腎臟內科國考複習

宋志建醫師

2022年01月12日

Harrison's Principles of Internal Medicine, 20e

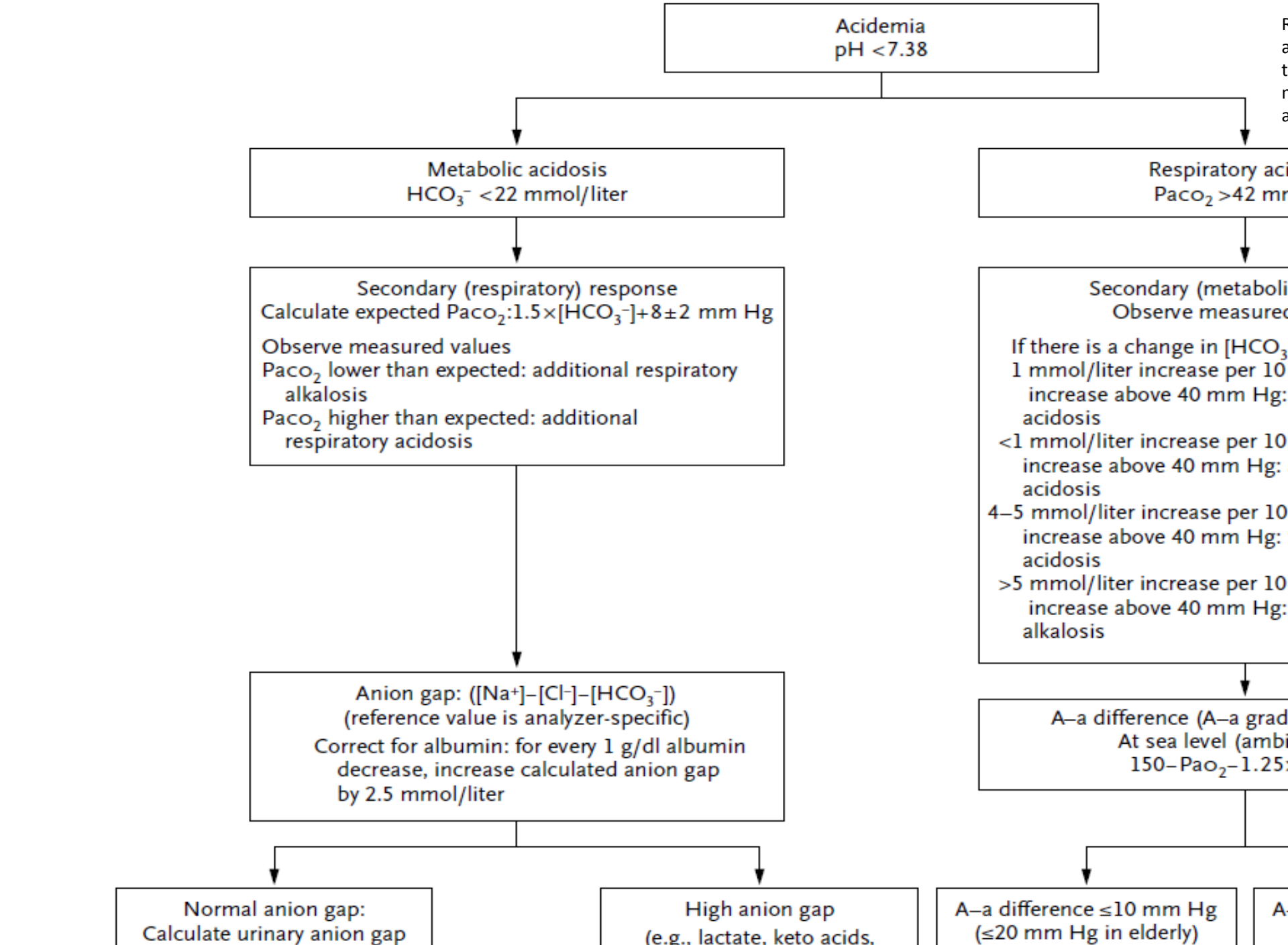
— Part 9: Disorders of the Kidney and Urinary Tract

Section 7: Alterations in Renal and Urinary Tract Function

Acidosis and alkalosis

Steps in Acid-Base Diagnosis

- 1. Obtain arterial blood gas (ABG) and electrolytes simultaneously.
- 2. Compare [HCO^-] on ABG and electrolytes to verify accuracy.
- 3. Calculate anion gap (AG), but correct to a normal albumin concentration of 4.5 g/dL.
- 4. Know four causes of high-AG acidosis (ketoacidosis, lactic acid acidosis, renal failure, and toxins).
- 5. Know two causes of hyperchloremic or nongap acidosis (bicarbonate loss from gastrointestinal tract, renal tubular acidosis).
- 6. Estimate compensatory response
- 7. Compare ΔAG and Δ$HCO\,3^-$
- 8. Compare change in [Cl] with change in [Na].


Acidemia
pH <7.38
Metabolic acidosis
HCO_3^- <22 mmol/liter
Respiratory aci
$Paco_2$ >42 mm
Secondary (respiratory) response
Calculate expected $Paco_2$:1.5×[HCO_3^-]+8±2 mm Hg
Observe measured values
$Paco_2$ lower than expected: additional respiratory alkalosis
$Paco_2$ higher than expected: additional respiratory acidosis
Secondary (metaboli
Observe measured
If there is a change in [HCO3
1 mmol/liter increase per 10
increase above 40 mm Hg:
acidosis
<1 mmol/liter increase per 10
increase above 40 mm Hg:
acidosis
4–5 mmol/liter increase per 10
increase above 40 mm Hg:
acidosis
>5 mmol/liter increase per 10
increase above 40 mm Hg:
alkalosis
Anion gap: ([Na^+]–[Cl^-]–[HCO_3^-])
(reference value is analyzer-specific)
Correct for albumin: for every 1 g/dl albumin decrease, increase calculated anion gap by 2.5 mmol/liter
A–a difference (A–a grad
At sea level (ambi
150–Pao_2–1.25
Normal anion gap:
Calculate urinary anion gap
High anion gap
(e.g., lactate, keto acids,
A–a difference ≤10 mm Hg
(≤20 mm Hg in elderly)
A-

Primary Acid–Base Disturbances with a Secondary ("Compensatory") Response-1

Metabolic acidosis

pH <7.38 and bicarbonate [HCO_3^-] <22 mmol per liter

Secondary (respiratory) response: $PaCO_2 = 1.5 \times [HCO_3^-] + 8 \pm 2$ mm Hg† or $[HCO_3^-]$ + 15 mm Hg‡

Complete secondary adaptive response within 12–24 hr

Superimposed respiratory acidosis or alkalosis may be diagnosed if the calculated $PaCO_2$ is greater or less than predicted

Metabolic alkalosis

pH >7.42 and [HCO_3^-] >26 mmol per liter

Secondary (respiratory) response: $PaCO_2 = 0.7 \times ([HCO_3^-] - 24) + 40 \pm 2$ mm Hg or $[HCO_3^-] + 15$ mm Hg‡ or $0.7 \times [HCO_3^-] + 20$ mm Hg§

Complete secondary adaptive response within 24–36 hr

Superimposed respiratory acidosis or alkalosis may be diagnosed if the calculated $PaCO_2$ is greater or less than predicted

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Prediction of Compensation

Disorder	Prediction of Compensation	Range of Values		
		pH	HCO3-	PaCO2
Metabolic acidosis	$PaCO_2=(1.5xHCO_3^-)+8$ $PaCO_2=HCO_3^-+15$ PaCO2=40-1.25x $deltaHCO_3^-$	Low	Low	Low
Metabolic alkalosis	$PaCO_2=HCO_3^-+15$ PaCO2=40+0.75x $deltaHCO_3^-$ PaCO2=40+6x($deltaHCO_3^-$/10)	High	High	High

Primary Acid–Base Disturbances with a Secondary ("Compensatory") Response-2

Respiratory acidosis

pH <7.38 and $PaCO_2$ >42 mm Hg

Secondary (metabolic) response

- Acute: $[HCO_3^-]$ is increased by 1 mmol/liter for each $PaCO_2$ increase of 10 mm Hg above 40 mm Hg
- Chronic: generally $[HCO_3^-]$ is increased by 4–5 mmol/liter for each $PaCO_2$ increase of 10 mm Hg above 40 mm Hg

Complete secondary adaptive response within 2–5 days

Superimposed metabolic alkalosis or acidosis may be diagnosed if the calculated $[HCO_3^-]$ is greater or less than predicted

Respiratory alkalosis

pH >7.42 and $PaCO_2$ <38 mm Hg

Secondary (metabolic) response

- Acute: $[HCO_3^-]$ is decreased by 2 mmol/liter for each $PaCO_2$ decrease of 10 mm Hg below 40 mm Hg
- Chronic: $[HCO_3^-]$ is decreased by 4–5 mmol/liter for each $PaCO_2$ decrease of 10 mm Hg below 40 mm Hg

Complete secondary adaptive response in 2–5 days

Superimposed metabolic alkalosis or acidosis may be diagnosed if the calculated $[HCO_3^-]$ is greater or less than predicted

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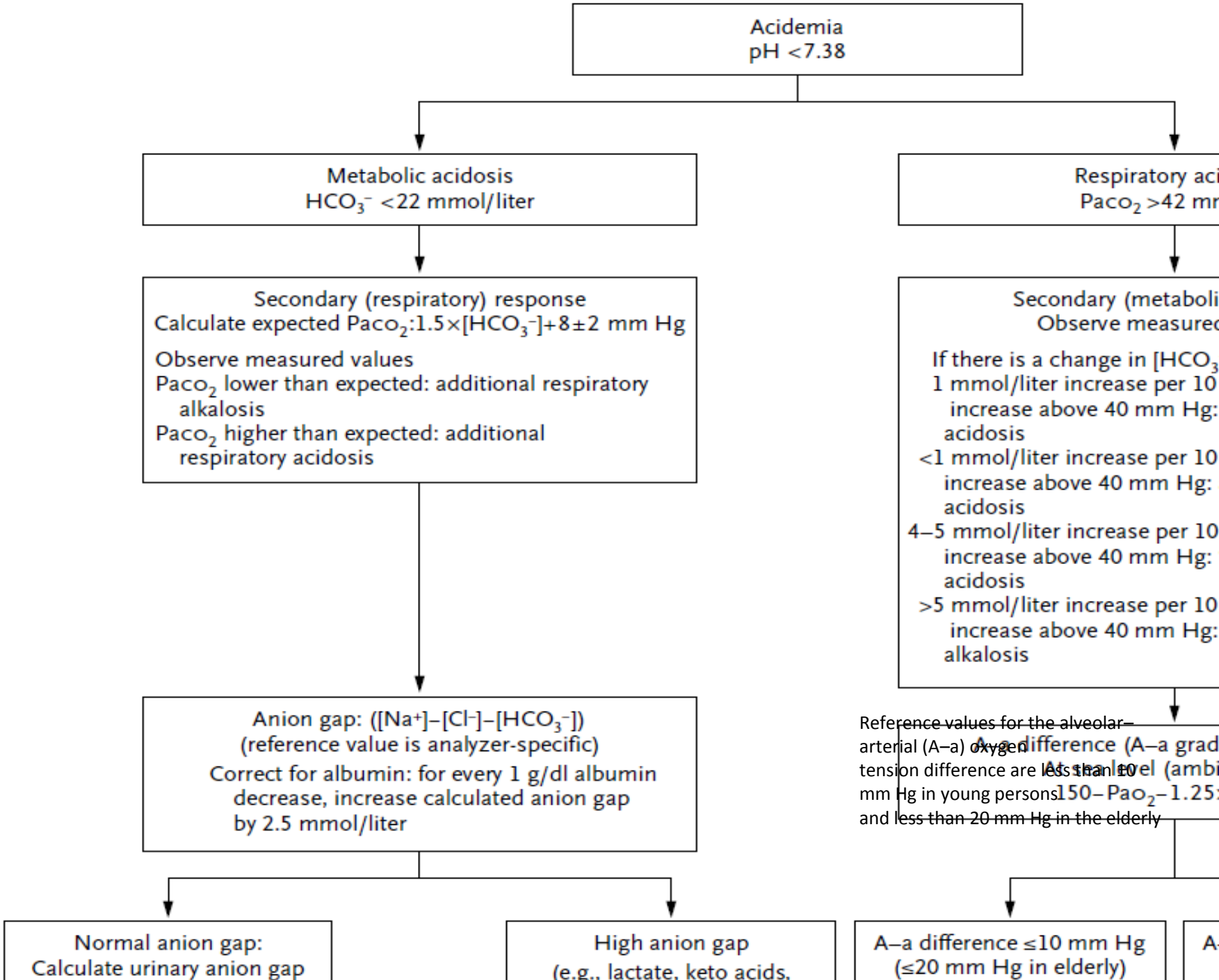
Henderson–Hasselbalch equation

$$\mathrm{pH} = 6.1 + \log \frac{\mathrm{HCO_3^-}}{\mathrm{PaCO_2} \times 0.03001}$$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1 mmol/liter increase per 10
increase above 40 mm Hg:
acidosis
<1 mmol/liter increase per 10
increase above 40 mm Hg:
acidosis
4–5 mmol/liter increase per 10
increase above 40 mm Hg:
acidosis
>5 mmol/liter increase per 10
increase above 40 mm Hg:
alkalosis
Anion gap: ([Na^+]–[Cl^-]–[HCO_3^-])
(reference value is analyzer-specific)
Correct for albumin: for every 1 g/dl albumin decrease, increase calculated anion gap by 2.5 mmol/liter
Reference values for the alveolar–arterial (A–a) oxygen tension difference are less than 10 mm Hg in young persons and less than 20 mm Hg in the elderly
A–a difference (A–a grad
At sea level (ambi
150–Pao_2–1.25
Normal anion gap:
Calculate urinary anion gap
High anion gap
(e.g., lactate, keto acids,
A–a difference ≤10 mm Hg
(≤20 mm Hg in elderly)
A-

AG calculation

[Na+] + [K+] +[Ca2+] + [Mg2+] + [H+] + unmeasured cations
= [Cl−]+ [HCO3−] + [$CO_3$2−] + [OH−] + albumin + phosphate+ sulfate + lactate + unmeasured anions

AG= unmeasured anions=[Na+] + [K+] +[Ca2+] + [Mg2+] + [H+] + unmeasured cations - [Cl−] - [HCO3−] - [$CO_3$2−] - [OH−] - albumin - phosphate - sulfate - lactate - unmeasured anions

AG= =[Na+] - [Cl−] - [HCO3−]

- A **low or negative** anion gap is observed when hyperchloremia is caused by high levels of cations, as seen in lithium toxicity, monoclonal IgG gammopathy, or disorders characterized by high levels of calcium or magnesium.
- A **negative** anion gap is caused by pseudohyperchloremia in bromide or iodide intoxication
- Correct for **albumin**: for every 1 g/dl albumin decrease, increase calculated anion gap by 2.5 mmol/liter

High anion gap

Overproduction of acid

- Ketoacidosis (diabetic ketoacidosis, alcoholic ketoacidosis, starvation)
- Lactic acidosis
  - L-Lactic acidosis
    - Type A — hypoxic (septic shock, mesenteric ischemia, hypoxemia, hypovolemic shock, carbon monoxide poisoning, cyanide)
    - Type B — nonhypoxic (thiamine deficiency, seizure, medications [nonnucleoside reverse-transcriptase inhibitors, metformin, propofol, niacin, isoniazid, iron], intoxication [salicylate, ethylene glycol, propylene glycol, methanol, toluene ingestion (early), paraldehyde])
  - D-Lactic acidosis in the short-bowel syndrome

Underexcretion of acid (advanced renal failure)†

Impaired lactate clearance in liver failure (also type B acidosis)

Cell lysis (massive rhabdomyolysis)

Use of penicillin-derived antibiotics

Pyroglutamic acid (5-oxoproline)[32]

ketonuria
(the nitroprusside test) reacts only with **acetoacetate**, not with **β-hydroxybutyrate**, the primary keto acid seen in alcoholic ketoacidosis.

Normal anion gap

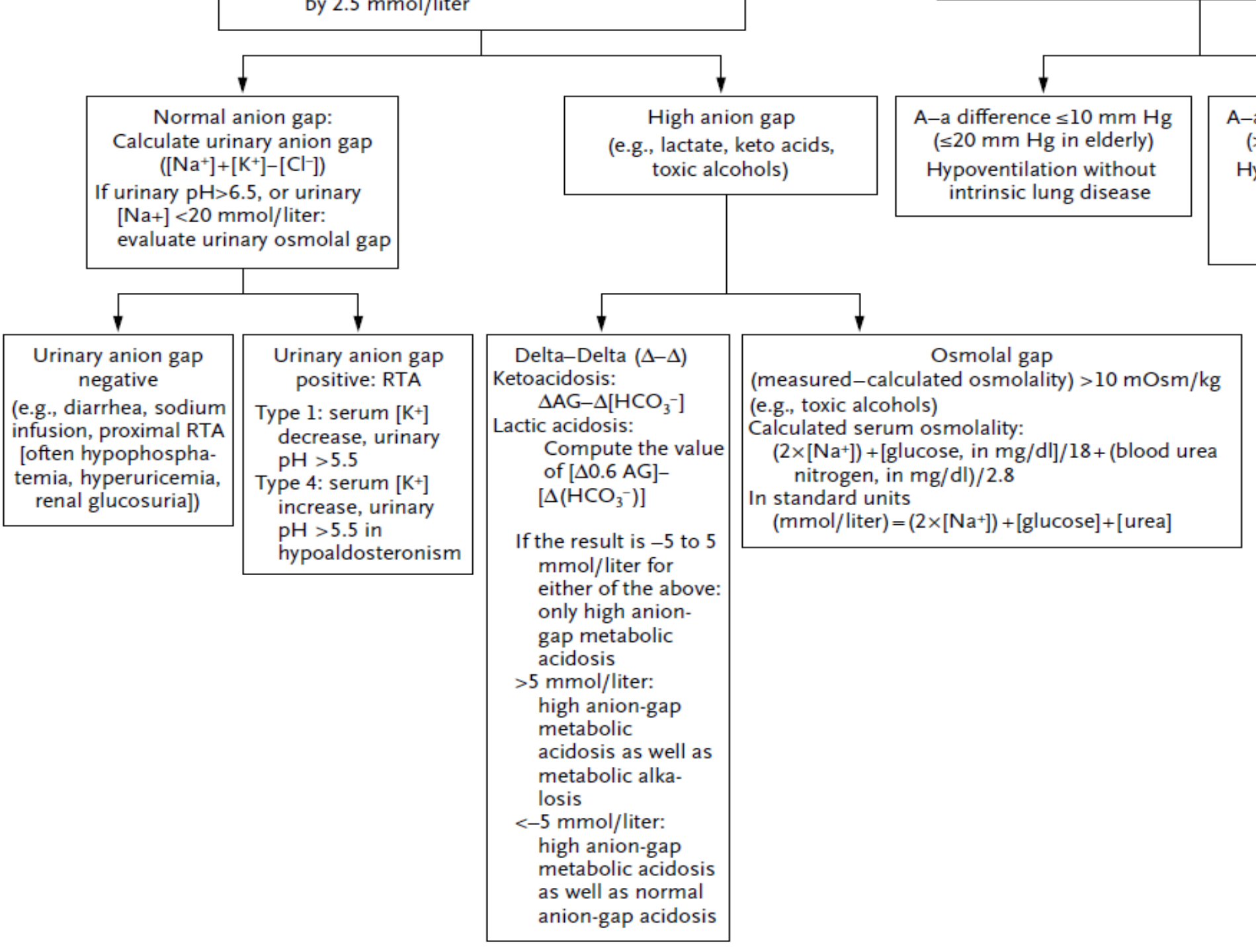
Loss of bicarbonate

- Gastrointestinal conditions (diarrhea, ureteral diversions, biliary or pancreatic fistulas)
- Renal conditions (type 2 [proximal] renal tubular acidosis, toluene ingestion [late in the process of toluene intoxication], conditions associated with medications [ifosfamide, tenofovir, topiramate, carbonic anhydrase inhibitors such as acetazolamide])[3,41]

Decreased renal acid excretion

- Early uremic acidosis
- Type 1 renal tubular acidosis (e.g., due to amphotericin, lithium, Sjögren's syndrome)[3]
- Type 4 renal tubular acidosis (hypoaldosteronism or pseudohypoaldosteronism)

Other causes: fluid resuscitation with saline, hyperalimentation (lysine, histidine, or arginine hydrochloride), administration of hydrochloride, ammonium chloride, cholestyramine, hippuric acid, sulfuric acid


by 2.5 mmol/liter
Normal anion gap:
Calculate urinary anion gap
([Na+]+[K+]–[Cl–])
If urinary pH>6.5, or urinary
[Na+] <20 mmol/liter:
evaluate urinary osmolal gap
High anion gap
(e.g., lactate, keto acids,
toxic alcohols)
A–a difference ≤10 mm Hg
(≤20 mm Hg in elderly)
Hypoventilation without
intrinsic lung disease
A–
(
Hy
Urinary anion gap
negative
(e.g., diarrhea, sodium
infusion, proximal RTA
[often hypophospha-
temia, hyperuricemia,
renal glucosuria])
Urinary anion gap
positive: RTA
Type 1: serum [K+]
decrease, urinary
pH >5.5
Type 4: serum [K+]
increase, urinary
pH >5.5 in
hypoaldosteronism
Delta–Delta (Δ–Δ)
Ketoacidosis:
ΔAG–Δ[HCO3–]
Lactic acidosis:
Compute the value
of [Δ0.6 AG]–
[Δ(HCO3–)]
If the result is –5 to 5
mmol/liter for
either of the above:
only high anion-
gap metabolic
acidosis
>5 mmol/liter:
high anion-gap
metabolic
acidosis as well as
metabolic alka-
losis
<–5 mmol/liter:
high anion-gap
metabolic acidosis
as well as normal
anion-gap acidosis
Osmolal gap
(measured–calculated osmolality) >10 mOsm/kg
(e.g., toxic alcohols)
Calculated serum osmolality:
(2×[Na+])+[glucose, in mg/dl]/18+(blood urea
nitrogen, in mg/dl)/2.8
In standard units
(mmol/liter)=(2×[Na+])+[glucose]+[urea]

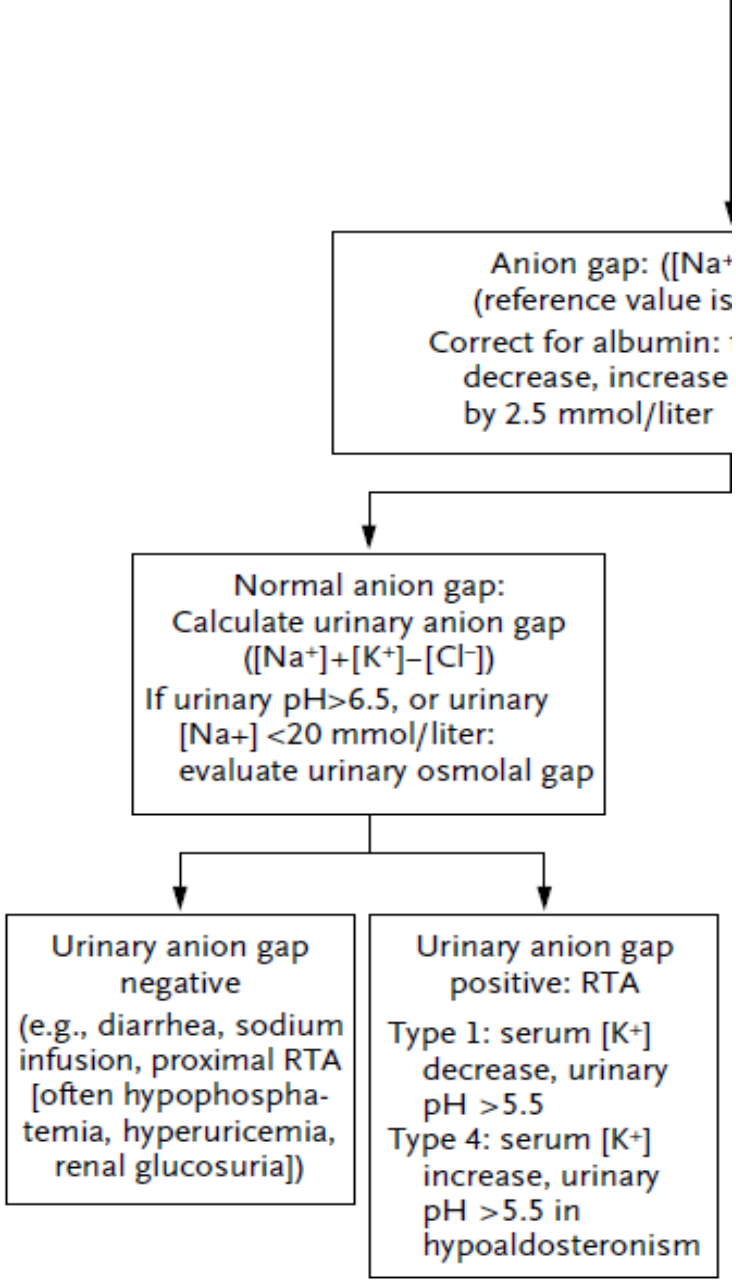
CONSIDERATION OF THE SERUM (OR PLASMA) OSMOLAL GAP

- Unexplained high anion-gap acidosis
- Coma
- Suspicion of ingestion of a (toxic) alcohol
- In hospitalized patients with an increased risk of iatrogenic propylene glycol intoxication

1. topical sulfadiazine silver cream, IV nitroglycerine, etomidate, enoximone, multivitamins, and phenytoin
2. lorazepam or diazepam

EVALUATION FOR THE PRESENCE OF MIXED METABOLIC ACID–BASE DISTURBANCES

- In high anion-gap metabolic acidosis, the magnitude of the increase in the anion gap (the delta AG, or ΔAG) is related to the decrease in the bicarbonate ions ($\Delta[HCO_3^-]$).
- To diagnose a high anion-gap acidosis with concomitant metabolic alkalosis or normal anion-gap acidosis, the so-called delta-delta (Δ-Δ) may be use
- A difference greater than 5 mmol per liter suggests a concomitant metabolic alkalosis, and if the difference is less than −5 mmol per liter, a concomitant normal anion-gap metabolic acidosis is diagnosed.


Anion gap: ([Na+
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If urinary pH>6.5, or urinary
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Urinary anion gap
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(e.g., diarrhea, sodium
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[often hypophospha-
temia, hyperuricemia,
renal glucosuria])
Urinary anion gap
positive: RTA
Type 1: serum [K+]
decrease, urinary
pH >5.5
Type 4: serum [K+]
increase, urinary
pH >5.5 in
hypoaldosteronism

Normal AG metabolic acidosis

Gastrointestinal bicarbonate loss	**1. Diarrhea**			
	2. External pancreastic or small bowel drainage			
	3. Ureterosigmoid ostomy			
	4. Drugs	**Calcium chloride**	**Magnesium sulfate**	**Cholestyramine**
Renal tubular acidosis				

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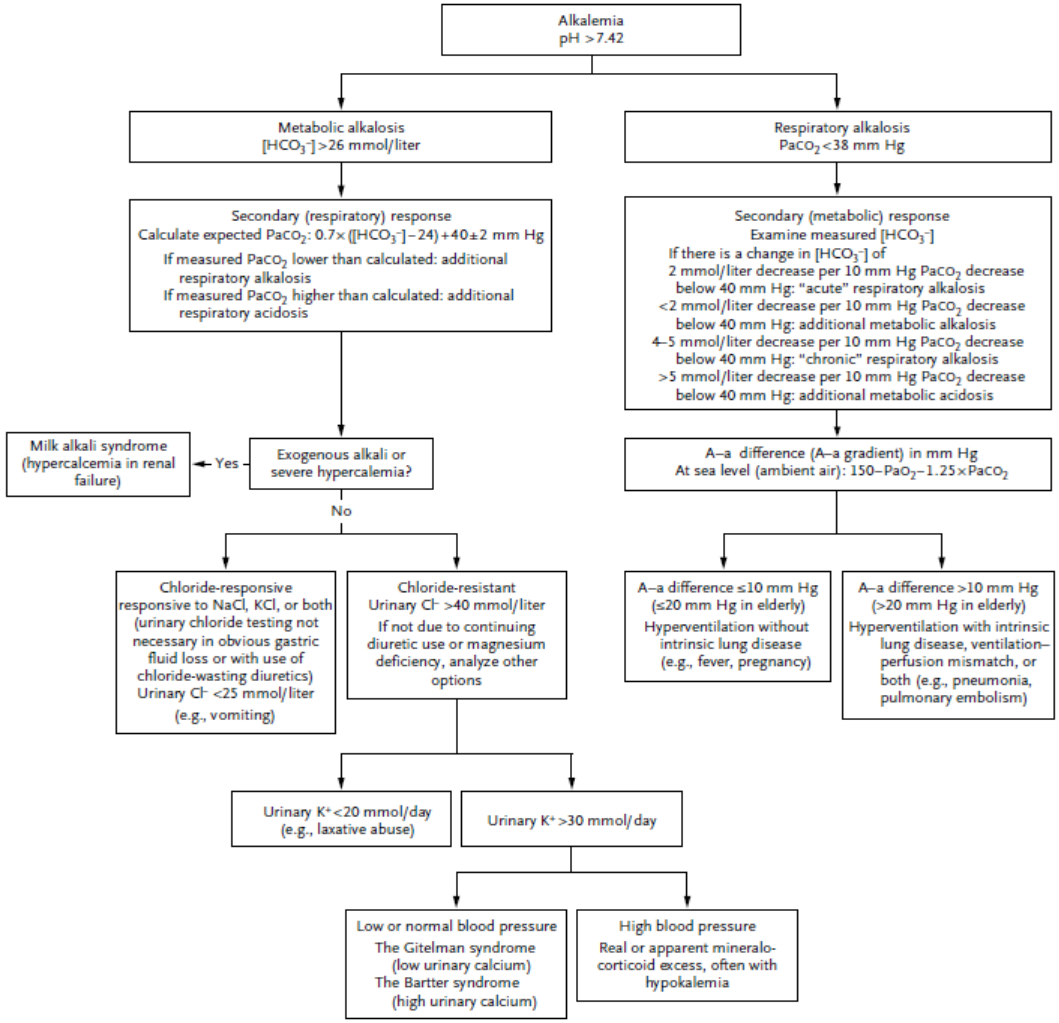
Urinary anion gap

- Urinary anion gap= $[Na^+]+[K^+]–[Cl^–]$
- Usually negative
- Positive when excretion of urinary ammonium ($NH4^+$) (as ammonium chloride [NH4Cl]) is impaired

Alkalosis

Table 3. Common Medical Conditions Characterized by Respiratory Acidosis and Alkalosis.*

Type of Acidosis	Common Medical Conditions
Respiratory acidosis	
Acute	
Normal alveolar–arterial O_2 difference	Depression of the central respiratory center by cerebral disease (encephalitis or trauma) or drugs (narcotics, barbiturates, or benzodiazepines)
High alveolar–arterial O_2 difference†	Airway obstruction related to acute exacerbations of asthma or pneumonia
Chronic	
Normal alveolar–arterial O_2 difference	Neuromuscular disease (e.g., myasthenia gravis, amyotrophic lateral sclerosis, Guillain–Barré syndrome, or muscular dystrophy), kyphoscoliosis
High alveolar–arterial O_2 difference†	Chronic obstructive pulmonary disease
Respiratory alkalosis	
Acute	
Normal alveolar–arterial O_2 difference	Pain, anxiety, fever, stroke, meningitis, trauma, severe anemia, salicylate toxicity
High alveolar–arterial O_2 difference†	Pneumonia, pulmonary edema, pulmonary embolism, aspiration, congestive heart failure, sepsis
Chronic	
Normal alveolar–arterial O_2 difference	Pregnancy, hyperthyroidism, hepatic failure
High alveolar–arterial O_2 difference†	Pulmonary embolism in pregnancy, liver failure with aspiration pneumonia



- **1.血陰離子隙(blood anion gap)是反應下列何項離子的多寡?**
- **A.未測量之陽離子(unmeasured cations)**
- **B.鈉離子+鉀離子(Na^++ K^+)**
- **C.未測量之陰離子(unmeasured anions)**
- **D.重碳酸離子+氯離子(HCO^-+ Cl^-)**
-

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-

Anion gap =Unmeasured anions=[Na+]−[Cl−] − [HCO_3−]=10

[Na+] + [K+] +[Ca2+] + [Mg2+] + [H+] + unmeasured cations

= [Cl−]+ [HCO3−] + [$CO_3$2−] + [OH−] + albumin + phosphate+ sulfate + lactate + unmeasured anions

- 一位病人血液氣體分析顯示**pH 7.51，P CO 49 mmHg，HCO - 38 mmol/L，**下列何者正確**? a23**
- **A.**代謝性酸中毒**(**酸血症**) B.**代謝性鹼中毒 **C.**呼吸性酸中毒 **D.**呼吸性鹼中毒

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Primary Acid–Base Disturbances with a Secondary ("Compensatory") Response-1

Metabolic acidosis

pH <7.38 and bicarbonate [HCO_3^-] <22 mmol per liter

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Complete secondary adaptive response within 12–24 hr

Superimposed respiratory acidosis or alkalosis may be diagnosed if the calculated $Paco_2$ is greater or less than predicted

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pH >7.42 and [HCO_3^-] >26 mmol per liter

Secondary (respiratory) response: $Paco_2 = 0.7 \times ([HCO_3^-] - 24) + 40 \pm 2$ mm Hg or $[HCO_3^-] + 15$ mm Hg‡ or $0.7 \times [HCO_3^-] + 20$ mm Hg§

Complete secondary adaptive response within 24–36 hr

Superimposed respiratory acidosis or alkalosis may be diagnosed if the calculated $Paco_2$ is greater or less than predicted

- 29 下列那一種是陰離子隙增加之代謝性酸中毒（high anion gap metabolic acidosis）？
- 玠A.腹瀉（diarrhea）
- 媳B.飢餓（starvation）
- 暟C.嘔吐（vomitting）
- 鬲D.輸尿管－乙形結腸造口術後（ureterosigmoidostomy）

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- **媳B.飢餓（starvation）**
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- 卼D.輸尿管－乙形結腸造口術後（ureterosigmoidostomy）metabolic acidosis

High AG metabolic acidosis

High AG				
Lactic acidosis				
Ketoacidosis				
Diabetic				
Alcoholic				
Starvation				
Toxin	Ethylene glycol	Methanol	Salicylates	Propylene glycol
Pyroglutamic acid				
Renal failure (acute and chronic)				

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Normal AG metabolic acidosis

Gastrointestinal bicarbonate loss	**1. Diarrhea**			
	2. External pancreastic or small bowel drainage			
	3. Ureterosigmoid ostomy			
	4. Drugs	**Calcium chloride**	**Magnesium sulfate**	**Cholestyramine**
Renal tubular acidosis				

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Harrison's Principles of Internal Medicine, 20e > Acidosis and Alkalosis

J. Larry Jameson, Anthony S. Fauci, Dennis L. Kasper, Stephen L. Hauser, Dan L. Longo, Joseph Loscalzo+

TABLE 51-6Causes of Metabolic Alkalosis

1. Exogenous HCO_3^- loads
1. Acute alkali administration
2. Milk-alkali syndrome
2. Effective ECFV contraction, normotension, K^+ deficiency, and secondary hyperreninemic hyperaldosteronism
1. Gastrointestinal origin
1. Vomiting
2. Gastric aspiration
3. Congenital chloridorrhea
4. Gastrocystoplasty
5. Villous adenoma
2. Renal origin
1. Diuretics
2. Posthypercapnic state
3. Hypercalcemia/hypoparathyroidism
4. Recovery from lactic acidosis or ketoacidosis
5. Nonreabsorbable anions including penicillin, carbenicillin
6. Mg^{2+} deficiency
7. K^+ depletion
8. Bartter's syndrome (loss of function mutations of transporters and ion channels in TALH)
9. Gitelman's syndrome (loss of function mutation of Na^+-Cl^- cotransporter in DCT)

Abbreviations: DCT, distal convoluted tubule; ECFV, extracellular fluid volume; TALH, thick ascending limb of Henle's loop.

- 一位酗酒病人因意識不清、劇烈嘔吐被送至急診室。其血液生化檢查及動脈血分析如下：pH：7.40、PaCO2：40 mmHg、HCO3：24 mEq/L、Glucose：120 mg/dL、BUN：10 mg/dL、Creatinine：0.7 mg/dL、Na：134 mEq/L、K：2.6 mEq/L、Cl：80 mEq/L、Acetone：3+，則下列何者為正確的診斷？
- 玠 A.血液酸鹼值正常無代謝性酸鹼疾病
- 媳**B.代謝性酸中毒合併代謝性鹼中毒**
- 暟 C.代謝性酸中毒合併呼吸性鹼中毒
- 鬲D.代謝性鹼中毒合併呼吸性酸中毒

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- 暟 C.代謝性酸中毒合併呼吸性鹼中毒
- 卼D.代謝性鹼中毒合併呼吸性酸中毒

- 下列那一個病例不符合所列之動脈血氣體分析和血清電解質的檢查結果？pH 7.49，PaO2 90 mmHg，PaCO2 48 mmHg，HCO_3^- 32 mEq/L；Na^+ 140，K^+ 2.7，Cl^- 92（電解質的單位是mmol/L）
- 琮 A.40 歲甲病人，血壓160/108 mmHg，血漿腎素活性0.12 ng/mL/hr（正常值1.0-3.5 ng/mL/hr）
- 媛 B.20 歲乙女性，使用利尿劑（hydrochlorothiazide）減重
- 暄 C.40 歲丙病人，血壓162/102 mmHg，長期食用甘草（licorice）
- **鳥 D.60 歲丁病人使用acetazolamide 治療青光眼**
- 32 承上題，那位病人給予生理食鹽水後可以矯正其電解質和酸鹼的不平衡？
- 琮 A.甲病人 媛**B.**乙病人 暄C.丙病人 鳥D.丁病人

- 下列那一個病例較符合所列之動脈血氣體分析和血清電解質的檢查結果？pH 7.32，PaO2 110 mmHg，PaCO2 30 mmHg，$HCO3^-$ 18 mEq/L；Na^+ 138，K^+ 3.5，Cl^- 97（電解質的單位是mmol/L）
- A.70 歲病人因便秘嚴重，服用 magnesium sulfate 導致腹瀉數天
- B.28 歲病人診斷為修格連氏症候群（Sjögren's syndrome），無意間發現腎鈣化（nephrocalcinosis），尿液酸鹼值為6.5；給予NH4Cl（0.1 g/kg 體重）後，尿液酸鹼值為6.0
- C.20 歲病人第一型糖尿病病史 5 年，血糖控制不佳，最近因為期末考胰島素注射次數減少
- D.60 歲病人因膽道阻塞放置引流管引流膽汁

- 下列那一個病例較符合所列之動脈血氣體分析和血清電解質的檢查結果？pH 7.32，PaO2 110 mmHg，PaCO2 30 mmHg，$HCO3^-$ 18 mEq/L；Na^+ 138，K^+ 3.5，Cl^- 97（電解質的單位是mmol/L）
- 玠A.70 歲病人因便秘嚴重，服用 magnesium sulfate 導致腹瀉數天
- 媳B.28 歲病人診斷為修格連氏症候群（Sjögren's syndrome），無意間發現腎鈣化（nephrocalcinosis），尿液酸鹼值為6.5；給予NH4Cl（0.1 g/kg 體重）後，尿液酸鹼值為6.0
- **C.20 歲病人第一型糖尿病病史 5 年，血糖控制不佳，最近因為期末考胰島素注射次數減少**
- 鬲D.60 歲病人因膽道阻塞放置引流管引流膽汁

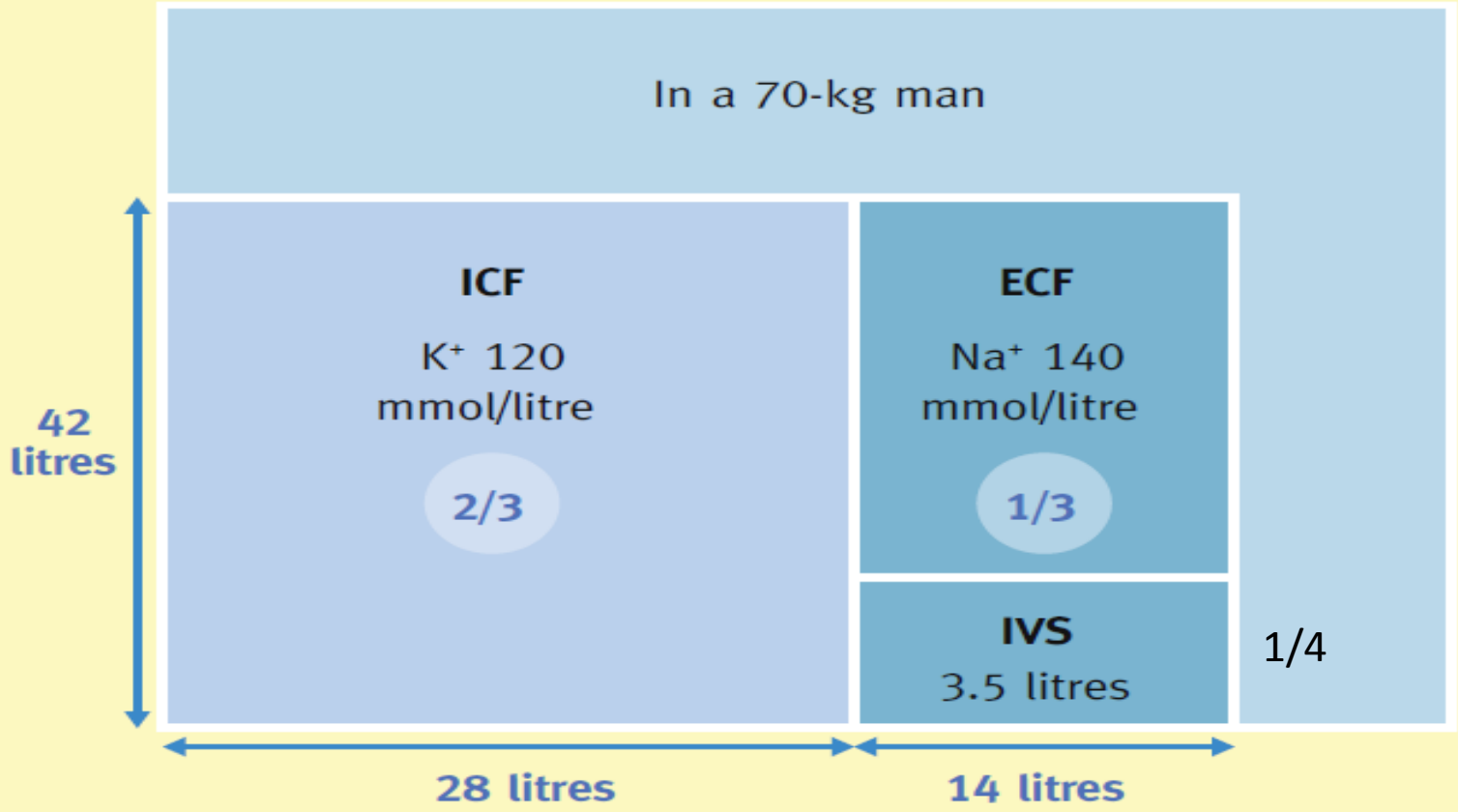
- **5.某70歲女性患者近2週嘔吐、腹痛漸增而至急診；過去病史：糖尿病10多年，一個月前腎功能正常，目前使用之藥物包括metformin 1.5 g daily，losartan 50 mg daily，以及simvastatin 20 mg daily。實驗室檢查發現：Na^+ 139 mmol/L，K^+ 4.9 mmol/L，Cl^- 103 mmol/L，glucose 216 mg/dL，cholesterol 220 mg/dL，Ca^{2+} 8 mg/dL，Cr 6.5 mg/dL；動脈血氣體pH 7.0，$HCO3^-$ 4.0 mEq/L，PCO2 14 mmHg，尿液無異常。下列何者為最可能之診斷？**
- A.diabetic ketoacidosis
- B.rhabdomyolysis
- C.lactic acidosis
- D.type 4 renal tubular acidosis

- **5. 某70歲女性患者近2週嘔吐、腹痛漸增而至急診；過去病史：糖尿病10多年，一個月前腎功能正常，目前使用之藥物包括metformin 1.5 g daily，losartan 50 mg daily，以及simvastatin 20 mg daily。實驗室檢查發現：Na^+ 139 mmol/L，K^+ 4.9 mmol/L，Cl^- 103 mmol/L，glucose 216 mg/dL，cholesterol 220 mg/dL，Ca^{2+} 8 mg/dL，Cr 6.5 mg/dL；動脈血氣體pH 7.0，$HCO3^-$ 4.0 mEq/L，PCO2 14 mmHg，尿液無異常。下列何者為最可能之診斷？**
- A. diabetic ketoacidosis
- B. rhabdomyolysis
- C. lactic acidosis
- D. type 4 renal tubular acidosis

Na

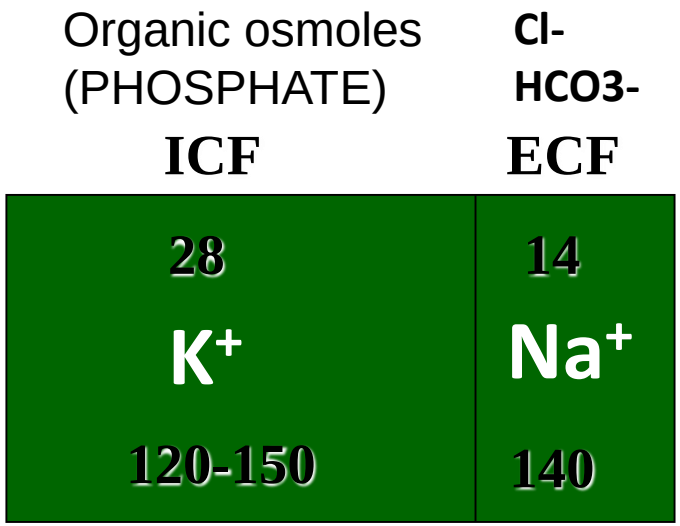
身體水分組成

Water moves freely between body fluid comparment



P_{Na} is an index of total body fluid osmolality.
ICF, intracellular fluid compartment; ECF, extracellular fluid compartment; IVS, intravascular space.

身體水分組成



- ECF volume: renal Na^+ regulation
- ICF volume: effective osmolality

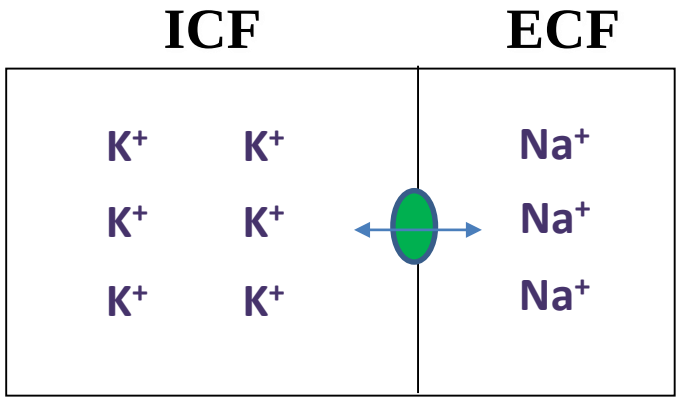
Water movement: osmotic equilibrium (滲透壓平衡)

Kevin M, et al. Ann Intern Med 1997;127:848-53

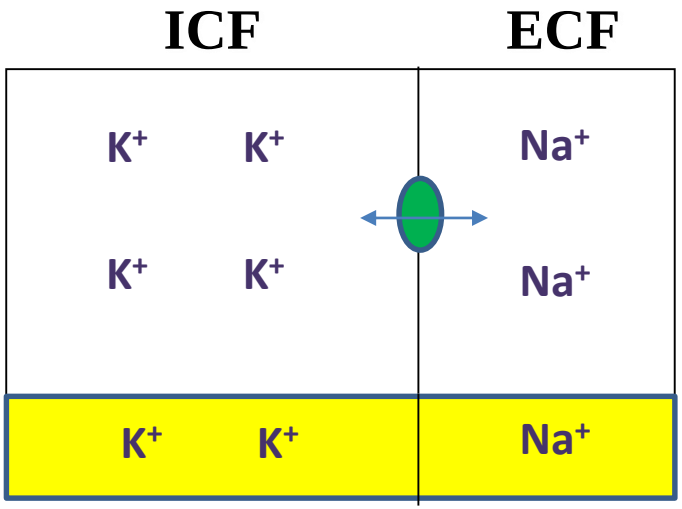
Changes in volumes of BFC

Na^+ content reflects ECF volume

Plasma [Na^+] reveals ICF volume

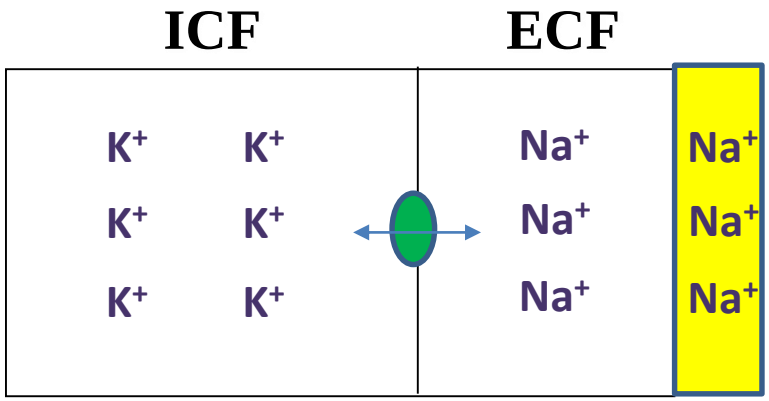


Water



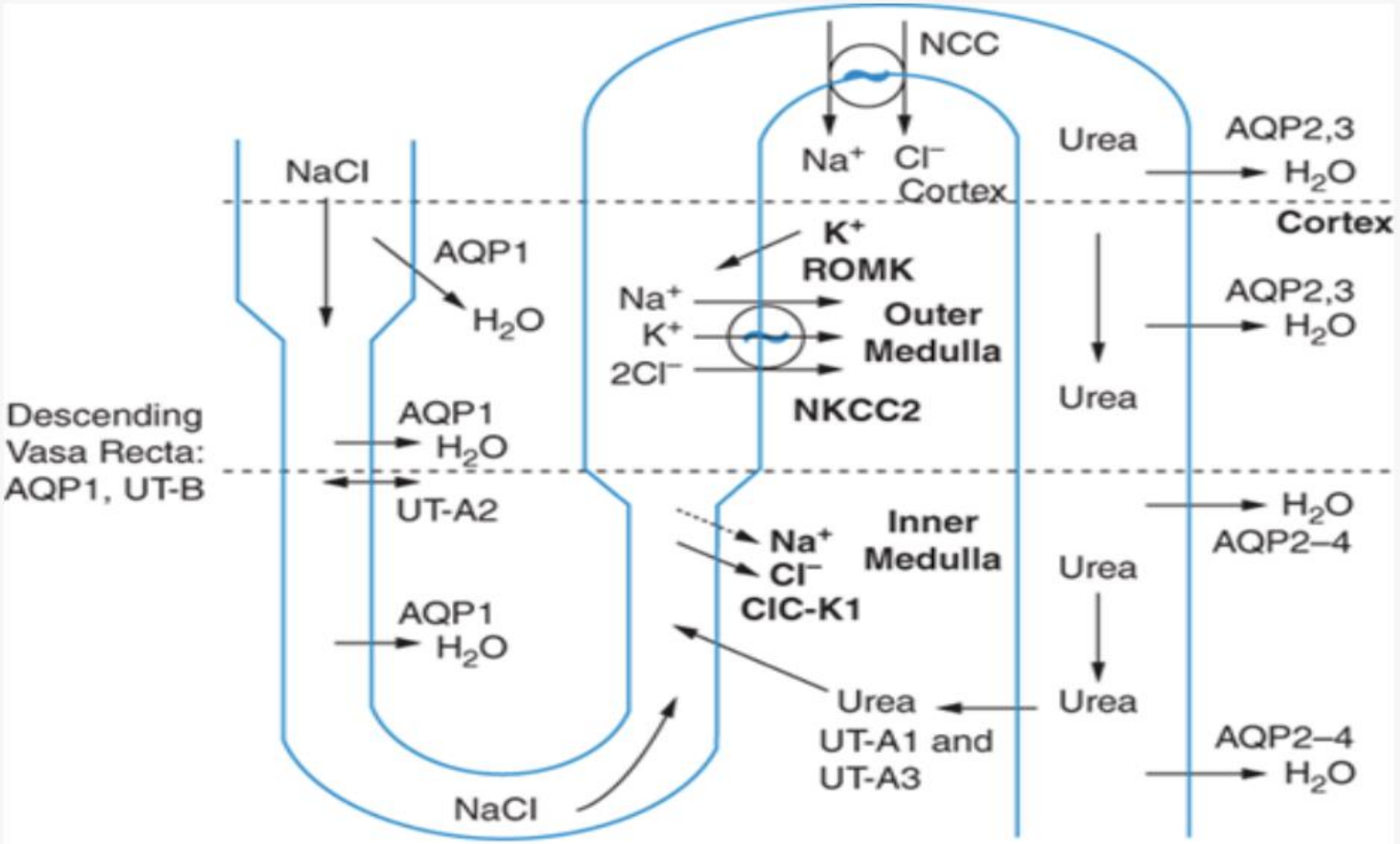
Hyponatremia 低血鈉

Isotonic saline

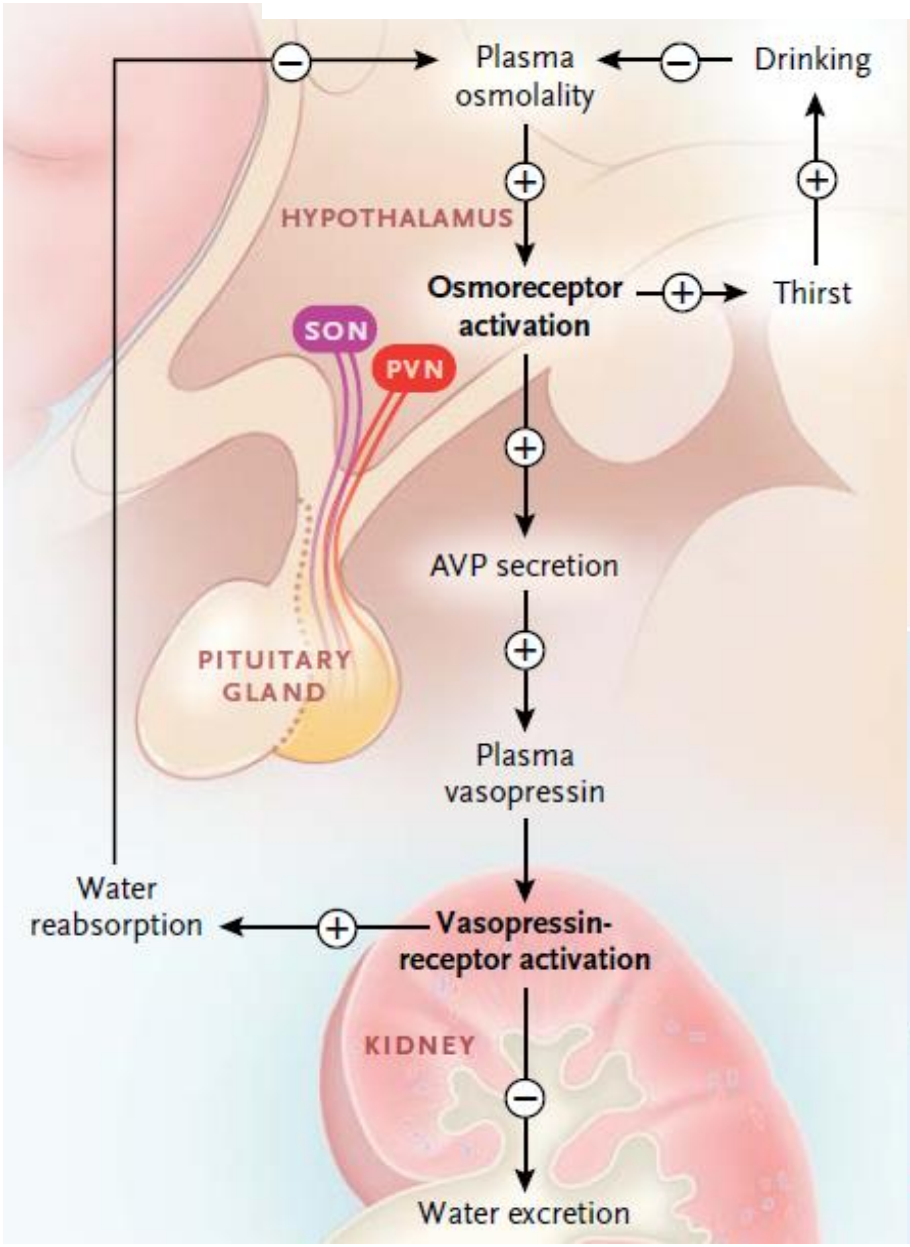


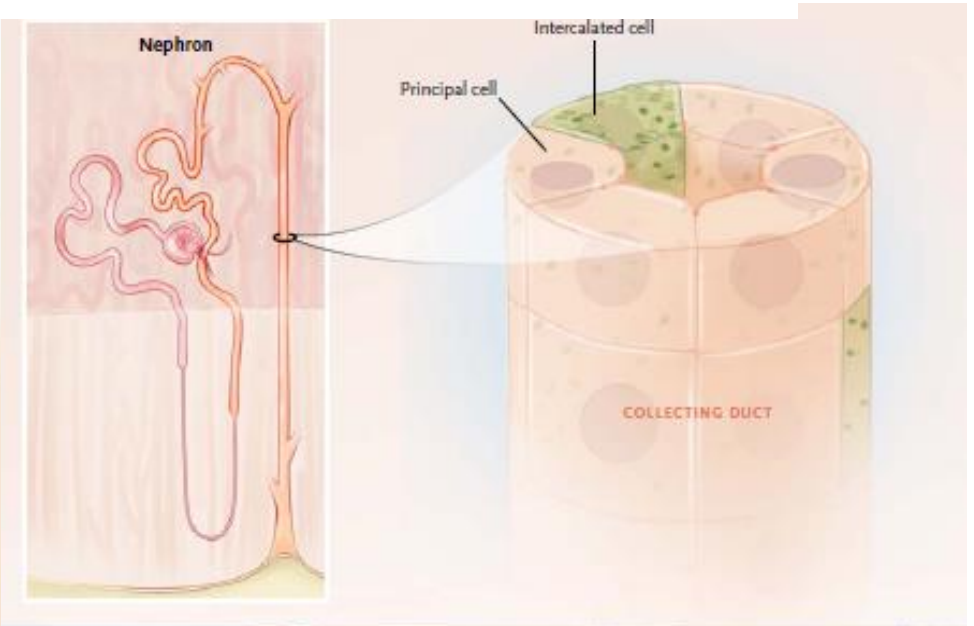
No change in P_{Na} or ICF

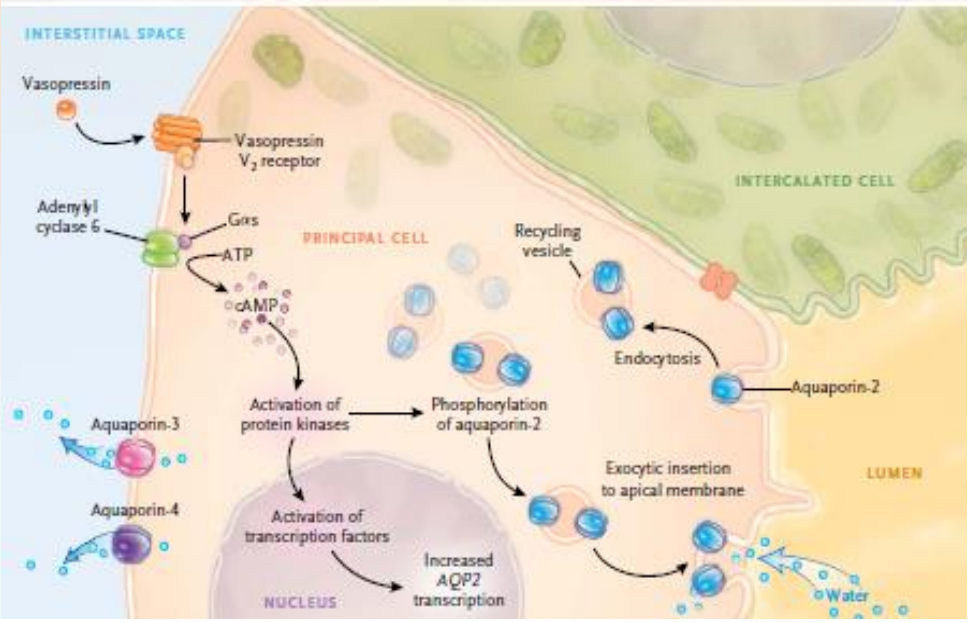
The renal concentrating mechanism.



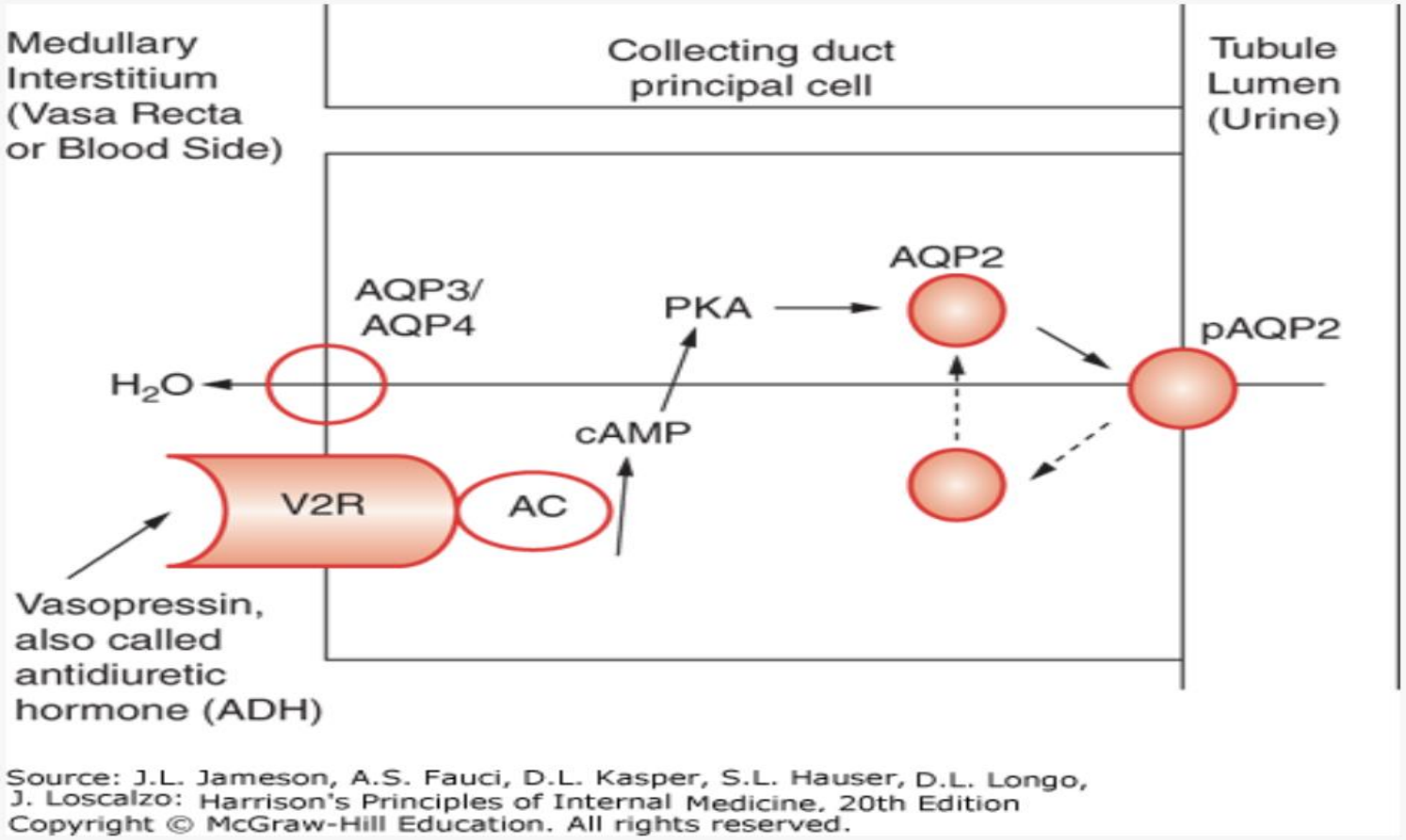
抗利尿激素Vasopressin (ADH)







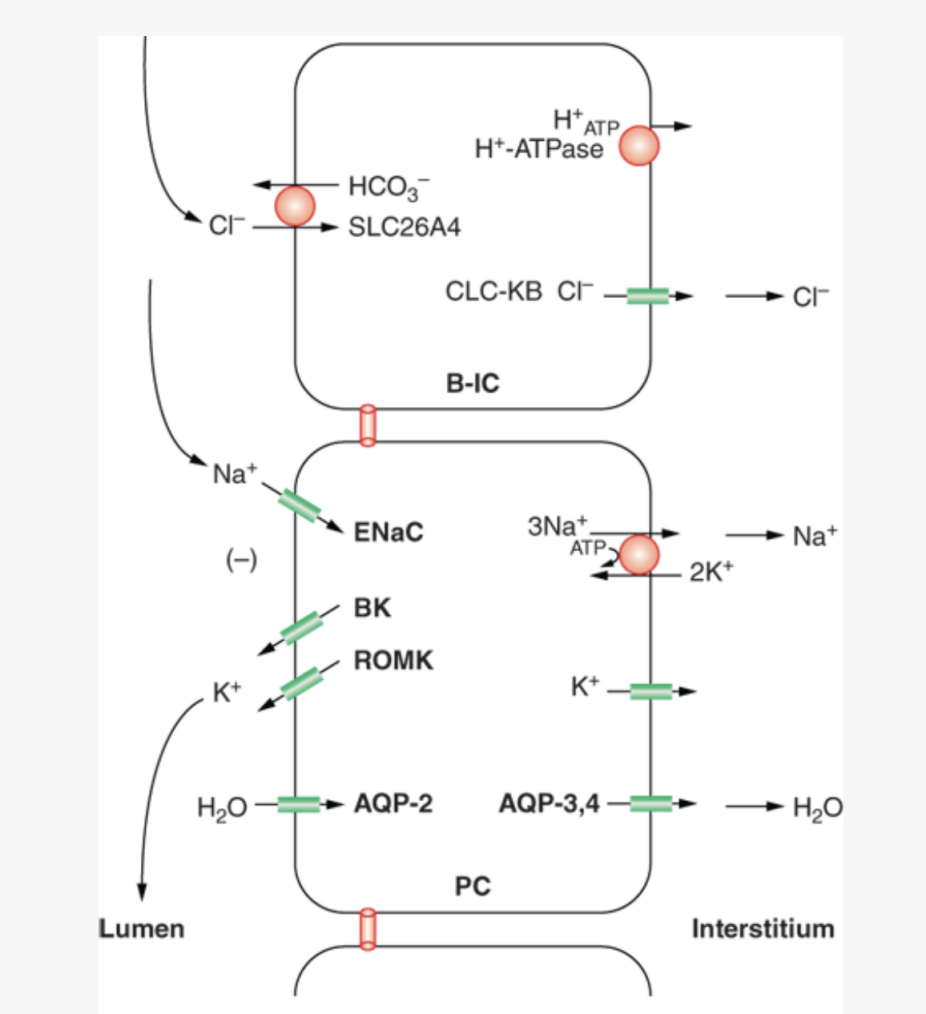
Vasopressin and the regulation of water permeability in the renal collecting duct.



