ASCITES AND HYPONATREMIA IN LIVER CIRRHOSIS: HOW AND WHEN TO INTERVENE

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Liver Cirrhosis: leading cause of death in general population worldwide

(e.g. 12th leading cause of mortality in USA)

Liver Transplantation: the only approach that reliably improves duration and quality of life

End-stage Liver Disease: primary focus is to keep patients alive and in the most stable condition

(very challenging!)

Natural History of Liver Cirrhosis

Chronic Liver Disease

(Viral, ETOH, Fatty liver)

↓

Compensated Liver Cirrhosis (median survival 12 years)

↓ 5-7 %/ year

Decompensated Liver Cirrhosis (median survival 2 years)

Jaundice, Variceal bleeding, Ascites, Hepatic encephalopathy, HRS or HCC

↓

Death

Ascites is one of the complications that mark the transition from a compensated to a decompensated stage of liver cirrhosis

Liver Cirrhosis

D' Amico's Clinical Staging & Prognostication

		1 year mortality
Stage 1	No varices No ascites	1%
Stage 2	Varices (non-bleeding) No ascites	3-4%
Stage 3	Varices Ascites	20%
Stage 4	Bleeding varices Ascites	50%

J Hepatology 2006
44: 217-231

Clinical Symptoms of Liver-Related Ascites

1. Increase in abdominal girth
2. Abdominal fullness, discomfort or ache
3. Shortness of breath
4. Early satiation
5. Sense of reduced mobility

Severity of Ascites

Grade I: 100mL (normal 25-50mL) by US studies

Grade II: 1000mL detected by P.E.
sagging flanks
shifting dullness
fluid wave
Puddle sign

Grade III: liters of ascitic fluid
"Tense" ascites, grossly distended abdomen

Patients with New Onset Ascites

1. History
2. Physical examination *

   spider angiomas

   palmar erythema

   muscle wasting

   jaundice

   signs of portal hypertension (e.g. splenomegaly, abdominal wall collaterals)

