IgA NEPHROPATHY

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- EDIPEMIOLOGY
- GENETICS
- PATHOGENESIS
- CILINICAL FEATURES AND NATURAL HISTORY
- LABORATORY FINDING
- PREGNANCY
- PROGNOSIS
- TREATMENT

- EPIDEMIOLOGY

- Most common forms of glomerulonephritis.
- Described by berger and hinglais.
- Asymptomatic hematuria to rapidly progressive glomerulonephritis.
- UP to 40% of patients may progress to ESRD.
- The primary and secondary forms.
- Most common in the 2nd and 3rd decades of life.
- Most common in males than females.
- *Brenner 2020*

Classification

Classification of Immunoglobulin A (IgA) Nephropathy	
Primary IgA Nephropathy (idiopathic)	
Secondary IgA Nephropathy *AssociatedDisorders*	
Henoch-Schönlein purpura Human immunodeficiency virus infection Toxoplasmosis Seronegative spondyloarthropathy Celiac disease Dermatitis herpetiformis Crohn's disease Liver disease Alcoholic cirrhosis	Neoplasia •Mycosi fungoides •Lung carcinoma •Mucin-secreting carcinoma Cyclic neutropenia Sicca syndrome Mastitis Leprosy Ankylosing spondylitis Reiter's syndrome
Familial IgA Nephropathy	

- GENETICS

- Multipel genes is combination with environmental factors.
- Polymorphisms in a number of genes, including those coding for ACE, angiotensin, angiotensin II receptor, T cell receptor, uteroglobin, nitric oxide synthase and TNF.
- Most transmission autosomal dominant.
- 4% to 14% cases have a family history of kidney disease.
- Polymorphisms of the genes for the enzymes responsible for glycosylation of IgA.
- *Brenner 2020*

- کدام یک از جملات زیر در مورد IgA نفروپاتی غلط است؟
- ۱) در دهه دوم و سوم زندگی شایع‌تر است.
- ۲) ۱۰ درصد بیماران به سمت ESRD پیشرفت می‌کنند.
- ۳) در آقایان شایع‌تر از خانم‌ها می‌باشد.
- ۴) بیشتر به فرم اتوزومال غالب به ارث می‌رسد

PATHOLOGY:

