Kidney diseases
Cortical nephrons: 85%
Peritubular capillaries encircling all nephron sections

Juxtamedullary nephrons: 15%
Some peritubular capillaries and vascular loops (vasa recta) which surround loop of Henle descend into medulla
Kidney function under physiological and pathophysiological conditions

- Excretes the waste products of metabolism
  - Defective function: increased urea-nitrogen, uric acid and creatinine in blood

- Regulates water, Na and K homeostasis
  - Defective function: hypertension, edema, hyperkalemia

- Regulates acid-base balance
  - Defective function: metabolic acidosis

- Endocrine function
  - Defective function: anemia, chronic kidney disease – mineral and bone disorder
Urine analysis – sample collection

- First void in the morning (concentrated, ideal for casts)
  - Cleanse with antiseptic solution – midstream sample (discard first 15-30 ml) then collect appr. 50-100 ml
- Store at 2-8 °C (for max 4 hr)
- Other sampling methods
  - Catheter
  - Transcutaneous, suprapubic
- Appearance: clean, shiny, pearly, yellow color
  - Cloudy: Indicative of presence of large amounts of protein, blood cells, bacteria and pus
  - Dark color: May be due to hematuria, excessive bilirubin content, highly concentrated urine
  - Unpleasant or unusual odor: May indicate infection; ammonia odor due to bacterial decomposition of urea
Color of urine, 9-10 parameters (dipstick test) and urine sediment

- **Normal, supposedly no renal dysfunctions**

- **Proteinuria**

- **Leukocyturia:** Infection, prostate and genital cytology (malignancy)

- **Hematuria:** Renal hematuria or prerenal origin (myoglobinuria, porphyria)

- **Positive 24 hr collected urine**
Proteinuria

- Healthy adults excrete <150 mg of protein in the urine daily
  - 30[20-60]% albumin, 30% serum globulins and 40% tissue proteins, of which the major component is Tamm-Horsfall protein

<table>
<thead>
<tr>
<th>Albuminuria</th>
<th>Proteinuria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Albumin excretion (mg/day)</strong></td>
<td><strong>Albumin-creatinin ratio (mg/mmol)</strong></td>
</tr>
<tr>
<td>&lt; 10</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>A1</td>
<td>&gt; 10 - &lt; 30</td>
</tr>
<tr>
<td>A2</td>
<td>30-300</td>
</tr>
<tr>
<td>A3</td>
<td>&gt; 300</td>
</tr>
<tr>
<td>&gt; 2200</td>
<td>&gt; 220</td>
</tr>
</tbody>
</table>
Forms of proteinuria

- 1. Prerenal due to overproduction or overflow (increased plasma concentrations of a proteins)
  - Hemolysis – hemoglobin (no free haptoglobin)
  - Rhabdomyolysis – myoglobin, electrolyte disturbances (hypo K, P_i, Mg)
  - Paraproteinemia – Bence Jones protein (immunoglobulin light chain)

- Renal
  - Glomerular
  - Tubular
2. Glomerular
   ○ The albumin in the ultrafiltrate is taken back cubilin and megalin receptors in the proximal tubules
   ○ Increased glomerular capillary permeability
     ■ Benign (functional) proteinuria: transient increase upon strenuous physical activity, fever, pregnancy, congestive heart failure
     ■ Orthostatic proteinuria: protein excretion abnormally elevated in the standing position (less than 1 g/day). Occurs in 2-5% of adolescents
     ■ Significant proteinuria: over 1 g/day - kidney disease
     ■ Selective (albumin, transferrin) or non-selective (IgG, albumin)
   ○ Mechanisms: see later

3. Tubular – failure to reabsorb normally filtered proteins of low molecular weight such as immunoglobulins (microglobulin, lysozim)
   ○ Seldom exceeds 2 to 3 g
   ○ Burns, heavy metal intoxication, renal graft ejection, chronic pyelonephritis

4. Postrenal (α₂ macroglobulin, Tamm-Horsfall protein)
   ○ Infection, malignant tumor
Plasma concentration, mg/L

Filtered load, mg/day if GFR – 150L/day

% reabsorbed

Daily excretion, mg

Normal

Glomerular proteinuria

Tubular proteinuria

Albumin

Low molecular weight proteins
Laboratory detection of proteinuria

○ Qualitative
  ■ 3% sulfosalicylic acid
    □ Moderate cloudiness 1+
    □ Explicit cloudiness 2+
    □ Flocculent precipitation 3+
    □ Curd precipitation 4+
  ■ False positive: penicillin, salicylate

○ Dipstick (short, plastic strips with small marker pads that are impregnated with different chemical reagents that react with abnormal substances in the urine to produce a colorimetric change)
  ■ Tetra-bromophenol blue in presence of protein
    □ Color change from yellow to various shades of green

○ Quantitative (24-hour urinary collection)
  ■ Protein electrophoresis or immunoassay for specific proteins
Leukocyturia / pyuria (pus in urine)

- Donné’s test
  - KOH → WBC destruction in urine → viscosity ↑ - air bubble entrapment on a single shake
- Leukocyturia & positive urine bacteriological specimen → infection: pyelitis, pyelonephritis, lower urinary tract infection: cystitis, prostatitis, urethritis, gonorrhea
- Sterile pyuria or aseptic leukocyturia
  - Pyuria upon repeated negative (bacteriological) specimen
  - Kidney stone, urinary tract tumor
  - Chronic interstitial nephritis (analgesics abuse)
  - TB, Chlamydia, Mycoplasma, Candida, Ureaplasma urealyticum
- Leukocyte esterase activity – WBC detection in the urine
  - Catalyzes the hydrolysis of an indoxyl carbonic acid ester to indoxyl – oxidizes a diazonium salt chromogen on the dipstick to produce a color change
Bacteriuria

- Nitrites in the urine – bacteriuria
  - Nitrites can readily be detected in the urine because they react with the reagents on the dipstick and undergo diazotization to form a red azo dye

- Urinary tract infection
  - Significant bacteriuria: more than $10^5$ colony-forming units (CFU) of bacteria per mL of urine in midstream urine sample – mainly *E. coli*

- Asymptomatic bacteriuria
  - More than $10^5$ organisms/ml in midstream urine
    - 1% of children under age 1
    - 1% of schoolgirls
    - 0.03% schoolboys
Schematic set up of a dip-slide container

- Paddle-holding stopper
- Agar
- Moist sponge

Interpretation after 24-hour incubation at 37°C

Nonsignificant

- $10^3$
- $10^4$

Significant

- $10^5$
- $10^6$
- $10^7$
Hematuria

- Forms: macroscopic or microscopic hematuria
  - Hemoglobinuria
    - Centrifuged urine – supernatant will be pink
    - Hemolysis (see later), paroxysmal cold hemoglobinuria, paroxysmal nocturnal hemoglobinuria, marches (march) hemoglobinuria, burns, venoms (snake, spider)
- Benzidine test
  - The hydrogen peroxide oxidizes benzidine and hemoglobin catalyzes the process; positive test: prussian blue color
- Dipstick
  - Myoglobin and hemoglobin reacts (due to their peroxidase-like activity); so if the test positive, light microscopic examination is justified
- Three glass voiding test & its significance
● Glomerular hematuria; main age group: children and young adults
  ○ Urinary sediment: dysmorphic erythrocytes, red blood cell casts
  ○ Proteinuria
  ○ Causes of glomerular hematuria
    ■ IgA nephropathy (Berger’s disease)
    ■ Mesangioproliferative glomerulonephritis (GN)
    ■ Focal segmental GN
    ■ Familial nephritis (e.g., Alport’s syndrome)
    ■ Membranous GN
    ■ Mesangiocapillary GN
    ■ Focal segmental sclerosis
    ■ SLE
    ■ Post infectious GN

● Non glomerular hematuria
  ○ Urinary sediment: casts, uniformly round shape erythrocytes (isomorphic); isomorphic / dysmorphic erythrocyte ratio should be determined
  ○ Significant proteinuria

● Causes of hematuria are age-dependent
  ○ > 35: the prevalence of asymptomatic hematuria is 13% (> 1 RBC/hpf)
  ○ > 40: only <5% glomerular disease; 15-20% neoplasms, mainly bladder carcinoma (2/3)
Glucose detection

- $T_m$ glucose: glucose is detected in the urine if blood sugar is over 8 mmol/l
- Qualitative: Nylander’s test
  - At alkaline pH, due to the reducing effects of sugars; bismuth nitrate $\rightarrow$ metal bismuth (black color)
- Dipstick
  - Glucose in the urine reacts with glucose oxidase on the dipstick $\rightarrow$ gluconic acid and hydrogen peroxide
  - In the second reaction, hydrogen peroxide reacts with peroxidase, causing oxidation of the chromogen on the dipstick, producing a color change (greenish-blue)
  - This double-oxidative reaction is specific for glucose, and there is no cross-reactivity with other sugars
    - False positive: vitamin C, aspirin
• Glucose is detected in urine
  ○ Hyperglycemia
    ▪ DM, acute MI, acute abdomen,
    ▪ Fructosuria, lactosuria, pentosuria
  ○ Normoglycemia
    ▪ Enzyme defects
    ▪ Drugs (false positive or false negative)
Ketone bodies

- **Legal test**
  - Na nitroprusside in the presence of ketone bodies (acetoacetate and β-hydroxybutyric acid) produce a burgundy color in an alkaline urine

- **Dipstick**
  - Na nitroprusside on the dipstick reacts with acetoacetic acid to produce a burgundy color