   palpable left lobe of liver

* Pathognomonic of liver cirrhosis

2006
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New-Onset Ascites

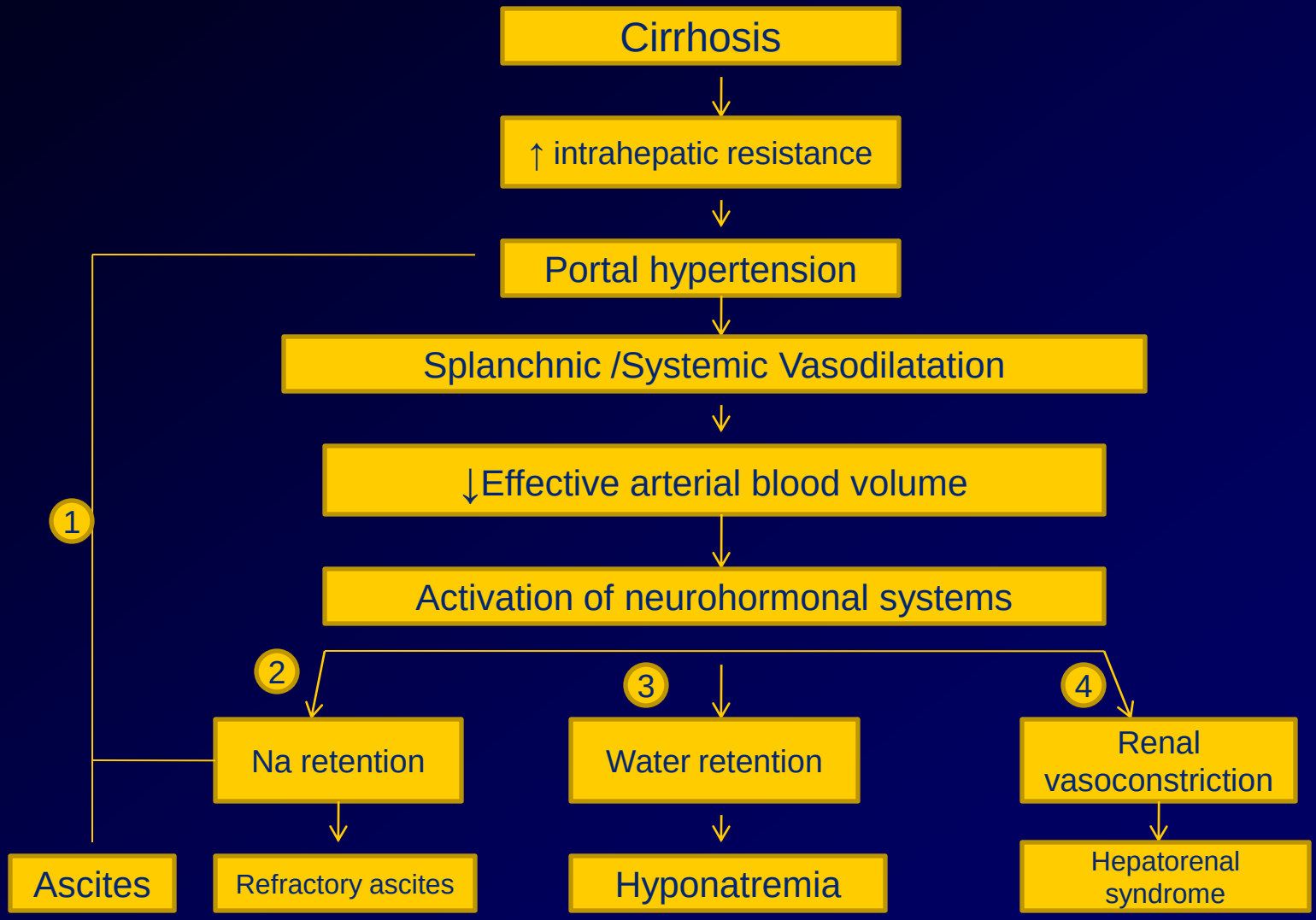
Diagnostic Paracentesis

Tests Performed in Diagnostic Paracentesis

- Gross appearance
- Total protein
- Albumin (with simultaneous serum albumin)
- WBC & differential count
- Bacteriological cultures
- Cytology
  - *Amylase (if pancreatic ascites is suspected)
  - *AFB staining & culture (if peritoneal TB is suspected)
  - *Glucose & LDH (if secondary peritonitis is suspected)
  - *Triglycerides (milky appearance e.g. chylous)
  - *RBC (bloody)

