# Renal Tubular Acidosis

- Disease state characterized by a normal anion gap metabolic acidosis resulting from either impaired bicarbonate reabsorption or impaired urinary acid (hydrogen ion) excretion.
- Both inherited and acquired forms exist.
- There are 3 main forms of RTA:
  1. distal (type I) RTA
  2. proximal (type II) RTA
  3. hyperkalemic (type IV) RTA.
  - ♥ type III RTA Mixed lesions (type I and II RTA), which occur in patients with inherited carbonic anhydrase deficiency.
- The RTA syndromes : characterized by a normal GFR do not progress to renal failure.

NOTE:
**Blood anion gap** = $[Na^+]$ - $[Cl^-+HCO_3^-]$
- ✓ <12 : the absence of an anion gap.
- ✓ >20 : highly suggestive of anion gap.

## Distal (Type I) Renal Tubular Acidosis

- Is the result of impaired distal urinary acidification (hydrogen ion secretion)
- Hereditary or secondary to a systemic disorder (e.g., obstructive uropathy, sickle cell nephropathy, toxins).
- **features**:
  1. urine pH cannot be reduced below 5.5
  2. severe non-anion gap metabolic acidosis
  3. hyperchloremia
  4. hypokalemia
  5. **Hypercalciuria → nephrocalcinosis or nephrolithiasis** ≒ distinguishing features
  6. **Hypocitraturia** (cause chronic metabolic acidosis)→ risk of Ca deposition in tubules.
  7. growth failure.
  8. absent of phosphate & massive bicarbonate wasting (characteristic of proximal RTA )
- Treatment is easily achieved with 1–3 mEq/kg/day $NaHCO_3$ ,a characteristic which distinguishes it from type II RTA.
- **Medullary sponge kidney**: characterized by cystic dilatation of the terminal portions of the collecting ducts.
  - ♥ US: medullary nephrocalcinosis .
  - ♥ Typically maintain normal renal function through adulthood
  - ♥ complications include hyposthenuria (inability to concentrate urine) and distal RTA.
  - ♥ Associations of medullary sponge kidney with Beckwith-Wiedemann syndrome.

## Proximal (Type II) Renal Tubular Acidosis

- Impaired proximal tubule bicarbonate reabsorption.
- hereditary (Fanconi syndrome) or a secondary (tubular immaturity in premature infants).
- **Fanconi syndrome**: global proximal tubular dysfunction (low molecular weight proteinuria+ glycosuria+ phosphaturia+ aminoaciduria+ proximal RTA).
- **Lowe syndrome** *(oculocerebrorenal syndrome of Lowe)* is a rare X-linked disorder characterized by congenital cataracts, mental retardation, and Fanconi syndrome.
- **Features:**
  1. Growth failure in the 1st year of life.
  2. polyuria
  3. dehydration (due to sodium losses)
  4. anorexia, vomiting, constipation
  5. hypotonia
  6. if with primary Fanconi syndrome→ rickets.
  7. non-anion gap metabolic acidosis
  8. **The urine pH is acidic (<5.5)** because distal acidification mechanisms are intact.
  9. Fanconi syndrome demonstrates: phosphaturia, aminoaciduria, glycosuria, uricosuria, and ↑urinary sodium or potassium.

## Hyperkalemic (Type IV) Renal Tubular Necrosis

- Impaired aldosterone production (hypoaldosteronism) or impaired renal responsiveness to aldosterone ("pseudo" hypoaldosteronism).
- mineralocorticoid deficiency (e.g., adrenal failure, congenital adrenal hyperplasia [CAH], diabetes mellitus, pseudohypoaldosteronism, interstitial nephritis).
- **Features**:
  1. growth failure in the first few years of life like those with type I and II RTA.
  2. Polyuria and dehydration (from salt wasting)
  3. Life-threatening hyperkalemia rarely,(especially those with pseudo hypoaldosteronism type 1)
  4. hyperkalemic non-anion gap metabolic acidosis
  5. Urine alkaline or acidic.
  6. Elevated urine Na levels + low urine K levels→ no aldosterone effect.