- **Causes of ketonuria**
  - Metabolic: DM, renal glycosuria, glycogen storage disease, increased metabolism (hyperthyroidism, fever, pregnancy or lactation)
  - Dietary: starvation, high protein, or low carbohydrate diets, prolonged vomiting
  - Other: acute illness, severe stress
UBG and bilirubin

- Normal urine contains **no bilirubin** and only very **small** amounts of **urobilinogen**
- Different dipstick reagents
  - Binding of bilirubin or urobilinogen to a diazonium salt to produce a colorimetric reaction
- False-negative results
  - Ascorbic acid – decreases the sensitivity for detection of bilirubin
- False-positive results
  - Phenazopyridine (relieve pain)
    - Colors the urine orange and, similar to the colorimetric reaction for bilirubin, turns red in an acid medium
Urinary sediment

- Semi quantitative analysis of the urinary sediment
  - Use freshly voided, concentrated (1st void in the morning) urine (appr 10-12 ml); sediment (1500 rpm for 5 min); leave 1 ml supernatant and re-suspend; assessment: in Bürker’s chamber under 100 and 400x magnification

- Organic components
  - Epithelial cells, white and red blood cells
  - Casts (hyaline, RBC, WBC, pigment, myoglobin)

- Separate kits for detection of inorganic materials and crystals
  - Uric acid, urate, calcium, cystine, cholesterol

- Negative sediment, if
  - 1-4 WBC, 1-2 hyaline cylinders / hpf, little Ca oxalate, amorphous urate or phosphate crystals & may be sperm (♂) found
  - ♀: above + 1-2 RBC and some epithelial cells / hpf
# Casts

<table>
<thead>
<tr>
<th>Types</th>
<th>Practical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyaline</td>
<td>If above normal (1-2) limits: GN, pyelonephritis, chronic kidney disease, heart failure, physical stress</td>
</tr>
<tr>
<td>RBC</td>
<td>GN, physical stress, exercise</td>
</tr>
<tr>
<td>WBC</td>
<td>Pyelonephritis</td>
</tr>
<tr>
<td>Epithelial cell</td>
<td>Renal tubular damage</td>
</tr>
<tr>
<td>Granular</td>
<td>Urinary tract obstruction or infection, chronic kidney disease</td>
</tr>
<tr>
<td>Waxy</td>
<td>Urinary tract obstruction</td>
</tr>
<tr>
<td>Fatty</td>
<td>Nephrotic syndrome</td>
</tr>
<tr>
<td>Broad</td>
<td>Urinary tract obstruction</td>
</tr>
<tr>
<td>Pseudo</td>
<td>Not a real cast</td>
</tr>
</tbody>
</table>
Red blood cells

Hyaline casts

RBC casts

Dismorphic RBC-s
WBC cast

Epithelial cell cast
Waxy, fine and coarse granular casts
Nephrolithiasis (Kidney stones)

- Affects 1-5% of population (males with 2x risk) Classic presentation: severe colicky flank pain with radiation to lower abdomen
- Stone formation occurs with
  - Super-saturation of the urine with those substances that are components of the stone
    - Ca (hypercalciuria)
    - Oxalate (hyperoxaluria)
    - Uric acid (hyperuricosuria)
     - Ca stones are radiopaque* (uric acid stones are not)
  - Disbalance between stone-forming and inhibiting factors

*Inability of X-ray to pass through
### Nephrolithiasis – risk factors

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Promote stone formation</th>
<th>Inhibit stone formation</th>
</tr>
</thead>
</table>
| **Nutritional** | • ↑ animal protein, oxalate (spinach, rhubarb, potato), Na, sucrose, fructose  
• Ca and C-vitamin supplementation  
• ↓ fluid intake (urine < 1l/day)  
• Obesity | • Diet related K and Ca (Ca inhibits intestinal oxalate reabsorption) fruits & vegetables (citrate source)  
• Coffee, tea, beer |
| **Non nutritional** | • Middle aged male  
• Hot climate, increased vitamin D exposure | ~50% less frequent in blacks |
| **Urinary** | • ↓ urine amount or citrate content  
• ↑ urinary Ca, oxalate, uric acid content  
• Urine pH:  
  ≤ 5.5 uric acid stone  
  ≥ 6.5 Ca-phosphate stone  
  Ca-oxalate stone: no pH dependency | • Urinary citrate: natural inhibitor of Ca stones  
• Nephrocalcin, Tamm-Horsfall protein, uropontin |
The forms of kidney stones

● 1. Ca stones (~ 90 %) formation is promoted by absorptive hypercalciuria and increased loss of renal Ca
  ○ Ca oxalate (~75%)
    ■ High amount of urinary calcium and oxalate and low levels of citrate. Rarely: primary oxaluria (autosomal recessive disease: the liver is the source of oxalate overproduction)
  ○ Ca phosphate (~15%)
    ■ High amount of urinary calcium and phosphate and low levels of citrate, urinary pH ≥ 6.5. Frequent in primary hyperparathyroidism and distal renal tubular acidosis type 1 (RTA-1: decreased urinary citrate and total acid levels)
2. Uric acid stones (~8%); development is determined by 2 factors: high uric acid excretion in the urine, and permanently low urine pH (≤ 5.5)
   - The high uric acid excretion is determined by
     - High purine intake (e.g., organ meats, fish, meat extracts)
     - Malignancy (i.e., rapid cell turnover: myeloproliferative disease)
     - Diarrhea increases the risk because of dehydration and the acidic urine
   - 25% of patients with uric acid stone have gout

3. Struvite (magnesium ammonium phosphate) stones (~1%)
   - Infection stone: urinary tract infection (e.g., cystitis)
     - *Ureaplasma urealyticum, Proteus, Staphylococcus, Klebsiella, Providencia, Pseudomonas*
   - More common in women (as the urinary tract infections are more frequent
   - Staghorns: involve the renal pelvis and extend into at least 2 calyces
4. Cystine stones (< 1%)

○ Rare, autosomal recessive condition: failure of renal tubular reabsorption of cystine, ornithine, lysine, and arginine. Since cystine is the worst-soluble amino acid, cystinuria and cystine stones are formed

○ Requires life-long therapy to prevent cystine stones
  ■ Low-methionine diet (unpleasant)
  ■ Cystine binders: penicillamine
  ■ Large amounts of urinary volume and alkalinizing agents

5. Drug-derived stones

○ Anti-viral therapy: acyclovir, indinavir
Oliguria, anuria, polyuria

- **Oliguria**: < 400 ml /day
  - Urea, \( \text{SO}_4^{2-} \), \( \text{HPO}_4^{2-} \) & other waste products of metabolism: \( \sim 550 \text{ mOsm/day} \)
  - Maximal urinary concentration attainable: \( \sim 1400 \text{ mOsm/L} \)
    
    \[
    \text{Minimal volume of urine water} = \frac{550 \text{ mOsm/day}}{1400 \text{ mOsm/L}} \approx 0.4 \text{ L}
    \]
  - Azotemia is inevitable with daily urine output < 400 ml

- **Azotemia**: blood urea-N (BUN or carbamide) and serum creatinine (seCr) level ↑ due to inadequate RPF and intraglomerular hydrostatic pressure to support normal GFR
  - Nephron loss (pyelonephritis, TB, polycystic kidney)
  - With normal tubular function (dehydration, edema)
  - With tubular damage (acute tubular necrosis, acute GN)
○ BUN/creatinine ratios are helpful clinically
  ■ High BUN/seCr ratio
    □ Pre-renal azotemia – CHF, volume depletion
    □ Post-renal azotemia – urinary tract obstruction
  ■ Normal BUN/seCr ratio
    □ Usually indicates primary renal disease as the cause of decreased GFR (e.g. renal failure)

● Anuria: urine amount < 100 ml /day
● Polyuria: urine amount > 3000 ml/day
  ○ Water loss
    ■ Diabetes insipidus (central and peripheral)
    ■ Osmotic diuresis (glucose, mannitol, urea)
  ○ Primary increase in water intake (psychogenic polydipsia)
Kidney function assessment

● Assessment of glomerular function
  ○ Clearance techniques (UxV)/P
    ■ Endogenous creatinine clearance
    ■ Isotope clearance: Cr$^{51}$-inulin, Co-B$_{12}$ (Decrease in radioactivity in blood sample)
  ○ Cystatin C – small mw protein; better candidate, than endogenous creatinine

● Assessment of tubular function – Concentration and dilution test (1.001-1.025 pond/cm$^3$)
  ○ Decrease in specific gravity
    ■ Increased fluid intake or administration of diuretics
    ■ Decreased renal concentrating ability, diabetes insipidus
  ○ Increase in specific gravity
    ■ Decreased fluid intake or dehydration owing to fever, sweating, vomiting, and diarrhea
    ■ DM (glucosuria)
    ■ Inappropriate secretion of antidiuretic hormone (SIADH)
Acute kidney injury [AKI] (acute renal failure)

- Heterogeneous group of disorders with rapid, usually reversible decrease in renal function that results in the need for dialysis
  - Failure of excretory function, fluid, electrolyte, acid-base metabolism and endocrine function
  - Increase in BUN & serum creatinine & reduction in urine volume

- Forms
  - Prerenal azotemia
    - Renal perfusion is compromised; glomerular and tubular function is intact
  - Intrinsic renal parenchymal disease
    - Primary intrarenal cause
  - Postrenal obstruction
    - Obstruction to the urinary flow
Acute kidney injury

Prerenal
60-70%

Intrinsic/renal
(25-35%)

Postrenal
(5-15%)

