Introduction to Glomerular disease

Dr H Bierman

- Glomerular disease ranges from asymptomatic hematuria and/or proteinuria to fulminant disease with AFR and extra-renal disease.
- Dramatic symptomatic presentations are uncommon.
- Asymptomatic urine abnormalities are common but not so specific – this may also indicate wide range of non-glomerular renal tract disease.

Clinical presentations of glomerular disease

Asymptomatic

Proteinuria 150 mg to 3 g per day

Hematuria > 2 red blood cells per high-power field in spun urine or > 10×10^6 cells/L (red blood cellsusually dysmorphic)

Macroscopic hematuria

Brown/red painless hematuria (no clots); typically coincides with intercurrent infection

Asymptomatic hematuria ± proteinuria between attacks

Nephrotic syndrome

Proteinuria: adult > 3.5 g/day; child > 40 mg/h per m^2

Hypoalbuminemia < 3.5 g/dL

Edema

Hypercholesterolemia

Lipiduria

Nephritic syndrome

Oliguria

Hematuria: red cell casts

Proteinuria: usually < 3 g/day

Edema

Hypertension

Abrupt onset, usually self-limiting

Rapidly progressive glomerulonephritis

Renal failure over days/weeks

Proteinuria: usually < 3 g/day

Hematuria: red cell casts

Blood pressure often normal

May have other features of vasculitis

Chronic glomerulonephritis

Hypertension

Renal insufficiency

Proteinuria > 3 g/day

Shrunken smooth kidneys

Clinical evaluation of glomerular disease

- History
- Physical examination
- Laboratory studies
- Imaging
- Renal biopsy

The aim is to:

- exclude non-glomerular disease,
- finding evidence of associated multisystem disease,
- establishing glomerular function

Glomerular Disease: History

- Family history – hearingloss (Alport); familial IgA nephropathy, FSGS, HUS.
- Drugs and toxins – NSAIDS and IF (Minimal change disease), membranous nephropathy (gold, NSAIDS, Hg in skin lightning creams), FSGS(heroin) or HUS (cyclosporin, tacrolimus, oral contraceptive).
- Recent or persistent infection – streptococcal, IE, viral.
- Malignancies – lung, breast, GIT (membranous); non-Hodgkins (MPGN); renal carcinoma (amyloid). Occasionally first manifestation of malignancy.
- Multisystem disease: Diabetes, amyloid, lupus, vasculitis.

Physical examination:

- Dependent pitting edema – nephrotic syndrome, CCF or cirrhosis. Often peri-orbital edema in morning in nephrotic syndrome.
- Edema of abdominal wall and dependent areas like genitals, pleural effusions and ascitis
- > 20% increase in body weight due to fluid accumulation not uncommon

Physical examination:

- Pulmonary signs – think of pulmonary renal syndrome
- Palpable purpura – vasculitis, SLE, cryoglobulinemia, endocarditis
- Low albumin – white nails or white bands (Muercke's bands)

Laboratory studies:

- Renal function
- Careful examination of urine
- Amount of proteinuria
- Presence or absence of dysmorphic RBC’s and casts
- Serology: ASOT, ANF, anti-dsDNA Ab’s, cryoglobulins and RF, anti-GBM Ab’s, ANCA
- Serum and urine electrophoresis
- Blood cultures, hep B, C HIV
- Complement C3, C4, CH50 (50% hemolyzing dose of complement)

Imaging:

- U/S : ensure 2 kidney's present, obstruction, anatomical abnormalities, kidney size.
- Renal size usually normal in GN but can be lanrge >14cm in nephrotic syndrome ass with DM, HIV, amyloid or acute severe GN.
- Small kidney's <9cm suggest chronic renal disease and should limit enthusiasm fro renal biopsy or aggressive immunosuppressive therapy.

Renal biopsy:

- Establish type of renal disease and guide therapy
- In children with typical nephrotic syndrome usually no biopsy initially – minimal change disease most common diagnosis
- In typical post Strep GN esp in epidemic biopsy usually not needed unless poor treatment response
- Anti-GBM GN with pulmonary hemorrhage and high anti-body titres biopsy not needed unless need for prognostic info.
- ANCA with biopsy at other site confirming vasculitis – can withhold biopsy.
- Long standing diabetics with characteristic findings of diabetic nephropathy
- Mild disease – biopsy sometimes not indicated when prognosis good

Asymptomatic urine abnormalities

- Increase with age
- Mostly found coincidently during routine medical examinations
- No evidence for routine population wide screening of urine – renal biopsy and or therapeutic intervention rarely required if renal function is normal

Asymptomatic microscopic hematuria

- > 2 RBC's per HPF
- Common in glomerular disease esp IgA nephropathy and thin membrane disease
- Glomerular origin should be thought of if red cells are dysmorphic, RBC casts are present or proteinuria are present.

Asymptomatic microscopic hematuria: evaluation

- U-MC+S to exclude UTI and prostatitis
- Renal imaging to exclude anatomic lesions like PCK, stones, tumor, AV-malformations
- Proteinuria or decreased GFR – suggest glomerular disease
- Sickle cell screen inappropriate populations
- TB
- Serum and urine calcium and uric acid – calsium and uric acid crystals
- Over 40 yrs – always cystoscopy to exclude uroepithelial malignancy

Asymptomatic microscopic hematuria: evaluation

- If all negative glomerular origin in form of IgA nephropathy and thin membrane disease is the most common at any age
- Biopsy will confirm diagnosis but with normal renal function in asymptomatic patient and low-grade proteinuria < 0.5 g/day not needed
- Repeat evaluation every 12 months however needed for rare cases of progression

Asymptomatic non-nephrotic proteinuria

- Hallmark of glomerular disease – proteinuria
- Normal = 150mg protein/24hr

(20-30mg albumin, 10-20 mg LMW protein freely filtered, 40-60 mg secreted protein like Tamm-Horfall protein and IgA)

- Microalbuminuria = 30-300mg albumin/24 hr – used to detect diabetics at risk fro diabetic nephroapthy
- Non-nephrotic proteinuria = < 3.5 g/24 hrs or protein:creat ratio of < 3, not specific for glomerular disease

Asymptomatic non-nephrotic proteinuria

- Selectivity of proteinuria – ratio of IgG to albumin . If highly selective (ratio <10%) is typical of minimal change disease (loss of glom charge barrier but intact glom size barrier)
- In non-selective proteinuria - loss of size and charge barriers is more common.
- Routine testing for protein selectivity is not done.
- Proteinuria can result from increased glomerular permeability or tubulointerstitial disease – but not result in nephrotic syndrome
- Also increased filtration through normal glomeruli – overflow proteinuria

Overflow proteinuria

- Typical of urinary light chain excretion
- Myeloma
- Release of lysozyme by leukemic cells
- Negative dipstick for protein but large amount by other tests

Tubular proteinuria

- Tubular interstitial disease - < 2g/d
- Tubular protein – b2-microglobulin and some albumin due to impaired reabsorption of filtered protein

Glomerular proteinuria

1. Functional proteinuria

- Transient non-nephrotic proteinuria with fever, exercise, CCF, hyperadrenergic or hyper-reninemic states.
- Is benign
- Due to increaed single nephron flow/pressure

1. Orthostatic proteinuria

- Children and young adults low grade glom proteinuria may be orthostatic.
- No protein in first morning sample.
- < 1g/24 hrs
- Pathogenesis unknown
- Biopsy not indicated

