ASCITES

- It is the **pathological** presence of free fluid within the peritoneal cavity. It forms because of conditions directly involving the peritoneum **“local”** (infection, malignancy), or diseases away from the peritoneum **“systemic”** (liver disease, heart failure).
- **Median survival** of cirrhotic patient is 9 years → ‘d be once develop ascites → 1.6 years.

Q. Is there fluids physiologically inside peritoneal cavity? → YES, there is a thin layer of fluid & its role is to be between the two layers of peritoneum to **minimize any shearing force.**
Q. What is ascites? → Xss accumulation of the fluids.
Q. What are the types of causes of ascites? → Local causes & Systemic causes.
→ **Local causes** as infection “TB”, Malignancy & Local obstruction of lymphatic system.
→ **Systemic causes** as liver disease, heart failure & renal failure.

#### Differential Diagnosis Cirrhotic Ascites
- Malignant Ascites.
- Tuberculous Ascites
- Chylous.
- Constrictive pericarditis.
- Hepatic Venous Obstruction.
- Ovarian Tumor.
- Bowel perforation.

#### Circulatory changes in Cirrhotics

**Increased**
- Plasma/total bl volume "due to ↑ fluids but no. of blood cells not ↑ ".
- Non Central bl volum " Extravascular"
- Cardiac output "HeamodilutionV.D→ ↑ SV"
- Portal pressure & flow "from portal HT"

**Decreased**
- EffectiveCentral bl Volume {leads to ↓ O2 adeq. supply}
- Arterial Bl Pressure {by V.D by nitric oxide}.
- Splanchnic vascular resistance {by V.D by nitric oxide}.
- Systemic vascular resistance {by V.D by nitric oxide}.
- Renal Bl Flow {leads to ↑ RAAS--→ Na/H2o retention}.

The abnormalities associated with ascites formation in cirrhotic patients:
- Portal hypertension.
- Renal retention of sodium.
- Splanchnic arterial vasodilatation.
- Systemic vascular changes.
- Splanchnic and hepatic lymph formation.
- Hypoalbuminemia. (Exaggerated by Na/H2o retention).

**Pathogenesis of ascites formation and hepatorenal syndrome in patients with cirrhosis.**

N.B: Lymph is the difference between artery & vein → So when there is V.D in arteries & constriction in portal vein → ↑ lymph formation.
MECHANISMS OF ASCITES

3 different factors or hypothesis

1- Under Fill & Peripheral Vasodilation
- Vascular changes.
- Vasodilators.
- Renal changes.

Cirrhosis

2- Over Fill Theory
- Hepatic signal
  (Baroreceptor, other)

Renal Na & H2O Retention

This will lead to
- Over flow into peritoneal cavity

3- Other Renal Factors
- Atrial natriuretic factor (ANF)
- Prostaglandins

In another way (a sum up for all of the above 3)

Cirrhosis

- Hepatic venous outflow obstruction
  - ↑ Sinusoidal pressure
    - HVPG > 10 – 12 mmhg

- Na & H2O retention

- ↓ arteriolar resistance
  (vasodilation)

- ↑ Activation of neurohormonal system (RAAS, etc.)
CLINICAL FEATURES

- Onset may be “Accumulating” TB, malignancy OR “Acute” as in VOD.
- Examination “Is there other precipitating causes?”
- Secondary Effects
  - Pleural Effusion.
  - Spontaneous Bacterial Peritonitis (SBP).
- Ascetic Fluid Examination. (To confirm SBP).

WORKUP OF ASCITIES

- Diagnostic Paracentesis
  - Routine (must be done):
    - Protein/Albumin cirrhotic ascites
    - PMN count
  - Selective diagnostic parameter acc.to the case & findings
    - If SBP then do:
      - Culture
      - Glucose, LDH for secondary infection.
    - If pancreatic ascites then do Amylase.
    - If malignant ascites then do Cytology
- Indications (when to do Diagnostic Paracentesis)
  - New-onset ascites
  - Admission to hospital
  - Symptoms/signs of SBP
  - Renal dysfunction
  - Unexplained encephalopathy

TREATMENT OVERVIEW

- Bed rest: (primary in all management plans) to ↓ burden of byproducts that occur by physical activity & ↑ RBF → ↑ excretion.
- 70-90 mmol Na diet.
- Weigh daily, and check urinary volume.
- If no response go for
  - Spironolactone 100-200 mg daily
  - Furosemide 40 mg daily
  - Stop diuretics in pre-coma, hypokalemia or alkalosis.

Q: WHY no complete Na restriction?
1) Cerebral edema 2) Palatability 3) ↓QOL 4) imp. for diuretics action.

- SO ADVICE: to ↓ soda & preservatives & use yeast-baked NOT Na bicarbonate.

