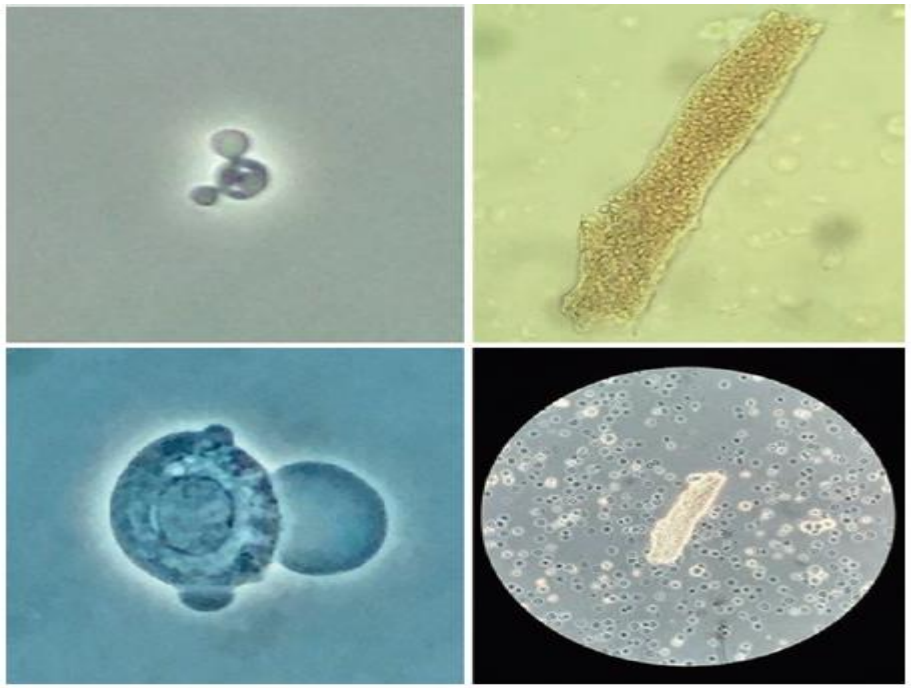
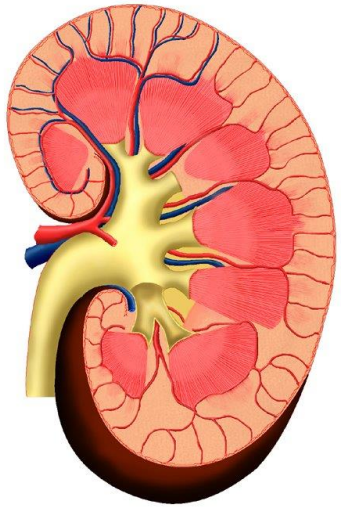
Glomerular Diseases





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Learning objectives

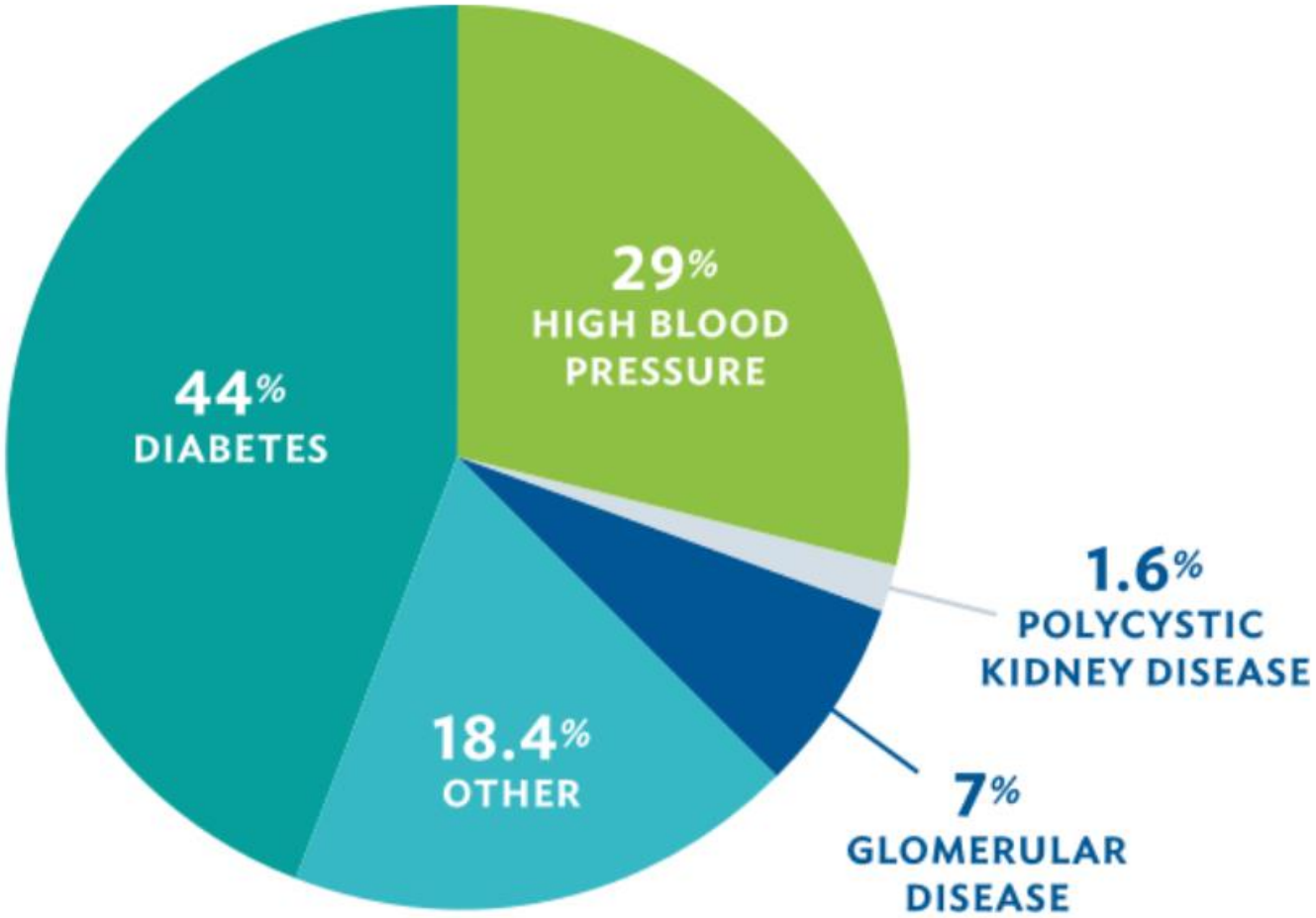
1. Appreciate the fact that glomerular diseases fall onto a wide spectrum
2. Be able to define the nephritic and nephrotic syndromes
3. Understand the pathology of 4 key glomerular diseases which serve as archetypal examples of nephritic and nephrotic syndrome
4. Know how to assess and manage a patient with suspected glomerular disease
5. Understand the various outcomes associated with these diseases

The study of kidney diseases is facilitated by dividing them into those that affect the

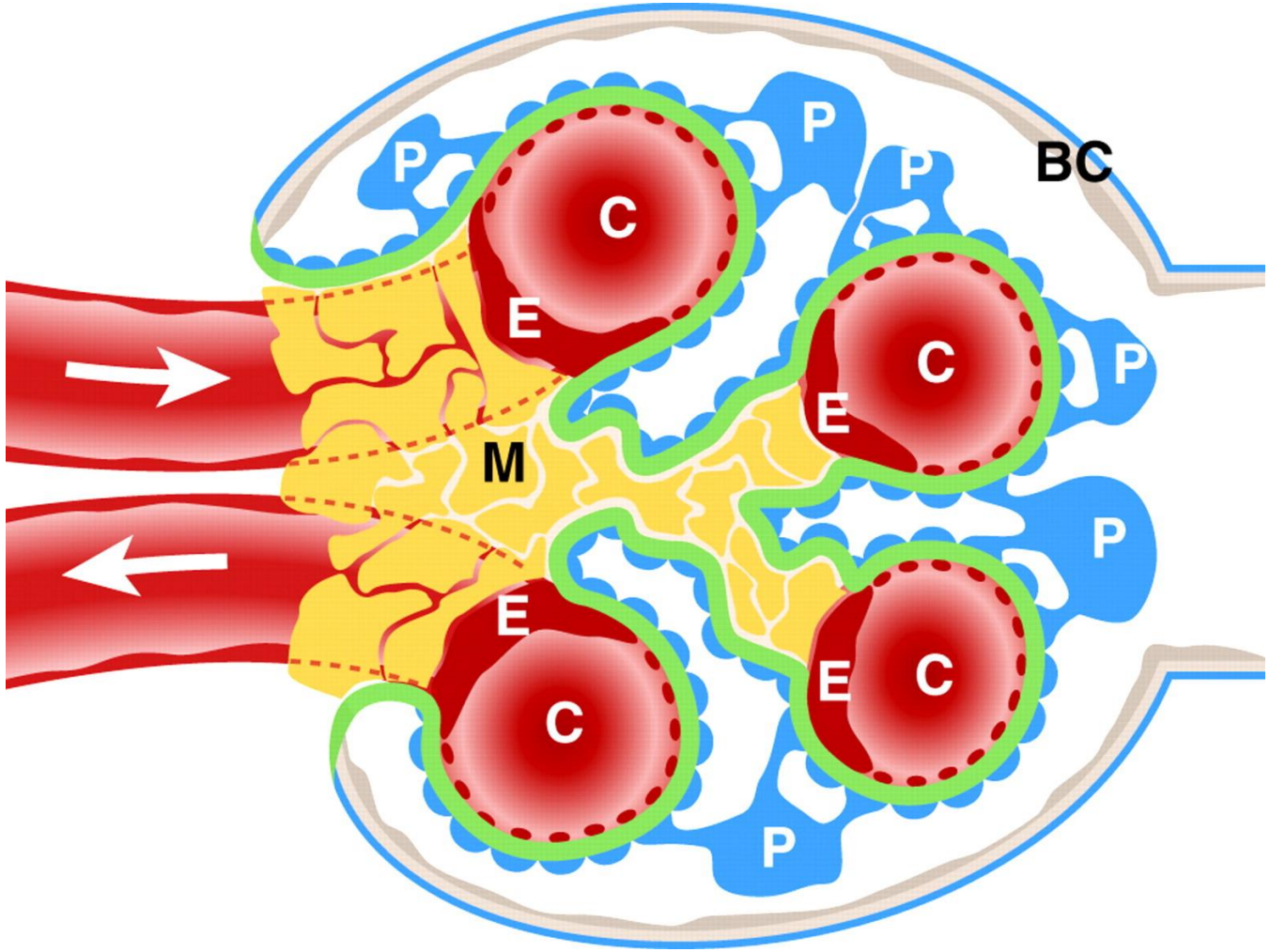
Four basic morphologic components:

1. Glomeruli
2. Tubules
3. Interstitium
4. Blood vessels

Causes of ESRD



Exercise 1: Histology of the Glomerulus



Bowman's Capsule

Capillaries

Endothelial cells

Mesangium

Podocytes

(Foot processes)

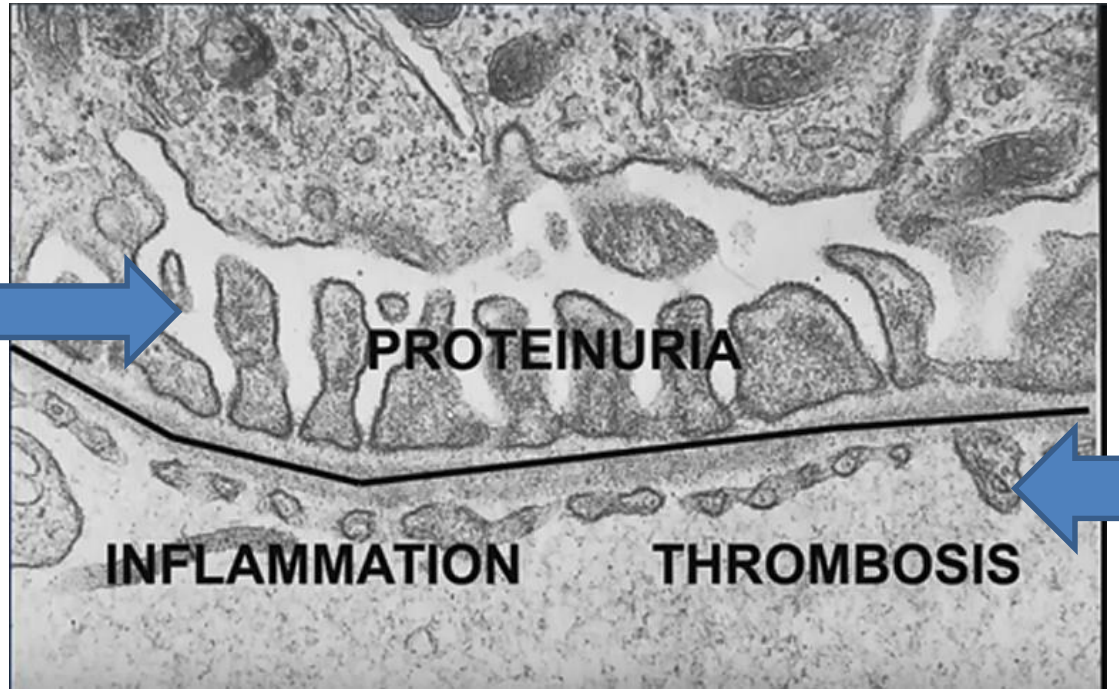
(GBM)

