Pharmacokinetics of Polymyxin B in Adult Patients with Cystic Fibrosis

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Contents

1. Project Summary

This is a single-center, open-label, non-interventional study to characterize the pharmacokinetics and safety of fixed-dose polymyxin B (PMB) in adult patients with cystic fibrosis (CF).

2. Abbreviations

ADL – activities of daily living
AKI – acute kidney injury
CF – cystic fibrosis
FEV1 – forced expiratory volume in 1 second
FiO_2 – fraction of inspired oxygen
GCS – Glasgow Coma Scale
KDIGO – Kidney Disease: Improving Global Outcomes
LC-MS/MS – liquid chromatography-tandem mass spectrometry
MDR – multidrug-resistant
NCI:CTCAE – National Cancer Institute: Common Terminology Criteria for Adverse Events
PK – pharmacokinetics
PMB – polymyxin B
Scr – serum creatinine

3. Background Information

Cystic fibrosis is a genetic disease affecting multiple organ systems; however, pulmonary disease is the cause of the majority of morbidity and mortality.[1] Pulmonary CF is a chronic, progressive disease process punctuated by episodes of acute exacerbation that require treatment. *Pseudomonas aeruginosa* is the predominant pathogen isolated in patients with acute exacerbations of cystic fibrosis, and guidelines from the Cystic Fibrosis Foundation recommend combination treatment directed against this pathogen as initial therapy.[2] Such therapy traditionally consists of an antipseudomonal beta-lactam with either an antipseudomonal fluoroquinolone or an aminoglycoside.

The demographics of patients with cystic fibrosis have shifted, and this shift has important implications for antimicrobial therapy. Once considered primarily a childhood disease, improvements in care have substantially increased the proportion of CF patients surviving into adulthood. In 1986, 70.8% of patients with CF were under 18 years of age. Data from 2016 CF Foundation Patient Registry Annual report show that that the majority of patients currently living with CF are adults (52.7%) and that median survival is now well into middle age (47.7 years).[1] The prevalence of positive cultures for MDR *P. aeruginosa* is less than 10% in pediatric patients with CF, but increases steadily in to around 20% in adults age 30-40 years.[1] This increase in drug-resistance over time likely reflects recurrent exposure to antipseudomonal antibiotics resulting in a severely limited armamentarium of active antibiotics to treat these patients into adulthood.

The polymyxins are cyclic peptide antibiotics which are positively charged at physiologic pH and exert bactericidal activity through binding to the lipopolysaccharide component of gram-negative bacterial membranes.[3] Colistin, which is commercially available as the prodrug colistimethate sodium, has historically been the most commonly used polymyxin in patients with and without CF.[4,5] There has been renewed interest into these compounds in the patients without CF due to the epidemic of antibiotic resistance. Population PK studies in critically ill patients have demonstrated high inter-patient variability in the exposure of formed colistin and inadequate attainment of therapeutic levels in patients with adequate or augmented renal function.[6,7] The variability between patients in colistin exposure is due to variable conversion from colistimethate, which requires removal of five pro-drug functional groups, as

well as the differential pathways of elimination for colistimethate and formed colistin. Colistimethate is freely filtered and excreted in urine whereas formed colistin as avidly reabsorbed in the kidney and eliminated by non-renal mechanisms.[8] The renal elimination of the inactive prodrug before conversion to the pharmacologically active form makes achieving colistin exposures associated with effective bacterial killing challenging in patients with adequate renal function. Patients with CF generally exhibit augmented clearance of renally eliminated compounds placing them at increased risk for underexposure.[9] Polymyxin B, which is administered directly as active drug and reabsorbed in the kidney in a manner analogous to formed colistin, has demonstrated more consistent PK in critically ill patients.[10-12]

The impact of patient-specific variables on the PK of the polymyxins has been an area of active investigation. As highlighted above, patient renal function has a significant bearing on the PK of colistin, through its prodrug colistimethate sodium, but has negligible impact on polymyxin B.[10-12] Therefore, despite the fact that the polymyxin B label includes renal dose adjustments, this agent is dosed without respect to patient renal function in clinical practice.[13] The only PK study of polymyxin B in patients with CF included 9 patients with only a median of 2 samples analyzed per patient (31 samples total).[14] Interestingly, this study did identify a relationship between polymyxin B CL and creatinine clearance; however, the validity and magnitude of this relationship are uncertain given that most of the observed effect was due to a single patient. The other patient-specific factor which has traditionally informed the dosing of these agents is patient body weight. Population PK studies of colistin from the modern era of use have challenged the traditionally held belief that the clearance and volume of distribution scale with patient weight.[6,7] In fact, the updated European Medicines Agency labeling for colistin recommends fixed-doses stratified by patient renal function based on these data.[15] Similarly, the most recent PK studies of polymyxin B have failed to demonstrate an impact of patient body weight on the clearance of polymyxin B; however, the majority of polymyxin B dosing in clinical practice is still weight-based.[11,12]

