Supplementary Appendix

Study Protocol and Statistical Analysis Plan

Trial:	Antibiotic Choice On ReNal outcomes (ACORN) trial
Manuscript:	Effect of Cefepime versus Piperacillin-tazobactam in Adults Hospitalized with Acute Infection: A Randomized Clinical Trial
ClinicalTrials.gov:	NCT05094154
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This Supplementary Appendix contains the following items:

1) Initial Protocol [dated 10/19/2021]
2) Final Protocol [dated 7/27/2022]
3) Summary of changes to Study Protocol
4) Original Statistical Analysis Plan [submitted 7/27/2022]
5) Final Statistical Analysis Plan [published BMJ Open 3/10/2023]
6) Summary of changes to the Statistical Analysis Plan

Effect of Antibiotic Choice On ReNal Outcomes (ACORN)

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Study Schema

1.0 Study Summary

Title: Effect of Antibiotic Choice On ReNal Outcomes (ACORN)

Background: Sepsis is one of the most common causes of acute illness and death in the United States. Early, empiric broad-spectrum antibiotics are a mainstay of sepsis treatment. Two classes of antibiotics with activity against *Pseudomonas*, anti-pseudomonal cephalosporins and anti-pseudomonal penicillins, are commonly used for acutely ill adults with sepsis in current practice. Recent observational studies, however, have raised concern that anti-pseudomonal penicillins may cause renal toxicity. Anti-pseudomonal cephalosporins, by comparison, may be associated with a risk of neurotoxicity. Rigorous, prospective data regarding the comparative effectiveness and toxicity of these two classes of medications among acutely ill patients are lacking. We propose a randomized trial comparing the impact of anti-pseudomonal cephalosporins and anti-pseudomonal penicillins on renal outcomes of acutely ill patients.

Primary Aim:

- To compare the effect of anti-pseudomonal cephalosporins versus anti-pseudomonal penicillins on the incidence of acute kidney injury among acutely ill patients

Primary Hypothesis:

- Among acutely ill patients with sepsis, use of anti-pseudomonal cephalosporins will decrease the incidence of acute kidney injury (AKI), compared to anti-pseudomonal penicillins.

Inclusion Criteria:

1. Age ≥ 18 years old
2. Located in a participating emergency department or medical intensive care unit
3. Less than 12 hours from presentation to study hospital
4. Treating clinician initiating an order for an anti-pseudomonal cephalosporin or anti-pseudomonal penicillin

Exclusion Criteria:

1. Known receipt of > 1 dose of an anti-pseudomonal cephalosporin or anti-pseudomonal penicillin during the last 7 days
2. Current documented allergy to cephalosporins or penicillin
3. Known to be a prisoner
4. Treating clinicians feel that either an anti-pseudomonal cephalosporin or anti-pseudomonal penicillin is required or contraindicated for the optimal treatment of the patient, including for more directed antibiotic therapy against known prior resistant infections or suspected sepsis with an associated central nervous system infection

Consent:

- Given that both anti-pseudomonal cephalosporins and anti-pseudomonal penicillins are routinely used in usual care, the lack of established risk or benefit with either treatment group, the impracticability of obtaining informed consent prior to initiating antibiotics for acutely ill patients, a waiver of informed consent will be requested.

Randomization:

- Using a best-practices advisor embedded within the electronic health record, patients meeting all inclusion criteria and no exclusion criteria will be randomized in a 1:1 ratio to receive an anti-pseudomonal cephalosporin (treating clinicians' choice of cefepime or ceftazidime) or anti-pseudomonal penicillin.

Study Interventions:

- Anti-pseudomonal cephalosporin group: patients assigned to the anti-pseudomonal cephalosporin group will receive the treating clinicians' choice of either cefepime or ceftazidime.
- Anti-pseudomonal penicillin group: patients assigned to the anti-pseudomonal penicillin group will receive piperacillin-tazobactam or ticarcillin-clavulanate.
- For patients in both groups, treating clinicians will determine the dose and duration of the assigned antibiotic class. An EHR-based advisor will alert treating clinicians of group assignment and collect data regarding any adverse events and the reason for modification or discontinuation of antibiotics in the 7 days after randomization

Primary Efficacy Outcome:

- The primary outcome will be the highest stage of acute kidney injury (AKI) between enrollment and 14 days after enrollment. Stage of AKI will be defined by Kidney Disease: Improving Global Outcomes (KDIGO) AKI creatinine criteria. Death will be classified as worse than the highest stage of AKI. The outcome will be defined using the following 5-value ordinal scale ranging from the lowest value (0 = alive without having experienced AKI) to the highest value (4 = died).
    - 0 = No AKI
    - 1 = Stage 1 AKI (Creatinine increase by 1.5-1.9 times baseline OR increase by >= 0.3 mg/dL)
    - 2 = Stage 2 AKI (Creatinine increase by 2.0-2.9 times baseline)
    - 3 = Stage 3 AKI (Creatinine increase by >= 3.0 times baseline OR increase to >= 4.0 mg/dL OR New RRT)
    - 4 = Death

Exploratory Outcomes:

- Exploratory Renal Outcomes: acute kidney injury of stage 2 or higher as defined in the KDIGO criteria for creatinine level, new receipt of renal-replacement therapy, days alive and free of renal-replacement therapy during the 28 days after enrollment, the highest creatinine level during the 28 days after enrollment, the change from baseline to the highest creatinine level, the final creatinine level, and dialysis dependence at hospital discharge.
- Exploratory Neurologic Outcomes: Glasgow Coma Scale score during the 14 days after enrollment, neurologic component of SOFA score, Coma and Delirium Free Days in 14 days after enrollment
- Exploratory Clinical Outcomes: ICU-free days, ventilator-free days, vasopressor-free days, interaction between patients admitted to the ICU vs ward

Sample Size Considerations:

- Using data obtained from 820 patients during the creation and testing of the enrollment advisor, we measured the distribution of outcomes expected among patients in the anti-pseudomonal penicillin group. We calculated that enrolling 2,050 patients would provide 80% power at an alpha of 0.05 to detect an odds ratio for highest stage of AKI of 0.65.

2.0 Background

Sepsis is a common condition associated with high mortality and morbidity[1]. Antibiotics are an integral component of the management of patients with sepsis[2]. Each hour delay in antibiotic administration in sepsis is associated with an increase in mortality[3]. Clinical guidelines recommend early management bundles, including early broad-spectrum antibiotics, for patients with presumed sepsis in the emergency department and intensive care unit[2,4]. Since the specific organism causing an infection is rarely known at

clinical presentation, empiric broad-spectrum antibiotics are commonly prescribed[5]. For patients at risk for resistant organisms, the most common regimens include vancomycin (to cover gram-positive organisms including methicillin-resistant *Staphylococcus aureus*) and an anti-pseudomonal cephalosporin or anti-pseudomonal penicillin (to cover gram-negative organisms including *Pseudomonas*).

2.1 Anti-Pseudomonal Cephalosporins as Part of an Empiric Broad Spectrum Regimen

Cephalosporins are beta-lactam antibiotics that act by inhibiting the synthesis of the peptidoglycan layer of bacterial cell walls. They are commonly used for a variety of infections including empiric broad spectrum coverage for sepsis, suspected nosocomial infections, and meningitis. Several cephalosporins have anti-pseudomonal activity, including cefepime, a fourth-generation cephalosporin, and ceftazidime, a third-generation cephalosporin. Anti-pseudomonal cephalosporins have replaced anti-pseudomonal penicillins as the preferred agent for empiric antibiotic regimens based on observational evidence that anti-cephalosporins are associated with a lower incidence of AKI[6]. However, others have argued against this approach given the lack of randomized trials comparing the relative efficacy and safety of the two agents as well as observational data suggesting that cephalosporins may be associated with neuro-toxicity[7–9].

2.2 Anti-Pseudomonal Penicillins as Part of an Empiric Broad Spectrum Regimen

Penicillins are also beta-lactam anti-biotics with similar mechanisms of action to cephalosporins. Anti-pseudomonal penicillins, such as piperacillin, ureidopenicillin, and ticarcillin are typically administered with a beta-lactamase inhibitor such as tazobactam or clavulanate. In the United States the most commonly used anti-pseudomonal penicillins are piperacillin-tazobactam and ticarcillin-clavulanate. Anti-pseudomonal penicillins are the preferred agents for empiric broad spectrum coverage at many centers, and piperacillin-tazobactam, specifically, has the added benefit of treating anaerobic organisms. Conversely, penicillins do not cover meningitis due to poor central nervous system penetration.

2.3 Acute Kidney Injury during Critical Illness

Acute Kidney Injury (AKI) is a common complication of ICU admission. AKI is associated with a six to eight fold increase in mortality in ICU populations, [10,11] is therefore a common target of critical care trials. There are many potential contributors to AKI in critical illness including isotonic fluids[12], IV contrast administration, medication toxicities[13], and acute illnesses like sepsis. Sepsis is the most common cause of AKI and accounts for 40-50% of AKI in the intensive care unit (ICU)[14,15]. As the primary treatment for the underlying cause of sepsis, antibiotics are a critical treatment for acutely ill patients, but antibiotics may cause renal injury, and renally-cleared antibiotics may reach supratherapeutic levels in the setting of AKI.

2.4 Prior Evidence of the Effect of Antibiotic Choice on Acute Kidney Injury

Vancomycin has long been associated with AKI[16,17]. Recently, a number of retrospective observational analyses have examined a potential association between the concurrent administration of vancomycin and piperacillin-tazobactam and the development of AKI, compared with vancomycin alone[18–21]. These data, however, are likely to be confounded by indication bias and studies evaluating whether piperacillin-tazobactam causes more AKI than other anti-pseudomonal antibiotics have been inconclusive.[18,22–30]. Studies that limited their analyses to the first 72 hours of treatment (when antibiotic choices are empiric and not yet tailored based on microbiologic data), have not shown any association between piperacillin-tazobactam and kidney injury[31].

Based on this preliminary, observational data, however, some institutions have elected to change their preferred broad spectrum antibiotic regimens from one including an anti-pseudomonal to one including an anti-pseudomonal cephalosporins.

2.5 Rationale for a Trial of Anti-Pseudomonal Cephalosporins vs Anti-Pseudomonal Penicillins

Tens of thousands of patients each year receive either anti-pseudomonal cephalosporins and penicillins, but no randomized trials have ever compared their relative effectiveness or safety. Each class of medications has been hypothesized to have toxicities that may be relevant for acutely ill patients. Because the relationship between antibiotic choice (anti-pseudomonal cephalosporins or anti-pseudomonal penicillins) and clinically relevant outcomes, such as AKI, are unknown, clinical trial data is urgently needed. Rigorous high-quality evidence that anti-pseudomonal cephalosporins, compared to anti-pseudomonal penicillins, decreases, increases or has no impact on the risk of AKI would have the potential to change the care received by thousands of acutely ill adults each year.

To address this knowledge gap, we will conduct a prospective, randomized trial of acutely ill adults undergoing initiation of empiric antibiotics in the ED or ICU, comparing anti-pseudomonal cephalosporins vs anti-pseudomonal penicillins with regard to renal outcomes.

3.0 Rationale, Aims, and Hypotheses

In order to determine the effect of an anti-pseudomonal cephalosporin, compared to an anti-pseudomonal penicillin, on the incidence of acute kidney injury among acutely ill patients, a randomized trial is needed.

Study Aims:

- Primary:
    - To compare the effect of anti-pseudomonal cephalosporins versus anti-pseudomonal penicillins on the incidence of acute kidney injury among acutely ill patients
- Secondary:
    - To compare the effect of anti-pseudomonal cephalosporins vs anti-pseudomonal penicillins on in-hospital mortality, ICU length of stay, and ventilator days

Study Hypotheses

- Primary Hypothesis:
    - The use of anti-pseudomonal cephalosporins, compared to the use of anti-pseudomonal penicillins, will decrease the incidence of acute kidney injury among acutely ill adults

4.0 Study Description

In order to address the aims outlined above, we propose a randomized trial evaluating the impact of anti-pseudomonal cephalosporins versus anti-pseudomonal penicillins in the treatment of sepsis in acutely ill adults. Patients admitted to a study unit who are deemed by their clinical team to require empiric broad spectrum antibiotics and fulfill inclusion criteria without meeting exclusion criteria will be enrolled and randomly assigned to an anti-pseudomonal cephalosporin vs an anti-pseudomonal penicillin. Randomization, group assignment and delivery of the intervention will occur within the electronic health record (details in section 7). All other decisions regarding treatment will remain at the discretion of the

treating provider. Data will be collected prospectively from the medical record to determine the effect of the assigned interventions on procedural, physiologic, and clinical outcomes.

5.0 Inclusion/Exclusion Criteria

5.1 Inclusion Criteria:

1. Age ≥ 18 years old
2. Located in a participating emergency department or medical intensive care unit
3. Less than 12 hours from presentation to study hospital
4. Treating clinician initiating an order for an anti-pseudomonal cephalosporin or anti-pseudomonal penicillin

5.2 Exclusion Criteria:

1. Known receipt of > 1 dose of an anti-pseudomonal cephalosporin or anti-pseudomonal penicillin during the last 7 days
2. Current documented allergy to cephalosporins or penicillin
3. Known to be a prisoner
4. Treating clinicians feel that either an anti-pseudomonal cephalosporin or anti-pseudomonal penicillin is required or contraindicated for the optimal treatment of the patient, including for more directed antibiotic therapy against known prior resistant infections or suspected sepsis with an associated central nervous system infection

6.0 Enrollment/Randomization

6.1 Study Sites:

Emergency Department and Medical Intensive Care Unit at Vanderbilt University Medical Center

6.2 Study Population:

All adults with sepsis located in a participating unit for whom the treating clinician orders either an anti-pseudomonal cephalosporins or anti-pseudomonal penicillin within 12 hours of hospital presentation unless determined to meet an exclusion criteria. All eligible patients will be included and there will be no selection based on gender, race, weight or other clinical factors.

6.3 Enrollment:

At the time that a treating clinician in a participating emergency department or medical intensive care unit initiates an order for an anti-pseudomonal cephalosporin or anti-pseudomonal penicillin for a patient who meets all inclusion criteria, an advisor within the electronic health record (details in section 7) will prompt treating clinicians to record whether the patient meets any exclusion criteria. Patients not meeting any exclusion criteria will be enrolled and randomized. For patients who are determined to be ineligible, the advisor will track the number and reasons for exclusion. The time of randomization will be defined as "time zero" on "study day 0."

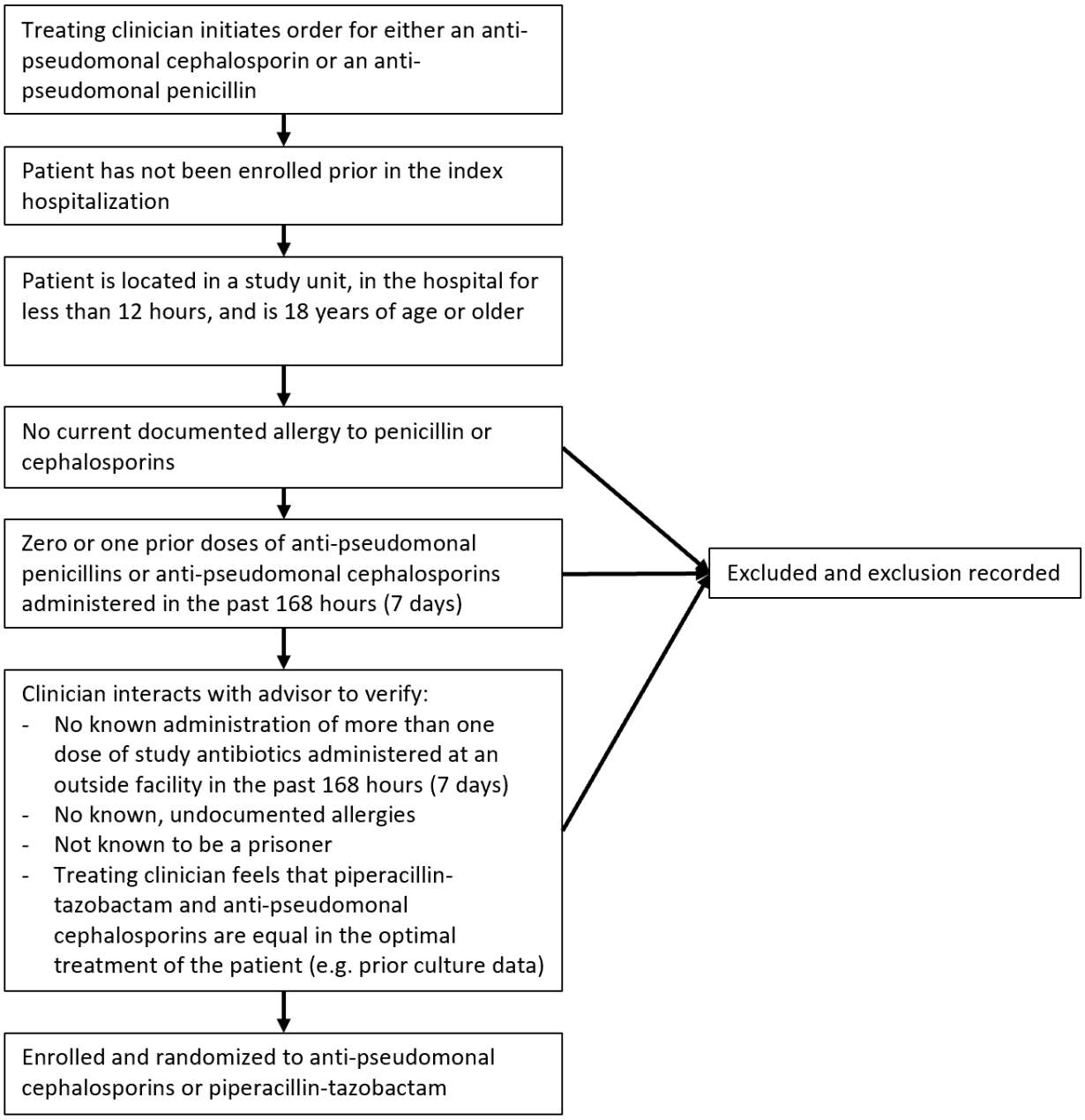

Figure 6: Enrollment Schema – When a treating clinician orders an anti-pseudomonal cephalosporin or anti-pseudomonal penicillin, tools within the electronic health record (details in section 7) will evaluate if the patient meets inclusion criteria (order placed within 12 hours of hospital presentation, age ≥ 18, and located in a participating unit), and the presence of documented allergy to penicillin or cephalosporins (an exclusion criteria). If the patient has not been previously enrolled in the trial during the index hospitalization, appears to meet all inclusion criteria, does not have a documented allergy to penicillin or cephalosporins, an ordering advisor will prompt the clinician to determine whether the patient meets any exclusion criteria. If the

treating clinician confirms that the patient does meet an exclusion criterion, the patient will be enrolled and randomized. The ordering advisor will track all exclusions.

6.4 Consent:

Anti-pseudomonal cephalosporins and anti-pseudomonal penicillins are routinely used in the care of acutely ill patients with sepsis in the emergency department and intensive care units at Vanderbilt University Medical Center. Currently, choice of empiric gram-negative coverage is based primarily on provider preference as there are no large randomized trials or evidence-based guidelines to support the choice of one empiric anti-pseudomonal therapy for sepsis over another. The concept of a randomized trial comparing anti-pseudomonal cephalosporins versus anti-pseudomonal penicillins has been discussed with the leaders of emergency department and intensive care units and representation from the infectious diseases and nephrology programs who agree that clinical equipoise exists regarding the choice of empiric anti-pseudomonal therapy for acutely ill adults with sepsis.

