Sodium Correction in Hyponatremia

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Objectives

- Utilize applicable labs, physical exam findings, and patient history to diagnose and classify hyponatremia
- Compare and contrast guideline recommendations for the management of hyponatremia
- Discuss data regarding safety and efficacy of vasopressin receptor antagonists and oral urea
- Design a therapeutic regimen for the management of hypovolemic, hypervolemic, and euvolemic hypotonic hyponatremia

Sodium

- Normal range: 135-145 mEq/L
- Main extracellular cation
- Functions:
  - Extracellular volume and water distribution
  - Membrane potential
  - Active transport

Chessman et al. Pharmacotherapy: a pathophysiologic approach.

Sodium regulation

- Serum sodium is regulated by changes in water balance
  - Increased water → hyponatremia
  - Decreased water → hypernatremia

- Processes affecting serum sodium level:
  - Osmoregulation
    - Antidiuretic hormone (ADH); thirst
  - Volume regulation
    - Renin-angiotensin-aldosterone system (RAAS); atrial natriuretic peptide (ANP); ADH

Rennke et al. Renal pathophysiology: the essentials

Sodium regulation

- Osmoregulation
  - Increased plasma osmolality → increased ADH
  - Decreased plasma osmolality → decreased ADH
- Volume regulation
  - Decreased effective circulating volume →
    - RAAS activation → sodium reabsorption
    - ANP release → sodium excretion
    - ADH secretion → water retention

Rennke et al. Renal pathophysiology: the essentials

Hyponatremia

- Na < 135 mEq/L
- Risk factors:
  - More common in patients > 30 years old
  - Medications
  - Low solute/protein diet
  - Significant solute-free fluid intake

Chessman et al. Pharmacotherapy: a pathophysiologic approach.

Classification

- Severity
  - Mild: > 125-135 mEq/L
  - Moderate: 115-125 mEq/L
  - Severe: < 115 mEq/L
- Symptoms
  - Mild: attention, gait, and posture impairments
  - Moderate: headache, nausea, vomiting, fatigue, confusion
  - Severe: seizures, respiratory arrest, coma, obtundation

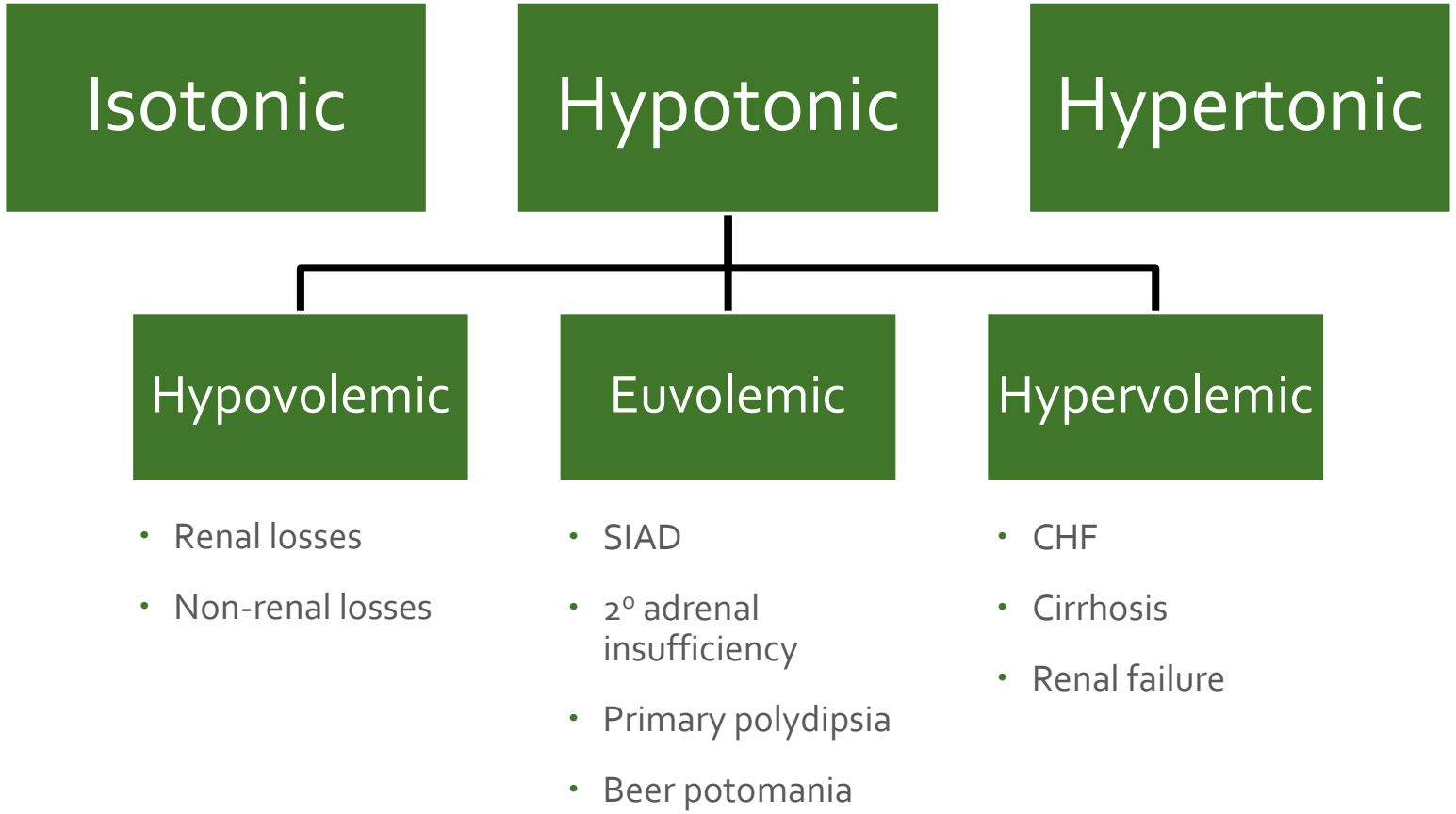
Verbalis et al. *Am J Med*. 2013 Oct;126(10):S1-S42

Classification

- Duration
  - Hyperacute: within the previous few hours
  - Acute: within the previous 24 hours
  - Subacute: within 24-48 hours
  - Chronic: more than 48 hours OR duration unknown

