Renal Disease

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Overview
- Aetiology, pathophysiology, clinical signs and symptoms of acute (ARF), chronic (CRF) & end-stage renal failure (ESRF)
- Renal Replacement Therapy: CAPD, APD, Haemodialysis, Transplantation, Conservative Management
- Medical Management of ARF, CRF, & ESRF

Basic Anatomy & Physiology
- Regulate volume and concentration of fluids in the body by producing urine by a process called glomerular filtration
- Involves the removal of waste products, minerals, and water from the blood.
- The kidneys maintain the volume and concentration of urine by filtering waste products and reabsorbing useful substances and water from the blood.

Other main renal functions:
- Detoxify harmful substances (e.g., free radicals, drugs)
- Increase the absorption of calcium from the gut by producing calcitriol (activated form of vitamin D)
- Produce erythropoietin (hormone that stimulates red blood cell production in the bone marrow)
- Secrete renin (hormone that regulates blood pressure and electrolyte balance)
The components of the kidney tubule are:
- Proximal tubule
- Loop of Henle
  - Descending limb of loop of Henle
  - Ascending limb of loop of Henle
- Distal Convoluted Tubule

Tubule component functions

- Proximal tubule:
  - Reabsorption of salt (Na+) and H2O
  - Approximately 2/3 of filtered salt and water reabsorption occurs here
  - ALL filtered organic solutes (primarily glucose and amino acids) reabsorbed

- Loop of Henle:
  - Descending – permeable to water, but completely impermeable to salt. Water dragged out into hypertonic interstitium (i.e. concentration of urine occurs here)
  - Ascending – impermeable to water. Pumps salt out into the interstitium to maintain the osmotic gradient between medulla and loop of Henle; the so-called "counter-current exchange."

- Distal Convoluted Tubule:
  - Cells have numerous mitochondria to produce energy to produce ATP for active transport to occur.
  - Much ion exchange regulated by the endocrine system
  - In presence of parathyroid hormone, DCT absorbs more calcium & excretes more phosphate
  - In presence of Aldosterone, DCT re-absorbs more Na & more K excreted
  - Adjusts urinary concentration of Hydrogen and Ammonium to regulate acidity of urine (and blood)

- Collecting Ducts
  - Normally impermeable to water
  - In presence of Antidiuretic Hormone (ADH), becomes water permeable ie. Levels of ADH determine whether urine will be dilute or concentrated.
  - Increased ADH indicates dehydration
  - Water overload – low ADH and dilute urine
Normal Biochemical Parameters

- **Na**: 135-145 mmol/l
- **K**: 3.5-5.0 mmol/l
- **Urea**: 2.5-6.7 mmol/l
- **Creat**: 70-150 micromol/l
- **HCO₃**: 18-28 mmol/l
- **Ca**: 2.12-2.65 mmol/l

Normal Haematological Parameters

- **Hb**
  - men: 13-18 g/dl
  - women: 11.5-16 g/dl

Investigations in Renal Disease

- **Blood biochemistry & haematology**
- **Urine dipstick**
  - Protein (abnormal when >500 mg/day)
  - Blood (infection, glomerular inflammation)
  - Leucocytes (white cells)

Renal Ultrasound

- **Useful for assessing renal size & perfusion**
  - Large kidneys in obstruction, diabetes, amyloid
  - Small kidneys in chronic renal disease
  - Dilated pelvicalyceal system in obstruction
Renal Perfusion Scan

- Normally, at least half of the injected radioisotope dye is excreted by 20 minutes.
- If there is obstruction, dye hold-up will occur in the pelvicalyceal system and the peak will be prolonged & excretion delayed.
- Useful in assessment of perfusion of newly transplanted kidneys.

Renal Biopsy

- Mainly used when intrinsic renal disease is suspected to provide a pathological diagnosis.

