HYPERTENSION

90-95% Essential Hypertension
• Affects 26% of adults > 18 years
• Incidence increases sharply with age (90% of 90 year olds are hypertensive)
• 35% polygenic
• 65% environmental
  – BMI and sodium most important environmental risk factors
  – Insulin resistance and the metabolic syndrome common

5-10% Secondary Causes
• Chronic kidney disease
• Primary renal disease
• Primary aldosteronism
• Renovascular disease
• Obstructive Sleep Apnoea
• Phaeochromocytoma
• Coarctation of the aorta
• Drugs
• Cushings Syndrome
• Primary hyperparathyroidism
• Hyper and Hypothyroidism
# Rare Causes of Hypertension (0.1%)

## Monogenic
- Glucocorticoid responsive hyperaldosteronism
- Apparent mineralocorticoid excess (Hereditary)
- Progesterone-induced hypertension (Activating MR Mutation)
- Liddle’s Syndrome
- Gordon’s Syndrome (PHA 2)
- Congenital adrenal hyperplasia

## Acquired
- Apparent mineralocorticoid excess (Acquired)
- Reninoma
Monogenic causes of hypertension

Characterised by abnormalities in steroid biosynthesis or metabolism or abnormalities of the CCT epithelial cell sodium channel

• present as real or apparent mineralocorticoid overactivity
• clinical phenotypes include hypertension from birth, apparent volume expansion, suppression of plasma renin, and variable hypokalaemia
Renin-angiotensin-aldosterone system

- Angiotensinogen → Angiotensin I → Angiotensin II
- Renin
- Decrease in renal perfusion (juxtaglomerular apparatus)
- Lungs
- Kidney
- Surface of pulmonary and renal endothelium: ACE
- Tubular Na⁺, Cl⁻ reabsorption and K⁺ excretion, H₂O retention
- Adrenal gland: cortex
- Aldosterone secretion
- Arteriolar vasoconstriction, increase in blood pressure
- Pituitary gland: posterior lobe
- ADH secretion
- Collecting duct: H₂O absorption
- Sympathetic activity

Legend
- Blue: Secretion from an organ
- Blue dashed: Stimulatory signal
- Red: Inhibitory signal
- Black: Reaction
- Black dashed: Active transport
- Dotted: Passive transport

Water and salt retention. Effective circulating volume increases. Perfusion of the juxtaglomerular apparatus increases.
Figure 1. Normal biosynthetic pathways for cortisol and aldosterone. 11βH₁ and aldosterone synthase are present only in the zona glomerulosa, and are regulated by angiotensin II. 11βH₂ is present solely in the zona fasciculata and is regulated by ACTH. 21H = 21-hydroxylase. 11βH₁₁ = 11β-hydroxylase isoenzymes 1 & 2; 18 = 18-hydroxylase/aldosterone synthase. 17αH = 17α-hydroxylase.
- 25 y/o male with new onset hypertension
- BP 200/115 HR 88, hypertensive retinopathy
- 1 + proteinuria
- Na 140 K 2.7 Cl 97 HCO3 30 pH 7.44 pCO2 45 Cr 90umol/l
- Spot urine K 40mmol/l
- Plasma renin 3mU/l (low) aldosterone 150ug/l (low)

**What is the diagnosis?**

**Clue:**
unresponsive to spironolactone, but responsive to low Na diet and triamterene
21 year old man with hypertension on 3 drugs and remains poorly controlled. Ongoing search for a secondary cause so far negative. Renin and Aldo levels are pending and in the meantime he is started on spironolactone 25mg daily which results in a severe exacerbation of his hypertension – necessitating urgent withdrawal of the drug.

Later that year, his 24 year old previously normotensive sister develops severe hypertension and hypokalaemia late in the second trimester of pregnancy. Her renin and aldosterone levels are both low.

What is the diagnosis?
17 year old boy from Glen Eden with extended family in Northland presents to ED with a minor sporting injury. BP noted to be 180/110. He is admitted and BP does not settle below 160/90. Auntie says there is a family history of high blood pressure and strokes on his father’s side.

Na 144 K 3.1 urea 5 creatinine 80 venous bicarb 31
Renin < 3mU/L (low) Aldosterone 650 ug/l (high)
Saline suppression test  aldo. non-suppressible
Contrast CT shows adrenals mildly hyperplastic but no focal ademoma
Kidneys normal size and shape

What are the 2 diagnostic possibilities?

