# Hyponatremia in cirrhosis

- A 49-year-old male, diagnosed patient of cryptogenic cirrhosis has been admitted with grade 3 HE (no localizing signs/CT head elsewhere normal). He has no fever.  His labs shows Hb-9g/dl, Plt-65 thousands, TLC-3400, TB-2.0mg%, S. Cr-2.0 mg%, S. Na- 117 meq/dl. There is h/o ascitic tap 4-5 liters elsewhere 4 days back.

| | | | |
|---|---|---|---|
| Hb | 9 | Ur | |
| TLC | 3400 | Cr | 2 |
| PLT | 65k | Na | 117 |
| INR | | K | 5.2 |
| T Bil | 2 | | |
| AST | | | |
| ALT | | | |

# Introduction

- 95 to 98% of total body sodium resides in the extracellular fluid (ECF)
- Serum sodium concentration is influenced by water metabolism rather than sodium intake and excretion
- Absolute or relative water retention causes hyponatremia, excessive fluid loss-hypernatremia
- Baroreceptors, osmoreceptors and neurohormonal system maintains total body water in constant state

# Introduction

- Hyponatremia is defined as a serum sodium concentration of less than 135 mEq/L.
- In cirrhosis by consensus, hyponatremia defined as a serum sodium of less than 130 mEq/L
- Most common electrolyte disorder in  cirrhosis.
- Predominantly hypervolemic or dilutional, hypovolumic (<10%)
- Patients with  hyponatremia usually have decompensated liver disease
- Predictor of poor outcomes

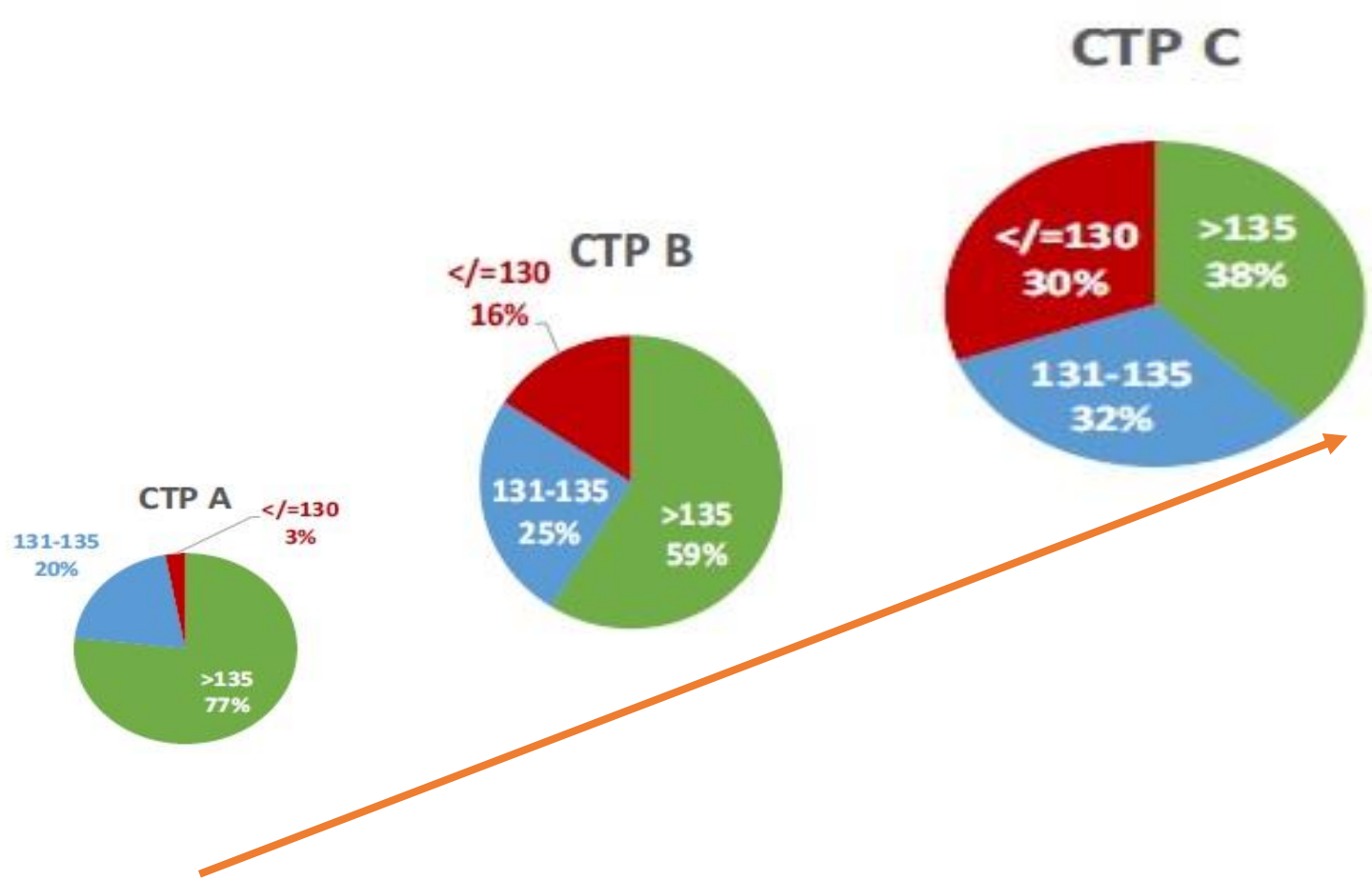
# Prevalence of hyponatremia in cirrhosis

Conventional definition: Serum sodium ≤135 meq/L
Hyponatremia in cirrhosis : Serum sodium ≤130 meq/L *

| **Author and Publication year** | **Patient characteristic** | **Prevalence (<135 meq/L)** | **Prevalence(<130 meq/L)** |
|---|---|---|---|
| Angeli et al (2006) | Outpatients | 40% | - |
| Angeli et al (2006) | In Patients | 57% | 21.6% |
| Kim et al (2009) | In patients | 20.8% | - |
| Jenq et al (2010) | In patients | 53.2% | 28.6% |
| Sheikh et al (2010) | In patients | 51.6% | 26.7% |

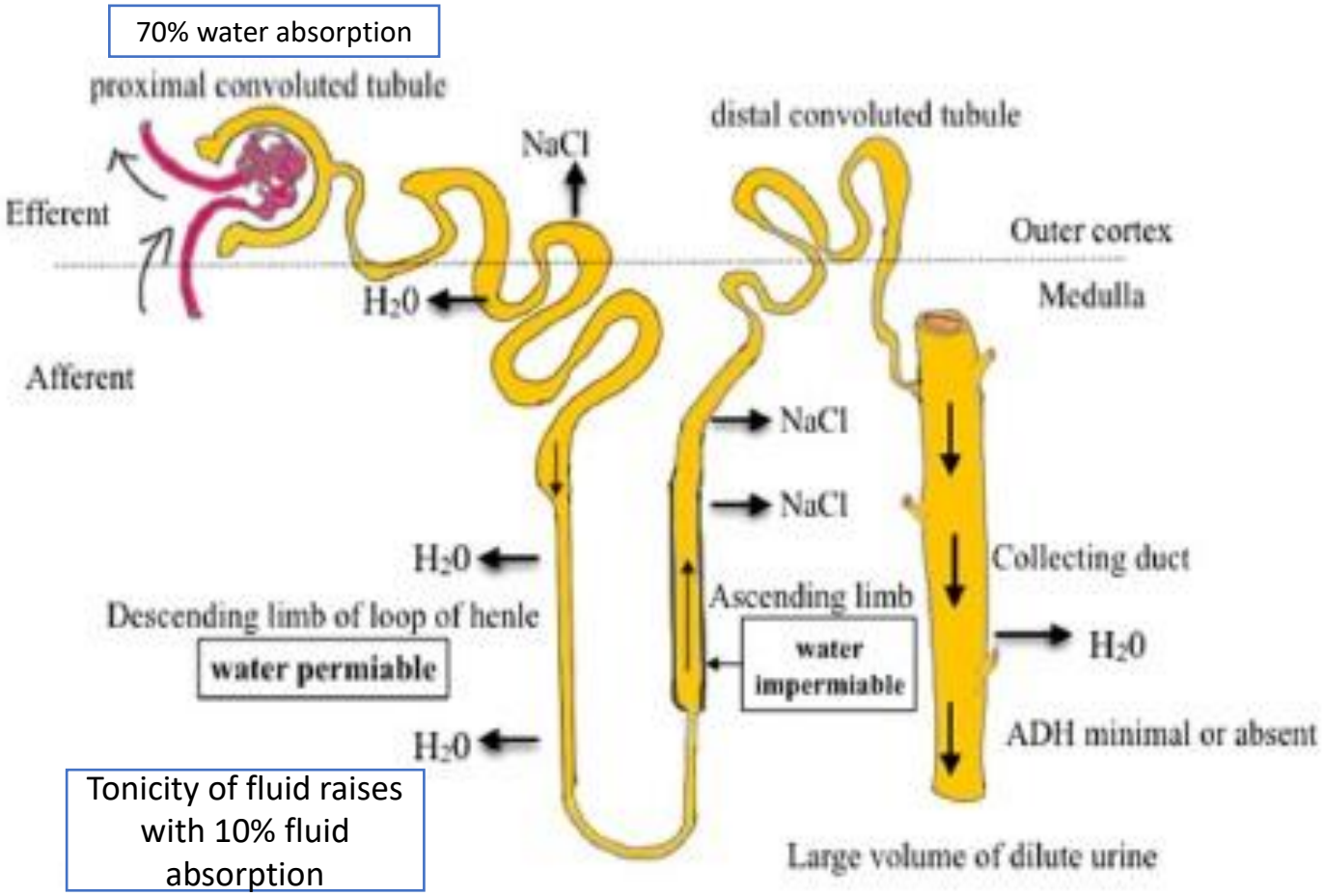
* Arroyo et al. *Digest Dis Sci*. 1976

# Prevalence of hyponatremia in cirrhosis




Bernardi M et al.*Hepatol Int*. 2018

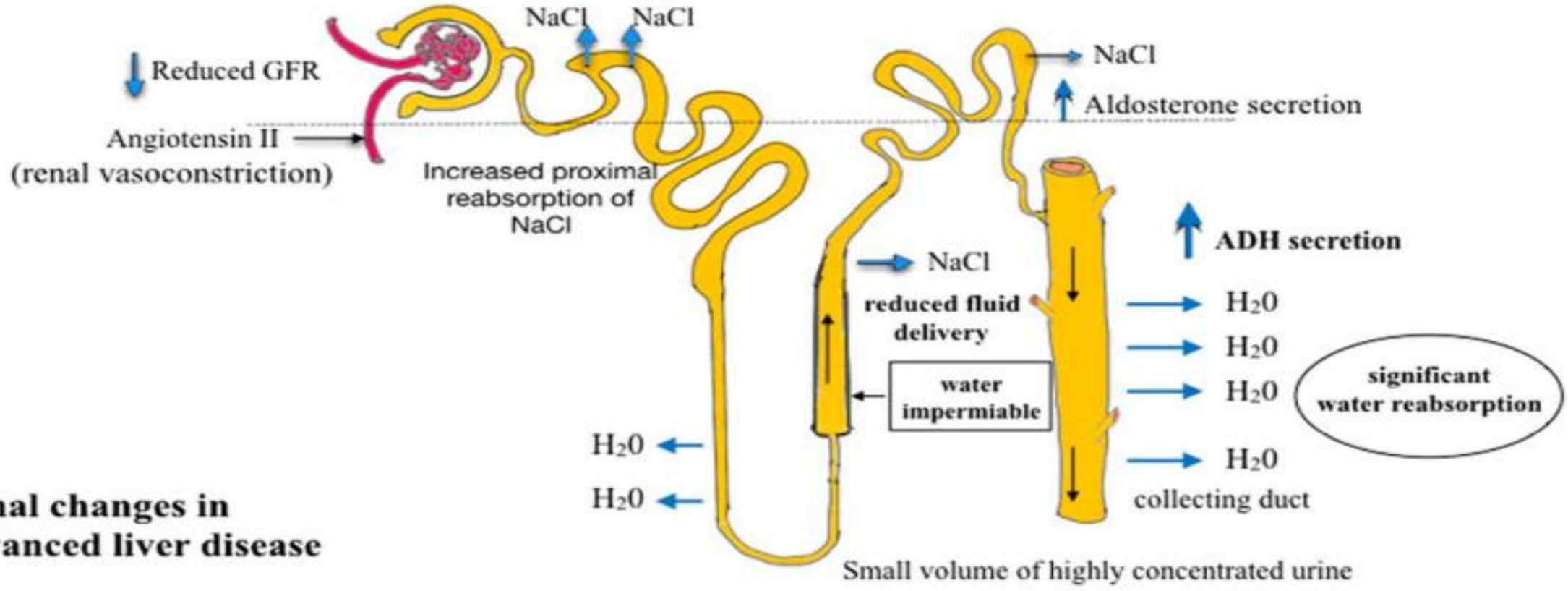
# Normal renal physiology of sodium and water homeostasis




- Multiple hormones are involved in renal regulation of water
  - Angiotensin
  - Aldosterone
  - Prostaglandin
  - ADH

