

Alport syndrome in children: moving towards early diagnosis and treatment

Articles

Original Review and recommendation

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REVIEW

Clinical practice recommendations for the treatment of Alport syndrome: a statement of the Alport Syndrome Research Collaborative

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2020 Update and current recommendation

Review > [Pediatr Nephrol. 2021 Mar;36\(3\):711-719. doi: 10.1007/s00467-020-04819-6.](#)

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

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Affiliations + expand

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Alport syndrome (AS) is a hereditary kidney disease resulting from defective or absent $\alpha3.\alpha4.\alpha5$ chains of type IV collagen in the glomerular basement membrane (GBM), eye, and cochlea.

AS can be transmitted as an X-linked (XLAS) (80%), autosomal recessive (ARAS) (15%) or autosomal dominant (ADAS) (5%) disorder.

Risk of end-stage kidney disease (ESKD)

In untreated males with XLAS, the risk of ESKD at age 25 is 50%, at age 40 is 90% and at age 60 is nearly 100%. Age at ESKD strongly correlates with *COL4A5* genotype: at age 30, the risk of ESKD is 90% for deletions and nonsense mutations, 70% for splicing mutations and 50% for missense mutations.

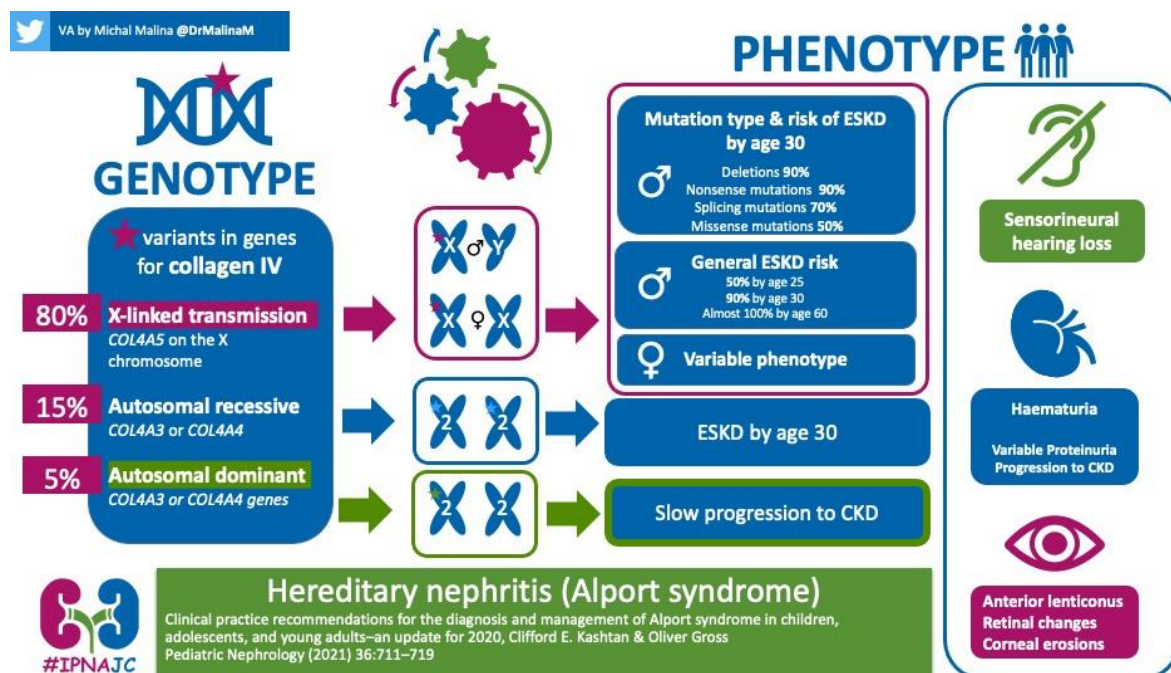
In most families with XLAS, age at ESKD in affected males is fairly similar. Therefore, the timing of ESKD can be predicted based on the timing of ESKD for older affected male relatives.

In contrast, the genotype-phenotype correlation is not observed in females with XLAS.

ARAS also carries a high risk of ESKD by age 30. Data on genotype-phenotype correlation in ARAS is more limited.

