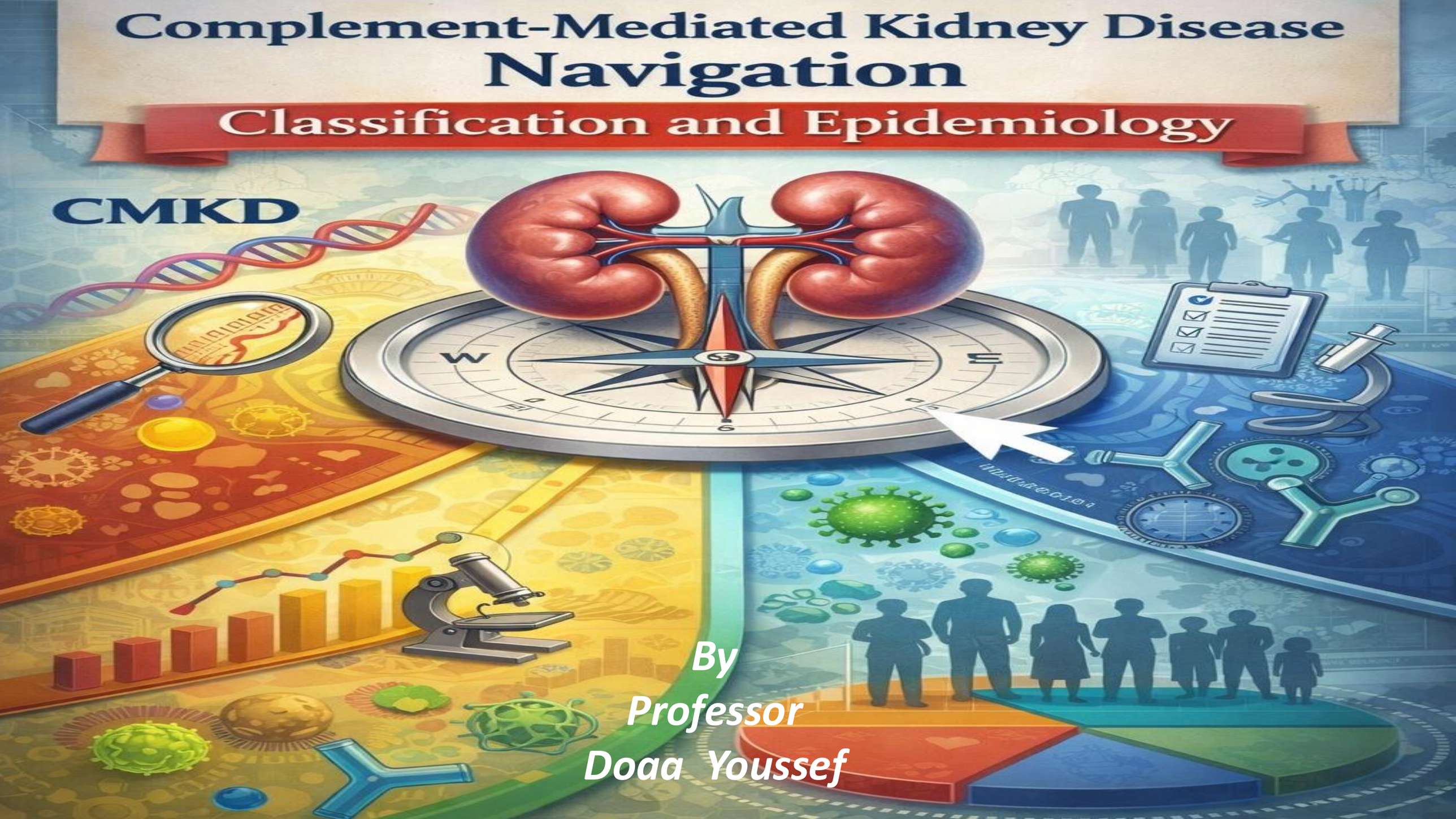
Complement-Mediated Kidney Disease Navigation

Classification and Epidemiology

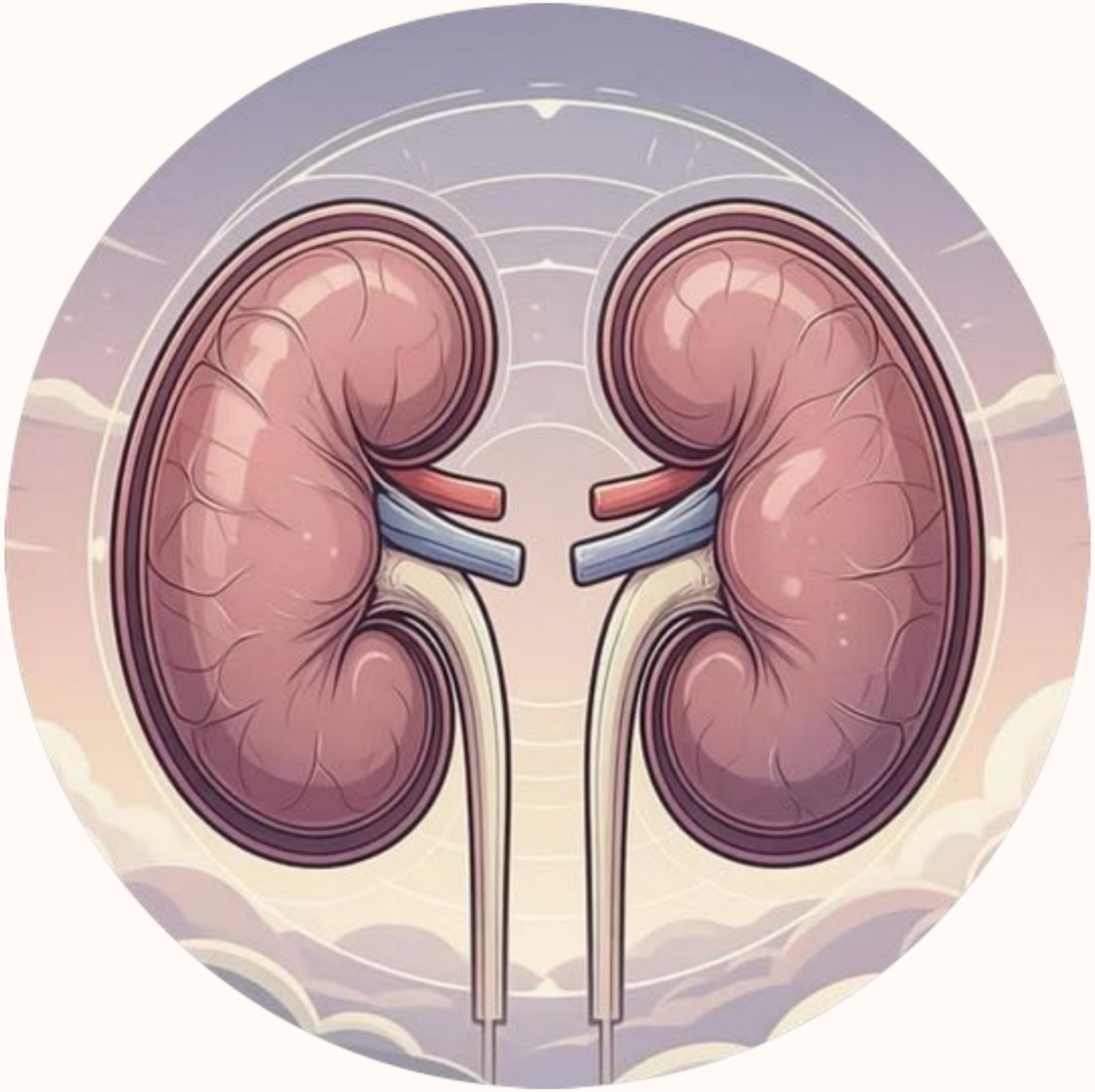


By
Professor
Doaa Youssef

Agenda

1- Introduction
2- Classification
3-Types of CMKD
4-Roadmap
5- Reflection on therapy

Introduction



- Complement-mediated diseases are often severe disorders arising from **genetic** mutations, acquired **autoantibodies**, or **deficiencies** in the complement system,
- They primarily affect the **kidneys** and **blood**,
- characterized by Involvement of **Complement** pathway leading to tissue **damage**.