The Cardinal Signs of Glomerular Dysfunction

- Proteinuria [dipstick, 24hr collection, Prot/Cr]
- Hematuria [dipstick, sediment]
- Loss of glomerular filtration rate [sCr; eGFR]

Disruptions of Normal Architecture

Nephrotic Syndrome



Active Urinary Sediments

Signs of Glomerular Dysfunction: Drop in GFR

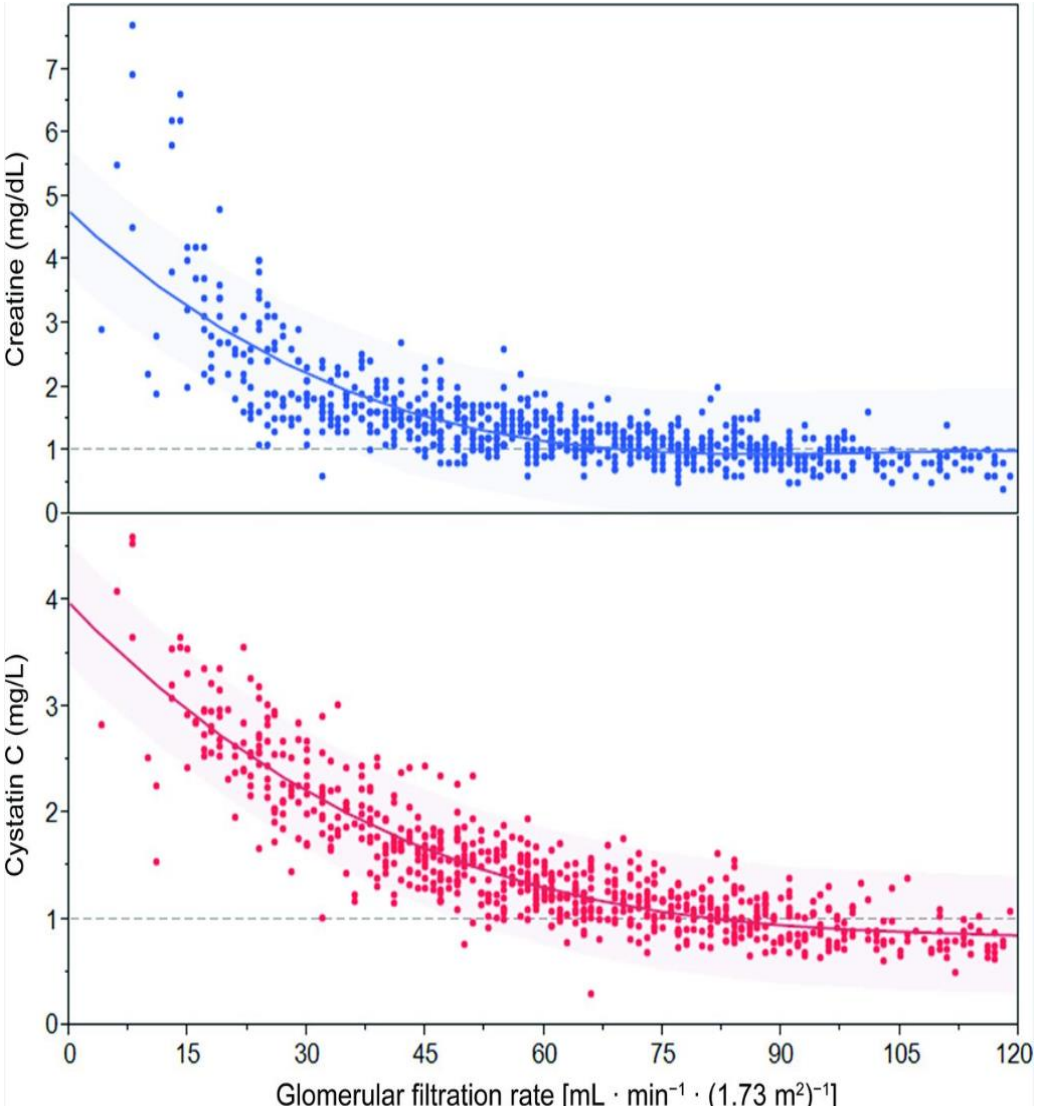
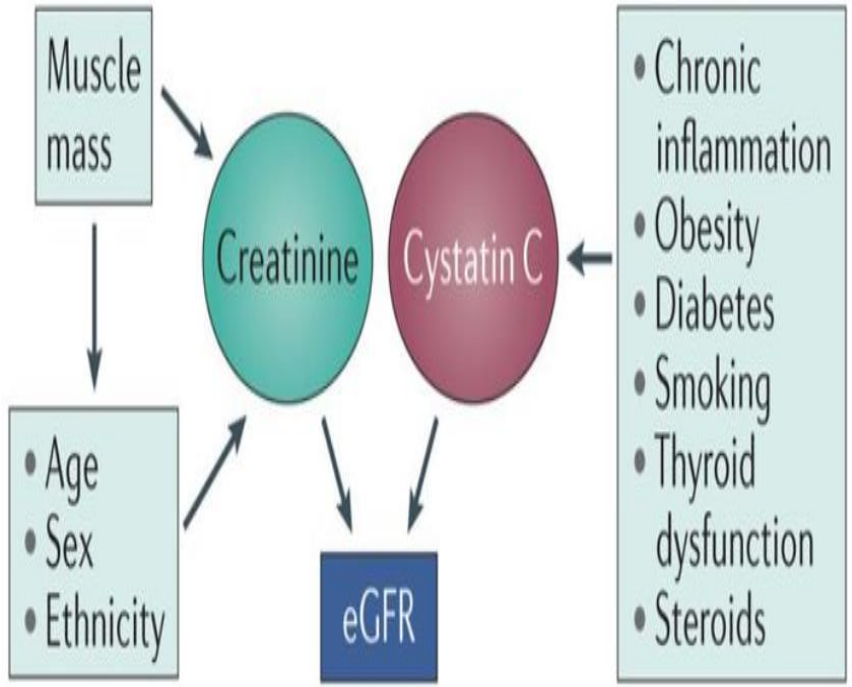


Figure 1: Non-GFR determinants that affect estimated GFR.



Nature Reviews | Nephrology

Signs of Glomerular Dysfunction: Drop in GFR

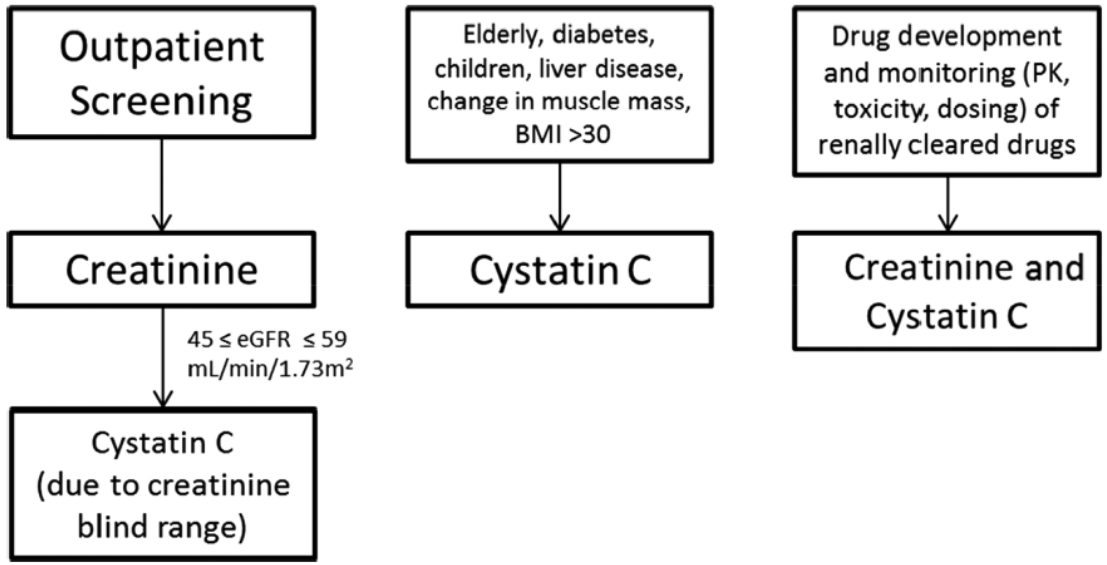
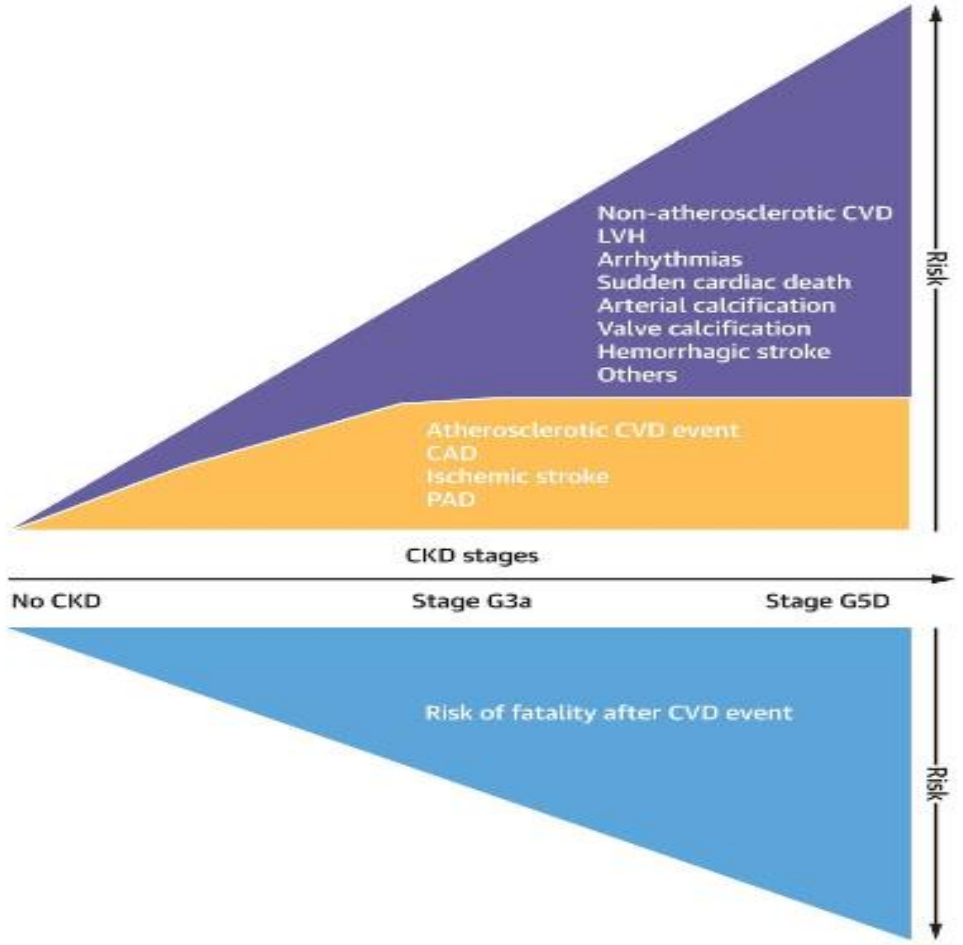


Figure 2. Recommendations for renal biomarker to use in different clinical settings. BMI, body mass index; eGFR, estimated glomerular filtration rate; PK, pharmacokinetics.

Creatinine has been studied much extensively across a much broader group of humans with different pathophysiology. The equation has been very well refined, so not much difference between the two studies, except in very specific patient populations

Changes in Cardiovascular Disease Risk with CKD Progression



Sarnak, M.J. et al. J Am Coll Cardiol. 2019;74(14):1823-38.