Na^+-Cl^- is reabsorbed

- Approximately two-thirds of filtered Na^+-Cl^- is reabsorbed by the renal proximal tubule, via both paracellular and transcellular mechanisms.
- The TALH subsequently reabsorbs another 25–30% of filtered Na^+-Cl^- via the apical, furosemide-sensitive Na^+-K^+-$2Cl^-$ cotransporter.
- The adjacent aldosterone-sensitive distal nephron, comprising the distal convoluted tubule (DCT), connecting tubule (CNT), and CD, accomplishes the "fine-tuning" of renal Na^+-Cl^- excretion.
- The thiazide-sensitive apical Na^+-Cl^-cotransporter (NCC) reabsorbs 5–10% of filtered Na^+-Cl^- in the DCT.
- Principal cells in the CNT and CD reabsorb Na^+ via electrogenic, amiloride-sensitive epithelial Na^+ channels (ENaC); Cl^- ions are primarily reabsorbed by adjacent intercalated cells, via apical Cl^- exchange (Cl^--OH^- and Cl^--HCO_3^- exchange, mediated by the SLC26A4 anion exchanger)

Sodium, water, and potassium transport in principal cells (PC) and adjacent β-intercalated cells (B-IC)



Case

- A 26-year-old man presented to the emergency department (ED) with nausea, vomiting, and epigastric pain for 1 week.
- Severe hyponatremia (106 mmol/L)
- Serum osmolality was recorded as 224 mOsm/kg

(reference range 275–295 mOsm/kg)

- Urine osmolality was 313 mOsm/kg

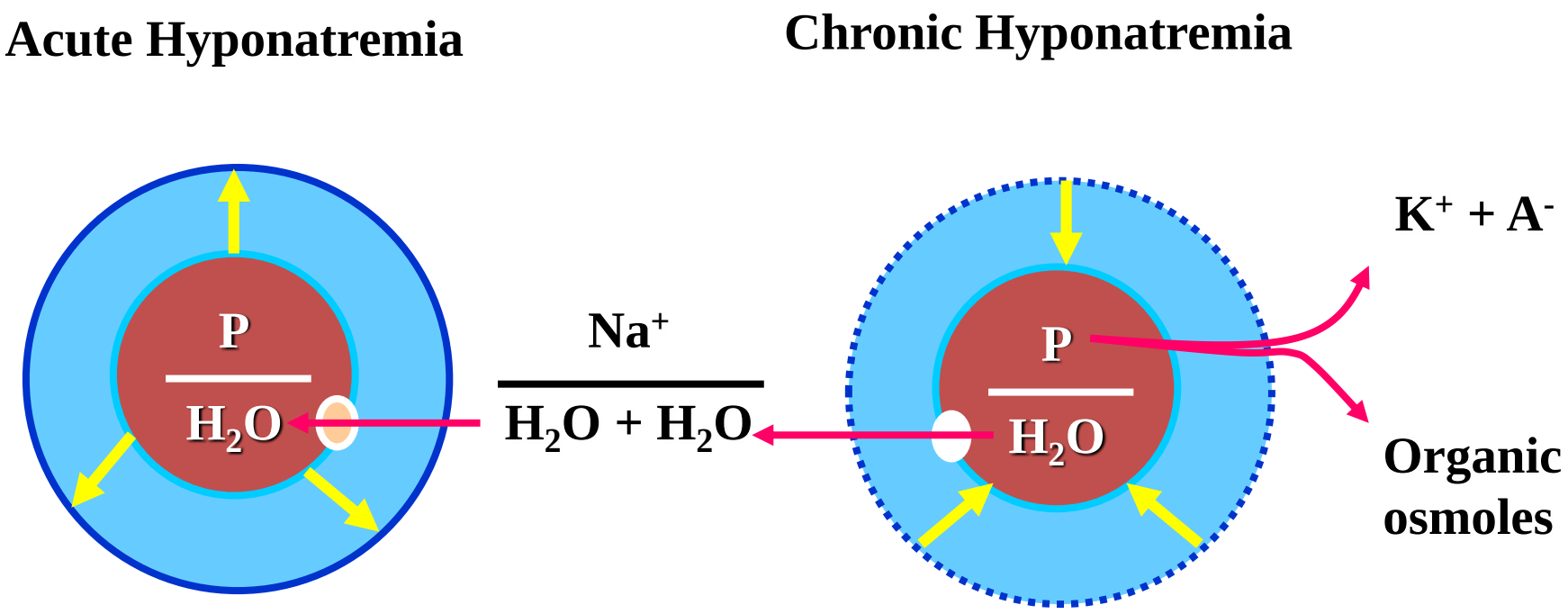
(reference range 300–900 mOsm/kg).

Question 1: The hyponatremia is?

1. Acute
2. Chronic

Time of development

- Cutoff 48 h



Question 2: What is the classification of hyponatremia in this patient?

1. **True hyponatremia**
2. **Pseudohyponatremia**
3. **Hyperosmolar hyponatremia**

Classification of hyponatremia

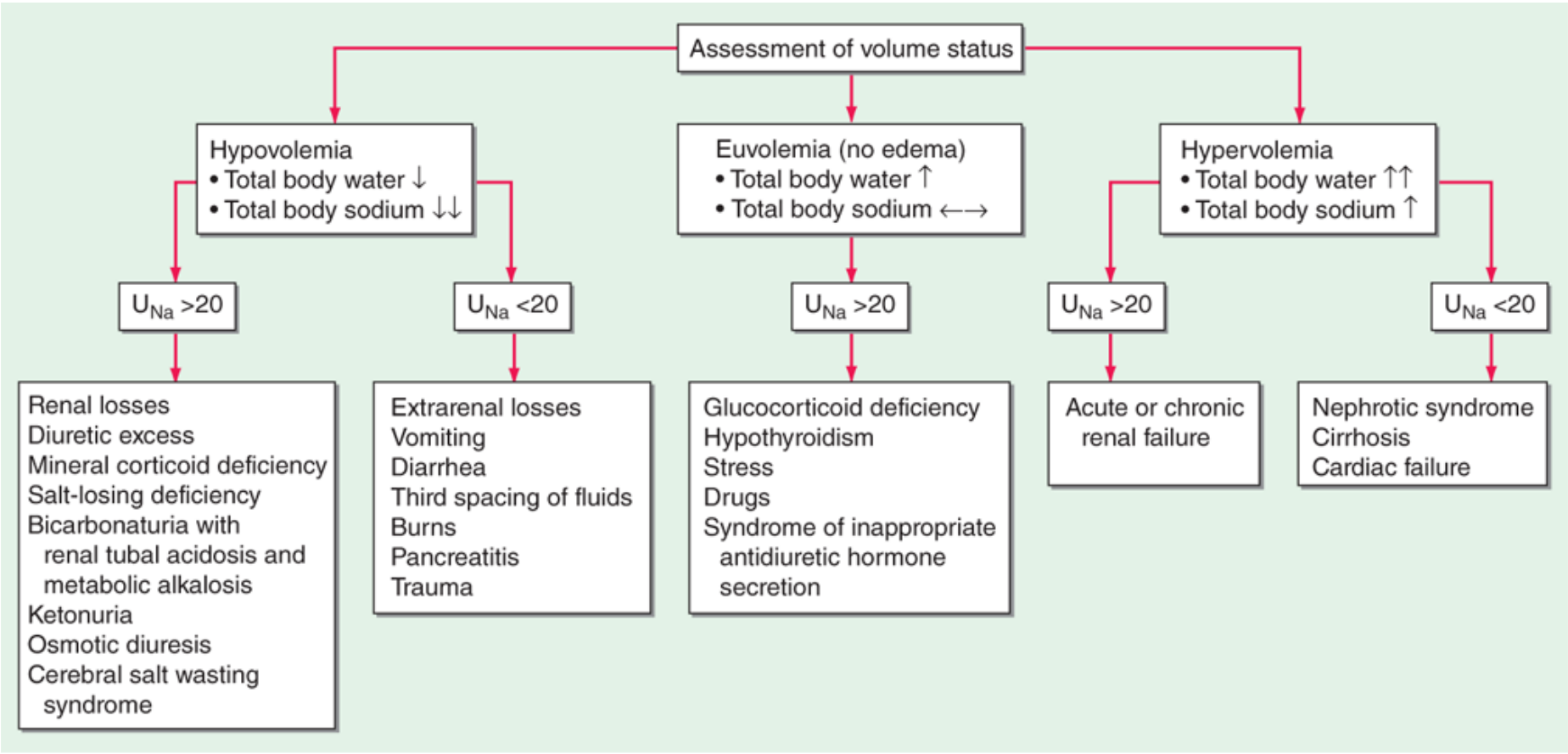
1. **Pseudohyponatremia: excess of lipids or abnormal protein (iron sensitive electrode-based methods of measurement)**
2. **Hyperosmolar hyponatremia: (Osmolality >290) hyperglycemia, mannitol, glycine**
3. **True hyponatremia: hypo-osmolar hyponatremia (Osmolality <285)**

低血鈉分類

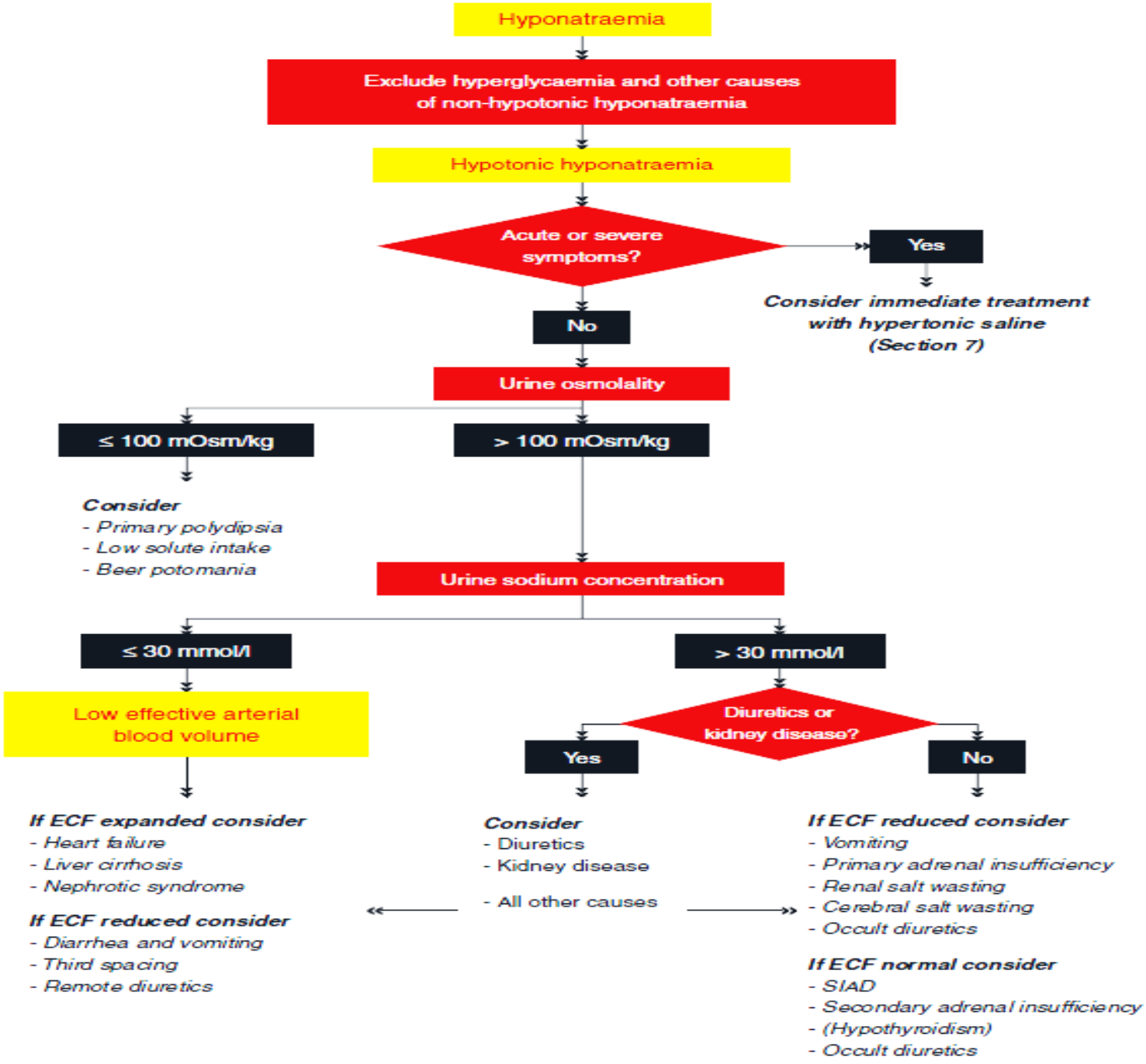
Classification	Criteria	Limitations of Clinical Utility
Moderate (125-129 mmol/L) versus Severe (<125 mmol/L)	**Absolute S_{Na}concentration**	**Symptoms do not always correlate with degree of hyponatremia**
Acute versus Chronic	**Time of development (48h)**	**Not always know**
Symptomatic versus asymptomatic	**Presence of symptoms**	**Aspecific symptoms, chronic may be symptomatic**
Hypotonic, isotonic, hypertonic	**Measure serum osmolality**	**Ineffective osmoles (urea, ethanol)**

Question 3: What is your diagnosis in this patient?

1. **Cerebral salt wasting**
2. **SIADH**
3. **Hypothyroidism**
4. **Adrenal insufficiency**



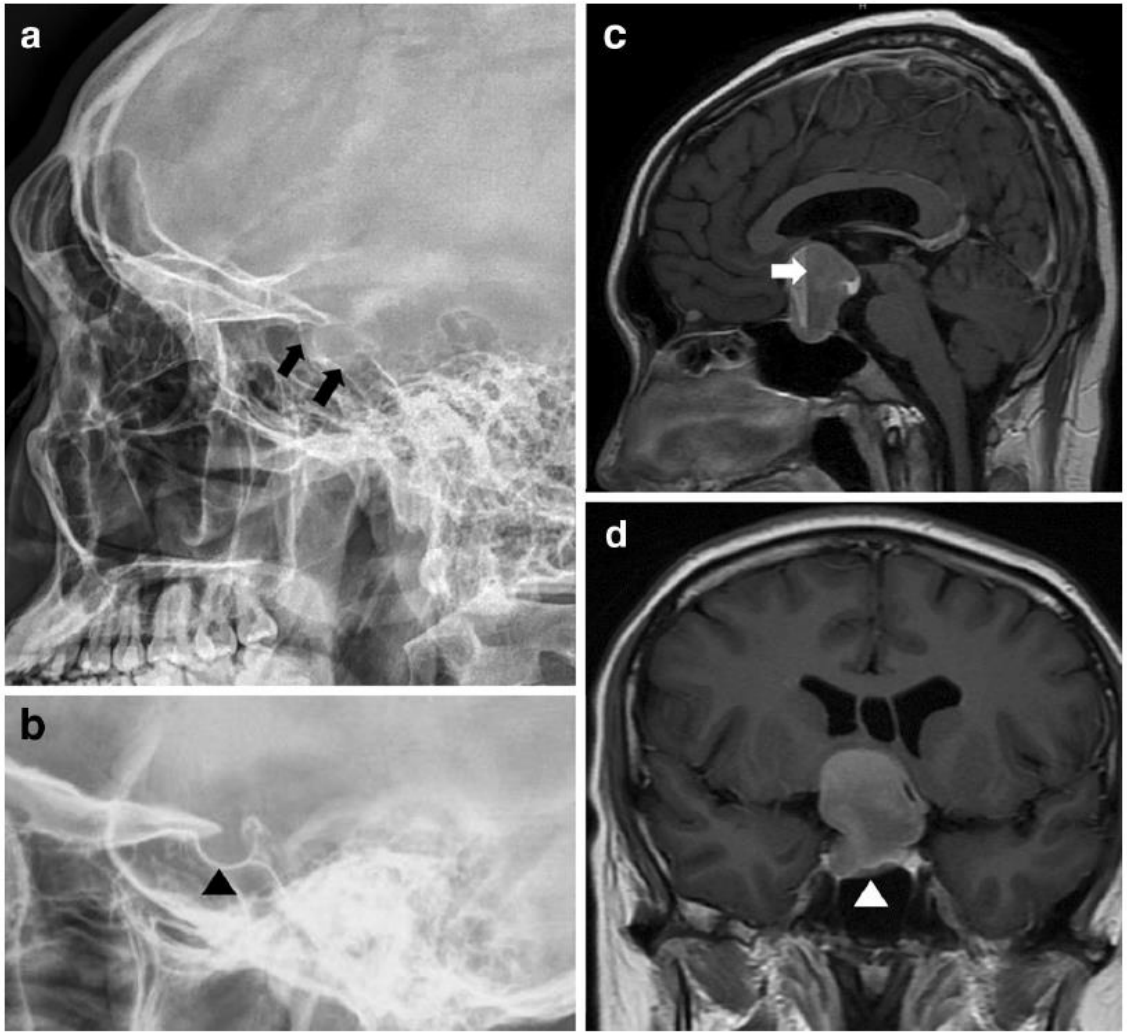
The diagnostic approach to hyponatremia. (From S Kumar, T Berl: Diseases of water metabolism, in Atlas of Diseases of the Kidney, RW Schrier [ed]. Philadelphia, Current Medicine, Inc, 1999; with permission.)


Hyponatraemia
Exclude hyperglycaemia and other causes of non-hypotonic hyponatraemia
Hypotonic hyponatraemia
Acute or severe symptoms?
Yes
Consider immediate treatment with hypertonic saline (Section 7)
No
Urine osmolality
≤ 100 mOsm/kg
> 100 mOsm/kg
Consider
- Primary polydipsia
- Low solute intake
- Beer potomania
Urine sodium concentration
≤ 30 mmol/l
> 30 mmol/l
Low effective arterial blood volume
Diuretics or kidney disease?
Yes
No
If ECF expanded consider
- Heart failure
- Liver cirrhosis
- Nephrotic syndrome
If ECF reduced consider
- Diarrhea and vomiting
- Third spacing
- Remote diuretics
Consider
- Diuretics
- Kidney disease
- All other causes
If ECF reduced consider
- Vomiting
- Primary adrenal insufficiency
- Renal salt wasting
- Cerebral salt wasting
- Occult diuretics
If ECF normal consider
- SIAD
- Secondary adrenal insufficiency
- (Hypothyroidism)
- Occult diuretics

Hormone study

- Prolactin at above 1000 ng/mL (reference range 2.1–17.7 ng/mL)
- LH level at 0.44 mIU/mL (reference range 1.5–9.3 mIU/mL); relative
- TSH at 1.22 uIU/mL (reference range 0.25–5.0 uIU/ mL);
- Free T4 level at 0.76 ng/dL (reference range 0.8–2 ng/dL);
- Testosterone level at 13 ng/ml (reference range 241–827 ng/dL)
- Low plasma cortisol level at 0.44 lg/dL (reference range 4.3–22.4 lg/dL)
- Low adrenocorticotropic hormone level at below 5 pg/mL (reference range 0.1–46.0 pg/mL), indicating panhypopituitarism except for prolactin.

Prolactinoma with hemorrhage consistent with pituitary apoplexy



抗利尿激素分泌失調綜合徵（syndrome of inappropriate antidiuretic hormone secretion, SIADH）

Essential criteria
Effective serum osmolality <275 mOsm/kg
Urine osmolality >100 mOsm/kg at some level of decreased effective osmolality
Clinical euvolaemia
Urine sodium concentration >30 mmol/l with normal dietary salt and water intake
Absence of adrenal, thyroid, pituitary or renal insufficiency
No recent use of diuretic agents
Supplemental criteria
Serum uric acid <0.24 mmol/l (<4 mg/dl)
Serum urea <3.6 mmol/l (<21.6 mg/dl)
Failure to correct hyponatraemia after 0.9% saline infusion
Fractional sodium excretion >0.5%
Fractional urea excretion >55%
Fractional uric acid excretion >12%
Correction of hyponatraemia through fluid restriction

Cause of SIADH

Malignant Diseases	Pulmonary Disorders	Disorders of the Central Nervous System	Drugs	Other Causes
Carcinoma	Infections	Infection	Drugs that stimulate release of AVP or enhance its action	Hereditary (gain-of-function mutations in the vasopressin V_2 receptor)
Lung	Bacterial pneumonia	Encephalitis	Chlorpropamide	Idiopathic
Small cell	Viral pneumonia	Meningitis	SSRIs	Transient
Mesothelioma	Pulmonary abscess	Brain abscess	Tricyclic antidepressants	Endurance exercise
Oropharynx	Tuberculosis	Rocky Mountain spotted fever	Clofibrate	General anesthesia
Gastrointestinal tract	Aspergillosis	AIDS	Carbamazepine	Nausea
Stomach	Asthma	Bleeding and masses	Vincristine	Pain
Duodenum	Cystic fibrosis	Subdural hematoma	Nicotine	Stress
Pancreas	Respiratory failure associated with positive-pressure breathing	Subarachnoid hemorrhage	Narcotics	
Genitourinary tract		Cerebrovascular accident	Antipsychotic drugs	
Ureter		Brain tumors	Ifosfamide	
Bladder		Head trauma	Cyclophosphamide	
Prostate		Hydrocephalus	Nonsteroidal anti-inflammatory drugs	
Endometrium		Cavernous sinus thrombosis	MDMA (“ecstasy”)	
Endocrine thymoma		Other	AVP analogues	
Lymphomas		Multiple sclerosis	Desmopressin	
Sarcomas		Guillain-Barré syndrome	Oxytocin	
Ewing’s sarcoma		Shy-Drager syndrome	Vasopressin	
		Delirium tremens		
		Acute intermittent porphyria		

Abbreviations: AVP, vasopressin; MDMA; 3,4-methylenedioxymethamphetamine; SSRI, selective serotonin reuptake inhibitor.
Source: From DH Ellison, T Berl: Syndrome of inappropriate antidiuresis. N Engl J Med 356:2064, 2007.

大腦耗鹽症候群
Cerebral salt wasting

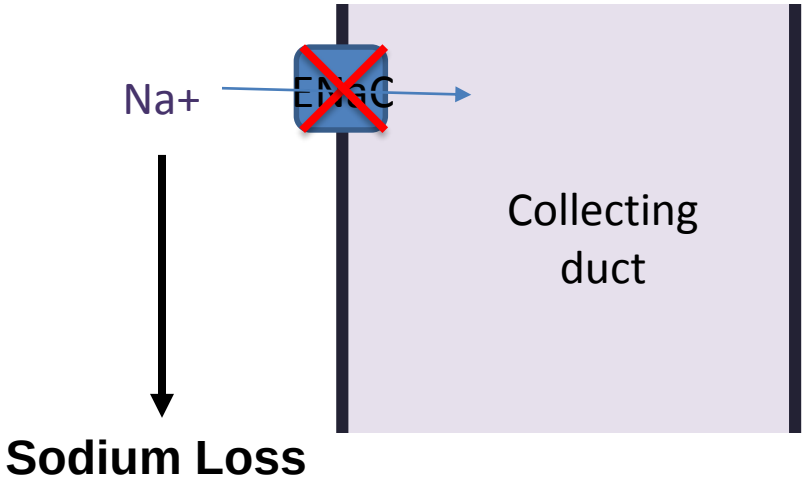
- Renal sodium loss
- Patients with intracranial disorders such as subarachnoid bleeding.
- Increased levels of brain natriuretic peptide
- Both inappropriate antidiuresis and secondary adrenal insufficiency are actually more common in this clinical setting
- Treatment requires volume resuscitation rather than water restriction.

SIADH or Cerebral salt wasting

	SIADH	Cerebral salt wasting
Serum urea concentration	Normal–low	Normal–high
Serum uric acid concentration	Low	Low
Urine volume	Normal–low	High
Urine sodium concentration	>30 mmol/l	≫30 mmol/l
Blood pressure	Normal	Normal–orthostatic hypotension
Central venous pressure	Normal	Low

Primary adrenal insufficiency

- Hypoaldosteronism causes renal sodium loss, contracted extracellular fluid volume (ECF)and hyponatraemia.



甲狀腺低下Hypothyroidism

- Only severe cases of clinically manifest hypothyroidism resulted in clinically important hyponatraemia.
- Development of hyponatraemia may be related to myxoedema, resulting from a reduction in cardiac output and glomerular filtration rate.

Question 4: What is your treatment for this patient?

1. Fluid restriction
2. SIADH
3. Hypothyroidism
4. Adrenal insufficiency

Subject	United States Guideline	European Guideline
Acute or symptomatic hyponatremia	Severe symptoms: Bolus 3% NaCl (100 ml over 10 min × 3 as needed)	Severe symptoms: Bolus 3% NaCl (150 ml over 20 min 2–3 times as needed)
	Moderate symptoms: Continuous infusion 3% NaCl (0.5–2 ml/kg per h)	Moderate symptoms: Bolus 3% NaCl (150 ml 3% over 20 min once)
Chronic hyponatremia		
SIAD	Fluid restriction (first line)	Fluid restriction (first line)
	Demeclocycline, urea, or vaptan (second line)	Urea or loop diuretics + oral NaCl (second line)
		Do not recommend or recommend against vaptan[a]
		Recommend against lithium or demeclocycline
Hypovolemic hyponatremia	Isotonic saline	Isotonic saline or balanced crystalloid solution
Hypervolemic hyponatremia	Fluid restriction	Fluid restriction
	Vaptans[b]	Recommend against vaptan
Correction rates	Minimum: 4–8 mmol/L per d, 4–6 mmol/L per d (high risk of ODS)	No minimum
	Limits: 10–12 mmol/L per d, 8 mmol/L per d (high risk of ODS)	Limit: 10 mmol/L per d
Management of overcorrection	Baseline $S_{Na} \geq 120$ mmol/L: probably unnecessary	Start once limit is exceeded
	Baseline $S_{Na} < 120$ mmol/L: start relowering with electrolyte-free water or desmopressin after correction exceeds 6–8 mmol/L per d	Consult an expert to discuss infusion containing electrolyte-free water (10 ml/kg) with or without 2 μg desmopressin iv

[a]"Do not recommend" when $S_{Na} < 130$ mmol/L, "recommend against" when $S_{Na} < 125$ mmol/L.
[b]In liver cirrhosis, restrict to patients where potential benefit outweighs risk of worsened liver function.[9]

Acute: hypertonic 3% saline (513 m*M*) to acutely increase plasma Na^+ concentration by 1–2 m*M*/h to a total of 4–6 m*M*

Chronic: slow in *chronic* hyponatremia (<8–10 m*M* in the first 24 h and <18 m*M* in the first 48 h)

Sodium Balance

- Typical Western diet: 150 mmol of NaCl each day
- Kidney excrete daily: around 150 mmol

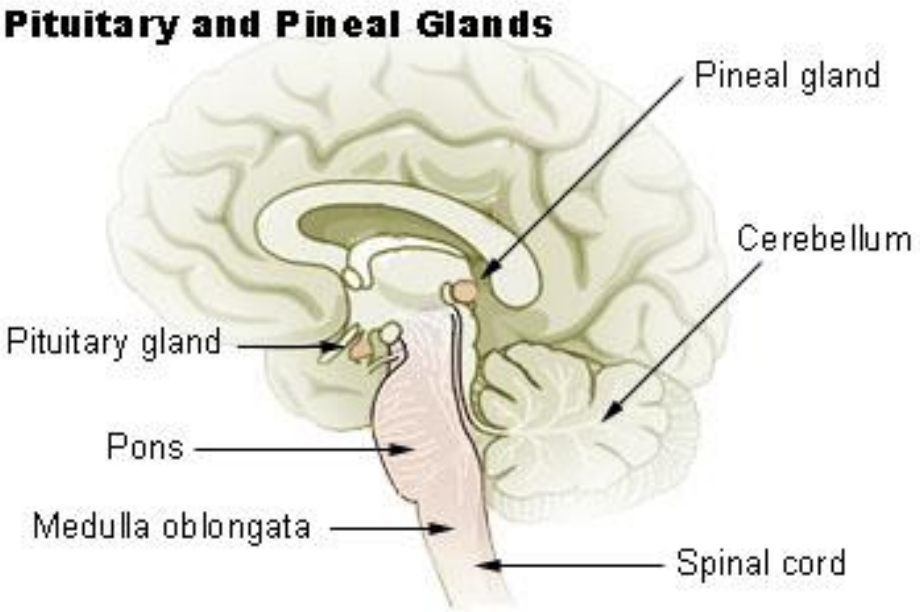
Sodium supplement

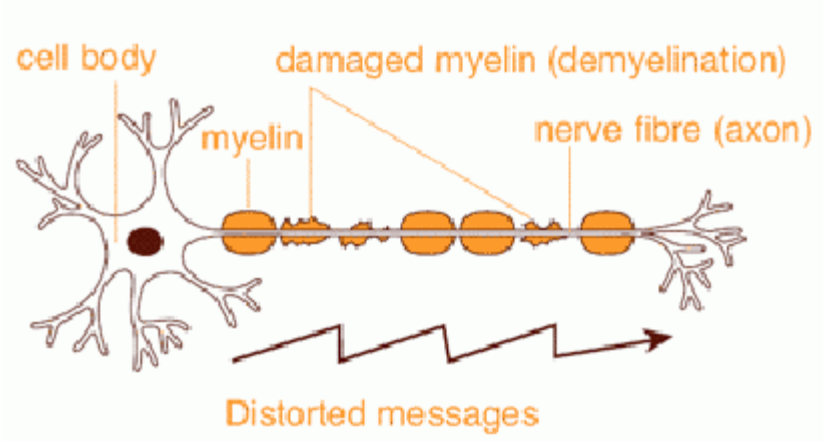
- 1g鹽片: 1000/58=17 meq
- 1顆鹽片: 10 meq
- Normal saline 500ml: 75 meq
- Half saline 500ml: 37 meq
- 3% 500ml:250 meq

100ml 3% 50 meq 10 min

滲透壓去髓鞘症候群 (Osmotic demyelination syndrome, ODS)

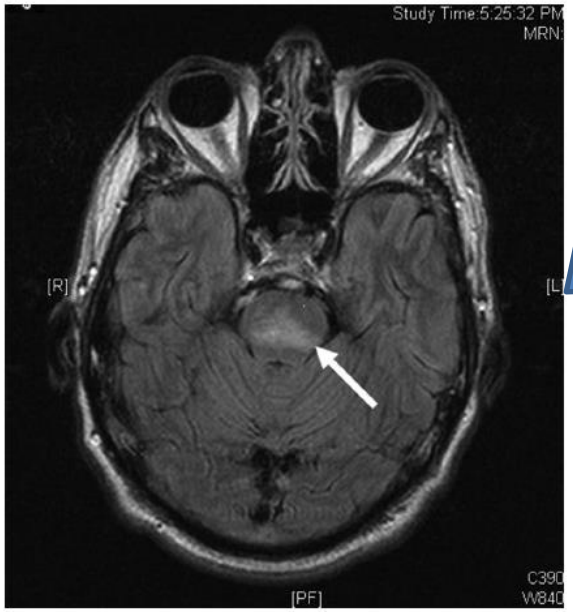
- Central pontine myelinolysis (CPM) was described by Adams and colleagues in 1959
- Extrapontine→osmotic demylination

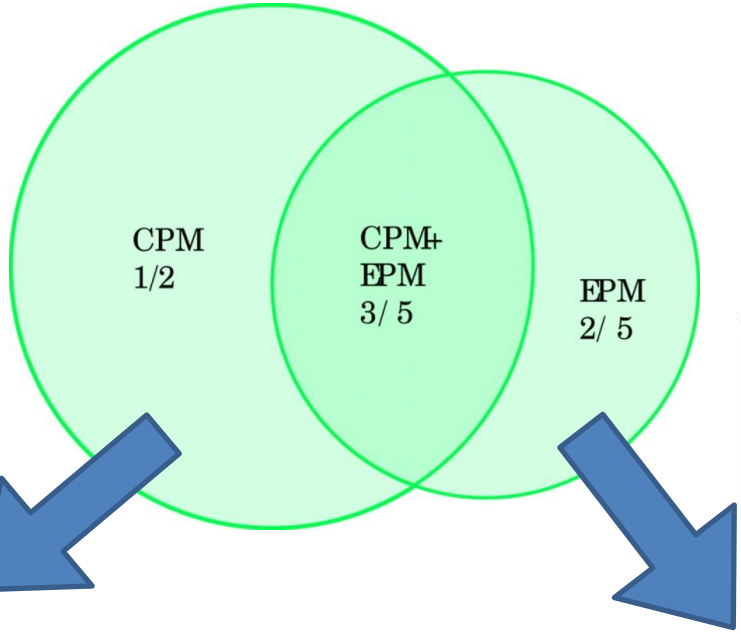


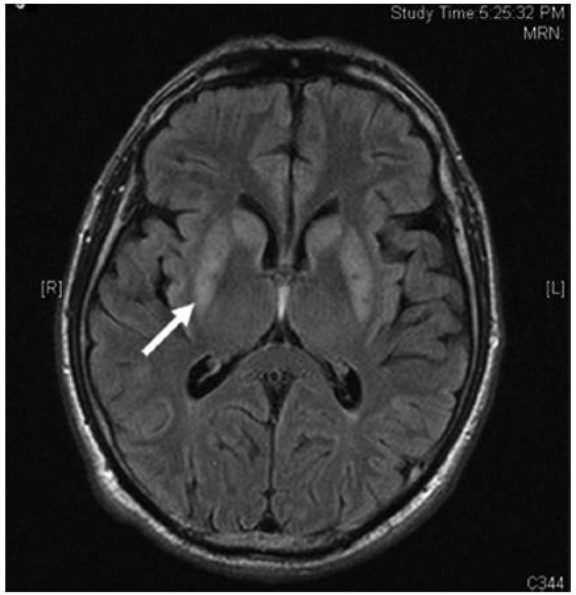


Am J Med Sci 2010;339(6):561–567

- **Central pontine myelinolysis (CPM)**
- **Extrapontine myelinolysis (EPM)**







J Neurol Neurosurg Psychiatry 2004;75:iii22-iii28

Osmotic demyelination syndrome, ODS

- Overly rapid correction of hyponatremia (>8–10 m*M* in 24 h or 18 m*M* in 48 h) is also associated with a disruption in integrity of the blood-brain barrier, allowing the entry of immune mediators that may contribute to demyelination.
- The lesions of ODS classically affect the pons, a neuroanatomic structure wherein the delay in the reaccumulation of osmotic osmolytes is particularly pronounced;
- clinically, patients with central pontine myelinolysis can present or more days after overcorrection of hyponatremia with paraparesis or quadriparesis, dysphagia, dysarthria, diplopia, a “locked-in syndrome,” and/or loss of consciousness.
- Other regions of the brain can also be involved in ODS, most commonly in association with lesions of the pons but occasionally in isolation; in order of frequency, the lesions of extrapontine myelinolysis can occur in the cerebellum, lateral geniculate body, thalamus, putamen, and cerebral cortex or subcortex.

Risk factors in ODS

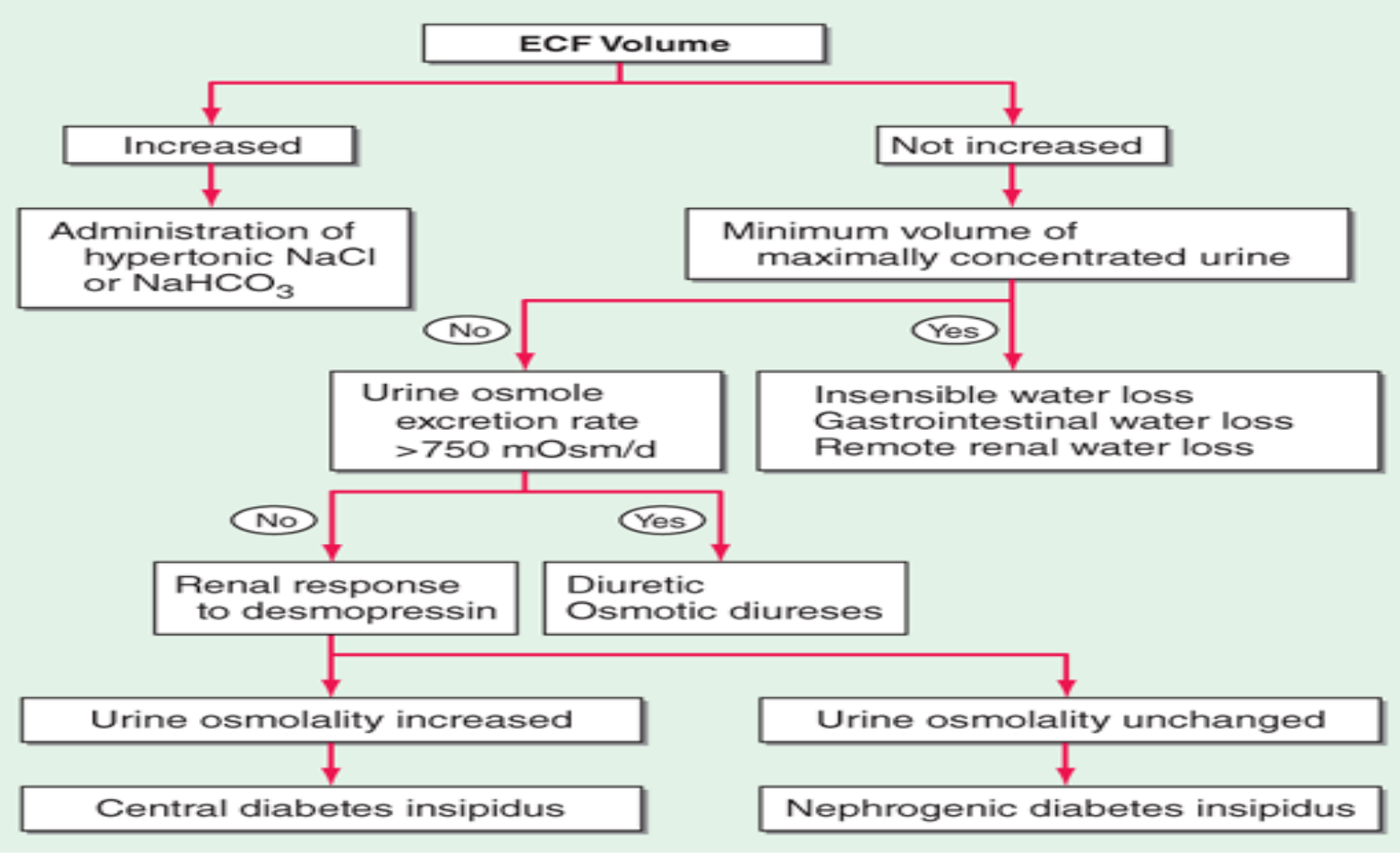
- Hypovolemic hyponatremia with hypertonic saline and/or normal saline
- Hypopituitarism or adrenal insufficiency upon the initiation of steroid therapy
- SIADH with hypertonic saline + loop diuretics
- Chronic hyponatremia in uremia treated with HD (ODS vs DDS)
- Cirrhosis of liver following withdrawal of pitressin

Lin SH, et al. Clin Nephrol 2002; 57: 86-88.

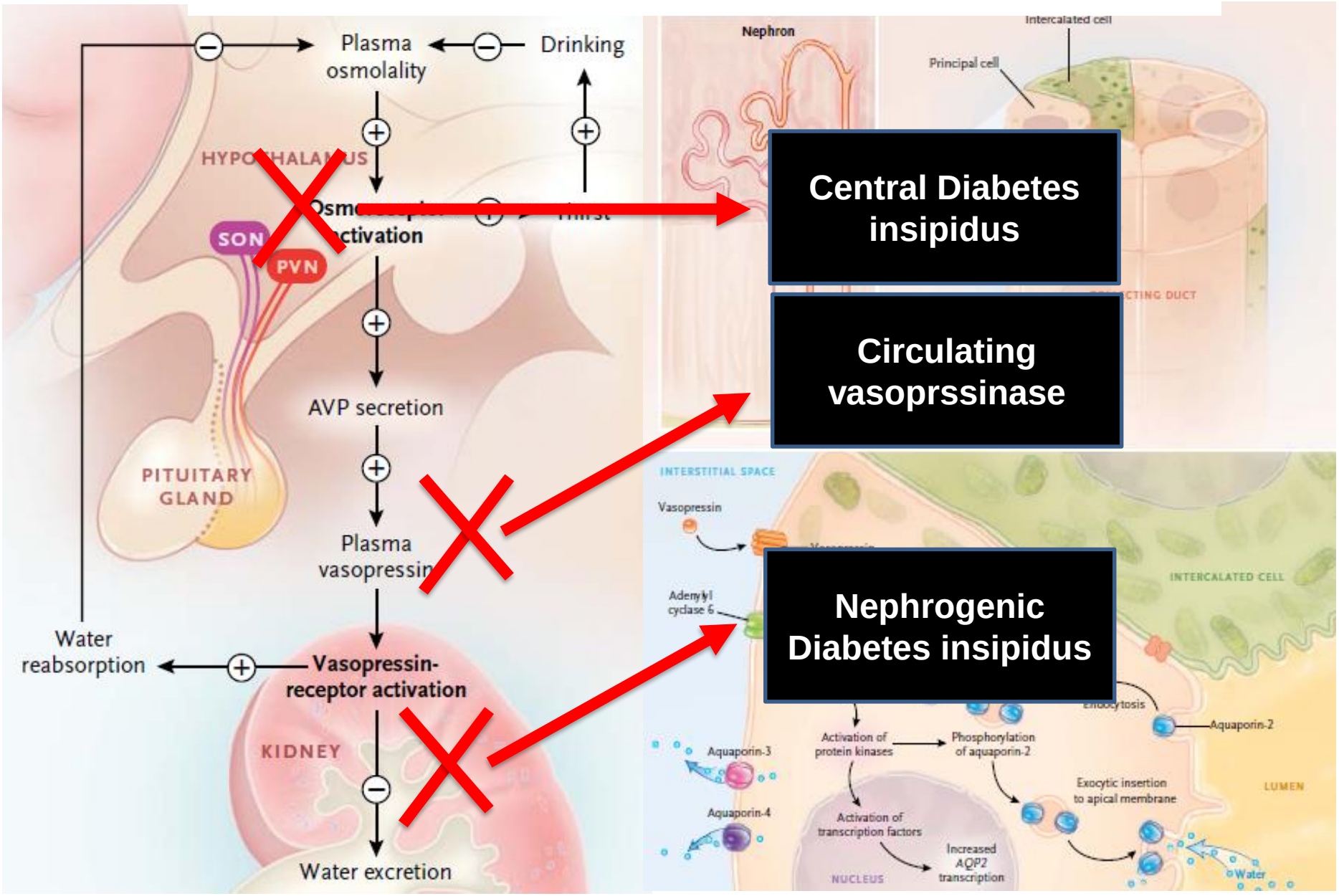
Hypernatremia的鑑別診斷

- Combined water and electrolyte deficit, with losses of H_2O in excess of Na^+ →Net water loss
- Renal water losses: Neurogenic or central diabetes insipidus, Nephrogenic diabetes insipidus, Renal losses (loop diuretics, osmotic diuresis.
- Non renal water losses: Hypodypsia, Respiratory or cutaneous, GI loss, hypertonic sodium gain

The diagnostic approach to hypernatremia



Diabetes insipidus 尿崩症



Central & Nephrogenic Diabetes insipidus

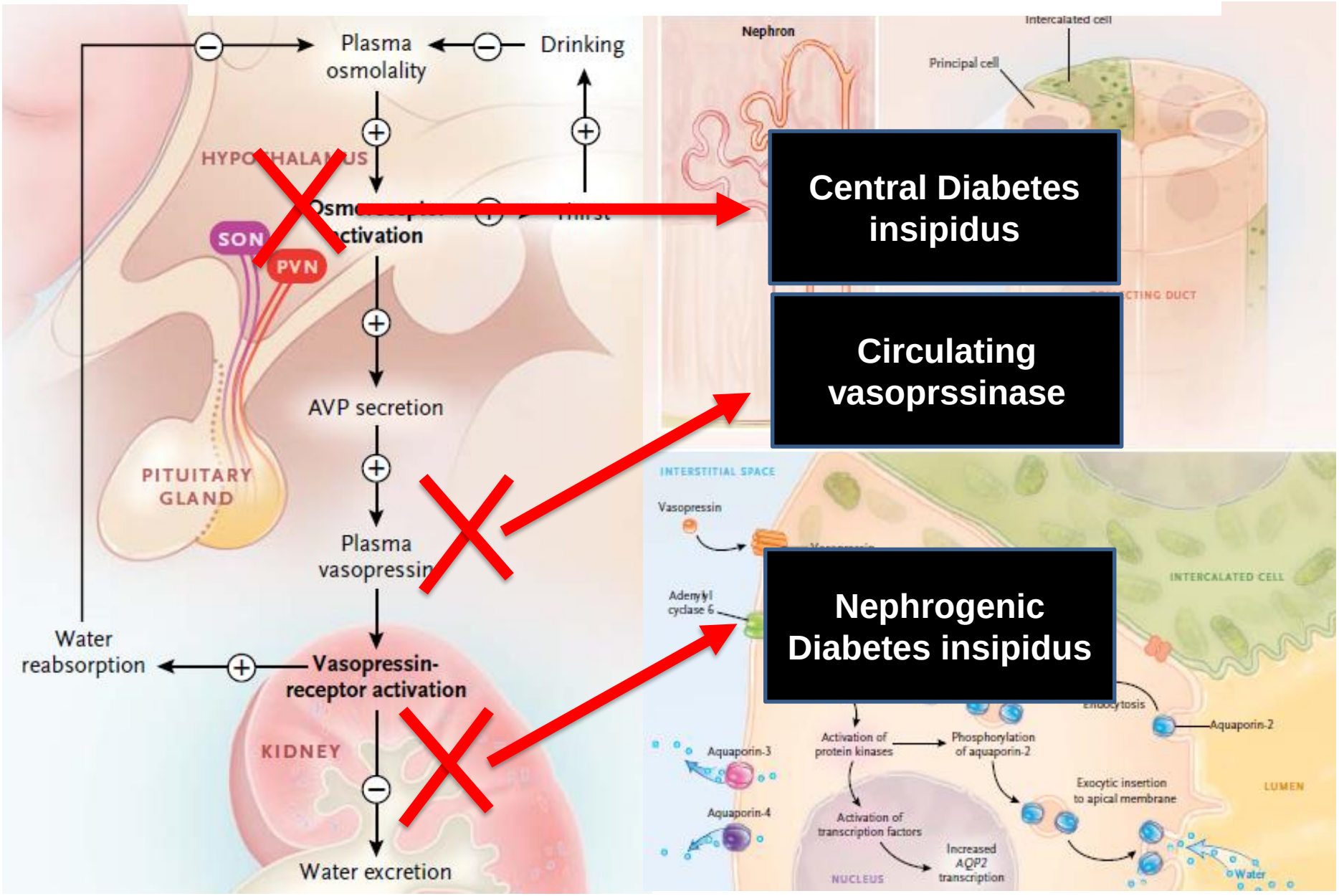
Table 1. Central Diabetes Insipidus vs Nephrogenic Diabetes Insipidus

	CDI	NDI
Vasopressin sensitivity	Sensitive	Resistant
Etiology		
Inherited	*AVP* gene mutations: autosomal dominant or recessive, 1%–2% (33) Wolfram syndrome: autosomal recessive, 1% (166)	*AVPR2* gene mutations: X-linked recessive, 90% (41, 167) *AQP2* gene mutations: autosomal recessive, 10% (168), or autosomal dominant <1% (42)
Acquired	Idiopathic (169) Trauma (surgery or accident) (170–172) Congenital disorders Tumors (benign + malignant; primary and metastatic) (173) Ischemic encephalopathy (174, 175) Infiltrative, autoimmune, and infectious diseases (169)	Drug-induced (eg, lithium ingestion) (40) Hypercalcemia (176), hypokalemia (177) Renal diseases (eg, autosomal dominant polycystic kidney disease and medullary cystic kidney disease) (36–39) Infiltrating lesions of kidney Sickle cell disease or trait (178)
Age of onset	Any age	Inherited form presents soon after birth Acquired forms present later and are often asymptomatic
Diagnosis dDAVP administration	Urine osmolality is restored to normal	Urine osmolality unaffected
Plasma AVP	Low or absent	Normal or elevated
Treatment	dDAVP is preferred over vasopressin	Hydrochlorothiazide and amiloride (the latter is substituted by indomethacin in children)

Na correction rate in hypernatremia

- Notably, the plasma Na^+ concentration should be corrected by no >10 m*M*/d, which may take longer than 48 h in patients with severe hypernatremia (>160 m*M*).
- A rare exception is patients with acute hypernatremia (<48 h) due to sodium loading, who can safely be corrected rapidly at a rate of 1 m*M*/h.
- Water should ideally be administered by mouth or by nasogastric tube, as the most direct way to provide free water, i.e., water without electrolytes. Alternatively, patients can receive free water in dextrose-containing IV solutions, such as 5% dextrose (D_5W); blood glucose should be monitored in case hyperglycemia occurs.
- Depending on the history, blood pressure, or clinical volume status, it may be appropriate to initially treat with hypotonic saline solutions (1/4 or 1/2 normal saline); normal saline is usually inappropriate in the absence of very severe hypernatremia, where normal saline is proportionally more hypotonic relative to plasma, or frank hypotension. Calculation of urinary electrolyte-free water clearance (Table 49-3) is required to estimate daily, ongoing loss of free water in patients with NDI or central DI, which should be replenished daily.

Diabetes insipidus 尿崩症



- 一位20歲男性，有嚴重多尿的現象。於禁水4小時後，小便滲透壓(osmolality)沒有明顯上升，注射 desmopressin(DDAVP)後，小便滲透壓亦沒有明顯上升，最可能的診斷為何?
- A.正常
- B.精神性多尿症
- C.中樞性尿崩症(central diabetes insipidus)
- D.腎性尿崩症(nephrogenic diabetes insipidus)

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- A.正常
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- C.中樞性尿崩症(central diabetes insipidus)
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- 一位21歲男性病人因長期多尿及夜尿至門診就診，血液檢查發現：鈉158 mmol/L，鉀3.7 mmol/L，氯124 mmol/L，尿液檢查發現鈉12 mmol/L，鉀6 mmol/L，肌酸酐32 mg/dL，滲透度60 mosm/kg HO，給予desmopressin（DDAVP）測試發現尿液滲透度上升至500 mosm/kg H22O，下列何者為正 確診斷？
- A.原發性多喝水症（Primary polydipsia）
- B.腎因性尿崩症（Nephrogenic diabetes insipidus）

C.中樞性尿崩症（Central diabetes insipidus） 鬲
D.滲透性利尿症（Osmotic diuresis）

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C.中樞性尿崩症（Central diabetes insipidus） 鳥

D.滲透性利尿症（Osmotic diuresis）

- 下列何種利尿劑可以用來治療先天性腎性尿崩症（congenital nephrogenic diabetes insipidus）所引起之多尿症？①thiazides ②loop diuretics ③acetazolamide ④amiloride
- 玠 A.①② 媳B.②③ 暯C.②④ 卤**D.①④**

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Central & Nephrogenic Diabetes insipidus

Table 1. Central Diabetes Insipidus vs Nephrogenic Diabetes Insipidus

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Vasopressin sensitivity	Sensitive	Resistant
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Age of onset	Any age	Inherited form presents soon after birth Acquired forms present later and are often asymptomatic
Diagnosis dDAVP administration	Urine osmolality is restored to normal	Urine osmolality unaffected
Plasma AVP	Low or absent	Normal or elevated
Treatment	dDAVP is preferred over vasopressin	Hydrochlorothiazide and amiloride (the latter is substituted by indomethacin in children)

- **26歲女性病人，最近一週有多喝和多尿。體重50公斤，血液osmolality 290 mOsmol/kg H2O，Na 140 mmol/L，K 3.8mmol/L。尿液osmolality 200 mOsmol/kg H2O，限水試2小時之體重47公斤，尿液osmolality 290 mOsmol/kg H2O，給予 ADH(DDAVP)後2小時內最高的尿液osmolality 320 mOsmol/kg H2O。下列敘述何者最正確?**
- **A.最可能的診斷是原發性多飲症(primary polydipsia)**
- **B.治療使用限水**
- **C.治療使用thiazides**
- **D.最可能的診斷是中樞型尿崩症(central diabetes insipidus)**

- **26歲女性病人，最近一週有多喝和多尿。體重50公斤，血液osmolality 290 mOsmol/kg H2O，Na 140 mmol/L，K 3.8mmol/L。尿液osmolality 200 mOsmol/kg H2O，限水試2小時之體重47公斤，尿液osmolality 290 mOsmol/kg H2O，給予 ADH(DDAVP)後2小時內最高的尿液osmolality 320 mOsmol/kg H2O。下列敘述何者最正確?**
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- **B.治療使用限水**
- **C.治療使用thiazides**
- **D.最可能的診斷是中樞型尿崩症(central diabetes insipidus)**

- 下列有關低血鈉症(hyponatremia)的描述，何者正確?
- A.如果血漿滲透壓(osmolality)偏低，應考慮是否有高血糖
- B.心臟衰竭可能造成細胞外體液(extracellular fluid)增加及低血鈉
- C.低血鈉及細胞外體液減少的病人，若尿液鈉離子濃度低於10 mmol/L，代表有Na wasting nephropathy
- D.抗利尿激素不適當分泌(SIADH)的病人通常血漿滲透壓正常，但細胞外體液減少

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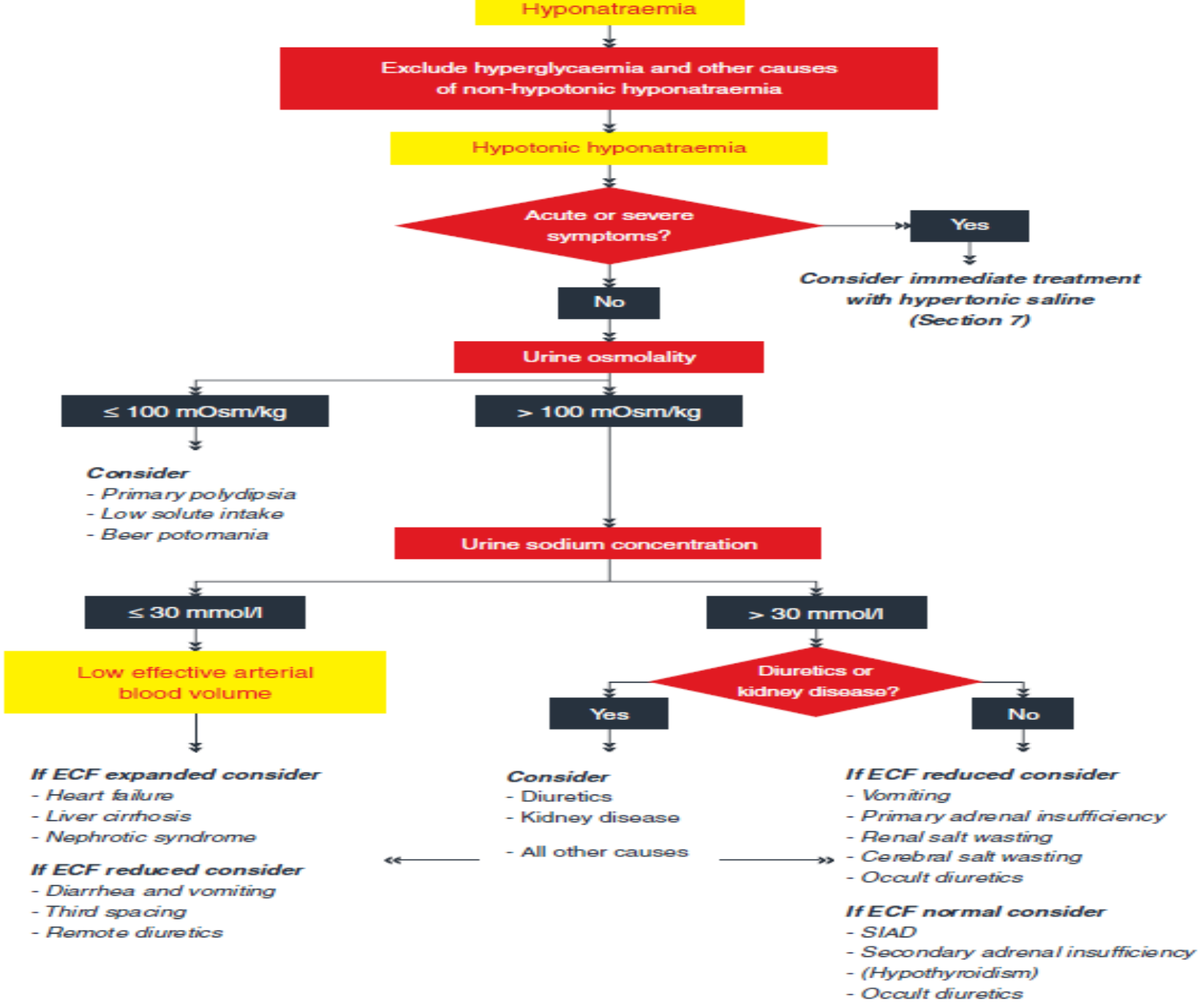
Hyponatraemia
Exclude hyperglycaemia and other causes of non-hypotonic hyponatraemia
Hypotonic hyponatraemia
Acute or severe symptoms?
Yes
Consider immediate treatment with hypertonic saline (Section 7)
No
Urine osmolality
≤ 100 mOsm/kg
> 100 mOsm/kg
Consider
- Primary polydipsia
- Low solute intake
- Beer potomania
Urine sodium concentration
≤ 30 mmol/l
> 30 mmol/l
Low effective arterial blood volume
Diuretics or kidney disease?
Yes
No
If ECF expanded consider
- Heart failure
- Liver cirrhosis
- Nephrotic syndrome
If ECF reduced consider
- Diarrhea and vomiting
- Third spacing
- Remote diuretics
Consider
- Diuretics
- Kidney disease
- All other causes
If ECF reduced consider
- Vomiting
- Primary adrenal insufficiency
- Renal salt wasting
- Cerebral salt wasting
- Occult diuretics
If ECF normal consider
- SIAD
- Secondary adrenal insufficiency
- (Hypothyroidism)
- Occult diuretics

抗利尿激素分泌失調綜合徵（syndrome of inappropriate antidiuretic hormone secretion, SIADH）

Essential criteria
Effective serum osmolality <275 mOsm/kg
Urine osmolality >100 mOsm/kg at some level of decreased effective osmolality
Clinical euvolaemia
Urine sodium concentration >30 mmol/l with normal dietary salt and water intake
Absence of adrenal, thyroid, pituitary or renal insufficiency
No recent use of diuretic agents
Supplemental criteria
Serum uric acid <0.24 mmol/l (<4 mg/dl)
Serum urea <3.6 mmol/l (<21.6 mg/dl)
Failure to correct hyponatraemia after 0.9% saline infusion
Fractional sodium excretion >0.5%
Fractional urea excretion >55%
Fractional uric acid excretion >12%
Correction of hyponatraemia through fluid restriction

- 下列何種引起低血鈉的情況，最適合以注射**0.9%**生理食鹽水來治療**?**
- **A.**高血糖**(hyperglycemia)**
- **B.**甲狀腺機能低下**(hypothyroidism)**
- **C.**皮質醛酮素缺乏**(aldosterone deficiency)**
- **D.SIADH(syndrome of inappropriate ADH secretion)**

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- C.皮質醛酮素缺乏(aldosterone deficiency)
- D.SIADH(syndrome of inappropriate ADH secretion)

- 63 歲男性，患有肺癌接受化學治療三天後，因意識不清被送至急診處。家人告知：病人食慾不好，有噁心但無嘔吐；身體診查：體溫36.8°C，血壓124/75 mmHg，脈搏78/min，呼吸18/min。病人除對時空有錯亂及嗜睡外，其他神經學檢查無異常；下肢無水腫；尿液檢查正常；尿素氮18 mg/dL，尿酸2.5 mg/dL，ALT 20 U/L，血糖108 mg/dL。血清電解質：Na+ 118，K+ 3.5，Cl- 79，free calcium 2.4（電解質單位mmol/L）；病人尿液的滲透壓是290 mOsmol/kg H2O。對此病人下列敘述何者錯誤？
- 琮A.病人的血清滲透壓估算大約是250 mOsmol/kg H2O
- 媦B.病人的抗利尿激素（antidiuretic hormone）是沒有分泌的
- 暟C.病人應該限制水分攝取
- 凅D.用高濃度的食鹽水靜脈輸注時，應該每2 小時監測血清鈉濃度，如果超過130 mmol/L 就應該停止

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- **媳B.病人的抗利尿激素（antidiuretic hormone）是沒有分泌的**
- 暟C.病人應該限制水分攝取
- 卼D.用高濃度的食鹽水靜脈輸注時，應該每2 小時監測血清鈉濃度，如果超過130 mmol/L 就應該停止

- 一位75歲女性，因昏迷而被送入院，其血清鈉（sodium）被發現為105 mEq/L。病史問起來，家中沒人照顧，昏迷可能有幾天之久了，提高血清鈉時需注意於第一天內（24小時內）提高血清鈉不可超過多少？
- A.12 mEq/L
- B.20 mEq/L
- C.24 mEq/L
- D.30 mEq/L

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- **A.12 mEq/L**
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- C.24 mEq/L
- D.30 mEq/L

Table 2. Comparison of the United States and European guidelines

Subject	United States Guideline	European Guideline
Acute or symptomatic hyponatremia	Severe symptoms: Bolus 3% NaCl (100 ml over 10 min × 3 as needed)	Severe symptoms: Bolus 3% NaCl (150 ml over 20 min 2–3 times as needed)
	Moderate symptoms: Continuous infusion 3% NaCl (0.5–2 ml/kg per h)	Moderate symptoms: Bolus 3% NaCl (150 ml 3% over 20 min once)
Chronic hyponatremia		
SIAD	Fluid restriction (first line)	Fluid restriction (first line)
	Demeclocycline, urea, or vaptan (second line)	Urea or loop diuretics + oral NaCl (second line)
		Do not recommend or recommend against vaptan[a]
		Recommend against lithium or demeclocycline
Hypovolemic hyponatremia	Isotonic saline	Isotonic saline or balanced crystalloid solution
Hypervolemic hyponatremia	Fluid restriction	Fluid restriction
	Vaptans[b]	Recommend against vaptan
Correction rates	Minimum: 4–8 mmol/L per d, 4–6 mmol/L per d (high risk of ODS)	No minimum
	Limits: 10–12 mmol/L per d, 8 mmol/L per d (high risk of ODS)	Limit: 10 mmol/L per d
Management of overcorrection	Baseline $S_{Na} \geq 120$ mmol/L: probably unnecessary	Start once limit is exceeded
	Baseline $S_{Na} < 120$ mmol/L: start relowering with electrolyte-free water or desmopressin after correction exceeds 6–8 mmol/L per d	Consult an expert to discuss infusion containing electrolyte-free water (10 ml/kg) with or without 2 μg desmopressin iv

[a] "Do not recommend" when $S_{Na} < 130$ mmol/L, "recommend against" when $S_{Na} < 125$ mmol/L.
[b] In liver cirrhosis, restrict to patients where potential benefit outweighs risk of worsened liver function.[9]

21.下列何種疾病不適合使用arginine vasopressin（AVP）拮抗劑（vaptans）？

A.抗利尿激素不適當分泌症候群（SIADH）

B.高體液低鈉血症（hypervolemic hyponatremia）

C.小細胞肺癌合併之低鈉血症

D.尿崩症（diabetes insipidus）

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D.尿崩症（diabetes insipidus）

- 1.一位40歲女性，因車禍接受頭部電腦斷層攝影檢查，發現腦下垂體部位有空蝶鞍(empty sella)現象。她目 前月經正常，飯前血糖90 mg/dL，PR 80/min，BP 130/80 mmHg，free T4 1.2 ng/dL(normal range 0.8~ 1.8 ng/dL)， TSH 1.0μIU/mL(normal range 0.1~2.0 μIU/mL)，early morning cortisol 15 μg/dL(normal range 8~18 μg/dL)。下列處置何者最恰當?
  A.經蝶鞍腦下垂體手術(transsphenoid surgery)
- B.放射治療(radiation therapy)
- C.藥物(bromocriptine therapy)
- D.說明病情使病患放心(reassurance)

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- 2.一位35歲的男性，因為意識不清被家人送至急診就醫，抽血檢查發現血鈉過高(160 mEq/L，參考值135~ 145 mEq/L)。有關高血鈉(hypernatremia)的處理，下列描述何者最適當?
- A.估算全身水量(total-body water):女性是體重的60%，而男性是體重的50%
- B.此病患若體重70公斤，計算free water缺乏量(free-water deficit)約5000 c.c.
- C.不易感知的水分流失(insensible losses)約5 mL/kg/day
- D.血鈉的矯正□　量不超過10 mM/day，以避免腦部水腫(cerebral edema)

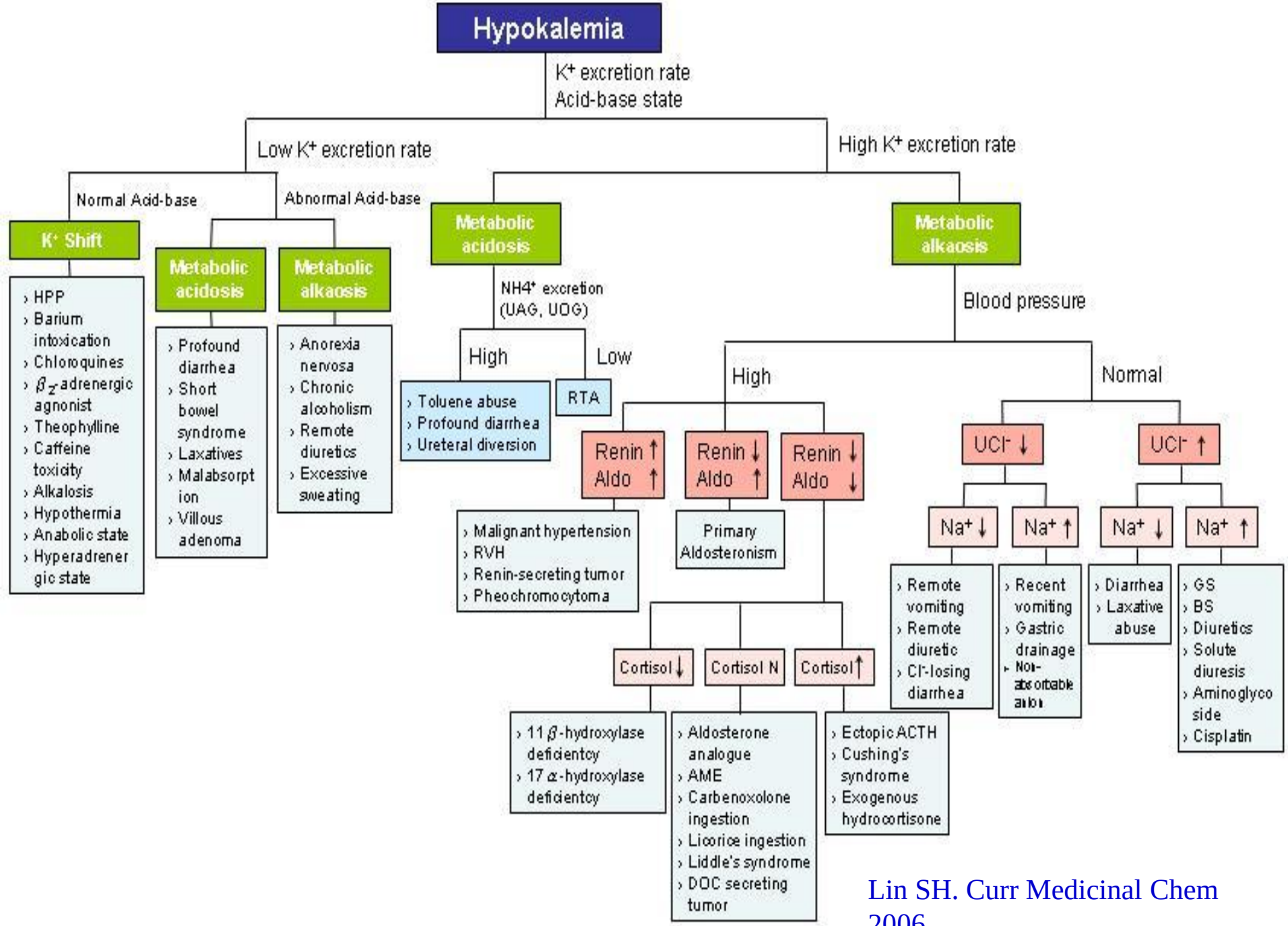
Water Deficit
1. Estimate total-body water (TBW): 50% of body weight in women and 60% in men 2. Calculate free-water deficit: $[(Na^+ - 140)/140] \times TBW$ 3. Administer deficit over 48–72 h, without decrease in plasma Na^+ concentration by >10 m*M*/24 h
Ongoing Water Losses
4. Calculate free-water clearance, C_eH_2O: $$C_eH_2O = V \times \left(1 - \frac{U_{Na} + U_K}{P_{Na}}\right)$$ where V is urinary volume, U_{Na} is urinary $[Na^+]$, U_K is urinary $[K^+]$, and P_{Na} is plasma $[Na^+]$
Insensible Losses
5. ~10 mL/kg per day: less if ventilated, more if febrile
Total
6. Add components to determine water deficit and ongoing water loss; correct the water deficit over 48–72 h and replace daily water loss. Avoid correction of plasma $[Na^+]$ by >10 m*M*/d.

