CHRONIC KIDNEY DISEASE (CKD)

Introduction

- CKD implies longstanding (more than 3 months), and usually progressive, impairment in renal function.
- In many instances, no effective means are available to reverse the primary disease process.

Introduction

- Wide geographical variations in the incidence of disorders causing CKD exist.
- The most common cause of glomerulonephritis in sub-Saharan Africa is malaria.
- Schistosomiasis is a common cause of CKD due to urinary tract obstruction in parts of the Middle East, including southern Iraq.
- ESKD is three to four times as common in black Africans in the UK and USA as it is in whites, and hypertensive nephropathy is a much more frequent cause of ESKD in this group.

Introduction

- The prevalence of diabetes mellitus and hence of diabetic nephropathy is higher in some Asian groups than in whites.
- The age is of relevance; CKD due to atherosclerotic renal vascular disease is much more common in the elderly than in the young.
- Over 70% of all cases with CKD are due to diabetes mellitus, hypertension and atherosclerosis.

Table 11. Definition of Chronic Kidney Disease

Criteria
1. Kidney damage for ≥3 months, as defined by structural or functional abnormalities of the kidney, with or without decreased GFR, manifest by *either*: • Pathological abnormalities; or • Markers of kidney damage, including abnormalities in the composition of the blood or urine, or abnormalities in imaging tests
2. GFR <60 mL/min/1.73 m^2 for ≥3 months, with or without kidney damage

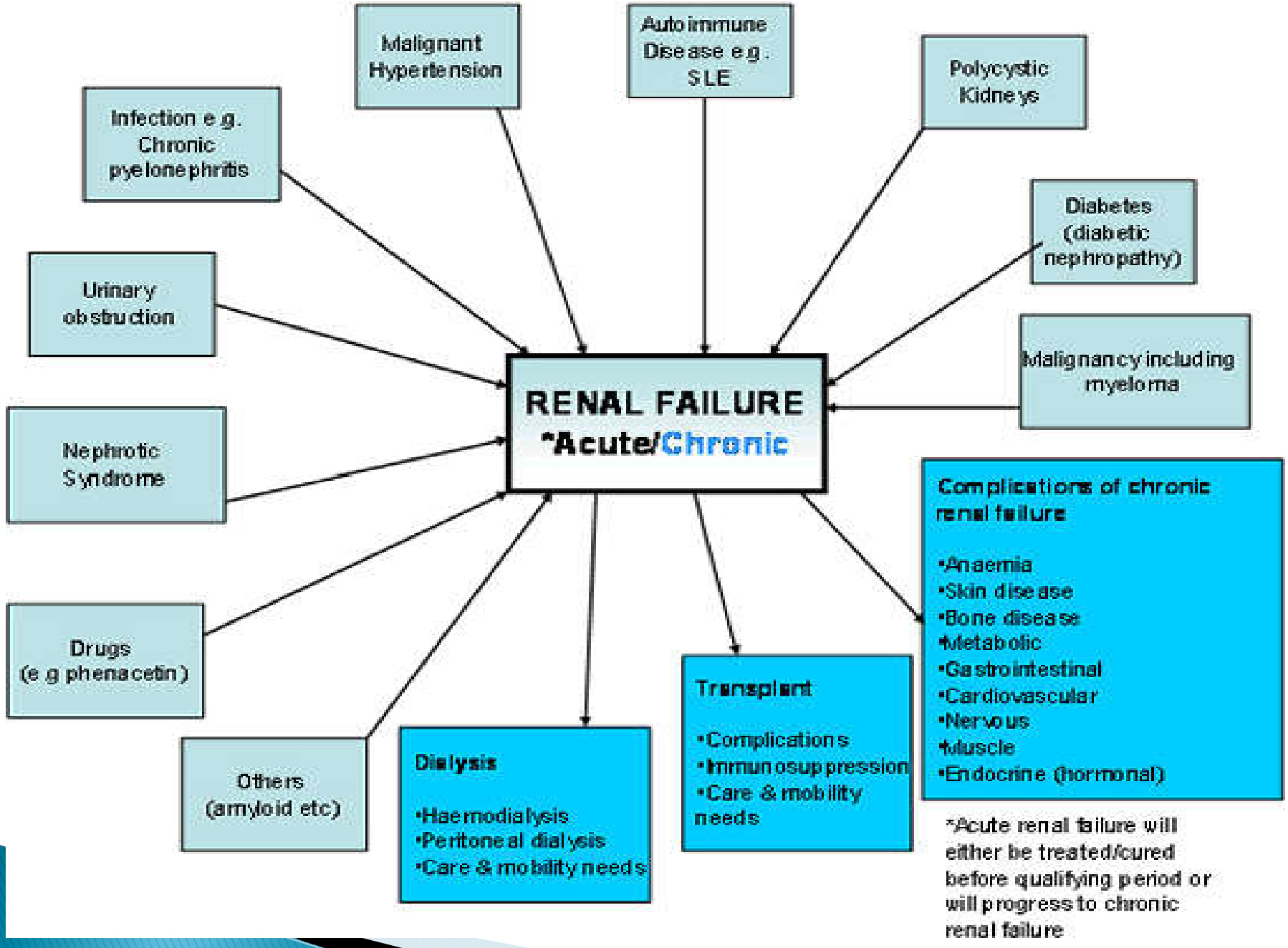
Methods to estimate GFR are discussed in Guideline 4. Markers of kidney damage are discussed in Guidelines 5–6.

