蛋白尿與腎絲球疾病的評估與處置

制定部門：腎臟內科

制訂日期：2016年07月 06日

修訂日期：2018年09月 19日

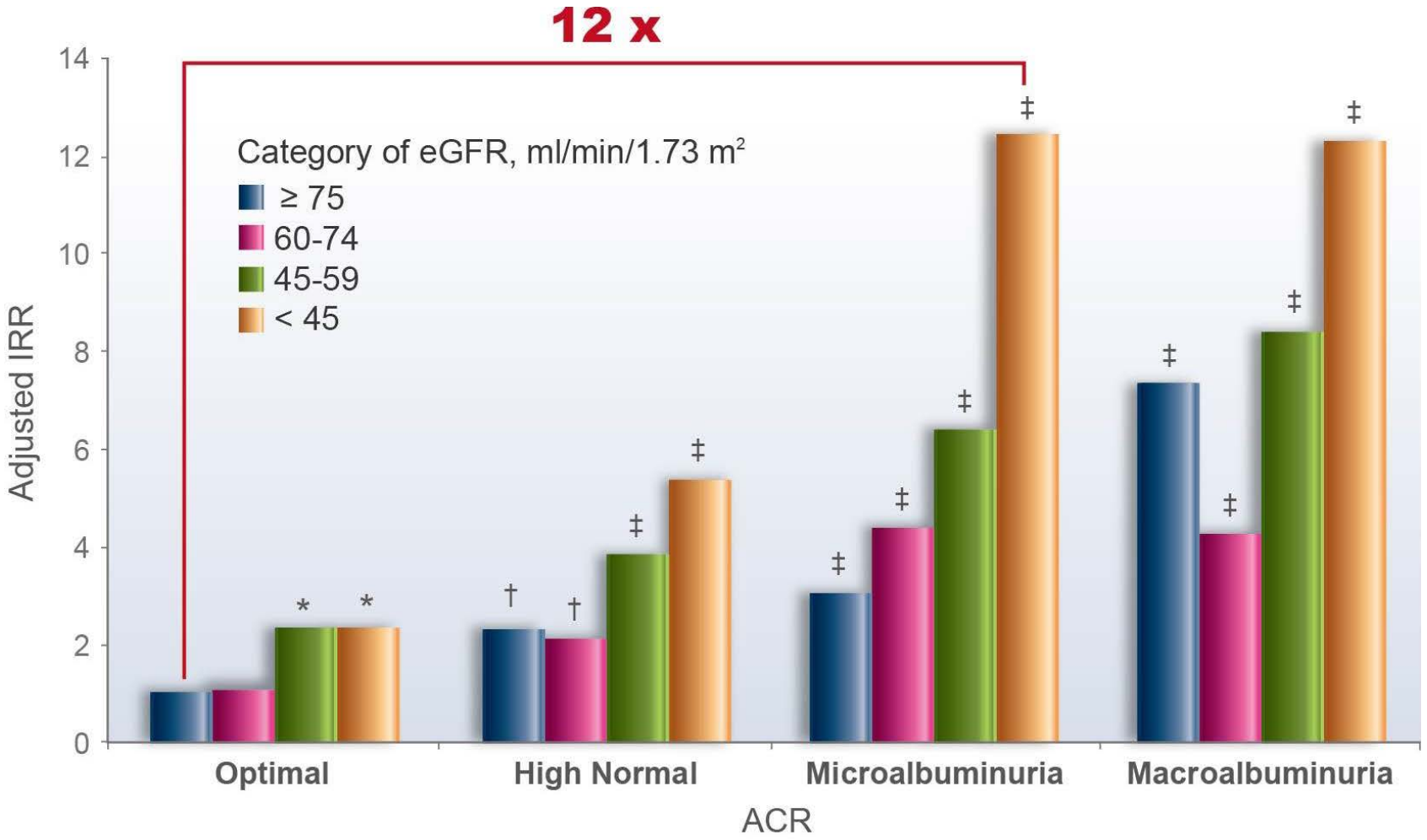
醫生阿 我尿尿有泡泡 怎麼辦 ??

Foamy Urine & Proteinuria

- **小便有無泡沫無法斷定一定有或沒有蛋白尿**
  - 尿中**含氮廢物**和**礦物質**上升時(改變了尿液的表面張力活性)易有泡泡
  - 晨尿 → **整晚尿液濃縮** + **尿液沖激到馬桶**(ex: 男生)易有泡泡
  - 正常生理形成的尿液泡沫一般會在數秒~數分鐘內消失
  - 真正的蛋白尿小便特徵 = **表面漂浮著一層細小的泡沫** + **久久不消失**
  - 真正的蛋白尿需經由客觀的評估 = **尿液分析**
- **正常的尿中有沒有蛋白？多少算正常？**
  - 正常的尿蛋白組成
    - **Tamm-Horsfall protein** (Loop of Henle上皮細胞分泌的Mucoprotein)
    - Albumin (~20%) (65,000 Daltons)
    - 少量Immnuoglobulin light chain & ß2-microglobulin
  - 正常尿蛋白量
    - **Total protein < 150mg/24hr & albumin < 30mg/24hr**

Reference: 基層醫學雜誌 第二十一卷 第六期 蛋白尿與微量白蛋白尿 (2003)

Reduced kidney function and MAU are risk factors for cardiovascular death



Reference: Hallan S, et al. Association of kidney function and albuminuria with cardiovascular mortality in older vs younger individuals: The HUNT II Study. Arch Intern Med 2007;167:2490-6.