CT Angiography

Acute Renal Failure

- Syndrome arising from rapid fall in Glomerular Filtration Rate (GFR)
- GFR – a measure of the "filtration capacity" of renal glomeruli, expressed in ml/min (corrected for body surface area). Normal is 100ml/min/1.73m²
- Characterized by retention of nitrogenous waste (urea, creatinine), non-nitrogenous products of metabolism, disordered electrolyte & fluid homeostasis, and acid-base disturbance

Acute Kidney Injury (AKI)

- Functional or structural abnormalities, or markers of kidney damage (including blood, urine, tissue tests or imaging studies) present for < 3 months
- Diagnostic Criteria: an abrupt (<48 hours) reduction in GFR, assuming adequate fluid resuscitation, and that obstruction has been excluded
The RIFLE classification

- Incidence:
  - 7% general hospital admission
  - 20-25% patients with sepsis & ~50% with septic shock
  - ~65% of ICU admissions, with a mortality of 43-88%

- Mortality
  - Dialysis-requiring acute renal failure, >50%

- Morbidity
  - Recovery of renal function depends on underlying cause
  - Irreversible in ~5% (~16% in the elderly)

Which patients are at risk?

- Elderly
- Pre-existing chronic renal disease
- Surgery
- Diabetes
- Volume depletion (NBM, bowel obstruction)
- Ischaemic heart disease
- Drugs: NSAIDS, ACE inhibitors, Immunosuppressants, IV contrast, Vancomycin, Gentamicin

How do we recognise ARF?

- Urea and Creatinine increased
- Oligo- or anuria (little or no urine)
- Volume depleted, or Volume overloaded
- Hyperkalaemia (K+)
- Hb often normal
- PO₂ often high
- Ca can be high or low

Causes & Classification

- Pre-renal
- Intrinsic Renal
- Post-renal
Pre-renal

- Decreased renal blood flow & GFR
- Can be secondary to hypovolaemia, or any cause of decreased effective renal blood flow (cardiac output, vasodilatation in sepsis) or intrarenal vasomotor changes (Non-steroidal medications, ACE inhibitors)
- Easily reversible by restoration of renal blood flow
- Kidneys remain structurally normal

Is it pre-renal ARF?

- Is the patient volume deplete?
- Is cardiac function good?
- Is the patient septic/vasodilated?

- Clinical signs:
  - BP, Heart rate, Peripheral perfusion, Urine output

Intrinsic Renal Failure

- Renal parenchyma damaged through injury to renal vasculature, glomerular filter, or tubulo-interstitium
- Commonest cause is Acute Tubular Necrosis (80-90% of cases, the end of product of an ischaemic or nephrotoxic injury)

Pre-renal: Treatment

- Fluid resuscitation, rate depends on degree of hypovolaemia, ongoing losses, whether oligo-anuric & cardiovascular status
- ?Inotropic support (Vasoconstrict in sepsis to increase mean arterial blood pressure)
Small renal vessels & glomeruli
- Glomerulonephritis (inflammation of the filter units). IgA disease, Membranous, Post-infective, Henoch Schonlein, Goodpasture’s disease
- Vasculitis (inflammation of the peritubular, afferent or efferent blood vessels). SLE, Wegener’s, Microscopic Polyangiitis

Glomerulonephritis (inflammation of the filter units). IgA disease, Membranous, Post-infective, Henoch Schonlein, Goodpasture’s disease
- Intravenous Contrast (used for CT scans)
- Clogging of renal tubules with casts (in myeloma, tumour lysis syndrome)

Post renal
- Kidneys produce urine, but there is obstruction to flow
- Increased back pressure results in decreased tubular function
- Can occur at any level in renal tract
- Eventually causes structural (and therefore permanent) damage

Management of ARF
- Hyperkalaemia
  - If urine output maintained, can treat medically
  - If anuric, may require haemodialysis

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Electrolytes and Acidosis
- Hyperphosphataemia
  - From decreased urinary PO4 excretion
  - Important clinically because it:
    - Contributes to hypocalcaemia
    - Encourages secondary hyperparathyroidism
    - Promotes soft tissue/vascular calcification
    - Causes itch
    - Can cause cardiac arrhythmias
- Hypocalcaemia (normal range 2.1 – 2.45)
  - Common in prolonged, or severe ARF
  - Mainly caused by decreased active vitamin D synthesis (1, 25-dihydroxyvitamin D3), but also by increased PO₄
  - Clinical features:
    - Paraesthesia, tetany, seizures
    - Managed by oral supplementation with alfa-calcidol (rocaltral, calcitriol)

- Hypokalaemia
  - Rare, but can occur in non-oliguric ATN caused by tubular toxins (vancomycin, gentamicin)
  - Also seen as GFR recovers, especially if patient becomes polyuric

- Hypomagnesaemia
  - Usually asymptomatic
  - Can cause neuromuscular instability, cramps, arrhythmias

