOMMENDED RENAL DOSAGE ADJUSTMENTS IN PATIENTS WITH SEPTIC SHOCK DUE TO GRAM NEGATIVE BACTEREMIA ON PATIENT OUTCOMES

2.1.1 Aim 1 Significance, Rationale and Hypothesis

Sepsis is a highly deadly and prevalent disease, resulting in 750,000 annual cases, with a mortality rate of 30%. (Rhodes, Evans et al. 2017) Timely administration of the correct antibiotic, and in the correct dose can improve outcomes for critically ill patient with sepsis. (Kumar, Roberts et al. 2006) (Liu, Fielding-Singh et al. 2017) Not only drug selection, but the appropriate dose needs consideration when treating patients with sepsis. Sepsis induces a dramatic change in the expected pharmacokinetic profile of beta-lactam antibiotics. (Goncalves-Pereira and Povoa 2011) Especially important, are the effects of acute kidney in sepsis on the ability to achieve therapeutic drug concentrations. In one study of AKI septic patients, the measured volume of distribution (Vd) was 2-fold larger for daptomycin (0.08L/kg increased to 0.23L/kg). (Khadzhynov, Slowinski et al. 2011) The PK changes in sepsis are especially challenging for beta-lactam antibiotics, and has been linked to poor patient outcomes. (Taccone, Laterre et al. 2010) Dosage adjustments are recommended for patients with reduced GFR. (package inserts) However, it is prudent to understand where these recommendations come from, and the limitation of the current regulatory approval process. (Crass, Rodvold et al. 2019) Poor microbiological outcomes have been linked to adherence to renal dosage adjustments in recent observations. (Kullar, Wagenlehner et al. 2017)

Aim 1: To determine the impact of routine currently recommended renal dosage adjustments in patients with septic shock due to gram negative bacteremia on patient outcomes

Aim 1 Hypothesis: The currently recommended renal function guided dosage regimens of beta-lactam antibiotics in septic shock patients with acute kidney injury is associated with

fewer vasopressor-free days alive in the ICU, when compared to those who receive unadjusted beta-lactam regimens.

2.1.2 Aim 1 Methods Impact of Dose Adjusted Beta-lactam Antibiotics in the First 48h of Sepsis Treatment: A Retrospective Multicenter Cohort Study

Design and Setting

To test the above hypothesis, we undertook a retrospective, observational, cohort study of critically ill adult patients admitted to an intensive care unit at a study site who received a broad-spectrum beta-lactam (cefepime, piperacillin/tazobactam, or meropenem) for at least 48 hours from 1/1/2013 to 4/30/2019.

Study Population

Inclusion criteria was age 18 years ≤, admission to the ICU for at least 48h, receipt of at least 48h of the same beta-lactam antibiotic, presence septic shock, defined according to Sepsis-3 definition (corroborated with the receipt of a vasoactive agent), positive blood culture with a gram negative organism, acute kidney injury at time of beta-lactam administration, AKI was defined according to the serum creatinine and urine output KDIGO criteria: (≥0.3mg/dL increase in serum creatinine or a total increase in ≥1.5mg/dl x baseline, or a decrease in urine output <0.5ml/kg/hour for 6 hours. Exclusion criteria included receipt of a continuous infusion beta-lactam, receipt of >1 beta lactam (meropenem, cefepime, piperacillin-tazobactam), receipt of an excluded beta-lactam within 48 hours (zebaxa, vabomere, avycaz), CRRT initiation within 48h of beta-lactam receipt, ECMO, transfer

from outside facility, non-susceptible cultured microorganism, concomitant gram-positive infection.

Definitions and Outcomes

The Cockcroft and Gault equation was used to estimate glomerular filtration rate (GFR) from serum creatinine. (Cockcroft and Gault 1976) Patients were grouped according to the dosing classification of the first 48 hours of therapy into 1) Adjusted or 2) Unadjusted. (Table 2.1). The primary study outcome was shock free survival up to 28d. Secondary outcomes included all-cause mortality at 28d, ventilator-free days at 28d, ICU length of stay and hospital length of stay. Shock free survival and ventilator free days were calculated as previously defined. (Yehya, Harhay et al. 2019) Several prior sub-group analyses of the primary outcome were planned: beta-lactam type, source of bacteremia, and infecting organism, and severity of AKI (GFR <50ml/min).

Table 2.1 Grouping scheme according to dosing classification of the first 48 hours of therapy

Beta-lactam	**Severe AKI** **CEF GFR 11-29 ml/min** **PTZ GFR 10-19 ml/min** **MEM GFR 10-25 ml/min**	**Mild AKI** **CEF GFR 30-60 ml/min** **PTZ GFR 20-40 ml/min** **MEM GFR 26-50 ml/min**
Cefepime (CEF)	Unadjusted ≥ 4 g EI or II Adjusted < 4g EI or II	Unadjusted ≥8 g Adjusted < 8 g
Piperacillin-tazobactam **(PTZ)**	Unadjusted ≥ 18g EI or II Adjusted <18g EI or II	Unadjusted ≥ 20.25g EI or 27g II Adjusted < 20.25g EI or 27g II
Meropenem **(MEM)**	Unadjusted ≥ 4 g EI or II Adjusted amount < 4g EI or II	Unadjusted ≥6 g Adjusted < 6 g

Statistical Analysis

Continuous variables were tested for distribution by histogram visualization and with the Shapiro-Wilk test. Continuous variables with normal distribution are presented as mean (SD); otherwise are presented as median (IQR). Continuous variables were analyzed using either the Student's T-test or the Wilcoxon Rank-sum test as appropriate. Categorical

variables are presented as frequencies and proportions and analyzed using the Pearson's Chi-square or Fisher's Exact test as appropriate.

Multivariable logistic regression was used to assess the effects of independent variables on the primary outcome, shock free survival, and secondary outcome mortality. All variables displaying a difference in the bivariate analysis (<0.2) were included for consideration into the final multivariable model, along with standard demographic/critical illness parameters, and variables identified a priori, or known to impact the outcome (e.g., timing of beta-lactam initiation, KDIGO stage, bacteria type).

The models were tested for assumptions of logistic regression as appropriate. Multicollinearity was tested using variance inflation factor (<2.5); normality of errors was assessed with the IQR test and visualization with the kernel density estimate. Constant variance by assessment with the Breusch-Pagan /Cook-Weisberg test for heteroskedasticity, and was adjusted using robust standard errors if appropriate. Model fit was assessed with the Hosmer-Lemeshow goodness of fit test. All other assumptions were met. Statistical analyses were done using Stata (version 14.2, Stata Corp, College Station, Texas, USA)

2.1.3 Aim 1 Results

Clinical Characteristics

A total of 179 patients were included in the final analysis (103 in the adjusted group, 76 in the unadjusted group). The subjects were evenly split with regards to gender (male) 49 (48%) vs. 41 (54%), p= 0.399, unadjusted vs adjusted respectively. The median age in years was 65 (50-74) unadjusted vs. 64 (58-74) adjusted, p= 0.245. The majority of patients

were admitted to a medical ICU >70% both groups, p=NS. Admission SOFA was 9 (5-11) in the unadjusted vs. 8 (5-10.5) in the adjusted group, p=0.864. KDIGO stage 1 AKI was the most common stage of AKI in both groups >50% both groups, however the serum creatinine at beta-lactam initiation was higher in the adjusted group 1.94 (1.29- 3.15) vs. 1.48 (1.08- 2.02) unadjusted, p <0.006. The most common source of infection was intra-abdominal 34% total cohort, followed by urinary 30% total cohort, followed by pulmonary (12% total cohort), p=0.474. The most commonly isolated bacterium was E.coli (44%), followed by K. pneumoniae (24%), and then P. aeruginosa (23%). Patients in the unadjusted group were more likely to have the beta-lactam antibiotic given within 1 hour of cultures drawn 52% vs. 45%, p=0.309. Baseline demographics are found in Table 2.2, baseline disease severity characteristics are found in Table 2.3, treatment characteristics are found in Table 2.4, Beta-lactam doses and infusion strategies are found in Table 2.5, and in Table 2.6, additional treatment characteristics.

Table 2.2 Baseline Characteristics

Characteristic	Total (n=179)	Unadjusted (n=103)	Adjusted (n=76)	p-value
Age (y), mean ± SD	64.5 (53-74)	65 (50-74)	64 (58-74)	0.245
Sex (m), n (%)	90 (50%)	49 (48%)	41 (54%)	0.399
Weight (kg), mean ± SD	78 (61.3- 92)	78.9 (62- 94)	74.65 (59.55-91.3)	0.511
BMI (kg/m2), mean ± SD	26.6 (21.8- 31.1)	26.45 (22.6- 30.9)	26.97 (20.88-31.81)	0.848
Admission ICU, n (%)				
Medical/respiratory	129 (72%)	76 (74%)	53 (70%)	0.521
Surgical (non-trauma)	31 (17%)	14 (14%)	17 (22%)	
Trauma	8 (4%)	6 (6%)	2 (3%)	
Cardiac/surg	3 (2%)	2 (2%)	1 (2%)	
Cardiac (non-surgery)	8 (4%)	5 (5%)	3 (4%)	
Admissions source				
ED	116 (74%)	70 (68%)	46 (61%)	0.518
Floor/PCU	40 (22%)	20 (19%)	20 (26%)	
Other	23 (13%)	13 (13%)	10 (13%)	
Past medical history, n (%)				
CHF	33 (18%)	16 (16%)	17 (22%)	0.244
CKD without dialysis	28 (16%)	13 (13%)	15 (20%)	0.195
HTN	99 (55%)	52 (51%)	47 (625)	0.131
Liver disease	27 (15%)	14 (14%)	13 (17%)	0.516
COPD	18 (10%)	7 (7%)	11 (15%)	0.091
Immunosuppressed (ANC 500 at admission)	27 (16%)	16 (16%)	11 (15%)	0.766
Neurological disorder (seizures, dementia, prior stroke)	29 (17%)	18 (18%)	11 (14%)	0.590
SOT	5 (3%)	2(2%)	3 (4%)	0.421
Malignancy (active)	74 (41%)	43 (42%)	31 (41%)	0.898
DM	51 (29%)	26 (25%)	25 (33%)	0.262
Other chronic lung condition	18 (10%)	11 (11%)	7 (9%)	0.747

Table 2.3 Disease severity characteristics

Disease severity	Total (n=179)	Unadjusted (n=103)	Adjusted (n=76)	p-value
Albumin at beta-lactam initiation (mg/dL), mean ± SD	2.33 (0.69)	2.40 (0.73)	2.23 (0.63)	0.114
Peak lactate median (IQR)	3.8 (2.25- 6.1)	3.85 (2.4- 6.1)	3.7 (1.8- 6.1)	0.381
SOFA score at ICU admission	8 (5-11)	9 (5-11)	8 (5-10.5)	0.864
Mechanical ventilation within 24 hours of beta-lactam initiation, n (%)	80 (46%)	39 (40%)	41 (54%)	0.072
AKI stage at initiation, n (%) **Stage 1** **Stage 2** **Stage 3**	102 (57%) 42 (23%) 35 (20%)	62 (60%) 27 (26%) 14 (14%)	40 (53%) 15 (20%) 21 (28%)	0.060
Baseline Scr	0.88 (0.65- 1.08)	0.82 (0.6- 1.03)	0.9 (0.75- 1.28)	0.0661
SCr at beta-lactam initiation, median (IQR)	1.62 (1.23- 2.56)	1.48 (1.08- 2.02)	1.94 (1.29- 3.15)	0.0060
Scr 24h	1.67 (1.14- 2.55)	1.54 (1.07- 2)	2.10 (1.42- 2.99)	0.0001
Scr 48h	1.42 (0.94- 2.49)	1.2 (0.9- 2.13)	1.96 (1.12- 2.84)	0.0022
CG CrCl at beta-lactam initiation, mean ± SD	46 (27-66)	50 (33- 67)	37 (22-58)	0.0076
CrCl at 24 h, mean ± SD	46 (28-65)	51 (32-71)	36 (24- 56)	0.0004
CrCl at 48 h, mean ± SD	50 (29- 79)	57 (36- 90)	41 (25- 69)	0.0030
Renal recovery within 48h n(%)	77 (43%)	47 (46%)	30 (40%)	0.411

Table 2.4 Treatment Characteristic

Treatment Characteristic	Total (n=179)	Unadjusted (n=103)	Adjusted (n=76)	p-value
Source of infection				
Pulmonary	20 (12%)	13 (12%)	7 (10%)	0.474
Intra-abdominal	57 (34%)	34 (35%)	23 (33%)	
Renal/GU	50 (30%)	24 (34%)	26 (27%)	
SSTI	10 (6%)	8 (8%)	2 (3%)	
CNS	1 (1%)	0 (0%)	1 (1%)	
Bone/joint	1 (1%)	1 (1%)	0 (0%)	
Unknown	30 (18%)	16 (16%)	14 (20%)	
Gram negative organism, n (%)				
E. coli	78 (44%)	41 (40%)	37 (49%)	0.852
K. pneumoniae	43 (24%)	28 (27%)	15 (20%)	
K. oxytoca	2 (2%)	1 (1%)	1 (1%)	
E. cloacae	9 (5%)	6 (6%)	3 (4%)	
P. aeruginosa	23 (23%)	13 (13%)	10 (13%)	
A. baumanii	1 (1%)	0 (0%)	1 (1%)	
B. cepacia	1 (1%)	1 (1%)	0(0%)	
C. spp	4 (2%)	3 (3%)	1 (1%)	
Proteus spp.	7 (4%)	4 (4%)	3 (4%)	
Other	11 (6%)	6 (6%)	6 (7%)	
Organism (2) n(%) (Total 17)	17 (9%)	12 (11%)	5 (7%)	0.082
Piperacillin MIC	8 (4-16)	8 (4-16)	8 (4-16)	0.069
Cefepime MIC	2 (1-2)	2 (1-2)	2 (1-2)	0.083
Meropenem MIC	1 (0.25-1)	1 (0.25- 1)	1 (0.25-1)	0.851
Location of patient at first dose **ICU** **ED** **Floor**	 72 (41%) 87 (50%) 15 (9%)	 43 (43%) 51 (51%) 6 (6%)	 29 (39%) 26 (49%) 9 (12%)	0.355
Beta-lactam given within 1 hour of cultures	88 (49%)	54 (52%)	34 (45%)	0.309
Median time from cultures drawn to BL given	1.16 (0.08- 7.8)	0.8 (0.067-6.35)	1.85 (0.91-14.33)	0.319
Beta-lactam received **Cefepime** **Meropenem** **Piperacillin/tazobactam**	 53 (30%) 42 (23%) 84 (47%)	 33 (32%) 14 (14%) 56 (54%)	 20 (26%) 28 (37%) 28 (37%)	0.001

Table 2.5 Beta-lactam doses and infusion strategy

Dose/strategy	Total (n= 179)	Unadjusted (n=103)	Adjusted (n=76)	p-value
Piperacillin/tazobactam				
Initial Piperacillin/tazobactam dose	3.64 (0.75)	3.61 (0.73)	3.69 (0.80)	0.648
EI strategy, n (%)	47/84 (56%)	31/56 (55%)	16/28 (57%)	0.876
Amount in first 24 h (g), mean ± SD	12.38 (4.06)	12.48 (3.89)	10.21 (3.54)	<0.001
Amount in first 48 h (g), mean ± SD	11.75 (3.9)	12.37(3.74)	10.47 (4.2)	0.039
Total amount in first 48h (g), mean ± SD	24 (7.39)	25.85 (6.54)	20.29 (7.71)	<0.001
Cefepime				
EI strategy, n (%)	13/ 53 (25%)	2/33 (6%)	11/20 (55%)	<0.001
Initial cefepime dose	1.59 (0.49)	1.75 (0.44)	1.35 (0.49)	0.0036
Amount in first 24 h (g), mean ± SD	3.85 (1.96)	4.87 (1.67)	2.15 (0.98)	<0.001
Amount in first 48 h (g), mean ± SD	3.64 (1.73)	4.57 (1.43)	2.1 (0.85)	<0.001
Total amount in first 48h (g), mean ± SD	7.49 (3.4)	9.45 (2.67)	4.25 (1.74)	<0.001
Meropenem				
Initial meropenem dose	0.88 (0.34)	1 (0.33)	0.82 (0.33)	0.116
EI strategy, n (%)	3/41 (7%)	1/14 (7%)	2/27 (7%)	0.975
Amount in first 24 h (g), mean ± SD	2.3 (0.97)	3.07 (0.97)	1.98 (0.75)	<0.001
Amount in first 48 h (g), mean ± SD	2.15 (0.91)	2.9 (1.0)	1.78(0.55)	<0.001
Total amount in first 48h (g), mean ± SD	4.5 (1.78)	5.96 (1.98)	3.77 (1.13)	<0.001

Table 2.6 Additional Treatment Characteristics

Characteristic	Total (179)	Unadjusted (n=103)	Adjusted (n=76)	p-value
Receipt of additional antibiotic with significant activity against MDR-GN within 48 h of beta-lactam initiation, n (%)	90 (51%)	49 (49%)	41 (54%)	0.474
Aminoglycoside, n (%)	45 (25%)	28 (27%)	17 (22%)	0.463
Fluoroquinolone, n (%)	25 (14%)	10 (10%)	15 (20%)	0.056
Number of IV vasopressor(s) received during initial episode of shock (n), median (IQR)	1 (1-2)	1 (1-2)	1 (1-2)	0.728
Vasopressor(s) received during shock, n (%)				
Norepinephrine	174 (97%)	100 (97%)	74 (97%)	0.910
Epinephrine	15 (8%)	6 (6%)	9 (12%)	0.151
Vasopressin	46 (26%)	28 (27%)	18 (24%)	0.596
Phenylephrine	14 (8%)	8 (8%)	6 (8%)	0.975
Dopamine	3 (2%)	2 (2%)	1(1%)	0.747
Norepinephrine equivalents at beta-lactam initiation (NEQ mcg/kg/min), median (IQR)	9.14 (5-20.79)	10.5 (4.9-16.38)	8.9 (5-24.1)	0.339
Maximum NEQ (for at least 1 h) in first 48 h after beta-lactam initiation (NEQ mcg/kg/min), median (IQR)	18 (7-33.4)	17.64 (6-30.93)	18.5 (7.91-35.83)	0.271
Change in pressor dose initial to max	7.8 (0.2- 20)	9 (1.26- 23.92)	7.25 (0-17.77)	0.342
Hydrocortisone ≤300 mg/d, n (%)	53 (31%)	27 (27%)	26 (36%)	0.225
IV thiamine ≥400 mg/d, n (%)	14 (8%)	7 (7%)	7 (9%)	0.547
Net fluid balance in first 24 h after beta-lactam initiation (mL), median (IQR)	2670 (1175-4621)	2802 (1249-4668)	2190 (933-4452)	0.465
Net fluid balance in second 24 h after beta-lactam initiation (mL), median (IQR)	1080 (184-2680)	993 (85- 2760)	1274 (189-2680)	0.951

Primary Outcomes

The primary outcome of shock-free survival at 28d was not different between the two groups: 25.56 days (0-27.16) unadjusted, vs. 25.32 days (0-27.04) adjusted, p=0.799. By 28 days 38 patients (37%) in the unadjusted group died, and 26 patients (34%) in the adjusted group died, p=0.77. VFD-28 was not different between groups, 26.74 days (0-28) vs. 26.45 days (0-28), unadjusted vs. adjusted accordingly. ICU and hospital length of stay were not different between groups, Table 2.7.

