UNIVERSITY OF PNG
SCHOOL OF MEDICINE AND HEALTH SCIENCES
DIVISION OF BASIC MEDICAL SCIENCES
DISCIPLINE OF BIOCHEMISTRY AND MOLECULAR BIOLOGY

PBL SEMINAR

RENAL TUBULAR ACIDOSIS – An Overview

What is Renal Tubular Acidosis (RTA)?

- Two simple definition of RTA:
  - RTA is a group of disorders of the Renal Tubules that result in a Normal Anion Gap Hyperchloremic Metabolic Acidosis in the presence of Normal Glomerular Function
  - RTA is a group of disorders in which there is Metabolic Acidosis due to defect in the Renal Tubular Acidification Mechanism used to maintain normal Plasma Bicarbonate (HCO_3^- ions) concentration and blood pH

Take Note:

- Control of pH in body fluids is significant for normal metabolism
- Large quantities of Anions (Sulphate, Phosphate, Lactate) are produced during metabolism
  - These anions are collectively called "Unmeasured Anions"
- Accumulation of such Anions may cause increase in Plasma Anion gap
- Renal Tubules play major role in elimination of:
  - Unmeasured anions"
  - H^+ ions and control of pH in body fluids
- Failure of renal tubules to regulate H^+ ions may cause metabolic acidosis

How do renal tubules regulate acid base balance?

- Renal acidification mechanism keeps the blood pH within a narrow range of 7.35 – 7.45 which is vital for normal functioning of cellular and tissue metabolism
- Renal tubules regulate acid base balance by the following mechanisms:
  - Reabsorption of Sodium Bicarbonate (Na HCO_3) by Proximal Renal Tubule (**Fig.1**)
    - Proximal tubule is responsible for reabsorption (reclaiming) of about 85 to 90% of filtered Bicarbonate ions (HCO_3^-)
    - Failure of this process leads to reduction of HCO_3^- ions in the systemic blood,
    - Resulting in Metabolic Acidosis
  - Regeneration of Bicarbonate ions (HCO^-_3) by Distal Tubule (**Fig. 2**)
    - Distal tubule reabsorbs the remaining filtered HCO_3^- ion (10 to 15%)
  - Secretion of H^+ ions by Distal Tubule
  - Production of Ammonia (NH_3) by Distal Tubule
  - Buffering of H^+ ions by Ammonium and Phosphate buffers **(Figs 3 & 4)** by Distal Tubule

What are the major conditions that can impair the handling of HCO_3^- by Kidneys?

- Renal Failure and
- Renal Tubular Acidosis
    - Both involve a defect in Renal tubule,
    - HCO_3^- ions reabsorption and regeneration are tubular functions
        - It is the tubular defect that causes metabolic acidosis
- In addition, Renal Failure also involves a marked defect in Glomerular Filtration

What are some of the possible causes of RTA in children?

- RTA in children in majority of cases is Congenital (from birth)
    - Can be Inherited as Recessive or Dominant trait
    - Can be associated with Genetic disorders like Salt Loosing Congenital Adrenal Hyperplasia,
- Sickle cell disease and
- Carbonic Anhydrase II deficiency
- Some cases are acquired due to drugs like outdated Tetracyclines, Heavy metals, etc,
- Withdrawal of the causative agent can result in cure

What are some suspected signs and symptoms of RTA in infants?

- Provided other disease conditions are excluded (such as Diarrhoea) a number of signs and symptoms can be considered, when due to no apparent cause an infant or a child:
    - Fails to put on weight or loses weight, Becomes Dehydrated, Excessive urine output (Polyuria), Excessive Thirst, Weakness, Poor appetite, Vomiting, Constipation and
    - Muscle weakness, which may be severe enough to cause Paralysis of respiratory muscles due to Low Serum Potassium levels (Hypokalemia)
    - Breathlessness with air hunger type of breathing due to Acidosis may be seen in severe cases
    - Rickets and Bony Deformities occur late in the disease
    - Skeletal deformities due to RTA occur because the Calcium from the bones is mobilized to buffer excess H^+ ions and bones become Demineralised, Deformed, Bowed and can sustain fractures
    - In clinically suspected cases, Arterial Blood Gas estimation will reveal Low Serum HCO^-_3 /TCO_2 level with Low blood pH and Normal Anion Gap
    - Urinary pH may be inappropriately high (>5.5) for the level of Acidosis in distal RTA

What is Anion Gap?

