IgA Nephropathy

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Subjects:

- Epidemiology
- Classification of Immunoglobulin A Nephropathy
- Pathology
- Clinical Features and Natural History
- Treatment

Epidemiology:

IgA nephropathy remains one of, if not the, most common forms of glomerulonephritis, especially in developed countries with a low prevalence of infectious diseases.

Although it was previously considered a benign disease, it is now clear that up to 40% of patients may progress to ESKD.

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Classification of Immunoglobulin A Nephropathy:

Primary immunoglobulin A (IgA) nephropathy
Secondary IgA nephropathy: Associated disorders
- IgA vasculitis (formerly Henoch-Schönlein purpura)
- Human immunodeficiency virus infection
- Toxoplasmosis
- Seronegative spondyloarthropathy
- Celiac disease
- Dermatitis herpetiformis
- Crohn disease
- Liver disease
- Alcoholic cirrhosis
- Ankylosing spondylitis
- Reiter syndrome
- Neoplasia
- Mycosis fungoides
- Lung CA

Continue……..

Mucin-secreting CA
Cyclic neutropenia
Immunothrombocytopenia
Gluten-sensitive enteropathy
Scleritis
Sicca syndrome
Mastitis
Pulmonary hemosiderosis
Berger disease
Leprosy
Familial IgA nephropathy

Epidemiology:

- IgA nephropathy occurs in individuals of all ages, but it is still most common in the 2nd and 3rd decades of life and is much more common in males than females .
- IgA nephropathy is uncommon in children younger than 10 years of age.

- In fact, 80% of patients are between the ages of 16 and 35 years at the time of kidney biopsy.
- The male to female ratio has been described as any where from 2 : 1 to 6 : 1.781

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Genetics:

Polymorphisms in a number of genes, including those coding for:

- angiotensin
- angiotensin II receptor
- T cell receptor
- IL-1
- IL-6
- IL receptor antagonist, TGF, mannose-binding lectin
- Nitric oxide synthase, and TNF
- ACE

Pathology:

- Immunofluorescence Microscopy:
- IgA nephropathy can be definitively diagnosed only by the immuneohistologic demonstration of glomerular immune deposits that stain dominantly or co dominantly for IgA compared with IgG and IgM .
- The staining is usually exclusively or predominantly mesangial, although a minority of specimens, especially from patients with severe disease, will have substantial capillary wall staining.

- By definition, 100% of IgA nephropathy specimens stain for IgA. On a scale of 0 to 4+, the mean intensity of IgA staining is approximately 3+.

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- IgM staining is observed in 84% of specimens with a mean intensity (when present) of only approximately 1+.
- IgG staining is observed in 62% of specimens, also with a mean intensity (when present) of approximately 1+.
- Early studies of IgA nephropathy described more frequent and more intense IgG staining than is seen today, but this probably was caused by the use of less specific antibodies that cross-react between IgA and IgG.

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- Almost all IgA nephropathy specimens have substantial staining for C3.
- In contrast, staining for C1q is rare and weak when present.
- If there is intense staining in a specimen that shows substantial IgA and IgG, the possibility of lupus nephritis rather than IgA nephropathy should be considered.
- Distinctive feature of IgA nephropathy is that unlike any other glomerular immune complex disease, the immune deposits usually have more intense staining for (Lambda)light chains than kappa (κ) light chains.

Electron Microscopy:

- Finding is mesangial electron-dense deposits that correspond to the immune deposits seen by immune histologic analysis .
- The mesangial deposits often are immediately beneath the peri mesangial basement membrane.
- They are accompanied by varying degrees of mesangial matrix expansion and hypercellularity.

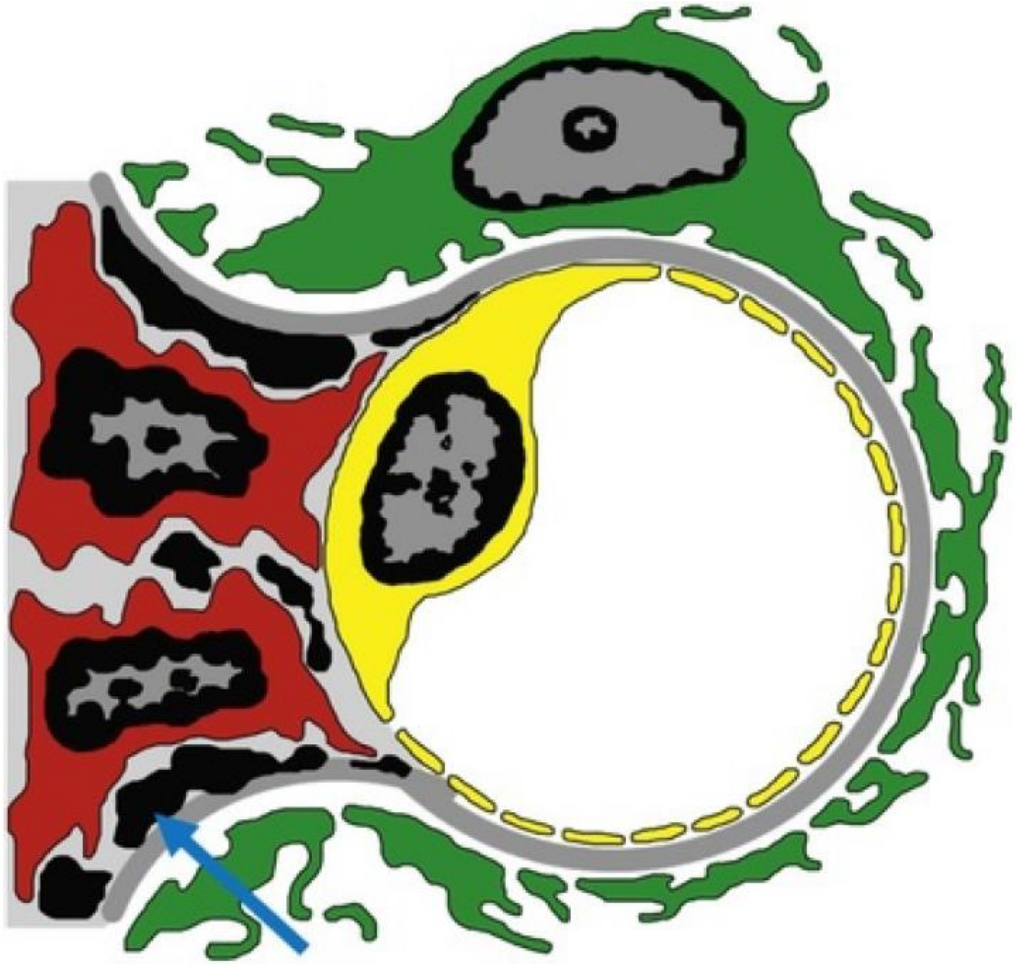
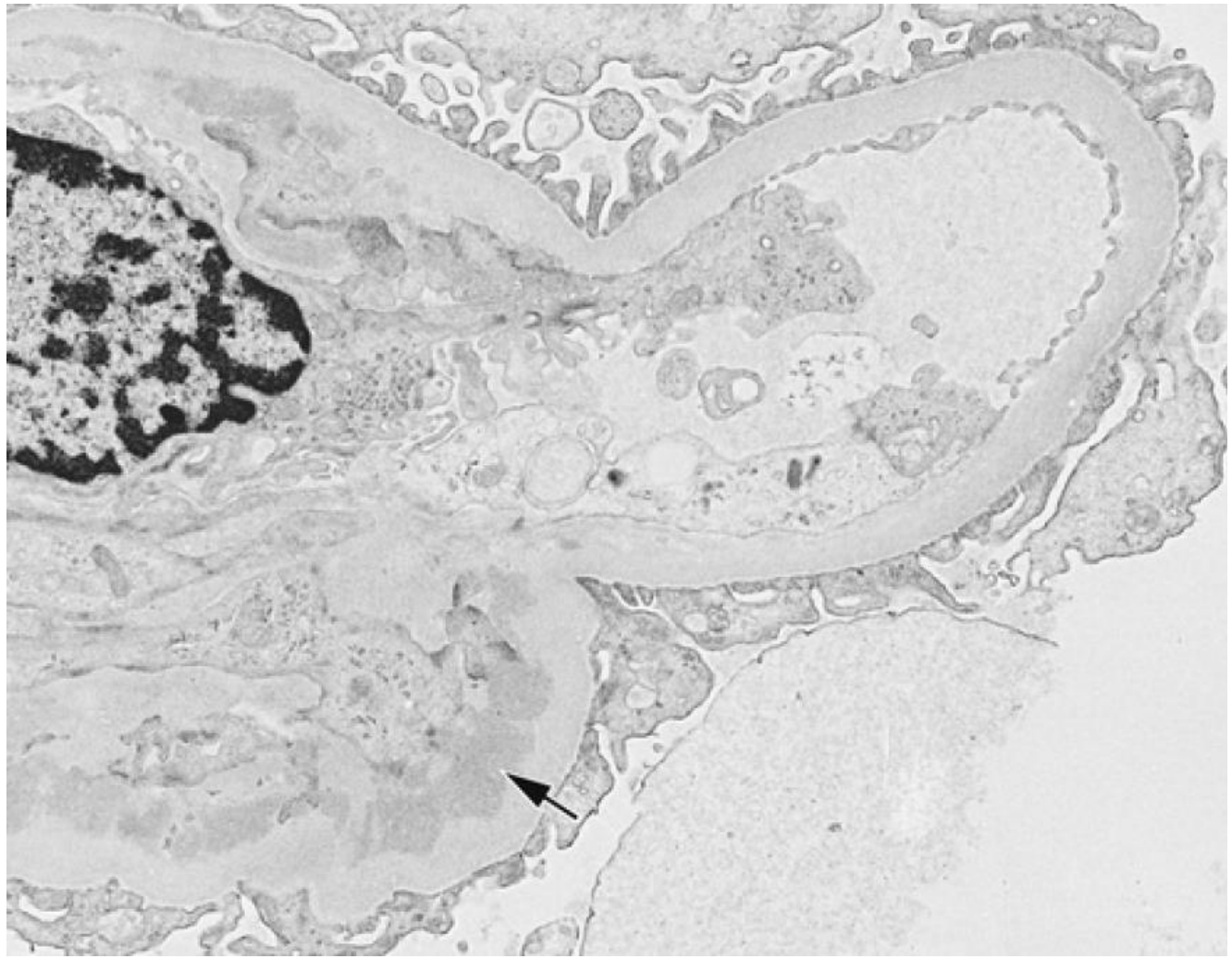


