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Nephrology and Hypertension

Board Review

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Wolters Kluwer

Nephrology and Hypertension Board Review

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Preface

A practicing nephrologist is expected to have a firm grasp of a large array of potentially life-threatening electrolyte and acid–base disturbances, a multitude of acquired and inherited kidney diseases, acute kidney injuries, complex chronic kidney disease–related metabolic, endocrinologic, skeletal/mineral, and cardiovascular complications, difficult-to-treat hypertension, kidney stones, all forms of renal replacement therapy including kidney transplantation, among many other topics.

Mastering the wide knowledge base and current literature required for the routine practice of nephrology can be a difficult task, particularly for those working in hectic private settings.

We intended to write this book as an abbreviated review for renal fellows and general nephrologists who have limited time to study for the nephrology board certifying examination or who simply wish to review and update their nephrology knowledge. The content presented herein closely reflects the American Board of Internal Medicine blueprint outlined for the Nephrology Certifying Examination.

In honor of our most loving and supportive parents, we direct all proceeds from this book to the Pham Family Patient Assistance Fund, created in September 2015, to help financially challenged patients pay for basic fees while seeking medical care.

Phuong-Chi T. Pham and Phuong-Thu T. Pham

Abbreviations

Na^+_e; K^+_e: exchangeable Na^+; exchangeable K^+
[HCO_3^-]: serum bicarbonate concentration
a.k.a.: also known as
Ab–Ag: antibody–antigen complex
ACC/AHA: American College of Cardiology/American Heart Association
ACEI: angiotensin-converting-enzyme inhibitor
ACKD: acquired cystic kidney disease
ACR: acute cellular rejection
ACS: acute compartment syndrome
ACTH: adrenocorticotropic hormone
AD: autosomal dominant
ADAMST13: a disintegrin and metalloproteinase with a thrombospondin type 1 motif
ADH: antidiuretic hormone
ADHF: acute decompensated heart failure
AE-1: anion exchanger I
AER: albumin excretion ratio
AFLP: acute fatty liver of pregnancy
AG: anion gap
AGE: advanced glycosylated end product
AGE:RAGE: advanced glycosylated end-product interaction with AGE receptor
aHUS: atypical hemolytic uremic syndrome
AII: angiotensin II
AKI: acute kidney injury
AKIN: Acute Kidney Injury Network
ALT: alanine aminotransferase
AME: apparent mineralocorticoid excess
AMR: acute antibody-mediated rejection
ANCA: antineutrophil cytoplasmic antibody
ANP: atrial natriuretic peptide
APP: abdominal perfusion pressure
APS: antiphospholipid syndrome
AQP: aquaporin
AR: autosomal recessive
ARB: angiotensin-receptor blocker
ARDS: acute respiratory distress syndrome
ARR: aldosterone–renin ratio
AST: aspartate aminotransferase
ATIN: acute tubulointerstitial nephritis
ATN: acute tubular necrosis
ATP: adenosine triphosphate
AV: atrioventricular
AVF: arteriovenous fistula
AVG: arteriovenous graft
AVN: avascular necrosis
AVP: vasopressin
AVR: vasopressin receptor
AVS: adrenal venous sampling
AZA: azathioprine
BKN: BK nephropathy
BMI: body mass index
BP: blood pressure
BUN: blood urea nitrogen
CA: cancer
CABG: coronary artery bypass grafting
CAD: coronary artery disease
CAII: carbonic anhydrase II
CAIV: carbonic anhydrase IV
CAPD: continuous ambulatory peritoneal dialysis
CaSR: calcium-sensing receptor
CCB: calcium channel blocker
CCT: cortical collecting tubule
CDC: complement-dependent cytotoxicity
cDI: central diabetes insipidus
CHF: congestive heart failure
CI-AKI: contrast-induced acute kidney injury
CKD: chronic kidney disease
CKD-EPI: chronic kidney disease epidemiology collaboration
CMV: cytomegalovirus
CNI: calcineurin inhibitor
CNS: central nervous system
CO: cardiac output
COPD: chronic obstructive pulmonary disease
C_{OSM}: osmolar clearance
CPK: creatine phosphokinase

