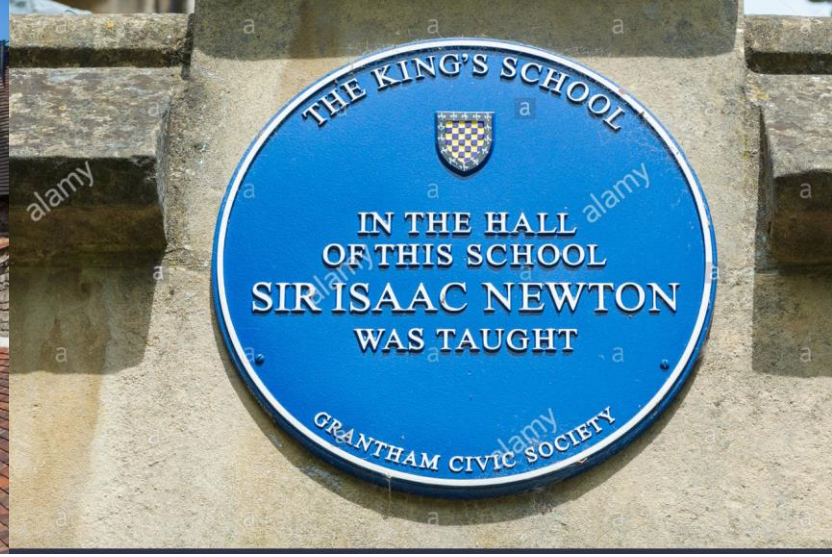

Funny Electrolytes: Overview of tubular physiology

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EMEESY Annual Network Study Day

Stoke Rochford

21 October 2017

Nottingham Children's Hospital


SALT

Renal tubular disorders

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Abstract

Renal tubular disorders are challenging and comprise a heterogeneous group of disorders. This review concentrates on those presenting in childhood with electrolyte abnormalities. Pattern recognition of these abnormalities is important in making diagnoses and a basic understanding of renal tubular physiology is helpful to understand why these patterns occur.

Clinical cases are used as illustrations in this review, supported by physiological descriptions of the disorders and notes about their management.

Although these disorders almost invariably come under the long-term management of paediatric nephrologists, they will just as invariably present to general paediatricians. This review should equip general paediatricians with the skills to request the appropriate initial investigations to make the correct diagnosis. There is also some advice on when to suspect a diagnosis of a renal tubular disorder and how to spot a child with a genuine polydipsia.

Keywords Bartter's; cystinosis; diabetes insipidus; Fanconi; Gitelman's; polydipsia; polyuria; pseudohypoaldosteronism; renal tubular acidosis; renal tubular disorder; tubulopathy

Introduction

Paediatricians find tubular disorders challenging: some embrace responsible for renal calculi or hypertension in otherwise healthy children.

Most commonly, paediatricians encounter renal tubular disorders in the context of investigating a child with abnormal electrolytes. The disorders are caused, directly or indirectly, through dysfunction of transporter proteins which are responsible for the tubular reabsorption or secretion of various electrolytes. Within recent years many genes encoding for these transporter proteins have been located and these genetic advances have served to improve our understanding of tubular physiology. However, as yet there is no gene therapy available for these challenging disorders.

A comprehensive review of all tubular disorders takes several chapters in paediatric nephrology texts so this article will offer a flavour of tubular disorders by focussing on several of the more common tubulopathies. The individual conditions are illustrated through case presentations but the names of patients have been changed.

At the end of this article, the reader should have a basic understanding of the role of the renal tubule in homeostasis, understand how tubular disorders deviate from the norm to result in their characteristic biochemical patterns and have confidence in how to begin to investigate a child presenting with electrolytic derangement.

Renal physiology

Faced with abnormal electrolyte results, there is a need for a foundational understanding of renal tubular physiology. The three major functions of the kidneys comprise:

- Maintenance of a constant extracellular environment for optimum cell functioning (homeostasis)

DOI: http://dx.doi.org/10.1016/j.paed.2014.03.005

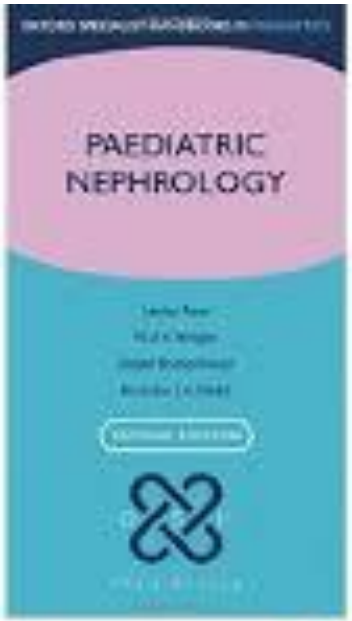

PAEDIATRIC
NEPHROLOGY

Table 7.1 Clinical and molecular characteristics of renal salt handling disorders

