ANZGMU

AUSTRALIA & NEW ZEALAND GENERAL MEDICINE UPDATE

ANZGMU 2021

Patient with low K: Is he acidotic or alkalotic?

Dr. Surjit Tarafdar

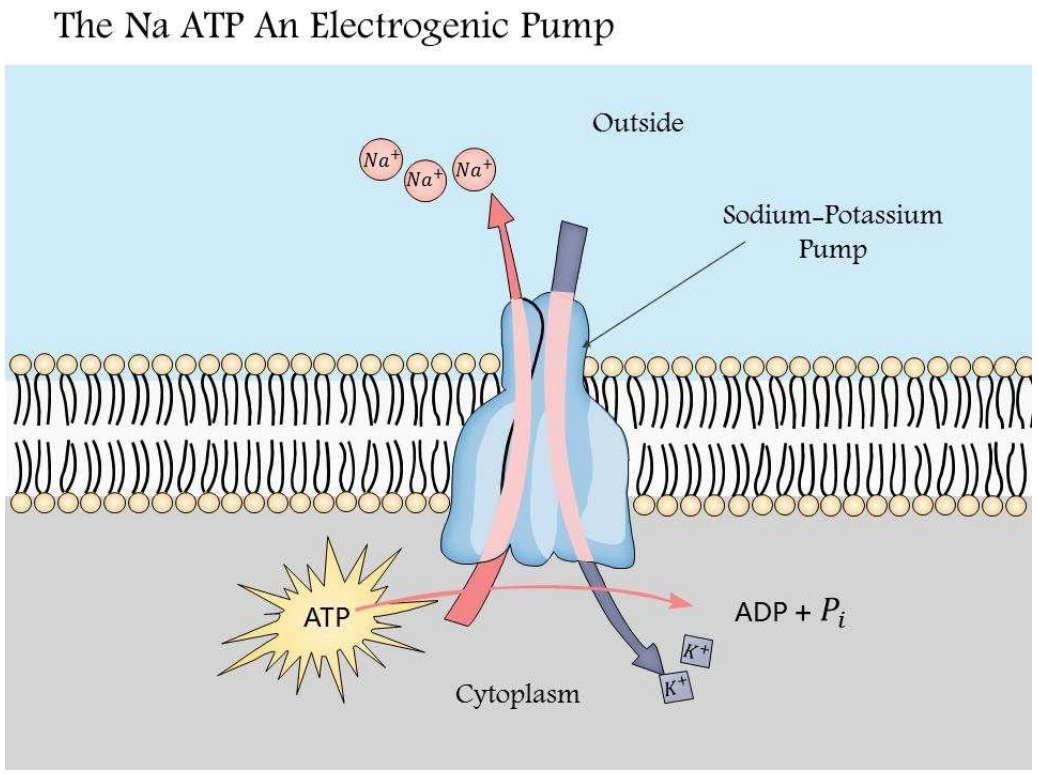
Blacktown and Mt. Druitt Hospital

Sydney

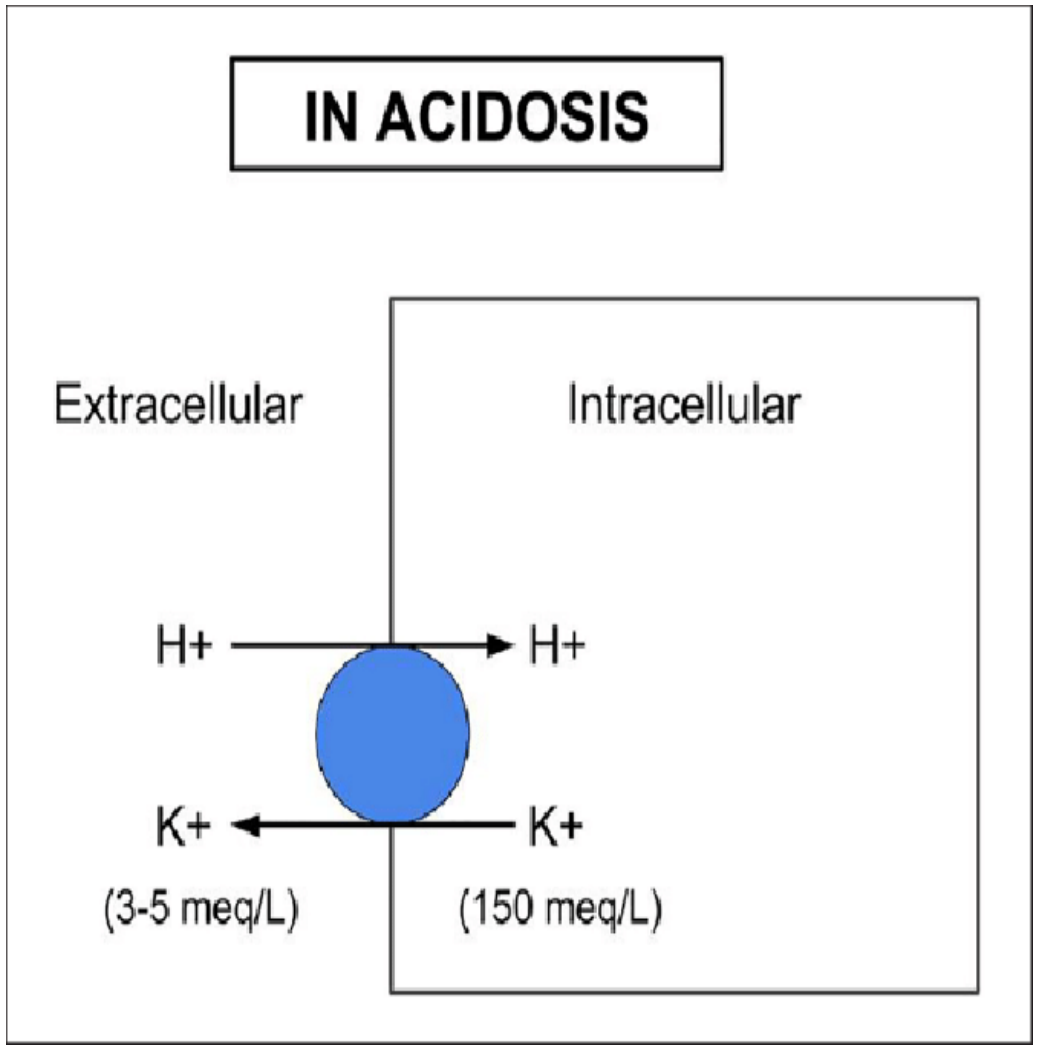
Conjoint Senior Lecturer
Department of Medicine Western Sydney University

Few key points to ponder before we proceed..

- Disorders of the renal tubules can lead to both **metabolic alkalosis and acidosis** as well as **hypokalemia or hyperkalemia**
- **K and H often move often together-** hyperkalemia predisposes to metabolic acidosis and vice versa……similarly metabolic alkalosis predisposes to hypokalemia
- **BUT**- hypokalemia can be associated with either **alkalosis or acidosis**
- The renal tubular cells are rich in K and low in Na due to the action of the basolateral Na-K-ATPase
- Ammonia is the chief buffer for H in urine