Tubulo-interstitial (94%)

Glomerular (5%)

Vascular (1%)

Sepsis / infection

Ischemia

Nephrotoxins

Glomerulonephritis

Vasculitis
Prerenal azotemia

- Azotemia develops due to severe hypotension with inadequate compensation processes
  - Decreased cardiac output (congestive heart failure, cardiogenic shock)
  - Hypovolemia
    - Vasodilation (septic shock)
    - Volume loss (burn, blood loss, diarrhea, diuretics)
    - Cirrhosis (hepatorenal syndrome type I)
  - Failure of renal autoregulation (rare, combined with other diseases)
    - Blockage of a. afferent-mediated vasodilation: PG synthesis inhibition of
    - Blockage of a. efferent-mediated vasoconstriction: ACE or ATR inhibition
Severe congestive heart failure, severe cirrhosis
Severe nephrosis, old patient (80+), severe dehydration, hemorrhage
Bi- or unilateral a. renalis stenosis

Compensatory vasodilation (guarantees the normal kidney function) is provided by kidney prostaglandins (PGI₂, PGE₁ & PGE₂), kinins and NO
Intrinsic renal parenchymal disease

- Tubular and interstitial involvement in AKI
  - Sepsis
  - Ischemia
  - Nephrotoxic agents
    - Exogenous
    - Endogenous
- It is called as acute tubular necrosis but necrosis is usually detected only with a nephrotoxic agents; in the first two, inflammation, apoptosis & changes in renal perfusion may be important

- Glomerular AKI
  - Acute GN: due to postinfectious [streptococcal, shunt] or systemic disease [HUS, SLE, pANCA AAV, Goodpasture’s syndrome]
  - Rare in adults, in children acute GN and HUS is frequent

- Vascular AKI
  - Arterial
    - Large vessels: stenosis, emboli, mural thrombi, atrial fibrillation
    - Small vessels: malignant hypertension, acute vasculitis, TTP-HUS
  - Venous occlusion
• AKI due to sepsis occurs in 50% of cases with severe sepsis
  ○ In addition to tubular damage, inflammation (endothelial injury, microvascular thrombosis, ROS, leukocyte activation), mitochondrial dysfunction and interstitial edema are present
  ○ Due to the generalized arterial vasodilatation → GFR ↓
    ■ In the kidney in the early stages of sepsis excessive a. efferent vasodilatation and at late stage excessive vasoconstriction (SNS, RAAS, vasopressin, endothelin) leads to AKI
• AKI due to ischemia is frequent if
  ■ The renal reserve capacity is decreased (elderly, existing nephropathy) and other damaging factors are also present (surgery, sepsis, nephrotoxic agents, burns, pancreatitis etc)
  ○ Due to the progression of prerenal azotemia, secondary ischemic AKI develops.
  ○ The decline of GFR is due to the constant pregglomerular vasoconstriction, back-leak of the filtrate and clogging of the tubules
• AKI due to nephrotoxic agents
  ○ Exogenous: heavy metal, ethylene glycol, drugs: amino glycosides, amphotericin-B, pentamidine, antivirals (acyclovir, tenofovir) chemotherapeutic agents (cisplatin, ifosfamide), I-containing x-ray contrast materials
    ■ Toxic and hypoxic damage
    ■ AKI may also occur as a secondary effect of medications (see acute allergic tubulointerstitial nephritis)
  ○ Endogenous (pigment): myoglobin, hemoglobin, myeloma protein
    ■ The amount of endogenous products are above the metabolic limit of the tubules & hypoperfusion → hypoxia + cast formation
Ischemic and nephrotoxic damage together → GFR ↓↓

1. Hemodynamic disturbances
   - A. afferent constriction (GFR ↓)
   - Mesangial contraction (GFR ↓)

2. Tubular damage and dysfunction
   - Due to tubular damage, NaCl reabsorption ↓ in the proximal tubules → ↑ NaCl reaches distal tubules and stimulates JGA (vasoconstrictor hormones) → a. afferent & mesangial contraction (abnormal tubulo-glomerular feedback) → snGFR↓↓
   - Urea, creatinine backflow (fluid backflow)
   - Tubular obstruction

3. Hormones responsible for decrease in GFR
   - Vasoconstrictors ↑: AT, ET-1, TxA₂, LT, PAF
   - Vasodilators ↓: NO, PGI₂
Intrarenal vasoconstriction – tubular cell damage (neutrophils and reperfusion injury to the loop of Henle and thick ascending segment) – integrin dysfunction – tubular cell desquamation (biochemical changes (Ca, purine depletion, phospholipase, apoptosis) – luminal obstruction – cast formation

Proliferation of viable tubular cells, regaining membrane polarity, restoring kidney function
Acute tubulointerstitial nephritis

- Acute tubulointerstitial nephritis: acute inflammation of kidney interstitium & tubules with or without renal failure
- Causes of acute tubulointerstitial nephritis
  - 1. Allergic acute tubulointerstitial nephritis
     - Antibiotics (ß-lactams, sulfonamides, penicillin, reintroduction of rifampicin), NSAID
     - Immune (hypersensitivity) reaction: tubular basement membrane or interstitial matrix
     - Mediators: cytokines, adhesion molecules
     - Symptoms: fever, rash, eosinophil granulocyte /cast accumulation
○ 2. Infections – acute pyelonephritis or part of a systemic inflammation
  ■ Acute cellular injury caused by infection often associated with obstruction or reflux
    □ Bacterial
    □ Viral (CMV, hantavirus, HIV, HBV
    □ Fungal (histoplasmosis), and parasitic (Leishmania, Toxoplasma)
  ■ Fever, pain, leukocytosis, pyuria, significant bacteriuria \(10^5/ml\)
○ 3. Immunologic diseases (SLE, Goodpasture syndrome)
○ 4. Acute transplant rejection
Postrenal acute renal failure

- Postrenal acute renal failure is due to partial or complete urinary tract obstruction

- Causes
  - Extra renal causes
    - Pyelon (calyx): kidney stones
    - Urether: kidney stones, pregnancy, tumor
    - Urethra and bladder neck: prostate diseases
  - Intra renal causes
    - Crystals: uric acid, methotrexate (folic acid antagonist)
• Clinical appearance of postrenal acute renal failure
  ○ Unilateral obstruction
    ■ Partial obstruction
      □ Pain, frequent urinary tract infection (UTI)
    ■ Complete obstruction
      □ Renin-mediated hypertension
  ○ Bilateral obstruction
    ■ Partial obstruction (ADH resistance, ↓Na+ reabsorption, K+ and H+ excretion)
      □ Polyuria, polydipsia
      □ Hyperkalemic metabolic acidosis and hypernatremia if water intake is not sufficient
      □ Upon resolving the obstruction: postobstructive diuresis
    ■ Complete obstruction
      □ Anuria, uremia
## Summary of AKI

<table>
<thead>
<tr>
<th>Prerenal</th>
<th>Intrarenal</th>
<th>Postrenal (obstructive uropathy/nephropathy)</th>
</tr>
</thead>
</table>
| ▪ Dehydration  
▪ Heart failure (cardiorenal syndrome)  
▪ Liver failure (hepatorenal syndrome) | ▪ Tubulointerstitial disease  
▪ Acute tubular necrosis  
▪ Acute (tubulo)interstitial nephritis  
▪ Intrinsic renovascular disease  
▪ Hypertensive emergency  
▪ Small vessel vasculitis  
▪ TTP/HUS  
▪ Glomerular diseases  
▪ Post-infectious GN | ▪ Ureteral obstruction  
▪ Neurogenic bladder  
▪ Urinary tract infection  
▪ Medications  
▪ Benign prostatic hypertrophy |
## Medications and AKI

<table>
<thead>
<tr>
<th>Prerenal</th>
<th>Intrarenal</th>
<th>Postrenal (obstructive uropathy/nephropathy)</th>
</tr>
</thead>
</table>
| ▪ Dehydration  
  Diuretics  
▪ Altered intrarenal regulation  
  a. afferent vasodilation **PGs**  
  (NSAID, sepsis, atherosclerosis)  
  a. efferent vasoconstriction **AT-II** (ACEI / ARB)  
  Calcineurin inhibitors*  
  (cyclosporin, tacrolimus) | ▪ Acute tubular necrosis  
  (aminoglycosides, cisplatin, tenofovir)  
▪ Acute interstitial nephritis  
  (β-lactams, vancomycin, sulfamethoxazole-trimethoprim, NSAIDs)  
▪ Crystal nephropathy  
  Acyclovir, ganciclovir, ciprofloxacin, sulfamethoxazole, methotrexate) | ↓ bladder sensation, ↓ detrusor muscle contraction, and/or  
  ↑ urinary sphincter tone  
▪ Opiates  
▪ Sympathomimetics  
▪ Anticholinergics |

### Risk factors for medications-induced nephrotoxicity

- Multiple exposure to drugs
- Preexisting renal insufficiency
- Volume depletion
- Age > 60 years
- Other diseases: sepsis, diabetes mellitus etc

* vasoconstrictive effect on both a. afferents & efferents
Classification of major glomerular diseases

● A. Histology
  ○ Non-proliferative / non-inflammatory glomerulonephritis (GN) / glomerulopathy (GP)
  ○ Proliferative / inflammatory GN

● B. Immune mechanism
  ○ Immune complex (antigen+ antibody+complement) mediated glomerular disease
  ○ Non-immune complex-mediated injury

● C. Clinical picture
  ○ Overlap between clinical syndromes is possible
Classification of glomerular diseases by immune mechanisms

