Research Prioritization Topic Brief: Comparative Effectiveness of Dietary Manipulation and Medications for the Prevention of Recurrent Kidney Stones

Assessment of Prevention, Diagnosis and Treatment Options

PCORI Scientific Program Area:

Comparative Effectiveness Research

Communication and Dissemination

Executive Summary

PCORI-proposed Comparative Research Question: What is the comparative effectiveness of dietary manipulation and medications for the prevention of recurrent kidney stones?

Brief Overview of the Topic: Kidney stones are hard masses that form within the kidney or urinary tract. Kidney stones are also called urolithiasis or nephrolithiasis. Treatments to prevent recurrent kidney stones include diet and medications.

Impact on Health and Populations: Five percent of the United States population is at risk of recurrent kidney stones. Older age, white race and males are more likely to be affected, although the prevalence of kidney stones in other populations is increasing.

Assessment of Current Options: There are no direct comparisons of diet versus medication treatment strategies alone or in combination.

Likelihood of Implementation of Research Results in Practice: Evidence-based treatment guidelines are produced by societies and updated regularly, so it is very likely that new research results would be used in practice.

Durability of Information: Results are likely to be relevant for years. There have been no new treatments to prevent recurrent kidney stones in decades. No potential break-through treatments are currently undergoing clinical trials. There are no ongoing studies that compare diet and medications directly.

Topic 2: Comparative effectiveness of dietary manipulation and medications for the prevention of recurrent kidney stones

1. Contributors:

Susan Hutfless. PhD. Johns Hopkins Evidence Based Practice Center
Brian Matlaga. MD. Johns Hopkins Medical Institutions
Stephen Sozio. MD, MHS. Johns Hopkins School of Medicine
Catalina Suarez-Cuervo. MD. Johns Hopkins Evidence Based Practice Center
Tianjing Li. MD, MHS, PhD. Johns Hopkins Evidence Based Practice Center
Eric Bass. MD, MPH. Johns Hopkins Evidence Based Practice Center

2. Introduction:

Kidney stones are hard masses that form within the kidney or urinary tract. Kidney stones are also called urolithiasis or nephrolithiasis, and may develop from metabolic causes or infectious causes.[1] The remainder of this report will focus on metabolic kidney stones. Metabolic kidney stone formation is a complex physiologic event. Their formation is augmented when crystal-forming substances that make up the stone (*i.e.,* calcium, oxalate, uric acid) are high and inhibitors of crystal formation (*i.e.,* citrate) are low.[2]

Kidney stones are thought to be caused by a combination of genetic and environmental factors. About half of people with kidney stones have a genetic predisposition. Dietary factors associated with increased risk include low fluid intake, low calcium intake, and high sodium intake, high fructose intake, while evidence is mixed for increased animal protein, increased sucrose, and low magnesium.[3]

Approximately 1 in 10 people in the United States has had at least one kidney stone. All patients who have a kidney stone should be provided with recommendations to change their diet to prevent future stones. Patients at increased risk for recurrent stones, patients requiring more invasive interventions such as those who have undergone multiple treatments to remove stones or patients who presented with multiple stones at the time of their first presentation are all considered for more intensive evaluations. About 50% of those with at least one kidney stone have recurrent stones. The prevalence of recurrent kidney stones in the United States is 5%.[4]

Medications prescribed to prevent the occurrence of future stones target the substances that make up the stones or inhibit their formation.[5,6] Laboratory tests of the urine or tests to determine the crystals that formed the stone are performed to identify the best match for the patient's stones.[7]

Guideline recommended treatments for recurrent kidney stones include the following.[5,8-10]

- Medications to prevent stone formation
  - Thiazide diuretics (for calcium stones)
  - Citrate (for calcium and oxalate stones)
  - Allopurinol (for uric acid stones)
  - Cystine binding thiol drugs (for cystine stones, which result from a genetic defect of the processing of cystine)
- Dietary guidance
  - Increasing water consumption
  - Decreasing sodium consumption
  - Decreasing consumption of foods with oxalate (*i.e.,* spinach, beets, rhubarb, chocolate, nuts, soy)
  - Decreasing calcium supplementation
  - Reduction in animal protein (evidence shows mixed results)
  - Increased intake of specific liquids (*i.e.,* lemonade)
- Lifestyle changes
  - Losing weight and decreasing sedentarism
  - Increasing exercise

