

Bon Secours Richmond
Pharmacy & Therapeutics Committees
Conivaptan (Vaprisol®)
6/06

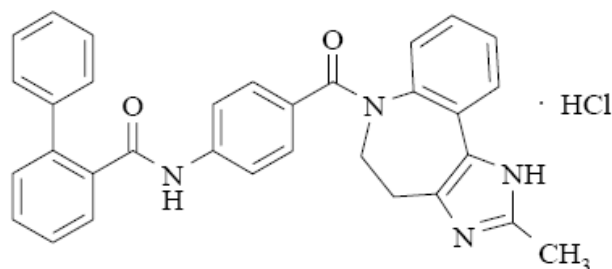
Overview:

Conivaptan is an injectable arginine vasopressin receptor antagonist (V_{1a} and V_2), which promotes excretion of free water (aquaretic) without increased electrolyte loss or activation of the renin-angiotensin-aldosterone system. It is FDA approved for euvoletic hypotonic hyponatremia in hospitalized patients. Studies in the package insert for conivaptan 40 mg/day demonstrated an increase of serum sodium of approximately 6 meq/l over 2-4 days. Conivaptan inhibits its own metabolism, displays non-linear kinetics and has high intersubject variability (94% coefficient of variation in clearance). It is a substrate and potent inhibitor of CYP3A4 and causes an increased AUC for simvastatin, midazolam, and digoxin. It is contraindicated with potent inhibitors of CYP3A4 (ketoconazole, itraconazole, ritonavir, indinavir, clarithromycin). It has a high rate of infusion site reactions (20%) and phlebitis (16%). Other common ADRs are: hypokalemia (10%), headache (12%), thirst (10%), and vomiting (6.6%). It should be given into a large vein and the IV site must be changed every 24 hours. Dosing: 20 mg loading dose in 100 ml D5W over 0.5 hour, then 20-40 mg/day in 250 ml of D5W for up to 4 days. Conivaptan is incompatible with 0.9% sodium chloride and lactated ringers injection. Conivaptan cost \$710 on day one of therapy and \$305-\$710 per day thereafter.

Recommendations:

- Conivaptan is not recommended for formulary addition at this time
 - Conivaptan is FDA approved for use in acute dilutional euvoletic hypotonic hyponatremia
- 3% Sodium Chloride injection may be used and is currently recommended for the following conditions
 - severe symptomatic euvoletic hypotonic hyponatremia when serum sodium is less than 125 mEq/l
 - severe symptomatic hypervolemic hypotonic hyponatremia with loop diuretics when serum sodium is less than 125 mEq/l
 - severe symptomatic hypovolemic hypotonic hyponatremia when serum sodium is less than 125 mEq/l

*severe symptomatic hypotonic hyponatremia : confusion, ataxia, seizures, obtundation, coma, respiratory arrest
- Dosing Tools for 3% Sodium Chloride will be created for physician use and will be placed on the pharmacy web site for easy access. (see attached)
- Patients will meet the following criteria to receive conivaptan
 - Serum sodium less than 130 mEq/l
 - Plasma osmolality less than 290 mOsm/kg H₂O
 - Euvoletic hyponatremia (absence of pitting edema or ascites)
- Conivaptan infusions should not exceed 96 hours per the package insert
- Patients receiving conivaptan will not have any of the following exclusion criteria:
 - Clinical evidence of dehydration or volume depletion
 - Hypervolemic hypotonic hyponatremia (CHF, cirrhosis with ascites, nephrotic syndrome, acute or chronic renal failure)
 - Contraindicated in hypovolemic hypotonic hyponatremia (burns, GI fluid losses, Addison's disease)
- Monitoring will include the following:
 - Serum sodium every 2 hours until the patient is asymptomatic then every 4-8 hours
 - Urine and serum osmolality and electrolytes (sodium and potassium) every 4-6 hours
 - Serum sodium should not increase any faster than 12 mEq/l in 1st 24 hours and less than 20 mEq/l in 1st 48 hours for acute hyponatremia, and less than 12 mEq/l 1st 24 hours and less than 18 mEq/l 1st 48 hours for chronic hyponatremia.
 - Urine volume
 - IV site for signs of phlebitis
- Conivaptan injection should be infused into a large vessel and the IV site should be changed every 24 hours.



- Cost analysis
 - Conivaptan costs \$710 for the first day and \$305-\$710 per day there after, with a complete treatment course costing up to \$2,840.
 - 3% Sodium Chloride cost \$1-\$4 for a complete treatment course.

- Serum and urine monitoring for 3% sodium chloride and conivaptan are comparable

Findings

- Conivaptan is an arginine vasopressin receptor antagonist (V_{1a} and V_2), which promotes excretion of free water (aquaretic) without increased electrolyte loss or activation of the renin-angiotensin-aldosterone system.
 - V_2 receptors are coupled to the aquaporin channels in the apical membranes of the cells lining the collecting ducts of the kidney
 - V_{1a} receptors are the most widely distributed receptor (physiological role ill-defined)
 - Conivaptan increases skin blood flow and inhibits AVP induced platelet aggregation
- Arginine vasopressin (formerly called antidiuretic hormone) is released from the pituitary and increases free water reabsorption in the renal collecting ducts.
- Pharmacokinetics:
 - Conivaptan inhibits its own metabolism, displays non-linear kinetics and has high intersubject variability (94% coefficient of variation in clearance)
 - CYP3A4 substrate and potent inhibitor
 - Increases blood levels/AUC of the following:
 - Midazolam 2-3 increase AUC
 - Simvastatin 3 fold increase AUC
 - Digoxin (specifics not stated in package insert)
 - Clearance 15.2 L/Hr
 - AUC 98 ng hr/ml
 - Creatinine Clearance < 60 ml/min, 80% increase in AUC
 - Cirrhosis 180% increase in AUC
 - Fraction Excreted Unchanged In Urine 1%
 - Half-life 12-14 hours
 - Protein binding 99% (10-1000 ng/ml serum concentration)
 - Contraindicated with potent inhibitors of CYP3A4 (ketoconazole, itraconazole, ritonavir, indinavir, clarithromycin)
- Adverse effects:
 - infusion site reactions (20.2%), infusion site phlebitis (15.8%), hypokalemia (10%), headache (12%), thirst (10%), vomiting (6.6%)
 - Overly rapid correction of serum sodium (defined as 12 mEq/l/24 hours) occurred in 9% of patients in clinical trials, none had permanent sequelae.
 - Two cases of rhabdomyolysis have been reported in patient on statins who were treated with conivaptan
- Dosing
 - Loading dose of 20 mg over 30 minutes in 100 ml of D5W
 - Maintenance dose of 20-40 mg by continuous infusion over 24 hours in 250 ml of D5W
 - Maximum length of therapy 4 days
- Average Increase Serum Sodium for 40 mg/day of conivaptan
 - Day 2 5.8 mEq/l
 - Day 4 6.4 mEq/l
- Cumulative effective water clearance by day 4 for 40mg/day of conivaptan
 - 2.9 liters versus 1.8 in placebo group
- Infusion Site: Large vein, change site every 24 hours
- Incompatible with Lactated Ringer's or 0.9% Sodium Chloride
- Pregnancy Category C
- Solubility 0.15 mg/ml in water

Vaprisol 40 mg IV every day versus standard care, which was primarily fluid restriction (2 liters or less per day)

