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PART B
STUDY DESCRIPTION

TITLE OF PROTOCOL	A pilot study of the effect of prophylactic antibiotics on hospitalized patients with advanced cirrhosis
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B1. PURPOSE OF PROTOCOL

In this pilot study, we aim to assess feasibility of subject identification and data collection, including specimen processing, as well as the rate of enrollment for a future, larger randomized, placebo controlled trial of the effect of prophylactic antibiotics for all patients with advanced cirrhosis admitted to the hospital without an existing indication for new antibiotic use. Specifically, we will assess the incidence of infection after the time of enrollment and associated outcomes.

B2. SIGNIFICANCE AND BACKGROUND FOR THE STUDY

Advanced chronic liver disease/cirrhosis creates a state of relative immune-compromise, and, indeed, infections are a key precipitant of clinical decline in patients with cirrhosis. Specifically, infections of any kind are a common cause of acute on chronic liver failure (ACLF) and complicate 20-40% of hospital admissions of patients with cirrhosis. Although other pathogens are also important, the vast majority of infections in patients with cirrhosis are of bacterial origin. In other high-risk hospitalized patient populations, early initiation of antibiotics has been shown to reduce the need for intensive care unit (ICU) admission and short-term mortality. Unfortunately, the presentation of infection in patients with cirrhosis is protean and may be subtle. Diagnosis may be delayed by the absence of classic signs of infection such as fever and absolute leukocytosis. Vital diagnostic studies, such as paracentesis or other culture (blood, urine, or sputum) may be delayed or may not yield results until days after presentation. Delaying antibiotics until such studies result is inadvisable in patients with infection; however, empiric administration of antibiotics to all patients with cirrhosis admitted to the hospital would result in waste and increased risk of antibiotic resistance, *Clostridium difficile* infection, and other adverse effects. Sub-groups of patients with cirrhosis are already known to benefit from empiric/prophylactic antibiotics including those with acute upper gastrointestinal hemorrhage and those with increased risk of spontaneous bacterial peritonitis. The risk of infection increases with more advanced cirrhosis, as marked by higher Model for End-stage Liver Disease – Sodium (MELD-Na).

There are also biomarkers of systemic infection that, although not specific, may be used to identify patients more likely to have an active infection and thus allow more targeted use of empiric antibiotics. Specifically, increase in serum C-reactive protein (CRP, >25 mg/L) and Procalcitonin (>0.5 ng/mL) are associated with acute bacterial infection.

These factors may permit identification of patients who would benefit from prophylactic/empiric antibiotics. There has not, however, been investigation of the effect of prophylactic antibiotics on hospitalized patients with advanced cirrhosis beyond the sub-populations described above.

B3. DESCRIPTION OF RESEARCH PROTOCOL

A. Study Design – Overview, Methods, Procedures

This is a blinded, randomized, placebo-controlled pilot trial to determine feasibility of subject identification, rate of enrollment, and data collection, including specimen processing, for a future, larger randomized trial of the effect of empiric antibiotics for all patients with advanced cirrhosis admitted to the hospital without an existing indication for new antibiotic use. Specifically, we will assess the incidence of infection after the time of enrollment and associated outcomes. Patients will be randomized to receive either ceftriaxone or placebo (normal saline). Study drug will be delivered in masked vials for daily IV administration.

Case finding and Screening: Eligible patients will be identified in the emergency department or by admitting physicians upon their initial medical assessment or by study personnel via daily review of the inpatient hepatology ward and consultative service census. Study personnel will screen each potential subject by review of medical record for potential eligibility.

Consent: If a patient meets basic eligibility criteria, a study investigator will meet with the potential subject/LAR to review the study protocol and obtain informed consent. Screening measures will be completed following consent and the balance of the baseline measures will be completed.

Extended Screening/Baseline: Evaluation for undiagnosed infection will be completed following consent and prior to randomization including: chest x-ray, venous blood culture, urine culture- all, if not already performed via routine care. These studies may be deferred if they have been done within 7 days of enrollment and there has been no change in clinical status. Subjects with infection identified upon enrollment will be excluded from further participation and have further treatment directed by their standard clinical providers.

Each subject's medical record will be reviewed to determine the presence or absence of diuretic-resistant ascites (defined by history of TIPS, large volume paracentesis within the past 3 months despite diuretics, or intolerance of diuretics).