definition

- It has been agreed by experts that:
- The current definition for CKD will be retained: GFR <60 mL/min per 1.73 m2 or a urinary albumin-to creatinine ratio >65 mg/mmol or protein creatinine ratio of 100 mg/mmol.
- The classification has been modified by adding albuminuria stage, subdivision of stage 3 into A and B, and emphasizing clinical diagnosis.

Classification of CKD

Stage	GFR (mL/min/1.73 m2)	Description
1	≥90	Normal or increased glomerular filtration rate (GFR), with other evidence of kidney damage
2	60–89	Slight decrease in GFR with other evidence of kidney damage
3A	45–59	Moderate decrease in GFR with or without other evidence of kidney damage
3B	30–44	
4	15–29	Severe decrease in GFR with or without other evidence of kidney damage
5	<15	Established renal failure


Malignant Hypertension
Autoimmune Disease e.g. SLE
Polycystic Kidneys
Infection e.g. Chronic pyelonephritis
Diabetes (diabetic nephropathy)
Urinary obstruction
Malignancy including myeloma
RENAL FAILURE
*Acute/Chronic
Nephrotic Syndrome
Complications of chronic renal failure
•Anaemia
•Skin disease
•Bone disease
•Metabolic
•Gastrointestinal
•Cardiovascular
•Nervous
•Muscle
•Endocrine (hormonal)
Drugs (e.g. phenacetin)
Transplant
•Complications
•Immunosuppression
•Care & mobility needs
Others (amyloid etc)
Dialysis
•Haemodialysis
•Peritoneal dialysis
•Care & mobility needs
*Acute renal failure will either be treated/cured before qualifying period or will progress to chronic renal failure

Basic Diagnosis	No.	%
Diabetic Nephropathy	3490	30.0
Undetermined	1819	15.6
CGN	1542	13.2
Hypertensive Nephrosclerosis	1313	11.3
TID	814	7.0
Obstructive Uropathy	316	2.7
Cystic Disease	276	2.4
Renovascular Disease	99	0.9
Congenital Disease	59	0.5
Heredofamilial	14	0.1
Vascular disease	1	0.01
Others	1899	16.3
Total:	11644	100.0

Causes of chronic kidney disease

Congenital and inherited disease
Polycystic kidney disease (adult and infantile forms)
Medullary cystic disease
Tuberous sclerosis Oxalosis Cystinosis
Congenital obstructive uropathy

Glomerular disease

Primary glomerulonephritides *including focal* glomerulosclerosis

Secondary glomerular disease *(systemic lupus,* polyangiitis, Wegener's granulomatosis, amyloidosis, diabetic glomerulosclerosis, accelerated hypertension, haemolytic uraemic syndrome, thrombotic thrombocytopenic purpura, systemic sclerosis, sickle cell disease)

