

الله أكبر





Alexandria University

# Alexandria University



**Mohamed Alaa Thabet**

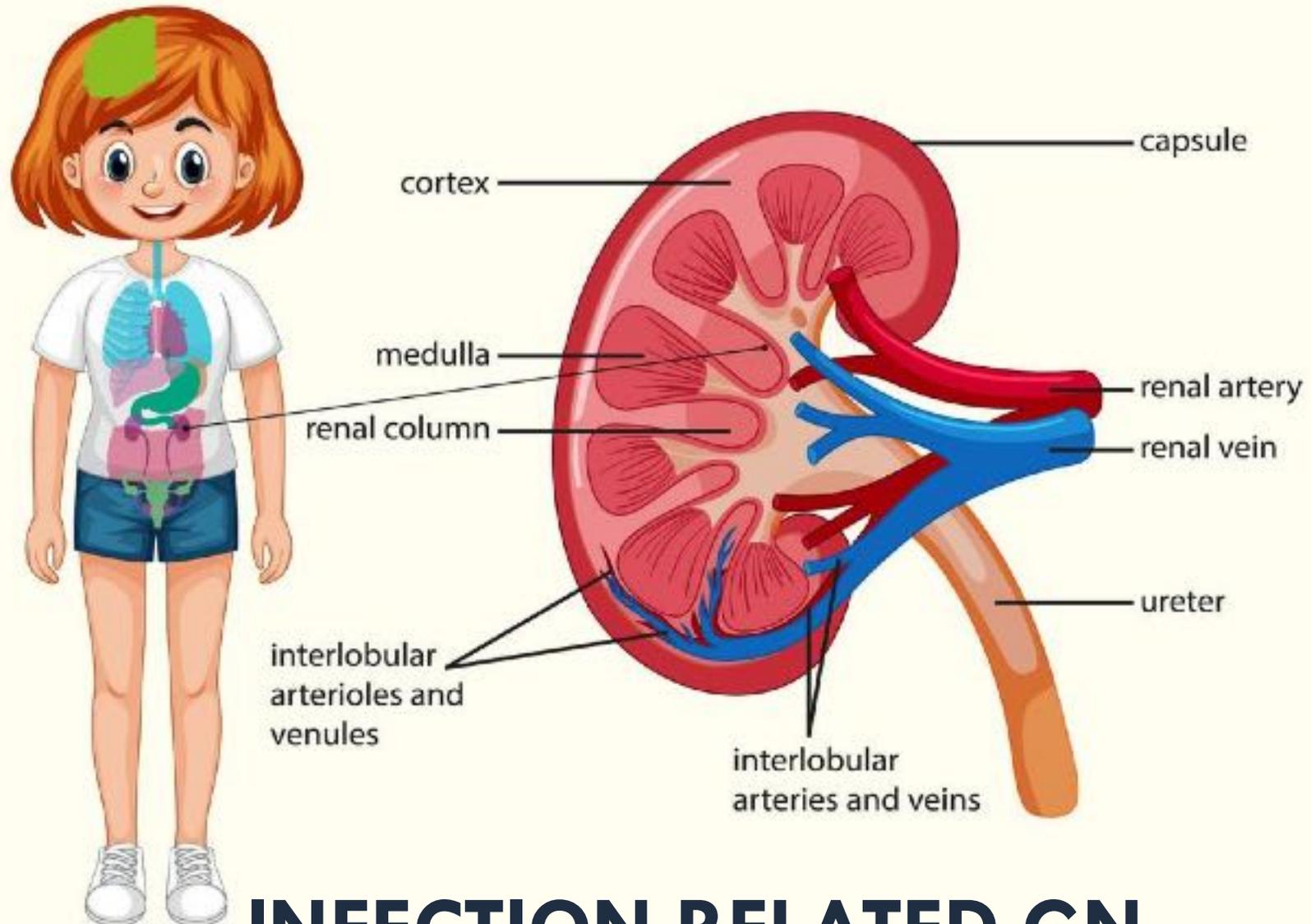
**Professor of Pediatrics**



A vibrant, multi-colored powder explosion against a black background. The explosion is centered and radiates outwards, with colors including bright pink, magenta, red, orange, yellow, green, cyan, blue, and purple. The particles are captured in mid-air, creating a sense of dynamic movement and energy.

**Exciting topics  
trying to understand  
the role of complement  
in glomerulonephritis**

## Human Kidney Anatomy



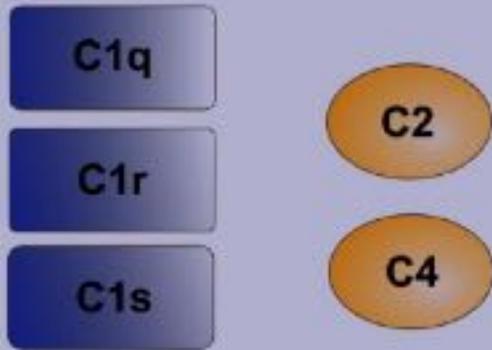
**INFECTION RELATED GN**

# OUR HERO TODAY



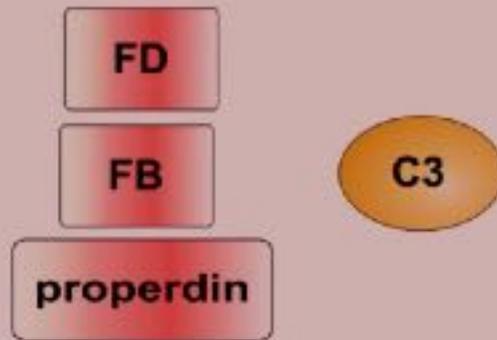
## THE COMPLEMENT SYSTEM

# Classical Pathway



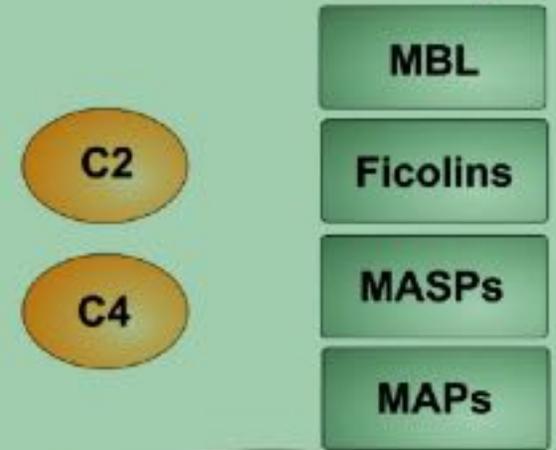
Immune complexes

# Alternative Pathway



Foreign surfaces

# Lectin Pathway

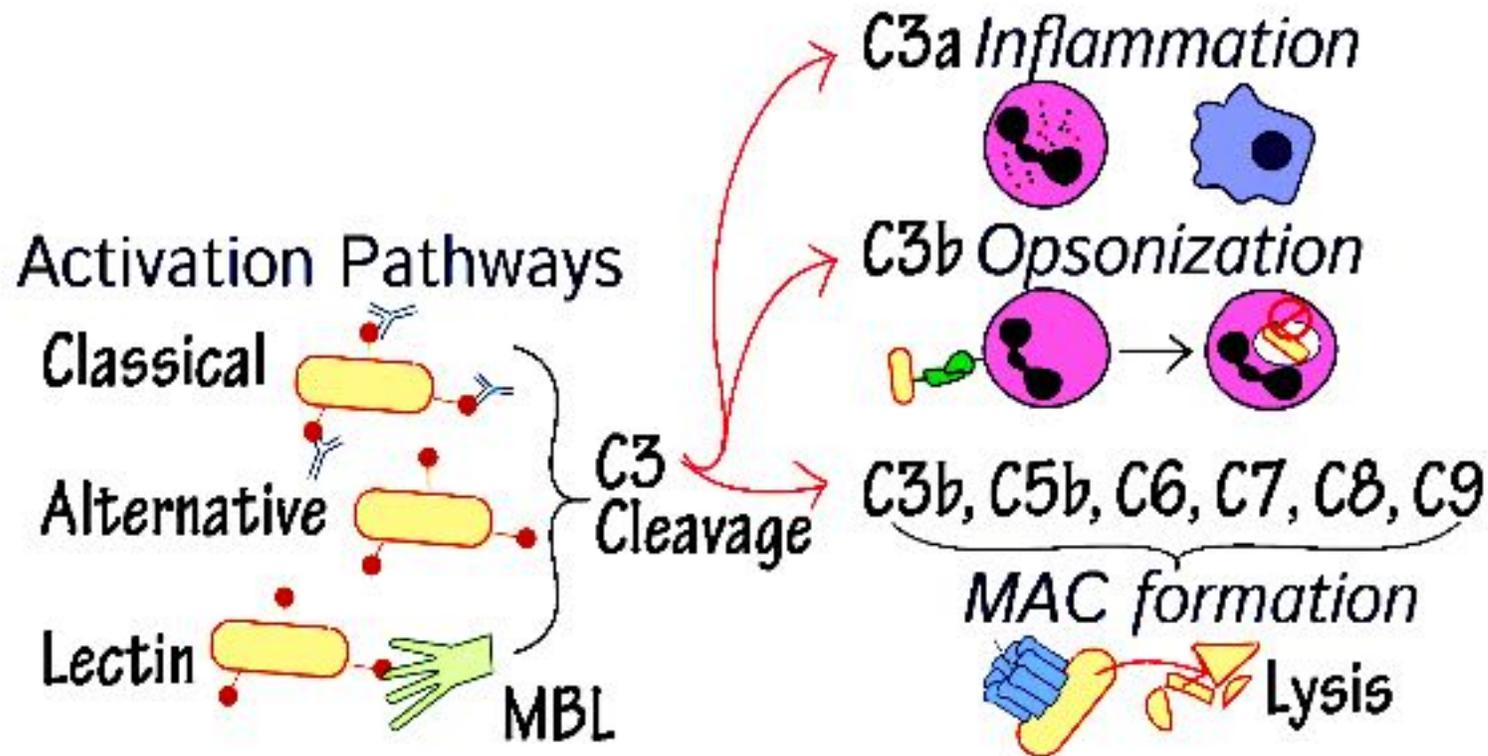


Sugar patterns



# INNATE IMMUNE DEFENSES

## Complement System



- Opsonization & Clear immune complexes
- Trigger inflammation
- Kill pathogens

# Functions of the complement system

## “OIL”

- **O**psonization → C3b
- **I**nflammation → C3a, C5a
- **L**ysis → C5b–C9 (MAC)

## COMPLEMENT

1. Immune surveillance
2. Bridge between innate & adaptive
3. Opsonization
4. Inflammation regulation
5. Direct killing of microbes
6. Self-tolerance & protection of host cells
7. Clearance of immune complexes and apoptotic cells



# Functions of the complement system

## TOLERANCE

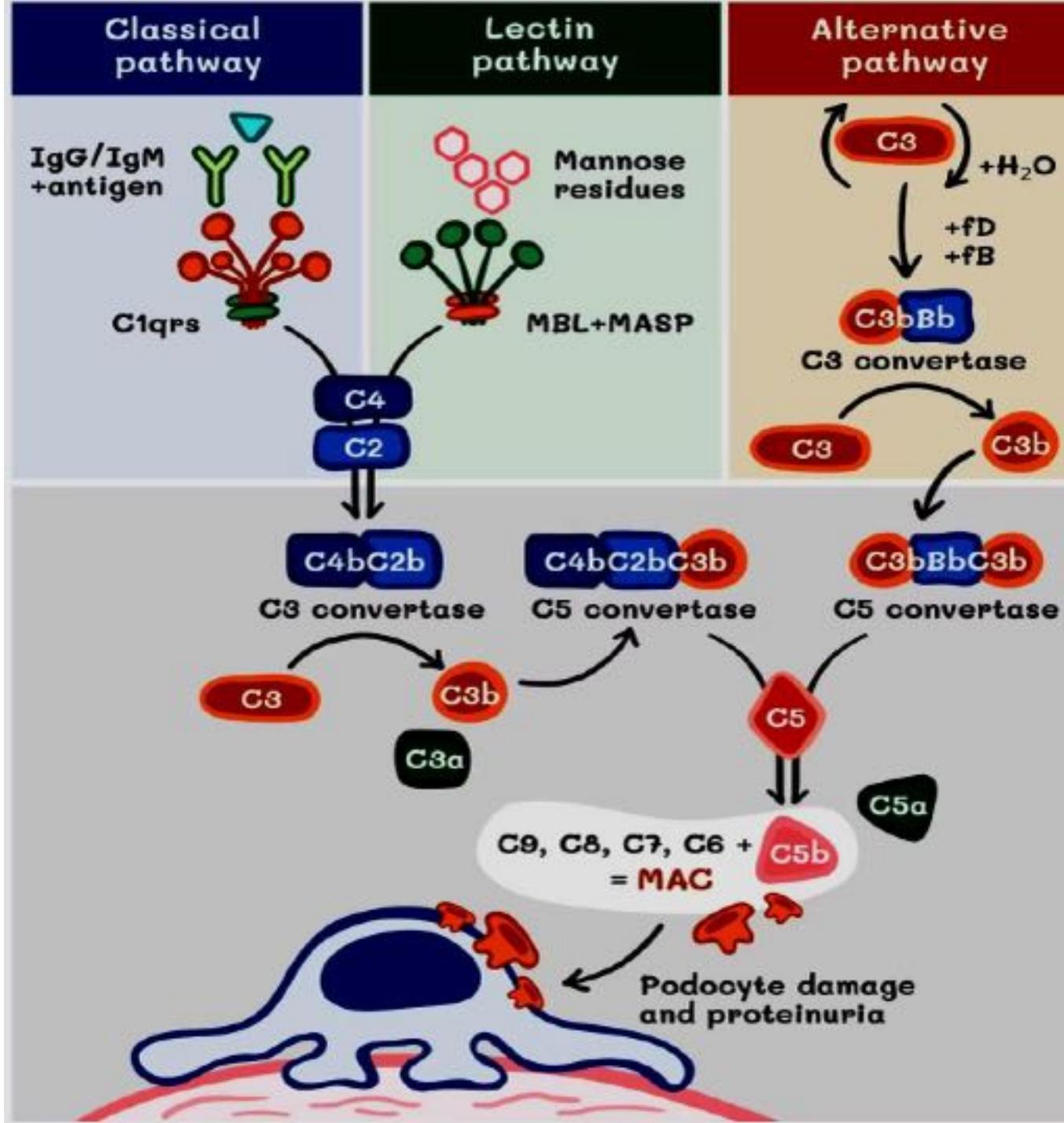
- T** – Tolerance to self
- O** – Own cells spared
- L** – Limits complement activation
- E** – Endogenous cell protection
- R** – Regulatory (DAF, CD59)
- A** – Avoids self-damage
- N** – No MAC on host cells
- C** – Controlled activation
- E** – Ensures self-safety

## CLEARANCE

- C** – Clears immune complexes
- L** – Labels debris (C3b)
- E** – Eliminates apoptotic cells
- A** – Aids phagocytosis
- R** – Removes waste
- A** – Assists macrophages
- N** – Non-inflammatory cleanup
- C** – Circulation cleanup
- E** – Efficient resolution

Early complement  
(C1q, C2, C4) =

TOLERANCE  
&  
SUSCEPTIBILITY



Late complement  
(C3, C5-9) =

INFLAMMATION  
&  
INJURY

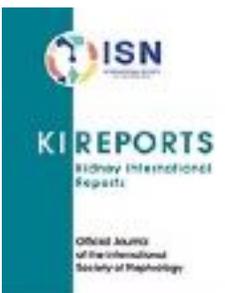


Figure by @CTeodosiu

# Complement System initiators

**Classical**

**Complexes**

**[1,4,2]**

**Lectin**

**Like** “sugar” 

**[L,4,2]**

**Alternative**

**Always**

**Active Alone**

**[3,D,B]**

Activation generates anaphylatoxins (C3a, C5a) and the Membrane Attack Complex, which directly damage kidney tissue.

