BMJ Best Practice

Alport's syndrome

The right clinical information, right where it's needed

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Summary

- Rare familial nephropathy due to abnormalities in type IV collagen.
- May be inherited in 1 of 3 patterns: X-linked, autosomal recessive, or autosomal dominant.
- Associated with considerable clinical variability of age of onset of chronic renal failure. Frequently associated with sensorineural hearing loss.
- Female carriers of X-linked mutations have a significant lifetime risk of developing HTN and renal disease.
- Strong genotype-phenotype correlations in X-linked Alport's syndrome have been described in male patients.
- Monitoring and treatment of renal disease is the main treatment.

BASICS

Definition

Alport's syndrome is an inherited disease of the glomerular basement membrane caused by abnormalities in type IV collagen.[1] It is associated with sensorineural hearing loss, lenticonus (bulging of the lens capsule and the underlying cortex[2]) and retinal abnormalities, as these tissues are additional sites of expression of type IV collagen. The classic thickening and lamellation of the glomerular basement produces a progressive haematuric nephritis that progresses to chronic renal failure in all males with the X-linked form of the disease.[3]

Epidemiology

Alport's syndrome is a rare disease and the prevalence is not well known. The estimated prevalence in the US is 20:100,000 and in Europe 1:100,000 to 9:100,000.[11] The majority of cases (85%) are X-linked, with the remainder being mainly autosomal recessive. The disease accounts for approximately 3% of children and 0.2% of adults with chronic renal failure and for >1% of patients receiving renal replacement therapy.[12] The majority of patients with chronic renal failure are male due to the X-linked inheritance pattern. No clear evidence for significant ethnic variation is available.

Aetiology

Alport's syndrome is due to mutations in the COL4A3, COL4A4, and COL4A5 genes.[1] They encode the alpha-3, alpha-4, and alpha-5 chains of type IV collagen, which is a major component of the glomerular basement membrane. The glomerular basement membrane is unique because of its thickness (300 to 350 nanometre) and its position between 2 cell layers, podocytes, and endothelial cells. Other components of the glomerular basement membrane are laminin, nidogen, and heparin sulphate proteoglycans. Each type IV collagen molecule is composed of 3 sub-units or alpha chains that intertwine to form a helical structure. These collagen chains are characterised by a repeating Gly-X-Y sequence with a non-collagenous domain at the C-terminus. Six different genes, COL4A1 to COL4A6, encode the different alpha chain isoforms, alpha-1(IV) to alpha-6(IV). Alpha-1(IV) and alpha-2(IV) are ubiquitously expressed, while alpha-3(IV), alpha-4(IV), and alpha-5(IV) are restricted to the glomerular basement membrane, distal tubular basement membrane, Descemet membrane (thin hyaline membrane between the substantia propria and endothelial layer of the cornea) and Bruch membrane (inner layer of the choroid, separating it from the pigmentary layer of the retina), anterior lens capsule, lung, and cochlea. This accounts for the phenotypic features seen in Alport's syndrome in the kidney, ear, and eye. Alpha-6(IV) is found in the epidermal basement membrane.

These genes are found as pairs in a 'head to head' orientation, COL4A1 to COL4A2 on chromosome 13, COL4A3 to COL4A4 on chromosome 2, and COL4A5 to COL4A6 on the X chromosome. Only mutations in COL4A3, COL4A4, and COL4A5 have been described in Alport's syndrome, as well as a contiguous gene deletion of COL4A5 to COL4A6.[10] Mutations cause loss of expression or mis-assembly of the alpha chains and hence failure of assembly and maturation of a normal basement membrane collagen network.

Pathophysiology

During early development alpha-1(IV) and alpha-2(IV) isoforms predominate in the glomerular basement membrane before switching to mainly alpha-3(IV), alpha-4(IV), and alpha-5(IV). These isoforms are thought to enhance the ability of the glomerular basement membrane to resist proteolytic degradation. Loss of these chains also leads to a compensatory increase in expression of other type IV, type V, and type VI collagens. Therefore, abnormalities in these components cause ultra-structural damage to the basement membrane, which is manifest as thinning, thickening, splitting, and

lamellation, the classic features seen under electron microscopy. This presumably results in the loss of the normal permselectivity of the glomerular basement membrane and the subsequent development of haematuria, proteinuria, glomerulosclerosis, and interstitial nephritis.

Classification

Genetic classification

Alport's syndrome is a genetically heterogeneous disease caused by mutations in genes encoding different alpha chains of type IV collagen.[1] It is one of a group of inherited disorders characterised by abnormalities in the glomerular basement membrane. Approximately 85% of cases are inherited as an X-linked trait and are due to mutations in the COL4A5 gene located at Xq22.3. The remaining 15% of cases are autosomal recessive and due to mutations in the COL4A3 and COL4A4 genes. Rare autosomal-dominant cases are also due to mutation of the COL4A3 and COL4A4 genes.

X-linked Alport's syndrome (XLAS)

- XLAS is the most common type of Alport's syndrome.[3] All male patients have haematuria and develop chronic renal failure. There is considerable allelic heterogeneity. Genotype-phenotype correlations have been described with 90% of male patients having loss-of-function mutations (large deletions, non-sense and frame-shifting mutations) and reaching chronic renal failure by 30 years of age.[3] [4]
- Haematuria develops in over 95% of female carriers with some developing chronic renal failure in later life.[5] A family history may be absent in about 10% of cases suggesting a de novo mutation.

Autosomal-recessive Alport's syndrome (ARAS)

- ARAS in a family is suggested by the presence of severe early disease in males and females, isolated haematuria in both parents and parental consanguinity.[6]

Autosomal-dominant Alport's syndrome (ADAS)

- ADAS is rare and suggested by a relatively mild phenotype and slow progression to chronic renal failure in affected patients.[7]

Alport's syndrome with diffuse leiomyomatosis (ASDL)

- In ASDL, genital leiomyomas are often seen in females. There may be a childhood history of cataracts, dysphagia, cough, or recurrent bronchitis. However, there is often no family history.
- Deletion in COL4A5 and COL4A6 is detected by multiplex ligation-dependent probe amplification (MLPA) and/or fluorescence in situ hybridisation (FISH) (if the deletion is large).