- I. Immune complex mediated glomerular disease
  - 1. *In situ* immune complex formation
    - Intrinsic tissue antigen (ie kidney related antigen)
      - Goodpasture antigen: NC-1 (non-collagenous) domain of type IV collagen
      - Neutral endopeptidase (alloimmune neonatal MN)
      - Phospholipase A$_2$ receptor (PLA$_2$-R1) (autoimmune MN)
    - Planted antigen (captured by the kidney)
      - Endogenous: DNA, IgA$_1$
      - Exogenous: cationic BSA from cow milk binds to anionic components of the GBM (early childhood MN)
  - 2. Circulating immune complex formation
    - Endogenous: DNA, tumor
    - Exogenous: *Streptococcal, Staphylococcal* and viral antigens
In situ complexes
subepithelial deposits

Preformed circulating complexes;
subendothelial deposits

Endothelia
Podocytes
C3/C5a MAC

Oxidants*
Proteases*

T_{H1/2}

Cytokines
Chemokines

Basement membrane damage

Endocapillary proliferation

Extracapillary proliferation

N

Me
II. Non-immune complex-mediated injury
   ○ 1. Toxic injury to podocytes (see nephrotic syndrome, minimal change NP)
   ○ 2. Abnormalities of the alternative complement pathway (see MPGN)
   ○ 3. Necrotic lesions
      ■ Anti-neutrophil cytoplasmic antibody (ANCA): neutrophil-mediated free radical and proteolytic lesions (see RPGN-III)
   ○ 4. Hyperfiltration injury (see FSGS)
   ○ 5. Atubular glomeruli
      ■ Glomerulo-tubular disconnection as proximal tubules are sensitive to hypoxia (due to ischemia or tubulointerstitial diseases)
Classification of glomerular diseases by clinical picture

1. Nephrotic syndrome
   ○ Nephrotic protein loss, hypoalbuminemia, edema, hyperlipidemia, lipiduria

2. Acute nephritic syndrome
   ○ Hematuria, RBC casts, leucocytes, sub-nephrotic proteinuria, azotemia, oliguria, edema, hypertension, renal insufficiency

3. Rapidly progressive GN (RPGN)
   ○ Acute nephritis with rapidly progressive renal failure & proteinuria

5. Asymptomatic hematuria and/or proteinurin
   ○ Glomerular proteinuria, subnephrotic proteinuria

5. Chronic renal failure
   ○ Azotemia progressing to uremia
Nephrotic syndrome

● 1. Selective proteinuria
   ○ Albuminuria + selective protein loss (see deficiencies and consequences)
     ■ Proteinuria in children > 1 g/day/m\(^2\)
     ■ Proteinuria in adults > 3.5 g/day/1.73 m\(^2\)

● 2. Hypoproteinemia
   ○ Hypoalbuminemia if se albumin < 25 g/l (children), < 35 g/l (adult)

● 3. Edema formation – generalized
   ○ RAAS and ADH activation
   ○ Low level of ANP and BNP
● 4. Hyperliporoteinemia, lipiduria
  ○ Increased synthesis and secretion of LDL-C in the liver
  ○ Lp(a) ↑
  ○ Decreased catabolism of VLDL-C (TG ↑)
    ■ Apo CIII (LPL inhibitor) synthesis ↑ → block of VLDL-C metabolism
    ■ Apo CII (LPL activator) loss in urine → VLDL-C ↑
  ○ HDL3-C is increased, but it is lost into the urine before acquiring cholesterol into HDL2-C
  ○ Maltese cross in urine
● 5. Blood pressure and kidney function is usually normal
  ○ High blood pressure can develop in some cases
  ○ Conditions with high protein loss may lead to rapid decrease in GFR
● 6. Minimal hematuria may also occur
7. Deficiencies and diseases due to selective protein loss
   ○ Lipoprotein loss in urine → VLDL-C↑ (see Apo C-s before)
   ○ Thyroxin-binding globulin loss → „low thyroxin” syndrome
   ○ 25-OH cholecalciferol-binding globulin loss → lack of vitamin D, impaired bone mineralization
   ○ 1α-hydroxylation is impaired due to kidney disease → deficient vitamin D metabolism → low se Ca → secondary hyperparathyroidism
   ○ Transferrin loss → microcytic anemia
   ○ Other metal-binding protein loss → copper & zinc deficiency
○ Athero-thrombotic-embolic complications: in adults, renal or deep vein thrombosis
  ■ Increased clotting factor synthesis → ↑ viscosity
  ■ Increased fibrinogen level
  ■ Urinary loss of protein C, S and antithrombin-III
○ Increased susceptibility to infections (spontaneous bacterial peritonitis, cellulitis)
  ■ Loss of complement factor B and IgG
  ■ Defective opsonization
  ■ Altered T-cell function
○ Loss of light chains → kidney damage
Diseases with nephrotic syndrome

- Primary disease – see later
- Secondary (systemic) diseases
  - DM
  - Amyloidosis
  - Systemic lupus erythematosus (SLE)
  - Drugs (non-steroidal anti-inflammatory drugs, heroin)
  - Infections (malaria, syphilis, hepatitis B, C, HIV)
  - Malignant diseases (carcinoma, lymphoma)
  - Other (hereditary nephritis)
- Children: 95% primary, 5% secondary
- Adults: 60% primary, 40% secondary (DM, SLE, amyloidosis, pre-eclampsia)
• Podocytopathies
• 1. Minimal change disease
  ○ Altered innate & acquired \( \left( T_{\text{reg}} \downarrow \right) \) immune responses due to viral (?) infection
    ■ Cytokines are involved in generation of a plasma permeability factor(s) leading to reversible, steroid responsive podocyte injury
  ○ Other immunological abnormalities
    ■ IgE is often increased (food or inhalant allergies are implicated)
    ■ Often associated with primary immune diseases
  ○ Clinical presentation: classical nephrotic syndrome, usually reversible; rarely: hypertension, microscopic hematuria, atopy, GFR ↓
2. Focal segmental glomerulosclerosis (FSGS)
   ○ Focal: minority of glomeruli are involved; segmental: a portion of the glomerular globe is affected
   ○ Non-selective proteinuria or nephrotic syndrome (75-90% [children], 50-60 [adults]), oliguria, hypertension and progression to renal failure
   ○ Causes of FSGS
     ■ Primary: unknown cause, circulating plasma permeability factors mediated extensive podocyte injury
       □ Cardiotrophin-like cytokine 1, soluble urokinase-type plasminogen activator receptor (suPAR) or podocyte uPAR → activation of β₃-integrin in podocytes → foot process effacement & ↑ GBM permeability → proteinuria → FSGS & TGF-β-mediated cell and matrix proliferation
       □ Transcription factors & slit-pore membrane protein mutations (rare)
Circulating permeability factors ↑

Hereditary Proteinuria Syndromes

Transcription factor mutations: LMX1B (nail-patella sy), WT1 (Denys-Drash and Frasier’s sys)
Protein mutations: Nephrin, NEPH, podocin, CD2-AP, and α-actinin 4

HIV-1: direct damage to podocytes & tubular cells
Secondary causes of FSGS

- Apolipoprotein L1 (Apo-L1) variant mutations: very frequent in Yoruba ethnicity; this Apo-L1 can lyse *Trypanosoma brucei rhodesiense*, (a parasite causing sleeping sickness), but cause FSGS!
- Viral: HIV-1, CMV, EBV
- Drug-related: heroin, bisphosphonate, IFNs, Li, anabolic steroids
- Adaptive or hyperfiltration injury
  - With reduced kidney mass: low birth weight, ablation, aging kidney
  - With normal renal mass: hypertension, elevated BMI, vaso-occlusive diseases
  - In the short term compensate for the decrease in nephron numbers and provide optimal GFR, but in the long run FSGS develops
  - Decrease in a. afferent resistance – increased intracapillary hydrostatic pressure – proteinuria, EC matrix accumulation TGFβ, AT-II, PDGF, CTGF (connective-tissue growth factor), endothelin → glomerular hypertension
Decrease in nephron number $\rightarrow$ Primary kidney disease or resection

$\uparrow$ pressure & flow $\rightarrow$ DM*, Hypertension**

Proteinuria A2 (micro)albuminuria

*NO production abnormally $\uparrow$ in DM; development of glomerular hypertension and hyperfiltration $\rightarrow$ $\uparrow$ filtration pressure, podocyte stress & compromised tubulo-glomerular feedback (TGF)

**Abnormal response in hypertension: Physiologically: NO level $\uparrow$ upon salt ingestion to keep blood pressure normal

Decrease in nephron number

$\uparrow$ pressure & flow

FSGS

Kidney (nephron) protection

RAAS (renin receptor, ACE, AT2R) inhibition: $\downarrow$ glomerular hypertension and hyperfiltration $\rightarrow$ $\downarrow$ filtration pressure, podocyte stress & glomerular afterload

SGLT2 inhibition: normalization of filtration pressure, podocyte stress & restoration of TGF

$\downarrow$ protein intake
3. Membranous nephropathy (MN) / GP
   ○ Commonest nephrotic syndrome in adults often with microscopic hematuria, hypertension and impaired renal function (at the time of diagnosis chronic renal failure in 50% of the cases)
   ○ Causes
     ■ Primary (idiopathic)
       □ Antigen: neutral endopeptidase, PLA$_2$-R1 or BSA + genetic susceptibility
     ■ Secondary
       □ Infections: HBV, HCV, HIV, malaria, parasitic infestation, syphilis
       □ Tumors: lung, colon, gastric carcinoma
       □ Drugs: gold, captopril, NSAID
Antigen: e.g. PLA$_2$-R1 + antibody (IgG4)