Diagram depicting the ultrastructural features of immunoglobulin A nephropathy.



Electron micrograph of a capillary and adjacent mesangium from a patient with immunoglobulin A nephropathy

Light Microscopy:

- At the time of biopsy, IgA nephropathy usually manifests as a focal or diffuse mesangio proliferative or proliferative glomerulonephritis,
- Although specimens from a few patients will have no lesion by light microscopy, those from a few will show aggressive disease with crescents, and occasional specimens will already demonstrate chronic sclerosing disease.

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“Oxford-MEST score”

Four parameters emerged as independently predictive of clinical out comes:

- Mesangial hypercellularity—score ≤ 0.5 = 0 or score >0.5 = 1
- Endocapillary hypercellularity—absent = 0 or present = 1
- Segmental glomerulosclerosis: absent = 0 or present = 1
- Tubular atrophy–interstitial fibrosis—percentage of cortical area ≤ 25% = 0, 26% to 50% = 1, or >50% = 2

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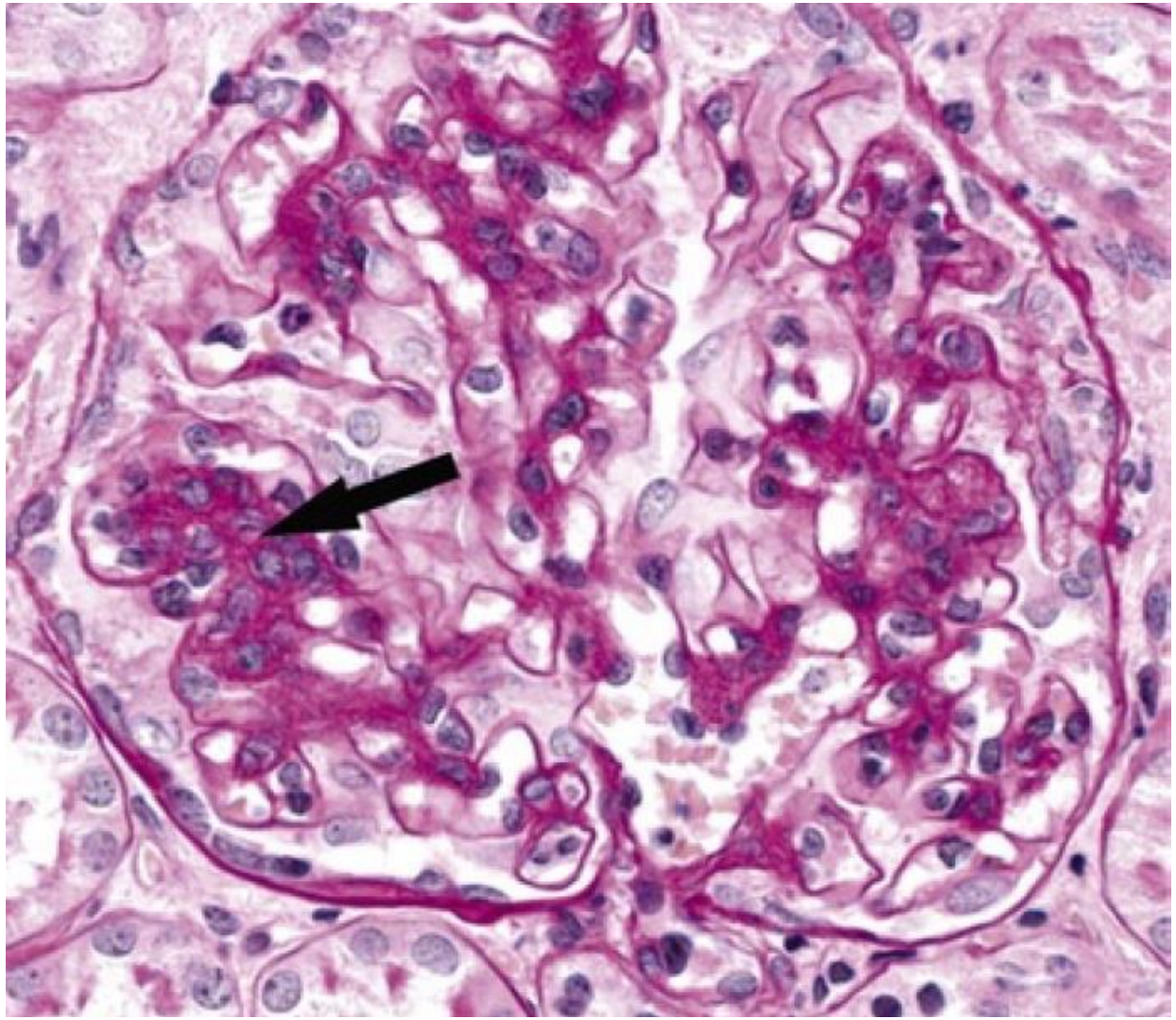