	Locus	Gene	Mode	Protein	renin	aldo	K^+	Cl^-	HCO_3^-	Other features/comments
Fanconi	*	*	*	*	⇑	⇑	⇓	⇑	⇓	*
Type I Bartter	15q15–21	SLC12A1	AR	NKCC2 co-transporter (furosemide-sensitive)	⇑	⇑	⇓	⇓	⇑	Nephrocalcinosis, often pre- or neonatal onset
Type II Bartter	11q24–25	KCNJ1	AR	K channel ROMK	⇑	⇑	⇓	⇓	⇑	Nephrocalcinosis, often pre- or neonatal onset
Type III Bartter	1p36	CLCNKB	AR	Cl channel CICKNB	⇑	⇑	⇓	⇓	⇑	Often hypomagnesaemia Mostly childhood onset
Type IV Bartter	1p31	BSND	AR	Barttin	⇑	⇑	⇓	⇓	⇑	Often hypomagnesaemia deafness. Usually neonatal onset
Gitelman	16q13	SLC12A3	AR	NCC (thiazide-sensitive)	⇑	⇑	⇓	⇓	⇑	Hypomagnesaemia, hypocalciuria Mostly childhood onset
EAST/SeSAME	1q23	KCNJ10	AR	KCNJ10/Kir4.1	⇑	⇑	⇓	⇓	⇑	Epilepsy, ataxia, sensorineural deafness, tubulopathy with hypomagnesaemia, hypocalciuria
CAH type I	6p21	CYP21A2 CYP21 CYP21B	AR	Subunits of 21-hydroxylase	⇑	⇓	⇑	⇑	⇓	Virilization
CAH type II	1p13	HSD3B2	AR	3-β-hydroxysteroic dehydrogenase	⇑	⇓	⇑	⇑	⇓	Hypospadias, male pseudohermaphroditism
PHA1	12p13 16p13 16p13 4q31	SCNN1A SCNN1B SCNN1G NR3C2	AR AR AR AD	EnaC sodium chanrel subunits A,B,G Mineralocorticoid receptor	⇑	⇓	⇑	⇑	⇓	Symptoms are severe in recessive form, milder in dominant form
PHA2	12p13 17q21	WNK1 WNK4	AD AD	WNK-kinases	⇓	⇑	⇑	⇑	⇓	
Liddle	16p13 16p13	SCNN1B SCNN1G	AD AD	EnaC sodium channel subunits B,G	⇓	⇓	⇓	⇓	⇑	
AME	16q22	HSD11B2	AR	11-β-hydroxysteroid dehydrogenase	⇓	⇓	⇓	⇓	⇑	Intrauterine growth retardation
GRA	8q21	CYP11B1 CYP11B2	AD	11-β-hydroxylases	⇓	⇑	⇓	⇓	⇑	
CAH type IV	8q21	CYP11B1	AR	11-β-hydroxylase	⇓	⇓	⇓	⇓	⇑	Virilization
CAH type V	10q24	CYP17A1	AR	17-alpha-hydroxylase	⇓	⇓	⇓	⇓	⇑	Ambiguous genitalia

Listed are disorders of tubular salt handling. The upper 10 rows (white) list disorders of salt wasting (hypovolaemia/low blood pressure), whereas the lower 6 rows (shaded) list disorders of salt retention (hypervolaemia/hypertension). aldo:aldosterone. AR: autosomal recessive, AD: autosomal dominant
(* for details of disorders in the proximal tubule see 'Disorders of renal salt handling: proximal tubule', p.144).

Funny electrolytes in paediatrics

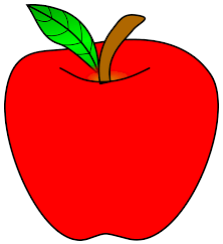
- Common!
  - Gastroenteritis
  - Medication
    - Gentamicin
    - Chemotherapy
    - Anti-epileptics
  - Neonatal period
    - Prematurity
    - Hypernatraemic dehydration
  - Pyloric stenosis

When to suspect tubulopathy?

