Dear Registry Participant,

Hello again, and welcome to the new edition of the Cystinuria newsletter. As you may well know, this newsletter was planned and written by the staff of the Cystinuria Registry at New York University, and patient advocates from the Cystinuria Support Network (CSN) and the International Cystinuria Foundation (ICF).

In this issue, you will find updates about the contact and disease registry and related clinical extensions like the biobank, quality of life assessment and smaller trials currently ongoing in New York. Our patient advocacy groups (PAG) members report about a meeting in Washington, "how to find a doctor, and give updates about the CSN and ICF. We also report about the grant renewal.

Your participation in the disease registry and all related substudies includes a few small tasks. Please make sure that our emails are not being directed to your Spam filter and please call us back when we leave a message on your voicemail. You can always email us at cystinuria@nyumc.org. Let us know if there is a topic that you would like us to discuss in the next issue which will be released in spring of 2014.

- Frank Modersitzki, MPH

Cystinuria Registry
Part of the Rare Kidney Stone Consortium

News

Frank Modersitzki and Dr. David Goldfarb, of NYU School of Medicine, published the results of a survey of health-related quality of life in cystinuria titled “Health-related quality of life (HRQoL) in cystine compared with non-cystine stone formers”. This paper was published by the journal Urolithiasis. In this paper, we discussed the health related quality of life for cystinuria and non-cystinuria stone formers in comparison to the US standard population.

For this online survey we collected information about health-related quality of life, stone events, medical history and some socio-economic information. We found that cystinuria stone formers have worse outcomes in health-related quality of life than the US standard and other non-cystine stone formers. In our survey, health domains like ‘pain’ show worse outcomes. Health domains like bodily pain, general health, vitality and mental health were significantly lower in cystinuria formers compared to non-cystinuria formers.

Interestingly, people with cystinuria had worse HRQoL because they had more stones, not because of some other factor related to cystinuria. While the result of the study may not be surprising, we think this is an important contribution to documenting what most people with cystinuria have told us. In addition, quality of life improved as time since the last stone increased. While this also may seem obvious, we wondered if people with cystinuria continued to have low HRQoL scores even after stones had resolved. As that was not the case, based on these data, we are reassured that effective prevention of new stones should lead to improved HRQoL even if dietary changes, fluid therapy and medications are significant impediments in the lives of people with cystinuria.

We plan to continue with the assessment of HRQoL and incorporate this information into the “disease registry”. Please see the next page for more detailed information. We plan to include over 200 cystinuria stoner formers. This is the largest sample of cystinuria stone formers ever surveyed for HRQoL.

Based on our results, we recommend that pain management and mental health consultants be considered during the treatment of cystinuria when needed. The paper may also be useful in documenting to other healthcare professionals, friends and family, that cystinuria is different than other forms of kidney stones. You can find a copy of this article on the ICF Facebook page or request it via email from cystinuria@nyumc.org.
Contact registry

Currently, we have more than 400 participants signed up with the contact registry. All should have received an informed consent form in the mail. All participants that signed up for the contact registry, at NYU, should have received consent forms (assent forms for children). The contact registry is used to get in touch with cystinuria patients. It only stores your contact information and your interest in receiving newsletters, email from the ICF or new study opportunities. We abide by our agreement, with you, not to request or store any medical information. If you would like to make any changes to your contact registry entry, please contact us.

Cystinuria registry update

The Cystinuria Registry is also referred to as the disease registry. To store your information, an informed consent (see above) and verification of your consent via telephone (or in person if possible) is needed. Currently, we have 250 participants enrolled in the disease registry. The disease registry does not include any information other than your gender and date of birth. We assign a unique patient number to you. Contact and Disease registry data are kept completely separate. The information in the disease registry is protected by a certificate of confidentiality, as outlined in the consent form. None of your personal identifiers will be collected and or shared with anyone. For the disease registry, we try to collect information about your medical history (or any change), regular blood work to monitor kidney function, 24-h urine results, renal image data and information about stone events and stone-related interventions. Some of this information is collected when a stone occurs and you are treated by a medical provider at another location (hospital or primary clinic). If you are aware that additional information, on your condition, is stored at another provider, please let us know when you sign a medical chart release form. We can provide additional blank medical release forms for you to obtain that information on our behalf.