# Complement System initiators

**Classical**

**Complexes**



**C1q**



**Lectin**

**Like** "sugar" 🍬



**MBL**



**Alternative**

**Always**



**C3b**



# Complement System initiators

**Classical**

**Complexes**



**Self care**



**Lectin**

**Like** "sugar" 🍬



**Infection**



**Alternative**

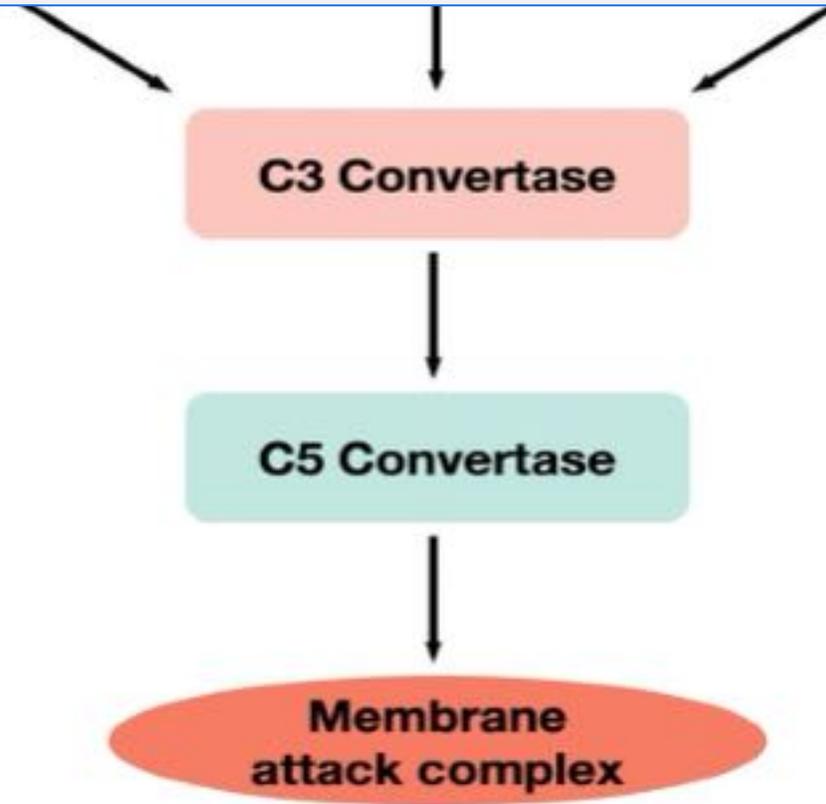
**Always**



**Surveillance**

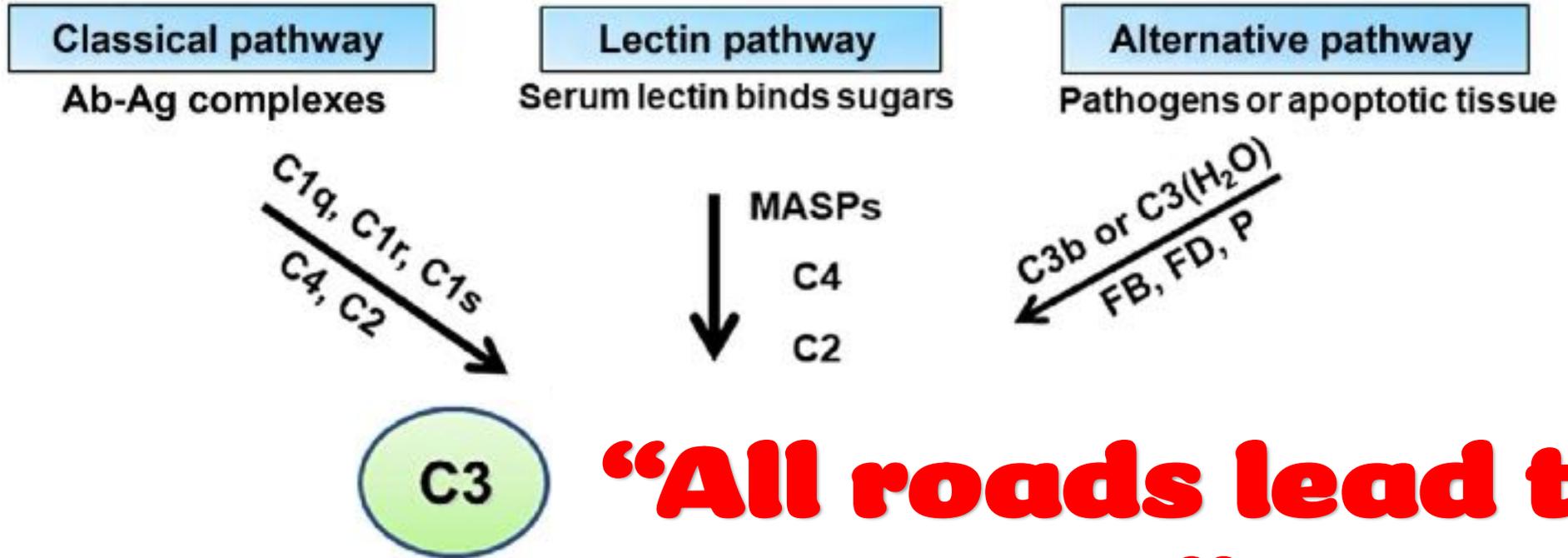


# Different starts → same ending



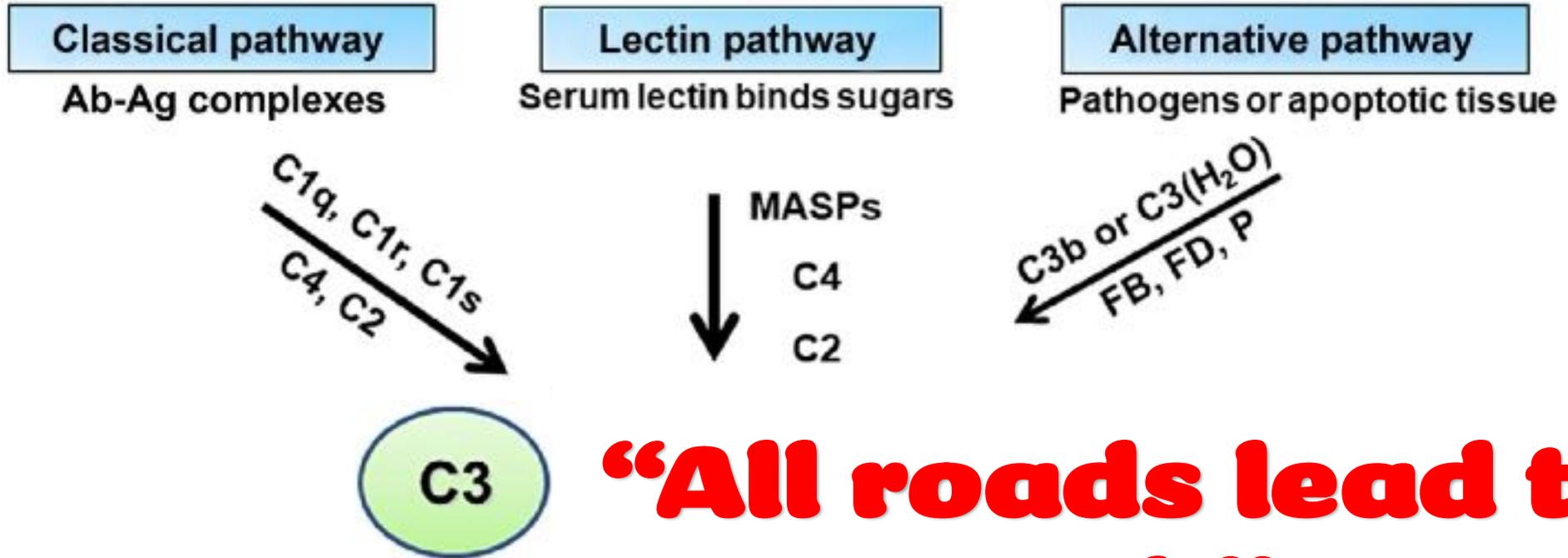
 @ghobby

# Complement cascade



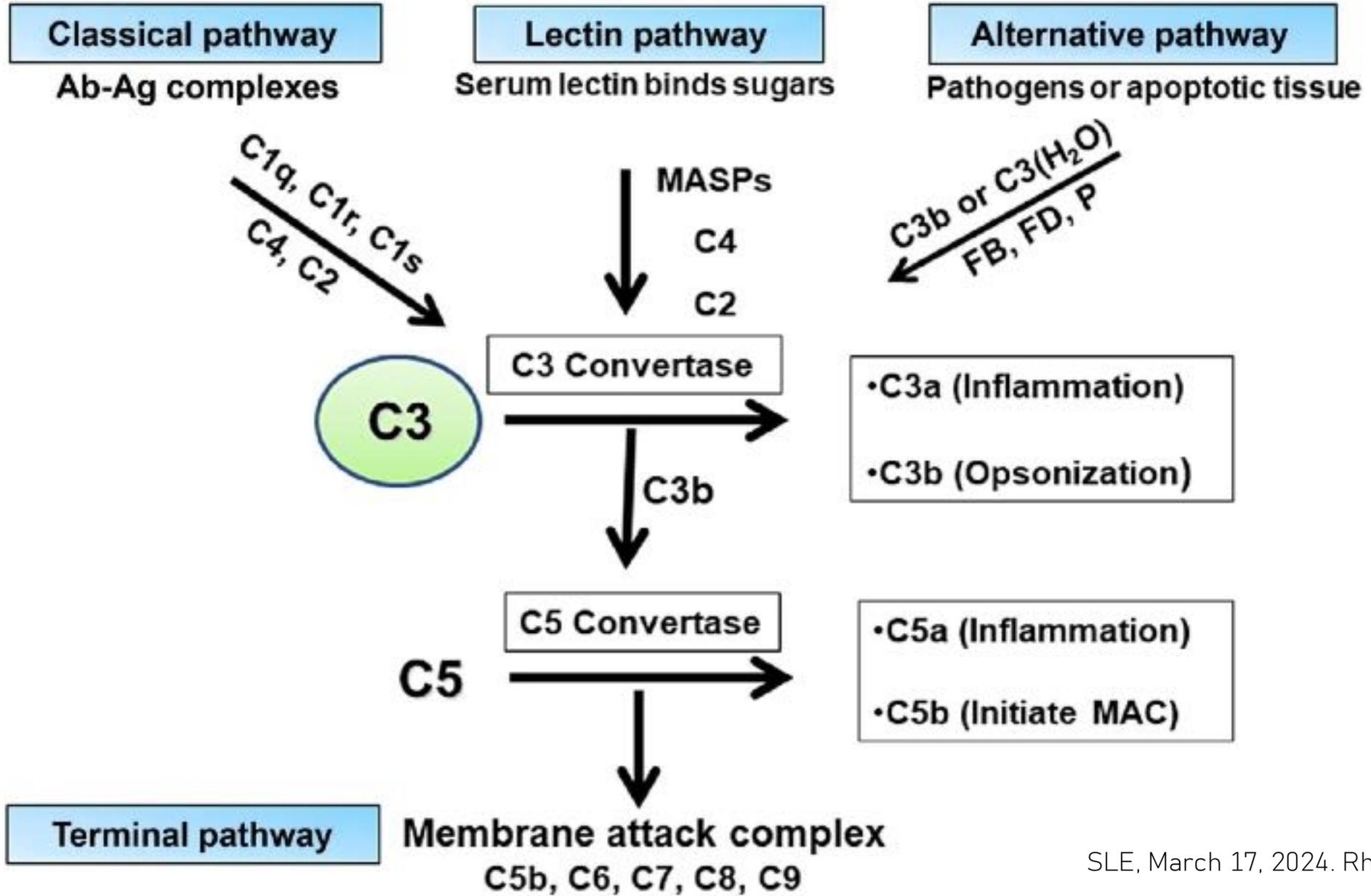
**“All roads lead to C3”**

# Complement cascade



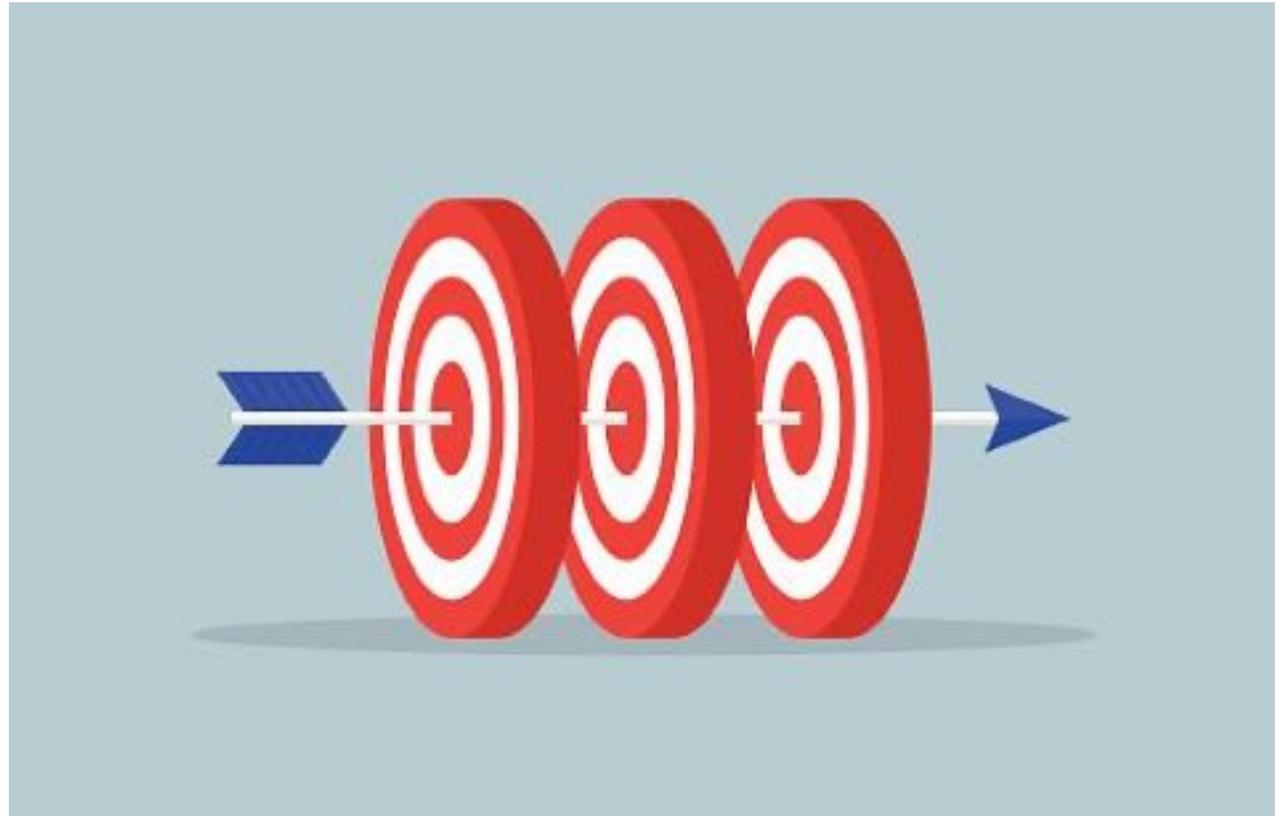
**“All roads lead to C3b”**

# Complement cascade



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**What  
C3b  
normally does?**





**What  
C3b  
normally does?**

OPSONIZATION

CLEARANCE

TOLERANCE

---

# Anaphylatoxins [C3a & C5a]

Chemotaxis of leukocytes, and increased vascular permeability

01

Mesangial cell proliferation and secretion of extracellular matrix

02

The inflammatory response

AWESOME!



3 A

---

*Each day, 1% of C3 undergoes hydrolysis to spontaneously activate the alternative pathway.*

*This allows C3 to recruit factor D, which cleaves factor B, to form Bb that cleaves C3 to C3a and C3b.*

*C3b associates with Bb to form C3 convertase*  
***C3bBb***

**THIS PROCESS IS CALLED  
"TICK OVER,"**



# Alternative pathway order

C3 → B → D → → C3b → P → Amplification

## “C3 Ticks Before Defending Properly”

- C3 → spontaneous Tick-over
- B binds
- D cleaves B → Bb → C3 → C3a & C3b
- Properdin (P) stabilizes



# C3b Amplification Loop

## Mnemonic: “Tick, Stick, Split, Rides, Repeat”

1. **Tick** → C3 tick-over → C3b
2. **Stick** → C3b sticks to microbial surface
3. **Split** → Factor D splits B → Bb
4. **Rides** → Bb rides C3b → C3bBb
5. **Repeat** → more C3 cleavage

Factor H

Factor I

DAF

MCP



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Tight regulation of the alternative pathway is the key to keep it in control.

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**Regulatory proteins include:**

**Factor H & I**: promotes the decay of C3 and C5 convertases

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**Membrane cofactor protein (MCP)**: cofactor for factor I, which cleaves and inactivates C3b

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**Complement receptor 1 (CR1)**: accelerates decay of C3 and C5 convertases; also a cofactor for serum factor I

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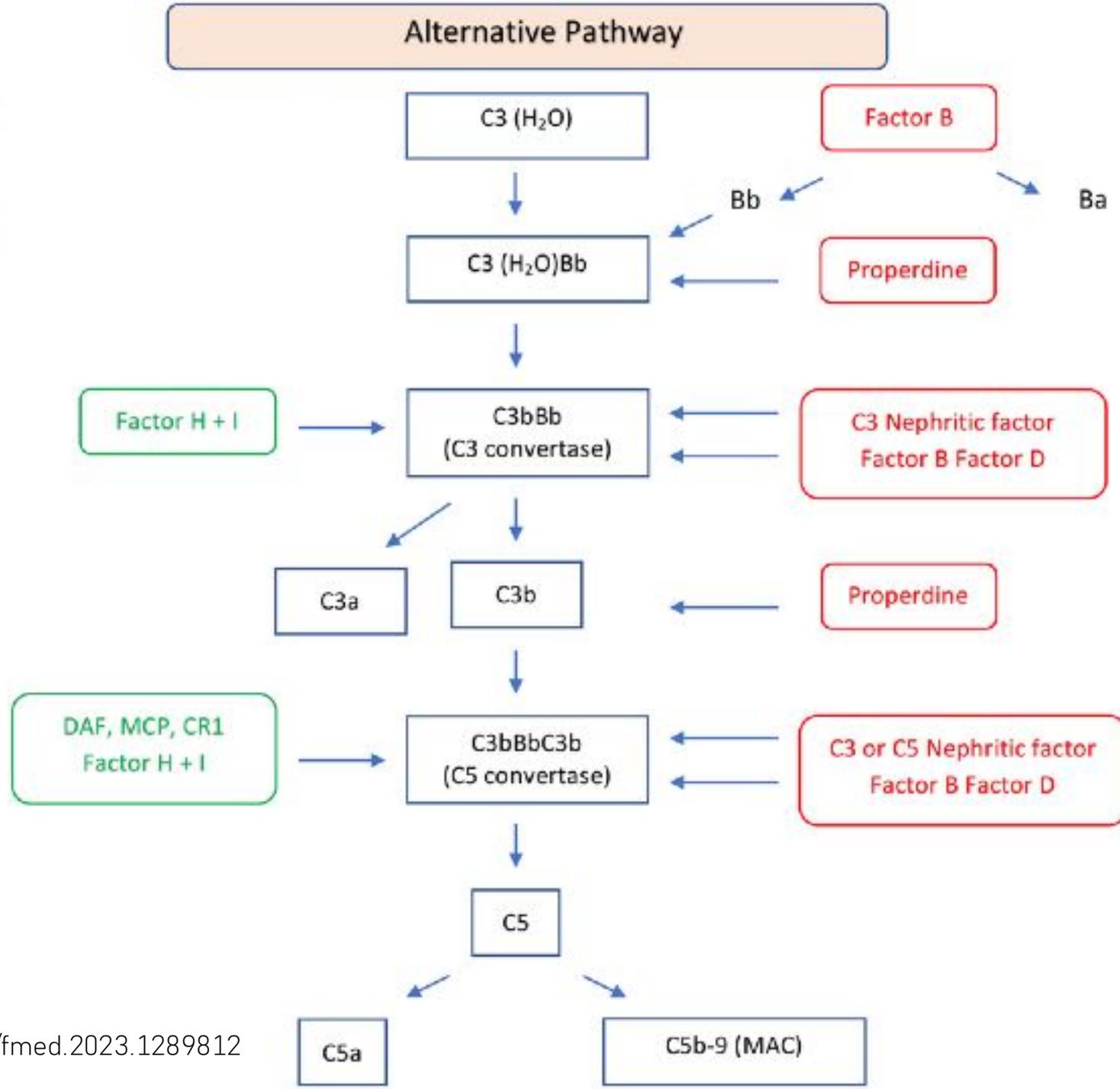
**Decay accelerating factor (DAF)**: accelerates decays of C3 and C5 convertases

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## Regulators of the Alternative Pathway

Regulator	Type / Location	Function	Mechanism / Notes
<b>Factor H</b>	Plasma glycoprotein	Cofactor for Factor I; inhibits AP	Binds C3b on host cells → Factor I cleaves C3b → prevents C3 convertase formation; accelerates decay of C3bBb
<b>Factor I</b>	Plasma serine protease	Cleaves C3b and C4b	Needs cofactors (Factor H, CR1, MCP) → inactivates C3b → stops convertase
<b>Properdin (Factor P)</b>	Plasma protein	Actually, <b>stabilizes</b> AP convertase (opposite of inhibitors)	Binds C3bBb → extends half-life (~10 min → 30 min)
<b>CR1 (CD35)</b>	Membrane receptor on RBCs, leukocytes	Cofactor for Factor I	Inactivates C3b, clears immune complexes
<b>MCP (CD46)</b>	Membrane cofactor protein on host cells	Cofactor for Factor I	Protects host cells from C3b deposition
<b>Decay-Accelerating Factor (CD55)</b>	Membrane protein on host cells	Dissociates C3/C5 convertase	Prevents formation/stability of C3bBb





Regulator	Type / Role	Deficiency / Dysfunction	Resulting Disease / Clinical Feature
<b>Factor H</b>	Plasma glycoprotein; AP inhibitor, cofactor for Factor I	Deficiency or mutations	<b>Atypical Hemolytic Uremic Syndrome (aHUS)</b> → uncontrolled AP activation, endothelial damage; low C3
<b>Factor I</b>	Plasma serine protease; cleaves C3b/C4b	Deficiency	<b>Recurrent pyogenic infections, low C3</b> (due to consumption), risk of <b>autoimmunity</b>
<b>CD55 (DAF)</b>	Membrane protein; breaks C3/C5 convertase	Deficiency	<b>Paroxysmal Nocturnal Hemoglobinuria (PNH)</b> → complement-mediated lysis of RBCs
<b>CD59 (Protectin)</b>	Membrane protein; blocks MAC	Deficiency	<b>PNH</b> → complement-mediated intravascular hemolysis
<b>MCP (CD46)</b>	Membrane cofactor protein; cofactor for Factor I	Mutation	<b>Atypical HUS (aHUS)</b> , sometimes recurrent microangiopathy
<b>Properdin (Factor P)</b>	Plasma protein; stabilizes AP convertase (activator)	Deficiency (X-linked)	<b>Recurrent meningococcal infections (Neisseria meningitidis)</b>
<b>CR1 (CD35)</b>	Membrane receptor; cofactor for Factor I, clears immune complexes	Rare deficiency	Impaired clearance of <b>immune complexes</b> , predisposes to <b>autoimmunity / SLE</b>
<b>CR2 (CD21)</b>	B-cell receptor; binds C3d	Rare mutation	Impaired <b>B-cell activation</b> , susceptibility to infections
<b>C1 inhibitor (C1-INH)</b>	Inhibits classical & lectin pathways	Deficiency (autosomal dominant)	<b>Hereditary Angioedema (HAE)</b> → bradykinin-mediated swelling

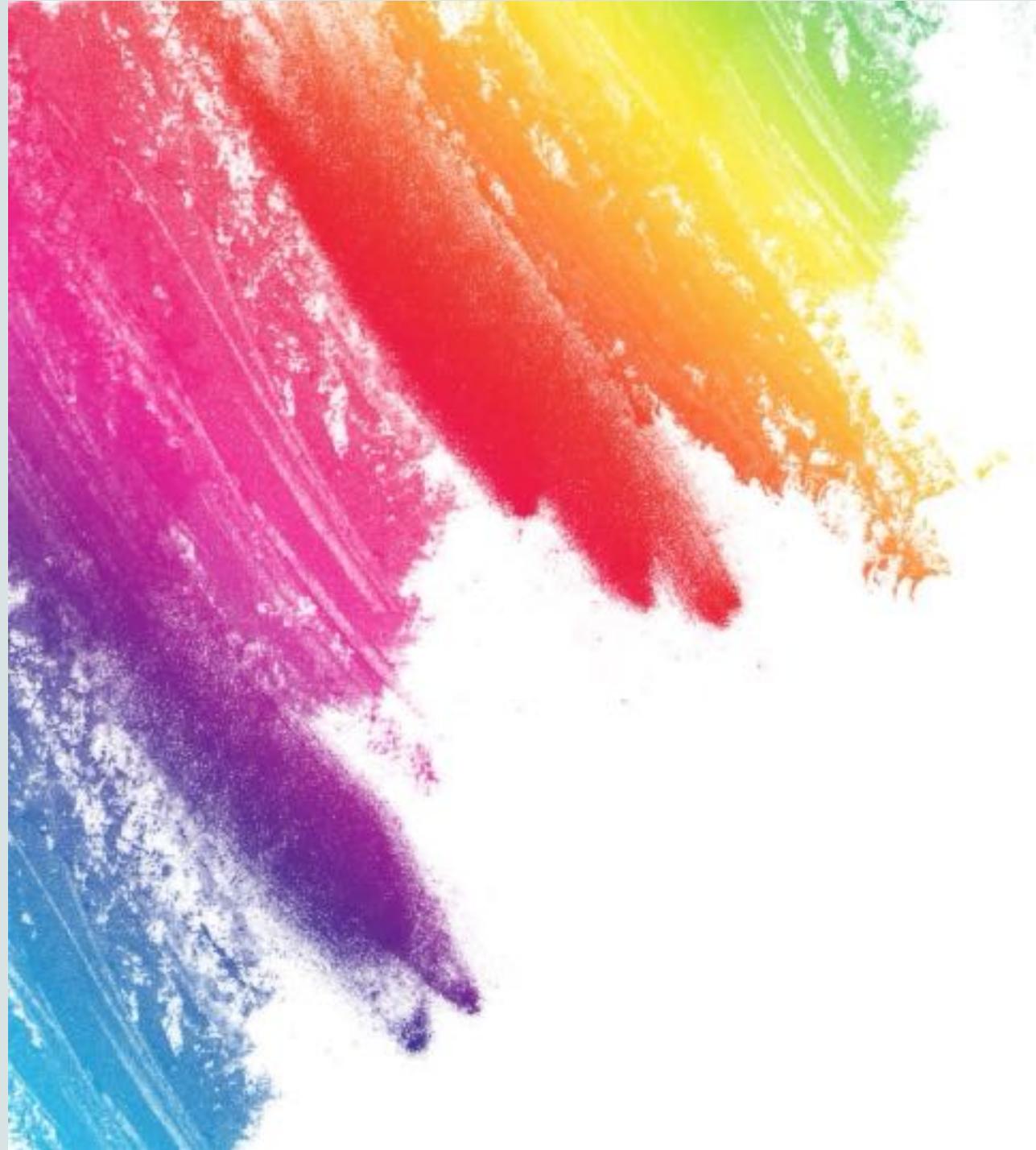
**C3 convertase**

**C3bBb**

**Why is this important?**



**Normally,  
It is  
short-lived.**



*Dysregulation  
of the  
alternative  
pathway*



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Dysregulation of  
the alternative  
pathway



***C3 nephritic factors (C3NeFs)***

***Loss of regulator activity***

1. Autoantibodies to **factor H**
2. Monoclonal Ig that inhibit **factor H**
3. Hereditary deficiency of **factor H**
4. Mutations in complement **factor H**

*C3 nephritic  
factor  
(C3nef)*



# What is C3 nephritic factor?

Autoantibody against the C3 convertase (C3bBb)

Stabilizes C3 convertase, preventing its normal breakdown.