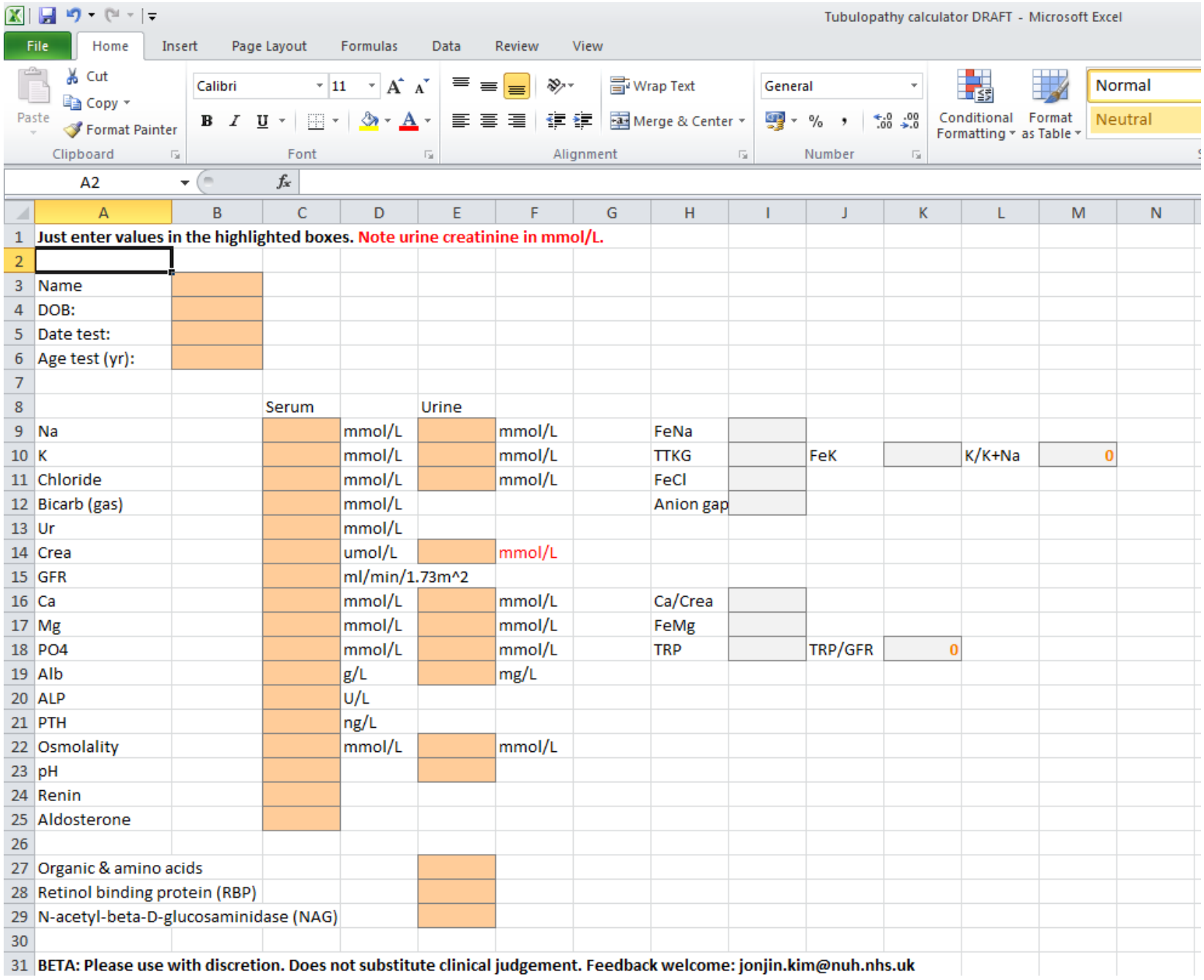
- Acute presentations:
  - Salt (water) wasting crises
  - Hyperkalaemia
  - Seizures
- Chronic presentations:
  - Failure to thrive
  - (true) polyuria polydipsia
  - Bone/muscle ache
  - Nephrocalcinosis
  - Part of multi-system disease
  - Constipation/intractable enuresis

Investigation of suspected salt-wasting tubular disorders

Test	Interpretation	Notes
Urine dipstick	Glycosuria implies a proximal tubulopathy.	Proteinuria may also be present. Frequently this is low molecular weight proteinuria in Fanconi syndrome. Requesting urine NAG or RBP may be helpful.
Venous blood gas	Metabolic alkalosis seen with Bartter's/Gitelman's. Metabolic acidosis seen with proximal and distal tubulopathies.	Metabolic acidosis can be investigated further to ascertain site of renal tubular acidosis.
Magnesium	Hypomagnesaemia occurs in Gitleman's.	
Renin and aldosterone	Elevated with volume-contracted states, especially Bartter's, Gitelman's and severely so with pseudohypoaldosteronism.	Vital information to interpret hypo- or hyperkalaemia.
Urinary chloride	High values (>10 mmol/litre) in association with hypochloraemia exclude non-renal causes of chloride loss.	
Urinary calcium	Hypercalciuria usually seen in Bartter's whereas hypocalciuria is usually seen in Gitleman's.	Consult tables for age-specific reference ranges. Ideally a spot sample should be the second voided sample of the day.
Urine pH	Should be performed in the laboratory with a glass electrode.	pH > 5.5 with a metabolic acidosis suggests dRTA.
Urine amino acids	Generalised aminoaciduria seen in proximal tubulopathies.	
Fractional excretion of sodium (FE_{Na})	In the face of volume contraction, FE_{Na} should be <1% (<2.5% in neonates). A result greater than this confirms a diagnosis of salt-wasting.	$FE_{Na} = 100 \times \left(\frac{U_{Na} \times P_{Cr}}{P_{Na} \times U_{Cr}}\right)$ Remember to convert U_{Cr} to μmol/litre.
Transtubular potassium gradient (TTKG)	Should be <2.5 with hypokalaemia and >7 with hyperkalaemia.	Use if distal tubular dysfunction is suspected as this is an indirect index of potassium secretory activity in the cortical collecting tubule. $TTKG = \frac{U_K \times P_{osm}}{P_K \times U_{osm}}$ where P_{osm} and U_{osm} are plasma and urinary osmolality respectively.
Tubular reabsorption of phosphate (TRP)	Values <80% in children >12 months implies phosphate leak which, in combination with hypokalaemia, acidosis, glycosuria and generalised aminoaciduria implies a Fanconi syndrome.	$TRP = 100 - \left(\frac{100 \times U_P \times P_{Cr}}{P_P \times U_{Cr}}\right)$
Hand/wrist X-ray	To look for rickets which may be present with Fanconi syndromes or in association with hypercalciuria.	
Renal ultrasound	To look for nephrocalcinosis and urinary tract malformations.	Nephrocalcinosis may be seen with Bartter's syndrome, Dent's disease and distal renal tubular acidosis.

