Hypertension, Cystic kidney disease and tubules

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FRACP course 2015

Basic concepts

- Defined statistically in children – above the 95th centile for age, height and gender as opposed to the adult definition that is by risk

- Severe untreated hypertension carries risk of end organ damage to kidneys, eyes and heart

Blood Pressure Tables for Children and Adolescents

from the Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents

**Blood Pressure Levels for Boys by Age and Height Percentile**

<table>
<thead>
<tr>
<th>Age (Year)</th>
<th>BP Percentile</th>
<th>Systolic BP (mmHg)</th>
<th>Diastolic BP (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>50th</td>
<td>80 81 83 85 87 88 89</td>
<td>54 55 56 57 58 59 60</td>
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<tr>
<td></td>
<td>90th</td>
<td>94 95 97 99 100 102 103</td>
<td>49 50 51 52 53 54 55</td>
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<td></td>
<td>95th</td>
<td>98 99 101 103 104 106 108</td>
<td>54 55 56 57 58 59 60</td>
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<td></td>
<td>96th</td>
<td>105 106 108 110 112 113 114</td>
<td>61 62 63 64 65 66 67</td>
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<td>50th</td>
<td>84 85 87 88 90 92 92</td>
<td>59 60 61 62 63 64 65</td>
</tr>
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<td>54 55 56 57 58 59 60</td>
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<tr>
<td></td>
<td>96th</td>
<td>109 110 111 113 115 117 117</td>
<td>66 67 68 69 70 71 71</td>
</tr>
<tr>
<td>3</td>
<td>50th</td>
<td>88 89 90 91 93 94 95</td>
<td>44 45 46 47 48 49 50</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>96th</td>
<td>111 112 114 116 118 119 120</td>
<td>71 72 73 74 75 76 77</td>
</tr>
</tbody>
</table>

Causes

- Renovascular
  - Renal artery stenosis
  - Renal vein thrombosis
  - Fibromuscular dysplasia
  - Mid-aortic syndrome
- Compressive effect (tumour/hydronephrosis)
- Renal Parenchymal Disease
  - Polycystic Kidney disease
  - MCKD
  - Interstitial nephritis, cortical necrosis
  - Glomerular disease
- Obstruction
Other causes of hypertension

- Coarctation of the aorta
- Wilms tumour, neuroblastoma
- Monogenic hypertension eg Liddle’s syndrome
- Cushings, Conn’s and phaeochromocytomas
- Raised BMI and Obstructive sleep apnoea

Exam scenarios

- White coat hypertension
- Dysplasia
- Acute GN

Exam scenario

- An 8 yo girl is seen in outpatients with 3 month history of headache.
- BP 150/100 but she is anxious
- ABPM average 145/90mmHg, with no nocturnal dip.
- Imaging shows small dysplastic kidneys
- No history of infections
- Creatinine 100umol/l
- Urine protein: creatinine 180mg/mmol
Ambulatory blood pressure monitoring

- Multiple recordings, improving reproducibility
- Better predictor of end organ damage
- Helps to define circadian BP profile – loss of nocturnal dipping predicts end organ damage
- Minimises white coat effect
- Gold standard – how to confirm if true hypertension

What would be your antihypertensive of choice?

A) ACE inhibitor  
B) Beta blocker  
C) Calcium channel antagonist  
D) Diuretic  
E) Exercise and diet

Answer A

- CKD due to bilateral renal dysplasia
  - BP >95%
  - Proteinuric
- Best choice for reduction of BP, proteinuria & preservation of renal function is ACEi.