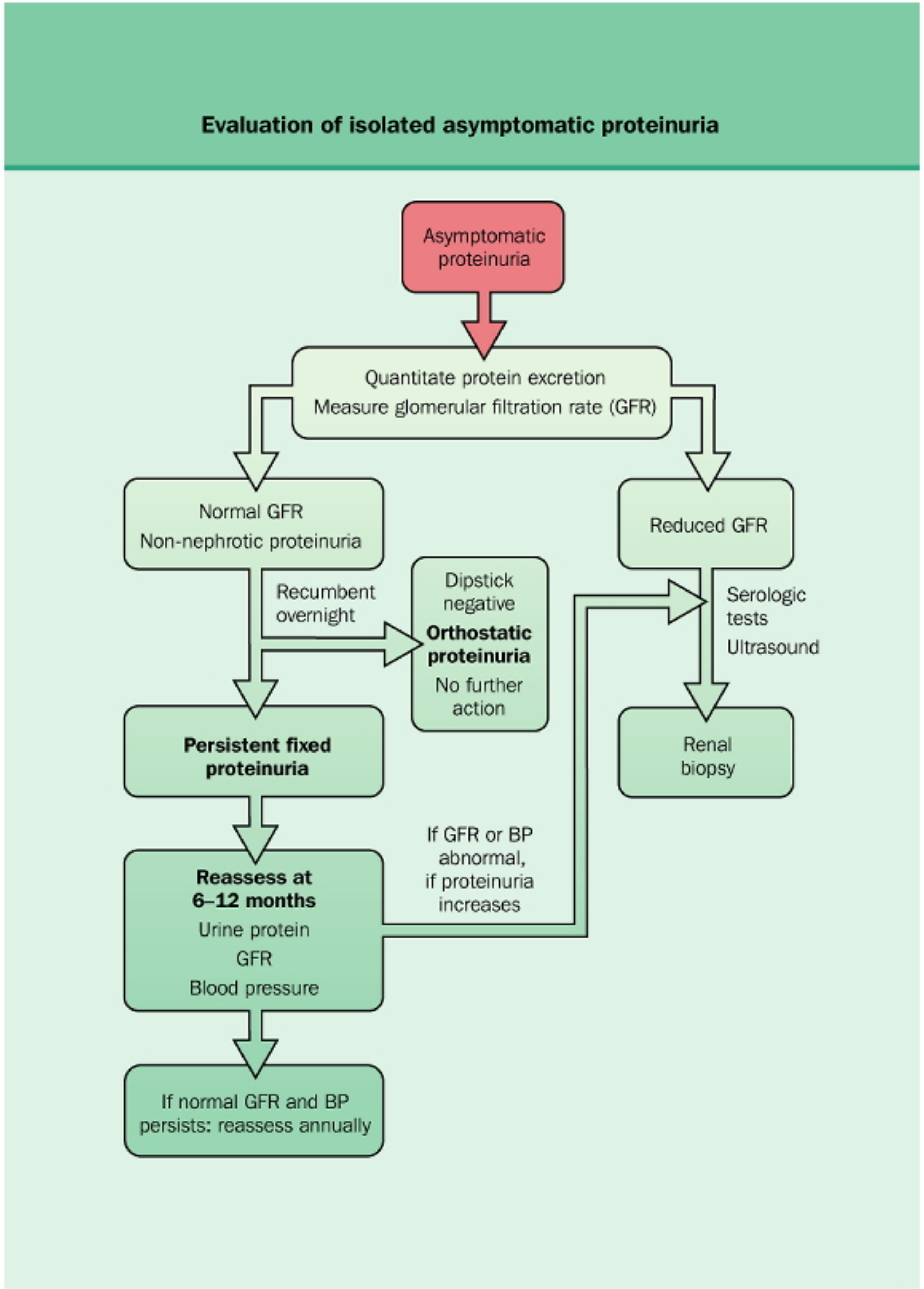
Glomerular proteinuria

<u>3. Fixed non-nephrotic proteinuria</u>

- Usually glomerular disease
- If normal GFR benefit of biopsy controversial
- Prolonged fowllow-up justified as long as proteinuria persists
- Same pathology as with nephrotic syndrome but milder like MPGN without immune deposits.
- Normal light microscopy with only effaced foot processes on EM common. Looks like minimal change but not steroid responsive. No tretamnet needed.

Asymptomatic proteinuria with hematuria

- Much greater risk for significant glomerular injury, hypertension, progressive renal dysfunction.
- Minor changes on histology less common
- Renal biopsy indicated even if proteinuria between 0.5 and 1 gram/24 hrs if microscopic hematuria present.



Evaluation of isolated asymptomatic proteinuria
Asymptomatic proteinuria
Quantitate protein excretion
Measure glomerular filtration rate (GFR)
Normal GFR
Non-nephrotic proteinuria
Reduced GFR
Recumbent overnight
Dipstick negative
Orthostatic proteinuria
No further action
Serologic tests
Ultrasound
Persistent fixed proteinuria
Renal biopsy
If GFR or BP abnormal, if proteinuria increases
Reassess at 6–12 months
Urine protein
GFR
Blood pressure
If normal GFR and BP persists: reassess annually

Macroscopic hematuria

- Episodic painless macroscopic hematuria ass with glom disease is often brown “smoky” rather than red
- Clots are unusual
- Exclude other causes of red/bown urine: hemoglobinuria, myoglobinuria, food dyes (beetroot)
- Macroscopic hematuria due to glom disease mainly seen in children and young adults and rarely over 40

Macroscopic hematuria

- Requires urological evaluation including cystoscopy unless history typical of glomerular disease
- IgA nephropathy most common but can occur with many other glomerular and non-glomerular diseases including acute interstitial nephritis
- Usually painless and loin-pain suggests other pathology like stones

Macroscopic hematuria

- IgA nephropathy – hematuria usually episodic occurring within a day of upper resp infection (synpharyngitic)
- Clear distinction between this history and the 2-3 week latency between infection and post strep GN
- Post strep GN usually also has other features of nephritic syndrome

Nephrotic syndrome

- Nephrotic syndrome is pathogenomic of glomerular disease.

Asymptomatic

teinuria 150 mg to 3 g per day

lematuria > 2 red blood cells

high-power field in spun urine

or > 10 × 10^6 cells/L

blood cellsusually dysmorphic)

naturia

hematuria

ncides with

ction

± proteinuria

cks

Nephrotic syndrome

Proteinuria: adult > 3.5 g/day; child > 40 mg/h per m^2

Hypoalbuminemia < 3.5 g/dL

Edema

Hypercholesterolemia

Lipiduria

ts

day

Rapidly progressive glomerulonephritis

Renal failure over days/weeks

Proteinuria: usually < 3 g/day

Hematuria: red cell casts

Blood pressure often normal

May have other features of vasculitis

Nephrotic syndrome

- Renal function can be normal but in many cases renal function progressively decline if left untreated.
- Nephrotic syndrome negatively affects renal function but also has metabolic effects leading to poor health.
- Disease can be self limiting or respond completely to treatment (minimal change disease).
- For most patients it is a chronic condition.
- Not all patients with >3.5g/24 hrs have the full syndrome and their serum albumin can be normal; this is due to varied protein metabolism and production between patients.

Nephrotic syndrome: Etiology

Common glomerular diseases presenting as nephrotic syndrome in adults		
Disease	**Associations**	**Serologic tests helpful in diagnosis**
Minimal change disease	Allergy, atopy, NSAIDs, Hodgkin's disease	None
Focal segmental glomerulosclerosis	African Americans	–
	HIV infection	HIV antibody
	Heroin	–
Membranous nephropathy	Drugs: gold, penicillamine, NSAIDs	–
	Infections: hepatitis B, C; malaria	Hepatitis B surface antigen, anti-HCV antibody
	Lupus nephritis	Anti-DNA antibody
	Malignancy: breast, lung, gastrointestinal tract	–
Membranoproliferative glomerulonephritis (Type I)	C4 nephritic factor	C3 ↓, C4 ↓
Membranoproliferative glomerulonephritis (Type II)	C3 nephritic factor	C3 ↓, C4 normal
Cryoglobulinemic MPGN	Hepatitis C	Anti-HCV antibody, rheumatoid factor, C3 ↓, C4 ↓, CH_{50} ↓
Amyloid	Myeloma	Serum protein electrophoresis, urine immunoelectrophoresis
	Rheumatoid arthritis, bronchiectasis, Crohn's disease (and other chronic inflammatory conditions), familial Mediterranean fever	–
Diabetic nephropathy	Other diabetic microangiopathy	None

Nephrotic syndrome: Etiology

- Nephrotic range proteinuria without low albumin and edema has the similar etiologies.
- Although predominant in childhood, minimal change disease remains common at all ages. Increased prevalence of FSGS in African Americans.
- FSGS is becoming more common and MPGN less common.

Age-related variations in nephrotic syndrome

	Prevalence (%)				
	Child	Young adult		Middle and old age	
	(<15 years)	Whites	Blacks	Whites	Blacks
Minimal change disease	78	23	15	21	16
Focal segmental glomerulosclerosis	8	19	55	13	35
Membranous nephropathy	2	24	26	37	24
Membranoproliferative glomerulonephritis (MPGN)	6	13	0	4	2
Other glomerulonephritis	6	14	2	12	12
Amyloid	0	5	2	13	11

Data adapted from Haas et al.[6] and Cameron[5].