Light micrograph of a glomerulus with immunoglobulin A

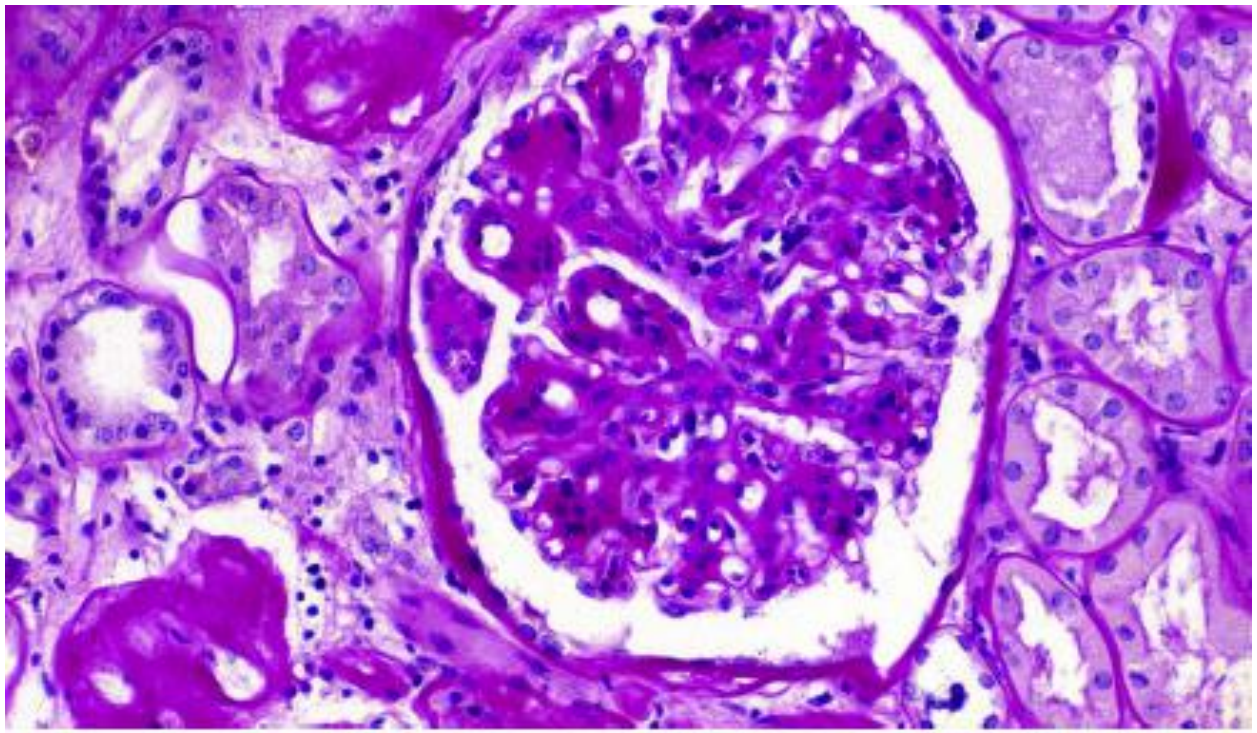

Figure 1. Immunoglobulin A nephropathy with moderat
ıesangial expansion and proliferation (periodic acid–Schi
tain). Reproduced with permission from *AJKD* 31(4):e1.

AJKD Atlas of Renal Pathology: IgA Nephropathy

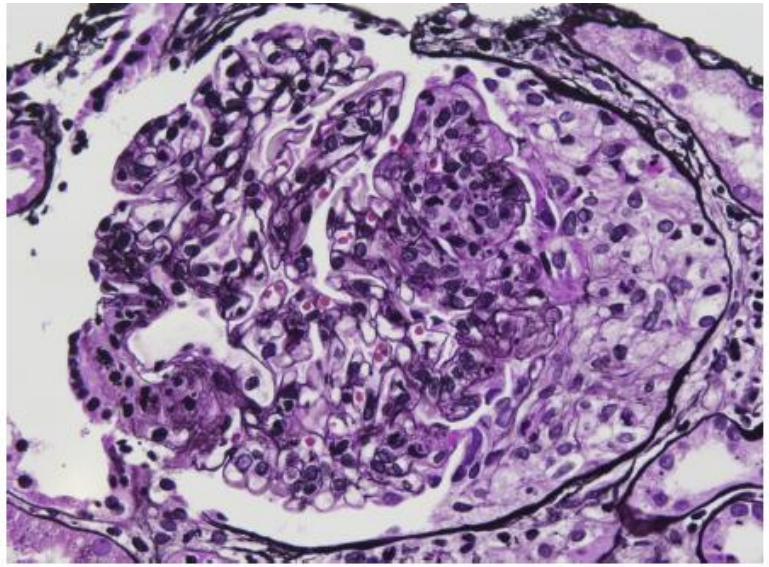

Figure 2. Immunoglobulin A nephropathy with endocapillary proliferation and cellular crescent formation (Jones silver stain).

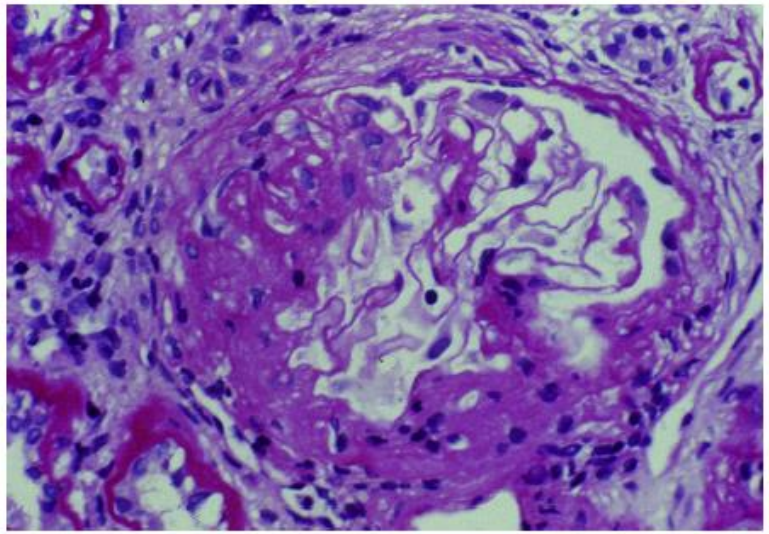

Figure 3. Immunoglobulin A nephropathy with segmental sclerosis (periodic acid–Schiff stain). Reproduced with permission from *AJKD* 31(4):e1.

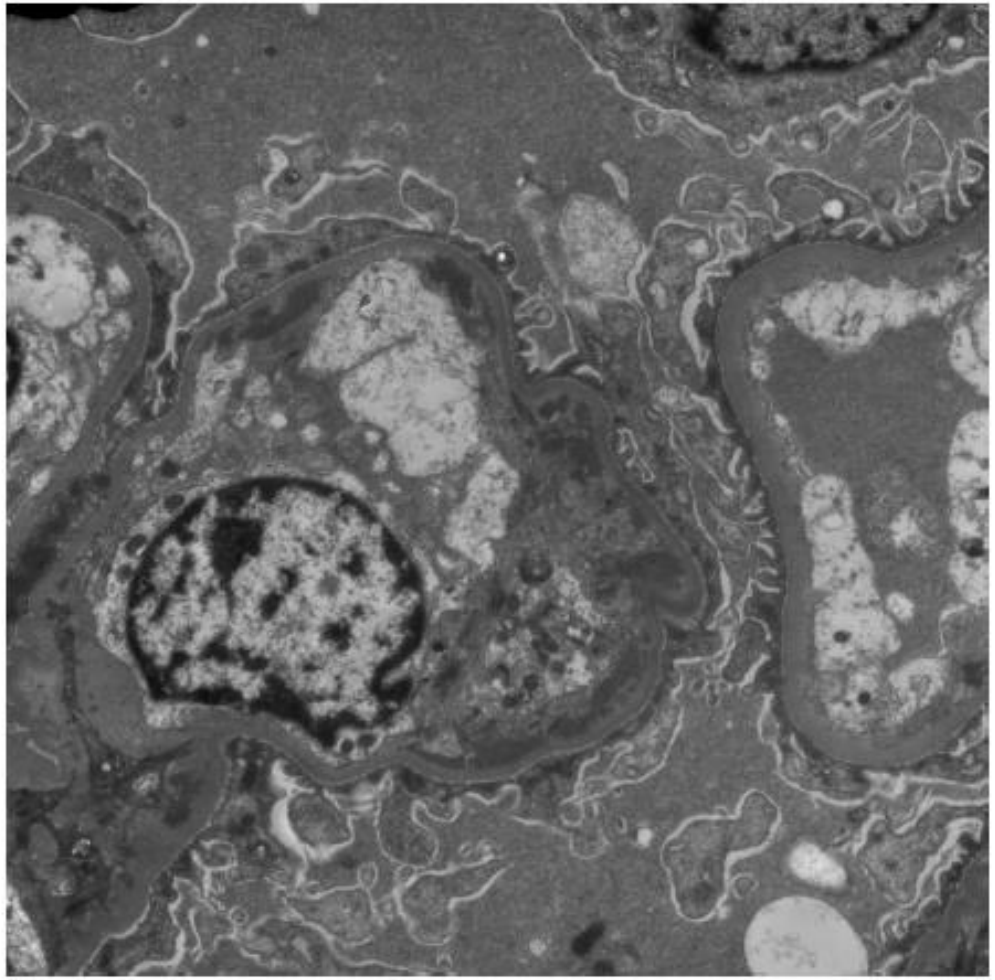

Figure 6. Subendothelial deposits in glomerular capillary walls can be seen in more active immunoglobulin A nephropathy (electron microscopy).