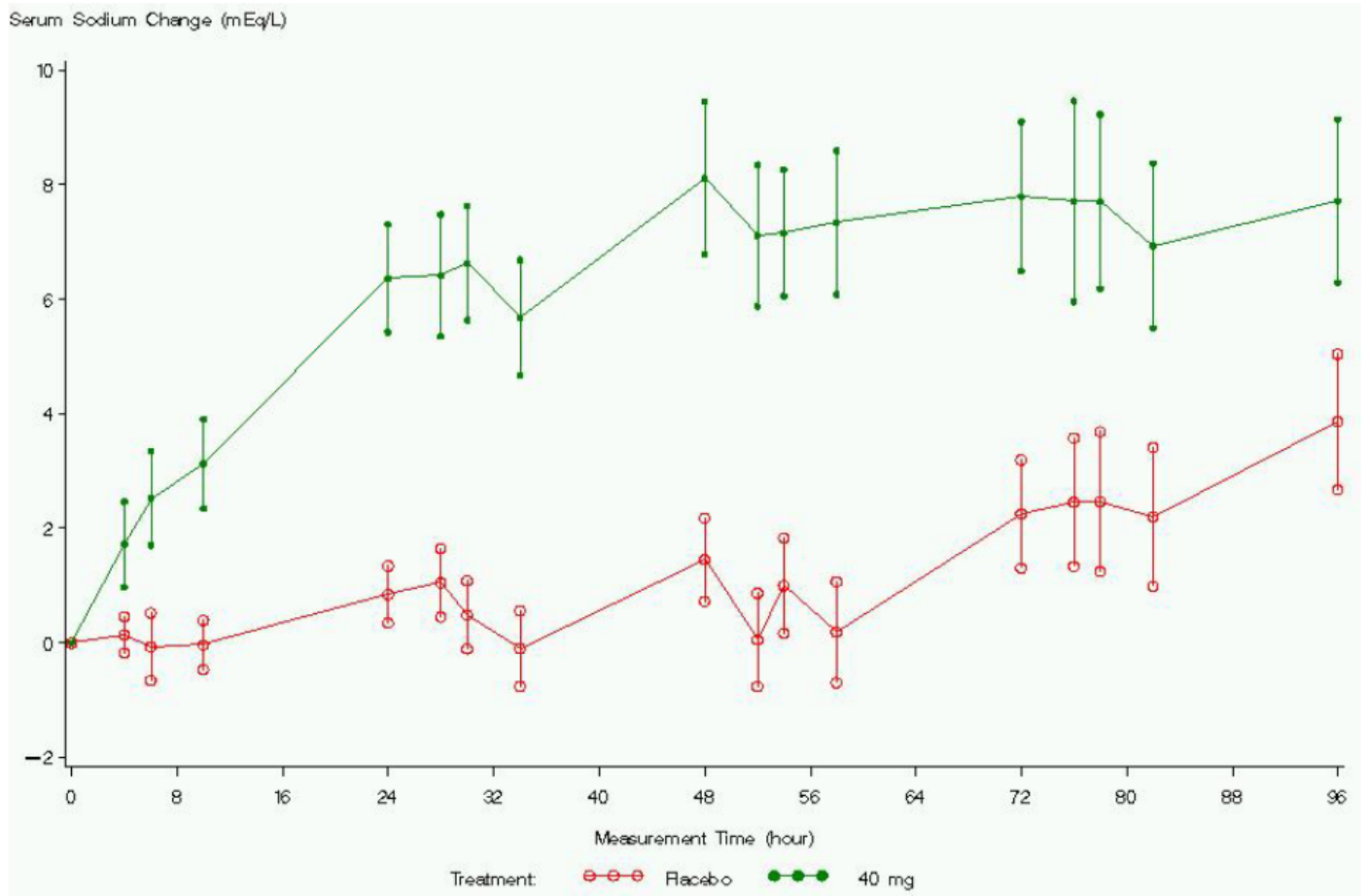


Table 3. Efficacy Outcomes of Treatment with VAPRISOL 40 mg/day

Efficacy variable	Placebo N=21		VAPRISOL 40 mg/d N=18	
	2 day‡	4 day	2 day ‡	4 day
Baseline adjusted serum Na ⁺ AUC over duration of treatment (mEq-hr/L)				
Mean (SD)	25.8 (83.19)	113.3 (258.19)	222.1 (166.31)	530.8 (399.49)
LS Mean ± SE	42.6 ± 31.89	152.9 ± 70.13	220.4 ± 34.24***	519.8 ± 75.31**
Number of patients (%) and median event time (h) from first dose of study medication to a confirmed ≥4 mEq/L increase from Baseline in serum Na ⁺ , [95% CI]	8 (38.1%) Not estimable		15 (83.3%) 21.0***, [6, 30]	

Total time (h) from first dose of study medication to end of treatment during which patients had a confirmed ≥ 4 mEq/L increase in serum Na^+ from Baseline				
Mean (SD)	2.5 (6.89)	17.6 (22.19)	24.5 (18.11)	52.5 (34.25)
LS Mean \pm SE	4.0 \pm 3.14	20.8 \pm 6.34	24.1 \pm 3.37***	52.1 \pm 6.81**
Serum Na^+ (mEq/L)				
Baseline mean (SD)	124.3 (3.93)	124.3 (3.93)	123.6 (4.24)	123.6 (4.24)
Mean (SD) at end of treatment	125.1 (4.32)	128.7 (4.82)	129.4 (4.43)	130.0 (4.27)
Change from Baseline to end of treatment				
Mean change (SD)	0.8 (2.56)	2.4 (4.83)	5.8 (4.23)	6.4 (5.23)
LS Mean change \pm SE	1.2 \pm 0.85	2.8 \pm 0.96	6.7 \pm 0.91**	6.1 \pm 1.03*
Number (%) of patients who obtained a confirmed ≥ 6 mEq/L increase from Baseline in serum Na^+ or a normal serum Na^+ concentration ≥ 135 mEq/L during treatment	0 (0)	6 (28.6%)	7 (38.9%)**	12 (86.7%)*

*P<0.05, **P<0.01, ***P<0.001 vs placebo

†efficacy variables were assessed on day 2 of a 4 day treatment period

)

Primary efficacy endpoint	20 mg/day N=11	40 mg/day N=93
Baseline adjusted serum Na^+ AUC over duration of treatment (mEq·hr/L)		
Mean (SD)	1000.2 (34.72)	648.9 (407.37)
Secondary efficacy endpoints		
Number of patients (%) and median event time (h) from first dose of study medication to a confirmed ≥ 4 mEq/L increase from Baseline in serum Na^+ , [95% CI]	10 (90.9) 12.0 [6.0, 24.8]	77 (82.8) 24.4 [24.0, 36.0]
Total time (h) from first dose of study medication to end of treatment during which patients had a confirmed ≥ 4 mEq/L increase in serum Na^+ from Baseline		
Mean (SD)	78.2 (27.38)	59.7 (32.94)
Serum Na^+ (mEq/L)		
Baseline mean (SD)	121.1 (4.16)	124.1 (4.60)
Mean (SD) at end of treatment	133.5 (2.56)	132.4 (4.20)
Mean Change (SD) from Baseline to End of Treatment	12.4 (4.75)	8.4 (5.38)
Mean (SD) at Follow-up Day 11	130.7 (9.44)	131.9 (5.80)
Mean Change (SD) from Baseline to Follow-up Day 11	9.5 (11.42)	8.0 (6.67)
Mean (SD) at Follow-up Day 34	135.6 (4.76)	134.4 (5.06)
Mean Change (SD) from Baseline to Follow-up Day 34	15.1 (7.77)	10.6 (6.70)
Number (%) of patients who obtained a confirmed ≥ 6 mEq/L increase from Baseline in serum Na^+ or a normal serum Na^+ concentration ≥ 135 mEq/L during treatment	10 (90.9%)	68 (73.1%)

|

Table 5		
IV VAPRISOL: Adverse Reactions Occurring in $\geq 2\%$ of Patients or Healthy Volunteers and VAPRISOL Incidence > Placebo Incidence Hyponatremia and Healthy Volunteer Studies		
Term	Placebo N=61 n (%)	40 mg N=183 n (%)
Blood and Lymphatic System Disorders		
Anemia NOS	2 (3.3%)	7 (3.8%)
Cardiac Disorders		
Atrial Fibrillation	0	5 (2.7%)
Gastrointestinal Disorders		
Constipation	2 (3.3%)	9 (4.9%)
Diarrhea NOS	0	10 (5.5%)
Dry mouth	2 (3.3%)	8 (4.4%)
Nausea	2 (3.3%)	7 (3.8%)
Vomiting NOS	0	12 (6.6%)
General Disorders and Administration Site Conditions		
Cannula site reaction	0	10 (5.5%)
Edema peripheral	1 (1.6%)	10 (5.5%)
Infusion site erythema	0	9 (4.9%)
Infusion site pain	1 (1.6%)	14 (7.7%)
Infusion site phlebitis	0	29 (15.8%)
Infusion site reaction	0	37 (20.2%)
Infusion site swelling	1 (1.6%)	5 (2.7%)
Pain NOS	0	4 (2.2%)
Pyrexia	0	7 (3.8%)
Thirst	1 (1.6%)	18 (9.8%)
Infections and Infestations		
Oral candidiasis	0	4 (2.2%)
Pneumonia NOS	0	5 (2.7%)
Urinary tract infection NOS	1 (1.6%)	6 (3.3%)
Metabolism and Nutritional Disorders		
Dehydration	0	4 (2.2%)
Hyperglycemia NOS	0	5 (2.7%)
Hypoglycemia NOS	0	6 (3.3%)
Hypokalemia	1 (1.6%)	18 (9.8%)
Hypomagnesemia	0	4 (2.2%)
Hyponatremia	0	6 (3.3%)
Nervous system disorders		
Headache	2 (3.3%)	22 (12.0%)
Psychiatric Disorders		
Confusional state	1 (1.6%)	7 (3.8%)
Insomnia	0	6 (3.3%)
Renal and urinary disorders		
Hematuria	1 (1.6%)	4 (2.2%)
Pollakiuria	0	11 (6.0%)
Polyuria	0	9 (4.9%)
Skin and subcutaneous disorders		

Erythema	0	5 (2.7%)
Vascular Disorders		
Hypertension NOS	0	10 (5.5%)
Hypotension NOS	1 (1.6%)	5 (2.7%)
Orthostatic hypotension	0	10 (5.5%)
Phlebitis NOS	1 (1.6%)	9 (4.9%)

)

- Hyponatremia is the most common disorder of fluid and electrolyte balance encountered in hospitalized patients.
 - Acute hyponatremia occurs when serum sodium levels fall rapidly to less than 135 mEq/l in under 48 hours. Symptoms occur due to brain swelling and can be mild to severe.
 - Chronic hyponatremia occurs when serum sodium levels fall gradually over greater than 48 hours.
- Symptomatic hyponatremia is defined as the presence of neurological symptoms in patients with hyponatremia. The speed at which hyponatremia develops rather than the magnitude of hyponatremia is most closely associated with degree of symptoms. Symptoms include: headache, lethargy, muscle cramps, confusion, ataxia, disorientation, restlessness, obtundation. Severe symptoms include: seizure, coma, respiratory arrest

TABLE 1-A. Clinical Classification of Hyponatremia

<i>ECF Volume Status</i>	<i>Hypovolemia</i>	<i>Euvolemia</i>	<i>Hypervolemia</i>
Fluid/Solute Mechanism	Extracellular sodium decreased Total body water decreased	Extracellular sodium normal Total body water slightly increased	Extracellular sodium increased Total body water greatly increased
Clinical Manifestations	Gastrointestinal fluid losses Burns Addison's disease Renal dysfunction	SIADH Hypothyroidism Adrenal insufficiency Pulmonary disorders Inappropriate IV therapy	Heart failure Cirrhosis with ascites Nephrotic syndrome Renal failure

ECF = extracellular fluid; IV = intravenous; SIADH = syndrome of inappropriate antidiuretic hormone. Adapted from *Int J Biochem Cell Biol*, Volume 35, Baylis PH, The syndrome of inappropriate antidiuretic hormone secretion, 1495–1499, © 2003, with permission (pending) from Elsevier.

