CIVIL HOSPITAL OF GUADALAJARA

FRAY ANTONIO ALCALDE

Protocol Title:
Infectious Prophylaxis with Trimethoprim–Sulfamethoxazole Following Severe Acute Kidney Injury: A Clinical Trial at the Old Civil Hospital of Guadalajara, from October 2025 to October 2026

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Table of Contents

Contents

(AKI) – Acute Kidney Injury
(ICU) – Intensive Care Unit
(KDIGO) – Kidney Disease: Improving Global Outcomes (Organization)
(SCr) – Serum Creatinine
(UO) – Urine Output
(CI) – Confidence Interval
(HR) – Hazard Ratio
(eGFR) – Estimated Glomerular Filtration Rate
(CKD) – Chronic Kidney Disease
(IQR) – Interquartile Range
(AE) – Adverse Events
(MAKE) – Major Adverse Kidney Events
(RRT) – Renal Replacement Therapy
(TMP-SMX) – Trimethoprim–Sulfamethoxazole

Introduction

Acute kidney injury (AKI) is a complex disorder characterized by a rapid decline in renal function, leading to the accumulation of metabolic waste products and fluid imbalance. It is a frequent and severe complication among critically ill patients, affecting approximately 30–50% of those admitted to intensive care units (ICUs). This syndrome

is associated with increased morbidity, mortality, and healthcare costs.

The prognosis of AKI depends on its severity and underlying cause. The worst outcomes are observed in patients who require renal replacement therapy (RRT), in whom mortality approaches 60%. AKI is often secondary to non-renal organ dysfunction such as sepsis, respiratory failure, or heart failure. These conditions may reduce renal perfusion and promote inflammation and oxidative stress, resulting in kidney injury.

Although the KDIGO consensus criteria provide a standardized definition of AKI based on changes in serum creatinine (SCr) and urine output (UO), these markers tend to appear late and lack sensitivity for early detection. Moreover, survivors of AKI have been shown to face a markedly increased risk of infections, particularly within the first three months after hospital discharge. This heightened susceptibility is mainly due to a state of multifactorial immunosuppression and cellular anergy.

Background

Following an episode of AKI, infections are a frequent complication.

In a retrospective Spanish cohort, infection surveillance began three months after the AKI episode. Over a median follow-up of nine months (IQR 2–56), 153 patients (42%) developed at least one infection. The most common were urinary tract infections [67 (44%)], respiratory tract infections [46 (30%)], soft tissue infections [14 (9%)], and abdominal infections [14 (9%)]. No specific baseline variable was associated with infection type.

Factors linked to infection during follow-up were analyzed using Cox regression. In univariate analysis, the following were associated with infection risk: older age {HR 1.18 [95% CI, 1.05–1.33], P = 0.005}, cognitive impairment [HR 1.51 (95% CI, 1.00–2.28), P = 0.050], lower eGFR three months post-AKI [HR 0.91 (95% CI, 0.86–0.97), P = 0.002], decline in eGFR from baseline to three months [HR 1.07 (95% CI, 1.01–1.14), P = 0.028], and transition from AKI to chronic kidney disease (CKD) [HR 1.55 (95% CI, 1.13–2.14), P = 0.007].

Baseline eGFR differed significantly between patients who developed infection and those who did not (P = 0.038), although the nadir and post-AKI eGFR values were similar between groups (P = 0.289 and P = 0.215, respectively).

Problem Definition

Study Rationale:

- Infections represent a serious yet understudied complication among patients who have experienced acute kidney injury (AKI). While kidney disease is known to increase susceptibility to infections—and infections are a major cause of mortality in this population—the precise relationship between AKI and infection risk, as well as the immunologic mechanisms underlying this vulnerability, remain poorly understood.
- Existing data indicate that postoperative AKI is associated with higher rates of infection-related hospitalizations, and that the transition from AKI to chronic kidney disease (CKD) further amplifies infectious risk. However, to date, no studies have evaluated the efficacy of antibiotic prophylaxis in preventing infections among patients recovering from severe AKI after hospital discharge.
- This research gap underscores the need for a clinical trial aimed at determining whether prophylactic administration of trimethoprim–sulfamethoxazole can reduce infection incidence in this high-risk group.