Signs of Glomerular Dysfunction

Proteinuria [dipstick, 24hr collection, Prot/Cr]

Summary of relative risks from categorical meta-analysis (dipstick included) (−, ±, +, ⩾++)

All-cause mortality

	ACR <10	ACR 10–29	ACR 30–299	ACR ⩾300
eGFR >105	1.1	1.5	2.2	5.0
eGFR 90–105	Ref	1.4	1.5	3.1
eGFR 75–90	1.0	1.3	1.7	2.3
eGFR 60–75	1.0	1.4	1.8	2.7
eGFR 45–60	1.3	1.7	2.2	3.6
eGFR 30–45	1.9	2.3	3.3	4.9
eGFR 15–30	5.3	3.6	4.7	6.6

Cardiovascular mortality

	ACR <10	ACR 10–29	ACR 30–299	ACR ⩾300
eGFR >105	0.9	1.3	2.3	2.1
eGFR 90–105	Ref	1.5	1.7	3.7
eGFR 75–90	1.0	1.3	1.6	3.7
eGFR 60–75	1.1	1.4	2.0	4.1
eGFR 45–60	1.5	2.2	2.8	4.3
eGFR 30–45	2.2	2.7	3.4	5.2
eGFR 15–30	14	7.9	4.8	8.1

Kidney failure (ESRD)

	ACR <10	ACR 10–29	ACR 30–299	ACR ⩾300
eGFR >105	Ref	Ref	7.8	18
eGFR 90–105	Ref	Ref	11	20
eGFR 75–90	Ref	Ref	3.8	48
eGFR 60–75	Ref	Ref	7.4	67
eGFR 45–60	5.2	22	40	147
eGFR 30–45	56	74	294	763
eGFR 15–30	433	1044	1056	2286

Acute kidney injury (AKI)

	ACR <10	ACR 10–29	ACR 30–299	ACR ⩾300
eGFR >105	Ref	Ref	2.7	8.4
eGFR 90–105	Ref	Ref	2.4	5.8
eGFR 75–90	Ref	Ref	2.5	4.1
eGFR 60–75	Ref	Ref	3.3	6.4
eGFR 45–60	2.2	4.9	6.4	5.9
eGFR 30–45	7.3	10	12	20
eGFR 15–30	17	17	21	29

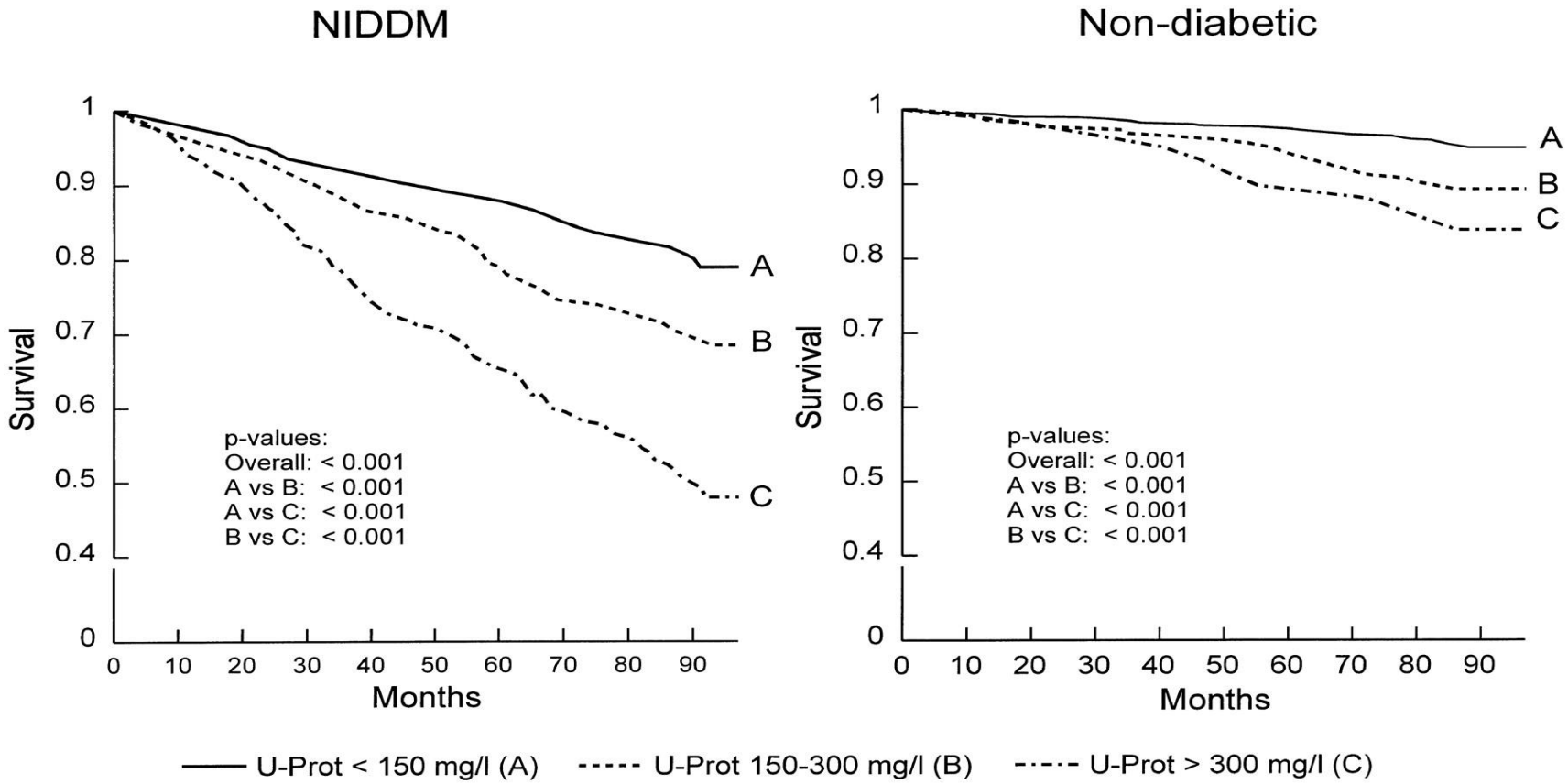
Progressive CKD

	ACR <10	ACR 10–29	ACR 30–299	ACR ⩾300
eGFR >105	Ref	Ref	0.4	3.0
eGFR 90–105	Ref	Ref	0.9	3.3
eGFR 75–90	Ref	Ref	1.9	5.0
eGFR 60–75	Ref	Ref	3.2	8.1
eGFR 45–60	3.1	4.0	9.4	57
eGFR 30–45	3.0	19	15	22
eGFR 15–30	4.0	12	21	7.7

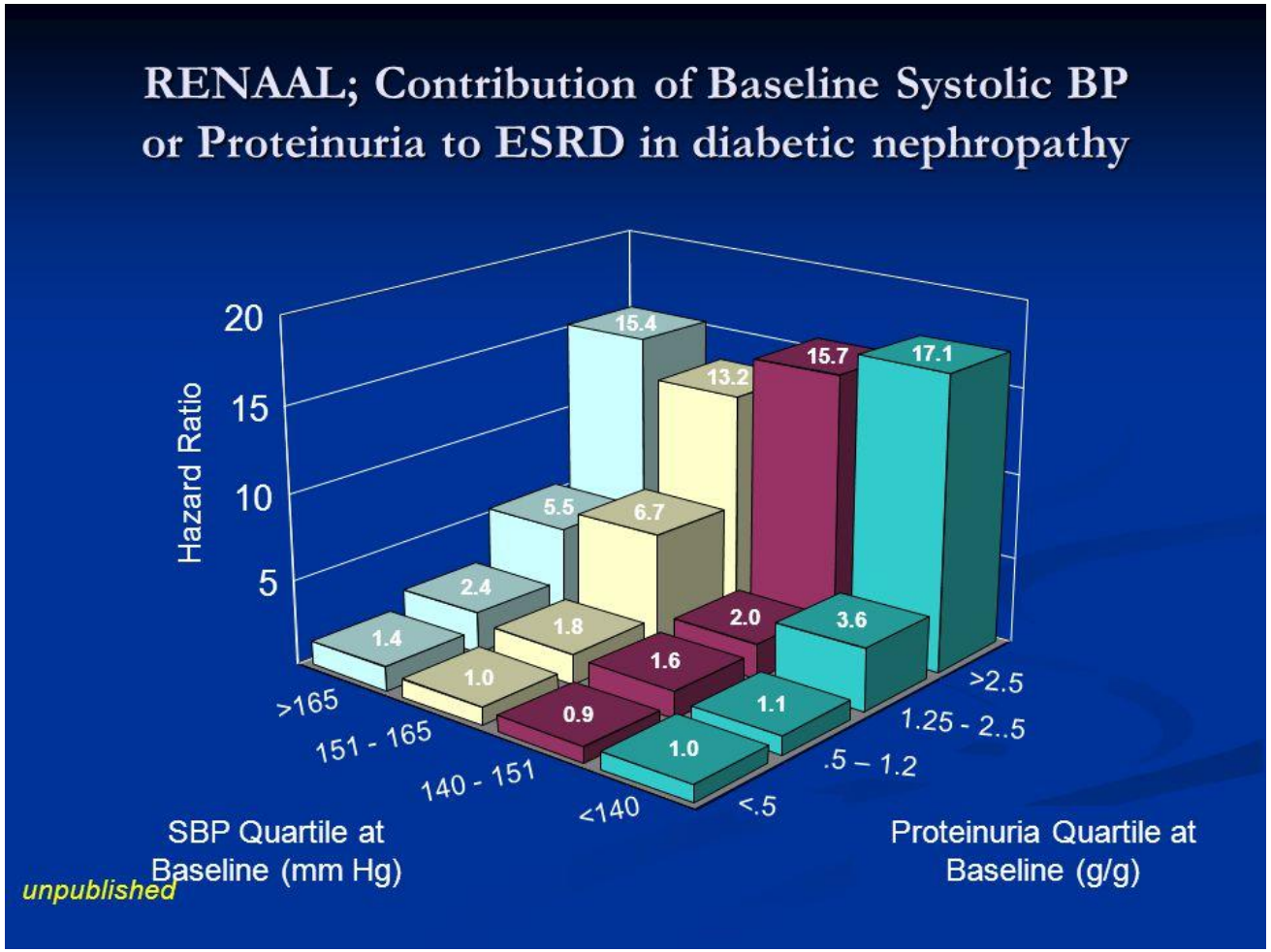
KDIGO Guidelines 2011

				Albuminuria stages, description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<3 mg/mmol	**3-29 mg/mmol**	**≥30 mg/mmol**
GFR stages, descriptions and range (ml/min per 1.73m²)	Stage 1 (G1)	Normal or high	**≥90**			
	Stage 2 (G2)	Mildly decreased	**60-90**			
	Stage 3 (G3a)	Mildly to moderately decreased	**45-59**			
	Stage 3 (G3b)	Moderately to severely decreased	**30-44**			
	Stage 4 (G4)	Severely decreased	**15-29**			
	Stage 5 (G5)	Kidney failure	**<15**			

Why is Proteinuria Important?



Contribution of Proteinuria to ESRD



Proteinuria has a larger contribution to ESRD then even hypertension

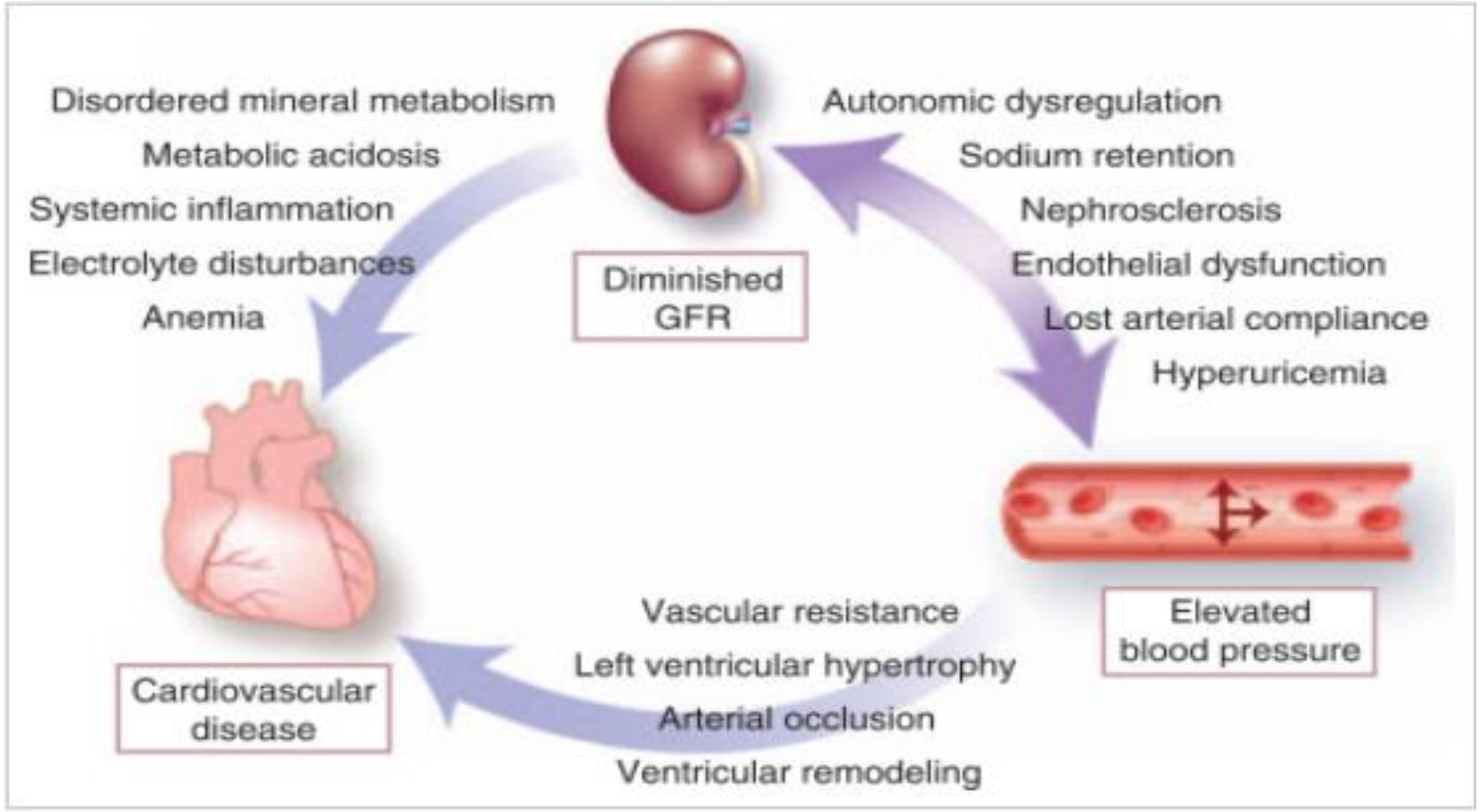
Signs of Glomerular Dysfunction: Hematuria

- Glomerulitis
  - Inflammation from complement activation via classical or lectin pathway by immune complexes in the proximal layer of the capillary wall (C4 and C3 are consumed)
  - Inflammation by activation of complement via the alternative pathway (Only C3 is consumed)
  - Inflammation through antibody-dependent cell cytotoxicity
  - Inflammation through cell-mediated immune mechanisms

- Capillary Fragility
  - Alport's or thin basement membrane

- Other causes
  - Sickle cell disease or trait
  - Stresses such as excessive exercise, fever, etc.

