

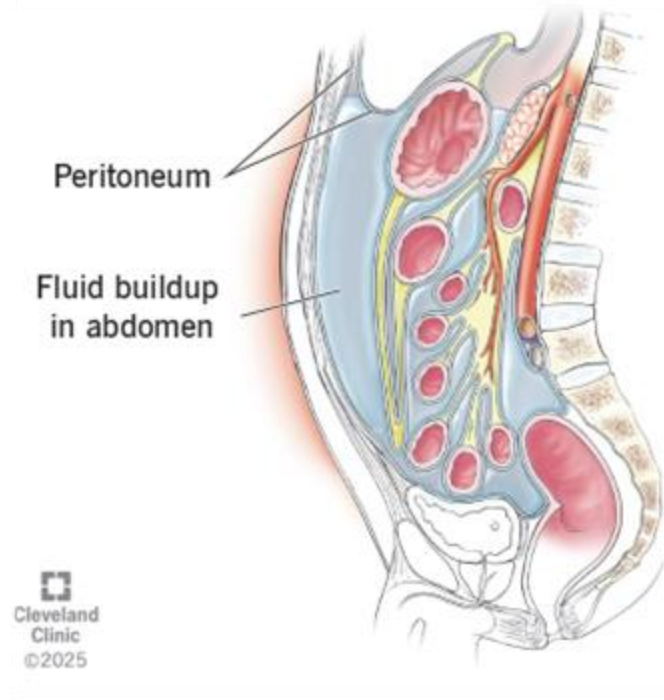
Management of Ascites in Patients with Decompensated Cirrhosis



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Definition and Causes of Ascites

- The peritoneum is a membrane that covers the abdominal organs
- Ascites is a build up of fluid between the 2 layers of the peritoneum
- Causes of ascites include:
 - Portosystemic hypertension
 - Congestive cardiac failure, constrictive pericarditis
 - Renal failure, nephrotic syndrome
 - Infections – tuberculosis
 - Malignancy – liver, ovarian, bladder, peritoneal metastases, pancreatic
 - Chronic pancreatitis
 - Severe malnutrition (kwashiorkor)
 - Low protein levels
- Hepatic cirrhosis is the most common cause of ascites



Ascites in Hepatic Cirrhosis

- Ascites:
 - Clinical manifestation of portal hypertension related renal dysfunction which leads to sodium and water retention and impaired free water clearance
 - Most frequent decompensating event in cirrhosis
 - Associated with reduced transplant free survival
- 5-10% of patients with compensated cirrhosis develop ascites every year

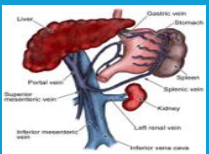
Pathophysiology of Portal Hypertension



Progressive fibrosis and hepatic necrosis result in a build up of scar tissue in the liver



Increasing scar tissue results in an increased pressure in the portal vein which is the large blood vessel carrying blood from the intestines into the liver