ESH/ESC guideline recommendation: tests for MAU are widely available and relatively inexpensive and highly predictive

Availability, prognostic value and cost of some markers of organ damage (scored from 0 to 4 pluses)			
Markers	CV predictive value	Availability	Cost
Electrocardiography	++	++++	+
Echocardiography	+++	+++	++
Carotid intima-media thickness	+++	+++	++
Arterial stiffness (pulse wave velocity)	+++	+	++
Ankle-Brachial index	++	++	+
Coronary calcium content	+	+	++++
Cardiac/vascular tissue composition	?	+	++
Circulatory collagen markers	?	+	++
Endothelial dysfunction	++	+	+++
Cerebral lacunae/white matter lesions	?	++	++++
Est. glomerular filtration rate or creatinine clearance	+++	++++	+
Microalbuminuria	+++	++++	+

Categories of CKD in KDIGO 2012

Prognosis of CKD by GFR and Albuminuria Categories: KDIGO 2012

GFR categories (ml/min/ 1.73 m²) Description and range				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
					Microalbuminuria	Macroalbuminuria
				<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol
	G1	Normal or high	≥90			
	G2	Mildly decreased	60-89			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	<15			

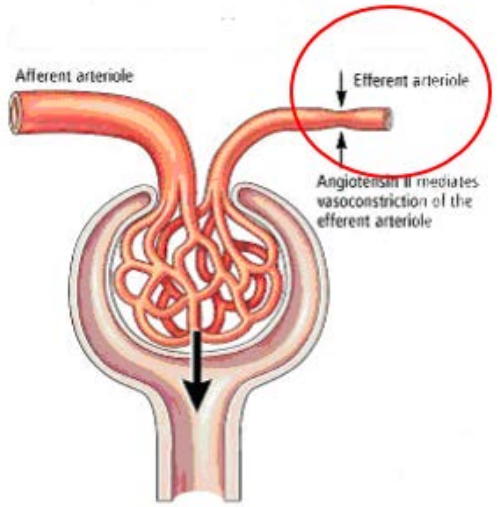
ther markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; F

KDIGO Clinical Practice Guideline for Chronic Kidney disease 2012

有蛋白尿就是腎臟有問題？

- **Transient proteinuria (or physiologic proteinuria)**
  - 因為**暫時性腎小球濾過量或壓力上升等hemodynamic change**造成
  - 見於fever, 運動後, CHF (venous congestion),懷孕,寒冷,情緒壓力 等
  - 解除後自動回復 & Urine daily protein loss 通常**小於 1 g/d**

- **Postural proteinuria**
  - 2%~5%青少年，30歲後多半會消失
  - 直立時發生，又稱orthostatic proteinuria
  - 可能機制：直立時norepinephrine及AT-II 增加
  - 通常<1g/d



Classification of Proteinuria

Measure	Categories		
	Normal to mildly increased	Moderately increased	Severely increased
AER (mg/24 h)	<30	30–300	>300
PER (mg/24 h)	<150	150–500	>500
ACR		**microalbuminuria**	**macroalbuminuria**
(mg/mmol)	<3	3–30	>30
(mg/g)	<30	30–300	>300
PCR			
(mg/mmol)	<15	15–50	>50
(mg/g)	<150	150–500	>500
Protein reagent strip	Negative to trace	Trace to +	+ or greater

Reference: KDIGO Clinical Practice Guideline for the Management of BP in CKD (2012)

尿蛋白的檢驗

- **Urinalysis (dipstick, 半定量法)**
  - **1+ 30mg/dL, 2+ 100mg/dL,3+ 300mg/dL, 4+ 1~2g/dL**
    - Se 32~46%, Sp 97~100%
  - **只能測Albumin; 需一天尿蛋白>300~500mg/d才會(+)**
    - 30mg/dL = 30mg/100ml x 1000~1500 ml(假設一天尿量) = 300~450mg
  - 一旦持續Positive就已經是Macroalbuminuria(>300mg/day)
    - **無法早期偵測Diabetic kidney disease的Microalbuminuria (30~300mg/d)**
      - 在Microalbuminuria時開始用ACEI/ARB有機會改善DKD/延緩腎功能惡化
  - False positive
    - Sp. gravity >1.020 (太濃) or Urine Ph >7 or pyuria/hematuria
    - 24hr內用過含碘顯影劑
  - False negative
    - Sp. gravity <1.005 (太稀) or Urine Ph 太低(ex: <5.0)

Reference: 基層醫學雜誌 第二十一卷 第六期　蛋白尿與微量白蛋白尿 (2003)

尿蛋白的檢驗

- **定量法才能早期發現Microalbuminuria**
- **24 hr urine total protein/albumin & creatinine**
  - Gold standard & avoid circadian variation & 可測各種protein
  - 標準 = **"empty to empty"** (開始留前解尿解乾淨, 結束前解尿解乾淨)
    - 起算時第一泡尿必需要捨棄，因為這是之前時間所製造和累積的尿液。
  - 較不方便/費時 & 收集檢體易出錯
  - **驗証：由total urine Cr，判定檢體收的好不好(Cr產量: <50y/o, 男 20~25mg/kg/d & 女 15~20mg/kg/d; >50y/o 10~20mg/kg/d)**

Reference: DOQI Clinical Practice Guidelines for CKD (2002)