- Diuretics – acute GNs
- Dietary advice with raised BMI

- Which other organs would you screen?
Assessment of end organ damage

**Ophthalmology**
- para-foveal and intraretinal haemorrhages
- arteriolar attenuation with focal occlusions
- hypertensive retinopathy
- retinal infarction

**Echocardiography**
- LVH is most common sign of end organ damage
- Patients with established HTN should have LV mass assessed at diagnosis & periodically thereafter
- Persistent increased LV mass – increase drug therapy
- Direct correlation between severity of HTN & atherosclerotic lesions in aorta and coronaries in adolescents with sudden death from trauma
- Carotid intimal thickness and large artery compliance correlate with severity of HTN

**Another scenario**
- 6 year old in CED with headache
- BP 140/100
- History of sore throat a few weeks ago
- Oedema
- Haematuria

**What would be your antihypertensive of choice?**

A) ACE inhibitor
B) Beta blocker
C) Calcium channel antagonist
D) Diuretic
E) Exercise and diet
Then he has a seizure.

Primary vs secondary hypertension
- Primary HTN remains a diagnosis of exclusion
- Increasing prevalence of obesity means that age of primary HTN is lower than 2 decades ago
- Obesity being recognised as a cause in itself
- Renal disease remains most common cause of secondary
- Secondary HTN tend to have abnormal renal function tests, renal US or echocardiograms
- Some studies show that children with primary HTN have higher BMI but not all

Reversible Posterior leucoencephalopathy- PRES

Hypertension in Type 2 diabetes
- Common in adults with T2DM, ~ 70%
- Prevalence of HTN in children and adolescents unknown ~ 8-36%
- Blunted nocturnal dipping common in association with increased incidence of microalbuminuria
- Obese adolescents show greater reduction in BP when shifting from a high to low sodium intake –Sodium retention parallels plasma insulin concn.
- Salt sensitivity is associated with increased sympathetic activity
RENAL CYSTIC DISEASES

Cystic Kidney Diseases

- **Simple benign cysts** – up to 1-2 per kidney in childhood (5 in adults). Dx requires otherwise normal appearing parenchyma, function and no associated disorders (eg NF, Meckel, VHL, TS).

- **Cystic dysplastic kidneys** – in utero developmental anomaly, small echogenic kidneys, may have abnormal shape, impaired renal function (if bilat). May have urological anomalies / genetic syndrome.

- **MCDK** – generally a unilateral non-functional cystic mass (large non communicating cysts of various sizes), no identifiable parenchyma & loss reniform shape, atretic prox ureter. If <5cm often involute up to ~ 2 years of age. 1/4000 live births (2xM>F), non-heritable. ~25% contralateral side have VUR & also ↑ risk UPJ obstruction & dysplasia. If bilateral (v rare) – fatal in newborn period.

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  - ~25% contralateral side have VUR & also ↑ risk UPJ obstruction & dysplasia.
  - If bilateral (v rare) – fatal in newborn period.

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Exam scenario

- 2 year old boy presents with developmental delay and seizures.
- There are hypopigmented macules on his chest and abdomen.
- Normal electrolytes and renal function
BP 110/60
Renal USS shows large kidneys with multiple cysts

What is the most likely diagnosis?

A) Autosomal recessive polycystic kidney disease
B) Nephronophthisis
C) Bilateral multicystic dysplastic kidneys
D) Tuberous Sclerosis related cystic kidney disease
E) Autosomal dominant polycystic kidney disease

Answer D

- ARPKD – cysts are small, kidneys are large and BP is high
- Kidneys in nephronophthisis usually not enlarged and no large cysts
- Bilateral MCDK not compatible with life
  - Nb not the same as bilateral cystic dysplastic kidneys
- Most likely is ADPKD or TS - skin is the clue for TS
**Tuberous Sclerosis & Kidney disease**
- Mutation TSC1 & 2 genes.
  - TSC2 adj to PKD1, some patients found to have contiguous deletions of both genes.
  - Renal manifestations of TS:
    - Angiomyolipoma: benign fatty vascular malform, 80% TS pts, from early childhood, if large can bleed/obstruct
    - Cystic disease – 20% have epithelial cysts, polycystic disease in <5% (may result in ESRD)
    - Renal cell carcinoma - <1%
- Management guidelines:
  - Annual BP and assessment of GFR
  - Monitor PKD/angiomyolipomata
  - Renal MRI at presentation, then annually if abnormality found

