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Randomized Trial of Empiric Versus Selective Prevention Strategies for Kidney Stone Disease

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Randomized Trial of Empiric Versus Selective Prevention Strategies for Kidney Stone Disease

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1.0 Background

Kidney stone prevalence over the last few decades has dramatically risen in all demographic groups, especially among women, children, and minorities.¹⁻³ Severe, debilitating flank pain is the clinical hallmark of a kidney stone event, often associated with acute kidney injury, urinary symptoms, and infection. After the first stone episode, symptomatic recurrence occurs in 20% at 5 years and 31% at 10 years.⁴ Over 20% of stone formers have had ≥ 3 stone events.⁵ The recurrent, episodic nature of this condition leads to multiple healthcare encounters in planned and unplanned settings, contributing to the >\$10 billion annual cost of care.⁶

Dietary and pharmacologic interventions for preventing future kidney stone episodes are effective.^{7,8} To help clinicians choose among the various interventions, clinical guideline panels recommend *selective therapy*: performing 24-hour urine testing to direct specific interventions to correct abnormal urinary parameters.⁹⁻¹¹ However, 24-hour urine testing is limited in its ability to predict stone recurrence, burdensome, complex for clinicians to interpret, costly, and potentially delays therapy initiation.¹²

An alternative strategy is *empiric therapy*: applying interventions without 24-hour urine testing.¹³ The efficacy of empiric therapy is supported by multiple dietary and pharmacologic trials showing reduction in stone events compared to placebo regardless of baseline urine testing results, and trials that did not require testing of urine chemistry.^{12,14-17}

To date, the efficacy of selective versus empiric therapy for kidney stone prevention has not been studied. We propose two randomized clinical trials of selective versus empiric therapy for patients with idiopathic calcium stone disease, representing >80% of the kidney stone population.^{18,19} The primary outcome is change in urinary supersaturation, which associates with symptomatic stone recurrence.^{20,21}

2.0 Rationale and Specific Aims

The aims of this study are to:

1. Conduct a randomized clinical trial of selective versus empiric dietary therapy in low-risk stone formers.
2. Conduct a randomized clinical trial of selective versus empiric diet plus pharmacologic therapy in high-risk stone formers.

3.0 Previous Human Studies

Both dietary and pharmacologic interventions have been shown to be effective in reducing kidney stone recurrence in patients with kidney stone disease.^{7,8} However, these interventions can be costly, burdensome, and have side effects – this is important because these interventions are often made over a lifetime since kidney stone disease is a chronic condition with a lifetime of risk. Therefore, in current practice, clinical guidelines recommend 24-hour urine testing to identify urinary abnormalities and enable clinicians to select specific diet and pharmacologic interventions.⁹⁻¹¹

This current strategy of identifying and intervening on specific abnormalities from urine testing is called selective therapy, which has been the dominant strategy to prevent kidney stone recurrence over the last 4 decades.²² While this approach to stone prevention is rational, 24-hour urine testing has several drawbacks that limit its utility.¹² The test results are complex to interpret. Clinicians are intimidated by urinary chemistry and renal physiology, which contributes to the neglect of 24-hour urine utilization: only 7% of Americans at high-risk for recurrence receive 24-hour urine testing.²³ In addition, the test has limited ability to predict stone recurrence and response.¹² Often repeat testing is needed to confirm borderline values,^{24,25} monitor compliance and treatment effect,⁹⁻¹¹ or address inadequate collection completeness^{26,27} – adding to the cost burden of testing.

The 2015 NIDDK symposium “Urinary Stone Disease: Research Challenges and Opportunities” included basic scientists, nephrologists, and urologists charged with prioritizing clinical and basic research needs for stone disease.^{28,29} During a panel discussion on “Strategies to Prevent Urinary Stone Disease Recurrence”, a conclusion was that “the role of 24-hour urines to guide therapy should be systemically assessed”. The panel recommended an effort to “undertake a practical trial in calcium stone formers with three arms to compare diet/fluids versus diet/fluids plus thiazide versus diet/fluids plus citrate, with an analysis of baseline urine chemistries to determine whether they influenced the response and thus were necessary”.

