# WATER METABOLISM: Made easier

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## INTRODUCTION:

Water is important to our health and makes up approximately two-thirds of our body by weight. Physicians often find this subject intimidating and difficult to comprehend, because most teachers teach it poorly. On clinical rotations and ward rounds, we have taught our students and residents to remember lists of facts, protocols for diagnosis and treatment, and "check their minds at the door". Systems integration is often ignored. Detailed physiologic facts are studied without understanding the "big picture". In reality, you learned most of what you needed to know about water metabolism by the end of second year medical school. By understanding basic principles of normal water metabolism and solute balance along with how diseases interfere with normal health, you can rationally deduce differential diagnosis, diagnostic strategy, and therapeutic management. I purposefully try and keep this discussion focussed on major principles, and highly admire the basic scientists and clinicians that have contributed to this subject. Students are encouraged to review major textbooks, review articles and recent articles.[1-3]

## CAN YOU MEASURE WATER?

How is water content and distribution measured? Patients with hyponatremia or hypernatremia have an imbalance of water, but the sodium concentration simply indicates that there is an abnormal concentration of sodium. It tells us nothing about the total amount of water in the body. We cannot send a blood sample to the lab for "water". Osmolality measures the solute concentration per kg, and is an indirect indicator of the "concentration" of water. Measuring total water content of the body can be done by expensive and/or time consuming research methods, but simple bedside examination is more practical.

## FLUID COMPARTMENTS

Don't fall asleep or click to a new web-site yet – this is critical! About two thirds of the body is water. Two thirds of the water is intracellular and one third is extracellular. Two thirds of the extracellular water is interstitial and one third is intravascular. What determines the volume of the different fluid compartments? (Hint – it is NOT water) Fluid compartment volume is determined by the content of the major solute in each compartment. What are the major solutes? Potassium and magnesium are the major intracellular solutes. Sodium is the major extracellular solutes. Serum protein is the additional "solute" of the intravascular component. The body controls the content of each fluid compartment by regulating the amount of each major solute.

For all practical purposes, water is in equilibrium among all of the fluid compartments. If the osmolality changes in any of the compartments, water will redistribute among compartments until osmolality equilibrates. Testing the osmolality in plasma estimates osmolality of all body fluid compartments.

## EXTRACELLULAR FLUID COMPARTMENT CONTROL

The normal human is beautifully designed for regulating extracellular fluid volume by regulating body sodium content. (Here's the part that explains why nephrologists are so rabid about distinguishing volume depletion from dehydration. "Volume depletion" means extracellular volume depletion. Let's say that a patient with volume depletion presents after 48 hours of diarrhea, 10-pound weight loss, tachycardia, hypotension, "tilt" positive, normal serum sodium and plasma osmolality (Posm), and concentrated urine. Clinicians often mislabel this condition "dehydration", but all of you Greek scholars out there will know that "de" "hydro" means "lack of" and "water", and should be applied to patients presenting with hypernatremia. Hyponatremic patients, unless they are severely water and sodium depleted, are usually "hyperhydrated". OK, back to extracellular sodium regulation.

Your body has two major systems for balancing sodium content – the "affector" and "effector" systems. The affector (or sensing) system monitors whether there is too much, too little, or just the right content of sodium. It does this through the baroreceptors in the aortic arch, carotid arteries, atria, brain, and liver. If the sodium content is incorrect, the effector systems go to work. The renin-angiotensin-aldosterone, catecholamine, and vasopressin systems increase blood pressure and sodium retention. The atrial natriuretic peptide (ANP) system causes renal sodium loss. When you first examine a patient with hyponatremia and get initial lab tests, you are attempting to estimate the extracellular fluid volume and status of the extracellular effector systems. Two patients, one with diuretic abuse and another with cardiogenic shock will both be tachycardic, sweaty, pale, and tremulous indicating that their catecholamine system is turned on. The same two patients will often have low urine sodium concentration, high urinary potassium, acid urine, hypokalemia, and hypochloremic metabolic alkalosis indicating that the renin-angiotensin-aldosterone system is active. Finally, hyponatremia in both cases indicates that the vasopressin system is active independent of plasma osmolality. In the patient with diuretic abuse, the effector system is turned on "appropriately" due to true volume depletion. In the case of cardiogenic shock, the effector system is turned on "inappropriately" due to cardiac disease disrupting the normal extracellular volume sensing system.