Verbalis et al. *Am J Med*. 2013 Oct;126(10):S1-S42

Types of hyponatremia



Verbalis et al. *Am J Med*. 2013 Oct;126(10):S1-S42

SIAD

- Type of euvolemic hypotonic hyponatremia
- Pathophysiology
  - Increased activity of ADH results in water retention and excretion of concentrated urine
    - Labs: urine osmolality > 100 mOsm/kg, urine sodium > 30 mEq/L
- Management
  - Correction of underlying cause
  - Fluid restriction
  - NaCl ± loop diuretic
  - Oral urea

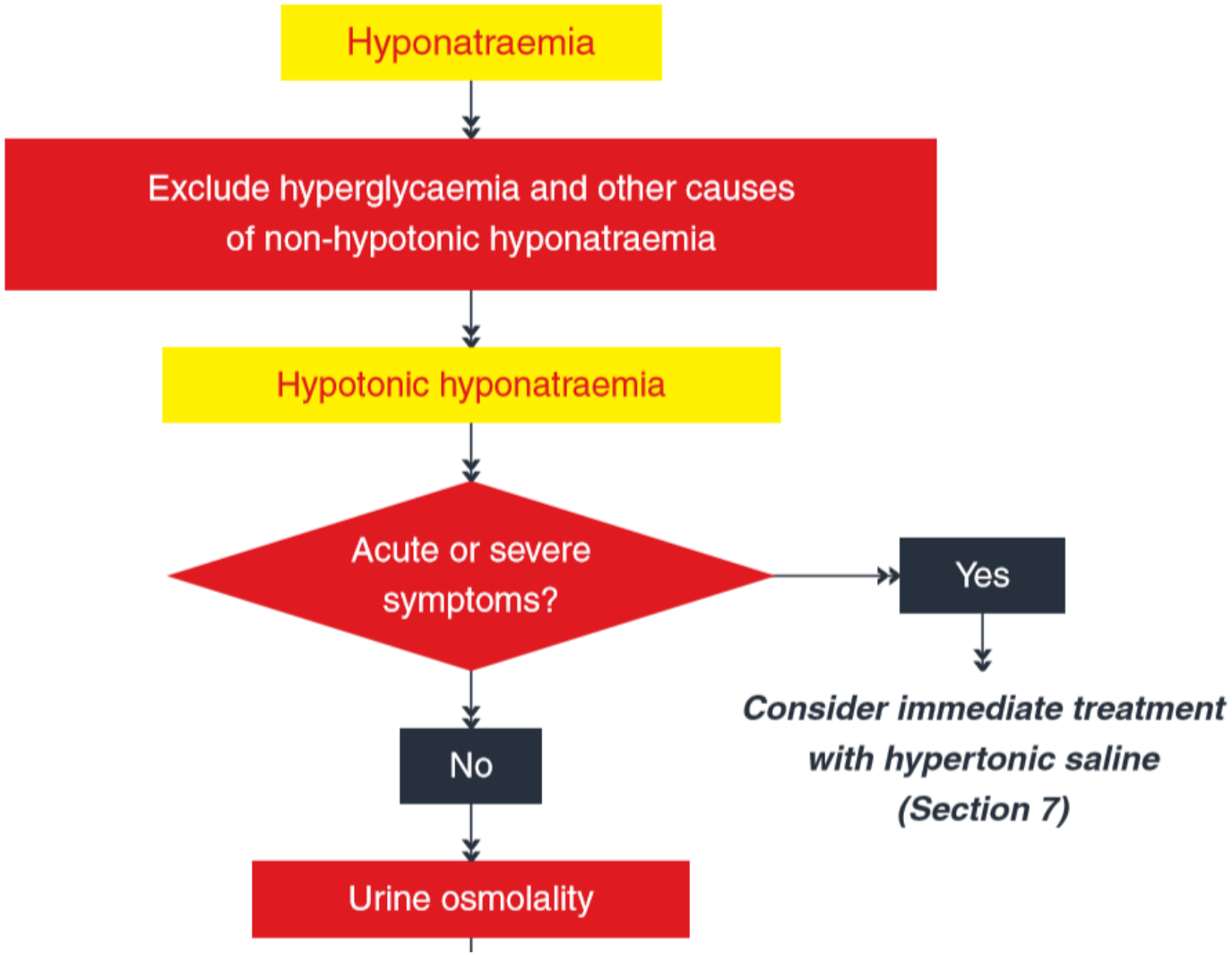
Sanghvi et al. *Am J Kidney Dis.* 2007 Oct;50(4):673-80

Beer potomania

- Type of euvolemic hypotonic hyponatremia
- Pathophysiology
  - Fluid intake exceeds kidneys' ability to excrete the extra fluid
  - Poor diet; low sodium intake
  - Decreased activity of ADH
    - Labs: urine osmolality < 100 mOsm/kg, urine sodium < 30 mEq/L
- Management
  - Fluid restriction
  - IV fluids ONLY if symptomatic

