RENAL AT A GLANCE
Day 2 ebook 2023

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1: Secondary Hypertension

Indications for screening:

- Severe or resistant HTN: persistent HTN despite adequate doses of 3 antihypertensive from different classes including a diuretic
- Malignant HTN: severe HTN with signs of end-organ damage: retinal haemorrhages /papilledema, heart failure, neurologic disturbance, or AKI
- An acute rise in blood pressure developing in a patient with previously stable values or onset of hypertension after the age of 55
- Hypokalaemia and/or metabolic alkalosis in a hypertensive patient
- Adrenal incidentaloma in a hypertensive patient (screen for endocrine causes of hypertension i.e., Primary hyperaldosteronism, Cushing syndrome and Pheochromocytoma)
- Age less than 30 years in non-obese with negative family history

Major causes of sec HTN

- Primary aldosteronism – Suspect in co-existent low or low-normal K, and/or metabolic alkalosis (causes hypertension in up to 10% essential hypertension)
- Renovascular hypertension – Characterised by stenosis of the renal artery, relatively common in those with severe and acute hypertension especially after >55 years age.
- Cushing's syndrome
- Pheochromocytoma – Relatively uncommon cause of hypertension with about half the patients presenting with paroxysmal hypertension
- Drugs- OCP, NSAID, glucocorticoids, decongestants e.g., pseudoephedrine, cyclosporine, tacrolimus, EPO, amphetamines, and cocaine
- Primary renal disease – Both acute and chronic kidney disease, particularly with glomerular or vascular disorders, can lead to hypertension.

Rarer causes:

- Endocrine disorders- Hypothyroidism and hyperparathyroidism
- Coarctation of aorta
- Polyarteritis Nodosa or Takayasu Arteritis
- *Conditions other than primary aldosteronism leading to hypertension with metabolic alkalosis and hypokalaemia*:
  - Liddle Syndrome
  - Chronic liquorice ingestion
  - Apparent mineralocorticoid excess (AME)
  - Familial Hyperaldosteronism e.g., Glucocorticoid remediable hypertension

Primary Aldosteronism (Conn's Syndrome)

- Characterised by hypokalaemia and metabolic alkalosis (potassium low normal in > 50% cases)
- ***Incidence in the 'essential hypertensive' population may be as high as 10%***
- Types:
  - Bilateral idiopathic hyperaldosteronism (60 to 70 percent)
  - Unilateral Aldosterone producing adenoma (30 to 40 percent)
- Diagnosis:
  - Plasma aldosterone concentration to plasma renin activity ratio (PAC/PRA) ratio above 30 strongly predictive (**this ratio is denominator dependent- while the aldosterone level may be high normal, the renin is severely suppressed**
  - Confirmatory test: oral sodium loading, or saline infusion test shows non-suppression of aldosterone.
  - Adrenal CT scan followed by adrenal vein sampling to differentiate adenoma (treatment surgical) vs hyperplasia (medical treatment) may be needed.

Renovascular HTN

- 10 to 45 % of those with acute or severe hypertension especially after 55 years age
- Two types: fibromuscular dysplasia (FMD) in 10-15% and most of remaining atherosclerotic renal artery stenosis (RAS)
  - FMD: Commoner in women below 50 years age and unrelated to lipid status (**lesions distal to proximal 2 cms of aortic origin of renal artery**) and String of beads appearance of renal artery on imaging
  - RAS: Usually after 50 years and cholesterol plaque obstructs renal artery (**lesions usually within 2 cms of origin from aorta**)
- Presentation:
  - Elevation in serum creatinine by > 30 % within a week of starting ACEI or ARB
  - Severe hypertension in a patient with an unexplained atrophic kidney or asymmetry in renal sizes of >1.5 cm
  - Onset of severe and usually rapid hypertension after the age of 55
  - A systolic-diastolic abdominal bruit that lateralizes to one side: low sensitivity (40 %) but very high specificity (99 %)
  - Hypokalemia and alkalosis classically associated with primary aldosteronism may be seen in renovascular HTN (effect of secondary hyperaldosteronism due to activated
  - Recurrent unexplained flash pulmonary oedema

- Duplex Doppler ultrasonography, computed tomography angiography (CTA) and/or magnetic resonance angiography (MRA) are all useful for detection of renovascular hypertension-CTA is preferable for FMD.
- Diagnostic tests **justified only if** a corrective procedure would be performed as treatment.
- For patients with atherosclerotic RAS, revascularization procedures have not been shown to confer clinical benefit when compared to medical therapy BUT are often considered useful in patients with FMD.
- Revascularization should be offered to those with a short duration of blood pressure elevation, failure or intolerance to medical therapy, recurrent flash pulmonary oedema or otherwise unexplained renal failure

Cushing Syndrome

- Prescribed oral prednisolone is the commonest cause but inhaled, topical or injected corticosteroids can also be causative.
- ACTH dependent causes (up to 80% cases)
    - Cushing disease: hypersecretion of ACTH by pituitary gland seen in 65 to 70 %of all Cushing's syndrome.
    - Ectopic ACTH secretion by non-pituitary tumours e.g., by bronchial carcinoid, small cell Ca lung etc. causes 10 to 15% of all cases.
- NON-ACTH dependent causes (20% cases)
    - Adrenocortical adenomas and carcinomas cause 18 to 20 % of all cases.
    - bilateral adrenal micronodular or macronodular hyperplasia cause < 2% of all cases
- Investigation: For initial screening, 2 of the following 3 tests should be positive
    - mid-night salivary cortisol
    - 24-hours urinary cortisol
    - low-dose dexamethasone suppression test
- If Cushing's diagnosed follow up with serum ACTH levels
    - Low ACTH- CT scan adrenal gland
    - Normal to high ACTH- High dose Dexamethasone Test and if positive then follow with MRI pituitary gland. In equivocal cases petrosal venous sinus catheterisation to demonstrate central-to-peripheral ACTH gradient