The polymyxins are associated with significant toxicities, namely, nephrotoxicity and neurotoxicity, which limit their clinical use. Therefore, it is important to assess the relative toxicity of colistin and PMB to ensure that shifting use to PMB for its PK advantages does not lead to increased toxicity. The comparative nephrotoxic potential of colistin and polymyxin B has been extensively investigated in non-CF populations, primarily the critically ill, and a meta-analysis of recent observational studies found an increased risk for acute kidney injury (AKI) with colistin relative to polymyxin B (RR 1.55, 95% CI 1.36-1.78).[16] Only two studies assessing nephrotoxicity of both colistin and polymyxin B have included patients with CF. Phe and colleagues included 38 patients with CF and found that CF was actually protective against colistin associated AKI (aOR 0.03, 95% CI 0.001-0.79) in multivariable analysis.[17] Unfortunately, no CF patients in this study received polymyxin B, so the relative rates of kidney injury between the two agents in this population could not be assessed. A 2017 study investigated the association between polymyxin treatment and kidney injury in 220 adult CF patients, 29 treated with PMB and 191 treated with colistin.[18] The study found no difference in rates of AKI between PMB and colistin (34.5% vs 29.8%, p = 0.77) in patients nor in the rates of renal recovery by hospital discharge (90.0% vs 91.2%, p = 1.00). Neurotoxicity with the polymyxins are poorly characterized in patients with and without CF, especially with polymyxin B. Studies with colistin in pediatric patients with CF have found rates of neurotoxicity between 0 – 97.3% with many demonstrating higher rates of neurotoxicities than AKI.[5] The most common manifestation of neurotoxicity with polymyxins is mild-moderate perioral paresthesia followed by weakness, ataxia, and in rare cases respiratory compromise.[5,19,20] Neurotoxicity has not been evaluated in studies comparing colistin and PMB.

We propose to measure the plasma concentrations of PMB in adult patients with CF receiving intravenous therapy as a part of their routine care and to use these measured concentrations to build population pharmacokinetic models. The population pharmacokinetic modeling approach will allow the assessment of the impact of patient specific covariates (i.e. weight, renal function) on pharmacokinetic parameters. Patients will be monitored for nephrotoxicity and neurotoxicity to ensure that PMB has an acceptable

margin of safety in this patient population. This investigation will be the first to prospectively assess the pharmacokinetics and toxicities of PMB in this patient population and will facilitate optimal use of this compound in the management of acute pulmonary exacerbations of CF.

4. Specific Aim/Hypothesis

4.1. Measure the plasma concentration of PMB in adult CF patients receiving intravenous therapy. Adult patients with CF often receive multiple courses of antipseudomonal antibiotics over the course of their disease resulting in the evolution of multi-drug resistant (MDR) *P. aeruginosa* pulmonary colonizers. The polymyxins, colistin and PMB, frequently retain activity against MDR gram-negative bacteria. Colistin has historically been the most commonly used polymyxin in patients with CF; however, new pharmacokinetic (PK) and toxicity data obtained from non-CF populations suggest that PMB may achieve more consistent exposure with lower associated toxicity. We aim to measure concentrations of PMB in plasma samples obtained from adult CF patients treated with polymyxin B using liquid chromatography–tandem mass spectrometry (LC-MS/MS).

4.2. Characterize the pharmacokinetics of PMB in adult CF patients. There are three major population PK studies which inform the dosing of PMB and one small study including patients with CF. These studies suggest that the clearance of PMB is not related to patient body weight and have discordant results regarding patient renal function. Therefore, underweight patient populations with excellent renal function, such as CF, may be at risk for underdosing with traditional weight-based regimens. We aim to use population pharmacokinetic modeling to characterize the PK of fixed-dose PMB in this special population and assess the effect of patient-specific covariates (e.g., body weight, renal function) on PK parameters.