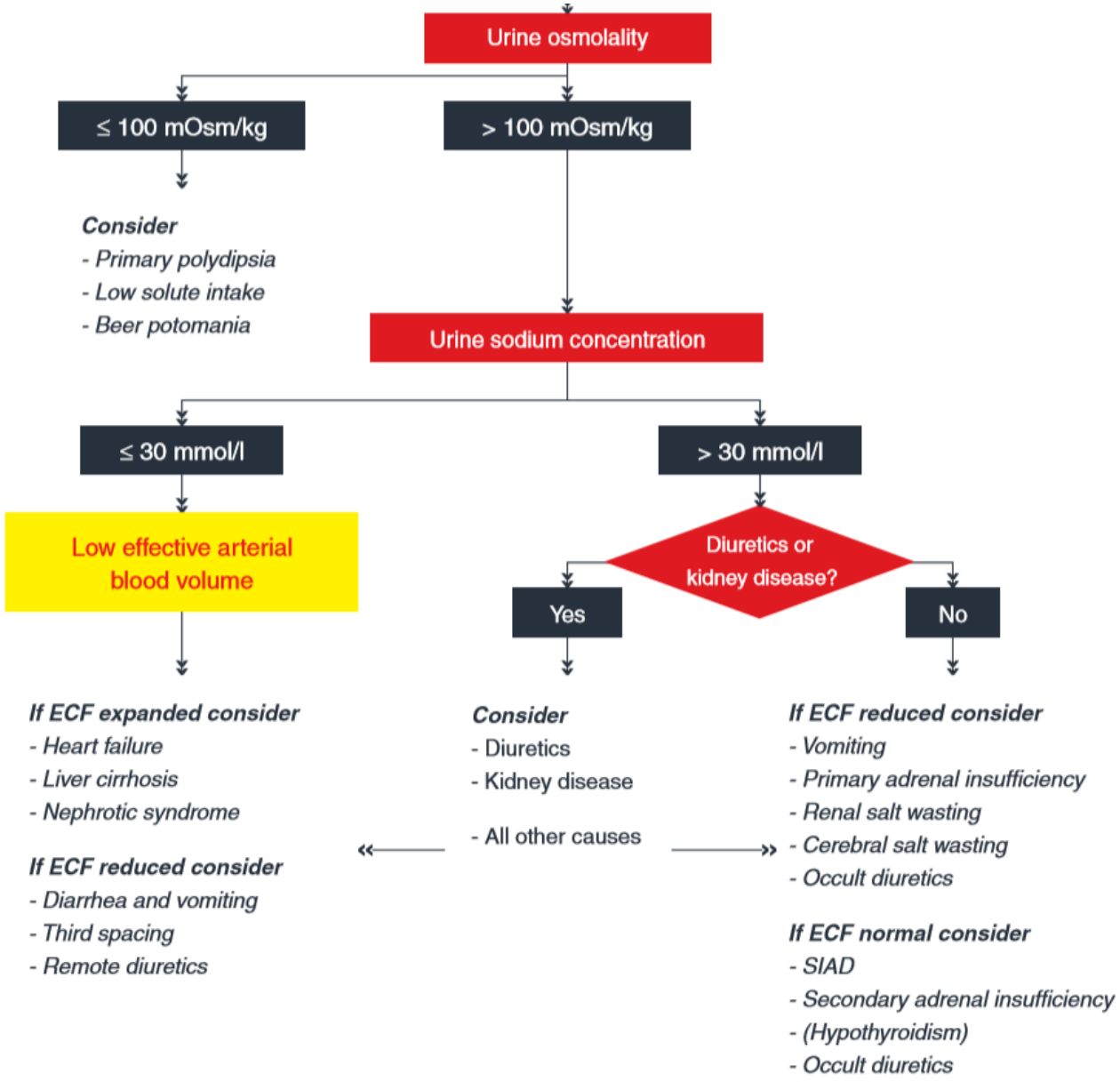
Sanghvi et al. *Am J Kidney Dis.* 2007 Oct;50(4):673-80

2014 European Guidelines diagnostic strategy



Spasovski et al. *Intensive Care Med*. 2014;40:320-331

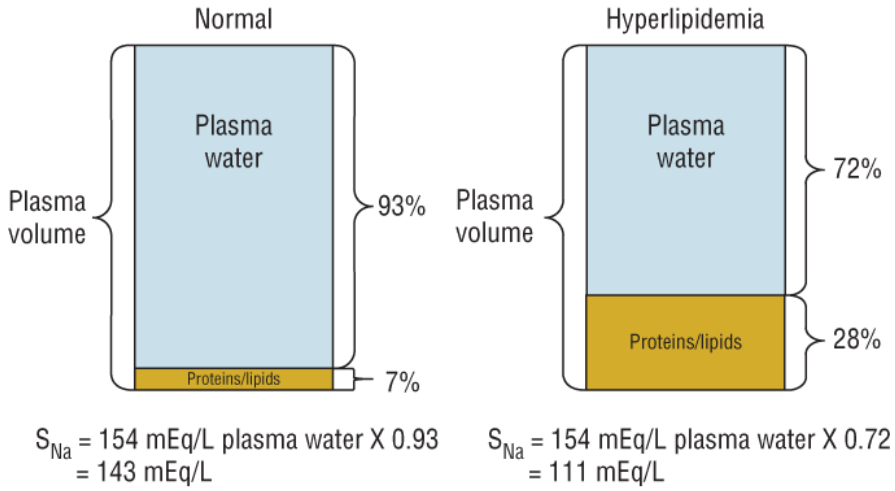
2014 European Guidelines diagnostic strategy



Spasovski et al. *Intensive Care Med*. 2014;40:320-331

Isotonic hyponatremia

- Lab value breakdown
  - Serum osmolality: ~280 mOsm/kg
- "Pseudohyponatremia"
  - Associated with an outdated lab test used to measure Na
  - Seen in patients with hyperlipidemia or hyperproteinemia



Sterns RH. *N Eng J Med*. 2015;372:55-65
Chessman et al. Pharmacotherapy: a pathophysiologic approach.

Isotonic hyponatremia

- Lab value breakdown
  - Serum osmolality: ~280 mOsm/kg
- "Translocational" hyponatremia
  - Presence of additional osmoles causes extracellular fluid shift
  - Example:
    - Glucose (hyperglycemia)

Verbalis et al. *Am J Med*. 2013 Oct;126(10):S1-S42

Hypertonic hyponatremia

- Lab value breakdown
  - Serum osmolality: > 280 mOsm/kg
- "Translocational" hyponatremia
  - Presence of additional osmoles causes extracellular fluid shift
  - Examples:
    - Glucose (severe hyperglycemia)
    - Mannitol
    - Intravenous immunoglobulin (IVIG)

Verbalis et al. *Am J Med*. 2013 Oct;126(10):S1-S42

Hypotonic hyponatremia

- Lab value breakdown
  - Serum osmolality: < 280 mOsm/kg

Verbalis et al. *Am J Med*. 2013 Oct;126(10):S1-S42

Hypovolemic hypotonic hyponatremia

- Lab value breakdown
  - Serum osmolality: < 280 mOsm/kg
  - Urine osmolality: > 450 mOsm/kg
    - Urine sodium: > 30 mEq/L
      - Renal losses
    - Urine sodium: < 30 mEq/L
      - Non-renal losses

Verbalis et al. *Am J Med*. 2013 Oct;126(10):S1-S42

Hypovolemic hypotonic hyponatremia

- Etiology
  - Renal losses
    - Diuretics
    - Primary adrenal insufficiency
    - Cerebral salt wasting
    - Kidney disease
  - Non-renal losses
    - Vomiting*
    - Diarrhea
    - Blood loss
    - Sweating
  - Third-spacing

Verbalis et al. *Am J Med*. 2013 Oct;126(10):S1-S42

Hypervolemic hypotonic hyponatremia

- Lab value breakdown
  - Serum osmolality: < 280 mOsm/kg
  - Urine osmolality: > 100 mOsm/kg
    - Urine sodium: < 30 mEq/L

- Etiology
  - CHF
  - Cirrhosis
  - Renal failure
  - Pregnancy

Verbalis et al. *Am J Med*. 2013 Oct;126(10):S1-S42
Adrogué et al. *N Eng J Med.* 2000;342:1581-89

