Facilitating Antimicrobial Stewardship in the Outpatient Hemodialysis Setting

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ABSTRACT

Antimicrobial stewardship (AMS) encourages appropriate antimicrobial use to improve outcomes. Initiatives include preventing infection and optimizing antimicrobial use (i.e., right drug, dose, and duration). Infections are associated with significant morbidity and mortality among patients receiving hemodialysis. Although this population would benefit from AMS, initiatives are limited. In response, three studies were conducted.

The first was a study of hemodialysis bloodstream isolates (n = 1024). Pathogen distributions and antimicrobial susceptibilities were used to evaluate empiric antimicrobial combinations. Most isolates (>70%) were gram-positive. Using cefazolin over vancomycin reduced gram-positive coverage by >30%. Gram-negative coverage varied by <1%, with no advantage for broader agents, e.g., meropenem. These findings assist in optimizing empiric antimicrobial selection for bloodstream infections (BSIs) in the hemodialysis setting.

The second was a study of hemodialysis catheter-related exit-site infections (ESIs, n = 113) and BSIs (n = 64). The impact of new infection prevention measures on infection rates and risk factors for infection were evaluated. ESIs dropped by 60% with new measures, then increased slightly over time. BSIs declined by 85% over time, which was associated with new measures and reduced temporary catheter use. ESIs preceded one-third of BSIs. These findings highlight the necessity for ongoing surveillance, reinforcement of prevention measures, and strategies to address ESIs to reduce BSI risk.

The third was a pharmacokinetic study of cefazolin (n = 20) and ceftazidime (n = 18) in patients receiving hemodialysis. The pharmacokinetics, pharmacodynamics, and toxicodynamics were characterized and used to evaluate current dosing practices. For both drugs, the protein binding and volume of distributions were similar to other populations, while the elimination half-lives were >15-fold longer compared to patients with normal kidney function. In the cefazolin cohort, there was greater interindividual variation in half-life

attributed to residual kidney function. The analysis identified limitations in using a one-dose-fits-all approach. It highlighted the importance of considering residual kidney function, body weight, the interdialytic period, and pathogen susceptibility to optimize dosing. These findings can be used to develop adaptive dosing approaches that improve the treatment of infections in this high-risk population.

Given the lack of data, this work represents significant progress in facilitating AMS in the hemodialysis setting.

PREFACE

The initial proposal for this thesis was an expanded version of **CHAPTER 4**. However, due to the significant impact of the COVID-19 pandemic on clinical research, the study presented in **CHAPTER 4** was delayed and had to be scaled down. While clinical research was suspended during the pandemic, I, CK Lawrence, took on leading roles in two other relevant research studies, which are presented in **CHAPTERS 2** and **3**. Additionally, I conducted a study with SA Zelenitsky and collaborators titled *Adverse drug effects during community-based intravenous antimicrobial therapy*, which aligns with my area of interest in outpatient antimicrobial therapy. However, as the aims of this study did not align with the overarching theme of my thesis, it is not included.

A version of **CHAPTER 2** has been published in the Canadian Journal of Hospital Pharmacy. I obtained written permission from the Canadian Journal of Hospital Pharmacy to include this copyrighted article in this thesis. The article is titled *Clinical blood isolates from hemodialysis patients: distribution of organisms and antimicrobial resistance, 2007–2014* by CK Lawrence, C Sathianathan, M Verrelli, P Lagacé-Wiens, R Ariano, G Badejo, ML Boyce, JC Davis, and SA Zelenitsky (2020;73(4):266–71). Author affiliations are listed below. SA Zelenitsky was the principal investigator for this study. C Sathianathan, M Verrelli, P Lagacé-Wiens, R Ariano, and JC Davis facilitated the study, interpreted the results, and reviewed the manuscript. G Badejo and ML Boyce were undergraduate pharmacy students who performed data collection and summarized the preliminary results. I cleaned and analyzed the data, interpreted the results, and wrote the manuscript. This study did not require research ethics approval as the data were not linked to individual patients.

A version of **CHAPTER 3** has been published in the Journal of Vascular Access. Inclusion of this published article in my thesis meets the published "Sage's Author Archiving and Re-Use Guidelines". The article is titled *Impact of practice changes on catheter-related exit-site and bloodstream infection rates in a Canadian hemodialysis center: a retrospective study* by CK Lawrence, ML Boyce, S Weisensel, C Sathianathan, M

Verrelli, and SA Zelenitsky (2025;online ahead of print:1-7). Author affiliations are listed below. SA Zelenitsky was the principal investigator for this study. C Sathianathan and M Verrelli facilitated the study, interpreted the results, and reviewed the manuscript. ML Boyce and S Weisensel were undergraduate pharmacy students who performed data collection and summarized the preliminary results. I cleaned and analyzed the data, interpreted the results, and wrote the manuscript. Statisticians from the Biostatistics Group at the George & Fay Yee Centre for Healthcare Innovation and the Department of Community Health Sciences at the University of Manitoba assisted with statistical modelling. Research approvals were granted by the University of Manitoba Health Research Ethics Board (HS20491) and St. Boniface Hospital Research Review Committee (2017/1643), details of which are provided in **APPENDICES 3A** and **3B**, respectively. The Protocol and Data Collection Sheet used for this study are provided in **APPENDICES 3C** and **3D**, respectively.

The study presented in **CHAPTER 4** was the main focus of my thesis and has yet to be published. Originally, this study was to include a third antimicrobial, ciprofloxacin. However, due to significant delays related to the COVID-19 pandemic and low enrollment, we decided to discontinue the study of ciprofloxacin. SA Zelenitsky, my graduate advisor, was the principal investigator for this study and obtained funding through an Allied Health Research Grant from the Kidney Foundation of Canada. TM Lakowski was a co-principal investigator, and R Ariano, CJ Davis, DZ D'Argenio, W Luo, C Sathianathan, M Verrelli, and J Walters were other collaborators. Collaborator affiliations are listed below. CJ Davis, C Sathianathan, M Verrelli, and J Walters facilitated the study. TM Lakowski and W Luo led the pharmaceutical analyses. R Ariano and DZ D'Argenio were involved in the pharmacokinetic analyses. I obtained research approvals, enrolled patients, collected clinical data, oversaw blood sample collection, processed blood samples, assisted with pharmaceutical analyses, analyzed the data, including pharmacokinetic and pharmacodynamic analyses, interpreted the results, and wrote all documents. Research approvals were granted by the University of Manitoba Health Research Ethics Board (HS22503) and St. Boniface Hospital Research Review Committee (2019/1840), details of which are provided in **APPENDICES 4A** and **4B**, respectively.

This study is also registered on ClinicalTrials.gov (NCT04319328). The Protocol, Research Participant Information and Consent Form, and Data Collection Sheet used for this study are provided in **APPENDICES 4C, 4D,** and **4E**, respectively.

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Finally, I want to express my heartfelt gratitude to my family and friends for their endless support. A special thank you to my loving husband, Connor Joseph, for always believing in me. Without all of you, reaching this milestone would have been unimaginable.

DEDICATION

This thesis is dedicated to my parents, Cindy and Stephen Lawrence. I am sincerely grateful for everything you have done for me over the years. The values of perseverance, resilience, and a strong work ethic that you have instilled in me have been crucial in helping me reach where I am today.

TABLE OF CONTENTS

LIST OF TABLES

CHAPTER 2

Supplementary Tables

CHAPTER 3

Supplementary Tables

CHAPTER 4

Cefazolin

Ceftazidime

Supplementary Tables

Cefazolin

Ceftazidime

APPENDICES

LIST OF FIGURES

CHAPTER 2

Supplementary Figures

CHAPTER 3

Supplementary Figures

CHAPTER 4

Cefazolin

Ceftazidime

Supplementary Figures

Cefazolin

Ceftazidime

APPENDICES

LIST OF ABBREVIATIONS

ABW	Adjusted body weight
AMR	Antimicrobial resistance
AMS	Antimicrobial stewardship
AUC	Area under the concentration-time curve
AV	Arteriovenous
AVF	Arteriovenous fistula
AVG	Arteriovenous graft
BMI	Body mass index
BSI	Bloodstream infection
CANWARD	Canadian Ward Surveillance Study
CDC	Centers for Disease and Control
CPhA	Canadian Pharmacists Association
CL	Clearance
CLSI	Clinical and Laboratory Standards Institute
C_{max}	Maximum concentration
CoNS	Coagulase-negative staphylococci
COP	College of Pharmacy
CR	Catheter-related
CrCl	Creatinine clearance
CVC	Central venous catheter
DW	Dosing weight
ED	Equilibrium dialysis
EPS	Extracellular polymeric substances
ESBL	Extended-spectrum β-lactamase
ESI	Exit-site infection
ESKD	End-stage kidney disease
HD	Hemodialysis
iHFHD	Intermittent high-flux hemodialysis
IBW	Ideal body weight
IDSA	Infectious Diseases Society of America
IM	Intramuscular

IQR	Interquartile range
IRR	Incidence rate ratio
IS	Internal standard
IV	Intravenous
kg_{DW}	Kilograms based on dosing weight
KDOQI	Kidney Disease Outcomes Quality Initiative
LLOQ	Lower limit of quantification
LSS	Least sum of squares
MIC	Minimum inhibitory concentration
MIC_{90}	Minimum inhibitory concentration covering 90% of isolates tested
MRP	Manitoba Renal Program
MRSA	Methicillin-resistant *Staphylococcus aureus*
MS	Mass spectrometry
MSSA	Methicillin-susceptible *Staphylococcus aureus*
n	Sample size
NA	Information not available
N/C	Non-computable
NHSN	National Healthcare Safety Network
NOCHD	Nocturnal hemodialysis
PAR	Peak area ratio
PB	Protein binding
PD	Pharmacodynamic, pharmacodynamics
PK	Pharmacokinetic, pharmacokinetics
PSA	*Pseudomonas aeruginosa*
r	Pearson correlation coefficient
R^2	Coefficient of determination
rho	Spearman's correlation coefficient
RMSE	Root mean square error
SBH	St. Boniface Hospital
SD	Standard deviation
SDHD	Short daily hemodialysis
t½	Half-life

$t_{1/2_{off\text{-}HD}}$	Half-life between dialysis sessions
$t_{1/2_{on\text{-}HD}}$	Half-life during dialysis
TBW	Total body weight
TCPS 2: CORE	Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans Course on Research Ethics
TDM	Therapeutic drug monitoring
UF	Ultrafiltration
UHPLC	Ultra-high-performance liquid chromatography
UM	University of Manitoba
Vd	Volume of distribution
VRE	Vancomycin-resistant *Enterococcus* spp.
$\%fT_{>MIC}$	Percentage of time that free antimicrobial concentrations exceed a pathogens minimum inhibitory concentration

CHAPTER 1: Introduction

Preamble: This chapter aims to introduce the overarching themes and research objectives of this thesis. Also, to provide sufficient background information to support the scientific rationale for the research presented in **CHAPTERS 2, 3** and **4**. **REFERENCES** are merged at the end of this document. **APPENDICES 1A**, **1B**, **1C**, **1D, 1E,** and **1F** are referred to in this chapter.

1.1. Antimicrobial Stewardship

According to the World Health Organization, antimicrobial resistance (AMR) is one of the most serious threats to global public health.[1] In 2019, it was estimated that AMR resulted in or contributed to over 6 million deaths globally.[1] In addition to significant morbidity and mortality, AMR is also associated with increased healthcare spending. The World Bank predicts that without interventions to contain AMR, by 2050, annual healthcare expenditures could increase by 0.33–1.2 trillion US dollars globally.[2] AMR also threatens advancements in modern medicine, as without effective treatments for resistant pathogens, procedures such as surgery, cancer chemotherapy, and dialysis would come with significant risks.[1]

Unfortunately, over the past two decades, AMR has increased while the number of new antimicrobial agents making their way to the market each year has decreased.[3,4] Compared with drugs for chronic diseases, there is less commercial interest in developing antimicrobials for acute illnesses that threaten to become resistant. Antibiotic drug discovery has shifted to costly therapies that have a niche role in therapy. In treating multi-drug resistant infections, we rely upon last resort agents with well-defined toxicities, such as the detergent-like polymyxin colistin.[5] Penicillin, the first antimicrobial discovered in 1928, still has a significant role in clinical practice and is still considered the first-line agent for treating many infectious diseases.[4] Given the limited pipeline of new anti-infectives, existing antimicrobials are the mainstay for treating infectious diseases today and in the future. It is essential to develop strategies to preserve therapies such as penicillin before they are no longer effective.

As antimicrobial misuse and overuse are the main drivers in the development of AMR, promoting optimal use of antimicrobials can be considered one of the most important methods to combat resistance.[1,6] Suboptimal antimicrobial use not only drives AMR but can also threaten patient safety via increased toxicity, increased treatment failure resulting in infection-related morbidity and mortality, *Clostridioides difficile* infection, and longer hospital stay.[7] This is where antimicrobial stewardship (AMS) comes into play. AMS has been defined as "coordinated interventions designed to improve and measure the appropriate

use of antimicrobial agents by promoting the selection of the optimal antimicrobial regimens including dosing, duration of therapy, and route of administration."[8] The main goals of AMS are to improve patient outcomes and safety related to antimicrobial use while minimizing the development of AMR.[7,8] AMS initiatives aim to prevent or limit infection transmission or avoid unnecessary or suboptimal antimicrobial use. In the process, AMS may reduce healthcare costs associated with unnecessary or suboptimal antimicrobial use.[8] As the benefits of AMS have been well described in the literature and are broadly recognized, Accreditation Canada has included AMS as a required practice for hospitals in Canada.[9] Urgent calls for AMS have also been made in Canada's Federal Action Plan on AMR and Use.[10]

1.1.1. Optimal Antimicrobial Use

Optimal antimicrobial use involves initiating therapy only when indicated, appropriate selection and de-escalation, timely initiation and discontinuation, and optimal dosing.[7] Prescribers must clearly understand when antimicrobial treatment is required. Decisions should be directed by guidelines that utilize diagnostic criteria such as presenting signs and symptoms, point-of-care test results, or laboratory findings. Antimicrobials are not clinically indicated in certain situations, such as for uncomplicated asymptomatic bacteriuria and many upper respiratory tract infections.[11] When indicated, appropriate empiric therapy can be selected by considering patient factors (i.e., contraindications such as allergies or risk factors for resistant infections), most likely pathogens, and local resistance rates. Once available, culture and sensitivity results allow for the selection of targeted therapies that can often permit de-escalation from broader- to narrower-spectrum agents. For example, methicillin-sensitive *Staphylococcus aureus* (MSSA) would permit de-escalation from vancomycin to a more narrow-spectrum agent such as cloxacillin or cefazolin. Antimicrobials can also be de-escalated from intravenous (IV) to oral options when appropriate, which can reduce IV catheter-related (CR) infections, duration of hospitalization, and healthcare costs.[12]

Antimicrobial sensitivity is determined by *in vitro* minimum inhibitory concentration (MIC) testing, which determines the lowest antimicrobial concentration required to inhibit the visible growth of bacteria.[13,14] Notably, the minimum bactericidal concentration, the lowest concentration needed to kill bacteria, can be four to five times higher than the MIC. MIC breakpoints were developed to translate this information to clinical practice, determining if a specific antimicrobial would effectively treat a particular pathogen and infection type based on the MIC result. A MIC at or below the susceptible breakpoint implies that the pathogen should be inhibited using recommended doses based on the typical achievable concentrations at the site of infection. An intermediate result indicates microorganisms with MICs that may be above achievable concentrations at the site of infection. However, clinical efficacy may be possible if higher doses are used or the antimicrobial concentrates at the infection site. A resistant result implies that clinically achievable concentrations are unlikely at recommended doses, resistance mechanisms are present, or clinical studies have not established consistent efficacy.

Another aspect of optimal antimicrobial use, timely initiation of treatment, can be critical for treatment outcomes, especially for severe infections. For example, delaying treatment for meningitis or septic shock can significantly increase the risk of morbidity and mortality.[15] Timely discontinuation is also essential to reduce unnecessary antimicrobial exposures. As such, antimicrobials should be used for the shortest effective duration. Increasing evidence has shown that shorter treatment durations are non-inferior to longer durations for infections such as Gram-negative bloodstream infections, pyelonephritis, community-acquired pneumonia, and intraabdominal infections.[16]

1.1.1.1. Optimal Antimicrobial Dosing:

Optimal antimicrobial dosing has improved effectiveness, safety, and survival in patients with severe infections.[17–20] Optimal dosing is established based on pharmacokinetics (PK), which describes drug concentrations in patients over time and pharmacodynamics (PD), which defines relationships between

drug concentrations and response.[17,18] Evidence-based, PKPD-directed, antimicrobial dosing optimizes antibacterial activity, thereby maximizing microbiological and clinical cures while minimizing the risks of toxicity and AMR.[21,22] PKPD methods are used in drug development to determine MIC breakpoints and to adjust dosing in special populations (e.g., obesity, kidney dysfunction, critically ill).

Parameters such as half-life ($t_{1/2}$), volume of distribution (Vd), and protein binding are used to mathematically describe the PK of drugs.[13,23,24] These parameters are specific to each drug and can vary extensively between patient populations. Protein binding describes the fraction of drug bound to plasma proteins, primarily albumin.[13,23,24] Protein binding is significant as only unbound or "free" drug is typically pharmacologically active. Small changes in protein binding (e.g. due to hypoalbuminemia) can have substantial impacts on the unbound concentrations of highly protein-bound antimicrobials such as ceftriaxone (>85%), ertapenem (95%) or clindamycin (>85%).[14]

The elimination $t_{1/2}$ describes the time for drug concentrations to decrease by 50%. Drugs are primarily excreted into the urine as unchanged drug by the kidney or metabolized by the liver.[13,14,23,24] Changes in kidney and liver function can affect the $t_{1/2}$ of drugs depending on their primary routes of elimination. Notably, kidney function naturally declines with age. Many antimicrobials are excreted unchanged in the urine. Therefore, kidney function must be considered to optimize dosing adjustments.

The Vd describes the apparent volume a drug distributes within the body and can be determined from the dose (mg), the extent of absorption or bioavailability, and the resulting concentration (mg/L). The Vd is highly dependent on a drug's chemical characteristics, including hydrophilicity and lipophilicity. Highly lipophilic drugs often have large Vd as they can more easily pass through the lipid bilayers of cell membranes. Generally, males have a higher percentage of lean muscle mass, while females tend to have a higher percentage of adipose tissue. This results in differences in Vd. Obese patients may have higher Vd; however, dose requirements do not increase linearly with weight. This is attributed to a higher relative

increase in adipose tissue compared to lean body mass. The Vd of drugs into both muscle and adipose tissue is unequal. Therefore, adjustment factors are used to adjust dosing based on the properties and predicted Vd of drugs into different types of tissues.

Moreover, three main PKPD indices are predictive of antimicrobial efficacy: the ratio of peak concentration to a pathogen's MIC (C_{max}/MIC), the ratio of exposure or area under the concentration-time curve to MIC (AUC/MIC), and the percentage of time that free drug concentrations exceed a pathogens MIC (%fT$_{>MIC}$).[14,18,25] Generally, PKPD indices are identified in pre-clinical studies using *in vitro* dynamic or *in vivo* animal infection models, which may be later validated in a clinical setting.[26,27] Importantly, achieving these targets has been shown to improve clinical cure and survival in patients with infection.[28–34]

An understanding of these PKPD indices can be used to optimize various antimicrobial regimens. For example, as β-lactam efficacy is predicted by %fT$_{>MIC}$, therapies can be optimized using shorter dosing intervals or prolonged or continuous infusions as they extend the time drug concentrations exceed a pathogens MIC over a dosing interval. This has been demonstrated in a clinical setting where stepwise increases in meropenem %fT$_{>MIC}$ resulted in stepwise increases in the probability of clinical response in febrile neutropenic patients with bacteremia.[19] McKinnon *et al.* also demonstrated that optimal microbiological and clinical cure was achieved when cefepime and ceftazidime %fT$_{>MIC}$ exceeded 100% in patients with severe infections.[20] As for resistance suppression, limited data has shown that targeting β-lactams concentrations greater than four times a pathogens MIC for extended durations may be most appropriate.[25]

The PKPD describing antimicrobial toxicity, or toxicodynamics, is less clear. As an example, cephalosporins have been associated with neurological effects, including confusion, dizziness, agitation, hallucinations, and seizures that appear to be concentration-related.[35–37] A study of cefepime toxicity described a 50% increase in the risk of neurotoxicity with trough concentrations >22 mg/L.[36] Neurotoxicity

has primarily been reported in patients with kidney impairment and those on dialysis, attributed to reduced drug elimination.[38–46] This example highlights the need for optimal dosing adjustments in those with reduced kidney function.

In practice, the most basic dosage adjustments can be performed when evidence exists on how clinical covariates (e.g., body weight and kidney function) influence PK.[47] Further, evidence-based nomograms are used to simplify dosage adjustments.[48] While nomograms are superior to standard dosing, they do not incorporate all possible covariates.[49] Unfortunately, in special populations, body weight and kidney function alone often cannot fully describe the complex PK and PD changes that occur. These patients experience variability in PK between patients and within a patient during different stages of their disease.[50] In addition, during the drug development process, special populations are poorly represented in clinical studies. Therefore, post-market studies in these groups have a prominent role in describing the PKPD changes and dosing required to maintain optimal outcomes.[50,51]

Therapeutic drug monitoring (TDM) is another helpful tool for individualized dosage adjustment, especially in special populations. TDM is particularly useful in antimicrobial pharmacotherapy as there are no measurable immediate and direct effects as with other conditions (e.g. blood pressure monitoring for hypertension).[50] TDM is most beneficial for antimicrobials that display significant intra and inter-individual PK variability, have a well-defined therapeutic range (i.e., for efficacy and toxicity), and have the availability of an accurate and timely bioanalytical method.[49] Recently, TDM has expanded from antimicrobials monitored for toxicity, i.e., the aminoglycosides and vancomycin, to include other antimicrobials monitored for efficacy.[47] TDM has become a standard of care in many intensive care units, not only for aminoglycosides and vancomycin but also for β-lactams, linezolid, teicoplanin, and voriconazole.[49,51] Richter *et al.* showed that in critically ill patients, 10% were underdosed, and 30% were overdosed. However, with the implementation of TDM, target attainment significantly improved from 34%

to 62%.[52] Also, clinical benefits of TDM have been described for gentamicin and voriconazole and exceed that of clinical cure, including reduced duration of therapy, length of stay, toxicity, and mortality.[49]

Overall, there are significant opportunities to extend the benefits of PKPD to existing antimicrobials and special patient populations. Optimal antimicrobial dosing is crucial for the latter where appropriate adjustments are needed to maintain efficacy, mitigate toxicity risk, and reduce AMR development.[47]

1.2. Dialysis for End-Stage Kidney Disease

Dialysis is a lifesaving treatment that replaces kidney function by removing waste and fluid from the body. Dialysis is most often utilized by patients with end-stage kidney disease (ESKD) but may be necessary for patients with acute kidney injury, medication-resistant fluid overload, or toxic ingestions.[53–55] ESKD is most commonly caused by diabetes, followed by hypertension, and glomerulonephritis.[55] Patients with ESKD have lost over 85% of their kidney function. Patients require dialysis once medication can no longer manage fluid overload or uremic symptoms (e.g. nausea, vomiting, fatigue, severe itch) caused by the accumulation of urea in the body.[55]

There are two main types of dialysis: hemodialysis (HD) and peritoneal dialysis.[55] HD machines filter blood through a porous dialysis membrane called a dialyzer. Pressure and concentration gradients between blood and dialysate (cleaning fluid) flowing on opposite sides of the dialyzer removes waste and fluid. Typically, patients receive 4-hour HD treatments thrice weekly. HD requires direct access to the bloodstream, which is achieved through the creation of vascular access sites. These sites can be established using a central venous catheter (CVC), an arteriovenous (AV) graft (AVG), or an arteriovenous fistula (AVF). A CVC may be permanent and tunnelled under the skin (i.e., cuffed), or temporary and uncuffed. AVFs and AVGs involve surgical procedures that connect an artery and a vein to create an area with high blood flow.

Alternatively, peritoneal dialysis utilizes the peritoneal membrane in the abdomen to filter waste and fluid from the body. Patients undergoing peritoneal dialysis administer approximately 2 litres of dialysate into their peritoneal cavity through a catheter in their abdomen. Concentration gradients allow waste and fluid in the blood to move across the peritoneal membrane into the dialysate in the peritoneal cavity. The dialysate is exchanged four to five times during the day for continuous ambulatory peritoneal dialysis or is exchanged multiple times overnight through an automated peritoneal dialysis machine called a cycler. Of note, peritoneal dialysis will not be discussed further.

Patients with ESKD receiving chronic dialysis are classified as a high-risk population by the Centre for Disease Control and Prevention (CDC), along with other immunosuppressed populations such as patients undergoing organ transplants, cancer chemotherapy, and treatment for rheumatoid arthritis.[56] These patients are at high risk of developing infection including AMR infections, as well as infection-related morbidity and mortality. The procedures and treatments required by these patient populations would be extremely risky without effective antimicrobial therapy.

1.2.1. Risk Factors for Infection

Patients receiving chronic HD are particularly susceptible to infectious diseases and infection-related morbidity and mortality. A case-control study showed that patients receiving HD had a relative risk of 2.4 (95% CI 1.8–3.2) for developing hospital-acquired infections compared to healthy controls.[57] They are particularly susceptible due to vascular access required for HD, immunodeficiencies associated with ESKD, multiple co-morbidities, and frequent exposure to pathogens in healthcare settings.[56,58–62]

Vascular access remains one of the most significant risk factors for infection in patients receiving HD.[63] CVCs predispose patients to exit-site infections (ESIs) and bloodstream infections (BSIs). While less severe, ESIs are a notable risk factor and source of bacteremia in patients receiving HD.[2] AVFs or AVGs are preferred over CVCs, which are more prone to complications, including infection.[2,7–11] Infection risk is even higher in temporary versus permanent CVC and those inserted in the lower extremities.[64,65] Higher infection risk associated with catheters is logical as they remain in place between HD sessions, providing a direct route for pathogens to enter the body and a foreign object to adhere to (i.e., biofilms). Nevertheless, CVCs are an essential option that may be more feasible, preferred by the patient, or required to start HD urgently.[10,11]

Immunodeficiencies due to ESKD further predispose HD patients to infection. Immune dysfunction in ESKD is complex and not fully understood; however, it is thought to involve both immune activation and suppression, partly attributed to uremia.[66] Immune activation contributes to chronic inflammation, leading to cardiovascular problems which is the leading cause of mortality in this population. In contrast, immune suppression predisposes to infection which is the second leading cause of mortality in this population.[66,67]

As diabetic nephropathy is the leading cause of ESKD, many HD patients also suffer from other diabetic complications. Neuropathy increases the risk of injury, while peripheral vascular disease delays wound healing.[68] People with diabetes also have impaired immune responses as a result of factors including decreased neutrophil chemotaxis, phagocytosis, intracellular bactericidal activity, and cell-mediated immunity.[69] In fact, a meta-analysis by Guo *et al.* found that patients with diabetes undergoing HD had significantly higher odds of developing CR-BSIs (odds ratio 2.52, 95% CI 1.95–3.25).[70]

Autoimmune conditions are another notable cause of ESKD, and in these cases, immunosuppressive medications are often required. In a study by Hoen *et al.,* receipt of immunosuppressive therapy was associated with a higher risk of BSI (relative risk 3.0, 95% CI 1.0–6.1).[71] In general, a greater Charlson comorbidity index has also been significantly associated with the development of infections in the HD population.[57]

Frequent contact with healthcare settings also predisposes HD patients to infection.[72,73] Most patients receive HD thrice weekly in outpatient units. Without perfect hygiene and infection control measures, pathogens may be transmitted between patients. In addition to HD treatments, patients also commonly require surgeries to gain vascular access and are frequently hospitalized due to their complicated health status.[74] Notably, Fram *et al.* identified that previous hospitalization was associated with a 6.6-fold risk of developing a BSI in the HD setting.[75]

1.3. Infections in the Outpatient Hemodialysis Setting

1.3.1. Types and Incidence

The most common infections in the outpatient HD setting are related to vascular access. AV access infections range from mild cellulitis to BSI.[76] Signs and symptoms include redness, discharge that may be purulent, skin breakdown, and exposed graft for those with AVG.[76] Whenever possible, culture and sensitivity results are recommended to direct treatment.[76] Imaging is occasionally used to corroborate the diagnosis and determine the extent of AV access involvement.[76] Metastatic complications such as BSI, endocarditis, spinal abscess, and septic arthritis are closely monitored, particularly for infections caused by high-risk pathogens, including *S. aureus* and fungi.[76]

CVC-related infections include BSIs and ESIs that may extend to tunnel infections. As discussed above, culture and sensitivity results and monitoring for metastatic complications are recommended.[76] Standardized definitions for CVC-related infections exist to enable consistent reporting. The CDC, IDSA, and National Kidney Foundation have proposed several definitions. Based on the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines by the National Kidney Foundation, CR-BSI requires the following criteria: clinical manifestations (e.g., fever, chills, hemodynamic instability, CVC dysfunction, hypothermia, nausea, vomiting, or malaise), no other apparent source of infection, at least one positive peripheral blood culture, and a positive culture from the CVC hub, tip, or segment of the same organism isolated peripherally.[76] KDOQI define a CR-ESI as hyperemia, induration, or tenderness ≤2 cm from the CVC exit-site with or without drainage or concurrent BSI. CR-ESIs may extend to tunnel infections which are defined as tenderness, hyperemia, or induration that extends along the subcutaneous tunnel with or without drainage or concurrent BSI.

BSIs are the most severe dialysis-related infections, as they result in substantial morbidity and mortality.[61] Published infection rates are variable due to differences in patient populations, vascular access type, infection control, and infection definitions. In the United States, 119 patients receiving HD with various

access types were observed for infection over 16 years; the overall infection rate was 2.1 per 1000 days with a BSI rate of 0.44 per 1000 days.[77] Notably, additional studies have reported significantly higher rates of BSI in patients with CVC (0.26–1.86 per 1000 days)[62,78–84] than those with AVG (0.13–0.25 per 1000 days)[62,83] or AVF (0.09 per 1000 days)[62,83].

Infections in patients receiving HD are not limited to vascular access-related infections. Other common infections include skin and soft tissue infections, pneumonia, urinary tract infections, and *C. difficile* infections.[57,77,85] A study by Berman *et al.* reviewed infections in 433 patients receiving HD over nine years; the overall infection rate was 5.7 per 1000 days, with over 82% of infections acquired in the community.[85] The most common infections were vascular access-related (20.5%), followed by below-the-knee infections (19.3%), pneumonia (13%), and other skin and soft-tissue infections (9%). Diabetes was the cause of ESKD in 56% of patients, notably, the infection rate in this cohort was higher compared to those without diabetes (6.72 versus 4.79 per 1000 days, respectively). The higher infection rate in those with diabetes was primarily due to a higher rate of below-the-knee infections and other skin and soft tissue infections.

As mentioned previously, patients requiring dialysis often face hospitalization due to their complicated health status.[74] In a matched case-control study, nosocomial infections were significantly more frequent in the HD versus the non-HD group (relative risk 2.4, 95% CI 1.8–3.2).[57] Urinary tract infections were the most common nosocomial infections in the HD group, with a rate of 4.2 per 1000 days. The rate of *C. difficile* infection was 0.6 per 1000 days in the HD group, which was significantly higher than the non-HD group (relative risk 3.6, 95% CI 0.7–11). *C. difficile* infection may be more prevalent in the HD population due to frequent antimicrobial use and healthcare exposures.

1.3.2. Microbiology

As vascular access is the primary source for BSI in the outpatient HD setting, BSIs are most often associated with gram-positive skin flora, primarily staphylococci, followed by gram-negative bacteria and occasionally yeast.[62] Gram-positive bacteria account for approximately 60%–75% of BSI in the outpatient HD setting, compared to approximately 50% in the general population.[62,81,83,86,87] The etiology differs from other populations where gram-negative bacteria (e.g., *Escherichia coli*) from urinary or gastrointestinal sources are more common. BSIs in patients receiving HD is most often associated with *S. aureus*, accounting for 28%–44% of infections, while *E. coli* only accounts for 1%–13% of infections.[62,79,81,83,87,88] In a study of blood isolates from Canadian hospitals, *E. coli* was the most common, accounting for 22.6% of isolates, while *S. aureus* accounted for 17.7%.[86] Moreover, the microbiology of BSIs and superficial vascular access-related infections such as ESIs are similar, with gram-positive skin flora accounting for most infections.[78,83]

Common pathogens in the HD population are associated with resistance concerns, such as methicillin-resistant *S. aureus* (MRSA), vancomycin-resistant *Enterococcus* spp. (VRE), extended-spectrum β-lactamase (ESBL) producing Enterobacterales, and multidrug-resistant *Pseudomonas* spp. and *Acinetobacter* spp.[56,89] Notably, higher rates of AMR have been reported, attributed to healthcare exposures, high infection rates, frequent and long-term antimicrobial use, and indwelling catheters.[85] For example, the incidence of invasive MRSA infections among patients receiving dialysis was reported to be 100-fold higher than the general population.

Similarly, for the same reasons listed above, high colonization rates with AMR organisms have been reported in the HD population.[72,73] Notably, colonization with AMR organisms can significantly increase the risk of developing AMR infections. Studies in the HD population have shown that colonization with VRE increased the risk of VRE infection up to 22 times.[72,73,90] VRE colonization was linked to recent

antimicrobial use and hospitalization.[73,90] Similarly, colonization with MRSA increased the risk of MRSA infection up to 11 times.[72,73,91]

Resistance rates in the outpatient HD setting are variable and depend on timeframe and location. Studies of BSIs in patients receiving HD have reported MRSA rates of 10%–14% in Canada and Australia[83,88], 40%–46% in the United States[62,81], and 0% in Denmark[87]. A Canadian study reported no cases of VRE between 1998 and 1999[88], whereas more recent studies in Australia and the United States have reported rates of 11%–22%[62,81,83]. In studies from Australia and the United States, reported rates of *E. coli* resistant to 3rd generation cephalosporins were 9%–18%.[62,81,83] Compared to the general population, a study of blood isolates from Canadian hospitals reported a 24.4% MRSA and 4.6% VRE rate, with 6.5% of *E. coli* resistant to ceftriaxone.[86]

1.3.3. Management

The general treatment approach for vascular access-related infections includes antimicrobial therapy and source control. Monitoring for metastatic complications and infection persistence or recurrence is also critical. Antimicrobial treatment includes initial empiric selection based on the most likely pathogens and local resistance patterns, followed by targeted selection directed by culture and sensitivity results. The treatment duration is individualized based on the offending pathogen(s), infection severity and extent, and source control.

Due to the presence of biofilms, device removal (i.e., CVC or AVG) may be warranted for source control. Biofilms are highly treatment-resistant, resulting in persistent or recurrent infections, metastatic spread of disease, and increased morbidity and mortality.[92–95] Biofilms form when organisms firmly adhere to a surface by producing a slimy matrix of extracellular polymeric substances (EPS), mainly composed of polysaccharides.[96–98] Organisms within a biofilm often have low metabolic activity, while those on the

surface may detach and disseminate. These factors complicate treatment.[92,96–98] First, the strong EPS matrix protects pathogens from immune cells and also limits the penetration of antimicrobials. Another challenge is that many antimicrobials target processes occurring in growing and metabolically active pathogens.

For AV access infections, the recommended treatment includes timely initiation of systemic empiric broad-spectrum antimicrobial therapy covering gram-positive and gram-negative pathogens, followed by targeted therapy directed by culture and sensitivity results.[76] Treatment duration is individualized and may extend up to 6 weeks.[76] Surgical intervention is determined based on the offending pathogen(s), infection severity and extent, AV access type, and future HD vascular access options. AVG infections can rarely be treated with antimicrobials alone because source control becomes nearly impossible once the prosthetic material becomes infected.[76] A CVC may need to be inserted during treatment until the infection resolves or a new AV access can be established.[76]

For CR-ESIs, the recommended treatment includes topical or systemic empiric antimicrobial therapy with gram-positive coverage followed by targeted therapy directed by culture and sensitivity results for a total of 7–14 days.[76,99] Generally, ESIs do not require CVC removal.[76] As CR-tunnel infections are typically more extensive, recommended treatment includes systemic empiric antimicrobial therapy covering gram-positive and gram-negative pathogens followed by targeted therapy directed by culture and sensitivity results for a total of 10–14 days.[76,99] If the infection is not effectively treated with antimicrobials, it is recommended to exchange the CVC over a guidewire at the same site with a new tunnel, or if not possible, CVC removal and replacement at a new site.[76,99]

For CR-BSI, the recommended treatment includes immediate initiation of systemic empiric broad-spectrum antimicrobial therapy covering gram-positive and gram-negative pathogens.[76,92,99] Empiric antimicrobial therapy is followed by targeted therapy directed by culture and sensitivity results. Treatment durations are individualized and depend on source control. Guidelines recommend 2–6 weeks for *S. aureus*, 1–3 weeks

for gram-negative bacilli, coagulase-negative staphylococci (CoNS), or enterococci, and ≥2 weeks for *Candida* spp.[76,92,100] Optimal source control involves CVC removal and replacement at a new site.[76] After removing an offending CVC, a temporary CVC may be inserted to delay the placement and prevent contamination of a new permanent CVC.[76] As less effective, CVC exchange over a guidewire at the same site or CVC salvage are only used when necessary (e.g., vascular access options have been exhausted).[76] CVC removal is encouraged in the presence of clinical or hemodynamic instability, fever or bacteremia persisting after 48–72 hours of effective antimicrobial therapy, recurrence, metastatic complications, tunnel infections, and the following virulent or difficult-to-eradicate pathogens: *S. aureus*, *Pseudomonas aeruginosa*, mycobacteria, fungi, *Bacillus* spp., micrococci, or cutibacteria.[76,92,99–101]

Antimicrobial CVC lock solutions administered into catheter lumens between HD sessions have been used to improve CVC salvage and prevent contamination of newly placed CVCs.[76,92,99,100,102] Success rates for CVC salvage with antimicrobial lock solutions vary from 87% to 100% for gram-negative pathogens, 75% to 84% for *S. epidermidis,* and only 40% to 55% for *S. aureus*.[92] Antimicrobial concentrations must be 100 to 1000 times higher than required for systemic antimicrobial treatment to kill bacteria within a biofilm. Therefore, antimicrobials in CVC lock solutions are highly concentrated.[92] Examples of catheter lock solutions used locally by the Manitoba Renal Program (MRP) include cefazolin 5 mg/mL with heparin 2500 units/mL, gentamicin 2.5 mg/mL in 4% sodium citrate, and vancomycin 2.5 mg/mL in 4% sodium citrate (**APPENDIX 1A**).[100]

As far as empiric antimicrobial selection for CR-BSI, clinical practice guidelines recommend broad gram-positive coverage with vancomycin plus gram-negative coverage based on local susceptibility data (i.e., a third-generation cephalosporin such as ceftazidime, a carbapenem, or a β-lactam/β-lactamase combination such as piperacillin-tazobactam).[92] Cefazolin is listed as an alternative to vancomycin in HD units with a low prevalence of MRSA.[92] Targeted antimicrobial selection is directed by culture and sensitivity results. For example, cefazolin alone would be used for MSSA and CoNS. In contrast, vancomycin alone would be

used for severe cefazolin allergy and MRSA and CoNS. For gram-negatives, de-escalating to the safest narrow-spectrum agent is best practice. The empiric and targeted treatment protocols used locally by the MRP are included in **APPENDIX 1A**.[100] Generally, vancomycin plus tobramycin is used empirically. Ceftazidime is suggested as an alternative to tobramycin for aminoglycoside allergies or to prevent toxicity (i.e., aminoglycloside-associated otovestibular toxicity or nephrotoxicity in those with acute kidney injury).[100]

1.3.4. Implications

In the outpatient HD setting, infectious diseases are associated with significant morbidity and mortality. The United States Renal Data System 2023 report states that infectious causes were the second leading cause of mortality in patients with ESKD receiving HD, second only to cardiovascular causes.[103] A study by Berman *et al.* reported that 44% of community-acquired infections in dialysis patients resulted in hospitalization.[85] The USRDS states that in 2021, infections were responsible for 0.34 hospital admissions per person-year, a burden similar to cardiovascular causes at 0.40 admissions per person-year.[103]

In particular, BSIs in the dialysis setting are associated with high treatment failure rates, poor clinical outcomes, and substantial healthcare costs.[83] Significantly, BSIs can also compromise vascular access and lead to metastatic complications.[104] Compared to the general population, sepsis-related mortality has been reported to be 100 to 300 times higher in dialysis patients.[105] Risk factors for BSI-associated morbidity and mortality in patients receiving HD were investigated by Fram *et al.* in a nested case-control study.[75] BSI caused by *S. aureus* was associated with an 8.7 times higher risk (95% CI 2.5–30.1) of death or hospitalization, while BSI caused by multi-drug resistant organisms increased morbidity and mortality by 2.75 times (95% CI 1.0–7.5). Failed CVC salvage, hypoalbuminemia, and infected exit-sites have also been associated with an increased mortality risk.[61] Even though less severe, the implications of ESI are significant as they increase the risk of BSI.[58,106]

1.4. Antimicrobial Stewardship in the Outpatient Hemodialysis Setting

AMS has become a high priority in healthcare, demonstrated by the exponential increase in the number of publications relating to AMS over the past decade.[107] However, AMS initiatives in the outpatient HD setting have been limited, even though this population would greatly benefit from AMS. This is an area where future research and efforts should focus.[6,108–110]

One of the most effective AMS strategies to reduce the burden of infection is prevention. Most AMS initiatives in the outpatient HD setting have been related to infection prevention.[73] Optimal infection control practices are fundamental in the HD population to prevent CR-infections. The KDOQI guidelines endorse vital interventions recommended by the CDC to reduce infection rates and complications in patients requiring dialysis; these include: (1) infection surveillance with feedback, (2) optimal hand hygiene, (3) optimal vascular access care, (4) staff education and competency, (5) patient education and engagement, (6) reduction in CVC use when possible, (7) chlorohexidine for skin antisepsis, (8) CVC hub disinfection, and (9) preventative use of topical antimicrobials.[76,99]

A recent systematic review by Lazarus *et al.* demonstrated that over 80% of interventional studies aimed at preventing CR-BSIs had favourable outcomes.[111] One example of success was a CDC-sponsored initiative aimed at preventing BSI.[112] Seventeen HD units in the United States implemented an evidence-based intervention bundle that included catheter care, staff training and competency assessments, hand hygiene, vascular access care audits, and infection surveillance and feedback. Results comparing the 12-month pre-intervention and 15-month post-intervention periods showed a 54% decrease in vascular access-related BSIs. Another multicentre study in 422 HD facilities demonstrated decreased CR-BSI with a “scrub the hub” disinfection protocol.[80] The intervention was associated with a 21% reduction in CR-BSI, a 22% reduction in antimicrobial starts, and a 27% reduction in the rate of sepsis-related hospitalization.

Many observational studies have identified other areas where AMS can be improved in the outpatient HD setting. Snyder *et al.* assessed the appropriateness of 926 antimicrobial doses administered to patients receiving HD in the United States.[113] Almost one-third were deemed inappropriate, mostly because antimicrobial use was not or no longer indicated based on guidelines. Also, many inappropriate cases were associated with failure to de-escalate therapy, often for MSSA infections where vancomycin should have been stepped down to cefazolin, a more narrow-spectrum agent with increased activity. Inappropriate vancomycin use in this population, primarily due to failure to de-escalate therapy, has also been described by Zvonar *et al*.[114] A second study by Snyder *et al.* identified that almost 58% of patients receiving chronic HD and antimicrobial treatment received at least one inappropriate antimicrobial dose.[115] Similarly, Hui *et al.* assessed the appropriateness of antimicrobial regimens prescribed to patients receiving HD.[116] Overall, 29% and 21% of oral and IV regimens, respectively, were deemed inadequate. An inadequate classification was due to an incorrect dose or frequency for 87% of oral and 68% of IV regimens. Al Himali *et al.* also reported frequent inappropriate antimicrobial dosing (29.5%) in patients receiving HD.[117]

A model presented by D'Agata *et al.* predicted that implementation of AMS programs in outpatient HD settings on a national level in the United States would result in 2182 fewer multi-drug-resistant infections, a 4.8% reduction in *C. difficile* infections, a 4.6% reduction in infection-related deaths, and a 5% reduction in healthcare costs (assuming a 20% reduction in inappropriate antimicrobial use).[118] A study published by the same author demonstrated a 54% reduction in antimicrobial use following the implementation of AMS programs in six outpatient HD units, with no adverse effects.[119,120]

Still, there are many challenges when executing and evaluating AMS in the outpatient HD setting. As this population is at high risk of infection-related morbidity and mortality, prescribers may air on the side of caution and initiate antimicrobials when infection is suspected rather than confirmed. This may subsequently increase inappropriate use where antimicrobials may not be indicated based on guidelines. Another challenge is the lack of data describing resistance patterns in HD units, especially in Canada. This

information is beneficial to guide empiric antimicrobial selection. Also, drug choice is limited to agents with associated data supporting dosing adjustments, to ensure safety and efficacy in this population. During the drug development process, special populations, such as patients receiving HD, are poorly represented in clinical studies. Therefore, post-market studies have a prominent role in describing PK and PD alterations and, subsequently, dosing requirements to maintain optimal outcomes.[50,51] Thus, without high-quality data, dosing guidelines are extremely variable, and choosing the "right regimen" remains controversial.

1.4.1. Infection Surveillance: An Introduction to CHAPTERS 2 and 3

Infection surveillance is vital in the outpatient HD setting. Surveillance of causative organisms and resistance can inform the selection of empiric antimicrobial therapies before obtaining culture and sensitivity results. This is essential as prompt initiation of effective therapy improves clinical outcomes. Despite the value of microbiological surveillance, studies in patients receiving HD are limited,[62,81,83,87] and there are no current data for Canada. In addition, surveillance of infection rates can assess the effectiveness or need for infection prevention measures. Whereas programs such as the National Healthcare Safety Network (NHSN) Dialysis Event Surveillance and ESKD Quality Incentive Program are available to support surveillance in the United States[81,112], coordinated efforts and access to longitudinal surveillance data in Canada are limited.