**Exam scenario**
- A 10 year old girl is seen with nocturia
- On examination she is hypertensive with BP 130/90
- No issues with vision or development
- She has hepatosplenomegaly
- Urea 12, Creatinine 140umol/L.
- Hb 90, Platelets 98

**What is the most likely diagnosis?**

- Ultrasound shows 2 large echogenic kidneys with multiple small cysts
- Her spleen is 18cm and she is found to have oesophageal varices

A) Autosomal dominant polycystic kidney disease
B) Autosomal recessive polycystic kidney disease
C) Nephronopthisis
D) Bilateral cystic dysplasia
E) Bardet Biedl’s syndrome
Congenital Disorders of the Kidney

- Cystic Disease -genetic
  - ARPKD
  - ADPKD
  - FJN/MCD
  - Associated with other Syndromes

ADPKD

- Mutations of PKD1 & 2, affects 1/1000
- Wide phenotypic variability
- Detected antenatally/incidentally/screening
- Cannot exclude until >40yrs
- In childhood usually asymptomatic, may develop HTN/proteinuria
- Extrarenal: cysts in liver & pancreas, cerebral aneurysms
- General policy is to council against screening of minors: annual BP & UA only.

ARPKD

- Mutation of PKHD1, 1/20,000
- Cystic dilations of collecting ducts (multiple microscopic cysts) and congenital hepatic fibrosis
- May also have intrahepatic bile duct dilatation (“Caroli’s syndrome”).
- USS – kidneys large, echogenic, may see scattered small cysts (1-2mm).
- Presentation:
  - Antenatally - large bright kidneys and oligohydramnios/pulmonary hypoplasia if severe
  - Postnatally - palpable kidneys/HTN/CHF/liver disease/renal impairment.
- Hepatomegaly & portal HTN will develop in most

Nephropnophthisis

- Triad: disruption of TBM, tubulo-interstitial fibrosis, cyst formation.
- NPH presents infancy, childhood, adolescence. MCKD typically adult onset.
- Inherited (NPH AR (>10 identified mutations in NPHP loci at last count), MCKD AD)
- NPH most freq genetic cause CKD in <20yro, classic presentation is CKD (progresses to ESRD by 20yr), polyuria/polydipsia, bland urine, disproportionate anaemia.
- Normal/small sized kidneys, echogenic, poor CM differentiation, may see small cysts at CM junction.
- Extrarenal manifestations often assoc with NPH (esp visual and dev delay – eg Senior Loken syndrome, Joubert’s)
Renal Tubular Acidosis

- Normal anion gap
- Hyperchloraemic metabolic acidosis
- Inappropriately acidic urine

### Features of the Renal Tubular Acidosis (RTA) Syndromes

<table>
<thead>
<tr>
<th>Feature</th>
<th>Proximal RTA</th>
<th>Classic Distal RTA</th>
<th>Hyperchloraemic RTA</th>
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</thead>
<tbody>
<tr>
<td>Plasma bicarbonate &amp; alkalinisation</td>
<td>Decreased</td>
<td>Normal</td>
<td>Increased</td>
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<tr>
<td>Plasma chloride &amp; acidification</td>
<td>Increased</td>
<td>Increased</td>
<td>Increased</td>
</tr>
<tr>
<td>Plasma potassium</td>
<td>Normal or decreased</td>
<td>Decreased</td>
<td>Increased</td>
</tr>
<tr>
<td>Plasma uric acid</td>
<td>Increased</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Chloride excretion ratio</td>
<td>Normal or increased</td>
<td>Normal or increased</td>
<td>Increased</td>
</tr>
<tr>
<td>Urine pH at alkalosis</td>
<td>Increased</td>
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<td>Normal</td>
</tr>
<tr>
<td>D/P ratio bicarbonate</td>
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<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Furosemide response</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Urinary HCO₃⁻ excretion</td>
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<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Urinary pH</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Radiographs</td>
<td>Abnormal</td>
<td>Normal</td>
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<tr>
<td>Cryptorchidism</td>
<td>Present</td>
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<td>Present</td>
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<tr>
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<td>Absent</td>
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<td>Absent</td>
</tr>
<tr>
<td>Abnormality</td>
<td>High above</td>
<td>Low above</td>
<td>Low above</td>
</tr>
</tbody>
</table>