- Fe  = $\dfrac{\text{Urine}}{\text{CreaUrine}} \Big/ \dfrac{\text{Serum}}{\text{CreaSerum}}$

$$= \frac{\text{Apple(Urine) x Crea(Serum)}}{\text{Apple(Serum) x Crea(Urine)}}$$



Tubulopathy calculator DRAFT - Microsoft Excel

File Home Insert Page Layout Formulas Data Review View

Cut Copy Format Painter Paste Clipboard

Calibri 11 Font

Wrap Text Merge & Center Alignment

General Number

Conditional Formatting Format as Table

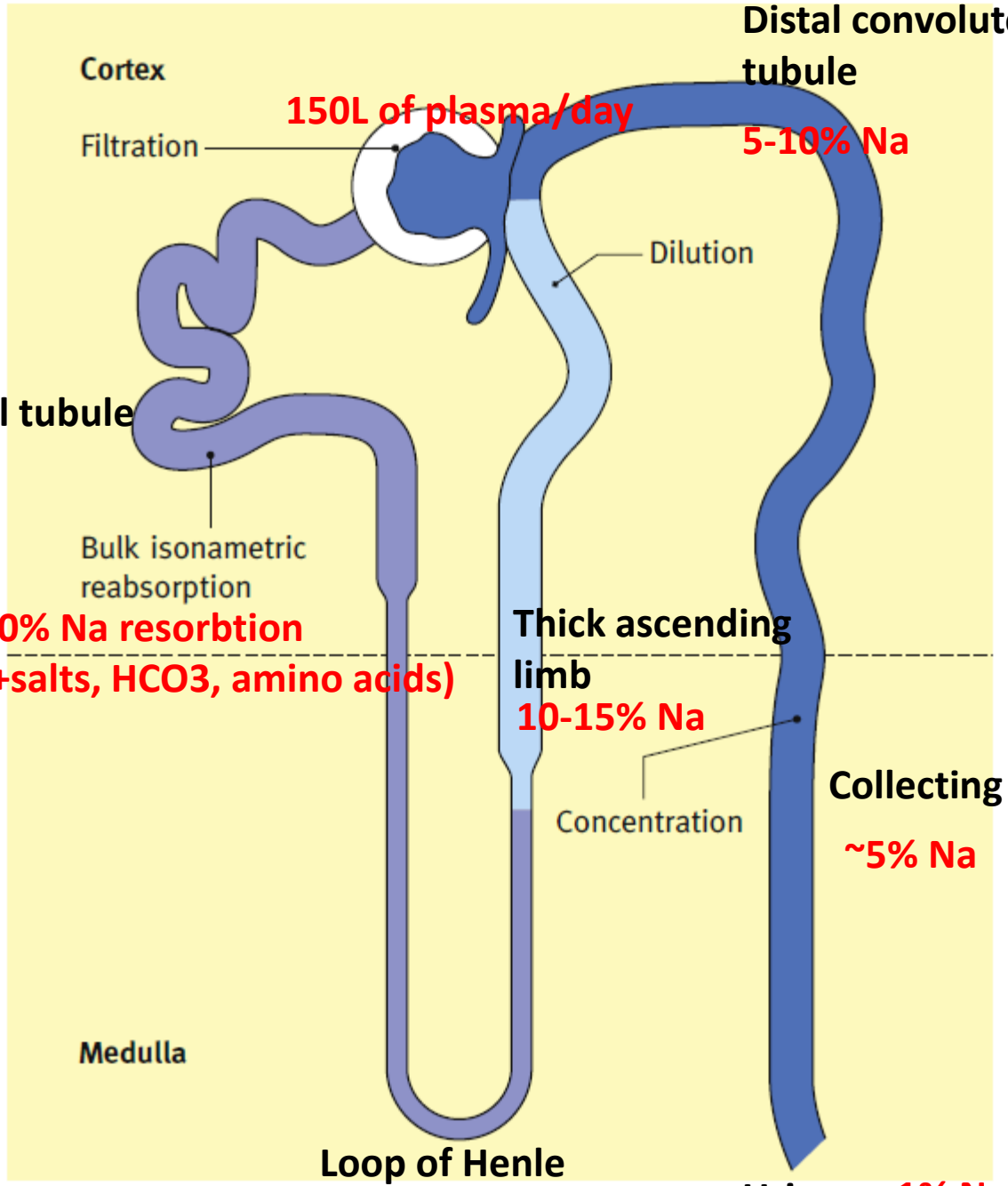
Normal Neutral

A2

	A	B	C	D	E	F	G	H	I	J	K	L	M	N
1	**Just enter values in the highlighted boxes.** Note urine creatinine in mmol/L.													
2														
3	Name													
4	DOB:													
5	Date test:													
6	Age test (yr):													
7														
8			Serum		Urine									
9	Na			mmol/L		mmol/L		FeNa						
10	K			mmol/L		mmol/L		TTKG		FeK		K/K+Na	0	
11	Chloride			mmol/L		mmol/L		FeCl						
12	Bicarb (gas)			mmol/L				Anion gap						
13	Ur			mmol/L										
14	Crea			umol/L		mmol/L								
15	GFR			ml/min/1.73m^2										
16	Ca			mmol/L		mmol/L		Ca/Crea						
17	Mg			mmol/L		mmol/L		FeMg						
18	PO4			mmol/L		mmol/L		TRP		TRP/GFR	0			
19	Alb			g/L		mg/L								
20	ALP			U/L										
21	PTH			ng/L										
22	Osmolality			mmol/L		mmol/L								
23	pH													
24	Renin													
25	Aldosterone													
26														
27	Organic & amino acids													
28	Retinol binding protein (RBP)													
29	N-acetyl-beta-D-glucosaminidase (NAG)													
30														
31	**BETA: Please use with discretion. Does not substitute clinical judgement. Feedback welcome: jonjin.kim@nuh.nhs.uk**													

Rules of thumb

- Na = Water = BP
- Na loosing disorders lead to low (normal) BP
- Kidneys don’t sense Na
  - Na is regulated by osmoreceptors in the brain (BP)
  - Salt loosing disorders have normal Na
  - Salt loosing disorders tend to have normal FeNa (compensatory mechanisms)


Cortex
Filtration
150L of plasma/day
Distal convoluted tubule
5-10% Na
Dilution
Proximal tubule
Bulk isonametric reabsorption
80% Na resorbtion
(+salts, HCO3, amino acids)
Thick ascending limb
10-15% Na
Concentration
Collecting duct
~5% Na
Medulla
Loop of Henle
Urine
<1% Na

Case 1

Hugh presented at 17 months of age with a 1-month history of vomiting and weight loss. On admission, despite clinical signs of dehydration, he remained polyuric with 8 heavy nappies a day. He had signs suggestive of rickets with splayed wrists and ankles and rachitic rosary. Weight and height were both below the 0.4th centile. Urinalysis showed glycosuria and proteinuria ++. His initial biochemistry showed:

Na	127 mmol/litre
K	1.8 mmol/litre
HCO_3	15 mmol/litre
Urea	8.6 mmol/litre
Creatinine	78 μmol/litre
Calcium	2.34 mmol/litre
PO_4	0.71 mmol/litre

Fanconi syndrome

- Generalised salt loss, acidosis and amino aciduria
- Multiple causes & multi-system disorders
  - Drugs
- Infancy
  - Cystinosis
  - Lowes (oculo-cerebro-renal)
- Childhood
  - Cystinosis
  - Dent's