Gines et al,Hepatology,1998
Alukal et al,Am J Gastroenterol,2020

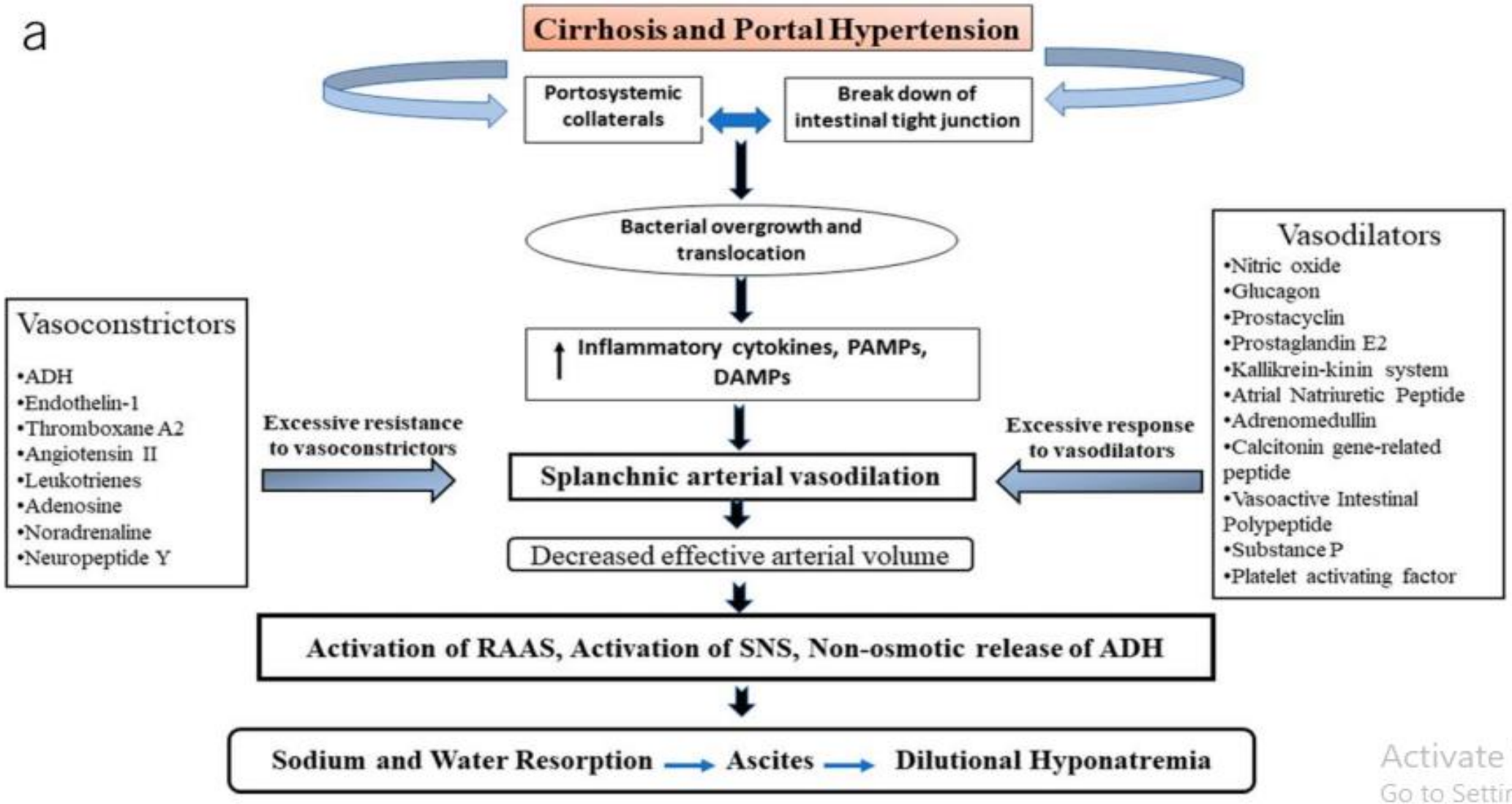
# Renal changes in portal hypertension leading to decrease in water clearance

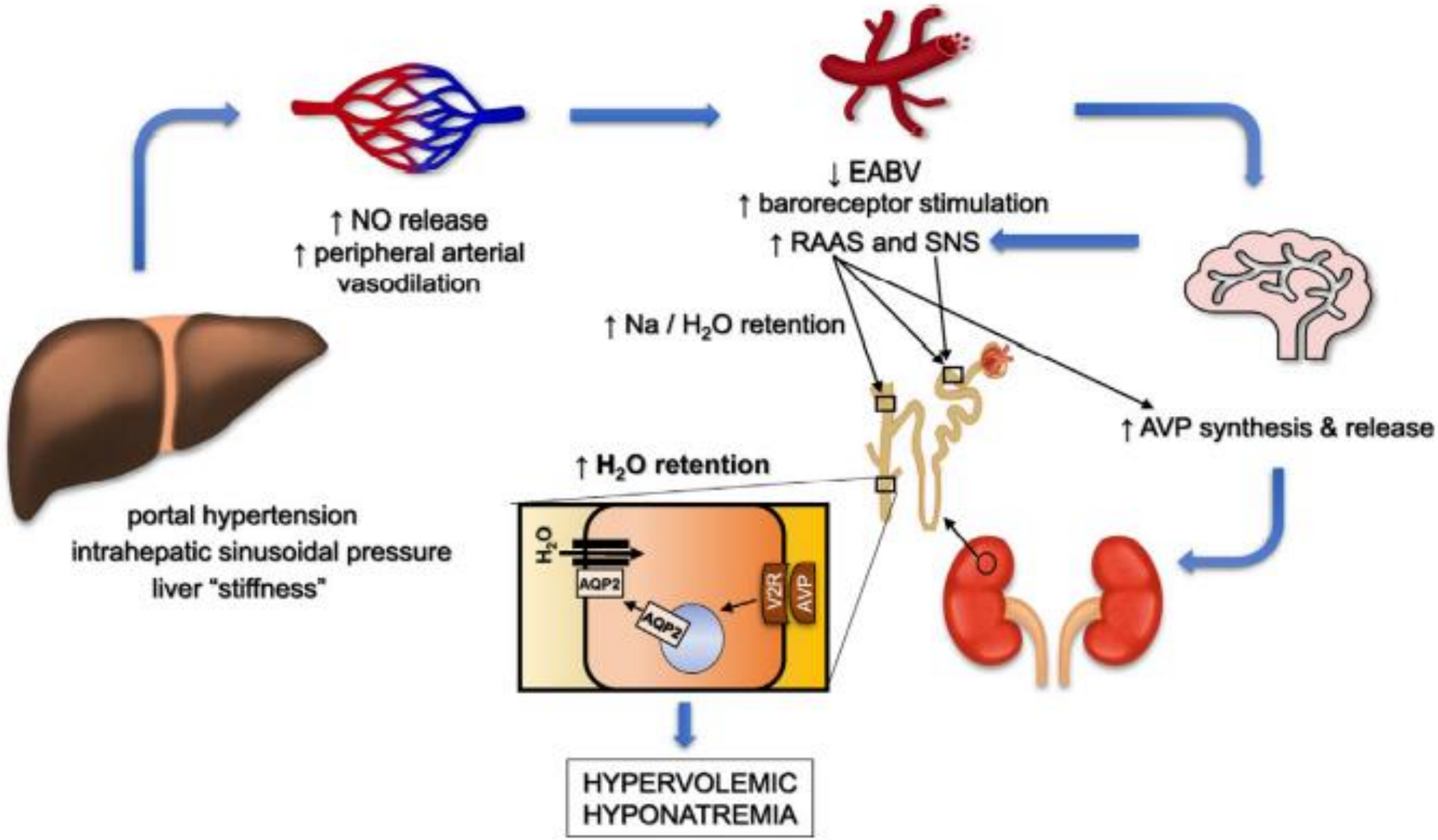



**Renal changes in advanced liver disease**

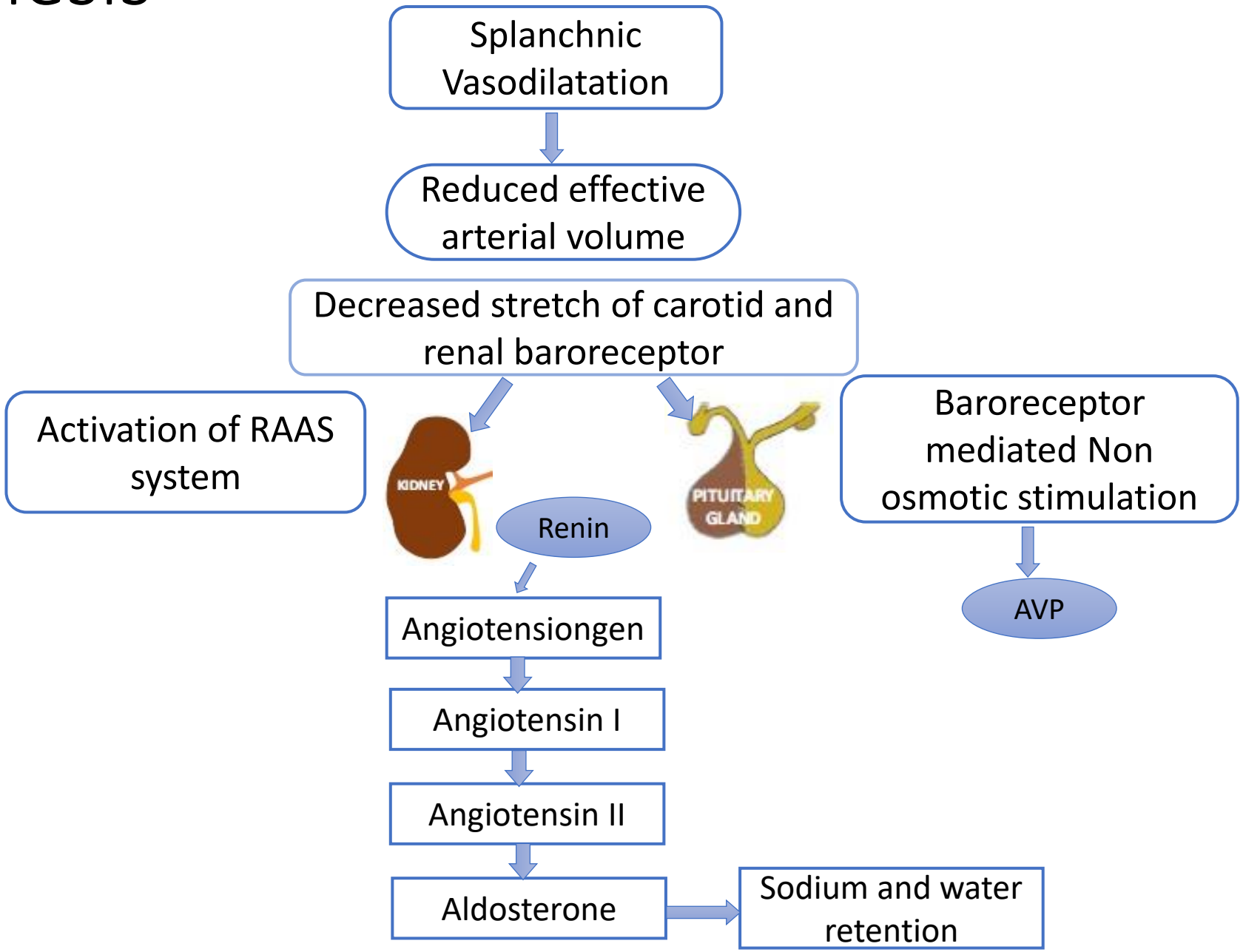
b

# Pathogenesis



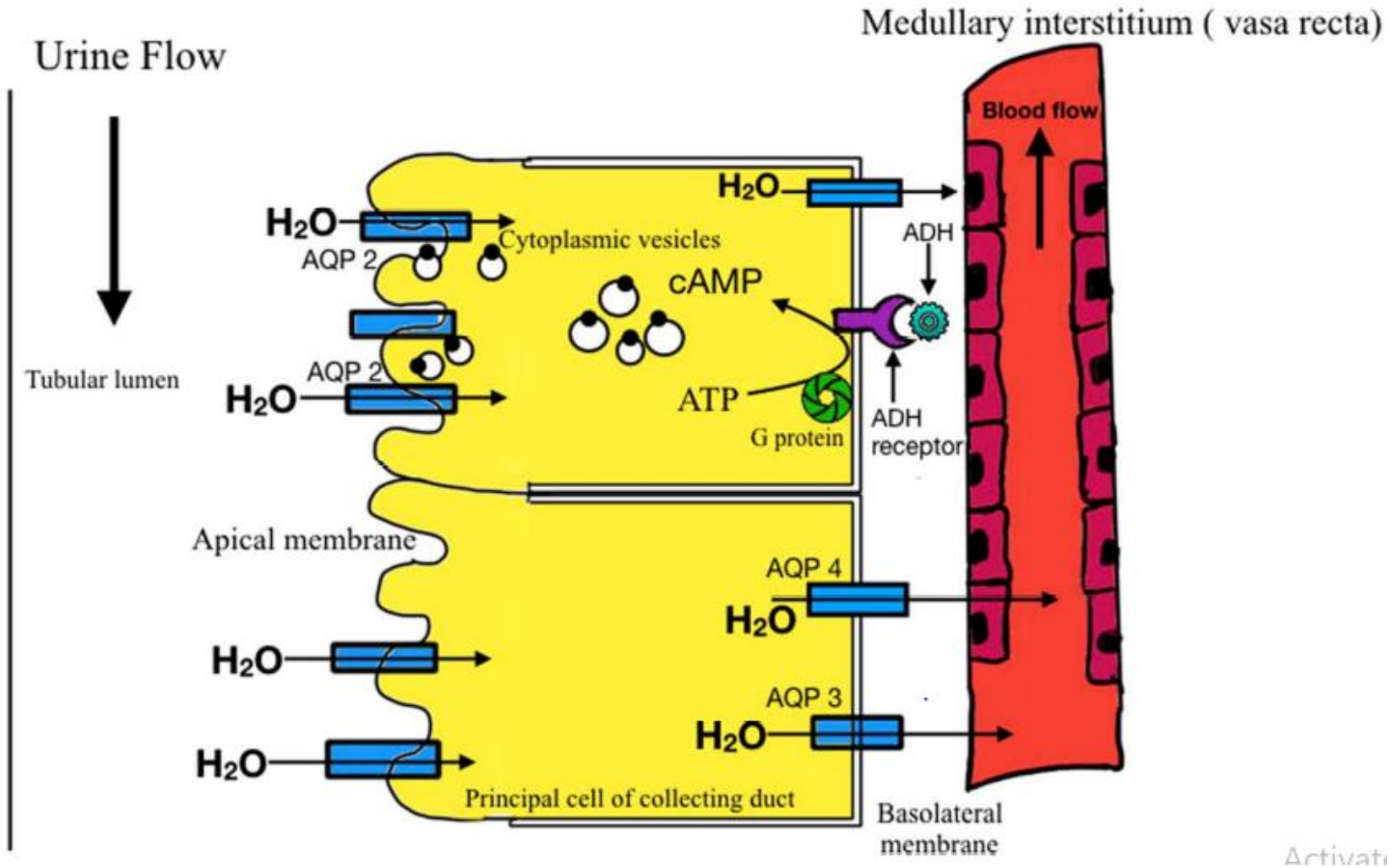

↑ NO release
↑ peripheral arterial vasodilation
↓ EABV
↑ baroreceptor stimulation
↑ RAAS and SNS
↑ Na / H2O retention
↑ AVP synthesis & release
↑ H2O retention
portal hypertension
intrahepatic sinusoidal pressure
liver "stiffness"
H2O
AQP2
AQP2
V2R
AVP
HYPERVOLEMIC
HYPONATREMIA