## BASIC WATER BALANCE

Now let's turn our attention to how the body normally handles water. Most cells and biological systems seem to work best within a narrow range of Posm. Normal Posm is 286 - 294 mOsm/kg. Three major systems are required to work properly: a) normal vasopressin (VP) production and release, b) a kidney that responds normally to VP, and c) normal thirst and water intake. Let's review each of these three systems.

## VASOPRESSIN (VP)

The supraoptic nuclei and paraventricular nuclei are clusters of magnocellular neuron nuclei located in the hypothalamus. These highly specialized neurons produce vasopressin (also called antidiuretic hormone or ADH). After transcription and translation, VP is packaged into vesicles and travels to the neuron endings located in the posterior pituitary and pituitary stalk. The vesicles release VP into the circulation normally due to increasing Posm. Non-osmotic stimuli for VP release include severe volume depletion, nausea, and pain. The "osmostat" is a poorly understood structure closely associated with the magnocellular neurons that acts like a thermostat, except it responds to osmolality instead of temperature. When Posm increases, the osmostat signals the magnocellular neurons to release VP, and when Posm decreases, the osmostat signals the magnocellular neurons to reduce VP release. Hyponatremia and hypernatremia can occur when either VP production or release is altered. If the majority of VP producing cells is damaged, central diabetes insipidus can occur with polyuria, dilute urine, polydipsia, and high normal Posm. Patients with Syndrome of Inappropriate ADH (SIADH) release VP into the circulation when they should not. Normally in pregnancy, the threshold for VP release and thirst is shifted to the left causing lower serum sodium than when the patient is not pregnant.

**THIRST**

Thirst is one of the most poorly understood parts of water balance. The thirst center is separate, but closely associated with the magnacellular neurons and the osmostat. Normally, it stimulates the sensation of thirst when Posm increases. Habit, medications, emotions, and culture also affects thirst. The threshold for thirst is "to the right" of the threshold for VP release. If it were reversed, you would spend your day in the bathroom and at the water fountain. When you think about it, patients with hyponatremia must have two disorders – one involving a reduced ability to excrete a water load (usually due to VP being present when it should not be) and the second being an abnormally set thirst threshold. I use as example anephric dialysis patients. Although they have a severely reduced ability to excrete water (they have no kidneys), they rarely develop hyponatremia because they have a normal thirst center. The thirst center is supposed to prevent you from taking in more water than you can lose in urine, sweat, and breath. For hyponatremia to develop and be maintained, water intake must exceed ability to excrete or lose water, and therefore suggests an abnormal thirst threshold.

**THE KIDNEY**

As a nephrologist, I tend to think that the kidney is the seat of the soul. In addition to performing nitrogenous waste removal, acid-base balance, sodium, potassium, and divalent ion balance, erythropoietin and 1,25 dihydroxy-D3 production, the kidney can produce urine with osmolality between 40 and 1200 mOsm/kg, allowing wide range of water intake. The average osmolar excretion needed to maintain osmolar balance is 600 mOsms per day. Ever wonder how someone decided that urine output less that 500 cc/day was "oliguria"? If the maximum urine concentration is 1200 mOsm/kg and you need to excrete 600 mOsm/day, then 500 cc is the smallest amount of urine you can produce and maintain "osmolar balance". If your kidney can only achieve a maximum urine concentration of 600 mOsm/kg, then "oliguria" is less than 1,000 cc/day. If you have nephrogenic diabetes insipidus and can only concentrate urine to 100

mOsm/kg, then you must drink over six liters of water per day to account for urine and insensible water losses, or risk becoming hypernatremic.

How can the kidney change urine concentration so drastically? The kidney is subdivided into a cortex and medulla. The osmolality of the cortex is roughly the same as plasma. The osmolality of the medulla increases toward the tip of the papilla to a maximum of approximately 1200 mOsm/kg. The nephron consists of a glomeruli and renal tubule. The major tubular segments consist of proximal tubule, loop of Henle with thin and thick segments; distal convoluted tubule and collecting duct. Urine formation begins with ultrafiltration of plasma at the glomerulus. Final urine produced is only 1-2% of the volume of glomerular ultrafiltrate. As tubular fluid travels through the various tubular segments through the cortex and medulla, the fluid is modified through active and passive transport mechanisms occurring at different parts of the tubule. Tubular fluid is absorbed isotonically until it gets to the loop of Henle. As urine travels down the loop toward the hairpin turn, the urine becomes progressively concentrated, as water is passively absorbed and salt remains in the tubular lumen. After the turn at the tip, urine becomes progressively dilute, as solute is absorbed, passively at first, and then actively against gradients throughout the medullary thick ascending loop and distal tubule. The urine, now maximally diluted begins travel through the collecting duct and medulla. At the risk of oversimplification, let me state that the urine can remain dilute or concentrated depending on the presence or absence of VP. If VP is present, water will move from the collecting duct lumen into the medullary interstitium and be returned to the circulation. The end result will be a smaller amount of concentrated urine.