Nephrotic syndrome: Hypoalbuminemia

- The result of:

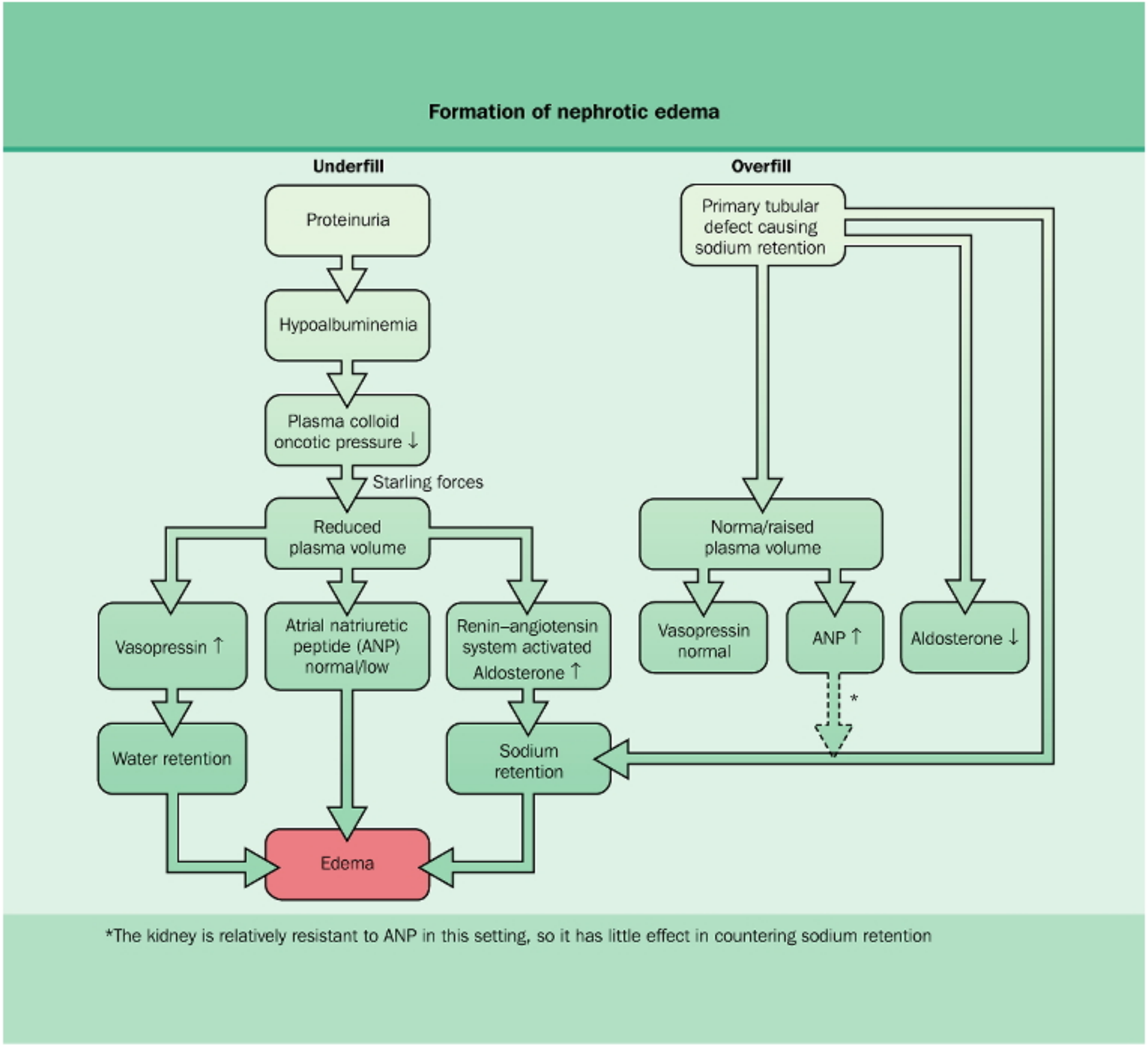
1. Urinary losses
2. Increased reabsorption and catabolism by tubular cells in proximal tubuli
3. Increased synthesis by liver is blunted by nephrotic syndrome

- Increased protein intake does not improve protein metabolism – the hemodynamic response is increased glomerular pressure, increasing protein losses.

Nephrotic syndrome: Hypoalbuminemia

- Consequence: fall in serum albumin.
- Increased protein synthesis in response to renal losses is non-discriminatory – proteins not lost may actually increase.
- Determined by molecular weight – the larger the molecule, the less likely it will be lost through kidney – increased plasma levels the result.
- This leads specifically to hypercoagulability and hyperlipidemia.

Nephrotic syndrome:
Edema



Formation of nephrotic edema
Underfill
Overfill
Proteinuria
Hypoalbuminemia
Plasma colloid oncotic pressure ↓
Starling forces
Reduced plasma volume
Vasopressin ↑
Atrial natriuretic peptide (ANP) normal/low
Renin–angiotensin system activated Aldosterone ↑
Water retention
Sodium retention
Edema
Primary tubular defect causing sodium retention
Norma/raised plasma volume
Vasopressin normal
ANP ↑
Aldosterone ↓
*
*The kidney is relatively resistant to ANP in this setting, so it has little effect in countering sodium retention

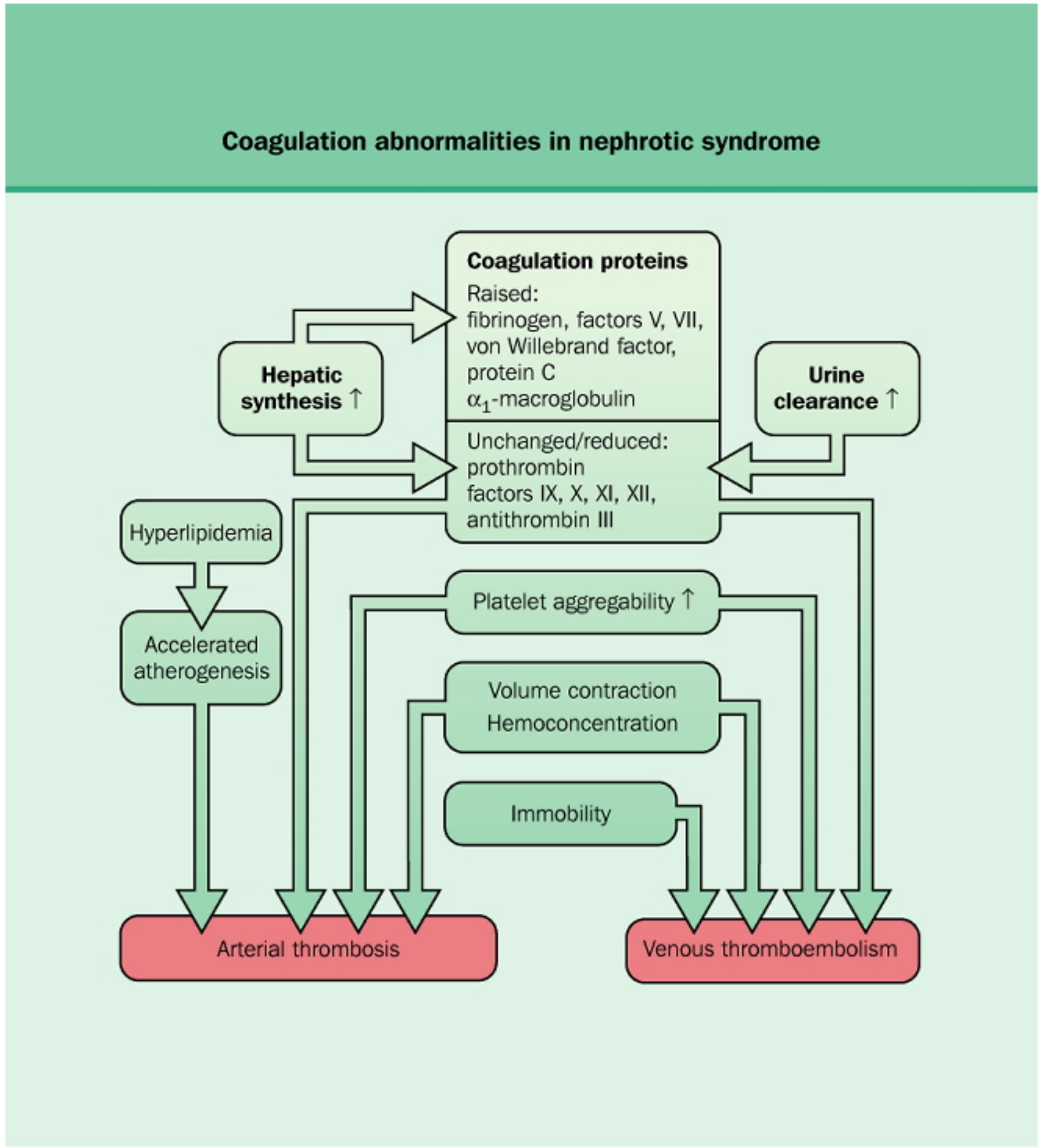
Metabolic consequences of nephrotic syndrome:

1. Negative nitrogen balance
2. Hypercoagulability
3. Hyperlipidemia and lipiduria
4. Endocrine

Metabolic consequences of nephrotic syndrome: negative nitrogen balance

- Measured by low S-albumin
- Wasting illness – muscle wasting masked by edema
- Loss of 10-20% of lean body mass common
- Albumin turnover increased by tubular catabolism of filtered protein rather than merely protein loss.
- Increased intake increases synthesis but also loss and aggravates disease.
- Low protein diet reduce proteinuria but in long run can worsen negative nitrogen balance.