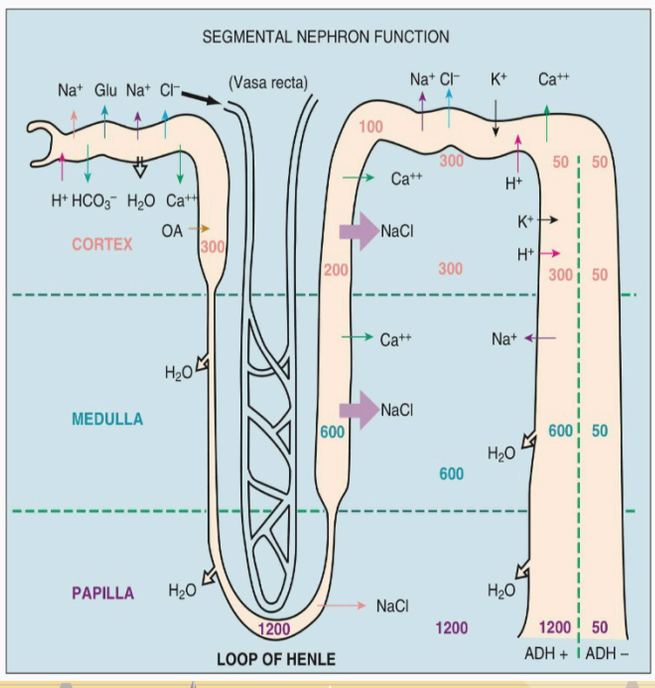
## NOTES:

- D/D: diarrheal dehydration - Metabolic acidosis : acidosis improve with correction of volume depletion.
- normal or low potassium suggests type I or II.
- A urine pH <5.5 in the presence of acidosis suggests proximal RTA, whereas patients with distal RTA typically have a urine pH >6.0.
- **urine anion gap** ([urine $Na^+$+urine $K^+$] - urine $Cl^-$) is calculated to confirm the diagnosis of distal RTA( positive gap). IF negative gap = proximal tubule bicarbonate wasting.
- The mainstay of therapy in all forms of RTA is bicarbonate replacement.

**Table 11-2**
**Types of Renal Tubular Acidosis (RTA)**

| Type of RTA | Characteristic Features | Causes or Associations | Clinical Presentation | Treatment |
|---|---|---|---|---|
| **Distal RTA (Type I)** | • Inability of the distal renal tubular cells to excrete acid ($H^+$) | • Isolated inherited defect<br>• Associated with nephrotic syndrome, sickle cell anemia, connective tissue disorders<br>• Associated with toxins, drugs (amphotericin) | • Vomiting<br>• Growth failure<br>• Acidosis<br>• Nephrocalcinosis and nephrolithiasis | • Small doses of oral alkali |
| **Proximal RTA (Type II)** | • Impaired bicarbonate reabsorption by the proximal renal tubular cells | • Isolated inherited defect<br>• Intoxication (heavy metals)<br>• Prematurity<br>• Drugs (gentamicin)<br>• Associated with more global defects in tubular reabsorption (Fanconi syndrome*) | • Vomiting<br>• Growth failure<br>• Acidosis<br>• Muscle weakness | • Large doses of oral alkali |
| **Type IV RTA** | • **Transient** acidosis in infants and children<br>• *Hyperkalemia is the hallmark* | • Associated with renal disorders such as obstructive uropathy and interstitial nephritis<br>• Diabetes mellitus<br>• Associated with mineralocorticoid deficiency states | • Patients may be asymptomatic or may present with failure to thrive | • Furosemide to lower serum potassium; oral alkali |

*Findings associated with Fanconi syndrome: proximal RTA, hyperphosphaturia, aminoaciduria, glucosuria, and potassium wasting.




| Renal tubular acidosis | | | |
|---|---|---|---|
| **Type** | **1 (Distal)** | **2 (Proximal)** | **4** |
| **Primary defect** | Poor hydrogen secretion into urine | Poor bicarbonate resorption | Aldosterone resistance |
| **Urine pH** | ≥5.5 | <5.5 | <5.5 |
| **Serum potassium** | Low-normal | Low-normal | High |
| **Causes** | • Genetic disorders<br>• Medication toxicity<br>• Autoimmune disorders (eg, Sjögren syndrome, rheumatoid arthritis) | Fanconi syndrome (glucosuria, phosphaturia, aminoaciduria) | • Obstructive uropathy<br>• Congenital adrenal hyperplasia |