Na-K-ATPase pumps 3 Na out and pulls 2 K into cells



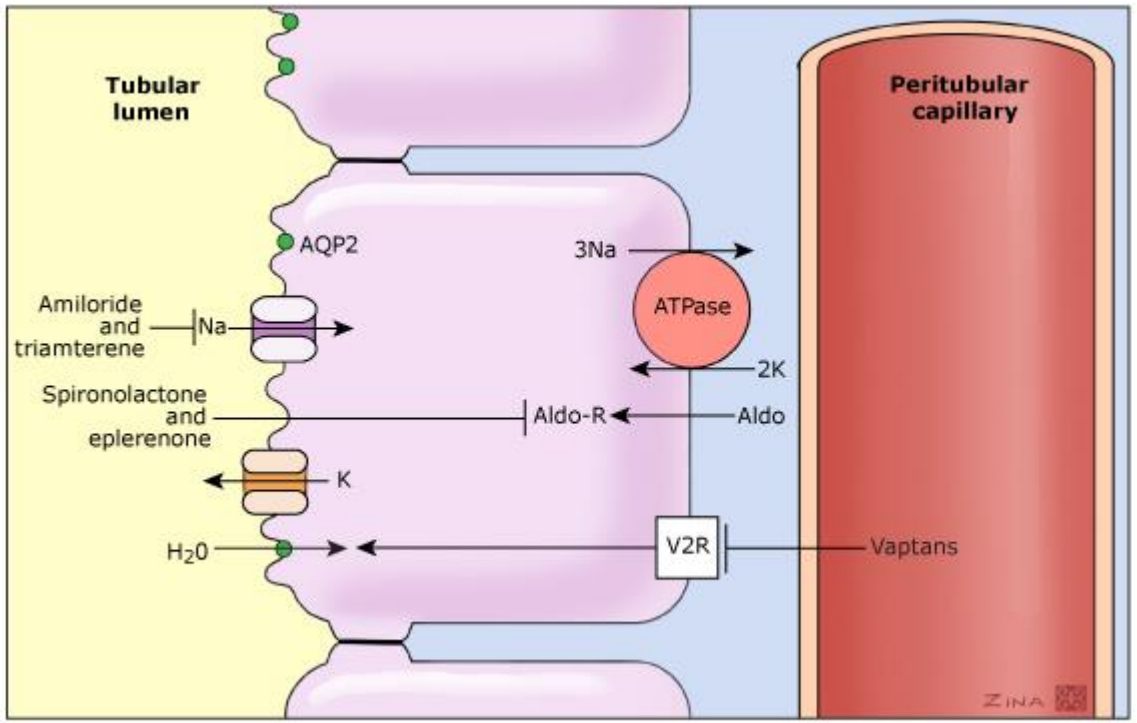
Cellular shifts between H and K……

metabolic acidosis leads to hyperkalemia AND vice versa

With a GFR of 125 ml/min, why don't we make 180 L urine everyday?

Because:

- Tubular cells are hungry for Na(due to Na-K-ATPase pumping 3 Na out and pulling in 2 K)
- Water passively follows the Na



Aldosterone

- Absorption of Na
- Excretion of K
- Water passively absorbed with the Na
- *Indirect* excretion of H

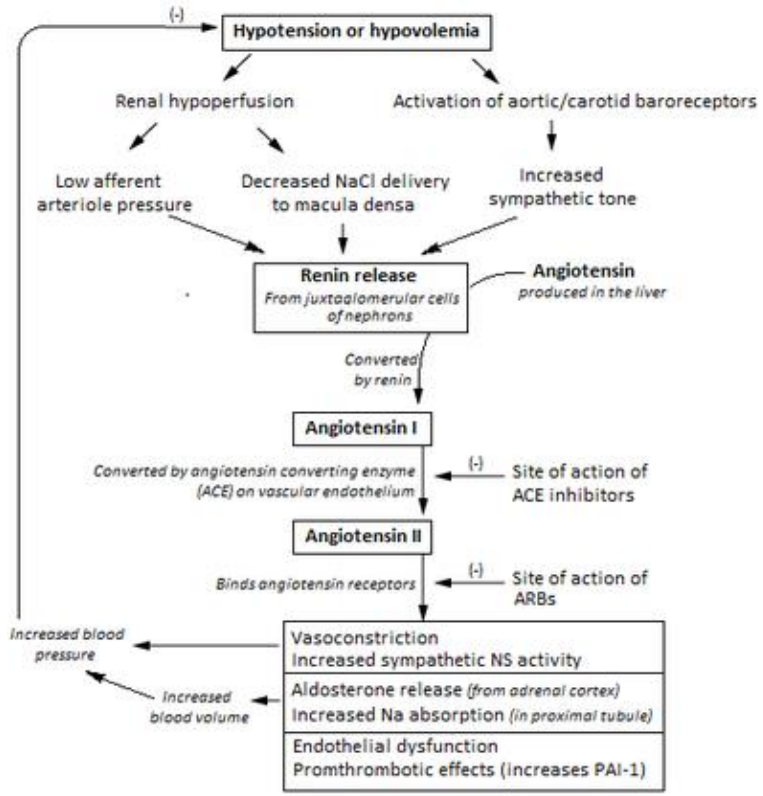
H in the urine needs buffer

- H+ in the urine needs buffers otherwise urine would quickly become saturated
- Chief buffer is ammonia which becomes ammonium after accepting the H^+
  $\{ NH_3 + H^+ \leftrightarrow NH_4^+ \}$
- Ammonia is derived from breakdown of glutamine by glutaminase in the PCT
- Hyperkalemia decreases glutaminase activity and therefore decreases ammonia production
- Therefore, in hyperkalemia, tubules unable to secrete H due to absence of enough ammonia to buffer it
- **End result: hyperkalemia leads to metabolic acidosis**

Summing up the K and H relation…….