Pheochromocytoma

- Catecholamine-secreting tumours that arise from chromaffin cells of the adrenal medulla and the sympathetic ganglia.
- Uncommon condition; <0.2% of patients with HTN

Rule of 10: 10% extra-adrenal, multiple, malignant (more likely to be bilateral or recurrent in familial cases)

- Presentation:
    - Triad: episodic headache, sweating and tachycardia (50% paroxysmal HTN)
    - Incidental finding of adrenal tumour in a hypertensive
    - family history of pheochromocytoma or predisposing genetic syndrome (about 40%) namely von Hippel-Lindau (VHL) syndrome, multiple endocrine neoplasia type 2 (MEN2) and less commonly, neurofibromatosis type 1 (NF1)
- Plasma fractionated metanephrines have a sensitivity = 96 to 100 % and specificity = 85 to 89%
- 24 hours urinary fractionated metanephrines and catecholamines has sensitivity = 98 percent and specificity = 98 percent
- So, high index of suspicion- first line test is plasma fractionated metanephrines and low index of suspicion- first line test is urinary fractionated metanephrines and catecholamines.
- Both CT and MRI are quite sensitive (98-100 %) but are only 70 %specific because of the high prevalence of adrenal "incidentalomas".

Polyarteritis Nodosa

- Check eBook chapter on vasculitis.

Takayasu Arteritis

- Check eBook chapter on vasculitis.

Conditions other than primary aldosteronism leading to HTN with metabolic alkalosis and hypokalaemia.

- Liddle Syndrome
- Chronic liquorice ingestion
- Apparent mineralocorticoid excess (AME)
- Glucocorticoid remediable hypertension

Liddle Syndrome

- Autosomal dominant condition with mutation in the ENAC channel (sodium reabsorbing channel in the collecting duct under control of aldosterone) rendering it resistant to normal degradation.
- Persistent sodium reabsorption and resultant hypertension
- Presentation at young age and may develop hypokalaemia with metabolic alkalosis.
- Genetic testing diagnostic; plasma aldosterone and renin both low.

Apparent mineralocorticoid excess (AME)

- Cortisol binds as avidly as aldosterone to the aldosterone receptor.
- Plasma cortisol concentration >>> aldosterone concentration
- In kidney 11-beta-hydroxysteroid dehydrogenase enzyme type 2 isoform (11-beta-HSD2) converts cortisol to the inactive cortisone
- Deficiency of 11-beta-HSD2 leads to elevated levels of cortisol in the kidneys which simulates hyperaldosteronism.
- Both plasma aldosterone levels and plasma renin activity low
- 24 hours urine collection reveals abnormally high urine cortisol to cortisone levels in AME.

Chronic Liquorice ingestion (think of an acquired AME)

- Liquorice contains glycyrrhetinic acid, which inhibits 11-beta-HSD2, the same enzyme that is deficient in AME.

Glucocorticoid remediable aldosteronism (GRE)

- While normally synthesis of cortisol but NOT aldosterone in under the control of adrenocorticotrophic hormone (ACTH), mutation of 11-beta-hydroxylase causes both cortisol and aldosterone synthesis to be controlled by ACTH.
- Plasma aldosterone elevated and plasma renin activity suppressed, though the aldosterone-renin ratio is typically not as high as with primary aldosteronism.
- Autosomal dominant condition usually presents in younger age and genetic testing is diagnostic.
- Treated with exogenous steroids while an alternative approach is treatment with mineralocorticoid receptor antagonists.

2: Thrombotic microangiopathies- HUS and TTP

Microangiopathic hemolytic anemia (MAHA)

- MAHA is hemolytic anemia due to intravascular RBC fragmentation and is characteristically Coombs-negative.
- MAHA is mostly caused due to abnormalities in the arteries and capillaries when it is termed thrombotic microangiopathy (TMA) **BUT** can be due to intravascular devices such as a prosthetic heart valve.
- Characteristic laboratory findings in MAHA-
    - Hemolytic anemia (low haptoglobin, high reticulocytes, raised LDH and indirect bilirubin)
    - Negative Coombs test
    - Schistiocytes (fragmented RBCs) on peripheral blood film
- *Remember not all MAHA is caused by TMA, but nearly all TMAs cause MAHA and thrombocytopenia.*

Thrombotic Microangiopathy (TMA)

- While TMA is microvascular thrombosis due to abnormalities in the vessel walls where injury to the endothelial cells is the central event, it is a **histological diagnosis (typically kidney biopsy)** characterised by:

    - Platelet microthrombi within small arterioles and capillaries

    - Characteristically swollen endothelial cells and subendothelial space, along with vessel wall thickening

- Clinically TMA presents with

    - MAHA (hemolytic anemia with schistocytes) AND thrombocytopenia

    - Variable signs of organ injury due to platelet thrombosis e.g., AKI, and neurological involvement etc.

