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Speaker Disclosures

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Astellas Pharma US, Inc.,
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MANAGEMENT OF HYPONATREMIA WITH FORMULA AND BEYOND

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Initial approach to Hyponatremia ($[Na^+]_s$ <136 mEq/l)

Hypotonic (dilutional) ?

Non-hypotonic ?

Non-hypotonic Hyponatremia

Translocational	(e.g., hyperglycemia, hypertonic mannitol)
Isotonic	(e.g., isotonic Na^+ free irrigant solutions for TURP or uterine bleeding)
Pseudohyponatremia	(spurious, laboratory artifact)

Populations/settings/conditions with increased prevalence of hyponatremia

- Elderly
- Drug-induced: Thiazide diuretics, antidepressants, antipsychotics, anticonvulsants, antineoplastic drugs, methamphetamines, NSAIDS, etc.
- Postoperative state
- Selected conditions:
  Alcoholism/liver cirrhosis
  Congestive heart failure
  HIV infection
  Pneumonia
- Exercise-associated hyponatremia (EAH)
- Emergency Department
- ICU

Main determinants of tonicity and $[Na^+]_s$

$$\text{Serum tonicity} \cong 2 \times [Na^+]_s$$

$$\text{Serum tonicity} \cong \frac{2 \times Na^+_E + 2 \times K^+_E}{\text{total body water}}$$

$$[Na^+]_s \cong \frac{Na^+_E + K^+_E}{\text{total body water}} \; *$$

* Edelman IS et al. J. Clin Invest 1958;37:1236-56.

PATHOGENESIS OF HYPONATREMIA

Represents an excess of water in relation to Na^+/K^+ stores

- Very low Na^+ intake
  (negative Na^+ balance)
- Renal Na^+ loss
  (e.g. diuretics, RTA, salt wasting)
- Extrarenal Na^+ loss
  (e.g., GI loss, "third space")

- Very low K^+ intake
  (e.g., alcoholics, tea and toast diet)
- Renal K^+ loss (e.g., diuretics)
- Extrarenal K^+ loss
  (e.g., cirrhosis with laxatives , diarrhea)

$$\downarrow [Na^+]_s \cong \frac{\downarrow Na^+_E \quad + \quad \downarrow K^+_E}{\uparrow TBW}$$

Impaired renal water excretion: ECF volume?

Decreased

Renal Na^+ loss (e.g., diuretics, RTA)

Extrarenal Na^+ loss (e.g., GI losses)

~ Normal (e.g., thiazides, SIADH)

Increased (e.g., CHF, cirrhosis, nephrosis)

Excess water intake

Primary polydipsia

Dilute infant formula,

Na^+ free irrigant solutions,

"Swimming lessons",

Multiple-tap water enemas

How pathogenesis is determined?

- **Medical history**
  - Underlying disease (e.g., CHF, cirrhosis)
  - Recent acute illness (e.g., diarrhea, pneumonia)
  - Fluid intake and losses (changes in body weight)
  - Medications (e.g., thiazides, antipsychotics)
  - Other pertinent information (e.g., previous diagnosis of hyponatremia, recent serum electrolytes)
- **Physical examination**
  - Blood pressure, skin turgor, overall volume status
- **Ancillary tests**
  - Serum electrolytes, BUN, creatinine, uric acid
  - Posm, cortisol level, thyroid panel
  - Uosm (e.g., 200 ~1.006; 400 ~ 1012; 600 ~ 1.018)
  - Urinary electrolytes
  - CT head, MRI

Management of Hyponatremia

1. Initial treatment

2. Long-term management

How does pathogenesis guide therapy?