In response, two surveillance studies were conducted to facilitate AMS in the outpatient HD setting. **CHAPTER 2** presents a retrospective study of bloodstream isolates from patients receiving HD. The objective of this study was to use the distribution of pathogens and their antimicrobial susceptibilities to evaluate microbiological coverage for empiric antimicrobial regimens that are recommended to treat BSIs. **CHAPTER 3** presents a retrospective study of CR-ESIs and CR-BSIs in an outpatient HD unit. Notably, the study period was selected to coincide with the implementation of new CR-infection prevention measures

at the midpoint. The objective of this study was to evaluate the impact of practice changes on infection rates as well as identify modifiable risk factors for infection.

1.4.2. Optimal Antimicrobial Dosing: An Introduction to CHAPTER 4

Unfortunately, patients receiving HD are more likely to fail antimicrobial therapy, resulting in infection-rated morbidity and mortality.[72,73] In addition to reduced immune function, therapy is complicated by the effects of ESKD and HD on antimicrobial PK. The elimination of drugs that are primarily excreted by the kidneys is decreased considerably in ESKD. During HD, the elimination depends on drug properties, with more efficient removal of small hydrophilic drugs with low protein binding and small volume of distribution (Vd). Factors including HD duration, dialyzer type, and blood and dialysate flow rates influence drug removal. Relatively newer high-flux dialyzers have larger pores, allowing larger drugs to pass.[121] Therefore, dosing recommendations based on studies of low-flux HD, may need to be empirically increased by 25%–50% as they underestimate the impact of HD on drug levels.[121] However, HD only accounts for a small portion of dosing intervals (e.g., 4 hours out of a 48–72 hour thrice weekly post-HD dosing interval).

Moreover, drug Vd can fluctuate due to fluid retention in ESKD and fluid removal during HD.[121,122] Infection itself can result in expanded Vd as well as increased drug clearance. Reduced protein binding as a result of uremia and hypoalbuminemia has also been described.[123] Uremia is a result of accumulation in ESKD, while hypoalbuminemia is common in the HD population due to malnutrition, decreased synthesis, exogenous loss, and the dilutional effects of fluid retention.[124]

Another challenge is the variability in PK due to diversity in patient characteristics such as age, gender, residual kidney function, body weight, and HD factors. Unfortunately, evidence to support appropriate dosage adjustments in the outpatient HD setting is sparse. Most studies available to date have employed stringent exclusion criteria to restrict PK variability, thereby limiting translatability to clinical practice.

Further, the absence of TDM for many antimicrobials prevents dose individualization. Whereas PKPD has been widely used to optimize antimicrobial dosing for other high-risk populations such as the immunocompromised, critically ill, and morbidly obese, such progress has not been made for patients receiving HD.[19,25,125]

The cephalosporins, cefazolin and ceftazidime, are among the most common prescribed IV antimicrobials in the outpatient HD setting.[85,113,116,126,127] In 2017, cefazolin and ceftazidime accounted for 49% of IV antimicrobial courses locally in the HD unit at St. Boniface Hospital (SBH) (unpublished audit data, **APPENDIX 1B**). Unlike the significant data available to direct dosing of vancomycin and the aminoglycosides, due to the availability for TDM, high-quality PK data is lacking for cefazolin and ceftazidime (**APPENDICIES 1C** and **1D**). Due to the scarcity of evidence, doses used in practice are variable and speculative. Dosing guidelines for cefazolin range from daily doses of 0.5–1 g, weight-based doses of 15–20 mg/kg thrice weekly post-HD, to fixed doses of 2–3 g thrice weekly post-HD (**APPENDIX 1E**), while dosing guidelines for ceftazidime range from daily dosing of 0.5–1 g to 0.5–2 g thrice weekly post-HD (**APPENDIX 1F**). Moreover, without evidence to direct dosage adjustments, HD programs adopt one-dose-fits-all protocols that do not consider patient factors that influence PK.[121,128] For example, the MRP uses a standard protocol of 2 g thrice weekly post-HD for both cefazolin and ceftazidime (**APPENDIX 1A**).[100] The lack of TDM for cephalosporins in the practice setting further limits clinical decisions regarding appropriate and individualized dosage adjustments. Consequently, poor clinical outcomes due to inappropriate antimicrobial dosing may be overlooked or erroneously attributed to patient factors such as ESKD. Despite being a high-risk population likely to benefit from evidence-based antimicrobial dosing, there are no data to support current approaches to cefazolin and ceftazidime dosing in the outpatient HD setting.

In response, a PK study was conducted to facilitate AMS in the outpatient HD setting. **CHAPTER 4** presents a prospective non-interventional PK study of cefazolin and ceftazidime in patients receiving HD.

The objective of this study was to evaluate antimicrobial concentrations to determine if current dosing protocols of 2 g thrice weekly post-HD are optimal to treat clinically relevant infections. Also, if needed, to investigate adaptive antimicrobial dosing strategies to optimize the treatment of severe infections in this high-risk and understudied population.

CHAPTER 2: Clinical blood isolates from hemodialysis patients: distribution of organisms and antimicrobial resistance, 2007–2014.

Preamble: A version of this chapter is published in the Canadian Journal of Hospital Pharmacy.[129] Additional data excluded from the submitted manuscript are included in this chapter's **Supplementary Tables & Figures** section. **REFERENCES** are merged at the end of this document.

2.1. Abstract

Background: Given the morbidity and mortality associated with bloodstream infections in hemodialysis patients, understanding the microbiology is essential to optimizing treatment in this high-risk population.

Objectives: To conduct a retrospective surveillance study of clinical blood isolates from adult hemodialysis patients, and to predict the microbiological coverage of empiric therapies for bloodstream infections in this population.

Methods: Clinical blood isolate data were collected from the 4 main outpatient hemodialysis units in Winnipeg, Manitoba, from 2007 to 2014. The distribution of organisms and antimicrobial susceptibilities were characterized. When appropriate, changes over time were tested using time series analysis. Study data were used to predict and compare the microbiological coverage of various empiric therapies for bloodstream infections in hemodialysis patients.

Results: The estimated annual number of patients receiving chronic hemodialysis increased steadily over the study period (p <0.001), whereas the number of blood isolates increased initially, then decreased significantly, from 180 in 2011 to 93 in 2014 (p = 0.04). Gram-positive bacteria represented 72.6% (743/1024) of isolates, including *Staphylococcus aureus* (36.9%, 378/1024) and coagulase-negative staphylococci (23.1%, 237/1024). Only 26.1% (267/1024) of the isolates were gram-negative bacteria, the majority Enterobacterales. The overall rate of methicillin resistance in *S. aureus* was 17.5%, and although annual rates were variable, there was a significant increase over time (p = 0.04). Antibiotic resistance in gram-negative bacteria was relatively low, except in *Escherichia coli* where 13.5% and 16.2% of isolates were resistant to ceftriaxone and ciprofloxacin, respectively. Empiric therapy with vancomycin plus an agent for gram-negative coverage was predicted to cover 98.8% to 99.7% of blood isolates from hemodialysis patients, whereas cefazolin plus an agent for gram-negative coverage would cover only 67.5% to 68.4%.

Conclusions: In an era of increasing antimicrobial resistance, data such as these and ongoing surveillance are essential components of antimicrobial stewardship in the hemodialysis population.

2.2. Introduction

Infectious diseases are associated with significant morbidity and are the second leading cause of death among patients receiving hemodialysis (HD).[130] Notable risk factors for infection include comorbidities (e.g., diabetes), immunosuppression associated with kidney disease, and the requirement for vascular access.[62] Bloodstream infections in HD patients can also lead to serious complications such as septic thrombosis, osteomyelitis, and endocarditis.[104] In general, the treatment of bloodstream infections in this population is associated with high failure rates, poor clinical outcomes, and substantial health care costs.[83]

It is important to understand the microbiology of infections in high-risk populations where antimicrobial resistance rates and emerging trends can inform the selection of empiric therapy. Such surveillance is especially relevant in HD patients given their regular contact with health care settings, high rates of infection, and frequent use of antibiotics.[72,83] Bloodstream infections in HD patients are most often associated with gram-positive skin flora, followed by gram-negative bacteria and occasionally yeast.[62] The more common pathogens in this population are associated with resistance concerns such as methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* spp. (VRE), extended-spectrum β-lactamase-producing (ESBL) Enterobacterales, and multidrug-resistant *Pseudomonas* spp. and *Acinetobacter* spp.[56,89] Clinical practice guidelines for the management of intravascular catheter-related infections in HD patients are broad, recommending "vancomycin and coverage for gram-negative bacilli, based on the local antibiogram (e.g., third-generation cephalosporin, carbapenem, or β-lactam/β-lactamase combination)" and cefazolin as an alternative to vancomycin in units with a low prevalence of MRSA.[92]

Despite the value of microbiological surveillance, studies in HD patients are limited,[62,81,83,87] and there are no current data for Canada. Our primary objective was to conduct a retrospective surveillance study of clinical blood isolates from the 4 main HD units serving adult patients in Winnipeg, Manitoba, from 2007 to 2014. The secondary objective was to use these data to predict the microbiological coverage of empiric therapies for bloodstream infections in the HD population.

2.3. Methods

Surveillance data of clinical blood isolates from the 4 main outpatient HD units serving adult patients in Winnipeg, Manitoba, from January 2007 to December 2014 were extracted from the provincial microbiology information system (Delphic LIS, Auckland, New Zealand). Because the data were not linked to individual patients, research ethics approval was not required. During the study period, the 4 main HD units —the Sherbrook Centre Dialysis Unit and Central Dialysis Unit in the Health Sciences Centre, St Boniface Hospital Dialysis Unit, and Seven Oaks Hospital Dialysis Unit— served approximately 68% of patients receiving chronic HD in the Manitoba Renal Program. These data primarily represent outpatients; however, a limited number of patients may have continued to HD in the units as inpatients.

Information on each clinical blood isolate was documented, specifically the date, location (HD unit), vascular site, organism identification, and antimicrobial susceptibilities. Importantly, these data excluded likely contaminants such as skin flora, unless culture results were positive in 2 sets of blood samples. Given the de-identified nature of surveillance data, additional steps were taken to exclude duplicate isolates (i.e., those with identical susceptibilities collected from different vascular sites at the same time in the same HD unit).[92]

The clinical blood isolates were characterized, and the distribution of organisms was detailed. Trends in the annual number of clinical isolates relative to the estimated number of HD patients were tested using a time series analysis with the Mann-Kendall trend test ($\alpha = 0.05$). Antimicrobial susceptibility rates were determined for the most common and clinically relevant pathogens (e.g., resistance concerns). Trends in antimicrobial resistance were also tested using time series analysis when the sample size exceeded 10 isolates of an organism in each year. All statistical analyses were conducted using SYSTAT 13 (Systat Software Inc., San Jose, California).

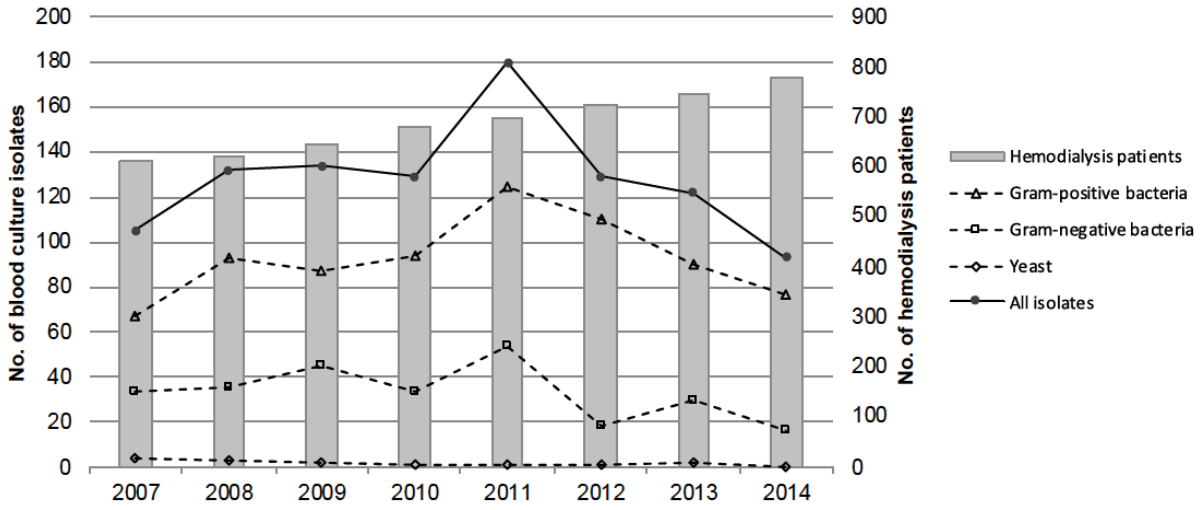
The study data were used to predict the microbiological coverage of various empiric therapies for bloodstream infections in HD patients. The predictions were based on our distribution of clinical blood isolates for organisms with at least 15 isolates. Empiric regimens were selected based on the aforementioned clinical practice guidelines and included vancomycin or cefazolin plus ceftazidime, piperacillin-tazobactam, meropenem, ciprofloxacin, tobramycin, or gentamicin for gram-negative coverage.[92] The predicted coverage of each empiric regimen was calculated by weighting the likelihood of each organism and summing the percentage of isolates susceptible to each antibiotic.

2.4. Results

A total of 1024 clinical blood isolates (from 953 blood cultures) met the inclusion criteria. Of these isolates, the largest percentage were gram-positive bacteria (72.6%, 743/1024), followed by gram-negative bacteria (26.1%, 267/1024) and yeast (1.4%, 14/1024).

Most blood cultures (93.2%, 888/953) contained a single isolate. While the estimated annual number of patients receiving chronic HD increased steadily over the study period (p <0.001), the annual number of clinical blood isolates increased initially, then decreased significantly, from 180 in 2011 to 93 in 2014 (p = 0.04) (**Figure 2A**). This trend was largely explained by a reduction in gram-positive bacterial isolates.

Figure 2A. Annual number of clinical blood isolates and estimated annual number of patients receiving chronic hemodialysis, 2007 to 2014.



As detailed in **Table 2A**, staphylococci accounted for 60.1% (615/1024) of clinical blood isolates, including *S. aureus* (36.9%, 378/1024) and coagulase-negative staphylococci (CoNS; 23.1%, 237/1024) (**Figure S2A**). The most common gram-negative bacteria were *Enterobacter* spp. (4.5%, 46/1024), *Klebsiella* spp. (4.2%, 43/1024), and *Escherichia coli* (3.6%, 37/1024) (**Figure S2A**). Antimicrobial susceptibility data are shown in **Table 2B** (**Figure S2B**). The overall rate of oxacillin (methicillin) resistance in *S. aureus* (i.e.,

MRSA) was 17.5% (66/378), with a significant upward trend from 6.7% (2/30) in 2007 to 26.0% (13/50) in 2014 ($p = 0.04$) (**Figure 2B**).

Table 2A. Distribution of clinical blood isolates, 2007–2014.

Organism	**No. of Isolates* (*n* = 1024)**	**% of Isolates***
Gram-positive bacteria		
Staphylococcus spp.	615	60.1
S. aureus	(378)	(36.9)
S. epidermidis	(182)	(17.8)
Other CoNS†	(55)	(5.4)
Enterococcus spp.	59	5.8
E. faecalis	(45)	(4.4)
E. faecium	(12)	(1.2)
Streptococcus spp.	31	3.0
Other	38	3.7
Gram-negative bacteria		
Enterobacter spp.	46	4.5
E. cloacae	(35)	(3.4)
Klebsiella spp.	43	4.2
K. pneumoniae	(29)	(2.8)
E. coli	37	3.6
Pseudomonas spp.	35	3.4
P. aeruginosa	(29)	(2.8)
Acinetobacter spp.	19	1.9
A. baumannii	(8)	(0.8)
Serratia spp.	19	1.9
Other	68	6.6
Yeast		
Candida spp.	14	1.4

*Isolate numbers and percentages for individual species are shown within parentheses.

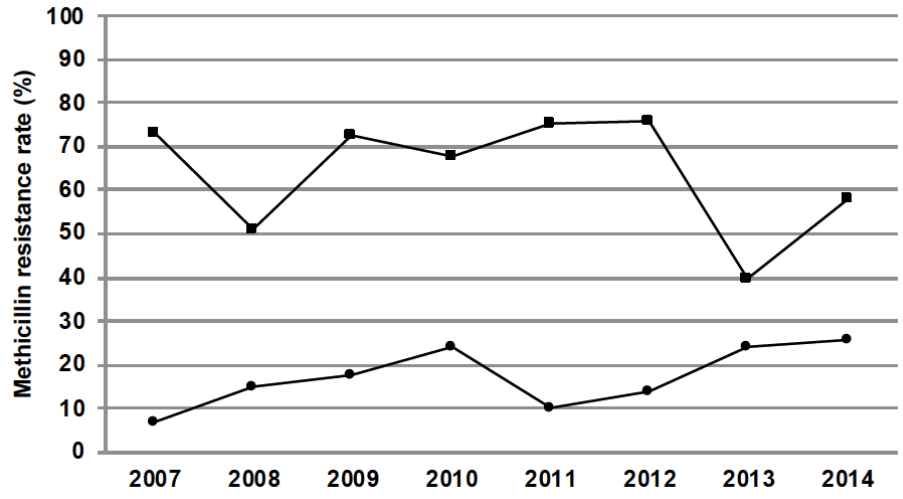
Table 2B. Antimicrobial susceptibilities of clinical blood isolates, 2007–2014.

Isolate	No. of isolates*	Susceptibility (%)										
		Oxacillin	Ampicillin	Vancomycin	Cefazolin	Ceftriaxone	Ceftazidime	Piperacillin-tazobactam	Meropenem	Ciprofloxacin	Gentamicin	Tobramycin
S. aureus	378	82.5	–	100	–	–	–	–	–	–	–	–
S. *epidermidis*	182	31.3	–	100	–	–	–	–	–	–	–	–
Other CoNS†	55	49.1	–	100	–	–	–	–	–	–	–	–
E. faecalis	45	–	91.1	100	–	–	–	–	–	–	–	–
E. faecium	12	–	16.7	83.3	–	–	–	–	–	–	–	–
Enterobacter spp.	46	–	–	–	–	–	–	97.8	100	100	100	100
Klebsiella spp.	43	–	–	–	88.4	100	100	100	100	100	100	100
E. coli	37	–	–	–	75.7	86.5	89.2	94.6	100	83.8	94.6	94.4
Pseudomonas spp.	35	–	–	–	–	–	94.3	94.3	97.1	94.3	97.1	100
Acinetobacter spp.	19	–	–	–	–	–	94.7	100	100	94.7	100	100

† Coagulase-negative staphylococci other than *S. epidermidis.*

* Number of isolates, except for tobramycin (for which numbers of isolates were as follows: 42 for *Enterobacter* spp., 41 for *Klebsiella* spp., 36 for *E. coli*, and 34 for *Pseudomonas* spp.).

Figure 2B. Rates of methicillin resistance in *Staphylococcus aureus* (*n* = 378, circles) and coagulase-negative *staphylococci* (*n* = 237, squares), 2007 to 2014.



The overall rate of oxacillin (methicillin) resistance in CoNS was 64.6% (153/237), but annual rates were variable with no notable trend over time (**Figure 2B**). Only 2 VRE isolates (both *Enterococcus faecium*) were identified during the study. All gram-negative bacteria except *E. coli* had susceptibility rates above 90% for the third-generation cephalosporins, piperacillin-tazobactam, meropenem, ciprofloxacin, gentamicin, and tobramycin. For *E. coli*, ceftriaxone and ceftazidime resistance was identified in 13.5% (5/37) and 10.8% (4/37) of isolates, respectively, including 2 isolates that were ESBL producers. *E. coli* also had the highest rate of ciprofloxacin resistance among the gram-negative bacteria (16.2%, 6/37).

The predicted microbiological coverage of empiric therapies was based on the current study's distribution of staphylococci, *Enterococcus faecalis*, *E. faecium*, *Streptococcus* spp., *Klebsiella* spp., *E. coli*, *Enterobacter* spp., *Serratia* spp., *Pseudomonas* spp., and *Acinetobacter* spp., which accounted for 88.1% (902/1024) of all isolates (**Table S2A**). The combinations of vancomycin with any of the agents for gram-negative coverage were predicted to cover 98.8% to 99.7% of the clinical blood isolates, whereas cefazolin plus an agent for gram-negative coverage would cover 67.5% to 68.4%. There were no differences based on the gram-negative coverage, whereby meropenem would cover less than 1% more isolates than ceftazidime, piperacillin-tazobactam, ciprofloxacin, tobramycin, or gentamicin.

2.5. Discussion

The current study provides important information about the microbiology of clinical blood isolates from HD patients over 8 years in Manitoba. There was a steady increase in the number of patients receiving chronic HD, whereas the number of isolates peaked in 2011 and then declined significantly. The reason for a spike in the number of isolates in 2011 is unclear. As expected, gram-positive bacteria accounted for most blood isolates (72.6%), followed by gram-negative bacteria (26.1%), and yeast (1.4%). In comparison, a Canadian Ward Surveillance Study (i.e., CANWARD) of clinical blood isolates from hospitalized patients reported distributions of 51% and 46% for gram-positive and gram-negative bacteria, respectively.[86] Whereas *S. aureus* was the most common organism in HD patients (i.e., 36.9% in our study compared with 17.7% in CANWARD), *E. coli* was most prevalent in hospitalized patients (i.e., 22.6% in CANWARD compared with 3.6% in our study).[86]

Notably, our distribution of blood isolates was similar to reports of clinically confirmed bloodstream infections in HD patients from Australia (2008–2015),[83] the United States (2007–2011 and 2014),[62,81] and Denmark (1995–2010).[87] The percentages of *S. aureus* (36.9%) and CoNS (23.1%) in our study were also similar to their infection rates of 28% to 33% for *S. aureus* and 25% to 31% for CoNS.[62,81,83] Although our percentage of gram-negative bacteria was comparable to the aforementioned studies, *E. coli* was less common (3.6%) compared to the infection rates in Australia (8.1%)[83] and Denmark (12.6%).[87]

Our overall rate of methicillin resistance in *S. aureus* was 17.5%. This compared to 22.5% in clinical isolates (all specimen types) from hospitalized patients in Canada during the same time period (**Figure S2C**).[131] Our increase in methicillin resistance from 6.7% in 2007 to 26.0% in 2014 is also consistent with a significant rise in community-acquired MRSA bloodstream infections observed in Canada between 2012 and 2017.[132] As expected, there was considerable geographic variability in MRSA resistance in clinically confirmed bloodstream infections in HD patients reported elsewhere, including none in Denmark (1995–2010),[87] 14% (2008–2015)[83] and 40% (2014)[62] in Australia, and 46% in the United States (2007–2011).[81]

Our rate of vancomycin resistance in enterococci was only 3.4%, lower than the rates of 11.4% to 21.7% reported in those studies.[62,81,83] Our rate of ceftriaxone resistance in *E. coli* of 13.5% was comparable to theirs of 9% to 18%; our study was the only one to report ESBL status.[62,81,83] Despite global concerns about multidrug resistance in *Pseudomonas* spp. and *Acinetobacter* spp., there are limited susceptibility data in the HD population. Although our numbers were small, resistance rates for these organisms were relatively low compared to clinical blood isolates from hospitalized patients in Canada (CANWARD).[86]

Our predictions of microbiological coverage with empiric therapies showed that replacing vancomycin with cefazolin, in combination with an agent for gram-negative coverage, would reduce the overall coverage of clinical blood isolates in HD patients by more than 30%. Although our rate of methicillin resistance in *S. aureus* was only 17.5%, the high prevalence of methicillin resistance in CoNS (i.e., 64.6%) suggests that all staphylococcal pathogens should be considered to ensure appropriate empiric therapy. Conversely, there was no advantage to using the broader-spectrum agents such as piperacillin-tazobactam or meropenem to cover gram-negative pathogens. Our predictions also found that vancomycin plus ciprofloxacin would cover 98.8% of clinical blood isolates in HD patients and may be an acceptable alternative for those with serious β-lactam allergy or aminoglycoside intolerance.

When interpreting the findings of the current study, it is important to consider the specific geographic context, particularly in terms of resistance rates. Even so, these data are informative and fill a notable gap in the study of infectious diseases in dialysis patients. Because our study was limited to the characterization of clinical blood isolates, not clinically confirmed infections, steps were taken to maintain clinical relevance by excluding duplicate cultures. Without access to patient identifiers, the possibility of repeat culture(s) of the same isolate on days following the index culture could not be ruled out. Therefore, the data were re-examined to identify the number of potential repeat isolates using a broad definition of the same organism, with identical susceptibilities, collected in the same HD unit within 7 days. According to this analysis, the number of possible repeats would not have exceeded 6% of all isolates. Our interpretation of some

resistance patterns was limited by changes made to the cephalosporin and carbapenem susceptibility breakpoints against Enterobacterales and *Pseudomonas* spp. in 2012 (**Figure S2D**). Most importantly, continued surveillance in HD patients is needed to maintain the relevance of this initial work, particularly given the trends in methicillin resistance and the emergence of VRE and ESBL-producing organisms near the end of our study.

2.6. Conclusion

This study provides insight on the distribution of organisms and antimicrobial susceptibilities of clinical blood isolates from multiple HD units in Manitoba over 8 years. The large sample size allowed for a longitudinal analysis, which is rarely available for this patient population. In an era of increasing antimicrobial resistance, data such as these and ongoing surveillance are essential components of antimicrobial stewardship in the HD population.

2.7. Supplementary Tables & Figures

Figure S2A. Clinical blood isolates from patients receiving hemodialysis in Manitoba between 2007 to 2014 (N = 1,024).

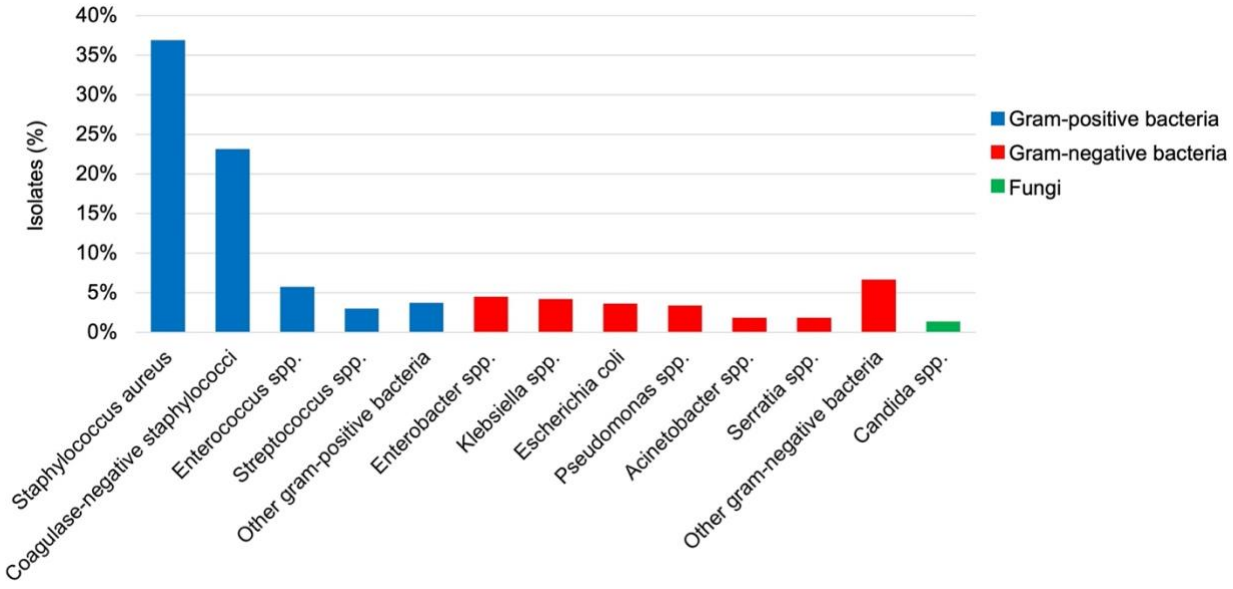


Figure S2B. Changes in antimicrobial susceptibility rates from 2007 to 2010 compared with 2011 to 2014 for gram-positive bacteria with 20 or more isolates collected including A) *Staphylococcus aureus*, B) *Staphylococcus epidermidis*, and C) *Enterococcus faecalis*.

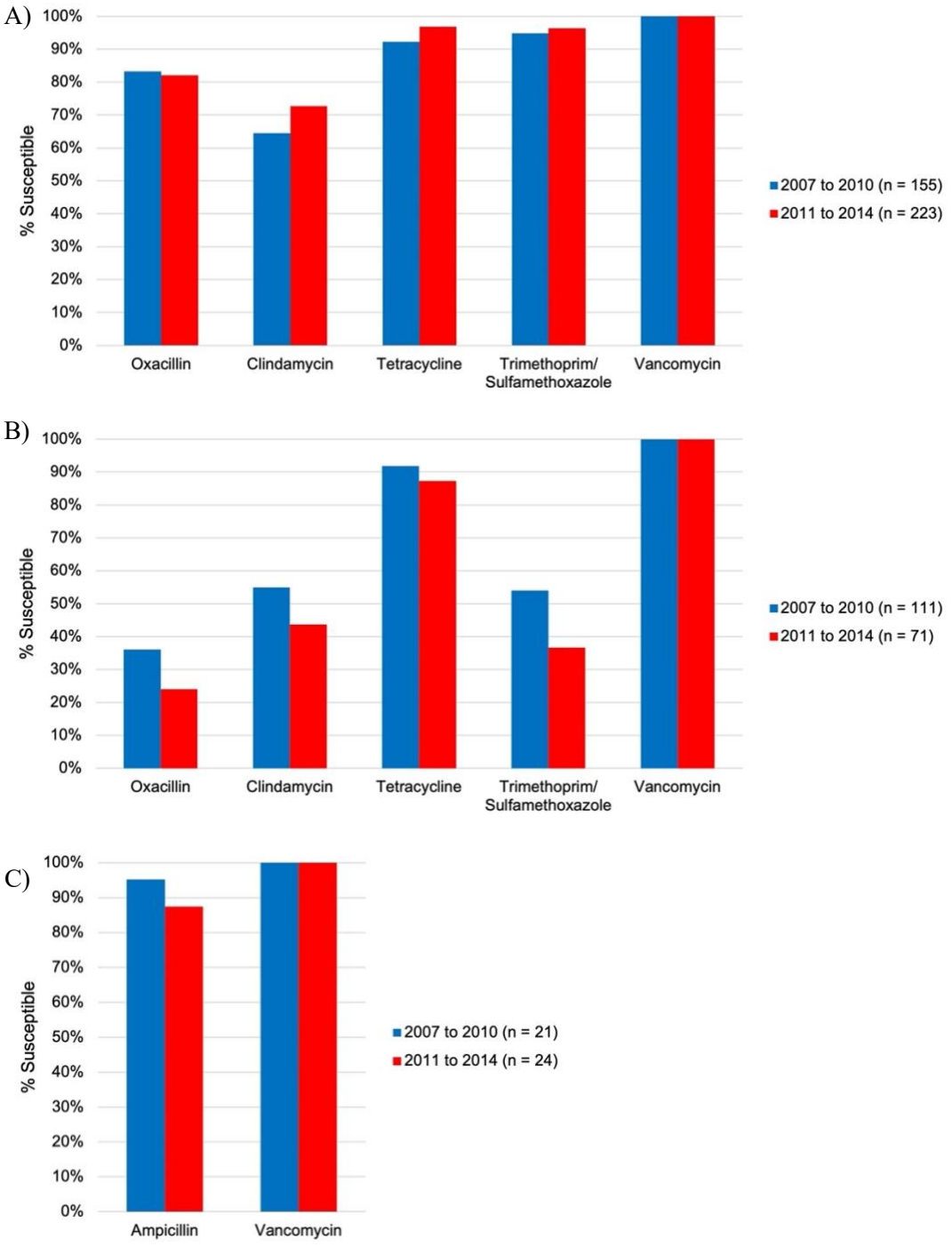


Table S2A. Predicted microbiological coverage of empirical antibiotic therapies.

	Gram-positive coverage	
Gram-negative coverage	Vancomycin	Cefazolin
Meropenem	99.7%	68.4%
Gentamicin	99.4%	68.1%
Tobramycin	99.2%	67.9%
Piperacillin-tazobactam	99.2%	67.9%
Ceftazidime	98.8%	67.5%
Ciprofloxacin	98.8%	67.5%

[a] Based on observed pathogen distribution and antimicrobial susceptibility.

Figure S2C. Methicillin-resistant *Staphylococcus aureus* rate in blood isolates from patients receiving hemodialysis (circles) compared to isolates from all specimen types in hospitalized patients (squares).[86]

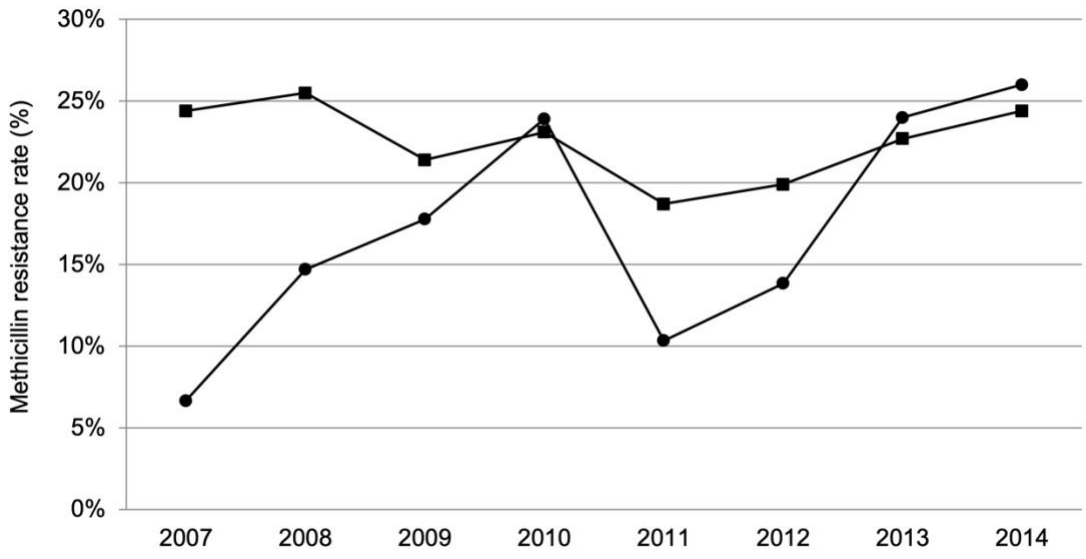
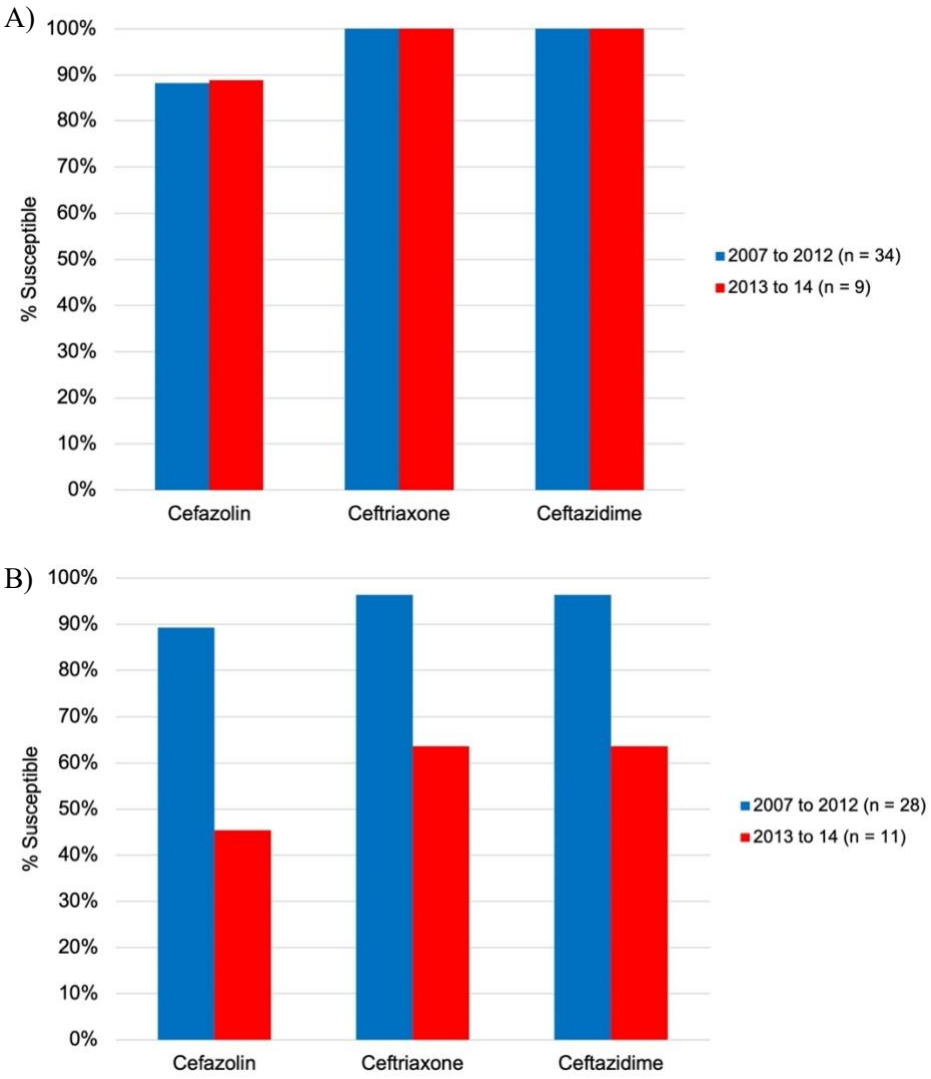


Figure S2D. Cephalosporin susceptibilities for A) *Klebsiella* spp. and B) *Escherichia coli* before and after the change in susceptibility breakpoint from 8 mg/L to 2 mg/L in 2012.



CHAPTER 3: Impact of practice changes on catheter-related exit-site and bloodstream infection rates in a Canadian hemodialysis center: a retrospective study.

Preamble: A version of this chapter is published in the Journal of Vascular Access.[133] Additional data excluded from the submitted manuscript are included in this chapter's **Supplementary Tables & Figures** section. **REFERENCES** are merged at the end of this document. **APPENDICES 3A**, **3B**, **3C**, and **4D** are referred to in this chapter.

3.1. Abstract

Background: Hemodialysis vascular access predisposes patients to exit-site infections (ESIs) and bloodstream infections (BSIs), resulting in significant morbidity and mortality. The objective was to characterize hemodialysis catheter-related (CR) ESIs and BSIs while considering potential factors associated with infection.

Methods: The study period was selected to coincide with new CR-infection prevention measures at the midpoint. These included masking during exit-site care, using chlorhexidine-alcohol versus povidone-iodine antiseptic, administering cefazolin prophylaxis with central venous catheter (CVC) insertions, and reducing temporary CVC use for chronic hemodialysis starts. Data were collected retrospectively, including patient characteristics, hemodialysis history, CVC details, and CR-infections. Quarterly infection rates were calculated per 1000 CVC days, and potential factors associated with infection were investigated. Modelling was used to characterize infection rates and covariates over time.

Results: Over 39 months, data for 267 patients, 499 CVCs, and 114,825 CVC days were captured. During the study period, there were 113 ESIs and 64 BSIs, with >80% of infections caused by gram-positive bacteria. ESI and BSI rates were 0.98 and 0.56 per 1000 CVC days, respectively. There were significant reductions in infection rates over time. The ESI rate dropped when new CR-infection prevention measures were introduced (P <0.01), from a mean of 1.28 to 0.73 per 1000 CVC days (P = 0.003). The rate of BSI trended downward to a low of 0.10 per 1000 CVC days in the last quarter of the study. The BSI rates associated with temporary and permanent CVCs were 1.25 and 0.53 per 1000 CVC days, respectively (P = 0.1). There was a strong correlation between the declining BSI rates and declining temporary CVC use over time (rho = 0.73, P = 0.005).

Conclusions: CR-ESI rates dropped significantly when new hemodialysis CR-infection prevention measures were introduced. CR-BSI rates declined over the study period, as did the use of temporary CVCs.

3.2. Introduction

In patients receiving hemodialysis (HD), infection is the second leading cause of mortality.[74] The population is particularly susceptible to infections due to immunosuppression caused by end-stage kidney disease (ESKD), comorbidities such as diabetes, frequent exposure to healthcare settings, and, most importantly, the need for vascular access.[58–61,75] Access through arteriovenous fistulas or grafts is preferred over central venous catheters (CVCs), which are more prone to complications, including infection.[58,65,83,84,112,134] Nevertheless, CVCs are an important option that may be more feasible, preferred by the patient, or required to start dialysis urgently.[65,134]

CVCs predispose patients to both catheter-related (CR) exit-site infections (ESIs) and bloodstream infections (BSIs). While less severe, CR-ESIs are a notable risk factor and source of bacteremia in patients receiving HD.[58] The microbiology of CR-ESIs and CR-BSIs are similar, with gram-positive skin flora (i.e., staphylococci) accounting for 60–80% of infections.[78,83] The etiology of BSIs differs from other patient populations, where gram-negative bacteria (e.g., *Escherichia coli*) from urinary or gastrointestinal sources are more common.[129] CR-BSIs often require CVC replacement and are associated with considerable morbidity, mortality, and healthcare costs.[104]

The published rates of CR-infections are variable due to differences in patient populations, vascular access type, infection control, and reporting criteria. Furthermore, while most investigations focus on BSIs, there are limited data on ESIs. Studies of patients receiving HD in North America, Australia, and Europe between 1999 and 2015 report CR-ESI rates of 0.46 to 0.80 per 1000 CVC days[78,83] and CR-BSI rates of 0.26 to 2.26 per 1000 CVC days[62,78–84,135]. Infection control practices are essential to prevent CR-infections in the HD population. A recent systematic review by Lazarus *et al.* showed that over 80% of interventional quality improvement studies to prevent CR-BSIs had favourable outcomes.[111] More specifically, CR-infection prevention measures such as aseptic CVC insertion[64,134,136], antimicrobial prophylaxis with CVC

insertion[137], aseptic techniques during catheter manipulations[64,136], and exit-site care[64,78,134,136] have been associated with lower infection rates.[80,84,112]

The surveillance of CR-infections in patients receiving HD is vital to monitor infection rates, assess the effectiveness of infection control measures, and optimize the selection of empiric antimicrobial therapies. Whereas programs such as the National Healthcare Safety Network (NHSN) Dialysis Event Surveillance and ESKD Quality Incentive Program are available to support dialysis-related infection control in the United States,[81,112] coordinated efforts and access to longitudinal surveillance data in Canada are limited. The objective of the current study was to characterize the microbiology and rates of CR-ESI and CR-BSI over 39 months in a Canadian HD center while considering potential factors associated with infection. These data were presented at the 31st European Congress of Clinical Microbiology and Infectious Diseases, July 2021 (online), Abstract #2773 (328945).

3.3. Methods

3.3.1 Study design & setting

A retrospective observational study of CR-infections was conducted in adult patients receiving HD through a CVC at St. Boniface Hospital (SBH) in Winnipeg, Manitoba. Study approvals were granted by the University of Manitoba Health Research Ethics Board (#HS20491) and the SBH Research Review Committee (#2017/1643).

The 39-month study period was selected so the midpoint coincided with the introduction of new CR-infection prevention measures. At the time, the HD unit served 145 to 160 patients, with 60-70% receiving dialysis through a CVC. CVC insertions were performed by interventional radiologists or nephrologists using guidewires, ultrasound, fluoroscopy, and contrast (radiologists only) to access the vessel and verify placement. If required, CVCs were replaced at a new site, i.e., not exchanged over a guidewire. Covidien Palindrome™ heparin-coated catheters were used for permanent placements, while Bard Niagara™ Vas-Cath or Slim-Cath catheters were used for temporary placements. Standard CVC care throughout the study period included using aseptic techniques during CVC and exit-site manipulations, Tegaderm™ dressings for exit-sites, and heparin lock solutions for interdialytic periods. Also, Polysporin® Triple was applied to CVC exit-sites for the first three dressing changes post-insertion. The new CR-infection prevention measures introduced at the midpoint of the study period included masking (patient and nurse) during exit-site care, using 2%-chlorhexidine/70%-alcohol antiseptic instead of povidone-iodine to clean CVC hubs and exit-sites, and administering cefazolin prophylaxis for CVC insertion. There was also an overall effort to reduce the use of temporary CVCs for chronic HD starts.

3.3.2. Data collection

Information on patient characteristics, HD history, CVC details, and CR-infections was collected from electronic Renal Program databases. To be included, patients had to have received acute or chronic HD for at least two weeks during the study period. Data were collected starting from January 1, 2011, for patients

already active in the HD program or later for those who joined the program after. Data were collected to March 31, 2014, or sooner for patients who left the HD program due to kidney recovery or transplant, switching to peritoneal dialysis, transferring to another location for HD, withdrawing care, or loss of life. Patient characteristics, including age, sex, etiology of kidney disease, dialysis start date, and comorbidities of diabetes or hypertension, were collected. Each CVC was documented according to the type (i.e., temporary-uncuffed or permanent-cuffed), location, and insertion and removal dates. The total number of CVC in place at any given time was determined based on insertion and removal dates. Total CVC days and the relative proportion of temporary and permanent CVCs in use were determined quarterly.