- **Hyperkalaemia leads to metabolic acidosis by three mechanisms-**
  - Excess K^+ enters the cell and in exchange H^+ comes out of cells
  - K^+ competes with H^+ for secretion by the collecting duct in exchange for Na^+
  - Hyperkalaemia by decreasing renal ammonia production inhibits H^+ excretion in urine (ammonia is the chief buffer for urinary H^+)
- **Metabolic acidosis leads to hyperkalaemia by-**
  - Excess H^+ enters the cell and in exchange K^+ comes out of cells
  - H^+ competes with K^+ for secretion by the collecting duct in exchange for Na^+

Quick review- renin angiotensin aldosterone system



Hypokalaemia associated with metabolic alkalosis

Divided into two groups depending on the blood pressure:

High BP

- Primary hyperaldosteronism (Commonest cause in this group)
- Liddle syndrome
- Chronic liquorice ingestion
- Apparent mineralocorticoid excess
- Familial Hyperaldosteronism (including Glucocorticoid-remediable hyperaldosteronism)

Low-normal BP

- Bartter syndrome
- Gitelman syndrome (milder disease and commoner in adult population)

K and metabolic acidosis

- Hypokalaemia with normal anion gap metabolic acidosis
  - Renal tubular acidosis type 1 (distal RTA)
  - Renal tubular acidosis type 2 (proximal RTA)
  - *Beware of chronic diarrhoea*

- *Might as well cover this too as we are talking RTAs…*

  Hyperkalaemia with normal anion gap metabolic acidosis
  - Renal tubular acidosis type 4 (type 4 RTA)

Primary aldosteronism (PA)

- 5-13% of all patients with hypertension have PA
- Aldosterone producing adenoma (35%) or bilateral idiopathic hyperplasia (>60%)
- Suspect in HTN and metabolic alkalosis with hypo or normokalemia (K normal but on the lower side) OR in HTN with adrenal incidentaloma
- Initial test: Plasma aldosterone to renin ratio (PAC/PRA) of >30 suggestive (denominator dependent)
- Confirmatory tests show non-suppression of aldosterone production after IV saline infusion (2 L over 4 hours) or heavy oral salt loading (1 g salt tablets tds x 3 days)
- CT adrenal and adrenal vein sampling

Liddle Syndrome (Pseudohyperaldosteronism)

- Rare autosomal dominant condition
- Presents in young age with HTN and hypokalemic metabolic alkalosis
- Mutation in the ENAC channel (Na^+ reabsorbing channel in the collecting duct) renders it resistant to normal degradation- look at diagram on slide no.7
- Characteristically associated with low plasma renin and aldosterone
- Therapy consists of Na^+ restriction and K^+ supplementation and Triamterene or Amiloride (why not spironolactone??)

Apparent mineralocorticoid excess (AME) and Chronic Liquorice Ingestion

- Cortisol binds avidly to the renal aldosterone receptor and the plasma cortisol concentration is 100-fold > plasma aldosterone concentration
- In kidney, 11-beta-hydroxysteroid dehydrogenase enzyme type 2 isoform (11-beta-HSD2) converts cortisol into the inactive cortisone
- **AME:** defective 11-beta-HSD2 causes high renal concentration of cortisol which leads to excess stimulation of aldosterone receptor

- Autosomal recessive and presents in childhood with HTN, low K and metabolic alkalosis

- Both plasma aldosterone and renin low while urinary free cortisone levels are very low or undetectable