- Immunoflurescence microscopy:
- 100% of IgA nephropathy specimens stain for IgA.
- 84% of specimens for IgM and 62% for IgG staining.
- Almost all IgA nephropathy specimens staining for C3.
- Staining for C1q is rare and weak.
- Intense staining for IgA and IgG, the possibility of lupus nephritis rather than IgA nephropathy.
- *Brenner 2020*
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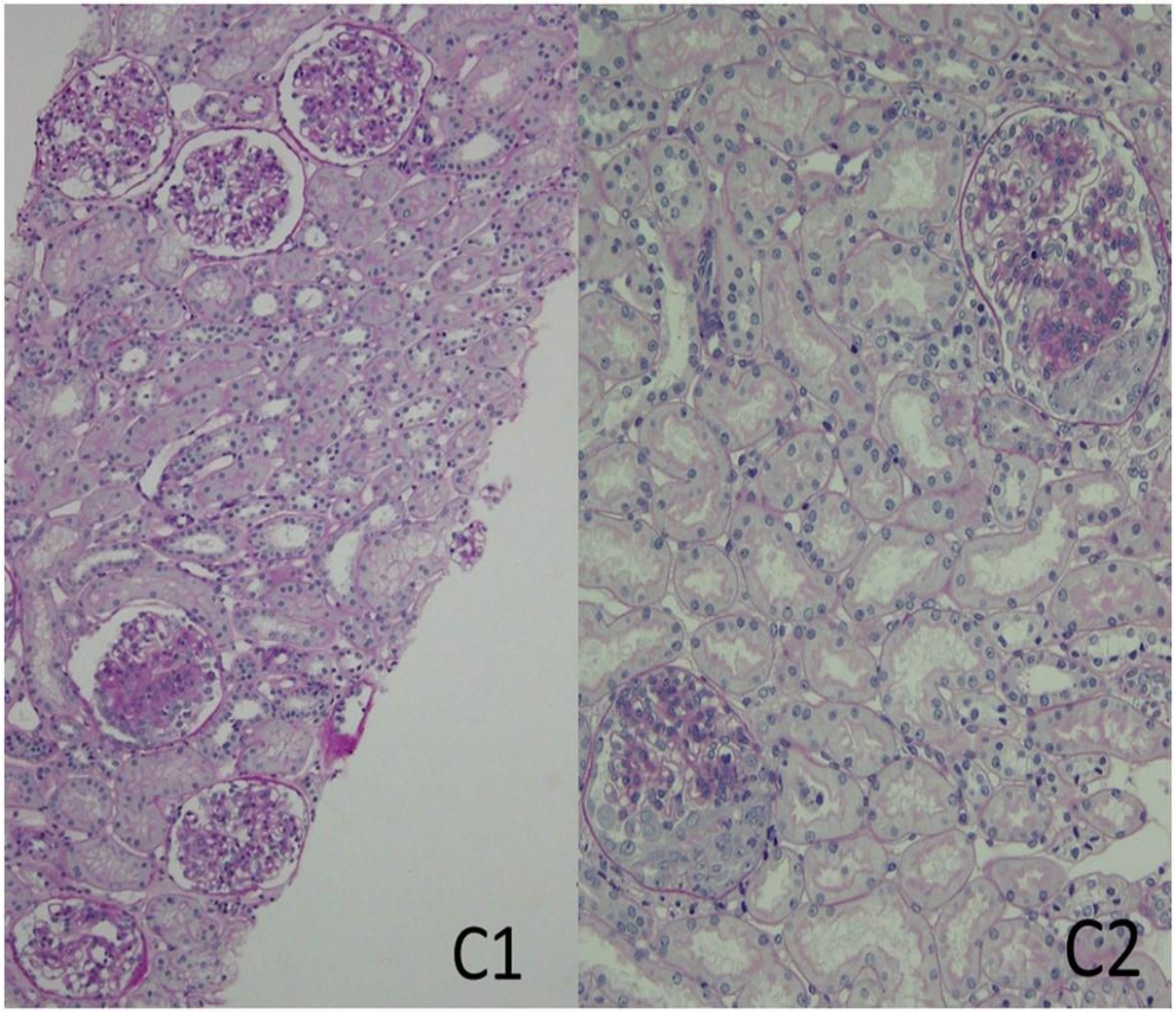
- Electron microscopy:
- The mesangial deposits the perimesangial basement membrane.
- Mesangial matrix expansion and hyper cellularity.
- Epithelial foot process effacement in patients with substantial proteinuria.
- *Brenner 2020*

- Light microscopy:
- Proliferative glomerulonephritis or no histologic changes.
- Althougth seen crescentic glomerulonephritis and glomerulosclerosing.
- Oxford-MEST score predictive of clinical outcomes.
- - Mesangial hyper cellularity – score $\leq$ 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 $\leq$ 25% = 0, 26% to 50% = 1 or > 50% = 2.