AJKD Atlas of Renal Pathology: IgA Nephropathy

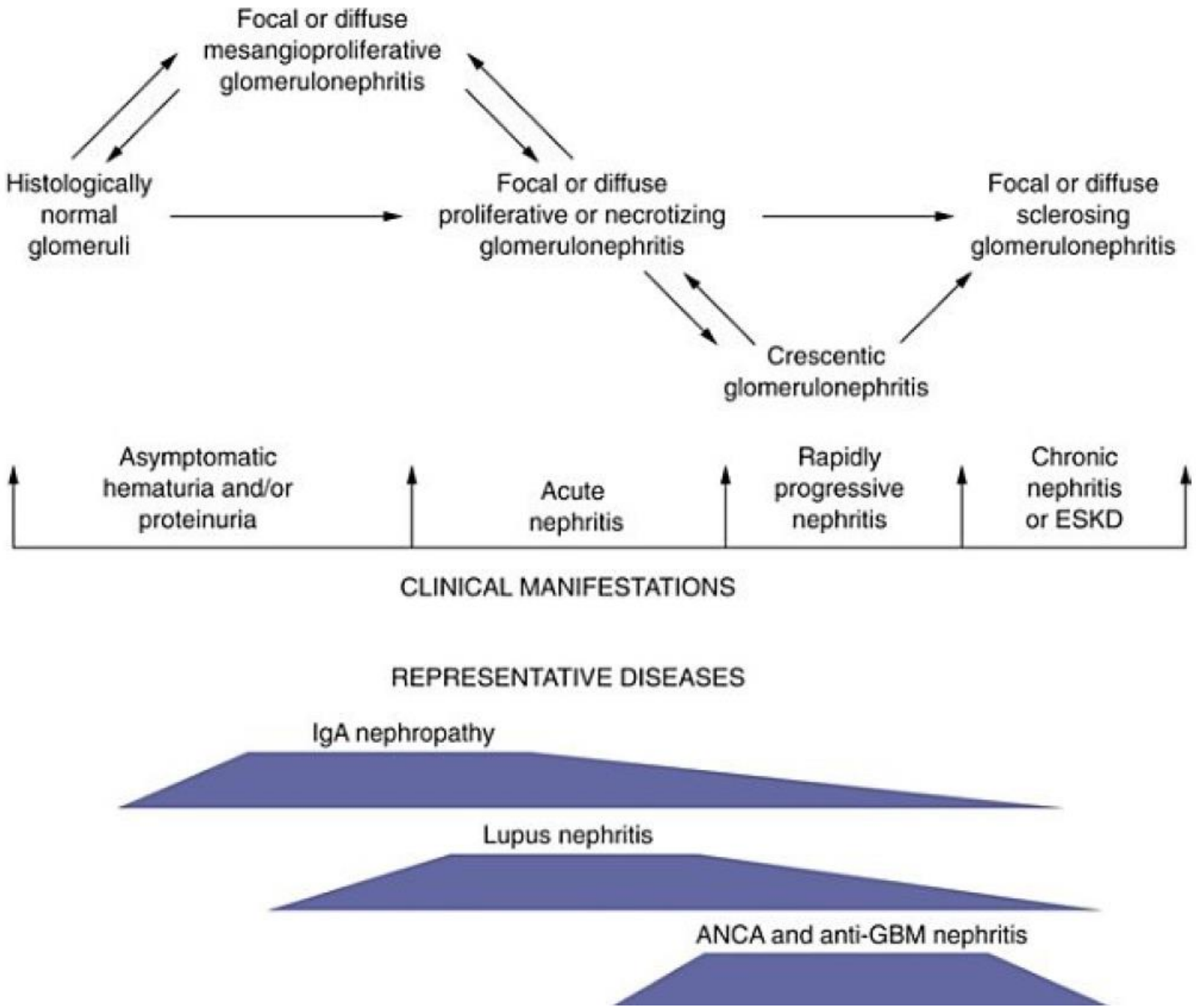

Diagram depicting the continuum of histological changes

FSGS:

- Occasional patients with IgA nephropathy will have focal glomerular sclerosis by light microscopy that is indistinguishable from FSGS until the IF microscopic findings are taken into consideration.

- Because of the episodic nature of IgA nephropathy, many patients have combinations of focal sclerotic lesions and focal active proliferative lesions.
- Patients with the most severe IgA nephropathy have crescent formation because of extensive disruption of capillaries.

Clinical Features and Natural History:

- Approximately 40% to 50% of these patients have macroscopic hematuria at the time of their initial presentation.
- The episodes tend to occur in close temporal relationship to upper respiratory infection, including tonsillitis and pharyngitis.
- This synchronous association of pharyngitis and macroscopic hematuria has been given the name syn pharyngitic nephritis.

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- Systemic symptoms are frequently found, including nonspecific symptoms such as malaise, fatigue, myalgia, and fever.
- patients have abdominal or flank pain.
- In a minority of patients (<5%), malignant hypertension may be an associated presenting feature.
- In the most severe cases (fewer than 10%), acute glomerulonephritis results in acute renal insufficiency.

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Macroscopic hematuria :

- Macroscopic hematuria due to IgA nephropathy occurs more often in children than in young adults.

- When it occurs in older individuals, it should raise the possibility of the more common causes of urinary tract bleeding, such as stones or malignancy.

Laboratory Findings:

- To date, there are no specific serologic or laboratory tests diagnostic of IgA nephropathy or IgA vasculitis.

The identification of abnormally galactosylated IgA1 has led to the development of a potential diagnostic test based on the detection of increased lectin binding in patients with IgA nephropathy.

Although the serum IgA levels are elevated in up to 50% of patients, the presence of elevated IgA in the circulation is not specific for IgA nephropathy.

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- A typical finding is microscopic hematuria on urinalysis that may persist, even at very low levels of macroscopic hematuria.
- The finding of dysmorphic erythrocytes in the urine is typical.
- Proteinuria is found in many patients with IgA nephropathy although, in most of them, protein excretion is less than 1 g/day.
- Mesangial and endocapillary hypercellularity, segmental glomerulosclerosis, and extra capillary proliferation are strongly associated with proteinuria.

Treatment:

Treatment is indicated for patients with urinary protein excretion of more than 0.5 g of protein/day.

- 1) RAAS blockade
- 2) oral and/or intravenous glucocorticoids
- 3) combined immunosuppressive (cytotoxic) therapy.

Angiotensin II Inhibition:

- Slower rate of loss of kidney function and a higher frequency of remission of proteinuria compared with either no therapy.
- High-dose ARB therapy was most efficacious in reducing proteinuria
- The current first line of treatment consists of escalating doses of an ARB to achieve a target urinary protein excretion of less than 1 g/day, along with dietary sodium restriction, for patients of any age with IgA nephropathy and proteinuria of more than 500 mg of protein excretion/day.

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Glucocorticoids:

- In summary, glucocorticoid therapy is a reasonable option for the treatment of patients with adverse prognostic features with well-preserved kidney function (GFR >60 mL/min/1.73 m2) who remain proteinuric despite a 3- to 6-month trial of angiotensin II inhibitors or patients with features of MCD and nephrotic syndrome.

