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Medical Management of Kidney Stones

Kidney stone disease (nephrolithiasis) is a common condition affecting approximately 1 in 11 individuals in the United States.[1] Kidney stones form in the upper urinary tract. If the stone moves into the ureter, it can obstruct the urinary tract and lead to mild to severe flank pain, infection, blood in the urine, nausea, vomiting, painful urination, and/or urgency.[2,3] Kidney stone disease is burdensome physically and financially. Acute pain from the passage of a kidney stone is one of the leading causes of emergency room visits,[2] and the annual overall cost of caring for individuals with kidney stone disease in the U.S. is estimated at $2.1 billion.[4]

The overall incidence of kidney stones is increasing and the lifetime prevalence among Americans is two times greater than it was 40 years ago.[2] Although kidney stones are more prevalent in men than women, recent studies indicate that the incidence is increasing for both groups.[5] Stone recurrence is also common; in about 50% of first-time stone formers, if the underlying cause(s) of the stone formation are not addressed, then kidney stones have a high likelihood of recurrence within 10 years.[6]

Medical management of individuals with kidney stone disease aims to prevent the growth of existing stones and the formation of new ones. While not all kidney stones are caused by dietary factors, prevention with nutritional measures targeted at urinary or dietary risk factors is useful in many cases. Accordingly, medical management may include general lifestyle/diet modifications [e.g., increased fluid intake, weight loss, consumption of less salt (sodium chloride), decreased protein intake, reduced oxalate intake, increased intake of fruit and vegetable], drug therapy, or both.[7] Additional preventive measures may also be recommended for individuals with specific stone types. Some risk factors reflect intrinsic metabolic abnormalities, and correction of these abnormalities with pharmacologic therapy may be indicated. Medical management ideally begins with an initial evaluation of metabolic risk factors and baseline 24-hour urine evaluation. It also often includes monitoring via regular imaging and additional 24-hour urine assessments.[7]

Four Clinical Practice Guidelines (CPGs) related to this topic have been published since 2019.[8-11] However, none are undergirded by a published systematic review and all were produced by non-US medical societies. Recent systematic reviews (published since 2020) are only partially relevant to the topic having assessed a narrow set of interventions.[12-22] Meanwhile, new randomized control trials[23-35] and observational studies[36-75] have accumulated in the last ten years but none have been incorporated in a recent, relevant review on treatment.[21]

Therefore, a new, high-quality systematic review on this topic that fully addresses all the KQs, updates the evidence, grades the strength of evidence, and supports an updated CPG produced by a US medical society, may be useful to the field and improve the quality and consistency of care of individuals with kidney stone disease in the U.S.

The Patient-Centered Outcomes Research Institute (PCORI) is partnering with the Agency for Healthcare Research and Quality (AHRQ) to develop a systematic evidence review on Medical Management of Kidney Stones based on nomination of the topic by the American Urological Association (AUA). The AUA

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published a guideline on this topic in 2014 informed by an AHRQ review, and plans to use the findings of this new systematic evidence review to update that guideline.

Draft Key Questions

KQ1: In children and adults with a history of nephrolithiasis, do results of baseline stone composition, diet assessment, and blood and urine chemistries predict the effectiveness of diet and/or pharmacological treatment for reducing stone recurrence, improving health outcomes, and reducing adverse effects?

KQ2: In children and adults with a history of nephrolithiasis, what are the comparative effectiveness and harms of pharmacological therapies, dietary therapies, or both in combination, compared to placebo or each other, in reducing stone recurrence and improving health outcomes?

KQ3: In children and adults with a history of nephrolithiasis who are treated with dietary and/or pharmacologic interventions to prevent stone recurrence, do results of follow-up blood and urine chemistries predict reduction in stone recurrence and health outcomes?

KQ4: What are the comparative harms and benefits of different imaging strategies to detect stone recurrence (i.e., imaging modality, interval of imaging)?

PICOTS

The Population, Interventions, Comparators, Outcomes, Timing, and Settings are described in Table 1 and Figures 1 and 2.