- Euvolemic hyponatremia occurs when arginine vasopressin (AVP) is secreted independently of the body's need to conserve water, and is most often seen in patients with the syndrome of inappropriate antidiuretic hormone (SIADH). See chart below
 - Features of SIADH
 - Hyponatremia
 - Hypo-osmolality of the serum
 - Inappropriately high urine osmolality
 - Renal excretion of sodium despite hyponatremia
 - Absence of clinical evidence of volume depletion or edema forming states

TABLE 1-B. Common Etiologies of SIADH

Tumors

Bronchogenic carcinoma
Mesothelioma
Thymoma
Duodenal carcinoma
Pancreatic carcinoma
Ureteral/prostate carcinoma
Uterine carcinoma
Nasopharyngeal carcinoma
Leukemia

CNS Disorders

Mass lesions (tumors, brain abscesses, subdural hematoma)
Inflammatory diseases (encephalitis, meningitis, systemic lupus, acute intermittent porphyria, multiple sclerosis)
Degenerative/demyelinative diseases (Guillain-Barré, spinal cord lesions)
Miscellaneous (subarachnoid hemorrhage, head trauma, acute psychosis, delirium tremens, pituitary stalk section, transphenoidal adenomectomy, hydrocephalus)

Drugs

Stimulated AVP release (nicotine, phenothiazines, tricyclics)
Direct renal effects and/or potentiation of AVP diuretic effects (dDAVP, oxytocin, prostaglandin synthesis inhibitors)
Mixed or uncertain actions (angiotensin converting enzyme inhibitors, carbamazepine and oxcarbazepine, chlorpropamide, clofibrate, clozapine, cyclophosphamide, 3,4-methylenedioxymethamphetamine (ecstasy), omeprazole, serotonin reuptake inhibitors, vincristine)

Pulmonary Disease

Pneumonia
Lung abscess
Bronchiectasis
Tuberculosis

Other

AIDS
Prolonged strenuous exercise (marathon, triathlon, ultramarathon, hot-weather hiking)
Senile atrophy
Idiopathic SIADH in the elderly

AIDS = acquired immunodeficiency syndrome; AVP = arginine vasopressin; CNS = central nervous system; dDAVP = desmopressin; SIADH = syndrome of inappropriate antidiuretic hormone.

Adapted from *Best Pract Res Clin Endocrinol Metab*, Volume 17, Verbalis JG, Disorders of body water homeostasis, 471–503, © 2003, with permission (pending) from Elsevier.

- Hyponatremia classification
 - Excess of body water relative to body solute
 - Dilutional
 - Total body water increases diluting serum sodium
 - Is more common than depletional
 - Euvolemic:
 - extracellular fluid volume is normal, no signs of fluid retention (pitting edema, ascites), total body water is increased
 - Most common type of hyponatremia
 - Hypervolemic: Volume of extracellular fluid compartment is expanded with associated edema and pitting.
 - CHF
 - Cirrhosis with ascites
 - Nephritic syndrome
 - Renal failure (acute, chronic)
 - Depletional is usually hypovolemic
 - Depletion of body sodium by renal or non-renal losses
 - Diuretic use
 - Salt wasting nephropathy
 - Mineralcorticoid deficiency (aldosterone)
 - GI losses due to diarrhea, vomiting, pancreatitis or bowel obstruction
 - Cutaneous losses from sweating or burns or blood loss
- Medications
 - Stimulate AVP release
 - Carbamazepine, oxcarbazepine
 - Antidepressants
 - Clofibrate
 - Chlorpropamide
 - Nicotine
 - Opioids
 - Phenothiazines
 - Tricyclics
 - Drugs that potentiate AVP in the kidneys
 - NSAID
 - Cyclophosphamide
 - Mechanism unclear
 - Haloperidol
 - Amitriptyline
 - Ecstasy (methylenedioxymethamphetamine)
 - Others
 - Vincristine
 - Oxytocin
 - Phenothiazines
 - Diuretics
 - Thiazide diuretics are the most common cause of hypovolemic hyponatremia.
 - SSRIs
 - Acetaminophen
 - Antipsychotics
 - Barbiturates

Table 2. Clinical Parameters to Differentiate Cerebral Salt Wasting Syndrome (CSWS) and Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH)

	CSWS	SIADH
Blood urea	↑	↓ or ↔
Blood pressure	↔ or ↓	N or ↔
Central venous pressure	↓	N or ↔
Urine volume	↑	↓
Thirst	↑	N

Control of Water Balance and Serum Sodium Concentration

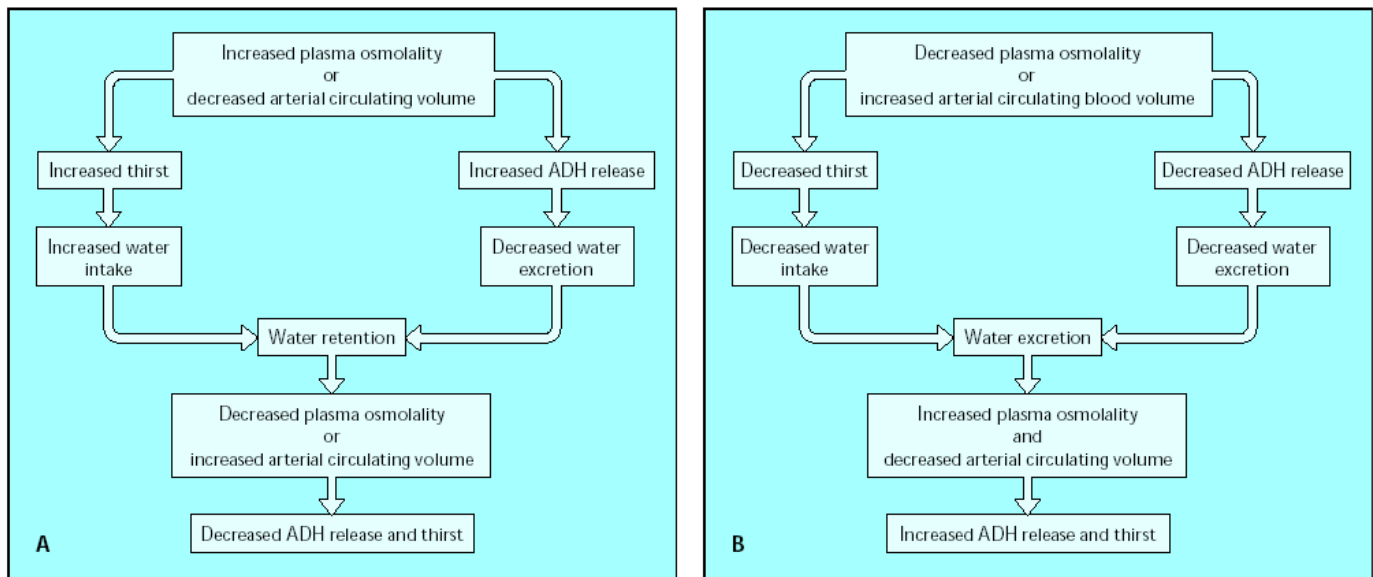


FIGURE 1-12

Pathways of water balance (conservation, **A**, and excretion, **B**). In humans and other terrestrial animals, the thirst mechanism plays an important role in water (H_2O) balance. Hypertonicity is the most potent stimulus for thirst: only 2% to 3% changes in plasma osmolality produce a strong desire to drink water. This absolute level of osmolality at which the sensation of thirst arises in healthy persons, called the *osmotic threshold for thirst*, usually averages about 290 to 295 mOsm/kg H_2O (approximately 10 mOsm/kg H_2O above that of antidiuretic hormone [ADH] release). The so-called thirst center is located close to the osmoreceptors but is

anatomically distinct. Between the limits imposed by the osmotic thresholds for thirst and ADH release, plasma osmolality may be regulated still more precisely by small osmoregulated adjustments in urine flow and water intake. The exact level at which balance occurs depends on various factors such as insensible losses through skin and lungs, and the gains incurred from eating, normal drinking, and fat metabolism. In general, overall intake and output come into balance at a plasma osmolality of 288 mOsm/kg, roughly halfway between the thresholds for ADH release and thirst [10].

