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Urinary Stone Disease: Research Challenges and Opportunities

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Executive Summary

Introduction

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Urinary stone disease (USD) is an important and increasingly common problem. It is the most expensive urological condition, with annual medical costs of approximately $10 billion. Nonmonetary burdens to patients such as pain and loss of quality of life also are enormous. In the United States, 1 in 11 individuals have USD. In the last 15 years, the rate has doubled in men as has the rate of admittance for USD to emergency departments. According to the NIDDK-funded study *Urological Diseases in America*, USD prevalence has increased by 50 percent in the past decade. Obesity and diabetes are associated with USD, and these conditions also are increasing in prevalence. USD is most common in Whites and in men, although USD prevalence is growing in all races and both sexes. Recurrence is common with USD, with one in three USD patients having two or more stone episodes.

Despite the high prevalence and expense of the disease, little is known about how stones form or which are likely to be passed. Advances in treatments in the past 30 years have evolved from open surgery to remove large stones to new technologies. Current treatments to prevent recurrence include increasing fluid intake, modifying diet, and medications, but these measures have not decreased prevalence, suffering, recurrence rates, USD-related chronic kidney disease (CKD) incidence, or cost, representing limited progress in USD, especially compared to diseases such as cancer and cardiovascular disease. Few of the American Urological Association's and American College of Physicians' guidelines for USD treatment recommendations are based on level-one evidence. To assess gaps in knowledge and evidence-based treatment, this meeting's goals include presenting information on the epidemiology and pathophysiology of USD, as well as evidence for management strategies; discussing and prioritizing the areas in which additional USD research is needed, including studies to better understand the role of the microbiome, genetics, and exposome; and providing recommendations to inform potential future funding initiatives by NIDDK, including recommendations on the key question of the types of studies needed to inform management of USD.

Increasing Urinary Stone Frequency

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When examining the prevalence of USD, factors to consider include the source population (e.g., general population vs. hospitalization); the definition of USD; and age, sex, and race data. The National Health and Nutrition Examination Survey (NHANES) data, which represent prevalence in the U.S. general population, showed an increase from 3.2 to 8.8 % from 1976 to 2010. The number of people in the United States with a reported history of USD in 2010 is 19 million. Prevalence by sex in 2010 was 10 percent of men and 7 percent of women. Women tend to have lower oxalate in urine than men, which might explain part of this difference. Regarding the possible protective role of estrogen, surgically induced menopause increases the risk for USD in women, but natural menopause does not. There also is no difference in USD prevalence in women with post-menopausal estrogen use. In the most recent NHANES data, the prevalence of USD is 20 percent for men and 10 percent for women in the 60- to 69-years-old age group. Prevalence is higher in Caucasians than African Americans and increases in both groups with age. One possible reason for racial differences is that African Americans have lower levels of calcium in urine.

Incidence rates indicate how likely an individual is to develop a disease. In the Nurses' Health Study II (a cohort of

women in the United States), the highest incidence rate was 2.5/thousand/year and depended on age. A study of pediatric nephrolithiasis showed incidence rates that were approximately one-tenth those of adults, having increased over the past decade as well. Potential reasons why prevalence is increasing are body mass index (BMI), diet, and diabetes prevalence. Relative risk for USD strongly increases with BMI in women and to a lesser degree in men. Patients who have received bariatric surgery also are at increased risk of developing USD. Diabetes increases the risk of nephrolithiasis, particularly in women, independently of BMI and dietary risk factors. In addition, higher fructose intake confers USD risk. An increased Dietary Approaches to Stop Hypertension (DASH) diet score was associated with lower USD risk. Extremely high-protein diets modify urine chemistry, but normal protein intake is not associated with USD. Poor-quality diets with large amounts of fast food may be problematic, however. These data indicate that USD is likely to be largely preventable.

Data on stone types can be used to answer the question of whether stone types change over time. Data from France comparing first occurrence and recurrent stones show highest prevalence of calcium oxalate stones followed by calcium phosphate and uric acid stones, with the percentage of calcium oxalate stones lower and calcium phosphate and uric acid stones higher in recurrent stones. Overall stone type distributions are similar in France and the United States. Stone type distributions vary by age and sex. There has been no change in the fraction of all stones containing calcium phosphate over the past 3 decades. It is uncertain whether stone type is changing over time.

Increased prevalence has implications for patient suffering, costs, and long-term sequelae (e.g., fracture, end-stage renal disease [ESRD], coronary heart disease). Stone formers have been shown to be at increased risk of ESRD compared with controls. The hazard ratios for ESRD remain elevated when adjusted from multiple variables. Fracture incidence is another risk for stone formers at all ages. Kidney stones formers also are at elevated risk of incident coronary heart disease, although the excess risk is small and potentially due to shared lifestyle mechanisms between kidney stone formers and patients with heart disease. USD therefore has a substantial risk of morbidity.

Recurrence is an important topic of research. It is unknown whether preventing recurrence of USD decreases morbidity risk.