Because the interventions studied (1) are used as a part of routine care, (2) are interventions the patient would be exposed to even if not participating in the study, (3) have no prior high-quality data to suggest the superiority of one approach over the other, and (4) are equivalent options from the perspective of the treating provider (otherwise the patient is excluded), we feel the study presents minimal risk.

In addition to the minimal risk posed by the study, obtaining informed consent prior to participation would not be feasible or practicable. Sepsis is a medical emergency. Each hour of delay in the initiation of antibiotics for acutely ill patients with sepsis increases mortality by about 7%. For patients presenting with sepsis to the participating units, the average time between initiation of an order for an anti-pseudomonal antibiotic and its administration to the patient is 28 minutes. Obtaining prospective written informed consent during this interval is impracticable and risks delaying antibiotic administration. Moreover, acutely ill patients with sepsis are commonly delirious or unconscious, and a legally authorized representative (LAR) is not consistently present at the time of initiation of antibiotics. Because the trial determines choice of the initial anti-pseudomonal antibiotic, but defers decisions regarding subsequent doses of antibiotics (e.g., duration of therapy, escalation, de-escalation) to treating clinicians, the primary study procedure will be completed within 1 hour of meeting eligibility criteria.

Because the study presents minimal risk, would not adversely affect the welfare or privacy rights of the participant, and consent would be impracticable, we will request a waiver of informed consent.

6.5 Randomization:

A series of study group assignments will be generated by computerized randomization in a 1:1 ratio of intervention to control. Study group assignment will remain concealed to study personnel and treatment team until after the study team has confirmed that the patient does not meet any exclusion criteria and the patient has been enrolled. Following randomization, treating clinicians will be notified via the ordering advisor.

7.0 Study Procedures

7.1 Electronic Health Record (EHR) Based Screening for Eligible Patients

For the duration of the study, when a provider initiates an order for the administration of an intravenous anti-pseudomonal cephalosporin or anti-pseudomonal penicillin, a software application in the EHR will assess if the patient is eligible for the study. The application will assess that the patient meets all the inclusion criteria (located in study unit, age ≥ 18, in the hospital for less than 12 hours, and has not been previously enrolled during the hospitalization) and none of the exclusion criteria (current documented allergy to cephalosporin or penicillin class antibiotics, more than one prior administration of study antibiotics during the last 7 days). If the above criteria are met, an order advisor (Figure 7) will: 1) Inform the provider of the study, 2) solicit the presence of contraindications to either study drug, 3) (if patient meets all eligibility criteria) enroll and randomize the patient. If there are contraindications which were not established electronically, the advisor will ask the provider to select the reason.

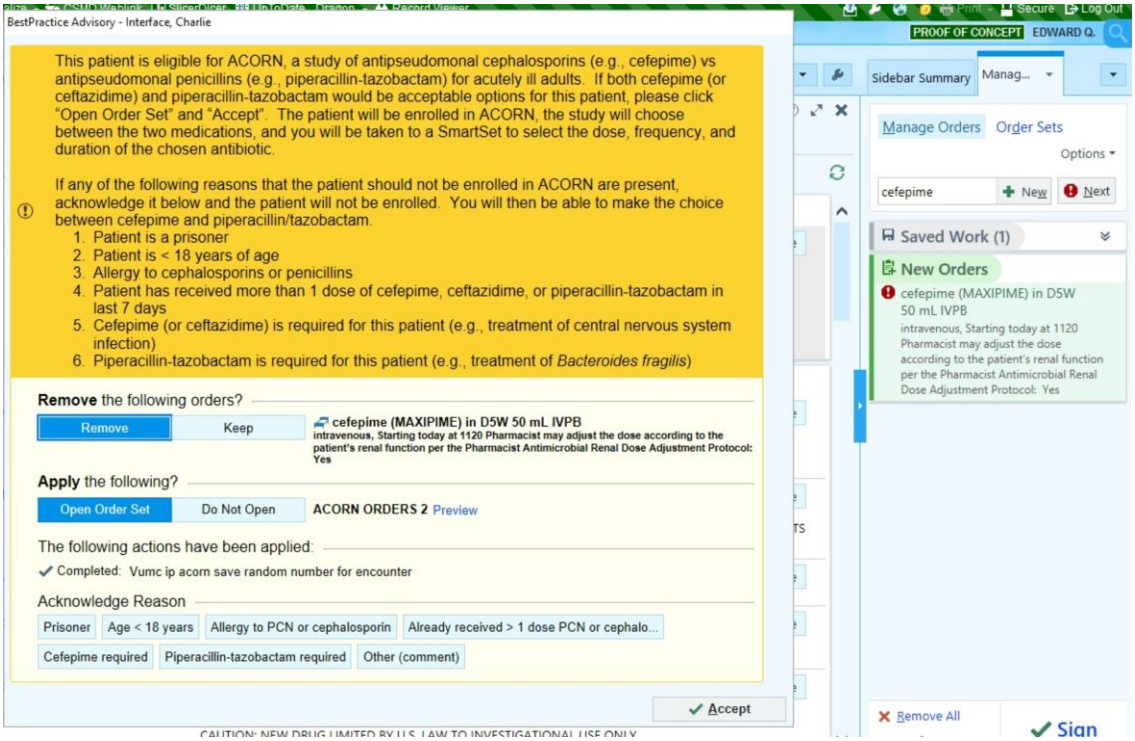

Figure 7: Order advisor informing providers of the study and soliciting other exclusion criteria

7.2 Antibiotic Ordering after Randomization

Once the participant is enrolled and randomized, the ordering advisor will guide the provider to the order one of the assigned study antibiotics. Dose, frequency, and duration will be at the discretion of treating clinicians and not affected by the advisor.

7.3 EHR-Based Tool to Capture Data on Antibiotic Modification and Adverse Events

In the 7 days after enrollment, if a clinician attempts the discontinue the study-related antibiotic order, an EHR-based advisor will remind the clinician of the treatment arm and if the treating clinician chooses to discontinue the antibiotic from the assigned group, the clinician will be asked for the rationale:

- Antibiotic tailoring (escalation or de-escalation) based on microbiologic data
- Undocumented or newly apparent allergy to either penicillins or cephalosporins

- Treating clinicians feel that either anti-pseudomonal cephalosporins or anti-pseudomonal penicillins are superior in the optimal treatment of the patient (provide reason why)
- Other (provider input rationale)
- Antibiotic induced adverse event

Data provided by the treating clinicians will be used for prospective safety monitoring and adverse event reporting.

7.4 Duration of the Intervention

Patients will be allocated to the anti-pseudomonal cephalosporin or anti-pseudomonal penicillin groups which will determine their initial antibiotic choice only. All further antibiotic decisions including, but not limited to, duration of antibiotics, changing based on new clinical or microbiological data, and switching between classes of anti-pseudomonal antibiotics will be left to the discretion of the treating team.

As described above, an EHR-based advisor will alert treating clinicians to group assignment and collect data for monitor for adverse events occurring in the seven days after randomization. The advisor will not impede the ability to change classes of antibiotic and will be used primarily for safety monitoring.

7. 5 Blinding:

It would be impractical to pursue blinding for the study. The medicines involved in this study are given at different doses with varying volumes of IV infusion. They are also given on different schedules varying as widely as 4 times a day to once daily. Furthermore, these dosing variations are impacted by renal function. Given the nature of the study intervention, patients, clinicians, and investigators will not be blinded to group assignment.

8.0 Data Collection:

8.1 In-Hospital Outcomes:

Primary Efficacy Outcome: Acute Kidney Injury Score between randomization and day 14. The acute kidney injury score is an ordinal outcome containing the stages of AKI as defined by KDIGO creatinine criteria, new renal replacement therapy (RRT), and death:

0 = No AKI
1 = Stage 1 AKI (Creatinine increase by 1.5-1.9 times baseline OR increase by >= 0.3 mg/dL)
2 = Stage 2 AKI (Creatinine increase by 2.0-2.9 times baseline)
3 = Stage 3 AKI (Creatinine increase by >= 3.0 times baseline OR increase to >= 4.0 mg/dL OR New RRT)
4 = Death

Death is defined as in-hospital mortality from any cause prior to hospital discharge, censored at 14 days. New RRT is defined as receipt of RRT at any point between ICU admission and hospital discharge, censored at 14 days. Baseline creatinine level will be determined by using a previously described hierarchical approach in which creatinine values obtained during the year before hospitalization are given priority over in-hospital measurements obtained before antibiotic administration. When no pre-enrollment

measurements are available, the baseline creatinine level is estimated with a previously described three-variable formula[32,33]. It is important to note that those patients with End-Stage Renal Disease (ESRD) would only be eligible to meet the "Death" component of the primary outcome.

Justification for the Primary Efficacy Outcome
This outcome is 1) validated for electronic assessment, 2) uses outcome thresholds for renal dysfunction defined by international nephrology organizations, 3) incorporates patient-centered outcomes (new RRT and death) that would be missed by a purely laboratory-based outcome, and 4) uses a hierarchal approach to analysis that counts rare but important patient-centered outcomes (new RRT, death) as worse than purely laboratory-based measures (stage 2 AKI).

Exploratory Outcomes:
- Exploratory Renal Outcomes: acute kidney injury of stage 2 or higher as defined in the KDIGO criteria for creatinine level within 14 days, acute kidney injury of stage 2 or higher as defined in the KDIGO criteria for creatinine level within 28 days, new receipt of renal-replacement therapy at 28 days, new receipt of renal-replacement therapy at 14 days, days alive and free of renal-replacement therapy during the 28 days after enrollment, days alive and free of renal-replacement therapy during the 14 days after enrollment, the highest creatinine level during the 28 days after enrollment, the change from baseline to the highest creatinine level, and the final creatinine level before hospital discharge.
- Exploratory Neurologic Outcomes: Glasgow Coma Scale (GCS) score during the 28 days after enrollment, neurologic component of SOFA score, Coma and Delirium Free Days in 28 days after enrollment
- Exploratory Clinical Outcomes: ICU-free days, ventilator-free days, vasopressor-free days, 28-day mortality, 14-day mortality, interaction between outcomes of patients admitted to the ICU vs wards

8.2 Baseline data:
Age, gender, height, weight, body mass index, race, APACHE II score, active medical problems at the time of admission, active comorbidities, comorbidities and medications known to increase risk of kidney or neurologic injury at enrollment (receipt of IV contrast in the previous 24 hours, receipt of ACE inhibitor or Angiotensin Receptor Blocker in the previous 24 hours), mean arterial pressure and vasopressor use prior to antibiotic receipt, analgesia and sedation use prior to antibiotic receipt (propofol, dexmedetomidine, fentanyl, hydromorphone, ketamine), pH, PaO2, PaCO2, respiratory rate, heart rate, oxygen saturation, temperature, lactic acid, elements of a basic metabolic panel (Na, K, Cl, HCO3, BUN, Creatinine, Glucose), magnesium, elements of a complete blood count (white blood cell count, hemoglobin, hematocrit, platelets), Confusion Assessment Method – ICU (CAM-ICU), Richmond Agitation Sedation Score (RASS), mechanical ventilation status and variables related to ventilation (FiO2, PEEP, respiratory rate, tidal volume), on renal replacement therapy prior to receipt of antibiotics, admission to ICU vs ward

8.3 Data from enrollment to hospital discharge:
Mean arterial pressure and vasopressor use, pH, PaO2, PaCO2, respiratory rate, heart rate, oxygen saturation, temperature, lactic acid, elements of a basic metabolic panel (Na, K, Cl, HCO3, BUN, Creatinine, Glucose), magnesium, elements of a complete blood count (white blood cell count,

hemoglobin, hematocrit, platelets), all microbiologic culture data (blood, urine, respiratory, wound, surgical, aspirate, body fluid), CAM-ICU, RASS, mechanical ventilation status and variables related to ventilation (FiO2, PEEP, respiratory rate, tidal volume), new-start renal replacement therapy, medications known to increase risk of kidney injury (receipt of IV contrast ACE inhibitor or Angiotensin Receptor Blocker, NSAIDs, trimethoprim-sulfamethoxazole, acyclovir, amphotericin B, diuretics), medications known to increase risk of neurologic injury (metronidazole, benzodiazepines, barbiturates, opiate pain medicines, typical and atypical anti-psychotics, propofol, dexmedetomidine, ketamine, corticosteroids), days spent in ICU, days spent in the hospital, date of intubation and extubation, date of death

8.4 Outcome Data:

Primary Outcome: All creatinine values from presentation to day 14, creatinine values prior to hospitalization, and dates and times of the following events, if applicable: presentation to the hospital, receipt of new renal replacement therapy, admission to the hospital, discharge from the hospital, death

Exploratory Renal Outcomes: All creatinine values from presentation to hospital discharge, creatinine values prior to hospitalization, and the dates and times of the following events, if applicable: presentation to the hospital, receipt of new renal replacement therapy, admission to the hospital, discharge from the hospital, death

Exploratory Neurologic Outcomes: All RASS values/dates/times from presentation to day 28, all CAM-ICU values/dates/time from presentation to day 28, all GCS values/dates/times from presentation to day 28

Exploratory Clinical Outcomes: Date and time of the following events, if applicable: presentation to the hospital, admission to the hospital, admission to the ICU, transfer from the ICU, discharge from the hospital, receipt of mechanical ventilation, discontinuation of mechanical ventilation, receipt of vasopressors, discontinuation of vasopressors, death

9.0 Risks and Benefits

In patients for whom the treating team has decided empiric broad spectrum antibiotics are required for the treatment of sepsis, there are currently no established risks or benefits to using anti-pseudomonal cephalosporins or anti-pseudomonal penicillins as empiric gram negative coverage. At this time, there is no reason to believe that participation in this study would expose patients to greater medical risks or benefits than those experienced by acutely ill patients requiring antibiotics as a part of routine care. The greater benefit of the study would be to society in the form of improved understanding of safe and effective empiric antibiotic selection for acutely ill patients with sepsis.

A potential risk to patients participating in this study involves the collection of protected health information (PHI). In order to limit the associated risks, the minimum amount of PHI necessary for study conduct will be collected. After collection, the data will be stored in a secure online database (REDCap) only accessible by the investigators. After publication, a de-identified database will be generated to protect participant privacy.

10.0 Statistical Considerations

Sample size considerations
Using data captured during the development and testing of the enrollment advisor (trial intervention) from 820 patients who would have been eligible for ACORN, we estimated the distribution of the primary outcome in the anti-pseudomonal penicillin group. A total of 61.2% of patients did not experience AKI or death, 4.9% had Stage I AKI, 4.3% had Stage II AKI, 8.0% had Stage III AKI or new RRT, and 21.5% died within 30 days of ICU admission. We calculated that obtaining 80% power at an alpha of 0.05 to detect an odds ratio of 0.65 for patients assigned to anti-pseudomonal cephalosporins would require a sample size of 2010. Assuming missing data for 40 patients, or < 5%, we plan to enroll 2050 patients.

Sample size re-estimation
At the planned interim analysis after 1025 patients, or roughly half of the intended enrollment, the DSMB will evaluate the distribution of the primary outcome in the anti-pseudomonal penicillin group. If required by the observed distribution of the primary outcome in the anti-pseudomonal penicillin group, the DSMB may recommend that the investigators increase the total sample size of the trial to maintain 80% power and an alpha of 0.05 to detect an odds ratio of 0.65.

Statistical Analysis:
Analysis principles
- Primary analysis will be conducted on an intention-to-treat basis (patients with protocol violations are analyzed per the assigned treatment arm).
- All hypothesis tests will be two sided, with an α of 0.05 unless otherwise specified.
- All analyses will be unadjusted unless otherwise specified.
- Pre-specified analyses of heterogeny of treatment effect based on baseline variables will be performed irrespective of treatment efficacy.

Trial profile:
We will present a Consolidated Standards of Reporting Trials diagram to detail the movement of patients through the study. This diagram will include total number of patients meeting inclusion criteria, number excluded and reason for exclusion, number enrolled and randomized in the study, number followed, and number analyzed.

Baseline Characteristics:
To assess randomization success, we will summarize in Table 1 the distribution of baseline variables across the study arms. Categorical variables will be reported as frequencies and percentages and continuous variables as either means with SDs or medians with interquartile ranges. Variables reported will include Demographics (age, gender, race, BMI, co-morbidities); Indication for antibiotics; Severity of Illness (APACHE II score); Acute Kidney Injury at enrollment; Delirium at enrollment

Primary Efficacy Outcome Analysis:
We will compare the primary outcome, the AKI ordinal outcome, between patients randomized to the anti-pseudomonal cephalosporins versus anti-pseudomonal penicillins groups. It is important to note that those patients with End-Stage Renal Disease (ESRD) would only be eligible to meet the “Death” component of the primary outcome.

The main analysis will be an intention-to-treat comparison of the primary outcome between the anti-pseudomonal cephalosporin and anti-pseudomonal penicillin groups. To do this, we will use an unadjusted, proportional odds model with group assignment (anti-pseudomonal cephalosporin, anti-pseudomonal penicillin) as the independent variable. For the purposes of declaring a statistically significant difference between groups in the primary endpoint, we will consider a two-sided P value of 0.05 as significant.

Secondary Analyses of the Primary Outcome
To account for potential confounders, we will develop an adjusted proportional odds regression model with the AKI ordinal outcome score (primary outcome) as the dependent variable and independent covariate of groups assignment, and relevant confounders (age, baseline creatinine, gender, mechanical ventilation at enrollment, receipt of inotropes at enrollment, AKI at enrollment, presence of CKD, admission location).

Secondary Analyses:
Analysis of Secondary and Exploratory Outcomes
We will conduct an intention-to-treat comparison of all secondary and exploratory outcomes between patients randomized to anti-pseudomonal cephalosporins and patients randomized to anti-pseudomonal penicillins. Continuous outcomes will be compared with the Mann-Whitney U test and categorical variables with the chi-square test or Fischer's exact test, as appropriate.

Heterogeny of Treatment Effect
We will examine the effect of group assignment on the primary outcome relative to a set of pre-specified baseline variables. These variables will be prespecified as part of a formal statistical analysis plan completed and made public prior to the completion of enrollment. A formal test of interaction will be used to evaluate for effect modification.

Presentation of Statistics
Continuous variables will be described as mean and standard deviation or median and interquartile range or bootstrapped 95% confidence intervals as appropriate. Categorical variables will be given as number and percentage. All between-group comparisons with continuous variables will be performed using Mann-Whitney U tests; categorical variables will be compared with chi-square testing or Fisher's exact test as appropriate.

Interim Analysis
We will plan for the DSMB to conduct a single interim analysis for efficacy and safety at the anticipated halfway point of the trial, after enrollment of 1025 patients. The stopping boundary for efficacy will be met if the P value for the difference between groups in the primary outcome is 0.001 or less. Use of the conservative Haybittle-Peto boundary ($P < 0.001$) will allow the final analysis to be performed using an unchanged level of significance ($P = 0.05$). Given the minimal risk nature of the study and current use of both interventions as a part of usual care, there will be no stopping boundary for futility. At the interim analysis, the DSMB will also monitor the distribution of the AKI ordinal outcome within the anti-pseudomonal penicillin group and may propose to increase the planned sample size to maintain the pre-planned power to detect an odds ratio of 0.65.

11.0 Reporting of Adverse Events or Unanticipated Problems

Assuring patient safety is an essential component of this protocol. All medications used in this trial are approved by the Food and Drug Administration and used in clinical practice with an established safety profile. This protocol further ensures safety of its participants through:

a) Exclusion criteria designed to prevent enrollment of patients likely to experience adverse events from the study antibiotics;
b) Systematic collection of safety outcomes relevant to the use of anti-pseudomonal cephalosporins and anti-pseudomonal penicillins in this setting;
c) Structured monitoring, assessment, recording, and reporting of adverse events.