Each subject's medical record will be reviewed to determine the calculated baseline CLIF-C ACLF score (Chronic Liver Failure Consortium (CLIF-C) Acute on Chronic Liver Failure). This will be computed using data (laboratory and physical examination) collected as part of standard of care. These data points include:

- bilirubin,
- creatinine,
- INR,
- West Haven grade of encephalopathy,
- mean arterial pressure, and
- peripheral oxygen saturation (SpO2).

A peripheral or central venous blood sample will be taken after consent is obtained. Approximately thirty milliliters (2 tablespoons) of whole blood will be collected. We will measure serum procalcitonin and C-reactive protein for the research study and store remaining specimen for potential future testing.

Patients will be excluded if there is a clinical indication for new treatment with antibiotics, e.g. upper gastrointestinal hemorrhage or apparent infection, Standard of care treatment will never be delayed.

Randomization: Each subject will be randomized to receive antibiotic treatment (ceftriaxone) or placebo (normal saline). Randomization will be blinded to patients, study investigators, and study staff. Only the BIDMC Research pharmacist will know treatment assignment. Randomization will be stratified by the presence of either serum creatinine >= 2.0 mg/dL and/or diuretic-refractory ascites.

Study Intervention: The research pharmacy staff will provide antibiotic or placebo in the form of masked vials of intravenous solution. This will consist of either 1 gr ceftriaxone or an equal volume of normal saline (approximately 100 mL). This administration will begin as soon as possible after enrollment and will be repeated once daily. If a subject is prescribed an equivalent intravenous antibiotic during the hospitalization (i.e., ceftriaxone, piperacillin/tazobactam, or a carbapenem), the study-treatment (ceftriaxone/placebo) will be withheld on those days. If the clinically prescribed antibiotic is subsequently discontinued prior to discharge, the study-treatment/placebo may be resumed. Study treatment will be discontinued on study treatment day 7, or at the time of discharge or liver transplantation, if such events occur earlier than treatment day 7.

Monitoring during Study Intervention: Monitoring during study treatment will utilize routine vital sign monitoring and standard care labs conducted as indicated (typically daily) during the patient's in patient stay. Standard care monitoring may also include radiographic or microbiology studies (e.g. culture) or special procedures such as therapeutic or diagnostic paracentesis at the discretion of the inpatient care team. No additional monitoring will be required per the study protocol. Standard care monitoring/labs that will be of interests include vital signs (e.g. blood pressure, mean arterial pressure, and oxygen saturation), CBC with WBC differential, bilirubin, INR, serum creatinine, sodium, albumin.

Incidental Findings: In the event that a clinically significant incidental finding is discovered during a research procedure, findings will be immediately reported to the attending on service for treatment or referral; results will be in OMR. These would be also be available to the in-patients care team via OMR. Examples of incidental findings include previously un-identified lung findings on chest x-ray, such as infection, pulmonary nodule, fracture, etc.

Safety Monitoring: The PI is ultimately responsible for protecting the rights, safety, and welfare of subjects enrolled into the trial. Study intervention will last for 7 days during the patient's inpatient stay for conditions related to the diagnosis of advanced cirrhosis/end stage liver disease. Safety monitoring will be conducted daily during the intervention phase; post-intervention procedures will continue daily during the patient's admission and on day 30 post end of intervention. The PI and/or a co-physician investigator will review all safety parameters including clinical safety laboratory assessments. Clinical laboratory values that fall outside of the pre-specified safety ranges will be brought to the PIs attention the day the reports are final to assess clinical significance.

Patients in the trial will be under the care of the in-patient liver service and these medical staff will be responsible for care of the patient throughout the admission.

The study PI will review data of all non-serious adverse events after randomization of the first 5 subjects, and every additional 10 subjects thereafter until the study is complete.

Monitoring for AE: Subjects will be monitored for the occurrence of adverse events during their participation in the study. Reporting procedures will comply with BIDMC IRB policies; US Federal Regulations (21CFR 312), and ICH Guideline E-6: *Guidelines for Good Clinical Practice.*

Adverse events will be coded and graded according to the NIH/NCI Common Terminology Criteria for Adverse Events version 4.03 (June 2010). All adverse events will be classified on seriousness (mild, moderate, serious), expectedness (expected, non-expected), and relatedness to trial (not related, possibly related, related).