- Metabolic Acidosis
  - Unmeasured anions from dietary and metabolic sources accumulate and cause acidic environment
  - Blood alkali "buffers" this, and is consumed
  - The kidney is unable to reabsorb alkali from the urine or generate new alkali (by production and excretion of ammonium)

Nutrition in ARF
- Pre-existing and hospital acquired malnutrition increases mortality and morbidity in the critically ill
- When prescribing supplements, enteral & parenteral feeds, consider particularly:
  - Potassium
  - Phosphate
  - Volume

Acute Renal Failure: Summary
- Rapid decline in GFR
- Usually associated with anuria
- Hyperkalaemia, Fluid overload, Acidosis are main disturbances
- High mortality and morbidity
- Pre-renal, Intrinsic & Post-renal
Chronic Renal Failure

- The US NKF-DOQI (National Kidney Federation – Outcomes Quality Initiative) classification of chronic kidney disease; adopted internationally
- Divides chronic kidney disease (CKD) into 5 stages according to GFR

- Many cases or early, asymptomatic CKD are unrecognized and therefore untreated
- Prevalence increases with age
- Most common identifiable causes are diabetes and vascular disease
- More common in many ethnic minorities
- Majority of patients with CKD stages 1-3 will NOT progress to ESRF. Risk of death from cardiovascular disease is higher than their risk of progression

Pathophysiology

- Diabetes (19%)
- Glomerulonephritis (13%)
- Reflux nephropathy (10%)
- Renovascular disease (7%)
- Hypertension (7%)
- Polycystic Kidney Disease (7%)

Mechanisms

- Decline in GFR usually progressive
- Series of interacting processes results in:
  - Glomerulosclerosis
  - Proteinuria
  - Tubulointerstitial fibrosis

- Raised Intraglomerular Pressure
  - As nephrons scar and ‘drop out’, remaining nephrons undergo compensatory adaptation with increased blood flow through each nephron attempting to normalize GFR
  - Increased pressure increases endothelial cell injury, with deposition of ‘pro-fibrotic’ biochemical elements

<table>
<thead>
<tr>
<th>Description</th>
<th>Stage</th>
<th>GFR (mL/min/1.73 m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney damage with normal or high GFR</td>
<td>1</td>
<td>&gt; 60</td>
</tr>
<tr>
<td>Kidney damage with mild decrease in GFR</td>
<td>2</td>
<td>45-59</td>
</tr>
<tr>
<td>Moderate decrease in GFR</td>
<td>3</td>
<td>30-44</td>
</tr>
<tr>
<td>Severe decrease in GFR</td>
<td>4</td>
<td>15-29</td>
</tr>
<tr>
<td>Kidney failure</td>
<td>5</td>
<td>&lt; 15 (or dialysis)</td>
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Proteinuria
- May be due to underlying glomerular lesion, or result from increased intraglomerular pressure
- Proteins or factors bound to filtered albumin (fatty acids, growth factors, metabolic end-products) may lead to:
  - Direct injury to proximal tubular cells
  - Recruitment of inflammatory cells (cause scarring)

Tubulointerstitial Scarring
- Chronic ischaemia implicated
  - Damaged glomerular capillaries
  - Intrarenal vasoconstriction (and decreased effective renal blood flow)
  - Intratubular capillary loss and increased diffusion distance

Diagnosis of CKD
- Why identify patients?
  - CV risk; modifiable – smoking reduction, cholesterol lowering, BP control
  - Some would benefit from further treatment
  - Complications of CKD recognised & treated early
  - Those who do go on to ESRF & require dialysis or transplantation can be prepared early

Progression of CKD
- Once established, tends to progress regardless of underlying cause
- Decline in GFR tends to be linear
- Factors influencing progression
  - Underlying disease
  - Race (faster progression in blacks)
  - BP
  - Level of Proteinuria
  - Dystipidaemia
  - Hyperphosphataemia
  - Uncontrolled Metabolic Acidosis
  - Anaemia
  - Smoking
  - Blood Glucose Control (if diabetic)
Preventing Progression of CKD

- **Blood Pressure**
  - Treat aggressively
  - Poor BP control causes GFR to decline more rapidly and increases cardiovascular risk
- ** Targets**
  - Without Proteinuria: 130/80
  - With Proteinuria: 120/75
  - Diabetics: 120/75