Linkage between Cardiac and Renal Disease



The Clinical Syndromes

1. The Nephrotic Syndrome
2. Acute Nephritic Syndrome
3. Rapidly Progressive GN
4. Asymptomatic Hematuria/Proteinuria
5. The Chronic Nephritic Syndrome (Chronic Renal Failure)

Terminology

Glomerulonephritis = inflammation of the glomeruli
'Glomerulopathy' is a more accurate term

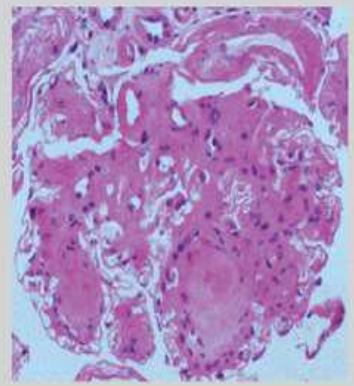
NEPHRITIC SYNDROME
Collection of symptoms and signs associated with inflammatory glomerular disorders

- **Hematuria**
- **Hypertension**
- **Oliguria**
- **Edema**

NEPHROTIC SYNDROME
Collection of symptoms and signs associated with proliferative glomerular disorders

- **Overt proteinuria (> 3.5g/24h)**
- **Hypoalbuminemia (< 3.0 g/dL)**
- **Edema**
- **Ascites**
- **Hypercoaguable state: Renal vein thrombosis**
- **Hyperlipidemia**

Spectrum of glomerular diseases



Nephrotic

Mechanism

- Injury to podocytes
- Changed architecture:
  - Scanning
  - Deposition of matrix or other elements

SLE

IgA nephropathy

Minimal change nephropathy

FSGS

Membranous nephropathy

Diabetic nephropathy

Amyloidosis

MPGN

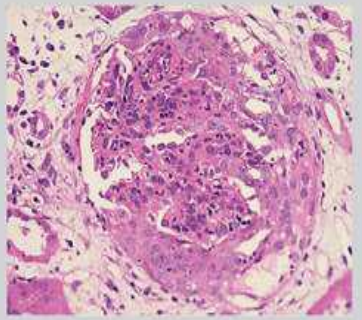
Post-streptococcal glomerulonephritis

Small vessel vasculitis

Anti-GBM disease

Haematuria

Proteinuria



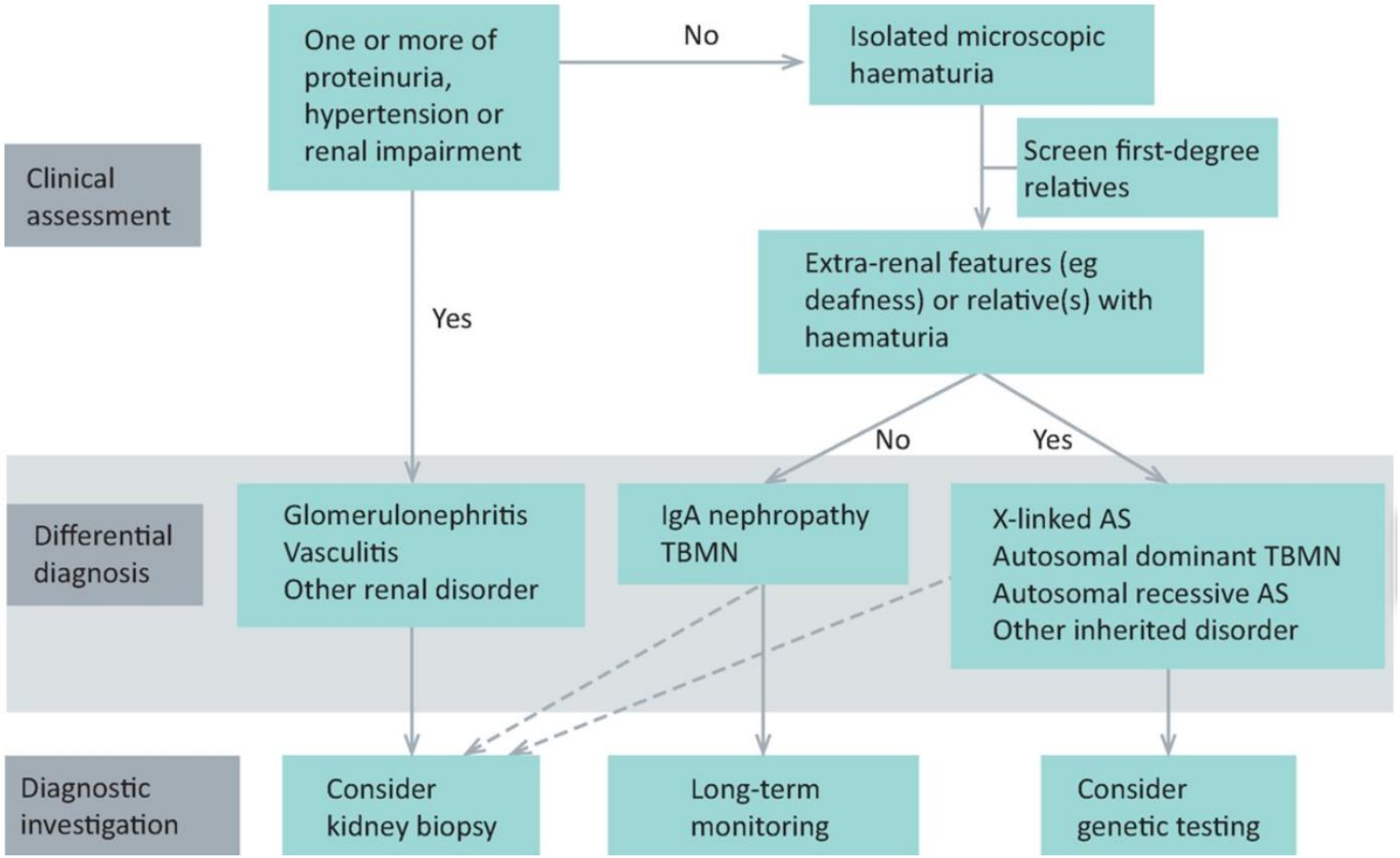
Nephritic

Mechanism

- Inflammation
- Reactive cell proliferation
- Breaks in GBM
- Crescent formation

* Adapted from Davidson's Principles and Practice of Medicine, 20th Edition

Glomerulonephritis Workup



- **Primary Glomerular Diseases**
  - Minimal Change disease
  - Membranous Nephropathy
  - Focal Glomerulosclerosis
  - IgA nephropathy
  - Fibrillary

- **Secondary Glomerular Diseases**
  - Lupus
  - Immune Complex related
    - Post Infectious related GN
      - Shunt nephritis
      - Bacterial endocarditis
    - Drugs
    - Goodpasture's
  - Infections
    - HIV, Hepatitis C, Syphilis
  - Diabetes
  - Amyloidosis
  - Vasculitis
    - Cryoglobulinemic vasculitis
    - Henoch-Schonlein purpura
    - ANCA vasculitis
  - Bee sting allergy
  - Malignancy

Investigations in Glomerular Disease

Bedside tests

Urine dipstick

Laboratory tests

CBC, CMP, HbA1C, complement, ANCA, ANA, anti-dsDNA, anti-GBM, ASO Titer, HIV, Hepatitis B surface Ag, Hepatitis C, anti-PLA-2R

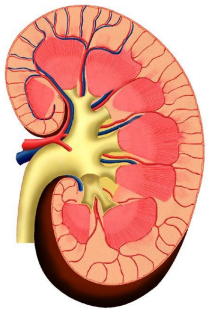
Urine microscopy, urine albumin:creatinine ratio, 24h protein

Imaging

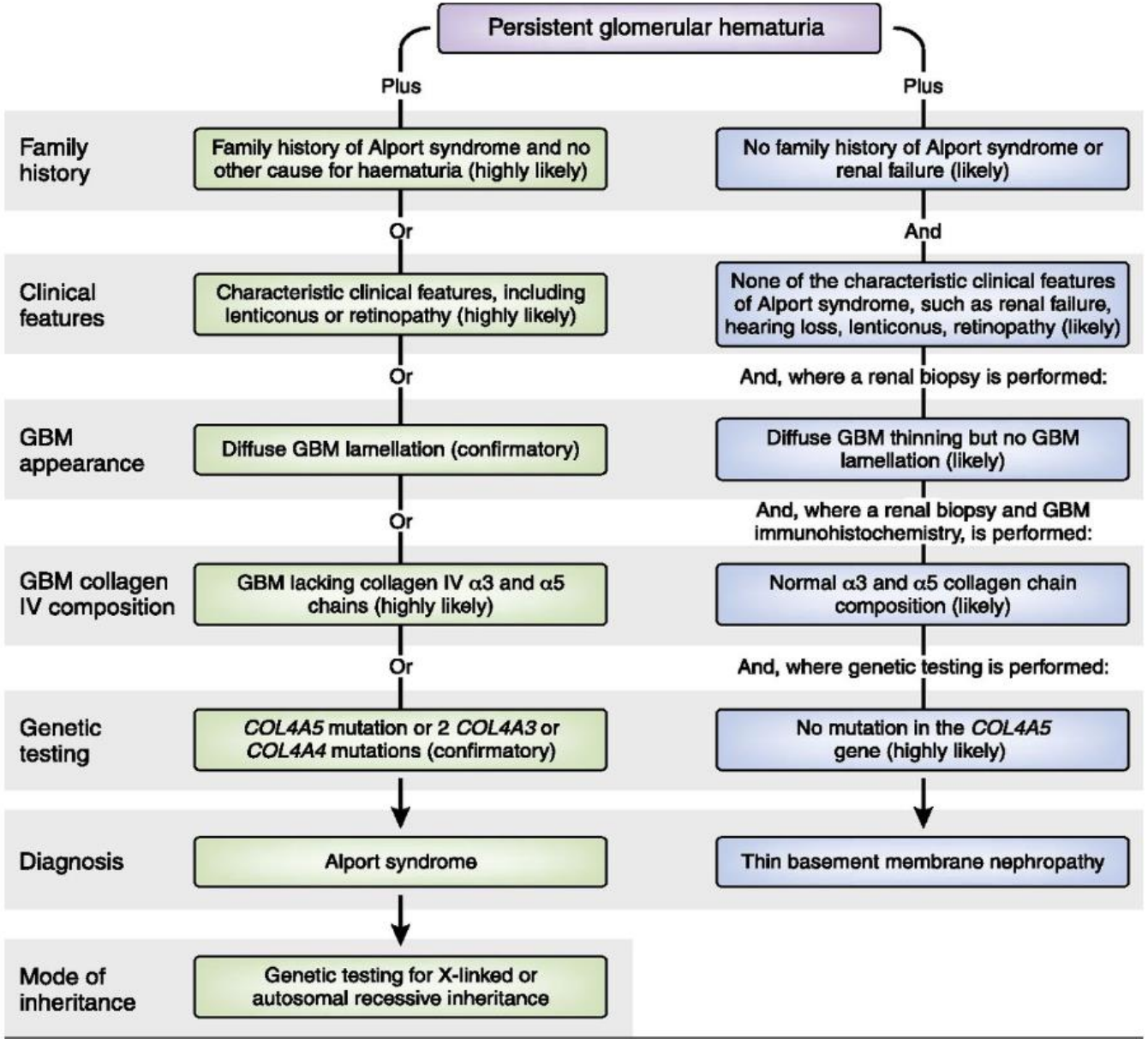
Renal ultrasound

Invasive tests

Renal biopsy



Thin Basement Membrane Disease



- Linkage between thin basement membrane disease and Alport's syndrome
- Both result from mutations in collagen Type 4
- Question if thin basement membrane disease is a heterozygous form Alport's syndrome