C3NeF keeps (C3bBb) persistently active

Chronic alternative complement pathway activation

Complement-mediated kidney damage

Excessive consumption of C3

Low C3 / normal C4

*Anti-FB  
antibodies*



Anti-FB  
antibodies

Act like C3 nephritic factor (C3NeF), but the target is *Factor B* instead of the *C3 convertase* itself.

# What is Anti-factor B antibodies?

Autoantibody against **Factor B**

Stabilizes C3 convertase, preventing its normal breakdown.

keeps (C3bBb) persistently active

Chronic alternative complement pathway activation

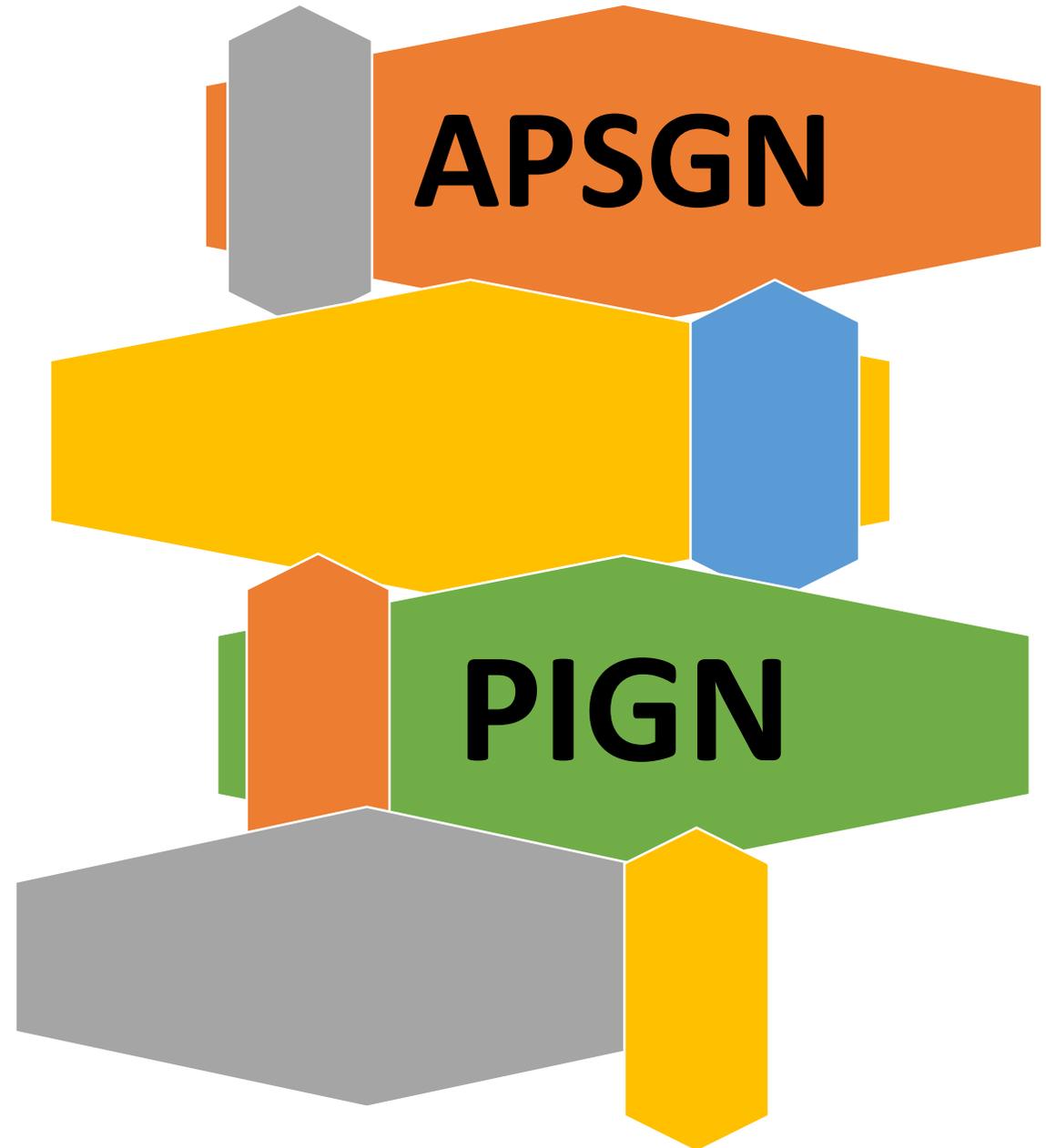
Complement-mediated kidney damage

Excessive consumption of C3

Low C3 / normal C4



# SIMPLE





**APSGN :The very old disease**

**Do we really know it ?**

**A little is known ?**





" وَمَا أُوتِيتُمْ مِّنَ الْعِلْمِ إِلَّا قَلِيلًا "

" MANKIND HAVE NOT BEEN GIVEN OF KNOWLEDGE EXCEPT A LITTLE."

# Poststreptococcal Glomerulonephritis

# Postinfectious Glomerulonephritis

**APSGN**



Hypertension  
Oliguria  
Edema

History of tonsillitis or skin infection



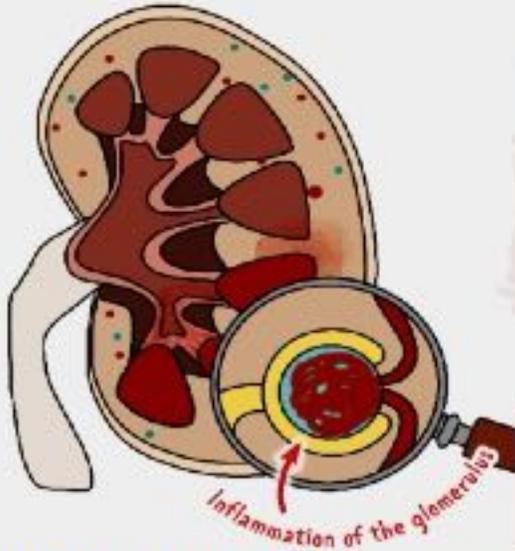
**Hematuria**

*Proteinuria  
Kidney  
dysfunction*



Malaise  
Anorexia

# ACUTE GLOMERULONEPHRITIS (POSTSTREPTOCOCCAL)



## PATHOLOGY

- 1 Untreated strep
- 2 Immune system response by creating **antigen-antibody complexes** (14 days after infection)
- 3 These antibodies get "lodged" in the glomeruli
- 4 Inflammation & scarring
- 5 ↓ GFR

It's not the strep that causes the inflammation of the kidneys. It's the **antigen-antibody complexes** that form due to the strep that causes the inflammation & damage to the glomeruli

## SIGNS & SYMPTOMS

- Hematuria → Blood in the urine
- Azotemia → Excessive nitrogenous waste in the blood (too elevated urine feels color)
- Malaise
- Headache
- Proteinuria (mild)
- Hypoalbuminemia
- ↓ GFR = Oliguria
- Edema
  - Swelling in the face/eyes
  - ↑ Blood pressure
  - Retaining sodium
  - ↑ Urine specific gravity
  - ↑ BUN & creatinine
  - (+) ASD (Antistreptolysin) Titer



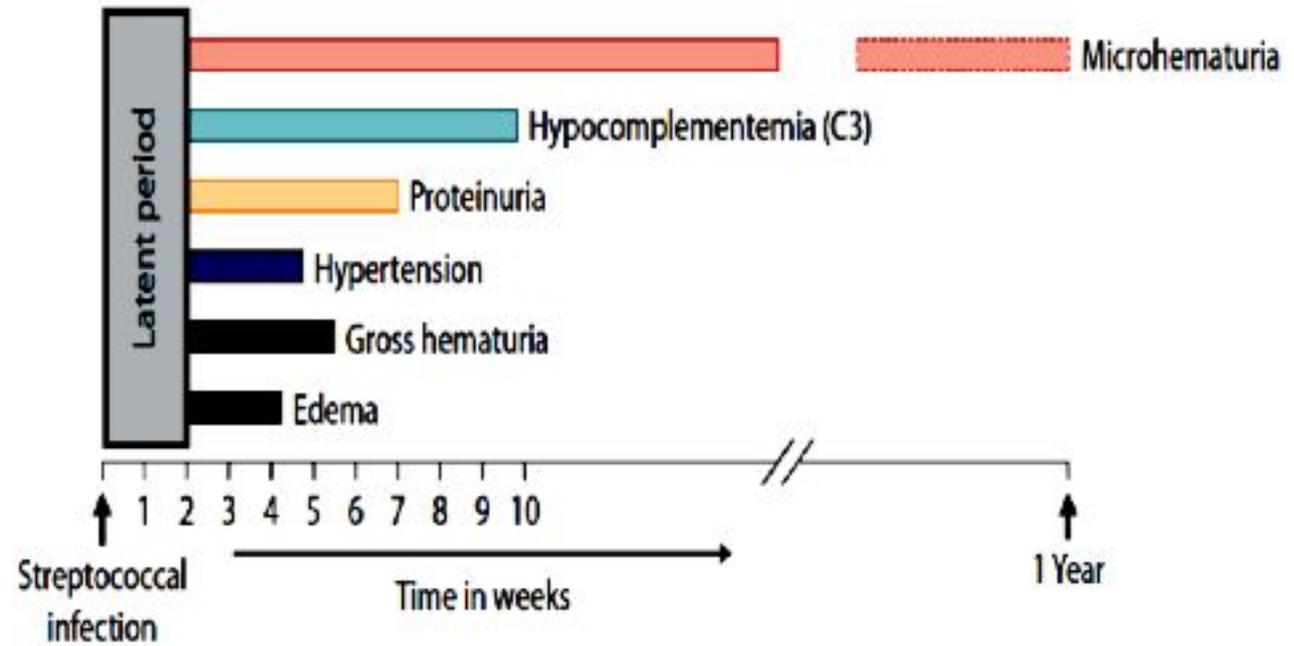
**MAIN CAUSE:**  
RECENT GROUP A BETA-HEMOLYTIC  
STREPTOCOCCAL INFECTION

## INTERVENTIONS

- Fix the cause! (strep)
- Diet modifications
  - Fluid restriction
  - Sodium restriction
  - ↓ Protein
  - Provide a lot of carbohydrates
- Monitor
  - Daily intake & output
  - Daily weight
- Bed rest
- Monitor blood pressure
  - Antihypertensives
  - Diuretics

Carbohydrates provide energy & stop the breakdown of protein

A weight gain of 2 kg is equal to 1,000 mL of retained fluid



**APSGN**  
Self limited  
No recurrence

what is the **morphology** of PSGN ?



**LIGHT MICROSCOPY**

GLOMERULI

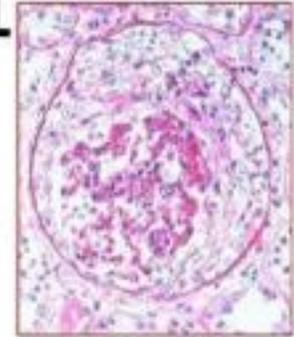
Enlarged **Hypercellular** glomeruli

Glomerular involvement  
**DIFFUSE & GLOBAL**

Infiltration of  
inflammatory cells

Proliferation of  
endothelial and  
mesangial cells

Crescent  
formation  
( in severe cases )



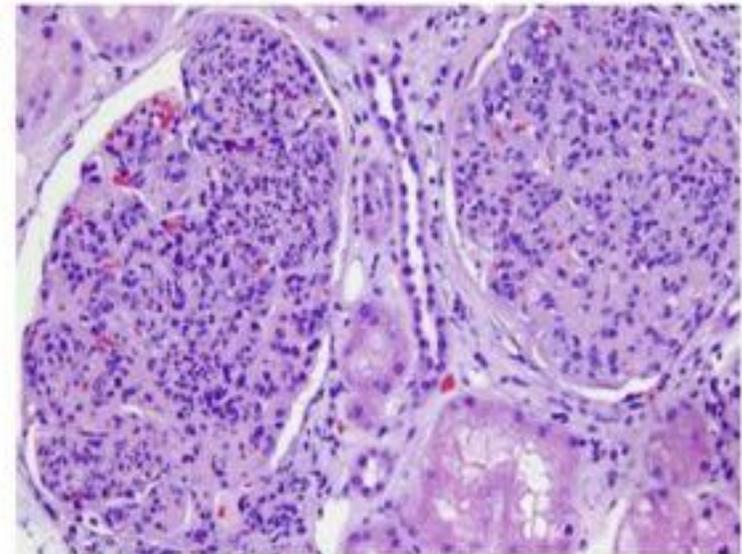
**Results in obliteration of capillary lumen**

TUBULES

may contain red  
cell casts

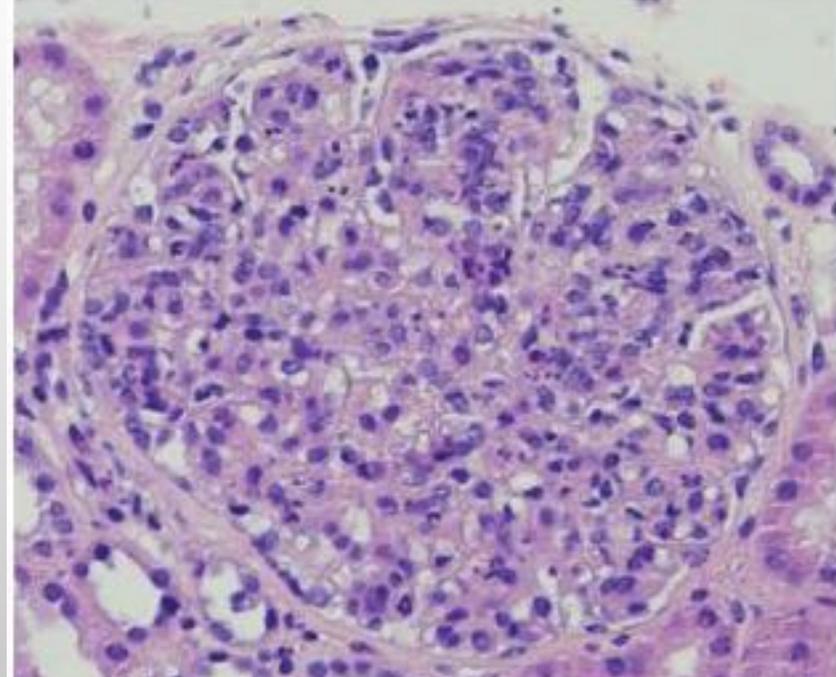
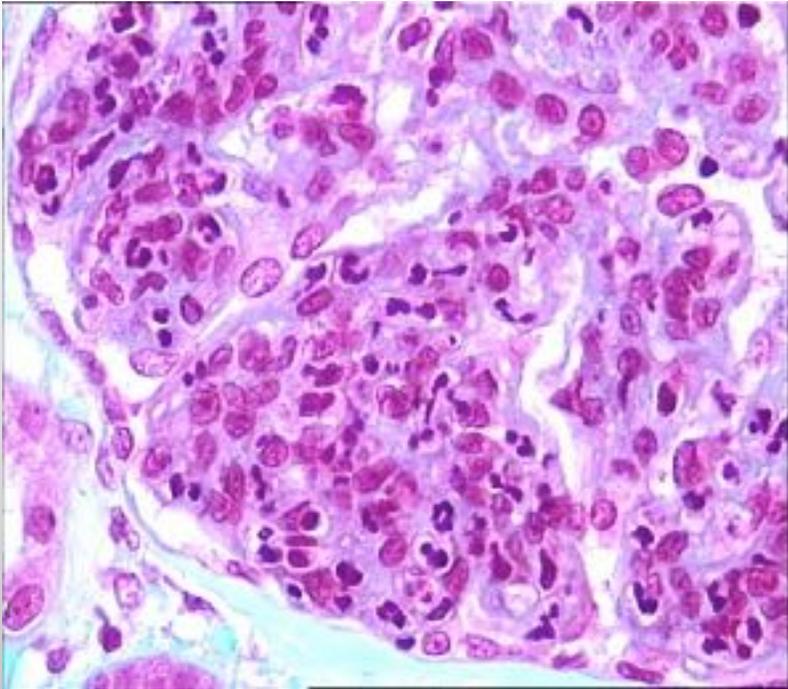
INTERSTITIUM

Interstitial edema and  
inflammation



# Light Microscopy

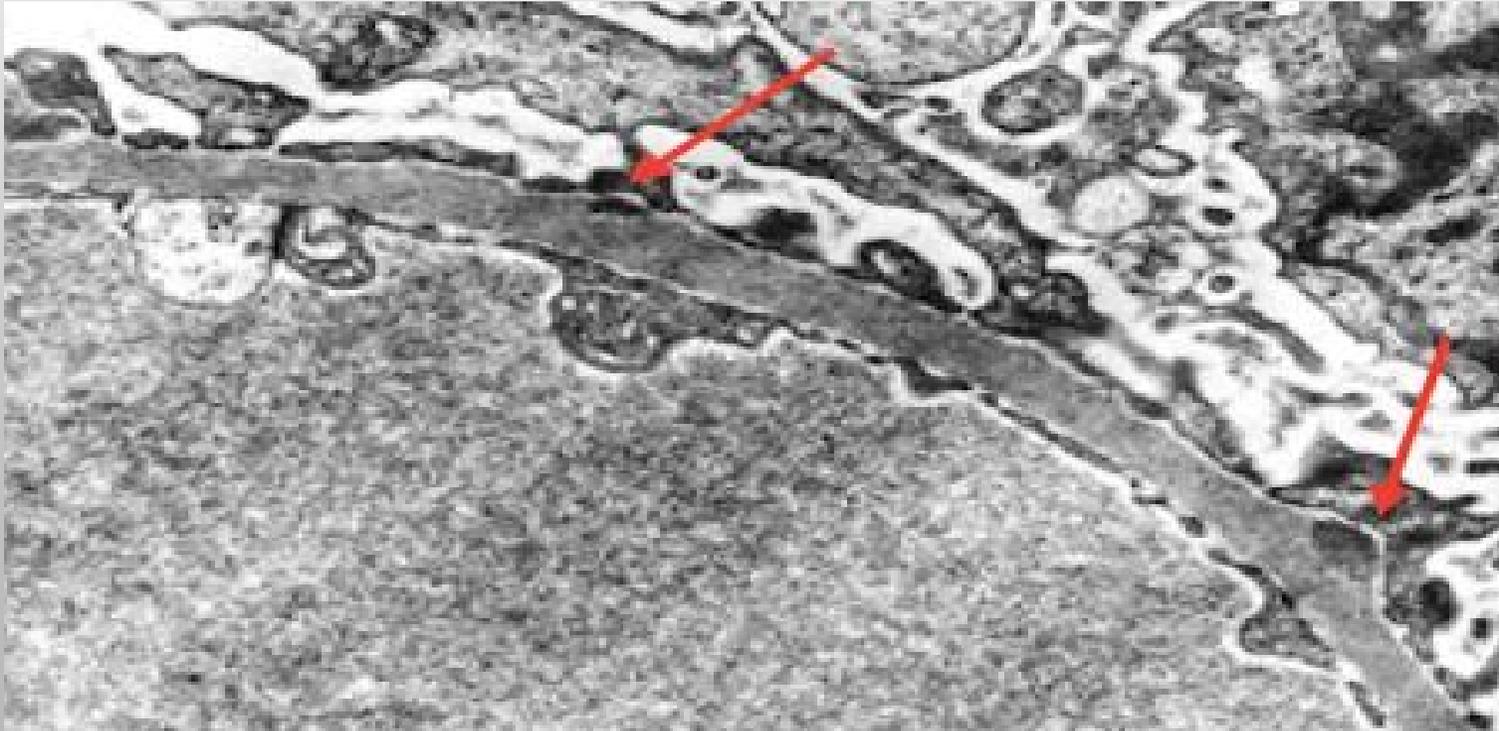
## Diffuse proliferative GN (DPGN)



- Diffuse endocapillary & mesangial cell proliferation
- Narrowing of the glomerular capillary lumens
- Infiltration of the glomeruli with neutrophils & monocytes
- Complete histologic resolution usually occurs by 1 year after onset.

# Electron Microscopy

- Electron-dense deposits (humps) in the subepithelial space
- Characteristic of APSGN.



# Immunofluorescence microscopy

Granular staining of the capillary loops with IgG and complement C3.