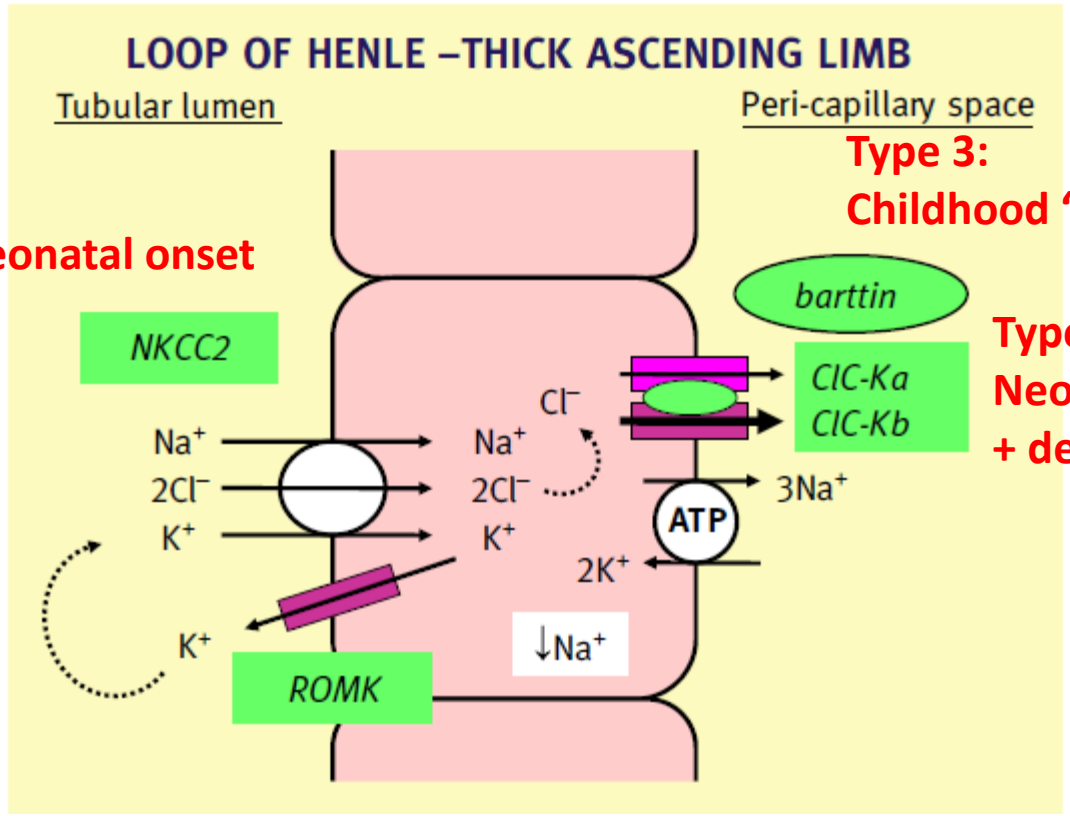
Case 2

- 8 mth old boy, consanguinous parents, 2 week history of vomiting, no diarrhoea

Serum	
Na	133
K	2.3
Ur	13
Crea	40
Ca	2.33
HCO3	31
Cl	88

Bartter's

- Urine
  - K (FE>15%), Cl (FE>1%), Ca (variable), Mg (high)
- Pseudo-Bartter's
  - Cystic fibrosis
  - Congenital chloride diarrhoea
- Treatment
  - Salt replacement
  - K>2.5
  - Indomethacin +/- chlorothiazide/spironolactone
  - Feeds