cPRA: calculated cytotoxicity panel of reactive antibodies
CR: complete remission
CrCl: creatinine clearance
CRRT: continuous renal-replacement therapy
CRS: cardiorenal syndrome
CSA: cyclosporine
CSW: cerebral salt wasting
CT: computed tomogram
CTG: chronic transplant glomerulopathy
CTIN: chronic tubulointerstitial nephritis
CTLA-4: cytotoxic T-lymphocyte–associated antigen-4
CVD: cardiovascular disease
CVP: central venous pressure
CVVH or CAVH: continuous venovenous (or arteriovenous) hemofiltration
CVVHDF: continuous venovenous hemodiafiltration
CYC: cyclophosphamide
D5: 5% dextrose solution
DBP: diastolic blood pressure
DCT: distal convoluted tubule
DDAVP: desmopressin acetate
DDD: dense deposit disease
DEXA: dual energy X-ray absorptiometry
DGF: delayed graft function
DHP: dihydropyridine
DI: diabetes insipidus
DIC: disseminated intravascular coagulation
DKD: diabetic kidney disease
DM: diabetes mellitus
DOPPS: dialysis outcomes and practice patterns study
DR: diabetic retinopathy
dRTA: distal renal tubular acidosis
DSA: donor-specific antibodies
DVT: deep vein thrombosis
EBV: Epstein–Barr virus
ECG: electrocardiogram
EF: ejection fraction
EFWC: electrolyte-free water clearance
EGF: epithelial growth factor
eGFR: estimated glomerular filtration rate
eKT/V: equilibrated KT/V
EM: electron microscopy
ENaC: sodium epithelial channel
EPO: erythropoietin
ESA: erythropoiesis-stimulating agent
ESRD: end-stage renal disease
ESWL: extracorporeal shock-wave lithotripsy
ET: endothelin
EVAR: endovascular aortic aneurysm repair
FBS: fasting blood sugar
$FeHCO_3$: fractional excretion of bicarbonate
FeMg: fractional excretion of magnesium
FeNa: fractional excretion of sodium
$FePO_4$: fractional excretion of phosphate
FeUrea: fractional excretion of urea
FGF-23: fibroblast growth factor 23
FHH: familial hyperkalemic hypertension (Gordon) or familial hypocalciuric hypercalcemia
FIO_2: fraction of inspired oxygen
FLC: free light chain
FMD: fibromuscular dysplasia
FSGS: focal segmental glomerulosclerosis
FWC: free water clearance
GBM: glomerular basement membrane
GFR: glomerular filtration rate
GI: gastrointestinal
GN: glomerulonephropathy
GRA: glucocorticoid remediable aldosteronism
GU: genitourologic
HAART: highly active antiretroviral therapy
hANP: human atrial natriuretic peptide
Hb: hemoglobin
HbA1C: hemoglobin A1C
HBV: hepatitis B virus
HCTZ: hydrochlorothiazide
HCV: hepatitis C virus
HD: hemodialysis
HDL: high-density lipoproteins
HELLP: hemolysis, elevated liver enzymes, low platelets syndrome of pregnancy
HF: heart failure
HIT: heparin-induced thrombocytopenia
HIV: human immunodeficiency virus
HLA: human leukocyte antigen
HMGCoA: hydroxymethylglutaryl-CoA
HPF: high power field
hPTH: hyperparathyroidism
HR: hazard ratio
HRS: hepatorenal syndrome
HSP: Henoch–Scholein purpura
HSS: hypertonic saline
HTN: hypertension
HUS: hemolytic uremic syndrome
IAH: intra-abdominal hypertension
IAP: intra-abdominal pressure
IC: immune-complex
ICP: intracranial pressure
ICU: intensive care unit
IDH: isolated diastolic hypertension
IDWG: interdialytic weight gain
IF: immunofluorescent microscopy
IgAN: IgA nephropathy
IGIV: intravenous immunoglobulin