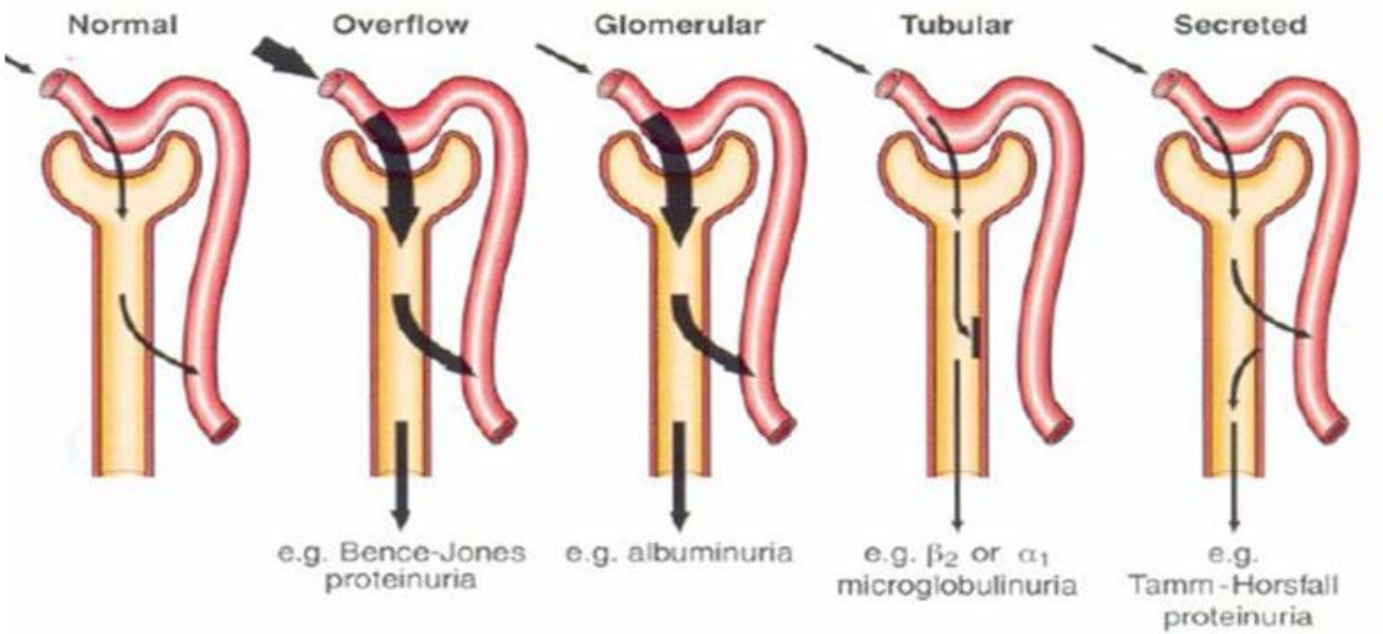
尿蛋白的檢驗

- **Spot urine albumin/creatinine ratio (ACR) or PCR**
  - Spot urine ACR: Urine Albumin/urine Cr
    - ACR≒24hrs urine albumin **成立於24hrs urine cr稍>1g**
      - 單次的尿蛋白/尿肌酸酐比(PCR)僅僅代表了該病人一天排出1000mg 肌酸酐時所同時排出的尿蛋白量
    - 肌肉量很多，一天排出的肌酸酐很可能會遠超過 1000 mg

    ➔ACR(PCR)低估了一天腎臟實際排出的Albumin(protein)
    - 體型瘦小, PCR 則會高估
    - 取清晨第一尿，可得到整晚的平均結果，降低個體生理週期波動的問題

Classification of Persistent proteinuria

- **Secretory(or situational) & Tubular基本 < 2g/d**
- **>2g/d → 考慮glomerular or overflow**



Reference: Brenner & Rector's The Kidney, 10th ed. Ch. 31

Persistent pathological proteinuria

Types	Types of urine proteins
Glomerular proteinuria	Albumin, large molecules (≧ 68 kD) : transferrin, anti-thrombin, immunoglobulin G
Tubular proteinuria	LMW (≦ 25 KD) proteinuria: α_1-microglobulin (A1M) or retinol-binding protein (RBP), ß2-microglobulin (B2M)
Overflow proteinuria	immunoglobulin light chains (Bence-Jones protein) , hemoglobinuria, myoglobiuria, lysozyme

Tubular proteinuria

- Tubularinterstitial disease or tubular injury/dysfunction
  - Acute hypersensitivity interstitial nephritis(ATIN)
  - NSAID, antibiotics
  - Gouty nephropathy
  - Heavy metals
  - Sick cell disease
  - Fanconi syndrome(proximal tubule injury; congenital, drug toxicity, heavy metals)

Overflow proteinuria

- Overproduction of immunoglobulin light chains, myoglobin, hemoglobulin
  - Multiple myeloma
  - Amyloidosis
  - Hemoglobinuria
  - Myoglobinuria

Glomerular Disease

- **ESRD in Taiwan (2011)**
  - Causes: **1st DKD**, 2nd GN, 3rd Hypertensive nephropathy
- **Glomerular disease**: **a spectrum of disease groups**
- **Nephrotic syndrome vs Nephritic syndrome**
  - 是依據**表現型態**上的區分(proteinura/hematuria/HTN/GFR decreasing)
  - 某些腎絲球疾病則可能具有跨越兩種Syndrome的表現