4.3. Determine the safety of PMB therapy in adult CF patients. Polymyxin use is limited to salvage therapy for MDR gram-negative bacterial infections and cases of allergy, intolerance, or adverse effects to alternative agents due to the significant toxicities related to these compounds. Nephrotoxicity is the most common dose-limiting toxicity; however, it has been poorly characterized with PMB in patients with CF. Neurotoxicity has also been reported and occurs with moderate frequency with colistin in studies of patients with CF. We aim to characterize PMB-associated nephrotoxicity using the Kidney Disease: Improving Global Outcomes (KDIGO) criteria and neurotoxicity via patient self-report.

5. Study Methodology

5.1. Study design: Single-center, open-label, non-interventional, pharmacokinetic study.

5.2. Inclusion criteria: Study subjects will be identified by investigators in the course of providing clinical care or by means of reports built in TheraDoc® Clinical Surveillance software (version 4.4; Premier Inc, Salt Lake City, UT) or built directly into the electronic medical record (EPIC Systems, Madison, WI). Subjects fulfilling the following criteria will be eligible for inclusion:

5.2.1. Adults, greater than 18 years of age

5.2.2. Diagnosed with cystic fibrosis

5.2.3. Treated with intravenous polymyxin B for a suspected or confirmed infection as part of routine care

5.3. Exclusion criteria

5.3.1. Extra-corporeal organ support systems that would alter drug distribution including renal replacement (e.g., hemodialysis, peritoneal dialysis, continuous renal replacement) or extra-corporeal membrane oxygenation

5.3.2. Pregnancy

5.3.3. Unable to provide informed consent

5.4. Study Timeline

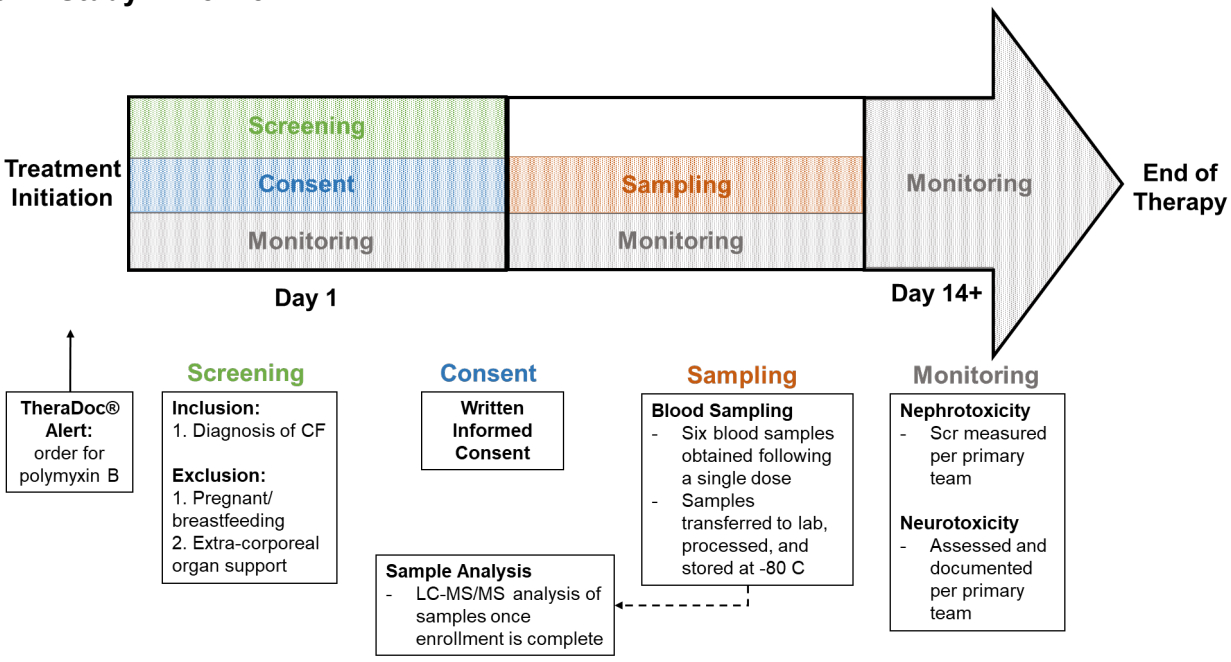

Figure 1: Study Timeline and Procedures. Abbreviations: CF, cystic fibrosis; LC-MS/MS, liquid chromatography tandem mass spectrometry, Scr, serum creatinine