Alport's syndrome with mental retardation

- This is classified as the presence of nephropathy with mental retardation. There is often no family history but the characteristic facial appearance of mid-face hypoplasia is seen[8] along with elliptocytosis on blood film.
- Whole gene COL4A5 micro-deletion is detected by FISH.

Primary prevention

Genetic testing offers the opportunity for early pre-symptomatic diagnosis and antenatal testing. Patients with a confirmed or suspected diagnosis should be referred for genetic counselling, where the different options for antenatal diagnosis can be explained and genetic testing carried out.

Direct sequencing and deletion analysis of all the Alport's syndrome-associated genes is available. It should ideally be carried out after genetic counselling. The mutation detection rate in Alport's syndrome-associated genes is high for patients who meet diagnostic criteria. Therefore, it is valuable to confirm the clinical diagnosis and to provide information for other family members. Ideally genetic testing is used only when clinical suspicion of Alport's syndrome is high and not as a screening test. Interpretation of results may be problematic if a sequence variant of unknown significance is found. Genotype-phenotype correlations are strong for X-linked Alport's syndrome (XLAS). Positive linkage or mutation analysis can be used to provide predictive, diagnostic, or prenatal testing. For predictive and prenatal testing referral to a clinical geneticist is required. In some centres, in addition to prenatal diagnosis, pre-implantation genetic diagnosis may be offered.

Screening

Family screening

- Relatives of an index case with suspected or confirmed Alport's syndrome can be offered screening. Identification of at-risk relatives will depend on the likely mode of inheritance. If this is unclear then all first-degree relatives can be offered screening with urinalysis, BP estimation, and assessment of renal function.
- In X-linked Alport's syndrome (XLAS) all affected family members should be identified using cascade testing where possible.[14] The daughters of affected males will be obligate carriers. This can initially be carried out using urinalysis and BP screening, and where the familial mutation is known this can be used to offer predictive and diagnostic tests. A single urine test can be offered to males but up to 3 are required in females.
- Early detection of hypertension, renal failure, and proteinuria offer the opportunity to intervene and potentially slow the progression of the renal disease and reduce the risk of developing cardiovascular disease. Screening in males and females is indicated, as the lifetime risk of developing renal failure is 100% and 15%, respectively.
- The age of screening depends on gender and the presence of symptoms and comorbidities. Male siblings of an affected male, who are at 50% risk, should be screened as early as possible after discussion with the parents in parallel with screening the mother if she has not previously been tested. Female siblings may be screened when they are able to give informed consent, usually during the teens or as a young adult, as symptoms typically appear later; however, urinalysis can be used earlier than this, or predictive genetic testing offered after discussion with parents, as use of an ACE inhibitor may slow disease progression.
- Children of a female carrier of XLAS should also be offered screening as above, boys as early as possible with parental consent and girls during the teens or as a young adult. Again, girls may now be screened earlier after discussion with parents.
- Screening advice is typically based on individual clinical assessment by nephrologists and clinical geneticists. American Society of Nephrology expert guidelines for the management of Alport's syndrome also contain guidance on family screening.[14]
- In autosomal-recessive Alport's syndrome (ARAS) cascade screening should be offered to parents and siblings. All offspring of a patient with ARAS are obligate carriers and therefore have microscopic haematuria. Both parents

may have microscopic haematuria. Siblings have a 1:4 chance of having ARAS and a 2:3 chance of being a carrier if they do not clinically have ARAS. All carriers have microscopic haematuria. Carriers of autosomal-recessive ARAS may be considered as potential kidney donors after careful clinical, pathological, and molecular evaluation.[14]

- In autosomal-dominant Alport's syndrome, all first-degree relatives should be offered screening as above.

Population screening

There are no indications for screening the healthy population. The diagnosis may rarely be made during population screening for hearing loss and microscopic haematuria.

Secondary prevention

Secondary prevention is mostly concentrated on preventing the complications associated with hypertension and chronic renal failure. A low-salt, high-fibre, low-cholesterol diet that is tailored to renal function should be followed and reviewed yearly. Smoking must be avoided and full support given to encourage cessation. All new symptoms such as ankle oedema, urinary discomfort and pain, chest pain, visual disturbance, and hearing loss should be reported to a physician for further evaluation. This may allow early intervention and treatment of medical complications.

Case history

Case history #1

An 18-year-old man presents to his primary care physician with a non-specific history of malaise. Mild sensorineural hearing loss had been diagnosed during his early education, although hearing aids were not required. Investigations reveal haematuria, heavy proteinuria, and hypertension. There was a history of macroscopic haematuria in infancy associated with an intercurrent infection and high fever. As the patient's family had moved frequently he was lost to follow-up.

Other presentations

Large family-based studies of X-linked Alport's syndrome, the most common form, show that in male patients the most common clinical presentation is microscopic or macroscopic (gross) haematuria with or without proteinuria (about 80% of cases).[3] Other presentations were proteinuria, deafness, chronic renal failure, and hypertension. Gross haematuria occurs in about 60% of cases. Proteinuria is eventually found in most patients (>95%). Hearing loss is present in about 80% of cases and eye signs in about 35%. In women with X-linked Alport's syndrome, more than 95% will have microscopic haematuria and 75% will develop proteinuria.[5] Approximately 30% will have some hearing impairment and 15% will have eye signs. Chronic renal failure will develop in 12% before 40 years of age, which is correlated with the presence of proteinuria and deafness. Many females are identified through family studies after the diagnosis is made in an affected male relative. Deletions of COL4A5 or COL4A6 can also cause Alport's syndrome and diffuse leiomyomatosis. This is defined by the association of Alport's syndrome with oesophageal, gastric, vulvovaginal, and bronchial leiomyomas, and clitoral hypertrophy.[9] Symptoms include dysphagia, recurrent bronchitis and altered bowel habit. Cataract has also been described.[10] A rare syndrome of Alport's syndrome with mental retardation, mid-face hypoplasia and elliptocytosis has also been described due to a contiguous gene deletion involving COL4A5.[8]

