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An Overview on Pathogenisis and Management of Iga Nephropathy

Shaik Shakeela, Guntur Venkata Srilekha, Vinjamuri Glory Nissy, Bandhamravuri Naga Sneha, Kotla Renuka Sai Priya
Assistant professor, Department of pharmacy practice, Hindu College of Pharmacy,

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ABSTRACT:
IgA Nephropathy is the most common primary glomerulonephritis, which is recognized by the deposition of mesangial IgA[1]. It is also called as Bergers disease. IgA is also called immunoglobulin A and nephropathy refers to the damage of glomeruli[2]. Worldwide 20-40% of the patients are developing end stage renal disease due to IgAN[1,3,4]. Studies found that proteinuria is the common symptom seen in asymptomatichaematuria [2]. The pathogenesis of IgAN has four steps called "four-hit hypothesis", this is used for the production of galactose deficient IgA1[3,4]. Diagnosis requires thrombotic microangiopathy, podocytopathy, C4 staining. On using of biomarkers, it is noted that proteinuria, hypertension and decreased GFR are the adverse outcomes of the patient. Modulation of renin angiotensin system in IgAN has shown disease progression in the patients along with-it sodium-glucose transporter 2 inhibition and endothelium-receptor antagonism shows effectiveness in patients[4,5]. Budesonide has been most effective drug, shows less severity in adverse effects and reversible[6].

INTRODUCTION:

The treatment of primary IgA nephropathy (IgAN) is undergoing rapid change, based on new insights and novel approaches to care. Science its description by Hinglais and Berger, IgAN became established as the most common form of primary glomerular disease worldwide. [7-9] Though heterogeneous, it is increasingly recognized as a major cause of progressive kidney dysfunction and failure, which occurs in 20%-50% of affected patients over 10to 20 years [9]. At highest risk are those with glomerular inflammation, interstitial fibrosis, increasing degrees of proteinuria, and kidney dysfunction [10].

The pathogenesis of IgAN has become clear over the decades as research findings accumulate. Pathophysiologic changes, commonly referred to as "hits"; to develop and progress the disease [11-13] Galactose deficient IgA (GD-IgA) is produced in the mucosa after stimulation by various antigens, including microbes such as bacteria. Individuals prone to IgA-directed auto-antibodies can be stimulated. This leads to circulating immune complexes containing the auto-antibody and the GD- IgA. Through specific and nonspecific interactions, these complexes accumulate in the glomerular mesangium. Once there, are able togenerate molecular and cellular response, including cytokine-,chemokine-, and complement-mediated cellular inflammation and injury[11-14] over time, this process can lead to the characteristic findings of haematuria and proteinuria, and also drives glomerular and tubulointerstitial sclerosis. Ultimately, kidney dysfunction and failure ensue.

Pathogenesis of IgA Nephropathy

IgA Nephropathy is a common cause of CKD and is characterized by the deposition of IgA1 immune complexes in the glomeruli.
The pathogenesis of IgA Nephropathy is described by the four-hit hypothesis:
Hit 1: Hereditary increase in galactose deficient circulation IgA1
Hit 2: Circulating antibodies directed against galactose deficient IgA1
Hit 3: Formation of pathogenic IgA1 containing immune complexes
Hit 4:mesangial deposition of IgA1 containing immune complexes, cell activation, and initiation of glomerular injury [17]