Potassium depletion	→	Potassium supplementation
Excessive water intake (polyuria with dilute urine, e.g., Uosm <200 mOsm/kg)	→	Fluid restriction alone (condition tends to "self correct" the hyponatremia at rapid pace)
Impaired water excretion (oliguric with concentrated urine, e.g., Uosm >400 mOsm/kg with ECF volume depletion)	→	Fluid restriction plus isotonic saline (volume repletion promotes water diuresis that "speeds up" correction)
Impaired water excretion (oliguric with concentrated urine, e.g., Uosm >400 mOsm/kg with normal or increased ECF volume)	→	Fluid restriction plus/minus 3% NaCl (513 mEq/l) furosemide AVP-receptor antagonists (condition does not tend to "self correct" the hyponatremia)

Intensive Care Med (1997) 23: 309–316
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ORIGINAL

H. J. Adrogué
N. E. Madias

Aiding fluid prescription for the dysnatremias

N Engl J Med 342:1581-1589, 2000.

N Engl J Med 342:1493-1499, 2000.

PRIMARY CARE

Review Article

Primary Care

HYPONATREMIA

HORACIO J. ADROGUÉ, M.D., AND NICOLAOS E. MADIAS, M.D.

Primary Care

HYPERNATREMIA

HORACIO J. ADROGUÉ, M.D., AND NICOLAOS E. MADIAS, M.D.

JASN, 15:781A, 2004.

Adrogué HJ, Madias NE. Quantitative Projection of the Impact of Measured Water and Electrolyte Losses on Serum Sodium Concentration for Managing Hyponatremia and Hypernatremia.

(1) Aims, (2) rationale, (3) use, and (4) expectations of formulas

(1) Provision of quantitative guidance for the prevention and management of dysnatremias

(2) Na^+ and K^+ represent the dominant cationic osmoles of ECF and ICF, respectively. Since these compartments are in osmotic equilibrium, total body cationic osmoles may be estimated as the product of TBW and $[Na^+]_s$

(3) The impact on $[Na^+]_s$ of cationic osmoles contained in 1 liter of infusate is conveniently and precisely estimated with the "formula for infusates"; alternatively, the impact on $[Na^+]$ of 1 liter of fluid loss is achieved with the "formula for losses"

(4) Expectations of formulas

- Formulas for "infusates" and "losses"should be used only as *auxiliary instruments* to facilitate implementation of fluid therapy
- The patient is regarded as a *closed system* without gain or loss of water and electrolytes other than the infusate or fluid loss being calculated
- An estimate of *TBW* is required and represents only a *rough approximation*
- The formulas predict effects after *complete equilibration* of all body fluids
- *Failure to account for other ongoing changes* in fluid and electrolyte balance (commonly substantial) result in a *substantial deviation* of the actual level of [Na^+] obtained compared to the value projected by the equations.

Formula predicting Δ $[Na^+]_s$ with infusates

Projects the impact of 1 l of any infusate on the patient's $[Na^+]_s$

$$\Delta [Na^+]_s = \frac{[Na^+ + K^+]_{inf} - [Na^+]_s}{\text{total body water} + 1}$$

Because of intercurrent fluid losses and other uncertainties, $[Na^+]_s$ should be closely monitored and adjustments to the prescription made (type of infusate, rate of infusion)

Formula predicting Δ $[Na^+]_s$ with fluid losses *

Projects the expected $\Delta[Na^+]_s$ in response to losing 1 l of fluid (fl) from the renal or extrarenal route

$$\Delta [Na^+]_s = \frac{[Na^+]_s - [Na^+ + K^+]_{fl}}{\text{total body water} - 1}$$

* "Reverse formula", compared to that of effects of infusates

Adrogué HJ, Madias NE. Quantitative Projection of the Impact of Measured Water and Electrolyte Losses on Serum Sodium Concentration for Managing Hyponatremia and Hypernatremia.

JASN, 15:781A, 2004.

Formulas Predicting $\Delta [Na^+]_s$

(1) Formula for Infusates

$$\Delta [Na^+]_s = \frac{[Na^+ + K^+]_{inf} - [Na^+]_s}{\text{total body water} + 1}$$

(2) "Reverse Formula" (for Fluid Losses)

$$\Delta [Na^+]_s = \frac{[Na^+]_s - [Na^+ + K^+]_{fl}}{\text{total body water} - 1}$$

Effects of 1 liter of fluid loss on $[Na^+]_s$ (e.g., initial $[Na^+]_s$ 110 mEq/l, TBW 30 liters)