# ACUTE RENAL FAILURE

- ARF is defined as an abrupt and significant decrease in GFR or in tubular function.
- Urine output may be low, normal, or high.
- ARF often is subdivided into two forms:
  3. **oliguric renal failure** (<1 mL/kg/hr in neonates and infants, <0.5 mL/kg/hr in others)
  4. **nonoliguric renal failure**: urine output is maintained in the nonoliguric variant, complicated by fluid and electrolyte disturbances & azotemia. Urinary osmolality is typically similar to serum osmolality in such patients.
- Causes:
  1. **prerenal** causes, characterized by renal underperfusion.
  2. **intrinsic renal** causes: vascular, immunologic, ischemic, or toxic injury to the kidney
  3. **postrenal** causes, which typically relate to urinary tract obstruction.
- If a patient has an acutely elevated serum creatinine +no period of oliguria= not prerenal .
- If a child has renal underperfusion (prerenal) or obstruction (postrenal) for an extended period, there is a high probability of intrinsic renal disease being present.
- Sepsis is a major morbid complication of ARF.

| Prerenal, Hypovolemic, Hypotension | Postrenal (Obstruction) | Intrinsic |
|---|---|---|
| Dehydration | Urethral obstruction | Acute tubular necrosis |
| Septic shock | Stricture | Nephrotoxins (drugs) |
| Heart failure | Posterior urethral valves | Acute cortical necrosis |
| Hemorrhage | Diverticulum | Glomerulonephritis |
| Burns | Ureteral obstruction | Interstitial nephritis |
| Peritonitis, ascites, cirrhosis | Calculi/crystals | Vascular |
| | Clot | Renal vein thromboembolism |
| | Ureterocele | Arterial thromboemboli (umbilical artery catheter) |
| | Extrinsic tumor compressing bladder outlet | Disseminated intravascular coagulation |
| | Extrinsic urinary tract tumors | Immune-mediated (scleroderma) |
| | Neurogenic bladder | Pigmenturia |
| | Tumor lysis syndrome | Hemoglobinuria |
| | | Myoglobinuria |

- **Acute tubular necrosis** is the most common cause of ARF in children and is usually the consequence of renal underperfusion.
  - poor perfusion → hypotensive ischemia (or hypoxia) resulting → early vasoconstriction → tubular injury.
  - Toxic injury secondary to drugs, exogenous toxins (ethylene glycol, methanol), or endogenous toxins (myoglobin, hemoglobin) cause ATN .
  - Severe vascular compromise may lead to arterial or venous thrombosis with **acute cortical necrosis**.
  - Acute tubular necrosis is commonly reversible, but acute cortical necrosis represents tissue death(permanent loss of renal function).

## Clinical Manifestations

- Precipitating illness associated with vomiting and diarrhea and an inadequate oral intake → hypotension and oliguria → prerenal causes.
- Obstructive causes; Flank masses or a distended & absent of dehydration .
  - with 2 functioning kidneys, obstruction must be bilateral to result in ARF.
- Intrinsic renal failure associated with hypertension, cardiac enlargement, or a gallop rhythm, which would suggest volume overload.
  - Urine output characteristically is decreased.
  - Signs of systemic involvement (systemic lupus erythematosus, Henoch-Schönlein purpura, HUS).
  - Urinalysis : RBC and granular casts, with mild to moderate proteinuria.