- Historically linked to glomerular **immune** complexes
- New research links it to **non-immune-mediated** diseases

- **<u>Primary</u> Complement Diseases** are typically **ultra-rare**. **?????**
- **aHUS** and **C3G** are the **prototypical** examples.
- Complement is the **primary** driver of injury.
- Caused by dysregulation of the **alternative** pathway
- Pathophysiology and clinical courses are **distinct**

Understanding Complement Pathway Activation

Lectin Pathway Activation

- Phylogenetically the **oldest** pathway
- Activated by pattern recognition PROTEINS like **MBL**.
- Binds to sugars on **bacteria** or **damaged host cells**
- Recognizes specific glycans on **injured kidney cells.**
- Involved in the pathogenesis of several kidney diseases.

Lectin

Common Effector

Initiators & Unique Factors

Classical Pathway Activation

- Initiated by IgG or IgM bound to target antigens.
- Commonly activated in **immune complex** glomerulonephritis
- **C1q** binds to clusters of antibodies to start the process.
- Triggers the sequential cleavage of proteins.
- Leads to the formation of **C3-convertases**

Classical

Alternative Pathway Activation

- Characterized by continuous low-level "**tickover**“ activation.
- **Amplifies** activity from the other **two** pathways.
- Forms a **positive** feedback loop via C3b.
- Also activated by proteases like **thrombin**
- **E.g. Factor** D levels increase in CKD, exacerbating activity

Alternative

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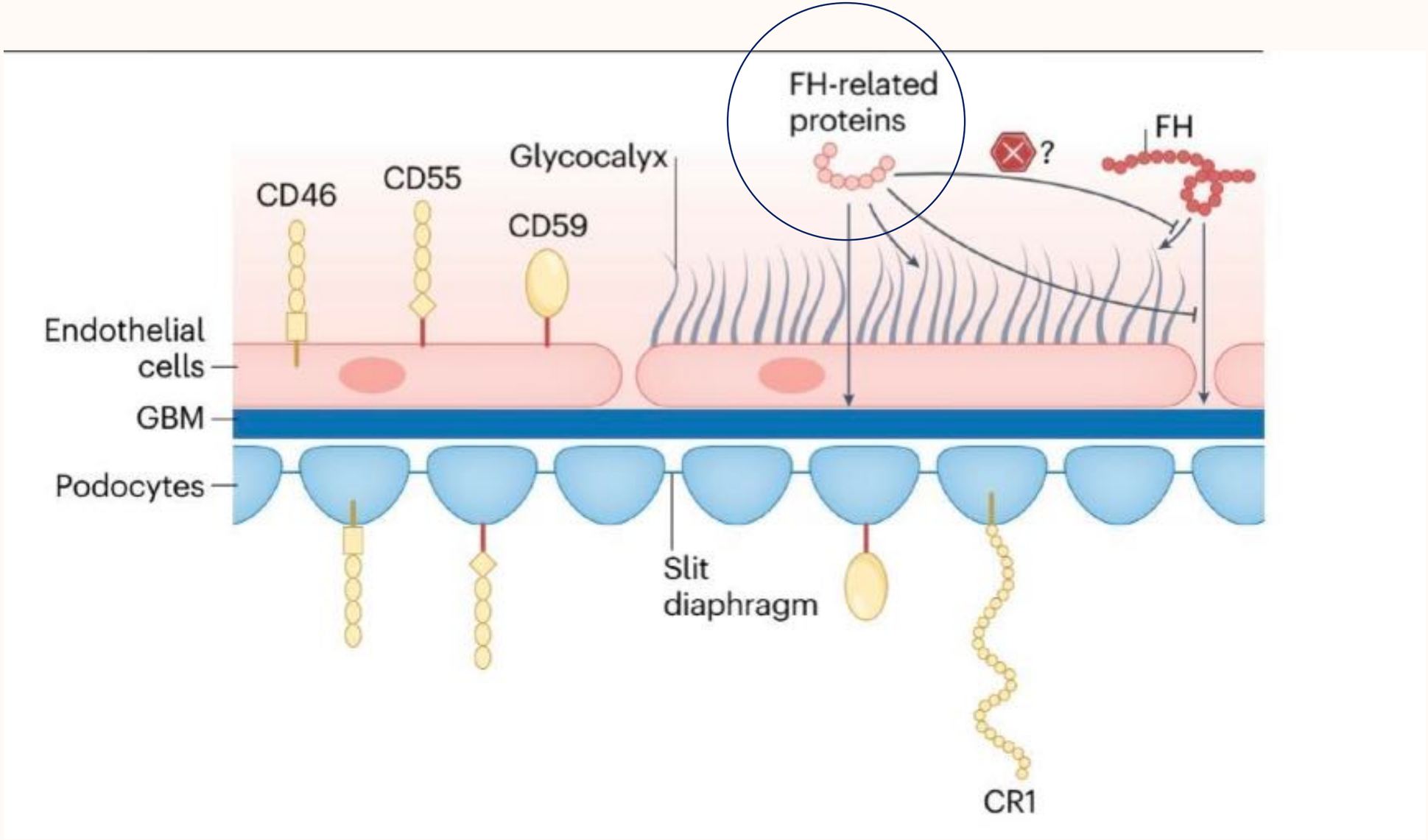
Complement Regulation



Classification

2025

www.kidney-international.org KDIGO executive conclusions

The role of complement in kidney disease: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference

OPEN

Marina Vivarelli[1], Jonathan Barratt[2], Laurence H. Beck Jr[3], Fadi Fakhouri[4,5], Daniel P. Gale[6], Elena Goicoechea de Jorge[7,8], Marta Mosca[9], Marina Noris[10], Matthew C. Pickering[11], Katalin Susztak[12], Joshua M. Thurman[13], Michael Cheung[14], Jennifer M. King[14], Michel Jadoul[15], Wolfgang C. Winkelmayer[16] and Richard J.H. Smith[17,18,19]; for Conference Participants[20]

