Promoting Early Diagnosis and Treatment of Alport Syndrome

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Back in the day (the 1990s and early 2000s) the idea that Alport syndrome should be diagnosed early in life was not universally accepted. "Why make the diagnosis?" colleagues would ask me. "There's nothing you can do about it, the parents will be terrified, and the family will never get health insurance." Fast forward to 2019: a diagnosis of Alport syndrome can still be terrifying, but we now know that early intervention can delay progression to ESRD (Gross et al, Kidney Int 2012;81:494-501; Temme et al Kidney Into 2012;81:779-783), and the Affordable Care Act, at least for now, prevents health insurance companies from denying coverage to people with Alport syndrome or charging them higher premiums. So how can nephrologists best take advantage of these opportunities in caring for people with Alport syndrome?

The first step is to create an inclusive diagnostic framework that promotes early diagnosis and initiation of effective prophylactic therapy. This was our motive in establishing an Alport Syndrome Classification Working Group, which produced a report entitled "Alport syndrome: a unified classification of genetic disorders of collagen IV α345" (Kashtan et al, *Kidney Int* 2018;93:1045-1051, PMD 29551517). We proposed that the diagnosis of Alport syndrome should be applied to individuals with any genetic mutation that interferes with the normal synthesis, deposition and function of the collagen IV α345 network of basement membranes. According to this scheme the Alport phenotype ranges from a non-progressive, kidney-limited disorder to a progressive multisystem disease, with a genetic spectrum that includes X-linked, autosomal recessive, autosomal dominant and digenic inheritance (Table).

Inheritance	**Affected gene(s)**	**Genetic State**
X-linked	*COL4A5*	Hemizygous (male) Heterozygous (female)
Autosomal recessive	*COL4A3* or *COL4A4*	Homozygous or compound heterozygous
Autosomal dominant	*COL4A3* or *COL4A4*	heterozygous
Digenic	*COL4A3, COL4A4* or *COL4A5*	*COL4A3* & *COL4A4* mutations in *trans* *COL4A3* & *COL4A4* mutations in *cis* Mutations in *COL4A5* and in *COL4A3* or *COL4A4*

This approach relies primarily on the results of gene sequencing, with less emphasis on specific extra-renal signs and symptoms and kidney pathological findings than previous classification schemes. In addition, this approach changes some of the ways we think about people with mutations that affect the collagen IV $\alpha345$ network in terms of diagnosis and patient outcome:
-- Women with heterozygous mutations in *COL4A5* are not "carriers" of X-linked Alport syndrome; they have X-linked Alport syndrome and are at risk for progressive kidney disease.
-- Similarly, subjects with heterozygous mutations in *COL4A3* or *COL4A4* are not "carriers" of autosomal recessive Alport syndrome; they have autosomal dominant Alport syndrome and are at risk for progressive kidney disease.
-- Subjects with glomerular basement membrane thinning and a mutation in *COL4A3, COL4A4* or *COL4A5* have Alport syndrome, with the result that "thin basement membrane nephropathy" (a pathological description rather than a distinct disease entity) is eliminated as a diagnosis.
-- Subjects with focal segmental glomerulosclerosis (FSGS) on biopsy and mutation in *COL4A3, COL4A4* or *COL4A5* have Alport syndrome, not some genetic form of FSGS.

There are multiple advantages to this approach:
-- Making the diagnosis of Alport syndrome establishes that an individual has a familial disease that carries the risk of progression to ESRD, which should result in close monitoring of the patient and evaluation of at-risk relatives.
-- Early diagnosis of Alport syndrome facilitates monitoring for the onset of albuminuria and proteinuria, the current indications for initiating treatment with angiotensin II antagonists (Kashtan et al, *Pediatr Nephrol* 2013;28:5-11).
-- A diagnosis of Alport syndrome allows connection with strong patient advocacy and support groups such as the Alport Syndrome Foundation.

Early (perhaps a better word is "expedited") diagnosis is important in adults as well as children. The higher the GFR when treatment is initiated, the greater the delay in ESRD (see Gross et al referenced above). In addition, diagnosis in adults, even those who have already advanced to ESRD, creates the opportunity to establish the diagnosis in related adults and children.

There are also obstacles to this approach. Insurance coverage for gene sequencing is variable and the cost may exceed a family's financial means. Some mutations in *COL4A3, COL4A4* and *COL4A5* will go undetected by current sequencing methods. People may fear a return to pre-ACA days, when those with pre-existing conditions could be denied health insurance or charged enormous premiums. When a genetic diagnosis is not possible the clinician can still follow published treatment recommendations when a diagnosis of Alport syndrome is suspected. We can all contribute to improved outcomes in patients with Alport syndrome through early diagnosis and initiation of treatment, ideally before kidney function begins to decline.

At the time this article was published, Dr. Kashtan was Professor of Pediatrics in the Division of Nephrology, Department of Pediatrics at the University of Minnesota Medical School. Dr. Kashtan had consulting relationships with Regulus Therapeutics, Reata Pharmaceuticals, Retrophin, Boehringer-Ingelheim and Daiichi Sankyo. He had been a site investigator for the CARDINAL trial (Reata) and the HERA trial (Sanofi-Genzyme) and had in the past received research support from the Novartis Institute for Biomedical Research. Dr. Kashtan retired from clinical service December 2020. He still serves on the Medical Advisory Committee for Alport Syndrome Foundation.