iMGN: idiopathic membranous glomerulonephropathy
INR: prothrombin time/international normalized ratio.
IRRT: intermittent renal-replacement therapy
ISH: isolated systolic hypertension
IV: intravenous
IVC: inferior vena cava
KDIGO: kidney disease: improving global outcomes organization
KDOQI: kidney disease outcomes quality initiative
LDH: lactate dehydrogenase
LDL: low-density lipoproteins
LM: light microscopy
LN: lupus nephritis
LVEAD: left ventricular end diastolic area
MAG3: mercaptoacetyltriglycine (used in nuclear renal scanning)
MAHA: microangiopathy ad hemolytic anemia
MAP: mean arterial pressure
MARS: molecular adsorbent recycling system
MBD: mineral bone disease
MCD: minimal change disease
MDRD: modification of diet in renal disease study
MELD: model for end-stage liver disease
MFI: mean fluorescence intensity
MGN: membranous glomerulonephropathy
MHC: major histocompatibility complex
MM: multiple myeloma
MMF: mycophenolate mofetil
MPA: mycophenolic acid
MPGN: membranoproliferative glomerulonephropathy
MPO: myeloperoxidase
MRA: mineralocorticoid-receptor antagonist
MRI: magnetic resonance imaging
mTOR: mammalian target of rapamycin
NBC: sodium bicarbonate cotransporter
NCC: sodium chloride cotransporter
nDI: nephrogenic diabetes insipidus
NE: norepinephrine
NFAT: nuclear factor of activated T cells
NHE3: sodium–hydrogen exchanger 3
NODAT: new-onset diabetes mellitus after transplant
NOS: not otherwise specified
NPT: sodium–phosphate transporter
NS: normal saline
NSAIDS: nonsteroidal anti-inflammatory drugs
NSF: nephrogenic systemic fibrosis
NSIAD: Nephrogenic syndrome of inappropriate antidiuresis
NT-proBNP: N-terminal of the prohormone brain natriuretic peptide
ODS: osmotic demyelinating syndrome
OGTT: oral glucose tolerance test
OPTN/UNOS: Organ Procurement and Transplantation Network/United Network of Organ Sharing
P[K^+]: plasma potassium
P[Na^+]: plasma sodium concentration
PA: pulmonary artery
PAI-I: plasminogen-activating-factor inhibitor
PAN: polyarteritis nodosa
PAoP: pulmonary arterial occlusion pressure
PaO_2: arterial partial pressure
PCR: polymerase chain reaction
PCR: protein-to-creatinine ratio
PD: peritoneal dialysis
PDG: phosphate-dependent glutaminase
PEEP: positive end–expiration pressure
PEPCK: phosphoenolpyruvate carboxykinase
PGL: paraganglioma
PGNMID: proliferative glomerulonephropathy with monoclonal Ig deposits
PH: primary hyperoxaluria
PHA: pseudohypoaldosteronism
PHEO: pheochromocytoma
PMN: polymorphonuclear leukocytes
POSEIDON trial: left ventricular end-diastolic pressure–guided fluid administration among patients undergoing cardiac catheterization trial
PPAR: peroxisome proliferator-activated receptor
PPV: pulse pressure variation
PR: partial remission
PR3: proteinase 3
PRA: cytotoxicity panel-reactive antibodies
PRA: plasma renin activity
PRCA: pure red cell aplasia
PRES: reversible posterior leukoencephalopathy syndrome
pRTA: proximal renal tubular acidosis
PTF: pentoxifylline
PTH: parathyroid
PTHrp: parathyroid hormone–related peptide
PTLD: posttransplant lymphoproliferative disease
PTRA: percutaneous transluminal renal angioplasty

