Infection related Glomerulonephritis

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Overview

- Epidemiology
- Definitions
  - Post-infectious (PIGN) vs. Infection related (IRGN)
  - Post-infectious (PIGN) vs. Post-streptococcal GN (PSGN)
- Other IRGN
- PSGN
  - Pathology, Pathogenesis, Clinical manifestations, Outcome
- Comparison with other GN
- Atypical PIGN/C3GN

Global incidence

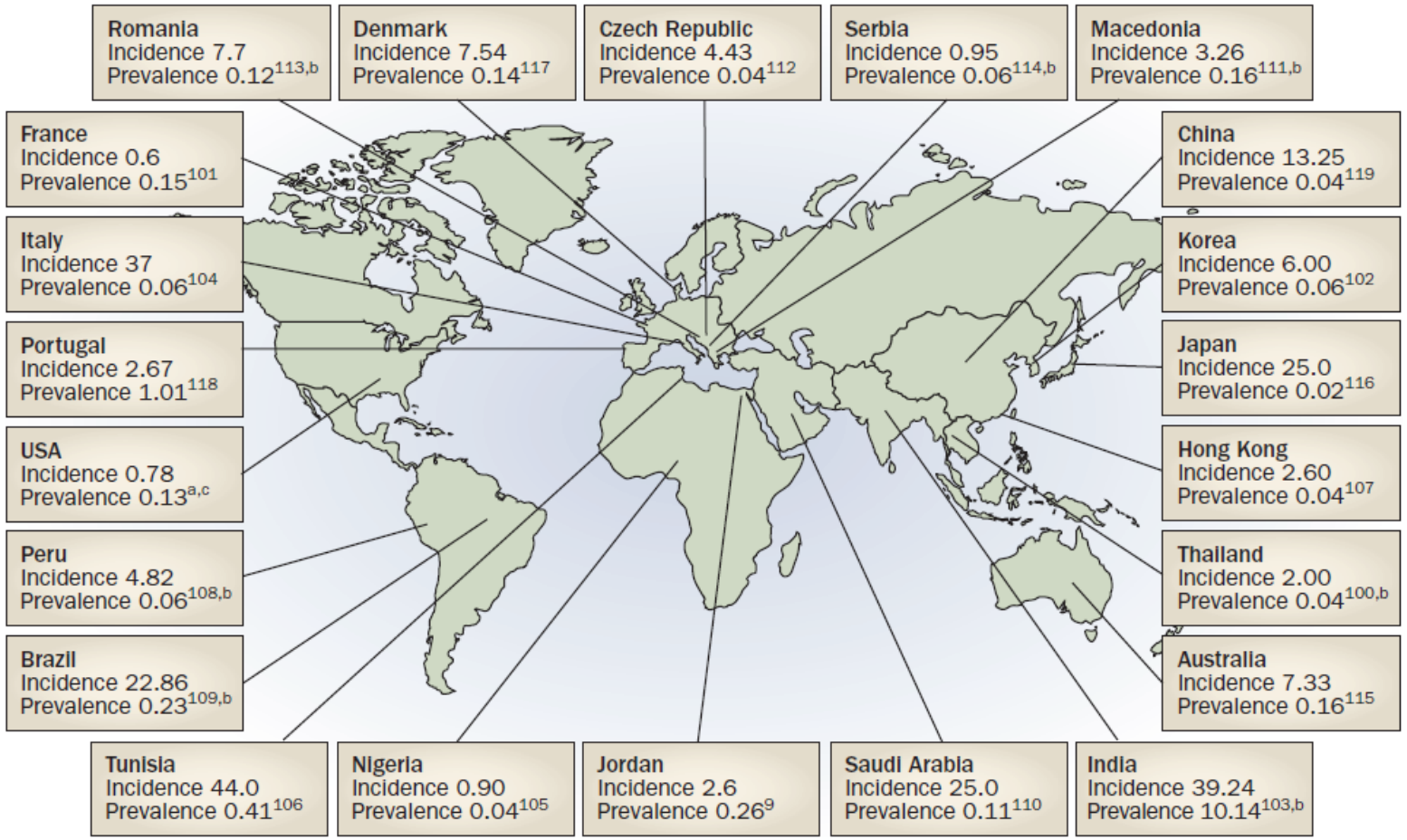
Est annual incidence ~ 9.3/100,000 (Carapetis etal)

X 4 Low resource setting in adults

Highest: Indigenous Australians 239/100,000

Caveats

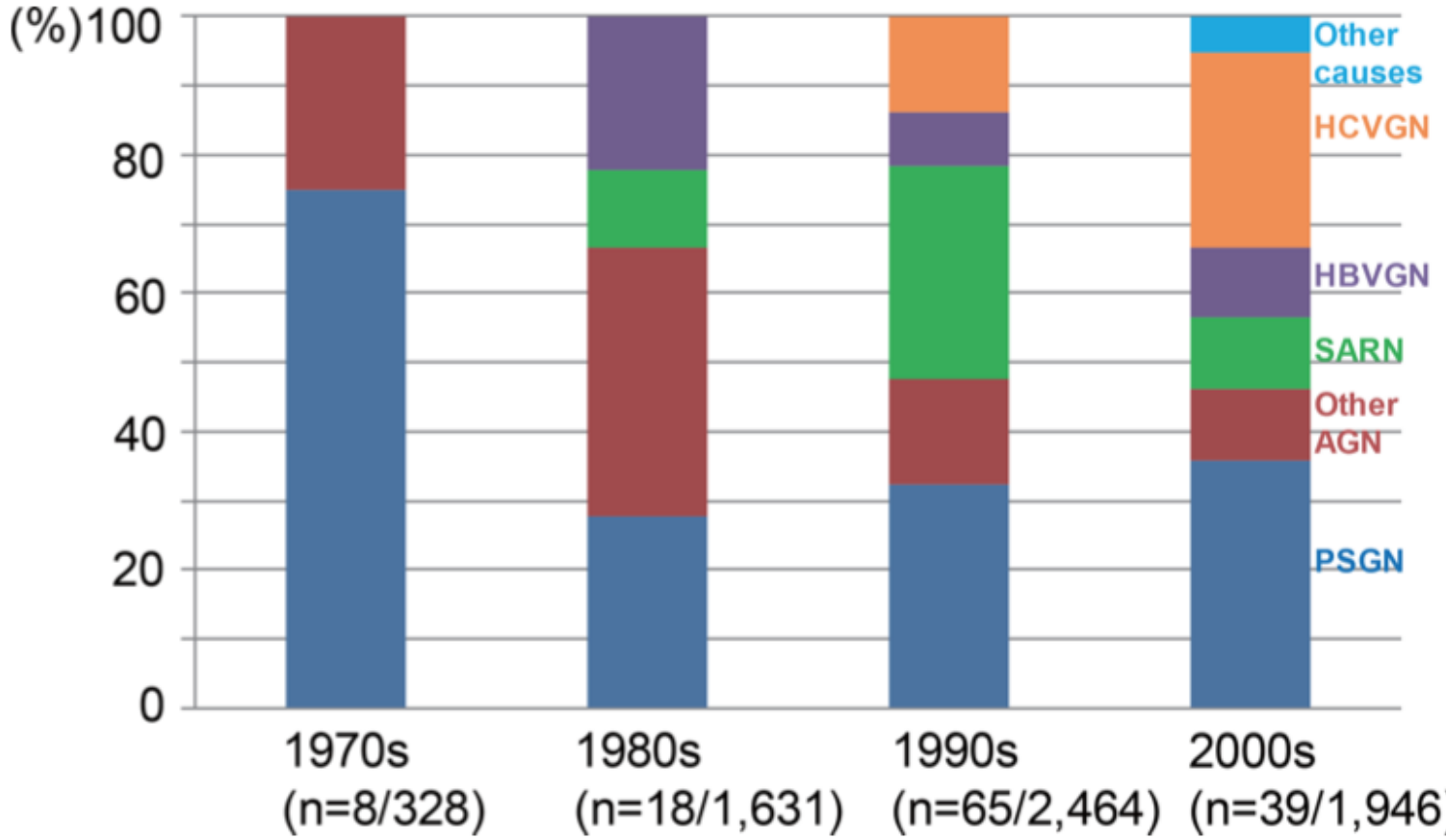
- Definition
- Under-reporting
- Sporadic vs. epidemic
- Paediatric vs. adult



