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Management of ascites and AKI in cirrhosis

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Outline

- Introduction
- Pathogenesis
- Evaluation of ascites
- Management of uncomplicated ascites
- Refractory ascites: diagnosis and management
- SBP: definitions and management
- AKI in cirrhosis

Introduction

- Most common of the 3 major complications of cirrhosis
- ~50% of patients with “compensated” cirrhosis develop ascites during 10 years of observation
- ~15% of patients with ascites succumb in 1 year and 44% succumb in 5 years

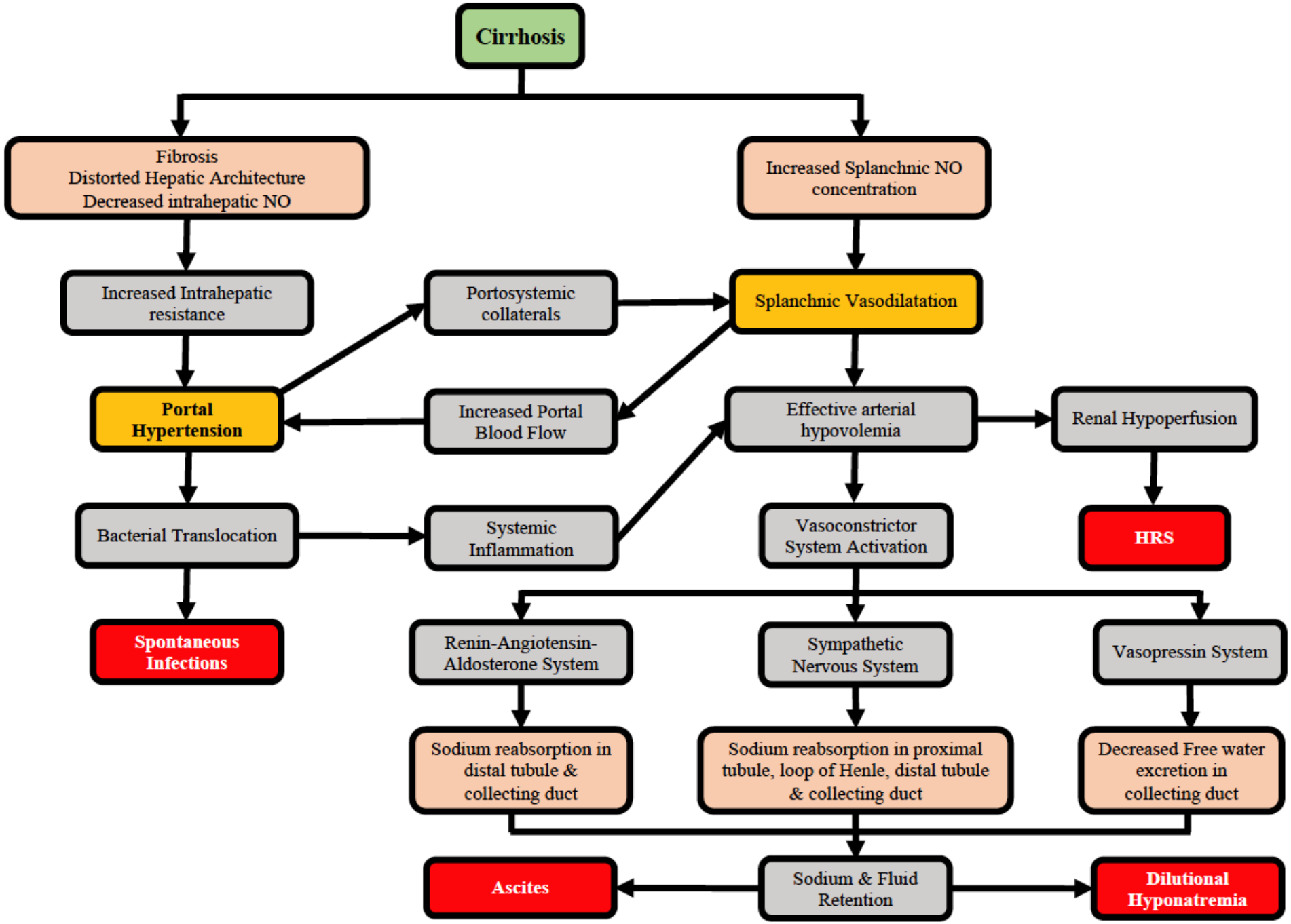
Pathogenesis

- Two older theories of ascites formation:
  - Underfill theory
  - Overflow theory

	Underfill Theory	Overfill Theory
Primary event	Vascular	Renal
Secondary Event	Renal	Vascular

Currently **vasodilation** hypothesis, is the most widely accepted theory

Pathogenesis



Grading of ascites: IAC

Grade 1.	**Mild ascites: only detectable by ultrasound**
Grade 2.	Moderate ascites: manifested by moderate symmetrical distension of abdomen
Grade 3.	Large or gross ascites: marked abdominal distension

Evaluation of Patients with Cirrhosis and Ascites

Evaluation of liver disease

- Etiologic tests
- Liver-function and coagulation tests
- CBC
- Imaging
- UGIE
- Liver biopsy in selected patients

Evaluation of renal and circulatory function

- Measurement of serum creatinine and electrolytes
- Measurement of urinary sodium (preferably from a 24-hour urine collection)
- Measurement of urinary protein (from a 24-hr urine collection)
- Spot urine sodium/potassium
- Arterial blood pressure

Ascitic fluid work up

Diagnostic paracentesis

- Recommended in all patients with
  - new onset grade 2 or 3 ascites
  - hospitalised for worsening of ascites or any complication of cirrhosis, AKI

- Extremely safe procedure-
  - routine prophylactic use of FFP or platelets not recommended
  - clinically evident DIC is a contraindication

Culture- 10 ml of ascitic fluid inoculated in blood culture bottle prior to antibiotic exposure

Cytology- 50 ml of fresh ascitic fluid; 3 samples from different paracentesis

Asymptomatic pt undergoing seral paracentesis- only cell count with differentials

ROUTINE	SELECTED CASES
Cell count and differential	AFB smear and culture, GeneXpert, TB-PCR
Total protein, glucose	Cytology
Culture	Triglyceride, Bilirubin
Albumin & SAAG	Amylase
ADA	Cholesterol

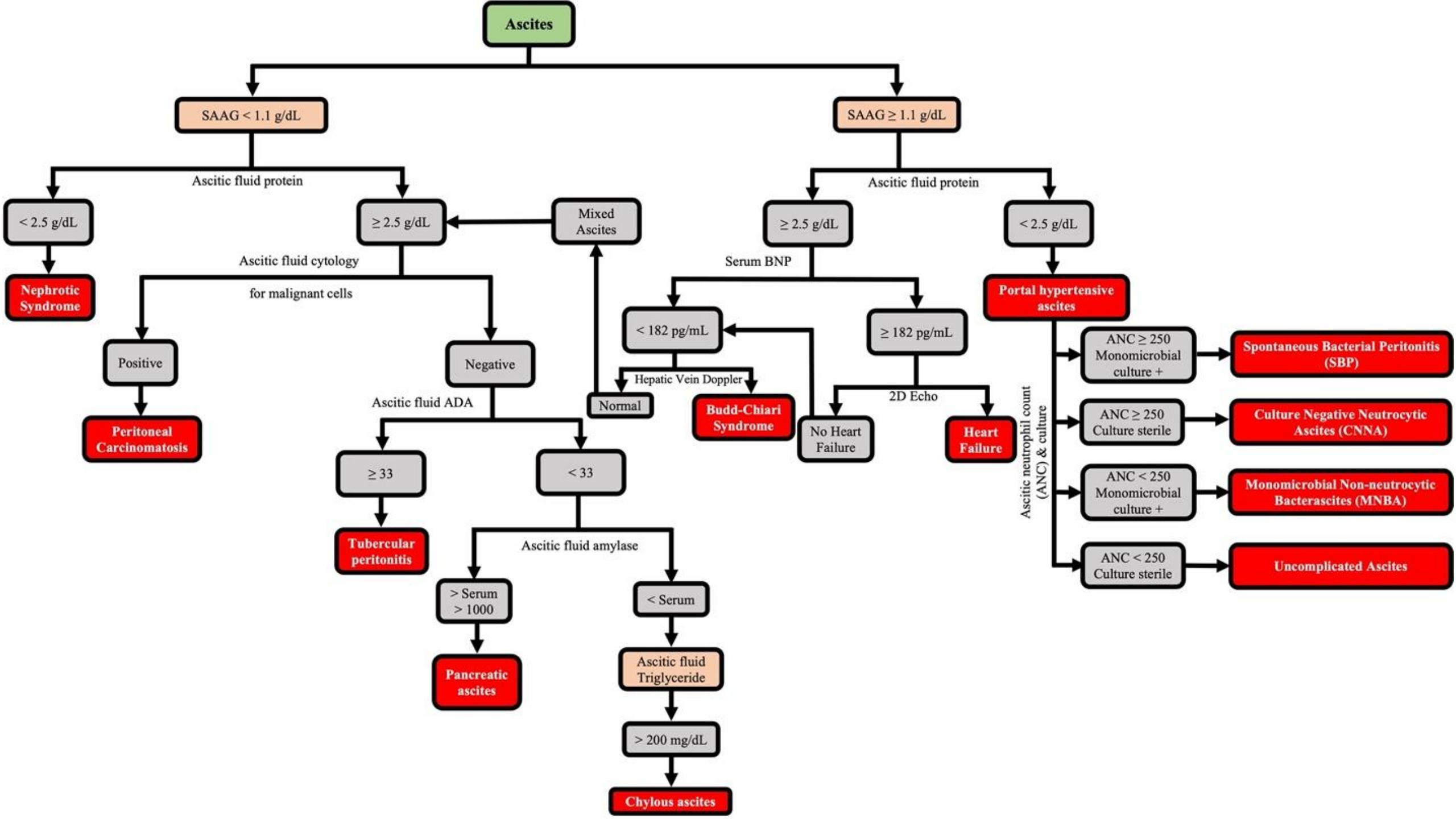
Role of SAAG

High Gradient(≥1.1 g/dl)	Low gradient(<1.1g/dl)
•Cirrhosis	•Peritoneal carcinomatosis
•Alcoholic hepatitis	•Tuberculous peritonitis
•Cardiac ascites	•Pancreatic ascites
•Massive liver metastases	•Bowel obstruction or infarction
•Fulminant hepatic failure	•Biliary ascites
•Budd-Chiari syndrome	•Nephrotic syndrome
•Portal vein thrombosis	•Postoperative lymphatic leak
•Sinusoidal obstruction syndrome	•Serositis in connective tissue disease
•Fatty liver of pregnancy	
•Myxedema	
•Mixed ascites	