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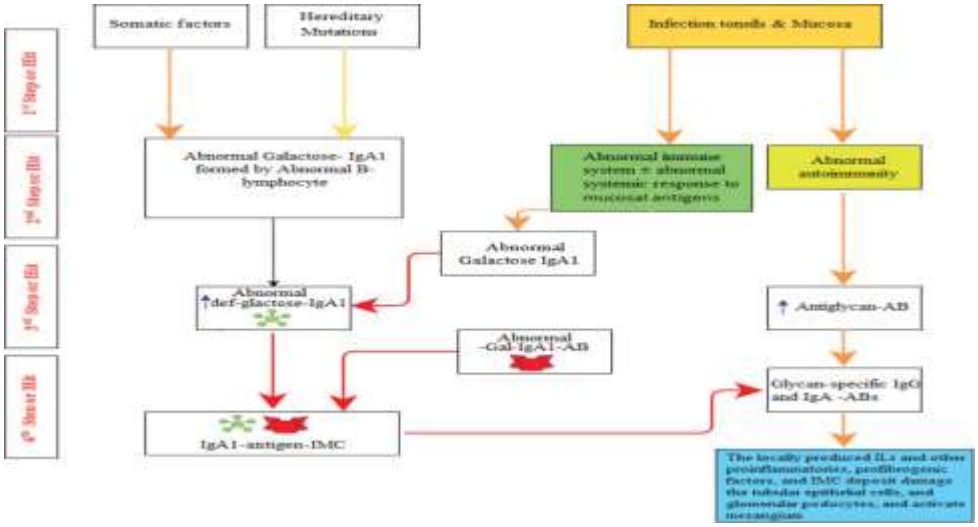

Fig:1

Hit 1:

1. As in the case for other immunoglobulins, IgA1 is glycosylated.
2. An altered pattern of its glycosylation has been recognised as a potentially pathogenic abnormality in IgA Nephropathy for nearly 20hrs
3. The key feature is the deficiency of galactose in the hinge region ofIgA, heavy chains. The hinge region of IgA, extends by 13 amino acids longer than hinge region of IgA2 and is found only in humans and higher primates.
4. Patients with IgA Nephropathy have increased circulating levels of IgA, with abbreviated glycans composed of n- acetyl galactosamine (Ga1NAc), with or without sialic acid, that are devoid of galactose moiety.
5. A Ga1NAc- specific lectin, helix aspersa agglutinin, is frequently used in an ELISA to measure the amount of galactose deficient IgA, after treatment of IgA1 with neuraminidase to remove terminal sialic acid.
6. In patients with IgA Nephropathy, the predominant sites where the cells secreting galactose deficient IgA, originate from and reside remain uncertain.
7. Circulatory IgA1 is produced mainly in bone marrow, whereas aberrantly glycosylated IgA1may be synthesized in response to mucosal infection, and thus abnormalities in the mucosal response to common microbial or food antigens may be involved in the production of galactose deficient IgA1
8. Serum levels of galactose deficient IgA1 are the 90th percentile for healthy controls in as many as 70 to 80% of IgA Nephropathy patients
9. Furthermore, 40to 50% of first-degree relatives of IgA Nephropathy patients have elevated levels comparable to that patient, demonstrating significant heritability of this trait.
10. GWAS data have identified a major locus on chromosome 22q12.2 influencing susceptibility to IgA Nephropathy
11. This locus is also associated with variation in serum IgA levels and has been previously associated with risk of inflammatory bowel disease, further implicating this interval in the regulation of mucosal inflammation
12. Two cytokine genes within the associated region,LIF and OSM, are excellent positional candidates, as both are expressed in B cells and may participate in the regulation of mucosal immunity
13. It is not yet known if this locus also influences aberrant IgA glycosylation[18]

Hit 2:

1. Aberrantly glycosylated IgA1 in the blood of patients with IgA Nephropathy is found nearly exclusively with immune complexes bound to IgG or IgA1 antibodies
2. The IgG auto antibodies exhibit unique features in the complementarily determining their heavy chains
3. Specifically, the third position in CDR3 is typically serine in patients with IgA Nephropathy, a feature necessary for efficient binding of the IgG to galactose deficient IgA1

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4. Importantly, serum levels of IgG antibodies specific for galactose deficient IgA1 correlated with disease severity, as assessed by the magnitude of proteinuria.
5. These antibodies are also present in sera of healthy individuals, albeit at lower levels
6. One can postulate that these antibodies are produced in response to bacterial or viral cell surface Ga1NAc containing glycol conjugates on commensal or infectious micro-organisms and then cross react with galactose deficient O linked glycans on IgA1
7. The strongest signals in the recent GWAS for IgA Nephropathy were localised within the MHC complex, a region highly associated with risk for many auto immune disorders