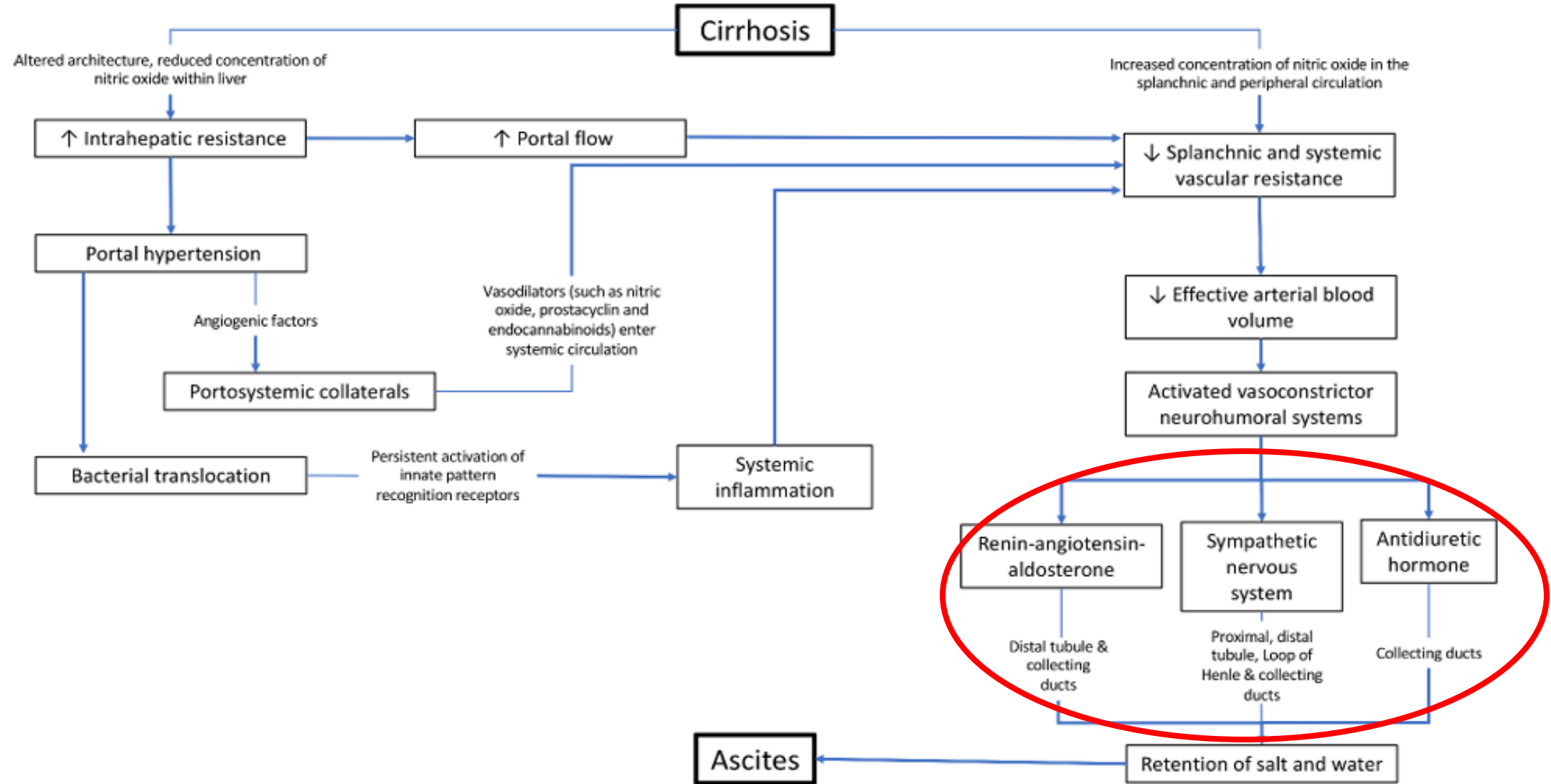


Increased resistance to portal flow triggers a cascade of events which ultimately leads to the development of ascites, varices and hepatic encephalopathy

Pathways Triggering the Development of Ascites

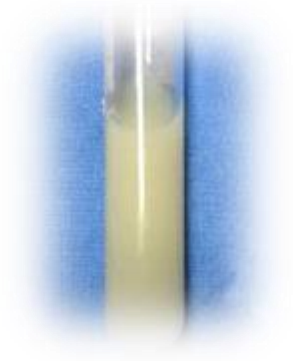
- As a result of the increased portal pressure:
 - Leakage of fluid from the portal vein and its branches into the peritoneal cavity
 - Increased hormonal signals to increase sodium and water retention
 - Renal retention of Na and water which results in a spill over into the peritoneal cavity
 - Reduced hepatic albumin synthesis and the consequent reduced oncotic pressure result in increased fluid leaking from the capillaries into the peritoneal cavity

Pathophysiology of Ascites in Liver Disease



Composition of Ascites

- Ascites is a mix of:
 - Proteins (albumin)
 - Electrolytes (Na)
 - Enzymes (lactate dehydrogenase)
 - Glucose
 - Bile acids
 - Lipids



Implications of Ascites in Individuals with Cirrhosis

- Associated with poor prognosis
- Approximately 20% die within 12 months of presentation
- Associated with systemic inflammation
 - Release of proinflammatory cytokines
- Increased risk of infection
 - Increased intestinal permeability
 - Spontaneous bacterial peritonitis (SBP)
 - Followed by urinary tract and respiratory tract infections
- Trigger for the development of acute on chronic liver failure

Potentially Modifiable Factors in Ascites

- Dysbiosis:
 - Systemic inflammation
 - Strong association between bacterial translocation and systemic inflammation
 - Main driver of disease progression and increasing portal hypertension
 - Small bowel bacterial overgrowth (prevalence >50% in cirrhosis)
 - Reduced bile acid secretion
 - Bacterial translocation
- Nutrition:
 - Provision of adequate energy and protein with ultimate goals of:
 - Improving nutritional status
 - Increasing hepatic synthetic function as measured by serum albumin levels
- Hepatic recompensation

