



Sultanate of Oman
Ministry of Health



Infection Related GN

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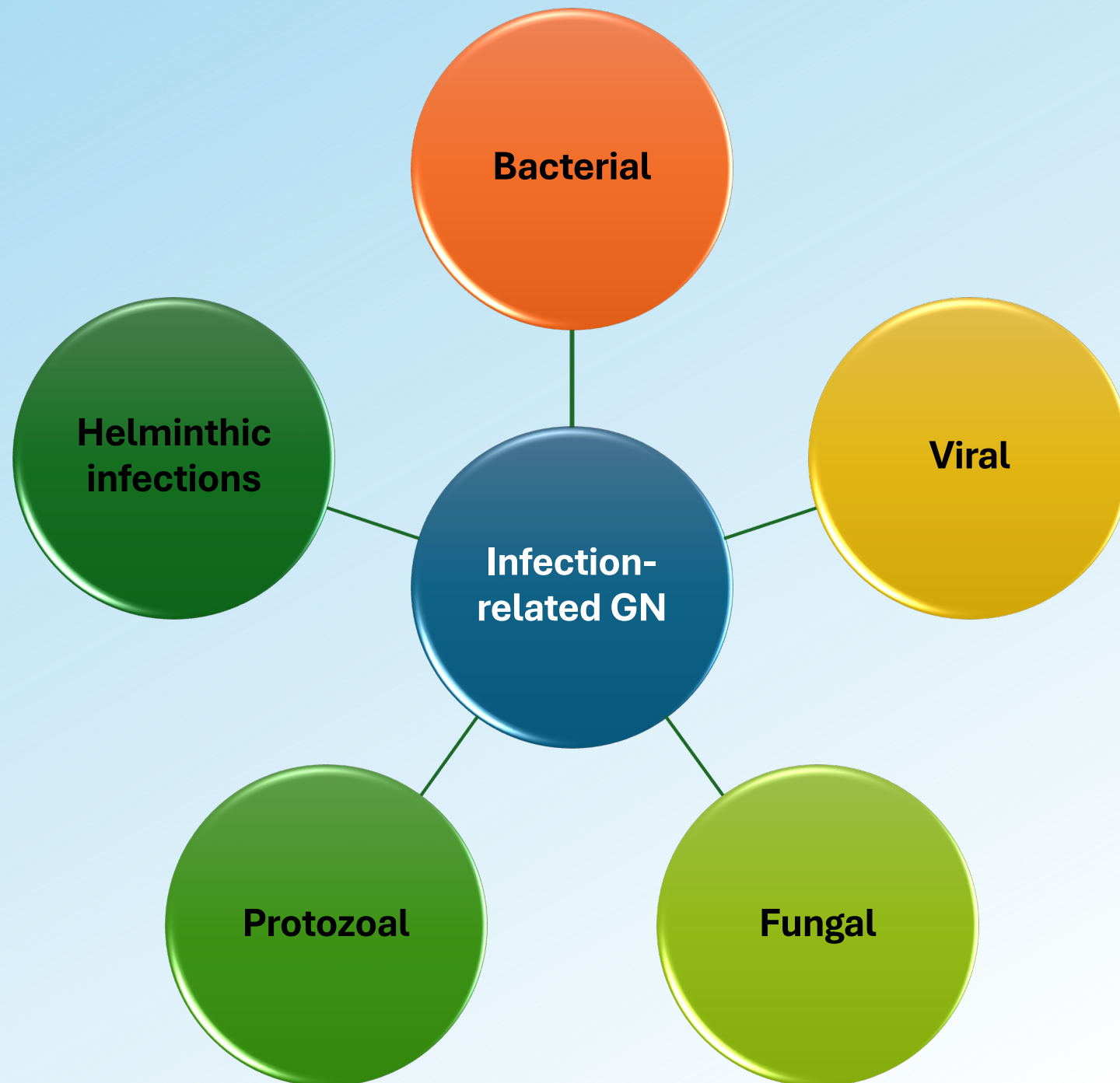
Introduction

Immune-Mediated

IRGN is glomerulonephritis due to an immunologic kidney response caused by a nonrenal infection.

The disease's epidemiology, morphology and progression are significantly influenced by:

- The timing of the infection
- The patient's age
- The pathogen involved
- Comorbid conditions
- Socioeconomic conditions
- Healthcare access
- Changing patterns in infectious diseases



Types of IRGN



Post-Infectious Forms

Occur after the infection has resolved.



Parainfectious Forms

Occur during an active, often persistent infection lasting weeks. (increasing importance in older patients).

Epidemiology Misnomer

Streptococcal Infections

In modern times it accounts for only 28%- 47% of postinfectious acute GN.

Staphylococcus Infections

aureus or epidermidis: isolated in 12%-24% of cases.