Table 2.7. Primary study outcomes

Outcome	Total (n=179)	Unadjusted (n=103)	Adjusted (n=76)	OR	95% CI	p-value
Duration of shock-free survival in the first 28 days (d), mean ± SD	25.54 (0-27.06)	25.56 (0-27.16)	25.32 (0-27.04)	0.452	-3.04-3.95	0.799
Duration of MV-free survival in the first 28 days (d), mean ± SD	26.48 (0-28)	26. 74 (0-28)	26.45 (0-28)	0.02	-3.67-3.7	0.648
Duration of MV-free survival in the first 90 days (d), mean ± SD	87.02 (0-90)	86.11 (0-90)	87.09 (0-90)	2.92	-9.55-15.40	0.644
ICU mortality, n (%)	48 (27%)	26 (25%)	22 (29%)	1.21	0.62-2.35	0.580
28-day mortality, n (%)	65 (36%	38 (37%)	26 (34%)	0.88	0.48-1.65	0.77
ICU LOS (d)	5.83(2.92-11.99)	5.92 (3.04-12.83)	5.5 (2.75-10.74)	2.66	-29.24-34.58	0.457
Hospital LOS (d)	12.81 (6.95-23.92)	12.83 (7.16-24.98)	11.95 (6.31-22.06)	23.81	-4.88-52.52	0.768
Shock resolved during ICU stay	150 (84%)	85 (82%)	65 (87%)	1.37	0.59-3.18	0.454
CRRT, n (%)	13 (7%)	9 (9%)	4 (5%)	0.56	0.164-1.878	0.344
Dialysis dependent at discharge n (%)	9 (6%)	4 (4%)	5 (7%)	1.76	0.456-6.837	0.405
Return of renal function to baseline, n (%)	114 (67%)	66 (67%)	48 (67%)	0.969	0.507-1.851	0.926
CDI, n (%)	8 (4%)	5 (5%)	3 (4%)	0.805	0.186-3.479	0.772

Multivariate regression modeling

The results of the multivariate linear regression for pressor free days at 28d is found in Table 2.8. Controlling for all variables in the model, three variables emerged as statistically significant predictors of pressor-free days at 28d: lactate, KDIGO stage 2 AKI, and maximum vasopressor dose. For every 1-unit increase in lactate, the number of pressor free days decreased by 0.97 (β -0.97, [95% CI -1.67, -0.27], p=0.007). KDIGO Stage 2 AKI was associated with 7.77 fewer pressor-free days, as compared to KDIGO Stage 1, (β -7.77, [95% CI 13.15, -2.40], p= 0.005). For every mcg/kg/min unit increase in maximum vasopressor dose, the number of vasopressor-free survival days decreased by 0.07 (β -0.07, [95% CI -0.13, -0.01], p=0.033).

The multivariate logistic regression for mortality is shown in Table 2.9. Peak lactate, Stage 2 AKI, and immunosuppressed on admission were all associated with increased mortality. Every 1-unit increase in peak lactate, was associated with an 18% increase in mortality (OR 1.18, [95% CI 1.00, 1.38], p= 0.047). KDIGO Stage 2 AKI was associated with a 456% increase in mortality, when compared to those with KDIGO stage 1 AKI (OR 4.56, [95% CI 1.33, 15.69], p=0.016). Those who were immunosuppressed on admission (ANC <500) had a 4.47 -fold increase in mortality, as compared to those with an ANC >500, (OR 4.47, [95% CI 1.13, 17.65], p=0.032).

Table 2.8. Multivariate linear model for pressor free days at 28d.

Variable	β Coef	P>|t|	95% Confidence Interval
Adjusted BL dose	-2.11	0.356	-6.62, 2.41
Age	0.03	0.334	-2.23, 6.52
Male gender	2.14	0.334	-2.24, 6.52
Lowest serum albumin	1.96	0.289	-1.69, 5.62
Peak serum lactate	-0.97	0.007	-1.67, -0.27
SOFA score	-0.16	0.643	-0.86, 0.53
KDIGO Stage[a]			
Stage2	-7.77	0.005	13.15, -2.40
Stage 3	1.03	0.727	-4.78, 6.83
Immunosuppressed at admission (ANC <500)	-2.28	0.455	-8.32, 3.76,
Beta-lactam Giving within 1hour of cultures	-2.15	0.347	-6.66, 2.36
Bacteria Isolated[b]			
K. pneumoniae	-0.34	0.902	-5.74, 5.06
E. cloacae	-3.76	0.498	-14.77, 7.24
P. aeruginosa	-6.26	0.052	-12.58, 0.06
B. cepacia	11.47	0.335	-12.05, 34.99
C. spp	9.13	0.265	-7.04, 25.30
Proteus spp.	-4.24	0.613	-20.84, 12.34
Other	-7.72	0.096	-16.84, 1.40
Extended Infusion	3.08	0.257	-2.28, 8.44
Double coverage of non- BL	-0.75	0.772	-5.87, 4.37
Maximum pressor dose in NE equivalents	-0.07	0.033	-0.13, -0.01
24h fluid balance	0.00	0.246	-0.00, -.001

[a] Referent category KDIGO stage 1
[b] Referent Category E. coli
Model Adj R^2= 0.21 p=0.002 Obs 114

Table 2.9. Multivariate logistic model for mortality

Variable	Odds Ratio	P>|t|	95% Confidence Interval
Adjusted BL dose	1.10	0.839	0.41, 2.99
Age	1.00	0.809	0.97, 1.03
Male gender	0.42	0.092	0.15, 1.15
Lowest serum albumin	0.84	0.665	0.38, 1.85
Peak serum lactate	1.18	0.047	1.00, 1.38
SOFA score	9.89	0.131	0.75, 1.04
KDIGO Stage[a]			
Stage2	4.56	0.016	1.33, 15.69
Stage 3	1.38	0.613	0.38, 4.96
Immunosuppressed at admission (ANC <500)	4.47	0.032	1.13, 17.65
Beta-lactam administered within 1 hour of cultures	1.32	0.589	0.47, 3.72
Bacteria Isolated[b]			
K. pneumoniae	0.70	0.575	0.21, 2.35
E. cloacae	0.44	0.553	0.03, 6.36
P. aeruginosa	3.66	0.055	0.97, 13.80
Proteus spp.	0.95	0.979	0.04, 22.85
Other	3.63	0.172	0.57. 23.20
Extended Infusion	0.46	0.223	0.13, 1.59
Double coverage of non- BL	1.07	0.901	0.34, 3.39
Maximum pressor dose in NE equivalents	1.02	0.060	0.99, 1.04
24h fluid balance	0.99	0.948	0.99, 1.00

[a] Referent category KDIGO stage 1
[b] Referent Category E. coli
Model R2= 0.21 p=0.031 Obs 111

Secondary outcomes

Several prior sub-group analyses of the primary outcome were planned, including beta-lactam type, infection with *Pseudomonas* spp, and categorizing GCR <50ml/min. There

were no differences seen in any of the three primary outcomes, with regards with any sub-group. (Table 2.10) Patients with a CrCl <50ml/min at the time of beta-lactam initiation were analyzed in multivariate regression. Controlling for other variables in the model, including sofa score, bacteria isolated, immune status, those with a dose adjusted beta-lactam had 6 fewer days alive and free from vasopressors than those without dosage adjustment in the first 48h, (β -5.94, [95% CI -11.07, -0.81], p=0.042). The full multivariate model is found in Table 2.11.

Table 2.10 Sub-group analysis of primary and secondary outcomes

Sub-group (n)	Outcome Median (IQR)	Unadjusted	Adjusted	P-value
GFR <50ml/min (100)	Shock-free survival at 28h	25.6 (20.95- 27.16)	26.01 (0-27.38)	0.775
	VFD-28	26.39 (13.25-28)	26.42 (0-28)	0.380
	Mortality	17/51 (33%)	19/49 (39%)	0.571
Cefepime (53)	Shock-free survival at 28h	26.28 (0-27.54)	24.89 (10.25-26.73)	0.281
	VFD-28	28 (0-28)	26.46 (10.41-28)	0.725
	Mortality	11/33 (33%)	6/20 (30%%)	0.801
Piperacillin-tazobactam (84)	Shock-free survival at 28h	25.43 (0-26.61)	26.02 (20.94-26.88)	0.550
	VFD-28	24.21(0-28)	26.73 (13.86-28)	0.564
	Mortality	21/56 (38%)	7/28 (25%)	0.252
Meropenem (41)	Shock-free survival at 28h	25.74 (22.38-26.78)	25.32 (0-27.44)	0.759
	VFD-28	28 (0-28)	24.69 (0-28)	0.251
	Mortality	9/14 (43%)	13/28 (46%)	0.826
Pseudomonas (23)	Shock-free survival at 28h	23.45 (0-26.38)	24.51 (0-26.59)	0.897
	VFD-28	0 (0-28)	25.74 (0-28)	0.548
	Mortality	10/13 (77%)	4/10 (40%)	0.072

Table 2.11. Multivariate Linear regression model of shock-free survival in patients with a CrCl <50ml/min

Model of shock free survival, limited to CrCl <50ml/min at time of BL dose Variable	**β coef.**	**P>|t|**	**95% Confidence Interval**
Dose adjusted BL	-5.94	0.024	-11.07, -0.81
Peak lactate	-0.83	0.085	-1.79, 9.11
SOFA score	-0.003	0.993	-0.77, 0.76
Immunosuppressed at admission (ANC <500)	-1.29	0.757	-9.64, 7.05
Beta-lactam administered within 1 hour	-2.97	0.273	-8.35, 2.41
Bacteria Isolated[b]			
K. pneumoniae	-2.55	0.499	-9.39,4.21
E. cloacae	-14.16	0.024	-26.43, -1.89
P. aeruginosa	-12.97	0.001	-20.12, -5.81
C. spp	0.87	0.933	-20.06, 21.81
Proteus spp.	-23.43	0.027	-44.09, -2.76
Other	-13.24	0.005	-22.34 -4.15
Extended Infusion	-0.59	0.845	-6.65, 5.46
Maximum pressor dose in NE equivalents	-0.06	0.086	-0.12, 0.00
24h fluid balance	0.00	0.129	-0.00, 0.00

[b] Referent Category E. coli
Model R^2 0.25, p = 0.03, Obs 66

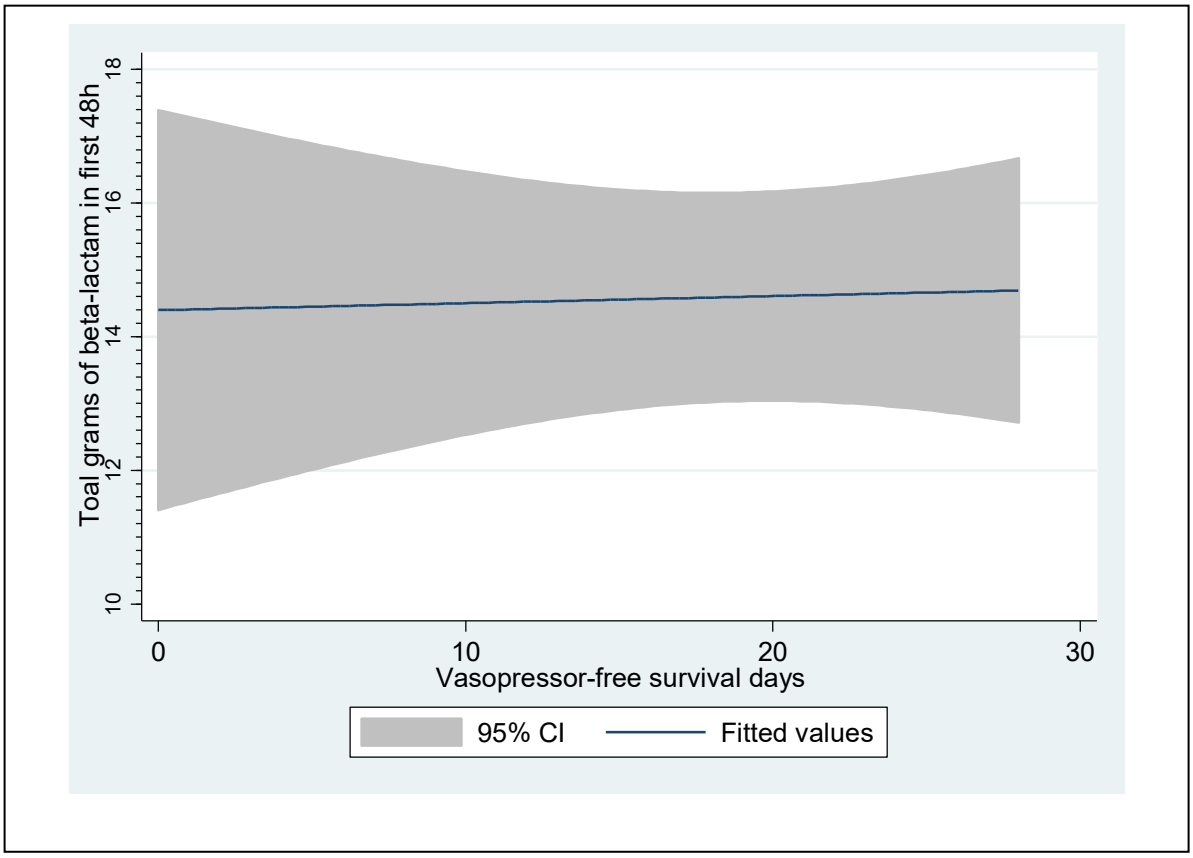
2.1.4 Aim 1 Discussion and Conclusion

Dose adjusting of cefepime, piperacillin-tazobactam or meropenem was not associated with clinical outcomes in this cohort of critically ill patients with septic shock and AKI (KDIGO stage1 and higher). In a prespecified sub-group of those with a CrCl <50ml/min at the time of beta-lactam initiation, dosage adjustment was statistically significantly associated with fewer days alive and free from vasopressor agents. These finds are

supported by previous observations made by Kullar and colleagues, where an exploratory analysis of a predefined cut point of <50ml/min was associated with poor microbiological response in patients enrolled in the ASPECT trials (complicated intra-abdominal infections and complicated urinary tract infection) trials. (Kullar, Wagenlehner et al. 2017) The patients in ASPECT-cIAI and cUTI et al were less critically ill, than our current population. (Solomkin, Hershberger et al. 2015, Wagenlehner, Umeh et al. 2015) Fewer than 10% had bacteremia, and the >80% had an APACHE of <10. Of the patients in both trials, a combined 94 (36 from ASPECT-cIAI and 58 from ASPECT-cUTI) had a CrCl <50ml/min on admission.

The construct of transient AKI has been discussed in expert circles of late, with the premise that dosage adjusting should not occur in a patient with a transient AKI. In a large retrospective study by Crass et al, records of patients with infections requiring antibiotics were reviewed for rates of transient AKI. (Crass, Rodvold et al. 2019) Of 18,650 records reviewed, 17.5% (3256) had AKI on admission. Of those with AKI on admission, 57.2% were transient, recovering with in 48h of index admission. A leading hypothesis as to the nature of these observations of improved microbiologic and clinical outcomes in non-dosage adjustments, is the notion that transient AKI does not require dose adjusting of a beta-lactam antibiotic. (Crass, Rodvold et al. 2019) Therefore, according to the above authors, in the presence of rapid recovery of renal function, and severe infections- dose adjusting the beta-lactam should not be recommended. The total dose of beta-lactam over the first 48h may be an important predictor of microbiologic and clinical outcomes in larger cohorts, as seen in Figure 2.1.