Metabolic consequences of nephrotic syndrome: Hypercoagulability



Metabolic consequences of nephrotic syndrome: Hypercoagulability

- Altered levels of coagulation factors and altered platelet function
- Netto result = hypercoagulable state aggrevated by:

1. Immobility
2. Infection
3. hemoconsentration

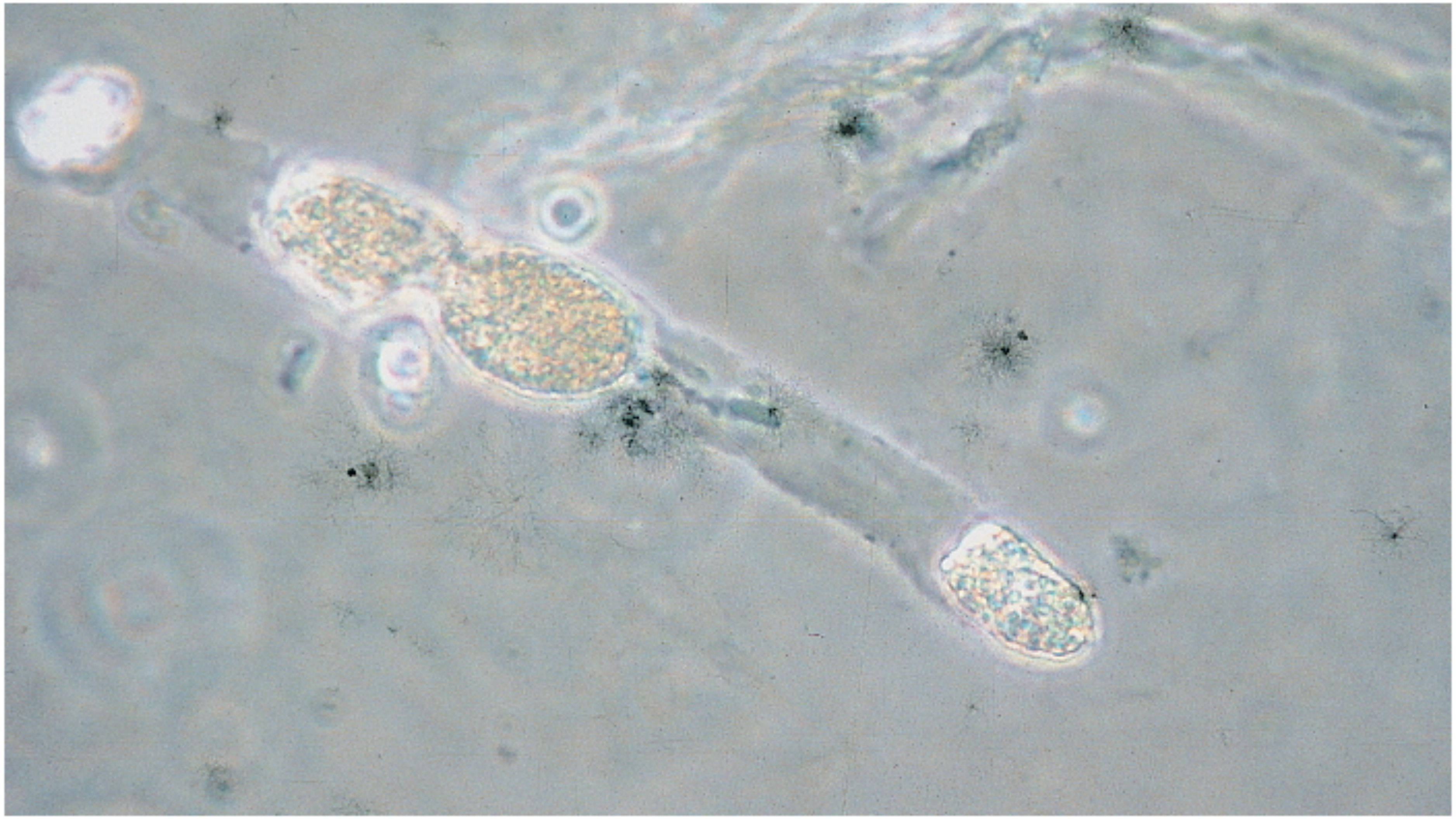
Metabolic consequences of nephrotic syndrome: Hypercoagulability

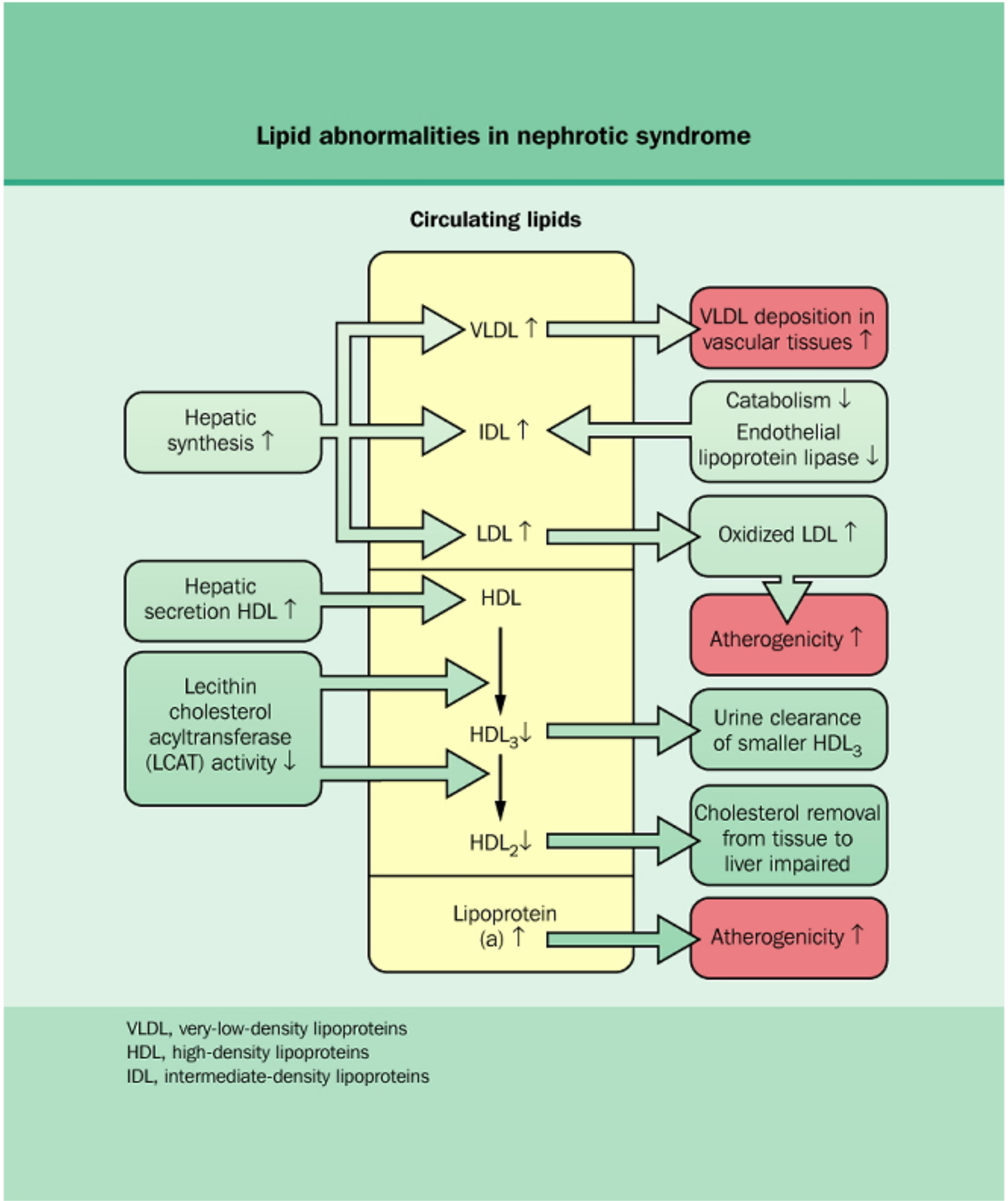
- Venous thrombosis and embolism is common as well as arterial thrombosis.
- 10% of adults and 2% of children will have thrombotic event.
- Increased fibrinogen causes increased ESR – levels of >100 not uncommon – ESR loses it's clinical value as marker of acute phase response.

Metabolic consequences of nephrotic syndrome: Hypercoagulability

- Renal vain thrombosis (RVT) is an NB complication of nephrotic syndrome.
- occurs in 8% of nephrotic individuals but if sought for specifically the prevalence increases to 10-50%.
- More common in membranous nephropathy - ? Why.
- Acute RV-thrombosis symptoms – flank pain, hematuria, ARF (if bilateral).
- More often develops slowly and asymptomatic.
- RVT should not be screened for routinely.
- Pulmonary embolism = NB complication.