Glomerular Disease Classifcation

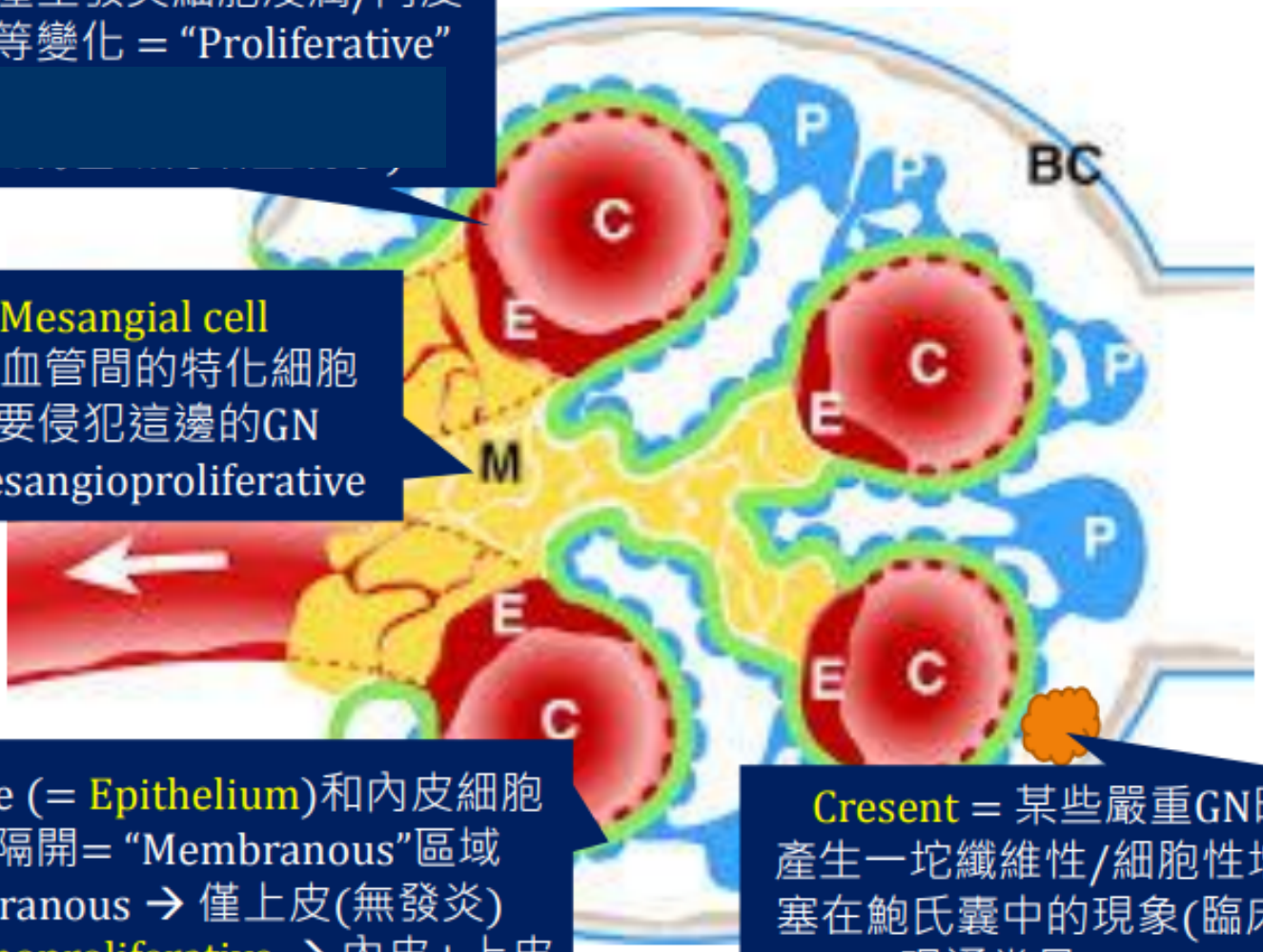
- **Nephrotic syndrome (小球阻擋蛋白流失能力↓↓為主)**
  - **定義: Proteinuria>3.5g/d & Alb<3.5mg/dL & edema/dyslipidemia**
  - **較少高血壓** & **U/A僅蛋白尿而無大量RBC** & **較少一開始就有AKI**
  - 蛋白流失太多 → malnutrition & immune compromised (Ig loss)
  - 流失AT-III及其他抗凝血因子 → thrombosis risk (~25%)
- **Nephritic syndrome (小球發炎 + 合併阻擋蛋白流失能力↓)**
  - Proteinuria未達Nephrotic level → **Subnephrotic proteinuria <3.5g/d**
  - **常表現高血壓** & **U/A gross/microscopic hematuria (+/- RBC cast)**
  - **常一開始有dysmorphic RBC** & **AKI(也可水腫)** & 可能有WBC cast

Reference: Brenner & Rector's The Kidney, 10th ed. Ch. 32

- 依病理:IgA nephropathy, MCD, membranous GN, FSGS, MPGN
- 依臨床進展：RPGN, CGN
- 相同病因可造成不同病理：
  - NSAID: MCD, membranous GN
- 相同病理可由不同病因造成：
  - membranous GN:NSAID,HBV, SLE, malignancy

Endothelium 內皮細胞
大多數GN侵犯的部分
GN時產生發炎細胞浸潤/內皮增生等變化 = “Proliferative”