## VASSOPRESSIN ACTION AT THE KIDNEY

This has been an exciting area for research recently.4-12 When VP reaches the kidney, it interacts with V2 receptors on the basolateral surface of the principal cells. Stimulation of the V2 receptors causes cell-signaling events that result in Aquaporin-2 water channel-rich vesicles to attach to the apical membrane of the principal cells. The apical membrane surface area and permeability increases. When VP levels diminish, the Aquaporin-2 water channels reform into cytoplasmic vesicles for storage, and the permeability of the principal cell decreases. There have been at least 5 types of Aquaporins identified in the kidney, brain, salivary, and sweat glands. Extensive review of this exciting area is beyond the scope of this outline.

## INTEGRATION OF NORMAL WATER BALANCE MECHANISMS

Now let’s summarize by describing what happens when a normal individual drinks a water load and then takes in no water for several hours. The individual starts with a normal state of hydration, electrolytes, and Posm, then drinks 2 liters of water in 30 minutes. The water is absorbed, reduces serum sodium and Posm, and suppresses VP release. The low VP causes the renal collecting ducts to become relatively impermeable to water and a large output of maximally diluted urine ensues. If the individual drinks nothing for several hours, water is lost in the urine, breath and sweat causing the Posm to increase. VP levels increase when the threshold for VP release is reached. Increasing VP causes the collecting ducts become more permeable to water, until maximal urinary concentration is reached. Water continues to be lost in breath, sweat and urine raising Posm further until the threshold for thirst is reached. When drinking again

satisfies thirst, water is absorbed from the gut, reducing Posm, thirst drive, VP levels and urine concentration. (I've just described the normal physiological response to a water load and water deprivation test.) Most of the time, our Posm remains in a tight range between the threshold for VP release and thirst, and urine is moderately concentrated, finely balanced without us having to think about it.

## CLINICAL APPROACH TO HYPONATREMIA

With the above as background, let's review the approach to patients with hyponatremia. The following discussion is geared toward general clinical problem solving for hyponatremia. Students are invited to read review articles and textbook chapters for the etiologies of hyponatremia in different volume states (low, normal, and high). When hyponatremia is detected in the clinic or ward, repeat the serum electrolytes and perform a directed history and physical to determine hyponatremia etiology and general extracellular volume status of the patient. Laboratory testing is relatively simple and designed to supplement your bedside assessment and assess the status of the "effector systems". Initial labs should include Posm, Uosm, and urine sodium concentration. If measured Posm is normal, pseudohyponatremia may be present. Causes include severe hyperlipidemia and hyperproteinemia. If euvolemia is suspected by physical exam, Supplemental lab testing for thyroid and adrenal disease should be considered. In some cases, determination of "electrolyte-free water clearance" may be helpful, but discussion of this fine point is beyond the scope of this discussion. Now let's review some cases to illustrate the major points:

## HYPONATREMIA – CASE #1

A young adult presents with severe gastroenteritis of 3 days duration with nausea, vomiting, and diarrhea. The patient is weak, sweaty, dizzy, pale, tachycardic, mildly hypotensive, and has 10 kg weight loss. He was told by an advice nurse 2 days ago to drink lots of clear liquids. Serum sodium 128meq/l, Posm 269mOsm/kg, Uosm 1100mOsm/kg, and urine sodium <10meq/l.

What is your assessment of the extracellular volume status? Answer – low. What is the status of the "effector systems"? Answer – catecholamine, renin-angiotensin-aldosterone, and VP systems are appropriately very active trying to preserve circulation to vital organs. Why is the patient hyponatremic? Answer – VP is probably elevated due to severe volume depletion and nausea, reducing urinary dilution capacity. Water intake and absorption was greater than ability to excrete water, causing dilution of body fluid compartments. Extracellular volume status and total water content are both reduced, but sodium content is reduced more than water thus causing hyponatremia. What is the therapy of choice and why? Answer – give isotonic IVF's until extracellular volume status is normal, and treat nausea. This will suppress the non-osmotic stimulus for VP release. With suppressed VP levels, Uosm will decrease and urine output will increase until excess water is excreted and normal water balance is restored.