Single-Gene Mutations: Implications for Personalized Medicine

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Disease causation runs the spectrum between purely genetic causes to purely environmental ones such as trauma. More than 15 percent of USD is caused by single-gene mutations. Single-gene or monogenic disease is caused by mutations in a single gene and can be recessive or dominant. There are more than 30 monogenic causes of USD, 17 of which are recessive, 5 of which are dominant, 5 of which are autosomal recessive/autosomal dominant, and 3 of which are x-linked. Disease gene identification allows doctors to offer genetic diagnosis, provides novel insights into pathogenesis and physiology, and potentially permits personalized treatments. In monogenic disorders, a single mutation confers 100 percent of the risk, whereas for complex disorders, multiple mutations each contribute a small fraction of the variance and confer much less risk. In a cohort of patients recruited from USD clinics, 40 out of 268 patients (15%) with USD had likely causative mutations in 14 of the 30 candidate USD genes, demonstrating that 15 percent of all cases had a monogenic cause. Eleven percent of adults and 21 percent of children had established monogenic causes. The total figure of 15 percent is likely an underestimate because of confusion with polygenic and sporadic "non-genetic" causes. Penetrance of monogenic alleles can be age-related, with treatment shifting the time-dependent penetrance curve toward older ages. To determine the true fraction of monogenic causation of USD will require testing of all alleles in animal models and identifying additional monogenic genes that cause USD by whole exome sequencing (WES). It is desirable to examine every USD patient for monogenic causes of disease to make an etiologic diagnosis if the patient is among the 15 percent with monogenic causes, initiate proper treatment and/or prophylaxis, and make a correct prognosis.

An example of identifying novel monogenic disease genes and pathogenic pathways by WES is the *SLC26A1* gene. *SLC26A1* mutations were found in three families with USD. In the future, every patient with the potential of monogenically caused USD should be given the opportunity to have the mutation identified because it provides an unequivocal diagnosis, might reveal a potential treatment or prophylaxis, allows etiologic classification for therapeutic trials, and enables the generation of gene-specific animal models. Whole genome testing will allow the number of candidate genes to grow. Precise phenotyping, particularly of severe phenotypes, should guide WES testing toward

those patients most likely to have monogenic causes for USD. Finding common variants will require a different type of study design with a large cohort.

The Exposome for Urinary Stone Disease

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The exposome is the measure of all of the exposure of an individual in a lifetime and how those exposures, including insults from environmental and occupational sources, relate to health. Exposure modified by each individual's unique characteristics (e.g., genetic factors, physiology) leads to disease. Non-modifiable risk factors for kidney stones include family history and the structural anatomy of the urinary system. Potentially modifiable risk factors for kidney stones include low fluid intake, a low-calcium diet, a high animal protein diet, high oxalate intake, a high sodium diet, hot weather, obesity, decreased exercise, and certain drugs. Hypocitraturia, hyperuricosuria, hypercalciuria, hyperoxaluria, and high or low pH are all urine chemistry risk factors for kidney stones, but it is not clear whether and to what extent some of them are modifiable. Employment in certain professions that require restricted urination may confer occupational risk for nephrolithiasis and urinary tract infections (e.g., "Taxi Cab Syndrome," infrequent voiders' syndrome in nurses, increased history of USD in operating room staff vs. other health care workers). A prospective study revealed an inverse relationship between fluid intake and the relative risk of symptomatic kidney stones. Potassium citrate is a potential preventative treatment for occupational kidney stones for those who cannot increase fluid intake. The Department of Defense and National Aeronautics and Space Administration (NASA) have funded research on this topic, which is of interest for deployed soldiers for several reasons (e.g., hot ambient temperature, salty animal protein rations, wearing body armor) and for astronauts. The effect of employment on USD is under-studied, however, and occupational data are not commonly included in a patient's electronic health record (EHR).

Regarding hot weather, a modeling study predicted a climate-related increase in prevalence in the United States at higher latitudes. Prevalence rates for men increased more than for women as mean annual temperature by state increased. There appear to be gender differences in the seasonal variation of urine stone risk factors that are hypothesized to be caused by women replacing sodium and water lost by sweating more effectively than men. The continued trend of global population migration to urban heat islands from rural areas might be a cause of increased USD prevalence in the past and projected into the future. The effects of urbanization on USD incidence, including time spent indoors in air-conditioned spaces, are numerous, however, making it difficult to study. An effect of urbanization is that more of the population may live in urban food deserts, where access to fresh fruits and vegetables is limited.

An additional risk factor may be the effect of antibiotic use on the microbiome. Antibiotic treatment for *Helicobacter pylori* reduced the intestinal colonization rate of *Oxalobacter formigenes*, the presence of which is associated with reduced urinary oxalate excretion. More widespread use of antibiotics could therefore be a part of the exposome that constitutes a risk for stone disease.

Dietary Recommendations

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Dietary recommendations (e.g., increase fluid intake to 1.5 to 2.0 L/day, decrease sodium intake, decrease animal protein intake, moderate dietary calcium intake) and medications to treat metabolic derangement (e.g., hypercalciuria, hypocitraturia) are cornerstones of stone prevention. Greater fluid intake is important because it dilutes the urine and prevents urine stagnation. An early prospective randomized, controlled trial (RCT) of calcium stone formers showed that increased fluid intake reduced stone recurrence, but higher baseline urinary calcium also predicted stone recurrence, indicating that hypercalciuria also should be treated. Very excessive sodium intake leads to calcium excretion, but sodium also is a marker of poor dietary choices. High animal protein lowers urine pH and causes excess uric acid, and may lead to gastrointestinal calcium absorption. Calcium intake impacts oxalate absorption, and very excessive intake may spill calcium into the urine. A 5-year RCT of men with recurrent calcium oxalate stones and hypercalciuria placed on a low-calcium diet or normal calcium plus low sodium/animal protein diet resulted in lower urinary calcium but increased oxalate (low-calcium diet), and lower sodium and sulfate and supersaturation of calcium oxalate (normal calcium, low sodium/animal protein). Overall, the risk of stone recurrence was 50 percent lower in the subjects on the normal calcium, low sodium/animal protein diet. Longitudinal observational data support the benefits of increased fluid intake and lower sodium but not lower animal protein. Very high sodium intake therefore may be a risk factor, but it

also is a marker of dietary choices. Animal protein intake may not be a major risk factor for most patients. Urine chemistry is poor in patients who are consuming a high-protein Adkins diet, although weight loss from the diet may be associated with decreased risk of recurrence.