Gram-negative bacteria

Isolated in up to 22% of cases

Global Incidence

Is difficult to determine, as it is often transient and is likely underreported or unrecognized.

Incidence and Prevalence

Decline in Developed Countries

The incidence of acute post-streptococcal glomerulonephritis (APSGN), historically the most common form of IRGN, has seen a marked decline in developed countries.

WHO Estimates

WHO estimates approximately 470,000 new cases of APSGN annually worldwide, with 97% occurring in low-socioeconomic regions.

Incidence Rates

- In developing countries, the median incidence of APSGN is reported at 24.3 cases per 100,000 person-years among children.
- In affluent communities, this figure drops to 6.2 cases per 100,000 person-years.

Changing Demographics

Shifting Profile

Prevalence of *Staph* RGN is **higher than** acute poststreptococcal GN in geographic areas with **adequate resources**.

Increase in Adult Cases

Particularly among older adults with comorbidities such as diabetes and hypertension...etc

Comorbidities

Approximately **1/3** adults with postinfectious glomerulonephritis have at least one comorbid condition

Prognosis



Children

Generally, have favorable outcomes with complete recovery of kidney function post-infection.



Healthy Adults

Also tend to recover well but may experience more complications if underlying health issues are present.



Older Adults & Comorbidities

Often face a more guarded prognosis due to chronic disease. Studies indicate that adults with comorbid factors may experience more chronic kidney injury following
IRGN

Pathophysiology

In Situ Formation

Positively charged circulating antigens cross the negatively charged basement membrane and bind to antigen-specific antibodies, forming subepithelial immune complexes.

Circulating Immune Complex Deposition

Antigens already bound to antibodies in circulation that deposit in glomeruli.

Plasmin Binding

Antigens deposited in glomeruli can bind plasmin, activating immunological processes such as:

- Complement activation (via alternative or classical pathways)
- Recruitment of inflammatory cells, particularly neutrophils.

Superantigens & Neutrophil extracellular traps (NETs)

Superantigens

produced by pathogens like Staph. & Chlamydia pneumoniae → polyclonal T-cell activation, → release of pro-inflammatory cytokines such as IL-2, IFN- γ , and TNF- α . → autoantibodies and immune complexes may deposit in the glomeruli, triggering complement activation and inflammatory damage.

Excessive or dysregulated NET formation contributes to glomerular injury by:

- Inducing endothelial damage.
- Acting as a scaffold for immune complex deposition.
- Triggering complement activation (via the alternative or lectin pathway).
- Exposing autoantigens (e.g., histones or MPO), promoting autoimmune responses.

Genetic Susceptibility and Predisposition

The Major Histocompatibility Complex (MHC) region

Specific HLA types, such as HLA-DRB1*03011, have been found at higher frequencies in patients with acute poststreptococcal glomerulonephritis (APSGN) compared to healthy individuals

Pathogenesis of Post-infectious/Post-streptococcal glomerulonephritis (PIGN)

Key nephritogenic antigens include:

- Nephritis-associated plasmin receptor (GAPDH).
 - Streptococcal pyrogenic exotoxin B (SPEB).
-
- They activate the alternate complement pathway, resulting in hypocomplementemia
 - Have an affinity towards plasmin and glomerular proteins.

Clinical and Diagnostic Features

Clinically

Include acute nephritic syndrome, transient arterial hypertension (50%), or nephrotic syndrome in 5–10% of cases.

Serologically

C3 consumption occurs in ~90% of cases and resolves within 6–8 weeks.

Anti-streptococcal antibodies

(e.g., antistreptolysin O, DNase B) are key diagnostic markers.

Possible biomarkers:

- Nephritis-associated plasmin receptor, (streptococcal glyceraldehyde-3-phosphate dehydrogenase)
- Streptococcal pyrogenic exotoxin B (SPE-B)

Histopathological Characteristics:

1

Early stages

Diffuse global intra-/endocapillary proliferation with neutrophilic infiltration (exudative GN). Occasional crescents.

2

Immunofluorescence

typically reveals C3-dominant or codominant glomerular staining

3

Later stages

Mesangial expansion and hypercellularity may precede full resolution.

1. Nasr SH, et al KI 2013.

2. Kanjanabuch T et al Nature Reviews Nephrology.2009

IRGN in Adults

IRGN in adults

differs significantly,
becoming more
parainfectious due to
persistent infections.

Management

prioritizes treating the
underlying infection.

Common Infections

Sites:

Respiratory tract, skin, urinary
tract, and systemic infections like
sepsis.

Etiology:

Predominantly Staphylococcus
species, gram-negative bacteria,
and fewer Streptococcus cases.

Histological Patterns

■ Acute phase

Diffuse intracapillary proliferation and neutrophil-rich exudates.

■ Chronic progression

Mesangioproliferative or membranoproliferative patterns.