Research Question:

Does administration of trimethoprim–sulfamethoxazole 800/160 mg every 48 hours for 90 days reduce the risk of infections in patients who have experienced severe acute kidney injury after hospital discharge?

Justification

The justification for this study lies in the absence of previous clinical trials evaluating the effectiveness of antibiotic prophylaxis in reducing infection risk following acute kidney injury (AKI) among discharged patients. Identifying infections as one of the most underestimated complications in AKI highlights the urgent need to address this research gap. Implementing a clinical trial to evaluate the administration of trimethoprim–sulfamethoxazole could provide crucial data regarding its efficacy and contribute to improving medical care and health outcomes in this vulnerable population.

The significance of this study is reflected in its potential to influence clinical practice and improve the management of AKI patients. Reducing infections may not only decrease morbidity but also enhance quality of life and lessen the healthcare system's burden. As the first study of its kind, its findings could establish a precedent for future research and guide the development of antibiotic prophylaxis protocols in similar clinical contexts.

The feasibility of the study is supported by its design—a randomized, double-blind, placebo-controlled clinical trial—which aligns with current recommendations for addressing AKI. The selection of Hospital Civil de Guadalajara "Fray Antonio Alcalde" as the research center ensures access to a relevant AKI patient population. Furthermore, clearly defined inclusion criteria and randomization methods suggest adequate planning to ensure successful recruitment and adherence to the protocol.

Potential vulnerabilities of the study include the possibility of bias during randomization or outcome assessment, as well as limited generalizability of findings to other populations due to cultural, socioeconomic, or healthcare delivery differences. Additionally, since this study targets a critically ill population, adverse

events related to antibiotic use will represent an important consideration. Addressing these aspects is essential for the validity and interpretation of the study's findings.

Theoretical and Conceptual Framework

Infections are among the least studied consequences of AKI. Although kidney diseases are well-recognized risk factors for infections—and infections remain one of the leading causes of death among patients with renal disease—the underlying mechanisms of this secondary immunodeficiency remain poorly defined [Steiger S]. Regarding the bidirectional relationship between AKI and infections, the recently published NARA-AKI prospective study demonstrated that postoperative AKI in non-cardiac surgery was associated with increased hospitalizations due to infections [Tagawa M, Kellum JA]. Beyond AKI, patients with chronic kidney disease (CKD) are more vulnerable to infections and exhibit worse outcomes than cohorts without CKD [Xu H, Su G]. Interestingly, not only the progression from AKI to CKD but also the decline in eGFR—independent of baseline or post-AKI eGFR—was independently associated with infection risk.

Several mechanisms may explain this increased susceptibility to infection. The immune dysfunction of CKD—characterized by impaired innate and adaptive immunity, decreased clearance of proinflammatory cytokines, and even epigenetic modifications in hematopoietic stem cells—adds to the alterations seen in AKI, such as disrupted kidney-immune system crosstalk, changes in immune cell composition and function, and an exaggerated inflammatory response [LaFavers K, Syed-Ahmed M]. Nevertheless, the precise pathophysiology of the elevated infection risk in patients transitioning from AKI to CKD remains incompletely understood.

Finally, a retrospective cohort study (Griffin BR) showed that recovery from AKI was associated with a 4.5-fold increase in the likelihood of infection (OR 4.53 [95% CI, 2.43–8.45]; $p < 0.0001$) within 30 days after hospital discharge. Moreover, the association between AKI and subsequent infection remained significant at 31–60 days and 91–365 days post-discharge, but not during the 61–90-day interval.

