Clinical Practice Recommendations for the Treatment of Alport Syndrome in Children, Adolescents and Young Adults – An Update for 2020 (Kashtan C and Gross O, *Pediatric Nephrology* 2021;36:711-719

A Synopsis for Individuals and Families with Alport syndrome

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In 2013 the Alport Syndrome Research Collaborative, a group of nephrologists interested in Alport syndrome, published recommendations for the treatment of Alport syndrome (1). The goal of these recommendations was to slow down the loss of kidney function and delay the need for dialysis or kidney transplantation. We recommended that people with Alport syndrome receive treatment using medications that block the activity of the renin-angiotensin-aldosterone-system, or RAAS, once they started to show elevated levels of albumin and other proteins in the urine. RAAS blockers include angiotensin converting enzyme inhibitors (ACE inhibitors) and angiotensin receptor blockers (ARBs).

We were asked to review these recommendations in 2020 by the editors of the journal *Pediatric Nephrology.* Two of us, Oliver Gross and myself, have updated the recommendations based on new information that had emerged since 2013, when the original set of recommendations was published (2, 3).

There are two major pieces of new information. First, Japanese investigators, led by Dr. Tomohiko Yamamura, confirmed the findings of Dr. Gross and his colleagues, published in 2012, that treatment with RAAS blockers delays kidney failure in boys and men with Alport syndrome. Dr. Gross's group had found that RAAS blockade, started when kidney function was still normal, delayed kidney failure by about 18 years, compared to subjects who had not received treatment with a RAAS blocker (4). Dr. Yamamura and coworkers showed a similar delay in kidney failure when they compared boys and men who received RAAS blocker treatment to boys and men who were not treated with a RAAS blocker (5). In addition, the Japanese researchers found that RAAS blockade was beneficial regardless of the type of variant in the *COL4A5* gene causing X-linked Alport syndrome in the person receiving treatment. This is a very important finding, because many of us had wondered if RAAS blockade would be effective in everyone with Alport syndrome, or only in those with relatively mild changes, called missense variants, in the *COL4A5* gene. Dr. Yamamura and his colleagues showed that RAAS blockade delayed kidney failure by about 17

years in subjects with these milder *COL4A5* variants, and by about 12 years in subjects with more severe *COL4A5* variants (so-called "truncating" variants that prevent production of a full-length alpha-5 collagen IV chain).

The second event was the publication of the results of the EARLY-PROTECT trial conducted by Dr. Gross and his collaborators in Europe and the United States (6). EARLY-PROTECT aimed to determine if starting RAAS blockade during the earliest stage of Alport kidney disease, when there is only blood in the urine (isolated hematuria), can delay the next phase of Alport kidney disease, when there are elevated urine levels of albumin (microalbuminuria) and other, larger proteins (proteinuria). In the EARLY-PROTECT trial, children with Alport syndrome aged 2-18 years who had hematuria alone or hematuria and microalbuminuria were treated with the RAAS blocker ramipril or a placebo and followed for as long as 6 years. Data from this randomized, placebo-controlled trial was supplemented by data from children with Alport syndrome who were treated with ramipril outside of the study, and from a group of children who were followed in the early 2000s and who were not receiving RAAS blockade. The results showed that ramipril treatment reduced progression from isolated hematuria to hematuria plus microalbuminuria, or from hematuria plus microalbuminuria to hematuria plus proteinuria, by greater than 40%. The study also showed that significant side effects from early ramipril treatment were rare.

Over the course of a lifetime, the risk of kidney failure (the need for dialysis or kidney transplantation) is essentially 100% for boys and men with X-linked Alport syndrome, and for people of either sex with autosomal recessive Alport syndrome. Although we cannot yet prevent kidney failure in these people, we know that early RAAS blockade can safely (and inexpensively) delay kidney failure by 10-20 years. This delay provides children and teenagers with more time to grow without dietary restrictions, postpones the risks of dialysis and kidney transplantation and may allow people with Alport syndrome to benefit from new treatments that further delay kidney failure. **For these reasons, in boys and men with X-linked Alport syndrome, and in people of either sex with autosomal recessive Alport syndrome, we now recommend that RAAS blocker treatment start at the time of diagnosis of Alport syndrome, regardless of the levels of urine proteins, as long as the affected person is 1-2 years of age or greater.**

Girls and women with X-linked Alport syndrome, and people of either sex with autosomal dominant Alport syndrome due to variants in one copy of the *COL4A3* or *COL4A4* gene, are also at risk for developing kidney failure, although the risk is much lower than in boys and men with X-linked Alport syndrome or in people with autosomal recessive Alport syndrome. The kidney disease of many girls and women with X-linked Alport syndrome, and people with autosomal dominant Alport syndrome, will never progress beyond isolated hematuria. Even though RAAS blocker treatment is generally safe it is difficult to justify the risk of any possible side effect if treatment is not needed to prevent kidney failure. Also, girls and women who are menstruating must be using effective contraception to take RAAS blockers safely, since these medications can cause severe damage to a developing fetus if taken during pregnancy. Since we know that the appearance of elevated albumin levels in the urine is a sign that Alport kidney disease is progressing, **we recommend that girls and women with X-linked Alport syndrome, and people of either sex with autosomal dominant Alport syndrome, start RAAS blocker treatment once**

they show persistent microalbuminuria (a urine microalbumin-to-creatinine ratio of greater than 30 mg/g). This approach will limit the risks of treatment to those people who have a significant risk of eventually developing kidney failure.

The updated recommendations are summarized in the accompanying table. Like the previous set of recommendations, we included specific suggestions for medications, dosing and follow-up. Nephrologists are ultimately responsible for prescribing these medications and monitoring for side effects. We also included recommendations for evaluation by audiology and ophthalmology, based on the Alport syndrome type and the gender of the affected person. Our hope is that widespread adoption of these recommendations will delay kidney failure in many people with Alport syndrome.

TABLE: When should RAAS blocker treatment start in people with Alport syndrome?

	When should treatment start?
Boys and men with XLAS	At time of diagnosis, if age > 12 to 24 months
Girls and women with XLAS	Persistent microalbuminuria
People of either sex with ARAS	At time of diagnosis, if age > 12 to 24 months
People of either sex with ADAS (variant in one copy of *COL4A3* or *COL4A4)*	Persistent microalbuminuria

Abbreviations
XLAS: X-linked Alport syndrome
ARAS: Autosomal recessive Alport syndrome
ADAS: Autosomal dominant Alport syndrome

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3. Kashtan CE, Gross O. Correction to: Clinical practice recommendations for the diagnosis and management of Alport syndrome in children, adolescents, and young adults-an update for 2020. Pediatr Nephrol. 2021;36(3):731.
4. Gross O, Licht C, Anders HJ, Hoppe B, Beck B, Tönshoff B, et al. Early angiotensin-converting enzyme inhibition in Alport syndrome delays renal failure and improves life expectancy. Kidney Int. 2012;81(5):494-501.
5. Yamamura T, Horinouchi T, Nagano C, Omori T, Sakakibara N, Aoto Y, et al. Genotype-phenotype correlation and the effects of treatment with angiotensin-targeting drugs in Japanese patients with male X-linked Alport syndrome. Kidney Int. 2020:in press.

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