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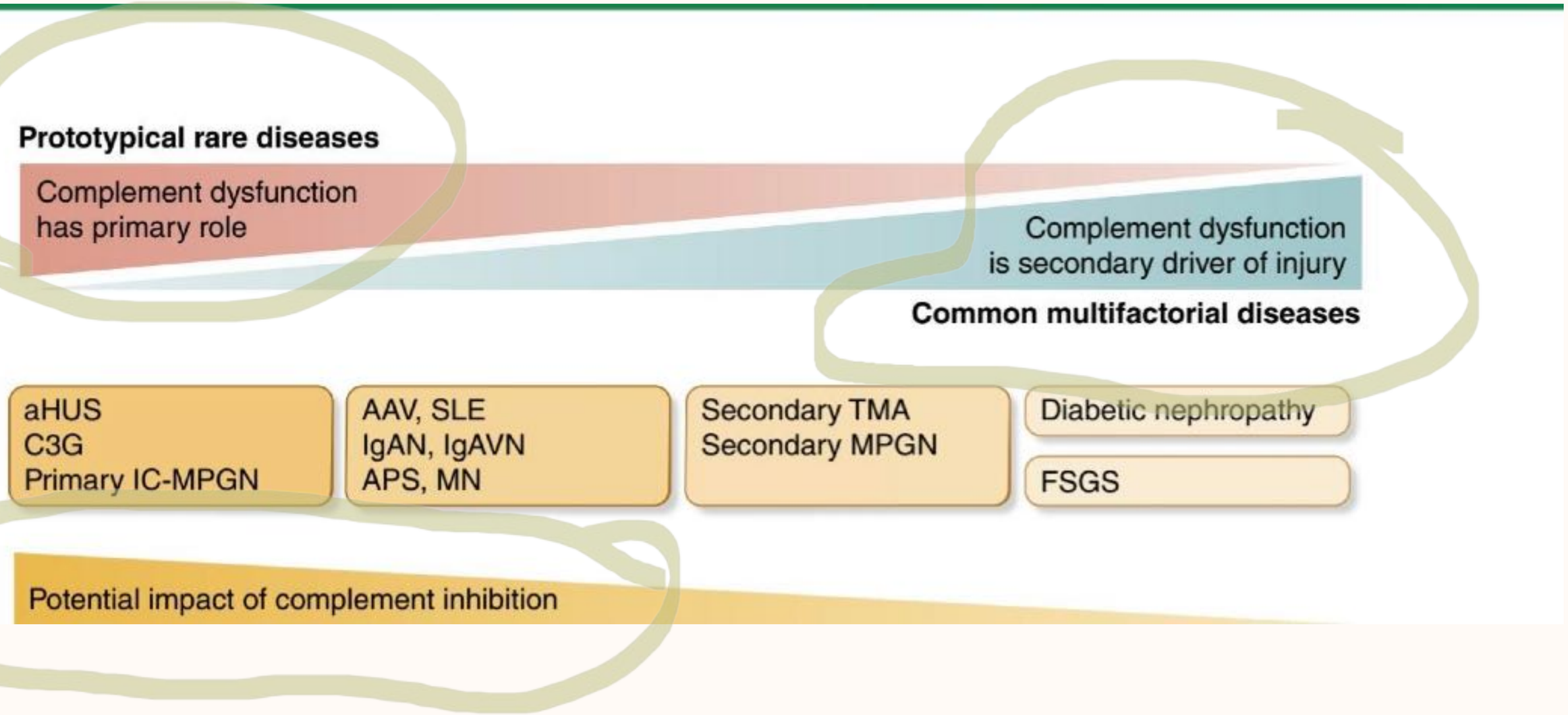
nature reviews nephrology

2023

Review article

The role of complement in kidney disease

Vojtech Petr[1,2] & Joshua M. Thurman[2]


Prototypical rare diseases
Complement dysfunction has primary role
Complement dysfunction is secondary driver of injury
Common multifactorial diseases
aHUS
C3G
Primary IC-MPGN
AAV, SLE
IgAN, IgAVN
APS, MN
Secondary TMA
Secondary MPGN
Diabetic nephropathy
FSGS
Potential impact of complement inhibition

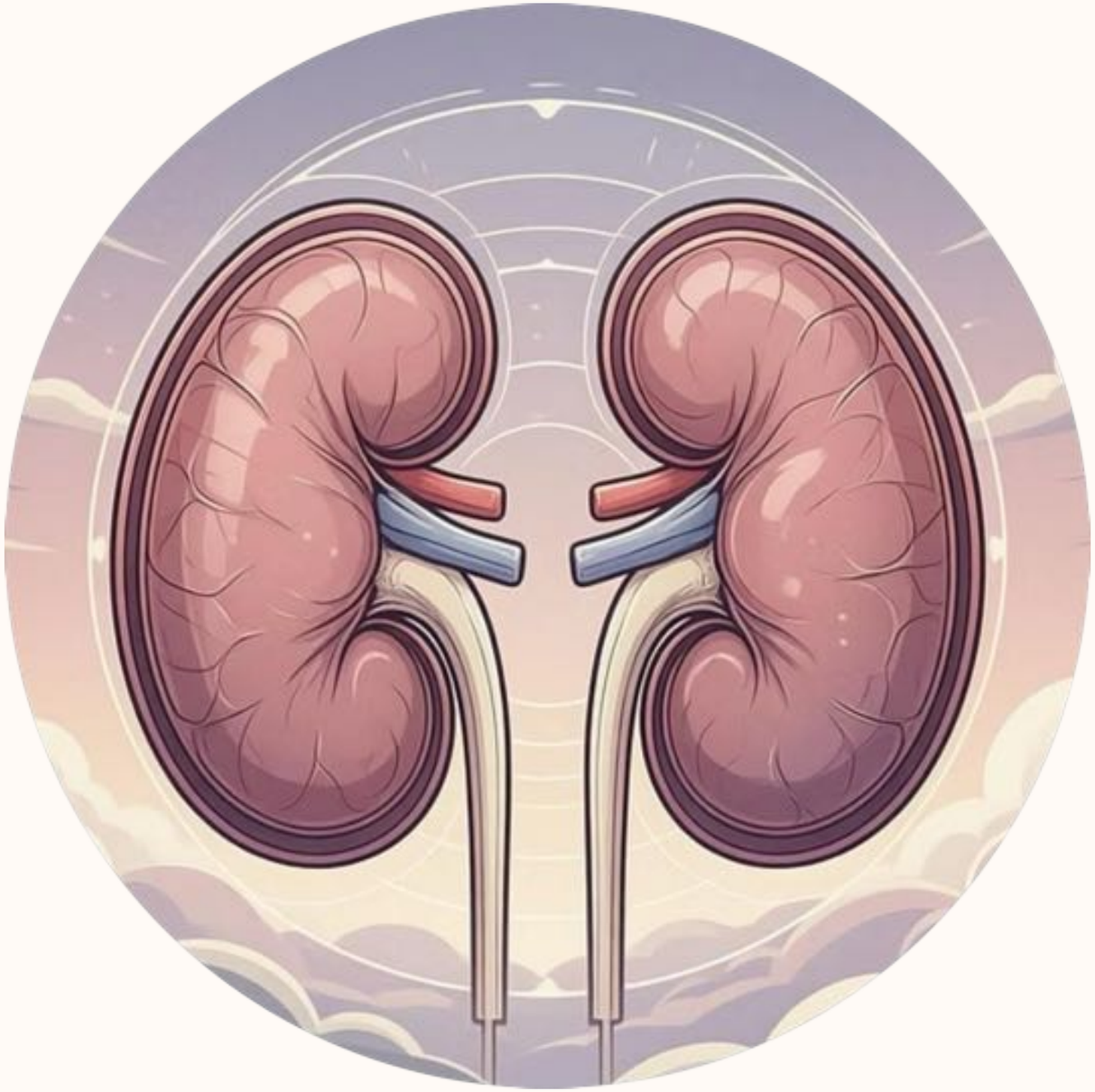
1. Atypical Haemolytic–uraemic Syndrome (aHUS)
2. C3 Glomerulopathy (C3G)
3. C1q Nephropathy
4. Immune Complex-mediated Membranoproliferative Glomerulonephritis (IC-MPGN)