MAHA with thrombocytopenia

- MAHA with thrombocytopenia may be due to primary TMA syndromes or secondary causes.
- *Primary* TMA:
    - Thrombotic thrombocytopenic Purpura (TTP)
    - Shiga toxin-mediated hemolytic uremic syndrome (ST-HUS)
    - Complement-mediated TMA (previously called atypical HUS)
    - Drug-induced TMA (DITMA) syndromes
    - Disorders of vitamin B12 metabolism mediated TMA

- *Secondary* causes *of MAHA with thrombocytopenia*
    - Pregnancy-associated (severe preeclampsia, HELLP syndrome)
    - Autoimmune disorders (SLE, SS, anti-phospholipid)

- Severe hypertension
- Systemic infections (bacterial endocarditis, HIV, CMV)
- DIC
- Haematopoietic stem cell transplant or organ transplantation
- Bone marrow ablation (e.g., total body radiation, high-dose chemotherapy)
- Immunosuppressive drugs (e.g., calcineurin inhibitors*)*

Thrombotic thrombocytopenic Purpura (TTP)

- Caused by severe deficiency of ADAMTS13 (VWF- cleaving protease) to typically <10%
- Deficiency of ADAMTS13 causes VWF to accumulate which provides a nidus for platelet trapping leading to thrombocytopenia
- RBCs fragmented as they make their way through these platelet rich plugs causing formation of schistocytes
- AKI usually **NOT severe** and anuria unlikely (Creatinine usually <176 µmol/L)
- Severe thrombocytopenia **very common** (platelets usually <30,000/microL)
- Neurologic dysfunction common e.g., headache to seizures, stroke, and coma
- Classic textbook pentad of thrombocytopenia, MAHA, neurological abnormalities, fever and renal dysfunction rarely seen (<5 %)
- High fatality rate without prompt treatment with plasma exchange
- If ADAMTS13 result not available and patient deteriorating, use PLASMIC score to estimate the pretest probability and diagnosis of TTP.
- PLASMIC score 5 or higher should be empirically treated for TTP with therapeutic plasma exchange (TPE)
- Diagnosed TTP treated with TPE, prednisolone and rituximab.
- Caplacizumab: anti-VWF antibody used in severe cases.

Shiga toxin-mediated hemolytic uremic syndrome (ST-HUS)

- Simultaneous occurrence of MAHA, thrombocytopenia, and AKI with history of recent diarrhoea
- Commoner in children
- Shiga toxin-producing E. coli (mostly O157:H7) HUS (STEC HUS) is the commonest worldwide but in Australia 50 % of post-diarrhoeal HUS are due to E. coli 0111where uncooked meat is the commonest culprit.
- Streptococcus pneumoniae associated HUS in 5-15% childhood cases.
- **Although one-half to two-thirds of patients require dialysis during the acute phase, the overall renal prognosis is good.**
- Supportive treatment and indication for dialysis same as in patients with AKI due to other causes
- Eculizumab used for severe CNS involvement.
- While mortality rates are less than 5%, another 5% may be left with significant sequelae (e.g., stroke or ESRD)

Complement-mediated TMA (CM-TMA, previously called atypical HUS)

- Previously called atypical HUS (aHUS) arises from excess activation of the alternative complement pathway.
- May result from either loss-of-function mutation in a regulatory gene (*CFH, CFI,* or *CD46*) or a gain-of-function mutation in an effector gene (*CFB* or *C3*) of the alternative complement pathway; no mutation identified in up to 50%
- Need to rule out HUS and TTP before considering diagnosis.
    - AKI usually severe in comparison to TTP
    - Thrombocytopenia usually not as severe as in TTP
    - No history of diarrhoea differentiates from HUS
    - Has known association with pregnancy; remember pregnancy associated HELLP or severe preeclampsia can lead to MAHA with thrombocytopenia.
- Life-threatening syndrome requiring prompt initiation of therapy.
- Treatment with either eculizumab or ravulizumab (monoclonal antibodies directed against the C-5 complement component)
- Ensure meningococcal antimicrobial prophylaxis in addition to vaccination when using eculizumab or ravulizumab
- Optimum duration of therapy uncertain

Drug induced TMA

- Immune-mediated: Quinine most common, other drugs being quetiapine, oxaliplatin and gemcitabine.
- Drug dose dependent:
    - Chemotherapeutic agents (such as gemcitabine and mitomycin), immunosuppressive agents (CNIs-cyclosporine and tacrolimus), vascular endothelial growth factor (VEGF) inhibitors (sirolimus and bevacizumab), and narcotics taken inappropriately or illegal agents (oxymorphone and cocaine)
    - Presentation might be acute, caused by a toxic dose of an approved or illegal drug, or chronic when the patient may present after weeks to months of drug exposure.

Metabolism-mediated TMA

- Hereditary disorders of intracellular vitamin B12 metabolism can cause **TMA.**

3: Glomerulonephritis

- Nephrotic and nephritic both involve the glomeruli. Key differences-
    - Nephrotic syndrome: **(*not an inflammatory condition*)** increased glomerular permeability to proteins causing >3.5 g proteinuria/24 hours, hypoalbuminemia, and oedema.
    - Nephritis/GN: ***glomerular inflammation*** causing hematuria ***with dysmorphic RBCs/RBC casts*** and often (not always though...) associated with reduced GFR, non-nephrotic proteinuria, oedema, hypertension.
- GN may be smouldering and slowly progressive or ***rapidly progressive (days, weeks, or months)*** and associated with extensive crescent formation i.e., rapidly progressive glomerulonephritis **(RPGN)**
- What is microscopic hematuria, dysmorphic RBC and RBC cast?
    - Microscopic hematuria is >2 RBCs per high power field in spun urine.
    - Mechanical damage caused by passage of RBC through the GBM followed by osmotic injury sustained by RBCs during passage through the hypotonic tubular segment cause ***dysmorphic RBC.***
    - Dysmorphic RBCs >5% of total urinary RBCs needed to diagnose nephritis/GN.
    - RBC casts are RBCs embedded in Tamm-Horsfall protein (THP) which is secreted by the TAL cells and is the most abundant protein in urine.

