§ 3 Chronic Renal Failure (CRF)

1. Concept

CRF is a complex pathophysiologic process and is an important clinical syndrome. It is characterized by progressive and irreversible destruction of renal tissue. The consequences of renal destruction exhibit in progressive deterioration of the filtration, reabsorptive functions and endocrine functions of the kidney. It is characterized by disorders of water, electrolyte, acid-base balance, besides endocrine dysfunction. Damage usually proceeds slowly, terminating in death when a sufficient number of nephrons have been destroyed.

The end stage of CRF is uremia.
Feature suggesting CRF

① Symptoms lasting longer than 3 months (e.g., malaise, nocturia);
② Increased BUN or serum creatinine documented months earlier. A previous systemic disease (e.g., diabetes mellitus, hypertension) or a history of kidney disease suggests that the azotemia may be chronic;
③ Normocytic normochromic anemia;
④ *Small kidneys* (less than 10 cm) on renal ultrasound.
Figure 13.39. Left, Chronic glomerulonephritis (granular shrunken kidney). Right, Normal kidney.
3. Clinical Course of CRF

The clearance rate of endogenous creatinin is the best diagnostic parameter of chronic renal failure.

\[ \text{Clearance creatinine} = \frac{U_{cr} \times V}{P_{cr}} \approx \text{GFR} \]

(1) Stage of decreased renal reserve (Silent stage)

- \( C_{cr} > 30\% \);
- The \( \text{GFR} \) is reduced to 50 to 75% of the normal value.
- \( \text{Serum creatinine} \) (Cr) and \( \text{BUN} \) are in normal range without symptoms and signs nomal,
- Renal reserve ↓.
(2) Stage of renal insufficiency

Ccr = 25~30% ;

The GFR declines to less than 50% of normal value in this stage.

Serum creatinine concentrations and BUN begin to rise significantly,

Evidences at this stage are mild anemia, Polyuria, Nocturia, hyposthenuria, and an elevation of the serum concentration of parathyroid hormone (PTH).

Azotemia and metabolic acidosis can occur at this stage with dehydration and infection.
(3) Stage of renal failure

Ccr = 20~25%;

This stage is associated with a further reduction of the GFR to 10 to 25% of normal value. Cr and BUN are obviously elevation.

Aggravating symptoms of CFR may appear, such as Marked anemia, severe acidosis, hyperphosphatemia, hypocalcemia.
(4) **Stage of uremia**

**Ccr < 20%;**

Uremia is the end-stage of renal failure that occurs when about **90%** of the nephron mass has been destroyed. The **GFR** is **less than 10%** of normal value. The **serum creatinine** and **BUN** levels **rise very sharply** in this stage.

A series of **uremic symptoms**.

The homeostasis **dysfunction** of **water, electrolyte, acid-base** and **endocrine dysfunction** are always accompanied with **autotoxication syndrome of endogenous poisons**.

The uremic syndrome affects every system in the body.
4. Pathogenesis of CRF

1. Intact nephron hypothesis

Intact nephron↓/Destroyed nephron↑↑→ CRF

Intact nephron:
- Glomerular hypertrophy
- Renal tubule dilation
(2) *Trade-off hypothesis*

“Trade-off” refers a process that organism develops a new lesion by correcting an old damage. As the nephrons are progressively destroyed, increased blood concentration of some solutes stimulates secretion of some related regulatory factors (such as hormones) in order to maintain the excretion function. At the same time, however, high blood levels of the regulatory factors will result in further metabolic disorder. It is termed “trade-off”.
Serum P (Normal) ← Urinary P ↑ ← P absorption ↓

Nephron↓ ↓
→ P. F↓ → S. P ↑ → S Ca^{2+} ↓ → PTH ↑

GFR ↓ ↓ ↑ ↓
P release ← dissolution of bone → Ca^{2+} release

Osteodystrophy

(surviving nephrons)
(3) Glomerular hyperfiltration hypothesis

In the single nephron compensatory intraglomerular hyperfusion and hyperfiltration, together with intraglomerular hypertension result in progressive glomerular sclerosis and eventual glomerular death. Several hormones, growth factor, cytokines (AT II, TGF-β, IL-1, TNF) influence mesangial and interstitial cell proliferation and extracellular matrix deposition → nephrons ↓ → vicious circle → CRF
Lesion of tubular and interstitial cells