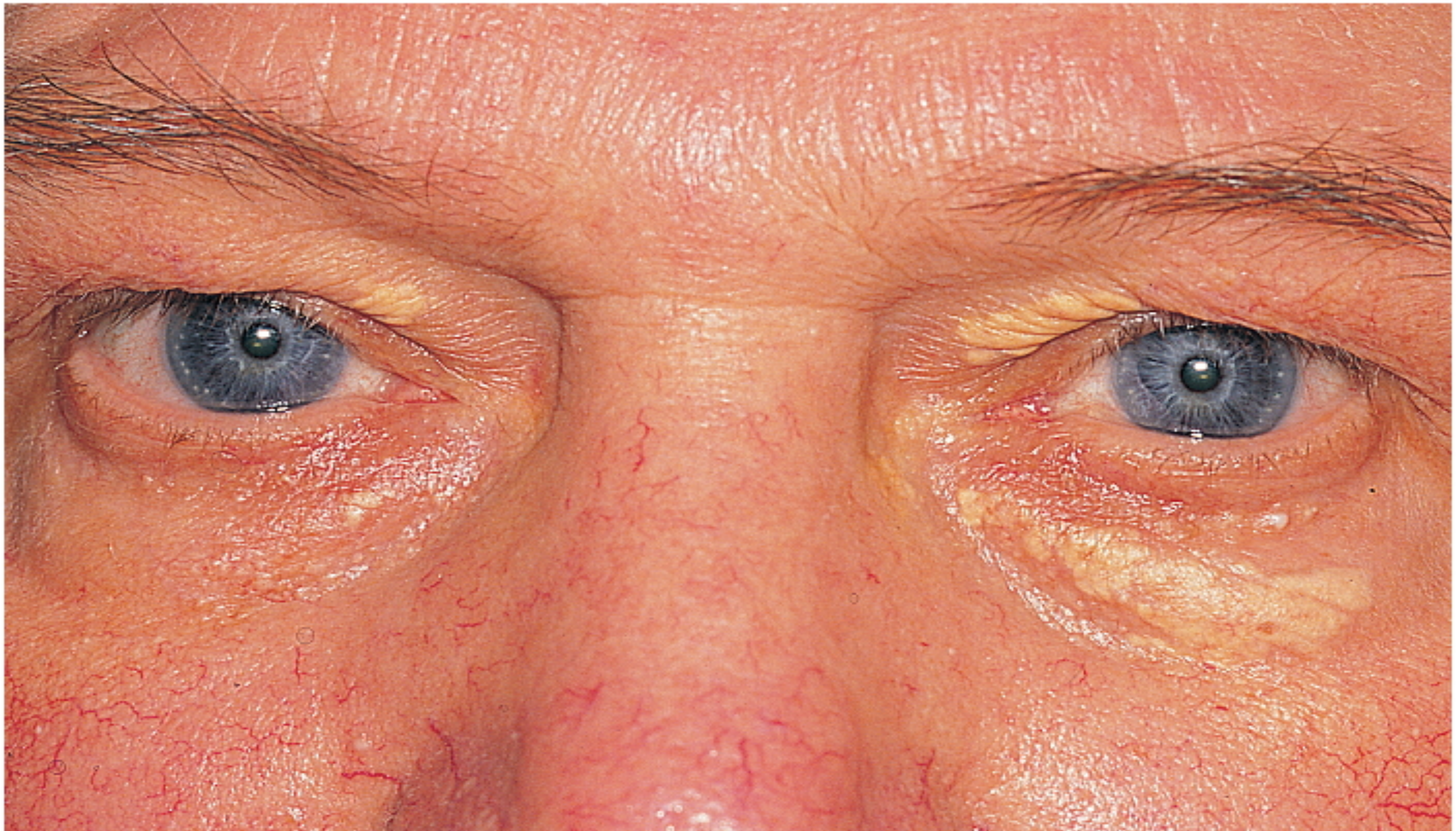
Hyperlipidemia and lipiduria




Lipid abnormalities in nephrotic syndrome
Circulating lipids
VLDL ↑
IDL ↑
LDL ↑
HDL
HDL$_3$↓
HDL$_2$↓
Lipoprotein (a) ↑
Hepatic synthesis ↑
Hepatic secretion HDL ↑
Lecithin cholesterol acyltransferase (LCAT) activity ↓
VLDL deposition in vascular tissues ↑
Catabolism ↓
Endothelial lipoprotein lipase ↓
Oxidized LDL ↑
Atherogenicity ↑
Urine clearance of smaller HDL$_3$
Cholesterol removal from tissue to liver impaired
Atherogenicity ↑
VLDL, very-low-density lipoproteins
HDL, high-density lipoproteins
IDL, intermediate-density lipoproteins

Hyperlipidemia and lipiduria

- Integral part of nephrotic syndrome.
- Clinical stigmata like xanthelasma may have rapid onset.

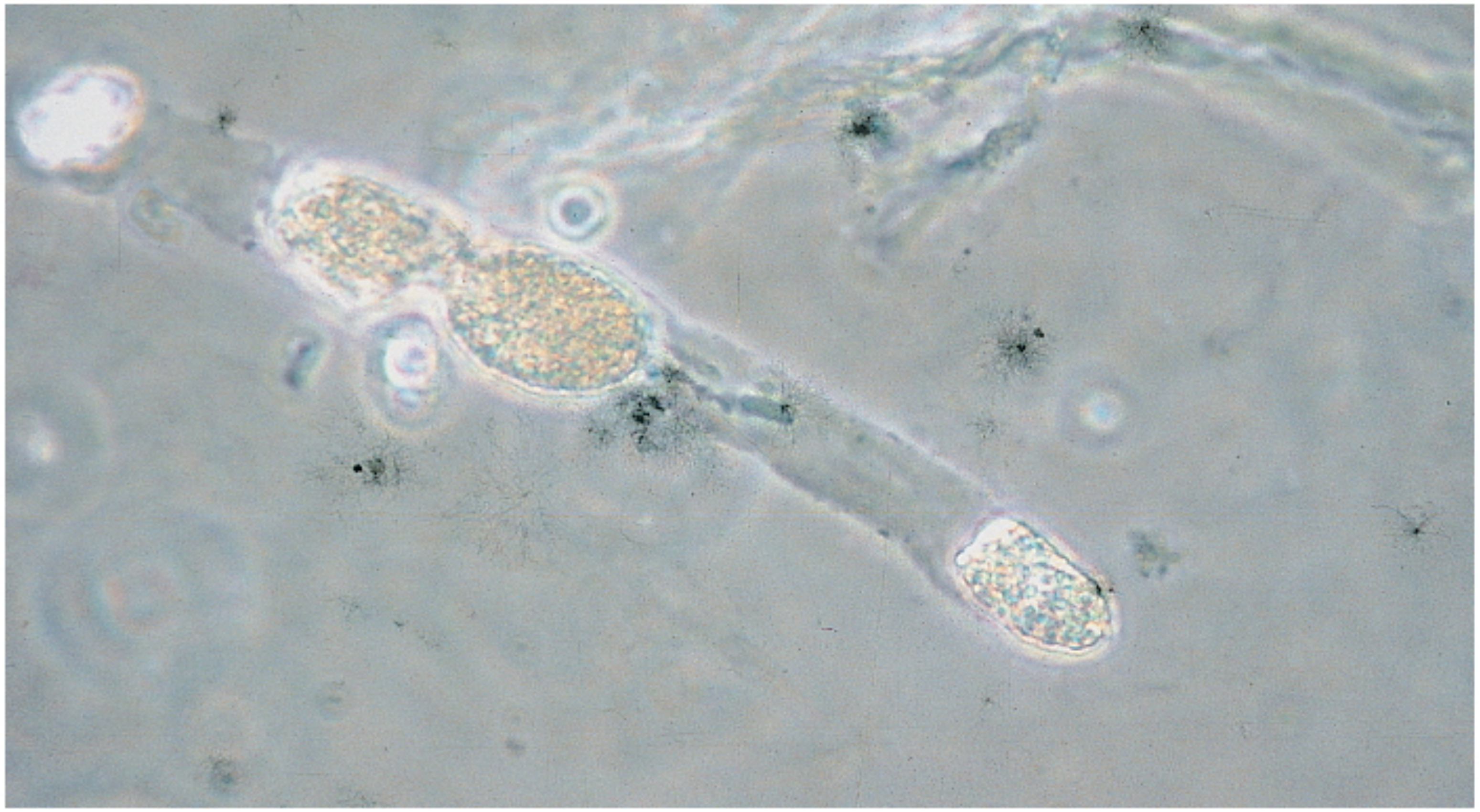


Hyperlipidemia and lipiduria

- Levels of s-cholesterol > 13 is common.
- Highly atherogenic lipid profile.
- 5-fold increase in coronary risk – except minimal change disease patients (short duration of illness).
- Contribute to progressive renal disease – lipid deposition in glomeruli and interstitium.
- Protection against CVS risk and renal risk via statins. May slow progression of renal disease.

