IgA nephropathy and IgA vasculitis

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History

- IGAN first decribed-Berger and Hinglais in 1968
- HSP or IGAV now-first described by Heberden in 1801
- Shonlein - in 1837 called it “peliosis rheumatica”
- Henoch-in 1868 descibed GI symptoms with arthalgia & 30 yrs later nephritis
- ***In the 2nd Chapel hill consensus classification in 2012-nomenclature changed to IGAV***

Epidemiology IgAN

- Varies according to regions
- Pacific rim (far east) contributes to 50% of all GN
- In Europe 20-30% & 2-10% in USA
- Lower prevalence in Africans, African Americans
- Seen in all ages but more common during 2nd & 3rd decades
- More common in males (M:F 2-3:1 ratio)

- Retrospective study from Kuwait - 356 biopsies with diagnosis of GN in > 12 yrs patients, 85 (23.9%) with IGAN; only 9.7%< 18 yrs had IGAN

BMC Nephrol. 2020;21:186

- Nationwide survey of kidney biopsies over 11-year period(2004 -2014); 7962 children <18 yrs from 115 hospitals across China with biopsy-proven glomerular diseases showed the prevalence of IGAN as 17%

Clin J Am Soc Nephrol. 2018;13

- Data from India prevalence ***7-16%***

Renal Failure. 2011, 33:1, 102-107

Table 1. IgA nephropathy studies from India.

Author	Biopsies (*n*)	Prevalence of IgA (%)	IgAN (*n*)	Clinical presentation (%)			
				NS	NiS	HTN	Renal failure
Chacko et al.[24]	5415	8.6	478	55	16	58	60
Bhuyan et al.[5]	1146	7.24	83	24	NA	39	34
Sehgal et al.[6]	106	10.37	11	NA	NA	NA	NA
Chandrika[7]	1592	14.26	227	36.7	18.9	3.5	5.7
Vanikar et al.[8]	4132	16.2	120	NA	NA	NA	NA
Muthukumar et al.[31]	NA	NA	98	25.6	5.1	9.2	13.5

HTN, hypertension; NA, not available; NiS, nephritic syndrome; NS, nephrotic syndrome

Western India

Clinical presentation- IgAN

- Data from the Japanese renal registry (2007-12); 5679 patients diagnosed as IGAN

Chronic nephritic syndrome in 88.5%, acute nephritic syndrome in 1.3%, recurrent or persistent hematuria in 1.4% & nephrotic syndrome in 3%

Clin Exp Nephrol. 2016 ;20

- Amongst 426 children with IGAN 7% presented as NS

Pediatr Nephrol. 2017;32

- Gross hematuria, persistent isolated microscopic hematuria, hematuria with proteinuria or recurrent gross or microscopic hematuria with ARI

- Japanese cohort of 258 children, 62% microscopic hematuria with or without asymptomatic proteinuria & 26% had macroscopic hematuria, 12% presented with ANS or NS

Child Nephrol Urol. 1988;9

- Study by South West Pediatric nephrology group from USA (n=218) (1972-1988)- 79% children had gross hematuria at diagnosis & proteinuria of 2+ or more in 51% biopsy

Kidney Int. 1982;22

Etiopathogenesis

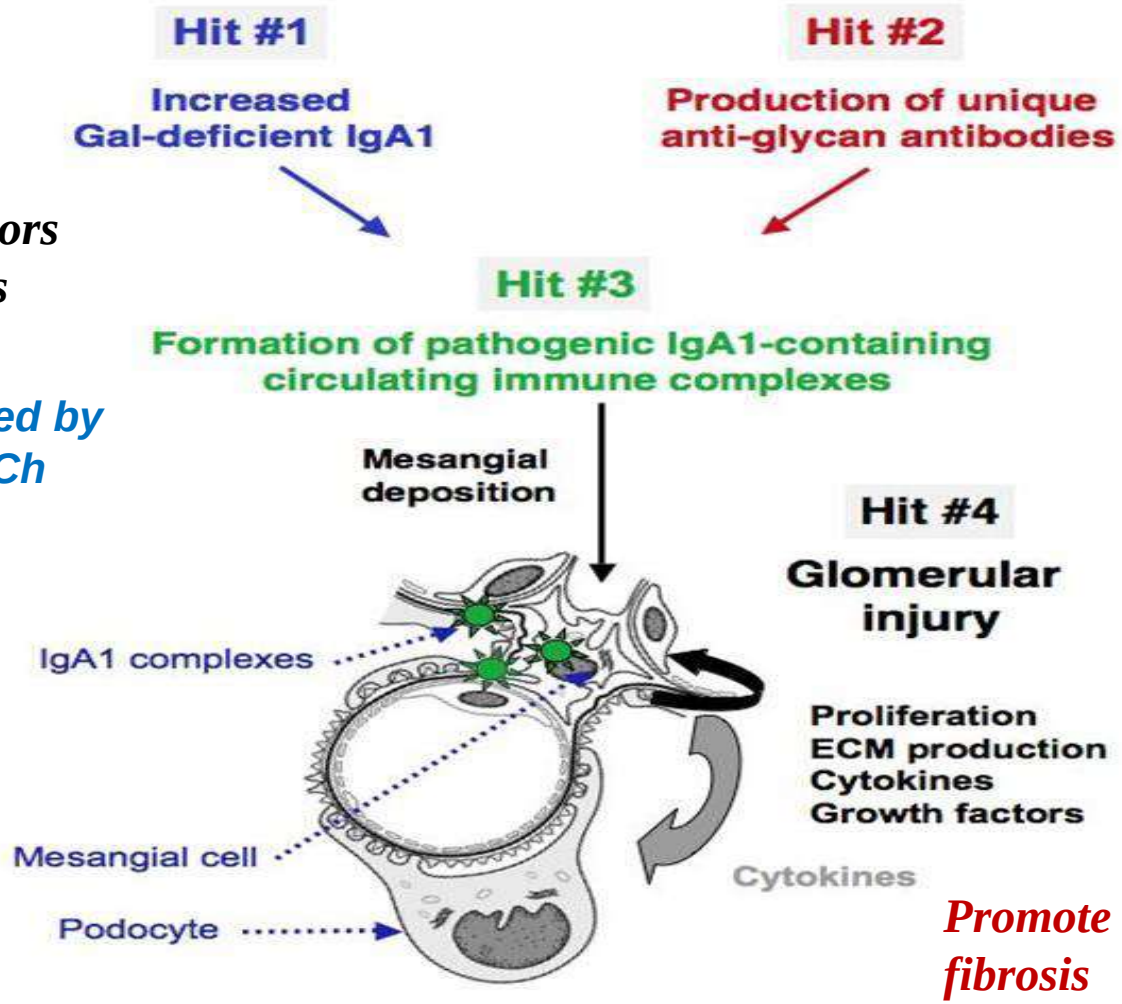
- **Multi-hit pathogenesis model** -galactose-deficient IgA1 in serum, anti-glycan response, decreased clearance of defective IGA1 by liver, formation & deposition of IgA1- immune complexes
- Serum IGA levels increased in 5-70% patients
- Elevated levels of Gd-IGA1 seen in patients with IGAN & IGAV