3.3.3. Infections

Episodes of infection were retrospectively identified in a quality assurance database of CR-ESIs and CR-BSIs that had been documented in real-time by designated personnel in the HD program. The culture date, microbiology, time since CVC insertion, and time to CVC removal were collected for all infections. A CR-ESI required local signs or symptoms of infection (i.e., at least two of redness, tenderness, or pus), a positive culture, and treatment with topical or systemic antimicrobials. A subsequent CR-ESI involving the same catheter was considered a new episode if it occurred at least two months later. A CR-BSI required systemic signs or symptoms of infection, a positive blood culture with no other apparent source of infection, and treatment with parenteral antimicrobials. All CR-BSIs were considered new episodes unless the same pathogen was cultured within three months in a previously infected catheter that was not removed.

3.3.4. Statistical analysis

Patients, CVCs, and infections were characterized using descriptive statistics, i.e., mean ± standard deviation, median [interquartile range], or number (percentage) as appropriate. Trends in characteristics over time were analyzed using the Mann-Kendall trend test. Quarterly infection rates were calculated as the number of infections per 1000 CVC days. Differences in infection rates between time periods were compared using the two-sided Student's t-test. In addition, potential factors associated with infection,

including new CR-infection prevention measures and CVC characteristics, were investigated. Patient characteristics were also considered including age, sex, comorbidities, and duration on dialysis. Univariate analyses were performed with two-sided Student's *t*-tests, Mann-Whitney *U*-tests, Chi-square or Fisher's exact tests, or incidence rate ratios (IRR) as appropriate. Pearson's correlations were used to investigate associations over time.

Modelling was performed to describe the rates of CR-ESI and CR-BSI over the 39-month period while considering potential covariates. Various models were tested, including generalized multiple regression with Poisson distribution and multiple linear regression with and without autocorrelated error. Models were inspected for homoscedasticity, stationarity, and normality. Covariates were considered, including the proportion of temporary CVCs, the number of newly inserted CVCs, and new CR-infection prevention measures. Covariates were tested for collinearity using Pearson's correlations. Only covariates with statistical significance ($P < 0.05$) were retained in the models. The final models were selected for goodness-of-fit based on the root mean square error (RMSE), coefficient of determination (R^2), and adjusted R^2.

Statistical analyses were performed using SAS® software (SAS Institute Inc.), SYSTAT 13 (Systat Software Inc., San Jose, California), and MedCalc Software Ltd. with a significance level (α) of 0.05.

3.4. Results

3.4.1. Patients & central venous catheters

Two-hundred and sixty-seven patients and 499 CVCs representing 114,825 CVC days were captured during the study period. The patient and CVC characteristics are detailed in **Tables 3A** and **3B**, respectively. Most CVCs were permanent (78.2%, 390/499), with a significant downward trend in the use of temporary CVCs over time (**Figure 3A**, $P = 0.004$). The proportion of temporary CVCs in place at any given time declined from an average of 5.7% in the first half of the study to 2.0% in the second half. Most CVCs were inserted in the right (77.4%, 386/499) versus the left (17.2%, 86/499) internal jugular vein, and only 1.2% (6/499) were located in the femoral vein.

Table 3A. Patient characteristics (n = 267).

Age (years)[a]	62.9 ± 15.4
Sex	
Male	131 (49.1%)
Female	117 (43.8%)
Undocumented	19 (7.1%)
Comorbidities	
Hypertension	164 (61.4%)
Diabetes	145 (54.3%)
Etiology of kidney disease	
Diabetes	122 (45.7%)
Tubulointerstitial disease	49 (18.4%)
Glomerulonephritis	37 (13.9%)
Hypertension/renovascular disease	33 (12.4%)
Polycystic kidney disease	7 (2.6%)
Reflux	3 (1.1%)
Other	42 (15.7%)
Undocumented	20 (7.5%)
Duration on any type of dialysis (months)	16 [3, 42]
Duration of data collection (months)	9 [2, 25]
Reason for discontinuation of data collection	
End of study	11 (41.6%)
Removed from HD[b]	54 (20.2%)
Transferred to another location for HD	54 (20.2%)
Loss of life	48 (18.0%)

Reported as number (%), mean ± standard deviation, or median [interquartile range].

[a] Start of study.

[b] Kidney recovery or transplant, switched to peritoneal dialysis, transferred to another hemodialysis unit, care withdrawn.

Table 3B. Central venous catheters (*n* = 499 in 267 patients).

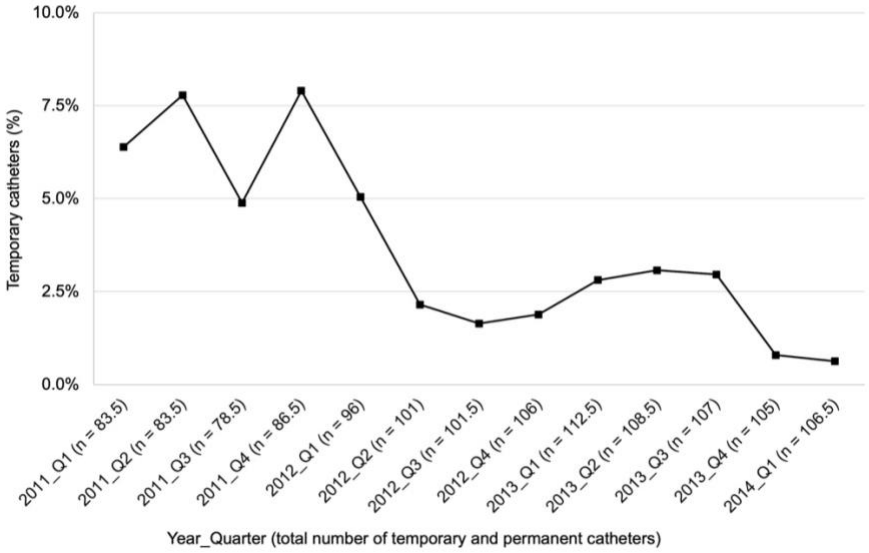
Type	
Permanent (cuffed)	390 (78.2%)
Temporary (uncuffed)	109 (21.8%)
Time in place (months)	
Permanent	7 [3, 18]
Temporary	1 [0.5, 1]
Location	
Right internal jugular vein	386 (77.4%)
Left internal jugular vein	86 (17.2%)
Other[a]	27 (5.4%)
Insertion time	
Prior to study	78 (15.6%)
During study	421 (84.4%)
Status	
Removed and replaced during study	232 (46.5%)
In place at end of study	102 (20.4%)
Other[b]	165 (33.1%)

Reported as number (%) or median [interquartile range].

[a] External jugular vein, femoral vein, or subclavian vein.

[b] Kidney recovery or transplant, switched to peritoneal dialysis, transferred to another hemodialysis unit, care withdrawn, loss of life.

Figure 3A. Temporary central venous catheter use over time.



3.4.2. Catheter-related infections

During the 39-month study period, 113 CR-ESIs involving 61 patients and 85 CVCs were identified (**Table 3C, Figures S3A** and **S3B**). The overall rate of CR-ESI was 0.98 per 1000 CVC days. Most were monomicrobial infections (85.8%, 97/113), with gram-positive bacteria, gram-negative bacteria, and yeast accounting for 81.2% (108/133), 12.8% (17/133) and 1.5% (2/133) of the pathogens, respectively (**Table S3A**). The most common organisms were *Staphylococcus aureus* (42.1%, 56/133), coagulase-negative staphylococci (24.8%, 33/133), *Corynebacterium* spp. (9.0%, 9/133), *Pseudomonas aeruginosa* (6.0%, 8/133), *Serratia marcescens* (3.8%, 5/133), and *Streptococcus* spp. (3.8%, 5/133).

During the study period, 64 CR-BSIs involving 38 patients and 51 CVCs were identified (**Table 3C, Figures S3A** and **S3B**). The overall rate of CR-BSI was 0.56 per 1000 CVC days. There was only one polymicrobial infection. Most pathogens were gram-positive bacteria (83.1%, 54/65), including *S. aureus* (53.8%, 35/65), coagulase-negative staphylococci (16.9%, 11/65), and *Streptococcus* spp. (4.5%, 3/65) (**Table S3A**). Gram-negative CR-BSIs were less common (15.4%, 10/65), with *P. aeruginosa* and *S. marcescens* accounting for 6.2% (4/65) and 3.1% (2/65) of the organisms, respectively. Almost one-third of CR-BSIs (32.8%, 21/64) were preceded by a CR-ESI within three months. Most cases (85.7%,18/21) were caused by the same pathogen, usually *S. aureus* (16/18).

Table 3C. Catheter-related exit-site and bloodstream infections.

CR-infections	Permanent CVCs (*n* = 390)	Temporary CVCs (*n* = 109)
CR-ESIs (*n*)	112	1
CR-ESI rate (per 1000 CVC days)	1.01	0.25
Time from CVC insertion to CR-ESI (months)	8.0 [3.8, 17.0]	4
CVCs involved in one / multiple CR-ESIs (*n*)	63 / 21	1
CR-BSIs (*n*)	59	5
CR-BSI rate (per 1000 CVC days)	0.53	1.25
Time from CVC insertion to CR-BSI (months)	9.0 [5.0, 17.5]	2.0 [1.0, 3.0]
CVCs involved in one / multiple CR-BSIs (*n*)	37 / 10	3 / 1

Reported as number or median [interquartile range].

BSI bloodstream infection, *CR* catheter-related, *CVC* central venous catheter, *ESI* exit-site infection.

3.4.3. Factors associated with infections

Infection rates were significantly lower after the new CR-infection prevention measures were introduced (1.28 versus 0.73 CR-ESIs per 1000 CVC days [$P = 0.003$] and 0.72 versus 0.50 CR-BSIs per 1000 CVC days [$P = 0.05$]). The CR-BSI rates associated with temporary and permanent CVCs were 1.25 and 0.53 per 1000 CVC days, respectively (IRR = 0.42, $P = 0.1$). There was a strong correlation between the declining CR-BSI rates and the declining use of temporary CVCs over time (**Figure 3A**, rho = 0.73, $P = 0.005$). The CR-BSI rates associated with CVCs located in the left versus right internal jugular vein were 0.82 versus 0.49 per 1000 CVC days, respectively (IRR = 0.59, $P = 0.09$). No infections were associated with CVCs located in the lower extremities. Compared to those without a documented infection during the study period ($n = 188$), patients with an infection ($n = 79$) tended to be on dialysis longer (41 [25.5, 64.5] versus 8 [2.0, 27.5] months, $P < 0.001$) and had more CVCs (2.8 ± 1.5 versus 1.5 ± 0.7, $P < 0.001$).

3.4.4. Modelled infection rates over time

The rates of CR-ESI and CR-BSI were best described by multiple linear regression with autocorrelated error. All homoscedasticity and normality assumptions were satisfied. Covariates for infection were tested but did not significantly improve the models. The proportion of temporary CVCs was not incorporated into the models as it was strongly correlated with time (r = -0.83, P <0.001).

The final models describing the rates of CR-ESI and CR-BSI are depicted in **Figures 3B** and **3C**, respectively. There was an abrupt and significant drop in CR-ESIs at the midpoint of the study with no further decline (**Figure 3B**, P <0.01). This corresponded to CR-ESI rates of 1.28 compared to 0.73 per 1000 CVC days before and after the new CR-infection prevention measures, respectively (P = 0.003). Of note, the rates of CR-ESI appeared to increase in the last two quarters of the study. The rate of CR-BSI decreased throughout the study period, with a more rapid decline starting the quarter after the new CR-infection prevention measures were introduced (**Figure 3C**, P <0.01). The CR-BSI rates were 0.70 per 1000 CVC days before and 0.37 per 1000 CVC days after (P = 0.007).

Figure 3B. Catheter-related exit-site infections over time, modelled using multiple linear regression with autocorrelated error (RMSE = 0.19).

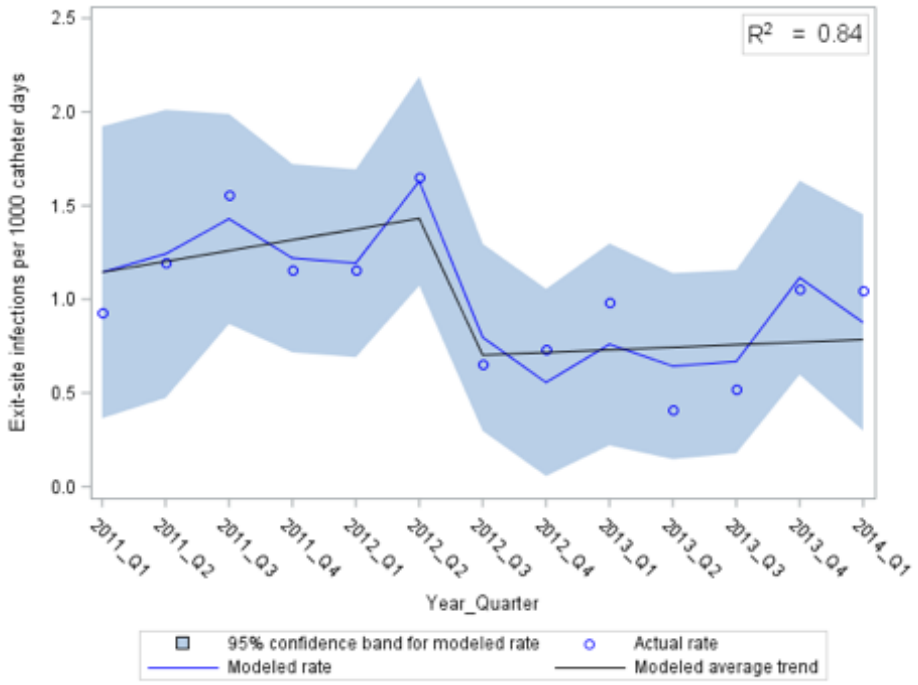
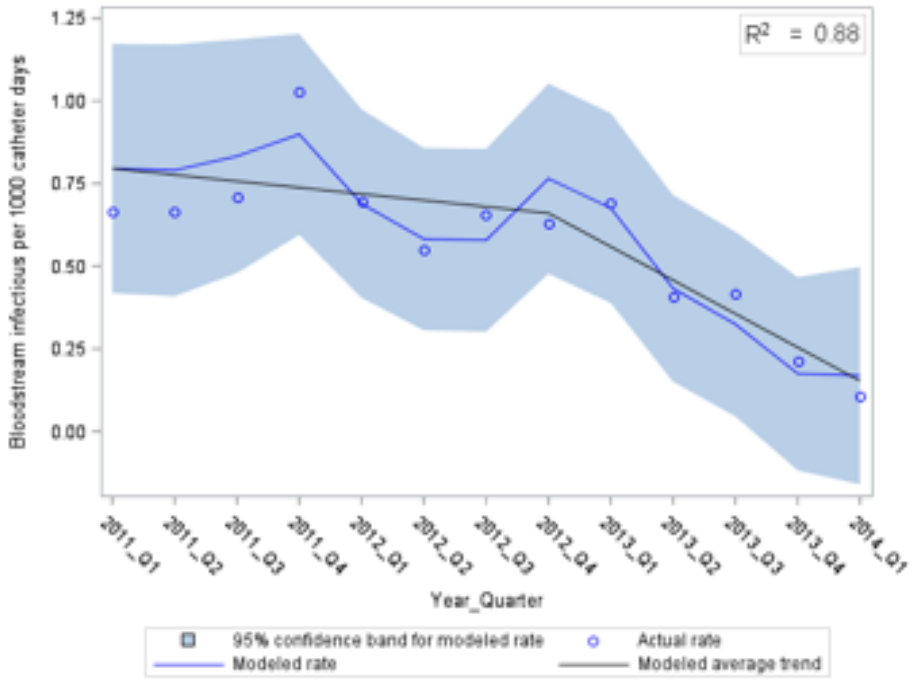


Figure 3C. Catheter-related bloodstream infections over time, modelled using multiple linear regression with autocorrelated error (RMSE = 0.11).



3.5. Discussion

The current study describes a significant reduction in CR-infections over 39 months in patients receiving HD. Notably, the decline coincided with the introduction of new CR-infection prevention measures at the midpoint of the study. The measures included masking during exit-site care, using chlorhexidine-alcohol versus povidone-iodine antiseptic, administering cefazolin prophylaxis with CVC insertions, and reducing temporary CVC use for chronic HD starts. They were selected based on feasibility and evidence available at the time. The use of chlorhexidine-alcohol was supported by strong evidence of superiority over povidone-iodine.[64,134,138–140] Guidelines did not recommend the routine use of antimicrobial prophylaxis during CVC insertion due to resistance concerns and limited evidence of benefit.[65,134] However, a study by Huddam *et al.* showed a reduction in CR-infections when 1 g of cefazolin was administered pre-insertion.[137] Also, a survey by Smyth *et al*. published in 2019 revealed that 21% of HD units used antimicrobial prophylaxis, usually a first-generation cephalosporin.[141] However, due to limited evidence, the routine use of antimicrobial prophylaxis for HD CVC insertions was discontinued at our site. The effort to reduce temporary CVC use was based on substantial evidence of higher infection rates for temporary compared to permanent CVCs.[65] Likewise, we found a higher rate of CR-BSI in temporary CVCs.

We observed an abrupt drop in CR-ESIs after the new CR-infection prevention measures were introduced, with no further decline. This corresponded to an overall 43% reduction in the rate of CR-ESI. However, there was an increase in CR-ESIs in the last two quarters of the study, which may have signalled weakened compliance with infection prevention measures. The rate of CR-BSI declined steadily throughout the study but more rapidly starting the quarter after the new CR-infection prevention measures were introduced (P <0.01). Notably, the decline in the rate of CR-BSI during the study was strongly correlated with the declining temporary CVC use over time (rho = 0.73, P = 0.005).

The rates of CR-infection in the current study were comparable to the values in the literature. Our overall CR-BSI rate of 0.56 per 1000 CVC days was comparable to the range of 0.26 to 1.86 per 1000 CVC days

reported by other studies in North America, Australia, and Europe during a similar time frame.[62,78–84] Of note, the rate of CR-BSI in the last quarter of our study, 0.1 per 1000 CVC days, was relatively low. Although there is less published data on CR-ESIs, our rate of 0.98 per 1000 CVC days was comparable to the 0.46 to 0.80 per 1000 CVC days observed by others.[78,83] Differences in rates may be explained by variability in patient characteristics, CVC type, and infection control measures. Also, it is important to consider that the criteria used to define CR-ESI and CR-BSI in the literature are inconsistent. The depth of catheter data collected in the current study was novel and prevented over-estimation of infection rates. More specifically, our data allowed for the identification of infection relapses when the same pathogen was cultured from a catheter that was not removed.

The microbiological etiology of CR-infections in our study was consistent with older reports in Canada.[78,88] Over 80% of infections were caused by gram-positive bacteria, primarily skin flora, with *S. aureus* and coagulase-negative staphylococci accounting for 46% and 22% of cases, respectively. The microbiology was similar between CR-BSIs and CR-ESIs, again demonstrating the important connection between the two infection types (**Figure S3C**). These data help direct the selection of appropriate empirical therapy, especially since prompt antimicrobial therapy significantly improves treatment outcomes.

In our study, potential factors associated with infection were also explored. Consistent with other studies, we observed a higher CR-BSI rate for CVCs located in the left versus right internal jugular vein, although the mechanism remains unclear.[65,142,143] In addition, patients who developed infection tended to be on dialysis longer and, therefore, "at risk" for longer. Those with an infection also had more CVCs since infected catheters are often replaced. Finally, almost one-third of CR-BSIs were preceded by a CR-ESI within three months. Most of these cases were caused by *S. aureus*, known to produce biofilms on indwelling devices. Taylor *et al.* also described a significantly increased BSI risk following HD access site infection (Odds Ratio = 4.36, $P = 0.002$).[58] Overall, CR-ESIs remain an understudied risk factor for CR-

BSIs. Our findings highlight the significance of optimal exit-site care, effective CR-ESI treatment, and ongoing surveillance.

One limitation of the current study is that data were collected retrospectively. As such, it is possible there were unidentified biases or confounders. For instance, the use of immunosuppressive agents was not available in our data; however, their use significantly increases infection risk. Also, the nature of our data did not allow for the determination of causation, only association. Finally, it is important to consider the geographical context and time period when interpreting the study results. Even so, these data are enlightening and fill a substantial gap in the study of CR-infections in patients receiving HD, particularly for CR-ESIs. Moving forward, further surveillance is necessary to maintain the applicability of this initial work, especially given the evolving nature of infection control measures. This is particularly true given notable changes in infection control following the COVID-19 pandemic.

3.6. Conclusions

In summary, the current study describes a significant decline in CR-infections over 39 months in patients receiving HD. More specifically, there was an abrupt drop in CR-ESIs after new CR-infection prevention measures were introduced. However, by the end of the study, ESI rates began to rise. Also, during the study, there was a steady decline in CR-BSIs, which was highly correlated with a concurrent decrease in temporary CVC use. Notably, ESIs preceded one-third of BSIs, primarily caused by the same pathogen. These findings emphasize the need for ongoing surveillance, reinforcement of CR-infection prevention measures, and optimal CR-ESI prevention and treatment to reduce the risk of CR-BSIs.

3.7. Acknowledgements

The authors would like to acknowledge statistical support from Dr. Depeng Jiang (BSc, MSc, PhD, Professor) and Yixiu Liu (MSc, PhD candidate) with the Biostatistics Group at the George & Fay Yee Centre for Healthcare Innovation and Department of Community Health Sciences at the University of Manitoba.

3.8. Supplementary Tables & Figures

Table S3A. Pathogens associated with exit-site and bloodstream infections in patients receiving hemodialysis with central venous catheters.

	Exit-site infection (*n* = 113)[b]	**Bloodstream infection (*n* = 64)[a]**
Staphylococcus aureus	56 (42.1%)	35 (53.8%)
Coagulase-negative *staphylococci*	33 (24.8%)	11 (16.9%)
Streptococcus spp.	5 (3.8%)	3 (4.5%)
Corynebacterium spp.	12 (9.0%)	1 (1.5%)
Enterococcus spp.	2 (1.5%)	1 (1.5%)
Other gram-positive pathogens	-	3 (4.6%)
Pseudomonas aeruginosa	8 (6.0%)	4 (6.2%)
Serratia marcescens	5 (3.8%)	2 (3.1%)
Other gram-negative pathogens	4 (3.0%)	4 (6.2%)
Yeast	2 (1.5%)	-
Unknown	6 (4.5%)	1 (1.5%)
Total	133	65

[a] One (1.6%) polymicrobial bloodstream infection

[b] Sixteen (14.2%) polymicrobial exit-site infections

Figure S3A. Time from central venous catheter insertion to exit-site (ESI) or bloodstream (BSI) infection.

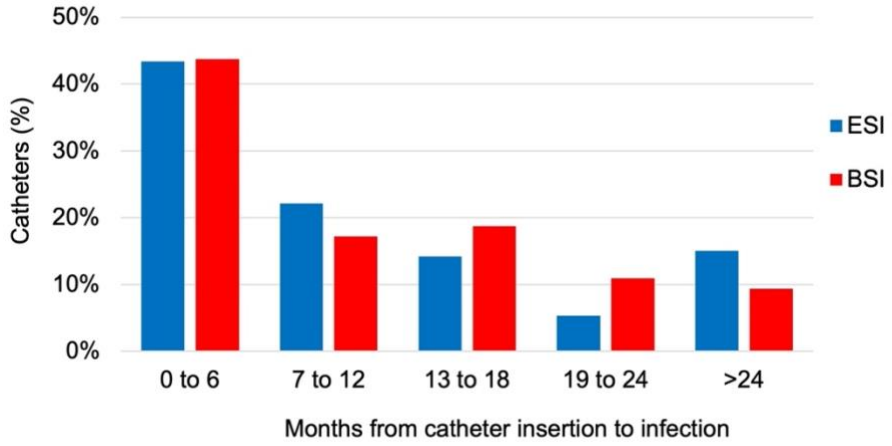


Figure S3B. Time from exit-site (ESI) or bloodstream (BSI) infection to central venous catheter removal.

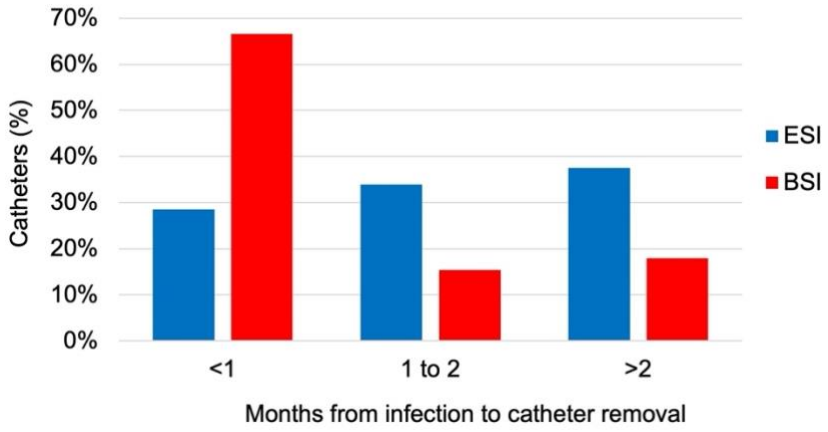
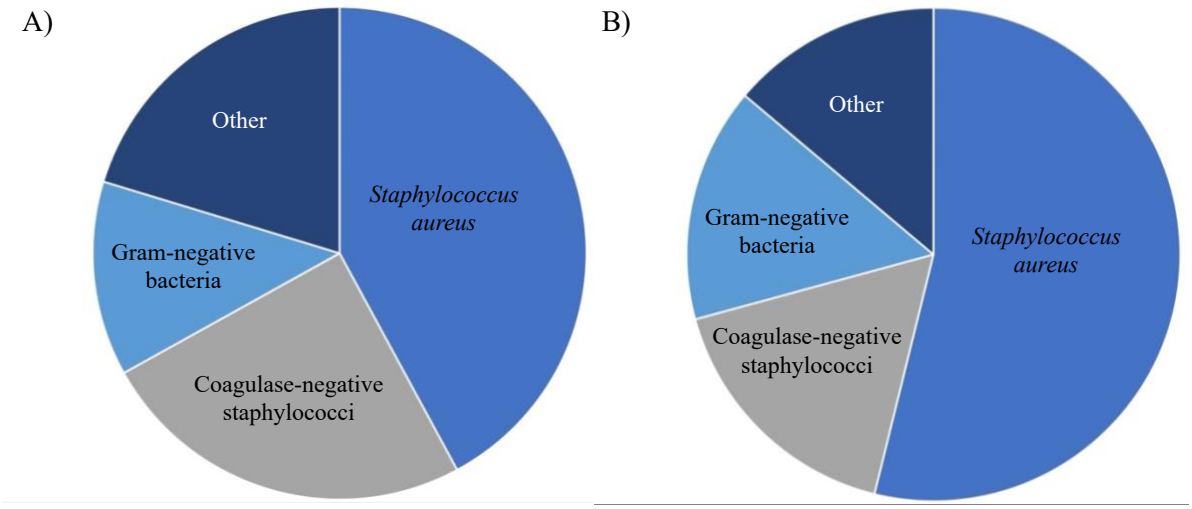


Figure S3C. Comparative etiology of A) exit-site infections and B) bloodstream infections.



CHAPTER 4: Antimicrobial dosing in the outpatient hemodialysis setting: a pharmacokinetic, pharmacodynamic, and toxicodynamic evaluation of cefazolin and ceftazidime.

Preamble: Of note, the study presented in this chapter was to originally include a third antimicrobial, ciprofloxacin. However, the study of ciprofloxacin was discontinued due to significant delays related to the COVID-19 pandemic and low enrollment. **REFERENCES** are merged at the end of this document. **APPENDICES 1A**, **1B**, **1C**, **1D, 1E, 1F, 4A, 4B, 4C, 4D, 4E,** and **4F** are referred to in this chapter.

4.1. Abstract

Background: Infections result in significant morbidity and mortality in patients receiving HD. Despite considerable use, the current one-dose-fits-all approach to cefazolin and ceftazidime dosing has not been validated. This study aimed to determine whether cefazolin and ceftazidime dosing are optimal to treat infections in the HD setting.

Methods: A PK study was conducted at the SBH outpatient HD unit. Patients receiving chronic HD and treatment with cefazolin or ceftazidime (2 g thrice weekly post-HD) were enrolled. Clinical data and blood samples were collected. Total and free antimicrobial concentrations were measured in serum. Maintaining free pre-HD troughs above a pathogen's MIC (100%$fT_{>MIC}$) and 100%$fT_{>4xMIC}$ were used to predict efficacy. Free pre-HD troughs >10x a pathogen's MIC were considered supratherapeutic.

Results: For cefazolin, 20 participants were enrolled and 19 completed the study (60.0% female, 60 ± 13 years old, 86.8 ± 24.2 kg weight, 18 [8–36] months dialysis vintage). Two participants produced no urine, 30.0% ≤1 cup daily, and 60.0% >1 cup daily. Total peak and pre-HD trough concentrations were 237.3 ± 47.7 mg/L and 70.1 ± 37.7 mg/L, respectively. Protein binding was concentration-dependent, averaging 81.8% ± 5.6% in trough samples. The Vd was 10.2 ± 2.6 L, correlating with body weight (P = 0.05). The $t_{½off\text{-}HD}$ was 31.4 ± 12.0 hours but was shorter in participants with higher urine production (P = 0.04) and those newer to dialysis (P = 0.05). Overall, 90.0%–100% of participants achieved 100%$fT_{>MIC}$, while 50.0%–95.0% achieved 100%$fT_{>4xMIC}$. Target attainment was lower for Enterobacterales, three-day interdialytic periods, and shorter $t_{½off\text{-}HD}$ (P <0.001). Supratherapeutic levels were observed in 15.0%–30.0% of participants. Three-day interdialytic periods, longer $t_{½off\text{-}HD}$ (P = 0.05) and higher dose by weight (P = 0.03) predicted excessive concentrations.

For ceftazidime, 18 participants were enrolled, and 15 completed the study (61.1% female, 65 ± 14 years old, 79.0 ± 20.7 kg weight, 33 [12–65] months dialysis vintage). Two participants produced no urine, 66.7%

≤1 cup daily and 22.2% >1 cup daily. Total peak and pre-HD trough concentrations were 122.5 ± 36.9 mg/L and 31.7 ± 10.9 mg/L, respectively. Protein binding was concentration-independent, averaging 10.3% ± 4.3%. The Vd and $t_{½off\text{-}HD}$ were 19.0 ± 5.6 L and 28.1 ± 4.8 hours, respectively. Compared to cefazolin, $t_{½off\text{-}HD}$ was less variable, likely attributed to lower residual kidney function (i.e., longer dialysis vintage and lower urine production). All participants achieved 100%$fT_{>MIC}$, while 0%–100% achieved 100%$fT_{>4xMIC}$. Target attainment was lower for *P. aeruginosa*, three-day interdialytic periods, shorter $t_{½off\text{-}HD}$ (P = 0.02), higher urine production (P = 0.009), and larger Vd (P = 0.02). No supratherapeutic levels were observed.

Conclusions: This study demonstrates the limitations of using one-dose-fits-all regimens in the HD setting. It identifies the importance of considering residual kidney function, body weight, interdialytic period, and pathogen MIC to optimize antimicrobial therapy. Although TDM of cefazolin and ceftazidime is not standard practice, it would improve dose individualization and the treatment of infections in patients receiving HD.

4.2. Introduction

PKPD research has demonstrated the importance of dosing for clinical outcomes, particularly for treating infectious diseases.[17,18,34,144] PKPD-directed antimicrobial dosing has improved efficacy, safety, and survival in patients with severe infections.[21,22] Whereas PKPD is widely used to optimize antimicrobial dosing for other high-risk populations, such as the critically ill, such progress has not been made for patients receiving HD.[19,25,125]

Patients receiving HD are among the most vulnerable to infectious diseases, which results in significant infection-related morbidity and mortality. Their susceptibility arises from several factors, including vascular access necessary for HD, immunodeficiencies associated with ESKD, comorbidities, and frequent exposures in healthcare settings. In addition to compromised immunity, treatment is complicated by the effects of ESKD and HD on the PK of antimicrobials. Unfortunately, there is a lack of evidence to guide appropriate dosage adjustments in the outpatient HD setting. Most studies conducted to date have employed strict exclusion criteria to minimize variability in PK, which limits the applicability of their findings to real-world clinical practice. Furthermore, the lack of TDM for many antimicrobials impedes dose individualization.

Cefazolin and ceftazidime are two of the most frequently prescribed antimicrobials in the outpatient HD setting.[85,113,116,126,127] Despite significant use, dosing is based on limited data that have not been validated. Because of the lack of evidence, dosing guidelines vary (**APPENDICES 1E and 1F**), and the doses used in practice are largely speculative. Additionally, without evidence guiding dosage adjustments, HD programs often implement one-dose-fits-all protocols that do not account for patient-specific factors that impact PK (**APPENDIX 1A**).[100,121,128] The lack of TDM for cephalosporins in practice further restricts decision-making related to personalized dosage adjustments. As a result, poor clinical outcomes due to suboptimal antimicrobial dosing may be overlooked and wrongly attributed to patient factors, such as ESKD.

Although patients receiving HD patients are a high-risk population that would benefit from evidence-based antimicrobial dosing, there are currently no data to support the existing approaches to cefazolin and ceftazidime dosing in this setting. Given the significant knowledge gap, this study aimed to characterize the concentrations and PK of cefazolin and ceftazidime in patients receiving chronic HD to determine whether current dosing strategies are optimal to treat the most clinically relevant infections in this population.

4.2.1. Hypothesis

The current one-dose-fits-all approach for cefazolin and ceftazidime does not reliably attain therapeutic concentration targets in the outpatient HD setting, thereby increasing the risk of adverse outcomes such as treatment failure, antimicrobial-associated toxicity, and AMR.

4.2.2. Objectives

1. To measure and describe the total and free serum concentrations of cefazolin and ceftazidime in a study population of infected adults receiving chronic intermittent high-flux HD (iHFHD).
2. To characterize the PK of cefazolin and ceftazidime in the study population, including protein binding, half-life, and volume of distribution.
3. To determine whether current dosing strategies are optimal to treat the most clinically relevant infections in the outpatient HD setting.

4.3. Methods

4.3.1. Study design

This study was a prospective, non-interventional PK study of cefazolin and ceftazidime in adults undergoing chronic iHFHD and receiving treatment for proven or suspected infection. It was conducted at the SBH HD unit in Winnipeg, part of the provincial MRP and was funded by an Allied Health Grant from the Kidney Foundation of Canada.

Before enrollment, approvals were granted by the University of Manitoba Health Research Ethics Board (#HS22503, **APPENDIX 4A**) and the SBH Research Review Committee (#2019/1840, **APPENDIX 4B**). Per correspondence with Health Canada, a Clinical Trial application was not required. The study Protocol, Participant Information and Consent Form, and Data Collection Sheet are included in **APPENDIX 4C, 4D**, and **4E**, respectively. Research personnel that had direct contact with research participants, i.e., the principal investigator, Dr. SA Zelenitsky, and the author, CK Lawrence, completed the Panel on Research Ethics Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans Course on Research Ethics (TCPS 2: CORE). To enable public access and transparency, the study was registered on ClinicalTrials.gov (NCT04319328).

Sample Size Determination: A sample size of 20 participants on iHFHD was selected, representing the most extensive PK study of cefazolin and ceftazidime to date. The sample size for each antimicrobial was calculated using:

$$\boldsymbol{n = \frac{Z^2 \delta^2}{E^2}}$$

Where n is the number of participants, Z is the 95% confidence interval of a standard normal distribution (i.e., 1.96), δ is the estimated standard deviation of the outcome variable, and E is the desired margin of error for the outcome variable (i.e., 15%).[145] Drug clearance (CL) was used as the PK outcome variable, with estimates based on the limited data available from a PK study of cefazolin, i.e., 30.9 ± 6.5 mL/min

during HD and 2.9 ± 0.7 mL/min between HD sessions.[146] Since sample size (n) is typically used to determine the number of participants required in each arm of comparative studies, the number was doubled in the context of conducting a descriptive PK study. Therefore, the sample size calculations included 20 participants with three blood samples per participant (i.e., 60 total) for each cohort, i.e., cefazolin and ceftazidime. The numbers were comparable to a previous PK study of 22 participants and 49 blood samples used to successfully construct a PK model of vancomycin in patients receiving iHFHD.[147]

4.3.2. Participant recruitment & consent

Before recruitment, the study was presented to staff at the SBH HD unit. Information posters were circulated to staff and posted in common areas (**APPENDIX 4F**). Recruitment started in October 2019 and finished in April 2023. Due to safety precautions during the COVID-19 pandemic, enrollment was suspended from March to July 2020 and November 2020 to July 2021.

Patients prescribed cefazolin or ceftazidime for proven or suspected infection in the SBH HD unit were identified by HD pharmacists. Patients were approached by a pharmacist, nurse, or nephrologist to ask for permission to be contacted by study personnel. A standardized script was provided for all staff as follows: *"Hi, Ms./Mr. ____, my name is ____. I'm a pharmacist/nurse/nephrologist in the hemodialysis unit. I'm aware you are receiving treatment with cefazolin/ceftazidime. I wanted to inform you that an optional study is taking place in our hemodialysis unit, which looks at cefazolin/ceftazidime blood levels in patients on dialysis. May I provide your name to one of the study members so they can discuss the study with you? Your decision to provide your name will in no way affect your care in the hemodialysis unit."*

Adult patients receiving chronic iHFHD were considered eligible if they could provide informed consent and their antimicrobial course allowed sufficient time for sample collection. Individuals could only participate once for a given antimicrobial. With separate informed consent, participants were eligible to participate in the study of the other antimicrobial. Patients with acute kidney injury or recovering kidney

function were excluded, as the intention was to study patients receiving chronic HD for ESKD. Patients were also excluded if they had chronic liver disease (Child-Pugh Class C or higher), which could confound drug elimination.

Once eligibility was confirmed, study personnel met with the patient during their HD session to discuss the study. The study personnel then inquired about their willingness to participate and obtained informed written consent if agreeable. The participant was given a copy of the Participant Information and Consent Form, and the original signed copy was retained in confidential study files. Following enrollment, the participant was assigned a study number to keep all subsequent data collected de-identified. A master list of participant names linked to study numbers was stored securely and separately from other study files to minimize the risk of a confidentiality breach. Study participation was documented directly in the patient's HD chart to inform staff.

4.3.3. Data collection

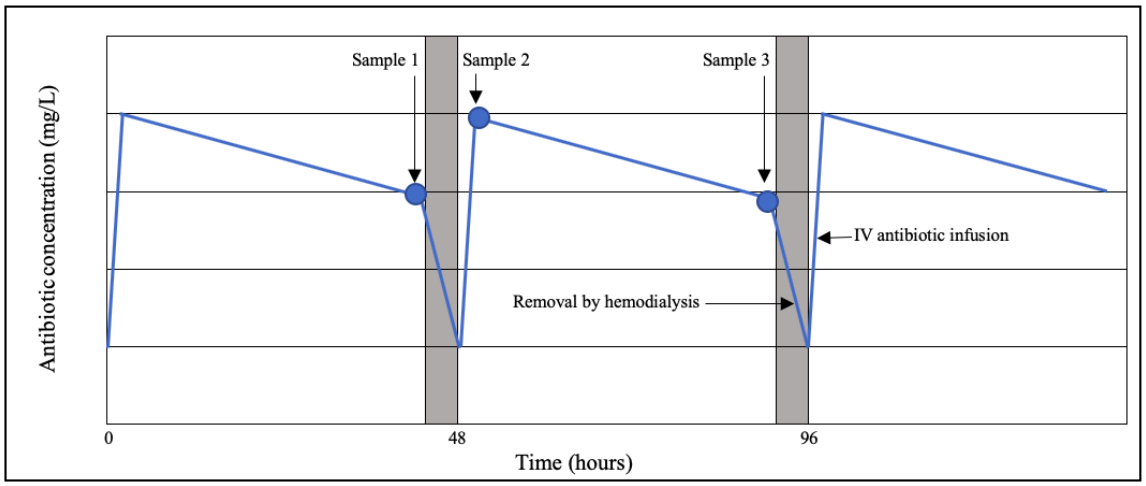
Data were collected by a single individual (CK Lawrence) using a standardized Data Collection Sheet. The following participant information was recorded: age, sex, height, dry body weight (i.e., estimated weight without excess fluid), dialysis vintage (i.e., duration of time on any type of dialysis), comorbidities, etiology of ESKD, concurrent medications that may interact with study drugs (i.e., heparin, probenecid, chloramphenicol), and albumin plasma concentrations. All HD sessions from the initiation of antimicrobial therapy to the completion of blood sample collection were documented, including dialyzer type, blood and dialysate flow rates, effective HD time, HD adequacy as indicated by Kt/V (where K is dialyzer clearance of urea, t is HD time, and V is volume of distribution of urea), and pre-HD and post-HD body weight. To estimate residual kidney function, participants were asked whether they produced no urine, ≤1 cup per day, or >1 cup per day.

The cefazolin and ceftazidime therapies were recorded, including doses and administration times. The MRP uses standard dosing protocols of cefazolin 2 g thrice weekly post-HD and ceftazidime 2 g thrice weekly post-HD (**APPENDIX 1A**).[100] Dosage adjustments are at the discretion of the prescribing nephrologist. Doses were administered by the HD nurse as a 5-minute IV push into the HD vascular access site, i.e., central venous catheter, AVF, or AVG directly after HD.

4.3.4. Sample collection & processing

Three blood samples (~6 mL), including two pre-HD troughs and one post-HD post-dose peak, were collected from each participant. The two pre-HD trough samples were collected on different days immediately before HD. The post-HD post-dose peak sample was collected 15 minutes after administering the post-HD antimicrobial dose. If a sample was missed, it was collected during a subsequent HD session. **Figure 4-i** depicts the sampling scheme using a simplified one-compartment plasma concentration profile.

Figure 4-i. Sample collection scheme.



HD nurses drew blood samples from participants' HD vascular access sites. They were collected in labelled 10 mL plain red-topped glass BD Vacutainer® tubes without anticoagulants or other additives (BD Canada,

Mississauga, Canada). Each sample was inverted five times and allowed to clot for 1 hour. Clotted whole blood was centrifuged in an accuSpin™ 8C centrifuge at 1300 g for 10 minutes at room temperature to separate the serum layer. One peak and one pre-HD trough sample from 10 participants were further processed to obtain ultrafiltrate to measure free antimicrobial concentrations. One millilitre of serum was transferred to a Centrifree® device (EMD Millipore Corporation, Massachusetts, United States) and centrifuged at a fixed 45-degree angle at 2000 g for 45 minutes at room temperature. Sterile disposable pipettes were used to transfer serum and ultrafiltrate to labelled cryogenic vials and then stored at -80°C until pharmaceutical analysis.

4.3.5. Pharmaceutical analysis

4.3.5.1 Cefazolin:

Using a previously validated method, Ultra-High Performance Liquid Chromatography tandem Mass Spectrometry (UHPLC-MS/MS) was used to measure total and free cefazolin concentrations in serum and ultrafiltrate, respectively.[148] A Shimadzu Nexera UHPLC connected to a Shimadzu LCMS-8040 triple quadrupole mass spectrometer (Shimadzu Corp., Kyoto, Japan) was used. The curves were linear (>0.99) and quantitative, from 1 to 400 mg/L for total cefazolin concentrations (93% accuracy, 97% precision) and 1 to 400 mg/L for free cefazolin concentrations (98% accuracy, 96% precision).

Stable isotope-labeled cefazolin ($^{13}C_2{}^{15}N$, Toronto Research Chemicals Inc, Ontario, Canada (TRC-C242502)) was used as an internal standard (IS) because its chemical properties are the same as, but mass is 3 amu higher than, natural abundance cefazolin so the two can be easily differentiated using mass spectrometry. Analytical-grade cefazolin (natural abundance) (Sigma-Aldrich Canada Co, Ontario, Canada) was used for external standardization and quantification using a peak area ratio (PAR) of the IS. Stock solutions were prepared in water, and aliquots were stored at -80°C. For total levels, standard curve and quality control samples were prepared with cefazolin and IS in blank pooled human serum (Innovative

Research Inc., Michigan, United States). For free levels, standard curve and quality control samples were prepared with cefazolin and IS in blank pooled human serum ultrafiltrate, which was processed using the Centrifree® device (same methods as described above).

To measure total serum concentrations, samples were thawed, and 50 µL of a 100 mg/L IS solution in water was added to 50 µL of the sample and vortexed to mix. Proteins were then precipitated using 1 mL of analytical-grade acetonitrile at -20°C, and the solution was vortexed and centrifuged (15,000 g, 10 minutes).[145] The supernatant was transferred to a new tube and dried for 40 minutes at 45°C in a Savant SPD1010 vacuum centrifuge (Thermo Fisher Scientific, Massachusetts, United States). The samples were then reconstituted in 100 µL of mobile phase A (0.1% aqueous formic acid) and then re-centrifuged (15,000 g, 15 minutes) in a 0.2 µm VWR Centrifugal Filter 82031-358 (VWR International LLC, Pennsylvania, United States) to remove any additional particulates. To measure free concentrations, 50 µL of IS solution in water was added directly to 50 µL of the ultrafiltrate samples, dried as described above and then reconstituted in 100 µL mobile phase A. All standard curves and quality controls were prepared and analyzed on each day of analysis. All study samples were prepared and analyzed in duplicate on different days. The prepared samples were then transferred to HPLC vials, and 5 µL injected in the UHPLC-MS/MS for analysis.