Current sources of information on strategies to prevent recurrent kidney stones

Current sources of patient information on strategies to prevent recurrent kidney stones come from foundations, institutions and companies. Websites have information for patients on the diagnosis and treatment of kidney stones, including strategies for prevention. These include the National Kidney Foundation,[11] Mayo Clinic,[12] companies, and Google.[13] The most common source of information provided to patients at clinic visits are pamphlets created by companies that have kidney stone prevention programs, such as LithoLinkStone.[14]

Dietary counseling is often performed by a physician, physician assistant, nurse practitioner or nurse during the clinic visit and not by a dietitian. The lack of access to a provider trained in administering a dietary intervention is thought to be one of the reasons for poor adherence to dietary interventions.[15] Access to a dietitian may be impeded by insurance coverage or no dietitian trained to treat recurrent kidney stone patients.

3. Symptoms and Patient-Centered Outcomes:

Kidney stones are usually asymptomatic until they enter the urinary tract. The major symptom is pain, manifest usually as bouts of pain that occur unexpectedly and transiently. Patients require pain relievers including nonsteroidal anti-inflammatory drugs (NSAIDs) and sometimes narcotics. [16]

Patients with kidney stones often experience such extreme pain that they go to the emergency room. If immediate surgical treatment is required, the emergency room visit may result in a hospital admission.[16]

Many people experience their first kidney stone while they are in middle age starting around age 40. The symptoms associated with kidney stones interfere with home and social life, work and professional activities, personal finances, and emotional and mental health.[17,18]

The majority of studies find that kidney stones are associated with increased risks of other diseases including chronic kidney disease,[19,20] bone loss[21] and fractures.[22] Whether treatment after recurrent kidney stones modifies this risk is unclear.

4. Impact/Burden of the Condition:

Approximately 1 in 10 people in the United States has had at least one kidney stone. Because 50% of those with at least one kidney develop a second, the prevalence of recurrent kidney stones in the United States is 5%.[4,7,23] Kidney stones increase with age. Among individuals 70 years and older approximately 19% of men and 9% of women have had at least one stone.

Based on the results of NHANES surveys that asked participants their kidney stone history between 2007 and 2010 the following populations have differing risks of stones

- Men are more likely to have stones than women: 11% vs 7%;
- Obese individuals are more likely to have kidney stones than normal weight individuals: 11% vs 6%;

- Individuals with diabetes are more likely to have kidney stones (odds Ratio 1.6);
- Individuals from households with incomes below $35,000 are more likely to have kidney stones than households with incomes greater than $75,000 (odds Ratio 1.6);
- Non-Hispanic whites are more likely to have kidney stones than Hispanics and non-Hispanic blacks;

	Men vs Women
Non-Hispanic whites	13% vs 8%

Hispanics	7%	vs	6%
Non-Hispanic blacks	5%	vs	4%

- Based on surveys conducted between 1988 through 1994, Asians had lower rates of kidney stones than non-Hispanic whites.[24]

The prevalence of kidney stones is increasing with time.[24]

2007 – 2010	10%
1988 – 1994	5%
1976 – 1980	4%
1964 – 1972	3%

The burden of kidney stones on the health care system is great. In 2006, approximately $10 billion was spent on hospital admissions for kidney stones. There are additional costs from outpatient visits and testing and indirect costs from lost time from school and work.[25,26] Although there is no information on variation in care for recurrent stones, there is evidence of variation in care for kidney stones treated in the emergency department.[27] Fewer than 1 in 5 patients received guideline recommended medications. There is no information on variation in utilization of dietary counseling.