Step-by-step diagnostic approach

In most cases of suspected Alport's syndrome meeting diagnostic criteria, clinical, molecular, or pathological approaches are used after careful consideration, often based on local availability.[14] Therefore, a full clinical and family evaluation is usually combined with either molecular or pathological examination. Direct gene testing is recommended if patients have 2 or more diagnostic criteria for Alport's syndrome.[15] [16] Targeted molecular examination (e.g., detection of a COL4A5/6 contiguous gene deletion) may be used where symptoms and signs suggest a diagnosis of Alport's syndrome with diffuse leiomyomatosis.

Clinical evaluation

Diagnosis should be considered in any child or adult (male or female) who presents with features compatible with a diagnosis of Alport's syndrome. These include haematuria, proteinuria, deafness, hypertension, and renal failure. Symptoms may be vague and only relate to the development of renal failure such as fatigue, breathlessness, peripheral oedema, growth retardation, hypertension, and signs and symptoms of acidosis. If renal disease is associated with deafness then there is a high suspicion of the diagnosis, especially in males. A family history of these features should always be sought and screening for haematuria offered to first-degree relatives, especially parents, as this may identify familial disease. Patients should be screened for high-frequency sensorineural hearing loss and lenticonus (bulging of the lens capsule and the underlying cortex[2])/retinopathy even in the absence of symptoms. The presence of the

characteristic central retinopathy, present in 40% to 70% of males, is said to be pathognomonic of the disease.[3] [17]

Aortic abnormalities have also been described in affected males and may be found with echocardiogram.[18]

Further rare signs and symptoms associated with Alport's syndrome are learning disability, dysphagia (caused by oesophageal leiomyomas) and cough or recurrent bronchitis (caused by bronchial leiomyomas).

Audiometry and ophthalmoscopy are done in all cases of suspected Alport's syndrome to support diagnosis.

Molecular genetic testing

If after a full clinical and family evaluation there is a strong clinical suspicion of Alport's syndrome, molecular diagnosis can be offered by direct mutation or linkage analysis, which can confirm the mode of inheritance.[14] It can also be used to predict phenotype, and to help in offering prenatal and pre-implantation genetic diagnosis. Genetic counselling should be sought before testing. [ASTOR: Alport Syndrome Treatments and Outcomes Registry] However, for reasons of cost, availability, and occasional limitations in identifying and interpreting gene variants, it may not be suitable for all families.[19] The current mutation detection rate in COL4A5 is high when direct sequencing and deletion screening strategies are used in patients who fulfil 2 or more diagnostic criteria.[15] [20] [21] Many genetic testing laboratories now deposit COL4A5 variants in a fully curated and standardised database, with the aim of improving the accuracy of genetic testing and prediction of phenotype.[22]

The diagnostic criteria are:[16]

1. Positive family history of haematuria with or without progression to chronic renal failure
2. Progressive sensorineural hearing loss
3. Characteristic ocular changes (anterior lenticonus (bulging of the lens capsule and the underlying cortex[2])/maculopathy)
4. Typical ultrastructural changes in the glomerular basement membrane.

cDNA may also be tested and can be obtained from hair root and skin biopsy samples.[23] Testing can confirm linkage to COL4A5 in X-linked Alport's syndrome or COL4A3/4 in autosomal-recessive Alport's syndrome.

Renal investigations and complication monitoring

Renal biopsy with electron microscopy and immunohistochemical analysis for type IV collagens allows for diagnosis of Alport's syndrome to be confirmed in most cases. Occasionally renal biopsy is contraindicated, which would prevent a pathological diagnosis being made. It is the characteristic electron microscopic changes of thinning, thickening, splitting, and lamellation of the glomerular basement membrane that should be sought in renal biopsies where Alport's syndrome is a possible diagnosis. Renal ultrasound also excludes any structural abnormality of the renal tract that may suggest an alternative diagnosis.

Routine investigations for renal disease are also done. They can also be used to monitor decline in renal function:

- FBC
- Urinalysis
- Fasting lipid panel

- Metabolic panel
- Serum intact PTH
- ECG
- Echocardiogram.

Skin biopsy

Skin biopsy is less invasive than renal biopsy, and where immunohistochemistry for type IV collagens is available it can be considered as part of the diagnostic approach. It is also faster than molecular testing. Total absence of alpha-5(IV) staining in the epidermal basement membrane is seen in males, and focal absence (or mosaic distribution) in females is seen in 50% to 60% of families.[19] Skin biopsy is of little value in autosomal forms of Alport's syndrome.

Risk factors

Strong

FHx of Alport's syndrome

- Family history will identify those members at risk of inheriting the condition, who should be offered screening, and in most cases will clarify the mode of inheritance. This may lead to earlier diagnosis and detection of complications such as hypertension. It may also allow the opportunity to consider antenatal diagnosis.

Weak

FHx of thin basement membrane nephropathy

- Thin basement membrane nephropathy may be seen in up to 20% of cases of X-linked Alport's syndrome and is also a manifestation of the carrier status of autosomal-recessive Alport's syndrome (ARAS) due to mutations in the COL4A3 and COL4A4 genes.[13] Unless there is family history of consanguinity, the risk of having children with ARAS for someone with thin basement membrane disease is very low (around 1:400), as the population carrier frequency is low (≤1%). However, simple screening with urinalysis can be offered to partners of patients with, or suspected of having, thin basement membrane nephropathy.

