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GUIDELINES

Clinical practice recommendations for the diagnosis and management of Alport syndrome in children, adolescents, and young adults–an update for 2020

Clifford E. Kashtan[1] · Oliver Gross[2]

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Abstract
In 2013, we published a set of clinical practice recommendations for the treatment of Alport syndrome in this journal. We recommended delaying the initiation of angiotensin-converting enzyme inhibition until the onset of overt proteinuria or, in some cases, microalbuminuria. Developments that have occurred over the past 7 years have prompted us to revise these recommendations. We now recommend the initiation of treatment at the time of diagnosis in males with X-linked Alport syndrome and in males and females with autosomal recessive Alport syndrome. We further recommend starting treatment at the onset of microalbuminuria in females with X-linked Alport syndrome and in males and females with autosomal dominant Alport syndrome. This article presents the rationale for these revisions as well as recommendations for diagnostic tactics intended to ensure the early diagnosis of Alport syndrome.

Keywords Alport syndrome · Collagen IV · Hematuria · Microalbuminuria · Proteinuria · Treatment recommendations · Angiotensin-converting enzyme inhibition

The Opportunity

Introduction

In 2013, we and several of our colleagues published "Clinical Practice Recommendations for the Treatment of Alport Syndrome" in this journal [1]. We recommended angiotensin-converting enzyme inhibition (ACEi) as first-line therapy in any patient with a diagnosis of Alport syndrome and overt proteinuria. For some patients—males with X-linked Alport syndrome (XLAS) and a truncating *COL4A5* variant or family history of kidney replacement therapy or renal death prior to age 30, and males and females with autosomal recessive Alport syndrome (ARAS)—we recommended consideration of ACEi at the time of detection of microalbuminuria. We suggested specific dosing regimens, therapeutic targets, and second-line therapies.

We have been prompted to revisit and update these recommendations by developments that have occurred in the 7 years since their publication. These developments include insights regarding the genetics of Alport syndrome arising from unbiased sequencing studies, new ideas about the classification of phenotypes associated with collagen IV gene variants and the results of retrospective and prospective studies of responses to ACEi treatment in patients with Alport syndrome. Here, we also emphasize that a significant percentage of patients with the histological changes of focal segmental glomerulosclerosis (FSGS) are found to have pathologic collagen IV gene variants and therefore should be diagnosed with Alport syndrome, in order to avoid ineffective and potentially harmful immunosuppressive therapy.

It has become increasingly clear that ACEi therapy for Alport syndrome is most effective when initiated before kidney function begins to decline, delaying the need for kidney replacement therapy by years and even decades [2]. Consequently we have an opportunity to radically alter the natural history of Alport kidney disease by early treatment with medications that are relatively safe, inexpensive, and

✉ Clifford E. Kashtan
kasht001@umn.edu

[1] Department of Pediatrics, Division of Pediatric Nephrology, University of Minnesota Medical School, 2450 Riverside Avenue, Minneapolis, MN 55454, USA

[2] Department of Nephrology and Rheumatology, University Medical Center Goettingen, Goettingen, Germany

widely available. In this monograph, we will present the rationale for early ACEi therapy in Alport syndrome. Since early therapy requires early diagnosis, we will discuss the diagnostic challenge and propose a scheme to achieve early diagnosis in as many patients as possible. Finally we will present specific treatment recommendations based on biological sex, genotype, and phenotype.

Rationale for early ACEi therapy

The cloning of the *COL4A5* gene and its implication in the pathogenesis of XLAS [3], followed by the discovery of the *COL4A3* and *COL4A4* genes and their involvement in autosomal forms of Alport syndrome [4, 5], allowed the generation of transgenic Alport mouse models that closely mimic the human Alport kidney phenotype [6–8]. Gross and colleagues studied ramipril therapy in a mouse model of ARAS in which untreated animals died of kidney failure at about 10 weeks of age [9]. Mice treated with ramipril starting at 4 weeks of age survived to about 20 weeks of age, a 100% prolongation of survival. Treated mice showed decreased proteinuria and kidney fibrosis compared with untreated mice. Ramipril treatment starting at 7 weeks of age decreased proteinuria but did not prolong survival. This study provided the first indication that the natural history of Alport kidney disease might be amenable to treatment. In a subsequent study, these investigators compared ramipril therapy to treatment with the AT1 receptor blocker (ARB) candesartan or placebo [10]. Ramipril increased lifespan by 111% while candesartan increased lifespan by only 38%. While numerous studies of a variety of interventions have shown benefit in murine Alport syndrome [11], none thus far has matched the efficacy of early ramipril therapy.