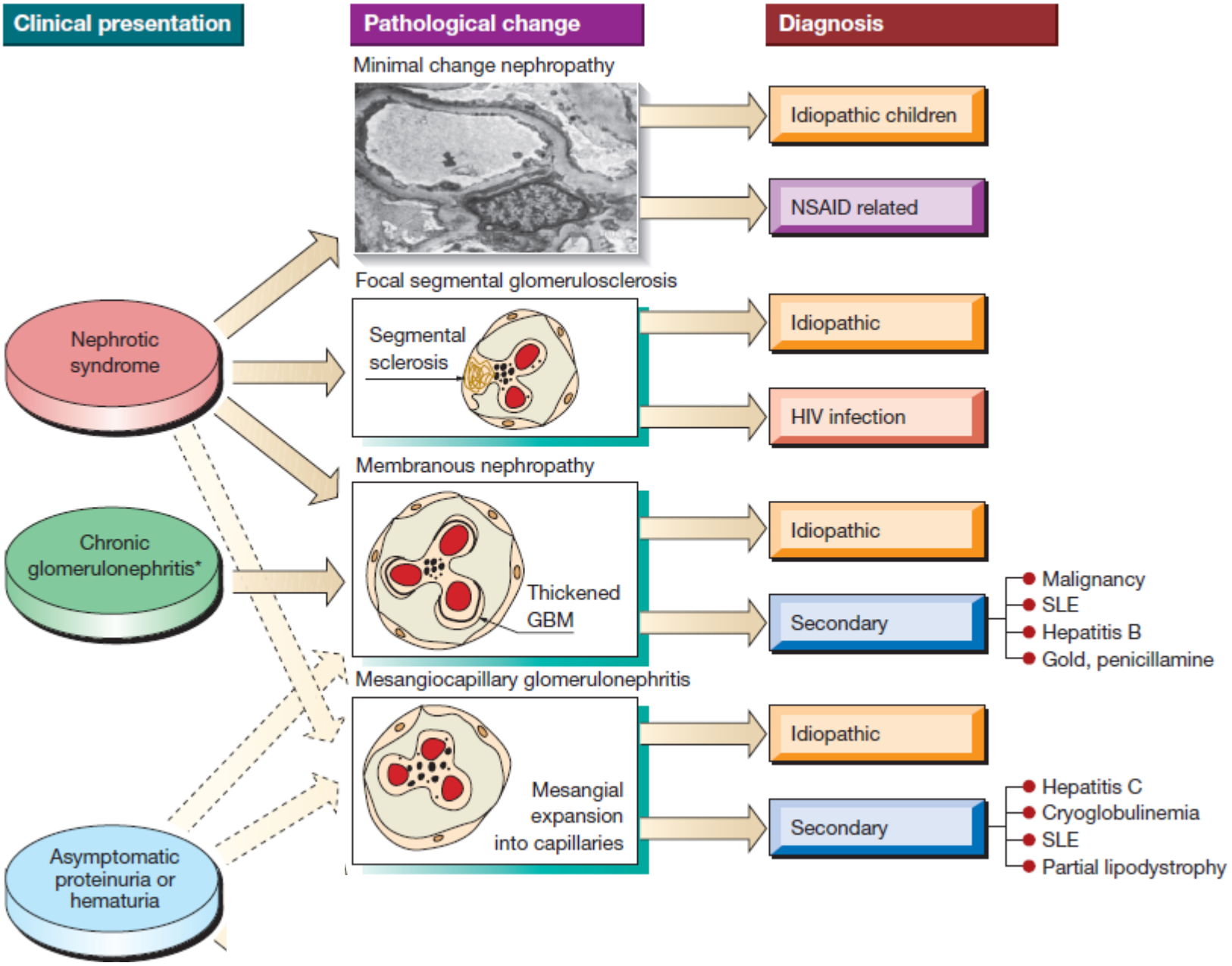
Mesangial cell
在微血管間的特化細胞
主要侵犯這邊的GN
= Mesangioproliferative

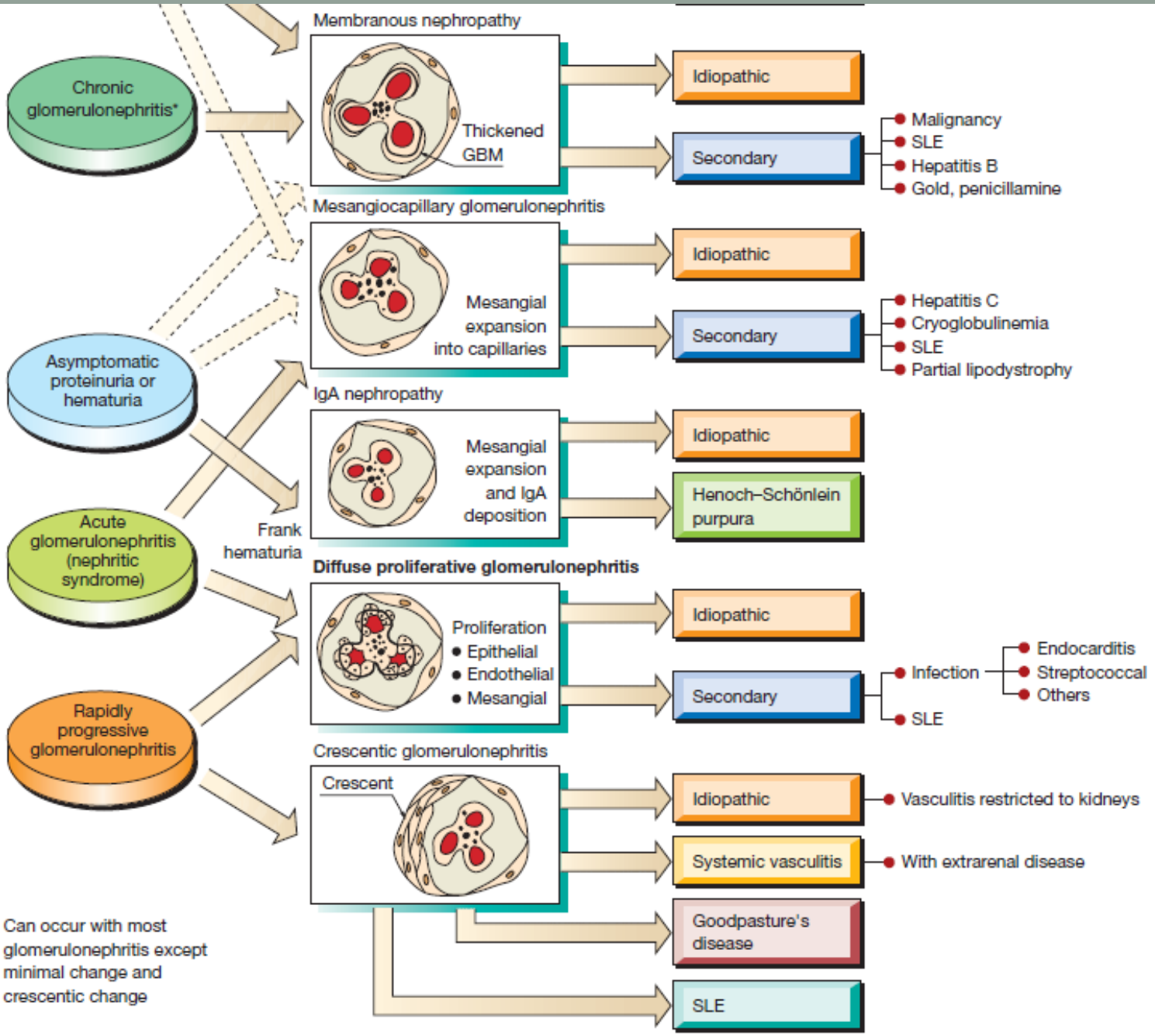


Podocyte (= Epithelium)和內皮細胞以BM隔開= “Membranous”區域
Membranous → 僅上皮(無發炎)
Membranoproliferative → 內皮+上皮