# Pathogenesis



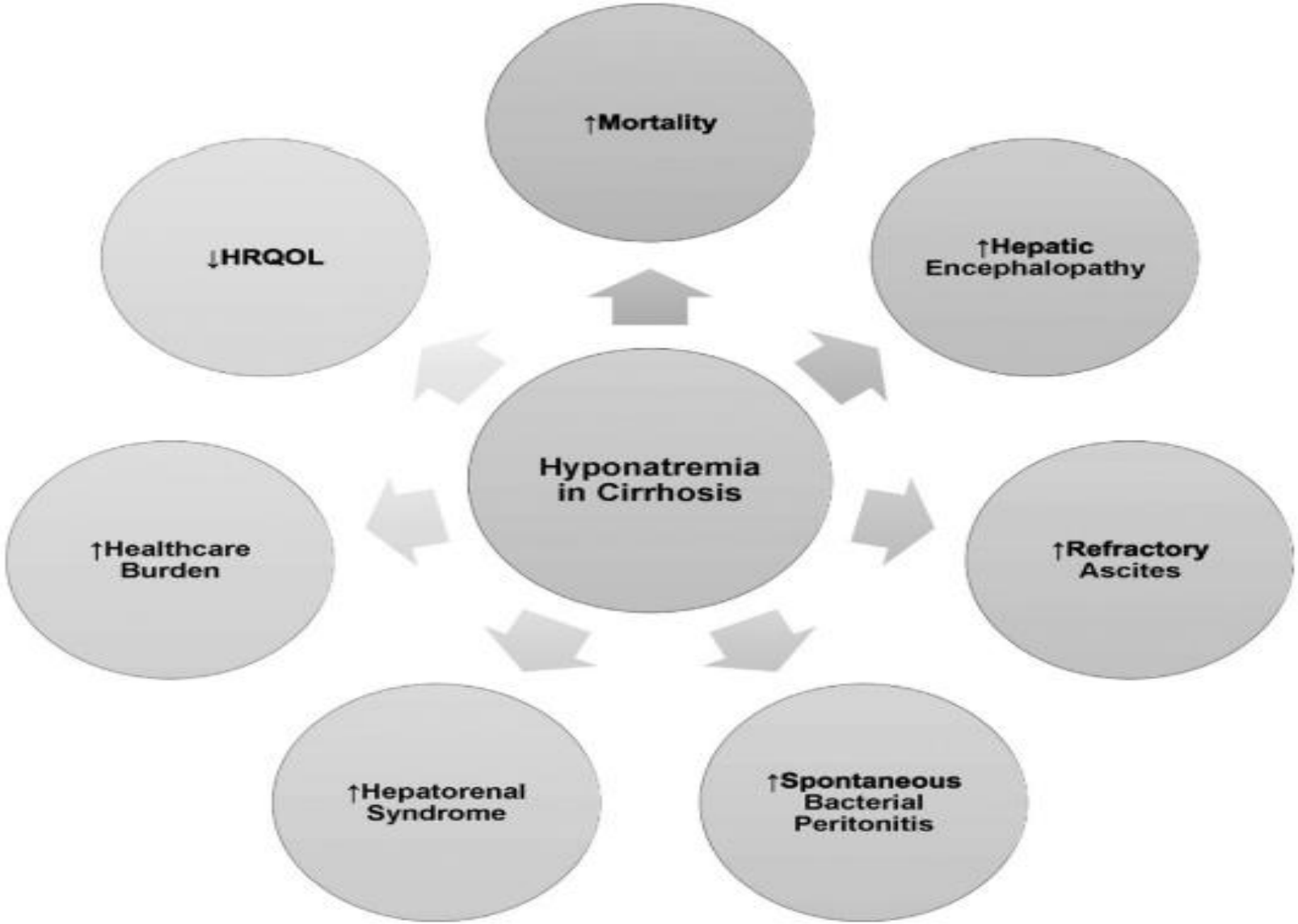

Alukal et al.Am J Gastroenterol,2020

# Mechanisms of excessive water absorption mediated by the release antidiuretic hormone (ADH).

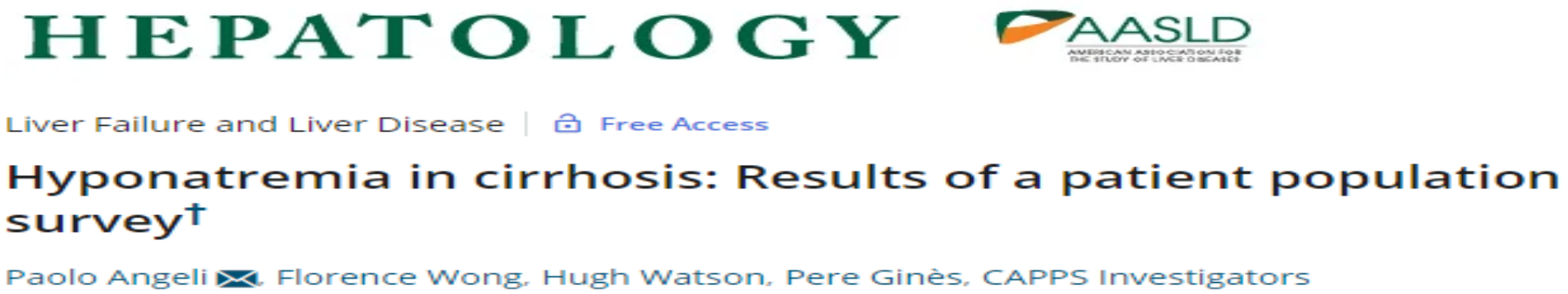


# Why addressing hyponatremia is important?

# Clinical outcomes of hyponatremia of cirrhosis



# Association between HRS, SBP and hyponatremia: Multiple issues in a sick patient

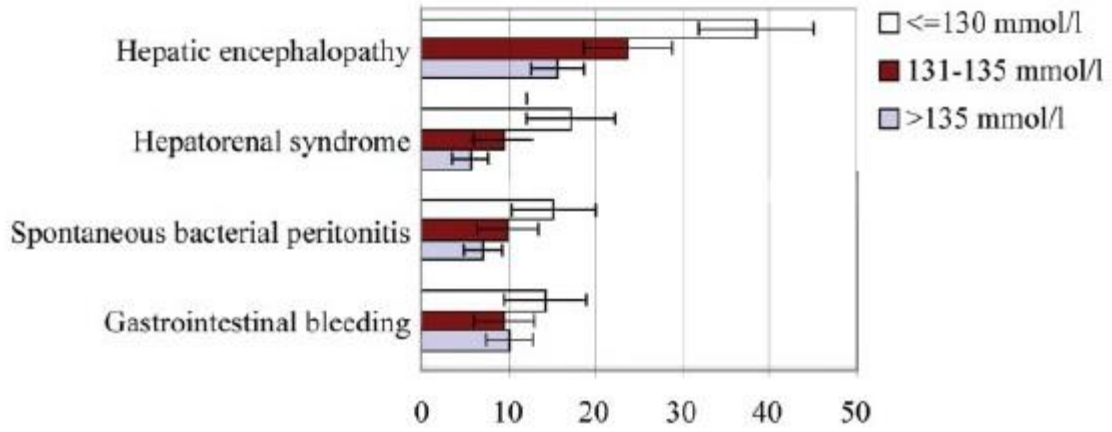



- A large prospective multicenter study included (n-995) cirrhotic patients
- hyponatremia was associated with
  - higher prevalence of refractory ascites,
  - higher requirement of large-volume paracentesis,
  - shorter time interval between paracentesis.
  - higher incidence of HE,SBP,HRS

# Association between HRS, SBP and hyponatremia: Multiple issues in a sick patient

## Hyponatremia in Cirrhosis: Results of a Patient Population Survey

Paolo Angeli,[1] Florence Wong,[2] Hugh Watson,[3] Pere Ginès,[4] and the CAPPS Investigators




| | 131–135 mmol/L (95% CI) | ≤130 mmol/L (95% CI) |
|---|---|---|
| Hepatic encephalopathy | 1.69 (1.16–2.45) | 3.40 (2.35–4.92) |
| Hepatorenal syndrome | 1.75 (1.00–3.05) | 3.45 (2.04–5.82) |
| Spontaneous bacterial peritonitis | 1.44 (0.85–2.43) | 2.36 (1.41–3.93) |
| Gastrointestinal bleeding | 0.93 (0.56–1.54) | 1.48 (0.91–2.41) |

NOTE. The group of patients with serum sodium >135 mmol/L was used as a reference.

**Angeli P *et al. Hepatology 2006***

# Hyponatremia and Complications

Odds Ratios for Different Variables of Critically Ill Cirrhotic Patients According to Serum Sodium Concentration

| Major Complications | > 135 mmol/L n (%) | ≤ 135 mmol/L n (%) | Odds Ratios (95% CI) | *P* |
|---|---|---|---|---|
| Hospital mortality | 33 (56) | 49 (73) | 2.145 (1.018-4.521) | 0.043 |
| Hepatic encephalopathy, ICU first day | 35 (59) | 52 (78) | 2.377 (1.096-5.157) | 0.027 |
| Ascites, ICU first day | 21 (36) | 48 (72) | 4.571 (2.154-9.702) | < 0.001 |
| Sepsis, ICU first day | 18 (31) | 32 (48) | 2.083 (1.001-4.333) | 0.048 |
| Renal failure, ICU first day | 34 (58) | 56 (84) | 3.743 (1.637-8.562) | 0.001 |
| Gastrointestinal bleeding, ICU first day | 42 (71) | 42 (63) | 0.680 (0.321-1.440) | NS (0.313) |
| EV bleeding, ICU first day | 30 (51) | 28 (42) | 0.694 (0.343-1.404) | NS (0.309) |
| Peptic ulcer bleeding, ICU first day | 19 (32) | 21 (31) | 0.961 (0.453-2.038) | NS (0.918) |
| Both EV and peptic ulcer bleeding | 7 (12) | 7 (10) | 0.867 (0.285-2.634) | NS (0.801) |

The group of patients with serum sodium concentration > 135 mmol/L was used as a reference.
CI indicates confidence intervals; EV, esophageal varices; ICU, intensive care unit; NS, not significant.

**Angeli P *et al. Hepatology 2006***

LIVER, PANCREAS AND BILIARY TRACT: ORIGINAL ARTICLES

# Serum Sodium Predicts Prognosis in Critically Ill Cirrhotic Patients

Jenq, Chang-Chyi MD*; Tsai, Ming-Hung MD†; Tian, Ya-Chung PhD*; Chang, Ming-Yang PhD*; Lin, Chan-Yu MD*; Lien, Jau-Min PhD†; Chen, Yung-Chang MD*; Fang, Ji-Tseng MD*; Chen, Pan-Chi MD†; Yang, Chih-Wei MD*

Author Information

- Comparing with serum sodium >135 mmol/L, patients with serum sodium ≤135 mmol/L had a greater in-hospital mortality (55.9% vs. 73.1%, *P*=0.043).
- at 6-month follow-up after hospital discharge differed significantly (*P*<0.05) between both groups
- Low serum sodium levels in critically ill cirrhotic patients are associated with high complications of liver cirrhosis, in-hospital mortality, and poor short-term prognosis

# Hyponatremia and hepatic encephalopathy

Astrocytes contains glutamine synthase → Detoxify ammonia

Hyperammonemia

↓

increased intracellular content of glutamine

↓

Increased cellular osmolality

↓

Astrocyte swelling

↓

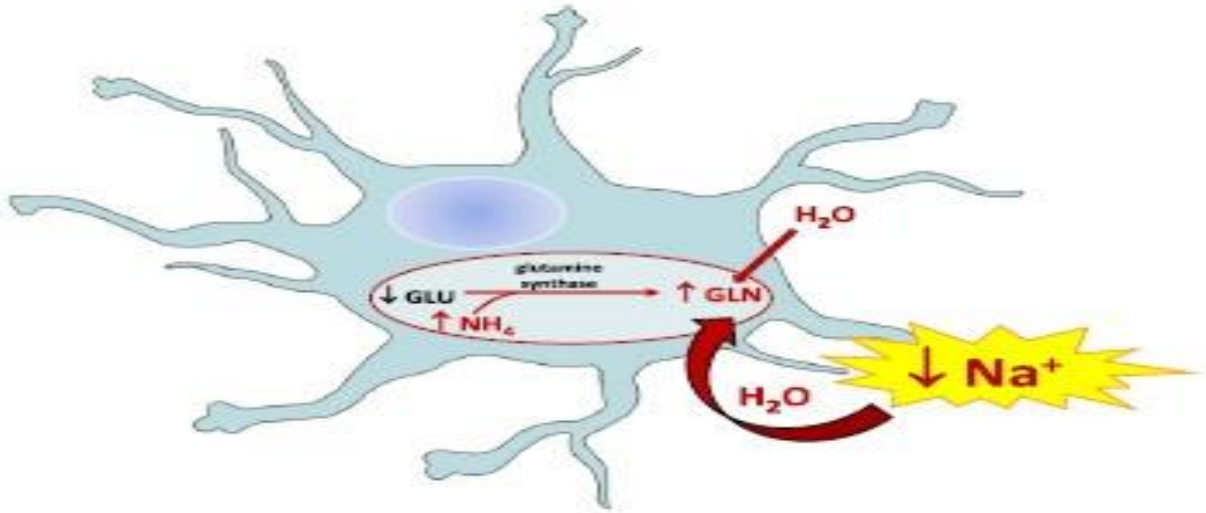
Astrocyte dysfunction

↓

HE

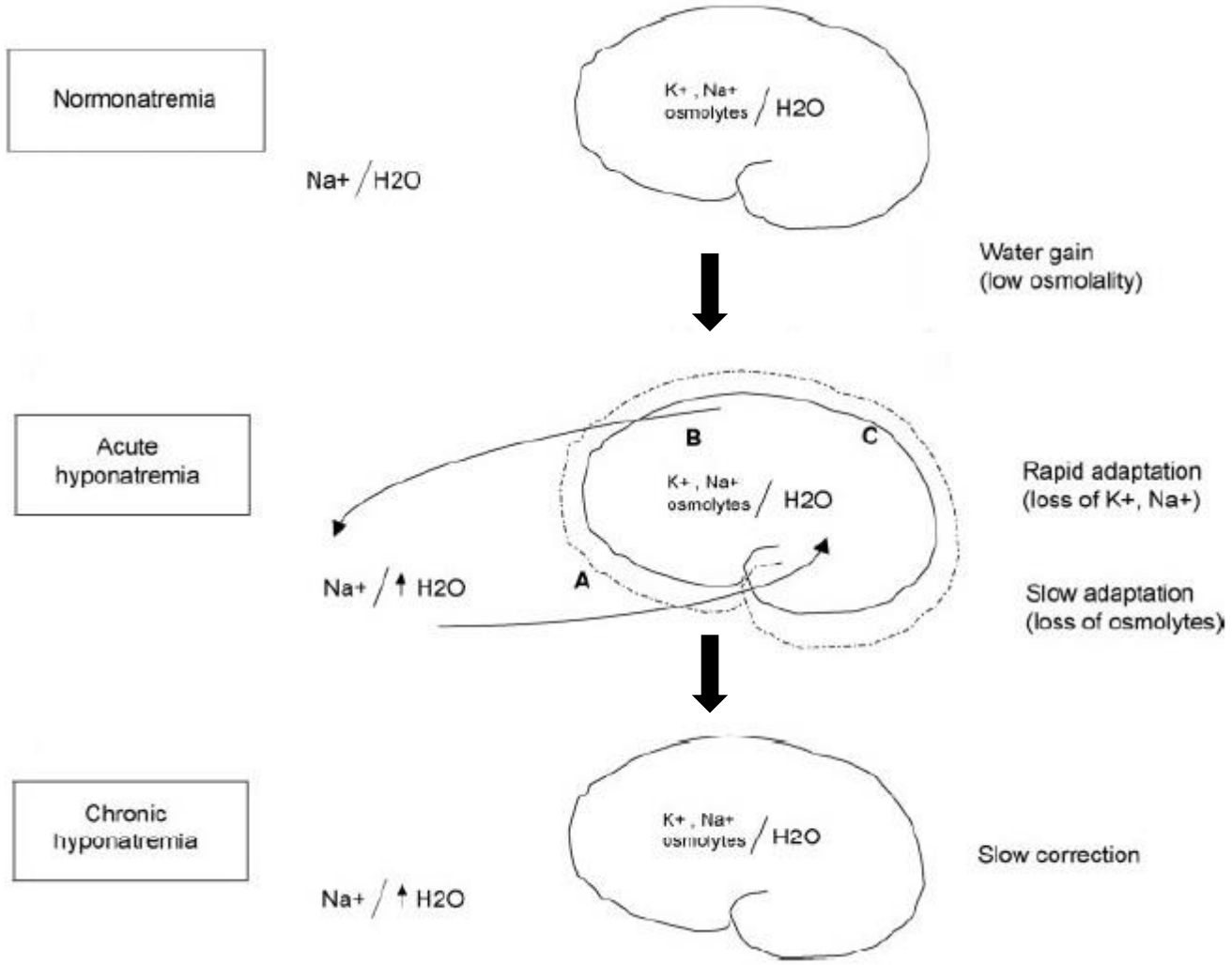
Low grade cerebral edema is one of the factor associated with HE

Deranged osmotic balance in cirrhotic brain, hyponatremia is second osmotic hit to astrocytes, can cause cell swelling and dysfunction




Bernardi M et al.*Hepatol Int*. 2018

# Cerebral adaptation to hyponatremia




- Brain and extracellular fluid osmolality are in balance
- When serum Na falls, water moves inside brain
- The cell swelling leads to extrusion of intracellular solutes
- Organic osmolytes-Glutamine,glutamate,taurine and myo-inositol are involved in long term adaptation of osmotic changes

Ginès P, Cárdenas A. *Semin Liver Dis*. 2008

# Hyponatremia Is a Risk Factor of Hepatic Encephalopathy in Patients With Cirrhosis: A Prospective Study With Time-Dependent Analysis

Mónica Guevara[1–3,7], M.E. Baccaro[1–3,7], Aldo Torre[1], Beatriz Gómez-Ansón[4], José Ríos[5], Ferrán Torres[5], Lorena Rami[6], Gemma C. Monté-Rubio[4], Marta Martín-Llahí[1–3], Vicente Arroyo[1–3] and Pere Ginès[1–3]

**Table 3. Variables with independent predictive value in the development of overt HE in the multivariate analysis (Prentice, Williams, and Peterson models)**

| | HR | 95% CI | *P* value |
|---|---|---|---|
| *Model 1* | | | |
| Hyponatremia | 10.69 | (4.39;26.03) | <0.001 |
| Earlier hepatic encephalopathy | 2.94 | (1.30; 6.61) | 0.009 |
| Bilirubin ≥ 2.1 mg/dl | 2.4 | (0.88;6.60) | 0.089 |
| *Model 2* | | | |
| Hyponatremia | 9.36 | (4.66;18.80) | <0.001 |
| Earlier hepatic encephalopathy | 1.78 | (1.10; 2.87) | 0.018 |
| Creatinine ≥ 1.2 mg/dl | 2.31 | (1.22;4.38) | 0.01 |
| *Model 3* | | | |
| Hyponatremia | 8.36 | (3.52; 19.82) | <0.001 |
| Earlier hepatic encephalopathy | 2.23 | (1.09; 4.56) | 0.029 |
| Creatinine ≥ 1.2 mg/dl | 2.36 | (1.11; 5.00) | 0.025 |
| Bilirubin ≥ 2.1 mg/dl | 2.74 | (1.16; 6.47) | 0.022 |

CI, confidence interval; HE, hepatic encephalopathy; HR, hazard ratio.

- 61 patients with cirrhosis were followed for 1 year for development of overt HE
- 27 patients developed 57 episodes of HE
- Hyponatremia( NA <130 meq/L),Overt HE,Bilirubin and creatinine were independent predictors

**Guevara *et al. Am J Gastroentero 2009***

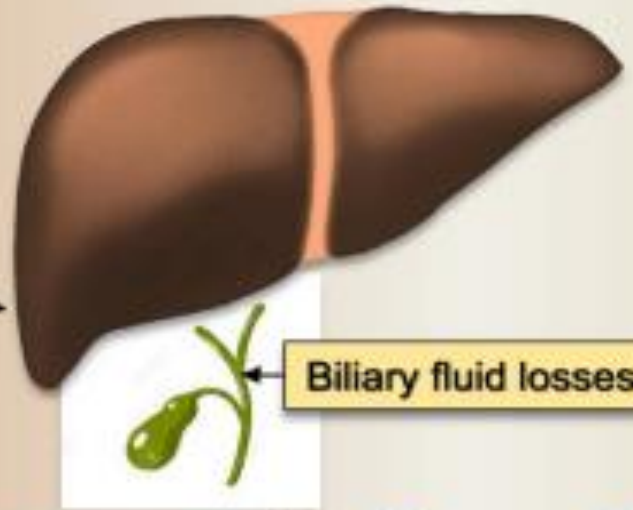
# Etiology-causes of Hyponatremia

- Cirrhosis Itself
- GI fluid losses
- Renal sodium losses
- Adrenal insufficiency
- Terlipressin
- Low solute intake
- Pseudohyponatremia

**HYPERVOLEMIC**
**with primary AVP release**

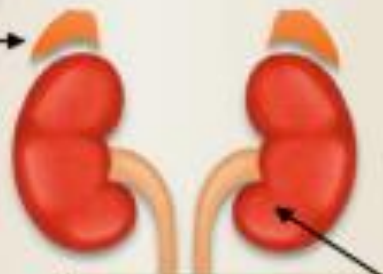
**HYPOVOLEMIC**
**with secondary AVP release**

Portal hypertension
↓ SVR



Biliary fluid losses

Hepato-adrenal insufficiency



Lactulose-induced-intestinal fluid losses


Aldosterone antagonist-induced urinary losses

EUVOLEMIC
due to low solute intake (not AVP-mediated)

# Terlipressin precipitates hyponatremia

JGH Open An open access journal of gastroenterology and hepatology Open Access JGHF

doi:10.1002/jgh3.12254

ORIGINAL ARTICLE

**A retrospective analysis of hyponatremia during terlipressin treatment in patients with esophageal or gastric variceal bleeding due to portal hypertension**

Xv Han, Jia Li, Ji-Ming Yang, Min Gao and Lei Wang

Tianjin Second People's Hospital, Tianjin Hepatopathy Research Institute, Tianjin, China

- During the treatment, serum sodium levels decreased from 137.78 to 126.59 mmol/L ($P < 0.05$), with an average decrease of 11.19 mmol/L.
- The serum sodium level decreased by
  - less than 5 mmol/L in 12 patients (27.27%),
  - 5–10 mmol/L in 13 patients (27.27%),
  - more than 10 mmol/L in 19 patients (43.18%)

J Clin Gastroenterol. 2015 Aug;49(7):607-12. doi: 10.1097/MCG.0000000000000217.

# Risk Factors for Developing Hyponatremia During Terlipressin Treatment: A Retrospective Analyses in Variceal Bleeding

Sun Young Yim [1], Yeon Seok Seo, Chang Ho Jung, Tae Hyung Kim, Eun Sun Kim, Bora Keum, Ji Hoon Kim, Hyonggin An, Hyung Joon Yim, Jong Eun Yeon, Yoon Tae Jeen, Hong Sik Lee, Hoon Jai Chun, Kwan Soo Byun, Soon Ho Um, Chang Duck Kim, Ho Sang Ryu

n-151 patients

- Hyponatremia was defined as a decrease in serum sodium (Na) level of >5 mEq/L from the baseline level
- Younger age, lower Child-Pugh score(child A), higher serum Na level, and longer duration of terlipressin treatment were independent risk factors.
- lower body mass index was an additional risk factor in this group.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# Terlipressin plus Albumin for the Treatment of Type 1 Hepatorenal Syndrome

F. Wong, S.C. Pappas, M.P. Curry, K.R. Reddy, R.A. Rubin, M.K. Porayko, S.A. Gonzalez, K. Mumtaz, N. Lim, D.A. Simonetto, P. Sharma, A.J. Sanyal, M.J. Mayo, R.T. Frederick, S. Escalante, and K. Jamil, for the CONFIRM Study Investigators*

## CONFIRM trial

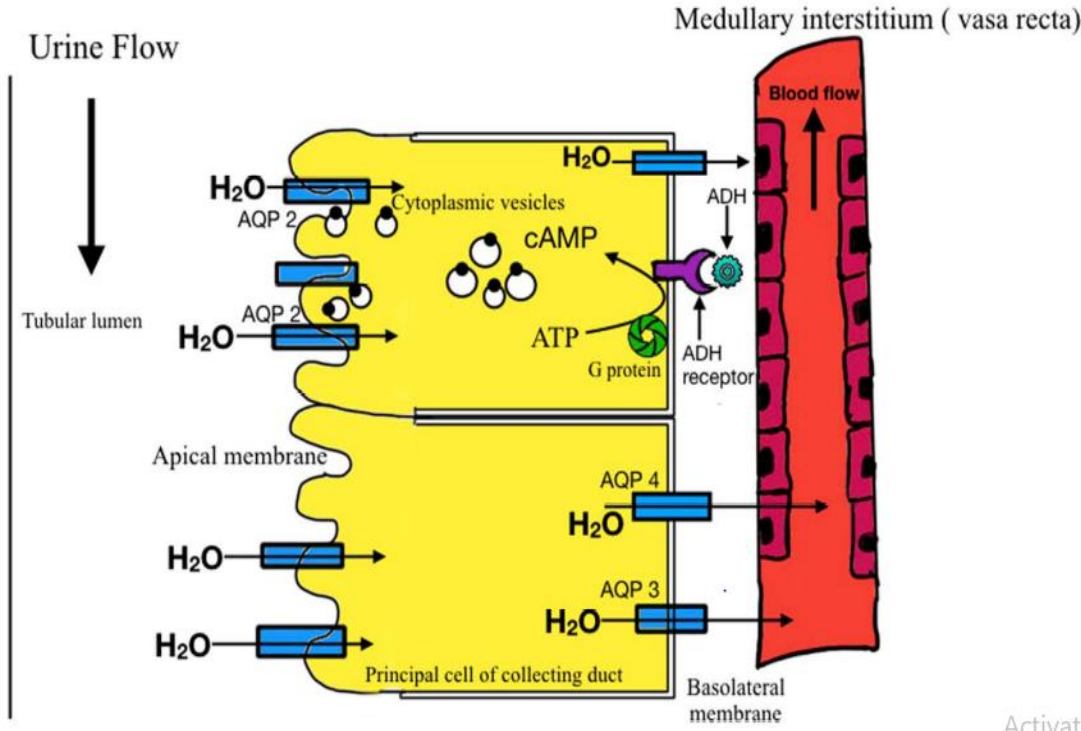
- Randomized placebo controlled trial testing the use of terlipressin for HRS-1 in North America (CONFIRM trial)
- Hyponatremia was not reported to be more common in terlipressin-treated subjects.

# Mechanism

- vasopressin analogue with greater affinity for the V2 receptor (VR) than that for the V1a receptor.
- mimic the actions of AVP in the renal collecting duct.
- mechanism may be related to endogenous vasopressin preconditioning.
- by binding to the V1 receptor on vascular smooth muscle, can contract blood vessels (mainly visceral blood vessels), leading to the redistribution of blood flow and contributing to the increase in arterial blood pressure and renal perfusion and the increase of sodium hydrochloride excretion in patient

- terlipressin also activates the V2 receptors of the basal lateral membrane of the main cells of the renal collecting duct

- Water permeability increases by 8–10 times, which could lead to dilution hyponatremia.



# Hyponatremia in liver transplant recipients

- From January 2016, United Network for Organ Sharing(UNOS) incorporated sodium to the MELD score as it is better score to predict waiting list mortality.
- It was seen that in the patients, who are on the LT waiting list with sNa (125–140 mmol/L), each millimole reduction in sNa was associated with a HR of 1.05.

*Kim WR, Biggins SW, Kremers WK, et al. Hyponatremia and mortality among patients on the liver-transplant waiting list. N Engl J Med. 2008*

- Hyponatremia prior to LT is associated with a
  - longer hospital stay
  - long ICU stay, and neurological complications.

- There may be an increase in 1-year mortality in patients with severe hyponatremia (sNa< 120) before LT.

# Addition of Sodium to MELD- MELD Na score

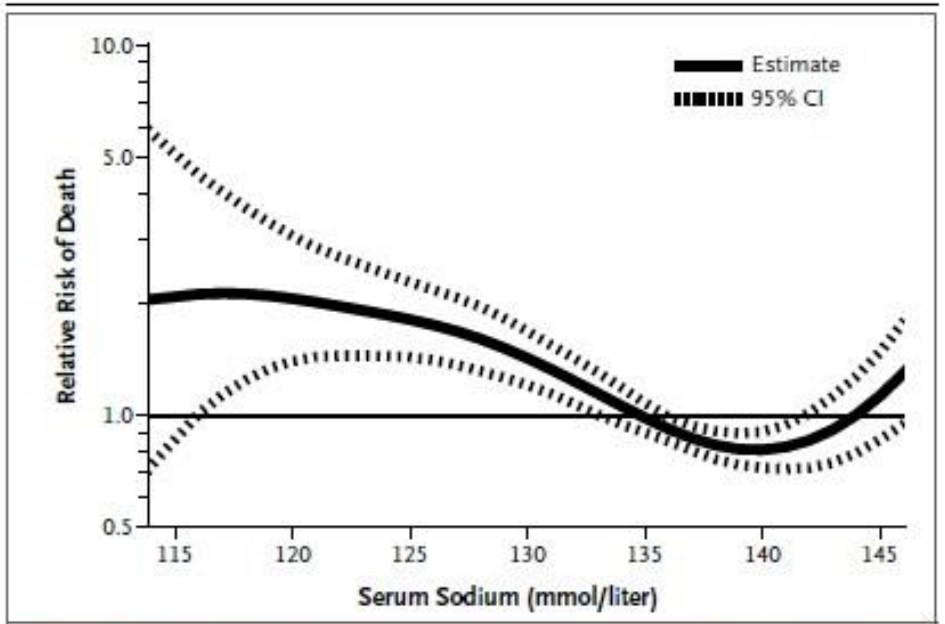



Figure 1. Serum Sodium Concentration and the Relative Risk of Death after Adjustment for the MELD Score.

- Decrease in serum sodium was associated with an increase in the risk of death while patients were on the waiting list
- Most meaningful differential effect of hyponatremia on mortality at a serum sodium concentration between 125 and 140 mmol per liter

Kim et al,New Eng J Med; 2006

# MELD Na over MELD

**Advantages**

- More predictive of risk of death
- MELD Na can reduce waiting list mortality
- Complications like HRS and refractory ascites which usually associated with hyponatremia are better covered

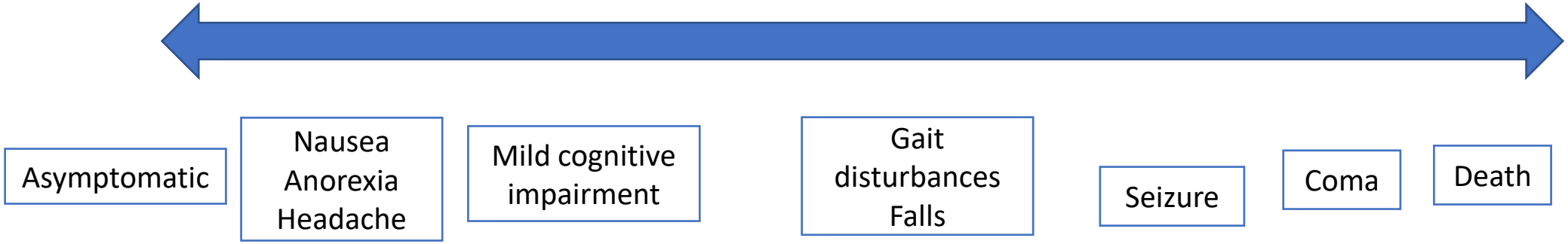
**Disadvantages**

- Sodium concentration depends upon use of diuretics and fluid status
- Modest efficacy due to limited population having hyponatremia among transplant list candidate
- Score changes only in sodium range of 120-135 meq/L
- Possibility of ‘gaming’ by altering sodium value

# Clinical features of hyponatremia

- The severity of clinical symptoms due to hyponatremia roughly correlates with serum osmolality and level of serum sodium in extracellular fluid.

- The rate of fall rather than the absolute fall in serum sodium from baseline is the most important predictor of the severity of symptoms.



# What has possibly happened to this patient?

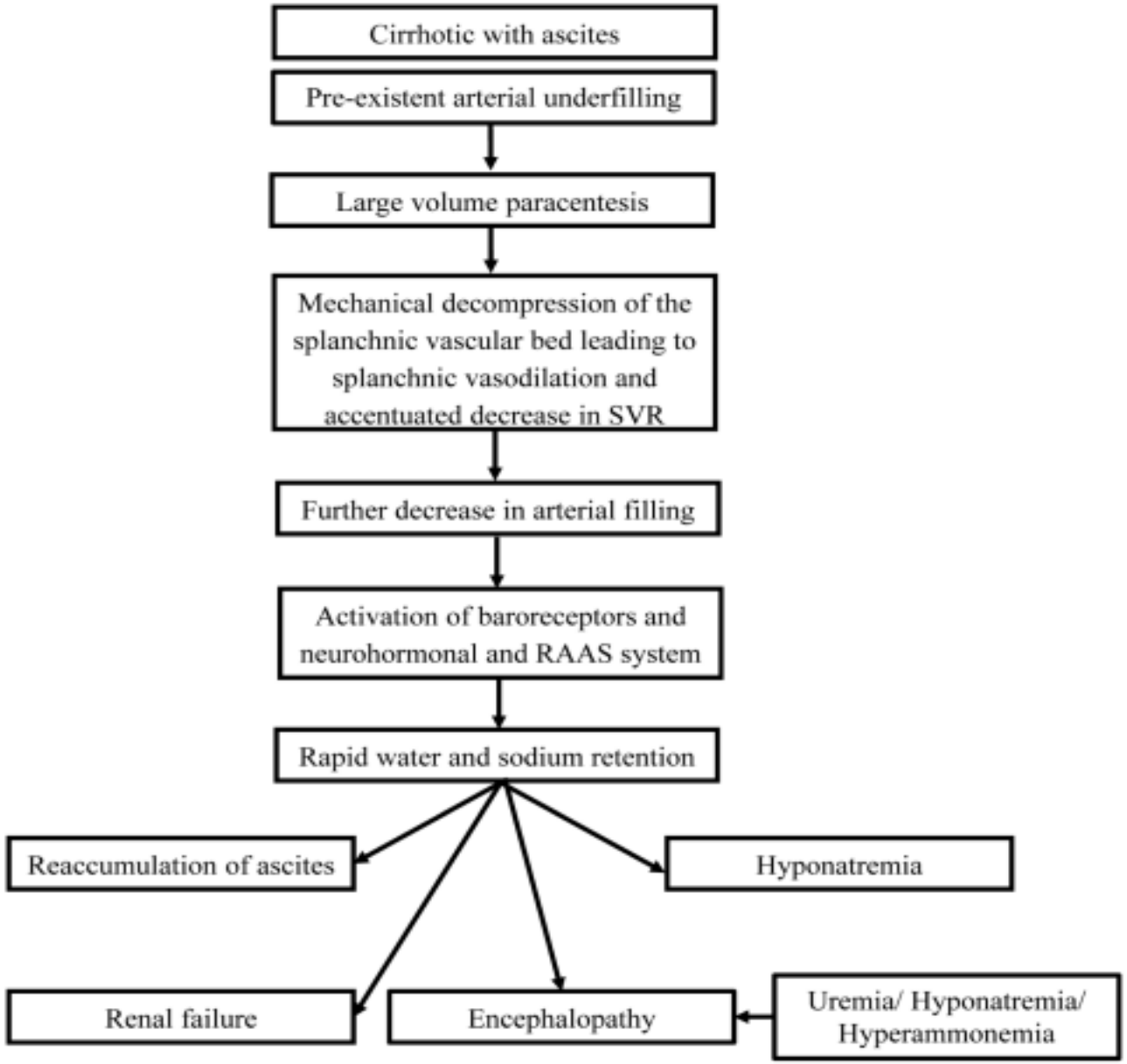
## PICD

- Increases of >50% of baseline plasma renin activity to a value more than 4 ng/mL/h on the fifth to sixth day after paracentesis.
- Refractory ascites (10% cirrhotics) required LVP
- safe method, sometimes with circulatory dysfunction in a significant percentage of patients (PICD)
- PICD usually occurs following LVP (>5–6 L)
- PICD results in
  - faster reaccumulation of ascites
  - hyponatremia
  - renal impairment
  - shorter survival

*Gines et al*

- PICD is a dreaded complication of paracentesis and is associated with a high incidence of morbidity and mortality.
- often overlooked and is a commonly missed diagnosis.
- The differentials in any patient presenting with worsening of complications of cirrhosis should include PICD.
- The diagnosis is clinical, and the measurement of PRA may or may not aid in diagnosis.
- PICD should be redefined as any complication (kidney injury, hyponatremia, encephalopathy, variceal bleed) developing after paracentesis with or without a concurrent rise in PRA.

# Pathophysiology of PICD



# Differential diagnosis of PICD complication

| Complication of PICD | Common differentials in practice |
|---|---|
| Hyponatremia | Diuretic induced/dilutional |
| Encephalopathy | Type B/C encephalopathy<br>Dyselectrolytemia<br>Uremia |
| Acute kidney injury | Diuretic-induced |

# Prevention of PICD

- Plasma volume expansion with intravenous salt poor albumin at a dose of 8 g per liter of ascitic fluid removed, when more than 5 L of ascitic fluid is removed at any single session, has been shown to prevent not only PPCD but also hyponatremia and mortality

| | | |
|---|---|---|
| Albumin | Evidence from a higher number of trials | Cost<br>Need for IV infusion |
| Terlipressin | Efficacy similar to albumin | Evidence from small pilot studies |
| Noradrenaline | Efficacy similar to albumin Economical | Adverse events are common<br>Need for IV infusion/ admission |
| Midodrine | Good oral bioavailability<br>Maintains MAP effectively<br>Can be given in daycare/outpatient | Small pilot studies<br>Less studied<br>Efficacy still controversial |

# Diagnosis and classifcation of Hyponatremia

# CLASSIFICATION

- **Based on total body water (TBW):**

  Hypervolemic ( ascites/anasarca/pedal edema) -90%

  Hypovolemic (No ascites/pedal edema) overuse of diuretics or diarrhea -10%

- **Based on clinical severity :**

  Moderately severe (nausea, confusion, and headache)

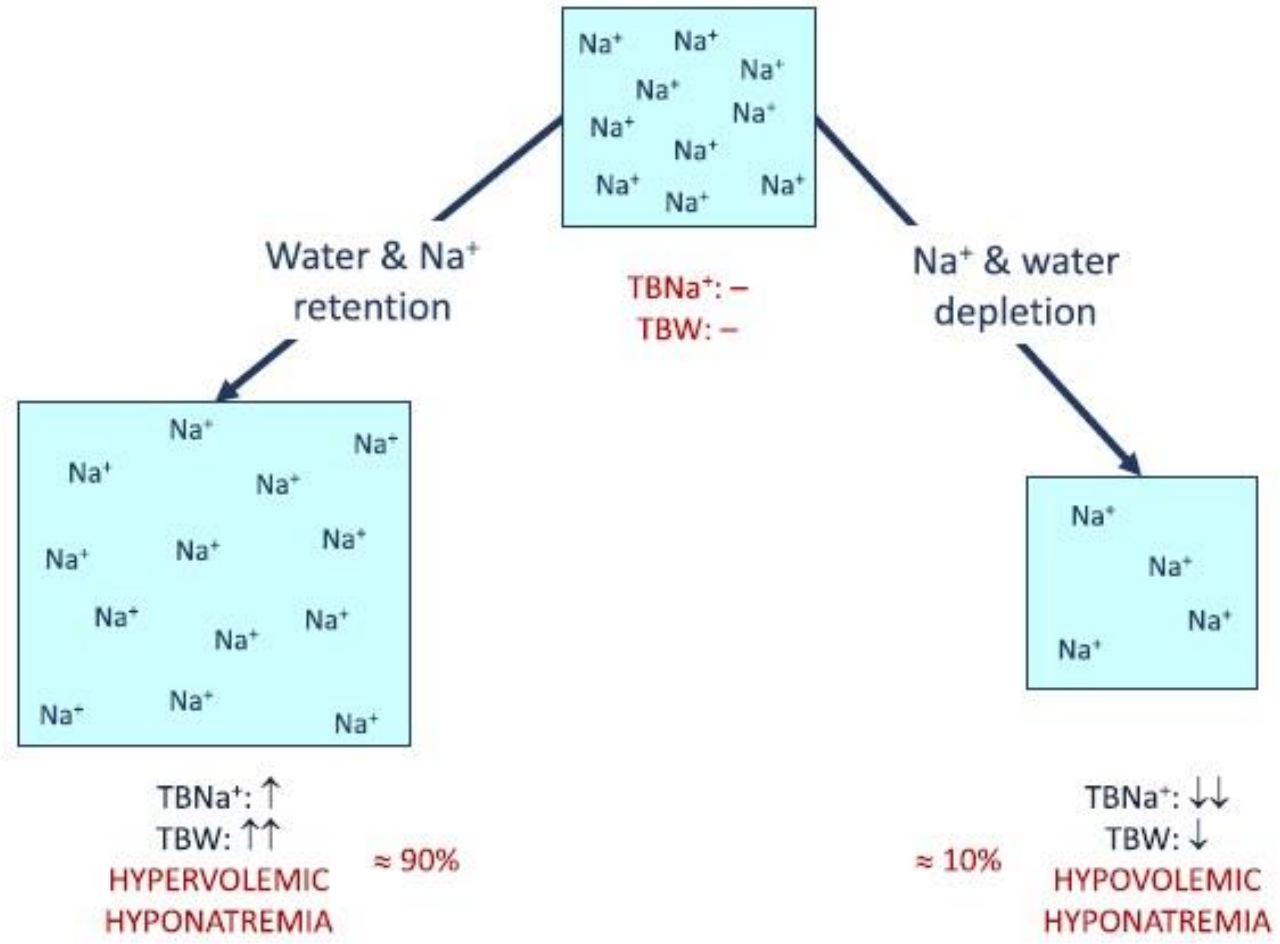
  Severe/profound (vomiting, cardio respiratory collapse, seizures, and coma)

- **Based on duration:**

  Acute (<48 h)

  Chronic (>48 h)

# Types of hyponatremia in cirrhosis

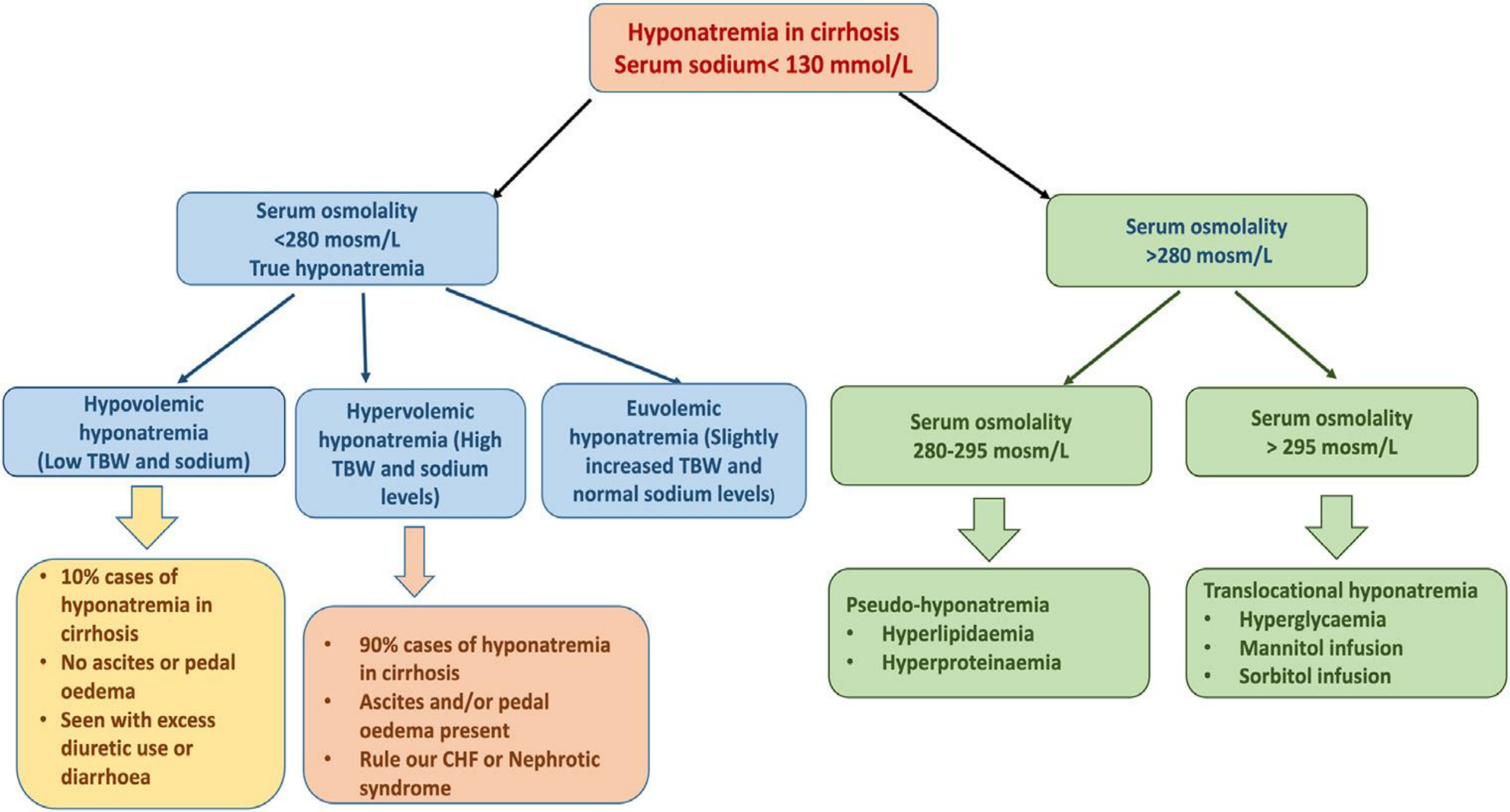



- Hypovolemic hyponatremia
- Hypervolemic hyponatremia
- Euvolemic hyponatremia

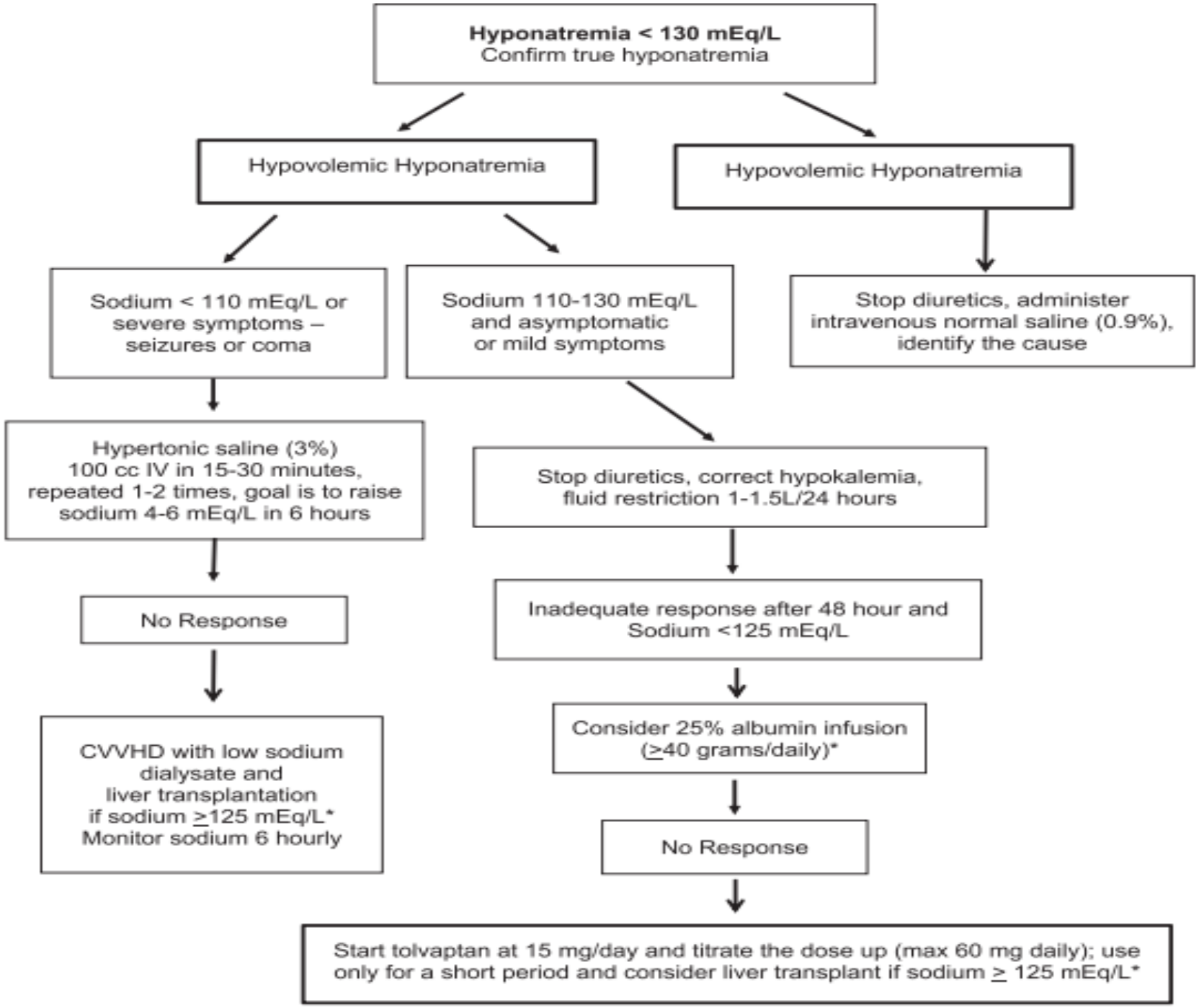
- Acute-Onset <48 hour
- Chronic-Onset >48 hour

- Mild,(135-125 meq/L)
- Moderate(125-120 meq/L)
- Severe(<120 meq/L)

Bernardi M et al,*Hepatol Int*. 2018


Hyponatremia in cirrhosis
Serum sodium< 130 mmol/L
Serum osmolality
<280 mosm/L
True hyponatremia
Serum osmolality
>280 mosm/L
Hypovolemic hyponatremia (Low TBW and sodium)
Hypervolemic hyponatremia (High TBW and sodium levels)
Euvolemic hyponatremia (Slightly increased TBW and normal sodium levels)
Serum osmolality
280-295 mosm/L
Serum osmolality
> 295 mosm/L
• 10% cases of hyponatremia in cirrhosis
• No ascites or pedal oedema
• Seen with excess diuretic use or diarrhoea
• 90% cases of hyponatremia in cirrhosis
• Ascites and/or pedal oedema present
• Rule our CHF or Nephrotic syndrome
Pseudo-hyponatremia
• Hyperlipidaemia
• Hyperproteinaemia
Translocational hyponatremia
• Hyperglycaemia
• Mannitol infusion
• Sorbitol infusion

# Management


Hyponatremia < 130 mEq/L
Confirm true hyponatremia
Hypovolemic Hyponatremia
Hypovolemic Hyponatremia
Sodium < 110 mEq/L or severe symptoms – seizures or coma
Sodium 110-130 mEq/L and asymptomatic or mild symptoms
Stop diuretics, administer intravenous normal saline (0.9%), identify the cause
Hypertonic saline (3%) 100 cc IV in 15-30 minutes, repeated 1-2 times, goal is to raise sodium 4-6 mEq/L in 6 hours
Stop diuretics, correct hypokalemia, fluid restriction 1-1.5L/24 hours
No Response
Inadequate response after 48 hour and Sodium <125 mEq/L
CVVHD with low sodium dialysate and liver transplantation if sodium ≥125 mEq/L* Monitor sodium 6 hourly
Consider 25% albumin infusion (≥40 grams/daily)*
No Response
Start tolvaptan at 15 mg/day and titrate the dose up (max 60 mg daily); use only for a short period and consider liver transplant if sodium ≥ 125 mEq/L*

# Hypervolemic  hyponatremia in cirrhosis-whom to treat?

- All patients do not require treatment.
- Most of the patients remain asymptomatic due to chronicity and neurological adaptation.
- No clear  serum sodium level is defined for initiation of treatment.

- Universally accepted criteria

➢Patient with severe hyponatremia (sNa<120 mmol/L) and/or

➢Hyponatremia with neurological symptoms

# Treatment options for hyponatremia

Free water restriction

Diuretics withdrawal and correction of hypokalemia

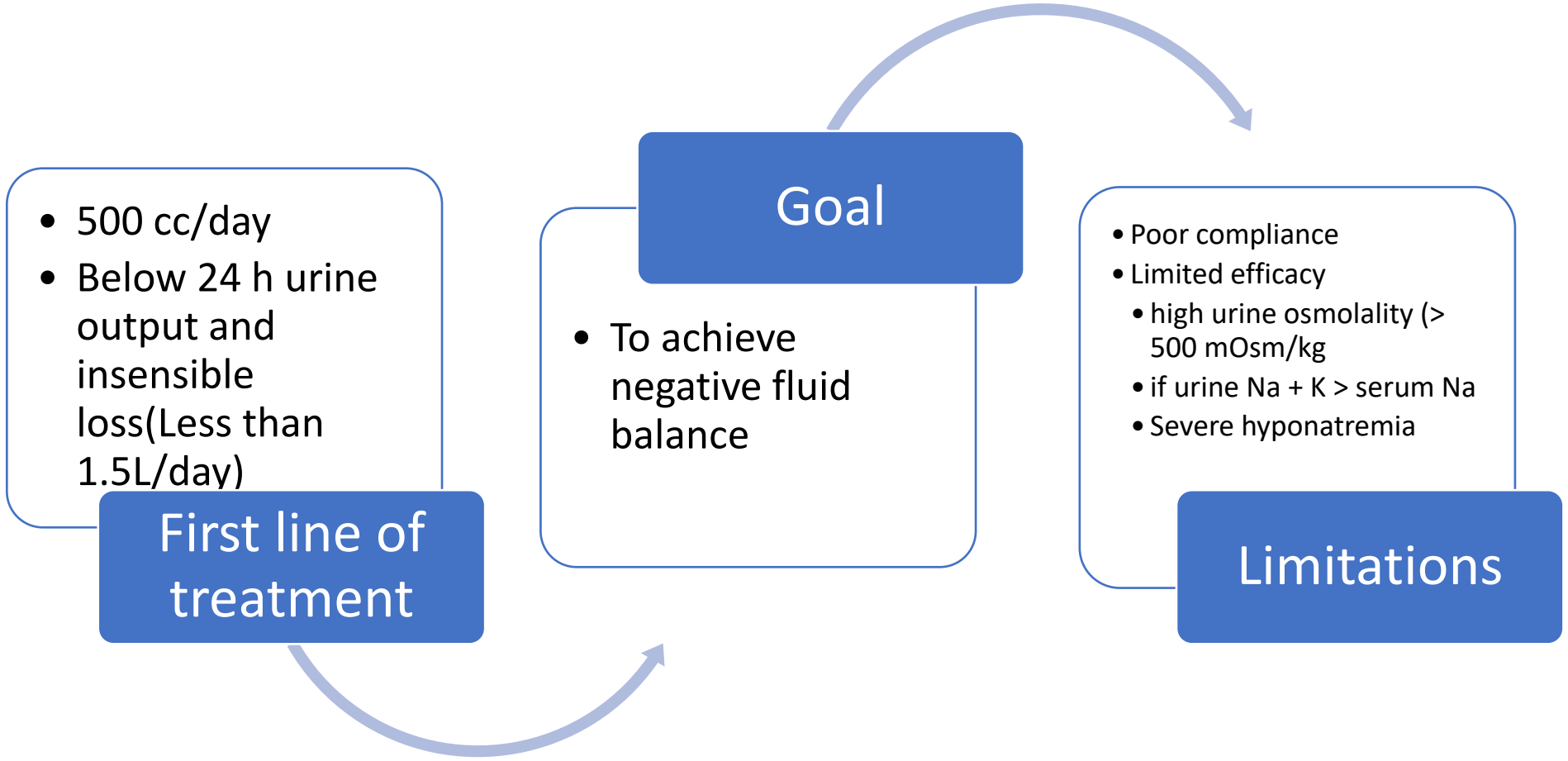
Albumin infusion

Hypertonic(3%) Saline

Vaptans

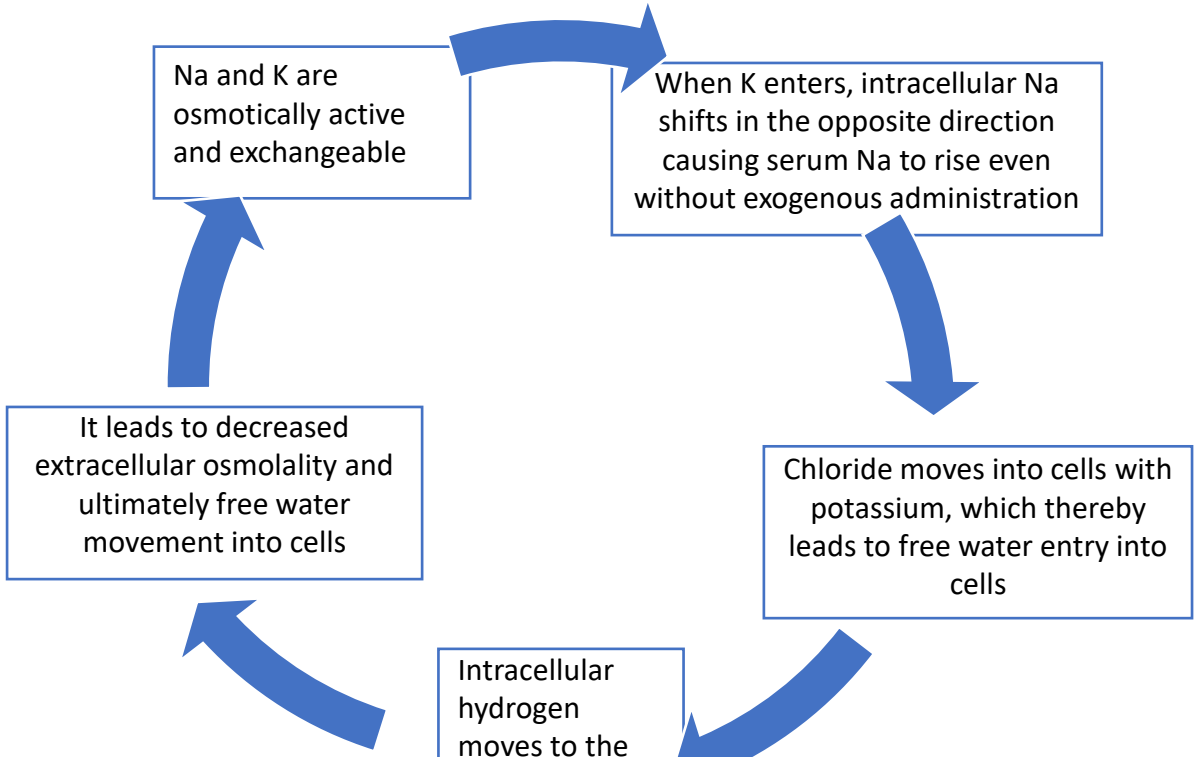
TIPSS

# Water restriction




If no improvement in 24-48 hours, other options need to be considered

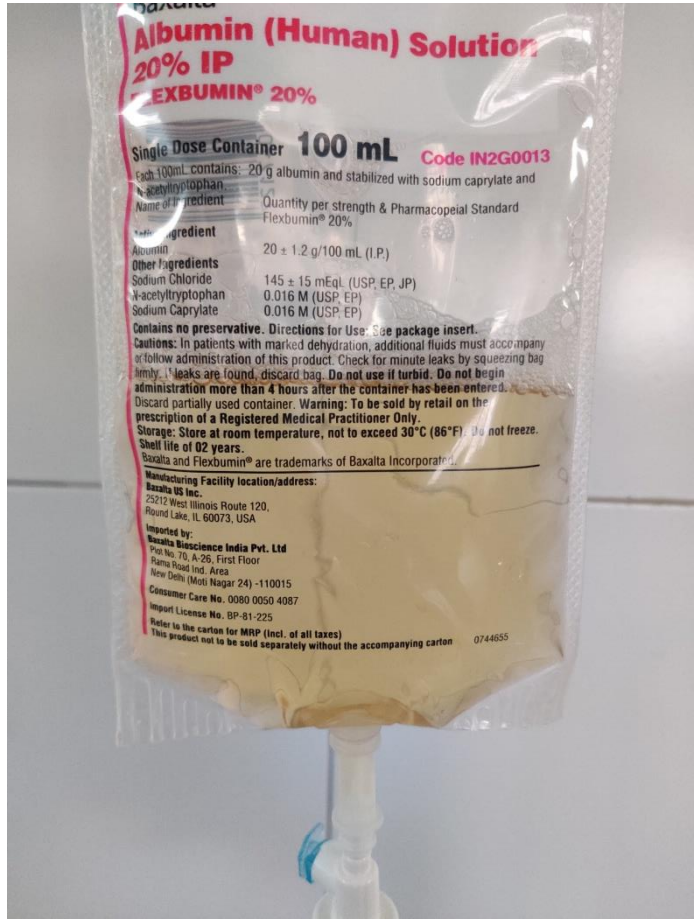
# Discontinuation of diuretics and correction of hypokalemia




Hypokalemia is also known to precipitate and worsen HE through increased ammoniagenesis in the kidney via production of renal glutaminase

# Role of Albumin

- Intravenous albumin can increase urinary free-water clearance by expanding intravascular volume, leading to a rise in serum sodium
- Human albumin Sodium content- 145± 15 meqL
- Recommended dose for this purpose- 40g/day




Bajaj et al, *Am J Gastroenterol,2018*

# Impact of albumin in resolution of hyponatremia

**Table 1 Continued**

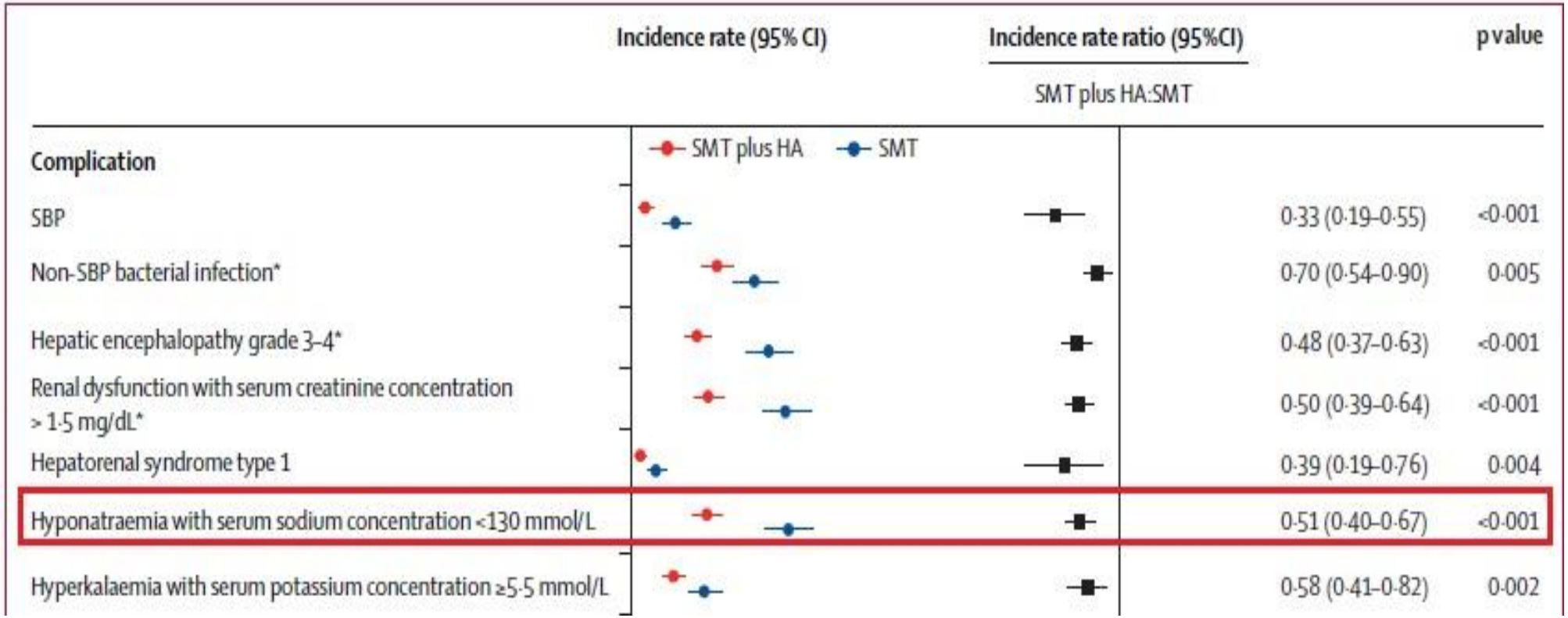
| | Albumin− ($n=349$) | Albumin+ ($n=777$) | $p$-value |
|---|---|---|---|
| NACSELD-ACLF | 5% (16/349) | 16% (121/776) | <0.0001 |
| Length of stay (days) | 9.11 (9.67) | 16.80 (18.60) | <0.0001 |
| In-hospital mortality | 4% (14/349) | 8% (64/777) | 0.01 |
| 30-day mortality | 8% (27/349) | 16% (126/777) | 0.0001 |
| Resolution of hyponatremia | 61% (213/347) | 69% (537/774) | 0.0085 |

NACSELD-ACLF score [13] is defined as the occurrence of two of the following: brain failure defined by grade 3 or 4 hepatic encephalopathy, circulatory failure defined by shock requiring vasopressors, renal failure defined by need for renal replacement therapy, and respiratory failure defined by use of BiPAP or mechanical ventilation

- 1126 patients with hyponatremia were evaluated in prospective series
- Resolution of hyponatremia was associated with a higher 30-day survival independent of acute-on-chronic liver failure and renal function

Bajaj et al, *Am J Gastroenterol,2018*

# Long-term albumin administration in decompensated cirrhosis (ANSWER): an open-label randomised trial




Incidence of hyponatremia (Na , 130 mEq/L) in the albumin group was lower than the SMT group with an incidence rate ratio of 0.51

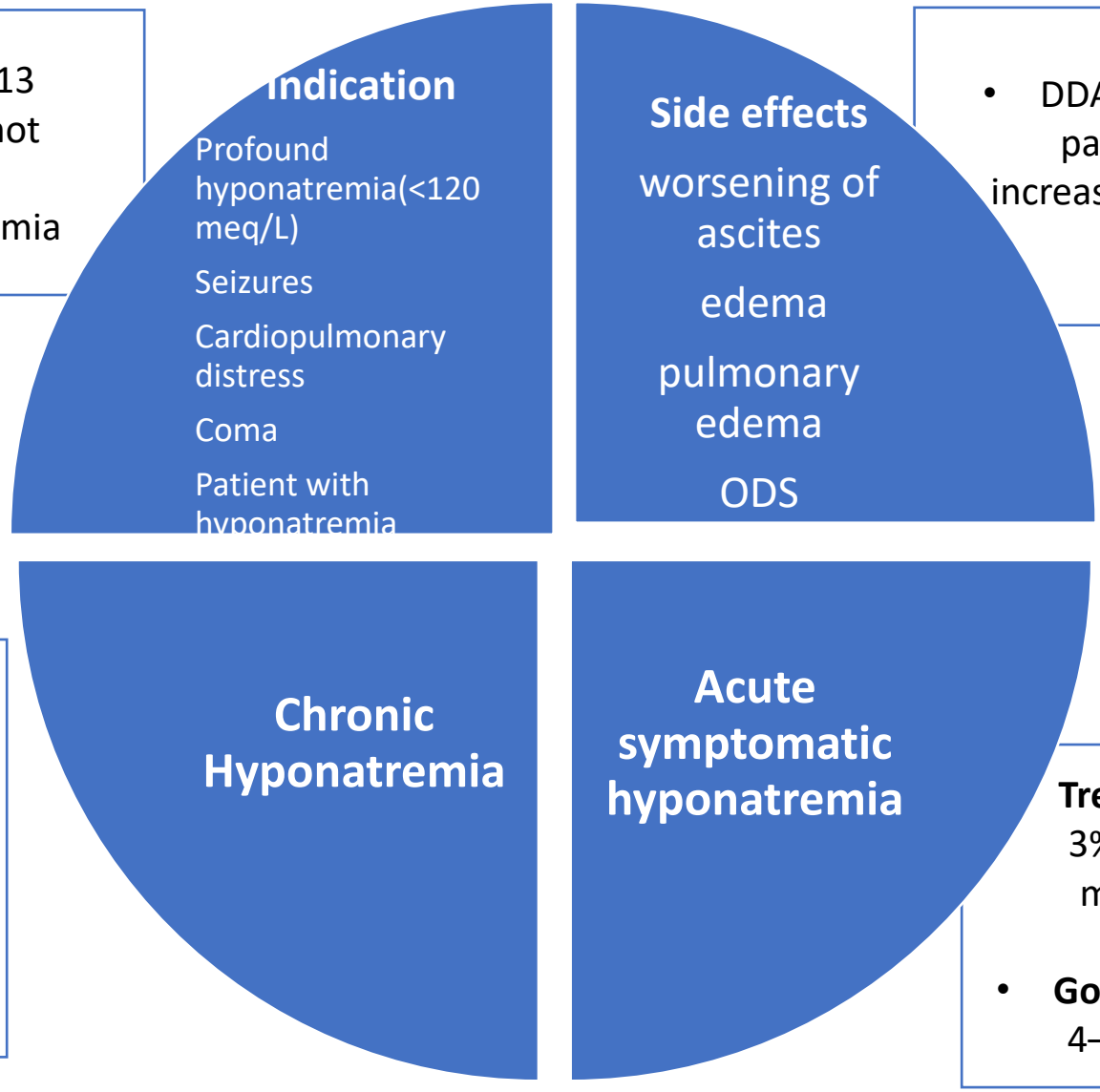
Caraceni et al; The Lancet;2018

# Role of midodrine

- Despite stopping diuretics and NSBB,some patients may continue to have systemic hypotension.
- In this subset of patients, midodrine can be used to increase MAP .
- Electrolyte free water clearance also increased ultimately mean serum sodium  also increased