- Which antihypertensives do we use?
  - Calcium channel blockers: amlodipine, nifedipine, verapamil, diltiazem
  - Beta-blockers: atenolol, metoprolol
  - ACE inhibitors: ramipril, enalapril, lisinopril
  - Angiotensin II Receptor Antagonists: losartan, candesartan
  - Others: clonidine, hydralazine

Experimental work suggests hyperlipidaemia accelerates decline in GFR

No clear evidence for use of cholesterol lowering drugs (statins) in patients with CKD

Ongoing multi-centre, international trial (SHARP trial) aiming to determine this

Hyperphosphataemia

- Concept of the Calcium-Phosphate product
- Calcium phosphate deposition in the renal tissue may contribute to progression of CKD

Acidosis

- No current clinical evidence that correction of acidosis decreases renal decline
- Oral Sodibic (bicarbonate, buffer) often given to decrease resistant Hyperkalaemia

Drugs, toxins & infections

- In patients with CKD, remaining kidney function is highly susceptible to further damage from:
  - Hypovolaemia
  - Obstruction or recurrent urinary tract infections
  - Nephrotoxins – NSAIDS, IV Contrast

Preventing Progression
Dietary Protein Restriction
- Animal Models; lowering protein intake protects against development of glomerulosclerosis by decreased intraglomerular pressure
- In humans, controversial
- Ongoing debate regarding optimal intake of protein. ~0.8 – 1.0g/kg protein/day.

Complications of CKD
- Anaemia
- Bone Disease
- Fluid & Electrolytes
- Malnutrition

Complications of advanced CKD
- Fluid Overload
  - Salt and water overload
  - Dietary salt restriction
  - Fluid intake restriction
  - Diuretics

Complications of advanced CKD
- Hyperkalaemia
  - Decreased Na delivery to DCT decreases aldosterone induced K+ excretion
  - Dietary K+ restriction
  - Loop diuretics (promote urinary K losses)
  - Drug withdrawal – ACE inhibitors
  - Correct acidosis
  - May need chronic dialysis

Complications of advanced CKD
- Acidosis
  - Bone – reabsorption increased
  - Metabolism – muscle weakness, fatigue
  - Hyperkalaemia
  - Nutrition – promotes catabolism by induction of proteolysis & resistance to growth hormone

Complications of advanced CKD
- Anaemia
  - Red cell production tightly regulated by a number of growth factors
  - EPO (erythropoietin); essential for maturation of immature red cells. Produced in outer renal medulla & deep cortex.
  - Decreased EPO in CKD
EPO (Erythropoietin)
- Prior to introduction, patients were transfusion dependent
- Enhanced quality of life scores
- Reduced Fatigue
- Reduced LVH
- Improved cognitive function
- Improved sexual dysfunction
- Improved sleep quality

Preparation for EPO therapy
- Ensure iron replete
- Iron deficiency found in up to 40% patients with advance CKD
- If GFR <50ml/min, supplementation likely to be needed
  - Pre-dialysis give orally
  - If on dialysis use parenteral iron

Renal Bone Disease
- Diminished bone strength in patients with diminished GFR
- A function of bone turnover, density, mineralization & architecture

Pathway of Renal Bone Disease

Hyperparathyroidism
- End result of prolonged stimulation of parathyroid glands in neck in response to low serum Ca
- Eventually results in clonal proliferation of the gland which requires suppression, either with artificial Vitamin D analogues, or surgical resection
- PTH release stimulated by low Ca, low vitamin D & high PO4
Treatment
- Decrease serum PO₄ with binders (often Calcium containing compounds)
- Increase serum Ca with calcium salts, or vitamin D analogues
- Suppress PTH secretion directly (calcimimetic agents)

Hyperphosphataemia
- Phosphate binders
  - Taken few minutes before meal to bind PO₄ in gut
  - Should not be taken at same time as iron supplements
- Dietary restriction
  - Meats, milk, eggs, cereals
  - Difficult balance between restriction & adequate protein intake

Malnutrition in CKD
- It’s common! ~50% dialysis patients
- Powerful predictor of survival

Factors contributing to malnutrition in renal failure
- Decreased Intake
  - Anorexia
  - Gastroparesis
  - Intraperitoneal instillation of dialysate in CAPD
  - Uraemia
  - Increased Leptin