Figure 2.1 Linear relationship between total grams of beta-lactam received in the first 48h and shock-free survival at d28.



Making dosing decisions based on serum creatinine in critically ill patients has been criticized for a long time. Serum creatinine-based equations are limited to interpretation in populations with steady production and elimination of creatinine. (Baptista, Neves et al. 2014) Critically ill patients with sepsis requiring antibiotics exhibit dynamic Pk parameters, including rapid changed in Vd and Cl. The wide therapeutic index of beta-lactam drugs, coupled with the emerging data of harm due to under dosing should compel

the clinician to re-evaluate empiric these dosage adjustments. Without direct TDM of beta-lactam antibiotics, full labeled dosing should be used in all patient with septic shock.

We did not evaluate microbiologic outcomes in this current study, as we hypothesized, in a sicker population a difference in a hard-clinical outcome such as days alive and free of vasopressors could be observed. However, when solely evaluating the group of patients with a CrC <50ml/min (n= 100), the data were underpowered to detect a difference in mortality. Future studies testing this hypothesis should use the cut of off (CrCl<50ml/min) as the defining criteria for AKI regardless of KDIGO criteria. This is an important threshold in the dosing package inserts for many beta-lactam antibiotics. As we have observed in the current study, KDIGO class was less informative of a population of patients who would be harmed by empiric dosage adjustments of the beta-lactam, antibiotics. We found no difference in the rates of C. difficile infection, and rates of neurotoxicity were extremely low. The concern for toxicity has been raised in several studies (Huwyler, Lenggenhager et al. 2017) which may be a result of prolonged dosing rather than empiric dosage selection.

Our study has key limitations to be explored. The retrospective data collection allows for selection bias on the treatment groups that is not readily obvious. Limiting our cohort to bacteremia reduced the sample size of our study, and reduces external validity- as many septic patients with AKI do not have concomitant bacteremia. The impact and negative consequences of prematurely dosage adjusting in an AKI could extend to non-bacteremia populations, which has been seen in prior studies of UTI and intraabdominal studies. (Solomkin, Hershberger et al. 2015, Wagenlehner, Umeh et al. 2015) There was very low rates of toxicities, which is likely a result of missing information bias, inherent to retrospective study designs. The selection of whom to dose adjust and whom not to, was left up to the clinical care team. This strengthens our study design, as none of the

participating sites had a protocol for dosage adjustments in the first 48h of therapy. However, particular clinical information about each patient is impossible to determine who would get a dosage adjustment, and who would not. It is likely that the sickest patients were dose adjusted, as reflected in the higher mortality rates in this group.

Strengths of the study include the multi-center design, and selection of the sickest patients who would plausibly be impacted by dose adjusting which increased internal validity. Limiting the inclusion to bacteremia with susceptible MIC concentrations minimized the impact of non-susceptible confounding. The groups were well balanced in the unadjusted analysis, and applying regression modeling was successful in controlling for measured confounders of the outcome.

In conclusion, the current study was able to demonstrate an association between shock-free survival in AKI patients (CrCl <50ml/min), without dosage adjustments of beta-lactam therapy within the first 48h. This hypothesis should be tested in a prospective randomized study to confirm these findings.

CHAPTER 3. AIM 2: TO EXAMINE THE RELATIONSHIP OF BETA-LACTAM PK/PD TARGET ATTAINMENT ACHIEVEMENT, AS MEASURED BY THERAPEUTIC DRUG MONITORING, WITH CLINICAL OUTCOMES IN PATIENTS ADMITTED TO THE ICU FOR SEPSIS

3.1.1 Aim 2 Significance, Rationale and Hypothesis

Aim 2: To examine the relationship of beta-lactam PK/PD target attainment achievement, as measured by therapeutic drug monitoring, with clinical outcomes in patients admitted to the ICU for sepsis

Aim 2 Hypothesis: Achieving the beta-lactam PK/PD target attainment (100%T>4xMIC) is associated with improved clinical outcomes in ICU patients with sepsis as compared to those who fail to achieve the PK/PD target

3.1.2 Aim 2 Methods Impact of Beta-lactam Target Attainment on Outcomes of Critically Ill Patients with Sepsis: A Retrospective Cohort Study

To test the hypothesis that beta-lactam trough concentrations are associated with clinical outcomes, a retrospective cohort study was performed on adult patients, admitted to the University of Kentucky Medical ICU from July 2017- December 2017. Patients were included in the study if they received a beta-lactam antibiotic and therapeutic drug monitoring during this time frame. Patients were excluded if they were incarcerated, pregnant, or did not have beta-lactam concentrations available. At the time of the study, beta-lactam TDM was non-protocolized and left to the treating healthcare team, however when done, 2 levels were commonly drawn: a mid-dosing interval level, and a trough level. This study was approved by the University of Kentucky institutional review board with a waiver of informed consent.

Definitions and Outcomes

The primary outcome was PK/PD target attainment, defined as a trough concentration of 100%T>4xMIC. The MIC threshold used in this study is 16 for piperacillin/tazobactam and 2 for meropenem, both of which are the breakpoint, respectively, for *Pseudomonas* aeruginosa. Secondary outcomes include 50%T>4xMIC, and clinical cure as defined previously (Roberts, Paul et al. 2014) as completion of the

antibiotic regimen without need for escalation or additional of antibiotics within 48h of cessation. Mortality, ICU and hospital length of stay were also assessed. Creatinine clearance was assessed with the Cockcroft-gault equation, and ARC was defined as a CrCl of ≥130ml/min. (Cockcroft and Gault 1976, Sime, Udy et al. 2015)

Statistical Analysis

Continuous variables were tested for distribution by histogram visualization and with the Shapiro-Wilk test. Continuous variables with normal distribution are presented as mean (SD); otherwise are presented as median (IQR). Continuous variables were analyzed using either the Student's T-test or the Wilcoxon Rank-sum test as appropriate. Categorical variables are presented as frequencies and proportions and analyzed using the Pearson's Chi-square or Fisher's Exact test as appropriate. Statistical analyses were done using Stata (version 14.2, Stata Corp, College Station, Texas, USA).

3.1.3 Aim 2 Results

A total of 43 patients were evaluated in this study, comprising 80 measurements. The primary outcome was reached in 25/43 (58%) of patients, which then defined the two cohorts (achieved the PK/PD goal, and did not achieve the PK/PD goal). The mean age (SD) in years was 58 (17) vs 61 (15), in the not-achieved and achieved groups, respectively, p=0.595. The majority of patients were male 75% vs 60%, p= 0.323 and white 94% vs 88%, p= 0.545, which did not differ between groups (PK/PD not achieved vs PK/PD achieved respectively). Admission SOFA score was slightly higher in the PK/PD achieved group 7.84 (4.11) vs 5.25 (3.8) as compared to the PK/PD not achieved group, however this did not reach statistical difference in the bivariate analysis, p=0.51. Piperacillin-tazobactam was the most commonly monitored beta-lactam 41(95%), followed by

meropenem 2(5%). Of the total 43 patients, 330 (82.5%) also met the secondary PK/PD outcome of 50%T>4xMIC. Those achieving the PK/PD goal had a statistically significantly lower CrCl than those not achieving the goal: 73ml/min (41-104) vs 109.5 ml/min (86.5- 146), and were more likely to be in shock 16(64%) vs 4 (25%), p=0.015. Augmented renal clearance was more common in the PK/PD not achieved group, yet this did not reach statistical significance: 6 (38%) vs 5(20%), p=0.217. Baseline characteristics are displayed in Table 3.1.

Infection type, and treatment characteristics are summarized in Table 3.2. The type of infection, use of concomitant aminoglycoside, total 24-hour dose of piperacillin received at the time of TDM sampling, and use of extended interval dosing (infusion over 3+ hours) was not different in the two groups. In those not achieving the PK/PD goal, the dose required to achieve this goal exceeded the FDA labeling in 8/13 (62%).

Table 3.1 Baseline characteristics by group, PK/PD not achieved and PK/PD achieved

Characteristic	N= 43	PK/PD not achieved (n=16)	PK/PD achieved (n=25)	p
Age	60 (15)	58 (17)	61 (15)	0.595
Gender (male)	28 (65%)	12 (75%)	15 (60%)	0.323
Race				
White	40 (93%)	15 (94%)	22 (88%)	0.545
AA	3 (7%)	1 (6%)	3 (12%)	
Weight	83.58 (25.18)	91.45 (22)	78.5 (26.16)	0.109
SOFA Score	6.9 (4.25)	5.25 (3.8)	7.84 (4.11)	0.051
Co-morbidities				
Diabetes	13 (32%)	7 (50%)	6 (24%)	0.098
Hypertension	23 (56%)	9 (64%)	13 (52%)	0.458
CHF	8 (20%)	2 (14%)	6 (24%)	0.471
Cirrhosis	5 (12%)	0 (0%)	4 (16%)	0.114
CKD	3 (7%)	0 (0%)	3 (12%)	0.177
COPD	13 (32%)	6 (43%)	6 (24%)	0.221
Immunosuppressed	22 (54%)	9 (64%)	12 (48%)	0.957
Other	22 (54%)	9 (64%)	13 (52%)	0.458
Admission KDIGO stage				
0	22 (52%)	10 (63%)	11 (44%)	0.244
1	12 (28%)	5 (31%)	6 (24%)	
2	5 (12%)	1 (6%)	4 (16%)	
3	4 (9%)	0(0%)	4 (16%)	
Shock	20 (49%)	4 (25%)	16 (64%)	0.015
Number of nephrotoxins	2.2 (0.85)	2 (0.65)	2.32 (0.95)	0.256
CrCl at time of TDM	94 (51-133)	109.5 (86.5- 146)	73 (41-104)	0.019
ARC (CrCl ≥130ml/min)	11 (27%)	6 (38%)	5 (20%)	0.217
ARC (CrCl ≥170ml/min)	7 (17%)	3 (19%)	4 (16%)	0.929
50%T>4xMIC	33 (82.5%)	9 (56%)	24 (100%)	0.001

Table 3.2. Treatment characteristics

Characteristic	N= 43	PK/PD not achieved (n=16)	PK/PD achieved (n=25)	p
Infection type				0.444
Pneumonia	24 (58%)	8(89%)	15 (60%)	
UTI	4 (10%)	2 (12.5%)	2 (8%)	
Other	4 (10%)	2 (12.5%)	2 (8%)	
Bacteremia	2 (5%)	1 (6%)	1 (4%)	
SSTI	2 (5%)	2 (12.5%)	0 (0%)	
Bone/joint	2 (5%)	0 (0%)	2 (8%)	
Intraabdominal	2 (5%)	0 (0%)	2 (8%)	
SBP/Medical prophylaxis	1 (2%)	0 (0%)	1 (4%)	
Concomitant aminoglycoside	12 (32%)	5 (33%)	7 (30%)	0.851
Total daily dose of piperacillin	13.5 (13.5-13.5)	13.5 (13.5-18)	13.5(13.5-13.5)	0.056
Total daily dose of meropenem	6 (6-6)	-	6 (6-6)	NS
Extended Infusion (3 or 4 hours)	30 (73%)	12 (75%)	18 (72%)	0.833
Gram negative bacteria isolated	12 (29%)	5 (32%)	7 (28%)	0.823
Bacteria susceptible to beta-lactam	10/15 (67%)	5 (83%)	5 (56%)	0.264
MIC	8 (1-16)	5 (1-8)	6 (1.01- 16)	0.88
Type of bacteria isolated				
GNR	7 (30%)	3 (33%)	4 (29%)	0.511
NF-GNR	6 (26%)	3 (33%)	3 (21%)	
Gram positive	7 (30%)	3 (33%)	4 (29%)	
Yeast	3 (13%)	0 (0%)	3 (21%)	

The clinical outcomes are summarized in Table 3.3. There was no difference in the incidence of a positive clinical outcome in the two groups, 69% PK/PD not achieved vs 62% PK/PD achieved, p=0.666. Length of stay in the ICU, and the hospital were both longer in the PK/PD achieved group. ICU length of stay 5(3.5-8) days in the PK/PD not

achieved vs 11(7-15) day in those who achieved the PK/PD goal, p=0.009. Hospital length of stay was 10(5-14.5) days in those who did not achieve the PK/PD goal, and 24(11-33) in those who achieved, p=006. In-hospital mortality was similar in both groups, (21%), p=0.965.

Table 3.3. Clinical outcomes

Clinical Outcome	Total N=43	PK/PD not achieved (n=16)	PK/PD achieved (n=25)	P-value
Positive clinical outcome	24 (65%)	11 (69%)	13 (62%)	0.666
ICU Length of Stay	7.5 (4.5-12.5)	5 (3.5-8)	11 (7-15)	0.009
Hospital Length of Stay	13.5 (8-27)	10 (5-14.5)	24 (11-33)	0.006
Mortality	9 (23%)	3 (21%)	5 (21%)	0.965

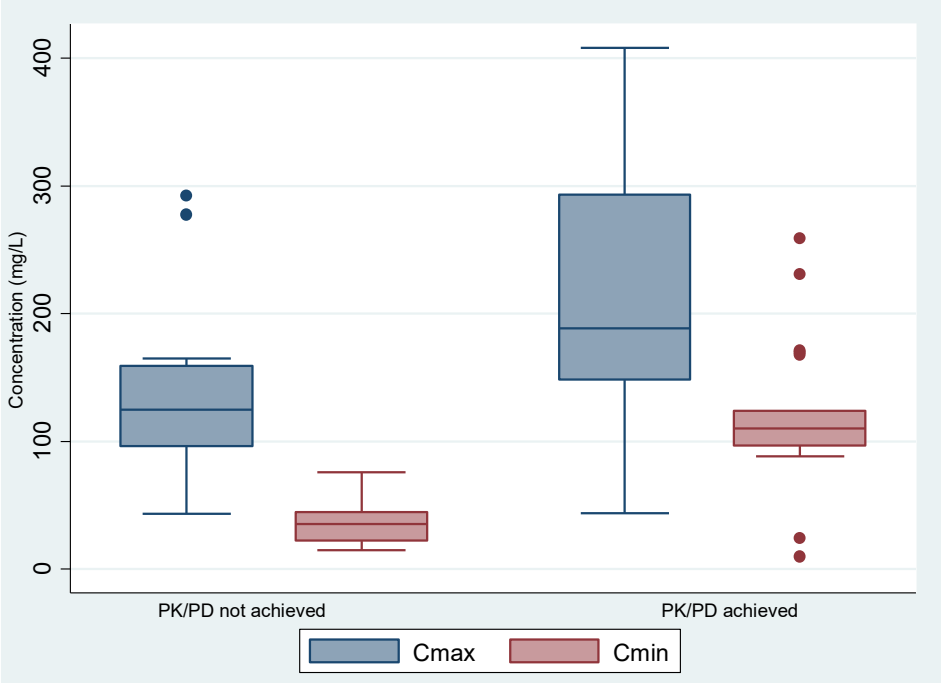
Population pharmacokinetic evaluations are found in Table 3.4. The elimination coefficient (Ke) was higher and elimination half-life (T1/2) was shorter in the PK/PD not achieved group, as compared to the PK/PD achieved group: (Ke) 0.34 (0.24- 0.51) vs 0.12 (0.07- 0.19), p <0.001, and T ½ 1.78 hours (1.37- 2.87) vs 5.77 hours (3.69- 9.53), p= 0.001, respectively. The Vd was similar between groups 27.29 L (11.51- 46.73) PK/PD not achieved vs 26.22 L (21.5-39) PK/PD achieved, p= 0.545. However, the total body clearance (Cl) was significantly higher in the PK/PD not achieved group: 8.38 L/hr (0.57-10.41) vs 3.56 L/hr (2.7- 5.3), p<0.001. The median (IQR) Cmin in the PK/PD not achieved group was 35.44(22.1- 44.52), as compared to the PK/PD achieved group: 110 (97-124), p <0.001. The Cmax was also lower in the PK/PD not achieved group: 125.46

mg/L (96.16- 165.1) vs 188.59 mg/L (147.77- 293.29), p= 0.055. The Cmin and Cmax are visually represented in Figure 3.1.

Table 3.4. Pharmacokinetic calculations

Characteristic	N= 43	PK/PD not achieved (n=16)	PK/PD achieved (n=25)	p
Ke	0.19 (0.11-0.37)	0.34 (0.24- 0.51)	0.12 (0.07- 0.19)	<0.001
T ½	3.65 (1.9- 6.32)	1.78 (1.37- 2.87)	5.77 (3.69- 9.53)	0.001
Cmax	161.85 (114-277.73)	125.46 (96.16- 165.1)	188.59 (147.77- 293.29)	0.055
Cmin	90 (31.5- 113)	35.44(22.1- 44.52)	110 (97-124)	<0.001
Vd	26.22 (16.4-41.4)	27.29 (11.51- 46.73)	26.22 (21.5-39)	0.545
Vd (L/kg)	0.38 (0.23-0.58)	0.29 (0.14-0.53)	0.43 (0.28-0.71)	0.089
Cl (L/hr)	5.36 (2.85- 7.85)	8.38 (0.57- 10.41)	3.56 (2.7- 5.3)	<0.001

Figure 3.1. Boxplot of Cmax, Cmin by group (PK/PD achieved and PK/PD not achieved)



The correlation table of covariates and pharmacokinetic parameters (Volume and Clearance) is found in Figure 3.2. Increasing age was not significantly correlated to volume (correlation coefficient 0.18), or clearance (correlation coefficient -0.063). Creatinine clearance had a low correlation to clearance (0.49), and negligible correlation with volume (correlation coefficient 0.08). Weight highly correlates with volume (correlation coefficient 0.82), and has negligible correlation to clearance (correlation coefficient 0.22). A visual representation of observed vs predictions is found in Figure 3.3. The majority of individual observations fall within the 90% prediction interval.