Combinations of Angiotensin II Inhibition, Glucocorticoid Therapy, and Immuno supprression

- Aliskiren, a direct inhibitor of renin, has been investigated as an antiproteinuric agent in IgA nephropathy.
- In a 3-year prospective controlled trial of cyclophosphamide, dipyridamole, and low-dose warfarin, it was reasonably clear that this treatment has very little long-term benefit in patients with IgA nephropathy.
- Three randomized trials of MMF have shown conflicting results. beneficial effect of MMF on proteinuria and hyperlipidemia
- Long-term follow-up of this cohort suggested better preservation of kidney function in the MMF-treated group.

Omega-3 Fatty Acids:

- By inhibiting cytokines, leukotriene Br
- platelet activating factor formation
- fish oil may play a role in suppressing cell-mediated inflammation and limit glomerular injury

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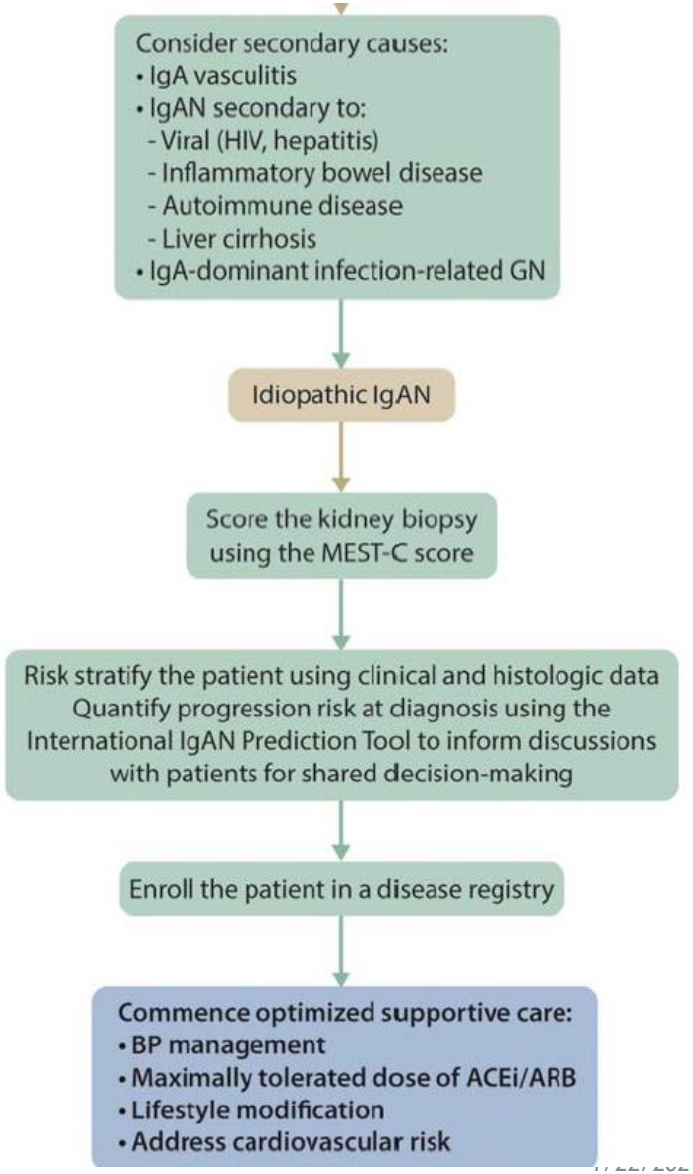
- Therefore, if omega-3 fatty acids should be used at all in the treatment of IgA nephropathy, they should be used adjunctively in combination with angiotensin II inhibition and not a monotherapy.

KDIGO 2021 CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF GLOMERULAR DISEASES

IgA Nephropathy :



Recommendation:

Recommendation 2.3.2: We recommend that all patients with proteinuria >0.5 g/d, irrespective of whether they have hypertension, be treated with either an ACEi or ARB *(1B)*.

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)*.

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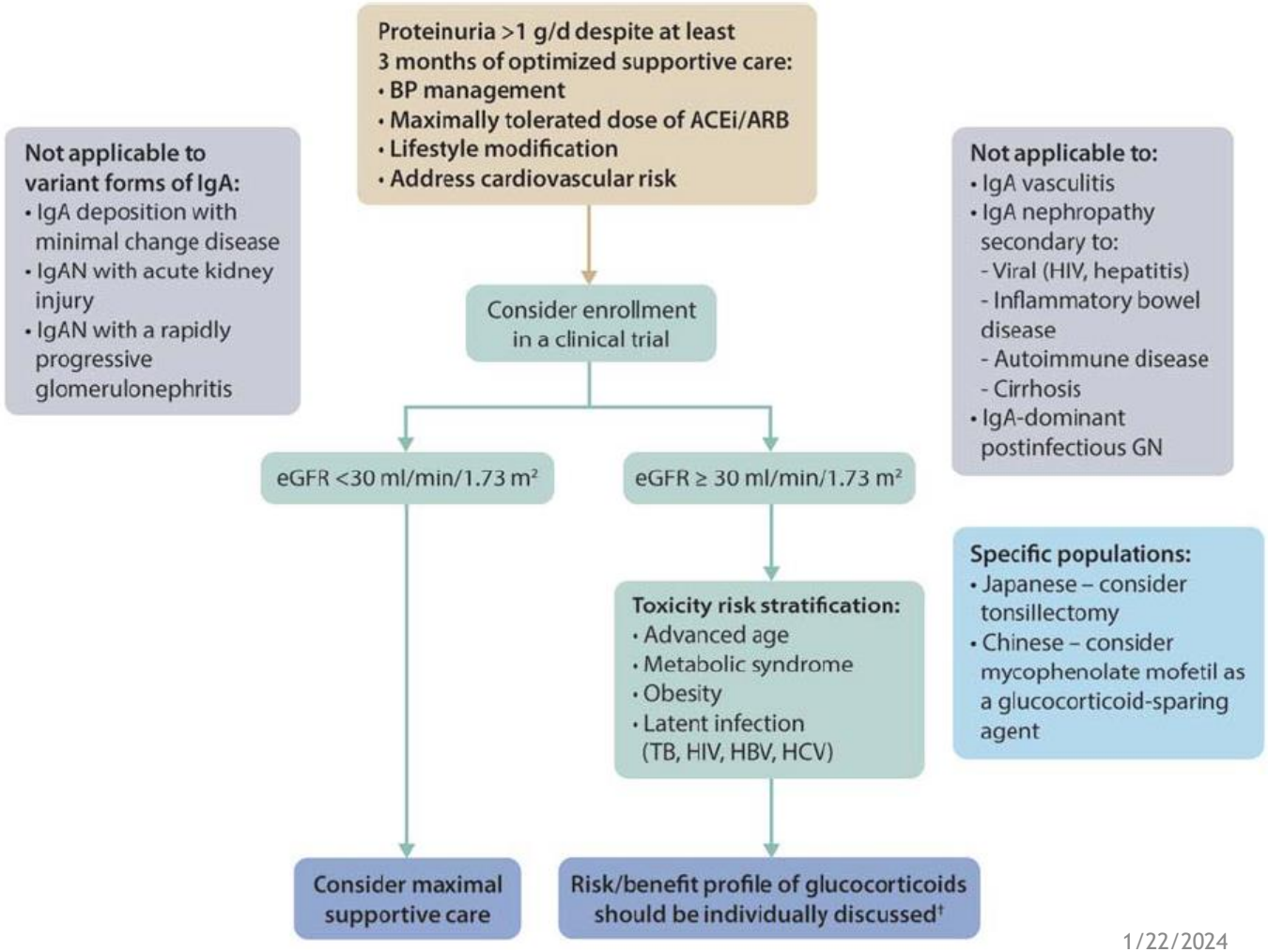
Clinical benefit of glucocorticoids in IgA N is not established and should be given with extreme caution:

eGFR <30 ml/min/1.73 m^2*
Diabetes
Obesity (BMI >30 kg/m^2)†
Latent infections (e.g., viral hepatitis, TB)
Secondary disease (e.g., cirrhosis)
Active peptic ulceration
Uncontrolled psychiatric illness
Severe osteoporosis

Practice Point 2.3.1.4: Management of patients with IgAN who remain at high risk for progression after maximal supportive care (Figure 24)



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 clinical 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-dose 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.