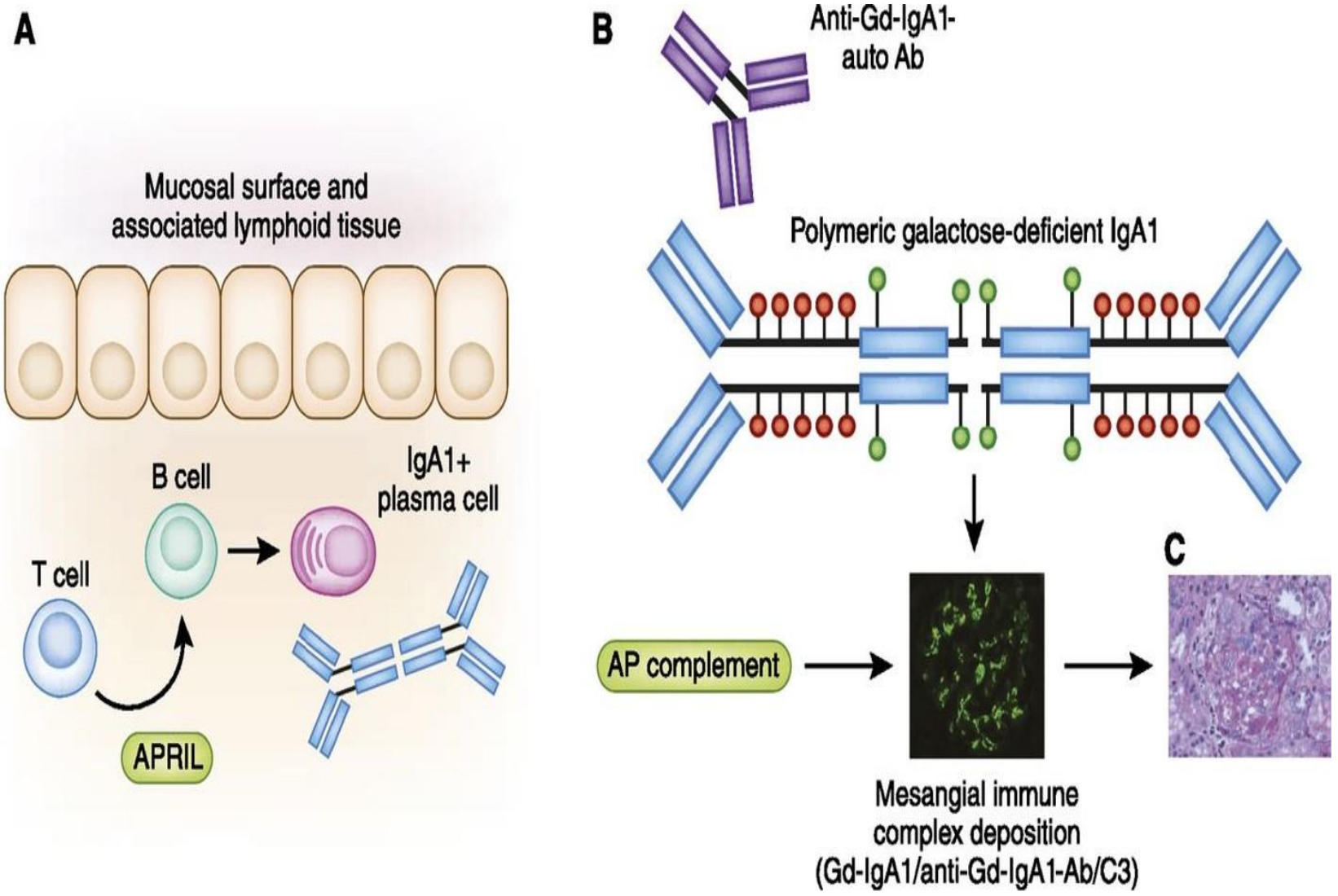
- in 2016 changing the MEST score to the MEST-C score (C for crescents)
- M, S, T and C associated with ESRD and not responsive to immunosuppressive therapy against E.
- *Brenner 2020*


C1
C2

- کدام یک از پاتولوژی‌های زیر در IgAنفروپاتی با پروگنوز مطلوب همراه است؟
- ۱) Mesangial hypercellularity
- ۲) Endocapillary hypercellularity
- ۳) Tubular atrophy
- ۴) Interstitial fibrosis

- PATHOGENESIS

- Patients with IgAN have increased circulating levels of galactose-deficient IgA_1.
- Antiglycan auto antibodies target Gd-IgA_1.
- Circulating immune complexes contain Gd-IgA_1.
- The Gd-IgA_1 – antiglycan IgG immune complexes deposit in the mesangium.
- *ajkd 2021*


A
Mucosal surface and
associated lymphoid tissue
B cell
IgA1+
plasma cell
T cell
APRIL
B
Anti-Gd-IgA1-
auto Ab
Polymeric galactose-deficient IgA1
C
AP complement
Mesangial immune
complex deposition
(Gd-IgA1/anti-Gd-IgA1-Ab/C3)

Clinical manifestations

- - Asymptomatic hematuria:
- The most common presentation of IgAN in adults.
- With varying degrees of proteinuria, with or without progressive kidney disease.
- Routin screening urinanalysis is not part of most health check guide lines.
- Urinary screening programs for school-age children in Japan, South Korea and Taiwan.
- Follow-up evaluation of individuals with abnormal urinanalysis is essential
- *ajkd 2021*

- - synpharyngitic macroscopic hematuria:
- Gross hematuria with upper respiratory tract infection or less commonly gastrointestinal tract infections.
- The 2-to-3 week gap between the onset of infection and gross hematuria.
- Occurs in only 10% to 15% of adult patients with IgAN.
- Most commonly in patients under 40 years old.
- Favorable prognosis but follow-up observation is required.
- *ajkd 2021*