The UHPLC-MS/MS was operated in positive ion mode using the DUIS interface (dual electrospray and atmospheric pressure chemical ionization) and multiple reaction monitoring events. Previously described MS transitions were used.[148] The precursor and product ion transitions as well as collision energies and pre-rod bias for cefazolin and the cefazolin IS are listed in **Table 4-i**. Nitrogen drying and nebulizing gas were at 15 L/min and 2 L/min, respectively. The desolvation line temperature was 250°C, and the heating block was 400°C. An Acquity UHPLC BEH C_{18} 1.7 µm 2.1 x 100 mm column (Waters Corp, Connecticut, United States) was used for separation at 40°C. The mobile phases comprised (A) 0.1% aqueous formic

acid and (B) acetonitrile with 0.1% formic acid. A flow rate of 0.4 mL/min was used with a 0% to 85% mobile phase B gradient over 1 minute, 85% mobile phase B held for 2 minutes, then stepped up to 100% mobile phase B and held for 2 minutes (to wash the column) and stepped back to 0% mobile phase B and held for 2 minutes (to recondition the column) for a total run time of 7 minutes. The retention time for cefazolin and the IS was 2.23 minutes. Optimization, data collection, and analysis were performed with LabSolutions software (Shimadzu, Kyoto, Japan).

4.3.5.2. Ceftazidime:

UHPLC-MS/MS measured total and free ceftazidime concentrations in serum and ultrafiltrate, respectively. An assay method was developed based on protocols published by others.[149–151] A Shimadzu Nexera UHPLC apparatus with a Shimadzu LCMS-8040 triple quadrupole mass spectrometer (Shimadzu Corp., Kyoto, Japan) was used. The curves were linear (>0.99) and quantitative from 1 to 400 mg/L for total ceftazidime concentrations (>85% accuracy, >88% precision) and 1 to 400 mg/L for free ceftazidime concentrations (>89% accuracy, >87% precision).

Ceftazidime-d5 (Toronto Research Chemicals Inc, Ontario, Canada (TRC-C244102)) was used as an IS because it has the same chemical properties as, but its mass is 5 amu higher than, natural abundance ceftazidime and therefore the two can be easily differentiated using mass spectrometry. Analytical-grade ceftazidime (natural abundance) (Sigma-Aldrich, MO, USA) was used for external standardization and quantification using the IS's PAR. Stock solutions were prepared in water, and aliquots were stored at -80°C. For total levels, standard curve and quality control samples were prepared with ceftazidime and IS in blank pooled human serum (Innovative Research Inc., Michigan, United States). For free levels, standard curve and quality control samples were prepared with ceftazidime and IS in blank pooled human serum ultrafiltrate, which was processed using the Centrifree® device (same methods as described above).

To measure ceftazidime concentrations, samples were thawed, and 15 µL (serum or ultrafiltrate) were added to 45 µL ice-cold methanol with 200 mg/L IS to precipitate proteins. Samples were vortexed and centrifuged (21,000 g, 15 minutes). The supernatants were then transferred to HPLC vials, and 1 µL injected into the UHPLC-MS/MS for analysis. All standard curves and quality controls were prepared and analyzed on each day of analysis. All study samples were prepared and analyzed in duplicate on different days.

The UHPLC-MS/MS was operated in positive ion mode using the DUIS interface (dual electrospray and atmospheric pressure chemical ionization) and multiple reaction monitoring. The precursor and product ion transitions as well as collision energies and pre-rod bias for ceftazidime are shown in **Table 4-i**. Nitrogen drying and nebulizing gas flow rates were 15 L/min and 2 L/min, respectively. The desolvation line and heating block temperatures were 250°C and 400°C, respectively. An Acquity UHPLC BEH C_{18} 1.7 µm 2.1 x 100 mm column (Waters Corp, Connecticut, United States) was used for separation at 40°C. The mobile phases consisted of (A) 0.1% aqueous formic acid in water and (B) 0.1% formic acid in methanol with a flow rate of 0.4 mL/min. A mobile phase B gradient was elevated from 2% to 20% over 1 minute, then stepped up to 98% and held for 3.3 minutes, and stepped down to 2% B and held for 1.9 minutes. The retention time for ceftazidime and the IS was 6.5 minutes. Optimization, data collection, and analysis were performed with LabSolutions software (Shimadzu, Kyoto, Japan).

UHPLC-MS/MS assay method validation for free and total levels of ceftazidime followed the *Food and Drug Administration Guidance for Industry: Bioanalytical Method Validation*.[152,153] Inter-day and intra-day variations were measured to validate the method. Standard curves (10 concentrations including and between 1 to 400 mg/L) and quality controls (2 mg/L, 80 mg/L, 320 mg/L) were prepared as described above and analyzed daily for three consecutive days. Intra-day variability was evaluated by six repeated injections at quality control concentrations. The lowest limit of quantification (LLOQ) was also assessed by six repeated injections to ensure both precision and accuracy were maintained at ≥80%. The intra- and inter-day

precision and accuracy were ≥80% for the LLOQ and ≥85% for the standard curve and quality controls. Therefore, the method presented acceptable accuracy and precision.

Table 4-i. Ultra-High Performance Liquid Chromatography tandem Mass Spectrometry parameters

Analyte	Precursor ion (*m/z*)	Product ion (*m/z*)	Q1 Pre Bias (V)	Collision energy (eV)	Q3 Pre Bias (V)
Cefazolin	455.2	156.0	-22	-17	-18
Cefazolin-$^{13}C_2$,^{15}N (IS)	458.2	156.0	-23	-16	-19
Ceftazidime	547.1	468.1	-28	-12	-27
Ceftazidime-d5 (IS)	552.3	468.1	-28	-12	-19

IS internal standard.

4.3.6. Data analysis

4.3.6.1. Participants, hemodialysis details, & dosing:

A descriptive analysis of participant characteristics, HD details, and antimicrobial dosing was conducted. The participant's total body weight (TBW) was calculated as the mean post-HD weight recorded during the study. The change in TBW from before to after HD was also computed. BMI (kg/m^2) was calculated and classified as underweight (<18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2), or obese (≥30 kg/m^2).[154] For participants with below-the-knee amputations, BMI was adjusted by increasing the participant's weight by 3.26%, i.e., the estimated total body mass attributed to the amputation.[155]

Antimicrobial doses were described relative to dosing weight (DW), i.e., TBW for non-obese individuals or adjusted body weight (ABW) for those classified as obese (i.e., BMI ≥30 kg/m^2) where:

$$\boldsymbol{ABW = IBW + 30\%(TBW - IBW)}$$

And where ideal body weight (IBW) is 50 kg + 2.3 kg for each inch over 5 feet for males and 45.5 kg + 2.3 kg for every inch over 5 feet for females. The correction factor of 30% is based on an approximation of the

relative distribution of β-lactams into adipose tissue.[156] The use of ABW for obese individuals allowed for a more reliable comparison of dosing among participants.

4.3.6.2. Serum concentrations & pharmacokinetics:

Descriptive analyses of total and free cefazolin and ceftazidime serum concentrations were conducted. Protein binding was calculated from total (serum) and free (ultrafiltrate) concentrations where:

$$\textbf{\textit{Protein binding}}\ (\%) = \frac{\textbf{\textit{total concentration} - \textit{free concentration}}}{\textbf{\textit{total concentration}}}\ \textbf{\textit{x}}\ \mathbf{100}\%$$

Differences in protein binding between peak and pre-HD trough samples were investigated. Relationships between protein binding and potential covariates, including age, sex, DW, albumin plasma concentration, daily urine production, and heparin administration during HD, were tested.

Various methods were utilized to describe the PK of cefazolin and ceftazidime. As described in the initial study protocol (**Appendix 4C**), PK analyses were first attempted using population-PK modelling with Pmetrics™ software (University of Southern California, Los Angeles).[157] However, this approach could not produce acceptably robust and reliable PK models for either cefazolin or ceftazidime. Next, individual PK modelling was conducted using ADAPT 5 software (University of Southern California, Los Angeles).[158] Whereas this method provided reasonable estimates for $t_{½\text{off-HD}}$ and Vd, it gave unreliable values for intradialytic half-life during HD ($t_{½\text{on-HD}}$).

Alternatively, an iterative fitting technique, the Sawchuk-Zaske with least sum of squares (Sawchuk-Zaske LSS) method, was developed to describe the PK. The initial PK parameters for each individual were estimated, where $t_{½\text{off-HD}}$ was calculated using the Sawchuk-Zaske method, and $t_{½\text{on-HD}}$ and Vd priors were based on literature values of 3.1 hours and 0.15 L/kg for cefazolin and 3.3 hours and 0.25 L/kg for ceftazidime, respectively.[146,159] PK parameters for a one-compartment model were estimated by minimizing the residual sum of squares between the observed and fitted concentrations. First, Vd was adjusted and then,

$t½_{off\text{-}HD}$ and Vd were adjusted sequentially to minimize the sum of squares. Finally, $t½_{on\text{-}HD}$ was added and all parameters were adjusted sequentially until the nadir was reached. Relationships between $t½_{off\text{-}HD}$ or Vd and potential covariates, including age, dialysis vintage, DW, sex, and daily urine production, were investigated.

4.3.6.3. Pharmacodynamics:

For comparison, all measured total pre-HD trough concentrations were extrapolated to both two- and three-day interdialytic periods using:

$$C_{day3} = C_{day2}\, x\, e^{-\left(\frac{0.693}{t1/2_{off-HD}}\, x\, 24\, h\right)}$$

Where C_{day3} is the pre-HD trough concentration for a three-day interdialytic period, C_{day2} is the pre-HD trough concentration for a two-day interdialytic period, and $t½_{off\text{-}HD}$ is the half-life off HD modelled by the Sawchuk-Zaske LSS method. If required, concentrations were adjusted to represent the standard cefazolin and ceftazidime dosing protocol of 2 g thrice weekly post-HD. Finally, all total pre-HD trough concentrations were converted to free levels using the study mean protein binding.

Pre-HD trough concentrations were analyzed to determine whether they were optimal to treat the most clinically relevant infections in the outpatient HD setting, i.e., cefazolin against MSSA and Enterobacterales and ceftazidime against Enterobacterales and *Pseudomonas aeruginosa*. The PD activity was predicted based on the established PKPD index for cephalosporins, the percentage of time that free plasma concentrations exceed a pathogen's MIC, i.e., $\%fT_{>MIC}$. A PKPD threshold of $100\%fT_{>MIC}$ during interdialytic periods was selected along with a higher threshold of $100\%fT_{>4xMIC}$, which was shown to improve efficacy in other high-risk populations and reduce the development of AMR.[17,18]

MIC values were based on Clinical Laboratory Standards Institute (CLSI) MIC susceptibility breakpoints for relevant pathogens.[160] Since there is no breakpoint for cefazolin against MSSA, a MIC covering 90%

of isolates tested (MIC_{90}) was used, aligning with methodologies in other similar studies.[161,162] Therefore, for cefazolin against MSSA, the PKPD thresholds translated to maintaining free pre-HD trough concentrations >1 mg/L or >4 mg/L based on a MIC_{90} of 1 mg/L.[161] For cefazolin against Enterobacterales, the PKPD thresholds were >2 mg/L or >8 mg/L based on the susceptible MIC breakpoint of ≤2 mg/L. For ceftazidime against Enterobacterales and *P. aeruginosa*, the PKPD thresholds were >4 mg/L or >16 mg/L (i.e., susceptible MIC breakpoint of ≤4 mg/L) and >8 mg/L or >32 mg/L (i.e., susceptible MIC breakpoint of ≤8 mg/L), respectively. These thresholds were analyzed for both two- and three-day interdialytic periods. Relationships between subtherapeutic concentrations and potential covariates, including sex, age, DW, daily urine production, $t½_{off\text{-}HD}$, Vd, dose (in mg/kg_{DW}), and interdialytic period, were also investigated.

4.3.6.4. Toxicodynamics:

The toxicodynamics of cefazolin and ceftazidime are not well described. However, high cephalosporin trough concentrations have been associated with neurotoxicity.[163,164] In patients with ESKD, reduced drug elimination can lead to increased exposures if dosages are not appropriately adjusted. As such, supratherapeutic trough levels and excessive antimicrobial exposure in study participants were analyzed.

Supratherapeutic or unnecessarily high trough levels were defined as those not expected to further improve microbiological or clinical response, i.e., $100\%fT_{>10xMIC}$. Others have also used this upper limit to determine when a dose reduction is required.[165] Therefore, total pre-HD cefazolin trough concentrations ≥100 mg/L, based on ten times the breakpoint of ≤2 mg/L for Enterobacterales and estimated protein binding of 80%, were considered excessive.[35] The upper limit for ceftazidime was total pre-HD trough concentrations ≥90 mg/L, based on ten times the breakpoint of ≤8 mg/L for *P. aeruginosa* and estimated protein binding of 10%.[166] The toxicodynamic upper limits were analyzed for both two- and three-day interdialytic periods. Relationships between supratherapeutic concentrations and potential covariates, including sex, age, DW, daily urine production, $t½_{off\text{-}HD}$, Vd, dose (in mg/kg_{DW}), and interdialytic period, were also investigated.

Excessive antimicrobial exposure was assessed by comparing exposure in study participants relative to controls with normal kidney function (i.e., creatinine clearance [CrCl] ~100 mL/min). Exposure was calculated based on the area under the concentration versus time curve over 48 hours (AUC_{48h}) using:

$$\frac{\boldsymbol{Dose}}{\boldsymbol{Vd} \times \frac{\boldsymbol{0.693}}{\boldsymbol{t_{1/2}}}}$$

Where *Dose* is the total dose administered over 48 hours; *Vd* is the volume of distribution; and *t½* is the antimicrobial half-life elimination. For each participant, the observed AUC_{48h} of either cefazolin or ceftazidime (2 g thrice weekly post-HD) was calculated based on their Vd and *t½* between dialysis sessions as per the Sauchuk-Zaske LLS method. For comparison, a predicted AUC_{48h} assuming normal kidney function was calculated using the study Vd, a *t½* of 1.8 hours based on literature values for cefazolin and ceftazidime in controls with normal kidney function, and the standard cefazolin or ceftazidime dosing of 2 g every 8 hours for severe infections.[35,166] The relative antimicrobial exposure was calculated as the ratio of the observed AUC_{48h} in participants divided by the predicted AUC_{48h} in controls with normal kidney function.

4.3.6.5. Statistics:

Study data were characterized using descriptive statistics. Continuous variables were reported as mean ± SD or median [interquartile range (IQR)] as appropriate. Categorical variables were presented as number and percentage. The Student's t-test and Mann-Whitney U-test were used to analyze continuous parametric and non-parametric data, respectively. Chi-square or Fisher's exact tests were used to investigate differences between dichotomous data as appropriate. Correlations were tested using Spearman's rho test. Correlations were described as weak if r was <0.3, moderate if r was between 0.3 and 0.7, and strong if r was >0.7. Statistical analyses were performed using SPSS (Version 29.0.1.1).

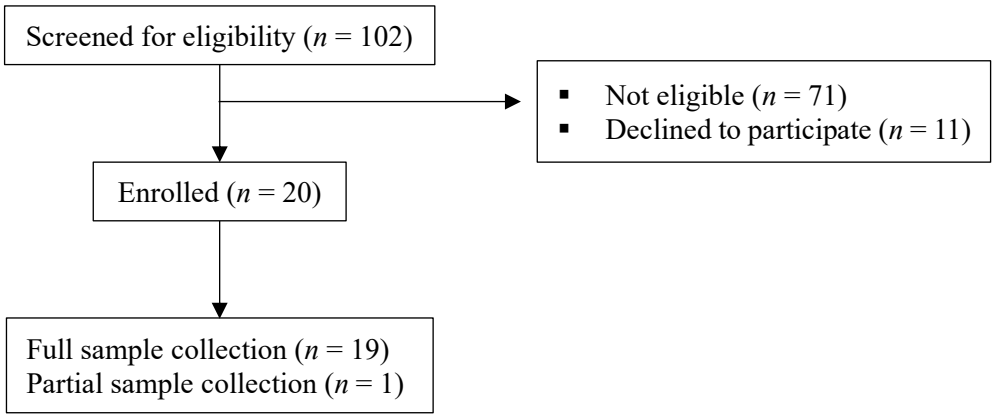
4.4. Results

4.4.1. Cefazolin

4.4.1.1. Participants, hemodialysis details, & cefazolin dosing

Twenty participants receiving cefazolin were enrolled, and 19 completed the study (**Figure 4A**). One individual did not complete sample collection due to early cessation of their antimicrobial course; therefore, only two of three blood samples were collected. Nonetheless, their data were included in analyses where appropriate.

Figure 4A. Study flow diagram for the cefazolin cohort.



The characteristics of study participants are summarized in **Table 4A**. Most were female (60.0%, 12/20), with a mean age of 60 ± 13 years. Half of the participants were classified as obese, with a mean TBW of 86.8 ± 24.2 kg. The most common comorbidities were diabetes and hypertension in 90.0% (18/20) and 85.0% (17/20) of participants, respectively. Participants had received dialysis for a median of 18 [8–36] months. Two participants reported no urine production, whereas 30.0% (6/20) reported ≤1 cup per day, and 60.0% (12/20) reported >1 cup per day.

Table 4A. Characteristics of participants in the cefazolin cohort (n = 20).

Female sex	12 (60.0%)
Age (years)	60 ± 13
TBW (kg)	86.8 ± 24.2
DW (kg)[a]	71.3 ± 12.0
BMI (kg/m^2)	31.3 ± 8.6
BMI class	
Underweight (<18.5 kg/m^2)	0
Normal (18.5–24.9 kg/m^2)	5 (25.0%)
Overweight (25–29.9 kg/m^2)	5 (25.0%)
Obese (≥30 kg/m^2)	10 (50.0%)
Comorbidities	
Diabetes	18 (90.0%)
Hypertension	17 (85.0%)
Heart disease	11 (55.0%)
Dyslipidemia	11 (55.0%)
Dialysis vintage (months)	18 [8–36]
Daily urine production	
None	2 (10.0%)
≤1 cup	6 (30.0%)
>1 cup	12 (60.0%)

Reported as n (%), mean ± SD, or median [IQR].

BMI body mass index, *DW* dosing weight, *TBW* total body weight.

[a] Adjusted body weight used for obese individuals and total body weight for non-obese individuals.

The HD sessions participants underwent during the study are detailed in **Table 4B**. The Fresenius Optiflux F250NRe and F160NRe high-flux dialyzers were used in 95.0% (19/20) of HD sessions. Seventy-five percent (15/20) of participants were administered heparin during HD to prevent clotting within the apparatus. On average, HD sessions were 3.6 ± 0.6 hours in duration. The most common dialysate flow rate was 500 mL/min (70.0%, 14/20) versus 800 mL/min. The mean dialysis blood flow rate was 328.5 ± 30.0 mL/min, and the HD adequacy (Kt/V) was 1.5 ± 0.3. Based on the change in TBW, a mean of 2.1 ± 0.9 L of fluid was removed during HD.

Table 4B. Details of hemodialysis sessions for participants in the cefazolin cohort (*n* = 20).

High-flux dialyzer	
Fresenius Optiflux F250NRe	12 (60.0%)
Fresenius Optiflux F160NRe	7 (35.0%)
Baxter Revaclear	1 (5.0%)
Mean HD session duration (h)	3.6 ± 0.6
Dialysate flow rate	
500 mL/min	14 (70.0%)
800 mL/min	6 (30.0%)
Mean blood flow rate (mL/min)	328.5 ± 30.0
Mean Kt/V	1.5 ± 0.3
Mean TBW change (kg)	2.1 ± 0.9

Reported as n (%) or mean ± SD.

HD hemodialysis, *h* hours, *TBW* total body weight, *Kt/V* dialysis adequacy where K is dialyzer clearance of urea, t is dialysis time, and V is urea distribution volume.

All but one participant received the standard dosing protocol of 2 g cefazolin thrice weekly post-HD. The other participant (TBW 84.9 kg, BMI 28.7 kg/m^2, urine production >1 cup per day, HD duration ~4.5 hours) was prescribed 2 g before two-day interdialytic periods and 3 g before three-day interdialytic periods. However, all study samples were collected following 2 g doses. The mean cefazolin dose was 28.8 ± 4.5 mg/kg$_{DW}$. Overall, a median of 3 [3–5] doses of cefazolin were recorded per participant.

4.4.1.2. Cefazolin serum concentrations & pharmacokinetics

A total of 59 blood samples were collected from the 20 study participants, including 19 post-HD post-dose peaks and 40 pre-HD troughs. In all samples, total cefazolin serum concentrations were measured. Free cefazolin levels were also measured in a subset of 20 samples (comprising 10 peak and 10 pre-HD trough samples from 10 participants). Concentration data are summarized in **Table 4C** and **Figures 4B** and **4C**. **Figure 4D** depicts free relative to total concentrations. The mean total and free peak concentrations were 237.3 ± 47.7 mg/L and 96.7 ± 42.8 mg/L, respectively. The total pre-HD trough concentration varied from

3.7 to 149.4 mg/L with a mean of 70.1 ± 37.7 mg/L. The free pre-HD trough concentrations were 15.0 ± 8.9 mg/L.

Table 4C. Total and free cefazolin serum concentrations.

	N	Mean ± SD	Median [IQR]	Range
Total (mg/L)				
Peaks	19	237.3 ± 47.7	246.0 [207.1–261.5]	141.9–316.8
Pre-HD troughs	40	70.1 ± 37.7	72.2 [38.3–90.6]	3.7–149.4
Free (mg/L)				
Peaks	10	96.7 ± 42.8	89.7 [73.3–116.0]	45.0–185.3
Pre-HD troughs	10	15.0 ± 8.9	11.9 [8.8–23.1]	2.1–28.8

HD hemodialysis.

Figure 4B. Total cefazolin peak (n = 19) and pre-hemodialysis trough (n = 40) serum concentrations.

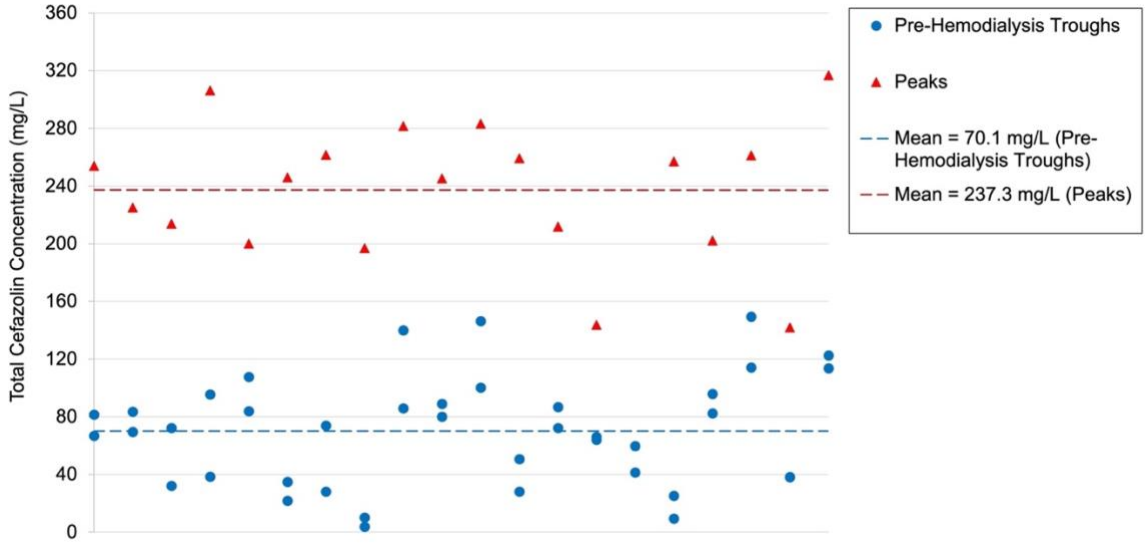


Figure 4C. Free cefazolin peak (n = 10) and pre-hemodialysis trough (n = 10) serum concentrations.

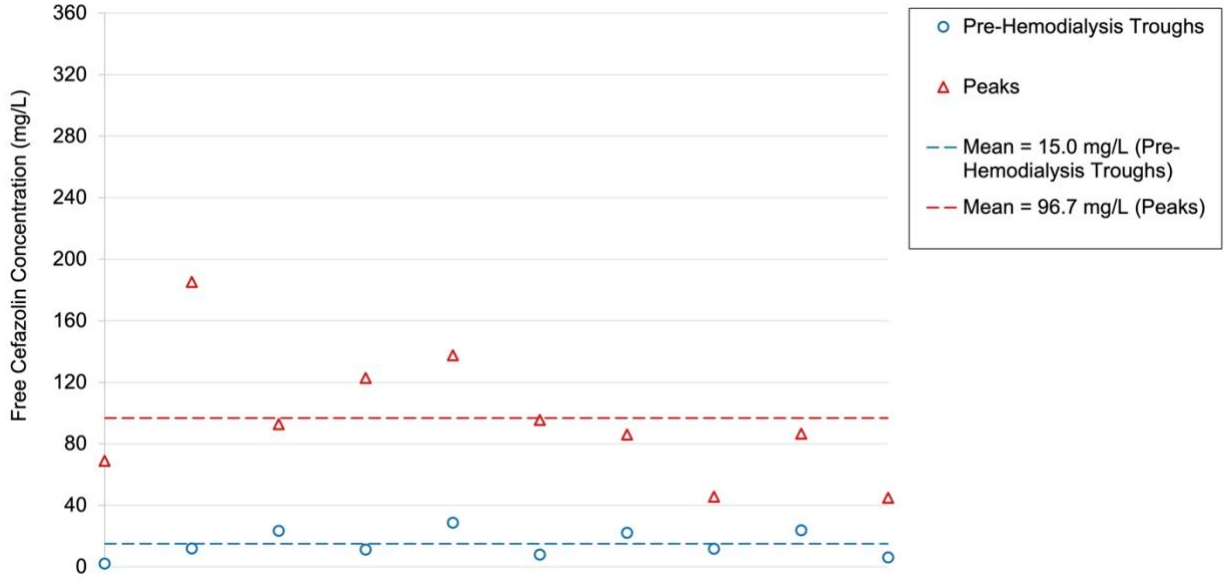
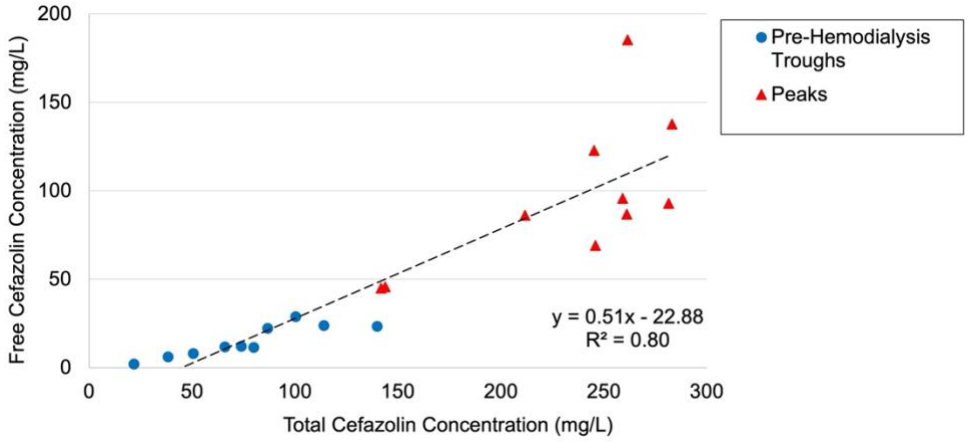


Figure 4D. Free relative to total cefazolin serum concentrations.



The mean cefazolin protein binding was 70.7% ± 15.0%. However, protein binding was significantly lower in peak (59.5% ± 12.9%) versus pre-HD trough (81.8% ± 5.6%) samples (P <0.01). **Figure 4E** illustrates concentration-dependent cefazolin protein binding (R^2 = 0.62). Cefazolin protein binding in pre-HD troughs was also moderately correlated with albumin concentrations (rho = 0.67, P = 0.03) (**Figure 4F**, R^2 = 0.29). Protein binding was not statistically lower in peak samples collected from participants who received heparin

during HD (56.0% ± 14.0%) compared to those who did not (67.8% ± 4.4%) (P = 0.2, **Table S4A**). No significant relationships were identified between protein binding and age, DW, sex, or urine production (**Table S4A**).

Figure 4E. Cefazolin protein binding relative to total serum concentration.

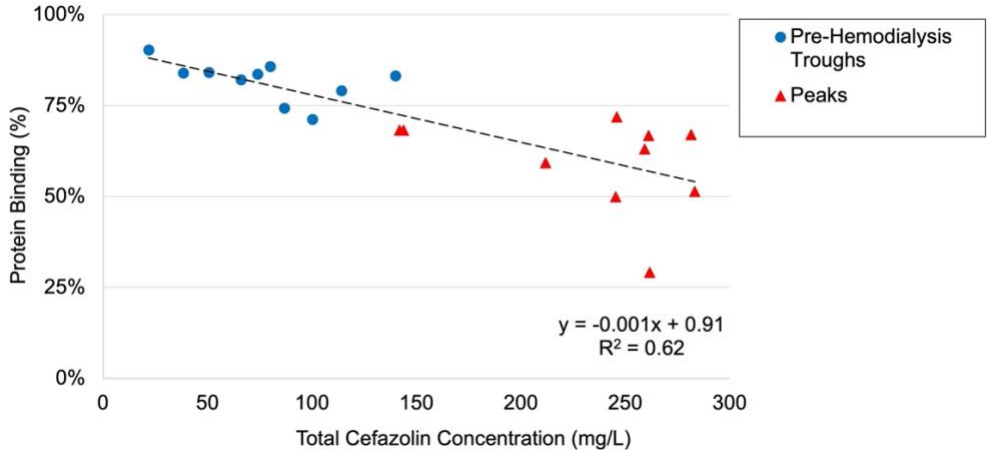
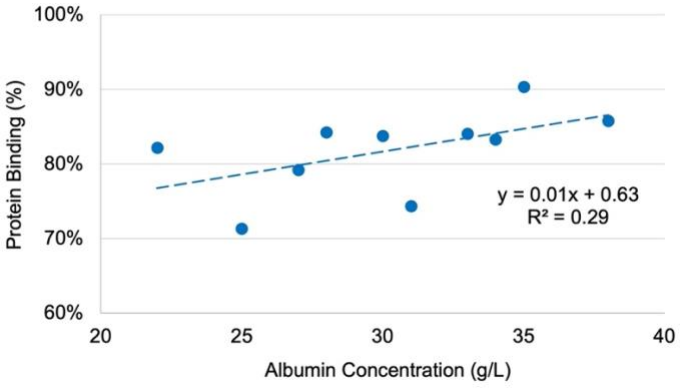


Figure 4F. Cefazolin protein binding in pre-hemodialysis troughs relative to albumin concentration (n = 10).



The modelled cefazolin PK parameters are reported in **Table 4D**. The mean $t_{½off\text{-}HD}$, $t_{½on\text{-}HD}$, and Vd were 31.4 ± 12.0 hours, 3.1 ± 0.5 hours, and 10.2 ± 2.6 L, respectively. There was a wide range in cefazolin $t_{½off\text{-}}$

$_{HD}$ from 10.5 to 53.4 hours. The $t½_{off\text{-}HD}$ was significantly shorter in participants that had received dialysis for less than 18 months (26.4 ± 10.8 hours) compared to those that had been on dialysis longer (37.0 ± 11.2 hours) (P = 0.05, **Table S4C**; **Figure 4G**). The $t½_{off\text{-}HD}$ was also shorter when urine production was >1 cup per day (27.2 ± 11.4 hours) as opposed to ≤1 cup per day (38.6 ± 9.9 hours) (P = 0.04, **Table S4C**; **Figure 4H**). No relationships were identified between $t½_{off\text{-}HD}$ and age, DW, or sex (**Table S4C**). Cefazolin Vd was moderately correlated with DW (rho = 0.46, P = 0.05) (**Table S4D**; **Figure 4I**, R^2 = 0.47), while no significant relationships were identified between Vd and age, dialysis vintage, sex, or urine production (**Table S4D**).

Table 4D. Cefazolin pharmacokinetic parameters (n = 19).[a]

	Mean ± SD	Median [IQR]	Range
$t½_{off\text{-}HD}$ (h)[b]	31.4 ± 12.0	29.5 [23.8–39.7]	10.5–53.4
$t½_{on\text{-}HD}$ (h)	3.1 ± 0.5	3.1 [3.0–3.3]	1.9–4.2
Vd (L) Vd (L/kg$_{DW}$)[c]	10.2 ± 2.6 0.14 ± 0.03	9.5 [8.5–11.3] 0.15 [0.13–0.15]	6.9–16.4 0.10–0.19

DW dosing weight, *HD* hemodialysis, *h* hours, $t½_{off\text{-}HD}$ half-life off hemodialysis, $t½_{on\text{-}HD}$ half-life on hemodialysis, *Vd* volume of distribution.

[a] Modelled using the Sawchuk-Zaske LSS method.

[b] For comparison, the calculated $t½_{off\text{-}HD}$ between measured peak and pre-HD trough values was 31.6 ± 13.1 hours, median 28.2 [23.9–40.3] hours, range 10.4–54.2 hours.

[c] Adjusted body weight used for obese individuals and total body weight for non-obese individuals.

Figure 4G. Cefazolin interdialytic half-life relative to dialysis vintage (box and whisker plot, n = 19).

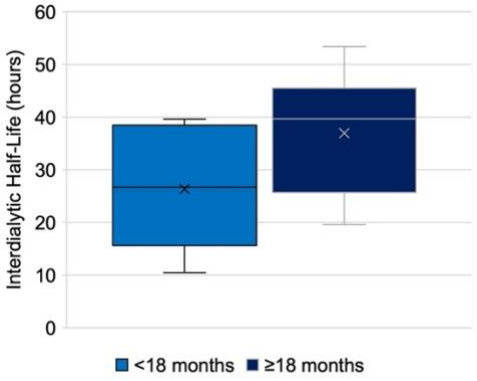


Figure 4H. Cefazolin half-life off hemodialysis relative to daily urine production (box and whisker plot, *n* = 19).

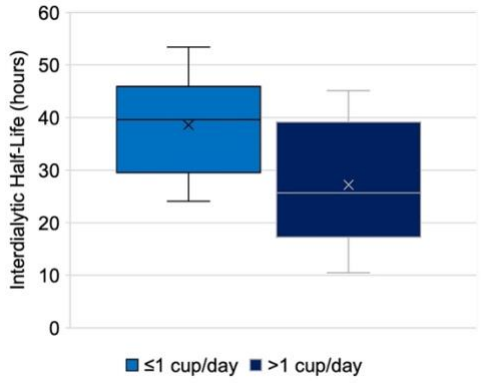
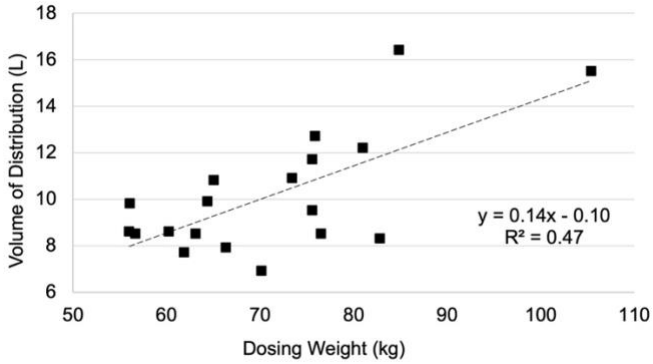


Figure 4I. Cefazolin volume of distribution relative to dosing weight (*n* = 19).



4.4.1.3. Cefazolin pharmacodynamics

Free pre-HD trough concentrations were significantly lower following three-day interdialytic periods (9.6 ± 6.1 mg/L) versus two-day periods (15.5 ± 7.6 mg/L, $P < 0.001$, **Figure 4J**). For cefazolin against MSSA, all participants achieved 100%$fT_{>MIC}$ (i.e., free pre-HD trough concentrations >1 mg/L) during two-day interdialytic periods, while 5.0% (1/20) did not for three-day periods (**Figure 4K**). Also, 5.0% (1/20) and 20.0% (4/20) of participants did not achieve the higher threshold of 100%$fT_{>4xMIC}$ (i.e., free pre-HD trough concentrations >4 mg/L) during two- and three-day interdialytic periods, respectively (**Figure 4K**).

For cefazolin against Enterobacterales, 5.0% (1/20) and 10.0% (2/20) of participants did not achieve 100%$fT_{>MIC}$ (i.e., free pre-HD trough concentrations >2 mg/L) during two- and three-day interdialytic periods, respectively (**Figure 4K**). Also, 20.0% (4/20) and 50.0% (10/20) of participants did not achieve the higher threshold of 100%$fT_{>4xMIC}$ (i.e., free pre-HD trough concentrations >8 mg/L) during two- and three-day interdialytic periods, respectively (**Figure 4K**).

In addition to 3-day interdialytic periods, shorter $t½_{off\text{-}HD}$ predicted subtherapeutic levels (*P* <0.001, **Table S4F**). There was also a strong correlation between pre-HD trough concentrations and $t½_{off\text{-}HD}$ (rho = 0.87, *P* <0.001, **Table S4E**; **Figure S4A**, R^2 = 0.68). Other factors, including sex, age, DW, urine production, Vd, and dose (in mg/kg_{DW}), were not predictive of subtherapeutic levels (**Tables S4F**, **S4G**, and **S4H**).

Figure 4J. Free cefazolin pre-hemodialysis trough concentrations extrapolated to a **A)** two- or **B)** three-day interdialytic period.

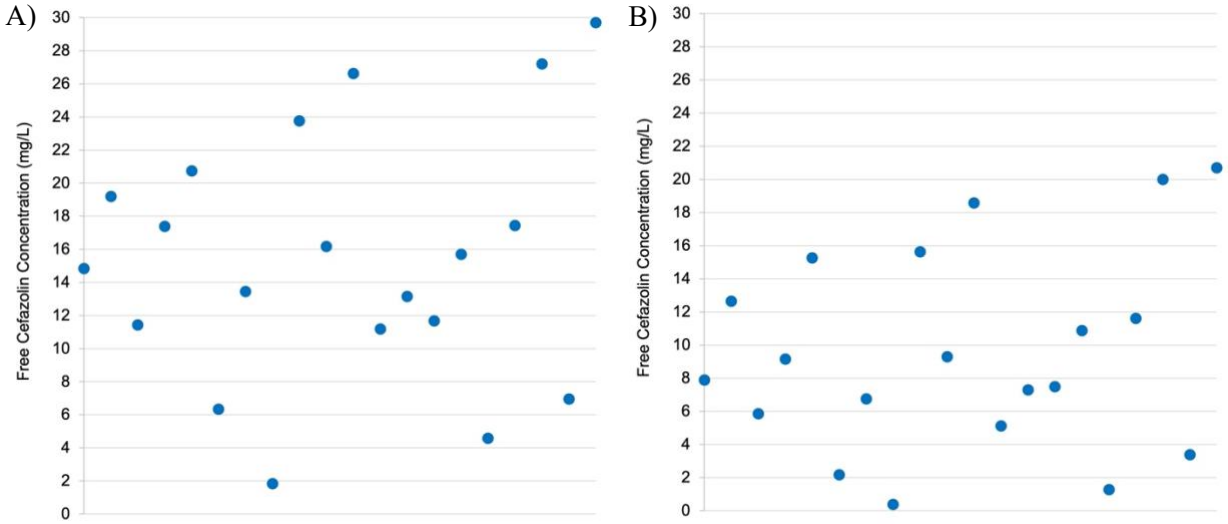
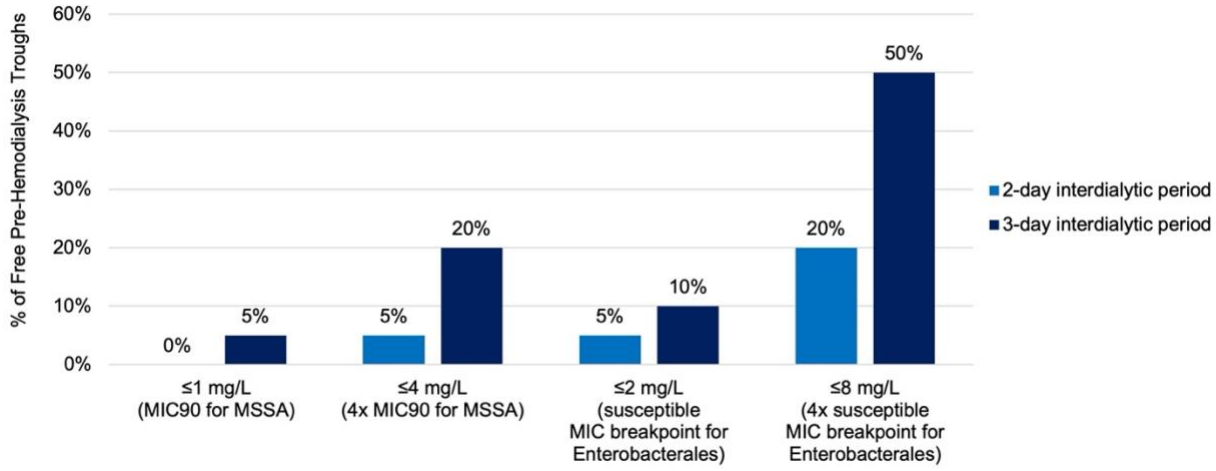


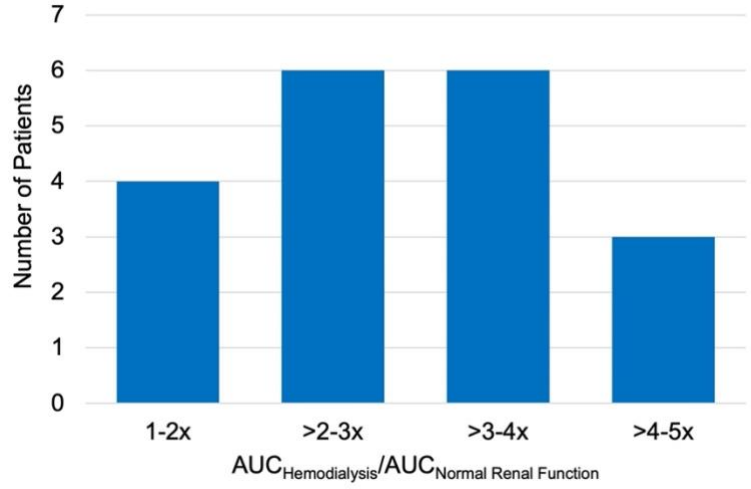
Figure 4K. Below target free cefazolin pre-hemodialysis trough concentrations (*n* = 20) against methicillin-susceptible *Staphylococcus aureus* (MSSA) and Enterobacterales.



4.4.1.4. Cefazolin toxicodynamics

Supratherapeutic cefazolin trough levels, defined as total pre-HD trough concentrations ≥100 mg/L, were observed in 30.0% (6/20) of participants following a two-day interdialytic period and 15.0% (3/20) following a three-day interdialytic period. The highest pre-HD trough concentration observed was 163.2 mg/L following a two-day interdialytic period. Longer $t_{½off\text{-}HD}$ (P = 0.05) and higher dose per kg_{DW} (P = 0.03) were predictors of supratherapeutic levels (**Table S4I**). Other factors, including sex, age, DW, urine production, and Vd, were not predictive of supratherapeutic levels (**Tables S4I** and **S4J**). Based on a comparison of AUC_{48h}, the relative exposure of cefazolin was 1.0 to 4.9 times higher in study participants than that predicted in controls with normal kidney function receiving 2 g every 8 hours (**Figure 4L**).

Figure 4L. Relative cefazolin exposure based on area under the concentration-time curve (AUC) over 48 hours in study participants than that predicted in controls with normal kidney function receiving 2 g every 8 hours.

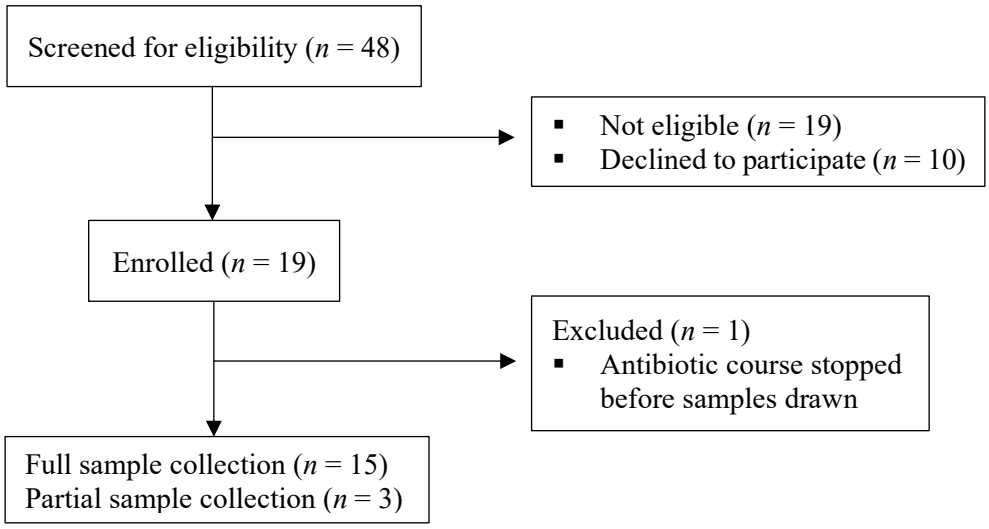


4.4.2. Ceftazidime

4.4.2.1. Participants, hemodialysis details, & ceftazidime dosing

Nineteen participants receiving ceftazidime were enrolled, and 15 completed the study (**Figure 4A-2**). One participant's antimicrobial course was stopped before sample collection, so they were excluded from the study. Three individuals did not complete sample collection due to early cessation of their antimicrobial course; therefore, only one of three blood samples were collected. Nonetheless, their data were included in analyses where appropriate.

Figure 4A-2. Study flow diagram for the ceftazidime cohort.



The characteristics of study participants are summarized in **Table 4A-2**. Most were female (61.1%, 11/18), with a mean age of 65 ± 14 years. Half of the participants were classified as obese, with a mean TBW of 79.0 ± 20.7 kg. Two participants had single below-the-knee amputations. The most common comorbidities were hypertension and diabetes in 83.3% (15/18) and 72.2% (13/18) of participants, respectively. Participants had received dialysis for a median of 33 [12–65] months. Two participants reported having no urine production, whereas 66.7% (12/18) reported producing ≤1 cup per day, and 22.2% (4/18) reported >1 cup per day.