What additional test is indicated before treatment plan is finalised?
17 year old girl with BP 170/110
Family history of difficult hypertension
Na 140 K 6.1 creatinine 70 Cl’ 114
pH 7.3 HCO3’ 14 PCO2 32
Renin 2mU/l (low) Aldosterone 175ug/l (low)

What is the diagnosis?
A 13 year old boy is referred from Samoa with severe hypertension
His father died in his 20’s of unknown cause.
He is hypokalaemic and alkalaemic
Plasma renin < 2miu/l
Aldosterone 50pmol/l (low)

He is unresponsive to most antihypertensive drugs but prior to referral has been
started on spironolactone which has been worked up to 200mg daily and his BP is
mow relatively well controlled

What is the diagnosis?
5 year old boy with precocious puberty hypertension and hypokalaemia

What is the likely diagnosis?
- 25 y/o male with new onset hypertension
- BP 200/115 HR 88, hypertensive retinopathy
- 1+ proteinuria
- Na 140 K 2.7 Cl 97 HCO3 30 pH 7.44 pCO2 45 Cr 90umol/l
- Spot urine K 40mmol/l
- Plasma renin 3mU/l (low) aldosterone 150ug/l (low)

What is the diagnosis?

**Clue:**
unresponsive to spironolactone, but responsive to low Na diet and triamterene
Liddle’s Syndrome
(Pseudohypoaldosteronism type 1)
Liddle’s Syndrome: Characteristic Features

- Prevalence < 1% hypertensives

- Mechanism

  Autosomal Dominant activating mutation(s) in ENaC of collecting duct

  Impaired regulatory mechanism leads to increased no. ENaC channels on luminal membrane

- Presentation: severe salt sensitive hypertension, hypokalaemia, low renin + aldosterone

- Presents in children and young adults

- Diagnosis – Genetic analysis of ENaC gene

- **Treatment**

  Responds to low protein diet and triamterene

  Cured by renal transplant
21 year old man with hypertension on 3 drugs and remains poorly controlled. Ongoing search for a secondary cause so far negative. Renin and Aldo levels are pending and in the meantime he is started on spironolactone 25mg daily which results in a severe exacerbation of his hypertension – necessitating urgent withdrawal of the drug

Later that year, his 24 year old previously normotensive sister develops severe hypertension and hypokalaemia late in the second trimester of pregnancy. Her renin and aldosterone levels are both low.

What is the diagnosis?
**Mineralocorticoid Receptor Mutation** *(Geller’s Syndrome) (Pregnancy-Associated Hypertension)*

Rare genetic familial disorder where there is point mutation of the mineralocorticoid receptor resulting in a partially activated receptor.

Causes severe hypertension

Progesterone and spironolactone act as partial agonists

Suspect in women who present with severe hypertension and hyopkalaemia in 2\textsuperscript{nd} or 3\textsuperscript{rd} trimester of pregnancy.

The syndrome was discovered in a young male hypertensive whose 2 sisters experienced severe exacerbations of hypertension in pregnancy.
17 year old boy from Glen Eden with extended family in Northland presents to ED with a minor sporting injury. BP noted to be 180/110. He is admitted and BP does not settle below 160/90. Auntie says there is a family history of high blood pressure and strokes on his father’s side.

Na 144  K 3.1 urea 5 creatinine 80 venous bicarb 31  
Renin < 3mU/L (low) Aldosterone 650 ug/l (high)  
Saline suppression test  aldo. non-suppressible  
Contrast CT shows adrenals mildly hyperplastic but no focal adenoma  
Kidneys normal size and shape

What are the 2 diagnostic possibilities?

What additional test is indicated before treatment plan is finalised?
Glucocorticoid Remediable Hyperaldosteronism

Suspect in patients with early onset familial hypertension

Biochemically indistinguishable from other causes of Primary Aldosteronism
- Adrenals normal or diffuse hyperplasia on CT

Diagnosis – PCR for the chimeric gene

Treatment
Low dose dexamethasone
Also responds to aldosterone antagonists and amiloride
Table 1. Algorithm for GRA diagnosis and treatment.

**Screening**
Recommended for hypertensive individuals who:
- are diagnosed with primary hyperaldosteronism without demonstrable tumor
- are young (especially children) and have suppressed plasma renin activity
- have a family history of cerebral hemorrhage or hypertension before age 30 years
- have refractory hypertension (hypertensive on 3 classes of agents including a diuretic)
- are members of known GRA kindreds