11.1 Adverse Event Definitions

Adverse Event – An adverse event will be defined as any untoward or unfavorable medical occurrence in a human subject temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research. Any adverse event occurring during the research will be classified according to the following characteristics:

- **Seriousness** – An adverse event will be considered "serious" if it:
  - Results in death;
  - Is life-threatening (defined as placing the patient at immediate risk of death);
  - Results in inpatient hospitalization or prolongation of existing hospitalization;
  - Results in a persistent or significant disability or incapacity;
  - Results in a congenital anomaly or birth defect; or
  - Based upon appropriate medical judgment, may jeopardize the patient's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

- **Unexpectedness** – An adverse event will be considered "unexpected" if the nature, severity, or frequency is neither consistent with:
  - The known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in the protocol-related documents, such as the IRB-approved research protocol; nor
  - The expected natural progression of any underlying disease, disorder, or condition of the subject experiencing the adverse event and the subject's predisposing risk factor profile for the adverse event.

- **Relatedness** – The strength of the relationship of an adverse event to a study intervention or study procedure will be defined as follows:
  - Definitely Related: The adverse event follows (1) a reasonable, temporal sequence from a study procedure AND (2) cannot be explained by the known characteristics of the patient's clinical state or other therapies AND (3) evaluation of the patient's clinical state indicates to the investigator that the experience is definitely related to study procedures.
  - Probably or Possibly Related: The adverse event meets some but not all of the above criteria for "Definitely Related".

- Probably Not Related: The adverse event occurred while the patient was on the study but can reasonably be explained by the known characteristics of the patient's clinical state or other therapies.
- Definitely Not Related: The adverse event is definitely produced by the patient's clinical state or by other modes of therapy administered to the patient.
- Uncertain Relationship: The adverse event does not fit in any of the above categories.

11.2 Monitoring for Adverse Events

The time interval during which patients will be monitored for the occurrence of adverse events begins at randomization and ends at the first of hospital discharge or 28 days. Adverse events occurring before randomization or after hospital discharge or 28 days will not be collected. In this trial, enrollment, randomization, intervention delivery, monitoring for safety and adverse events and outcome assessment will all take place within the electronic health record. As described an EHR-based advisor will continuously monitor for discontinuation of study drug and require that clinicians identify reason for discontinuation. Every time a study drug is discontinued, investigators will be notified in real-time using an automated lists within the EHR. Investigators will investigate and adjudicate potential adverse as close as feasible to 24 hours after initial report by treating clinicians. Investigators will assess any potential adverse events for whether the adverse event meets the criteria for recording and reporting outlined below.

11.3 Recording and Reporting Adverse Events

The following types of adverse events will be recorded and reported:

- Adverse events that are Serious and Definitely Related, Probably or Possibly Related, or of Uncertain Relationship.
- Adverse events that are Unexpected and Definitely Related, Probably or Possibly Related, or of Uncertain Relationship.

Adverse events that do not meet the above criteria will not be recorded or reported. Adverse events that the investigator assesses to meet the above criteria for recording and reporting will be entered into the adverse event electronic case report form in the trial database. The investigator will record a preliminary assessment of each characteristic for the adverse event, including seriousness, unexpectedness, and relatedness. For any adverse event that is **serious AND unexpected**, and definitely related, probably or possibly related, or of uncertain relationship, the investigator will report the adverse event to the principal investigator **within 24 hours** of the investigator becoming aware of the adverse event. For any other adverse event requiring recording and reporting, the investigator will report the adverse event to the principal investigator **within 72 hours** of the investigator becoming aware of the adverse event. The principal investigator will make the final determination regarding each characteristic for the adverse event, including seriousness, expectedness, and relatedness.

For adverse events that meet the above criteria for recording and reporting, the coordinating center will notify the DSMB, the IRB, and the sponsor in accordance with the following reporting plan:

Characteristics of the Adverse Event	**Reporting Period**

Fatal or life-threatening (and therefore serious), unexpected, and definitely related, probably or possibility related, or of uncertain relationship.	Report to the DSMB, IRB, and sponsor within 7 days after notification of the event.
Serious but non-fatal and non-life-threatening, unexpected, and definitely related, probably or possibly related, or of uncertain relationship.	Report to DSMB, IRB, and sponsor within 15 days of notification of the event.
All other adverse events meeting criteria for recording and reporting.	Report to DSMB in regularly scheduled DSMB safety reports.

The investigator will distribute the written summary of the DSMB's periodic review of reported adverse events to the IRB in accordance with NIH guidelines: (http://grants.nih.gov/grants/guide/notice-files/not99-107.html).

11.4 Clinical Outcomes that may be Exempt from Adverse Event Recording and Reporting

In this study of critically ill patients at high risk for death and other adverse outcomes due to their underlying critical illness, clinical outcomes, including death and organ dysfunction, will be systematically collected and analyzed for all patients. The primary, secondary, and exploratory outcomes will be recorded and reported as clinical outcomes and not as adverse events unless treating clinicians or site investigators believe the event is Definitely Related or Probably or Possibly Related to the study intervention or study procedures. This approach – considering death and organ dysfunction as clinical outcomes rather than adverse events and systemically collecting these clinical outcomes for analysis – is common in ICU trials. This approach ensures comprehensive data on death and organ dysfunction for all patients, rather than relying on sporadic adverse event reporting to identify these important events. The following events are examples of study-specific clinical outcomes that would not be recorded and reported as adverse events unless treating clinicians or site investigators believe the event was Definitely Related or Probably or Possibly Related to the study intervention or study procedures:

- Death (all deaths occurring prior to hospital discharge or 28 days will be recorded);
- Organ dysfunction
    - Circulatory failure, including hypotension, cardiac arrest or shock with or without receipt of vasopressors;
    - Acute renal failure
    - Delirium or coma
- Duration of mechanical ventilation;
- Duration of ICU admission;
- Duration of hospitalization

Note: A study-specific clinical outcome may also qualify as a reportable adverse event. For example, anaphylaxis that the investigator considers Definitely Related to an anti-pseudomonal penicillin would be both recorded as a study-specific clinical outcome and reported as a Serious and Definitely Related Adverse Event.

11.5 Unanticipated Problems involving Risks to Subjects or Others

Investigators must also report to the principal investigator Unanticipated Problems Involving Risks to Subjects or Others ("Unanticipated Problems"), regardless of severity, associated with study procedures

within 24 hours of the investigator becoming aware of the Unanticipated Problem. An Unanticipated Problem is defined as any incident, experience, or outcome that meets all of the following criteria:

- Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol; and (b) the characteristics of the subject population being studied; AND
- Definitely Related or Probably or Possibly Related to participation in the research (as defined above in the section on characteristics of adverse events); AND
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Upon becoming aware of any event that may represent an Unanticipated Problem, the investigator will assess whether the event represents an Unanticipated Problem by applying the criteria described above. If the investigator determines that the event represents an Unanticipated Problem, the investigator will record the Unanticipated Problem in the Unanticipated Problem electronic case report form in the trial database. The investigators will obtain information about the Unanticipated Problem and report the Unanticipated Problem to the DSMB, IRB, and sponsor within 15 days of becoming aware of the Unanticipated Problem.

12.0 Privacy/Confidentiality Issues

At no time during the course of this study, its analysis, or its publication will patient identities be revealed in any manner. The minimum necessary data containing patient or provider identities will be collected. As quickly as feasible, all data collected will be uploaded into a password-protected computerized database maintained within a secure, web-based application for building and managing online databases (REDCap), or stored on secure servers with user-level access control. All patients will be assigned a unique study number for use in the computerized database. At the time of publication all identifiers will be removed.

13.0 Follow-up and Record Retention

Patients will be followed after enrollment for 28 days or until hospital discharge, whichever occurs first. Data collected from the medical record will be entered into the secure online database REDCap. All data will be maintained in the secure online database REDCap until the time of study publication. At the time of publication, a de-identified version of the database will be generated.

14.0 Data and Safety Monitoring Board (DSMB)

The principal role of the DSMB is to assure the safety of patients in the trial. They will regularly monitor data from this trial, review and assess the performance of its operations, and make recommendations to the steering committee and sponsor with respect to:

- Participant safety and risk/benefit ratio of study procedures and interventions
- Protocol amendments (with specific attention to study population, intervention, and study procedures)
- Adherence to the protocol requirements
- Completeness, quality, and planned analysis of data
- Ancillary study burden on participants and main study
- Possible early termination of the trial because of new external information, early attainment of study objectives, safety concerns, or inadequate performance

The DSMB will consist of members with expertise in critical care medicine, infectious disease, biostatistics, and clinical trials. Appointment of all members is contingent upon the absence of any conflicts of interest. All the members of the DSMB are voting members. The Principal Investigator and unblinded study biostatistician will be responsible for the preparation of all DSMB and adverse event reports. The DSMB will develop a charter and review the protocol and patient notification forms during its first meeting. Subsequent DSMB meetings will be scheduled in accordance with the DSMB Charter with the assistance of the Principal Investigator. The DSMB will have the ability to recommend that the trial end, be modified, or continued unchanged.

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Effect of Antibiotic Choice On ReNal Outcomes (ACORN)

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Study Schema

1.0 Study Summary

Title: Effect of Antibiotic Choice On ReNal Outcomes (ACORN)

Background: Sepsis is one of the most common causes of acute illness and death in the United States. Early, empiric broad-spectrum antibiotics are a mainstay of sepsis treatment. Two classes of antibiotics with activity against *Pseudomonas*, anti-pseudomonal cephalosporins and anti-pseudomonal penicillins, are commonly used for acutely ill adults with sepsis in current practice. Recent observational studies, however, have raised concern that anti-pseudomonal penicillins may cause renal toxicity. Anti-pseudomonal cephalosporins, by comparison, may be associated with a risk of neurotoxicity. Rigorous, prospective data regarding the comparative effectiveness and toxicity of these two classes of medications among acutely ill patients are lacking. We propose a randomized trial comparing the impact of anti-pseudomonal cephalosporins and anti-pseudomonal penicillins on renal outcomes of acutely ill patients.

Primary Aim:

- To compare the effect of anti-pseudomonal cephalosporins versus anti-pseudomonal penicillins on the incidence of acute kidney injury among acutely ill patients

Primary Hypothesis:

- Among acutely ill patients with sepsis, use of anti-pseudomonal cephalosporins will decrease the incidence of acute kidney injury (AKI), compared to anti-pseudomonal penicillins.

Inclusion Criteria:

1. Age ≥ 18 years old
2. Located in a participating emergency department or medical intensive care unit
3. Less than 12 hours from presentation to study hospital
4. Treating clinician initiating an order for an anti-pseudomonal cephalosporin or anti-pseudomonal penicillin

Exclusion Criteria:

1. Known receipt of > 1 dose of an anti-pseudomonal cephalosporin or anti-pseudomonal penicillin during the last 7 days
2. Current documented allergy to cephalosporins or penicillin

3. Known to be a prisoner
4. Treating clinicians feel that either an anti-pseudomonal cephalosporin or anti-pseudomonal penicillin is required or contraindicated for the optimal treatment of the patient, including for more directed antibiotic therapy against known prior resistant infections or suspected sepsis with an associated central nervous system infection

Consent:

- Given that both anti-pseudomonal cephalosporins and anti-pseudomonal penicillins are routinely used in usual care, the lack of established risk or benefit with either treatment group, the impracticability of obtaining informed consent prior to initiating antibiotics for acutely ill patients, a waiver of informed consent will be requested.

Randomization:

- Using a best-practices advisor embedded within the electronic health record, patients meeting all inclusion criteria and no exclusion criteria will be randomized in a 1:1 ratio to receive an anti-pseudomonal cephalosporin (treating clinicians' choice of cefepime or ceftazidime) or anti-pseudomonal penicillin.

Study Interventions:

- Anti-pseudomonal cephalosporin group: patients assigned to the anti-pseudomonal cephalosporin group will receive the treating clinicians' choice of either cefepime or ceftazidime.
- Anti-pseudomonal penicillin group: patients assigned to the anti-pseudomonal penicillin group will receive piperacillin-tazobactam or ticarcillin-clavulanate.
- For patients in both groups, treating clinicians will determine the dose and duration of the assigned antibiotic class. An EHR-based advisor will alert treating clinicians of group assignment and collect data regarding any adverse events and the reason for modification or discontinuation of antibiotics in the 7 days after randomization

Primary Efficacy Outcome:

- The primary outcome will be the highest stage of acute kidney injury (AKI) between enrollment and 14 days after enrollment. Stage of AKI will be defined by Kidney Disease: Improving Global Outcomes (KDIGO) AKI creatinine criteria. Death will be classified as worse than the highest stage of AKI. The outcome will be defined using the following 5-value ordinal scale ranging from the lowest value (0 = alive without having experienced AKI) to the highest value (4 = died).
    - 0 = No AKI
    - 1 = Stage 1 AKI (Creatinine increase by 1.5-1.9 times baseline OR increase by >= 0.3 mg/dL)
    - 2 = Stage 2 AKI (Creatinine increase by 2.0-2.9 times baseline)
    - 3 = Stage 3 AKI (Creatinine increase by >= 3.0 times baseline OR increase to >= 4.0 mg/dL OR New RRT)
    - 4 = Death

Secondary Outcomes:

- Secondary Renal Outcome: Major Adverse Kidney Events within 14 days (MAKE14): Composite outcome of death within 14 days, new renal replacement therapy within 14 days, or stage 2 or higher AKI at day 14.
- Secondary Neurologic Outcome: The number of days alive and free of coma and delirium in the 14 days after enrollment (Delirium and Coma-Free Days to day 14).

Exploratory Outcomes:

- Exploratory Renal Outcomes: Major Adverse Kidney Events within 28 days (MAKE28), highest stage of AKI or death between randomization and day 7, stage 2 or higher acute kidney injury as defined in the KDIGO criteria for creatinine level within 14 and 28 days after enrollment, new receipt of renal-replacement therapy within 14 and 28 days after enrollment, days alive and free of renal-replacement therapy during the 14 and 28 days after enrollment, the highest creatinine level within 28 days after enrollment, the change from pre-illness creatinine to the highest creatinine level with 28 days after enrollment, the final creatinine level before hospital discharge at 28 days, and ongoing receipt of renal replacement therapy at hospital discharge or 28 days, nephrology consultation.
- Exploratory Neurologic Outcomes: Worst Glasgow Coma Scale score during the 7, 14, and 28 days after enrollment, Delirium and Coma Free Days in 28 days after enrollment
- Exploratory Clinical Outcomes: ICU-free days, hospital-free days, ventilator-free days, vasopressor-free days, 28-day mortality, 14-day mortality, disposition of patients admitted from the ED (ward vs ICU), escalation of antibiotics defined by subsequent receipt of meropenem, meropenem-vaborbactam, imipenem, imipenem-relebactam, cefiderocol, ceftazidime-avibactam, ceftolozane-tazobactam, tigecycline, amikacin, tobramycin, gentamicin

Sample Size Considerations:

- Our original sample size was calculated from 820 patients during the creation and testing of the enrollment advisor, where we measured the distribution of outcomes expected among patients in the anti-pseudomonal penicillin group. We calculated that enrolling 2,050 patients would provide 80% power at an alpha of 0.05 to detect an odds ratio for highest stage of AKI of 0.65.

  Near the midpoint of the trial, we determined that about 75% of our patients received concurrent vancomycin, a key subgroup of interest. We increased the sample size to 2,500 patients to estimate the enrollment of the original sample size (2,050) in the subgroup of patients receiving concurrent vancomycin.

2.0 Background

Sepsis is a common condition associated with high mortality and morbidity[1]. Antibiotics are an integral component of the management of patients with sepsis[2]. Each hour delay in antibiotic administration in sepsis is associated with an increase in mortality[3]. Clinical guidelines recommend early management bundles, including early broad-spectrum antibiotics, for patients with presumed sepsis in the emergency department and intensive care unit[2,4]. Since the specific organism causing an infection is rarely known at clinical presentation, empiric broad-spectrum antibiotics are commonly prescribed[5]. For patients at risk for resistant organisms, the most common regimens include vancomycin (to cover gram-positive organisms including methicillin-resistant *Staphylococcus aureus*) and an anti-pseudomonal cephalosporin or anti-pseudomonal penicillin (to cover gram-negative organisms including *Pseudomonas*).

2.1 Anti-Pseudomonal Cephalosporins as Part of an Empiric Broad Spectrum Regimen

Cephalosporins are beta-lactam antibiotics that act by inhibiting the synthesis of the peptidoglycan layer of bacterial cell walls. They are commonly used for a variety of infections including empiric broad spectrum coverage for sepsis, suspected nosocomial infections, and meningitis. Several cephalosporins have anti-pseudomonal activity, including cefepime, a fourth-generation cephalosporin, and ceftazidime, a third-generation cephalosporin. Anti-pseudomonal cephalosporins have replaced anti-pseudomonal

penicillins as the preferred agent for empiric antibiotic regimens based on observational evidence that anti-cephalosporins are associated with a lower incidence of AKI[6]. However, others have argued against this approach given the lack of randomized trials comparing the relative efficacy and safety of the two agents as well as observational data suggesting that cephalosporins may be associated with neuro-toxicity[7–9].

2.2 Anti-Pseudomonal Penicillins as Part of an Empiric Broad Spectrum Regimen

Penicillins are also beta-lactam anti-biotics with similar mechanisms of action to cephalosporins. Anti-pseudomonal penicillins, such as piperacillin, ureidopenicillin, and ticarcillin are typically administered with a beta-lactamase inhibitor such as tazobactam or clavulanate. In the United States the most commonly used anti-pseudomonal penicillins are piperacillin-tazobactam and ticarcillin-clavulanate. Anti-pseudomonal penicillins are the preferred agents for empiric broad spectrum coverage at many centers, and piperacillin-tazobactam, specifically, has the added benefit of treating anaerobic organisms. Conversely, penicillins do not cover meningitis due to poor central nervous system penetration.

2.3 Acute Kidney Injury during Critical Illness

Acute Kidney Injury (AKI) is a common complication of ICU admission. AKI is associated with a six to eight fold increase in mortality in ICU populations, [10,11] is therefore a common target of critical care trials. There are many potential contributors to AKI in critical illness including isotonic fluids[12], IV contrast administration, medication toxicities[13], and acute illnesses like sepsis. Sepsis is the most common cause of AKI and accounts for 40-50% of AKI in the intensive care unit (ICU)[14,15]. As the primary treatment for the underlying cause of sepsis, antibiotics are a critical treatment for acutely ill patients, but antibiotics may cause renal injury, and renally-cleared antibiotics may reach supratherapeutic levels in the setting of AKI.

2.4 Prior Evidence of the Effect of Antibiotic Choice on Acute Kidney Injury

Vancomycin has long been associated with AKI[16,17]. Recently, a number of retrospective observational analyses have examined a potential association between the concurrent administration of vancomycin and piperacillin-tazobactam and the development of AKI, compared with vancomycin alone[18–21]. These data, however, are likely to be confounded by indication bias and studies evaluating whether piperacillin-tazobactam causes more AKI than other anti-pseudomonal antibiotics have been inconclusive.[18,22–30]. Studies that limited their analyses to the first 72 hours of treatment (when antibiotic choices are empiric and not yet tailored based on microbiologic data), have not shown any association between piperacillin-tazobactam and kidney injury[31].

Based on this preliminary, observational data, however, some institutions have elected to change their preferred broad spectrum antibiotic regimens from one including an anti-pseudomonal to one including an anti-pseudomonal cephalosporins.