* Special tests

Pathogenesis of Cirrhosis



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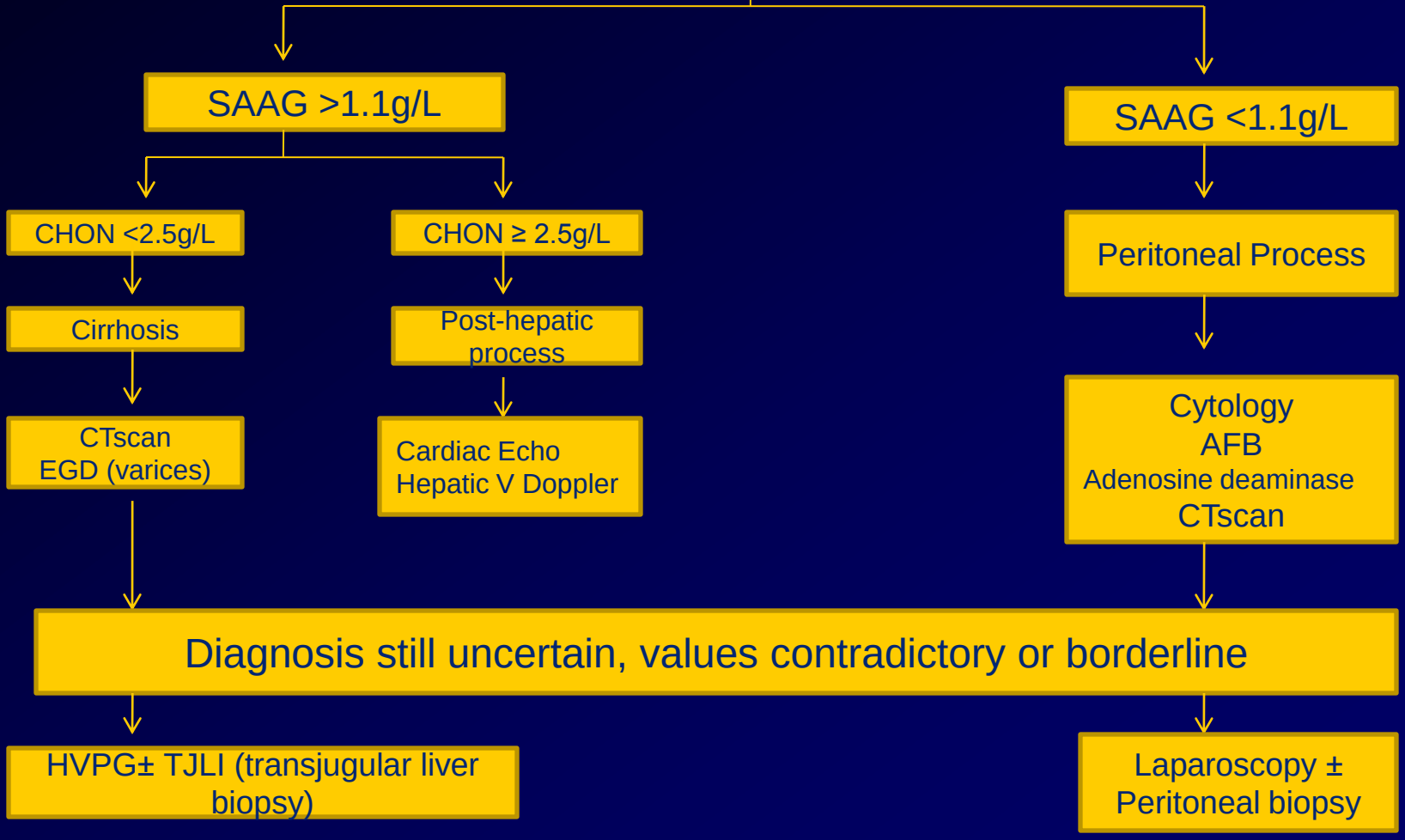
Serum-Ascites Albumin Gradient



