CLASSIFICATION OF RENAL DISEASE

The “Zwisus Christ, I can’t believe anyone would classify disease according to the physician who treats it” system for classifying renal disease:

1. Generalised parenchymal diseases
   a. Glomerular
      i. Congenital – congenital nephrotic, Alport’s syndrome
      ii. Immune/Inflammatory – glomerulonephritis, amyloidosis
      iii. Metabolic – diabetic glomerulosclerosis (diffuse and nodular)
   b. Tubulointerstitial
      i. Tubular transport abnormalities – congenital, acquired
      ii. Acute tubular necrosis – vascular, toxic
      iii. Interstitial nephritis – drugs, infection, urate, radiation, myeloma
   c. Vascular
      i. Hypertensive kidney disease – benign/malignant nephrosclerosis
      ii. Renal artery stenosis
      iii. Vasculitis
      iv. Disseminated intravascular coagulation

2. Acquired collecting system abnormalities
   a. Acute pyelonephritis
   b. Chronic pyelonephritis – reflux/obstructive nephropathy
   c. Nephrolithiasis, hydronephrosis

3. Focal lesions
   a. Infarcts, abscesses, scars, cysts (simple, parasitic, neoplastic)
   b. Tumours – Wilm’s (nephroblastoma), RCC, TCC

4. Congenital structural lesions
   a. Agenesis and hypoplasia
   b. Anomalous position, ureters, vessels
   c. Cystic diseases – renal dysplasia, polycystic kidney, medullar cystic disease

5. End stage kidney

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GENERALISED PARENCHYMAL DISEASES – CLINICAL ASPECTS

*Pathophysiology of Renal Clinical Manifestations*

Note that glomerular filtration rate (total amount of fluid filtered through all functional glomeruli) is the most important measure of renal function. Under normal conditions more than 98% of the glomerular filtrate is resorbed by the tubular system, so urine output does not reflect GFR.

1. **Extrarenal causes** – prerenal (e.g. heart failure) and post-renal (e.g. carcinoma of the cervix)
2. **Blocked filter (renal insufficiency)**
   a. Arterial blockage
      i. Main renal artery → decreased blood flow to glomeruli and decreased GFR – if severe and chronic, this leads to tubular atrophy
         1. Bilateral – hypertensive effects results in decreased renal function
         2. Unilateral – ischaemia of JGA releases renin (RAAS) causing hypertensive changes in the non-affected kidney
ii. Small vessel diseases are nearly always diffuse and bilateral

b. **Glomerular blockage**
   i. Reversible blockage occurs in types of acute glomerulonephritis
      1. Mechanisms – endothelial swelling, cell proliferation, inflammatory exudates, thrombosis, crescent formation
   ii. Permanent blockage – glomerulosclerosis
      1. Organisation of acute inflammatory/thrombotic lesions
      2. Accumulation of material in mesangium/GBM – nodular diabetic glomerulosclerosis, amyloidosis

c. **Tubulointerstitial blockage**
   i. Reversible blockage – acute tubular necrosis, acute interstitial nephritis, intratubular precipitates (uric acid, light chains in myeloma)
   ii. Permanent blockage – tubular atrophy (after interstitial fibrosis)
      1. Tubular atrophy, interstitial fibrosis and glomerulosclerosis are hallmarks of permanent parenchymal damage

3. **Leaky filter**
   a. Haematuria and proteinuria
      i. Haematuria does not necessarily imply glomerular disease except in younger patients or where other manifestations are present
         1. Leakage of RBCs from glomeruli indicates a lesion in the GBM sufficient to allow RBCs to pass through
      ii. Proteinuria almost always implies diffuse parenchymal disease
         1. Normally the glomerulus passes a small amount of protein which is resorbed by the proximal tubule
         2. Tubulointerstitial diseases fail to resorb this (<1g/day)
         3. Immunofluorescence shows extensive loss of heparin sulphate proteoglycan (poylanion which repels albumin)
      iii. Haematuria and proteinuria correlate fairly closely with inflammatory glomerular diseases and non-inflammatory glomerular diseases – a combination of the two is associated with renal insufficiency
   b. Failure of tubular absorption
      i. Generally causes little human disease, but may be important in mediating polyuria with salt wasting and fluid depletion
      ii. Causes include:
         1. Congenital tubular transport abnormalities
         2. Recovery phase of acute tubular necrosis – regenerated tubular cells are immature and incapable of proper function
         3. Chronic failure with interstitial fibrosis obstructing movement of fluid and decreasing the number of functional nephrons