2.5 Rationale for a Trial of Anti-Pseudomonal Cephalosporins vs Anti-Pseudomonal Penicillins

Tens of thousands of patients each year receive either anti-pseudomonal cephalosporins and penicillins, but no randomized trials have ever compared their relative effectiveness or safety. Each class of medications has been hypothesized to have toxicities that may be relevant for acutely ill patients. Because the relationship between antibiotic choice (anti-pseudomonal cephalosporins or anti-pseudomonal

penicillins) and clinically relevant outcomes, such as AKI, are unknown, clinical trial data is urgently needed. Rigorous high-quality evidence that anti-pseudomonal cephalosporins, compared to anti-pseudomonal penicillins, decreases, increases or has no impact on the risk of AKI would have the potential to change the care received by thousands of acutely ill adults each year.

To address this knowledge gap, we will conduct a prospective, randomized trial of acutely ill adults undergoing initiation of empiric antibiotics in the ED or ICU, comparing anti-pseudomonal cephalosporins vs anti-pseudomonal penicillins with regard to renal outcomes.

3.0 Rationale, Aims, and Hypotheses

In order to determine the effect of an anti-pseudomonal cephalosporin, compared to an anti-pseudomonal penicillin, on the incidence of acute kidney injury among acutely ill patients, a randomized trial is needed.

Study Aims:

- Primary:
    - To compare the effect of anti-pseudomonal cephalosporins versus anti-pseudomonal penicillins on the incidence of acute kidney injury among acutely ill patients
- Secondary:
    - To compare the effect of anti-pseudomonal cephalosporins vs anti-pseudomonal penicillins on in-hospital mortality, ICU length of stay, and ventilator days

Study Hypotheses

- Primary Hypothesis:
    - The use of anti-pseudomonal cephalosporins, compared to the use of anti-pseudomonal penicillins, will decrease the incidence of acute kidney injury among acutely ill adults

4.0 Study Description

In order to address the aims outlined above, we propose a randomized trial evaluating the impact of anti-pseudomonal cephalosporins versus anti-pseudomonal penicillins in the treatment of sepsis in acutely ill adults. Patients admitted to a study unit who are deemed by their clinical team to require empiric broad spectrum antibiotics and fulfill inclusion criteria without meeting exclusion criteria will be enrolled and randomly assigned to an anti-pseudomonal cephalosporin vs an anti-pseudomonal penicillin. Randomization, group assignment and delivery of the intervention will occur within the electronic health record (details in section 7). All other decisions regarding treatment will remain at the discretion of the treating provider. Data will be collected prospectively from the medical record to determine the effect of the assigned interventions on procedural, physiologic, and clinical outcomes.

5.0 Inclusion/Exclusion Criteria

5.1 Inclusion Criteria:

1. Age ≥ 18 years old
2. Located in a participating emergency department or medical intensive care unit
3. Less than 12 hours from presentation to study hospital
4. Treating clinician initiating an order for an anti-pseudomonal cephalosporin or anti-pseudomonal penicillin

5.2 Exclusion Criteria:

1. Known receipt of > 1 dose of an anti-pseudomonal cephalosporin or anti-pseudomonal penicillin during the last 7 days
2. Current documented allergy to cephalosporins or penicillin
3. Known to be a prisoner
4. Treating clinicians feel that either an anti-pseudomonal cephalosporin or anti-pseudomonal penicillin is required or contraindicated for the optimal treatment of the patient, including for more directed antibiotic therapy against known prior resistant infections or suspected sepsis with an associated central nervous system infection

6.0 Enrollment/Randomization

6.1 Study Sites:

Emergency Department and Medical Intensive Care Unit at Vanderbilt University Medical Center

6.2 Study Population:

All adults with sepsis located in a participating unit for whom the treating clinician orders either an anti-pseudomonal cephalosporins or anti-pseudomonal penicillin within 12 hours of hospital presentation unless determined to meet an exclusion criteria. All eligible patients will be included and there will be no selection based on gender, race, weight or other clinical factors.

6.3 Enrollment:

At the time that a treating clinician in a participating emergency department or medical intensive care unit initiates an order for an anti-pseudomonal cephalosporin or anti-pseudomonal penicillin for a patient who meets all inclusion criteria, an advisor within the electronic health record (details in section 7) will prompt treating clinicians to record whether the patient meets any exclusion criteria. Patients not meeting any exclusion criteria will be enrolled and randomized. For patients who are determined to be ineligible, the advisor will track the number and reasons for exclusion. The time of randomization will be defined as "time zero" on "study day 0."

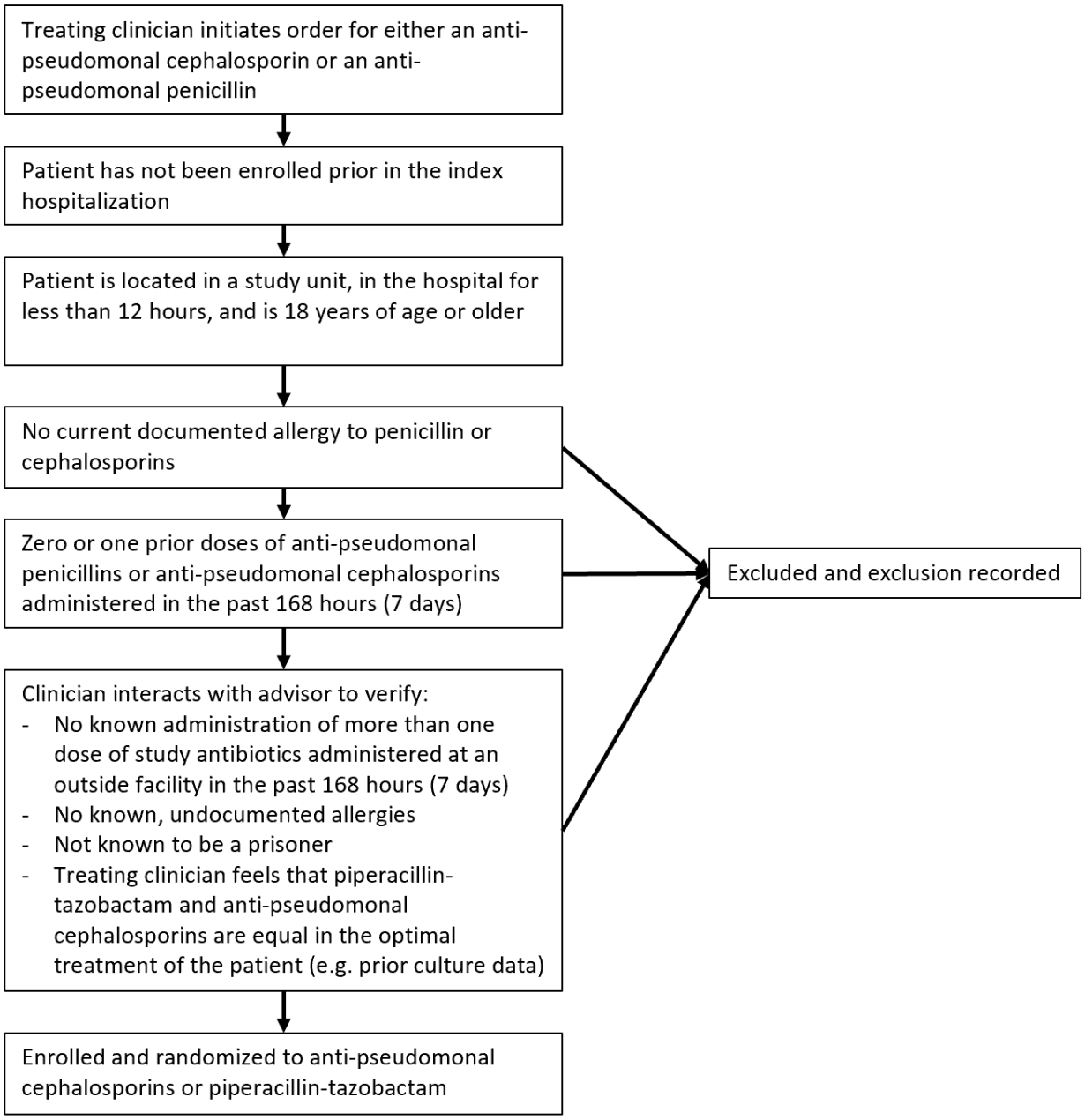

Figure 6: Enrollment Schema – When a treating clinician orders an anti-pseudomonal cephalosporin or anti-pseudomonal penicillin, tools within the electronic health record (details in section 7) will evaluate if the patient meets inclusion criteria (order placed within 12 hours of hospital presentation, age ≥ 18, and located in a participating unit), and the presence of documented allergy to penicillin or cephalosporins (an exclusion criteria). If the patient has not been previously enrolled in the trial during the index hospitalization, appears to meet all inclusion criteria, does not have a documented allergy to penicillin or cephalosporins, an ordering advisor will prompt the clinician to determine whether the patient meets any exclusion criteria. If the

treating clinician confirms that the patient does meet an exclusion criterion, the patient will be enrolled and randomized. The ordering advisor will track all exclusions.

6.4 Consent:

Anti-pseudomonal cephalosporins and anti-pseudomonal penicillins are routinely used in the care of acutely ill patients with sepsis in the emergency department and intensive care units at Vanderbilt University Medical Center. Currently, choice of empiric gram-negative coverage is based primarily on provider preference as there are no large randomized trials or evidence-based guidelines to support the choice of one empiric anti-pseudomonal therapy for sepsis over another. The concept of a randomized trial comparing anti-pseudomonal cephalosporins versus anti-pseudomonal penicillins has been discussed with the leaders of emergency department and intensive care units and representation from the infectious diseases and nephrology programs who agree that clinical equipoise exists regarding the choice of empiric anti-pseudomonal therapy for acutely ill adults with sepsis.

Because the interventions studied (1) are used as a part of routine care, (2) are interventions the patient would be exposed to even if not participating in the study, (3) have no prior high-quality data to suggest the superiority of one approach over the other, and (4) are equivalent options from the perspective of the treating provider (otherwise the patient is excluded), we feel the study presents minimal risk.

In addition to the minimal risk posed by the study, obtaining informed consent prior to participation would not be feasible or practicable. Sepsis is a medical emergency. Each hour of delay in the initiation of antibiotics for acutely ill patients with sepsis increases mortality by about 7%. For patients presenting with sepsis to the participating units, the average time between initiation of an order for an anti-pseudomonal antibiotic and its administration to the patient is 28 minutes. Obtaining prospective written informed consent during this interval is impracticable and risks delaying antibiotic administration. Moreover, acutely ill patients with sepsis are commonly delirious or unconscious, and a legally authorized representative (LAR) is not consistently present at the time of initiation of antibiotics. Because the trial determines choice of the initial anti-pseudomonal antibiotic, but defers decisions regarding subsequent doses of antibiotics (e.g., duration of therapy, escalation, de-escalation) to treating clinicians, the primary study procedure will be completed within 1 hour of meeting eligibility criteria.

Because the study presents minimal risk, would not adversely affect the welfare or privacy rights of the participant, and consent would be impracticable, we will request a waiver of informed consent.

6.5 Randomization:

A series of study group assignments will be generated by computerized randomization in a 1:1 ratio of intervention to control. Study group assignment will remain concealed to study personnel and treatment team until after the study team has confirmed that the patient does not meet any exclusion criteria and the patient has been enrolled. Following randomization, treating clinicians will be notified via the ordering advisor.

7.0 Study Procedures

7.1 Electronic Health Record (EHR) Based Screening for Eligible Patients

For the duration of the study, when a provider initiates an order for the administration of an intravenous anti-pseudomonal cephalosporin or anti-pseudomonal penicillin, a software application in the EHR will assess if the patient is eligible for the study. The application will assess that the patient meets all the inclusion criteria (located in study unit, age ≥ 18, in the hospital for less than 12 hours, and has not been previously enrolled during the hospitalization) and none of the exclusion criteria (current documented allergy to cephalosporin or penicillin class antibiotics, more than one prior administration of study antibiotics during the last 7 days). If the above criteria are met, an order advisor (Figure 7) will: 1) Inform the provider of the study, 2) solicit the presence of contraindications to either study drug, 3) (if patient meets all eligibility criteria) enroll and randomize the patient. If there are contraindications which were not established electronically, the advisor will ask the provider to select the reason.

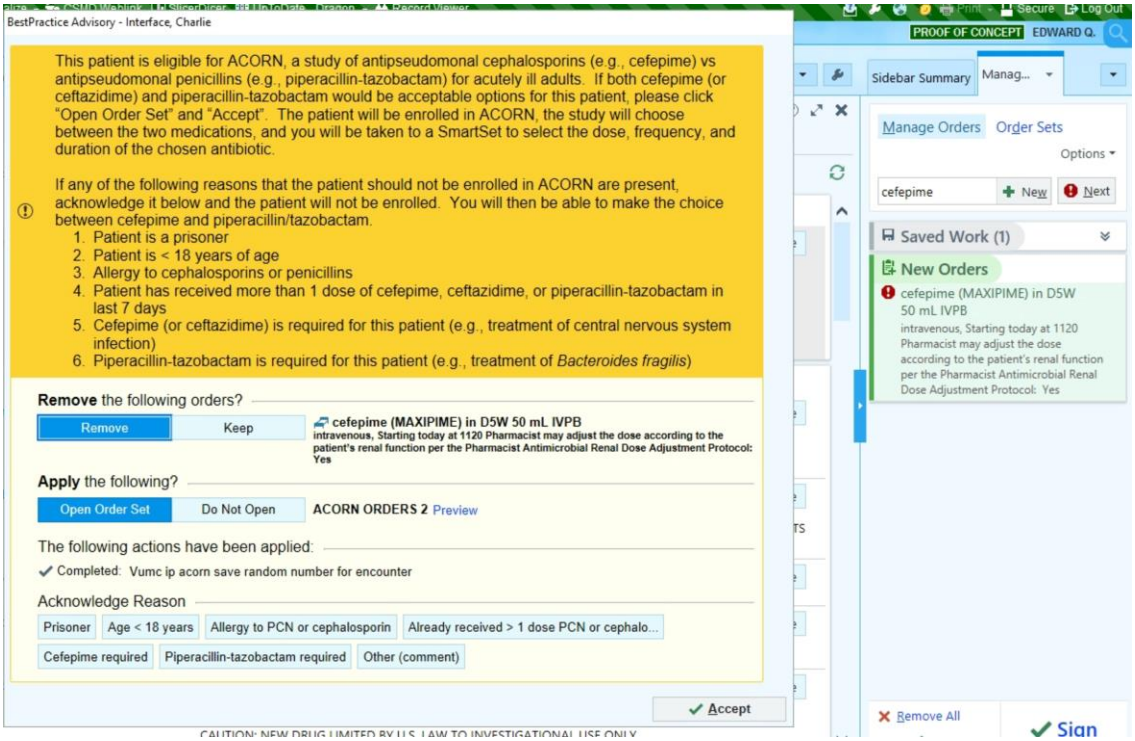

Figure 7: Order advisor informing providers of the study and soliciting other exclusion criteria

7.2 Antibiotic Ordering after Randomization

Once the participant is enrolled and randomized, the ordering advisor will guide the provider to the order one of the assigned study antibiotics. Dose, frequency, and duration will be at the discretion of treating clinicians and not affected by the advisor.

7.3 EHR-Based Tool to Capture Data on Antibiotic Modification and Adverse Events

In the 7 days after enrollment, if a clinician attempts the discontinue the study-related antibiotic order, an EHR-based advisor will remind the clinician of the treatment arm and if the treating clinician chooses to discontinue the antibiotic from the assigned group, the clinician will be asked for the rationale:

- Antibiotic tailoring (escalation or de-escalation) based on microbiologic data
- Undocumented or newly apparent allergy to either penicillins or cephalosporins

- Treating clinicians feel that either anti-pseudomonal cephalosporins or anti-pseudomonal penicillins are superior in the optimal treatment of the patient (provide reason why)
- Other (provider input rationale)
- Antibiotic induced adverse event

Data provided by the treating clinicians will be used for prospective safety monitoring and adverse event reporting.

7.4 Duration of the Intervention

Patients will be allocated to the anti-pseudomonal cephalosporin or anti-pseudomonal penicillin groups which will determine their initial antibiotic choice only. All further antibiotic decisions including, but not limited to, duration of antibiotics, changing based on new clinical or microbiological data, and switching between classes of anti-pseudomonal antibiotics will be left to the discretion of the treating team.

As described above, an EHR-based advisor will alert treating clinicians to group assignment and collect data for monitor for adverse events occurring in the seven days after randomization. The advisor will not impede the ability to change classes of antibiotic and will be used primarily for safety monitoring.

7. 5 Blinding:

It would be impractical to pursue blinding for the study. The medicines involved in this study are given at different doses with varying volumes of IV infusion. They are also given on different schedules varying as widely as 4 times a day to once daily. Furthermore, these dosing variations are impacted by renal function. Given the nature of the study intervention, patients, clinicians, and investigators will not be blinded to group assignment.

8.0 Data Collection:

8.1 In-Hospital Outcomes:

Primary Efficacy Outcome: Acute Kidney Injury Score between randomization and day 14. The acute kidney injury score is an ordinal outcome containing the stages of AKI as defined by KDIGO creatinine criteria, new renal replacement therapy (RRT), and death:

0 = No AKI
1 = Stage 1 AKI (Creatinine increase by 1.5-1.9 times baseline OR increase by >= 0.3 mg/dL)
2 = Stage 2 AKI (Creatinine increase by 2.0-2.9 times baseline)
3 = Stage 3 AKI (Creatinine increase by >= 3.0 times baseline OR increase to >= 4.0 mg/dL OR New RRT)
4 = Death

“Baseline” creatinine values are defined as the lowest prior creatinine values from three different timepoints: the pre-illness creatinine value, the peri-enrollment creatinine value, and the lowest prior on-study creatinine value. Death is defined as in-hospital mortality from any cause prior to hospital discharge, censored at 14 days. New RRT is defined as receipt of RRT at any point between ICU admission and hospital discharge, censored at 14 days.

Pre-illness creatinine level will be determined by using a previously described hierarchical approach in which creatinine values obtained during the year before hospitalization are given priority over in-hospital measurements obtained before antibiotic administration. When no pre-enrollment measurements are available, the pre-illness creatinine level is estimated with a previously described three-variable formula[32,33]. It is important to note that those patients with End-Stage Renal Disease (ESRD) would only be eligible to meet the "Death" component of the primary outcome.

Patients' peri-enrollment creatinine will be defined hierarchically using the creatinine value closest to enrollment in: (first) the 24 hours prior to enrollment, if available, and (second) the six hours after enrollment (if no value is available prior to enrollment). Prevalent AKI, or AKI that is present on admission and unrelated to the study intervention, will be defined by comparing the peri-enrollment creatinine to the pre-illness creatinine.

On-study creatinine will be defined as any creatinine value occurring after both the time of enrollment and the time of the peri-enrollment creatinine value. On-study creatinine values will be used to identify incident AKI and calculate the stage of AKI for the primary outcome.

Justification for the Primary Efficacy Outcome
This outcome is 1) validated for electronic assessment, 2) uses outcome thresholds for renal dysfunction defined by international nephrology organizations, 3) incorporates patient-centered outcomes (new RRT and death) that would be missed by a purely laboratory-based outcome, and 4) uses a hierarchal approach to analysis that counts rare but important patient-centered outcomes (new RRT, death) as worse than purely laboratory-based measures (stage 2 AKI).