PTT: activated prothrombin time
PVR: peripheral vascular resistance
RAAS: renin–angiotensin–aldosterone system
RBC: red blood cells
RCC: renal cell carcinoma
RIFLE: risk, injury, failure, loss of kidney function classification of acute kidney injury, and end-stage renal disease
ROMK: renal outer medullary kidney channel
RRT: renal-replacement therapy
RTA: renal tubular acidosis
RUA: routine urinalysis
S[K^+]: serum potassium
S[Na^+]: serum sodium concentration
SAG: serum anion gap
SBP: systolic blood pressure
SCa: total serum calcium
SCD: sickle cell disease
SCr: serum creatinine
SCUF: slow continuous ultrafiltration
$SCvo_2$: central venous oxygen saturation
sFLt1: soluble fms-like tyrosine kinase 1
SGLT2: sodium–glucose cotransporter 2
SIADH: syndrome of inappropriate secretion of antidiuretic hormone
SLE: systemic lupus erythematosus
SLEDD: sustained low-efficiency daily dialysis
SNAT3: sodium-dependent amino acid transporter
SNS: sympathetic nervous system
SOG: serum osmolality gap
S_{OSM}: serum osmolality
SPEP: serum protein electrophoresis
S_{PO_4}: serum phosphate concentration
SRC: scleroderma renal crisis
SSRI: serotonin reuptake inhibitors
SVR: systemic vascular resistance
SV: stroke volume
SVV: stroke volume variation
t½: half-life
TAC: tacrolimus
TB: tuberculosis
TBM: tubular basement membrane
TBMN: thin basement membrane nephropathy
TEB: thoracic electrical bioimpedance
TG: triglycerides
TGF: tumor growth factor
TIPS: transjugular intrahepatic portosystemic shunt
TLS: tumor lysis syndrome
TMP: transmembrane pressure
TRALI: transfusion-related acute lung injury
TRIM: transfusion-related immunomodulation
TRPV5: transient receptor potential cation channel, subfamily V, member 5
TSAT: serum transferrin saturation
TTP: thrombotic thrombocytopenic purpura
TZD: thiazolidinedione
U[K^+]: urine potassium concentration
U[Na^+]: urine sodium concentration
UCreat: urine creatinine concentration
UF: ultrafiltration
$U_{GLUCOSE}$: urine glucose concentration
U_{OSM}: urine osmolality
uPCR: urine protein-to-creatinine ratio
UPEP: urine protein electrophoresis
U_{PO_4}: urine phosphate concentration
URR: urea-reduction ratio
UT: urea transporter
U_{UREA}: urine urea concentration
Vd: volume of distribution
VDRA: vitamin D-receptor agonist
VEGF: vascular endothelial growth factor
VZV: varicella zoster
WBC: white blood cells
WCH: white coat hypertension
WNK: with-no-lysine kinase
WRN: warfarin-related nephropathy
XO: xanthine oxidase