nature REVIEWS NEPHROLOGY

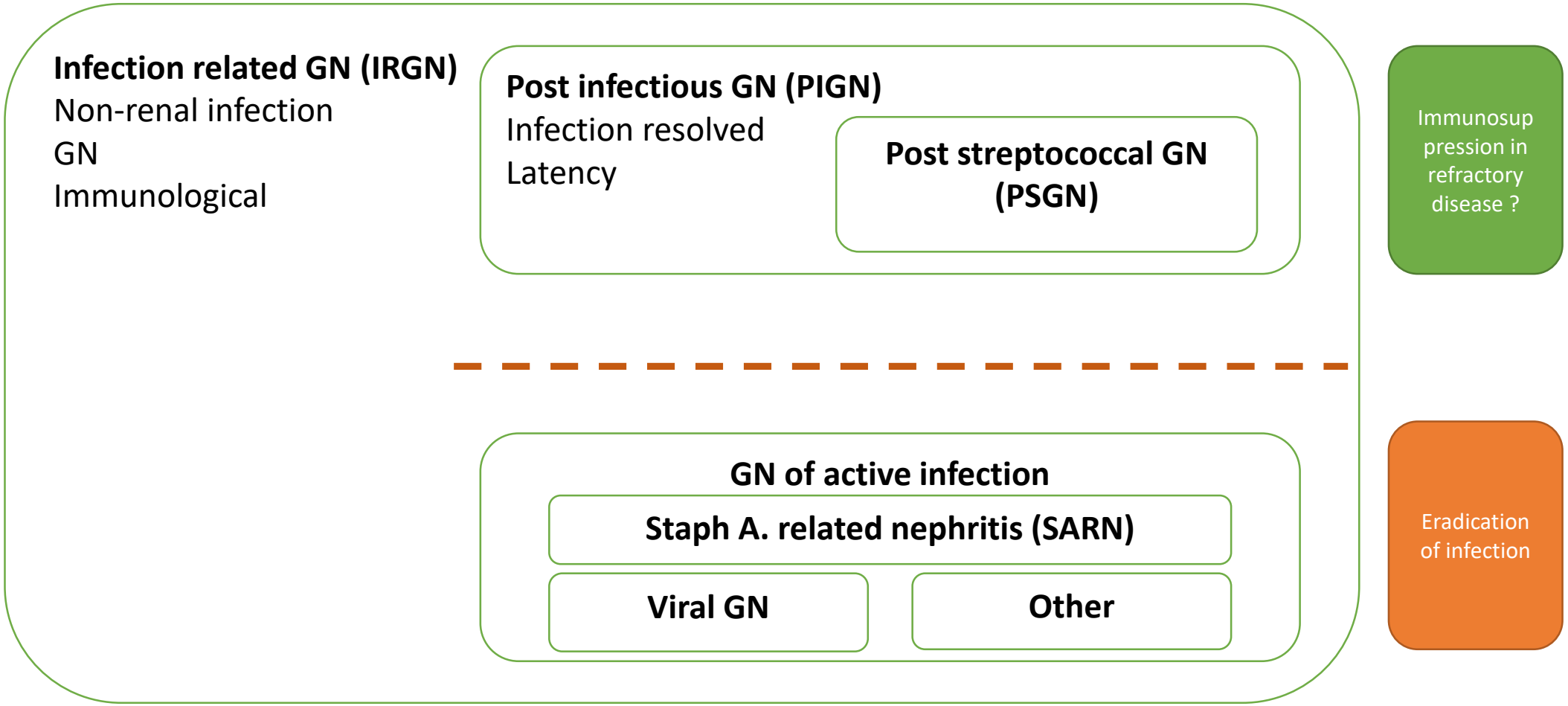
Kanjanabuch T, Kittikowit W, Eiam-Ong S. An update on acute postinfectious glomerulonephritis worldwide. Nat Rev Nephrol. 2009 May;5(5):259-69. doi:10.1038/nrneph.2009.44. Review. PubMed PMID: 19384327.

Changing epidemiology



Usui J, etal Temporal Changes in Post-Infectious Glomerulonephritis in Japan (1976-2009). PLoS One. 2016 Jun10;11(6):e0157356

Proposed definitions

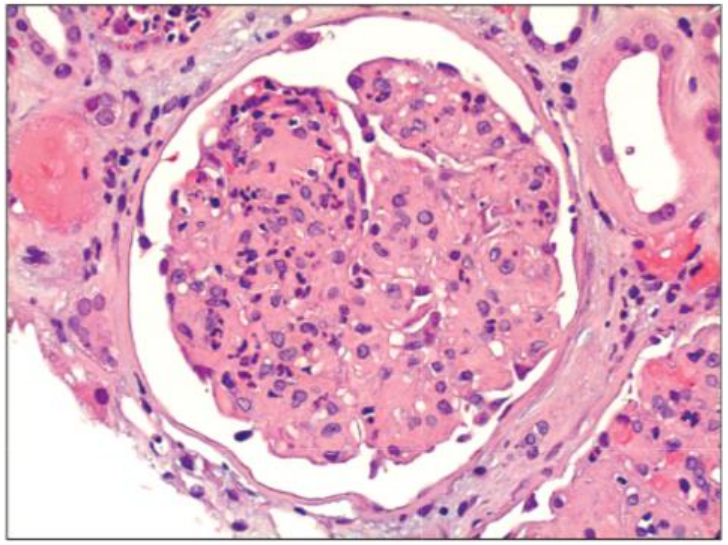


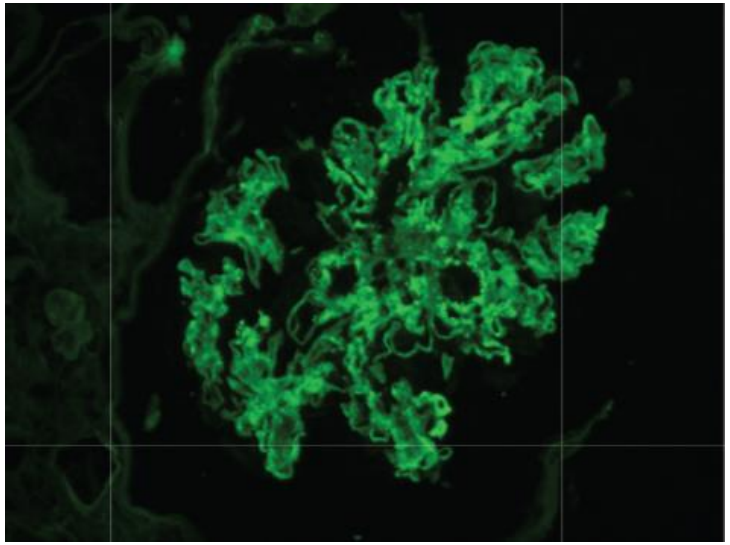
AJKD Official Journal of the National Kidney Foundation
AMERICAN JOURNAL OF KIDNEY DISEASES

Glassock RJ, Alvarado A, Prosek J, et al. Staphylococcusrelated glomerulonephritis and poststreptococcal glomerulonephritis: why defining "post" is important in understanding and treating infection-related glomerulonephritis. Am J Kidney Dis. 2015;65(6):826-832.

Staph A related GN

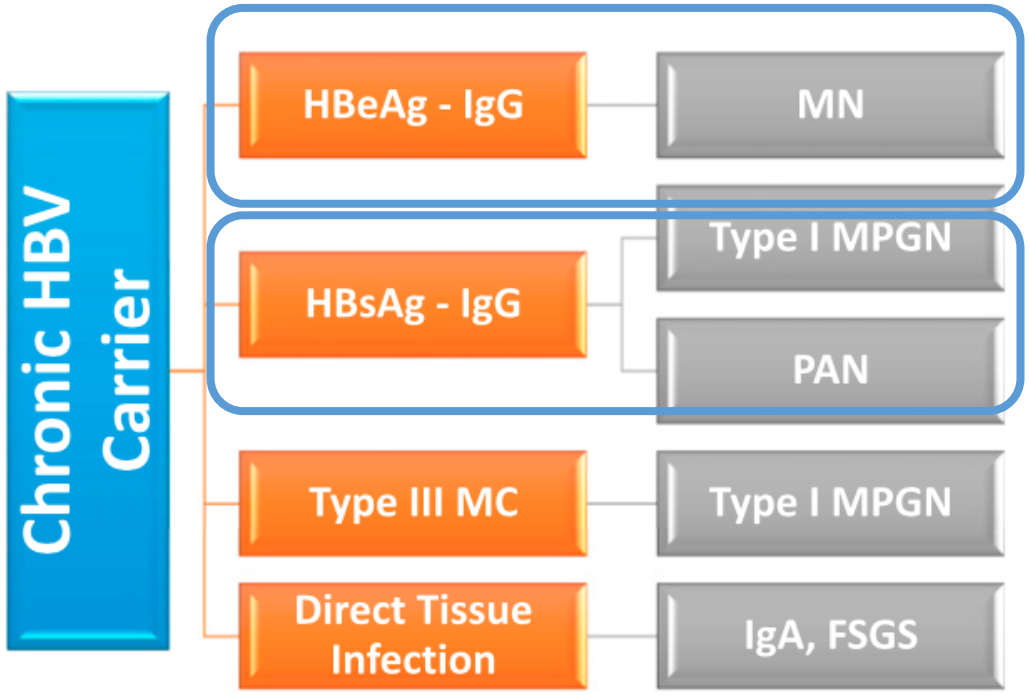
- In elderly and diabetics
- Concurrent infection
- MRSA
- IgA dominant IC GN
- Triggered by super-antigens
  - Enterotoxin A , C
  - Toxic shock syndrome toxin-1