4. **Blockage and leakage occurring together**
   a. Acute nephritic syndrome includes renal insufficiency plus haematuria with varying degrees of proteinuria.
      i. This may be due to partial obstruction of glomeruli, with leakage of blood/protein from inflammatory activity
      ii. Proteinuria may be sufficient to cause the nephrotic syndrome
   b. Renal failure with polyuria cannot be explained on the basis of each nephron responding the same way – while a large number of nephrons have been inactivated, there must be other nephrons that are excessively leaky

- **Assessment of Renal Function**

  **Serum markers**
  1. **Serum creatinine** (0.06-0.12 mmol/L)
     a. Creatinine is produced by non-enzymatic dehydration of muscle (about 2% of total pool turned over daily). Total daily production reflects muscle mass, and dietary creatinine is usually <1% of the body pool.
     b. At normal GFR, small changes in serum creatinine may be indicative of large GFR changes (the opposite for renal failure)
     c. Creatinine clearance is more sensitive to problems at low serum creatinine
  2. **Serum urea** (3.2-7.7mmol/L)
Renal

- Elevated by dehydration, low urine flow rate (tubular resorption), protein catabolism (starvation, trauma) and high dietary protein loads
- Not reliable on its own as a measure of renal function, but in the steady state on a fairly constant diet it is reasonably sensitive measurement
- Note BUN (blood urea nitrogen) converts to mmol/L by multiplying by 0.357

**Glomerular filtration rate and creatinine clearance** (1.4-2.5ml/s; 84-150mL/min)

1. Although inulin clearance is the gold standard for estimating GFR, it is more practical to measure creatinine clearance (though this overestimates due to tubular secretion)
   - Radionuclides can be used (e.g. 51 Chromium EDTA) – plasma decay curve
   - $C_{Cr}$ declines with age, and needs a blood sample and 24hr urine (usually estimated)
     1. $C_{Cr} = \frac{\text{Urine creatinine}}{\text{serum creatinine}}$
     2. Cockcroft-Gault formula: $C_{Cr} = \frac{(140 - \text{age}) \times \text{weight} \text{[kg]}}{50,000 \times \text{serum Cr} \text{[mmol/L]}}$
        Multiply by 0.85 for females
        For mL/min use 815 instead of 50,000
     3. Drug pharmacodynamics: $C_{Cr} \text{[L/hr/70kg]} = \frac{160 - \text{age} \text{[yr]}}{250 \times \text{serum Cr} \text{[mmol/L]}}$

**Other tests:**

1. Renal plasma flow
   - Can be measured using clearance of para aminohipurate or using scintigraphy
   - Clinical use limited to renovascular disease e.g. renal artery stenosis, transplant
2. Renal concentrating ability – urine osmolarity (60-1200mOsm/kg depending on hydration)
   - Note that urine osmolarity tends to decrease with age >65yrs → oliguria, nocturia
   - Used clinically if a tubulointerstitial disease is suspected e.g. diabetes mellitus

**Urine examination:**

1. **Protein** – dipsticks, 24hr protein (<200mg/day), functional proteinuria (orthostatic)
   - Albumin : creatinine should be <2.5 in normal patients
   - Microalbuminuria not used in renal disease except for diabetes mellitus
2. **Cells** – RBCs (and dysmorphic RBCs), white cells, epithelial cells
3. **Casts** – cellular (RBC, WBC), granular, hyaline, broad
4. **Others** – crystals, bacteria (acid-fast culture), cytology

**Organ imaging** – basic is USS and plain X-ray if stones suspected

1. **Renal ultrasound** – non-invasive, accurate size/position, good for obstruction and masses
2. **IV urogram** – useful for showing anatomy of bladder, ureter and collecting system
3. **Renal scintiscan** – RBF, GFR, urine excretion including post-operative leaks
4. **Arteriography** – necessary to show the arterial tree (digital subtraction – less contrast)
5. **CT scanning** – complementary to IVU/USS, useful for tumours and calculi
6. **Anterograde/retrograde pyelograms** – high density shadows for renal pelvis, ureter, bladder
7. **Micturating cystourethograms** – vesicoureteric reflux, bladder and urethral problems

• **Acute Renal Failure**

**Acute renal failure** is characterised by a rapid decrease in renal function, commonly with anuria (urine output <100mL/day) or oliguria (urine output <400mL/day) but normal or increased urine output may occur. It is a dramatic clinical syndrome with a wide variety of serious and potentially lethal complications, and is one of the few forms of major organ failure that is potentially reversible.