- Dosing calculations for 3% Sodium Chloride Injection (sodium 513 mEq/liter) for hypotonic hyponatremia with severe symptoms
 - Calculate the patients lean body weight (LBW)
 - Males (kg) = 50 + (Height in inches above 60 inches * 2.3)
 - Females (kg) = 45.5 + (Height in inches above 60 * 2.3)
 If patient weighs less than calculated lean body weight use patient weight as lean body weight
 - Calculate Total Body Water (TBW) in liters
 - Total Body Water (liters) = Lean Body Weight_{kg} * 0.6
 - Some authors suggest using the following to calculate total body water (liters)
 - 0.6 * lean body weight for children and men less than 70 years old
 - 0.5 * body weight for men greater than and equal 70 years old and females less than 70 years old
 - 0.45 * body weight for women greater than and equal to 70 years old
 - Calculate Sodium Deficit (goal serum sodium 130 mEq/l)
 - Sodium Deficit (meq) = Lean Body Weight_{kg} * 0.6_{l/kg} * (130 – Current Serum Sodium_{mEq/l})
 - Calculate total dose in ml of 3% Sodium Chloride (Sodium 513 meq /liter) required to correct sodium deficit
 - Dose (ml) = (Sodium Deficit_{meq} / 513_{mEq/l})*1000_{ml/liter}
 - Calculate infusion rate
 - To raise sodium 0.5 meq/liter/hour
 - Infusion rate (ml/hr)= (LBW_{kg} * 0.6_{l/kg} * 0.5_{meq/liter/hour} / 513_{mEq/l}) * 1000_{ml/liter}
 - Usual infusion rate 0.5 ml/kg/hour
 - Maximum infusion rate 2 ml/kg/hour, reduce to 0.5 ml/kg/hour when symptoms are controlled
 - Maximum rate of sodium increase 12 mEq/liter in 24 hours and 20 mEq/liter in 48 hours.
 - Normalization of serum sodium should be avoided for the first 48 hours.
 - Calculate expected duration of infusion
 - Duration of Infusion (hours) = Dose_{ml} / Infusion rate_{ml/hr} or
 - Duration of Infusion (hours)= (130-Serum Sodium) / 0.5_{meq/liter/hour} desired rise in serum sodium
- Calculation of negative fluid balance (liters) to achieve desired sodium of 130 mEq/l
 - Negative Fluid Balance (liters) = TBW – [(130 /current serum sodium) * TBW]
= LBW_{kg} * 0.6_{l/kg} * [(130/ current serum sodium) –1]
- Calculation of volume of 0.9% sodium chloride necessary to replace extra cellular fluid deficit calculation in hypovolemic hypotonic hyponatremia
 - Liters of 0.9% NaCl = Extra Cellular Fluid Volume Normal – Extra Cellular Fluid Volume Current
 - Liters of 0.9% NaCl = [Total Body Weight normal_{kg} * 0.6 * 0.33] – [Total Body Weight current_{kg} *0.6 * 0.33]
 - Liters of 0.9% NaCl = [Total Body Weight Normal_{kg} –Total Body Weight Current_{kg}]*0.6*0.33
- Calculation of Electrolyte free water clearance = urine volume(ml/day) * (1- [(U_{Na}+ U_K)/(P_{Na}+P_K)])
- Calculation of change of serum sodium induced by one liter of fluid in Hypovolemic hypotonic hyponatremia
 - Change in Na mEq/l= (infused concentration Na_{mEq/l} – serum Na_{mEq/l}) / ((0.6_{l/kg}*LBW_{kg}) + 1_{liter})
- Hyperosmolar hyponatremia: Hyponatremia in the presence of elevated serum osmolality may be caused by the following: hyperglycemia, glycine bladder irrigation, maltose, and mannitol ingestion. These substances led to diffusion of water from the cells into the extracellular compartment resulting in hyponatremia. Each 100 mg/dl rise in glucose concentration serum sodium decreased by 1.6 mEq/l and serum osmolality rises by 2 mOsm/kg.
 - Sodium corrected = Serum Na + (1.6 *(Blood Sugar –100)/100)
 - The presence of unmeasured osmoles should be suspected in osmolal gap exceeds 15 mOsm/kg
 - = measured – calculated
- Solutes that are permeable across cell membranes (eg, urea, methanol, ethanol, isopropyl alcohol, and ethylene glycol) do not cause water movement and cause hypertonicity without causing cell dehydration or changing serum sodium.
- Serum osmolality is comprised primarily of sodium and accompanying anions chloride and bicarbonate
 - Calculated Sosm = (2* Serum Na) + (Blood glucose/18) + (BUN/2.8)
- The sodium content of the infusion must exceed the sum of sodium and potassium concentration in the urine for the serum sodium to rise after infusion of the solution and to effect net free water excretion.
- Patients with SIADH often have urinary concentration of osmotically effective cations that exceed the sodium concentration of 0.9% saline and should be preferentially treated with 3% saline. When urine osmolality exceeds 300 mOsm/kg it is generally advisable to add an intravenous loop diuretic to increase excretion of solute free water and to prevent volume overload.

Hypotonic Hyponatremias

Category	<i>Euvolemic</i> Hypotonic Hyponatremia	<i>Hypovolemic</i> Hypotonic Hyponatremia	<i>Hypervolemic</i> Hypotonic Hyponatremia
Description	Euvolemic hyponatremia is characterized by an increase in body water with total body sodium stores that remain normal. Serum sodium levels are decreased and there is not evidence of fluid retention. Patient appears euvolemic. Normal or slight decrease in ECF sodium content and increased total body water. Most common type of hypotonic hyponatremia.	Total body water and extracellular sodium are decreased, but sodium deficit exceeds that of water	Total body water greatly increased, total body sodium increased.
Signs	No signs of peripheral or pulmonary edema	Decreased skin turgor, orthostatic hypotension, tachycardia, dry mucous membranes.	
Causes	SIADH: tumors, head trauma, stroke, meningitis, pituitary surgery, pulmonary disease, drugs: chlorpropamide, carbamazepine, cyclophosphamide, NSAIDs, SSRIs, Ecstasy; adrenal insufficiency, hypothyroidism	GI losses due to diarrhea, excessive sweating, vomiting, pancreatitis, or bowel obstruction, diuretics, mineralcorticoid deficiency, cerebral salt wasting (hyponatremia, hypovolemia, natriuresis, and diuresis)	Increase in ECF volume, and edema, but a decreased effective arterial blood volume, renal sodium and water excretion are impaired, nonosmotic release of ADH causes retention of water in excess of sodium Cirrhosis, CHF, nephrotic syndrome, renal failure (acute, chronic)
Differential Diagnosis	Renal insufficiency, glucocorticoid deficiency, hypothyroidism and psychogenic polydispsia		
Goal of Therapy	Dependent on cause and symptoms. Patients who develop hyponatremia rapidly are at greatest risk for cerebral edema and require more aggressive therapy to correct hyponatremia. Asymptomatic patients do not require rapid correction of serum sodium and treatment is dictated by underlying etiology.	Correct ECF volume deficit, which will restore organ perfusion, blood pressure, and hyponatremia. Once ECF volume is restored, ADH secretion will cease and diuresis will occur. This may make the serum sodium rise greater than 12 mEq/l/day, change to 0.45% saline if necessary.	Dependent on cause and symptoms Asymptomatic: Water restriction, restrict dietary intake of sodium chloride to 1-2 gm/day CHF: contractility agents (digoxin, etc), ACEI, ARB
Treatment	Asymptomatic: Water restriction and treatment of underlying cause. Induce negative water balance, fluid restriction, less than 800 ml/day will increase serum sodium by 1-2 mEq/liter. Sodium chloride or urea intake and/or loop diuretics. Demeclocycline 900-1200 mg/day then 600-900 mg per day. Symptomatic (confusion, ataxia, seizures, obtundation): 3% Sodium Chloride, rate of rise in serum sodium not greater than 12 mEq/liter in 24 hours and 20 mEq/liter in 48 hours. Serum sodium concentration should be increased upward at a rate of 1.5-2 mEq/l/h for the first few hours until life threatening symptoms are resolved. Remove causative agent	0.9% NaCl to correct ECF volume deficit. Rarely associated with CNS symptoms. 3% Sodium Chloride if symptomatic in ICU setting. Remove causative agent	Fluid restriction, 3% Sodium Chloride if symptomatic, and loop diuretics Remove causative agent
Diuretics	Loop diuretic if urine osmolality exceeds 300 mOsm/kg		
Monitor	Symptomatic: Serum sodium every 2-4 hours Asymptomatic: Serum sodium every 24-48 hours.	Serum sodium every 2-4 hours	

Total body water, 2/3 is intracellular, 1/3 is contained in the extracellular space

- Symptoms of hyponatremia and hypernatremia are primarily related to alterations in cell volume.
- Osmoregulation of body fluid is primarily mediated by changes in water balance, not electrolyte balance. Water balance is determined by the circulating levels of AVP.
- Under normal circumstances, the body regulates plasma sodium by adjusting the water content of the extracellular fluid. Hyponatremia is usually due to a defect in water balance.
 - Sodium does not freely cross cell membranes.
 - Addition of an isotonic solution to the ECF will result in no change in the intracellular volume because there is no change in the effective osmolality of the ECF.
 - Addition of hypertonic solute to ECF will result in a decrease in cell volume.

1 liter	Dextrose	Sodium mEq/l	Chloride mEq/l	Tonicity	% ECF	% ICF	Free Water
D5W	5%	0	0	Hypotonic	40	60	1000 ml
0.45% NaCl	0	77	77	Hypotonic	73	27	500 ml
0.9% NaCl	0	154	154	Isotonic	100	0	0 ml
3% NaCl*	0	513	513	Hypertonic	100	0	-2311 ml

*Water will be removed from intracellular space

- Serum sodium concentration is tightly regulated and usually varies by no more than 2-3% (serum osmolality 275-290 mOsm/kg) by pituitary release of antidiuretic hormone and reabsorption of water through the aquaporin channel in renal tubules.
- Nonosmotic release of AVP occurs when effective arterial blood volume (EABV) decreases by 5-10%. Angiotensin II stimulates both nonosmotic release of AVP and thirst.
- Serum sodium concentration may bear no relationship to the ECF volume and sodium content. Hypo- and hypernatremia may be associated with conditions of high, low or normal ECF sodium and volume.
- Brain injury results from either the acute effects of hypo-osmolality or from too rapid correction of hypo-osmolality in patients with symptomatic hyponatremia and is associated with a 20% incidence of significant morbidity.
- Hyponatremia is usually caused by excess of extracellular water relative to sodium because of impaired water excretion.
- Non-osmotic release of ADH can cause water retention and drop in serum sodium concentration and intracellular osmolality.
- Causes of nonosmotic release of ADH include hypovolemia, decreased EABV as seen in patients with CHF, nephrosis, and cirrhosis, and syndrome of inappropriate ADH (SIADH) release.
- The normal kidneys can excrete 20-30 liter/day and it is unusual for an individual with an intact diluting mechanism to become hyponatremic. Patients who ingest water in amounts that exceed the kidneys capacity for excretion will have urine osmolality < 100 mOsm/l.
- Pseudohyponatremia: Hyponatremia in patient with normal serum osmolality caused by hyperlipidemia or hyperproteinemia
- Hyperosmolar hyponatremia: Hyponatremia in the presence of elevated serum osmolality may be caused by the following: hyperglycemia, glycine bladder irrigation, maltose, and mannitol ingestion. These substances led to diffusion of water from the cells into the extracellular compartment resulting in hyponatremia. Each 100 mg/dl rise in glucose concentration serum sodium decreased by 1.6 mEq/l and serum osmolality rises by 2 mOsm/kg.
 - Sodium corrected = Serum Na + (1.6 *(Blood Sugar -100)/100)
 - The presence of unmeasured osmoles should be suspected in osmolal gap exceeds 15 mOsm/kg
 - = measured – calculated
- Solutes that are permeable across cell membranes (eg, urea, methanol, ethanol, isopropyl alcohol, and ethylene glycol) do not cause water movement and cause hypertonicity without causing cell dehydration or changing serum sodium.
- Serum osmolality is comprised primarily of sodium and accompanying anions chloride and bicarbonate
 - Calculated Sosm = (2* Serum Na) + (Blood glucose/18) + (BUN/2.8)
- In low plasma osmolality (hypotonicity) clinical assessment of the extracellular fluid volume is required and patients are categorized as hypovolemic, euvolemic or hypervolemic.
- Diuretic induced hypovolemic hypotonic hyponatremia occurs more frequently with thiazide diuretics than loop diuretics. Usually seen two weeks after starting diuretic.
- Diuretic therapy can cause either a low or a high urinary-sodium concentration, depending on the timing of last diuretic dose.
- Patients with serum sodium values greater than 125 mEq/l are generally asymptomatic except when hyponatremia develops in less than 24 hours.
- Symptoms of hyponatremia result from increase in neuronal cell volume and cerebral edema.
- Severity of symptoms of hyponatremia is proportional to the rate of decrease in serum sodium and the degree of hyponatremia.
- Euvolemic hypotonic hyponatremia is the most common form of hypo-osmolar hyponatremia seen in hospitalized patients.
- Neurologic symptoms and permanent brain damage are unusual following slow-onset hyponatremia, even if the decreases in the sodium concentration are large.
- Causes of hyponatremia