## HYPONATREMIA – CASE #2

A 65 yo male with known CAD presents to ED in severe CHF from MI that probably occurred 2 weeks earlier. Patient is thirsty, and has edema, ascities, distended neck veins, rales and S3/S4.

He is pale, sweaty, and "nervous". He takes no medications. Labs show serum sodium of 128, Posm 269, Uosm 1100, and urine sodium <10. (If some of the symptoms, signs, and labs look familiar, I'm trying to make a point here).

What is your assessment of the extracellular volume status? Answer – high. What is the status of the "effector systems"? Answer – just as in the previous case, all of the effector systems are turned on, but in this case it is because the cardiac disease has fooled the extracellular volume sensors. Why is the patient hyponatremic? Answer – VP elevated due to severe CHF causing the volume sensors to believe that "effective circulating volume" is severely decreased. The elevated VP reduces urinary dilution capacity despite hyponatremia. Water intake is greater than ability to excrete water, causing dilution of body fluid compartments. High aldosterone causes sodium retention, hypokalemia, and alkalosis. Extracellular volume status and total water content are both elevated, but water content is elevated more than sodium thus causing hyponatremia. (Hyponatremia in the setting of CHF is associated with increased mortality, probably because it indicates more severe CHF.) What is the therapy of choice and why? Answer – "Restrict water and sodium and treat CHF. As CHF and heart disease is treated, "effective circulating volume" will improve, decreasing the effector systems activity (including excessive VP). Urine output and sodium excretion will increase, and Uosm will decrease until water balance improves.

**HYPONATREMIA – CASE #3**

Middle age male with long smoking history presents with cough, hemoptysis, and 20-pound weight loss over the last 6 months. No medications. Viral gastroenteritis during last 2-3 days caused anorexia and precipitated clinic visit. Patient looks ill and tired, but otherwise has normal examination. Serum sodium 120, Posm 250, Uosm 600, urine sodium 12. Thyroid panel and cortrosyn stimulation test pending. Patient given 2 liters of IV normal saline in clinic and CXR ordered. CXR shows large perihilar mass consistent with lung cancer. Blood and urine chemistries repeated after IVF's and return identical to the first set except that urine sodium now greater than 40.

What is your assessment of extracellular volume status? Answer – on bedside exam, patient appears euvolemic, but initial urine sodium was low indicating subtle volume depletion from the recent viral syndrome. IV saline corrected this volume depletion (demonstrated by repeat urine sodium greater that 40). Is urine concentration "appropriate"? Answer – no. The low Posm and normal extracellular volume status should suppress VP levels and cause the urine concentration to become maximally diluted. The current Uosm is inappropriate to the Posm. If thyroid and adrenal disease is excluded, then patient probably has Syndrome of Inappropriate ADH (SIADH) caused by the lung cancer. Are elevated VP levels sufficient to explain the hyponatremia? Answer – no. There is probably an altered thirst threshold, and water intake must be exceeding water losses. (This fact is rarely discussed in review articles and textbooks.) What is the treatment/management plan? Diagnose and treat the lung disease and place patient on water restriction. Rapid correction is not necessary and potentially dangerous. How much water restriction is needed? Answer – until the Posm rises to an acceptable range (near lower range of normal). What explains Posm not increasing on a water restriction? Answer – water intake remains the same or more than water losses because a) patient is not following water restriction, or b) water restriction is not tight enough.

Many authors write about how to estimate water excess, and the controversy surrounding the treatment of severe and symptomatic hyponatremia. Those interested should read recent excellent reviews on this subject13. Although oversimplifying, I could sum this subject up with the following "pearls":

a.) If symptomatic and severe, you can raise the sodium concentration by a few meq/l quickly until major symptoms (i.e. seizures) stop. At that point,
b.) go slow, or start slow if there are no major symptoms, and
c.) whatever you do, evaluate the patient frequently and DO NOT over-correct the serum sodium level.