IgA nephropathy: the lectin pathway and implications for targeted therapy

OPEN

Jonathan Barratt[1], Richard A. Lafayette[2], Hong Zhang[3], Vladimir Tesar[4], Brad H. Rovin[5], James A. Tumlin[6], Heather N. Reich[7] and Jürgen Floege[8]

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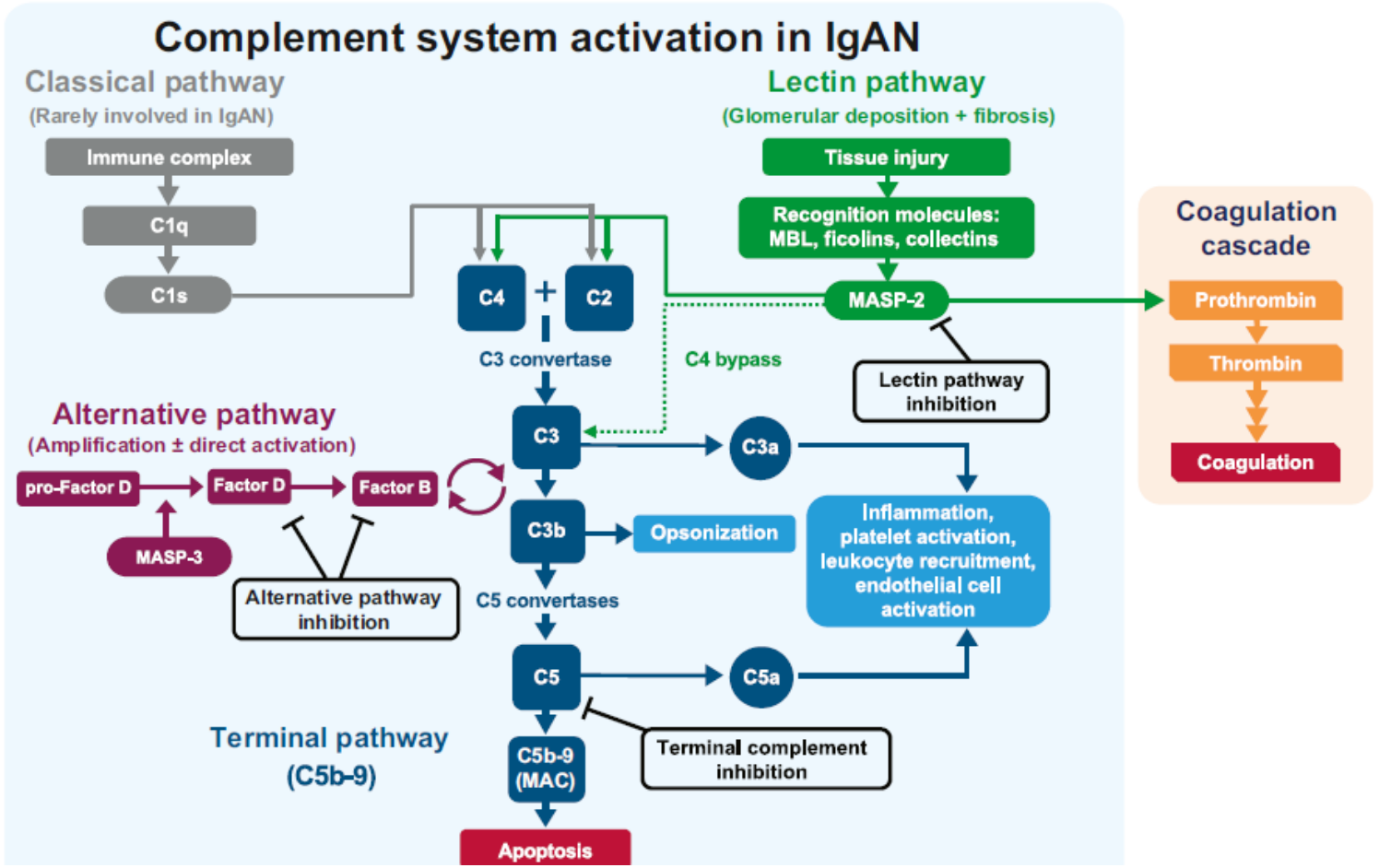
Many patients with immunoglobulin A nephropathy (IgAN) progress to kidney failure even with optimal supportive care. An improved understanding of the pathophysiology of IgAN in recent years has led to the investigation of targeted therapies with acceptable tolerability that may address the underlying causes of IgAN or the pathogenesis of kidney injury. The complement system—particularly the lectin and alternative pathways of complement—has emerged as a key mediator of kidney injury in IgAN and a possible target for investigational therapy. This review will focus on the lectin pathway. The examination of kidney biopsies has consistently shown glomerular deposition of mannan-binding lectin (1 of 6 pattern-recognition

Immunoglobulin A nephropathy (IgAN) is the most commonly occurring glomerular disease, and many patients progress to kidney failure even with optimal supportive care and currently available therapy.[1,2] Patients with IgAN and persistent proteinuria (>0.75 g/d) have a high risk of progressive loss of kidney function.[3] Systemic corticosteroids may temporarily slow the progression of kidney disease in these patients, but the data are not consistent and toxicity remains an issue.[3] When possible, patients with persistent proteinuria should be considered for participation in a clinical trial, in the hopes of discovering safer, effective therapy.[3] There is clearly an unmet medical need for additional treatment options to slow or even reverse the loss of kidney function. An


Complement system activation in IgAN
Classical pathway
(Rarely involved in IgAN)
Immune complex
C1q
C1s
Lectin pathway
(Glomerular deposition + fibrosis)
Tissue injury
Recognition molecules: MBL, ficolins, collectins
MASP-2
C4
C2
C3 convertase
C4 bypass
Lectin pathway inhibition
Coagulation cascade
Prothrombin
Thrombin
Coagulation
Alternative pathway
(Amplification ± direct activation)
pro-Factor D
Factor D
Factor B
MASP-3
Alternative pathway inhibition
C3
C3a
C3b
Opsonization
Inflammation, platelet activation, leukocyte recruitment, endothelial cell activation
C5 convertases
C5
C5a
Terminal pathway
(C5b-9)
C5b-9 (MAC)
Terminal complement inhibition
Apoptosis