Euvolemic hypotonic hyponatremia

- Lab value breakdown
  - Serum osmolality: < 280 mOsm/kg
  - Urine osmolality: > 100 mOsm/kg
  - Urine osmolality: < 100 mOsm/kg

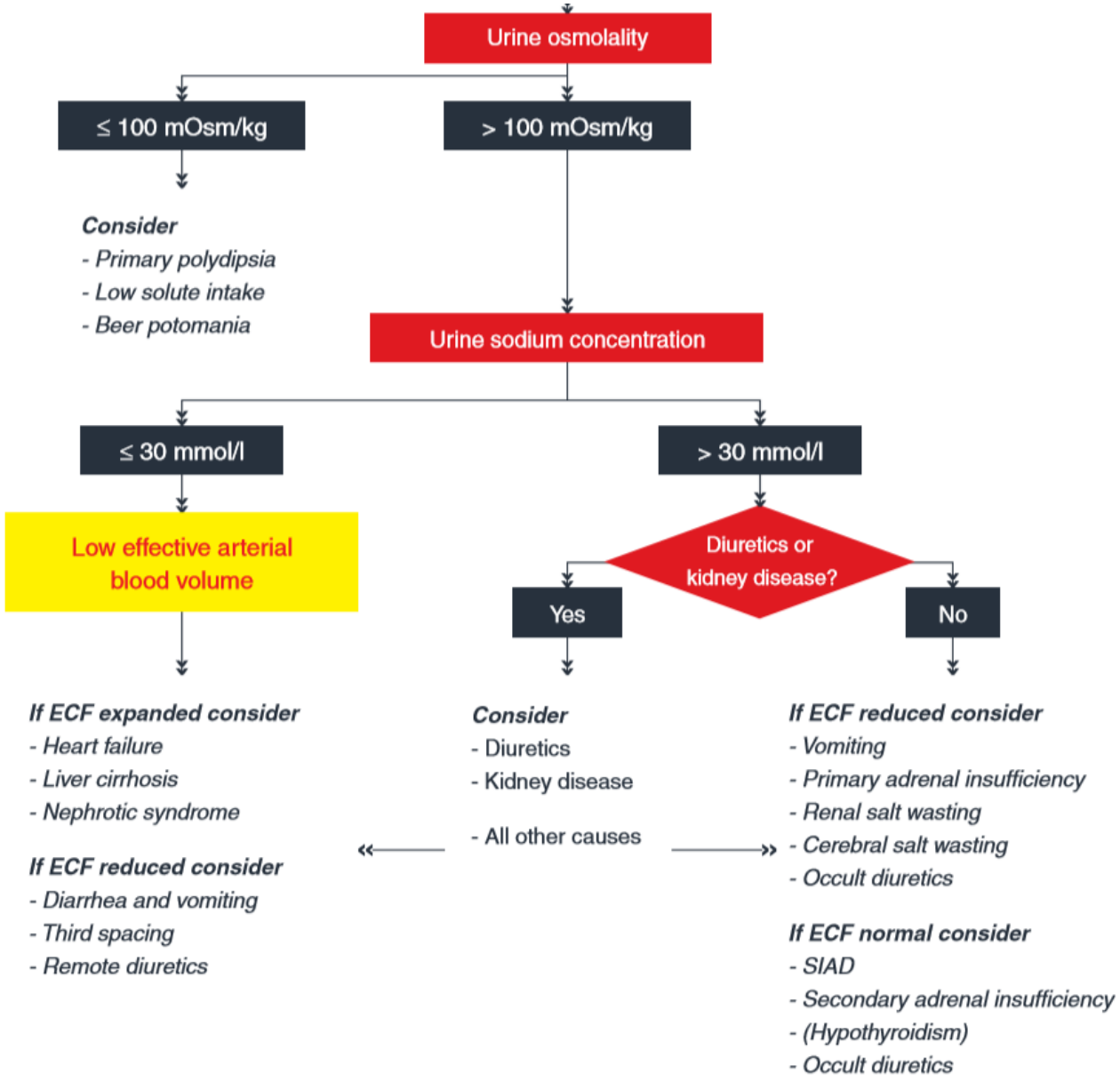
Verbalis et al. *Am J Med*. 2013 Oct;126(10):S1-S42

Euvolemic hypotonic hyponatremia

- Lab value breakdown
  - Serum osmolality: < 280 mOsm/kg
  - Urine osmolality: > 100 mOsm/kg
    - Urine sodium: > 30 mEq/L
      - SIAD, secondary adrenal insufficiency, hypothyroidism(?)
  - Urine osmolality: < 100 mOsm/kg
    - Urine sodium: < 30 mEq/L
      - Primary polydipsia, low Na intake, beer potomania

Verbalis et al. *Am J Med*. 2013 Oct;126(10):S1-S42
Adrogué et al. *N Eng J Med.* 2000;342:1581-89