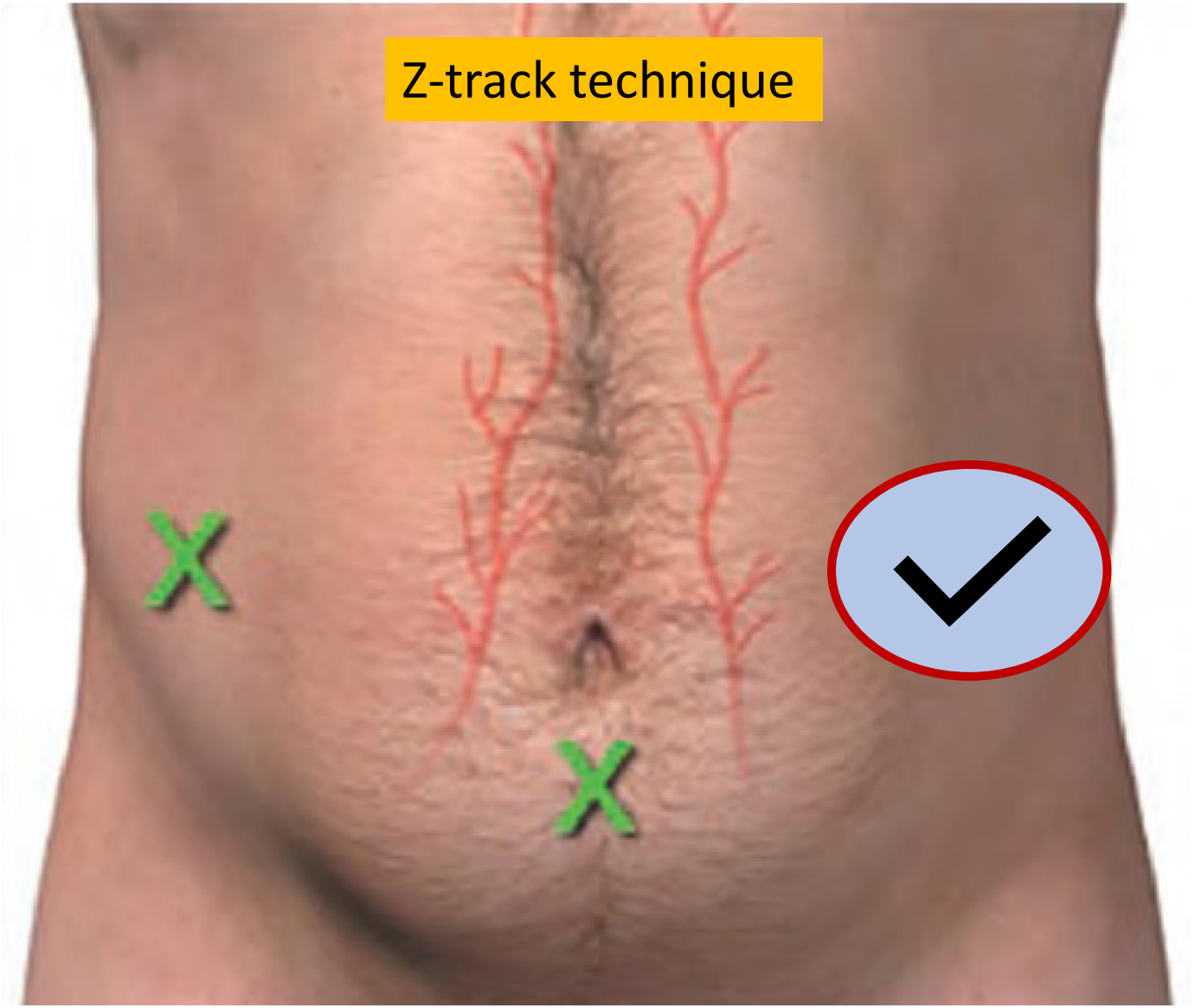
Mixed ascites (e.g: cirrhotic + tubercular + cirrhotic ascites): usually high SAAG and high protein

Why ascites in cirrhosis is low protein but high protein in early BCS?

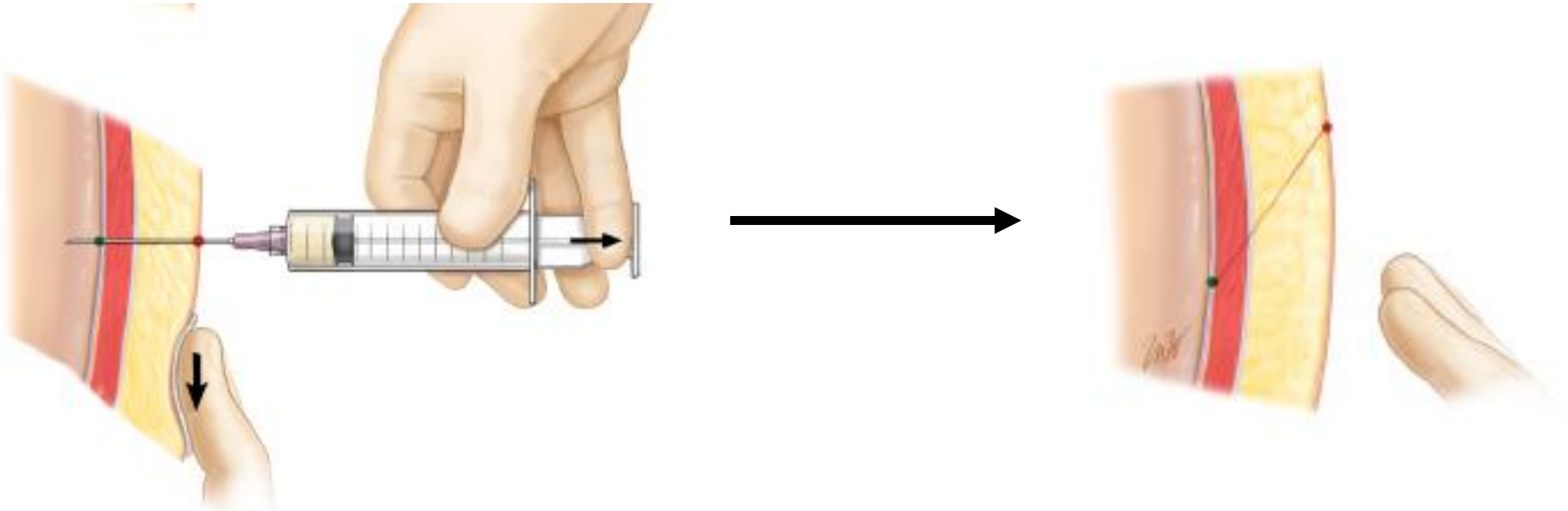
- Unlike capillaries, normal sinusoids do not have basement membrane allowing free exchange with space of disse
- In cirrhosis, sinusoids get “capillarised” i.e. they acquire a basement membrane which hinders exchange of protein
- Hence, low protein ascites in cirrhosis and late BCS
- However, in early BCS, sinusoids are not yet “capillarised”; hence high protein


Ascites
SAAG < 1.1 g/dL
SAAG ≥ 1.1 g/dL
Ascitic fluid protein
Ascitic fluid protein
< 2.5 g/dL
≥ 2.5 g/dL
Mixed Ascites
≥ 2.5 g/dL
< 2.5 g/dL
Nephrotic Syndrome
Ascitic fluid cytology for malignant cells
Serum BNP
Portal hypertensive ascites
Positive
Negative
< 182 pg/mL
≥ 182 pg/mL
Peritoneal Carcinomatosis
Hepatic Vein Doppler
2D Echo
Normal
Budd-Chiari Syndrome
No Heart Failure
Heart Failure
Ascitic fluid ADA
Ascitic neutrophil count (ANC) & culture
ANC ≥ 250 Monomicrobial culture +
Spontaneous Bacterial Peritonitis (SBP)
ANC ≥ 250 Culture sterile
Culture Negative Neutrocytic Ascites (CNNA)
≥ 33
< 33
ANC < 250 Monomicrobial culture +
Monomicrobial Non-neutrocytic Bacterascites (MNBA)
Tubercular peritonitis
Ascitic fluid amylase
ANC < 250 Culture sterile
Uncomplicated Ascites
> Serum > 1000
< Serum
Pancreatic ascites
Ascitic fluid Triglyceride
> 200 mg/dL
Chylous ascites

Site for diagnostic paracentesis



Z-track technique for paracentesis



Treatment

First-Line

- Cessation of alcohol use
- Other treatable etiologies
- Sodium restricted diet and diet education
- Diuretics
- Discontinue NSAIDS, ACE inhibitors and ARBs; No aminoglycosides
- Evaluation for liver transplantation

Second-Line

- Dose reduction in beta blockers
- Consider adding midodrine especially in the profoundly hypotensive patient
- Serial therapeutic paracenteses
- Evaluation for liver transplantation
- Transjugular intrahepatic portasystemic stent-shunt (TIPS)

General measures

- Moderate sodium restriction (80–120 mmol/ day)
  - generally equivalent to no added salt diet with avoidance of pre-prepared meals
  - to avoid sodas, pickles, bakery items
- Avoid diets with very low sodium content (<40 mmol/day)
- Prolonged bed rest not recommended

Clinical Trial > J Clin Gastroenterol. 1981;3 Suppl 1:73-80.

doi: 10.1097/00004836-198100031-00016.

Diuresis in the ascitic patient: a randomized controlled trial of three regimens

M R Fogel, V K Sawhney, E A Neal, R G Miller, C M Knauer, P B Gregory

PMID: 7035545 DOI: 10.1097/00004836-198100031-00016

Frusemide inferior to Spironolactone and combination of Spironolactone + Frusemide

Ascites mobilisation and the incidence of diuretic-induced complications similar in both regimens.
Sequential treatment required less dose adjustments

Spironolactone alone or in combination with furosemide in the treatment of moderate ascites in nonazotemic cirrhosis. A randomized comparative study of efficacy and safety

Justiniano Santos [1], Ramon Planas, Albert Pardo, Rosa Durández, Eduard Cabré, Rosa Maria Morillas, Maria Luisa Granada, José Angel Jiménez, Enrique Quintero, Miquel Angel Gassull

Randomized Controlled Trial > Gut. 2010 Jan;59(1):98-104. doi: 10.1136/gut.2008.176495.

Combined versus sequential diuretic treatment of ascites in non-azotaemic patients with cirrhosis: results of an open randomised clinical trial

P Angeli [1], S Fasolato, E Mazza, L Okolicsanyi, G Maresio, E Velo, A Galioto, F Salinas, M D'Aquino, A Sticca, A Gatta

Combined regimen: quicker resolution of ascites and lower hyperkalemia

Diuretics

Sequential Schedule	Combined Schedule
SP 100 → 200 → 300 → 400 mg/d	SP 100 mg/d + FRU 40 mg/d
↓	↓
SP 400 mg/d + Fr 40 → 80 → 120 → 160 mg/d	SP 200 → 300 → 400 mg/d + FRU 80 → 120 → 160 mg/d

Doses should be administered in the morning

Pts with 1st episode of Grade II ascites can be treated with sequential schedule

Pts with long standing or recurrent ascites- combined schedule

Other diuretics

- Torsemide
  - higher cumulative 24 hour natriuresis than frusemide
  - 5 mg torsemide equivalent to 20 mg frusemide

- Amiloride
  - Alternative to spironolactone in tender gynaecomastia
  - 10 mg amiloride equivalent to 100 mg spironolactone

Ratio of drugs

- Spironolactone + Frusemide (Lasilactone)- 50:20
- Spironolactone + Torsemide (Dytor Plus)- 50:5

Diuretic monitoring

- Maximum weight loss of 0.5 kg/day in patients without oedema and 1 kg/day in patients with oedema
- Escalation of dose not earlier than 72 hours
- Ascites largely resolved- reduce dose of diuretics to lowest effective dose
- Initial few weeks of treatment- frequent clinical and biochemical monitoring (serum electrolytes and renal functions)
- Urinary sodium in those with inadequate response

Discontinuation of diuretics

- Discontinue diuretics- serum Na <125 mmol/L, AKI, HE, or incapacitating muscle cramps
- Potassium <3meq/L- stop loop diuretic
- Potassium >6meq/L- stop anti-mineralocorticoids
- Severe muscle cramps- albumin infusion or baclofen (10 mg/day, with a weekly increase of 10 mg/day up to 30 mg/day)

Urinary sodium

- 24 hour urinary Na >78meq/L or spot urine Na/K >1
  - Adequate natriuresis
  - Pt should be losing weight
  - Lack of clinical response- dietary incompliance