Infection Related GN (rather than Post Infectious GN)

- Often refers to post-streptococcal (common in children) **but** in adults Staphylococcus associated GN as common especially in the developed world.
- Post-streptococcal GN occurs 2 weeks after skin or pharyngeal infection while staphylococcus associated GN occurs simultaneously with infection (so titled as infection related GN and NOT post-infectious GN)
- Staph GN commoner in elderly, diabetics, and alcoholics and ***>half develop CKD or ESRD*** (unlike excellent prognosis in post-step GN)
- Hypocomplementaemia (usually low C3 with normal C4 suggest activation of alternate pathway)
- Biopsy shows glomerular proliferative changes with ***hump shaped sub-epithelial deposits*** (NOT the spike and dome feature of subepithelial deposits in membranous nephropathy)
- Treatment: antihypertensive drugs, diuretics, and dietary salt restriction to control hypertension and fluid overload and antibiotics as appropriate

IgA Nephropathy (IgAN)

- Commonest glomerular disease in the developed countries
- Peak incidence in 2nd and 3rd decades and commoner in Caucasians and presents as:
    - Episodic macroscopic hematuria in **40-50%** (often within 24-48 hours of URTI)
    - Microscopic hematuria in **30- 40%** (usually with some proteinuria)
    - Nephrotic syndrome in 5% and RPGN in 5%

- Rarely as AKI or malignant hypertension
- Characterised by mesangial deposition of IgA with mesangial proliferation in the absence of any changes in the endothelium, GBM or podocytes.
- Diseases associated with IgAN
  - Celiac disease
  - Rheumatic disorders: RA, ankylosing spondylitis, Reiter syndrome
  - Cirrhosis: Alcoholic liver disease, NASH, Hepatitis B and C
  - Lung: Sarcoidosis
  - Infection: HIV
- Management
  - Proteinuria and/or HTN: ACEI or ARB and SGLT2 inhibitors
  - Proteinuria> 1g/day and GFR> 50 ml/min despite 3-6 months ACEI/ARB: 6-month course of prednisolone
- ESRF can occur in up to 50% patients with maximum risk in those with ***persistent proteinuria> 1g/day, HTN and CKD***

Anti- GBM antibody (Goodpasture) disease

- Circulating antibodies against NC1 domain of the alpha-3 chain of type IV collagen found in GBM and alveolar membranes.
- Present with RPGN as well as pulmonary haemorrhage in 40 to 60%: additional insult needed for lung manifestation -smoking, infection, cocaine inhalation, fluid overload or hydrocarbon exposure.
- ***Systemic complaints typically absent (presence suggests vasculitis)***
- Diagnosis: Anti-GBM antibody in plasma and biopsy shows characteristic ***linear deposition of IgG along the GBM on IF***
- 10 to 40% may also be MPO ANCA + and they have worse prognosis.
- **Treatment:**
  - Plasma exchanges up to two weeks + prednisolone and cyclophosphamide up to three months.
  - Rituximab if refusal/contraindication to cyclophosphamide
  - Plasma exchange is absolute indication in pulmonary haemorrhage independent of severity of renal disease.
  - Maintenance therapy usually not advised.
  - Untreated more than 90% result in death or dialysis.
- **NOTE:**
  - *Goodpasture syndrome is RPGN + lung haemorrhage from any cause (ANCA vasculitis, HSP, lupus, cryoglobulinemia etc.)*
  - *Goodpasture disease is RPGN+ lung haemorrhage + **anti-GBM antibody**.*
  - NOTE: Only 20-40% of hemoptysis with RPGN is due to Goodpasture disease

Alport Syndrome

- Commonest form of hereditary nephritis and often associated with sensorineural deafness and ocular abnormalities.
- Mutation in type IV collagen effect the GBM and basement membranes in the eye and ear.
- Usual presentation in childhood or young adulthood with asymptomatic haematuria or progressive GN
- More than 80% X linked so usually males have worse prognosis.
- Characteristic biopsy findings include splitting/thinning and thickening/basket weaving of GBM.
- No specific treatment (usual CKD strategy including ACEI/ARB for proteinuria)
- Renal transplantation is the only definitive therapy though up to 3% patients develop anti-GBM disease post-transplant.

Rapidly Progressive Glomerulonephritis (RPGN)/Crescentic GN

- GN with rapid progression of renal failure (days to weeks to months)
- Histologically defined by crescents in the glomeruli which are defined as two or more layers of proliferating parietal epithelial cells in Bowman's space (normally there is only one layer of parietal epithelium)
- Crescent formation is a nonspecific inflammatory response to severe glomerular injury.
- RPGN associations include:
    - Pauci immune RPGN: Negative staining on IF due to ANCA-associated vasculitis causes more than 50% of all RPGN.
    - Anti-GBM antibody associated RPGN: Positive anti-GBM antibodies and linear staining of the GBM on IF, this leads to 20% of all RPGN.
    - Immune complex mediated RPGN: IF characteristically shows presence of coarse immune deposits in the glomeruli; about 25% of all RPGN and may be due to lupus (commonest), IgAN, infectious GN, or MCGN
- Treatment: IV methylprednisolone for 3 days followed by daily oral prednisone, oral or IV cyclophosphamide or rituximab, and plasmapheresis in some settings e.g., anti GBM positive with haemoptysis AND treat the underlying renal disease
- Circumferential crescents in > 80 % glomeruli respond very poorly to treatment.

4: Lupus

Prof. Sanjay Swaminathan

What is SLE?