**Diagnosis**

<table>
<thead>
<tr>
<th>Test</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexamethasone suppression test</td>
<td>Easily performed. Dexamethasone 0.5mg every 6hrs x 2 days, normally aldosterone</td>
</tr>
<tr>
<td></td>
<td>&lt; 4ng/dl on day 3 at 8am</td>
</tr>
<tr>
<td>Genetic Test</td>
<td>Can be arranged through the international GRA registry</td>
</tr>
<tr>
<td></td>
<td>(<a href="http://www.brighamandwomens.org/gra">http://www.brighamandwomens.org/gra</a>)</td>
</tr>
<tr>
<td>24 hour urinary 18-hydroxycortisol &amp;</td>
<td>Impractical since assays only available in specialized centers. Elevated &gt; 2x upper limit of normal; a urinary level of 18-hydroxycortisol &gt; 10nmol/l is diagnostic (5)</td>
</tr>
<tr>
<td>18-oxocortisol levels</td>
<td></td>
</tr>
</tbody>
</table>

**Treatment**

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucocorticoids</td>
<td>Dexamethasone 0.125-0.25mg, or prednisolone 2.5-5mg daily, titrated to normotension.</td>
</tr>
<tr>
<td>Mineralocorticoid receptor antagonists</td>
<td>Eplerenone and spironolactone are effective treatment choices.</td>
</tr>
<tr>
<td>Sodium epithelial channel antagonists</td>
<td>Amiloride and triamterene have also been used successfully.</td>
</tr>
<tr>
<td>Non-directed anti-hypertensives</td>
<td>β-blockers and ACE-inhibitors are less likely to be efficacious in the setting of a suppressed renin-angiotensin system (9). Dihydropyridine calcium channel blockers can be useful adjunctive treatments to the above diuretic agents.</td>
</tr>
</tbody>
</table>
17 year old girl with BP 170/110
Family history of difficult hypertension
Na 140 K 6.1 creatinine 70 Cl’ 114
pH 7.3 HCO3’ 14 PCO2 32
Renin 2mU/l (low) Aldosterone 175ug/l (low)

What is the diagnosis?
Gordon’s Syndrome (Pseudohypoaldosteronism type 2)

Familial hypertension/ Autosomal Dominant

Hyperkalaemia + metabolic acidosis (one of the few causes of persistent hyperkalaemia with completely normal renal function)

Normal (low) aldosterone levels

Responsive to NaCl restriction

Responsive to diuretics – especially thiazides

Possible mechanisms:

• Too much NaCl absorption by DCT

• Too much Cl⁻ absorption by collecting duct/ shunting voltage with less K secretion

• Impaired collecting duct apical K channel – less K secretion causes more NaCl absorption

(Mutant WNK proteins are though to be involved + could underlie any of these mechanisms)
A 13 year old boy is referred from Samoa with severe hypertension
His father died in his 20’s of unknown cause.
He is hypokalaemic and alkalaemic
Plasma renin < 2miu/l
Aldosterone 50pmol/l (low)

He is unresponsive to most antihypertensive drugs but prior to referral has been started on spironolactone which has been worked up to 200mg daily and his BP is mow relatively well controlled

What is the diagnosis?
Apparent Mineralocorticoid Excess (Hereditary)
Apparent Mineralocorticoid Excess – Hereditary

• Prevalence < 1%

• Mechanism: Autosomal dominant inheritance of inactivating mutation in 11beta hydroxysteroid dehydrogenase 2

• Presentation
  - Severe salt-dependent hypertension with hypokalaemia, low plasma renin and aldo, usually in childhood, can present in adulthood

• Diagnosis: Increase ratio of urinary tetrahydrocortisol (THF + 5 alpha THF) to tetrahydrocortisone (THE): range 6-50 (N = 1)

• Treatment High dose MR antagonists
Figure 6. Flowsheet with guidelines for detecting Apparent Mineralocorticoid Excess (AME) syndrome. THF = tetrahydrocortisol; aTHF = allo-tetrahydrocortisol; THE = tetrahydrocortisol; UFF = urinary free cortisol; UFE = urinary free cortisone.
5 year old boy with precocious puberty hypertension and hypokalaemia

What is the likely diagnosis?
Congenital Adrenal Hyperplasia
Figure 1. Normal biosynthetic pathways for cortisol and aldosterone. 11βH₁ and aldosterone synthase are present only in the zona glomerulosa, and are regulated by angiotensin II. 11βH₂ is present solely in the zona fasciculata and is regulated by ACTH. 21H = 21-hydroxylase. 11βH₁₈₂ = 11β-hydroxylase isoenzymes 1 & 2; 18 = 18-hydroxylase/aldosterone synthase. 17αH = 17α-hydroxylase.
Rare Causes of Hypertension – Acquired

- Apparent Mineralocorticoid Excess
- Reninoma
62 year old woman with D2M for 12 years and hypertension for 10 years
Office BP 180/110