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Contents

1 Sodium/Water 1
Phuong-Chi T. Pham and Phuong-Thu T. Pham

2 Acid–Base/Potassium 29
Phuong-Chi T. Pham and Phuong-Thu T. Pham

3 Calcium, Phosphorus, Magnesium, and Kidney Stones 61
Phuong-Chi T. Pham, Monica S. Deshmukh, and Phuong-Truc T. Pham

4 Chronic Kidney Disease 100
Golriz Jafari, Phuong-Thu T. Pham, and Phuong-Chi T. Pham

5 Hypertension 151
Phuong-Mai T. Pham, Cynthia C. Nast, Son V. Pham, and Phuong-Anh T. Pham

6 Tubular, Interstitial, and Cystic Disorders 185
Phuong-Chi T. Pham, Monica S. Deshmukh, and Cynthia C. Nast

7 Glomerular/Vascular Diseases 217
Phuong-Chi T. Pham, Cynthia C. Nast, Jeffrey M. Miller, and Phuong-Thu T. Pham

8 Kidney Transplantation 286
Phuong-Thu T. Pham, Jennifer Q. Zhang, and Cynthia C. Nast

9 Pharmacology 334
Anita Kamarzarian, Phuong-Mai T. Pham, Phuong-Thu T. Pham, and Phuong-Chi T. Pham

10 Acute Kidney Injury/ICU Nephrology 355
Phuong-Chi T. Pham, Cynthia C. Nast, Phuong-Anh T. Pham, and Son V. Pham

Core Resources and Selected Readings 389

Index 394

CHAPTER 1

Sodium/Water

Phuong-Chi T. Pham and Phuong-Thu T. Pham

HYPONATREMIA

Background

- Plasma sodium concentration (P[Na^+]) refers to [Na+] in the plasma in vivo or in the plasma of anticoagulated blood ex vivo. Serum sodium concentration (S[Na^+]) refers to [Na+] measured in the serum of coagulated blood ex vivo. P[Na+] and S[Na^+] are often used interchangeably. Hyponatremia is typically defined as having S[Na^+] < 136 mEq/L.
- Clinical significance of hyponatremia:
  - Increased mortality
  - Impaired attention, mentation slowing even with mild hyponatremia
  - Predictor of hepatorenal syndrome (HRS), hepatic encephalopathy, and death in patients with liver disease
  - Increased risks for osteoporosis, gait instability, fall, and fracture
  - Associated with marked bone loss, myocardial fibrosis, and evidence of early senescence in rats
- The early Edelman equation predicts P[Na^+] as follows:

$$P[Na^+] = 1.11 \times (Na^+_e + K^+_e)/(\text{total body water}) - 25.6,$$

where ($Na^+_e + K^+_e$) represents the sum of total body *exchangeable* Na^+ and K^+ and the *constant 25.6* represents the pool of *osmotically inactive* Na^+ and K^+ (e.g., *"inexchangeable" Na^+ and K^+ sequestered in bones, nonfluid phase*).

- The Edelman equation indicates that disorders of water balance can cause changes in P[Na^+]. Indeed, "sodium disorders" typically reflect disorders of water balance.
- Note that body fluid tonicity = plasma tonicity = cell tonicity. Cell tonicity reflects plasma tonicity. Any change in plasma tonicity leads to a matching change in cell tonicity via free water shift, thus cell volume. Essentially, plasma tonicity determines cell volume.
- In acute hyponatremia, free water shifts into brain cells causing brain swelling. Severe neurologic complications and death can ensue due to the confinement of the brain within the skull.
- Two major determinants of body tonicity: antidiuretic hormone (ADH), a.k.a. arginine vasopressin and thirst
- Arginine vasopressin (AVP):
  - Synthesized in the paraventricular neurons of hypothalamus as pre-pro-AVP and proteolytically cleaved into vasopressin (a.k.a. ADH), neurophysin II, and *copeptin*. These molecules are stored in secretory granules in the posterior

pituitary and released upon osmotic (e.g., hyperosmolality) and nonosmotic stimuli (e.g., volume depletion, stress, drug-induced, nausea, etc.).
  - ADH may be seen as a "pituitary bright spot" or hyperintense T1 signal within the posterior pituitary on brain MRI. The loss of this "pituitary bright spot" is consistent with the lack of ADH, thus central diabetes insipidus (cDI).
- *Copeptin* as a surrogate for ADH:
  - Blood levels of copeptin are more easily measured than ADH (greater stability than ADH) and have been suggested to be a good ADH surrogate.
  - Copeptin levels have been shown parallel to ADH levels in various clinical settings, including increased levels in heart failure (HF), syndrome of inappropriate ADH secretion (SIADH), and sepsis, and reduced levels in cDI.
  - Copeptin level has been shown to increase earlier than troponin in acute myocardial infarction and has been suggested to be used as an early marker for its diagnosis.
  - Copeptin measurement is not yet commercially available in the United States.