The DASH Diet has been compared to a low oxalate diet to evaluate the effects on reducing calcium oxalate supersaturation. In one study, the DASH Diet was found to be more effective in reducing calcium oxalate supersaturation despite being higher in oxalate. An observational study found that participants with a high DASH score had decreased incidence of USD. Oxalate is a very complicated dietary risk factor as our understanding is incomplete in regard to the role of endogenous, exogenous, and absorption variation, as well as *Oxalobacter* metabolism. There is a need to study the whole diet, including factors influencing oxalate bioavailability.

Comparing the value of dietary versus supplemental calcium in prospective studies has shown no relationship between decreased stone risk and calcium supplements. In a RCT of calcium and vitamin D supplements, there was an increased risk of stones associated with supplements. RCTs of allopurinol and potassium citrate both showed fewer stones with these interventions.

It is likely that a comprehensive dietary intervention would be more valuable for reducing USD and metabolic risk factors. Personalized dietary advice may prove effective in controlling USD, but there is evidence that offering many dietary recommendations results in a lack of compliance with any of the recommendations. We appear to have a good understanding of which dietary factors are risk factors associated with stone formation; the challenge now is implementing and maintaining a comprehensive modification of the diet of stone-forming patients.

The Microbiome

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The understanding of the microbiome has changed dramatically, resulting in an understanding that microbes are essential to their human hosts. The cells comprising the microbiome are highly numerous; contribute to the human body’s genome; and are organized into complex communities, 70 percent of which live in the colon. Most of the microbes in the microbiome cannot be cultured in the laboratory, but evolving sequencing technologies have allowed the sequencing of DNA in the microbiome. The 16S rRNA gene, which is required for cell function and conserved within bacterial species, has been used to characterize the species composition of the microbiome. This approach has revealed that different regions of the gut are colonized by different bacteria. Microbial community function has been mapped with metagenomics, an approach in which gene expression is compared to databases to count the number of genes per function. Using this approach, toxins have been shown to alter microbial function.

The microbiome is relevant to USD because urinary oxalate excretion is related to stone incidence, oxalate is only degraded by microbes, and gut microflora may play a key role in USD incidence. *Oxalobacter* bacteria, which convert oxalate to carbon dioxide and formate, are gram-negative, anaerobic, and sensitive to antibiotics. Researchers have studied the role of bacteria that digest oxalate in mammals such as the white-throated woodrat that are able to survive on a high-oxalate diet. *Lactobacillus,* which are potential oxalate degraders and are very common, have been found concentrated in the foregut of the woodrat. Rare bacteria taxa that can degrade oxalate, including *Oxalobacter,* have been found in all sections of the woodrat gut. Different species cultured from different regions of the gut have shown varying abilities to degrade oxalate. The ability to degrade oxalate was found to be correlated with the relative abundance of *Oxalobacter*. Further evidence of the importance of the microbiome in oxalate degradation is that microbial transplants from woodrats to laboratory rats improved the ability of laboratory rats to digest oxalate and increased oxalate consumption. *Oxalobacter* remains detectable in laboratory rats 9 months after the transplants.

The importance of microbes in oxalate degradation in humans remains an area of future study. Woodrats have a foregut, unlike humans, and oxalate digestion primarily occurs there. It is not known how *Oxalobacter* might modulate urinary excretion of oxalate, but *Oxalobacter* populations increase with increased dietary oxalate. It also is not known whether alteration of the gut microbiome by antibiotics might contribute to USD. In addition, the effect of citrate on the microbiome is a potential area of future study.

Animal Models

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Vertebrate and invertebrate animal models show potential for answering key questions in USD. Invertebrate models such as the fruit fly have the advantage of relatively straightforward genetic manipulation, short lifespan, and low maintenance costs. Vertebrate models include rodents (i.e., mice and rats), as well as canine and feline models. Animal models allow precise control of diet, facilitated study of recurrence because of short lifespan, multi-papillary anatomy in some models, and investigation of new drugs. In fruit flies, it was found that the zinc chelator N,N,N′,N′-tetrakis(2-pyridylmethyl)ethylenediamine (TPEN) reduced concretion formation. The inhibition of zinc transporters also reduced the percent mineralized area, decreasing incidence. A variety of knockout models for zinc transporters also rescued survivorship.

Both rat and mouse models exist for USD. Most models investigate the role of hyperoxaluria, and rats and humans have similar oxalate metabolism. In rats, males are used to model calcium oxalate stones, whereas females are used as models of calcium phosphate stones. A variety of modes of delivery and agents have been used in rat calcium oxalate models, including giving hyperoxaluric agents along with ammonium chloride to reduce urinary pH, a critical aspect of stone formation. In one study of chronic hyperoxaluria in rats in which ethylene glycol was administered with ammonium chloride, urinary calcium, magnesium, and citrate increased, and crystalluria was followed by the formation of calcium oxalate stones. Another study of intraperitoneal sodium oxalate succeeded in inducing calcium oxalate stones. There are problems with rats and mice calcium oxalate models, however, including that rats require higher urinary oxalate levels than humans to produce calcium oxalate crystals and have much higher urinary citrate, implying a possible protective mechanism. For rat calcium phosphate models, females spontaneously form calcium phosphate stones, with dietary calcium, phosphate, and magnesium levels being key in stone formation. In mice, SLC3A1 knockouts show cystinuria and formation of bladder stones in male mice. There also are other deficient mouse models that produce oxalate crystals.