## HYPERNATREMIA AND SYNDROMES OF WATER DIURESIS

Most teachers teach as though hypernatremia and hyponatremia are different subjects instead of different parts of the spectrum of the same subject – water balance. If you understand the normal physiology of water balance and how the various systems are integrated, you can think through the rationale for evaluating and treating patients with hypernatremia. Let me illustrate with a couple of cases.

## HYPERNATREMIA CASE #1

Elderly patient is sent to you from nursing home because he is "deteriorating". He fell several weeks ago and sustained severe hip fracture. Complications from healing and his social situation required him to be placed into a nursing home where he was confined to bed. The nurse practitioner that calls you says that the patient is alert and oriented, thin, wasted, has dry mucous membranes, and has no edema. The NP had sent labs (serum sodium 150, Posm 309). You go to evaluate the patient.

What are the first two questions you should ask after you introduce yourself and establish rapport? Answer – first question is "are you thirsty", and the second is "are you urinating a little or a lot?" Let’s review some hypothetical patient answers. Patient answers, "I’m thirsty as heck, those jokers at the Home won’t bring me anything to drink, and my urine isn’t enough to water a cactus". You order Uosm and it returns 850. In this case, the patient’s physiological systems may be totally normal, and the problem may be that the nursing home is neglecting the patient. Elderly patients may lose a little maximal urine concentrating ability, which explains why the Uosm is only 850. Treatment would be providing food and water along with the other basic human necessities, and the patient’s exam and labs will correct. What if the patient had answered, "thirsty? No – should I be? And now that you mention it, I rarely need to urinate." The explanation may be that VP levels may be appropriately elevated and urine concentrated (Uosm returns 850), and that he has a rare case of damage (by stroke, tumor, granulomatous disease, trauma, or infection) to the thirst center with an intact magnocellular neuron, osmostat, and kidney. Management would also include appropriate fluid intake but also getting an anatomic

study of the hypothalamic area. What if the patient had answered, "I'm thirsty as heck, I'm drinking all the time, and I'm peeing enough to swamp a battleship"? Allow an ad lib fluid intake and measure 1500cc urine output over the next 4 hours. The Uosm of this collection is 70 mOsm/kg. There is no glycosuria, hypokalemia, palpable bladder, or enlarged prostate. In this case, the Posm was elevated and should cause high levels of VP, which should have caused urine to be concentrated (but it wasn't). There is either not enough VP in the circulation or the kidney is not responding. How do you sort out this problem? Administer IV vasopressin at the end of the water deprivation test. Over the next 2 hours, urine output stays high and repeat Uosm is only 80. What is the diagnosis? The patient clearly has an inappropriate water diuresis that is unresponsive to VP, thus making the diagnosis of nephrogenic diabetes insipidus. What are the causes of acquired nephrogenic DI that you have not tested for yet? (Partial bilateral urinary obstruction, hypcalcemia, drugs and other things on "lists".) Renal ultrasound shows no hydronephrosis and the serum calcium returns elevated at 12.9mg/dl. Pursue a hypercalcemia evaluation and give appropriate medical treatment. Success achieved after a few days, and urine concentrating ability and water balance are restored.

**CASE #2 – "POLYURIA, RULE-OUT DI"**

(This is a case that represents the most common cause for polyuria and water diuresis that I see). A 40 yo male is referred for excessive urination. Primary care provider has been evaluating patient for high urine output that started gradually over the past 4 months. There was a history of bipolar affective disorder treated with lithium several years ago. The patient is currently on no therapy, but complains of dry mouth and needing to drink constantly. He gets up several times per night to urinate. Urine output is measured at 10 liters per day. There is no hyperglycemia, hypokalemia, hypercalcemia, diuretic or lithium use, or hydronephrosis. Serum sodium is 137, Posm 281, Uosm 60. Primary provider performed water deprivation test (results not actually available to review) and said that patient concentrated urine significantly with VP administration. MRI of head showed no abnormality of hypothalamus or pituitary gland, and all endocrine tests were normal. The primary provider put the patient on DDAVP, the urine output decreased for a couple of days, then the patient developed a headache and repeat serum sodium was 129. The DDAVP was stopped and serum sodium became normal, but polyuria remains. The primary provider asks, "what should I do now?"