5. Evidence Gaps:

We searched for systematic reviews on strategies to treat recurrent kidney stones produced by the Agency for Healthcare Research & Quality's Evidence-based Practice Center Program and the Cochrane Collaboration. One Evidence-based Practice Center report and two Cochrane reviews were identified. We identified the research questions, findings and the evidence gaps identified in these reports. The American Urological Association relied on these and other sources to produce management recommendations for its members.[7]

Recurrent Nephrolithiasis in Adults: Comparative Effectiveness of Preventive Medical Strategies[3]

AHRQ Publication No. 12-EHC049-EF July 2012 Revised March 2013 and May 2013

Research Questions:

1. In adults with a history of nephrolithiasis, do results of baseline stone composition and blood and urine chemistries predict the effectiveness of diet and/or pharmacological

treatment on final health outcomes and intermediate stone outcomes, and reduce treatment adverse effects?

2. In adults with a history of nephrolithiasis, what is the effectiveness and comparative effectiveness of different dietary therapies on final health outcomes and intermediate stone outcomes?
3. In adults with a history of nephrolithiasis, what is the evidence that dietary therapies to reduce risk of recurrent stone episodes are associated with adverse effects?
4. In adults with a history of nephrolithiasis, what is the effectiveness and comparative effectiveness of different pharmacological therapies on final health outcomes and intermediate stone outcomes?
5. In adults with a history of nephrolithiasis, what is the evidence that pharmacological therapies to reduce risk of recurrent stone episodes are associated with adverse effects?
6. In adults with a history of nephrolithiasis being treated to prevent stone recurrence, do results of follow-up blood and urine biochemistry measures predict final health outcomes and intermediate stone outcomes?

Conclusions: (directly taken from the report abstract)

Increased fluid intake, reduced soft drink consumption, thiazide diuretics, citrate pharmacotherapy, and allopurinol reduce risk of recurrent calcium stones. Effects of other dietary interventions appear mixed. We identified no RCTs for uric acid or cystine stones. Data regarding whether baseline or follow-up biochemistries predict treatment efficacy is extremely limited.

Evidence Gaps:

No trials compared diet treatment with pharmacological treatment. Instead, nearly all pharmacological trials reported that all groups were assigned a common dietary co-intervention of increased fluid intake with or without additional dietary changes, so that the studies were designed to evaluate the effect of pharmacological treatment when added to this diet therapy. Few trials directly compared active pharmacological treatments. No trials directly compared thiazide versus citrate, thiazide versus allopurinol, or citrate versus allopurinol.

Since the vast majority of patients in the community with kidney stones have calcium stones, empirically increasing fluid intake in all patients with kidney stones with or without adding thiazide or citrate therapy might significantly reduce recurrence risk. However, we found no trials that tested this strategy.

Fluid and diet studies did not examine stone recurrence risk as a function of follow-up or change in urine supersaturation levels (and no pharmacological trials even reported follow-up urine supersaturation levels). These results suggest that future studies to formally test these follow-up measures as predictors of stone recurrence risk may be warranted.
Results from this review may not be generalizable to patients with non-calcium kidney stones (i.e., uric acid or cystine stones), to children, or to older adults. Further, results may not be generalizable to patients with underlying biochemical abnormalities, and may have limited generalizability to those with comorbid conditions not reported (though not explicitly excluded in most cases) in eligible trials (e.g., obesity, pregnancy, hypertension, history of bariatric surgery, chronic kidney disease, solitary kidney, renal transplant, or coronary artery disease). Because both trials of increased fluid intake versus control were conducted in participants with a single past stone episode, treatment effectiveness could differ in patients with multiple past stone episodes. While we don't know whether kidney stone patients followed in specialty centers differ from those followed in primary care, the reduction in stone recurrence risk with thiazide versus control appears similar in both populations. This suggests that the effect of this treatment, at least, may be insensitive to recruitment source.
Executive summary Table C provides 29 future research directions.

Citrate salts for preventing and treating calcium containing kidney stones in adults[28]
Editorial Group: Cochrane Kidney and Transplant Group, Published Online 6 OCT 2015, Assessed as up-to-date 29 JUL 2015
Objective:
"The objective of this review was to determine the efficacy and adverse events associated with citrate salts for the treatment and prevention of calcium containing kidney stones."
Conclusions:
"Citrate salts are an effective intervention in the treatment and prevention of kidney stones. The evidence from seven RCTs included in this review has demonstrated good efficacy with citrate therapy compared to control (placebo, usual care). However, this review was unable to demonstrate the most effective type and dose of citrate salt needed to achieve this clinical benefit. The precise duration of treatment remains to be defined. Interestingly, dropout rate due to side effects is low."