Nutritional Features of Patients with Cirrhosis and Ascites

- Malnutrition
- Sarcopenia
- Frailty
- Depletion of subcutaneous adiposity
- Poor oral intake
 - Nausea
 - Early satiety
- Micronutrients



There are no reported adverse events associated with provision of adequate nutrition in patients with ascites

Nutrition related Symptoms of Ascites

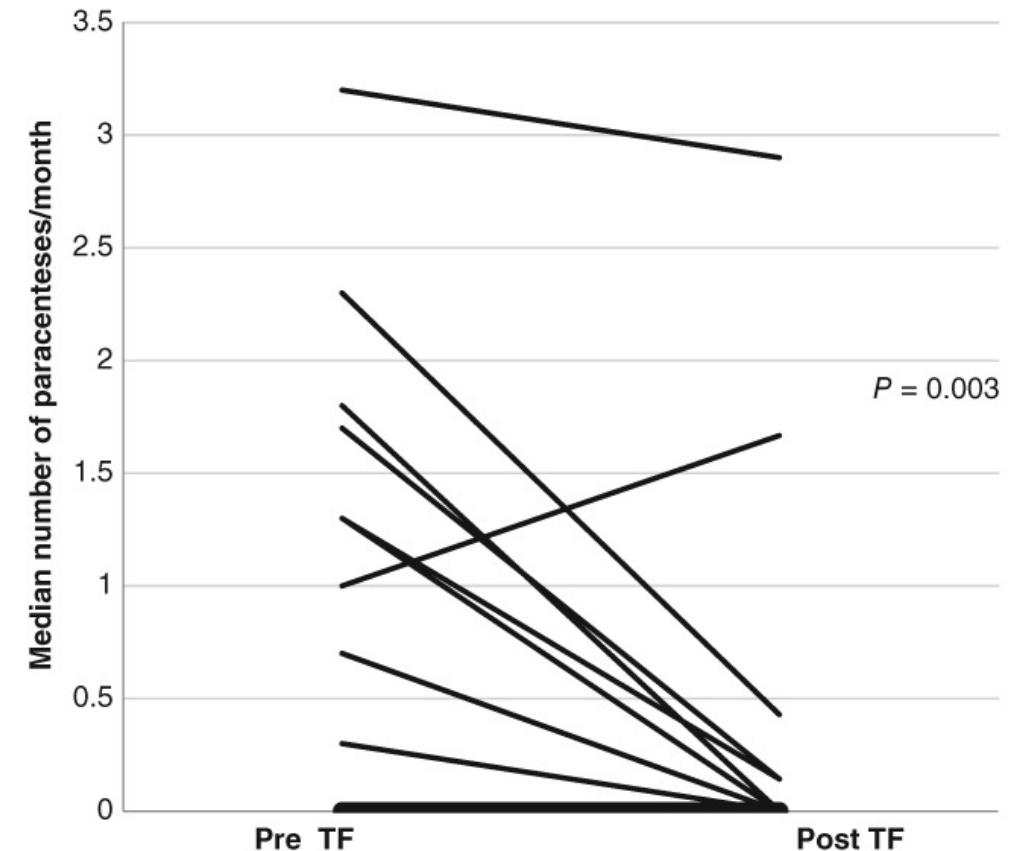
- Malnutrition secondary to:
 - Poor oral intakes
 - Early satiety
 - Nausea
 - Post-prandial fullness
 - Reduced post-prandial volumes
- After large volume paracentesis, total tolerated volume of spontaneous food intake and total energy intake increases

Evidence for Nutrition Support in Ascites

- French study (2005): investigated the factors associated with survival in a group of 63 severely malnourished inpatients with Childs Pugh C cirrhosis
- Patients whose spontaneous food intake $< 25\text{kcal/kg/}$ were commenced on enteral feeds according to their estimated nutritional requirements
- Normal diet + oral nutritional supplements maintained during feeding
- In severely malnourished patients with advanced disease, NG feeding was associated with:
 - Reduced disease severity
 - Improved liver function
 - Increased spontaneous food intake
- Bilirubin > 74 associated with poor outcomes/survival