Cresent = 某些嚴重GN時產生一坨纖維性/細胞性增生塞在鮑氏囊中的現象(臨床表現通常是RPGN)

Reference: Brenner & Rector’s The Kidney, 10th ed. Ch. 32


Clinical presentation
Pathological change
Diagnosis
Minimal change nephropathy
Idiopathic children
NSAID related
Focal segmental glomerulosclerosis
Segmental sclerosis
Idiopathic
HIV infection
Membranous nephropathy
Thickened GBM
Idiopathic
Secondary
Malignancy
SLE
Hepatitis B
Gold, penicillamine
Mesangiocapillary glomerulonephritis
Mesangial expansion into capillaries
Idiopathic
Secondary
Hepatitis C
Cryoglobulinemia
SLE
Partial lipodystrophy
Nephrotic syndrome
Chronic glomerulonephritis*
Asymptomatic proteinuria or hematuria


Chronic glomerulonephritis*
Asymptomatic proteinuria or hematuria
Acute glomerulonephritis (nephritic syndrome)
Rapidly progressive glomerulonephritis
Frank hematuria
Membranous nephropathy
Thickened GBM
Idiopathic
Secondary
Malignancy
SLE
Hepatitis B
Gold, penicillamine
Mesangiocapillary glomerulonephritis
Mesangial expansion into capillaries
Idiopathic
Secondary
Hepatitis C
Cryoglobulinemia
SLE
Partial lipodystrophy
IgA nephropathy
Mesangial expansion and IgA deposition
Idiopathic
Henoch–Schönlein purpura
Diffuse proliferative glomerulonephritis
Proliferation
• Epithelial
• Endothelial
• Mesangial
Idiopathic
Secondary
Infection
Endocarditis
Streptococcal
Others
SLE
Crescentic glomerulonephritis
Crescent
Idiopathic
Vasculitis restricted to kidneys
Systemic vasculitis
With extrarenal disease
Goodpasture's disease
SLE
* Can occur with most glomerulonephritis except minimal change and crescentic change

Nephritic Syndrome

- 依照**病因分類及螢光染色/抗體**區分
- **Pauci-immune, minimal staining** (沒有明顯螢光染色)
  - **ANCA (Anti-Neutrophil Cytoplasmic Antibody) (+)**
    - **GPA = Wegener's, EGPA = Churg-Strauss, Microscopic polyangiitis**
- **Linear staining** (線狀螢光染色)
  - Anti-GBM disease, Goodpasture syndrome
- **Granular staining** (顆粒狀螢光染色)
  - 可以依據**C3 level**分成兩群 → 再各自分成**systemic vs renal-limited**

Reference: Brenner & Rector's The Kidney, 10th ed. Ch. 32

Nephritic Syndrome

- 依照**病因分類及螢光染色/抗體**區分
- **Pauci-immune, minimal staining** (沒有明顯螢光染色)
  - 佔全部GN的40~45% (西方人) & 腎臟多以**RPGN**表現 & **可能肺出血**
  - **ANCA (Anti-Neutrophil Cytoplasmic Antibody) (+)**
    - 這群疾病會有ANCA (+), 但生理意義仍未明; C3/C4正常
  - Trigger factors: bacterial infection, drug
    - 常見藥物包含hydralazine, allopurinol, contaminated cocaine

口訣:
WC洗屁屁
(W/C-C/P/P)

ANCA-associated Vasculitis (GPA = Wegener's, EGPA = Churg-Strauss)

Disease	Granuloma	Renal	Pulmonary	Asthma	Ab type	ANCA(+)
Granulomatosis with polyangiitis (GPA)	(+)	80%	90%(+ENT)	(-)	**c-ANCA** (anti-PR3)	90%
Eosinophilic GPA	(+)	45%	70%	(+)	**p-ANCA** (anti-MPO)	50%
Microscopic polyangiitis	(-)	90%	50%	(-)		70%

Reference: Brenner & Rector's The Kidney, 10th ed. Ch. 32

Nephritic Syndrome

- 佔全部GN的~15% (西方人) & 腎臟多以**RPGN**表現 & **可能肺出血**
- **Anti-GBM (Anti-Glomerular Basement membrane Antibody) (+)**
  - 此類抗體的病生理意義仍未明; **本院無法驗**; C3/C4正常
- RPGN/Acute GN +/- Lung hemorrhage
  - Medical emergency (RPGN + 咳血者要想到肺出血 & 可能須插管)
  - Need early diagnosis (ex: biopsy) & treatment (ex: plasmaphresis)
  - **首先排除ANCA-associated vasculitis & Anti-GBM disease**
  - 其他: systemic vasculitis in SLE, uremic bleeding with pulm. edema

Anti-GBM Disease (young male, 5~40 y/o, M:F 6:1)			
Disease	**GN**	**Lung hemorrhage**	**Anti-GBM Ab**
Goodpasture's	(+)	(+)	(+)
Anti-GBM disease	(+)	(-)	(+)