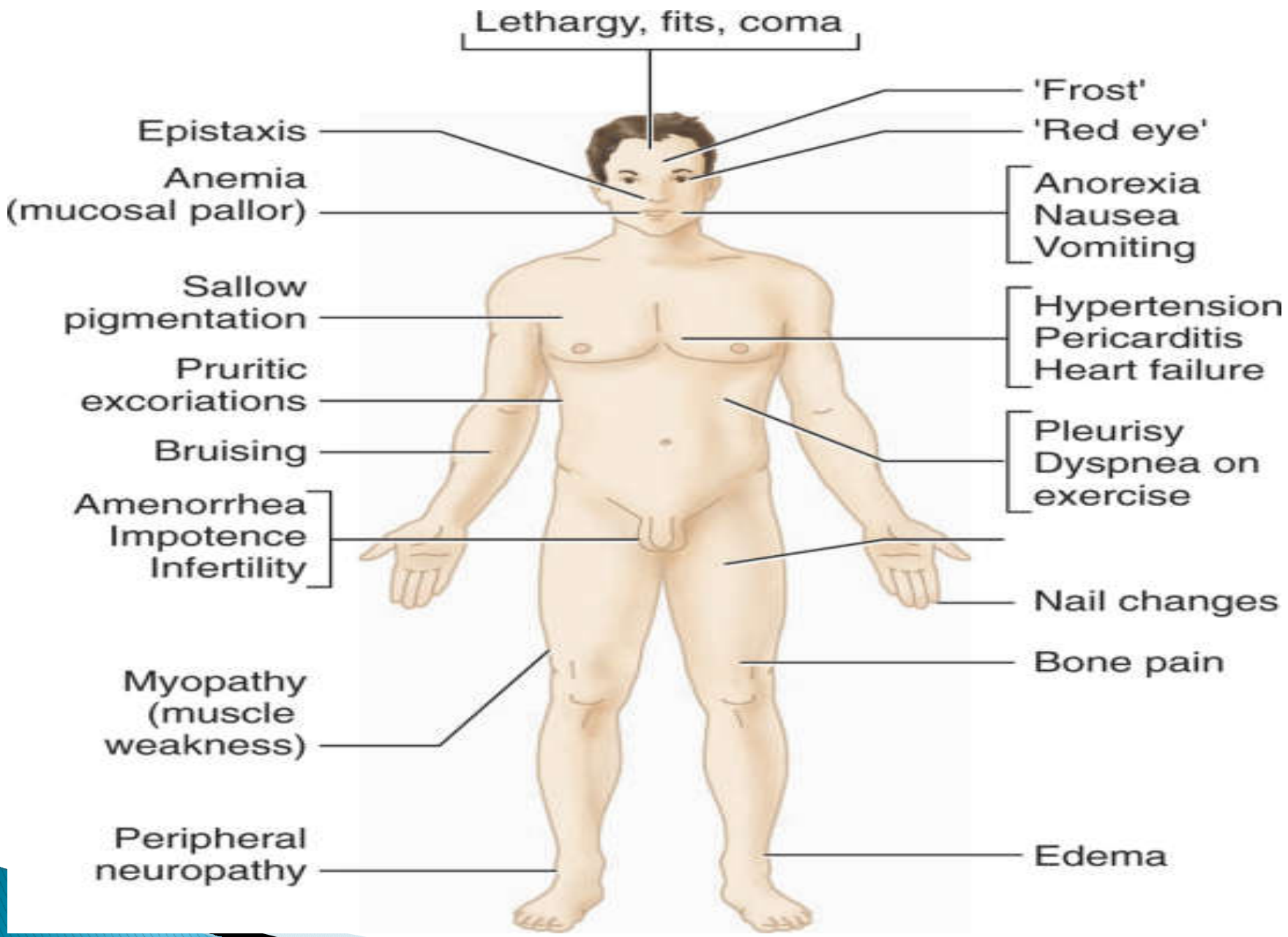
Causes of chronic kidney disease

Vascular disease
Hypertensive nephrosclerosis (common in black Africans)
Renovascular disease Small and medium-sized vessel vasculitis
Tubulointerstitial disease
Tubulointerstitial nephritis – idiopathic, due to drugs (especially nephrotoxic analgesics), immunologically mediated
Reflux nephropathy
Tuberculosis
Schistosomiasis
Nephrocalcinosis
Multiple myeloma (myeloma kidney)
Renal papillary necrosis (diabetes, sickle cell disease and trait, analgesic nephropathy) Chinese herb nephropathy
Urinary tract obstruction
Calculus disease
Prostatic disease
Pelvic tumours
Schistosomiasis