- Pre hospital
 - Overhydration, diarrhea, vomiting, surgery, head injury, CNS infection, liver failure, renal failure, CHF, drugs, SIADH
- Inhospital
 - Overhydration, chemotherapy, surgery, liver failure, renal failure, SIADH, CHF,
- Symptoms are a better indicator for therapy than the absolute value of serum sodium
 - Serum sodium 125-130 mEq/l: gastrointestinal (anorexia, nausea, vomiting)
 - Serum sodium < 125 mEq/l: most symptoms are due to cerebral edema
 - Mild: apathy, headache, lethargy
 - Moderate: Agitation, ataxia, confusion, disorientation, psychosis
 - Severe: Stupor, seizures, pseudobulbar palsy, tentorial herniation, Cheyne-Stokes respiration, coma, death
- Decreases in plasma tonicity result in movement of water into cells until the osmolality of the cells equals that of the extracellular fluid.
- Neurons adapt to increased cell volume over hours to days by transporting potassium, taurine, glutamine, and inositol out of the cells. Intraneuronal water then redistributes to the extracellular space.
- Hyponatremia should not be corrected too rapidly (greater than 12 mEq/liter/day). An acute decrease in brain cell volume may contribute to demyelinating brain injury (central pontine myelinolysis). Paralysis or coma may develop 5-7 days after treatment. Pontine myelinolysis is rarely seen in patients with a serum sodium greater than 120 mEq/l or in those who have hyponatremia for less than 48 hours.
- The sodium content of the infusion must exceed the sum of sodium and potassium concentration in the urine for the serum sodium to rise after infusion of the solution and to effect net free water excretion.
- Patients with SIADH often have urinary concentration of osmotically effective cations that exceed the sodium concentration of 0.9% saline and should be preferentially treated with 3% saline. When urine osmolality exceeds 300 mOsm/kg it is generally advisable to add an intravenous loop diuretic to increase excretion of solute free water and to prevent volume overload.
- Patients with symptomatic hypotonic hyponatremia should be admitted to the intensive care unit or a highly monitored setting.
- Serum urine osmolality, sodium, and potassium should be measured every 4-6 hours on the first day of therapy.
- Furosemide induced diuresis is equivalent to ½ isotonic saline.

References:

1. Kian Pen Goh, Management of Hyponatremia, Am Fam Physician 2004;69:2387-94
2. Vachharajani TJ, Hyponatremia in Critically Ill Patients, J Intensive Care Medicine 2003;18:3-8
3. Yeates KE, Salt and water: a simple approach to hyponatremia, CMAJ 2004;170:365-9
4. Kumar S, Disease of Water Metabolism, Kidney Atlas
5. Adroque HJ, Hyponatremia, NEJM 2000; 342:1581-1589
6. Palmer BF, Causes and Management of Hyponatremia, Ann Pharmacother 2003;37:1694-702



Comment in:

- [Am Heart J. 2003 Mar;145\(3\):377-9.](#)

Effects of high-dose furosemide and small-volume hypertonic saline solution infusion in comparison with a high dose of furosemide as bolus in refractory congestive heart failure: long-term effects.

[Licata G](#), [Di Pasquale P](#), [Parrinello G](#), [Cardinale A](#), [Scandurra A](#), [Follone G](#), [Argano C](#), [Tuttolomondo A](#), [Paterna S](#).

Department of Internal Medicine, University of Palermo, Palermo, Italy.

BACKGROUND: Diuretics have been accepted as first-line treatment in refractory congestive heart failure (CHF), but a lack of response to them is a frequent event. A randomized, single-blind study was performed to evaluate the effects of the combination of high-dose furosemide and small-volume hypertonic saline solution (HSS) infusion in the treatment of refractory New York Heart Association (NYHA) class IV CHF and a normosodic diet during follow-up. **Materials and Methods** One hundred seven patients (39 women and 68 men, age range 65-90 years) with refractory CHF (NYHA class IV) of different etiologies, who were unresponsive to high oral doses of furosemide, angiotensin-converting enzyme inhibitors, digitalis, and nitrates, were enrolled. Inclusion criteria included an ejection fraction (EF) <35%, serum creatinine level <2 mg/dL, blood urea nitrogen level < or =60 mg/dL, reduced urinary volume, and low natriuresis. The patients were randomized in 2 groups (single-blind). Patients in group 1 (20 women and 33 men) received an intravenous (IV) infusion of furosemide (500-1000 mg) plus HSS (150 mL of 1.4%-4.6% NaCl) twice a day in 30 minutes. Patients in group 2 (19 women and 35 men) received an IV bolus of furosemide (500-1000 mg) twice a day, without HSS, during a period lasting 6 to 12 days. Both groups received IV KCl (20-40 mEq) to prevent hypokalemia. At study entry, all patients underwent a physical examination and measurement of body weight (BW), blood pressure (BP), and heart rate (HR), an evaluation of signs of CHF, and measurement of control levels of serum Na, K, Cl, bicarbonate, albumin, uric acid, creatinine, urea, and glycemia daily during hospitalization, and measurements of the daily output of urine for Na, K, and Cl. A chest radiograph, electrocardiogram, and echocardiogram were obtained at study entry, during hospitalization, and at the time of discharge from the hospital. During the treatment and after discharge, the daily dietary Na intake was 120 mmol in group 1 versus 80 mmol in group 2, with a fluid intake of 1000 mL daily in both groups. An assessment of BW and 24-hour urinary volume, serum, and urinary laboratory parameters were performed daily until patients reached a compensated state, when IV furosemide was replaced with oral administration (250-500 mg/d). After discharge from the hospital, patients were observed as outpatients weekly for the first 3 months and, subsequently, once a month. **RESULTS:** The groups were similar in age, sex, EF, risk factors, treatment, and etiology of CHF. All patients showed a clinical improvement. Ten patients in both groups had hyponatremia at entry. A significant increase in daily diuresis and natriuresis was observed in both groups, but it was more significant in the group receiving HSS ($P < .05$). The serum Na level increased in group 1 and decreased in group 2 ($P < .05$). The serum K level was decreased in both groups ($P < .05$). BW was reduced in both groups ($P < .05$). Group 2 had an increase in serum creatinine level. Serum uric acid levels increased in both groups. BP values decreased and HR was corrected to normal values in both groups. In the follow-up period (31 +/- 14 months), 25 patients from group 1 were readmitted to the hospital for heart failure. In group 2, 43 patients were readmitted to the hospital at a

higher class than at discharge. Twenty-four patients in group 1 died during follow-up, versus 47 patients in group 2 ($P < .001$). CONCLUSION: This treatment is effective and well tolerated, improves the quality of life through the relief of signs and symptoms of congestion, and may delay more aggressive treatments. The effects were also beneficial in a long period for mortality reduction (55% vs 13% survival rate) and for clinical improvement.

Publication Types:

- [Clinical Trial](#)
- [Randomized Controlled Trial](#)

PMID: 12660669 [PubMed - indexed for MEDLINE]

2: [Eur J Heart Fail](#). 2000 Sep;2(3):305-13.

[Related Articles](#), [Links](#)



Effects of high-dose furosemide and small-volume hypertonic saline solution infusion in comparison with a high dose of furosemide as a bolus, in refractory congestive heart failure.

[Paterna S](#), [Di Pasquale P](#), [Parrinello G](#), [Amato P](#), [Cardinale A](#), [Follone G](#), [Giubilato A](#), [Licata G](#).

Department of Internal Medicine, University of Palermo, Palermo, Italy.