End of treatment: The study intervention will continue for 7 consecutive days (unless interrupted by equivalent antibiotic treatment for a new clinical indication). If the study intervention is interrupted the study intervention may be restarted following completion of the open label antibiotic treatment to complete the 7 days of study intervention.

Follow-up Procedures: Monitoring will continue until 30 days post-intervention.

End of study: Subject data will be recorded for up to 30 days post-intervention.

Data/Tissue Repository: A data and bio-specimen repository will be created to permit future research on this topic. De-identified data for each subject will be stored in a restricted access, password-protected folder on the BIDMC network drive. This access will be limited to study personnel. A master-code which links patient medical record number to the coded study subject ID will be stored in a separate location and available only to the PI and study personnel, as required for data entry. A blood specimen will also be collected from each subject upon enrollment for storage such that additional testing may be completed if preliminary results or subsequent knowledge suggest that another biomarker might have added prognostic significance. These specimens will be stored in a locked unit in the Liver Research Center (LMOB4) and coded with study ID only. Further testing on these specimens will not become part of the medical record.

B. Statistical Considerations

Sample Size Justification: We estimate there will be a small prevalence of occult infection among patients who are believed to be eligible after initial screening is completed. Patients with identified infection at the time of enrollment will not be randomized and instead be treated as per standard of care at the discretion of the medical staff. We estimate there may be 5-10 such patients who are thus enrolled but not randomized.

We aim to randomize a total of 40 subjects, assigned to active intervention vs. placebo; hence as many as 50 may be screened / consented to determine eligibility. This is a pilot study intended to assess feasibility of patient identification, administration of required testing and enrollment processing, and the rate thereof. The magnitude of observed effect will permit sample size estimation for a larger, more definitive study which we hope to complete subsequently. It is unknown how many subjects will need to be screened to complete this planned enrollment. We will also obtain information on the dropout rate and/or rate of use of therapeutic antibiotics which may alter enrollment goals for a future study.

Data Analysis: As stated elsewhere, the proposed study is a pilot study, not intended to provide definitive results. However, there are multiple outcomes of interest that will be recorded in order to permit planning of a future study.

The primary outcome is incident bacterial infection identified after randomization

screening (as defined below).

Secondary outcomes include:

1. In-hospital mortality;
2. 30-day mortality;
3. Incident acute on chronic liver failure (ACLF) defined as two or more of:
   - Grade 3-4 hepatic encephalopathy,
   - Need for renal replacement therapy,
   - Need for mechanical ventilation,
   - Need for vasopressors, or mean arterial pressure (MAP) <60 mmHg, or decrement of >40 mmHg in systolic blood pressure after volume resuscitation.
4. Change in calculated CLIF-C ACLF score;
5. Length of stay (LOS) after randomization;
6. Intensive Care Unit (ICU) transfer after randomization;
7. C difficile infection (positive stool polymerase chain reaction (PCR) or toxin-assay in the setting of diarrhea);
8. Increment in MELD-Na >= 3 points between randomization and discharge;
9. Acute kidney injury (increase in creatinine >= 0.3 mg/dL in 48 hr or >50% from baseline (within previous 3 months) occurring after randomization;
10. Variceal hemorrhage.

Covariates recorded/measured

- Procalcitonin at enrollment
- C-reactive protein at enrollment
- Other antibiotic use in-hospital (type and duration)
- Fungal infections (by positive culture) or use of systemic anti-fungal medications.

We will monitor daily for the incidence of the outcomes above via review of the medical record and discussions with the inpatient providers (when necessary). For any subject with a positive culture result, the site, organism, and antibiotic susceptibility will be recorded when available.