1. Starry sky (generalized distribution),
  2. Tree stalk (mesangial),
  3. Garland (capillary wall).
-

# Mesangial

# Garland GBM

# Starry Sky Diffuse

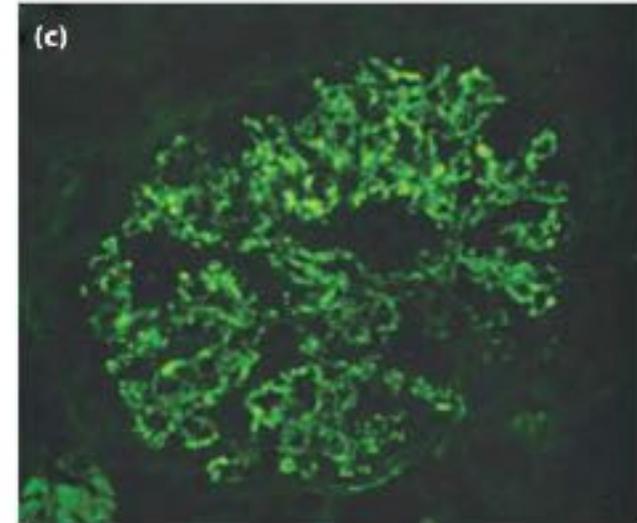
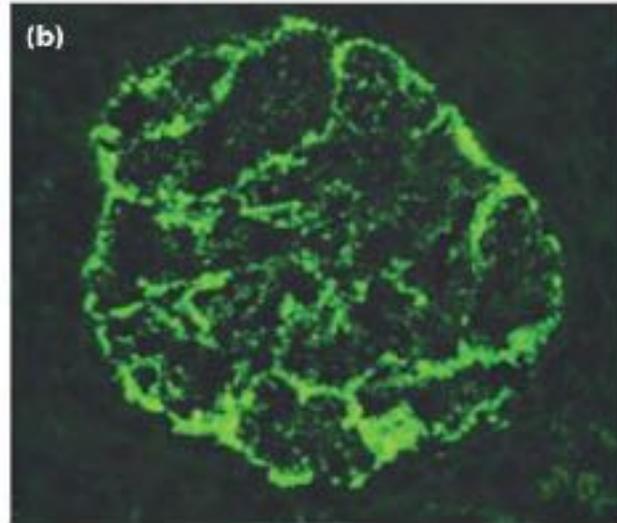
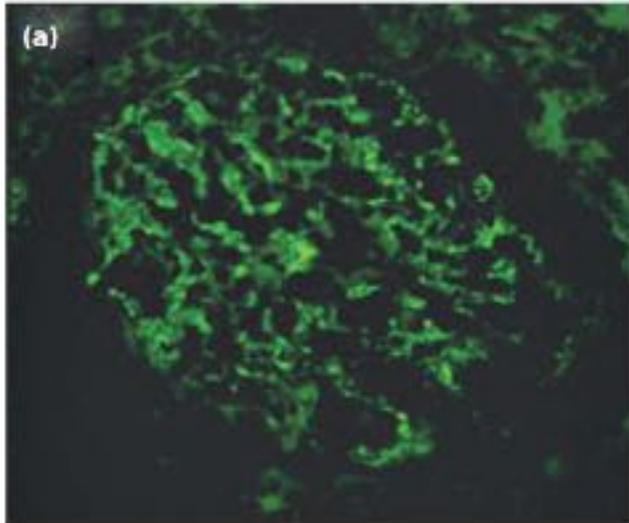
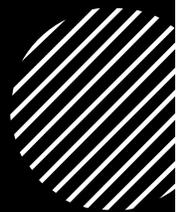


Figure 21.4 Illustrative patterns of complement C3 immunofluorescence observed in renal biopsy samples from patients with postinfectious glomerulonephritis. (a) Mesangial pattern: Mesangial C3 deposits are present, particularly toward the axial region of the glomerulus. (b) Garland or capillary wall pattern: Heavy C3 deposits are present along the glomerular basement membrane (GBM). (c) Starry sky or diffuse pattern: Many small deposits of C3 are present along the GBM and in the mesangium. (Reproduced with permission from: Kanjanabuch T, Kittikowit W, Eiam-Ong S. An update on acute postinfectious glomerulonephritis worldwide. *Nat Rev Nephrol.* 2009;5:259–69.)

Immunofluorescence typically shows "starry sky" or "garland" patterns of **bright C3 staining**



# The Pathogenesis of IRGN



Deposition of circulating immune-complexes in glomeruli



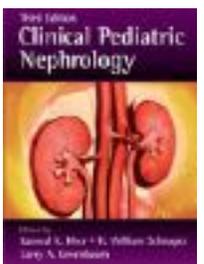
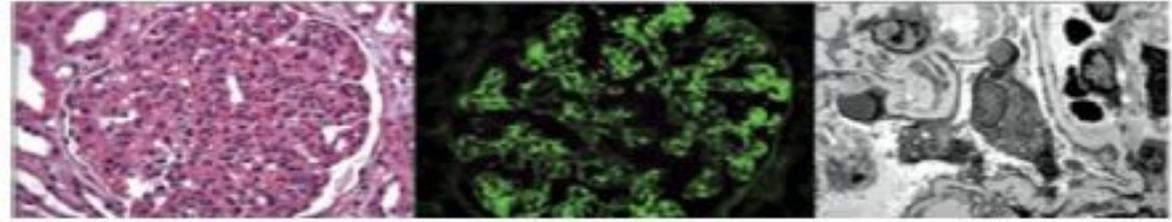
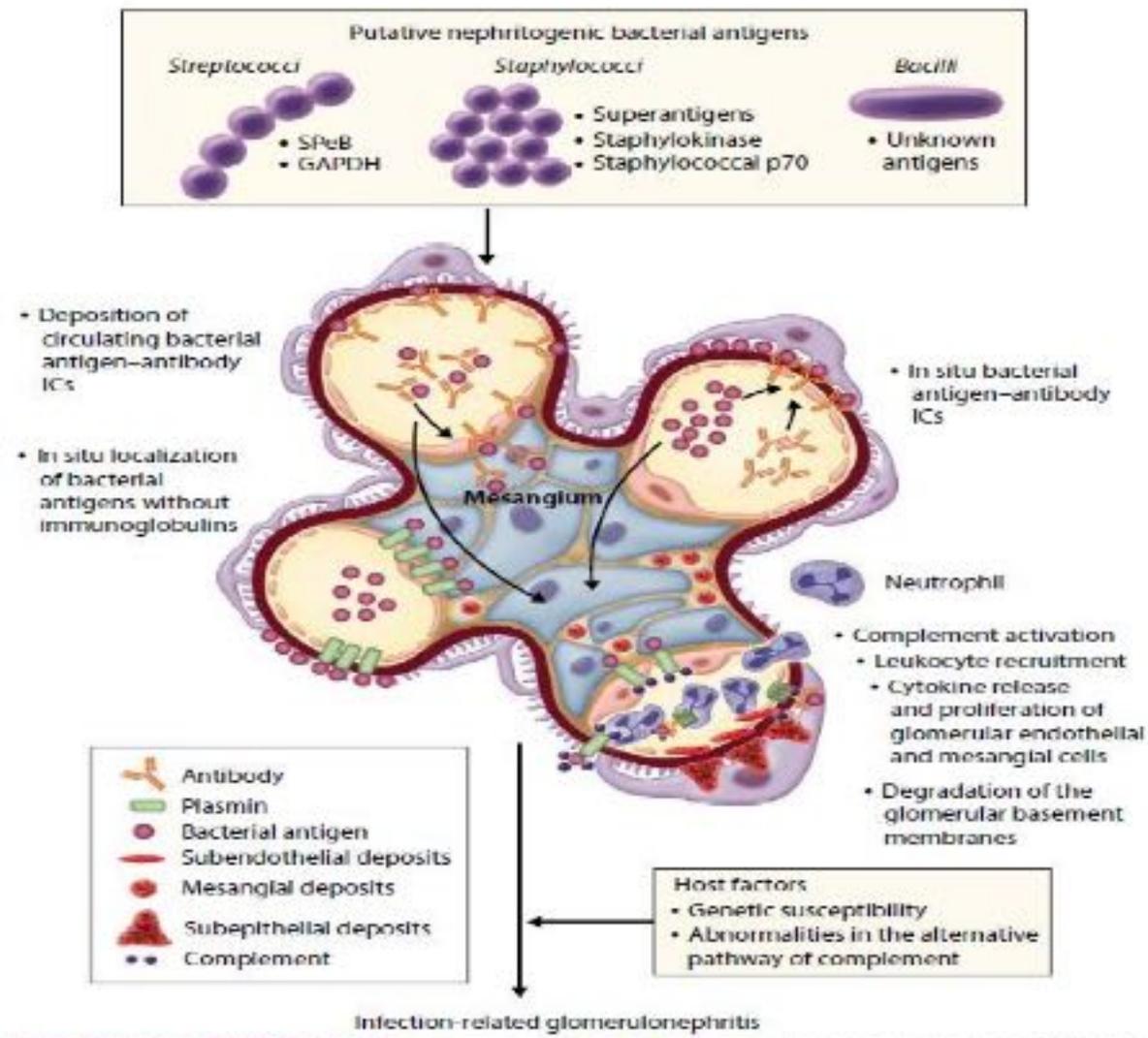
Implantation of antigen in glomeruli initiating immune-complexes in situ



Modifications of native glomerular structures, which become autoantigens



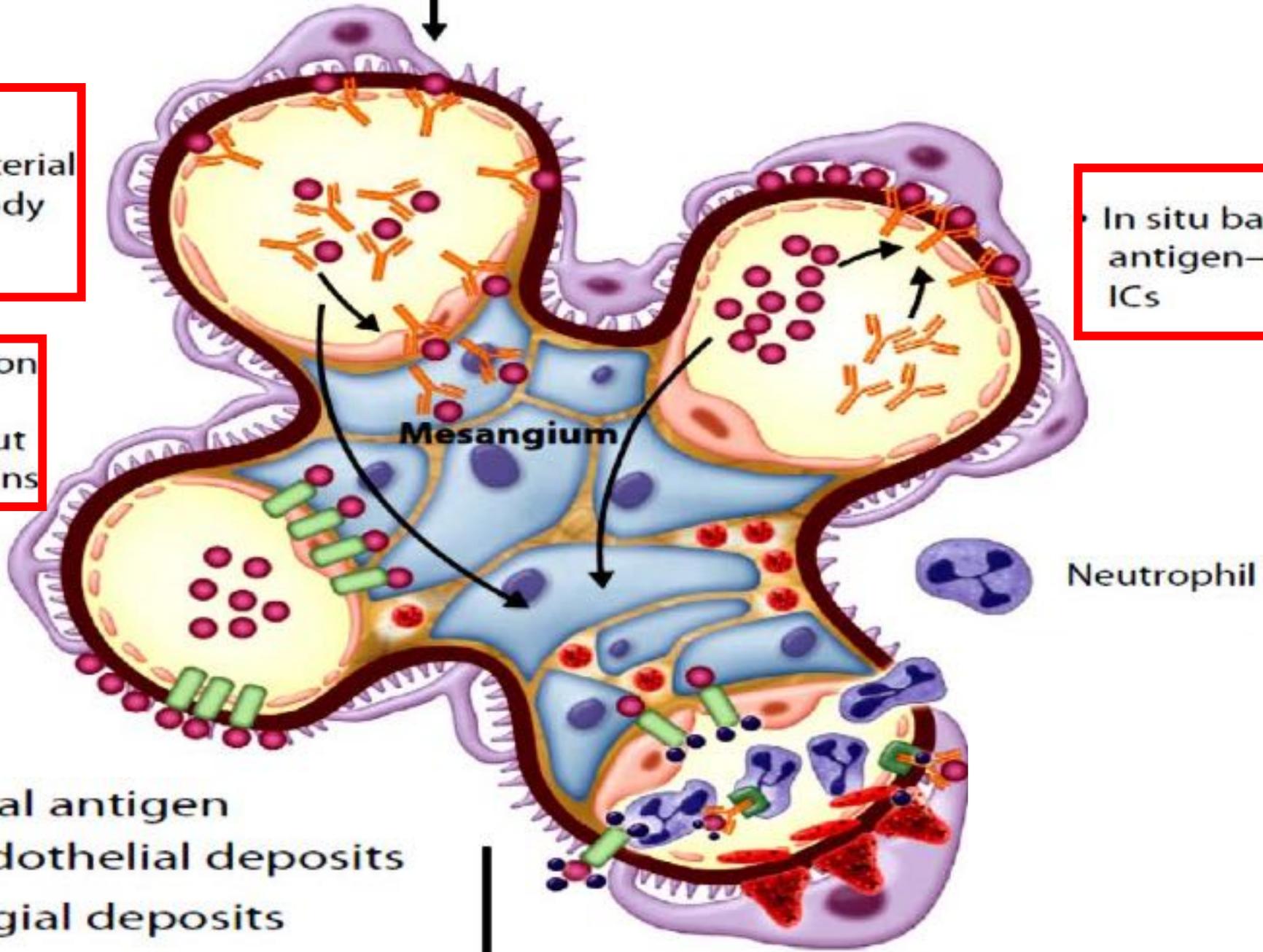
Direct activation of the complement system by implanted antigens.



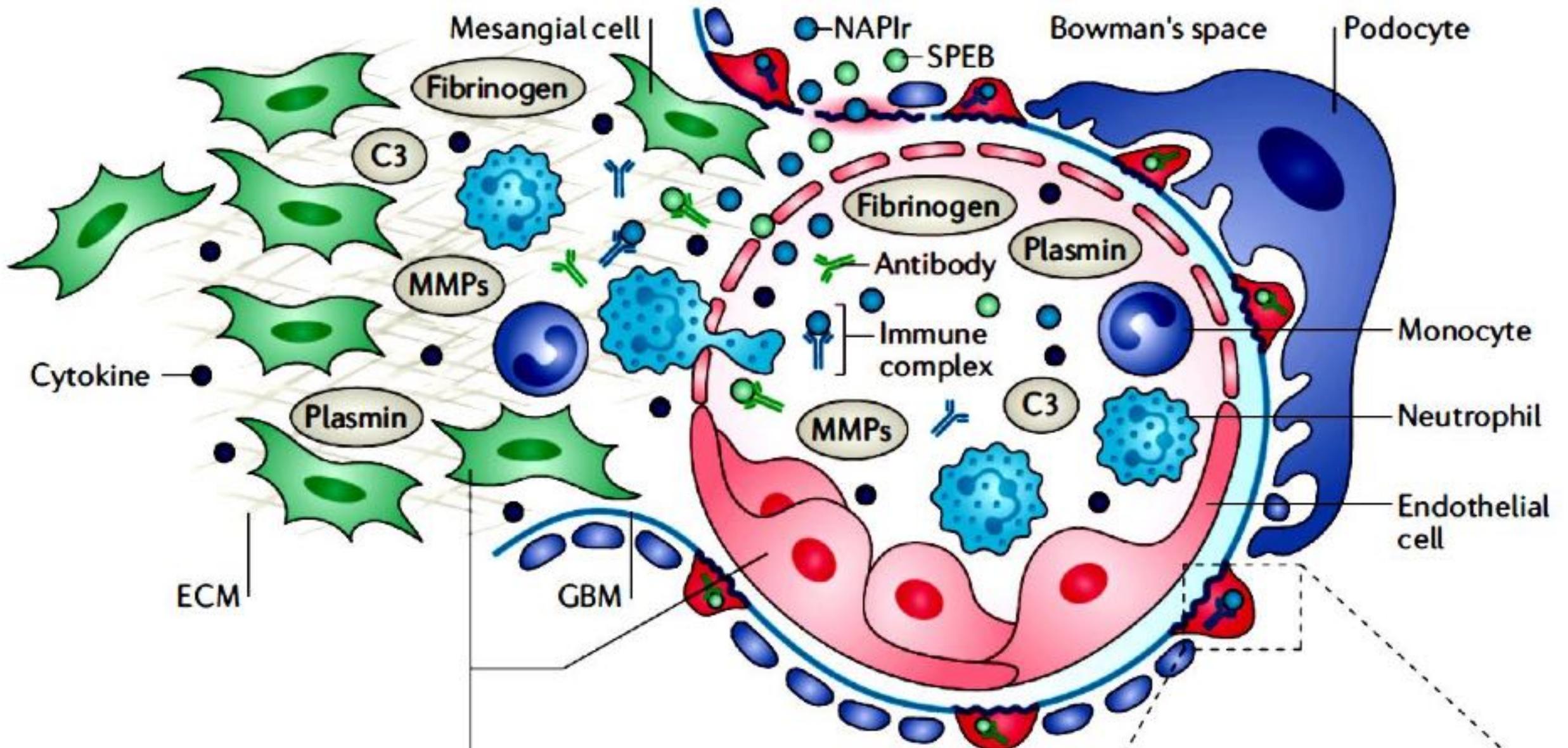
Deposition of circulating bacterial antigen-antibody ICs

In situ localization of bacterial antigens without immunoglobulins

In situ bacterial antigen-antibody ICs



- Bacterial antigen
- Subendothelial deposits
- Mesangial deposits
- ▲ Subepithelial deposits



Satoskar A, Parikh S and Nadasdy T. Epidemiology, pathogenesis, treatment and outcomes of infection associated glomerulonephritis. NATURE REVIEWS | NEPHROLOGY volume 16 | January 2020.

# Glomerular inflammation and injury in APSGN

AS A CONSEQUENCE OF STREPTOCOCCAL  
INFECTION

COMPLEMENT  
ACTIVATION

PLASMIN-INDUCED TISSUE  
INJURY

**MAC**

**IMMUNE COMPLEXES**

Cytokines & cellular immune factors initiate an inflammatory response manifested by cellular proliferation and edema of the glomerular tuft

Clinical manifestation of APSGN.



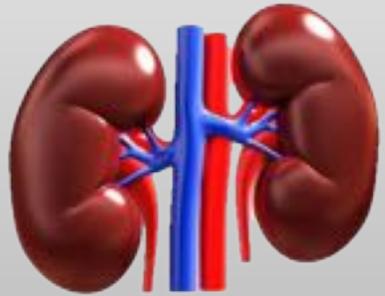
**HOST RESPONSE & SUSCEPTIBILITY**

**PIGN**

**APSGN**

**Asymptomatic**

**Symptomatic**



**Classical**

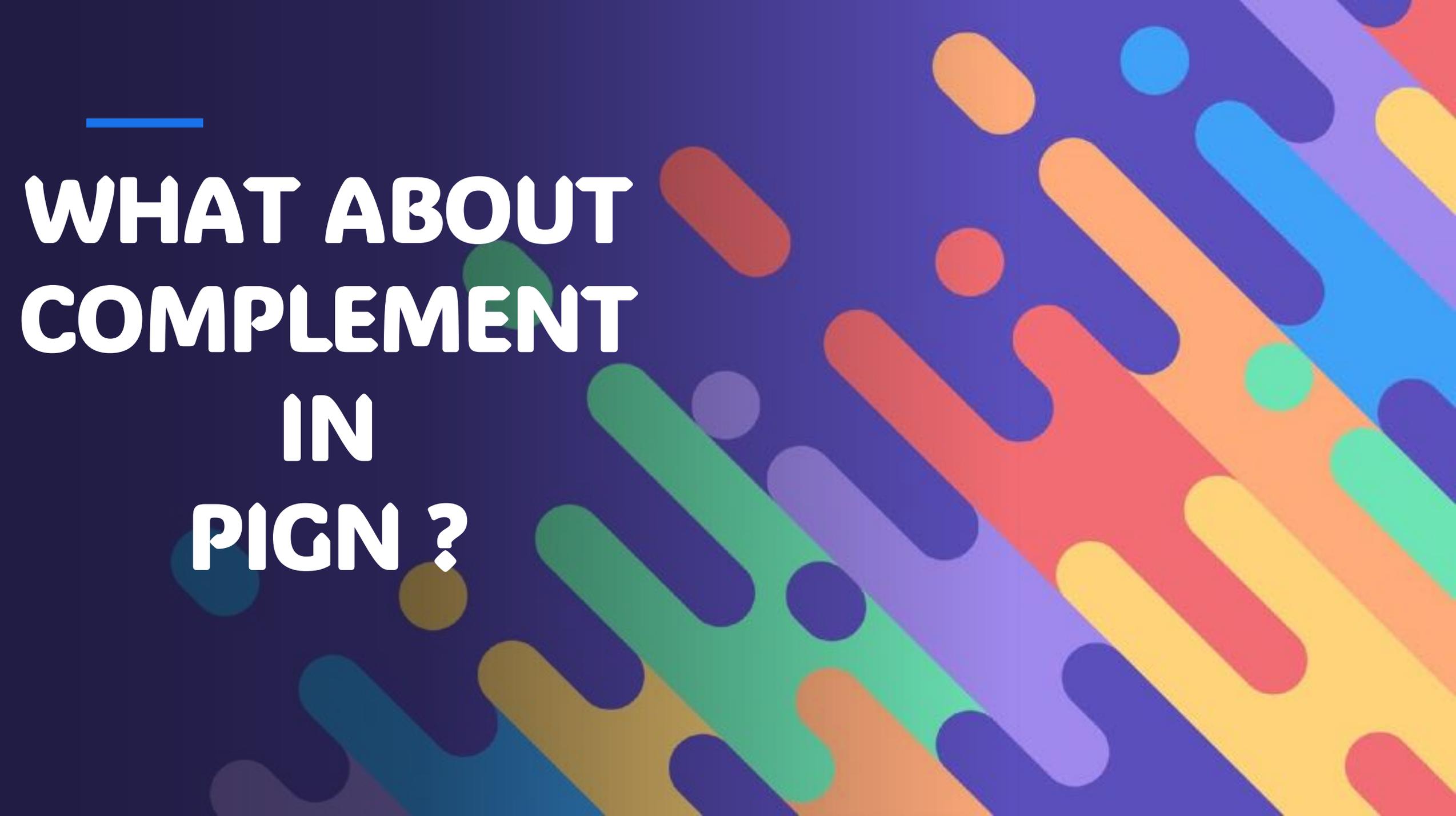
**Atypical**

**Complications**



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# WHAT ABOUT COMPLEMENT IN PIGN ?



