KENYA MEDICAL TRAINING COLLEGE NAKURU

RENAL MEDICINE

BY

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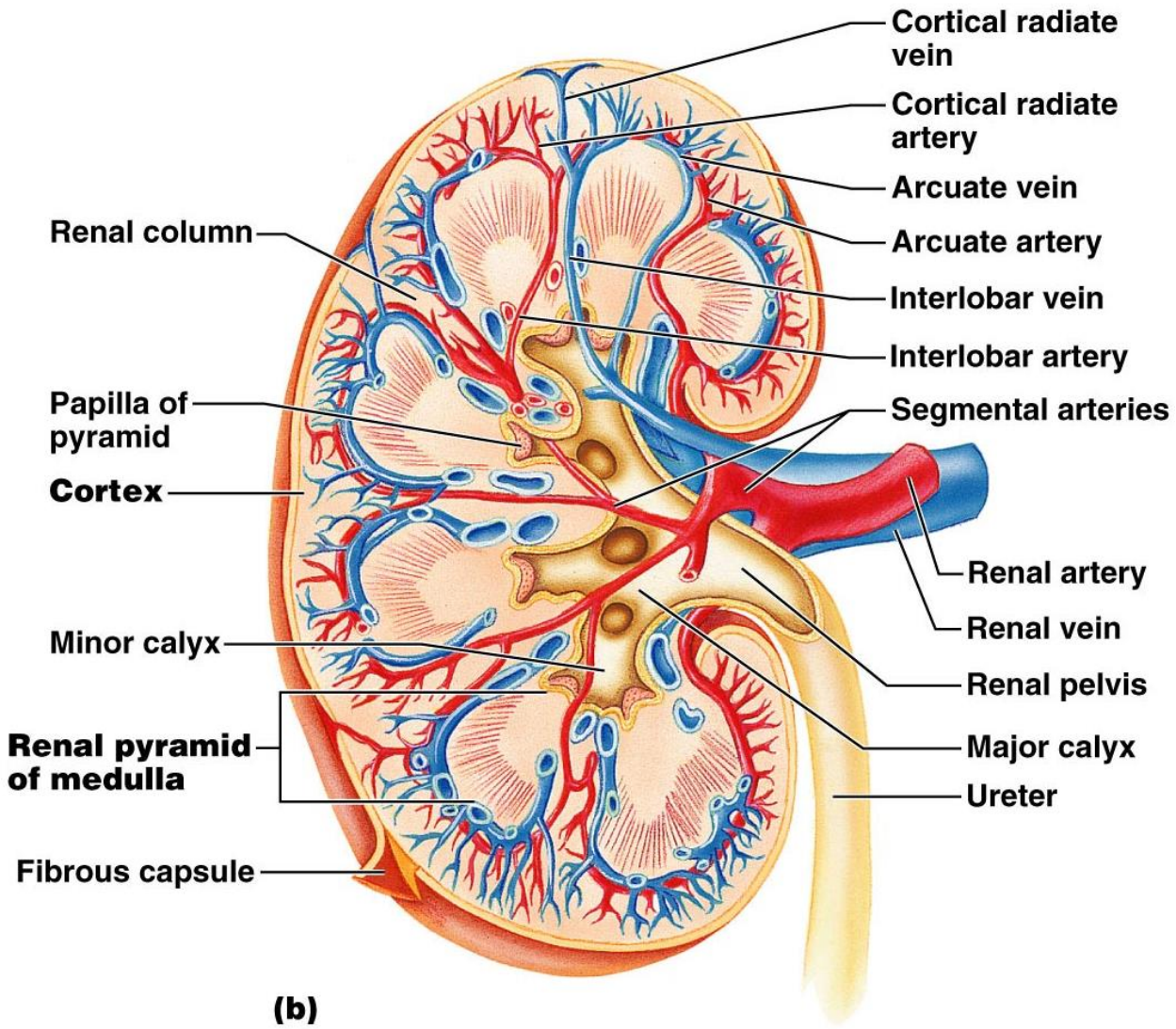
FIRST EDITION

ANATOMY

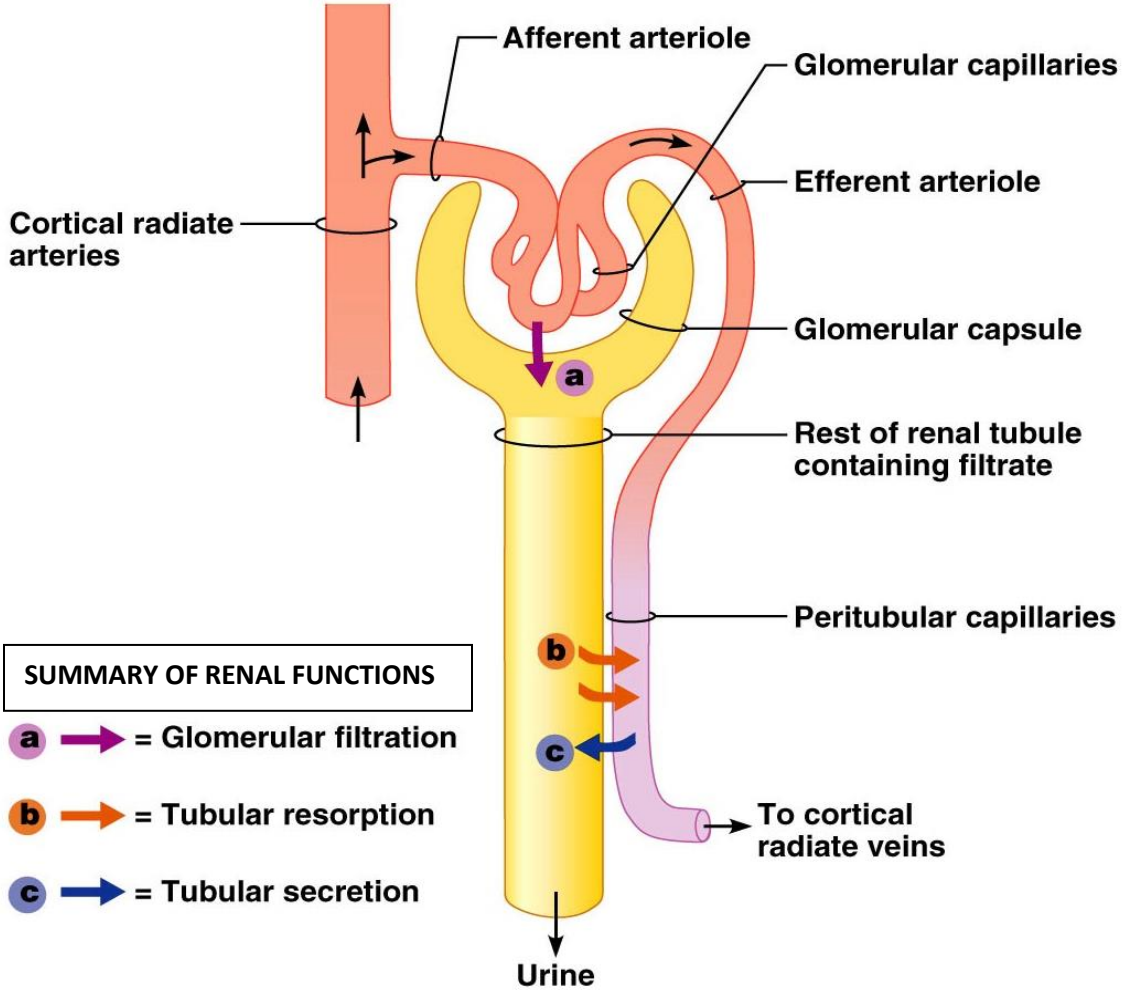


The kidneys perform a variety of important functions:

1. They regulate the osmotic pressure (osmolality) of the body fluids by excreting osmotically dilute or concentrated urine.
2. They regulate the concentrations of numerous ions in blood plasma, including Na^+, K^+, Ca^{2+}, Mg^{2+}, Cl^-, bicarbonate (HCO_3^-), phosphate, and sulfate.
3. They play an essential role in acid base balance by excreting H^+ when there is excess acid or HCO_3^- when there is excess base.
4. They regulate the volume of the ECF by controlling Na^+ and water excretion.
5. They help regulate arterial blood pressure by adjusting Na^+ excretion and producing various substances (e.g., renin) that can affect blood pressure.
6. They eliminate the waste products of metabolism, including urea (the main nitrogen-

containing end product of protein metabolism in humans), uric acid (an end product of purine metabolism), and creatinine (an end product of muscle metabolism), bilirubin (end product of hemoglobin degradation)

7. They remove many drugs (e.g., penicillin) and foreign or toxic compounds.
8. They are the major sites of production of certain hormones, including erythropoietin and 1, 25-dihydroxy vitamin D_3 , thrombopoietin
9. They degrade several polypeptide hormones, including insulin, glucagon, and parathyroid hormone.
10. They synthesize ammonia, which plays a role in acid base balance.
11. They synthesize substances that affect renal blood flow and Na^+ excretion, including arachidonic acid derivatives (prostaglandins, thromboxane A_2) and kallikrein (a proteolytic enzyme that results in the production of kinins).



Approach to a patient with a genito urinary problem.

1. History

- Change in appearance of urine e.g. blood in urine (Haematuria) or change in urine volume or stream
    - Polyuria
    - Nocturia
    - Anuria
    - Decrease in urine stream
    - Hesitancy
    - Dribbling
    - Strangury
    - Urine retention or incontinence
- Dysuria, frequency, urgency
- Loin pain – R/o renal infection, renal infarction
- Renal / ureteric colic – May be due to renal pelvis / ureteric calculi or blood clot. Pain often radiates to the iliac fossa, groin and genitalia.
- Urethral discharge
- Fever / hotness of the body
- Scrotal swelling
- Leg swelling
- Others- Anorexia, vomiting, fatigue, hiccup, insomnia especially in chronic renal failure.
- Genital rash, impotence, ↓ libido
- Drugs; Steroids, immunosuppresants, fluid or salt restriction, use of NSAIDS which can worsen an already existing renal function,
- Past medical histroy; previous episodes, recurrent UTI, renal calculi. History of DM, HTN, childhood enuresis,vascular diseases like MI or CVA.
- Family history; Polycytic kidneys, DM, HTN.

NB. Causes of polyuria are;

- Excess fluid intake
- Osmotic, e.g. hyperglycaemia, hypercalcaemia
- Cranial diabetes insipidus (reduced antidiuretic hormone (ADH) secretion)
    - Idiopathic (50%), mass lesion, trauma, infection
- Nephrogenic diabetes insipidus (tubular dysfunction)
    - Genetic tubular defects
    - Drugs/toxins, e.g. lithium, diuretics
    - Interstitial renal disease
    - Hypokalaemia, hypercalcaemia

2. **On examination**

- General - Pallor, fatigued patient, brown line pigmentation of nails, hyperventilation, hicupping, ammoniacal fish breath, a dirty brown appearance or yellow complexion, reduced skin turgor due to dehydration, ankle oedema.
- Hands – Leuconychia
  -Muehrcke's nails (paired white transverse lines near the end of nails (R/o nephrotic syndrome).
  -Mee's lines – Single transverse white bands in the nails (R/o Arsenic poisoning, renal failure)
  - Beau's lines; non pigmented indented transerve bands in nails.
  -Asterixis
  -Pallor
- Vital signs
  -BP, temperature,RR and depth

Systemic examination:

P/A – Tenckhoff catheter

- Scars - dialysis, surgery, ascites
- Enlarged kidneys, transplanted kidney, ballotment
- Local lumbar tenderness
- Renal or other arterial bruit
- Examine the liver for hepatomegally
- DRE- Prostate, frozen pelvis etc

R/S – Hyperventilation, crepitations
CVS – JVP, Heaving apex, pulmonary oedema, extra –heart sounds, pericardial friction rub.
Others – Fundoscopy

Investigations for renal and urinary tract diseases.