↓

In situ subepithelial immune complex deposition

Complement system activation (C5b-9)

↓

Damage to the glomerular filtration barrier

↓

Mild, non-selective proteinuria & microscopic hematuria
Acute nephritic syndrome

- Due to immune mechanism (immune complex, anti-BM antibody or vasculitis) structural glomerular injury develops
- Major symptoms of acute nephritic syndrome (w rapid start)
  - 1. Hematuria – macroscopic, dysmorphic RBC-s in sediment
  - 2. Proteinuria < 3 g/day
  - 3. Azotemia, oliguria – see acute renal failure
  - 4. Edema around face, eye-lids – due to decreased filtration and Na retention (plasmin activates ENaC in principal cells of cortical collecting ducts)
  - 5. Hypertension
- Diseases with acute nephritic syndrome
1. Post-streptococcal GN (acute postinfectious GN)
   ○ After infections with β-hemolytic streptococci (impetigo, pharyngitis)
   ○ Circulating immune complex + complement fixation & PMN attraction and activation
   ○ Endothelial cell swelling (oliguria, edema, hypertension)
   ○ Increased anti-streptolysin-O [ASO] titer (1/3 of cases are normal !), decreased C3 level
2. Subacute bacterial endocarditis second (ongoing infection [Staphylococcus] when GN develops)
   ○ Immune complex-mediated disease
3. Lupus nephritis
STREPTOCOCCAL INFECTION

ANTIBODY FORMATION
Several weeks later – elevated ASO and ASK titer

ANTIGEN - ANTIBODY COMPLEX
Deposits in glomerulus

ACUTE INFLAMMATION AND DAMAGE

INCREASED PERMEABILITY OF CAPILLARY
Hematuria
Albuminuria

GLOMERULUS SWELLING
CONGESTION–DECREASED GFR
Oliguria and elevated serum urea

CELL PROLIFERATION

STIMULATION OF RENIN SECRETION
Elevated BP and edema

Majority

A few

Some

FULL RECOVERY
ACUTE RENAL FAILURE
CHRONIC GLOMERULONEPHRITIS (fibrosis)

DEATH
CHRONIC RENAL FAILURE
2. Membranoproliferative GN (MPGN)
   ○ Variable clinical manifestation: nephritic / nephrotic syndrome, asymptotic hematuria, proteinuria, RPGN, chronic renal failure with poor prognosis
   ○ Histological classification (see pathology)
   ○ Pathophysiology – common findings: low levels of complement
     ■ 1. Activation of the classical complement pathway by circulating or locally formed immune complexes
        □ Infections: viral (HBV, HCV, EBV [HHV-4]), bacterial* (endocarditis, shunt nephritis, abscesses), fungal, parasitic infestation
        □ Autoimmune disorders: SLE, Sjögren’s, RA
        □ Monoclonal gammopathy

*Mycobacterium tuberculosis, Coxiella burnetti, Mycolpasma pneumoniae, streptococci, nocardia, meningococcus
2. Increased and abnormal activation of the alternative complement pathway; mutation of or antibodies against to complement factors or regulatory proteins (C3GP/GN)

**Causes**

- Mutations of complement factor (C3) or complement regulatory proteins (Factor H, I)
- Antibody formation against
  - C3 convertase (C3 nephritic factor – C3NeF): blocks C3 convertase inactivation; deposition in GBM → nephritis
  - Factor H, I
- Partial lipodystrophy (laminin A / C mutation)
- PPARγ mutation in metabolic syndrome
Rapidly progressive glomerulonephritis (RPGN)

- Rapid loss of renal function (50% loss over 3 months)
- Nephritic syndrome
  - Proteinuria < 1 g/day
  - Hematuria, RBC casts
  - Blood pressure – often normal
- Classification of RPGN
  - RPGN-I: anti-GBM disease (5-20%)
    - Goodpasture’s syndrome (anti-GBM disease + pulmonary hemorrhage)
    - Anti-GBM disease (less common than Goodpasture)
    - Masugi nephritis (experimental)
○ RPGN-II: RPGN superimposed on any **immune complex** disease (25-45%)
  - Severe immune complex disease (IgA, post-Streptococcal, SLE, endocarditis, cryoglobulins – any of these disease can produce RPGN if it is severe enough)
○ PRGN-III: (pauci-immune) - **without immune complex** (34-65%); usually systemic vasculitis (ANCA positive)
  - Vasculitis syndromes (segmental necrotizing glomerulo-nephritis)
  - Anti-neutrophil cytoplasmic antibodies [ANCA]
    - pANCA to myeloperoxidase
    - cANCA to proteinase-3
Asymptomatic hematuria and/or proteinuria

- Asymptomatic (oligosymptomatic) hematuria (macroscopic) and/or proteinuria < 3 g/day
- Forms
  - 1. IgA nephropathy (Berger’s disease)
  - 2. Diffuse mesangial proliferative GN
    - Focal or diffuse (involving 50 percent or more of glomeruli)
    - Mesangial-cell proliferation is the dominant abnormality
  - 3. Focal proliferative and necrotic GN
    - Less than 50 percent of glomeruli have increased numbers of mesangial, endothelial, or epithelial cells
  - 4. Thin basement membrane GN
  - 5. Alport nephropathy
1. IgA nephropathy: the most common primary glomerular disease; mainly idiopathic; but can develop as a secondary disease
   - Primary/idiopathic: nephropathy of young man with sore throat, or after GI infection (food allergy and anti-α-galactosyl antibody (IgA₁) can be detected) with gross hematuria
   - Secondary: Henoch-Schönlein purpura, infections, liver, celiac, Chron’s and rheumatic diseases
   - Abnormal glycosylation of IgA₁ – defective elimination of immune complexes in the liver → the complexes deposited in the kidneys and cause GN
   - Renal failure in 1/3 of cases
A bnormalities of mucosal immune system

Galactose deficient IgA₁ → Galactose deficient IgA₁ autoantibody

Immune complex formation and deposition in the kidney

Activation of inflammatory pathways and the complement system in the kidney
Activation of mesangial cells, cytokine production,
ECM & mesangial cell proliferation

Complement activation
Mesangial immunedeposits

Glomerular sclerosis
2. Diffuse mesangial proliferative GN
   ○ Minor illness (mild SLE, resolving post-streptococcal disease) with good prognosis, often focal disease (< 50% involvement)
   ○ Mainly mesangial cells proliferate
   ○ IgA and IgM level is increased
   ○ Poor prognosis: Zuni Indians - 2-3% of the tribe is affected (IgG, IgM, IgA, and C3 ↑) – quick renal failure
There is a continuum between these syndromes. Diseases of glomerular injury can be placed along the spectrum from *nephrotic* to *nephritic*, with MCD, MN and FSGS on the nephrotic end.
Chronic glomerulonephritis – Chronic renal failure

- Irreversible loss of kidney function
  - Hematuria, proteinuria and hypertension are often detected
  - The progression is closely correlated with hypertension, proteinuria, smoking, obesity, dyslipidemia
  - In the background, often hyperfiltration damage and serum TGF-β, connective-tissue growth factor (CTGF) ↑

- Early start of multiplex therapy is justified to protect the kidney
  - Diminish progression of hypertension and proteinuria – ACE inhibitor, AR blocker
  - Cessation of smoking
  - Treat dyslipidemia – statins
  - Decrease salt and protein intake
  - Increase physical activity – achieve normal BMI
Chronic Renal Failure

- Diabetes mellitus
- Glomerulonephritis
- Other urologic cause
- Hypertension
- Cystic disease
- Unknown

- Poststreptococcal
- Rapidly progressive GN
- Membranous GN
- Focal glomerulosclerosis
- Membranoproliferative GN
- IgA

991
### Stages of chronic kidney disease

**Stages of chronic kidney disease**

<table>
<thead>
<tr>
<th>GFR categories (ml/min/1.73 m²)</th>
<th>Persistent albuminuria categories description and range</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A1</td>
</tr>
<tr>
<td></td>
<td>Normal to mildly increased</td>
</tr>
<tr>
<td>G1 Normal or high</td>
<td>≥90</td>
</tr>
<tr>
<td>G2 Mildly decreased</td>
<td>60–89</td>
</tr>
<tr>
<td>G3a Mildly to moderately decreased</td>
<td>45–59</td>
</tr>
<tr>
<td>G3b Moderately to severely decreased</td>
<td>30–44</td>
</tr>
<tr>
<td>G4 Severely decreased</td>
<td>15–29</td>
</tr>
<tr>
<td>G5 Kidney failure</td>
<td>&lt;15</td>
</tr>
</tbody>
</table>

**Slow progression of kidney disease**
- Asymptomatic
- Abnormal urine test: albuminuria, proteinuria, hematuria; ± hypertension

**Early renal insufficiency**
- Asymptomatic → fatigue, edema, nocturia
- Edema, anemia

**Late renal insufficiency**
- Loss of appetite, fatigue; dyspnea, worsening edema, pruritus
- MODS, electrolyte abnormalities
- Renal failure, uremia, ESRD
- Loss of appetite, fatigue; dyspnea, altered mental status
- **Life-threatening complications**: severe hypertension, pulmonary edema, acidosis, hyperkalemia, encephalopathy

**KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease**

Kidney International Supplements (2013) 3, 5–14; doi:10.1038/kisup.2012.77
Adaptive changes in chronic renal disease