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Table 1. PICOTS

	KQ1 Baseline stone composition, diet assessment, and blood and urine chemistries	KQ2: Therapy Effectiveness	KQ3: Follow-up blood and urine chemistries	KQ4: Detection
Population	Non-pregnant children and adults with a history of nephrolithiasis (results stratified by age--children and adults). *Exclusion criteria: Children and adults without a history of nephrolithiasis, pregnant adults.*	Non-pregnant children and adults with a history of nephrolithiasis (results stratified by age--children and adults). *Exclusion Criteria: Children and adults without a history of nephrolithiasis, pregnant adults.*	Non-pregnant children and adults with a history of nephrolithiasis (results stratified by age--children and adults) treated with dietary and/or pharmacologic interventions to prevent stone recurrence. (Dietary (both targeted and empiric) and/or pharmacological treatment, including over-the-counter (OTC) medications or supplements.) *Exclusion Criteria: Children and adults without a history of nephrolithiasis, pregnant adults.*	Non-pregnant children and adults with a history of nephrolithiasis (Include children and adults with a history of nephrolithiasis who have undergone pharmacological and/or dietary interventions as a subgroup). *Exclusion criteria: Children and adults without a history of nephrolithiasis; pregnant adults.*

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	KQ1 Baseline stone composition, diet assessment, and blood and urine chemistries	KQ2: Therapy Effectiveness	KQ3: Follow-up blood and urine chemistries	KQ4: Detection
Intervention	OBTAINING AT BASELINE: stone composition/diet assessment/blood and urine chemistries before treatment (diet/pharmacological) is started. (Dietary and/or pharmacological treatment, including over-the-counter (OTC) medications or supplements. Dietary therapies include both targeted (e.g., to urinary risk factors and/or to findings of diet assessment) and empiric and may include monitoring of fluid, dietary calcium, sodium, bicarbonate precursors, and non-dairy animal protein intake; multicomponent diets. Pharmacologic therapies may include thiazide diuretics, potassium citrate, alkali citrate or bicarbonate, allopurinol, cystine-binding thiol, acetohyroxamic acid, Lumasiran, nedosiran. *Exclusion criteria: Non-dietary and non-pharmacological interventions.)*	Dietary (both targeted and empiric) and/or pharmacological treatment, including over-the-counter (OTC) medications or supplements. *Exclusion Criteria: Non-dietary and non-pharmacological interventions.*	OBTAINING IN FOLLOW-UP: blood and urine chemistries. *Exclusion criteria: Non-dietary and non-pharmacological interventions.*	Follow-up imaging to detect stone recurrence at specific intervals and (CT scans, renal ultrasounds, and abdominal radiograph, MRI, X-rays (KUB)) to evaluate stone size, stone composition, stone location, and stone shape. *Exclusion criteria: Imaging not used as a follow-up measure (e.g., diagnostic imaging at initial appointment).*
Comparators	NOT OBTAINING AT BASELINE: stone composition / diet assessment / blood and urine chemistries before treatment (diet/pharmacological) is started. (Placebo-controlled or comparative effectiveness studies of interventions where results are reported or stratified by baseline stone composition, baseline diet assessment, and/or blood and urine chemistries, or single-arm or observational studies of interventions where results are reported or stratified by baseline stone composition,	Dietary treatment (targeted and empiric) and/or pharmacological treatment, including over-the-counter (OTC) medications or supplements; placebo. *Exclusion Criteria: Non-dietary and non-pharmacological treatment, together or alone.*	NOT OBTAINING IN FOLLOW-UP: blood and urine chemistries. (No surgery, sham surgery, no treatment, dietary (both targeted and empiric) and/or pharmacological treatment, including over-the-counter (OTC) medications or supplements, no dietary therapy, placebo, treatments compared to each other.)	Other imaging modality to detect stone recurrence or other interval for imaging. Follow-up imaging (CT scans, renal ultrasounds, and abdominal radiograph) to predict stone size, stone composition, stone location, and stone shape. *Exclusion criteria: Imaging not used as a follow-up measure (e.g., diagnostic imaging at initial appointment).*