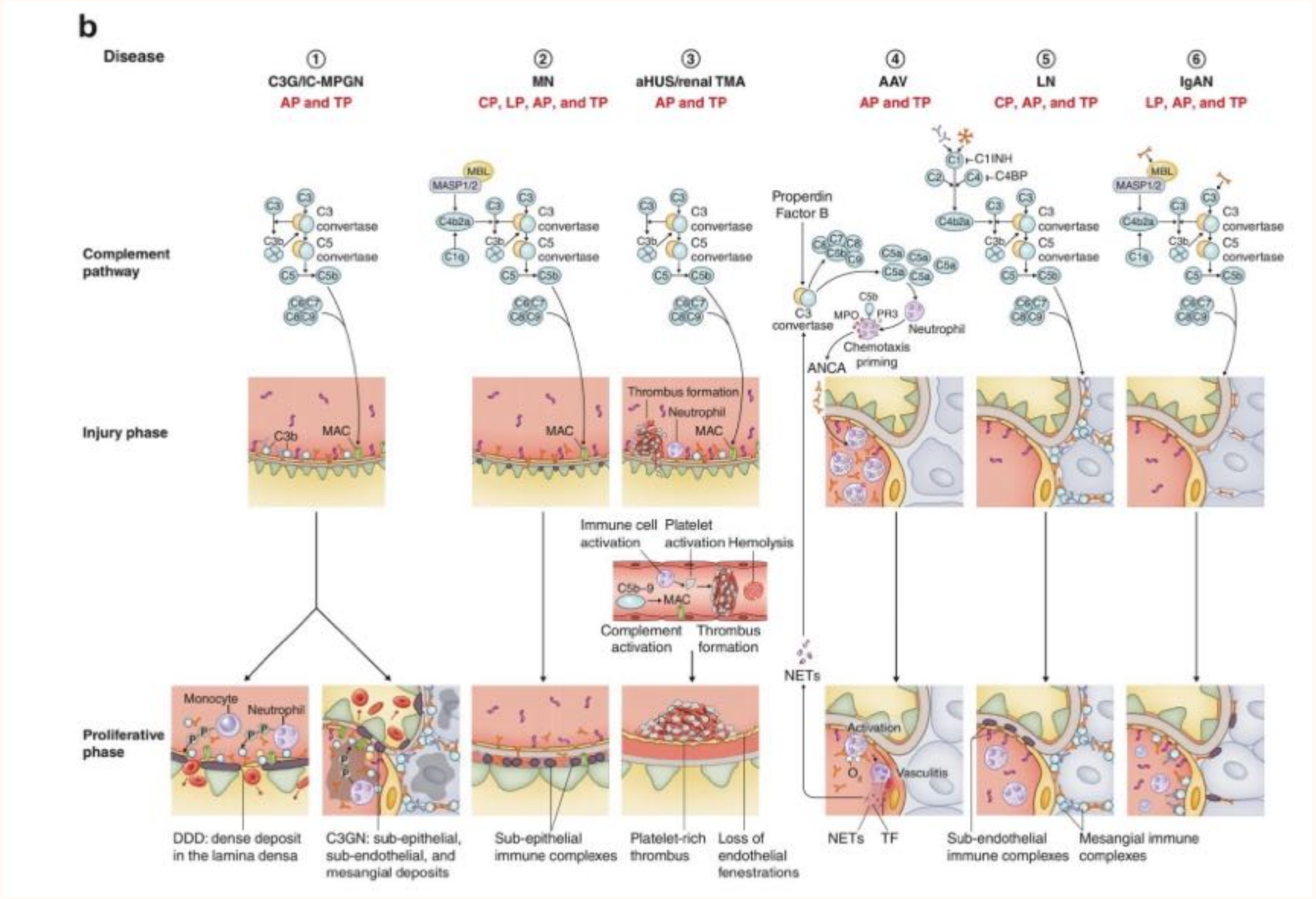
1. Lupus Nephritis
2. ANCA-associated Vasculitis (AAV)
3. Anti-glomerular Basement Membrane (Anti-GBM) Disease
4. Transplant Rejection

1. Diabetic Kidney Disease (DKD)
2. Focal Segmental Glomerulosclerosis (FSGS)

1. Membranous Nephropathy (MN)
2. IgA Nephropathy (IgAN)
3. Acute Kidney Injury (AKI) In models of ischaemia–reperfusion
4. Polycystic Kidney Disease (PKD): C3 is upregulated in the kidneys of PKD models
5. Glomerulonephritis associated with Monoclonal Gammopathies
6. Shiga Toxin-producing Escherichia coli infection-associated Haemolytic–uraemic Syndrome (STEC-HUS)

List of CMKD





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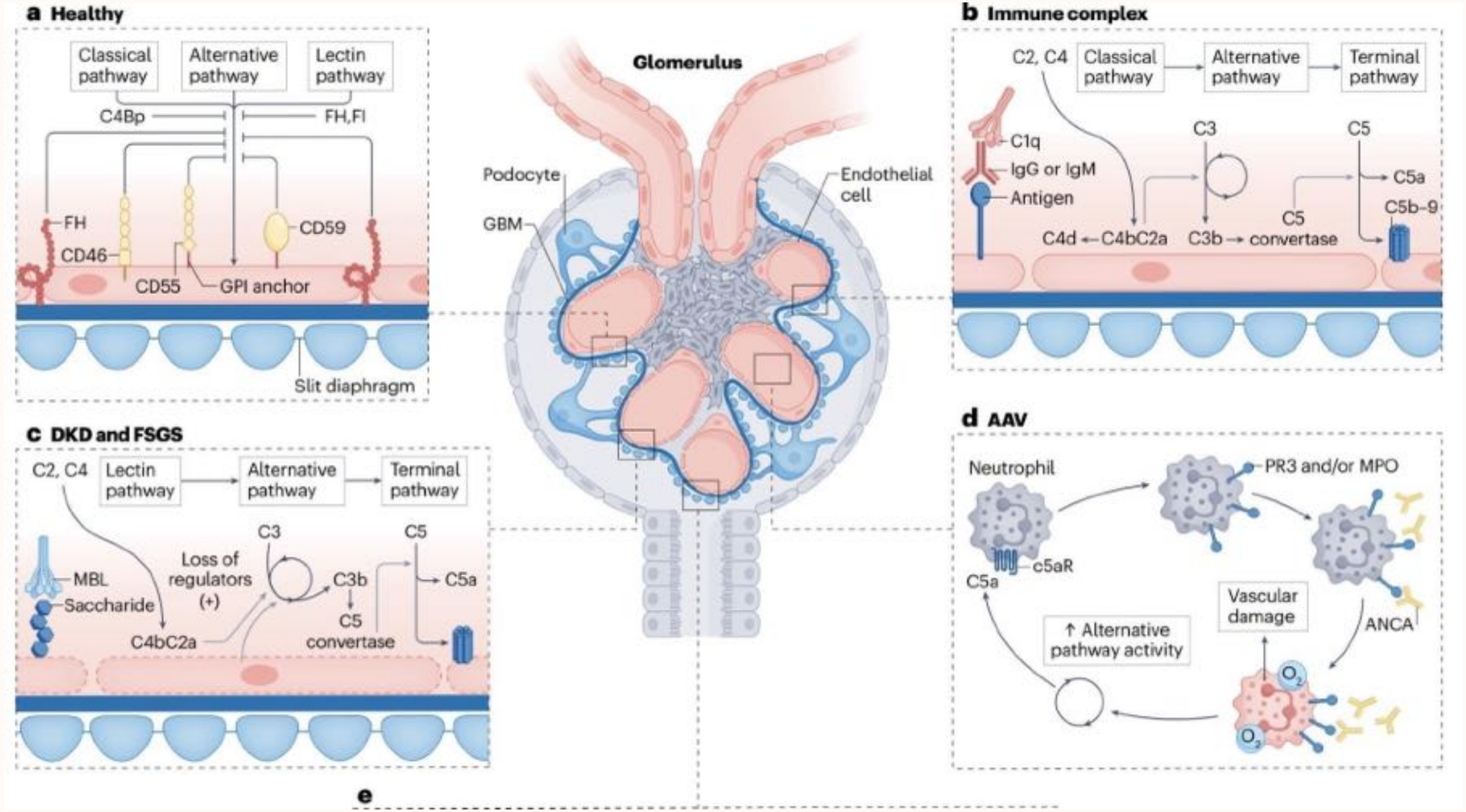

a Healthy
Classical pathway
Alternative pathway
Lectin pathway
C4Bp
FH,FI
FH
CD46
CD55
GPI anchor
CD59
Slit diaphragm
Glomerulus
Podocyte
GBM
Endothelial cell
b Immune complex
C2, C4
Classical pathway
Alternative pathway
Terminal pathway
C1q
IgG or IgM
Antigen
C3
C5
C5a
C5b–9
C4d
C4bC2a
C3b
C5 convertase
c DKD and FSGS
C2, C4
Lectin pathway
Alternative pathway
Terminal pathway
MBL
Saccharide
Loss of regulators (+)
C3
C3b
C5
C5a
C4bC2a
C5 convertase
d AAV
Neutrophil
PR3 and/or MPO
c5aR
C5a
Vascular damage
ANCA
↑ Alternative pathway activity
e