PLOS ONE 2016

- Associated with adenoviruses, staph, streptococci, H. Parainfleunza, measles, rubella etc…
- Stap aureus cell envelop antigen identified in glomeruli of 68.1% (79/116) IGAN biopsy specimen from Japan

Kidney Int 2004; 66

Multi hit hypothesis



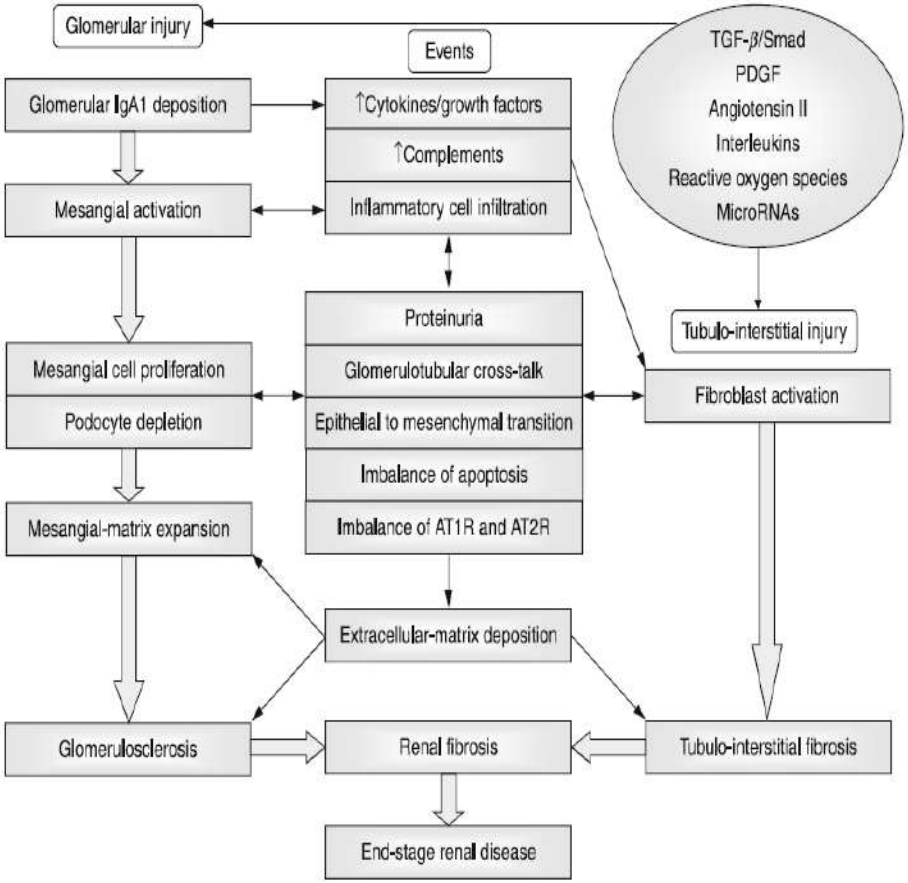
Genetic factors & Infections

Hit 2,3 Regulated by 3 MHC loci on Ch 6p21

Hit 3&4-affected by complement factor H locus on ch1q32 that regulates complement cascade

Promote glomerular & TI fibrosis

Progression of Damage



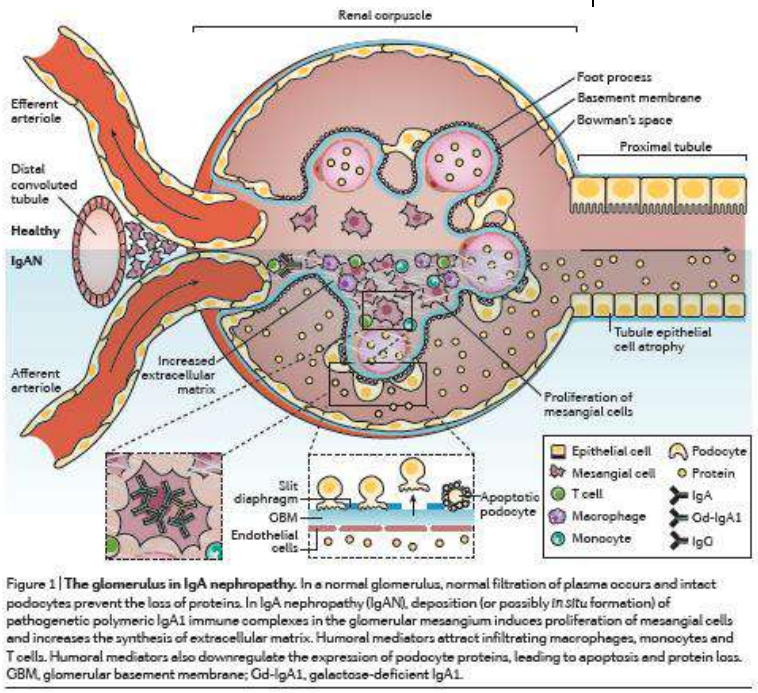


Figure 1 | **The glomerulus in IgA nephropathy.** In a normal glomerulus, normal filtration of plasma occurs and intact podocytes prevent the loss of proteins. In IgA nephropathy (IgAN), deposition (or possibly *in situ* formation) of pathogenetic polymeric IgA1 immune complexes in the glomerular mesangium induces proliferation of mesangial cells and increases the synthesis of extracellular matrix. Humoral mediators attract infiltrating macrophages, monocytes and T cells. Humoral mediators also downregulate the expression of podocyte proteins, leading to apoptosis and protein loss. GBM, glomerular basement membrane; Gd-IgA1, galactose-deficient IgA1.

Imbalance of Angiotensin II subtypes 1 & 2 has role in inflammation; direct toxic damage of tubules by IgA

IgA1 accelerates podocyte apoptosis through direct & indirect pathways

Genetic predisposition of IgAV

- ***ACE, IL18 & HLA-B *35*** associated with worst renal prognosis
- Specific genes coding for inflammatory pathways within blood vessels & Kidney
- Racial presdiposition especially more in Asians

Genetic susceptibility	Genetic protection
HLA-B*15	HLA-B*7
HLA-B*35	HLA-B*40
HLA-B*4102	HLA-B*49
HLA-B*52	HLA-B*50
HLA-A*2	HLA-A*1
HLA-A*11	HLADRB1*3
HLA-A*26	HLADRB1*7
HLA-DRB1*0103	Agtrs699M235T
HLA-DRB1*11	MEFV
HLA-DQA1*0301	PONI
HSPA21267GG	
IL1815187238-137G	
MCP1-2518TT	
MCP1-2518T	
TGF beta rs1800469-509TT	
Agt	
ACE	
C1GALT1rs	
NOS2A	
eNOS	
PONI192QQ	
MEFV	

Rhematol Int 2013; 33

Biopsy classifications

- Semiquantitative & single grade like LEE & Haas classifications have been used in past; they suffer from problem of reproducibility
- Lee used biopsy material from 142 Korean patients with IgAN; primarily used glomerular changes for prediction of progression