Type 1:
Pre-/neonatal onset

Type 2:
Pre-/neonatal onset

Type 3:
Childhood 'classic' onset

Type 4:
Neonatal onset
+ deafness

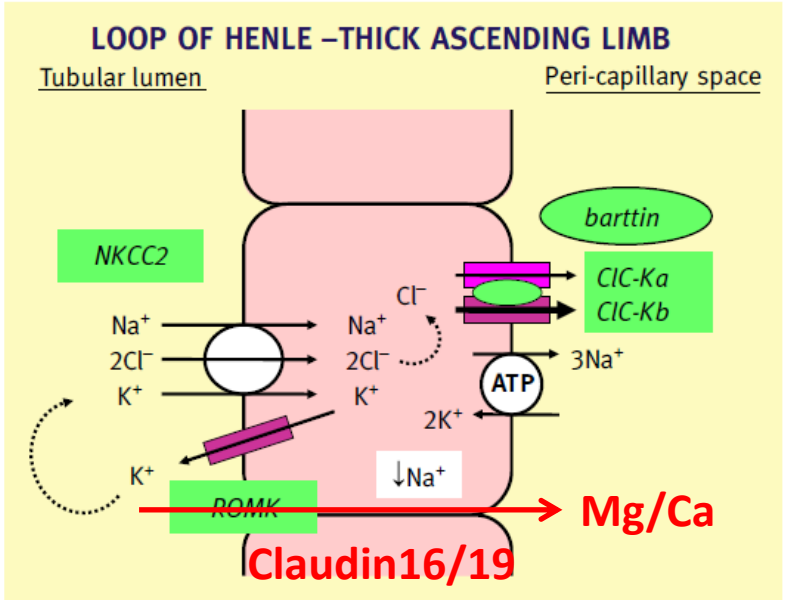
Case 3

- 6 month old girl, consanguinous parents, generalized seizures, needing PICU admission and IV salt replacement

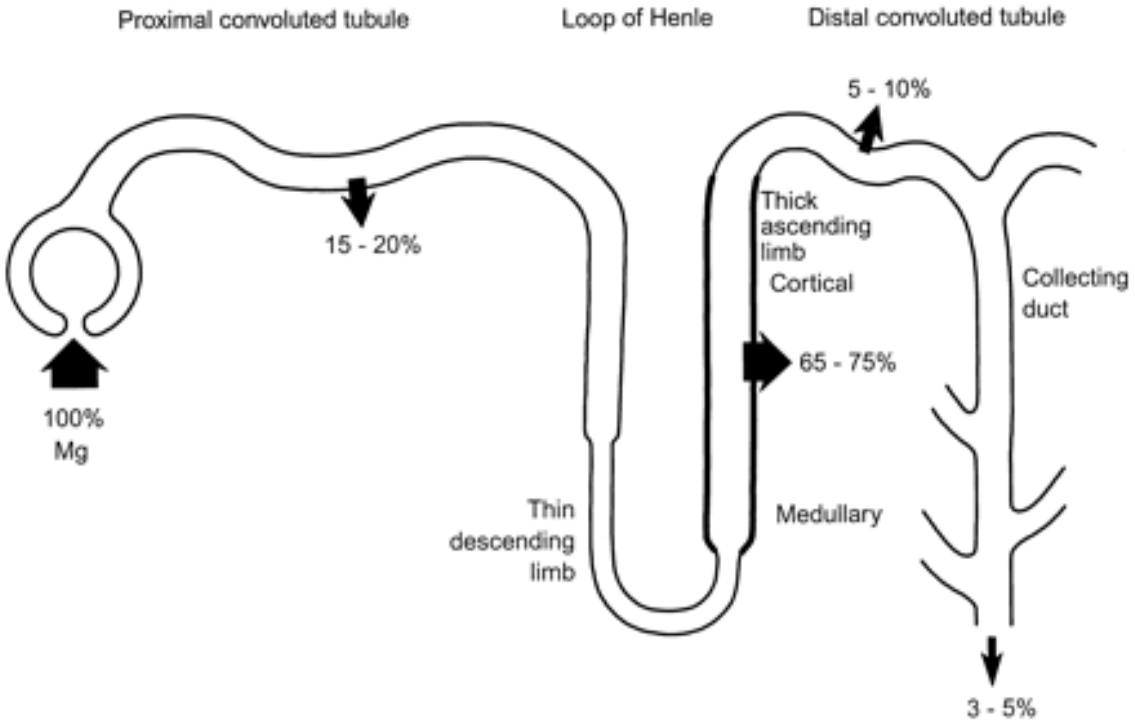
Serum		Urine
Na	133	FeNa 1%
K	4	TPMT 4%
Ur	5	
Crea	40	
Ca	1.9	Ca/Crea Up
Mg	0.4	FeNa Up
HCO3	24	
Cl	104	