*The syndrome signifies generalised proximal tubule dysfunction and is characterised by impaired reabsorption of glucose, uric acid, all organic acids.

### Case

- 15 month old boy referred for failure to thrive
- Normal pregnancy. Routine prenatal care.
- Normal delivery, no NICU

- Proteinuria, glucosuria
- No weight gain for > 6 months
- Two episodes of dehydration requiring hospitalization
- Blue eyes and blonde

Distinguish by the story

- If they lose Calcium in the urine and have nephrocalcinosis think DISTAL RTA.

- If they have rickets, lose phosphate, have glycosuria, think PROXIMAL RTA

- The post obstructive diuresis baby has a HYPERKALAEMIC distal RTA.
Case

- Initial bloods:
  - Na 138, K 3.0, Cl 114
  - Bicarbonate 15, PO4 0.8
  - Urea 4, Creatinine 40umol/l
  - Glucose normal, Albumin normal
  - TSH/T4 normal
  - Urine protein/creatinine ratio 350mg/mmol
  - Glycosuria

Generalised proximal tubule dysfunction

- the Fanconi syndrome
  - Salt wasting causes polyuria and polydipsia
  - Hypokalaemia due to attempts to correct massive distal salt delivery
  - Hypophosphataemia leading to rickets
  - Acidosis
  - Failure to thrive
  - Glycosuria

Generalised proximal tubule dysfunction

- Idiopathic - variable inheritance
- Inborn errors of metabolism
  - Cystinosis, Galactosemia, Hereditary fructose intolerance, Tyrosinemia (type I), Wilson disease
- Lowe's oculocerebrorenal syndrome
  - Bilateral congenital cataracts, glaucoma, hypotonia, hyporeflexia, severe mental retardation
- Dent's Disease
- Mitochondrial cytopathies
- Heavy metal poisoning
- Cadmium, lead, mercury, platinum, and uranium.
- Chinese herbs
- Drugs
  - Tetracycline (anhydro-4-epitetracycline), Aminoglycosides, Cisplatin, Nitroimidazole, 6-mercaptopurine, Valproic acid, Etanercept, a reverse transcriptase inhibitor
- Dysproteinemias
  - Multiple myeloma, amyloidosis, light-chain nephropathy, benign monoclonal gammopathy
- Immunologic injury of the proximal tubules
  - c- interstitial nephritis, renal transplantation
**Urine electrolytes**

- **SODIUM**
  - Useful for assessing ECF depletion
  - Confirmation of hypovolaemia
  - Urine Na and Chl usually retained in parallel.
  - Would expect <20 if hypovolaemia only issue.
  - Can have higher urine Na losses if vomiting leads to metabolic alkalosis – need to excrete bicarbonate, but Chl will remain low.

- **CHLORIDE**
  - High with diuretic abuse.
  - High with Barrters, Gitelman’s
  - Low with vomiting (lose in vomit) and laxative abuse

**Hypochloraemic Hypokalaemia Metabolic Acidosis**

- Cystic fibrosis
- Barrters Disease
- Pyloric stenosis
- Diuretic abuse
- Chloridorrhoea
- Persistent vomiting & diarrhoea

**Barrter’s**

- FTT, polyuria, polydipsia, constipation, muscle weakness, nephrocalcinosis

- Hypokalaemic hypochloraemic metabolic acidosis
  - Decreased serum Na, K and Cl
  - Increased urinary Ca, Cl, prostaglandin E2
  - Raised renin and aldosterone
  - Normal blood pressure & renal function

- Treat with Na, K supplements & indomethacin

**Pseudo Bartter’s**

- Cystic fibrosis
- Hypokalaemic alkalosis with dehydration ie ECF depletion, Na and water reaborption, K+ and H+ excretion.