Canine and feline models provide information about the genetics and prevention of urate stones. Dalmatian dogs commonly have a genetic defect in uric acid transport due to a mutation in the SLC2A9 gene, leading to liver and kidney problems. Other breeds are hyperuricosuric as well, requiring dietary management using low-purine diets. Some breeds tend toward silica urolithiasis. Silica management is achieved by increasing moisture in the diet, administering diets low in carbohydrates, and avoiding high-silica foods. Males of certain breeds are predisposed for calcium oxalate stones. In felines, urate urolithiasis is common. Some breeds of felines are at risk for calcium oxalate stones.

Animal models in USD can inform human studies, including recognizing patterns and identifying themes, exploring new possibilities, and refining study designs. Models are most valuable in learning about disease mechanisms rather than serving as a model for clinical trials. Although studies are more time-consuming, using the pig as a model can allow testing of new drugs and approaches to management.

Pediatric Urinary Stone Disease

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During the past 25 years, the incidence rate of urinary stones in adolescents ages 12 to 17 has increased dramatically. Although adult men are more likely to develop USD, in children, the prevalence of USD is higher among females than males. Pediatric USD also seems to have a high hereditary component, with 79 percent of children with urinary stones having a positive family history. The composition of adult and pediatric stones are similar except that children have a higher proportion of calcium oxalate and calcium phosphate stones, as well as a lower proportion of uric acid stones. Pediatric urinary stone patients tend to have low urine output, hypercalciuria, and hypocitraturia. However, most children with idiopathic hypercalciuria do not form urinary stones. USD is a risk factor in children for low bone mineral density (BMD), which is important because childhood is the period of developing peak bone mass. Although adult urinary stones are associated with increased osteoporosis, CKD, and vascular disease, the natural history of pediatric urinary stones has not been well defined. It is unclear whether extra-renal manifestations and kidney stones are the result of the same underlying condition or whether kidney stones are causative.

Regarding prevention, evidence-based dietary modifications are not currently available. There are no pediatric equivalents of the Nurses' Health Studies I and II or the Health Professionals Follow-Up Study. RCTs are needed to determine when pharmacological management is indicated for children. Currently, about one-half of all pediatric

patients are prescribed citrate, but diet modification is recommended much more commonly. Key pediatric stone issues that need to be better understood include the reason for female predominance in adolescence; the reason why some hypercalciuric children form stones while others do not; the natural history of pediatric urinary stones; the genetic contribution to incidence; whether there is a unifying mechanism behind urinary stones, vascular calcifications, and BMD; and evidence-based management guidelines.

Diagnostic imaging is an area of concern for children with USD. Although computed tomography (CT) is the current gold standard for suspected nephrolithiasis, it increases the risk of malignancies, making ultrasound an attractive alternative. Ultrasound is a good first choice for children because although it is operator-dependent and is less sensitive and less specific than CT, it identifies most kidney and ureteral stones in children. Additionally, ultrasound is the preferred initial imaging study because most children with suspected stones do not have them, multiple imaging studies are obtained during each stone episode, and children are often exposed to radiation after the initial diagnosis. However, CT use at the first imaging study remains high nationwide, indicating that current practices deviate substantially from recommended best practices.

The surgical indications for ureteroscopy (URS) and extracorporeal shock wave lithotripsy (SWL) are similar between adults and children, with outcomes favoring URS over SWL. Comparative effectiveness considerations should include efficacy, harms (e.g., the need for secondary procedures), patient/family preference, and cost-effectiveness.

Recurrence risk involves modifiable risk factors in the environment and behavior, as well as non-modifiable risk factors. Low water intake and high sodium intake are possible causes for the rising USD incidence in children. Water intake decreases kidney stone recurrence in adults and is an appealing intervention for children because it is risk-free, readily available, and inexpensive. Approximately 75 percent of 9- to 18-year-old children have insufficient water intake. Barriers to water intake may differ between adults and children, including that adolescents consume more alternative beverages than adults. Although changing behavior is difficult even for adults, enhanced educational and behavioral strategies, as well as use of text messaging and mobile health interventions, have shown promise in children. Interventions that increase water intake among children and adolescents with USD should be explored. Other possible interventions include pairing the recommendation to increase fluid intake with smart-watch and dipstick technologies. Game and monetization incentives have proven effective in children. There are existing research infrastructures and opportunities such as the NIH Adherence Network and mHealth 2015 that may facilitate exploration of age-appropriate interventions for adolescents with USD.

Pragmatic Clinical Trials

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In 2012, a study of clinical trials registered in ClinicalTrials.gov revealed that 50 percent of NIH-funded trials did not result in published main results within 2.5 years of completion. The study raised concerns in the U.S. Congress. A report about studies funded by NHLBI found that studies with clinical endpoints were published much more quickly than those with surrogate endpoints. To maximize the return on research dollars, there was a call for funding more large trials with clinical endpoints. This was not a new argument; previously, an editorial suggested that realignment of funding toward practical clinical trials and away from small clinical trials would increase the value of clinical research in decision making.