What can you do to help with the collection of medical charts?

- Return the medical chart release form to us. This gives us permission to contact your doctor’s office and request a copy of your records. If you see a different urologist or nephrologist for the treatment of cystinuria, please request an additional release form.
- At your doctor’s office, you can always ask for a copy of your lab results and the doctor’s notes regarding your visit. You may want to keep copies of this information at your home, in case you have a stone-related event and need to go to a different location that does not have access to your medical records. You could share this information with the registry, if you like.
- If you know that your blood results are only at the hospital or primary care office, please share this with us.
- If you take any cystinuria-related medication, keep a medication journal at home and note any changes that you or your doctor may make.
- Keep a log on any stone event, stone-related pain, stones passed, image studies and potential stone procedures.
- Talk to your renal doctor and tell him/her that you are part of the Registry and that you consented to the release of your information to the Registry.

Biobank

The cystinuria biobank is still enrolling participants. This involves an additional informed consent. If you want to participate, email us (cystinuria@nyumc.org) and request an informed consent form. We try to collect blood, urine and stones (if any are available) on annual basis and bank these specimens at the Mayo Clinic for future research. For participants that are not seen in your practice in New York, we will mail collection kits to your home. The collection should be done at your next regular doctor visit. The phlebotomist should collect one additional tube of blood and a urine sample, and mail it with a included return label to the Mayo clinic. Collection kits will soon be mailed to participants that have already signed up for the biobank.

Quality of life study

The quality of life study was fully activated (Oct 2013) and we are starting to recruit participants. The assessment of quality of life will be done with a highly standardized questionnaire, SF-36v2 (for adults) and SF-10 (for children). These questionnaires will be done online annually and will take 20 minutes of your time. Parents will complete this questionnaire for their children. All information will be collected on a secure NYU web site and questionnaire results will be included in the registry. If you want to be part of the of the quality of life assessment, email is at cystinuria@nyumc.org; include ‘quality of life’ in the subject line.
Application for Renewal of the Rare Kidney Stone Consortium (RKSC)
David S. Goldfarb MD

On November 7, 2013, the RKSC submitted its application for renewal for another 5 years. The RKSC consists of 4 projects: studying genetic causes of kidney stones: primary hyperoxaluria, cystinuria, APRT deficiency and Dent disease. RKSC is one of 17 funded consortia, currently in the 5th year of 5 years of funding. No one is sure of how many consortia will be funded in 2014 for another 5 years, but we put together a good grant, describing all the progress we have made in the last 4.5 years and our plans for the future. The grant includes hundreds of pages of proposals, letters of support, biographical sketches of all the participants, and plans for sharing our data and collecting specimens. We included biographies of Janice O’Connor and Katie Jewell, and letters of support from George Brown of the International Cystinuria Foundation, and from Janice and Katie, representing ICF and Cystinuria Support Network too. Below are the specific aims for the coming 5 years we described in the grant. Some of it might seem technical, and the details are not spelled out here, but I am happy to share them with you.

Specific Aim #1: Work collaboratively with our Patient Advocacy Groups (ICF and CSN) to engage patients to improve disease outcomes.

a. Identify patient-centered concerns and problems that can be addressed through study.
b. Systematically assess Health-Related Quality of Life (HRQoL).
c. Achieve robust participation in clinical studies, including patient reported outcomes.
d. Improve disease awareness of patients, family and other practitioners.

Hypothesis: An active partnership of patients, medical providers and research scientists will more effectively identify concerns and problems that merit study, engage patients and families, advance scientific discovery, and improve patient outcomes and quality of life.

Specific Aim #2: Identify patients with cystinuria at high risk of recurrent stones and progressive loss of kidney function.

a. Generate robust longitudinal outcome data through expansion of a prospective longitudinal cohort and expansion of the cystinuria registry.
b. Expand the cystinuria biobank for blood, urine, DNA, stones.

Hypothesis: Outcome data and biologic specimens from well-defined groups of patients with cystinuria will: (1) Generate and allow testing of new hypotheses regarding loss of kidney function and stone formation in patients with cystinuria. (2) Predict which patients are at high risk of stone recurrence and progression of CKD and thus best suited for future clinical trials of novel therapeutic agents. (3) The variables associated with chronic kidney disease in cystinuria include cystine excretion and cystine capacity (CysCap).