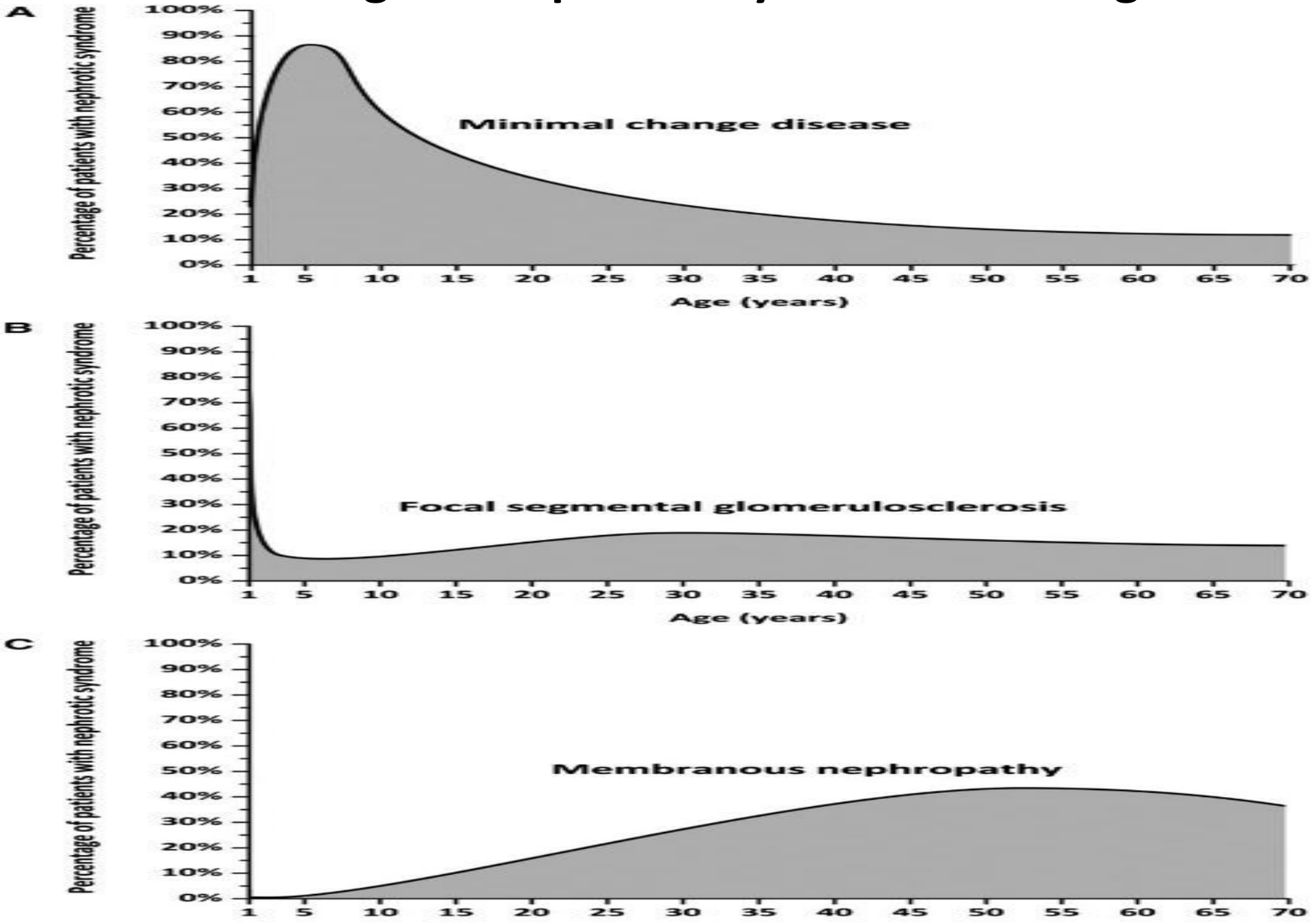
Thin Basement Membrane Disease

- Long term prognosis is good with isolated hematuria and thin GBM
- Presence of heterozygous COL4A3/COL4A4 mutation in patient with hematuria and thin GBM should be considered a risk factor for CKD
- Family history of CKD or proteinuria also portend a poor prognosis

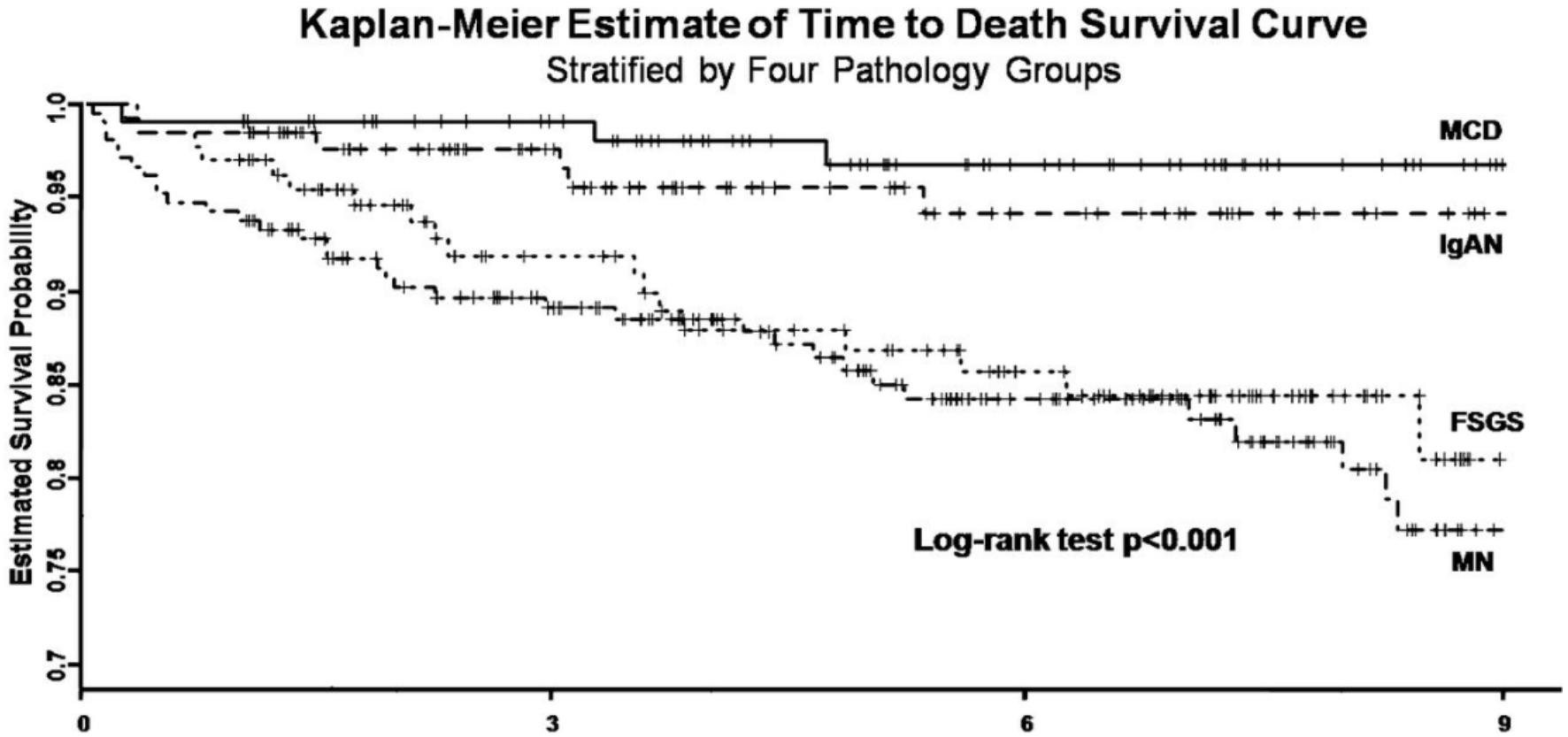
Nephrotic Syndromes

- Membranous
  - Can be associated with lupus
- Minimal change disease
- Diabetic Nephropathy
- Focal Segmental Glomerulonephritis
- Amyloidosis

Percentage of Nephrotic Syndrome with Age



Death Survival Curve in Minimal Change Disease, IgA, FSGS, and Membranous



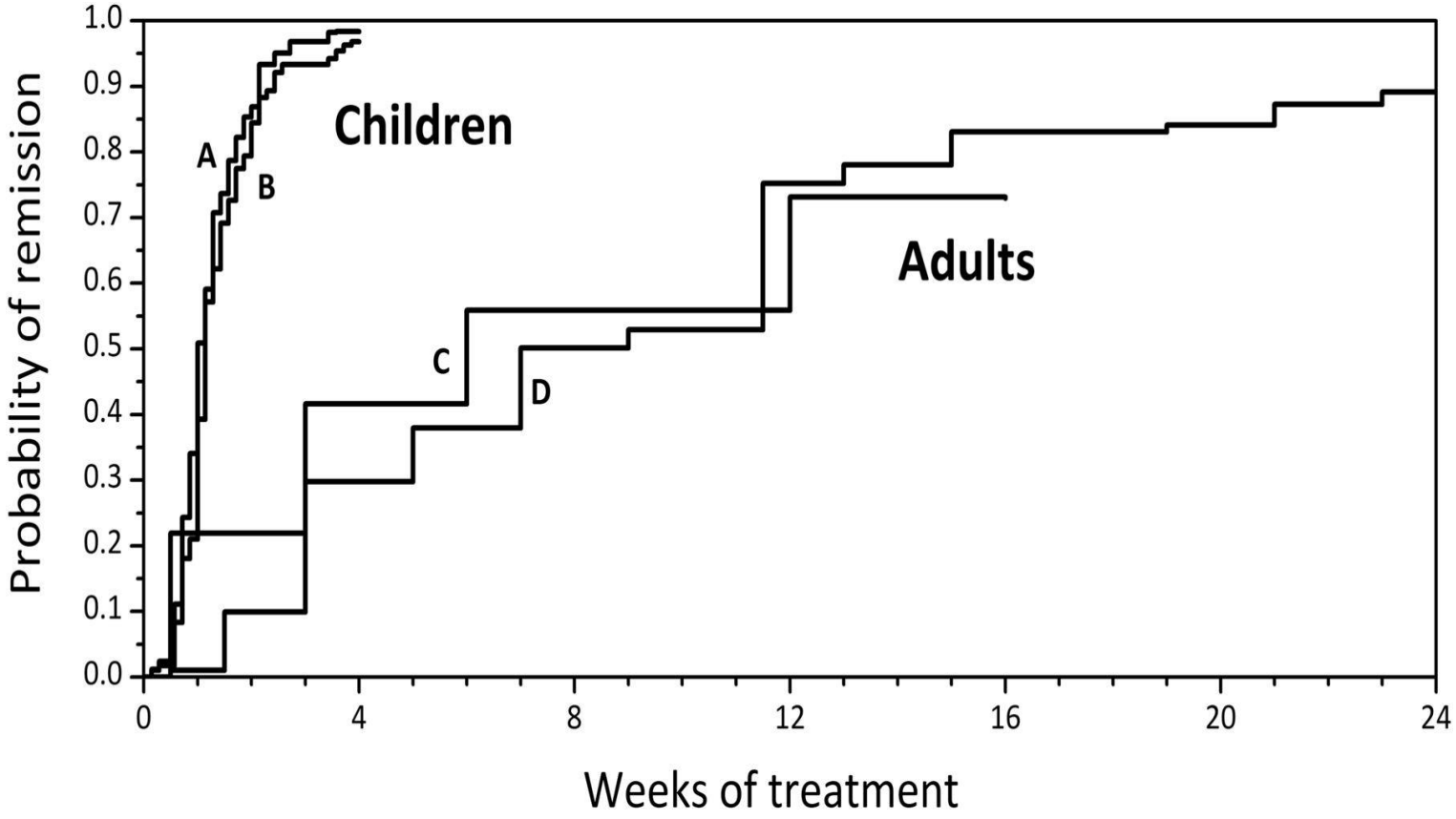
Events in Next Period/Subjects Currently at Risk				
MCD	1/109	2/94	0/62	1/32
IgAN	3/130	3/95	0/64	0/45
FSGS	10/130	6/95	2/68	0/15
MN	22/209	7/156	5/94	1/36

Glomerular Diseases 1

Minimal change nephropathy

- Commonest cause of nephrotic syndrome in children
- Accounts for 25% adult nephrotic syndrome
- Proteinuria usually remits on high dose steroids
- Does not progress to CKD
- Issues: nephrotic syndrome and complications of treatment

Very Responsive to Prednisone



- Very good prognosis
- If patient does not respond to steroid, thought process is that most likely it is FSGS with a sampling error that missed that lesion
- In pediatric population, most nephrologist empirically treat nephrotic syndrome with steroids for presumed minimal change disease, since it is very common and only consider biopsy if they don’t respond to steroids. In adults, majority of patient’s are biopsied

Secondary Causes of Minimal Change Disease

Idiopathic	87%
Secondary	13%
Drugs	• NSAID • Alpha Interferon • Lithium • Gold (Usually Membranous)
Allergy	1. Pollens 2. House dust 3. Immunisations 4. Insect stings
Malignancy	1. Hodgkins 2. Mycosis fungoides 3. CLL (but usually MPGN)