The evaluation of ACEi therapy for Alport syndrome was then expanded to retrospective studies of cohorts of individuals with Alport syndrome in Europe. First, age at kidney failure, defined as the need for dialysis or kidney transplantation, was assessed in males with XLAS and in patients with ARAS who were divided into three groups based on the disease stage when ACEi therapy was initiated—(1) hematuria and microalbuminuria, (2) proteinuria with normal kidney function, and (3) impaired kidney function—and compared to patients who received no treatment [2]. ACEi treatment significantly delayed kidney failure by 3 years in the impaired kidney function group and by 18 years in the proteinuria group, while none of the patients in the hematuria and microalbuminuria group, who were younger at the onset of treatment and had shorter follow-up, had progressed to kidney failure. Among patients with heterozygous mutations in *COL4A3, COL4A4*, or *COL4A5*, those who received ACEi treatment showed a lower incidence of kidney failure, later age at kidney failure, and improved survival, compared to untreated patients [12].

In males with XLAS, *COL4A5* genotype exerts a profound effect on age at kidney failure. Various truncating variants (e.g., large rearrangements, nonsense and frameshift variants) are associated with much earlier need for kidney replacement therapy than non-truncating variants such as missense mutations, with splicing variants showing an intermediate effect that depends on whether the splicing anomaly is truncating or non-truncating [13–15]. A crucial question is whether response to ACEi or ARB treatment is also influenced by *COL4A5* genotype. This question was addressed in a recent study of a large cohort of genotyped males with XLAS in Japan [16]. In the entire group, treatment with ACEi or ARB was associated with a mean age at kidney failure of greater than 50 years, compared to 28 years in untreated patients, consistent with the prior study in European patients. In patients with non-truncating variants, the mean age at kidney failure was 33 years for untreated patients, while in over 50% of treated patients kidney failure was delayed beyond 50 years of age. Patients with truncating variants who received no treatment had a mean age at kidney failure of 16 years, compared to 28 years in treated patients. Thus, ACEi/ARB treatment delayed kidney failure by 17 years in patients with non-truncating *COL4A5* variants and by 12 years in patients with truncating *COL4A5* variants. This study was not designed to examine the effect of the timing of treatment.

Alport kidney disease progresses through a consistent series of phases that vary in duration according to genotype. An initial phase of isolated hematuria is followed at some point by microalbuminuria, proceeding eventually to overt proteinuria and ultimately declining kidney function. In the 2013 clinical practice recommendations, the initiation of ACEi therapy was predicated on the appearance of evidence of progression, namely microalbuminuria or proteinuria [1]. Since then, a question has arisen—can initiation of ACEi therapy during the isolated hematuria phase delay progression to microalbuminuria and proteinuria? This question was addressed prospectively by the EARLY PRO-TECT trial of ramipril treatment in pediatric Alport patients (mean age 8.8 ± 4.2 years) with isolated hematuria or hematuria and microalbuminuria [17]. This trial included a randomized, placebo-controlled arm (20 children) and open-label, "real world" cohorts of treated and untreated subjects (42 children), with follow-up as long as 6 years (216.4 patient-years of follow-up). Recruitment to the randomized, placebo-controlled arm of the trial was hindered by parents' concerns regarding randomization to placebo, and by the difficulty of identifying subjects who had not already developed overt proteinuria. Ramipril-treated subjects reached mean daily doses of 4.5–4.8 mg/m^2 with minimal adverse effects, normal blood pressure, and stable estimated glomerular filtration rates. The primary outcome measure was progression to the next phase of disease, i.e., isolated hematuria to microalbuminuria or microalbuminuria to proteinuria. Ramipril therapy reduced

progression to the next phase of disease by greater than 40% in both the randomized and real-world arms. These efficacy data, although not significant by the classical mathematical definition, combined with the critically important safety data, support an argument in favor of preemptive ACEi therapy designed to delay and prevent chronic kidney disease and kidney failure in the Alport population.