BACKGROUND: Diuretics, have been accepted as first-line treatment in refractory heart failure, but a lack of response is a frequent event. A randomised single blind study was performed to evaluate the effects of the combination of high-dose furosemide and small-volume hypertonic saline solution (HSS) infusion in the treatment of refractory NYHA class IV congestive heart failure (CHF). **MATERIALS AND METHODS:** Sixty patients (21 F/39 M) with refractory CHF (NYHA class IV) of different etiologies, unresponsive to high oral doses of furosemide, ACE-inhibitors, digitalis, and nitrates, aged 65-90 years, were enrolled. They had to have an ejection fraction (EF) $< 35\%$, serum creatinine < 2 mg/dl, BUN ≤ 60 mg/dl, a reduced urinary volume and a low natriuresis. The patients were randomised in two groups (single blind): group 1 (11 F/19 M) received an i.v. infusion of furosemide (500-1000 mg) plus HSS (150 ml of 1.4-4.6% NaCl) b.i.d. in 30 min. Group 2 (10 F/20 M) received an i.v. bolus of furosemide (500-1000 mg) b.i.d., without HSS, during a period lasting 6-12 days. Both groups received KCl (20-40 mEq.) i.v. to prevent hypokalemia. All patients underwent at entry a physical examination, measurement of body weight (BW), blood pressure (BP), heart rate (HR), evaluation of signs of CHF, and controls of serum Na, K, Cl, bicarbonate, albumin, uric acid, creatinine, urea and glycemia and daily during hospitalization, as well as the daily output of urine for, Na, K and Cl measurements. Chest X-ray, ECG and echocardiogram were obtained at entry during and at the discharge. During the treatment and after discharge the daily dietary Na intake was 120 mmol with a drink fluid intake of 1000 ml daily. An assessment of BW and 24-h urinary volume, serum and urinary laboratory parameters, until reaching a compensated state, were performed daily, when i.v. furosemide was replaced with oral administration (250-500 mg/day). After discharge, patients were followed as outpatients weekly for the first 3 months and subsequently once per month. **RESULTS:** The groups were similar for age, sex, EF, risk factors, treatment and etiology of CHF. All patients showed a clinical improvement. Six patients in both groups had hyponatremia (from 120 to 128 mEq./l) at entry. A significant increase in daily diuresis in both groups was observed (from 390 ± 155 to 2100 ± 626 , and from 433 ± 141 to 1650 ± 537 ml/24 h, $P < 0.05$). Natriuresis (from 49 ± 15 to 198 ± 28 mEq./24 h) was higher in group 1 vs. group 2 (from 53.83 ± 12 to 129 ± 39 mEq./24 h, $P < 0.05$). Serum Na (from

135.9+/-6.8 to 142.2+/-3.8 mEq./l, P<0.05) increased in the group 1 and decreased in the group 2 (from 134.7+/-7.9 to 130.1+/-4.3 mEq./l). Serum K was decreased (from 4.4+/-0.6 to 3.9+/-0.6, and 4.6+/-9 to 3.6+/-0.5 mEq./l, P<0.05) in both groups. BW was reduced (from 73.8+/-9.1 to 63.8+/-8.8, and from 72.9+/-10.2 to 64.5+/-7.5 kg, P<0.05) in both groups. Group 2 showed more patients in NYHA class III than group 1 (18 vs. 2 patients, P<0.05). Group 2 showed an increase of serum creatinine. Serum uric acid increased in both groups. BP values decreased, and HR was corrected to normal values in both groups. Group 2 showed a longer hospitalization time than group receiving HHS infusion (11.67+/-1.8 vs. 8.57+/-2.3 days, P<0.001). In the follow-up (6-12 months), none of the patients from group 1 were readmitted to the hospital and they maintained the NYHA class achieved at the discharge. Group 2 showed 12 patients readmitted to hospital and a higher class than at discharge. **CONCLUSION:** Our data suggest that the combination of furosemide with HSS is feasible and it appears that this combination produces an improvement of hemodynamic and clinical parameters, reduces the hospitalization time and maintains the obtained results over time in comparison with those receiving high-dose furosemide as bolus.

[Congest Heart Fail.](#) 2006 Jan-Feb;12(1):55-60.

[Related Articles, Links](#)



Hyponatremia and heart failure--treatment considerations.

[Sica DA.](#)

Departments of Medicine and Pharmacology, Section of Clinical Pharmacology and Hypertension, Division of Nephrology, Medical College of Virginia of Virginia Commonwealth University, Richmond, VA 23298-0160, USA. dsica@hsc.vcu.edu

Hyponatremia as it occurs in the heart failure patient is a multifactorial process. The presence of hyponatremia in the heart failure patient correlates with both the severity of the disease and its ultimate outcome. The therapeutic approach to the treatment of hyponatremia in heart failure has traditionally relied on attempts to improve cardiac function while at the same time limiting fluid intake. In more select circumstances, hypertonic saline, loop diuretics, and/or lithium or demeclocycline have been used. The latter two compounds act by retarding the antidiuretic effect of vasopressin but carry with their use the risk of serious renal and/or cardiovascular side effects. Alternatively, agents that selectively block the type 2 vasopressin receptor increase free water excretion without any of the adverse consequences of other therapies. Conivaptan, lixivaptan, and tolvaptan are three such aquaretic drugs. Vasopressin receptor antagonists will redefine the treatment of heart failure-related hyponatremia and may possibly evolve as adjunct therapies to loop diuretics in diuretic-resistant patients.

Publication Types:

- [Review](#)

PMID: 16470095 [PubMed - indexed for MEDLINE]

2: [Am J Cardiol.](#) 2005 May 2;95(9A):14B-23B.

[Related Articles, Links](#)



Current treatments and novel pharmacologic treatments for hyponatremia in

congestive heart failure.

Goldsmith SR.

University of Minnesota Medical School, Minneapolis, Minnesota 55415, USA. srg_hcmc@yahoo.com

Hyponatremia in congestive heart failure (CHF) is associated with increased morbidity and mortality, underlining the importance of adequate assessment and treatment of this electrolyte imbalance in patients with CHF. Current treatment options for hyponatremia in CHF include hypertonic saline solution, loop diuretics, fluid restriction, and other pharmacologic agents, such as demeclocycline, lithium carbonate, and urea. Hypertonic saline solution must be administered with extreme caution because excessively slow or rapid sodium correction can lead to severe neurologic adverse effects. Loop diuretics are useful for reducing the water retention caused by CHF. However, the potent diuresis induced by agents such as furosemide results in loss of sodium and other essential electrolytes, which may exacerbate hyponatremia. Fluid restriction is only moderately effective and often difficult to implement in the hospital setting. Agents such as demeclocycline and lithium have potentially serious renal and cardiovascular side effects. The arginine vasopressin (AVP) receptor antagonists are a promising new class of aquaretic agents that increase free-water excretion while maintaining levels of sodium and other essential electrolytes. Tolvaptan (OPC-41061), lixivaptan (VPA-985), and conivaptan (YM-087) are currently under development for the treatment of hyponatremia. Although tolvaptan and lixivaptan are selective for the vasopressin-2 (V(2)) receptor responsible for the antidiuretic actions of AVP, conivaptan demonstrates activity at both the V(2) receptor and the V(1a) receptor responsible for the vasoconstricting properties of AVP. This dual receptor activity may be particularly useful in patients with CHF. These patients may benefit from the increased cardiac output, reduced total peripheral resistance, and reduced mean arterial blood pressure that results from V(1a) receptor blockade as well as the reduced congestion, reduced cardiac preload, and increased sodium concentrations induced by V(2) receptor antagonism.

Publication Types:

- [Review](#)

PMID: 15847853 [PubMed - indexed for MEDLINE]

3: [Crit Care Nurse](#). 2004 Oct;24(5):36-8, 40-4, 46 passim.

[Related Articles](#), [Links](#)

Full text article at
ccn.aacnjournals.org

Pass the salt: indications for and implications of using hypertonic saline.

Johnson AL, Criddle LM.

trauma/neuro intensive care unit at Oregon Health & Science University, Portland, Ore, USA.

Sodium is the most abundant extracellular ion. Historically, therapy with hypertonic saline was widely used for a variety of conditions. Currently, there are 3 primary indications for its use in critical care: hyponatremia, volume resuscitation, and brain injury. SIADH and CSW syndrome may require sodium replacement, but most cases of hyponatremia can be managed without administration of hypertonic saline. Studies of use of hypertonic saline in hypovolemia and brain injury are promising, but additional research is needed to better define optimal dosing regimens and to determine the relative risks associated with hypertonic saline versus conventional treatment for the management of patients with head injuries

and for volume resuscitation in shock states.

Publication Types:

- [Review](#)

PMID: 15526489 [PubMed - indexed for MEDLINE]

- 4: [Am J Med Sci](#). 2003 Jul;326(1):25-30.

[Related Articles](#), [Links](#)



Treatment of symptomatic hyponatremia.

[Decaux G](#), [Soupart A](#).

Hopital Universitaire Erasme, Bruxelles, Belgium. guy.decaux@skynet.be

Inadequate treatment of severe hyponatremia (<120 mEq/L) can be associated with severe neurological damage. In acute (<48 hours) hyponatremia, usually observed in the postoperative period, prompt treatment with hypertonic saline (3%) can prevent seizures and respiratory arrest. For patients with chronic (>48-72 hours) symptomatic hyponatremia, correction must be rapid during the first few hours (to decrease brain edema) followed by a slow correction limited to 10 mmol/L over 24 hours to avoid the development of osmotic demyelinating syndrome. In patients with asymptomatic hyponatremia, slow correction is the appropriate approach. When patients are overtreated, neurologic damage can be prevented by relowering the serum sodium (SNa) so that the daily increase in SNa remains below 10 mmol/L/24 hours. Frequent measurements of SNa during the correction phase of SNa are mandatory to avoid overcorrection. The use of urea to treat hyponatremia represents an advantageous alternative to hypertonic saline.

Publication Types:

- [Review](#)

PMID: 12861122 [PubMed - indexed for MEDLINE]

- 5: [Pediatr Rev](#). 2002 Nov;23(11):371-80.

[Related Articles](#), [Links](#)

Full text article at
www.pedsinreview.org

Disorders of water metabolism in children: hyponatremia and hypernatremia.

[Moritz ML](#), [Ayus JC](#).

Children's Hospital of Pittsburgh, Pittsburgh, PA, USA.