Table 4A-2. Characteristics of participants in the ceftazidime cohort (*n* = 18).

Female sex	11 (61.1%)
Age (years)	65 ± 14
TBW (kg)	79.0 ± 20.7
DW (kg)[a]	65.1 ± 11.6
Amputation	2 (11.1%)[b]
BMI (kg/m^2)	29.2 ± 7.9
BMI class	
Underweight (<18.5 kg/m^2)	1 (5.6%)
Normal (18.5–24.9 kg/m^2)	6 (33.3%)
Overweight (25–29.9 kg/m^2)	2 (11.1%)
Obese (≥30 kg/m^2)	9 (50.0%)
Comorbidities	
Hypertension	15 (83.3%)
Diabetes	13 (72.2%)
Heart Disease	10 (55.6%)
Dyslipidemia	8 (44.4%)
Dialysis vintage (months)	33 [12–65]
Daily urine production	
None	2 (11.1%)
≤1 cup	12 (66.7%)
>1 cup	4 (22.2%)

Reported as n (%), mean ± SD, or median [IQR].

BMI body mass index, *DW* dosing weight, *TBW* total body weight.

[a] Both participants had single below-the-knee amputations.

[b] Adjusted body weight used for obese individuals and total body weight for non-obese individuals.

The HD sessions participants underwent during the study are detailed in **Table 4B-2**. The Fresenius Optiflux F250NRe and F160NRe high-flux dialyzers were used in 94.4% (17/18) of HD sessions. Most participants (66.7%, 12/18) were administered heparin during HD to prevent clotting of the apparatus. On average, HD sessions were 3.5 ± 0.4 hours in duration. The most common dialysate flow rate was 500 mL/min (77.8%, 14/18) versus 800 mL/min. The mean dialysis blood flow rate was 332.5 ± 20.0 mL/min, and the HD

adequacy (Kt/V) was 1.5 ± 0.4. Based on the change in TBW, a mean of 1.7 ± 0.8 L of fluid was removed during HD.

Table 4B-2. Details of hemodialysis sessions for participants in the ceftazidime cohort (*n* = 18).

High-flux dialyzer	
Fresenius Optiflux F250NRe	10 (55.6%)
Fresenius Optiflux F160NRe	7 (38.9%)
Nipro Elisio-19H	1 (5.6%)
Mean HD session duration (h)	3.5 ± 0.4
Dialysate flow rate	
500 mL/min	14 (77.8%)
800 mL/min	4 (22.2%)
Mean blood flow rate (mL/min)	332.5 ± 20.0
Mean Kt/V	1.5 ± 0.4
Mean TBW change (kg)	1.7 ± 0.8

Reported as n (%) or mean ± SD.

HD hemodialysis, *h* hours, *TBW* total body weight, *Kt/V* dialysis adequacy where K is dialyzer clearance of urea, t is dialysis time, and V is urea distribution volume.

All but one participant received the standard dosing protocol of 2 g ceftazidime thrice weekly post-HD. One participant (TBW 42.6 kg, BMI 20.8 kg/m^2, urine production ≤1 cup per day, HD duration ~4 hours) was prescribed 1 g thrice weekly post-HD. The mean ceftazidime dose was 30.2 ± 5.3 mg/kg$_{DW}$. Overall, a median of 5 [4–6] doses of ceftazidime were recorded per participant.

4.4.2.2. Ceftazidime serum concentrations & pharmacokinetics

A total of 48 blood samples were collected from the 18 participants, including 15 post-HD post-dose peaks and 33 pre-HD troughs. In all samples, total ceftazidime serum concentrations were measured. Free ceftazidime levels were also measured in a subset of 16 samples (comprising seven peak and nine pre-HD trough samples from eight participants). Concentration data are summarized in **Table 4C-2** and **Figures**

4B-2 and **4C-2**. **Figure 4D-2** depicts free relative to total concentrations. The mean total and free peak concentrations were 122.5 ± 36.9 mg/L and 114.7 ± 41.7 mg/L, respectively. Total pre-HD trough concentrations ranged from 13.0 to 51.8 mg/L with a mean of 31.7 ± 10.9 mg/L. The free pre-HD trough concentrations were 29.4 ± 6.4 mg/L.

Table 4C-2. Total and free ceftazidime serum concentrations.

	N	Mean ± SD	Median [IQR]	Range
Total (mg/L)				
Peaks	15	122.5 ± 36.9	113.6 [94.9–149.6]	74.7–203.2
Pre-HD troughs	33	31.7 ± 10.9	31.4 [25.9–37.4]	13.0–51.8
Free (mg/L)				
Peaks	7	114.7 ± 41.7	105.7 [88.4–132.3]	66.9–188.6
Pre-HD troughs	9	29.4 ± 6.4	29.8 [27.5–31.3]	19.0–39.1

HD hemodialysis.

Figure 4B-2. Total ceftazidime peak (n = 15) and pre-hemodialysis trough (n = 33) serum concentrations.

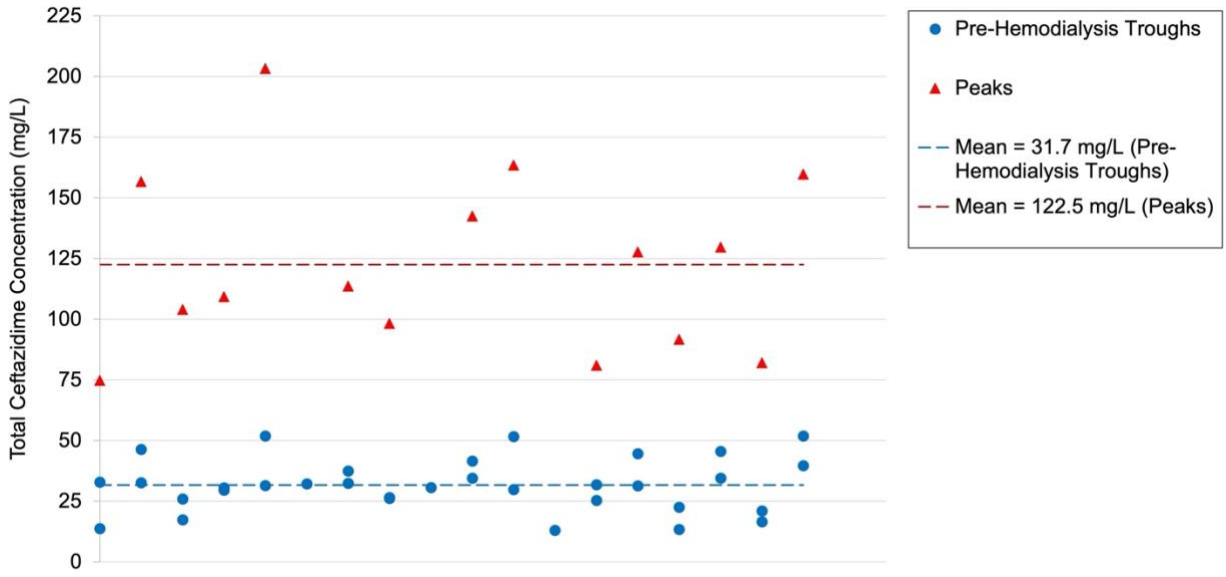


Figure 4C-2. Free ceftazidime peak (n = 7) and pre-hemodialysis trough (n = 9) serum concentrations.

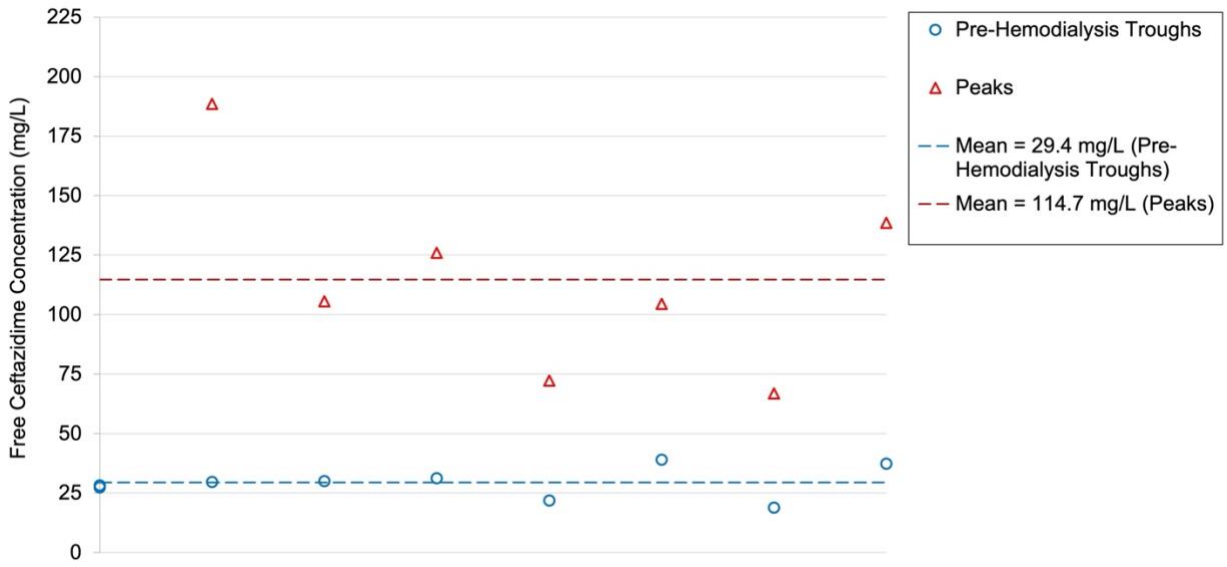
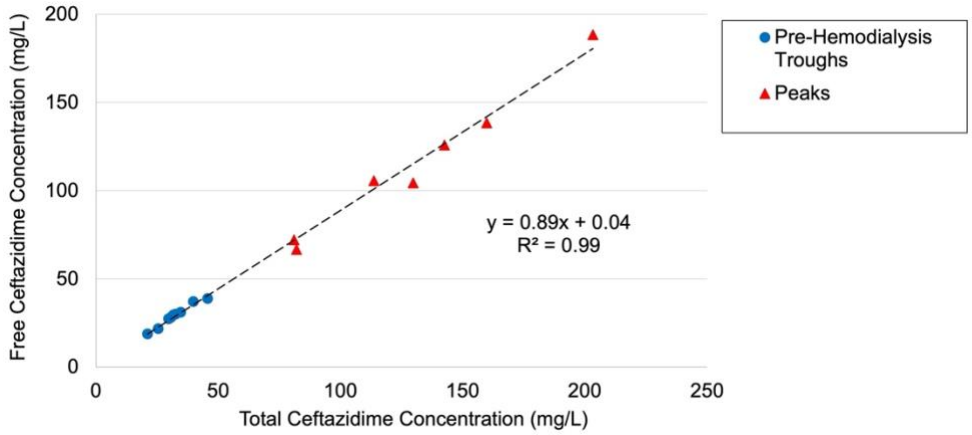
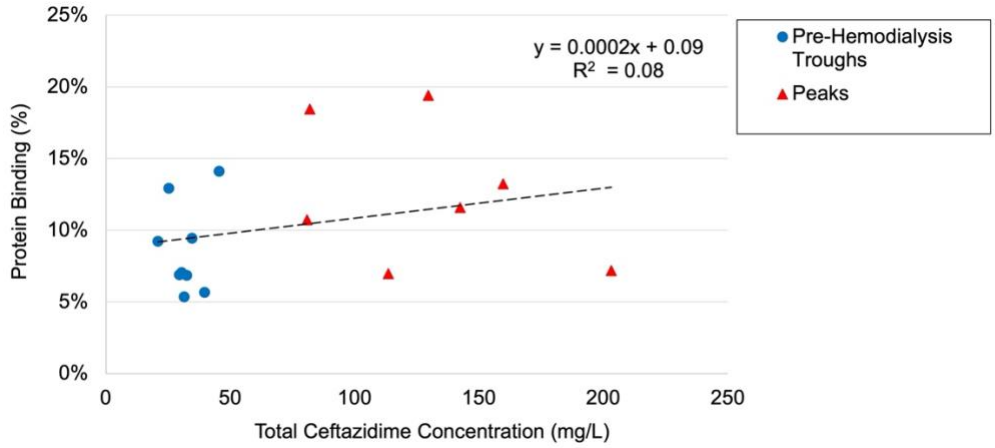


Figure 4D-2. Free relative to total ceftazidime serum concentrations.



The mean ceftazidime protein binding was 10.3% ± 4.3%. Protein binding was not significantly different in peak (12.5% ± 4.9%) versus pre-HD trough (8.6% ± 3.1%) samples (P = 0.08). **Figure 4E-2** illustrates that ceftazidime protein binding was concentration-independent (R^2 = 0.08). No significant relationships were identified between protein binding and participant age, DW, albumin concentration, sex, or urine production (**Table S4A-2**).

Figure 4E-2. Ceftazidime protein binding relative to total ceftazidime serum concentration.



The modelled ceftazidime PK parameters are reported in **Table 4D-2**. The mean $t½_{off\text{-}HD}$, $t½_{on\text{-}HD}$, and Vd $t½_{off\text{-}HD}$ were 28.1 ± 4.8 hours, 3.7 ± 0.8 hours, and 19.0 ± 5.6 L, respectively. While the $t½_{off\text{-}HD}$ appeared shorter when urine production was >1 cup per day (23.5 ± 1.1 hours) as opposed to ≤1 cup per day (29.3 ± 4.7 hours), there was no statistical difference (P = 0.06, **Figure 4F-2**). In addition, no significant relationships were identified between $t½_{off\text{-}HD}$ and age, dialysis vintage, DW, or sex (**Table S4C-2**). Ceftazidime Vd was not related to any covariates tested (**Table S4D-2**).

Table 4D-2. Ceftazidime pharmacokinetic parameters (n = 15).[a]

	Mean ± SD	Median [IQR]	Range
$t½_{off\text{-}HD}$ (h)[b]	28.1 ± 4.8	27.4 [24.1–30.8]	22.2–38.9
$t½_{on\text{-}HD}$ (h)	3.7 ± 0.8	3.3 [3.3–3.5]	3.2–5.9
Vd (L)	19.0 ± 5.6	18.6 [14.2–22.8]	10.4–28.9
Vd (L/kg_{DW})[c]	0.30 ± 0.08	0.32 [0.21–0.35]	0.18–0.43

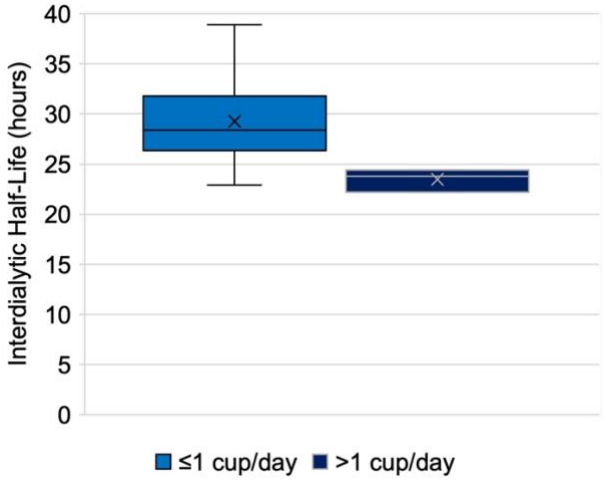
DW dosing weight, *HD* hemodialysis, *h* hours, $t½_{off\text{-}HD}$ half-life off hemodialysis, $t½_{on\text{-}HD}$ half-life on hemodialysis, *Vd* volume of distribution.

[a] Modelled using the Sawchuk-Zaske LSS method.

[b] For comparison, the calculated $t½_{off\text{-}HD}$ between measured peak and pre-HD trough values was mean 28.3 ± 6.5 hours, median 26.6 [24.5–29.3] hours, range 22.2–47.5 hours.

[c] Adjusted body weight used for obese individuals and total body weight for non-obese individuals.

Figure 4F-2. Ceftazidime half-life off hemodialysis relative to daily urine production (box and whisker plot, n = 15).



4.4.2.3. Ceftazidime pharmacodynamics

Free pre-HD trough concentrations were significantly lower following three-day interdialytic periods (22.8 ± 6.8 mg/L) versus two-day periods (41.6 ± 10.8 mg/L, P <0.001, **Figure 4G-2**). For ceftazidime against Enterobacterales and *P. aeruginosa,* all participants achieved 100%$fT_{>MIC}$ (i.e., free pre-HD trough concentrations >4 mg/L or >8 mg/L, respectively) during both two- and three-day interdialytic periods

(**Figures 4H-2**). While all participants achieved the higher threshold of 100%$fT_{>4xMIC}$ against Enterobacterales (i.e., free pre-HD trough concentrations >16 mg/L) during two-day interdialytic periods, 26.7% (4/15) did not for three-day periods (**Figure 4H-2**). Also, 33.3% (5/15) and 100% (15/15) of participants did not meet 100%$fT_{>4xMIC}$ against *P. aeruginosa* (i.e., free pre-HD trough concentrations >32 mg/L) during two- and three-day interdialytic periods, respectively (**Figure 4H-2**).

In addition to 3-day interdialytic periods, shorter $t½_{off\text{-}HD}$ (P = 0.02), higher daily urine production (P = 0.009), and larger Vd (P = 0.02) predicted subtherapeutic levels (**Tables S4F-2** and **S4G-2**). This is explained by the relationship between lower pre-HD trough concentrations and higher daily urine production (P = 0.02) and larger Vd (P = 0.002) (**Table S4E-2**, **Figures S4A-2** and **S4B-2**). Other factors, including sex, age, DW, and dose (in mg/kg_{DW}), did not predict subtherapeutic levels (**Tables S4F-2** and **S4G-2**).

Figure 4G-2. Free ceftazidime pre-hemodialysis trough concentrations extrapolated to a **A)** two- or **B)** three-day interdialytic period.

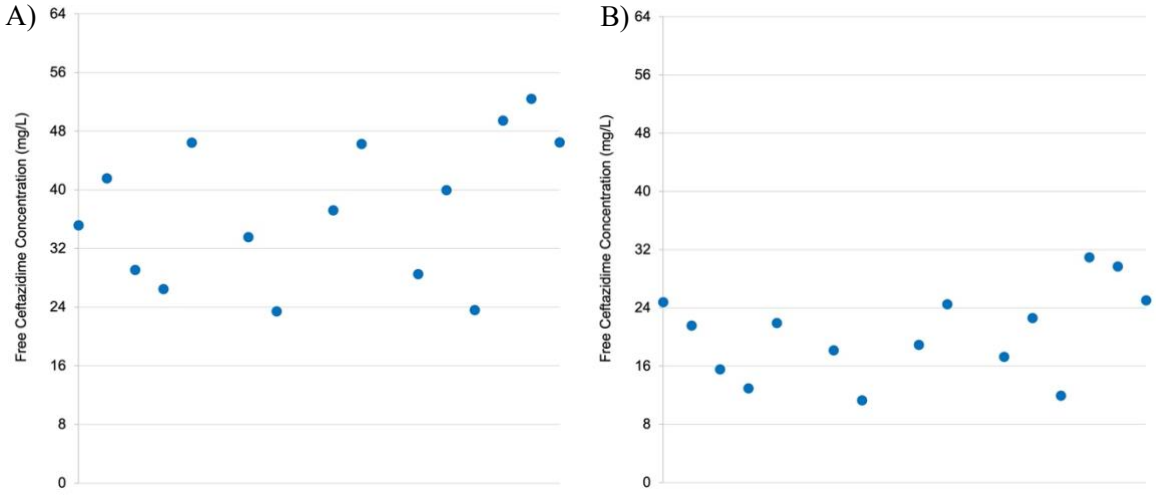
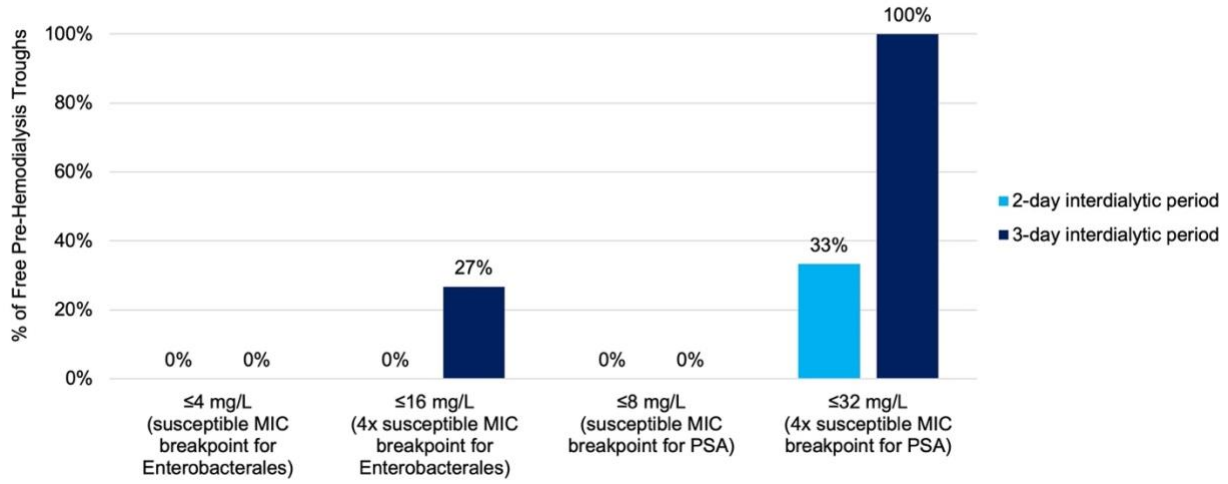


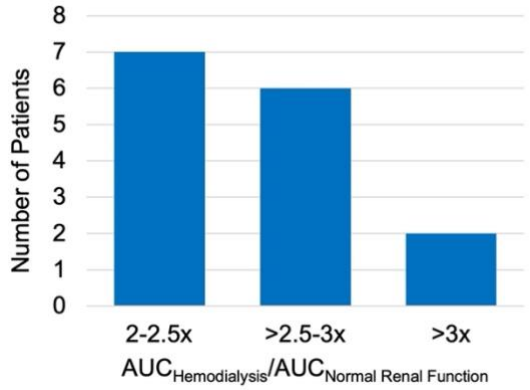
Figure 4H-2. Below target free ceftazidime pre-hemodialysis trough concentrations (*n* = 15) against Enterobacterales and *Pseudomonas aeruginosa* (PSA).



4.4.2.4. Ceftazidime toxicodynamics

No supratherapeutic ceftazidime trough levels were observed, defined as total pre-HD trough concentrations ≥90 mg/L. The highest pre-HD trough concentration observed was 52.4 mg/L following a two-day interdialytic period. However, based on a comparison of AUC_{48h}, the relative exposure of ceftazidime was 2.1 to 3.6 times higher in study participants than that predicted in controls with normal kidney function receiving 2 g every 8 hours (**Figure 4I-2**).

Figure 4I-2. Relative ceftazidime exposure based on area under the concentration-time curve (AUC) over 48 hours in study participants than that predicted in controls with normal kidney function receiving 2 g every 8 hours.



4.5. Discussion

Despite the significant use of cefazolin and ceftazidime to treat infections in patients receiving chronic iHFHD, the current one-dose-fits-all dosing approach is based on limited data. In clinical practice, the absence of TDM for cephalosporins is another barrier. Consequently, it is difficult to ascertain whether suboptimal antimicrobial dosing or patient-specific factors, such as ESKD, are responsible for the poor clinical outcomes. To our knowledge, this is the most extensive and largest clinical PK study of cefazolin and ceftazidime in patients receiving iHFHD. It was conducted in infected patients in a real-world setting, enhancing its applicability and translatability to clinical practice. Diverging from the conventional approach of many PK studies, we did not restrict PK variability by employing stringent exclusion criteria. As a result, the participants accurately represented the diversity of our HD population, which includes both male and female individuals with infections, as well as those with varying degrees of residual kidney function and body weight, ranging from non-obese to obese. Overall, the current study offers crucial insights into the dosing of cefazolin and ceftazidime in the outpatient HD setting, highlighting the need for individualized dosing strategies to improve clinical outcomes.

4.5.1. Cefazolin

4.5.1.1. Cefazolin serum concentrations

The average cefazolin dose in the study was 28.8 ± 4.5 mg/kg_{DW}, which resulted in total peak concentrations of 237.3 ± 47.7 mg/L (15 minutes post-dose). For logistical reasons, our peak samples were collected shortly after dose administration. A PK study conducted by Sowinski *et al.* of cefazolin administered post-HD demonstrated that the distributional phase is complete within 15 minutes after IV bolus administration. This finding suggests that our peak samples were collected during the post-distributional phase.

We observed total cefazolin pre-HD trough concentrations of 70.1 ± 37.7 mg/L (44 to 68 hours post-dose). Despite differences in dosing, sample timing, and subject characteristics, these concentrations align with other studies of cefazolin in adults receiving HD, as summarized in **APPENDIX 1C**.[146,167–174] Kuypers *et*

al. studied a dosage of 2 g of cefazolin administered post-HD, reporting concentrations of 97 ± 27 mg/L and 61 ± 22 mg/L at 44 and 68 hours after the dose, respectively. These values are comparable to our extrapolated concentrations of 85.0 ± 41.9 mg/L and 52.5 ± 33.3 mg/L at the corresponding time points. One of the most prominent observations in our study was the wide variability in pre-HD trough concentrations, which ranged from 3.7 to 149.4 mg/L. This variability was linked to the diverse residual kidney function among participants, unlike other studies that usually include anuric subjects.

4.5.1.2. Cefazolin protein binding

Free cefazolin concentrations in ultrafiltrate were used to determine the extent of protein binding. The traditional reference method for measuring free concentrations is equilibrium dialysis (ED).[175,176] However, ultrafiltration (UF) is favoured in clinical research due to its simplicity and rapid processing time of approximately 45 minutes compared to 4 hours for ED.[175,176] A systematic review by Jongmans *et al.*, which encompassed 24 *in vivo* studies of cefazolin protein binding in serum or plasma from various patient populations, reported that most studies (87.5%, 21/24) used UF methods. Notably, a recent study by Ahmed *et al.* demonstrated comparable protein binding of cefazolin using ED and UF methods.[177]

Another benefit of UF is the ability to process samples before freezing. As ED is run in batches, freezing and thawing samples is often required before analysis, which can affect protein stability, folding, and cause percipitation.[178] Cuhadar *et al.* support this concern, finding a significant reduction in albumin concentrations after storing samples at -20°C for three months.[179] As UF allows for individual samples to be processed rapidly, freezing can be avoided before UF.

Non-specific drug adsorption is a concern in both ED and UF, which may result in inaccurately low measurements of free drug concentrations. Centrifree® devices were chosen to mitigate this issue because their regenerated cellulose membranes exhibit minimal drug adsorption.[180,181] Indeed, cefazolin has not been

shown to significantly adsorb to Centrifree® UF membranes.[182,183] As such, several clinical studies have used Centrifree® devices to measure cefazolin protein binding.[146,184–192]

Previous research has explored how temperature and pH influence drug protein binding.[175,193,194] A potential limitation of our analysis was that we did not maintain physiological conditions, including temperature (~37°C) and pH (~7.4), following the sample collection. Nonetheless, the difference in protein binding at physiological versus ambient temperatures is expected to be minimal.[175] Moreover, by conducting analyses immediately post-collection, we minimized the time for CO_2 degassing from blood, which could decrease the pH.[175,180] Additionally, to further prevent CO_2 degassing, Centrifree® devices were capped.

In our study, cefazolin protein binding was concentration-dependent, where protein binding was lower in peak (59.5% ± 12.9%) versus pre-HD trough (81.8% ± 5.6%) samples (P <0.01). Studies of cefazolin protein binding in other patient populations have observed similar differences between peak and trough samples.[189,195–198] One explanation is the saturation of protein binding sites. A population-PK model of cefazolin by Chung *et al.* found that maximum protein binding occurred at a concentration of 175 ± 51 mg/L (n = 12, age 64 ± 13 y, weight 87 ± 15 kg, CrCl 80 ± 68 mL/min, albumin 30 ± 8 g/L).[199] Another explanation is heparin co-administration. Importantly, heparin has been shown to reduce protein binding due to an increase in free fatty acids that competitively bind to albumin.[200,201] Overall, 75.0% of our study participants received heparin anticoagulation during HD. However, we did not find a statistically significant difference in protein binding between peak samples from patients who received heparin (56.0% ± 14.0%) compared to those who did not (67.8% ± 4.4%) (P = 0.2).

Overall, protein binding of 81.8% ± 5.6% in pre-HD trough samples was most consistent with typical values reported for cefazolin, i.e., approximately 74% to 86%.[202] This finding contrasts with previous data suggesting reduced protein binding in patients receiving HD.[192,203] It is proposed that the lower protein

binding is related to hypoalbuminemia, which is common in patients receiving HD due to malnutrition, decreased synthesis, exogenous loss, and the dilutional effects of fluid retention.[124] Notably, 80.0% of our study participants had hypoalbuminemia, defined as albumin concentrations <35 g/L. We identified a moderate correlation between protein binding in pre-HD trough samples and albumin concentrations (rho = 0.67, $P = 0.03$), although these effects may not be clinically significant. Other studies have also reported similar correlations between cefazolin protein binding and albumin concentrations.[190,201,204–207] Although we explored other potential covariates, none, including weight or obesity, significantly influenced protein binding, supporting the conclusions of previous research in this area.[184,185,188,198]

The available information on the protein binding of cefazolin in the HD setting is limited to four studies. The first, by Greene *et al.,* investigated the *in vitro* protein binding of cefazolin in human serum collected from 12 subjects receiving HD.[123] Samples were spiked with 92 mg/L of cefazolin, and free concentrations were determined using UF. Protein binding was lower in peak (22.4% ± 20.9%) versus pre-HD trough (72.5% ± 13.4%) samples (P <0.005), which was attributed to subjects receiving heparin during HD. Craig *et al.* used ED to study the *in vivo* protein binding of cefazolin in 11 subjects with kidney impairment, including two receiving HD.[208] At an average cefazolin concentration of 45 mg/L, protein binding ranged from 61.6% to 84.7%. Studies by Sowinski *et al.* and Duke *et al*. used Centrifree® UF devices to determine the *in vivo* protein binding of cefazolin in clinical samples from patients receiving HD (**APPENDIX 1C**).[146,192] The former reported average protein binding of 63% ± 12%. The latter identified lower binding in peak (63.5% ± 6.8%) versus pre-HD trough (75.5% ± 14.3%) samples, also thought to be due to heparin administration during HD. Our results were comparable to the values reported in these studies. As Sowinski *et al.* and Duke *et al*. froze samples before UF, this may explain their slightly lower values. Albumin levels were only reported by Duke *et al*., where median albumin concentrations were 38.5 [35.5–40] g/L, yet this would not explain the differences. The lack of comprehensive methods and results in the other two studies limits our ability to compare results.

4.5.1.3. Cefazolin pharmacokinetic modelling

We employed several approaches to delineate the PK of cefazolin. Initially, we conducted nonparametric population-PK modelling with Pmetrics™ software. This method does not assume a normal distribution for PK parameters, enabling us to identify sources of PK variability. This approach, therefore, highlights differences in dosing requirements and facilitates dose individualization based on specific patient characteristics.[209] After facing challenges in developing a robust population-PK model, we proceeded with individual PK modelling using ADAPT 5 software. Although both approaches allowed for reliable modelling of the t½ between HD sessions and Vd, they could not accurately estimate the t½ during HD. Without an intradialytic or post-HD sample, we hypothesize that neither modelling method could provide reliable estimates of t½ during HD. This insight is essential when designing future PK studies in the outpatient HD setting. As an alternative, an iterative fitting technique, the Sawchuk-Zaske LSS method, was developed to characterize the PK of cefazolin. Using standardized procedures, we aimed to optimize the accuracy and limit bias, thereby enhancing the reliability of our results.

Our values for the t½ between HD sessions, t½ during HD, and Vd were 31.4 ± 12.0 hours, 3.1 ± 0.5 hours, and 10.2 ± 2.6 L, respectively. The modelled t½ between HD sessions using the Sawchuk-Zaske LSS method was similar to that calculated using the Sawchuk-Zaske method alone, i.e., 31.6 ± 13.1 hours. Furthermore, our findings using the Sawchuk-Zaske LSS method aligned with those from ADAPT 5 modelling, which estimated an average t½ between HD sessions of 32.3 ± 12.6 hours and Vd of 11.2 ± 2.8 L (**Table S4B**). The consistency across different methods confirms the validity of our Sawchuk-Zaske LSS method. To test the robustness of our Sawchuk-Zaske LSS method, we determined that changes in t½ during HD did not significantly impact the modelled values of t½ between HD sessions or Vd. Given the limitations in determining t½ during HD (i.e., no intradialytic or post-HD sample), covariate analyses for t½ during HD were not performed.

In our study, the cefazolin t½ was 31.4 ± 12.0 hours between HD sessions, compared to a t½ of approximately 1.8 hours (range = 1.2–2.2 hours) in subjects with normal kidney function.[35,208,210–213] Over 80% of an administered cefazolin dose is excreted unchanged in the urine, explaining the significantly prolonged t½ in patients with ESKD. Studies in the HD setting have reported cefazolin t½'s ranging from 25.7 to 36.9 hours between HD sessions, as detailed in **APPENDIX 1C**.[146,167,169,173,174] The cefazolin t½ during HD was 3.1 ± 0.5 hours in our study. These findings are consistent with two studies, which reported cefazolin t½'s of 3.2 ± 1.2 hours and 3.4 ± 1.0 hours during iHFHD (**APPENDIX 1C**).[146,167]

One of our key findings was the wide variation in t½ between HD sessions among participants, ranging from 10.5 to 53.4 hours. The variability was primarily explained by residual kidney function. The t½ between HD sessions was shorter in participants with higher daily urine production (P = 0.04). This observation aligns with findings reported by Fogel *et al.*, where one individual with high residual urine output had substantially higher cefazolin elimination between HD sessions.[167] Similarly, Palmer *et al*. found that subjects with residual kidney function (measured via 24-hour urine creatinine) had a much shorter t½ between HD sessions (25.0 [21.3–27.7] hours) compared to those without (49.3 [26.7–82.4] hours).[174] Overall, in our study, the significant variability in t½ between HD sessions explained the wide range in pre-HD trough concentrations (P <0.001).

We also found that the t½ between HD sessions was shorter in participants newer to dialysis (P = 0.05). This trend suggests that residual kidney function progressively declines with increasing dialysis vintage. Supporting this, Duke *et al*. found that dialysis vintage was inversely related to cefazolin elimination between HD sessions and was the only covariate that significantly improved their population-PK model.[192] In summary, urine output and dialysis vintage are indicators of residual kidney function, which can predict cefazolin elimination between HD sessions.

Regarding the t½ during HD, it is important to acknowledge that variations in HD factors, including dialyzer filter type and flux, dialysate and blood flow rates, and duration, influence drug elimination.[122,214–216] These factors must be considered when translating our results to different practice settings. Since the beginning of the 21st century, there has been a transition from low- to high-flux dialyzers. This shift was driven by evidence of superior clinical outcomes, ultimately establishing high-flux dialyzers as the new standard of care.[121] High-flux membranes have larger pores that allow larger drugs to pass, thereby increasing drug elimination during HD.[121] However, the clinical significance of this advancement is not adequately described in the literature.[121]

In our study, the Vd of cefazolin was 10.2 ± 2.6 L (0.14 ± 0.03 L/kg_{DW}), which correlated with DW (P = 0.05). Our results are comparable to the Vd reported in healthy subjects.[212,213] Our Vd also compares to the 0.09–0.13 L/kg reported in studies of cefazolin in patients receiving chronic HD (**APPENDIX 1C**).[146,167,173,174] While the Vd of many drugs increases in patients undergoing chronic HD due to fluid retention between sessions, our findings show that the Vd of cefazolin remains similar to that of healthy individuals.[121] However, our models did not account for the dynamic nature of Vd, which may fluctuate with cumulative fluid retention between HD sessions and fluid removal during HD. Notably, we observed that 2.1 ± 0.9 L of fluid was removed during HD, which represents approximately 20% of the Vd of cefazolin. Therefore, fluid retention could significantly increase the distributional space for hydrophilic drugs that have a small volume of distribution, such as cefazolin. To our knowledge, no models have accounted for a dynamic Vd in patients receiving HD. Theoretically, the expanded Vd with fluid retention between HD sessions could dilute drug concentrations.

4.5.1.4. Cefazolin pharmacodynamics

We analyzed pre-HD cefazolin trough concentrations to assess if the current one-dose-fits-all dosing approach of 2 g cefazolin thrice weekly post-HD was adequate to treat the most clinically relevant infections, i.e., MSSA and Enterobacterales, in the outpatient HD setting. We assessed whether PKPD

thresholds of 100%$fT_{>MIC}$ and 100%$fT_{>4xMIC}$ were met during interdialytic periods. Our thresholds were informed by a select number of studies, where ≥60%–70%$fT_{>MIC}$ was required for efficacy of cephalosporins in pre-clinical studies and ≥45%–100%$fT_{>MIC}$ in clinical studies.[18–20,25,217] Higher thresholds up to 100%$fT_{>1-5xMIC}$ have been recommended to improve clinical outcomes in critically ill and immunocompromised patients and suppress the development of AMR.[17,18,25,30,31,218,219]

In the context of HD, PKPD thresholds have not been validated in clinical outcome studies.[216] Given that the cephalosporins provide minimal post-antimicrobial effect, re-growth can occur shortly after concentrations fall below a pathogens MIC.[18] Furthermore, thresholds less than 100%$fT_{>MIC}$ do not translate in the same way to thrice weekly post-HD dosing. For instance, achieving 70%$fT_{>MIC}$ over an eight-hour dosing interval represents 2.4 hours of sub-MIC antimicrobial concentrations. Comparatively, during a 48-to-72-hour post-HD dosing interval, this threshold would result in 14.4 to 21.6 hours of sub-MIC concentrations. Given the heightened risk of infection-related morbidity and mortality among patients receiving chronic HD, higher PKPD thresholds are justified. While the absence of clinical outcome studies is a limitation, our PKPD thresholds were based on the best available evidence and aimed at optimizing clinical outcomes while minimizing the development of AMR in this high-risk population.

Overall, for cefazolin, 90.0% to 100.0% of study participants achieved 100%$fT_{>MIC}$, depending on the pathogen (i.e., MSSA or Enterobacterales) and interdialytic period (i.e., two- or three-days). Target attainment was lower for the higher threshold of 100%$fT_{>4xMIC,}$ i.e., 50.0% to 95.0%. In general, target attainment was lower against Enterobacterales due to the higher MIC breakpoint of 2 mg/L compared to the MIC_{90} of 1 mg/L used for MSSA. As expected, target attainment was also lower during three-day interdialytic periods. Subtherapeutic cefazolin concentrations were also predicted by a shorter t½ between HD sessions (P <0.001). These findings highlight the limitations of using a one-dose-fits-all dosing approach. We identified the importance of considering residual kidney function, the time between HD sessions, and pathogen MIC to optimize PKPD target attainment. This is particularly important for

achieving a threshold of 100%$fT_{>4xMIC}$, which may improve clinical outcomes and help prevent the development of AMR, especially when treating severe, life-threatening, or deep-seated infections.

4.5.1.5. Cefazolin toxicodynamics

The toxicodynamics of β-lactams are not well defined. Neurological effects, including confusion, dizziness, agitation, delirium, hallucinations, and seizures, have been described.[35,163,164] Notably, in early 2023, Health Canada released a Summary Safety Review concluding that there may be a link between cephalosporin use and seizures.[220] Cephalosporin neurotoxicity is thought to be concentration-dependent and may involve the blockade of gamma-aminobutyric acid receptors.[221] Differences in central nervous system penetration between cephalosporins may account for varying toxicity potential.[164] A concern is that antimicrobial-induced neurotoxicity can often be overlooked or misinterpreted.[36]

Most information on cefazolin toxicity is derived from individual case reports.[38–46,222–224] Symptoms of neurotoxicity have been reported to develop several days after initiating cefazolin treatment and resolve a few days following discontinuation of therapy.[164] Elevated total cefazolin trough concentrations have been reported in patients experiencing neurotoxicity, with values ranging from 150 to 1000 mg/L.[39,41–44,46] Neurotoxicity has been primarily reported in patients with kidney impairment and those on dialysis, attributed to reduced cefazolin elimination.[38–46] Other proposed risk factors include advanced age, pre-existing central nervous system disorders, high doses, disruption of the blood-brain barrier (e.g., meningitis), and concurrent drugs that lower the seizure threshold.[163,164,225,226]

We assessed whether the current cefazolin dosing protocol resulted in supratherapeutic levels. As there is no clear upper limit for cefazolin toxicity, we defined supratherapeutic or unnecessarily high trough levels as those not predicted to provide additional benefit, i.e., 100%$fT_{>10xMIC}$. This translated to total pre-HD cefazolin trough concentrations ≥100 mg/L. Using this definition, supratherapeutic concentrations were observed in 15.0% to 30.0% of participants, depending on the interdialytic period. The highest pre-HD

trough concentration was 163.2 mg/L. Two-day interdialytic periods, longer t½ between HD sessions (P = 0.05), and higher dose per kg_{DW} (P = 0.03) were predictors of supratherapeutic concentrations. Additionally, excessive antimicrobial exposure was assessed by comparing relative AUC_{48h} in study participants to that expected in controls with normal kidney function (i.e., CrCl ~100 mL/min, receiving 2 g cefazolin every 8 hours). The relative cefazolin exposure was 1.0 to 4.9 times higher in study participants than controls. Again, these findings highlight the limitations of using a one-dose-fits-all dosing approach. We identified the importance of considering patient factors to prevent supratherapeutic cefazolin exposures and potential toxicity.

4.5.1.6. Knowledge translation: cefazolin dosing in the outpatient hemodialysis setting

Due to a lack of evidence to direct dose individualization, HD programs often adopt one-dose-fits-all protocols, overlooking factors that influence PK. Specifically, within the MRP, a standard dosing protocol of 2 g cefazolin thrice weekly post-HD is used (**APPENDIX 1A**).[100] In our study, this protocol produced greater than 40-fold variation in total pre-HD trough concentrations. The significant variation was attributable to t½, which ranged from 10.5 to 53.4 hours due to varying residual kidney function among study participants. Based on our lower PKPD threshold of 100%$fT_{>MIC}$ and our upper limit of 100 mg/L, target attainment ranged from 65.0% to 80.0% depending on the pathogen (i.e., MSSA or Enterobacterales) and interdialytic period (i.e., two- or three-days). Given that a probability of target attainment ≥90% is typically considered optimal in PKPD research, our current cefazolin dosing protocol would be regarded as suboptimal.

In search of adaptive dosing strategies, we reviewed cefazolin dosing guidelines for adults receiving thrice-weekly iHFHD, as outlined in widely recognized clinical dosing resources (**APPENDIX 1E**). Recommendations ranged from daily dosing of 0.5–1 g, weight-based dosing of 15–20 mg/kg thrice weekly, to fixed doses of 2–3 g thrice weekly. While a 3 g cefazolin dose, primarily before three-day interdialytic periods, may reduce subtherapeutic levels in some patients, it would also expose other patients to

supratherapeutic levels. Conversely, weight-based dosing could reduce supratherapeutic levels in patients with lower body weight. Moreover, lower doses given more frequently, i.e., daily dosing rather than thrice weekly, would enhance cefazolin PKPD based on improved $\%fT_{>MIC}$. However, this approach may raise logistical concerns. Unfortunately, none of the current guideline recommendations address residual kidney function, which was predictive of subtherapeutic and supratherapeutic cefazolin levels in our study.

We found that considering residual kidney function is essential for appropriately adjusting cefazolin dosing, as small changes in residual kidney function led to substantial variations in concentrations. While we identified that urine output and dialysis vintage were indicators of remaining residual kidney function, these remain surrogate measures. A more accurate measure of residual kidney function (i.e., 24-hour urine creatinine) linked to cefazolin PK may more appropriately guide cefazolin dose individualization. The preferable alternative would be TDM, allowing for dose individualization in all patients regardless of covariates influencing PK.

4.5.2. Ceftazidime

4.5.2.1. Ceftazidime serum concentrations

The average ceftazidime dose in the study was 30.2 ± 5.3 mg/$kg_{DW,}$ which resulted in total peak concentrations of 122.5 ± 36.9 mg/L (15 minutes post-dose). Our values were similar to the 148.2 ± 19.4 mg/L reported by Hoffler *et al*. 30 minutes after a single 2 g dose of ceftazidime administered post-HD. The higher levels in their study may be explained by lower body weight compared to ours (65.0 ± 4.7 kg versus 79.0 ± 20.7 kg, respectively).[227] Based on previous PK studies of ceftazidime administered as an IV bolus, the distributional phase is complete in approximately 30 to 60 minutes. Ceftazidime's larger Vd may explain the prolonged distributional phase.[227–229] Therefore, as our peak samples were collected 15 minutes post-dose, it is possible they were collected during the distributional phase.

We observed total ceftazidime pre-HD trough concentrations of 31.7 ± 10.9 mg/L (44 to 68 hours post-dose). Despite differences in dosing, sample timing, and subject characteristics, these concentrations align with other studies of ceftazidime in adults receiving HD, as summarized in **APPENDIX 1D**.[159,227,229–232] Goh *et al.* studied a dosage of 2 g of ceftazidime administered post-HD, reporting concentrations of 49 [39–71] mg/L and 26 [21–41] mg/L at 44 and 68 hours after the dose, respectively.[231] These values are comparable to our extrapolated concentrations of 41.6 ± 10.8 mg/L and 22.8 ± 6.8 mg/L at the corresponding time points.