- Genetic testing available

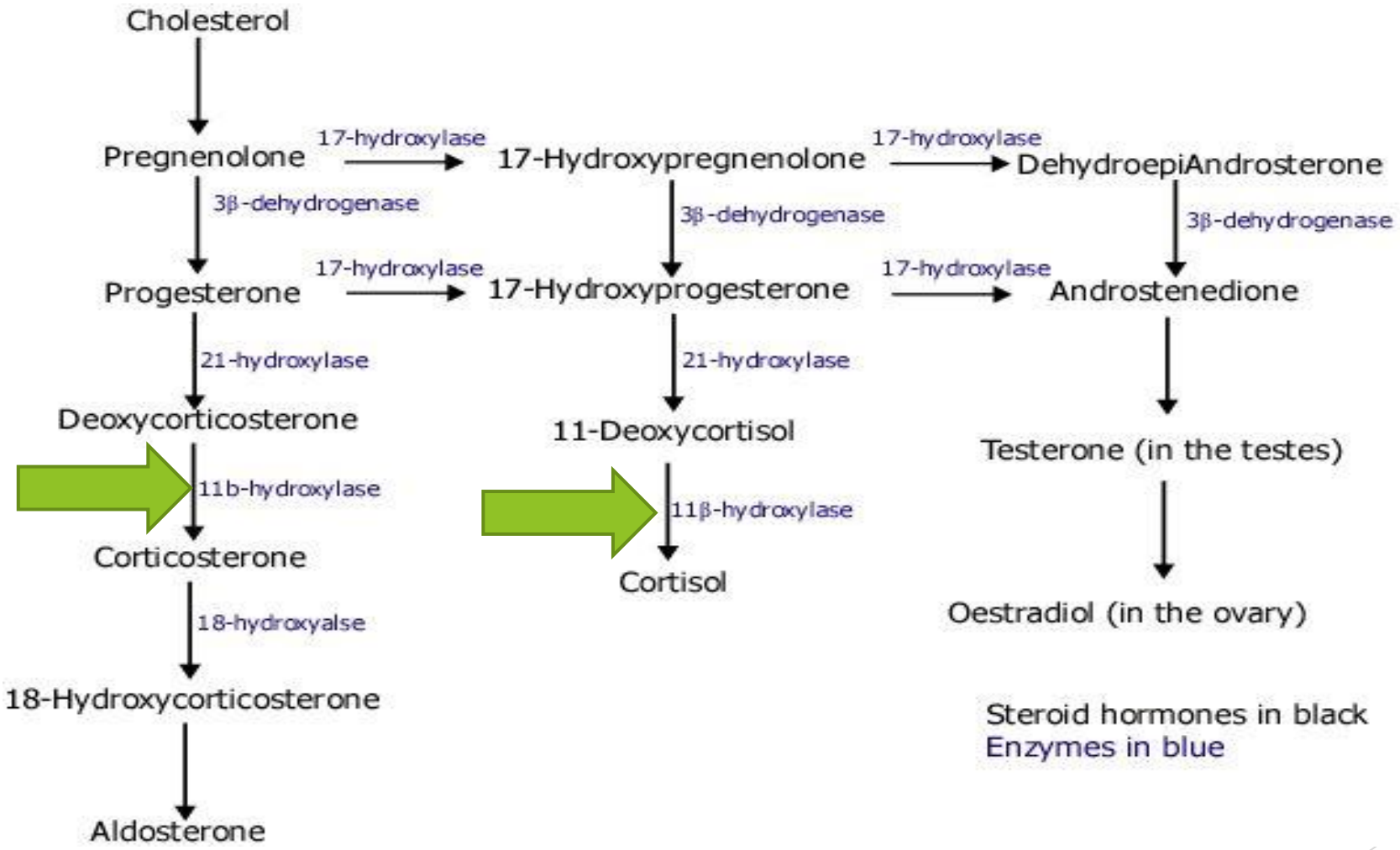
- *Liquorice inhibits 11-beta-HSD2 and so causes an acquitted AME like condition*

Familial Hyperaldosteronism

- FH type I or **glucocorticoid-remediable aldosteronism (GRA)** due to a *CYP11B1/CYP11B2* chimeric gene
- FH type II: This is the largest group and has autosomal dominant inheritance. Is clinically indistinguishable from sporadic primary aldosteronism. While the exact mutation not known, it is suspected to have linkage to chromosome 7p22
- FH type III: Caused by germline mutations in the potassium channel subunit KCNJ5, patients usually present early with massive adrenal hyperplasia.
- FH type IV caused by germline mutations in the *CACNA1H* gene, which encodes the alpha subunit of an L-type voltage-gated calcium channel (Cav3.2). While CT may show cortical adenoma, bilateral hyperplasia, or normal-appearing adrenal glands, adrenal venous sampling shows bilateral aldosterone hypersecretion

