Guidelines for approach to a child with

Metabolic acidosis (including RTA)

Children's Kidney Centre
University Hospital of Wales
Cardiff CF14 4XW

DISCLAIMER: These guidelines were produced in good faith by the authors reviewing available evidence/opinion. They were designed for use by paediatric nephrologists at the University Hospital of Wales, Cardiff for children under their care. They are neither policies nor protocols but are intended to serve only as guidelines. They are not intended to replace clinical judgment or dictate care of individual patients. Responsibility and decision-making (including checking drug doses) for a specific patient lie with the physician and staff caring for that particular patient.

Version 1, S. Hegde/Sept 2007

Metabolic acidosis

Normal acid base balance

Maintaining normal PH is essential for cellular enzymatic and other metabolic functions and normal growth and development. Although it is the intracellular PH that matter for cell function, we measure extra cellular PH as
1. It is easier to measure
2. It parallels changes in intracellular PH
3. Subject to more variation because of lesser number of buffers extra cellularly.

Normal PH is maintained by intra and extra cellular buffers, lungs and kidneys.
Buffers attenuate changes in PH when acid or alkali is added to the body and they act by either accepting or donating Hydrogen ions. Buffers function as base when acid is added or as acid when base is added to body. Main buffers include either bicarbonate or non-bicarbonate (proteins, phosphates and bone).
Source of acid load:

1. CO2- Weak acid produced from normal metabolism, dealt with by lungs pretty rapidly(within hours)
2. Endogenous acid (2-3meq/kg of H ions produced/day) from dietary protein metabolism, incomplete metabolism of carbohydrates and fats and stool losses of bicarbonate (only the stomach secretes H ions, rest of the GIT secrete bicarbonate). Kidneys deal with these changes more slowly (days).

There is a clear interrelationship and independence of the lungs and kidneys in regulating PH. Both the lungs and kidneys can affect the H ion concentration (and hence PH). However only the lungs can regulate the CO2 concentration and only the kidneys can regulate the bicarbonate concentration.
Renal Mechanisms: Is two step process

1. Reabsorption of bicarbonate -85% in proximal tubule and rest in collecting tubule. Increased reabsorption of bicarbonate (leading to metabolic acidosis) is seen in volume depletion, hypokalemia and in the presence of increased PCO2. Reduced reabsorption is seen in hyperparathyroidism, with drugs like acetazolamide and in those with low PCO2.
2. Tubular secretion of Hydrogen ions: requires the presence of urinary buffers, namely
    a. Phosphate- The amount of urinary phosphate is proportional to dietary intake, urinary concentration is more than serum concentration, but there is no inbuilt mechanism to increase the concentration in the event of acidosis.
    b. Ammonia- effective buffer, the production of which can be increased to ten fold in severe acidosis.

Response to acid load/acidosis: As a result of increased tubular H ion secretion the urinary PH drops, but not below 4.5. If the acidosis persists ammonia is essential to buffer, the production of which could be increased by many fold.
Acid excretion in collecting tubule is increased by acidic blood PH (metabolic or respiratory acidosis), aldosterone (which also increases serum bicarbonate) and hypokalemia. Increased urinary bicarbonate loss is seen in alkalosis.

Metabolic acidosis

Metabolic acidosis (MA) occurs when there is either net gain of H ion or net loss of bicarbonate ions. Patients with MA have low serum bicarbonate levels but not all with low bicarbonate have MA (e.g. those with resp alkalosis). Respiratory compensation to correct acidosis is always incomplete i.e. will not normalise the PH.
Normal PH with low bicarbonate= MA with some degree of respiratory alkalosis.
Low PH with low bicarbonate = MA

Mechanisms- 3 basic mechanisms

1. Loss of bicarbonate from the body- e.g. proximal RTA, diarrhoea
2. Increased acid generation- by internal mechanism- inborn errors of metabolism
   By external agent- salicylates
3. Decreased ability excrete acid (H + ion) - distal RTA, type 4 RTA

Table 1. Causes of Metabolic Acidosis

I Normal anion gap (with hyperchloraemia)