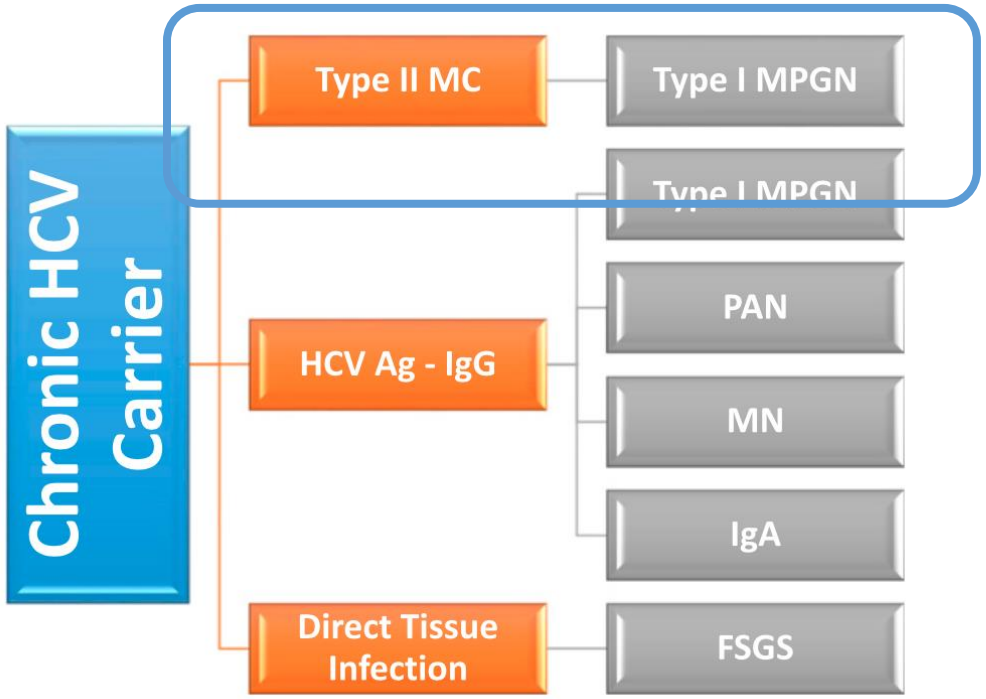


Viral associated GN

Hep B Virus



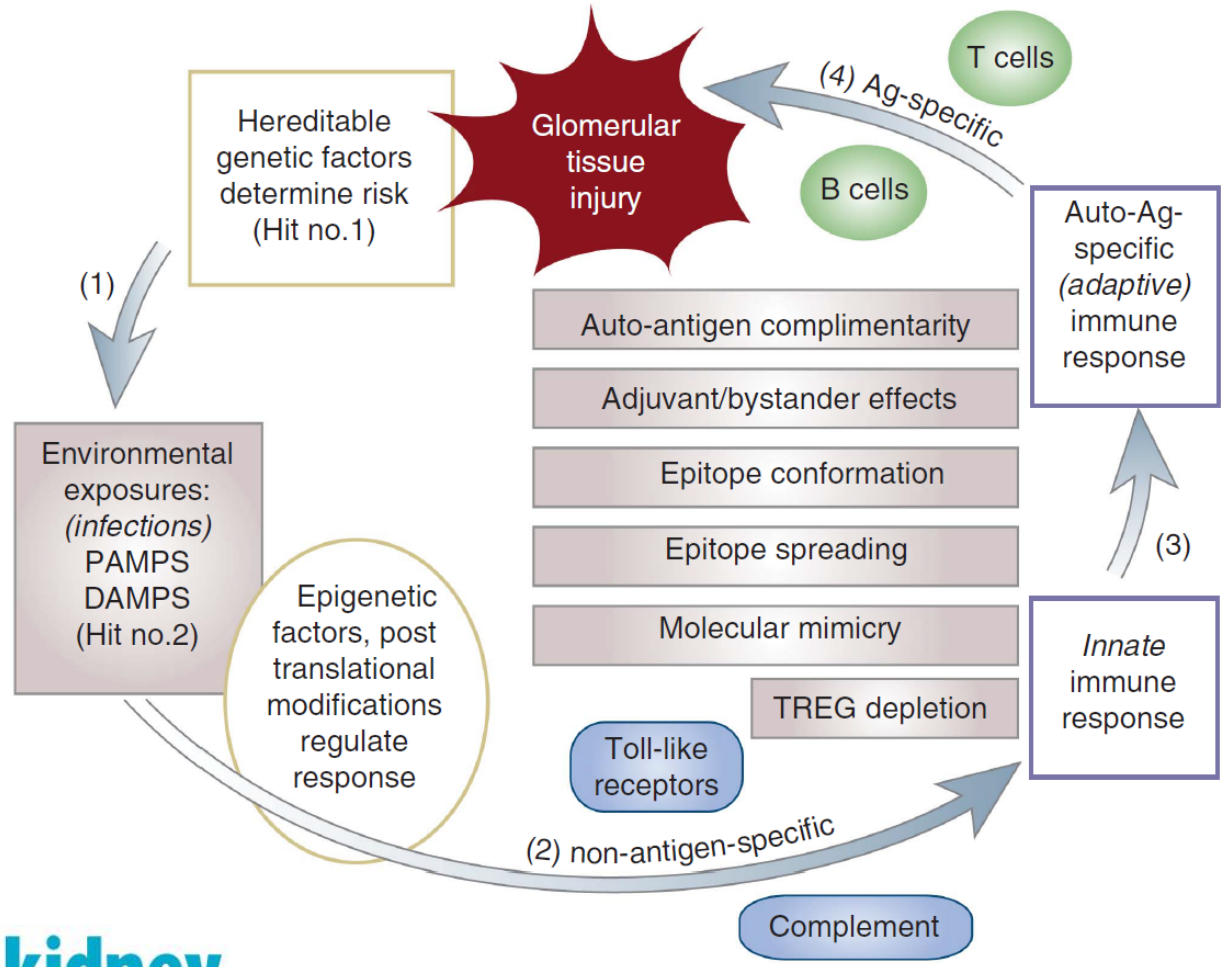
Hep C Virus



CJASN

Kupin WL. Viral-Associated GN: Hepatitis B and Other Viral Infections. Clin J Am Soc Nephrol. 2016 Oct 18. pii: CJN.09180816.
Kupin WL. Viral-Associated GN: Hepatitis C and HIV. Clin J Am Soc Nephrol.2017 Aug 7;12(8):1337-1342. doi: 10.2215/CJN.04320416

Infection & Autoimmunity



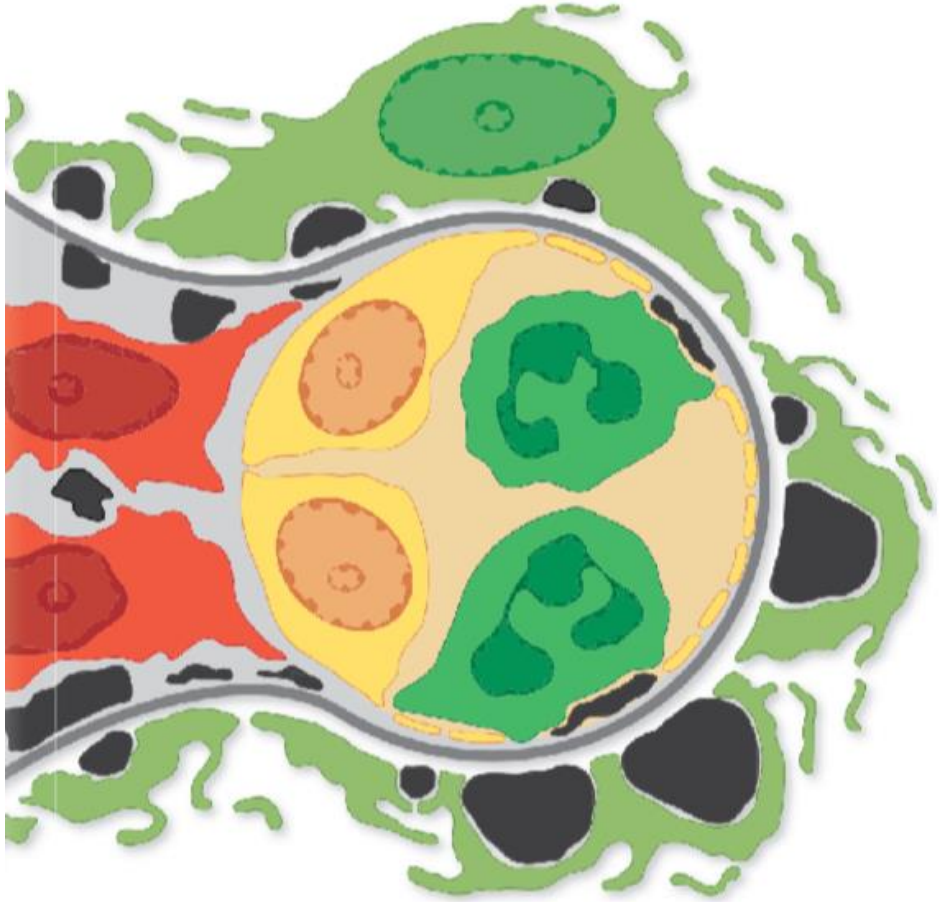
Disease
Post-streptococcal GN
IgA nephropathy
Anti-GBM nephritis
ANCA-positive GN
Lupus nephritis
MPGN I
MCD/FGS
Membranous nephropathy
Dense deposit disease
C3 nephropathy

ISN kidney INTERNATIONAL
OFFICIAL JOURNAL OF THE INTERNATIONAL SOCIETY OF NEPHROLOGY

Couser WG, Johnson RJ. The etiology of glomerulonephritis: roles of infection and autoimmunity. Kidney Int. 2014 Nov;86(5):905-14. doi: 10.1038/ki.2014.49.