- 2.一位35歲的男性，因為意識不清被家人送至急診就醫，抽血檢查發現血鈉過高(160 mEq/L，參考值135~ 145 mEq/L)。有關高血鈉(hypernatremia)的處理，下列描述何者最適當? A.估算全身水量(total-body water):女性是體重的60%，而男性是體重的50%
- B.此病患若體重70公斤，計算free water缺乏量(free-water deficit)約5000 c.c.
- C.不易感知的水分流失(insensible losses)約5 mL/kg/day
- D.血鈉的矯正□　量不超過10 mM/day，以避免腦部水腫(cerebral edema)

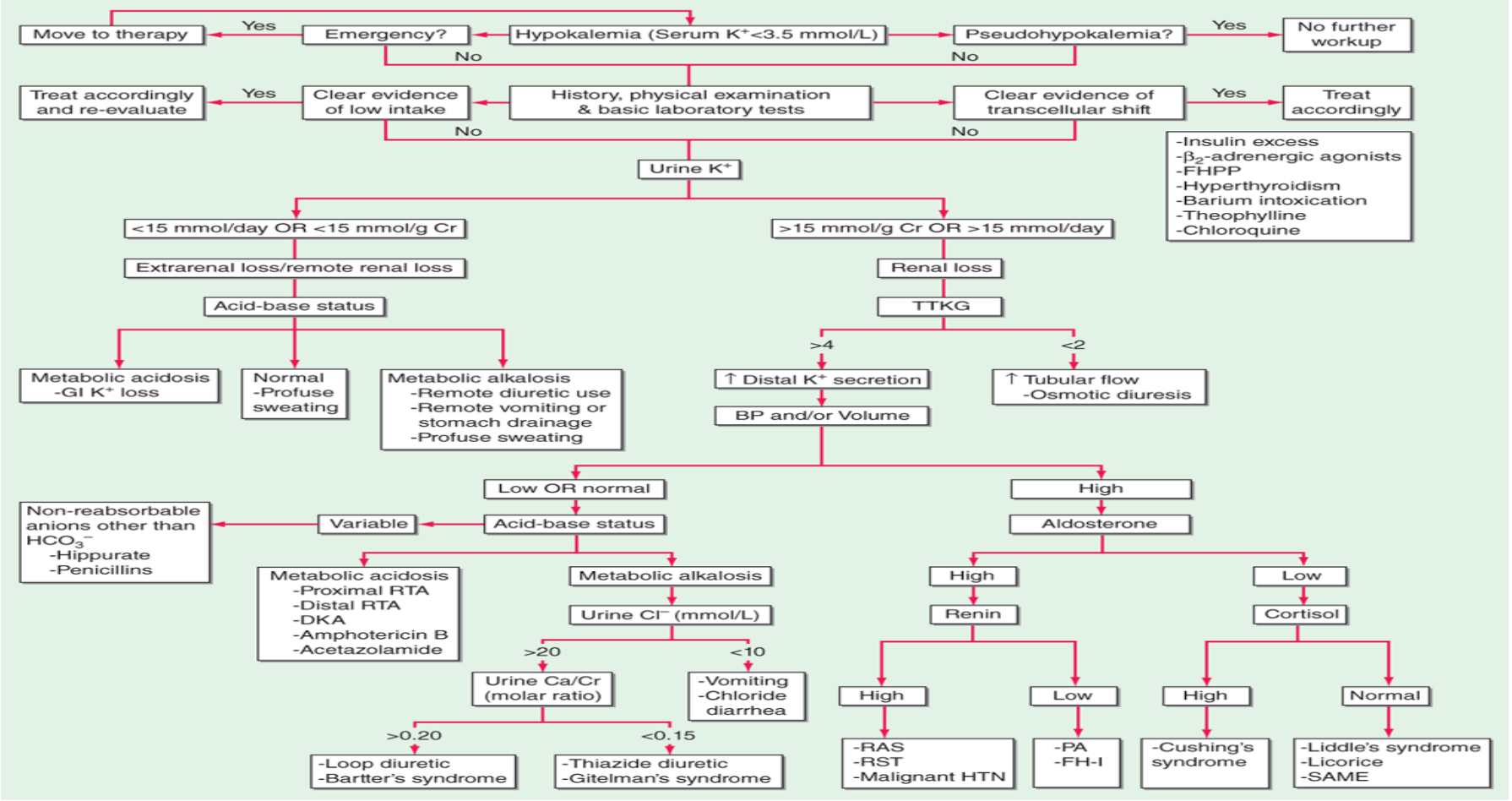
Water is the most abundant constituent in the body, comprising approximately 50% of body weight in women and 60% in men. Total-body water is distributed in two major compartments: 55–75% is intracellular (intracellular fluid [ICF]), and 25–45% is extracellular (extracellular fluid [ECF]). The ECF is further subdivided into intravascular (plasma water) and extravascular (interstitial) spaces in a ratio of 1:3.

Evaporation of water from the skin and respiratory tract (so-called "insensible losses") constitutes the major route for loss of solute-free water, which is typically 500–650 mL/d in healthy adults.

K



Lin SH. Curr Medicinal Chem 2006



The diagnostic approach to hypokalemia. See text for details. AME, apparent mineralocorticoid excess; BP, blood pressure; CCD, cortical collecting duct; DKA, diabetic ketoacidosis; FH-I, familial hyperaldosteronism type I; FHPP, familial hypokalemic periodic paralysis; GI, gastrointestinal; GRA, glucocorticoid remediable aldosteronism; HTN, hypertension; PA, primary aldosteronism; RAS, renal artery stenosis; RST, renin-secreting tumor; RTA, renal tubular acidosis; SAME, syndrome of apparent mineralocorticoid excess; TTKG, transtubular potassium gradient. (Used with permission from DB Mount, K Zandi-Nejad K: Disorders of potassium balance, in Brenner and Rector's The Kidney, 8th ed, BM Brenner [ed]. Philadelphia, W.B. Saunders & Company, 2008, pp 547–587.)

Potassium

K^+ Daily intake

- WHO: The recommended level of intake of ≥90 mmol/day is a conditional recommendation for adults
- US National Academies:120 mmol/day
- **Taiwan:**

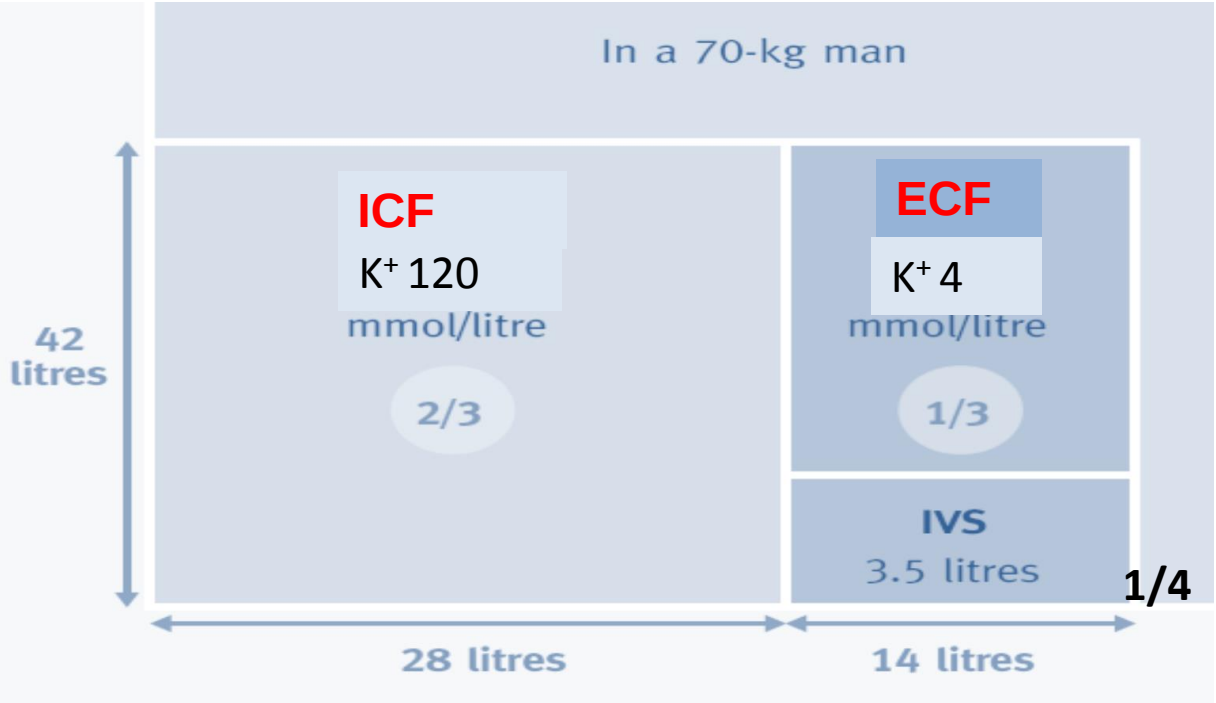
Male 67 mmol/day
Female 52 mmol/day

The National Academies Press: Washington, DC, 2005; 186-268

Potassium Homeostasis

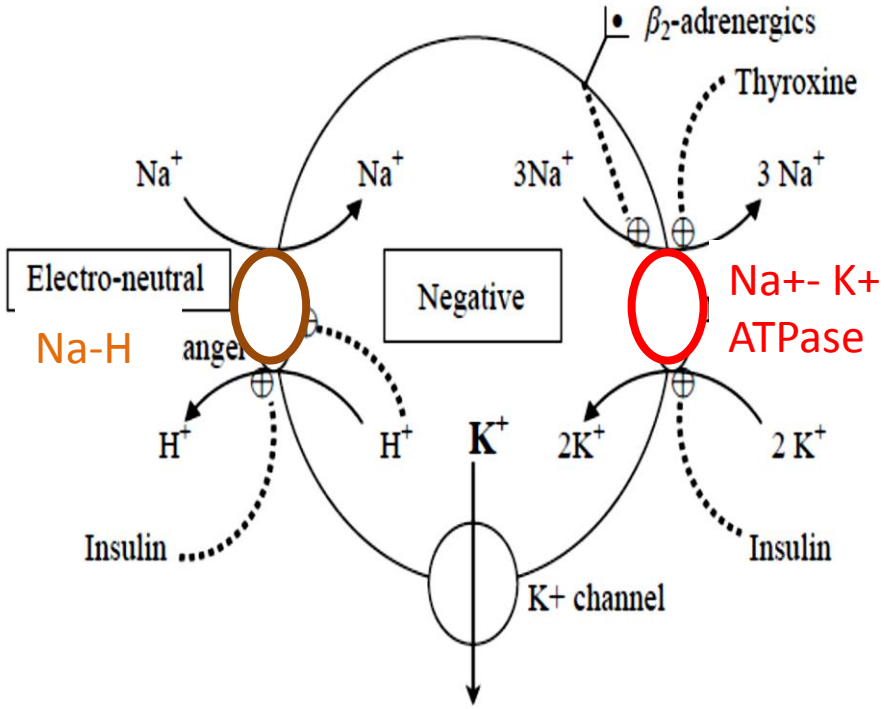
- Potassium is the most abundant intracellular cation
- 98% intracellular: 3000-4000 mmol/L (50 mmol/Kg)

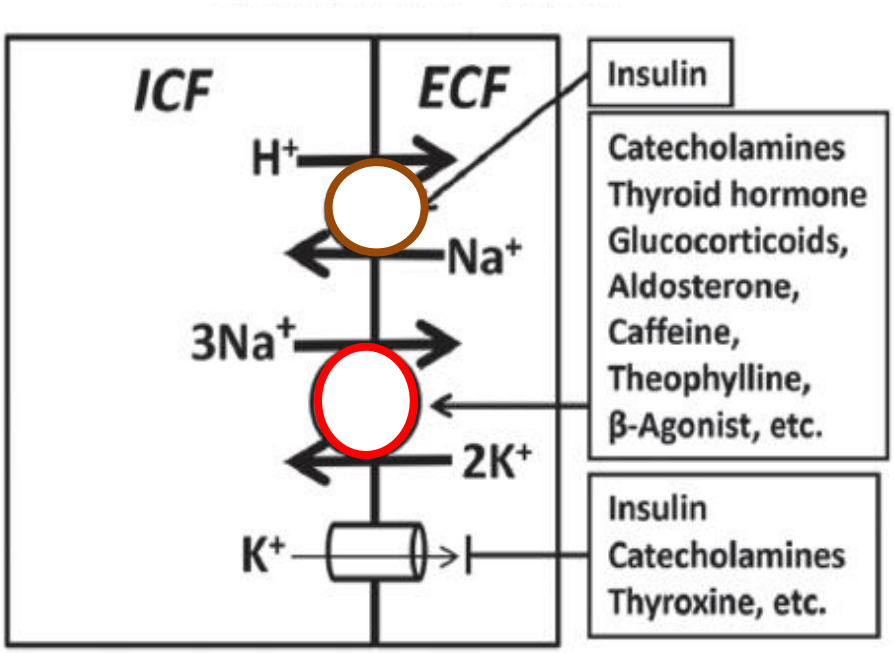
  Muscle (3000 mmol), RBC (200 mmol) and liver (200 mmol)
- 2 % Extracellular: 60-80 mmol



Halperin ML et al Lancet 1998

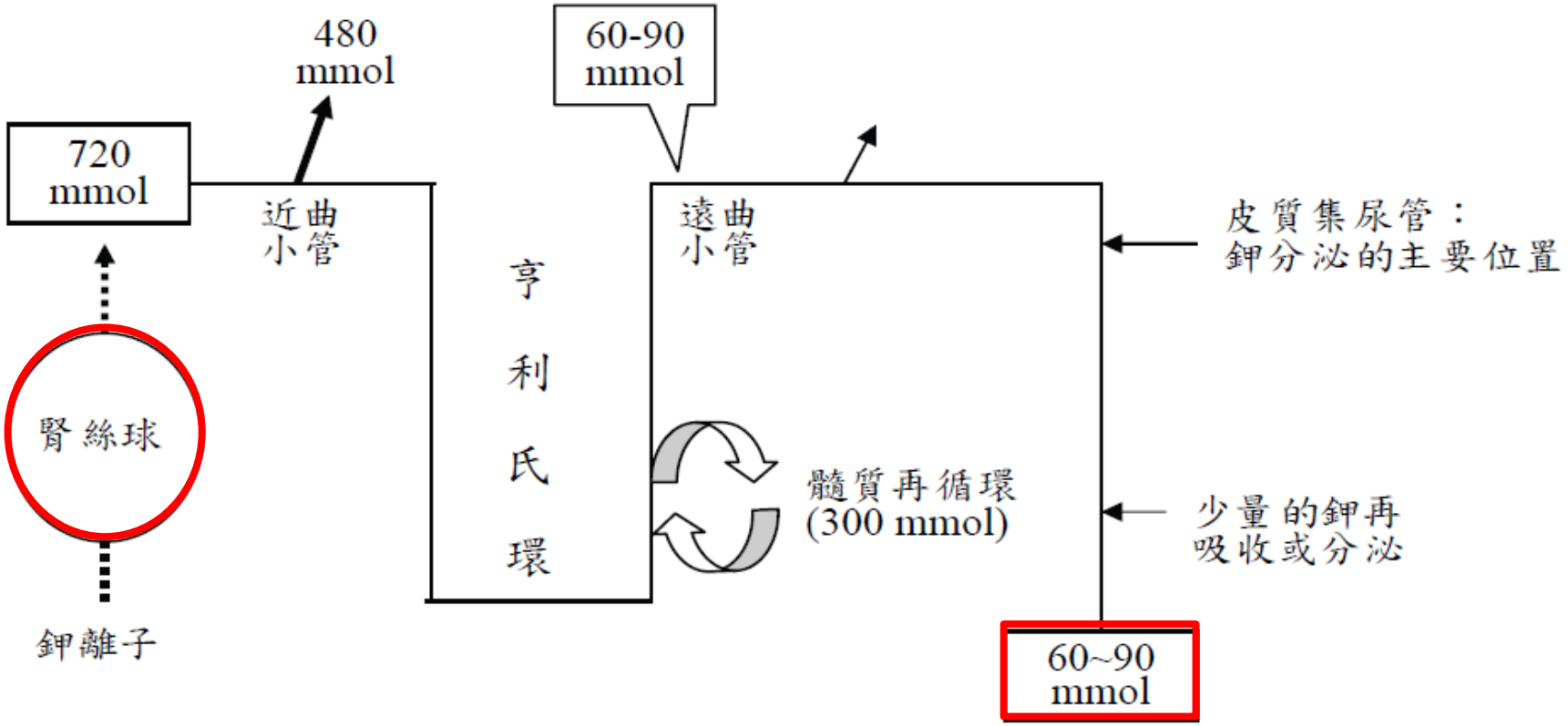
Intracellular regulation





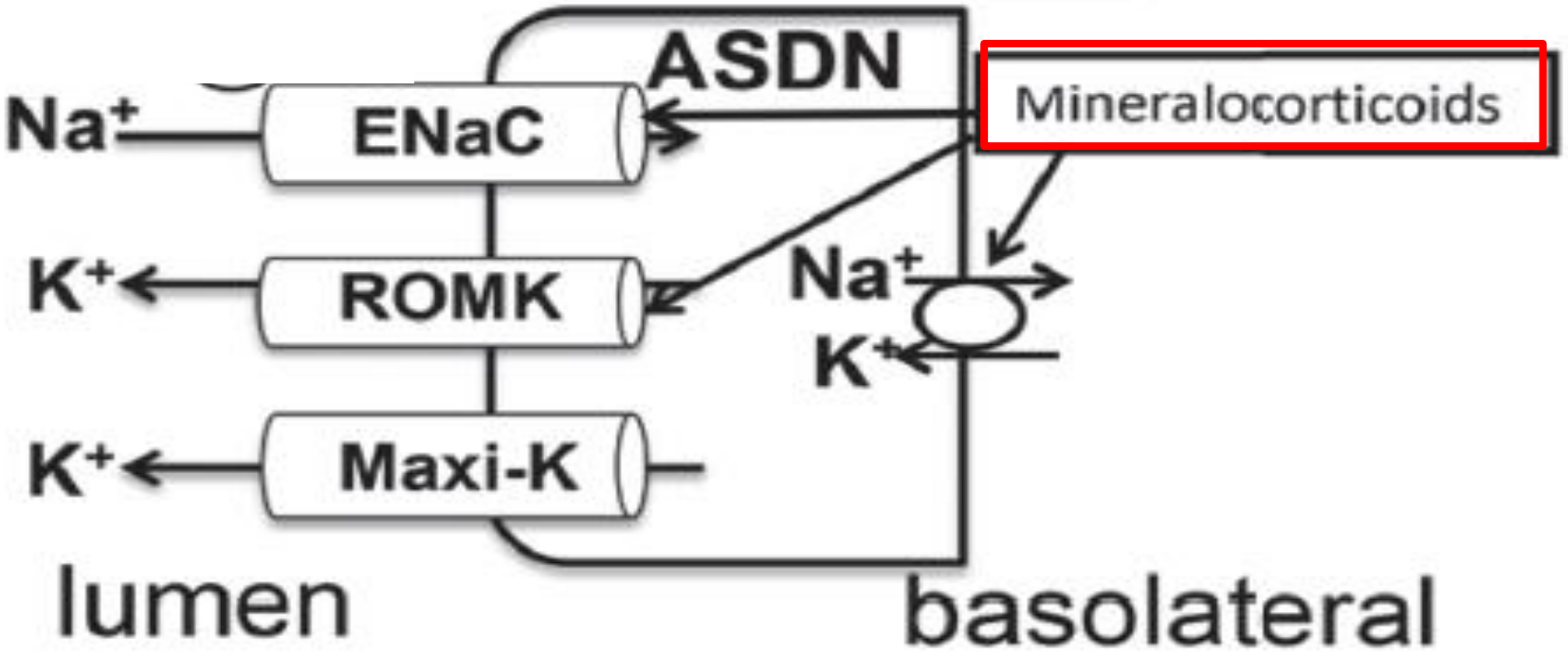
Wei KY, Cheng CJ, Lin SH. Kidney and Dialysis

Renal K^+ excretion



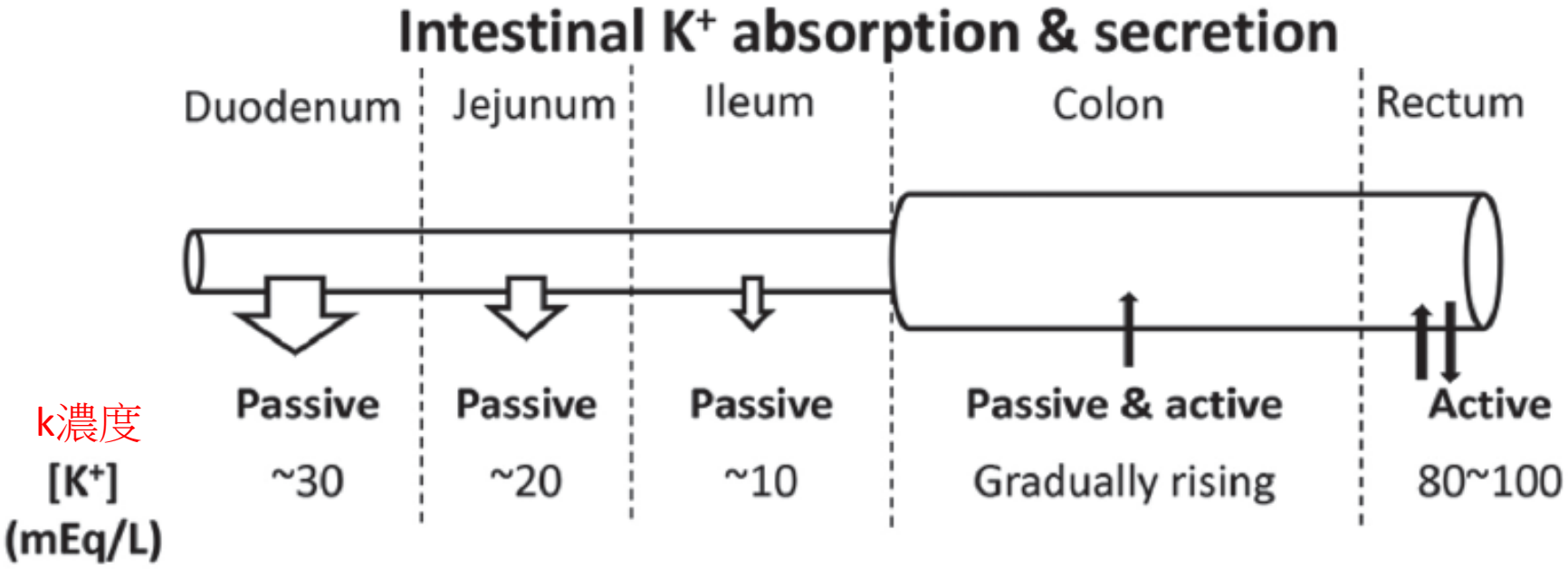
Lee CC, Huang WT, Lin SH. Intern Med Taiwan 2010

遠端腎小管鉀分泌



Wei KY, Cheng CJ, Lin SH. Kidney and Dialysis 2018

Intestinal K absorption and secretion



- Absorption: 80-90% in duodenum and jejunum
- Daily K excretion: 5-15 mmol

Wei KY, Cheng CJ, Lin SH. Kidney and Dialysis

低血鉀的臨床症狀與表徵

心臟 心律不整、心肌收縮力下降、血壓上升、增加毛地黃類藥物毒性。

腎臟 在慢性低血鉀狀況下，腎絲球濾過率及腎血流下降、腎臟濃縮小便能力下降導致多尿、腎臟對鈉、檸檬酸(citrate) 及重碳酸根(HCO3-)重吸收增加導致高血壓、低檸檬酸尿症(hypocitraturia) 及代謝性鹼中毒、腎囊泡(renal cyst) 形成，甚至導致慢性腎臟病。

肌肉 腸胃道蠕動減少、膀胱收縮力減少導致膀胱擴大、橫紋肌溶解、肌肉無力癱瘓。

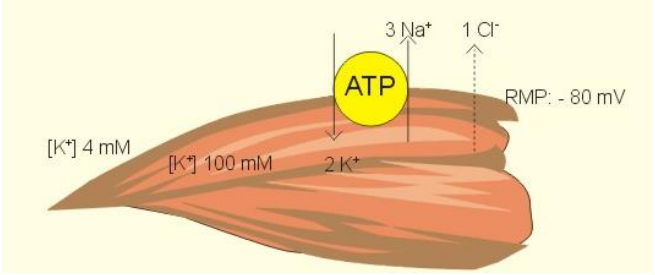
周邊神經 感覺異常、肌腱反射(deep tendon reflex) 減少。

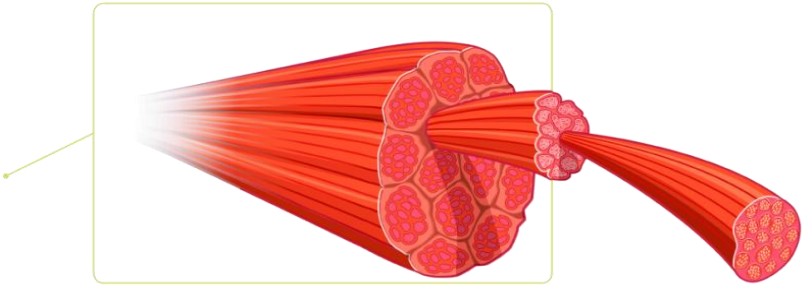
新陳代謝 (慢性低血鉀狀況下) 醛固酮(aldosterone) 分泌減少、增加胰島素抗性、增加腎素(renin) 分泌、增加胺離子生成(ammoniagenesis)。

J Intern Med Taiwan 2010; 22: 31-39

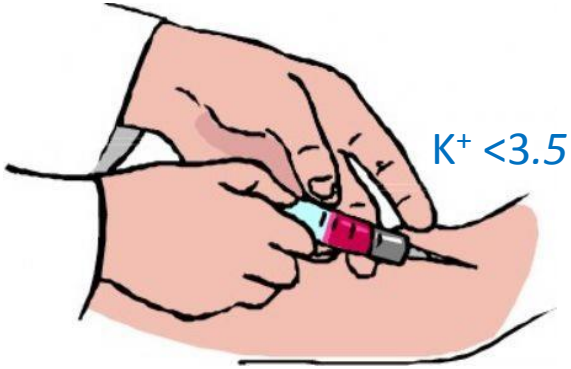
Hypokalemic Paralysis

- Abrupt muscle weakness and even paralysis associated with acute hypokalemia





RMP more negative



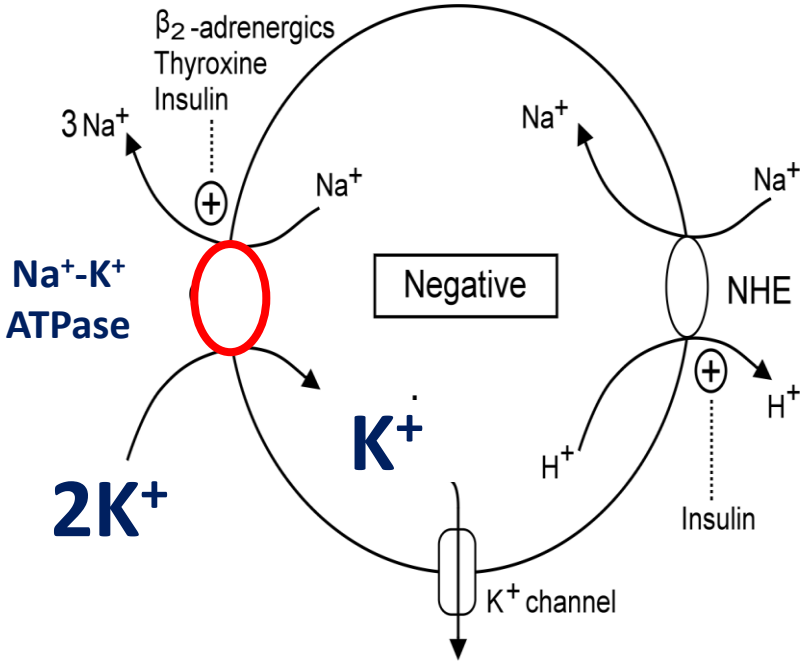
K^+ <3.5 mEq/l

Paralysis

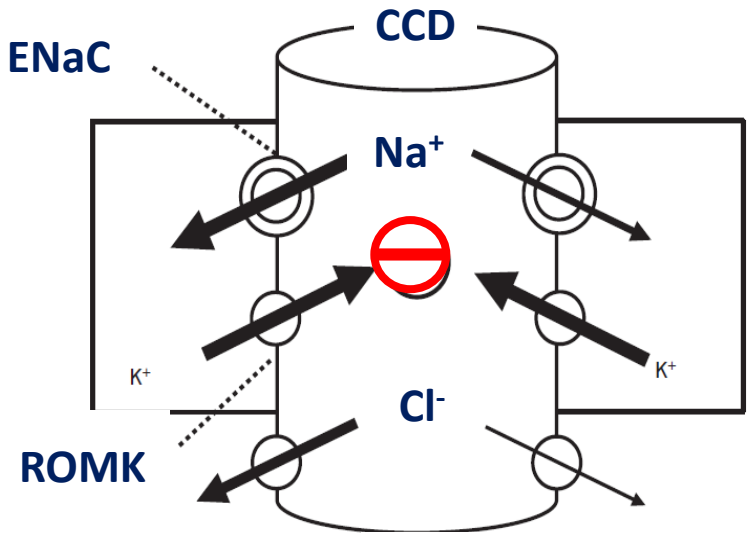
Arch Intern Med 2004;164:1561-1566.

Where is the K^+ going?

Increased K^+ shift



Increased Renal K^+ Excretion



Fast Na^+ — **High BP**

High K^+ — **Normal or low BP**

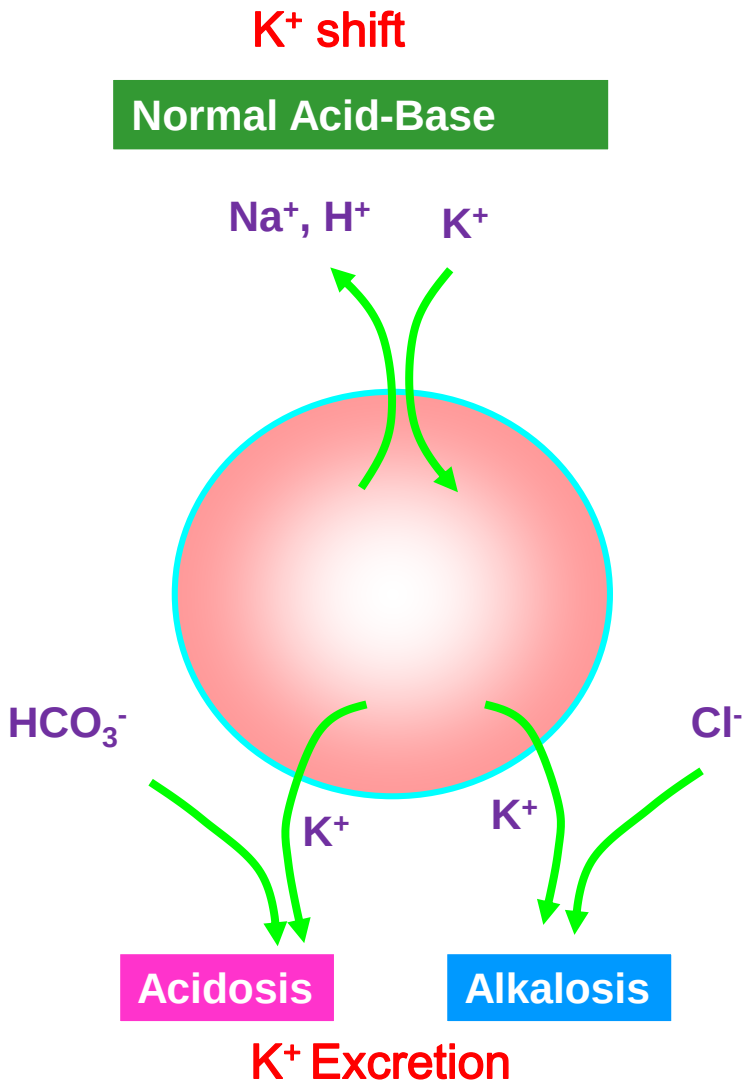
Slow Cl^- — **Urine Na, Cl, divalents**

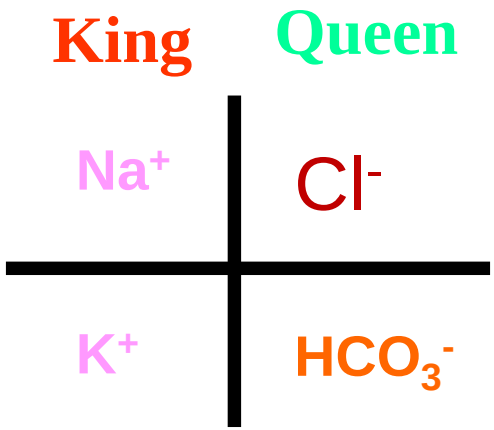
MES: PRA, Aldo, cortisol

Acute hypokalemia with K^+ shift

Chronic hypokalemia with K^+ deficit

Acid-Base in Hypokalemia





Clues: NH_4 excretion (UAG, UOG, pH)

BP, PRA, Aldo, Cortisol
UNa^+, K^+, Cl^-, Mg^{+2}, Ca^{+2}, Cr, Osm

What is Urine K^+ Excretion Rate?

24 hour Urine

- Time-consuming
- Inconvenient
- Inadequate urine collection
- Influenced by K^+ supplement and/or saline administration
- Influenced by drugs
- Assess by K^+ concentration (15-25 mmol/L) or excretion rate (15-20 mmol/day)?
- Less useful for K^+ shift disorders
- Do not reveal hour to hour K^+ excretion rate (8 hr vs 16hr)

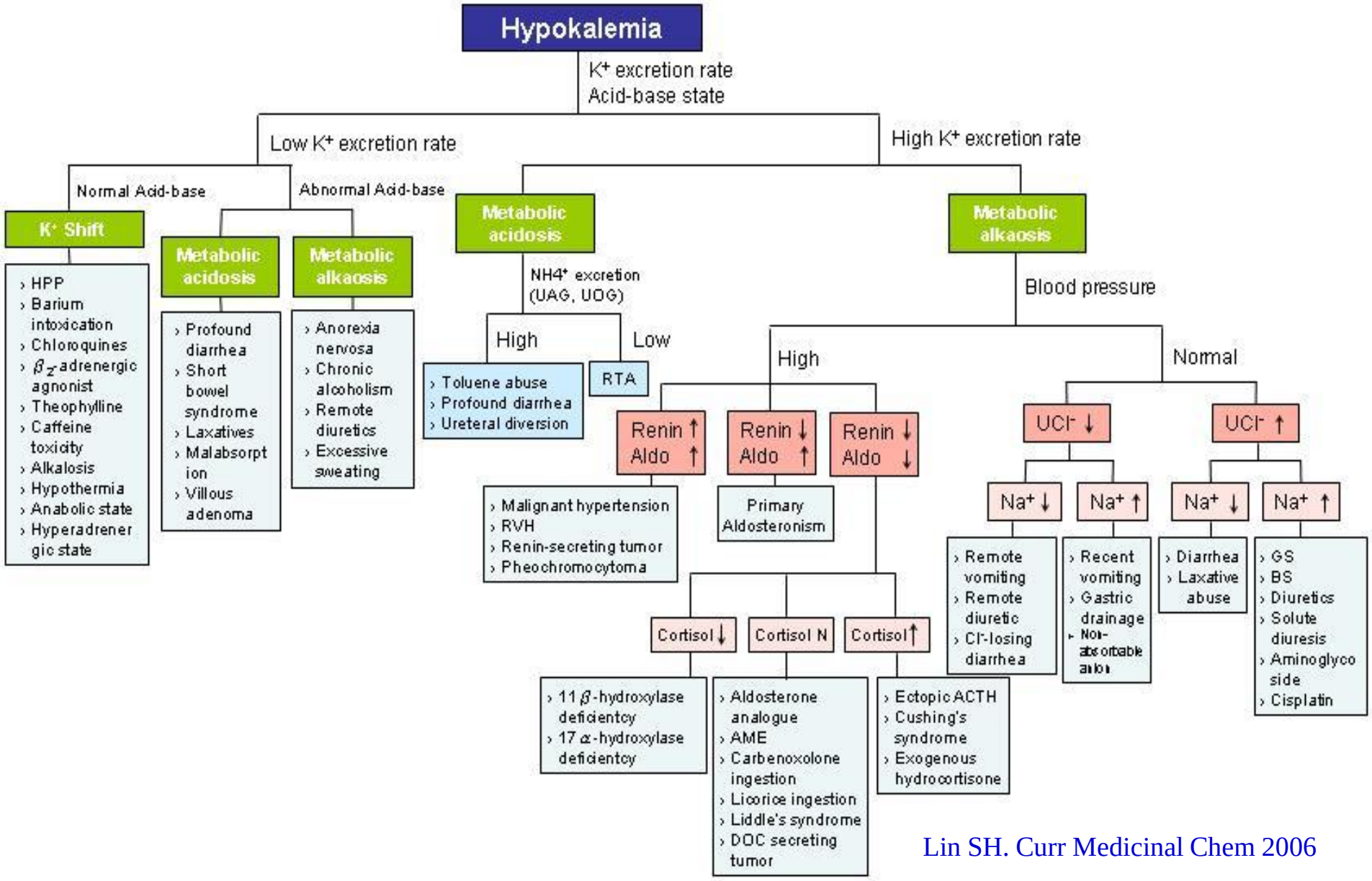
Therapeutic course

Spot Urine

- Urine K^+ concentration (polyuria): 20 mM
- FEK: (U/P) K/(U/P) Cr (3%)
- TTKG: (U/P) K/(U/P) Osm (3)
- **UK^+/Cr: (mmol/l/mg/dl) (0.18) or mmol/mmol (2)**

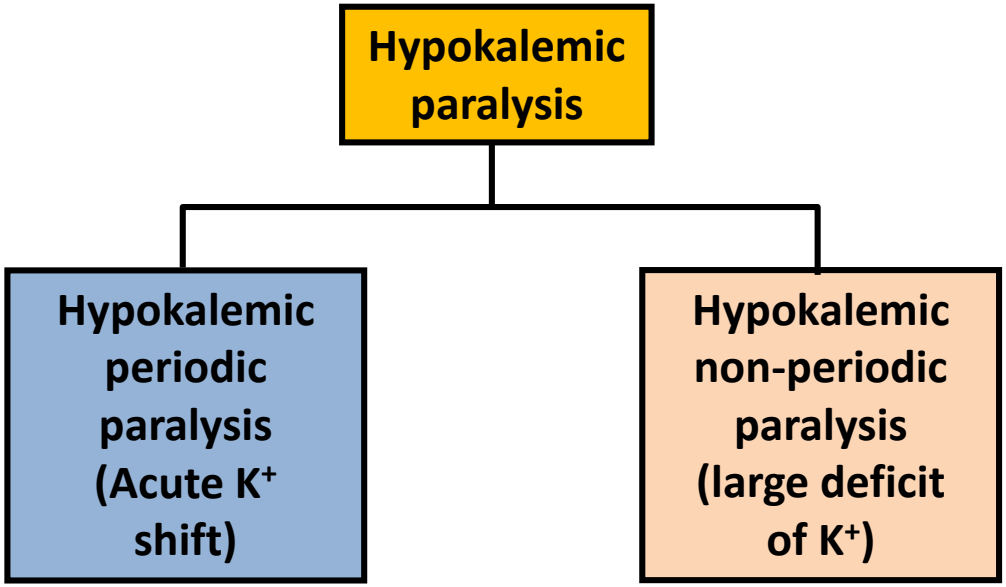
Disease state

Lin SH, et al. QJM 2003; 96: 935-947.



Lin SH. Curr Medicinal Chem 2006

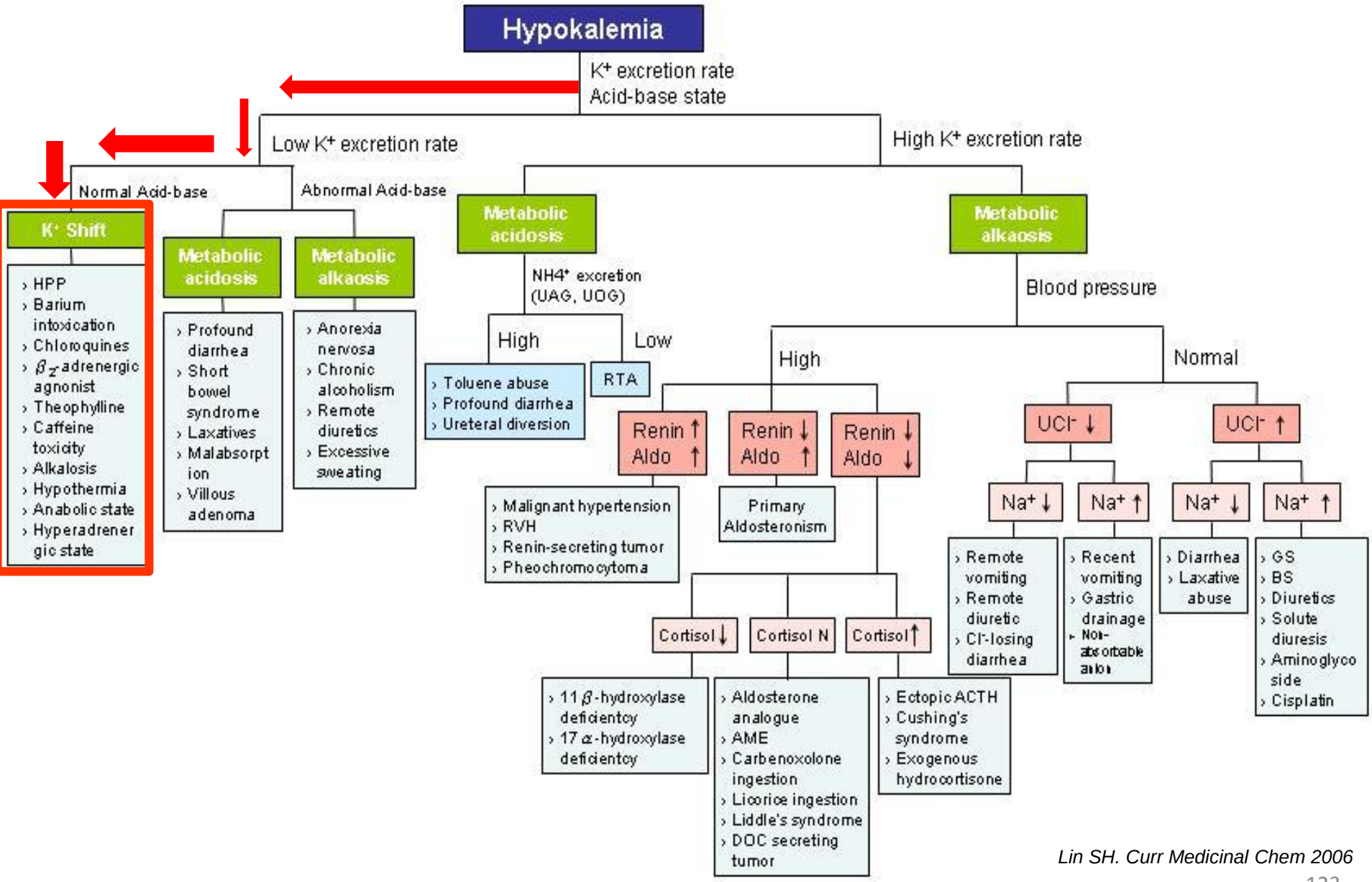
Etiologies of Hypokalemic Paralysis



- Hypokalemic periodic paralysis due to acute shift of K^+ into cells
- Hypokalemic non-periodic paralysis due to a large deficit of K^+

Lin SH et al Arch Intern Med. 2004

K^+ Shift



Lin SH. Curr Medicinal Chem 2006

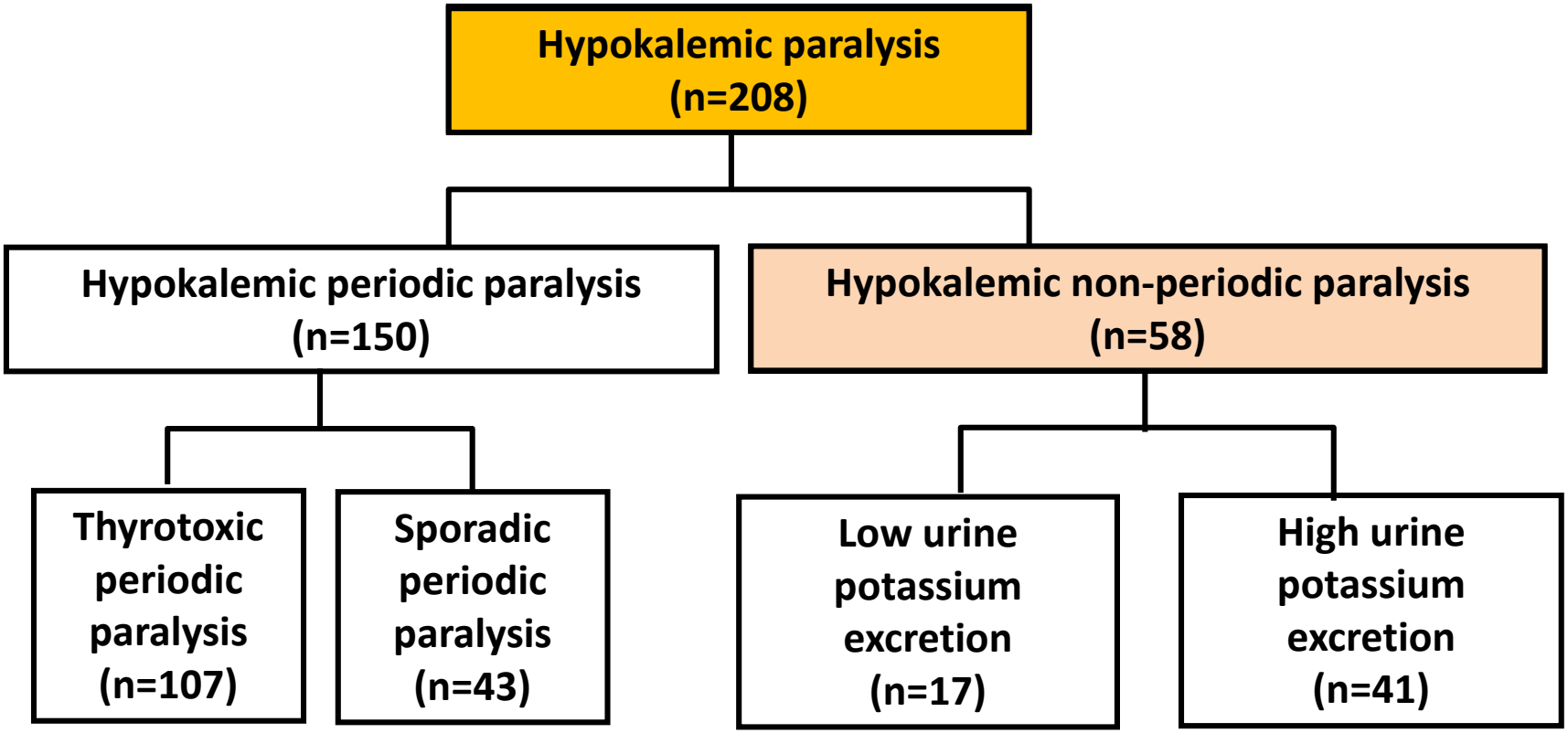
Drug-induced hypokalemia with low urine K^+ excretion rate

Increased shift of extracellular fluid potassium to intracellular fluid

1. Drugs with **ß2-adrenergic activity**: salbutamol (albuterol)
2. **Thyroid hormone**: levothyroxine, tri-iodothyronine
3. **Insulin**
4. Drug overdose: barium, lithium, verapamil, chloroquine, thiopental sodium
5. **Calcium channel blockers**: nifedipine, nitredipine
6. Hydroxocobalamin, granulocyte-macrophage colony-stimulating factor (**G-CSF**)

Sung et al Adverse Drug Reaction Bulletin. 2012;273:1051-1054

The causes and number in patients with hypokalemic paralysis



Sung CC and Lin SH et al.The American Journal of Medicine (2015) 128, 289-296

- **32歲男性病患，過去身體健康良好。此次因為近一日來四肢無力到急診求診。診視時發現病患在病床上意識清醒，呼吸正常，心跳為每分鐘 124次，規則;血壓120/78 mmHg;四肢無法舉離病床，輕觸和疼痛的感覺雙側相同，深部肌腱反射(deep tendon reflex)下降。實 室檢 發現血鉀為1.5 meq/L;血中 creatine kinase 671 IU/L(參考值，38~174 IU/L);甲狀腺刺 激素(thyroid stimulating hormone)為 0.013 μIU/mL(參考值，0.35~5.5 μIU/mL)和游離T 4甲狀腺素(free T4 thyroxine)為4.51 ng/dL(參考值，0.89~1.80 ng/dL)。此病患最有可能的診斷為何?**
- **A.原發性皮質醛酮過多症(primary aldosteronism)**
- **B.甲狀腺毒性週期性麻痺症(thyrotoxic periodic paralysis)**
- **C.利尿劑使用過多**
- **D.第一型及第二型腎小管酸血症(renal tubular acidosis)**

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Drug-induced hypokalemia with low urine K^+ excretion rate

Gastrointestinal tract potassium loss

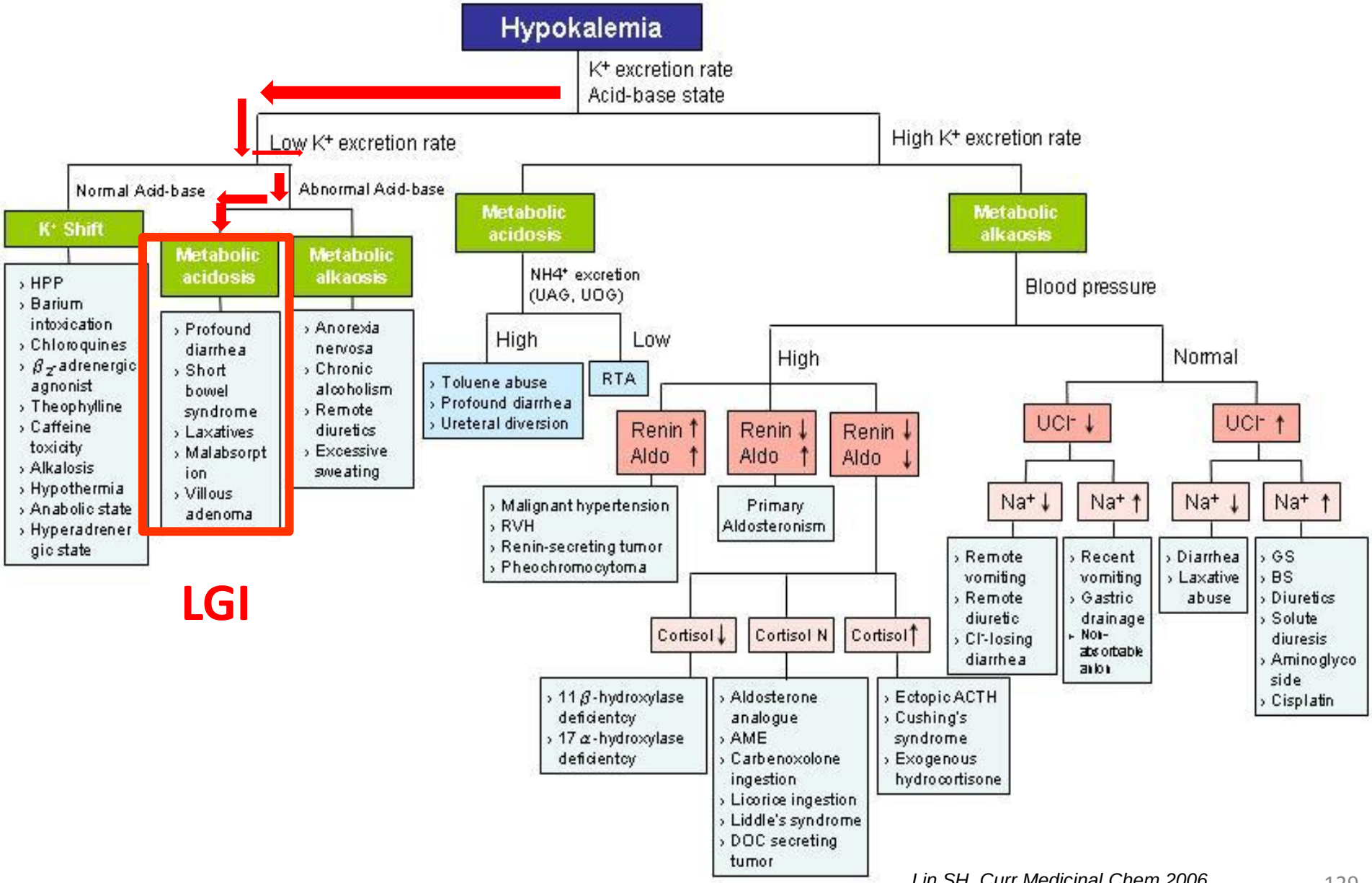
1. Diarrhoea-associated: laxatives, antibiotics causing pseudomembranous colitis
2. Vomiting-associated: quinine, chemotherapy agents, narcotics and other anaesthesic agents
3. Cation-exchange resin: sodium polystyrene sulphonate (Kayexalate or Resonium-A), calcium polystyrene sulphonate (Kalimate)

Former renal potassium wasting

1. Diuretics '**off**' action

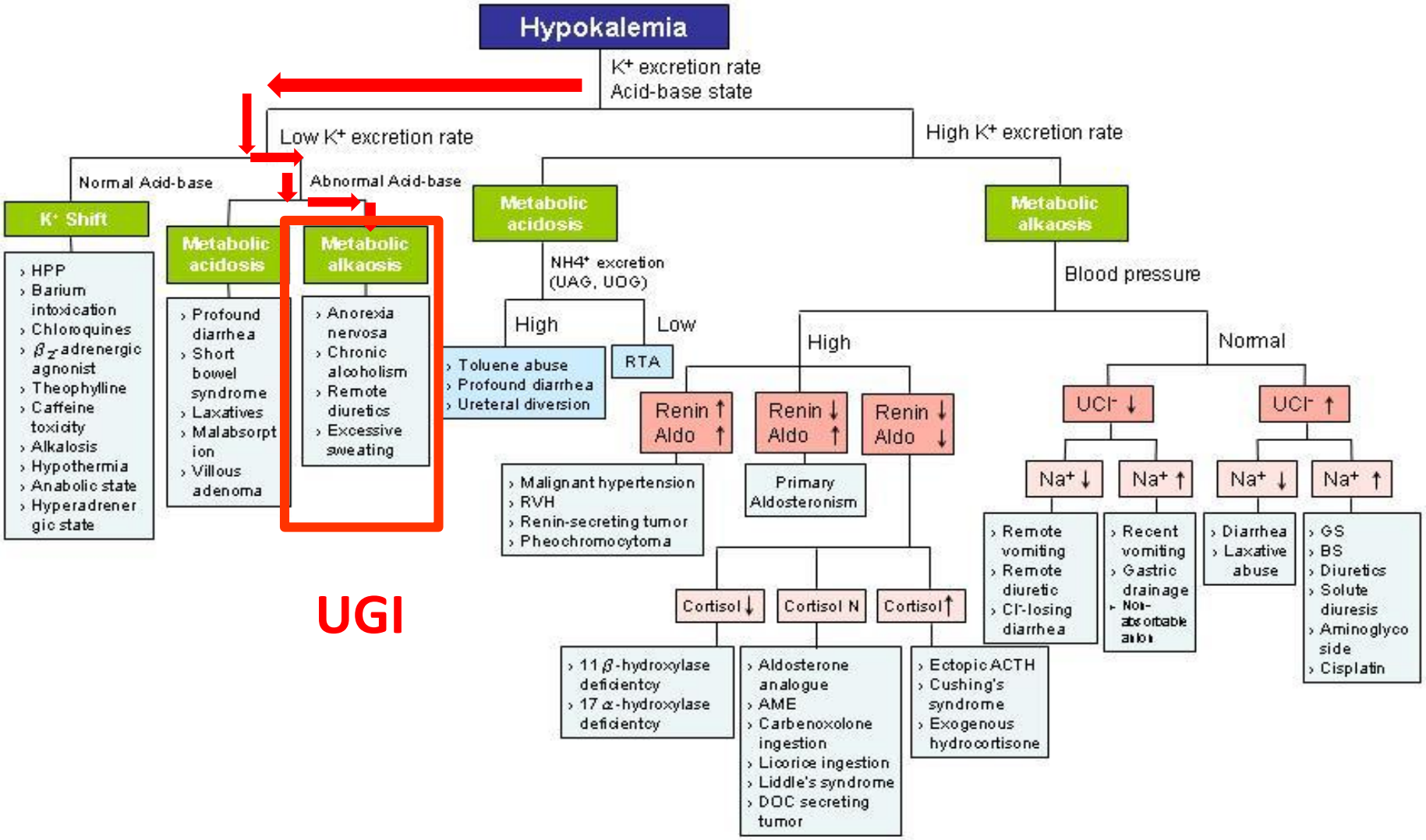
Sung et al Adverse Drug Reaction Bulletin. 2012;273:1051-1054

Low urine K^+ with metabolic acidosis

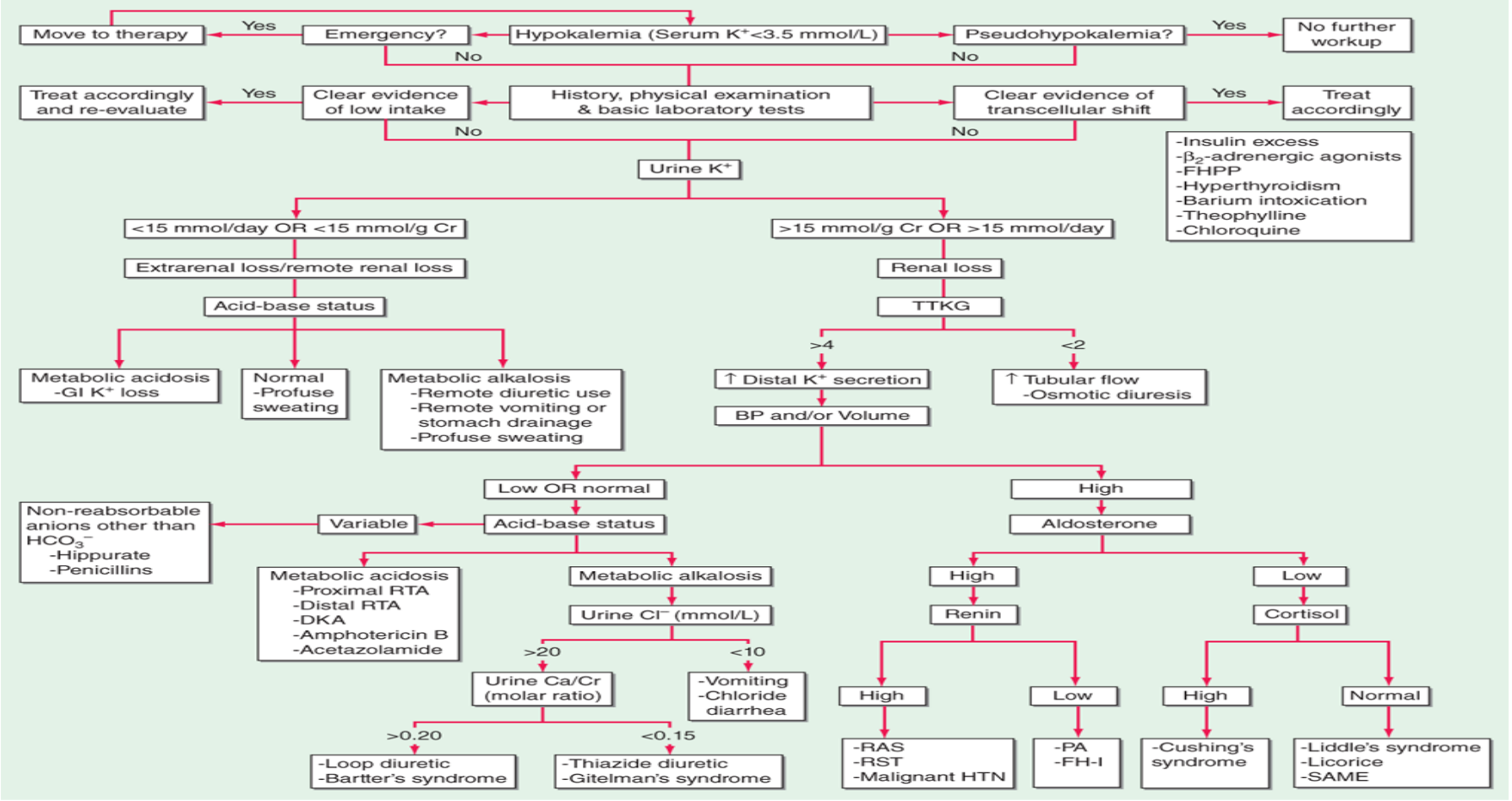


Lin SH. Curr Medicinal Chem 2006

Low urine K^+ with metabolic alkalosis



Lin SH. Curr Medicinal Chem 2006



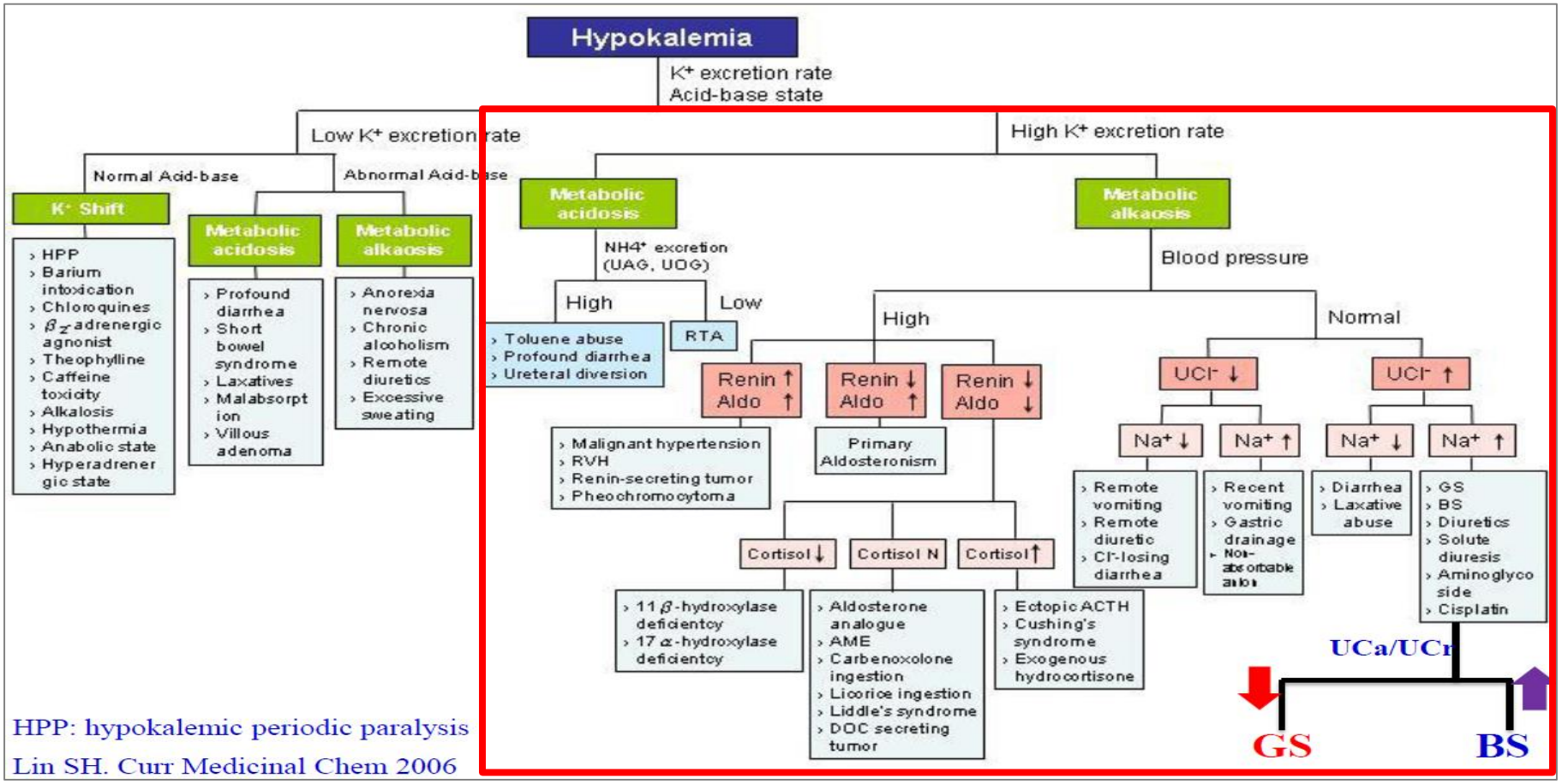
The diagnostic approach to hypokalemia. See text for details. AME, apparent mineralocorticoid excess; BP, blood pressure; CCD, cortical collecting duct; DKA, diabetic ketoacidosis; FH-I, familial hyperaldosteronism type I; FHPP, familial hypokalemic periodic paralysis; GI, gastrointestinal; GRA, glucocorticoid remediable aldosteronism; HTN, hypertension; PA, primary aldosteronism; RAS, renal artery stenosis; RST, renin-secreting tumor; RTA, renal tubular acidosis; SAME, syndrome of apparent mineralocorticoid excess; TTKG, transtubular potassium gradient. (Used with permission from DB Mount, K Zandi-Nejad K: Disorders of potassium balance, in Brenner and Rector's The Kidney, 8th ed, BM Brenner [ed]. Philadelphia, W.B. Saunders & Company, 2008, pp 547–587.)

