

## Guidelines on the Investigation and Management of Renal Tubular Disease

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**Please note: The following guidelines have not been assessed according to the AGREE (Appraisal of Guidelines for Research and Evaluation) criteria. This will take place at the next guideline review.**

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## 1. Introduction

The renal tubule has many varied and complex physiological functions and it is therefore not surprising that renal tubular disease has a wide range of presentation. This document has been developed by clinicians within the Renal Unit.

## 2. Disturbances of Tubular Phosphate Reabsorption

The renal handling of phosphate is best described by the maximum tubular phosphate reabsorption corrected for GFR.  $TMP/GFR = \frac{PIPO_4 - [UPO_4 \times PICr]}{[Ucr]}$ . This may be estimated by the determination of phosphate and creatinine in a fasting blood and simultaneously obtained urine sample. (Reference range: Brodehl J. Paediatric Nephrology 1994 (8): 645).

The commonest cause of an isolated defect in tubular phosphate reabsorption is X linked hypophosphataemic rickets (XLH). In this condition vitamin D metabolism is also abnormal since the level of 1,25 DHCC should be elevated in the presence of hypophosphataemia but is either normal or slightly reduced. XLH presents in late infancy with

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clinical and radiological rickets and growth retardation is a major feature. The diagnosis is confirmed by the finding of persistent hypophosphataemia in the absence of a generalised tubulopathy and a low TMP/GFR.

### 3. Management

These patients should receive neutral phosphate (Phosphate Sandoz) 50-100mg/kg per day given in five divided doses. In addition either one alpha DHCC or 1,25 DHCC should be given in order to increase intestinal calcium and phosphate reabsorption. Monitoring should be with intermittent plasma calcium measurements and early morning urine calcium/creatinine ratios and if necessary 24hr. urinary calcium excretion (should not exceed 0.1mmol/kg/day).

### 4. Renal Tubular Acidosis (RTA)

RTA describes a group of transport defects in bicarbonate reabsorption, H<sup>+</sup> ion excretion or both. Presentation is that of a metabolic acidosis associated with hyperchloraemia and a normal plasma anion gap. Other causes of a normal plasma anion gap acidosis are GI bicarbonate loss, bowel augmentation cystoplasty/ileal loop diversion, adrenal insufficiency, TPN and drugs e.g. carbonic anhydrase inhibitors, cholestyramine.

### 5. Diagnostic Procedures in Metabolic Acidosis

The first step in the evaluation of a patient with metabolic acidosis is to calculate the **plasma anion gap** [Na - (CL + HCO<sub>3</sub>)]. The mean normal value varies from lab to lab but averages 9 +/- 3mEq/l. Albumin is the major unmeasured anion and a fall in plasma albumin of 1g/dl decreases the anion gap by 2.5mEq/l.

**Urine pH**, preferably early morning is useful since this is a measurement of the small amount of free H<sup>+</sup> ions in the urine, and it is essential to measure urine pH using a pH meter. In the presence of a significant metabolic acidosis, if the distal tubular function is intact the urine pH should be < 5.5 at all ages and < 5.0 in older children.

The next step should be calculation of the **urine anion gap** [ Na<sup>+</sup> + K<sup>+</sup> - CL<sup>-</sup> ], which has been proposed as an indirect index of urinary NH<sub>4</sub> excretion. The algorithms in tables 2 and 3 show the evaluation of a patient with a normal plasma anion gap acidosis who has either a negative or positive urinary anion gap.

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## 6. Nephrogenic Diabetes Insipidus

### 6.1 Introduction to NDI

Nephrogenic diabetes insipidus (NDI) refers to an impairment of urine concentrating capacity consequent on a resistance to the action of ADH. The problem can reflect resistance at the ADH site of action in the collecting duct or interference with the countercurrent mechanism due for example to medullary injury or decreased sodium chloride reabsorption in the medullary aspect of the loop of Henle. A mild form is relatively common in patients with chronic renal insufficiency. Inherited NDI in children is a rare disorder resulting in variable degrees of resistance to ADH. It is generally transmitted in an X linked fashion with the genetic defect involving a number of different mutations in the V2 reception gene. A rarer autosomal form of NDI has been described in which defect is post receptor and lies in the ADH sensitive water channel Aquaporin 2.