Paracentesis: its disadv. is loss protiens & solutes. So if > 5L → Replace with protiens.
A- Uncomplicated Ascites:

- **Definition:** Ascites responsive to diuretics in the absence of infection and renal dysfunction.

- **How to manage**
  - **Sodium restriction**
    - Effective in 10-20% of cases.
    - 2 g (or 5.2 g of dietary salt) a day.
    - **Goal:** *negative sodium balance* (*But not –ve fluid balance*).
    - **Side effect:** unpalatability may compromise nutritional status.
    - **Predictors of response:** mild or moderate ascites, Urine Na excretion > 50 mEq/day.
  - **Diuretics**
    - Should be spironolactone-based.
    - A progressive schedule (spironolactone → furosemide requires fewer dose adjustments than a combined therapy (spironolactone + furosemide).
    - **Dosage**
      - Spironolactone 100-400 mg/day.
      - Furosemide (40-160 mg/d) for inadequate weight loss or if hyperkalemia develops.
    - **Increase diuretics if** weight loss <1 kg in the first week and < 2 kg/week thereafter.
    - **Decrease diuretics if** weight loss >0.5 kg/day in patients without edema and >1 kg/day in those with edema.
    - **Side effects**
      - Hyponatremia, hyperkalemia, encephalopathy,
      - Gynecomastia

B- Refractory Ascites

- Occurs in —10% of cirholtic patients.

- **Types:**
  - **Diuretic-intractable ascites**
    - Therapeutic doses of diuretics cannot be achieved because of *diuretic-induced complications*.
  - **Diuretic-resistant ascites**
    - *No response to maximal diuretic therapy* (400 mg spironolactone + 160 mg furosemide/day).

- **How to manage**
  - **LVP + Albumin**
  - **TIPS**
  - **PVS** (in non-TIPS, non-transplant candidates)

LVP: Large volume Paracentesis.
PVS: Peritoneovenous shunt.
Summary

### TTT of Ascites:

- Portal HTN with no Ascites
- Uncomplicated ascites
- Refractory Ascites

**Complications**

<table>
<thead>
<tr>
<th>A- Hepatorenal Syndrome</th>
<th>B- Spontaneous bacterial peritonitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal failure in patients with cirrhosis, advanced liver failure and severe sinusoidal portal hypertension.</td>
<td>Clinical features may be absent and TLC in blood normal.</td>
</tr>
<tr>
<td>Absence of significant histological changes in the kidney (<em>&quot;Functional&quot; renal failure</em>)</td>
<td>o Ascetic proteins usually&lt;1gr/dl</td>
</tr>
<tr>
<td>Marked arteriolar vasodilation in the extra-renal circulation.</td>
<td>o Local defense mechanism→more risk of SBP</td>
</tr>
<tr>
<td>Marked renal vasoconstriction leading to reduced glomerular filtration rate.</td>
<td>o Usually monomicrobial Gram —Ve</td>
</tr>
<tr>
<td>Marked arteriolar vasodilation in the extra-renal circulation.</td>
<td>o Antibiotics if ascites&gt;250 polymorphs</td>
</tr>
<tr>
<td>Marked renal vasoconstriction leading to reduced glomerular filtration rate.</td>
<td>o 50% die.</td>
</tr>
<tr>
<td>o Absence of significant histological changes in the kidney (<em>&quot;Functional&quot; renal failure</em>)</td>
<td>o 69% recur in 1 year.</td>
</tr>
<tr>
<td>o Marked arteriolar vasodilation in the extra-renal circulation.</td>
<td></td>
</tr>
<tr>
<td>o Marked renal vasoconstriction leading to reduced glomerular filtration rate.</td>
<td></td>
</tr>
</tbody>
</table>

**Management of Hepatorenal Syndrome**

- Proven efficacy
- Liver transplantation
- Under investigation
  - Vasoconstrictor + albumin {to flush kidney}
  - Transjugular intrahepatic portosystemic shunt (TIPS)
  - Vasoconstrictor + TIPS
  - Extracorporeal albumin dialysis (ECAD)
- Ineffective
  - Renal vasodilators (prostaglandin, dopamine)
  - Hemodialysis

**Notes:**

- Indications for Prophylactic Antibiotics to Prevent Spontaneous Bacterial Peritonitis:
  - 1) Cirrhotic patients hospitalized with GI hemorrhage (short-term) → Norfloxacin 400 mg p.o. BID x 7 days
  - 2) Patients who have recovered from SBP (long-term) → Norfloxacin 400 mg p.o. daily, indefinitely=longterm.
  - Weekly quinolones not recommended (lower efficacy, development of quinolones resistance)
  - 3) Patients who have ascitic albumen less than 1 gm/dl. (long-term) → Norfloxacin 400 mg p.o. daily, indefinitely=longterm