Study Objectives

Primary Objective:

To reduce the risk of infections within 90 days following hospital discharge after a severe episode of acute kidney injury (AKI).

Secondary Objectives:

To evaluate the risk of rehospitalization, infection-related rehospitalization, septic shock, major adverse kidney events (MAKE) at 90 days, incidence of hyperkalemia, and new episodes of acute kidney injury. Adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and classified as mild, moderate, or severe. AEs of special interest include skin rash, erythema, nausea, vomiting, headache, and tachycardia.

Working Hypothesis

Hypothesis: Administration of trimethoprim–sulfamethoxazole 800/160 mg every 48 hours for 90 days reduces the risk of infections.

Null Hypothesis: Administration of trimethoprim–sulfamethoxazole 800/160 mg every 48 hours for 90 days does not reduce the risk of infections.

Materials and Methods

• This study will be a phase 2, randomized, prospective, double-blind, investigator-initiated, parallel-group, placebo-controlled clinical trial conducted at the Hospital Civil de Guadalajara “Fray Antonio Alcalde”, Guadalajara, Mexico. All patients with AKI receiving nephrology consultation will be considered for inclusion.
• The diagnosis of AKI will follow the Kidney Disease: Improving Global Outcomes (KDIGO) serum creatinine criteria. In accordance with the recommendations of the 31st Acute Disease Quality Initiative Group regarding the design of clinical trials for AKI treatments, the subphenotype of patients at the highest risk of post-AKI infections will be selected. This study will be considered a phase 2 randomized, double-blind, placebo-controlled trial meeting efficacy (AKI trajectory and eGFR evaluation), feasibility (patient recruitment and protocol adherence), and safety (adverse events and drug reactions) objectives.
• Group randomization will be performed using the clinical trial randomization tool available at http://www.winepi.net/f108.php, employing traditional block randomization. Sequences for each arm and stratum will be generated using maximal asymptotic randomization.
• Patients will be recruited on an outpatient basis to document any infectious event of any kind occurring within the first 90 days, as well as cases of rehospitalization due to infection within the same period at the Hospital Civil de Guadalajara “Fray Antonio Alcalde”.

Study Population

Patients diagnosed with severe acute kidney injury (AKI) who have been discharged from the hospital and receive nephrology follow-up at the Hospital Civil de Guadalajara “Fray Antonio Alcalde”, Guadalajara, Mexico. This group will include patients with diverse demographic and clinical characteristics who meet the inclusion criteria established in the study protocol.

Observation Unit

Patients diagnosed with severe AKI will be monitored for a period of 90 days after hospital discharge. Each participant will be evaluated based on infection incidence, rehospitalization, adverse events, and other health outcomes related to trimethoprim–sulfamethoxazole administration. Observation will focus on collecting clinical data and health outcomes specific to each participant.

Sample Size

To determine, with a 95% confidence level and 90% statistical power, whether the proportion of 59% in sample A differs from 29.5% in sample B, a total of 60 individuals per group will be required.
This study aims to detect a clinically significant difference of 0.8 ($Z\alpha/2 = 1.96$, $Z\beta = 0.84$) with a standard deviation of 1.5. Sample size calculations are based on the assumption

that approximately 30% of patients with AKI will experience a subsequent infection.

Sampling Method

Potential participants for this study will be identified during routine hospital rounds for patients with acute kidney injury (AKI) and through concurrent review of medical records to confirm eligibility. If a patient is deemed eligible, the principal investigator will contact them to explain the study and provide a participant information and consent form.

After discussion with the patient and family members, the nephrology staff will obtain written informed consent prior to any study-related evaluations.

The intervention drug will be trimethoprim–sulfamethoxazole 800/160 mg, administered under double-blind conditions. Blinding will be achieved by ensuring that participants do not witness preparation of the study medication, and by assigning unblinded study personnel—who will not participate in outcome assessments—to handle preparation and administration.