Secondary Outcomes:
- Secondary Renal Outcome: Major Adverse Kidney Events within 14 days (MAKE14): Composite outcome of death within 14 days, new renal replacement therapy within 14 days, or stage 2 or higher AKI at day 14.
- Secondary Neurologic Outcome: The number of days alive and free of coma and delirium in the 14 days after enrollment (Delirium and Coma-Free Days to day 14).

Exploratory Outcomes:
- Exploratory Renal Outcomes: Major Adverse Kidney Events within 28 days (MAKE28), highest stage of AKI or death between randomization and day 7, stage 2 or higher acute kidney injury as defined in the KDIGO criteria for creatinine level within 14 and 28 days after enrollment, new receipt of renal-replacement therapy within 14 and 28 days after enrollment, days alive and free of renal-replacement therapy during the 14 and 28 days after enrollment, the highest creatinine level within 28 days after enrollment, the change from pre-illness creatinine to the highest creatinine level with 28 days after enrollment, the final creatinine level before hospital discharge at 28 days, and ongoing receipt of renal replacement therapy at hospital discharge or 28 days, nephrology consultation.
- Exploratory Neurologic Outcomes: Worst Glasgow Coma Scale score during the 7, 14, and 28 days after enrollment, Delirium and Coma Free Days in 28 days after enrollment
- Exploratory Clinical Outcomes: ICU-free days, hospital-free days, ventilator-free days, vasopressor-free days, 28-day mortality, 14-day mortality, disposition of patients admitted from the ED (ward vs ICU), escalation of antibiotics defined by subsequent receipt of meropenem, meropenem-

vaborbactam, imipenem, imipenem-relebactam, cefiderocol, ceftazidime-avibactam, ceftolozane-tazobactam, tigecycline, amikacin, tobramycin, gentamicin

8.2 Baseline data:

Age, sex, height, weight, body mass index, race, SOFA score, active medical problems at the time of admission, active comorbidities, comorbidities and medications known to increase risk of kidney or neurologic injury at enrollment, mean arterial pressure and vasopressor use prior to antibiotic receipt, analgesia and sedation use prior to antibiotic receipt, presence of sepsis define by Sepsis-3 criteria, transplant recipient status, presumed source of infection, on renal replacement therapy prior to receipt of antibiotics, admission to ICU vs ward

8.3 Data from enrollment to hospital discharge:

Mean arterial pressure and vasopressor use, pH, PaO2, PaCO2, respiratory rate, heart rate, oxygen saturation, temperature, lactic acid, elements of a basic metabolic panel, magnesium, elements of a complete blood count, all microbiologic culture data, CAM-ICU, RASS, GCS mechanical ventilation status and variables related to ventilation, nephrology consultation, new-start renal replacement therapy, indications for new renal replacement therapy among patients who received new renal replacement therapy, medications known to increase risk of kidney injury, medications known to increase risk of neurologic injury, days spent in ICU, days spent in the hospital, date of intubation and extubation, date of death

8.4 Outcome Data:

Primary Outcome: All creatinine values from presentation to day 14, creatinine values prior to hospitalization, and dates and times of the following events, if applicable: presentation to the hospital, receipt of new renal replacement therapy, admission to the hospital, discharge from the hospital, death

Exploratory Renal Outcomes: All creatinine values from presentation to hospital discharge, creatinine values prior to hospitalization, and the dates and times of the following events, if applicable: presentation to the hospital, receipt of new renal replacement therapy, admission to the hospital, discharge from the hospital, death, nephrology consultation

Exploratory Neurologic Outcomes: All RASS values/dates/times from presentation to day 28, all CAM-ICU values/dates/time from presentation to day 28, all GCS values/dates/times from presentation to day 28

Exploratory Clinical Outcomes: Date and time of the following events, if applicable: presentation to the hospital, admission to the hospital, admission to the ICU, transfer from the ICU, discharge from the hospital, receipt of mechanical ventilation, discontinuation of mechanical ventilation, receipt of vasopressors, discontinuation of vasopressors, death, antibiotic receipt

9.0 Risks and Benefits

In patients for whom the treating team has decided empiric broad spectrum antibiotics are required for the treatment of sepsis, there are currently no established risks or benefits to using anti-pseudomonal

cephalosporins or anti-pseudomonal penicillins as empiric gram negative coverage. At this time, there is no reason to believe that participation in this study would expose patients to greater medical risks or benefits than those experienced by acutely ill patients requiring antibiotics as a part of routine care. The greater benefit of the study would be to society in the form of improved understanding of safe and effective empiric antibiotic selection for acutely ill patients with sepsis.

A potential risk to patients participating in this study involves the collection of protected health information (PHI). In order to limit the associated risks, the minimum amount of PHI necessary for study conduct will be collected. After collection, the data will be stored in a secure online database (REDCap) only accessible by the investigators. After publication, a de-identified database will be generated to protect participant privacy.

10.0 Statistical Considerations

Sample size considerations
Using data captured during the development and testing of the enrollment advisor (trial intervention) from 820 patients who would have been eligible for ACORN, we estimated the distribution of the primary outcome in the anti-pseudomonal penicillin group. A total of 61.2% of patients did not experience AKI or death, 4.9% had Stage I AKI, 4.3% had Stage II AKI, 8.0% had Stage III AKI or new RRT, and 21.5% died within 30 days of ICU admission. We calculated that obtaining 80% power at an alpha of 0.05 to detect an odds ratio of 0.65 for patients assigned to anti-pseudomonal cephalosporins would require a sample size of 2010. Assuming missing data for 40 patients, or < 5%, we planned to enroll 2050 patients.

Sample size re-estimation
At the planned interim analysis after 1025 patients, or roughly half of the intended enrollment, the DSMB will evaluate the distribution of the primary outcome in the anti-pseudomonal penicillin group. If required by the observed distribution of the primary outcome in the anti-pseudomonal penicillin group, the DSMB may recommend that the investigators increase the total sample size of the trial to maintain 80% power and an alpha of 0.05 to detect an odds ratio of 0.65.

Near the midpoint of the trial, we determined that about 75% of the total population received concurrent vancomycin, an important subgroup of interest. We increased the sample size from the original 2,050 patients to 2,500 patients to estimate the original sample size in the subgroup of the receipt of concurrent vancomycin. Given our faster than expected enrollment, the trial is estimated to complete at the originally proposed endpoint. This would provide 92% power to detect and OR of 0.75 at an alpha of 0.05 in the primary analysis cohort. This was presented to the DSMB at the interim analysis who agreed with the sample size increase.

Statistical Analysis:
Analysis principles
- Primary analysis will be conducted on an intention-to-treat basis (patients with protocol violations are analyzed per the assigned treatment arm).
- All hypothesis tests will be two sided, with an α of 0.05 unless otherwise specified.
- All analyses will be unadjusted unless otherwise specified.

- Pre-specified analyses of heterogeny of treatment effect based on baseline variables will be performed irrespective of treatment efficacy.

Trial profile:
We will present a Consolidated Standards of Reporting Trials diagram to detail the movement of patients through the study. This diagram will include total number of patients meeting inclusion criteria, number excluded and reason for exclusion, number enrolled and randomized in the study, number followed, and number analyzed.

Baseline Characteristics:
To assess randomization success, we will summarize in Table 1 the distribution of baseline variables across the study arms. Categorical variables will be reported as frequencies and percentages and continuous variables as either means with SDs or medians with interquartile ranges. Variables reported will include Demographics (age, gender, race, BMI, co-morbidities); Indication for antibiotics; Severity of Illness (APACHE II score); Acute Kidney Injury at enrollment; Delirium at enrollment

Primary Efficacy Outcome Analysis:
We will compare the primary outcome, the AKI ordinal outcome, between patients randomized to the anti-pseudomonal cephalosporins versus anti-pseudomonal penicillins groups. It is important to note that those patients with End-Stage Renal Disease (ESRD) would only be eligible to meet the "Death" component of the primary outcome.

The main analysis will be an intention-to-treat comparison of the primary outcome between the anti-pseudomonal cephalosporin and anti-pseudomonal penicillin groups who received at least one dose of a study drug. To do this, we will use an unadjusted, proportional odds model with group assignment (anti-pseudomonal cephalosporin, anti-pseudomonal penicillin) as the independent variable. For the purposes of declaring a statistically significant difference between groups in the primary endpoint, we will consider a two-sided P value of 0.05 as significant.

Secondary Analyses of the Primary Outcome
To account for potential confounders, we will develop an adjusted proportional odds regression model with the AKI ordinal outcome score (primary outcome) as the dependent variable and independent covariate of groups assignment, and relevant confounders (age, peri-enrollment creatinine, sex, mechanical ventilation prior to enrollment, receipt of inotropes prior to enrollment, receipt of RRT prior to enrollment, SOFA score, presumed source of infection, enrollment location).

Secondary Analyses:
Analysis of Secondary and Exploratory Outcomes
We will conduct an intention-to-treat comparison of all secondary and exploratory outcomes between patients randomized to anti-pseudomonal cephalosporins and patients randomized to anti-pseudomonal penicillins. Continuous outcomes will be compared with the Mann-Whitney U test and categorical variables with the chi-square test or Fischer's exact test, as appropriate.

Heterogeny of Treatment Effect
We will examine the effect of group assignment on the primary outcome relative to a set of pre-specified baseline variables. These variables will be prespecified as part of a formal statistical analysis plan

completed and made public prior to the completion of enrollment. A formal test of interaction will be used to evaluate for effect modification.

Presentation of Statistics
Continuous variables will be described as mean and standard deviation or median and interquartile range or bootstrapped 95% confidence intervals as appropriate. Categorical variables will be given as number and percentage. All between-group comparisons with continuous variables will be performed using Mann-Whitney U tests; categorical variables will be compared with chi-square testing or Fisher's exact test as appropriate.

Interim Analysis
We will plan for the DSMB to conduct a single interim analysis for efficacy and safety at the anticipated halfway point of the trial, after enrollment of 1025 patients. The stopping boundary for efficacy will be met if the P value for the difference between groups in the primary outcome is 0.001 or less. Use of the conservative Haybittle-Peto boundary ($P < 0.001$) will allow the final analysis to be performed using an unchanged level of significance ($P = 0.05$). Given the minimal risk nature of the study and current use of both interventions as a part of usual care, there will be no stopping boundary for futility. At the interim analysis, the DSMB will also monitor the distribution of the AKI ordinal outcome within the anti-pseudomonal penicillin group and may propose to increase the planned sample size to maintain the pre-planned power to detect an odds ratio of 0.65.

11.0 Reporting of Adverse Events or Unanticipated Problems

Assuring patient safety is an essential component of this protocol. All medications used in this trial are approved by the Food and Drug Administration and used in clinical practice with an established safety profile. This protocol further ensures safety of its participants through:

a) Exclusion criteria designed to prevent enrollment of patients likely to experience adverse events from the study antibiotics;
b) Systematic collection of safety outcomes relevant to the use of anti-pseudomonal cephalosporins and anti-pseudomonal penicillins in this setting;
c) Structured monitoring, assessment, recording, and reporting of adverse events.

11.1 Adverse Event Definitions

Adverse Event – An adverse event will be defined as any untoward or unfavorable medical occurrence in a human subject temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research. Any adverse event occurring during the research will be classified according to the following characteristics:

- **Seriousness** – An adverse event will be considered "serious" if it:
  - Results in death;
  - Is life-threatening (defined as placing the patient at immediate risk of death);
  - Results in inpatient hospitalization or prolongation of existing hospitalization;
  - Results in a persistent or significant disability or incapacity;
  - Results in a congenital anomaly or birth defect; or

  - Based upon appropriate medical judgment, may jeopardize the patient's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

- **Unexpectedness** – An adverse event will be considered "unexpected" if the nature, severity, or frequency is neither consistent with:
  - The known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in the protocol-related documents, such as the IRB-approved research protocol; nor
  - The expected natural progression of any underlying disease, disorder, or condition of the subject experiencing the adverse event and the subject's predisposing risk factor profile for the adverse event.

- **Relatedness** – The strength of the relationship of an adverse event to a study intervention or study procedure will be defined as follows:
  - Definitely Related: The adverse event follows (1) a reasonable, temporal sequence from a study procedure AND (2) cannot be explained by the known characteristics of the patient's clinical state or other therapies AND (3) evaluation of the patient's clinical state indicates to the investigator that the experience is definitely related to study procedures.
  - Probably or Possibly Related: The adverse event meets some but not all of the above criteria for "Definitely Related".
  - Probably Not Related: The adverse event occurred while the patient was on the study but can reasonably be explained by the known characteristics of the patient's clinical state or other therapies.
  - Definitely Not Related: The adverse event is definitely produced by the patient's clinical state or by other modes of therapy administered to the patient.
  - Uncertain Relationship: The adverse event does not fit in any of the above categories.

11.2 Monitoring for Adverse Events

The time interval during which patients will be monitored for the occurrence of adverse events begins at randomization and ends at the first of hospital discharge or 28 days. Adverse events occurring before randomization or after hospital discharge or 28 days will not be collected. In this trial, enrollment, randomization, intervention delivery, monitoring for safety and adverse events and outcome assessment will all take place within the electronic health record. As described an EHR-based advisor will continuously monitor for discontinuation of study drug and require that clinicians identify reason for discontinuation. Every time a study drug is discontinued, investigators will be notified in real-time using an automated lists within the EHR. Investigators will investigate and adjudicate potential adverse as close as feasible to 24 hours after initial report by treating clinicians. Investigators will assess any potential adverse events for whether the adverse event meets the criteria for recording and reporting outlined below.

11.3 Recording and Reporting Adverse Events

The following types of adverse events will be recorded and reported:

- Adverse events that are Serious and Definitely Related, Probably or Possibly Related, or of Uncertain Relationship.

- Adverse events that are Unexpected and Definitely Related, Probably or Possibly Related, or of Uncertain Relationship.

Adverse events that do not meet the above criteria will not be recorded or reported. Adverse events that the investigator assesses to meet the above criteria for recording and reporting will be entered into the adverse event electronic case report form in the trial database. The investigator will record a preliminary assessment of each characteristic for the adverse event, including seriousness, unexpectedness, and relatedness. For any adverse event that is **serious AND unexpected**, and definitely related, probably or possibly related, or of uncertain relationship, the investigator will report the adverse event to the principal investigator **within 24 hours** of the investigator becoming aware of the adverse event. For any other adverse event requiring recording and reporting, the investigator will report the adverse event to the principal investigator **within 72 hours** of the investigator becoming aware of the adverse event. The principal investigator will make the final determination regarding each characteristic for the adverse event, including seriousness, expectedness, and relatedness.

For adverse events that meet the above criteria for recording and reporting, the coordinating center will notify the DSMB, the IRB, and the sponsor in accordance with the following reporting plan:

Characteristics of the Adverse Event	**Reporting Period**
Fatal or life-threatening (and therefore serious), unexpected, and definitely related, probably or possibility related, or of uncertain relationship.	Report to the DSMB, IRB, and sponsor within 7 days after notification of the event.
Serious but non-fatal and non-life-threatening, unexpected, and definitely related, probably or possibly related, or of uncertain relationship.	Report to DSMB, IRB, and sponsor within 15 days of notification of the event.
All other adverse events meeting criteria for recording and reporting.	Report to DSMB in regularly scheduled DSMB safety reports.

The investigator will distribute the written summary of the DSMB's periodic review of reported adverse events to the IRB in accordance with NIH guidelines: (http://grants.nih.gov/grants/guide/notice-files/not99-107.html).

11.4 Clinical Outcomes that may be Exempt from Adverse Event Recording and Reporting

In this study of critically ill patients at high risk for death and other adverse outcomes due to their underlying critical illness, clinical outcomes, including death and organ dysfunction, will be systematically collected and analyzed for all patients. The primary, secondary, and exploratory outcomes will be recorded and reported as clinical outcomes and not as adverse events unless treating clinicians or site investigators believe the event is Definitely Related or Probably or Possibly Related to the study intervention or study procedures. This approach – considering death and organ dysfunction as clinical outcomes rather than adverse events and systemically collecting these clinical outcomes for analysis – is common in ICU trials. This approach ensures comprehensive data on death and organ dysfunction for all patients, rather than relying on sporadic adverse event reporting to identify these important events. The following events are examples of study-specific clinical outcomes that would not be recorded and reported as adverse events unless treating clinicians or site investigators believe the event was Definitely Related or Probably or Possibly Related to the study intervention or study procedures:

- Death (all deaths occurring prior to hospital discharge or 28 days will be recorded);
- Organ dysfunction
    - Circulatory failure, including hypotension, cardiac arrest or shock with or without receipt of vasopressors;
    - Acute renal failure
    - Delirium or coma
- Duration of mechanical ventilation;
- Duration of ICU admission;
- Duration of hospitalization

Note: A study-specific clinical outcome may also qualify as a reportable adverse event. For example, anaphylaxis that the investigator considers Definitely Related to an anti-pseudomonal penicillin would be both recorded as a study-specific clinical outcome and reported as a Serious and Definitely Related Adverse Event.

11.5 Unanticipated Problems involving Risks to Subjects or Others

Investigators must also report to the principal investigator Unanticipated Problems Involving Risks to Subjects or Others ("Unanticipated Problems"), regardless of severity, associated with study procedures **within 24 hours** of the investigator becoming aware of the Unanticipated Problem. An Unanticipated Problem is defined as any incident, experience, or outcome that meets all of the following criteria:

- Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol; and (b) the characteristics of the subject population being studied; AND
- Definitely Related or Probably or Possibly Related to participation in the research (as defined above in the section on characteristics of adverse events); AND
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Upon becoming aware of any event that may represent an Unanticipated Problem, the investigator will assess whether the event represents an Unanticipated Problem by applying the criteria described above. If the investigator determines that the event represents an Unanticipated Problem, the investigator will record the Unanticipated Problem in the Unanticipated Problem electronic case report form in the trial database. The investigators will obtain information about the Unanticipated Problem and report the Unanticipated Problem to the DSMB, IRB, and sponsor within 15 days of becoming aware of the Unanticipated Problem.

12.0 Privacy/Confidentiality Issues

At no time during the course of this study, its analysis, or its publication will patient identities be revealed in any manner. The minimum necessary data containing patient or provider identities will be collected. As quickly as feasible, all data collected will be uploaded into a password-protected computerized database maintained within a secure, web-based application for building and managing online databases (REDCap), or stored on secure servers with user-level access control. All patients will be assigned a unique study number for use in the computerized database. At the time of publication all identifiers will be removed.

13.0 Follow-up and Record Retention

Patients will be followed after enrollment for 28 days or until hospital discharge, whichever occurs first. Data collected from the medical record will be entered into the secure online database REDCap. All data will be maintained in the secure online database REDCap until the time of study publication. At the time of publication, a de-identified version of the database will be generated.

14.0 Data and Safety Monitoring Board (DSMB)

The principal role of the DSMB is to assure the safety of patients in the trial. They will regularly monitor data from this trial, review and assess the performance of its operations, and make recommendations to the steering committee and sponsor with respect to:

- Participant safety and risk/benefit ratio of study procedures and interventions
- Protocol amendments (with specific attention to study population, intervention, and study procedures)
- Adherence to the protocol requirements
- Completeness, quality, and planned analysis of data
- Ancillary study burden on participants and main study
- Possible early termination of the trial because of new external information, early attainment of study objectives, safety concerns, or inadequate performance

The DSMB will consist of members with expertise in critical care medicine, infectious disease, biostatistics, and clinical trials. Appointment of all members is contingent upon the absence of any conflicts of interest. All the members of the DSMB are voting members. The Principal Investigator and unblinded study biostatistician will be responsible for the preparation of all DSMB and adverse event reports. The DSMB will develop a charter and review the protocol and patient notification forms during its first meeting. Subsequent DSMB meetings will be scheduled in accordance with the DSMB Charter with the assistance of the Principal Investigator. The DSMB will have the ability to recommend that the trial end, be modified, or continued unchanged.