As large trials became more popular in cardiovascular disease, trials became more complex, with the unintended consequence that the existence of RCTs was threatened, leading to the suggestion of embedding randomization in large trials and EHR-based registries. An example of such a trial is the Thrombus Aspiration in ST-Elevation myocardial infarction (TASTE) trial, which took advantage of high-quality registries in Sweden that had all of the necessary information except informed consent. Seventy percent of patients with heart attacks who were cared for in participating hospitals were randomized in the trial with an incremental cost of only $300,000. Embedded trials may be more difficult to implement in the United States, but some have been carried out within registries (e.g., STS National Database, National Cardiovascular Data Registry [NCDR]). In Canada, an embedded study of transfusion outcomes enrolled 24,000 patients at an additional cost of less than $2 million. A U.S. insurance company even has conducted an embedded trial on the effect of full drug coverage on myocardial infarction that was profitable to the company because it reduced hospitalizations. An embedded trial using cluster randomization to study intensive care unit strategies to

reduce infections cost only $40 per patient. The Patient-Centered Outcomes Research Institute (PCORI) is building a research network by taking advantage of large health plans. The NIH Collaboratory funded the Time to Reduce Mortality in End-Stage Renal Disease (TiME) Demonstration Project, a pragmatic clinical trial, and a living textbook on pragmatic trials. NHLBI is participating in a funding opportunity for low-cost, embedded, randomized, controlled, pragmatic trials.

Pragmatic trials face some unique challenges. Some of the EHR data are of good quality and some are not. Depending on specifics, written, informed consent is needed for participation in some trials. Including a large number of providers and sites increases variability but reflects real-world practice. Pragmatic trials are most useful when studying approved interventions rather than pre-approval interventions. Pilot trials help in study design (e.g., planning for power analysis), and because pragmatic trials are relatively inexpensive, it is affordable to conduct more pilots.

Pharmacological Management of Urinary Stones

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The prevalence of USD is positively correlated with BMI, and the disease is more prevalent in men than women in all BMI categories (i.e., normal, overweight, and obese). The risk of recurrent stones also is higher in men than in women. In 1985, potassium citrate was approved by the U.S. Food and Drug Administration (FDA) for stone prevention and is now widely used either alone or in combination with thiazide or thiazide analog diuretics for the treatment of calcium nephrolithiasis. The thiazide diuretic was shown in 1959 to reduce urinary calcium excretion, and in 1970, thiazide-treated hypercalciuric stone formers were shown to have a decrease in the number of stone episodes. RCTs have shown the effectiveness of thiazides and citrate in reducing recurrence, although not all had the statistical power to reveal a significant effect of treatment. Trials have shown higher withdrawal rates for thiazide and citrate compared to controls as a result of adverse events. One potential adverse event from citrate therapy is an increase in calcium phosphate stone formation. Calcium phosphate in stones increases with age and stone event number. Although the formation of calcium-citrate soluble complexes decreases calcium oxalate and calcium phosphate saturation, an increase in urinary pH is thought to increase precipitation of brushite and hydroxyapatite. Drug development has been limited by the incorrect perception that USD is not a chronic disease, as well as incomplete understanding of the pathophysiology and molecular genetic basis.

Future innovative therapies may arise from advances in understanding of calcium and oxalate transport, the role of insulin resistance, renal lipotoxicity in uric acid nephrolithiasis, and the potential role of V2 vasopressin receptor (V2R) antagonists. Another potential therapeutic approach, the use of phosphate binders, has not been studied yet in randomized trials. An understanding of calcium transport is needed before considering the use of an inhibitory agent for calcium absorption because interfering with calcium absorption raises the risk of a negative calcium ion balance. Oxalate also is potentially as important as calcium in propensity for calcium stone formation. Urinary oxalate is regulated by endogenous production, dietary ingestion, metabolism by *Oxalobacter* in the gut, and uptake by the kidney from the plasma. The pharmacological approach to treat hyperoxaluria includes upregulation of intestinal luminal secretion, intestinal luminal oxalate complexation, and intestinal luminal oxalate degradation and secretion. Reversal of insulin resistance in patients with idiopathic uric acid nephrolithiasis using insulin sensitizing drug (pioglitazone) has been shown to increase urine pH and ammonium levels. Proposed strategies for the development of new therapies include expanding knowledge of the pathophysiology and molecular genetic basis of kidney stone disease, developing a surrogate marker to predict the risk of kidney stone disease, including stone analysis before and after treatment in data registries to determine if “stone transformation” occurs, and designing prospective studies. In designing studies, bone density should be considered as one of the outcomes because of the dangers of bone fractures.

When considering treatment, both thiazide and citrate are first-line drugs. Some patients tolerate one better than the other. For citrate treatment, dosage should be adjusted to maintain a urinary pH lower than 6.7.

Urinary Stone Removal Strategies

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Current best practices in urinary stone removal depend on the stone location and size. For renal stones in the upper/mid/pelvis regions, percutaneous nephrolithotomy (PNL) is preferred for stones greater than 20 mm, and

secondarily, retrograde intrarenal surgery (RIRS), or SWL is considered; SWL or endourology is preferred for 10 to 20 mm stones; and SWL or RIRS are considered equally for less than 10 mm stones, with PNL a secondary treatment option. For renal stones located in the lower pole, trials comparing treatments are of only moderate quality. For ureteral stones, evidence favors the use of URS for stone removal, with HM3 lithotriptor being more effective than SWL at breaking up stones. Relevant outcomes for stone removal strategies are the stone-free rate, which involves defining "stone-free" (i.e., whether residual 1 or 2 mm stone fragments are acceptable); the need for additional procedures; stent use, which is a common patient complaint; complications, including long-term effects; and length of stay, which often is not generalizable from health system to health system. Imaging technologies used after fragmentation to assess outcomes includes kidneys, ureters, bladder (KUB) X-ray plus renal ultrasound, or if radiolucent, renal ultrasound followed by contrasted CT if hydronephrosis is present. Additional outcomes include economic outcomes (i.e., the cost of care for the entire episode); unplanned care such as emergency department visits or hospitalizations, which are common and expensive; and patient-reported outcomes (e.g., satisfaction, quality of life, return to normal functioning, indirect costs such as loss of work).