Evidence for Nutrition Support in Ascites

- Supplementary continuous TF:
 - Improves nutritional status
 - Reduces ascites
 - Reduces paracentesis requirements
- Supplementary continuous TF should be considered as a treatment for malnourished patients with decompensated cirrhosis and refractory ascites



Albumin and the Liver

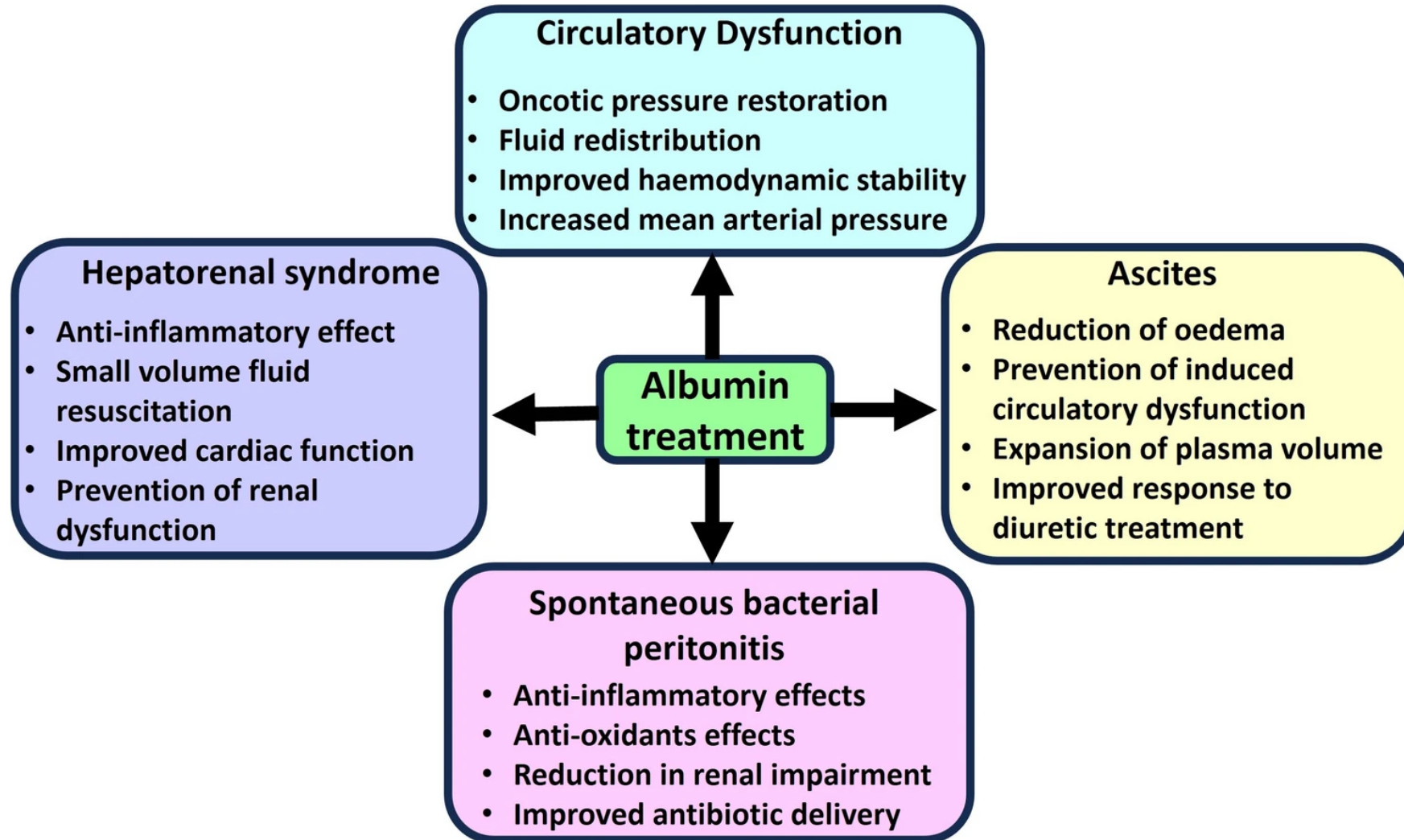
- Albumin:

- Synthesised by hepatocytes and continuously secreted into the circulation
- It is not stored in the liver
- 50% of circulating protein is albumin
- Accounts for 75% of plasma oncotic pressure which is principally responsible for fluid distribution in the body's compartments
- Both the quantity and quality of albumin produced by the cirrhotic liver are reduced
- Hypoalbuminaemia in cirrhosis arises as result of:
 - Reduced synthesis
 - Increased catabolism
 - Haemodilution related to expanded total plasma volume