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Antibiotic Choice On ReNal outcomes (ACORN) trial

Study Protocol Revision Sequence

10/19/2021	Original Protocol, version 1.0
11/10/2021	First patient enrolled
2/11/2021	**Amendment to Study Protocol, version 1.1** Exploratory outcomes were updated to match clinicaltrials.gov (with addition of disposition from the Emergency Department). Secondary outcome definitions were revised for clarity and internal inconsistencies in outcomes were resolved.
7/27/2022	**Amendment to Study Protocol, version 1.2** Sample size was increased to 2,500 at the time of the interim analysis to ensure sufficient patients in the subgroup receiving vancomycin at baseline. Protocol revision also included changes to match the pre-specified statistical analysis plan: 1. Approach to calculation of baseline creatinine was clarified. 2. Clarified outcome windows for existing exploratory outcomes. 3. Inclusion of additional exploratory outcomes: a. 7- day and 28-day renal and neurologic outcomes b. Escalation of antibiotics c. Hospital-free days d. Nephrology consultation 4. Changed the covariables included in the adjusted analysis of the primary outcome (a secondary analysis) to include enrollment SOFA score, presumed source of infection, and receipt of kidney replacement therapy at enrollment. 5. Clarified the definition of the primary analytic population
10/7/2022	Enrollment complete

Protocol and statistical analysis plan for the Antibiotic Choice On ReNal outcomes (ACORN) randomized clinical trial

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Abstract:

Introduction: Antibiotics are time-critical in the management of sepsis. When infectious organisms are unknown, patients are treated with empiric antibiotics to include coverage for gram-negative organisms, such as anti-pseudomonal cephalosporins and penicillins. However, in observational studies some anti-pseudomonal cephalosporins (e.g. cefepime) is associated with neurologic dysfunction while the most common anti-pseudomonal penicillin (piperacillin-tazobactam) is associated with acute kidney injury. No randomized control trials have compared these regimens. This manuscript describes the protocol and analysis plan for a trial designed to compare the effects of anti-pseudomonal cephalosporins and anti-pseudomonal penicillins among acutely ill patients receiving empiric antibiotics.

Methods and Analysis:

The Antibiotic Choice On ReNal outcomes (ACORN) trial is a prospective, single-center, non-blinded randomized trial being conducted at Vanderbilt University Medical Center. The trial will enroll 2,500 acutely ill adults receiving gram-negative coverage for treatment of infection. Eligible patients are randomized 1:1 to receive cefepime or piperacillin-tazobactam upon first order entry of a broad-spectrum antibiotic covering gram-negative organisms. The primary outcome is the highest stage of acute kidney injury and death occurring between enrollment and 14 days after enrollment. This will be compared between patients randomized to cefepime and randomized to piperacillin-tazobactam using an unadjusted proportional odds regression model. The secondary outcomes are Major Adverse Kidney Events through day 14 and number of days alive and free of delirium and coma in 14 days after enrollment. Enrollment began on November 10, 2021 and is expected to be completed in December 2022.

Ethics and Dissemination:

The trial was approved by the Vanderbilt University Medical Center institutional review board with a waiver of informed consent. Results will be submitted in a peer-reviewed journal and presented at scientific conferences.

Trial Registration:

This trial was registered with ClinicalTrials.gov (NCT05094154) on October 26, 2021, prior to enrollment of the first patient on November 10, 2021.

Strengths and Limitations:

- This ongoing pragmatic trial will compare the effects of cefepime vs piperacillin-tazobactam on acute kidney injury and death among acutely ill adults receiving gram-negative antibiotic therapy in the Emergency Department or Intensive Care Unit.
- Strengths: Broad eligibility criteria, inclusion of a range of indications for antibiotic therapy, and use of the electronic health record to screen for eligible patients and facilitate delivery of the assigned intervention will increase the external validity of the findings
- Limitations: After concealed randomization, patients, clinicians, and investigators are unblinded to study group assignment. Because urine output is not systematically available across all care, the outcome of AKI is based on creatinine measurements.

Introduction:

Antibiotics are necessary for management of patients with sepsis[1] but can cause unintended adverse effects on organ function[2]. Since specific organisms causing infection is often unknown, empiric broad-spectrum antibiotics are commonly prescribed. For patients at risk for resistant organisms, common regimens include gram-positive coverage (i.e. vancomycin) and gram-negative coverage with an anti-pseudomonal cephalosporin or penicillin, predominantly cefepime or piperacillin-tazobactam[1].

Because the medications are considered to have comparable anti-pseudomonal activity, discussion surrounding choice has focused on adverse effects. Some observational studies have reported an association between receipt of piperacillin-tazobactam and acute kidney injury (AKI)[3,4], particularly among patients receiving vancomycin[5–7]. Other studies have shown no relationship between piperacillin-tazobactam and AKI[8,9]. AKI is common during hospitalization[10], and there are many potential contributors including isotonic fluids[11,12], medications, and acute illnesses like sepsis[13,14].

Similarly, an association between cephalosporins and neurotoxicity manifesting as delirium and coma has been observed.[15–17] Delirium, acute brain dysfunction characterized by fluctuations in mental status, inattention, altered consciousness, and disorganized thinking,[18] is also a common complication of hospitalization. In Intensive Care Unit (ICU) populations, delirium is predictive of mortality, prolonged length of stay, and long-term cognitive impairment[19,20]. The incidence of cephalosporin-induced neurotoxicity is unknown but has been reported to increase in-hospital mortality[21].

A randomized controlled trial would overcome limitations of observational data, but none are known to exist[22]. Rigorous, high-quality evidence assessing risk of AKI and neurotoxicity after exposure to anti-pseudomonal antibiotics would have potential to change care received by thousands of acutely ill adults annually. To address the lack of available evidence, we are conducting a prospective, randomized trial comparing anti-pseudomonal cephalosporins and anti-pseudomonal penicillins among acutely ill adults in the Emergency Department (ED) or ICU.

Methods and Analysis:

This manuscript was written in accordance with Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines (Table 1, Supplement 1)[23]. The Learning Healthcare System (LHS) Platform at Vanderbilt University Medical Center conducts research studies using a unique model that leverages pragmatic, randomized, controlled clinical trials embedded within usual care[24]. The LHS Platform is composed of stakeholders from across the enterprise and supports projects in both the pediatric and adult inpatient and outpatient settings (Supplement 2). LHS Platform studies focus on comparative effectiveness, implementation science, and programmatic evaluation approaches[25,26].

Study Design

The Antibiotic Choice On ReNal outcomes (ACORN) trial is a pragmatic, single-center, unblinded, parallel-group, randomized trial comparing anti-pseudomonal cephalosporins to anti-pseudomonal penicillins among acutely ill adults receiving gram-negative antibiotics in the ED and ICU. At this center, the predominant anti-pseudomonal cephalosporin is cefepime and the predominant anti-pseudomonal penicillin is piperacillin-tazobactam. The primary outcome is highest stage of AKI or death in 14 days. The trial protocol was approved by the institutional review board at Vanderbilt University Medical Center and registered prior to initiation of enrollment (NCT05094154). An independent data and safety monitoring board (DSMB) monitors the progress and safety of the trial.

	STUDY PERIOD				
	Eligibility Screen	**Randomization & Allocation**	**Post-allocation**		**Final Outcome Assessment**
TIMEPOINT	*Order entry for CEF or PTZ*	EHR enrollment advisor	*7 days after enrollment*	*14 days after enrollment*	*Discharge or 28 days after enrollment*
ENROLLMENT:		X			
EHR-based inclusion criteria screening	X				
Manual screening for exclusion criteria by treating clinicians	X				
Allocation		X			
INTERVENTIONS:					
Cefepime		X	X		
Piperacillin-tazobactam		X	X		
ASSESSMENTS:					
Baseline variables	X	X			
Adverse events		X	X	X	X
Primary and secondary outcome		X	X	X	
Exploratory outcomes			X	X	X

Table 1. Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist. Enrollment, interventions, and assessments. CEF, Cefepime; PTZ, piperacillin-tazobactam; EHR, Electronic health record;

Study Population

Inclusion criteria:

1. Age ≥ 18 years old
2. Located in a participating ED or ICU
3. Less than 12 hours between presentation to study hospital
4. Treating clinician initiating an order for an anti-pseudomonal cephalosporin or anti-pseudomonal penicillin

Exclusion criteria:

1. Known receipt of > 1 dose of an anti-pseudomonal cephalosporin or anti-pseudomonal penicillin during the last 7 days
2. Current documented allergy to cephalosporins or penicillin
3. Known to be a prisoner
4. Treating clinicians feel that either an anti-pseudomonal cephalosporin or anti-pseudomonal penicillin is required or contraindicated for the optimal treatment of the patient, including for more directed antibiotic therapy against known prior resistant infections or suspected sepsis with an associated central nervous system infection

Screening and Enrollment

When a treating clinician in a participating ED or ICU initiates an order for cefepime or piperacillin-tazobactam for a patient who meets all inclusion criteria, a clinical decision support (CDS) tool will 1) inform the provider of the study, 2) query the provider regarding the presence of any exclusion criteria, and if none are present, 3) enroll and randomize the patient. For patients who meet an exclusion criterion, the reason is recorded (Fig. 1).

Analysis population

The primary goal is the exploration of uncommon safety effects, therefore the population for primary analysis will include all patients who were randomized and received at least one dose of either study drug in the 168 hours (7 days) after

randomization. A sensitivity analysis will include all patients randomized, including those who never received either cefepime or piperacillin/tazobactam.

Randomization and Treatment Allocation

Study group assignments are generated by computerized randomization in a 1:1 ratio of intervention to control. Study group assignment will remain concealed until the team has confirmed the patient does not meet any exclusion criteria and the patient has been enrolled. The CDS tool will advise the clinician of group assignment following randomization.

Study Interventions

For patients assigned to cefepime, the CDS tool will guide providers to intravenous cefepime. For patients assigned to piperacillin-tazobactam, the CDS tool will guide providers to intravenous piperacillin-tazobactam. The CDS tool will display a standardized table of dose by glomerular filtration rate, but decisions regarding dose, frequency, and duration will be the treating clinician's discretion.

In the 168 hours (7 days) following enrollment, any new order for cefepime or piperacillin-tazobactam will open a CDS tool, which displays group assignment and allows clinicians to (re)order the assigned antibiotic or provide a reason for ordering the non-assigned antibiotic. Similarly, if the assigned antibiotic is discontinued, the CDS tool will solicit a rationale for discontinuation, including antibiotic tailoring, newly apparent allergy to either cephalosporins or penicillins, or clinician preference.

The CDS tool influences only the choice of the initial anti-pseudomonal antibiotic. Treating clinicians determine concurrent administration of other antibiotics (e.g., vancomycin, metronidazole), duration of therapy, escalation, de-escalation, approach to source control, and use of culture and laboratory data to modify antibiotic therapy.

Data Collection

Trial personnel will monitor for adverse events daily and will record the following data elements at the time of enrollment by manual review of the health record (Supplement 3 and 4):

- Presence of sepsis, defined by Sepsis-3 criteria[27]
- Transplant recipient status
- Receipt of renal replacement therapy (RRT) prior to enrollment
- Presumed source of infection organized into groups based on previously published data[28]

All other data will be obtained using electronic exports from the health record. The following variables are collected:

1. Collected at baseline: Age, sex, height, weight, body mass index, race, Sequential Organ Failure Assessment (SOFA) score, active medical problems at the time of admission, active comorbidities, comorbidities and medications known to increase risk of kidney or neurologic injury at enrollment, mean arterial pressure and vasopressor use prior to antibiotic receipt, analgesia and sedation use prior to antibiotic receipt, admission to ICU vs ward
2. Collected from randomization to hospital discharge: Mean arterial pressure and vasopressor use, pH, PaO2, PaCO2, respiratory rate, heart rate, oxygen saturation, temperature, lactic acid, elements of a basic metabolic panel, magnesium, elements of a complete blood count, antibiotic receipt, all microbiologic culture data, Confusion Assessment Method for the ICU (CAM-ICU), Richmond Agitation Sedation Score (RASS), Glasgow Coma Scale (GCS), mechanical ventilation status and variables related to ventilation, nephrology consultation, receipt of new RRT, indications for new RRT among patients who received new RRT, medications known to increase risk of kidney injury, medications known to increase risk of neurologic injury, admitting team, date of admission, days spent in the ICU, days spent in the hospital, date of intubation(s) and extubation(s), date of discharge, and date of death.

Primary Outcome

The primary outcome will be a combination of the highest stage of AKI and death between randomization and day 14. The stages of AKI are defined using creatinine

measurements and the “Kidney Disease: Improving Global Outcomes (KDIGO)”[29] criteria. The score will range from 0 (best value) to 4 (worst value):

0 = No AKI

1 = Stage 1 AKI (Creatinine increased by 1.5-1.9 times baseline OR increase by >= 0.3 mg/dL)

2 = Stage 2 AKI (Creatinine increased by 2.0-2.9 times baseline)

3 = Stage 3 AKI (Creatinine increased by >= 3.0 times baseline OR increase to >= 4.0 mg/dL OR New RRT)

4 = Death

“Baseline” creatinine values are defined as the lowest prior creatinine values from three different timepoints: the pre-illness creatinine value, the peri-enrollment creatinine value, and the lowest prior on-study creatinine value as defined below. Death is defined as mortality from any cause occurring prior to or on the end of study day 14, censored at hospital discharge. RRT is defined as receipt of RRT at any point between randomization and the end of study day 14, censored at hospital discharge. Patients who are receiving RRT prior to enrollment can only experience values of 0 (patient did not die) or 4 (patient died) because they are ineligible to experience changes in creatinine or new receipt of RRT that define levels 1 through 3.

Patients’ pre-illness creatinine will be defined as the lowest serum creatinine between 12 months and 24 hours prior to enrollment. For patients for whom a value is unavailable, a pre-illness creatinine value will be estimated using a previously-described three-variable formula [creatinine = 0.74 − 0.2 (if female) + 0.08 (if African American) + 0.003 × age (in years)][30]. There are no validated estimations of creatinine without race but we will evaluate the effect of social constructs by fitting models both with and without race in a sensitivity analysis.

Patients’ peri-enrollment creatinine will be defined hierarchically using the creatinine value closest to enrollment in: (first) the 24 hours prior to enrollment, if available, and (second) the six hours after enrollment (if no value is available prior to enrollment). Prevalent AKI, or AKI that is present on admission and unrelated to the

study intervention, will be defined by comparing the peri-enrollment creatinine to the pre-illness creatinine.

On-study creatinine will be defined as any creatinine value occurring after both the time of enrollment and the time of the peri-enrollment creatinine value. On-study creatinine values will be used to identify incident AKI and calculate the stage of AKI for the primary outcome.

The primary outcome will be calculated as follows:

- Patients who survive without new RRT and do not experience an on-study creatinine value that is at least 0.3 mg/dL higher than the peri-enrollment value or any preceding on-study value, and whose on-study creatinine is never more than 1.5 times the peri-enrollment value or any preceding on-study value, will be considered not to have experienced incident AKI and will receive a value of 0 for the primary outcome.
- Among patients who survive and experience AKI (have on-study creatinine value that is at 1.5 times or at least 0.3 mg/dL higher than the peri-enrollment value or any preceding on-study value), the score for the primary outcome will be determined by the stage of AKI and classified as follows:
    a. A value of 1 if the highest on-study creatinine after qualifying for AKI is less than 2.0 times the lowest of the pre-illness creatinine value, the peri-enrollment creatinine value, and the lowest prior on-study creatinine value (baseline creatinine);
    b. A value of 2 if the highest on-study creatinine after qualifying for AKI is at least 2.0 times and less than 3.0 times the lowest of the pre-illness creatinine value, the peri-enrollment creatinine value, and the lowest prior on-study creatinine value (baseline creatinine); and
    c. A value of 3 if the highest on-study creatinine after qualifying for AKI is at least 3.0 times the lowest of the pre-illness creatinine value, the peri-enrollment creatinine value, and the lowest prior on-

study creatinine value (baseline creatinine), with a maximum creatinine above 4 mg/dL, or receive new RRT

- Patients who die will receive a value of 4

The mechanisms and extent of AKI with antibiotic exposure are not well understood. The primary outcome window of 14 days was chosen as it was felt to capture the period most likely to be affected by controlling antibiotics choice for 168 hours (7 days).

Secondary Outcomes

We have prespecified two secondary outcomes. Major Adverse Kidney Events within 14 days (MAKE14), is the composite outcome of death within 14 days, new RRT within 14 days, or stage 2 or higher AKI at day 14, according to KDIGO creatinine criteria. The second is number of days alive and free of delirium and coma in the 14 days after enrollment (Delirium and Coma-Free Days to day 14). Delirium is defined as a positive assessment on the CAM-ICU[31] and coma is defined as a RASS of -4 or -5[32] at any point during that study day.

Exploratory Outcomes

- Exploratory Renal Outcomes
    - Major Adverse Kidney Events within 28 days (MAKE28)
    - Highest stage of AKI or death between randomization and day 7
    - Stage 2 or higher AKI as defined in the KDIGO criteria for creatinine level within 14 days and 28 days after enrollment
    - New receipt of RRT within 14 days and 28 days after enrollment
    - Days alive and free of RRT during 14 days and 28 days after enrollment
    - Highest creatinine level within 28 days after enrollment
    - Change from pre-illness creatinine to the highest creatinine level within 28 days after enrollment
    - Final creatinine level before hospital discharge at 28 days
    - Ongoing receipt of RRT at hospital discharge or 28 days
    - Nephrology consultation

- Exploratory Neurologic Outcomes
    - Worst GCS score during the 7 days, 14 days, and 28 days after enrollment
    - Delirium and Coma-Free Days in the 28 days after enrollment
- Exploratory Clinical Outcomes
    - ICU-free, Hospital-free, Ventilator-free, and Vasopressor-free days in the 28 days after enrollment
    - 14-day mortality
    - 28-day mortality
    - Disposition of patients admitted from the ED (ward vs ICU)
    - Escalation of antibiotics defined by subsequent receipt of meropenem, meropenem-vaborbactam, imipenem, imipenem-relebactam, cefiderocol, ceftazidime-avibactam, ceftolozane-tazobactam, tigecycline, amikacin, tobramycin, gentamicin.

Definition of Supportive Therapy-Free days is available in Supplement section 5.

DSMB and Interim Analysis

A DSMB composed of experts in critical care medicine, infectious disease, and biostatistics has overseen the design of the trial and is monitoring its conduct (Supplement 6). The DSMB conducted a single interim analysis, prepared by the study biostatistician, at the anticipated halfway point of the trial after enrollment of 1025 patients. The meeting was held on July 14, 2022, and the DSMB recommended continuing the trial to completion without alteration. The stopping boundary for efficacy was prespecified as p-value for the difference between groups in the primary outcome of 0.001 or less. Given current use of both interventions as a part of usual care, there was no stopping boundary for futility. Use of a conservative Haybittle-Peto boundary for efficacy will allow the final analysis to be performed using an unchanged level of significance (P = 0.05). The DSMB retains the authority to recommend stopping the trial at any point, request additional data or interim analyses, or request modifications of study protocol to protect patient safety.