- Systemic, multisystem autoimmune disease
- Strong female:male preponderance (~8:1)
- Considerable ethnic differences in frequency
  - More common in Africa, Asian population than Caucasian populations
  - Globally, estimates of SLE prevalence in adults range from 30-150/100 000, and incidence ranges from 2·2 to 23·1/100 000 per year
- Characterised by autoantibodies directed against nuclear components

Pathophysiology:

- Defining feature is autoantibodies directed against chromatin or DNA
- Antibody-antigen complexes may lodge in small blood vessels, leading to disease manifestations
- Exposure to DNA may occur by aberrant apoptosis and release of DNA into the circulation
  - This may, in some individuals, lead to an auto-reactive immune response
  - Also thought to be a defect in clearance of immune complexes and persistence of apoptotic cell debris

B cell responses in SLE:

- Persistently active B cell responses may be partly driven by B cell activating factor, BAFF (targeted by new SLE drug, Belimumab).
- Innate immune responses may be also involved, with Toll like receptors (TLRs) binding to DNA or RNA ligands
- Pathogens, such as viruses or bacteria, may lead to innate immune activation and disease progression

Clinical Features:

- Constitutional symptoms: fevers, weight loss (or gain), fatigue, myalgias
- Cutaneous and joints manifestations are the commonest:
  - Malar rash, discoid lupus, photosensitive rash
  - Arthralgias/arthritis of hands, wrist, feet, knees
- Raynaud's phenomenon
- Oral ulceration
- Alopecia
- Sicca symptoms
- Serositis
- Neurological complications
- Renal (nephrotic range proteinuria)
- Can affect any organ!

Laboratory Tests:

- Tests can be divided into those useful in <u>diagnosis</u> or in <u>monitoring</u>

Diagnostic tests:

  - Anti-nuclear antibody (ANA)
  - Extractable nuclear antigens (ENA)
  - DNA antibodies (both diagnostic and monitoring)
  - Antiphospholipid antibodies: Lupus anticoagulant, Cardiolipin antibodies and β_2-glycoprotein 1 Ab

Monitoring tests:

  - ESR, CRP

  - C3, C4 levels
  - Urine dipstick; microscopy for casts, testing for proteinuria

ANA testing:

- ANA testing is performed by indirect immunofluorescence (IIF)
  - Patient's serum is added to slides fixed with human cells
  - If serum contain antibodies, they bind to various target proteins; following washing steps, an anti-immunoglobulin with a fluorescent tag is added and cells are visualised under a fluorescent microscope
  - A number of staining patterns can be observed including homogeneous, speckled and nucleolar patterns
  - Patient's serum are commonly diluted at 1:40;
    - if no fluorescence is seen, then this is called negative
    - A positive result means that the serum is diluted further 4 fold (1:40, 1:160, 1:640, 1:2560)
- An ANA titre is the dilution of serum that results in a positive result
  - Titres are commonly reported as positive if ≥1:40, although the higher the titre, the more significant the result; commonly our patients will have a titre of ≥1:640.

Antibodies to Extractable nuclear antigens (ENA):

- Used as a supplementary test to ANA tests to try and ascertain the targets of a positive ANA result
- Most common ENAs tested include:
  - SS-A (Ro), SS-B (La) and Ro-52 (seen in SLE or Sjogren's syndrome)
  - **Sm (Smith) – highly specific for SLE**
  - RNP (positive in mixed connective tissue disease)
  - Scl-70 (seen in systemic sclerosis)
  - Jo-1 (dermatomyositis, anti-synthetase syndrome)

DNA antibodies:

- Presence of DNA antibodies is a very specific marker of SLE
- Measured in several ways, including by a radioimmunassay (Farr), which is the most specific way of measuring this
- In many labs (including Westmead), assay has been switched to an ELISA type assay (non-radioactive) which is less specific
- ACR criteria states that a positive DNA antibody result is one criteria for SLE classification, but if ELISA is used, the DNA Ab result needs to be >2 x the upper range of normal

Other tests:

- Low C3 and C4 indicate that complement is being consumed, presumably by antibody and antigen complexes being deposited in small blood vessels
  - Sign of active lupus
- Always check for antiphospholipid antibodies
- Inflammatory markers: ESR may be a better marker of disease activity than CRP, which can be normal even in active SLE; although low level rises in CRP are often seen
- Check for urinary sediment, proteinuria
- Renal biopsy – see later section

Classification systems in SLE:

- American College of Rheumatology (ACR) classification criteria often used as a diagnostic aid, first developed in 1982 (revised in 1997)
- Need to meet 4 of 11 criteria to be classified as SLE, with 95% sensitivity and 85% specificity
- Mostly used in trial settings to make sure patients are "standardised"
- Patients can still have SLE without necessarily having met 4 criteria
- Other classification schemes exist, such as SLICC (require 4/17 criteria but at least 1 clinical and 1 laboratory or biopsy proven lupus nephritis with positive ANA or DNA antibodies).
- New classification scheme introduced in 2019: EULAR/ACR criteria
  - Need to meet entry criteria and reach 10 points for a classification of SLE

My approach to diagnosis:

- SLE diagnosis is not an exact science!
- Screen patients who have signs/symptoms compatible with SLE with appropriate lab tests (ANA, ENA, DNA Ab, C3,C4 etc)
- Patients with a high titre ANA, with suggestive ENA antibodies or raised DNA antibodies **and** an appropriate history are more likely to have SLE
- Although ANA negative lupus does exist, it is a rare entity; vast majority will be ANA +

Management of SLE:

- Patient education
- Advice regarding sun exposure, sunscreen, wearing broad brimmed hats
- Exercise and stopping smoking
- Addressing CV risk factors
- Skin and joint manifestations often respond well to hydroxychloroquine (Plaquenil)
- Many lupus specialists put all their patients on Plaquenil:
  - Very safe drug, with no regular blood testing required
  - Can cause retinal toxicity but this is dose and time dependent
- Further management depends on the disease manifestation
- Low to medium dose corticosteroids are often used
- If doses can't be reduced to <7.5 mg/day of prednisolone, then a steroid sparing agent needs to be considered
- Target to treat approach with aim of achieving lupus low disease activity state (LLDAS) or remission is a new concept in last few years
- The steroid sparing agents most commonly used in SLE are azathioprine or mycophenolate, although methotrexate can also be used, particularly for synovitis
- Belimumab has been licenced but its exact role in treating patients with lupus has yet to be established; probably use will be those with active musculoskeletal or cutaneous disease