Today: Na 144 K 2.6 Bicarb 35 Cl 95

6 months ago: Na 138 K 4.5 Bicarb 26 Cl 101

Meds  Valsartan, Frusemide, Verapamil, Vitamin E, Vitamin C, Ibuprofen, Herbal preparation
20 year old woman with BP 170/110 on routine check. BMI 23

Na 142mmol/l K 3.0mmol/l urea 5mmol/l creatinine 66umol/l
Plasma metanephrines normal
24-hour urinary free cortisol normal
renin 350miu/l, aldosterone 800pmol/l

Duplex ultrasound – no evidence or renal artery stenosis

What to do next?
62 year old woman with D2M for 12 years and hypertension for 10 years
Office BP 180/110

**Today:** Na 144 K 2.6 Bicarb 35 Cl 95

**6 months ago:** Na 138 K 4.5 Bicarb 26 Cl 101

**Meds** Valsartan, Frusemide, Verapamil, Vitamin E, Vitamin C, Ibuprofen, Herbal preparation
Apparent Mineralocorticoid Excess – acquired

Glycyrrhizic Acid (Licorice)

- Blocks 11BHSD 2
- Increases access of cortisol to mineralocorticoid receptor causing sodium retention + potassium loss

Glycyrrhizic Acid (50x sweeter than sugar) present in many herbal preparations to improve palatability, candies, medications, chewing tobaccos, teas, and present in 2/3 of Chinese herbal formulas
20 year old woman with BP 170/110 on routine check. BMI 23

Na 142mmol/l  K 3.0mmol/l  urea 5mmol/l  creatinine 66umol/l
Plasma metanephrines normal
24-hour urinary free cortisol normal
renin 350miu/l, aldosterone 800pmol/l

Duplex ultrasound – no evidence or renal artery stenosis

What to do next?
CT shows a 2cm solid renal mass in subcapsular location, lower pole of right kidney

What is the likely diagnosis?

How to proceed?

Bilateral renal vein sampling shows lateralisation of renin secretion in a ratio of 6:1 for the right kidney

CT-guided biopsy showed a renal tumour composed of uniform polygonal cells with little nuclear polymorphism or mitotic activity. Renin production confirmed by immunofluorescence antibody testing.

At surgery encapsulated tumour identified and excised

Subsequently BP normal on no treatment
Reninoma

Rare
Tumour of JG apparatus producing renin autonomously
Hypotension and hypokalaemia
50% present before age 20
High renin and aldosterone
Imaging – often see a small renal mass in subcapsular location
Tumours occasionally extrarenal (eg in pelvis)

Treatment – partial nephrectomy usually curative
Hypertension and hypokalaemia
↓
Measure renin and aldosterone
↓

<table>
<thead>
<tr>
<th>↑ renin + aldo</th>
<th>N or ↓ renin + ↑aldo</th>
<th>↓ renin + ↓aldo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignant hypertension</td>
<td>Primary aldosteronism</td>
<td>Apparent mineralocorticoid excess</td>
</tr>
<tr>
<td>Renovascular</td>
<td>Idiopathic aldosteronism</td>
<td>– genetic (11BHSD2 mutation)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>Glucocorticoid remediable hyperaldosteronism</td>
<td>– acquired (glycerrhetinic acid)</td>
</tr>
<tr>
<td>Coarctation</td>
<td>Congenital adrenal hyperplasia</td>
<td>Cushing’s Syndrome</td>
</tr>
<tr>
<td>Renin-secreting tumour</td>
<td></td>
<td>DOC Excess</td>
</tr>
<tr>
<td>Renal infarct</td>
<td></td>
<td>Liddle’s Syndrome</td>
</tr>
<tr>
<td>Vasculitis</td>
<td></td>
<td>Activating MR Mutation</td>
</tr>
</tbody>
</table>
Urine [Cl⁻]

- <20 mEq/L
  - Chloride-responsive alkaloses
    - Gastric fluid loss
    - Nonreabsorbable anion delivery
    - Diuretics*
    - Posthypercapnia
    - Villous adenoma
    - Congenital chloridorrhea

- >20 mEq/L
  - Chloride-unresponsive alkaloses
    - Urine K⁺
      - <30 mEq/d
        - Laxative abuse
          - Severe K⁺ depletion
      - >30 mEq/d
        - Blood pressure
          - Low/normal
          - High
            - Bartter or Gitelman syndrome, or diuretic abuse
            - Plasma renin
              - High
              - Low
                - Primary aldosteronism, bilateral adrenal hyperplasia, or licorice abuse
              - High
                - Cushing syndrome
          - High
            - Plasma cortisol
              - Normal
              - Yes
                - Renovascular HTN
                  - JGA tumor
              - No
                - Malignant or accelerated HTN

* After diuretic therapy