Clinical Manifestations

- Risk and severity of neurologic effects depend on the degree and rate of change of $S[Na^+]$.
- Mild: $S[Na^+] \geq 125$ mEq/L: usually asymptomatic to minimally symptomatic
- Moderate: lethargy, headaches, nausea/vomiting, disorientation, muscle cramps, reduced reflexes
- Severe: hyponatremic encephalopathy, seizures, coma, respiratory arrest, brain stem herniation, death

Broad Categorization of Hyponatremia

- Pseudohyponatremia:
  - Refers to falsely low-measured $S[Na^+]$. Flame photometric assay is an old method used to detect sodium content via intensity of flame color divided by serum volume. In patients with falsely elevated serum volume due to space-occupying paraproteins or lipids, the $S[Na^+]$, defined as sodium content ÷ serum volume, will be falsely low. Newer methods of measuring $S[Na^+]$ are now widely used to avoid pseudohyponatremia:
    - Ion-specific electrodes which measure $S[Na^+]$ directly from the serum
    - Supracentrifugation of serum to remove paraproteins/lipids prior to measuring $S[Na^+]$
  - Conditions with falsely high plasma volume leading to "pseudohyponatremia":
    - Severe hyperlipidemia
    - Hyperparaproteinemia (multiple myeloma, Waldenstrom macroglobulinemia)
- Hyponatremia due to extracellular free H_2O shift with osmotically active agents:
  - Hyperglycemia
  - Hypertonic mannitol
  - Sucrose, maltose (mixed in intravenous IgG solutions)
- True hyponatremia: truly low Na^+ content per unit volume, due to increased free water retention, excessive Na^+ loss, or both leading to a hypoosmolar state

Differential Diagnoses of True Hyponatremia

Hypovolemic hyponatremia:

- Appropriate increase in ADH secretion + high H_2O intake + increase renal salt reabsorption (Table 1.1):
  - Bodily fluid loss, chronic diuretics (thiazides), third-spacing

  - Typical presentation: hypovolemia, urine Na^+ concentration (U[Na^+]) < 20 mEq/L (unless poor kidney function with inability to maximally reabsorb Na^+), urine osmolality (U_{OSM}) typically >300 mOsm/kg
- Renal salt wasting → volume depletion → appropriate increase in ADH secretion + high H_2O intake:
  - Acute, recent diuretic use
  - Mineralocorticoid insufficiency
  - Cerebral salt wasting (CSW)
  - Typical presentation: hypovolemia, U[Na^+] > 20 to 30 mEq/L, U_{OSM} typically >300 mOsm/kg

Euvolemic hyponatremia:

- ADH-dependent, but ADH secretion is inappropriate (i.e., ADH is not secreted in response to volume loss or hyperosmolar state):
  - SIADH: central nervous system (CNS) or pulmonary pathology, drugs affecting CNS, antipsychotics, antiepileptics, antidepressants, nonsteroidal anti-inflammatory drugs (NSAIDS), cyclophosphamide, acute pain, nausea/vomiting, symptomatic HIV
  - Severe hypothyroidism (myxedema coma or thyroid-stimulating hormone > 50 mIU/mL) → reduced cardiac output, peripheral vascular resistance, and renal perfusion → ↑ADH secretion

Table 1.1 Differential diagnoses of true hyponatremia

	ADH-Dependent U_{OSM} > 100–150 mOsm/kg		ADH-Independent Variable U_{OSM}	
	Appropriate ADH secretion	Inappropriate or dysregulated ADH secretion	U_{OSM} < 100 mOsm/kg	U_{OSM} > 100 mOsm/kg
Sodium retention U[Na+] < 20 mEq/L	Chronic thiazides Bodily fluid losses Third-spacing Mineralocorticoid deficiency	SIADH + low salt intake Congestive heart failure Cirrhosis Nephrotic syndrome		Nephrogenic SIAD + low salt intake
No sodium retention U[Na+] > 30 to 40 mEq/L	Mineralocorticoid deficiency Renal salt wasting Recent diuretic use Bodily fluid loss + poor kidney function Cerebral salt wasting	SIADH + normal salt intake Hypocortisolism Severe hypothyroidism		Kidney failure (U_{OSM} is typically ~300 mOsm/kg) Nephrogenic SIAD + normal salt intake
Variable sodium excretion: Diet-dependent	Pregnancy (physiologically appropriate—see text)		Polydipsia Low solute intake Hypotonic fluids	
			Reset osmostat	