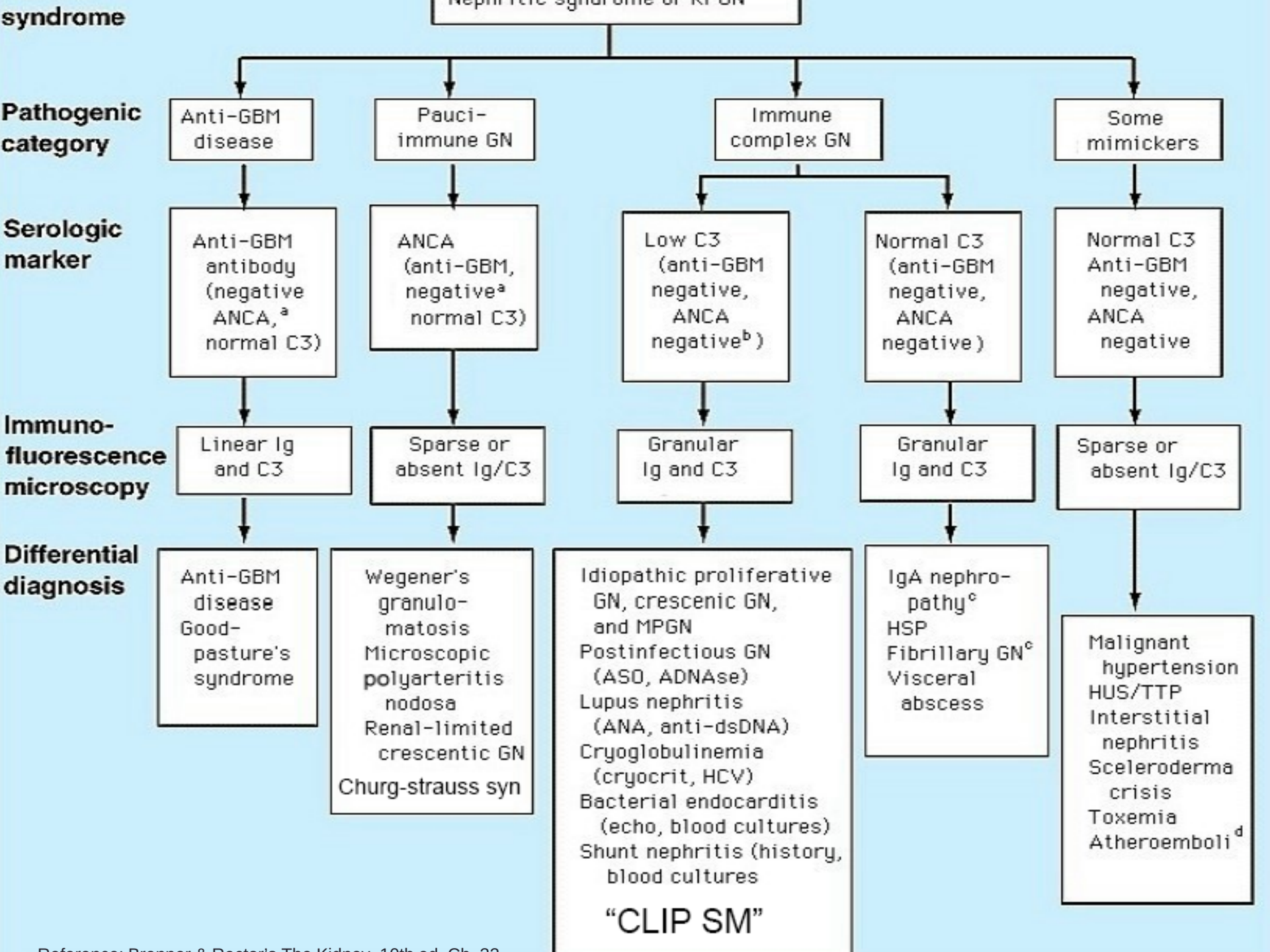
Reference: Brenner & Rector's The Kidney, 10th ed. Ch. 32

Nephritic Syndrome

- **Granular staining** (顆粒狀螢光染色)
  - 佔全部GN的40~45 % (西方人) & variable presentation
  - **Immune complex disease** (IC disease, 腎絲球內有IC deposition)
  - 可以依據**C3 level**分成兩群 → 再各自分成**systemic vs renal-limited**

Immune Complex Disease			
Low C3 ("CLIP-SM" + C)		**Normal C3**	
Systemic	**Renal-limited**	**Systemic**	**Renal-limited**
Cryoglobulinemia (HCV/RF/Cryo+,SPEP)	Poststreptococcal GN (PSGN)(10~14d, ASLO+)	HSP (Henoch-Schonlein Purpura) (血尿,腹痛, 紫斑)	IgA nephropathy
SLE (Lupus) (ANA/ds-DNA Ab+)	Shunt nephritis (VP shunt Hx)		Fibrillary GN
Endocarditis (IE) (fever, B/C+, valvular dx)	Membranoproliferative GN (MPGN)		
Other: idiopathic proliferative GN/Crescentic GN 註: Cholesterol emboli造成的蛋白尿C3/C4也會低		註: HSP = IgA nephropathy + systemic vasculitis	

Reference: Brenner & Rector's The Kidney, 10th ed. Ch. 32



References: Brenner & Rector's The Kidney, 10th ed. Ch. 32

Nephrotic Syndrome

- 分為Primary glomerular disease vs Systemic disease

Primary Glomerular Disease	Systemic Disease
MCD (minimal change disease)(20%) 小兒腎病症候群最常見原因 Primary & Secondary (**NSAID**, Hodgkin's)	**DM** (**HbA1C**, Kimmelsteil-Wilson) (**Retinopathy** 60% in T2DM)
MN (Membranous nephropathy)(30%) 成人腎病症候群最常見原因 Primary: **phospholipase A2 receptor Ab** Secondary: **HBV, HCV, Syphilis, Cancer**,SLE	**Amyloidosis** (AL = **light chain disease**) (AA = **inflammation dx**)
FSGS (focal segmental glomerulosclerosis) (40%) Primary (**suPAR**) & secondary (**HIV**, Heroin, etc)	**SLE** (Typically WHO class V)
MPGN (5%) (**HCV +/- Cryo**; HBV, etc)	**Cryoglobulinemia** (Typically MPGN in kidney)
Fibrillary-immunotactoid glomerulopathy (1%)	
其他: Mesaingial proliferative GN, IgM/C1q nephropathy	