Specific Aim #3: Identify pathways of kidney injury associated with cystinuria.

a. Measure plasma and urine levels of injury and inflammatory markers, estimate rates of marker elevation in cystinuria, and compare with patients with hyperoxaluria, Dent disease and APRT deficiency.
b. Correlate biomarker panels with cystinuria disease severity.
c. Correlate biomarker panels with cystinuria disease outcome.

Hypothesis: (1) Urinary markers of inflammation are increased in cystinuria (2) Patterns of biomarkers will predict injury pathways and potential treatment targets; (3) Biomarkers can be used to predict and monitor progression cystinuria-induced kidney injury and stone risk.

Specific Aim #4: Identify novel therapeutic targets for potential pilot studies.

a. Continue to plan for a possible phase I study of cystine dimethyl ester (CDME).

Hypothesis: in vitro inhibitors of cystine crystallization will have meaningful clinical effects

The current schedule is that we would hear about a funding decision by June or July 2014. We certainly put a lot of work into this proposal and really appreciate the help offered us by George, Katie and Janice. Of course we will let you all know as soon as we hear about our proposal.
Finding Strength in Numbers
Highlights and Hope from the Rare Diseases Clinical Research Network’s Coalition of Patient Advocacy Groups Annual Meeting
By Kathryn Jewell and Janice O’Connor

On Oct. 1, we had the honor of representing the cystinuric community at the Rare Diseases Clinical Research Network (RDCRN) Coalition of Patient Advocacy Groups (CPAG) annual meeting in Rockville, MD. Due to the government shutdown that began on that day, some key federal organizations, such as the National Institutes of Health and the Office of Rare Diseases Research, unfortunately were prevented from attending. Despite that turn of events, the meeting proved an enormous success as it provided more time and opportunity to share with and learn from attendees representing a host of rare diseases, as well as the coalition working on behalf of us all.

At times, when we can feel isolated in our disease, it was most reassuring to realize - we are not alone. Across the U.S. and around the world, patients, caregivers, physicians, researchers, and organizations are advocating for better health care, enhanced treatment and, ultimately, cures for life-threatening and/or life-altering rare diseases and disorders.

The RDCRN suggested that we should all visit their website and encourage our members to join the RDCRN’s contact registry: http://rarediseasesnetwork.epi.usf.edu. This will help with the research for our disease as the information can provide demographics of where most of the cystinurics are located. We currently have connection to the contact registry through Dr. Goldfarb’s NYU website: http://medicine.med.nyu.edu/nephrology/research/current/join+the+cystinuria+registry.

The RDCRN represents 246 rare diseases, has 12,247 registrants, and represents 97 countries as of Oct 1, 2013. Let us join them and show researchers we are out there, add to their numbers, and demonstrate that cystinuria is worth the research.

During a session on advocacy, we also learned how organizations like ours have taken their cause to Capitol Hill to educate public officials and get legislation passed for improved healthcare, which in turn has meant more funding and more research. The United Mitochondrial Disease Foundation (UDMDF) started small and now has a full-time paid staff member with an office in Washington, DC that is fighting for research, legislation and funding for their rare disease. This work took a few decades, but they are making strong strides for their disease and the families. Can you imagine if we work together, and had a walk, then a meeting with multiple political figures for discovery with our disease? Could Cystinuria become a household recognized named such as Cystic Fibrosis? Yes it could, but not without getting members of our community involved with registering for the Rare Kidney Stone Consortium, joining the RDCRN (so they realize how many of us are out there), then gathering on Capitol Hill someday.

Did you know there are pharmaceutical companies and industries that focus solely on rare diseases for orphan drug development? Dr. Chris Adams, founder of a company named Cydan Development, Inc., spoke about his company’s and their goals for developing these orphan drugs, and the practical steps to partnering with the industry.

The meeting also included reports from the various organizations that make up the Coalition of Patient Advocacy Groups. Of those 12 individual reports, Kim Hollander of the Oxalosis and Hyperoxaluria Foundation (OHF), spoke on behalf of the Rare Kidney Stone Consortium, which represents the cystinuric community. Our consortium has accomplished many of the goals that were set out four years ago, and is now in the process of reappraising for federal funding to keep research in a forward moving motion.