4.5.2.2. Ceftazidime protein binding

Free ceftazidime concentrations in ultrafiltrate were used to determine the extent of protein binding. Previous data has shown that ceftazidime does not significantly adsorb to regenerated cellulose membranes, making Centrifree® devices suitable for our study.[233] Other clinical studies have also used Centrifree® devices to measure ceftazidime protein binding.[234] As discussed previously, a potential limitation of our analysis was that we did not maintain physiological conditions, including temperature (~37°C) and pH

(~7.4), following the sample collection. However, Lam *et al.* reported that temperature, pH, and concentration did not significantly affect ceftazidime protein binding.[233]

In our study, ceftazidime protein binding was 10.3% ± 4.3% and linear for the range of concentrations studied. In a systematic review by Jongmans *et al.*, five *in vivo* studies of ceftazidime protein binding in serum or plasma from various patient populations were summarized, four of which used UF methods.[203] The average binding in these studies ranged from 0% to 21%, comparable to our findings.[233–238] Although we investigated potential covariates (e.g., albumin concentration), none had a significant effect on protein binding, likely due to the relatively low protein binding of ceftazidime.

The available information on the protein binding of ceftazidime in the HD setting is limited to two studies. The first, by van Dalen *et al*., used UF to determine the *in vivo* protein binding of ceftazidime in samples from critically ill patients with varying degrees of kidney dysfunction, including HD.[235] The average protein binding was 5.9% ± 9.8%. Matzke *et al.* used Centrifree® UF devices to determine the *in vivo* protein binding of ceftazidime in clinical samples from eight patients receiving chronic HD.[234] The average protein binding was 17% ± 7%. Overall, our ceftazidime protein binding is comparable to studies in various patient populations, including healthy volunteers, the critically ill, and those with varying degrees of kidney dysfunction.

4.5.2.3. Ceftazidime pharmacokinetic modelling

As described previously, the Sawchuk-Zaske LSS method was used to delineate the PK of ceftazidime. Our modelled values for the t½ between HD sessions, t½ during HD, and Vd were 28.1 ± 4.8 hours, 3.7 ± 0.8 hours, and 19.0 ± 5.6 L, respectively. The modelled t½ between HD sessions using the Sawchuk-Zaske LSS method was similar to that calculated using the Sawchuk-Zaske method alone, i.e., 28.3 ± 6.5 hours. Furthermore, our findings using the Sawchuk-Zaske LSS method aligned with those from ADAPT 5 modelling, which estimated an average t½ between HD sessions of 28.0 ± 4.7 hours and Vd of 20.3 ± 5.6

L (**Table S4B-2**). Given that our peak samples may have been collected during the distribution phase, our one-compartment PK model may have slightly overestimated the values for t½ between HD sessions.

In our study, the ceftazidime t½ was 28.1 ± 4.8 hours between HD sessions, compared to a t½ of approximately 1.8 hours (range = 1.3–2.0 hours) in subjects with normal kidney function.[166,239–241] Over 80% to 90% of an administered ceftazidime dose is excreted unchanged in the urine within 24 hours, explaining the significantly prolonged t½ in patients with ESKD. Studies in the HD setting have reported ceftazidime t½'s ranging from 15.1 to 38.0 hours between HD sessions, as detailed in **APPENDIX 1D**.[159,229–231] The ceftazidime t½ during HD was 3.7 ± 0.8 hours in our study. No other studies have reported the t½ of ceftazidime during iHFHD (**APPENDIX 1D**).[159,229]

The variation in t½ between HD sessions among participants, ranging from 22.2 to 38.9 hours, may be explained by residual kidney function. While the $t½_{off\text{-}HD}$ appeared shorter when urine production was >1 cup per day (23.5 ± 1.1 hours) as opposed to ≤1 cup per day (29.3 ± 4.7 hours), there was no statistical difference ($P = 0.06$). It is important to consider that our sample size may not have been large enough to identify a statistical difference, therefore, further investigation may be warranted. Overall, compared to cefazolin, there was less variability in the t½ between HD sessions and pre-HD trough concentrations, likely attributed to lower residual kidney function in this cohort. Comparatively, participants in the ceftazidime versus cefazolin cohort had lower daily urine production (22.2% versus 60.0% of participants produced >1 cup of urine per day, respectively) and had been on dialysis longer (median dialysis vintage 33 [12–65] months versus 18 [8–36] months, respectively). Still, urine output may indicate remaining residual kidney function, which could predict ceftazidime elimination between HD sessions.

Concerning the t½ during HD, variations in HD factors, including dialyzer filter type and flux, dialysate and blood flow rates, and duration, are likely to influence drug elimination.[122,214–216] It is reasonable to

assume that ceftazidime elimination may increase during high- versus low-flux HD. The abovementioned factors must be considered when translating our results to different practice settings.

In our study, the Vd of ceftazidime was 19.0 ± 5.6 L (0.30 ± 0.08 L/kg_{DW}). Our results are similar to the reported Vd of ceftazidime in healthy subjects of approximately 14–20 L.[166,239–241] Additionally, our Vd compares to the 0.24 ± 0.03 L/kg reported in studies of ceftazidime in patients receiving chronic HD (**APPENDIX 1D**).[229] Although we explored potential covariates, none significantly influenced Vd. The fluid retention between HD sessions is less likely to impact the Vd of ceftazidime as it is relatively large. We observed that 1.7 ± 0.8 L of fluid was removed during HD, which represents approximately 9% of the Vd of ceftazidime.

4.5.2.4. Ceftazidime pharmacodynamics

We analyzed pre-HD ceftazidime trough concentrations to assess if the current one-dose-fits-all dosing approach of 2 g ceftazidime thrice weekly post-HD was adequate to treat the most clinically relevant infections, i.e., Enterobacterales and *P. aeruginosa*, in the outpatient HD setting. We assessed whether PKPD thresholds of 100%$fT_{>MIC}$ and 100%$fT_{>4xMIC}$ were met during interdialytic periods. As discussed previously, our thresholds were informed by a select number of studies identifying the PKPD thresholds required for the efficacy of cephalosporins, some of which were specific to ceftazidime.[20,218,242]

Loo *et al.* studied PKPD target attainment of various ceftazidime regimens in patients receiving HD using previously published PK data during low-flux HD. However, this study used PKPD thresholds of 45%$fT_{>MIC}$ and 70%$fT_{>MIC}$.[243] We argue that thresholds less than 100%$fT_{>MIC}$ do not translate to thrice weekly post-HD dosing. Achieving 45% to 70%$fT_{>MIC}$ over a 48-to-72-hour dosing interval would result in 15 to 39 hours of sub-MIC antimicrobial concentrations. Also, given the heightened risk of infection-related morbidity and mortality among patients receiving chronic HD, higher PKPD thresholds are justified.

Overall, for ceftazidime, all study participants achieved 100%$fT_{>MIC}$, regardless of the pathogen (i.e., Enterobacterales or *P. aeruginosa*) or interdialytic period (i.e., two- or three-days). Target attainment was lower for the higher threshold of 100%$fT_{>4xMIC}$ ranging from 0% to 100%. In general, target attainment was lower against *P. aeruginosa* due to a MIC breakpoint of 8 mg/L compared to 4 mg/L for Enterobacterales. As expected, target attainment was also lower during three-day interdialytic periods. Subtherapeutic concentrations were also predicted by shorter t½ between HD sessions (P = 0.02), higher daily urine production (P = 0.009), and larger Vd (P = 0.02). These findings highlight the limitations of using a one-dose-fits-all dosing approach. We identified the importance of considering residual kidney function, the time between HD sessions, and pathogen MIC to optimize PKPD target attainment. This is particularly important for achieving a threshold of 100%$fT_{>4xMIC}$, which may improve clinical outcomes and help prevent the development of AMR, especially when treating severe, life-threatening, or deep-seated infections.

4.5.2.5. Ceftazidime toxicodynamics

We assessed whether the current ceftazidime dosing protocol resulted in supratherapeutic levels. As there is no clear upper limit for ceftazidime toxicity, we defined supratherapeutic or unnecessarily high trough levels as those not predicted to provide additional benefit, i.e., 100%$fT_{>10xMIC}$. This translated to total pre-HD ceftazidime trough concentrations ≥90 mg/L. Additionally, excessive antimicrobial exposure was assessed by comparing relative AUC_{48h} in study participants to that expected in controls with normal kidney function (i.e., CrCl ~100 mL/min, receiving 2 g ceftazidime every 8 hours). No supratherapeutic concentrations were observed, with the highest level being 52.4 mg/L. However, the relative ceftazidime exposure was 2.1 to 3.6 times higher in study participants than controls.

As with cefazolin, ceftazidime has been associated with a risk for neurotoxicity. Most information originates from individual case reports. A recent article by Vanneste *et al*. summarized 32 cases of ceftazidime-related neurotoxicity reported in the literature.[244] Of these, most patients (75%) had some

degree of kidney impairment. Few case reports included ceftazidime levels; however, in 8 patients, trough levels ranged from 36.9 to 402 mg/L. Most cases improved within two to three days after reducing or discontinuing ceftazidime with or without interventions such as dialysis or antiseizure medication. Using an ROC analysis, the authors identified a trough value of <78 mg/L for the improvement of neurological symptoms in patients experiencing ceftazidime-related neurotoxicity. This value compares to our upper limit of 90 mg/L.

4.5.2.6. Knowledge translation: ceftazidime dosing in the outpatient hemodialysis setting

Due to a lack of evidence to direct dose individualization, HD programs often adopt one-dose-fits-all protocols, overlooking factors that influence PK. Specifically, within the MRP, a standard dosing protocol of 2 g ceftazidime thrice weekly post-HD is used (**APPENDIX 1A**).[100] Based on this protocol, target attainment was 100% in our study based on our lower PKPD threshold of 100%$fT_{>MIC}$ and upper limit of 90 mg/L. However, for the higher PKPD threshold of 100%$fT_{>4xMIC}$, target attainment against Enterobacterales was 100% and 73.3% during two- and three-day interdialytic periods, respectively, and against *P. aeruginosa* was 66.6% and 0% during two- and three-day interdialytic periods, respectively. Given that a probability of target attainment ≥90% is typically considered optimal in PKPD research, our current ceftazidime dosing protocol would be regarded as suboptimal based on our higher PKPD threshold of 100%$fT_{>4xMIC}$.

In search of adaptive dosing strategies, we reviewed ceftazidime dosing guidelines for adults receiving thrice-weekly iHFHD, as outlined in widely recognized clinical dosing resources (**APPENDIX 1F**). Recommendations included daily dosing of 0.5–1 g and 0.5–2 g thrice weekly. While not recommended in the guidelines, a 3 g ceftazidime dose, primarily before three-day interdialytic periods, may reduce subtherapeutic levels in some patients but could also expose others to supratherapeutic levels. Moreover, lower doses given more frequently, i.e., daily dosing rather than thrice weekly, would enhance ceftazidime PKPD based on improved %$fT_{>MIC}$. However, this approach may be limited by logistics. Importantly, none

of these methods address residual kidney function, which was predictive of subtherapeutic ceftazidime levels in our study.

We found that participants in the ceftazidime versus cefazolin cohort had lower residual kidney function, as predicted by lower daily urine production and longer dialysis vintage. In a cohort with higher residual kidney function, we may have observed higher ceftazidime elimination between HD sessions and, subsequently, worse PKPD target attainment. Therefore, a more accurate measure of residual kidney function (i.e., 24-hour urine creatinine) linked to ceftazidime PK may more appropriately guide ceftazidime dose individualization. A preferable alternative would be TDM, allowing for dose individualization in all patients regardless of covariates influencing PK.

4.6. Conclusions

The current study demonstrates the limitations of using one-dose-fits-all cefazolin and ceftazidime regimens in the outpatient HD setting. It identifies the importance of considering residual kidney function, body weight, and the time between HD sessions to optimize antimicrobial therapy. Although TDM of cefazolin and ceftazidime is not standard practice, it would considerably enhance dose individualization, especially given the significant PK variability among patients receiving chronic HD. In closing, the current approach to cefazolin and ceftazidime dosing is suboptimal in the outpatient HD setting, thereby increasing the risk of adverse outcomes such as treatment failure, antimicrobial-associated adverse effects, and AMR. These findings will be used to investigate adaptive antimicrobial dosing strategies that can improve the treatment of severe infections in this high-risk and understudied population.

4.7. Acknowledgements

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4.8. Supplementary Tables & Figures

4.8.1. Cefazolin

Table S4A. Relationships between cefazolin protein binding and participant characteristics.

	Pre-HD troughs (*n* = 10)	**Peaks (*n* = 10)**
Spearman's rho	**rho (*P* value)**	
Age (years)	rho = 0.33 (*P* = 0.4)	rho = 0.18 (*P* = 0.6)
DW (kg)[a]	rho = 0.39 (*P* = 0.3)	rho = 0.52 (*P* = 0.1)
Albumin plasma concentration (g/L)	**rho = 0.67 (*P* = 0.03)**	rho = 0.09 (*P* = 0.8)
Student's t-test	**Protein binding (*P* value)**	
Sex Female (*n* = 5) Male (*n* = 5)	(*P* = 0.2) 79.4% ± 6.1% 84.3% ± 4.2%	(*P* = 0.2) 65.1% ± 8.7% 54.0% ± 15.0%
Daily urine production ≤1 cup (*n* = 4) >1 cup (*n* = 6)	(*P* = 0.5) 80.1% ± 4.4% 83.0% ± 6.4%	(*P* = 0.5) 55.6% ± 18.0% 62.2% ± 9.3%
Heparin during hemodialysis No heparin (*n* = 3) Heparin (*n* = 7)	NA	(*P* = 0.2) 67.8% ± 4.4% 56.0% ± 14.0%

Reported as mean ± standard deviation.

DW dosing weight.

[a] Adjusted body weight used for obese individuals and total body weight for non-obese individuals.

Table S4B. Cefazolin pharmacokinetics modelled using ADAPT 5 (*n* = 19).

	Mean ± SD	**Median [IQR]**	**Range**
$t_{½off\text{-}HD}$ (h)	32.3 ± 12.6	30.0 [23.9–41.9]	10.5–53.3
$t_{½on\text{-}HD}$ (h)	N/C	N/C	N/C
Vd (L) Vd (L/kg$_{DW}$)[a]	11.2 ± 2.8 0.16 ± 0.04	10.5 [9.4–13.9] 0.16 [0.13–0.17]	6.5–16.2 [0.09–0.26]

DW dosing weight, *HD* hemodialysis, *h* hours, *N/C* non-computable, *IQR* interquartile range, *SD* standard deviation, $t_{½off\text{-}HD}$ half-life off hemodialysis, $t_{½on\text{-}HD}$ half-life on hemodialysis, *Vd* volume of distribution.

[a] Adjusted body weight used for obese individuals and total body weight for non-obese individuals.

Table S4C. Relationships between cefazolin half-life off hemodialysis ($t½_{off\text{-}HD}$) and participant characteristics (n = 19).

Spearman's rho	**rho (*P* value)**
Age (years)	rho = 0.06 (P = 0.8)
Dialysis vintage (months)	rho = 0.39 (P = 0.1)
DW (kg)[a]	rho = -0.09 (P = 0.7)
Student's t-test	**$t½_{off\text{-}HD}$ (*P* value)**
Sex	(P = 0.6)
Female (n = 11)	32.8 ± 12.7
Male (n = 8)	29.5 ± 11.4
Dialysis vintage	**(P = 0.05)**
<18 months (n = 9)	**26.4 ± 10.8**
≥18 months (n = 10)	**37.0 ± 11.2**
Daily urine production	**(P = 0.04)**
≤1 cup (n = 7)	**38.6 ± 9.9**
>1 cup (n = 12)	**27.2 ± 11.4**

Reported as mean ± standard deviation. *DW* dosing weight.

[a] Adjusted body weight used for obese individuals and total body weight for non-obese individuals.

Table S4D. Relationships between cefazolin volume of distribution (Vd) and participant characteristics (n = 19).

Spearman's rho	**rho (*P* value)**
Age (years)	rho = -0.07 (P = 0.8)
Dialysis vintage (months)	rho = -0.08 (P = 0.8)
DW (kg)[a]	**rho = 0.46 (P = 0.05)**
Mann-Whitney U	**Vd (*P* value)**
Sex	(P = 0.7)
Female (n = 11)	8.6 [8.5–10.9]
Male (n = 8)	9.7 [8.5–13.0]
Daily urine production	(P = 0.5)
≤1 cup (n = 7)	9.8 [8.6–11.3]
>1 cup (n = 12)	9.5 [8.4–11.5]

Reported as median [IQR]. *DW* dosing weight.

[a] Adjusted body weight used for obese individuals and total body weight for non-obese individuals.

Table S4E. Relationships between total cefazolin pre-hemodialysis trough concentrations and participant characteristics, dosing, and pharmacokinetics (n = 20).[a]

Spearman's rho	**rho (*P* value)**
Age (years)	-0.07 (P = 0.8)
DW (kg)[b]	-0.25 (P = 0.3)
Cefazolin dose (mg/kg$_{DW}$)[b]	0.25 (P = 0.3)
$t_{½off\text{-}HD}$ (h)[c]	**0.87 (*P* <0.001)**
Vd (L)[c]	-0.02 (P = 1)
Student's t-test	**Pre-HD trough concentration (*P* value)**
Sex	(P = 0.3)
Female (n = 12)	93.5 ± 42.0
Male (n = 8)	72.3 ± 40.9
Daily urine production	(P = 0.2)
≤1 cup (n = 8)	101.7 ± 28.2
>1 cup (n = 12)	73.9 ± 46.7

Reported as mean ± standard deviation.

DW dosing weight, *HD* hemodialysis, *h* hours, $t_{½off\text{-}HD}$ half-life off hemodialysis, *Vd* volume of distribution.

[a] The second pre-HD trough from each participant was extrapolated to a two-day interdialytic period.

[b] Adjusted body weight used for obese individuals and total body weight for non-obese individuals.

[c] n = 19.

Figure S4A. Total cefazolin pre-hemodialysis trough concentrations relative to interdialytic half-life (n = 19).

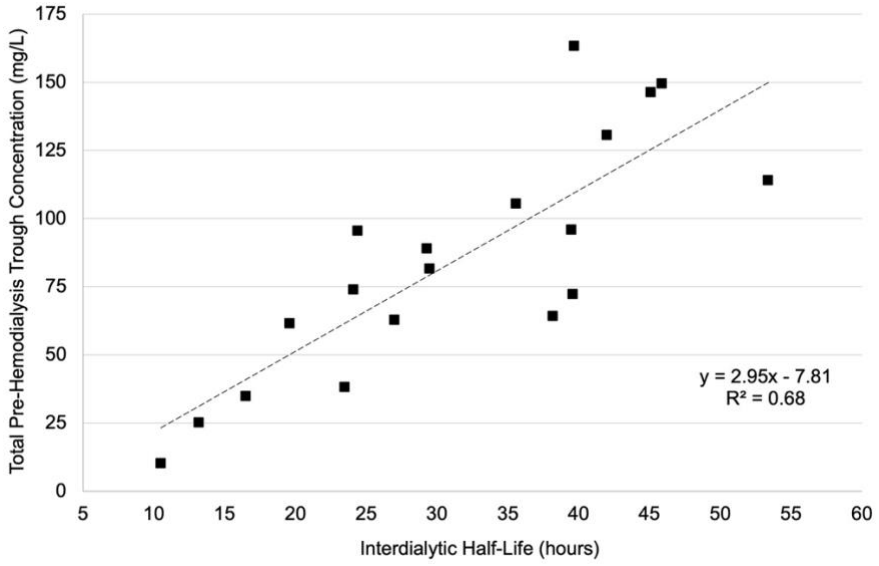

Table S4F. Factors associated with free cefazolin pre-hemodialysis trough concentrations below 2 mg/L three days post-dose.

Factor	Free cefazolin pre-HD trough		*P* value
	<2 mg/L (*n* = 2)	**≥2 mg/L (*n* = 18)**	
Female sex	1 (50.0%)	11 (61.1%)	1
Age (years)	69.5 ± 3.5	59.3 ± 13.6	0.3
DW (kg)[a]	63.1 ± 1.8	72.2 ± 12.3	0.3
Urine production ≤1 cup per day	0 (0%)	8 (44.4%)	0.5
$t½_{off\text{-}HD}$ (h)	**11.9 ± 1.9**	**33.7 ± 10.4[b]**	**<0.001**
Vd (L)	8.8 [8.3–9.4]	9.5 [8.5–11.7][b]	0.5
Dose (mg/kg$_{DW}$)[a]	31.7 ± 0.9	28.4 ± 4.6	0.3

n (%), mean ± standard deviation, or median [interquartile range].

DW dosing weight, *HD* hemodialysis, *h* hours, $t½_{off\text{-}HD}$ half-life off hemodialysis, *Vd* volume of distribution.

[a] Adjusted body weight used for obese individuals and total body weight for non-obese individuals.

[b] *n* = 17.

Table S4G. Factors associated with free cefazolin pre-hemodialysis trough concentrations below 4 mg/L three days post-dose.[a]

Factor	Free cefazolin pre-HD trough		*P* value
	<4 mg/L (*n* = 4)	**≥4 mg/L (*n* = 16)**	
Female sex	1 (25.0%)	11 (68.8%)	0.3
Age (years)	65.8 ± 8.1	59.0 ± 14.2	0.4
DW (kg)[b]	78.6 ± 20.1	69.4 ± 9.1	0.4
Urine production ≤1 cup per day	0 (0%)	8 (50.0%)	0.1
$t½_{off\text{-}HD}$ (h)	**15.9 ± 5.6**	**35.5 ± 9.5[c]**	**0.001**
Vd (L)	9.1 [8.2–11.3]	9.5 [8.5–11.3][c]	0.7
Dose (mg/kg$_{DW}$)[b]	26.6 ± 6.2	29.3 ± 4.0	0.3

Reported as n (%), mean ± standard deviation, or median [interquartile range].

DW dosing weight, *HD* hemodialysis, *h* hours, $t½_{off\text{-}HD}$ half-life off hemodialysis, *Vd* volume of distribution.

[a] These results also apply to maintaining free pre-HD cefazolin trough concentrations above 8 mg/L two days post-dose.

[b] Adjusted body weight used for obese individuals and total body weight for non-obese individuals.

[c] *n* = 15.

Table S4H. Factors associated with free cefazolin pre-hemodialysis trough concentrations below 8 mg/L three-days post-dose.

Factor	Free cefazolin pre-HD trough		*P* value
	<8 mg/L (*n* = 10)	**≥8 mg/L (*n* = 10)**	
Female sex	5 (50.0%)	7 (70.0%)	0.7
Age (years)	62.2 ± 9.9	58.5 ± 16.4	0.6
DW (kg)[a]	73.6 ± 14.6	68.9 ± 8.8	0.4
Urine production ≤1 cup per day	3 (30.0%)	5 (50.0%)	0.7
$t½_{off\text{-}HD}$ (h)	**24.2 ± 9.8**	**39.4 ± 8.8[b]**	**0.002**
Vd (L)	9.2 [8.5–11.5]	9.5 [8.6–10.9][b]	1
Dose (mg/kg$_{DW}$)[a]	28.0 ± 5.0	29.5 ± 4.0	0.5

Reported as n (%), mean ± standard deviation, or median [interquartile range].

DW dosing weight, *HD* hemodialysis, *h* hours, $t½_{off\text{-}HD}$ half-life off hemodialysis, *Vd* volume of distribution.

[a] Adjusted body weight used for obese individuals and total body weight for non-obese individuals.

[b] *n* = 9.

Table S4I. Factors associated with supratherapeutic total cefazolin pre-hemodialysis trough concentrations three days post-dose.

Factor	Total cefazolin pre-HD trough		*P* value[a]
	<100 mg/L (*n* = 17)	**≥100 mg/L (*n* = 3)**	
Female sex	10 (58.8%)	2 (66.7%)	1
Age (years)	60.5 ± 13.7	59.7 ± 13.3	0.9
DW (kg)[a]	73.3 ± 11.7	59.5 ± 5.9	0.06
Urine production ≤1 cup per day	7 (41.2%)	1 (33.3%)	1
$t½_{off\text{-}HD}$ (h)	**29.1 ± 11.6[b]**	**43.6 ± 3.4**	**0.05**
Vd (L)	9.7 [8.5–11.8][b]	8.6 [8.3–9.2]	0.4
Dose (mg/kg$_{DW}$)[a]	**27.9 ± 4.1**	**33.8 ± 3.2**	**0.03**

Reported as n (%), mean ± standard deviation, or median [interquartile range].

DW dosing weight, *HD* hemodialysis, *h* hours, $t½_{off\text{-}HD}$ half-life off hemodialysis, *Vd* volume of distribution

[a] Adjusted body weight used for obese individuals and total body weight for non-obese individuals.

[b] *n* = 17.

Table S4J. Factors associated with supratherapeutic total cefazolin pre-hemodialysis trough concentrations two days post-dose.

Factor	Total cefazolin pre-HD trough		*P* value[a]
	<100 mg/L (*n* = 14)	**≥100 mg/L (*n* = 6)**	
Female sex	7 (50.0%)	5 (83.3%)	0.3
Age (years)	58.6 ± 13.8	64.5 ± 12.2	0.4
DW (kg)[a]	74.1 ± 12.4	64.7 ± 8.6	0.1
Urine production ≤1 cup per day	4 (28.6%)	4 (66.7%)	0.2
$t½_{off\text{-}HD}$ (h)	**25.8 ± 9.5[b]**	**43.6 ± 6.1**	**<0.001**
Vd (L)	9.5 [8.5–11.7][b]	9.2 [8.6–10.6]	0.9
Dose (mg/kg_{DW})[a]	27.6 ± 4.3	31.4 ± 4.1	0.09

Reported as n (%), mean ± standard deviation, or median [interquartile range].

DW dosing weight, *HD* hemodialysis, *h* hours, $t½_{off\text{-}HD}$ half-life off hemodialysis, *Vd* volume of distribution.

[a] Adjusted body weight used for obese individuals and total body weight for non-obese individuals.

[b] *n* = 13.

4.8.2. Ceftazidime

Table S4A-2. Relationships between ceftazidime protein binding and participant characteristics (*n* = 8).

Spearman's rho	**rho (*P* value)**
Age (years)	rho = -0.23 (*P* = 0.6)
DW (kg)[a]	rho = -0.02 (*P* = 1)
Albumin plasma concentration (g/L)	rho = -0.56 (*P* = 0.2)
Student's t-test	**Protein binding (*P* value)**
Sex	(*P* = 0.9)
Female (*n* = 3)	10.1% ± 4.0%
Male (*n* = 5)	10.6% ± 3.9%
Daily urine production	(*P* = 0.4)
≤1 cup (*n* = 7)	10.8% ± 3.7%
>1 cup (*n* = 1)	7.0%

Reported as mean ± standard deviation.

DW dosing weight.

[a] Adjusted body weight used for obese individuals and total body weight for non-obese individuals.

Table S4B-2. Ceftazidime pharmacokinetics modelled using ADAPT 5 (*n* = 15).

	Mean ± SD	**Median [IQR]**	**Range**
$t½_{off\text{-}HD}$ (h)	28.0 ± 4.7	27.2 [23.9–30.2]	22.7–37.0
$t½_{on\text{-}HD}$ (h)	N/C	N/C	N/C
Vd (L)	20.3 ± 5.6	20.2 [16.2–24.0]	11.4–31.7
Vd (L/kg_{DW})[a]	0.32 ± 0.10	0.30 [0.23–0.39]	[0.19–0.48]

DW dosing weight, *HD* hemodialysis, *h* hours, *IQR* interquartile range, *N/C* non-computable, *SD* standard deviation, $t½_{off\text{-}HD}$ half-life off hemodialysis, $t½_{on\text{-}HD}$ half-life on hemodialysis, *Vd* volume of distribution.

[a] Adjusted body weight used for obese individuals and total body weight for non-obese individuals.

Table S4C-2. Relationships between ceftazidime half-life off hemodialysis ($t_{½off\text{-}HD}$) and participant characteristics (n = 15).

Spearman's rho	**rho (*P* value)**
Age (years)	rho = -0.47 (P = 0.1)
Dialysis vintage (months)	rho = 0.08 (P = 0.8)
DW (kg)[a]	rho = -0.05 (P = 0.9)
Student's t-test	**$t_{½off\text{-}HD}$ (*P* value)**
Sex	(P = 0.8)
Female (n = 9)	27.7 ± 4.0
Male (n = 6)	28.4 ± 5.5
Daily urine production	(P = 0.06)
≤1 cup (n = 12)	29.3 ± 4.7
>1 cup (n = 3)	23.5 ± 1.1

Reported as mean ± standard deviation.

DW dosing weight.

[a] Adjusted body weight used for obese individuals and total body weight for non-obese individuals.

Table S4D-2. Relationships between ceftazidime volume of distribution (Vd) and participant characteristics (n = 15).

Spearman's rho	**rho (*P* value)**
Age (years)	-0.18 (P = 0.5)
Dialysis vintage (months)	-0.10 (P = 0.7)
DW (kg)[a]	0.29 (P = 0.3)
Student's t-test	**Vd (*P* value)**
Sex	(P = 0.9)
Female (n = 9)	18.7 ± 3.3
Male (n = 6)	19.2 ± 6.9
Daily urine production	(P = 0.3)
≤1 cup (n = 12)	18.2 ± 6.0
>1 cup (n = 3)	22.2 ± 1.5

Reported as mean ± standard deviation.

DW dosing weight.

[a] Adjusted body weight used for obese individuals and total body weight for non-obese individuals.

Table S4E-2. Relationships between total ceftazidime pre-hemodialysis trough concentrations and participant characteristics, dosing, and pharmacokinetics (n = 15).[a]

Spearman's rho	**rho (*P* value)**
Age (years)	rho = -0.13 (P = 0.6)
DW (kg)[b]	rho = -0.48 (P = 0.07)
Cefazolin dose (mg/kg$_{DW}$)[b]	rho = 0.15 (P = 0.6)
$t_{½off\text{-}HD}$ (h)[c]	rho = 0.28 (P = 0.3)
Vd (L)[c]	**rho = -0.74 (*P* = 0.002)**
Student's t-test	**Pre-HD trough concentration (*P* value)**
Sex	(P = 0.7)
Female (n = 9)	40.3 ± 11.6
Male (n = 6)	42.5 ± 10.8
Daily urine production	**(*P* = 0.02)**
≤1 cup (n = 12)	**44.7 ± 9.8**
>1 cup (n = 3)	**29.4 ± 3.1**

Reported as mean ± standard deviation.

DW dosing weight, *HD* hemodialysis, *h* hours, $t_{½off\text{-}HD}$ half-life off hemodialysis, *Vd* volume of distribution.

[a] The second pre-HD trough from each participant was extrapolated to a two-day interdialytic period.

[b] Adjusted body weight used for obese individuals and total body weight for non-obese individuals.

[c] n = 15.

Figure S4A-2. Total ceftazidime pre-hemodialysis trough concentrations relative to volume of distribution (n = 15).

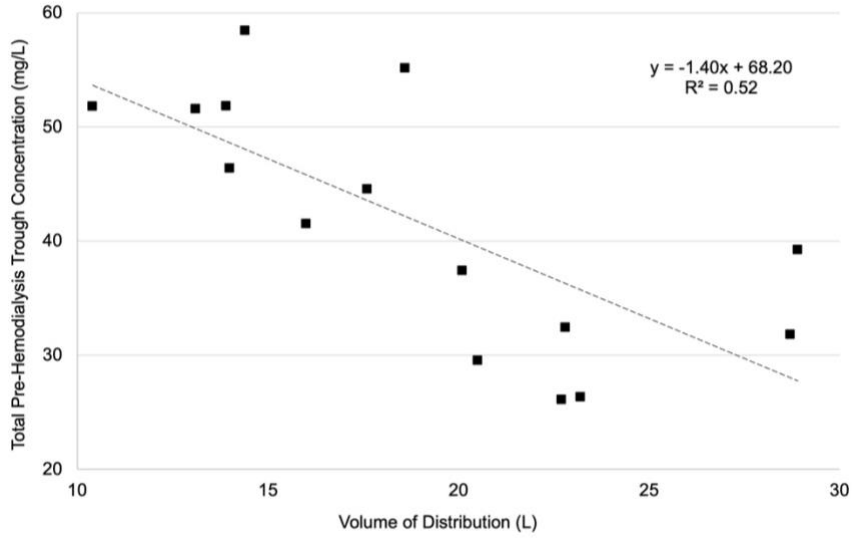

Figure S4B-2. Box and whisker plot of total ceftazidime pre-hemodialysis trough concentrations for participant daily urine production (n = 15).

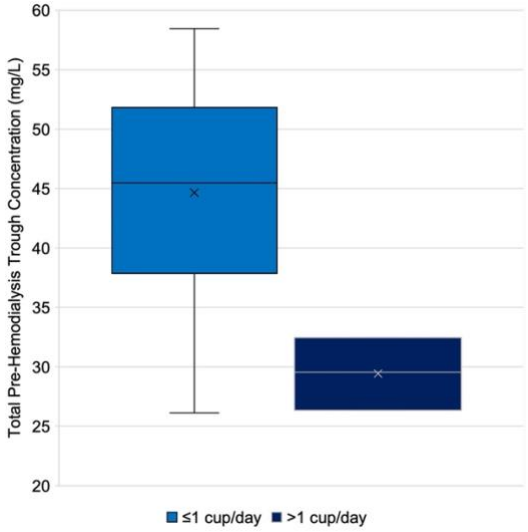

Table S4F-2. Factors associated with free ceftazidime pre-hemodialysis trough concentrations below 32 mg/L two days post-dose.

Factor	**Free ceftazidime pre-HD trough**		***P* value[a]**
	<32 mg/L (*n* = 5)	**≥32 mg/L (*n* = 10)**	
Female sex	3 (60.0%)	6 (60.0%)	1
Age (years)	69.6 ± 12.4	63.9 ± 16.1	0.5
DW (kg)[a]	72.1 ± 8.2	61.7 ± 11.7	0.1
Urine production ≤1 cup per day	**2 (40.0%)**	**10 (100.0%)**	**0.02**
$t½_{off\text{-}HD}$ (h)	25.8 ± 5.4	29.3 ± 4.3	0.2
Vd (L)	**23.6 ± 3.1**	**16.7 ± 5.1**	**0.02**
Dose (mg/kg$_{DW}$)[a]	27.8 [27.8–30.5]	29.0 [28.2–34.5]	0.3

Reported as n (%), mean ± standard deviation, or median [interquartile range].

DW dosing weight, *HD* hemodialysis, *h* hours, $t½_{off\text{-}HD}$ half-life off hemodialysis, *Vd* volume of distribution.

[a] Adjusted body weight used for obese individuals and total body weight for non-obese individuals.

Table S4G-2. Factors associated with free ceftazidime pre-hemodialysis trough concentrations below 16 mg/L three days post-dose.

Factor	**Free ceftazidime pre-HD trough**		***P* value[a]**
	<16 mg/L (*n* = 4)	**≥16 mg/L (*n* = 11)**	
Female sex	2 (50.0%)	7 (63.6%)	1
Age (years)	72.8 ± 11.8	63.3 ± 15.5	0.3
DW (kg)[a]	72.1 ± 9.5	62.6 ± 11.6	0.2
Urine production ≤1 cup per day	**1 (25.0%)**	**11 (100.0%)**	**0.009**
$t½_{off\text{-}HD}$ (h)	**23.4 ± 0.9**	**29.8 ± 4.5**	**0.02**
Vd (L)	22.3 ± 1.2	17.8 ± 6.1	0.2
Dose (mg/kg_{DW})[a]	29.2 [26.7–30.5]	28.4 [28.0–33.4]	0.6

Reported as n (%), mean ± standard deviation, or median [interquartile range].

DW dosing weight, *HD* hemodialysis, *h* hours, $t½_{off\text{-}HD}$ half-life off hemodialysis, *Vd* volume of distribution.

[a] Adjusted body weight used for obese individuals and total body weight for non-obese individuals.

CHAPTER 5: Discussion and conclusions.

Preamble: This chapter aims to demonstrate how the findings presented in **CHAPTERS 2**, **3**, and **4** add to current knowledge in the research area. **REFERENCES** are merged at the end of this document.

As previously highlighted, patients requiring HD are at high risk of developing infections as well as infection-related morbidity and mortality. HD vascular access is a notable risk factor predisposing patients to ESIs and BSIs. Although this population would benefit significantly from AMS, current initiatives to prevent infection and optimize antimicrobial use are limited. In response, three studies were conducted to facilitate AMS in the outpatient HD setting. The studies presented in **CHAPTERS 2**, **3**, and **4** represent significant progress in the area. Notably, the studies were designed to answer clinically relevant questions such as: What is the most appropriate empiric antimicrobial regimen? Is AMR a concern? How effective are infection prevention measures? What are the modifiable risk factors for infection that can be addressed? Is antimicrobial dosing optimal? How can antimicrobial dosing be improved? As answers to these questions are important to practicing clinicians, there has been significant interest and engagement in our research. As our findings are clinically relevant, they can be translated "from bench to bedside" and positively impact practice.

CHAPTER 2 presents a retrospective study of bloodstream isolates (n = 1024) from patients receiving HD. The objective of this study was to use the distribution of pathogens and their antimicrobial susceptibilities to evaluate microbiological coverage for empiric antimicrobial regimens recommended for the treatment of BSIs. Over 70% of isolates were gram-positive, primarily staphylococci (60.1%, 615/1024), including *S. aureus* (36.9%, 378/1024) and CoNS (23.1%, 237/1024). The MRSA rate was 17.5%, although rates significantly increased from 6.7% to 26.0% over time. Methicillin resistance in CoNS was higher at 64.6%. VRE were only identified at the end of the study. Gram-negative bacteria were highly susceptible; however, ESBL-producers were only identified at the end of the study. Microbiological coverage was predicted for regimens recommended in clinical practice guidelines[92], including vancomycin or cefazolin for gram-positive coverage plus ceftazidime, piperacillin-tazobactam, meropenem, ciprofloxacin, tobramycin, or gentamicin for gram-negative coverage. Using cefazolin over vancomycin was predicted to reduce overall coverage by >30% from 98.8%–99.7% to 67.5%–68.4%. This finding was primarily attributable to methicillin resistance in CoNS. The predicted gram-negative coverage varied by <1%, with no advantage

for broader-spectrum agents such as piperacillin-tazobactam or meropenem. Notably, the predicted coverage of vancomycin plus ciprofloxacin was 98.8%; therefore, this regimen may be an acceptable alternative for severe β-lactam allergy and aminoglycoside intolerance. These data will direct appropriate empiric antimicrobial selection, thereby supporting AMS in the outpatient HD setting. Also, given the increasing AMR observed over time, these data highlight the necessity for ongoing local surveillance.

CHAPTER 3 presents a retrospective study of CR-ESIs (n = 113) and CR-BSIs (n = 64) in an outpatient HD unit. Notably, the study period was selected to coincide with the implementation of new CR-infection prevention measures at the midpoint, including masking during exit-site care, using chlorhexidine-alcohol versus povidone-iodine antiseptic, administering cefazolin prophylaxis with CVC insertions, and reducing temporary CVC use for chronic HD starts. The main objectives of this study were to evaluate the impact of practice changes on infection rates and identify risk factors for infection. Immediately after implementing new infection prevention measures, ESI rates dropped by 60%. However, by the end of the study, ESI rates began to rise. Over the study period, BSI rates declined by 85%, which was strongly correlated with reduced temporary catheter use over time. Notably, ESIs preceded one-third of BSIs, primarily due to the same pathogen. These findings demonstrate the effectiveness of CR-infection prevention measures as an AMS initiative to reduce antimicrobial use in outpatient HD settings. With the increase in ESI observed by the end of the study, ongoing local surveillance and reinforcement of prevention strategies are essential. Furthermore, these data highlight the need for further investigations into ESI prevention and treatment strategies to reduce the risk of BSIs.

CHAPTER 4 presents a prospective non-interventional PK study of cefazolin (n = 20) and ceftazidime (n = 18) in patients receiving HD. Despite the considerable use of these antimicrobials in the outpatient HD setting, there is limited evidence to validate the current dosing protocols (2 g thrice weekly post-HD). The objective of this study was to characterize the PK, PD, and toxicodynamics and evaluate whether current dosing protocols are optimal to treat clinically relevant infections. For both drugs, the protein binding and

volume of distributions were similar to other populations, while the elimination half-lives were >15-fold longer compared to patients with normal kidney function. In the cefazolin cohort, there was more interindividual variation in half-life and pre-HD trough concentrations. The variability was attributed to residual kidney function. Overall, the analysis identified limitations in using a one-dose-fits-all approach. It highlighted the importance of considering residual kidney function, body weight, interdialytic period, and pathogens MIC to improve dosing. While urine output and dialysis vintage were identified as indicators of residual kidney function, these remain surrogate measures. A more accurate measure of residual kidney function (i.e., 24-hour urine creatinine) linked to PK may more appropriately guide dosage adjustments. A preferable alternative would be TDM. Although TDM is not standard for cefazolin and ceftazidime, it would significantly enhance dose individualization due to notable PK variability within the HD population. As the current approach to cefazolin and ceftazidime dosing is suboptimal, the risk of adverse outcomes, including treatment failure, toxicity, and AMR, may be increased. These data will direct appropriate antimicrobial dosing, an important and understudied component of AMS in the outpatient HD setting. Further investigations should be conducted to establish adaptive dosing strategies for cefazolin and ceftazidime in this high-risk and understudied population.

While this work provides a foundation for future research, there are many opportunities to enhance AMS in the outpatient HD setting. Ongoing surveillance of infections and AMR is vital to maintain the relevance and applicability of this initial work. This is especially true as AMR changes over time, impacting appropriate antimicrobial selection. As well, infection control measures are constantly evolving with notable practice changes following the COVID-19 pandemic. Surveillance is critical to determine the need for and effectiveness of infection prevention strategies. In addition, future research should focus on optimizing antimicrobial dosing, including TDM, for patients receiving HD. Finally, the studies, methodologies, findings, and experiences presented in this thesis may aid the investigation of other understudied antimicrobials and enhance the ongoing development of AMS in the outpatient HD setting.

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APPENDICES

APPENDIX 1A. Manitoba Renal Program Order Sets[100]

kidneyhealth.ca
manitoba renal program

SUSPECTED CENTRAL VENOUS CATHETER RELATED BACTEREMIA ORDER SHEET FOR PATIENTS RECEIVING 3 TIMES PER WEEK HEMODIALYSIS USING TOBRAMYCIN

• Do not add or change orders in any section where orders have previously been written

*Elder alert (lower dose/treatment recommended if patient greater than 65 years old)

■ Standard Orders ☐ Requires a check (☑) for activation

Drug Allergies/Intolerances

See Clinical Circumstances Sheet

ORDER TRANSCRIBED AND ACTIVATED ⇓ | TEST DONE

Patent's Height .....

Patient's Weight .....

MEDICATION and INTRAVENOUS ORDERS

DATE _____ TIME _____

PATIENT'S DRY WEIGHT: _____

Empiric Antibiotic Protocol:

■ vancomycin - weight based dosing:

- ☐ **40 kg - 69.9 kg** vancomycin 1 g IV over last 60 min of hemodialysis x 1 dose then 500 mg IV over last 30 min of hemodialysis x 1 dose
- ☐ **70 kg - 100.9 kg** vancomycin 1.25 g IV over last 90 min of hemodialysis x 1 dose then 750 mg IV over last 60 min of hemodialysis x 1 dose
- ☐ **101 kg - 130 kg** vancomycin 1.5 g IV over last 90 min of hemodialysis x 1 dose then 1 g IV over last 60 min of hemodialysis x 1 dose
- ☐ **If weight less than 40 kg or greater than 130 kg:** dose should be at the nephrologist's discretion: vancomycin _____ **mg** IV x 1 dose then _____ **mg** IV during next hemodialysis x 1 dose

If patient is allergic to vancomycin:

- ☐ ceFAZolin 2 g IV push post-hemodialysis x 2 doses

■ tobramycin - weight based dosing:

- ☐ **40 kg - 80.9 kg** tobramycin 1.5 mg/kg = _____ **mg** IV x 1 dose then 1 mg/ kg = _____ **mg** IV push post-hemodialysis x 1 dose
- ☐ **81 kg - 100.9 kg** tobramycin 120 mg IV x 1 dose then 80 mg IV push post-hemodialysis x 1 dose
- ☐ **101 kg - 120.9 kg** tobramycin 130 mg IV x 1 dose then 90 mg IV push post-hemodialysis x 1 dose
- ☐ **121 kg - 140 kg** tobramycin 140 mg IV x 1 dose then 100 mg IV push post-hemodialysis x 1 dose

If weight less than 40 kg or greater than 140 kg dose should be at Nephrologists discretion:

- ☐ tobramycin _____ mg IV x 1 dose then _____ mg IV x 1 dose.

If patient is allergic/otovestibular toxicity to gentamicin or tobramycin or if patient has possible acute kidney injury:

- ☐ ceftAZidime 2 g IV push post-hemodialysis x 2 doses

All dosing recommendations are for patients on conventional hemodialysis (3 x/week). Patients on alternative modalities of hemodialysis (e.g., short daily dialysis or dialysis greater than 3 x/week) may require individualized antibiotic dosing.

GENERAL ORDERS

Suspected systemic central venous catheter related bacteremia:

Prior to administering antibiotic:

- ■ Blood cultures (follow MRP Policy 30.20.16)
- ■ CBC
- ■ swab exit site for C & S (if exudate present)
- ■ Notify Nephrologist

■ If nursing staff suspects central venous catheter related bacteremia for reasons other than those noted above notify Nephrologist.

■ Physician reassessment of cultures and sensitivities to occur within 72 hours.