Evidence Gaps:
"Overall, evidence for specific citrate treatment is limited due to use of different citrate salts at varying dosage, varying follow-up periods, and varying follow-up imaging protocols. Despite

significant benefit of citrate salts in prevention and treatment of kidney stones these limitations, make it difficult to recommend a specific salt in day-to-day practice.
This review highlights the lack of good quality reported literature in the use of citrate salts for kidney stone management. A multi-centre study which compares different citrate salts in patients who are stone-free, recurrent stone formers or have residual fragments < 4 mm to placebo is required. The primary outcomes should be new stone formation, stone growth, visits to the emergency department, proven renal colic or intervention for stones. Alterations in the urinary parameters should be included as secondary outcomes. A complete metabolic work up according to European guidelines at baseline, and six monthly thereafter should be considered. Gold standard CT KUB should be used for assessment allowing all types of stones to be studied. The study should incorporate interval reporting at 6, 12 and 24 months so evidence can be gathered on the long term benefits of using citrate salts. Adverse events should be reported thoroughly and specify if patients dropped out due to an event. Future studies should report on the health economics of citrate salts in preventing new stone formation after interventions (ESWL, PCNL and ureteroscopy) and their impact on the growth of residual fragments."

Water for preventing urinary stones[29]

Editorial Group: Cochrane Kidney and Transplant Group, Published Online: 13 JUN 2012, Assessed as up-to-date: 18 APR 2012

Objective

This review aims to look at the benefits and harms of:

1. increased water intake for the primary prevention of urinary stones in a population without a history of the disease; and
2. increased water intake for the secondary prevention of urinary stones in patients with a history of the disease.

Conclusions:

The evidence from only one study indicates that increased water intake reduces the risk of recurrence of urinary stones and prolongs the average interval for recurrences. However further research is required. Due to the lack of appropriate RCTs, no conclusions can be drawn on increased water intake for the primary and secondary prevention of urinary stones.

Evidence Gaps:

Large, multi-centre long-term RCTs of good quality are required to answer the questions concerning increased water intake for the primary and secondary prevention of urinary stones.

Future studies should be designed to evaluate how much water and what kind of water is best for the primary and secondary prevention of urinary stones.
The effect of increased water intake on different kinds of stone formers should also be evaluated.

6. Ongoing Research:

We searched ClinicalTrials.gov, NIH Reporter and PCORI's website to identify ongoing research.

ClinicalTrials.gov results

- 11 studies found for recurrent kidney stones or recurrent nephrolithiasis. One was unrelated to the topic (NCT02346500). Of the relevant studies, none specifically aimed to prevent recurrent stones. Instead they focused on expulsion of existing stones, changing urine concentrations of the common components of stones or examining genetic risk factors.
- 6 completed
  - With results
    - NCT00831701: Tamsulosin vs placebo to expel single distal ureteral stones. There was no difference between tamsulosin and placebo. Completed in 2008. A publication also reported no statistically significant difference between the treatment groups.[30]
  - Without results
    - NCT00004284: Potassium citrate vs potassium phosphate. No primary outcome provided. Last updated in 2000.
    - NCT00120731: All patients received potassium citrate, acetazolamide and a diet low in oxalate and purines to change urine pH, citrate, calcium and bicarbonate. Completed in May 2007.
    - NCT01022060: Renalof, a couch grass extract, vs placebo to dissolve renal calculi. Completed in 2010.
    - NCT01650935: DASH diet vs oxalate restricted diet to change urinary concentrations of oxalate. DASH is a diet high in fruits, vegetables, whole grains, and low-fat dairy products and low in saturated fat, total fat, cholesterol, refined grains, sweets and meat. Completed in 2013. A publication that reported on calcium oxalate as the primary outcome found no statistically significant difference between the groups in the as-treated analysis.[31]
    - NCT02289755: All patients received ALLN-177, an oxalate decarboxylase, to reduce urinary oxalate excretion. Completed in February 2015.