Hypokalemic nonperiodic paralysis-low urine K^+ excretion (n=17)

	Number	Age (years)	Gender (M:F)
Low urinary K^+ excretion rate	17	42.5 ± 6.1	15:2
Hyperchloremic metabolic acidosis	2		
Remote toluene abuse	1	45	1:0
Remote acetazolamide use	1	35	1:0
Hypochloremic metabolic alkalosis	15		
Chronic alcoholism	7	46.7 ± 8.2	7:0
Remote loop diuretics & thiazides use	4	60.8 ± 24.9	3:1
Anorexia/bulimia nervosa	2	19.5 ± 0.7	2:0
Profound diarrhea	1	57	1:0
Chronic laxative use	1	34	0:1

Sung CC and Lin SH et al.The American Journal of Medicine (2015) 128, 289-296

High urine K^+ excretion

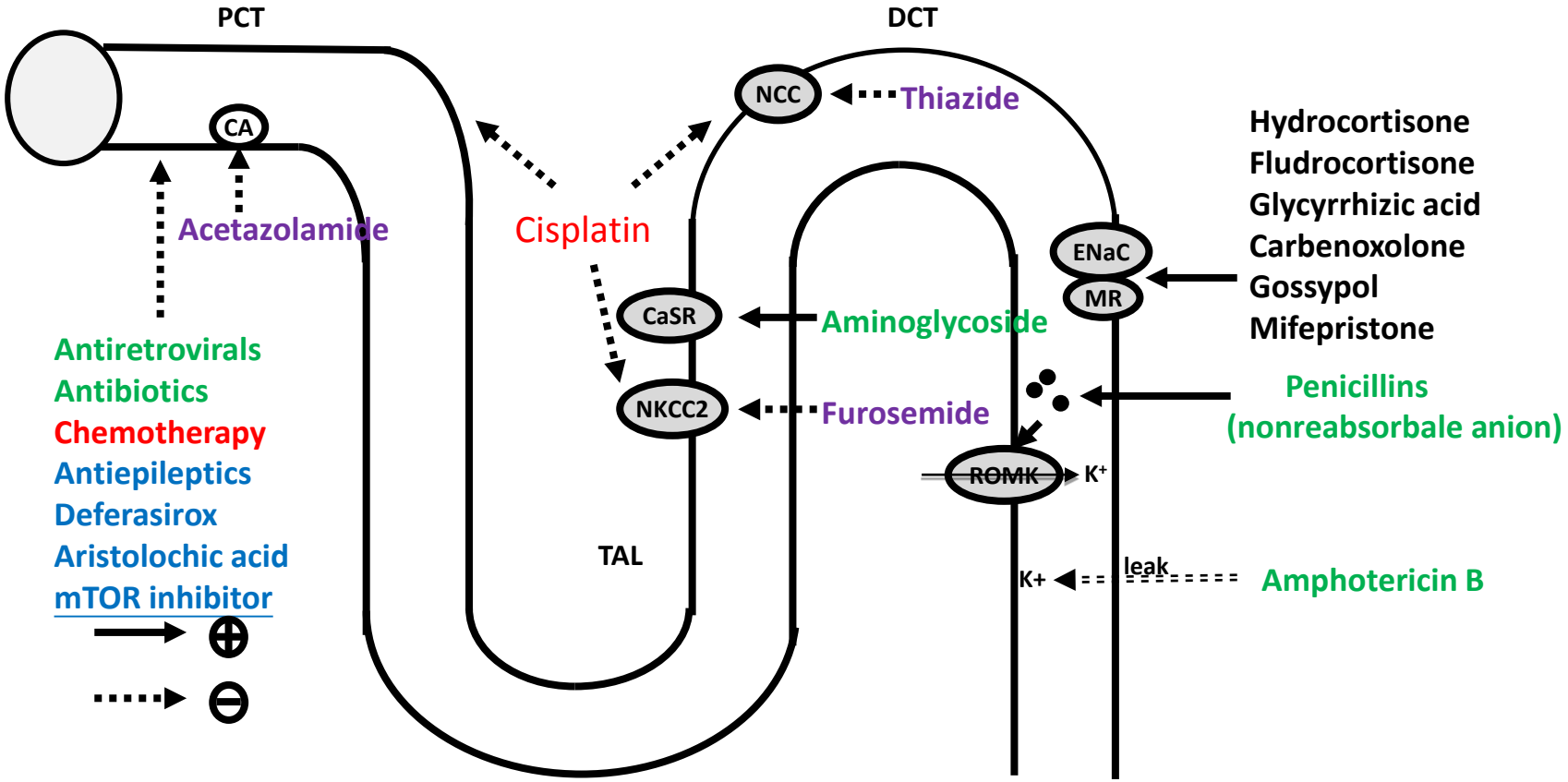


HPP: hypokalemic periodic paralysis

Lin SH. Curr Medicinal Chem 2006

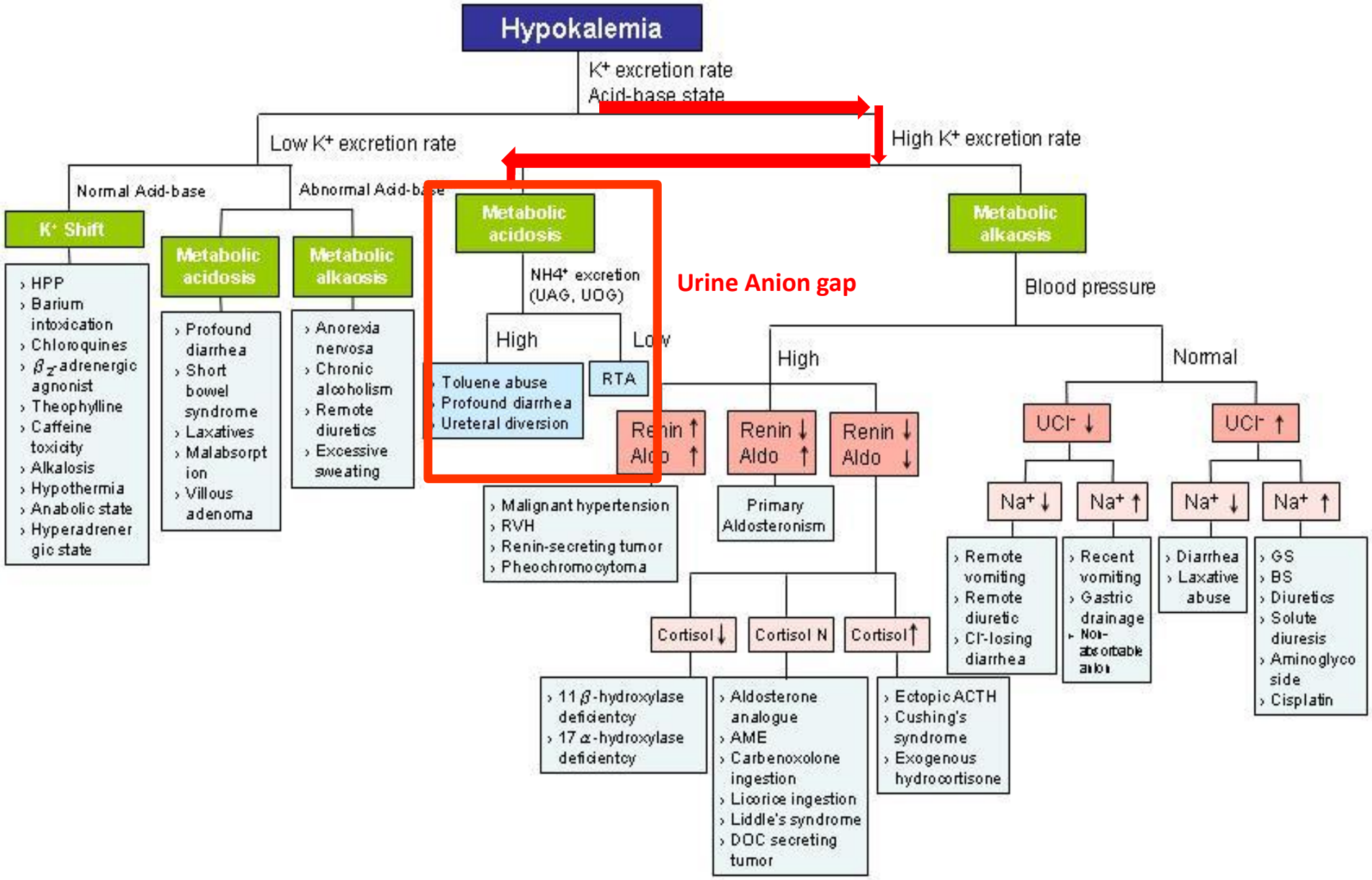
Lin SH et al Arch Intern Med. 2004

Drug-induced hypokalemia with high urine K^+ excretion rate



Sung et al .Adverse Drug Reaction Bulletin. 2012;274:1055-1058.

High urine K^+ with metabolic acidosis



Lin SH. Curr Medicinal Chem 2006

- 下列那一個病例較符合所列之動脈血氣體分析和血清電解質的檢查結果**[pH:7.32，PaO2:110 mmHg，PaCO :33 mmHg，HCO - :18; Na+ 138，K+ 3.0，Cl- 109(電解質的單位是mmol/L)]? A.19歲女學生為第一型糖尿病，因期末考熬夜兩天，忘記注射胰島素**
- **B.39歲女性經理服用作用於遠端腎小管之利尿劑減重**
- **C.59歲女性有第五期慢性腎臟病**
- **D.69歲女性腹瀉三天**

- 下列那一個病例較符合所列之動脈血氣體分析和血清電解質的檢查結果**[pH:7.32，PaO2:110 mmHg，PaCO :33 mmHg，HCO -:18;Na+ 138，K+ 3.0，Cl- 109(電解質的單位是mmol/L)]? 23**
- **A.19歲女學生為第一型糖尿病，因期末考熬夜兩天，忘記注射胰島素 B.39歲女性經理服用作用於遠端腎小管之利尿劑減重**
- **C.59歲女性有第五期慢性腎臟病**
- **D.69歲女性腹瀉三天**

Hypokalemic nonperiodic paralysis-high urine K^+ excretion with metabolic acidosis(n=11)

	Number	Age (years)	Gender (M:F)
High urinary K^+ excretion rate	41	33.5± 4.2	29:12
Hyperchloremic metabolic acidosis	11		
Renal tubular acidosis	8	35.0 ± 19.1	2:6
Recent toluene abuse	2	35.5 ± 0.7	2:0
Ureteral diverson	1	47	1:0

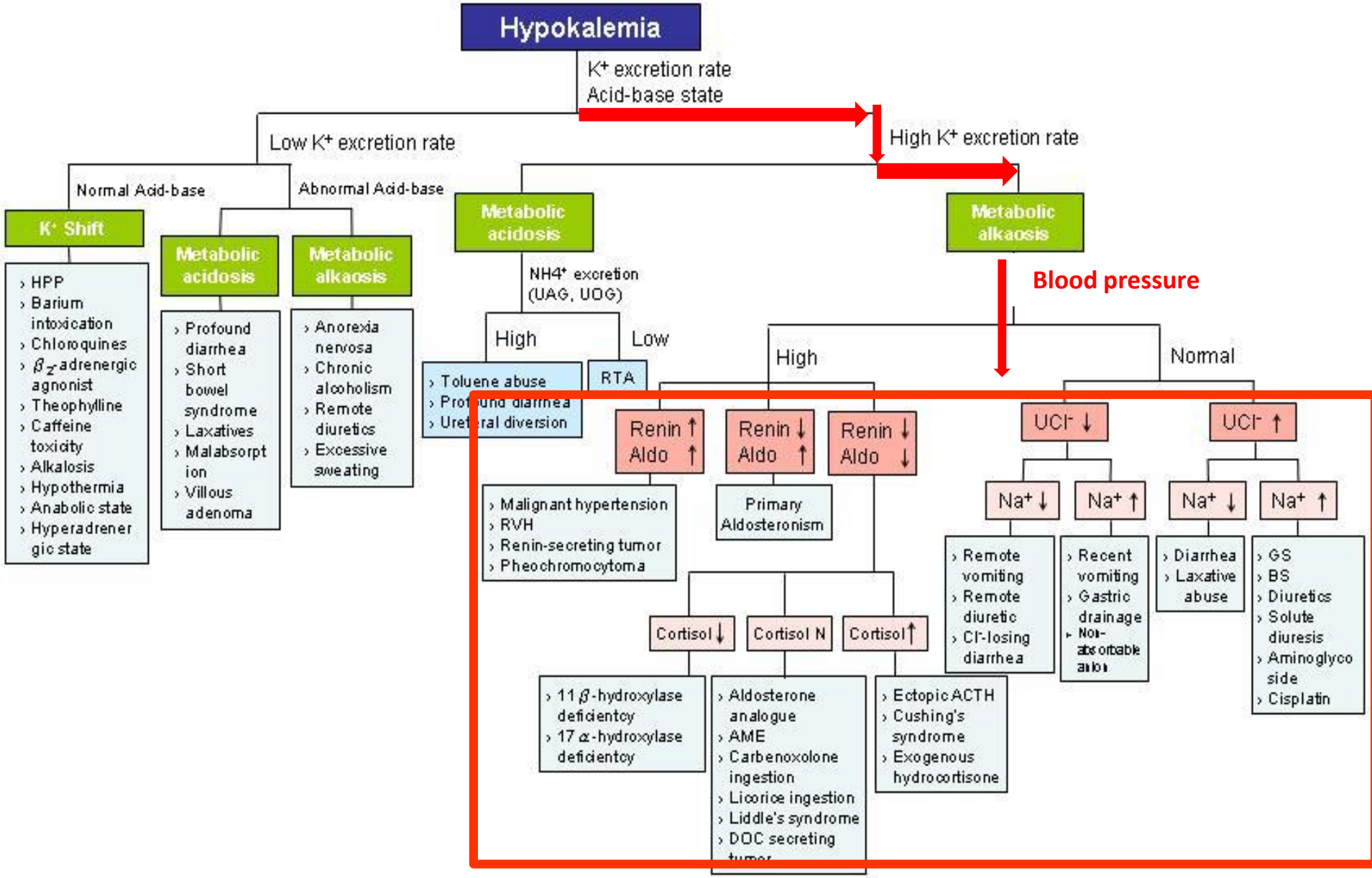
Renal tubular acidosis:

Distal=Primary Sjögren's syndrome (n = 7)

Proximal=Fanconi syndrome (n = 1)

Sung CC and Lin SH et al.The American Journal of Medicine (2015) 128, 289-296

High urine K^+ with metabolic alkalosis

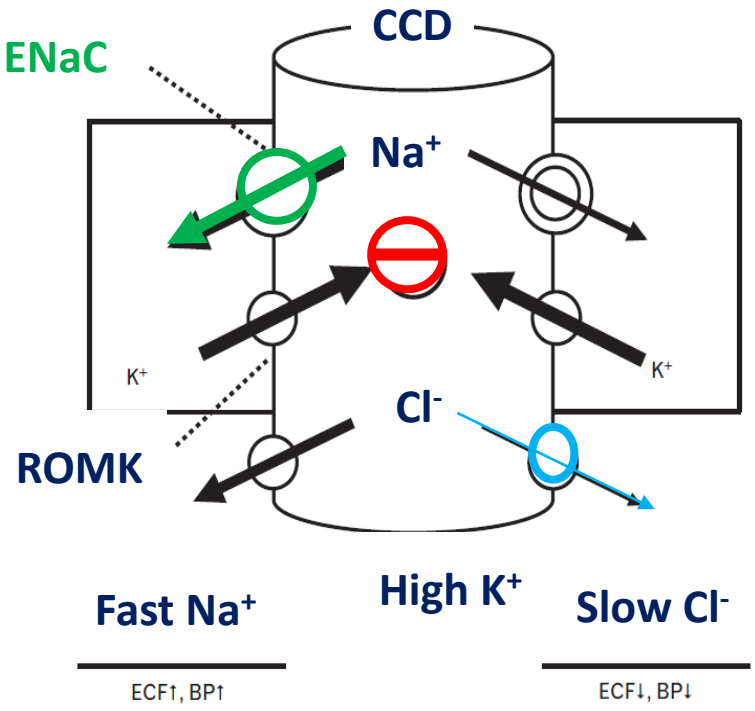


Lin SH. Curr Medicinal Chem 2006

Renal K^+ Excretion and Blood Pressure

Increased Renal K^+ Excretion

High BP



Normal or low BP

MES: PRA, Aldo, cortisol

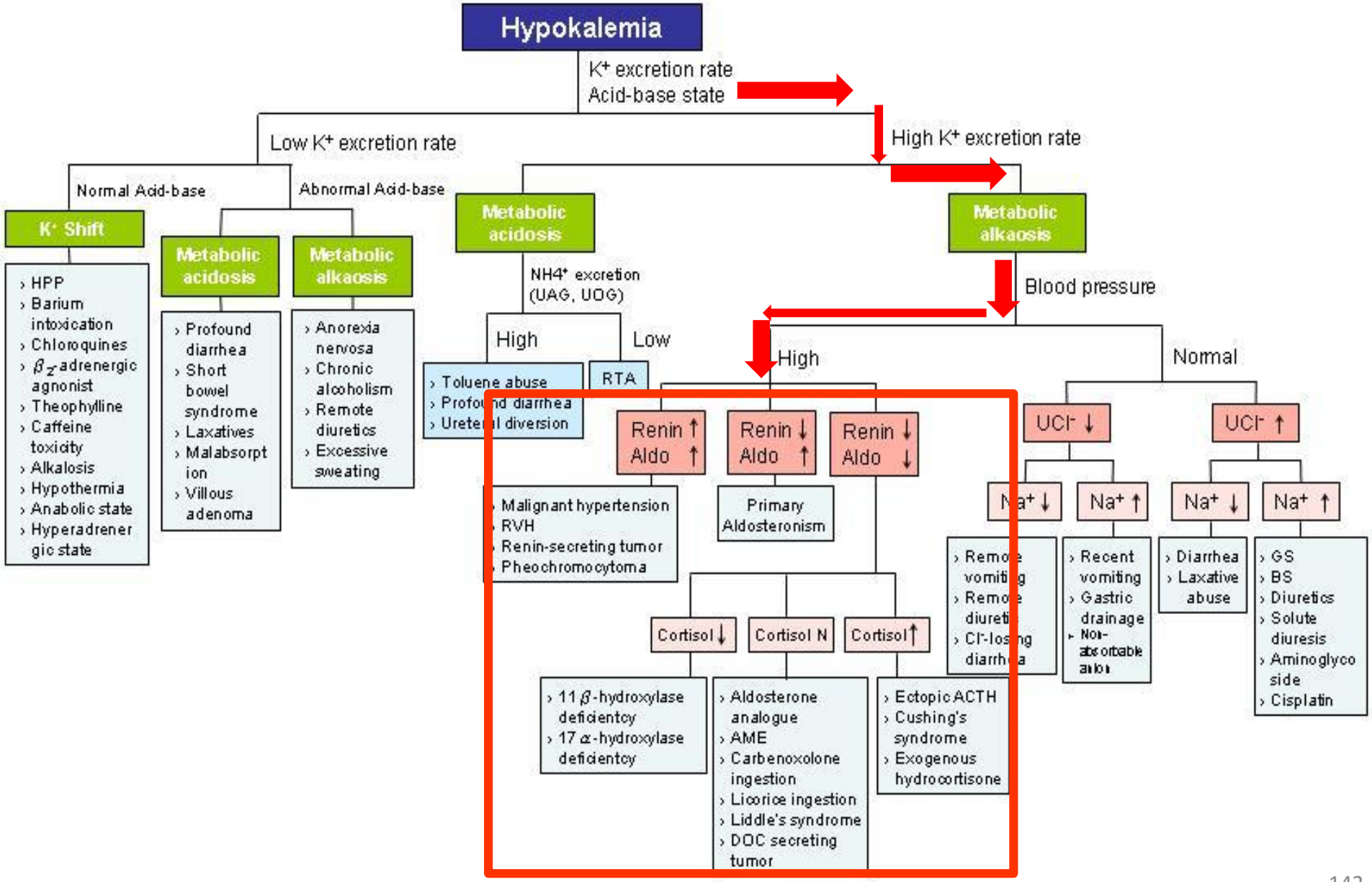
Urine Na, Cl, divalents

Hypokalemic nonperiodic paralysis- high urine K^+ excretion with metabolic alkalosis (n=30)

	Number	Age (years)	Gender (M:F)
High urinary K^+ excretion rate	41	33.5± 4.2	29:12
Hypochloremic metabolic alkalosis	30		
High blood pressure	11		
Primary aldosteronism	**9**	**44.5 ± 12.4**	**6:3**
Chronic licorice ingestion	1	40	0:1
Ectopic adrenocorticotropin hormone syndrome	1	60	1:0
Normal blood pressure	19		
Gitelman's syndrome	11	21.1 ± 10.1	11:0
Classic Bartter's syndrome	1	20	1:0
Recent loop diuretics & thiazides use	5	67.8 ± 17.6	4:1
Bulimia nervosa	2	20.0 ± 2.8	1:1

Sung CC and Lin SH et al.The American Journal of Medicine (2015) 128, 289-296

High BP with mineralocorticoid excess



Lin SH. Curr Medicinal Chem 2006

ECF ↑ + Metabolic alkalosis

Renin
Aldo
Cortisol

↑ Renin
↑ Aldo

- MH
- RVH
- RST

↓ Renin
↑ Aldo

- PA

↓ Renin
↓ Aldo

Cortisol

High

Ectopic ACTH
Cushing syndrome
Exogenous H

Normal

Licorice
Liddle's S
AME
DOC

Low

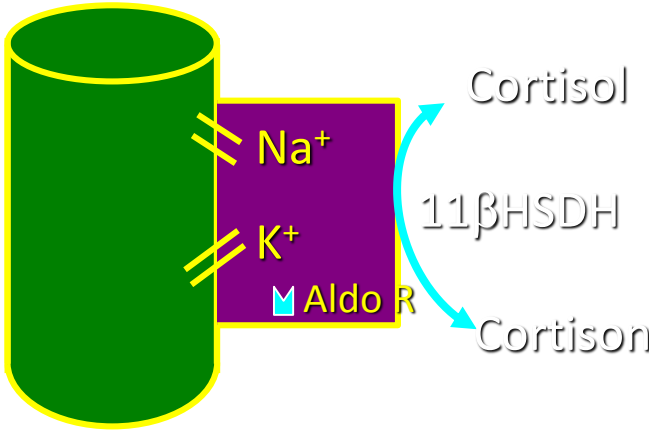
Sex Hormone

High

11β hydroxylase D

Low

17α hydroxylase D



I. Endogenous aldosterone-like substance (DO
II. Exogenous aldosterone analogue (HC, FC)
III. Na^+ channel activation (Liddle's syndrome)
IV. 11βHSDH problems (defect by AME, inhibition by licorice, saturation by excessive cortisol)

- 一名35歲女性因夜尿(nocturia)就診，身體檢查:血壓150/94 mmHg，脈搏78/min，其它檢查無異常。實 室檢 :blood urea nitrogen 15 mg/dL，creatinine 1.0 mg/dL，空腹血糖97 mg/dL，血鈉142 mmol/L，血鉀 2.8 mmol/L，血氯90 mmol/L，尿沉渣正常，尿鉀排泄量50 mmol/day，動脈氣體pH 7.45，[HCO -] 30 3 mmol/L，PaCO2 44 mmHg，則本病人最可能罹患?
- A.腎小管酸血症(renal tubular acidosis)
- B.巴特氏症候群(Bartter’ s syndrome)
- C.絨毛狀腺瘤(villous adenoma)
- D.原發性皮質醛酮症(primary aldosteronism)

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- D.原發性皮質醛酮症(primary aldosteronism)

- .一位52歲男性因反覆發生下肢癱瘓入院，血壓168/98 mmHg，血液檢查發現:鈉146
- mmol/L，鉀2.0 mmol/L，氯100 mmol/L，酸鹼值7.56，重碳酸根38 mmol/L，腎素(renin) 0.1 ng/mL/hr(正常值0.3~3 ng/mL/hr)，血清醛固酮(aldosterone)8 ng/dL(正常值2~9 ng/dL);則下列敘述何者錯誤?
  A.病患為留鹽激素過多狀態(mineralocorticoid excess state)
- B.應補充大量鉀離子直到病患肌肉力量恢復
- C.因血清腎素偏低，可以排除腎素分泌腫瘤(renin-secreting tumor)及續發性高醛固酮症
- D.因血清醛固酮正常，可以排除原發性高醛固酮症

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- 24 歲女性有難控制的高血壓，從二年前診斷之後就不斷增加使用的藥物與劑量，目前使用藥品包括labetalol 1000 mg bid，lisinopril 40 mg qd，clonidine 0.1 mg bid，amlodipine 5 mg qd。身體診查：血壓168/100 mmHg，心跳每分鐘84 次，沒有呼吸窘迫，心臟檢查沒有心雜音或心摩擦音。週邊動脈脈搏對
- 稱且正常，四肢沒有水腫，沒有多毛，無脂肪異常分布或生殖器異常。實驗室檢查：鉀2.8 mEg/dL，空腹血糖值114 mg/dL，若依上述情況，最可能的診斷是：
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- 暪C.先天性腎上腺增生（congenital adrenal hyperplasia）
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- 一位19歲大一學生，新生健康檢查血壓160/100 mmHg，在無服用藥物下，之後一個月家裡自量血壓介於130/88至170/106 mmHg之間，鉀離子2.8 mmol/L，鈉離子140 mmol/L，氯離子98 mmol/L。此一高血壓應首先考慮下列那一種？
- 琮 A.白袍高血壓（white coat hypertension）
- 媳 B.本態性高血壓（essential hypertension）
- 暟 C.腎動脈狹窄（renal artery stenosis）
- 鬲 D.腎上腺瘤（adrenal adenoma或primary hyperaldosteronism）

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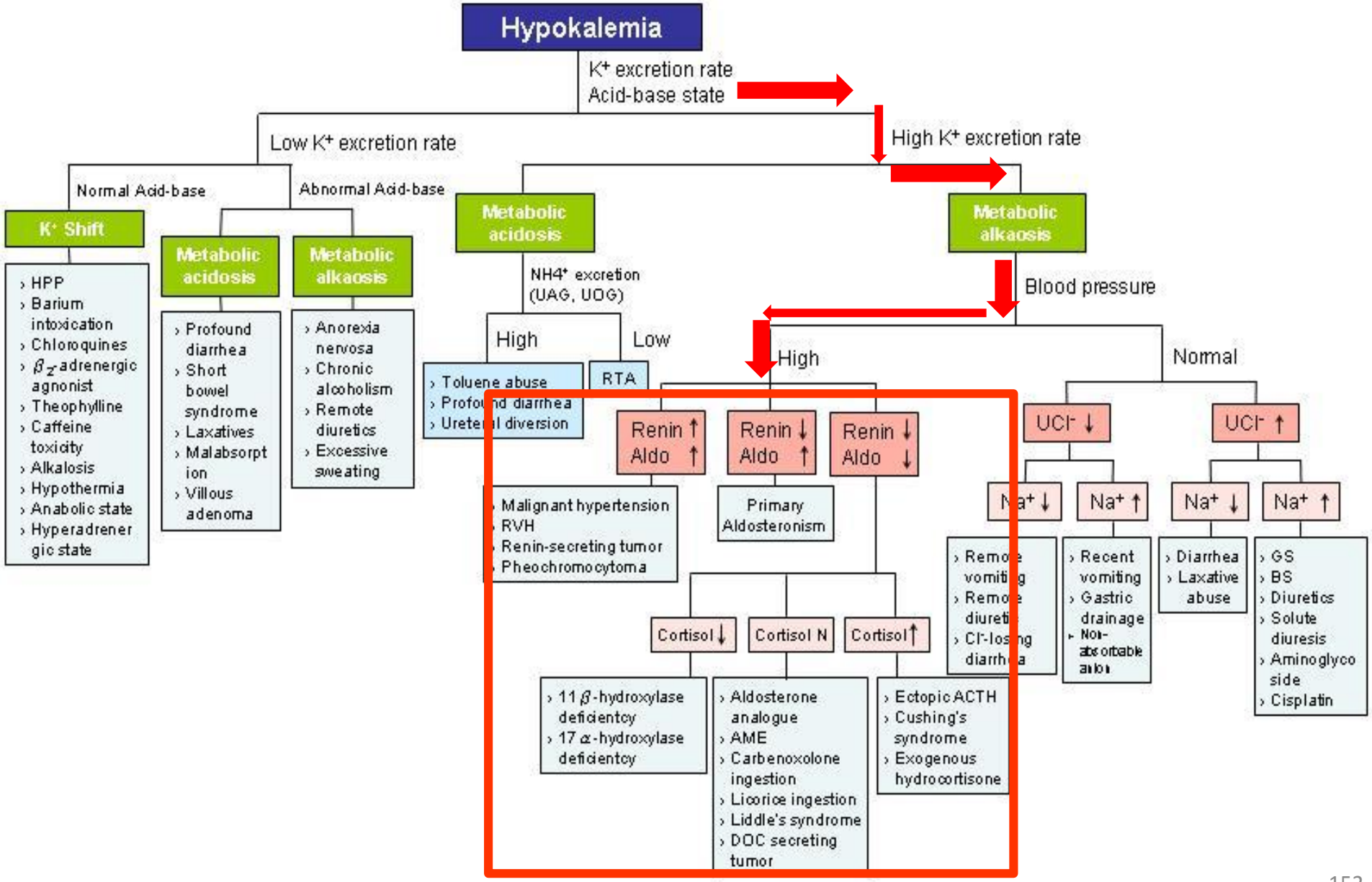
High BP with mineralocorticoid excess



Lin SH. Curr Medicinal Chem 2006

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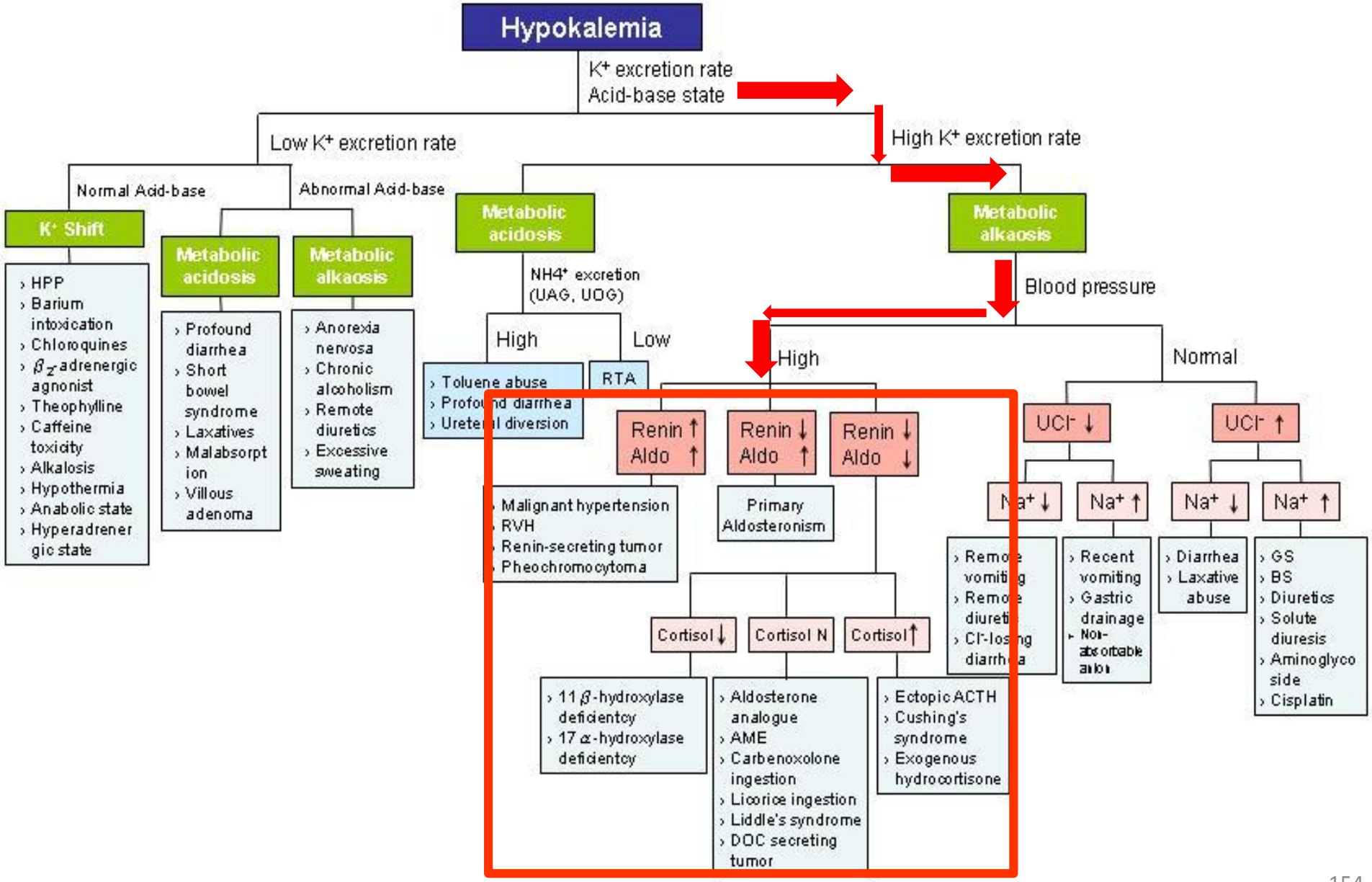
- A.檢查尿液的鉀離子濃度和滲透壓，以及血清滲透壓
- B.檢查甲狀腺功能
- C.檢查血漿皮質醛固酮（aldosterone）濃度
- D.心臟超音波檢查
- 28 承上題，此病人最不需考慮下列那個診斷？
- A.原發性皮質醛固酮症（primary aldosteronism）
  B.巴特氏症候群（Bartter’ s syndrome）
- C.葛拉夫思氏疾病（Graves’ disease）
  D.高安氏動脈炎（Takayasu’s arteritis）

High BP with mineralocorticoid excess



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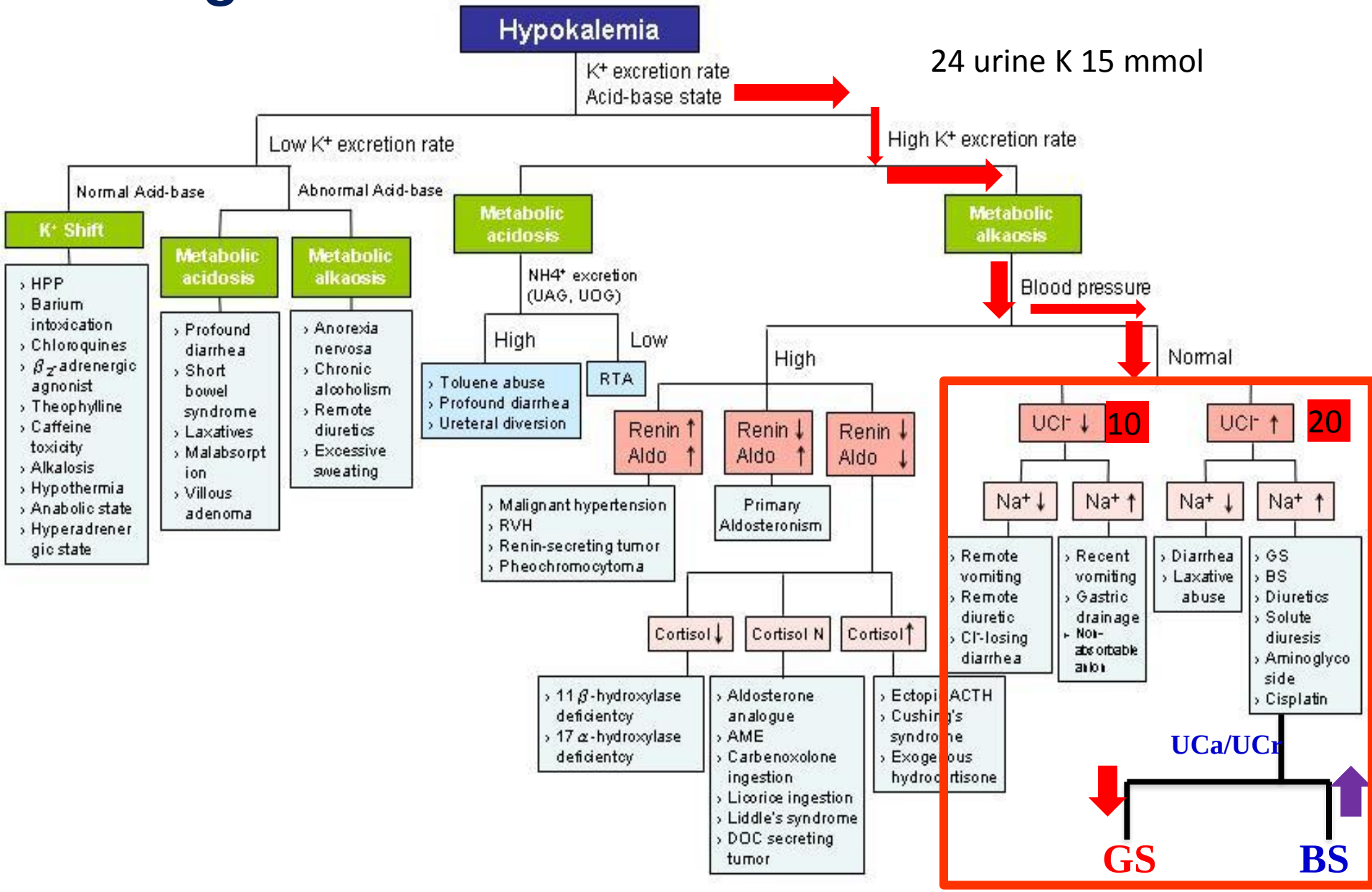
  D.高安氏動脈炎（Takayasu’s arteritis）

- 32 下列何種疾病不會有低血鉀合併代謝性鹼中毒？
- 玠 A.Bartter’ s syndrome 媳
  - B.Primary aldosteronism 暯
  - C.Liddle’ s syndrome 鬲
  - **D.Gordon’ s syndrome**

- 下列那一個病例最不符合所列之動脈血氣體分析和血清電解質的檢查結果**[pH:7.49，PaO2:90 mmHg， PaCO :43 mmHg，HCO -:28;Na+ 139，K+ 3.0，Cl- 89(電解質的單位是mmol/L)]?**
- **B.急性腹瀉三天**
- **C.原發性皮質醛酮症**
- **D.噁心嘔吐兩天**

High urine K with alkalosis and normal BP



Lin SH. Curr Medicinal Chem 2006

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- **A.血清滲透壓應該>310 mOsmol/kg H2O**
- **B.尿液的鉀離子應該<10 mmol/L**
- **C.尿液的滲透壓應該>500 mOsmol/kg H2O**
- **D.尿液氯離子應該>20 mmol/L**

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Bulimia nervosa	2	20.0 ± 2.8	1:1

Sung CC and Lin SH et al.The American Journal of Medicine (2015) 128, 289-296

Treatment--You need to count: K^+ supplement

- **Slow-K(Potassium chloride):1# 5 meq**
- **Radi-K (Potassium gluconate):1# 2.5meq**
- **Destone (potassium citrate): 1# 5 meq**
- **KCl:2 meq/ml**
- **Dietary K^+: 0.6-0.7 meq/kg/Day= 50-60 meq/Day**

K^+ supplement rate in severe hypokalemia

- **Intravenous KCl: rate of 10-20 mmol/hour**
- **Infused rate could be increased to 30 mmol/hour through a CVP if the patient developed ventricular arrhythmias, respiratory failures, or a fall in plasma K^+ concentration during therapy.**
- **Lowered to < 10 mmol/hour when muscle strength recovered enough for the patient to ambulate.**

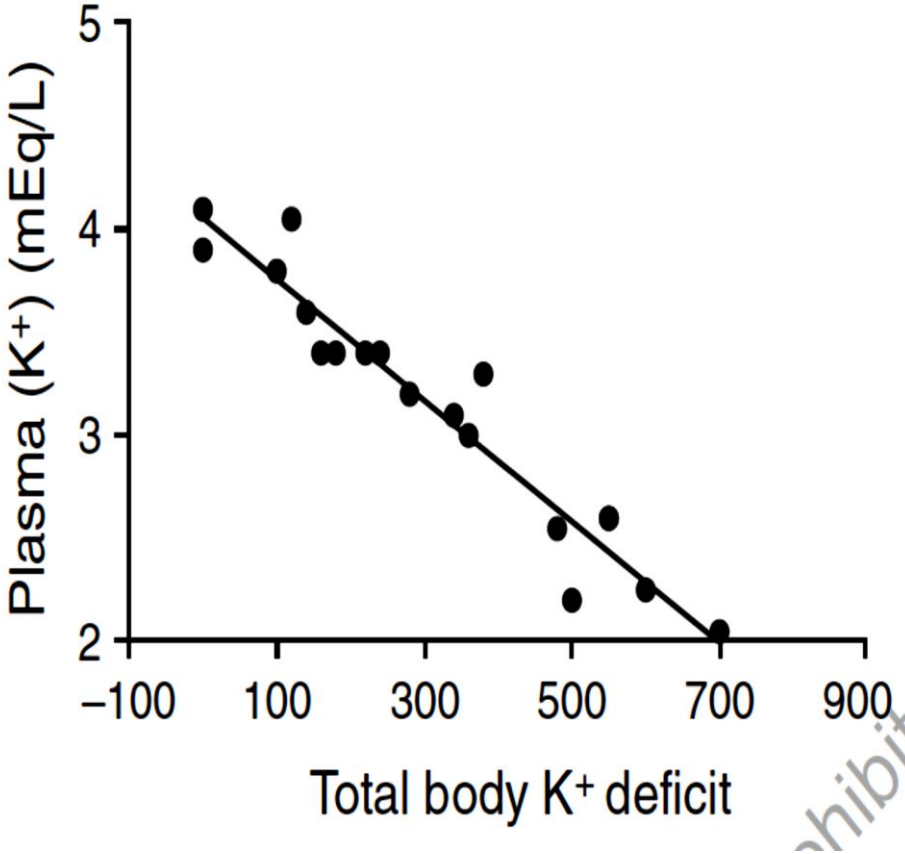
Sung CC and Lin SH et al.The American Journal of Medicine (2015) 128, 289-296

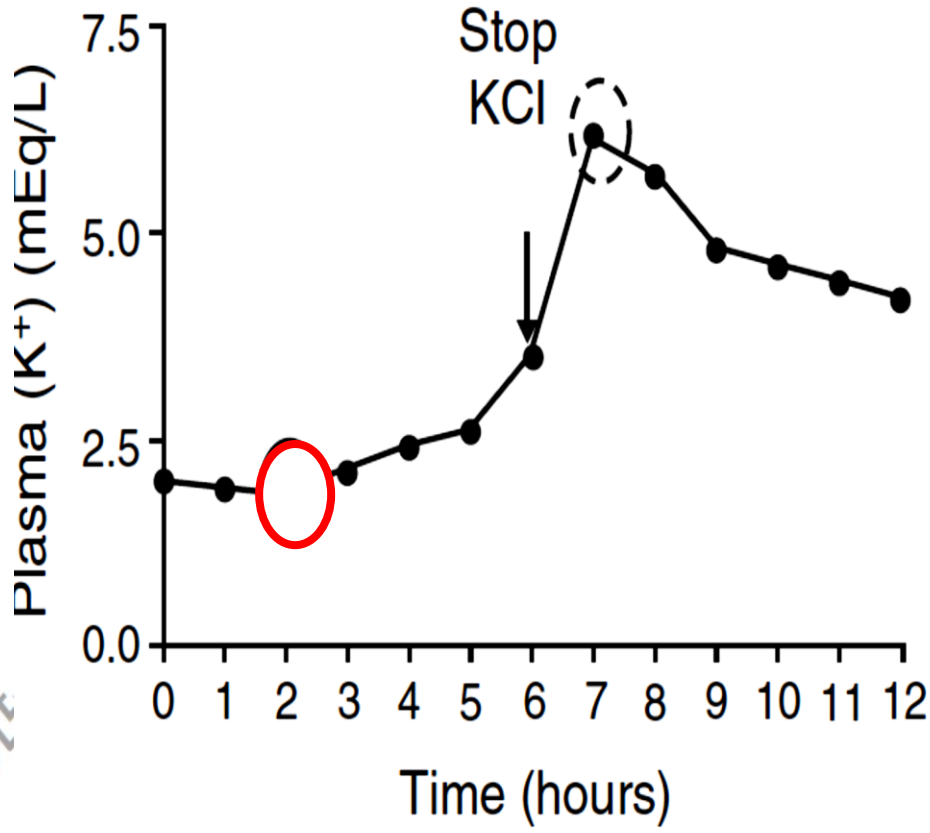
Hypokalemic non-periodic paralysis

- Understanding the common etiologies of hypokalemic non-periodic paralysis may aid in early diagnosis.
- Patients with initial lower plasma K^+, renal K^+ wasting, and hypovolemia required higher recovery K^+ dosage.
- Paradoxical hypokalemia is prone to develop in hypovolemic patients even during K^+ supplementation with volume repletion.

Sung CC and Lin SH et al.The American Journal of Medicine (2015) 128, 289-296

Rebound hyperkalemia in Hypokalemic periodic paralysis





Cheng CJ and Lin SH. TPP in Book Chapter 13, p145-151. Endocrine Press 2014

Quick facts to separate K^+ Shifting disorders from K^+ wasting disorders

	K^+ Shifting 疾病	K^+ wasting 疾病
發生時間	快速	漸進性
恢復時間	較短	通常較長
低血鉀原因	K+ 移入細胞內	K^+流失
尿 K+ 排出	低	通常高
常合併Ca, Mg 離子的異常	少	常常
酸鹼平衡	相對正常	異常

Kidney and Dialysis Vol.29, No.1, pp. 17-24 (March, 20

Rebound hyperkalemia v.s. Paradoxical Hypokalemia

Table Comparison Between Hypokalemic Nonperiodic Paralysis and Thyrotoxic Periodic Paralysis

	Hypokalemic nonperiodic paralysis	Thyrotoxic periodic paralysis
Presenting serum K (mEq/L)	1.8 ± 0.2	2.1 ± 0.2
Recovering serum K (mEq/L)	2.6 ± 0.2	3.1 ± 0.3
K replacement (mmol)	243 ± 75	63 ± 32
Recovery time (h)	13.0 ± 3.6	6.3 ± 3.2
Rebound hyperkalemia (%)	0	59%
Paradoxical hypokalemia (%)	55%	26
Risk factors for paradoxical hypokalemia	Higher serum renin activity and aldosterone level	Higher systolic blood pressure, heart rate, and free T4 level

K = potassium.

The American Journal of Medicine, Vol 128, No 3, March 2015

- 41 一位 20 歲男性因突發四肢無力至急診室就診，血壓150/90 mmHg，心跳110 次/分鐘，血液檢查發現：鈉138 mmol/L，鉀2.4 mmol/L，氯106 mmol/L，肌酸酐0.9 mg/dL，滲透度290 mOsmol/kgH2O，pH 值7.40，重碳酸根23 mmol/L；尿液檢查發現：肌酸酐98.5 mg/dL，鈉102 mmol/L，鉀10.4 mmol/L，氯98 mmol/L，滲透度600 mOsmol/kg H2O。則下列敘述，何者錯誤？
- A.病患可能罹患甲狀腺功能亢進，需檢測病患之甲狀腺功能
- B.病患因尿液排泄大量鉀離子，需大量補充鉀離子
- C.鉀離子之補充加入生理食鹽水（normal saline）比加入5%葡萄糖要好
- D.需密切監測血鉀，以避免反彈性高血鉀

- 41 一位 20 歲男性因突發四肢無力至急診室就診，血壓 150/90 mmHg，心跳110 次/分鐘，血液檢查發現：鈉138 mmol/L，鉀2.4 mmol/L，氯106 mmol/L，肌酸酐0.9 mg/dL，滲透度290 mOsmol/kgH2O，pH 值7.40，重碳酸根23 mmol/L；尿液檢查發現：肌酸酐98.5 mg/dL，鈉102 mmol/L，鉀10.4 mmol/L，氯98 mmol/L，滲透度600 mOsmol/kg H2O。則下列敘述，何者錯誤？
- 珧A.病患可能罹患甲狀腺功能亢進，需檢測病患之甲狀腺功能
- **嫕B.病患因尿液排泄大量鉀離子，需大量補充鉀離子**
- 暯C.鉀離子之補充加入生理食鹽水（normal saline）比加入5%葡萄糖要好
- 鬲D.需密切監測血鉀，以避免反彈性高血鉀

- 下列有關低血鉀的治療敘述，何者錯誤？
- A.腎小管酸血症引起的低血鉀補充potassium citrate 優於potassium chloride
- B.週邊靜脈輸注potassium chloride 時，注射速度每小時不應超過20 mmol
- C.potassium chloride 可加在normal saline 或 dextrose solution，輸注後升鉀的效果一樣
- D.中心靜脈補充鉀離子時，potassium chloride 注射液濃度可至60 mmol/L

- 下列有關低血鉀的治療敘述，何者錯誤？
- 珧A.腎小管酸血症引起的低血鉀補充potassium citrate 優於potassium chloride
- 媦B.週邊靜脈輸注potassium chloride 時，注射速度每小時不應超過20 mmol
- 暪**C.potassium chloride 可加在normal saline 或dextrose solution，輸注後升鉀的效果一樣**
- 凅D.中心靜脈補充鉀離子時，potassium chloride 注射液濃度可至60 mmol/L

Management for Hypokalemia

I. **Medical emergency:** cardiac arrhythmia, respiratory insufficiency

II. **Avoid risk of K^+ shift into cells:** do not give glucose, insulin and $NaHCO_3$

III. **Magnitude of K^+ deficit:** large vs small dose of K^+

IV. **Route of K^+ administration:** central, peripheral or oral

V. **K^+ preparations:** KCl vs $KHCO_3$ (K^+ citrate) vs K^+ phosphate

VI. **Adjuncts to therapy:** K^+-sparing agents, ACEI, AIIA

VII. **Associated settings:** HPP, chronic hyponatremia, hypomagnesemia, volume depletion, severe metabolic acidosis, low muscle mass

VIII. **Initial lower serum K^+, volume depletion, and high urinary K^+ excretion were associated with higher recovery KCl dosage.**

Take Home message for hypokalemia

- Recognize K^+ shift and K^+ deficit diseases.
- Calculate urine K^+ excretion: spot > 24hr.
- Measure acid-base and do not forget Cl^-.
- Blood pressure is the clue for mineralocorticoid excess syndrome.
- Avoid Paradoxical Hypokalemia or rebound hyperkalemia during K^+ supplement.
- Genetic diagnosis may be considered.

Hyperkalemia

TABLE 49-5Causes of Hyperkalemia

1. Pseudohyperkalemia

1. Cellular efflux; thrombocytosis, erythrocytosis, leukocytosis, in vitro hemolysis
2. Hereditary defects in red cell membrane transport

2. Intra- to extracellular shift

1. Acidosis
2. Hyperosmolality; radiocontrast, hypertonic dextrose, mannitol
3. β_2-Adrenergic antagonists (noncardioselective agents)
4. Digoxin and related glycosides (yellow oleander, foxglove, bufadienolide)
5. Hyperkalemic periodic paralysis
6. Lysine, arginine, and ε-aminocaproic acid (structurally similar, positively charged)
7. Succinylcholine; thermal trauma, neuromuscular injury, disuse atrophy, mucositis, or prolonged immobilization
8. Rapid tumor lysis

3. Inadequate excretion

1. Inhibition of the renin-angiotensin-aldosterone axis; ↑ risk of hyperkalemia when used in combination

1. Angiotensin-converting enzyme (ACE) inhibitors
2. Renin inhibitors; aliskiren (in combination with ACE inhibitors or angiotensin receptor blockers [ARBs])
3. Angiotensin receptor blockers (ARBs)
4. Blockade of the mineralocorticoid receptor: spironolactone, eplerenone, drospirenone
5. Blockade of the epithelial sodium channel (ENaC): amiloride, triamterene, trimethoprim, pentamidine, nafamostat
2. Decreased distal delivery

1. Congestive heart failure
2. Volume depletion
3. Hyporeninemic hypoaldosteronism

1. Tubulointerstitial diseases: systemic lupus erythematosus (SLE), sickle cell anemia, obstructive uropathy
2. Diabetes, diabetic nephropathy
3. Drugs: nonsteroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase 2 (COX2) inhibitors, β-blockers, cyclosporine, tacrolimus
4. Chronic kidney disease, advanced age
5. Pseudohypoaldosteronism type II: defects in WNK1 or WNK4 kinases, Kelch-like 3 (KLHL3), or Cullin 3 (CUL3)
4. Renal resistance to mineralocorticoid

1. Tubulointerstitial diseases: SLE, amyloidosis, sickle cell anemia, obstructive uropathy, post–acute tubular necrosis
2. Hereditary: pseudohypoaldosteronism type I; defects in the mineralocorticoid receptor *or* the epithelial sodium channel (ENaC)
5. Advanced renal insufficiency

1. Chronic kidney disease
2. End-stage renal disease
3. Acute oliguric kidney injury
6. Primary adrenal insufficiency

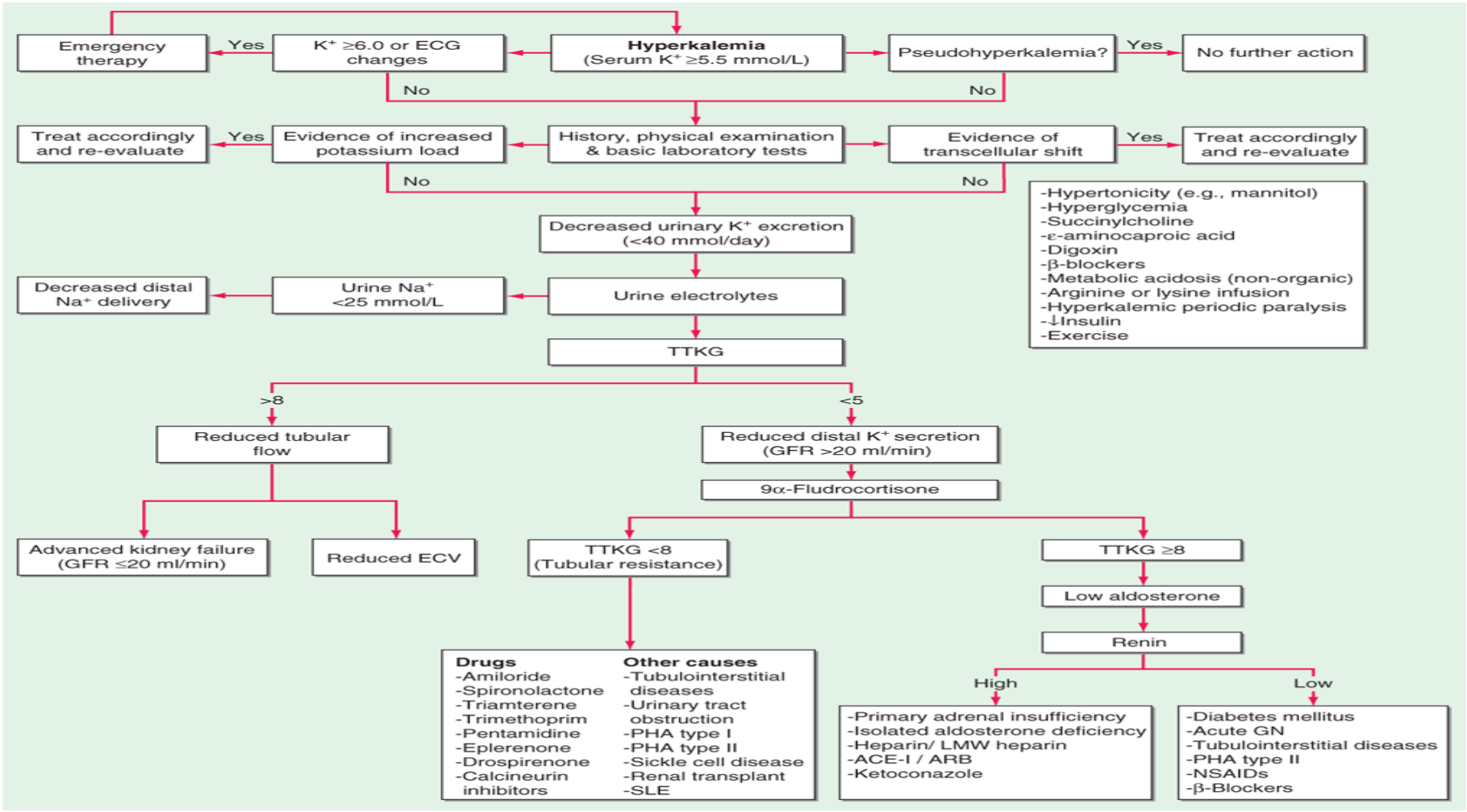
1. Autoimmune: Addison’s disease, polyglandular endocrinopathy
2. Infectious: HIV, cytomegalovirus, tuberculosis, disseminated fungal infection
3. Infiltrative: amyloidosis, malignancy, metastatic cancer
4. Drug-associated: heparin, low-molecular-weight heparin
5. Hereditary: adrenal hypoplasia congenita, congenital lipoid adrenal hyperplasia, aldosterone synthase deficiency
6. Adrenal hemorrhage or infarction, including in antiphospholipid syndrome

Hypoaldosteronism and Hyperkalemia

- Aldosterone release from the adrenal gland may be reduced by hyporeninemic hypoaldosteronism, medications, primary hypoaldosteronism, or isolated deficiency of ACTH (secondary hypoaldosteronism). Primary hypoaldosteronism may be genetic or acquired **(Chap. 379)** but is commonly caused by autoimmunity, either in Addison's disease or in the context of a polyglandular endocrinopathy. HIV has surpassed tuberculosis as the most important infectious cause of adrenal insufficiency. The adrenal involvement in HIV disease is usually subclinical; however, adrenal insufficiency may be precipitated by stress, drugs such as ketoconazole that inhibit steroidogenesis, or the acute withdrawal of steroid agents such as megestrol.
- Hyporeninemic hypoaldosteronism is a very common predisposing factor in several overlapping subsets of hyperkalemic patients: diabetics, the elderly, and patients with renal insufficiency. Classically, patients should have suppressed PRA and aldosterone; ~50% have an associated acidosis, with a reduced renal excretion of NH_4^+, a positive urinary anion gap, and urine pH <5.5. Most patients are volume expanded, with secondary increases in circulating atrial natriuretic peptide (ANP) that inhibit both renal renin release and adrenal aldosterone release.

pseudohypoaldosteronism (PHA).

- PHA type I (PHA-I) has both an autosomal recessive and an autosomal dominant form. The autosomal dominant form is due to loss-of-function mutations in the MLR; the recessive form is caused by various combinations of mutations in the three subunits of ENaC, resulting in impaired Na^+ channel activity in principal cells and other tissues. Patients with recessive PHA-I suffer from lifelong salt wasting, hypotension, and hyperkalemia, whereas the phenotype of autosomal dominant PHA-I due to MLR dysfunction improves in adulthood.
- PHA type II (PHA-II; also known as *hereditary hypertension with hyperkalemia*) is in every respect the mirror image of GS caused by loss of function in NCC, the thiazide-sensitive Na^+-Cl^- cotransporter (see above); the clinical phenotype includes hypertension, hyperkalemia, hyperchloremic metabolic acidosis, suppressed PRA and aldosterone, hypercalciuria, and reduced bone density. PHA-II thus behaves like a gain of function in NCC, and treatment with thiazides results in resolution of the entire clinical phenotype. However, the NCC gene is not directly involved in PHA-II, which is caused by mutations in the WNK1 and WNK4 serine-threonine kinases or the upstream Kelch-like 3 (KLHL3) and Cullin 3 (CUL3) proteins, two components of an E3 ubiquitin ligase complex that regulates these kinases; these proteins collectively regulate NCC activity, with PHA-II-associated activation of the transporter.



The diagnostic approach to hyperkalemia. See text for details. ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCD, cortical collecting duct; ECG, electrocardiogram; ECV, effective circulatory volume; GFR, glomerular filtration rate; GN, glomerulonephritis; HIV, human immunodeficiency virus; LMW heparin, low-molecular-weight heparin; NSAIDs, nonsteroidal anti-inflammatory drugs; PHA, pseudohypoaldosteronism; SLE, systemic lupus erythematosus; TTKG, transtubular potassium gradient. (Used with permission from DB Mount, K Zandi-Nejad K: Disorders of potassium balance, in Brenner and Rector's The Kidney, 8th ed, BM Brenner [ed]. Philadelphia, W.B. Saunders & Company, 2008, pp 547–587.)

- 下列有關低腎素醛固酮分泌不足症（hyporeninemic hypoaldosteronism）之特徵敘述，何者正確？
- 玠 A.代謝性鹼中毒和高鉀血症
- 媳B.代謝性酸中毒和高鉀血症
- 暟 C.代謝性鹼中毒和低鉀血症
- 卼D.代謝性酸中毒和低鈉血症

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- 玠 A.代謝性鹼中毒和高鉀血症 媦**B.代謝性酸中毒和高鉀血症**
- 暟 C.代謝性鹼中毒和低鉀血症 鬲D.代謝性酸中毒和低鈉血症

22.56歲男性糖尿病人因胸部不適至急診，初步檢查血中creatinine 2.0 mg/dL、K^+ 5.8 mEq/L、Na^+ 139 mEq/L、Cl^- 116 mEq/L、HCO_3^- 18 mEq/L、osmolality 290 mOsm/kg・H_2O、尿中creatinine 12 mg/dL、K 9.6 mEq/dL、osmolality 580 mOsm/kg・H_2O，病人最可能的診斷是：

A.第二型腎小管酸血症（type 2 renal tubular acidosis）

B.metformin引發酸血症（metformin related acidosis）

C.低腎素低醛固酮血症（hyporeninemic hypoaldosteronism）

D.糖尿病酮酸血症（diabetic ketoacidosis）

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D.糖尿病酮酸血症（diabetic ketoacidosis）

3.