Atypical Haemolytic–Uraemic Syndrome (aHUS)

- A form of (TMA)
- Endothelial damage is driven by **alternative** pathway activity.
- Primarily affects kidney **endothelium**
- Associated with **genetic** variants in CFH, CFI, and CD46
- C5 inhibitors like **eculizumab** are the standard of care

C3 Glomerulopathy (C3G)

- Primary injury is confined to the **glomeruli**
- Associated with **nephritic FACTORS** that stabilize convertases.
- Impaired regulation occurs in the **fluid** phase or **GBM**
- C5 inhibitors have **not** shown clear benefit in trials.
- Possible pathogenic role for upstream fragments like **C3a**

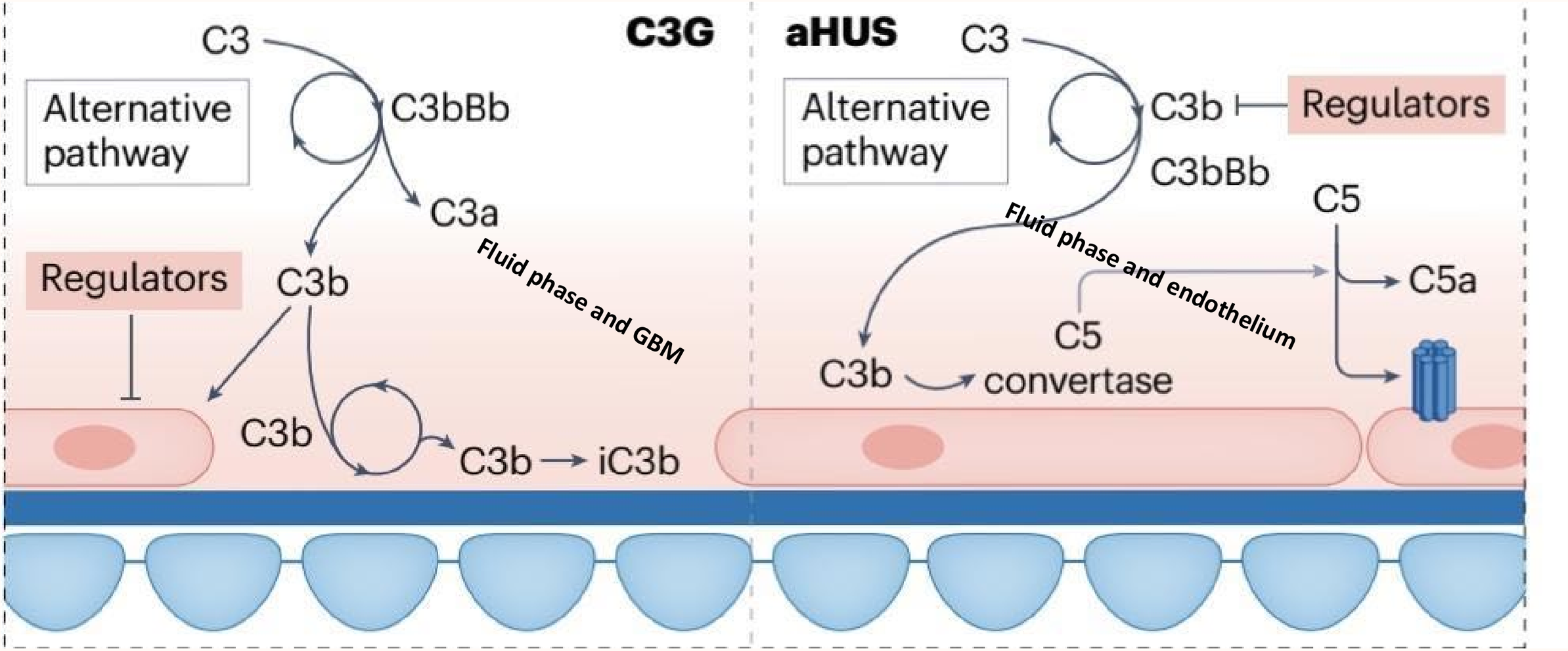

C3G
C3
Alternative pathway
C3bBb
C3a
Regulators
C3b
Fluid phase and GBM
C3b
C3b → iC3b
aHUS
C3
Alternative pathway
C3b
Regulators
C3bBb
C5
Fluid phase and endothelium
C5a
C5
C3b
convertase

Table 1 | Atypical haemolytic–uraemic syndrome and C3 glomerulopathy

Parameter	aHUS[203]	C3G[204]
Clinical course	Acute	Chronic
Incidence	0.2–1.9/million/year[205]	1–3/million/year[206]
Associated infectious disease	Shiga toxin-producing *Escherichia coli* infection associated with haemolytic–uraemic syndrome	Post-infectious glomerulonephritis
Complement activation phase	Endothelial cell and/or glycocalyx	Fluid phase and/or glomerular basement membrane
Triggers	Autoimmunity, transplantation, pregnancy, infections, drugs and metabolic disease[207]	Infection[65,208]
Kidney failure	60–70% without complement inhibition; 10–15% with complement inhibition[203,209]	50% at 10 years[67]
Post-transplant recurrence	Variable; depends on genetic risk factors[210]	Very high[204]
Extrarenal manifestations	Systemic thrombotic microangiopathy; retinal drusen are rare	Partial lipodystrophy[211], retinal drusen[212]
C3 levels	Low in 30–50% of patients[213]	Low in up to 75% of patients[67,214]
Acquired drivers	Anti-factor H autoantibodies[215]	Nephritic factors[216], anti-factor H autoantibodies[215], monoclonal immunoglobulin[53,217]

aHUS, atypical haemolytic–uraemic syndrome; C3G, C3 glomerulopathy.