Adequacy of 24 hour urine collection- urinary creatinine

- Men >15 mg/kg/day
- Females >10 mg/kg/day

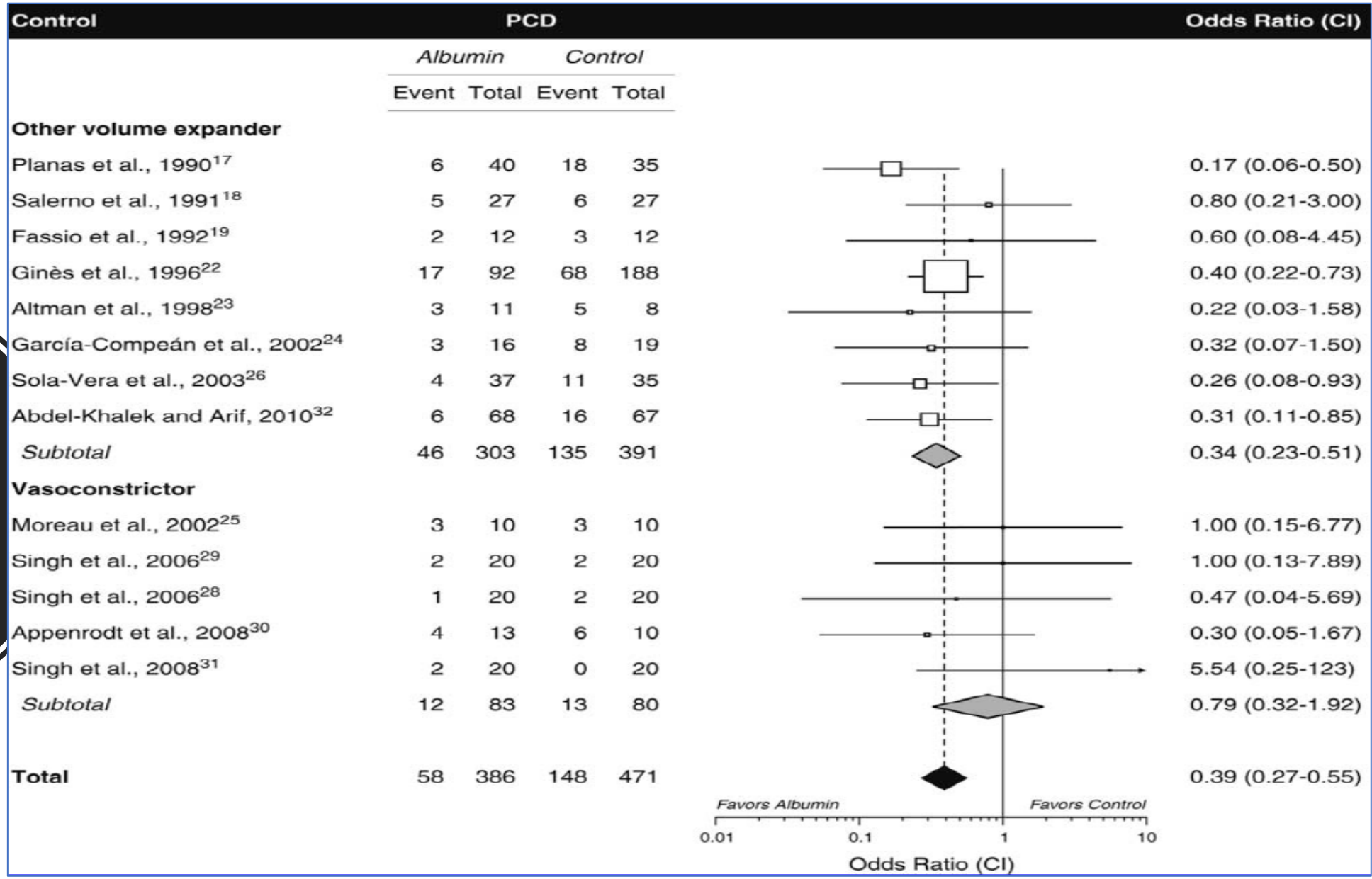
Large Volume Paracentesis (LVP)

- By definition LVP implies removal of > 5 L of ascitic fluid in a single session
- 1st line therapy in grade III ascites
- Removal of >5 L of fluid: plasma volume expansion with albumin (6-8 g/L of ascites removed) to prevent PICD
- Albumin infusion may not be necessary for a **single** modest volume paracentesis of less than 5 L
  - **Except** in patients with ACLF

Paracentesis induced circulatory dysfunction (PICD)

- Following LVP: early beneficial hemodynamic changes
- This is often followed by circulatory dysfunction (PICD) with intense **activation of RAAS** due to **arterial vasodilatation**
  - Increased nitric oxide synthesis in vascular endothelium
  - Mechanical changes of decompression
- PICD: elevation of plasma renin activity by >50% to a level of >4ng/ml on **day 6** after paracentesis
- Occurs in 75-80% patients undergoing LVP without volume expansion
- Potential approaches to prevention:
  - volume expansion (albumin, dextran, polygeline)
  - Vasoconstriction (terlipressin, noradrenaline, midodrine)

Albumin: best for preventing PICD



Following LVP albumin (8g/l) decreases incidence of PICD to 15-20% compared to 75-80% without albumin

Bernardi et al, Hepatology 2012

HEPATOLOGY

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Original Article

Paracentesis-Induced Circulatory Dysfunction With Modest-Volume Paracentesis Is Partly Ameliorated by Albumin Infusion in Acute-on-Chronic Liver Failure

Vinod Arora, Rajan Vijayaraghavan, Rakhi Maiwall, Amrish Sahney, Sherin Sarah Thomas, Rehmat Ali, Priyanka Jain, Guresh Kumar, Shiv Kumar Sarin ✉ ... See fewer authors

- In ACLF, PICD occurs in 70% patients of ACLF (without albumin) following modest volume paracentesis
- Albumin decreases the risk of PICD following MVP in ACLF (OR: 0.068; p = 0.005)

How frequently will LVP be required: the mathematics

You removed 10 litre of ascitic fluid in a patient today who has a serum sodium of 130 mmol/l, 24-hour urinary Na 20 mmol/l, with dietary salt intake of 5 g/day……..when will he again require LVP?

- 5 g dietary salt (NaCl) = 2 g of dietary Na = 88 mmol of Na = 88 mEq of Na
- Non-urinary sodium excretion: 10 mmol/day
- Our patient's urinary Na excretion: 20 mmol/day
- Therefore, Na retention per day: 88 – (20+10) = 58 mmol/day

- Ascitic fluid sodium concentration = serum sodium concentration
- Therefore, 10-L paracentesis removes 130 x 10 = 1300 mmol sodium
- Time taken to reaccumulate 10-L of ascites: 1300/58 = 22 days

Patient with serum sodium of 130 and "0" urinary sodium excretion will require 10-L of ascitic tap every 16-days

Refractory ascites: definition (IAC)

"ascites that cannot be mobilised or the early recurrence of which (i.e., after LVP) cannot be satisfactorily prevented by medical therapy"

Diuretic-resistant ascites	**Ascites that cannot be mobilized or the early recurrence of which cannot be prevented because of a lack of response to sodium restriction and maximal diuretic treatment**
Diuretic-intractable ascites	Ascites that cannot be mobilized or the early recurrence of which cannot be prevented because of the **development of diuretic induced complications** that preclude the use of an effective diuretic dosage

Recurrent or recidivant ascites: ascites requiring LVP on at least 3 occasions within 12-months despite dietary sodium restriction and adequate diuretic dosage; precedes refractory ascites

Diagnostic criteria of refractory ascites

Treatment duration	Intensive diuretic therapy (spironolactone 400 mg/day and frusemide 160 mg/day) for **at least one week** and on a **salt-restricted diet** of less than 90 mmol/day
Lack of response	Mean **weight loss of <0.8 kg over four days** and **urinary sodium output less** than the sodium intake
Early ascites recurrence	Reappearance of grade 2 or 3 ascites **within four weeks of initial mobilisation**
Diuretic-induced complications	• Diuretic-induced HE- development of HE in the absence of other precipitating factor • Diuretic-induced renal impairment- increase of serum creatinine by >100% to >2 mg/dl • Diuretic-induced hyponatremia- decrease of serum Na by >10 mmol/L to a serum Na of <125 mmol/L • Diuretic-induced hypo- or hyperkalemia- serum K <3 mmol/L or >6 mmol/L • Invalidating muscle cramps

Refractory ascites: management

- Urgent evaluation for LT as median survival only ~6 months
- Repeated LVP plus albumin (8 g/L of ascites removed)- first line treatment for refractory ascites
- Discontinue diuretics in patients not excreting >30 mmol/day of sodium under diuretic treatment

Controversy of beta-blockers

	N/BB vs No BB	Study cohort	RA %/Dose of NSBB	%CTP C No BB vs BB	MELD No BB vs BB	MAP No BB vs BB	Adjusted HR for mortality with BB
Sersté et al.	151/77/ 74	RA	151/120- 1.3%,,160- 46.7% 40-11.7%,,80- 40.3%	61% vs. 74%	18.8 vs. 18.9	123 vs. 103	2.61 (1.63-4.19)
Mandorfer et al.	182	SBP	NS,100 mg: 1%,,120 mg: 4%, ≤40 mg: 39%, 50–80 mg: 30%	53% vs. 67%	20.0 vs. 21.6	83 vs. 77	1.64 (1.1-2.3)
Leithead et al.	322 (208 matched)	transplant list	117 (76 matched) 80 mg (10–240)	NS	16 vs. 17	89 vs. 86	0.35 (0.14-0.86)
Mookerjee et al.	349	ACLF	NS	NS	29 vs. 27	79 vs. 78	0.60 (0.36-0.98)
Kimer N et al	61	RA	61,80 (40–200)	NA	15.5 VS 15	NA	No difference in mortality

- Very high dose of NSBB
- Lower MAP in pts on NSBB

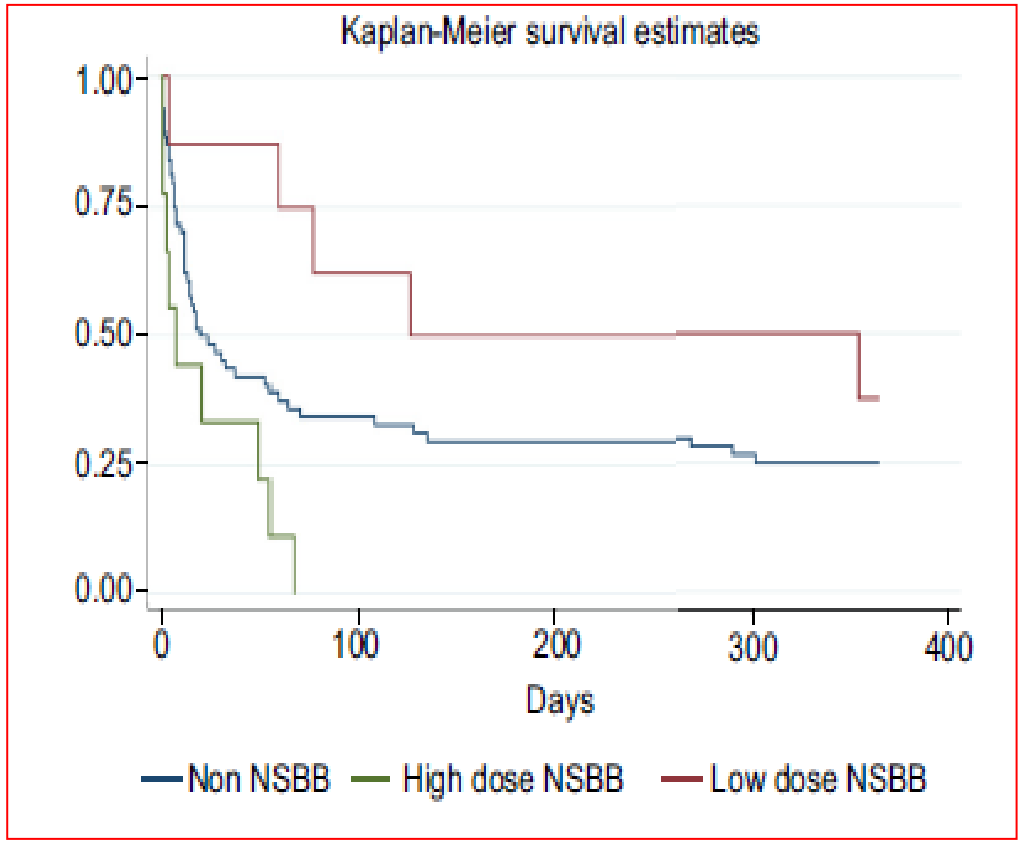
Dose of NSBB and outcome in SBP

- 81 patients
- 75% -male , mean age-60 ± 10 years , 75% -alcohol
- CTP A:2, B:16, C:63