Glucocorticoid-remediable aldosteronism (GRA)

- While both cortisol and aldosterone are synthesised in the adrenal cortex, only cortisol is under the control of ACTH
- 11B- hydroxylase involved in the pathways of both cortisol and aldosterone synthesis (isoenzymes B-1 in cortisol synthesis and B-2 in aldosterone synthesis) has 95% homology between the two isoenzymes
- Unequal meiotic crossovers in chromosome 8 produces a hybrid 11B-hydroxylase enzyme which is involved in both cortisol and aldosterone synthesis and therefore, **both cortisol and aldosterone production are controlled by ACTH**
- Genetic testing diagnostic


Cholesterol
Pregnenolone
17-hydroxylase
17-Hydroxypregnenolone
17-hydroxylase
DehydroepiAndrosterone
3β-dehydrogenase
3β-dehydrogenase
3β-dehydrogenase
Progesterone
17-hydroxylase
17-Hydroxyprogesterone
17-hydroxylase
Androstenedione
21-hydroxylase
21-hydroxylase
Deoxycorticosterone
11-Deoxycortisol
Testerone (in the testes)
11b-hydroxylase
11β-hydroxylase
Corticosterone
Cortisol
Oestradiol (in the ovary)
18-hydroxyalse
18-Hydroxycorticosterone
Aldosterone
Steroid hormones in black
Enzymes in blue

Bartter syndrome and Gitelman Syndrome

- Bartter syndrome usually presents in perinatal period or childhood
- Gitelman syndrome is mostly a disorder of adulthood with hypomagnesaemia a striking feature
- Prevalence of Gitelman syndrome is 1 in 40,000 compared with 1 in 1,000,000 for Bartter syndrome
- Having Bartter and Gitelman syndromes is the same as being born on loop and thiazide diuretics respectively
- Volume contraction leads to RAAS activation and the secondary aldosteronism leads to urinary loss of K and H

Bartter and Gitelman Syndrome

Bartter Syndrome

- Defect in Na^+ reabsorption in the TAL of loop of Henle
- Normal to increased urinary Ca
- Increased renal vasodilatory prostaglandins
- Treatment: NSAIDs, K supplementation and K-sparing diuretic e.g. spironolactone
- Type III classically grow to adulthood and may develop CKD due to nephrocalcinosis and NSAIDs use
- Often growth and mental retardation

Gitelman Syndrome

- Defect in thiazide-sensitive Na^+-Cl^- cotransporter in DCT
- Low urinary Ca
- Hypomagnesaemia: high urinary Mg loss due to down regulation of Mg^+ channel TRPM6
- Treatment: K-sparing diuretic and Mg and K supplementation
- No growth or mental retardation

What can mimic Gitelman or Bartter syndromes?

- **Surreptitious self-induced vomiting**

  - Urinary Cl^- is characteristically low as hypovolemia leads to increased Na^+ reabsorption with the accompanying Cl^- reabsorption

  - Often scarring on the dorsum of the hand and dental erosions

- **Surreptitious diuretic use**

  - Variable urinary Cl^- levels depending on the timing of diuretic use

  - Urine diuretic screen may be helpful

Renal tubular acidosis (RTA)

- Group of disorders characterized by normal anion gap metabolic acidosis with either hypokalemia or hyperkalemia and relatively well preserved GFR
- **Normal anion gap metabolic acidosis with hypokalemia:**

- Proximal RTA (type 2) caused by reduced ability to reabsorb bicarbonate (HCO_3) in the proximal tubules

- Distal RTA (type 1) caused by defects in distal H ion excretion

- **Normal anion gap metabolic acidosis with hyperkalemia:**

-Type 4 RTA is due to either aldosterone deficiency or tubular resistance to the action of aldosterone and is the commonest among RTAs

Proximal RTA (Type 2 RTA)