Hyperlipidemia and lipiduria

- Lipiduria – refractile accumulation of lipid in cellular debris and casts (oval fat bodies and fatty casts).
- This is a consequance of proteinuria and not plasma lipid abnormalities.



Endocrine and other effects of nephrotic syndrome: Vitamin D

- Loss of Vit D binding protein – low plasma 25-OHVitD.
- Free Vit D usually normal and overt osteomalasia or uncontrolled hyperparathyroidism is very unusual unless renal failure present.

Endocrine and other effects of nephrotic syndrome: thyroid

- Loss of thyroid binding globulin – reduced total circulating thyroxine. Normal free thyroxine and TSH.
- No clinical alteration in thyroid status.
- Occasional cases of copper, iron, or zinc deficiency have been described due to loss of binding proteins.

Endocrine and other effects of nephrotic syndrome

- Drug binding might be altered by decreased albumin.
- Most drugs don’t need dose adjustments except clofibrate which can cause severe myopathy in nephrotic patients at normal dosages.
- Altered protein binding may change dosage of warfarin required for adequate antcoagulation.

Nephrotic syndrome: infection

- Prone to bacterial infection
- Before steroids sepsis was major cause of death in nephrotic children; still problem in developing world
- Primary peritonitis caused by pneumococci is characteristic of nephrotic children
- Over age 20 most people have antibodies against pneumococci capsular Ag therefore less common after this age
- Also sterptococci and gram negative bacilli (not staphylococcus)

Endocrine and other effects of nephrotic syndrome

- Cellulitis in areas of severe edema is common – B-hemolytic streptoccci
- Explanation for increased infection risks:

1. Large fluid collections – bacteria grow easily
2. Nephrotic skin is fragile – site of entry
3. Edema dilute local humoral immune factors
4. Loss of IgG and complement factor B (of alternative pathway) in urine – loss of ability to eliminate encapsulated organisms such as pneumococci
5. Zn and fe lost – needed for normal lymphocyte function
6. Polymorph and T-cell dysfunction are also present

Acute and chronic changes in renal function in nephrotic syndrome:
Acute renal failure

Acute Renal Failure

Acute renal failure in nephrotic syndrome
Pre-renal failure due to volume depletion
Acute tubular necrosis due to volume depletion and/or sepsis
Intrarenal edema
Renal vein thrombosis
Transformation of underlying glomerular disease, e.g., crescentic change superimposed on membranous nephropathy
Adverse effects of drug therapy
Acute allergic interstitial nephritis secondary to various drugs, including diuretics
Hemodynamic response to NSAIDs and ACE inhibitors

Chronic Renal Failure

- With exeption of minimal change disease most cases are at risk of progressive renal failure
- Degree of proteinuria one of biggest risk factors for progression
- Risk less if < 2g/day and increases in proportion to degree of proteinuria
- Marked risk if > 5g/day
- Because proteinuria identifies severe glomerular disease and causes renal damage *per se* via toxic interstitial nephritis
- Measures that reduce protienuria reduce disease progression – ACE inhibitors

Nephritic syndrome

- In nephrotic syndrome the glomerular injury manifests as increased capillary permeability to protein
- By contrast – in nephritic syndrome there is evidence of glomerular inflammation with:

1. Reduced GFR
2. Non-nephrotic proteinuria
3. Edema
4. hypertension (secondary to sodium retention)
5. Hematuria with RBC casts

Nephritic syndrome

- Classical presentation seen in acute post-streptococcal GN in children
- Rapid onset over a few days of:

1. Oliguria
2. Weight gain
3. Generalized edema
4. Brown urine with no clots
5. Urine with protein, RBC's and RBC casts
6. Serum albumin is normal – rarely nephrotic range proteinuria
7. Increased circulating volume with hypertension and pulmonary edema without signs of cardiac disease

Nephritic syndrome

Differentiation between nephrotic syndrome and nephritic syndrome

Typical features	Nephrotic	Nephritic
Onset	Insidious	Abrupt
Edema	++++	++
Blood pressure	Normal	Raised
Jugular venous pressure	Normal/low	Raised
Proteinuria	++++	++
Hematuria	May/may not occur	+++
Red-cell casts	Absent	Present
Serum albumin	Low	Normal/slightly reduced

Nephritic syndrome

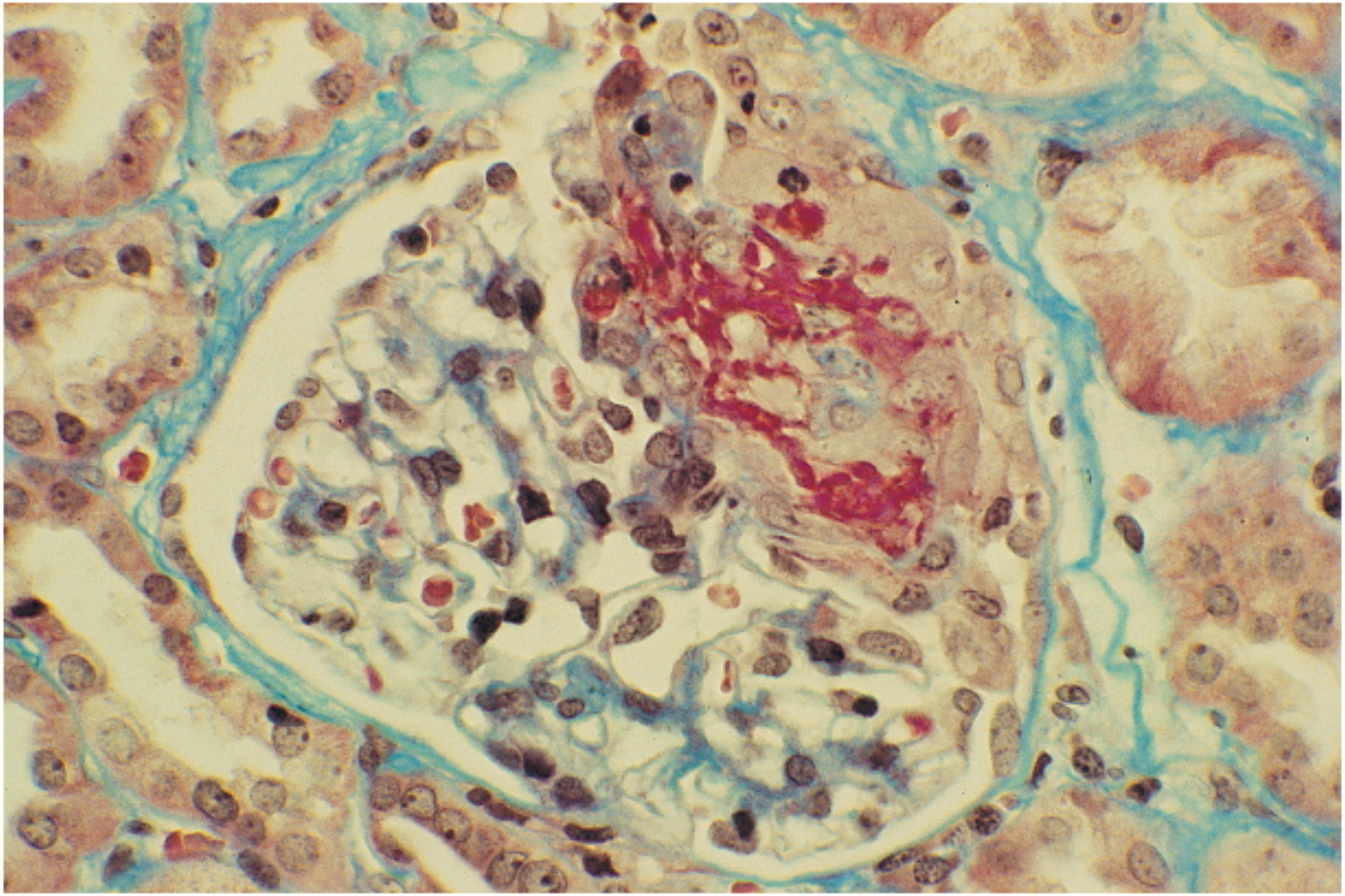
- This differentiation is usually straightforward but can overlap esp in MPGN

Nephritic syndrome: Etiology

Common glomerular diseases presenting as nephritic syndrome		
Disease	**Association**	**Serologic tests helpful in diagnosis**
Poststreptococcal glomerulonephritis	Pharyngitis, impetigo	ASO titer, streptozyme antibody
Other postinfectious disease		
Endocarditis	Cardiac murmur	Blood cultures, C3 ↓
Abscess	–	Blood culture, C3, C4 normal or raised
'Shunt'	Treated hydrocephalus	Blood cultures, C3 ↓
IgA nephropathy	Upper respiratory or gastrointestinal infection	Serum IgA ↑
Systemic lupus	Other multisystem features of lupus	Antinuclear antibody, anti-double stranded DNA antibody, C3 ↓, C4 ↓