PHYSICIAN'S SIGNATURE _____

PRINTED NAME _____

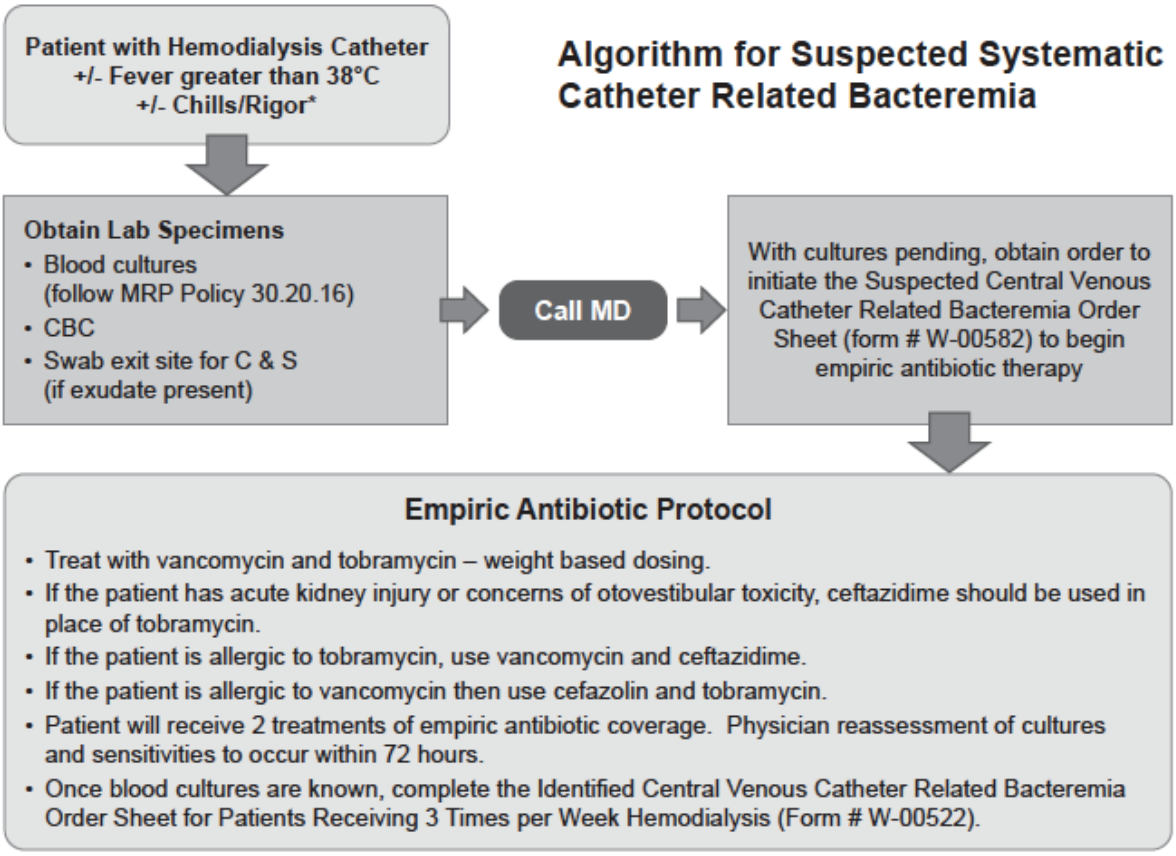
GENERIC EQUIVALENT AUTHORIZED

☐ Order faxed by _____ Date/Time _____

☐ Order transcribed by _____ Date/Time _____

☐ Order verified by _____ Date/Time _____

SAP # 295070 (W-00582) March 2020


Patient with Hemodialysis Catheter
+/- Fever greater than 38°C
+/- Chills/Rigor*
Algorithm for Suspected Systematic Catheter Related Bacteremia
Obtain Lab Specimens
• Blood cultures (follow MRP Policy 30.20.16)
• CBC
• Swab exit site for C & S (if exudate present)
Call MD
With cultures pending, obtain order to initiate the Suspected Central Venous Catheter Related Bacteremia Order Sheet (form # W-00582) to begin empiric antibiotic therapy
Empiric Antibiotic Protocol
• Treat with vancomycin and tobramycin – weight based dosing.
• If the patient has acute kidney injury or concerns of otovestibular toxicity, ceftazidime should be used in place of tobramycin.
• If the patient is allergic to tobramycin, use vancomycin and ceftazidime.
• If the patient is allergic to vancomycin then use cefazolin and tobramycin.
• Patient will receive 2 treatments of empiric antibiotic coverage. Physician reassessment of cultures and sensitivities to occur within 72 hours.
• Once blood cultures are known, complete the Identified Central Venous Catheter Related Bacteremia Order Sheet for Patients Receiving 3 Times per Week Hemodialysis (Form # W-00522).
* If nursing staff suspects central venous catheter bacteremia for any other reason, notify the nephrologist.

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IDENTIFIED CENTRAL VENOUS CATHETER RELATED BACTEREMIA ORDER SHEET FOR PATIENTS RECEIVING 3 TIMES PER WEEK HEMODIALYSIS

- Do not add or change orders in any section where orders have previously been written

*Elder alert (lower dose/treatment recommended if patient greater than 65 years old)

■ Standard Orders ☐ Requires a check (☑) for activation

Drug Allergies/Intolerances

See Clinical Circumstances Sheet

ORDER TRANSCRIBED AND ACTIVATED ⇓ | TEST DONE

Patent's Height .....

Patient's Weight .....

MEDICATION and INTRAVENOUS ORDERS

DATE _____ TIME _____

PATIENT'S DRY WEIGHT: _____

☐ ***Continue* vancomycin** – weight based dosing

- ☐ **40 kg - 69.9 kg** vancomycin 500 mg IV 3 times per week over last 30 min of hemodialysis **x** _____ **doses**
- ☐ **70 kg - 100.9 kg** vancomycin 750 mg IV 3 times per week over last 60 min of hemodialysis **x** _____ **doses**
- ☐ **101 kg - 130 kg** vancomycin 1 g IV 3 times per week over last 60 min of hemodialysis **x** _____ **doses**

If weight less than 40 kg or greater than 130 kg:

- ☐ vancomycin _____ **mg** IV 3 times per week during hemodialysis **x** _____ **doses** (dose at nephrologist's discretion)

☐ ceFAZolin 2 g IV push post-hemodialysis 3 times per week **x** _____ **doses**

☐ cefTAZidime 2 g IV push post-hemodialysis 3 times per week **x** _____ **doses**

☐ Other: _____

IV 3 times per week in hemodialysis **x** _____ **doses**

Antibiotic locks should be used in conjunction with systemic antibiotics if attempting catheter salvage or awaiting catheter removal/ conversion

Start Antibiotic Lock below:

☐ gentamicin 2.5 mg/mL in 4% sodium citrate
☐ vancomycin 2.5 mg/mL in 4% sodium citrate
☐ ceFAZolin 5 mg/mL and heparin 2500 units/mL
x _____ treatments. **Fill volume of arterial & venous ports post-dialysis**

1) fax order to inpatient Pharmacy Department for preparation
*2) **indicate patient's dialysis schedule:***

All dosing recommendations are for patients on conventional hemodialysis (3 x/week). Patients on alternative modalities of hemodialysis (e.g., short daily dialysis or dialysis greater than 3 x/week) may require individualized antibiotic dosing.

GENERAL ORDERS

■ Blood Cultures 1 week after completion of antibiotic (follow MRP Policy 30.20.16)

■ ***Drug Levels:***
vancomycin or tobramycin drug levels will be ordered on a patient specific basis.

For patients on a vancomycin or gentamicin antibiotic lock:
drug levels should be drawn from a peripheral blood sample.

If a peripheral blood sample cannot be obtained:
Initiate dialysis. Wait 5 minutes then swab arterial blood line injection port with alcohol and draw blood sample for tobramycin or vancomycin drug level.

■ Fax this completed form to the Vascular Access Nurse

☐ ECHO (TTE)

Blood Cultures drawn on _____ (date) are positive for:

☐ Coagulase Negative Staphylococcus
- ☐ Methicillin-sensitive
- ☐ Methicillin-resistant

☐ Staphylococcus aureus
- ☐ Methicillin-sensitive (MSSA)
- ☐ Methicillin-resistant (MRSA)
- ☐ Vancomycin intermediately resistant (VISA)

☐ Streptococcus Viridans

☐ Enterococcus _____
- ☐ Vancomycin-resistant

☐ Gram negative, **specify organism**
_____

☐ Other, **specify organsim**
_____

☐ Infectious diseases (Dr. _____) was consulted regarding treatment plan on _____ (date)

PHYSICIAN'S SIGNATURE _____

PRINTED NAME _____

GENERIC EQUIVALENT AUTHORIZED

☐ Order faxed by _____ Date/Time _____

☐ Order transcribed by _____ Date/Time _____

☐ Order verified by _____ Date/Time _____

SAP # 295053 (W-00522) March 2020

Appendix I

Antibiotic Protocol for Tunneled Catheter Associated Bacteremia (CAB)*
(Please refer to Appendix II antibiotic dosing guidelines)

Specific to Organism

Coagulase Negative Staphyloccoccus

(IV Antibiotic x 2 weeks if catheter exchanged; x 3 weeks if catheter salvage with antibiotic lock):
- If methicillin-sensitive: ceFAZolin x 2–3 weeks
- If methicillin-resistant: vancomycin x 2–3 weeks total

Enterococcus

(IV Antibiotics x 2 weeks if catheter exchanged; x 3 weeks if catheter salvage with antibiotic lock):
- Antibiotic therapy guided by cultures and sensitivities
- If recurrent infection then an ECHO (TTE) should be ordered to rule out endocarditis

Gram Negative

(IV Antibiotics x 2 weeks if catheter exchanged; x 3 weeks if catheter salvage with antibiotic lock):
- Antibiotic therapy guided by cultures and sensitivities

Staphyloccoccus aureus

(IV Antibiotic x 4 - 6 weeks as per nephrologist. All staph aureus infections should be covered with antibiotic lock even if line is to be removed:
- Catheter should be removed/exchanged unless limited access
- An ECHO (TTE) should be ordered on all patients with Staphylococcus aureus positive blood cultures to rule out endocarditis
- If MSSA positive: ceFAZolin x 4–6 weeks
- If MRSA positive (or allergy to penicillins/cephalosporins): vancomycin x 4–6 weeks

Streptococcus viridans

(IV Antibiotic x 2 weeks if catheter exchanged; x 3 weeks if catheter salvage with antibiotic locks):
- ceFAZolin x 2–3 weeks
- If allergy to penicillins/cephalosporins: vancomycin x 2–3 weeks
- If recurrent infection then an ECHO (TTE) should be ordered to rule out endocarditis

- All patients with positive blood cultures should be placed on an antibiotic lock. Choice of antibiotic locking solution should complement the chosen antibiotic therapy. The antibiotic lock should be continued until antibiotic therapy is complete or until line removal. If catheter is exchanged the decision to continue the antibiotic lock is at the discretion of the nephrologist.

Repeat blood cultures 1 week after completion of antibiotic therapy

***Decisions regarding catheter removal/catheter exchange are at the discretion of the nephrologist and vascular nurse. It is suggested that catheter should be removed/exchanged unless limited vascular access for Staphylococcus aureus, Pseudomonas, or fungal, there is evidence of metastatic complications (e.g., endocarditis, osteomyelitis or septic thrombosis), or patient has a recurrent catheter infection.**

Appendix II

Antibiotic Dosing Guidelines

- **ceFAZolin** 2 g IV qHD
- **tobramycin** Dosing Protocol (this protocol is intended to be limited to a 2-dose regimen providing four days of empiric therapy. Additional aminoglycoside therapy should be limited to cases without alternatives or where the benefits outweigh the current and cumulative risks of toxicity).

Body Weight	Loading Dose (after dialysis session)	2nd Dose (after next dialysis session)
Less than 40 kg	Dose is at the discretion of the Nephrologist	
40 - 80.9 kg	1.5 mg/kg	1 mg/kg
81 - 100.9 kg	120 mg	80 mg
101 - 120.9 kg	130 mg	90 mg
121 - 140 kg	140 mg	100 mg
Greater than 140 kg	Dose is at the discretion of the Nephrologist	

If weight less than 40 kg or greater than 140 kg dose should be at Nephrologist's discretion:
tobramycin _____ mg IV x 1 dose then _____ mg IV x 1 dose.

Target tobramycin predialysis level: 1.5 - 3 mg/L (~50% removed by high flux dialyzers so provides a trough level of 0.75 - 1.5 mg/L). The risk for otovestibular with tobramycin increases with duration of therapy (especially after 7 - 10 days of use). **Notify renal pharmacist if tobramycin is ordered for 4 or more doses so that patient can be monitored.**

- **vancomycin** – weight based dosing: (monitor predialysis level q2weeks Target predialysis levels: 10 - 20 mg/L) to avoid resistance; 15-20 mg/L for MRSA or deep seeded infection)
  - 40 kg - 69.9 kg vancomycin 1 g IV x 1 (loading dose) then 500 mg IV qHD
  - 70 kg - 100.9 kg vancomycin 1.25 g IV x 1 (loading dose) then 750 mg IV qHD
  - 101 kg - 130 kg vancomycin 1.5 g IV x 1 (loading dose) then 1 g IV qHD
  - If weight less than 40 kg or greater than 130 kg, the dose is at the discretion of the nephrologist
- **cefTAZidime** 2 g IV qHD

**All dosing recommendations are for patient on conventional hemodialysis (3 x/week). Patients on alternative modalities of hemodialysis (e.g., short daily dialysis or dialysis greater than 3 x/week) may require individualized antibiotic dosing.*

APPENDIX 1B. Antimicrobial Usage at St. Boniface Hospital Hemodialysis Unit

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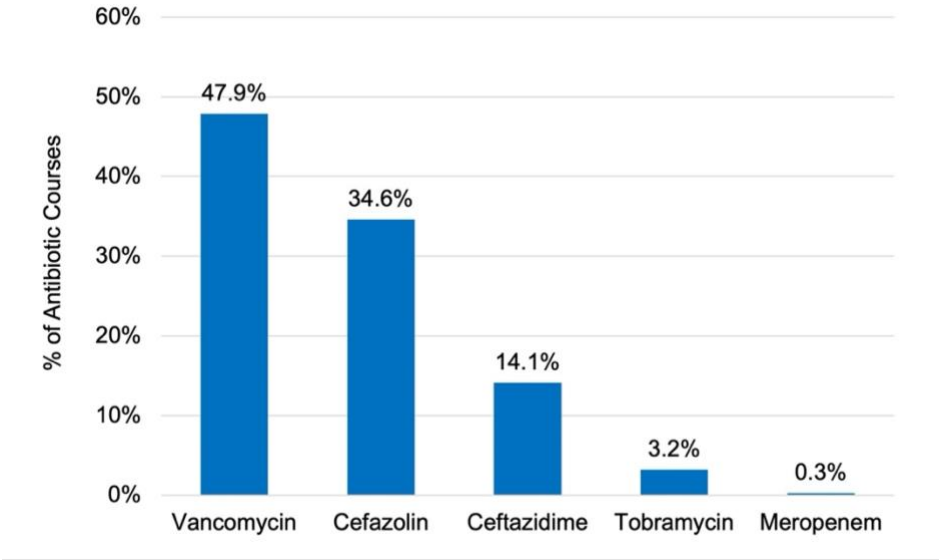
Figure A1B. St. Boniface Hospital hemodialysis unit outpatient intravenous antimicrobial courses in 2017 that were at least 3 days or longer.



APPENDIX 1C. Studies of Cefazolin Concentrations and Pharmacokinetics in Adults Receiving Intermittent Hemodialysis

Table A1C. Studies of cefazolin concentrations and pharmacokinetics in adults receiving intermittent hemodialysis.[a]

Author Year	Dialysis Details	Cefazolin Dosing[b]	Subjects	Analysis	Total Conc (mg/L)	PK Parameters
McCloskey 1973[168]	Low-flux IHD Biweekly, ~6 h, UF145 dialyzer	0.5 g during HD x 1 dose	*n* = 7; uninfected	PK analysis using manual methods	72 h post-dose: 9.9 ± 5.1	$t½_{on\text{-}HD}$ = 6.5 h
Brogard 1977[169]	Low-flux IHD Biweekly, ~6 h, UF145 dialyzer	0.5 g IM post-HD x 1 dose	*n* = 10; uninfected	Conc evaluation & PK analysis using manual methods (1-compartment model)	24 h post-dose: 34.2 ± 3.2	$t½_{off\text{-}HD}$ = 25.7 h $t½_{on\text{-}HD}$ = 3.3 h
Marx 1998[170]	High-flux IHD Thrice weekly, ~4 h, F60 or F80 dialyzer	20 mg/kg[c] post-HD x 1 week	*n* = 5; 4 female, infected, 58 ± 20 y, 78 ± 21 kg, 19 ± 5 mg/kg dose	Conc evaluation	44–68 h post-dose: 41.6 ± 23.9	NA
Fogel 1998[167]	High-flux IHD Thrice weekly, duration NA, F80 dialyzer	1–2 g post-HD x multiple doses	*n* = 15; all anuric, infected	Conc evaluation & PK analysis using manual methods	1 h post-dose: (79–452) 24–72 h post-dose: (8.9–176)	$t½_{off\text{-}HD}$ = 26.4 ± 5.5 h $t½_{on\text{-}HD}$ = 3.2 ± 1.2 h Vd = 9.0 ± 3.9 L (0.13 ± 0.05 L/kg)
Kuypers 1999[171]	High-flux IHD Thrice weekly, ~4 h, dialyzer type NA	2 g post-HD x 1 week	*n* = 15; 14 male, 8 anuric, uninfected, 41–77 y, 53–104 kg, 19.2–37.7 mg/kg dose	Conc evaluation	44 h post-dose: 97 ± 27 (52–145) 68 h post-dose: 61 ± 22 (26–99)	NA

Table A1C. (Continued) Studies of cefazolin concentrations and pharmacokinetics in adults receiving intermittent hemodialysis.[a]

Author Year	Dialysis Details	Cefazolin Dosing[b]	Subjects	Analysis	Total Conc (mg/L)	PK Parameters
Sowinski 2001[146]	High-flux IHD Thrice weekly, ~4 h, CT190 or CT110 dialyzer	15 mg/kg[d] post-HD x 1 dose	*n* = 10; all male, 8 anuric/2 with urine output ~50 mL/day, uninfected, 48 ± 18 y, 83.3 ± 17.2 kg (pre-HD), 14.5 ± 0.7 mg/kg dose	PK analysis & conc simulations using Adapt 2 (2-compartment model)	Simulated levels 44 h post-dose: 59.8 ± 19.4 68 h post-dose: 36.2 ± 17.0	$CL_{off\text{-}HD}$ = 0.17 ± 0.04 L/h $CL_{on\text{-}HD}$ = 1.9 ± 0.4 L/h $t½_{off\text{-}HD}$ = 34.7 ± 5.9 h $t½_{on\text{-}HD}$ = 3.4 ± 1.0 h Vd = 8.8 ± 1.6 L (0.11 ± 0.01 L/kg) PB = 63% ± 12%
Ahern 2003[172]	Low- & high-flux IHD Thrice weekly, duration NA, CT190, CA110, F80B, or F8 dialyzer	20 mg/kg[d] post-HD x 1–2 weeks	*Group 1: n* = 25; 15 female, infected, 67 ± 17 y, 71.3 ± 17.4 kg, 21.1 ± 4.1 mg/kg dose *Group 2: n* = 9; 5 female, infected, 72 ± 10 y, 72.3 ± 21.0 kg, 19.9 ± 1.0 mg/kg dose	Conc evaluation	72 h post-dose *Group 1:* 56.6 ± 37.1 (9.7–139.0) *Group 2:* 42.9 ± 25.8 (9.2–98.0)	NA
Maynor 2008[245]	High-flux IHD Thrice weekly, duration NA, F180 dialyzer	1 g 30 min pre-HD x 1 dose	*n* = 5; 4 male, non-infected, 49 ± 9 y, 75 ± 15 kg	Dialytic CL analysis	NA	$CL_{on\text{-}HD}$ = 3.2 ± 1.0 L/h
Law 2014[173]	High-flux NOCHD Five to seven times weekly, ~8 h, Xenium 170 dialyzer	2 g post-HD x 2 doses	*n* = 15; 6 female, non-infected, 46 ± 7 y, 71 [63–81] kg, dialysis vintage: 4 [2–14] y	PK analysis using manual methods (1-compartment model)	16 h post-dose: 159.8 [125.3–198.5]	$CL_{off\text{-}HD}$ = 0.13 [0.07–0.18] L/h $CL_{on\text{-}HD}$ = 1.7 [1.4–2.2] L/h $t½_{off\text{-}HD}$ = 36.9 [21.3–60.6] h $t½_{on\text{-}HD}$ = 3.4 [2.9–4.4] h Vd = 7.6 [6.8–11.3] L, 0.13 [0.08–0.16] L/kg

Table A1C. (Continued) Studies of cefazolin concentrations and pharmacokinetics in adults receiving intermittent hemodialysis.[a]

Author Year	Dialysis Details	Cefazolin Dosing[b]	Subjects	Analysis	Total Conc (mg/L)	PK Parameters
Palmer 2019[174]	High-flux SDHD Six times weekly, ~2 h, F80A dialyzer	1 g post-HD x 2 doses	*n* = 10; 4 female, 6 anuric, non-infected, 69 [61–74] y, 75 [63–86] kg, dialysis vintage: 4.1 [1.1–7.6] y	PK analysis using manual methods (1-compartment model)	22 h post-dose: 96 [73 - 116]	$CL_{off\text{-}HD}$ = 0.16 [0.11–0.21] L/h $CL_{on\text{-}HD}$ = 2.0 [1.7–2.5] L/h $t½_{off\text{-}HD}$ = 28.1 [23.5–59.3] h $t½_{on\text{-}HD}$ = 2.3 [1.7–2.7] h Vd = 7.0 [6.5–7.8] L, 0.09 [0.08–0.12] L/kg
Duke 2024[192]	High-flux IHD Thrice weekly, ~4 h, FX80, FX100, or FX120 dialyzer	2 g post-HD x multiple doses	*n* = 16; 14 female, infected, 51.0 [38.8–62.3] y, 69.5 [58.5–76.3] kg, dialysis vintage 59 [24.3–120] months, albumin 38.5 [35.5–40] g/L	PK analysis using Pmetrics (2- compartment model)	44 h post-dose: 98.7 [76.6–114.3] 68 h post-dose: 53.0 [38.2–67.2]	PK based on total conc NA PB = 75.5% ± 14.3%

Reported as mean ± standard deviation, median [interquartile range], or (range).

$CL_{off\text{-}HD}$ clearance off dialysis, *$CL_{on\text{-}HD}$* clearance on dialysis, *conc* concentration, *h* hours, *IHD* intermittent hemodialysis, *IM* intramuscularly, *NA* information not available, *NOCHD* nocturnal hemodialysis, *PB* protein binding, *PK* pharmacokinetic, *SDHD* short daily hemodialysis, *$t½_{off\text{-}HD}$* half-life off dialysis, *$t½_{on\text{-}HD}$* half-life on dialysis, *Vd* volume of distribution.

[a] Studies of the critically ill or those with acute kidney injury were excluded.

[b] Intravenous administration unless otherwise specified.

[c] Based on actual body weight, rounded to the nearest 500 mg (doses between 1–2 g).

[d] Based on actual body weight, rounded to the nearest 100 mg (max 2 g).

APPENDIX 1D. Studies of Ceftazidime Concentrations and Pharmacokinetics in Adults Receiving Intermittent Hemodialysis

Table A1D. Studies of ceftazidime concentrations and pharmacokinetics in adults receiving intermittent hemodialysis.[a]

Author Year	Dialysis Details	Cefazolin Dosing[b]	Subjects	Analysis	Total Conc (mg/L)	PK Parameters
Hoffler 1984[227]	Low-flux IHD Frequency, duration, & dialyzer type NA	2 g post-HD x 1 dose	*n* = 6; 1 female, infected, 65.0 ± 4.7 kg	Conc evaluation	0.5 h post-dose: 148.2 ± 19.4 24 h post-dose: 56.5 ± 8.5	NA
Leroy 1984[229]	Low-flux IHD Frequency NA, ~6–8 h, Travenol coil dialyzer	15 mg/kg during HD x 1 dose	*n* = 4; non-infected, anuric	PK analysis using manual methods (2-compartment model)	NA	$t½_{off\text{-}HD}$ = 25.3 ± 4.1 h $t½_{on\text{-}HD}$ = 2.8 ± 0.2 h Vd = 0.24 ± 0.03 L/kg
Nikolaidis 1985[159]	Low-flux IHD Thrice weekly, ~4 h, Cordis Dow C-Dak 3.5 dialyzer	1 g 1 h pre-HD x 1 dose	*n* = 9; 3 female, non-infected, anuric, 49.1 ± 5.3 y, 59.9 ± 4.0 kg	PK analysis using manual methods (2-compartment model)	1 h post-dose: 64.3	$t½_{off\text{-}HD}$ = 33.9 ± 1.5 h $t½_{on\text{-}HD}$ = 3.3 ± 0.4 h
Ohkawa 1985[230]	Low-flux IHD Frequency & duration NA, NC-8, EX-23, or AM-10 dialyzers	0.5 g post-HD x 1 dose	*n* = 6; non-infected	Conc evaluation & PK analysis using NONLIN (2- compartment model)	0.25 h post-dose: 57.9 ± 11.7 6 h post-dose: 33.1 ± 6.4	$t½_{off\text{-}HD}$ = 15.1 ± 5.6 h
Goh 2016[231]	Low-flux IHD Thrice weekly, ~4 h, Polyflux L	1–2 g post-HD x 2 doses	*Group 1 (1 g dose): n* = 6; 2 female, non-infected, anuric (<200 mL urine/day), 61 [56–65] y, BMI 25 [22–28] kg/m^2, dialysis vintage 38 [19–61] *Group 2 (2 g dose): n* = 8; 3 female, non-infected, anuric (<200 mL urine/day), 59 [53–64] y, BMI 22 [21–24] kg/m^2, dialysis vintage 36 [25–53]	Conc evaluation & PK analysis using manual methods (1-compartment model)	*Group 1 (1 g dose):* 2 h post-dose: 78 [60–98] 44 h post-dose: 37 [23–37] 68 h post-dose: 13 [12–20] *Group 2 (2 g dose):* 2 h post-dose: 158 [128–196] 44 h post-dose: 49 [39–71] 68 h post-dose: 26 [21–41]	*Group 1 (1 g dose):* $t½_{off\text{-}HD}$ = 38 h *Group 2 (2 g dose):* $t½_{off\text{-}HD}$ = 33 h

Table A1D. (Continued) Studies of ceftazidime concentrations and pharmacokinetics in adults receiving intermittent hemodialysis.[a]

Author Year	Dialysis Details	Cefazolin Dosing[b]	Subjects	Analysis	Total Conc (mg/L)	PK Parameters
Maxwell-Scott[232] 2019	High-flux IHD Thrice weekly, duration & dialyzer type NA	2–3 g post-HD x multiple doses	*n* = 1; female, infected, anuric, ~45 y, 95 kg, dialysis vintage 11 y	Conc evaluation	Post 2 g dose: 105 45 h post 2 g dose: 25 70 h post 2 g dose: 7 70 h post 3 g dose: 15	NA

Reported as mean ± standard deviation or median [interquartile range].

BMI body mass index, *conc* concentration, *h* hours, *IHD* intermittent hemodialysis, *NA* information not available, *PK* pharmacokinetic, $t½_{off\text{-}HD}$ half-life off dialysis, $t½_{on\text{-}HD}$ half-life on dialysis,

Vd volume of distribution.

[a] Studies of the critically ill and those with acute kidney injury were excluded.

[b] Intravenous administration unless otherwise specified.

APPENDIX 1E. Cefazolin Dosing Recommendations in the Outpatient Hemodialysis Setting

Table A1E. Intravenous cefazolin dosing recommendations for adult patients receiving thrice weekly intermittent high-flux hemodialysis listed in commonly used clinical dosing references.

Dosing Reference	Cefazolin Regimen
CPhA Monograph[202]	15–20 mg/kg thrice weekly post-HD
Health Canada Monograph[35]	NA
IDSA Guidelines[92]	20 mg/kg thrice weekly post-HD[a]
Lexi-Drug Monograph[246]	0.5–1 g once daily, post-HD on HD days[170] **OR** 2 g thrice weekly post-HD[122,171] **OR** 20 mg/kg (max 2 g) thrice weekly post-HD[146,172] **OR** 2 or 3 g thrice weekly post-HD prior to two- or three-day interdialytic periods, respectively[247]
Micromedex[248]	2–3 g thrice weekly post-HD[171,249] **OR** 20 mg/kg thrice weekly post-HD[a,92]
The Renal Dosing Handbook[250]	NA

CPhA Canadian Pharmacists Association, *HD* hemodialysis, *IDSA* Infectious Diseases Society of America, *NA* information not available.

[a] Based on actual body weight, rounded to the nearest 0.5 g.

APPENDIX 1F. Ceftazidime Dosing Recommendations in the Outpatient Hemodialysis Setting

Table A1F. Intravenous ceftazidime dosing recommendations for adult patients receiving thrice weekly intermittent high-flux hemodialysis listed in commonly used clinical dosing references.

Dosing Reference	Ceftazidime Regimen
CPhA Monograph	NA
Health Canada Monograph[166]	1 g loading dose then 0.5–1 g thrice weekly post-HD
IDSA Guidelines[92]	1 g thrice weekly post-HD
Lexi-Drug Monograph[251]	NA[a]
Micromedex[252]	1 g loading dose then 1 g thrice weekly post-HD
The Renal Dosing Handbook[250]	0.5–2 g thrice weekly post-HD

CPhA Canadian Pharmacists Association, *HD* hemodialysis, *IDSA* Infectious Diseases Society of America, *NA* information not available.

[a] Dosing only available for low-flux HD: 0.5–1 g daily, post-HD on HD days (1 g recommended for empiric therapy or critical illness due to increased probability of pharmacodynamic target attainment)[243] **OR** 1 g thrice weekly post-HD (2 g recommended prior to three-day interdialytic periods or concerns for resistance)[159,229]

APPENDIX 3A. University of Manitoba Health Research Ethics Board Approval (HS20491)

P126-770 Bannatyne Avenue
Winnipeg, Manitoba
Canada, R3E 0W3
Telephone : 204-789-3255
Fax: 204-789-3414

UNIVERSITY OF MANITOBA | Research Ethics - Bannatyne
Office of the Vice-President (Research and International)

HEALTH RESEARCH ETHICS BOARD (HREB)
CERTIFICATE OF FINAL APPROVAL FOR NEW STUDIES
Delegated Review

PRINCIPAL INVESTIGATOR:	INSTITUTION/DEPARTMENT:	ETHICS #:
Dr. Sheryl Zelenitsky	U of M/Pharmacy	HS20491 (H2017:046)
APPROVAL DATE: February 21, 2017	**EXPIRY DATE:** February 21, 2018	
STUDENT PRINCIPAL INVESTIGATOR SUPERVISOR (If applicable):		

PROTOCOL NUMBER:	PROJECT OR PROTOCOL TITLE:
N/A	"Infection-Prevention Bundle" for Hemodialysis Catheter Insertion
SPONSORING AGENCIES AND/OR COORDINATING GROUPS: NA	

Submission Date of Investigator Documents:	HREB Receipt Date of Documents:
January 20 and February 13, 2017	January 24 and February 13, 2017

THE FOLLOWING ARE APPROVED FOR USE:

Document Name	Version(if applicable)	Date
Protocol: Protocol Clarification Letter received February 13, 2017 Revised REB Submission Form dated February 10, 2017		Jan 20, 2017
Consent and Assent Form(s):		
Other: Data Collection Sheet		Jan 20, 2017

CERTIFICATION
The above named research study/project has been reviewed in a ***delegated manner*** by the University of Manitoba (UM) Health Research Board (HREB) and was found to be acceptable on ethical grounds for research involving human participants. The study/project and documents listed above was granted final approval by the Chair or Acting Chair, UM HREB.

HREB ATTESTATION
The University of Manitoba (UM) Research Board (HREB) is organized and operates according to Health Canada/ICH Good Clinical Practices, Tri-Council Policy Statement 2, and the applicable laws and regulations of Manitoba. In respect to clinical trials, the HREB complies with the membership requirements for Research Ethics Boards defined in Division 5 of the Food and Drug Regulations of Canada and carries out its functions in a manner consistent with Good Clinical Practices.

QUALITY ASSURANCE
The University of Manitoba Research Quality Management Office may request to review research documentation from this research study/project to demonstrate compliance with this approved protocol and the University of Manitoba Policy on the Ethics of Research Involving Humans.

CONDITIONS OF APPROVAL:

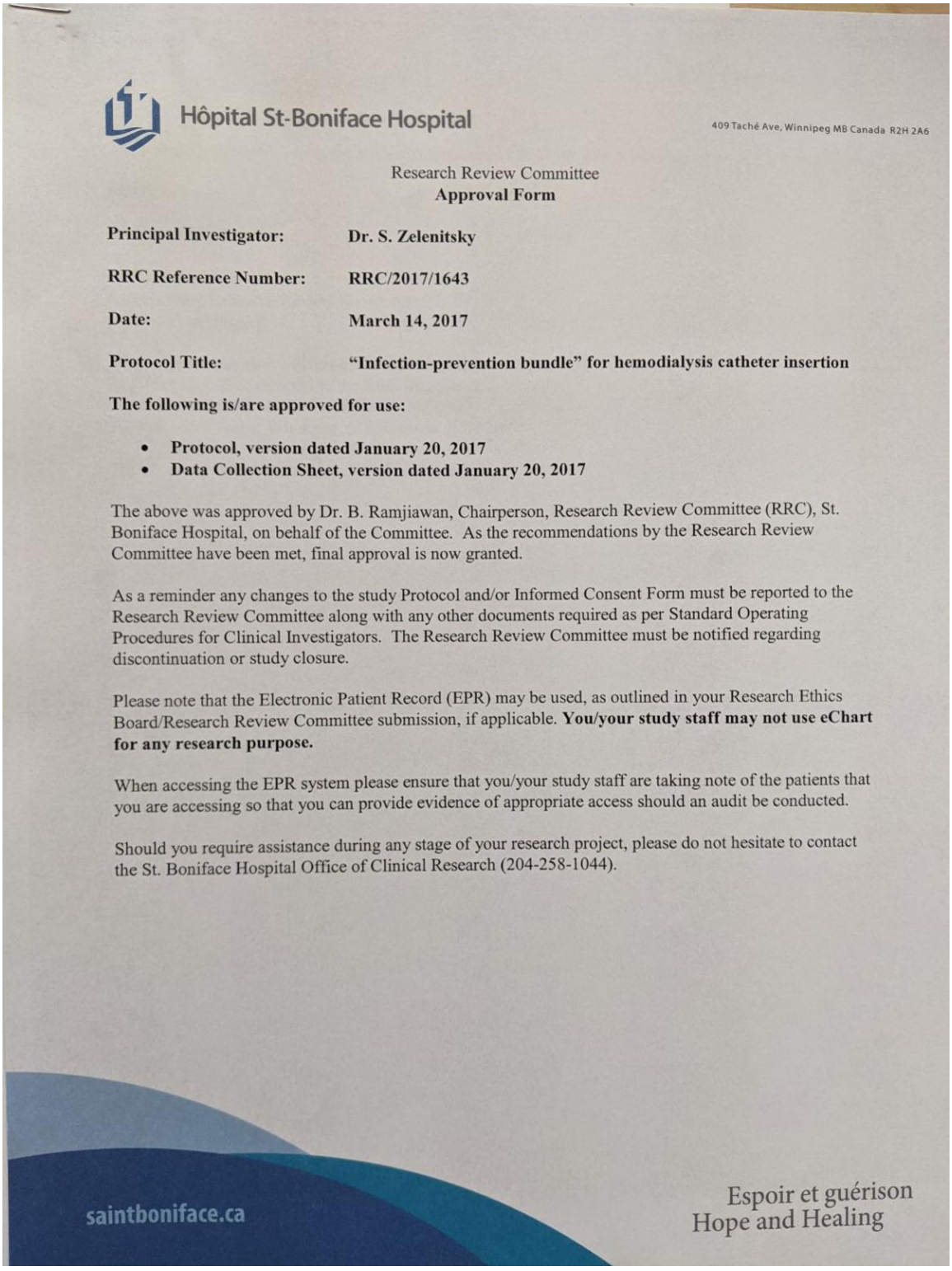
1. The study is acceptable on scientific and ethical grounds for the ethics of human use only. ***For logistics of performing the study, approval must be sought from the relevant institution(s).***
2. This research study/project is to be conducted by the local principal investigator listed on this certificate of approval.
3. The principal investigator has the responsibility for any other administrative or regulatory approvals that may pertain to the research study/project, and for ensuring that the authorized research is carried out according to governing law.
4. **This approval is valid until the expiry date noted on this certificate of approval. A Bannatyne Campus Annual Study Status Report** must be submitted to the HREB within 15-30 days of this expiry date.
5. Any changes of the protocol (including recruitment procedures, etc.), informed consent form(s) or documents must be reported to the HREB for consideration in advance of implementation of such changes on the **Bannatyne Campus Research Amendment Form.**
6. Adverse events and unanticipated problems must be reported to the HREB as per Bannatyne Campus Research Boards Standard Operating procedures.
7. The UM HREB must be notified regarding discontinuation or study/project closure on the **Bannatyne Campus Final Study Status Report**.

Sincerely,

[redacted]

Chair, Health Research Ethics Board
Bannatyne Campus

APPENDIX 3B. St. Boniface Hospital Research Review Committee Approval (2017/1643)



Hôpital St-Boniface Hospital

409 Taché Ave, Winnipeg MB Canada R2H 2A6

Research Review Committee
Approval Form

Principal Investigator:	**Dr. S. Zelenitsky**
RRC Reference Number:	**RRC/2017/1643**
Date:	**March 14, 2017**
Protocol Title:	**"Infection-prevention bundle" for hemodialysis catheter insertion**

The following is/are approved for use:

- **Protocol, version dated January 20, 2017**
- **Data Collection Sheet, version dated January 20, 2017**

The above was approved by Dr. B. Ramjiawan, Chairperson, Research Review Committee (RRC), St. Boniface Hospital, on behalf of the Committee. As the recommendations by the Research Review Committee have been met, final approval is now granted.

As a reminder any changes to the study Protocol and/or Informed Consent Form must be reported to the Research Review Committee along with any other documents required as per Standard Operating Procedures for Clinical Investigators. The Research Review Committee must be notified regarding discontinuation or study closure.

Please note that the Electronic Patient Record (EPR) may be used, as outlined in your Research Ethics Board/Research Review Committee submission, if applicable. **You/your study staff may not use eChart for any research purpose.**

When accessing the EPR system please ensure that you/your study staff are taking note of the patients that you are accessing so that you can provide evidence of appropriate access should an audit be conducted.

Should you require assistance during any stage of your research project, please do not hesitate to contact the St. Boniface Hospital Office of Clinical Research (204-258-1044).

saintboniface.ca

Espoir et guérison
Hope and Healing

APPENDIX 3C. Protocol *(Version: 04/17/2017)*

"Infection-Prevention Bundle" for Hemodialysis Catheter Insertion

Dr. Sheryl Zelenitsky, Professor, College of Pharmacy, University of Manitoba (PI)
Dr. Chris Sathianathan, St. Boniface Hospital Renal Program
Dr. Mauro Verrelli, St. Boniface Hospital Renal Program
Research assistants (to be determined): 4th year Pharmacy Research Elective student; 3rd year Pharmacy Research Summer student, College of Pharmacy, University of Manitoba

Background

Infections are associated with considerable morbidity and mortality in patients undergoing hemodialysis. In particular, indwelling catheters present a significant risk for exit site, bloodstream and other serious infectious complications.[1] The catheter type, insertion procedures and exit site care are important factors in the risk of developing subsequent catheter-related infection.[2] In 2012, the St. Boniface Renal Program implemented an infection-prevention bundle for hemodialysis catheter insertion that included: (1) patient and nurse masking during exit site care, (2) chlorhexidine/alcohol (instead of iodine) application to catheter hubs and to exit site with dressing changes and (3) systemic antimicrobial prophylaxis with cefazolin 1 g given after the first two dialysis sessions post-catheter insertion. There is limited study of the clinical impact of such preventative measures particularly as a bundle for hemodialysis catheter insertion.[3,4]

Goal

To compare the rate of exit site and catheter-related bloodstream infections in patients who had hemodialysis catheters present during the 18 months pre- (Jan 2011 - June 2012) and 18 months post-implementation (Oct 2012 - Mar 2014) of an "infection-prevention bundle" in the St. Boniface Renal Program. The addition of these data will increase the power of study to analyze infection rates in regard to the intervention.

Hypothesis

Implementation of the bundle for hemodialysis catheter insertion resulted in a significant reduction in subsequent catheter-related infections.

Methods

This study will be conducted at the St. Boniface Hospital, Winnipeg, Canada and will rely on data collected from the St. Boniface Renal Program database. The study will include data on patients undergoing hemodialysis including 18 months pre- (Jan 2011 - June 2012) and 18 months post-implementation (Oct 2012 - Mar 2014) of the infection-prevention bundle. Since the practice changes occurred from July to Sept 2012, these data will be collected and categorized as pre- or post-bundle where appropriate. The time frame was selected based on data related to catheter-associated infections that is available in quality control records of the St. Boniface Renal Program. It is predicted that patient data will be collected on 300 patients undergoing hemodialysis between Jan 2011 and Mar 2014.

No patient identifiers will be collected. Only the following patient data (source), will be recorded during the study:

- Hemodialysis patients: age, sex, months of hemodialysis, etiology of renal disease. (St. Boniface Renal Program/Manitoba Renal Program database)
- Catheter insertions: catheter type, new or replacement catheter, insertion date, elements of prevention bundle or other infection-prevention measures for catheter insertion. (St. Boniface Renal Program/Manitoba Renal Program database)
- Catheter-related infections: exit site, bloodstream, or other catheter-related infection such as tunnel infection. Date and pathogen will be recorded if available. (Quality control records of the St. Boniface Renal Program)

Descriptive statistics for all variables pre- and post-bundle will be calculated. Data with Gaussian distributions will be presented as mean and standard deviation, whereas other data will be reported as median and interquartile range (IQR). Univariate statistics will be used to compare characteristics pre- and post-bundle using the two-tailed Student's t-test, Mann–Whitney U-test, Pearson's $\chi 2$ test or Fisher's exact test, as appropriate. Monthly infection rates will be calculated, and further analyzed pre- and post-bundle using a Poisson regression model. All statistical analyses will be conducted using SYSTAT 12 (SYSTAT Software Inc., San Jose, CA).

References:

1. Li PK et al. Infectious complications in dialysis--epidemiology and outcomes. Nat Rev Nephrol. 2011;8(2):77-88.
2. Bohlke M et al. Hemodialysis catheter-related infection: prophylaxis, diagnosis, and treatment. J Vasc Access 2015;16(5):347-55.
3. Kosa S et al. The economics of hemodialysis catheter-related infection prophylaxis. Seminars in Dial 2013:26(4):482-93.
4. Huddam B. The efficacy of prophylactic antibiotic administration prior to insertion of tunneled catheter in hemodialysis patients. Renal Fail 2012:34(8):998-1001.

APPENDIX 3D. Data Collection Sheet *(Version: 04/17/2017)*

Data Collection Sheet

Infection Prevention Bundle for hemodialysis catheter insertion

YEAR	ID#	AGE	SEX
Dialysis Access			CORR database

ETIOLOGY
Main dx:
Comorbidities:
CORR database

CATHETER TYPE	INSERTION DATE (M/Y)
eKHR database	

DURATION OF HEMODIALYSIS		
Start Date (M/Y)	End Date (M/Y)	Reason
CORR database		

INFECTION TYPE	DATE ACQUIRED (M/Y)	PATHOGEN(S)
QA data collection		

APPENDIX 4A. University of Manitoba Health Research Ethics Board Approval (HS22503)

UNIVERSITY OF MANITOBA | Research Ethics and Compliance

Research Ethics - Bannatyne
P126-770 Bannatyne Avenue
Winnipeg, MB
Canada R3E 0W3
Phone +204-789-3255
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HEALTH RESEARCH ETHICS BOARD (HREB)
CERTIFICATE OF FINAL APPROVAL FOR NEW STUDIES
Delegated Review

PRINCIPAL INVESTIGATOR:	INSTITUTION/DEPARTMENT:	ETHICS #:
Dr. Sheryl Zelenitsky	U of M/Pharmacy	HS22503 (H2019:031)
APPROVAL DATE: February 7, 2019	**EXPIRY DATE:** February 7, 2020	
STUDENT PRINCIPAL INVESTIGATOR SUPERVISOR (if applicable): NA		

PROTOCOL NUMBER:	PROJECT OR PROTOCOL TITLE;
NA	Is Cefazolin and Ceftazidime Dosing Optimal in Hemodialysis Patients?
SPONSORING AGENCIES AND/OR COORDINATING GROUPS: University of Manitoba	

Submission Date of Investigator Documents:	HREB Receipt Date of Documents:
January 4 and January 31, 2019	January 4 and January 31, 2019

THE FOLLOWING ARE APPROVED FOR USE:

Document Name	Version(if applicable)	Date
Protocol: Protocol including Clarifications as per Letter dated January 31, 2019	V. 1	01/04/2019
Consent and Assent Form(s): Research Participant Information and Consent Form	V. 1	01/04/2019
Other: Data Collection Sheet	V. 1	01/04/2019
Master List	V. 1	01/04/2019

CERTIFICATION
The above named research study/project has been reviewed in a ***delegated manner*** by the University of Manitoba (UM) Health Research Board (HREB) and was found to be acceptable on ethical grounds for research involving human participants. The study/project and documents listed above was granted final approval by the Chair or Acting Chair, UM HREB.

HREB ATTESTATION
The University of Manitoba (UM) Research Board (HREB) is organized and operates according to Health Canada/ICH Good Clinical Practices, Tri-Council Policy Statement 2, and the applicable laws and regulations of Manitoba. In respect to clinical trials, the HREB complies with the membership requirements for Research Ethics Boards defined in Division 5 of the Food and Drug Regulations of Canada and carries out its functions in a manner consistent with Good Clinical Practices.