**Pre-renal acute renal failure** is characterised by no renal parenchymal damage. The kidneys function appropriately in a pathological environment (e.g. decreased RBF), and removal of the pathology results in a return to normal renal function.

1. **Aetiology:**
   - Hypovolaemia 2° to volume loss (haemorrhage, burns, renal/GI fluid loss)
   - Diminished RBF 2° to cardiac pump failure (i.e. 1° cardiac disease)
   - Liver failure (renal vasoconstriction ± RBF), septicaemia (systemic vasodilation)
2. **Pathophysiology:**
   - Volume receptors at cardiac, arterial and CNS sites → effector mechanisms
     i. Humoral – RAAS, catecholamines, prostaglandins, ANP, ADH

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Renal

ii. Neural – renal autonomic nervous system
iii. Intrinsic – afferent arteriolar myogenic reflex

b. Renal response:
   i. Increased proximal tubular Na⁺/H₂O reabsorption (2° to increased filtration fraction → increased peritubular oncotic pressure)
   ii. Increased distal Na⁺ reabsorption (2° to increased aldosterone levels)
   iii. Increased collecting tubule free H₂O reabsorption (2° to decreased medullary blood flow, sow distal tubule flow and increased ADH)
   iv. Probably redistribution of RBF towards salt-avid juxtamedullary nephrons

3. Clinical features – orthostatic hypotension, cool peripheries, low JVP, granular casts ± RBCs
4. Biochemistry reflects salt-poor, low volume, concentrated urine
   a. Urine Na⁺ <20mmol/L (usually <10mmol/L)
   b. Fractional excretion Na⁺ <1%
   c. Urine/Plasma osmolality >1.2, Urine/Plasma creatinine >40
5. Treatment:
   a. Aggressive volume replacement (0.9% NaCl)
   b. Monitor urine output, clinical state, biochemical indices
   c. ATN prevented → renal function restored

Intrinsic renal disease:

1. Acute tubular necrosis
   a. Aetiology:
      i. Ischaemia – major reduction in RBC, usually prolonged but may be brief
      ii. Nephrotoxins – drugs (aminoglycosides, amphotericin B), rhabdomyolysis, haemolysis, contrast agents, heavy metals
   
   b. Pathophysiology and clinical features
      i. Tubular damage → tubular obstruction → leaky tubules
         1. Decreased RBF, decreased glomerular filtration coefficient (Kᵢ)
         2. Decreased filtration fraction, GFR → loss of tubular function
      ii. Oliguria in 25% (usually within 24 hours but may take days, lasts 1-2 weeks)
      iii. Return of renal function takes weeks to months:
         1. Recovery characterised by daily doubling of urine output
         2. Residual ↓GFR and concentration/acidification defects

   c. Prognosis:
      i. Mortality 50% overall – high with burns, multi-organ failure and sepsis; low with obstetric-related and aminoglycoside toxicity
      ii. Death generally caused by septicaemia and/or haemorrhage

   d. Biochemical features:
      i. Urine Na⁺ >40mmol/L
      ii. Fractional excretion Na⁺ >1.0 (most sensitive/specific test for ATN)
      iii. Urine/Plasma osmolality = 1.0, Urine/Plasma creatinine 10-20
   
   e. Treatment:
      i. Maintain fluid and electrolyte balance, dialyse as indicated
      ii. Maintain nutrition –may need parenteral feeding
      iii. Modify drug regimen, prevent and treat infection

2. Acute glomerulonephritis (see glomerulonephritis lecture)
   a. Biochemistry similar to pre-renal picture
   b. Sediment – active, red cells, granular/red cell casts

3. Acute interstitial nephritis (see lecture on tubulo-interstitial nephritis)
   a. Urine biochemistry similar to ATN
   b. Sediment – eosinophils, red blood cells

4. Vasculopathies
   a. Large vessels (e.g. renal emboli) similar to pre-renal
   b. Small vessels (e.g. vasculitis) similar to glomerulonephritis

Post-renal acute renal failure:

1. Aetiology – ureteric calculi, sloughed papillae, neoplastic disease, retroperitoneal fibrosis, lower urinary tract trauma or surgery
2. Clinical features:
   a. Polyuric, anuric, viable high/low urinary output
Renal

b. Clinical examination and suggestive history – e.g. stones, neoplastic disease
c. Renal ultrasound → dilated collecting system, ureter or residual urine
d. Urine sediment → red cells and/or granular cells

3. Treatment – remove obstruction, fluid replacement if post-obstructive diuresis

- Chronic Renal Failure

Chronic renal failure is characterised slowly progressive and non-reversible loss of renal function that may be excretory, homeostatic and endocrine. It usually results in uraemia (end-stage renal disease) which requires renal replacement treatment.