PSGN

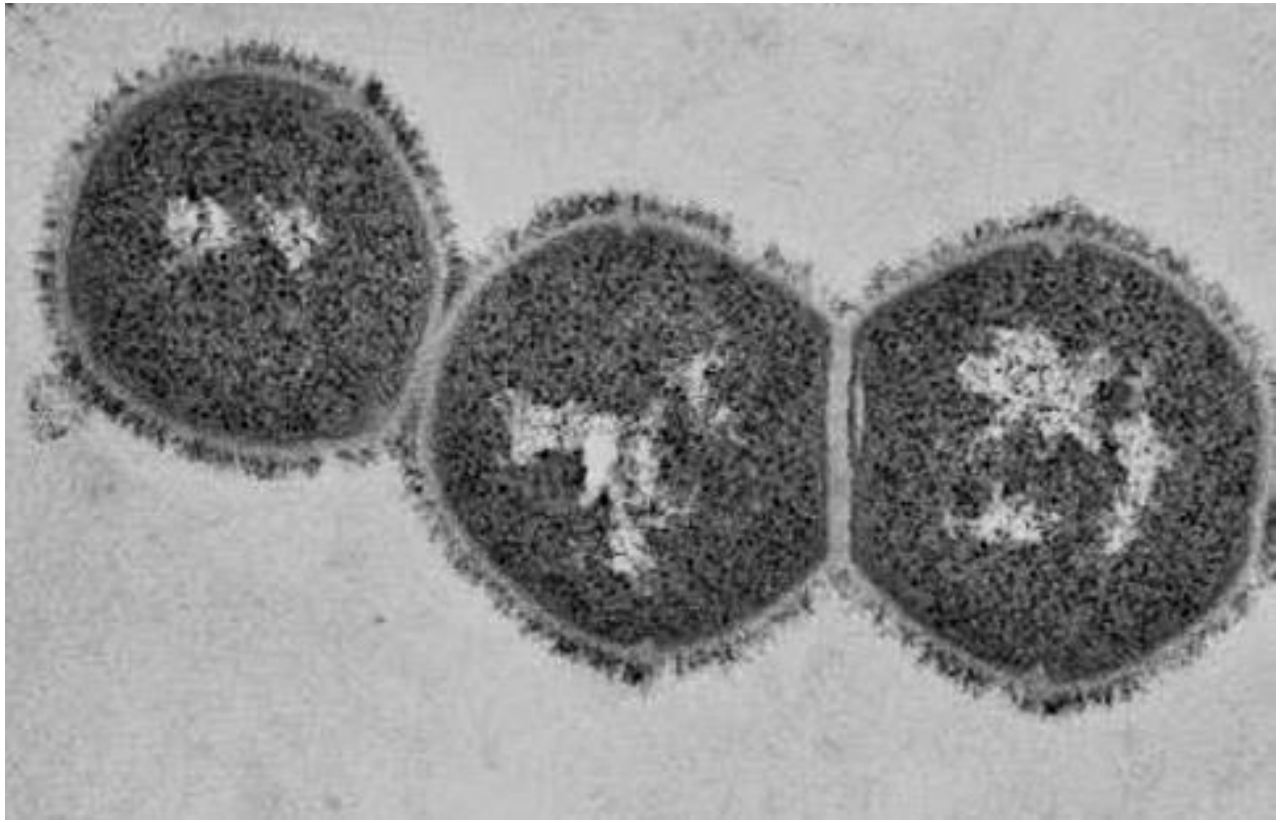
Pathogenesis



Reproduced from Heptinstall's pathology of the kidney 7th edition

- Group A Strep. (GAS) [Strep. Pyogenes]
- No animal model, GAS human pathogen
- In-situ sub-epithelial Immune complex (IC) deposition
  - No correlation to circulating IC
  - Preformed IC – largely sub-endothelial
- Alternative complement (AP) pathway activation
- Cellular immunity

Pathogenesis : mechanisms

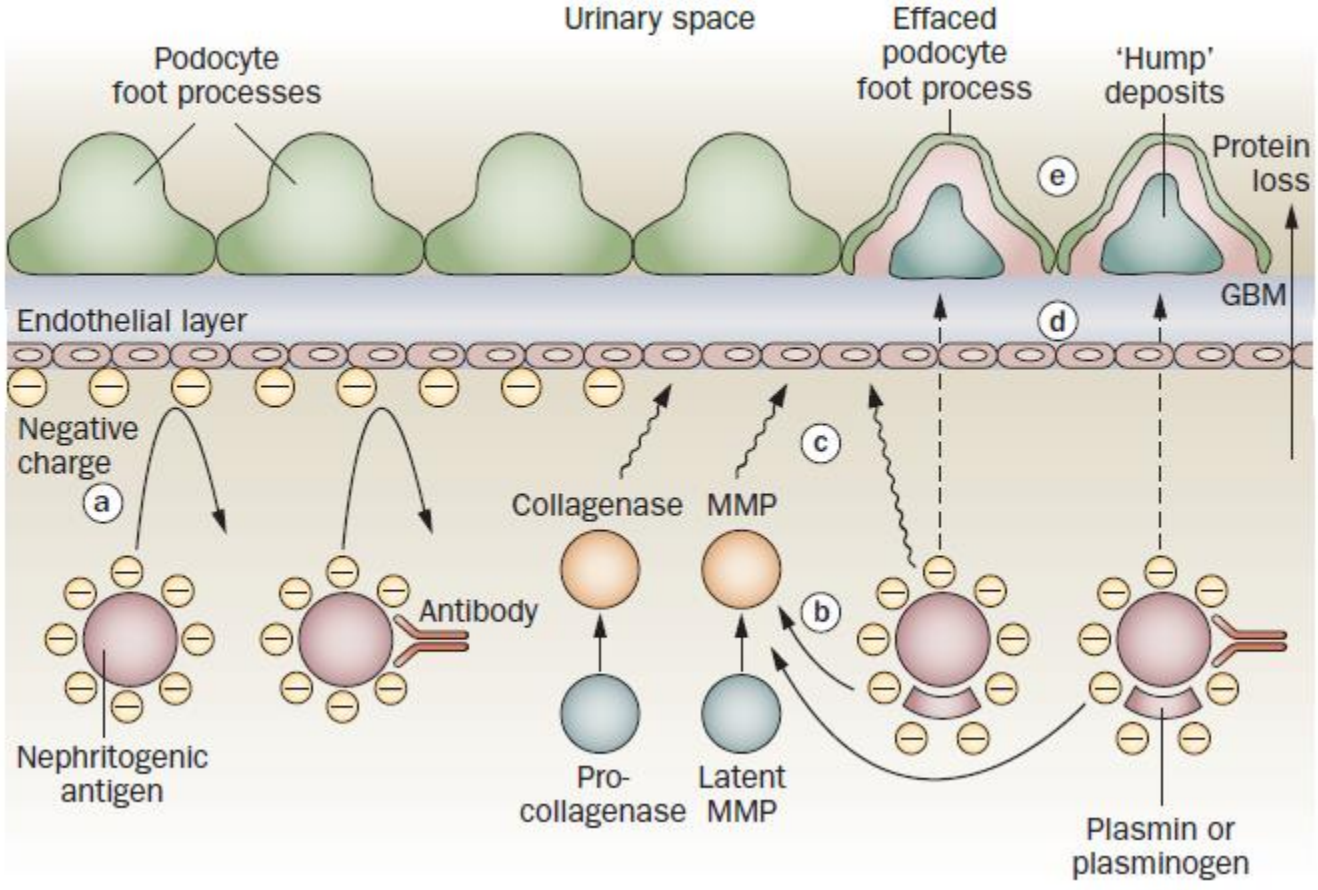


- Nephritogenic strains
  - URTI (M types **1, 2, 4, 12, 18,25)**
  - **Skin (M types 49, 55, 57,60)**
- Nephritogenic antigens
  - M proteins, streptokinase are unlikely
- Autoimmunity
  - Anti-IgG
  - Epiphenomenon ?
- Molecular mimicry
  - M protein in Rheumatic caditis

kidney INTERNATIONAL
OFFICIAL JOURNAL OF THE INTERNATIONAL SOCIETY OF NEPHROLOGY

Rodríguez-Iturbe B, Batsford S. Pathogenesis of poststreptococcal glomerulonephritis a century after Clemens von Pirquet. Kidney Int. 2007 Jun;71(11):1094-104.

Pathogenesis: Penetrating the GBM



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Kanjanabuch T, Kittikowit W, Eiam-Ong S. An update on acute postinfectious glomerulonephritis worldwide. Nat Rev Nephrol. 2009 May;5(5):259-69.

Pathogensis : Nephritogenicity

SpeB/zSpeB
28 kDa

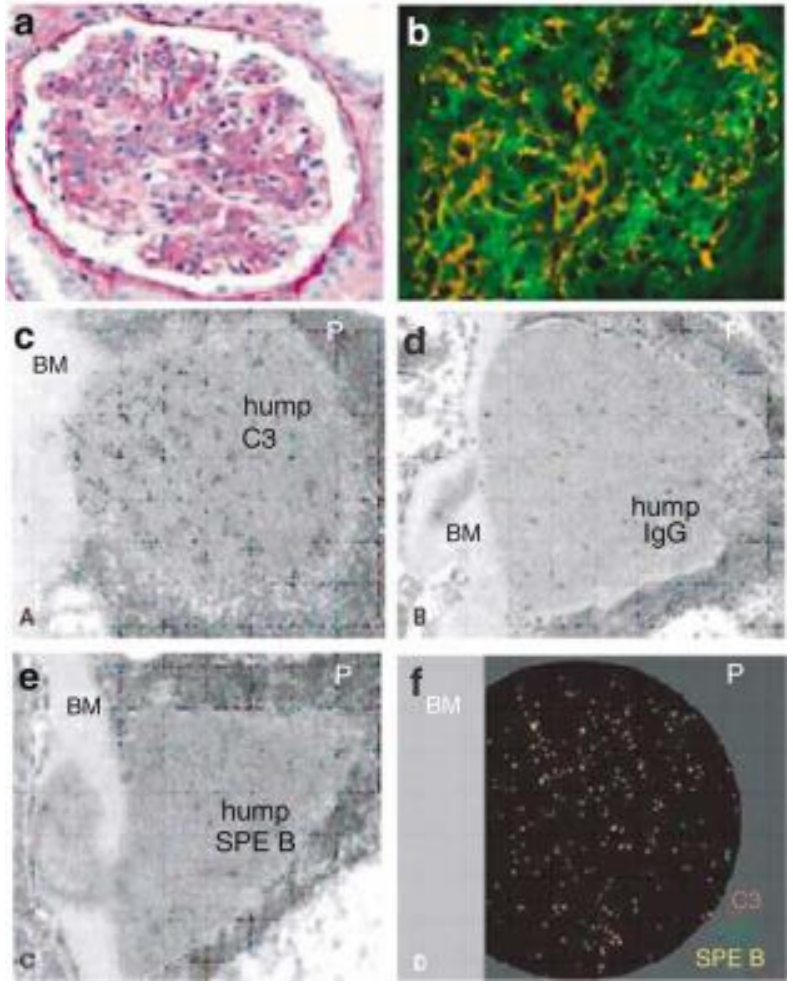
GAPDH (NAPlr)
43 kDa

Serological : Specific Antibody response

Histological: Co-localization

Plasmin binding receptor protein
Activates collagenase & MPP

Immune complex GN



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Rodríguez-Iturbe B, Batsford S. Pathogenesis of poststreptococcalglomerulonephritis a century after Clemens von Pirquet. Kidney Int. 2007 Jun;71(11):1094-104.