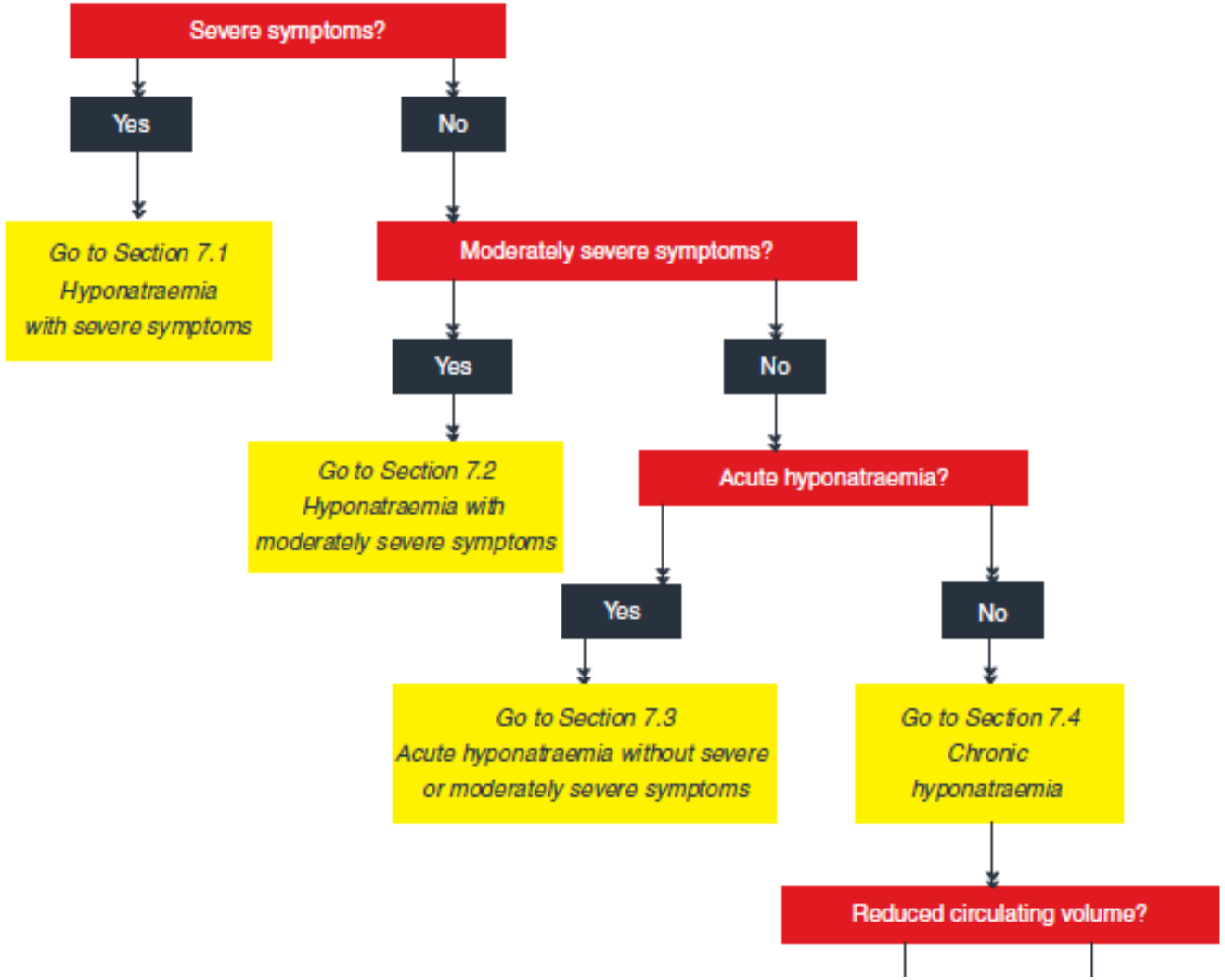
2014 European Guidelines diagnostic strategy



Spasovski et al. *Intensive Care Med*. 2014;40:320-331

Management

2014 European Guidelines management algorithm



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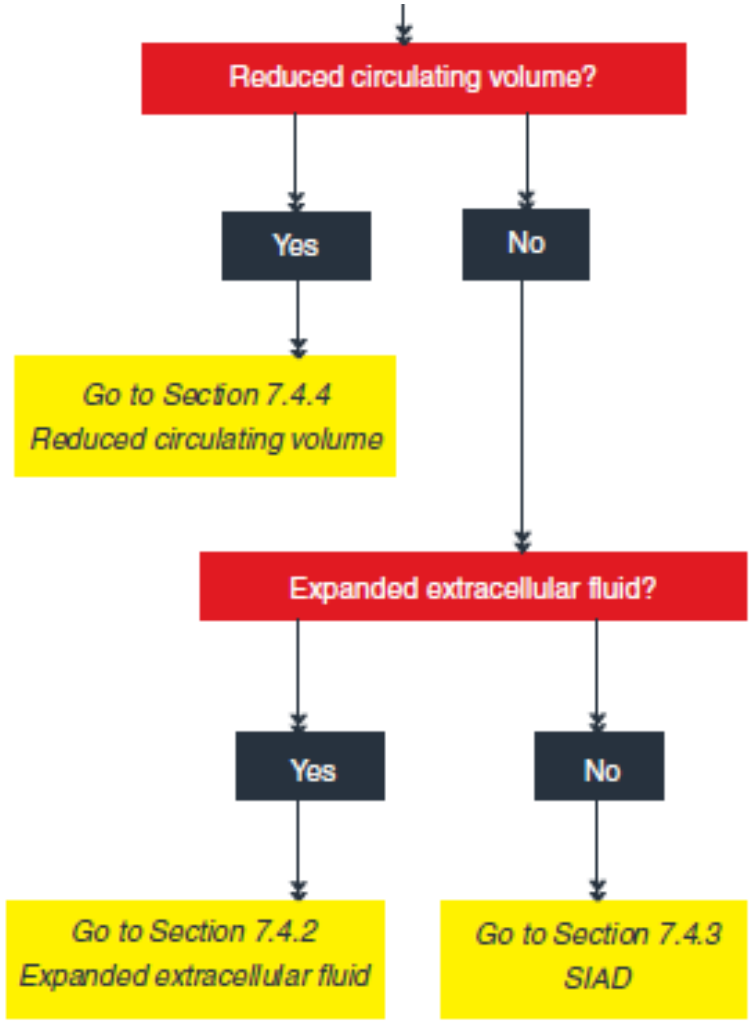
2014 European Guidelines management algorithm



Spasovski et al. *Intensive Care Med*. 2014;40:320-331

Severe symptoms

- Goal: rapid increase in serum sodium concentration within 1 hour
  - Immediate risk of cerebral edema outweighs risk of ODS
- Guideline recommendations:
  - 100-150 mL of 3% hypertonic saline over 10-20 min
    - *Consider 2 mL/kg in patients who are significantly under- or overweight
  - Repeat boluses 2-3 times every 20-30 min as needed to reach target serum sodium concentration increase of 5 mEq/L within the first hour
- Alternative: sodium bicarbonate ("6% saline")
  - 1 amp (50 mL) of sodium bicarb ≈ 100 mL of 3% saline
    - Osmolarity of 3% saline = 1027 mOsm/L
    - Osmolarity of 8.4% sodium bicarb = 2000 mOsm/L

Spasovski et al. *Intensive Care Med*. 2014;40:320-331
Verbalis et al. *Am J Med*. 2013;126:S1-S42
Bourdeaux & Brown. *Neurocrit Care*. 2010 Aug;13(1):24-8

Severe symptoms

- Symptomatic improvement after 5 mEq/L increase in serum sodium concentration
  - Stop hypertonic saline infusion
  - Determine etiology of hyponatremia and initiate cause-specific management
  - Limit further serum sodium increase
    - First 24 hours: ≤ 10 mEq/L total (including initial 5 mEq/L)
    - First 48 hours: ≤ 18 mEq/L total (including initial 5 mEq/L)