The placebo will consist of magnesium tablets, administered at the same frequency—one tablet every 48 hours for three months.

Control Group Definition

The control group will include patients who, during hospitalization at the Old Civil Hospital of Guadalajara “Fray Antonio Alcalde”, were identified by the Nephrology Service as having severe acute kidney injury that had resolved or was in the process of recovery. These patients will have been discharged with standard post-AKI management and care, without the addition of antibiotic prophylaxis.

Inclusion Criteria

Patients with severe AKI and known baseline serum creatinine (SCr) levels—defined as the most recent SCr value within the six months preceding hospitalization—will be included. Participants must also have available serum creatinine data for the months following discharge to assess major adverse kidney events (MAKE) at 90 days post-AKI.

Exclusion Criteria

Patients will be excluded if they: Experienced AKI within the previous three months, Are younger than 18 years, Have CKD stage 5, chronic dialysis, or kidney transplant, Had a hospital stay shorter than 48 hours, Have incomplete data preventing full análisis

Elimination Criteria

- Patients who partially or completely discontinue the prophylactic antibiotic before completing three months of treatment
- Patients rehospitalized for non-infectious causes within the first three months
- Patients who take a different dose of prophylactic antibiotic than prescribed

Operationalization of Variables

Independent Variable:

- Treatment: Administration of the study drug versus placebo (categorical variable with two levels: active treatment or placebo).

Dependent Variables (Primary Outcomes):

- Development of gastrointestinal infections — categorical nominal binary variable (yes/no)

- Development of upper respiratory infections — categorical nominal binary variable (yes/no)
- Development of lower respiratory infections — categorical nominal binary variable (yes/no)
- Development of urinary tract infections — categorical nominal binary variable (yes/no)
- Development of soft tissue infections — categorical nominal binary variable (yes/no)
- Rehospitalization due to infection — categorical nominal binary variable (yes/no)
- Development of septic shock — categorical nominal binary variable (yes/no)
- Requirement for long-term renal replacement therapy — categorical nominal binary variable (yes/no)
- Death from any cause — categorical nominal binary variable (yes/no)
- Progression to chronic kidney disease or ≥50% decline in eGFR — categorical nominal binary variable (yes/no)
- Worsening renal function with ≥25% decline in eGFR due to infection — categorical nominal binary variable (yes/no)
- Presence of hyperkalemia — categorical nominal binary variable (yes/no)
- Adverse drug reactions — categorical nominal variable

Data Collection and Observation Techniques

Data will be collected through automated extraction from the institutional electronic medical record system. Additional potential contributors to AKI—such as nephrotoxic medications (aminoglycosides, nonsteroidal anti-inflammatory drugs, and vancomycin)—will also be considered.

The presence of anaphylactic shock will be documented, and relevant biochemical parameters, such as serum iron levels and transferrin saturation, will be recorded for analysis.

Indications for renal replacement therapy (RRT) will include:

- Fluid overload refractory to diuretics
- Severe hyperkalemia
- Severe metabolic acidosis
- Uremic manifestations such as encephalopathy, pericarditis, or seizures

The study will be submitted to the Institutional Review Board (IRB) of the Hospital Civil de Guadalajara “Fray Antonio Alcalde” and registered at ClinicalTrials.gov with the corresponding registration number.

This research will adhere to the ethical principles outlined in the Declaration of Helsinki and will be designed in accordance with CONSORT (Consolidated Standards of Reporting Trials) guidelines.

Statistical Analysis

An intention-to-treat approach will be adopted, including all randomized participants who receive the intervention, for both primary and secondary outcomes.

Categorical variables will be expressed as counts and percentages (%) and compared using either the chi-square test or Fisher’s exact test, as appropriate.

Continuous variables will be reported as median values (IQR), since normal distribution is not expected according to the Shapiro–Wilk test; between-group comparisons will be performed using the Mann–Whitney U test.