HYPO Magnesaemia

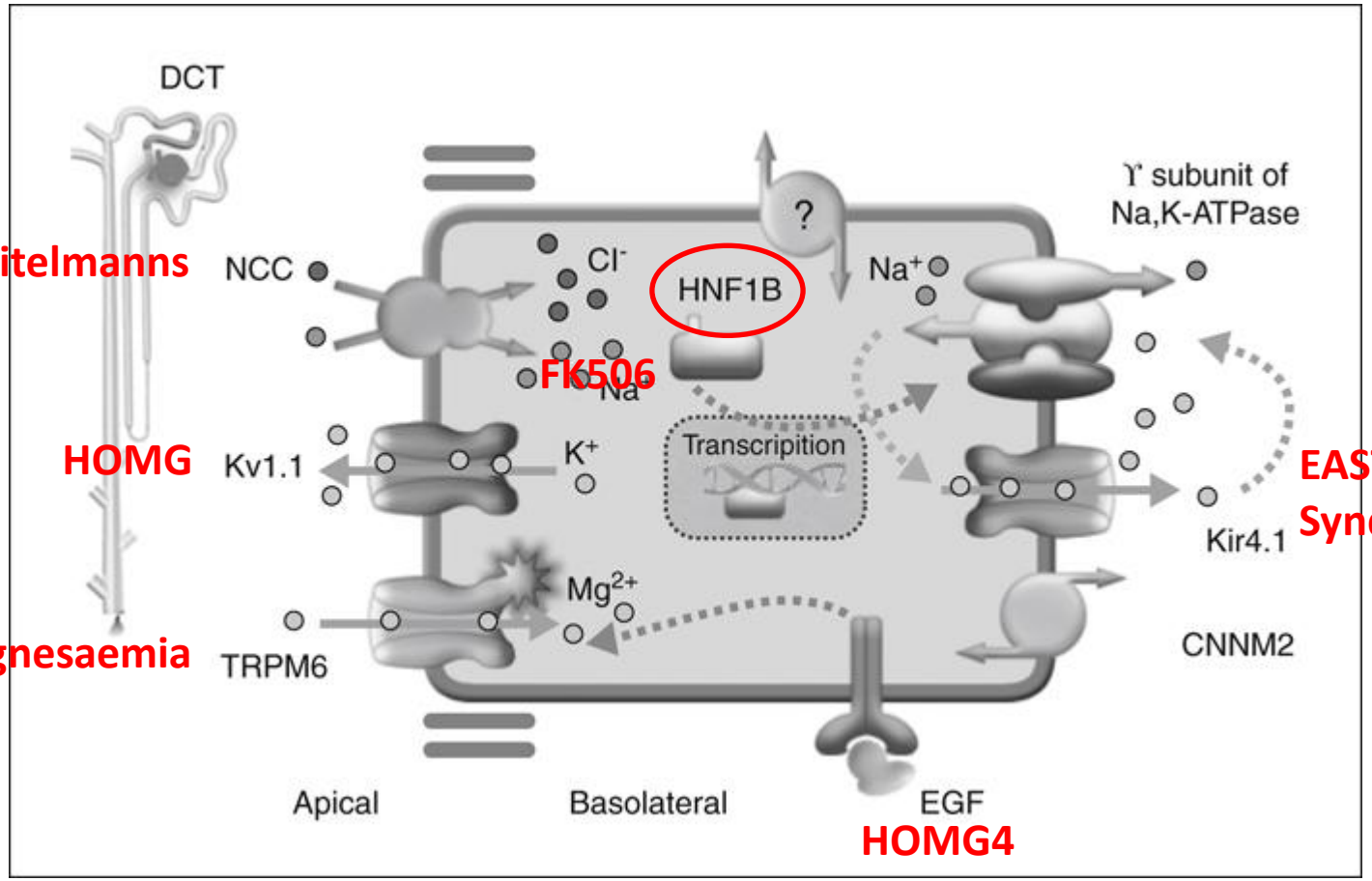
- Familial hypomagnesaemia with hypercalciuria and nephrocalcinosis (Manz syndrome)



Reabsorption of Mg



Distal convoluted tubule



Case 2

Charlie's hypokalaemia was picked up following routine blood tests for investigation of left thigh pain under the care of orthopaedic surgery at his local hospital. He was a 14-year-old boy with short stature, delayed puberty and persistent nocturnal enuresis despite multiple therapies.