- 一位35歲女性，因為最近血壓升高來就診。生化初步檢查都在正常值範圍內，除了血清鉀離子是2.5 mmol/L。下列那一個診斷最不可能考慮?
- A.單側腎動脈狹窄(unilateral renal arterial stenosis)
- B.服用甘草(licorice)
- C.高登症候群(Gordon’ s syndrome)
- D.原發性皮質醛酮症(primary aldosteronism)

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- D.原發性皮質醛酮症(primary aldosteronism)

- 32 下列何種疾病不會有低血鉀合併代謝性鹼中毒？
- A.Bartter’ s syndrome
  - B.Primary aldosteronism
  - C.Liddle’ s syndrome
  - D.Gordon’ s syndrome

- 32 下列何種疾病不會有低血鉀合併代謝性鹼中毒？
- A.Bartter’ s syndrome
  - B.Primary aldosteronism
  - C.Liddle’ s syndrome
  - **D.Gordon’ s syndrome**

- 下列何種疾病不會合併有低血鎂？
- 琼 A. Gitelman’ s症候群（Gitelman’ s syndrome）
- 媳 B. Claudin 16 or 19突變（Claudin 16 or 19 mutations）
- 暖 C.再餵食症候群（Refeeding syndrome）
- **鬲 D.甲狀腺功能低下（Hypothyroidism）**

- 下列何者較不會導致低血鈣（hypocalcemia）？
- 玠 A.低血鎂（hypomagnesemia） 媳B.副甲狀腺低下症（hypoparathyroidism）
- **暟 C.服用利尿劑（thiazide）** 卼D.慢性腎衰竭

- **9. 一位26歲患者，外觀正常，身體質量指數（BMI）為20 kg/m2，無不適。健檢發現高血壓、低血鉀、心跳正常。為了探討次發性高血壓的可能，此病患宜安排下列何種檢查最合適？**
- A. 抽血檢驗aldosterone和plasma renin activity
- B. 抽血檢驗ACTH和cortisol
- C. 測量24小時尿液的VMA和catecholamines
- D. 抽血檢驗fT4（free thyroxine）和TSH

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- 109-2
- **1.一位25歲男性，突然發現下肢無力、無法站立與走路、需家人攙扶，遂在隔天早上由家屬陪同就醫。實驗室檢查發現低血鉀（2.0 mEq/L）及低血磷（1.8 mg/dL），而血清肌酸酐（creatinine 0.6 mg/dL）、鈉（139mEq/L）、鈣（2.2 mmol/L）及血清滲透壓（serum osmolality 290 mOsm/kg）則在正常範圍。同時尿液中的鉀與滲透壓分別為10 mEq/L與580 mOsm/kg。下列敘述何者最適當？**
- A. TTKG（transtubular potassium gradient）計算後等於2.0
- B. 此病患低血鉀是因腎臟排出過多鉀離子
- C. 需加驗甲狀腺功能
- D. 經由周邊靜脈補鉀時，應將氯化鉀加在葡萄糖水裡，鉀離子濃度儘量不超過20～40 mmol/L
-

109-2

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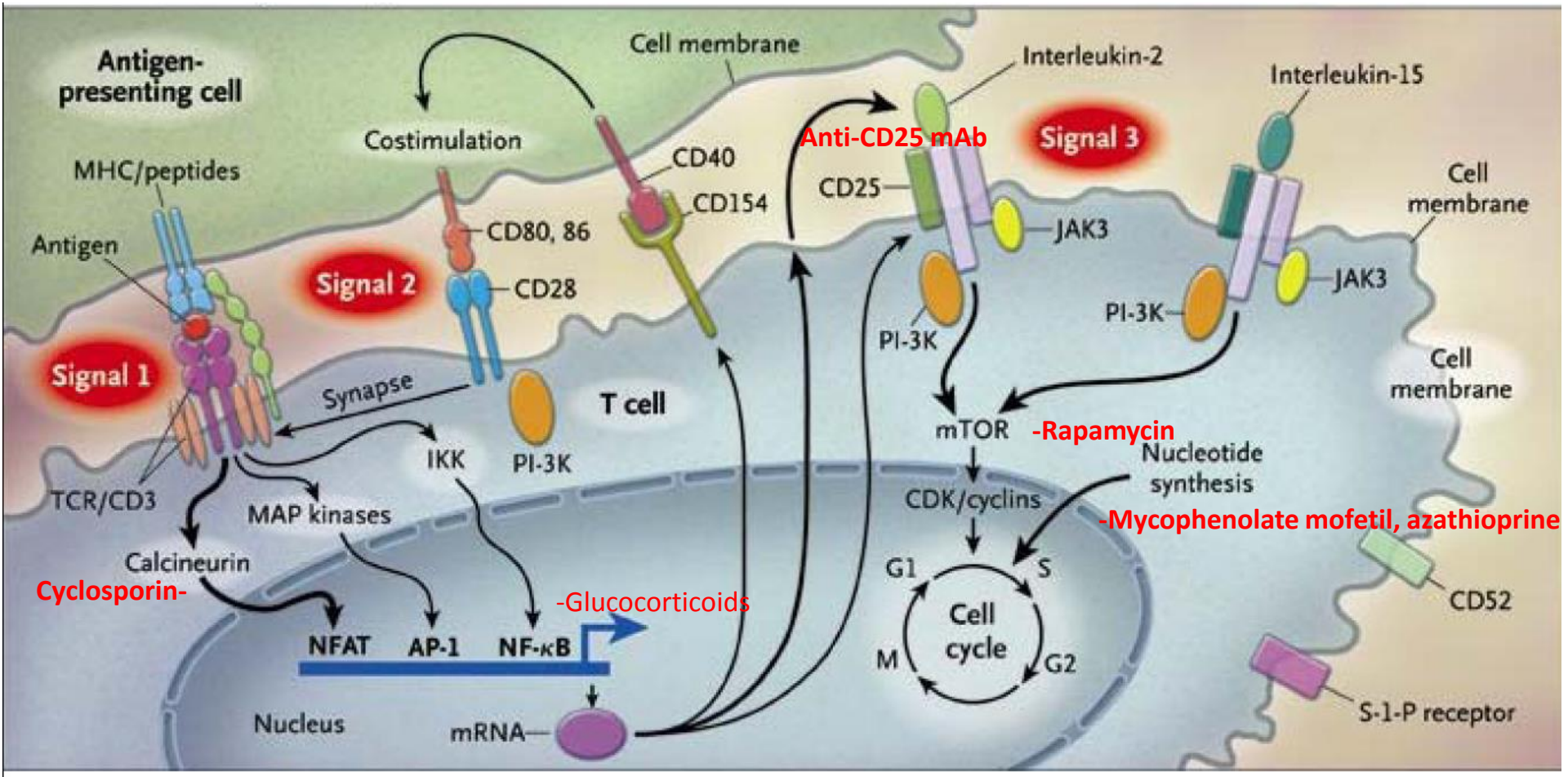
-

Kidney transplantation

Immunosuppressive Agent

Immunosuppressive Agent	Target	Outcome
Cyclosporin A, FK506	**Calcineurin**	**Inhibit calcineurin phosphatase activity, preventing dephosphorylation of NFAT and IL-2 transcription**
Rapamycin	**mTOR**	**Inhibits growth factor signaling, blocks cell-cycle transition and cell survival**
Mycophenolate mofetil, azathioprine	**Purine synthesis**	**Inhibit proliferation of T and B lymphocytes**
Glucocorticoids	**Gene transcription**	Inhibits NF-κBB nuclear translocation and production of proinflammatory cytokines
Anti-CD25 mAb	**CD25**	**Saturates IL-2 receptorand prevents T cell activation**
Campath-1	**CD52**	Depletes mature peripheral lymphocytes, monocytes, natural killer cells, and subset of granulocytes
ATG, ALS	**T cells**	**Broad lymphocyte depletionand immunomodulatoryactivities**



Halloran, NEJM 2004,351:2715

CNI side-effects

- Nephrotoxicity
- Hepatotoxicity
- Diabetogenic effect (FK > CsA)
- Tremor, seizure (FK > CsA)
- Hirsutism (CsA), hair loss (FK)
- Gingival hypertrophy (CsA)
- Hyperuricemia
- Hyperlipidemia (CsA>FK)
- Bone toxicity

FK (Tacrolimus, prograf)
CsA

MMF side effect

- Diarrhea
- Nausea
- Vomiting
- Anemia
- Leukopenia
- Abdominal pain
- Sepsis

Rapamycin-side effect

- Thrombocytopenia
- Granulocytopenia
- Hyperlipidemia
- Diarrhea
- Edema
- Arthralgia
- Proteinuria
- Pneumonitis

- 最容易造成移植後糖尿病之免疫抑制劑為:
  A.cyclosporine
- B.tacrolimus
- C.mycophenolate mofetil
- D.sirolimus

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- B.tacrolimus
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- D.sirolimus

- **7.下列有關腎移植抗排斥藥物與其副作用之配對，何者錯誤？**
- A.類固醇（glucocorticoid）：骨質疏鬆
- B.環孢靈（cyclosporine）：腎毒性
- C.普樂可復（tacrolimus）：移植後糖尿病
- D.斥消靈（sirolimus）：高尿酸血症
-

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- B. 環孢靈（cyclosporine）：腎毒性
- C. 普樂可復（tacrolimus）：移植後糖尿病
- D. 斥消靈（sirolimus）：高尿酸血症
-

- **2.55歲女性病人，因慢性腎絲球腎炎導致末期腎病，5年前接受親屬捐贈活體腎移植，長期接受tacrolimus、mycophenolate mofetil治療，一個月前血中肌酸酐0.8 mg/dL，3天前噁心、嘔吐，肌酸酐升至3.3 mg/dL，腎切片檢查呈現腎小球、腎小管有C4d沉積，內皮細胞損傷，目前最佳治療方式是：**
- A. 增加tacrolimus和mycophenolate mofetil劑量
- B. 類固醇脈衝治療（methylprednisolone pulse therapy）
- C. 降低tacrolimus劑量加血液透析
- D. 血漿置換術加免疫球蛋白注射

- **2. 55歲女性病人，因慢性腎絲球腎炎導致末期腎病，5年前接受親屬捐贈活體腎移植，長期接受tacrolimus、mycophenolate mofetil治療，一個月前血中肌酸酐0.8 mg/dL，3天前噁心、嘔吐，肌酸酐升至3.3 mg/dL，腎切片檢查呈現腎小球、腎小管有C4d沉積，內皮細胞損傷，目前最佳治療方式是：**
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- D. 血漿置換術加免疫球蛋白注射

- 24.48歲男性末期腎病病人，接受長期免疫抑制劑治療，移植前無糖尿病病史，移植3個月後血中肌酸酐0.8
- mg/dL，飯前血糖210 mg/dL，下列何種藥物最有可能產生此種合併症?
  A.mycophenolate mofetil
- B.tacrolimus
- C.sirolimus
- D.everolimus

- 24.48歲男性末期腎病病人，接受長期免疫抑制劑治療，移植前無糖尿病病史，移植3個月後血中肌酸酐0.8
- mg/dL，飯前血糖210 mg/dL，下列何種藥物最有可能產生此種合併症?
  A.mycophenolate mofetil
- B.tacrolimus
- C.sirolimus
- D.everolimus

CKD

- 一位**50**歲病人罹患慢性腎絲球腎炎**20**年，現出現尿毒症狀，且血中肌酸酐為**11.0 mg/dL**，**BUN 120 mg/dL**， 病人選擇血液透析，下列敘述何者錯誤**?**
- **A.**長期血液透析，單次透析其尿素氮**(BUN)**減少的比率達到**60%**是足夠的
- **B.**大多數臺灣病人接受每週**3**次，每次**4**小時的治療
- **C.**所用透析液一般用重碳酸鹽來矯正尿毒病人的酸中毒**(**酸血症**)**
- **D.**肌肉痙攣**(muscle cramps)**是透析時常見的併發症

- 一位50歲病人罹患慢性腎絲球腎炎20年，現出現尿毒症狀，且血中肌酸酐為11.0 mg/dL，BUN 120 mg/dL， 病人選擇血液透析，下列敘述何者錯誤?
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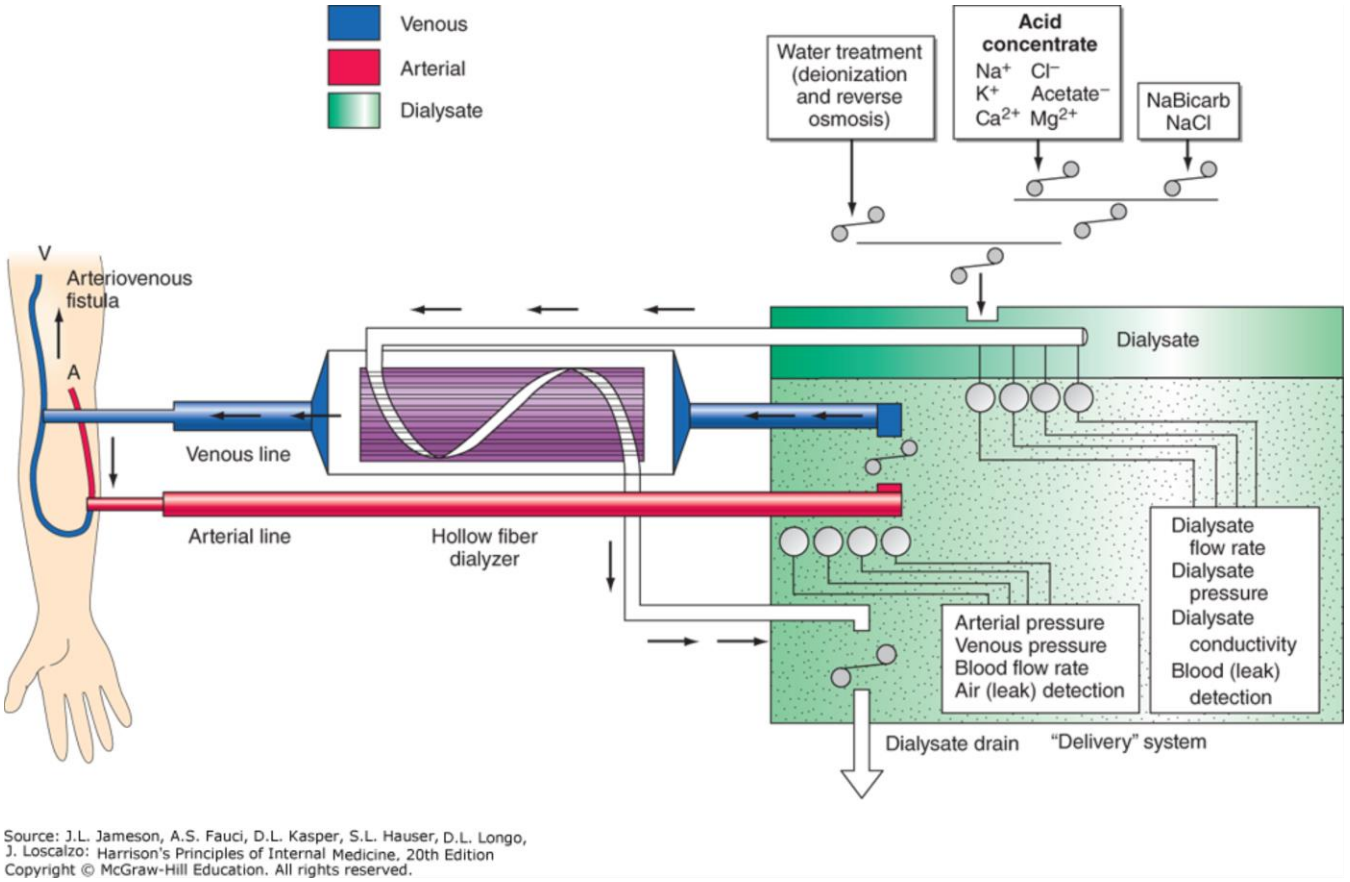
- C.所用透析液一般用重碳酸鹽來矯正尿毒病人的酸中毒(酸血症)
- D.肌肉痙攣(muscle cramps)是透析時常見的併發症

- Current targets include a urea reduction ratio (the fractional reduction in blood urea nitrogen per hemodialysis session) of >65–70% and a body water–indexed clearance × time product (Kt/V) >1.2 or 1.05, depending on whether urea concentrations are “equilibrated.”



Source: J.L. Jameson, A.S. Fauci, D.L. Kasper, S.L. Hauser, D.L. Longo, J. Loscalzo: Harrison's Principles of Internal Medicine, 20th Edition

Schema for hemodialysis.

- 6 一位 45 歲男性末期腎病患者選擇腹膜透析（peritoneal dialysis），下列敘述何者錯誤？
- 珚A.每兩天執行一次腹膜透析
- 媳B.腹膜透析單次注入腹腔2 公升透析液是可以的
- 暟C.腹膜透析脫水靠滲透壓（osmolality），最常用來提供滲透壓的物質是高濃度葡萄糖
- 鬲D.肌酸酐廓清率每週70 L 是足夠的

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Target of WKt/V, WnCcr

	CAPD		CCPD	NIPD
	L, LA	H, HA		
Weekly Kt/V	>1.7	>2.0	>2.1	>2.2
Weekly nCCr	>50 L/week	>60 L/week	>63 L/week	>66 L/week

- 35下列何者是血液透析過程中最常見之急性併發症？
- 玠 A.高血壓 媳B.低血壓 暟C.抽筋 卼D.嘔吐

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- 玠 A.高血壓 媳**B.低血壓** 暯C.抽筋 鬲D.嘔吐

- 下列有關慢性腎病(chronic kidney disease)所引發之次發性副甲狀腺機能亢進(secondary hyperparathyroidism)機轉之敘述，何者錯誤?

A.腎臟衰竭造成高磷血症(hyperphosphatemia)

B.Fibroblast growth factor 23抑制腎臟1-alpha hydroxylase，降低活性維他命D之合成

C.高磷血症(hyperphosphatemia)促進活性維他命D之產生

D.低鈣血症(hypocalcemia)刺激副甲狀腺荷爾蒙之產生

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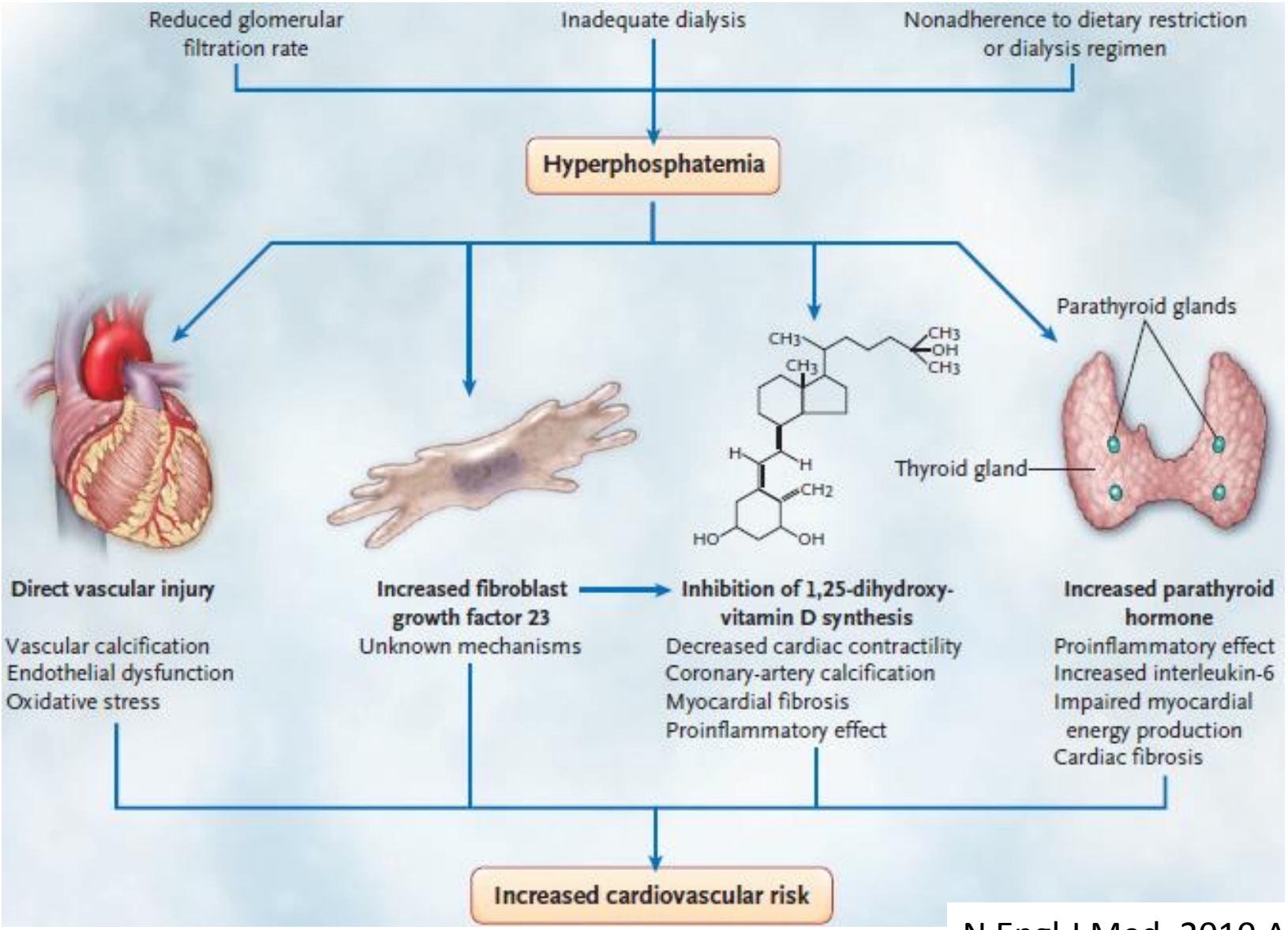
高血磷對於心血管風險



N Engl J Med. 2010 Apr 8;362

- Fibroblast growth factor 23 (FGF-23) is part of a family of phosphatonins that promotes renal phosphate excretion. Recent studies have shown that levels of this hormone, secreted by osteocytes, increases early in the course of CKD. It may defend normal serum phosphorus in at least three ways: (1) increased renal phosphate excretion; (2) stimulation of PTH, which also increases renal phosphate excretion; and (3) suppression of the formation of 1,25(OH)2D3, leading to diminished phosphorus absorption from the gastrointestinal tract.

- 下列何種腎臟替代療法為末期腎病之最佳治療**(treatment of choice)?**
- **A.**血液透析**(hemodialysis)**
- **B.**腹膜透析**(peritoneal dialysis)**
- **C.**腎臟移植**(kidney transplantation)**
- **D.**血液過濾透析**(hemodiafiltration)**

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- D.血液過濾透析(hemodiafiltration)

- 有關腹膜透析和血液透析的優劣點，下列何者錯誤?
- A.血液透析對於超過濾(ultrafiltration)的控制比較正確
- B.腹膜透析比較容易發生血脂肪升高
- C.血液透析比較常有白蛋白流失
- D.腹膜透析比較容易有低血鉀情況

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- 治療慢性腎病(chronic kidney disease)合併之高血壓時，首選藥物為:
- **A.利尿劑(diuretics)**
- **B.鈣離子阻斷劑(calcium channel blockers)**
- **C.β-阻斷劑(β-blockers)**
- **D.血管張力素轉化酶阻斷劑(angiotensin-converting enzyme inhibitors)或血管張力素接受器阻斷劑(angiotensin receptor blockers)**

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減緩慢性腎臟病惡化—血壓調控

Control systemic blood pressure to reduce Intraglomerular Hypertension and Proteinuria

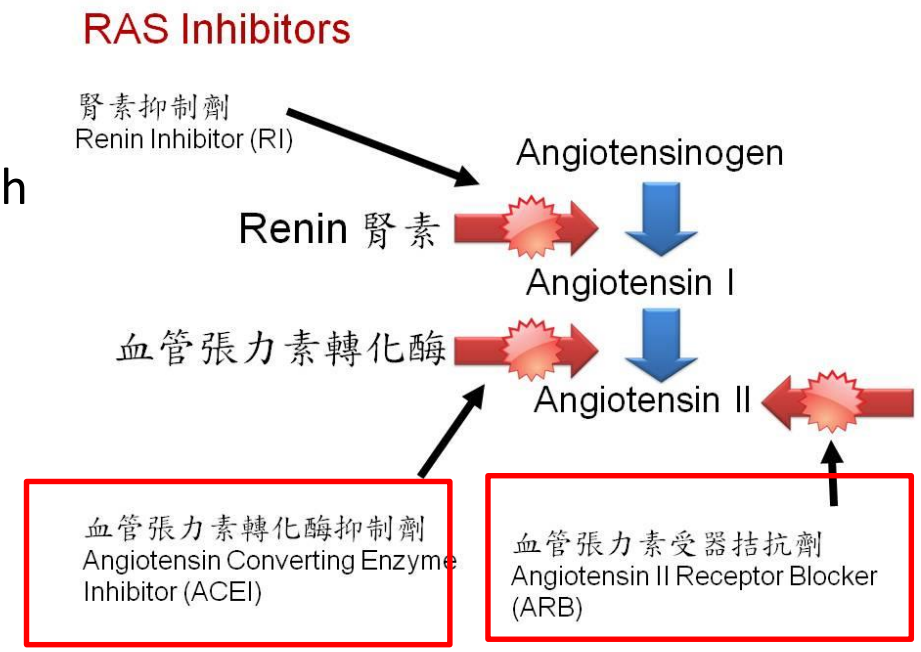
- Lowering protein excretion results into less decline in GFR.
- Elevated blood pressure increases proteinuria.
- ***130/80 mmHg as the target blood pressure in non-proteinuric CKD patients.***
- ***125/75 mmHg as the target blood pressure in proteinuric CKD patients.***

Avoiding further renal injury

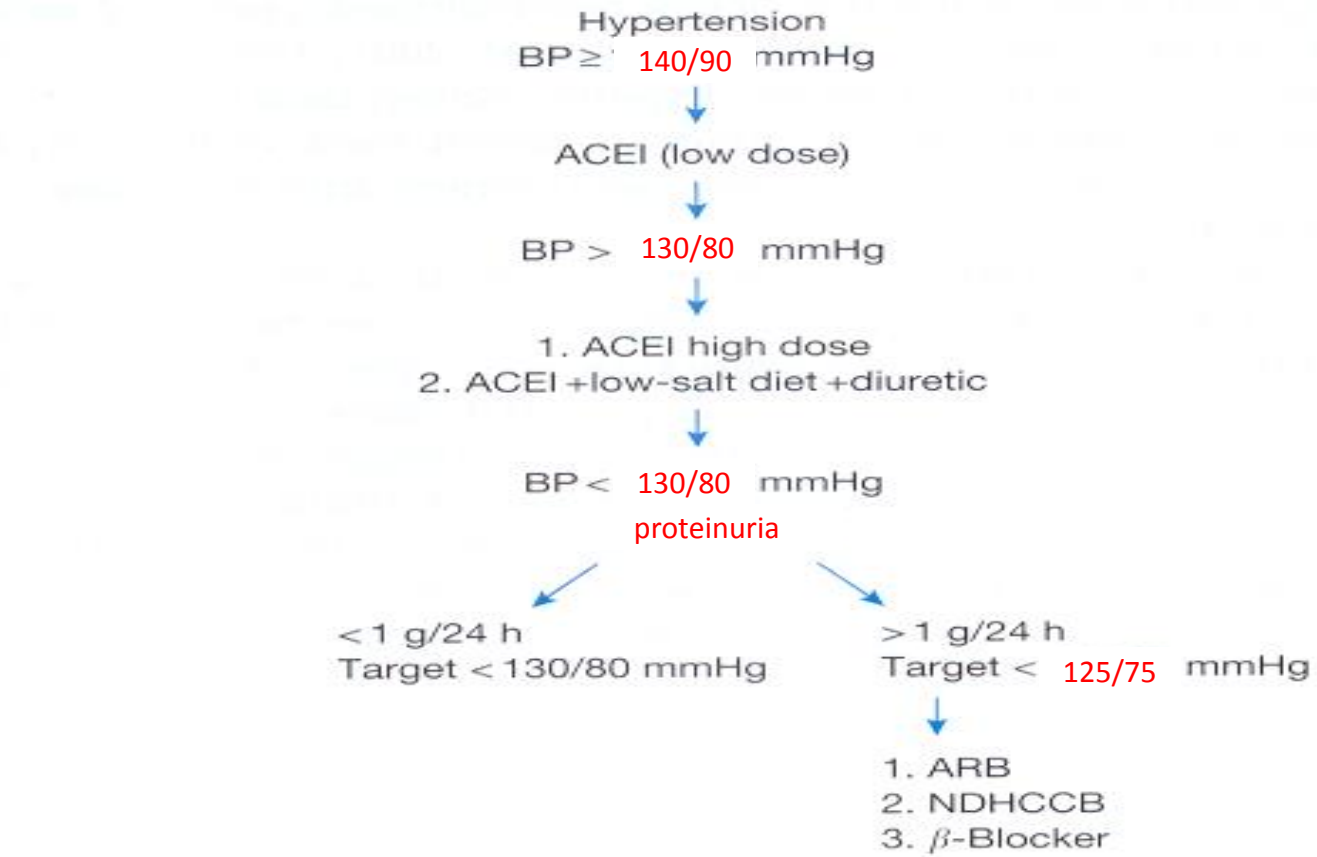
- Dehydration
- Renal toxic agents
  - NSAIDs (non-steroid anti-inflammatory drugs)
  - Amionoglycosides
  - Contrast medium

慢性腎臟病為什麼要使用ACEIs/ARB?

- **Lowering both systemic and intraglomerular hypertension to decrease proteinuria**
- Several controlled studies showing ACEI/ARBs are effective in slowing th progression in both diabetic and nondiabetic CKD patients, esp. with protienuria
- Adverse effects
  - ACEIs: cough and angioedema
  - ACEI/ARB: anaphylaxis, and hyperkalemia
  - A progressive increase in plasma creatinine after the use may suggest the presence of renovascular disease within the large or small arteries.



慢性腎臟病—高血壓處理流程



ACEI = Angiotensin converting enzyme inhibitors
NDHCCB = Non-dihydropyridine calcium channel blocker
ARB = Angiotensin receptor blocker

- 腎絲球過濾率可藉由自主控制(autoregulation)在血壓變化時，仍能保持穩定之腎絲球過濾率，下列有關腎絲球過濾率自主控制之敘述，何者正確?
  A.出球小動脈(efferent arteriole)之自主控制來自肌源性(myogenic)反射
- B.腎小管腎絲球回饋(tubuloglomerular feedback)，會影響出球小動脈(efferent arteriole)之收縮與舒張
- C.腎小球旁器(juxtaglomerular apparatus)釋出腎素(renin)，引發入球小動脈(afferent arteriole)之收縮
- D.抑制腎小管產生腺苷(adenosine)，可造成入球小動脈(afferent arteriole)之擴張

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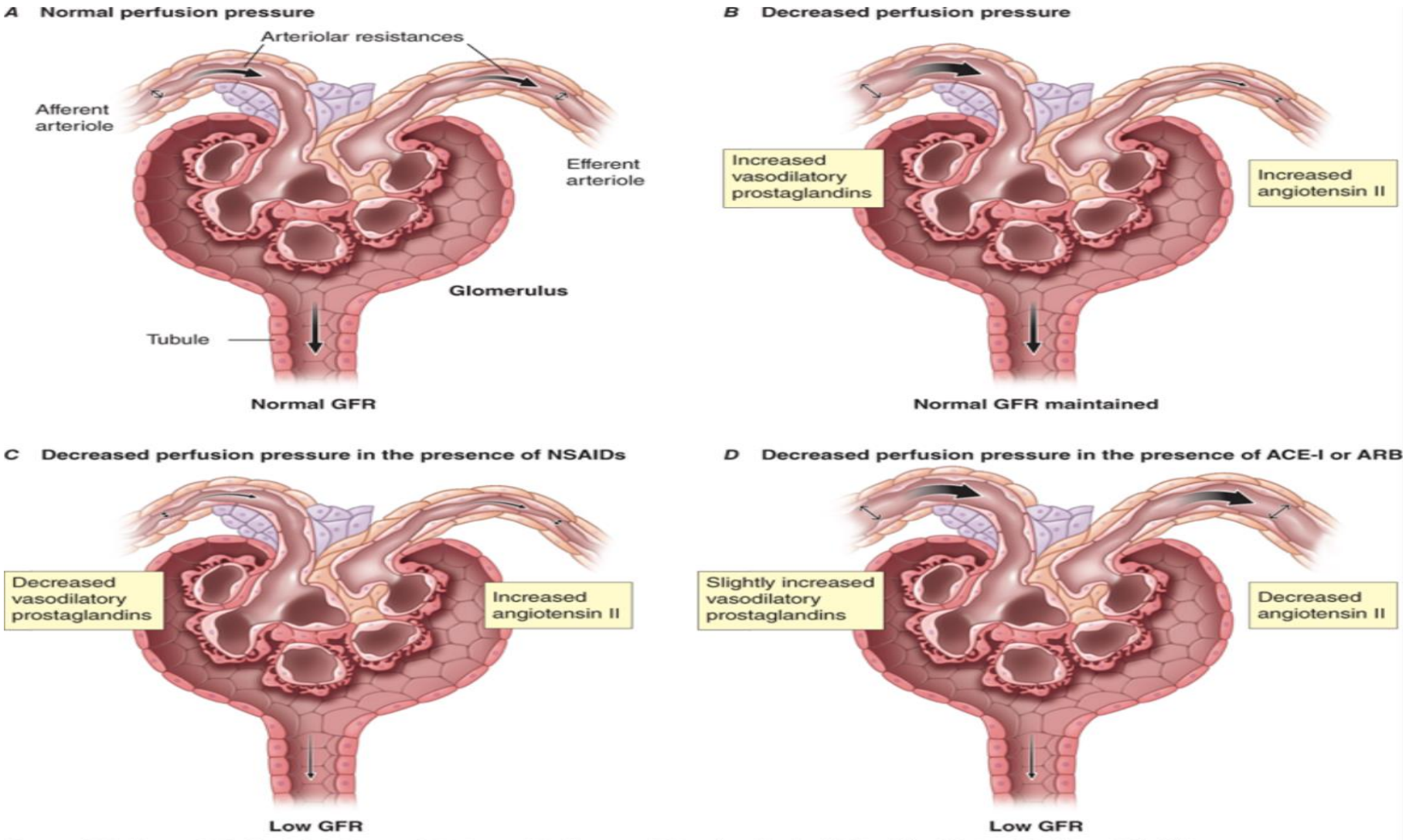
Autoregulation of the glomerular filtration rate (GFR)



Source: D. L. Kasper, A. S. Fauci, S. L. Hauser, D. L. Longo, J. L. Jameson, J. Loscalzo: Harrison's Principles of Internal Medicine, 19th Edition.
www.accessmedicine.com

- 有關angiotensin-converting enzyme inhibitors的腎臟保護作用，下列何者錯誤?
- A.可以降低血壓
  B.可以降低蛋白尿
  C.可以增加腎絲球過濾速率
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- 下列藥物可能引起急性腎臟損傷，而主要的作用是腎血管的影響，何者例外?
- A.非類固醇消炎劑(nonsteroidal anti-inflammatory drugs)
- B.血管張力素阻斷劑(angiotensin-converting enzyme inhibitors)
- C.含鉑的抗癌製劑(如cisplatin)
- D.腎素抑制劑(renin inhibitors)

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- 一位 50 歲男病人，患慢性腎臟病8 年，一個月前血清肌酸酐（creatinine）為3.0 mg/dL 現因身體虛弱而就診，抽血發現血清肌酸酐6.0 mg/dL，血鉀（K）7.2 mmol/L，心電圖呈現高而尖的T 波及QRS期間（duration）延長的變化，下列敘述何者錯誤？
- A.給予口服鉀離子交換樹脂（potassium exchange resin）
- B.給予重碳酸鈉靜脈注射
- C.給予口服氧化鎂
- D.緊急血液透析治療

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Potassium Homeostasis (鉀離子)

- Compensation of impaired potassium secretion in CKD (which is not necessary) includes increased secretion through GI tract
- Conditions in which easily developing hyperkalemia:
  - increased dietary potassium intake, protein catabolism, hemolysis, hemorrhage, transfusion of stored red blood cells
  - metabolic acidosis
  - Use of ACE inhibitors, ARBs, and spironolactone and other potassium-sparing diuretics.
- Hyperkalemia can be treated by
  - avoidance of
    - dietary potassium
    - potassium supplements (including occult sources, such as dietary salt substitutes)
    - potassium-retaining medications (especially ACE inhibitors or ARBs)
  - use of
    - kaliuretic diuretics.
    - Potassium-binding resins (calcium resonium or sodium polystyrene)
  - Dialysis in intractable hyperkalemia

- 下列治療高血鉀症方法中，何者能夠有效降低體內的鉀量？
- A.beta 2 受體促效劑（beta 2 agonist）
- B.樹脂（resins）
- C.氯化鈣（calcium chloride）
- D.葡萄糖＋胰島素（glucose + insulin）

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- 28 一位52歲女性，在急診處被發現血鉀7.2 mmol/L，其心電圖出現高的T波，QRS延長。第一步需要給予何種處理？
- A.給予calcium gluconate靜脈注射
- B.給予β2-交感神經促進劑（β2-adrenergic agonists）
- C.給予離子交換劑（cation exchange resins）
- D.給予insulin加葡萄糖靜脈輸注

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- 下列何項是第2 型糖尿病腎病變最早期的臨床表現？
- A.尿液白蛋白排泄量>30 mg/day
- B.血清肌酸酐（creatinine）>1.2 mg/dL
- C.腎絲球過濾率>120 mL/min
- D.血壓>130/80 mmHg

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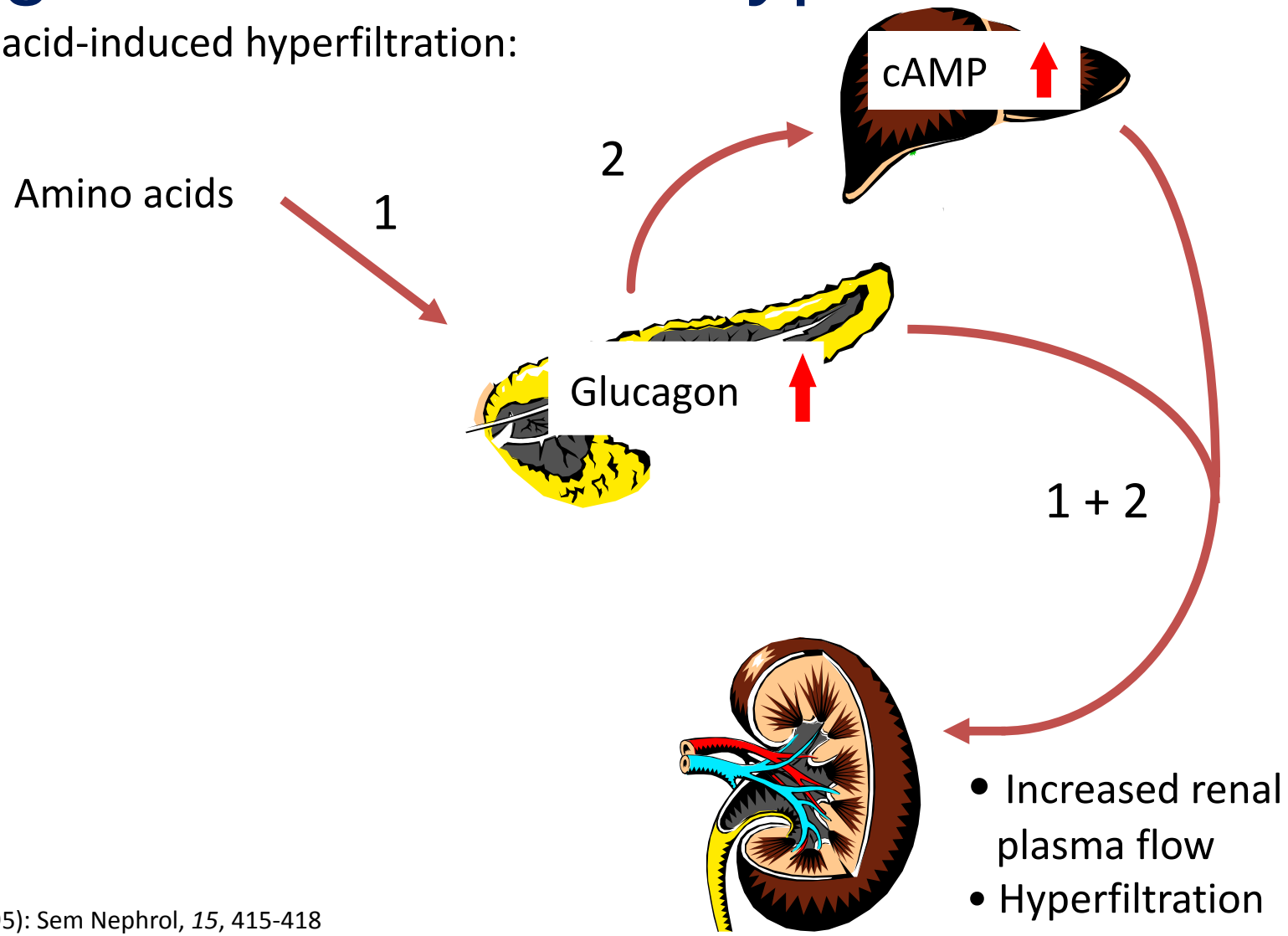
- D.血壓>130/80 mmHg

糖尿病腎病變分成五個階段

- 第一期:高過濾期，腎臟會肥大，也會腎絲球過濾率會增加，然而白蛋白尿排出量也些微增加，但在正常範圍內(一天小於30毫克)；大部分糖尿病病患於血糖控制良好之下，白蛋白尿情形可改善。
- 第二期:靜止期，在糖尿病診斷確定後數年，腎絲球開始有細小的結構性損傷，但是其肌肝酸無明顯上升，腎功能無明顯惡化，白蛋白尿的排出量也在正常範圍內(每天小於30毫克)，臨床上無明顯其他症狀。
- 第三期:微量白蛋白尿期，通常在診斷8~10年後，腎絲球結構損傷嚴重，開始有白蛋白尿增加的情形(一天30~300毫克)，臨床上病患常合併血壓上升；雖然這階段有白蛋白尿增加，但在血糖嚴格控制之下，其微量白蛋白尿是可逆的，而回到正常白蛋白尿期。
- 第四期:巨量白蛋白尿期，通常在糖尿病發生後的15~20年，此時白蛋白尿顯著增加(一天大於300毫克)，同時無法藉由血糖嚴格的控制，而明顯改善白蛋白尿的程度；另外高血壓不易控制，腎臟功能會快速惡化，血中肌肝酸上升速率加快。
- 第五期:末期腎臟病變，此時病患若有尿毒症的症狀(食慾不振、倦怠、水腫、寡尿、呼吸喘、貧血、酸血症、高血鉀…等)，則需要腎臟替代療法(血液透析或腹膜透析)。

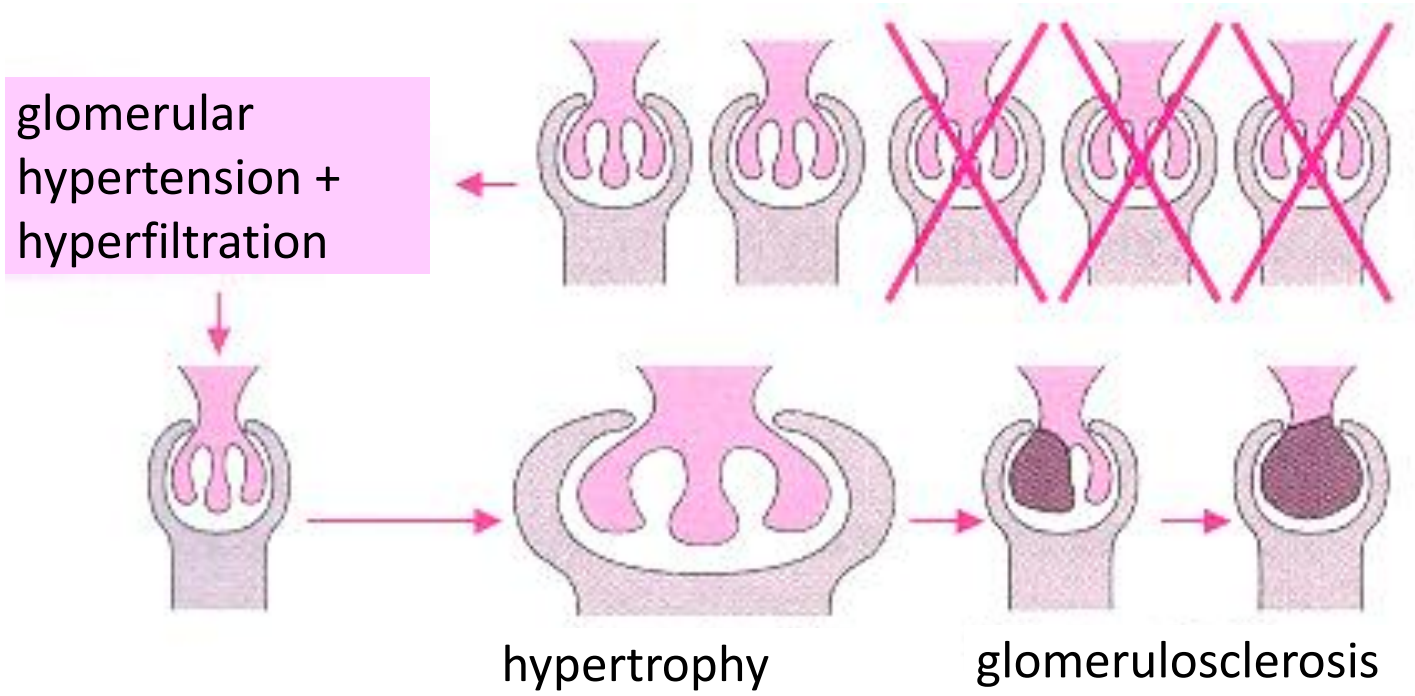
慢性腎臟病惡化-腎絲球的高過濾率
Progression of CKD-Hyperfiltration

Amino acid-induced hyperfiltration:



Lang et al. (1995): Sem Nephrol, *15*, 415-418

慢性腎臟病惡化Progression of CKD



減緩慢性腎臟病惡化–限制蛋白
Protein restriction

Dietary principles	CKD 1-3 stage	CKD 4-5
Energy	**30-35 kcal/kg/d**	**30-35 kcal/kg/d**
Protein	**0.8-1.0 g/kg/day**	**0.6-0.75 g/kg/day**
Fat	25-35% healthy fat selection	25-35% healthy fat selection
Carbohydrate	Adjusted based on glycemic control	Adjusted based on glycemic control
Low salt	Yes	Yes
Low Potassium	-	Depend on lab values
Low phosphorus	-	Depend on lab values

Principles modified based on
K/DOQI 2000 year, J Am Diet Assoc 2004(104)404-409, 1993-1996 NAHSIT

- 40 下列何者不是腎臟製造的荷爾蒙？
- A.腎素（renin）
- B.皮質醛固酮（aldosterone）
- C.紅血球生成素（erythropoietin）
- D.活性維生素D3（calcitriol）

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腎臟基本生理功能

- 分泌尿液、排出代謝產物、藥物及廢物
  - 腎功能
- 調節體內體液、電解質及酸鹼平衡
  - 水分、電解質異常
  - 代謝性酸鹼中毒
- 荷爾蒙之分泌
  - 紅血球生成素 (Erythropoietin)
  - 維生素D (Vitamin D3)
  - 腎素（Renin）

- 一位長期血液透析的尿毒病人，接受紅血球生成素（erythropoietin）注射，每週三次，每次2000 U，打了3個月，血色素（hemoglobin）不見上升。尋找原因時，下列何者最不需要考慮？
- A.慢性腸胃道出血
- B.透析效率不良
- C.缺鐵
- D.缺鈣

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- C.缺鐵
- **D.缺鈣**

Anemia in CKD慢性腎臟病貧血

- A normocytic, normochromic anemia is almost universal by CKD stage 4.
- Causes of anemia in CKD
  - Relative deficiency of erythropoietin
  - Diminished red blood cell survival
  - Bleeding diathesis
  - Iron deficiency
  - Hyperparathyroidism/bone marrow fibrosis
  - "Chronic inflammation“
  - Folate or vitamin B12 deficiency
  - Hemoglobinopathy
  - Comorbid conditions: hypo/hyperthyroidism, pregnancy, HIV-associated disease, autoimmune disease, immunosuppressive drugs
- Treatment of anemia for CKD is to reverse all the causes above if possible

- 下列何者不是延緩慢性腎病進展的治療方式？
- A.低蛋白飲食
- B.控制血壓
- C.非類固醇抗發炎藥物
- D.血管張力素阻斷劑（angiotensin receptor blocker）

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總結:
減緩慢性腎臟病惡化的策略

A: Education衛教:

- **No smoking, no alcohol**
- **On low salt, low protein diet (0.6-0.8g/Kg/Day)**
- **Avoid nephrotoxic agents and unnecessary drugs**
- **Obesity →reduce body weight: close to IBW**
- **Consult a Nephrologist early: Team with the nephrologist for care if GFR is less than 30 mL/min/1.73 m2**

B: Medication藥物調整:

- **Use of ACEI, ARB etc**
- **Control BP (pressure less than 130/80 mmHg, proteinuria 125/75 mmHg)**
- **Control sugar (HbA1c < 8%)**
- **Electrolyte balance**
- **Fluid control**
- **Control dyslipidemia**
- **Phosphate blinder, vitamin D**
- **Sodium bicarbonate**
- **Supplement of EPO or *HIF***
- **Ketosteril use(reduce urea production, reduce urea to kidney burden, improve nutrition status, and improve immunity)**
- **Kremezin (*Spherical Adsorptive Carbon)***
- **Pentoxifyllin use [slow down(prevent) renal fibrosis]**

- 關於慢性腎臟病（chronic kidney disease）的敘述，下列何者最不正確？
- A.根據目前國際所認知的分期，一位70歲72公斤的男性病人，他的血清肌酸酐為2.5 mg/dL，應該是第四期
- B.使用captopril可以延緩慢性腎病衰竭的速度，主要是可以增加腎絲球內壓力，提高腎絲球過濾速率
- C.目前最被研究和腎臟衰竭相關的基因是angiotensin-converting enzyme。具有deletion（D）的同質接合者（DD），其腎功能比較會進展至衰竭
- D.有蛋白尿的慢性腎臟病人，血壓的控制目標是在125/75 mmHg

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- A.腎臟切片檢查
- B.透析治療
- C.以angiotensin-converting enzyme inhibitor治療
- D.以脈衝式類固醇（pulse methylprednisolone）治療

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- 31.腎衰竭病人常有出血傾向，其中最重要的機轉為：
- A.血小板數目減少
- B.血小板凝集功能不正常
- C.肝內凝血蛋白質合成減少
- D.血管完整性異常

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- 19.下列那一項治療在減緩慢性腎衰竭的進行速率上，沒有效果？
- A.服用ACEI（Angiotensin converting enzyme inhibitors）或ARB（Angiotensin receptor blockers）來治療高血壓
- B.糖尿病患者嚴格控制血糖，維持HbA1C＜7%
- C.服用Kayexalate
- D.低蛋白飲食

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- D.低蛋白飲食

- **8.有關尿毒性出血（uremic bleeding）的敘述，下列何者錯誤？**
- A.尿毒性出血常導因於血小板凝集功能不良
- B.若尿毒性出血病患合併貧血，輸血也有助於凝血
- C.可輸注desmopressin、cryoprecipitate來治療尿毒性出血
- D.若持續出血，可考慮給與androgen幫助止血，但須注意可能有血栓栓塞（thromboembolism）的風險

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26.有關慢性腎臟病所併發之腎性貧血（renal anemia），下列敘述何者錯誤？

A.腎性貧血之紅血球型態常為正常血球大小（normocytic）與正常色素性（normochromic）

B.腎性貧血常出現虛弱、運動耐受力不良（exercise intolerance）、心衰竭與認知功能異常等症狀

C.因慢性腎臟病病患常合併血液凝集功能異常，故造成腎性貧血最主要的原因為胃腸道出血

D.將腎性貧血病患之血色素值矯正至正常人標準值（≥13 g/dL），無法改善病患之心血管併發症

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27.下列有關慢性腎臟病的敘述，何者錯誤？

A.糖尿病乃目前臺灣新發生長期透析病患最常見之原發病因

B.慢性腎臟病患合併糖尿病，其血壓值應控制在130/80 mmHg以下

C.敗血症為最常造成慢性腎臟病患死亡的原因

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24.一名40歲男性糖尿病患者，定期接受降血糖（metformin）和血壓藥物（amlodipine）治療，其居家血壓維持138/86 mmHg，最近HbA1c為6.8%，血紅素10.7 g/dL，尿蛋白1.5 g/day，estimated GFR 59 mL/min per 1.73 m^2，下列治療策略何者正確？

A.輔以低劑量長效型胰島素

B.使用紅血球生成素減緩腎功能惡化

C.加上血管張力素受器阻斷劑

D.進行低蛋白飲食合併胺基酸補充品

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- 22.72歲男性為慢性腎病病人，血中肌酸酐(creatinine)6.3 mg/dL，下列何種酸鹼電解質狀態最少發生在此病 人?
- A.鈉(Na+)148 mEq/L
- B.鉀(K+)5.6 mEq/L
- C.磷(PO 3-)5.5 mg/dL 4
- D.鈣(Ca++)8.0 mg/dL

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- 23.
- 65歲女性病人因長期糖尿病腎病變，接受規則血液透析治療已5年，透析前血中磷(PO 3-)6.8 mg/dL、鈣 (Ca++)10.8 mg/dL、副甲狀腺賀爾蒙(PTH)88 pg/mL。對此病人，下列何者為最適當治療?
- A.使用磷結合劑(phosphate binder)
- B.使用維他命D3(vitamin D3)
- C.使用擬鈣劑(calcimimetic)
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AKI

Epidemiology of AKI

- Incidence of less severe AKI: 2,000-3,000 per million population per year
- AKI treated with renal replacement therapy: 200-300 per million population per year
- 4-5% of general intensive care unit patients will be treated with renal replacement therapy
- Up to two thirds of intensive care unit patients will develop AKI defined by the RIFLE classification

Crit Care Med. 2008 Apr;36(4 Suppl):S146-51.

Changing landscape of AKI

- **1978**, Tufts Medical Center
  - 4.9% incidence per hospitalization
- **1996**, Rush Presbyterian-St Luke's Medical Center
  - 7.2% incidence per hospitalization
- **2002**, ARIC cohort
  - 17% incidence
- Increased in more recent time period and age >65

Grams et al. Clin J Am Soc Nephrol 2014 Jan 23 [Epub]

Hou et al. Am J Med 1983;74:243-8

Nash et al. Am J Kidney Dis 2002;39:930-6

Case

- M/40 year-old
- BW 72kg
- DM, hypertension
- Pneumonia
- Daily urine output: 2000 ml
- 3 days later, septic shock with inotropic agent
- Urine output 100 ml daily
- Serum creatinine (1.0→2 mg/dl)

What is your clinical evaluation?

Q2: Is this patient HAVE

- 1. Oliguria
- 2. Pre-renal azotemia
- 3. Acute kidney injury

Is this patient HAVE

- Oliguria: Urine volume to 0.5 ml/kg/h
- Pre-renal azotemia: spot urine Na < 20meq/L, FeNa < 1%, urine osmolality > 500 mOsm.kg, Serum BUN/Crea>20
- Acute kidney injury

Oliguria

- Generally reflects a decreased GFR
- Normal GFR: approximately 125 ml/min

(approximately 107 ml/kg/h for a 70-kg adult),

- Urine volume to 0.5 ml/kg/h

Q3: How much of GFR for this patient?

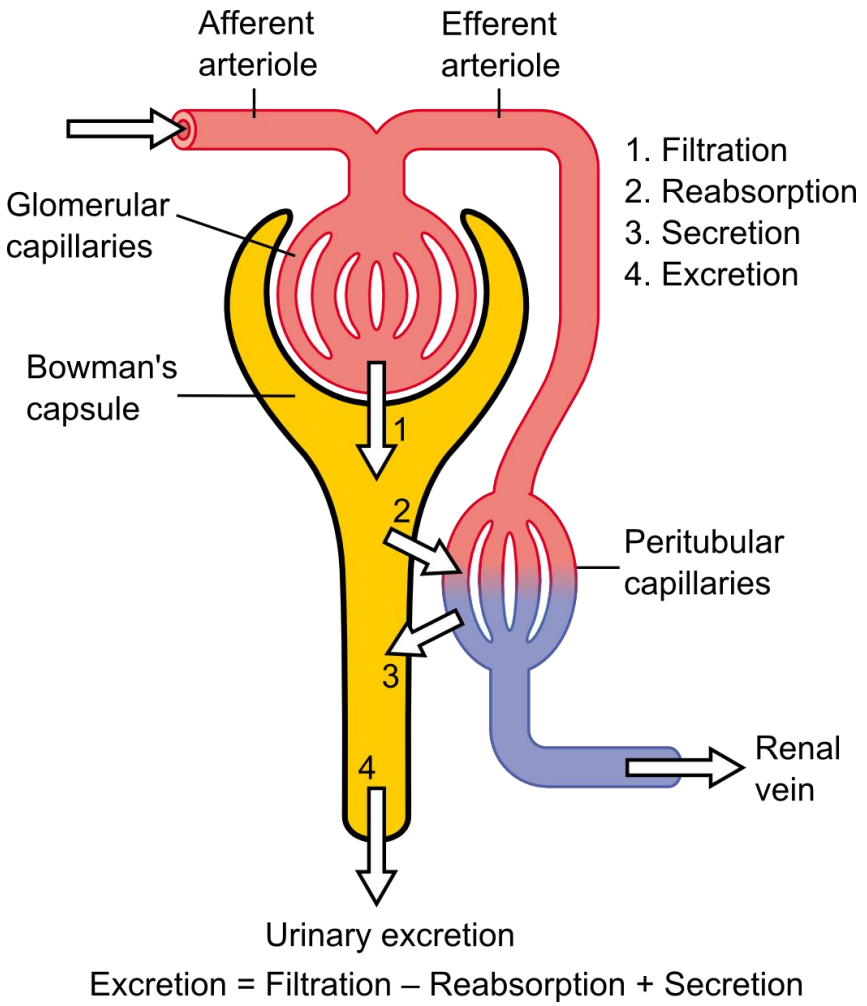
1: 125 ml/min

2: 50 ml/min

3: 25 ml/min

4: 0 ml/min

Glomerular filtration rate (GFR)



- Renal blood flow accounts for 20% of the cardiac output

- GFR is about 125 mL/min (10% less for women), or 180 L/day.
- About 99% of the filtrate (178 L/day) is reabsorbed, and the rest (2 L/day) is excreted.

- Total GFR= sum of the SNGFRs in each of the functioning nephrons

Arch Intern Med 1924;34:243-57

腎絲球過濾率Glomerular Filtrate Rate (GFR)

GFR measurement

1. Creatinine clearance rate: 24 hours urine clearance rate

Estimated GFR (eGFR)

1. Equation from the Modification of Diet in Renal Disease (**MDRD**) study

   eGFR (mL/min per1 .73 m2) = $1.86 \times (PCr)^{-1.154} \times (age)^{-0.203}$

   - Multiply by 0.742 for women
   - Multiply by 1.21 for African Americans

2. **Cockcroft-Gault equation**

   eGFR=(140-age)x body weight /(72xcreatinine)

   - Multiply by 0.85 for women

GFR- current applications

Diagnostic marker: Epidemiology-USA

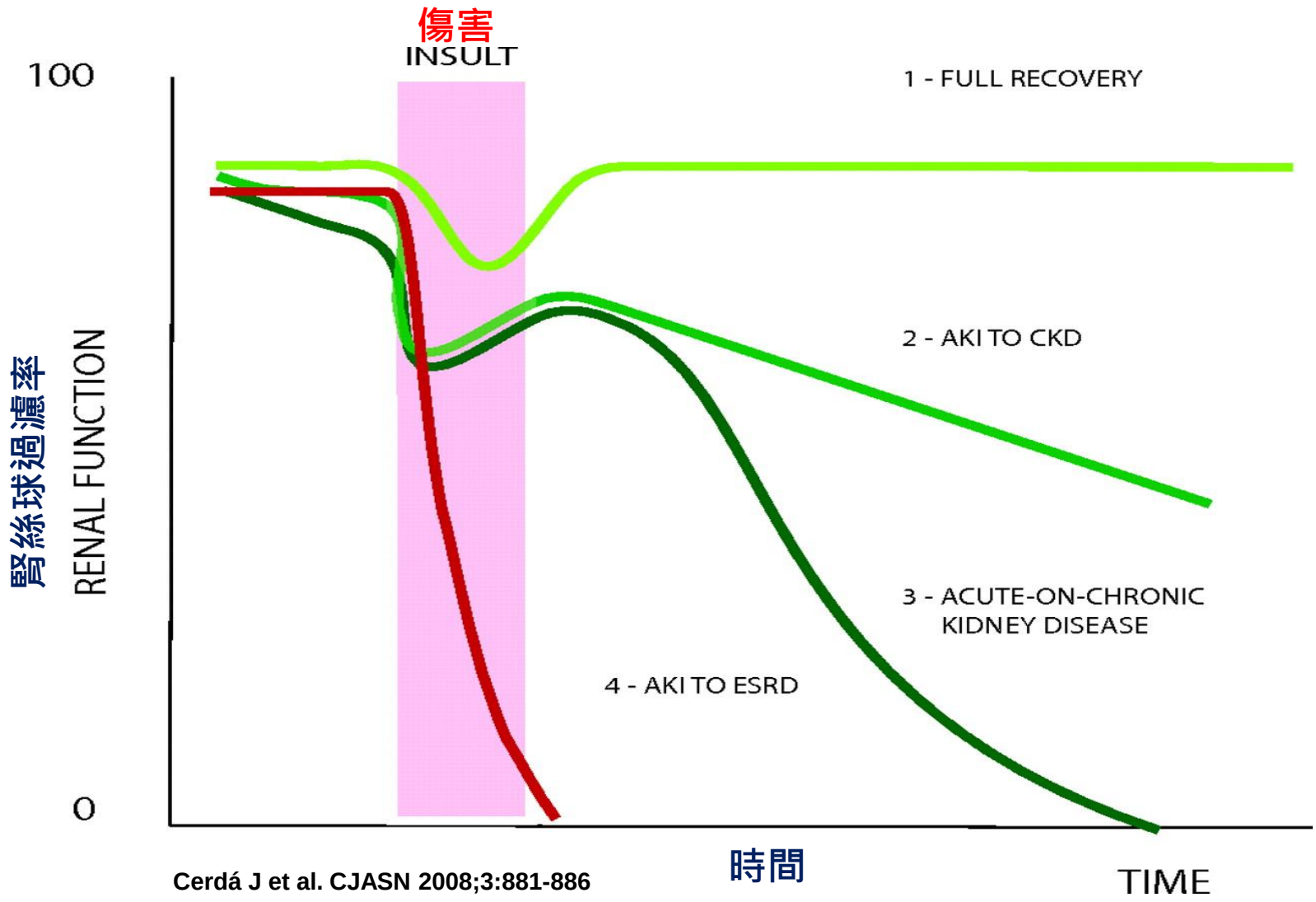
Stage of CKD	Description	GFR		Prevalence†
			%	No. of Cases (95% CI)
		ml/min/1.73 m²		*millions*
1	Kidney damage with normal or increased GFR	>90	2.8	5.6 (4.0–7.2)
2	Kidney damage with mild decrease in GFR	60–89	2.8	5.7 (4.2–7.2)
3	Moderate decrease in GFR	30–59	3.7	7.4 (6.0–8.9)
4	Severe decrease in GFR	15–29	0.1	0.30 (0.02–0.5)
5	Kidney failure	<15	0.2	0.30‡

N Engl J Med 2006;354:2473-83

Q4: Is this patient has AKI?

- 1.Yes
  2.No
  3.CKD
  4. I do not know

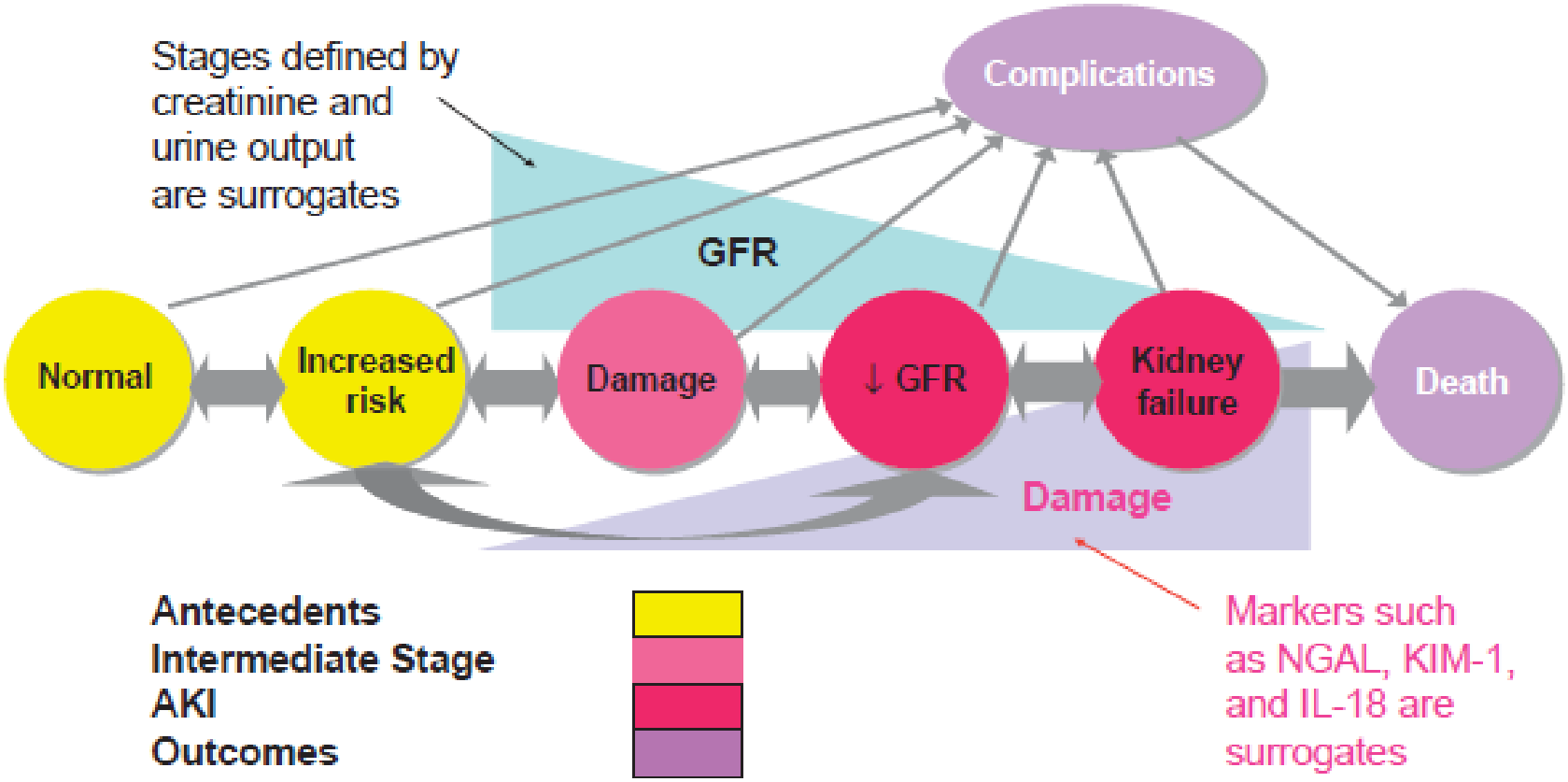
急性腎損傷後的發展



Cerdá J et al. CJASN 2008;3:881-886

CJASN

Conceptual model of acute kidney injury (AKI).



Cerdá J et al. CJASN 2008;3:881-886

CJASN

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Q4: Is this patient has AKI?

- **1.Yes**
  2.No
  3.CKD
  4. I do not know

The RIFLE Criteria

- In 2002, a group of experts known as the Acute Dialysis Quality Initiative (ADQI)
- 3 severity categories and 2 clinical outcome categories.

Categories	Serum Creatinine Criteria	Urine Output Criteria†
RIFLE:		
Risk	↑ in SCr to 1.5–<2 × baseline	UO: <0.5 mL/kg/hr for 6 hrs
Injury	↑ in SCr to 2–<3 × baseline	UO: <0.5 mL/kg/hr for 12 hrs
Failure	↑ in SCr to ≥3 × baseline	UO: <0.3 mL/kg/hr for 24 hrs or anuria for 12 hrs
Loss	Loss of kidney function for >4 wks	
ESRD	Loss of kidney function for >3 mos	

Marino's The ICU Book fourth Edition

Limitations of RIFLE criteria

- The RIFLE criteria have 2 limitations:

(a) there is no defined time period for the change in serum creatinine

(b) the minimum change in serum creatinine required for the diagnosis of AKI is considered too large.

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AKIN Criteria

- In 2005, Acute Kidney Injury Network (AKIN)
- A smaller change in creatinine (≥ 0.3 mg/dL) for the diagnosis of AKI
- A time limit of 48 hours is imposed on the change in serum creatinine.