Condition	$[Na^+ + K^+]_{fl}$	Effect on $[Na^+]_s$
Water diuresis(e.g., polydipsia)	20 mEq/l	↑ 3.0 mEq/l
Viral/bacterial diarrhea	50 mEq/l	↑ 2.0 mEq/l
Diuretics (e.g., furosemide)	55 mEq/l	↑ 1.8 mEq/l
Gastric fluid	70 mEq/l	↑ 1.3 mEq/l

Other formulas for calculating saline infusion rates

	Step 1	*Step 2*
Traditional	$\text{Na required} = \text{TBW} \times ([\text{Na}]_2 - [\text{Na}]_1)$	$\text{Volume (liter)} = \dfrac{\text{Na required (mmol)}}{513 \text{ mmol/liter}}$
Barsoum and Levine	$\Delta[\text{Na}]_s = \dfrac{(V_{inf})\,[\text{Na}]_{inf} - (V_u)\,[E]_{urine} - (\Delta V)\,[\text{Na}]_1}{\text{TBW} + \Delta V}$	$\text{Volume (liter)} = \dfrac{\text{Desired } \Delta[\text{Na}]_s}{\Delta[\text{Na}]_s \text{ (with 1 liter)}}$

Nguyen and Kurtz

$$\text{Volume (liter)} = \frac{\text{TBW} \times \left(1 - \dfrac{[\text{Na}]_1 + 23.8}{[\text{Na}]_2 + 23.8}\right) + V_{input} - \dfrac{[E]_{input} \times V_{input}}{[E]_{urine}}}{\dfrac{[E]_{inf}}{[E]_{urine}} - 1}$$

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Original Article

NDT
Nephrology Dialysis Transplantation

Therapeutic approach in patients with dysnatraemias

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Department of Internal Medicine, Medical School, University of Ioannina, 45110 Ioannina, Greece

Nature Clinical Practice Nephrology 2:674, 2006

PRACTICE POINT

www.nature.com/clinicalpractice/neph

Does the Adrogue–Madias formula accurately predict serum sodium levels in patients with dysnatremias?

	Anticipated serum Na^+ concentration (meq/l)	Achieved serum Na^+ concentration (meq/l)	*P*-value
Volume depletion			
12 h (*n* = 45)	130.2 ± 4.1	131.3 ± 5.2	NS
24 h (*n* = 15)	130 ± 4	135.6 ± 3.3	0.002
36 h (*n* = 6)	135.5 ± 3.8	136.8 ± 4.3	NS
SIADH			
12 h (*n* = 10)	127.4 ± 5.7	128.9 ± 5.9	NS
24 h (*n* = 4)	129.4 ± 6.3	131.4 ± 6.4	NS
Diuretics			
12 h (*n* = 29)	123.8 ± 6	125.5 ± 5.6	NS
24 h (*n* = 15)	125.2 ± 5.1	127.3 ± 6.1	NS
36 h (*n* = 8)	129.3 ± 4.9	132.1 ± 5.3	NS
Primary polydipsia			
12 (*n* = 2)	122.5 ± 0.7	127.8 ± 1.4	0.02
Hypernatraemia			
12 h (*n* = 92)	153.6 ± 7.5	156.5 ± 8.9	0.021
24 h (*n* = 67)	151.5 ± 6.4	153.3 ± 8.3	NS
36 h (*n* = 34)	149 ± 6.2	150.7 ± 6.8	NS

Clin J Am Soc Nephrol 2:1110-1117, 2007

Original Articles

Hypertonic Saline for Hyponatremia: Risk of Inadvertent Overcorrection

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Editorial

The Adrogue-Madias Formula Revisited

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Clin J Am Soc Nephrol 2: 1098–1099, 2007. doi: 10.2215/CJN.03300807

Table 2. Clinical features of the overcorrectors[a]