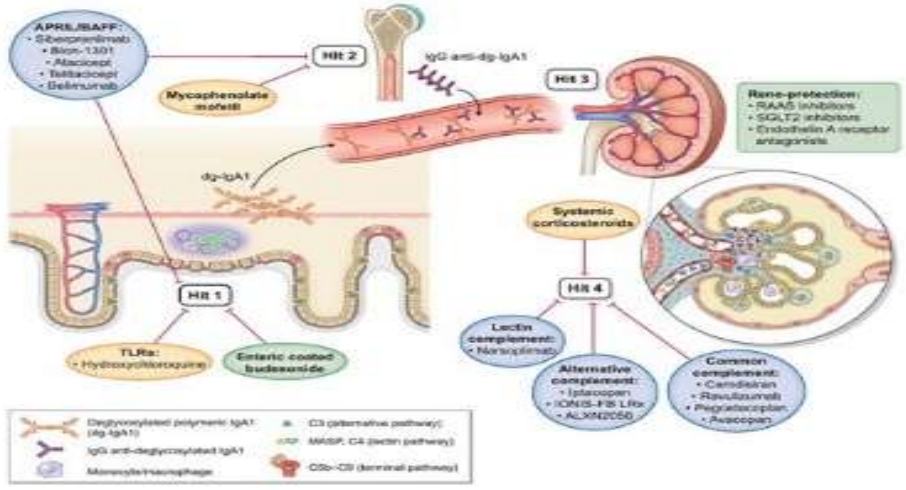

Fig 2(2)

8.
9. Thestrongest genetic effect was observed for the MHC11 locus containing the HLA-DQB1, DQA1 and DRB1 genes
10. This effect appeared to be conveyed by a highly protective haplotype DRB1*1502-DQA1*O1O2-DQB1*0602
11. Specifically, the DQB1*0602 allele reduced the odds of disease by over 50% per copy
12. This is a relatively common classical HLA allele, present in 10 to 20% of Europeans and 2 to 10% Asians
13. Taken together, these new genetic findings strongly implicate adaptative immunity in the pathogenesis of IgA Nephropathy and define the genetic context required of galactose deficient IgA1 as an antigen and for generation of pathogenic anti glycan anti bodies

Hit 3:

1. It is generally agreed that in IgA Nephropathy, the Mesangial cells represent the primary target of pathogenic deposits formed by circulating immune complexes or bylanthanic deposits of aberrantly glycosylated IgA1, followed by binding of newly generated anti glycan antibodies to form immune complexes and insitu.
2. The presence of circulating IgA1 containing immune complexes is not unique to patients with IgA Nephropathy
3. Such complexes can be detected in persons without apparent renal disease, including healthy individuals and patients with Heno-Schoenleinpurpura without nephritis
4. The complexes in patients with Heno-Schoenleinpurpura without nephritis consist of IgA, but not IgG, and are of smaller mass than complexes found in patients with IgA Nephropathy
5. By analogy with other human disease caused by immune complexes, it is likely that, in IgA Nephropathy, the molecular proportion of antigens and antibodies determines the size of the formed immune complexes and consequently, their rate of removal from the circulation as well as biologic activity
6. The pathogenic Circulating IgA1 –IgG immune complexes in patients with IgA Nephropathy are relatively large (>800kd) and thus may be excluded from entry into the

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hepatic space of disse to reach the as aloglycoprotein receptor (ASGP-R) on hepatocytes, the normal catabolic pathway for circulatory IgA1
7. As a result, these immune complexes enter the renal circulation
8. While it is not completely understood that determines the entry of circulating immune complexes into the mesangium, the factors involved likely include the size of immune complexes, their amount and local hemodynamic factors
9. The biologic activity of large circulating immune complexes with galactose deficient IgA1 increasing in IgA Nephropathy patients during episodes of macroscopic haematuria
10. However, it is not known whether this increase in activity is due to Greater production of galactose deficient IgA1, antiglycan anti bodies, or other undefined factors influencing the formation of these complexes and/or their composition
11. MHC risk alleles may participate in this step by influencing the efficiency of antigens presentation, recognition and processing and subsequent activation of auto reactive B cells

Hit-4:

1. The pathogenic importance of immune complexes has been shown by invitro studies
2. The glomerular injury of IgA Nephropathy histologically manifests as proliferation of Mesangial ells andexpansion of extra cellular matrix components
3. Immune complexes from patients with IgA1 bind to cells more effectively than do uncomolexedIgA1orimmune complexes from healthy controls
4. Complexes with galactose deficient IgA1 induce cultured human mesangial cells to proliferate, secrete extra cellular matrix components, and release humoral factors such as TNF- alpha,IL-6 and TGF beta
5. These factors can inturn, alter podocyte gene expression and glomerular permeability
6. The cellular receptors on Mesangial cells involved in the binding of IgA1 are not well characterised
7. IgA1 containing complexes display a high affinity for the extra cellular matrix components fibronectin and type IV collagen in the mesangium, and preferentially bind and activate Mesangial cells
8. Moreover, CD71 on human Mesangial cells effectively binds immune complexes containing galactose deficient IgA1, leading to enhanced expression of CD71
9. Activation of complement system in glomeruli augments the inflammatory cascade and potentiates tissue injury in IgA1 Nephropathy
10. The immune complexes with IgA1 can activate compliment via the alternative or lectin pathway
11. Our recent GWAS identified a major IgA Nephropathy susceptibility locus within the complement factor H gene (CFH) cluster on chromosome 1q32
12. Products of CHF and it's neighbouring CFHR (CFH related) genes participate in the modulation pf the alternative pathway by binding c3a and c5a convertase
13. Mutations in CFH lead to uncontrolled activation of alternative pathway and cause inherited forms of membrano proliferative glomerulonephritis type II, a disease pathologically distinct from IgA Nephropathy
14. However, carriers of a common deletion encompassing the neighbouring CFHR1 and CFHR3 genes had an approximately 30% decreased risk of developing IgA Nephropathy
15. The risk was almost 60% lower in the rare individuals who carry two copies of this deletion
16. Based on early experimental data, however, CFHR1 and CFHR3, the key activator of the terminal portion of the complement pathway
17. Therefore, a relative loss of CFHR1 and CFHR3 may enhance the inhibitory action of CHF and thus convey protection against local inflammation
18. These mechanistic issues have important clinical and therapeutic implications because sub clinical findings consistent with IgA Nephropathy [19]

MANAGEMENT OF IgA NEPHOPATHY:

The management of IgA nephropathy involves non immunosuppression therapy and immunosuppression therapy

1] NON IMMUNOSUPRESSION THERAPY:
A] Conservative Strategies that may reduce disease progression include Life style modifications
Sodium intake of less than 2g/day,
Low protein diet
Weight management,
Smoking cessation,
Regular physical activity
Fluid management
Lipid management

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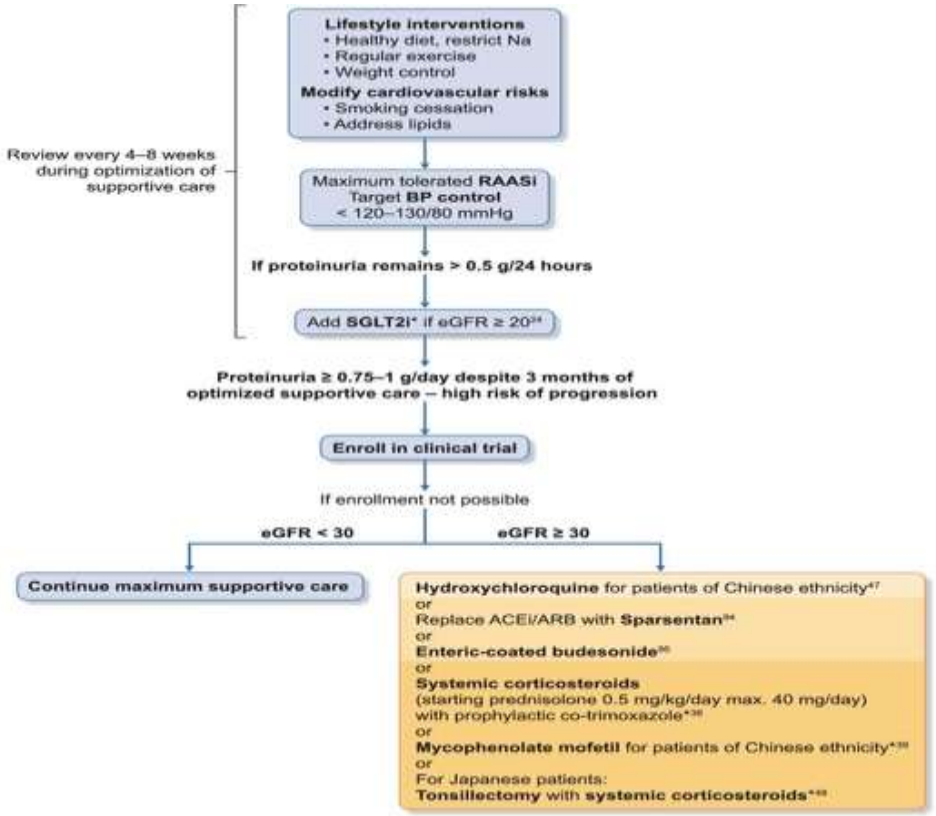
Avoidance of nonsteroidal anti-inflammatory medications.