This alternative strategy of administering diet and/or pharmacologic interventions without identification of abnormal urinary parameters is called empiric therapy.¹³ This strategy is supported by several randomized controlled diet and pharmacologic trials in which the identification of baseline urinary calcium, oxalate, and citrate did not predict symptomatic kidney stone recurrence.⁸ Some positive trials of citrate therapy did not require the intervention group to have hypocitraturia.^{14,15} The same was true for several thiazide trials that did not require hypercalciuria as an inclusion criteria.^{16,17} The only positive dietary intervention trial by Borghi et al did not require more than hypercalciuria among eligible participants.³⁰

No trials have compared selective versus empiric pharmacologic intervention strategies. Evidence to support any form of selective therapy is lacking. The only study comparing empiric versus selective therapy was a dietary intervention study by Kocvara et al. among first-time stone formers.³¹ At 3 years, stone recurrence occurred in 7% of the selective therapy group and 23% of the empiric therapy group. However, the major flaw was significant follow-up bias: only follow-up visits were performed in the selective therapy group. This bias is well-described as the “stone-clinic effect”, where follow-up visits with fluid and dietary reminders result in reduced recurrence rates. The stone-clinic effect has been consistently observed in placebo arms of numerous intervention trials.^{12,14-17,32-40} Based on the methodologic flaws of the Kocvara et al. study, a 2012 AHRQ (Agency for Healthcare Research Quality) report on research gaps in recurrent stone prevention highlighted the need to “evaluate effectiveness and harms of single and/or multicomponent biochemistry screening strategies followed by a comparison of different diet and/or pharmacological treatment strategies (e.g., targeted treatment or empiric treatment or control) with adequate power for clinical outcomes”.⁴¹

For low risk patients, clinical guidelines recommend 24-hour urine testing in interested first-time stone formers.⁹ If empiric therapy were at least equivalent to selective strategies in reducing recurrence risk, avoiding the 24-hour urine test would reduce the cost of care for these patients due to less testing and fewer office visits. For high risk patients, only 7% of Americans at high-risk for recurrence receive 24-hour urine testing,²³ despite strong recommendations from clinical guidelines⁹⁻¹¹ (a “Standard” according to the American Urological Association⁹). Evidence to support selective therapy and 24-hour urine testing is needed to change clinical practice and increase the rate of appropriate testing in populations that would benefit.

4.0 Inclusion/Exclusion Criteria

- Inclusion criteria for the dietary intervention study
 - 1 lifetime symptomatic kidney stone event, or one having had 1 event in the last 5 years
- Exclusion criteria for the dietary intervention study

Medullary sponge kidney or renal tubular acidosis	Untreated urinary obstruction
Primary hyperparathyroidism or hyperoxaluria	Cancer in the past 5 years
Inflammatory bowel disease or bowel resection	Pregnancy
Sarcoidosis, cystinuria	Change in diuretic dosing within 30 days
Prior stone composition with uric acid, struvite, cystine, carbonate apatite	Pharmacologic treatment for stone prevention within 3 months

- Inclusion criteria for the dietary and pharmacologic intervention study
 - 2 symptomatic kidney stone events in the last 5 years
- Exclusion criteria for the dietary and pharmacologic intervention study

Medullary sponge kidney or renal tubular acidosis	Untreated urinary obstruction
Primary hyperparathyroidism or hyperoxaluria	Cancer in the past 5 years
Inflammatory bowel disease or bowel resection	Pregnancy
Sarcoidosis, cystinuria	Change in diuretic dosing within 30 days
Prior stone composition with uric acid, struvite, cystine, carbonate apatite	Pharmacologic treatment for stone prevention within 3 months

- will additionally exclude those with use of specific medications (thiazides, topiramate, xanthine oxidase inhibitors, citrate, bicarbonate), a history of chronic kidney disease stage 3 or higher (eGFR<60), gouty arthritis or 3 gout episodes in 1 year, known allergy to study medications, or hypokalemia or hyponatremia at screening.

5.0 Enrollment/Randomization

Recruitment will occur at the Vanderbilt University Medical Center urology clinic. We will distribute flyers on the Vanderbilt campus and through the Vanderbilt Research Notification Distribution List. Allocation concealment will be ensured. We will randomize stratified by sex in to blocks of 4 participants. This will ensure that equal numbers by sex are allocated to each group.

6.0 Study Procedures

In the dietary intervention only study, both groups will undergo visits at baseline and at 1-month. These can be in-person or virtual. As part of routine clinical care, participants will have already completed 24hr urine testing and BMP within 12 months of enrollment. Testing of 24-hour urine collections will occur just prior to 1-month and finally at 2 months (2 collections total). This ensures similar follow-up and testing in both groups. The empiric therapy group will have identical instructions given at baseline and 1 month (see Table 1 below). The selective therapy group will have targeted dietary instructions at baseline and at 1 month based on 24-hour urine testing (see Table 2), enabling iterative adjustment at 1-month. Allocation to treatment will be concealed to investigators and subjects. In addition, 24-hour urine results will not be provided to investigators or subjects; we designed the selective interventions to be formulaic and free of interpretation or bias as much as possible.