Clinical features

Oliguria(~60%)/Oedema(~70%)
Hypertension (~80%)/CCF
Intra-glomerular blood flow
⇣ FeNa →Na/water retention
⇣ Renin state

Proteinuria(~70%)
Sub-nephrotic

Haematuria (~100%)
Microscopic 2/3

Serology
ASOT : URTI > skin
Anti DNAseB : skin > URTI
Anti-hyaluronidase : skin > URTI
Autoantibodies (RF, AntiDNA, ANCA)

Complements
Predominantly AP (C3)

Culture (~25%)

GAS infection

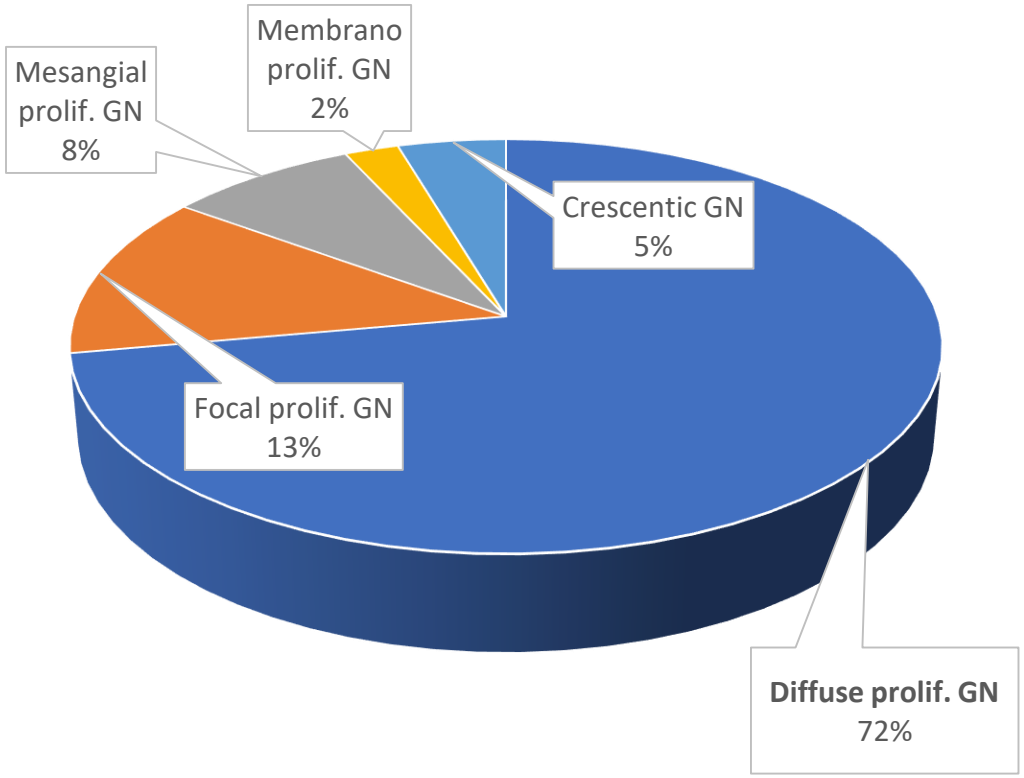
Latency (pharyngitis :2 weeks, skin: >2 weeks)

Acute Nephritic syndrome

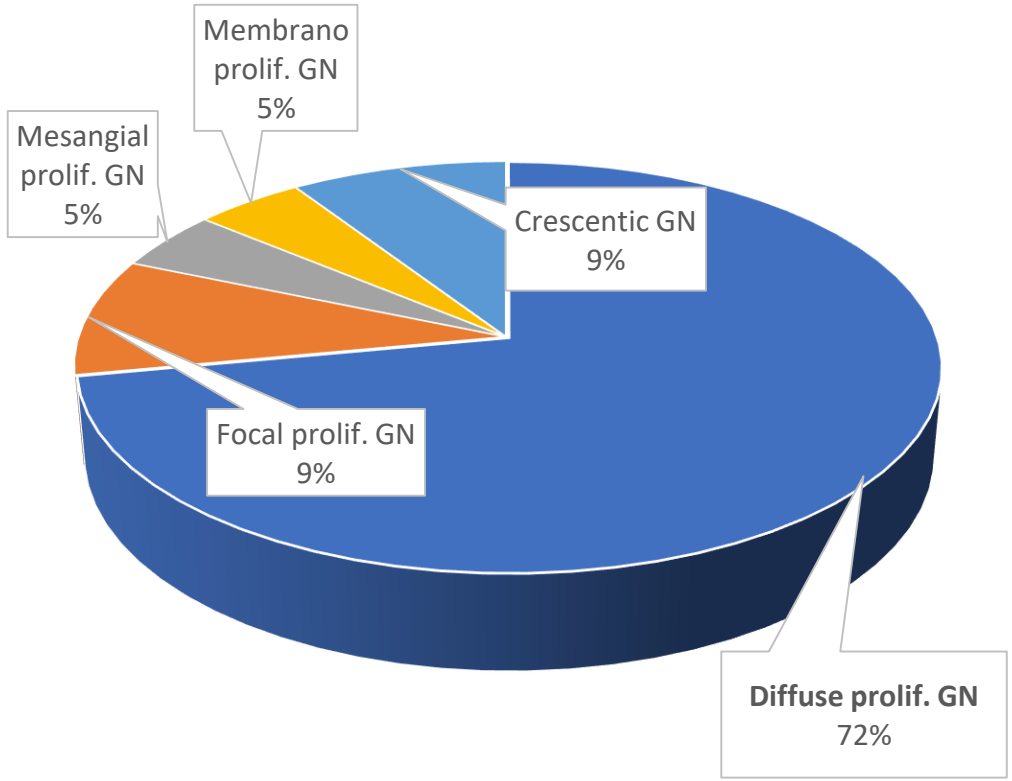
Recovery

Histology

Nasr etal. 1995-2005
(N=86) : NY, USA

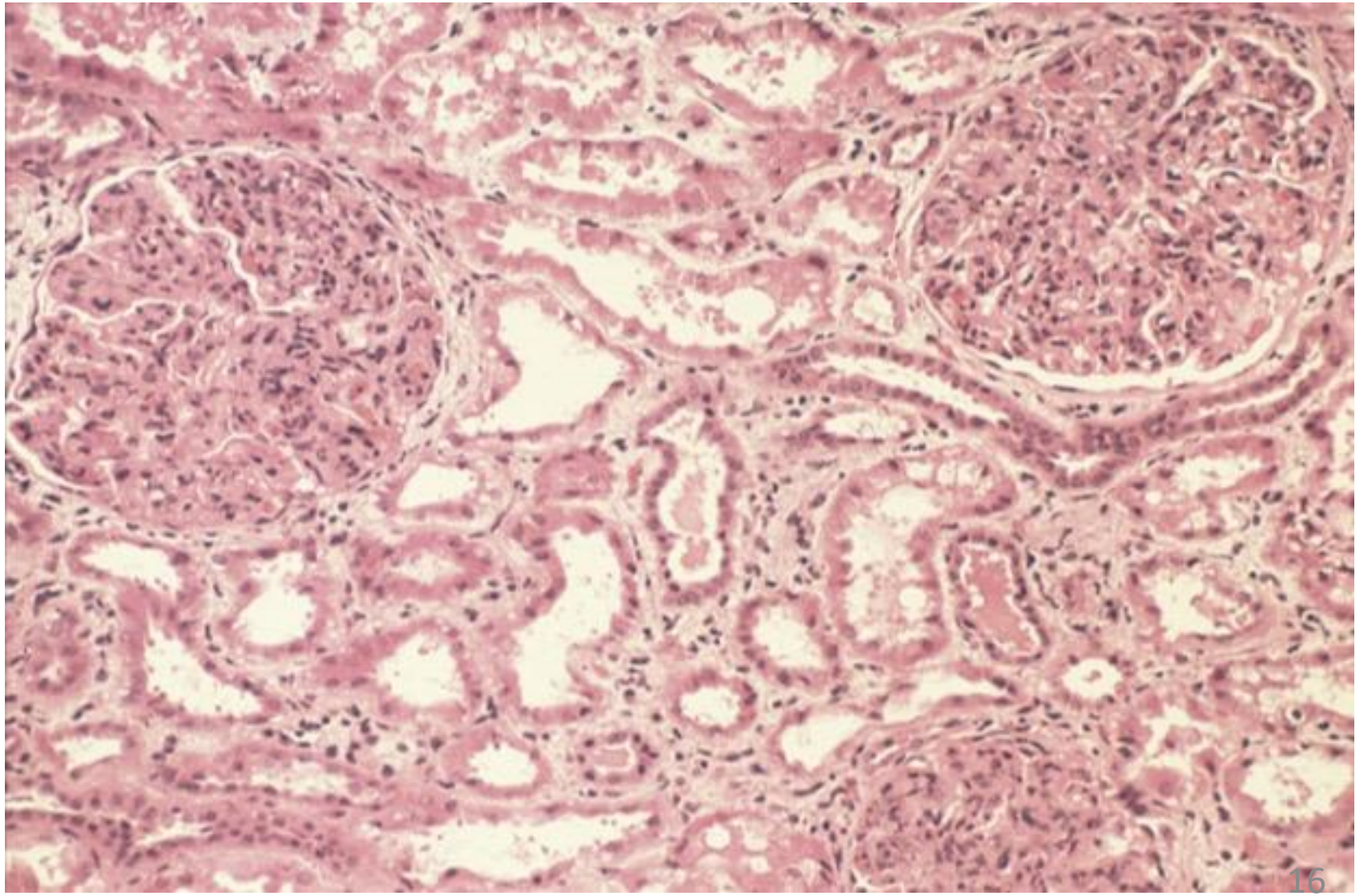


Ramanathan etal. 2004-2014
(N=43) : NT Aus



Histology : LM : Glomeruli

- Diffuse, monomorphic
- Hypercellularity
- Lobular expansion
- Crescents are rare