Sample Size Estimation

As specified in the initial trial protocol, at the time of the single, planned interim analysis the DSMB oversaw a re-estimation of the planned sample size. Because [1] concurrent receipt of vancomycin has been hypothesized to be in the proposed mechanistic pathway between receipt of an anti-pseudomonal penicillin and AKI and [2] approximately 75% of patients in the trial concurrently receive vancomycin, the sample size was increased by 25% from 2,050 to 2,500 patients. The increase in sample size ensures the number of patients receiving concurrent vancomycin will be approximately 2,050, consistent with the original sample size estimation. Assuming a two-sided alpha of 0.05 and a distribution of the primary outcome with approximately 70% of patients experiencing no AKI, 10% of patients experiencing stage I AKI, 7% of patients experiencing stage II AKI, 7% of patients experiencing stage III AKI, and 6% of patients experiencing death, we calculated that enrollment of a total of 2,500 patients would provide 92% statistical power to detect an odds ratio of 0.75 in the primary analysis.

Statistical Analysis Principles

Analyses will be conducted following reproducible research principles using R (R Foundation for Statistical Computing, Vienna, Austria)[33]. Continuous variables will be reported as mean ± SD or median and IQR; categorical variables will be reported as frequencies and proportions. As a randomized controlled trial, there will be no comparison of baseline characteristics. A two-sided p-value of < 0.05 will be used to indicate statistical significance; with just one primary outcome, no adjustment for multiplicity will be made. Two secondary outcomes are specified, one safety outcome for each treatment regimen. Since hypothesized safety concerns are independent, we will not adjust our secondary outcomes for multiplicity. For all other outcomes, emphasis will be placed on magnitude of differences between groups rather than statistical significance.

Main Analysis of the Primary Outcome

The main analysis will be an unadjusted, intention-to-treat comparison of the primary outcome between patients randomized to receive anti-pseudomonal

cephalosporins versus anti-pseudomonal penicillins who received at least one dose of a study drug using a proportional odds regression model. The unadjusted common odds ratio (cOR) with confidence intervals will be the primary treatment effect. If departures from the proportionality assumption are observed, then a partially proportional odds model will be constructed.

Secondary Analyses of the Primary Outcome

Multivariable modeling to account for covariates

To account for participants' baseline status, we will include covariates in the proportional odds regression model. The following prespecified baseline covariates will be considered: age; sex; peri-enrollment creatinine; receipt of RRT prior to enrollment; receipt of vasopressors; receipt of mechanical ventilation; SOFA score; presumed source of infection; enrollment location (ED vs ICU). Source of infection will be categorized as: lung, intra-abdominal (perforated viscus, ischemic bowel, cholecystitis/cholangitis, peritonitis/abscess/small bowel obstruction, *Clostridium difficile* colitis, spontaneous bacterial peritonitis, pancreatitis, enterocolitis/diverticulitis, other intra-abdominal infections), urinary (pyelonephritis, obstructive urinary tract infection), skin and soft tissue (cellulitis/abscess/necrotizing fasciitis/decubitus ulcer, surgical site infection), other (bone/joint, primary blood stream infection, intravascular catheter, disseminated infection, central nervous system infection, endocarditis, other), and unknown.

Effect Modification

We will test the interaction between the treatment effect of anti-pseudomonal cephalosporins vs anti-pseudomonal penicillins and baseline variables expected to modify effects of treatments on the outcomes. The effect modifiers will be tested one by one by including both the main effect and the interaction term in the adjusted model. Because this study is not formally designed or powered to test for interaction, a less conservative two-sided p value for the interaction term will be used, with values less than 0.10 considered suggestive of potential interaction and values less than 0.05 considered conclusive evidence. The following variables will be considered:

1. Location at randomization (ED vs ICU)
2. Presence of sepsis (meeting Sepsis-3 criteria) at randomization
3. Receipt of vancomycin (defined as an order for vancomycin in the 12 hours before or 6 hours after randomization)
4. Source of infection
5. AKI at randomization
6. CKD at randomization
7. Neutropenia at randomization
8. Admitting team (medicine vs surgical)

Sensitivity Analyses of the Primary Outcome

To assess robustness of findings, the main analysis of the primary outcome will be repeated in several alternative populations. First, we will include all patients who were identified by the CDS tool as meeting eligibility criteria, regardless of receipt of any doses of anti-pseudomonal cephalosporins or anti-pseudomonal penicillins. Second, many patients are initiated on antibiotics in the acute setting, which are stopped as a more likely cause for their illness becomes known (e.g. pulmonary embolism). We will repeat the main analysis restricted to the subset of patients that received more than 2 days (48 hours) of anti-pseudomonal therapy. Third, because race is a social construct, we will repeat the main analysis with those whose pre-illness creatinine was estimated by an equation without race as a factor. Fourth, to avoid uncertainty around the calculations of pre-illness creatinine, we will repeat the main analysis excluding patients with calculated pre-illness creatinine values. Because group assignment might influence recovery from prevalent AKI in a way that could affect calculations of the primary outcome, we will recalculate the primary outcome as a repeated measure assessed daily from randomization to day 14 using only the pre-illness creatinine as the baseline creatinine.

Analysis of the Secondary Outcomes

Analysis of secondary outcomes will follow a similar framework to the primary analysis, with a systematic assessment of unadjusted models, adjusted models using

the same set of covariates. The secondary outcome of MAKE14 will be compared between groups using a logistic regression model. Delirium and coma-free days to day 14 will be compared between groups using a proportional odds regression model, and will include the additional covariate of coma on enrollment for the adjusted model. Delirium and coma free days to day 14 will be assessed for effect modification using the same approach as the primary outcome replacing receipt of vancomycin with baseline coma.

Analyses of Exploratory Outcomes

Exploratory outcomes will proceed using unadjusted analyses only, with presentation of effect sizes and confidence intervals as well as p-values. Continuous outcomes will be compared with the Mann-Whitney U test and difference in medians reported. For categorical variables, groups will be compared with the chi-square test or Fischer's exact test as appropriate and results will be expressed as a difference in proportions or odds ratios, each with 95% confidence intervals.

Handling of Missing Data

In the case that a patient is enrolled, never receives RRT, and is discharged alive without having a creatinine value measured following enrollment, the patient will be assumed to have no AKI. When data are missing for secondary or exploratory outcomes, complete-case analysis, excluding cases where data for the analyzed outcome are missing, will be performed. There will be no imputation of missing data for these outcomes. In adjusted analyses, missing data for covariates will be imputed using multiple imputations.

Trial status

The ACORN trial is currently enrolling and started enrollment on November 10, 2021.

Ethics and Dissemination

Waiver of Informed Consent

Acutely ill patients for whom the provider is ordering broad-spectrum antibiotics in the ED or ICU are at significant risk for morbidity and mortality from their underlying illness. Most patients receiving empiric gram-negative antibiotics in routine clinical care receive either anti-pseudomonal cephalosporins or anti-pseudomonal penicillins. Any benefits or risks of these two approaches are experienced by patients receiving gram negative antibiotics in clinical care, outside the context of research. As a requirement for enrollment in the ACORN trial, the patient's treating clinician must have made the decision to order either anti-pseudomonal cephalosporins or anti-pseudomonal penicillins as part of routine clinical care and affirmed that either would be a safe and reasonable approach for the patient (otherwise the patient is excluded). Therefore, making the decision between the two approaches randomly through study group assignment rather than by a provider who thinks either approach is safe and reasonable for the patient was proposed to pose no more than minimal incremental risk.

Obtaining informed consent for participation in the study would be impracticable. Receipt of antibiotics in sepsis is time sensitive. Each hour delay in antibiotics in patients with sepsis is associated with an increase in mortality[34]. Attempting to obtain prospective written informed consent from patients presenting to the ED or ICU during the interval between the placement of an order for empiric antibiotics and their administration risks delaying antibiotic delivery. Moreover, acutely ill patients with sepsis are commonly delirious or unconscious, and a legally authorized representative is not consistently present at the time of initiation of antibiotics. Because the trial determines only the choice of the initial anti-pseudomonal antibiotic and defers decisions regarding subsequent doses of antibiotics (e.g., duration of therapy, escalation, de-escalation) to treating clinicians, enrollment, trial group assignment, and the primary study procedure (administration of the assigned antibiotic) commonly occurs within 1 hour of meeting eligibility criteria.

Because the study was expected to pose minimal risk and prospective informed consent was considered to be impracticable, a waiver of informed consent was requested and granted from the Vanderbilt University Medical Center IRB.

Protocol Changes

ClinicalTrials.Gov will be updated with any amendments to the protocol as per SPIRIT guidelines (Supplement 7).

Dissemination Plan

Trial results will be submitted to a peer-reviewed journal for consideration of publication and will be presented at one or more scientific conferences. Data will be made available following publication (Supplement 8).

Conclusion

To allow for a clearer and more objective interpretation of trial results, this description delineates the ACORN trial methods and analysis prior to the conclusion of enrollment.

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Figure 1. Electronic health record-based enrollment advisor

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Protocol and statistical analysis plan for the Antibiotic Choice On ReNal outcomes (ACORN) randomised clinical trial

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ABSTRACT

Introduction Antibiotics are time-critical in the management of sepsis. When infectious organisms are unknown, patients are treated with empiric antibiotics to include coverage for gram-negative organisms, such as antipseudomonal cephalosporins and penicillins. However, in observational studies, some antipseudomonal cephalosporins (eg, cefepime) are associated with neurologic dysfunction while the most common antipseudomonal penicillin (piperacillin–tazobactam) is associated with acute kidney injury (AKI). No randomised control trials have compared these regimens. This manuscript describes the protocol and analysis plan for a trial designed to compare the effects of antipseudomonal cephalosporins and antipseudomonal penicillins among acutely ill patients receiving empiric antibiotics.

Methods and analysis The Antibiotic Choice On ReNal outcomes trial is a prospective, single-centre, non-blinded randomised trial being conducted at Vanderbilt University Medical Center. The trial will enrol 2500 acutely ill adults receiving gram-negative coverage for treatment of infection. Eligible patients are randomised 1:1 to receive cefepime or piperacillin–tazobactam on first order entry of a broad-spectrum antibiotic covering gram-negative organisms. The primary outcome is the highest stage of AKI and death occurring between enrolment and 14 days after enrolment. This will be compared between patients randomised to cefepime and randomised to piperacillin–tazobactam using an unadjusted proportional odds regression model. The secondary outcomes are major adverse kidney events through day 14 and number of days alive and free of delirium and coma in 14 days after enrolment. Enrolment began on 10 November 2021 and is expected to be completed in December 2022.

Ethics and dissemination The trial was approved by the Vanderbilt University Medical Center institutional review board (IRB#210591) with a waiver of informed consent. Results will be submitted to a peer-reviewed journal and presented at scientific conferences.

Trial registration number NCT05094154.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This ongoing pragmatic trial will compare the effects of cefepime versus piperacillin–tazobactam on acute kidney injury (AKI) and death among acutely ill adults receiving gram-negative antibiotic therapy in the emergency department or intensive care unit.
⇒ Strengths: Broad eligibility criteria, inclusion of a range of indications for antibiotic therapy and use of the electronic health record to screen for eligible patients and facilitate delivery of the assigned intervention will increase the external validity of the findings.
⇒ Limitations: After concealed randomisation, patients, clinicians and investigators are unblinded to study group assignment. Because urine output is not systematically available across all care, the outcome of AKI is based on creatinine measurements.

INTRODUCTION

Antibiotics are necessary for the management of patients with sepsis,[1] but can cause unintended adverse effects on organ function.[2] Since specific organisms causing infection are often unknown, empiric broad-spectrum antibiotics are commonly prescribed. For patients at risk for resistant organisms, common regimens include gram-positive coverage (ie, vancomycin) and gram-negative coverage with an antipseudomonal cephalosporin or penicillin, predominantly cefepime or piperacillin–tazobactam.[1]

No prospective randomised trials have compared the efficacy of cefepime versus piperacillin–tazobactam head to head. When administered empirically in clinical practice, both antibiotics are commonly considered to have comparable activity against gram-negative organisms, including *Pseudomonas*, although cefepime does not cover anaerobic organisms and piperacillin–tazobactam does. Whether coverage of anaerobic

organisms in acutely ill patients is associated with higher[3] mortality, lower[4–7] mortality or no difference in mortality is uncertain.

In the absence of evidence that efficacy differs between cefepime and piperacillin–tazobactam, discussion surrounding the choice between the two has focused on adverse effects. Some observational studies have reported an association between receipt of piperacillin–tazobactam and acute kidney injury (AKI),[8 9] particularly among patients receiving vancomycin.[10–12] Other studies have shown no relationship between piperacillin–tazobactam and AKI.[13 14] Adverse kidney events are common during hospitalisation,[15] and there are many potential contributors including isotonic fluids,[16 17] medications and acute illnesses such as sepsis.[18 19]

Similarly, an association between cephalosporins and neurotoxicity manifesting as delirium and coma has been observed.[20–22] Delirium, acute brain dysfunction characterised by fluctuations in mental status, inattention, altered consciousness and disorganised thinking,[23] is also a common complication of hospitalisation. In intensive care unit (ICU) populations, delirium is predictive of mortality, prolonged length of stay and long-term cognitive impairment.[24 25] The incidence of cephalosporin-induced neurotoxicity is unknown but has been reported to increase in-hospital mortality.[26]

A randomised controlled trial would overcome limitations of observational data, but none is known to exist.[27] Rigorous, high-quality evidence assessing the risk of AKI and neurotoxicity after exposure to antipseudomonal antibiotics would have the potential to change care received by thousands of acutely ill adults annually. To address the lack of available evidence, we are conducting a prospective, randomised trial comparing antipseudomonal cephalosporins and antipseudomonal penicillins among acutely ill adults in the emergency department (ED) or ICU.

METHODS AND ANALYSIS

This manuscript was written in accordance with Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines (table 1, online supplemental file 1).[28] The Learning Healthcare System (LHS) Platform at Vanderbilt University Medical Center conducts research studies using a unique model that leverages pragmatic, randomised, controlled clinical trials embedded within usual care.[29] The LHS Platform is composed of stakeholders from across the enterprise and supports projects in both the paediatric and adult inpatient and outpatient settings (online supplemental file 2). LHS Platform studies focus on comparative effectiveness, implementation science and programmatic evaluation approaches.[30 31]

Study design

The Antibiotic Choice On ReNal outcomes (ACORN) trial is a pragmatic, single-centre, unblinded, parallel-group, randomised trial comparing antipseudomonal cephalosporins to antipseudomonal penicillins among acutely ill adults receiving gram-negative antibiotics in the ED and ICU. At this centre, the predominant antipseudomonal cephalosporin is cefepime and the predominant antipseudomonal penicillin is piperacillin–tazobactam. The primary outcome is the highest stage of AKI or death in 14 days. The trial protocol was approved by

Table 1 Standard Protocol Items: Recommendations for Interventional Trials checklist

	Study period				
	Eligibility screen	**Randomisation and allocation**	**Post allocation**		**Final outcome assessment**
Timepoint	Order entry for CEF or PTZ	EHR enrolment advisor	7 days after enrolment	14 days after enrolment	Discharge or 28 days after enrolment
Enrolment:		X			
EHR-based inclusion criteria screening	X				
Manual screening for exclusion criteria by treating clinicians	X				
Allocation		X			
Interventions:					
Cefepime		X	X		
Piperacillin–tazobactam		X	X		
Assessments:					
Baseline variables	X	X			
Adverse events		X	X	X	X
Primary and secondary outcomes		X	X	X	
Exploratory outcomes			X	X	X

Enrolment, interventions and assessments.
CEF, cefepime; EHR, electronic health record; PTZ, piperacillin–tazobactam.

the institutional review board at Vanderbilt University Medical Center and registered prior to initiation of enrolment (NCT05094154). An independent data and safety monitoring board (DSMB) monitors the progress and safety of the trial.

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research. Patient and community representatives participated in the steering committee for the LHS in which the trial was conducted.

Study population

Inclusion criteria

1. Age≥18 years old.
2. Located in a participating ED or ICU.
3. Less than 12 hours between presentation to study hospital.
4. Treating clinician initiating an order for an antipseudomonal cephalosporin or antipseudomonal penicillin.

Exclusion criteria

1. Known receipt of >1 dose of an antipseudomonal cephalosporin or antipseudomonal penicillin during the last 7 days.
2. Current documented allergy to cephalosporins or penicillin.
3. Known to be a prisoner.
4. Treating clinicians feel that either an antipseudomonal cephalosporin or antipseudomonal penicillin is required or contraindicated for the optimal treatment of the patient, including for more directed antibiotic therapy against known prior resistant infections or suspected sepsis with an associated central nervous system infection.

Screening and enrolment

When a treating clinician in a participating ED or ICU initiates an order for cefepime or piperacillin–tazobactam for a patient who meets all inclusion criteria, a clinical decision support (CDS) tool will (1) inform the provider of the study, (2) query the provider regarding the presence of any exclusion criteria, and if none is present, (3) enrol and randomise the patient. For patients who meet an exclusion criterion, the reason is recorded (figure 1).

Analysis population

The primary goal is the exploration of uncommon safety effects, therefore the population for primary analysis will include all patients who were randomised and received at least one dose of either study drug in the 168 hours (7 days) after randomisation. A sensitivity analysis will include all patients randomised, including those who never received either cefepime or piperacillin/tazobactam.

Randomisation and treatment allocation

Study group assignments are generated by computerised randomisation in a 1:1 ratio of intervention to control. Study group assignment will remain concealed until the team has confirmed the patient does not meet any exclusion criteria and the patient has been enrolled. The CDS tool will advise the clinician of group assignment following randomisation.

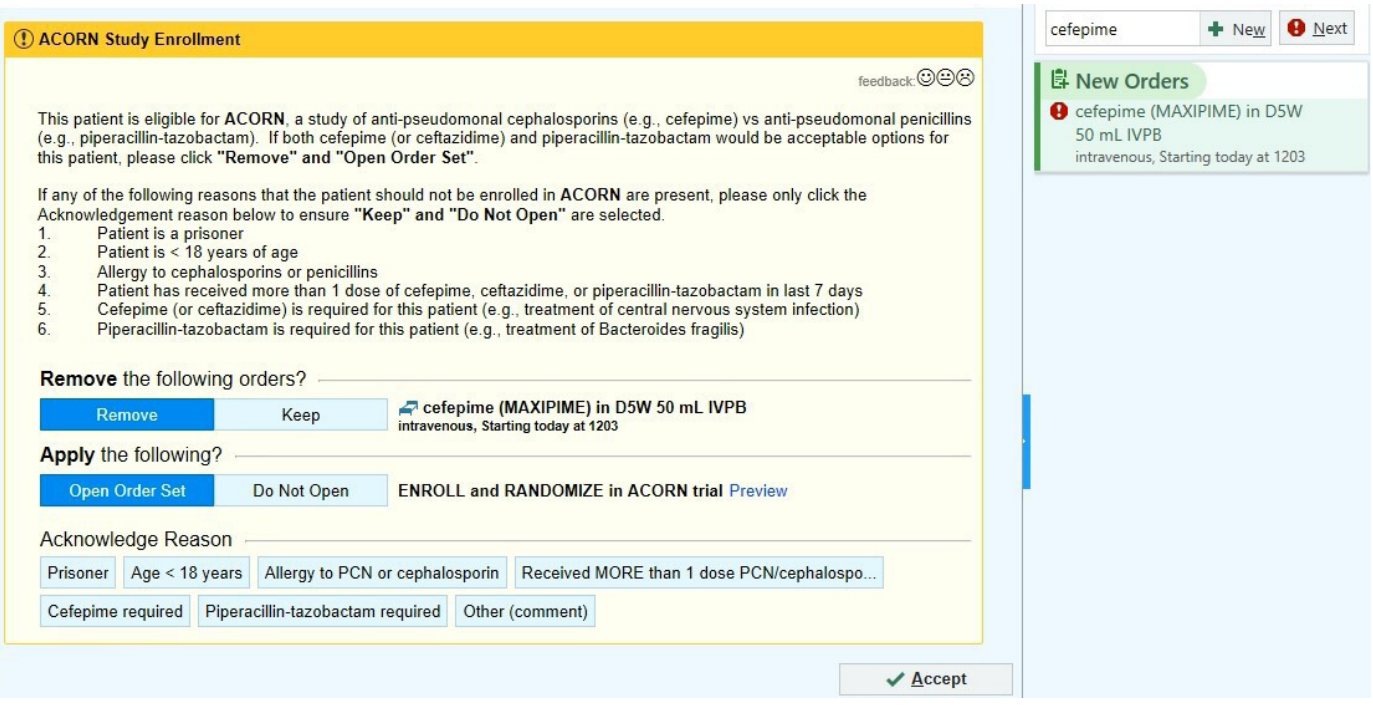

Figure 1 Electronic health record-based enrolment advisor. ACORN, Antibiotic Choice On ReNal outcomes. D5W - Dextrose 5% in Water; IVPB - Intravenous Piggyback; PCN - penicillin

Study interventions

For patients assigned to cefepime, the CDS tool will guide providers to intravenous cefepime. For patients assigned to piperacillin–tazobactam, the CDS tool will guide providers to intravenous piperacillin–tazobactam. The CDS tool will display a standardised table of dose by glomerular filtration rate, but decisions regarding dose, frequency and duration will be the treating clinician's discretion.