1. Renal loss of bicarbonate
   Carbonic anhydrase inhibitors
   Renal tubular acidosis
   Post-hypocapnic acidosis
2. GI loss of bicarbonate
   Diarrhoea
   Ileostomy, digestive fistula
   Ureterosigmoidostomy, ileal bladder or conduits
   Cation exchange resins
3. Miscellaneous
   Administration of HCl & NH4Cl
   TPN, dilution acidosis

II. Increased anion gap (with hyperchloraemia)

1. Increased acid production
   Ketoacidosis
   Lactic acidosis and other organic acidosis
   Toxins (salicylate, methanol, paraldehyde)
2. Decreased excretion of acid
   Acute renal failure
   Chronic renal failure

(Renal failure causes a variable picture in which the anion gap may be normal or raised.)

Compensatory response

1. Lungs try to compensate by hyperventilating, the washing out of CO2 can only help to raise the PH partially. Newborns and infants have limited capacity to compensate for acid load.
2. Urine PH- The appropriate response of the kidneys is to increase the urinary acid excretion with urine PH falling below 5, but not below 4.5.

If the urinary PH is higher than expected (inappropriate) for the degree of MA, suspect RTA. Urinary PH is low in the presence of diarrhoea but it could be >6 if the diarrhoea is associated with hypokalemia, simulating RTA.

Clinical manifestations- Includes those of underlying problems and of acidosis.
MA can manifest (depending on severity) as poor feeding, failure to thrive, hypotonia, abdominal pain, vomiting, lethargy, tacchypnoea, impaired cardiac contractility, pulmonary hypertension etc.

Clinical evaluation- should include recognition of clinical presentation and manifestation of MA, determination of underlying cause and recognition of severe MA that needs early treatment.

Investigations- depend on the possible cause. It should include

Blood- Urea & electrolytes, Glucose, blood gas, bicarbonate, chloride, LFT, Ca & Phosphate, osmolality & calculation of plasma anion gap
Urine- PH (lab), dipsticks, analysis, Urea & electrolytes, chloride, osmolality and Calculation of urinary anion gap

Plasma Anion Gap-
To keep the electro neutrality of the extra cellular fluid, the sum of the cation concentration must be equal to that of the anions, which can be expressed as-
Sodium + unmeasured cations= Chloride+ bicarbonate + unmeasured anions.
Unmeasured cations include potassium, calcium and magnesium and unmeasured anions include phosphate, sulphate, proteins and organic anions.
Serum anion gap (SAG) = serum Sodium – (serum Bicarbonate+ serum chloride)
The normal values vary from 8 to 16 mmol/l.
It represents the difference between measured cation and measured anion. Calculating AG is important step in approaching the differential diagnosis of metabolic acidosis.
Abnormally decreased anion gap is seen in hypoalbuminemia, lithium intoxication and multiple myeloma.

Urine anion gap
A related concept, which needs measuring the urinary electrolytes.
Measurement of urinary PH (is of limited values) can not reliably differentiate acidosis of renal origin from that of extra renal origin. Measurement of urinary ammonium excretion (which is produced in response to acidosis –it combines with chloride to produce NH4Cl) can help to differentiate. The extra- renal causes of MA are associated with an appropriate increase in urine acid (ammonium) excretion. In contrast, the net acid excretion and urinary ammonium levels are low in MA of renal origin. Unfortunately measurement of urinary ammonium excretion is cumbersome and not readily available. Urinary AG is a rough and inverse estimate of ammonium (NH4) eliminated in urine during metabolic acidosis.
Urinary anion gap (UAG) = (urine Sodium + urine Potassium) - urine Chloride

i.e. Positive UAG = Urine (Na + K) >Cl

Negative UAG = Urine (Na + K) < Cl

Under normal circumstances, urine anion gap is positive (with values between 20-50 meq/l) due to the presence of dissolved anions *e.g.,* sulfates, phosphates. A negative value suggests presence of increased renal excretion of unmeasured renal cation (other than sodium or potassium) like ammonium. Urine (Na + K) < Cl (Negative UAG) suggests increased urinary

ammonium excretion and is characteristic of a normal renal response to acidosis (with normal or elevated SAG). This is usually seen with acidosis due to GI loss (vomiting, GI drainage and all diarrhoeas except congenital chloride diarrhoea), there by indicating normal response of kidneys (compensatory rise in urinary NH_4+ excretion) in acidosis of extra-renal origin.