We learned that the grant money, research, orphan drug interest, and interest in cystinuria, has to come from the patients and family promoting the disease. If we do not have a team of like minds that want a cure, or a better quality of life at the very least, we cannot do this. We must have a passion for cystinuria, in order to spark an interest to fuel the fire that is needed for a cure.

Dr. David Goldfarb has the passion. He attended another RDCRN meeting the following day. He is fighting for us, lecturing and promoting on our behalf, and is involved in research for this disease for us. We must also be proactive to keep this research rolling. Our goal should be to make everyone aware of cystinuria and what this disease is. We should promote knowledge of cystinuria to the world, and then we will get the help that we are crying out for. That is what the other organizations are doing. It is our time to do the same.

One upcoming way to make a difference is to join forces with the RKSC and organizations like the National Organization for Rare Diseases (NORD) to advocate for widespread recognition of rare diseases on Rare
FINDING A DOCTOR FOR CYSTINURIA
By Katie Jewell

I have moved 36 or more times in my life dealing with Cystinuria. I am one of the patients that have a high cystine output, and make stones quite frequently. I have lived overseas in Denmark, Holland, Scotland, and England. My residence is in the United States. I am also the patient advocate for the Cystinuria Support Network, and have been involved with the CSN and the ICF for over a decade. In other words, I am well qualified for the advice I am sharing from my experiences.

- A NEPHROLOGIST AND UROLOGIST IS NEEDED.

You need a Nephrologist, and an Urologist. The Nephrologist will keep you from seeing the Urologist, and is priority in all Cystinurics' lives. The Urologist is a surgeon that will be removing your stones, finding infections and blockages, placing stents, and nephrostomy tubes, among many other things. The Nephrologist is proactive in your care to help prevent you from having surgery, and losing kidney function. They work hand and hand and they should both work out of the same hospital preferably, and work well together.

- TEACHING HOSPITALS ARE MOST KNOWLEDGABLE FOR CYSTINURIA

Contacting a teaching hospital for a Nephrologist and Urologist for your care is the first place to look for the most qualified Dr. for Cystinuria. I lived in many rural areas where this was not an option, and it caused problems with my care. They just do not have the knowledge that you need to deal with this rare disease, and they treat you as they have been trained as normal kidney stone protocol.

- A GOOD BEDSIDE MANNER IS IMPORTANT

Like your Dr. If he does not have a good bedside manner, then he is not going to understand our issues with Cystinuria. I had a Dr. tell me that since I seemed to like the care that I received at Jackson Memorial in Miami, then I should move back to Miami. He was a great Dr. But he had no compassion. I moved on to another Dr. that listened to me, and cared about me.

- DO NOT PUT UP WITH ERRORS

If you like your Dr. and they make serious errors, find another Dr. I had a Dr. that was very nice, and had compassion, but she did not comprehend the seriousness of my disease. I was in ER once, and she insisted that I knew how to care for myself at home. I knew I was too sick for that. Her associate kept me in the hospital and I ended up in ICU for a week because I had Urosepsis. You know your body, and if you think it is serious, then your Dr. should also.

- MAKE AN APPOINTMENT TO INTERVIEW THE DOCTOR

Set up an appointment with the Dr. and let them know when you book the appointment that you are interviewing him to see if he is the best Dr. for your situation. Most Drs. respect this, and if they do not, then keep looking.

- INTERVIEW QUESTIONS

Ask them questions about availability, if you have an emergency can they get you in for a ultrasound that day without going to the ER, have they had a patient with Cystinuria before, would they be willing to help you if you are involved with research, if you feel you may have an infection can you call and just have the nurse run a urine test for you, how long does it normally take the nurse to return a call, what is his plan of treatment if you feel you may have a stone, what is their pain medication for protocol for stones, does he understand that you do not want a CT every time you feel like you have a stone, and is he willing to use ultrasound first with you, which Nephrologist does he work best with ...and you can add to this list. Have this list of questions ready for this interview and take notes while speaking to him. This is an interview. Rate him on experience, personality, accessibility, and quality of care you believe you will get from him.