- NO symptomatic improvement after 5 mEq/L increase in serum sodium concentration
  - Investigate alternative explanations for symptoms
    - Give hypertonic saline for additional 1 mEq/L increase in serum sodium
  - Do not exceed 10 mEq/L limit in 24 hours
    - If symptoms not improved after 10 mEq/L increase in serum sodium and/or if after reaching serum sodium of 130 mEq/L, hyponatremia unlikely to be the cause of the symptoms

Spasovski et al. *Intensive Care Med*. 2014;40:320-331

Moderately severe symptoms

- Goals:
  - Prevent further decrease in sodium level
  - Determine etiology of hyponatremia and initiate cause-specific management
- Guideline recommendations for initial management:
  - US: continuous infusion of 3% hypertonic saline at 0.5-2 mL/kg/hr
  - European: 150 mL bolus of 3% hypertonic saline over 20 min x 1
    - *Alternative: sodium bicarbonate

Spasovski et al. *Intensive Care Med*. 2014;40:320-331
Verbalis et al. *Am J Med*. 2013;126:S1-S42

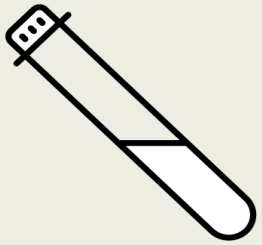
Bourdeaux & Brown. *Neurocrit Care*. 2010 Aug;13(1):24-8

JAMA Internal Medicine

RCT: Risk of Overcorrection in Rapid Intermittent Bolus vs Slow Continuous Infusion for Symptomatic Hyponatremia

POPULATION

80 Men, 98 Women

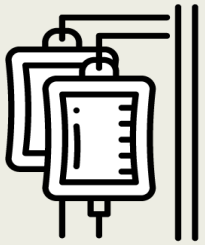


Adults aged >18 y with symptoms of hyponatremia and glucose-corrected serum sodium ≤125 mmol/L

Mean (SD) age: 73.1 (12.2) y

INTERVENTION

178 Patients randomized

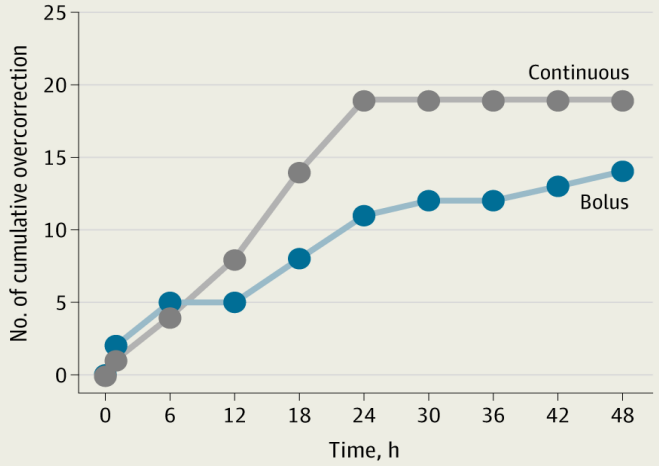


87 Rapid intermittent bolus
Hypertonic saline, 3%, infusion of 2 mL/kg over 20 min every 6 h

91 Slow continuous infusion
Hypertonic saline, 3%, continuous infusion at a rate of 0.5-1 mL/kg/h

FINDINGS

Both rapid intermittent bolus and slow continuous infusion for treating symptomatic hyponatremia are effective and safe with no difference in overcorrection risk (17.2% vs 24.2%, respectively; absolute risk difference, −6.9% (95% CI, −18.8% to 4.9%); *P* = .26)



SETTINGS / LOCATIONS

3 General hospitals in the Republic of Korea

PRIMARY OUTCOME

Overcorrection at any given period, defined as increase in serum sodium level by >12 mmol/L within 24 h or >18 mmol/L within 48 h

Baek SH, Jo YH, Ahn S, et al. Risk of overcorrection in rapid intermittent bolus vs slow continuous infusion therapies of hypertonic saline for patients with symptomatic hyponatremia: the SALSA randomized clinical trial. *JAMA Intern Med.* Published online October 26, 2020. doi:10.1001/jamainternmed.2020.5519

Baek et al. *JAMA Intern Med*. Published online October 26, 2020

Moderately severe symptoms

- Goals:
  - Prevent further decrease in sodium level
  - Determine etiology of hyponatremia and initiate cause-specific management
- Guideline recommendations for initial management:
  - US: continuous infusion of 3% hypertonic saline at 0.5-2 mL/kg/hr
  - **European: 150 mL bolus of 3% hypertonic saline over 20 min x 1**
    - *Alternative: **sodium bicarbonate**
- Rate of correction:
  - Suggest aiming for 5 mEq/L increase in the first 24 hr
  - Suggest limiting to 10 mEq/L increase in the first 24 hr
  - Suggest limiting to 8 mEq/L increase on subsequent days until serum sodium reaches 130 mEq/L

Spasovski et al. *Intensive Care Med*. 2014;40:320-331
Verbalis et al. *Am J Med*. 2013;126:S1-S42
Bourdeaux & Brown. *Neurocrit Care*. 2010 Aug;13(1):24-8

Acute hyponatremia*

*without severe or moderately severe symptoms

- Goals:
  - Determine etiology of hyponatremia and initiate cause-specific management
  - Prevent further decrease in sodium level
- Guideline recommendations for initial management:
  - 150 mL bolus of 3% hypertonic saline over 20 min x 1
    - *Alternative: sodium bicarbonate
- Rate of correction
  - No suggested limitations or aims in regards to rate of correction

Spasovski et al. *Intensive Care Med*. 2014;40:320-331

Chronic hyponatremia*

*without severe or moderately severe symptoms

- Goals:
  - Determine etiology of hyponatremia and initiate cause-specific management
  - Avoid harm through treatment
- Guideline recommendations:
  - Stop non-essential fluids, medications, and other factors that may contribute to hyponatremia
  - Mild hyponatremia
    - Recommend against treating for the sole purpose of increasing sodium level
  - Moderate or profound hyponatremia**
    - Recommend limiting to 10 mEq/L increase in the first 24 hr
    - Recommend limiting to 8 mEq/L increase every 24 hr thereafter

**weigh risks vs. benefits of correcting based on severity of hyponatremia and underlying diagnosis

Spasovski et al. *Intensive Care Med*. 2014;40:320-331

Reduced circulating volume

- Unique characteristics:
  - Deficits in both sodium and water
  - Appropriate ADH secretion → simultaneous dilutional hyponatremia
    - Places patients at higher risk for overcorrection of sodium level