- Low urine chloride - CF, laxative abuse, chloride diarrhoea.

- Normal/ High - loop diuretic abuse
Salt and water

- Serum Osm/L = (serum Na x 2) + urea + glucose
- Normal serum value - 280-300 mOsm/Kg
- Normal urine Osm – 250 – 900 mOsm / kg
- Reflects hydration status
- Measured by serum and urine
- Solutes measured - mainly urea, glucose, and sodium
- Measured as solute concentration/Kg

Factors that affect Osmolality

- **Plasma osmolality**
  - Predominantly determined by Na, Chl, HCO3, glucose and urea.
  - Calculated plasma osmolality = 
  - (2xplasma sodium) + glucose + urea
  - Difference in measured and calculated is the osmol gap

- **Urine osmolality**
  - Measure of urine concentration.
  - Determined by ADH
  - Can work it out roughly by multiplying the last two figures on the SG on the dipstick by 40.
SIADH

- Plasma osmolality below 270mosm
- Inappropriately concentrated urine (>100osm)
- Clinical euvoalema
- Increased urine Na to try to lose volume
- Plasma Na will improve after fluid restriction

HYPONATRAEMIA

Plasma osmolality

High → ?factitious

Normal → Pseudohypo

Hyperglycaemia Hyperlipidaemia

ECF volume assessment

Decreased → loss of Na>water

Reduced

Extrarenal

GI loss
Skin loss
3rd spacing
Expect Urine Na<20

Renal

Diuretics
Bicarbonaturia 2dry to vomiting
Recovery ATN
Post obstruction
Salt losing
Expect Urine Na=20

Normal → Gain of water>salt

Renal failure
Urine Na>20

SIADH

XS water intake
Hypothyroidism
Glucocorticoid deficiency
Urine Na >20

Hypernatraemia

ECF assessment

Decreased

Losing water>Na

Urine osmolality

>800 (concentrated)
Non renal loss eg GI
Expect urineNa<20

<800

Diabetes insipidus

Hyperglycaemia
Intrinsic renal disease
Expect urine Na>20

Normal/increased

Gaining Na> water

Variable urine osmo

Excess oral sodium
Excess iv fluid
Mineralocorticoid xs
Cushing's
Conn's
Expect urine Na >20

Some hopefully self explanatory slides regarding diuretics in case there are questions on them
II. Types of Diuretics

a) Osmotic Diuretics

Examples: Mannitol, Urea, Glycerol and loop diuretics

Mechanism of Action:
Osmotic diuretics...
...are freely filterable at the glomerulus...
...undergo limited reabsorption by the renal tubule...
...are relatively biologically inert.

Therefore, their osmotic force retains H2O in the proximal convoluted tubule resulting in diuresis. The retained H2O makes the [Na+] in the tubule lower than that in the interstitium. This concentration gradient decreases proximal tubular Na+ reabsorption resulting in a small natriuresis with a net H2O loss.