Clinical approach to the patient with CKD or any other form of renal disease

- **History**
- Particular attention should be paid to:
- *Duration of symptoms*
- *Drug ingestion, including non-steroidal antiinflammatory*
- agents, analgesic and other medications, and unorthodox treatments such as herbal remedies
- *Previous medical and surgical history, e.g. previous*
- chemotherapy, multisystem diseases such as SLE, malaria
- *Previous occasions on which urinalysis or* measurement of urea and creatinine might have been performed, e.g. pre-employment or insurance medical examinations, new patient checks
- *Family history of renal disease.*

- **Symptoms**
- The early stages of CKD are often completely asymptomatic, despite the accumulation of numerous metabolites.
- Serum urea and creatinine concentrations are measured in CKD,
- a rough correlation exists between urea and creatinine concentrations and symptoms.
- The nature of the metabolites that are involved in the genesis of symptoms is unclear.


Lethargy, fits, coma
'Frost'
'Red eye'
Epistaxis
Anemia
(mucosal pallor)
Anorexia
Nausea
Vomiting
Sallow
pigmentation
Hypertension
Pericarditis
Heart failure
Pruritic
excoriations
Bruising
Pleurisy
Dyspnea on
exercise
Amenorrhea
Impotence
Infertility
Nail changes
Bone pain
Myopathy
(muscle
weakness)
Peripheral
neuropathy
Edema

- Symptoms are common when the serum urea concentration exceeds 40 mmol/L, but many patients develop uraemic symptoms at lower levels of serum urea. Symptoms include:
- Malaise, loss of energy
- Loss of appetite
- Insomnia
- Nocturia and polyuria due to impaired concentrating
- ability
- Itching
- Nausea, vomiting and diarrhoea
- Paraesthesiae due to polyneuropathy

- ‘Restless legs’ syndrome (overwhelming need to frequently alter position of lower limbs)
- Bone pain due to metabolic bone disease
- Paraesthesiae and tetany due to hypocalcaemia
- Symptoms due to salt and water retention – peripheral or pulmonary oedema
- Symptoms due to anaemia
- Amenorrhoea in women; erectile dysfunction in men.
- In more advanced uraemia CKD stage 5, these symptoms become more severe and CNS symptoms are common:

- Mental slowing, clouding of consciousness and seizures Myoclonic twitching.
- Severe depression of glomerular filtration can result inoliguria. This can occur with either acute kidney injury or in the terminal stages of CKD. However, even if the GFR is profoundly depressed, failure of tubular reabsorption may lead to very high urine volumes; the urine output is therefore not a useful guide to renal function.