Clin Nephrol. 1987; 27

- Haas classification -histologic features of 244 cases of IgAN (1980 -1994) reviewed & subclassified using classification based on glomerular changes (mesangial hypercellularity & glomerular sclerosis)

Am J Kidney Dis. 1997; 29

original article http://www.kidney-international.org

see commentary on page 477

The Oxford classification of IgA nephropathy: rationale, clinicopathological correlations, and classification

A Working Group of the International IgA Nephropathy Network and the Renal Pathology Society: Daniel C. Cattran[1,†], Rosanna Coppo[2,†], H. Terence Cook[3,†], John Feehally[4,†], Ian S.D. Roberts[5,†], Stéphan Troyanov[6,†], Charles E. Alpers[7], Alessandro Amore[2], Jonathan Barratt[4], Francois Berthoux[8], Stephen Bonsib[9], Jan A. Bruijn[10], Vivette D'Agati[11], Giuseppe D'Amico[12], Steven Emancipator[13], Francesco Emma[14], Franco Ferrario[15], Fernando C. Fervenza[16], Sandrine Florquin[17], Agnes Fogo[18], Colin C. Geddes[19], Hermann-Josef Groene[20], Mark Haas[21], Andrew M. Herzenberg[22], Prue A. Hill[23], Ronald J. Hogg[24], Stephen I. Hsu[25], J. Charles Jennette[26], Kensuke Joh[27], Bruce A. Julian[28], Tetsuya Kawamura[29], Fernand M. Lai[30], Chi Bon Leung[31], Lei-Shi Li[32], Philip K.T. Li[31], Zhi-Hong Liu[32], Bruce Mackinnon[19], Sergio Mezzano[33], F. Paolo Schena[34], Yasuhiko Tomino[35], Patrick D. Walker[36], Haiyan Wang[37], Jan J. Weening[38], Nori Yoshikawa[39] and Hong Zhang[37,*]

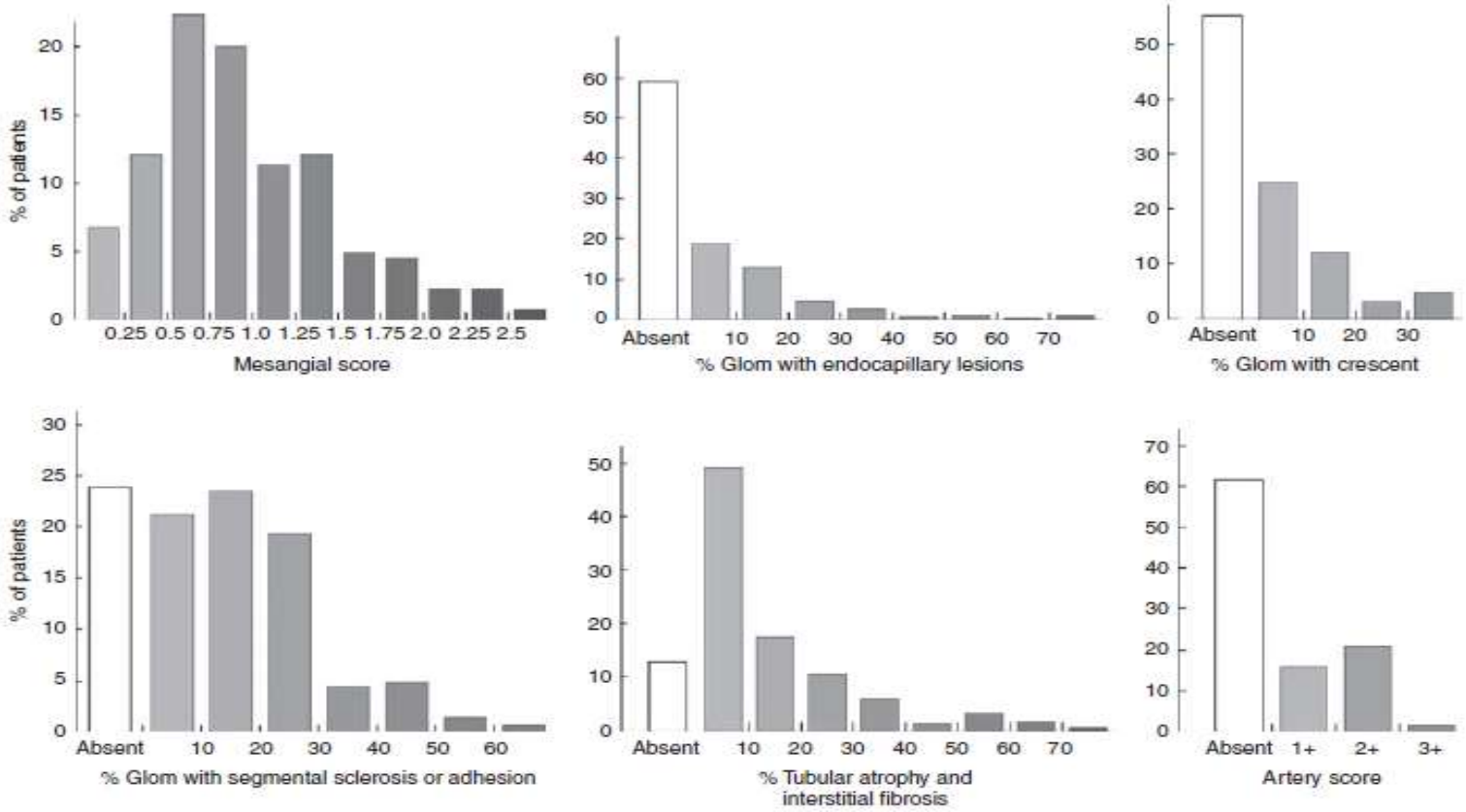
Table 1 | Age and geographical origin of the study cohort of 265 cases of IgA nephropathy

		Adults	Children (age < 18 years at biopsy)
Total	265	206	59
Asia		*48*	*14*
China	Beijing	12	2
	Hong Kong	9	1
	Nanjing	7	1
Japan	Tokyo	19	1
	Wakayama	1	9
Europe		*73*	*21*
France	St Etienne	23	1
Italy	Bari	23	1
	Milano	16	3
	Roma	–	9
	Torino	3	7
United Kingdom	Glasgow	8	–
North America		82	24
Canada	Toronto	32	0
United States	Birmingham	12	1
	Mayo Clinic	14	4
	South West Study Group	24	19
South America		*3*	*0*
Chile	Santiago	3	0

Proportion of children ~22.3%; from 8 countries on 4 continents

- Median follow up 5years, median proteinuria 1.7gm/d, 90% FU > 3yrs
- 29% (***47% children*** & 23% adults) were on immunosupressants, mostly steroids & other agents only in 9%

Biopsy findings



igure 1| Frequency of pathological features in 265 renal biopsies. Percentage of patients with each pathological feature. he six pathological features illustrated are those with sufficient reproducibility and frequency to merit evaluation for association with linical outcome. Glom, glomeruli.