**Q.** What is the features of the best antibiotics in SBP?

1) **Broad spectrum** with high potency against Gm-ve.
2) **Hydrophilic** "to be secreted in peritoneal cavity"
3) **Not affect or damage the kidney**

**N.B:** For prophylaxis, we want to use oral not injection form, SO: **NOT USE 3rd generation cephalosporin BUT USE Oral Quinolone** "has long t1/2"

**Q.** What is preferred daily or 2/weeks regimen?

→ **Daily regimen.**

**CASE:** Pt. with ascites on diuretics his Scr baseline is 1.2mg/dl. Later on, the Scr becomes 1.7 mg/dl. → That's means that the case is deteriorating due to severe hyponatremia→ So increased risk of SBP & risk of developing Hepatorenal syndrome.

**SO BEST SOLUTION IS PREVENTION.**

**Q. What is the difference between peritonitis and SBP?**

→ **No pain:** due to 1) Very diluted cytokines in fluids. 2) Huge amount of fluids between the 2 layers of peritoneum → No Shearing → No pain.

**NO Fever:: Because the pt. is Immunocompromised.**
HEPATIC ENCEPHALOPATHY

Hepatic Encephalopathy Nomenclature

- **Type A**: Associated with Acute liver failure
- **Type B**: Associated with porto-systemic Bypass without intrinsic hepatocellular disease
- **Type C**: Associated with **Cirrhosis** “liver cell failure, so can’t detoxify nitrogenous cpd.” and **porto-systemic shunting** “shunting of nitrogenous cpd. into brain directly”.
  - **Type C** is the Encephalopathy of Cirrhosis
    - Neuropsychiatric complication of cirrhosis
    - Results from spontaneous or surgical radiological portal-systemic shunt + chronic liver failure
    - Failure to metabolize neurotoxic substances
    - Alterations of astrocyte morphology and function (Alzheimer type II astrocytosis)

PATHOGENESIS

- Failure to metabolize NH3
- Bacterial action
- Protein load
- GABA-BD receptors
- NH3 Shunting
- Toxins

STAGES OF HEPATIC ENCEPHALOPATHY

1. Confusion
2. Drowsiness
3. Somnolence “sleep disturbance”
4. Coma

MINIMAL HEPATIC ENCEPHALOPATHY

- Occurs in 30-70% of cirrhotic patients without overt hepatic encephalopathy
- Detected by psychometric and neuro-psychological testing
- Patient has **only delayed response** → So driving is prohibited.
- Not have the severe classical form “NO previous 4 stages”.
  - **May improve with lactulose or synbiotics (probiotics and fermentable fiber)**

TREATMENT

- **Identify and treat precipitating factor**
  - Infection
  - GI hemorrhage
  - Pre renal azotemia
  - Sedatives
  - Electrolyte dist. (diuretics, diarrhea, vomiting).
  - High protein diet.
  - Constipation “increase protein & bacterial contact.”

- **Lactulose** (adjust to 2-3 bowel movements/day to avoid diarrhea)
- **Protein restriction <40 g. short-term (if at all)** (N.B: Not complete restriction → increase muscles breakdown → more & more increase in nitrogenous byproduct.
- **TIPS**
  - **Local antibiotics**: (neomycin, Rifaximin or metronidazole)
  - **Flumazenil** “BDZ antidote” → in case of sedation

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Actions of lactulose

1. Increase ammonia fixation in liver:
   - Ornithine aspartate
   - Benzoate
   **N.B:** Ornithine & Benzoate not used if Scr >2.5 mg/dl

2. Decrease ammonia production in gut:
   - Antibiotics
   - Adjustment in dietary protein
   - Urease-producing bacteria
   - Increase cathartic effect

3. Shunt occlusion or reduction

**CHILD PUGH SCORE**

Each measure is scored 1-3, with 3 indicating most severe derangement.

<table>
<thead>
<tr>
<th>Measure</th>
<th>1 point</th>
<th>2 points</th>
<th>3 points</th>
<th>units</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilirubin total</td>
<td>&lt;2</td>
<td>2-3</td>
<td>&gt;3</td>
<td>mg/dl</td>
</tr>
<tr>
<td>Serum albumin</td>
<td>&gt;35</td>
<td>28-35</td>
<td>&lt;28</td>
<td>g/l</td>
</tr>
<tr>
<td>INR</td>
<td>&lt;1.7</td>
<td>1.71-2.20</td>
<td>&gt;2.2</td>
<td>No unit</td>
</tr>
<tr>
<td>Ascites</td>
<td>None</td>
<td>mild</td>
<td>Severe</td>
<td>No unit</td>
</tr>
<tr>
<td>Hepatic encephalopathy</td>
<td>none</td>
<td>Grade I- II ( or suppressed by medication )</td>
<td>Grade III- IV ( or refractory )</td>
<td>No unit</td>
</tr>
</tbody>
</table>