Infection definitions

- Bacteremia (positive blood culture not felt to be a skin flora contaminate)
- Spontaneous bacterial peritonitis (ascites PMN count >250/□L or positive ascites culture in the setting of new abdominal pain, or unexplained leukocytosis, fever, hypotension, fever, acute kidney injury, or exacerbation of hepatic encephalopathy, i.e., increase in West Have grade)
- Pneumonia: Pulmonary infiltrate on chest x-ray (CXR) or computed tomography (CT) in the presence of A) respiratory symptom(s) (cough, pleuritic pain, or dyspnea) or B) auscultation findings, abnormal body temperature (>38C or< 36C), or newly abnormal leukocyte count >10,000/microL or < 4,000/microL (if baseline leukocyte count > 4,500/microL).
- Skin or Soft Tissue Infection (SSTI): Superficial erythema, warmth, or fluctuance in the

skin/soft tissues felt to be secondary to infection by the inpatient team, excluding mild superficial thrombophlebitis from IV catheter insertion
- UTI: Urine leukocytes > 10/hpf, bacteruria, positive urine culture, urinary leukocyte esterase or nitrite in the presence of symptoms/signs of infection (dysuria, unexplained increased urinary frequency, fever, or leukocytosis)
- Other infections as identified by the primary medical team

For purposes of analysis, deidentified subject clinical data documenting the metrics above will be stored in a password protected file within the BIDMC network. Analysis will be conducted at BIDMC using R-studio software. There are no additional statistical consultants currently affiliated with this study. Descriptive statistics will include the incidence of the primary and secondary categorical outcomes in each arm with comparison via Chi-square test or Fisher's exact test for rare events. As noted elsewhere, we do not anticipate this study will provide sufficient statistical power to demonstrate statistically significant differences between groups, but we will need to have an idea of the magnitude of effect prior to planning such a study and hope to obtain this information here.

C. Subject Selection

Potential subjects will be identified by attending hepatologists on the ward/consultation service during the course of clinical care and/or by study personnel via daily review of these patient lists in OMR. Patients meeting eligibility criteria below will be reviewed and approached to discuss the study, if appropriate.

Inclusion Criteria:
- Age >= 18
- Cirrhosis, as defined by liver biopsy (completed as standard care) or a composite assessment of available results from imaging or elastography, prior records, and laboratory studies
- MELD-Na >= 18 (Model for End Stage Liver Disease-Sodium, incorporating components of serum sodium, bilirubin, International Normalized Ratio (INR), and creatinine

Exclusion Criteria:
- Inability to obtain consent from subject or next of kin/legal authorized representative (LAR)
- Allergy to cephalosporins
- Pregnancy (due to limited prospective data regarding safety of ceftriaxone)
- Presence of ascites amenable to paracentesis without paracentesis performed as SOC for exclusion of infection
- Existing indication for new antibiotics, e.g. upper gastrointestinal hemorrhage or apparent infection
- Use of major immunosuppressive medications (e.g. prednisone 20 mg/day or greater, immunosuppression for solid organ transplant)
- History of recurrent *C.difficile* infection within the past year (>2 episodes) or requiring prior fecal microbiota transplant (FMT)
- Enrollment in the study protocol during a previous admission

There are no specific limitations regarding gender or racial distribution of the planned population studied and as such, our intended sample will reflect a subset of these patients

without selection based on either parameter. The only exception to this is pregnant women will be excluded due to theoretical risk of adverse effect of ceftriaxone exposure (Pregnancy category B). Please note that is exceptionally rare to encounter a pregnant patient with this degree of chronic liver illness.

There are no specific requirements for contraception during this short study conducted with patients admitted to the hospital.

B4. POSSIBLE BENEFITS

Subjects *may* receive benefit via reduction in the risk or severity of infection during the admission. There *may* also be reduction in length of hospital stay or other complications such as indirect benefits such as rate of ICU transfer, variceal hemorrhage, or death. These will be identified in comparison to similar outcomes among subjects receiving placebo, noting, as above, that this is a pilot study, not intended to confirm such a benefit.

The benefit to society would be validating the design of a larger trial which could confirm such benefits and thus improve medical care and metrics important to patients, such as length of stay and mortality.

B5. POSSIBLE RISKS AND ANALYSIS OF RISK/BENEFIT RATIO

Risks of participation in the study include reaction to the antibiotic used in the trial: Ceftriaxone is commonly used to treat patients with end stage liver disease, and subjects may be prescribed ceftriaxone as routine care even if they do not participate in this trial.

Regardless of which treatment the subject is assigned, the study medication will be administered intravenously (IV), peripherally or via central venous catheter if one is already in place for routine care.