Other Phenomena:
• Osmotic diuretics result in dehydration of the eye and brain.
• Diuresis is mitigated by subsequent H2O reabsorption in the distal nephron.
• Mannitol increases medullary blood flow, thereby decreasing the medullary urea gradient and enhancing the diuretic effect.
• Osmotic diuretics may cause hyperosmolality.
• Osmotic diuretics may cause that overtied (e.g., 1 g/kg of mannitol in a 75-kg person requires an infusion of 300 to 1,500 mL).

b) Carbonic Anhydrase Inhibitors

Examples: Acetazolamide, Dichlorphenamide, Methazolamide

Mechanism of Action:
One mechanism of proximal tubular Na+ reabsorption is passive accompaniment with HCO3−, the reabsorption of which depends on tubular carbonic anhydrase. Therefore, inhibition of carbonic anhydrase results in:
• diuresis
• natriuresis
• alkaline urine
• normal anion gap metabolic acidosis

Other Phenomena:
• Carbonic anhydrase inhibitors also dehydrate the eye and decrease CSF production.
• Diuretic efficacy is mitigated by subsequent distal HCO3− reabsorption.
• Effectiveness of carbonic anhydrase inhibitors is increased by metabolic alkalosis and decreased by metabolic acidosis.
• Na+ salvage in the distal nephron results in hypokalemia.
• Inhibition of red blood cell carbonic anhydrase limits CO2 transport and results in hypercapnia.

III. High-Volume Loop Diuretics

Examples: Furosemide, Bramandine, Ethacrynic Acid

Mechanism of Action:
The loop diuretics are a diverse group of drugs which block reabsorption of Na+ and Cl− in the thick ascending loop of Henle. This causes a less hypertonic urine to enter the collecting duct with a lower gradient for ADH dependent H2O reabsorption. This results in a diuresis and natriuresis. The loop diuretics also interfere with the generation of a hypertonic medullary interstitium which reduces ADH dependent H2O reabsorption and augments their efficacy.

Other Phenomena:
• Loop diuretics, particularly ethacrynic acid, perturb endolymph electrolyte composition causing transient or permanent deafness.
• Na+ salvage in the distal nephron results in hypokalemia.
• Loop diuretics decrease systemic vascular resistance thereby augmenting their dehydrating effect.
• Loop diuretics do not differ in their maximal effect.
• Loop diuretics will displace protein bound drugs (e.g., warfarin).
• Nephrotic syndrome decreases loop diuretic efficacy as urinary protein binds and inactivates the diuretics.
• Loop diuretics decrease urate excretion and may worsen hyperuricemia.
• Loop diuretics may cause hyperglycemia.
• Loop diuretics increase both Mg2+ and Ca2+ excretion.
• Loop diuretics may cause idiopathic interstitial nephritis.
• Hypochloremia may decrease loop diuretic efficacy.
d) Thiazide Diuretics

Examples: Chlorothiazide, Hydrochlorothiazide, Metolazone (thiazide-like)

Mechanism of Action:
The thiazides block a specific site in the early distal tubule which would normally reabsorb Na+ and Cl-. Like the loop diuretics, this causes a less hypotonic urine to enter the collecting duct with a lower gradient for ADH dependent H2O reabsorption. This results in a diuresis and natriuresis. Unlike the loop diuretics, the thiazides do not interfere with the generation of a hypotonic medullary interstitium. This, and the fact that the majority of the generation of hypotonic tubular fluid occurs before the distal tubule, makes these diuretics less effective than the loop diuretics.

Other Phenomena:
• Some thiazides have carbonic anhydrase inhibitor activity, but this does not cause significant diuresis.
• Na+ salvage in the distal nephron results in hypokalemia.
• Thiazide diuretics do not differ in their maximal effect.
• Thiazides decrease urea excretion and may worsen hyperuricemia.
• Thiazides increase Mg** excretion but decrease Ca** excretion.
• Thiazides may cause idiopathic interstitial nephritis.

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e) Potassium-Sparing Diuretics

Examples: Spironolactone (aldosterone antagonist), Triamterene (aldosterone independent)

Mechanism of Action:
The K+ sparing diuretics block either the aldosterone dependent or independent pumps in the late distal tubule and early collecting duct. This results in a mild diuresis. In normal conditions there is little change in the K+ output, however these drugs are very effective in mitigating an ongoing kaliuresis. These drugs should never be used in combination with K+ supplements.