The mounting evidence that early ACEi therapy dramatically improves kidney outcomes in Alport syndrome has prompted us to revise the clinical practice recommendations originally published in 2013. Before presenting the new recommendations, the challenges to making an early diagnosis of Alport syndrome need to be discussed, since early treatment is not possible without early diagnosis.

Challenges to early diagnosis

Although specific data on the diagnostic evaluation of isolated hematuria in children around the world is lacking, we can say from our own experiences that it is not unusual for patients to be managed by observation, without a specific diagnosis, as long as other signs of glomerular disease such as albuminuria and proteinuria are absent. Given the prevailing recommendations for pharmacologic intervention in children with isolated glomerular hematuria, the clinician may reasonably conclude that kidney biopsy is not justified since it is unlikely to reveal treatable pathology. In addition, the diagnostic modalities needed to distinguish between various etiologies of isolated glomerular hematuria, such as electron microscopy and immunohistology, may be unavailable, and the availability and expense of molecular genetic testing may be prohibitive.

However, the balance of the benefit versus the risk and expense of diagnostic modalities shifts if a consensus develops in support of treatment of certain causes of isolated glomerular hematuria at the time of diagnosis. Identification of patients who would benefit from early therapeutic intervention would require a more aggressive approach to diagnosis. At this time, a more aggressive approach may be aspirational in many parts of the world, because limitations on diagnostic capacity cannot be immediately eliminated.

The diagnostic tactics

Workup of isolated glomerular hematuria

Our position is that clinicians should pursue a specific diagnosis in every patient with isolated glomerular hematuria, using the tools available. We will present what we consider the "ideal" approach, as well as modifications that may be needed to address the practical obstacles to this approach that exist in many parts of the world. We focus on isolated glomerular hematuria because the presence of additional evidence of kidney dysfunction typically provokes an aggressive diagnostic evaluation.

The majority of pediatric-age patients with isolated glomerular hematuria will fall into one of four diagnostic groups: IgA nephropathy, genetic variants of *COL4A3/COL4A4/COL4A5* (Alport syndrome and so-called thin basement membrane nephropathy—see discussion in next section), C3 glomerulopathy and hematuria with thin glomerular basement membranes but without an identifiable genetic variant. The diagnostic algorithm presented in Fig. 1 presents an approach that aims to generate the highest yield from molecular genetic testing and kidney biopsy, recognizing that a conclusive diagnosis of IgA nephropathy currently requires kidney biopsy. Like many diagnostic algorithms, ours has limitations.

The algorithm funnels patients with a family history of hematuria or chronic kidney disease toward molecular genetic testing. It must be recognized that a negative family history cannot exclude a diagnosis of Alport syndrome, and a positive family history of chronic kidney disease is not proof of Alport syndrome. The algorithm also recommends molecular genetic testing in patients found to have bilateral sensorineural hearing loss or ocular abnormalities such as anterior lenticonus and maculopathy. The appearance of these findings is highly dependent on age, biological sex, and genotype, so while their presence is very helpful diagnostically, the absence of such findings does not exclude Alport syndrome.

In the absence of a suggestive family history or extrarenal abnormalities, diagnostic approaches differ according to local health insurance systems, availability of electron microscopy, and the accessibility of genetic testing. In Europe, for example, clinicians in some countries will prefer genetic testing to confirm a diagnosis of Alport syndrome. In other countries, an approach in which the first step is kidney biopsy, intended primarily as a means of diagnosing IgA nephropathy, may be preferred. Of course, electron microscopy showing basket-weave changes in glomerular basement membranes is highly suggestive of a diagnosis of Alport syndrome, but the capacity to perform electron microscopy is not universal. Electron microscopy may reveal thin glomerular basement membranes, but this finding does not have prognostic value in the pediatric population, and is of limited prognostic value even in adults, because the finding of thin glomerular basement membranes is not a guarantor of non-progressive disease.