- - rapidly progressive glomerulonephritis:
- RPGN by a ≥ 50% decline in eGFR over 3 month or less.
- Presentation during the course of IgAN or absence clinical features of IgA vasculitis.
- It is frequently associated of crescents in ≥ 50% glomeruli.
- Crescent are commonly observed in IgAN and not necessarily accompanied by RPGN.
- Presence of crescent does not use of immunotherapy in the absence of other high risk clinical features.
- RPGN portends a poor kidney prognosis.
- *ajkd 2021*

- Nephrotic syndrome

- Nephrotic syndrome is a rare presentation of IgAN.
- Patients clinical features of nephrotic syndrom who present with minimal change disease.
- Kidney biopsy demonstrates mesangial deposition of IgA and extensive foot process effacement.
- *ajkd 2021*

- Acute kidney injury in IgA nephropathy

- Decrease in kidney function in IgAN are usually chronically progressive.
- AKI in IgAN are 2 specific cause:
- 1) RPGN
- 2) Acute tubular injury from red blood cell cast obstruction and/ or heme toxicity.
- AKI not improvement with 1 to 2 weeks required kidney biopsy

- A cause of AKI and hematuria in IgAN anticoagulant related nephropathy.
- Patients with diabetes may present with AKI due to a PSGN dominated by IgA deposits.
- IgAN may occur in the context of systemic IgA vasculitis (Henoch – Schönlein purpura).
- *ajkd 2021*

LABORATORY FINDINGS

- There are no specific serologic or laboratory tests diagnostic of IgA nephropathy or IgA vasculitis.
- Presence of elevated IgA in the circulation is not specific for IgA nephropathy.
- Decreased C3 level and an elevated $^{\mathrm{IgA}}/_{\mathrm{C3}}$ ratio.
- Proteinuria is found in many patients with IgA nephropathy.
- *Brenner 2020*

PREGNANCY

- Women with IgA nephropathy tolerate pregnancy well.
- Only women with uncontrolled hypertension, eGFR of less than 70 $^{\mathrm{ml}}/_{\mathrm{min}}$, or severe arteriolar or interstitial damage on kidney biopsy are at risk for kidney dysfunction.
- Women with creatinine levels higher than 1/4 $^{\mathrm{mg}}/_{\mathrm{dl}}$ have increase in creatinine level during the course of Pregnancy, and pregnancy-related loss of maternal kidney function occurs in 43% of these patients.
- The infant survival rate was 93%, preterm delivery occurred in almost two-thirds and growth retardation in one-third of infants.
- *Brenner 2020*

PROGNOSIS

- Proteinuria is a dominant risk factor for disease progression in IgAN (above 1 $^{\mathrm{gr}}/_{\mathrm{day}}$).
- Decreased kidney function at presentation and hypertension are risk factors.
- Obesity and smoking contribute directly and indirectly to kidney risk.
- Presentation of macroscopic hematuria is a good prognosis.
- *ajkd 2021*

Prognostic Markers at Presentation in IgA Nephropathy

Clinical	Histopathologic
Poor Prognosis	
Hypertension	Mesangial hypercellularity
Renal impairment	Endocapillary proliferation
Severity of proteinuria	Segmental glomerulosclerosis
Hyperuricemia	Tubular atrophy
Gross obesity	Interstitial fibrosis
Duration of preceding symptoms	Capillary loop IgA deposits
Increasing age	Crescents (controversial)
Good Prognosis	
Recurrent macroscopic hematuria	
No Impact on Prognosis	
Gender	Intensity of IgA deposits
Serum IgA level	

- ایمنوگلوبولین شرکت کننده در کمپلکس ایمنی به همراه $Gd\text{-}IgA_1$در IgAN از چه کلاسی است؟
- ۱) IgM ۲) IgG ۳) IgA ۴) IgE