FHx of microscopic haematuria

- Most likely found in the mother of males with X-linked Alport's syndrome (XLAS) (father will be negative). All daughters of a man with XLAS will eventually manifest haematuria. Only about 50% of carriers of ARAS will have haematuria and may be completely asymptomatic. However, there are other genetic causes of familial haematuria such as familial IgA disease and other types of familial glomerulonephritis.

microscopic haematuria

- Alport's syndrome is an uncommon cause of microscopic haematuria with or without proteinuria. However, features of Alport's syndrome and a family history should be sought in all patients with undiagnosed microscopic haematuria. About 10% of cases of X-linked Alport's syndrome are due to new mutations so there is no family history.

History & examination factors

Key diagnostic factors

presence of risk factors (common)

- Hx of microscopic haematuria in a first-degree relative, especially in mother or both parents, is a strong risk factor for Alport's syndrome. A male relative with Hx of renal failure and/or deafness may also suggest the diagnosis. Most cases of Alport's syndrome are X-linked, so male-to-male transmission does not occur. Autosomal-recessive Alport's syndrome typically occurs in siblings of either sex. About 10% of cases of X-linked Alport's syndrome are due to new mutations, meaning no family history.

gross haematuria (common)

- A common symptom is the presence of gross haematuria, often precipitated by an intercurrent infection in a young child.

hearing impairment (common)

- Complications such as renal failure and deafness typically more common in young males in X-linked Alport's syndrome but affect males and females equally in the autosomal-recessive form.[3] [5] [24] [25]

Other diagnostic factors

fatigue (common)

- Vague symptom related to the development of renal failure. May be due to anaemia. Complications such as renal failure and deafness typically more common in young males in X-linked Alport's syndrome but affect males and females equally in the autosomal-recessive form.[3] [5] [24] [25]

breathlessness (common)

- Vague symptom related to the development of renal failure. Complications such as renal failure and deafness typically more common in young males in X-linked Alport's syndrome but affect males and females equally in the autosomal-recessive form.[3] [5] [24] [25]

peripheral oedema (common)

- Vague symptom related to the development of renal failure or nephritic syndrome. May result from impaired renal salt excretion. Complications such as renal failure and deafness typically more common in young males in X-linked Alport's syndrome but affect males and females equally in the autosomal-recessive form.[3] [5] [24] [25]

hypertension (common)

- Sign of chronic renal failure.

foamy-appearing urine (common)

- Indicates proteinuria.

visual disturbance (uncommon)

- Often due to cataracts or corneal erosions. Cataracts have been described as a presenting symptom.[10]

learning disability (uncommon)

- Associated with Alport's syndrome with mental retardation.

dysphagia (uncommon)

- Caused by oesophageal leiomyomas seen in Alport's syndrome with mental retardation.

cough or recurrent bronchitis (uncommon)

- Caused by bronchial leiomyomas seen in Alport's syndrome with mental retardation.

growth retardation (uncommon)

- Sign of chronic renal failure.

menorrhagia (uncommon)

- Can be a symptom of genital leiomyomas in Alport's syndrome with diffuse leiomyomatosis.

irregular firm central pelvic mass (uncommon)

- Can be a sign of genital leiomyomas in Alport's syndrome with diffuse leiomyomatosis.

Diagnostic tests

1st test to order

Test	Result
FBC • Done as part of the routine investigation of any patient with suspected renal disease. Performed at least annually or more frequently as renal function declines. • Elliptocytosis may suggest a diagnosis of Alport's syndrome with mental retardation, although this is extremely rare.	**possible anaemia or leukocytosis; elliptocytosis if with mental retardation**
metabolic panel • Part of the routine investigation of any patient with suspected renal disease. At least annually or more frequently as renal function declines. Serum creatinine can screen for abnormalities in GFR.	**may show abnormalities consistent with renal failure such as low bicarbonate, elevated potassium or serum creatinine, or low calcium; may show metabolic acidosis**
fasting lipid panel • Part of the routine investigation of any patient with suspected renal disease. At least annually or more frequently as renal function declines.	**possible dyslipidaemia**
urinalysis • Shows large numbers of red cells per high power field. • Morphology may suggest a glomerular origin. • Also carried out to quantify level of proteinuria. This is an important indicator of likely progression of renal disease. • Proteinuria can also be assessed by calculating the ratio of urinary protein to serum creatinine. • May be repeated annually or more frequently if proteinuria heavy or nephrotic syndrome develops.	**haematuria and/or proteinuria**

Test	Result
serum intact PTH • With renal impairment there is loss of 1-alpha-hydroxylase in the kidney, which results in a decreased conversion of 25-hydroxyvitamin D to the active 1,25-dihydroxyvitamin D. This then causes hyperphosphataemia and hypocalcaemia with a consequent rise in PTH.	**may be elevated in cases of renal failure**
audiometry • Done in all cases of suspected Alport's syndrome.	**possible high-tone sensorineural hearing loss**
ophthalmoscopy • Done in all cases of suspected Alport's syndrome where additional diagnostic criteria are required.	**possible corneal and/or retinal abnormalities; lenticonus (bulging of the lens capsule and the underlying cortex), maculopathy and early-onset cataract**
renal ultrasound • Also excludes any structural abnormality of the renal tract that may suggest an alternative diagnosis.	**normal-sized or small smooth kidneys**
renal biopsy • Part of the diagnostic work-up of a patient with suspected Alport's syndrome or any abnormality warranting renal biopsy (e.g., undiagnosed chronic renal insufficiency or unexplained proteinuria and haematuria).[24]	**features on electron microscopy typical of Alport's syndrome; immunohistochemical analysis of type IV collagen chain distribution may reveal loss of staining in males and absent or discontinuous staining in females**
ECG • Routine investigation for a patient with underlying renal disease and hypertension.	**normal or may show evidence of LVH**