Patient	Gender	Age (yr)	Volume Status	Thiazide Diuretic	Urine Osmolality (mOsm/L)	Volume of Hypertonic Saline (ml)	Sodium before Infusion (mEq/L)	Rise in Serum Sodium (mEq/L) at		Water Diuresis?	Dextrose Water Used?
								24 h	48 h		
3	F	69	Euvolemic	Yes	228	N/D	106	16	21	Yes	Yes
15	F	81	Indeterminate	Yes	429	292	115	14	16	N/D	N/D
19	F	84	Euvolemic	No	480	744	118	15	17	N/D	N/D
29	F	57	Indeterminate	No	271	195	109	11	21	N/D	Yes
37	F	63	Euvolemic	No	425	48	112	16	20	Yes	N/D
43	M	53	Hypovolemic	Yes	–	60	108	12	20	Yes	N/D
49	F	87	Euvolemic	Yes	90	N/D	109	16	18	Yes	Yes
51	F	91	Euvolemic	Yes	472	460	107	13	19	N/D	N/D
56	F	58	Indeterminate	Yes	272	376	116	10	19	N/D	N/D
57	F	75	Euvolemic	No	–	540	119	13	14	N/D	N/D

[a]N/D, not documented.

Mohmand HK, et al. Clin J Am Soc Nephrol 2:1110-1117, 2007

Recommendations for the correct use of Adrogué –Madias formula for infusates

1) Estimation of total body water should be conservative ("not generous") since equilibration within body fluids may be incomplete at the time $[Na^+]_s$ is measured

2) Always add the effect of potassium supplementation (including oral intake) on $[Na^+]_s$

3) Recognize that ongoing hypotonic fluid losses promote correction of hyponatremia beyond the prediction of the formula for infusates

4) If ongoing fluid losses are substantial, an estimate of their effect on $[Na^+]_s$ should be done using the "reverse" formula

Therapy of Hyponatremia

- The optimal treatment of hypotonic hyponatremia requires balancing the risks of hypotonicity against those of therapy
- The presence of symptoms and their severity largely determine the pace of correction, that should be sufficient to reverse the manifestations of hypotonicity, but not so rapid as to risk osmotic demyelination (e.g., CPM)
- Increases in $[Na^+]_s$ of 3 to 6 mEq/l are sufficient to overcome the complications of cerebral edema caused by hyponatremia (clinical observations)

Recommended Δ $[Na^+]_s$ in the Management of Hyponatremia

1. Projected limit of correction: ≤ 8 mEq/l per 24 hrs

2. Projected goal of active treatment: ~ 4-6 mEq/l per 24 hrs

   If symptoms are severe: ~ 1 mEq/l per hr for 2-4 hrs

   If symptoms not severe: ~ 4-6 mEq/l over 10-24 hrs

3. Anticipated or reached > 8 mEq/l per 24 hrs: Initiate therapy with: D5W/DDAVP

Recommended monitoring of $[Na^+]_s$ and urine output during active treatment of Hyponatremia

Initial phase	every 2-4 hours
Intermediate phase	every 6-8 hours
Late phase	every 12-24 hours

Illustrative case #1

- 28-year-old woman with stupor and grand mal seizures 2 days after appendectomy; euvolemic
- Wt 67 kg; $[Na^+]$ 113 mEq/l, $[K^+]$ 4.5 mEq/l
- Sosm 229 mosmol/kg H_2O
- Uosm 550 mosmol/kg H_2O
- Diagnosis and initial treatment plan?

Case #1 (continued)

Diagnosis → Postoperative hyponatraemia

Initial treatment plan

- diazepam 20 mg IV
- phenytoin 250 mg IV
- laryngeal intubation
- oxygen administration
- mechanical ventilation
- fluid restriction
- furosemide 20 mg IV
- 3% NaCl to increase $[Na^+]_s$ by 2 mEq/l over 2 hrs

Case #1 (continued)

Estimate of 3% NaCl initial infusion

TBW, $0.5 \times 67 = 33.5$ liters

$$\Delta\,[Na^+]_s = \frac{513 - 113}{33.5 + 1} = 11.6 \text{ mEq/l per 1 liter infusate}$$

For an initial goal of $\Delta\,[Na^+]_s$ of 2 mEq/l over 2 hours,

$2 \div 11.6 = 0.172$ liter is required, or 172 ml $\div$ 2

or ~ 86 ml/hour

Case #1 (continued)