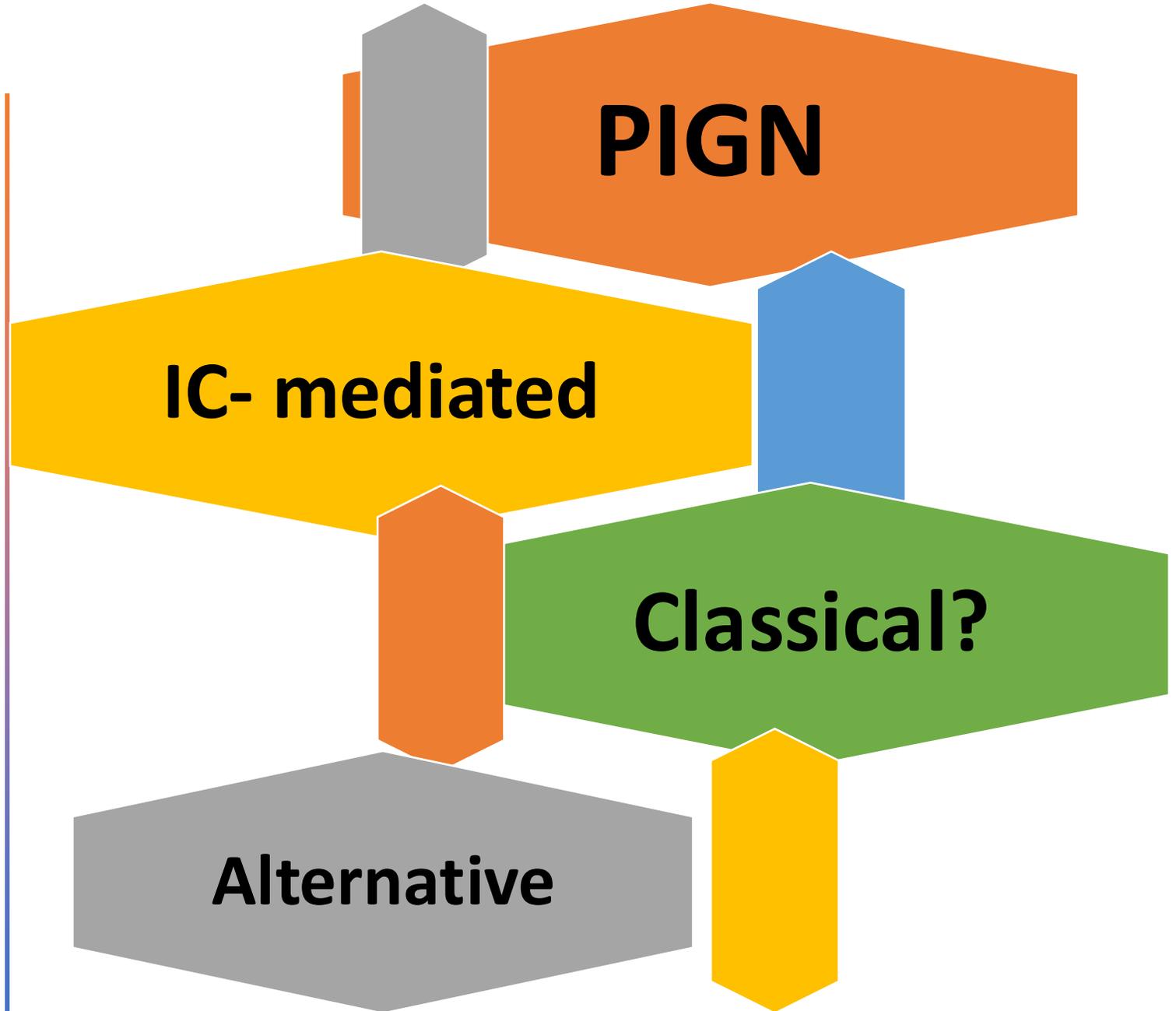
## Complement profile in PSAGN

- **Complement activation is the hallmark of APSGN.**
- **Alternative pathway is the predominant**
- **Lectin pathway may be involved in some.**

Confused

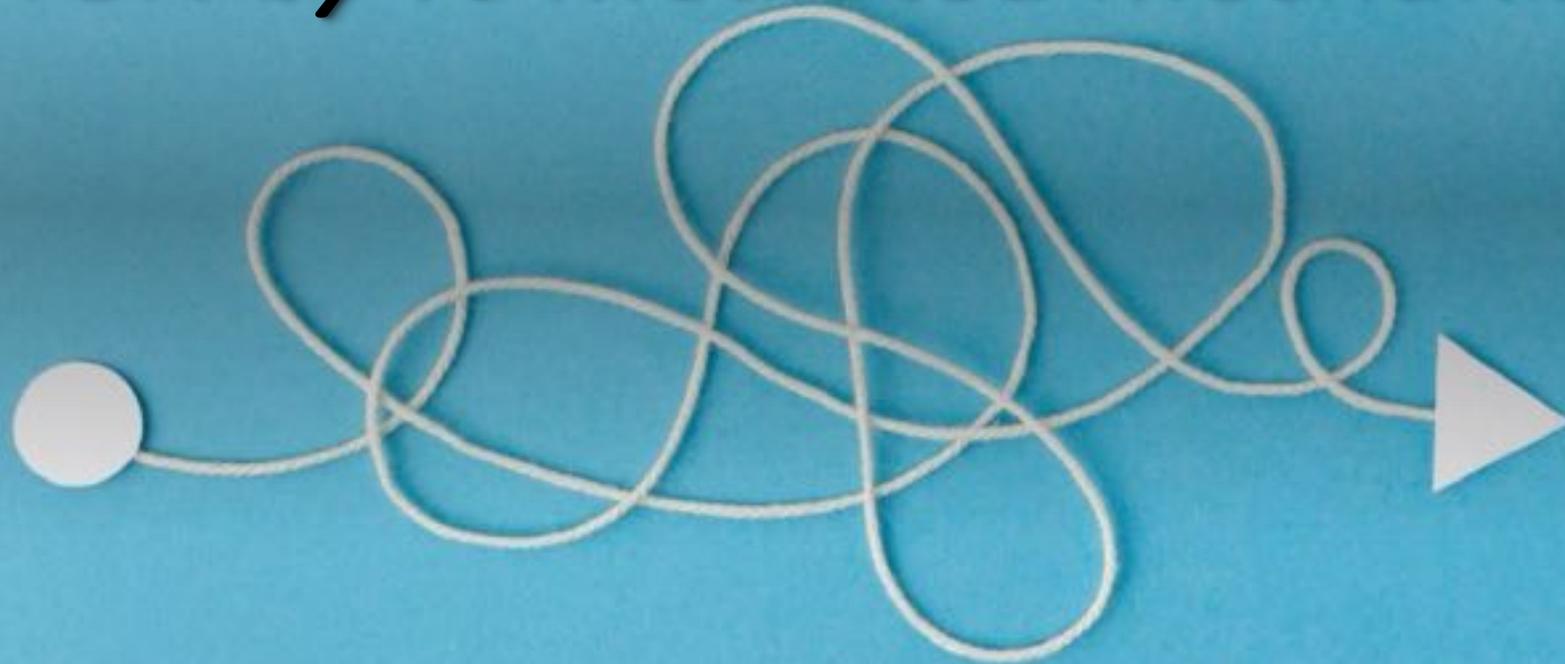


CONFUSED



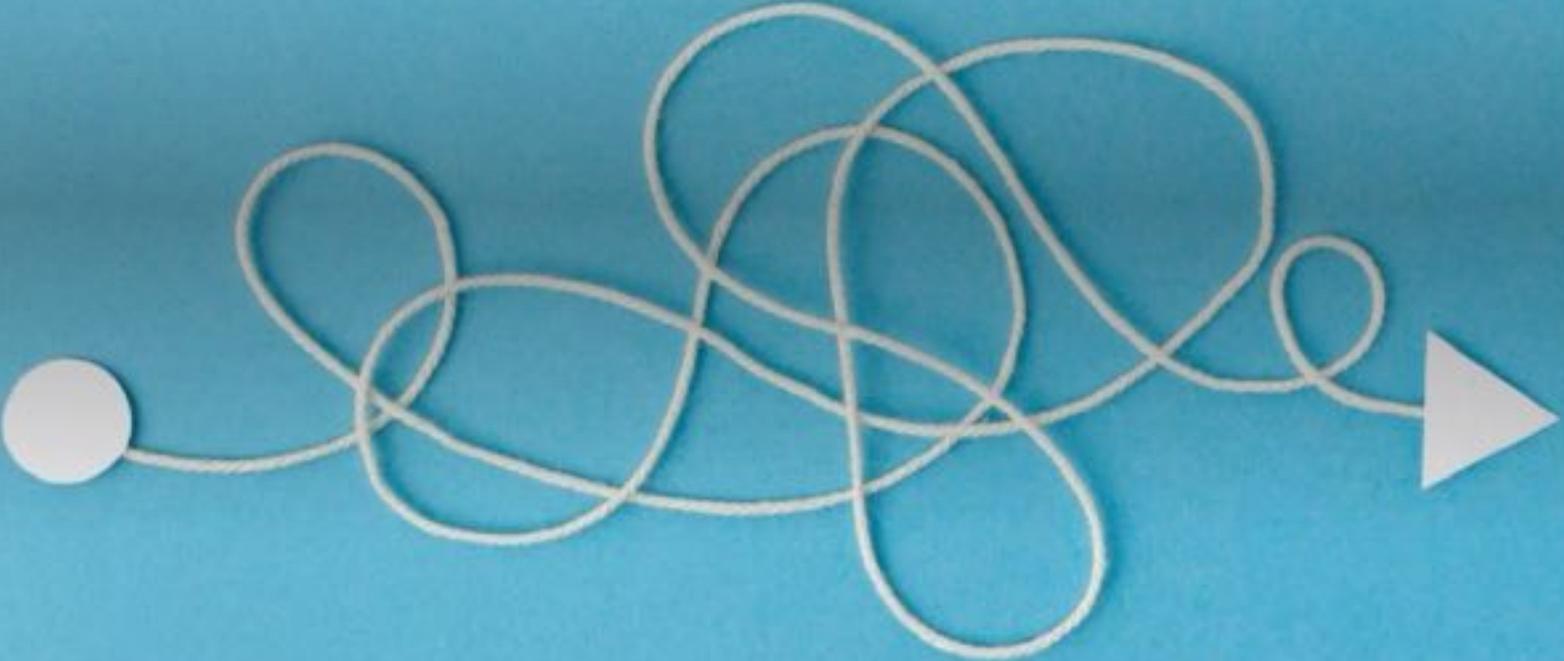


***1) How is the Alternative Pathway activated in PIGN by IC mediated mechanism ?***



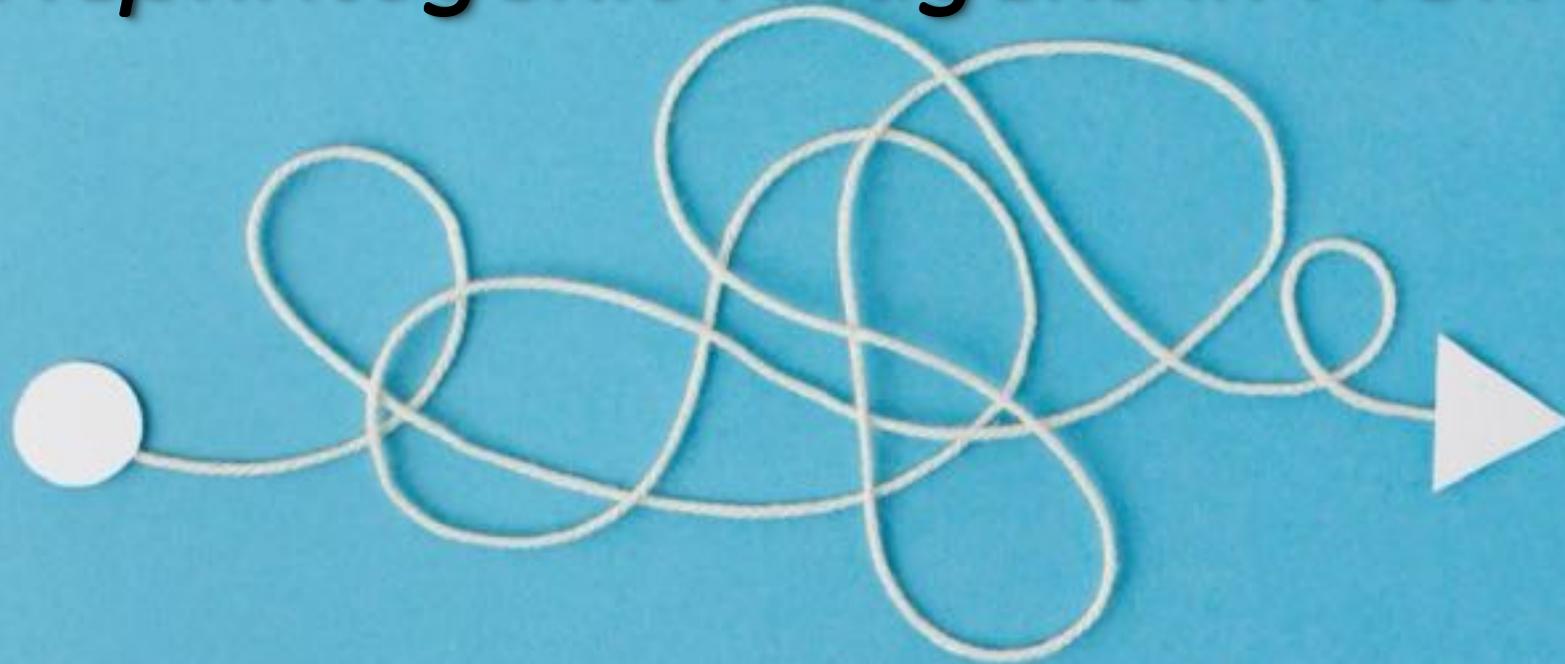


***2) How ICs containing streptococcal antigens activate alternative pathway in PIGN?***





***3) Does activation of the C- P in is suppressed by Nephritogenic Antigens in PIGN?***

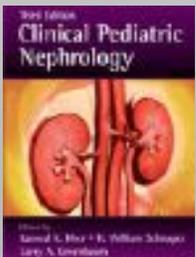
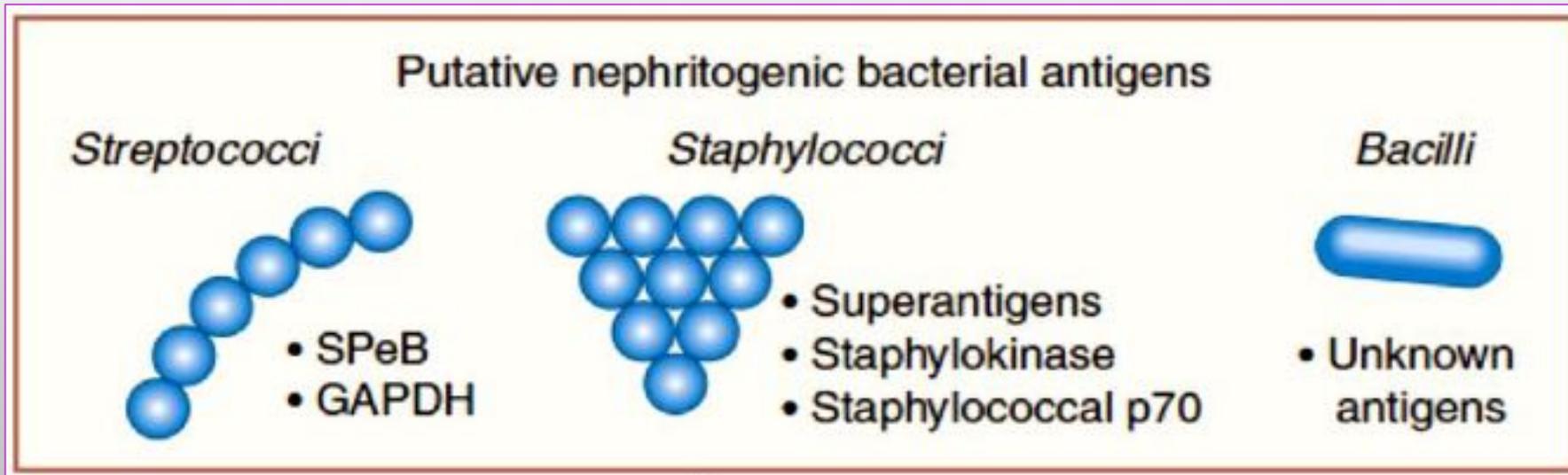




# **Nephritogenic Antigens**

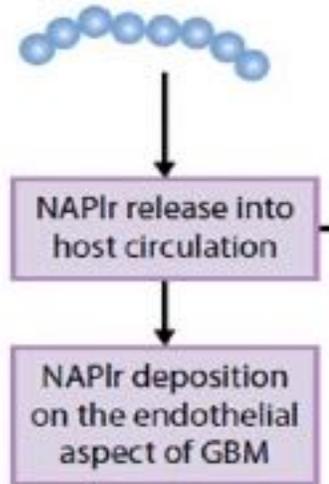


# NEPHRITOGENIC ANTIGENS IMPLICATED IN THE PATHOGENESIS OF PIGN

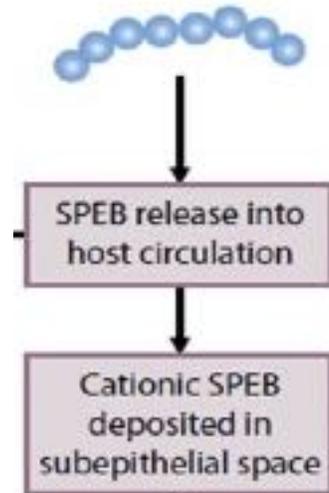
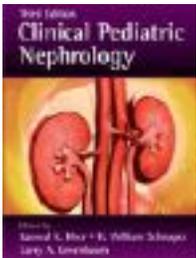


Streptococcal glyceraldehyde-3-phosphate dehydrogenase (GAPDH)

# Nephritogenic antigens in APSGN



**Nephritis-associated plasmin receptor (NaPIr)**



**Streptococcal pyrogenic exotoxin B (SPEB)**

The common pathway for both antigens is binding to plasmin, which activates complement, and promotes chemotaxis and degradation of GBM.



**What Is Your  
Secret Weapon?**



# PLASMIN

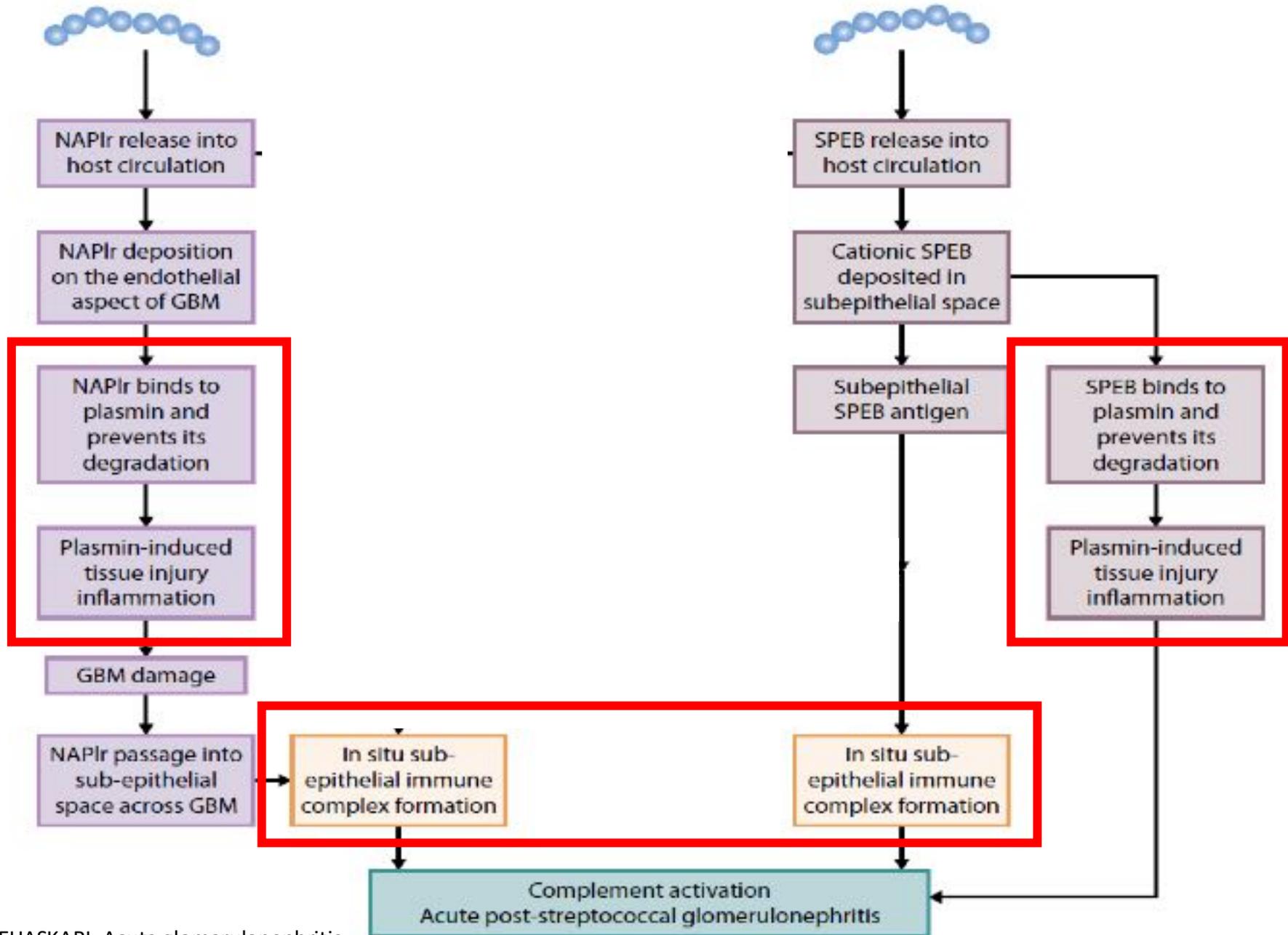


**POWERFUL TISSUE DESTRUCTION**

**DIRECT**

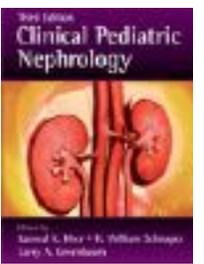
**COMPLEMENT**

**INFLAMMATION**



**SECRET WEAPON**

**SECRET WEAPON**



# Nephritogenic antigens in APSGN

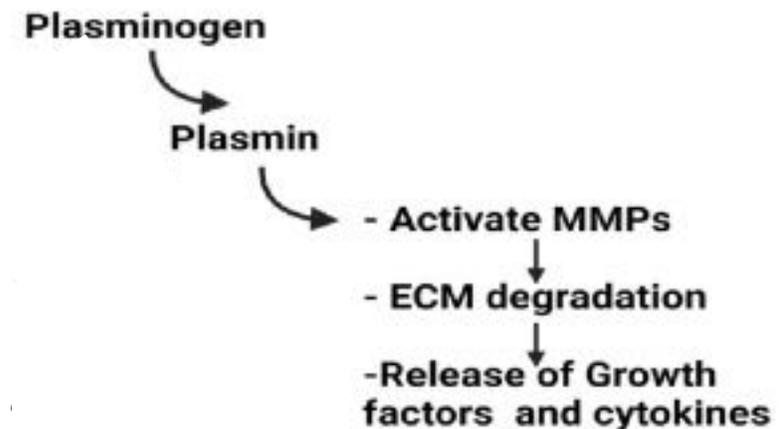
Plasmin-induced glomerular tissue damage