Factor H & Related Proteins

- Factor H regulates complement on acellular surfaces
- **Protects** the **GBM** and endothelial glycocalyx
- FHR proteins may antagonize Factor H binding.
- FHR proteins can promote activation on tissues.
- Variants in CFH and CFHR genes **link** to **aHUS/C3G.**

Lupus Nephritis (LN)

- Intra-renal activation via the **classical** pathway
- Driven by deposited immune **complexes**
- **Paradoxically**, classical pathway **deficiency** is a risk for SLE.
- "**Full house“ s**taining shows C1q, C4, and C3.
- Complement **blockade** might reduce inflammation but risk **autoimmunity**

ANCA-Associated Vasculitis (AAV)

- Described as "**pauci-immune**" due to sparse deposits.
- **Alternative** pathway is the dominant driver of injury.
- **C5a** mediates glomerular injury via neutrophils.
- Avacopan (C5aR1 antagonist) is an **approved** adjunct therapy, Allows for significant **reduction** in glucocorticoid use

Focal Segmental Glomerulosclerosis (FSGS)

- **Podocytopathy** where **IgM** and **C3** are often detected.
- Deposited **IgM** activates the **classical** pathway
- **CD55** EXPRESSION is lower in FSGS glomeruli.
- Complement activation is likely a **secondary** event **after** injury.
- Therapeutic inhibition **may** attenuate disease progression

Membranous Nephropathy (MN)

- Characterized by **subepithelial** immune **complexes**
- Autoantibodies are predominantly **IgG4**
- Activation may occur via the **lectin** pathway
- Recent studies suggest all **three** pathways can be involved.
- **C3a blockade <u>may</u>** prevent podocyte morphological changes

IgA Nephropathy (IgAN)

- **IgA1** can activate the **alternative** pathway directly.
- **Galactose-deficient** glycans are targeted by autoantibodies.
- MBL may bind to these glycans, activating the **lectin** pathway
- **FHR1** and **FHR5** deposits correlate with **worse** prognosis.
- The **alternative** pathway plays a crucial disease-causing role

C1q Nephropathy

* Defined by intense glomerular **C1q** staining
* Patterns of injury often **mimic minimal change disease**
* Whether C1q indicates **classical** pathway activation is **unclear**.
* **Co-deposition** of IgM, IgG, or C3 is frequent.
* C1q positivity may associate with **frequent relapse**s in children.

Acute Kidney Injury (AKI)

* **Alternative** pathway is activated in the **post-ischaemic** tubules
* **Lectin** PATHWAY activation via collectin-11 and l-fucose.
* Injured **tubules** lose regulation while increasing **C3** synthesis
* Urinary **Factor B** and Ba fragments **predict** development.
* **Ravulizumab** is being tested for **post-cardiac** surgery AKI

Diabetic Kidney Disease (DKD)

- **Complement** deposits are associated with **worse** outcomes
- **Lectin** pathway may be activated by **glycated** proteins.
- Hyperglycaemia impairs complement regulators like **CD59**
- In podocytes, loss of **CD55** exacerbates kidney disease.
- **Genetic** variants in Factor **H** are **risk** factors for DKD

Polycystic Kidney Disease (PKD)

* **C3** is strongly upregulated in PKD mouse models.
* C3 **deficiency** in mice **attenuates cystogenesis**
* C3 fragments are detectable in human cyst fluid and urine
* **Suggests** complement contributes to cyst growth.
* Currently no active clinical trials with inhibitors for PKD

Which part of the kidney more susceptible to injury by CMKD ?

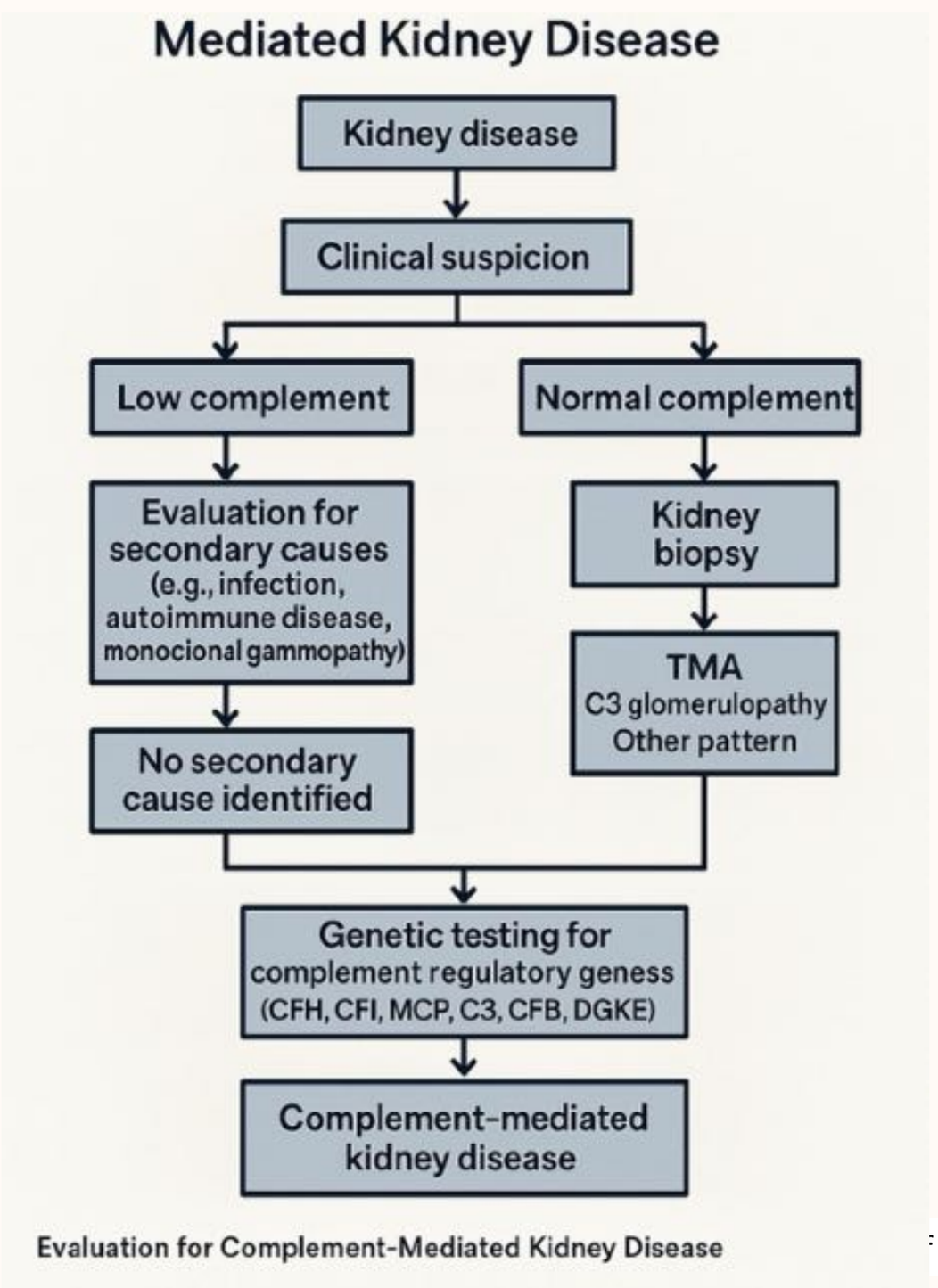
Susceptibility: The Glomerulus

* Glomeruli are "**inward-facing**" and exposed to plasma **proteins**.
* Rely on a threshold of cell-surface **regulators**.
* The GBM is **fully** dependent on soluble **Factor H.**
* This dependence explains sensitivity to Factor H defects
* Regulatory mechanisms can be overwhelmed by **immune complexes**

Susceptibility: The Tubulointerstitium

* Tubular epithelial cells promote activation **when injured.**
* Injury reduces surface regulation like **CD46**
* Cells can **locally** synthesize C3 and lectins
* May have evolved as a **defense** against urinary pathogens
* Activation occurs **independently** of the glomerulus.

Road map



Evaluation for Complement-Mediated Kidney Disease

Laboratory Work-up: Key Biomarkers and Genetic Testing

Biomarkers: Tissue Immunostaining

* **Biopsies** are stained for **C3c, C4d, and C1q**

* Comparing **deposits** identifies the **active** pathways

Genetic and Acquired Drivers

* Variants in alternative pathway genes are risk factors.

* Infections may decrease regulators or increase substrates.

* Genetic analysis provides **prognostic** information for aHUS.