ADAS progresses slower than the other two types.

Here is an infographic summarizing genotype-phenotype relation in AS by [M. Malina](#)



Rationale for early angiotensin converting enzyme inhibitors (ACEi) therapy

AS progresses through a consistent series of phases that vary in duration according to genotype. An initial phase of isolated hematuria is followed by microalbuminuria, then overt proteinuria, and eventually progresses to kidney failure.

ACEi therapy is most effective when initiated before kidney function decline and delays ESKD and the need of kidney replacement therapy (KRT) by years or decades.

Animal mouse models of AS

Untreated mice died of kidney failure at about 10 weeks of age, while mice treated with [ramipril](#) started at 4 weeks of age survived to ~20 weeks of age (doubling the survival). Treated mice showed decrease in proteinuria and kidney fibrosis. If ramipril was started at 7 weeks, it decreased proteinuria but did not increase survival.

Another study compared [ramipril to candesartan](#) (an angiotensin receptor blocker) and placebo. Ramipril increased lifespan by 111% while candesartan increased only by 38%.

Clinical trials in AS

Retrospective cohort studies in patients with AS

Age at kidney failure was assessed in males with XLAS and in patients with ARAS who were divided in 3 groups, based on disease stage when ACEi was started: 1) hematuria and microalbuminuria, 2) proteinuria and normal kidney function, and 3) impaired kidney function, and compared to patients with no treatment.

Treatment with ACEi delayed kidney failure by 18 years in the proteinuria group and by only 3 years in the impaired kidney function group. None of the patients with hematuria and microalbuminuria (younger and with shorter follow-up) progressed to kidney failure.

Among patients with heterozygous mutations in any of the 3 genes, treated patients showed a [lower incidence and later age](#) at kidney failure and improved survival, compared to untreated patients.

In males with XLAS, genotype exerts a profound effect on age at kidney failure. Truncating variants are associated with an earlier need of KRT than non-truncating variants. Splicing variants show an intermediate effect.

Genotype appears to also influence response to therapy. In a [large cohort of XLAS males in Japan](#), treatment with ACEi or angiotensin receptor blockers (ARB) was associated with a mean age at kidney failure of >50 years, compared to 28 years in untreated patients. In patients with non-truncating variants, treatment delayed kidney

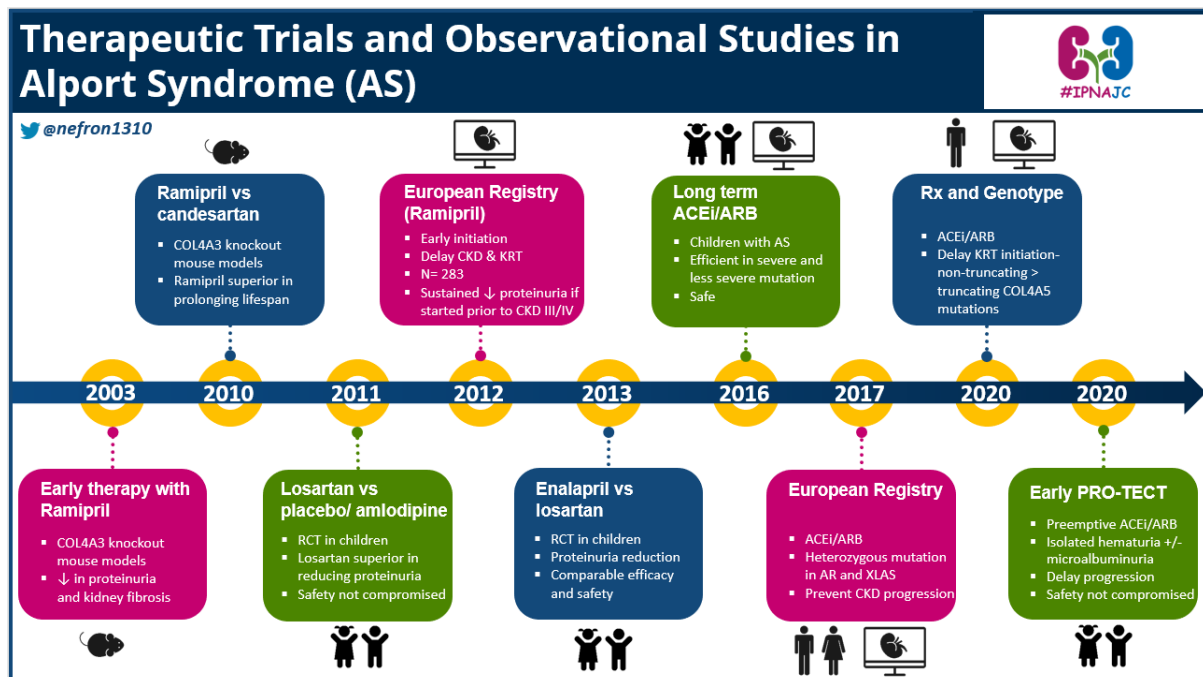
failure by 17 years and by 12 years in patients with truncating variants compared to untreated patients.