Diet Restrictions
- Loss of nutrients in dialysate
- Concurrent illness and hospitalizations
- Increased inflammatory and catabolic cytokines
- Chronic blood loss
- Acidosis
- Accumulation of toxins such as aluminum
- Endocrine disorders
  - Insulin resistance
  - Hyperglucagonemia
Management of ESRF
- As for most of the complications of CKD
- Renal Replacement Therapy
- Conservative Treatment

Indications for Dialysis in CRF
- GFR < 15ml/min with uraemic symptoms
- GFR < 10ml/min whether symptomatic or not
- Refractory hyperkalaemia, acidosis, pulmonary oedema, pericarditis, encephalopathy
- Pre-emptive transplantation is treatment of choice. Should be considered when GFR < 20ml/min

Renal Replacement Therapy
- Number of people receiving RRT expected to double in next 10 years
- Will eventually reach "steady state"
- 3 forms:
  - Haemodialysis
  - Peritoneal dialysis
  - Transplantation

Haemodialysis
Blood is exposed to dialysate (a solution containing physiological concentrations of electrolytes) across a semi-permeable membrane (the dialyser).

- Pores in the membrane allow small molecules and electrolytes to pass through.
- Concentration differences allow molecules to diffuse down gradients, thereby expelling waste products, and replacing desirable molecules or ions.
- Water can be driven through the membrane by hydrostatic force (ultrafiltration); the means by which we control fluid status.

Requirements for Haemodialysis:

- Vascular access (indwelling catheter, arterio-venous fistula or graft)
- Anti-coagulation
- Dialysis membrane
- Dialysate

Complications of Haemodialysis:

- Line infections (infection risk 100-300 fold higher in dialysis patients compared to general population)
- Clotted fistulae
- Intradialytic Hypotension
- Cardiac arrhythmias
- Cramps

Long term survival on HD
Peritoneal Dialysis

- Semi-permeable membrane of the peritoneum used as the dialyser membrane
- Dependent on diffusion along concentration gradients across peritoneum
- Fluid removal (ultrafiltration) depends on presence of a high intraperitoneal osmotic gradient as generated by glucose

Types of PD

- CAPD (Continuous Ambulatory Peritoneal Dialysis)
  - 3-5 exchanges per day with dwell times of 4-10 hours
  - Patient connects and disconnects to PD dialysate bags

- Automated PD (APD)
  - Automated machine performs exchanges at night whilst patient is sleeping
  - Performs at least 4 exchanges over ~8 hours
  - Can be programmed to leave patient dry, or to do a last fill

APD is generally performed over night while you sleep.
Complications of PD
- PD peritonitis
- Exit site infections
- Sclerosing encapsulating peritonitis
  - Symptoms of intermittent bowel obstruction
  - Poor Ultrafiltration
  - Malnutrition

Renal Transplantation
- Compatibility
  - Blood Group
  - Tissue typing
  - Antibodies
  - Donor-recipient characteristics

Benefits of Transplantation
- Decreased cardiovascular risk
- Normalisation of anaemia, bone disease, electrolyte imbalance, acid-base balance, normal cellular function
- Lifestyle!

Complications of Transplantation
- Surgical complications
- Graft dysfunction: “chronic allograft nephropathy,” recurrent glomerulonephritis.
- Acute rejection
- Post-transplant infections; CMV, HSV, Shingles, EBV, BK
- Post transplant malignancy
  - ~50% recipients 20yrs post transplant will have had a skin cancer
  - Post-transplant lymphoproliferative disorders in 1-5%: (NHL, Myeloma, Hodgkin’s Disease)
  - Cervical and vulval cancers
  - Solid organ tumours

Conservative Therapy
- Symptomatic control
- Optimal medical therapy
  - Diuretics
  - Anaemia treatment
  - K+ control
  - Dietary
  - Palliative Care
- 5 year survival rate for elderly patients 39.8% (compared to 79.8% for younger controls)
- Lengthier hospital admissions
- More complications - infections
- Conservative therapy may not shorten lifespan and can result in improved quality of life measures

Summary
- Acute renal failure
- Chronic renal failure
  - Anaemia
  - Bone disease
  - Fluid & Electrolyte disturbances
- Renal Replacement
  - Haemodialysis
  - Peritoneal Dialysis
  - Transplantation
  - Conservative Therapy

Questions?

Summary
- Multiple medical problems requiring input from multiple medical teams
- Often associated with social and financial difficulties
- Present real multidisciplinary challenge requiring input from all allied health professionals, social workers, spiritual leaders, friends, families….