- Guideline recommendations:
  - Continuous IV infusion for volume repletion
    - Normal saline or balanced crystalloid
    - 0.5-1.0 mL/kg/hr
  - In the setting of hemodynamic instability
    - Need for rapid fluid resuscitation overrides concern over rapid increase in serum sodium level
  - In the setting of imminent overcorrection
    - If additional fluid resuscitation still needed, suggest changing to glucose solution (i.e. D5W)

Spasovski et al. *Intensive Care Med*. 2014;40:320-331

Expanded extracellular fluid

- Guideline recommendations:
  - Expand recommendation against treating for the sole purpose of increasing sodium level to hyponatremia that is moderate
    - Refrained from making any recommendations for profound hyponatremia in this patient population
  - Suggest fluid restriction to avoid worsening fluid overload
  - Recommend against vasopressin receptor antagonists (vaptans)
  - Recommend against demeclocycline or lithium

Spasovski et al. *Intensive Care Med*. 2014;40:320-331

SIAD

- Guideline recommendations:
  - First line: fluid restriction
  - Second line: increase solute intake
    - Oral urea (0.25-0.50 g/kg per day)
    - Oral sodium chloride + low-dose loop diuretic
  - Recommend against demeclocycline or lithium
  - Regarding vasopressin receptor antagonists (vaptans)
    - In moderate hyponatremia: do not recommend
    - In profound hyponatremia: recommend against

Spasovski et al. *Intensive Care Med*. 2014;40:320-331

Vasopressin receptor antagonists

- Tolvaptan (PO)
  - Selective vasopressin V2-receptor blocker
  - FDA-approved for euvolemic and hypervolemic hyponatremia
- Conivaptan (IV)
  - Mixed vasopressin V1- and V2-receptor blocker
  - FDA-approved for euvolemic hyponatremia
- Promote excretion of electrolyte-free water in order to increase serum sodium levels
- Included in the US guidelines for SIAD and hypervolemic hyponatremia

Otsuka Pharmaceutical Co., Ltd. 2012
Astellas Pharma US, Inc. 2005

Vasopressin receptor antagonists

- Concerns:
  - Unable to predict extent of free water excretion
  - Samsca® (tolvaptan) associated with overly rapid correction of sodium levels (US Boxed Warning)
  - Tolvaptan linked to serious hepatic injury (US Boxed Warning)
    - REMS program for Samsca® (tolvaptan) in autosomal dominant polycystic kidney disease due to risk of hepatotoxicity
    - Jynarque® (tolvaptan) is only available through a REMS program due to risk of serious liver injury
  - Cost

- Consistently not recommended or recommended against in the European guidelines

Otsuka Pharmaceutical Co., Ltd. 2012
Astellas Pharma US, Inc. 2005

Oral urea

- Osmotic agent that increases urinary free water excretion and decreases ongoing natriuresis
  - Used for treatment of euvolemic and hypervolemic hyponatremia
- Classified as medical food and Generally Recognized as Safe (GRAS) by the FDA
- Available as ure-Na® powder
  - 15 g USP urea per pouch
  - Should be mixed with water or juice
  - Lemon-lime flavor to improve tolerability
- Significantly less expensive than vasopressor receptor antagonists

Nephcentric LLC. 2020
Soupart et al. *CJASN.* 2012 May;7(5):742-47

Oral urea: efficacy

- Comparison study of urea vs. vasopressin receptor antagonists:
  - 13 patients with chronic SIADH first received a vaptan for 1 year followed by an 8-day holiday period, after which they received oral urea for 1 year
  - Urea demonstrated similar efficacy, with both agents increasing serum sodium levels to ~135 mEq/L

- Retrospective study of urea in the ICU
  - Mild hyponatremia group (n = 50; initial sodium 128 ± 4 mEq/L) received urea
    - Mean increase of 4 mEq/L in the first 24 hours and 7 mEq/L in 48 hours
  - Severe hyponatremia group (n = 35; initial sodium 111 ± 3 mEq/L) received isotonic saline + urea
    - Mean increase of 11 mEq/L in the first 24 hours
    - 2 patients received desmopressin to re-lower sodium
    - No cases of ODS

Soupart et al. *CJASN.* 2012 May;7(5):742-47
Decaux et al. *Crit Care*. 2010;14(5):R184

Oral urea: safety

- Provides "limited and predictable" excretion of free water
  - Less likely to cause sodium overcorrection and ODS
- Data from animal studies indicate that oral urea may actually protect against ODS
  - Rapid correction of hyponatremia with urea compared with lixivaptan or hypertonic saline:
    - Significantly decreased brain microglial activation
    - Significantly reduced changes in blood brain barrier permeability
    - Increased astrocyte viability
    - Reduced brain histological evidence of demyelination 6 days after the beginning of correction of hyponatremia

Nervo et al. *Clin Endocrinol (Oxf)*. 2019 Jun;90(6):842-48
Gankam et al. *Kidney Int.* 2015;87(2):323-31