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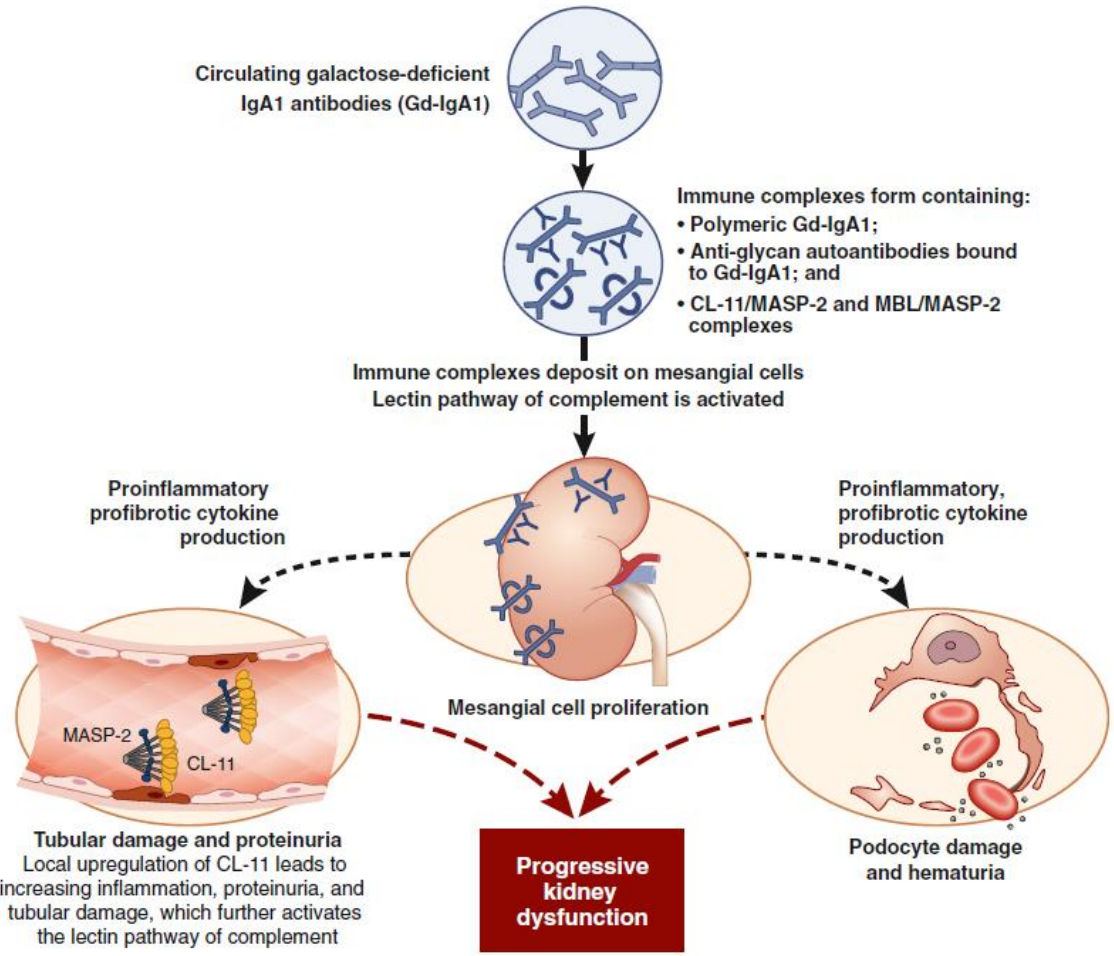

e 3 | Activation of the lectin pathway contributes to both tubular and podocyte damage in immunoglobulin A nephropa

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Targeting the alternative and lectin pathways in IgA N:

- The Factor B inhibitor iptacopan was well tolerated, strongly inhibited activity of the alternative pathway, and reduced proteinuria through 6 months in a phase 2 study.

- As discussed above, lectin pathway activation is not seen in all cases of IgA N, but it is associated with more severe disease progression. Given the role of MASP-2 activation of the lectin pathway
- in the pathophysiology of IgA N, the MASP-2 inhibitor, narsoplimab, is being assessed as a possible treatment for IgA N.

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REVIEW

Novel Treatment Paradigms: Primary IgA Nephropathy

Haresh Selvaskandan[1,2], Jonathan Barratt[1,2] and Chee Kay Cheung[1,2]

[1]Mayer IgA Nephropathy Laboratories, Department of Cardiovascular Sciences, University of Leicester, Leicester, UK; and [2]John Walls Renal Unit, University Hospitals of Leicester NHS Trust, Leicester, UK

IgA nephropathy (IgAN) is the most common primary glomerulonephritis worldwide. Approximately 30% to 45% of patients progress to kidney failure (KF) within 20 to 25 years of diagnosis, and there has long been a lack of effective treatments. The therapeutic landscape in IgAN is rapidly evolving, driven in large part by the acceptance of the surrogate clinical trial end point of proteinuria reduction by regulatory authorities for the accelerated approval of new therapies. Two drugs, targeted release formulation (TRF)-budesonide (nefecon) and sparsentan, have recently been approved under this scheme. Advancing insights into the pathophysiology of IgAN, including the roles of the mucosal immune system, B-cells, the complement system, and the endothelin system have driven development of therapies that target these factors. This review outlines current, recently approved, and emerging therapies for IgAN.

Kidney Int Rep (2023) ■, ■–■; https://doi.org/10.1016/j.ekir.2023.11.026
KEYWORDS: APRIL; BAFF; clinical trials; complement; endothelin; IgA nephropathy

First described in 1968, IgAN represents the most common primary glomerulonephritis worldwide.[1] Patients present with a wide spectrum of clinical manifestations, including isolated nonvisible hematuria, progressive chronic kidney disease (CKD), nephrotic syndrome, or rapidly progressive glomeru- progression of IgAN made clinical trials unattractive. In 2019, the Kidney Health Initiative performed an analysis of 13 controlled trials that demonstrated a clear association between an early treatment effect on proteinuria and a composite of time to doubling of serum creatinine, KF, and death.[12] Regulatory authorities now

Table 1. Parameters required by the international IgA nephropathy prediction tool to predict 50% decline in eGFR or kidney failure up to 80 months from biopsy

Parameters required by the IIgANPT
eGFR at biopsy
Systolic blood pressure at biopsy
Diastolic blood pressure at biopsy
Proteinuria at biopsy
Age at biopsy
Race
ACE inhibitor or ARB at biopsy
MEST score[a]
Immunosuppression at or prior to biopsy

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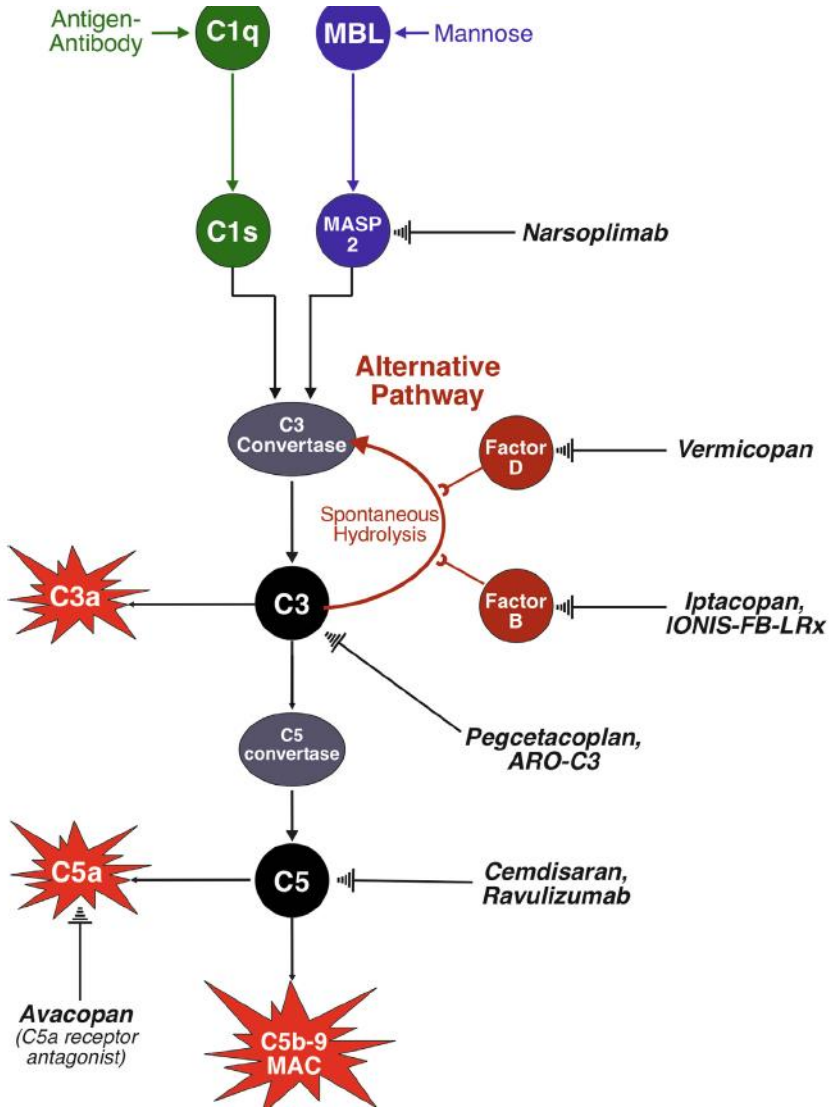
- Sodium-Glucose Co-Transporter-2 Inhibitors (SGLT2is)