1. Urinalysis (midstream urine; MSU)

- Dipstick
  - Haematuria
  - Protenuria; NB: Microalbuminuria is undetectable on dipstick.
  - Glucose; R/o DM, pregnancy, sepsis, renal tubular damage
  - Ketones; starvation, ketoacidosis
  - Leucocytes
  - Nitrites; UTI, High protein meal
  - Bilirubin
  - Urobilinogen
  - Specific gravity (normal 1.000 – 1.030)
  - PH- normal 4.5 -8
- **Microscopy**
  - Leucocytes >10/mm^3 (unspurn urine)
  - Red cells > 2/mm^3
  - Finely granular and hyaline casts R/o Fever, exercise, loop diuretics

- Densely granular casts R/0 glomerular disease, tubular disease, interstitial nephritis
- Fatty casts, Red cell casts – consider glomerular disease, glomerulonephritis, vasculitis, malignant HTN
- White cell casts – consider pyelonephritis
- Tubular cell casts – acute tubular necrosis
- Crystals; oxalate crystals in fresh urine may indicate a predisposition to form calculi.

2. 24hr urine for Na^+, K^+, Ca^{++}, urea, creatinine + protein excretion.
3. Renal function

- Serum urea; A poor guide to renal excretory fxn as it varies with protein intake, liver metabolic capacity and renal perfusion
- Serum creatinine; more reliable than urea as it is produced from muscle at a constant rate. It is almost completely filtered at the glomerulus.
- Urine creatinine clearance – provides a reasonable approximation of the GFR. It is a measure of GFR. Normal; 10-20mmol/24hrs
- ^{51}Cr- labelled EDTA; A more accurate measurement of GFR.

NB: Estimating creatinine clearance using Cockcroft- Gault equation:-

$$\text{Creatinine clearance (ml/min)} = \frac{140 - \text{age in yrs}) \times \text{Bwt in kg}}{72 \times \text{serum creatinine in mg/dl}}$$

For women multiply above by 0.85

It is unreliable in

- ❖ Unstable renal fxn
- ❖ Very obese patients
- ❖ Oedematous patients

4. Imaging studies

i. U/S – Renal size, position, dilatation of collecting system, distinguish tumours and cysts.

You can image prostate, bladder; estimate complete empting in suspected bladder outflow obstruction.

- Doppler U/S – Renal artery stenosis

ii) IVU – Being replaced by U/S but can provide excellent definition of collecting system, ureters. Its superior to U/S in examining renal papillae, stones, urothelial malignancy.

- Can demonstrate renal perfusion in patients with adequate renal arterial supply. It is dependent on adequate renal fxn for good images and has risk of irradiation.

iii) Renal arteriography and venography – In suspected renal artery stenosis or haemorrhage

iv) CT scan – Useful for characterizing masses within kidney e.g. cysts. Good even in obese patients. It is the first radiological investigation for renal colic in advanced centres but has risk of exposure to irradiation.

v) MRI– It provides excellent resolution and distinction between tissues. Has no risk of irradiation.

5. **Radionuclide studies**

6. **Biopsy (renal biopsy**)

- To establish nature and extent of renal disease in order to judge the prognosis and need for treatment.

Indications for percutaneous needle biopsy include;
(1) unexplained acute renal failure or chronic kidney disease;
(2) acute nephritic syndromes;
(3) unexplained proteinuria and hematuria;
(4) previously identified and treated lesions to plan future therapy;
(5) systemic diseases associated with kidney dysfunction, such as systemic lupus erythematosus, Goodpasture's syndrome, and Wegener's granulomatosis, to confirm the extent of renal involvement and to guide management;
(6) suspected transplant rejection, to differentiate it from other causes of acute renal failure; and
(7) to guide treatment.
Relative contraindications include a solitary or ectopic kidney (exception: transplant allografts),

- horseshoe kidney,
- uncorrected bleeding disorder,
- severe uncontrolled hypertension,
- renal infection, renal neoplasm,
- hydronephrosis,
- ESRD,
- congenital anomalies,
- multiple cysts,
- uncooperative patient.
-

HAEMATURIA

- Refers to blood in urine
- It may arise from anywhere in the renals upto the urethral tract.
- Haematuria may be macroscopic or microscopic. Macroscopic (visible) haematuria is more likely to be caused by tumours, severe infxns or renal infarction.
- Haematuria with dysuria is usually from UTI while painless haematuria is more ominous e.g. bladder cancer or glomerulonephritis. Recurrent episodes of painless gross haematuria in association with respiratory infxns are characteristic of IgA nephropathy.

Causes of haematuria

1. Renal causes
    - Glomerulonephritis – often IgA
    - Analgesic nephropathy
    - Tubulointerstitial nephritis
    - Tumours; renal cell carcinoma
    - Polycystic kidney disease
    - Papillary necrosis
    - Infection; pyelonephritis
    - Renal infarction – infective endocarditis
    - Vascular malformations

- Renal trauma
- Coagulopathies / clotting disorders

2. Extra – renal causes

- Ureteric causes
  - Tumours
  - Stones / calculi
  - Trauma
- Bladder causes
  - Infxns e.g. cystitis, schistosomiasis
  - Neoplasm, transitional cell carcinoma
- Prostatic causes
  - Prostatitis
  - BPH
  - Ca prostate
- Urethral causes
  - Urethritis
  - Trauma
  - Instrumentation
- Others
  - DIC
  - Haemophilia
  - Drugs etc

Urinary tract infection (UTI)

Aetiology and risk factors

- Urine is an excellent culture medium for bacteria; in addition, the urothelium of susceptible persons may have more receptors to which virulent strains of *Escherichia coli* become adherent.
- In women, the ascent of organisms into the bladder is easier than in men; the urethra is shorter and absence of bactericidal prostatic secretions may be relevant.
- Sexual intercourse may cause minor urethral trauma and transfer bacteria from the perineum into the bladder.
- Instrumentation of the bladder may also introduce organisms.
- Multiplication of organisms then depends on a number of factors, including the size of the inoculum and virulence of the bacteria.

Typical features of cystitis and urethritis include:

- abrupt onset of frequency of micturition and urgency
- scalding pain in the urethra during micturition (dysuria)
- suprapubic pain during and after voiding
- intense desire to pass more urine after micturition, due to spasm of the inflamed bladder wall (strangury)
- urine that may appear cloudy and have an unpleasant odour
- microscopic or visible haematuria.

The spectrum of presentations of urinary tract infection

- Asymptomatic bacteriuria
- Symptomatic acute urethritis and cystitis
- Acute pyelonephritis
- Acute prostatitis
- Septicaemia (usually Gram-negative bacteria)

Risk factors for urinary tract infection

1. **Incomplete bladder emptying**
   - Bladder outflow obstruction
   - Neurological problems (e.g. multiple sclerosis, diabetic neuropathy)
   - Gynaecological abnormalities (e.g. uterine prolapse)
   - Vesico-ureteric reflux

2. **Foreign bodies**
   - Urethral catheter or ureteric stent

3. **Loss of host defences**
   - Atrophic urethritis and vaginitis in post-menopausal women
   - Diabetes mellitus

<u>Investigation of patients with urinary tract infection</u>

1. **All patients**
   - Dipstick- estimation of nitrite, leucocyte, esterase and glucose
   - Microscopy/cytometry of urine for white blood cells, organisms
   - Urine culture

2. **Infants, children, and anyone with fever or complicated infection**
   - Full blood count; urea, electrolytes, creatinine
   - Blood cultures

3. **Pyelonephritis; males; children; women with recurrent infections**
   - Renal tract ultrasound or CT
   - Pelvic examination in women, rectal examination in men

4. **Continuing haematuria or other suspicion of bladder lesion**
   - Cystoscopy

Treatment

Antibiotic regimens for urinary tract infection (UTI) in adults

Scenario	Drug	Regimen	Duration
Cystitis and uncomplicated UTI			
First choice	Trimethoprim	200 mg 12-hourly	3 days in women, 10 days in men
Second choices*	Amoxicillin	250 mg 8-hourly	
	Nitrofurantoin	50 mg 6-hourly	
	Cefalexin	250 mg 6-hourly	
	Ciprofloxacin	100 mg 12-hourly	
	Co-amoxiclav	250/125 mg 8-hourly	
In pregnancy	Cephalexin	250 mg 6-hourly	7 days
	Amoxicillin (Avoid trimethoprim and quinolones)	250 mg 8-hourly	
Prophylactic therapy			
First choice	Trimethoprim	100 mg at night	Continuous
Second choices	Nitrofurantoin	50 mg at night	
	Co-amoxiclav	250/125 mg at night	
Pyelonephritis and complicated UTI (i.e. with associated systemic toxicity)			
First choices	Co-amoxiclav	500/125mg 8-hourly	10 days
	Ciprofloxacin	500 mg 12-hourly	
Second choices*	In seriously ill patients start		
	i.v. treatment, e.g.		
	Cefuroxime	750 mg 8-hourly	7-14 days
	Gentamicin	Dose adjusted to renal function and plasma gentamicin levels	
Epididymo-orchitis			
First choice	Ciprofloxacin	500 mg 12-hourly	14 days
Second choice	Consider screening and treatment for chlamydia in young men		
Acute prostatitis			
First choice	Trimethoprim	200 mg 12-hourly	28 days
Second choice*	Ciprofloxacin	500 mg 12-hourly	

Prophylactic measures to be adopted by women with recurrent urinary infections

- Fluid intake of at least 2 L/day
- Regular complete emptying of bladder
- Good personal hygiene
- Emptying of the bladder before and after sexual intercourse
- Cranberry juice may be effective

GLOMERULAR DISEASES:

These account for a significant number of acute and chronic renal failure cases. Glomerular damage may follow several insults;

a) Inherited abnormalities as in
   i) Alport's syndrome
   ii) Thin basement membrane disease (TBM)
b) Acquired disorders
   i) Inflammatory conditions
   ii) Non –inflammatory conditions

INHERITED GLOMERULAR DISEASES

i) Alport's syndrome

- A congenital disorder associated with genetic mutations on x- chromosome which encodes type IV collagen leading to x –linked dorminant disease.
- The pathogeniss involves progressive degeneration of the glomerular basement membrane.
- Affected patients progress from haematuria to ESRF in their late teens or twenties.
- Female carriers (COL4A5) have haematuria but rarely develop significant renal disease.
- The disease is also associated with a sensorineural deafness and ocular abnormalities (lenticonus, cataracts).
- Biospy shows degeneration of the basement membrane.
- Treatment - usually none
  -Renal transplant may be beneficial

ii) Thin GBM disease

- Inherited as autosomal dorminant.
- It presents with microhaematuria with no associated HTN, Proteinuria or reduction in GFR
  LM – glomerular appears normal
  EM –Abnormally thin basement membrane.

-Prognosis is good as the condition is usually benign.

ACQUIRED GLOMERULAR DISEASE:

GLOMERULONEPHRITIS

Def: Inflamation of the glomeruli. Most types of glomerulonephritis are immunologically mediated e.g. anti –GBM antibodies seen in Good pastures disease.

Classification

A. Acute nephritic syndrome

1. Acute glomerulonephritis – glomerular injury occurs over days to weeks.
   i) Post streptococcal GN
   ii) Non streptococcal GN
2. Rapidly progressive GN

3. Membrano-proliferative GN

   i) Diffuse proliferative GN – more than 50% of glomeruli is affected.
   ii) Diffuse proliferative GN may result from several causes.
      - Streptococcal infxn
      - SLE
      - Vasculitides e.g. PAN
      - Subacute bacterial endocarditis
   iii) Focal proliferative GN – Less than 50% of the glomeruli is affected. It commonly results from:
      - IgA, nephropathy
      - Thin membrane disease
      - Henoch schonlein purpura
   iv) Mesangiocapillary – rare, Biospy shows large glomeruli, mesangial proliferation and thickened capillary walls (Tramline appearance of a double basement membrane).