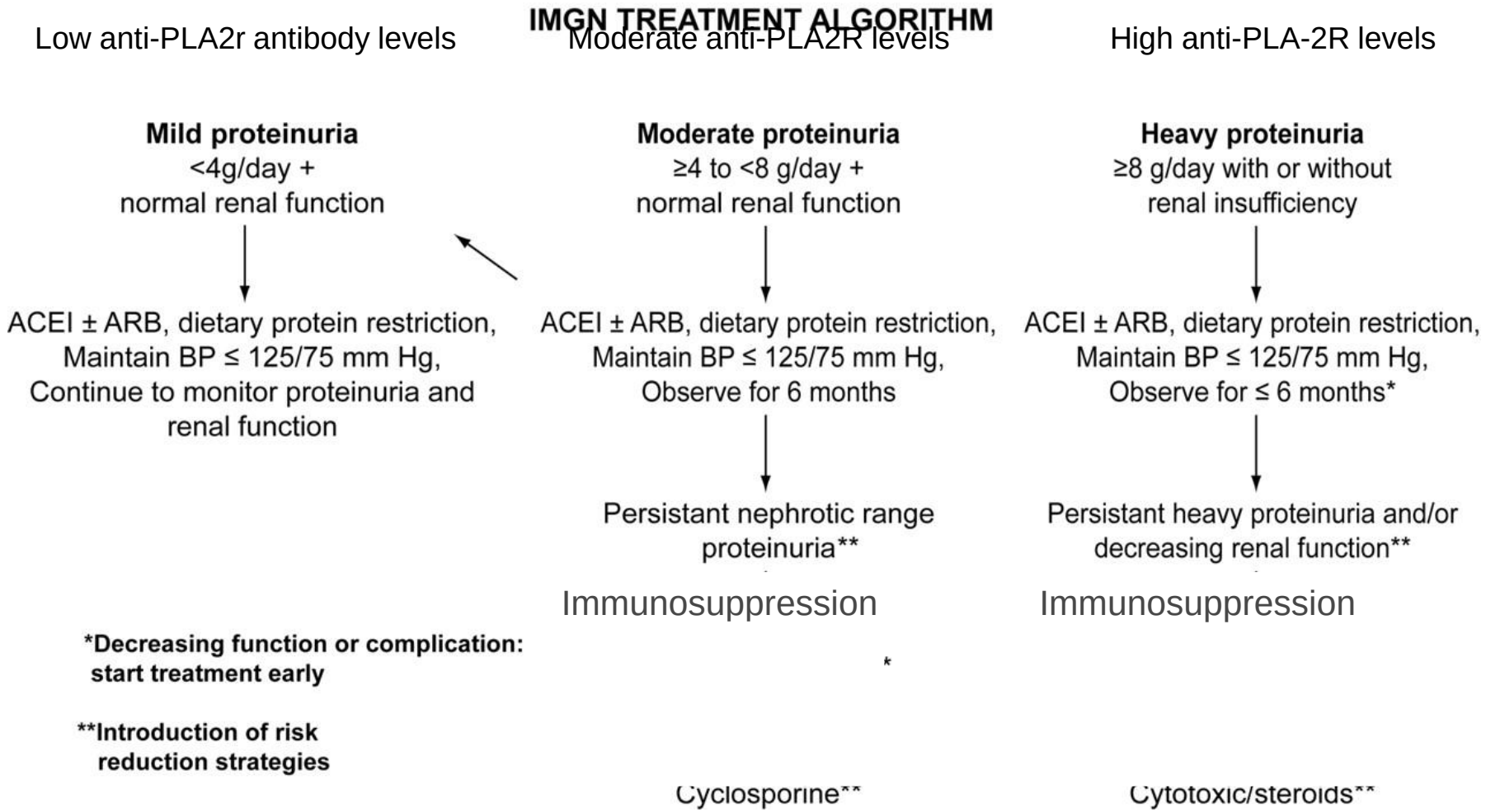
Membranous Nephropathy

- Commonest cause of nephrotic syndrome in adults
- 1/3 spontaneous resolution within 6 months, 1/3 remain in nephrotic state, 1/3 progress to CKD
- Anti-phospholipase A2 receptor antibodies have been implicated in 70-80% of primary membranous nephropathy
- Anti- thrombospondin domain containing 7a is seen in 5-10% of primary membranous

Secondary Causes of Membranous Nephropathy

- **Systemic lupus erythematosus (SLE)**
  Class V Lupus Nephritis (10-20%)
- Drugs: penicillamine, gold, high dose Captopril, and NSAIDs, Anti-TNF
- Infections: Hepatitis B, Hepatitis C, syphilis
- **Malignancy**: **solid tumors** prostate, lung, or GI track

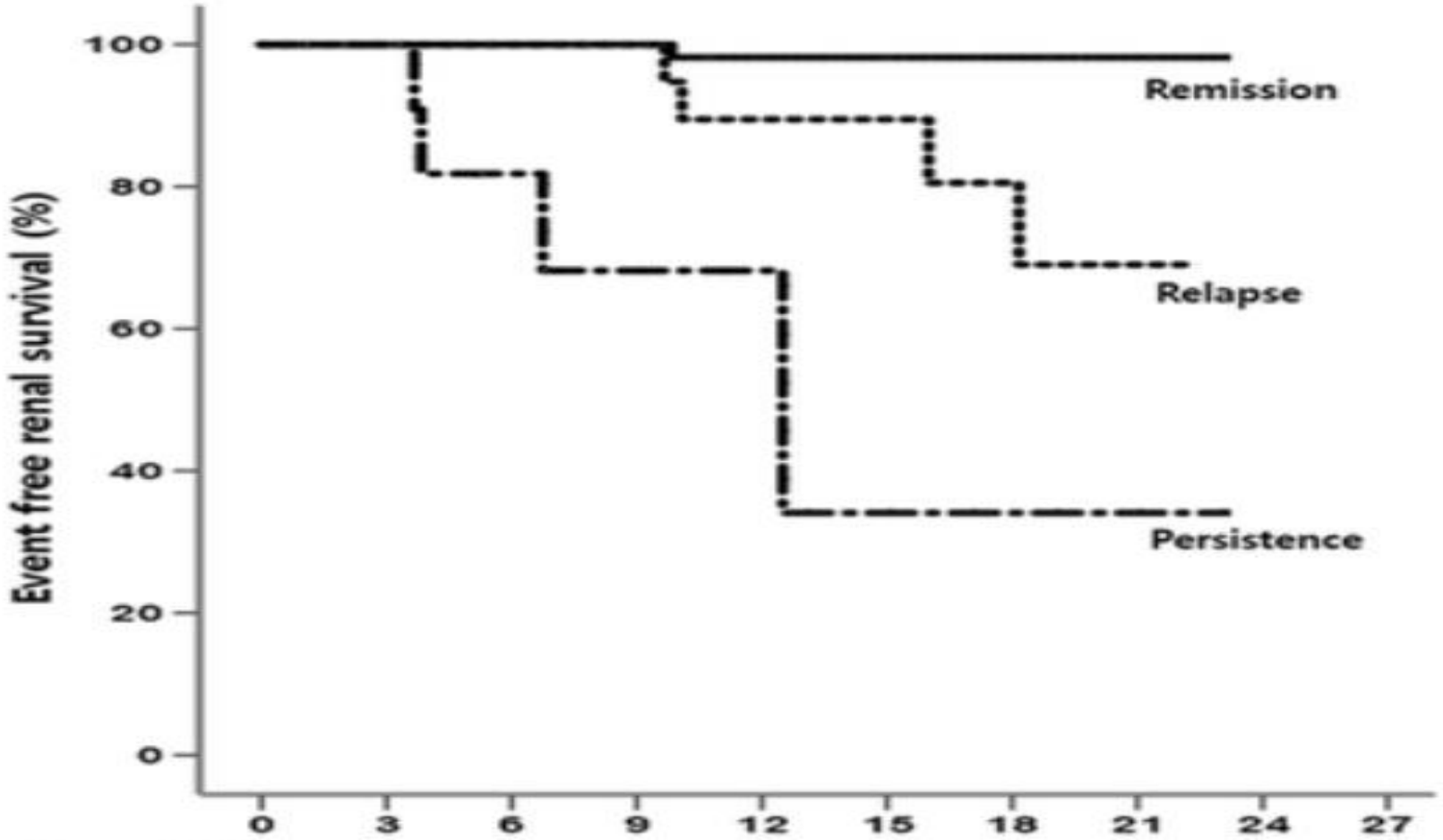
Treatment Algorithm for Membranous Nephropathy



Treatments for Membranous Nephropathy

- Cytoxan
- Rituximab
- Calcineurin Inhibitors
- Corticosteroids
- Cholesterol Medications
- Blood pressure management
- Blood Thinners

Renal Outcomes Data



No. at Risk								
Remission	98	88	75	60	43	35	23	12
Relapse	26	26	25	21	14	13	8	3
Persistence	41	18	12	6	3	2	2	2

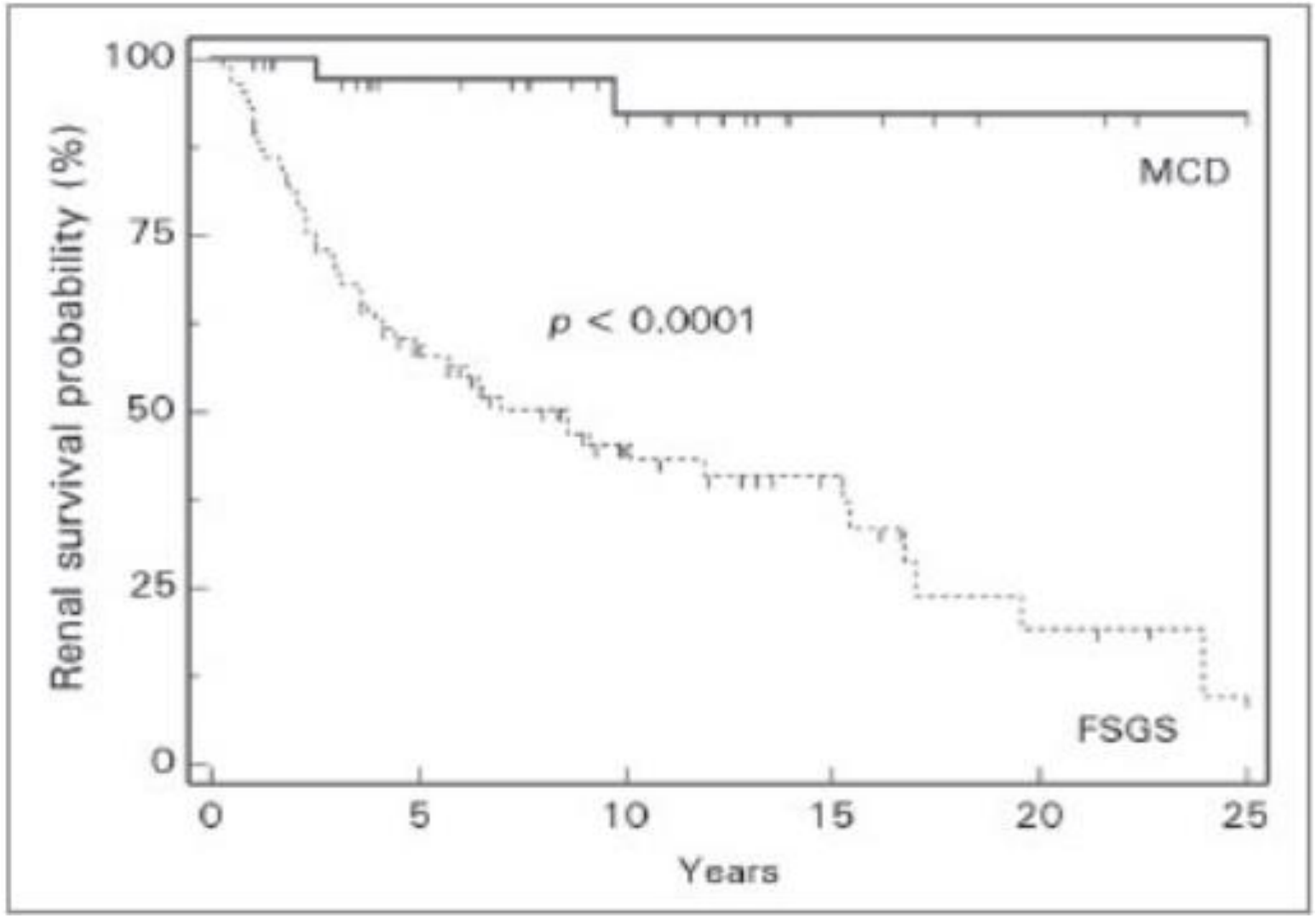
Focal Segmental Glomerulosclerosis

Idiopathic or primary disease

Secondary

1. Hereditary (mutations on genes for podocyte proteins)
2. Virus: HIV, parvovirus
3. Medication: heroin, interferon-alpha, lithium, pamidronate
4. Adaptive changes (hyperfiltration)
   a. Loss of kidney mass: agenesis, vesicoureteral reflux, nephrectomy
   b. Hypertension, diabetes, obesity, cyanotic cardiopathy
5. Tumours: lymphoma
6. Added to glomerular diseases
   a. Focal proliferative glomerulonephritis: IgA, lupus nephritis, extracapillary proliferative GN
   b. Alport's Syndrome
   c. Membranous GN
   d. Thrombotic microangiopathy

Renal Outcomes in Steroid Resistant Nephrotic Syndrome (FSGS)