Median survival time
Non-NSBB - 20 days,
Low dose NSBB -126 days
High dose NSBB-8 days

Bleeding rates - 8/64 non-NSBB, 0/8 low dose NSBB, 1/9 high dose NSBB, p = 0.57

HRS during f/u- 23/60 non-NSBB, 1/8 low dose NSBB, 5/9 high dose NSBB, p = 0.18



Madsen et al, J Hepatol 2016

Non-Selective Beta Blockers

- Refractory ascites and SBP- not absolute contraindications for NSBBs
- Avoid high doses of NSBBs (>160mg/day of propranolol or >80mg/day of nadolol)- possible worse outcomes
- Decrease dose/ withhold NSBB in RA with severe circulatory dysfunction
  - SBP < 90 mm Hg
  - serum Na < 130 meq/L
  - AKI
- Can be reintroduced if circulatory dysfunction improves
- Carvedilol not recommended in this setting

TIPS vs LVP- RCTs

	Refractory/ Recividant Ascites (%)	TIPS (N)	LVP (N)	Ascites improved (%)		HE (%)		Survival (%)	
				TIPS	LVP	TIPS	LVP	TIPS	LVP
Lebrec et al., 1996	100/0	13	12	38	0	15	6	29	60
Rössle et al., 2000	55/45	29	31	84	43	23	13	58	32
Ginès et al., 2002									
Sanyal et al., 2003									
Salerno et al., 2004	68/32	33	33	79	42	61	39	59	29
Narahara et al, 2011	100/0	30	30	87	30	20	5	20	5

TIPS- conslusions

- Better control of ascites with less recurrence at 3 and 12 months
- Higher incidence of HE
- ??improved survival: outcomes may be different in recividant vs refractory ascites

TIPS: PTFE covered vs bare stent

Acta Gastroenterol Belg. 2010 Jul-Sep;73(3):336-41.

Covered stents are better than uncovered stents for transjugular intrahepatic portosystemic shunts in cirrhotic patients with refractory ascites: a retrospective cohort study.

Maleux G[1], Perez-Gutierrez NA, Evrard S, Mroue A, Le Moine O, Laleman W, Nevens F.

J Gastroenterol Hepatol. 2015 Feb;30(2):389-95. doi: 10.1111/jgh.12725.

Long-term clinical outcome of patients with cirrhosis and refractory ascites treated with transjugular intrahepatic portosystemic shunt insertion.

Tan HK[1], James PD, Sniderman KW, Wong F.

Retrospective studies- better control of ascites and 1 year or 2 year survival with covered vs bare stents

TIPS

- Consider in patients with recurrent or refractory ascites or when paracentesis ineffective
- Small-diameter PTFE (8 mm)-covered stent recommended for TIPS
- Continue diuretics and salt restriction after TIPS till resolution of ascites
- Close clinical follow up

TIPS- when to avoid

- MELD >15-18
- Current overt HE
- Recurrent unprecipitated or chronic HE
- Active infection
- Unrelieved biliary obstruction
- Multiple hepatic cysts
- Moderate pulmonary hypertension
- Progressive renal failure
- Severe systolic or diastolic dysfunction
- Bilirubin >3mg/dl and platelets <75,000
- Severe coagulopathy
- PVT

Midodrine (alpha 1 agonist)

Midodrine	Time	MAP	Urine output	UNaE	PRA	PA	NE	GFR	Clinical effect|outcome
Ascites **Singh 2013, 22.5 mg/day* vs SMT**	1 month	↑	↑	↑	↓	↓	NA	=	Haemodynamic improvement Better ascites control
Singh 2012, 22.5 mg/day* vs SMT	1 month	↑	↑	↑	↓	↓	NA	=	Haemodynamic improvement
	3 month	=	↑	↑	NA	NA	NA	=	Better ascites control 3 month
	6 month	=	=	=	NA	NA	NA	=	Survival improvement
Ka							NA	=	Haemodynamic improvement
Kalambokis 2005, 22.5 mg/day * octreotide vs octreotide plus midodrine	11 days	↑	=	=	↓	↓	NA	=	Haemodynamic improvement
Angeli 1998, 15 mg/day†	0-3 h|3-6 h	↑	NA	↑|=	↓	=	NA	=	Haemodynamic improvement
Moreau 1987 0.15 mg/day* i.v, single dose vs placebo	Single dose	↓	NA	NA	=	=	↓		↓Sympathetic activity Hemodynamic improvement

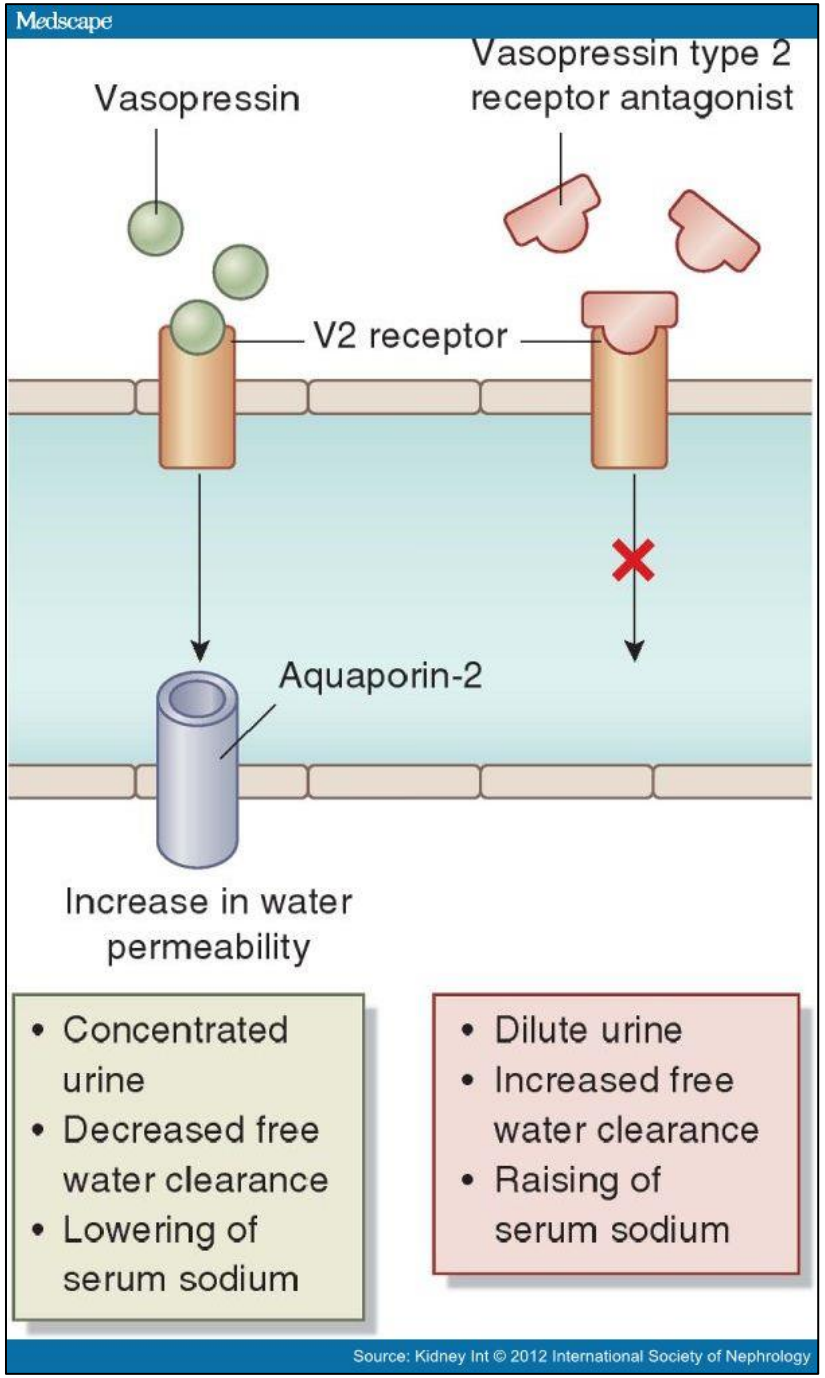
Consider midodrine in RA with low MAP; Dose: 5-15 mg TDS

Vaptans: vasopressin antagonists

Receptor	Localization	Functions
V1a	Vascular smooth muscle	Vasoconstriction, myocardial hypertrophy
	Platelets	Platelet aggregation
	Hepatocytes	Glycogenolysis
	Myometrium	Uterine contraction
V1b[a]	Anterior pituitary	ACTH release
V2	Basolateral membrane collecting tubule	Insertion of AQP2 water channels into apical membrane, induction of AQP2 synthesis
	Vascular endothelium	vWF and factor 8 release
	Vascular smooth muscle	Vasodilatation

ACTH, adrenocorticotropin hormone; AQP2, aquaporin-2.
[a]Termed V3 in some classification schemes.

Vaptans: vasopressin antagonists



Vaptans: US- FDA Recomendations

- Limitation of the duration of Vaptan treatment to 30 days.
- **Removal of the indication for use in patients with cirrhosis**
- Should be avoided because the ability to recover from liver injury may be impaired.
- Description of liver injuries seen in clinical trials of patients with ADPKD
- Recommendation to discontinue Tolvaptan in patients with symptoms of liver injury

Meta-analysis: safety and efficacy of vaptans

- Debated
- 2 trials were terminated due to adverse events.
  - Satavapatan trial - interim analysis found
    - mortality(31% vs 22% in the placebo group)
  - 2nd Satavaptan trial
    - 3x increase in serum bilirubin
    - increased creatinine and
    - prolonged QTcF.

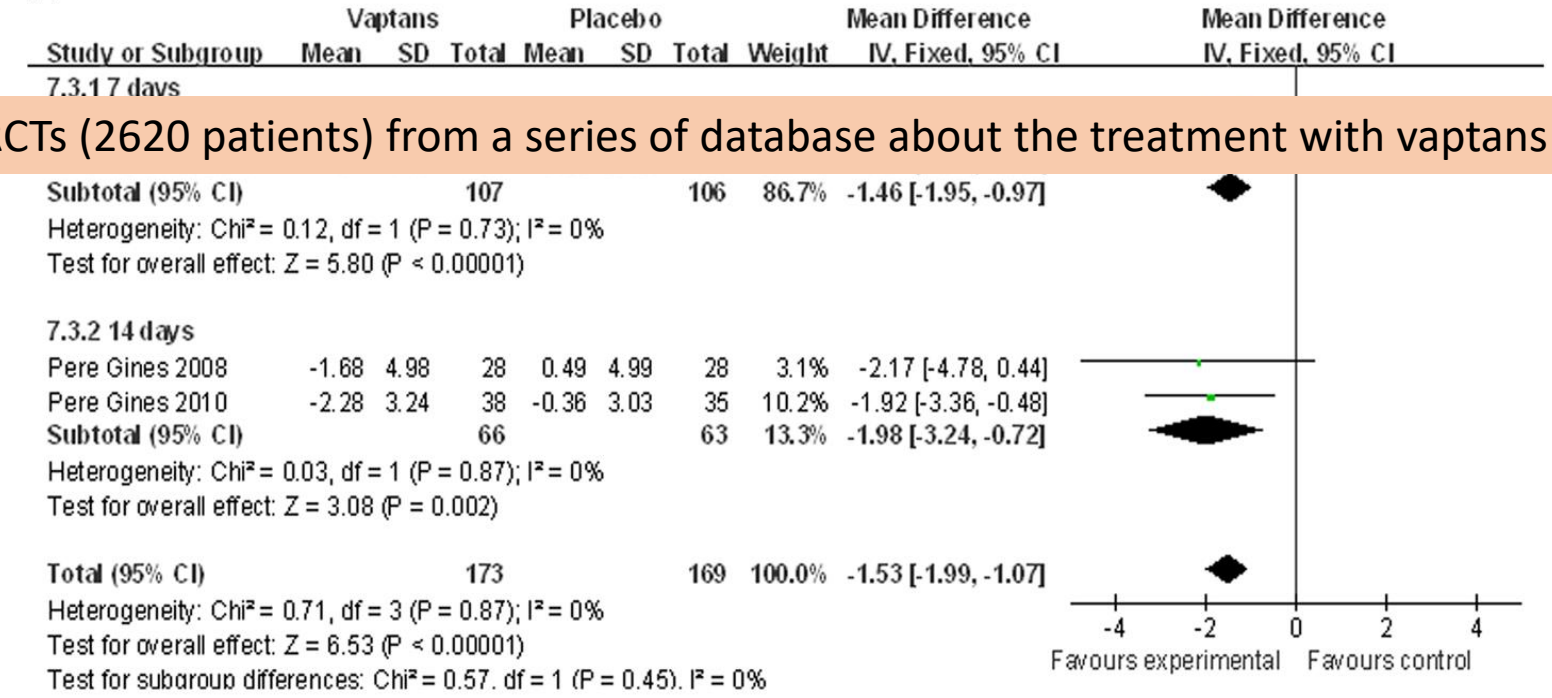
- Meta-analysis did not show
  - increased mortality or
  - complications to cirrhosis or
  - increased risk of serious adverse events
    - (statistical power of the included trials and the duration of follow-up in included trials limit the strength)