HYPERAMMONEMIA

Increased glutamine synthesis

↑ intracellular osmolality

Water shift from extracellular space

HYPONATREMIA

↓ extracellular osmolality

Water shift from extracellular space

Astrocyte

Astrocyte swelling

Reduction of intracellular osmolytes

Astrocyte dysfunction

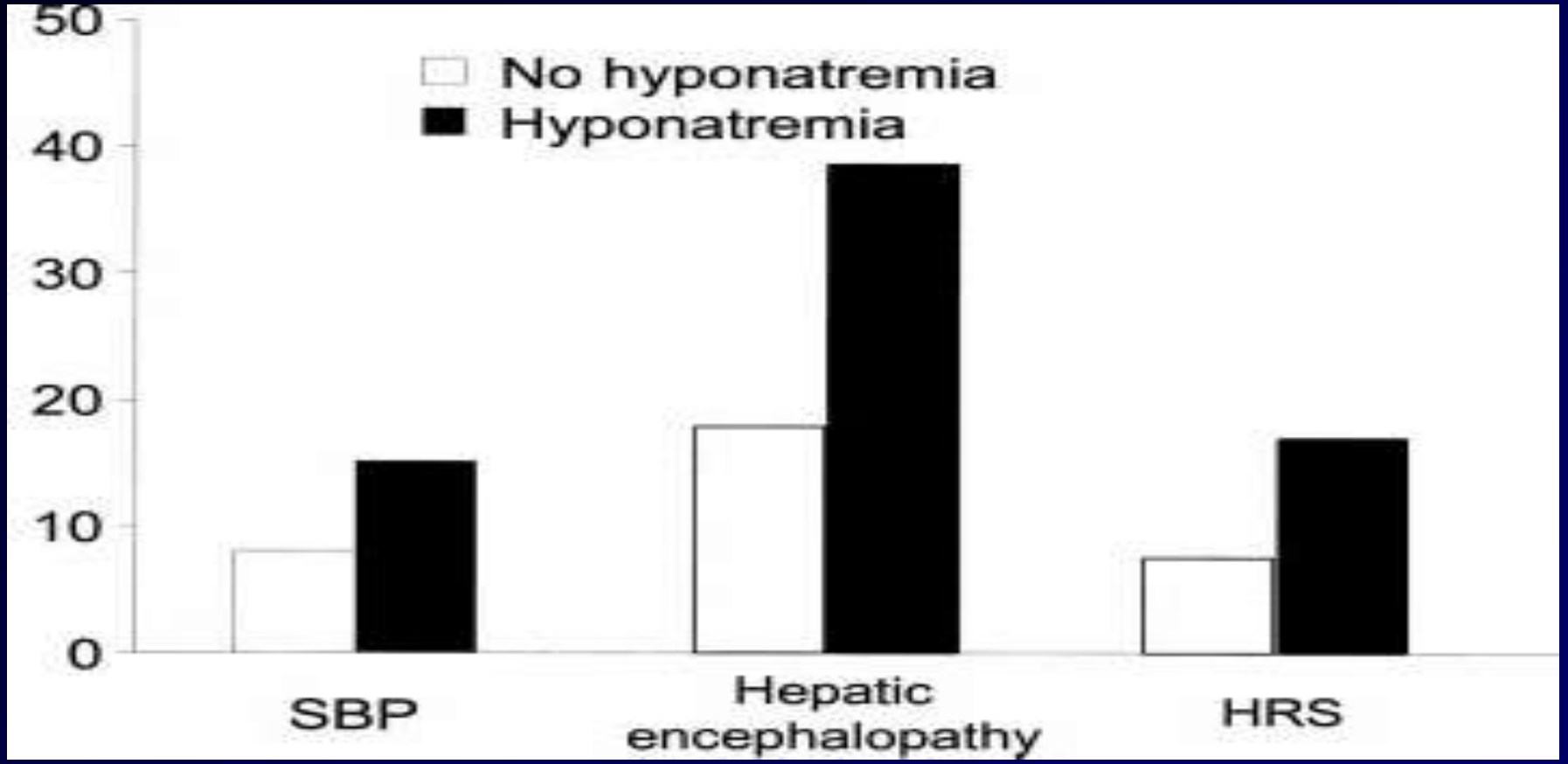
factors increasing ammonic synthesis;

progressive hyponatremia

HEPATIC ENCEPHALOPATHY

Gines, P,Guevara M.Hyponatremia in Cirrhosis.Hepatol. 2008:1002-1010.

Presence of Hyponatremia is associated with increased morbidity



Angeli P, et al. Hyponatremia in cirrhosis: results of a patient population survey. Hepatology 2006; 44:1535-1542

Site of Action of Different Therapies for Ascites

CIRRHOSIS

↓

↑ Intrahepatic resistance

↓

Portal hypertension

↓

Splanchnic/systemic vasodilatation

↓

↓ effective arterial blood volume

↓

Activation of Neurohormonal systems

↓

Sodium retention

↓

Ascites

- Liver Transplant
- TIPS
- Vasoconstrictors?
- Albumin
- Spironolactone
- Furosemide, V2 antagonists
- LVP, PVS

Patients with Cirrhosis and New Ascites

Sodium restriction(2gm Na/day= 5.2gm dietary salt)