## Laboratory Studies and Imaging

- **anemia** (dilutional or hemolytic, as in SLE, renal vein thrombosis, HUS)
- **leukopenia** (SLE)
- **thrombocytopenia** (SLE, renal vein thrombosis, HUS)
- **hyponatremia** (dilutional)
- serum C3 level may be depressed (postinfectious glomerulonephritis, SLE, or membranoproliferative glomerulonephritis)
- **antibodies :**
  1. streptococcal (poststreptococcal glomerulonephritis)
  2. nuclear (SLE),
  3. neutrophil cytoplasmic (Wegener granulomatosis, microscopic polyarteritis),
  4. glomerular basement membrane (Goodpasture disease) antigens.
- The **fractional excretion of sodium** ($FE_{Na}$) : is the percent of sodium filtered by the glomeruli that is reabsorbed by the tubules. calculated as follows:

  $$[U/P\ Na \div U/P\ creatinine] \times 100$$

  A. Values less than 1% : prerenal azotemia.
  B. Values that exceed 3% : tubular and intrinsic renal dysfunction.
- ratio of serum **BUN** and **creatinine**
- **Urinalysis**:
  1. hematuria, proteinuria, or casts suggests intrinsic ARF.
  2. WBC and WBC casts + low-grade hematuria & proteinuria→ tubulointerstitial disease.
- **Hyperkalemia** :in ARF as a result of increased catabolism & absence of K excretion.
- **Acidosis** is due to catabolism and the impaired secretion of hydrogen ions.
- **Hypocalcemia** & **hyperphosphatemia** in ARF.
- Ultrasound imaging: increased echogenicity in children with ATN, loss of cortico-medullary differentiation when cortical necrosis, Enlarged kidneys when nephritis.
- Radiologic studies (ultrasound, VCUG, CT, nuclear imaging) are often helpful to determine the cause of obstruction if it is the suspected cause of renal failure.
- **Renal biopsy**, performed percutaneously, may be indicated if:
  1. the presentation is atypical
  2. assess the severity of systemic disease involvement (systemic lupus erythematosus)
  3. guide therapy
  4. establish a prognosis

| | PRERENAL ARF | INTRINSIC ARF |
|---|---|---|
| SPECIFIC GRAVITY | elevated (>1.020) | High(<1.010) |
| URINE OSMOLALITY | Elevated(>500 mOsm/kg) | Low(<350 mOsm/kg) |
| URINE SODIUM | Low(<20 mEq/L) | High(>40 mEq/L) |
| AND FRACTIONAL EXCRETION OF SODIUM | 1% (<2.5% in neonates) | > 2% (>10% in neonates) |

| | HYPOVOLEMIA | ACUTE TUBULAR NECROSIS | ACUTE INTERSTITIAL NEPHRITIS | GN | OBSTRUCTION |
|---|---|---|---|---|---|
| SEDIMENT | Bland | Broad, brownish granular casts | WBC, eosinophils, cellular casts | RBC, red blood cell casts | Bland or bloody |
| PROTEIN | None or low | None or low | Minimal / increased with NSAIDs | Increased, >100 mg/dL | Low |
| URINE SODIUM, MEQ/L* | <20 | >30 | >30 | <20 | <20 (acute)<br>>40 (few days) |
| URINE OSMOLALITY, MOSM/KG | >400 | <350 | <350 | >400 | <350 |
| $FE_{Na}$ %† | <1 | >1 | Varies | <1 | <1 (acute)<br>>1 (few days) |