One could reasonably ask why molecular genetic testing should not be the first step in all patients with isolated glomerular hematuria, since such testing carries a high likelihood of identifying those who would benefit from pharmacologic intervention. We agree that this could be a reasonable practice in a clinical environment where molecular genetic testing is easily available and covered by health insurance. However, a universal genetic testing strategy will likely result in a greater

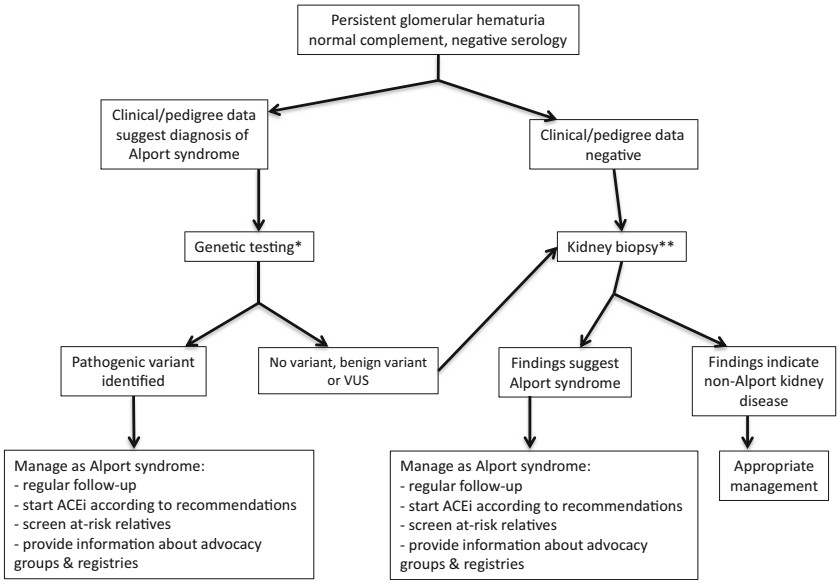

Fig. 1 An approach to diagnosis of individuals with persistent glomerular hematuria using genetic testing and/or kidney biopsy. * The genetic testing approach may vary based on the level of suspicion of a diagnosis of Alport syndrome. When suspicion is high, next-generation sequencing (NGS) of *COL4A3*, *COL4A4*, and *COL4A5* is indicated. When suspicion of a diagnosis of Alport syndrome is moderate or low, a broad NGS panel including focal segmental glomerulosclerosis and polycystic kidney disease genes, or whole exome sequencing, should be considered. ** Kidney biopsy should, if possible, always include routine transmission electron microscopy (TEM). When TEM shows glomerular basement membrane changes suggestive of Alport syndrome, or when TEM is not available, immunofluorescence studies of collagen IV alpha-chain expression can provide useful diagnostic and prognostic information [18]. VUS variant of uncertain significance, ACEi angiotensin-converting enzyme inhibitor

number of results that are not easily interpretable, such as a variant of uncertain significance (VUS) in a single affected member of a family. Sequencing of exons and flanking intronic regions will not identify all pathogenic variants, so some individuals with clinical and pathological findings consistent with Alport syndrome will have negative genetic testing. The genetic counseling resources needed to provide robust molecular genetic services may not be available to nephrology practices, especially those not affiliated with academic centers. Effective testing of relatives of an index case is difficult without genetic counseling support.

Classification

We previously presented a proposal, supported by the results of clinical, pathological, genetic, and treatment studies, for classifying all kidney disorders associated with pathogenic *COL4A3*, *COL4A4*, or *COL4A5* variants as Alport syndrome [18]. This scheme, summarized in Table 1, does not require a positive family history, extrarenal findings, or evidence of progressive kidney disease in order to make a diagnosis of Alport syndrome. Girls and women with heterozygous *COL4A5* variants are classified as having Alport syndrome, rather than being labeled as "carriers" of the disease. Patients with hematuria and heterozygous variants in *COL4A3* or *COL4A4* are considered to have autosomal dominant Alport syndrome, eliminating the diagnosis of thin basement membrane nephropathy. It should be noted that there is not universal agreement on this latter point among investigators in the field [19]. Disagreement over the appropriate classification of patients with hematuria and

Table 1 Indications for treatment of Alport syndrome in children, adolescents, and young adults

	Indication for treatment
XLAS males	At time of diagnosis, if age > 12 to 24 months
XLAS females	Microalbuminuria
ARAS	At time of diagnosis, if age > 12 to 24 months
ADAS (heterozygous variant in *COL4A3* or *COL4A4*)	Microalbuminuria

XLAS, X-linked Alport syndrome; *ARAS*, autosomal recessive Alport syndrome; *ADAS*, autosomal dominant Alport syndrome

heterozygous variants in *COL4A3* or *COL4A4* should not preclude regular monitoring for kidney disease progression and early intervention, as described below.