If the acidosis (of normal SAG) is of renal origin (e.g. proximal or distal RTA), urinary ammonium excretion is low (failure to acidify-kidneys unable to mount a normal response to acid load) and the UAG is positive (Urine (Na + K) >Cl).

Urine osmolal gap (UOG):
Interpretation of the UAG is confounded if large quantities of bicarbonate or other organic anions are present in the urine. A potential criticism of UAG as an indirect measure of NH.4 excretion is that it assumes that the predominant accompanying ion is chloride. NH4, excreted as a response to acidosis will contribute to the urine osmolality resulting in increased osmolal gap (calculated osmolality differ from measured osmolality by >15 mosmol/kg).

Urine Anion Gap (UOG) = measured urine osmolality- calculated urine osmolality
= (Osm) urine - [2(.Na + K) + Urea + Glucose] urine

A UOG of > 40 mosm/kg suggest significant ammonia excretion. However UAG can not be used if there is volume depletion (urine Na <25) or in neonates (immature acidification)

Renal tubular acidosis (RTA)

This term is applied to a group of transport defect in the reabsorption of bicarbonate, excretion of hydrogen ions or both. The RTA syndromes are characterized by a relatively normal GFR, hyperchloraemic metabolic acidosis with normal serum anion gap. The hyperchloraemia is a part of compensatory mechanism following bicarbonate loss.
Those with MA in the following circumstances should not be considered and investigated for RTA

1. Those who are systemically unwell
2. who have fluid depleting states or clinically volume depleted
3. Those in renal failure
4. those having UTI with urea splitting organism (proteus)

It is essential to rule out other causes of normal anion gap MA (see table 1). Rule out gastrointestinal cause for MA (suggestive symptoms like diarrhea & negative UAG).

Table 2. Features Suggesting Tubular Disorders

Clinical	**Laboratory**
Growth retardation, failure to thrive	Hyperchloremia metabolic acidosis
Polyuria, polydipsia, preference for savory foods	Metabolic alkalosis ± alkalosis
Refractory rickets	Hyponatremia with hyperkalemia
Renal calculi, nephrocalcinosis	Normocalcemic hypercalciuria
Unexplained hypertension	

Table 3 Features of RTA

	Proximal RTA	With bicarb wasting (mixed/type3)	Distal classic RTA	Hyperkalemic distal RTA	RTA 4 with normal GFR
Diagnostic testing	Bicarbonate response		Acid load, bicarbonate response		Renin aldosterone
Serum HCO3 untreated	15-20		10-15	10-15	15-20
Unstressed urine PH	>7	6-7.5	5.8-7	>5.5	<5.5
During metabolic acidosis (spontaneous or acid load)					
Serum potassium	Normal/Low	Normal/Low	Normal/Low	Increased	Increased
Urine PH	<5.5	>5.5	>5.5	>5.5	<5.5
Urine anion gap	Positive	Positive	Positive	Positive	Positive
Urine NH4+ V	Normal	Decreased	Decreased	Decreased	Decreased
FE Potassium	Normal or increased	Increased	Increased	Decreased	Decreased
UrineCa V	Normal	Increased	Increased	Increased	Normal/low
UrineCitr V	Normal or increased	Decreased	Decreased	Decreased	Normal/low
During Normal serum HCO3 concentration (or after alkaline load)					
FE Bicarbonate	>10-15%	>5-15%	<5%	<5%	>5-15%
Urine -Blood PCO2	>20 mm Hg	<20 mm Hg	<20 mm Hg	<20 mm Hg	<20 mm Hg
Other tubular defects	Common	Rare	Rare	Rare	Rare
Nephrocalcinosis	-/+	++	++	+	_
Rickets	+	_	-/+	_	_
Response to 2 mmol/kg of Bicarbonate	Refractory	Refractory	Good	Good	Variable
Bicarb needed to correct Serum PH (mmol/kg)	4-10	10-15	1-2 child 4-15 adult	2-3	2-4

Urine NH4+ V, Ca V, Citr V-Urinary excretion of ammonium, calcium & citrate respectively
FE-Fractional excretion, + often, ++ very common, - rare or absent, HCO3- Bicarbonate

Investigation of RTA

A. Investigation to confirm presence, type of and look for manifestations of RTA

Urine

1. Dipstick urinalysis for - glycosuria and proteinuria (suggestive of glomerular or proximal tubular dysfunction) urinary pH (laboratory PH meter should be used, *not by dipstick*).