Initial blood results were

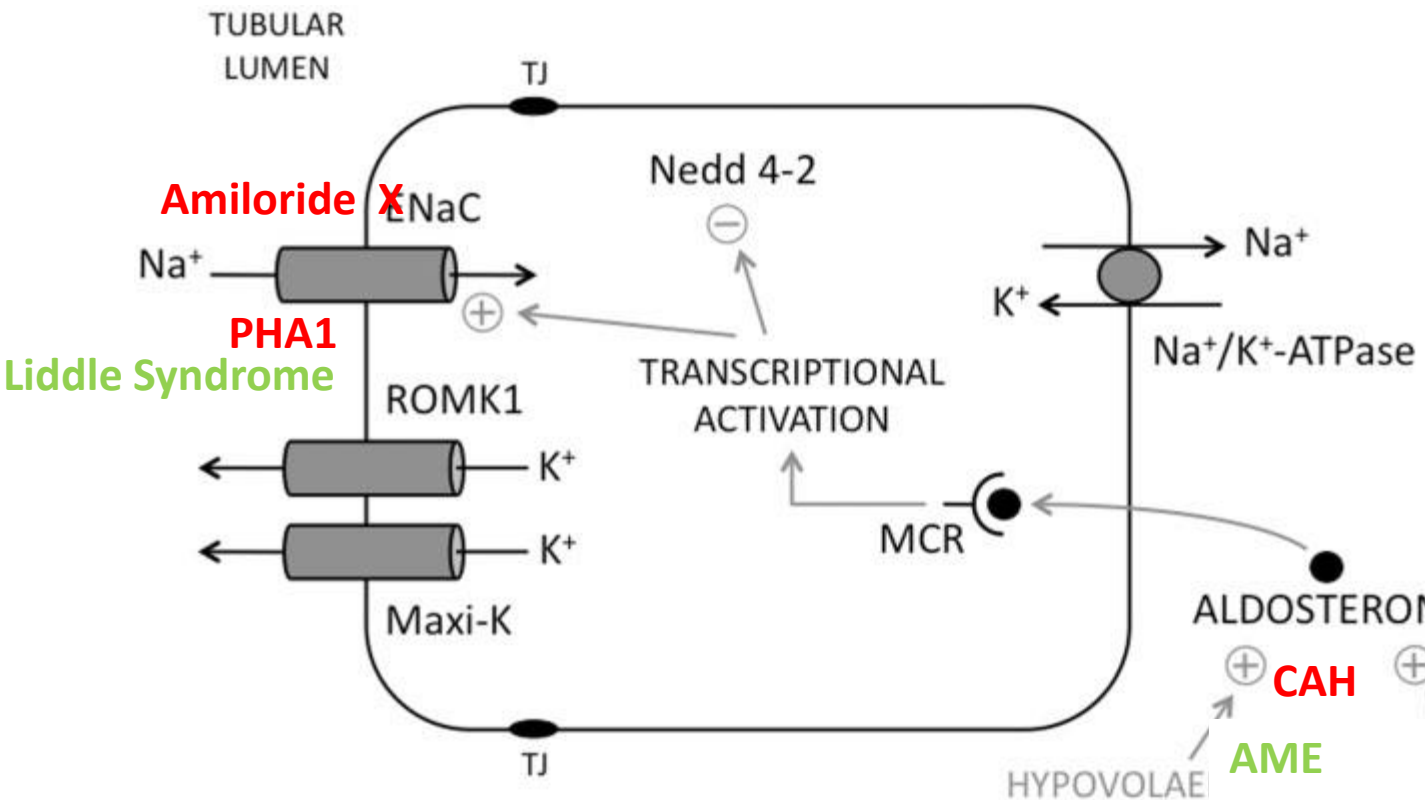
Na	136 mmol/litre
K	2.8 mmol/litre
HCO_3	31 mmol/litre
Cl	90 mmol/litre
Urea	6.7 mmol/litre
Creatinine	42 μmol/litre
Ca	2.41 mmol/litre
PO_4	1.5 mmol/litre
Albumin	36 g/litre
Mg	0.64 mmol/litre

Urine calcium excretion was low and plasma renin and aldosterone were elevated.

Gitelman's

- Thiazide diuretics
- HYPOmagnesium
  - Muscle cramps/joint aches
  - Prolonged QT (10%)
- Electrolytes similar to Bartter's

Collecting duct



Summary

1. Na = Water = BP

2. Clinical history and presentation is important

3. Tubulopathy calculator is available

Funny Electrolytes

- “What kind of work do you do?”
- “Oh, I work with kidneys.”
- “So do you work in nephrology or pediatric orthopedics?”