- **Examination**
- There are few physical signs of uraemia per se.
- Findings include: short stature (in patients who have had CKD in childhood);
- pallor (due to anaemia); increased photosensitive pigmentation
- (which may make the patient look misleadingly healthy);
- scratch marks due to uraemic pruritus; signs of fluid overload.
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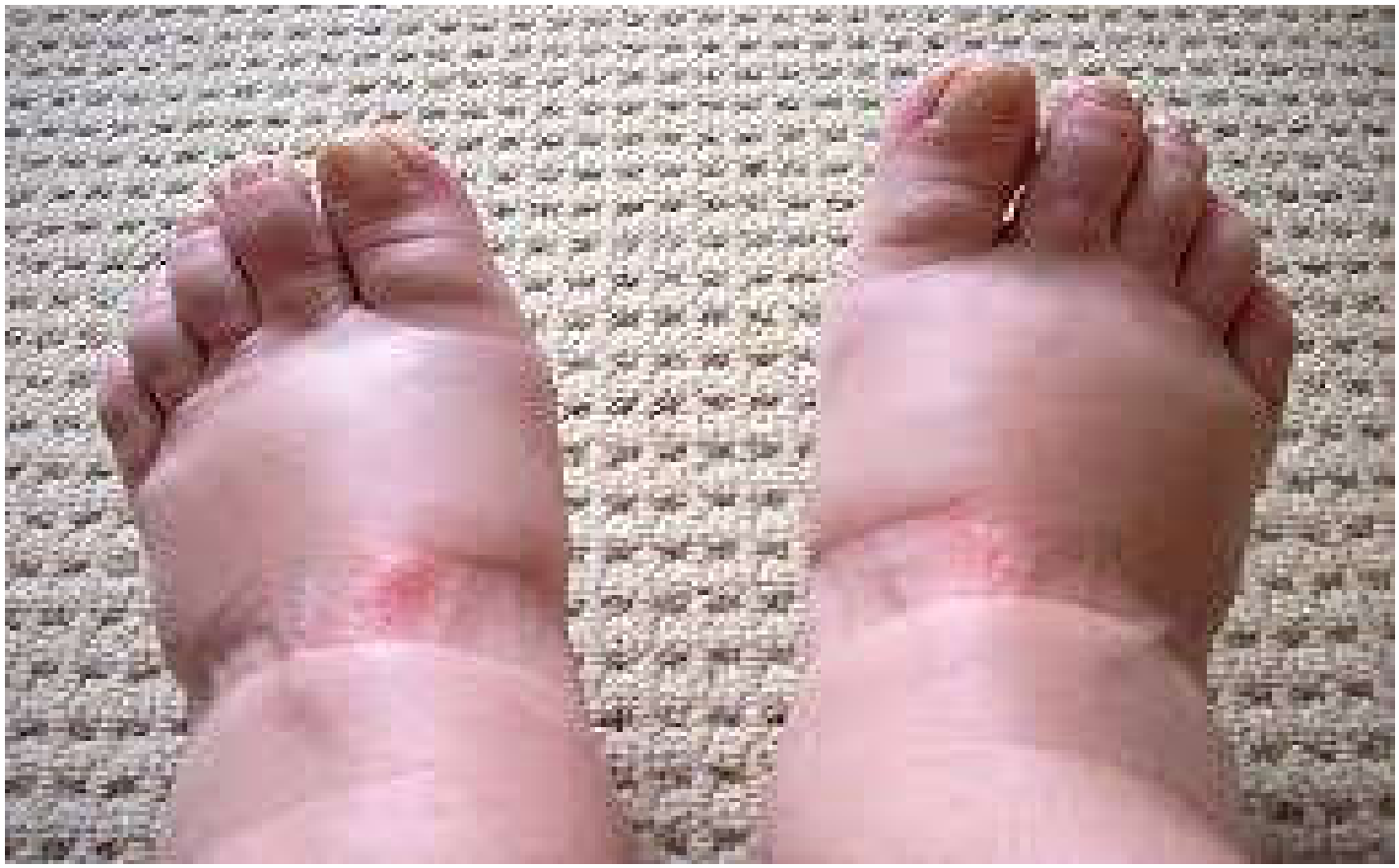
CHRONIC RENAL FAILURE (CRF)

- RENAL INSUFFICIENCY -

- Edema
- Headaches
- GFR - progressively decreases from 90 to 30 ml/min
- ↓ Ability to Concentrate Urine
- Mild Anemia
- Polyuria → Oliguria
- ↑ BP
- ↑ BUN & Serum Creatinine
- Weakness & Fatigue

- pericardial friction rub; flow murmurs (mitral regurgitation due to mitral annular calcification; aortic and pulmonary regurgitant murmurs due to volume overload);
- and glove and stocking peripheral sensory loss (rare).
- The kidneys themselves are usually impalpable unless grossly enlarged as a result of polycystic disease, obstruction or tumour

- In addition to these findings, there may be physical signs of any underlying disease which may have caused the CKD,
- for instance:
- Cutaneous vasculitic lesions in systemic vasculitides
- Retinopathy in diabetes and hypertensive retinopathy in hypertension.
- An assessment of the central venous pressure, skin turgor, blood pressure both lying and standing and peripheral circulation should also be made.