2. **Urine culture**- rule out UTI with urea splitting organisms

3. **Random urine sample**- for electrolytes, chloride, calcium, citrate, creatinine, amino acids and tubular reabsorption of phosphate (a corresponding plasma sample for phosphate and creatinine is also required for this calculation) and potassium.

Calculate citrate: creatinine and calcium: creatinine ratio.

4. **Early morning urine** –for osmolality to check of renal concentrating ability
Calculate **urine anion gap: UAG =**Urinary (Na+K) - Chloride.
It is positive in RTA
Calculate urine **osmolal gap (UOG)**
UOG = measured urine osmolality- calculated urine osmolality
= (Osm) u-[2(.Na+.K) + Urea+ Glu] u

Plasma

Electrolytes (sodium, potassium, and chloride), urea, creatinine, bicarb, calcium, magnesium and phosphate, PTH, uric acid, blood gas, ammonia, Vitamin D levels
In hyperkalemic RTA- also do plasma rennin and aldosterone

Calculate serum anion gap (SAG). **SAG = serum Na - (serum chloride + serumHCO3)**

Blood	**Urine**
Sodium, potassium, chloride, urea, creatinine, bicarbonate Calcium, Phosphate, Magnesium, LFT, uric acid Blood gas, ammonia, Vitamin D levels Renin & Aldosterone- in hyperkalemic RTA Calculate Anion Gap	Dipstick, Urine analysis, culture, Laboratory PH Random sample-Chloride, U&E, calcium, citrate, Phosphate, aminoacids, creatinine, protein Early morning osmolality Calculate anion gap & solute:creatinine ratios

Tests for phosphate handling-

For solutes that do not undergo any tubular secretion,
The amount filtered =amount reabsorbed in the tubules + amount excreted in urine
= % of solute reabsorbed in tubules + % of solute excreted in urine
=% of solute reabsorbed in tubules + fraction excretion of solute (FEsol)
So, % of solute reabsorbed in tubules = 100- FE*sol*

1. **Tubular reabsorption of phosphate (TRP) = 100 - FE*phos***

TRP = 100 - [(Urine *phos*/Serum *phos*) x (Serum *creat*/Urine *creat*)]

TRP represents the percentage of filtered phosphate that is reabsorbed in proximal tubule.

2. Frequently, the phosphate handling is best expressed as TMP/GFR, as phosphate reabsorption is dependant on GFR

For a child on western diet (plenty of phosphate), the amount reabsorbed =tubular maximum reabsorption of phosphate (TMP), if the GFR is normal.

TMP = GFR x (Ser phosphate – urine phosphate) x V

Calculation of TMP/GFR

a. **using a normogram based on serum phosphate and TRP**

b. **TMP/GFR = TRP x serum *phosphate***
= [1- (Urine *phos*/Serum *phos*) x (Serum *creat*/Urine *creat)*] x Serum *phos*

Tests for potassium handling-

Potassium balance is regulated by changing it's secretion in distal nephron. It depends on aldosterone and amount of sodium & water delivered to distal nephron. The renal ability to retain K+ is not as efficient as that of sodium.

Assessment:

1. Random **urine K level** (> 20 mmol/l in those with hypokalemia, is wasting)
2. Spot sample for **urinary potassium: creatinine ratio**. Normal values are age dependant.
3. Fractional excretion of potassium (FE ***K***+)

FE*K*+ = (Urine *K*+ / Serum *K*+) x (Serum *creat* / Urine *creat*)

Normally 10-15%
Potassium loosing (renal) states > 10-15%
> 100% in renal failure

4. **Transtubular potassium gradient (TTKG)**

TTKG provides an estimation of the regulatory mechanisms of K+ secretion in distal nephron, an assessment of renal response to hypo and hyperkalemia, and hence most widely used approach in children with disordered K+ balance. It attempts to evaluate the gradient between luminal and peritubular K+ concentration in distal nephron as a reflection of aldosterone bioactivity.