It has recently become clear that patients with FSGS on biopsy frequently exhibit pathologic variants in *COL4A3*, *COL4A4*, or *COL4A5*. Gast and colleagues found that variants in *COL4A3–5* genes were the most common form of genetic variation in adult FSGS patients, including 3% of patients with sporadic FSGS and 38% of families with "familial FSGS" [20]. In a study by Groopman and colleagues, variants in *COL4A3–5* accounted for 30% of the genetic mutations identified in a cohort of patients with chronic kidney disease, including a number of patients who previously carried a diagnosis of FSGS [21]. Individuals with FSGS-like changes on kidney biopsy who have pathogenic variants in the *COL4A3–5* genes should be classified and treated as having Alport syndrome. This will help prevent ineffective and potentially harmful immunosuppressive treatment and facilitate prompt evaluation of at-risk family members.

The goals of this classification scheme are to maximize early diagnosis of Alport syndrome and to promote effective monitoring to detect kidney disease progression, with the ultimate goal of preserving kidney function by enabling early pharmacologic intervention. Simply put, we aim to make a diagnosis of Alport syndrome as early as possible, in order to initiate therapy in every patient in whom the risk and expense of treatment are outweighed by the benefit of delaying loss of kidney function.

The treatment recommendations

Angiotensin converting enzyme inhibition

These treatment recommendations for the use of angiotensin-converting enzyme inhibition are modeled on the protocols employed in the ESCAPE trial in children with chronic kidney disease [22] and the EARLY PROTECT trial in children with Alport syndrome [17]. We have extrapolated from these protocols and other published pediatric studies [23, 24] to suggest dosing parameters for lisinopril, in order to provide an alternative to ramipril with a similar duration of action, in the event that lisinopril is the more readily available agent.

Males with X-linked Alport syndrome (hemizygous *COL4A5* variants)

We recommend starting treatment of males with XLAS at the time of diagnosis. For very young patients, we recommend withholding treatment until age 12–24 months. For ramipril, we recommend a starting dose of 1 mg/m^2/day with up-titration over 3 to 4 months to 6 mg/m^2/day or until the maximum tolerated dose is achieved. In the case of lisinopril, we recommend a starting dose of 0.2 mg/kg/day (maximum dose 10 mg daily) with up-titration to 0.6 mg/kg/day (maximum dose 40 mg daily), or until the maximum tolerated dose is achieved, over 3 to 4 months. For both ramipril and lisinopril, the dose should be adjusted as needed as the child grows in order to maintain a constant mg/m^2 or mg/kg dose, up to the maximum recommended or tolerated dose. Note that these dosing regimens do not consider the level of albuminuria or proteinuria; we will address the proteinuria response when discussing dual angiotensin blockade below.

Females with X-linked Alport syndrome (heterozygous *COL4A5* variants)

We recommend starting treatment of females with XLAS when microalbuminuria, defined as a urine microalbumin-creatinine ratio greater than 30 mg/mg, is detected in repeated measures in the absence of infection. We postulate that the onset of microalbuminuria identifies those heterozygous females at significant risk for progression to chronic kidney disease and kidney failure. At this time, a reliable measure of X-inactivation balance in the kidney has not been validated; such a tool could refine the application of prophylactic treatment.

We recommend the same dosing protocols of ramipril and lisinopril as for males with XLAS. Female patients who are menstruating must be using effective contraception to avoid fetopathy secondary to angiotensin blockade during pregnancy.

Males and females with autosomal recessive Alport syndrome (homozygous or compound heterozygous *COL4A3* or *COL4A4* variants)

We recommend starting treatment of males and females with ARAS at the time of diagnosis. Ramipril and lisinopril should be dosed according to the protocols for males with XLAS described above. Female patients who are menstruating must be using effective contraception to avoid fetopathy secondary to angiotensin blockade during pregnancy.