Investigations

- The following investigations are common for all renal patients.
- This includes patients with glomerular or non-glomerular
- disease, renal involvement in systemic diseases, AKI and
- CKD, as renal symptoms and signs are nonspecific.
- **Urinalysis**
- *Haematuria may indicate glomerulonephritis, but other* sources must be excluded
- *Proteinuria, if heavy, is strongly suggestive of glomerular* disease. Urinary infection may also cause proteinuria.
- *Glycosuria with normal blood glucose is common in CKD.*
- *Urine culture, including early-morning urine samples* for TB.

- ***Urine microscopy***
- ***White cells in the urine usually indicate active bacterial*** urinary infection, but this is an uncommon cause of CKD; sterile pyuria suggests papillary necrosis or renal tuberculosis.
- ***Eosinophiluria is strongly suggestive of allergic*** tubulointerstitial nephritis or cholesterol embolization.
- ***Casts. Granular casts are formed from abnormal cells*** within the tubular lumen, and indicate active renal disease.
- *Red-cell casts are highly suggestive of* glomerulonephritis.
- ***Red cells in the urine may be from anywhere between*** the glomerulus and the urethral meatus

- **Serum biochemistry**
- Urea and creatinine.
- Calculation of eGFR.
- Elevations of creatine kinase and a disproportionate elevation in serum creatinine and potassium compared with urea suggest rhabdomyolysis.
- **Haematology**
- *Eosinophilia suggests vasculitis, allergic* tubulointerstitial nephritis, or cholesterol embolism.
- *Markedly raised viscosity or ESR suggests myeloma or* vasculitis.
- *Fragmented red cells and/or thrombocytopenia* suggest intravascular haemolysis due to accelerated hypertension, haemolytic uraemic syndrome or thrombotic thrombocytopenic purpura.

- **Radiological investigation**
- *Ultrasound. Every patient should undergo* ultrasonography (for renal size and to exclude hydronephrosis), and plain abdominal radiography and CT (without contrast) to exclude low-density renal stones or nephrocalcinosis, which may be missed on ultrasound.
- *CT is also useful for the diagnosis of retroperitoneal* fibrosis and some other causes of urinary obstruction, and may also demonstrate cortical scarring.
- *MRI. Magnetic resonance angiography in renovascular* disease.
- **Renal biopsy**
- This should be performed in every person with unexplained CKD and normal-sized kidneys, unless there are strong contraindications.
- If rapidly progressive glomerulonephritis is possible, this investigation must be performed within 24 h of presentation if at all possible.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Complications of chronic kidney disease

- ***Anaemia***
- Several factors have been implicated:
- *Erythropoietin deficiency (the most significant)*
- *Bone marrow toxins retained in CKD*
- *Bone marrow fibrosis secondary to* hyperparathyroidism
- *Haematinic deficiency – iron, vitamin B12, folate*
- *Increased red-cell destruction*
- *Abnormal red-cell membranes causing increased* osmotic fragility
- *Increased blood loss – occult gastrointestinal bleeding,* blood sampling, blood loss during haemodialysis or because of platelet dysfunction
- *ACE inhibitors (may cause anaemia in CKD, probably* by interfering with the control of endogenous erythropoietin release).
- Red-cell survival is reduced in CKD. Increased red-cell destruction may occur during haemodialysis owing to mechanical, oxidant and thermal damage.

Bone disease: renal osteodystrophy

- The term ‘renal osteodystrophy’, more appropriately described as bone mineral disorder, embraces the various forms of bone disease that may develop alone or in combination in CKD – hyperparathyroid bone disease, osteomalacia, osteoporosis, osteosclerosis and adynamic bone disease
- Most patients with CKD are found, histologically, to have mixed bone disease.
- renal osteodystrophy is present in many patients with moderate CKD and in almost all of those with ESKD.

- ***Pathogenesis of bone disease***
- Phosphate retention owing to reduced excretion by the kidneys occurs in the very early stages of CKD.
- This results in the release of fibroblast growth factor 23 (FGF 23) and by osteoblasts as a compensatory mechanism. FGF 23 causes phosphaturia to bring the plasma phosphate level to within the normal range.
- FGF 23 also downregulates 1α-hydroxylase in an attempt to reduce intestinal absorption of phosphate. However, consistently elevated levels of FGF 23 after a while cannot control phosphate levels and its effects are overwhelmed by development of secondary hyperparathyroidism.
- Elevated FGF 23 levels are the strongest independent predictor of mortality in patients with CKD.