Figure 3.2. Covariate values of age, sex, CrCl plotted against population Volume and Clearance

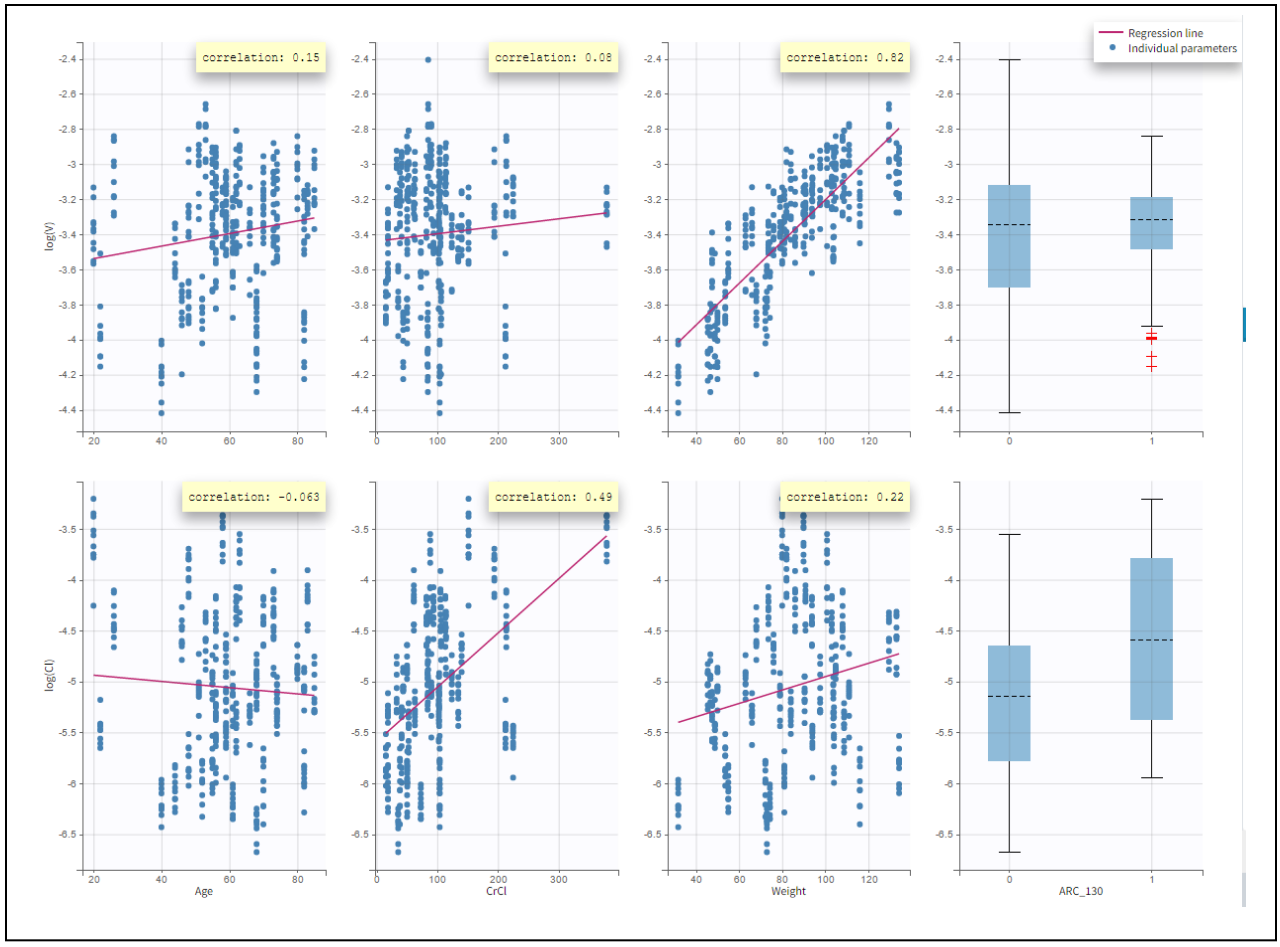
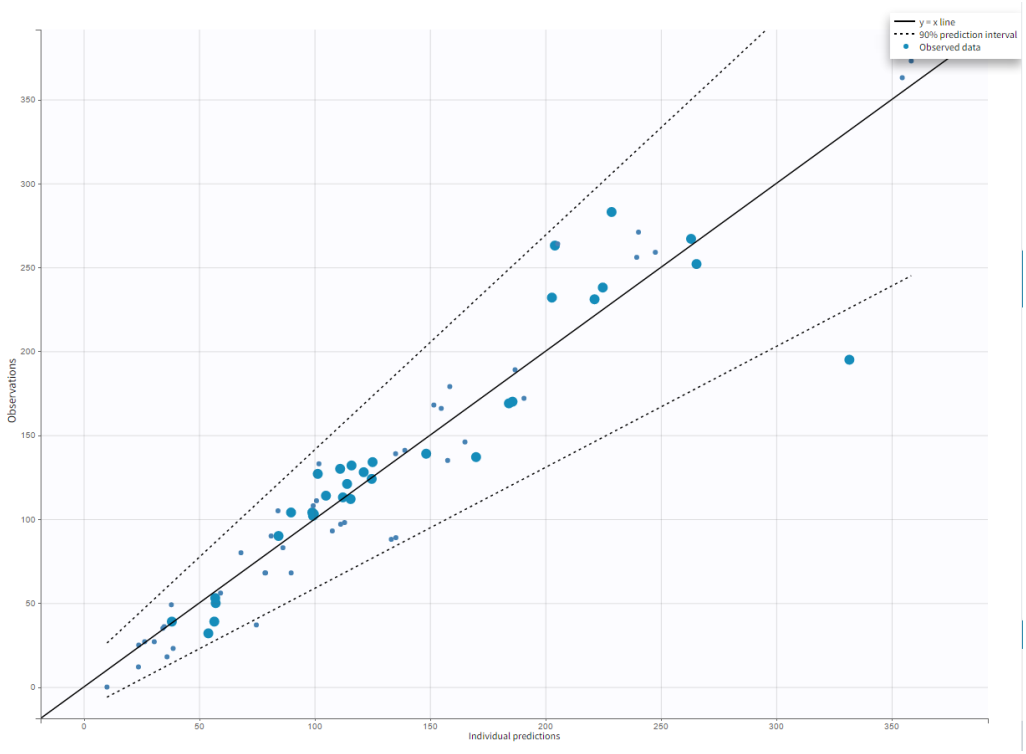


Figure 3.3. Plot of individual predictions vs. observed values



Multivariate logistic regression

The results of the multivariate logistic regression model of PK/PD achieved are found in Table 3.5. The original model started with the following variables: Serum creatinine at TDM, Presence of shock, SOFA score, gender, age, weight, ARC, history of diabetes, AKI at admission. Controlling for other variables in the model, for every point increase in serum creatinine at the time of TDM, the odds of achieving the PK/PD goal increased by 3.83- fold [OR 3.83, (95% CI 1.298, 11.2960), p=0.015]. Controlling for other variables in the model, the presence of shock at the time of TDM increased the odds of PK/PD achieved by 11.81- fold [OR 11.81, (05% CI 1.806, 77.29), p=0.010]. A past medical history of diabetes was associated with an 87% decreased chance of achieving the PK/PD goal, [OR 0.13, (95% CI 0.018, 0.940), p=0.043].

Table 3.5. Multivariate logistic regression model of predictors of PK/PD achieved

PK/PD Achieved	Odds Ratio	P>|z|	[95% Confidence Interval]
Serum Creatine at TDM	3.83	0.015	1.298, 11.296
Shock (Y/N)	11.81	0.010	1.806, 77.29
History of diabetes	0.13	0.043	0.018, 0.940

39 observations
Model p <0.001
R2 0.34
VIF 1.02
Hosmer-Lemeshow goodness of fit test p=0.396
Breusch-Pagan / Cook-Weisberg test for heteroskedasticity p= 0.0076
Final model adjusted for Robust Standard Errors

A multivariate logistic regression model was built with the same initial variables, also including PK/PD goal achieved. The results are summarized in Table 3.6. Controlling for other variables in the model, admission SOFA score and male gender were the only variables significantly associated with a positive clinical outcome. For every 1- unit increase in admission SOFA score, the odds of achieving a positive clinical outcome decreased by 47% [OR 0.53, (95% CI 0.331, 0.855), p=0.009]. Male gender was associated with a 94% decrease in a positive clinical outcome [OR 0.06, (95% CI 0.005, 0.889), p=0.040].

Table 3.6. Multivariate logistic regression model of predictors of a good clinical outcome

Good clinical outcome	Odds Ratio	P>|z|	[95% Confidence Interval]
SOFA score	0.53	0.009	0.331, 0.855
Male gender	0.06	0.040	0.005, 0.889
Shock	16.59	0.075	0.756, 364.14

35 observations
Model p <0.001
R2 0.37
VIF 1.02
Hosmer-Lemeshow goodness of fit test p=0.594
Breusch-Pagan / Cook-Weisberg test for heteroskedasticity p= 0.172

3.1.4 Aim 2 Discussion and Conclusion

In this small retrospective cohort study of septic patients receiving beta-lactam antibiotics, goal PK/PD target attainment was achieved by roughly 2/3 of patients (58%). Target attainment was not associated with a positive outcome in this cohort, however it was associated with a longer hospital and ICU length of stay. This finding is likely due to the overall sicker population represented in those who achieved PK/PD target attainment (the higher baseline SOFA score and higher proportion of patients with shock, and lower CrCl).

The overall target attainment of 58% is higher than expected, as compared to prior reports published in the literature. In a large point prevalence study (DALI) of beta-lactam TDM in the ICU, the aggressive PK/PD target of 100%T>4xMIC was reached by only 35 % of patients. (Roberts, Paul et al. 2014) Another prospective study of 18 critically ill patients published this target attainment reached 10-20% of the time. (Kaska, Havel et al. 2018) Another study evaluating TDM of meropenem in patients with KPC-producing *Klebsiella pneumoniae* infections reported that only 50% of cases reached the target

attainment of 100%T>4xMIC, which was the target in our study. (Pea, Della Siega et al. 2017) Overall, the ability of standard dosing of beta-lactams to reach this PK/PD target is consistently poor. Factors associated with not reaching this goal are the presence of ARC, younger age, volume status, and intermittent bolus dosing regimens. (Carrie, Legeron et al. 2018, Carrie, Petit et al. 2018, Kaska, Havel et al. 2018) In our study, we determined increasing serum creatinine and a presence of shock to be positively associated with achieving the PK/PD goal. A past medical history of diabetes, however, was significantly associated with not achieving the PK/PD goal. Increasing serum creatinine can reflect impaired GFR is a common finding throughout the literature, however the diagnosis of shock is a more difficult finding to explain in this study, and may represent unmeasured confounding. The role of diabetes in predicting target attainment, outside of a disease severity assessment tool, is unclear and also likely represents statistical noise in this small cohort.

Achieving the PK/PD goal in this study was not associated with a positive outcome. This is dissimilar to the finding of the DALI study, and others which have demonstrated a clinical outcome benefit to achieving this aggressive PK/PD goal. (Roberts, Paul et al. 2014) (Carrie, Petit et al. 2018) This discrepant finding could be attributed to multiple factors. Our patients had documented infection in fewer than 30% of cases. This present cohort also received a high proportion of empiric aminoglycoside double coverage therapy. The rationale behind empiric dual gram-negative therapy is to provide coverage for possible resistant organisms, and to augment bactericidal killing, however the benefit of this practice remains controversial. (Kumar, Safdar et al. 2010)

Strengths of the current study include the empiric dosing and infusion strategy of the beta-lactams. Piperacillin was most commonly dosed at 3.375 grams every 6 hours, and

infused over 3 hours in >70% patients in both groups, despite apparent CrCl. Both meropenem patients received the highest dose, with extended infusion interval. These homogenous dosing regimens minimized a treatment effect with the smaller chance of reaching target attainment with intermittent infusion regimens. Complete, 2 level TDM data were available for the majority of patients, allowing for a robust pharmacokinetic assessment.

The most important limitation of this study is the analytic method used to detect the beta-lactam concentrations. The bioactivity assay method of detection utilizes a bacterial probe to determine the antibiotic concentration based on the zone of inhibition. This method can have high intra-rater reliability, but is subject to interfering substances which can contaminate the sample, augmenting the killing effect. (Shaw 1979) One study evaluated ciprofloxacin concentrations measured by HPLC or bioassay in serum and urine. The serum measurements were comparable; regression slope difference 1.0 (99.9% confidence limits: 0.984 <slope < 1.035). However, in urine the bioassay overestimated the antibiotic concentration 30.2 +/- 8.5 HPLC vs 38.2 +/- 5.9 bioactivity assay. Slope difference was 1.327 < slope < 1.698. (Joos, Ledergerber et al. 1985) Another study compared ciprofloxacin concentrations in serum by HPLC or bioactivity assay, and found a similar finding. The microbiologic assay reported higher concentrations than HPLC, owed to detection of active metabolites according to the authors. (Khan, Khan et al. 2012) The presence of concomitant antibiotics with similar bioactivity could have falsely elevated the beta-lactam concentrations in our study, which would explain the higher proportion of target attainment achieved.

In conclusion, at standard doses, target attainment was low at 58% in this study. Use of a bioactivity assay method of detection may overinflate the concentration result.

Prospective studies of higher dosage regimens should be done to achieve a higher proportion of target attainment, and a chromatographic analytic method should be considered. Set the stage for renal biomarkers in the next session.

CHAPTER 4. AIM 3: TO DEVELOP A LABORATORY DEVELOPED TEST USING LC-MS TO MEASURE BETA-LACTAM CONCENTRATIONS IN HOSPITALIZED PATIENTS

4.1.1 Aim 3 Significance, Rationale and Hypothesis

Laboratory developed tests (LDT) are an important tool to aid in patient care for the clinician. In the absence of an FDA approved test, the LDT is developed internally, validated, maintained by the institution, and used for in-house patient care. (Genzen 2019) For example, all beta-lactam assays are considered an LDT. The LDT is regulated by the Centers for Medicare and Medicaid, and abide by all Clinical Laboratory Improvements Amendments (CLIA) regulations. The requirements of laboratory developed test include a laboratory director with a MD or PhD with specific board certification. The test must be approved with proper validation, ongoing performance assessments, and provide interpretations to the ordering physicians. Laboratory developed tests are commonly seen in settings where commercial tests are unavailable to meet a clinical need, including new drug monitoring, or advanced genetic testing. The landscape of federal regulation over laboratory developed test has begun to change over the years, with the FDA desiring more regulatory control over these tests. (Genzen 2019) Therefore, to meet the needs of the

patients at UKHC, an LDT for beta-lactam assay measurements will be developed and implemented into clinical practice.