Other tests to consider

Test	Result
molecular genetic testing • Can confirm mode of inheritance and predict phenotype, and help in offering prenatal and pre-implantation genetic diagnosis.[14] Direct sequencing and multiplex ligation-dependent probe amplification (MLPA) analysis of all the Alport's syndrome associated genes is available. Should ideally be carried out after clinical genetics review. • Linkage analysis can be performed if sufficient family members of known disease status are available for study.[15] [16]	**identification of pathogeneic mutation in COL4A5 (in X-linked Alport's syndrome) or COL4A3/4 (in autosomal-recessive Alport's syndrome)**
echocardiogram • Routine investigation for a patient with underlying renal disease and hypertension.	**possible LVH and aortic abnormalities**

Emerging tests

Test	Result
skin biopsy • Should be considered if immuno-fluorescent staining for alpha-5(IV) is available locally as part of the diagnostic work-up for X-linked Alport's syndrome (XLAS) in males and females.[19] [26] In XLAS, staining for alpha-5(IV) is absent in 80% of males and absent or discontinuous in about 60% of females.	**abnormal discontinuous staining for alpha-5(IV) in the epidermal basement membrane**

Differential diagnosis

Condition	Differentiating signs / symptoms	Differentiating tests
MYH9 disorders (Epstein's syndrome and Fechtner's syndrome)	• Hx of easy bruising and bleeding. FHx may suggest autosomal-dominant inheritance.[27]	• FBC reveals macro-thrombocytopenia. Due to mutations in the MYH9 gene.[27] [28]
Branchio-oto-renal syndrome	• Autosomal-dominant disorder characterised by hearing loss; structural defects of the outer, middle, and inner ear; branchial fistulas or cysts; and renal disease. The condition shows reduced penetrance and variable expressivity, making diagnosis in some cases difficult.	• Hearing loss may be sensorineural, conductive, or mixed on formal testing. Renal abnormalities ranging from mild hypoplasia to complete absence may be seen on ultrasound. Mainly due to mutations in the EYA1 and SIX1 genes.[29]
Thin basement membrane nephropathy	• Usually no FHx of renal failure except in consanguineous families. Rarely associated with other types of glomerulonephritis. Hx is negative except for persistent microscopic haematuria.	• All tests normal except for presence of haematuria of glomerular origin. Thin glomerular basement membrane on electron microscopy and normal immunohistochemical staining for type IV collagens in skin and kidney. COL4A3 and COL4A4 testing is available.
Familial focal segmental glomerulosclerosis	• Usually no FHx of hearing loss and most likely autosomal dominant or recessive. No microscopic haematuria.	• Diagnosis on renal biopsy. Mutations described in INF2, ACTN4, TRPC6, CD2AP, NPHS1, NPHS2, and PLCE1 have been identified, though it is highly genetically heterogeneous.
Maternally inherited diabetes and deafness	• Maternally inherited and associated with a FHx of diabetes.	• Mutation screening for mutations in MTTL1, MTTE, and MTTK.
IgA nephropathy	• Usually no FHx. Absence of haematuria in relatives, although rare familial cases have been reported. No other associated features.	• Renal biopsy reveals glomerular deposition of IgA.

Diagnostic criteria

Historical and symptomatic criteria[16]

At least 3 of the following are required to make a diagnosis of Alport's syndrome:

1. Positive family history of haematuria with or without progression to chronic renal failure
2. Progressive sensorineural hearing loss
3. Characteristic ocular changes (anterior lenticonus (bulging of the lens capsule and the underlying cortex[2])/maculopathy)
4. Typical ultra-structural changes in the glomerular basement membrane.

Additional criteria now include diffuse leiomyomatosis and abnormal distribution of type IV collagens in skin or kidney.[30]

Chronic renal failure stages[31]

- Stage 1: GFR greater than 90 mL/minute/1.73 m^2, and evidence of kidney damage based on pathological diagnosis, abnormalities of radiographic imaging or laboratory findings such as haematuria and/or proteinuria.
- Stage 2: reduction in GFR of 60 to 89 mL/minute/1.73 m^2.
- Stage 3A: reduction in GFR of 45 to 59 mL/minute/1.73 m^2.
- Stage 3B: reduction in GFR of 30 to 44 mL/minute/1.73 m^2.
- Stage 4: reduction in GFR of 15 to 29 mL/minute/1.73 m^2.
- Stage 5: reduction in GFR less than 15 mL/minute/1.73 m^2. [GFR MDRD calculators for adults]

Step-by-step treatment approach

Patients with X-linked, autosomal-recessive, or autosomal-dominant Alport's syndrome should be managed lifelong by a nephrologist with a focus on management of hypertension, proteinuria, and dyslipidaemia. Treatment with ACE inhibitors should be offered. They should also be offered referral to a clinical geneticist.[14] Patients are commonly managed according to current local guidelines for hypertension, chronic renal failure, and cardiovascular risk.[31] [32] Monitoring for progression of renal disease is essential. Routine monitoring involves investigations for serum creatinine (for GFR abnormalities), fasting lipid panel, FBC, calcium/phosphate/PTH, uric acid, and urinalysis. Testing should be at least annually or more frequently as renal function declines.[31] No informative disease-specific controlled clinical trials in Alport's nephropathy have been carried out, although there is strong evidence for ACE inhibitors delaying the onset of end-stage renal disease (ESRD) and improving survival.[33]

Although evidence for the use of specific agents in Alport's syndrome from properly conducted clinical trials does not exist, a new set of management guidelines has been published.[14] These guidelines recommend treatment using blockade of the renin-angiotensin system in patients with proteinuria.

Renal disease

Hypertension and proteinuria

- Hypertension is secondary to the underlying renal disease. Frequent monitoring and early treatment are required to achieve a target based on current guidelines (i.e., <130/80 mmHg). First-choice treatment for proteinuria with or without hypertension consists of an ACE inhibitor and/or an angiotensin-II receptor antagonist. They are also used to slow the progression of renal disease. In children, the ACE inhibitor ramipril has been suggested as a first-line option, and either an angiotensin-II receptor antagonist (e.g., losartan) or an aldosterone antagonist (e.g., spironolactone) as a second-line option.[34] Losartan has been found to be effective in reducing proteinuria in children with Alport's syndrome with or without hypertension although further trials are required to evaluate its effect on the rate of decline in renal function.[35] Regular monitoring for adverse events such as orthostatic hypotension and hyperkalaemia is recommended.