Table 1. Empiric dietary therapy

High water intake – at least 2 liters daily (3 liters in warm weather)
Reduce soda intake to less than 3 cans per week.
Moderate salt intake for goal <2000mg sodium daily
Restriction of animal protein intake
Normal calcium intake (3-4 servings per day)
Increase vegetable and fiber intake
Avoid intake of the highest oxalate foods: spinach, rhubarb, beets, almonds

Table 2. Selective dietary therapy

Urinary parameter	Intervention
Volume <2.5L	Drink water to reach 2.5L based on specific urine volume
Calcium >250mg male, >200mg female	Restrict animal proteins, reduce sugar intake, reduce salt intake, avoid calcium and vitamin D supplements
Oxalate >40mg	Restriction of dietary oxalates, maintain intake of dairy products, increase fiber intake
Citrate <450mg male, <550mg female	Restrict animal proteins, increase fruit, and vegetable intake
pH<5.8	Restrict animal proteins, increase fruit, and vegetable intake
Uric acid >800mg male, >750mg female	Restrict animal proteins, increase fruit, and vegetable intake
Sodium >150mmol	Reduce salt intake for goal <2000mg sodium daily
Sulfate > 80mEq or urine urea nitrogen >14g	Restrict animal proteins, increase fruit, and vegetable intake

In the dietary and medical intervention only study, both groups will undergo visits at baseline, 1-month, and 2 months. The baseline visit can be virtual if participants have had 24hr urine testing and blood work (serum BMP, uric acid, magnesium) done as part of routine clinical care within 12 months of enrollment. Subjects will undergo 24-hour urine testing prior each visit (prior to 1 month visit and prior to 2 month visit). Dietary recommendations in the respective selective and empiric groups will be given as in the dietary only study. Selective pharmacologic therapy (see Table 3) will target specific abnormalities identified by the 24-hour urine, as recommended by clinical guidelines.⁹⁻¹¹ At the baseline visit, the urinary parameter with the most severe abnormality (n times above reference range) will be targeted at the baseline visit. At the 1-month visit, persistent abnormalities will have adherence assessed and may have dose adjustment (Table 3 right column). Empiric pharmacologic therapy will be once daily indapamide 1.25mg daily with potassium citrate 15mEq given throughout the 2-month duration. Indapamide is effective in decreasing urinary calcium levels and reduces stone recurrence.⁵⁹⁻⁶¹ Potassium citrate is given to reduce the risk of hypokalemia from indapamide, with a small benefit from the citrate component at this dose.^{14,15} We minimize the side effect profile of indapamide by choosing the lower dose (1.25mg rather than 2.5mg daily) while maintaining efficacy in reducing urinary calcium and stone events;^{59,60} and this is also the

most common dose prescribed in general (Vanderbilt data: 47% 1.25mg vs 36% 2.5mg vs 5mg 16% daily). Allocation to treatment will be concealed to both investigators and subjects, but we acknowledge that patients and researchers may be able to deduce their group assignment. Visits at baseline, 1 month, and 2 months will assess adherence, safety (side effects), blood pressure, and serum tests (e.g. potassium, sodium, random glucose).

Table 3 Selective pharmacologic therapy (all doses are daily)

Urinary parameter	Baseline or 1 month (newly identified)	At 1 month (if persistent ^a)
Calcium >250mg male, >200mg female	Indapamide 1.25mg + potassium chloride 20mEq ^{b,c}	Indapamide 2.5mg + potassium chloride 20mEq
Oxalate >40mg	None	None
Citrate <450mg male, <550mg female	Potassium citrate 15mEq BID	Potassium citrate 30mEq BID
pH<5.8	Potassium citrate 15mEq BID	Potassium citrate 30mEq BID
Uric acid >800mg male, >750mg female	Allopurinol 300mg	Continue Allopurinol 300mg

^a If persistent abnormality then will first check adherence with baseline medication

^b If both elevated calcium and low pH: indapamide 1.25mg and potassium citrate 15mEq BID

^c If both elevated calcium and low citrate: indapamide 1.25mg and potassium citrate 15mEq BID

To assess for adherence to diets, we will ask participants to complete a self-reported, written food diary or on a secure web portal in REDCap within 24-48 hrs of the 24hr urine collection. This is so that we can analyze this data if there is a concern for poor adherence based on the 24hr urine results.

7.0 Outcomes and Power Analysis

The primary outcome will be mean calculated calcium oxalate supersaturation at compared 2 months. Secondary outcomes compared at 2 months are: calcium phosphate urinary supersaturation, uric acid urinary supersaturation, urinary volume, calcium, oxalate, potassium, citrate, pH, uric acid, and sodium. In the 2-month timeframe of the study, we would expect the occurrence of symptomatic stone events to be very rare in this low-risk population. We will explore the change in urinary parameters from baseline to 1-month in both groups. In the selective group we will explore changes from 1-month to 2-months to assess iterative dietary adjustment. We will also assess adherence to medications determined by pill counts, adverse events, and symptomatic stone events, although this is unlikely to occur in the short timeframe.