MEST-C classification

Table 8 | Recommended elements in renal biopsy report for a case of IgA nephropathy

Detailed description of the features present on
- Light microscopy
- Immunohistochemistry
- Electron microscopy

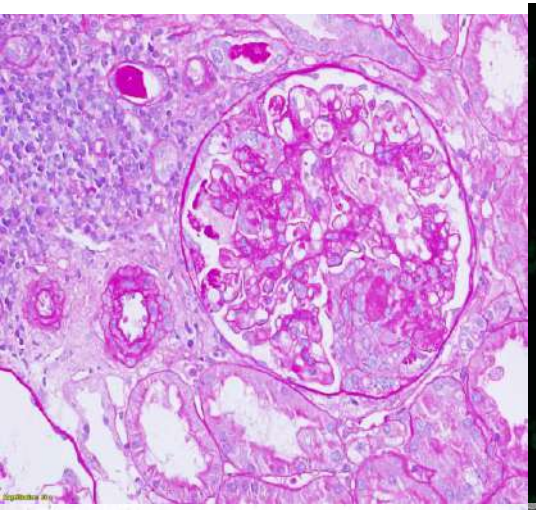
Summary of four key pathological features
- Mesangial score ⩽0.5 (M0) or >0.5 (M1)
- Segmental glomerulosclerosis absent (S0) or present (S1)
- Endocapillary hypercellularity absent (E0) or present (E1)
- Tubular atrophy/interstitial fibrosis ⩽25% (T0), 26-50% (T1), or >50% (T2)

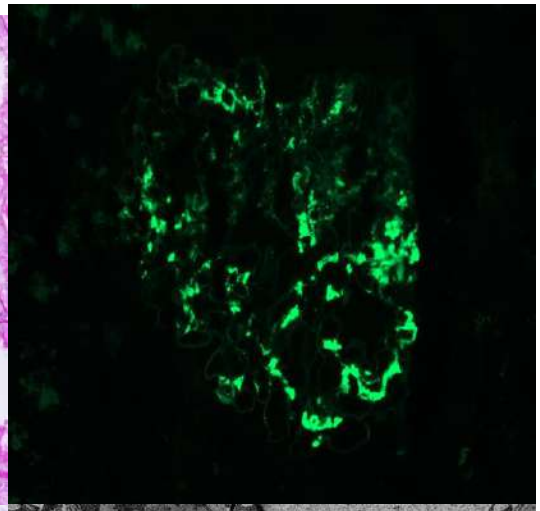
Total number of glomeruli
Number of glomeruli with endocapillary hypercellularity, extraca proliferation, global glomerulosclerosis, and segmental glomerul sclerosis

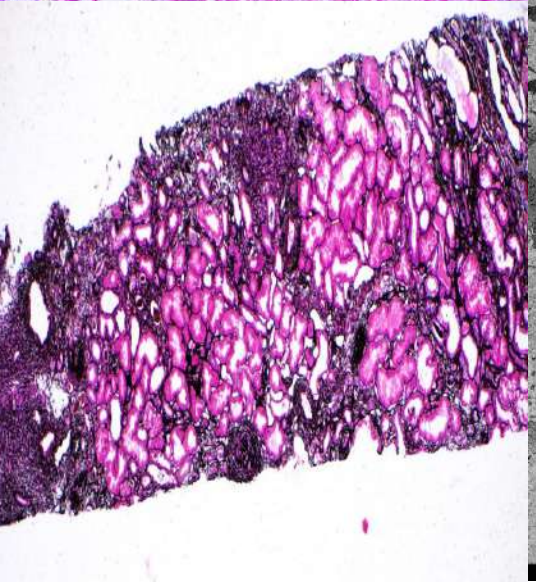
OXFORD CLASSIFICATION OF IGA NEPHROPATHY

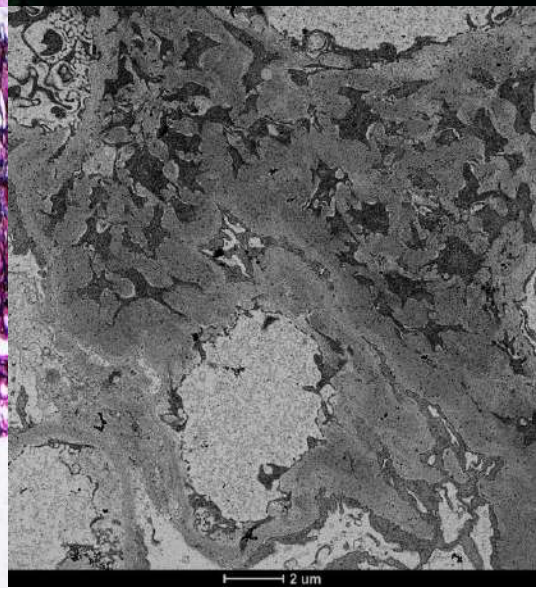
MEST	DESCRIPTION	SCORE
M	Mesangial Hypercellularity	M0: <50% Glomeruli M1: >50% Glomeruli
E	Endocapillary Hypercellularity	E0: Absent E1: Present
S	Segmental Glomerulosclerosis	S0: Absent S1: Present
T	Tubular Atrophy	T0: Absent or <25% tubules T1: 26-50% tubules T2: >50% tubules
C	Crescent	C0: Absent C1: 1-24% Glomeruli C2: >25%

MEST-C ; 2016 update based on pooled cohort of 3096 patients from 4 retrospective studies (original Oxford cohort, VALIGA, 1 each from China & Japan)









Microscopy Examination:- The kidney biopsy show 13 glomeruli out of which 7 are globally sclerosed. The viable glomeruli show increase in mesangial matrix and cellularity. One glomerulus shows an area of segmental fibrinoid necrosis. The basement membrane appears unremarkable on silver methenamine stain. No crescent is identified.

Tubules show injury inform of lowering of epithelium. Focal acute tubular necrosis is also identified. Interstitium show as dense chronic inflammatory cell infiltrate. Blood vessels show medial sclerosis. About 40% of tubulointerstitial compartment show chronic parenchymal damage on MT stain.

IF:- The tissue sent for IF showed 5 glomeruli of which 2 are globally sclerosed the viable glomeruli show coarse granular mesangial deposits of IgA. These deposits show greater intensity of staining for lambda (2+) over kappa (0). Non specific C3 deposits are identified in the sclerosed glomeruli IgG, IgM, and C1q are negative.

Impression: Findings are consistent with IgA nephropathy with focal acute tubular necrosis, interstitial nephritis & moderate degree of chronic parenchymal damage

MEST Score = M1,E1, S0, T1.