- Hypocortisolism → ↑synthesis of corticotropin-releasing hormone, which is co-expressed with ADH, hence ↑ADH
- Pregnancy: reduced threshold for ADH secretion + increased thirst
- Typical presentation for all conditions associated with "inappropriate" ADH secretion above: euvolemia, $U[Na^+] > 30$ to 40 mEq/L (on normal dietary water and sodium intake), $U_{OSM} > 100$ mOsm/kg, low serum uric acid. NOTE: In the presence of hyponatremia, the kidneys are expected to maximally dilute the urine to <100 mOsm/kg. Any urine osmolality > 100 mOsm/kg indicates suboptimal urine dilution, which implies either presence of ADH or poor kidney function.
- For the diagnosis of SIADH: In addition to typical presentation above, hypothyroidism, hypocortisolism, diuretic use (particularly thiazides), and renal insufficiency must also be ruled out.

- ADH-independent:
  - Reset osmostat: normal variant (lower osmotic threshold for ADH release), hypothalamic injury, malnutrition. Urine sodium and osmolality vary according to volume status and serum osmolality (S_{OSM}).
  - Primary polydipsia (psychogenic polydipsia – psychiatric patients +/– phenothiazines with associated dry mouth, hypothalamic infiltrative disease such as sarcoidosis affecting thirst center)
  - Tea and toast syndrome, beer potomania: insufficient solute intake to provide the necessary solute load required by kidneys to excrete water. Kidneys cannot excrete pure free water. Kidneys need a minimum of 50 to 100 mOsm of solute to excrete every 1 L of water (i.e., maximal diluting capacity of healthy kidneys is typically 50 to 100 mOsm/kg).
  - Increase H_2O absorption from the use of irrigation fluids with various procedures (transurethral resection, hysteroscopy, nephrolithotomy):
    - Hypoosmotic 1.5% glycine solution, osmolality = 200 mOsm/kg. Of interest, the use of >1.5 to 2.0 L of 1.5% glycine solution may also directly stimulate ADH.
    - Hypoosmotic 3% sorbitol, osmolality = 165 mOsm/kg. Sorbitol is metabolized to glucose + fructose in liver, then to CO_2 and H_2O.
    - Isoosmotic 5% mannitol, osmolality = 275 mOsm/kg. 5% mannitol solution usually does not cause hyponatremia because it is isotonic to plasma.
  - Typical presentation for all ADH-independent conditions above: euvolemia, $U[Na^+]$ variable depending on sodium intake; $U_{OSM} < 100$ to 150 mOsm/kg.
  - Constitutively activated ADH-receptor without presence of ADH: Nephrogenic syndrome of inappropriate antidiuresis (NSIAD). Not to be confused with SIADH
    - X-linked gain of function mutation of vasopressin 2 (AVP2) receptor
    - Clinically, patients resemble those with SIADH, but no stimulus for the ADH secretion is found and plasma ADH level is undetectable (in contrast to SIADH where ADH levels are high). In SIAD, the ADH receptor is activated without actual ADH binding. Diagnosis of SIAD is possible in older age (e.g. 70's).
    - Typical presentation: similar to SIADH, except ADH level is undetectable
    - Diagnosis requires sequencing of the *AVP2* receptor gene.
    - Carriers of the mutation have abnormal response to water-loading test.

Hypervolemic hyponatremia:

- ADH-dependent: dysregulated continuing ADH secretion due to conditions associated with reduced effective circulating volume (e.g. heart failure, cirrhosis, nephrotic syndrome)
- ADH-independent: kidney failure with poor diluting capacity.