Nephritic syndrome: RPGN

- Glomerular injury is so severe that renal function deteriorates over days or weeks
- Patient may present as uremic emergency with progressive disease and renal failure or develop renal failure while being investigated for extra-renal disease associated with GN
- Histology in RPGN is Crescentic GN: proliferative cellular response outside glomerular tuft but inside Bowman’s space know as crescent because of it’s shape on cross section



RPGN:Etiology

Common glomerular diseases presenting as rapidly progressive glomerulonephritis (RPGN)		
Disease	**Association**	**Serologic tests helpful in diagnosis**
Goodpasture's disease	Lung hemorrhage	Antiglomerular basement membrane (anti-GBM) antibody (occasionally antineutrophil cytoplasmic antibodies (ANCA) present)
Vasculitis		
Wegener's granulomatosis	Upper and lower respiratory involvement	cANCA (cytoplasmic)
Microscopic polyangiitis	Multisystem involvement	pANCA (perinuclear)
Pauci-immune crescentic glomerulonephritis	Renal involvement only	pANCA
'Immune complex'		
Systemic lupus	Other multisystem features of lupus	Antinuclear antibody, anti-double stranded DNA antibody, C3 ↓, C4 ↓
Poststreptococcal glomerulonephritis	Pharyngitis, impetigo	Asotiter, streptozyme antibody, C3 ↓, C4 normal
IgA nephropathy/Henoch–Schönlein purpura (HSP)	Characteristic rash ± abdominal pain in HSP	Serum IgA ↑ (30%), C3 and C4 normal
Endocarditis	Cardiac murmur; other systemic features of bacteremia	Blood cultures, ANCA (occasionally) C3 ↓, C4 normal

Note the overlap between the diseases in this figure and those in Table 19.5. A number of glomerular disease may present with either a nephritic syndrome or with RPGN.

Treatment of glomerular disease

- General supportive

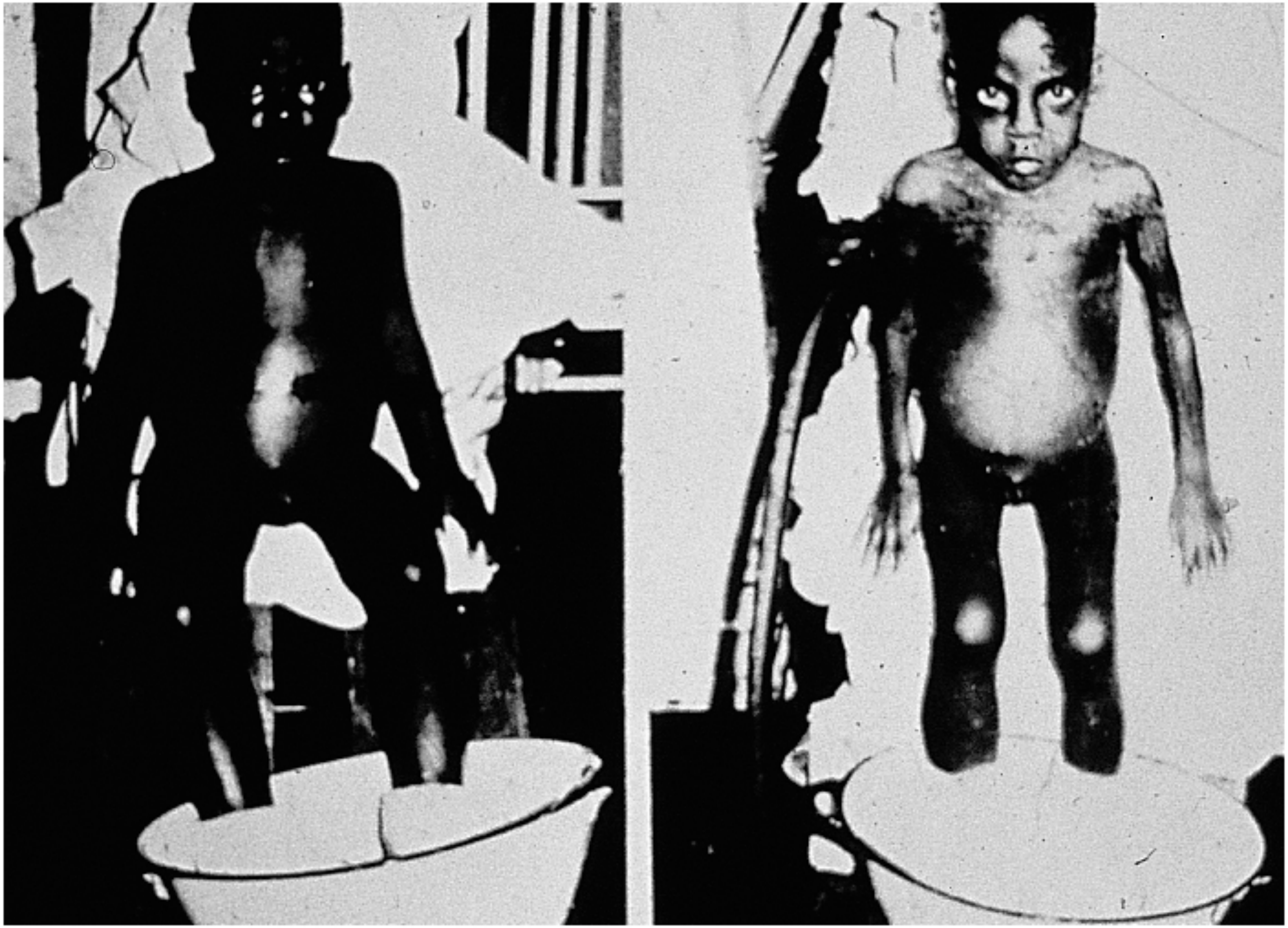
1. Reduce proteinuria
2. Control edema
3. Treat blood pressure
4. Treat metabolic consequences

- Disease specific

1. Immunosuppressive therapy
2. Plasma exchange
3. Adequate treatment of infection to eliminate persistent presence of AG

Treatment of nephrotic edema

- Before the days of diuretics small tubes were inserted under the skin via needles and the patient stood in drum while fluid seeps out. Not very SATISFACTORY!



Treatment of nephrotic edema

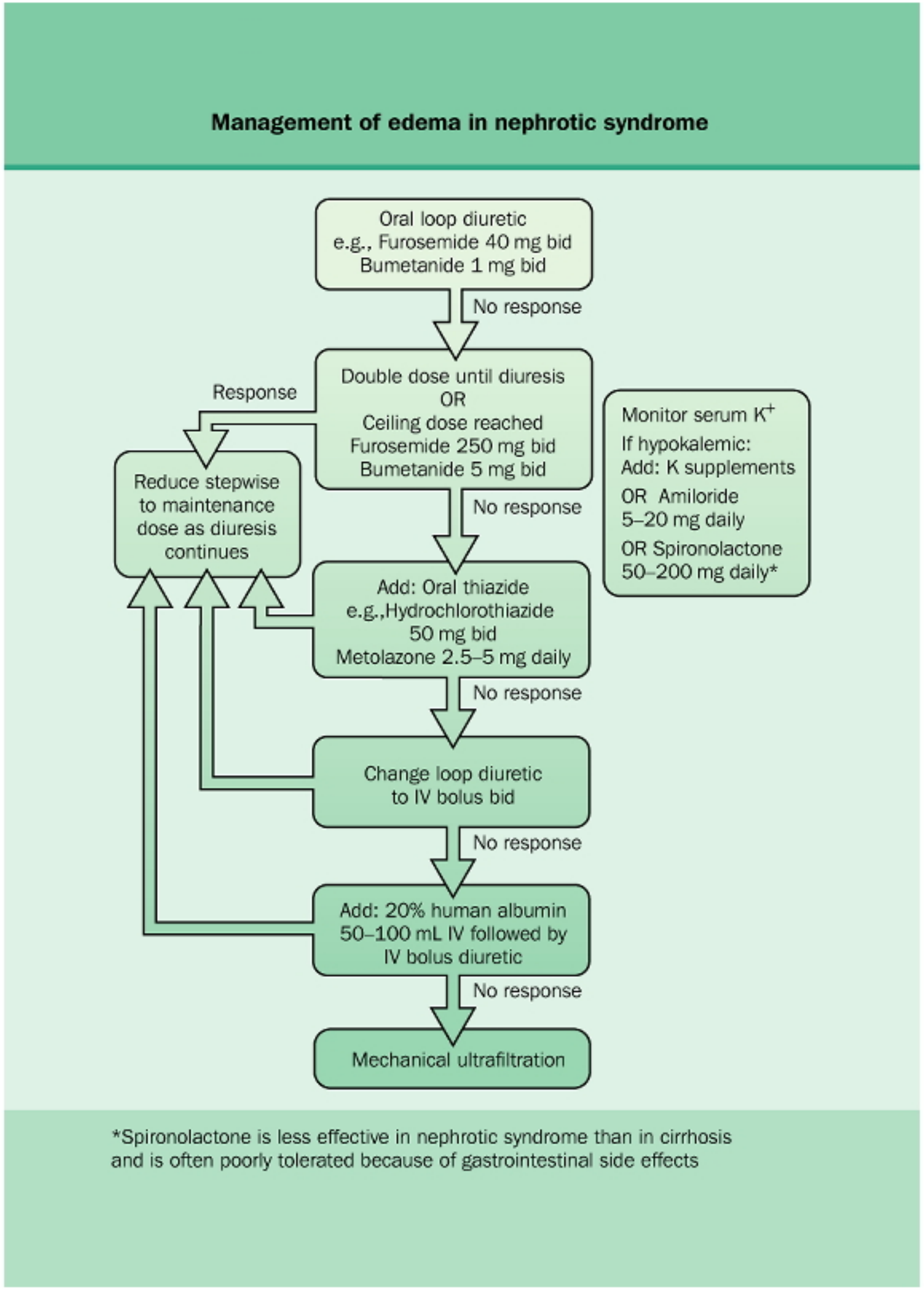
- MAINSTAY of treatment is moderate sodium restriction (60-80 mmol/24hrs) together with diuretics
- Hypovolemia usually not a problem provided fluid removal is gradual and controlled
- Weigh patient daily to measure progress
- Children – be cautious – more prone to hypovolemic shock

