5-Part Series on Alport Syndrome
by Dr. Clifford Kashtan

Dr. Clifford Kashtan is the director of the Alport Syndrome Treatments and Outcomes Registry (ASTOR) and a member of the ASF Medical Advisory Committee. He is a practicing physician and a researcher with extensive knowledge regarding Alport Syndrome.

Dr. Kashtan wrote a 5-part series of brief articles about Alport Syndrome in connection with the first-ever Alport Awareness Month in March 2014. The series was posted weekly on ASF social media during the month, but is shared here in its entirety. Dr. Kashtan updated some information in March 2015.

Part 1: Hope for people with Alport syndrome

For the past 40 years there has been slow but steady progress in understanding Alport syndrome, thanks to the efforts of many investigators working in clinics and laboratories all over the world. In the 1970s we learned that Alport syndrome is a genetic disease of tissue structures called basement membranes. In the 1980s, we found out that the basement membrane abnormalities are caused by defects in type IV collagen, a major basement membrane protein. And in the 1990s, researchers identified the type IV collagen genes COL4A3, COL4A4 and COL4A5 as the sites of the mutations that cause Alport syndrome.

In the 2000s, studies of mice genetically engineered to have Alport syndrome have informed us about the processes that cause kidney failure and demonstrated that the kidney failure can be delayed by several types of treatment. We also have evidence that treatment can postpone the need for dialysis and kidney transplantation in people with Alport syndrome.

Although there is still much work to be done before we will be able to completely prevent kidney failure and deafness in people with Alport syndrome, therapies that are being developed now promise to improve the treatment of Alport kidney disease. In order to insure that people with Alport syndrome get the best treatment available, we need to promote early, accurate diagnosis and start our current treatment early in the course of the disease. We need to support Alport syndrome advocacy groups, patient registries and basic and clinical research, to spread knowledge about the disease and to develop new, more effective treatments. We will cover these areas in posts over the next several weeks.

Part 2: Early, accurate diagnosis

Early and accurate diagnosis of Alport syndrome is crucial for several reasons. First, uncertainty about the cause of symptoms such as blood in the urine causes families unnecessary anxiety. Second, the risk to relatives and children depends on the
genetic type of Alport syndrome that affects a family. Finally, early diagnosis allows close monitoring for changes that indicate the need to begin treatment to delay kidney failure.

People with Alport syndrome have blood in the urine. When a diagnosis of Alport syndrome is made in one member of a family, other members of the family are at risk of having the disease. A physician and/or a genetic counselor can help screen relatives of people with Alport syndrome for blood in the urine. Sometimes people at risk are reluctant to have their urine or their children’s urine screened because of concerns about health insurance coverage, or because they believe there is no treatment for Alport syndrome, or because they feel fine and believe they don't need any treatment. These are all misconceptions. First, people cannot be denied health insurance coverage or be charged higher premiums because they have genetic conditions. Second, there is treatment for Alport syndrome (discussed in the next post) and if the treatment is started while kidney function is still normal it will be more effective in delaying kidney failure. Finally, people with chronic kidney diseases lose most of their kidney function before they start to have symptoms like fatigue, poor appetite or trouble breathing. By the time symptoms like these develop it is often too late to prevent kidney failure. So there is every reason to make the diagnosis of Alport syndrome early.

It is just as important to diagnose Alport syndrome in girls as in boys. Alport families know that affected boys will someday develop kidney failure, but they often believe that affected girls have no risk of kidney failure. Women with Alport syndrome may think that they are only carriers of a mutation, not a disease, and have no need for regular monitoring. The fact is that over 95% of women with Alport syndrome have blood in the urine, so they have the disease. Although the risk of kidney failure is much lower in women with Alport syndrome compared to men, there is a significant risk. About 20-30% of women with the X-linked form of Alport syndrome reach end-stage kidney disease by the age of 60. Women with Alport syndrome can also develop deafness.

If you're reading this on Facebook you probably have Alport syndrome in your family. Of course there are families with Alport syndrome who don’t know it yet. The Alport Syndrome Foundation has devoted a lot of time and energy to spreading awareness of Alport syndrome as a cause of chronic kidney disease. For example, the Foundation has a booth at the annual meeting of the American Society of Nephrology. Thousands of nephrologists from all over the world pass by that booth every day of the meeting. Even if they don't stop (and many do) these physicians are reminded about Alport syndrome as a potential diagnosis in their patients. This is just one example of the great work being done by the Foundation.

Part 3: Current treatment

In mice Alport syndrome is a fatal disease, causing death due to kidney failure at a few months of life. If these mice begin treatment with a type of medication called an
angiotensin converting enzyme inhibitor (ACE inhibitor) while they still have normal kidney function, they survive twice as long as untreated mice. ACE inhibitors have been used for many years to safely treat high blood pressure in children and adults with kidney disease, and they are relatively inexpensive. Studies of people with Alport syndrome indicate that treatment with an ACE inhibitor can delay the development of end-stage kidney disease, especially if treatment is started when kidney function is still normal. These human studies are not conclusive, because they are retrospective (they look backward, not forward) and uncontrolled, but they are very encouraging.

We are still learning about the ways in which these medications protect the kidneys of animals and people with Alport syndrome. We believe there are at least two effects. First, these medications may directly prevent the formation of scar tissue in kidneys of animals and people with Alport syndrome. Second, by lowering urine protein levels these medications may prevent the harmful effects of high urine protein levels on kidney cells.