In normal children the plasma osmolality is maintained in the range 275 – 285 msom/kg despite variations in water and solute intake. In patients with NDI episodic dehydration and hypernatraemia is frequent. Assessment of a patient with suspected urinary concentration defect should conclude plasma electrolytes, calcium and urinary tract ultrasound. Assuming these investigations are normal assessment of the urine concentrating capacity by controlled water deprivation with or without DDAVP is warranted. One of the major advantages of a water deprivation test is the recognition of partial defects in ADH secretion/action. However, a water deprivation test is a potentially hazardous procedure and should under no circumstances be done in the presence of hypernatraemia and increased Posm. In these circumstances DDAVP should be administered at a dose of 0.5ug/m<sup>2</sup> by the intravenous, intramuscular or subcutaneous route or 5ug/m<sup>2</sup> intranasally. Uosm should be repeated in four hours and if the response is adequate the Uosm should be > 800msom/kg.

If the patient is adequately hydrated and the PNa is normal, a careful water deprivation test should be carried out over 6-8 hours or until 3% of the body weight is lost should this occur first. Each sample of urine passed within this period should be collected for measurement of volume and osmolality and if at any point the Uosm exceeds 800msom/kg, the test can be aborted. At the end of the deprivation period, the Uosm and Posm should be estimated and if the Uosm is < 800mosm/kg, DDAVP should be given and a further Uosm and Posm checked four hours later. In central DI (CDI), secondary to a complete defect in ADH secretion and NDI there will be no significant change in Uosm during water deprivation but the Posm often rises to > 300msom/kg. Following DDAVP, the Uosm should be > 800mosm/kg in CDI but will remain unchanged in NDI. In partial CDI the Uosm will be 300-800mosm/kg but will show an adequate response to DDAVP.

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## 6.2 Management of NDI

All complications of NDI are prevented by the provision of an adequate fluid intake and in particular a target fluid intake should be prescribed. In addition to a low sodium diet, of Thiazide diuretics and NSAID may reduce urine output. The favoured combination at present is Chlorthiazide and Amiloride but Indomethacin may be added if this combination is not successful.

## 7. TUBULAR DISORDERS OF ELECTROLYTE REGULATION

### 7.1 Bartter and Gitelman Syndromes

These syndromes are rare disorders with a characteristic set of metabolic abnormalities including hypokalaemia, metabolic alkalosis, hyperreninaemia, hyperaldosteronism, and in some patients hypomagnesaemia. The primary defect in Bartter and Gitelman syndromes appears to be impaired sodium reabsorption in the loop of Henle and distal tubule respectively.

#### 7.1.1 Clinical Features

Classical Bartter's syndrome presents in early life and is often but not always associated with growth retardation and developmental delay. In addition to the biochemical abnormalities referred to above polyuria and polydipsia and decreased urinary concentrating ability are also common. Urinary calcium excretion is increased and the plasma magnesium concentration is either normal or mildly reduced in most patients.

Gitelman syndrome is a more benign condition and may not diagnosed until late childhood or adult life. Hypomagnesemia and urinary magnesium wasting are almost always present and patients may present with tetany.

#### 7.1.2 Diagnosis

The diagnosis of these disorders is to a large extent one of exclusion. Surreptitious vomiting and diuretic abuse are the two major causes of unexplained hypokalaemia and metabolic alkalosis in normotensive patients. Vomiting is generally associated with a low urinary chloride concentration and the diagnosis of diuretic abuse can be confirmed (in the absence of a positive history) by urinary toxicology. Patients with Bartter and Gitelman syndromes tend to euvolaemic with chloride excretion being equal to intake. The net effect is a urinary chloride concentration of > 40mmol/l.

#### 7.1.3 Management

In both conditions a combination of NSAID and potassium sparing diuretic usually brings the plasma potassium concentration into the low normal

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range and largely reverses the metabolic alkalosis. Most patients also require oral potassium, sodium and perhaps magnesium supplementation.

## 7.2 Pseudohypoaldosteronism and Liddle's syndrome

The cortical collecting tubule contains two cell types with very different functions, the principal cell and the intercalated cell. The principal cell has sodium and potassium channels in the apical membrane and, as in all sodium reabsorbing cells Na-K-ATPase pumps in the basolateral membrane. The entry of luminal sodium into these cells primarily occurs down a concentration gradient through an ion specific sodium channel in the apical membrane. Aldosterone plays a central role in these transport processes, primarily by increasing the number of open sodium channels in the apical membrane. The sodium channel is characterised by a sensitivity to Amiloride and administration of this diuretic leads to closure of the sodium channels. These observations have now been followed by the identification of two genetic disorders characterised by abnormal function of the sodium channel. Firstly, decreased function or resistance to aldosterone in pseudohypoaldosteronism (PHA) and increased function in Liddle's syndrome.