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	KQ1 Baseline stone composition, diet assessment, and blood and urine chemistries	KQ2: Therapy Effectiveness	KQ3: Follow-up blood and urine chemistries	KQ4: Detection
	baseline diet assessment, and/or blood and urine chemistries. *Exclusion Criteria: _______*		*Exclusion Criteria: None.*	
Outcomes	Effectiveness of diet and pharmacological treatments at preventing stone recurrence. **(**Formation of new stones, growth of existing stones, passage of previously unaccounted for stones, need for surgical intervention, and complications related to stone events; adverse events, broadly defined. *Exclusion criteria: Studies for which only outcome(s) are acute pain management and/or treatment to promote expulsion of stones.)*	Formation of new stones, growth of existing stones, passage of previously unaccounted for stones, need for surgical intervention, and complications related to stone events; adverse events, broadly defined. *Exclusion Criteria: Studies for which only outcome(s) are acute pain management and/or treatment to promote expulsion of stones.*	Final health outcomes and intermediate stone outcomes. (Formation of new stones, growth of existing stones, need for surgical intervention, and complications related to stone events; adverse events of the intervention, broadly defined. *Exclusion criteria: Studies for which only outcome(s) are acute pain management and/or treatment to promote expulsion of stones.)*	Formation/detection of new stones, stone recurrence, growth of existing stones, need for surgical intervention, and complications related to stone events; adverse events, broadly defined – should include radiation dose/exposure. *Exclusion criteria: Studies for which only outcome(s) are acute pain management and/or treatment to promote expulsion of stones.*
Timing	Follow-up not limited.	Follow-up not limited.	Follow-up not limited.	Follow-up not limited.
Settings	Setting not limited.	Setting not limited.	Setting not limited.	Setting not limited.
Study Design	RCT, CT, observational studies with comparator group, case-control studies, observational studies including post-only and pre-post studies, case-series for harms and as determined during Topic Refinement. *Exclusion criteria: exclude studies with population less than 30 per study arm.*	RCT, CT, observational studies with comparator group, case-control studies, observational studies including post-only and pre-post studies, case-series for harms and as determined during Topic Refinement. *Exclusion criteria: exclude studies with population less than 30 per study arm.*	RCT, CT, observational studies with comparator group, case-control studies, observational studies including post-only and pre-post studies, case-series for harms and as determined during Topic Refinement. *Exclusion criteria: exclude studies with population less than 30 per study arm.*	RCT, CT, observational studies with comparator group, case-control studies, observational studies including post-only and pre-post studies, case-series for harms and as determined during Topic Refinement. *Exclusion criteria: exclude studies with population less than 30 per study arm.*

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Figure 1. Draft Analytic Framework (Key Questions 1, 2, 3)