B. Chronic GN – duration months to years

C. Non –inflammatory GN leading to Nephrotic syndrome

1. Minimal change disease – most common in children.
2. Membranous GN – Most common in adults
3. Focal segmental GN (FSGN)
4. Diabtetic nephropathy
5. Amyloidosis

D. Chronic renal failure

Pathophysiology of glomerular disease:

The glomerular filters includes:-

- Vascular endothelium
- Basement membrane
- Slit diaphragm (fenestrations)
- Foot processes.

The main ways of glomerular injury are:-

1. Immunologic mechanisms via:-
   i) Antibody mediated glomerular injury as;
   a) Immune complex disease where glomerular deposits are formed by
      - Local immune complex deposits
      - Circulating immune complex deposits

      Examples include acute DPGN, membranous GN, MPGN, IgA nephropathy and secondary glomerular disease in SLE, malaria etc.
   b) Anti –GBM disease – good pastures disease.
   c) Alternate pathway disease as in membrano- proliferative GN type II.
   d) Others – Anti-neutrophil cytoplasmic antibodies and in focal segmental glomerulosclerosis resulting from anti –endothelial cell antibodies.

ii) Cell mediated glomerular injury – Pauci immune GN (type III RPGN).

iii) Secondary pathogenetic mechanisms as in mediate glomerular injury in various primary and secondary glomerular diseases.

2. Non –immunologic mechanisms as in:
   i) Metabolic problems – Diabetic nephropathy, Fabry's disease.
   ii) Haemodynamic disturbances as in hypertensive nephrosclerosis
   iii) Deposition problems – Amyloid nephropathy
   iv) Infxns as in HIV nephropathy (HIVAN) and immune complex GN in SABE.
   v) Drugs as in NSAIDS associated minimal change disease.

Based on the size and charge of the antigen, the pathology will depend on the negative charge of the basement membrane and the space size of the filters. A large antigen that is negatively charged will repell by the basement membrane & in the subendothelial space, this antigen stimulates the production of inflammatory mediators.
In the blood; leucocytes, monocytes and endothelial factors →inflammation → GN.

Following an ab/ag interaction there is activation of complement –→ activation of inflammatory cells. Mesangial cells release protease →free radicals' damage. Neutrophils attraction → protease release, free oxygen radicals →platelets activation and blood coagulation disturbance.

Basement membrane's response to injury is via;
i) Thickening
ii) Cellular proliferation
iii) Hyalinization or sclerosis →scarring

The number of ag/ab and size usually determines the pattern and outcome of the glomerulonephritis commonly resulting into:

- Haematuria (H)
- Oliguria (O)
- Hypertension (H)
- Oedema (O) Plus proteinuria (non nephrotic range)

ACUTE NEPHRITIS

This represents one of the spectrums of glomerular disease. It results from glomerular injury disease. It results from glomerular injury of about 10-20 days (few days to weeks).

Common causes:

1. Post streptococcal glomerulonephritis
2. Anti – GBM disease
3. Small vessel vascilitis – PAN
   - Henoch schonlein purpura etc
4. Mesangiocapillary
5. IgA nephropathy
6. SLE

PATHOLOGY

Nephritis follows acute clogging of the glomerular filter, usually by immune complex deposits resulting in decreased glomerular filtration rate. There are also circulating complex or antigens which are exogenous and often related to infxns; bacteria, viruses etc.
The mechanisms resulting into nephritic syndrome include:-

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

Clinical presentation:
Acute nephritic syndrome usually presents with;

1. Haematuria – may be microscopic usually smoky (coca –cola like) urine in appearance; haematuria may be gross in some cases.
2. Oliguria due is GFR
3. Hypertension
4. Oedema due to sodium and water retention.
5. Protenuria may not be gross – variable degrees of protenuria; commonly less than 3g/24hrs.

Investigations:

- Urinalysis – microscopic haematuria, protenuria usually <3g/day, RBC casts.
- U/E/C
- FBC & ESR
- ASOT
- Auto-antibodies – ANCA, Anti- GBM antibodies etc
- Complement (C3 C_4).
- Renal biospy – LM, EM and immunoflurescence microscopy to confirm diagnosis.

<u>POST –STREPTOCOCCAL GLOMERULONEPHRITIS</u>:

An acute prolireferative glomerulonephritis that usually follows 1-4 weeks (average 10 days) after throat, ear or skin infxns by Beta-haemolytic strepcocci Lancefield group A mainly types 1,2,3,4,12,18,25,49,55,57 and 60.
It is most common in children between 6-10yrs but it can occur in adults of any age.

Pathology:
The disease follows an immune mechanism rather than direct infxn. Following an infxn, there is about 7-10/7 delay or latency before antibody production occurs. This results into a rising ASOT and streptozyme titres. The immune complex induces an acute nephritis that manifests as oliguria and azotemia due to ↓GFR, Oedema and HTN due to salt and water retention. Smoky urine is due to RBCs, proteins and WBC casts. All these factors lead to protenuria.

Antibody production to streptcocci →ASOT and ↓serum concentration of C3 & C4 due to complement activation and consumption.
The main pathology in diffusehypercellularity of glomeruli→Diffuse proliferative glomerulonephiritis. There is proliferation of both endothelial and mesangial cells with

infiltration of neutrophils.
In children, the condition may resolve completely while in others it may end to glomerula sclerosis and after several years→ ESRF.

Clinical presentation:
Typically presents 7- 14/7 after sore throat infxn. Most patients present with:

- Haematuria – Red or smoky urine due to RBCs, proteins and WBC casts.
- Oliguria
- Hypertension
- Oedema – Usually mild and especially peri-orbital

Investigations:

- Urinalysis – Nephritic sediments, protenuria (non NS)
- Throat swabs
- U/E - ↑ urea (Azotemia)
- ASOT, Anti- DNase B, Anti –Hyaluronidase and streptokinase titres.
- Serum concentration of C3 and C4 levels
- FBC
- Renal biopsy
    - LM – Diffuse proliferative glomerulonephritis with proliferation of endothelial and mesangial cells, infiltration by neutrophils and macrophages and there may be cresent formation.
    - Immunofluoresence – granular deposits (star –sky appearance) and IgG & C3
    - EM – Subendothelial deposits

NON- STREPTOCOCCAL AGN:

Occurs in association with other infectious agents such as:

- Bacterial – Staph. endocarditis, pneumococcal pneumonia, meningococaemia, TB, salmonella typhi of leptospirosis.
- Viral – Hepatitis B, mumps, varicella, infectious mononucleosis
- Parasitic – Malaria, toxoplasmosis, schistosomiasis and leishmaniasis

The pathology is similar to post –strep GN

NB: Lesions similar to DPGN may follow drug reactions and SLE.
In most non –streptococcal case, the antigen – antibody reaction is unknown.

DDX in GN associated with low serum complement:

1. Post- infection GN
2. Subacute bacterial infxn especially endocarditis
3. SLE
4. Cryoglobulinaemia
5. Mesangiocapillary GN- Usually type II

Treatment of Post- infectious AGN

- Fluid and sodium restriction
- Loop diuretics
- Anti hypertensive to control HTN – ACE –I
- Treat underlying cause

RAPIDLY PROGRESSIVE (CRESCENTIC) GN:

An extreme inflammatory nephritis that causes rapid loss of renal function over days to weeks. There is severe destruction of glomeruli causing renal failure.
It is typically seen in:

- Good pastures disease
- Small vessel vasculitides
- SLE
- IgA nephropathy
- May be idiopathic (50% case)

Pathology:
Crescenteric glomerulonephritis seen as cellular crescentic cells - macrophages, T- cells, fibrin which may arise because of leakage of blod in the Bowman's space (Half- moon shaped deposits or crescents). The crescentic lesions are often associated with necrotizing lesions in the glomerulus (focal segmental necrotizing GN).
The affected glomeruli eventually scar and if untreated, renal failure occurs within weeks.

Treatment

Depend on type. Type I-IV.

GLOMERULAR DISEASES ASSOCIATED WITH SYSTEMIC DISORDERS:

SLE nephropathy (lupus nephritis)
SLE is an auto –antigen driven T-cell dependent and B- cell mediated autoimmune disease.
SLE nephropathy may manifest as nephritis or nephrotic syndrome. About 75% of SLE patients have some renal abnormality with or without clinical manifestations. About 25% have no clinical features – Silent lupus nephritis.
Many cases are diagnosed by renal biopsy and the outcome is very good.
The antigen is a double strand DNA nucleosome and the antibodies found against it are anti-SM abs, SSB, SS-A C1q or subendothelial immune complex deposits or pure basement membrane disease.
LM –Shows a wide variety of lesions.
Haematoxylin bodies are pathognomonic.
Immunofluorescence shows full house pattern IgG, IgA, C3, C4

Treatment

- Anti –HTN –Angiotensin receptor blockers or ACE- I
- Lipid lowering agents in case of CRF (A coronary equivalent just like diabetes).
- IV pulsed cyclophosphamide 1 dose monthly for 6/12 at $0.75g/m^2$ in normal saline.
- Methylprednisolone 0.5 -1g IV monthly for 6/12
- Check on vitals & control BP

Maintenace therapy:

Usually 4 wks after stopping cyclophosphamide. Maintenance drugs include:

- Mofetil (MMF)
- Azathioprine
- Cyclosporine

Keep on monitoring; every 3/12; serology, urinalysis to detect relapse.

NB: A relapse requires a fresh start up of treatment
Most of the lupus nephritis has a lot of relapses.

- Remission – control of;
  - Renal
  - Extrarenal
  - Serologic findings with resolution of haematuria, pyuria of cellular casts and stabilization of serum creatinine.

Other systemic diseases associated with glomerular diseases;

- DM
- RA
- Anmyloidosis
- Vascular disease

NEPHROTIC SYNDROME

DEF: Nephrotic syndrome is a condition characterized by:-

(i) Albuminuria (heavy proteinuria) >3.5g/day – nephrotic range proteinuria.
(ii) Hypoalbuminemia
(iii) Oedema
(iv) Lipidimia
(v) Hyperlipidemia

Causes of nephrotic syndrome

A. Primary glomerular disease

(i) Minimal change disease (lipoid nephrosis or nil disease)
(ii) Membranous GN
(iii) Focal segmental glomerulosclerosis (FSGS)
(iv) Membranoproliferative GN
(v) Mesangiocapillary GN
(vi) Immuno-tactoid GN

B. Secondary causes

a) Systemic diseases

(i) Diabetes mellitus
(ii) SLE, HSP
(iii) Amyloidosis

b) Systemic infections

(i) Bacterial – bacterial endocarditis, syphilis, leprosy
(ii) Protozoal – P.falciparum malaria, filariasis
(iii) Viral – HBS, HCV, HIV

c) Hypersensitivity reactions

(i) Drugs – heavy metal compounds, penicillamine, heroin, tolbutamide
(ii) Bee stings, snake bite , poison

d) Malignancies

(i) Carcinomas
(ii) Myeloma (multiple myeloma)
(iii) Hodgkins disease

e) Others

(i) Cong. Disorders
(ii) Alport's disease, Fabry's disease, nail patella syndrome
(iii) Circulatory disturbance; renal vein thrombosis, constrictive pericarditis
(iv) Pregnancy; toxaemia of pregnancy.