Males and females with autosomal dominant Alport syndrome (heterozygous *COL4A3* or *COL4A4* variants)

We recommend starting treatment of males and females with ADAS when microalbuminuria, defined as a urine microalbumin-creatinine ratio greater than 30 mg/mg, is detected in repeated measures in the absence of infection. We postulate that the onset of microalbuminuria identifies those heterozygous individuals at significant risk for progression to chronic kidney disease and kidney failure. Female patients who are menstruating must be using effective contraception

to avoid fetopathy secondary to angiotensin blockade during pregnancy.

Additional interventions

Dual renin-angiotensin-aldosterone system blockade

There are no studies in human Alport syndrome that correlate magnitude of proteinuria with kidney functional outcomes. Lacking this data, we must infer proteinuria goals from experimental studies using Alport models and from trials involving heterogenous disease cohorts.

Jarad et al. created a mouse line in which both the *col4a3* and albumin genes were knocked out, generating an Alport mouse unable to synthesize albumin [25]. Survival was enhanced by 60% in the double knockout mice compared to Alport mice with either one or two normal albumin alleles. These results indicate that in the Alport setting, urine albumin is deleterious to kidney survival, suggesting that proteinuria should be aggressively suppressed in patients with Alport syndrome.

Data from the ESCAPE trial of ramipril therapy in children with chronic kidney disease suggest that a urine protein-creatinine ratio of 1.0 mg/mg or less confers a significant kidney survival advantage over higher levels of proteinuria [26]. So, in an Alport patient with urine protein-creatinine ratio greater than 1.0 despite maximal ACEi dosing, additional measures to suppress proteinuria are reasonable, if tolerated by the patient. Possible additional measures include an angiotensin receptor blocker or an aldosterone antagonist. There is limited data on the efficacy and safety of dual angiotensin blockade in the pediatric population. Addition of losartan at an initial dose of 0.8 mg/kg/day to ACEi in a small group of pediatric patients reduced proteinuria by about 60% [27]. Dual angiotensin blockade is not without risks. In the EARLY PRO-TECT trial, reversible acute kidney failure and hyperkalemia occurred in one child receiving dual angiotensin blockade, requiring hospitalization [17]. In two small case series of children with Alport syndrome, the addition of aldosterone inhibition to angiotensin blockade resulted in significant decreases in proteinuria [28, 29].

Blood pressure goals and life-style habits

Children with Alport syndrome are typically normotensive, but hypertension frequently develops in adolescent and young adult patients. We recommend a blood pressure goal of about the 50th percentile in Alport patients. Certain life-style habits, including moderation of dietary intake of meat protein and salt, maintaining a body mass index less than 25 kg/m^2, and avoidance of smoking, are also recommended.

Finally, patients who have been diagnosed with FSGS and are found to have pathogenic variants in *COL4A3-5* genes should not be treated with immunosuppressive agents, including calcineurin inhibitors [30]. There are likely to be patients with FSGS on biopsy who have heterozygous VUSs in *COL4A3* or *COL4A4*; in such patients, a finding of thin or lamellated glomerular basement membranes by electron microscopy would support a diagnosis of Alport syndrome. If ultrastructural findings are not definitive, the clinician should consider the totality of the available clinical information and family history, along with genetic studies, to determine appropriate intervention.

Hearing evaluation and augmentation

About 30% of males with XLAS will have detectable hearing loss by age 10, increasing to about 60% by age 20 [13]. The risk of hearing loss in children with ARAS is about 20% by age 10, with a higher rate of hearing loss in children with at least one truncating variant in *COL4A3* or *COL4A4* [31]. Therefore, for males with XLAS, and children with ARAS, formal hearing evaluation should begin at age 5 to 6 years with annual follow-up examination. Earlier hearing evaluation should be considered in patients with overt proteinuria or in children who fail hearing screening or who exhibit delayed acquisition of speech skills or other signs suggestive of a hearing deficit.