- TREATMENT

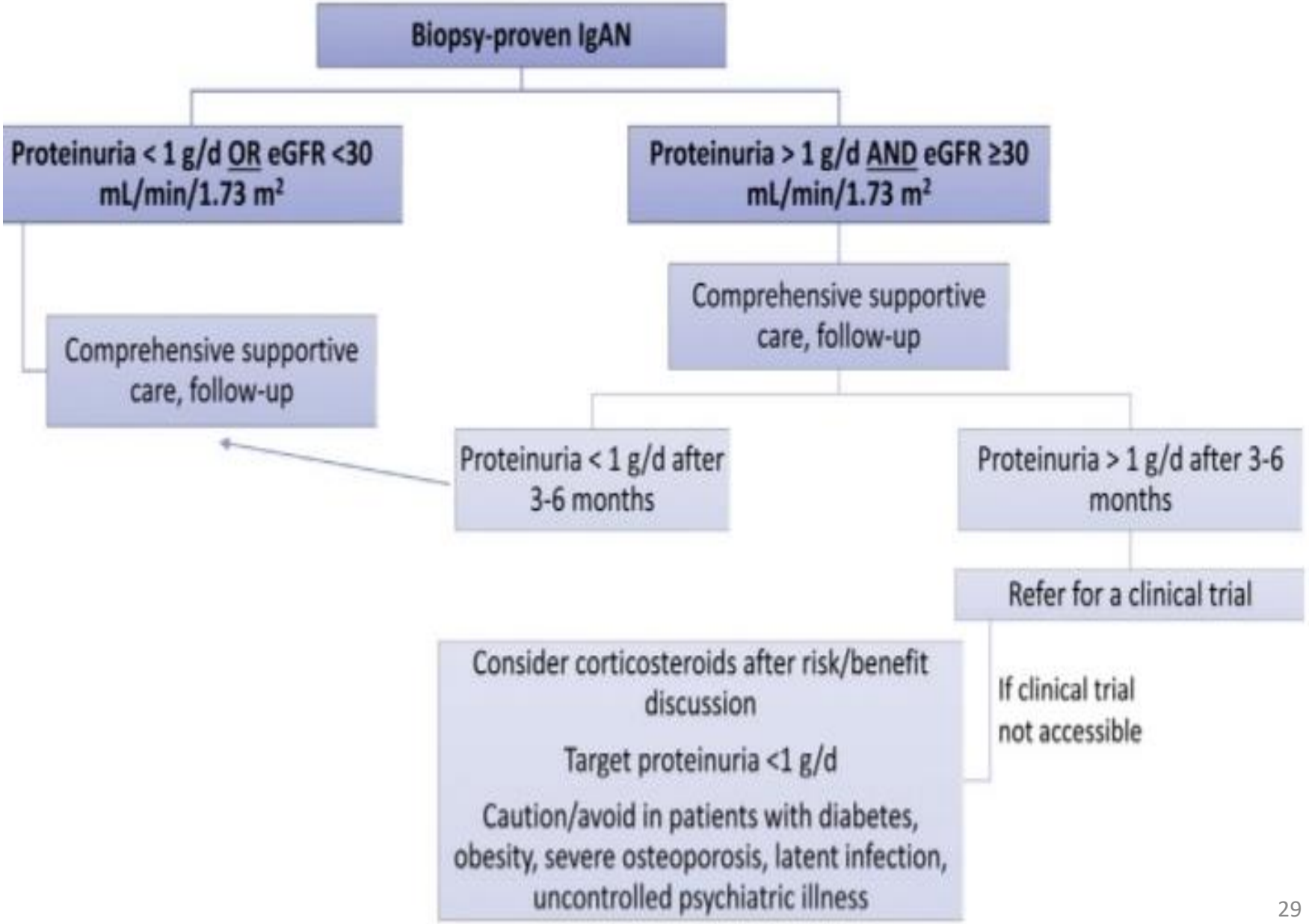
- **Conservative treatment**:
- Supportive care is particularly important in the management of IgAN.
- Supportive care is the first-line treatment in the absence of rapidly progressive decline of kidney function.
- Includes blood pressure control, use of RAS blockade, treatment of dyslipidemia, low-salt diet, weight reduction, smoking cessation and avoidance of nephrotoxic drugs.
- Use of RAS blockade effectively decrease the risk of kidney failure in proteinuric kidney disease.
- *ajkd 2021*

Box 1. Comprehensive Supportive Care in IgAN

- ACEI or ARB irrespective of whether patients have high blood pressure
  - ◇ Target: blood pressure 120/75 mm Hg and proteinuria <0.5 g/d
- Statin therapy if persistent hyperlipidemia
- Low-sodium diet (<2 g/d)
  - ◇ 24-hour urinary sodium excretion can be used to verify dietary consumption
- Advice on smoking cessation
- Avoidance of NSAIDs and other nephrotoxic drugs
- Target of healthy weight

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; IgAN, immunoglobulin A nephropathy; NSAIDs, nonsteroidal anti-inflammatory drugs.