Concomitant:
GI hemorrhage
HE
Renal deficiency
SBP/Infection

Yes

Resolve complication before specific treatment

Tense ascites

Yes

Single LVP * ± albumin

No

Assess Transplant Candidacy

Spironolactone 100mg ± Furosemide 40mg

Weight loss 1-1.5kg/week

Continue same dose

Ascites eliminated
Titrate down diuretics

Weight loss < 1kg/wk

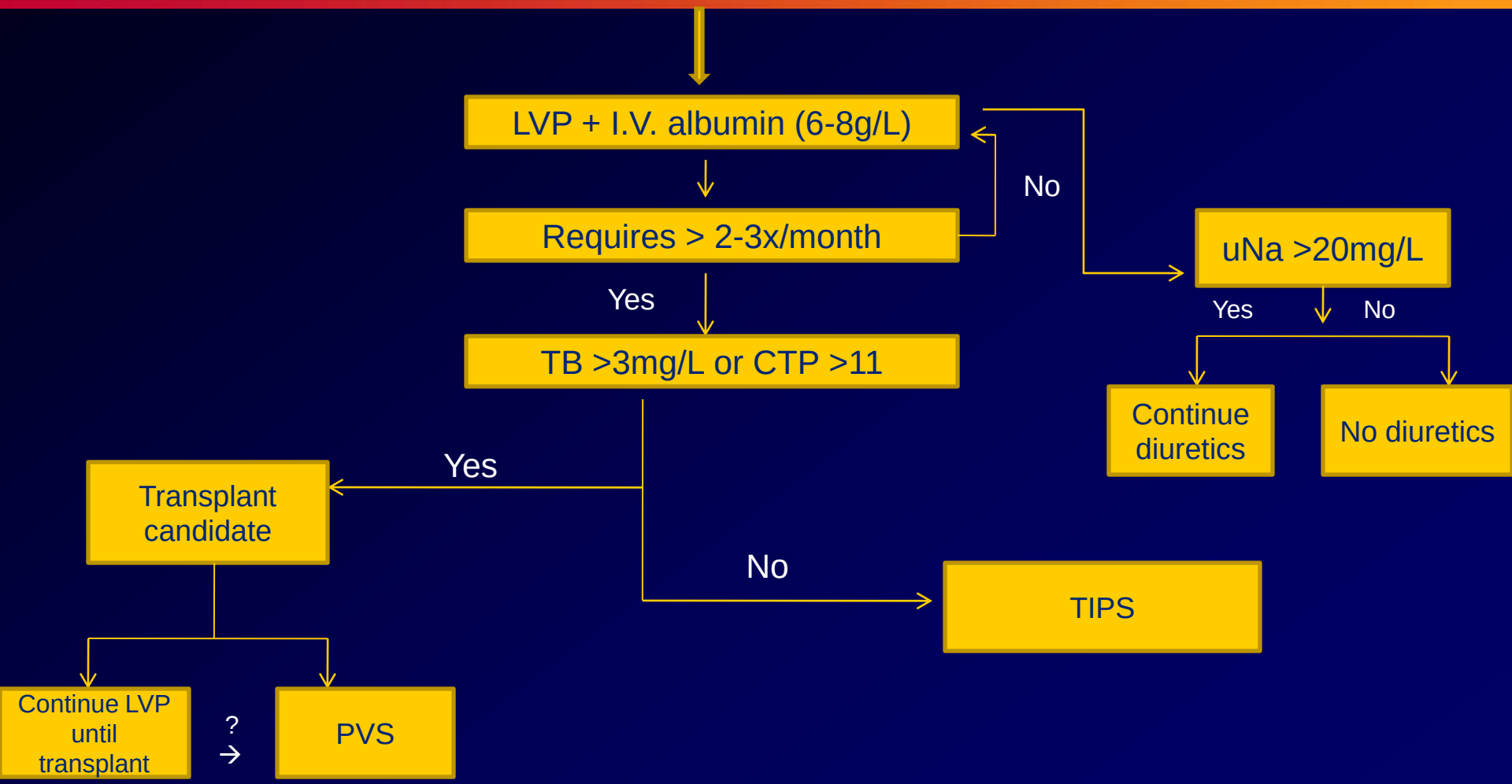
Increase dose (x2) every 1-2 wks

Weight loss >0.5kg/day ± complication

Decrease dose or discontinue

* large volume paracentesis

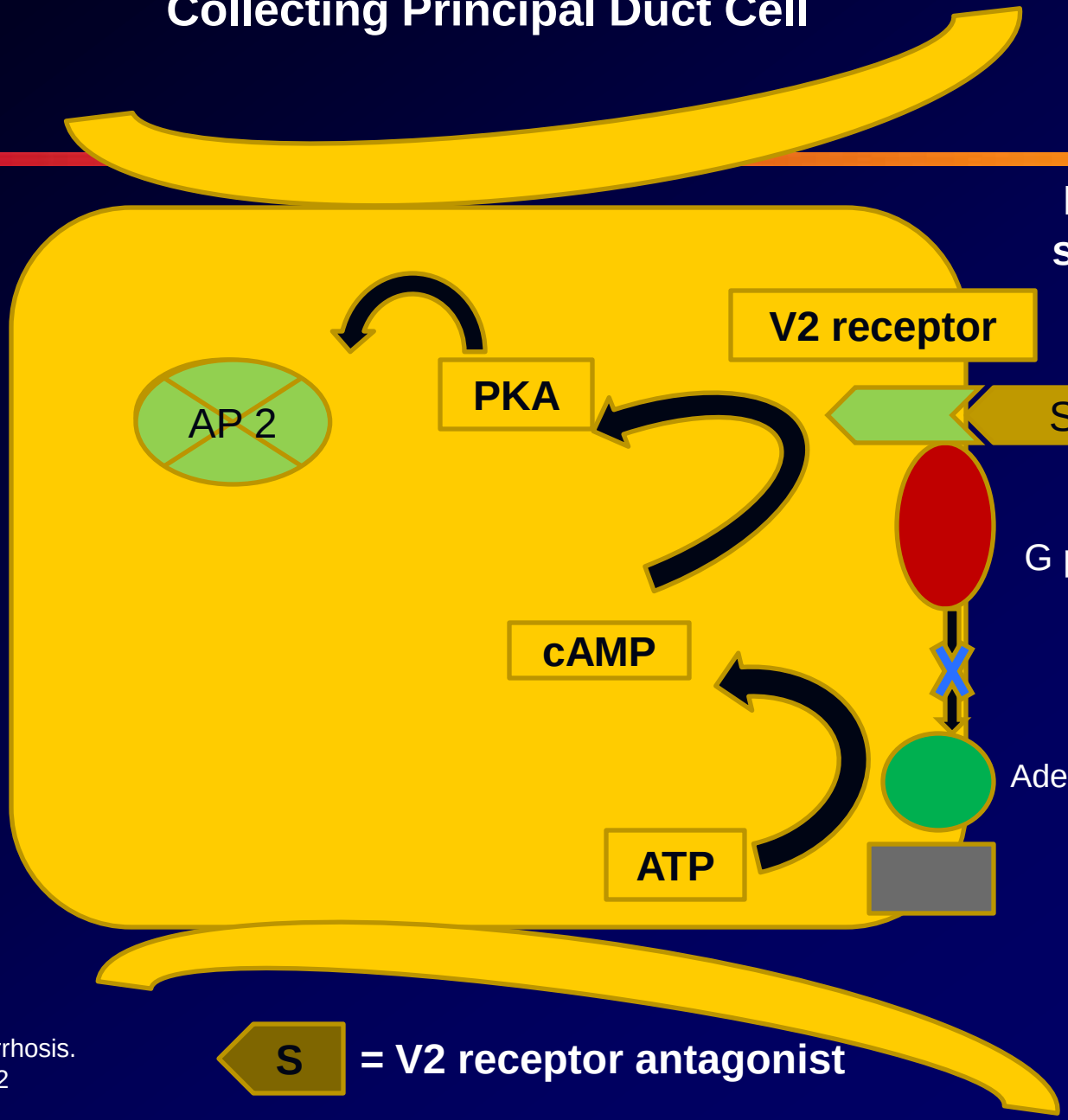
Refractory Ascites



Treatment of Hypervolemic Hyponatremia in Cirrhosis

1. Fluid restriction
2. Aldosterone antagonists
3. Loop diuretics
4. Vasopressin receptor antagonists

Collecting Principal Duct Cell



Wong, F. Hyponatremia in Cirrhosis. Hepatology 2006; 44: 1535-42

Six Vaptans

1. Mozavaptan (OPC-31260)
2. Lixivaptan (VPA-985)
3. Tolvaptan (OPC-40161)
4. SPD556 (M0002/RWJ 351647)
5. Satavaptan (No longer being developed)
6. Conivapatan (V1 & V2 receptor antagonist)