Aliment Pharmacol Ther 2012

Vaptans in cirrhosis patients with ascites: meta-analysis of RCTs

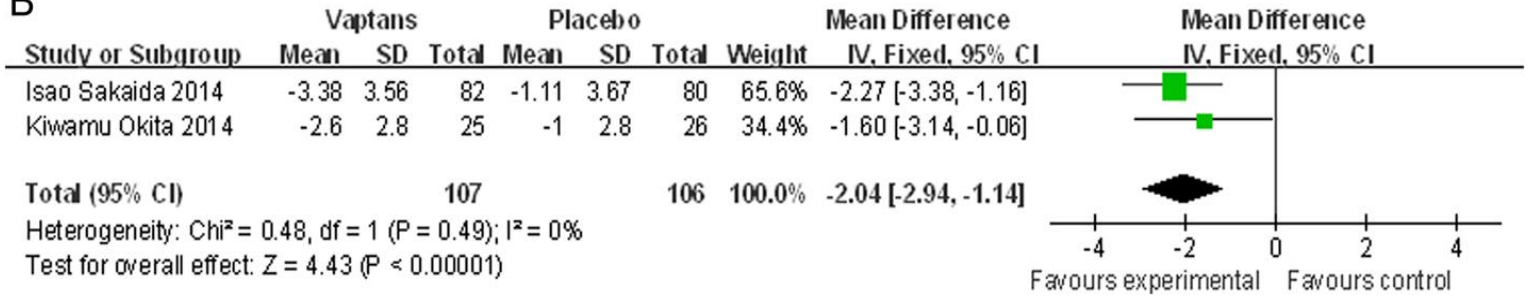
16 RCTs (2620 patients) from a series of database about the treatment with vaptans for cirrhosis with ascites patients

A



S.Na conc.

B

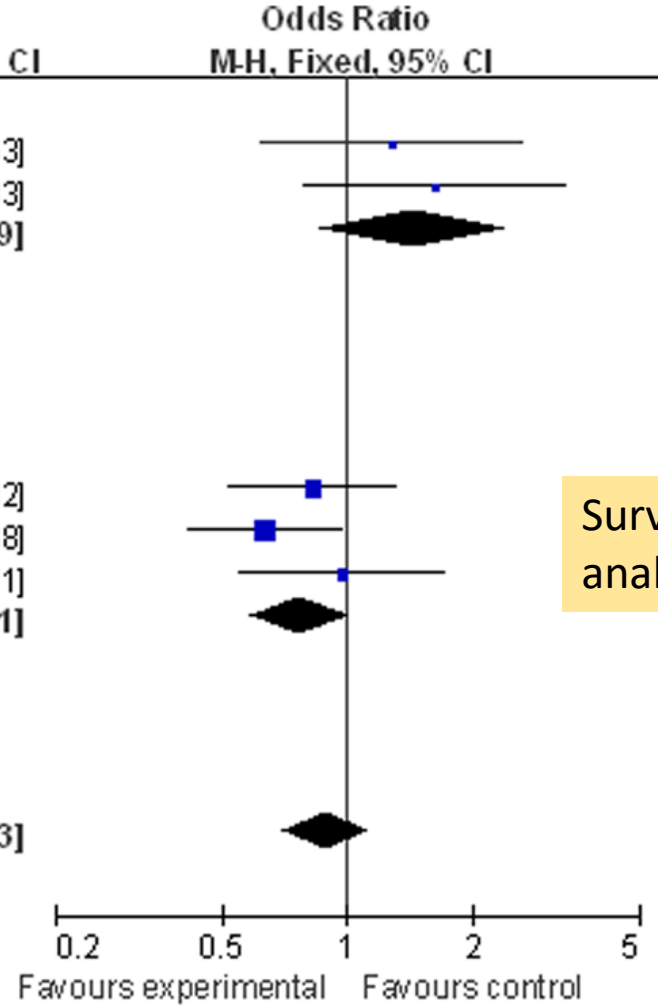


Ascites

Yan et al, BMC Gastro 2015

Vaptans in cirrhosis patients with ascites: meta-analysis of RCTs

Study or Subgroup	Vaptans Events	Total	Placebo Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
11.1.1 diuretics						
Florence Wong 2009	144	186	35	48	8.9%	1.27 [0.62, 2.63]
Pere Gines 2008'	30	47	48	92	8.4%	1.62 [0.79, 3.33]
Subtotal (95% CI)		233		140	17.3%	**1.44 [0.87, 2.39]**
Total events	174		83			
Heterogeneity: Chi² = 0.21, df = 1 (P = 0.65); I² = 0%						
Test for overall effect: Z = 1.41 (P = 0.16)						
11.1.2 no diuretics						
Florence Wong 2012 a	185	232	190	230	27.5%	0.83 [0.52, 1.32]
Florence Wong 2012 b	227	328	131	168	37.9%	0.63 [0.41, 0.98]
Florence Wong 2012 c	105	160	53	80	17.3%	0.97 [0.55, 1.71]
Subtotal (95% CI)		720		478	82.7%	**0.77 [0.58, 1.01]**
Total events	517		374			
Heterogeneity: Chi² = 1.51, df = 2 (P = 0.47); I² = 0%						
Test for overall effect: Z = 1.86 (P = 0.06)						
Total (95% CI)		953		618	100.0%	**0.89 [0.70, 1.13]**
Total events	691		457			
Heterogeneity: Chi² = 6.09, df = 4 (P = 0.19); I² = 34%						
Test for overall effect: Z = 0.99 (P = 0.32)						
Test for subgroup differences: Not applicable						



Survival analysis

Yan et al, BMC Gastro 2015

Research Article

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

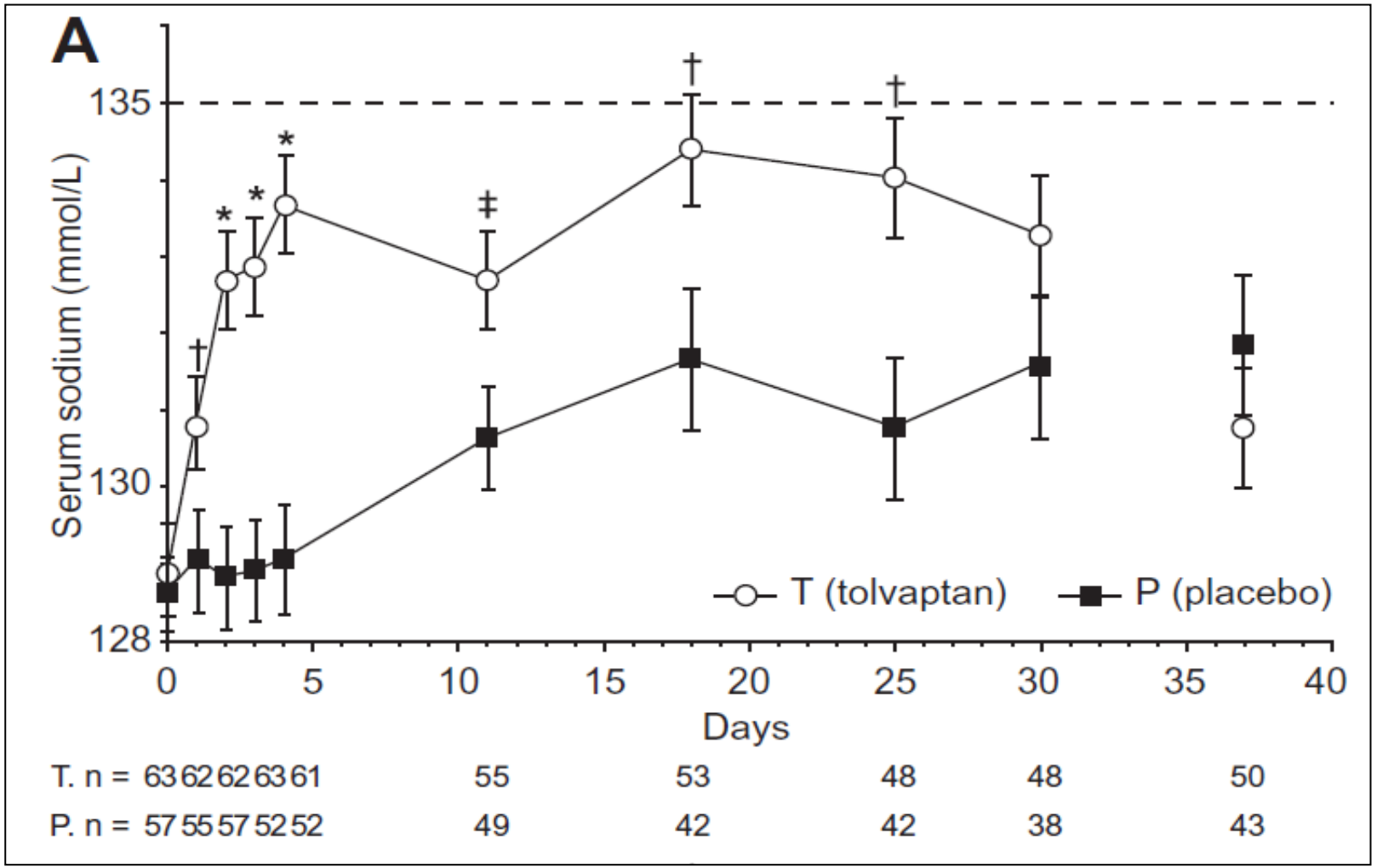
Tolvaptan, an oral vasopressin antagonist, in the treatment of hyponatremia in cirrhosis

Andrés Cárdenas[1,2,*,†], Pere Ginès[2,3,†], Paul Marotta[4,†], Frank Czerwiec[5,†], John Oyuang[5,†], Mónica Guevara[2,3,†], Nezam H Afdhal[6,†]

- Aims: Safety and efficacy of tolvaptan in patients with cirrhosis and hyponatremia
- Study: multicenter, double-blind, randomized, controlled
- Methods: This sub-analysis of the Study of Ascending Levels of Tolvaptan trials examined cirrhotic patients with hyponatremia who received 15 mg oral tolvaptan (n = 63; increased to 30 or 60 mg if needed) or placebo (n = 57) once-daily for 30 days

Cardenas et al, J Hepatol 2012

Tolvaptan for hyponatremia in cirrhosis: sodium trends



Conclusions:

Improved serum sodium levels

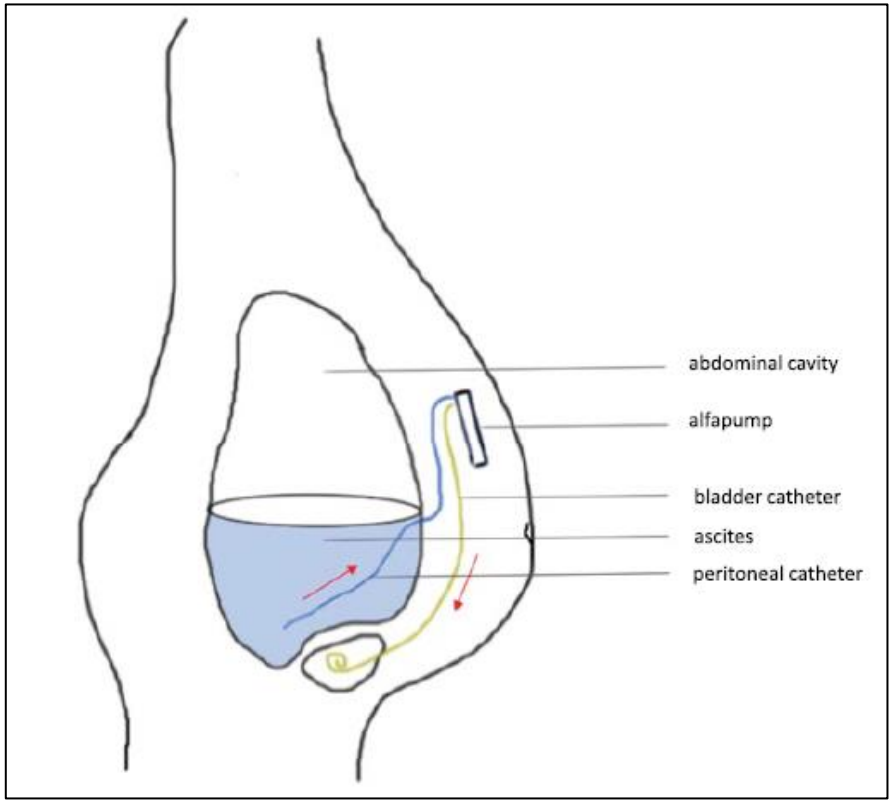
Hyponatremia recurred in tolvaptan-treated patients after discontinuation.

Tolvaptan recommended for RA in the Japanese guidelines

Cardenas et al, J Hepatol 2012

Automated Low-flow Ascites Pump (Alfapump®)

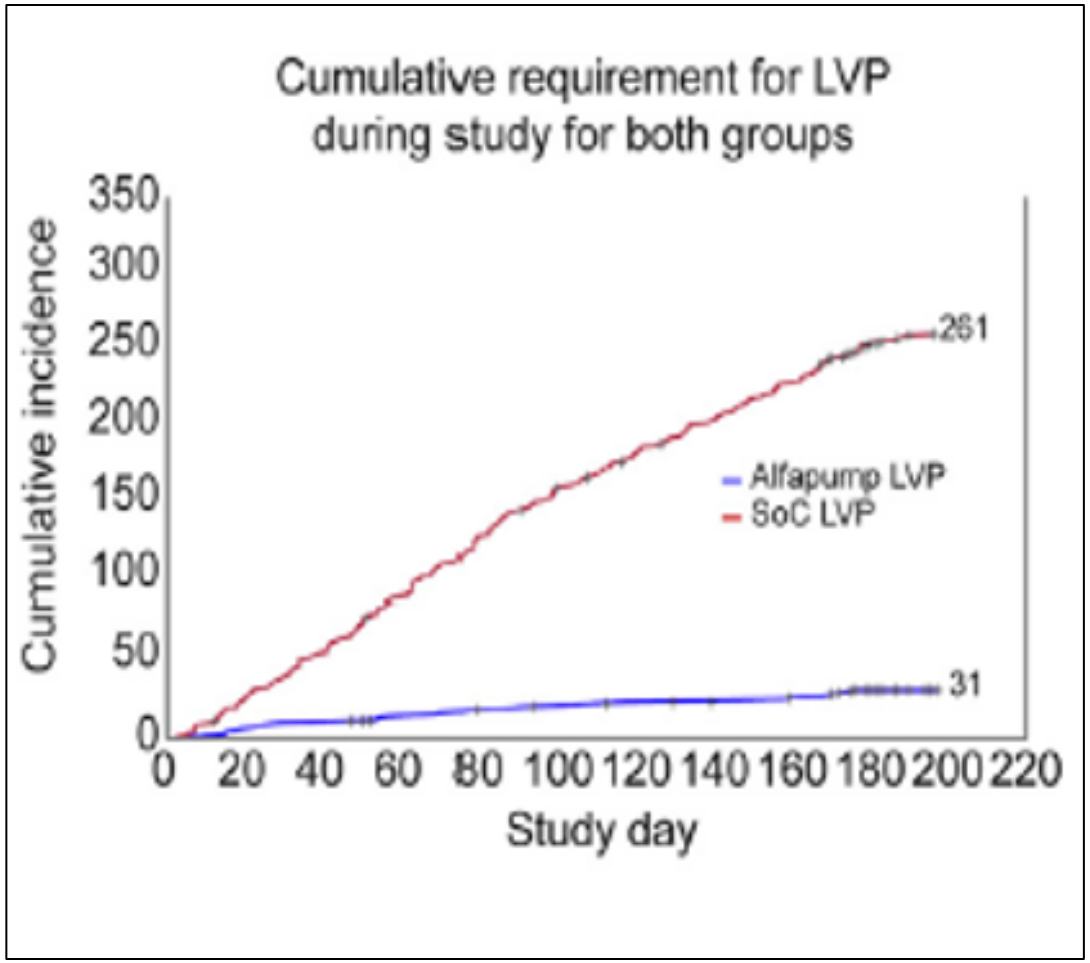
- Battery-powered pump implanted subcutaneously in the abdominal wall that aspirates and transports ascitic fluid through a subcutaneous catheter into the urinary bladder
- Works in cycles of small volumes (generally 5–10 ml) that are pumped every 5–10 min into the urinary bladder, without the obligatory administration of albumin
- The pump has in-built sensors that monitor peritoneal and bladder pressure to stop pump operation in the event of ascites resolution or full urinary bladder
- Up to 4 L ascitic fluid (usually 500 ml to 2.5 L) can be removed by the pump in a day
- Contraindications: loculated ascites, active infection or severe abdominal adhesions from previous surgery
- Due consideration should also be given to surgical morbidity and mortality in patients with advanced cirrhosis.



Research Article

EASL | JOURNAL OF HEPATOLOGY

Alfapump® system *vs.* Large volume paracentesis for refractory ascites: A multicenter randomized controlled study



Significant reduction in LVP requirement for the AlfaPump patients

- AlfaPump patients reported adverse events (AEs; 96.3% vs. 77.4%, p = 0.057) and serious AEs (85.2 vs. 45.2%, p = 0.002)
  - Mostly AKI
  - Treatable in most cases
- Survival was similar in AlfaPump and standard of caregroups.

Long term albumin for ascites

	ANSWER trial	MACHT trial
Type	Randomised Open label	Randomised Placebo controlled
Interventional treatment	HA 40 g twice a week for 2 weeks, then 40 g every week.	HA 40 g every 15 days plus midodrine.
Total number of patients (number of patients in each group)	431 (218 HA/213 SMT)	173 (87 HA+midodrine/86 SMT)
Number (%) of patients in waiting list for LT at enrolment	34 (8)	173 (100)
MELD at enrolment (HA/SMT)	12/13	17/18
Duration of interventional treatment	17.6 (8.0–18.0) months*	63 days†
Number (%) of patients under-going LT during the follow-up	37 (9)	106 (61)
Effect of interventional treatment on serum albumin concentration	Increase in serum albumin concentration (0.6–0.8 g/dL) in the first month.	No significant change.
Outcomes according to the interventional treatment	Reduction of mortality and complications.	No effect on mortality or complications.

Caraceni et al, Lancet 2018; Solà, et al.J Hepatol. 2018

Spontaneous bacterial peritonitis (SBP)

SBP	ANC>250/mm^3 and ascitic culture single organism	Antibiotics + albumin
CNNA	ANC>250/mm3 but culture negative	Treat like SBP
MNBA	ANC<250/mm^3 but culture single organism	Treat if symptomatic or SIRS Else, repeat ascitic fluid work up and treat if repeat culture positive or ANC>250/mm^3

Clinical Trial > N Engl J Med. 1999 Aug 5;341(6):403-9. doi: 10.1056/NEJM199908053410603.

Effect of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis

P Sort [1], M Navasa, V Arroyo, X Aldeguer, R Planas, L Ruiz-del-Arbol, L Castells, V Vargas, G Soriano, M Guevara, P Ginès, J Rodés

Affiliations + expand

PMID: 10432325 DOI: 10.1056/NEJM199908053410603

Cefotaxime + **Albumin (1.5 g/kg at diagnosis f.b 1g/kg on D3)** vs Cefotaxime alone:

- AKI: 10% vs 33%; p=0.002
- In-hospital mortality: 10% vs 29%; p=0.001

SBP management

Immediate empirical antibiotics as soon as diagnosis of SBP made; modify as per sensitivity

Uncomplicated SBP	IV Ceftriaxone 1g Q12H for 5 days
Complicated SBP	IV Carbapenems
Nosocomial SBP	Additional gram-positive cover

Albumin infusion 20-40 gm/day for duration of treatment in all patients

SBP management

- Duration of treatment atleast 5-7 days
- Persistent symptoms or organ dysfunction- repeat diagnostic tap at 48 hours
  - Failure to decrease ANC by 25% suggest failure of antibiotic therapy (upgrade antibiotics)
- ANC <250/mm^3 resolved SBP
  - No need to document resolution in all cases
- SBE treated similar to SBP

SBP prophylaxis

Primary prophylaxis
- Norfloxacin (400 mg/day) in patients with ascitic fluid protein <than 1.5 g/dL with Child-Pugh score ≥9 and serum bilirubin level ≥3 mg/dl, with either impaired renal function or hyponatremia
- Stop prophylaxis- long lasting improvement of clinical condition and disappearance of ascites

Secondary prophylaxis
- Norfloxacin (400 mg/day) 1st line prophylactic agent
- Intermittent prophylaxis to be avoided
- Life long prophylaxis
- Evaluation for transplant
- Restrict PPI to those with clear indication; adjust dose of NSBB