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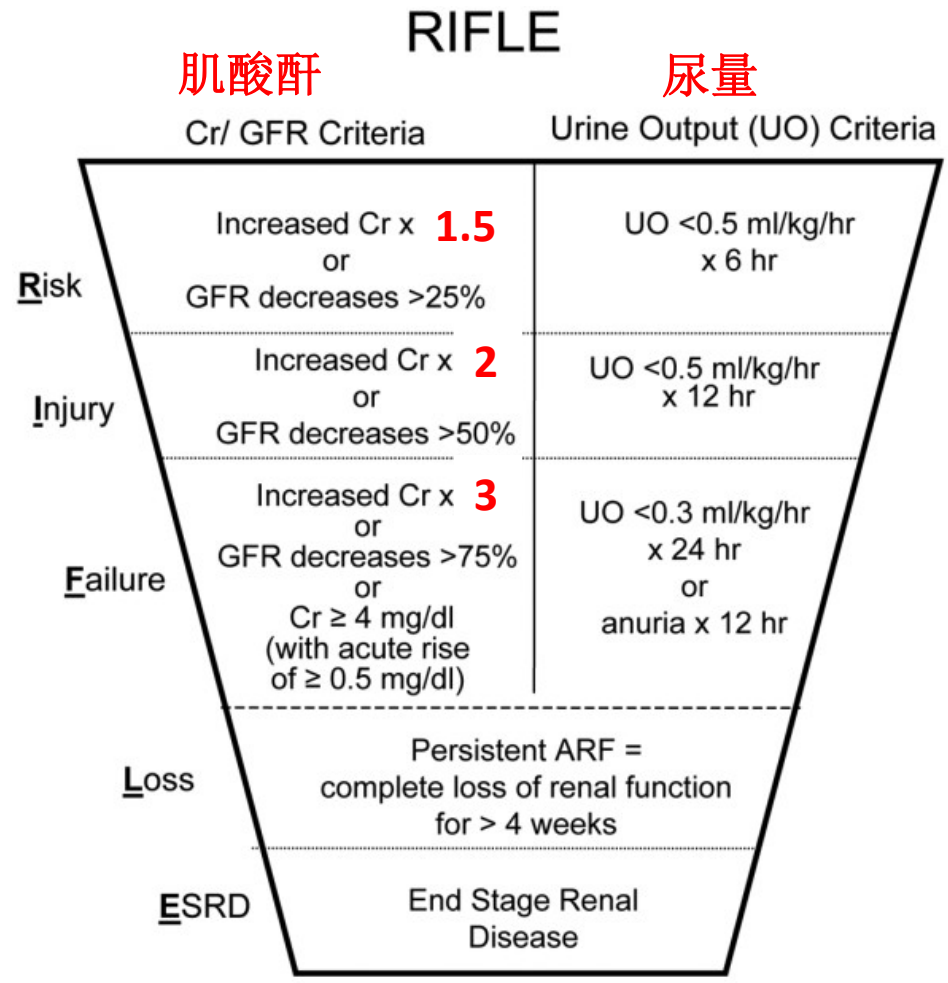
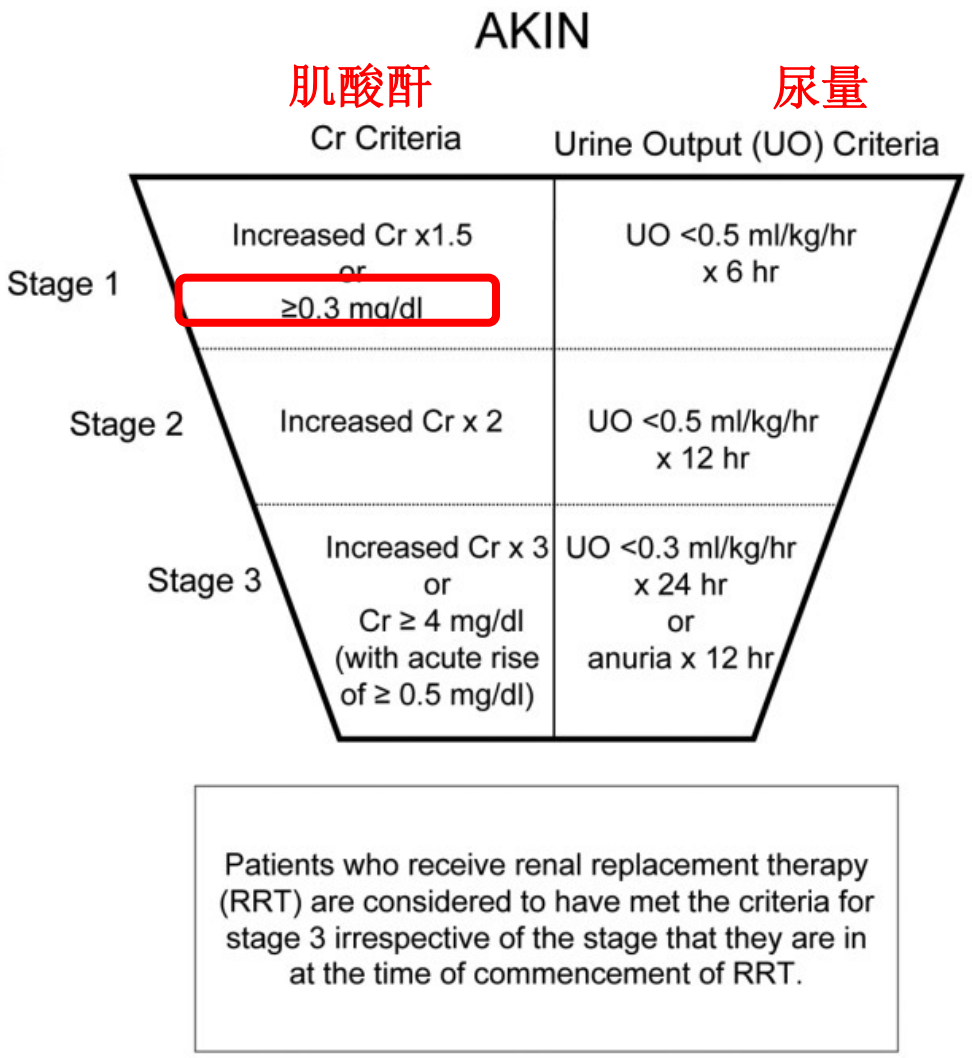
急性腎損傷分級





2002 Acute Dialysis Quality Initiative Group, ADQI

2005 Acute Kidney Injury Network，AKIN

Comparison of RIFLE and AKIN Criteria

AKI staging	Urine output	RIFLE	
Serum creatinine	(common to both)	Class	Serum creatinine or GFR
Stage 1 Increase of more than or equal to 0.3 mg/dl (≥26.5 μmol/l) or increase to more than or equal to 150% to 200% (1.5- to 2-fold) from baseline	Less than 0.5 ml/kg/h for more than 6 hours	Risk	Increase in serum creatinine × 1.5 or GFR decrease >25%
Stage 2 Increased to more than 200% to 300% (>2- to 3-fold) from baseline	Less than 0.5 ml/kg per hour for more than 12 hours	Injury	Serum creatinine × 2 or GFR decreased >50%
Stage 3 Increased to more than 300% (>3-fold) from baseline, or more than or equal to 4.0 mg/dl (≥354 μmol/l) with an acute increase of at least 0.5 mg/dl (44 μmol/l) or on RRT	Less than 0.3 ml/kg/h for 24 hours or anuria for 12 hours	Failure	Serum creatinine × 3, or serum creatinine >4 mg/dl (>354 μmol/l) with an acute rise >0.5 mg/dl (>44 μmol/l) or GFR decreased >75%
		Loss	Persistent acute renal failure=complete loss of kidney function >4 weeks
		End-stage kidney disease	ESRD >3 months

Confusion in definition

- The diagnosis of AKI includes prerenal conditions (e.g., hypovolemia) where there is no “injury” in the kidneys.
- Oliguria is required for the diagnosis of AKI, which neglects cases of nonoliguric acute renal failure (e.g., interstitialnephritis, myoglobinuric renal failure).
- There is a lack of agreement about the minimum increase in serum creatinine required for the diagnosis of AKI.

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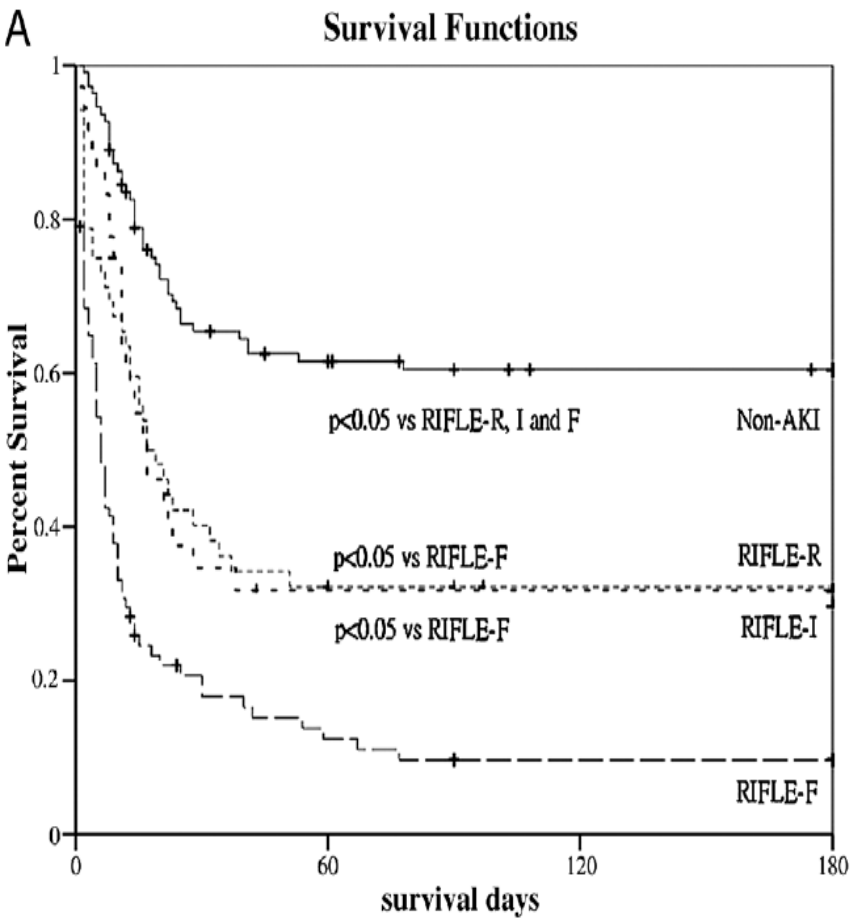
Clinical outcomes: RIFLE vs AKIN criteria

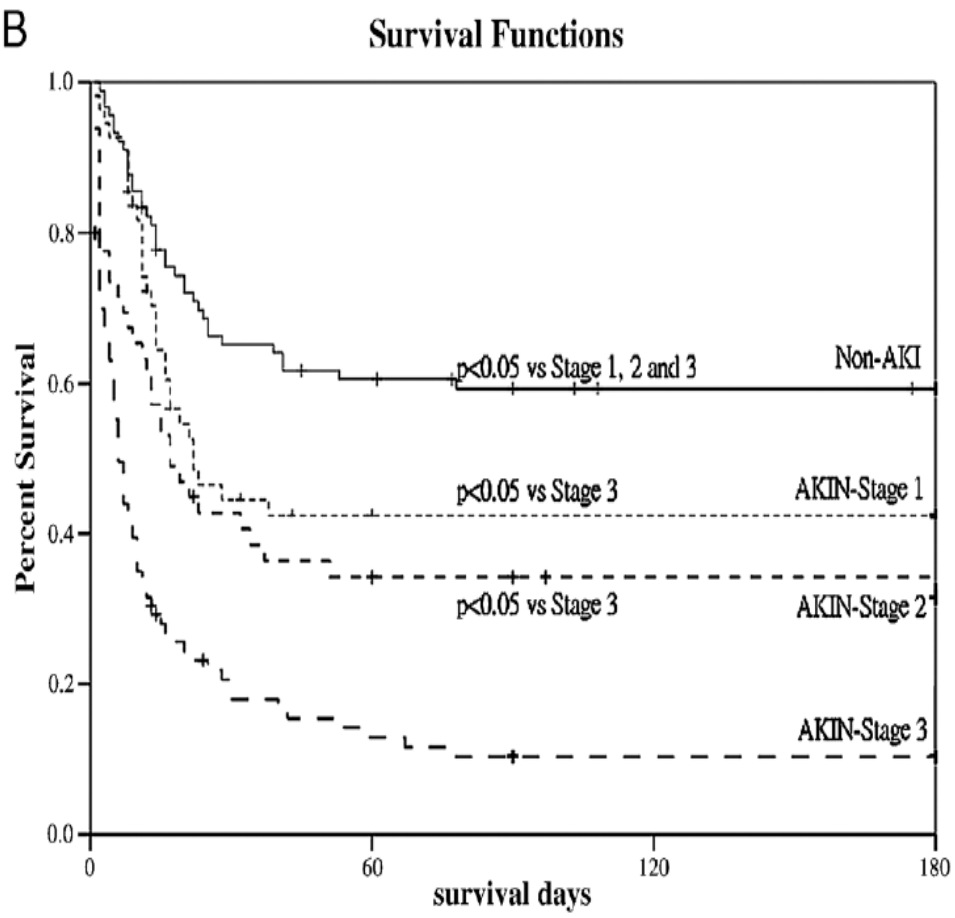
	All patients (n = 291), n (%)	Hospital survivors (n = 114), n (%)	Hospital nonsurvivors (n = 177), n (%)
RIFLE*			
Non-AKI	114 (39.2)	72 (63.2)	42 (23.7)
Risk	38 (13.1)	14 (12.3)	24 (13.6)
Injury	52 (17.9)	16 (14.0)	36 (20.3)
Failure	87 (29.9)	12 (10.5)	75 (42.4)
Total	291	114 (39.2)	177 (60.8)
AKIN*			
Stage 0	93 (32.0)	57 (50.0)	36 (20.3)
Stage 1	57 (19.6)	27 (23.7)	30 (17.0)
Stage 2	49 (16.8)	16 (14.0)	33 (18.6)
Stage 3	92 (31.6)	14 (12.3)	78 (44.1)
Total	291	114 (39.2)	177 (60.8)

*Chi-square for trend; $P < 0.001$.

Shock. 2010 Mar;33(3):247-52.

Clinical outcomes: RIFLE vs AKIN criteria





Shock. 2010 Mar;33(3):247-5

Case

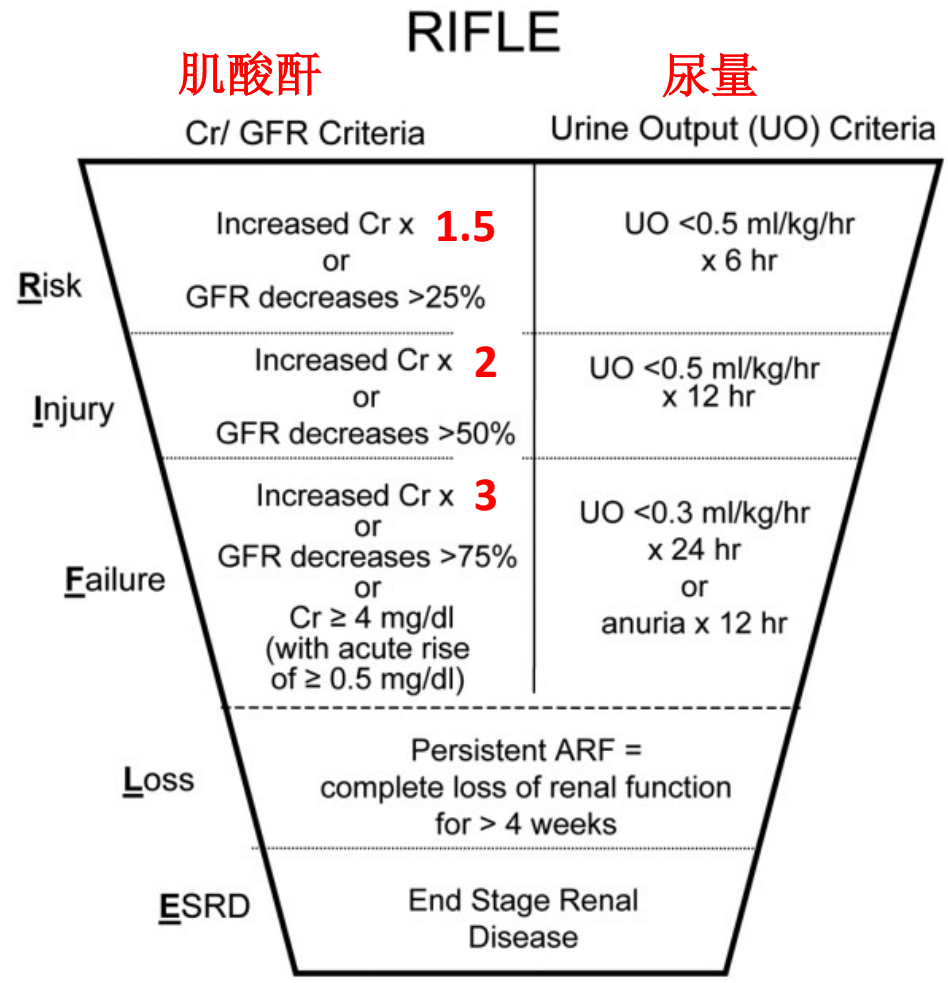
- M/40 year-old
- BW 72kg
- DM, hypertension
- Pneumonia
- Daily urine output: 2000 ml
- 3 days later, septic shock with inotropic agent
- Urine output 100 ml daily
- Serum creatinine (1.0→2 mg/dl)

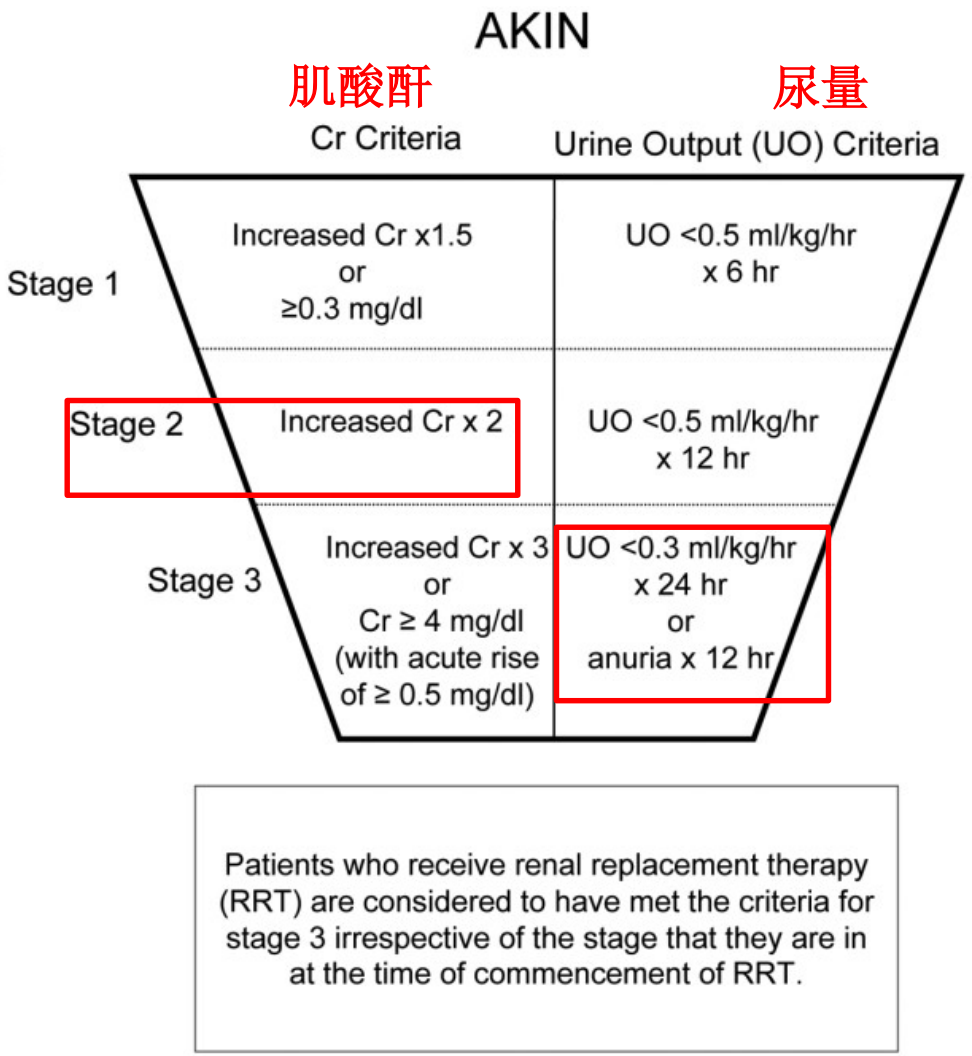
What is your clinical evaluation?

Q5: What's stage of AKIN in this patient?

- 1. Stage I
- 2. Stage II
- 3. Stage III
- 4. None of above

急性腎損傷分級





2002 Acute Dialysis Quality Initiative Group, ADQI

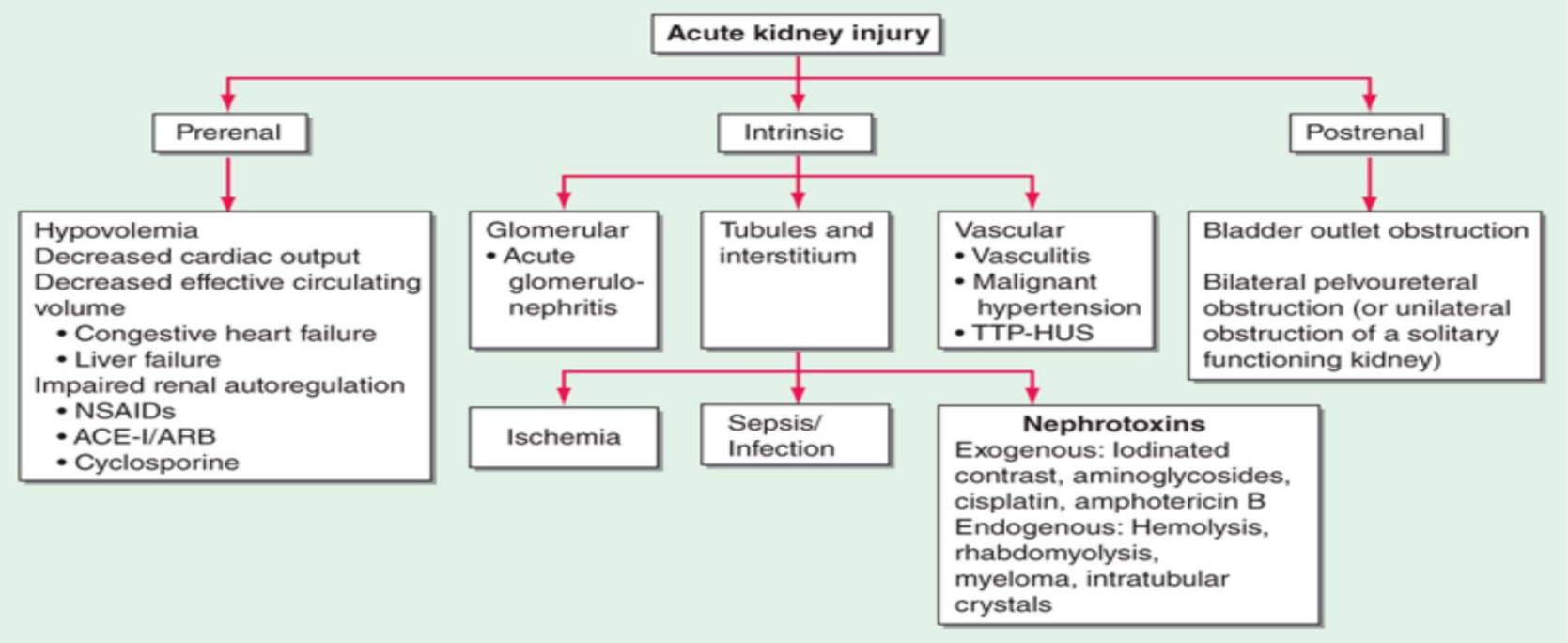
2005 Acute Kidney Injury Network，AKIN

Q5: What's stage of AKIN in this patient?

- 1. Stage I
- 2. Stage II
- 3. Stage III
- 4. None of above

Clinical phenotype of AKI

- Prerenal Disorders
- Renal Disorders (Intrinsic)
- Postrenal Obstruction



Source: D. L. Kasper, A. S. Fauci, S. L. Hauser, D. L. Longo, J. L. Jameson, J. Loscalzo: Harrison's Principles of Internal Medicine, 19th Edition.
www.accessmedicine.com

Citation: Acute Kidney Injury, Kasper D, Fauci A, Hauser S, Longo D, Jameson J, Loscalzo J. *Harrison's Principles of Internal Medicine, 19e;* 2015. Available at: https://accessmedicine.mhmedical.com/content.aspx?sectionid=79746409&bookid=1130&Resultclick=2 Accessed: August 13, 2018

Common causes of AKI

Most Common Causes†	Other Common Causes
Sepsis*	Increased Abdominal Pressure
Major Surgery	Cardiopulmonary Bypass
Hypovolemia	Trauma
Low Cardiac Output	Rhabdomyolysis
Nephrotoxic Agents	

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Prerenal Disorders

- The insult in prerenal disorders is a decrease in renal blood flow
- Prerenal disorders are responsible for 30 – 40% of cases of AKI
- Hypovolemia and low-output heart failure
- Responds to interventions that augment systemic blood flow (e.g., volume resuscitation), but the response can be lost when the low flow state is severe (e.g., hypovolemic shock).

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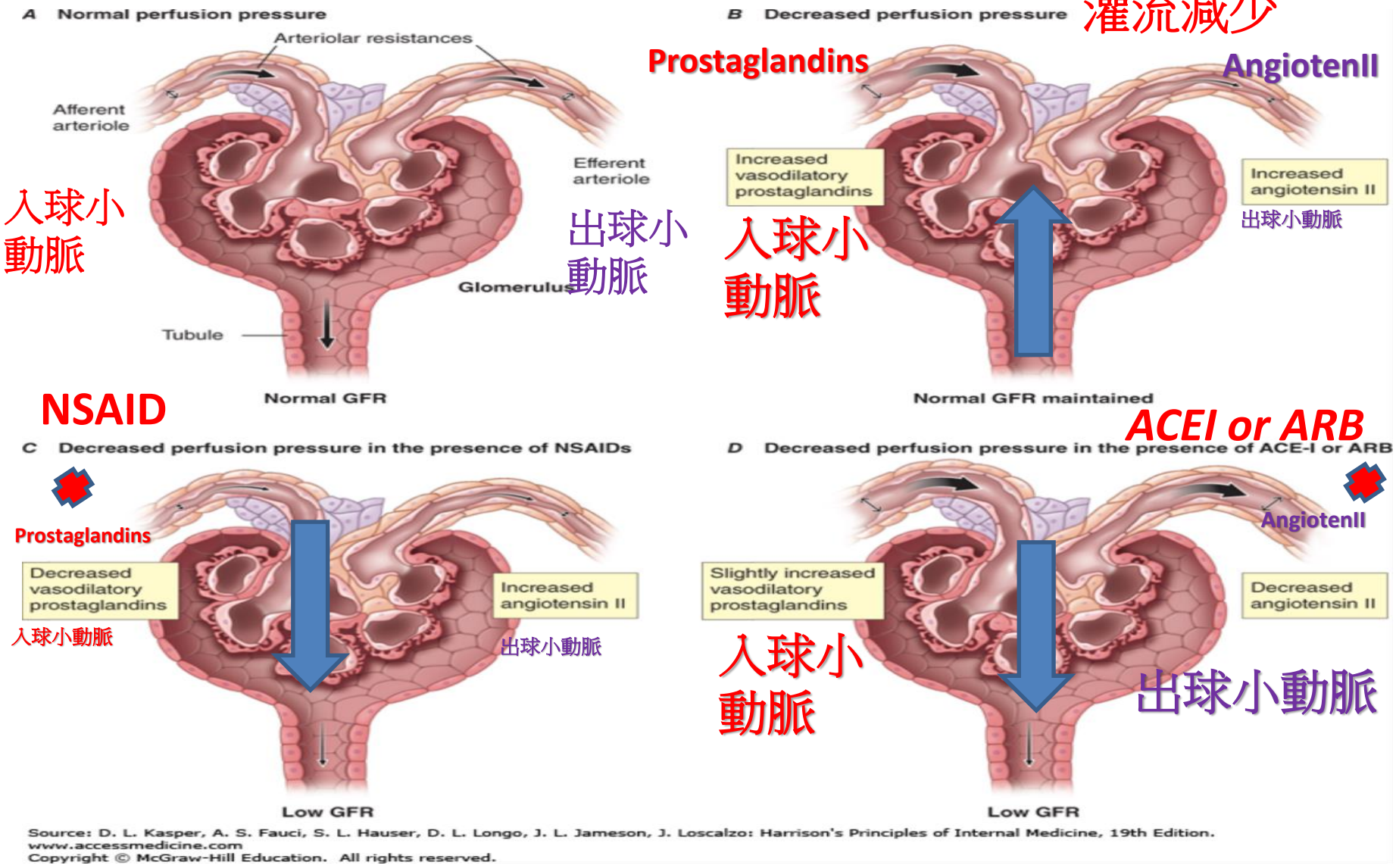
Autoregulation of the glomerular filtration rate (GFR)



Source: D. L. Kasper, A. S. Fauci, S. L. Hauser, D. L. Longo, J. L. Jameson, J. Loscalzo: Harrison's Principles of Internal Medicine, 19th Edition.
www.accessmedicine.com

- **Q6: 下列情況使用angiotensin-converting enzyme inhibitor(ACEI)比較容易發生急性腎衰竭，但何者例外?**
- **1.雙側腎動脈狹窄**
- **2.合併使用鈣離子阻斷劑**
- **3.使用大量利尿劑治療鬱血性心衰竭**
- **4.合併使用非類固醇消炎劑**

- 下列情況使用**angiotensin-converting enzyme inhibitor(ACEI)**比較容易發生急性腎衰竭，但何者例外?
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- **2.**合併使用鈣離子阻斷劑
- **3.**使用大量利尿劑治療鬱血性心衰竭
- **4.**合併使用非類固醇消炎劑

Renal Disorders (Intrinsic AKI)

- Prerenal azotemia advances to tubular injury
- Acute tubular necrosis (ATN)
- Acute interstitial nephritis (AIN): inflammatory injury, but the injury is located in the renal interstitium rather than the renal tubules

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Acute tubular necrosis (ATN)

- ATN is responsible for over 50% of cases of AKI
- Inflammatory (oxidative) injury in the epithelial cell lining of the renal tubules
- Damaged cells are sloughed into the lumen of the renal tubules, where they create an obstruction

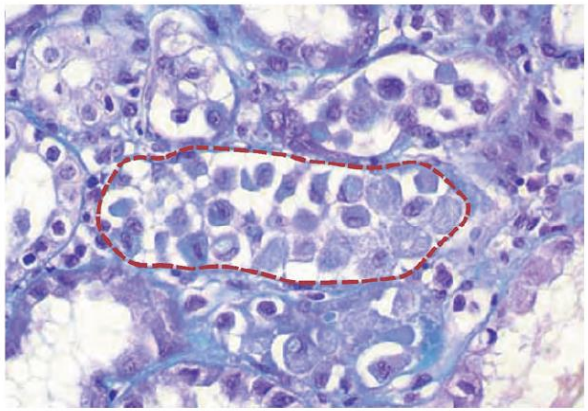

FIGURE 34.2 Photomicrograph of acute tubular necrosis (ATN) showing a proximal tubule (outlined by the dotted line) filled with exfoliated renal tubular cells.

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Reduces the glomerular filtration rate (GFR) in ATN

- The luminal obstruction creates a back pressure on the luminal side of the glomerulus
- This decreases the net filtration pressure across the glomerulus
- Reduces the glomerular filtration rate (GFR).
- This process is called *tubuloglomerular feedback* .

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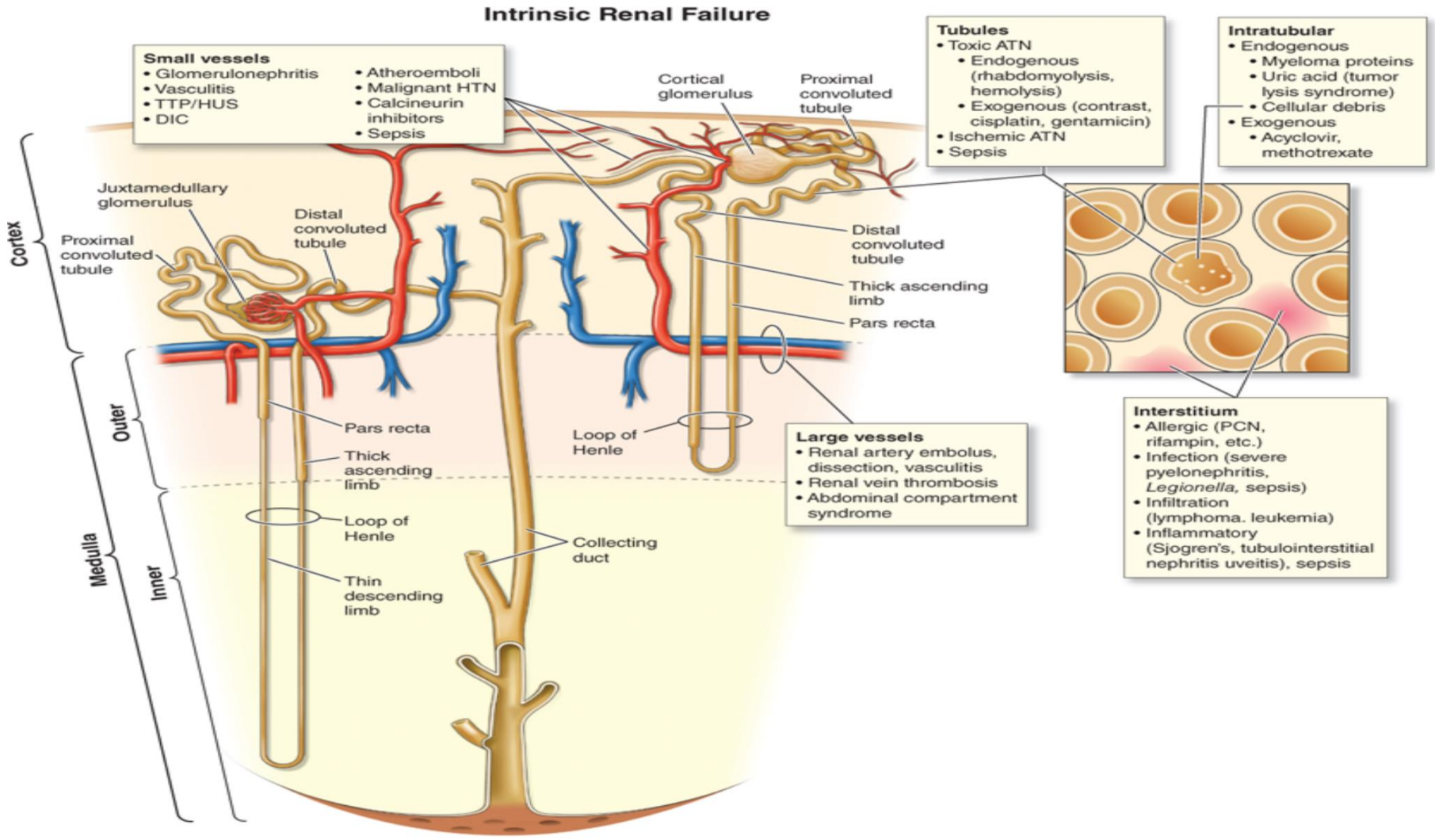
Major causes of intrinsic acute kidney injury.



ATN is a manifestation of

- Severe sepsis and septic shock
- Radiocontrast dye
- Nephrotoxic drugs (e.g., aminoglycoside)
- Rhabdomyolysis with myoglobinuric renal injury.

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Sepsis-associated AKI

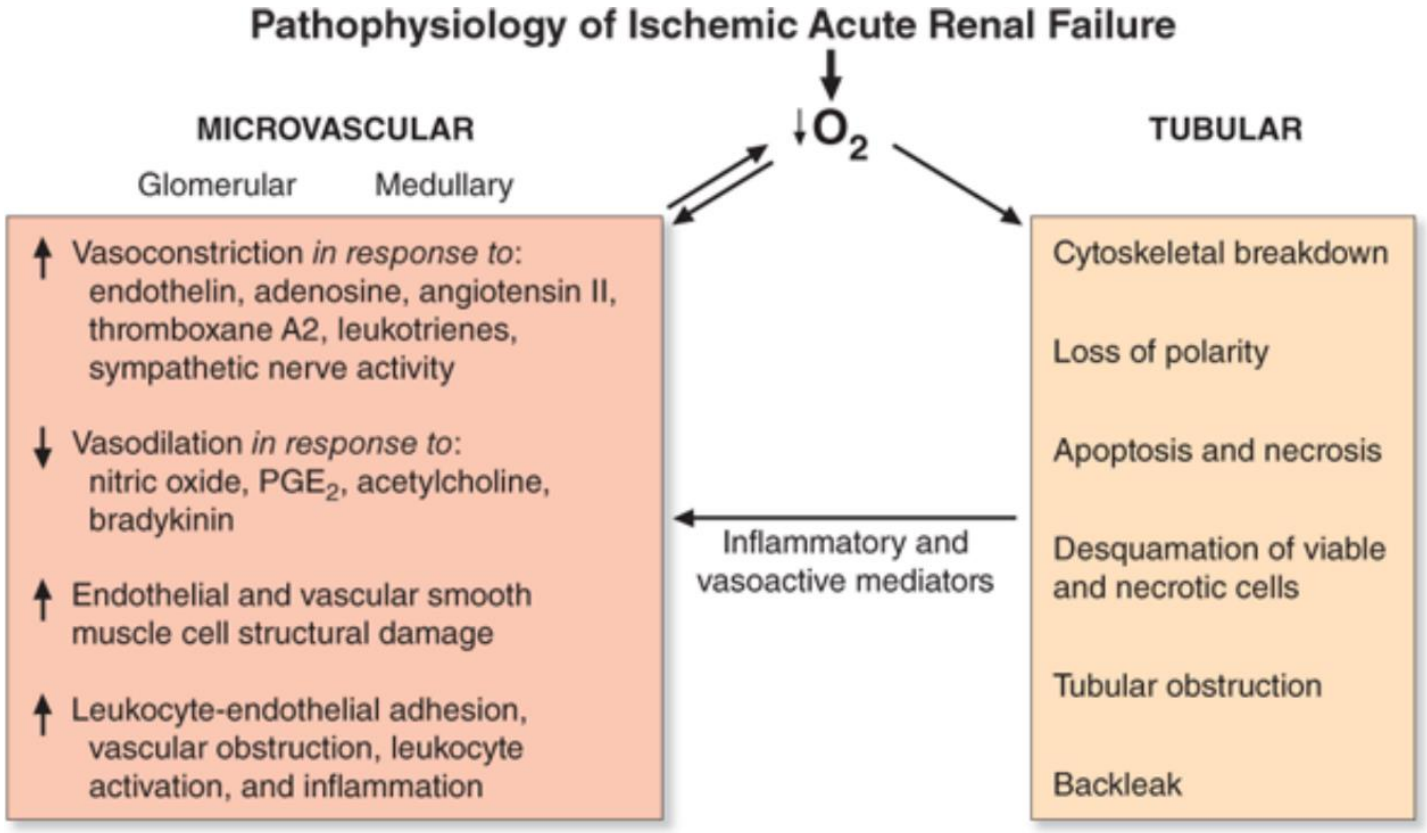
- Decreases in GFR with sepsis can occur even in the absence of overt hypotension
- Tubular injury associated with AKI in sepsis as manifest by the presence of tubular debris and casts in the urine
- Inflammation, mitochondrial dysfunction, and interstitial edema, must be considered in the pathophysiology of sepsis-induced AKI.

Sepsis-associated AKI

- Cytokines that upregulate the expression of inducible NO synthase in the vasculature—can lead to a reduction in GFR
- Sepsis may lead to endothelial damage, which results in microvascular thrombosis, activation of reactive oxygen species, and leukocyte adhesion and migration, all of which may injure renal tubular cells.

Ischemia-associated AKI

- Healthy kidneys receive 20% of the cardiac output and account for 10% of resting oxygen consumption, despite constituting only 0.5% of the human body mass
- The outer medulla is particularly vulnerable to ischemic damage because of the architecture of the blood vessels that supply oxygen and nutrients to the tubules.



Interacting microvascular and tubular events contributing to the pathophysiology of ischemic acute kidney injury. PGE_2, prostaglandin E_2. (From JV Bonventre, JM Weinberg: J Am Soc Nephrol 14:2199, 2003.)

Postoperative AKI

- Ischemia-associated AKI is a serious complication in the postoperative period
- The procedures most commonly associated with AKI are cardiac surgery with cardiopulmonary bypass
- Severe AKI requiring dialysis occurs in approximately 1% of cardiac and vascular surgery procedures.
- Common risk factors for postoperative AKI include underlying chronic kidney disease, older age, diabetes mellitus, congestive heart failure, and emergency procedures.

Burns and Acute Pancreatitis

- Extensive fluid losses into the extravascular compartments of the body frequently accompany severe burns and acute pancreatitis.
- AKI is an ominous complication of burns, affecting 25% of individuals with more than 10% total body surface area involvement.
- abdominal compartment syndrome, where markedly elevated intraabdominal pressures, usually higher than 20 mmHg, lead to renal vein compression and reduced GFR.

Risk factors for nephrotoxicity

- Older age
- Chronic kidney disease (CKD)
- Prerenal azotemia.
- Hypoalbuminemia: increased free circulating drug concentrations.

Nephrotoxin-associated AKI

- **Contrast Agents:** Iodinated contrast agents
- **Antibiotics:**Aminoglycosides. amphotericin B, Vancomycin
- **Chemotherapeutic Agents:** Cisplatin, Ifosfamide, bevacizumab, gemcitabine
- **Toxic Ingestions:** Ethylene glycol, Diethylene glycol, Aristolochic acid
- **Endogenous Toxins:** myoglobin, hemoglobin, uric acid, and myeloma light chains.

Contrast Nephropathy

- A rise in SCr beginning 24–48 h following exposure, peaking within 3–5 days, and resolving within 1 week.
- Low fractional excretion of sodium and relatively benign urinary sediment without features of tubular necrosis (see below) are common findings.

Q7:一位55歲病人因腫瘤而安排須注射顯影劑(contrast medium)的電腦斷層攝影(CT scan)，下列敘述何者錯誤?

- **A.** 顯影劑腎病變產生的原因包括腎小管阻塞或腎血行動力學改變
- **B.**顯影劑腎病變很少出現尿液**fractional excretion of sodium(FeNa)<1%**
- **C.**糖尿病是產生顯影劑腎病變的危險因子之一
- **D.**高危險病人一定要做含顯影劑之檢查時，可先適度補充液體**(hydration)**

Q7:一位55歲病人因腫瘤而安排須注射顯影劑(contrast medium)的電腦斷層攝影(CT scan)，下列敘述何者錯誤?

- **A.** 顯影劑腎病變產生的原因包括腎小管阻塞或腎血行動力學改變
- **B.顯影劑腎病變很少出現尿液fractional excretion of sodium(FeNa)<1%**
- **C.**糖尿病是產生顯影劑腎病變的危險因子之一
- **D.**高危險病人一定要做含顯影劑之檢查時，可先適度補充液體**(hydration)**

Contrast nephropathy1

- The most common clinical course of contrast nephropathy is characterized by a rise in SCr beginning 24–48 hours following exposure, peaking within 3–5 days, and resolving within 1 week.
- preexisting chronic kidney disease, often in association with congestive heart failure or other coexisting causes for ischemia-associated AKI.

Contrast nephropathy2

- Contrast nephropathy is thought to occur from a combination of factors, including

(1) hypoxia in the renal outer medulla due to perturbations in renal microcirculation and occlusion of small vessels;

(2) cytotoxic damage to the tubules directly or via the generation of oxygen free radicals, especially since the concentration of the agent within the tubule is markedly increased; and

(3) transient tubule obstruction with precipitated contrast material.

- Other diagnostic agents implicated as a cause of AKI are high-dose gadolinium used for MRI and oral sodium phosphate solutions used as bowel purgatives.
- use of statins, bicarbonate, N-acetylcysteine (NAC), ascorbic acid, the adenosine antagonists theophylline and aminophylline, vasodilators, forced diuresis, and renal replacement therapy.

Postrenal Obstruction

- Obstruction distal to the renal parenchyma is responsible for only about 10% of cases of AKI
- The obstruction can involve the most distal portion of the renal collecting ducts (papillary necrosis), the ureters (extraluminal obstruction from a retroperitoneal mass), or the urethra (strictures).
- Ureteral obstruction from stones does not cause AKI unless there is a solitary functional kidney.

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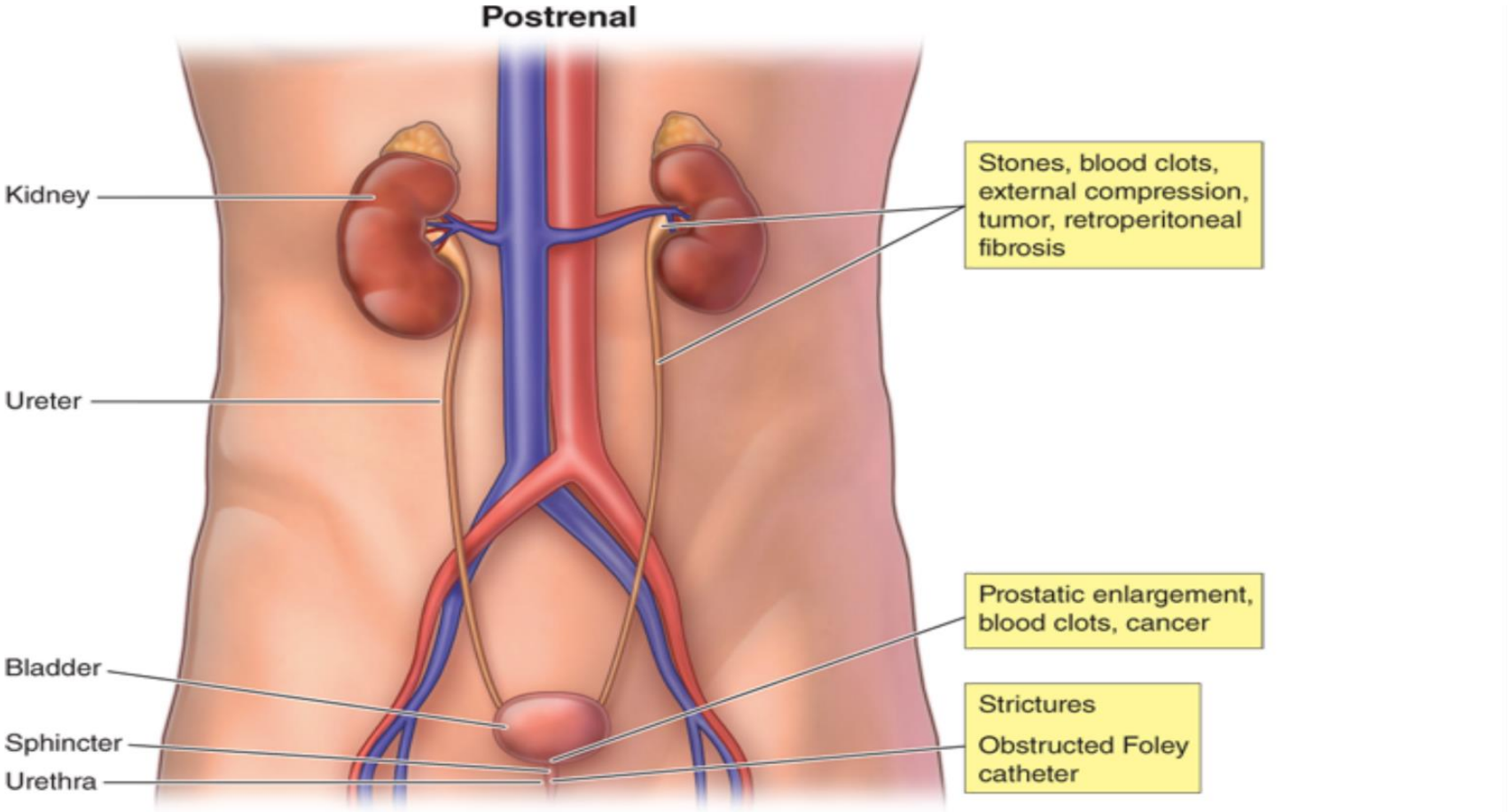
Causes of obstruction leading to postrenal AKI



Source: D. L. Kasper, A. S. Fauci, S. L. Hauser, D. L. Longo, J. L. Jameson, J. Loscalzo: Harrison's Principles of Internal Medicine, 19th Edition.
www.accessmedicine.com

Diagnostic Evaluation for AKI

- Bedside ultrasound evaluation of the kidneys for evidence of postrenal obstruction.

- Monitor Volume status, spot Urine Sodium

- Urine sediment, serologic and hematologic test

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Urinary Measurements for the evaluation of AKI

Measurement	Prerenal Disorder	Renal Disorder
Spot Urine Sodium	<20 mEq/L	>40 mEq/L
Fractional Excretion of Na	<1%	>2%
Fractional Excretion of Urea	<35%	>50%
Urine Osmolality	>500 mOsm/kg	300–400 mOsm/kg
U/P Osmolality	>1.5	1–1.3

- A prerenal disorder can be associated with a high urine sodium (> 40 mEq/L) if there is ongoing diuretic therapy, or the patient has chronic renal disease (where there is "obligatory" sodium loss in the urine).

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Harrison's Principles of Internal Medicine, 20e > Azotemia and Urinary Abnormalities

J. Larry Jameson, Anthony S. Fauci, Dennis L. Kasper, Stephen L. Hauser, Dan L. Longo, Joseph Loscalzo+

TABLE 48-2Laboratory Findings in Acute Renal Failure

INDEX	PRERENAL AZOTEMIA	OLIGURIC ACUTE RENAL FAILURE
BUN/P_{Cr} ratio	>20:1	10–15:1
Urine sodium U_{Na}, meq/L	<20	>40
Urine osmolality, mosmol/L H_2O	>500	<350
Fractional excretion of sodium[a]	<1%	>2%
Urine/plasma creatinine U_{Cr}/P_{Cr} Urinalysis (casts)	>40 None or hyaline/granular	<20 Muddy brown

[a] $FE_{Na} = \frac{U_{Na} \times P_{Cr} \times 100}{P_{Na} \times U_{Cr}}$

- Q8:下列何種檢查結果代表病人可能有腎前性氮血症(prerenal azotemia)?
- **1.blood urea nitrogen /plasma creatinine(BUN/PCr)ratio< 10:1**
- **2.urine sodium(UNa)>40 meq/L**
- **3.urine osmolality <350 mOsmol/kg H2O**
- **4.urine creatinine/plasma creatinine(UCr/PCr)>40**

Q8:

- 下列何種檢查結果代表病人可能有腎前性氮血症**(prerenal azotemia)?**
- **1.blood urea nitrogen /plasma creatinine(BUN/PCr)ratio< 10:1**
- **2.urine sodium(UNa)>40 meq/L**
- **3.urine osmolality <350 mOsmol/kg H2O**
- **4.urine creatinine/plasma creatinine(UCr/PCr)>40**

- Q9:一位40歲病人原來腎功能正常，現其血肌酸酐(creatinine)上升至2.1 mg/dL，下列何種狀況最可判斷此病人傾向腎因性急性腎衰竭，而不是腎前性(prerenal)急性腎衰竭?
- 1.尿中出現透明圓柱體(hyaline casts)
- 2.血中尿素氮(BUN)48 mg/dL
- 3.尿鈉(Na)濃度為8 mmol/L
- 4.尿鈉排泄分率(fractional excretion of sodium, FeNa)為2%

- Q9:一位40歲病人原來腎功能正常，現其血肌酸酐(creatinine)上升至2.1 mg/dL，下列何種狀況最可判斷此病人傾向腎因性急性腎衰竭，而不是腎前性(prerenal)急性腎衰竭?
- 1.尿中出現透明圓柱體(hyaline casts)
- 2.血中尿素氮(BUN)48 mg/dL
- 3.尿鈉(Na)濃度為8 mmol/L
- 4.尿鈉排泄分率(fractional excretion of sodium, FeNa)為2%

- Q10:下列何項在腎前腎衰竭（Prerenal azotemia）最不常見？
- 1.排鈉分率（FENa）小於1%
- 2.尿鈉大於10 mmol/L
- 3.尿比重大於1.018
- 4.出現玻璃圓柱（Hyaline casts）

Q10:下列何項在腎前腎衰竭（Prerenal azotemia）最不常見？

- 1.排鈉分率（FENa）小於1%
- 2.尿鈉大於10 mmol/L
- 3.尿比重大於1.018
- 4.出現玻璃圓柱（Hyaline casts）

How to management?

- M/40 year-old
- BW 72kg
- DM, hypertension
- Pneumonia
- Daily urine output: 2000 ml
- 3 days later, septic shock with inotropic agent
- Urine output 100 ml daily
- Serum creatinine (1.0→2 mg/dl)

What is your clinical evaluation?

Q11:How to management?

1. The use of Loop diuretics
2. Renal replacement therapy
3. Both
4. Do not need any management

Use of Loop diuretics

- Decrease oxygen consumption in the loop of Henle by inhibiting sodium transport, thus potentially lessening ischemic injury
- Inhibit the Na-K-2Cl cotransporter → resulting in a loss of the high medullary osmolality and decreased ability to reabsorb water.
- High-dose furosemide (>1 g/d)

Renal Replacement therapy

Table 17 | Potential applications for RRT

Applications	Comments
Renal replacement	This is the traditional, prevailing approach based on utilization of RRT when there is little or no residual kidney function.
緊急處理	
Life-threatening indications	No trials to validate these criteria.
Hyperkalemia	高血鉀 alemia is effective in removing potassium; however, it requires frequent monitoring of potassium ent of concurrent medical management to prevent relapses.
Acidemia	酸血症 due to AKI is often aggravated by the underlying condition. Correction of metabolic acidosis with tions depends on the underlying disease process.
Pulmonary edema	肺水腫 to prevent the need for ventilatory support; however, it is equally important to manage pulmonary d patients.
Uremic complications (pericarditis, bleeding, etc.)	尿毒症 ractice it is rare to wait to initiate RRT in AKI patients until there are uremic complications.
Nonemergent indications	
Solute control	BUN reflects factors not directly associated with kidney function, such as catabolic rate and volume status. SCr is influenced by age, race, muscle mass, and catabolic rate, and by changes in its volume of distribution due to fluid administration or withdrawal.
Fluid removal	Fluid overload is an important determinant of the timing of RRT initiation.
Correction of acid-base abnormalities	No standard criteria for initiating dialysis exist.
Renal support	This approach is based on the utilization of RRT techniques as an adjunct to enhance kidney function, modify fluid balance, and control solute levels.
Volume control	Fluid overload is emerging as an important factor associated with, and possibly contributing to, adverse outcomes in AKI. Recent studies have shown potential benefits from extracorporeal fluid removal in CHF. Intraoperative fluid removal using modified ultrafiltration has been shown to improve outcomes in pediatric cardiac surgery patients.
Nutrition	Restricting volume administration in the setting of oliguric AKI may result in limited nutritional support and RRT allows better nutritional supplementation.
Drug delivery	RRT support can enhances the ability to administer drugs without concerns about concurrent fluid accumulation.
Regulation of acid-base and electrolyte status	Permissive hypercapnic acidosis in patients with lung injury can be corrected with RRT, without inducing fluid overload and hypernatremia.
Solute modulation	Changes in solute burden should be anticipated (e.g., tumor lysis syndrome). Although current evidence is unclear, studies are ongoing to assess the efficacy of RRT for cytokine manipulation in sepsis.

AKI, acute kidney injury; BUN, blood urea nitrogen; CHF, congestive heart failure; SCr, serum creatinine; RRT, renal replacement therapy.

- Q12下列何者不是急性腎衰竭病人接受緊急血液透析治療的適應症？

1..BUN 120 mg/dL，creatinine 2.5 mg/dL

2..血鉀值大於7 mEq/L，且Kayexalate（sodium polystyrene sulfonate）治療效果不佳

3.心包膜積水

4.肺水腫

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- **6. 下列有關急性腎損傷（acute kidney injury）的敘述，何者錯誤？**
- A. 腎前性（prerenal）急性腎損傷之血清尿素氮（BUN）與肌酸酐（creatinine）比值常大於20
- B. 敗血症為造成腎因性（intrinsic）急性腎損傷常見原因之一
- C. 泌尿道阻塞造成之腎後性（postrenal）急性腎損傷，解決阻塞為最首要的治療方式
- D. 慢性腎臟病患併發急性腎損傷，若尿鈉排出分率（fractional excretion of sodium, FeNa）大於1%，則可排除腎前性（prerenal）急性腎損傷
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- 25.針對嘔吐導致急性腎損傷的病人，欲區分prerenal或intrinsic病因，下列何項指標最為適合?
- A.fractional excretion of sodium
- B.urine-to-plasma urea ratio
- C.fractional excretion of chloride
- D.urine osmolality

- 27.依照2012年最新之KDIGO(Kidney Disease:Improving Global Outcomes)準則，下列診斷急性腎損傷 (acute kidney injury)之定義何者錯誤?
- A.血清肌酸酐值於48小時內上升幅度大於或等於0.3 mg/dL
- B.血清肌酸酐值於5天內上升幅度大於或等於25%
- C.血清肌酸酐值於一星期內上升幅度大於或等於50%
- D.尿液每小時之排出量少於0.5 mL/kg，並持續6小時

25.下列有關預防顯影劑腎病變的敘述，何者正確？

A.通常血清肌酸酐於注射顯影劑後24～48小時開始上升，有高於1%病人需接受透析治療

B.以生理鹽水預防顯影劑腎病變，可於施打顯影劑後開始給與，持續6～24小時

C.統合分析顯示N-acetylcysteine預防顯影劑腎病變的效果佳且副作用低，建議臨床上常規使用

D.其致病機轉包括腎臟outer medulla缺氧、腎小管細胞自由基傷害及暫時性腎小管阻塞等因素

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- 61.一位20歲運動員參加馬拉松比賽約2小時後因昏倒與痙攣被救護車送醫治療。抵達醫院時，意識呈昏迷，心 跳每分□　120次，血壓98/52毫米汞柱(mmHg)，體溫攝氏40.8度。驗血發現:aspartate aminotransferase (AST)110 U/L、alanine aminotransferase(ALT)123 U/L、肌酸酐(creatinine)2.2 mg/dL、鈉143 mmol/L、鉀4.7 mmol/L、鈣2.4 mmol/L、葡萄糖75 mg/dL。病人過去健康情況良好，比賽前無不適症狀。比 賽當日氣溫為攝氏37度。請依前述情況回答下列3題。 此病人最可能的診斷為何?
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- B.熱衰竭(heat exhaustion)
- C.中暑(heat stroke)
- D.熱昏厥(heat syncope)
- 62.上述病人的處置，何者最不適宜?
- A.使用acetaminophen降低體溫
- B.置入氣管內管
  C.補充生理食鹽水
- D.必要時使用lorazepam治療痙攣
- 63.兩天後，上述病人抱怨兩腿酸痛、腫脹，並且發現茶色尿，但尿量沒有明顯變少。下肢檢查發現肌肉有壓 痛。血中肌酸激酶(creatine kinase)42,700 U/L、肌酸酐(creatinine)2.8 mg/dL、鉀5.0 mmol/L、鈣2.07 mmol/L;尿液潛血反應呈4+，但顯微鏡檢查未看到紅血球。下列處置何者最適當?
- A.維持每小時尿量200~300 mL
  B.酸化尿液
  C.每天補充2,500 mL生理食鹽水
- D.開始透析治療

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- D.開始透析治療

GN

Definition of glomerular diseases

Etiology

Primary glomerular diseases
- IgA nephropathy
- Pauci-immune glomerulonephritis[a]
- Antiglomerular basement membrane antibody disease[b]
- Membranoproliferative glomerulonephritis (types I, II, and III)

Secondary glomerular diseases
- Postinfectious glomerulonephritis
- Lupus nephritis
- Wegener's granulomatosis[a]
- Microscopic polyangiitis[a]
- Cryoglobulinemia[c]
- Henoch-Schönlein purpura

[a]Antibody-reactivity with cytoplasmic antigens (ANCA)-associated; [b]Includes Goodpasture's syndrome when pulmonary involvement; [c]Most often hepatitis C virus-related

Javaid et al, Kidney Int 2005:67:1692-1703

Pathology

Glomerular involvement
All glomeruli (diffuse) or only some (focal)
Extent of disease within involved glomeruli: patchy (segmental) or general

Cell involvement
Increases in cell number (proliferative)
Neutrophil accumulation (exudative)

Cell damage
Cell necrosis visible by light microscopy (necrotising)
Ultrastructural damage visible only by electronmicroscopy (foot-process effacement, membrane thinning)

Changes in non-cellular glomerular components
Matrix accumulation (hyalinosis) or immune deposits
Site of deposition (mesangial, subendothelial, subepithelial)

Chadban et al Lancet 2005:356:1797-1806

Definition of glomerular diseases

Asymptomatic urinary abnormalities
Subnephrotic-range proteinuria, and/or microscopic haematuria, not accompanied by renal impairment, oedema, or hypertension

Nephritic syndrome
Recent onset of haematuria and proteinuria, renal impairment, and salt and water retention, causing hypertension

Rapidly progressive glomerulonephritis
Progression to renal failure over days to weeks, in most cases in the context of a nephritic presentation, typically associated with the pathological finding of extensive glomerular crescent formation on renal biopsy

Nephrotic syndrome
Nephrotic-range proteinuria (more than 3·5 g per 1·73 m^2 in 24 h), hypoalbuminaemia, hyperlipidaemia, and oedema, in many cases complicated by predisposition to venous thrombosis and bacterial infection

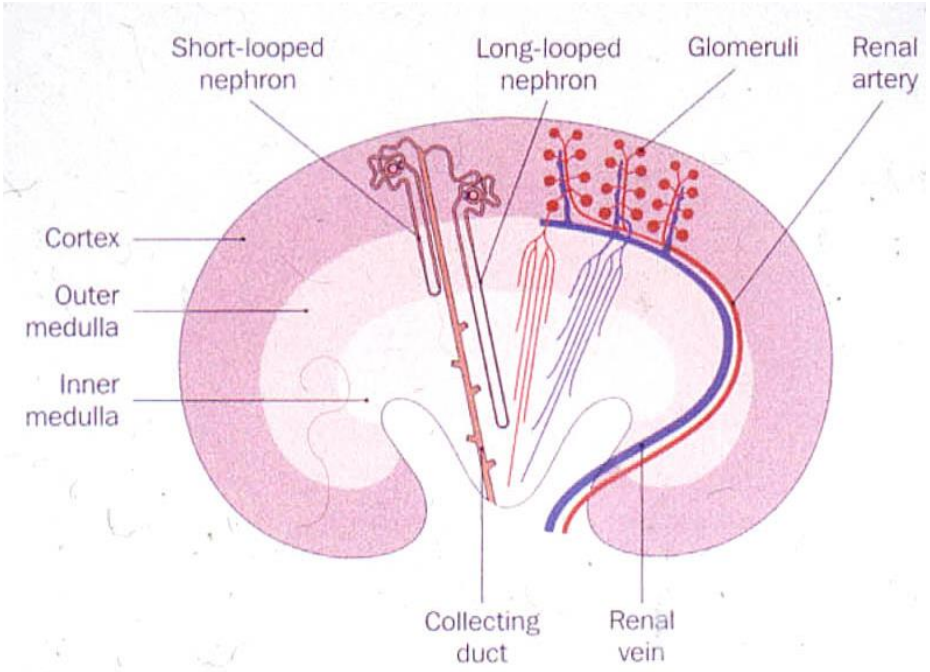
Chronic glomerulonephritis
Persistent proteinuria with or without haematuria and slowly progressive impairment of renal function

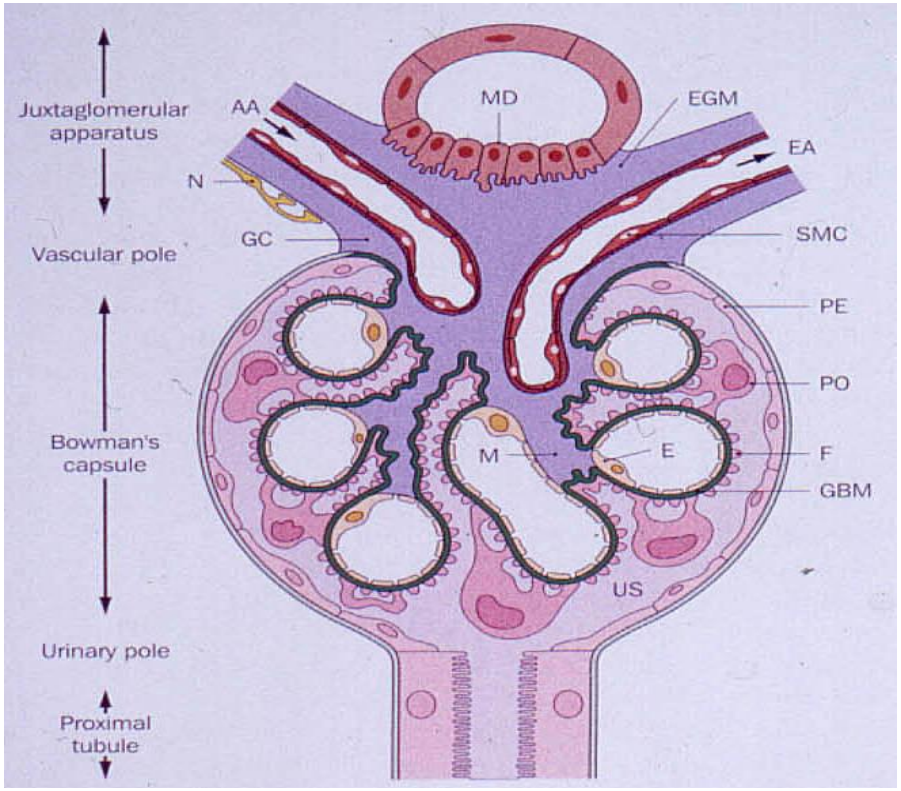
Chadban et al Lancet 2005:356:1797-1806

➔ **Classification according to the clinical manifestation is the simplest and most effective tool for the clinical.**

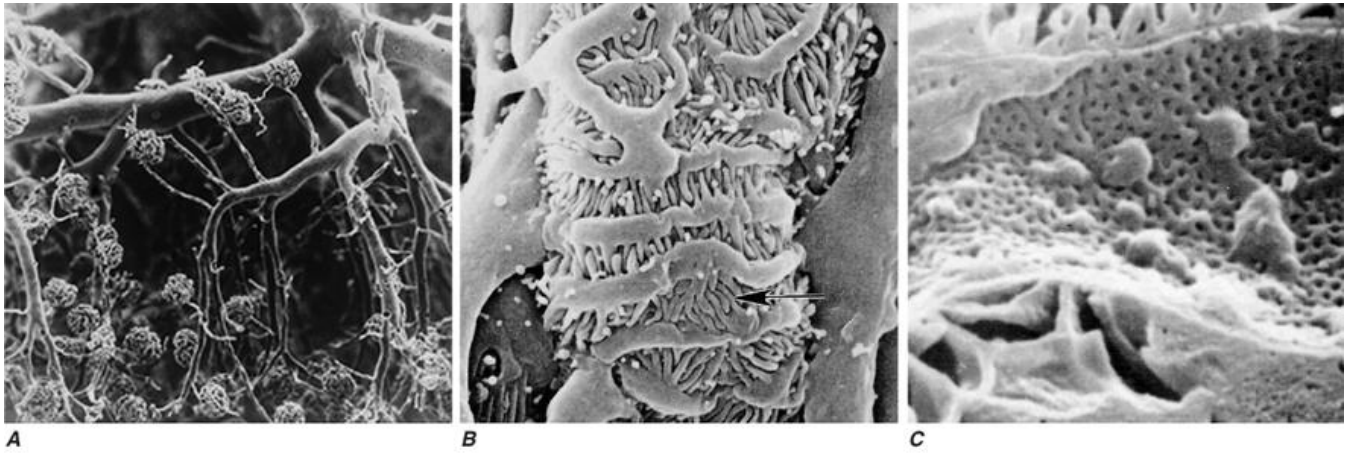
Chadban et al Lancet 2005:356:1797-1806

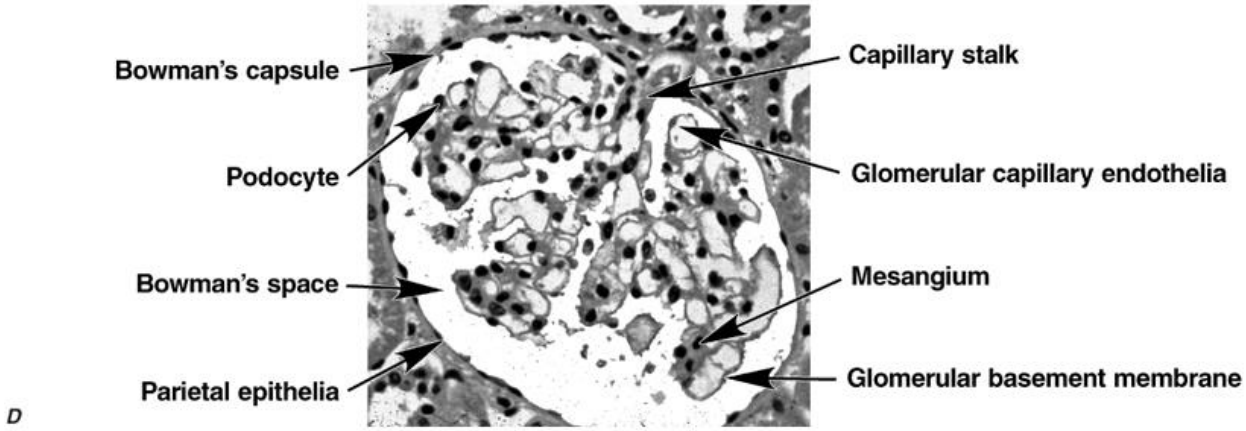
Pathogenesis of glomerular diseases



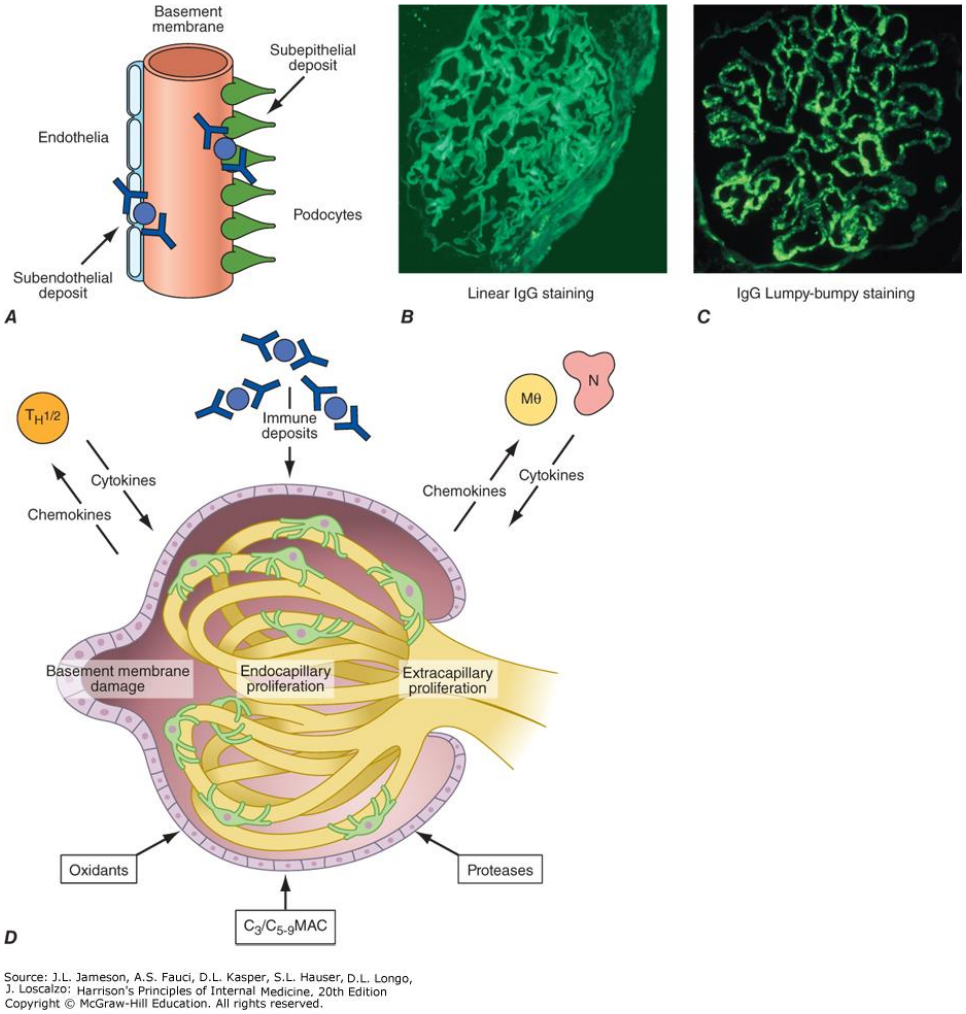


➔Why dose glomerular injury occur? Primary and secondary





Glomerular architecture. A. The glomerular capillaries form from a branching network of renal arteries, arterioles, leading to an afferent arteriole, glomerular capillary bed (tuft), and a draining efferent arteriole. (From VH Gattone II et al: Hypertension 5:8, 1983.) B. Scanning electron micrograph of podocytes that line the outer surface of the glomerular capillaries (arrow shows foot process). C. Scanning electron micrograph of the fenestrated endothelia lining the glomerular capillary. D. The various normal regions of the glomerulus on light microscopy. (A–C: Courtesy of Dr. Vincent Gattone, Indiana University; with permission.)