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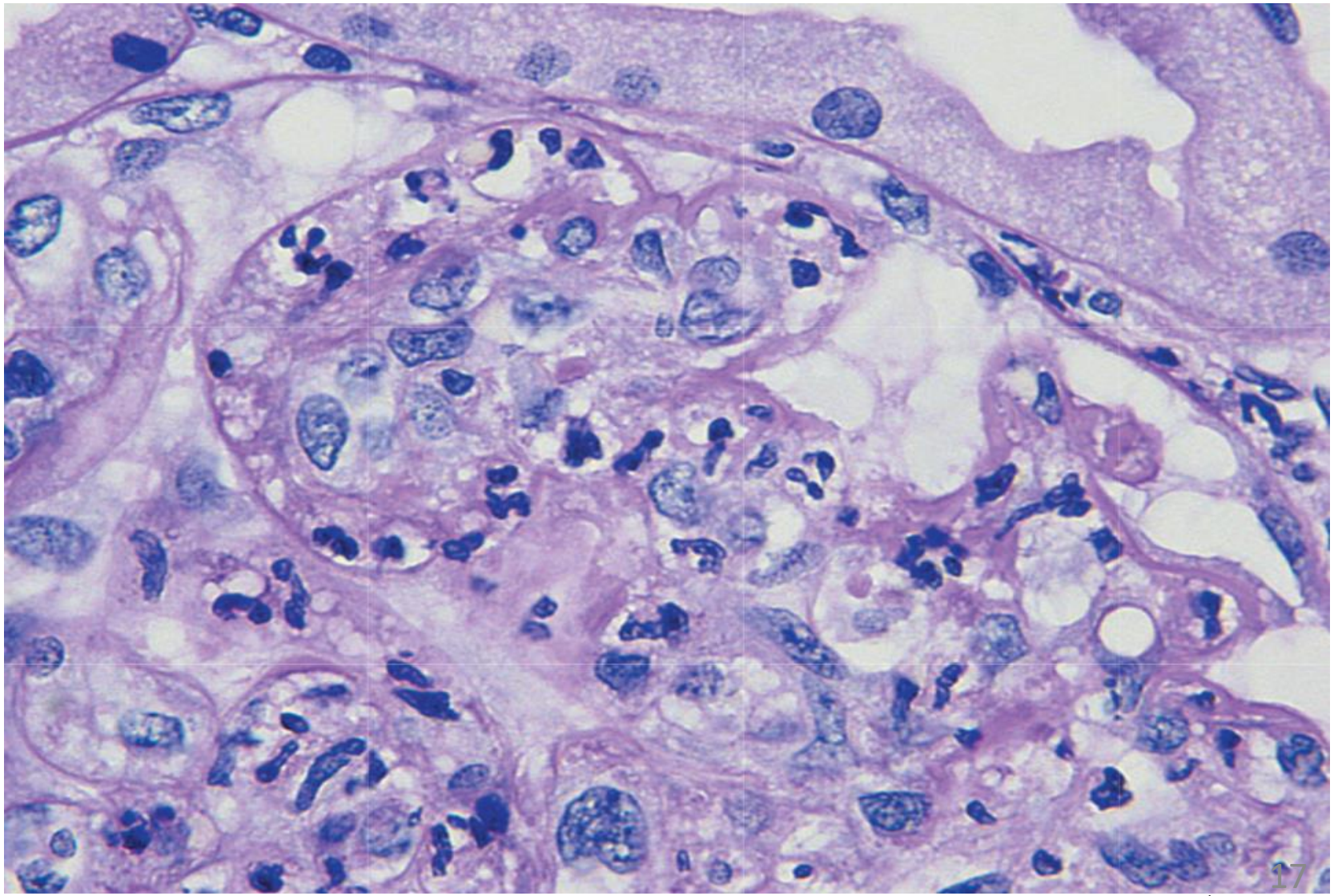
Histology : LM : Glomeruli

- GBM is not thickened
- Hypercellularity
  - External (predominant, early)
    - PMN
    - Monocytes
    - Lymphocytes, eosinophils unusual
  - Internal (late stage)
    - Mesangial
    - Epithelial
    - Endothelial



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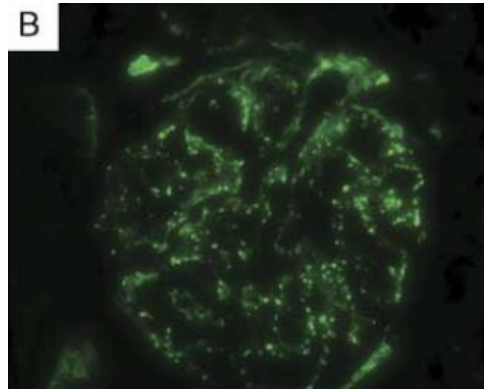
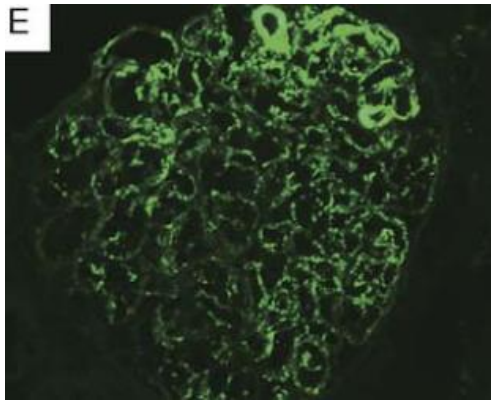
Histology : LM : Tubules, interstitium, blood vessels

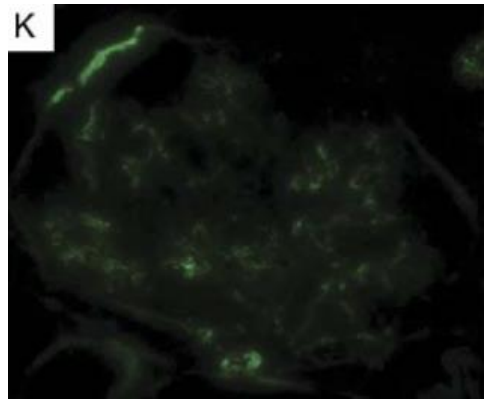
- Not directly affected
- Proteinuria -> hyaline droplets
- Casts
- ATN
- IF/TA in extensive crescentic
- Arteritis rare

Histology : IF

- Sorger etal :
  - Starry sky : early cases
  - Garland : assoc heavy proteinuria, more dense subepithelial
  - Mesangial : resolving
- No evidence that different aetiological factors are responsible
- Likely related to host and stage of the disease





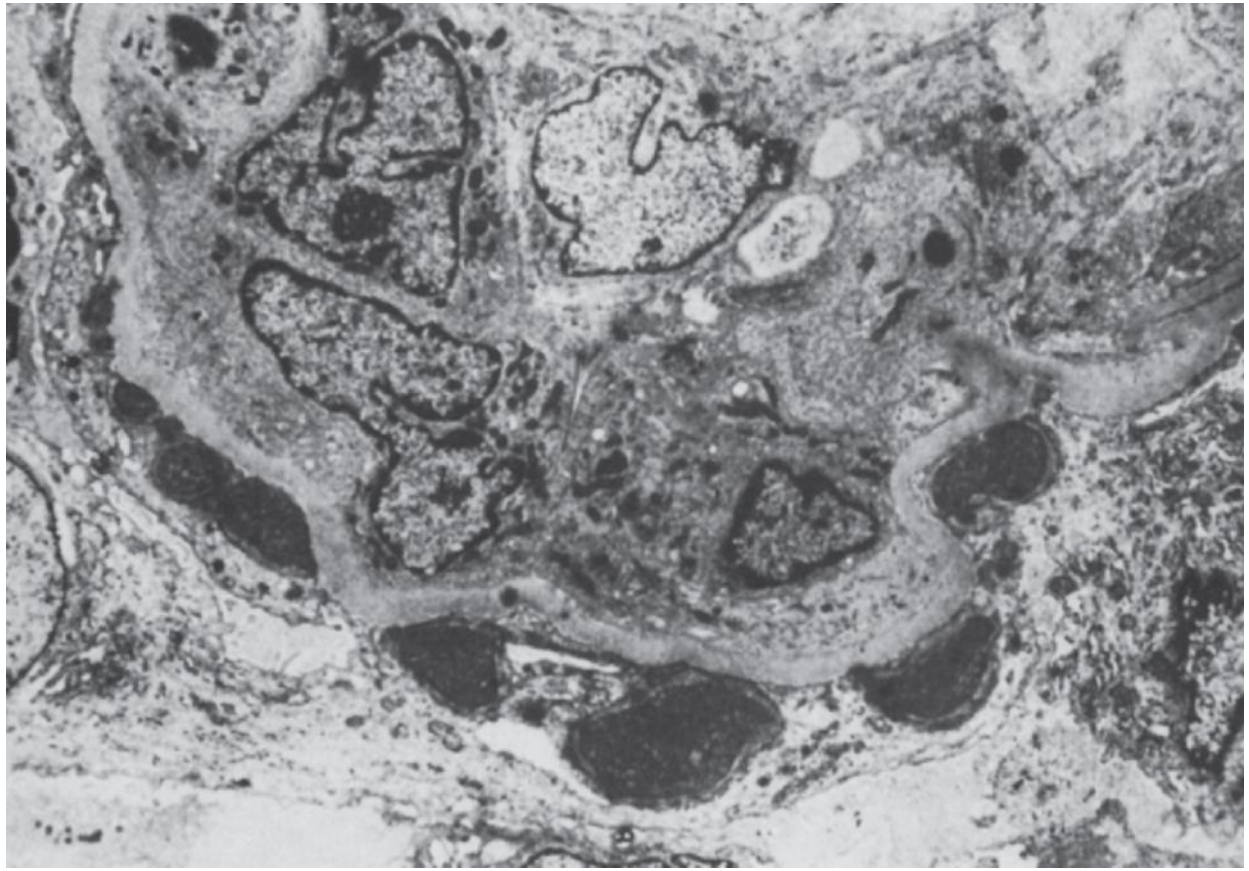


Histology : IF

- Anti-C3
  - More intense than anti-IgG, sometimes only anti-C3
- IgM in 50%
- IgA in staph
- C1q-C4 absent ; suggestive of alternate pathway