Prospective studies in patients with AS

The [EARLY PRO-TECT trial](#) addressed the question whether initiation of ACEi therapy at the early stage of hematuria with or without microalbuminuria can delay progression to more advanced disease. The trial included a randomized, placebo-controlled arm and open-label cohorts of treated and untreated children with follow-up as long as 6 years. Primary outcome measure was progression to the next phase of disease. Ramipril reduced progression by >40% in both randomized and open-label arms.

In summary, there is mounting evidence that early ACEi improves kidney outcomes in AS. Thus, there is a need to start **early treatment**, which requires an **early diagnosis**.

Here is the infographic summarizing clinical trials by [Shweta Shah](#).



Challenges to early diagnosis

There are no clear guidelines or recommendations for the assessment and treatment of patients with glomerular hematuria who do not have proteinuria. If patients with AS and early disease (without overt proteinuria) may benefit significantly from early treatment, there is a need for early diagnosis of AS in patients who present with isolated glomerular hematuria.

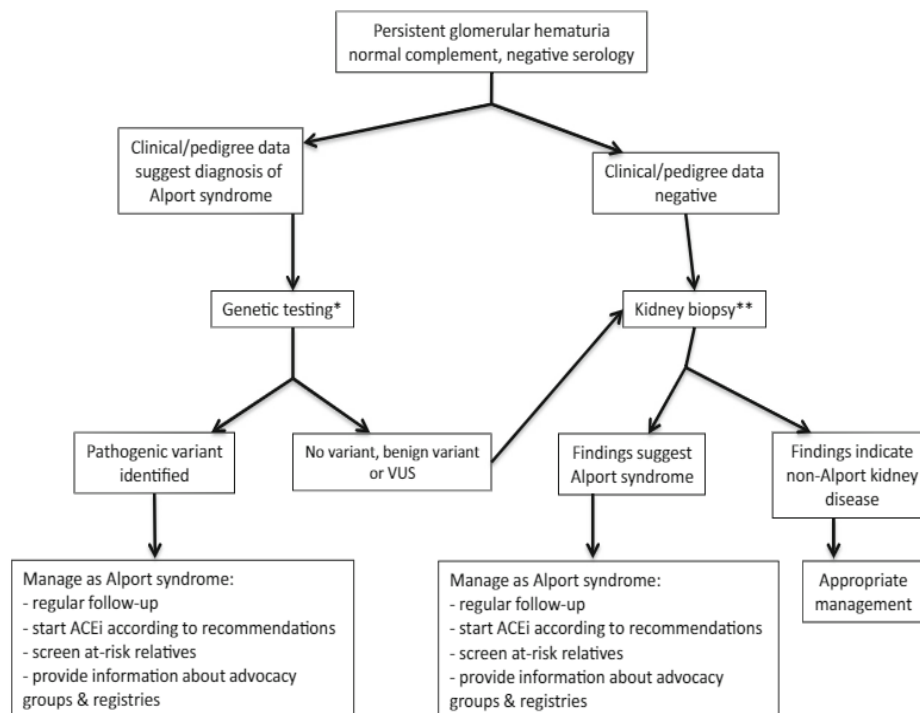
Work-up of isolated glomerular hematuria

The majority of children with isolated glomerular hematuria with fall in one of four categories:

- 1) IgA nephropathy
- 2) Genetic variants of COL4A3/A4/A5 [AS]
- 3) C3 glomerulopathy
- 4) Thin basement membrane (TBM) disease without identifiable genetic variant

In AS, the most common presentation is asymptomatic microscopic hematuria. Therefore, the authors advocate that a specific diagnosis be pursued in every patient with isolated glomerular hematuria and propose an ideal approach (see algorithm below).