Source: J.L. Jameson, A.S. Fauci, D.L. Kasper, S.L. Hauser, D.L. Longo, J. Loscalzo: Harrison's Principles of Internal Medicine, 20th Edition

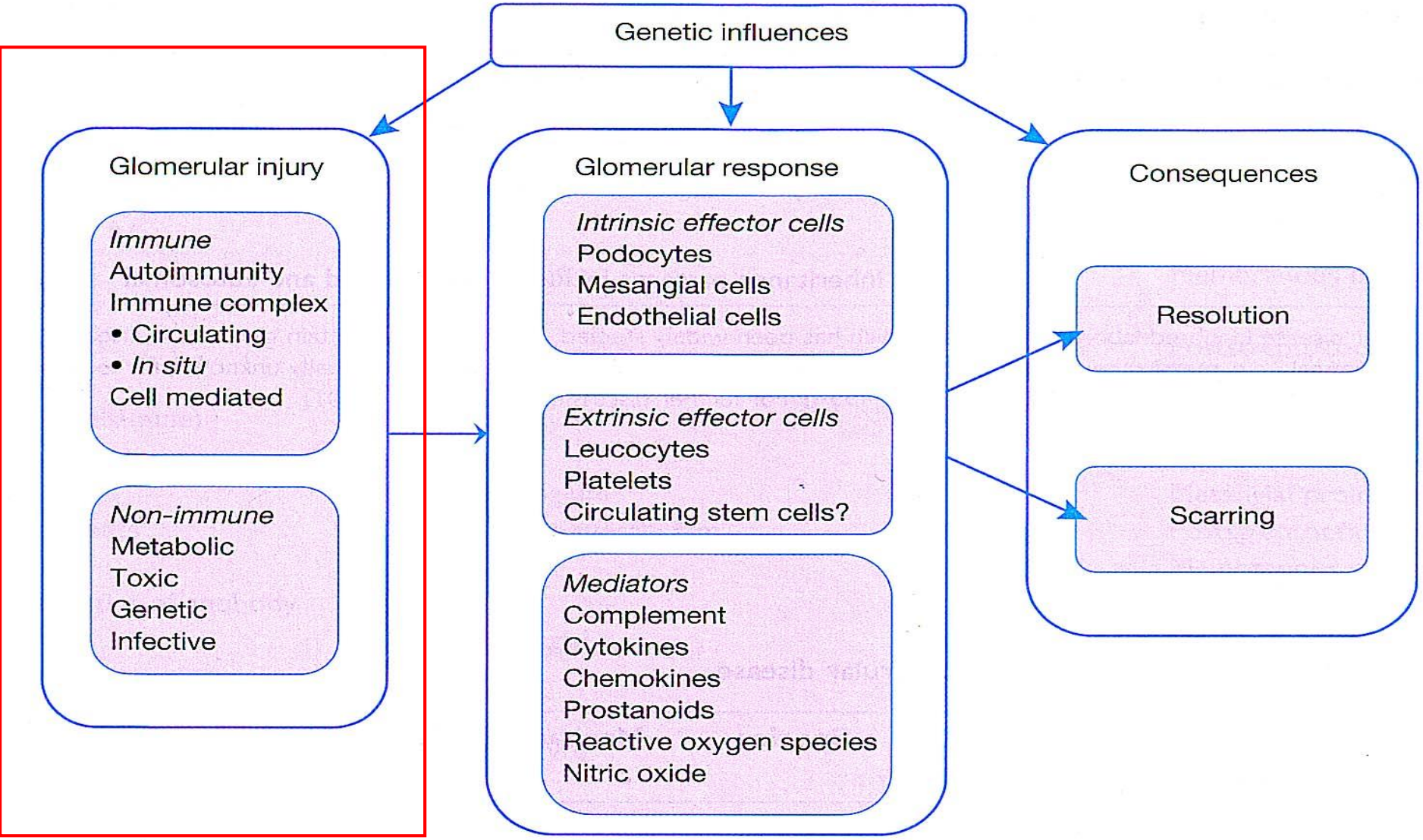
The glomerulus is injured by a variety of mechanisms. A. Preformed immune deposits can precipitate from the circulation and collect along the glomerular basement membrane (GBM) in the subendothelial space or can form in situ along the subepithelial space. B. Immunofluorescent staining of glomeruli with labeled anti-IgG demonstrating linear staining from a patient with anti-GBM disease or immune deposits from a patient with membranous glomerulonephritis. C. The mechanisms of glomerular injury have a complicated pathogenesis. Immune deposits and complement deposition classically draw macrophages and neutrophils into the glomerulus. T lymphocytes may follow to participate in the injury pattern as well. D. Amplification mediators as locally derived oxidants and proteases expand this inflammation, and, depending on the location of the target antigen and the genetic polymorphisms of the host, basement membranes are damaged with either endocapillary or extracapillary proliferation.

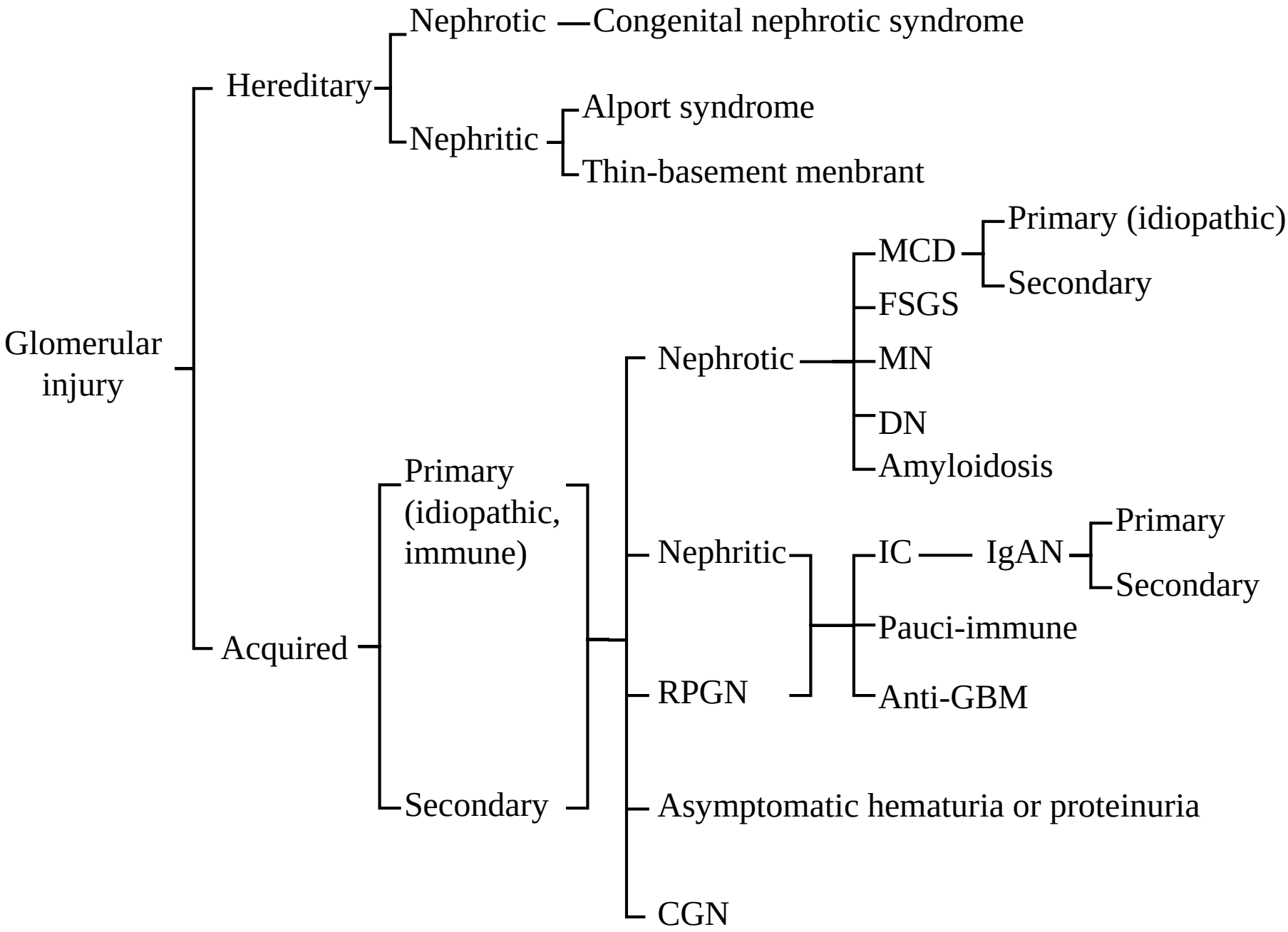
Table 1. Classification of renal diseases based on 13,519 renal biopsies

	No. of cases	%
Primary glomerular diseases	9278	68.64
Secondary glomerular diseases	3359	24.84
Systemic diseases	2673	19.77
Metabolic diseases	345	2.55
Vascular diseases	244	1.80
Infections	97	0.72
Hereditary and congenital renal diseases	131	0.97
Tubulointerstitial diseases	464	3.43
Rare renal disease	37	0.27
Sclerosing glomerulonephritis	132	0.98
Unclassified	118	0.87
Total	13,519	100.00

Kidney International, Vol. 66 (2004), pp. 920–923

Pathogenesis of glomerular diseases




Glomerular injury
Hereditary
Nephrotic
Congenital nephrotic syndrome
Nephritic
Alport syndrome
Thin-basement menbrant
Acquired
Primary (idiopathic, immune)
Secondary
Nephrotic
MCD
Primary (idiopathic)
Secondary
FSGS
MN
DN
Amyloidosis
Nephritic
IC
IgAN
Primary
Secondary
Pauci-immune
Anti-GBM
RPGN
Asymptomatic hematuria or proteinuria
CGN

Clinical Manifestations of GN

TABLE 8.1. Definition and categorization of glomerular diseases

Clinical syndrome	Manifestations	Major etiologies
GN	RBCs, RBC casts, proteinuria, hypertension, renal dysfunction	Acute poststreptococcal GN Other postinfectious GN (abscess, endocarditis) IgA nephropathy Lupus nephritis (WHO class III/IV)
Rapidly progressive GN	Presents as GN with acute renal failure (oliguria, rising serum creatinine)	Antiglomerular basement membrane nephritis (Goodpasture's) Vasculitis syndromes (Wegener's, microscopic polyangiitis, Henoch-Schönlein purpura, mixed cryoglobulinemia) Immune complex–associated (IgA, poststreptococcal GN)
Nephrotic syndrome	Proteinuria (>3.5 g/day), edema, high serum cholesterol, low serum albumin, urine lipids	Minimal change disease Focal segmental glomerulosclerosis MN MPGN Diabetic nephropathy Amyloid (myeloma, light-chain deposition disease) Fibrillary GN
Asymptomatic proteinuria	Urinary protein excretion <2 g/day	Low-grade glomerular disease (IgA nephropathy, MN, or MPGN) Hereditary glomerular disease (Alport's syndrome) Tubulointerstitial disease (see Chapter 6)
Asymptomatic hematuria	Urinary RBCs >2/high-power field (spun sediment)	Low-grade glomerular disease (IgA nephropathy, thin basement membrane disease) Other (see Chapter 5)

GN, glomerulonephritis; IgA, immunoglobulin A; MN, membranous neuropathy; MPGN, membranoproliferative glomerulonephritis; RBC, red blood cell; WHO, World Health Organization.

腎絲球疾病

1. 依照臨床表現
   - AGN
   - RPGN
   - Nephrotic syndrome
   - Hematuria

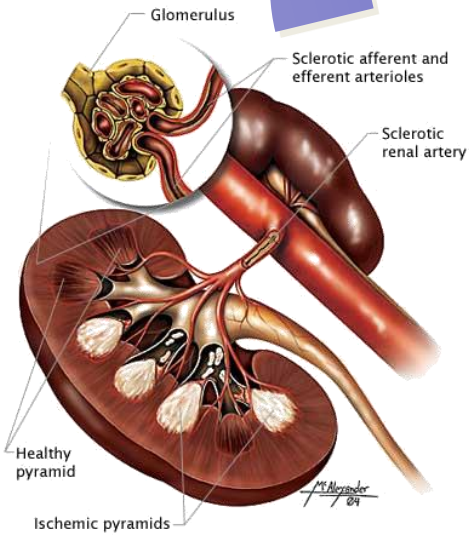
2. 介紹AGN常見疾病
- **IgAN**

3. 介紹RPGN常見疾病
- **以螢光染色做區分**

--linear: Anti-GBM
--granular: immune-complex (Lupus)
--pauci-immune: Renal vasculitis

4. 介紹Nephrotic syndrome常見疾病
   - MCD, FSGS, MN, MPGN
   - Fibrillay GN, Amyloidosis

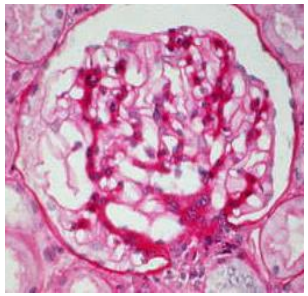
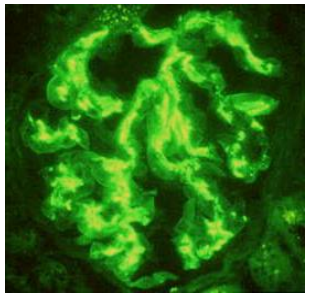
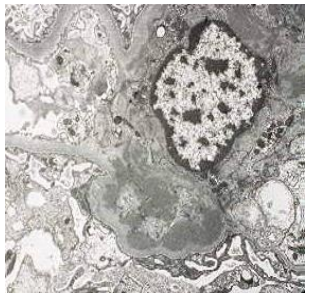
5. 介紹Hematuria常見疾病
   - Thin-basement membrane diseases
   - Alport's syndrome



解剖 → 生理 → 病生理 → 疾病 → 診斷 → 治療 → 預後

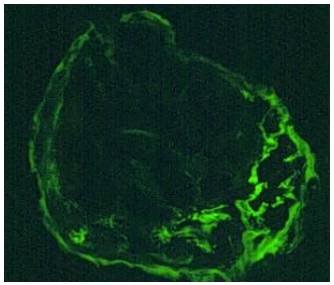
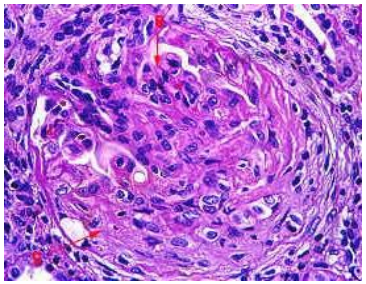
Acute Nephritic syndrome

- Sudden onset of acute renal failure (days to weeks) and oligouria (400 ml/day)
- Extracellular fluid volume expansion, edema and hypertension
- Urinalysis: RBC casts, dysmorphic RBCs, leukocytes and subnephrotic proteinuria (<3.0 g/24 hrs), hematuria is often macroscopic

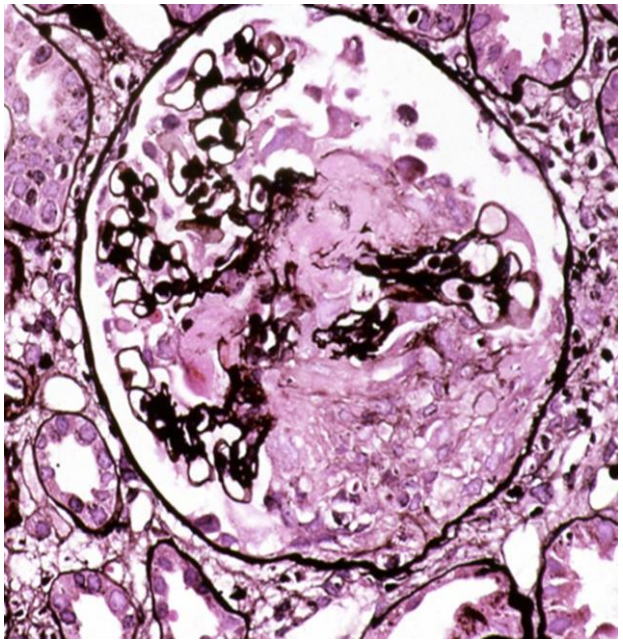
Rapid Progressive GN (RPGN)

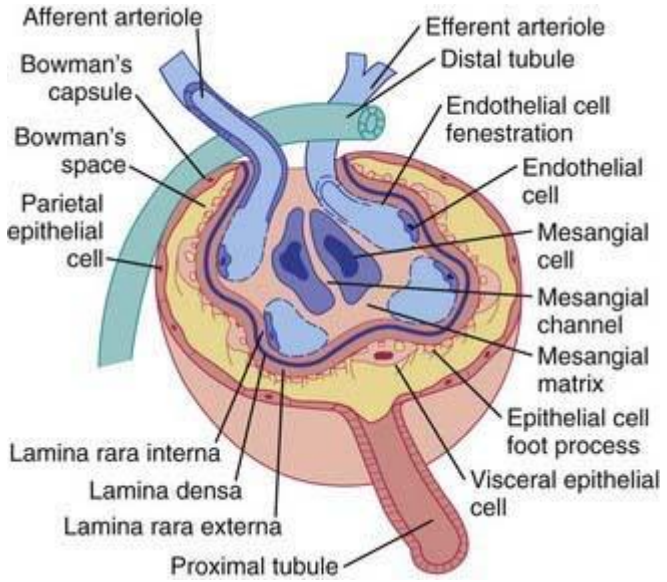
- Subacute of renal failure (weeks to months)
- Nephritic urinary sediments, subnephrotic proteinuria and variable oligouria
- Hypervolemia, edema and hypertension

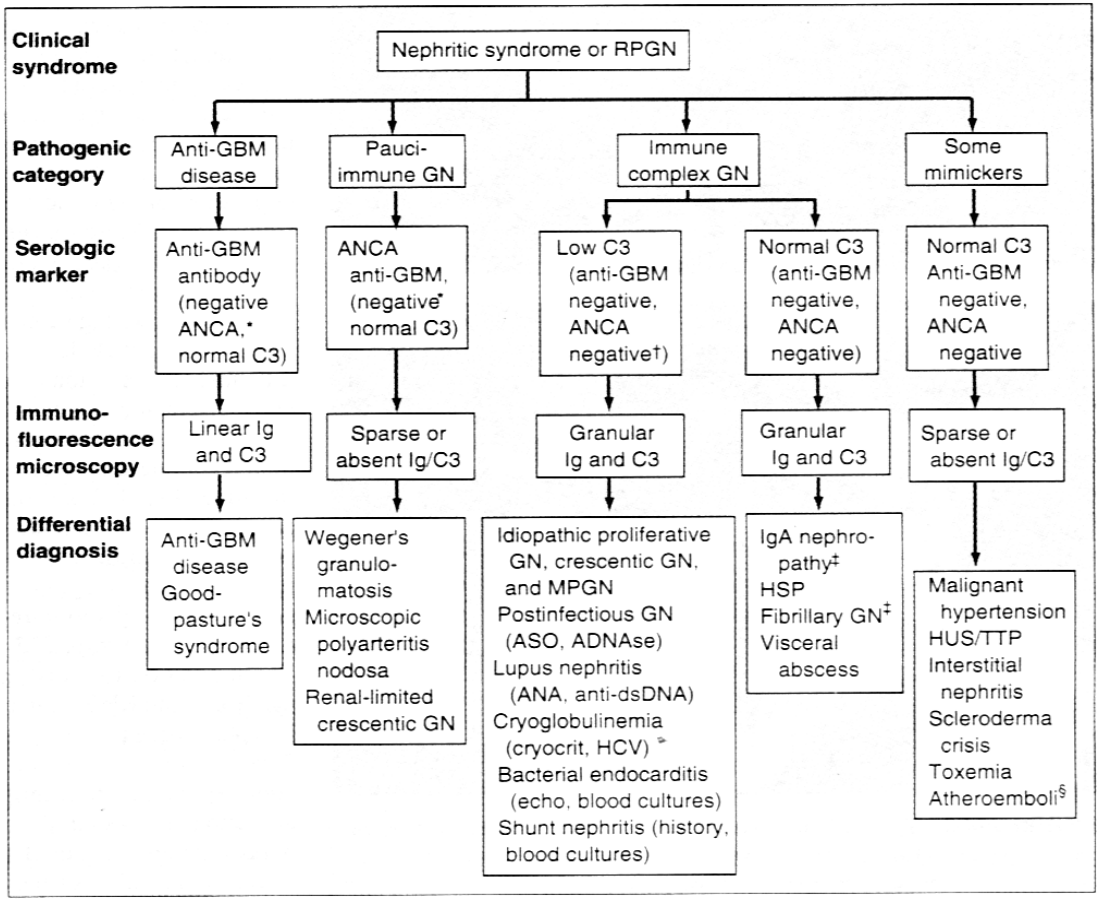
Crescentic glomerulonephritis

- Severe glomerular injury, resulting in rupture of the glomerular capillary loops(Figure), with accumulation of leucocytes and blood constituents in Bowman's space, which in turn induces visceral epithelial cell proliferation, together forming a cellular crescent.





Etiology and differential diagnosis



- **AGN**
  - Immune complex GN: >70%
  - Pauci-immune GN: <30%
  - Anti-GBM: rare (<1%)
- **RPGN**
  - Immune complex GN: 45%
  - Pauci-immune GN: 45%
  - Anti-GBM: <10%

Immune complex GN

Infection: Streptococcal
Non-streptococcal
Non-infection: Systemic
Primary (IgA nephropathy)

Causative Factors of the Syndrome of Acute Glomerulonephritis

- Infectious
  - Acute poststreptococcal glomerulonephritis (group A, β-hemolytic streptococcal infection)
  - Nonpoststreptococcal glomerulonephritis
    - Infective endocarditis
    - Staphylococcal bacteremia
    - Pneumococcal pneumonia
    - Meningococcemia
    - Typhoid fever
    - Secondary syphilis
    - Acute viral infection (cytomegalovirus, varicella, Epstein-Barr, hepatitis B, coxsackie)
    - Mycoplasma (rare)
    - Trichinosis
    - Toxoplasmosis
    - Falciparum malaria
- Noninfectious
  - Multisystem diseases
    - Systemic lupus erythematosus
    - Henoch-Schönlein purpura
    - Necrotizing vasculitis
    - Goodpasture's disease
    - Alport's syndrome
  - Primary glomerular disease
    - IgA nephropathy (Berger's disease)
    - Mesangial proliferative glomerulonephritis
    - Membranoproliferative glomerulonephritis

IgA Nephropathy and Henoch-Scholein Purpura (HSP)

Incidence

- Most common glomerulopathy worldwide: 10-40% of GN
- 30% prevalence along the Asian and Pacific Rim and 20% in southern Europe, compared to a much lower prevalence in northern Europe and North America.
- Renal-limited form of GN
- IgA-containing immune deposits (abnormal IgA1 glycosylation) in the glomerular mesangium
- IgM, IgG, C_3, or immunoglobulin light chains may be codistributed with IgA. IgA deposited in the mesangium is typically polymeric and of the IgA1 subclass
- HSP: petechial rash on the extremities, arthropathy, abdomen pain and GN

Clinical pictures

- Nephritic urine sediment and moderate proteinuria
- Hypertension
- Gross hematuria, often 24 or 48 hrs after a pharyngeal or GI infection, vaccination or strenuous exercise
- Precipitating factors

Precipitating factors

Table 1 Precipitating factors for haematuria in IgA nephropathy

Upper respiratory tract infections
Tonsillitis
Pharyngitis
Bronchitis
Acute gastroenteritis
Hepatitis A/B
Periostitis
Staphylococcal osteomyelitis
Septic arthritis
Peritonitis
Lobar pneumonia
Erysipelas
Erythema polymorphus
Staphylococcal sepsis
Typhoid fever
Brucellosis
Infectious mononucleosis
Influenza-like syndromes
Rubella
Mumps
Herpes zoster
Tonsillectomy
Tooth extraction
Appendicectomy
Heavy physical exercise
Vaccine
BCG overdose

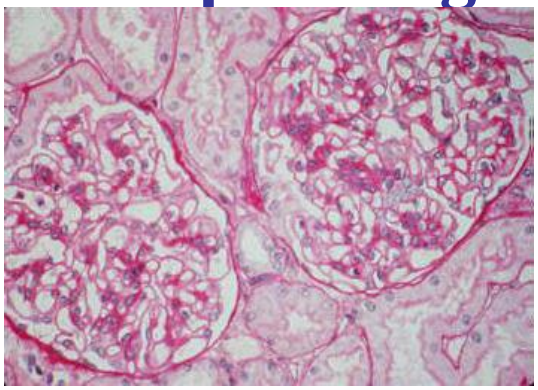
Etiology

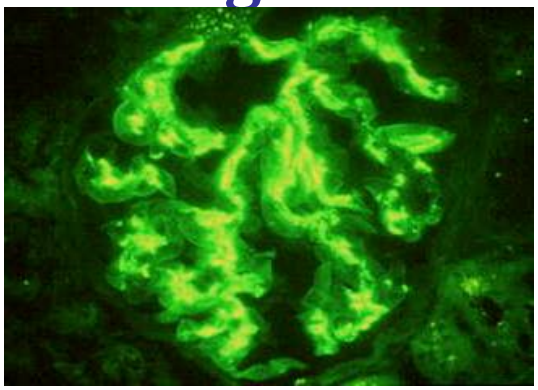
TABLE 264-7 Diseases Associated with IgA Nephropathy

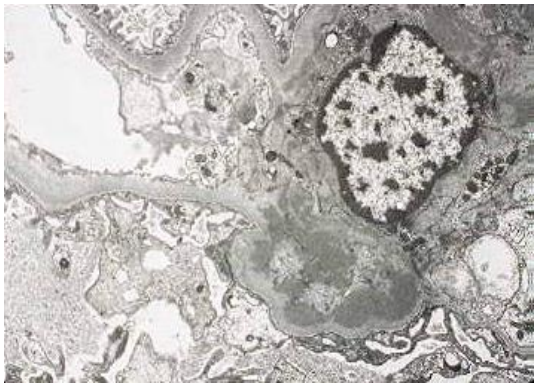
Idiopathic (majority)	
Renal-limited or as component of Henoch-Schönlein purpura	
In association with systemic diseases or drugs[a]	
Liver	Chronic liver disease with involvement of biliary tree
Gastrointestinal	Celiac disease, Crohn's disease, adenocarcinoma
Respiratory	Idiopathic interstitial pneumonitis, obstructive bronchiolitis, adenocarcinoma
Skin	Dermatitis herpetiformis, mycosis fungoides, leprosy
Eyes	Episcleritis, anterior uveitis
Miscellaneous	Ankylosing spondylitis, relapsing polychondritis, Sjögren's syndrome, monoclonal IgA gammopathy, schistosomiasis

Although prominent deposition of IgA has been reported with each of these conditions, significant glomerular inflammation and dysfunction are rare.

Renal pathological findings

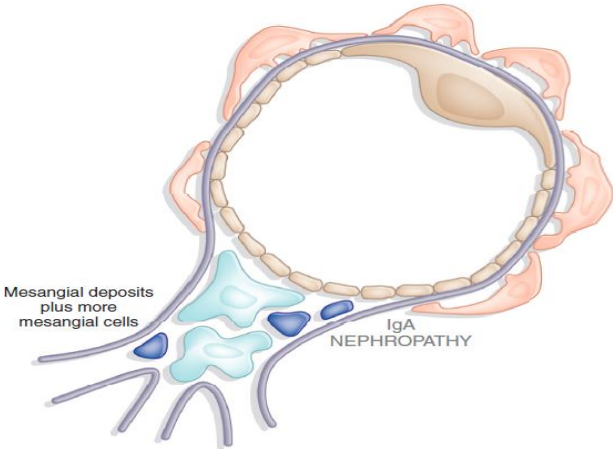






Glomerular schematic 2

Treatment



- **Supportive**
  - BP control and proteinuria reduction (ACEI & ARB)
  - Fish oil (Omega fatty acid)
- **Immunosuppressive**
  - Glucocorticoid
  - Cyclophosphamide and mycophenolate mofetil: severe disease
- **20-50% ESRD**
  - poor prognostic factors: older age, male, hypertension, nephrtoic range proteinuria, renal insufficiency, tubulointerstial and crescent lesions
  - renal failure seen in only 25–30% of patients with IgA nephropathy over 20–25 years

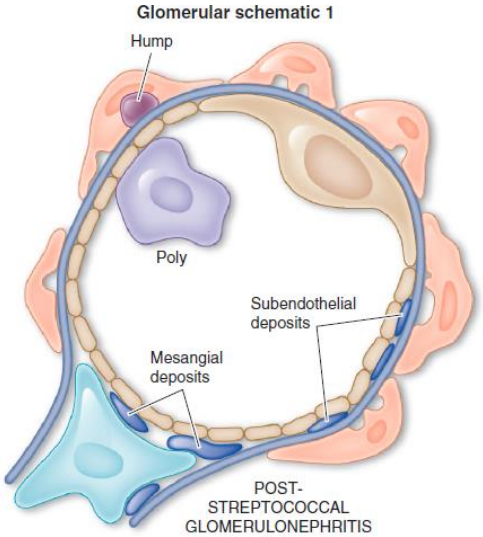
Postinfectious glomerulonephritis

- Most common cause of glomerular diseases in children between 5 and 15 yr
- Rare: < 2 yr, and > 40 yr
- Caused by nephritogenic strains:
  - Group A beta-hemolytic streptococcus: type 12(pharyngitis), type 49 (impetigo)
    Latency: 6-12 days
  - Non-streptococcus: bacterial endocarditis, ventriculoatrial shunt infection
- Mechanism: unknown
- S/Sx: nephritic syndrome

Postinfectious glomerulonephritis

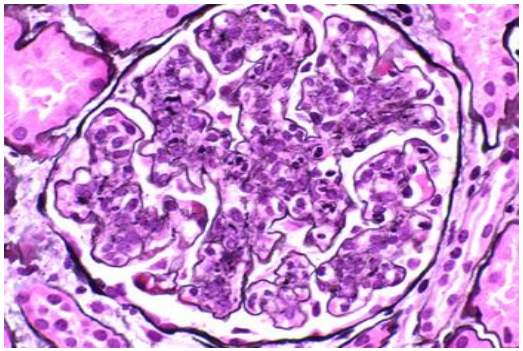
Diagnosis

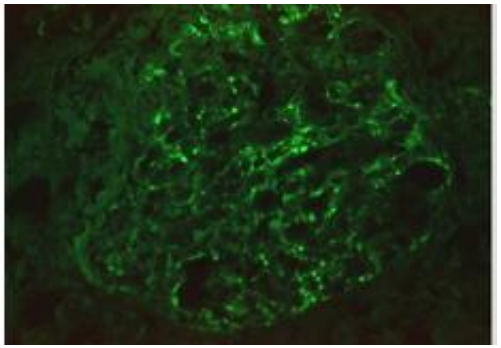
- Serum: antistreptolysin O (ASO), 75% pharyngitis, 50% impetigo
  Lower C3, but return to normal within 6 to 8 weeks
- Urine: nephritic pictures
- Biopsy: MsPGN, RPGN

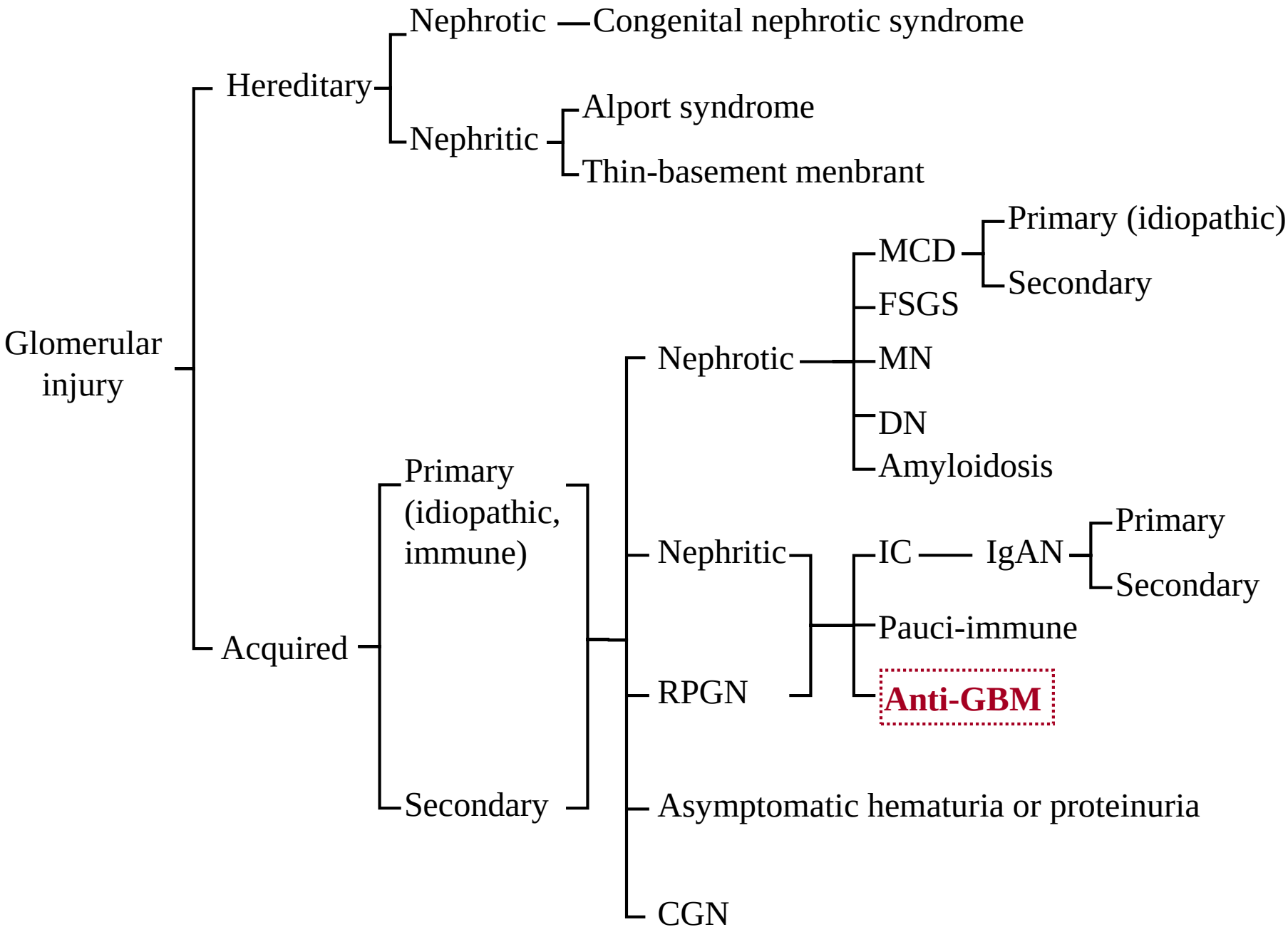


Prognosis and treatment

- No specific treatment: supportive care
- Anti-microbial therapy: within 36 hrs of infectio
- 85-95%: return to normal
- 10%: RPGN






Glomerular injury
Hereditary
Nephrotic
Congenital nephrotic syndrome
Nephritic
Alport syndrome
Thin-basement menbrant
Acquired
Primary (idiopathic, immune)
Secondary
Nephrotic
MCD
Primary (idiopathic)
Secondary
FSGS
MN
DN
Amyloidosis
Nephritic
IC
IgAN
Primary
Secondary
Pauci-immune
Anti-GBM
RPGN
Asymptomatic hematuria or proteinuria
CGN

Anti-GBM disease (Goodpasture's syndrome)

Incidence

- Autoimmune disease
- Autoantibodies directed against type IV collagen
  (noncollagenous domain of α3 chain of type IV collagen)
  α3 NC1 domain of collagen IV

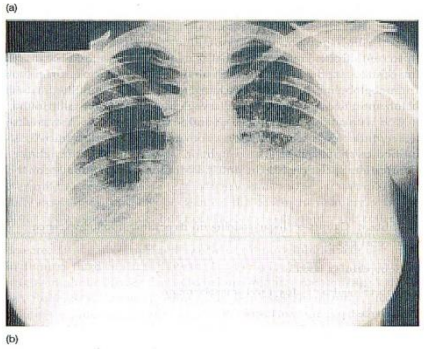
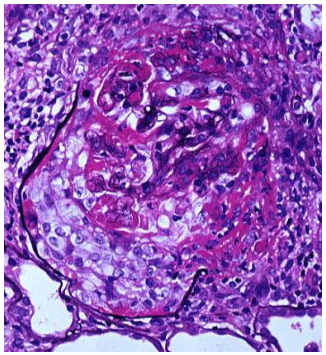
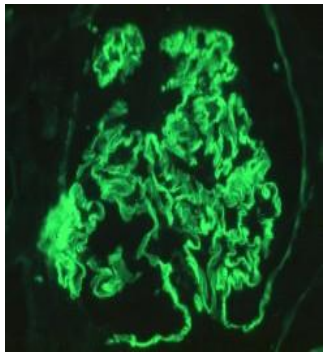
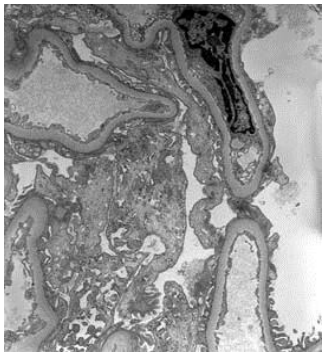
Clinical pictures

- Acute nephritic syndrome is rare
- RPGN, nephritic urinary sediments, subnephrotic proteinuria
- Hypertension is unusual
- Anti-GBM antibody in serum: >90%
- 50-70% with lung hemorrhage
- Anti-GBM nephritis + lung hemorrhage: Goodpasture's syndrome
- Young male (5-40 years)
- Male: Female = 6:1

Renal pathological findings

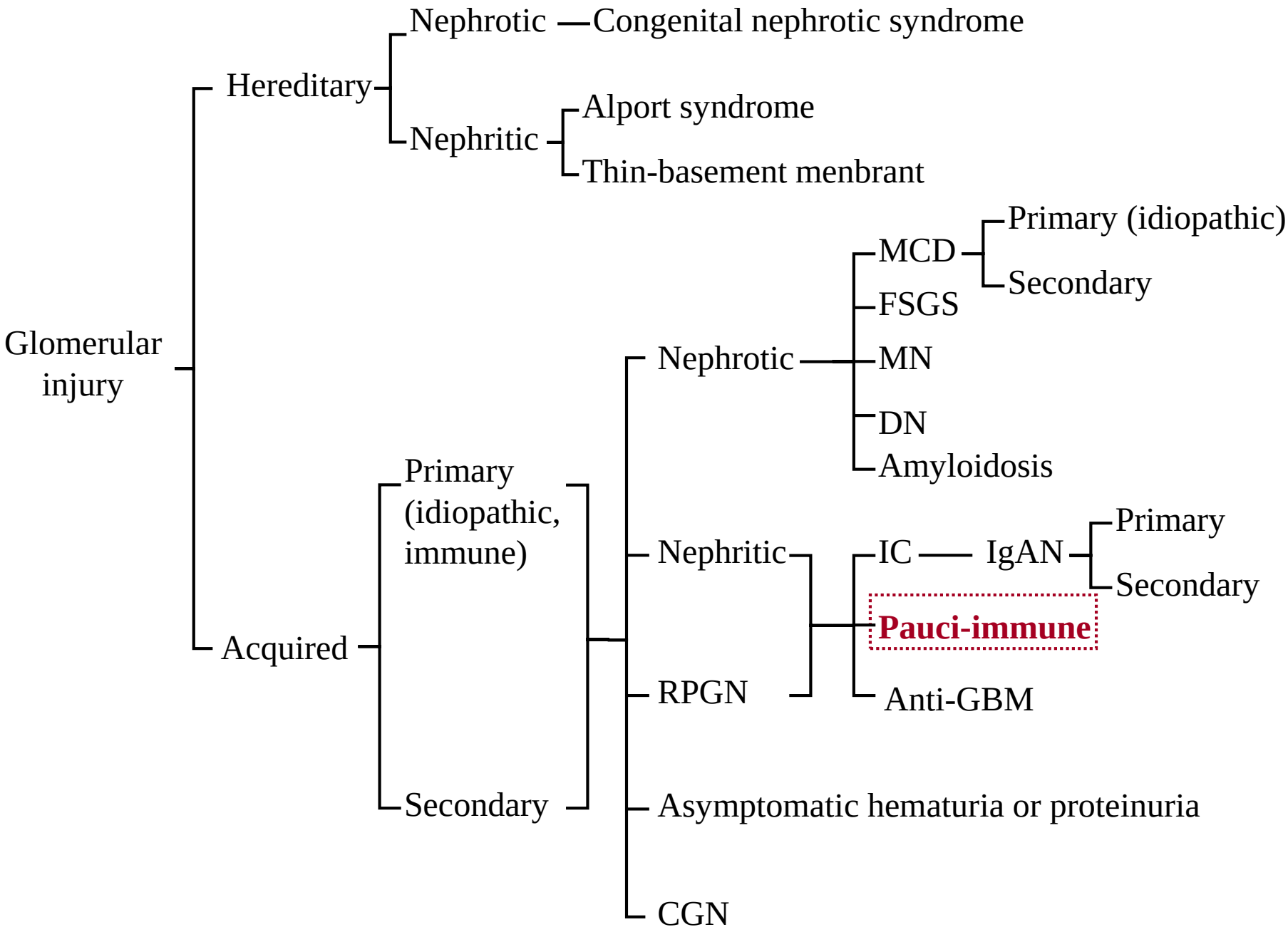
- Gold standard

  IF: linear deposition of immuoglobulin along the GBM

Treatment

- Early and aggressive use of plasmapheresis, glucocorticoid, cyclophosphamide and azathioprine
  - Plasmapheresis: 1-2 weeks (daily or alternate day)
    until anti-GBM antibody not detected
  - Glucocorticoid: prednisolone (1 mg/kg/day),
    in combination with either cyclophophamide (2-3 mg/kg/day)
    or azathioprine (1-2 mg/kg/day)
- The speed of initiation of therapy is a critical determinant of outcome
- In patients with ESRD: kidney transplantation


Glomerular injury
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Nephrotic
Congenital nephrotic syndrome
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Acquired
Primary (idiopathic, immune)
Secondary
Nephrotic
MCD
Primary (idiopathic)
Secondary
FSGS
MN
DN
Amyloidosis
Nephritic
IC
IgAN
Primary
Secondary
Pauci-immune
Anti-GBM
RPGN
Asymptomatic hematuria or proteinuria
CGN

Pauci-immune GN

- RPGN is a more common clinical presentation than acute nephritic syndrome

c-ANCA anti-proteinase 3 (PR3) :granulomatosis with polyangiitis

P-ANCA anti-myeloperoxidase (MPO): microscopic polyangiitis or Churg-Strauss.

Renal pathological findings

- Necrotizing GN
- Absence of immune deposition

ANCA-associated vasculitis

- Vaculitis: inflammation and necrosis of blood vessels
- Common in white people and older patients (mean aged: 57 years)
- Non-specific S/Sx:
  Lethargy, malaise, anorexia, weight loss, fever, arthralgia and myalgia
- Non-specific laboratory:

RPGN/ Pauci-immune GN

TABLE 8.3. Rapidly progressive glomerulonephritis: major categories

Immunofluorescence pattern of immunoglobulin G	Major etiologies	Serologic tests
Linear staining	Goodpasture's disease	Anti-GBM antibody positive
	Goodpasture's syndrome (with pulmonary hemorrhage)	
	Anti-GBM disease (restricted to the kidney)	
No staining	Vasculitis syndromes	
	Wegener's granulomatosis	C-ANCA positive
	Microscopic polyangiitis	P-ANCA positive
	Polyarteritis nodosa	ANCA negative
Granular staining	Immune complex diseases	
	Systemic lupus	Antinuclear antibody positive, low C3,C4
	Immunoglobulin A	Negative serologies
	Poststreptococcal glomerulonephritis	Streptozyme, low C3
	Membranoproliferative glomerulonephritis	Low C3, low C4

ANCA, antineutrophil cytoplasmic antibodies; anti-GBM, antiglomerular basement membrane.

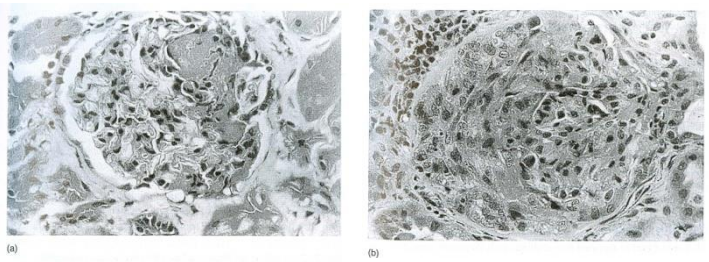
Wegener's granulomatosis (Small sized vasculitis)

c

Clinical pictures

- Middle-aged white people
- Classical triad: necrotizing granulomata of the upper and lower respiratory tract, and necrotizing glomerulonephritis
- c-ANCA(anti-PR3 antibodies): antineutrophil cytoplasm antibodies react with proteinase 3
- Urinalysis: hematuria, RBC casts, and proteinuria

Renal patholgocial findings



Treatment

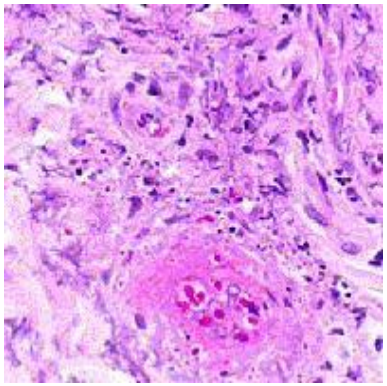
- Early and aggressive
  Should not be delayed until biopsy results are available
  The need of dialysis doesn't preclude the use of aggressive therapy
- Methylyprednisolone iv 7 mg/kg/day on 3 successive days, followed by oral prednisolone 1 mg/kg/day
- Cyclophosphamide: 2 mg/kg/day oral
- Plasmapheresis: (particularly in lung hemorrhage)
- ESRD: kidney transplantation (recurrence)

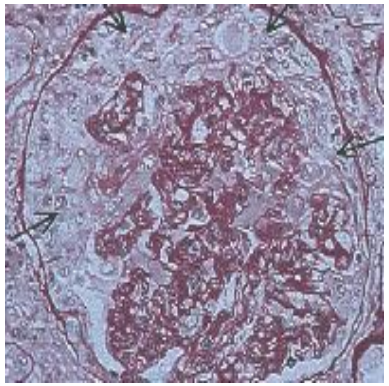
Microscopic polyangiitis (Smaller artiertis)

Clinical pictures

- Multisystemic involvement
- p-ANCA: anti-myeloperoxidase antineutrophilic cytoplasma antibodies
- proteinuria, RBC cast

Renal pathological findings





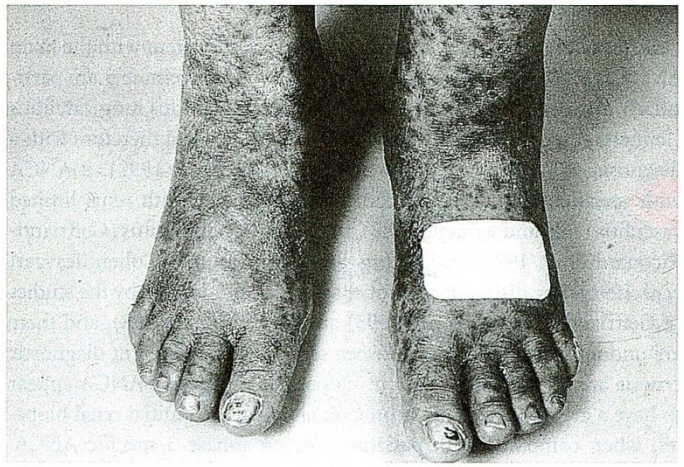


Fig. 6 Vasculitic rash in a patient with microscopic polyangiitis. A plaster covers the site of skin biopsy.

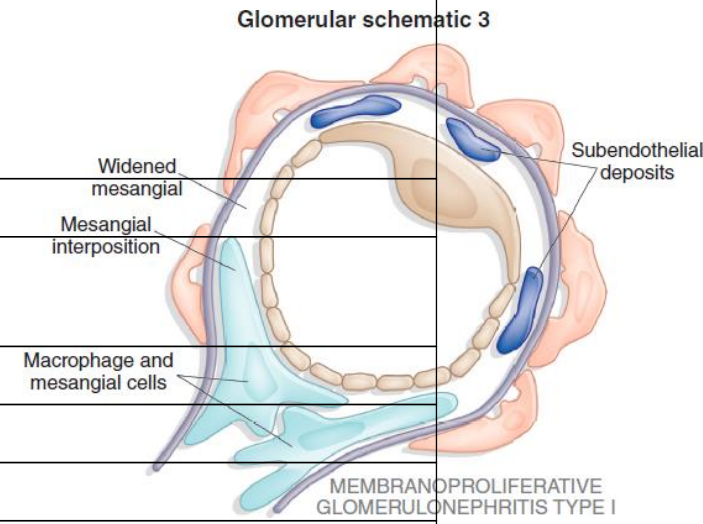
MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS

- immune-mediated glomerulonephritis characterized by thickening of the GBM with mesangioproliferative changes; 70% of patients have hypocomplementemia.
- Low serum C_3 and a dense thickening of the GBM containing ribbons of dense deposits and C_3 characterize type II MPGN*, dense deposit disease*

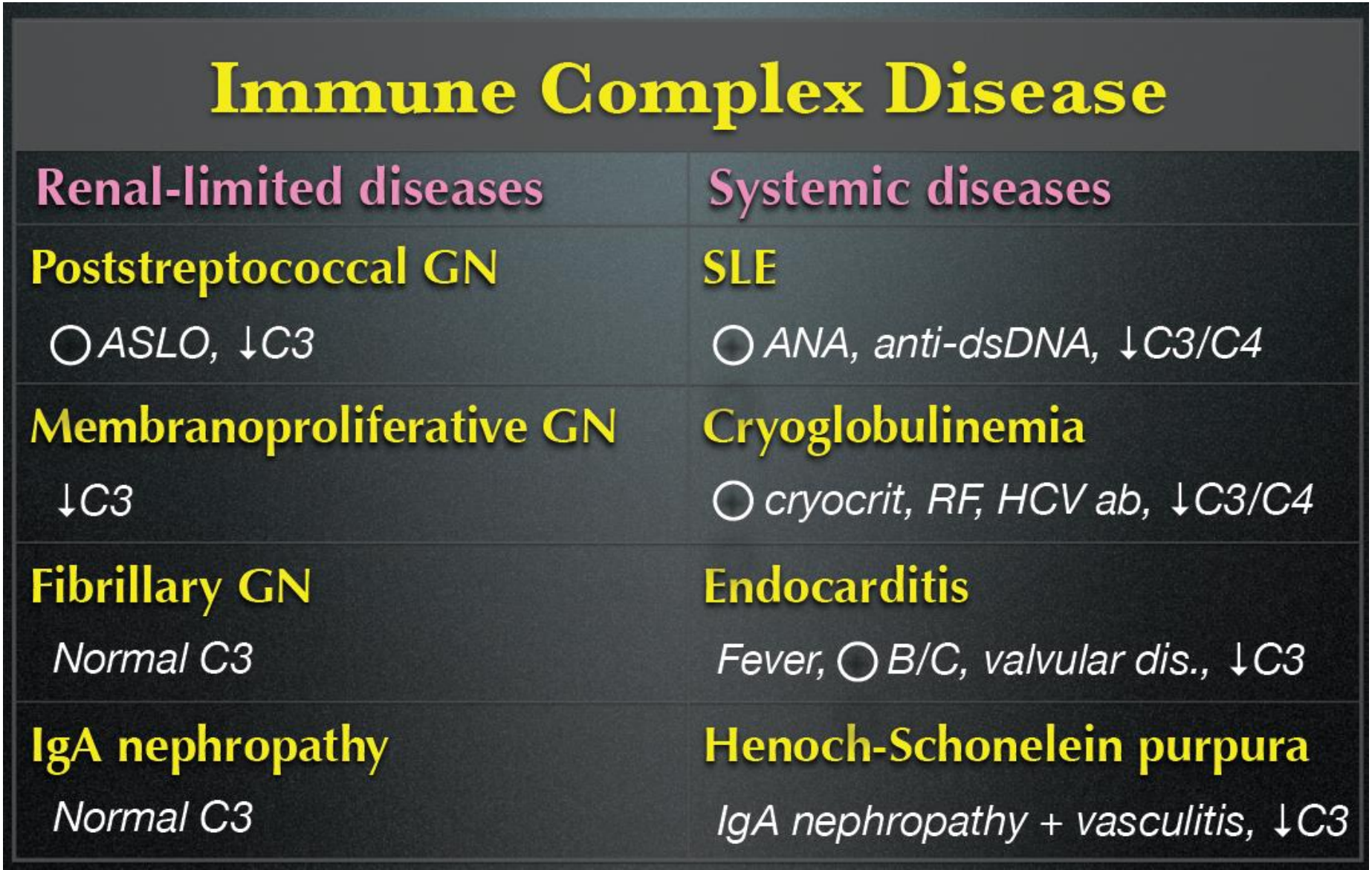
J. Larry Jameson, Anthony S. Fauci, Dennis L. Kasper, Stephen L. Hauser, Dan L. Longo, Joseph Loscalzo+

TABLE 308-4Membranoproliferative Glomerulonephritis: Immunoglobulin-Mediated

Type I Disease—Most Common
Idiopathic
Subacute bacterial endocarditis
Systemic lupus erythematosus
Hepatitis C and cryoglobulinemia
Mixed cryoglobulinemia
Hepatitis C
Cancer: lung, breast and ovary (germinal)
Type II Disease
Idiopathic
Dense Deposit Disease (immunoglobulin-mediated)
Type III Disease
Idiopathic
C_3 Glomerulopathy: C_3 Dominant, Non-Immunoglobulin-mediated
Dense Deposit Disease (C_3 dominant)
Idiopathic
Specific genetic mutations and/or autoantibodies to alternate complement pathway factors or regulatory
factors of alternate complement pathway
C_3 Glomerulonephritis
Specific genetic mutations and/or autoantibodies to alternate complement pathway factors or regulatory factors of alternate complement pathway



Summary for immune complex diseases



- 32 歲男性病人，最近數年內都沒有吃藥，平常體重60 kg，血壓120/80 mmHg，血液肌酸酐1.0 mg/dL。3週前開始出現水腫、少尿與咳血。目前體重65 kg，血壓140/100 mmHg，血色素8.0 g/dL，血液肌酸酐2.0 mg/dL，尿液紅血球20～30/HPF，紅血球圓柱體（RBC cast）+，蛋白質trace，胸部X 光有兩側肺泡浸潤（alveolar infiltrates）。最不可能的診斷是：
- A.快速進行性腎絲球腎炎
- B. Goodpasture 氏症候群
- C.急性腎小管壞死
- D.紅斑性狼瘡腎炎

腎小管壞死

- 32 歲男性病人，最近數年內都沒有吃藥，平常體重60 kg，血壓120/80 mmHg，血液肌酸酐1.0 mg/dL。3週前開始出現水腫、少尿與咳血。目前體重65 kg，血壓140/100 mmHg，血色素8.0 g/dL，血液肌酸酐2.0 mg/dL，尿液紅血球20～30/HPF，紅血球圓柱體（RBC cast）+，蛋白質trace，胸部X 光有兩側肺泡浸潤（alveolar infiltrates）。最不可能的診斷是：
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- B. Goodpasture 氏症候群
- **C.急性腎小管壞死**
- D.紅斑性狼瘡腎炎

Lupus nephritis

- Lupus nephritis is a common and serious complication of systemic lupus erythematosus (SLE) and most severe in African-American female adolescents.
- Thirty to 50% of patients will have clinical manifestations of renal disease at the time of diagnosis, and 60% of adults and 80% of children develop renal abnormalities at some point in the course of their disease.

Treatment

- if a remission—defined as a return to near-normal renal function and proteinuria ≤330 mg/dL per day—is achieved with treatment, renal outcomes are excellent.
- Current evidence suggests that inducing a remission with administration of high-dose steroids and either cyclophosphamide or mycophenolate mofetil for 2–6 months, followed by maintenance therapy with lower doses of steroids and mycophenolate mofetil or azathioprine, best balances the likelihood of successful remission with the side effects of therapy. There is no consensus on use of high-dose intravenous methylprednisolone versus oral prednisone, monthly intravenous cyclophosphamide versus daily oral cyclophosphamide, or other immunosuppressants such as cyclosporine, tacrolimus, rituximab, or belimumab.

Harrison's Principles of Internal Medicine, 20e > Glomerular Diseases

J. Larry Jameson, Anthony S. Fauci, Dennis L. Kasper, Stephen L. Hauser, Dan L. Longo, Joseph Loscalzo+

TABLE 308-3Classification for Lupus Nephritis

Class I	Minimal mesangial	Normal histology with mesangial deposits
Class II	Mesangial proliferation	Mesangial hypercellularity with expansion of the mesangial matrix
Class III	Focal nephritis	Focal endocapillary ± extracapillary proliferation with focal subendothelial immune deposits and mild mesangial expansion
Class IV	Diffuse nephritis	Diffuse endocapillary ± extracapillary proliferation with diffuse subendothelial immune deposits and mesangial alterations
Class V	Membranous nephritis	Thickened basement membranes with diffuse subepithelial immune deposits; may occur with class III or IV lesions and is sometimes called mixed membranous and proliferative nephritis
Class VI	Sclerotic nephritis	Global sclerosis of nearly all glomerular capillaries

Note: Revised in 2004 by the International Society of Nephrology-Renal Pathology Society Study Group.

- 一位45歲男性病人有慢性C型肝炎病史，因尿中泡沫多及水腫且體重增加5公斤而來求診，其24小時尿蛋白流 失為5公克，血中白蛋白(albumin)為 2.4 g/dL，血中補體(complement)濃度下降，下列敘述何者錯誤?
- A.其蛋白尿程度已達腎病症候群之標準
- B.病人血液中常出現冷凝蛋白(cryoglobulin)
- C.較易出現腎動脈栓塞
- D.若做腎臟穿刺，病理診斷最可能是MPGN(membranoproliferative glomerulonephritis)

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- C.較易出現腎動脈栓塞 D.若做腎臟穿刺，病理診斷最可能是MPGN(membranoproliferative glomerulonephritis)

- Among these, thrombotic events including stroke, myocardial infarction, limb and bowel ischemia or infarction, thrombophlebitis, pulmonary emboli, and ocular thrombi including retinal arterial and/or venous occlusions, as well as gangrene, have been described

Cryoglobulinemia

- Cryoglobulins are cold-precipitable monoclonal or polyclonal immunoglobulins
- Systemic vasculitis characterized by palpable purpura, arthralgias, weakness, neuropathy, and glomerulonephritis
- Underlying disorders

Cryoglobulinemia-classification

Table 1: Classification and clinico-pathological characteristics of different cryoglobulinemias.

	Composition	Pathological findings	Clinical associations
Type I cryoglobulinemia	monoclonal Ig, mainly IgG, or IgM, or IgA self-aggregation through Fc fragment of Ig	tissue histological alterations of underlying disorder	-lymphoproliferative disorders: MM, WM, CLL, B-cell NHL
Type II mixed cryoglobulinemia	monoclonal IgM (or IgG, or IgA) with RF activity (often cross-idiotype WA-mRF) and polyclonal Ig (mainly IgG)	-leukocytoclastic vasculitis -B-lymphocyte expansion with tissue infiltrates	-infections (mainly HCV) -autoimmune/lymphoproliferative disorders -rarely 'essential'
Type II–III mixed cryoglobulinemia	oligoclonal IgM RF or mixture of poly/ monoclonal IgM (often cross-idiotype WA-mRF)	-leukocytoclastic vasculitis -B-lymphocyte expansion with tissue infiltrates	-infections (mainly HCV) -autoimmune/lymphoproliferative disorders -rarely 'essential'
Type III mixed cryoglobulinemia	polyclonal mixed Ig (all isotypes) with RF activity of one polyclonal component (usually IgM)	-leukocytoclastic vasculitis -B-lymphocyte expansion with tissue infiltrates	-infections (mainly HCV) -more often autoimmune disorders -rarely 'essential'

lymphoproliferative disorders: MM (multiple myeloma), WM (Waldenstrom's macroglobulinemia), chronic lymphocytic leukemia), B-cell non-Hodgkin's lymphoma;
Ig: immunoglobulin; RF: rheumatoid factor; HCV: hepatitis C virus

J Clin Pathol 2002, **55:4-13**

Cryoglobulinemia-Diagnosis

Table 3: Proposed criteria for the classification of mixed cryoglobulinemia (MC) patients.

Criteria	Serological	Pathological	Clinical
major	mixed cryoglobulins low C4	leukocytoclastic vasculitis	purpura
minor	rheumatoid factor + HCV + HBV +	clonal B-cell infiltrates (liver and/or bone marrow)	chronic hepatitis MPGN peripheral neuropathy skin ulcers

definite mixed cryoglobulinemia syndrome:

a) serum mixed cryoglobulins (± low C4) + purpura + leukocytoclastic vasculitis

b) serum mixed cryoglobulins (± low C4)+ 2 minor clinical symptoms
+ 2 minor serological/pathological findings

essential or secondary mixed cryoglobulinemia:

absence or presence of well-known disorders (infectious, immunological or neoplastic)

HCV+ or HBV+: markers of hepatitis C virus or hepatitis B virus infection (anti-HCV ± HCV RNA; HBV DNA or HBsAg); MPGN: membranoproliferative glomerulonephritis.