Biomarker Analysis

- Complement levels (C3, C4, Factor H, Factor I, MCP, B, D)
- Autoantibodies (e.g., C3 Nephritic Factor)
- Serum creatinine and urea for kidney function
- Urinalysis for protein and red blood cells

Genetic Testing

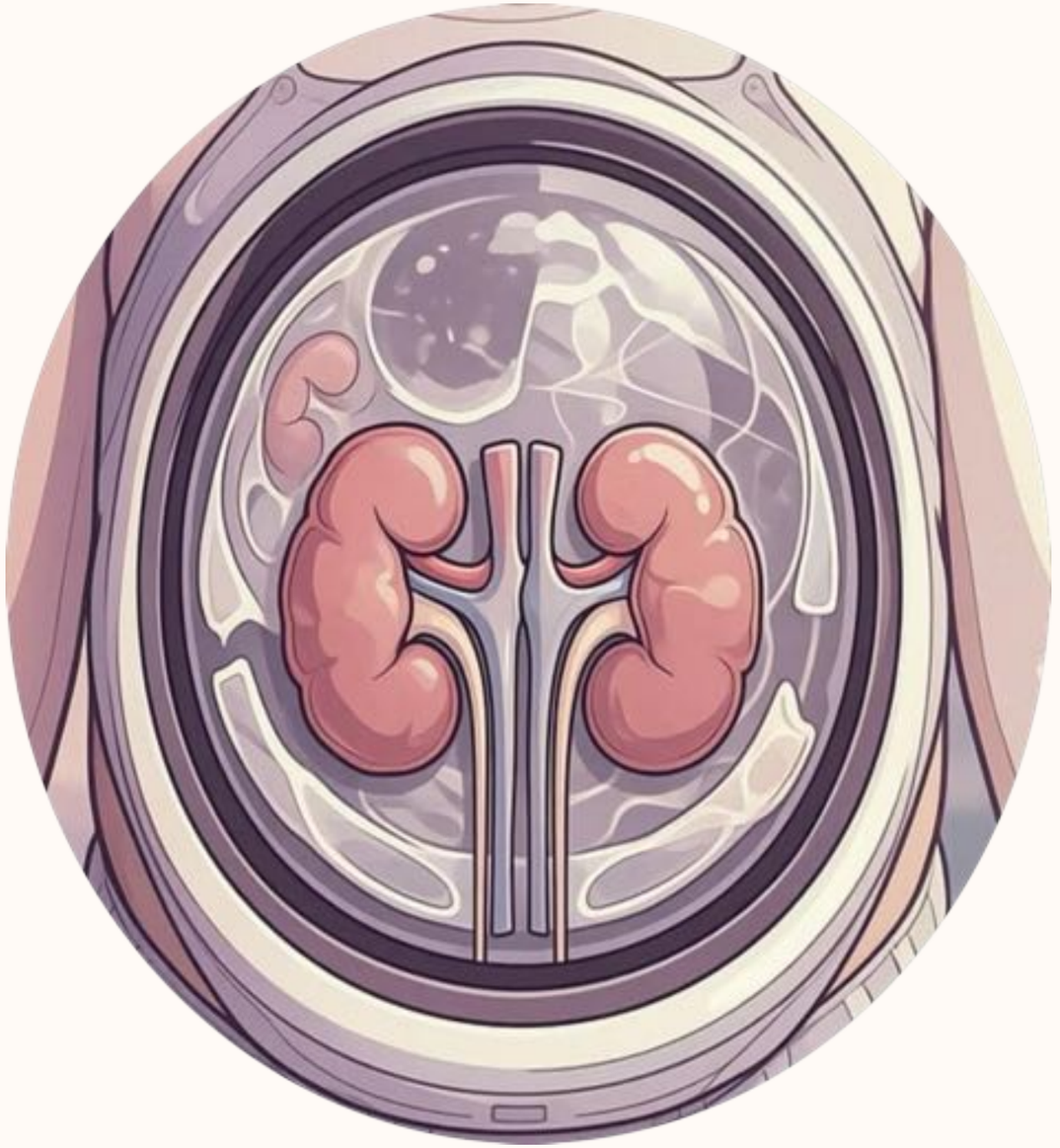
- *Identification of mutations in complement genes (CFH, CFI, C3, CD46, CFB)*
- Screening for associated risk alleles
- Helps confirm diagnosis and guide treatment

Differentiating Complement-Mediated GN from Other GN

Distinguishing complement-mediated glomerulonephritis (GN) from other forms of GN is paramount for effective treatment. Key clinical and laboratory features help in this differentiation.

Feature	Complement-Mediated GN	Other GN
Complement Levels	Often low C3, normal C4	Variable, often normal
Pathology	Dense deposits, C3 predominant staining	Variable immune complex deposition
Genetics	Mutations in complement genes (e.g., CFH, C3)	Less common or different genetic associations
Clinical Course	Recurrent, progressive	Variable, depending on specific GN type

Therapeutic Strategies - Overview



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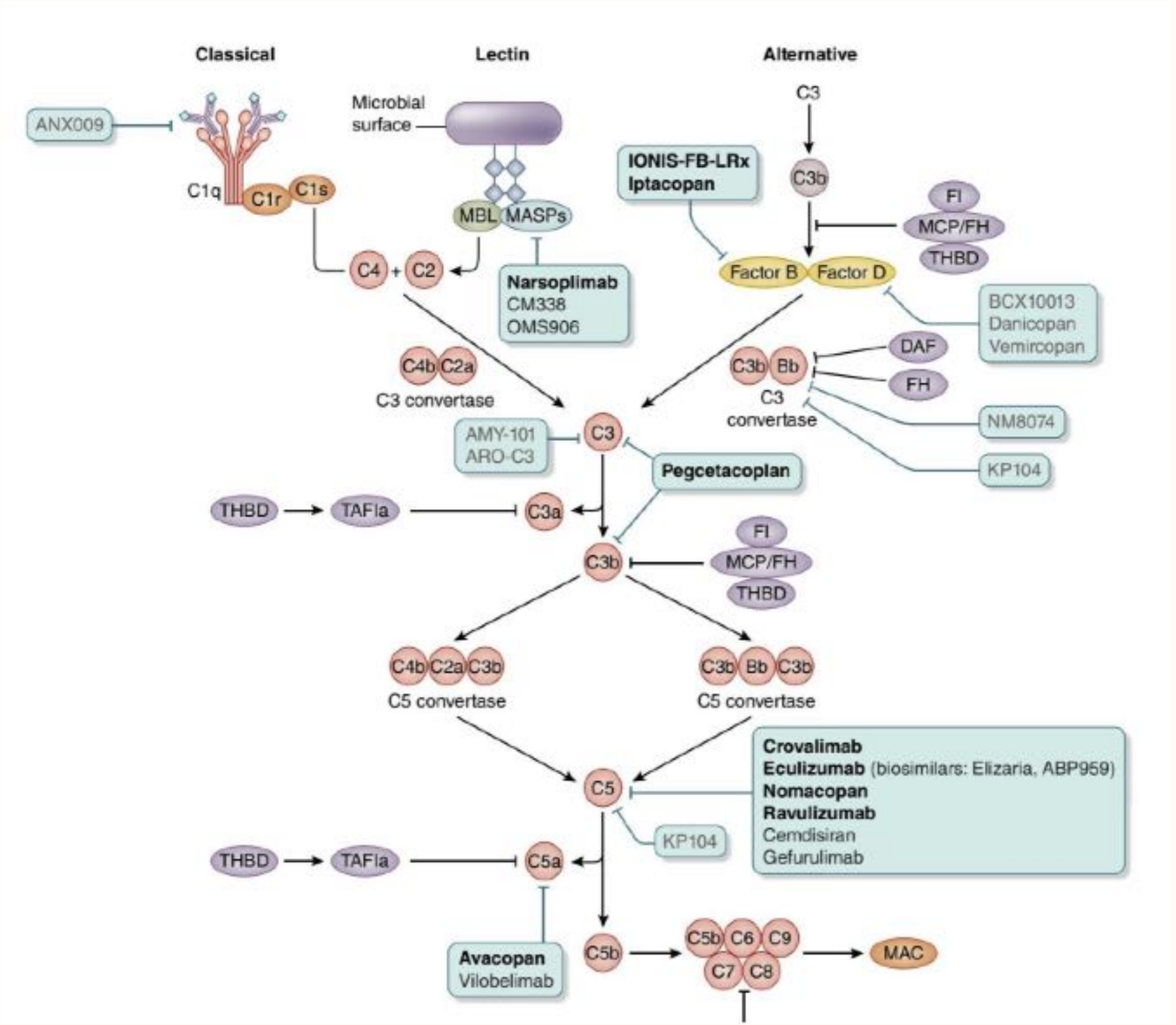
Classical
Lectin
Alternative
ANX009
C1q
C1r
C1s
Microbial surface
MBL
MASPs
C4 + C2
Narsoplimab
CM338
OMS906
C3
C3b
IONIS-FB-LRx
Iptacopan
FI
MCP/FH
THBD
Factor B
Factor D
BCX10013
Danicopan
Vemircopan
C4b C2a
C3 convertase
C3b Bb
C3 convertase
DAF
FH
NM8074
KP104
AMY-101
ARO-C3
C3
Pegcetacoplan
THBD
TAFIa
C3a
FI
MCP/FH
THBD
C3b
C4b C2a C3b
C5 convertase
C3b Bb C3b
C5 convertase
Crovalimab
Eculizumab (biosimilars: Elizaria, ABP959)
Nomacopan
Ravulizumab
Cemdisiran
Gefurulimab
C5
KP104
THBD
TAFIa
C5a
Avacopan
Vilobelimab
C5b
C5b C6 C9
C7 C8
MAC