● Adaptation by
  ○ I. Increased protein metabolites & falling GFR
    ■ 50% decrease in GFR; 50% increase of urea and creatinine levels (still within the reference range); \((U \times V = GFR \times P)\)
  ○ II. Increased tubular secretion
    ■ K excretion and ammonia genesis + H secretion
  ○ III. Decreased tubular reabsorption
    ■ Increased phosphate and Na excretion due to decreased reabsorption
  ○ Compensatory mechanisms are effective to ~90% GFR ↓, then uremia develops

● Maladaptation
  ○ Chronic kidney disease – mineral and bone disorder (formerly: renal osteodystrophy) and anemia
Urea-N (carbamid), creatinine: inverse relationships with GFR

PO$_4^{3-}$, urate, K$^+$, H$^+$: $\uparrow$ secretion, $\downarrow$ reabsorption

NaCl: constant plasma level
II. Increased tubular secretion
1. Ammonia genesis and H⁺ secretion ↑
   - if GFR falls to 25% - ammonia production increases by 4x
     - Initially: no pH abnormality (bones participate in buffering, bicarbonate level is low)
     - Later: non-anion gap metabolic acidosis: sulphate and phosphate level is normal
     - Late stage: anion-gap metabolic acidosis: sulphate and phosphate level is increased
2. K⁺ excretion↑
  ○ Aldosterone stimulates Na⁺-K⁺-ATPase in principal cells and colonic K⁺ excretion (~50%↑)
  ○ Osmotic diuresis: increased flow in the distal tubule

<table>
<thead>
<tr>
<th>K homeostasis</th>
<th>Physiologic conditions</th>
<th>Declining renal function</th>
</tr>
</thead>
<tbody>
<tr>
<td>GFR (ml/min)</td>
<td>125</td>
<td>5</td>
</tr>
<tr>
<td>Ultrafiltrate (l)</td>
<td>180</td>
<td>7,2</td>
</tr>
<tr>
<td>Se K⁺ level (mmol/l)</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Daily K⁺ handling by the kidney(mmol)</td>
<td>5 x 180=900</td>
<td>5 x 7,2=36</td>
</tr>
<tr>
<td>K⁺ intake / output (mmol)</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>K⁺ tubular secretion</td>
<td>11.1%</td>
<td>278%</td>
</tr>
</tbody>
</table>
III. Decreased tubular reabsorption

1. Disorders of phosphate metabolism

Mild, moderate (G 2-3) renal insufficiency

○ Less and less part of the filtered $P_i$ will be reabsorbed. The normal $P_i$ balance is maintained by PTH by inhibiting the tubular phosphate reabsorption (PTH stimulates $Na^+-P_i$ cotransporter endocytosis and $P_i$ is excreted) The PTH secretion is ensured by hypocalcemia due to the increased phosphate level

Severe (G4) renal insufficiency

○ 60-90% of the filtered amount of $P_i$ is excreted. Hyperphosphatemia develops because with standard $P_i$ intake the normal $P_i$ balance can not maintained due to the decrease in the number of functioning nephrons
Declining renal function

\[ \downarrow \text{1,25 (OH)}_2\text{D}_3 \]

\[ \downarrow \text{GI } \text{P}_i, \text{Ca}^{2+} \text{ reabsorption} \]

\[ \downarrow \text{blood } \text{iCa}^{2+} \text{ level} \]

PTH ↑

FGF-23 ↑

Phosphate excretion ↓

se phosphate level↑

Phosphaturia ↑

Bone resorption↑

Osteocytes FGF-23 production ↑

**Adaptive changes:** PTH & FGF-23 inhibits NaPi (NPT2) cotransporter function

Role of FGF-23 in maintaining normal se phosphate level

1. Increased renal phosphate excretion
2. Stimulation of PTH (renal phosphate excretion)
3. Suppression of calcitriol (GI phosphorus absorption↓)
2. NaCl and water metabolism disturbances

○ Nephron level
  ■ Decrease in Na and water reabsorption in the proximal tubules
  ■ Aldosterone is ineffective
  ■ Urea, creatinine level is increased → osmotic diuresis
  ■ Level of natriuretic factors – increased

○ Tubular level: Increased fractional water clearance in the functioning tubules
  ■ Isosthenurinla: urine specific gravity = protein-free plasma (1.008-1.012)
  ■ Nocturia is frequent due to compensatory polyuria
  ■ Decreased tolerance to water load or water deprivation
<table>
<thead>
<tr>
<th>Na homeostasis</th>
<th>Physiologic conditions</th>
<th>Declining renal function</th>
</tr>
</thead>
<tbody>
<tr>
<td>GFR (ml/min)</td>
<td>125</td>
<td>3</td>
</tr>
<tr>
<td>Ultrafiltrate (l)</td>
<td>180</td>
<td>4.3</td>
</tr>
<tr>
<td>Se Na level (mmol/l)</td>
<td>140</td>
<td>140</td>
</tr>
<tr>
<td>Daily Na handling by the kidney (mmol)</td>
<td>25200</td>
<td>602</td>
</tr>
<tr>
<td>NaCl intake / output (mmol)</td>
<td>120</td>
<td>120</td>
</tr>
<tr>
<td><strong>NaCl excretion</strong></td>
<td><strong>0.5%</strong></td>
<td><strong>20.0%</strong></td>
</tr>
<tr>
<td>Water homeostasis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ultrafiltrate (l)</td>
<td>180</td>
<td>4</td>
</tr>
<tr>
<td>Daily urine volume (l)</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Urine amount in % of ultrafiltrate</td>
<td>1.1%</td>
<td>50%</td>
</tr>
<tr>
<td>Osmolality (mOsmol/kg)</td>
<td>50-1200</td>
<td>250-350</td>
</tr>
<tr>
<td><strong>Possible daily urine volume (l)</strong></td>
<td><strong>15-0.5</strong></td>
<td><strong>2.4-1.7</strong></td>
</tr>
</tbody>
</table>
Uremia

- Uremia: clinical signs and symptoms of chronic renal failure [G 5]
  - Negligible GFR and all body systems are affected → azotemia [blood urea-N (BUN or carbamide) and creatinine level increased], oliguria, anuria, uremia
  - Requires dialysis and kidney transplantation
Major clinical signs in uremia

- Fluid electrolyte and acid-base disturbance
  - Volume overload
  - Metabolic acidosis
  - Hyperkalemia
- Ca, phosphorus problems
  - No active vitamin D
  - Phosphate retention → hypocalcemia
- Bone disturbances
  - Secondary hyperparathyroidism
  - Osteomalacia
- Cardiopulmonary
  - High blood pressure – over 80% of patients
  - Fibrinous pericarditis – constrictive pericarditis
  - Accelerated atherosclerosis
- Hemopoietic
  - Anemia
  - Poor platelet function
- GI
  - Nausea and vomiting
  - GI bleeding
  - Pancreatitis
- Skin
  - Pruritus
  - Uremic frost
  - Yellow color
- Neuromuscular
  - Peripheral neuropathy, encephalopathy, pica, poor appetite, emotional problems
- Infections
  - Staphylococcus, hepatitis C
- Other
  - Glucose intolerance
Progression of kidney disease

- Starvation
- Protein catabolism ↑
- Urea ↑
- Anorexia, nausea
- Vomiting
- Insufficient fluid intake
- Volume depletion
- GFR decrease
- Surgery
- Steroid administration
- Fever, GI bleeding
Bone physiology in a nutshell

- Normal bone: Normal bone mineralization depends on adequate supply of Ca and phosphate to the bone
  - Role of vitamin D in normal bone mineralization
    - Maintains Ca and phosphate homeostasis through its action on bone, GI tract and parathyroid gland
    - Vitamin D supplied in the diet or produced from sterol precursor (in skin upon UV exposure); active vitamin D is formed as a result of sequential hydroxylation (liver → kidney)
  - Dysfunction in any of the above metabolic steps may result in
    - Growing child: rickets and osteomalacia
    - Adults: osteomalacia and secondary hyperparathyroidism
Maladaptation in chronic kidney disease

I. Chronic kidney disease – mineral and bone disorder
   1. High bone turnover disease due to secondary hyperparathyroidism
      - ↓GFR leads to phosphate retention, which stimulates FGF-23 & PTH + parathyroid mass
      - FGF-23↑ & failing kidney → ↓calcitriol → ↓Ca^{2+} + phosphate retention stimulates PTH
         - ↓calcitriol stimulates PTH gene transcription
      - In the parathyroid gland due to FGF-23 receptor (klotho receptor) down-regulation, FGF-23 stops inhibiting PTH production
      - PTH is metabolized by kidney: progressive loss of kidney tissue leads to further increase of PTH level
      - Development of PTH resistance in the bones
      - PTH is uremic toxin: muscle weakness, cardiac fibrosis
Clinical picture of hyperparathyroidism
- Bone pain, fragility, brown tumors (bone cysts + blood), compression syndromes, erythropoietin resistance
- Hyperparathyroidism leads to development of osteitis fibrosa cystica (von-Recklinghausen’s disease) - pathology

2. Adynamic renal bone disease
- Low bone turnover in dialysis patients due to aluminum deposition (negatively affects osteoblastic activity and hydroxyapatite crystal formation) or excessive suppression of the parathyroid glands (relative hypoparathyroidism)
  - Relative hypoparathyroidism: ↑Ca load (Ca-containing phosphate binders, ↑Ca-dialysis solutions), vitamin D preparations, elderly (low bone turnover, osteoporosis, osteopenia), diabetics
3. Osteomalacia
   - **Low** bone turnover in combination with abnormally increased mineralization time (<35 → >100 days)
   - Aluminum, iron, cadmium and unknown factor deposition play a role
   - Now uncommon: no aluminum-containing antacids are used as phosphate binders and stringent & efficient techniques are used in preparing the dialysate (no Al)