## Treatment

- Fluid balance:
  - weight (at least every 12 hours in severely ill children)
  - If hypovolemia : IV administration of physiologic saline (0.9% sodium chloride) 20mL/kg over 30 to 60 minutes.
  - If hypervolemia, 2 mg/kg of furosemide, or an equal dose of other loop diuretics.
  - Severe fluid overload +marked oliguria or anuria = one indication for **dialysis**.
  - Urine output and serum and urine electrolytes levels should be determined frequently during the acute phase.
- Potassium:
  - The major risk of hyperkalemia is arrhythmia.
  - earliest electrocardiographic change seen in patients with developing hyperkalemia is the appearance of peaked T waves.
  - followed by widening of the QRS intervals, ST segment depression, ventricular arrhythmias, and cardiac arrest.
  - Procedures to deplete body potassium stores ():
    1. Exogenous sources of potassium (dietary, intravenous fluids, total parenteral nutrition) should be eliminated.
    2. Kayexalate, 1 g/kg, PO or by retention enema. exchanges sodium for potassium, several hours to take effect. single dose ↓ K by 1 mEq/LM ,repeated q 2 hr.
  - severe elevations in serum potassium (>7 mEq/L) require emergency measures in addition to Kayexalate. agents should be administered:
  1. Calcium gluconate 10% solution, 1.0 mL/kg IV, over 3-5 min - counteracts the K-induced increase in myocardial irritability but does not lower K level.
  2. Na bicarbonate, 1-2 mEq/kg IV, over 5-10 min - shift K extracellular - intracellular
  3. Regular insulin, 0.1 U/kg, with glucose 50% solution, 1 mL/kg, over 1 hr - shift K extracellular – intracellular.
- Acidosis:
  - common in ARF because of retention of hydrogen ions, phosphate, and sulfate
  - requires treatment If acidosis is severe (arterial pH <7.15; serum bicarbonate <8 mEq/L) or contributes to hyperkalemia.
  - sodium Bicarbonate counteracts, but ↑risk of fluid overload, hypernatremia, tetany and hypertension.
- hypocalcemia and hyperphosphatemia:
  - primarily involves efforts to lower the serum phosphorus level.
  - Dietary phosphorus restriction & administration of phosphate binders, calcium acetate, and calcium carbonate are the first therapeutic steps.
  - Symptomatic hypocalcemia → parenteral calcium/ given cautiously because it may precipitate in the body with circulating phosphorus.
- **dialysis** :
  - Indications for dialysis in ARF include the following:
    1. Volume overload with evidence of hypertension and/or pulmonary edema refractory to diuretic therapy
    2. Persistent hyperkalemia
    3. Severe metabolic acidosis unresponsive to medical management
    4. Neurologic symptoms (altered mental status, seizures)
    5. Blood urea nitrogen greater than 100-150 mg/dL (or lower if rapidly rising)
    6. Calcium/phosphorus imbalance, with hypocalcemic tetany
- Potential renal replacement therapies in children for ARF include peritoneal dialysis, hemodialysis, and the variations of continuous renal replacement therapy, such as continuous hemofiltration and hemodialysis or continuous venovenous hemodiafiltration.



# CHRONIC KIDNEY DISEASE

- defined as either renal injury (proteinuria) and/or a glomerular filtration rate <60 mL/min/1.73 $m^2$ for >3 mo.
- **Standardized Terminology for Stages of Chronic Kidney Disease**

| STAGE | DESCRIPTION | GFR (mL/min/1.73 $m^2$) |
|---|---|---|
| Stage 1 | Kidney damage with normal or increased GFR | >90 |
| Stage 2 | Kidney damage with mild decrease in GFR | 60-89 |
| Stage 3 | Moderate decrease in GFR | 30-59 |
| Stage 4 | Severe decrease in GFR | 15-29 |
| Stage 5 | Kidney failure | <15 or on dialysis |

- (ESRD) defining all patients treated with dialysis or kidney transplantation. subset of the patients with Stage 5 CKD.
- The etiologies of chronic renal disease in childhood relate to the age of the child at the time the kidney disease occurs.
  - ♥ younger than 5 yr is most commonly a result of :
    1. congenital abnormalities such as renal hypoplasia, dysplasia
    2. obstructive uropathy
    3. congenital nephrotic syndrome
    4. prune belly syndrome
    5. cortical necrosis
    6. focal segmental glomerulosclerosis
    7. polycystic kidney disease
    8. renal vein thrombosis
    9. hemolytic uremic syndrome.
  - ♥ After age 10, acquired diseases, such as :
    1. acquired diseases (various forms of glomerulonephritis including lupus nephritis)
    2. inherited disorders (familial juvenile nephronophthisis, polycystic kidney disease & Alport syndrome)
    3. metabolic disorders (cystinosis, hyperoxaluria)
- Children often present during late puberty as pubertal growth spurt increases demand on the damaged kidneys.

