Management of Hyponatremia
Liver Cirrhosis

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Hyponatremia / Cell Phone
Hyponatremia
Liver Cirrhosis

- The most common electrolyte disorder (*1,2)
- 20% have serum Na\(^+\) < 130 mmol/L\(^\text{*3}\) (current definition)
- 50% have serum Na\(^+\) < 135 mmol/L
- S. Na\(^+\) <126mmol/L is rare (prevalence 6%)
- Mostly in child-Pugh class C patients

Hyponatremia
Liver Cirrhosis
prognostic Importance

- Increased Prevalence of:
  ✓ Hepatic Encephalopathy
  ✓ Hepatorenal syndrome
  ✓ SBP

- Among ascites patients
  ✓ Lower response to diuretics
  ✓ Higher incidence of refractory ascites
  ✓ More need for therapeutic paracentesis at shorter intervals
Hyponatremia  Liver Cirrhosis OLT

- The risk of waitlist mortality appears to increase by 12% for each unit decrease in S.Na (120-135 mmol/L)\(^{(1)}\)*

- Risk of developing irreversible central pontine myelinolysis in early post-op period. \(^{(2)}\)*

- Need greater use of blood products, and longer hospital stay.

- Increased 3 month mortality\(^{(3)}\)*

- MELD-Na score provides better short term mortality prediction among candidates for OLT. It is the best drop-out predictor at three months \(^{(4)}\)*

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Hyponatremia Liver Cirrhosis

Total body H2O and S.Na
Homeostasis (Normal)

Complex interplay between
Baroreceptors-Osmoreceptors-Central Neurohormonal systems (AVP)
Hyponatremia Liver Cirrhosis

ADH

Osmotic Stimulation of ADH

![Graph showing osmotic stimulation of ADH](image-url)
Hyponatremia Liver Cirrhosis

ADH

Non-osmotic Stimulation of ADH

Plasma ADH, pg/mL

Blood volume depletion, %

Hypotension / Decrease Effective Circ Volume
Hyponatremia
Liver Cirrhosis
Hyponatremia Liver Cirrhosis

Clinical Types

- Hypovolemic Hyponatremia
- Hypervolemic Hyponatremia
Hypovolemic Hyponatremia
Liver Cirrhosis
Pathophysiology

- 10% of cirrhotics
- Na loss from diuretics + and GI tract (D ± V)
- Low S.Na + contraction of plasma volume ⇒ ↓ ECF volume ⇒ tachycardia ⇒ ↓ renal perfusion
Hypervolemic Hyponatremia
Liver Cirrhosis
Pathophysiology

Savio John, World J Gastroenterology 2015 March 21 ; 21(11): 3197-3205
Hypervolemic Hyponatremia Peripheral systemic vasodilation (splanchnic arterial vasodilation)

Vasodilators:
- Nitric oxide
- Glucagon
- Prostacyclin
- Prostaglandin E2
- Kallikrein-kinin system
- Atrial Natriuretic Peptide
- Adrenomedullin
- Calcitonin gene-related peptide
- Vasoactive Intestinal Polypeptide
- Substance P
- Platelet activating factor

Excessive response to vasodilators

Splanchnic arterial vasodilation

Vasoconstrictors:
- ADH
- Endothelin-1
- Thromboxane A2
- Angiotensin II
- Leukotrienes
- Adenosine
- Noradrenaline
- Neuropeptide Y

Resistance to vasoconstrictors

Savio John, World J Gastroenterology 2015 March 21; 21(11): 3197-3205
Peripheral systemic vasodilation (splanchnic arterial vasodilation) (continue)

Causes of (NO) Synthase Activity (Endothelial cells)

- Mechanical stimuli due to shear stress
- Vascular Endothelial growth factors
- TNF Alpha
- Endotoxins or Bacterial DNA (defective RES function)
Hyponatremia Liver cirrhosis
Clinical Manifestations

- Related to severity and rate of fall (chronic vs acute) (1)*
- Hyponatremia without liver cirrhosis- headache – disorientations, confusion, local neurologic deficits, seizures, cerebral herniation → death
- Hyponatremia generally develops slowly so that the brain can adjust to hypo-osmolality and hypotonicity of ECF → little clinical effect

- Defense Mechanisms: (2)*
  ✓ Rapid release of I.C electrolyte(K) within 24 hours.
  ✓ LMW organic compounds (myoinositol)

Hyponatremia Liver Cirrhosis

The Brain and Hyponatremia

Immediate effect of EC F hypotonicity

Brain cell Normal 290

Brain cell 290

Acute Hyponatremia 270

Proper therapy slow correction

Brain cell 270

Brain cell 270

Immediate effect of EC F hypotonicity

Brain cell 290

Brain cell 270

Rapid adaptation phase

Brain cell 285

Slow adaptation

Brain cell 270

Improper therapy fast correction = CPM!
Central pontine myelinolysis

- Osmotic demyelination syndrome
- Causes-
  - Rapid correction of hyponatremia, specially chronic
  - Associated with alcoholism, hyperemesis gravidarum, SCT
- S/s- due to myelinolysis of corticobulbar & corticospinal tracts, in pons- LOC, quadriplegia, dysarthria, dysphagia, diplopia etc.
- Dx- clinical + MRI
- Rx- supportive only
- Prevention- slow correction of hyponatremia- ~0.5 mEq/L/hr
Management of Hyponatremia in Cirrhosis

Hypovolemic Hyponatremia

- The most frequent cause is diuretic over treatment
- Daily B.wt. reduction should not exceed 500g-800gr\(^{(1)}\)
- Patients with peripheral edema (up to 2kg/day) tolerates B.wt. reduction better until edema disappear

Hypovolemic Hyponatremia

Treatment

- Hypovolemic Hyponatremia\(^{(1)}\)*
  - Removal of precipitating factor (Diuretic over treatment)
  - Administration of normal saline
  - Treatment of vomiting and diarrhea.

## Treatment of Hypervolemic Hyponatremia

<table>
<thead>
<tr>
<th>Asymptomatic</th>
<th>Severely symptomatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea without vomiting</td>
<td>-Vomiting</td>
</tr>
<tr>
<td>Confusion</td>
<td>-CR distress</td>
</tr>
<tr>
<td>Headache</td>
<td>-Somnolence</td>
</tr>
<tr>
<td></td>
<td>-Seizures</td>
</tr>
<tr>
<td></td>
<td>-Coma</td>
</tr>
<tr>
<td></td>
<td>-Glasgow coma scale B8</td>
</tr>
</tbody>
</table>
Treatment of Hypervolemic Hyponatremia

DETECTION OF HYponatremia

ASYMPTOMATIC MILDLY SYMPTOMATIC

Look for: diuretic overtreatment profuse vomiting diarrhea

YES
Hypovolemic hyponatremia

Stop diuretics (if given)
Volume expansion

Resolution
Implement preventive measures

NO
Hypervolemic hyponatremia

Look for & treat precipitating factors
Hypotonic fluid infusion
Polydipsia
Paracentesis
Bacterial infection
Hepatorenal syndrome

Persistence

Correct hyponatremia max speed: 2 mmol/h
Symptom resolution / attenuation

ASSAY

Consider & treat concomitant hepatic encephalopathy

Time of onset ≤ 24h

Assess the expected effect of hypertonic saline infusion

Correct hyponatremia max speed: 0.5 mmol/h

Time of onset > 24h
Unknown

## Hypervolemic Hyponatremia Prevention

<table>
<thead>
<tr>
<th>Condition</th>
<th>Prevention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ascites + impaired renal perfusion</td>
<td>Avoid hypotonic fluid</td>
</tr>
<tr>
<td>Large volume paracentesis</td>
<td>8g albumin/liter removed</td>
</tr>
<tr>
<td>SBP</td>
<td>1.5g/kg day 1 (albumin)</td>
</tr>
<tr>
<td></td>
<td>1g/kg day 3 + antibiotic</td>
</tr>
<tr>
<td>Hepatorenal syndrome</td>
<td>Terlipressin + albumin</td>
</tr>
</tbody>
</table>
Treatment of Hypervolemic Hyponatremia Severely Symptoms

First Hour management

- Promot IV 3% hypertonic saline 150ml over 20 min
- Check S.Na after 20min
- Repeat twice or until a target of 5mмо/L increase in S.Na, if not keep infusion at a rate of 1mmol/L/Hour
Treatment of Hypervolemic Hyponatremia

After 1st hour Management

- Stop hypertonic saline
- Keep 0.9% saline until cause specific treatment
- Limit ↑ in S.Na to a total of <10 mmol/L during 1st 24 hours and 8 mmol/L during every 24 hours later on until 130 mmol S.Na
- Check S.Na after 6 hours and 12 hour and daily afterwards.
Severe Hypervolemic Hyponatremia
Pharmacologic Treatment

- Demeclocyclin → unsuccessful (S.E) (1)* Nephrotoxic
- Niravoline (K-opioid receptor agonist)
  Inhibits ADH(central)
  0.5-1mg/day
  Higher dose → reversible personality disorders + mild confusion (2)*, (non sustainable effect)
- (Vaptans) Selective blockers of V2 receptor of AVP

Hyponatremia Liver cirrhosis VAPTAN

Savio John, World J Gastroenterology 2015 March 21; 21(11): 3197-3205
Vaptans (Vasopressin Receptor Antagonists)

Tolvaptan-satavaptan-lixivaptan → selective block V2 receptor
Conivaptan - V2+ V1 receptor blocking I.V

- **Tolvaptan**
  - Added to diuretic therapy for 25-60 days in heart failure patients →↓B.wt + edema (RCT) improve Na level \(^{(1,2)\ast}\)
  - Multicenter trials evaluating effect on progression of PKD→↑risk of liver failure in cirrhotic

- **Stavaptan:**
  - Increased mortality compared to placebo on one year follow up.

Vaptans- Summary

- Neither fluid restriction nor administration of saline should be used in combination with vaptans
- Duration of treatment not yet established
- In liver transplant setting with severe hypervolemic hyponatremia (Na<125mmol/L) vaptans may be considered
- Only Tolvaptan is approved by EMA for SIADH
- FDA → SIADH and heart failure.
Hyponatremia Liver Cirrhosis

Summary

- Hyponatremia is very common in cirrhosis but routine correction of asymptomatic patients is not recommended.
- The main indications for treatment are:
  - Neurologic symptoms
  - S.Na < 120 mEq/L
  - Pre transplantation S.Na < 130 mEq/L
- Precipitating factors have to be avoided or promptly recognized and corrected.
- Vaptans are only approved for use in pre-transplant setting.
Thank You