- Isolated defect in proximal HCO3 reabsorption or with impaired reabsorption of phosphate, glucose, uric acid, and amino acids (Fanconi syndrome)
- Urinary pH usually <5.5 due to compensatory increased H secretion by distal tubules
- Can be caused by myeloma due to tubular toxicity of filtered light chains
- Other causes include carbonic anhydrase inhibitors acetazolamide and topiramate, tenofovir, Wilson's disease, Cystinosis, Lowe syndrome, outdated tetracycline and lead or mercury poisoning
- **Fanconi syndrome often suspected in normal anion gap metabolic acidosis with hypokalaemia, glycosuria AND low plasma phosphate and uric acid**

Distal RTA (Type 1 RTA)

- Type 1 RTA is caused by inability of the distal tubules to secrete H
- Characterised by urinary pH >5.5 due to lack of H in urine THUS differentiating from type 2 RTA
- Causes: **Sjogren's syndrome**, SLE, hypergammaglobulinemic states, primary biliary cirrhosis, autoimmune hepatitis, chronic obstructive uropathy, renal transplantation and glue sniffing
- Drugs causing RTA type 1: lithium, ibuprofen, ifosfamide (chemo agent) and amphotericin
- Genetic associations: Marfan syndrome, Ehler Danlos syndrome and mutations in basolateral chloride-bicarbonate exchanger (*SLC4A1* gene) and apical hydrogen-ATPase (*ATP6V0A4* and *ATP6V1B1* genes)

My patient has diarrhea……

- Metabolic acidosis and hypokalaemia in diarrhea due to

  -Faecal loss of bicarbonate rich pancreatic secretions

  - Intravascular depletion and RAAS activation
- *How do I differentiate from RTA?*

Urine anion gap (UAG)

- UAG = Urine(Na + K − Cl)
- UAG is positive in healthy individuals
- NH3 in urine accepts H to form NH4 which combines with the negatively charge Cl to form NH4Cl
- With metabolic acidosis, the kidney will appropriately respond by excreting a heavy load of H *(except in type1 RTA where H excretion is characteristically defective)*
- **UAG is positive in type 1 RTA (lack of H and hence low NH4Cl) and negative in diarrhea (excess H and hence high NH4Cl)**

Treatment of types 1 and 2 RTA

- Alkali and potassium replacement
- Alkali therapy helps in growth in children, reduces stone formation and slows progress to CKD (sodium bicarbonate or potassium citrate)
- Higher doses of alkali needed in type 2 RTA
- Patients with severe or symptomatic hypokalemia should be given potassium prior to or concomitantly with sodium bicarbonate therapy

Recap of type 1 and 2 RTAs

Type 1 RTA (distal RTA)	Type 2 RTA (Proximal RTA)
Inability to secrete H+	Inability to reabsorb HCO3
Urine pH >5.5 (low H+ in urine)	Urine pH <5.5 (compensatory increase in distal tubular H^+ secretion)
Nephrolithiasis and nephrocalcinosis	No renal stones
No Fanconi syndrome	• May have Fanconi syndrome:glycosuria,phosphaturia, uric aciduria and aminoaciduria
Treat with alkali and K+ replacement	Same treatment but often need bigger doses of alkali

Type 4 RTA

- Normal anion gap metabolic acidosis and hyperkalaemia
- Hyporeninemic hypoaldosteronism as well as diminished tubular response to aldosterone
- Common in diabetics especially those with diabetic nephropathy
- Caused by ACEI, ARBs, K-sparing diuretics, Calcineurin inhibitors (cyclosporine and tacrolimus), NSAIDs, heparin, trimethoprim
- May be seen in chronic interstitial nephritis of any cause or sickle cell disease
- Synthetic mineralocorticoid such as fludrocortisone may be effective
- In patients with hypertension or fluid overload, thiazide or loop diuretic may help

Trumpisms ……..we are going to miss these..

- "There's nothing I love more than women, but they're really a lot different than portrayed. They are far worse than men, far more aggressive, and boy, can they be smart!“

- Trump held a joint news conference with the emir of Kuwait, Sheikh Sabah Ahmed al-Sabah, who complained about media coverage in his country. Trump said, "I'm very, very honoured and happy to know that you have problems with the media also.”

Thank you