Progression to chronic renal failure

- This is due to the underlying nephropathy. Early referral to a nephrologist is required for consideration of renal replacement therapy, which may consist of transplantation or dialysis.

Renal transplant

- Transplant is the only cure for chronic renal failure as it allows patients to stop dialysis. It can also reduce cardiovascular complications and therefore extend survival.
- Overt post-transplant anti-glomerular basement membrane (anti-GBM) disease occurs in 3% to 5% of Alport's syndrome patients.[36] Onset is usually within the first year after transplantation. Regular screening for anti-GBM antibodies can be offered, especially if there is an underlying loss-of-function mutation and loss of alpha-5(IV) expression by immunohistochemistry. Graft loss is high and recurrence in second grafts is high. Patients with graft dysfunction (especially males with X-linked Alport's syndrome, and males and females with autosomal-dominant Alport's syndrome) should undergo renal allograft biopsy with direct immunofluorescence for IgG and C3 and be screened for circulating anti-GBM antibodies. Presentation of anti-GBM disease varies

and ranges from asymptomatic increases in serum creatinine to gross haematuria, oliguria, and a rapidly progressive glomerulonephritis.

- Where living related kidney donation is being considered, special consideration should be given to which family members may be considered as potential donors.[36] Initial screening for haematuria should be carried out to detect other affected or carrier members prior to extensive clinical evaluation. Genetic testing can be used to guide donor selection. People who have been shown not to carry the familial mutation may be screened as potential donors. Few XLAS carrier females have been kidney donors.[37] Renal function may deteriorate in this group after donation but in exceptional circumstances donation may take place although the long-term prognosis remain unknown.[38]

Extra-renal disease

Sensorineural deafness

- Hearing loss should be managed according to current guidelines.

Visual disturbance

- Children with lenticonus (bulging of the lens capsule and the underlying cortex[2]) should be offered annual surveillance, although this does not need to be extended to adults, as the rate of complications is very low. Cataracts may require surgical extraction.

Diffuse leiomyomatosis

- In cases of Alport's syndrome with diffuse leiomyomatosis, surgery may also be required for any symptomatic leiomyomas.

Future trials

No well-powered and well-controlled clinical therapeutic trials have been carried out in Alport's syndrome. However, to provide an evidence base for the use of ACE inhibitors in Alport's syndrome, a double-blind randomised, placebo-controlled, multicentre phase III trial has been initiated to assess the safety and efficacy of early treatment with ramipril in children.[33] In murine and canine animal models of Alport's syndrome, blockade of the renin-angiotensin system had variable effects on the degree of proteinuria and rate of progression to chronic renal failure.[39] [40] This suggests that early intervention with agents that block different parts of the angiotensin system may have a beneficial effect in human disease. Losartan has been shown to have a beneficial effect on reducing proteinuria in children with Alport's syndrome with or without hypertension.[35] In a 3-year open-label extension phase of this study, losartan and enalapril both maintained the reduction in proteinuria seen in the initial study although the sample size in each group was small and no placebo arm was used.[41] The long-term effect of such intervention on the rate of decline in renal function is not known. Clinical trials are clearly needed to assess this. [ASTOR: Alport Syndrome Treatments and Outcomes Registry]

Treatment details overview

Consult your local pharmaceutical database for comprehensive drug information including contraindications, drug interactions, and alternative dosing. (see Disclaimer)

Ongoing (summary)

Patient group	Tx line	Treatment
all patients	1st	renal disease monitoring + ongoing management for complications
with proteinuria ± hypertension	plus	pharmacotherapy
with chronic renal failure	plus	dialysis + transplant eligibility study
	adjunct	renal transplant + anti-glomerular basement membrane (anti-GBM) antibody screening
with sensorineural deafness	plus	referral to audiologist
with visual disturbance	plus	referral to ophthalmologist
with symptomatic leiomyomas	adjunct	surgery

Treatment options

Ongoing

Patient group	Tx line	Treatment
all patients	**1st**	**renal disease monitoring + ongoing management for complications** » Monitoring for progression of renal disease is essential. Routine monitoring involves investigations for serum creatinine (for GFR abnormalities), fasting lipid panel, FBC, calcium/phosphate/PTH, uric acid, and urinalysis. Testing should be at least annually or more frequently as renal function declines.[31] » Management of manifestations of the disease such as hypertension, chronic renal failure, and cardiovascular risk should be according to current local guidelines.[31] [32]
with proteinuria ± hypertension	**plus**	**pharmacotherapy** » First-choice treatment for proteinuria with or without hypertension in adults consists of an ACE inhibitor and/or an angiotensin-II receptor antagonist. They are also used to slow the progression of renal disease. » In children, the ACE inhibitor ramipril has been suggested as a first-line option, and either an angiotensin-II receptor antagonist (e.g., losartan) or an aldosterone antagonist (e.g., spironolactone) as a second-line option.[34] » Frequent monitoring and early treatment are required to achieve a target based on current guidelines (i.e., <130/80 mmHg). Regular monitoring for adverse events such as orthostatic hypotension and hyperkalemia is recommended.