Although about 30% of females with XLAS will eventually exhibit hearing loss, the probability of hearing loss is less than 10% until about age 40 [32]. Proteinuria and hearing loss are independently associated with the probability of kidney failure in females with XLAS, likely reflecting the effect of X-inactivation balance [32]. Based on these observations, we recommend formal hearing evaluation for females with XLAS who exhibit overt proteinuria, or when impaired hearing is suspected clinically or because of a failed hearing screen. Hearing loss is relatively unusual in patients with ADAS, affecting only 4–13% of individuals [33, 34]. Therefore, we recommend hearing evaluation in patients with heterozygous variants in *COL4A3* or *COL4A4* when there is clinical suspicion of hearing impairment.

Patients with Alport syndrome should avoid exposure to loud noise and use effective protection when noise exposure is unavoidable. Hearing loss due to Alport syndrome usually responds well to amplification with hearing aids. Speech discrimination is typically well preserved. In the USA, a major obstacle to the optimal management of Alport-related hearing loss is the lack of coverage for hearing aids by many health insurers.

Ophthalmological assessment and follow-up

An initial ophthalmologic exam can be useful in the diagnosis of Alport syndrome [35]. Regular examination for anterior lenticonus should begin at about age 15 years in males with XLAS who have truncating variants in *COL4A5* and in males and females with ARAS, based on available genotype-phenotype correlations [13, 36]. Earlier examination is recommended in patients who demonstrate decreased visual acuity. Subsequent examinations should be scheduled annually. Ophthalmological assessment should be carried out in females with XLAS, and in patients who are heterozygous for *COL4A3* or *COL4A4* variants, if there is clinical suspicion of abnormal vision.

Investigational agents

Over the coming years, clinical trials of novel therapies for Alport syndrome will be conducted and completed, and results will be published. How will new treatments that demonstrate benefit be incorporated into therapeutic recommendations? At this point we can only offer speculation.

Safety will be a key consideration. Exposure to additional risk may be reasonable for patients with declining glomerular filtration rates (GFR) despite ACEi therapy but inappropriate for patients with stable kidney function. An agent that prevents or stabilizes hearing loss could justify acceptance of added risk. While no treatment is without some risk, the availability of kidney replacement therapy and the typically good outcomes of kidney transplantation in Alport patients [37] should take treatments that carry a risk of mortality off the table.

Timing of intervention is also likely to be important. An agent that increases GFR, such as the Nrf2-activator bardoxolone methyl [38], may be attractive for patients with declining GFR but undesirable for young patients with normal GFR. Anti-fibrotic therapies such as microRNA-21 antagonism [39, 40] may benefit younger as well as older patients, since declining GFR is closely associated with increasing interstitial fibrosis and tubular atrophy in boys and teenage males with Alport syndrome [41].

Another factor that will influence decisions about add-on therapies with be *COL4* genotype, especially in males with X-linked Alport syndrome. For example, males with missense variants in *COL4A5* may have less need for treatments in addition to ACEi than those with truncating variants.

To indulge speculation a bit further, we can ask whether there is an "ideal" range of GFR for patients with Alport syndrome who have lost some degree of kidney function. For example, perhaps a treatment regimen that stabilizes GFR around 75–80 ml/min could ameliorate glomerular hyperfiltration and thereby suppress glomerulosclerosis.

Conclusion

The ultimate goal for Alport syndrome therapy is a cure. While early ACEi treatment is not curative, it does offer the real possibility of delaying the need for dialysis and kidney transplantation until relatively late in life, or even preventing kidney failure, for substantial numbers of patients with Alport syndrome due to hemizygous missense variants in *COL4A5* or heterozygous variants in *COL4A3*, *COL4A4*, or *COL4A5*. Even males with truncating variants in *COL4A5* are likely to gain years of kidney function as a result of early ACEi therapy. Further improvements in kidney survival are possible from addition of novel anti-inflammatory, anti-fibrotic, and other interventions [38–40, 42, 43]. Ideally novel therapies will be tested in Alport-specific clinical trials. Widespread application of molecular diagnostic testing in the evaluation of patients with glomerular hematuria will identify those patients who are likely to benefit from conventional therapy with a well-established safety record, and those patients in whom the risks and expense of novel treatments may be justified by the greater likelihood of progression to kidney failure.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest. Neither the authors nor their immediate family members have any financial relationships or holdings that influenced the writing of this manuscript or that will be affected by the content of the manuscript if published.

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