- 4 recruiting
  - NCT01217372: Nephrolithiasis Prevention by Lemon Juice vs no intervention. One of the primary endpoints is occurrence of new stones. Estimated primary completion in March 2016.
  - NCT01690039: Influence of Polymorphisms in the ATP6V1 Gene of the V-ATPase on the Development of Incomplete Distal Renal Tubular Acidosis. Not related to the topic.
  - NCT02375295: A Prospective Randomized Trial of 2 Weeks vs 3 Months of Antibiotics Post Percutaneous Nephrolithotomy for the Prevention of Infection-Related Kidney Stones. Primary endpoint is recurrent kidney stones. Estimated primary completion in December 2017.
  - NCT02503345: Evaluate the Effect of ALLN-177 in Reducing Urinary Oxalate in Patients With Hyperoxaluria and Kidney Stones. Three doses of ALLN-177 were compared with placebo to change urinary oxalate. Estimated primary completion in March 2016.

NIH Reporter results

- 26 studies were identified based on searches for "recurrent kidney stones" and "recurrent nephrolithiasis"
  - 3 were unrelated to kidney stones
  - 8 included humans with the following titles. None compared dietary treatments to each other or dietary to medical treatments. No study mentioned novel dissemination strategies.
    - Identifying risk factors and improving risk assessment for nephrolithiasis
    - Improving stone disease treatment by accurate phenotyping and risk stratification
    - Epidemiology of kidney stone recurrence
    - Randall's plaque: pathogenesis and relationship to nephrolithiasis
    - Innovative strategies for improved outcomes in nephrolithiasis
    - Novel ultrasound modalities to detect, characterize and remove stones
    - Identifying and mitigating risk factors for dehydration-mediated nephrolithiasis in adolescents

    - Improving stone disease treatment by accurate phenotyping and risk stratification
    - Several of these ongoing studies are part of the George M. O'Brien Urology Cooperative Research Centers Program (U54). One of the goals of this program is to develop and test better treatments for urologic disorders, including kidney stones.

No PCORI-funded study is focused specifically on kidney stones.

7. Likelihood of Implementation of Research Results in Practice:

Results from new research optimizing the existing treatment strategies is likely to be noticed by the community if the results are appropriately disseminated. Alternative payment models may increase the desire to prevent recurrent stones, rather than relying on procedures to destroy or remove them. However, lack of insurance coverage for dietitians and the reliance on procedural interventions from some urologists may interfere with the adoption of non-procedural interventions.

Given the high disease burden, if the information is disseminated through guidelines and other resources that reach both academic and community physicians, it is very likely that the results will be implemented immediately.

8. Durability of Information:

There are no current innovations related to this topic. It is likely that the results will remain current for several years. There is a recognized need for information and educational tools. The American Urological Association updates their guidelines approximately every 5 years. The guidelines include a search for literature to support the recommendations. The majority of current recommendations are based on expert opinion. New information generated as part of PCORI-funded research is very likely to be incorporated into these guidelines, and then updated, if necessary, every 5 years.

9. Potential Research Questions:

- *Research Need:* There are no ongoing studies that compare dietary treatments to each other or dietary to medical treatments funded by NIH, PCORI or registered in ClinicalTrials.gov. The systematic reviews suggested head to head comparisons to address this gap.
  Research Question: What is the comparative effectiveness of diet versus diet combined with a medication to prevent recurrent stones? The diet and medication should be tested in a population that has stones related to the examined treatments.

- *Research Need:* No identified ongoing study mentioned novel education or dissemination strategies.

Research Question: No research question proposed at this time because no evidence exists comparing the treatment options directly.

- Research Need: The consulting experts noted that dieticians specialized at preventing recurrent stones are unavailable. Examining if special training increases the effectiveness or adherence with dietary interventions compared with non-specialized dieticians or physician-office administered counseling is needed.
  Research Question: Do patients who receive dietary interventions from dieticians with specialized training for kidney stone prevention have greater adherence and fewer future stones compared with the standard dietary intervention from a nurse practitioner or physicians?

- *Research Need:* Our experts stated that information on how best to manage workflows and treatment algorithms combining dietary and medical treatments and timing of future appointments are needed.
  Research Question: No research question proposed at this time because no evidence exists comparing the treatment options directly.