A challenge for efficacy trials is heterogeneity. Heterogeneity can include stone location and upper tract anatomy, devices for stone fragmentation, surgeon technique and expertise, varying definitions of "stone free," follow-up imaging regimens, stone composition, and patient characteristics such as obesity. Additional challenges include existing RCT quality, cost of RCTs, and the current funding environment.

Possible outcomes include improvements in efficacy (e.g., SWL technology, ureteroscopes, laser fibers, less-invasive percutaneous approaches) and effectiveness (e.g., outcomes in broad practice, adoption of best surgical practices). It is unclear what might be the magnitude of potential gains and what would change practice. Similar to the CRUSADE registry, which tracked adherence to treatment for patients with unstable angina or non-ST segment elevation myocardial infarction (NSTEMI) and improvements in practice, the Michigan Urologic Surgery Improvement Collaborative (MUSIC) is a quality improvement registry in urology that provides feedback to participating practices on radiographic staging in low-risk prostate cancer that resulted in a decline in bone scans and CT use in patients.

For new studies, key questions include what would constitute a change in practice or substantial improvement in outcomes. Determining the best study design (e.g., RCT vs. observational) needs to consider feasibility, cost, time, and opportunities for collaboration. Key outcomes need to be decided upon, including clinical, patient-centered, and policy-relevant outcomes. For example, what follow-up period in a clinical trial would be sufficient to determine if a patient is stone-free? When comparing imaging technologies that will be used in studies to determine the outcome of being stone-free, consideration needs to be paid to the superior image quality of CT compared to ultrasound and advances in technology that have decreased radiation exposure from CT scans. Clinical studies also need to be designed to assess the real-world spectrum of treatments, however, which includes KUB X-ray and ultrasound. A possible outcome to be studied might be the long-term effects of residual stone dust that is purposefully not removed after treatment. Patient preference also needs to be considered in trial outcomes, particularly patient dissatisfaction with stents.

Novel Urinary Stone Management Strategies for the Urologist

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New urinary stone management strategies for the urologist include ultrasound innovations, modifications to enhance SWL, and robotics. Surgery leaves fragments that may serve as stone nuclei and are unlikely to pass from the lower pole. Ultrasonic propulsion is an ultrasound innovation designed to reposition stones within the kidney. In a clinical trial of 15 patients who had de novo stones and post-lithotripsy fragments, as well as those were pre- or peri-URS surgery, ultrasound propulsion imaged and moved stones in all but one of the patients. Patients passed some of the post-lithotripsy stones; imaging showed that what were thought to be large stones (> 4 mm) in some cases actually were several smaller ones; and large stones (> 8 mm) were moved. There was no pain or adverse events associated with the procedure. This study showed that the procedure can be used to expel fragments and for diagnosis. A second trial with an additional 15 patients has been approved. The outcomes will include moving stones that are obstructing the kidney so that stone removal can be performed as elective rather than emergency surgery. A vortex ultrasound beam was able to pull a simulated kidney stone on a path. Ultrasound also was optimized to estimate stone size and avoid false positives. Burst wave lithotripsy (BWL), which uses an oscillating pressure pulse, was compared to SWL, which uses a single pressure pulse with a compressive spike. In simulations, fragment size decreased with increasing ultrasound burst

frequency, and at 330 Hz, all fragments were less than 2 mm in diameter. This technology is still in development prior to clinical testing. Ultrasound innovations in hardware have the potential to break up, move, and characterize stones.

In work supported by NIDDK, a new lens design was developed to improve the performance of SWL. The new lens results in a change in waveform, decrease in peak pressure, broader beam, and alignment of peak pressure/cavitation. In vitro experiments showed a rate-dependent efficacy in SWL stone comminution; the decrease in attenuation at lower frequency was attributed to residual cavitation bubble nuclei having more time to dissolve.

A new robot has been developed for flexible URS. The technology is in development and early clinical testing.

Imaging for Diagnosis and Management of Urinary Stone Disease

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Expectations for imaging are changing. Rather than just detecting the presence or absence of stones, imaging is being used in deciding on treatments, predicting outcomes, and estimating risk factors. The choice among the three imaging technologies—KUB X-ray, ultrasound, and CT—depends on multiple factors, including risk (i.e., radiation exposure is minimized for children and young adults), availability, cost, and performance. Success of imaging will depend on stone size, composition, location, body habitus, and operator skill. The composition of stones affects imaging performance. Some types of stones can be seen with radiographic techniques but cannot be detected by ultrasound.

In numerous studies, CT has been shown to detect approximately more than 90 percent of all stones. CT is widely available, produces thin images, and can visualize complications associated with stones. Coronal reformations are valuable because they can detect tiny stones that might be missed with ultrasound. Studies of CT sensitivity and specificity show a sensitivity of close to 100 percent, making it the test of choice for emergency departments. CT can distinguish heterogeneous and homogeneous stones, as well as total stone volume, making it useful for predicting treatment efficacy. CT also can be used in planning interventions, including the renal access and guiding fluoroscopic procedures. Dual-energy CT (DECT), which simultaneously uses two X-rays of different energies, can distinguish between calciferous and uric acid stones. A meta-analysis of 13 studies using single-source DECT (ssDECT) and dual-source DECT (dsDECT) found almost 100 percent accuracy in distinguishing uric acid stones, which is information that can be used in medical management decisions. Post-processing software of targeted DECT scans can be used to calculate the effective atomic number of a stone.