1. Major causes (2000 transplant data) include:
   a. Diabetes (40%)
   b. Glomerulonephritis (23%)
   c. Hypertensive nephrosclerosis (11%)
   d. Polycystic kidney disease (7%)
   e. Reflux nephropathy (3%)
   f. Analgesic nephropathy (<1%)
   g. Other – obstruction, calculi, systemic disease, idiopathic (7%)

2. Symptoms – note that many are asymptomatic with no signs until 2/3 of renal mass lost
   a. Progressive lethargy, anorexia and vomiting
   b. Hypertension and/or heat failure
   c. Anaemia
   d. Routine examination → hypertension, proteinuria, deranged biochemistry

Consequences of renal impairment:

1. Bone disease – 2° hyperparathyroidism (2° to low Ca\(^{++}\)), osteomalacia (↓1-25 OH-Vitamin D), both (renal osteodystrophy), adynamic bone disease, aluminium toxicity
   a. Treatment – phosphate binders, 1-25 OH-Vitamin D, parathyroidectomy, dialysis

2. Blood - anaemia (↓EPO), poor platelet function → bleeding
   a. Treatment – EPO, iron replacement

3. Endocrine – 2° hyperparathyroidism and low vitamin D, lowered testosterone, increased LH and prolactin, raised renin (5%), abnormal growth hormone cycles

4. Electrolytes and water balance – urine diluting/concentrating ability deranged (retention or excessive loss), acidosis, hyperkalaemia
   a. Judge fluid status by weight, JVP, BP and oedema
   b. Reduce K\(^+\) in diet and reconsider polypharmacy
   c. Citrates and bicarbonate

5. Other organ systems:
   a. Cardiovascular – hypertension, heart failure, pericarditis
   b. Gastrointestinal – anorexia, nausea and vomiting (urea), diarrhoea, uraemic fetor, oesophagitis and angiodysplasia more common
   c. Dermatological – pallor, pigmentation, pruritus, ecchymoses
   d. Neurological – fatigue, headache, lethargy, peripheral neuropathy, ‘restless leg syndrome’, terminal phase → stupor, coma, fits
   e. Psychological – depression, anxiety

Conservative management of renal failure:

1. Hypertension – target 130/80mmHg (note – no agent reduces intraglomerular pressure)
   a. ACE inhibitors first line
   b. Long-acting Ca\(^{++}\) channel blockers or loop diuretics second line
   c. β-blockers, α-blockers and thiazides are third line

2. Diet – adequate calories with reduced protein and fat (in line with cardiovascular guidelines)
   a. Protein restriction has minimal effects – reduces glomerular Hyperfiltration, BP, proteinuria, hyperlipidaemia, phosphate intake, hyperparathyroidism and acidosis
   b. Reduce total fat to <30% total energy intake and limit SFA to <10%

3. Hyperlipidaemia – similar to cardiovascular disease, animal models suggest → progression
   a. In nephrotic patients, HMG-CoA reductase inhibitors reduce cholesterol and triglyceride concentrations but show no benefit for renal function or proteinuria
   b. Fibrates may have adverse effects on renal function unless dose is reduced

4. Calcium and phosphate – prevent bone disease, but beware extraosseous calcification
   a. Some phosphate restriction achieved through decreased by dietary restriction
Renal

b. Monitor serum albumin, calcium (keep <5.5), phosphate and PTH:
   i. If serum calcium low, phosphate high \( \rightarrow \) CaCO\(_3\) 0.5-1.5 tds with meals
   ii. If PTH >20pmol/L, calcium/phosphate controlled \( \rightarrow \) calcitriol 0.25\( \mu \)g od

c. Adynamic bone disease – normal PTH, tendency to hypercalcaemia with vitamin D and calcium salts. May need Mg\(^{2+}\) and Al\(^{3+}\) salts may be needed to control phosphate