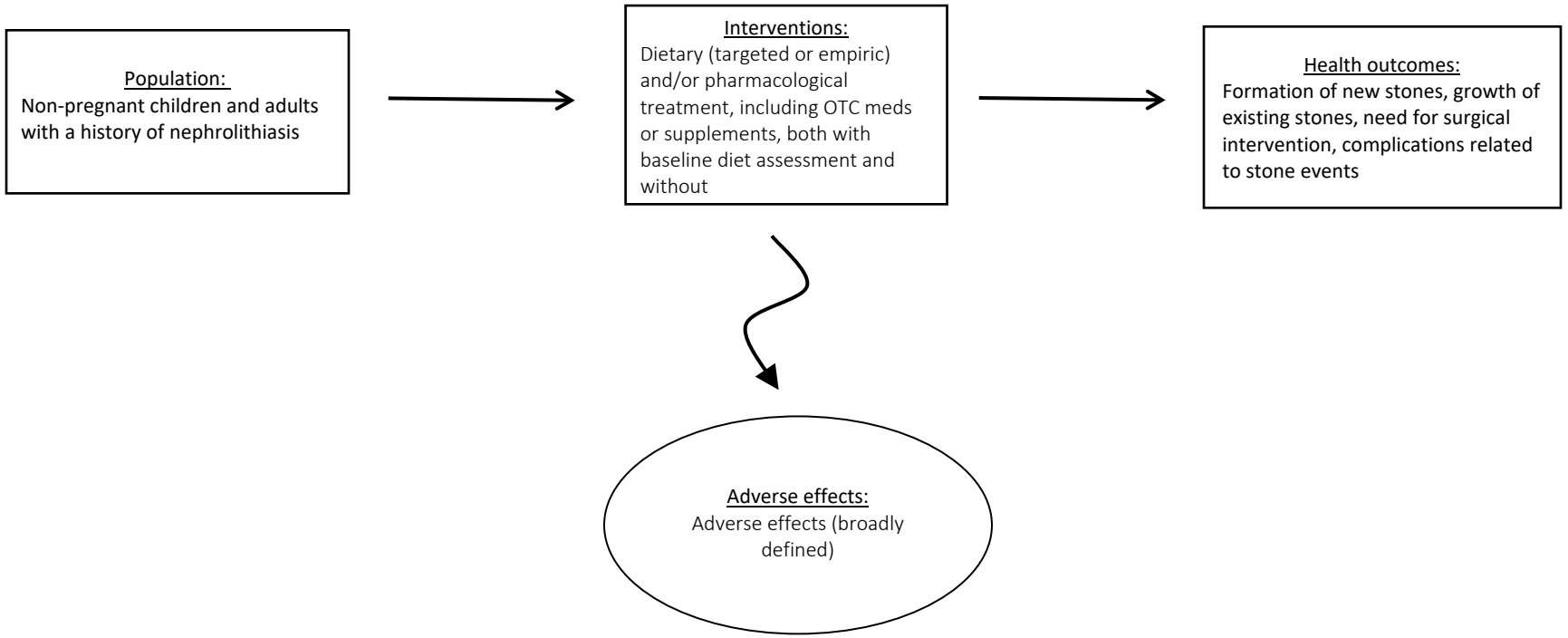

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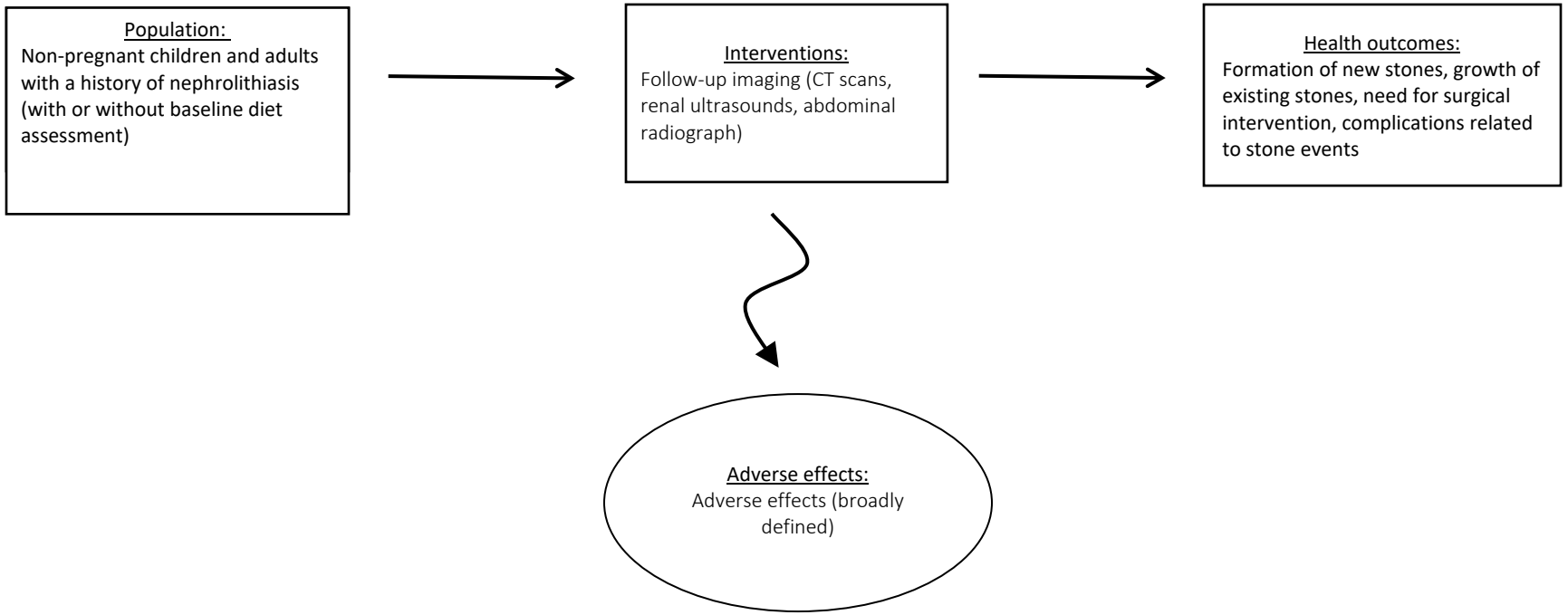
Figure 2. Draft Analytic Framework (Key Question 4)



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