Publication Types:

- [Review](#)

- 6: [Rev Med Brux.](#) 2001 Oct;22(5):413-9.

[Related Articles](#), [Links](#)

[Treatment of severe hyponatremia (<120mEq/l)]

[Article in French]

[Decaux G.](#)

Service de Medecine Interne Generale, Hopital Erasme, U.L.B.

Inadequate treatment of severe hyponatremia (< 120 mEq/l) can be associated with severe neurological damage. Acute hyponatremia (< 48 h) is usually observed in the postoperative period, these patients need prompt treatment with hypertonic saline (3%) to avoid epilepsy and respiratory arrest. Patients with chronic symptomatic hyponatremia (> 48-72 h) need a rapid correction of SNa the first hours (to decrease brain oedema) followed by a slow correction so that the daily increase in SNa stay under 10 mEq/l/24 h, to avoid the "Osmotic Demyelinating Syndrome" (ODS). Patients with asymptomatic hyponatremia need a slow correction. In patients who are overtreated, decreasing the SNa by giving hypotonic solutions (eventually with DDAVP) so that the daily increase in SNa stays under 10 mEq/l/24 h could protect them again ODS. Frequent measurements of SNa during the correction phase of SNa are mandatory to avoid overcorrection. The use of urea for the management of hyponatremia could represent a good alternative to hypertonic saline. In animals, urea treatment has been clearly shown to protect again ODS, this protective effect could be due to its ability to induce quickly brain "organic osmolytes" reaccumulation.

Publication Types:

- [Review](#)

PMID: 11723783 [PubMed - indexed for MEDLINE]

- 7: [J Am Soc Nephrol.](#) 2001 Feb;12 Suppl 17:S10-4.

[Related Articles](#), [Links](#)

Treatment of severe hyponatremia: conventional and novel aspects.

[Gross P](#), [Reimann D](#), [Henschkowski J](#), [Damian M](#).

Department of Medicine, Universitätsklinikum Carl Gustav Carus, Dresden, Germany.
peter.gross@mailbox.tu-dresden.de

Hyponatremia is a frequent electrolyte disorder. A hyponatremia is called acute severe (<115 mM) when the duration has been <36 to 48 h. Such patients often have advanced symptoms as a result of brain edema. Acute severe hyponatremia is a medical emergency. It should be corrected rapidly to approximately 130 mM to prevent permanent brain damage. In contrast, in chronic severe hyponatremia (>4 to 6 d), there is no brain edema and symptoms are usually mild. In such patients, a number of authors have recommended a correction rate <0.5 mM/h to approximately 130 mM to minimize the risk of cerebral myelinolysis. Sometimes it is not possible to diagnose whether a severe hyponatremia is

acute or chronic. In such cases, an initial imaging procedure is helpful in deciding whether rapid or slow correction should be prescribed. The modalities of treatment of severe hyponatremia have so far consisted of infusions of hypertonic saline plus fluid restriction. In the near future, vasopressin antagonists will become available. Preliminary experience has already demonstrated their efficiency of inducing a sustained water diuresis and a correction of hyponatremia.

Publication Types:

- [Review](#)

PMID: 11251026 [PubMed - indexed for MEDLINE]

8: [Clin Endocrinol \(Oxf\)](#). 2000 Jun;52(6):667-78.

[Related Articles](#), [Links](#)



Comment in:

- [Clin Endocrinol \(Oxf\)](#). 2003 Jul;59(1):142.

Hyponatraemia.

[Smith DM](#), [McKenna K](#), [Thompson CJ](#).

Academic Department of Endocrinology, Beaumont Hospital, Dublin, Republic of Ireland.

Publication Types:

- [Review](#)

PMID: 10848869 [PubMed - indexed for MEDLINE]

9: [N Engl J Med](#). 2000 May 25;342(21):1581-9.

[Related Articles](#), [Links](#)



Comment in:

- [N Engl J Med](#). 2000 Sep 21;343(12):886-7; author reply 888.
- [N Engl J Med](#). 2000 Sep 21;343(12):886; author reply 888.
- [N Engl J Med](#). 2000 Sep 21;343(12):886; author reply 888.
- [N Engl J Med](#). 2000 Sep 21;343(12):887-8.
- [N Engl J Med](#). 2000 Sep 21;343(12):887; author reply 888.
- [N Engl J Med](#). 2000 Sep 21;343(12):887; author reply 888.

Hyponatremia.

[Adrogué HJ](#), [Madias NE](#).

Department of Medicine, Baylor College of Medicine and Methodist Hospital, Houston, USA.

Publication Types:

- [Review](#)

PMID: 10824078 [PubMed - indexed for MEDLINE]

□ 10: [Neurosurg Rev.](#) 1996;19(3):193-6.

[Related Articles](#), [Links](#)

Cerebral salt wasting syndrome.

[Uygun MA](#), [Ozkal E](#), [Acar O](#), [Erongun U](#).

Department of Neurosurgery, Selcuk University School of Medicine, Konya, Turkey.

Hyponatremia following acute or chronic central nervous system injury which is due to excessive Na⁺ loss in the urine without an increase in the body fluid, has been described as Cerebral Salt Wasting Syndrome (CSWS). This syndrome is often confused with dilutional hyponatremia secondary to inappropriate ADH secretion. Accurate diagnosis and management are mandatory for to improve the course of the disease. In this study a patient with CSW Syndrome is presented and the treatment and diagnosis of this syndrome are discussed in view of the literature.

Publication Types:

- [Case Reports](#)
- [Review](#)

PMID: 8875510 [PubMed - indexed for MEDLINE]

□ 11: [BMJ.](#) 1993 Jul 31;307(6899):305-8.

[Related Articles](#), [Links](#)

Comment in:

- [BMJ. 1993 Sep 18;307\(6906\):736.](#)

Management of hyponatraemia.

[Arieff AI](#).

Department of Medicine, Veterans Affairs Medical Center, San Francisco, California 94121.

Publication Types:

- [Review](#)

- 12: [J Neurol Neurosurg Psychiatry](#). 1993 Jun;56(6):626-32.

[Related Articles](#), [Links](#)

Symptomatic hyponatraemia: can myelinolysis be prevented by treatment?

[Harris CP](#), [Townsend JJ](#), [Baringer JR](#).

Department of Neurology, University of Utah Medical Center, Salt Lake City 84132.

The treatment of hyponatraemia is controversial because of the risk of causing central or extrapontine myelinolysis (EPM). Rapid correction with hypertonic saline to a low normal sodium level has its proponents; others feel that slow correction to below normal sodium values is preventative. Most investigators feel that overcorrection should be avoided. It is not known whether the magnitude of serum sodium change is more important than the actual rate of correction. We present three patients with hyponatraemia ranging from 103 to 105 mmol/l who were corrected slowly with normal saline, corrected quickly with hypertonic saline, or rapidly overcorrected with hypertonic saline. All became comatose and died; all had EPM with or without central pontine myelinolysis (CPM). The rate of correction, the solution used, or the magnitude of correction did not seem to protect against demyelination. In a review of 67 reported CPM cases since 1983, no patients documented as having CPM or EPM by radiological studies or necropsy were treated with water restriction only. A group of 27 hyponatraemic patients treated only with water restriction and 35 with diuretic cessation alone did not develop CPM or EPM. This may be a reasonable approach to patients with symptomatic hyponatraemia and normal renal function.

Publication Types:

- [Case Reports](#)
- [Review](#)

PMID: 8509775 [PubMed - indexed for MEDLINE]

- 13: [Pol Tyg Lek](#). 1992 Jul 6-13;47(27-28):604-7.

[Related Articles](#), [Links](#)

[Hyponatremia--clinical aspects and treatment]

[Article in Polish]

[Pupek-Musialik D](#), [Raszeja-Wanic B](#).

Kliniki Nadcisnienia Tetniczego IK AM w Poznaniu.

Publication Types:

- [Review](#)

PMID: 1488338 [PubMed - indexed for MEDLINE]

□ 14: [Crit Care Med.](#) 1992 Apr;20(4):534-9.

[Related Articles](#), [Links](#)

Severe hyponatremia: the case for conservative management.

[Sterns RH.](#)

University of Rochester School of Medicine, Rochester General Hospital, NY.

Publication Types:

- [Review](#)

PMID: 1559369 [PubMed - indexed for MEDLINE]

□ 15: [Pediatr Clin North Am.](#) 1990 Apr;37(2):351-63.

[Related Articles](#), [Links](#)

Hyponatremia.

[Berry PL](#), [Belsha CW.](#)

Baylor College of Medicine, Houston, Texas.

This article provides a useful clinical classification of hyponatremic states based upon plasma tonicity and extracellular fluid volume. The pathophysiology of hyponatremia induced by hypovolemic, euvolemic, and hypervolemic conditions is discussed. An approach to the treatment of each category of hyponatremia is presented.

Publication Types:

- [Review](#)

PMID: 2184401 [PubMed - indexed for MEDLINE]

□ 16: [Am J Med.](#) 1990 Feb;88(2):161-6.