Management of AKI in cirrhosis

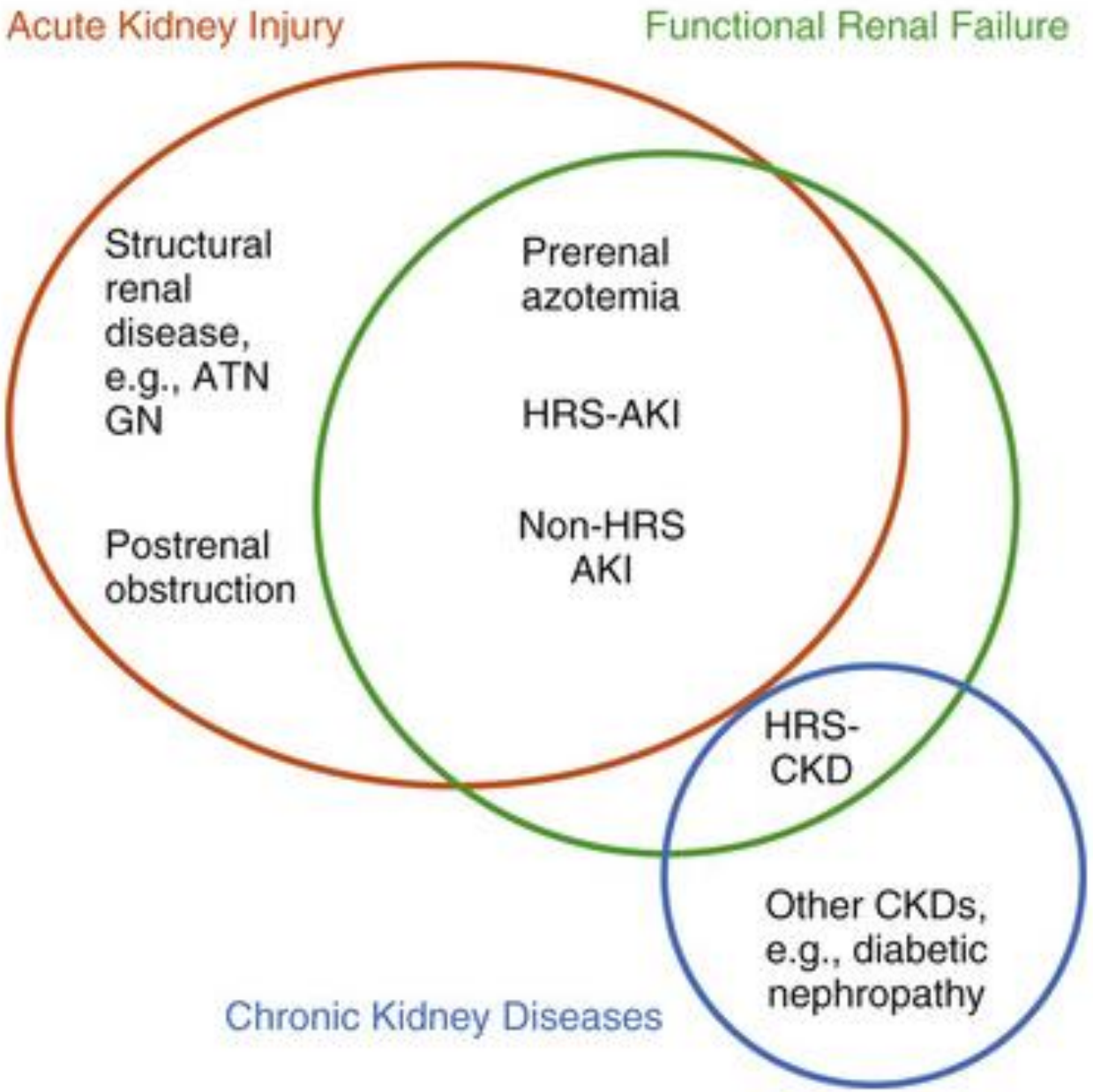
Incidence of renal dysfunction in cirrhosis

- AKI occurs in ~50% of admitted cirrhotic patient
- 5-80 % in ICU admitted patients
- Burden of AKI is increased by 200% in cirrhosis

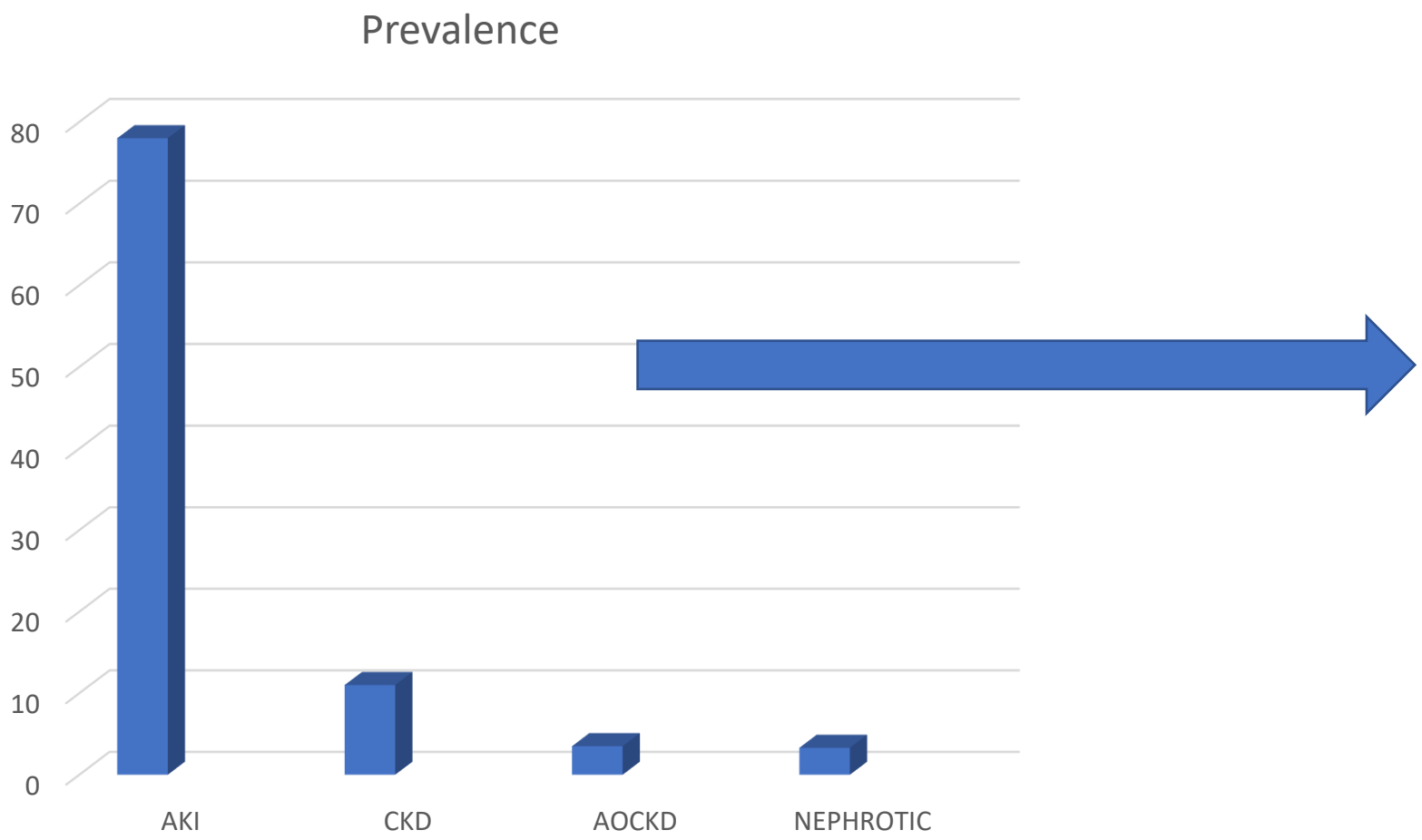
- Prevalence CKD is around 3.4%
- Burden of CKD as increased by 50%

Mitra et al, NEJM 2023

Spectrum of renal involvement in cirrhosis



Spectrum of AKI in cirrhosis



Spectrum OF AKI
Pre-renal: 47%
HRS: 28.2%
ATN: 17.4%

Cullaro G et al CJASN 2022

AKI definition (International Club of Ascites, 2017)

Definition of AKI	- Increase in **sCr ≥0.3 mg/dl within 48 h** - A percentage increase **sCr ≥50% above baseline** which is known, or presumed, to have occurred within the prior seven days
Baseline sCr	- value of sCr obtained in the previous three months - If more than one value , use value closest to admission - No previous values- use value at admission
Staging of AKI	- Stage 1: increase in sCr ≥0.3 mg/dl or an increase in sCr ≥1.5-fold to 2-fold from baseline - Stage 2: increase in sCr >2-fold to 3-fold from baseline; - Stage 3: increase of sCr >3-fold from baseline or sCr ≥4.0 mg/dl with an acute increase ≥0.3 mg/dl or initiation of RRT

AKI- response to therapy (ICA)

Progression- Progression of AKI to a higher stage and/or need for RRT Regression of AKI to a lower stage stage			
Response to treatment	No response	Partial response	Full response
	No regression of AKI	Regression of AKI stage **but sCr still ≥0.3 mg/dl above the baseline value**	Return of sCr to a value **within 0.3 mg/dl of the baseline value**

CKD- eGFR<60 ml/min with or without structural kidney damage for > 3 months

HEPATORENAL SYNDROME

OLD	NEW	CRITERIA
HRS-1	HRS-AKI	✓ ↑ in sCr ≥0.3 mg/dl (≥26.5µmol/L) in 48h; or ↑ ≥50% in 3 months ✓ No response after volume expansion with albumin 1g/kg/d x48H ✓ Cirrhosis with ascites ✓ Absence of shock ✓ No current or recent use of nephrotoxic drugs (diuretics, NSAIDs) ✓ Absence of parenchymal kidney disease ▪ No Proteinuria (>500 mg/d) ▪ No Hematuria (>50 RBC/HPF) ▪ Normal kidney ultrasonography
HRS-2	HRS-NAKI	**HRS-AKD** ✓ ↑ in sCr < 50% in 3 months ✓ eGFR < 60 ml/min/1.73 m^2 ✓ No other cause of kidney disease ✓ Cirrhosis with ascites **HRS-CKD** ✓ eGFR < 60 ml/min/1.73 m^2 ✓ No other cause of kidney disease ✓ Cirrhosis with ascites

Need of biomarkers for AKI

- *"A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention."*

- Limitations of serum creatinine in cirrhosis:
  - Influenced by age, sex, and ethnicity.
  - Sarcopenia: Reduced production of creatinine
  - Ascites: Increased total volume of distribution, lead to an overestimation of GFR
  - Demonstrates a slow kinetic increase in AKI (on the order of 12-24 hours), which delays diagnosis
  - Assay related- interference from serum bilirubin and albumin
  - Cannot distinguish between functional and tubular damage.

Goals of Novel Kidney Biomarkers

- **Prediction** of AKI development
- **Early identification** of AKI and triage of patients
- **Distinguish prerenal AKI from ATN**, thus limiting volume resuscitation to those with fluid responsive kidney injury.
- **Predicting AKI severity** by identifying those who will progress to a more severe AKI stage.