TTKG = [(Urinary K+) x (Plasma osmolality)] / [(Plasma K+) x (urine osmolality)]

The urine osmolality must be greater than the serum osmolality for the results to be valid.

A value > 5 indicates aldosterone is acting whereas a value <3 indicates lack of minaralocorticoid activity.
In normal K+ replete subjects TTKG should be 5-15.
In **hyperkalemia** TTKG should be > 10 assuming normal renal excretion of K+. If the TTKG is appropriate and the kidney function is normal, it suggests extra renal cause for hyperkalemia. If the TTKG is <8 during hyperkalemia, it suggests a defect in renal potassium excretion, usually due to aldosterone deficiency or resistance.
A value > 4 in the presence of **hypokalemia** suggest excessive urinary losses of K+, a lack of aldosterone suppression.

Radiology

1. A **renal ultrasound**
2. X-ray wrists if indicated

Formal loading (Dynamic) Tests

The loading tests are needed if diagnosis of RTA can not be made on the presenting signs & symptoms, initial tests and associated findings (e.g. generalized tubular dysfunction)

Bicarbonate loading test uses intravenous or oral sodium bicarbonate to increase serum bicarbonate to > 26mmol/l. The following two parameters are calculated

1. **Fractional excretion of Bicarbonate** (FEHCO3) expresses the percent of filtered bicarbonate that is excreted in the urine.

FEHCO3 = (U_{HCO3}/P_{HCO3}) x (P_{cr}/U_{cr}) X 100

U_{HCO3} *and* P_{HCO3}- urine & plasma concentration of HCO3

P_{cr} & U_{cr}- urine and plasma concentration of creatinine

<5%- Normal or distal RTA
>15% -Proximal RTA

2. **Urine to blood PCO2 difference (Urine PCO2- blood PCO2**) is good index of distal renal acidification. It is estimated when the urine is alkaline (PH >7.6) and acidosis is corrected.

A difference of > 20 mm Hg- Normal or proximal RTA
< 10 mm Hg- Distal RTA

Acidification Test is done using ammonium chloride in patients with suspected incomplete distal RTA and in some patients with type 4 RTA who are not significantly acidotic.
Useful parameters like urine PH, anion gap and titrable acidity are calculated once the acidosis is artificially induced.

B. Investigations to know the etiology

Appropriate tests as indicated

Diagnosis:

Proximal RTA-

1. Hyperchloraemic metabolic acidosis
2. Low serum *K*+ levels
3. Positive UAG and Urine PH <5.5 on early morning sample with acidosis
4. Rapid excretion of administered bicarbonate
5. Most have additional signs of proximal tubular dysfunction (hypophosphataemia, hypouricemia, renal glycosuria and amino aciduria)

If diagnosis is not obvious with above criteria alkali or acid load testing might be necessary.

Distal RTA-

1. Hyperchloraemic metabolic acidosis
2. Low/normal serum *K*+ levels
3. Positive UAG
4. Urine PH >6 with acidosis
5. Absence of proximal tubular dysfunction.
6. Alkali loading (to calculate FE of bicarbonate) or other dynamic tests might be needed to differentiate distal from proximal RTA

Treatment of RTA

A. Treatment of underlying cause
B. Alkali supplement

1. Usually as sodium and potassium citrate –provides K+ needed for patients with proximal RTA and also to compensate for increased urinary wasting of K+ associated with higher doses of alkali.
2. Larger doses are needed in proximal RTA than distal RTA
3. Use potassium citrate, not sodium citrate in those with calcium stones
4. Large doses might not be tolerated, addition of thiazides could help.

C. Potassium supplements/restriction

1. Usually needed in proximal RTA, but most with dRTA do not need long term K+ supplements.
2. K+ restriction /other measures to lower K in those with hyperkalemic RTA

D. Other supplements

Patients with proximal RTA and proximal tubular dysfunction (Fanconi syndrome) need phosphate and vit D supplements

Approach to a child with metabolic acidosis (including RTA)