B] SUPPORTIVE STRATEGIES:using maximal renin- angiotensin system[ras] blockade with angiotensin- converting enzyme inhibitors or inhibitors or angiotensin receptor blockers.
Blood pressure control-

a) ACE INHIBITORS:drugs like lisinopril, enalapril, captopril to reduce blood pressure and proteinuria
b) Angiotensin receptor blockers: (arbs) drugs like losartan, valsartan, candesartan to reduce blood pressure and proteinuria
c) Diuretics: drugs like furosemide or spironolactone to reduce fluid overload and blood pressure



Sodium-glucose cotransporter-2 inhibitors

Sodium-glucose cotransporter-2 inhibitors (SGLT2 inhibitors) have shown promising results in patients with CKD,
It is a class of oral hypoglycaemic agents used to treat type2 diabetic mellitus
They work by inhibiting the SGLT2 protein in the kidneys which reduces glucose excretion in the urine

Sparsentan

Sparsentan is an oral dual endothelin and angiotensin II receptor antagonist that was recently approved by the Food and Drug Administration (FDA) for high-risk IgANpatients.
The urine protein-to-creatinine ratio (UPCR) decreased by 49.8% (mean percentage decrease from baseline) in the sparsentan group compared with 15.1% in the irbesartan group at 36 weeks(between-group relative reduction of 41%, $p<0.0001$).

Adverse events- hypotension, dizziness, headache, fatigue.
Hydroxychloroquine: hcq is an antimalaria medication that has been used to treat various autoimmune disease. It resuses the inflammation and proteinuria in IgA nephropathy
It also modulates the immune system, reducing the producing of IgA antibodies
Dosage: typical dose of hcq for IgA nephropathy is 200-400mg/dl for to 7 months side effects include: git upset, nausea, vomiting and diarrhoea

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2] Immunosuppressant therapy:
Mycophenolatemofetil supresses T and B lymphocyte proliferation, reducing antibody synthesis, cytotoxic t cell formulation, and leukocyte migration to inflammatory areas.
Azathioprine and cyclophosamide also supress immune system and reduce IgA deposition

Table 1:
Drug therapies commonly used and/or approved for the treatment of primary IgAN.