Pathophysiology – Main pathology is distortion of glomerular architecture and function. The pathogenesis of nephrotic syndrome varies according to aetiological factors but in all cases the characteristic features are attributable to the same process;

1. **Albuminuria-** is due to immune complexes directed against endogenous antigens expressed on or near the foot processes leading to loss of anionic properties of the GBM with resultant inability of the membrane to repulse the negatively charged albumin molecules.
   Loss of albumin may also be due to defects in the slit diaphragms which results in loss of size of the barrier.
2. **Hypoalbuminemia** – results from urinary loss of albumin, increased renal catabolism and inadequate hepatic synthesis of albumin.
3. **Oedema** – attributable to 2 hypothesis
   (i) Arterial underfilling where there is low oncotic pressure that leads to plasma volume depletion. This is not a major determinant of oedema however because the parallel decline in interstitial oncotic pressure leads to little change in the transcapillary gradient. But in severe hypoalbuminemia (<1g/dl), volume depletion does occur causing the activation of the RAAS that then returns the plasma volume to normal at the expense of extracellular volume expansion leading to oedema.
   (ii) Primary sodium retention due to increased activity of the Na^+/K^+ ATPase pump leading to active Na^+ transport into the tubular capillary, relative resistance of ANP and increased activity of Na^+/H^+ exchanger.
   These could be due to associated tubulointerstitial inflammation which releases angiotensin II leading to reduced GFR and enhancing tubular reabsorption.
   1^o sodium retention is the main mechanism of oedema in majority of NS.
4. **Lipiduria** – due to hyperlipidaemia and loss of size barrier leading to excessive leakiness of the glomerular filtration barrier.
5. **Hyperlipidemia -** Results from a reduction in plasma oncotic pressure which triggers increased hepatic lipoprotein synthesis, reduced lipid catabolism and reduced lipid clearance.
   The severity is universely related to the fall in plasma oncotic pressure.
   The most common abnormalities are hypercholesterolemia and hypertriglyceridemias.
   HDL is either normal or reduced.
   Spontaneous or drug induced resolution of the NS reverses the hyperlipidemia.
6. **Other features:-**
   (i) **Hypercoagulability** – Due to urinary loss of anti-thrombin III, altered activity of protein C and S, increased synthesis of clotting factors; fibrinogen and platelets abnormality. The patients are prone to thrombo-embolism – DVT, renal vein thrombosis and pulmonary embolism.

(ii) **Anaemia** – Loss of protein and transferrin leads to microcytic hypochromic anaemia.

(iii) **Increased risk/susceptibility to infection** – Results from loss of immunoglobulms in urine or partly due to immunosuppressive agents used in Rx.

(iv) **Vitamin D def.** – From loss of cholecalciferol binding protein.

(v) Decreased thyroxine level from loss of thyroxin binding globulins.

Clinical features of NS

The characteristic features of NS in general are:-

1. Albuminuria >3.5g/day
2. Hypoalbuminemia
3. Oedema – usually generalized
4. Lipiduria
5. Hyperlipidemia

Most patients present with the following:-

a) Symptoms – H/o acute /chronic infection, drugs, allergies etc.
Facial puffiness plus swelling of legs

b) Signs on physical examination

(i) General

- Periorbital oedema or leg oedema or generalized oedema (anarsaca), usually pitting, non tender.
- Patient may be febrile
- May be pale (pallor)
- Vital signs – BP often normal. RR- variable; cardiopulmonary involvement, temperature normal or increased.

(ii) Systemic – Plus or minus ascites, may be in CCF. Pleural effusion, hepatomegally, xanthoma etc.

c) Lab features

- Urinalysis
  - Dipstick – albuminuria, proteinuria
  - Microscopy – lipiduria; sediments positive for fat droplets. Increased anti-thrombin III
- 24hrs urine measurement.
- Blood for
  - Cholesterol levels – hyperlipidemia
  - Protein/albumin levels (hypoalbuminemia (<1g/dl))
  - Urea albumin creatinine ratio (UACR)
  - U/E – increased NA^+, urea; may be normal or increased especially if moving towards ESRF.
  - FBC + PBF

- Hb decreased
- Microcytic hypochromic anaemia

➢ Transferrin level decreased

- Imaging studies
  - ➢ U/S of the kidney
- Renal biopsy for Lm, IF and EM
- Others; as per suspected underlying aetiology
  - ➢ MPs, serology; VDRL, HIV
  - ➢ HBsAg etc.

MANAGEMENT OF NEPHROTIC SYNDROME:-

A) Evaluation:-

- History – A thorough clinical history to rule out any systemic disease is essential.
- Physical examination
  - ➢ Periorbital oedema
  - ➢ Leg oedema; pitting usually non- tender
  - ➢ Anarsaca
- Investigations

I) Urinalysis

(i) Dipstic – measures albumin conc. By colorimetric reaction that produces different shades of green according to the conc. of albumin in the sample. It may be:-

- Negative
- Trace 15-30mg/dl
- 1^+ 30-100mg/dl
- 2+ 100-300mg/dl
- 3+ 300-1000mg/dl
- 4+ >1000mg/dl

The disadvantage of this test is that

a) It is insensitive to microalbuminuria
b) It is influenced by the urine volume and dehydration.

(ii) Microscopy

➢ Relatively bland sediment due to lack of inflammatory cell infiltrates in the glomeruli.

➢ Sediment is positive for fat droplets (lipiduria)

(iii) Quantitative methods

a) 24hrs urine protein measurement
Useful in determining prognosis; poor in sereve proteinuria.
Benign in mild proteinuria.

Good for monitoring response to therapy (Its very sensitive).
Disadvantage – Its cumbersome to collect the 24hrs urine for protein.

(iv) Urine albumin to creatinine ratio (UACR).

- Compares amount of albumin in urine and creatinine excretion.
- First morning specimens are preferred
- Useful for serial monitoring of protein excretion.
- Useful for detecting microalbuminuria
  - Microalbuminuria 20-200mg/g and 30-300mg/g for males and females respectively. This corresponds to urine albumin excretion of 20-200 and 30-300mg/day.
- When microalbuminuria >500-1000mg/day, perform the total protein to creatinine ratio.
- Disadvantages – It may be influenced by
  - Muscle mass
  - Heart failure
  - Fever

II) Renal ultrasound

- To rule out structural abnormalities.

III) Urea, electrolytes and serum creatinine

IV) Complement level

- Low in membranous nephropathy due to HBV and SLE and in MPGN due to consumption of C_3 by C_3 nephritic factor.

V) Investigate for secondary causes

- MPS
- HBsAg
- HIV
- Random sugar to rule out DM
- VDRL, toxicology – heavy metals, heroin
- FBC; pancytopenia in myeloma, lymphoma.

VI) Renal biopsy

Indication for biopsy

- Progressive disease
- Increasing protein excretion
- Elevation in plasma creatinine
- Significant elevation in BP.

B) Non-immunosuppressive treatment

(i) General

- Monitor vital signs; BP, temperature, PR, RR.
- Monitor urea and electrolytes
- Input/output chart for fluid balance.
- Take weight regularly/daily

(ii) Control sodium retention and oedema- most patients have anarsaca with peripheral oedema with one of the cavities involved.

- Dietary sodium restriction to less than 2g/day
- Diuretic therapy – loop diuretics are useful for removing the excess fluid and controlling oedema. Higher doses of loop diuretics are usually required for it to be effective due to relative diuretic resistance. Patients may require up to 80-120mg of IV frusemide with or without addition to a thiazide.
- If the patient still has poor response, increase the dose. Aim for about 1kg/day weight loss

(iii)Treat hyperlipidaemia

- Rationale
  - Decreases cardiovascular risk
  - Reduces progressive glomerular injury
  - Improves response to ACE-I
- Hyperlipidaemia is controlled with
  a) Dietary modification
     - Reduce saturated fats in diet
     - Increase mono and poly-unsaturated fats.
  b) Statins are the treatment of choice esp. if hyperlipidemia persist after treatment of the underlying kidney disorder with immuno-suppressants and ACE-I. These lower TC, LDL-C by 20-40%.

(iv)Treat hypercoagulability states

- No routine prophylactic anti-coagulation with nephrotic syndrome
- In cases of massive proteinuria, hyperalbuminemia <20g/l give prophylaxis if there is an additional risk factor for thrombosis e.g.
  - Prior idiopathic thromboembolic event
  - Immobilization
  - Severe heart failure
  - Morbid obesity
  - Surgery
- Give heparin and then warfarin
- Anti-coagulate patients with
  - Thrombosis
  - NS with non-renal thrombo-embolic event.

- Give thrombolytic therapy with or without catheter thrombectomy in acute renal vein thrombosis. renal vein thrombosis presents with
  - Haematiria
  - Flank pain
  - Testicular enlargement; usually left testis.
- In acute renal vein thrombosis – Do Doppler U/S and the main treatment is anti-thrombolytic therapy.
- Continue warfarin for as long as the patient remains nephrotic with minimum duration of 6-12 months with target INR goal of 2-3 till patient becomes stable.

(v) Decrease proteinuria and slow the progression to renal impairment

- Use ACE-I or ARBs.
- The role of ACE-I/ARBs is
  - Reduction in proteinuria causing a 10-20% decline in plasma levels of TC, LDL-C, LP
  - Reduction in lipids does not depend on class of drugs – ACE-I. ARB.
  - Reduction in proteinuria may cause increased sensitivity to diuretic therapy.

(vi) Treat any infection

- Antibiotics
- Pneumococcal vaccines.

C) Immunosuppressive therapy in NS

- Basically employs
  - Steroids (glucocorticoids)
  - Cytotoxics – cyclophosphamide/cyclosporine.
    - Prednisolone 1mg/kg/day max 60-80mg per day. If CR within 12wks, taper dose over 2-3 months
    - Cyclosporine plus low dose glucocorticoids as initial therapy in steroids. Increased risk of relapse.
    - In resistance, MMF 1g BD for 6/12.

Specific conditions of NS

(i) Minimal change GN (MCD) disease

Minimal change disease or lipoid necrosis or nil disease.

Is the most common cause of NS (90%) in children <10yrs and 10-15% of adult NS.

It is the primary cause of NS (65% cases).

Secondary causes include:-

- Drugs (NSAIDS, antibiotic, lithium, penicillamine, biophosphonate, immunizations)
- Malignancies – Hodgkins disease, non-hodgkins disease, leukaemia, rarely solid tumours- RCC, thymoma, colon, bronchogemic, lung, pancreas, duodemal, prostate.
- Infections; TB,HIV, HCV
- Atopy
- SLE
- Type 1 DM, PKD, HIVAN, Graves disease, GBS, myasthenia gravis

NB: In patients with MCD, always make sure that there is no systemic disease.

Investigations

- Selective proteinuria
- Renal biopsy

  LM – normal glomerulus or minimal change

  IF – no immune complexes

  EM – diffuse effacement of the epithelial foot processes.

Rx –

prednisolone on 1mg/kg/day, max 60mg/day.

Increase dose till proteinuria disappears, then continue for 30days before tappering to alt. day therapy for 2/12, then tapper every 2/52 by reducing by 15mg/day.

In frequent relapses; combine steroid with cyclophosphamide or cyclosporin or MMF or rituximab.

If urinalysis shows resistance – do renal biopsy to rule out other renal diseases especially FSGS or genetic causes of resistance.

<u>NB</u>

- 90% cases resolve spontaneously (complete remission)
- For children, no need for biopsy unless Rx failure. Relapses 50% cases.
- In adults; always do a renal biopsy.
- Proteinuria usually remits with high doses of steroids.
- Most do not progress to renal impairment/CRF

Membranous glomerulonephritis

Is the most common cause of NS in adults forming 15-33% of cases.