■ Immunohistochemistry and Electron Microscopy

Typical findings: C3-dominant or co-dominant patterns.

Acute phase deposits: Subepithelial "humps."

Chronic phase: Predominantly mesangial deposits.

IgA- dominant IRGN

Pathogens

MRSA, MSSA, E. coli, S. epidermidis, & Klebsiella bacteriaemia in patients with underlying comorbidities, especially diabetes

Presentation

- Bacteremia is often, but not always, found, although the presentation may be delayed.
- Reported in patients with skin and joint infections, pneumonia, osteomyelitis, and endocarditis

Hypocomplementemia

May be seen in 30%-50% of cases.

Key Features

IgA-dominant immune response with strong C3 reactivity

Differential Diagnosis

IgA nephropathy and ANCA-associated vasculitis due to overlapping serological and histological findings.

Kidney Biopsy

- A kidney biopsy is useful in adults, particularly when the culture evidence of infection is elusive, or the diagnosis is in doubt.
- In some cases, a biopsy may be critical at arriving at the correct diagnosis, as comorbidities (DM, HIV) contribute to the difficulty in making the diagnosis

Persistent Low C3

In classical postinfectious GN, a persistently low C3 in serum beyond 12 weeks may be an indication for kidney biopsy to exclude C3 glomerulonephritis (C3GN).

Infective Endocarditis-Associated IRGN

Prosthetic Valves

Prosthetic valves or structural heart valve lesions

Risk Factors

Substance abuse, Elderly, DM, HCV, HIV or Immunocompromised

Pathogens

Strep. viridans (low virulence, left heart) and **Staph. aureus** (high virulence, right heart).

Compatible IE History

- ECHO with vegetations, Fever, new or changed cardiac murmur
- Splenomegaly and other classical features

Blood Cultures

- + ve blood cultures (90-98%)
- Negative in 2-10%.

Histological Findings

Extracapillary proliferative GN with or without necrosis.

Shunt Nephritis

Associated with ventriculoatrial shunts

- Associated with **ventriculoatrial shunts** colonized by **Streptococcus epidermidis**.
- Lower risk with ventricular-jugular shunts.
- Least with ventricular-peritoneal shunts.
- May present after months or years following shunt placement & sometimes after shunt revision

Symptoms and Diagnosis

- Symptoms may be non-specific
- ANCA titers may be positive
- Presents as membranoproliferative GN with prominent IgM deposits.

Treatment of Bacterial IR-GN

Treat the underlying infection

- No RCT to guide treatment of any of the 4 infection-related GNs
- Treat the underlying infection with antibiotics directed against the organism
- Although this will not alter the course- it can prevent the spread of infection within the community

Manage Symptoms

- Treat oedema, hypertension- as well as persistent proteinuria
- May require the support of KRT

Glucocorticoids and Immunosuppression

The utility of glucocorticoids and immunosuppression is unproven and carries serious potential risk - even in cases with crescentic GN

HIV- related GN

Global Problem

As it contributing significantly to CKD

Biopsy Importance

Should be performed, when feasible, to evaluate the morphology- multiple pathologies that occurs

Outcome Factors

- Persistence of viral replication
- Response to ART
- (APOL1) Genetic predisposition
- Coinfection with other viruses
- Development of IC disease or TMA

ART Initiation

Current consensus data from the [TEMPRANO study](#), demonstrate benefit of ART initiation at diagnosis - regardless of CD4 count.

Kidney diseases associated with HIV

HIVAN

HIVICK

Non-HIVAN

- Non-collapsing FSGS
- TMA
- Amyloidosis (AA) skin poppers
- Crystalline tubulopathy
- Immunotactoid glomerulopathy

HIVAN

First Described

1984 from New York
University

Imaging Findings

Enlarged kidneys

Collapsing FSGS

- Microcystic dilatation
- Interstitial inflammation
- Endothelial tubuloreticular inclusions

HIV Location

Could be found in the podocytes and renal tubular epithelial cells

- Treatment with cART is effective at reversing HIVAN

Clinically

- Heavy proteinuria
- Rapid progression to ESKD
- Almost exclusively in African (Americans)

HIVICK

Lupus-like GN

- Mesangial and endocapillary hypercellularity
- Full-house patten

Other GN

- MN, IgAN, PIGN, MPGN, MesPGN, Cryo GN.

EM Findings

- Immune complex by EM
- Tubuloreticular bodies

Laboratory Findings

- Negative lupus serologies
- Hypergammaglobulinemia
- Hypocomplementemia
- Hematuria
- Proteinuria (less than HIVAN).

KDIGO recommend

Term HIVICK gets replaced with a specific description of the pattern of immune complex disease "in the setting of HIV.