USD is a risk factor for other conditions, including low BMD, diabetes, fatty liver, and metabolic syndrome. A benefit of CT scans is that results from CT scans can be used to motivate patients to change behaviors. CT can diagnose patients who have Randall’s plaque and are at risk for stones, leading to medical management and potentially halting stone formation. CT attenuation is a good predictor of whether radiography will be useful in routine follow-up. Moreover, KUB X-ray does not distinguish clusters and small fragments as well as CT.

Safety is a key aspect of imaging, especially in young patients. The effective radiation dose from a CT scan can be as high as 13 mSv for men. The dose depends on the CT scanning protocol, scan length, and body part. Doses can be lowered by limiting the scanning area, increasing slice thickness, lowering the energy of the scan, and lowering the current. Low-dose imaging has increased noise, however. New techniques can be used to reconstruct the image to improve quality. Studies have shown that radiation doses associated with CT scans have declined with time. An approach to decreasing dose is to use standard-dose CT for initial scans and ultra-low dose scans for follow-up scans. Ultra-low dose CT is used primarily in academic settings. A wider sharing of best practices and protocols is needed to broaden its adoption, but it is difficult to incentivize hospitals to adopt new technologies. Payers are helping change the model, however, as are the adoption of the new technologies by young radiologists. The current imaging strategy is to use ultrasound as a first-line approach for children and young adults and CT in adults.

CT has some significant drawbacks other than safety. It is expensive compared with other types of imaging. As an alternative, urinalysis can help to determine the type of stone. CT also is not needed for diagnosis if there is colic or blood in the urine.

Behavioral Economics of Urinary Stone Disease

Mitesh Patel, M.D., M.S., M.B.A., University of Pennsylvania Perelman School of Medicine
Medicine is shifting toward a new model of care that is proactive rather than reactive and visit-based. The new model passively monitors behaviors during everyday life and anticipates when action needs to be taken to address issues before the patient becomes ill. The new model of care is rooted in three evolving market trends: (1) widespread innovations in mobile technology; (2) a growing understanding about incentives; and (3) a shift in health care reimbursement toward fostering population health. The Affordable Care Act offers economic incentives that favor outcome-based incentives. Regarding the science of motivation, there is a shift toward the understanding that people act irrationally but predictably, which is changing the ways in incentives are delivered. Insights from behavioral economics suggest solutions to typical decision errors, including changing the path of least resistance, making rewards immediate and frequent, putting rewards at risk if a behavior is not achieved, making rewards tangible and in a familiar context, and telling individuals about the monetary incentives that they would have won had they been adherent.

Wearable devices are an emerging tool for changing health behaviors. Currently, 1 to 2 percent of the population uses wearable devices, but it is estimated that sales will increase over the next few years. At present, there is little evidence that these devices alone, however, can change behavior for those who need it most. Key challenges to changing behaviors via wearable devices include expense, which limits access for individuals that need them; sustainability; accuracy, which has not been evaluated for many devices; and motivation. In a recent study, smart phones and wearable devices were compared on a treadmill and almost all were found to be accurate.

Incentives have been tested as a way to change behavior. In a randomized trial that used monetary incentives to increase adherence of patients with diabetes, a decrease in glycated hemoglobin (HbA1c) was found that was greatest in the incentive groups but did not persist after the incentive was removed in the high-incentive group. Medication adherence has the largest potential use of incentives, with smart phone apps being a way to target behavior. Gamification such as a cartoon of a wilting plant to target hydration is another way to modify behavior.

Competition may be quite effective in providing social incentives for behavior change and is sustainable, whereas incentive use is not. The most effective interventions in terms of population health will target sedentary individuals, which may require reframing goals to focus on these individuals (e.g., 7,000 steps per day vs. 10,000 steps per day). Step tracking is viewed as a benign manipulation. A possible use for step tracking "big data" in research is to judge the success of targeted interventions.

Wearable devices may help facilitation monitoring health outcomes but by themselves may not drive behavior change. Effective engagement strategies must be combined with these technologies to build new healthy habits. Insights from behavioral economics can help design interventions that anticipate and leverage predictable barriers to health behavior change.

Breakout Sessions

Interactions of the Diet and/or Microbiome and Prevention Strategies

Moderator: Chris Ketchum, Ph.D., NIDDK, NIH
Reporter: Marshall Stoller, M.D., University of California, San Francisco
Both the urinary tract and gut microbiome are relevant to USD. There is a need to differentiate between biofilms and the microbiome. The fecal microbiome needs to be defined for non-stone and stone formers. Multiple clinics could be used to obtain samples that would be sent to a central repository; this approach would reduce costs. It might be possible to leverage other collaborative consortia through dietary questionnaires, 24-hour urine samples, accessing recurrent stone patients and patients with a positive family history, and segregating patients into groups that did or did not receive remote prophylactic antibiotics. More needs to be understood about the microbiota community involved in citrate and oxalate metabolism and whether there exists other microbe-derived metabolites that might impact USD. In addition, the question needs to be answered as to whether microbiota are involved in calcium metabolism. Relevant subpopulations include patients with inflammatory bowel disease, bariatric surgery, obesity, and early/late onset diabetes. Regarding diet, the effects of lowering oxalate need to be assessed, including definition of a low-oxalate diet. Another dietary question is whether it is possible to consistently increase fluid intake. To carry out a prospective trial with fluid intake, smart-phone apps could be used to assess urine concentration; the wilting plant app could be part of the trial; and a

dipstick would be a simple, cheap technology to assess urine pH and specific gravity. In addition, it is not known what happens long-term with a DASH diet.