J Clin Pathol 2002, **55:4-13**

- **C型肝炎的病人有高達30%會伴隨有腎臟病變，其中以下列何種變化最為少見?**
- **A.冷凝球蛋白腎小球腎炎(cryoglobulinemic glomerulonephritis)**
- **B.膜性腎病變(membranous glomerulonephritis)**
- **C.急性腎間質腎炎(acute interstitial nephritis)**
  D.第一型膜增生性腎小球腎炎(type 1 membranoproliferative glomerulonephritis)

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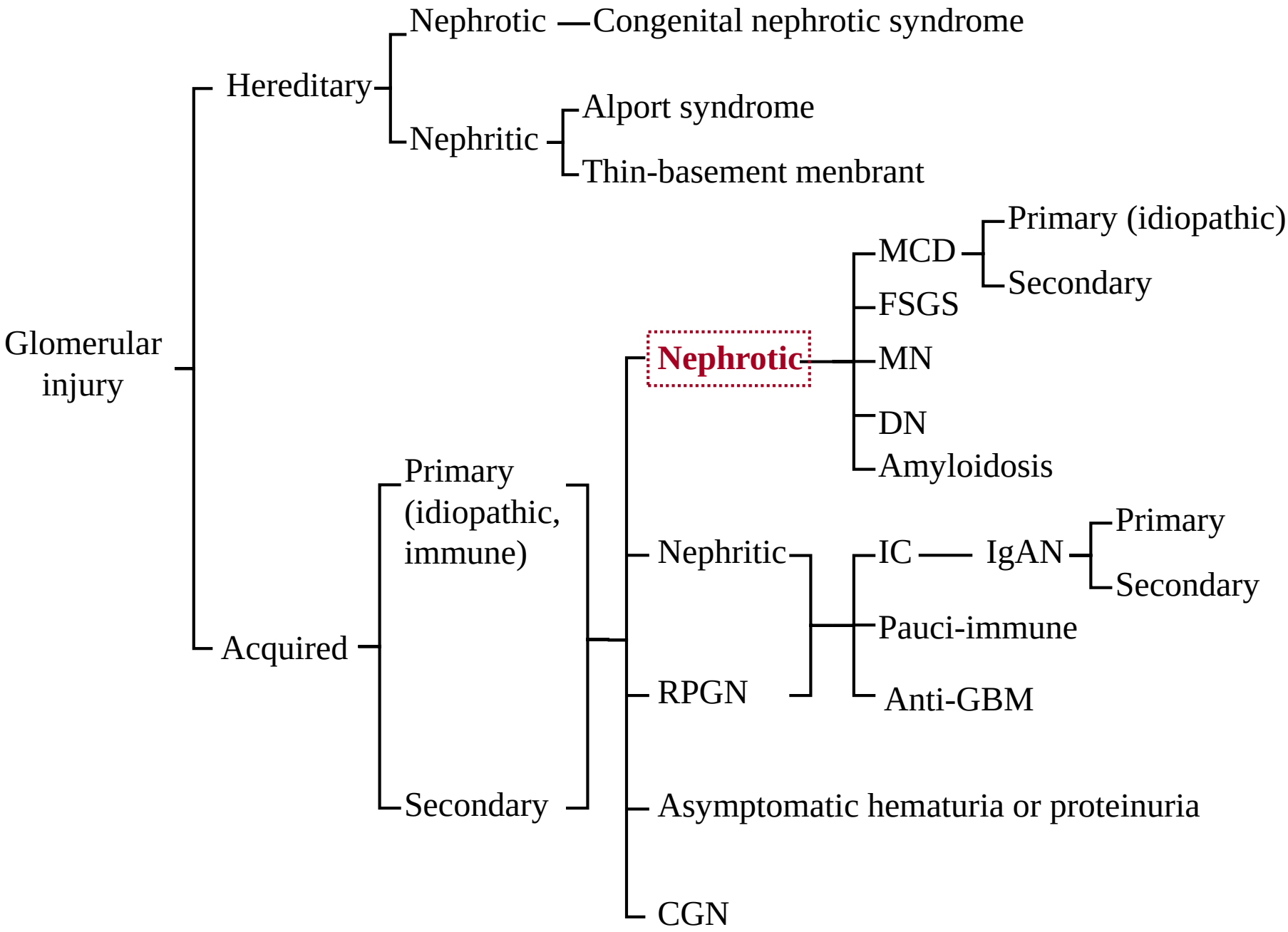
- *Clinical features* of chronic hepatitis C are similar to those described above for chronic hepatitis B. Generally, fatigue is the most common symptom; jaundice is rare. Immune complex–mediated extrahepatic complications of chronic hepatitis C are less common than in chronic hepatitis B (despite the fact that assays for immune complexes are often positive in patients with chronic hepatitis C), with the exception of essential mixed cryoglobulinemia **(Chap. 332)**, which is linked to cutaneous vasculitis and membranoproliferative glomerulonephritis as well as lymphoproliferative disorders such as B-cell lymphoma and unexplained monoclonal gammopathy. In addition, chronic hepatitis C has been associated with extrahepatic complications unrelated to immune-complex injury. These include Sjögren's syndrome, lichen planus, porphyria cutanea tarda, type 2 diabetes mellitus, and the metabolic syndrome (including insulin resistance and steatohepatitis).


Glomerular injury
Hereditary
Nephrotic
Congenital nephrotic syndrome
Nephritic
Alport syndrome
Thin-basement menbrant
Acquired
Primary (idiopathic, immune)
Secondary
Nephrotic
MCD
Primary (idiopathic)
Secondary
FSGS
MN
DN
Amyloidosis
Nephritic
IC
IgAN
Primary
Secondary
Pauci-immune
Anti-GBM
RPGN
Asymptomatic hematuria or proteinuria
CGN

Nephrotic syndrome

Definition

Complex of renal and extrarenal features

- Proteinruia: > 3.5 g/1.73 m^2/24 hrs
- Hypoalbuminemia
- Edema
- Hyperlipidemia
- Lipiduria
- Hypercoagulability

Six common entities: (> 90% in adults)

- Minimal change disease (MCD), Focal segmental glomerulosclerosis (FSGS) Membranous nephropathy (MN), Membranoproliferative glomerulonephritis (MPGN), Fibrillary GN, Diabetic nephropathy

Table 5

Complications of Nephrotic Syndrome

Complication	Contributing Factors
Edema (including ascites and pleural effusions)	Generalized capillary leak Possibly renal Na retention
Infection (especially cellulitis and, in 2 to 6%, spontaneous bacterial peritonitis)	Unknown Possibly loss of opsonins and immunoglobulins
Anemia	Loss of erythropoietin and transferrin
Changes in thyroid function test results (among patients previously hypothyroid, increased dose requirement for thyroid replacement hormone)	Loss of thyroid-binding globulin
Hypercoagulability and thromboembolism (especially renal vein thrombosis and pulmonary embolism, which occur in up to 5% of children and 40% of adults)	Loss of antithrombin III Increased hepatic synthesis of clotting factors Platelet abnormalities Hyperviscosity caused by hypovolemia
Protein undernutrition in children (sometimes with brittle hair and nails, alopecia, and stunted growth)	Loss of proteins Sometimes decreased oral intake secondary to mesenteric edema
Hyperlipidemia	Increased hepatic lipoprotein synthesis
Coronary artery disease in adults	Hyperlipidemia with atherosclerosis Hypertension Hypercoagulability
Hypertension in adults	Renal Na retention
Bone disorder	Corticosteroid use
Chronic kidney disease	Unknown Possibly hypovolemia, interstitial edema, and use of NSAIDs
Proximal tubular dysfunction (acquired Fanconi's syndrome), with glucosuria, aminoaciduria, K depletion, phosphaturia, and renal tubular acidosis	Toxic effects on proximal tubular cells secondary to large amounts of protein that they reabsorb

Nephrotic syndrome

Definition

Complex of renal and extrarenal features

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- Hypoalbuminemia
- Edema
- Hyperlipidemia
- Lipiduria
- Hypercoagulability

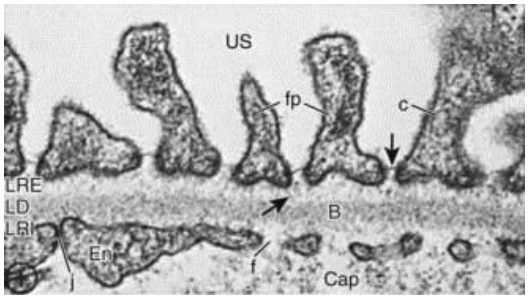
Six common entities: (> 90% in adults)

- Minimal change disease (MCD), Focal segmental glomerulosclerosis (FSGS) Membranous nephropathy (MN), Membranoproliferative glomerulonephritis (MPGN), Fibrillary GN, Diabetic nephropathy

Minimal Change Disease

Incidence

- Nephrotic syndrome: 80% in children (<16 years)
  20% in adults

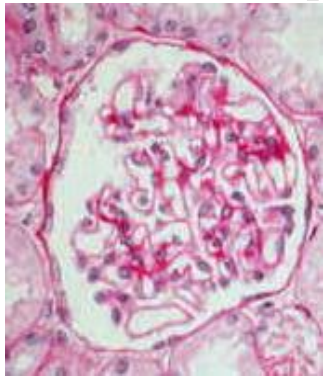


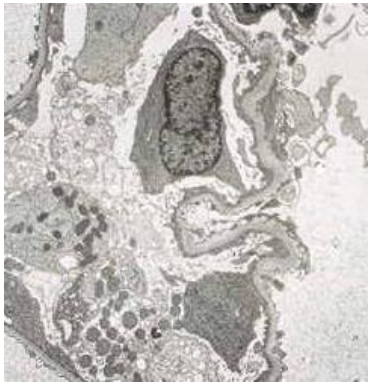
Clincial pictures

- Nephrotic syndrome: typical, selective proteinuria
- Hematuria: 20-30%
- Hypertension and renal failure: rare

Renal patholocial findings

- EM: diffuse effacement of the foot processes of visceral epithelial cell





Minimal Change Disease

Etiology

Causes of Minimal Change Disease (Nil Disease, Lipoid Nephrosis)
Idiopathic (majority)
In association with systemic diseases or drugs
Drug-induced interstitial nephritis induced by NSAIDs, rifampin, interferon α
Hodgkin's disease and other lymphoproliferative malignancy
Human immunodeficiency virus infection
IgA nephropathy
Diabetes mellitus
Fabry's disease
Sialidosis
Heroin use
Iron dextran administration

- Genetic predisposition: HLA-B12
- Immune
- mutation in nephrin, α-actinin-4, and podocin

Minimal Change Disease

Treatment

- Spontaneous remission: 30-40% in children
  Rare in adults
- Highly steroid-responsive
- 8 weeks high-dose oral glucocorticoid
  - Children: 60 mg/m2 qd x 4 weeks
    40 mg/m2 qod x 4 weeks
    --- 90% remission
  - Adult: 1 mg/kg/day x 4 weeks
    1 mg/kg qod x 4 weeks
    --- 50% remission
- steroid dependent: relapse during or shortly after withdrawal of steroid
- frequently relapse: relapse more than three times per years
  - added cyclophosphamide, chlorambucil, and cyclosporine

Focal Segmental Glomerulosclerosis

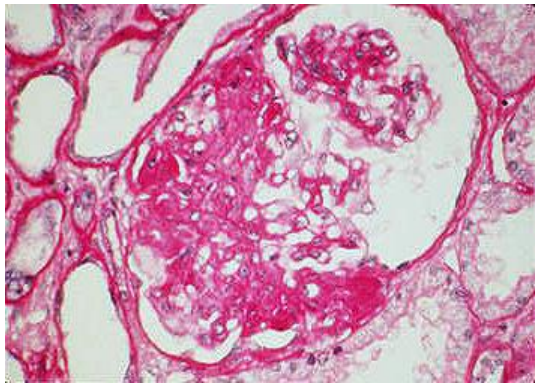
Incidence

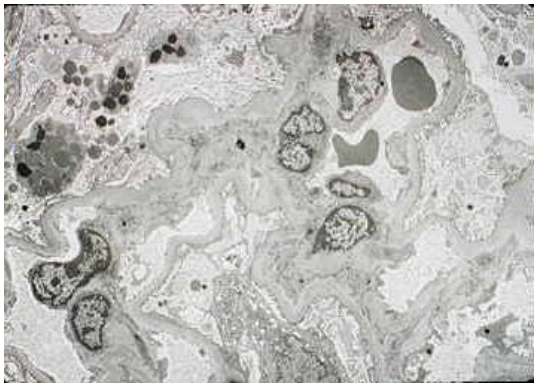
- One-thirds of cases of nephrotic syndrome in adults
- Sclerosis with hyalinosis involving portions (segmental) of fewer than 50% (focal) of glomeruli on a tissue section.

Clinical pictures

- Nephrotic syndrome: 66% of patients, non-selective
- Subnephrotic proteinuria: 33%
- Hypertension, abnormal urine sediment (RBC & WBC)

Renal pathological findings





Focal Segmental Glomerulosclerosis

Etiology

TABLE 264-4 Etiology of Focal and Segmental Glomerulosclerosis

- Idiopathic (majority)
- In association with systemic diseases or drugs
  - HIV infection
  - Diabetes mellitus
  - Fabry's disease
  - Sialidosis
  - Charcot-Marie-Tooth disease
- As consequence of sustained glomerular capillary hypertension
  - Congenital oligonephropathies
    - Unilateral renal agenesis
    - Oligomeganephronia
  - Acquired nephron loss
    - Surgical resection
    - Reflux nephropathy
    - Glomerulonephritis or tubulointerstitial nephritis
  - Other adaptive responses
    - Sickle cell nephropathy
    - Obesity with sleep apnea syndrome
    - Familial dysautonomia
  - Miscellaneous
    - Heroin use

- Primary FSGS: unclear, immunologic (partly)

Focal Segmental Glomerulosclerosis

Treatment

- Spontaneous remission: rare
- Renal prognosis is relatively poor
- Glucocorticoid therapy: 16-24 weeks
  - poor prognostic factors: hypertension, abnormal renal function, black race, and persistent heavy proteinuria
- adjuvant therapy: cyclosphosphamide, cyclosporine, and mycophenolate mofetil
- Renal transplantation: recurrence 50%, graft loss 10%
  - poor prognostic factors: a short time interval between the onset of the FSGS and ESRD, young age at onset, presence of mesangial hypercellularity on renal biopsy

congenital nephrotic syndrome

- congenital nephrotic syndrome from mutations in *NPHS1* (nephrin) and *NPHS2* (podocin) affect the slit-pore membrane at birth, and *TRPC6* cation channel mutations produce *focal segmental glomerulosclerosis* (*FSGS*) in adulthood;
- polymorphisms in the gene encoding apolipoprotein L1, *APOL1*, are a major risk for nearly 70% of African Americans with nondiabetic end-stage renal disease (ESRD), particularly FSGS;

- **34.20**歲男性，因下肢水腫住院，血清白蛋白是**2.3 g/dL**，血中尿素氮和血清肌酸酐各為**27/1.2 mg/dL**，**24**小時尿液蛋白質流失測 得**18 g**。腎臟切片 病理檢查，發現光學顯微鏡下腎絲球的結構正常。下列敘述何者正確**?**
- **A.**電子顯微鏡下應該看得到電子密集沈積
- **B.**通常血清補體是正常的
- **C.**如果治療有效，通常不會再發
- **D.**通常對類固醇治療的效果不佳，有效果的約只有**30%**

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- **D.**通常對類固醇治療的效果不佳，有效果的約只有**30%**

Membranous nephropathy

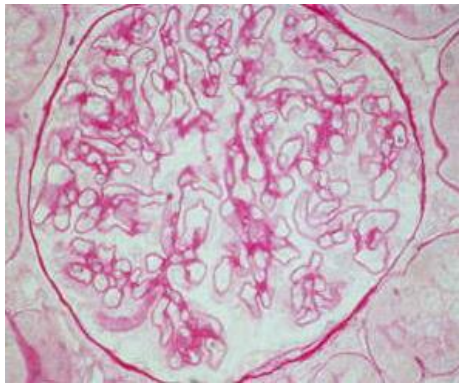
Incidence

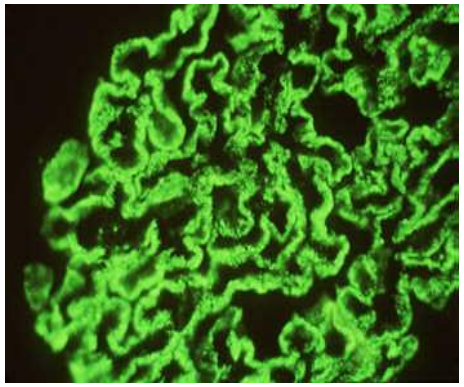
- Leading cause of idiopathic nephrotic syndrome in adults (30-40%, aged: 30-50 years)
- A rare cause in children: < 5%
- Male: Female = 2:1.

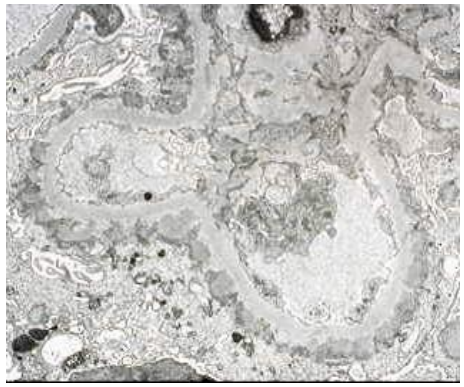
Clinical pictures

- Nephrotic syndrome:80%, non-selective
- Hematuria: 50%, associated with hypertension

Renal pathological findings







Membranous nephropathy

Etiology

TABLE 264-5 *Conditions Associated with Membranous Glomerulopathy*

Idiopathic (majority)
In association with systemic diseases or drugs
- Infection
  - Hepatitis B and C, secondary and congenital syphilis, malaria, schistosomiasis, leprosy, hydatid disease, filariasis, enterococcal endocarditis
- Systemic autoimmune diseases
  - SLE, rheumatoid disease, Sjögren's syndrome, Hashimoto's disease, Graves' disease, mixed connective tissue disease, primary biliary cirrhosis, ankylosing spondylitis, dermatitis herpetiformis, bullous pemphigoid, myasthenia gravis
- Neoplasia
  - Carcinoma of the breast, lung, colon, stomach, and esophagus; melanoma; renal cell carcinoma; neuroblastoma; carotid body tumor
- Drugs
  - Gold, penicillamine, captopril, NSAIDs, probenecid, trimethadione, chlormethiazole, mercury
- Miscellaneous
  - Sarcoidosis, diabetes mellitus, sickle cell disease, Crohn's disease, Guillain-Barré syndrome, Weber-Christian disease, Fanconi's syndrome, α_1 antitrypsin deficiency, angiofollicular lymph node hyperplasia

Note: SLE, systemic lupus erythematosus; NSAIDs, nonsteroidal anti-inflammatory drugs.

- Idiopathic: incompletely understood

Membranous nephropathy

Treatment

- Spontaneous remission: 40%
- ESRD: 10-20%
  - poor prognostic factors: male, older age, hypertension, severe proteinuria, and hyperlipidemia, and impaired renal function
- Immunosuppressive agents: glucocorticoid, cyclophosphamide, chlorambucil, and cyclosporine.
- Kidney transplantation: a successful treatment for ESRD

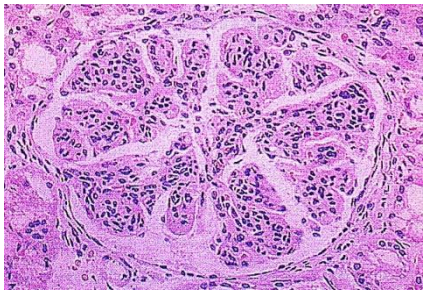
Membranoproliferative glomerulonephritis

- Also known a mesangiocapillary GN
- Thickening of the GBM and proliferative changes

Clinical pictures

- Type I MPGN: heavy proteinruia, nephrotic syndrome
  Active urinary sediments, C3 depressed
- Type II MPGN: nephrotic syndrome, nephritic syndromen and RPGN

Renal pathological findings



Membranoproliferative glomerulonephritis

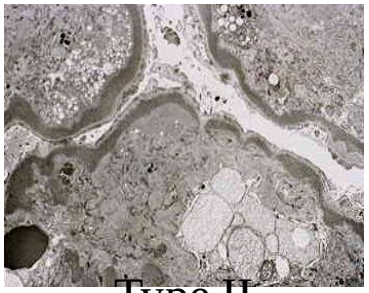
Table 3 Comparison between type I MCGN and dense deposit disease

Features	Type I MCGN	Dense deposit disease
Age (at clinical onset)	Older	Younger
Asymptomatic urinary findings (at clinical onset)	Asymptomatic proteinuria and haematuria	Less common
Nephrotic syndrome	Less common	More common
Acute nephritic syndrome	Less common	More common
Gross haematuria	Less common	More common
Low serum complement	Less common (less severe, less persistent)	Common (severe, persistent)
C3NeF	Less common	More common
Partial lipodystrophy (with hypocomplementaemia and C3NeF)	Rare	Mainly associated with this type
Recurrence in renal transplants	Less common (ca. 25%)	Frequent (80+%)
Renal prognosis	Better	Worse

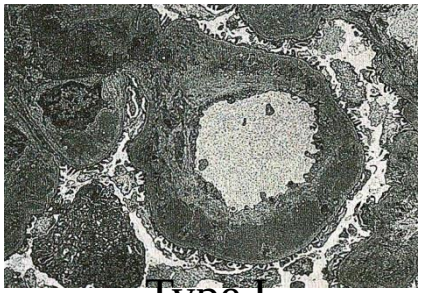
TABLE 264-6 Causes of Membranoproliferative (Mesangiocapillary) Glomerulonephritis (MPGN)

Idiopathic	
Type I	With subendothelial and mesangial immune deposits
Type II	With intramembranous dense deposits containing sparse or no Ig; associated with C3 nephritic factor
Type III	Features of type I MPGN and membranous nephropathy
In association with systemic diseases or drugs[a]	
Systemic immune-complex disease	SLE, mixed cryoglobulinemia, Sjögren's syndrome
Chronic infections	Hepatitis B and C, HIV, bacterial endocarditis, ventriculoatrial shunts, visceral abscess
Malignancy	Leukemias, lymphomas
Liver disease	Chronic active hepatitis and cirrhosis (usually associated with hepatitis B or C)
Miscellaneous	Partial lipodystrophy, heroin use, sarcoidosis, inherited C2 deficiency, thrombotic microangiopathies

[a] Usual with morphologic features of idiopathic type I MPGN (see above).
Note: SLE, systemic lupus erythematosus.



Type II



Type I

Membranoproliferative glomerulonephritis

Treatment

- No effective therapy for type I and type II MPGN
- 5-10 years to ESRD

Table 3 NIH treatment regimen

Induction
Prednisolone
1 mg/kg daily
Cyclophosphamide
2 mg/kg daily
Fulminant disease
Prednisolone
2 mg/kg daily
Cyclophosphamide
4–5 mg/kg daily
Maintenance
Prednisolone
tapering alternate day dose
Cyclophosphamide
starting dose maintained until remission >1 year

Poor prognosis factors

Table 4 Factors heralding a poor prognosis in MCGN

Clinical
Acute nephritic presentation
Hypertension
Nephrotic range proteinuria
Renal dysfunction at onset
Absence of clinical remission
Histological
Dense-deposit disease (type II)
Crescents
Tubulointerstitial fibrosis
Mesangial deposits
Glomerular sclerosis

腎絲球疾病

1. 依照臨床表現
- AGN
- RPGN
- Nephrotic syndrome
- Hematuria

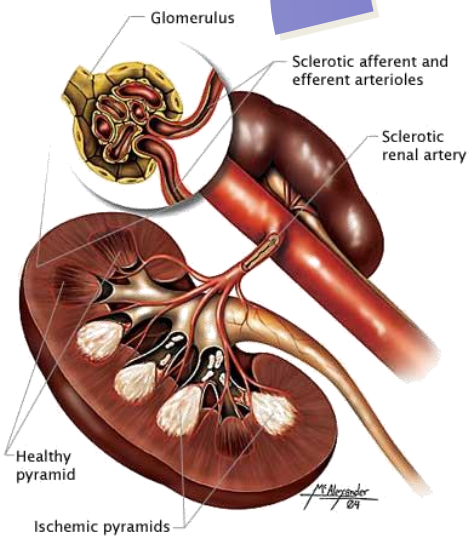
2. 介紹AGN常見疾病
- IgAN

3. 介紹RPGN常見疾病
- 以螢光染色做區分

--linear: Anti-GBM
--granular: immune-complex (Lupus)
--pauci-immune: Renal vasculitis

4. 介紹Nephrotic syndrome常見疾病
- MCD, FSGS, MN, MPGN
- Fibrillay GN, Amyloidosis

5. 介紹Hematuria常見疾病
- **Thin-basement membrane diseases**
- **Alport's syndrome**



解剖
↓
生理
↓
病生理
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疾病
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診斷
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治療
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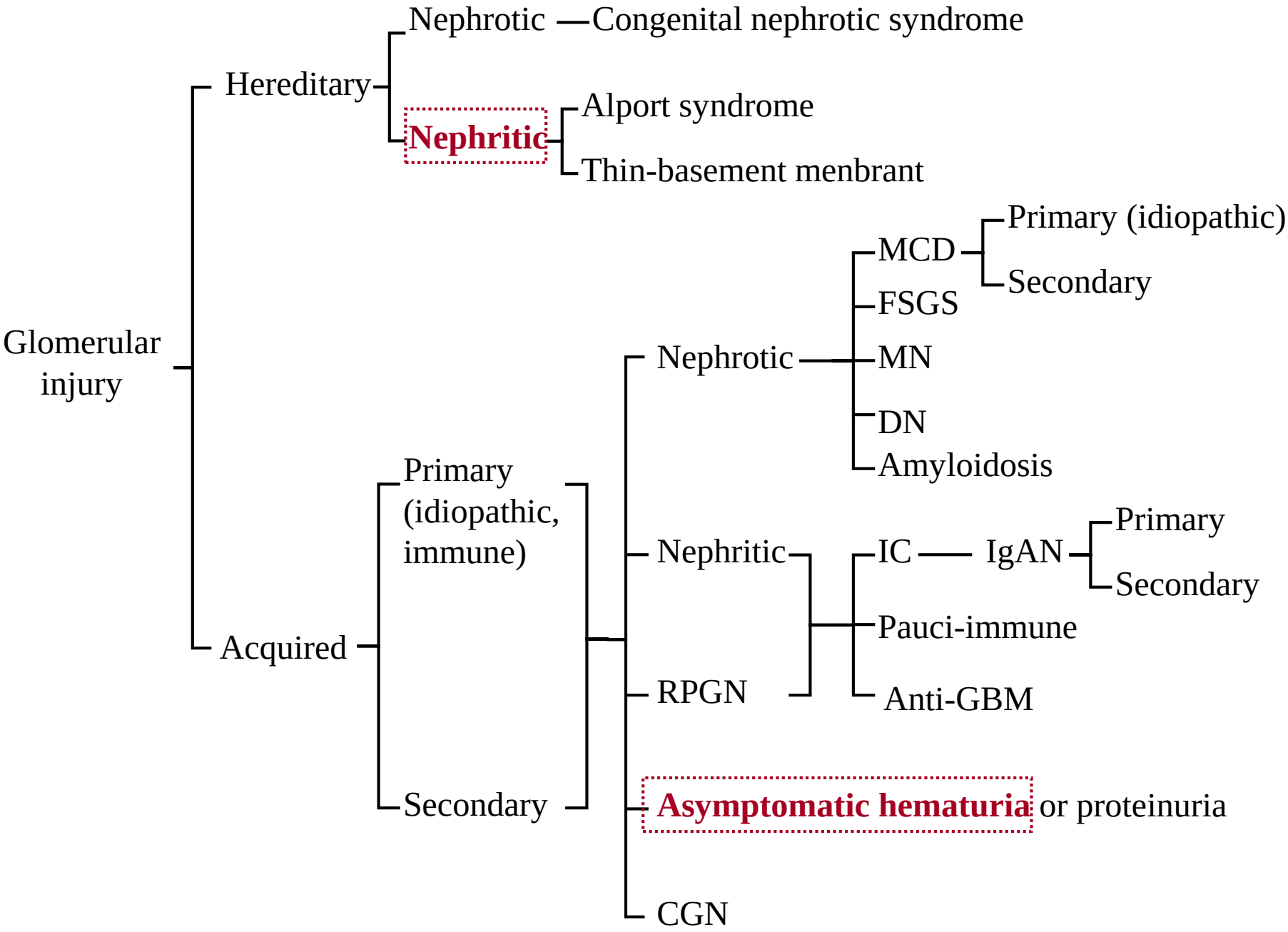
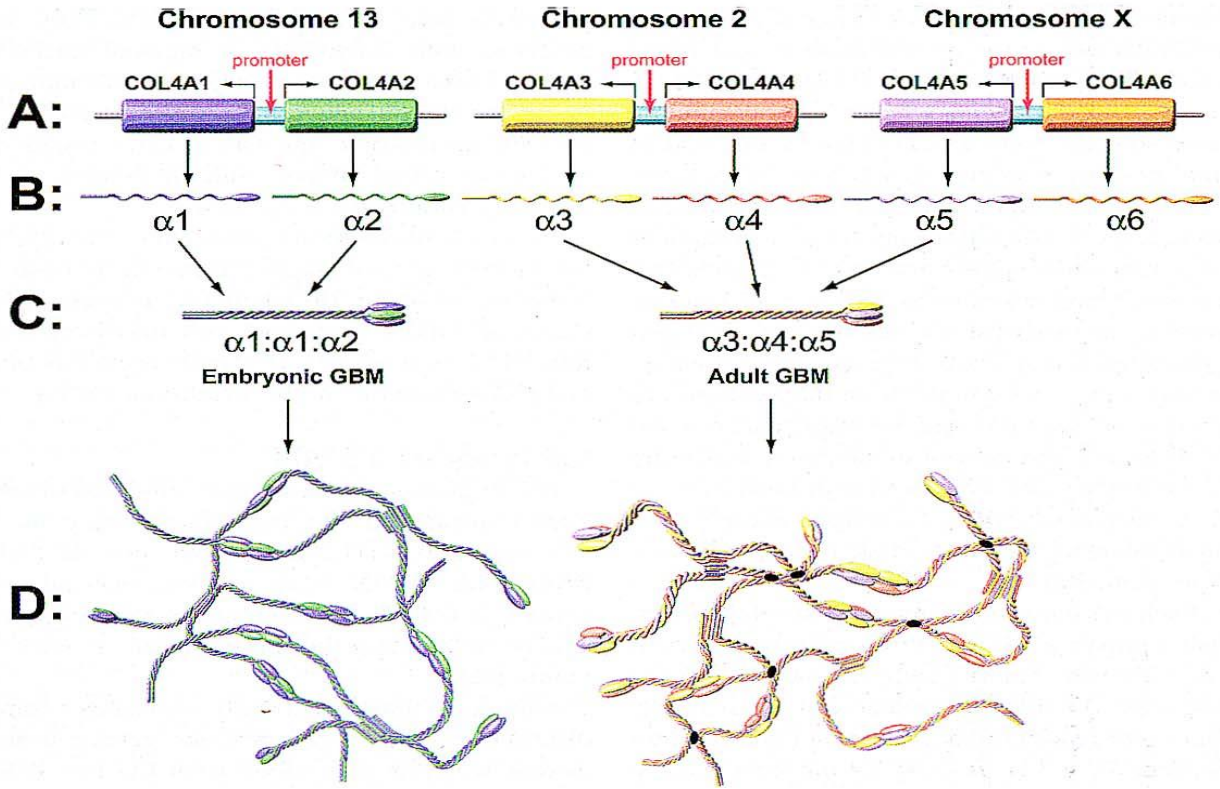
預後


Glomerular injury
Hereditary
Nephrotic
Congenital nephrotic syndrome
Nephritic
Alport syndrome
Thin-basement menbrant
Acquired
Primary (idiopathic, immune)
Secondary
Nephrotic
MCD
Primary (idiopathic)
Secondary
FSGS
MN
DN
Amyloidosis
Nephritic
IC
IgAN
Primary
Secondary
Pauci-immune
Anti-GBM
RPGN
Asymptomatic hematuria
or proteinuria
CGN

Asymptomatic hematuria

Common diseases

- IgA nephropathy
- Thin-basement membrane diseases
- Alport's syndrome



Thin Basement membrane disease

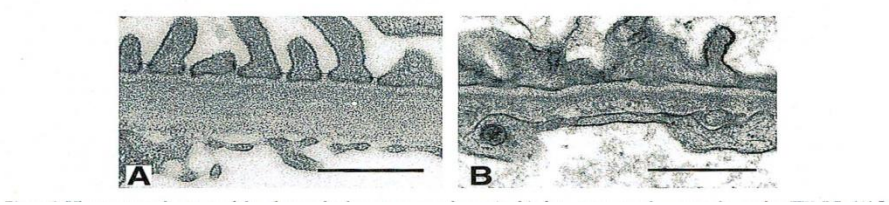
- Familial, autosomal dominant
- Defect in α4 chain of type IV collagen

Clinical pictures

- Persistent or intermittent hematuria
- Exacerbation of hematuria during URI

Renal Pathological findings

Normal 300 to 400 nanometers (nm) to 150 to 250 nm



Treatment

- No clear evidence-based treatment
- Monitored: hypertension, proteinruia, and renal insufficiency

Alport's syndrome

X-linked dominant trait

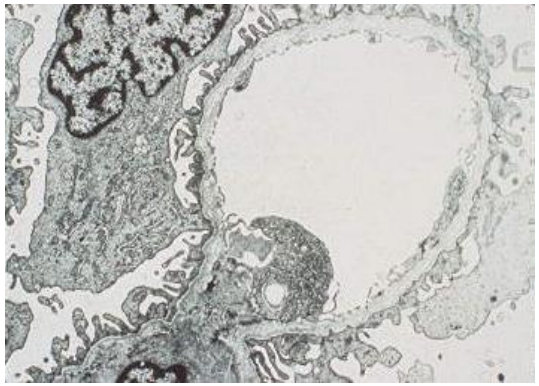
Defect in α5 chain of type IV collagen

Renal pathological findings

- EM: thickening, fragmentation and lamellation of the lamina densa of the GBM
- LM: mesangial hypercellularity, focal and segmental glomerulosclerosis, and tubulointerstitial fibrosis

Treatment

- Male tend to ESRD
- Transplantation:
  - Ideal treatment
  - 5% transplant recipients: anti-GBM



Diagnosis: glomerulonephritis

Table 1. Common presentations of glomerulonephritis

Presentation	Cause	Specific test
Nephritic syndrome	IgA nephropathy	
	Poststreptococcal GN	ASOT, anti-DNAase B, C3
	SLE	ANA, anti-ds DNA, C3, C4
	Anti-GBM disease	Anti-GBM antibody
	ANCA vasculitis	ANCA
	Mesangiocapillary GN	C3, HBsAg
Nephrotic syndrome	Minimal change disease	
	Membranous GN	HbsAg, chest X-ray, mammogram*
	FSGS	
	SLE	ANA, anti-ds DNA, C3, C4
	Diabetes	Fasting glucose
	Amyloid	Urine Bence-Jones protein, serum and urine protein electrophoresis
GN and infection		
• URTI	Flare of IgA nephropathy	
• Streptococcus	Poststreptococcal GN	
• Hepatitis B	Membranous GN	
• Hepatitis C	Mesangiocapillary GN	
• Endocarditis	Mesangiocapillary GN	
GN and drugs		
• NSAID	Minimal change disease	
• Gold, penicillamine	Membranous GN	
• OCP, quinine	HUS	FBE (schistocytes), LDH, haptoglobin
GN and purpuric skin rash	IgA/HSP	Skin biopsy with immunoflouresence
	SLE	
	ANCA vasculitis	
GN and cancer	Membranous GN	

Isbel, Aust Fam Physician 2005:34:907-913

Management: glomerulonephritis

Delayed progression

- Regular clinical follow up
- Blood pressure control
- ACEIs or/and ARBs for proteinuria > 1g/day
- Dietary protein
- Lipid lowering

Immunosuppressive agents

Management: glomerulonephritis

Type	Management strategy
Minimal-change disease	Oral prednisone 0·5–1·0 mg/kg daily for 6 weeks, then tapered;[86] cyclophosphamide or ciclosporin in steroid-resistant or frequently relapsing patients.[86,87]
Focal and segmental glomerulosclerosis	Oral prednisone 0·5–1·0 mg/kg daily for at least 6 months, may be tapered after first 3 months;[88] cyclophosphamide is indicated for steroid-resistant cases, with 50% chance of response; response reduces probability of progression to ESRD by 50%.[88,89]
Membranous nephropathy	Cyclophosphamide (or chlorambucil) orally combined with prednisolone,[90] achieves 50% remission rate; steroids alone are ineffective.[91]
Mesangiocapillary glomerulonephritis	Prednisone can be useful in children[92] but not in adults;[93] anti-CD20 can be effective in cryoglobulinaemia-associated disease.[94]
Proliferative lupus nephritis (class III and IV)	Pulse steroids, followed by monthly intravenous cyclophosphamide and daily oral prednisone for 3–6 months (remission induction), followed by oral azathioprine or mycophenolate mofetil and reduced-dose prednisone (maintenance).[95-98]
Rapidly progressive glomerulonephritis—anti-GBM	Plasmapheresis, pulse methylprednisolone, followed by oral cyclophosphamide and prednisone are effective.[1,99]
Rapidly progressive glomerulonephritis—vasculitis	Pulse methylprednisone followed by oral cyclophosphamide and prednisone.[100]
IgA nephropathy	Oral prednisone can be effective in retarding progression;[101] however, combined inhibition of ACE and angiotensin-receptor blockade should be first-line therapy.[83]

GFR=glomerular filtration rate; ESRD=end-stage renal disease; GBM=glomerular basement membrane; ANCA=antineutrophil cytoplasmic antibodies; ACE=angiotensin-converting enzyme.

Table 2: Management of primary glomerulonephritis with immunosuppressive agents

Chadban et al Lancet 2005:356:1797-1806

Mo Med. 2011 Jan-Feb;108(1):33-6.

Clinical presentation & management of glomerular diseases: hematuria, nephritic & nephrotic syndrome.

Khanna R.

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Abstract

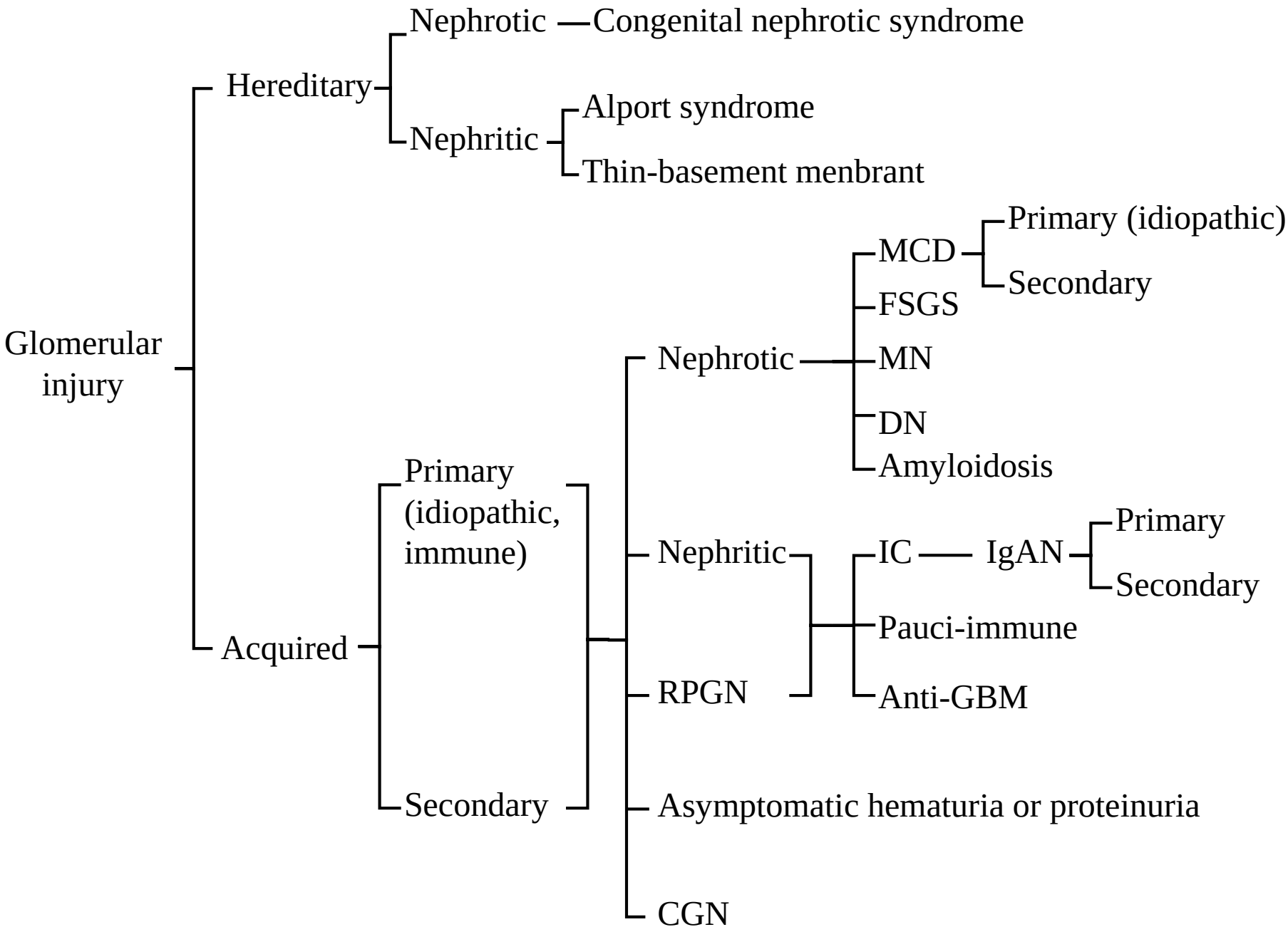
Because the differential diagnosis for glomerulonephritis (GN) is broad, using a classification schema is helpful to narrow the causes of GN in a systematic manner. The etiology of glomerulonephritis can be classified by their clinical presentation (nephrotic, nephritic, rapidly progressive GN, chronic GN) or by histopathology. GN may be restricted to the kidney (primary glomerulonephritis) or be a secondary to a systemic disease (secondary glomerulonephritis). The nephrotic syndrome is defined by the presence of heavy proteinuria (protein excretion greater than 3.0 g/24 hours), hypoalbuminemia (less than 3.0 g/dL), and peripheral edema. Hyperlipidemia and thrombotic disease may be present. The nephritic syndrome is associated with hematuria and proteinuria and abnormal kidney function and carries poorer prognosis and is typically associated with hypertension. The predominant cause of the nephrotic syndrome in children is minimal change disease. The most common causes of nephritic syndrome are post infectious GN, IgA nephropathy and lupus nephritis. Chronic GN is slowly progressive and is associated with hypertension and gradual loss of kidney function. Treatment includes non-specific measure aimed at controlling hypertension, edema, proteinuria and disease modifying immunosuppression.

Table 9. Histology of chronic renal failure ($N = 607$)

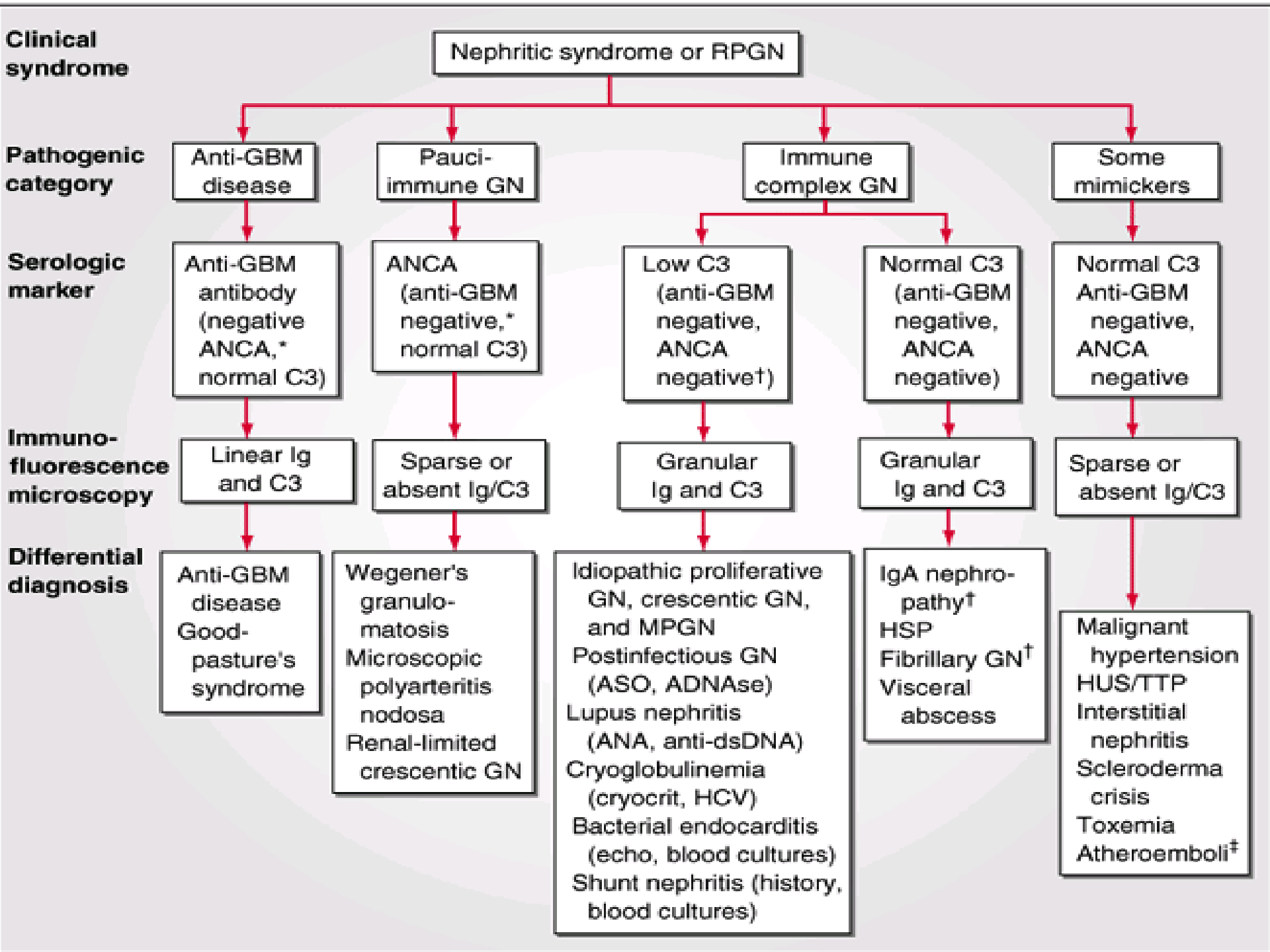
	No. of cases	%
Primary glomerular diseases	252	41.50
IgAN	162	26.70
FSGS	58	9.60
MPGN	27	4.40
MN	5	0.82
Secondary glomerular diseases	218	35.91
Renal vasculitis	87	14.33
HSPN	3	0.49
LN	66	10.88
DN	19	3.13
Multiple myeloma	8	1.32
Amyloidosis	8	1.32
Monoclonal immunoglobulin deposit disease	8	1.32
Benign/malignant nephrosclerosis	11	1.81
Toxemia in pregnancy	3	0.49
Hereditary renal disease	5	0.82
Chronic interstitial nephritis	71	11.70
Unclassified	66	10.87
Total	607	100.00

Abbreviations are: IgAN, IgA nephropathy; FSGS, focal segmental glomerulosclerosis; MPGN, mesangiocapillary glomerulonephrits; MN, membranous nephropathy; HSPN, Henoch-Schönlein purpura; LN, lupus nephritis; DN, diabetic nephropathy.

Kidney International, Vol. 66 (2004), pp. 920–923


Glomerular injury
Hereditary
Nephrotic
Congenital nephrotic syndrome
Nephritic
Alport syndrome
Thin-basement menbrant
Acquired
Primary (idiopathic, immune)
Secondary
Nephrotic
MCD
Primary (idiopathic)
Secondary
FSGS
MN
DN
Amyloidosis
Nephritic
IC
IgAN
Primary
Secondary
Pauci-immune
Anti-GBM
RPGN
Asymptomatic hematuria or proteinuria
CGN

- 34.一位55歲女性病人，過去無腎臟病史，因最近一週尿量漸減且體重增加而住院。身體診察: 血壓180/110 mmHg，脈搏72/min，呼吸次數16/min，呼吸音正常，心律規則無雜音，腹部 平坦無壓痛，下肢有顯壓陷性水腫。血液檢查:血紅素10 gm/dL，白血球10500 /μL，白蛋白2.5 g/dL，尿素氮35 mg/dL，肌酸酐3.0 mg/dL;尿液檢查:蛋白質(3+)，紅血球20 ~25顆/高倍視野，並可見到紅血球圓柱體。本病人接受腎臟切片檢查後，最適當治療方式 為?
- A.廣效性抗生素(broad-spectrum antibiotics)
- B.免疫抑制劑(immunosuppressive therapy)
- C.緊急血液透析(emergent hemodialysis)
- D.補充白蛋白(albumin infusion)


Clinical syndrome
Nephritic syndrome or RPGN
Pathogenic category
Anti-GBM disease
Pauci-immune GN
Immune complex GN
Some mimickers
Serologic marker
Anti-GBM antibody (negative ANCA,* normal C3)
ANCA (anti-GBM negative,* normal C3)
Low C3 (anti-GBM negative, ANCA negative†)
Normal C3 (anti-GBM negative, ANCA negative)
Normal C3 Anti-GBM negative, ANCA negative
Immuno-fluorescence microscopy
Linear Ig and C3
Sparse or absent Ig/C3
Granular Ig and C3
Granular Ig and C3
Sparse or absent Ig/C3
Differential diagnosis
Anti-GBM disease
Good-pasture's syndrome
Wegener's granulo-matosis
Microscopic polyarteritis nodosa
Renal-limited crescentic GN
Idiopathic proliferative GN, crescentic GN, and MPGN
Postinfectious GN (ASO, ADNAse)
Lupus nephritis (ANA, anti-dsDNA)
Cryoglobulinemia (cryocrit, HCV)
Bacterial endocarditis (echo, blood cultures)
Shunt nephritis (history, blood cultures)
IgA nephro-pathy†
HSP
Fibrillary GN†
Visceral abscess
Malignant hypertension
HUS/TTP
Interstitial nephritis
Scleroderma crisis
Toxemia
Atheroemboli‡

- .30歲的婦女，產前7天的血壓正常，血液肌酸酐 0.6 mg/dL。產後當天有出血、高血壓、少尿、水腫。理學檢查皮膚沒有紅斑或紫斑，血液Hb 8.0 g/dL，血小板70,000/mm3，血液抹片有fragmented RBCs，haptoglobin下降，BUN 100 mg/dL，肌酸酐3.6 mg/dL，尿液osmolality 400 mOsmol/kg H2O，尿液Na+ 10 mmol/L，尿液紅血球20~30/HPF，尿液蛋白質trace。最可能的診斷是:
- A.急性腎小管壞死(acute tubular necrosis)
- B.溶血性尿毒症候群(hemolytic uremic syndrome)
  C.Goodpasture氏症候群
- D.冷凝球蛋白血症(cryoglobulinemia)

Microvascular Thrombotic Crisis (Thrombotic Thrombocytopenic Purpura, Hemolytic-Uremic Syndrome)

- This syndrome of hemolysis, thrombocytopenia, and microvascular thrombosis in kidneys, brain, and other tissues carries a high mortality rate and occurs most commonly in young individuals with lupus nephritis.
- The most useful laboratory tests are identification of schistocytes on peripheral blood smears, elevated serum levels of lactate dehydrogenase, and antibodies to ADAMS13.
- Plasma exchange or extensive plasmapheresis is usually life-saving; most authorities recommend concomitant glucocorticoid therapy; there is no evidence that cytotoxic drugs are effective.

- 一位30歲女性病人尿液分析發現血尿，下列何項檢查結果支持是腎小球性(glomerular)血尿?
- A.尿沉渣看見顆粒性圓柱體
- B.24小時蛋白尿排泄量> 2.5克
- C.尿沉渣發現變形性紅血球
- D.紅血球數目> 50顆/高倍視野

- 一位30歲女性病人尿液分析發現血尿，下列何項檢查結果支持是腎小球性(glomerular)血尿?
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- D.紅血球數目> 50顆/高倍視野

- Hematuria with dysmorphic RBCs, RBC casts, and protein excretion >500 mg/d is virtually diagnostic of glomerulonephritis.
- RBC casts form as RBCs that enter the tubule fluid and become trapped in a cylindrical mold of gelled Tamm-Horsfall protein

- **40歲女性因為無痛性巨觀性血尿(painless gross hematuria)求診。下列那一項檢查最能夠判別血尿的來源 是腎絲球病變引起的?**
- **A.血清肌酸酐濃度**
- **B.血清補體C3濃度**
- **C.尿液紅血球的形態**
- **D.靜脈內泌尿攝影術(intravenous urography)**

- **40歲女性因為無痛性巨觀性血尿(painless gross hematuria)求診。下列那一項檢查最能夠判別血尿的來源 是腎絲球病變引起的?**
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- **D.靜脈內泌尿攝影術(intravenous urography)**

- **3.23歲女性病人，於上呼吸道感染後3天發現血尿，尿液檢查發現有血尿、蛋白尿，腎切片檢查發現腎小球膜基質（mesangium）有免疫球蛋白沉澱，此病人最可能之診斷為：**
- A.微小變化腎病變（minimal change disease）
- B.A型免疫球蛋白腎病變（IgA nephropathy）
- C.局部腎硬化（focal glomerulosclerosis）
- D.膜性腎病變（membranous nephropathy）

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- C.局部腎硬化（focal glomerulosclerosis）
- D.膜性腎病變（membranous nephropathy）

- **4.下列抗體和疾病之間的致病機轉組合，何者錯誤？**
- A.anti-proteinase-3 antibodies and granulomatosis with polyangiitis
- B.anti-hyaluronidase antibodies and poststreptococcal glomerulonephritis
- C.anti-phospholipase A2 receptor antibodies and primary membranous glomerulonephritis
- D.anti-α5 NC1 domain of collagen IV antibodies and Goodpasture syndrome

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- C.anti-phospholipase A2 receptor antibodies and primary membranous glomerulonephritis
- D.anti-α5 NC1 domain of collagen IV antibodies and Goodpasture syndrome

23.一名30歲女性，近2個月血清肌酸酐從1.0升至3.0 mg/dL，其血清anti-neutrophil cytoplasmic抗體呈陰性反應，血清C3降低，C4正常，經腎臟切片檢查確定為新月型腎絲球腎炎，電鏡檢查發現有subepithelial electron-dense沉積，glomerular basement membrane厚度正常，下列診斷何者正確？

A.membranous nephropathy

B.membranoproliferative glomerulonephritis, type II

C.lupus nephritis

D.poststreptococcal glomerulonephritis

23.一名30歲女性，近2個月血清肌酸酐從1.0升至3.0 mg/dL，其血清anti-neutrophil cytoplasmic抗體呈陰性反應，血清C3降低，C4正常，經腎臟切片檢查確定為新月型腎絲球腎炎，電鏡檢查發現有subepithelial electron-dense沉積，glomerular basement membrane厚度正常，下列診斷何者正確？

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C.lupus nephritis

D.poststreptococcal glomerulonephritis

- 28.一位18歲男性大學新生，一星期前入學體檢報告正常。三天前參加新生盃籃球比賽後關節酸痛，自行購買止 痛藥(diclofenac)服用後開始出現小便泡沫與腳腫，故至門診求診。無嘔吐、腹瀉、發燒與頻尿症狀。理 學檢查發現:血壓160/90 mmHg，呼吸速率每分□ 20下，四肢出現紅疹，雙下肢4+水腫。血液檢查:尿素 氮(BUN)52 mg/dL、肌酸酐:2.0 mg/dL，白蛋白1.8 g/dL，白血球7,000/μL，血色素10.2 g/dL，膽固醇 320 mg/dL，三酸□ 油脂(triglyceride)260 mg/dL。尿液檢查:紅血球2~3顆/HPF，白血球3~5顆/HPF， 尿液總蛋白質與肌酸酐比值為12 g/g Cr。下列何項為最可能的診斷?
- A.hemolytic uremic syndrome B.minimal change disease C.rapidly progressive glomerulonephritis D.IgA nephropathy

- 28.一位18歲男性大學新生，一星期前入學體檢報告正常。三天前參加新生盃籃球比賽後關節酸痛，自行購買止 痛藥(diclofenac)服用後開始出現小便泡沫與腳腫，故至門診求診。無嘔吐、腹瀉、發燒與頻尿症狀。理 學檢查發現:血壓160/90 mmHg，呼吸速率每分□ 20下，四肢出現紅疹，雙下肢4+水腫。血液檢查:尿素 氮(BUN)52 mg/dL、肌酸酐:2.0 mg/dL，白蛋白1.8 g/dL，白血球7,000/μL，血色素10.2 g/dL，膽固醇 320 mg/dL，三酸□ 油脂(triglyceride)260 mg/dL。尿液檢查:紅血球2~3顆/HPF，白血球3~5顆/HPF， 尿液總蛋白質與肌酸酐比值為12 g/g Cr。下列何項為最可能的診斷?
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下列何種狀況不是使用angiotensin-converting enzyme（ACE）inhibitors的禁忌？

- A.腎功能持續惡化
- B.低血鉀
- C.懷孕
- D.雙側腎動脈狹窄

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- C.懷孕
- D.雙側腎動脈狹窄

一位70歲男性糖尿病患，長期服用glimepiride、metformin、acarbose、pioglitazone控制血糖。接受血管攝影4天 後，因意識不清被送至急診。抽動脈血液檢驗結果顯示代謝性酸中毒（pH 6.8、Pco2 39.3 mmHg、HCO3 - 6.2 mEq/L）、BUN 86 mg/dL、creatinine 6.8 mg/dL、Na + 135 mEq/L、K + 6.0 mEq/L、Cl - 90 mEq/L、glucose 131 mg/dL、lactic acid 26.6 mmol/L（參考值 0.5～2.2 mmol/L）、ketone body（negative）。其所服用的藥物中，何 者與此急性病變最具相關性？

- A. glimepiride
- B. metformin
- C. acarbose
- D. pioglitazone

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- C. acarbose
- D. pioglitazone

18歲男性病人，10天前喉嚨痛，當時血液肌酸酐1.0 mg/dL。最近4天有發燒、高血壓、少尿、水腫、運動性 呼吸困難。血液肌酸酐1.6 mg/dL，明顯的補體下降，尿液紅血球25～40/HPF，紅血球圓柱體（RBC cast）+，蛋白質1+。最不可能的診斷是：

- A.鏈球菌感染後之腎絲球腎炎（poststreptococcal glomerulonephritis）
- B.韋氏肉芽腫（Wegener’s granulomatosis）
- C.紅斑性狼瘡腎炎（lupus nephritis）
- D.心內膜炎（infective endocarditis）

18歲男性病人，10天前喉嚨痛，當時血液肌酸酐1.0 mg/dL。最近4天有發燒、高血壓、少尿、水腫、運動性 呼吸困難。血液肌酸酐1.6 mg/dL，明顯的補體下降，尿液紅血球25～40/HPF，紅血球圓柱體（RBC cast）+，蛋白質1+。最不可能的診斷是：

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- C.紅斑性狼瘡腎炎（lupus nephritis）
- D.心內膜炎（infective endocarditis）

巴特氏症候群（Bartter’s syndrome）的腎小管上皮細胞功能失調出現在：

- A.近端腎小管
- B.亨利氏環粗上升支
- C.遠端腎小管
- D.集尿小管

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- A.近端腎小管
- B.亨利氏環粗上升支
- C.遠端腎小管
- D.集尿小管

一位50歲無糖尿病男性，生化檢驗結果呈現血清肌酸酐 3.5 mg/dL，尿素氮40.1 mg/dL，估算之腎絲球過濾率 20 mL/min，白蛋白4.0 g/dL，血鉀4.1 mmol/L，血鈣2.05 mmol/L，血磷4.5 mg/dL，25(OH) vitamin D 10 ng/mL，intact parathyroid hormone 255 pg/mL。下列治療何者最優先？

- A.cinacalcet
- B.cholecalciferol
- C.calcitriol
- D.ergocalcitriol

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- A.cinacalcet
- B.cholecalciferol
- C.calcitriol
- D.ergocalcitriol

王先生為54歲男性，因IgA nephropathy進展至末期腎臟病，無其他過去病史。若要為王先生建議腎臟替代療 法，下列何種療法的長期（大於1年）存活率及生活品質最佳？

- A.血液透析（hemodialysis）
- B.腹膜透析（peritoneal dialysis）
- C.連續性靜脈對靜脈血液過濾術（continuous venovenous hemofiltration）
- D.腎臟移植（renal transplantation）

王先生為54歲男性，因IgA nephropathy進展至末期腎臟病，無其他過去病史。若要為王先生建議腎臟替代療 法，下列何種療法的長期（大於1年）存活率及生活品質最佳？

- A.血液透析（hemodialysis）
- B.腹膜透析（peritoneal dialysis）
- C.連續性靜脈對靜脈血液過濾術（continuous venovenous hemofiltration）
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35歲女性病患，體檢時發現血壓偏高。她主訴近2個月來覺得頭痛、全身無力和倦怠。理學檢查除了血壓高（160/100 mmHg）以外，並無特殊發現。血液檢驗發現血中肌酸酐（creatinine）1.1 mg/dL，鈉離子137 mmol/L，鉀離子 2.6 mmol/L，動脈血液氣體檢查發現代謝性鹼中毒（metabolic alkalosis），血清中腎素（renin）為0.04 ng/mL/hr（參考值，1～5 ng/mL/hr）；血中皮質醛酮濃度（plasma aldosterone concentration）為39.2 ng/dL（參考值，5～30 ng/dL）；血中腎上腺刺激素（adrenocorticotropin）為12 pg/mL（參考值，10～ 65 pg/mL）。此病患最有可能的診斷為何？

- A.腎動脈狹窄（renal artery stenosis）
- B.甲狀腺亢進（hyperthyroidism）
- C.原發性皮質醛酮症（primary aldosteronism）
- D.庫欣氏症候群（Cushing's syndrome）

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一位55歲男性兩天來嘔吐不止送至急診處。病人過去有十二指腸潰瘍，兩天前開始噁心嘔吐，但無腹痛或發 燒。身體診察，脈搏每分鐘118，血壓88/50 mmHg，無貧血或黃疸；胸腔和心臟正常，上腹部稍有壓痛但無 反彈疼痛，腸動聲稍減，血清電解質（mmol/L）：Na + 136，K + 2.9，Cl - 89。動脈氣體分析如下：pH 7.49， PaCO2 45 mmHg，PaO2 98 mmHg，HCO3 - 32 mEq/L。下列有關對此病人的敘述何者最為正確？

- A.尿液的氯離子應該<20mmol/L
- B.尿液的滲透壓應該<300mOsmo/kgH_2O
- C.血液的滲透壓應該<270mOsmo/kgH_2O
- D.尿液的鉀離子應該<10mmol/L

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承上題，下列那個處置最為適合此病人？

- A.給與5%葡萄糖水1000 mL + 20 mmol KCl
- B.給與0.45% NaCl 1000 mL + 20 mmol KCl
- C.給與0.9% NaCl 1000 mL + 20 mmolKCl
- D.給與lactated Ringer’s solution 1000 mL

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關於低血鉀（hypokalemia）的敘述，下列何者最正確？

- A.利尿劑spironolactone（Aldactone）是造成低血鉀症的原因
- B.輕度且穩定的低血鉀症病人，補充鉀離子應該以口服方式為主
- C.低血鉀症可能同時合併有高血鎂（hypermagnesemia）的情形
- D.建議補充氯化鉀加入含有葡萄糖溶液中，以利鉀離子儘快吸收

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下列何種檢驗對區分腹瀉或腎小管酸血症（renal tubular acidosis）引起正常陰離子隙代謝性酸中毒最具診斷價 值？

- A.尿陰離子隙（urine anion gap）
- B.血陰離子隙（blood anion gap）
- C.血鉀濃度
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56歲男性病人因意識不清至急診，身體診察發現呼吸22次/分鐘且深沉，初步血液檢查K + 4.6 mEq/L、Na + 138 mEq/L、Cl - 99 mEq/L、HCO3 - 10 mEq/L，動脈血氣分析呈現pH 7.20、pCO2 22 mmHg，此病人最不可能的診 斷為：

- A.乳酸酸血症（lactic acidosis）
- B.酮酸血症（ketoacidosis）
- C.急性腹瀉
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65歲女性病人糖尿病已15年，1個月前血中肌酸酐（creatinine）為1.1 mg/dL，3天前開始咳嗽有痰、發燒、呼 吸困難、急促，今日意識不清、發燒持續，送至急診，血壓130/70 mmHg，身體診察右下胸有濁音，胸部X光 呈現右下肺浸潤病灶，血中白血球16,580 /μL、血中肌酸酐8.5 mg/dL、血中鉀離子6.5 mEq/L、HCO3 - 12 mEq/L，則病人此時最不適合接受何種治療？

- A.連續性靜脈血液過濾術（continuous venovenous hemofiltration）
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一名63歲有高血壓的女性病患經體外碎石後確診為草酸鈣結石，下列何項措施無法預防結石復發？

- A.喝水保持尿量＞2 L/day
- B.限制飲食鹽分攝取
- C.改用thiazide為降壓藥
- D.減少飲食鈣量攝取

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下列有關腎因性全身纖維化（nephrogenic fibrosing dermopathy）的敘述，何者錯誤？

- A.與使用gadolinium有關，病症類似scleromyxedema
- B.CKD第3期仍可減量使用gadolinium
- C.肝臟疾病是罹患此症的危險因子
- D.血液透析無法清除gadolinium

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關於急性腎損傷（acute kidney injury）的治療方式，下列何者錯誤？

- A.針對急性腎損傷的治療原則，目前以支持性療法為主
- B.可使用等張生理食鹽水來預防顯影劑造成之急性腎損傷
- C.急性腎損傷若併發高血鉀症，應停用血管張力素轉化酶抑制劑（ACEi）或血管張力素II型受體拮抗劑（ARB）
- D.羥乙基澱粉溶液（hydroxyethyl starch）可有效改善低血容積引發之急性腎損傷

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63歲女士因背痛服用diclofenac持續半年，因下肢水腫至門診求診，最近無噁心、嘔吐及腹瀉。身體診察查： 血壓126/66 mmHg，心跳每分鐘74下，雙側下肢水腫程度1+。血液檢查：白血球7,900/μL，血色素10.9 g/dL， 血小板282,000/μL，球蛋白3.9 g/dL，白蛋白3.0 g/dL，尿素氮12 mg/dL，肌酸酐0.63 mg/dL，血糖84 mg/dL， 乳酸去氫酶（LDH）288 U/L（正常值131～250 U/L），尿酸9.7 mg/dL，鈉離子136 mEq/L，鉀離子4.2 mEq/L，膽固醇260 mg/dL，三酸甘油脂80 mg/dL，低密度膽固醇175 mg/dL。尿液試紙檢查：尿蛋白陰性，尿 比重1.015，尿液沉渣無紅血球或白血球。尿液總蛋白質與肌酸酐比值為4.907克/克肌酸酐。下列有關此位病 患之敘述，何者正確？

- A.病患蛋白尿的原因可能是非類固醇抗發炎藥（NSAID）造成
- B.檢anti-phospholipase A2 receptor 抗體有助診斷病因
- C.檢測血清免疫電泳（immunoelectrophoresis）有助診斷病因
- D.此病患首選治療為低劑量血管張力素II型受體拮抗劑

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50歲女性，每日尿量5公升，限水測試後，尿滲透壓並無變化，每小時尿量並未減少。5小時後，靜脈注射 desmopressin acetate 2 μg，尿滲透壓上升，每小時尿量減少。下列何者是此病人最適當的診斷？

- A.原發性多飲症（primary polydipsia）
- B.滲透性利尿（osmotic diuresis）
- C.中樞性尿崩症（central diabetes insipidus）
- D.腎性尿崩症（nephrogenic diabetes insipidus）

50歲女性，每日尿量5公升，限水測試後，尿滲透壓並無變化，每小時尿量並未減少。5小時後，靜脈注射 desmopressin acetate 2 μg，尿滲透壓上升，每小時尿量減少。下列何者是此病人最適當的診斷？

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