Side effects rarely observed in patients receiving any type of fluid intravenously include fever, infection at the site of IV insertion, blood clot in the vein, or inflammation of the vein extending from the site of injection, IV fluid leakage into the tissue around the IV insertion, and fluid overload.

Subjects randomized to receive c**eftriaxone**, may experience side effects that have been observed in prior clinical trials.

- The most common side effects (>10%) observed in clinical trials of ceftriaxone include skin tightness, thickening of the skin, and a warm sensation around the site of the injection when ceftriaxone was administered as an intermuscular injection.
- Less common side effects (<10%) included pain and tenderness at the injection site when the drug is given as an intermuscular injection; skin rash, diarrhea, eosinophilia (excess of inflammatory/allergic blood cells), thrombocytopenia (excess of platelets/blood clotting-cells), leukopenia (low level of white/infection-fighting blood cells), increased serum transaminases (liver blood tests which may suggest liver injury) and increased blood urea nitrogen (a marker of kidney function).
- Allergic reaction to the study drug which can vary in severity from asymptomatic rash, to pruritic (itchy) rash, to hives, to anaphylaxis (a life threatening allergic reaction).
- Indirect adverse effect of the study drug: development of antibiotic resistance,

opportunistic infection- *C difficile* colitis or fungal infection. Diagnostic uncertainty related to treatment of subsequent infections.

Subjects randomized to receive **placebo**, will receive approximately 100 mL (less than 7 tablespoons) of normal saline. There are no additional side effects expected beyond those listed above.

Blood draw and receiving medication intravenously: The risks and discomforts of drawing blood from a vein include the possibility of pain or bruising at the site of the blood draw, occasional feeling of lightheadedness, and rarely, infection or blood clotting at the site of the blood draw.

Some participants may need one or all of the following tests for the study:

Chest X-Ray/Radiation Risk:

Some patients may get a chest x-ray to rule out infection at screening if one has not been completed as standard care. Radiation exposure from a single chest x-ray will deliver approximately 0.2 milliSieverts, a measure of radiation exposure. For comparison, the average person in the United States receives a radiation exposure of 3.2 milliSieverts per year from natural background and exposures we encounter in our everyday life. One possible effect from this additional radiation exposure is an increase in the risk of cancer. The estimated increase in the cancer risk due to this radiation exposure is 0.002%.

Other Tests, Imaging Studies, and Procedures: Based on the severity of your condition or if your disease worsens, you may be asked to undergo other diagnostic tests, imaging studies (e.g., ultrasound), and procedures as a standard of care for your condition. There may be risks associated with these tests, imaging studies, and procedures. Your doctor will explain the risks associated with each test/study/procedure and you may be asked to sign a separate informed consent form depending on the test/study/procedure being performed.

Loss of confidentiality: There is the potential for loss of confidentiality by participating in this study. Every effort will be made to protect the confidentiality of your identifiable information.

We feel that the potential benefit to this patient population of this type of treatment outweighs these risks. We have attempted to minimize risk by exclusion of subjects deemed to be at greater risk of adverse reaction (e.g. history of allergy to cephalosporins or recurrent clostridium difficile infection), permitted non-study clinical teams to provide treatment without limitation, and minimized the number of subjects exposed to the intervention. The potential benefit to future patients could include reduced admission length or mortality rate.

B6. RECRUITMENT AND CONSENT PROCEDURES

Recruitment: Study participants will be identified from among the ranks of patients admitted to the BIDMC (Emergency Department and/or Liver Service) with end stage liver disease and advanced cirrhosis.

The PI and physician co-Investigators will identify patients admitted to their Service (Liver / Transplant Services) who meet preliminary eligibility criteria. Thereafter, a physician investigator will meet with the potential participant to introduce the study. If the patient does not have capacity to consent, the Investigator will identify the patient's Health Care Proxy / Legally Authorized Representative (LAR) to introduce the study.

Due to the COVID-19 global pandemic and hospital wide visitor restriction policies, informed consent will be conducted remotely via telephone with the patient's LAR when necessary.

Once the potential participant/LAR indicates willingness to consider enrollment, the physician investigator will explain the study in clear, easy-to-understand language; review study purpose and goals, study treatment, procedures (including randomization), burdens and benefits, and schedules. Any questions from a potential participant/LAR regarding the study will be answered by the study investigator.