Newer agents/therapies being considered for SLE:

- Multiple newer agents are in various phases of clinical trials
  - Voclisporin, a calcineurin inhibitor, has been shown to be effective in lupus nephritis
  - Targeting Type I interferons
  - B cell depletion with rituximab
  - JAK Inhibition with baricitinib
  - B cell intracellular signaling (Bruton's tyrosine kinase)
  - T cell co-stimulation blockade
  - Immune complex inhibition
- CAR-T cells (targeting B cells) have emerged as an exciting new therapeutic that has been used in a handful of patients with severe SLE (including lupus nephritis)

Management of severe SLE:

- For SLE with potentially life threatening organ involvement, pulse methylprednisolone (1 gram x 3-5 days) is often employed, followed by oral steroids
- This may be followed by pulse IV cyclophosphamide
- Alternatives would be to use Mycophenolate mofetil
- Rituximab (B cell depletion) has also been used, although exact role in SLE has not been established

Lupus nephritis:

- Renal involvement is very common in SLE, with clinically relevant disease present in up to 50% of patients
- Most commonly diagnosed following a urine disptick but requires a renal biopsy (LM, EM and DIF) for definitive diagnosis
- Regular checks for increased proteinuria (with an albumin:creatinine ratio), red cell casts and checking of serum creatinine (and eGFR) should be performed in all patients with SLE
- Patients with elevated DNA antibodies and low C3/C4 are at higher risk of developing Lupus nephritis

Indications for a renal biopsy:

- Renal biopsy is only performed on selected patients:
  - Those with >0.5 grams of proteinuria/day
  - Patients with a rising serum creatinine (where other causes have been excluded)
  - Active urinary sediment with dysmorphic red blood cells

Classes of Lupus nephritis:

- Class I – minimal mesangial LN (not commonly diagnosed)
- Class II – mesangial proliferative LN
  - manifests as microscopic haematuria and/or proteinuria
- Class III – focal proliferative LN
  - <50% of glomeruli affected
  - presents with haematuria and/or proteinuria with some of the following: ↓GFR, ↑BP, nephrotic syndrome
- Class IV – diffuse proliferative LN
  - >50% glomeruli affected
  - Most patients have present with haematuria and proteinuria and ↓GFR, ↑BP, nephrotic syndrome frequently seen
- Class V – membranous LN
  - Present with nephrotic syndrome
- Class VI – advanced sclerosing LN
  - Slowly progressive renal dysfunction with bland urinary sediment

Renal biopsy findings in Class IV lupus nephritis:

- Typical light microscopy findings:
  - >50% of glomeruli are affected on LM
  - Diffuse wire loop changes and mesangial proliferation
- Typical direct immunofluorescence findings:
  - Usually the “full house” of immunglobulins (IgG, IgA and IgM), with C3 and C1q. C1q staining is very specific for SLE and background staining for C1q is very weak in normal tissue
- Typical electron microscopy findings:
  - Subendothelial deposits

Management of lupus nephritis

- Data is mostly for Type III or IV LN
- Induction therapy
  - IV Cyclophosphamide for 3- 6 months (although exact duration is not known
  - Eurolupus protocol is 500 mg every 2 weeks
  - Most specialists would also pulse with methylprednisolone, followed by tapering oral steroids
- Alternative induction agent would be using mycophenolate, particularly in patients with less severe renal disease (near normal kidney function)
    - Maintenance is usually with azathioprine or mycophenolate for 2 – 3 years
- Also one may use an alternate combination of mycophenolate with a calcineurin inhibitor (voclisporin, tacrolimus or cyclosporin) OR mycophenolate plus belimumab OR cyclophosphamide plus belimumab

Choice of immune suppression in consideration of pregnancy or preserving fertility in the future:

- Choice of immune suppressants is very important in young SLE patients as they are often female and of child bearing age
  - Ideally SLE is well controlled for >6 months before pregnancy is attempted
  - Severe disease flares need to be factored in, as well as transitioning patients from one regimen to another
- Drugs such as mycophenolate, methotrexate and cyclophosphamide are contraindicated
- Azathioprine, hydroxycholoroquine and low dose steroids can be continued throughout pregnancy; suggested that patients be on hydroxycholoroquine

Preserving fertility in SLE patients:

- If co-existing antiphospholipid antibody syndrome is present, recommended to use concurrent aspirin and low molecular weight heparin
- EULAR guidelines in 2019: In women with high risk aPL profile but without a history of thrombosis or pregnancy complications (with or without SLE), treatment with 100 mg/day of aspirin should be considered
- In preserving fertility, the Eurolupus protocol (500 mg cyclophosphamide 2 weekly) provides much better protection in preserving fertility than higher dose regimens
  - Consideration of sperm or egg freezing

5: Vasculitis and Kidney

- ***Inflammation of vessel walls causing damage to the walls***
- Clinical manifestations due to:
    - Vessel wall rupture- bleed
    - Luminal compromise- downstream ischemia/necrosis
- Classified depending on the size of the blood vessel involved