Reference: Brenner & Rector's The Kidney, 10th ed. Ch. 32

Glomerular Disease Approach

- **Recent infection/fever**
  - **Infective endocarditis**
  - **PSGN (10~14 days after GAS)**
  - **IgA nephropathy (5~7 days after URI)**
  - **SLE**
- **Skin purpura/ecchymosis**
  - TTP/HUS
  - PSGN
  - IE
  - HSP
  - Cryoglobulinemia
- **成年人最多之GN**
  - **IgA nephropathy**
- **成年人最多之nephrotic syndrome**
  - **Membranous nephropathy**
- **IVDU**
  - **Infective endocarditis**
  - **HIV-related FSGS**
- **Nephrotic syndrome**
  - 年輕人MCD most common
  - MPGN/MN/SLE
  - 合併 **HBV** → **MN**
  - 合併 **HCV** → **Cryoglobulinemia**
  - **Solid tumor cancer** → **MN**
- **合併lymphoma**
  - RPGN, Amyloidosis
- **兒童 & 合併血便 → HUS**
- **腎衰竭/意識混亂/溶血/血小板低**
  - **Thrombocytopenic Purpura(TTP)**
  - **Atypical HUS**

Glomerular Disease Approach

- **是否合併Hemoptysis**
  - 先排除感染、氣道問題、嚴重肺水腫、凝血異常
  - **考慮Pulmonorenal syndrome**
    - Check **ANCA**(檢查M25-223) & **Anti-GBM** (本院無)
    - Check **ANA** & **Anti-ds-DNA Ab** (L72-241) & **C3/C4**
- **ANCA/Anti-GBM disease not likely or negative**
  - Check C3/C4 level → **Low C3 level then: check CLIP-SM**
    - **ASLO (L72-109), Cryo.(L72-239), ANA** & **Anti-ds-DNA Ab**
    - **B/C +/- 2D-ECHO, HBsAg/HCV Ab/RPR/HIV, RF** (L72-134)
- **排除GN mimics**
  - TTP/HUS/aHUS → **↓Hb/PLT/haptoglobin, MAHA in PB smear, ↑LDH**
  - Cholesterol emboli → **↓C3/C4**, toe cyanosis, cath., eos., livedo.
  - MM → Hb, Ca, **S/U IFE(L72-204)/PEP(L72-201) or SFLC (L72-214)**
  - AIN → rash, new drug, urine WBC + WBC cast

Glomerular Disease Approach

- **考慮Renal echo → 腎臟超音波為nephromegaly**
  - **考慮Amyloidosis, Sarcoidosis, HIV, DM, PKD**
- **考慮Renal biopsy**
  - IF (immunofluorescence) +/- EM (electric microscopy)
- **For nephrotic syndrome**
  - HbA1C (for DM)
  - ANA/C3/C4/Anti-ds-DNA Ab (for SLE)
  - Serum+Urine IFE or serum IFE + serum free light chain (for MM/AL)
  - Cryoglobulin test (for Cryoglobulinemia)
  - HBsAg(MN), HCV Ab (MPGN/Cryo), HIV (FSGS), RPR (MN)
  - PLA2 receptor Ab (本院無法驗)(for MN)
  - suPAR (本院無法驗) (for FSGS)
  - Cancer screen if MN

Glomerular Disease Treatment

- **General**
  - Dietary protein (average daily need + average loss amount)
  - **Albumin (1pc = 12.5g) + Diuretics for edema & Na restriction (<2g/d)**
  - Diet + Statin for dyslipidemia in nephrotic syndrome
  - **ACEI/ARB** → ↓ proteinuria, slow non-immunologic progression
  - Consider influenza/pneumococcus vaccination
- **Primary**
  - Nephrotic syndrome: consider steroid, cytotoxic agents
  - Acute GN/RPGN: consider pulse steroid x 3 days then maintain dose
  - Lupus: **steroid + endoxan (or MMF) +/- plasmapheresis**
  - ANCA-associated vasculitis/Anti-GBM disease
    - **Pulse steroid + endoxan (or rituximab) +/- plasmapheresis**
- **Secondary**
  - Treat underlying disease (ex: Antibitoics for IE/PSGN)

Steps of Proteinuria Approach

- **排除False (+) & transient & admixture proteinuria**
- **Repeat U/A +/- TP/Cr or ACR (or 24hr urine TP/Cr)**
- **年輕人 & TP/Cr <1g/mg → 排除Postural proteinuria**
  - **Split urine measurement** = 活動 (7am~11pm) + 平躺 (11pm~7am)

  → 如果**平躺8hr期間的尿蛋白<50mg**而活動時有顯著蛋白尿則可確診
- **Persistent proteinuria → 進一步檢查其他原因**
  - Clinical: DM, HTN, edema, CKD, hematuria, fever/infection/URI
  - Lab: **urinalysis, spot urine ACR(L72-338)/TPCr or 24hr urine TP/Cr**

  → **>2g/d** (1g/g) 先考慮**Glomerular proteinuria / overflow proteinuria**

  → **<2g/d** (1g/g) 先考慮**Tubular proteinuria / early glomerular disease**
  - Edema, no HTN/AKI/hematuria → **nephrotic** likely
  - HTN/AKI/hematuria, edema, recent fever/infection → **nephritic** likely
    - AKI的BUN/Cr大多>20/FeNa<1% (可和ATIN/ATN等區分)

Reference: 基層醫學雜誌 第二十一卷 第六期 蛋白尿與微量白蛋白尿 (2003)

Reference

1. 基層醫學雜誌 第二十一卷 第六期 蛋白尿與微量白蛋白尿 (2003)
2. ESH/ESC hypertension guideline 2013
3. KDIGO Clinical Practice Guideline for Chronic Kidney disease 2012
4. KDIGO Clinical Practice Guideline for the Management of BP in CKD (2012)
5. DOQI Clinical Practice Guidelines for CKD (2002)
6. Brenner & Rector’s The Kidney, 10th ed. Ch. 32


Thank You !