Very effective in normalization of Na concentration

*** Recurrence of hyponatremia when stopped

No long term data on safety & efficacy

High cost

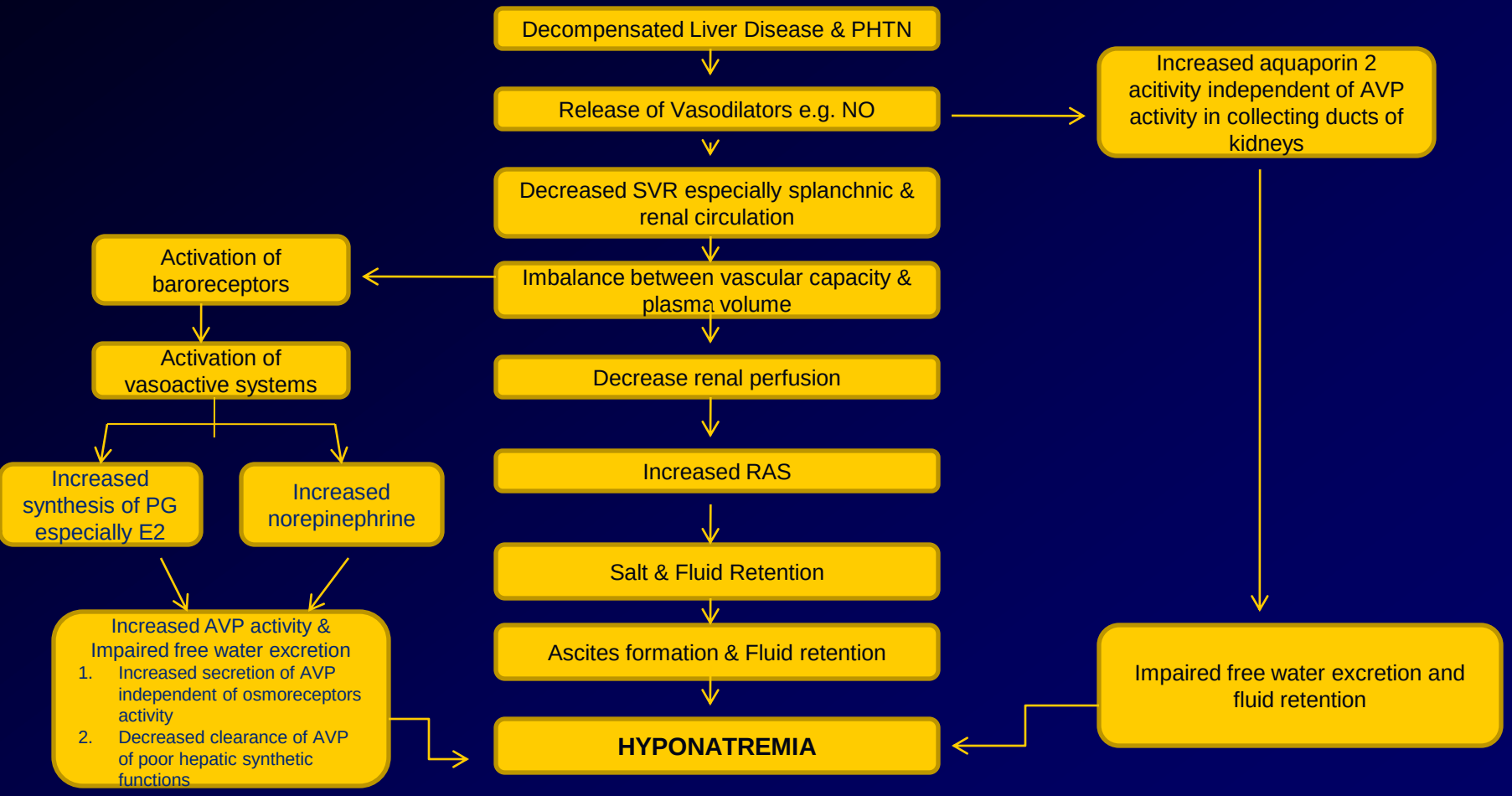
Can not be recommended for general use

SUMMARY

1. Ascites and dilutional hyponatremia are frequent complications in cirrhotic patients and are associated with poor renal function and poor quality of life
2. Aldosterone antagonists (spironolactone) and loop diuretics (furosemide) are the treatment of choice
3. Some non-responders to conventional treatment, new therapeutic options are necessary e.g. Vaptans
4. Algorithms for management of uncomplicated and complicated ascites

Thank you

Pathogenesis of Hyponatremia in Cirrhosis



Habib S., T. Boyer. Vassopressin V2-receptor antagonists in patients with cirrhosis, ascites and hyponatremia. Ther Adv Gastroenterol. 2012: 189-197.