- *Research Need:* We did not identify literature that assessed access to care, practice variation or compliance with the existing treatment guidelines.
  Research Question: Do patient characteristics and demographics (i.e., age, sex, race, setting) affect the types of providers prescribing effective medications or dietary counseling for recurrent kidney stones?
  Research Question: What is the adherence to treatment guidelines based on provider recommendations?
  Research Question: What is the patient adherence with the treatment prescribed by providers?

10. Conclusion:

Despite the large societal burden (approximately 10% of the population), there have been no new treatments for kidney stones in decades and no major trials or other studies to optimize

the current treatment strategies to prevent recurrent kidney stones. The absence of innovation makes this topic especially compelling. Comparative effectiveness research to optimize the current treatment strategies or test the effectiveness of alternative strategies should be given high priority.

APPENDIX

Methods

Literature search:

From December 2015 to February 2016, we conducted a literature review to identify evidence-based research around the effectiveness of dietary manipulation and medications for the prevention of recurrent kidney stones. We used PubMed, Google Scholar and the Cochrane Database of Systematic Reviews to identify systematic reviews, meta-analyses and research reports and the most current reviews. We also searched the websites for government agencies, such as the CDC, the NIH and relevant professional associations (American Urological Association, European Urological Association, National Kidney Foundation), patient advocacy groups as likely to contain relevant material on the current prevalence and available treatment services as well as any references or sites suggested by our experts.

Clinical trials and NIH Funding Announcements:

In January 2016, we conducted a search on clinicaltrials.gov and the NIH reporter for open clinical trials related to the topic. We used the broad search terms “recurrent kidney stones” and “recurrent nephrolithiasis”. The results are described above.

References for topic: Comparative effectiveness of dietary manipulation and medications for the prevention of recurrent kidney stones

1. European Urological Association. Guidelines on Urolithiasis. 2015; http://uroweb.org/wp-content/uploads/EAU-Guidelines-Urolithiasis-2015-v2.pdf. Accessed January 10, 2016.
2. Sakhaee K, Maalouf NM, Sinnott B. Kidney Stones 2012: Pathogenesis, Diagnosis, and Management. *J Clin End Met.* 2012/06/01 2012;97(6):1847-1860.
3. Fink HA, Wilt TJ, Eidman KE, et al. AHRQ Comparative Effectiveness Reviews. *Recurrent Nephrolithiasis in Adults: Comparative Effectiveness of Preventive Medical Strategies. Comparative Effectiveness Review No. 61. (Prepared by the University of Minnesota Evidence-based Practice Center under Contract No. 290-02-0009.)* AHRQ Publication No. 12-EHC049-EF. ed. Rockville (MD): Agency for Healthcare Research and Quality (US); 2012.
4. Scales CD, Jr., Smith AC, Hanley JM, Saigal CS. Prevalence of kidney stones in the United States. *Eur Urol.* Jul 2012;62(1):160-165.
5. Meschi T, Nouvenne A, Borghi L. Lifestyle Recommendations to Reduce the Risk of Kidney Stones. *Urologic Clinics of North America.* 8// 2011;38(3):313-320.
6. Kok DJ. The preventive treatment of recurrent stone-formation: how can we improve compliance in the treatment of patients with recurrent stone disease? *Urolithiasis.* Dec 14 2015.
7. Pearle MS, Goldfarb DS, Assimos DG, et al. Medical management of kidney stones: American Urological Association guideline. *J Urol.* Aug 2014;192(2):316-324.
8. Eisner BH, Goldfarb DS, Pareek G. Pharmacologic treatment of kidney stone disease. *Urologic Clinics of North America.* Feb 2013;40(1):21-30.
9. Heilberg IP, Goldfarb DS. Optimum nutrition for kidney stone disease. *Adv Chronic Kidney Dis.* Mar 2013;20(2):165-174.
10. Yuvanc E, Yilmaz E, Tuglu D, Batislam E. Medical and alternative therapies in urinary tract stone disease. *World J Nephrol.* Nov 6 2015;4(5):492-499.
11. National Kidney Foundation. Diet and Kidney Stones. 2015; https://www.kidney.org/atoz/content/diet. Accessed February 2, 2016.
12. Mayo Clinic. Diseases and Conditions - Kidney stones. 2016; Mayo Foundation for Medical Education and Research http://www.mayoclinic.org/diseases-conditions/kidney-stones/basics/definition/con-20024829. Accessed February 2, 2016.
13. Google. Kidney Stones prevention. 2016; https://www.google.com/webhp?sourceid=chrome-instant&ion=1&espv=2&ie=UTF-8#q=kidney+stones+prevention. Accessed February 2, 2016.
14. LithoLink. Kidney Stone Prevention Program. 2014; http://www.litholink.com/en/PreventionProgram. Accessed February 2, 2016.
15. Parks JH, Asplin JR, Coe FL. Patient adherence to long-term medical treatment of kidney stones. *J Urol.* Dec 2001;166(6):2057-2060.
16. Wang RC. Managing Urolithiasis. *Ann Emerg Med.* Nov 23 2015.
17. Penniston KL, Nakada SY. Development of an instrument to assess the health related quality of life of kidney stone formers. *J Urol.* Mar 2013;189(3):921-930.