Large vessel vasculitis

- Takayasu Arteritis
- Giant Cell Arteritis

Medium sized vessels vasculitis

- Polyarteritis Nodosa
- Kawasaki Disease

Small vessels vasculitis

- Pauci-immune **:** *Granulomatosis with polyangiitis (Wegener's)*
  Eosinophilic granulomatosis with polyangiitis (Churg-Strauss)
  Microscopic polyangiitis
- Immune complex-mediated: *Cryoglobulinemic vasculitis.*
  IgA nephropathy/HSP
  Anti-glomerular basement membrane (anti-GBM) disease
  Hypocomplimentemic urticarial vasculitis (anti-C1q vasculitis)

Renal involvement in vasculitis

- Small vessel vasculitis- effect glomerular capillaries and thus lead to glomerulonephritis.
- Medium vessel vasculitis- Inflammation of interlobar/arcuate arteries causing thrombosis or rupture leading to renal infarction or haemorrhage respectively.
- Large vessel vasculitis – effects aorta/main renal arteries leading to renovascular hypertension- ***almost like a renal artery stenosis.***

Takayasu Arteritis

- Primarily affects the aorta and its primary branches.
- Women affected in 80 to 90% of cases and Asians more effected.
- Age of onset usually before 40 years of age
- Primarily granulomatous inflammation of aorta and its branches- initial proximal subclavian artery involvement common
- Abdominal aorta effected eventually in 50%
- Renal involvement: Involvement of the renal arteries leads to renovascular hypertension in > 50% cases
- Diagnosis**:** Angiography/CTA/MRA helpful
- American College of Rheumatology criterion needs 3 out of following 6:
    - Age at disease onset ≤40 years

        - Claudication of the extremities
        - Decreased pulsation of one or both brachial arteries
        - Difference of at least 10 mmHg in systolic blood pressure between the arms
        - Bruit over one or both subclavian arteries or the abdominal aorta
        - Arteriographic narrowing or occlusion of the entire aorta, its primary branches, or large arteries in the proximal upper or lower extremities
- Mainstay of treatment is glucocorticoids
- 50% need steroid sparing agents like methotrexate, azathioprine etc.

Giant cell arteritis : Histologically similar to Takayasu arteritis

- As per American College of Rheumatology three positive out of following five criterions help to diagnose GCA:
    - *Age greater than or equal to 50 years at time of disease onset*
    - *Localized headache of new onset*
    - *Tenderness or decreased pulse of the temporal artery*
    - *Erythrocyte sedimentation rate (ESR) greater than 50 mm/hour*
    - *Biopsy revealing a necrotizing arteritis with a predominance of mononuclear cells or a granulomatous process with multinucleated giant cells*

Polyarteritis Nodosa (PAN)

- Systemic vasculitis that typically affects medium-sized muscular arteries
- ANCA negative/ lung characteristically NOT involved/no granulomas
- Involvement of arterioles, veins and capillaries excludes PAN….so does GN exclude PAN? (YES)
- Aetiology unknown, 20-30% association with Hepatitis B
- Recessive loss of function mutations of the gene encoding adenosine deaminase 2 (ADA2)

PAN presentation

- Systemic features- fever/malaise- 80%
- Peripheral neuropathy- 75%
- Arthralgia/myalgia- 65%
- Skin- livedo reticularis, purpura-50%
- Kidney- AKI due to infarct/bleed- 50%
- GI- abdominal pain, PR bleed- 40%
- Hypertension- 35%
- Orchitis- 20%
- Stroke- 20%
- Cardiomyopathy, pericarditis- 10%

PAN Diagnosis

- Biopsies of medium-sized vessels are not safe or practical and so uncommon.
- **Mesenteric or renal arteriography often diagnostic- multiple aneurysms and irregular constrictions in medium sized vessels**
- *REMEMBER- No diagnostic laboratory test ,no GN, no lung involvement, no ANCA, no involvement of arterioles/capillaries/veins and no granuloma on biopsy.*

PAN Treatment

- Depends on disease severity and presence/absence of hepatitis B.
- **Mild disease**- arthritis, anaemia, and skin lesions but NO renal, cardiac, GI, neurologic involvement are treated with prednisolone.
- **Moderate to severe disease**- involvement of above or life-threatening complication treated with prednisolone and second immunosuppressive agent, typically cyclophosphamide initially followed by prednisolone and azathioprine for upto 18 months of total treatment.
- **Hep B or C positive**- antiviral rather than immunosuppressant, if severe PAN then short-term treatment with glucocorticoids and plasma exchange until antiviral therapy becomes effective.

ANCA Associated small vessel vasculitis

- Granulomatosis with polyangiitis (Wegener's previously):**90% ANCA +**[mostly PR3]
- Microscopic polyangiitis:**70% ANCA+** [mostly MPO]
- Eosinophilic granulomatosis with polyangiitis (Churg-Strauss): **50% ANCA+** [MPO slightly > PR3]
- Renal-limited vasculitis (uncommon): Pauci-immune vasculitis limited to the kidney with **75 to 80 % MPO-ANCA +**
- **Beware-**

  -10-40% of Anti-GBM antibody disease ANCA+ [mostly MPO]

  - Drug associated ANCA vasculitis: most commonly anti-thyroid drugs, minocycline, hydralazine, cocaine contaminated with levamisole, penicillamine, clozapine and isoniazid

Granulomatosis with polyangiitis (GPA)

- **Lung and tracheal involvement in 90%**- pulmonary haemorrhage, nodular or cavitating lesions radiologically with tracheal or subglottic stenosis
- **ENT involvement in 90%**- sinusitis, rhinitis, subglottic stenosis, ocular inflammation, septal perforation and saddle nose deformity
- **Kidney involvement in 80%**- GN with/without proteinuria and renal failure, RPGN