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Review

Crescents and IgA Nephropathy: A Delicate Marriage

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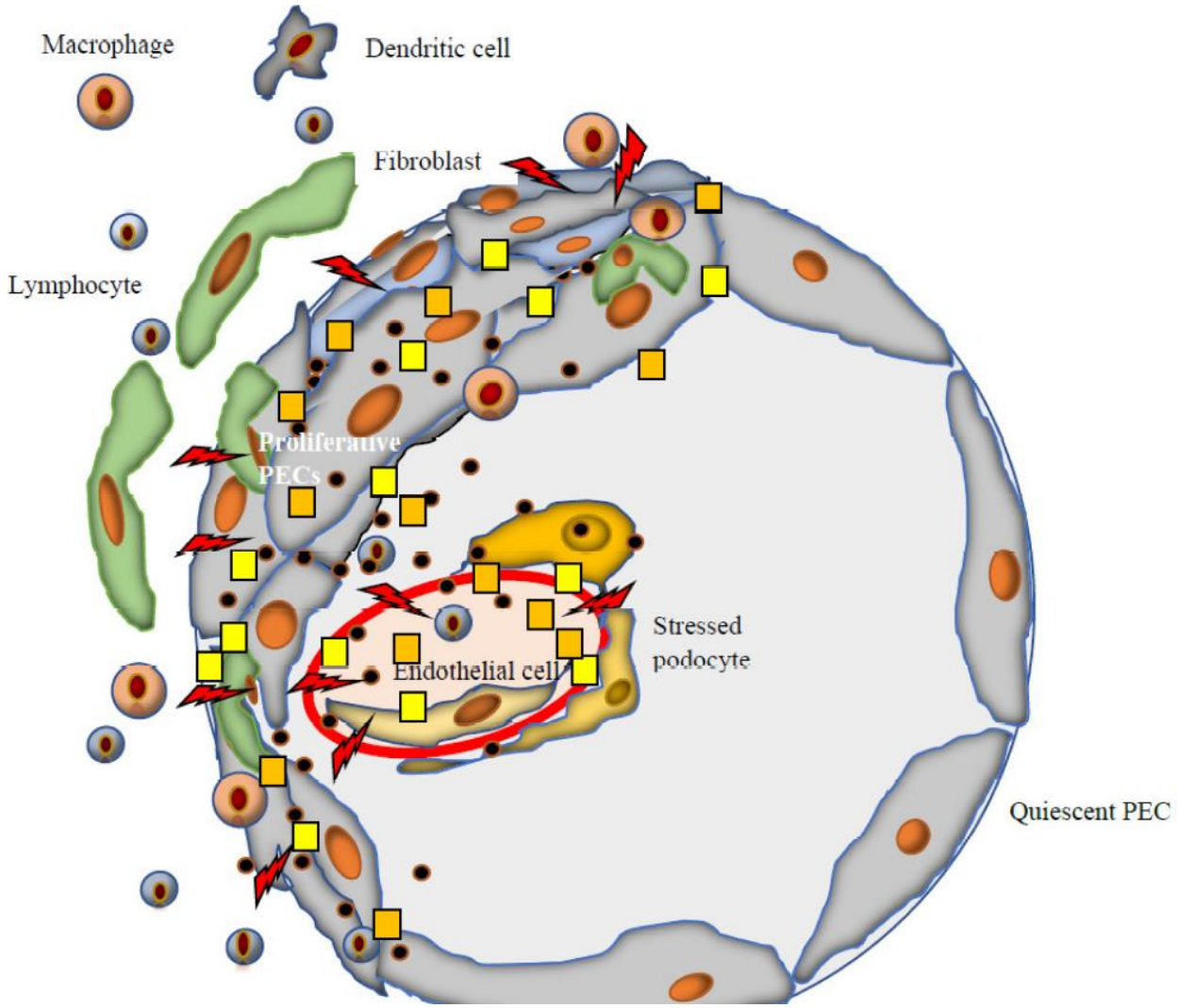
Abstract: IgA nephropathy (IgAN) is a progressive disease with great variability in the clinical course. Among the clinical and pathologic features contributing to variable outcomes, the presence of crescents has attracted particular interest as a distinct pathological feature associated with severity. Several uncontrolled observations have led to the general thought that the presence and extent of crescents was a prognostic indicator associated with poor outcomes. However, KDIGO 2021 guidelines concluded that either the presence or the relative number of crescents should not be used



journal/jcm2022/Hernán Trimarchi

Turning from MEST to MEST-C Score:

- A revised version of the Oxford classification for IgA nephropathy published in 2017 includes a C (crescent) score in addition to the original MEST scores:
- C0 (no cellular or fibrocellular crescents)
- C1 (crescents in <25% of glomeruli
- suggesting a poor prognosis in patients not receiving immunosuppressive therapy)
- C2 (crescents in≥ 25% of glomeruli)

Crescents and IgA Nephropathy/jcm2022

frontiers in Immunology

REVIEW
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Immunoglobulin A Nephropathy. Recurrence After Renal Transplantation

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IgA nephropathy (IgAN) is the most common primary glomerular disease worldwide. The disease generally runs an indolent course but may lead to ESRD in 20–30% of patients in 20 years or more after diagnosis. Patients with IgA nephropathy are ideal candidates for renal transplant because they are generally relatively young and with few comorbidities. Their graft survival is better or comparable to that of controls at 10 years, though few data are available after 10 years of follow-up. Recurrence of the original disease in the graft is a well-known complication of transplant in IgAN and is a significant cause of deterioration of graft function. Recurrent IgAN rarely manifests clinically before 3 years post transplantation. Recurrence rate is estimated to be around 30% with considerable

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Edited by:
Niels Olsen Saraiva Camara, University of São Paulo, Brazil

Reviewed by:
Viktoria Woronik,

HISTOLOGICAL FEATURES OF IgA N RECURRENCE :

- Some studies suggest that, the Oxford classification of histological features of IgA N in the native kidney, applied to biopsies of recurrent IgA N has prognostic value for graft failure

INCIDENCE OF IgA N RECURRENCE:

- The rate of graft loss due to recurrence is reported to range from 1.3 to 17%

PREDICTORS OF IgA N RECURRENCE:

- Young age at renal transplantation
- male gender
- rapidly progressive course of the original disease before transplantation
- This study demonstrated that normalized serum levels of galactose deficient -IgA1–specific IgG autoantibody was an independent risk factor for recurrence of the disease in the allograft.

TREATMENT OF GRAFT RECURRENCES

- suggested that steroid withdrawal may increase graft loss risk because of recurrence of IgA N.
- At present treatment should aim to reduce proteinuria, to optimize blood pressure and to reduce inflammation as suggested by the KDIGO Transplant guidelines.

- Studies from Japan report favorable outcomes after tonsillectomy in patients with recurrent IgA N.

https://doi.org/10.1186/s12882-019-1628-z

BMC Nephrology

RESEARCH ARTICLE Open Access

Graft failure of IgA nephropathy in renal allografts following living donor transplantation: predictive factor analysis of 102 biopsies

Jin Zhang[1†], Guo-dong Chen[2†], Jiang Qiu[2*], Guo-chang Liu[1], Li-zhong Chen[2], Kai Fu[1] and Zi-xuan Wu[2]

Abstract

Background: To investigate predictive factors related to graft failure of IgA nephropathy(IgAN) in renal allografts

Continue……

- IgA N is the most common de novo or recurrent nephropathy, especially in living donor transplantation
- occurs frequently within 5 years after transplantation.
- The color doppler ultrasound and blood flow imagine were valuable in diagnosing and evaluating the graft dysfunction.

- The risk of graft failure should be taken seriously in patients who exhibit heavy proteinuria (24-h urinary protein level > 2 g) and/or a declined eGFR as the initial symptoms, especially with hypoproteinemia, a high lesion grade (grade IV-V of Lee's classification) and/or mesangial C1q deposition.

Conclusions:

- Several factors may account for the variable results regarding the impact of crescents on clinical outcomes in IgA N.
- (a) the different patient ethnicities
- (b) different timing of the renal biopsy after onset of clinical manifestations
- (c) the histologic type of crescents included in each study, either cellular, fibrocellular, or fibrous

THANK YOU


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