Hypermetabolism

↓

Calcium overload; oxygen free radical↑

↓

Renal tubule and mesenchymocyte injury

↓

Renal tubule atrophy; mesenchmal fibrosis

↓

CRF
5. Alterations of metabolism add function

(1) Disturbance of water, electrolyte and acid-base

① Disorders of water balance

* **Nocturia** (the urine volume in night time is about 2~3 times in day time, or more than 750ml) at GFR < 40ml/min

* **Polyuria** (>2000ml/d) at GFR < 30ml/min

* **Hyponatremia** (<1.020)

* **Isosthenuria** (1.008 ~ 1.012→1.010, 285mOsm/L)

* **Oliguria** (<400ml/d) at GFR = 5~10ml/min

* **Proteinuria**, **Cylindruria**
Urinary osmolality

- Hyposthenuria
- Isostheuria

Graph showing normal urinary specific gravity compared to hyposthenuria and isostheuria.
*Mechanisms of Polyuria*

a. Surviving hypertroph glomerulus compensatory filtration

b. Henle’s loop injury → dysfunction of urinous concentration

c. Osmotic diuresis due to compensative increase of solute in the crude urine filtrated through the surviving nephrons.
Disorders of electrolyte metabolism

- Disorders of **sodium metabolism**
  - **Hyponatremia** (when polyuria)
  - ↓
  - **Hypernatremia** (When oliguria)

- Disorders of **potassium metabolism**
  - Serum potassium concentration is usually maintained within normal range until GFR < 25%.
  - Polyuria in early CRF → **hypokalemia**.
  - Oliguria in end-stage CRF → **hyperkalemia**.
Disorders of **calcium-phosphate metabolism**

**Hyperphosphatemia**

Serum [P] in adult > 1.61 mmol / L  
Serum [P] in children > 1.90 mmol / L

**Mechanism**

1. **GFR**:  
   CFR → The nephrons progressively destroyed → GFR↓↓↓→ < 20~30 ml/min → phosphorus retention ↑  
   → serum [P]↑

2. **Secondary elevation of PTH**:  
   Serum [P]↑ → serum [Ca]↓ → PTH ↑ → osteolysis  
Hypocalcemia

Serum level of free calcium < 1 mmol/L

or

Total calcium level < 2.2 mmol/L

Mechanism

a. Hyperphosphatemia: \([\text{Ca}] \times [\text{P}] = \text{coefficient}\), 
   
   \([\text{P}] \uparrow \rightarrow [\text{Ca}] \downarrow\)

b. Disorder in Vit.D activation: \(1\alpha\) hydroxylase \(\downarrow\)

c. PTH↑↑↑ → Bone resistant to PTH and abnormal calcification.

d. Calcitonin secretion↑

e. Some toxic substances damage GI to reduce \(\text{Ca}^{2+}\) absorption.
Metabolic acidosis

Impaired ability of the kidney to excrete, $\text{H}^+/\text{NH}_4^+$ excretion is decreased

$\text{GFR} \downarrow \rightarrow \text{retention of phosphate, sulfate and other organic anions}$
(2) **Azotemia**

- Non-protein nitrogens (NPN) > 28.6 mmol/L or > 40 mg/dl
- Blood urea nitrogen (BUN) > 3.75~7.14 mmol/L or > 10~20 mg/dl
- Plasma creatinine (Scr) > 0.9~1.8 mg/dl
  - [Creatance clearance = Ucr \times V\text{(ml/min)} / Pcr ≈ GFR.]
- Blood uric acid > 3~5 mg/dl
Renal hypertension

a. Sodium-dependent hypertension
b. Renin-dependent hypertension
c. $\text{PGE}_2 \downarrow, \text{PGA}_2 \downarrow$ and KK-K↓→hypertension
Renal diseases

↓

GFR ↓ Renal blood flow ↓ kidneys injury

↓

Na⁺,H₂O excreted ↓ Renin ↑ PGE₂,PGA₂ ↓

↓

Na⁺,H₂O retention ← ADS ↑ ← AT II ↑

↓

Blood volume ↑ Peripheral resistance ↑

↓

C.O ↑ → Hypertension
(4) Renal osteodystrophy
   Children $\rightarrow$ renal rickets
   Adult $\rightarrow$ osteoporosis, osteomalacia, fibrosa osteitis
Chronic Renal Failure