Medical Management of Ascites

- Diuretics
 1. Spironolactone
 2. Furosemide
- Fluid restriction in the presence of hyponatraemia ($\text{Na} < 125 \text{ mmol/L}$)
- Intravenous albumin replacement
 - Goal: increase plasma albumin levels
- Paracentesis (ascitic taps)
 - IV albumin infusion
- Transjugular intrahepatic portosystemic shunt (TIPS)
 - Creates a vascular channel between the portal and hepatic veins
 - Restores effective arterial blood volume and ultimately improves renal perfusion and Na excretion
 - Complications
 - Cardiac dysfunction
 - Cardiac assessment prior to TIPS
 - Hepatic encephalopathy
 - Reduce diameter of the stent to prevent HE
- Benefits
 - Improved nutritional status
 - Increased muscle mass

IV Albumin Replacement (ANSWER Protocol)



ANSWER Protocol

- 40g IV 20% albumin for 2 weeks then,
- 40g IV 20% albumin 1/week
- Long term IV albumin administration results in:
 - 50% reduction in incidence of refractory ascites
 - Increased survival
 - Reduced incidence of SBP, hepatic encephalopathy, renal dysfunction
 - Reduced incidence of hyponatraemia and hyperkalaemia
 - Normalisation of plasma albumin concentrations after 1 month
- In addition to the improvements in the level of ascites and the frequency of paracentesis requirements, IV albumin is associated with reduced hospital admissions

Complications Associated with Medical Management

- Hyponatraemia
 - Diuretic
 - Low salt diet
- Acute renal failure
 - Elevated creatinine in association with cirrhosis
- Hepatorenal failure
 - Management: Terlipressin
 - Splanchnic bed vasodilator
 - Associated with poor survival/increased mortality

Nutritional Recommendations in Ascites

- Sodium
- Fluid
- Energy
- Protein
- Cramps



Ascites ... Let's talk about salt (NaCl)



Salt and fluid retention

- Humans have a basic physiological requirement for sodium: 460-920mg Na/d (1-2g salt – Na Cl)
- Sodium intakes > 2000mg/d are associated with increasing blood pressure, renal disease and cardiovascular disease
- Approximately 90% of Na consumed is excreted in the urine
- The renin-angiotensin-aldosterone hormone system and the sympathetic nervous system are intimately involved in Na-homeostasis
- Activation of these systems in patients with ascites results in fluid retention

Ascites ... Let's talk about salt (NaCl)



- Sodium restriction is frequently recommended as a first-line therapy for the management of ascites
- Diuretic therapy:
 - Furosemide
 - Spironolactone
- What do the guidelines say about salt intake and ascites?
 - ESPEN, EASL, AASLD, BASL

But it's not all about salt ...!

Salt Restriction and Ascites: EASL 2019

- Recommendation:

- *80-120 mmol Na/d which corresponds to 4.6–6.9g of salt/day*
- *A more severe reduction in dietary sodium content is considered unnecessary and even potentially detrimental*
- *This is generally equivalent to a no added salt diet with avoidance of pre-prepared meals*
- *Take care to improve diet palatability as this may cause a reduction in calorie intake*

- Advice to patient:

- *“You should try not to add too much salt to your food.*
- *It may take some time to adjust, but it usually gets easier with time.*
- *However, if you keep feeling that this makes your food unpleasant to eat, and that it makes you eat less, please report to your doctor or dietitian”*

Salt Restriction and Ascites: ESPEN 2019



- *“Although common practice, the evidence to restrict dietary sodium is poor and conflicting”*
- Hyponatraemia is common in patients with cirrhosis and is more likely to occur when the intake of sodium is low
- Sodium intake **should not** < 60 mmol/d (3.5g salt), as this makes the diet unpalatable, potentially compromising energy and protein intake

ESPEN 2020 - It's not all about salt ...!