**ACTIVATES  
COMPLEMENT**

**DIRECT TISSUE  
DESTRUCTION**

**INDIRECT TISSUE  
DESTRUCTION**

**[SECRET  
WEAPON]**



# Nephritogenic antigens in APSGN

Plasmin-induced glomerular tissue damage

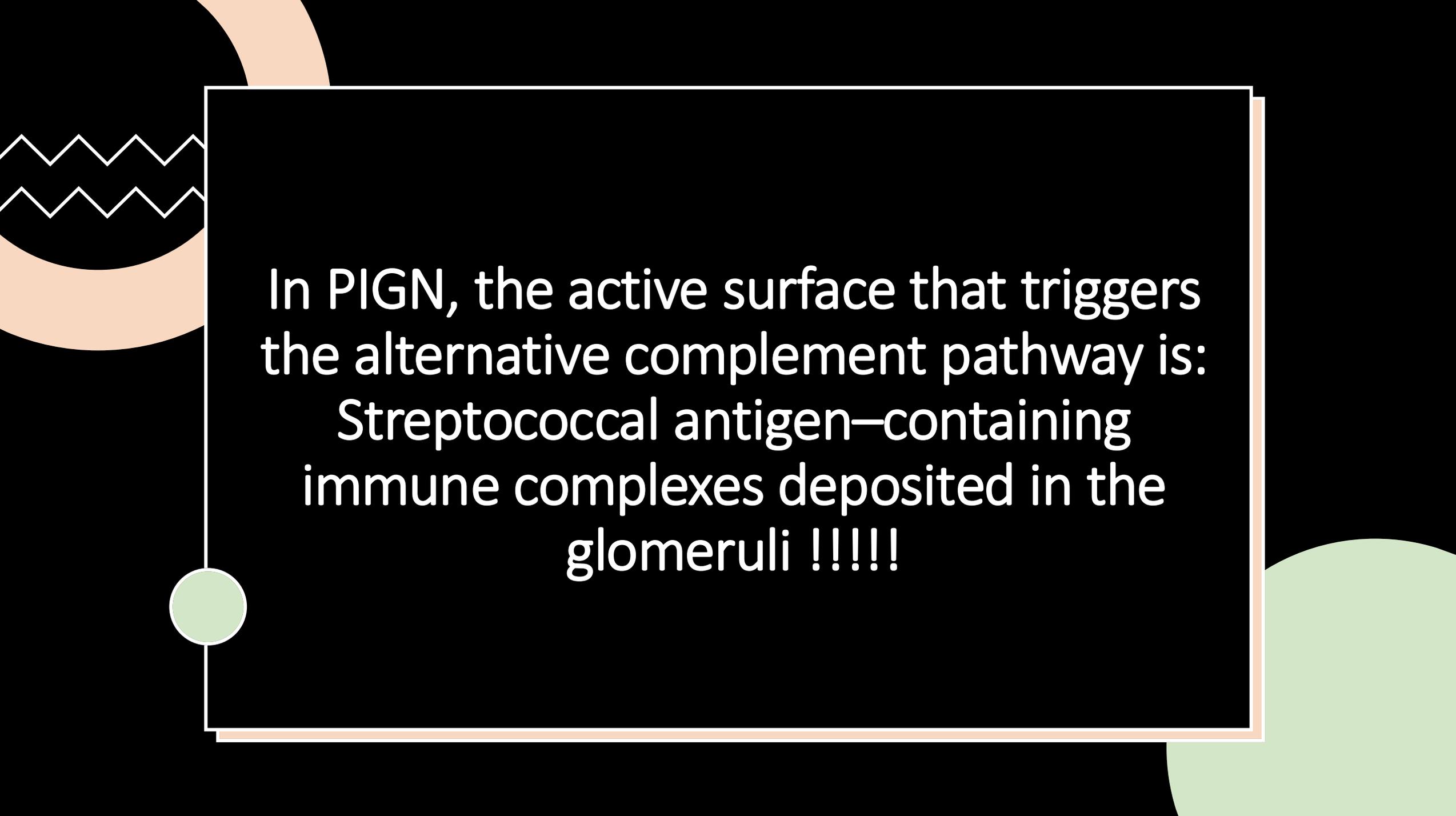
DEGRADING  
EXTRACELLULAR  
MATRIX PROTEINS.

INDIRECT ACTIVATION  
OF MATRIX  
METALLOPROTEINASES.

CIRCULATING ICs  
TRANSIT THE  
DAMAGED GBM

HUMPS

**[SECRET  
WEAPON]**



In PIGN, the active surface that triggers the alternative complement pathway is:  
Streptococcal antigen–containing immune complexes deposited in the glomeruli !!!!!

# Glomerular inflammation and injury in APSGN



**Glomerular in situ immune complex formation by antibodies against planted cationic bacterial antigens (SpeB)**



**Entrapment of circulating bacterial antigen-antibody immune complexes**



**Deposition of bacterial antigens (NAPlr) that bind to plasminogen, inducing local tissue injury**

# *Nephritogenic antigens as a driver of kidney injury*

## **Immune complex DEPOSITION**

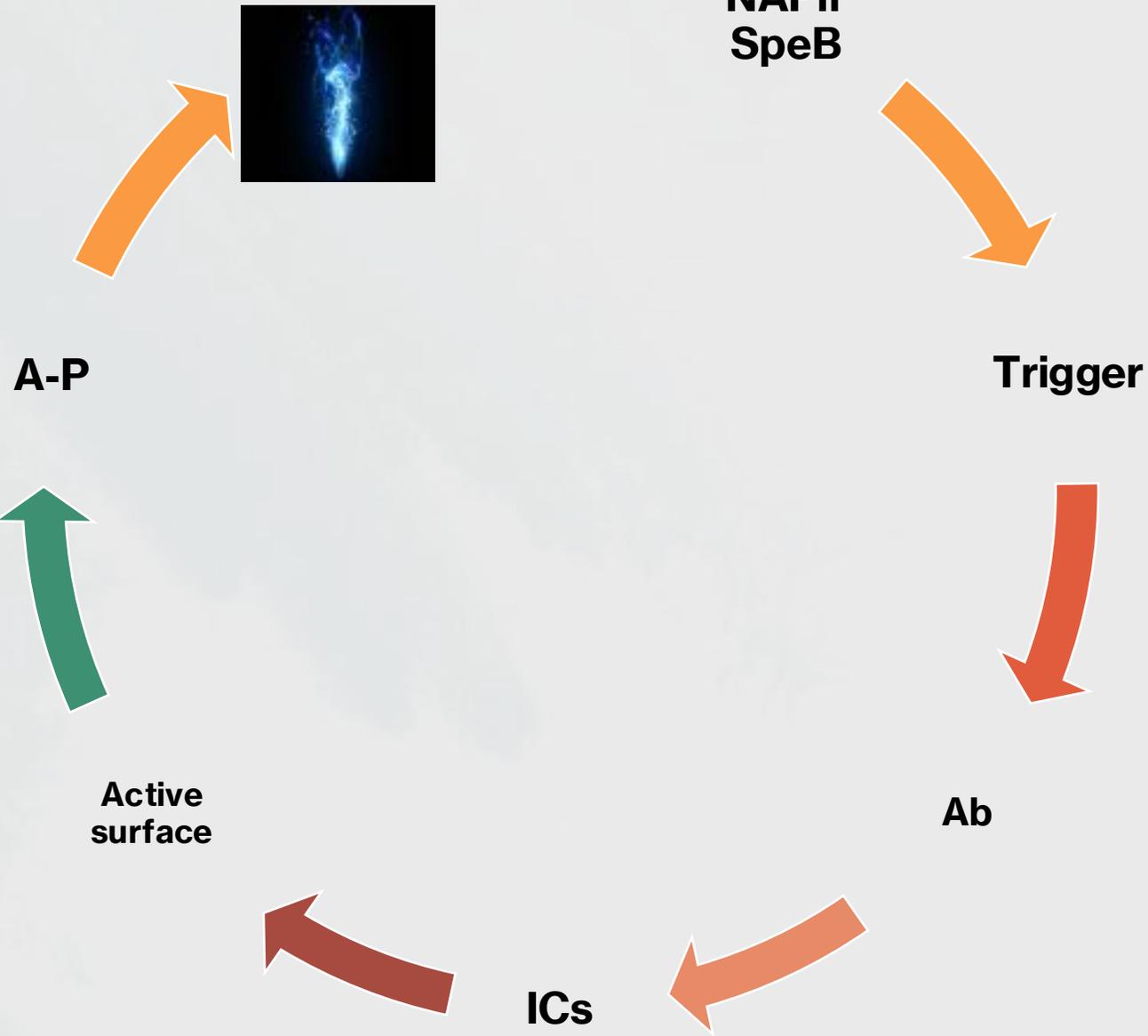
Active surface for  
alternative  
complement  
pathway

## **Complement ACTIVATION**

DIRECT  
&  
INDIRECT

## **Glomerular INJURY**

DIRECT  
&  
INDIRECT





NAP1r  
SpeB



bind



plasmin



direct

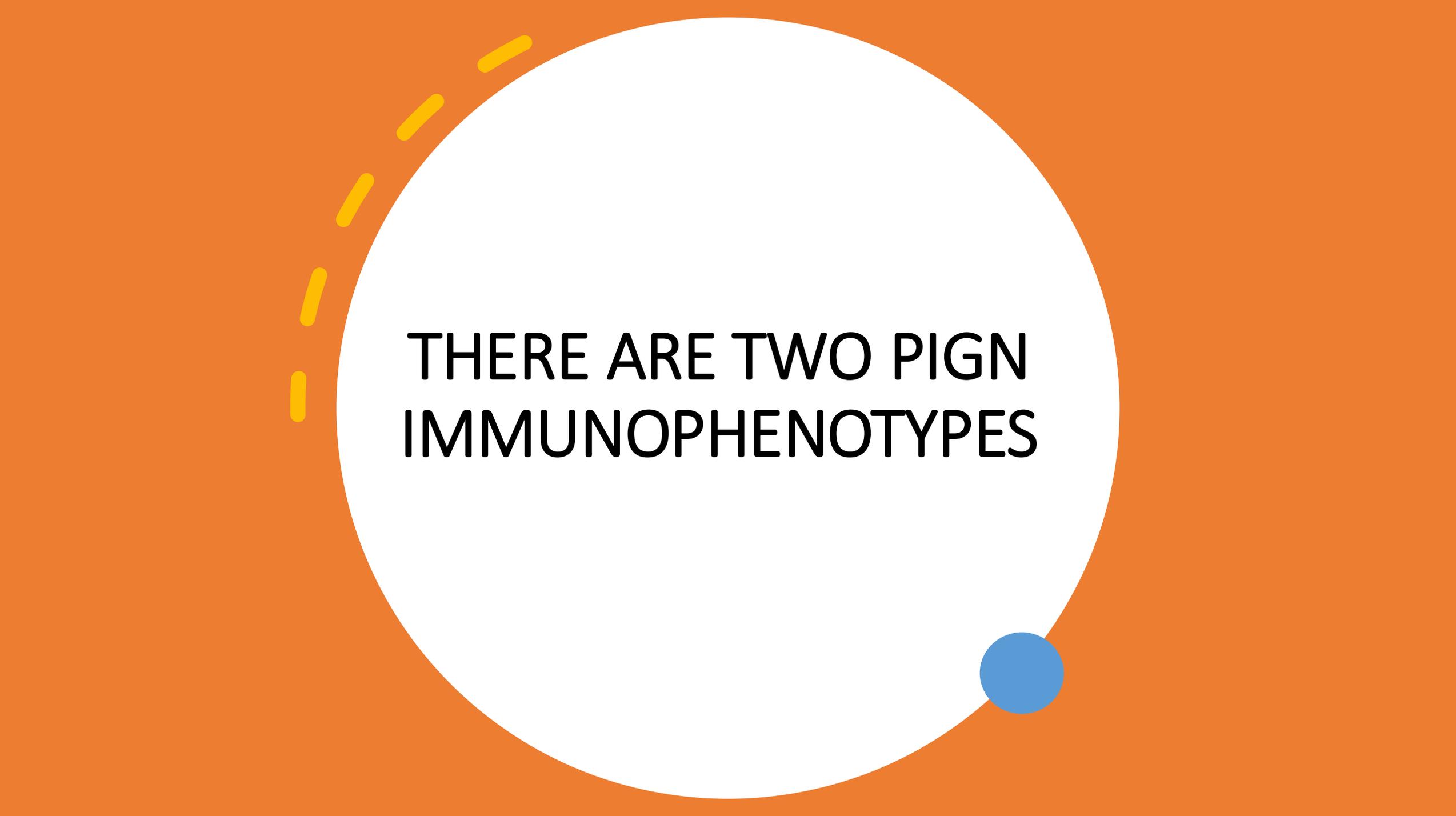


indirect

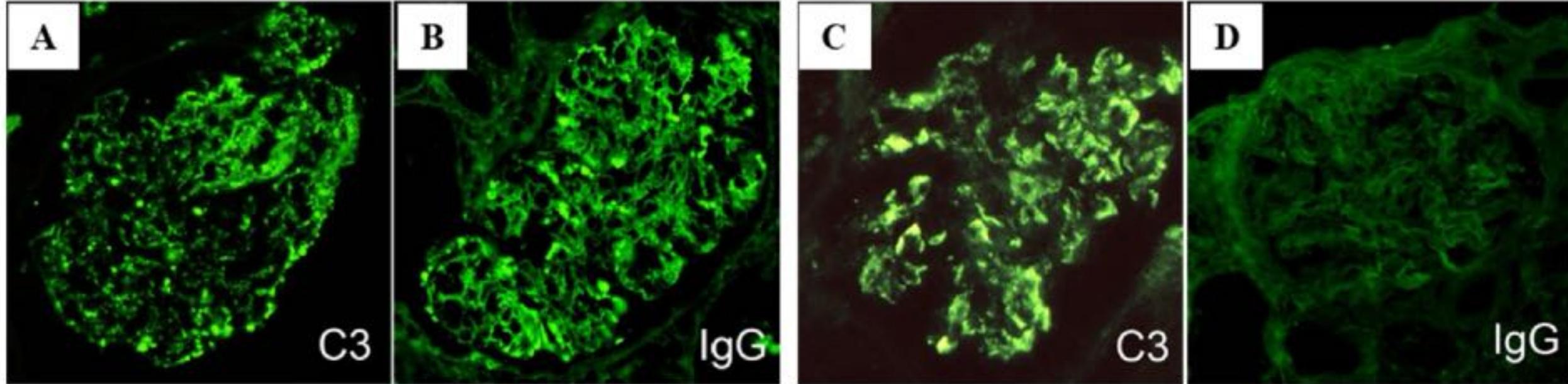


A-P





**THERE ARE TWO PIGN  
IMMUNOPHENOTYPES**



**Two different patterns of glomerular C3 and IgG deposits in PIGN:**

1. (A,B): C3 with IgG deposits, positive granular staining for C3 (A) and for IgG (B).
2. (C,D): C3 without IgG deposits, positive granular staining for C3 (C) but completely negative for IgG (D).

# The two main immune-patterns of PIGN:

## 1. Immune complex–dominant PIGN (IC-dominant PIGN)

- ✓ The “classic” post-infectious GN
- ✓ IgG + C3 (sometimes IgM or IgA) in a granular pattern
- ✓ Subepithelial “hump” deposits on EM

## 2. C3-dominant PIGN

- ✓ PIGN with complement dysregulation

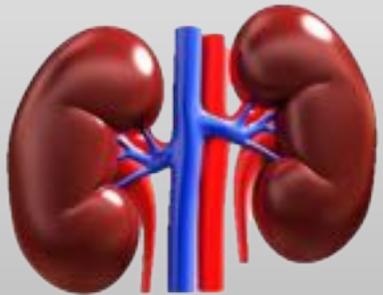
# ***GN with dominant C3***

**PIGN**

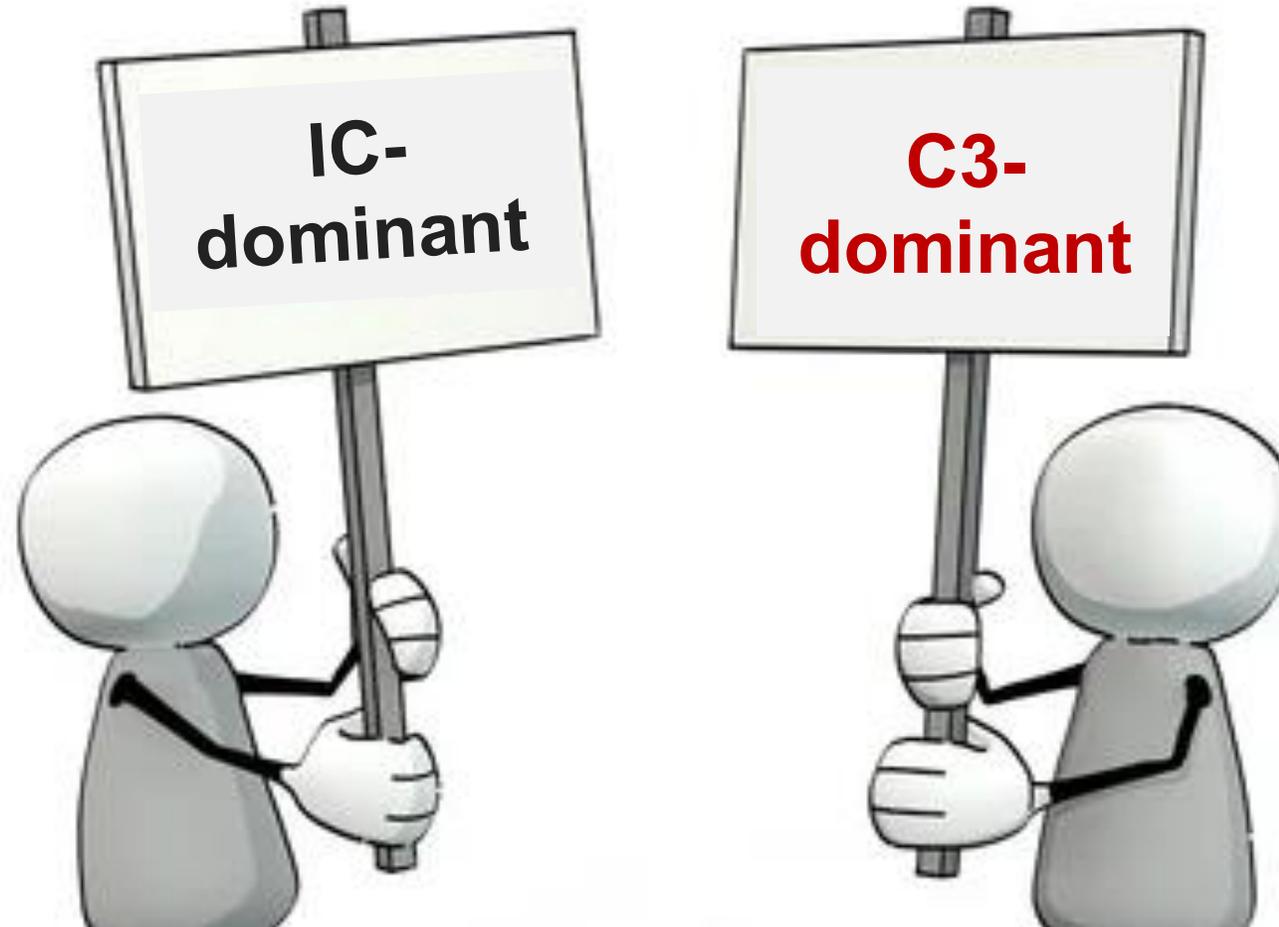
**C3 glomerulopathy**

**DDD**

**C3GN**



C3-dominant glomerular deposition was previously considered to represent a later stage of PIGN.