5.5. Informed Consent

5.5.1. **Procedures:** A member of the study team will review the study and informed consent with the potential participant and answer any questions. Written informed consent will be obtained from the patient prior to enrollment in the study. Informed consent documents will outline the risk associated with obtaining the blood samples as well as the anticipated benefits of the study. A copy of the signed informed consent will be given to the participant. Subjects will be free to opt out of the study at any time for any reason after enrollment.

5.5.2. **Storage:** Informed consent documents will be stored in a locked cabinet in a locked office. Copies of the informed consent documents will be uploaded onto M+Box with access restricted to IRB-authorized study personnel, and will also be uploaded to participant's medical record in MiChart.

5.6. Dosing and Administration

5.6.1. The dose and duration of infusion for PMB will determined at the discretion of the prescribing physician in the course of routine clinical care. There is no study intervention on the dosing and administration of PMB.

5.6.2. The recommended dosing schedule for intravenous polymyxin B at Michigan Medicine consists of an initial weight-based loading dose (2 mg/kg, maximum of 200 mg) followed by 100 mg every 12 hours for the duration of therapy as determined by the clinician. A reduction of the maintenance dose to 75 mg every 12 hours is recommended for patients with total body weight less than or equal to 50 kg.

5.7. Sampling:

5.7.1. Blood samples will be collected from enrolled patients at 5 time points during a single dosing interval under steady-state conditions. Sampling will occur on any day of therapy immediately prior to and following a single dose of PMB. The infusion time is selected at the discretion of the prescribing physician; thus the sampling schema is described based on the duration of infusion (Table 1).

Table 1: Sample collection times

Sample Code	Collection Timepoint	Collection Time Relative to Duration of Infusion (t_{inf})
C_0	Prior to Start of Infusion	0 hour
C_1	End of Infusion	t_{inf} + 0 hour
C_2	One Hour after End of Infusion	t_{inf} + 1 hour
C_3	Three Hours after End of Infusion	t_{inf} + 3 hours
C_4	Eight Hours	8 hours

5.7.2. Blood samples will be collected via one of three sampling methodologies: peripheral venipuncture, peripheral intravenous catheter, or a central venous catheter (e.g., PICC, Port). The method of obtaining blood samples will be determined by study personnel and will consider patient preference, patient safety, and the likelihood of obtaining adequate samples. Insertion of, care for, and sampling from indwelling catheters will be performed per hospital policy.

5.7.3. The procedure for obtaining and processing blood samples can be found in the Laboratory Protocol document in the Appendix (10.1).

5.8. Demographic and Clinical data: Study team members will obtain demographic and clinic data needed to describe the study population and build pharmacokinetic models. Data will be abstracted from DataDirect or obtained directly from the medical record for each index encounter. Data recorded directly from the medical record will be stored in REDcap.

5.8.1. Demographic: comprehensive demographic data will be obtained from DataDirect. Examples of variables of interest include race and sex.

5.8.2. Encounter: comprehensive encounter data will be obtained from DataDirect. Example variables of interest include age, weight, height, body mass index, admission and discharge dates, and sites of care.

5.8.3. Diagnosis: comprehensive codified diagnosis data will be obtained from DataDirect. Example diagnoses of interest include comorbid conditions, admission diagnoses, and discharge diagnoses

5.8.4. Procedures: comprehensive procedure data will be obtained from Data Direct. Example variables of interest include procedure codes related to renal replacement therapy or source control procedures

5.8.5. Medications: comprehensive medication orders and administration data will be obtained from DataDirect. Example medications of interest include polymyxin B, aminoglycosides, beta-lactams, other anti-infectives, vasopressors, albumin, fluid, immunosuppressants, corticosteroids, intravenous contrast dye, and chemotherapies

5.8.6. Laboratory: comprehensive laboratory information, including microbiology, will be obtained from DataDirect. Example laboratory values of interest include aminoglycoside or vancomycin drug concentrations, serum creatinine, blood urea nitrogen, sodium, potassium, CO_2, albumin, total bilirubin, white blood cell count, platelet count, hemoglobin, hematocrit, total lymphocyte count, pH, PaO_2, bicarbonate, procalcitonin, erythrocyte sedimentation rate, c-reactive protein, and culture results.