Target	Drug	Disease	Clinical trial #
Alternative pathway			
Factor B	Iptacopan	aHUS	NCT04889430, NCT05795140
		C3G and/or post-Tx recurrence of C3G	NCT03955445, NCT03832114[c], NCT04817618
		IC-MPGN	NCT05755386
		LN	NCT05268289
		IgAN	NCT03373461[c], NCT04557462, NCT04578834
	IONI-FB-LRx	IgAN	NCT04014335
Factor D	Danicopan (ALXN2040)	C3G, IC-MPGN	NCT03124368[c], NCT03369236[c], NCT03459443[c]
	Vemircopan (ALXN2050)	IgAN, LN	NCT05097989
C3	Pegcetacoplan	TA-TMA	NCT05148299
		C3G, IC-MPGN	NCT05067127, NCT05809531
		Post-Tx recurrence of C3G or IC-MPGN	NCT04572854
Classical pathway			
C1s	Sutimlimab (BIVV009)[a]	Cold agglutinin disease	NCT05132127[c], NCT03347396[c], NCT03347422[c]
C1INH	Cinryze, Berinert, Ruconest	AMR	NCT02547220[c], NCT03221842[c], NCT01147302[c], NCT01134510[c]
		Ischaemia–reperfusion injury, delayed graft function in kidney transplantation	NCT02134314[c], NCT04696146
Lectin pathway			

		kidney transplantation	
Lectin pathway			
MASP2	Narsoplimab (OMS721)	TA-TMA	NCT05855083
		C3G, IgAN, LN, MN	NCT02682407
		IgAN	NCT03608033
		TMA including aHUS	NCT02222545[c], NCT03205995
Terminal pathway			
C5	Eculizumab	AMR	NCT01399593[c]
		STEC-HUS	NCT01410916[c]
		Delayed graft function	NCT02145182[c]
		aHUS	NCT01193348[c], NCT05726916
	Ravulizumab (ALXN1210)	TMA	NCT04743804
		TA-TMA	NCT04543591, NCT04557735
		IgAN, LN	NCT04564339
		aHUS	NCT03131219[c]
		Acute kidney injury following cardiac surgery	NCT05746559
	Nomacopan (rVA576)[b]	TA-TMA	NCT04784455
		IgAN	NCT03841448
C5a	Vilobelimab	ANCA-associated vasculitis	NCT03895801[c]
C5aR1	Avacopan	C3G	NCT03301467[c]
		ANCA-associated vasculitis	NCT02994927[c], NCT01363388[c], NCT02222155[c]
		IgAN	NCT02384317[c]

* **Eculizumab** was the first approved for aHUS in **2011**.

* New drugs target specific pathways or **terminal** components

* These agents **differ** from standard immunosuppressants

* Provide rapid anti-inflammatory effects for antibody diseases.

* Can be **used** as **monotherapies** or **adjuncts**.

FDA Approved Complement Inhibitors

* *Eculizumab/Ravulizumab*: Block C5 cleavage.

* *Avacopan*: Blocks the C5a receptor 1 (C5aR1).

* *Pegcetacoplan*: Blocks at the level of C3.

* *Sutimlimab*: Targets C1s (**classical** pathway inhibitor).

* These are **<u>expanding</u>** therapeutic options in nephrology

C3 vs. C5 Inhibition

* **C3 inhibitors (**e.g., **Pegcetacoplan**) block **all three** pathways

Suppress all downstream FRAGMENTS (C3a, C3b, C5a, C5b–9).

* **C5 inhibitors (**e.g., Eculizumab) block **only terminal** fragments

Leaves the proximal complement pathway intact.

* Choice **depends** on whether **upstream** fragments cause injury

Pathway-Specific Inhibition

* Selective drugs may have **fewer side** effects

* However, **multiple pathways are often active in one disease**

Monotherapy vs. Adjunct Therapy

* Monotherapy: For diseases **not** driven by autoantibodies.
* Examples: aHUS, or secondary drivers in DKD/FSGS.
* **Adjunct** Therapy: For antibody-mediated autoimmune diseases.
* Used with cyclophosphamide or rituximab (e.g., AAV).
* Reduces injury **while** autoantibodies are **cleared**

Risks of Complement Blockade

* Primary risk is increased susceptibility to **infection**
* Risk **level** depends on the target in the cascade
* **Combined** immunosuppression further **increases** this risk.
* **Vaccination** and **antibiotics** are essential mitigations.
* Long-term risk of inducing **autoimmunity** is a concern.

Challenges in the Field

* Many complement-associated diseases are **rare** and slow

* Clinical **trials** are **complicated** and difficult to conduct.

* Predictive **biomarkers** to identify responders are needed.

* High **cost** of drugs limits global availability.

* Pharmacologic **monitoring** could tailor doses and save costs.

Concerns

- Kidney diseases for which the role of complement dysregulation is pivotal often have no known effective treatment options, leading to kidney failure and risk of recurrence after kidney transplant
- Kidney diseases involving complement overactivation can have a profound impact on the daily lives of patients and caregivers, limiting participation in important or meaningful activities
- For young patients, the lack of natural history data leads to uncertainty regarding course and impact of disease, which can influence decisions on career and family planning
- Evidence on the correct management of many complement-mediated nephropathies is limited in quantity and quality, and awareness of innovative therapies (either in clinical trials or marketed) is often insufficient
- Approved agents are not universally available due to limited affordability
- Lack of awareness of complement-mediated diseases among health care professionals delays diagnosis and hinders optimal management
- Because complement blocking therapies increase the risk of infection, their long-term use is potentially concerning

Conclusions

Careful analysis of SAFTY and EFFICACY remains paramount.

Thank You