Suggested algorithm for isolated glomerular hematuria (depending on local resources and choices)



In patients with family history of hematuria, chronic kidney disease (CKD) or history of bilateral sensorineural hearing loss, genetic testing is recommended as initial

study. In patients without a positive history, a kidney biopsy, that includes electron microscopy, is recommended first.

Caveats

- 1) A negative family history does not exclude AS.
- 2) A positive family history of CKD is not proof of AS.
- 3) Absence of specific findings (hearing loss or ocular abnormalities) does not exclude AS as the extra-renal findings are dependent on age, genotype and biological sex.
- 4) Finding a TBM on EM does not guarantee non-progressive disease.
- 5) Some patients with clinical and pathological findings of AS may have negative genetic testing.

Classification of AS

All kidney disorders associated with pathogenic COL4A3-5 variants should be classified as Alport syndrome. Females with heterozygous COL4A5 are classified as Alport syndrome (not carriers). Patients with heterozygous variants in COL4A3-4 have ADAS (not TBM) (note: there is no universal agreement on this concept).

A significant percentage of patients with histologic focal segmental glomerulosclerosis (FSGS) are found to have pathologic collagen IV gene variants and should be diagnosed with AS. These patients should not be treated with immunosuppressive medications.

The ultimate goal is to maximize early diagnosis of AS in order to initiate treatment in every patient that can benefit from delaying progression to kidney failure.

Treatment goals

The authors postulate that the onset of microalbuminuria identifies patients at significant risk of progression to CKD and kidney failure and recommend starting ACEi/ ARB therapy in these patients.

	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 <i>COL4A3</i> or <i>COL4A4</i>)	Microalbuminuria

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

Blood pressure goals

BP goal of ~50th percentile in patients with AS.

Hearing evaluation

Males with XLAS (risk of detectable hearing loss of 30% by age 10) and children with ARAS (risk of 20% by age 10) should start formal hearing evaluation at age 5 -6 years with annual follow up.

Females with XLAS (risk <10% before age 40) should be evaluated if they develop overt proteinuria or when hearing impairment is suspected clinically.

Patients with ADAS should be evaluated if there is clinical suspicion of hearing impairment.

Ophthalmologic evaluation













Males with XLAS (with truncating variants) and patients with ARAS should begin evaluation by ~15 years of age.

Females with XLAS and patients with heterozygous variants for COL4A3 and COL4A4, should be evaluated if clinical suspicion.

Reproductive counselling

Females who are menstruating must use effective contraception to avoid fetopathy due to ACEi.

Check out this infographic on diagnostic challenges & treatment goals by [Swasti Chaturvedi](#)

Therapeutic Recommendations for Alport Syndrome (AS)		 #IPNAJ
Diagnostic Recommendations	When to start ACEi/ARB Treatment?	What to monitor?
 <p>Consider AS Diagnosis if</p> <ul style="list-style-type: none">Isolated persistent glomerular haematuriaNormal complementsNegative serology (ANA, ANCA, Anti-GBM etc.)	 <p>X-linked AS (XLAS) male</p> <ul style="list-style-type: none">At diagnosis (age > 12 to 24 m)	 <ul style="list-style-type: none">Target BP: 50th percentile for age, ht & sexBMI < 25kg/m²Moderate intake of meat protein & salt
 <p>Genetic testing</p> <ul style="list-style-type: none">If family history of AS	 <p>XLAS female</p> <ul style="list-style-type: none">Classify as Alport syndrome & NOT as carriersMicroalbuminuria > 30 mg/g	 <p>Annual hearing evaluation</p> <ul style="list-style-type: none">from 5-6 yrsXLAS males & ARAS
 <p>Kidney Biopsy</p> <ul style="list-style-type: none">If no family history of ASOr genetic testing is inconclusive	 <p>Autosomal recessive AS (ARAS)</p> <ul style="list-style-type: none">At diagnosis (age > 12 to 24 m)	 <p>Annual eyes exam</p> <ul style="list-style-type: none">from 15yrsXLAS males & ARAS
	 <p>Autosomal dominant AS (ADAS)</p> <ul style="list-style-type: none">Microalbuminuria > 30 mg/g	 <p>Contraception</p> <ul style="list-style-type: none">Menstruating Females (prevent fetopathy from ACEi/ARB)