- IF findings-predominant or codominant IgA in all, IgG 32%, IgM in 8% & both in 11%

Child Nephrol Urol 1988;9

- C3 deposits in mesangium in 64%, early components of classical pathway- C4, C1q absent;fibrin or fibrinogen related antigens present in 25-70%-diffuse mesangial distribution

Clin Exp Immunol 1985; 62

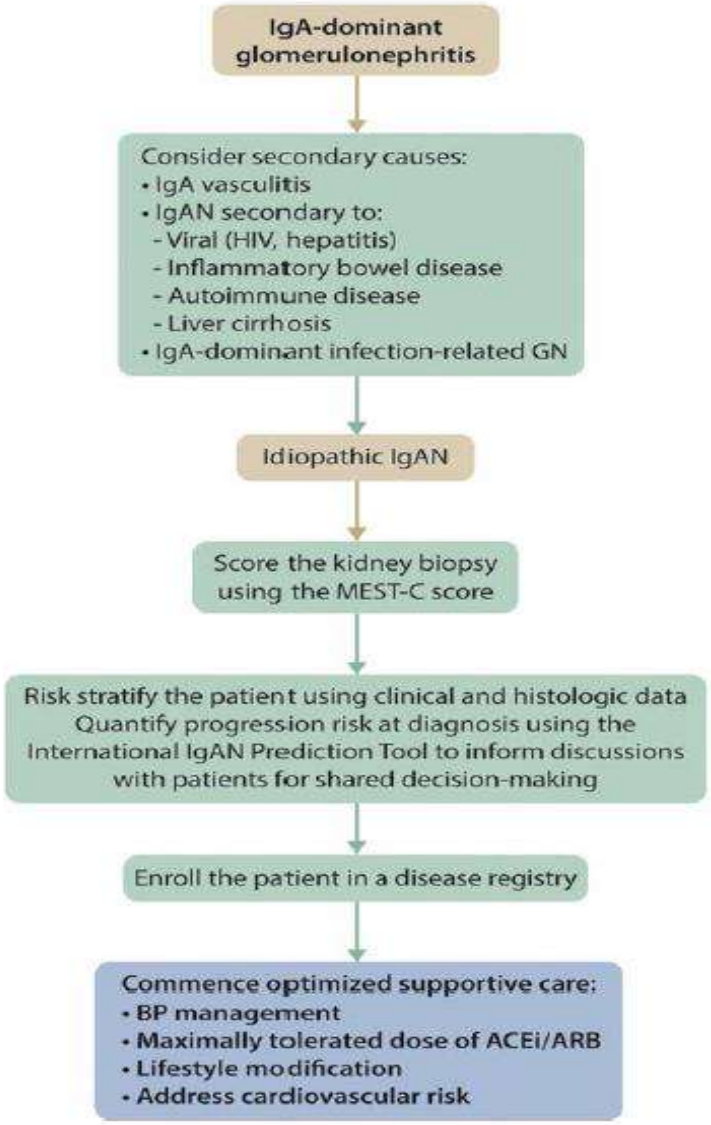
- EM not essential to make a diagnosis

Lab parameters

- Serum IGA levels in increased in 30-50% adults but only 8-16% children
- Galactose deficient IgA1 levels elevated
- ASLO/C3 done to R/O PIGN
- Serum IgA/C3 appears as a better marker to differentiate IGA from non IgA GN
- Serum IgA/C3 ratio >4.5 associated with worse outcomes

Intern Med 2004; 43

- Increased urinary excretion of EGF, MCP-1, IL-6, LMW, mannose binding proteins, proteonomic data being evaluated



KDIGO clinical practice guidelines on management of chronic glomerulonephritis 2021

International IgAN prediction tool

- Uses clinical & histological data at the time of biopsy to risk stratify
- Quantifies risk of progression

- Equations derived from multi-ethnic international cohort- 2781 patients with biopsy proven idiopathic IgAN & designed to predict risk of 50% decline in eGFR or ESKD after biopsy

KDIGO 2021 clinical practice guidelines for glomerular diseases

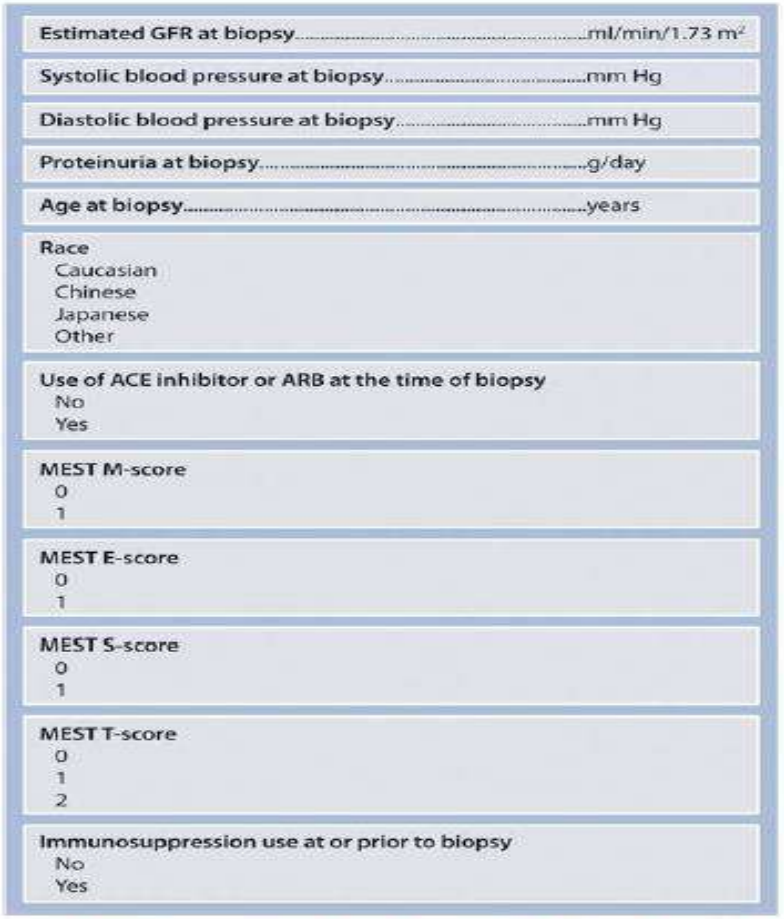


Figure 20 | The data elements included in the International IgAN Prediction Tool. Using clinical and histologic data at biopsy, users can determine a 50% decline in eGFR or kidney failure at selected time intervals. The tool is not validated for use with data obtained

Calculator | About | References

International IgAN Prediction Tool at biopsy - Adults

Determine prognosis in adults with IgA nephropathy

Questions

1.	Estimated GFR at biopsy	47 ml/min/1.73m2
2.	Systolic blood pressure at biopsy	140 mmHg
3.	Diastolic blood pressure at biopsy	90 mmHg
4.	Proteinuria at biopsy	2.5 g/day
5.	Age at biopsy	25 Years
6.	Race	Other
7.	Use of ACE inhibitor or ARB at the time of biopsy	Yes
8.	MEST M-score	1
9.	MEST E-score	1
10.	MEST S-score	0
11.	MEST T-score	1
12.	Immunosuppression use at or prior to biopsy	No
13.	At how many months after renal biopsy would you lik...	60 Months

13/13 completed

Results

Save Copy Results

Risk of Progression

The risk of a 50% decline in estimated GFR or progression to end-stage renal disease 5.0 years after renal biopsy is 49.02%

Copy Results

Updating the International IgA Nephropathy Prediction Tool for use in children

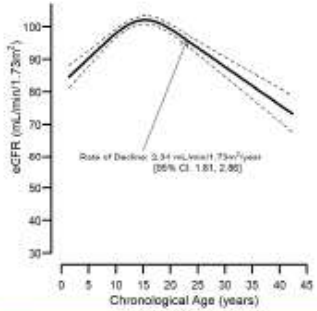
International cohort

Update the Prediction Tool

N=1,060 children with IgAN

Followed into adulthood

In contrast to adults, children have a non-linear eGFR trajectory



To account for eGFR trajectory:

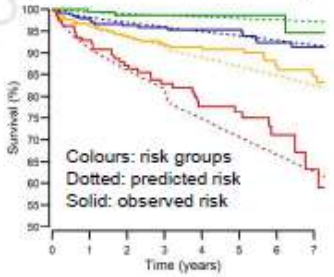
1. Modified outcome: 30% decline eGFR or ESKD
2. Updated model coefficients and baseline survival

The International IgA Nephropathy Network

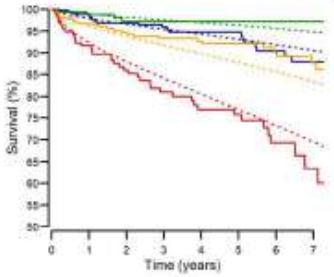
Calibration

(Agreement between predicted and observed risk)

Model with race/ethnicity



Model without race/ethnicity



Prediction performance

	Model with race/ethnicity	Model without race/ethnicity
Model fit (R^2_D)	30.3%	22.2%
Discrimination (C-statistic)	0.74 (95% CI 0.73, 0.75)	0.68 (95% CI 0.67, 0.69)

CONCLUSION:

The updated pediatric International IgAN Prediction Tool models can accurately predict the risk of a 30% decline in eGFR or ESKD in children with IgAN.

ISN kidney INTERNATIONAL
OFFICIAL JOURNAL OF THE INTERNATIONAL SOCIETY OF NEPHROLOGY

Barbour, 2020

Recommendation 2.3.1.1: We suggest that patients who remain at high risk of progressive CKD despite maximal supportive care be considered for a 6-month course of glucocorticoid therapy. The important risk of treatment-emergent toxicity must be discussed with patients, particularly those who have an eGFR <50 ml/min per 1.73 m^2 *(2B)*.

Agent	Suggested usage	Remarks
Antiplatelet agents	Not recommended	No documented evidence of efficacy
Anticoagulants	Not recommended	No documented evidence of efficacy
Azathioprine	Not recommended	No evidence for efficacy as monotherapy or when combined with glucocorticoids
Cyclophosphamide	Not recommended	Unless in the setting of rapidly progressive IgAN
Calcineurin inhibitors	Not recommended	No documented evidence of efficacy
Rituximab	Not recommended	No documented evidence of efficacy
Fish oil	Not recommended	Patients who wish to take fish oil should be advised of the dose and formulation used in the published clinica trials that reported efficacy.
Mycophenolate mofetil (MMF)	**Chinese patients** In those patients in whom glucocorticoids are being considered MMF may be used as a glucocorticoid-sparing agent	In a single RCT conducted in China, MMF with low-dos glucocorticoids was noninferior to standard-dose glucocorticoids for the treatment of incident IgAN presenting with proliferative histologic lesions (E or C lesions with or without necrosis) on kidney biopsy and proteinuria >1.0 g/d. There were significantly fewer glucocorticoid-related side effects in the combination-therapy arm.[1,5]
	Non-Chinese patients There is insufficient evidence to support the use of MMF	In the RCTs of MMF in non-Chinese patients there was no evidence for efficacy of MMF monotherapy.[2–5]
Hydroxychloroquine	**Chinese patients** In those patients who remain at high risk of progression in spite of optimized supportive care	In a small, short-term RCT conducted in China, hydroxychloroquine introduced to patients with proteinuria of 0.75–3.5 g/d despite optimized ACEI/ARB reduced proteinuria by 48% versus 10% in the placebo group at 6 months.[6]
	Non-Chinese patients There is insufficient evidence to support the use in those patients	Hydroxychloroquine has not been evaluated in non-Chinese patients.

	Japanese IgAN	Chinese IgAN	Caucasian IgAN
Clinical practice	Performed routinely (often with pulsed glucocorticoids)	Not routinely performed	Not performed
Remarks	Multiple cohort studies,[1-5] including a large retrospective study with propensity matching,[3] report improved kidney survival following tonsillectomy. A single RCT failed to show a difference in eGFR at 1 year comparing tonsillectomy vs. tonsillectomy and pulsed glucocorticoids, and no longer term data are available from this study.[6]	Inconsistent data from small retrospective cohort studies and a small single-center RCT	Very few data available in this population. Available data do not support the efficacy of tonsillectomy as a treatment for IgAN in Caucasian patients

- ***Steroids >0.5 mg/kg/d for 6 mo along with ACEI/ARB***
- ***Tonsillectomy not recommended***
- ***For RPGN- steroids, IV CP***

Study	Medication	Start dose	Duration high dose	Taper	Total exposure
TESTING[1]	Methylprednisolone	0.6–0.8 mg/kg/d (per investigator), rounded to nearest 4 mg. Max 48 mg/d	2 months	8 mg/month	6–8 months
Manno[2]	Prednisone	1 mg/kg/d, max 75 mg/d	2 months	0.2 mg/kg/ month	6 months
Lv[3]	Prednisone	0.8–1 mg/kg/d	8 weeks	5–10 mg/d every 2 weeks	8 months

- Therapeutic Evaluation of Steroids in IGAN Global study- Had to be stopped after 1.5 yrs due to serious adverse effects

- STOP IGA nephropathy trial-162 adults, decrease in proteinuria more in steroid group but at 3 yrs the fall in eGFR was similar

NEJM,2015;373

- All children with proteinuria >0.2mg/mg should be treated with ACEI/ARB
- For proteinuria >1gm/d; prednsisolone 1-2 mg/kg/d for 4 weeks followed by A/D tapering over 4-6months
- MP pulses & IV CP for RPGN
- In severe IGAN in Japanese patients-steroids, ACEI/ARB, AZA/mizoribine, anticoagulants for 2yrs

Clin Exp Nephrol 2016; 20

Newer agents

- Phase 3 PROTECT study-antiproteinuric & renoprotective effects of ***Sparsentan*** (dual acting angiotensin II & endothelin type A receptor antagonist)

- 270 participants with IgAN, 137 randomized to dapagliflozin & 133 to placebo- FU median 2.1 yrs; eGFR decline was -3.5 & -4.7 mL/min/yr, Dapa reduced UP/UC ratio by 26% relative to placebo

Kidney Int. 2021;100(1)

- Safety & efficacy of a novel ***targeted-release formulation of budesonide*** designed to deliver drug to distal ileum-150 pts received 16mg, 8mg or placebo; TRF 16 mg/d, added to RAS blockade, reduced proteinuria (27.3%↓)

Lancet. 2017;389(10084)

Course & Prognosis

- ESKD develops in 20% after 10 yr, 30% after 20 yr
- 10% children CKD (4 or 5) by 15 yr after initial diagnosis
- ***Poor prognostic indicator***
  - Heavy proteinuria, Persistent hypertension, Male , Crescentic GN