Consent: Consent procedures will be completed for patients in a private setting beyond the ear shot of others. The physician investigator will review all study procedures, and risks and benefits will be discussed. The patient/LAR will be given ample time to ask questions and all questions will be answered. If the patient/LAR wishes to discuss participation with others, arrangements will be made to facilitate/expedite these discussions as time from subject identification to treatment is of importance.

Patients/LAR willing to consent to participation will be required to sign and date the BIDMC CCI approved consent; the Investigator completing consent procedures will also sign and date the consent document. The original consent will be maintained in the subject's research record, a copy will be placed in the subject's medical record, and a copy of the signed consent will be given to the subject.

When conducting consent remotely, a consent document will be emailed to the patient's LAR. Once the investigator and LAR both have a hard copy of the consent document in front of them, the consent document will be reviewed according to the same standards as outline above. If the LAR is willing to consent to study participation, they will sign the consent document and email or fax return a picture of the consent document signature page to study staff. The signature page signed by the LAR will be filed in the patient's research record alongside the consent document signed by the Investigator. A copy of both signed documents will be emailed to the LAR for their records.

If informed consent is obtained from a LAR, capacity for consent will be documented in the medical record. Once the subject's condition improves such that s/he regains capacity, informed consent for continued study participation will be obtained from the subject at that time. A separate ICF will be used to complete this consent. **Subject Protection**: We do not believe potential participants are vulnerable to coercion or undue influence. Patients admitted to the hospital with advanced chronic liver disease frequently present with hepatic encephalopathy. To exclude these patients would exclude a substantial group for whom the study is specifically intended to help. When investigators encounter a patient who does not have capacity to consent, the LAR will be identified and approached to obtain consent on

behalf of the potential subject. At such time as the patient regains capacity, the investigator will complete consent procedures directly with the subject.

We will not enroll prisoners into the study.

B7. STUDY LOCATION

Privacy: Consent procedures will be completed in a private hospital setting, beyond earshot of others by study investigators during the patient's hospital admission, e.g. private exam room, in-patient hospital room, etc.

Study procedures will be completed in various hospital settings, outpatient clinic or on the telephone. Patient privacy will be maintained in accordance with hospital policy and procedures. Medical record reviews will be completed by study staff at workstations in BIDMC research and clinical staff offices. Information collected will be limited to the minimum amount of data necessary to accomplish the research purposes.

All investigators and study staff are trained in HIPAA guidelines and requirements as well as Human Subjects Protections best practices. Only the investigators and study staff have access to data that identifies subjects by name. Subjects are assigned a unique study identifier and all subject records will be void of subject identifiers.

Only investigators listed will be able to connect individual subject information with research data. Data will be kept on a password protected database on a firewall-protected, BIDMC password protected computer in a restricted access location.

Physical Setting: Study investigators will interact with potential subjects during a hospitalization and following outpatient clinic visits in the Liver Center or Transplant Center. Subjects may be contact by phone in the event they do not return to the Center for a follow up visits prior to Day 30 post study treatment.

B8. DATA SECURITY

Study staff is trained in human subject protections regulation including hospital mandated CITI and HIPAA standards. Access to clinical medical records used for the trial is strictly limited in accordance with hospital policies. Data abstracted from medical records will be managed in compliance with clinical research best practices; both hard copy and electronic data collected for the investigation will be stored in restricted access files in the Division's Clinical Research Offices and in electronic files and folders behind hospital firewalls. Data included in analytic files will be de-identified and the key linking data to patient identity will be maintained by the investigators in a separated restricted access location.

B9 Multi-Site Studies

Is the BIDMC the coordinating site? ☐ Yes ☒ No *Not applicable*

Is the BIDMC PI the lead investigator of the multi-site study? ☐ Yes ☒ No *Not applicable*

B10 Dissemination of Research Results

In this pilot study to determine feasibility of case finding, rate of enrollment, data capture, and specimen collection and processing for a future, larger study of the effect of empiric antibiotics for all patients with advanced cirrhosis admitted to the hospital without an existing indication for new antibiotic use. There will be no subject specific outcomes to present to participants.

The results of this study may be published and/or presented at scientific meetings in accordance with customary academic, editorial, and ethical practices and requirements.