↓

GFR↓

↓

Elimination of phosphate↓

Acidosis

↓

Plasma phosphate↑

↓

Gastrointestinal absorption of calcium↓

↓

Hypocalcemia

↓

Secondary Hyperparathyroidism

↓

Renal osteodystrophy
Chronic renal failure

↓

Loss of nephron mass

↓

Renal biosynthetic capacity

↓

Renal excretory function↑

↓

Renal production

↓

Retention of toxic metabolites

↓

Metabolic acidosis

↓

Hyperphosphatemia

↓

Hypocalcemia

↓

Calcium x phosphate producte > 60

↓

Circulating 1,25(OH)₂D₃

↓

Responsiveness of bone to 1,25(OH)₂D₃

↓

Dissolution of bone buffers

↑

PTH secretion

↓

Gut absorption

↓

Impaired bone growth

↓

Osteomalacia

↓

Bone decalcification and osteoporosis

↓

Remodeling and redistribution of bone (osteosclerosis)

↓

Pathogenesis of renal osteodystrophy

↓

Gut absorption impairment of calcium

↓

Impaired bone growth in children (renal rickets)

↓

Osteitis

↓

Matastatic calcification
Renal osteodystrophy
(5) Renal anemia

**Mechanism:**

a. Reducing erythropoieten;

b. Cumulation of toxic substances → inhibit the ability of the bone marrow to make RBCs;

c. Bleeding induced by inhibiting of renal poisons on platelet function;

d. Toxic substances destroy RBCs;

e. Reducing absorption or utilization of iron and protein.

(6) Tendency to hemorrhage

**Mechanism:**

a. Platelet coagulation decreased

b. Renal poisons accumulation (such as urea, Carbamidine, etc.) inhibit platelet to release PF$_3$
§ 4 *Uremia

1. **Concept** of uremia

Uremia is the most severe stage of acute or chronic renal failure. Besides disorders of water and electrolyte metabolism and acid-base imbalance, and renal endocrine function, the patients with uremia will manifest a series of *autotoxication syndroms* caused by accumulation of endogenous poisons.
2. **Clinical manifestation** of uremia

(1) **Neurological signs**

- **Uremic encephalopathy**
  
  From mild sleep disorders, impairment of mental concentration, loss of memory, errors in judgment, and neuromuscular irritability to asterixis, stupor, seizures, and coma in end uremia.

- **Uremic peripheral neuropathy**
  
  "Restless legs syndrome" should be regarded.

(2) **Cardiovascular signs**

- **Hypertension, arrhythmia, pericarditis** → pericardial friction rub, and/or pericardial tamponade.
(3) **Respiratory signs**

- **Dyspnea**
- **Kussmaul breath** — deep and big breath
- **Uremic pneumonia**, fibrinous pleurisy
- **Pulmonary edema**

Urea is decomposed into ammonia by salivary enzyme, resulting in the smell of ammonia in exhalation.

(4) **Gastrointestinal signs**

- **Anorexia**, **Nausea**, **Vomiting**, **diarrhoea**.

Uremic gastroenteritis is characterized by **mucosal ulcerations** with blood loss.

(5) **Endocrine signs**

- **Sexual dysfunction**, including infertility in women
(6) Signs of skin

Pallor due to anemia; gray discoloration.

When urea concentration is extremely high, evaporation of sweat leaves a residue of urea termed “uremic frost”.

![Image of uremic frost](image-url)
(7) **Immunity signs**
   Immunosuppression
   Increased susceptibility to infections

(8) **Disorders of metabolism**
   ① **Glucose metabolism**
      In about 50% patients appear the **glucose intolerance**
   ② **Protein metabolism**
      The patients with uremia often appear signs of **negative nitrogen balance**. such as hypoproteinemia, emaciate, cachexia etc..
   ③ **Fat metabolism**
      Patients with uremia have increased content of triglyceride in blood resulting in **hyperlipidemia**.
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<td>Electrolytic</td>
<td>Hyperkalemia, Metabolism, edema, Hyperphosphatemia, Metabolism, edema, Hyperphosphatemia</td>
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3. **Pathogenesis** of uremia

(1) **Uremic Toxins**
   ① Urea
   ② Guanidine compound
   ③ Amines and phenols
   ④ Middle molecules (mol. wt. 500~5000D)

(2) **Overproduction of counter-regulatory Hormones**
   Parathyroid hormone (PTH)

(3) **Underproduction of renal hormones**
   Erythropoietin, 1-hydroxylation of vitamin D₃
§ 5 Principles of treatment for chronic renal failure and uremia

1. **Conservative management**

   The conservative treatment consists of measures to prevent or retard the deterioration in renal function and to help the body in compensating for the existing impairment.