Overall Aim 3: To develop a Laboratory Developed Test using LC-MS to measure beta-lactam concentrations in hospitalized patients

Aim 3 Hypothesis: A Laboratory Developed Test utilizing LC-MS technology will improve beta-lactam concentration accuracy over available detection methods, and facilitate personalized dosing of beta-lactam antibiotics for UKHC hospitalized patients with sepsis

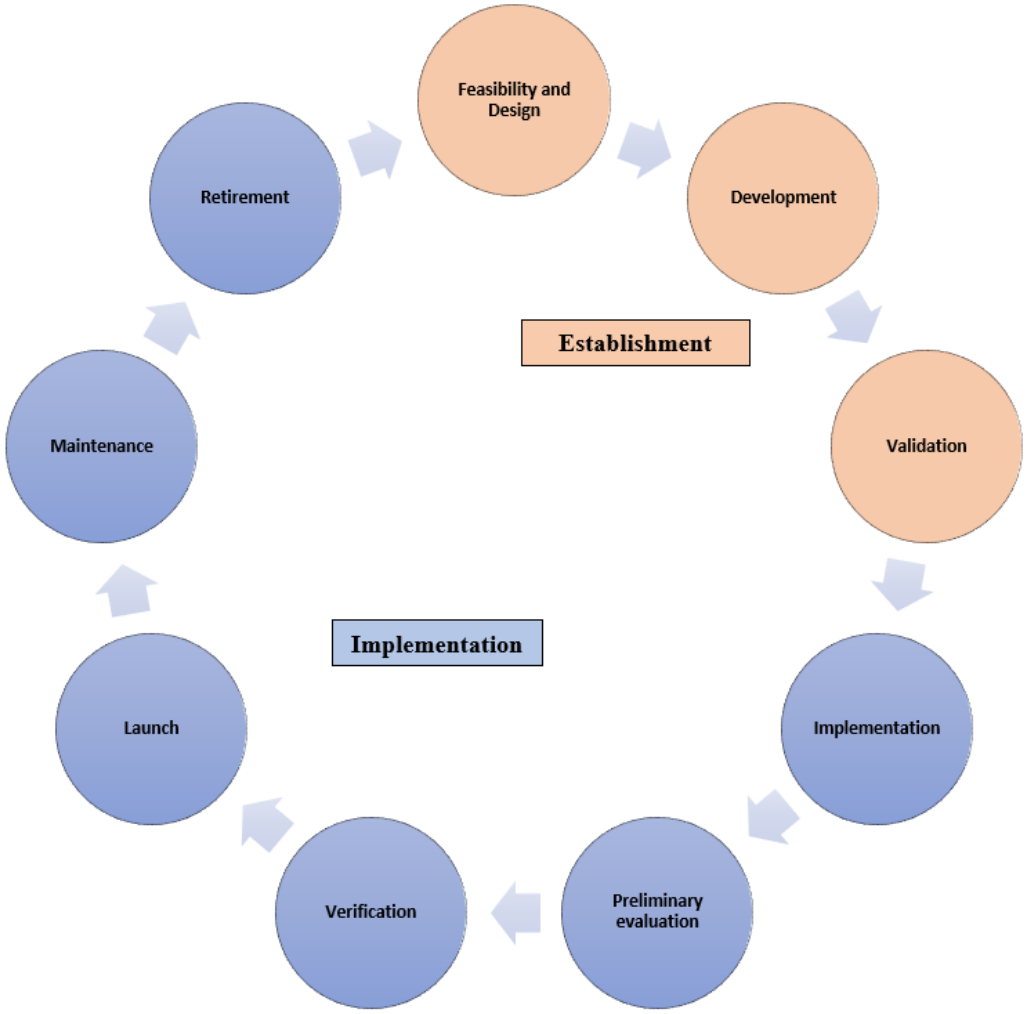
4.1.2 Aim 3: Methods

4.1.2.1 Background and Rationale for a Laboratory Developed beta-lactam assay

The Clinical and Laboratory Standards Institute (CLSI) regulates laboratory developed tests, including beta-lactam assays. (CLSI 2014) CLSI provides guidance for development of liquid chromatography-mass spectrometry (LC-MS) methods for laboratory developed test. Mass spectronomy measures the size of a compound, therefore allowing for identification and quantification. LC-MS is advantageous over traditional gas chromatography (GC-MS) for several reasons, including a wider range of molecular weights able to measure, with lower limits of detection. Cleaning the ion source is easier and requires fewer parts, and the run times are generally shorter. While the clinical lab will employ multiple testing platforms, the LC-MS is optimal for beta-lactam measuring. Pitfalls of the LC-MS method includes requiring advanced technician training with special technical skills. The throughput can be limited in number, as compared to the immunoassay method, and LC-MS comes with high instrumentation costs. The CLSI has set forth

guidance in the EP19 document for development and validation of a laboratory developed test. (CLSI 2014) This process includes two overarching themes with specific steps in each: Establishment and Implementation, depicted in Figure 4.1.

Figure 4.1 Testing Lifecycle



Step 1. Feasibility and design assess use of the test, patient population, clinical demand and volume. This includes consultation with clinicians on how the test will be used through a literature review and marketing assessment of the center. Essentially, there must be a clinical need and the ability of the laboratory to meet the need, as well as a way to bill/pay for the test.

Step 2. Development assess the materials needed and technical features required to establish the test. Development uses CLSI method evaluation standard (EP), and determine precise requirements of the test. Each batch of reagent requires manufacturing records. The end of the development phase, is the design output. This is a test that will work, prior to validation.

Step 3. Validation is defined as the 'Objective evidence that the requirements for a specific use or application of the test have been fulfilled'. (CLSI 2014) Validation confirms the final test is suitable for the measurement, the population and in the specific condition. The steps of validation include: precision, accuracy (measurement against a gold standard), measuring interval, reference interval (normal range), sensitivity, limit of detection/ detection capacity, analytical specificity (identification of interfering substances), clinical validation (testing in the target population works), reagent and sample stability (storage conditions of plasma/serum), and risk assessment. These steps essentially inform the package insert, if the test were to be commercially available.

Step 4: Preliminary evaluation includes a small batch testing to confirm the calibration and quality control is working. This is a step to ensure the test performance is satisfactory.

Step 5: Verification is objective criteria that the test performs in the way the manufacturer (or internal laboratory) claims. Specifically, it is the evidence that the specific requirements are completed. Verification includes optimal performance in a variety of settings: different operators, equipment changes, room changes, space configuration changes, storage conditions (ex: -20c or -80c freezer) and in different patient populations. Verification should be done by a laboratory in which the similar patient conditions are met, a CLIA laboratory, not a research laboratory if the test is to be done for patient care.

Step 6: Launch is the transition of the test into patient care. This step includes training of end users, clinicians who will order the test. Streamlining education of staff, and incorporation of informatics and IT for test ordering.

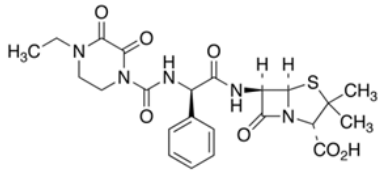
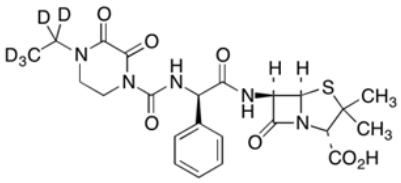
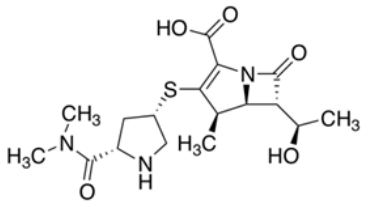
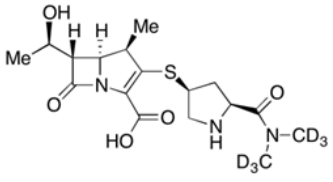
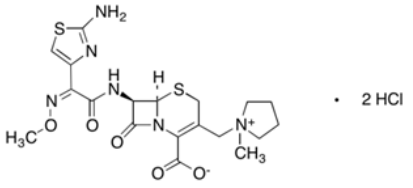
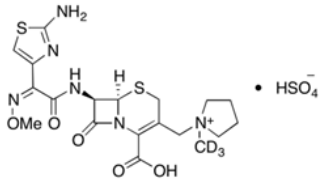
Step 7: Maintenance phase describes the phase of normal clinical use. Ongoing quality assurance and quality control, evaluate of precision, accuracy, results review and follow-up. This step is the same as a commercially available test, and does not differentiate between the origin.

Step 8: Retirement is the sunsetting of the test, which includes maintaining document control and records of the test. Test retirement can occur for any reason, mostly due to advances in technology and replacement with a newer more advanced test.

4.1.2.2 Beta-Lactam Measurements by Liquid Chromotagraphy/ Tandem Mass Spectromonony: A Laboratory Developed Test

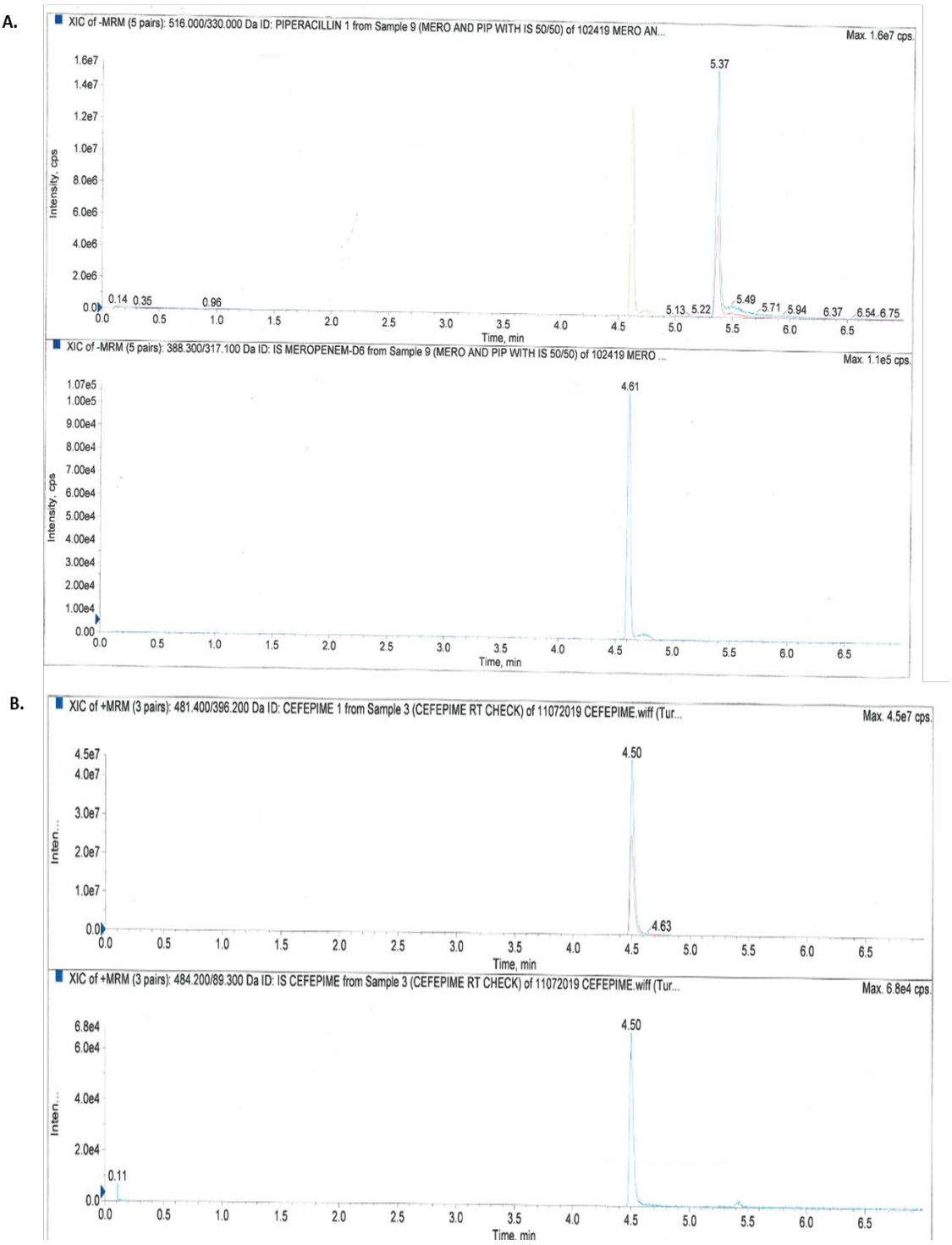
The following outline our steps for the successful development of a novel LC-MS/MS method for determining concentrations of cefepime, meropenem and piperacillin in human blood. Drug reagent standards were obtained from Sigma-Aldrich in the forms: Piperacillin Monohydrate USP Reference Standard, Meropenem USP Reference Standard, Cefepime Hydrochloride USP Reference Standard. Additional reagents for liquid chromatography (LC) including HPLC grade acetonitrile and methanol were also obtained from Sigma Aldrich. Internal standard material in the form of the deuterated beta lactam drugs including piperacillin-d5, meropenem-d6 and cefepime-d3 sulfate (Table 4.1) were obtained from Toronto Research Chemicals.

Table 4.1. Standards used for beta lactam method development

Standard	Structure	Molecular Formula	Molecular Weight (Da)
Piperacillin		$C_{23}H_{27}N_5O_7S$	517.55
Piperacillin-d5 (IS)		$C_{23}H_{22}D_5N_5O_7S$	522.59
Meropenem		$C_{17}H_{31}N_3O_8S$	437.51
Meropenem-d6 (IS)		$C_{17}H_{19}D_6N_3O_5S$	389.5
Cefepime		$C_{19}H_{24}N_6O_5S_2 \bullet 2(HCl)$	480.56
Cefepime –d3 sulfate (IS)		$C_{19}H_{23}D_3N_6O_9S_3$	581.66

The beta lactam method at the University of Kentucky Clinical laboratory was developed on a Sciex 6500 LC-MS/MS platform. Identification of the beta lactam antibiotics for this study by mass spectrometry was first achieved by finding the appropriate MS parameters to identify unique qualifier (Q1)/quantifier (Q3) ion pairs for each of the standard materials and the respective internal standards. Piperacillin and meropenem yielded optimal fragmentation patterns in negative ion mode with a Q1/Q3 (Da) of 516/330 or 516/232.9 and 382/311.1 or 382/267, for piperacillin and meropenem, respectively. Importantly, the deuterated internal standard material did not reveal a unique fragmentation pattern between the non-deuterated USP standard and the deuterated IS, therefore, the meropenem-d6 was adopted as the internal standard for both piperacillin and meropenem with an internal standard Q1/Q3 of 388/317.1 Fragmentation and identification of cefepime was optimal in positive ion mode with a Q1/Q3 of 481.4/396.2 or 481.4/86.1 with the cefepime-d3 Q1/Q3 established at 484.2/89.3. Instrument parameters were set to switch polarization modes to accommodate the detection of all three beta lactams within the same run. In addition, the final method was established using a scheduled MRM scan type with the Q1/Q3 ion pairs identified above. The LC methodology was developed and optimized on a Kinetex 2.6 µm reverse phase C18 100 Å Phenomenex column with the dimensions of 150 x 4.6 mm. The LC method optimized with a flow rate of 0.4 mL/min and a linear solvent gradient of water to 50:50 MeOH to MeCN from 5%-90% for a total method duration of 7 minutes, including a re-equilibration phase to prepare the column for subsequent injections. LC-MS/MS chromatography traces for the completed method demonstrating optimized conditions and peak resolution are shown in Figure 4.2.

Figure 4.2. LC-MS/MS chromatography traces from the beta lactam method development



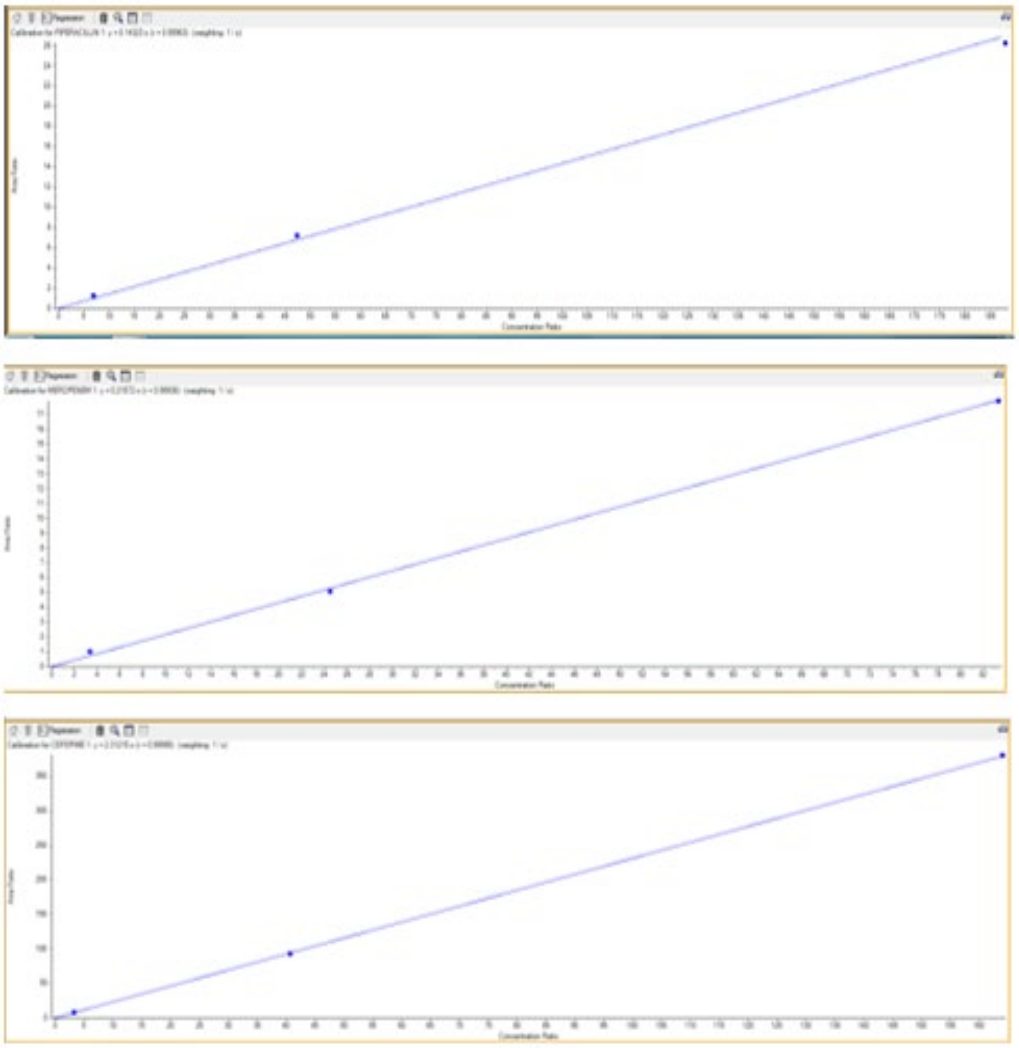
The optimized sample preparation protocol for serum specimens includes an extraction/protein precipitation step with a 100% acetonitrile solvent solution with rigorous vortexing, followed by centrifugation. The resulting supernatant is removed from the centrifuged sample and dried down with dry air using a standard hood manifold. Following this step, the residual sample is reconstituted in LC mobile phase consisting of 0.1% formic acid in distilled water, prior to injection into the LC-MS/MS instrument. The complete beta-lactam method was calibrated using commercially available standards from Chromsystems diagnostics.