[Related Articles](#), [Links](#)



Comment in:

- [Am J Med. 1990 Jun;88\(6\):702.](#)

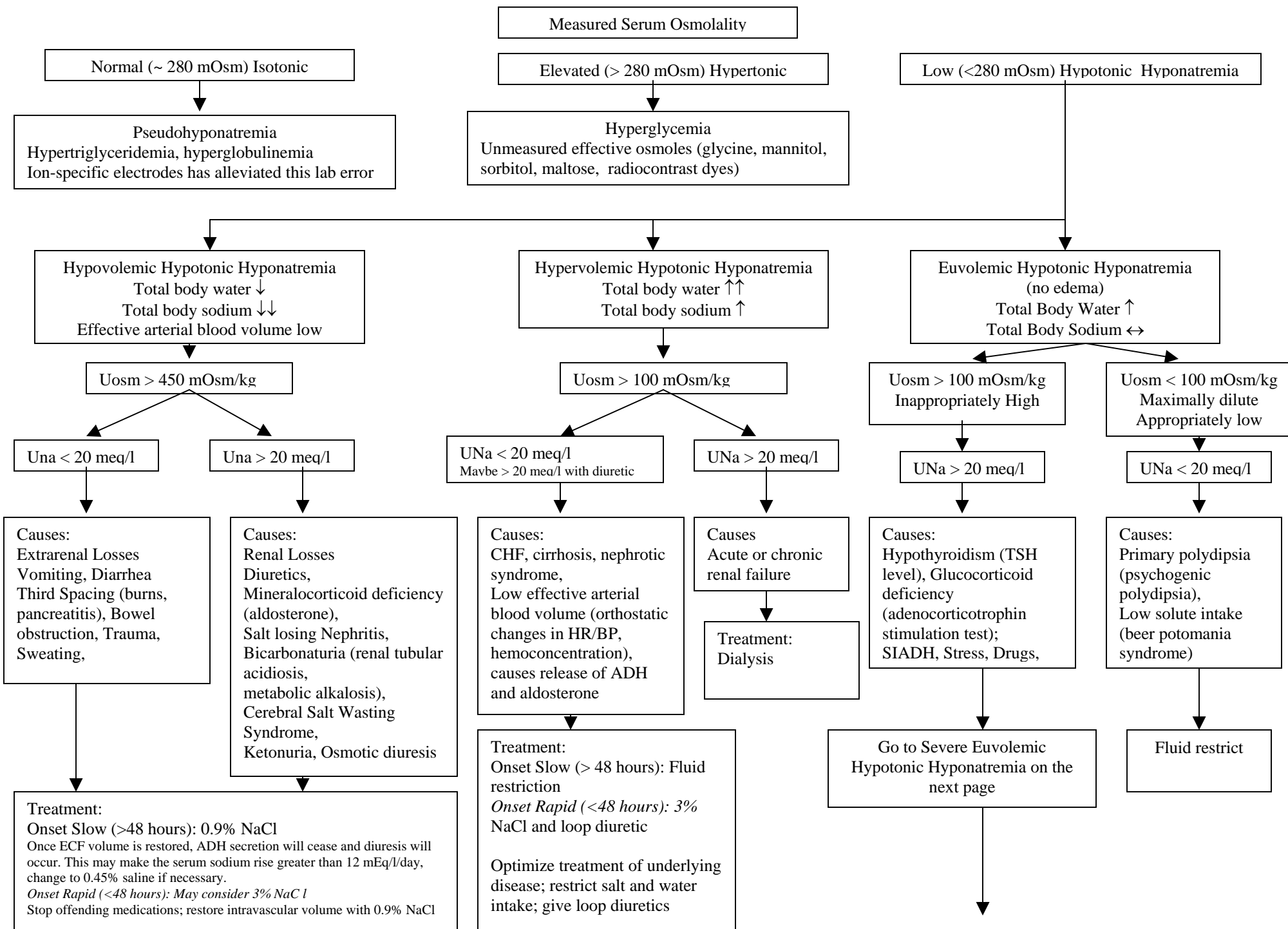
Management of severe hyponatremia: rapid or slow correction?

[Cluitmans FH](#), [Meinders AET.](#)

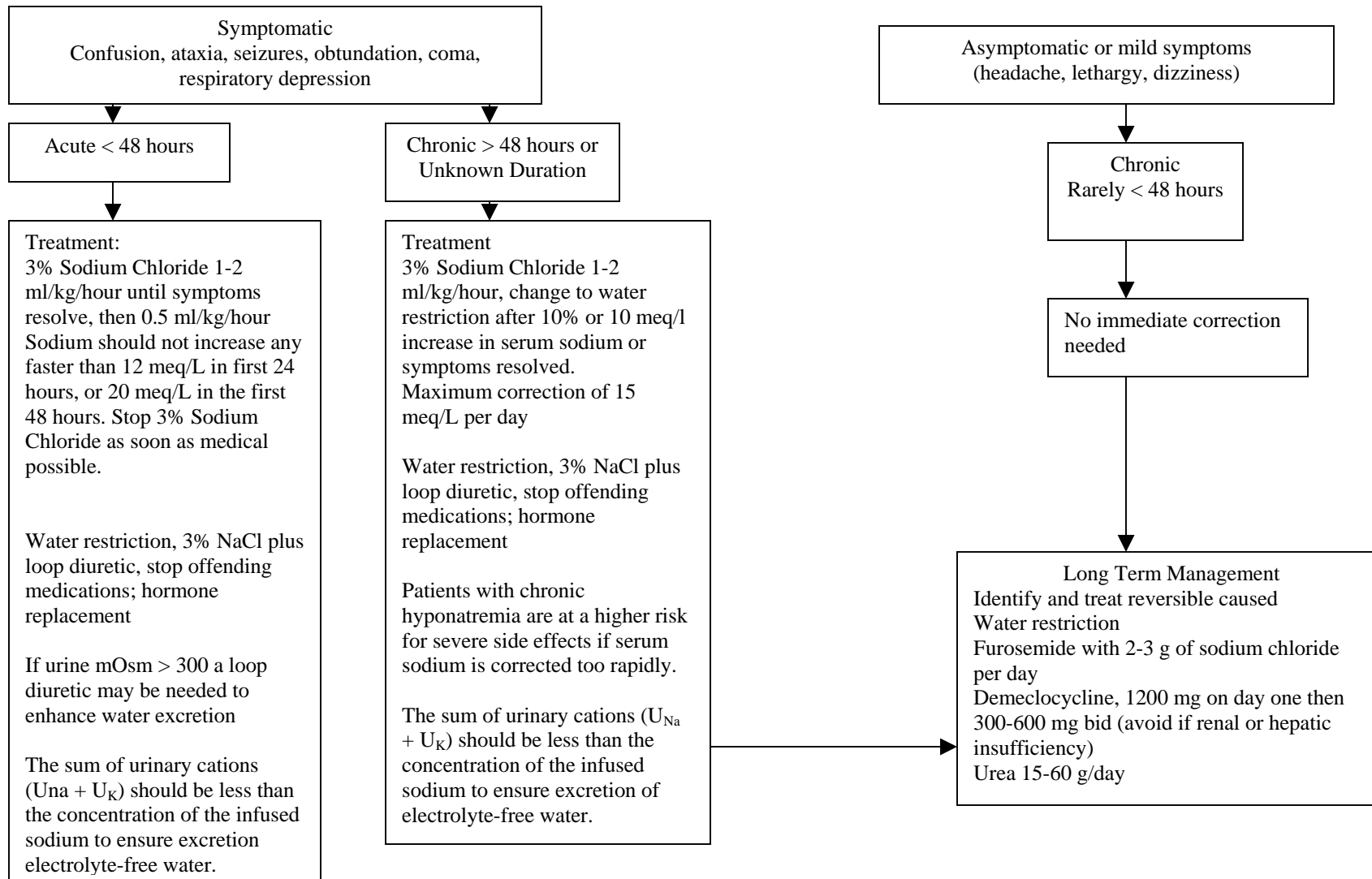
Department of General Internal Medicine, University Hospital of Leiden, The Netherlands.

Case reports and the literature on the treatment of severe hyponatremia were reviewed. It appeared that the conflicting opinions with respect to the rate of correction of severe hyponatremia could be reduced to not differentiating between acute and chronic hyponatremia, to using different criteria for this distinction, and to differences in treatment strategy. After reviewing the available data in the literature, it is suggested that hyponatremia should be classified as acute whenever the rate of decrease of serum sodium exceeds 0.5 mmol/L/hour. If it is unknown at which rate the hyponatremia has developed, it can be assumed to be acute if within a short period of time (two to three days), large quantities of fluid are ingested orally or administered parenterally, especially hypotonic fluids in the presence of impaired water excretion. In other cases, chronic hyponatremia is probable. It is concluded that acute hyponatremia should be treated without delay and rapidly at a rate of at least 1 mmol/L/hour, to prevent severe neurologic damage or death. With respect to chronic hyponatremia, it appeared that severe neurologic complications almost exclusively occurred in patients who were treated with hypertonic or isotonic saline without the addition of furosemide or an osmotic diuretic agent, resulting in a (rapid) correction rate of 0.5 mmol/L/hour or more. In contrast, patients with severe chronic hyponatremia treated with furosemide and isotonic or hypertonic saline almost uniformly did well after rapid correction. Uneventful recovery is also the rule when severe chronic hyponatremia is corrected slowly, at a rate less than 0.5 mmol/L/hour. On pathophysiologic grounds, and bearing in mind that slow correction was used in the majority of reported patients in the literature with severe chronic hyponatremia who recovered without neurologic complications, this treatment modality is preferable. Whenever the available data do not permit a differentiation between acute or chronic hyponatremia, rapid correction has to be pursued by means of administration of hypertonic or isotonic saline together with furosemide.

Hyponatremia Algorithm



Severe **Euvolemic** Hypotonic Hyponatremia (Serum Sodium < 125 meq/l)



There is no consensus about the optimal treatment of symptomatic hyponatremia. Correction should be of a sufficient pace and magnitude to reverse the manifestations of hypotonicity, but not so rapid and large as to pose a risk for developing osmotic demyelination. The speed at which hyponatremia develops rather than the magnitude of hyponatremia is most closely associated with degree of symptoms. Normalization of serum sodium should be avoided for the first 48 hours.

For mild symptoms of hyponatremia, or asymptomatic patients with serum sodium above 125 meq/l, use a conservative approach. (Water restriction less than 1-1.25 l/day) If serum sodium continues to decline 0.9% NaCl may be given to clarify diagnosis. If the patient has SIADH, hyponatremia will worsen and if they are ECF volume contracted serum sodium will improve.