It may remit spontaneously. Short term treatment with steroids and ankylating agents may improve NS and long term prognosis.
It may be

1. Idiopathic
2. Secondary to
   a.) Diabetes mellitus.
   b.) Drugs – gold, penicillamine, heroin, NSAIDS, mercury, captopril, probenizid
   c.) Connective tissue disorders
   SLE, HSP, sjogren's syndrome, RA, mixed connective diseases, ankylosing spondylosis
   d.) Infections – bacteria, syphilis
   Viral – HBV, HCV
   Parasites – mal, schistosomiasis, hydatid disease
   e.) Neoplasma – adenocarcinoma of lungs, colon, stomach, breast, Hodgkins disease
   f.) Autoimmune diseases –thyroid diseases, 1^{o} biliary sclerosis, myasthenia gravis
   g.) Others – sarcoidosis, fanconi's syndrome, amyloidosis.

Focal segmental glomenlosclerosis

There is little response to corticosteroid therapy and there is rapid progression to renal failure. It can occur after renal transplants with proteinuria recurring almost immediately. It may be mistaken for MCD.
It is the most common cause of idiopathic 1^{o} NS in adults: 35% of all cases. It presents as acute onset NS.
Black patients are at increased risk due to genetic, socio-economic and environmental factors. In nephrotic patients, about 50% renal survival at 10yrs.
Secondary FSGS presents with non-nephrotic proteinuria, renal insufficiency, with or 5 hypoalbuminemia and oedema. It is induced by physiologic response to intraglomenular hypertrophy/hypertension or healing of a previous glomerular injury.
The aetiologisal causes include:

- HIV disease
- Heroine use
- Vesicourethral reflux
- Reduced renal mass/renal agenesis
- Sickle cell disease
- Others – renal resection, DM, fabry's disease, tubular interstitial nephritis

HIV - ASSOCIATED NEPHROPATHY

HIV nephropathy can give any form of glomerulonephritis. The commonest pathological manifestation is focal segmental glomerulosclerosis (FSGS); one of the main cause of glomerular collapse and sclerosis. Other lessions include tubulo-reticular structures lessions.

DIABETIC NEPHROPATHY:-

A common cause of end stage renal failure. Prevention is the key to management. About 30% of type 1 DM develop diabetic nephropathy 20yrs but thereafter the risk falls to <1% per year.

Risk factor

- Poorly controlled glucose
- Long standing DM
- Presence of micro-vascular cmx
- Race-more common in Asians
- Pre-existing HTN
- Family history of DM nephropathy
- Family h/o-HTN

Rx – Dilatiazin or verapamil are suitable but ACE – I are assoc. with hyperkalaemia and renal artery stenosis!

AMYLOIDOSIS NEPHROPATHY

Results from extracellular aggregates and deposits of a number of proteins that are characteristically associated to amyloid fibrin. The deposits take Congo red stain and contain aminoglycans and glycoprotein, serum amyloid – P (SAP) favoured by the production of abnormal proteins or over- production or accumulation in certain types. No HAEMATURIA. The abnormal protein leads to a rare amyloid syndrome, Prian disease (protein sequence is normal but pathologically it is alternatively folded proteins – it is infections!)
Amyloidosis may occur in Alzheimers disease, type II DM and haemolysis related disease.

Myeloma and other paraproteinemias

In multiple myeloma, the glomerular traps abnormal proteins called Bence Jones protein - light chain proteins. These together with other paraproteins damages the glomerular membrane leading to leakage of proteins and nephrotic syndrome.

NOTE:

a) In**dications for glucocorticoids in Minimal change disease**

(i) Age 1-10yrs
(ii) No HTN, gross haematuria or elevation in serum creatinine.
(iii) Normal complement levels
(iv) No extra-renal symptoms e.g. malar rash or purpura.

b) Indicators of poor prognosis

(i) Massive proteinuria
(ii) Severe renal dysfunction
(iii) Interstitial fibrosis, collapsing FSGS at presentation.
(iv) Poor initial response to therapy.

C) Causes of ARF in NS

(i) Concurrent ATN
(ii) Collapsing FSGS due to glomerular and tubular injury.
(iii) Patient on NSAIDS – These reduce GFR (decreased formation of vasodilator prostaglandins inducing renal vasoconstriction) – Reversible after stopping the medication.
(iv) Diuretics (loop, thiazides) may lead to reduced plasma volume.
(v) Bilateral renal vein thrombosis – Renal infarction and flank pain.
(vi) Use of radio-contrast
(vii) Use of herbal medicines.

PROTEINURIA

Passage of proteins in urine may be:-

1. Functional <150mg/day as in
    - Exercise
    - Fever
    - CCF
    - Burns
    - Post-operative
    - Acute alcohol abuse
2. Orthostatic – Proteinuria occurs only during the day when patient is standing and the first morning specimen/sample is negative
3. Pathological – Most due to glomerular disease as in
    - Nephrotic syndrome
    - DM
    - GN
    - SLE etc.

DDX of NS

- Nephritc syndrome
- Kwashiorkor
- Allergic reaction
- CCF
- Liver disease
- Beri-beri
- ARF/CRF

ACUTE RENAL FAILURE (ARF)

Def: Is a syndrome characterized by a rapid onset of decreased renal function with oliguria or anuria and a sudden increase in urea or creatinine in the blood (uremia).

In acute renal failure, there is a sudden and usually reversible loss of renal function which develops over a period of days or weeks and is usually accompanied by a reduction in urine volume. The term acute kidney injury has now been adopted and replaces ARF.

Epidemiology

Acute kidney injury complicates 5% of all hospital admissions and 30% of ICU admission.

Incidence is about 100 – 600 million people/yr and 50% of these patients have oliguria.

Aetiology of acute kidney injury.

The causes of acute renal failure are often maltifactorial and usually occur secondary to a circulatory dysfunction.

The causes can be grouped into:

1. **Prerenal causes:-**

Local – renal artery occlusion/stenosis.

-Diseases affecting arterioles (thromboembolic disease)

-Drugs e.g amphotericin B which causes vasoconstrictions of the renal vessels.

Systemic - Fluid or blood loss as in severe h'ge, diarrhoea, vomiting, dehydration, severe burns.

- Severe hypoalbuminaemia

- Hypotesion fron MI, septicaemic shock, Drugs, heart failure.
- Hepatorenal syndrome (increased renal vascular resistance). All the blood is diverted to the splanchnic vessels.
- Malignant HTN
- Haemolytic uraemic syndrome.
- Pericardial tamponade and massive PE.

N/B: Renal failure from pre-renal causes usually results from a sudden decrease in blood flow →renal ischaemia and decreased GFR→ disordered renal fxn. An inadequate CO and hypovolaemia → reduced perfusion of the kidneys. The underperfusion initially causes reversible changes but subsequently "acute tubular necrosis" or other changes cause longer lasting but usually temporary intrinsic renal failure.

2. **Intrinsic renal diseases/ renal causes.**

- Acute tubular necrosis (85%) 2^0
    - Ischemia
    - Toxins – toxic renal failure
    - Drugs; aminoglycosides
- Antibiotics (cephalosporins)
- Radiocontrast materials.
- Chemotherapy – cisplatin
- Heavy metals
- Rhabdomyolysis.
    - Glomerular disease, 1^o or as a component of a systemic disease e.g SLE.
    - Interstitial nephritis.
- Cancers; lymphomas
- Leukaemias.
- Drugs – NSAIDS, proton pump inhibitors, sulfonamides, glycosponia and beta-lactams.
- Infxns e.g.
    - CMV
    - Acute pyelonephritis (rare)
    - Multiple myeloma
    - Scleroderma.

3. **Post renal causes**

Commonly due to obstructive uropathy

- Urethral obstructions; calculus, blood clot, sloughed papillae, trauma etc.
- BPH or Ca prostate.
- Bilateral ureteric obstruction; pelvic tumor, surgery,uterine prolapse.

Causes of rapidly progressive renal failure (wks to months)

1. Urinary tract obstruction
2. Rapidly progressive glomerulonephrites.
3. Bilateral renal artery stenosis which may be precipitated by ACE-I.
4. Multiple myeloma
5. Scleroderma.
6. Malignant HTN
7. Haemolytic uraemic syndrome.

Diagnostic criteria:

a. Kidney at risk
- Abrupt increase in serum creatinine within 48 hours of 26mmol/l from baseline.
- Oliguria of less than 0.5ml/kg/hour for more than 6 hours.

b. Acute kidney injury.
- Increase in serum creatinine > 2-3 fold from baseline.
- Urine output <0.5ml/kg/hr for >12hrs

c. Kidney failure
- Serum creatinine >3 fold from baseline
- Urine output <0.3ml/kg/hr for more than 24 hrs or
- Anuria >12 hrs.

Reversible pre-renal acute renal failure

The kidney can regulate its own blood flow and GFR over a wide range of perfusion pressures.

Decreased perfusion pressure (hypovolaemia, shock, heart failure) →dilatation of resistance vessels in the kidney to facilitate flow. Vasodilator prostaglandins are important and this mechanism is markedly impaired by NSAIDS.

If autoregulation of blood flow fails, the GFR can still be maintained by selective constrictions of post – glomerular (efferent) arteriole mediated via renin- angiotensin mechanism. ACE-I interfere with this response. More severe or prolonged under-perfusion of the kidneys may lead to failure of the compensatory mechanisms and hence an acute decline in GFR.

Clinical assessment:

Marked hypotension and signs of poor peripheral perfusion. But pre-renal ARF may occur with systemic hypotension esp. in pts on NSAIDS or ACE-I

Postural hypotension; fall in blood pressure > 20/10mmhg from lying to standing is a valuable sign of early hypotension.

N/B: The combination of sepsis and NSAIDS is a potent cause of ARF.

If treatment is given early and hypoperfusion (arterial pressure < 80mmhg) corrected, renal function will usually improve rapidly and residual renal impairment is therefore unlikely.

Anti-diuretic hormones → better kidney blood supply; thirst is stimulated → ↑water uptake, ANS is activated, efferent vasoconstriction occurs and afferent vasodilatation by prostacyclins to keep the kidneys working.

Established acute renal failure:

May develop following severe or prolonged under-perfusion of the kidney. In such cases, the histological pattern of acute tubular necrosis is usually seen.

Acute tubular necrosis (ATN):

Results from ischemia or nephrotoxicity.

The ischaemic insult ultimately causes death of tubular cells which later causes tubular obstructions.

Acute tubular necrosis goes thro' several stages:-

1. Pre-renal phase fails to correct after prolonged under-perfusion of the kidney.
2. Initiation phase- Takes hours of hypoperfusion. Decreased renal blood flow →renal tubular epithelium necrosis →epithelial damage →blockage by epithelial cells.
   Decreased ATP, Na+ transport → decreased transportation → swelling of cells and generation of free O2 radicals and increased intracellular calcium → further cell necrosis.

3. Maintenance phase – From 2 – 3weeks.
   Renal cell injury is established; GFR 5-10ml/mm.

   Pts is oliguric (urine Vol <400ml/24hrs), increased Na+ retention → uraemic complications. GFR remains low despite reperfusion and this is due to release of vaso-active peptides (endothelium)

4. Recovery phase – About 4 weeks after insult.
   There is replenishing and regeneration of epithelium, normalization of GFR, marked diuresis of Na+ and water (polyuria) due to loss of the medullary concentration gradient.

Features of established ARF:

Usually detected by the underlying aetiology with features of renal failure.

S**ymptoms:**

- Anorexia, nausea, vomiting, drowsiness, apathy, confusion.
- Hiccups, fits, seizures or coma
- Oliguria
- Anuria (rare and usually indicates acute urinary tract obstruction or vascular occlusion)

N/B: In about 20% cases, urine volume is normal or increased but with a low GFR and a reduction of tubular reabsorption (Non-oliguric AFR)

Signs:

- Marked hypotension decreased capillary return.
- Postural hypotension (BP decreases 20/10mmHg from lying down to standing position)
- Metabolic acidosis, hyperkalaemia.
- Arrhythmia accompanies sepsis.
- On gen examination; anaemia,↑RR,&↑PR, tachycardia but thready pulse, decreased skin turgor, cold clammy skin, oedema esp. leg oedema.