Drug	Dose	Marker of response	Precaution	Toxicity
RAASi	ACEi:e.g. enalapril 5 mg OD PO up titrated to 40 mg/day as tolerated. ARB: e.g. valsartan 80 mg OD PO up titrated to 160 mg/day as tolerated	Reduction in proteinuria reduction in BP reduced eGFR slope	Hold during acute illness (e.g. dehydration, infection) check for a rise in serum creatinine>30% or hyperkalaemia.	Hyperkalaemia hypotension AKI (e.g. in setting of bilateral renal artery stenosis, volume depletion, sepsis)
SGLT2i	Dapagliflozin 10 mg OD PO (DAPA-CKD) (23) Empaglifozin 10 mg od po (EMPA-Kidney) (24)	Reduction in proteinuria reduction in BP reduced eGFR slope	Hold during acute illness (e.g. dehydration, infection) caution in patients with history of UTI	Genital fungal infection urinary tract infection glycaemic diabetic ketoacidosis
Dual ERA/ARB	Sparsentan 200mg OD PO uptitrated to 400 mg OD PO as tolerated stop other ACEi/ARB	Reduction in BP reduction in proteinuria	Hold during acute illness (e.g. dehydration, infection) check for a rise in sr.cr .30% or hyperkalemia 7-10 days after starting	Hyperkalemia Hypotension AKI (e.g. in setting of bilateral renal artery artery stenosis, volume depletion, sepsis) Oedema
Systemic cortico steroids	Methylprednisolone PO 0.4 mg/kg/day max 32 mg/kg/day for 2 months followed by 4 mg/day taper each month for total 6-9 months (TESTIN G-2 protocol) (36) (or prednisolone equivalent)	Reduction in proteinuria resolution of haematuria reduced eGFR slope	Prevalent chronic infections (e.g. TB, HBV) prior to initiation cautious use in patients with obesity	Glucose intolerance/DM Opportunistic infection weight gain osteoporosis/avascular necrosis Acne altered appearance (stretch marks/buffalo hump/moon facies/hirsutism) mood/psychosis
MMF	MMF 1.5g/day for 12 months then taper to 0.75-1g/day for upto 2 years (MAIN protocol) (39)	Reduction in proteinuria resolution of haematuria reduced eGFR slope	Screen for and treat prevalent chronic infections (e.g. TB, HBV) Prior to Initiation VZV vaccination.	Diarrhoea pneumonia Shingles Leukopenia

ACEi = angiotensin-converting enzyme inhibitor; ARB= angiotensin-II receptor blockers; OD= Once per day: PO= administer orally; AKI= acute kidney injury; TB= tuberculosis; HBV= hepatitis B virus; VZV= varicella-zoster virus; M= male; F= female; Bp = blood pressure; IS= immunosuppression; IV= intravenously; PCR= protein-creatinine ratio; OR= odds ratio.

FISH OIL:

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Omega-3 is a polyunsaturated fatty acid that acts decrease leukotrienes and platelet aggregation, reducing IgAN progression.
Omega-3 is prescribed to IgAN patients in combination with other drugs.
It is given in higher doses, such as 12g/d, especially for worsened renal function IgAN patients however, the response is inconsistent.

Targeted therapy;
Tonsillectomy is a common practice in many parts of the world for recurrent severe tonsilitis.
Tonsillectomy is conducted in >50% of IgAN Asian patients.

Due to the genetic differences in IgAN susceptibility and therapeutic responses,

Studies showed that combined pulsed steroid therapy and tonsillectomy improve protein urine loss and the clinical course of IgAN patients, leading to improved patient's outcomes.

Life style recommendations:

- There are many other steps you can take help manage your IgAN and lower your risk of worsening CKD:
- If you smoke and / or use tobacco products, stop. Smoking can speed up the kidney disease process and increase your risk of getting kidney failure. It also increases your risk for other serious health problems, including high blood pressure, heart disease, cancers, and stroke.
- If you are overweight, losing weight through a balanced diet and physical activity can help improve your health in many ways.
- Exercise regularly. Remember, its okay to start slowly- taking short walks is a great way to begin.
- Limit your sodium(salt) intake to less than 2300 mg per day(about 1 teaspoon of salt from all the food and drinks you consume each day).

Diet

Although there is no proof, it is advised that IgA kidney deposit patients should avoid meals that enhance antigen exposure of the intestinal mucosa, such as gluten, meat, and milk-based items.

It is believed that low-protein diets delay the IgAN progression; however, there are no large trials explicity designed to study the significant benefit of minimal protein diets in preventing or reducing kidney function in IgAN patients.

The modification od Diet in Renal Disease(MDRD) study was the only significant clinical study that assessed the benefit of a low protein content diet on the deterioration of renal function in CKD patients.

Unfortunately, the MDRD study did not specifically test for IgAN patients. Even so, the MDRD study did not show a significant advantage of a low protein diet in impairing kidney function deterioration.
Hence, it appears that a low protein diet cannot be strongly recommended, while it may lead to protein diet cannot be strongly recommended, while it may lead to protein malnutrition, especially if the urine protein loss is high.

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