Risk factors associated with HIVAN and HIVICK

HIVAN

- Younger
- African
 - APOL1 (G1 and G2) risk alleles (75% have both alleles)
- CART naïve
 - Low CD4 (<200/ml)
 - High viral load
- Develops early in the HIV infection

HIVICK

- Older
- Non-Africans outside of Africa
- CART (5-fold higher)
 - Lower viral load
 - Higher CD4 count
- Develops late in HIV infection
- More common than HIVAN since cART

Treatment

HIVAN

- CART
- RAS inhibition
 - Prevents ESKD
 - Reverses AKI
 - May prevent the development of HIVAN
- Glucocorticoids*
 - IDSA recommends a trial of steroids
 - UpToDate does not recommend routine use
 - Lower creatinine and proteinuria
 - Increase infection
 - Relapse after discontinuation

HIVICK

- Benefits unclear
 - CART
 - RAS blockade
 - Immunosuppression
 - Treat other infections (hepatitis B, C)

HBV associated kidney diseases

Prevalence

3-20% of chronic hepatitis B patients may develop HBV-GN

Types of Glomerulonephritis

- Membranous nephropathy
- MPGN
- Mes PGN
- IgA nephropathy
- Cryoglobulinemia
- Polyarteritis nodosa

Pathogenesis

Endemic Areas

More common in endemic areas

- Male children

Genotype Role

- Genotype A is more common in MN and MPGN

Chronic Hepatitis Infection

- Hepatitis B antigen-antibody complexes
- Hepatitis B surface and core antigen can be found on GBM and mesangium.

Membranous Nephropathy

- Seroconversion from HBeAg to anti-HBe
- Spontaneous remission is uncommon in adults
- Anti-PLA2R and THSD7A are positive in HBV-MN patients probably in the same proportion as non-HBV infected patients

KDIGO, 2021

- Patients with HBV (**DNA levels >2000 IU/ml**) & **GN** receive nucleos(t)ide analogues as recommended as per HBV treatment.(1C)
- **Pegylated interferon** should **not** be used to treat patients with replicative HBV infection and GN
- **Rituximab and cyclophosphamide** should be **avoided** in patients with simultaneous HBV infection and anti-PLA2R antibody-mediated MN **until a sustained virologic remission** has been obtained by nucleos(t)ide analogue therapy as it may accelerate HBV replication.

Note:

- Plasma exchange may be tried in patients with accompanying cryoglobulinemic vasculitis
- HBV Vaccination
 - Ideally all individuals should be vaccinated

HCV-Associated Kidney Diseases

Cryoglobulinemic GN

- Diffuse mesangial proliferative
- MPGN

Membranous nephropathy

Others

- Fibrillary glomerulonephritis
- Focal segmental glomerulosclerosis
- IgA nephropathy
- Immunotactoid glomerulopathy
- PAN*

Treatment of HCV-Associated GN

DAA

- Complete remission has been achieved by sofosbuvir and daclatasvir

Immunosuppressive therapy

To start 1 - 4 months prior to antiviral therapy

- Plasma exchange
- Cyclophosphamide
- Mycophenolate mofetil
- Glucocorticoid
- RAS blockade*

Rituximab

For cryoglobulinemic vasculitis

- Superior to immunosuppressive therapy
- Effective in patients who failed antiviral therapy
- Doubles the effectiveness of antiviral therapy alone

Schistosomiasis associated GN

Immune response can start once the egg deposited after infection.

1

2

Pathology: mesangial proliferative glomerulonephritis.

3

Clinically: proteinuria, hematuria, & sometimes nephrotic syndrome.

4

Treatment:

- Antiparasitic medications for underlying schistosomiasis
- Supportive care for associated kidney disease

Malaria associated GN

Acute malaria-associated GN occurs most commonly with *Plasmodium falciparum*

1

2

Clinically: NS, transient mild proteinuria, microscopic hematuria, and occasionally low complement

3

Pathology: MPGN or mesangioproliferative GN

4

Chronic GN occurs mainly with *P. malariae*: has been associated with irreversible and progressive GN. Previously known as tropical nephritis or "quartan malarial nephropathy" - children are most commonly affected.

5

Malarial infection + GN should be treated with an appropriate antiparasitic agent eradicate the organism from blood and hepatosplenic sites.

6

There are no indications for use of immunosuppressive agents in malarial nephropathy



Conclusion

- Despite global advancements in healthcare, IRGN remains prevalent in regions with high rates of infection and limited access to healthcare.
- The evolving spectrum of IRGN has shifted towards non-streptococcal and adult-onset cases, requiring heightened vigilance and tailored management.
- Early recognition and appropriate treatment of underlying infections are critical to improving patient outcomes.
- Prevention strategies, such as vaccination and improved sanitation, can significantly reduce the disease burden.
- Ongoing research into pathophysiology and biomarkers will pave the way for targeted therapies.

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