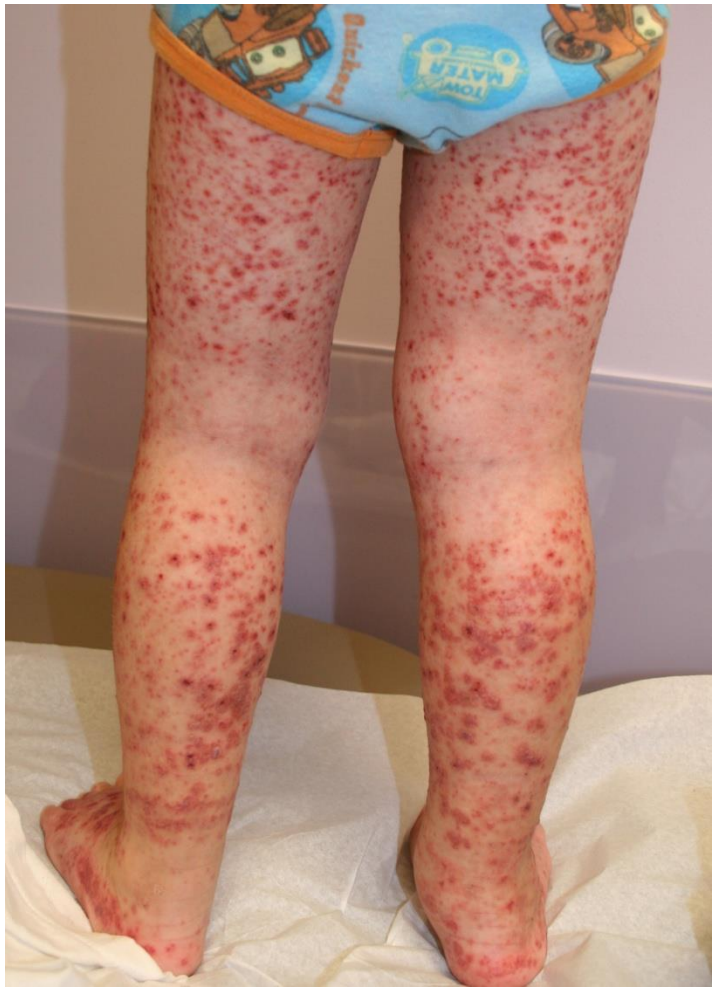
Nephritic Syndromes

- Membranoproliferative Glomerulonephritis
- IgA nephropathy
- Rapidly Progressive Glomerulonephritis (Crescentic GN)

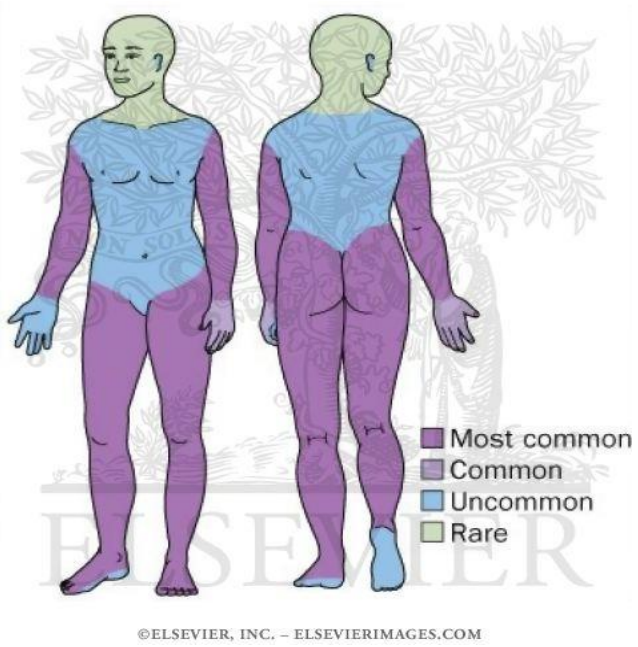
IgA Nephropathy

- 40% glomerulonephritis
- Acute exacerbations can occur, particularly with respiratory infections
- Mild variant associated with HSP in children
- Poor response to immunosuppressive therapy, so steroids are first line after failing conservative therapy with RAAS blockade and blood pressure control

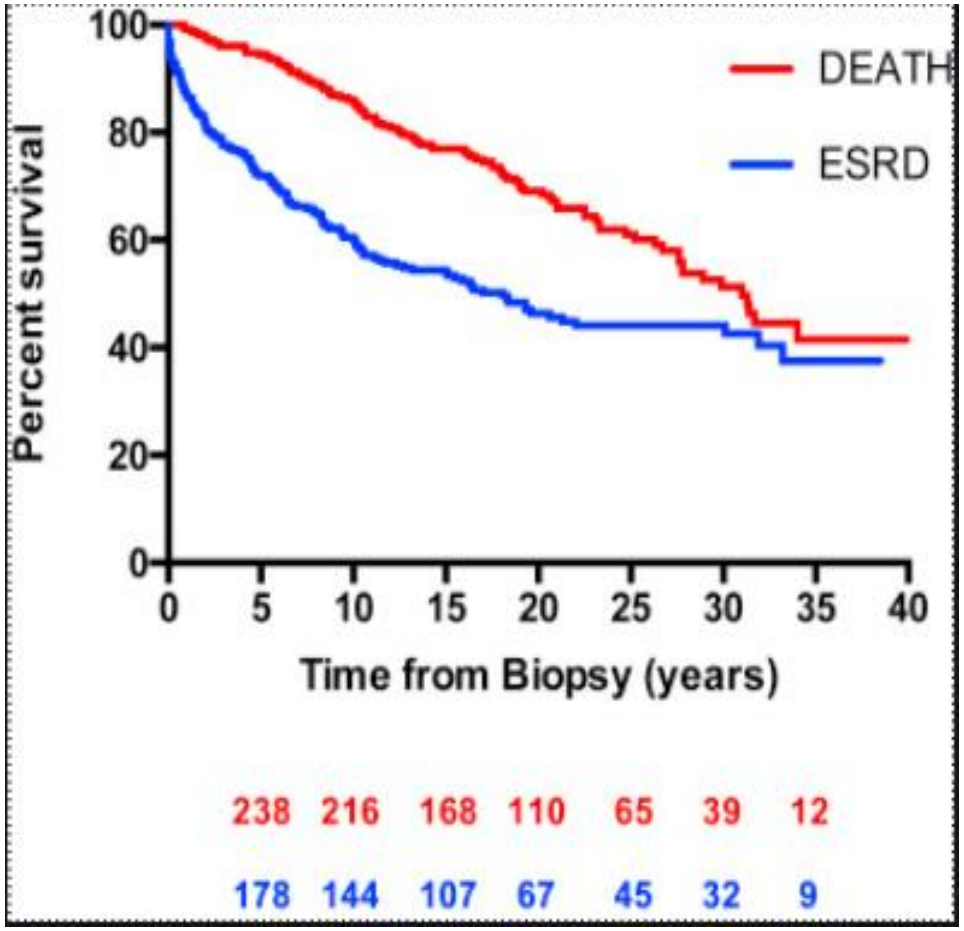
Henoch-Schonlein Purpura

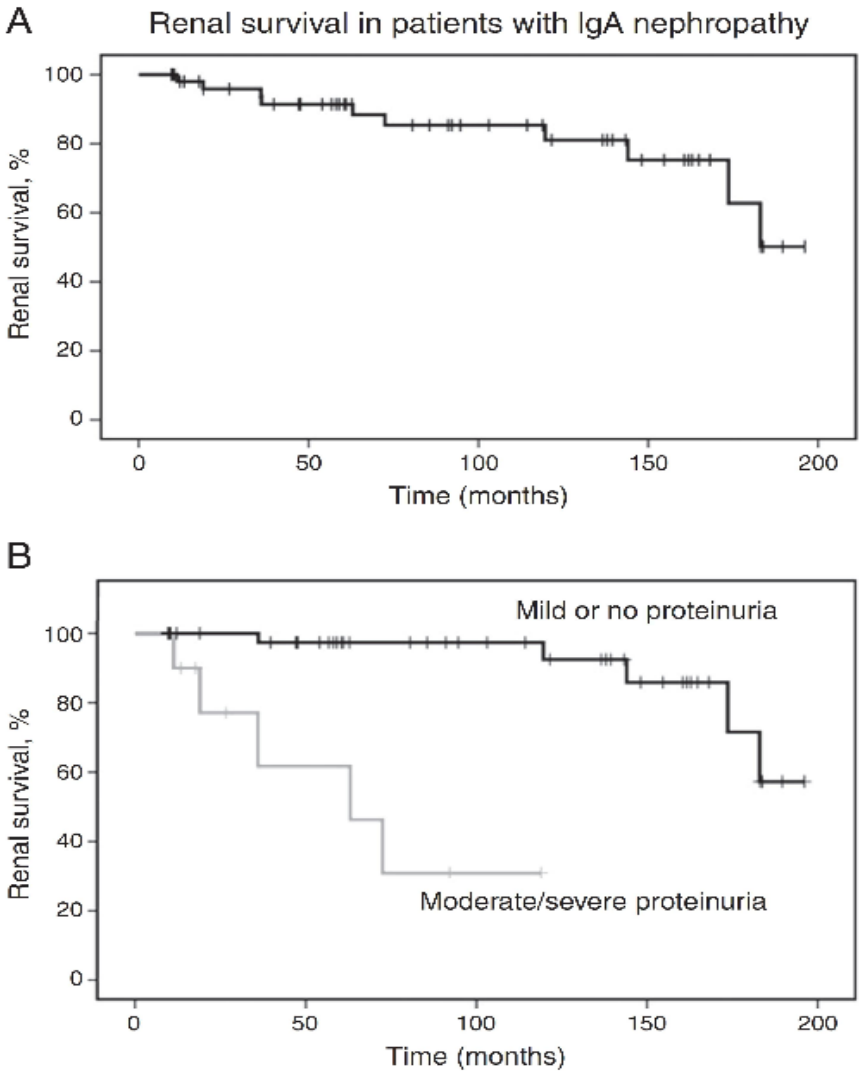


- Systemic vasculitis version of IgA
- 3-10 years M:F 2:1
- Skin rash, arthralgia, abdominal pain



Renal Outcomes for IgA Nephropathy





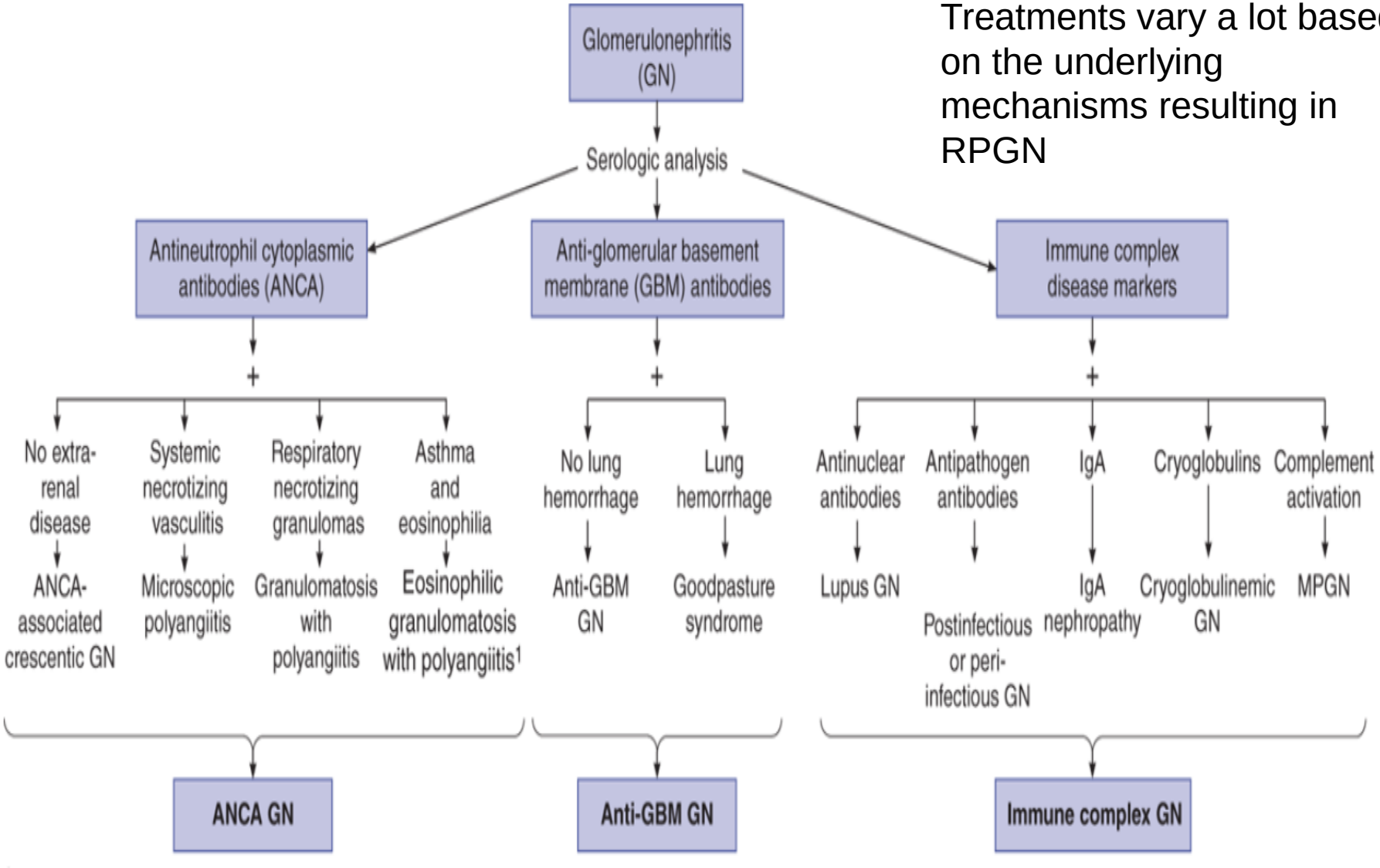
Rapidly Progressive GN (RPGN)