We recommend regular measurement of urine protein levels in children with Alport syndrome (boys and girls), starting at 1 year of age and then at least annually. In order to start treatment early we need to make the diagnosis of Alport syndrome early, as discussed in the previous post. The test we use to measure urine protein levels is called the urine protein-creatinine ratio and requires only a small amount of urine. Children with urine protein-creatinine ratios above 0.2 should be treated with an ACE inhibitor with the goal of reducing the protein-creatinine ratio as much as possible. A more detailed discussion of treatment can be found here (EMBED LINK TO TREATMENT SUMMARY).

**Part 4: Advocacy groups and registries**

Although there is evidence that early treatment with ACE inhibitors can delay end-stage renal disease (ESRD) in people with Alport syndrome, we do not have evidence that ESRD can be completely prevented. Kidney transplantation is usually very successful in people with Alport syndrome, but some people will be unable to get new kidneys, and kidney transplantation can result in severe illnesses and, in some cases, death. There is no evidence that ACE inhibitors prevent deafness in people with Alport syndrome, and hearing does not improve after kidney transplant. For all of these reasons we need to find more effective treatments that are also safe. In this post and the next one we will discuss the tools we will need to develop these new treatments: advocacy groups, registries, basic research and clinical research.

Advocacy groups like the Alport Syndrome Foundation are made up of volunteers who are affected by Alport syndrome as patients or relatives of patients. Advocacy groups are vital for educating the public and healthcare providers about the disease. Advocacy groups can raise money to support research aimed at increasing our understanding of the disease and finding new treatments. Advocacy groups can also lobby lawmakers and federal agencies to provide funds for research. Drug makers
often reach out to advocacy groups to seek their support for studies of new therapies. The Alport Syndrome Foundation has been tremendously effective in all of these efforts.

Registries are databases of people with certain diseases or conditions that store confidential data such as name, contact information and medical condition. Registries can be national or international in scope. Registries are particularly important for rare diseases like Alport syndrome, because no one medical center will have access to enough people with the disease to carry out valid research studies. Registries are especially valuable for treatment trials because they are able to quickly identify and contact eligible individuals willing to participate in research.

The Alport Syndrome Treatments and Outcomes Registry (ASTOR) was founded at the University of Minnesota in 2007 and is now the largest Alport syndrome registry in the world, with about 800 participants in North America and China, and connections to registries in France, Germany and other countries (EMBED ASTOR LINK HERE). ASTOR has funding from the National Institutes of Health to demonstrate that clinical trials in Alport syndrome are feasible and are not likely to fail because of inadequate participation. ASTOR is working with pharmaceutical companies to develop new treatments for Alport syndrome. ASTOR and the Alport Syndrome Foundation have formed a strong alliance based on our shared goal to improve the lives of people with Alport syndrome by supporting the development of safe new treatments for the disease.

Part 5: Basic and clinical research

Basic research is research performed in a laboratory that focuses on the mechanisms of normal and abnormal biological processes and typically uses cells and animals. Clinical research involves people and is often used to test treatments for a disease. Scientists and doctors in many countries are conducting basic and clinical research studies in order to better understand Alport syndrome and develop more effective treatments for Alport kidney disease and hearing loss.

Basic researchers are focusing on how abnormal type IV collagen changes the behavior of kidney cells, how these changes in behavior lead to scarring of the kidneys and ways to alter the behavior of kidney cells to prevent or at least suppress scarring processes. Promising treatments can be developed into medications and other biological agents (for example stem cells) that can be tested in people with Alport syndrome.

In theory it may be possible to correct the genetic defects that cause Alport syndrome by introducing normal type IV collagen genes into kidney and inner ear cells. There are significant technical barriers and safety issues that will make development of gene therapy a very challenging project.
It is becoming standard practice to start ACEI therapy when patients with Alport syndrome show elevated urine protein levels. It is possible that earlier onset of treatment would be more effective. This possibility is being tested in a European clinical trial in which patients with Alport syndrome who have normal urine protein levels receive an ACEI or placebo, in order to determine if the development of elevated urine protein levels can be delayed by treatment.

Trials of new treatments are likely to be carried out first in adults with Alport syndrome who have started to lose kidney function. It is very possible that trials of one or more new agents will start within the next several years. ASTOR and other registries are participating in the Athena study (EMBED LINK TO ATHENA SITE HERE) that aims to establish the rate of loss of kidney function in people with advanced Alport syndrome, in preparation for a clinical trial of anti-microRNA therapy for Alport syndrome.

Successful clinical trials will require the close cooperation of advocacy groups and registries to help minimize risks and to rapidly identify eligible individuals. Advocacy groups and registries provide the interface between scientists and companies with treatments to test and the people who may participate in clinical trials.

There is a strong spirit of collaboration and mutual support in the international Alport community that involves advocacy groups, registries and researchers around the world. This spirit of cooperation motivated the recent international Alport workshop held in Oxford, UK in January 2014 and the follow-up meeting that occurred in Philadelphia in November 2014. The next workshop will take place in Goettingen, Germany in September 2015. The primary goal of these workshops is to develop and carry out a collaborative research plan that will lead to major improvements in the treatment of Alport syndrome and in the lives of people with the disease.