Primary options

adults

» enalapril: 5-20 mg orally daily
-or-
» fosinopril: 10-80 mg orally daily
-or-
» lisinopril: 10-80 mg orally daily

--AND/OR--

» candesartan: 16 mg orally daily
-or-
» irbesartan: 150-300 mg orally daily
-or-
» losartan: 50-100 mg orally daily

OR

children

Ongoing

Patient group	Tx line	Treatment
		» ramipril: consult specialist for guidance on dose
		Secondary options
		children
		» losartan: consult specialist for guidance on dose
		OR
		children
		» spironolactone: consult specialist for guidance on dose
with chronic renal failure	**plus**	**dialysis + transplant eligibility study**
		» Due to underlying nephropathy. Early referral to a nephrologist for consideration of renal replacement therapy, which may consist of transplantation or dialysis.
	adjunct	**renal transplant + anti-glomerular basement membrane (anti-GBM) antibody screening**
		» Transplant is the only cure for chronic renal failure as it allows patients to stop dialysis. It can also reduce cardiovascular complications and therefore extend survival.
		» Overt post-transplant anti-GBM disease occurs in 3% to 5% of Alport's syndrome patients.[36] Onset is usually within the first year following transplantation. Regular screening for anti-GBM antibodies can be offered, especially if there is an underlying loss-of-function mutation and loss of alpha-5(IV) expression by immunohistochemistry. Graft loss is high and recurrence in second grafts is high.
		» Patients with graft dysfunction (especially X-linked Alport's syndrome males, and autosomal-recessive Alport's syndrome males and females) should undergo renal allograft biopsy with direct immunofluorescence for IgG and C3 and be screened for circulating anti-GBM antibodies.
		» Presentation of anti-GBM disease may be very variable, ranging from asymptomatic increases in serum creatinine to gross haematuria, oliguria, and a rapidly progressive glomerulonephritis.
with sensorineural deafness	**plus**	**referral to audiologist**
		» Occurs in up to 80% of male patients with X-linked Alport's syndrome by 30 years of age.[3] Also dependent on the type of mutation in the COL4A5 gene. Earlier onset if a loss-of-function mutation present.

Ongoing

Patient group	Tx line	Treatment
with visual disturbance	**plus**	**referral to ophthalmologist** » May be due to anterior lenticonus (bulging of the lens capsule and the underlying cortex)[2] and predisposes to axial myopia and cataract. Ophthalmological review is necessary. » Children with lenticonus should be offered annual surveillance, although this does not need to be extended to adults, as the rate of complications is very low. Cataracts may require surgical extraction.
with symptomatic leiomyomas	**adjunct**	**surgery** » In cases of Alport's syndrome with diffuse leiomyomatosis, surgery may also be required for any symptomatic leiomyomas. Often genital leiomyomas in females.

Emerging

Combination of aldosterone receptor blockade

One small study has suggested a beneficial effect of the combination of aldosterone with blockade of the renin-angiotensin system on proteinuria.[42] Five patients with Alport's syndrome were enrolled. Urinary protein to creatinine ratio was reduced at 3, 6, 12, and 18 months, while estimated GFR did not change. A drop in systolic and diastolic BPs was statistically significant, and serum potassium level was slightly elevated. None of the patients showed signs of severe hyperkalaemia (>5.0 mmol/L [5.0 mEq/L]). These results suggest that aldosterone receptor blockade combined with ACE inhibitors and angiotensin-II receptor antagonists could offer a valuable adjuvant treatment for the reduction of proteinuria in patients with Alport's syndrome, as in those with other chronic kidney diseases.

Ciclosporin (cyclosporine)

One small study has suggested that the nephrotoxicity of ciclosporin (cyclosporine) is likely to outweigh its potential therapeutic benefit in reducing proteinuria.[43] After a 6-month period, mean proteinuria decreased from 2±1.06 g/day to 0.65±0.73 g/day, and mean albuminaemia had increased from 29±5.2 g/L to 35±6.5 g/L. Mean inulin clearance decreased from 102±29 mL/minute/1.73 m^2 to 74±16.3 mL/minute/1.73 m^2.

Recommendations

Monitoring

Once a diagnosis of Alport's syndrome has been confirmed, patients should be managed by a specialist, usually a nephrologist.

- Patients should be reviewed dependent on the presence of hypertension and the degree of renal impairment present. Early detection and treatment of the complications of Alport's syndrome is likely to improve quality of life and life expectancy. Particular attention should be paid to cardiovascular complications, which are the most common cause of morbidity and mortality in chronic renal failure. In children with chronic renal failure, monitoring of growth is also essential.
- Once hypertension is diagnosed the treatment should be ongoing. Patients with hypertension should be followed up every 6 to 12 months to ensure BP is controlled (i.e., <130/80 mmHg). Additional monitoring may be necessary as complications arise.
- Patients should be referred to a nephrologist according to local guidelines dependent on the level of renal function. This will allow for monitoring of the rate of decline of renal function, adjustment of diet and antihypertensive medicines, preparation for renal replacement therapy and management of the metabolic abnormalities associated with chronic kidney disease progression. Additional therapies for proteinuria may also be considered.
- Early referral to a nephrologist is likely to lead to an improvement in estimated GFR. A longer duration of regular nephrology care in the non-chronic renal failure period is associated with decreased hospitalisation and better long-term survival once the patient begins dialysis. [GFR MDRD calculators for adults]
- Erythrocyte-stimulating agents should be started to maintain target haemoglobin of 110 to 120 g/L (11 to 12 g/dL).
- Depression is frequent among patients with chronic renal failure. It has a significant impact on morbidity and mortality, justifying awareness and screening.
- Lenticonus (bulging of the lens capsule and the underlying cortex[2]), present in 10% to 15% of patients, is associated with more rapid progression to chronic renal failure and loss-of-function mutations in the COL4A5 gene. Lenticonus in children should also be followed up regularly by an ophthalmologist.

Patient instructions

Information should be provided to patients about the variable course and disease manifestations of Alport's syndrome, and the importance of early detection and modification of risk factors such as hypertension and proteinuria that influence that rate of progression to renal failure. This information can also be passed on to other family members who may wish to consider screening and genetic counselling. [Alport Syndrome Foundation]

It is generally appropriate to describe to the patient the following complications: haematuria, proteinuria, nephrotic syndrome, hypertension, progression to renal failure, hearing loss, and eye complications.