Prior studies have shown that a calcium oxalate supersaturation difference of 3.3 is clinically meaningful and associates with clinical stone events.^{20,21,54} We estimate the standard deviation of calcium oxalate supersaturation at 3.6 based on prior studies.^{26,55,56}

For the dietary only study, if we set the non-inferiority margin at a supersaturation of 3.3, the required sample size needed is n=20 per group for 80% power. We will therefore aim to recruit 24 subjects per arm to ensure adequate sample size is attained. Block randomization with block sizes of 2 and 4 will ensure sex will be balanced. At Vanderbilt,

there is roughly equivalent 1:1 male: female ratio undergoing 24-hour urine testing. Patient characteristics on all randomized patients will be summarized. A regression model will be fit for calcium oxalate supersaturation with treatment and sex as covariates. The treatment difference will be estimated using this regression model, and non-inferiority will be concluded if a 95% two-sided confidence interval for the treatment difference is wholly above -3.3. For non-inferiority design analysis, we will perform both intention-to-treat and per-protocol (only non-dropouts), as recommended for non-inferiority designs,^{57,58} and require both analyses to show non-inferiority to conclude non-inferiority of the interventions.

For the dietary and pharmacologic study, the power analysis is similar in this superiority study for 80% power to detect a difference of calcium oxalate supersaturation 3.3. If the superiority threshold is not met, we will perform a non-inferiority analysis with the same non-inferiority margin as in Aim 1. There is no multiplicity penalty for testing both superiority and non-inferiority.⁶² We will aim to recruit 24 patients per arm, and use the intention-to-treat analysis as the primary approach. We do not anticipate difficulty with recruitment, as over one-third of patients undergo 24-hour urine testing at Vanderbilt have had 2 stone events in the last 5 years.

8.0 Risks

The safety risk from the dietary interventions would be expected to be extremely low, as they are considered health-promoting dietary changes. In the study where pharmacologic interventions are performed, we anticipate minimal risk, since all of the medications and all of their doses are already commonly prescribed for the last >20 years of clinical practice and in use for kidney stone prevention and for other conditions (e.g. preventing gout attacks, treatment of hypertension). All medications are given at the lowest dose to achieve efficacy in order to minimize side effects. Even if side effects to medications were to occur, we have adopted appropriate strategies to minimize possibility these risks would occur, and even if they did occur, the risk would be minimal. Subjects will be given direct contact methods to reach our research nurse or Dr. Hsi should any adverse events occur. At each study visit, we will assess adherence (pill counts), safety (side effects), blood pressure, serum basic metabolic panel (e.g. potassium, sodium, calcium, random glucose), serum uric acid, and serum magnesium. We will assess for the following safety outcomes:

- Hypokalemia, defined as blood potassium level < 3 mmol/L.
- Hyponatremia, defined as blood sodium level < 125 mmol/L.
- Hypomagnesemia, defined as blood magnesium level < 0.5 mmol/L.
- Gouty arthritis or requiring uric acid lowering therapy.
- Newly developed overt diabetes mellitus (defined as fasting glucose level $\geq$ 7 mmol/L or random Glucose $\geq$ 11 mmol/L).
- Allergic reaction if considered by the local investigator to be potentially related to the study medication.
- Heart rate, systolic and diastolic blood pressure at the right arm in sitting position after at least 5 min rest will be recorded at all study visits.

9.0 Reporting of Adverse Events or Unanticipated Problems involving Risk to Participants or Others

In the event of adverse effects on participants, Dr. Hsi will ensure necessary medical or professional intervention promptly. Serious or unanticipated complications will be promptly reported to the IRB within 48 hours, including serious medication side effects, any breach in confidentiality that may involve risk to the subject, any complaints of a subject that indicates an unanticipated risk or that cannot be resolved by the principal investigator, and any new information that indicates an unexpected change to the risk/benefit ratio of the research.

10.0 Study Withdrawal/Discontinuation

Study participants can stop the medications and withdraw from the study at any time and for any reason, including the occurrence of serious adverse events. If necessary, the study can be stopped early if there is an ethical or safety concern based on the potential to minimize harm and maximize benefit for the subjects.

11.0 Privacy/Confidentiality Issues

Risks to privacy and confidentiality will be minimized in this study. All study personnel will have training in procedures to ensure patient privacy, confidentiality and in the HIPAA privacy rule. Only persons directly involved in the study will have access to data identifying individual patients. Forms are kept in file cabinets within locked rooms when not in use. All data to be analyzed will be de-identified and labeled with only with a unique research code for each participant. The electronic data will be stored in the REDCap (Research Electronic Data Capture) database. This database is secure and password protected.

12.0 Follow-up and Record Retention

Research data will be kept for 5 years after the study is finished, and then the data will be deleted.

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