Genetic Information for Personalized Urinary Stone Disease Prevention

Moderator: Marva Moxey-Mims, M.D., NIDDK, NIH
Reporter: Friedhelm Hildebrandt, M.D., Boston Children's Hospital
A cost-effective approach to fostering the use of genetic information for personalized USD prevention would be to examine existing cohorts for monogenic causes. This technique could be applied to such data sets as the Women's Health Initiative (WHI), NHANES-3, and Rare Kidney Stone Consortium (RKSC), among others. In large, prospective cohorts, the cost to obtain genotype data for the 30-plus monogenic mutations that are known to cause USD would be approximately $30 per patient or $1,000 per patient for whole exome data. Possible gains from collecting these data include the abilities to assign disease causation and the deleteriousness of a mutated allele for each of the 30-plus monogenic genes, to define adult-onset mutations, and to conduct genetic epidemiology. The 30-plus genes could be converted to biomarkers, permitting genetic counseling and mutation analysis for family members, prophylactic recommendations, therapeutic recommendations, and etiologic stratification for future trials. Tailored treatment would involve personalized management and established correlations between genotype and phenotype (e.g., age of initial stone, recurrence, treatment response). Basic science studies with animal models would inform treatment as well.

Strategies to Prevent Urinary Stone Disease Recurrences

Moderator: Paul Kimmel, M.D., NIDDK, NIH
Reporter: John Lieske, M.D., Mayo Clinic
Several themes emerged in the discussion of diet and drug strategies to prevent stone disease recurrences, as well as how the strategies should be evaluated. There is a need to develop a collaborative trials network with a common database and common protocol. Emergency departments are a common entry point for USD and ideally would be included in the network, as should centers with pediatric USD. Because of poor awareness, a national USD education project should be considered with a goal that primary care physicians could ultimately care for many USD patients with less complicated disease. The role of 24-hour urines to guide therapy should be systematically assessed. The role of imaging for monitoring patients and as a trial outcome needs to be better understood. Fluid is a known treatment, but it is not known how much intake is enough, what the barriers to increased intake are, and whether rescue or additive therapies such as citrate could possibly be used for times when patients have unavoidably low fluid intake. The role of weight loss in stone risk needs further study. The role of citrate in calcium phosphate stone formers is not well understood. Final recommendations included the following: (1) develop a clinical trials network that encompasses emergency departments, as well as nephrology and urology centers; (2) undertake a practical trial in calcium stone formers (ages 12 years old or greater) 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 (stone events would be the hard outcome); and (3) launch a USD education project.

Impact of Surgical Stone Removal Therapies on Stone Clearance

Moderator: Ziya Kirkali, M.D., NIDDK, NIH
Reporter: Charles Scales, Jr., M.D., M.S.H.S., Duke University School of Medicine
The discussants identified 25 key clinical problems that they narrowed to four consensus priorities. These four were the following: (1) long-term outcomes of residual stones, (2) stent pain, (3) antibiotic prophylaxis for PNL, and (4) the safety of anticoagulants for PNL. Additional important opportunities were patient-centered outcomes, a platform for technology assessment, non-obstructive renal stones associated with pain, and fragment retrieval versus dusting. For stent pain, there was a consensus that it is common, has the potential for use as a patient-centered outcome, potentially has broad impacts, and needs to be better understood. Facets of possible study design would include a prospective cohort, an approach that would maximize EHR data capture, embedded focused questions within a larger study, a biorepository, and use of the Lower Urinary Tract Dysfunction Research Network (LURN) as a model for patient phenotyping. Embedded focus questions could include anticoagulant safety, antibiotic prophylaxis, imaging protocols, active removal versus dusting, small residual fragments, and small asymptomatic stones.

Conclusions

Robert Star, M.D., NIDDK, NIH
This meeting succeeded in establishing a conversation among representatives of three groups who typically do not interact: nephrologists, urologists, and basic scientists/engineers. The participants recognized the need for overarching tools to advance the field, including the following:

- The development of patient-centered outcomes such as pain scores specific to kidney stones.
- Phenotyping (e.g., low-cost, low-dose CT imaging for determination of residual stones; urine chemistry; changes to the microbiome), especially establishing a computable phenotype that can be characterized by interrogating EHRs to capture stone events.
- Animal models across species, including the fruit fly and pig, to investigate USD physiology and assist with phenotyping.
- Collaborative networks.
- An education program to disseminate new results.

The topics of the four breakout sessions were overlapping as well as complementary; for example, increased fluid intake as treatment was a topic for genetics-informed treatment and stone recurrence prevention. Key points made during the four breakout sessions included that genetic information based on 30-plus known monogenic mutations can be used in existing and future prospective cohorts to define phenotypes and lead to personalized counseling and treatment; exome sequencing can be used to expand the understanding of the genetic contribution to USD. Regarding the effects of diet and the microbiome on USD, there is a need to better understand oxalate metabolism in the microbiome and the functional effects of the urinary tract versus gastrointestinal microbiome on USD. Prevention is difficult; there was interest in a pragmatic study of the effectiveness of different methods to increase water intake. For individuals who cannot increase fluid intake, the efficacy of citrate needs to be assessed. With respect to surgical treatment, reduction of stent pain is a patient-centered outcome that needs to be a focus of surgical treatment. There was a need to better understand the long-term outcome for small, asymptomatic stones (de novo and remnants of treatment). A better understanding of the critical size of stones will inform imaging detection limits. The results of this meeting will inform future endeavors sponsored by the NIDDK. The NIDDK is committed to the support of the advancement of prevention and treatment of USD, as will be reflected in upcoming funding opportunities.