- Us a syndrome associated with severe glomerular injury but does not denote a specific etiology

- Characterized by rapid and progressive loss of renal function associated with severe oliguria and signs of nephritic syndrome

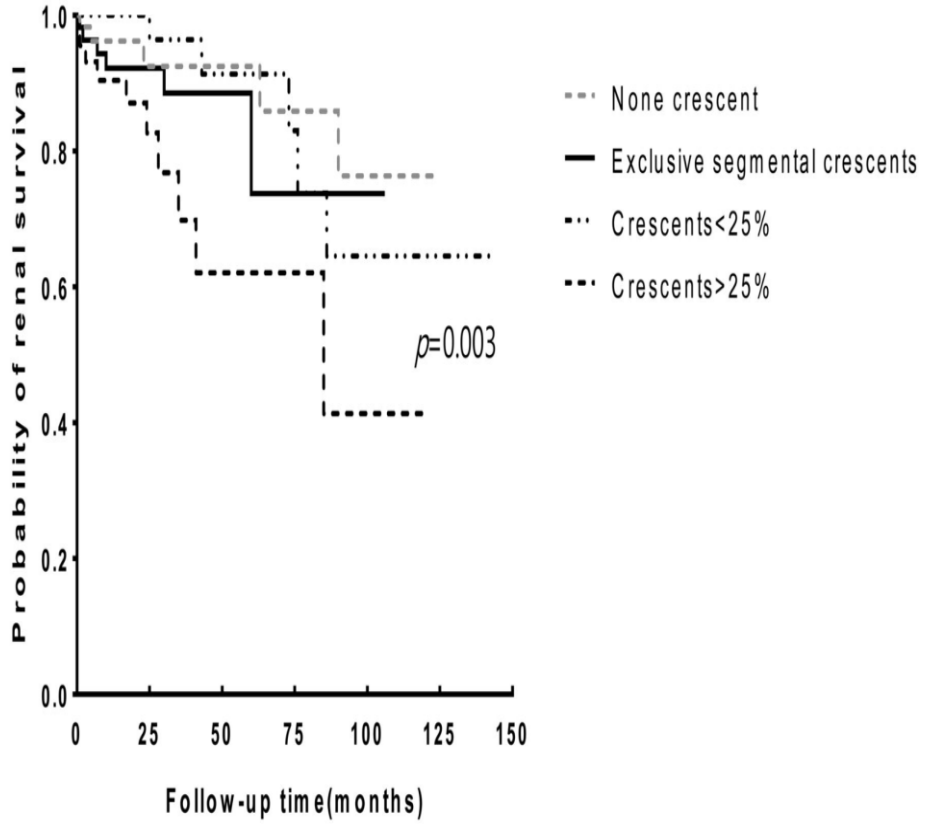
- Tends to have crescents on renal biopsy

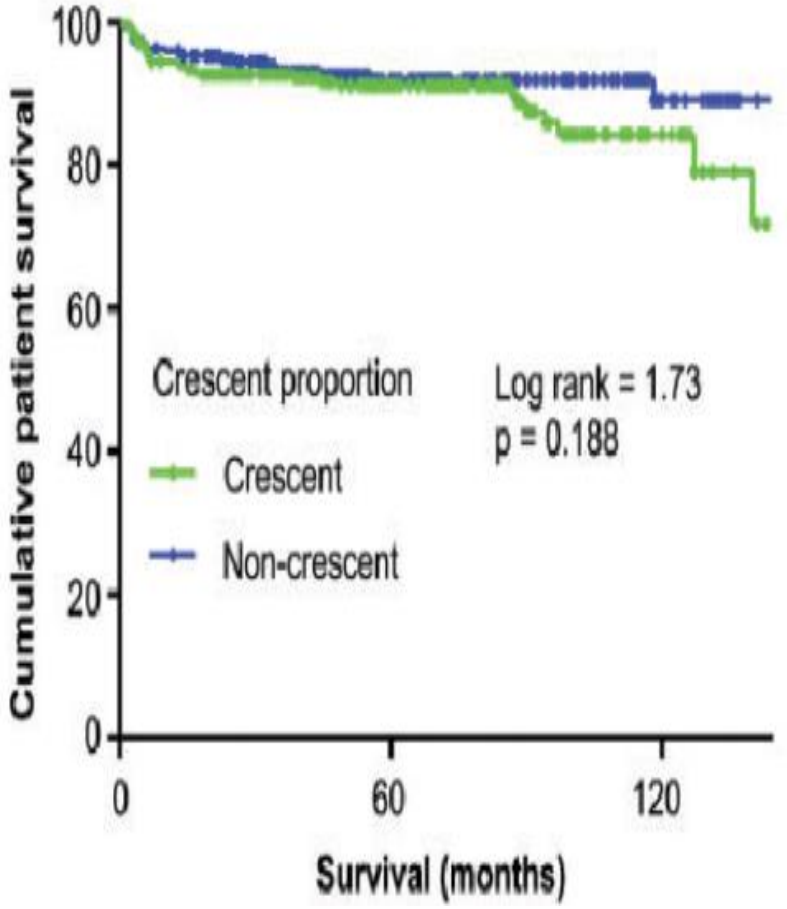
Rapidly Progressive GN (RPGN)



Treatments vary a lot based on the underlying mechanisms resulting in RPGN

Crescents Have a Big Implications when it comes to Renal Outcomes

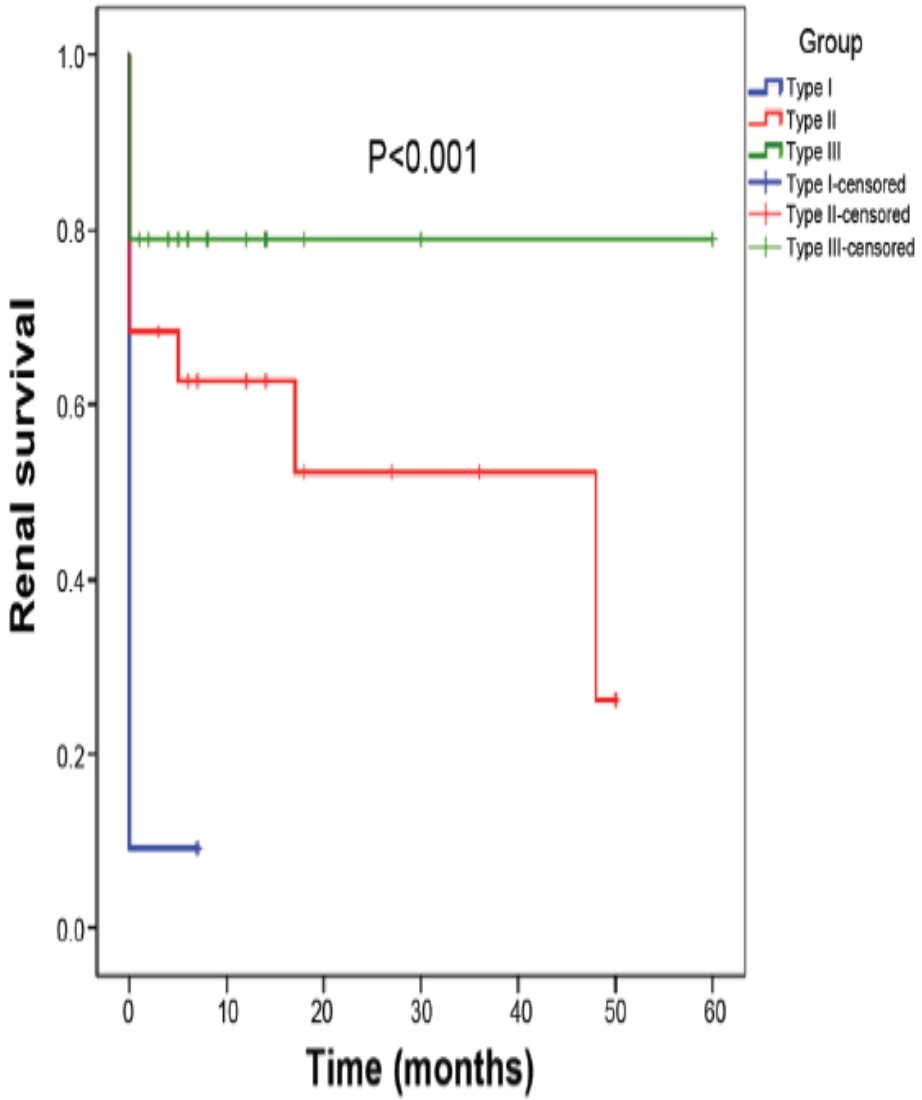


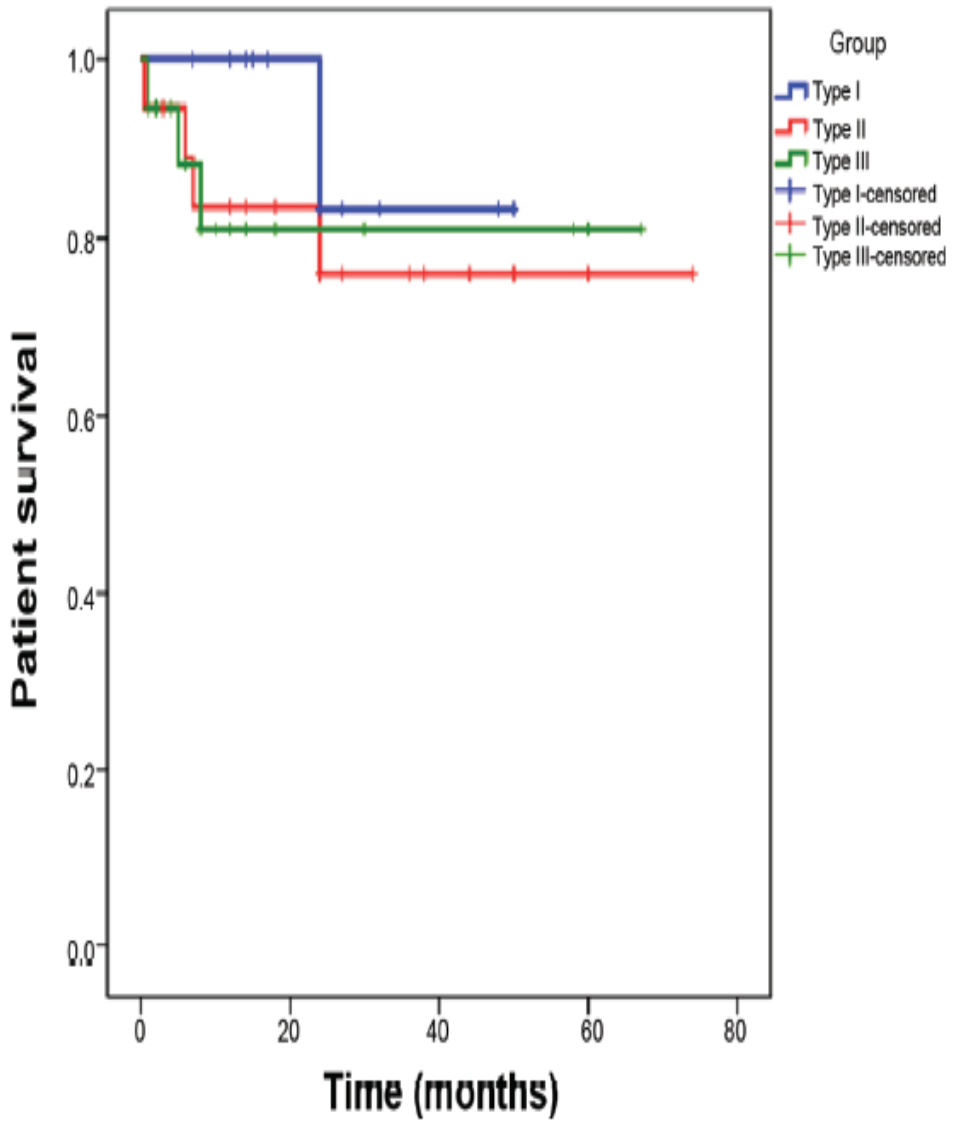


Infection Related Glomerulonephritis

- More common in children, now rare in developed world
- 10 day latency,
- Historically streptococcal throat infection but antibiotics being very common place currently seen with any long term infection and more now associated with staph infections
- Renal function improves spontaneously after 10-14 days
- Management by fluid and sodium restriction and treatment of the infection

- Type 1 = Anti-GBM disease
- Type 2 = Immune Complex Mediated (Lupus/IgA/Infectious Related GN/MPGN)
- Type 3 = ANCA vasculitis





Biggest Predictors for Renal Survival and Mortality

- Degree of proteinuria
- Hypertension control
- Current GFR
- Cause

Thank you

Any questions?