4.1.2.3 Aim 3 Results

Clinical Method Validation

Method validation for a laboratory developed test that will be used in patient care involves a number of steps to assess the analytical performance of the assay. In brief, the studies necessary to complete a laboratory developed test include, determining the limit of quantification (LOQ), simple and complex precision to assess the random error of the assay, accuracy and linearity to examine the performance of the assay over the desired analytical measuring range of the assay, comparison studies to a reference laboratory or method to assess the relative performance of the assay and identify any biases that would contribute the systematic error of the assay, interference studies and stability studies to determine the optimal handling and storage conditions for clinical samples. The calibration curve for our method validation is found in Figure 4.3.

Figure 4.3. Calibration Curve



Acquisition and Laboratory Processing of Patient Blood Specimens for Clinical Method Validation Experiments

The University of Kentucky Clinical Laboratory has policies and procedures to follow when handling human samples for research. In conjunction with the Enterprise Pre-analytic coordinator, a process was established to receive human samples, and process them in the Clinical lab for the beta-lactam study. Institutional review board (IRB) approval was obtained for this study. Enrollment criteria for patient eligibility for the validation arm of the study included 1) ≥ 18 years old, non-pregnant, non-incarcerated with admission to a non-COVID MICU 2) diagnosis of sepsis and being treated with a beta-lactam of interest (cefepime, meropenem, piperacillin). Patients were excluded if they 1) Comfort care decision to limit support or imminent death, as decided by MICU team or withdrawal of MICU care by family within 72h of enrollment 2) Planned antibiotic duration <48 hours (surgical or medical prophylaxis) 3) acute kidney injury on admission, defined as a KDIGO Stage 1 or higher.

The procedure for handling samples is outlined below, and in Figure 4.4 Processing Request Form.

Using the Processing Request Form

1. Collect 1 red top from patient, labeled with the subject ID and sample ID as the two patient identifiers.

2. Send red top labeled with the two patient identifiers and a copy of the BETALAC Processing request form with matching identifiers to the lab.

3. The lab will then order the processing charge with this information.

4. The lab will then centrifuge the red top and make three aliquots to store at -70ºC until picked up by Dr. Schuler or the designated special chemistry staff for sample analysis.

    a. Aliquot 1: ARUP aliquot requiring sterile processing

    b. Aliquot 2: Aliquot for Florida

    c. Aliquot 3: Aliquot for– special chemistry in-house testing

For a select number of initial blood draws, 5 aliquots will be done. The additional specimens will be used for an internal comparison study between green (Li-heparin) and red top (Serum-no additive) tubes. This comparison study is to facilitate the transition to patient care, where the commonest labs drawn, "AM labs" are in a green top tube, thus negating the need for drawing additional blood specimens from our patients. With the transition to green top tubes, clinical pharmacists and providers will be able to place an 'add on order' to AM labs, for a beta-lactam level. Acceptance of this proposed work-flow is pending the final stability and comparison results, as the results of these studies will dictate how long a sample can remain at room temperature, and still be eligible for a beta-lactam level 'add-on'.

To facilitate the patient comparison studies with reference laboratories, contracts and billing accounts were created with the University of Florida (UF) and ARUP Laboratories. A two-way comparison study will be done with ARUP laboratory, and the

University of Florida Infectious Disease Pharmacokinetics Laboratory. A total of 40 samples will be sent to ARUP and 40 samples will be sent to University of Florida Infectious Disease Pharmacokinetics Laboratory representing the identical time points for each of the unique patient samples to complete the comparison studies. The University of Florida Infectious Disease Pharmacokinetics Laboratory will serve as the reference laboratory for our method validation. Their laboratory utilizes a LC-MS/MS method for beta-lactam detection, and is a CLIA certified, College of American Pathologists (CAP) accredited laboratory for patient care. The UF laboratory specifications for sample handling are for the blood (0.5ml) to be drawn in a red top tube, avoiding a gel separator. After the blood clots, centrifuge the samples, and freeze at -70°C. Use a different tube for each test and time of collection, and label the tubes with the patient's name, date and time of collection, and the drug(s) to be assayed. Samples should be packed in dry ice, and sent to the laboratory with the requisition form via overnight delivery Monday through Friday. The listed stability from UF is 1 year at -80°C. Results will be available via fax within 48 hours.

A second reference laboratory comparison to the ARUP bioactivity method will also be performed. ARUP is a CLIA certified, CAP accredited reference laboratory. The analytic method for beta-lactams is the bioactivity assay. Specific handling instructions include: draw 2 ml of serum (1ml minimum), centrifuge at ambient temperature, and process into a sterile container. This will minimize the risk of interfering substances. The sample should be frozen at -70°C, and shipped on dry ice to ARUP within 7 days, according to their internal stability. Since the bioactivity assay uses a bacterial probe and zone of inhibition to measure the concentration, the requisition form must contain concomitant antibiotics the patient is receiving.

Figure 4.4. Processing request form

Beta-lactam TDM - IRB45733 IRB45805 - Processing Request Form

HealthCare

BETALAC
Beta-lactam TDM Research
Account#: 026182618-9900

UKHealthCare Clinical Laboratory Client Services
800 Rose Street; HA619
Lexington, KY 40536
Phone: (859) 323-5432
Fax: (859) 257-7696

Section Completed by Study

BETALAC PI: Melissa Thompson Bastin, PharmD **COI:** Dr. Erin Schuler
Contact Phone: 843-364-4124

Patient Demographics:

7124412 Place patient demographic label here or hand-write the two patient identifiers 7124412

Collection date: _____
Collection time: _____
Subject ID: _____
Sample ID: _____
Date of Birth: _____
Sex: Male Female

Samples Requested:

☑ **PRCS1** Processing Level 1

It is imperative that plasma & serum be denoted on the corresponding aliquot.

☑ **Check all aliquots that are needed from this collection**

Both red & green containers should be centrifuged at ambient temperature, and each container aliquotted into a separate send-out container with screw caps based on number of aliquots checked. Freeze immediately at -70ºC.

1 - Green Container

- ☐ **Aliquot 1** **Write plasma on the aliquot with a permanent marker**
  Volume: Preferred:1.0 mL plasma Minimum: 0.5 mL plasma

1 - Red Container

- ☐ **Aliquot 2** ***Requires sterile processing into sterile ARUP container.***
  Volume: Preferred: 2.0 mL serum Minimum: 1.0 mL serum
- ☐ **Aliquot 3** **Write serum on the aliquot with a permanent marker**
  Volume: Preferred: 1.0 mL serum Minimum: 0.5 mL serum
- ☐ **Aliquot 4** **Write serum on the aliquot with a permanent marker**
  Volume: Preferred: 0.5 mL serum Minimum: 0.2 mL serum
- ☐ **Aliquot 5** **Write serum on the aliquot with a permanent marker**
  Volume: Any remaining serum

Section Completed by Lab Central

Use Institutional Code BETALAC- when ordering in Sunquest.

1. Enter BETALAC-(allowing system to auto-assign the next sequential number)
2. Enter the patient's last name as BETALAC the first name as the subject ID, and the middle name as the sample ID.
3. Enter the Date of Birth and Sex.
4. Enter 020136 for the ordering physician & delete the OSADD.
5. Order PRCS1 and process red & green containers as described above.
6. Immediately freeze the plasma & serum denoted aliquots in the -70ºC freezer in the BETALAC rack.

4.1.3 Aim 3 Discussion and Conclusion

We were able to develop and validate a LC-MS based beta-lactam assay as a Laboratory Developed Test for the University of Kentucky. The specimen stability and comparison studies are currently underway. A patient care protocol for use at the University of Kentucky, and education plan for providers and front-end users of the test is underway.

CHAPTER 5. CONCLUSIONS AND FUTURE DIRECTIONS

5.1.1 Conclusions and Future Directions

In conclusion, through an extensive review of the literature, we were able to demonstrate a significant gap in the science of understanding of beta-lactam dosing in critically ill patients with sepsis, and the optimal methods of measuring beta-lactam concentrations. We demonstrated, by accomplishing Aim 1, the current practice of following FDA renal function labeling for beta-lactam dosing in septic patients with AKI is associated with poorer outcomes. In accomplishing Aim 2, we confirmed that optimal beta-lactam target attainment is inconsistently achieved in septic patients. However, we recognize the significant and important limitation of the sampling methods done in this study, which greatly interferes with the interpretation of the concentrations, therefore restricting the generalizability of this study. By accomplishing Aim 3, we were able to advance the science of understanding of beta-lactam dosing by funding a Laboratory Developed Test to be developed and used in clinical practice at the University of Kentucky. The future directions of this work include to validate the laboratory developed test, and

perform a prospective trial testing these hypotheses prospectively. The role and implications of protein binding alterations of beta-lactam antibiotics should be explored in future studies of pharmacokinetic evaluations in critically ill patients.

The next steps for this area of research would be a prospective randomized controlled trial. To overcome the important confounder of dual empiric coverage of gram-negative infections, we would randomize to double coverage with an aminoglycoside vs. no aminoglycoside. Participants would be randomized into 4 groups, 1) beta-lactam TDM plus concomitant aminoglycosides, 2) standard beta-lactam dosing plus concomitant aminoglycosides, 3) beta-lactam TDM with no aminoglycoside and 4) standard beta-lactam dosing and no concomitant aminoglycoside. There is clinical equipoise with the practice of prescribing empiric aminoglycosides, and this study design could also help answer the role of this practice. To overcome ethical considerations of provider preference, providers could decline entry into the study, should they feel strongly about prescribing an aminoglycoside. The TDM targets in the study should be the more aggressive target of 100%t>4xMIC. Clinical outcomes would include microbiologic cure, mortality, ICU and hospital LOS. With the aminoglycoside arm of the study, a robust analysis on nephrotoxicity risk of this practice could be evaluated as well.

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Woodward, C. W., J. Lambert, V. Ortiz-Soriano, Y. Li, M. Ruiz-Conejo, B. D. Bissell, A. Kelly, P. Adams, L. Yessayan, P. E. Morris and J. A. Neyra (2019). "Fluid Overload Associates With Major Adverse Kidney Events in Critically Ill Patients With Acute Kidney Injury Requiring Continuous Renal Replacement Therapy." Crit Care Med **47**(9): e753-e760.
Yehya, N., M. O. Harhay, M. A. Q. Curley, D. A. Schoenfeld and R. W. Reeder (2019). "Reappraisal of Ventilator-Free Days in Critical Care Research." Am J Respir Crit Care Med **200**(7): 828-836.

VITA

MELISSA L. THOMPSON BASTIN, PHARMD, BCPS

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EDUCATION

06/16- Present	PhD candidate in Clinical and Translational Science University of Kentucky College of Medicine Department of Behavioral Science Qualifying Exam completed 7/2018 Anticipated graduation 5/2021
08/06 – 05/10 Pharmacy	Medical University of South Carolina (South Carolina College of MUSC Campus) Charleston, SC *Doctor of Pharmacy*, 2010
08/01 – 05/05	College of Charleston, Charleston SC *Bachelor of Science* in Psychology, 2005 NCAA varsity athlete, Equestrian Team *(01-05)*

POST GRADUATE TRAINING

07/11-06/12 Resident	Postgraduate Year Two Critical Care Specialty Pharmacy Chief Pharmacy Resident University of Kentucky HealthCare, Lexington, KY Program Director: Jeremy Flynn, PharmD, BCPS, FCCP, FCCM Advisor: Kelly Smith, PharmD, BCPS, FACP
06/10- 07/11	Postgraduate Year One Pharmacy Resident (R380) University of Kentucky HealthCare, Lexington, KY Program Director: Aaron Cook, PharmD, BCPS Advisor: Amber Lawson, PharmD, BCOP

CERTIFICATION/LICENSURE

11/14	ACLS Experienced Provider Course completed
5/14- 19	ACLS Instructor Certification
10/13-Present	Board Certified Pharmacotherapy Specialist

06/12	Post-Graduate Year Two Critical Care Specialty Residency Certificate University of Kentucky HealthCare
06/11	Post-Graduate Year One Pharmacy Practice Residency Certificate University of Kentucky HealthCare
06/11	Scholarship of Teaching and Learning Certificate University of Kentucky College of Pharmacy
07/10- Present	Kentucky Pharmacist License (Preceptor) # 015175
06/10- Present	ACLS for Health Care Providers

PHARMACY PRACTICE EXPERIENCE

08/12- Present *(MICU)*	*Clinical Pharmacist, Pulmonary Critical Care/Medicine ICU* University of Kentucky HealthCare Supervisor: Aaron Cook, PharmD, BCPS
08/13- Present	*Assistant Professor, adjunct series* University of Kentucky College of Pharmacy
07/11- 06/12	*Chief Pharmacy Resident* University of Kentucky HealthCare
06/10- 6/12	*Assistant Professor (Residency appointment)* University of Kentucky College of Pharmacy
07/10- 07/12	*Staff Pharmacist: Centralized/Decentralized ICU Pharmacist* University of Kentucky HealthCare
08/04-03/08	*Pharmacy Technician CPhT/Student Pharmacist Intern (05/06-03/08)* MUSC Adult Inpatient Pharmacy, Charleston, SC Supervisor: Rich Ottmar, RPh
10/03-03/06	*Pharmacy Technician, CPhT* Eckerd Pharmacy, Charleston, SC Supervisor: Scott Wink, PharmD

CURRENT POSITION

Clinical Pharmacist, Pulmonary Critical Care/MICU University of Kentucky HealthCare: This position is a clinical pharmacy specialist position in which I round with the medical ICU teams. Responsibilities also include education, committee service, precepting. Specific job functions, committee involvement and projects are listed below.

10/20- Present	UK HealthCare COVID Subcommittee Taskforce member
03/20- Present	Advancing BEST Care Sepsis Team lead and EPIC transition team lead
09/19- Present	Scientific Member of UK Institutional Review Board (IRB)
04/19- Present	eICU Steering Committee member
06/17- Present	UK HealthCare Medical ICU lead pharmacist
06/16- 10/18	UK HealthCare Enterprise Sedation committee member • Education committee coordinator
07/15- Present	MICU Operations Quality Improvement • Development of oral sedation analgesia protocol for MICU • Development of RN driven diuresis protocol for MICU • Review of DKA management/protocol in the MICU
10/14- 10/18	Medication Utilization and Outcomes / Cost Reduction Initiatives (CRI) • Albumin Coalition, Respiratory medication coalition
07/15- Present	UK HealthCare Pharmacy member of the enterprise Sepsis resuscitation committee
01/14- Present	UK COP PPS 973 Critical Care Elective, course coordinator
08/13- Present	University of Kentucky College of Pharmacy APPE preceptor (MICU) • Preceptor for APPE students since 2013
07/13- Present	University of Kentucky PGY1 Pharmacy resident preceptor (MICU) • Preceptor for PGY1 Residents since 2013
08/13- Present	University of Kentucky PGY2 Critical Care resident preceptor (MICU) • Preceptor for PGY2 Residents since 2013
05/13- Present	UK HealthCare Anti-microbial Subcommittee: ICU Pharmacy representative • CRRT dosing guidelines, C.diff bundle, formulary approval of new antimicrobials
04/14- 07/16	UK Medication History (MARQUIS) training coordinator • Training for new pharmacists, APPE students, interns, technicians. • Development of WBT (web-based training) for yearly competency
05/13- 07/16	UK HealthCare Pharmacy Intern Program: Clinical liaison
05/13- 07/16	UK HealthCare Pharmacy Intern Program: Chandler Hospital Manager • Manager of the Chandler hospital branch of the intern program • Responsible for 2 Direct reports, 3 indirect reports and 32 student interns.