QUALITY ASSURANCE

The University of Manitoba Research Quality Management Office may request to review research documentation from this research study/project to demonstrate compliance with this approved protocol and the University of Manitoba Policy on the Ethics of Research Involving Humans.

CONDITIONS OF APPROVAL:

1. The study is acceptable on scientific and ethical grounds for the ethics of human use only. ***For logistics of performing the study, approval must be sought from the relevant institution(s).***
2. This research study/project is to be conducted by the local principal investigator listed on this certificate of approval.
3. The principal investigator has the responsibility for any other administrative or regulatory approvals that may pertain to the research study/project, and for ensuring that the authorized research is carried out according to governing law.
4. **This approval is valid until the expiry date noted on this certificate of approval. A Bannatyne Campus Annual Study Status Report** must be submitted to the HREB within 15-30 days of this expiry date.
5. Any changes of the protocol (including recruitment procedures, etc.), informed consent form(s) or documents must be reported to the HREB for consideration in advance of implementation of such changes on the **Bannatyne Campus Research Amendment Form.**
6. Adverse events and unanticipated problems must be reported to the HREB as per Bannatyne Campus Research Boards Standard Operating procedures.
7. The UM HREB must be notified regarding discontinuation or study/project closure on the **Bannatyne Campus Final Study Status Report.**

Sincerely,

[redacted]

Chair, Health Research Ethics Board
Bannatyne Campus

APPENDIX 4B. St. Boniface Hospital Research Review Committee Approval (2019/1840)

Hôpital St-Boniface Hospital

409 Taché Ave, Winnipeg MB Canada R2H 2A6

Research Review Committee
Approval Form

Principal Investigator:	**Dr. S. Zelenitsky**
RRC Reference Number:	**RRC/2019/1840**
Date:	**June 12, 2019**
Protocol Title:	**Is Cefazolin and Ceftazidime Dosing Optimal in Hemodialysis Patients?**

The following is/are approved for use:

- **Protocol, version 2 dated May 3, 2019**
- **Research Participant Information and Consent Form, version 2 dated May 3, 2019**
- **Data Collection Sheet, version 2 dated May 3, 2019**

The above was approved by Dr. B. Ramjiawan, Chairperson, Research Review Committee (RRC), St. Boniface Hospital, on behalf of the Committee. As the recommendations by the Research Review Committee have been met, final approval is now granted.

As a reminder any changes to the study Protocol and/or Informed Consent Form must be reported to the Research Review Committee along with any other documents required as per Standard Operating Procedures for Clinical Investigators. The Research Review Committee must be notified regarding discontinuation or study closure.

Please note that the Electronic Patient Record (EPR) may be used, as outlined in your Research Ethics Board/Research Review Committee submission, if applicable. **You/your study staff may not use eChart for any research purpose.**

When accessing the EPR system please ensure that you/your study staff are taking note of the patients that you are accessing so that you can provide evidence of appropriate access should an audit be conducted.

Should you require assistance during any stage of your research project, please do not hesitate to contact the St. Boniface Hospital Office of Clinical Research (204-258-1044).

The Research Review Committee wishes you much success with your study.

Sincerely yours,

[redacted]

Chairperson, Research Review Committee
St. Boniface Hospital

Please quote the above reference number on all correspondence.
Inquiries should be directed to the RRC Secretary
Telephone: (204) 258-1044 **Fax**: (204) 237-9860
N1008 – 409 Taché, Winnipeg, MB, Canada R2H 2A6

BR/ar

PROTOCOL

Is Cefazolin, Ceftazidime and Ciprofloxacin Dosing Optimal in Hemodialysis Patients?

Summary and Significance

Despite being one of the highest-risk populations and most likely to benefit from evidence-based antibiotic therapy, there is very limited information on whether current approaches to antibiotic dosing in dialysis patients are safe and effective. By measuring plasma concentrations of cefazolin, ceftazidime and ciprofloxacin and constructing population-pharmacokinetic models we will be able to translate our findings to patient care by developing the first evidence-based dosing recommendations for one of the most commonly used antibiotics in patients on intermittent high-flux hemodialysis (iHFHD).

Background

Drug dosing is established based on pharmacokinetics (PK) which describe drug concentrations in patients over time and pharmacodynamics (PD) which describe relationships between drug concentrations and response or clinical outcomes.[1,2] Particularly for the treatment of infectious disease, PK-PD research has clearly displayed the importance of antibiotic dosing and clinical outcomes.[1–4] Evidence-based, PK-PD directed, antibiotic dosing helps maximize antibacterial activity and clinical cure, while minimizing the risks of toxicity and antibiotic resistance.[5,6] Due to the emergence of increasingly resistant infections in complex patients and the relatively slow production of new antibiotics, optimizing current therapies has become a topic of high priority in healthcare.[7] Whereas PK-PD has been used to optimize antibiotic dosing for other high-risk populations such the immunocompromised and critically ill, such progress has not been made for the treatment of infectious diseases in dialysis patients.[8–10]

Dialysis patients are particularly susceptible to infectious diseases due to their complicated health status, invasive catheters that are required to administer dialysis, and frequent visits to healthcare settings. Consequently, they often receive antibiotics further increasing the risk of developing resistant infections.[11,12] They are also more likely to fail antibiotic therapy leading to infection-associated morbidity and mortality.[11,12] Therapy is complicated by compromised immune function in patients with kidney disease and altered antibiotic pharmacokinetics (i.e., altered antibiotic concentrations due to dialysis and decreased kidney function).

The cephalosporins, cefazolin and ceftazidime, and the fluroquinolone, ciprofloxacin are among the most commonly prescribed antibiotics. Cefazolin and ceftazidime accounted for 49% of intravenous antibiotic courses in our hemodialysis unit at St. Boniface Hospital in 2017. The fluroquinolones provide one of the broadest oral antibiotics, ciprofloxacin accounted for 52% of all oral courses prescribed in our unit during this time. Despite significant use the dosing of cefazolin and ceftazidime in patients on iHFHD is based on limited data that have not been validated in this patient population. Current dosing guidelines for cefazolin are supported by a single PK study of 10 non-infected patients, while no relevant and current data exists for ceftazidime or ciprofloxacin.[13] Due to the scarcity of evidence dialysis programs often adopt one-dose-fits-all antibiotic therapy regardless of patient factors that influence PK such as age, gender, body weight, and dialysis specifics.[14,15]

Our study aims to optimize the dosing of intravenous (iv) cefazolin, ceftazidime and oral (po) ciprofloxacin to improve the treatment of infectious disease in patients on iHFHD. By measuring plasma concentrations

and constructing population-PK and PK-PD models we will develop dosing strategies that will be utilized in clinical practice to improve outcomes and decrease toxicity and the emergence of antibiotic resistance.

Objectives

1. To measure total and free plasma concentrations of iv cefazolin, ceftazidime, and po ciprofloxacin in adult patients on iHFHD receiving antimicrobial therapy for proven or suspected infection.
2. To characterize the pharmacokinetics of iv cefazolin, ceftazidime and po ciprofloxacin in iHFHD patients using population-PK modeling.
3. To translate findings to practice by evaluating current antibiotic dosing and developing evidence-based recommendations which optimize dosing of iv cefazolin, ceftazidime and po ciprofloxacin in patients on iHFHD.

Hypothesis

Current antimicrobial dosing is suboptimal in intermittent high-flux hemodialysis patients, a high-risk population, therefore increasing the risk of poor outcomes including treatment failure, toxicity, and antibiotic resistance.

Methods

This prospective, non-interventional PK study will be conducted at the St. Boniface Hospital outpatient hemodialysis unit. We will study iv cefazolin, ceftazidime and po ciprofloxacin in adult patients undergoing chronic iHFHD and receiving antimicrobial therapy for suspected or proven infection. Our study will follow best practices and will be approved by St. Boniface Hospital Research Review Committee and the University of Manitoba Biomedical Research Ethics Board. Individuals will only participate once in the study of a particular antibiotic. With separate informed consent, patients may participate in the study of a second antibiotic.

***Study subjects*:** Adult patients on iHFHD receiving iv cefazolin, ceftazidime, or po ciprofloxacin for the treatment of proven or suspected infection will be included in our study. Patients will only be enrolled if their treatment course allows for the collection of three 6 mL blood samples before their treatment is completed (as per sample collection regimen described below). Patients will be excluded if they have chronic liver disease (Child Pugh Class C or higher) and if they are unable to provide informed consent. Patients with acute kidney injury or recovering renal function will be excluded as our intention is to study patients receiving chronic hemodialysis for end-stage renal disease. In addition, we will exclude patients who have received study drug as part of a different treatment course a week preceding the start of the treatment course observed in our study, as our model will assume the study drug blood levels start from zero at the beginning of treatment.
Note: Our study will not affect patients' therapy, only those who have already been prescribed cefazolin, ceftazidime or ciprofloxacin will be considered for participation in our study.

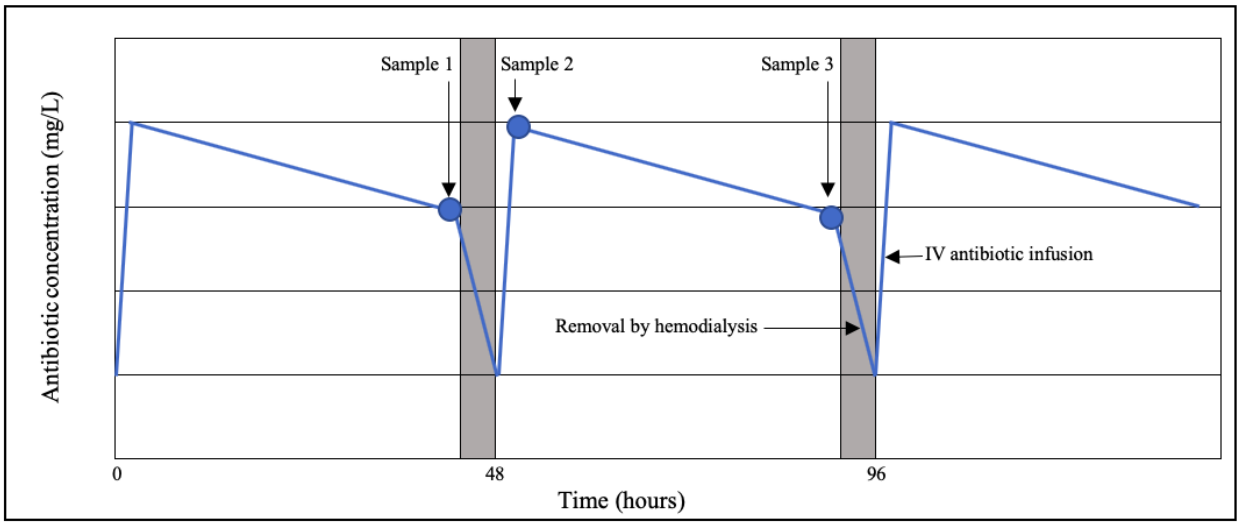
***Sample size*:** A sample size of 20 patients was selected and will represent the largest pharmacokinetic study to date of cefazolin, ceftazidime, and ciprofloxacin in infected patients on intermittent high-flux hemodialysis. The scope of this study is consistent with a Master's project and available resources. Sample size was calculated using $\frac{Z^2\delta^2}{E^2}$ where Z equals 1.96 (95% confidence interval of a standard normal distribution), δ is the standard deviation of the outcome variable, and E equals 15% (desired margin of error for the outcome variable).[16] Our predicted outcome variable was limited on one population-PK study of cefazolin where clearance was 30.9 ± 6.5 mL/min during dialysis and 2.9 ± 0.7 mL/min between dialysis.[13]

A sample size of 20 was calculated for each antibiotic where population-PK models will be developed from 60 samples (20 patients, 3 samples per patients).

***Patient enrollment and data collection*:** We will enroll 60 patients in our study (20 patients for each drug) and collect 3 blood samples. Patients will be required to have received at least one dose before sampling.

The sampling scheme for iv cefazolin and ceftazidime (see **Figure 1** below) will include a pre-dialysis sample within 60 minutes before starting dialysis. After dialysis, the next antibiotic dose will be administered, and a post-dose sample will be collected at least 15 minutes afterwards. Another pre-dialysis sample will be collected within 60 minutes before starting the next dialysis session. Missed samples will be collected at the subsequent dialysis session and will not compromise our analyses.

Figure 1: Sample Collection Scheme



Since po ciprofloxacin will not be administered in the hemodialysis unit and the time of dose administration will not be recorded in the patients' chart, patients will document the timing of each dose on a **"Cipro Dosing Card"**. Again, the sampling scheme will also include a pre-dialysis sample within 60 minutes before starting dialysis. After dialysis, a post-dose sample will be collected approximately 15 minutes afterwards. Another pre-dialysis sample will be collected within 60 minutes before starting the next dialysis session. Missed samples will be handled as described above.

Patient factors (e.g., age, sex, body weight, residual renal function, dialysis start date, comorbidities, cause of end stage renal disease, concurrent medications that may interact with study drugs), details of each dialysis session (dialyzer type, mean blood and dialysate flow rates, duration, and dose or K_t/V_{urea}), and antibiotic dose and administration time will be recorded. All dialysis sessions and antibiotic doses will be recorded from the start of therapy until 3 blood samples have been collected.

***Sample preparation and analysis (objective 1)*:** Whole blood will be centrifuged (1300 g, 4°C, 10 min) to isolate plasma which will be used to measure the total plasma concentration of cefazolin, ceftazidime, and ciprofloxacin. To describe protein binding in this patient population we will measure free concentrations of cefazolin and ceftazidime in the first 2 samples from the first 10 patients for each drug. Here samples will be centrifuged (2000 g, 45 min) in Centrifree® tubes to isolate ultrafiltrate. Samples will be stored at -80°C.

Cefazolin, ceftazidime, and ciprofloxacin concentrations will be measured using a Shimadzu LCMS 8040 triple quadrupole liquid chromatograph mass spectrometer (Shimadzu, Kyoto, Japan), as previously

described.[17–20] A stable isotope of cefazolin, $^{13}C_2{}^{15}N$ will be used as the internal standard (IS). Analytical-grade cefazolin, ceftazidime and ciprofloxacin will be obtained to create standard curves. Stock solutions will be prepared in water and aliquots stored at -80°C. Standard curve and quality control samples will be prepared in blank human serum.

For measuring total concentrations, prior to analysis IS will be added to samples to achieve a concentration of 2.5 mg/L. Proteins will be precipitated using analytical-grade acetonitrile and centrifuge (15,000 g, 10 min).[16] The supernatant will be dried and reconstituted in 100 µL of mobile phase, then re-centrifuged (15,000 g, 15 min) in a Centrifugal Filter. For measuring free concentrations, IS will be added to the ultrafiltrate samples and reconstituted in mobile phase prior to analysis.

The HPLC-MS/MS will be operated in positive mode using dual electrospray and atmospheric pressure chemical ionization (DUIS) and with multiple reaction monitoring events optimized using LabSolutions LCMS software (Shimadzu, Kyoto, Japan). Previously described MS transitions will be used.[17,19] All samples will be analyzed in duplicate.

Albumin concentrations will be measured in patient samples using an automated EasyRA® chemistry analyzer. As with free levels, we will measure the albumin concentration in the first 2 samples from the first 10 patients for each drug, in duplicate. As albumin is the main protein to which drugs bind, measuring concentrations will help describe differences in protein binding for cefazolin, ceftazidime, and ciprofloxacin between individuals.

***Data analysis (objective 2)*:** Population-PK models will be constructed using 60 concentrations (from the first objective) and the Pmetrics™ software with Nonparametric Adaptive Grid algorithm and expectation maximization methods (University of Southern California, Los Angeles, CA), as shown in previous works.[21–23]

The PK profiles of iv cefazolin and ceftazidime will be analyzed using one-compartment models with zero-order administration and first-order elimination and a two-compartment model with post-administration distribution and post-dialysis rebound. PK parameters for the one-compartment model including V_d (volume of distribution), k_e (drug elimination) during dialysis, k_e between dialysis sessions, and drug CL (clearance) will be described.

PK parameters for the two-compartment model including distribution rate constants between the central and peripheral compartment, central V_d, peripheral V_d, and drug CL will be determined. Covariates which influence PK and significantly improve the model will be incorporated, such as body weight, sex, age, dialyzer type, mean blood and dialysate flow rates, duration, and dose (K_t/V_{urea}) of dialysis. The best PK model will be selected using established goodness-of-fit tests, and then independently validated.

The PK profile of po ciprofloxacin will be analyzed according to one- and two-compartment models with first-order oral absorption and first-order elimination. Since the sampling scheme will not describe the absorption characteristics, *a priori* estimates will be used for the absorption rate constant and time to maximum concentration. PK parameters including V_d/F and drug CL/F will be determined, where F is the fraction of oral dose that is absorbed. Covariates will be investigated as described above.

Protein binding of cefazolin, ceftazidime, and ciprofloxacin will be calculated from the total (plasma) and free (ultrafiltrate) concentrations where:

$$\textbf{\textit{Protein binding}}\ (\%) = \frac{\textbf{\textit{free concentration in ultrafiltrate}}}{\textbf{\textit{total concentration in plasma}}}\ \textbf{\textit{x}}\ \mathbf{100}\%$$

Knowledge Translation (objective 3): Monte Carlo simulations will be used to predict the probability of attaining concentration targets with particular antibiotic regimens in our target population (iHFHD patients) and project the likelihood of achieving clinical outcomes such as cure and survival.[24] These simulations incorporate factors involving the patient (age, body weight, organ function, severity of illness), infection (infection site, pathogen minimum inhibitory concentration or MIC), and antibiotic PK-PD. Our simulation will generate a cohort of 5,000 subjects on iHFHD that are consistent with patients included in our PK study (e.g., age, sex, body weight, dialysis details). Antibiotic regimens will be simulated using our PK data (from **Objective 2**) to generate 5,000 individual concentration profiles. This simulated population will be used to evaluate current dosing guidelines for iv cefazolin, ceftazidime and po ciprofloxacin and investigate various other regimens.

The established PD target for cephalosporins is time that free concentrations exceed a pathogens MIC and for fluroquinolones AUC_{24}/MIC (the area under the concentration-time curve over 24 hours over a pathogens MIC). The Clinical Laboratory Standards Institute MIC breakpoint (highest MIC considered susceptible) for cefazolin and ceftazidime is 8 mg/L and 1 mg/L for ciprofloxacin. For cefazolin and ceftazidime regimens the probability of maintaining free concentrations above both 8 mg/L and 32 mg/L will be evaluated. A target above 32 mg/L is based on supporting evidence in immunocompromised patients for higher levels, here 4x the MIC breakpoint.[1,2] For dosing regimens of po ciprofloxacin the probability of achieving a free AUC_{24h}/MIC of at least 90, for an MIC breakpoint of 1 mg/L will be evaluated.[25,26]

MIC distributions of clinically relevant pathogens, *S. aureus* for cefazolin, and *E. coli* and *P. aeruginosa* for ceftazidime and ciprofloxacin will be obtained from surveillance data from the Canadian Antimicrobial Resistance Alliance and the European Committee on Antimicrobial Susceptibility Testing. The probability of target attainment at each MIC will be calculated as the proportion of 5,000 simulated subjects. Cumulative target attainment will integrate probabilities across the MIC distribution by multiplying each probability by the fraction of the pathogen displaying that each MIC and summing the values.

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RESEARCH PARTICIPANT INFORMATION AND CONSENT FORM

STUDY TITLE: Is Cefazolin, Ceftazidime, and Ciprofloxacin Dosing Optimal in Hemodialysis Patients?

Principal Investigator

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Additional Study Team Members

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St. Boniface Hospital/College of Pharmacy, University of Manitoba

Dr. Chris Sathianathan, MD, Nephrologist/Professor
St. Boniface Hospital/Manitoba Renal Program/University of Manitoba

Funding

This research is supported by an Allied Health Research Grant from the Kidney Foundation of Canada.

You are being asked to participate in a research study. Please take your time to review this consent form and discuss any questions you may have with the study staff. You may take your time to make your decision about participating in this study and you may discuss it with your friends, family, or your doctor before you make your decision. This consent form may contain words that you do not understand. Please ask the study staff to explain any words or information that you do not clearly understand.

Purpose of Study

Cefazolin, ceftazidime, and ciprofloxacin are common antibiotics used for treating infections. As medications are removed by dialysis and not as effectively removed by the kidneys in patients with end stage renal disease, they require special considerations to ensure their therapy remains similar to patients who are not receiving dialysis. For many medications there is little information describing how to change dosing for dialysis patients. The purpose of our study is to determine if the current dose of cefazolin, ceftazidime, and ciprofloxacin are optimal in hemodialysis patients. Our objectives include taking blood samples from patients receiving cefazolin, ceftazidime, or ciprofloxacin for the treatment of infection. We will measure blood levels of cefazolin, ceftazidime, or ciprofloxacin and determine how it is handled differently in the body. Our final objective is to share our research to benefit as many hemodialysis patients as possible by recommending changes to optimize the dosing of cefazolin, ceftazidime, and ciprofloxacin.

A total of 60 patients will participate in this study.

Study Procedures

The standard antibiotic treatment with cefazolin, ceftazidime, and ciprofloxacin in hemodialysis patients will not change for the study.

During this study and while you receive treatment with cefazolin, ceftazidime, or ciprofloxacin three 6 mL blood samples will be collected on days you are receiving dialysis in the St. Boniface Hospital Hemodialysis Unit. Each blood sample is equal to just over a teaspoon. The amount of cefazolin, ceftazidime, or ciprofloxacin in the blood samples will be measured. Certain health and medical information will be collected from charts/records.

If you take part in this study, you will have the following procedures:

During your treatment and after at least one dose of cefazolin, ceftazidime, or ciprofloxacin, three 6 mL blood samples will be collected including:

Sample A – taken just prior to one of your dialysis sessions
Sample B – taken 15 minutes after a dialysis session
(and after antibiotic is administered for cefazolin and ceftazidime only)
Sample C – taken just prior to another dialysis session

Blood samples will be drawn from an existing dialysis access site i.e., a catheter or tube in your blood vessel which is already in place to administer dialysis. Since blood samples will be collected from an existing access site, there are no additional needles or pokes required for this study. Six

milliliters (6 mL) of blood will be collected for each sample. Please note for one sample you will be asked to stay 15 minutes after your antibiotic is administered following dialysis. The blood samples will be labelled with a study number (without your name or any other identifiers) and stored in a secured freezer at the College of Pharmacy, University of Manitoba. Later, samples will be thawed and processed, and cefazolin, ceftazidime, or ciprofloxacin levels will be measured in a laboratory at the College of Pharmacy, University of Manitoba.

Certain personal health information will be collected from your medical/chart records. This information will be used to help explain the cefazolin, ceftazidime, or ciprofloxacin levels in your blood as well as the differences in levels observed in different individuals. We hope to use this information to identify the best cefazolin and ceftazidime dose to treat infections in hemodialysis patients.

The personal health information that will be collected includes: 1) study number, age (without your birthdate), sex, weight and height, the cause of your kidney disease, the date you started dialysis, the amount of urine you produce every day, other medical conditions you have, and medications you may be taking that may interact with cefazolin, ceftazidime, or ciprofloxacin. 2) Information related to your dialysis sessions including the timing, dialyzer type, flow rates of your blood and dialysis solution, and your dialysis dose (i.e. the adequacy of your dialysis). 3) Cefazolin, ceftazidime, or ciprofloxacin treatment details including dose and timing. If you are being treated with oral ciprofloxacin you will receive a **"Cipro Dosing Card"** to record the date and time you take this medication at home. The information will be documented on paper forms using your study number and transferred to computer files which will be password protected.

You will be assigned a study number which will be used on all study samples, forms, and files. Your name, age, phone number, and other identifying information will not appear. One paper copy of a master list linking you to your study number will be kept in a secure locked cabinet in the principal researcher's office separate from other study related forms and files. The master list will be destroyed after the study is completed within 4 years' time.

Your participation in the study will end once all 3 blood samples are collected.

You can stop participating at any time. However, if you decide to stop participating in the study, we encourage you to talk to the study researchers as soon as possible using the contact information provided on page 1.

Risk and Discomforts

The expected risk to study participants is minimal. Blood samples will be drawn from an existing dialysis blood access site, i.e. a catheter/tube in your blood vessel which is already in place to administer your dialysis.

As listed above, certain personal health information will be collected for the study. All precautions will be taken to respect and keep your personal information confidential. However, despite these efforts absolute confidentiality cannot be guaranteed.

Benefits

There may or may not be direct benefit to you from participating in this study. We hope the information learned from this study will benefit all hemodialysis patients who receive treatment with cefazolin, ceftazidime, and ciprofloxacin in the future.

After we analyze the data collected in this study, we will post results in the outpatient Hemodialysis Unit at St. Boniface Hospital. Results will also be available online at clinicaltrials.gov.

Costs

All the procedures, which will be performed as part of this study, are provided at no cost to you.

Payment for Participation

You will receive no payment or reimbursement for taking part in this study.

Alternatives

You do not have to participate in this study to receive treatment for your condition. Our study will not influence the choice of the prescribed treatment by your nephrologist. We will only include you in our study once you have been prescribed cefazolin, ceftazidime, or ciprofloxacin for the treatment of your condition. Please talk to your nephrologist if you have questions regarding your treatment.

Confidentiality

Medical records that contain your identity will be treated as confidential in accordance with the Personal Health Information Act of Manitoba. All paper and electronic records will be kept in a secure location and only authorised study personnel will have access to these records. All study related documents will bear only your assigned study number. A separate master list linking your study number and name will be kept in a separate location in a locked cabinet. Certain information will be entered into the computer using your study number in order to analyze our data and describe how cefazolin, ceftazidime, and ciprofloxacin levels differ in hemodialysis patients. This data will include; timing and details of dialysis sessions, timing and dose of cefazolin, ceftazidime, or ciprofloxacin administrated, and personal factors that affect levels of the antibiotic such as age, sex, body weight, and height.

Despite efforts to keep your personal information confidential, absolute confidentiality cannot be guaranteed. Information gathered in this research study may be published or presented in public forums, however your name and other identifying information will not be used or revealed.

Your personal information may be disclosed if required by law. The University of Manitoba Health Research Ethics Board or St. Boniface General Hospital Research Review Board may review and/or copy records related to the study for quality assurance and data analysis purposes. If any of

your medical/research records need to be copied to any of the above, your name and all identifying information will be removed.

Voluntary Participation/Withdrawal from the Study

Your decision to take part in this study is voluntary. You may refuse to participate, or you may withdraw from the study at any time. Your decision not to participate or to withdraw from the study will not affect your care at this centre. If the study staff feel that it is in your best interest to withdraw you from the study, they will remove you without your consent.

If you happen to be a student of the University of Manitoba or a healthcare employee of the Winnipeg Regional Health Authority your performance evaluation will not be affected by your decision not to participate.

We will tell you about any new information that may affect your health, welfare, or willingness to stay in this study.

Medical Care for Injury Related to the Study

Injury or illness resulting from this study is unlikely. However, in the case of injury resulting from collection of blood samples in this study the necessary medical treatment will be available at no additional cost to you.

Questions

You are free to ask any questions that you may have about your treatment and your rights as a research participant. If any questions come up during or after the study or if you have a research-related injury, contact the study researchers:

Dr. Sheryl Zelenitsky at [redacted] or [redacted]

OR

Courtney Lawrence at [redacted] or [redacted]

For questions about your rights as a research participant, you may contact the University of Manitoba, Bannatyne Campus **Research Ethics Board Office at [redacted]**.

Do not sign this consent form unless you have had a chance to ask questions and have received satisfactory answers to all of your questions.

Statement of Consent

I have read this consent form. I have had the opportunity to discuss this research study with Ms. Lawrence, Dr. Zelenitsky or other study researchers. I have had my questions answered by them in language I understand. The risks and benefits have been explained to me. I believe that I have not been unduly influenced by any study team member to participate in the research study by any statements or implied statements. Any relationship (such as employer, supervisor or family member) I may have with the study team has not affected my decision to participate. I understand that I will be given a copy of this consent form after signing it. I understand that my participation in this study is voluntary and that I may choose to withdraw at any time. I freely agree to participate in this research study.

I understand that information regarding my personal identity will be kept confidential, but that confidentiality is not guaranteed. I authorize the inspection of any of my records that relate to this study by The University of Manitoba Research Ethics Board for quality assurance purposes.

By signing this consent form, I have not waived any of the legal rights that I have as a participant in a research study.

Participant name: _____

Participant signature: _____ Date: _____

Relationship (if any) to study team members: _____

I, the undersigned, have fully explained the relevant details of this research study to the participant named above and believe that the participant has understood and has knowingly given their consent.

Name: _____

Signature: _____ Date: _____

Role in the study: _____

COVID-19 Consent Appendix

This appendix contains important information about in-person research during the COVID-19 public health crisis. COVID-19 (also called SARS-CoV2) is an illness caused by the coronavirus. Coronaviruses are most commonly spread from an infected person through: a) respiratory droplets when you cough or sneeze; b) close personal contact, such as touching or shaking hands; or c) touching something with the virus on it, then touching your eyes, nose or mouth before washing your hands.

The University of Manitoba is committed to taking measures to protect the health and safety of their campuses and the wider community. Your safety is important to us. The university has suspended most research that cannot be conducted remotely or virtually. This project requires in-person visits. Therefore, it is important to understand that your participation in this study may increase your exposure to COVID-19.

Our project has been approved to proceed by the Research Ethics Board, our Faculty, the COVID Recovery Response Team, the COVID Recovery Steering Committee, and the University Provost. In order to gain approval, we created policies to ensure the safety of the research team and participants. These plans were reviewed and approved by the parties above. Please note that no changes have been made to our original research protocol discussed above, however, we have implemented various precautions for your safety. These precautions include:

- *Use of 3-ply reusable or disposable masks, goggles, and gloves by researchers. You are also required to wear a mask as instructed by the St. Boniface Hospital and Hemodialysis Unit.*
- *Hand hygiene performed by researchers before and after any contact with research participants. You will also be offered hand-sanitizer before and after any interactions with researchers.*
- *Limited contact with researchers. Informed consent will take approximately 5 minutes, will involve a socially distanced conversation with a single researcher, and will take place in the Hemodialysis Unit during one of your regularly scheduled hemodialysis sessions. This will be the only contact you will have with researchers as blood draws will be completed by hemodialysis nurses during your regularly scheduled hemodialysis sessions.*
- *You are required to sign a consent form and COVID-19 consent appendix prior to participating in this study. A sanitized clip board and pen will be offered to you if you wish to sign these forms the Hemodialysis Unit, or you may take the forms home to sign and return to researchers at your next hemodialysis session.*
- *Researchers are required to screen themselves for symptoms daily before they come into work. The Hemodialysis Unit staff will continue to be responsible for screening you for symptoms during your regularly scheduled hemodialysis sessions.*
- *At the discretion of the Hemodialysis Unit staff and/or researchers you may be temporarily or permanently withdrawn from the study if you have confirmed or suspected COVID-19 infection (i.e., if you have had a positive test result or are exhibiting any symptoms of COVID-19), if you have been a close contact with someone with COVID-19 (or are awaiting tests results), or if you have been told by a health official to self-isolate.*

COVID-19 is a serious health threat, and the situation is evolving rapidly. If you feel that you are from a group that is more vulnerable to COVID-19 effects (e.g., a senior over the age of 60 years old or immunocompromised), please feel free to discuss your participation with the research team before providing your consent. You are under no obligation to participate and can change your mind about participating in the research at any time without consequence.

The University of Manitoba is closely watching the situation in Manitoba and may restrict in-person research at any time. We will continue to keep you informed as to changes that may occur to this study.

There is a possibility that during your participation in the study you could come into contact with someone with COVID-19. We are required to collect and retain your personal contact information in order to follow up with you and/or conduct contact tracing if you may have been exposed to COVID-19. **We cannot guarantee anonymity as the personal contact information identifies you as a participant and we may be required to disclose this information in the event of a possible exposure.** Your contact information will be kept separately from data collected through the research study to allow for de-identification of the research data. You maintain your right to withdraw from the study at any time, including your research data. If you do withdraw from the study, we will still need to continue to maintain your contact information and will only give it to Manitoba Health and/or the Hemodialysis Unit at St. Boniface Hospital if required for contact tracing. Please note, these parties will not have access to your research data.

If you have questions regarding this study, measures we are taking to keep all parties safe, or have any concerns, please do not hesitate to ask. You can contact any of the above-named researchers or the Bannatyne Campus Research Ethics Board office at [redacted]

Your signature on this form indicates that you have understood to your satisfaction the information regarding participation and the COVID-19 risk and agree to participate. In no way does this waive your legal rights nor release the researchers, sponsors, or involved institutions from their legal and professional responsibilities. Your continued participation should be as informed as your initial consent, so you should feel free to ask for clarification or new information throughout your participation.

Participant name: _____

Contact information (phone # or email): _____

Participant signature: _____ **Date:** _____

APPENDIX 4E. Data Collection Sheet ***(Version 3: 07/12/2019)***

DATA COLLECTION SHEET

*To be used with **Master List** which will be locked in a separate cabinet from the **Data Collection Sheet**

Protocol: Is Cefazolin, Ceftazidime, and Ciprofloxacin Dosing Optimal in Hemodialysis Patients?

STUDY DRUG: Cefazolin OR Ceftazidime OR Ciprofloxacin

PARTICIPANT NUMBER: _____
(Participant number will start at 1 for cefazolin, 101 for ceftazidime, and 201 for ciprofloxacin)

DATE OF INCLUSION (mm/dd/yyyy): _____

Participants Dialysis Schedule		
Days	MWF / TTS	Other:
Time	Morning / Afternoon / Evenings	Other:

Eligibility Criteria:
INCLUSION CRITERIA (all must be YES)

1. Adult patient (>18 years)? **Yes** □ **No** □
2. Proven or suspected infection? **Yes** □ **No** □
3. Receiving cefazolin/ceftazidime/ciprofloxacin for treatment? **Yes** □ **No** □
4. Treatment course allows collection of three 6 mL blood samples before completion as per protocol? **Yes** □ **No** □
5. Able to provide informed consent? **Yes** □ **No** □

EXCLUSION CRITERIA (all must be NO)

1. Chronic liver disease: Child Pugh Class C or higher? **Yes** □ **No** □
2. Received study drug as part of a different treatment course in 1-week preceding start of new treatment course? **Yes** □ **No** □
3. Acute kidney injury or recovering kidney function? **Yes** □ **No** □

PARTICIPANT DEMOGRAPHICS

Age (years)	**Sex** (M/F)	**Target Weight** (kg)	**Height** (cm)

Dialysis Start Date: _____

Residual Renal Function: □ ≥ 1 cup urine per day □ < 1 cup urine per day □ No urine
Cause of End Stage Renal Disease: _____

Comorbidities:

□ Diabetes mellitus □ Medication Controlled □ Insulin Dependent □ End-Organ Damage

□ Peripheral Vascular Disease □ Amputation _____

□ Heart Disease □ Ischemic Heart Disease □ CHF □ HTN □ Previous MI

□ Cerebrovascular Disease □ Previous CVA or TIA

□ Hemiplegia

□ Dementia

□ COPD

□ Peptic Ulcer Disease

□ Connective Tissue Disease

□ Liver Disease □ Mild □ Moderate

□ Autoimmune Disease _____

□ Neutropenia (ANC <500/μL)

□ HIV □ AIDS

□ Malignancy □ Solid Tumor □ Lymphoma □ Leukemia □ Multiple Myeloma □ Metastatic

Other: _____

Concurrent Medications (only those with potential interactions with cefazolin/ceftazidime/ciprofloxacin):

_____
_____
_____
_____

Participant Number: _____

DIALYSIS DETAILS

Dialyzer Type: _____

Dialysis Session[A]	Date (mm/dd/yyyy)	Start Time End Time	Mean Flow Rate (mL/min)	Weight (kg)	Kt/V	Notes
1		__ __ : __ __ __ __ : __ __	Blood: _____ Dialysate: _____	Pre-dialysis: _____ Post-dialysis: _____		
2		__ __ : __ __ __ __ : __ __	Blood: _____ Dialysate: _____	Pre-dialysis: _____ Post-dialysis: _____		
3		__ __ : __ __ __ __ : __ __	Blood: _____ Dialysate: _____	Pre-dialysis: _____ Post-dialysis: _____		
4		__ __ : __ __ __ __ : __ __	Blood: _____ Dialysate: _____	Pre-dialysis: _____ Post-dialysis: _____		
5		__ __ : __ __ __ __ : __ __	Blood: _____ Dialysate: _____	Pre-dialysis: _____ Post-dialysis: _____		

[A]Record all dialysis sessions starting after the first post-dialysis dose of study drug until 3 blood samples have been collected from the participant.

ANTIBIOTIC DOSES

Dose #[A]	Prescribed dose (mg)	Date (mm/dd/yyyy)	Time of Dose[B]	Pre-level Drawn	Post-Level Drawn	Notes
1			__ __ : __ __	□	□	
2			__ __ : __ __	□	□	
3			__ __ : __ __	□	□	
4			__ __ : __ __	□	□	
5			__ __ : __ __	□	□	

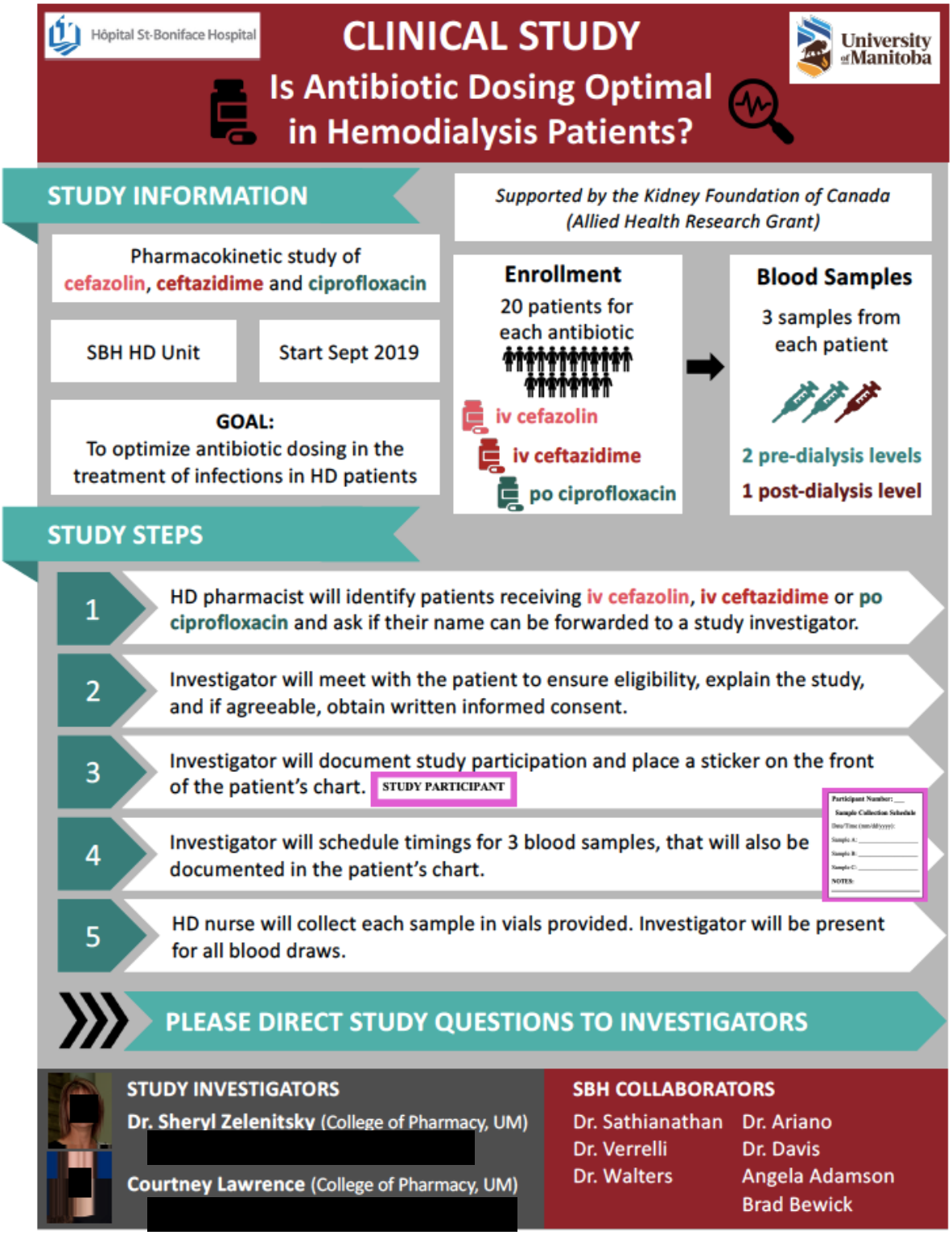
[A]Record all doses of study drug for the treatment course until 3 blood samples have been collected from the participant.
[B]For cefazolin and ceftazidime this data will be taken from the patients' chart. For ciprofloxacin, patients will record the timing of doses on a provided "Cipro Dosing Card".

SAMPLE COLLECTION

Sample Number	Sample Code[A]	Date of Collection (mm/dd/yyyy)	Time of Collection	Pre-Level	Post-Level	Notes
1	___A		__ __ : __	□	□	
2	___B		__ __ : __ __	□	□	
3	___C		__ __ : __ __	□	□	

[A]Based on participant and sample number, will be used to identify samples and recorded on vials.

APPENDIX 4F. Information Poster for Staff



HOW TO COLLECT SAMPLES

Pre-Dialysis Sample

Before dialysis, obtain blood sample as per standard collection procedures using the red BD Vacutainer and Luer-Lok device provided.

Fistula and graft: Insert dialysis needle to obtain sample.

Catheter: Remove lock and discard 5 mL of blood, then obtain sample.

Post-Dialysis Sample

For iv cefazolin and iv ceftazidime: Administer as per standard procedure (iv over 3-5 min). Obtain blood sample 15 min after dose. If administered directly via catheter or dialysis needle, flush with saline and discard 5 mL of blood, then obtain blood sample.

For po ciprofloxacin: Taken at home by patient. Obtain blood sample 15 min after dialysis.

Fistula and graft: Keep one dialysis needle in place to obtain sample.

Catheter: Obtain sample from catheter before placing lock.

MESSAGE FROM PRINCIPLE INVESTIGATOR

Thank you for your interest in our study on the pharmacokinetics of cefazolin, ceftazidime and ciprofloxacin in HD patients. I'm a pharmacy professor at the UM with a nil-salary appointment in pharmacy at the SBH. My research focuses on infectious diseases and optimizing antibiotic therapy in high-risk patient populations. I have conducted research with Dr.'s Verrelli and Sathianathan, and developed the current vancomycin and aminoglycoside dosing protocols for the MRP. The current study will also involve Courtney Lawrence, a graduate student and licensed pharmacist, and Christy Choi, an undergraduate pharmacy student with a degree in nursing. We will be on-site to manage the study, enroll patients, collect study data, and receive/process blood samples. We appreciate your involvement and contributions to this study. If you have any questions, please don't hesitate to contact me. *Best regards, Dr. Sheryl Zelenitsky* [redacted]

STUDY DETAILS

Background: Dialysis patients are particularly susceptible to infection-related complications, morbidity and mortality. They are more likely to receive antibiotics, experience treatment failure, and become colonized or infected with resistant pathogens. Pharmacokinetic (PK)/pharmacodynamic (PD) research is used to design antibiotic dosing regimens that maximize antibacterial activity, while minimizing the risks of toxicity and resistance. Despite significant advances for other high-risk populations, research to optimize antibiotic dosing for dialysis patients is limited. Data from 2017 show that cefazolin and ceftazidime accounted for half of IV antibiotics used in the SBH HD Unit, while ciprofloxacin accounted for 52% of all oral courses prescribed during that time. Despite significant use, the dosing of these agents during intermittent high-flux HD is based on limited data. Current dosing for cefazolin is supported by a single PK study of 10 non-infected patients, and there are no PK studies of ceftazidime or ciprofloxacin during high-flux HD. Clinical decisions on the dosing of these agents are further limited by the lack of therapeutic drug monitoring in the practice setting. As such, dialysis programs adopt "one-dose-fits-all" protocols (eg. ceftazidime 2 g post-dialysis) regardless of patient factors such as age, gender, weight, and dialysis variables.

Goal: To optimize the dosing of cefazolin, ceftazidime and ciprofloxacin to improve the treatment of serious, often life-threatening infections in HD patients.

Design: A non-interventional PK study of cefazolin, ceftazidime and ciprofloxacin in HD patients in the SBH HD Unit. Serum concentrations of cefazolin, ceftazidime and ciprofloxacin will be measured in 60 adult patients (20 each) who are receiving antibiotic therapy for suspected or proven infection. Three blood samples will be collected from each participant (2 pre-dialysis, 1 post-dialysis), processed in lab space at the Asper Clinical Research Institute, and analyzed using UHPLC-MS/MS at the College of Pharmacy. The PK of cefazolin, ceftazidime and ciprofloxacin will be characterized using population-PK modelling. Covariates that influence PK such as gender, age, body weight, dialyzer type, blood and dialysate flow rates, duration of dialysis, and Kt/V will be incorporated as appropriate. The PK findings will be translated to clinical practice using Monte Carlo simulations to evaluate conventional dosing and develop new optimized recommendations for cefazolin, ceftazidime and ciprofloxacin in HD patients. These data may also be extrapolated to inform dosing for modalities such as daily or nocturnal HD.

Significance: Despite being one of the highest-risk populations and most likely to benefit from evidence-based antibiotic therapy, there is little evidence that current approaches to antibiotic dosing in dialysis patients are optimal. By measuring plasma concentrations and constructing population-PK models, we will generate more PK information for cefazolin, ceftazidime and ciprofloxacin than available in all published literature to date. Most importantly, we will translate our findings to patient care by developing evidence-based dosing recommendations for these important antibiotics in HD patients.

Approvals: The study has been approved by the HREB at the UM and SBH RRC.