Histology : EM

- Sub-epithelial electron-dense deposits (“Humps”)
- Sub-endothelial early in disease
- Not pathognomonic
- Mostly in the mesangial notch near GBM reflection over mesangium
- Abundant in the first few weeks and then decline, usually disappear in 6 weeks



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Pathology : temporal profile

TABLE 1. Poststreptococcal GN: The Interval Between the Onset of Renal Symptoms and Renal Biopsy Determines the Histologic Features

	Early Biopsy (< 2 wk)	Typical Features	Late Biopsy (> 4-6 wk)
Clinical features	Mild albuminuria and hematuria	Acute nephritic syndrome	Persistent microscopic hematuria and/or proteinuria
Light microscopy	Glomerular endocapillary proliferation may be focal and segmental	Diffuse global proliferation ("exudative" early on; lymphocytes, monocytes along with mesangial and endothelial proliferation predominate later)	Mesangial proliferation
Immunofluorescence microscopy	C3 and IgG; starry sky pattern	C3 and IgG; starry sky or garland pattern*	C3 ± IgG; mesangial pattern
Electron microscopy	Mesangial, subepithelial (humps), and ± subendothelial deposits	Mesangial, subepithelial (humps), and ± subendothelial deposits	Mesangial and ± rare subepithelial humps in the mesangial "notch"

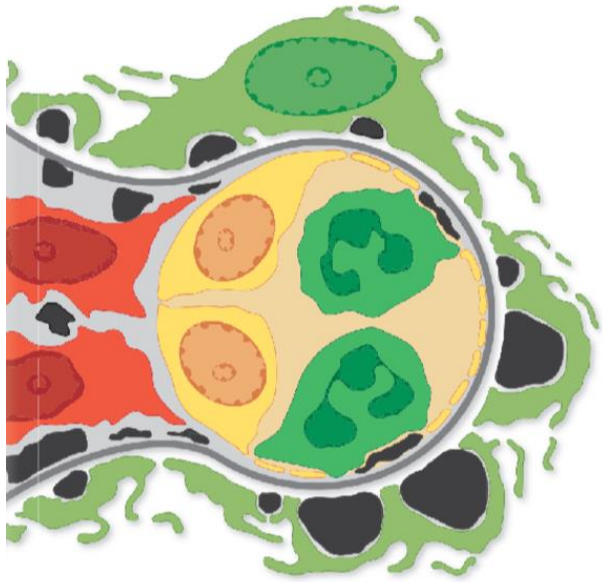
*Garland pattern with confluent subendothelial deposits in patients with nephrotic syndrome.
GN indicates glomerulonephritis; Ig, immunoglobulin.

ADVANCES IN ANATOMIC PATHOLOGY

Kambham N. Postinfectious glomerulonephritis. Adv Anat Pathol. 2012 Sep;19(5):338-47. doi: 10.1097/PAP.0b013e31826663d9. Review. PubMed PMID:22885383.

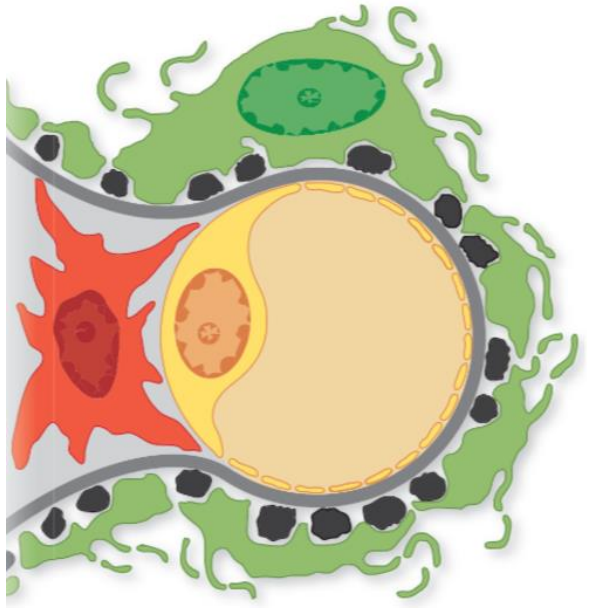
PSGN vs. Primary MGN : sub-epithelial deposits

- PSGN



- Variable sized sub-epithelial
- Sub-endothelial and mesangial deposits

- Membranous



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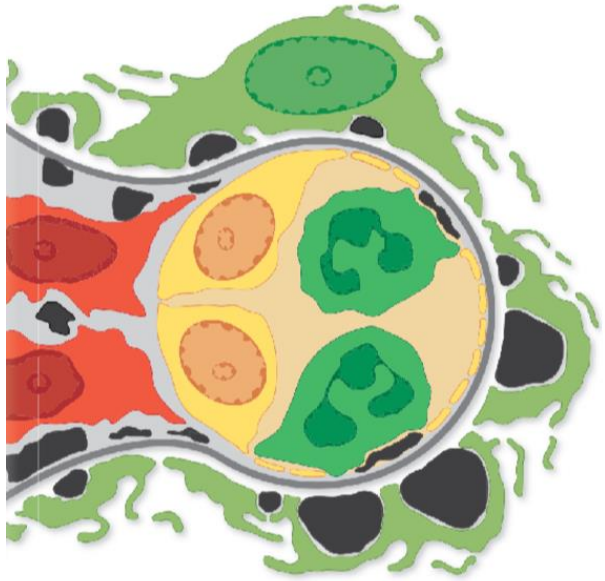
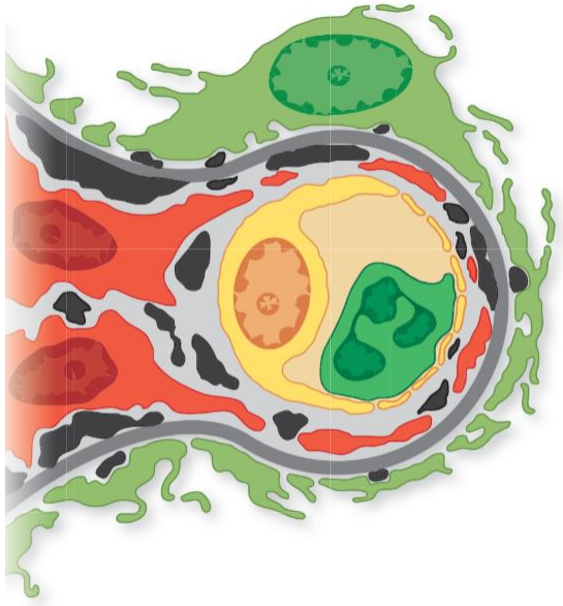
PSGN vs. MPGN type 1 :

- PSGN



- Predominant sub-epithelial
- Sub-endothelial and mesangial deposits

- MPGN type 1



- Predominant sub-endothelial
- Occasional ‘humps’

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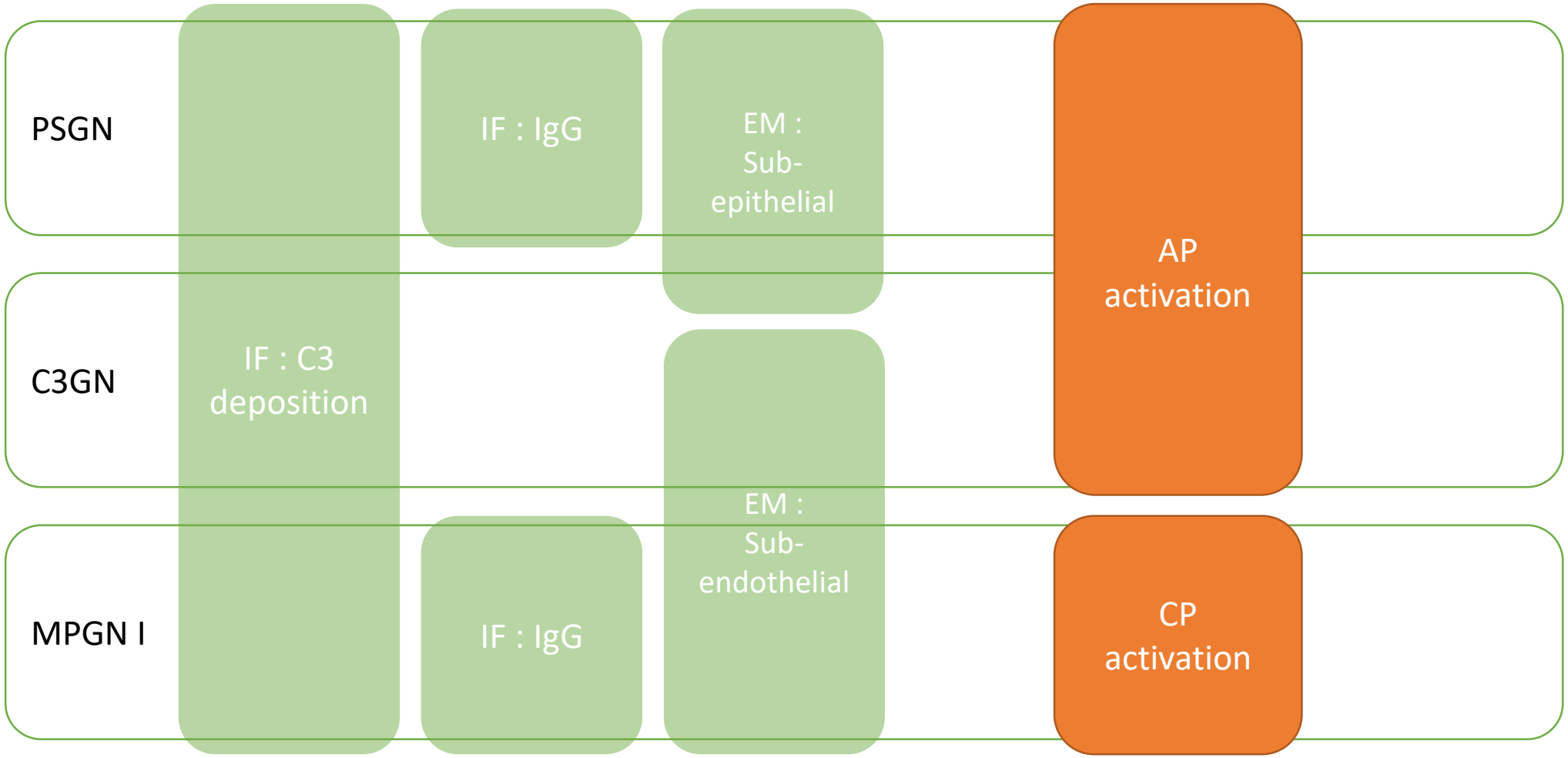
Comparison of C3 dominant GN