Investigations in acute renal failure.

- FBC,ESR
- PBF; fragmented RBCs
- Coagulation screen; DIC, hyperviscosity states
- GXM
- Assess kidney fxn
    - U/E
    - Serum creatinine
- Urinalysis,haematurai,proteinuria
- Blood cultures
- CRP
- Ca++, prosphates (Ca++ is normal in ARF unlike in CRF where it is raised).
- Hepatitis serology, HIV screening
- Imaging studies
    - Urgent renal U/S to confirm obstruction and size of kidneys
    - CXR
    - ECG esp. if >40yrs or has risk of cardiac disease.
- Others especially if diagnosis in not known.
    - Immunoglobulins and protein electrophoresis
    - Urinary Bence Jones protein
    - Complement
    - Auto – antibodies, ANA and dsDNA if ANA +ve.
    - Rheumatoid factor
    - Anti-streptolysin 0 titre
    - Renal biopsy.

Management of AFR:

1. Quick assessment of patient
- BP
- PR
- JVP
- Skin turgor
- Resp. rate

2. Emergency resuscitation. This is aimed at dealing with the emergencies in ARF that include:

(i) Hyperkalaemika
(ii) Metabolic acidosis
(iii) Pulmonary oedema
(iv) Hypovolaemia.

- Hyperkalemia (K+>6mm/l) must be treated immediately to avoid the risk of cardiac arrhythmias.
- Give 10mls of 10% calcium gluconate IV over 2min (slowly). This helps to stabilize the cell membrane potential but does not change the level of K+
- Inhaled (nebulized) sulbutamol helps to shift K+ from intra vascular space to cells.
- IV glucose 50mls of 50% solutions plus soluble insulin 10units also shifts k+ from intravascular into cells.
- IV sodium bicarbonate (100mls of 8.4%, solution) in severe metabloc acidosis.
- IV furosemide and normal saline or
- Ion exchange resin (resonium orally or rectaly or kayaxalate)
- Consider dialysis if methods to correct hyperkalaemia as above are not successful. Dialysis helps to remove sodium and water especially in pulmonary oedema
- Treat fluids and electrolyte imbalance.
- Hypokalaemia must be treated appropriately.
- In severe acidosis, give isotonic sodium bicarbonate 500mls of 1.26%
- Anuria or renal overload may require dialysis or renal replacement.
- Catheterize patient
- Keep strict input/output chart.

3. Address the underlying cause of ARF
    - Restore renal perfusion and treat the cause of ARF
    - Use of immunosuppressive therapy eg in interstitial renal diseases; progressive glomerulonephritis.
    - Treat diarrhea and vomiting with anti-emetics.
    - Post renal obstruction should be relieved urgently.
4. Supportive care in ARF

- Daily wt to check on fluids depletion or oedema.
- Manage anemia – transfuse if anaemic
- Restrict sodium and potassium intake
- Restrict dietary protein to about 40g/day and ↑fat and carbohydrate. Those on dialysis may be allowed up to 70g/day of proteins
- Infection control
- Aseptic techniques in burns
- Regular clinical examination
- Regular micro biological examination.

5. Drugs.
    - Avoid drugs that will cause further kidney injury e.g. NSAIDS, ACE-I, prostaglandin inhibitors and radio-contrast media.
    - Antibiotics may require dose adjustment to avoid accumulation.
6. Renal replacements
7. Monitoring for recovery in ARF

Indicators:-

- Gradual return of urine output
- A steady improvement in plasma biochemistry.

CHRONIC RENAL FAILURE:-

Def: A functional diseases characterized by a progressive and generally irreversible decline in GFR. Any renal failure for more than 3/12 is termed chronic renal failure.

End stage renal failure (ESRF) is a clinical state with irreversible endogenous loss of renal function leading to permanent dependence on renal replacement therapy in order to avoid life-threatening uraemia

Estimation of GFR

1. Cockcroft -Gault formular.

$$GFR = \frac{(140 - age) \times body\ weight\ (kg)}{72 \times plasma\ creatinine(mg/dl)}$$

In females; multiple by 0.85 normal values 120-130mls/min/M2

Modification of diet in renal disease (MDRD)

Is more accurate in estimating GFR.

It considers race, gender etc

$GRF = 1.86\ (Pcr\ mg/dl)^{-1.154} \times (age)^{-0.203}$

For women; multiply by 0.742

For blacks; multiply by 1.21

Epidemiology

CKI affects 0.1% of the population.

CRF is very common and about 6% have stage I-II and 4% have stages III – IV

About 11 – 16% of cases are undetected

Aetiology/ causes of CRF

1. Diabetes mellitus
2. Hypertension (Nephrosclerosis)
3. Glomerulonphrtis esp. chronic GN
4. Polycystic kidney disease
5. Obstructive uropathy
6. Infections, HIV, chronic pyelonephritis
7. Analgesic nephropathy
8. Others – tubular nephritis
   -Systemic inflammatory diseases; SLE , Vasculitis, Amyloidosis

   -Alport syndrome

   -Fabry's diseases.

   - Multiple myeloma
9. Sickle cell disease
10. Toxic nephropathy; amphotericin B, Aminoglycosides

Stages of chronic kidney failure.

Stage O - patients have risk factors for kidney disease; history of kidney disease, HTN, DM but has no kidney damage; GFR 120mls/min

Stage I – kidney damage with normal or increased GFR of >- 90ml/min/1.73m^2

Stage II – kidney damage, GFR 60 – 89ml/min/1.73m^2

Stage III – moderately low GFR 30 – 59mls/min/1.73m^2

Stage IV - severe low GFR 15 – 29 mls/min/1.73m^2

Stage V – kidney failure with GFR less than 15ml/min/1.73m^2 or pt is on dialysis. This is established renal failure

Pathogenesis

A disturbance in water, electrolytes and acid – base balance contributes to the clinical picture in chronic renal failure.

Chronic kidney injury results into irreversible nephron dysfxn and loss of fxn. The remaining nephrons take over the fxn of the lost nephrons leading to hyperfiltration and increased pressure. The hyperfiltration causes scarring

There is speedy progression and the development of uraemia. Up to 50% of nephrons could be lost without any features of kidney fxn impairment. But when GFR falls below 30mls/min/1.73m2 clinical features become apparent. The patient may be symptomatic because of a new state of azotaemia achieved.

Hyperfiltration accelerates the evolutions to ESRF. The patent can easily become uraemic in situations of dehydration, drugs, obstructions or any catabolic state with increased turnover of nitrogenous products.

There are retained products of metabolism and increased kidney hormones with loss of normal production of erythropoietin.

Clinical manifestations of CRF

May be:-

- Asymptomatic
- Symptomatic
- Symptoms
- Signs

Symptoms:-

- Tiredness or breathlessness
- Easy bruisisng
- Yellow complexion
- Muscle cramps
- Nocturia
- In ESRF; there is kussmaul resp, anorexia, nausea, hiccups, pruritus, vomiting, muscular twitching, fits, drowsiness and coma.

Signs/examination findings:

- Pallor /anemia

- Increased BP/HTN
- Brown line pigmentation of nails.
- Increased JVP esp. in fluid overload.
- Restless leg syndrome
- Proteinuria

Investigations

- FBC
- U/E
- Serum creatinine
- Calcium, phosphate and albumin
- Lipid profile
- Blood glucose levels
- Imaging studies;
    - U/S
    - CXR
    - ECG esp if >40yrs or has risk factors for cardiac disease
- Others; ANCA, Rh. Factors, Anti GBM, Protein electrophoresis.

TREATMENT OF CRF

Aims

1. Reverse the precipitant factors
- Volume depletion
- Uncontrolled HTN
- Infxn
- Nephrotoxic medications etc
- Urinary tract obstruction

Reversing the precipitants would inturn retard the progression of CRF

Therefore control:-

BP – aim to optimize BP control with ACE –I. This would not only control BP but also reduce proteinuria and reduces fibrosis. With ACE-I, always start with a lower dose. The dose can be raised by 25% every wk.

The same effect may be achieved by using non-dihydropyridine calcium antagonists.

If diabetic; optimize sugar control

Optimize nutrition status:-

Restrict dietary proteins of upto 60g/day or 0.6g/kg/day

Provide high carbohydrate diet

N/B: Ensure no malnutrition.

2. Manage associated complications

(i) HTN – goal of BP is 130/85mmHg
(ii) Anaemia – recombinant Epo etc,
(iii) Dyslipidaemia – HMG-COA reductace inhibitors; statins are useful
(iv) Infection
(v) Metabolic acidosis – maintain plasma bicarbonate above 22mmol/l
(vi) GIT bleeding due to decreased platelet fxn. Dialysis ma be necessary.
(vii) Renal osteodystrophy – restrict diet with high phosphate (milk, cheese, eggs) or use phosphate binders; calcium carbonate and aluminium hydroxide
(viii) Sensory uropathy – use of gaberpentin is useful for restless leg syndrome.
(ix) Depression – manage appropriately thro' counseling on possible progression and the possible need for renal replacement therapy. Also counsel family members.
(x) Fluid and electrolyte balance – depending on presentation; salt-wasting disease or fluid overload. These may require sodium and water intake supplementation or sodium and water restriction. In both cases input/output chart is necessary.

Clinical consequences of CRF.

1. Fluid and electrolytes imbalance.

- From sodium retention, H_2O retention which causes
    - Peripheral oedema
    - Increase BP
    - CCF features
    - Ascites
    - Weight gain

Patients may present with vomiting, general malaise, sweating, intravascular depletion worsens kidney fxn. GFR lower than 5mls/min/1.73m^2 causes hyperkalaemia. In such patients, avoid ACE-I and K+.

Causes of hyperkalaemia

- Metabolic acidosis
- Haemolysis
- Infections
- Drugs (K+ sparring medication), other drugs e.g. Beta blockers.
- Potassium rich foods
- Insulin deficiency.

2. Metabolic acidosis:-
   Due to decreased capacity of kidney to excrete acid and the inability to generate buffers leading to a fall in PH

   Tx – Iv sodium bicarbonate as bolus then ½ dose, then ½ dose as IVI. Total dose 1meq/kg/day.

3. GIT disorders
   - Anorexia, peptic ulcerations and GIT bleeding due to impaired platelets fxn.
   - Pt later develops ascites.

4. CVS CMXs
   Increase BP, cardiomyopathy and heart failure.

   CRF causes increased atherosclerosis due to hypercholesteraemia, DM and HTN.

   Coronary artery disease equivalent, anybody who has had a heart attack before has a risk of 50%

Traditional risk factors for heart attack

- Obesity
- Sedentary life style
- Low HDL (dyslipidaemia)
- HTN
- Smoking
- DM
- OCPS

Risk factors for chronic kidney disease.

- Proteinuria

- Anaemia
- Uraemic toxins
- Hypercoagulability states.
- Increased Ca++ and phosphataemia.

Reversible factors for CRF:-

- HTN
- Reduced renal perfusion as in
  - Renal artery stenosis
  - Hypotension due to drug Rx
  - Sodium and water depletion
- Poor cardiac function
- Urinary tract obstruction
- UTI
- Others – infxn causing increased catabolism and urea productions.
  -Nephrotoxic medication.

5. Anemia

Usually monocytic normochromic anaemia.

The causes of anaemia in CRF include:-

- Deficiency of erytropoietn due to decreased production (failure of erythropoietin response)
- Toxic effects of uraemia causing decreased erythropoeitin and decrease in BM fxn,.
- Reduced dietry intake.
- Reduced RBC survival
- Increasesd blood loss due to capillary fragility and poor platelet fxn

Anemia causes LVF, increased mortality, progression of renal dz and DM CMx

Treatment:

- Recombinant human erythropoietn EPO (epoietin – alpha 50 – 150u/kg/wk in divided dose IV or sc or --Daepoetin alpha 0.45ug/kg IV or SC every 2/52.
- Correct concomitant iron deficiency by giving IV iron (oral iron has poor absorption). The commonly used iv iron is venofer at 50 – 100mg twice/wk for 6.52.
- Monitor serum ferritin, serum iron; do transferin saturation and if the indices are still low, repeat the treatment.
- Target Hb 11 – 12g/dl (110 120g/d) Hb > 13g/dl increases mortality rate.
- Others- red cell transfusion

-Continous erythropoesis Receptor activator – CERA

CERA is a pegylated EPO and is a monthly dosing.