	• Direct training, review scheduling, competency documentation, 90-day evaluations, and yearly evaluations (PE).
05/13- 07/16	Scholarship and Education Coordinator, UK HealthCare Pharmacy Intern Program • Direct the advisor-advisee program • Coordinate the monthly journal club, Summer Lecture Series, Fall Professional Development Series • Advise lead interns on "Intern-al Matters", the yearly newsletter publication • Connect students to preceptors on research and quality improvement projects
02/ 13- 01/16	UK HealthCare Critical Care Pharmacy Council: pharmacy work group targeting ICU guideline and protocol implementation and education
07/13- Present	UK HealthCare Pharmacy Residency Program resident advisor
11/12- 1/15	UK HealthCare Anticoagulation and National Patient Safety Goals committee
09/12- Present	UK HealthCare Student Intern Program, Mentor and Pharmacist preceptor

PEER REVIEWED PUBLICATIONS

1. **Thompson Bastin ML,** Adams P, Nerusu S, Morris PE, Mayer KP and Neyra JA. Association of phosphate containing solutions with incident hypophosphatemia in critically ill patients requiring continuous renal replacement therapy. *Blood Purification* [article accepted]

2. **Thompson Bastin ML**, Berger K, Adams CA, Altschuler J, Dixit D, Effendi MK, Heavner MS, Johnston JP, Lemieux DG, Lemieux SM, Littlefield AJ, Owusu KA, Rose C, Rouse GE. Adapting Clinical Pharmacy Staffing Models During the COVID-19 Pandemic: Lessons Learned and Considerations for Future Disaster Planning. *Journal of the American College of Clinical Pharmacy* [epub ahead of print DOI: 10.1002/jac5.1374]

3. Neyra JA, Yessayan L, **Thompson Bastin ML**, Willie K, Tolwani A. How to prescribe and troubleshoot continuous renal replacement therapy: A case-based review. Kidney 360 2020. [epub ahead of print DOI: 10.34067]

4. Mayer KP, **Thompson Bastin ML**, Montgomery-Yates AA, Pastva AM, Dupont-Versteegden EE, Parry SM and Morris PE. Acute skeletal muscle wasting and dysfunction predict physical disability at hospital discharge in patients with critical illness. *Critical Care* 2020;24(1):637 PMID: 33148301

5. Ruiz EF, Ortiz-Soriano V, Talbott M, Klein BA, **Thompson Bastin ML**, Price E, Taylor M, Hauschild CE, Dorfman R, Adams B, Fryman L and Neyra JA. Development, Implementation and Outcomes of a Quality Assurance System for the Provision of Continuous Renal Replacement Therapy. *Scientific Reports* 2020;10(1):20616 PMID: 33244053

6. Adams CA, Altschuler J, Barlow BL, Dixit D, Droege CA, Effendi MK, Heavner MS, Johnston JP, Kiskaddon AL, Lemieux DG, Lemieux SM, Littlefield AJ, Owusu KA, Rouse GE, **Thompson Bastin ML**, Berger K. Analgesia and Sedation Strategies in Mechanically Ventilated Adults with COVID-19. Pharmacotherapy 2020 [epub ahead of print] PMID: 33068459

7. Flannery AH, Owen GD, Coz A, **Thompson Bastin ML**, Patel K. Impact of Hyperoncotic Albumin on Duration of Vasopressor Support in Septic Shock: A Propensity Score Matched Analysis. *Annals of Pharmacotherapy* 2020 [epub ahead pf print] PMID: 33016080

8. Barlow B, Barlow A, **Thompson Bastin ML**, Berger K, Dixit D and Heavner M. Minimizing pharmacotherapy related healthcare worker exposure to SARS-CoV-2. *Am J Health Syst Pharm* 2020 Online ahead of print. doi: 10.1093/ajhp/zxaa190. PMID: 32469056

9. Flannery AH, Bissell BD, **Thompson Bastin ML**, Morris PE, Neyra J. Continuous versus intermittent infusion of vancomycin and the risk of acute kidney injury in critically ill adults: a systematic review and meta-analysis. *Critical Care Medicine* 2020;48(6):912-918 PMID: 32317590

10. Bissell BD, Laine ME, **Thompson Bastin ML**, Flannery AH, Kelly A, Riser J, Neyra JA, Potter J and Morris PE. Impact of Protocolized Diuresis for De-Resuscitation in the Intensive Care Unit Protocolized Diuresis in the Critically Ill. *Critical Care* 2020;24:70 PMID: 32111247

11. Nelson N, Strzelewicz MG and **Thompson Bastin ML**. Plasmapheresis Treatment for Osmotic Demyelination Syndrome: Case Report and Review of Current Literature. *Transfusion and Apheresis Science* 2019; ePub ahead of print. PMID 31759898

12. Magee CA, **Thompson Bastin ML**, Graves K, Burgess D, Nestor MA, Lamm JR and Cook AM. Fever Burden in Patients with Subarachnoid Hemorrhage. *J Stroke Cerebrovasc Dis.* 2019;28(11):104313 PMID 31405792

13. Laine ME, Flannery AH, Moody B and **Thompson Bastin ML**. Need for Expanded Candida Score for Empiric Antifungal Use in Medically Critically Ill Patients?

Critical Care 2019; 23:242 PMID 31272491

14. **Thompson Bastin ML**, Short GT, Cook AM, Rust K and Flannery AH. Perceptions of Television-Based Education in the ICU: A Survey Comparison among Patients and Care Providers. *American Journal of Critical Care* 2019;28(4):307-315 PMID: 31263014

15. Lat I, Daley MJ, Shewale A, Pangrazzi MH, Hammond D, Olsen KM, Teevan, C., Erdman, M., Milicevic, L., Hyche, S., Woolridge, J., Patel, G., DeMott, J., Dalton, K., Sokol, S., Bullard, H., Miller, M.K., Pierce, T., Flannery, A.H., Bissell, B.D., **Thompson Bastin, M.L** et al. DEFINE study group and the Discovery Research Network. A Multicenter, Prospective, Observational Study to Determine Predictive Factors for Multidrug-Resistant Pneumonia in Critically Ill Adults: The DEFINE Study. *Pharmacotherapy* 2019;39(3):253-60 PMID 30101412

16. Buzzard SL, Bissell BD and **Thompson Bastin ML**. Ehrlichiosis presenting as severe sepsis and meningoencephalitis in an immunocompetent adult. *Journal of Medical Microbiology Case Reports 2018;5(9)* (PMID 30425837)

17. Borchet J, Phillips J, **Thompson Bastin ML**, Livingood A, Anderson R, Brasher C, Bright D, Fahmi Armanious B, Leary M, Lee J and Hagemann T. ACCP White Paper: Best Practices: Incorporating Pharmacy Technicians and Other Support Personnel into the Clinical Pharmacist's Process of Care. *Journal of the American College of Clinical Pharmacy 2018 [epub ahead of print]* DOI: 10.1002/jac5.1029

18. Woolum JA, Abner EL, Kelly A, **Thompson Bastin ML**, Morris PE and Flannery AH. Effect of Thiamine Administration on Lactate Clearance and Mortality in Patients with Septic Shock. *Critical Care Medicine* 2018;46(11): 1747-52 (PMID: 30028362)

19. McCleary EJ, **Thompson Bastin ML**, Cook AM, Bissell BD, Pierce CA and Flannery AH. Development of a Co-Precepting Model for a Preceptor-in-Training Program for New Practitioners. *Hospital Pharmacy* 2019;54(4):246-49 (PMID 31320774)

20. Fu S, Flannery AH and **Thompson Bastin ML**. Acute Hepatotoxicity after High-Dose Cytarabine for the Treatment of Relapsed Acute Myeloid Leukemia: A Case Report. *Hospital Pharmacy* 2018;54(3):160-164 (PMID 31205325)

21. Flannery AF, **Thompson Bastin ML,** Montgomery-Yates A, Smith K, Hook C, Cassity E, Eaton P, Morris PE. Multidisciplinary Prerounding Meeting as a Continuous Quality Improvement Tool: Leveraging to Reduce Continuous Benzodiazepine Use at an Academic Medical Center. *J Intensive Care Med.* 2019;34(9):707-713(PMID: 29683053)

22. Magee CA, **Bastin MLT,** Laine ME, Bissell BD, Howington GT, Moran PR, McCleary EJ, Owen GD, Kane LE, Higdon EA, Pierce CA, Morris PE, Flannery AH. Insidious harm of medication diluents as a contributor to cumulative volume and hyperchloremia: a prospective, open-label, sequential period pilot study. *Crit Care Med.* 2018;46(8):1217-1223 (PMID: 29727367)

23. Bissell BD, Flannery AH, Adkins DA, and **Thompson Bastin ML**. Safe, Efficacious and Aggressive Treatment of Life-Threatening Hypophosphatemia During Recovery from Acute Fulminant Hepatic Failure. *Journal of Intensive Care Medicine* 2018;33(6):375-379 (PMID: 29088996)

24. Flannery AH, **Bastin MLT**, Magee CA, and Bensadoun ES. Vitamin C in Sepsis: When It Seems Too Sweet, It Might (Literally) Be. *Chest* 2017;152 (2):450-451 (PMID: 28797393)

25. La M, **Thompson Bastin ML**, Cousineau JT, Johnson CA and Flannery AF. Impact of home psychoactive medications on sedation requirements in Medical ICU patients. *Journal of Critical Care* 2017;43:102-107 (PMID: 28865338)

26. Bissell BD, Magee C, Moran PR, **Bastin MLT** and Flannery AH. Hemodynamic Instability Following Vasopressin Withdrawal in Septic Shock. *Journal of Intensive Care Medicine* 2019;34(9):761-765 (PMID: 28750598)

27. **Thompson Bastin ML**, Cook AM and Flannery AH. Training Pharmacy Residents for High-Stress, High-Impact Clinical Scenarios Using Simulation Training. *Am J Health Syst Pharm.* 2017 Mar 15;74(6):424-429 (PMID: 28274986)

28. **Thompson Bastin ML**, Neville NR, Parsons RE, Flannery AH, Tennant SJ and Johnson CA. An unusual case of *Salmonella* Enteritidis causing pneumonia, septic shock and multiple organ failure in an immunocompetent patient. *IDCases* 2016;6:85-89. (PMID: 27818944)

29. Smetana K, Cook AM, **Bastin ML** and Oyler D. Antiepileptic Dosing for Critically Ill Adult Patients Receiving Renal Replacement Therapy. *Journal of Critical Care* 2016;36:116-124 (PMID: 27546759)

30. Parli SE, **Thompson Bastin ML** and Lewis D. Use of Continuous Renal Replacement Therapy for Removal of Dabigatran in a Patient with Need for Emergent Surgery. *Case Reports in Critical Care* 2016;16: (PMID: 27313909)

31. Phillips H, Dangler A, Klem PM, Chu F, Pon T, Liewer S, **Thompson Bastin ML**, Halfpap JJ, Fish J, Stun L, Varughese CA. Preceptor development: Responses to frequently asked questions from preceptors in academic hospitals. *Am J Health Syst Pharm* 2016; 73:e261-e266 (PMID: 27099334)

32. Noel ZR, **Bastin MLT**, Montgomery AA and Flannery AH. Comparison of High-Dose vs Standard Dose Oseltamivir in Critically Ill Patients with Influenza. *Journal of Intensive Care Medicine* 2017;32(10):574-577 (PMID: 26992784)

33. Flannery AH, Willey MD, **Thompson Bastin ML**, Buch KP and Bensadoun ES. Eosinophilia and Fever with Levetiracetam: A Case Report. *Pharmacotherapy* 2015;35(8):e131-e135 (PMID: 26235978)

34. Kunka ME, Cady EA, Woo HC, and **Thompson Bastin ML**. Flucytosine Pharmacokinetics in a Critically Ill Patient Receiving Continuous Renal Replacement Therapy. *Case Reports in Critical Care* 2015 [epub ahead of print] (PMID: 26246919)

35. May CC, Arora S, Parli SE, Fraser JF, **Bastin MT**, Cook AM. Augmented Renal Clearance in Patients with Subarachnoid Hemorrhage. *Neurocritical Care* 2015;23(3):374-379 (PMID: 25761425)

36. Baker ML, **Bastin MT**, Cook AM, Fraser JF, Hessel EA. Hypoxemia associated with nimodipine in a patient with an aneurysmal subarachnoid hemorrhage. *American Journal Health-System Pharmacy* 2015;72(1): 39-43 (PMID: 25511836)

37. Flannery AH and **Thompson Bastin ML**. Oseltamivir Dosing in Critically Ill Patients with Severe Influenza. *Annals of Pharmacotherapy* 2014;48(8):1011-1018 (PMID: 24816209)

38. **Thompson Bastin ML,** Baker SN, Weant KA. Effect of Etomidate on Adrenocortical Suppression: A Review of Intubated Septic Patients. *Hospital Pharmacist* 2014;49(2):177–183 (PMID: 24623871)

39. **Thompson ML**, Flynn JD, Clifford TM. The Pharmacotherapy of Lung Transplantation: An Overview. *Journal of Pharmacy Practice* 2013;26 (1):5-13 (PMID: 23204148)

40. **Thompson ML** and Magnuson BW. Management of Postoperative Ileus. *Orthopedics* 2012; 35(3):213 (PMID: 22385598)

41. **Thompson ML** and Martin C. Treatment of Necrotizing Fasciitis Infections in Orthopedic Surgery Patients. *Orthopedics* 2011; 34(2):111-5 (PMID: 21323228)

42. Jennings DL and **Thompson ML**. Use of Combination Therapy with a Beta-blocker and Milrinone in Patients with Advanced Heart Failure. *Annals of Pharmacotherapy* 2009;43(11):1872-6 (PMID: 19789358)

SELECTED ABSTRACTS

Kressin C, **Thompson Bastin ML**, Ather A, Gopinath A, Pandya K. Cisatracurium for Acute Respiratory Distress Syndrome on Extracorporeal Membrane Oxygenation. SCCM Virtual Congress 2021

Dempsey J, Mayer K, Parry S, Morris PM, **Thompson Bastin ML**. Effect of Early Enteral Nutrition on Muscle Size, Quality, and Strength in Critically Ill Patients. Incidence and associated consequences of hyperchloremia in aneurysmal subarachnoid hemorrhage. SCCM Virtual Congress 2021

Barlow BL, **Thompson Bastin ML**, Bissell BD, Flannery AH, Cook AM. Incidence and associated consequences of hyperchloremia in aneurysmal subarachnoid hemorrhage. SCCM Virtual Congress 2021

McCleary E, Bulfin MP, **Thompson Bastin ML**, Naseman K, Pandya K. Retrospective Evaluation of Two Diabetic Ketoacidosis Protocols in Hospitalized Patients. SCCM Virtual Congress 2021

Thompson Bastin ML, Berger K, Adams CA, Altschuler J, Dixit D, Effendi MK, Heavner MS, Johnston JP, Lemieux DG, Lemieux SM, Littlefield AJ, Owusu KA, Rose C, Rouse GE, Hammond DA. Adapting Clinical Pharmacy Staffing Models During the COVID-19 Pandemic: Lessons Learned and Considerations for Future Disaster Planning. ACCP Annual meeting 2020

Thompson Bastin ML, Zhu M, McCleary E. Risk factors for diabetic ketoacidosis treatment failure in medically critically ill patients. *Critical Care Medicine* 2020;48(1):141

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Kelley J, Bissell B, **Thompson-Bastin M**, Flannery A. Renal Effects of Vasopressin on Cirrhotic Patients With Septic Shock. *Critical Care Medicine* 2020;48(1):680

Caroline E Hauschild, Eloy Ruiz, **Melissa L. Thompson Bastin**, Kirby Mayer, Brandi Adams, Lisa Fryman, Monica Talbott, Javier A Neyra. Development and implementation of a quality management program for continuous renal replacement therapy deliverables. Advances in Critical Care Nephrology 2020

Thompson Bastin ML, Nerusu S, Adams P, Morris P and Neyra JA. Phosphorus-containing Solutions Reduce Incident Hypophosphatemia and Associate with Better Outcomes in Critically Ill Patients Requiring Continuous Renal Replacement Therapy. American Journal of Respiratory and Critical Care Medicine 2019;199:A5994

Srinadh A, Flannery A, Kelly A, Bhattacharya D, **Thompson Bastin ML**, Nepal C, Cassity E, Gopinath A, Morris R. Pain Assessment and Sedation Delivery in

Mechanically Ventilated Patients: Can We Do It Better? *Critical Care Medicine* 2019;47(1):547

Bissell B, Flannery A, Pandya K and **Thompson Bastin ML**. Comparison of Sodium Acetate Buffering Capacity in Critically Ill Patients with and without Cirrhosis. ACCP Global Conference, Seattle, WA. Poster presentation at ACCP Global Conference on Clinical Pharmacy. [Oct 2018]

Wong A, Smith Z, **Thompson Bastin ML**, DeMott JM, Gross K, Bissell B, Heavner M, Droege M, Hohlfelder B. Development of pharmacy residency research resources within the Critical Care PRN. ACCP Global Conference, Seattle, WA. Poster presentation at ACCP Global Conference on Clinical Pharmacy. [Oct 2018]

Thompson Bastin ML, Short T, Cook A, Rust K, Flannery A. Perceptions of Television-Based Education in the ICU: A Comparison between Patients and Care Providers. *Critical Care Medicine* 2018; 46(1):176

Dave K, **Thompson Bastin ML**, Flannery AH, Cassity E, Kelley A, Morris P. Evaluation of Stress Ulcer Prophylaxis Indications at a Large Academic Medical Center. *Critical Care Medicine* 2018; 46(1):507

Thompson Bastin ML, Soper MK, Laine ME, Dhar S. Propylene Glycol Toxicity from Pentobarbital Infusion in Refractory Status Epilepticus. *Critical Care Medicine* 2018;46(1):455

Bissell B, Magee C, **Thompson Bastin ML** and Flannery A. Detrimental Effect of Supplemental Dextrose Infusions In The Intensive Care Unit. *Critical Care Medicine*. 2018; 46(1):200

Magee C, **Thompson Bastin ML**, Laine M, Bissell B, Moran P, Owen G, Morris P and Flannery AH. Insidious Harm of Medication Diluents As A Contributor To Cumulative Volume And Hyperchloremia. *Critical Care Medicine* 2018;46(1):6

* *Abstract received a Star Research Award (top 10 submissions)*

Laine M, Moody B, Flannery AH, Kalema A and **Thompson Bastin ML**. Need for expanded candida score for empiric antifungal use in medical critically ill patients? *Critical Care Medicine* 2018;46(1):323

Ali D, Clark J, Flannery AH, Kelly A, Oyler D, **Thompson Bastin ML**. De-Escalation of Dexmedetomidine-Based Sedation Utilizing Clonidine in Medical and Surgery ICU. *Critical Care Medicine* 2018;46(1):489

Flannery AH, Bissell B, Owen G, Moran P, Kelly A, **Thompson Bastin ML**. Assessing the Impact of Albumin Use on Vasopressor Duration And Mortality In Septic Shock. *Critical Care Medicine* 2018;46(1):687

Woolum, Jordan; **Thompson Bastin ML**, Kelley A, Flannery AH. Association of Thiamine Administration with Outcomes in Septic Shock Patients. *Critical Care Medicine* 2018;46(1):711

Fu SH, Flannery AH, **Thompson Bastin ML**. Acute Hepatotoxicity after High-Dose Cytarabine for the Treatment of Relapsed Acute Myeloid Leukemia: A Case Report 2017 ACCP Meeting