   For the treated of CRF and uremia are as following:
   1. To treat the primary renal disease.
   2. To treat reversible aggravating factor.
   3. To prevent or slow the progression of real disease.
   4. To prevent and treat end stage renal failure.
   5. Other treatment.
2. Dialysis or renal transplantation

(→) Dialysis

(1) Peritoneal dialysis
(2) Hemodialysis

(←) Transplantation
Case 1

Mr. Ma, Male, 22 years old, hospitalized in Oct. 27, 1997. **Left thigh trauma** and **endless bleeding**. **Dottiness**, pale, Bp was not detectable, Weak heart beats, wound on left thigh 5 × 5 cm, bleeding.

Treatment after hospitalized: Blood transfusion 8000 ml, operation to inosculate nerves and vessels, inject cedilanid, hydrogenate-cortisone and **isoproterenol**.

On Oct. 28, Bp 100/80mmHg, P 130/min, conscious, urine 2-30ml/h, Treatment with mannitol, duretics, take orally magnesium sulfate, inject sodium bicarbonate, glucose plus insulin, but still **anuria** with **aggravated azotemia**, **acidosis** and **hyperkalemia**.
On Nov. 6, Bp 120/80mmHg, P 128/min, NPN 168 mg/dl, CO₂ CP 40vol%, plasma K⁺ 6.2mmol/L, specific gravity of Urine 1.010, urinary protein (++), RBC(++++), WBC(++).

After dialysis for 7h, NPN 79mg%, CO₂ CP 38.1vol/dl, Plasma K⁺ 4.7mmol/L, Na⁺ 140mmol/L, Cl⁻ 100/mmol/L, AG=22.7mmol/L.

On Nov. 12, dialysis for another 5h, urine output was increasing.

On Nov. 19, urine 2000ml/d, S. G. 1.012, plasma NPN 95mg/dl, CO₂ CP 47 vol/dl, plasma K⁺ 3.3mmol/L, Na⁺ 150 mmol/L, Cl⁻ 114mmol/L, AG=14.6mmol/L.

In Dec., urinary output and other parameters restored to normal.
Discussions

1. Why the patient was still with oliguria when the Bp was almost back to normal detected on next day of hospitalized?

2. The mechanisms for increased NPN, decreased CO$_2$ CP and hyperkalemia?

3. The mechanisms for the formation of diuresis?

4. Having diuresis for a week, why the NPN was still high? CO$_2$ CP was still low? Still hyperkalemia?
5. Is diuresis phase safe to the patient?

6. Why did they use mannitol? Insulin plus glucose? And magnesium sulfate in treatment?

7. Did the patient suffer from functional or parenchyma ARF?
Case 2

Mr. Shi, male 68 year old, hospitalized in Jan.18, 1988

Main complains: Tired, lumbago for 3 years, nausea and vomit, little urinate for 10 days.

Present: Diuresis and nocturia since 3 years, back pain, tired, no edema. Feel dizzy, bone ache, limp. Proteins and casts were detected in urine, and the situation was worse day by day. Recently, feel nausea, vomit and itch everywhere, insomnia, decrease memory retention, faint reaction and gradually became comatose. Nosebleed twice, diarrhea with blood, the urine volume was decreasing and about 100ml/day in the recent 2 days.
Case 2

**History:** Hypertension for 13 year, with angina history.

**PE:** anemia, severe sick look, T37℃, R 30/min, deep, P 90/min, Bp 160/90mmHg, coma, halitosis, gum red and bleeding, ulcer in mouth mucus, Left heart enlarged, no edema of the lower limbs.

**Laboratory examinations:** RBC 20 thousand/cmm, Hb 6g%, platelet 1.28 thousand/cm³, BUN 92.2mg%, Pcr11.2mg%, CO₂CP 30Vol%, K⁺ 5.9%mEq/L, Na⁺ 123mEq/L, Ca²⁺ 7mg/L, P 7mg/dL, urine S.G 1.010, protein (++).
Discussion

1. What is the diagnosis of the disease?
2. Difference of the clinic progression from ARF?
3. Why from diuresis to oliguria?
4. Why the illness was aggravating year-by-year?
5. Mechanisms for the hypertension?
6. Mechanism for the anemia?
Discussion

7. Mechanisms for nausea, vomiting, halitosis and ulcer of alimentary tract?

8. Why the patient had no renal edema?

9. Why the patient showed no twitch with hypocalcemia?

10. Mechanisms for lumbago and bone aches?

11. Mechanisms for skin itching?

12. Mechanisms for dimmed reaction and coma?

13. The patient had diuresis, but why still showed disturbance of internal homeostasis?