In the 168 hours (7 days) following enrolment, any new order for cefepime or piperacillin–tazobactam will open a CDS tool, which displays group assignment and allows clinicians to (re)order the assigned antibiotic or provide a reason for ordering the non-assigned antibiotic. Similarly, if the assigned antibiotic is discontinued, the CDS tool will solicit a rationale for discontinuation, including antibiotic tailoring, newly apparent allergy to either cephalosporins or penicillins, or clinician preference.

The CDS tool influences only the choice of the initial antipseudomonal antibiotic. Treating clinicians to determine concurrent administration of other antibiotics (eg, vancomycin, metronidazole), duration of therapy, escalation, de-escalation, approach to source control and use of culture and laboratory data to modify antibiotic therapy.

Data collection

Trial personnel will monitor for adverse events daily and will record the following data elements at the time of enrolment by manual review of the health record (online supplemental files 3 and 4):

- Presence of sepsis, defined by Sepsis-3 criteria.[32]
- Transplant recipient status.
- Receipt of renal replacement therapy (RRT) prior to enrolment.
- Presumed source of infection organised into groups based on previously published data.[33]

All other data will be obtained using electronic exports from the health record. The following variables are collected:

1. Collected at baseline: age, sex, height, weight, body mass index, race, Sequential Organ Failure Assessment (SOFA) Score, active medical problems at the time of admission, active comorbidities, comorbidities and medications known to increase risk of kidney or neurologic injury at enrolment, mean arterial pressure and vasopressor use prior to antibiotic receipt, analgesia and sedation use prior to antibiotic receipt, admission to ICU versus ward.
2. Collected from randomisation to hospital discharge: mean arterial pressure and vasopressor use, pH, PaO_2, $PaCO_2$, respiratory rate, heart rate, oxygen saturation, temperature, lactic acid, elements of a basic metabolic panel, magnesium, elements of a complete blood count, antibiotic receipt, all microbiologic culture data, *Clostridium difficile* testing results, Confusion Assessment Method for the ICU (CAM-ICU), Richmond Agitation Sedation Score (RASS), Glasgow Coma Scale (GCS), mechanical ventilation status and variables related to ventilation, nephrology consultation, receipt of new RRT, indications for new RRT among patients who received new RRT, medications known to increase risk of kidney injury, medications known to increase risk of neurologic injury, admitting team, date of admission, days spent in the ICU, days spent in the hospital, date of intubation(s) and extubation(s), date of discharge and date of death.

Primary outcome

The primary outcome will be a combination of the highest stage of AKI and death between randomisation and day 14. The stages of AKI are defined using creatinine measurements and the 'Kidney Disease: Improving Global Outcomes (KDIGO)'[34] criteria. The score will range from 0 (best value) to 4 (worst value):

0=No AKI.

1=Stage 1 AKI (creatinine increased by 1.5–1.9 times baseline or increase by ≥0.3 mg/dL).

2=Stage 2 AKI (creatinine increased by 2.0–2.9 times baseline).

3=Stage 3 AKI (creatinine increased by ≥3.0 times baseline or increase to ≥4.0 mg/dL or new RRT).

4=Death.

'Baseline' creatinine values are defined as the lowest prior creatinine values from three different timepoints: the preillness creatinine value, the perienrolment creatinine value and the lowest prior on-study creatinine value as defined below. Death is defined as mortality from any cause occurring prior to or on the end of study day 14, censored at hospital discharge. RRT is defined as receipt of RRT at any point between randomisation and the end of study day 14, censored at hospital discharge. Patients who are receiving RRT prior to enrolment can only experience values of 0 (patient did not die) or 4 (patient died) because they are ineligible to experience changes in creatinine or new receipt of RRT that define levels 1 through 3.

Patients' preillness creatinine will be defined as the lowest serum creatinine between 12 months and 24 hours prior to enrolment. For patients for whom a value is unavailable, a preillness creatinine value will be estimated using a previously described three-variable formula (creatinine=0.74–0.2 (if female)+0.08 (if African American)+0.003×age (in years)).[35] There are no validated estimations of creatinine without race but we will evaluate the effect of social constructs by fitting models both with and without race in a sensitivity analysis.

Patients' perienrolment creatinine will be defined hierarchically using the creatinine value closest to enrolment in: (first) the 24 hours prior to enrolment, if available, and (second) the 6 hours after enrolment (if no value is available prior to enrolment). The prevalent AKI, or AKI that is present on admission and unrelated to the study intervention, will be defined by comparing the perienrolment creatinine to the preillness creatinine.

On-study creatinine will be defined as any creatinine value occurring after both the time of enrolment and

the time of the perienrolment creatinine value. On-study creatinine values will be used to identify incident AKI and calculate the stage of AKI for the primary outcome.

The primary outcome will be calculated as follows:

- Patients who survive without new RRT and do not experience an on-study creatinine value that is at least 0.3 mg/dL higher than the perienrolment value or any preceding on-study value, and whose on-study creatinine is never more than 1.5 times the perienrolment value or any preceding on-study value, will be considered not to have experienced incident AKI and will receive a value of 0 for the primary outcome.
- Among patients who survive and experience AKI (have on-study creatinine value that is at 1.5 times or at least 0.3 mg/dL higher than the perienrolment value or any preceding on-study value), the score for the primary outcome will be determined by the stage of AKI and classified as follows:
  a. A value of 1 if the highest on-study creatinine after qualifying for AKI is less than 2 times the lowest of the preillness creatinine value, the perienrolment creatinine value and the lowest prior on-study creatinine value (baseline creatinine).
  b. A value of 2 if the highest on-study creatinine after qualifying for AKI is at least 2 times and less than 3 times the lowest of the preillness creatinine value, the perienrolment creatinine value and the lowest prior on-study creatinine value (baseline creatinine).
  c. A value of 3 if the highest on-study creatinine after qualifying for AKI is at least 3 times the lowest of the preillness creatinine value, the perienrolment creatinine value and the lowest prior on-study creatinine value (baseline creatinine), with a maximum creatinine above 4 mg/dL, or receive new RRT.
- Patients who die will receive a value of 4.

The mechanisms and extent of AKI with antibiotic exposure are not well understood. The primary outcome window of 14 days was chosen as it was felt to capture the period most likely to be affected by controlling antibiotics choice for 168 hours (7 days).

Secondary outcomes

We have prespecified two secondary outcomes. Major adverse kidney events within 14 days (MAKE14) is the composite outcome of death within 14 days, new RRT within 14 days or stage 2 or higher AKI at day 14, according to KDIGO creatinine criteria. The second is number of days alive and free of delirium and coma in the 14 days after enrolment (delirium and coma-free days to day 14). Delirium is defined as a positive assessment on the CAM-ICU[36] and coma is defined as an RASS of −4 or −5[37] at any point during that study day.

Exploratory outcomes

- Exploratory renal outcomes.
  - Major adverse kidney events within 28 days (MAKE28).
  - Highest stage of AKI or death between randomisation and day 7.
  - Stage 2 or higher AKI as defined in the KDIGO criteria for creatinine level within 14 days and 28 days after enrolment.
  - New receipt of RRT within 14 days and 28 days after enrolment.
  - Days alive and free of RRT during 14 days and 28 days after enrolment.
  - Highest creatinine level within 28 days after enrolment.
  - Change from preillness creatinine to the highest creatinine level within 28 days after enrolment.
  - Final creatinine level before hospital discharge at 28 days.
  - Ongoing receipt of RRT at hospital discharge or 28 days.
  - Nephrology consultation.
- Exploratory neurologic outcomes.
  - Worst GCS Score during the 7, 14 and 28 days after enrolment.
  - Delirium and coma-free days in the 28 days after enrolment.
- Exploratory clinical outcomes.
  - ICU-free, hospital-free, ventilator-free and vasopressor-free days in the 28 days after enrolment.
  - 14-day mortality.
  - 28-day mortality.
  - Disposition of patients admitted from the ED (ward vs ICU).
  - Escalation of antibiotics defined by subsequent receipt of meropenem, meropenem–vaborbactam, imipenem, imipenem–relebactam, cefiderocol, ceftazidime–avibactam, ceftolozane–tazobactam, tigecycline, amikacin, tobramycin, gentamicin.

Definition of supportive therapy-free days is available in online supplemental section 5.

DSMB and interim analysis

A DSMB composed of experts in critical care medicine, infectious disease and biostatistics has overseen the design of the trial and is monitoring its conduct (online supplemental file 6). The DSMB conducted a single interim analysis, prepared by the study biostatistician, at the anticipated halfway point of the trial after enrolment of 1025 patients. The meeting was held on 14 July 2022, and the DSMB recommended continuing the trial to completion without alteration. The stopping boundary for efficacy was prespecified as p value for the difference between groups in the primary outcome of 0.001 or less. Given current use of both interventions as a part of usual care, there was no stopping boundary for futility. The use of a conservative Haybittle-Peto boundary for efficacy will allow the final analysis to be performed using an unchanged level of significance (p=0.05). The DSMB retains the authority to recommend stopping the trial at

any point, request additional data or interim analyses, or request modifications of the study protocol to protect patient safety.

Sample size estimation

As specified in the initial trial protocol, at the time of the single, planned interim analysis the DSMB oversaw a re-estimation of the planned sample size. Because (1) concurrent receipt of vancomycin has been hypothesised to be in the proposed mechanistic pathway between receipt of an antipseudomonal penicillin and AKI and (2) approximately 75% of patients in the trial concurrently receive vancomycin, the sample size was increased by 25% from 2050 to 2500 patients. The increase in sample size ensures the number of patients receiving concurrent vancomycin will be approximately 2050, consistent with the original sample size estimation. Assuming a two-sided alpha of 0.05 and a distribution of the primary outcome with approximately 70% of patients experiencing no AKI, 10% of patients experiencing stage 1 AKI, 7% of patients experiencing stage 2 AKI, 7% of patients experiencing stage 3 AKI and 6% of patients experiencing death, we calculated that enrolment of a total of 2500 patients would provide 92% statistical power to detect an OR of 0.75 in the primary analysis.

Statistical analysis principles

Analyses will be conducted following reproducible research principles using R (R Foundation for Statistical Computing, Vienna, Austria).[38] Continuous variables will be reported as mean±SD or median and IQR; categorical variables will be reported as frequencies and proportions. As a randomised controlled trial, there will be no comparison of baseline characteristics. A two-sided p value of <0.05 will be used to indicate statistical significance; with just one primary outcome, no adjustment for multiplicity will be made. Two secondary outcomes are specified, one safety outcome for each treatment regimen. Since hypothesised safety concerns are independent, we will not adjust our secondary outcomes for multiplicity. For all other outcomes, emphasis will be placed on the magnitude of differences between groups rather than statistical significance.

Main analysis of the primary outcome

The main analysis will be an unadjusted, intention-to-treat comparison of the primary outcome between patients randomised to receive antipseudomonal cephalosporins versus antipseudomonal penicillins who received at least one dose of a study drug using a proportional odds regression model. The unadjusted common OR with CIs will be the primary treatment effect. If departures from the proportionality assumption are observed, then a partially proportional odds model will be constructed.

Secondary analyses of the primary outcome

Multivariable modelling to account for covariates

To account for participants' baseline status, we will include covariates in the proportional odds regression model. The following prespecified baseline covariates will be considered: age; sex; perienrolment creatinine; receipt of RRT prior to enrolment; receipt of vasopressors; receipt of mechanical ventilation; SOFA Score; presumed source of infection; enrolment location (ED vs ICU). Source of infection will be categorised as: lung, intra-abdominal (perforated viscus, ischaemic bowel, cholecystitis/cholangitis, peritonitis/abscess/small bowel obstruction, *Clostridium difficile* colitis, spontaneous bacterial peritonitis, pancreatitis, enterocolitis/diverticulitis, other intra-abdominal infections), urinary (pyelonephritis, obstructive urinary tract infection), skin and soft tissue (cellulitis/abscess/necrotizing fasciitis/decubitus ulcer, surgical site infection), other (bone/joint, primary blood stream infection, intravascular catheter, disseminated infection, central nervous system infection, endocarditis, other) and unknown.

Effect modification

We will test the interaction between the treatment effect of antipseudomonal cephalosporins versus antipseudomonal penicillins and baseline variables expected to modify the effects of treatments on the outcomes. The effect modifiers will be tested one by one by including both the main effect and the interaction term in the adjusted model. Because this study is not formally designed or powered to test for interaction, a less conservative two-sided p value for the interaction term will be used, with values less than 0.10 considered suggestive of potential interaction and values less than 0.05 considered conclusive evidence. The following variables will be considered:

1. Location at randomisation (ED vs ICU).
2. Presence of sepsis (meeting Sepsis-3 criteria) at randomisation.
3. Receipt of vancomycin (defined as an order for vancomycin in the 12 hours before or 6 hours after randomisation).
4. Source of infection.
5. AKI at randomisation.
6. CKD at randomisation.
7. Neutropenia at randomisation.
8. Admitting team (medicine vs surgical).

Sensitivity analyses of the primary outcome

To assess robustness of findings, the main analysis of the primary outcome will be repeated in several alternative populations. First, we will include all patients who were identified by the CDS tool as meeting eligibility criteria, regardless of receipt of any doses of antipseudomonal cephalosporins or antipseudomonal penicillins. Second, many patients are initiated on antibiotics in the acute setting, which are stopped as a more likely cause for their illness becomes known (eg, pulmonary embolism). We will repeat the main analysis restricted to the subset of patients that received more than 2 days (48 hours) of antipseudomonal therapy. Third, because race is a social construct, we will repeat the main analysis with those whose preillness creatinine was estimated by an equation without race as a factor. Fourth, to avoid uncertainty around

the calculations of preillness creatinine, we will repeat the main analysis excluding patients with calculated preillness creatinine values. Because group assignment might influence recovery from prevalent AKI in a way that could affect calculations of the primary outcome, we will recalculate the primary outcome as a repeated measure assessed daily from randomisation to day 14 using only the preillness creatinine as the baseline creatinine.

Analysis of the secondary outcomes

Analysis of secondary outcomes will follow a similar framework to the primary analysis, with a systematic assessment of unadjusted models, adjusted models using the same set of covariates. The secondary outcome of MAKE14 will be compared between groups using a logistic regression model. Delirium and coma-free days to day 14 will be compared between groups using a proportional odds regression model, and will include the additional covariate of coma on enrolment for the adjusted model. Delirium and coma free days to day 14 will be assessed for effect modification using the same approach as the primary outcome replacing receipt of vancomycin with baseline coma.

Analyses of exploratory outcomes

Exploratory outcomes will proceed using unadjusted analyses only, with presentation of effect sizes and CIs as well as p values. Continuous outcomes will be compared with the Mann-Whitney U test and the difference in medians reported. For categorical variables, groups will be compared with the χ^2 test or Fischer's exact test as appropriate and results will be expressed as a difference in proportions or ORs, each with 95% CIs.

Handling of missing data

In the case that a patient is enrolled, never receives RRT and is discharged alive without having a creatinine value measured following enrolment, the patient will be assumed to have no AKI. When data are missing for secondary or exploratory outcomes, complete-case analysis, excluding cases where data for the analysed outcome are missing, will be performed. There will be no imputation of missing data for these outcomes. In adjusted analyses, missing data for covariates will be imputed using multiple imputations.

Trial status

The ACORN trial is currently enrolling and started enrolment on 10 November 2021.

Ethics and dissemination

Waiver of informed consent

Acutely ill patients for whom the provider is ordering broad-spectrum antibiotics in the ED or ICU are at significant risk for morbidity and mortality from their underlying illness. Most patients receiving empiric gram-negative antibiotics in routine clinical care receive either antipseudomonal cephalosporins or antipseudomonal penicillins. Any benefits or risks of these two approaches are experienced by patients receiving gram-negative antibiotics in clinical care, outside the context of research. As a requirement for enrolment in the ACORN trial, the patient's treating clinician must have made the decision to order either antipseudomonal cephalosporins or antipseudomonal penicillins as part of routine clinical care and affirmed that either would be a safe and reasonable approach for the patient (otherwise the patient is excluded). Therefore, making the decision between the two approaches randomly through study group assignment rather than by a provider who thinks either approach is safe and reasonable for the patient was proposed to pose no more than minimal incremental risk.

Obtaining informed consent for participation in the study would be impracticable. Receipt of antibiotics in sepsis is time sensitive. Each hour delay in antibiotics in patients with sepsis is associated with an increase in mortality.[39] Attempting to obtain prospective written informed consent from patients presenting to the ED or ICU during the interval between the placement of an order for empiric antibiotics and their administration risks delaying antibiotic delivery. Moreover, acutely ill patients with sepsis are commonly delirious or unconscious, and a legally authorised representative is not consistently present at the time of initiation of antibiotics. Because the trial determines only the choice of the initial antipseudomonal antibiotic and defers decisions regarding subsequent doses of antibiotics (eg, duration of therapy, escalation, de-escalation) to treating clinicians, enrolment, trial group assignment and the primary study procedure (administration of the assigned antibiotic) commonly occurs within 1 hour of meeting eligibility criteria.

Because the study was expected to pose minimal risk and prospective informed consent was considered to be impracticable, a waiver of informed consent was requested and granted from the Vanderbilt University Medical Center IRB.

Protocol changes

ClinicalTrials.Gov will be updated with any amendments to the protocol as per SPIRIT guidelines (online supplemental file 7).

Dissemination plan

Trial results will be submitted to a peer-reviewed journal for consideration of publication and will be presented at one or more scientific conferences. Data will be made available following publication (online supplemental file 8).

CONCLUSION

To allow for a clearer and more objective interpretation of trial results, this description delineates the ACORN trial methods and analysis prior to the conclusion of enrolment.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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Antibiotic Choice On ReNal outcomes (ACORN) trial

Statistical Analysis Plan Revision Sequence

7/27/2022	Original Statistical Analysis Plan complete and submitted for review at BMJ Open
10/7/2022	Enrollment Complete
3/10/2023	**Statistical Analysis Plan Published in BMJ Open** Qian ET, Casey JD, Wright A, et al. Protocol and statistical analysis plan for the Antibiotic Choice On ReNal outcomes (ACORN) randomised clinical trial. BMJ Open. 2023;13(3):e066995. Published 2023 Mar 10. doi:10.1136/bmjopen-2022-066995

*** No changes occurred to the Statistical Analysis Plan from initial submission to publication**