5. Anaemia
   a. EPO may have a role predialysis in severely symptomatic patients if blood pressure control is satisfactory
   b. May also be useful in patients with substantial co-morbidities that preclude dialysis

6. Metabolic acidosis and increased ammonium – administration of alkali in severe acidosis
   a. Excessive Na\(^+\) loading \( \rightarrow \) increased BP
   b. Sodium citrate increases aluminium absorption and should not be used with Al\(^{3+}\) salts

7. Nephrologist referral – refer all patients approaching end-stage renal failure (plasma creatinine 0.6-0.8mmol/L) 6-12 months pre-dialysis for treatment options and education

• Renal Replacement Therapy

Advanced chronic renal failure is characterised by accumulation of metabolic waste products, electrolyte and volume changes, and loss of endocrine and metabolic functions. Indications for renal replacement therapy include:

1. Signs and symptoms of uraemia
2. Change in nutritional status
3. Clearance criteria
4. Others – multicentre studies being done on early intervention (IDEAL study)

Dialysis provides treatment for waste product accumulation and fluid/electrolyte changes:

1. Haemodialysis involves an artificial kidney with passive diffusion of solutes across a membrane (high \( \rightarrow \) low concentration) and ultrafiltration of fluid (via pressure gradient)
   a. Intermittent therapy, usually 3 times a week for 4-5 hours (2-4L fluid removed)
   b. Blood is pumped from a preformed vascular access (large-bore cannula, artificial grafts or AV fistula) through the dialyser at 200-400mL/min then reinfused
   c. Blood and dialysate runs through a series of filters, and waste products diffuses across into the dialysate (similar composition to plasma)
   d. Patients encouraged to learn home haemodialysis (lower costs, less dependence)

2. Peritoneal dialysis uses native peritoneum with concentration gradients \( \rightarrow \) solute transfer
   a. ‘Continuous ambulatory’ – usually 4-5 times a day every day
   b. Dialysate is drained into the peritoneal space via a permanent soft silicone cuffed catheter, allowed to dwell for 4-8 hours before being drained and replaced
   c. Waste solute moves down a concentration gradient from the peritoneal circulation, acetate replaces base and dextrose induces H\(_2\)O removal (corrects volume overload)

3. Limitations of dialysis:
   a. At best, only provides up to 10% of native glomerular filtration (peritoneal > haemo), though this is sufficient for controlling uremic syndrome, appetite and nausea.
   b. Haemodialysis complications include headache, nausea, symptomatic hypotension, persistent bleeding, blocked vascular access and infection \( \rightarrow \) abscess, sepsis
   c. Peritoneal dialysis complications include exit site infection and peritonitis, obstruction, hernias, peritoneal fluid leaks and membrane changes (ultrafiltration failure)
   d. Diet and electrolyte balance should be monitored

Renal transplant is the most effective and cost-effective form of renal replacement therapy using a healthy donor kidney (living donor or brain-dead cadaver) matched for blood group and HLA.

1. Transplant operation takes 2-3 hours with 7-10 day hospital stay for the recipient
   a. 10-30% get acute tubular necrosis – dialysis until resolved (1-6 weeks)
   b. Most get massive polyuria (10-20L/day), settles as urea and creatinine decrease

2. Pharmacotherapy involves immunosuppressive agents (azathioprine and cyclosporin A), antimicrobials and antihypertensives.
   a. Cotrimoxazole (pneumocystic pneumonia), fungilin (candidiasis), acyclovir (herpetic ulceration) and famotidine (gastric ulceration) usually only used for first 4-6 weeks

3. Complications include wound infection, rejection \( \rightarrow \) stronger therapy, increased risk of skin cancer \( \sim \)50% incidence 15-years post-transplant

4. Prognosis – 5-year survival is \sim 70% for 20-54 year olds, \sim 20% for older patients (
Renal

- Lower with diabetes – 20% for 20-54 year olds, 10% for older patients
- Comorbid cardiovascular or neoplastic disease also reduce prognosis

Costs:
1. Central haemodialysis – >$50,000 per annum
2. Peritoneal dialysis or home haemodialysis – $20,000-30,000 per annum
3. Renal transplant - $70,000 in year one, $10,000-15,000 subsequently

**GENERALISED PARENCHYMAL DISEASE – SYNDROMES AND DISEASES**

The term *glomerulonephritis* is used to describe glomerular diseases associated with inflammation, although often it is used for all glomerular diseases (‘non-inflammatory glomerulopathies’ is better). These diseases are classified by clinical features, morphology (light, electron and immunofluorescent microscopy), pathogenesis and aetiology; but can also be divided into 1° and 2° disorders.