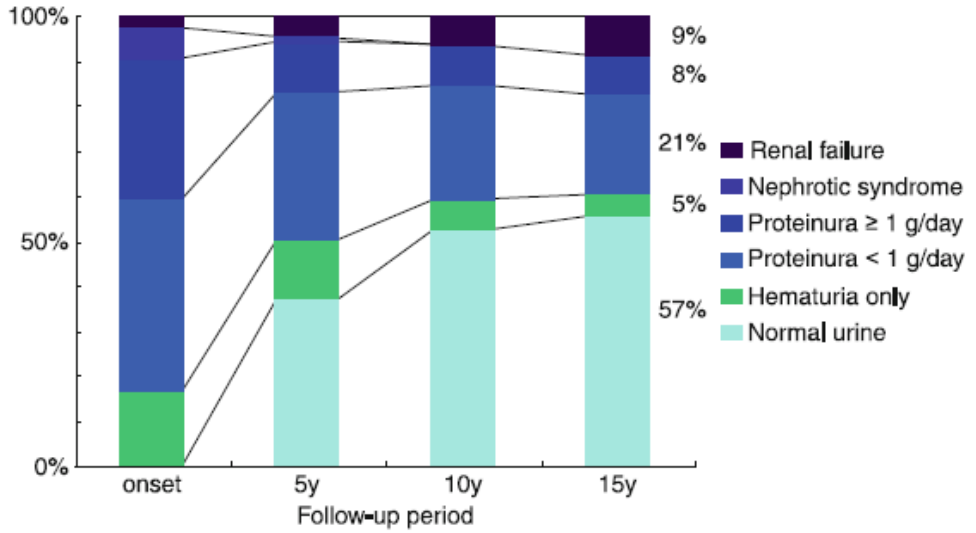


Fig. 7 Long-term prognosis of the 169 Japanese children with IgAN followed more than 10 years

IgAV

- Small-vessel vasculitis characterized by non-thrombocytopenic purpura -100%, arthritis - 68%, abdominal pain - 53%, & nephritis- 30-50%
- Approximately ***3-27 cases / 100,000*** school-aged children
- Peak incidence ***4-6 yrs*** (1.5:1; M:F)

Front Pediatr 2019

- Almost 97% develop renal involvement within 6 mo of onset; mild in majority
- Hematuria & low grade proteinuria commonest; nephritic syndrome or NS in <20%

IgAV Definition

The EULAR/PReS/PRINTO classification criteria for childhood IgA vasculitis.

Criterion	Description
Mandatory	Purpura or petechia with lower limb predominance
At least 1 out of 4	(1) Acute onset diffuse abdominal colicky pain (may include intussusception and gastrointestinal bleeding) (2) Histology showing leukocytoclastic vasculitis or proliferative glomerulonephritis with predominant IgA deposition. (3) Acute onset arthralgia or arthritis (4) Either proteinuria or haematuria

Histopathologicaly characterized by immunoglobulin A (IgA), C3, & immune complex deposition in arterioles, capillaries & venules

Validated in 872 children<18 yrs of HSP;
100% sensitivity & 87% specificity

RHEUMATOLOGY

Rheumatology 2019;58:1607–1616
doi:10.1093/rheumatology/kez041
Advance Access publication 16 March 2019

Original article

European consensus-based recommendations for diagnosis and treatment of immunoglobulin A vasculitis—the SHARE initiative

Single hub & access point for pediatric rheumatology in Europe

TABLE 1 SHARE recommendations for the diagnosis of IgAV

Number	Recommendations: Diagnosis	LoE	SoR
Classification criteria			
1.	The EULAR/PRINTO/PReS-endorsed Ankara 2008 criteria should be used to classify IgAV (formerly known as HSP) [26]	2A	B
Use of biopsy			
2.	A skin biopsy including specific immunofluorescence staining for IgA should be performed in case of atypical rash and/or to exclude alternative diagnoses; skin biopsy is not needed in a patient with the typical purpuric skin rash on lower limbs and buttocks	4	D
3.	Absence of IgA immunofluorescence staining on biopsy does not exclude the diagnosis of IgAV	3	C
Renal work-up			
4.	Renal involvement should be investigated using eGFR and urinalysis (haematuria and UP:UC ratio or UA:UC ratio)	2B	C
5.	A paediatric nephrologist should be consulted if an IgAV patient has moderate proteinuria[a] and/or impaired GFR[b]	4	D
6.	A renal biopsy should be performed if an IgAV patient has severe proteinuria (>250 mg/mmol for at least 4 weeks; although shorter duration of severe proteinuria is also a relative indication for biopsy), persistent moderate (100–250 mg/mmol) proteinuria[c] or impaired GFR[b]	2A	
Imaging			
7.	In severe abdominal pain, an US should be performed by an ultrasonographer with paediatric expertise to exclude intestinal intussusception	4	D

Biopsy classification

TABLE 2 Definitions of severity of IgAV nephritis

Severity of IgAV nephritis	Definition
Mild	Normal GFR[a] and mild[b] or moderate[c] proteinuria
Moderate	<50% crescents on renal biopsy and impaired GFR[d] or severe persistent proteinuria[e] [44]
Severe	>50% crescents on renal biopsy and impaired GFR[c] or severe persistent proteinuria[e] [44]
Persistent proteinuria [43]	• UP:UC ratio >250 mg/mmol for 4 weeks[e] [44] • UP:UC ratio >100 mg/mmol for 3 months • UP:UC ratio >50 mg/mmol for 6 months

Table 2 Morphologic classification of Henoch–Schönlein nephritis evolved by the International Study of Kidney Disease in Children

I	Minimal glomerular abnormalities	
II	Pure mesangial proliferation	(a) focal or (b) diffuse
III	Minor glomerular abnormalities or mesangial proliferation, with crescents or segmental lesions (sclerosis, adhesions, thrombosis, necrosis) in fewer than 50 % of glomeruli	(a) focal or (b) diffuse mesangial proliferation
IV	As III but with crescents or segmental lesions in 50–75 % of glomeruli	(a) focal or (b) diffuse mesangial proliferation
V	As III but with crescents/ segmental lesions in more than 75 % of glomeruli	(a) focal or (b) diffuse mesangial proliferation
VI	Membranoproliferative-like lesion	(a) focal or (b) diffuse mesangial proliferation

TABLE 3 SHARE recommendations for the treatment of IgAV

Number	Recommendations: Treatment	LoE	SoR
Analgesia			
1.	Adequate analgesia should be prescribed for IgAV-associated arthropathy[a]	4	D
2.	NSAIDs are not contraindicated if renal function is normal in IgAV	4	D
3.	Adequate analgesia should be prescribed for IgAV-associated abdominal pain	4	D
Use of CS			
4.	CS treatment is indicated in case of: • Orchitis • Cerebral vasculitis • Pulmonary haemorrhage • Other severe organ- or life-threatening vasculitis manifestations	4	D
5.	In patients with severe abdominal pain and/or rectal bleeding (in whom intestinal intussusception has been excluded), CS treatment could be considered	4	D
6.	The dose of oral CS (prednisolone/prednisone) should be 1–2 mg/kg/day	4	D
7.	If CS are indicated, pulsed i.v. methylprednisolone (e.g. 10–30 mg/kg with a maximum of 1 g/day on three consecutive days) may be considered for severe cases	4	D
8.	Prophylactic CS treatment to prevent the development of IgAV-associated nephritis is not indicated	1B	A