Flannery AH, **Thompson Bastin ML**, Fu S, Bissell BD, Morris PE and Neyra J. Continuous versus intermittent infusion of vancomycin and the risk of acute kidney injury in critically ill adults: a systematic review and meta-analysis" 2017 ACCP Annual Meeting

Bissell BD, Flannery AH, Adkins DA, **Thompson Bastin ML**. Safe, Efficacious and Aggressive Treatment of Life-Threatening Hypophosphatemia During Recovery from Acute Fulminant Hepatic Failure. American Journal of Respiratory and Critical Care Medicine 2017;195:A3835

Bissell BD, Magee C, **Thompson Bastin ML**, Moran PR, Flynn JD, Flannery AH. Hemodynamic Instability Following Vasopressin Withdrawal in Septic Shock. American Journal of Respiratory and Critical Care Medicine 2017;195:A5767

Thompson Bastin ML, Flannery AH, Montgomery-Yates AA, Smith KH, Hook C, Cassity EP, Eaton PM and Morris PE. ICU "Hotel Rounds" as a Quality Improvement Tool: Changing Practice in a Medical Intensive Care Unit. *Critical Care Medicine* 2016;44;108

Thompson Bastin ML, McLaughlin CP, Turner B, Williams MV and Li, J. Development of an ICU-Based Pharmacy Technician to Improve the Medication Distribution Process. *Critical Care Medicine* 2016;44:95

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Thompson Bastin ML, Cook AM and Flannery AH. Simulation Training to Prepare Pharmacy Residents for High-stress, High-impact Clinical Scenarios. *Critical Care Medicine* 2016;44(12)181

Thompson Bastin ML, Curlin A and Flannery AH. Angioedema from Combination Sitagliptin and Lisinopril in a Diabetic Patient. *Critical Care Medicine* 2016;44(12)542

Thompson Bastin ML, Neville NR, Parsons RE, Flannery AH, Tennant SJ, and Johnson CA. An Unusual Case of Salmonella Causing Pneumonia and Septic Shock in an Immunocompetent Patient. *Critical Care Medicine* 2016;44(12):524

La M, **Thompson Bastin ML**, Gisewhite J and Flannery AH. Impact of Restarting Home Neuropsychiatric Medications on Sedation Outcomes in Medical ICU Patients. *Critical Care Medicine* 2016;44(12)333

Magee C, **Thompson Bastin ML**, Burgess D, Nestor M and Cook AM. Effects of Fever burden and increased use of antibiotics in patients with Subarachnoid Hemorrhage. *Critical Care Medicine* 2016;44(12):262

Thompson Bastin ML, Gokun Y, Macaulay TE, Clifford T. Use of Fenoldopam in Calcineurin Inhibitor Induced Nephrotoxicity. *Critical Care Medicine* 2013;41(12)
** Abstract nominated as a Research Citation Finalist*

Noel Z, **Bastin MT**, Montgomery-Yates A, Flannery A. Comparison of high dose versus standard dose oseltamivir in critically ill patients with influenza. *Critical Care Medicine* 2015;43(12):114-115

May CC, Arora S, Parli SE, **Thompson Bastin MT**, Cook AM. Levetiracetam pharmacokinetics in subarachnoid hemorrhage patients with augmented renal clearance: a Monte Carlo Simulation. Pharmacotherapy 2014: 34

Thompson Bastin ML, Fugit A, Martin C. Challenges Associated With and Ways to Improve the Transition from Resident to Preceptor: A Pilot Study. Poster presented at the American Society of Health-System Pharmacists National Preceptors Conference May 2013. Washington, DC

Thompson ML, Weant K, Baker S. Effect of Etomidate on Adrenocortical Suppression: A Review of Intubated Septic Patients. Poster presented at the Society of Critical Care Medicine 41st Congress. February 2012. Houston, Tx

Thompson ML, Boan A, Blue AV. Knowledge and Attitude Changes of Health Profession Students Towards Pharmacy: Before and After Completion of an Interprofessional Education Fellowship. Poster presented at American College of Clinical Pharmacy Annual Conference October 2010. Austin, Tx

BOOK CHAPTERS

Cook AM and **Thompson Bastin ML.** "TDM of anti-infectives" in PK/PD in Special Populations and Prophylaxis, Infectious Disease Pharmacotherapy Self-Assessment Program, 2019; Marc Scheetz, editor.

Thompson Bastin ML and Bissell BD. "Corticotrophins, corticosteroids, and prostaglandins" in Side Effect of Drugs Volume 41, 2018; Sidhartha D. Ray, editor

Trobaugh KA, Flannery AH and **Thompson Bastin ML**. "Special Populations: Critical Care and Transplantation" in Demystifying Drug Dosing in Renal Dysfunction; Brandon Nemecek and Drayton Hammond, editors: American Society of Health-System Pharmacists, Bethesda, MD.

"Cardiovascular Critical Care" in ACCP Critical Care Prep and Review Course. Chapter reviewer. 2018- Present

SELECTED PRESENTATIONS
NATIONAL/STATE/REGIONAL

IRB Overview
August 2020
Preceptor's Playbook: Tactics, Techniques, and Strategies
American Society of Health-System Pharmacists

Publications and Presentations
August 2020
Preceptor's Playbook: Tactics, Techniques, and Strategies
American Society of Health-System Pharmacists

Research and Publication Opportunities for Students
August 2020
Preceptor's Playbook: Tactics, Techniques, and Strategies
American Society of Health-System Pharmacists

Pharmacy Implications of CRRT
August 2020
Baxter Healthcare webinar/training

Optimization of Beta-lactam Dosing in Critically Ill Patients: Ready for Prime Time?
March 2020
Kentucky Society of Health-System Pharmacists Spring meeting
Lexington, KY

Renal Replacement Therapy in the ICU: What Every Intensivist Should Know
October 2019
American College of Chest Physicians. CHEST Annual Meeting
New Orleans, LA

Solutions in CRRT
October 2019
Acute Therapies Summit, sponsored by Baxter Healthcare.
New York, NY

Antibiotic Dosing Concepts in CRRT
October 2019
Acute Therapies Summit
New York, NY

Overcoming Challenges of Medication Dosing in CRRT
October 2019
Baxter Healthcare Webinar series

Solutions in CRRT
November 2018
Acute Therapies Summit
Louisville, KY

Medication Dosing in CRRT
November 2018
Acute Therapies Summit
Louisville, KY

Role of ionized magnesium in the care of the ICU patient:
July 2018
implications for point of care, pharmacy utilization and clinical outcomes.
NOVA Biomedical Webinar series

Development of an ICU-based Specialty Technician to Improve the
October 2018 *Medication Distribution Process.*
Kentucky Society of Health-System Pharmacists Fall meeting
Lexington, KY

Sepsis: Treatment Considerations and Case Review
October 2016
Highlands Regional Sepsis Summit
Prestonsburg, KY

What is the Future of Epinephrine in Cardiac Arrest?: Pros and Cons
June 2015
American Heart Association Strive to Revive Symposium
Lexington KY

Ketamine: A review of the Contemporary Uses of an Old Medication
October 2013
Kentucky Society of Health-System Pharmacist Fall meeting
Indiana

Effect of Etomidate on Adrenocortical Suppression:
April 2011
A Review of Intubated Septic Patient
Great Lakes Residency Conference
West Lafayette IN.

Management of Atrial Fibrillation in the Intensive Care Unit
October 2011
University of Kentucky College of Pharmacy Grand Rounds
Lexington, KY

Developing Contemporary Pharmacy Practitioners Through
April 2011 *Interprofessional Education*.
University of Kentucky College of Pharmacy Grand Rounds
Lexington, KY

LOCAL

Pharmacotherapy of Pain, Agitation and Sedation in the ICU
July 2014- 2017
University of Kentucky Pulmonary/Critical Care Fellows Noon Conference

Airway Pharmacology: Review of Medications used in RSI.
July 2014- 2017
University of Kentucky Pulmonary/Critical Care Fellows Noon Conference

Pharmacotherapy of Sepsis Treatment in the MICU.
2014- 2016
University of Kentucky Pulmonary/Critical Care medical intensive care unit nursing staff

Pharmacotherapy of Sedation in the MICU
2014- 2016
University of Kentucky Pulmonary/Critical Care medical intensive care unit nursing staff

Sepsis
October 2013
University of Kentucky pharmacy department.

Acute Alcoholic Hepatitis
October 2013
UK HealthCare Pharmacy Residency program

Interprofessional Roles on the HealthCare Team: A Focus on Pharmacy
November 2011 University of Kentucky Interprofessional Education and Health Care Seminar Series

Use of Fenoldopam in Calcineurin Inhibitor Induced Nephrotoxicity
August 2011 University of Kentucky College of Pharmacy Grand Rounds

Effect of Etomidate on Adrenocortical Suppression:
August 2011
A Review of Intubated Septic Patients
University of Kentucky College of Pharmacy Grand Rounds

Journal Reviews

12/09- Present Annals of Pharmacotherapy
Critical Care Medicine
American Journal of Health Systems Pharmacists
Hospital Pharmacy
Journal of Pharmacy Technology

Abstract Reviews

8/2017- Present Society of Critical Care Medicine
10/2019- Present American College of Clinical Pharmacy

Grant Reviews

2018- Present Society of Critical Care Medicine DISCOVERY and Weil Grants
2018- Present American College of Clinical Pharmacy Critical Care PRN Grants
2017 TL1 University of Kentucky Pre-Doctoral Training Program

Book Chapter Reviews

07/17- Present ACCP Critical Care Pharmacy Preparatory Review and Recertification Course
09/09 ASHP Pharm-Prep Reviewer for PCAT preparatory book

Media Interviews

"Medication Dosing in CRRT"
August 2020
Society of Critical Care Medicine iCritical Care Podcast

"Critical care pharmacist shares experience from pandemic frontlines"
May 2020
University of Kentucky media relations
https://ukhealthcare.uky.edu/wellness-community/blog/critical-care-pharmacist-shares-experience-pandemic-frontlines

"Model placing pharmacy techs in MICU solved medication issues, boosted morale"
Sept 2017
AphA Pharmacy*Today*
https://www.pharmacytoday.org/article/S1042-0991(17)31346-4/fulltext

ORGANIZATION MEMBERSHIP

05/18- Present NIH PETAL Network: Southeastern Clinical Center Site Co-investigator
01/16-01/17 Critical Care Trials Network, (CCPTN) Site Investigator

02/11- Present Society of Critical Care Medicine (SCCM):
SCCM Discovery Network Steering Committee (2018-2021)
SCCM Discovery Network collaborator (01/17- Present)
Section of Clinical Pharmacy Practice (CPP):
Research committee member Charge-1 lead (2017- present)
Programming committee member (2017- present)
Communications committee member (2012- 2013)

08/09- Present American College of Clinical Pharmacy, Member (ACCP): Critical Care and Practice & Research Network
ACCP Certification Affairs Committee (2019-2020) Charge: Develop mechanisms to identify ACCP member-experts who could be recommended by the College to serve on interprofessional guideline/consensus panels.
ACCP Public and Professional Relations Committee (2017- 2018) Charge: Provide a recommendation to the Board of Regents on methods to increase the number of ACCP members actively engaged in the work of NIH study sections, national guideline panels, and similar interprofessional work groups.
ACCP Publications Committee (2016- 2017) Charge: Develop a white paper summarizing the future roles of pharmacy technicians
ACCP Critical Care PRN: Research Committee member:
Research Committee Chair elect (2019- Present)
Resident grant charge lead (2018- 2019)

08/06- Present American Society of Health Systems Pharmacists, Member (ASHP)
02/08- Present Phi Lambda Sigma, Beta Chi Chapter, Member (PLS)
01/08- Present Kappa Epsilon Professional Pharmacy Fraternity, Member (KE)
08/06- 08/10 American Pharmacists Association, Member (APhA)
03/09- 05/10 MUSC Presidential Scholar
05/08- 12/08 Health Speakers Toastmaster: Member
08/08- 05/10 Student Public Health Interest Group Member
04/07- 05/10 MUSC Student Government Association, Member (SGA)

Residency Leadership
06/11- 07/12 Residency Executive Committee, UK HealthCare: Chair
06/11- 07/12 Resident Advisory Committee, UK HealthCare: Member
06/11- 07/12 UK College of Pharmacy Curricular Reform: Committee member
06/10- 07/11 UK Residency Class Social Planning: Committee member
06/10- 07/11 UK Residency Class Recruitment: Committee member
06/10- 07/11 UK Chandler Hospital House Staff Council Pharmacy: Resident Representative
06/10- 07/11 UK Pharmacy Education Advisory Committee: Resident Representative

HONORS AND AWARDS

10/20	Kentucky Society of Health-system Pharmacists Innovative Health-System Pharmacy Practice Award
12/19	SCCM CPP Innovations in Patient and Medication Safety Award
08/19	CHEST Foundation Diversity Travel Grant winner
06/17	UK HealthCare Quality and Safety Award
02/17	UK Women's Forum Employee Educational Assistance Award
01/17	Society of Critical Care Medicine Star Research Star Achievement Award
07/15	UK HealthCare Robert Rapp Pharmacist of the Year Award: Nominee
01/14	Society of Critical Care Medicine Research Citation Finalist Award
06/12	Outstanding Pharmacy Resident Award, UK HealthCare
04/11	Served as Chief Pharmacy Resident, UK HealthCare
05/10	Eli Lily and Company Award, MUSC-SCCP
05/10	Dean's List member 2007-10, MUSC-SCCP
04/10	Inducted into the MUSC Student Leadership Society
03/10	South Carolina Society of Health System Pharmacy Scholarship
05/09	Inducted as a MUSC Presidential Scholar
10/09	MUSC ASHP Clinical Skills Competition: First place winner and national competition participant
10/09	MUSC ASP Patient Counseling Competition: Top 10 finalist
10/09 2009-10	"Who's Who Among Students in American Universities and Colleges"
04/09	Phi Lambda Sigma, Chapter of the Year 2008-09
02/09	Phi Lambda Sigma, Beta Chi Chapter Member of the Year 2008-09
12/08 2008-09	"Who's Who Among Students in American Universities and Colleges"
11/08	MUSC ASHP Clinical Skills Competition: Third place winner
11/08	MUSC ASP Patient Counseling Competition: Top 10 finalist
01/08	NCBI Diversity Workshop for Student Leaders: invited participant
03/07 the	Cambridge Who's Who Among Executive and Professional Women in Pharmaceutical Industry "Honors Edition" 2007- 10
08/06	National Scholars Honor Society Member 2006-10

VOLUNTEER ACTIVITIES

07/10- present Lexington, KY:

UK COP Salvation Army clinic, pharmacist volunteer

Leader of a Youth Mission Trip to Bowery Mission, Eastland Church

Created the Outreach Committee within the UK Residency class which coordinated outreach and volunteer activities of the residents and UK pharmacists with the

community. Including volunteers to the UK Children's Hospital, Christmas letters to soldiers abroad, and local charities

08/06- 05/10 Charleston SC:

Health Exposition in rural Spanish speaking communities
Educated families during Poison Prevention month
Phi Delta Chi clothing drive
American Cancer Society Hope Lodge
CARES free medical clinic
Crisis Ministries free medical clinic
Holiday Lighting in the horseshoe- visitor to the Children's Hospital
Carolina Youth Development Center- Christmas Crawl
Trot for the Cure, canine cancer research event
"Shop for the Cure" Susan G. Komen fundraiser
Baskets for Breast Cancer- Hollings Cancer Center
Colleges of Charleston Relay for Life
Northwoods Clinic painted the medical clinic
American Red Cross blood drive volunteer

RESEARCH SUPPORT (ongoing)

ASHP Foundation: Pharmacy Resident Practice Advancement Grant ($5,000)
Barlow (Co-I)
01/20- /1-21
Funded
"Pharmacist-driven Fluid Stewardship in the Neurointensive Care Unit"
Role: Co-Investigator and resident advisor

ASHP Foundation: Practice Advancement Initiative Grant ($75,000)
Thompson Bastin (PI)
06/18- 06/20
Funded
Implementing a personalized medicine dosing protocol for beta-lactam antibiotics in critically ill patients with sepsis: a prospective observational sequential period pilot study
Role: Principle Investigator

RESEARCH SUPPORT (completed)

ASHP Foundation: New Investigator Research Grant ($20,000)
Bissell (PI)
05/18- 05/20
Funded
Implementation and Evaluation of Pharmacist-Managed Diuresis in the Intensive Care Unit

This practice-based study will assess a pharmacist-managed diuresis protocol in a medical ICU (MICU) on ventilator days, and ICU length of stay in patients with recovering shock.
Role: Co-Investigator

Faculty Resources Grant, University of Kentucky ($12,000)
Flannery (PI)
06/16- 06/20
Funded
Effect of Albumin Administration of Vasopressor Duration in Resolving Septic Shock
The goal of this study is to assess the effects of albumin on vasopressor duration in septic shock recovering from their illness.
Role: Co-Investigator

NIH/NHLBI: 1U01HL123027-01
Morris (UK Site PI)
07/14-04/20

Clinical Centers (CC) for the NHLBI Prevention and Early Treatment of Acute Lung Injury (PETAL) Clinical Trials Network (U01)

University of Kentucky is a sub-site to this network. The goal of this project is to promote health by prevention and treatment of acute lung injury through PETAL network participation and innovative protocols. Ongoing trials (ASTER). Completed trials (ROSE, VIOLET, CLOVERS).
Role: Site Co-Investigator (University of Kentucky)