- *“Based on the pathophysiology of ascites a moderate dietary sodium intake (80-120 mmol/day) is usually recommended (4.6-6.9g salt/d)*
- *The potential benefit may be offset by a reduced intake of energy and protein due to poor palatability of such a diet*
- *Therefore, great care should be taken to ensure adequate nutrition when prescribing a sodium restricted diet*
- *In patients with cirrhosis and ascites on a low sodium diet morbidity and mortality rates were lower in patients receiving a balanced diet with BCAA with or without PN support compared to those recommended a low sodium diet alone”*

Interpretation: nutrition support in combination with a moderate Na restriction = reduced morbidity and mortality

Salt Restriction and Ascites: AASLD 2021

- *Moderate dietary sodium restriction (2g or 90 mmol/day) should be prescribed to achieve a negative sodium balance and net fluid loss*
- *Patient education for sodium restriction is essential to maximize adherence*
- *Advice should include information on sodium contents of pre-prepared meals, avoiding adding salt to cooked meals, and guarding against nutritional deficiency*
- *Liberalization of sodium restriction should be considered if a patient is unable to maintain nutritional targets*

Salt Restriction and Ascites: British Society of Gastroenterology and BASL, 2021

- *Patients with cirrhosis and ascites should have a moderately salt restricted diet with daily salt intake of no more than 5–6.5 g (87–113 mmol sodium).*
- *This translates to a no added salt diet with avoidance of precooked meals.*
- *Patients with cirrhosis and ascites should receive nutritional counselling on the sodium content in the diet*

Ascites ... Let's talk about salt (NaCl)

- There are other significant contributors to sodium in patients with cirrhosis and ascites:
- Dosage: 40g IV albumin – 200ml 20% albumin required to administer 40g albumin
- 20% albumin approximately 0.9% Na
 - 48-100mmol/L (2 x 100ml bottles) provides 9.6-20mmol/L $\equiv$ 0.5- 1.2g NaCl)
 - 30g cheese $\equiv$ 0.3-1.0g NaCl + 7-9g protein and approximately 120kcal



Ascites ... Let's talk about salt (NaCl)

- Let's not forget about the sodium content of commonly used medications in cirrhosis:
 - Piperacillin tazobactam (Tazocin)
 - Movicol
 - Bactrim
 - Ciprofloxacin
 - Amoxicillin
 - Prednisolone
 - Oxycodone
 - Levothyroxine sodium



Evidence Against Salt Restrictions in Ascites

- There are significant adverse events with salt restriction including
- Sodium restriction alone without nutrition support associated with :
 - Hyponatraemia
 - Reduced caloric intake
 - Increased risk of renal impairment
 - Increased risk of hepatic encephalopathy
 - Increased risk of hepatorenal syndrome
 - Increase in episodes of Subacute Bacterial Peritonitis (SBP)
 - Increased mortality
- Provision of post paracentesis parenteral nutrition in Sorrentino's group provided additional benefits to increased oral intake + late evening snack

Salt or No salt in the Management of Ascites

- 200 individuals with cirrhosis and ascites randomised to sodium unrestricted (SUD) group and sodium restricted group (SRD)
- Both groups received silymarin, IV albumin, furosemide, spironolactone
- After 30days there were statistically significant differences in:
 - Energy
 - intakes lower in sodium restricted group (-550kcal/d)
 - Hyponatraemia
 - improved in the sodium unrestricted group
 - Albumin
 - Increased in sodium unrestricted group; unchanged in sodium restricted group
 - Ascites
 - Improved in sodium unrestricted group
 - Renal impairment due to hyponatraemia
 - Nil in the sodium unrestricted group

Dietary Sodium Restriction in Ascites

- The evidence base for sodium restricted diets in the management of ascites is limited
 - Based on 1 early study and the pathophysiology of ascites
- 115 patients with grade 3 ascites randomised into 2 groups and followed for 6 months
 - Salt restricted diet
 - Salt unrestricted
- Results:
 - Severe sodium restriction:
 - Reduced ascites
 - Further compromised nutritional status and sarcopenia
 - Associated with a significantly higher risk of death ($p < 0.001$, OR = 1.65)



Fluid and Ascites

- Fluid restriction is not necessary in treating most patients with cirrhosis and ascites
- When it is, there is wide variation in recommended fluid intake
- Common practice in intractable ascites
- BASL: 1-1.5L fluid/d for hypovolaemic or hyponatraemic patients ($\text{Na} < 125 \text{ mmol/L}$)
- Fluid restriction should be stretched to accommodate oral sip supplements and HP fluids
 - i.e. do not count sip supplements as part of fluid intake