IgAVN

- ACEI for persistent proteinuuria
- ***Oral prednsiolone for mild IgAV-first line***
- Oral prednisolone/ MP pulses as first line in moderate nephritis
- AZA/MMF/IV CP as 2nd line for moderate nephritis & maintenance for severe nephritis
- CNI or oral CP not recommended

(4D)

KDIGO practice guidelines 2021

2.8.1 IgAV-associated nephritis in children

Practice Point 2.8.1.1: For the purposes of this practice point, children are defined as those aged <18 years. It is acknowledged that post-pubertal children in some respects may have a similar course and response to treatment as adults with IgAN, but there are insufficient data currently to recommend that they be managed as adults with IgAN. Indications for management of IgAVN in children have recently been published as the result of a European consortium initiative.[140] Briefly:

- There are no data supporting the use of glucocorticoids to prevent nephritis in children with IgAV but mild or absent evidence of kidney involvement.[153,154]
- Children >10 years of age more often present with non-nephrotic-range proteinuria and impaired kidney function, and they may suffer more chronic histologic lesions with delay in biopsy and delay in treatment longer than 30 days.[155]
- The majority of children who will develop nephritis will do so within 3 months of presentation. Urinary monitoring is necessary for ≥6 months and optimally 12 months from initial presentation of systemic disease.
- Children with IgAVN and persistent proteinuria for >3 months should be treated with an ACEi or ARB. A pediatric nephrologist should be consulted.
- A kidney biopsy should be performed in children with nephrotic-range proteinuria, impaired GFR, or persistent moderate (>1 g/d) proteinuria.
- Oral prednisone/prednisolone or pulsed intravenous methylprednisolone should be used in children with mild or moderate IgAVN.
- Children with IgAVN with nephrotic syndrome and/or rapidly deteriorating kidney function are treated in the same way as those with rapidly progressive IgAN.

Long term outcomes

- Primarily due to renal involvement
- 4 (11%) children of 122 with IgAV had CKD or death

Clin Nephrol 1987; 27

Estimated incidence of ESKD from 2 large series 2-5%

- 78 children with HSP (***FU 23.4 yrs***)-44% with NS/ ANS at presentation had HTN/impaired renal Fx,; 82% with hematuria/± proteinuria initially were normal, 16/44 (36.4%) pregnencies with HTN/proteinuria

Lancet. 1992;339

- Cresecents in biopsy an important prognostic indicator

Recurrence in allograft

- Clinical recurrence uncommon but mesangial IgA deposits occur frequently

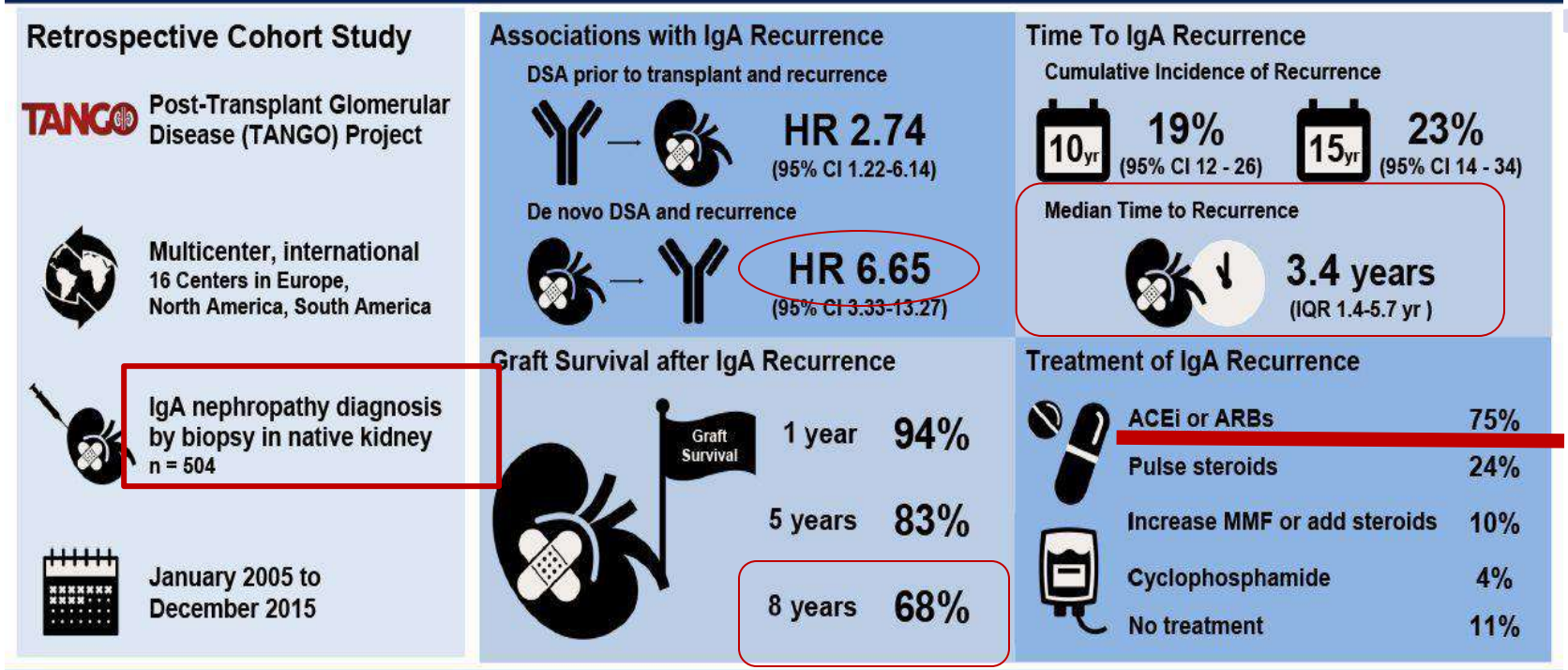
- Recurrent disease associated with live related donation

- Outcomes of 17 patients with HSP (19 renal transplants) with 38 controls; mean post-transplant FU 110 mo; actuarial 15-year pt Survival ***80% in HSP Vs 82% controls***, 42% with crescentic GN had recurrence & half graft loss

Nephrol Dial Transplant. 2008 ;23

What do we know about IgA recurrence in adult kidney transplant recipients?

CJASN
Clinical Journal of the American Society of Nephrology



Conclusions In this multicenter international cohort of kidney transplant recipients, cumulative incidence of recurrent IgA was 19% at 10 years, and 23% at 15 years after kidney transplantation.

Audrey Uffing, Maria José Pérez-Saéz, Thomas Jouve, et al. ***Recurrence of IgA after Kidney Transplantation in Adults***. CJASN doi: 10.2215/CJN.00910121.
Visual Abstract by Sinead Stoneman, MB BCh BAO, MRCPI

Clin J Am Soc Nephrol. 2021;16

IgAN & IgAV have good outcomes in pediatric age groups but have the propensity to progress into adulthood hence appropriate management is important to prevent long term consequences.....

THANK YOU