Glomerular diseases produce various combinations of proteinuria, haematuria, reduced glomerular filtration and alterations in sodium excretion leading to oedema and hypertension. The major clinical syndromes are:

1. **Acute nephritic syndrome** – haematuria, oliguria, ↓GFR, Na⁺ retention and hypertension
2. **Nephrotic syndrome** – proteinuria, hypoalbuminaemia, oedema, hypercholesterolaemia
3. **Persistent urinary abnormalities with few or no symptoms** is used for mild or moderate proteinuria (<3g/24h) ± haematuria but no other symptoms or signs
4. **Chronic glomerulonephritis** – progressive renal failure (proteinuria, haematuria, hypertension)
   - Presence of haematuria suggests glomerular aetiology, although only proteinuria may be found if there is 2° focal segmental glomerulosclerosis (Hyperfiltration injury)
   - Imaging shows small but not scarred kidneys (c.f. chronic pyelonephritis)

**Acute Nephritic Syndrome**

**Acute nephritic syndrome** is characterised by sudden onset acute renal failure with oliguria 2° to ECF volume expansion, oedema and hypertension (impaired GFR and enhanced tubular reabsorption of salt and water). Glomerular capillary wall damage also leads to characteristic urinalysis with RBC casts, dysmorphic RBCs, leukocytes and subnephrotic proteinuria. Typical clinical features include:

1. **Haematuria** – constant, usually macroscopic with pink or brown smoky urine
2. **Oliguria** – may be overlooked or absent in milder cases
3. **Proteinuria** – usually mild or moderate but may be massive → ‘mixed nephritic-nephrotic’
4. **Oedema** – usually mild, often just periorbital or with some non-specific weight gain
5. **Hypertension** – common (even if no oliguria/oedema) with raised urea and creatinine

**Aetiology:**

1. **Post-streptococcal glomerulonephritis** is the most common cause
   - Peak age incidence 6 years, uncommon under 2 years, M>F
   - Follows skin/throat infection with certain strains of Group A β-haemolytic *S. pyogenes*
2. Henoch-Schonlein purpura
3. Crescentic glomerulonephritis (rapidly progressive)
4. **Other** - Alport’s syndrome, diffuse proliferative GN, membranoproliferative GN, Goodpasture’s syndrome (anti-GBM), haemolytic uraemic syndrome, IgA nephropathy, vasculitis

**Management:**

1. **Investigations** – urinalysis, U&Es, creatinine, skin/throat swab, streptococcal serology, CXR
2. **Observations** – temperature, HR, RR, BP, urine output, daily weight
3. **Treatment:**
   - Treat significant hypertension
   - Restrict fluid intake (restrict K⁺ and protein in severe renal failure)
   - Treat streptococcal infection with penicillin
   - Diuretics e.g. frusemide occasionally useful to treat fluid overload and hypertension
4. **Prognosis** depends on the cause – post-streptococcal glomerulonephritis rarely progresses to chronic renal diseases in children (uncommonly in adults), otherwise prognosis α severity

**Complications:**

1. **Hypertensive encephalopathy** – seizures, coma, permanent neurological deficits, death
Renal

2. Heart failure – associated with massive pulmonary oedema needing assisted ventilation
3. Severe renal failure (requiring dialysis) – uncommon, may recover after dialysis

- Nephrotic Syndrome

Nephrotic syndrome is a group of symptoms and signs seen in patients with severe proteinuria – note that other manifestations are secondary to urine protein loss and can occur with lesser degrees of proteinuria, or may be absent in patients with massive proteinuria. It is defined as:

1. General oedema
2. Proteinuria >3.5 g/day in adults, >0.05 g/kg/day in children
3. Serum albumin <30 g/L

Pathophysiology:
1. Proteinuria (normal <150mg/day) – diffuse increase in glomerular permeability, often immune
2. Hypoalbuminaemia – loss exceeds liver’s ability to synthesise albumin (12-14 g/day)
3. Oedema – mechanism complex and in dispute, but in general:
   a. Underfill theory – lowered oncotic pressure → oedema (e.g. minimal change)
   b. Overflow theory – normal plasma volume with primary renal salt/water retention
4. Hyperlipidaemia – raised serum cholesterol and triglycerides 2° to hepatic synthesis
5. Hypercoagulation – hypovolaemia, loss of antithrombin III in urine, raised fibrinogen synthesis