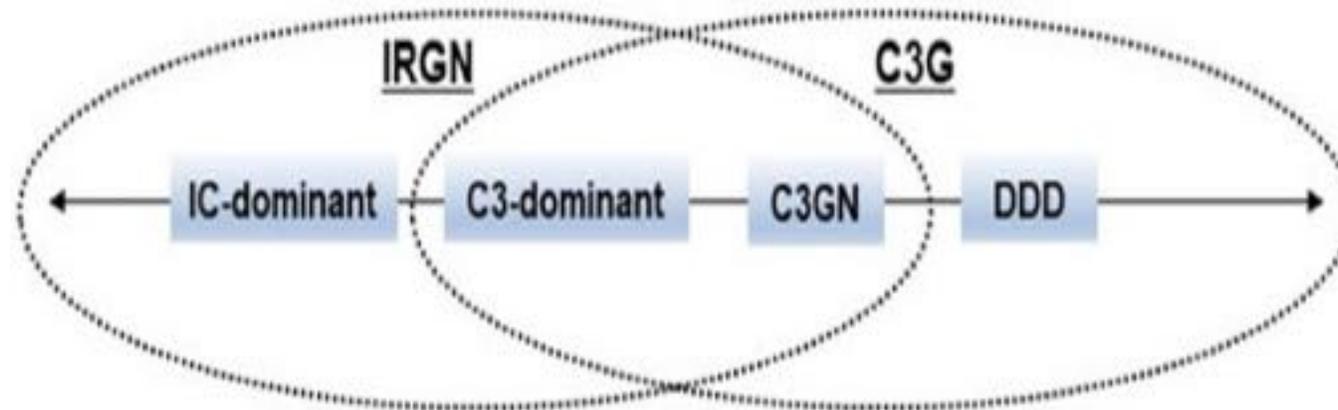
C3 positivity is dominant if it is at least two orders of magnitude greater than any other immunoreactant

**C3 dominance** with minimal immunoglobulin is the Diagnostic hallmark of C3G.

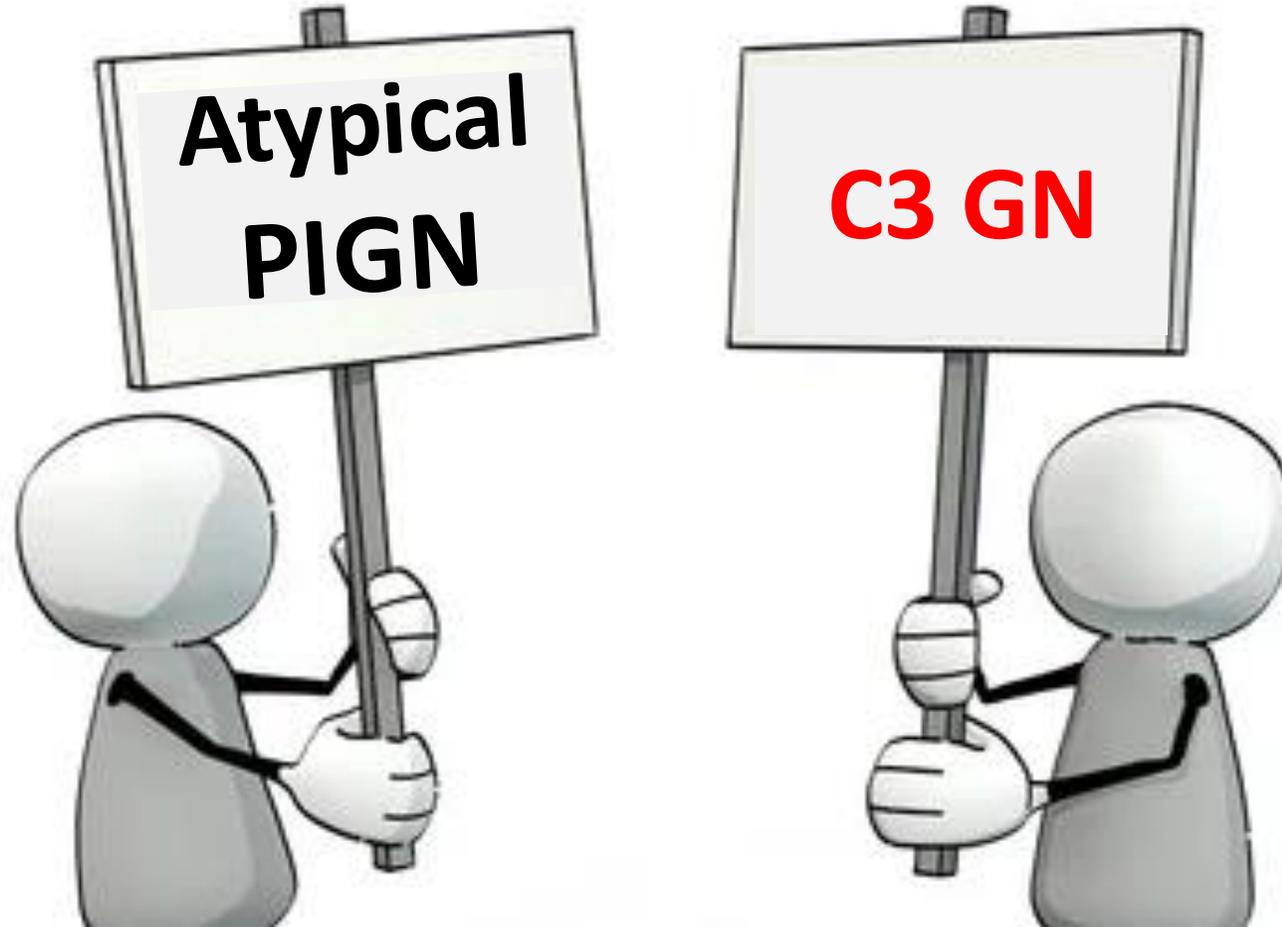
*“Does C3 G & PIGN define a disease spectrum ?”*



*“Does PSAGN represent a transient form of C3 GN ?”*



The overlapping clinico-pathological features of C3GN and PIGN have been attracting considerable attention



# *Does C3 G & PIGN define a disease spectrum ?*



PIGN usually follows a benign course, but few children have an atypical, severe presentation



These exceptional cases have been linked to the dysregulation of the complement alternative pathway.



There is a considerable overlap in the histopathological features of PIGN & C3G, which is also associated with A-P dysregulation but has a poorer outcome.



Some children with C3G may be misdiagnosed as PIGN before C3G become apparent.

# 3 Established C3G

•Pathogenesis: **primary alternative pathway dysregulation**

- Causes:
- C3 nephritic factor
  - Factor H/I antibodies
  - Complement gene variants (CFH, CFI, C3, CFB)

Persistent  
hypocomplementemia or  
recurrent “PIGN” is C3G until  
proven otherwise.

- Biopsy:
- **C3-dominant staining**
  - Minimal immunoglobulin
  - EM: dense intramembranous deposits (DDD) or mesangial/subendothelial

•Course: **Relapsing or progressive CKD**



**NAP1r**



**Anti-FB  
antibodies**



# Complex Mission of *NAPlr*

*Step 1: Invasion of Streptococci into Host*

*Step 2: Deposition of NAPlr in Glomeruli*

*Step 3: Plasmin Trapped by NAPlr*

*Step 4: Glomerular Inflammation*

*Step 5A: IC-Dominant Glomerular Injury*

*Step 5B: C3-Dominant Glomerular Injury*



**NAP1r**

**An Essential  
Inducer of  
C3-Dominant  
Glomerular  
Injury**





**Anti-FB  
antibodies**

**Streptococcal infection  
may cause transient or  
persistent  
anti-FB  
autoantibodies, which  
can overactivate  
complement.**





# Anti-FB antibodies

## **Anti-FB autoantibodies in PIGN:**

1. Promote ongoing alternative complement activation
  2. Help bridge classic PIGN into C3GN
- 



# Anti-FB antibodies

## Role in PIGN

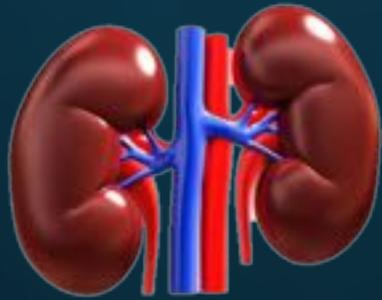
- Seen in a subset of PIGN, especially:
  1. Atypical or prolonged cases
  2. Cases that don't fully normalize C3 within 6–8 weeks



# Anti-FB antibodies

## May explain

1. Delayed recovery
  2. Relapsing or persistent hypocomplementemia
  3. Raises concern for evolution of C3 glomerulopathy
- 



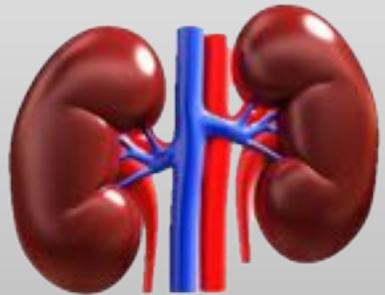
# Revisiting PIGN in the emerging era of CMKD

**PIGN**

**APSGN**

**Classical**

**Atypical**



**RECURRENT**

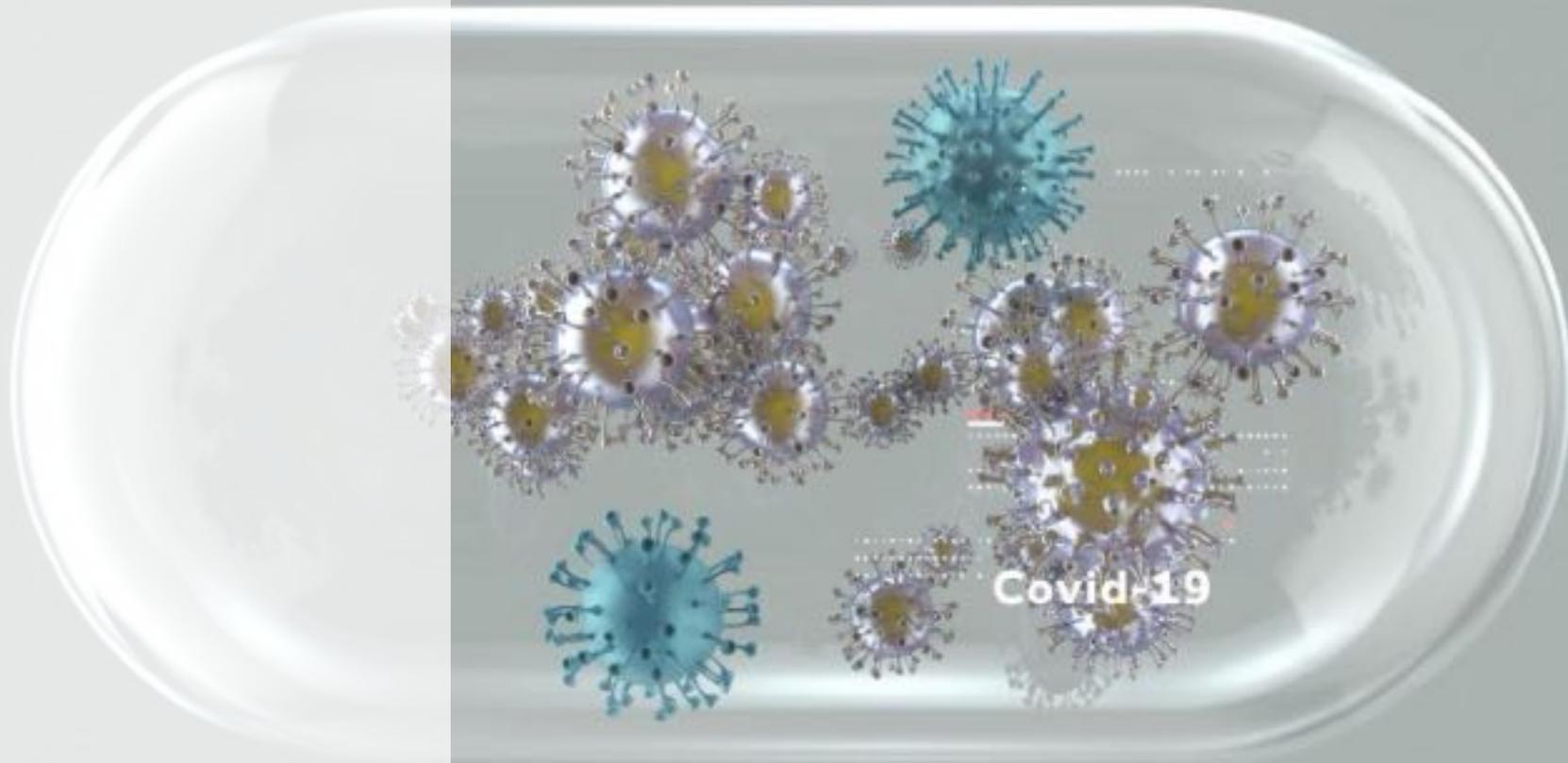
**PERSISTENT**

**ESKD**

**DEATH**

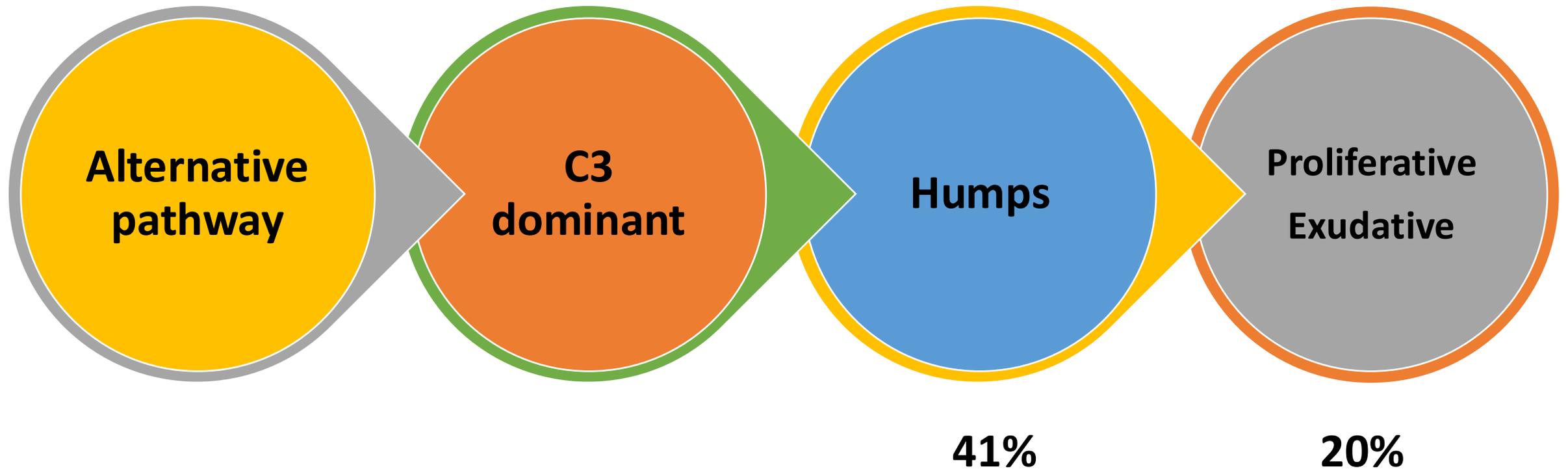


# PIGN & C3GN



**Similar Yet Dissimilar**

The overlap of clinical and pathologic features between PIGN and C3GN is striking.



Pathology  
of  
**G3GN**

Hypercellularity

Dominant C3 deposition

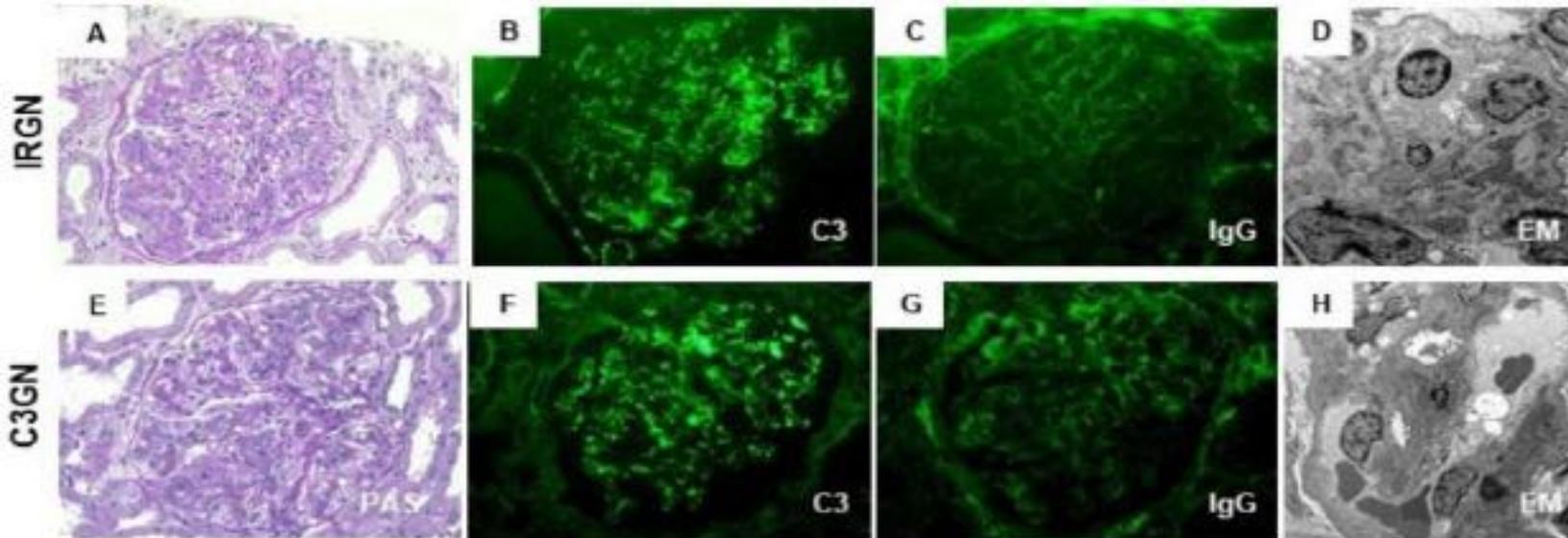
Intramembranous , mesangial &  
**subendothelial** deposits.

Pathology  
of  
**APSGN**

Hypercellularity

Dominant C3 deposition

**Subepithelial** deposits  
(Humps) .



Distinguishing  
**PIGN**  
from  
**C3GN**  
has become a  
diagnostic  
challenge

---

C3-dominant IF may represent late stages of IRGN, making it difficult to distinguish from C3G

---

Subepithelial humps commonly seen in IRGN is also a feature of C3G and insufficient to distinguish IRGN from C3G.

---

The current consensus recommends monitoring these patients clinically and with laboratory tests.

---

Patients with IRGN are expected to recover kidney function and resolve hypocomplementemia, proteinuria, and hematuria within 12 weeks

---

If clinical and laboratory abnormalities persist beyond 12 weeks, C3G should be suspected, and a kidney biopsy should be performed to help differentiate between these 2 conditions.

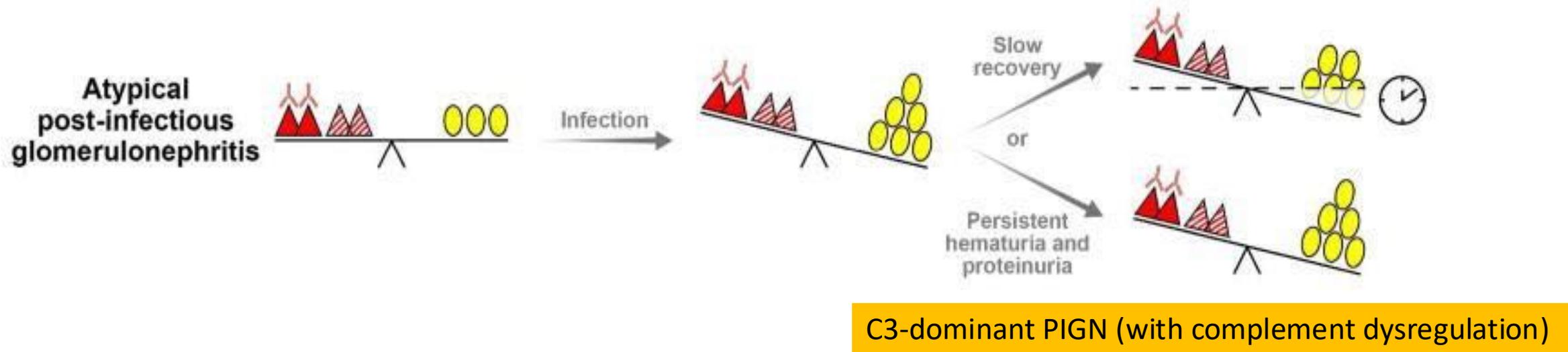
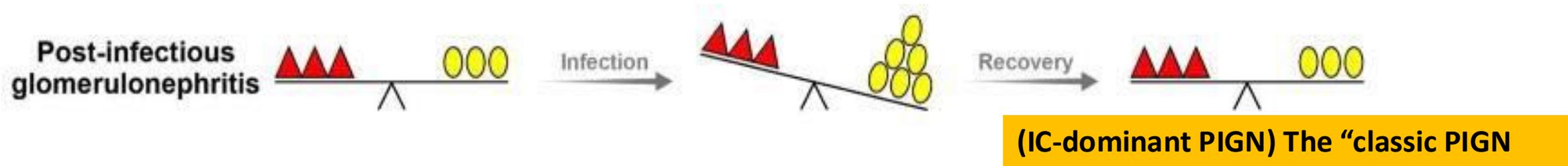


PIGN & C3G ARE NOW CONSIDERED PART OF A  
DISEASE SPECTRUM, NOT ENTIRELY SEPARATE  
ENTITIES !!!!!!!



# WHAT ABOUT COMPLEMENT IN PIGN ?





underlying defect in the alternative pathway of the complement, either autoantibodies against C3 convertase or mutations in complement regulatory genes.

# Atypical APSGN

Infographic by Anitha Rangan  
(@AnithaRangan)

Acquired and genetic factors

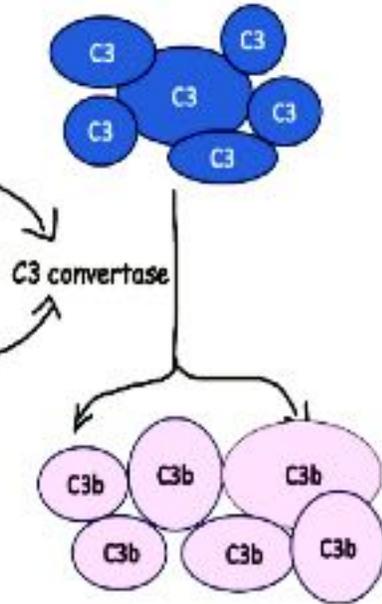
Dysregulation in the alternative complement pathway, resulting in overactivation of C3 convertase

Inflammation and glomerular injury

Persistent Proteinuria, Hematuria, Depressed C3

Gene mutations in regulatory proteins: Factor H, B, D

C3 Nephritic factors



## Dysregulation of A-P

AGN

Glomerular deposition of C3/IgG.

Classic APSGN

Latent period

C3

Self-limited  
One episode  
No recurrence

## "Atypical" PIGN & Complement Dysregulation



The disease persists or progresses to ESKD due to:

1. **Genetic Defects:** Mutations in AP regulatory proteins
2. **Acquired Defects:** Presence of (C3NeF), stabilize the C3 convertase

# PERSISTENT PIGN



Had underlying genetic mutations and/or auto-antibodies



Presence of C3Nef



Persistent activity of complement



Interestingly, demonstrating transformation of PIGN to C3G



Explaining initiation of C3G by streptococcal infection.





Does PIGN hide  
**Phoenix** under the  
ashes ?



# Yes

- **Some cases evolve into C3GN.**



Some cases of PIGN don't fully shut off complement after the infection clears.

Instead, they unmask an underlying defect in regulation of the alternative complement pathway, and the disease evolves into C3G.