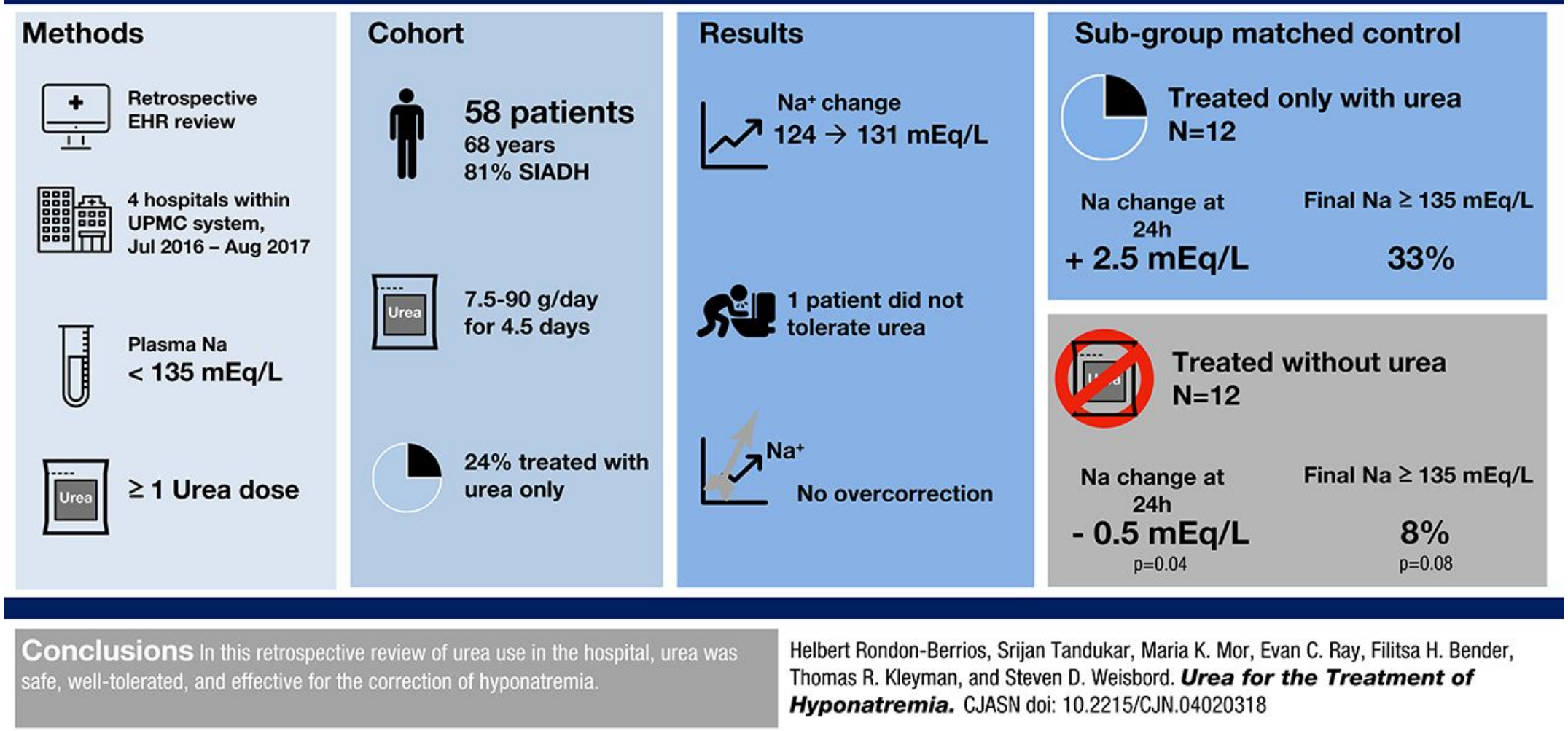
Oral urea: safety

- Not nephrotoxic or hepatotoxic
  - Expect to see isolated increase in BUN levels
    - NOT indicative of kidney function
    - Exogenous urea administration has been shown to be safe even in patients with advanced renal failure
  - Metabolism into ammonia
    - Concern that oral urea could trigger hepatic encephalopathy
    - However, given the complexity of the pathogenesis of hepatic encephalopathy, oral urea (and any resultant increase in ammonia) may be considered "probably safe" for many patients with cirrhosis
    - Some studies have successfully used oral urea for hyponatremic cirrhosis with ascites resistant to diuretics, without causing encephalopathy
- Data showing lack of toxicity even in long-term use

Decaux et al. *Crit Care*. 2010;14(5):R184
Johnson et al. *Mayo Clin Proc*. 1972;47(1):21-9
Decaux et al. *Nephron*. 1986;44(4):337-43
Soupart et al. *CJASN*. 2012 May;7(5):742-47

How safe and effective is oral urea for the treatment of hyponatremia in hospitalized patients?

CJASN
Clinical Journal of American Society of Nephrology



Conclusions In this retrospective review of urea use in the hospital, urea was safe, well-tolerated, and effective for the correction of hyponatremia.

Helbert Rondon-Berrios, Srijan Tandukar, Maria K. Mor, Evan C. Ray, Filitsa H. Bender, Thomas R. Kleyman, and Steven D. Weisbord. ***Urea for the Treatment of Hyponatremia.*** CJASN doi: 10.2215/CJN.04020318

Rondon-Berrios et al. *CJASN*. 2018 Nov;13(11):1627-1632

Overcorrection

- If increase in serum sodium concentration exceeds 10 mEq/L in the first 24 hours or 8 mEq/L in any subsequent 24 hour period

- Guideline recommendations:
  - Recommend re-lowering serum sodium concentration
  - Recommend stopping active hyponatremia treatment
  - Recommend consulting an expert to assist in determining appropriate next steps and options for re-lowering sodium
    - If appropriate, consider infusion of 10 mL/kg of electrolyte-free water over 1 hour
      - Should include strict monitoring of urine output and fluid balance
    - If appropriate, consider IV desmopressin (DDAVP) 2 mcg
      - Doses not to be repeated more frequently than every 8 hours

Spasovski et al. *Intensive Care Med*. 2014;40:320-331

Summary of guideline recommendations

Subject	United States Guideline (2013)	European Guideline (2014)
Acute or symptomatic hyponatremia	- Severe symptoms: bolus 3% saline (100 mL over 10 min x 3 prn) - Moderate symptoms: continuous infusion 3% saline (0.5-2 mL/kg/hr)	- Severe symptoms: bolus 3% saline (150 mL over 20 min x 2-3 prn) - Moderate symptoms: bolus 3% saline (150 mL over 20 min x 1)
Chronic hyponatremia		

SIAD	- Fluid restriction (1st line)
	- Demeclocycline, urea, or vaptan (2nd line)
		- Fluid restriction (1st line)
		- Urea or loop diuretic + PO NaCl (2nd line)
		- Vaptans:
		  - Na < 130: do not recommend
		  - Na < 125: recommend against
		- Recommend against lithium and demeclocycline

Hypovolemic hyponatremia	- Isotonic saline	- Isotonic saline or balanced crystalloid
Hypervolemic hyponatremia	- Fluid restriction - Vaptans (risk vs. benefit in liver cirrhosis)	- Fluid restriction - Recommend against vaptans

Hoorn & Zietse. *J Am Soc Nephrol*. 2017;28:1340-1349

Summary of guideline recommendations

Subject	United States Guideline (2013)	European Guideline (2014)

Correction rates	- Minimum: 4-8 mmol/L per day
	  - High risk of ODS: 4-6 mmol/L per day
	- Limit: 10-12 mmol/L per day
	  - High risk of ODS: 8 mmol/L per day
		- Minimum: (none)
		- Limit: 10 mmol/L per day

Management of overcorrection	- Baseline Na ≥ 120 mmol/L: probably unnecessary - Baseline Na < 120 mmol/L: start re-lowering with electrolyte-free water or desmopressin after correction exceeds 6-8 mmol/L per day	- Start once limit is exceeded - Expert consultation to discuss giving electrolyte-free water (e.g. D_5W) and/or desmopressin IV

Hoorn & Zietse. *J Am Soc Nephrol*. 2017;28:1340-1349

Questions?

Thank you!