### 7.2.1 Clinical Presentation and Genetics

PHA has two different modes of inheritance. Firstly autosomal recessive in which the defect is permanent and all aldosterone target organs are involved (kidney, lung, gut and salivary glands). Secondly autosomal dominant, in which the defect may improve with age in some cases and only involves the kidney. PHA typically presents in infancy with sodium wasting, hyponatremia and severe hyperkalemia. In addition to the typically severe fluid and electrolyte disturbance in the multiple target organ type, lung sodium channel activity is also impaired often leading to lower respiratory tract infection.

Liddle's syndrome is a rare autosomal dominant condition in which there is a primary increase in cortical tubular sodium re-absorption and in most cases an increase in potassium excretion. Patients present with hypertension, hypokalemia and metabolic alkalosis similar to disorders caused by mineralocorticoid excess.

### 7.2.2 Management

Therapy of PHA consists of a high salt diet that prevents volume depletion and, by enhancing sodium delivery to the potassium excretory site in the collecting tubule leads to increased potassium secretion and lowers plasma potassium concentration. Some patients respond to high dose Fludrocortisone or Carbenoxolone. The efficacy of Carbenoxolone in PHA is presumably related to its ability to antagonize corticosteroid metabolism thereby allowing cortisol that circulates in much higher concentration than aldosterone, to enhance mineralocorticoid activity peripherally. The management of Liddle's syndrome includes sodium restriction and Amiloride.

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## 8. FANCONI SYNDROME

### 8.1 Introduction

Fanconi syndrome is characterised by a generalised reduction in renal tubular function while GFR is not primarily affected. The key findings are excessive urinary loss of amino acids, glucose, phosphate, bicarbonate and other organic substrates handled by the proximal and distal tubule. Metabolic consequences are a normal anion gap metabolic acidosis, hypophosphataemia, hypokalaemia, dehydration, rickets, and growth retardation. The commonest cause of Fanconi syndrome in children is cystinosis. This is a metabolic condition characterised by accumulation of cystine in different organs and tissues. There are three forms of cystinosis, infantile (nephropathic), intermediate (adolescent) and adult (benign). Nephropathic cystinosis has been estimated to affect one in 100,000 children.

### 8.2 Clinical Manifestations

The first clinical signs of nephropathic cystinosis appear between 3 and 6 months of age and are largely due to impaired proximal tubular reabsorption. The major extra renal manifestations are growth retardation and delayed puberty. Cystine deposition in the cornea is demonstrable by slit lamp examination and may be responsible for photophobia and blepharospasm. Other manifestations are hypothyroidism, insulin dependent diabetes mellitus and myopathy and long term neuropsychiatric manifestations.

### 8.3 Diagnosis

The diagnosis of cystinosis can be confirmed by the determination of the cystine content of peripheral blood leucocytes or fibroblasts.

### 8.4 Management

The initial aim should be of symptomatic treatment with fluid, electrolyte, phosphate and bicarbonate supplementation. Tubular loss of electrolytes may be drastically reduced by the use of Indomethacin (1-3mg/kg/day). Activated Vitamin D, Thyroxine and growth hormone are also necessary. Specific treatment with cysteamine (Cystagon) is now well established and if introduced in infancy any subsequent decline in GFR should be delayed or halted.

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## 9. Ammonium Chloride Loading Test

- Ensure adequate urine flow by giving water at 60mls/m<sup>2</sup>/hour.
- After one or two baseline urine samples, give:  
**NH<sub>4</sub>Cl 75mEq/m<sup>2</sup> (infant) or 150 mEq/m<sup>2</sup> (child)**

via nasogastric tube over 15-30 minutes. (Mix with a minimum of 5mls water per 1 gram).

- **Sampling: Capillary gases - at 0 and 4 hours**  
**Urine specimens - hourly from 0 to 6 hours**

(for urinary pH, titratable acidity - TA - and NH<sub>4</sub>: in Universal containers - send to Biochemistry immediately)

### Test interpretation (normal ranges):

Age	pH	TA (μEq/min/ 1.73m <sup>2</sup> )	NH <sub>4</sub>
preterm 1-3/52	5.76 ± 0.5	24.9 ± 13.4	29.3 ± 6.4
term 1 - 3/52	5.0 ± 1.5	32.4 ± 8.2	55.8 ± 8.8
infant 1 - 12/12	5.0	62 (43-111)	57 (42-79)
child 3 - 15 years	5.5	52 (33-71)	73 (46-100)

see: **Pediatric Nephrology 3rd Edn (1994) - Holliday Ed. pp. 238ff**

## 10. Future Guideline Development

- Should any aspect of this guideline change before the planned review in April 2007 (i.e. new technology or procedural change) then this guideline should be updated accordingly.
- Future review of this guideline should make use of the AGREE document to ensure that up-to-date evidence and best clinical practice has been used to inform this guideline.

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