5.8.7. Vitals: comprehensive vital signs and fluid inputs and outputs will be obtained from DataDirect. Example vitals of interest include mechanical ventilation, fraction of inspired oxygen (FiO_2), oxygen saturation, temperature, blood pressure, heart rate, respiratory rate, urine output, Glasgow Coma Scale score (GCS), dietary information.

5.8.8. Outcome: hospital length of stay, mortality, readmission rate. Results of spirometry, including forced expiratory volume in 1 second (FEV1).

5.9. Assay: Plasma concentrations of polymyxin B, comprising both polymyxin B1 and B2 components, will be determined using LC-MS/MS.

5.10. Storage of data and samples

5.10.1. Sample storage: Samples will be labeled with a unique study identifier and stored at -80 C. No protected health information will be stored with the samples. Access to samples will be restricted to authorized research personnel.

5.10.2. Data storage: Sample information including subject name, medical record number, and date and time of collection will be recorded separately in the sample collection log. The sample collection log will be stored in a locked draw within a locked office, accessible only to study personnel. Electronic data will be maintained in a password-protected file within M+box. Access to this document will be restricted to approved members of the research team. Only codified data will be used in analysis.

5.11. Patient reimbursement: Patients will be reimbursed $100 for participation in the study.

6. Data Analysis

6.1. Population Pharmacokinetic Analysis

6.1.1. Pharmacokinetic Modeling: The PK data will be analyzed using a population PK modeling approach through the nonparametric adaptive grid (NPAG) algorithm in the Pmetrics™ package for the R environment.[21,22] Models will be parameterized as one- and two-compartment systems with zero-order infusion and elimination from the central compartment modeled as a first-order process. Michaelis-Menten and mixed-order linear/Michaelis Menten elimination will be tested if first-order processes alone do not display adequate fit of the data.

For all models, the inverse of the estimated assay variance will be used as the first estimate for weighting. Weighting will be accomplished by making the assumption that total observation variance is proportional to assay variance. Assay variance will be determined on a between-day basis. The analysis will be performed with adaptive γ, a scalar which is optimized with each cycle to produce the best approximation to the homoscedastic assumption.

Models will be run for at least 100 cycles and Bayesian estimates will be obtained for each patient. For each model, both the mean and median will be employed as measures of central tendency for the population parameter estimates and will be evaluated in the Bayesian analysis. Scatter plots will be examined for individual patients and for the population as a whole.

6.1.2. Monte Carlo Simulation: The parameter vector and covariance matrix from population PK modeling will be used as the prior distribution for the simulation function within Pmetrics™. 1000-subject Monte Carlo simulations will be performed for candidate dosing regimens.

The simulated plasma concentration-time curves will be used to calculate area under the concentration-time curve (AUC) values for different 24-hour increments through 96 hours. For each regimen examined, probability of efficacy will be the fraction of the simulated subjects at each time interval for which the 24-hour AUC is between 50 – 100 mg*h/L while the probability of toxicity will be the fraction of subjects with 24-hour AUC values ≥ 100 mg*h/L.[23,24]

6.2. Toxicity Analysis

6.2.1. Nephrotoxicity: Nephrotoxicity will be assessed using the KDIGO criteria to define AKI. The nephrotoxicity endpoint will be met if subjects meet criteria for any stage of AKI by the KDGIO criteria using measured serum creatinine (Table 2). The degree of AKI will also be described by KDIGO stage. Time to renal recovery after cessation of PMB and the proportion of patients with renal recovery by hospital discharge will also be assessed. Renal recovery is defined as resolution of all KDIGO criteria for AKI.