A repeated-measures analysis of variance (ANOVA) will be used to compare variables over time between groups. A Kaplan–Meier survival curve will be plotted for both groups and compared using the log-rank test. Missing data will be imputed using the mean linear interpolation method.

All statistical tests will be two-tailed, and a p-value < 0.05 will be considered statistically significant.

The analyses and figures will be performed using MedCalc software (Version 22.0.21, Ostend, Belgium) and GraphPad Prism (Version 10.2.3, Boston, Massachusetts, USA).

Presentation of Information

- Table of demographic characteristics comparing the intervention and control groups
- Quantitative comparison table of reported infections
- Kaplan–Meier comparative survival curve between intervention and control groups

Required Resources

- The database will be compiled by the supervising resident physician and the

assigned medical intern.

- Material resources required include:
    - Computer equipment for data collection
    - Supply of trimethoprim–sulfamethoxazole 800/160 mg tablets, administered every 48 hours for three months per patient
    - The trimethoprim–sulfamethoxazole tablets will be funded by the research team itself.

Dissemination

The study findings will be disseminated through scientific conferences, academic presentations, and peer-reviewed

Referencias Bibliográficas

- Molitoris BA. Low-Flow Acute Kidney Injury: The Pathophysiology of Prerenal Azotemia, Abdominal Compartment Syndrome, and Obstructive Uropathy. Clin J Am Soc Nephrol. 2022 Jul;17(7):1039-1049. doi: 10.2215/CJN.15341121. Epub 2022 May 18. PMID: 35584927; PMCID: PMC9269622.
- Lee SA, Cozzi M, Bush EL, Rabb H. Distant Organ Dysfunction in Acute Kidney Injury: A Review. Am J Kidney Dis. 2018 Dec;72(6):846-856. doi: 10.1053/j.ajkd.2018.03.028. Epub 2018 Jun 14. PMID: 29866457; PMCID: PMC6252108.
- Lysak N, Bihorac A, Hobson C. Mortality and cost of acute and chronic kidney disease after cardiac surgery. Curr Opin Anaesthesiol. 2017 Feb;30(1):113-117. doi: 10.1097/ACO.0000000000000422. PMID: 27841788; PMCID: PMC5303614.
- Matsuura R, Doi K, Hamasaki Y, Nangaku M. RRT Selection for AKI Patients With Critical Illness. Semin Nephrol. 2020 Sep;40(5):498-505. doi: 10.1016/j.semnephrol.2020.08.006. PMID: 33334463.
- Chávez-Iñiguez JS, Sánchez-Villaseca SJ, García-Macías LA. Síndrome cardiorrenal: clasificación, fisiopatología, diagnóstico y tratamiento. Una revisión de las publicaciones médicas [Cardiorenal syndrome: classification, pathophysiology, diagnosis and management. Literature review]. Arch Cardiol Mex. 2022 Apr 4;92(2):253-263. Spanish. doi: 10.24875/ACM.20000183. PMID: 34261129; PMCID: PMC9005172.
- Inker LA, Titan S. Measurement and Estimation of GFR for Use in Clinical Practice: Core Curriculum 2021. Am J Kidney Dis. 2021 Nov;78(5):736-749. doi: 10.1053/j.ajkd.2021.04.016. Epub 2021 Sep 11. PMID: 34518032.
- Claure-Del Granado R, Macedo E, Chávez-Íñiguez JS. Biomarkers for Early Diagnosis of AKI: Could It Backfire? Kidney360. 2022 Sep 8;3(10):1780-1784. doi: 10.34067/KID.0001012022. PMID: 36514722; PMCID: PMC9717653.
- Kuwabara S, Goggins E, Okusa MD. The Pathophysiology of Sepsis-Associated AKI. Clin J Am Soc Nephrol. 2022 Jul;17(7):1050-1069. doi: 10.2215/CJN.00850122. Epub 2022 Jun 28. PMID: 35764395; PMCID: PMC9269625.
- Achanti A, Szerlip HM. Acid-Base Disorders in the Critically Ill Patient. Clin J Am Soc Nephrol. 2023 Jan 1;18(1):102-112. doi: 10.2215/CJN.04500422. Epub 2022 Aug 23. PMID: 35998977; PMCID: PMC10101555.
- Cecconi M, Evans L, Levy M, Rhodes A. Sepsis and septic shock. Lancet. 2018 Jul 7;392(10141):75-87. doi: 10.1016/S0140-6736(18)30696-2. Epub 2018 Jun 21. PMID: 29937192.
- Chen L, Rackley CR. Diagnosis and Epidemiology of Acute Respiratory Failure. Crit Care Clin. 2024 Apr;40(2):221-233. doi: 10.1016/j.ccc.2023.12.001. Epub 2023 Dec 26. PMID: 38432693.
- Kurmani S, Squire I. Acute Heart Failure: Definition, Classification and Epidemiology. Curr Heart Fail Rep. 2017 Oct;14(5):385-392. doi: 10.1007/s11897-017-0351-y. PMID: 28785969; PMCID: PMC5597697.
- Vasques F, Cavazza A, Bernal W. Acute liver failure. Curr Opin Crit Care. 2022 Apr 1;28(2):198-207. doi: 10.1097/MCC.0000000000000923. PMID: 35142727.
- Matsuura R, Doi K, Rabb H. Acute kidney injury and distant organ dysfunction-network system analysis. Kidney Int. 2023 Jun;103(6):1041-1055. doi: 10.1016/j.kint.2023.03.025. Epub 2023 Apr 6. PMID: 37030663.