Treatment of nephrotic edema

- Nephrotic patients are resistant to diuretics:

1. Loop diuretics must reach tubuli to be effective
2. Transport from peritubular capillaries requires protein binding which is reduced in hypoalbuminemia
3. Once in renal tubuli 70% binds to protein in urine and is excreted and lost

- Oral diuretics are preferred – effect is dependent on AUC which is greater fro oral drugs
- In severe nephrosis reduced GIT absorption due to GIT edema – then rather IV infusion
- Remove </= 2kg/day – move on to next class of diuretic to achieve this goal


Management of edema in nephrotic syndrome
Oral loop diuretic e.g., Furosemide 40 mg bid Bumetanide 1 mg bid
No response
Double dose until diuresis OR Ceiling dose reached Furosemide 250 mg bid Bumetanide 5 mg bid
Response
Reduce stepwise to maintenance dose as diuresis continues
Monitor serum K+
If hypokalemic:
Add: K supplements
OR Amiloride 5–20 mg daily
OR Spironolactone 50–200 mg daily*
No response
Add: Oral thiazide e.g.,Hydrochlorothiazide 50 mg bid Metolazone 2.5–5 mg daily
No response
Change loop diuretic to IV bolus bid
No response
Add: 20% human albumin 50–100 mL IV followed by IV bolus diuretic
No response
Mechanical ultrafiltration
*Spironolactone is less effective in nephrotic syndrome than in cirrhosis and is often poorly tolerated because of gastrointestinal side effects

Treatment of proteinuria

- Benefits of reducing proteinuria:

1. If reduced below nephrotic range serum proteins normalize reversing metabolic consequences
2. Reduced renal impairment progression – ACE inhibition reduced intra-renal hypertension (seen in renal impairment)
3. Proteinuria is toxic to tubulo-interstitium
4. If proteinuria can be reduced with less toxic therapy less need for more disease specific treatment which could have other negative effects

Treatment of proteinuria

- Agents reducing proteinuria do so hemodynamically:

1. Reducing afferent arteriolar dilatation (NSAID's, low-protein diet, dipyridamole)
2. Blocking efferent arteriolar constriction (ACE, ARB, direct renin inhibitors)
3. ACE inhibitors also reduce increased glomerular capillary wall permeability

- This therapy reduce the GFR – reduction in GFR is however generally less than reduction in proteinuria

Treatment of proteinuria

- ACE-inhibitors most commonly used – reduce proteinuria 40-50%, esp. if patient on salt restricted diet
- Anti-Hpt drugs will reduce proteinuria in relation to drop in systolic BP but ACE/ARM's do so independently of BP
- ACE and ARB's have additive effect in reducing proteinuria (ON TARGET)

Treatment of proteinuria

- Therapy less commonly used:

1. NSAID's (reduce intra-renal PG synthesis – chemical nephrectomy)
2. Dipyridamole (adenosine mediated afferent arteriolar vasoconstriction)

- Caution: ACE and NSAID can cause severe drop in GFR with ARF. ACE – hyperkalemia, NSAIDS – salt retention and diuretic resistance.

Treatment of proteinuria

- Low protein diet will reduce proteinuria – caution – can induce malnutrition
- In rare cases where nephrotic syndrome is so severe that patinet is dying of it's complications one needs to resort to nephrectomy – usually chemically by NSAID/ACE. Reduce proteinuria by removing residual GFR.
- Bilateral renal artery embolization can be done if above not adequate.
- Bilateral nephrectomy – significant peri-operative mortality

Correction of hypo-proteinemia

- Difficult to increase protein intake to maintain positive protein balance – patients usually have anorexia and easy satiety due to gut edema and ascites
- Sustained high protein intake my be detrimental to renal function
- Low protein diet reduce proteinuria and my improve serum protein but take care to avoid malnutrition – YOU NEED A DIETICIAN EXPERINECED IN RENAL PATINET CARE.
- (0.8 – 1 mg/kg/d) with high carbohydrate intake to maximize protein utilization

Treatment of hypercoagulability

- Increased risk when albumin falls below 20
- Immobility and undercurrent illness aggravates the risk
- Analysis suggest benefit to anti-coagulate long term as long as albumin is below 20
- Anti-coagulate during hospitalization – prophylactic dosages
- Once thrombotic event occurs long term anti-coagulation for 6-12 months or longer should albumin not recover

Treatment of hypercoagulability

- Higher dosages of heparin may be needed – dependent on anti-thrombin III which is reduced in nephrotic syndrome
- Warfarin for long term anti-coagulation – careful – altered protein binding may reduce dose needed to achieve INR of 2-3
- Acute renal vain thrombosis may try thrombolytic therapy of embolectomy (surgical) – not convincing evidence that it improves renal survival long term

Treatment of hyperlipidemia

- Not direct evidence that nephrotic syndrome and hyperlipidemia increase CVS risk, extrapolation of evidence suggest benefit in treating hyperlipidemia
- Diet restriction only modest effect
- Statins reduce LDL and some may increase HDL and reduce Tgl
- Fibrates unacceptable myositis risk
- Bile acid sequestrants (cholestyramine) may lower LDL further and increase HDL but usually not tolerated due to GIT side affects
- Second line treatment = probucol, newer fibrates (closely monitor for muscle injury)
- Conventional dosing

Infection

- High index of suspicion
- Spontaneous bacterial peritonitis is common – ascites should be tested and cultured if suspicion of systemic infection
- Bacteremia is common even if signs are localized (cellulitis ex)
- ESR of little value (raised in Nephrotic syndrome)
- Raised CRP and PCT of value
- IV antibiotics stated as soon as cultures are taken (should include penicillin (pneumococci))
- With recurrent infections and IgG less than 600mg/dL – some proof to give monthly IV Ig 10-15g to keep levels > 600

Hypertension

- Common in GN
- Universal as chronic GN progress to end-stage renal disease
- Sodium and water retention NB and high-dose diuretic with dietary salt restriction is essential part of treatment
- Aim of treatment is to reduce CVS risk and renal disease progression
- MDRD study – patients with >1g proteinuria do better with BP <125/75
- ACE-inhibitors/ARB's = first choice
- Non-dihyropyridine calsium channel blockers also reduce proteinuria and BP

Disease specific therapy

General principles:

- Most glomerular diseases has immune pathogenesis – treatment aimed at suppressing systemic and local immune responses
- Where foreign antigen is ineffectively removed treatment aimed at eliminating it ex. IE (antibiotics), IF-alpha (cryoglobulinemia ass with Hep C)
- The more severe and acute the GN the more successful the immunosuppression
- Little success with chronic GN

Disease specific therapy

- With rapid deteriorating RF the toxicity of drugs acceptable for short period – “little to loose”
- Treatment is not specific and suppress immunity globally
- Mainstay of treatment:

1. Steroids
2. Azathioprine
3. Cyclophosphamide

Disease specific therapy

- Cyclosporine no proven place in GN but established in transplant
- Mycophenolate Mofetil newer anti-metabolite emerging as new agent in GN especially lupus
- Cancer risk with immunosuppression
- Time of exposure limited to as short as possible

That’s it