# Why does this happen?

## 1 Persistent alternative complement activation

- In patients who progress to C3 GN:
    - **No switch off**
    - **Alternative pathway keeps firing**, even after infection is gone
    - → **persistent low C3** and ongoing glomerular injury
-



# Why does this happen?

## **2** Underlying complement regulatory abnormalities

- 1. C3 nephritic factor (C3NeF) → stabilizes C3 convertase**
  - 2. Mutations or dysfunction in complement regulators**
-

# Why does this happen?

## 3 Infection as the “second hit”

### Two-hit model:

1. **Genetic or acquired complement dysregulation**  
(silent)
  2. **Infection** → massive complement activation →  
disease becomes clinically apparent
-



PIGN  
is often the first  
**"STRESS TEST"**  
of the alternative pathway.  
Failure to recover suggests  
underlying C3G.

# Clues it's no longer simple PIGN

C3 remains low beyond 8–12 weeks

Persistent hematuria/proteinuria

Repeat biopsy shows:

- **C3-dominant staining**
- Minimal or absent IgG
- No classic subepithelial humps

Diagnosis shifts to C3 GN

---

## **CLINICAL CLUES SUGGESTING C3G AFTER PIGN**

- **Recurrent “PIGN” episodes**
- **Progressive proteinuria or CKD**
- **Family history of complement-mediated disease**

Feature	<b>PIGN (Post-Infectious GN)</b>	<b>C3 Glomerulonephritis</b>
Primary mechanism	Immune-complex mediated	Alternative complement dysregulation
Trigger	Recent infection	Infection as “second hit”
Complement pathway	Alternative (transient)	Alternative (persistent)
Serum C3	Low → <b>normalizes in 6–8 wks</b>	<b>Persistently low</b>
Light microscopy	Diffuse endocapillary proliferative GN	MPGN / mesangial proliferative
Immunofluorescence	<b>C3 + IgG</b> (± IgM, IgA)	<b>C3 dominant / C3 only</b>
IF pattern	Granular “starry sky”	Granular, no Ig
EM deposits	<b>Subepithelial humps</b>	Mesangial + intramembranous
EM hallmark	Large discrete humps	Ribbon-like dense deposits (DDD)
Disease course	Self-limited	Progressive
Prognosis	Good (esp. children)	Variable, often poor
Key diagnostic clue	Ig present on IF	C3 ≥ 2 orders stronger than Ig

<b>Feature</b>	<b>PIGN</b>	<b>C3 GN</b>
<b>Trigger</b>	Infection	Complement dysregulation
<b>C3 level</b>	Low, then normalizes	Persistently low
<b>IF</b>	IgG + C3	C3 dominant
<b>Course</b>	Self-limited	Progressive

**PIGN = immune complexes + humps + recovery**

**C3 GN = complement only + persistence + progression**

## Why supportive care is NOT enough ?

**C3 GN →**

**Complement-targeted / immunomodulatory therapy**

- ❑ continuous alternative complement activation
  - ❑ You must interrupt the complement cascade or slow progression.
1. RAAS blockade → reduce proteinuria
  2. Immunosuppression:
    - ✓ Steroids ± mycophenolate
  3. Complement-targeted therapy (severe/refractory cases):
    - ✓ Eculizumab (C5 inhibitor)

<b>If misdiagnosed as...</b>	<b>Consequence</b>
PIGN instead of C3 GN	Missed chance to stop progression
C3 GN instead of PIGN	Unnecessary immunosuppression

**Why the distinction matters ?**



# Timeline

*Distinction based on morphology alone is difficult*

*Allow the clinical course and laboratory follow-up to dictate further differentiation.*

Feature	PIGN	C3 GN
C3 recovery	Normalizes in 6–8 weeks	Persistently low
Course	Self-limited	Progressive



**C3 Glomerulopathy and post-infectious  
glomerulonephritis define a disease  
spectrum**

---

THE CONCEPT OF  
PIGN & C3G  
AS PART OF  
**A SPECTRUM**

**PIGN & C3G are different outcomes of the same complement-mediated process.**

**Normal complement regulation → classic PIGN**

**Defective complement regulation → C3G**

**PIGN can be the first manifestation of C3G.**

---

THE CONCEPT OF  
PIGN & C3G  
AS PART OF  
**A SPECTRUM**

Both involve **dysregulation of the alternative complement pathway**

Infection (classically streptococcal) acts as a **trigger** → strong complement activation.

In most patients → complement regulation recovers → **PIGN resolves**.

In some → **complement control defects** → disease **persists or recurs**, leading to **C3G**.

---

## CONCLUSION

- Even in classic cases of PIGN, follow-up is needed to ensure that there is resolution & absence of recurrence.
- Differentiation between PIGN & C3GN is critical as the prognosis and management differ significantly.



ANNE GEDDES

”اللهم انفعنا بما علمتنا،  
وعلمنا ماينفعنا،  
وزدنا علما“

**Thank you**

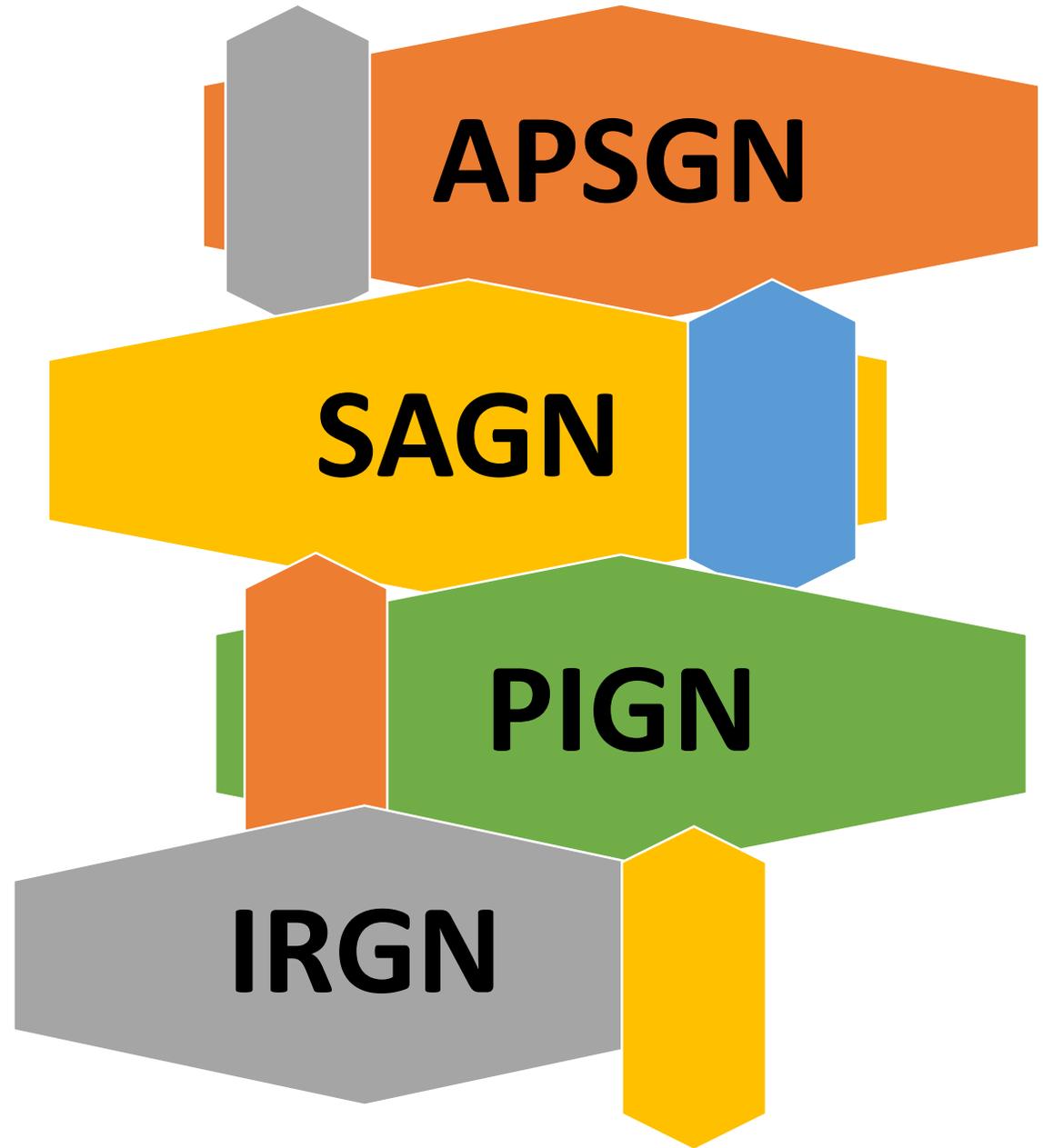




Confused



CONFUSED





# PIGN

The list of  
infective agents  
that may  
cause it is  
growing

- 1. Bacterial**
- 2. Viral**
- 3. Fungal**
- 4. Parasitic**





**PIGN is a subset of IRGN**



**“(IRGN)”**  
has replaced  
**(PIGN)**



GN of active infection is a subset of IRGN

# **Infection-related GN (IRGN)**

- 1. Postinfectious GN (PIGN)**
- 2. GN of active infection**

# IRGN

## PIGN

Broad group of acute nephritis that follows a variety of infectious events.

## APSGN

- Children: 2–15 years old.
- A  $\beta$ - haemolytic *Streptococci*
- Most patients recover

## GN of Active Infection

Ongoing infection

PERSISTENT BACTERAEMIA

1. BACTERIAL ENDOCARDITIS
2. SHUNT NEPHRITIS.
3. DEEP SEATED INFECTIONS

**Controlling infection is essential**





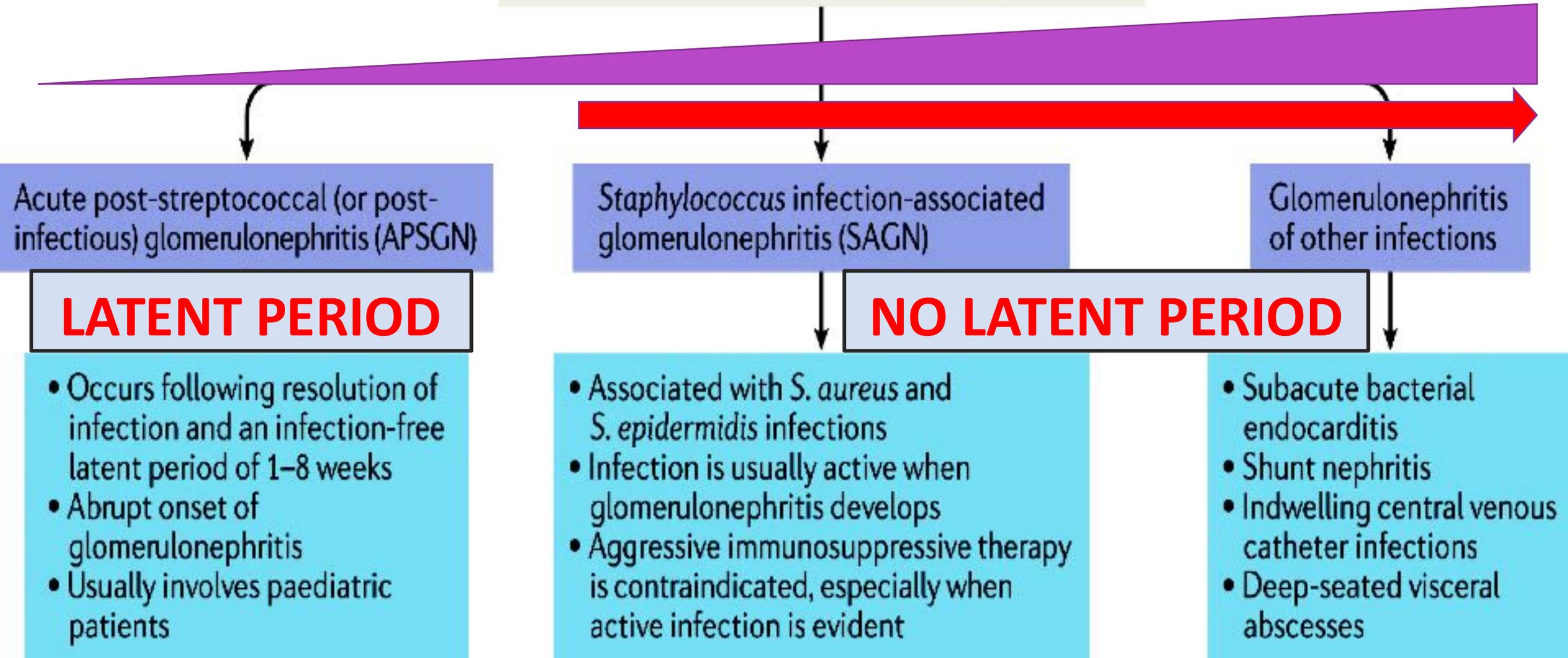
For over a century, (APSGN) was the  
typical form of  
PIGN

*Striking changes,  
particularly in developed countries.*

# Changing Trends

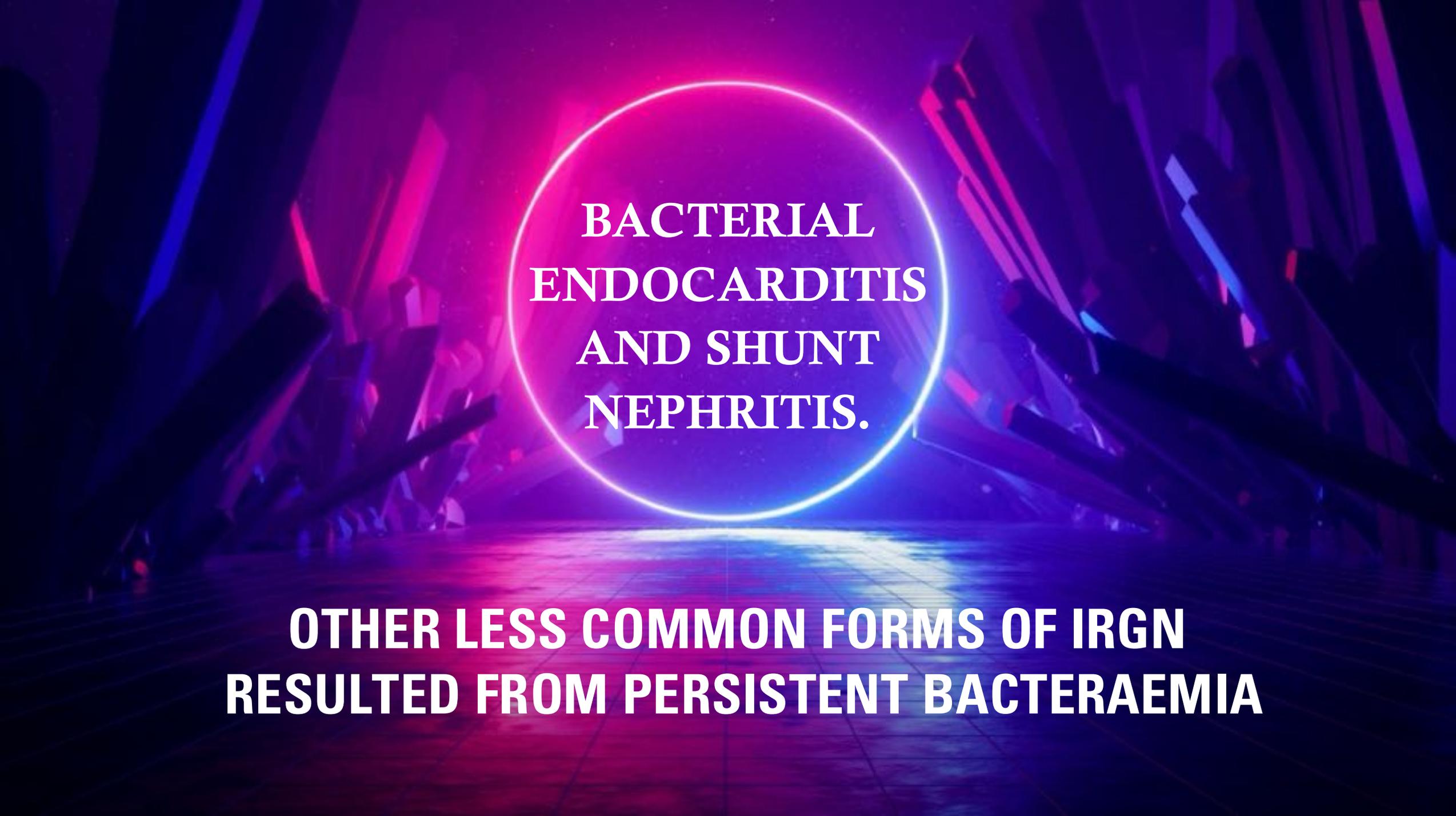
APSGN decreased in the Western world, whereas (SAGN) cases increased

## Bacterial infection-associated glomerulonephritis



Feature	APSGN	SAGN
Age group	Mainly paediatric age group (peak incidence in the first decade)	<ul style="list-style-type: none"> <li>• Mainly adults, between 50 and 80 years of age</li> <li>• Younger patients with IVDU</li> </ul>
Bacterial strain	Nephritogenic strains of <i>Streptococcus pyogenes</i> (GAS)	MRSA, MSSA, MRSE, MSSE
Type of infection	Streptococcal pharyngitis, tonsillitis, mastoiditis, peritonsillar abscess, otitis media, pyoderma, streptococcal superinfection of scabies	<u>Endocarditis</u> , skin infections (usually leg ulcers), cellulitis, skin abscesses, osteomyelitis, septic arthritis, pneumonia, <u>bacteraemia of unclear source</u> , post-surgical site infections
Infection-free latent period	<ul style="list-style-type: none"> <li>• 1–2 weeks for streptococcal sore throat</li> <li>• 3–6 weeks for pyogenic streptococcal skin infections</li> <li>• In many patients, GN may remain a subclinical disease</li> </ul>	<ul style="list-style-type: none"> <li>• <b>No infection-free latent period</b></li> <li>• Infections can be occult and deep-seated</li> <li>• Co-morbid conditions may mask signs of infection. Infection may come to attention after the patient presents with acute nephritis</li> </ul>

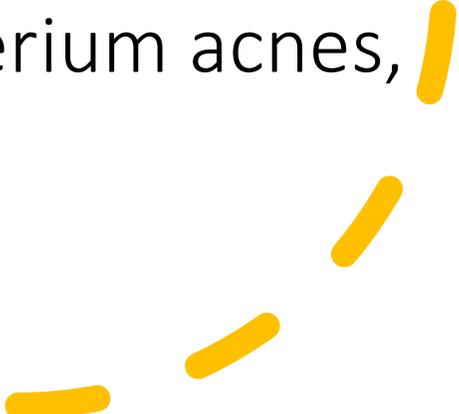
Feature	APSGN	SAGN
Clinical presentation	<ul style="list-style-type: none"> <li>• Renal function normal or mildly elevated serum creatinine levels. Dark-coloured urine ('cola-' or 'tea-coloured' urine). Proteinuria sub-nephrotic range</li> <li>• Abrupt onset oedema (prominent facial oedema)</li> <li>• HTN in half of the affected children</li> </ul>	<ul style="list-style-type: none"> <li>• AKI, microscopic haematuria, heavy proteinuria (<u>nephrotic range</u>)</li> <li>• Worsening of underlying co-morbid conditions such as diabetes mellitus, HTN, heart failure</li> <li>• Subset of patients present with <u>LCV rash</u></li> </ul>
Laboratory findings	<ul style="list-style-type: none"> <li>• Low C3, normal C4 levels</li> <li>• Rising ASO titres</li> </ul>	<ul style="list-style-type: none"> <li>• Low C3 in <u>30 to 50% of patients</u>, C4 usually normal</li> <li>• Positive ANCA serology in a subset of patients. Often dual positivity for myeloperoxidase and proteinase 3. Usually, titres are low positive</li> </ul>
Outcome	<ul style="list-style-type: none"> <li>• Usually complete recovery in paediatric patients</li> <li>• For adult patients, prognosis is less favourable. Rare cases can progress to chronic kidney disease when the kidney shows numerous crescents</li> </ul>	<ul style="list-style-type: none"> <li>• Prognosis is unpredictable</li> <li>• Poorly controlled diabetes, advanced age, endocarditis, ANCA positivity with crescents in the biopsy portend worse prognosis</li> </ul>



**BACTERIAL  
ENDOCARDITIS  
AND SHUNT  
NEPHRITIS.**

**OTHER LESS COMMON FORMS OF IRGN  
RESULTED FROM PERSISTENT BACTERAEEMIA**

# Shunt Nephritis

- Ventriculoperitoneal shunts
  - Low-grade fever may be the only sign
  - This may result in delay of diagnosis.
  - **Staphylococcus epidermidis** is the most common pathogen(75%).
  - **S. aureus, corynebacterium, listeria,** pseudomonas, Propionibacterium acnes, and Bacillus species
- 

# Shunt Nephritis

- Membranoproliferative pattern.
- Granular deposits of C3, IgM & IgG in subendothelial & mesangial locations.
- Persistent antigenemia is responsible for IC formation, but it is unclear whether they are formed in the circulation or *in situ*.
- Classical complement pathway activation
- C3a & C5a perpetuate local inflammation.

# Shunt Nephritis

The prognosis of is excellent, with normalization of kidney function & resolution of proteinuria,

if the infected shunt is removed and appropriate antibiotic treatment is administered.

## Endocarditis-associated GN

# Streptococcus viridians

- The kidney biopsy findings are diverse
- Focal segmental proliferation is the most common finding, followed by diffuse endocapillary proliferation.
- Exudative features are similar to APSGN.
- Crescents and glomerular necrosis may also be present, and in some patients may affect >50% of glomeruli

## Endocarditis- associated GN

- Immune complex disease
- Deposition of circulating immune complexes in the glomeruli, but also there is evidence for in situ formation of complexes.
- The nephritogenic bacterial antigens were identified within the affected glomeruli in *S. aureus* and streptococcal infections.

## Endocarditis-associated GN

- Treatment consists of antibiotic therapy and surgery to remove valvular vegetations and eradicate the infection.
  - Most complications resolve on treatment with appropriate antibiotics.
  - In a few patients with proliferative lesions and no improvement with antibiotics, corticosteroids and cyclophosphamide may be useful
  - Patients with crescentic GN may benefit from plasmapheresis.
- 