- Chávez-Íñiguez JS, Maggiani-Aguilera P, Pérez-Flores C, Claure-Del Granado R, De la Torre-Quiroga AE, Martínez-Gallardo González A, Navarro-Blackaller G, Medina-González R, Raimann JG, Yanowsky-Escatell FG, García-García G. Nephrologist Interventions to Avoid Kidney Replacement Therapy in Acute Kidney Injury. Kidney Blood Press Res. 2021;46(5):629-638. doi:
- Tagawa M, NishimotoM, KokubuMet al. Acute kidney injury as an independent predictor of infection and malignancy: the NARA-AKI cohort study. J Nephrol 2019;32:967–75
- Kellum JA, Romagnani P, Ashuntantang G et al. Acute kidney injury. Nat Rev Dis Primers 2021;7:52 Steiger S, Rossaint J, Zarbock A et al. Secondary immunodeficiency related to kidney disease (SIDKD) – definition, unmet need, and mechanisms. J Am Soc Nephrol 2022;33: 259–78
- Xu H, Gasparini A, Ishigami J et al. eGFR and the risk of community-acquired infections. Clin J Am Soc Nephrol 2017;12:1399–408
- Su G, Trevisan M, Ishigami J et al. Short- and long-term outcomes after incident pneumonia in adults with chronic kidney disease: a time-dependent analysis from the Stockholm CREAtinine Measurement project. Nephrol Dial Transplant 2020;35:1894–900
- LaFavers K. Disruption of kidney-immune system crosstalkin sepsis with acute kidney injury: lessons learned fromanimal models and their application to human health. Int J Mol Sci 2022;23:1702
- Syed-Ahmed M, Narayanan M. Immune dysfunction and risk of infection in chronic kidney disease. Adv Chronic Kidney Dis 2019;26:8–15
- Griffin BR, You Z, Holmen J, SooHoo M, Gist KM, Colbert JF, Chonchol M, Faubel S, Jovanovich A. Incident infection following acute kidney injury with recovery to baseline creatinine: A propensity score matched analysis. PLoS One. 2019 Jun 24;14(6):e0217935. doi: 10.1371/journal.pone.0217935. PMID: 31233518; PMCID: PMC6590794.