# Hypertonic saline

- Hypertonic saline (513 mEq/L Na) -usually not recommended for dilutional hyponatremia




- DDAVP can be used in patients who are at increased risk of developing ODS

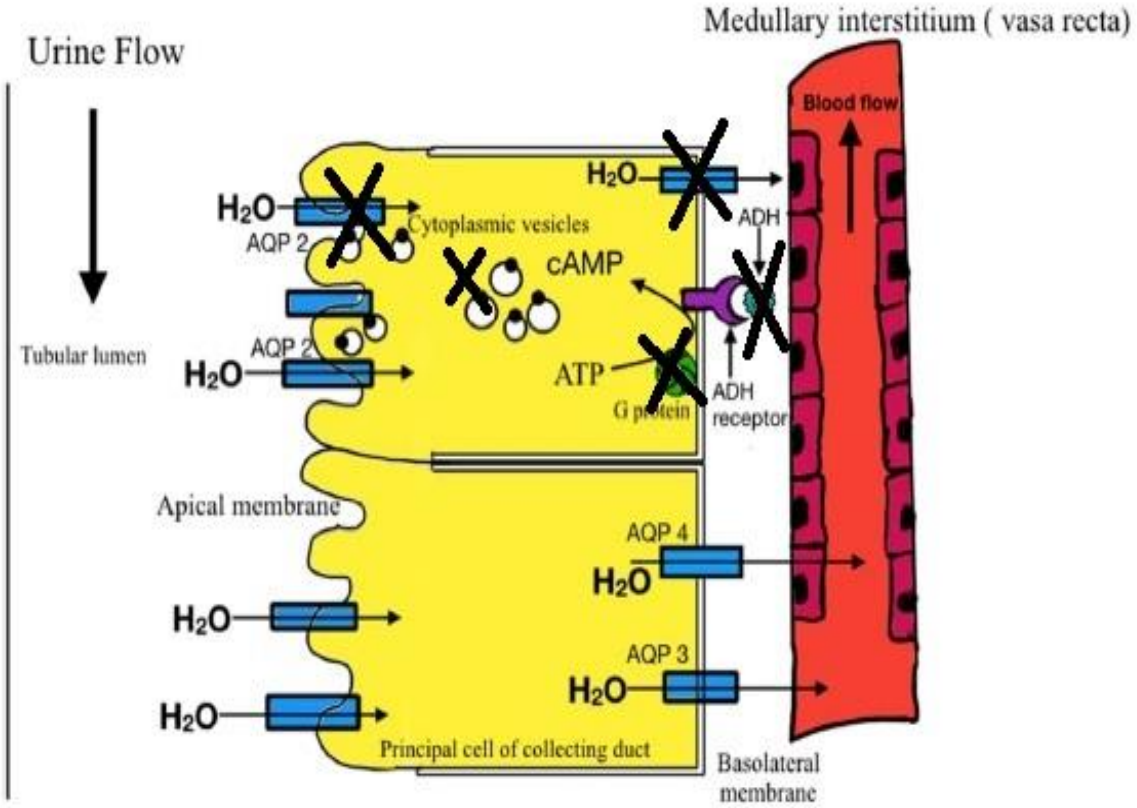
- Either symptomatic or severe (<110 mEq/L)-hypertonic saline may be administered through a continuous infusion at a rate of 15–30 cc/hr
- Na should not increase by more than 8 mEq/L per day

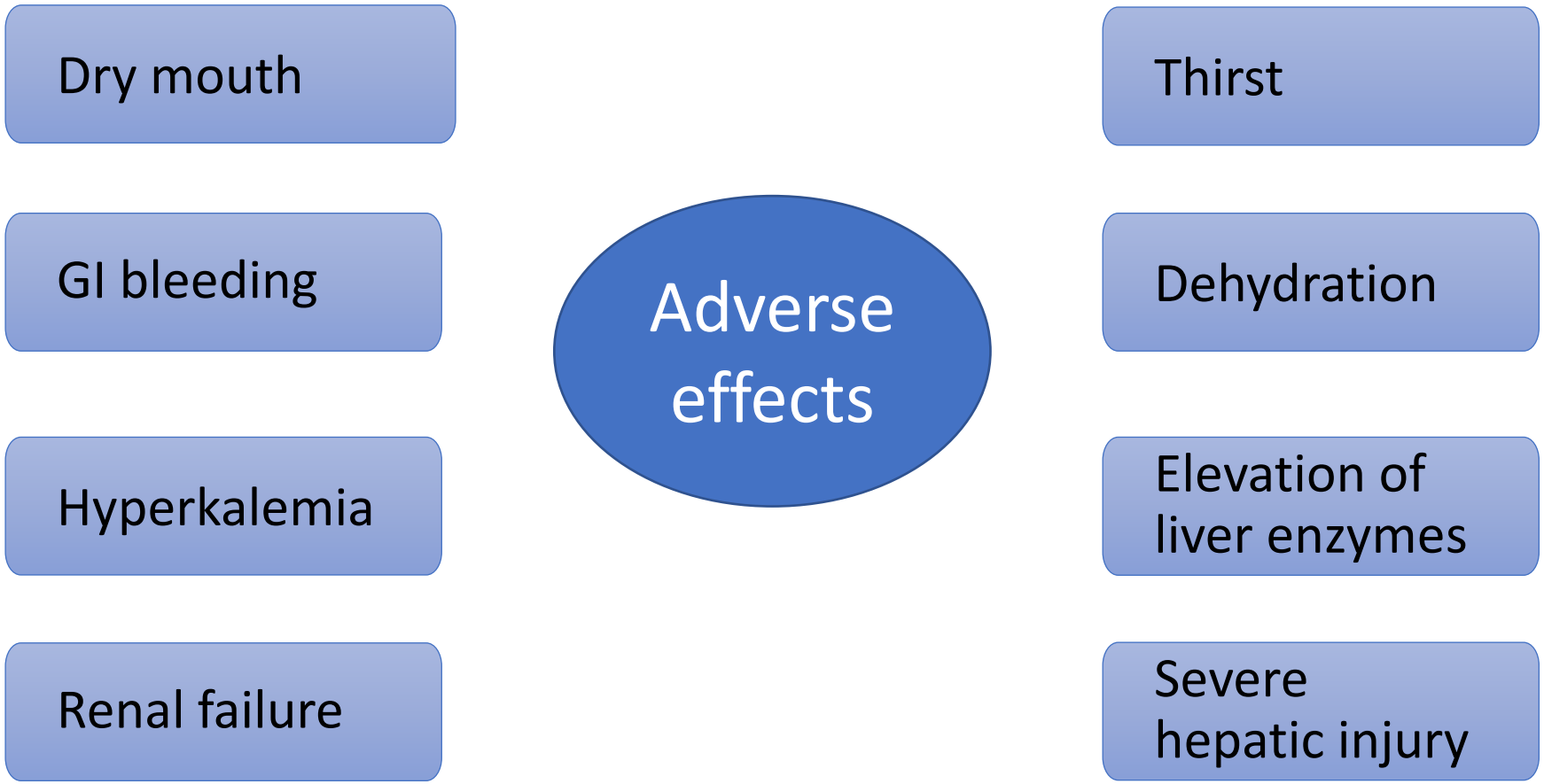
**Treated** with a 100 cc bolus of 3% saline (100 cc over 15–30 minutes),can be repeated 3 times
- **Goal**-to raise serum sodium by 4–6mEq/L in the first 6 hours

# Vasopressin receptor antagonist

- Vaptans are class of nonpeptide drug which blocks the action of ADH on V1 and V2 receptors
- Conivaptan nonselective antagonist of V1 and V2 receptor-more adverse events, not used in cirrhotic
- Tolvaptan-selective V2 receptor antagonist

- Increases the urine volume and solute free water excretion-**aquaretics**






**USFDA black box warning to use vaptans in cirrhosis in view of severe hepatic injury –this has been reported at very high dose 120 mg/day)**

Satavaptan-withdrawn due to high rate of GI bleed and renal failure in cirrhotics

# Guidelines to administer Tolvaptan

- Tolvaptan should be
  - started under close monitoring-preferably in hospital
  - started at lower dose-15 mg/day and gradual increase up to 60 mg/day based on serum Na response-optimal correction not more than 8-10 mmol/L /day
  - avoided in patient with encephalopathy or who can’t drink adequate water
  - administered carefully with CYP3A4 inhibitor drug- can potentiate the effect of vaptan

# Assessment of response to therapy

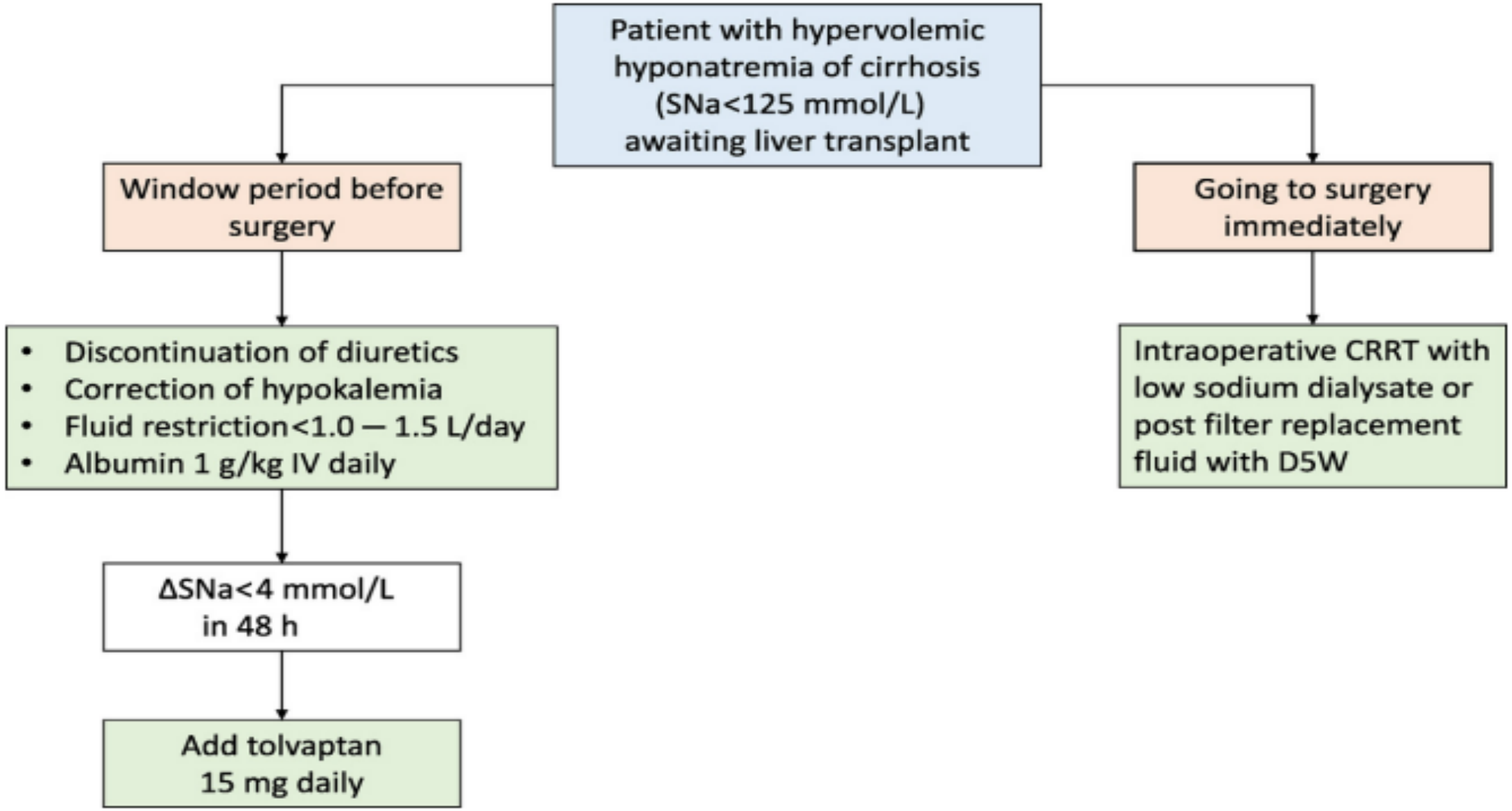
- Response to therapy is defined as achievement of absolute value of ≥ 130 meq of sodium or increase in 5 meq/L from base line

- Response rate of various therapies
  - Free water restrictions- 20-33%
  - Hypertonic saline- 78-10%
  - Tolvaptan- 68-81 %

Relapse rate- 55%

Sigal SH,et al,*Canadian Journal of Gastroenterology and Hepatology,2018*

# Hyponatremia in patients awaiting for LT



# Summary

- Hyponatremia in cirrhosis is very commonly encountered problem
- Associated with detrimental outcome in cirrhosis and is marker of poor prognosis
- Diagnosis requires thorough investigation
- Management options are limited specifically in hypervolemic hyponatremia
- Vaptans use may be beneficial in correction of lab values but not the survival
- Use of hypertonic saline(3%) should be judicious and overcorrection need to be avoided
- Patients undergoing liver transplantation are at higher risk for ODS, and slow SNa correction is recommended.

# THANK YOU

# Body volume status