Certain children, young adults, and adults should be encouraged to learn about the significance of systolic and diastolic BP readings and how to take their own BP. Target BP should be emphasised. Dietary advice should be given: 0.8 g/kg protein of ideal body weight per day; for patients with hypertension or hyper-cholesterolaemia, sodium restriction of 90 mEq per day, and low cholesterol intake (<200 mg/day) are advised.

Patients and their relatives should be offered genetic counselling to inform them of all reproductive choices, as well as family screening. Some families may proceed to antenatal diagnosis if molecular characterisation of the family has been carried out. This is usually offered by chorionic villous sampling (CVS) between 11 and 12 weeks' gestation. Pre-implantation genetic diagnosis may rarely be offered. In X-linked Alport's syndrome, fetal sexing may also be offered at about 8 weeks' gestation using maternal plasma screening. CVS is then offered only if the fetus is male. The risks to both sexes are equal in autosomal-recessive Alport's syndrome. [GeneTests]

Complications

Complications	Timeframe	Likelihood
chronic renal failure	**long term**	**high**
Complications of chronic renal failure include anaemia, hyper-parathyroidism, protein malnutrition, cardiovascular disease, metabolic acidosis, and hyperkalaemia. These are treated according to standard parameters. Early referral to a nephrologist is recommended for renal replacement therapy (transplant or dialysis).		
depression	**variable**	**medium**
Frequent among patients with chronic renal failure. It has a significant impact on morbidity and mortality so requires awareness and screening.		
complications during pregnancy	**variable**	**low**
Maternal and fetal complications are higher in pregnancies of women with Alport's syndrome and renal dysfunction/hypertension. New or worsening hypertension, pre-eclampsia, and oedema are more common. Women with pre-pregnancy serum creatinine of 106 micromol/L or greater (≥1.2 mg/dL) have higher risk of fetal or maternal complications.		

Prognosis

For a male with X-linked Alport's syndrome (XLAS), the disease follows a consistent but variable course. At present this seems to be uninfluenced by any intervention except when renal failure develops and renal replacement therapy (dialysis or transplantation) can be offered.[33] This is a lifesaving intervention. Microscopic haematuria with episodic gross haematuria develops from an early age. Proteinuria then develops, which is a prelude to the development of hypertension and progressive renal failure. All males will eventually develop chronic renal failure. The rate of progression to chronic renal failure is mutation dependent in XLAS. Over 90% will develop chronic renal failure before 30 years of age if they have a loss-of-function mutation in COL4A5.[3] In women with XLAS 12% may develop chronic renal failure before 40 years of age; significant hearing loss may also develop in 10%. In autosomal-recessive Alport's syndrome, the natural history of the disease is less well characterised. In one series of 40 individuals with autosomal-recessive Alport's syndrome, the median age was 31 years and the median age at end-stage renal disease (ESRD) was 22.5 years (range 10 to 38 years). A third of adults were found to have normal renal function.[44] Equal numbers were due to mutations in COL4A3 and COL4A4. The presence of at least one loss-of-function allele predicted an earlier onset of ESRD. Once chronic renal failure has developed, patients with all types of Alport's syndrome can be offered renal replacement therapy.

Diagnostic guidelines

Europe

Aetiological investigations into bilateral severe to profound permanent hearing loss in children

Published by: British Association of Audiovestibular Physicians; British Association of Paediatricians in Audiology **Last published:** 2009

Summary: Guidelines for the investigation of hearing loss in children.

International

Clinical practice guideline for the evaluation and management of chronic kidney disease

Published by: Kidney Disease: Improving Global Outcomes **Last published:** 2012

Summary: Evidence-based guideline on the evaluation of all patients with CKD; it updates the 2002 KDOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification.

North America

Expert guidelines for the management of Alport syndrome and thin basement membrane nephropathy

Published by: American Society of Nephrology **Last published:** 2013

Summary: Management guidelines based on expert opinion that cover the use of genetic testing as the key diagnostic tool and the need to identify and follow up all affected family members, including female carriers of COL4A5 mutations.

Treatment guidelines

Europe

European best practice guidelines for renal transplantation (Part 2). Section IV: long-term management of the transplant recipient. IV.2.4. Chronic graft dysfunction. De novo renal disease after transplantation

Published by: EBPG Expert Group on Renal Transplantation **Last published:** 2002

Summary: For transplant patients with Alport's syndrome, the possibility of anti-glomerular basement membrane (anti-GBM) glomerulonephritis should be considered in the case of graft dysfunction.

International

Clinical practice recommendations for the treatment of Alport syndrome

Published by: Alport Syndrome Research Collaborative **Last published:** 2013

Summary: Clinical practice recommendations for the treatment of children with Alport's syndrome who are not enrolled in clinical trials.

Clinical practice guideline for the evaluation and management of chronic kidney disease

Published by: Kidney Disease: Improving Global Outcomes **Last published:** 2012

Summary: Evidence-based guideline on the management and treatment of all patients with CKD; it updates the 2002 KDOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification.

North America

Expert guidelines for the management of Alport syndrome and thin basement membrane nephropathy

Published by: American Society of Nephrology **Last published:** 2013

Summary: Management guidelines based on expert opinion that cover the treatment of Alport's syndrome, including the use of renin-angiotensin blockade in patients with proteinuria and guidance for living-related kidney donation.

The seventh report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure (JNC 7)

Published by: National Heart, Lung, and Blood Institute **Last published:** 2003

Summary: For patients with hypertension and chronic renal disease, these guidelines recommend aggressive management, often with 3 or more drugs to reach a target BP of under 130/80 mmHg.

Online resources

1. ASTOR: Alport Syndrome Treatments and Outcomes Registry *(external link)*
2. GFR MDRD calculators for adults *(external link)*
3. Alport Syndrome Foundation *(external link)*
4. GeneTests *(external link)*

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