- Decreased renal production of the 1α-hydroxylase enzyme results in reduced conversion of 25-(OH)2D3 to the more metabolically active 1,25-(OH)2D3.
- Reduced activation of vitamin D receptors (VDR) in the parathyroid glands leads to increased release of parathyroid hormone (*secondary hyperparathyroidism).*

- 1,25-Dihydroxycholecalciferol deficiency also results in gut calcium malabsorption.

- Phosphate retention owing to reduced excretion by the kidneys, results in an increase in PTH synthesis and release.
- PTH promotes reabsorption of calcium from bone and increased proximal renal tubular reabsorption of calcium, and this opposes the tendency to develop hypocalcaemia induced by 1,25-(OH)2D3 deficiency and phosphate retention.

- This ‘secondary’ hyperparathyroidism leads to increased osteoclastic activity, cyst formation and bone marrow fibrosis *(osteitis fibrosa cystica).*

- 1,25-(OH)2D3 deficiency and hypocalcaemia result in impaired mineralization of osteoid *(osteomalacia).*

- ***Skin disease***
- Pruritus (itching) is common in severe CKD and is mainly due to retention of nitrogenous waste products of protein catabolism as it improves following dialysis.
- Other causes of pruritus include hypercalcaemia, hyperphosphataemia,
- elevated calcium $\times$ phosphate product, hyperparathyroidism (even if calcium and phosphate levels are normal) and Iron deficiency.
- In dialysis patients, inadequate dialysis is usually the cause of pruritus. Nevertheless, a significant number of dialysis patients who are well dialysed and in whom other causes of pruritus can be excluded suffer persistent itching.
- The cause is unknown and no effective treatment exists.

- **Nephrogenic systemic fibrosis (NSF)**
- NSF is a systemic fibrosing disorder with predominant skin involvement.
- It is seen only in patients with moderate to severe CKD (eGFR <30 mL/min), particularly patients on dialysis.
- Gadolinium-containing contrast agents, which are excreted exclusively by the kidney, have been implicated in the causation of over 95% cases of NSF.
- The *diagnosis is based upon a biopsy of an involved site,* showing proliferation of dermal fibrocytes with excessive collagen deposition. Special testing may show gadolinium.

- NSF usually follows a chronic and unremitting course, with 30% having no improvement, 20% having modest improvement and 30% dying.
- No single therapy or combination of therapies has shown consistent benefit in NSF with exception of improvement in renal function.
- Improvement in the NSF may follow renal transplantation.
- *Prevention is by* avoiding the use of gadolinium-based contrast agents in patients with severe CKD (eGFR <30 mL/min) or those on dialysis therapy.

- **Gastrointestinal complications**
- These include decreased gastric emptying and increased risk of reflux oesophagitis, peptic ulceration, acute pancreatitis and constipation, particularly in patients on continuous ambulatory peritoneal dialysis (CAPD).
- Elevations of serum amylase of up to three times normal may be found in CKD without any evidence of pancreatic disease, owing to retention of high-molecular-weight forms of amylase normally excreted in the urine.

- **Metabolic abnormalities**
- **Gout. Urate retention is a common feature of CKD.**
- **Treatment** of clinical gout is complicated by the nephrotoxic potential of NSAIDs.
- Colchicine is useful for the acute attack, and allopurinol should be introduced under colchicine cover to prevent further attacks.
- The dose of allopurinol should be reduced in CKD, e.g. 100 mg on alternate days.

- **Insulin.**
- **Insulin is catabolized by and to some extent** excreted via the kidneys. For this reason, insulin requirements in diabetic patients decrease as CKD progresses. By contrast, end-organ resistance to insulin is a feature of advanced CKD resulting in modestly impaired glucose tolerance.
- Insulin resistance may contribute to hypertension and lipid abnormalities.