Proposed GN classification based on Pathogenesis

Table 1. Classification of GN

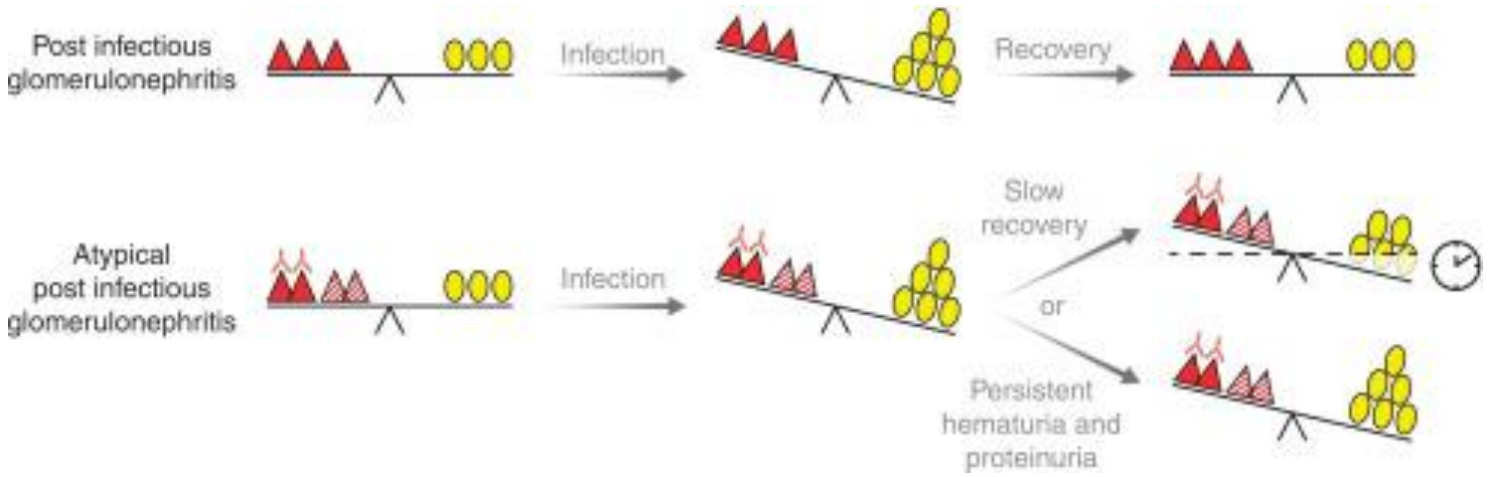
Pathogenic Type	Specific Disease Entity	Pattern of Injury: Focal or Diffuse	Scores or Class
Immune-complex GN[a]	IgA nephropathy, IgA vasculitis, lupus nephritis, infection-related GN, fibrillary GN with polyclonal Ig deposits	Mesangial, endocapillary, exudative, membranoproliferative, necrotizing, crescentic, sclerosing, or multiple[b]	Oxford/MEST scores for IgA nephropathy ISN/RPS class for lupus nephritis
Pauci-immune GN	MPO-ANCA GN, proteinase 3-ANCA GN, ANCA-negative GN	Necrotizing, crescentic, sclerosing, or multiple[b]	Focal, crescentic, mixed, or sclerosing class (Berden/EUVAS class)
Anti-GBM GN	Anti-GBM GN	Necrotizing, crescentic, sclerosing, or mixed[b]	
Monoclonal Ig GN[a]	Monoclonal Ig deposition disease, proliferative GN with monoclonal Ig deposits, immunotactoid glomerulopathy, fibrillary GN with monoclonal Ig deposits	Mesangial, endocapillary, exudative, membranoproliferative, necrotizing, crescentic, sclerosing, or multiple[b]	
C3 glomerulopathy	C3 GN, dense deposit disease	Mesangial, endocapillary, exudative, membranoproliferative, necrotizing, crescentic, sclerosing, or multiple[b]	

JASN

1: Sethi S, Haas M, Markowitz GS, D'Agati VD, Rennke HG, Jennette JC, Bajema IM, Alpers CE, Chang A, Cornell LD, Cosio FG, Fogo AB, Glassock RJ, Hariharan S, Kambham N, Lager DJ, Leung N, Mengel M, Nath KA, Roberts IS, Rovin BH, Seshan SV,Smith RJ, Walker PD, Winearls CG, Appel GB, Alexander MP, Cattran DC, Casado CA, Cook HT, De Vriese AS, Radhakrishnan J, Racusen LC, Ronco P, Fervenza FC. MayoClinic/Renal Pathology Society Consensus Report on Pathologic Classification,Diagnosis, and Reporting of GN. J Am Soc Nephrol. 2016 May;27(5):1278-87. doi:10.1681/ASN.2015060612. Epub 2015 Nov 13.

Atypical PIGN

- Rarely, persisting disease activity
- Role of C5i



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Sethi, S., Fervenza, F. C., Zhang, Y., Zand, L., Meyer, N. C., Borsa, N., … Smith, R. J. H. (2013). Atypical post-infectious glomerulonephritis is associated with abnormalities in the alternative pathway of complement. Kidney International, 83(2), 293–299. http://doi.org/10.1038/ki.2012.384

Outcome

Table 7 Summary of characteristics and outcomes from previous studies of APIGN compared with our study

	Study	Country	Year	Case	Biopsy incidence	Mean/ median age	Diabetes	Main organism	Site of infection	ESRF risk	Mortality risk
1	Richmond *et al.*[21]	New Zealand	1970–1987	41	N/A	36	N/A	Non-Streptococcal	URTI	34%	36%
2	Keller *et al.*[19]	Germany	1984–1993	30	4.5%	49	N/A	Streptococcal	Teeth	13%	3%
3	Montseny *et al.*[22]	France	1976–1993	76	4.5%	48	8%	Staphylococcus	URTI	8%	11%
4	Moroni *et al.*[23]	Italy	1979–1999	50	N/A	54	10%	Streptococcus	URTI	10%	10%
5	Srisawat *et al.*[24]	Thailand	1999–2005	36	3.6%	47	12%	Non-streptococcal	N/A	14%	0%
6	Nasr *et al.*[25]	USA	1995–2005	86	0.6%	56	21%	Streptococcus	URTI	17%	8%
7	Wen *et al.*[26]	Taiwan	2000–2008	20	N/A	61	25%	Staphylococcus	Skin	25%	30%
8	Nasr *et al.*[13]	USA	2000–2010	109	0.9%	>65	49%	Staphylococcus	Skin	11%	13%
9	Luo *et al.*[14]	China	2000–2009	64	N/A	29	2%	Streptococcus	URTI	4%	0%
10	Helal *et al.*[27]	Tunisia	1976–2004	148	N/A	36	4%	Streptococcus	URTI	3%	1%
11	Hamouda *et al.*[28]	Tunisia	1991–2007	50	N/A	37	10%	Streptococcus	URTI	0%	0%
12	Natarajan *et al.*[18]	India	2009–2011	102	N/A	33	3%	Streptococcus	URTI	≈1%	0%
13	Our study	Australia	2004–2014	43	11.4%	44	61%	Streptococcus	Skin	50%	14%

Modified from Luo *et al.*[14] with permission. We would like to thank the authors and Dustri-Verlag for permission to use their table. N/A, not applicable; URTI, upper respiratory tract infection

NEPHROLOGY

Ramanathan, G., Abeyaratne, A., Sundaram, M., Fernandes, D. K., Pawar, B., Perry, G. J., Sajiv, C., and Majoni, S. W. (2017) Analysis of clinical presentation, pathological spectra, treatment and outcomes of biopsy-proven acute postinfectious glomerulonephritis in adult indigenous people of the Northern Territory of Australia. Nephrology, 22: 403–411. doi: 10.1111/nep.12797.

Treatment

- PSGN
  - Supportive care
  - Steroids in crescentic GN ? Weak evidence
  - Emerging role of C5i in Atypical forms
- IRGN
  - Supportive care
  - Prevention of infection ; vaccination
  - Eradication of infection

Conclusion

- Classical PSGN is becoming rarer. Non-PSGN/IRGN increasingly recognized.
- Immune complex based pathology
- PSGN associated with Nephritogenic antigens (SpeB / NAPLR)
- Complement defects lead to Atypical/C3GN
- Outcome is dependent on co-morbidities.