Aetiology:
1. Glomerular disease – membranoproliferative GN, proliferative GN, minimal change disease, focal segmental glomerulosclerosis, membranous glomerulopathy
2. Systemic disease – diabetes, amyloidosis, SLE, other collagen diseases, HIV
3. Nephrotoxins – gold salts, penicillamine, mercury poisoning, IV drug abuse, NSAIDs
4. Allergies – bee stings, pollens, poison ivy
5. Cardiovascular – CHF, constrictive pericarditis, renal vein thrombosis (may be 2° to NS)
6. Neoplastic – leukaemia, lymphoma, solid tumours

Management:
1. Investigations to assess:
   a. Severity of nephrotic syndrome
   b. Severity of renal failure
   c. Specific disease responsible
   d. Underlying renal pathology (renal biopsy)
2. Treatment:
   a. Fluid and electrolyte balance:
      i. Na⁺ restriction (<60mmol/day, 1/3 of normal)
      ii. Water restriction
      iii. Diuretics if not volume depleted (frusemide ± amiloride, thiazides)
   b. Protein balance:
      i. Adequate dietary protein
      ii. IV albumin
   c. Specific therapy:
      i. Corticosteroids – minimal change, focal segmental glomerulosclerosis
      ii. Immunosuppressive drugs – combination of cyclophosphamide, chlorambucil and cyclosporin A (± corticosteroids)
3. Complications include infections and thrombosis
4. Prognosis varies by histological classification

- Investigation of Proteinuria

Proteinuria (± nephrotic syndrome) is usually evidence of significant renal disease and hence needs logical investigation.
1. Normally 50-150 mg/day is excreted consisting of mainly Tamm-Horsfall glycoprotein derived from cells in the loop of Henle (plus some serum protein).
2. Large amounts of protein are usually the result of abnormality in the glomerular filtration barrier, but modest proteinuria may be associated with tubular injury or glomerulonephritis
3. Proteinuria may only be present when the patient is upright (orthostatic proteinuria) – usually <1.5 g/day, associated with minor renal disease and good prognosis
Renal

The renal glomerulus responds to injury by decreased filtration, increased permeability to plasma proteins, by inflammatory changes or a combination of these. **Investigations** (particularly serum creatinine or creatinine clearance) and history/examination allows us to narrow the differential:

1. Red cell casts in the urine indicate haematuria of glomerular or tubular origin, and urine with many cells are said to have an ‘active sediment’ particularly if casts are also present
2. Renal function tests, quantitation of proteinuria and USS/IV urography are critical:
   a. Proteinuria >3 g/24h with active urine sediment, red cell casts → GN
   b. Abnormal renal architecture, pyuria, proteinuria 1-2 g/24h → interstitial disease
3. Renal biopsy is indicated in:
   a. Nephrotic syndrome in adults
   b. Steroid-resistant nephrotic syndrome in children
   c. Persistent proteinuria/haematuria and proteinuria of connective tissue disease

- **Pathology of Glomerular Diseases**

  **Pathogenesis of glomerular injury:**

  1. **Immune**
     a. Antibody to GBM component – anti-GBM disease
     b. Trapping antigen, fixing antibody – membranous GN
     c. Trapping immune complexes – SLE
     d. Trapping antibody complexes – IgA nephropathy
     e. T-cell or cytokine mediated – minimal change disease

  2. **Non-immune**
     a. Congenital abnormality in GBM components – Alport's nephropathy
     b. Metabolic change in GBM components – diabetes
     c. Trapping abnormal materials – amyloidosis
     d. Hyperfiltration injury – secondary FSGS

  **Progressive renal injury:**

  1. Continued disease activity – persistence of immune complexes e.g. SLE
  2. Hypertension – worsens itself, leading to more damage to vessels
  3. Hyperfiltration injury – nephrons cannot regenerate, so functional nephrons have an increase GFR but eventually become leaky, deranged or blocked (focal segmental glomerulosclerosis)
     a. Greater chance of getting renal failure with nephrectomy
     b. ACE inhibitors can save renal function, as decreased efferent pressure → decreased glomerular pressure → decreased GFR