Fluid Restrictions in Ascites

- Wide variation in recommended fluid intake
- EASL: not recommended unless serum Na < 125mmol/L
- ESPEN: not recommended unless serum Na < 120mmol/L
- AASLD: not necessary for ascites unless serum sodium $\leq$ 125 mmol/L
 - Overly strict fluid or sodium restriction can worsen malnutrition
- BASL: 1-1.5L fluid/d for hypovolaemic or hyponatraemic patients (Na<125mmol/L)

Energy Requirements in Ascites

- Cirrhosis is a state of accelerated starvation demonstrated by a rapid post absorptive physiology
- Characterised by a reduction in the respiratory quotient which marks a metabolic switch in fuel utilisation
- During this state of accelerated starvation, there is a reduction in protein synthesis with an increase in gluconeogenesis from amino acids
- Gluconeogenesis is energy expensive and may further increase REE

Energy Requirements in Ascites

- AASLD and BASL do not have a recommendation specific to the energy requirements in ascites
- AASLD recommended energy intakes based on BMI:
 - Normal BMI: 35 kcals/kg/d
 - BMI > 30-40: 25-35 kcals/kg/d
 - BMI > 40: 20-25 kcals/kg/d

Energy Requirements in Ascites

- ESPEN 2000:
- *“Cirrhotic patients during the natural course of the disease tend to spontaneously decrease their dietary intake*
- *Cirrhotic patients in conditions of increased energy expenditure (i.e. acute complications, refractory ascites) or malnutrition, should ingest an increased amount of energy*
- *Measurement of energy expenditure is recommended whenever possible*
- *Oral diet of cirrhotic patients with malnutrition and muscle depletion should provide 30-35kcal/kg/d and 1.5 g protein/kg/d*
- *Increased energy intake is not recommended in obese patients”*

Energy Requirements in Ascites

- EASL 2018
- 35 kcals/kg/d
- Obese individuals with cirrhosis: hypocaloric diet (-500-800 kcal/d)
- *Consider confounding effect of fluid retention*

REE in Ascites

- Dry weight or actual weight (weight + ascites)?
- REE is decreased after paracentesis -159 kcal /d ($p < 0.005$) ($n=10$)¹
 - Implication: ascites viable metabolic unit and underestimating requirements may contribute to protein-energy malnutrition
- Presence of ascites appears to increase REE ($n=19$)²
 - Deducting estimated weight of ascites underestimated energy requirements ($p=0.06$)
 - Including weight with ascites overestimated requirements ($p=0.69$)

¹Dolz C. Amer Gastroenterol Assoc, 1991

²AW Knudsen. Scandinavian J Gastroenterol, 2016

REE Before and After Paracentesis – unpublished

Baseline demographics

Participants	15
Age (yrs) (Median, IQR)	59.0 (52.5-63.5)
Gender	
Male (n)	7
Female (n)	8
Primary Disease	
MAFLD (n)	0
MetALD (n)	7
EtOH (n)	4
Viral (n)	1
Other (n)	3
MELD (Median, IQR)	18.0 (15-24)
CTP	
B (n)	5
C (n)	10
Hepatic encephalopathy (n)	10
Weight (kg) (median, IQR)	85.7 (91.7-68.5)
BMI (median, IQR)	27.2 (26.1-32.1)
SGA	
B (n)	12
C (n)	3
HGS (%predicted) (median, IQR)	56.5 (46.8-61.7)



Indirect calorimetry measured after a 4-hour fast

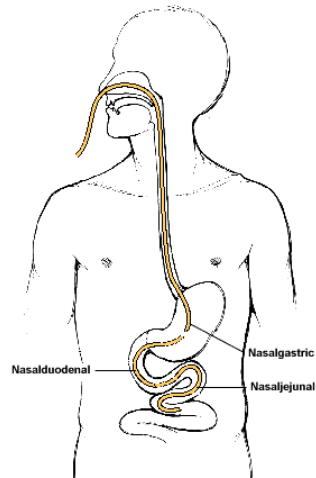
	Pre-paracentesis	Post-paracentesis
Participants (n)	15	12
Weight (kg) median, IQR)	85.7 (68.5-91.7)	81.5 (71.2-93.0)
Abdominal girth (cm) (median, IQR)	109.6 (102.8-121)	106.5 (100.9-120.3)
Volume drained (median, IQR)		6.7 (4.9-7.3)
REE (kcal) (median, IQR)	1566 (1451-1749)	1659 (1455-1872)
REE (kcal/kg (median, IQR)	18.8 (19-21.2)	20.4 (20.1-20.4)
Respiratory Quotient	0.80 (0.7-0.8)	0.80 (0.80-0.80)
Measured REE as %age predicted REE (median, IQR)	96 (92.5-107)	104.5 (100.5-110.3)