- # Endocrine abnormalities
- <u>These include:</u>
- **Hyperprolactinaemia**, which may present with galactorrhoea in men as well as women, Increased luteinizing hormone (LH) levels in both sexes, and abnormal pulsatility of LH release
- Decreased serum testosterone levels (only seldom below the normal level).
- Erectile dysfunction and decreased spermatogenesis are common
- Absence of normal cyclical changes in female sex hormones, resulting in oligomenorrhoea or amenorrhoea

- Complex abnormalities of ***growth hormone*** secretion and action, resulting in impaired growth in uraemic children (pharmacological treatment with recombinant growth hormone and insulin-like growth factor is used)
- Abnormal ***thyroid hormone*** levels, partly because of altered protein binding. Measurement of thyroid stimulating hormone (TSH) is the best way to assess thyroid function.
- True ***hypothyroidism*** occurs with increased frequency in CKD.
- ***Posterior pituitary*** gland function is normal in CKD.

- # Nervous system
- ***Central nervous system***
- *Severe uraemia causes an unusual combination of* depressed cerebral function and decreased seizure threshold.
- However, convulsions in a uraemic patient are much more commonly due to other causes such as accelerated hypertension, thrombotic thrombocytopenic purpura or drug accumulation.
- Asterixis, tremor and ***myoclonus*** are also features of severe uraemia.
- Rapid correction of severe uraemia by haemodialysis leads to *dialysis disequilibrium owing to osmotic cerebral swelling.*
- This can be avoided by correcting uraemia gradually by short, repeated haemodialysis treatments or by the use of peritoneal dialysis.
- ‘

- ***Autonomic nervous system***
- Increased circulating catecholamine levels and impaired efferent vagal function are common in CKD.
- Overactivity of the sympathetic nervous system in CKD is believed to play a part in the genesis of hypertension in this condition. All of these abnormalities improve to some extent after institution of regular dialysis and resolve after successful renal transplantation.
- ***Peripheral nervous system***
- *Median nerve compression in the carpal tunnel is*
- common, usually due to β2-microglobulin-related amyloidosis. ‘
- *Restless legs’ syndrome is common in* uraemia. The syndrome is difficult to treat.
- Iron deficiency should be treated if present. Attention should be paid to adequacy of dialysis. Symptoms may improve with the correction of anaemia by erythropoietin.
- *A polyneuropathy occurs in patients who are* inadequately dialysed.

Cardiovascular disease

- Life expectancy remains severely reduced compared with the normal population owing to a greatly increased (16-fold) incidence of cardiovascular disease, particularly myocardial infarction, cardiac failure, sudden cardiac death and stroke.

Risk factors

- Hypertension is a frequent complication of CKD.
- Diabetes mellitus is the commonest cause of CKD.
- Dyslipidaemia is universal in uraemic patients.
- Ventricular hypertrophy is common, as is systolic and diastolic dysfunction.
- Diastolic dysfunction is largely attributable to left ventricular hypertrophy and contributes to hypotension during fluid removal on haemodialysis.

- Systolic dysfunction may be due to:
- Myocardial fibrosis
- Abnormal myocyte function owing to uraemia
- Calcium overload and hyperparathyroidism
- Carnitine and selenium deficiency.
- Left ventricular hypertrophy is a risk factor for early deathbin CKD, as in the general population.
- Systolic dysfunction is also a marker for early death.

- **Coronary artery calcification.**
- **Traditional risk factors (e.g.**
- smoking, diabetes) can only partly explain the risk in patients with chronic nephropathies.
- Coronary artery calcification is more common in patients with ESKD than in normal individuals and it is highly likely that this contributes significantly to cardiovascular mortality.
- Vascular calcification is frequent in all sizes of vessel in CKD.
- In addition to the classical risk factors for atherosclerosis:
- A *raised (calcium × phosphate) product causes medial* calcification.

- ***Pericarditis***
- This is common and occurs in two clinical settings:
- Uraemic pericarditis is a feature of severe, pre-terminal uraemia or of underdialysis.
- Haemorrhagic pericardial effusion and atrial arrhythmias are often associated.
- There is a danger of pericardial tamponade, and anticoagulants should be used with caution.
- Pericarditis usually resolves with intensive dialysis.
- Dialysis pericarditis occurs as a result of an intercurrent illness or surgery in a patient receiving apparently adequate dialysis.

- **Malignancy**
- The incidence of malignancy is raised in patients with CKD and with dialysis.
- Malignant change can occur in multicystic kidney disease.
- Lymphomas, primary liver cancer and thyroid cancers also occur.