4. Mixed uremic osteodystrophy with high or low bone turnover and abnormal mineralization

5. CV diseases
   - PTH & FGF-23 ↑
     - □ Klotho deficiency: soft tissue calcification, ↑mortality, LV hypertrophy
     - □ PTH ↑: increased cardiomyocyte loss
   - Hyperphosphatemia and hypercalcemia → increased vascular calcification
   - Ischemic vascular diseases
   - Heart failure, hypertension, pericardial disease
II. Normocytic, normochromic anemia (G 3-4)

- Erythropoietin deficiency due to progressive loss of kidney tissue
- Other causes
  - Toxic effect of uremia on precursor cells
  - Reduced red cell survival
  - Increased blood loss due to hemodialysis, capillary fragility
  - Reduced iron, B$_{12}$ and folic acid intake
- Abnormal hemostasis
  - Prolonged bleeding time, platelet dysfunction etc
In the beginning of the disease, conditions such as DM, hypertension, chronic kidney disease, proteinuria, and albuminuria increase the risk of progression to chronic heart failure, coronary heart disease, left ventricular hypertrophy, and atherosclerotic CVDs. If left untreated, this progression can lead to end-stage kidney disease and chronic heart failure.
Renal tubular transport disorders

• 1. Selective proximal tubular transport disorders
  ○ 1. Selective glucosuria of genetic origin (autosomal recessive)
    ■ Primary renal glucosuria or benign glucosuria (up to 160 g/day)
      □ Glucose transporter gene (SGLT2) inactivating mutation
      □ In T2DM therapy: inhibition of SGLT2 → glucosuria; ↓blood sugar, ↓glucotoxicity, ↓bw, ↓blood pressure
    ■ Congenital glucose/galactose malabsorption
      □ Rare, glucose transporter gene (SGLT1) defect; intestinal/kidney glucose reabsorption is impaired
      □ Mild glucosuria (10 g/day)
Glucose transport is saturable! $T_m$ glucose

Other symporters:
- Na-Phosphate
- Na-Citrate
- Na-Amino acid
- Na-Lactate

Fanconi-Bickel syndrome: GLUT2 gene mutations

GLUT-2

GLUT-1

SGLT1

SGLT2
2. Aminoaciduria

<table>
<thead>
<tr>
<th>Amino acid</th>
<th>Disease</th>
<th>Manifestation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>α-amino acids</strong> (neutral tryptophan and others)</td>
<td>Hartnup disease</td>
<td>Pellagra like disorders</td>
</tr>
<tr>
<td><strong>Dibasic amino acids</strong> (cystine, lysine, ornithine and arginine)</td>
<td>Cystinuria</td>
<td>Recurrent nephrolithiasis</td>
</tr>
<tr>
<td><strong>Dicarboxylic acids</strong> (glutamic and aspartic acid)</td>
<td>Dicarboxylic aminoaciduria</td>
<td>Fasting hypoglycemia, ketoacidosis</td>
</tr>
<tr>
<td><strong>Iminoglycines</strong> (OH proline, glycine)</td>
<td>Iminoglycinuria</td>
<td>No known disease</td>
</tr>
</tbody>
</table>

3. Renal phosphate wasting

- X-linked hypophosphatemic rickets (osteomalacia)
  - Hypophosphatemia due to decreased proximal transport of phosphate to tubules in presence of humoral phosphaturic factor (FGF-23)
  - Low levels of calcitriol – disturbed vitamin D metabolism
- Oncogenic hypophosphatemia: humoral phosphaturic factor, different from PTH (does not act on cAMP)

4. Renal tubular acidosis (RTA-2)
Phosphaturic effect:
**PTH** increases Na\(^+\)-P\(_i\) symporter (NPT2) endocytosis → P\(_i\) reabsorption Ø → P\(_i\) excretion ↑,
**FGF-23**: inhibits NPT2 symporter

In chloride reabsorption **formate** plays an important role:
HCOO\(^-\) + H\(^+\) → CH\(_2\)O\(_2\) (formic acid)
Anion: formate (HCOO\(^-\)) hydroxide (OH\(^-\)), oxalate, bicarbonate, sulfate
II. Non-selective proximal tubular transport disorder: Fanconi syndrome
   ○ Increased membrane permeability allows back leak of solutes from the proximal tubular cell to tubular lumen: glucosuria, aminoaciduria, RTA-2, phosphaturia and uricosuria
      ■ Congenital: faulty genes, inborn error of metabolism (cystinosis)
      ■ Acquired: secondary to toxic insult (drug, light chain)

III. Henle loop thick ascending loop: Bartter syndrome

IV-V. Distal tubules & medullary collecting ducts (see table)
## Inherited disorders affecting renal tubular and solute transport in the distal tubule and collecting duct

<table>
<thead>
<tr>
<th>Disease</th>
<th>Mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gitelman syndrome</td>
<td>Sodium chloride cotransporter</td>
</tr>
<tr>
<td>Pseudoaldosteronism (Liddle’s syndrome)</td>
<td>Epithelial sodium channel β and γ subunits</td>
</tr>
<tr>
<td>Recessive pseudohypoaldosteronism type 1</td>
<td>Epithelial sodium channel, α, β and γ subunits</td>
</tr>
<tr>
<td>Pseudohypoaldosteronism type 2 (Gordon’s hyperkalemia-hypertension syndrome)</td>
<td>Kinases: WNK-1, WNK-4 [with-no-lysine kinase]</td>
</tr>
<tr>
<td>X-linked nephrogenic diabetes insipidus</td>
<td>Vasopressin V$_2$ receptor</td>
</tr>
<tr>
<td>Nephrogenic diabetes insipidus (autosomal)</td>
<td>Water channel, aquaporin-2</td>
</tr>
<tr>
<td>Distal renal tubular acidosis (RTA-1)</td>
<td>Anion exchanger-1(Cl-HCO$_3$ antiporter)</td>
</tr>
<tr>
<td></td>
<td>Anion exchanger-1(Cl-HCO$_3$ antiporter)</td>
</tr>
<tr>
<td></td>
<td>Proton ATPase, β1 subunit</td>
</tr>
<tr>
<td></td>
<td>Proton ATPase, 116-kD subunit</td>
</tr>
</tbody>
</table>
Thick ascending segment (TAL)
25% Na reabsorption
Na-K-2Cl cotransporter (NKCC)
Loop diuretics

Distal tubule
5% Na reabsorption
Na-Cl cotransporter (NCC)
Thiazide diuretics

Bartter’s syndrome

Gitelman’s syndrome
The kidney achieves normal acid/base balance using three main mechanisms:

I. Proximal tubular reabsorption of $\text{HCO}_3^-$; (No net acid excretion)

II. Proximal tubular synthesis, tubular transport and subsequent net excretion of ammonium ions ($\text{NH}_4^+$; $pK = 9.3$), which ensures $\text{HCO}_3^-$ regeneration within the kidney

III. Distal tubular secretion of $\text{H}^+$ with buffering, using predominantly phosphate ($pK = 6.8$), creatinine ($pK = 5.0$) and urate ($pK = 5.8$)
Bicarbonate transport in TAL is very similar to proximal tubule. On the basolateral side, an additional symporter $K^+\text{-HCO}_3^-$ facilitates bicarbonate transport.

1. Buffering $H^+$ ions
2. Conserving $\text{HCO}_3^-$
Role of intercalated cells in pH regulation

α intercalated cells – predominate in acidemia
Actively secrete hydrogen ions
Reabsorb bicarbonate

In the distal nephron the intercellular junctions are non-permeable, so it is possible to sustain a pH gradient (minimum pH is 4)

β intercalated cells – predominate in alakalemia
Secrete bicarbonate into the lumen (like type A cells turned around)

Type β intercalated cells are found in large numbers in animals whose metabolism generates base - e.g. ruminants

EC protein hensin mediates the adaptation

\[
\text{HPO}_4^{2-} + \text{H}^+ = \text{H}_2\text{PO}_4^-
\]

\[
\text{NH}_3 + \text{H}^+ = \text{NH}_4^+
\]
• Net acid excretion (NAE) \( NAE = (TA) + (NH^+_4)_u - (HCO^-_3)_u \)
  ○ \( TA = \) titratable acidity measured by the amount of alkali required to neutralize urine pH to physiological pH (7.4) - 20-30 mmol/day (about 40 % of maximum capacity)
  ○ \( (NH^+_4)_u = \) ammonium ion excretion - 50-60 mmol/day (about 15 % of maximum capacity)
  ○ \( (HCO^-_3)_u = \) negligible urine bicarbonate loss

<table>
<thead>
<tr>
<th>Increased ammonium synthesis</th>
<th>Decreased ammonium synthesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolic acidosis</td>
<td>Metabolic alkalosis</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>Hyperkalemia</td>
</tr>
<tr>
<td>Glucocorticoids</td>
<td>Low supply of glutamine</td>
</tr>
<tr>
<td></td>
<td>Reduced kidney mass</td>
</tr>
</tbody>
</table>

○ (HCO^-_3)_u = negligible urine bicarbonate loss
Ammonium ($\text{NH}_4^+$) generation

1. Secretion in the proximal tubules
2. Reabsorption in the loop of Henle
3. Diffusion and trapping in medullary collecting tubule
Renal tubular acidosis (RTA)

- In spite of normal or only mildly reduced GFR, normal anion gap (hyperchloremic) metabolic acidosis develops, because the tubules are not able to perform their physiologic role in acid-base regulation.