6. Infections

Susceptibility to infxns in pts with CRF is due to impaired cellular and hormonal immunity.

7. Disorders of bone metabolism

i) Renal oeteodystrophy

Results from decreased calcium absorption which causes overproduction of parathyroid hormones. Increase PHT causes osteitis fibrosa cystica

There are disorders of Vit D metabolism and chronic metabolic acidosis.

Hyperphosphataemia causes a diseased in calcium levels because phosphate binds to Ca++ -> hypercalcaemia and decreased calcium sensitive receptors (CASR).

N/B: Vit D is important for GIT Ca++absorption and reabsorption.

Phosphataemia is due to phosphate retention from nephron loss.

Clinical features include; bone pains, recurrent fractures, muscle aches and cramps.

Rx – calciphylaxiS if Ca – Po_4^{-3} product in blood exceeds 5.5mmol/l

Calcium phosphate product in blood should not be > 5.5mmol/l because this causes deposition of Ca++ in soft tissues with resultant necrosis and in blood vessels causing atherosclerosis.

For posphataemia; treatment includes

Phosphate restriction diet by limiting protein intake. Unfortunately, one of the consequences is malnutrition, so ensure high biological value proteins such as meat and eggs.

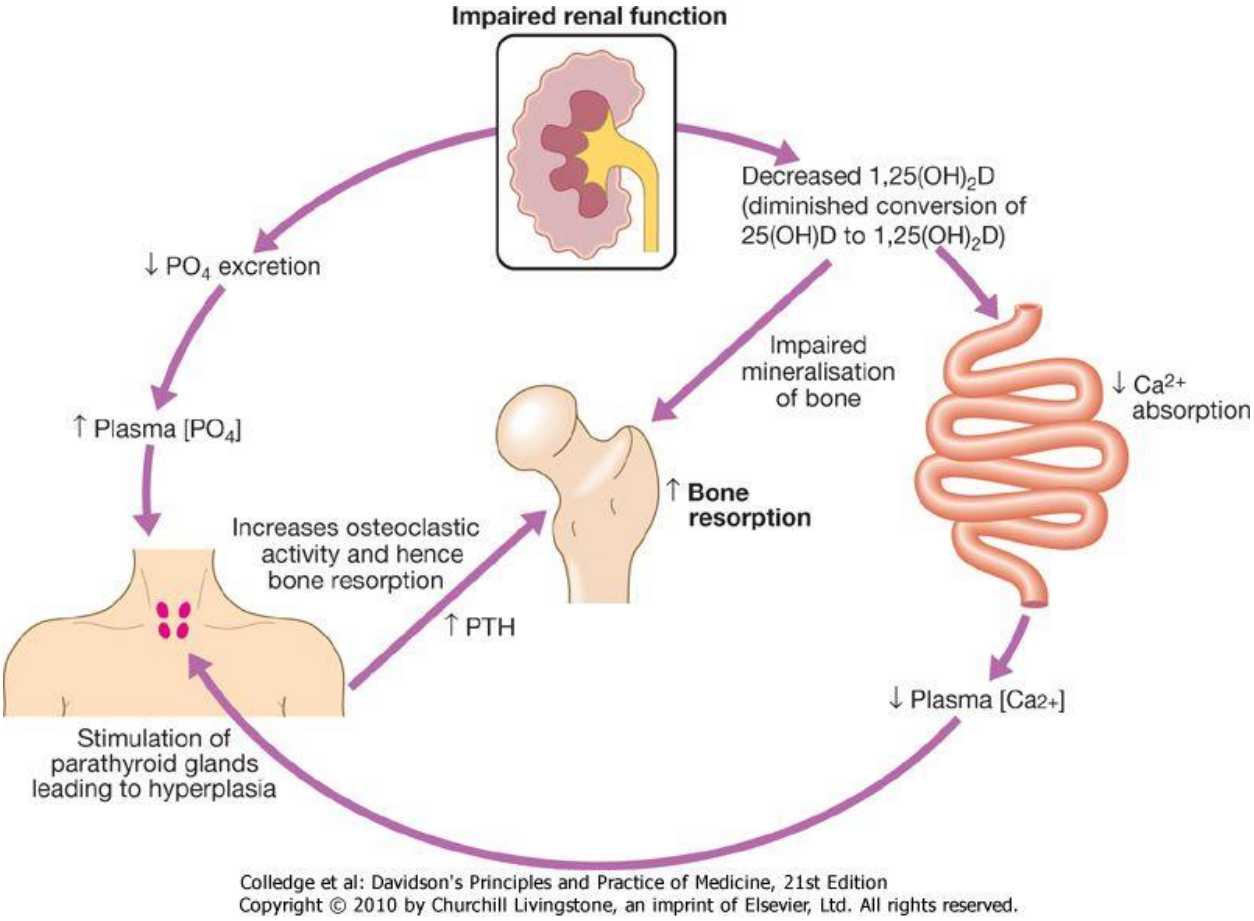
Avoid dairy products, phosphate containing additives, processed foods etc.

Phosphate binding agents – bind in GIT & decrease absorption. The binders include:-

Calcium containg buinders eg calcium carbonate and calcium acitate.

Ensure Ca – Po_4^{-3} product is < 5.5mmol per litre, when it goes more than 5.5mmol/l; give sevelamer.

Pathogenesis of renal osteodystrophy



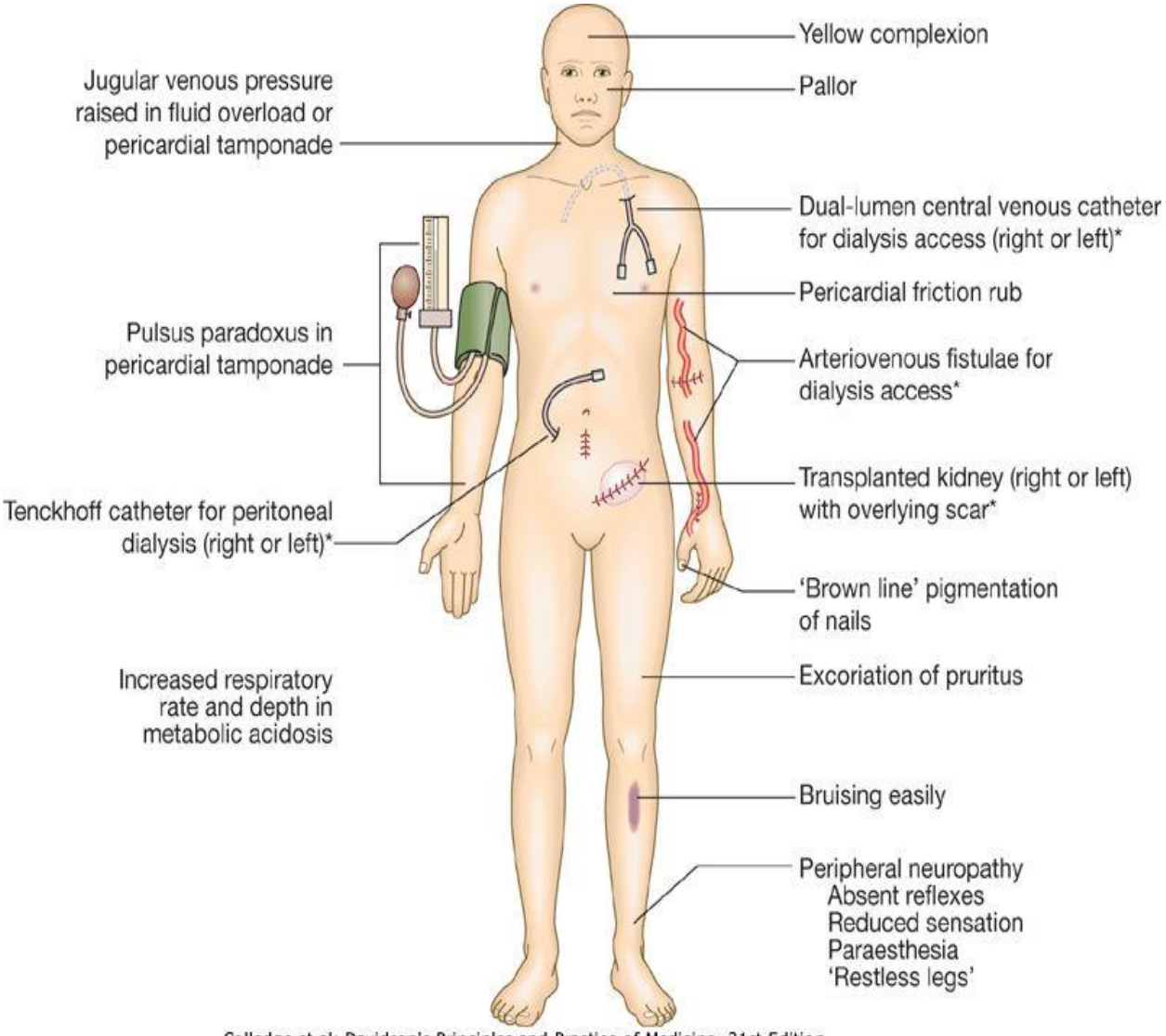
ii) Secondary hyperparathyroidism

Due to Vit D or Vit D analogues to correct hypocalcaemia.

These must be active Vit D analogues (calcitriol)

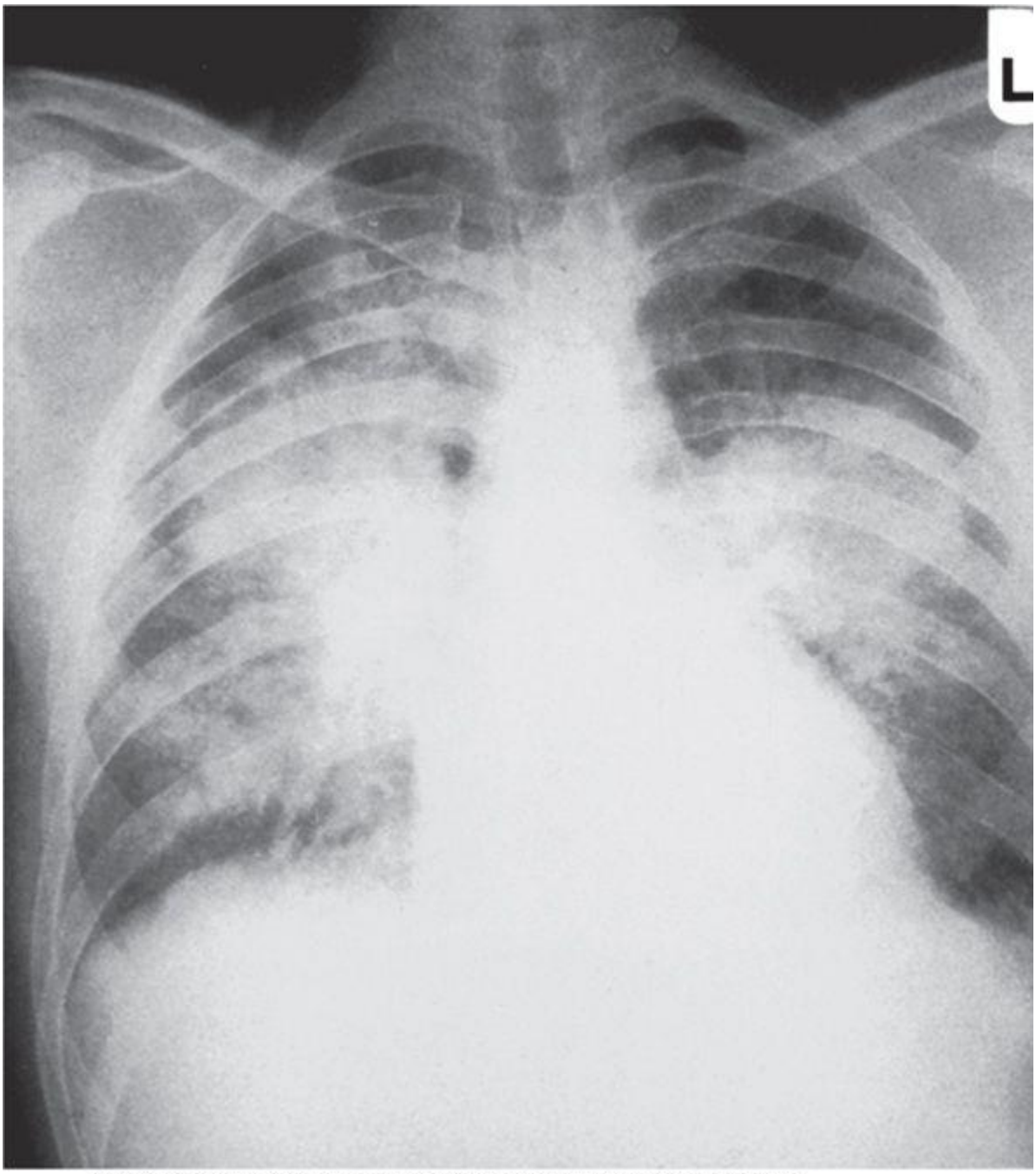
Others – calcimimetics e.g. cinacelet which mimics the calcium and binds to CASR in the parathyroid gland and prevents elevation of calcium levels.