- Immunosuppressive treatment:
- - Corticosteroids:
- Patients with persistent proteinuria of > 1 $^{\mathrm{gr}}/_{\mathrm{day}}$ despite at least 3 months of optimized supportive therapy including RAS blockade are considered to be at higher risk of progression.
- Corticosteroid is the only currently available immunosuppressive agent with evidence supporting it's efficacy.
- The 2012 KDIGO suggest a 6-month course of steroids therapy in patients who have over 1 $^{\mathrm{gr}}/_{\mathrm{day}}$ of proteinuria and eGFR > 50 $^{\mathrm{ml}/_{\mathrm{min}}}/_{1.73\ \mathrm{m}^2}$.
- ajkd 2021


Biopsy-proven IgAN
Proteinuria < 1 g/d OR eGFR <30 mL/min/1.73 m²
Proteinuria > 1 g/d AND eGFR ≥30 mL/min/1.73 m²
Comprehensive supportive care, follow-up
Comprehensive supportive care, follow-up
Proteinuria < 1 g/d after 3-6 months
Proteinuria > 1 g/d after 3-6 months
Refer for a clinical trial
Consider corticosteroids after risk/benefit discussion
Target proteinuria <1 g/d
Caution/avoid in patients with diabetes, obesity, severe osteoporosis, latent infection, uncontrolled psychiatric illness
If clinical trial not accessible

- - Immunosuppression beyond corticosteroids:
- KDIGO not using mycophenolate as a treatment for IgAN.
- There are recent data in Chinese population to support its use as a steroid sparing agent.
- Tonsillectomy not recommended but reduction in proteinuric and improved kidney survival in Japanese population.
- *ajkd 2021*

- **Experimental therapies**:
- - Targeted – release budesonide:
- A targeted – release formula of budesonide (Nefecon) was developed for use in IgAN.
- Release drug at the distal ileum where the largest site of Gd-IgA_1 secreting cells is located.
- Reduction in production of Gd-IgA_1 by mucosal – drived cells.
- *ajkd 2021*

- **Sparsentan:**
- A novel dual-acting angiotensin II and endothelin type A receptor antagonist.
- The anti proteinuric and renoprotective effects.
- In IgAN patients with eGFR $\geq$ 30 and proteinuria $\geq 1\ {}^{\mathrm{gr}}/_{\mathrm{day}}$.
- *ajkd 2021*
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- - **SGLT2 inhibitors**:
- The DIAMOND study of dapagliflozin.
- Included 53 patients with an average GFR 58 $^{\mathrm{ml}}/_{\mathrm{min}/_{1.73\ \mathrm{m}^2}}$, and proteinuria of 1.1 $^{\mathrm{gr}}/_{\mathrm{day}}$.
- Half had an underlying diagnosis of IgAN.
- Six weeks of treatment with dapagliflozin did not result in a reduction of proteinuria.
- But a reversible in measured GFR and favorable hemodynamic effects in diabetic nephropathy.
- Institution of this medication for instances where immunotherapy may not be appropriate or SGLT2 – inhibition with immunotherapy drugs potential for genitourinary infection complications.
- *ajkd 2021*

- **Fish oil**:
- There are conflicting data regarding the effectiveness of fish oil on slowing kidney disease progression.
- The total doses 3 to 12 $^{\mathrm{gr}}/_{\mathrm{day}}$ with eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA).
- The doses used in IgAN can be costly and not harmful.
- Therefore, to minimize medication burden prioritization of blood pressure control and institution od RAS blockade.
- *ajkd 2021*

- **Treatment of IgAN variants: nephrotic syndrome and rapidly progressive disease:**
- The 2012 KDIGO advised approaching the treatment of IgAN with overt nephrotic syndrome similarly to the treatment of minimal change nephropathy.
- corticosteroids were recommended, and a steroid – sparing regime is often required to maintain remission.
- In patients with RPGN, intravenous methylprednisolone followed by a combination of either oral or intravenous cyclophosphamide and corticosteroids as in ANCA – associated vasculitis.
- Plasmapheresis and rituximabe not recommended.
- *ajkd 2021*

- کدام یک از داروهای زیر در درمان IgAN جایگاهی ندارد؟

- ۱) پردنیزولون ۲) لوزارتان
- ۳) سیکلوسپورین ۴) سیکلوفسفامایید


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