If the following explanation makes sense, you probably understand the basics of water balance. The first thing to do is repeat the water deprivation test. The tip-off that the patient may not have DI is that the serum sodium initially is in the low range of normal. You perform another water deprivation test, but patient complains bitterly about thirst. It is important to check Posm and Uosm frequently during the test to ensure that normal physiological mechanisms are given a chance to work, and identify patients who cheat (patients can be quite creative). If the patient is compliant and water steadily lost, Posm will increase until the threshold for VP release is reached. Allow Posm to increase to the high 290's to make sure there is adequate stimulus for VP release. Psychogenic polydipsic patients can "wash out" their urinary gradient and may not be able to maximally concentrate their urine. As long as the patient is adequately supervised, the water deprivation test is safe. Psychogenic polydipsia patients probably have profound alteration of their thirst mechanism as part of their underlying psychiatric disorder. In this case, when Posm increased above 295, the urine output slowed and Uosm increased to >700. The diagnosis

of psychogenic polydipsia was made and the patient was referred to psychiatry. It is important not misdiagnose this patient. Why did the patient develop hyponatremia on DDAVP? The DDAVP caused the equivalent of "iatrogenic SIADH", and the patient's water intake was greater than his ability to excrete a water load resulting in a rapid decrease of serum sodium. Treatment should be focussed on treating the underlying psychiatric disorder and avoiding medications that decrease urinary dilution.

## CONCLUSIONS

I have reviewed water balance and the general cognitive approach toward disorders of hyponatremia, hypernatremia, and water diuresis. I have stressed general concepts, understanding of basic physiological principles, and system integration that allows the primary clinician to use basic problem solving skill to evaluate many patients. I apologize for oversimplifying many points, but have done so to illustrate important concepts that I believe are not adequately addressed in many textbooks and review articles on this subject. Serious students should review additional references. Thanks for taking the time to read this. Comments are appreciated.

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**BIBLIOGRAPHY**

1.Knepper MA, Rector FC. Urine Concentration and Dilution. In: Brenner BM, editor. The Kidney. 5th ed. Philadelphia: WB Saunders; 1996. P. 532-70.
2.Harris HW, Zeidel ML. Cell Biology of Vasopressin. In: Brenner BM, editor. The Kidney. 5th ed. Philadelphia: WB Saunders; 1996. P. 516-31.
3.Robertson GL, Berl T. Pathophysiology of Water Metabolism. In: Brenner BM, editor. The Kidney. 5th ed. Philadelphia: WB Saunders; 1996. P. 873-928.
4.Nielsen S, Pallone T, Smith BL, Christensen EI, Agre P, Maunsbach AB. Aquaporin-1 water channels in short and long loop descending thin limbs and in descending vasa recta in rat kidney. Am J Physiol 1995; 268: F1023-37.
5.Jamison RL, Buerkert J, Lacy F. A micropuncture study of collecting tulbule function in rats with hereditary diabetes insipidus. J Clin Invest 1971;50:2444-52.
6.Marples D, Christensen S, Christensen EI, Ottosen PD, Nielsen S. Lithium-induced downregulation of aquaporin-2 water channel expression in rat kidney medulla. J Clin Invest 1995;95:1838-45.
7.Frokier J, Marples D, Knepper MA, Nielsen S. Bilateral ureteral obstruction downregulates expression of vasopressin-sensitive AQP-2 water channel in rat kidney. 1996;270: F657-68.
8.Marples D, Frokier J, Dorup J, Knepper MA, Nielsen S. Hypokalemia-induced downregulation of aquaporin-2 water channel expresion in rat kidney medulla and cortex. J Clin Invest. 1996;97:1960-68.
9.Kanno K, Sasaki S, Hirata Y, Ishikawa S, Fushimi K, Nakanishi S, Bichet DG, Marumo F. Urinary excretion of aquaporin-2 in patients with diabetes insipidus. N Engl J Med 1995; 332:1540-5.
10.Nielsen S, Agre P. The aquaporin family of water channels in kidney. Kidney Intern 1995:48:1057-68
11.Maunsbach AB, Agre P, Nielsen S. Aquaporin-1 water channel expression in human kidney. J Am Soc Nephrol 1997;8:1-14.
12.Apostol E, Ecelbarger CA, Knepper MA. Reduced renal medullary water channel expression in puromycin aminosucleoside-induced nephrotic syndrome. J Am Soc Nephrol. 1997;8:15-24
13.Laureno R, Karp BI. Myelinolysis after correction of hyponatremia. Ann Intern Med. 1997;126:57-62.

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