- Forms of RTA
  - Hypokalemic forms
    - Proximal tubular or RTA type-2 (RTA-2)
    - Distal tubular or RTA type-1 (RTA-1)
  - Hyperkalemic forms or RTA-4 (distal tubular)
    - Hypoaldosteronisms (it is RTA-4 in the strict sense)
      - In general, acidosis and hyperkalemia less severe
    - Distal tubule voltage defects (Na reabsorption disturbances)
### Hyperchloremic (normal anion gap) metabolic acidosis in RTA

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Type 2 RTA</th>
<th>Type 1 RTA</th>
<th>Hyperkalemic RTA</th>
</tr>
</thead>
</table>
| **Primary defect** | Reduced **proximal** HCO₃ reabsorption | Impaired **distal** acidification | •RTA-4: ↓ aldosterone secretion  
• Aldosterone resistance  
• ↓ Na reabsorption in the distal tubule (voltage defect) |
| **Plasma HCO₃** | Low (12 to 20 mmol/L) | Low (may be below 10 mmol/L) | Low (> 17 mmol/L in hypoaldosteronism) |
| **Plasma K**    | Reduced, made worse by bicarbonaturia induced by alkali therapy | Usually hypokalemic; which largely **corrects** with alkali therapy | Increased |
| **Urine pH**    | > 5.3 if the se HCO₃ exceeds the tubule's HCO₃ reabsorptive threshold.  
< 5.3 when the se HCO₃ is reduced to levels that can be largely reabsorbed despite defective proximal tubule reabsorptive mechanisms | > 5.3 | > 5.3 with voltage defects  
< 5.3 with hypoaldosteronism |
### RTA etiology

<table>
<thead>
<tr>
<th></th>
<th>RTA-2</th>
<th>RTA-1</th>
</tr>
</thead>
</table>
| **Congenital**   | • Transporter disturbances responsible for acidification (isolated RTA-2)  
                   • Na-H antiporter                                                       | • Autosomal dominant and recessive disorder of basolateral Cl-HCO$_3$ antiporter |
|                  | • Na-HCO$_3$ (NBCe1) symporter: + ocular abnormalis and short stature   | • Disorder of apical H-ATPase with neural deafness or with normal hearing |
|                  | • Carbonic anhydrase type 2 (CA-II) deficiency: + osteopetrosis, brain calcification and mental retardation |                                                                       |
|                  | • Fanconi syndrome                                                      |                                                                       |
|                  | • Cystinosis                                                           |                                                                       |
| **Acquired**     | • Multiple myeloma/light chain disease                                 | • Autoimmune diseases                                                 |
|                  | • CA-II inhibitors: acetazolamide; topiramate                           |   • Sjögren’s syndrome (lack of H-ATPase or auto antibodies against CA-II) |
|                  | • Nephrotoxic drugs: ifosfamide                                        |   • RA                                                                |
|                  |                                                                       |   • Hypercalciuria                                                      |
|                  |                                                                       |   • Drugs: amphotericin-B, ifosfamide                                   |
|                  |                                                                       |   • Toluol (sniffing)                                                   |
|                  |                                                                       |   • Hereditary spherocytosis or ovalocytosis: Cl-HCO$_3$ antiporter is present in RBC membrane |
Proximal RTA
RTA-2

Bicarbonate, K and volume loss in the distal tubules

Na-Phosphate Na-Citrate
Na-Amino acid Na-Lactate

Na/H antiporter 66%
H-ATPase 33%

Na/3HCO₃ symporter

3Na-2K-ATPase

△ Indicates possible cellular mechanisms responsible for Type 2 proximal RTA
RTA-2

- Non-specific damage to the proximal tubular epithelium
  ○ Affects proximal cell acid secretion i.e. failure of bicarbonate reabsorption
- Dominant features: bicarbonaturia, hypovolemia & hypokalemia
  ○ Due to HCO₃⁻ loss: a new steady state of se HCO₃⁻ is achieved at a lower HCO₃⁻ level (14-20 mmol/l)
  ○ Hypokalemia: luminal flow of Na and HCO₃⁻ is high to the main site of K secretion in the distal tubules. Na and HCO₃⁻ loss causing moderate hypovolemia and secondary hyperaldosteronism; aldosterone takes back Na and increases K secretion
    - Alkaline therapy (NaHCO₃ or Na citrate), increases hypokalaemia, so K must be replenished, always!
  ○ No nephrocalcinosis! due to decreased citrate reabsorption in the proximal tubules
Distal RTA
RTA-1

Possible cellular causes of distal RTA-1

α intercalated cell (cortical and medullary collecting duct)

Amphotericin B

H^+-ATPase

H^+-K^+ ATPase

Blood

Lumen
RTA-1

- Proximal bicarbonate handling is intact (no bicarbonate loss) the disorder is confined to the distal part
- Causes of RTA
  - 1. Proton pump deficiency; cortical and medullary collecting duct $H^+$ handling is deficient in $\alpha$-intercalated cells. The deficiency is mainly due to absent or dysfunctional H-ATPase and lesser degree to H-K-ATPase dysfunction or absence
  - 2. Increased luminal permeability: the $H^+$ secretion is normal, followed by back leak of $H^+$ (amphotericin B)
Leading symptom: electrolyte depletion

○ Due to insufficient H\(^+\) secretion, hypokalemia develops
  □ Physiological explanation: the Na reabsorption in the collecting tubules based on the principle of electron neutrality: uptake with anions (Cl or HCO\(_3\)) or with cation depletion (H or K)
  ■ Further hypokalemic factor is that due to acidosis more Na enters into the distal tubule (Na loss → hypovolemia), and aldosterone causes loss of K
  ■ Alkaline therapy reduces / eliminates K loss (decrease of H loss, and inhibition of aldosterone secretion)

○ Progressive accumulation of acids over years → increased bone buffering → nephrocalciosinsis and kidney stone formation.

Possible mechanisms

■ Urine pH > 5.3
■ Hypercalciuria
■ Low urinary excretion of citrate – due to increased or normal proximal tubular reabsorption
Nephrocalcinosis and RTA-1

Hypokalemia

- Decreased urinary citrate excretion
  - Impaired urinary acidification
    - Alkaline urine
  - Hyperchloremic metabolic acidosis
    - Reduced renal tubular calcium reabsorption
      - Hypercalciuria
        - CaPO₄ precipitation
    - Resorption of bone mineral
      - Hypercalciuria
### Etiology of hyperkalemic RTA

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Details</th>
</tr>
</thead>
</table>
| **Reduced aldosterone production** | • Hyporeninemic hypoaldosteronism  
Kidney diseases: DM, chronic interstitial nephritis  
Drugs: NSAID, calcineurin inhibitors  
Volume expansion (acute GN)  
• RAAS inhibition (renin, ACE, ATR)  
• Chronic heparin Rx (impairs aldosterone synthesis, heparin damages *zona glomerulosa* cells)  
• Primary adrenal insufficiency (aldosterone and cortisol defect)  
• Congenital conditions  
  - Congenital hypoaldosteronism (21 hydroxylase deficiency and isolated hypoaldosteronism)  
  - Gordon syndrome (Pseudohypoaldosteronism type 2): increased function of distal tubular Na-Cl cotransporter (WNK defect)  
  - Lack of aldosterone: hyporeninemia or abnormal aldosterone synthesis |
| **Aldosterone resistance** | Inhibition of basolateral Na/K ATPase or apical ENaC  
  - Spironolactone, eplerenone, amiloride, and triamterene  
  - Antibiotics: trimethoprim, pentamidine  
Pseudohypoaldosteronism type 1 (mineralocorticoid receptor resistance or Na channel abnormalities)  
Voltage defects  
  - Markedly reduced distal Na delivery (severe hypovolemia)  
  - Acquired or congenital defects in Na reabsorption by the distal tubule principal cells (obstructive uropathy), SLE, and sickle cell disease |
**Distal RTA**

**RTA-4**

**Lumen**

- **Na⁺**
- **K⁺**
- **Cl⁻**
- **H⁺**
- **OH⁻**
- **H₂O**

**Blood**

- **3Na⁺**
- **2K⁺**

**α intercalated cell**

- **Mineralocorticoid receptor**

**Principal cell**

- **Potential difference**

**Aldosterone lack**

- **Aldosterone resistance**
RTA-4

- The most common RTA in adults
- In the collecting tubules, disrupted Na absorption results in metabolic acidosis and hyperkalemia
  - Na reabsorption is impaired → no luminal negativity for Na reabsorption → failure of H\(^+\) and K\(^+\) secretion → H\(^+\) and K\(^+\) ↑
  - Hyperkalemia reduces ammonia genesis in the proximal tubules
Water-reabsorption (main site)
Aldosterone – site of action
Na reabsorption
K secretion

K-sparing diuretics: amilorid, triamterene
Mineralocorticoid receptor Antagonists (spironolactone)

Type A:
\[ H^+ \text{ secretion} \]
\[ \text{HCO}_3^- \text{ reabsorption} \]

Type B:
\[ \text{HCO}_3^- \text{ secretion} \]
\[ H^+ \text{ reabsorption} \]

*Amilorid-sensitive epithelial Na channel (ENaC): upregulated by aldosterone; stimulated by proteolytic enzymes [eg plasmin] and blocked by potassium-sparing diuretics