2 hours follow-up

No further seizures; she responds to pain but not to commands; $[Na^+]_s$ 116 mEq/l (Δ $[Na^+]_s$ = 3 mEq/l)

Revised goal of additional Δ $[Na^+]_s$ of 2 mEq/l over 4 hrs, 2 ÷11.6 = 0.172 liter is required, or 172 ml ÷ 4 or ~ 43 ml/hr

Case #1 (continued)

6 hours follow-up

No seizure activity, patient responds to simple commands; $[Na^+]$ 118 mEq/l ($\Delta [Na^+]_s$ = 5 mEq/l)

Revised treatment plan:

Discontinue 3% NaCl
Continue withholding water
Close monitoring (clinical, laboratory)

Illustrative case #2

- 24-year-old man with schizoaffective disorder, on/off lithium. Past history of polydipsia and also of severe hypernatremia (188 mEq/l). Admitted now with grand mal seizure, $[Na^+]_s$ 106 mEq/l and pulmonary congestion on chest x-ray
- Urine: 225 mosmol/kg, $[Na^+]$ 77 mEq/l
- Diagnosis and initial treatment plan?

Case #2 (continued)

Diagnosis → Excessive water intake
(condition tends to "self correct" the hyponatremia at rapid pace)

Initial treatment plan (recommended) →
- Fluid restriction
- Close monitoring
- Antiseizure medication, airway intubation, oxygen therapy, mechanical ventilation

Initial treatment plan (actual) →
- Same as above plus
- 3% NaCl (300 ml over 5 hours, wt 60 kg; rate of infusate 60 ml/hr)

Data at 9 hours →
- $[Na^+]_s$ 133 mEq/l
- Urine output 14.2 liters

Δ $[Na^+]_s$ (133-106) = 27 mEq/l *!!!!!!*

Outcome: CPM (became apparent on day 5)

Illustrative case #3

- 35-year-old man with generalized weakness after one week of diarrhea and continued free water ingestion; normal mental status and neurological examination
- Wt 70 kg; $[Na^+]_s$ 117 mEq/l, $[K^+]$ 2.0 mEq/l
- Sosm 235 mosmol/kg H_2O
- Uosm 417 mosmol/kg H_2O
- Diagnosis and initial treatment plan?

Case #3 (continued)

Diagnosis **Asymptomatic hypovolemic hyponatremia**

Initial treatment plan

- **Isotonic saline with 30 mEq/l of KCl**
- **Estimate of initial infusate**
  TBW, 0.6 × 70 = 42 l

$$\Delta[Na^+]_s = \frac{(154 + 30) - 117}{42 + 1} = 1.6 \text{ mEq/l per 1 l of infusate}$$

- **Initial plan is 250 ml/hr of infusate for first 4 hrs. Vigilance is required because volume repletion will likely result in water diuresis**

Case #3 (continued)

4 hours follow-up

$[Na^+]_s$ 120 mEq/l ($\Delta [Na^+]$ 3 mEq/l) $[K^+]_s$ 2.8 mEq/l

Urine output: 400 ml

$[Na^+ + K^+]_u$ 30 mEq/l

Using the "reverse formula" (fluid losses)

$$\Delta [Na^+]_s = \frac{120 - 30}{42 - 1} = 2.2 \text{ mEq/l per liter of urine loss}$$

Revised treatment plan Half-istonic saline (77 mEq/l) with 30 mEq/l KCl add 125 ml/hr for the next 4 hrs

Re-evaluate in 4 hrs

Long-term Management of Hyponatremia

1. Severe heart failure: fluid restriction, ACE inhibitors, loop diuretics, consider vasopressin receptor antagonists
2. Cirrhosis: fluid restriction, consider vasopressin receptor antagonists
3. SIADH: fluid restriction, consider vasopressin receptor antagonists
4. Low solute intake: secure proper nutrition (electrolytes and protein)
5. Primary polydipsia: behavior modification, antipsychotic drugs (e.g., clozapine)
6. Glucocorticoid deficiency: replacement therapy
7. Hypothyroidism: replacement therapy

THANK YOU