Protein Requirements in Ascites

- AASLD:
 - 1.2-1.5g protein/kg body weight /d
 - Increase to 2.0g protein/kg body weight/d if sarcopenic
- ESPEN:
 - 1.2-1.5g protein/d
 - Sarcopenia: 1.5g protein/kg/d
- EASL:
 - 1.2-1.5g protein/kg/day
- BASL:
 - 1.2-1.5g protein/kg/d

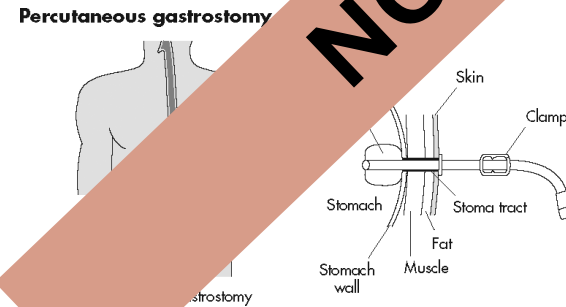
Enteral Feeding in Patients with Ascites

Nasogastric Feeding
Tube?



OR

Percutaneous
Endoscopic Gastrostomy
(PEG) Tube



Enteral Feeding in Liver Disease

(RPAH Experience - unreported)

- 9 patients with portal hypertension on nasogastric feeding + diet ad lib
- CTP improved in 8 patients
- 1 patient found did not improve (extra-hepatic spread HCC identified after 10 weeks)
- Frequency of ascitic taps reduced from every 7 – 14 days to nil in 8 patients
- Serum albumin levels improved (unsupported)
- 1/9 avoided TIPPS insertion
- Hand Grip Strength improved in 8 patients



Muscle Cramps in Cirrhosis

- Common in patients with chronic liver disease
 - Up to 88% of patients with cirrhosis
 - Related to disease severity
 - Can occur following large volume paracentesis
- Independent of
 - Aetiology of liver disease
 - Albumin, magnesium, sodium, potassium, zinc



Management

Taurine

- Supplementation with 2g taurine/day:
 - Reduced frequency of cramps:
 - 7.1 fewer cramps than placebo during treatment ($p=0.03$)
 - Reduced duration of cramps during treatment compared to placebo
 - 81.4 minutes per 2 weeks; 170 minutes/2weeks for placebo group ($p=0.02$)
 - Reduced intensity/cramp (Likert Scale)
 - 1.42 units less than placebo ($p=0.004$)

Pickle Juice

- US study:
 - 82 patients randomised to 2 arms:
 - “Sips” of pickle juice or water at onset of cramps
 - Reduced severity of muscle cramps
 - No change in frequency of cramps
 - No change in quality of life
 - What’s in pickle juice?
 - 75ml bottle of Australian pickle juice contains approximately 470mg of sodium
 - $\frac{1}{4}$ cup of pickle juice can contain between 500 and 1,000mg of sodium

Complications of Nutrition Support in Ascites

- There are significant complications associated with malnutrition in patients with ascites
- Nutritional interventions for ascites are felt to be essential to improved outcomes: mild-moderate Na restriction + adequate protein and calories. *Tapper E et al. Curr Hepatol Rep, 2021*
- Caveats:
 - Think about refeeding
 - Careful with nasogastric feeding in patients with worsening hepatic encephalopathy
 - Potential increased risk of aspiration

Dietary Prescription for Patients with Ascites

- Assess level of malnutrition
- Aim to maintain muscle status and improve hepatic synthetic function (albumin)
- Mild sodium restriction – no added salt at the most
- Energy: 30-35kcal/kg/d – ?consider BMI and fluid mass
- Protein: 1.5g-2.0/kg/d
- Fasting: avoid periods of prolonged fasting to reduce gluconeogenesis and preserve or improve muscle mass
- Sodium: ALWAYS prioritise meeting protein and energy requirements over Na restriction
- Fluid restrict in the presence of hyponatraemia ($\text{Na} \leq 125\text{mmol/L}$)

Response to Nutrition Support in Cirrhosis and Ascites

“Reduce sarcopenia and improve nutrition”

Piero Amodio ISHEN 2019

Enteral + Oral



8 weeks

Oral



12 months

24 months

And Reduce Ascites

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