- YOU CAN FIRE THEM

If you are not happy with him/her fire them and move on. They will earn money from you, and with this disease, depending on the severity, it could be quite a bit over time. Your life is in their hands, let it be in hands that you trust.
You are not alone, although it may seem like it at times. There is plenty of information on the internet available to you now. Check out the link [http://www.cystinuria.org](http://www.cystinuria.org) then go to the forums to find a Doctor in the general forum. There is a forum just for that! These Drs are often recommended by other Cystinurics, and it is a great place to place a question. Also [http://www.cystinuria.com](http://www.cystinuria.com) is available for more information on this disease and for a personal group email for support. There are several Facebook pages on Cystinuria, where you can ask questions, share information, or just vent frustration with others. Some of these groups are closed, and private, but others are not so be sure you know this before you put something out there for the whole world to see regarding your disease that you may be trying to hide from your employer, or others. My email is kathjewell@aol.com for more information regarding any Cystinuria links you may need. Good luck finding THE Nephrologist, and Urologist that are best for you and your individual situation.

**Effect on Increasing Doses of Cystine Binding Thiol Drugs on Cystine Capacity in Patients with Cystinuria**

by Nicola Sumorok

We are excited to announce that our newest study on cystinuria is up and running. This latest study is a study of CBTDs (binding thiol drugs, i.e. Thiola and d-Penicillamine), which are used in the prevention of stone formation in patients with cystinuria. The study hopes to find the best dosage at which these medications can help prevent kidney stones. Although CBTDs are normally standard of care in cystinuria, there are no set guidelines to the best prescribed dosage. Therefore, this allows dosages to be too small, resulting in kidney stones; or too large, resulting in side effects. The aim of the study is to determine what the effect of varying doses of CBTDs has on the urinary cystine capacity, one of the tests in the 24-hour urine that we follow to assess the effectiveness of treatment.

The study involves four separate periods in which subjects take their CBTD (either Thiola or d-penicillamine) at specified doses (0 grams per day, 1 gram per day, 2 grams per day, and 3 grams per day). Each study period is 7 days long, and subjects perform a 24-hour urine collection on the last day of each period. The order in which the periods are completed is randomly assigned to eliminate any bias the order of the study periods may have on the results. Subjects are asked to keep a food diary on the day before and the day of the first urine collection, which they replicate in the subsequent three study periods, in order to control for any effects diet may have on the urine tests.

Only patients who are already on a CBTD are being considered for inclusion in the study. We are actively recruiting patients at this time, and several people are already participating. We hope to enroll a total of ten-to-fifteen patients over the next 6 months. Ultimately, we hope the findings from the study can help physicians guide treatment in the future, and improve the quality of life for patients with cystinuria.

**Rare Kidney Stone Consortium meeting in Iceland**

The cystinuria registry joined the NIH-funded Rare Kidney Stone Consortium for a scientific and grant renewal meeting in Iceland. Our collaborators from the APRT registry hosted the Nordic Conference of Nephrology, bringing together nephrologists from Iceland, Denmark, Sweden, Finland and Norway. We used this opportunity to hold a RKSC planning meeting. The goal of this work meeting was to plan the NIH grant renewal, that was submitted on Nov 7, 2013.
Some of the attendees of the Rare Kidney Stone Consortium planning session, held in Reykjavik, Iceland, at the Childrens Hospital at Landspitali: The National University Hospital of Iceland: from left to right: Carrie Light, Dr. Dawn Milliner, Tammy Evans, Frank Modersitzki, Dr. Vidar Edvardsson, Dr. John Lieske, Dr. Eric Bergstralh, Dr. David Goldfarb. Not pictured: Dr. Lada Beara-Lasic and Dr. Runolfur Palsson.

**Internet Resources**

NYU School of Medicine, Division of Nephrology - main site for the cystinuria registry
http://medicine.med.nyu.edu/nephrology/research/current/cystinuriaregistry -

Cystinuria Support Network, active Yahoo email group

and http://www.facebook.com/groups/2225138217/?fref=ts

International Cystinuria Foundation

Rare Kidney Stone Consortium, main consortium web site
http://www.rarekidneystones.org

Rare Kidney Stone Consortium
http://www.rarekidneystones.org

Other Facebooks sites
en espanol: http://www.facebook.com/groups/153010944726588/
cystinuria awareness project: http://www.facebook.com/groups/309167699098336/?fref=ts

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