18. Bensalah K, Tuncel A, Gupta A, Raman JD, Pearle MS, Lotan Y. Determinants of quality of life for patients with kidney stones. *J Urol.* Jun 2008;179(6):2238-2243; discussion 2243.

19. Keddis MT, Rule AD. Nephrolithiasis and loss of kidney function. *Curr Opin Nephrol Hypertens.* Jul 2013;22(4):390-396.

20. Sigurjonsdottir VK, Runolfsdottir HL, Indridason OS, Palsson R, Edvardsson VO. Impact of nephrolithiasis on kidney function. *BMC Nephrology.* 2015;16:149.

21. Arrabal-Polo MA, Cano-Garcia Mdel C, Canales BK, Arrabal-Martin M. Calcium nephrolithiasis and bone demineralization: pathophysiology, diagnosis, and medical management. *Current Opin Urol.* Nov 2014;24(6):633-638.

22. Denburg MR, Leonard MB, Haynes K, et al. Risk of fracture in urolithiasis: a population-based cohort study using the health improvement network. *Clin J Am Soc Nephrol.* Dec 5 2014;9(12):2133-2140.

23. Uribarri J, Oh MS, Carroll HJ. The first kidney stone. *Ann Int Med.* Dec 15 1989;111(12):1006-1009.

24. Romero V, Akpinar H, Assimos DG. Kidney Stones: A Global Picture of Prevalence, Incidence, and Associated Risk Factors. *Rev Urol.* Spring-Summer 2010;12(2-3):e86-e96.

25. Scales CD, Jr. Practice patterns in the management of urinary lithiasis. *Curr Urol Rep.* Apr 2013;14(2):154-157.

26. Pearle MS, Calhoun EA, Curhan GC. Urologic Diseases in America Project: UROLITHIASIS. *J Urol.* 3// 2005;173(3):848-857.

27. Scales CD, Jr., Bergman J, Carter S, Jack G, Saigal CS, Litwin MS. Quality of Acute Care for Patients With Urinary Stones in the United States. *Urology.* Nov 2015;86(5):914-921.

28. Phillips R, Hanchanale VS, Myatt A, Somani B, Nabi G, Biyani CS. Citrate salts for preventing and treating calcium containing kidney stones in adults. *Cochrane Database Syst Rev.* 2015;10:Cd010057.

29. Bao Y, Wei Q. Water for preventing urinary stones. *Cochrane Database Syst Rev.* 2012;6:Cd004292.

30. Hermanns T, Sauermann P, Rufibach K, Frauenfelder T, Sulser T, Strebel RT. Is there a role for tamsulosin in the treatment of distal ureteral stones of 7 mm or less? Results of a randomised, double-blind, placebo-controlled trial. *Eur Urology.* Sep 2009;56(3):407-412.

31. Noori N, Honarkar E, Goldfarb DS, et al. Urinary lithogenic risk profile in recurrent stone formers with hyperoxaluria: a randomized controlled trial comparing DASH (Dietary Approaches to Stop Hypertension)-style and low-oxalate diets. *Am J Kidney Dis.* Mar 2014;63(3):456-463.