Microscopic Polyangiitis-

- **Kidney involvement in 80%**- GN with/without proteinuria and renal failure, RPGN
- Lung involvement in 40% , GI in 40%, ENT in 35% and neurologic system in 30%
- MPO/p-ANCA + in more than 80%
- NO asthma/eosinophilia/granulomas
- Churg-Strauss (EGPA)- asthma, eosinophilia and necrotising granulomatous inflammation involving respiratory tract, renal involvement less common
- Prevalence is 2.5, 2.5 and 1/100000 respectively
- Renal biopsy (COMMON IN ALL THREE PAUCI-IMMUNE VASCULITIS) shows segmental necrotizing glomerulonephritis often with crescents, IF negative

Treatment of GPA and MPA

- IV methylprednisolone for three days followed by oral prednisolone at 1g/kg and Rituximab or Cyclophosphamide for induction (3-6 months)
- Remission in 85-90% in 3 months (75% achieve complete remission)
- Avacopan — Increasing use of this complement C5a receptor inhibitor as an adjunctive agent (avoid in those with active liver disease).
- Plasmapheresis offered to those needing dialysis, RPGN on biopsy, haemoptysis or concurrent anti-GBM disease
- Maintenance therapy with azathioprine/rituximab and low dose prednisolone usually given for 12 to 24 months *(remember PJP prophylaxis with co-trimoxazole)*
- Patients with PR3-ANCA are more likely to relapse than those with MPO-ANCA
- RAVE and RITUXIVAS trial established non-inferiority of rituximab as induction therapy vs cyclophosphamide
- MAINRITSAN trial showed superiority of rituximab over azathioprine for maintenance therapy

Eosinophilic Granulomatosis with polyangiitis (EGPA or Churg-Strauss Syndrome)

- Mean age of diagnosis 50 years (GPA and MPA in older people)
- Develops in sequential phases with overlap at times-
  - *Prodromal phase:* In 2nd to 3rd decade with atopic disease/asthma
  - *Eosinophilic phase*: pulmonary opacities, asthma, and peripheral eosinophilia with eosinophilic infiltration of lungs and GIT
  - *Vasculitic phase*: In 3rd to 4th decade with vascular/extravascular granulomatosis and fever, weight loss, malaise, and lassitude
- Asthma precedes vasculitis by up to 10 years.
- ENT involvement reported in 70 to 85 % patients
- Kidney involvement in about 50% cases and less severe than GPA or MPA
- Cardiac involvement causes up to half of all deaths.
- Non severe EGPA, treated with mepolizumab (interleukin 5 antagonist monoclonal antibody) and systemic glucocorticoids.
- Those with severe disease need cyclophosphamide or rituximab with glucocorticoids as induction therapy followed by maintenance therapy with azathioprine or methotrexate for 12-18 months.

6: Renal Transplant

Dr Jagadish Jamboti

Renal transplantation is the preferred modality of treatment for patients with End Stage kidney disease. Successful kidney transplant improves the QOL and survival in kidney transplant recipients.

There are 2 types of kidney donors: live donors and deceased donors. Deceased donors in the ICU could be either donors after Neurologic determination of Death (DNDD donors-previously known as DBD donors) or after Circulatory Determination of Death (DCDD donors -previously known as DCD donors).

Recipients are waitlisted for deceased donor transplants after ensuring their suitability for transplant. Kidney allocation is based on

1) Wait-time
2) HLA match and absence of significant HLA antibodies.

HLA matching has shown a dose-dependent graft survival effect among multiple transplant registries, across various eras of immunosuppression.

HLA antibodies are produced upon exposure to new HLA antigens such as during pregnancy, blood transfusions or previous organ transplants.

Immune recognition leads to organ rejection. Acute Rejection is associated with an inferior long-term allograft and patient survival. Acute Rejection can be broadly divided into: T-cell mediated rejection and Antibody- mediated rejection. Cell-mediated rejection is treated with pulse intravenous methyl prednisolone and optimisation of immunosuppression. Steroid resistant cell-mediated rejection is treated with Anti-thymocyte Globulin. Antibody mediated rejection is treated with intravenous immunoglobulins and Plasma exchange.

Standard immunosuppression consists of Triple immunosuppression: CNI (Tacrolimus/Cyclosporine) plus anti-proliferative agent (Mycophenolate or Azathioprine) along with corticosteroids. Each medication has important side effects that can sometimes dictate change in the dose or formulations or medications. Low dose Tacrolimus with mycophenolate and steroids has been shown to provide maximal allograft survival with preserved GFR.

Use of CD-28 monoclonal antibody Belatacept avoids long term CNI toxicity.

Some native kidney diseases are prone to recur in the transplant. Example: primary FSGS, Membranoproliferative GN, membranous GN.

Use of pulsatile hypothermic perfusion of the allograft kidney has been shown to reduce delayed graft function (DGF) and improve 1- year graft survival.

Viral infections like CMV, BK Virus infection and PJP fungal pneumonia are commonly encountered post- transplant. mTOR inhibitors have shown anti-viral effects. Specific anti-viral medications are available for the treatment of CMV infection, including Marabavir for Ganciclovir resistant CMV. Treatment of BKV nephropathy consists of reduction of immunosuppression and anti-viral drugs with IVIG. TRANSFORM trial showed that patients receiving low dose tacrolimus with everolimus had similar graft survival as those receiving tacrolimus standard dose, with reduced incidence of viral infections.

NODAT/PTDM can occur in up to 30% of transplant recipients. Skin cancer incidence is reduced with the use of mTORi.

Kidney donors are at a slightly increased risk of developing gestational hypertension or pre-eclampsia. Mycophenolate is avoided in kidney transplant recipients who conceive to avoid teratogenicity.

There are several important drug interactions with CNI, based on cytochrome p450 metabolism.
ABO incompatible transplants are possible with the use of plasma exchange or immunosorbent columns.