Conclusions: Earlier Diagnosis, regular monitoring and early treatment can delay progression in Alport Syndrome

Kashtan CE, Gross O. Clinical practice recommendations for the diagnosis & management of Alport syndrome in children, adolescents & young adults- an update for 2020. Ped Nephrol, 2021. VA by Swasti Chaturvedi @SwastiThinks

Proteinuria target

The optimal target for lowering urine protein excretion is unknown. Recommendation is based on an arbitrary goal of P/C ratio < 0.5 mg/mg if baseline value is >1.0 mg/mg, or a 50% reduction if baseline value is >0.2 but <1.0.

In subjects treated for microalbuminuria, the recommended target is <50-100 mg/g creatinine. If urine protein levels persist at higher levels despite treatment, it is recommended to continue therapy with first and second-line agents.

Therapeutic agents

First line: ACEi

Second line: ARB or aldosterone antagonist

ACEi

Medications and dosages are based on protocols from the [ESCAPE trial](#) in children with CKD and the EARLY PROTECT trial in children with AS.

Ramipril, starting dose of 1 mg/m²/day up to a maximum of 6 mg/m²/day (or maximum tolerated dose) over 3-4 months. Lisinopril, starting dose of 0.2 mg/kg/day (maximum dose of 10 mg/day) up to a maximum of 0.6 mg/kg/day (maximum dose of 40 mg/day)

Note: dosing regimen does not consider level of albuminuria or proteinuria

Dual renin-angiotensin-aldosterone system (RAAS) blockade






There are no studies in human AS that correlate the degree of proteinuria and functional kidney outcomes. There is limited data on efficacy and safety of dual blockade in the pediatric population. Adding losartan in [one study](#) reduced proteinuria by ~60%. In the [EARLY PROTECT study](#), a reversible acute kidney injury (AKI) occurred in a child with dual blockade.

There are several ongoing trials for AS. [CARDINAL trial](#) studies bardoxolone methyl, [HERA trial](#) investigates Lademirsen and [AFFINITY study](#) evaluates Atrasentan.

This infographic by [Abdul Qader](#) depicts various pharmacological therapies for Alport syndrome.

What are the Treatments of Alport Syndrome ?



				
Goal of treatment	First- line ACE inhibitor	2nd- line ARB or Aldosterone antagonist	Adverse events	Ongoing clinical trials
<ul style="list-style-type: none"> Urine Protein: creatinine ratio <0.5mg/mg or 50% reduction from the baseline Urine Albumin: creatinine ratio < 50-100mg/g 	<ul style="list-style-type: none"> Ramipril 1-2 mg/m²/day; maximum 6mg/m²/day Enalapril 2X Ramipril dose Lisinopril 4X Ramipril dose 	<ul style="list-style-type: none"> Losartan 12.5 mg/m²/day; maximum 50mg/m²/day Candesartan 0.2X Losartan dose Irbesartan Spironolactone 25mg OD for > 10years old; Lower starting dose for <10 years 	<ul style="list-style-type: none"> Hyperkalaemia ✓ ACEi, ARB, AA Orthostatic hypotension ✓ ACEi, ARB Doubling serum creatinine ✓ ACEi & ARB Gynecomastia ✓ AA Dry cough (ACEi) Angioedema (ACEi) 	<ul style="list-style-type: none"> CARDINAL Study Bardoxolone methyl * Changes in eGFR at 48 weeks HERA Trial Lademirsen * Changes in eGFR at 48 weeks AFFINITY Study Atrasentan * Evaluate effect on proteinuria <p>* Primary outcome</p>

Conclusion: Early treatment may delay the need of RRT until late in life or even prevent kidney failure.

 @md_abdulqader83

Conclusions

Early treatment may delay the need of KRT until late in life or even prevent kidney failure. RAAS inhibition can delay the disease progression but does not cure the disease, which is the ultimate goal.

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