## CLINICAL MANIFESTATIONS:

- **Growth failure** is prominent. The factors include :
  1. undernutrition
  2. osteodystrophy
  3. hormonal abnormalities
  4. medications (steroids)
  5. acidosis.
- Increased calorie intake leads to a slight increase in growth in some children.
- progressive anemia :
  1. failure of the kidney to produce adequate **erythropoietin** in response to anemia
  2. impaired response to erythropoietin because of the uremia
- **Renal osteodystrophy** is common, associated with:
  1. hyperphosphatemia
  2. high serum alkaline phosphatase levels
  3. secondary hyperparathyroidism
  4. low levels of 1,25-dihydroxyvitamin D

## GROWTH

- Children with CKD have an apparent growth hormone (GH)-resistant state with elevated GH levels but decreased insulin-like growth factor 1 levels and major abnormalities of insulin-like growth factor-binding proteins.
- Children with CKD who remain less than -2 SD for height despite optimal medical support (adequate caloric intake and effective treatment of renal osteodystrophy, anemia, and metabolic acidosis) may benefit from treatment with pharmacologic doses of recombinant human GH (rHuGH).



- rHuGH continues until the patient
1. reaches the 50th percentile for midparental height
2. achieves a final adult height
3. Undergoes renal transplantation.

## RENAL OSTEODYSTROPHY

- spectrum of bone disorders seen in patients with CKD.
- The most common condition seen in children is high-turnover bone disease caused by secondary hyperparathyroidism→ pathologic finding: osteitis fibrosa cystica.
- GFR declines 50% of normal→ decline in renal 1α-hydroxylase activity+ decreased production of activated vitamin D (1,25-dihydroxycholecalciferol→ decreased intestinal calcium absorption→ hypocalcemia→ increased parathyroid hormone (PTH) → increase in bone resorption.
- Later,when the GFR declines to 20-25% of normal, compensatory mechanisms to enhance phosphate excretion become inadequate→ hyperphosphatemia, → further hypocalcemia → increased PTH secretion.
- **Clinical manifestations:**
  1. muscle weakness, bone pain, and fractures with minor trauma.
  2. rachitic changes, varus and valgus deformities of the long bones, and slipped capital femoral epiphyses
- **lab** : Hypocalcemia & hyper-phosphatemia, ↑alkaline phosphatase, and a normal PTH
- Radiographs of the hands, wrists, and knees show subperiosteal resorption of bone with widening of the metaphyses.
- **Treatment**:
  1. low phosphorus diet, and infants should be provided with a low-phosphorus formula such as Similac PM 60/40.
  2. phosphate binders: calcium carbonate and calcium acetate, non-calcium-based binders.
  3. aluminum may be absorbed from the gastrointestinal tract and can lead to aluminum toxicity, aluminum-based binders should be avoided.
  4. The cornerstone of therapy for renal osteodystrophy is vitamin D administration. indicated in patients with
     A. 25-hydroxy-vitamin D levels below the established goal range for his or her particular stage of CKD →treated with ergocalciferol.
     B. PTH levels above the established goal range for CKD stage→ calcitriol

## LAB RESULTS:

- hyperkalemia & hyponatremia (if volume overloaded)
- Acidosis
- Hypocalcemia & hyper-phosphatemia
- elevation in uric acid
- heavy proteinuria→hypoalbuminemia
- normochromic, normocytic anemia
- Serum cholesterol and triglyceride levels are elevated
- CKD from congenital lesions such as renal dysplasia, the urinalysis usually has a low specific gravity and minimal abnormalities.

## TREATMENT

- Recombinant-produced growth hormone is useful in children with chronic renal failure on or off dialysis.
- The initial therapy for **renal osteodystrophy** is to restrict phosphate in the diet.
- When the serum phosphorus is under control, therapy with either 1-hydroxylated vitamin D or its analogues is indicated.
- HTN with volume overload → salt-restricted diet (2-3 g/24 hr) and +Thiazide diuretics as initial diuretic class of choice for mild renal dysfunction (CKD stages 1-3)/GFR falls into stage 4 CKD loop diuretics (furosemide )become the diuretic class of choice.
- **Angiotensin-converting enzyme (ACE) inhibitors** (enalapril, lisinopril) and angiotensin II blockers (losar-tan) are the antihypertensive medications of choice in all children with

proteinuric renal disease because of their potential ability to slow the progression to ESRD.

- Recombinant-produced erythropoietin has resolved much of the anemia formerly seen in chronic renal failure.
- The optimal treatment of ESRD is **renal transplantation**.
- 93% of transplants of any type (living or deceased donor) are functioning 1 year post-transplant; 50% are still functioning 19 years later.

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