Table 2: Definition of AKI using the KDGIO criteria

Stage	Serum Creatinine
1	1.5 – 1.9 x baseline *OR* ≥ 0.3 mg/dL increase from baseline
2	2.0 – 2.9 x baseline
3	≥ 3.0 x baseline *OR*

	≥ 4 mg/dL *OR* Initiation of renal replacement therapy

6.2.2. Neurotoxicity: Neurotoxicities will be assessed by patient self-report. The type of toxicity, anatomic site of toxicity, and severity will be assessed by the study personnel using the National Cancer Institute: Common Terminology Criteria for Adverse Events (NCI:CTCAE) scale.[25]

Table 3: NCI:CTCAE terminology and definitions for potential neurotoxicities

CTCAE Term	Definition
Apnea	A disorder characterized by cessation of breathing
Ataxia	A disorder characterized by lack of coordination of muscle movements resulting in the impairment or inability to perform voluntary activities
Confusion	A disorder characterized by a lack of clear and orderly thought and behavior
Dizziness	A disorder characterized by a disturbing sensation of lightheadedness, unsteadiness, giddiness, spinning, or rocking
Dyspnea	A disorder characterized by an uncomfortable sensation of difficulty breathing
Hallucinations	A disorder characterized by a false sensory perception in the absence of an external stimulus
Hearing impairment	A disorder characterized by partial or complete loss of the ability to detect or understand sounds resulting from damage to ear structures
Muscle Weakness	A disorder characterized by a reduction in the strength of muscles in multiple anatomic sites
Paresthesia	A disorder characterized by functional disturbances of sensory neurons resulting in abnormal cutaneous sensations of tingling, numbness, pressure, cold, and/or warmth
Peripheral motor neuropathy	A disorder characterized by damage or dysfunction of peripheral motor nerves
Peripheral sensory neuropathy	A disorder characterized by damage or dysfunction of peripheral sensory nerves
Psychosis	A disorder characterized by personality change, impaired functioning, and loss of touch with reality.
Respiratory Failure	A disorder characterized by impaired gas exchange by the respiratory system resulting in hypoxia and a decrease in oxygenation of the tissues that may be associated with an increase in arterial levels of carbon dioxide
Seizure	A disorder characterized by sudden, involuntary skeletal muscle contractions of cerebral or brain stem origin

Table 4: NCI:CTCAE terminology and grade for potential neurotoxicities

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Apnea	-	-	Present; medical	Life-threatening respiratory or	Death

			intervention indicated	hemodynamic compromise; intubation or urgent intervention indicated	
Ataxia	Asymptomatic; clinical or diagnostic observations only	Moderate symptoms; limiting instrumental ADL	Severe symptoms, limiting self-care ADL; mechanical assistance indicated	-	-
Confusion	Mild disorientation	Moderate disorientation; limiting instrumental ADL	Severe disorientation; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	-
Dizziness	Mild unsteadiness or sensation of movement	Moderate unsteadiness or sensation of movement; limiting instrumental ADL	Severe unsteadiness or sensation of movement; limiting self-care ADL	-	-
Dyspnea	Shortness of breath with moderate exertion	Shortness of breath with minimal exertion; limiting instrumental ADL	Shortness of breath at rest; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death
Hallucinations	Mild hallucinations (e.g. perceptual distortions)	Moderate hallucinations	Severe hallucinations; hospitalization not indicated	Life-threatening consequences; threats of harm to self or others; hospitalization indicated	Death
Hearing Impairment	Subjective change in hearing in the absence of documented hearing loss	Hearing loss with hearing aid or intervention not indicated; limiting instrumental ADL	Hearing loss with hearing aid or intervention indicated; limiting self-care ADL	Decrease in hearing to profound bilateral loss; nonservicable hearing	-
Muscle weakness	Symptomatic; perceived by patient but not evident on physical exam	Symptomatic; evident on physical exam; limiting instrumental ADL	Limiting self-care ADL	-	-
Paresthesia	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms, limiting self-care ADL	-	-
Peripheral motor neuropathy	Asymptomatic; clinical or diagnostic	Moderate symptoms; limiting	Severe symptoms, limiting self-care ADL	Life-threatening consequences; urgent	Death

	observations only	instrumental ADL		intervention indicated	
Peripheral sensory neuropathy	Asymptomatic	Moderate symptoms; limiting instrumental ADL	Severe symptoms, limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	-
Psychosis	Mild psychotic symptoms	Moderate psychotic symptoms (e.g. disorganized speech; impaired reality testing)	Severe psychotic symptoms (e.g. paranoid, extreme disorganization); hospitalization not indicated, new onset	Life-threatening consequences, threats of harm to self or others; hospitalization indicated	Death
Respiratory Failure	-	-	-	Life-threatening consequences; urgent intervention, intubation, or ventilator support indicated	Death
Seizure	Brief partial seizure and no loss of consciousness	Brief generalized seizure	New onset seizures (partial or generalized); multiple seizures despite medical intervention	Life-threatening consequences; prolonged repetitive seizures	Death

Abbreviations: ADL, activities of daily living
*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden

6.3. Statistical Analysis

6.3.1. Baseline demographic and clinical data: Baseline demographic and clinical data will be assessed using descriptive statistics. Variables will be summarized as mean (standard deviation), median (5^{th}, 95^{th} percentile), or number (percentage) as indicated.

6.3.2. Population pharmacokinetic analysis: Model goodness-of-fit of the observed data will be assessed by regression with an observed-predicted plot. Between-subject variability will be quantified using coefficients of determination. Model discrimination will be based on log-likelihood (-2LL) and Akaike's Information Criterion (AIC) objective function values as well as diagnostic plots. Predictive performance evaluation will be based on weighted mean bias and the bias-adjusted weighted mean precision.

6.3.3. Toxicity analysis: Nephrotoxicity and neurotoxicity rates will be summarized as number (percentage). Time to renal recovery will be summarized as mean (standard deviation) or median (interquartile range) days as indicated while renal recovery by hospital discharge will be summarized as number (percentage).

7. Benefits and Risks

7.1. Benefits:

7.1.1. Current CF Foundation guidelines recommend that two antibiotics with activity against *P. aeruginosa* as the standard of care for treatment of acute pulmonary exacerbations. Many adult CF patients have had extensive lifetime exposure to antipseudomonal antibiotic therapy and may require therapy with last line agents due to multi-drug resistance in clinical isolates. The polymyxins, colistin and polymyxin B, are often required as combination salvage therapy for isolates with documented resistance to aminoglycosides or fluoroquinolones. Polymyxin B has significant pharmacokinetic advantages to colistin for CF patients; however, limited data exist in this patient subpopulation to guide dosing in practice. The data generated by this study will be used to confirm dosing of polymyxin B in this population and ensure safety with commonly administered doses extrapolated from non-CF patient populations. There is no direct benefit to patients enrolled in the study at the time of enrollment; however, patients treated with polymyxin B at the time of the study are at risk for re-infection with MDR organisms in the future. Therefore, PK data obtained in this study could inform the dosing of polymyxin B for the treatment of future infections with MDR organisms.

7.1.2. Patients will not experience direct benefit from this study. Patients will not be informed of study results.

7.2. Risks

This study poses no more than minimal risk to participants. Potential risks are as follows.

7.2.1. Accidental Disclosure of Protected Health Information (PHI)

7.2.1.1. Frequency: Rare

7.2.1.2. This investigation will involve the use of PHI. With any use of PHI, the potential for accidental disclosure exists.

7.2.2. Adverse Effects Due to Blood Sampling

7.2.2.1. Frequency: Rare

7.2.2.2. The only intervention outside of routine care in this study is blood sampling. Potential adverse effects of blood sampling include mild pain, anxiety/fear, bruising, hematoma, arterial puncture, nerve damage, re-bleeding, phlebitis, or vasovagal reactions.

7.3. Protection Against Risks

7.3.1. Accidental Disclosure of Protected Health Information (PHI)

We will follow standard practice for protecting research data (locked cabinets/offices requiring key access, restricted access, use of secure servers). Protection of participant confidentiality will be maintained by providing each subject a unique identification number. Only this number will be used on study documents that relate to the subject. All physical data will be stored in a locked cabinet within a locked office. Electronic study

data will be maintained on University of Michigan servers in M+Box and accessed through University devices or VPN. Access to PHI will be restricted to IRB-approved study personnel. All data will be codified prior to analysis.

7.3.2. Adverse Effects Due to Blood Sampling

To minimize the risks associated with blood sampling, blood samples will be obtained by a member of the study team who has received training specific to blood sampling. Best practice procedures for phlebotomy will be followed. A maximum of 5 mL of blood will be removed per sample for a maximum total volume of 30 mL per patient, which is less than 10% of the volume removed in a standard blood donation. When possible, existing indwelling central venous access will be used to obtain samples to avoid additional venipuncture.

8. Adverse Events

8.1. Reporting Plan

We will utilize a study specific adverse event (AE) reporting plan and only report adverse events directly related to the venipuncture or venous access to the IRB per the recommended guideline.

8.2. Other Reportable Information or Occurrence

Any breach of confidentiality will be reported immediately to the IRB.

9. References

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10. Appendices

10.1. Appendix I: Laboratory Protocol

Laboratory Protocol

1. Blood Collection Tubes

Plastic Lavender Top K2-EDTA Tube (BD, Franklin Lakes, NJ, Catalog# 367863)

2. Blood Collection Supply Quantities

Five blood samples are to be obtained and processed per subject on polymyxin B therapy. Samples will be collected at the time points listed below relative to the end of polymyxin B infusion (t_{inf})

Sample Code	Collection Timepoint	Collection Time Relative to Duration of Infusion (t_{inf})
C_0	Prior to Start of Infusion	0 hour
C_1	End of Infusion	t_{inf} + 0 hour
C_2	One Hour after End of Infusion	t_{inf} + 1 hour
C_3	Three Hours after End of Infusion	t_{inf} + 3 hours
C_4	Eight Hours	8 hours

Minimum Supplies Necessary:

Up to 20 subjects × 5 blood collection tubes =	100 Blood Collection Tubes
100 blood samples x 2 plasma aliquots/blood sample=	200 cryovials (Screw Capped Polypropylene, 1-2 mL)
200 cryovials × 1box/81 cryovials=	3 cryovial storage boxes

3. Pre-Study Preparation

- **a.** Plasma collection tubes
  - **i.** Label 5 plasma collection tubes per subject with:
    - **1)** study protocol number
    - **2)** the study subject code
      - **a)** color code with a highlighter pen (yellow, pink, green, orange) the subject code if more than one subject is to be studied on the same date
    - **3)** date of collection

4) sample code (i.e. C_0, C_1, etc.)

ii. Transfer plasma collection tubes to a test-tube rack

1) Individual test-tube racks should be used for each subject if more than one subject is to be studied on the same day

iii. Pre-chill (2-8°C) plasma collection tubes prior to blood collection

b. Cryovials

i. Label 10 cryovials per subject with:

1) study protocol number

2) the study subject code

a) color code with a highlighter pen (yellow, pink, green, orange) the subject code if more than one subject is to be studied on the same date

b) the color code should match the plasma collection tube for each subject to reduce the risk of potential transfer error

3) date of collection

4) sample code (i.e. C_0, C_1, etc.)

5) aliquot number (AQ-1, AQ-2)

ii. Transfer cryovials to a rack

1) Individual cryovial racks should be used for each subject if more than one subject is to be studied on the same day

c. Cryovial boxes

i. Label 2 cryovial boxes with:

1) study protocol number

2) date of collection

3) aliquot number (AQ-1 and AQ-2)

4. Blood Sample Collection and Processing

a. Collection

i. Collect venous blood in pre-labeled and chilled lavender top plasma collection tubes

ii. Invert the plasma collection tube ten times slowly and gently to ensure adequate mixing of the EDTA with the sample

iii. Immediately replace the sample tube upright in the test-tube rack within the study cooler

iv. Record actual time of sample collection in sample collection log

b. Processing

i. Centrifuge the whole blood at 3000 rpm for 12 minutes in a refrigerated centrifuge set to 4°C

ii. Transfer the supernatant (plasma) to pre-labeled cryovials in 0.5 – 1 mL aliquots of equal volume, taking care not to disturb the buffy coat.

1) See the section below for management of insufficient sample volume

iii. Place cryovials into the appropriate cryovial boxes ordered by subject and sample code

1) More than one subject can be stored in each cryovial box. **Do not divide a samples for a single subject between more than one cryovial box**

iv. Store cryovial boxes at -80°C until analysis

1) The time from blood collection until the plasma sample is stored at -80°C should be 90 minutes or less.

c. Potential Problems

i. Hemolysis

1) Samples with visible hemolysis may be processed as noted
2) The cryovials for hemolyzed samples should be marked with the term “Hemo”

ii. Insufficient sample volume

1) An insufficient sample volume is less than 0.5 mL of plasma
2) If between 0.25-0.5 mL:
    a) Transfer plasma to two labeled cryovials in aliquots of equal volume
3) If less than 0.25 mL:
    a) Transfer plasma into the cryovial labeled “AQ-1” only
    b) Mark the cryovial labeled “AQ-2” with the term “ISV”, which indicates “insufficient sample volume”
    c) Place the “AQ-2” cryovial labeled “ISV” in the appropriate slot in the “AQ-2” cryovial box inverted, so that the cap is facing downward rather than upward.