Physical signs in advanced chronic kidney disease. (Features of renal replacement therapy)



Pulmonary oedema in acute renal failure.

The appearances are indistinguishable from left ventricular failure but the heart size is usually normal. Blood pressure is often high.



Clinical terms.

Azotemia – retention of nitrogenous waste products, urea, urates, polyamines, indoles, phenols, hippurate.

Uraemia – nitrogenous compounds plus endocrine dysfxn and loss of normal products produced by kidney plus fluid dysfxn.

Excretory failure – increased fluid retention causing dysfxn in cellular structures.

N/B: uraemia causes decreased body temp, decreased lipoprotein lipase activity and fxn leading to hyperlipidemia.

Bence Jones proteinuria

Patients with a clone of B lymphocytes secreting free immunoglobulin light chains filter these freely into the urine, and this can be identified as 'Bence Jones protein' in fresh urine samples. This may occur in amyloidosis and in B cell disorders, but is particularly important as a marker for myeloma. Bence Jones protein is poorly identified by dipstick tests and relatively low quantities of protein may be associated with significant pathology, so specific immunodetection methods are required when Bence Jones proteinuria is suspected. Highly sensitive serum assays for free light chains are becoming available for monitoring treatment.

Microalbuminuria

Microalbuminuria describes the urinary excretion of small amounts of albumin

TUBULO-INTERSTITIAL DISEASES

Acute tubular necrosis is the most common cause of the clinical syndrome of acute renal failure

Interstitial nephritis

A group of inflammatory, inherited and other diseases affect renal tubules and the surrounding interstitium. The clinical presentation is often simply with renal impairment. Proteinuria is generally low level. Urine may contain red and white blood cells.

Acute interstitial nephritis (AIN)

Acute inflammation within the tubulo-interstitium is most commonly allergic, particularly to drugs, but other causes include toxins and a variety of systemic diseases and infections. Deterioration of renal function in drug-induced AIN may be dramatic and resemble rapidly progressive glomerulonephritis.

Causes of acute interstitial nephritis

1. **Allergic**

   Many drugs, but particularly
   - Penicillins
   - NSAIDs
   - Proton pump inhibitors
   - Mesalazine (delayed)

2. **Immune**
   - Autoimmune nephritis ± uveitis
   - Transplant rejection

3. **Infections**
   - Acute bacterial pyelonephritis
   - Leptospirosis
   - Tuberculosis
   - Hantavirus

4. **Toxic**
   - Myeloma light chains
   - Mushrooms (*Cortinarius*)

Management

Some patients with drug-induced AIN recover following withdrawal of the drug alone, but corticosteroids (e.g. prednisolone 1 mg/kg/day) accelerate recovery and may prevent long-term scarring. Dialysis is sometimes necessary but is usually only short-term.

Chronic interstitial nephritis

Chronic interstitial nephritis (CIN) is caused by a heterogeneous group of diseases

Causes of chronic interstitial nephritis

1. Acute interstitial nephritis

- Any of the causes of AIN

2. Glomerulonephritis

- Varying degrees of interstitial inflammation occur in association with most types of inflammatory glomerulonephritis

3. Immune/inflammatory

- Sarcoidosis
- Sjögren's syndrome
- SLE, primary autoimmune
- Chronic transplant rejection

4. Toxic

- Mushrooms (*Cortinarius*)
- Lead
- *Aristolochia*
- Balkan nephropathy

5. Drugs

- All drugs causing AIN
- Lithium toxicity
- Analgesic nephropathy
- Ciclosporin, tacrolimus

6. Infection

- Consequence of severe pyelonephritis

7. Congenital/developmental

- Vesico-ureteric reflux: is associated; causation not clear
- Renal dysplasias: often associated with reflux

- Inherited: now well recognised but mechanisms unclear
- Other: Wilson's disease, medullary sponge kidney, sickle-cell nephropathy

8. Metabolic and systemic diseases

- Hypokalaemia, hypercalciuria, hyperoxaluria

- Amyloidosis

Toxic causes of CIN

The combination of interstitial nephritis and tumours of the collecting system is seen in 'Chinese herb nephropathy' (a rapidly progressive syndrome caused by mistaken identity of ingredients in herbal preparations.), in analgesic nephropathy, and in Balkan nephropathy (an endemic chronic nephropathy). A plant toxin found in *Aristolochia clematis* (aristolochic acid) is probably responsible for the herb nephropathy and possibly also for Balkan nephropathy. Confusing *Cortinarius* species for wild edible or 'magic' mushrooms causes a devastating irreversible renal tubular toxicity encountered occasionally in Scandinavia and Scotland.

Papillary necrosis and analgesic nephropathy

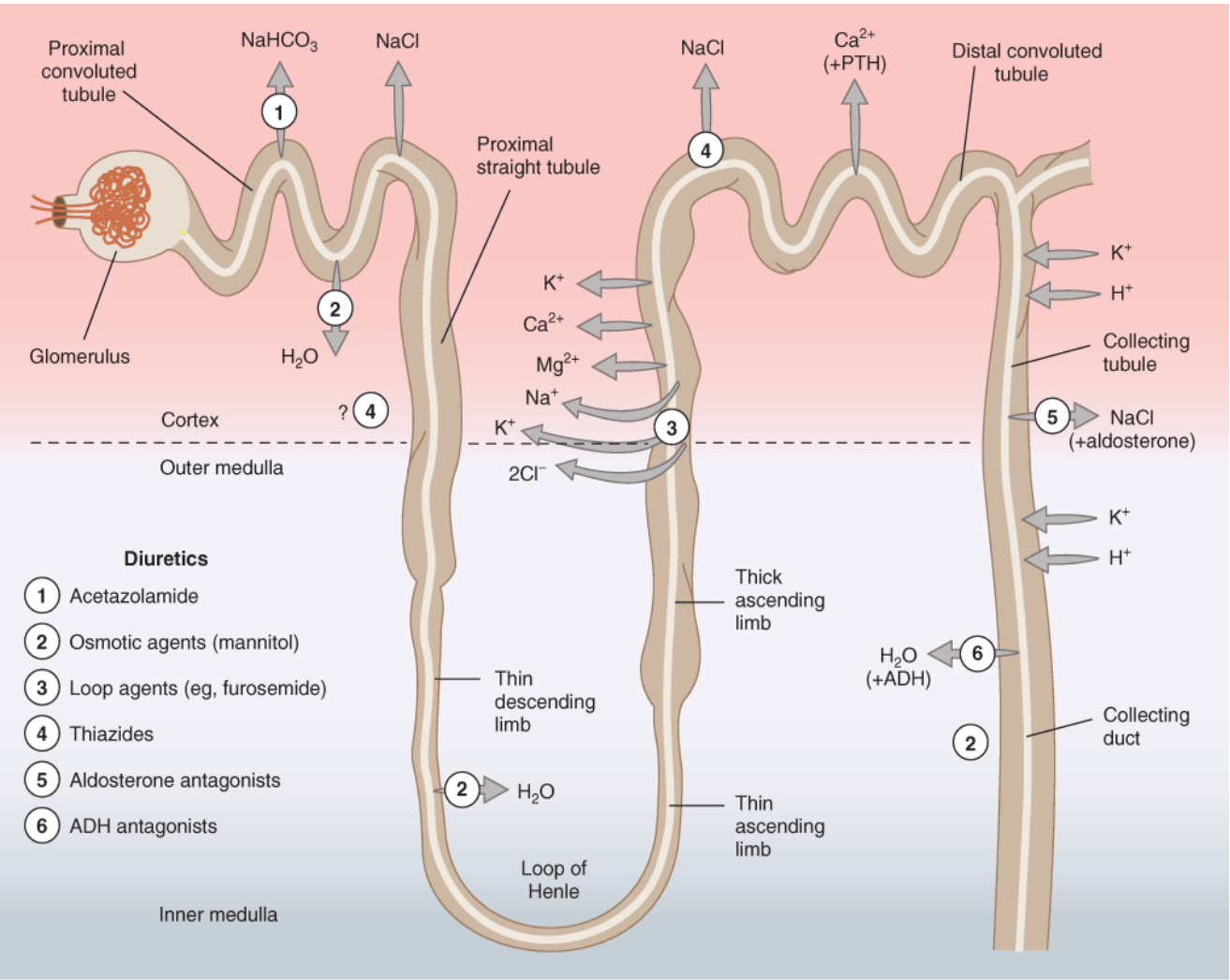
The renal papillae are at the end of the capillary distribution in the kidney, and may necrose in diabetes mellitus, rarely in infections, in sickle-cell disease and occasionally in other conditions. Necrosed papillae may cause ureteric obstruction and renal colic. Papillary necrosis is difficult to identify other than on pyelography.

Long-term ingestion (years to decades) of certain NSAIDs may cause CIN and renal papillary necrosis. In animals, lesions can be induced with almost any NSAID; however a dramatic fall in the incidence of analgesic nephropathy has been observed which appears to coincide with the withdrawal of phenacetin from compound analgesics.

Sickle-cell nephropathy

- The longer survival of patients with sickle-cell disease, means that a larger proportion live to develop chronic complications of microvascular occlusion.
- In the kidney these changes are most pronounced in the medulla, where the vasa recta are the site of sickling because of hypoxia and hypertonicity.
- Loss of urinary concentrating ability and polyuria are the earliest changes; distal renal tubular acidosis and impaired potassium excretion are typical.
- Papillary necrosis (as seen in analgesic nephropathy) is very common. A minority of patients develop ESRD.
- This is managed according to the usual principles, but response to recombinant erythropoietin is poor in the presence of haemoglobinopathy.
- Patients with sickle trait have an increased incidence of unexplained microscopic haematuria, and occasionally overt papillary necrosis.

DIURETICS



Source: Trevor AJ, Katzung BG, Masters SB: *Pharmacology Examination & Board Review, 9th Edition:* www.accesspharmacy.com

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