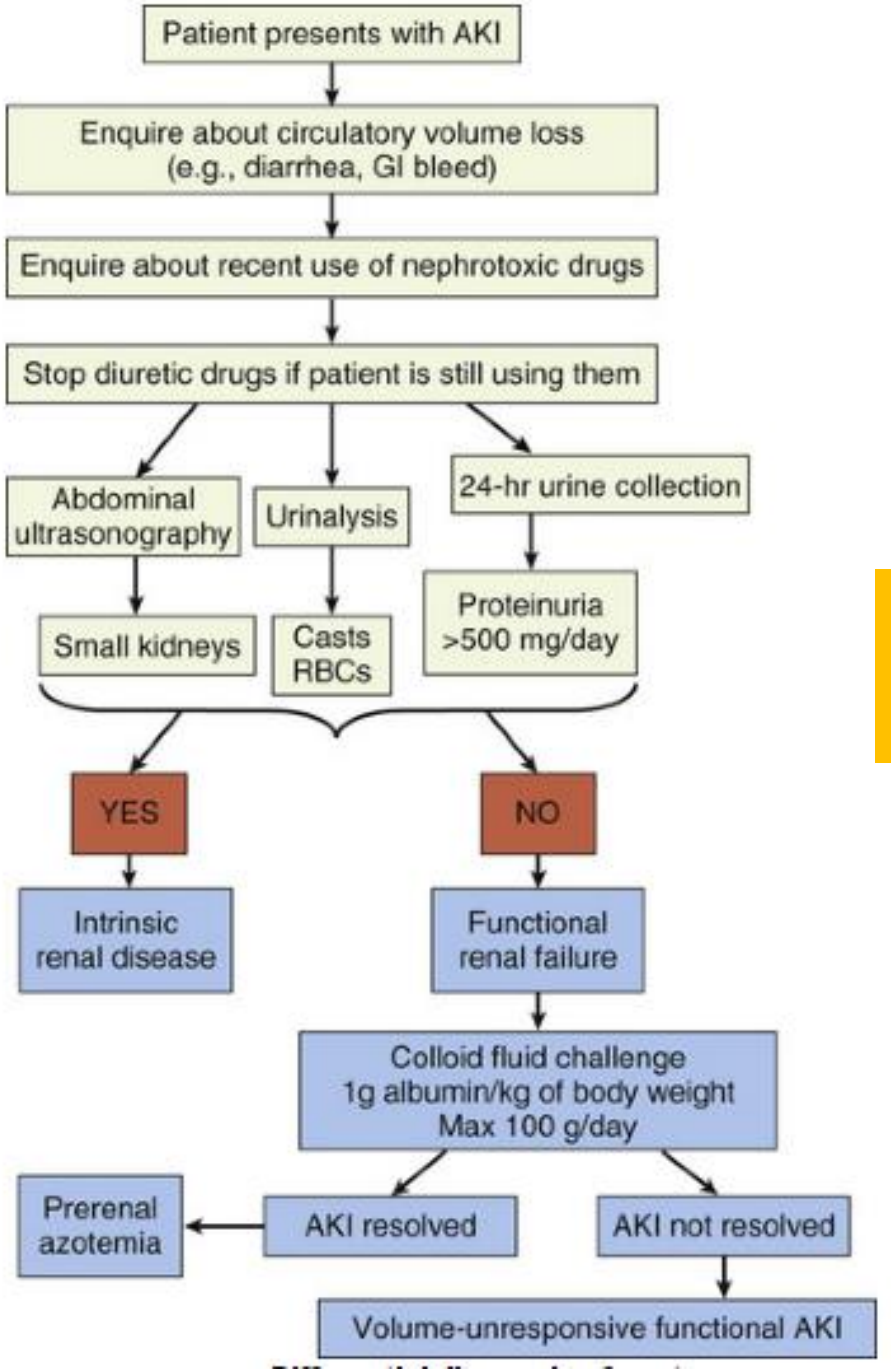
Classes of Kidney Biomarkers

Type	Examples	Testing Location	Time to Expression	Function	Nonrenal Expression and Limitations
Functional	Cystatin C[a,b]	Serum (urine)	12-24 h	Structural protein of cysteine protease inhibitor family	Similar to Scr, ↑ in CKD
Tubular injury	NGAL[b]	Urine (serum)	1-12 h	Innate immune regulation via iron sequestration	Infection (UTI), liver disease
	IL-18	Urine	1-12 h	Immune regulation	Infection
	KIM-1	Urine	1-12 h	Activates T_H cells, promotes apoptotic cell clearance	Clear cell carcinoma
	L-FABP	Urine	1-12 h	Free fatty acid transporter	Liver disease, PKD, sepsis
Cell cycle arrest	[TIMP-2] × [IGFBP-7][a,b]	Urine	<12 h	Regulate cell injury repair	Little evidence in cirrhosis

Cystatin C approved for clinical use in America and Europe
None of the biomarkers are routinely available in India

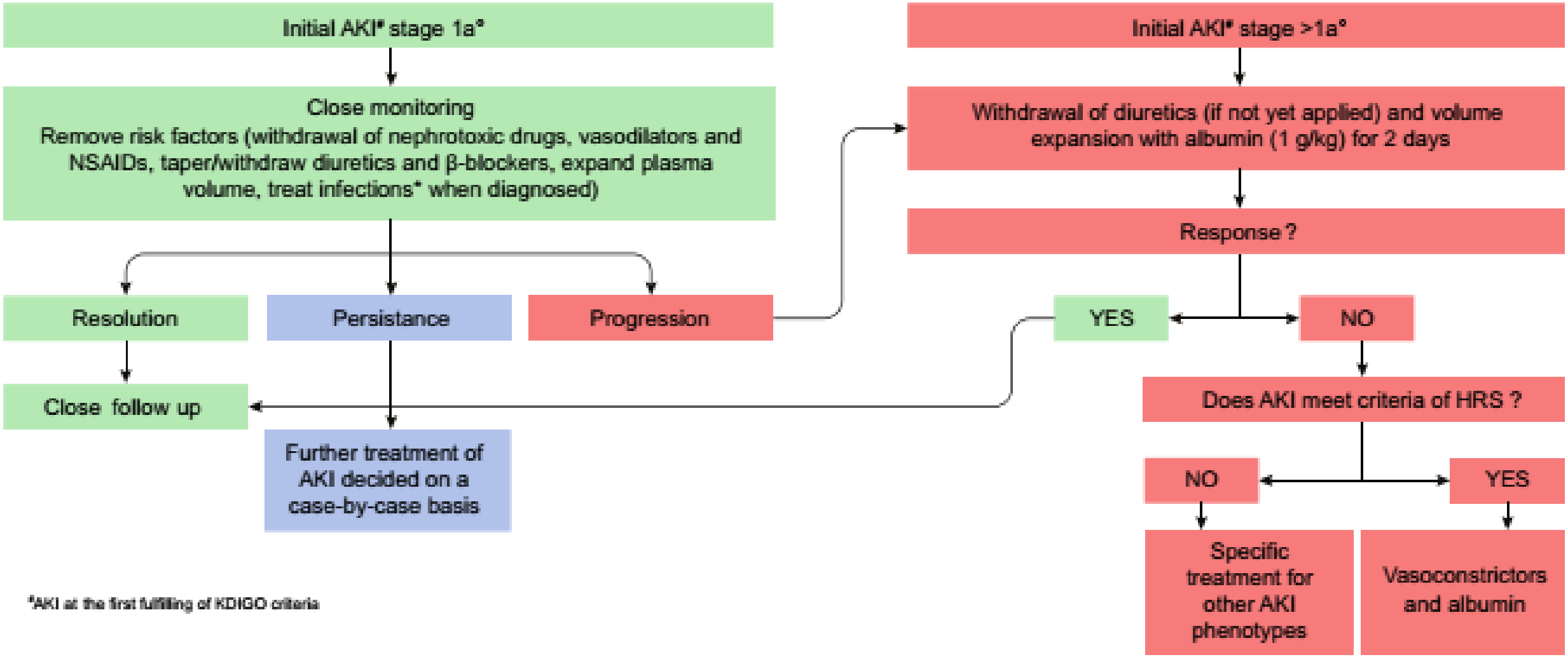
Allegretti et al, AJKD, 2020

Differential diagnosis of AKI



FENa <0.1 highly suggestive of functional AKI

Approach to AKI



*AKI at the first fulfilling of KDIGO criteria

Doses of vasoconstricors

Vasoconstrictor	Recommended Dosage
Terlipressin	
Bolus	Initially 0.5 mg intravenously every 4-6 hr. If no response by Day 3, can increase the dosage to 1.0 mg every 4-6 hr. Maximum dosage is 2.0 mg every 4-6 hr. Maximum duration 14 days.
Continuous infusion	Initially 2.0 mg/day. If no response by Day 3, can increase the dosage to 4.0 mg/day. Maximum dosage is 12.0 mg/day. Maximum duration 14 days.
Norepinephrine	
Continuous infusion	0.5-3 mg/hr continuously to achieve an increase in mean arterial pressure of 10 mmHg. Treatment is to be continued until serum creatinine concentration is < 1.5 mg/dL, or < 133 µmol/L.
Combination	
Midodrine	7.5 mg *per os* 3 times daily. Can increase to 12.5 mg *per os* 3 times daily. Aim at increasing systemic blood pressure to 120/80 mmHg.
Octreotide	100 µg subcutaneously 3 times daily. Can increase bolus followed by a continuous infusion at 50 µg/hr.

Duration of therapy- maximum 14 days or till complete response

Terlipressin: continuous infusion vs bolus in HRS-AKI

	Infusion regimen	Bolus regimen
Initial dose	2 mg/24 hours	0.5 mg q 4hourly
Escalation of dose	Serum creatinine decrease < 25% at 48 hours	
Maximum dose	12 mg/24 hours	2 mg q 4hourly

Dissolve terlipressin for infusion in 5% dextrose- maintained pH; better stability

Infusion group

- Lower rate of adverse events (35.39% vs 62.16%; p<0.025)
- Rate of treatment response- not different (76.47% vs 64.85%)
- Lower mean daily dose (2.23 6 0.65 versus 3.51 6 1.77 mg/day; P < 0.05)

Cavallin et al, Hepatology 2016

CONFIRM Trial

Table 2. Primary and

End Point	P Value
Primary end point of	0.006
Clinical success	
Clinical failure	
Competing event‡	
Liver transplantat	
Death	
Secondary end points adjustmen	
HRS reversal§	<0.001
Clinical success	
Clinical failure	
Competing event‡	
Liver transplar	
Death	
HRS reversal with no through 30	0.001
Clinical success	
Clinical failure	
Competing event‡	
Liver transplar	
Death	
HRS reversal in patie matory res	<0.001
Clinical success	
Clinical failure	
Competing event‡	
Liver transplar	
Death	
Verified reversal of H through 30	0.08
Clinical success	
Clinical failure	
Competing event‡	
Liver transplar	
Death	

Table 4. Adverse Events in the Safety Population.*

Event	Terlipressin (N=200)	Placebo (N=99)
	number of patients (percent)	
Adverse events of any grade†	176 (88)	88 (89)
Adverse events leading to discontinuation of the trial regimen	24 (12)	5 (5)
Serious adverse events with an incidence of ≥3% in either trial group‡		
Any	130 (65)	60 (61)
Cardiac disorders	8 (4)	6 (6)
Atrial fibrillation	1 (<1)	3 (3)
Gastrointestinal disorders	30 (15)	6 (6)
Abdominal pain	10 (5)	1 (1)
Gastrointestinal hemorrhage	8 (4)	0
General disorders and administration-site conditions	11 (6)	6 (6)
Multiple organ dysfunction syndrome	9 (4)	3 (3)
Hepatobiliary disorders	37 (18)	29 (29)
Chronic hepatic failure	9 (4)	8 (8)
Alcoholic cirrhosis	4 (2)	3 (3)
Hepatic cirrhosis	6 (3)	2 (2)
Hepatic failure	9 (4)	10 (10)
Worsening of HRS	3 (2)	3 (3)
Infections and infestations	19 (10)	5 (5)
Pneumonia	4 (2)	3 (3)
Sepsis	9 (4)	0
Nervous system disorders	13 (6)	3 (3)
Hepatic encephalopathy	9 (4)	3 (3)
Respiratory, thoracic, and mediastinal disorders§	33 (16)	8 (8)
Acute respiratory failure	8 (4)	2 (2)
Respiratory failure	20 (10)	3 (3)
Vascular disorders	10 (5)	4 (4)
Shock	5 (2)	3 (3)

Wong et al, NEJM 2021

HRS-AKI

- Baseline ECG; monitor for cardiovascular and ischemic side effects
- Monitoring for fluid overload prevention
- Recurrence in responders- repeat therapy
- Empirical antibiotics in all pending culture reports
- Insufficient data with TIPS in HRS-AKI
- Liver Transplant- best treatment irrespective of response to vasoconstrictors
- RRT- based on individual severity

Take home message

- SAAG is crucial for pinpointing portal HTN as cause of ascites
- Never forget BCS as a cause of portal hypertensive ascites; may be high or low protein
- Salt restriction is key for controlling portal hypertensive ascites
- Diuretic dose ratios (50:20 for Spiron : Fru; 50:5 for Spiron : Tor)
- Albumin in SBP and for LVP (MVP in ACLF)
- Refractory ascites: very poor prognosis
- AKI: differentiate pre-renal and HRS from ATN
- Vasoconstrictors and albumin in HRS

Further Reading

- AASLD: Biggins SW, Angeli P, Garcia-Tsao G, et al. Diagnosis, Evaluation, and Management of Ascites, Spontaneous Bacterial Peritonitis and Hepatorenal Syndrome: 2021 Practice Guidance by the American Association for the Study of Liver Diseases. Hepatology. 2021 Aug;74(2):1014-1048. doi: 10.1002/hep.31884.
- EASL: European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu; European Association for the Study of the Liver. EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis. J Hepatol. 2018 Aug;69(2):406-460. doi: 10.1016/j.jhep.2018.03.024.
- BSG: Aithal GP, Palaniyappan N, China L, et al. Guidelines on the management of ascites in cirrhosis. Gut. 2021 Jan;70(1):9-29. doi: 10.1136/gutjnl-2020-321790.
- Angeli P, Garcia-Tsao G, Nadim MK, Parikh CR. News in pathophysiology, definition and classification of hepatorenal syndrome: A step beyond the International Club of Ascites (ICA) consensus document. J Hepatol. 2019 Oct;71(4):811-822. doi: 10.1016/j.jhep.2019.07.002


Thank you