**Interpretation**

<table>
<thead>
<tr>
<th>Points</th>
<th>class</th>
<th>1 year survival</th>
<th>2 year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-6</td>
<td>A</td>
<td>100%</td>
<td>85%</td>
</tr>
<tr>
<td>7-9</td>
<td>B</td>
<td>81%</td>
<td>57%</td>
</tr>
<tr>
<td>10-15</td>
<td>C</td>
<td>45%</td>
<td>35%</td>
</tr>
</tbody>
</table>

**LIVER TRANSPLANTATION**

- Organ transplantation may be **living related** OR orthotopic (cadaveric).
- In Egypt all organs donated must be from **living related donors**.
- **The most common indications are decompensated liver cirrhosis post HCV (more than 90%), HBV or inherited liver disorders.**
- **Hepatitis C has high recurrence rate after liver transplantation.**
- Cadaveric: means brain dead but beating heart.

**CASE:** Hepatitis C patient develop decompensated cirrhotic patient, if listed in liver transplantation → **GIVE Anti HCV antiviral** drugs before transplantation to make patient is 30 days free of virus → **so decrease incidence of recurrence**.

- **Post Transplant Medications needed:**
  - Tacrolimus
  - Cyclosporine
  - Mycophenolate Mofetil
  - Sirolimus
  - Prednisone.
  - Antifungal (Fluconazole).
  - Antivirals (Valgancyclovir and Acyclovir.).
  - Antibiotics (Trimethoprim/ sulfamethoxazole, dapsone, pentamidine).
  - Diuretics.
  - Antiulcer Medications.
  - Anti-Hypertensives (Nifedipine Metoprolol, Amlodipine).

- **N.B:** The donor liver a must not to have steatosis OR presence of viral infection OR microvascular invasion.
- **After using immunosuppressive** may be there opportunistic infection as CMV or fungal disease or **reactivation** of the viral infection.
- **CHECK:** DDI, Drug-food interaction & severe S.E as “DM, HT, electrolyte dist.” → **SO BALANCE DOSE**

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PANCREATITIS

Acute pancreatitis

- It is a necro-inflammatory disease of the pancreas.
- It is a chemical NOT BACTERIAL inflammation.
- CAUSES (Risk factors):
  o Obstruction of the common bile duct by stones (increasing duct pressure and subsequent unregulated activation of digestive enzymes).
  o Alcohol abuse, ethanol directly sensitizes acinar cells to cholecystokinin stimulation.
  o Pancreas divisum (congenital anatomical variant of the pancreatic duct).
  o Endoscopic retrograde cholangiopancreatography (ERCP).
  o Hyperparathyroidism, Hypertriglyceridemia.
  o Dysfunction of sphincter of Oddi is controversial.
  o Trauma.

- Clinical Picture:
  o In most individuals, acute pancreatitis is a mild self-limiting disorder, but in up to 20% of the cases there are severe clinical complications and mortality.
  o The main presentation is acute abdominal pain (before diagnosis not use Analgesic, but refer the patient to hospital, ant there if diagnosis occur ➔ USE Morphine as analgesic).
  o There is massive fluid sequestration in peritoneal cavity in severe acute pancreatitis.
  o Severe acute pancreatitis is an intensely catabolic state & leads to hypovolemic shock & sever hypocalcemia.

- Lab tests: Serum/urinary lipase & amylase enzymes to confirm the diagnosis.

- Management:
  o A Variety of prognostic factors and scoring systems have been proposed for accurate assessment of the severity of acute pancreatitis and reliable prediction of high risk and potentially fatal cases (Glasgow’s or Ranson’s or APACHE) score.
  o Management is typically straightforward: intravenous fluids, Ca replacement, intravenous or enteral feeding, morphine analgesia, and nothing by mouth.
  o However, treatment of severe cases can be quite complex, particularly if multiple organ systems are involved or if there are local complications.
  o Prophylactic use of antibiotics in sterile necrosis is controversial (of no benefit).

Chronic pancreatitis

- Alcoholic chronic pancreatitis is a complex disease normally thought to have an early stage that is associated with recurrent attacks of acute pancreatitis.
- There are loss of exocrine & endocrine function.
- Late stage is characterized by steatorrhea, diabetes, fibrotic scarring, and pancreatic calcification.
- Accompanied with DM (due to loss of endocrine function).
- May need digestive enzyme replacement. (due to loss of exocrine function).