- Anion Gap (**AG**): sum of routinely measured Cations minus routinely measured Anions:
    - $\mathbf{(Na^+ + K^+) – (Cl^- + HCO_3^-)}$

- K^+ is a small value numerically, it is usually omitted from AG equation
- Equation is:

$$\mathbf{AG = Na^+ - (Cl^- + HCO_3^-)}$$

- Note: Venous value of HCO_3^- is used in the calculation
- Venous CO_2 can be used in place of the venous HCO_3^-

$$\mathbf{AG = Na^+ - (Cl^- + CO_2)}$$

- Normal AG calculated without K^+ is about 12.4 mEq/L

What causes the Anion Gap?

- Normal Physiological condition, there is Electrochemical balance
  - Total Anions = Total Cations
- Anion gap exists because not all Electrolytes are routinely measured
- Several Anions are not measured routinely, leading to Anion Gap
- Anion Gap is an Artefact of measurement, not Physiologic reality

How can Distal RTA (Type I RTA) be characterised?

- **Distal RTA (Type I RTA)**:
- Reduced capacity of Distal Tubule to lower pH in Luminal fluid
- Defect may be due to
  - Failure to eliminate H^+ ions
  - Failure in H^+ ions secretion or
  - Retention of H^+ ions in the lumen

- Consequences of Distal RTA:
  - High Urinary pH (above 5.5)
  - Reduced Excretion of Titratable Acid and Ammonium ions
  - Mild Bicarbonaturia (HCO_3^- ions in urine), because a small amount of HCO_3^- is reabsorbed distally
  - Plasma [HCO_3^-] is often below 10mmol/L
    - Severe Hypobicarbonatemia
  - Plasma [K^+] usually low, but may be normal
  - GFR relatively normal

- Subdivisions of Type I RTA:
  - Related to difficulties in maintaining a secretory H^+ ion gradient in Distal tubule

How can Proximal RTA (Type II RTA) be characterised?

- **Proximal (Type II) RTA**:

- Relative decrease in ability of Proximal Tubule to reabsorb filtered HCO_3^- ions causing metabolic acidosis
  - Associated with loss or failure to reabsorb HCO_3^-
- Decreased Ammonium excretion into Tubule lumen
- Type II RTA is often part of Fanconi syndrome
  - Proximal tubule loss of Glucose, Calcium, Phosphate, other Electrolytes, and Organic Acids

- Inhibitors of Carbonic Anhydrase also cause Type II RTA

- Consequences of Type II RTA:
  - Clinically associated with failure to thrive
  - Urine pH above 5.5 as Acidosis develops
  - Urine pH below 5.5 when Acidosis is fully established

- Plasma [HCO_3^-] typically 15 – 20mmol/L
  - Moderate Hypobicarbonatemia
- Plasma [K^+] usually low, but may be normal
- Substantial Bicarbonaturia (high amount of HCO_3^- in urine)
- GFR relatively normal

How can Type IV RTA be characterized?

- **Type IV (Hyperaldosteronism; Aldosterone resistance; Hyperkalemic RTA**):
- Typically diagnosed when RTA is associated with Hyperkalemia
- Causative defect is usually decreased Aldosterone Secretion, often secondary to Low Renal Renin secretion ("**Hyporeninemic Hypoaldosteronism**")
  - Cases Acidosis Inhibiting production of NH_4^+ ion
- Defect in Distal Tubule Aldosterone Receptor ("Aldosterone Resistance") may be present
- In some case, a receptor defect is the sole cause
- Type IV RTA can result from numerous causes:
  - Decreased Aldosterone,
  - Increased Renal Resistance to Aldosterone,
  - Presence of an Aldosterone Antagonist such as Spironolactone

- Consequences of Type IV RTA:
- Associated with Increased Renin Activity,
- Hyponatremia,
- Hyperkalemia and Volume Depletion
- Urine pH usually below 5.5
- Plasma [HCO_3^-] typically 15 – 20mmol/L
- Moderate Hypobicarbonatemia
- Plasma [K^+] High

Some Laboratory Tests Useful in Diagnosis of RTA

Urine pH:

- A urine pH greater than 5.5 in the presence of Acidosis is diagnostic of Type I RTA (Distal RTA) if the following conditions are excluded:

  - Urea-splitting UTI (which raises urine pH)
  - Hypokalemia (which stimulates NH_3 production, buffering free protons)
  - Avid salt retentive state

- **Net Acid Excretion**:
- **Urine Acidification Tests**:
- **Na_2 SO4 administration**:
- **Fractional Excretion of HCO_3^- (Fe_{HCO3^-})**: