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Reviewed by
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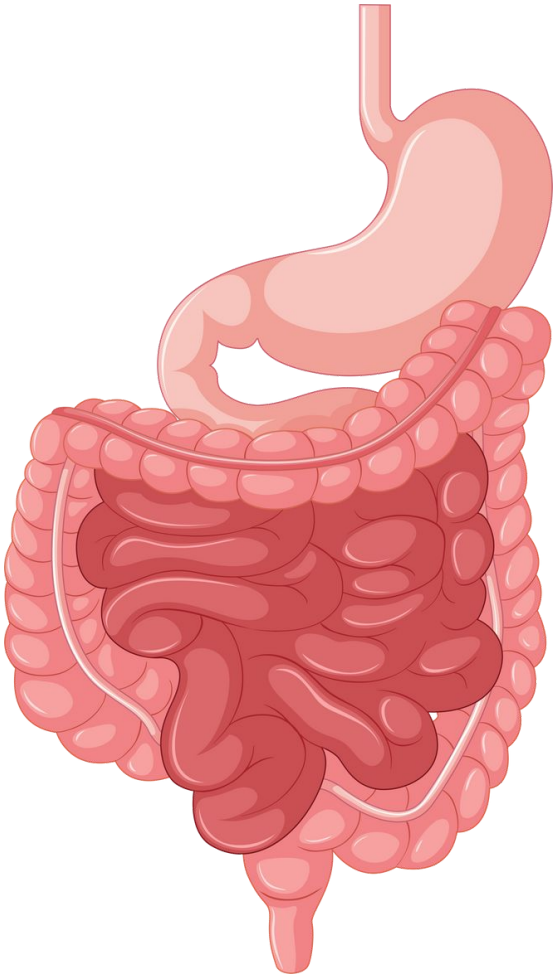
medicine 443

GNT443

Pathophysiology of Ascites



Editing File

Color index:

Main text (Black)

Female slides (Pink)

Male slides (Blue)

Important things (Red)

Dr's notes (Green)

Extra information (Grey)

OBJECTIVES

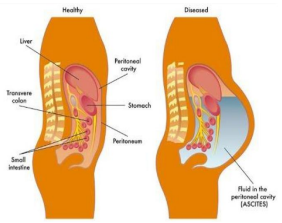
- To understand basic pathophysiologic steps in the development of ascites secondary to cirrhosis.
- To correlate the anatomic and pathophysiologic changes with clinical manifestations.
- To understand the general concepts in evaluation and management of patients with ascites.

Ascites in Cirrhosis

Ascites

1- The pathologic **accumulation of fluid in the peritoneal cavity.**
2- It is the most commonly complication of cirrhosis.
Ascite:

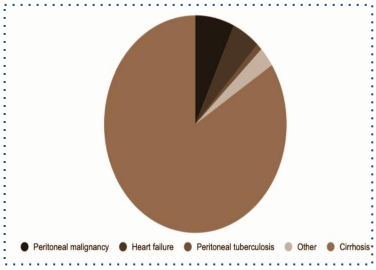
- Cirrhosis 85%
- Other causes 15%

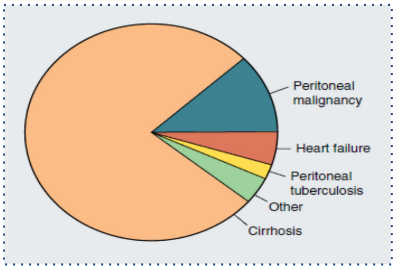


Causes of Ascites

Ranked from highest to lowest

1. Cirrhosis
2. Peritoneal malignancy
3. Heart failure
4. Other
5. Peritoneal tuberculosis

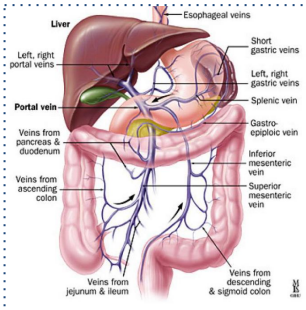


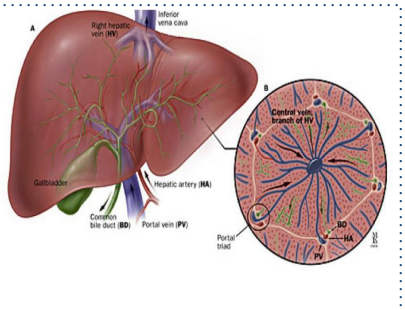


Anatomy of portal system:

Anatomical correlation:

1. Liver has dual blood supply mainly from the portal vein.
2. Most disruptions of the portal blood flow results in portal hypertension (keystep of developing ascites).





https://www.hopkinsmedicine.org/gastroenterology_hepatology/_pdfs/liver/alcoholic_liver_disease.pdf

Pathogenesis

1. The formation of ascites is governed by the **same** principles as **edema** formation at other sites: net **capillary permeability** and the **hydraulic** and oncotic pressure gradients.
2. First step is the development of portal hypertension (Portal hypertension → Ascites).
3. Ascites is the final consequence of a series of anatomic, pathophysiologic, and biochemical abnormalities occurring in patients with cirrhosis.

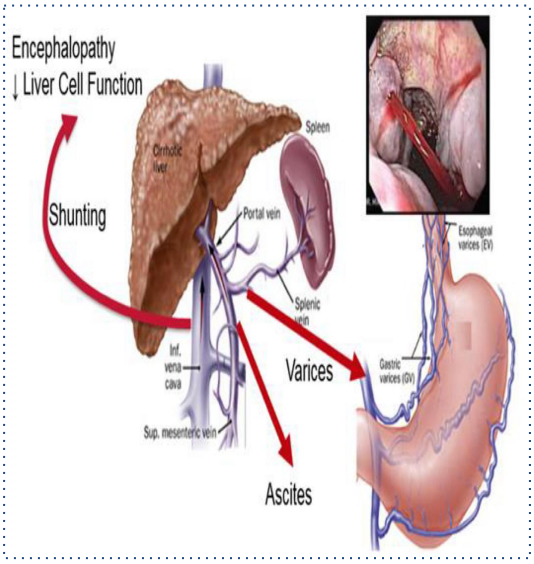
2 Ascites in Cirrhosis

Portal Hypertension

The development of portal hypertension is the **first** major step toward fluid retention in the setting of **cirrhosis.**

Patients with cirrhosis but **without portal hypertension do not** develop **ascites** or edema.

A portal pressure **above 12 mmHg** appears to be required for fluid retention. (not imp)



Macroscopic & Microscopic Anatomy Of The Liver Demonstrating Blood Flow & Level Of Obstruction (Flow Impairment)

01 Pre-hepatic

(e.g.. Portal vein thrombosis, Congenital venous abnormalities)

02 Hepatic (Pre-sinusoidal)

(e.g Hepatoportal sclerosis, Schistosomiasis, Granulomatous disease)

03 Hepatic (Sinusoidal)

(cirrhosis and many liver disease)

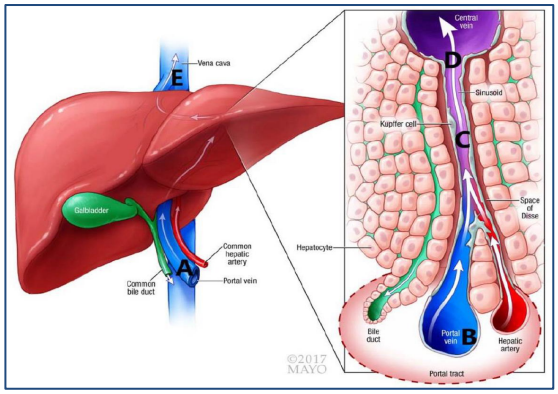
04 Hepatic (Post-sinusoidal)

(cirrhosis and many liver disease)

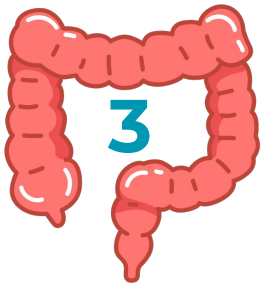
05 Post-hepatic

(e.g Budd-Chiari syndrome, Cardiac failure)

Budd-Chiari syndrome it is thrombosis of hepatic veins



Videos to help understanding

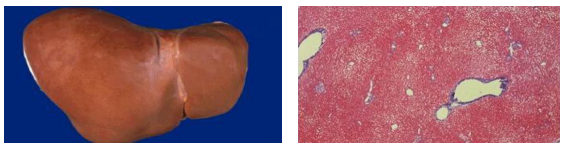


Cirrhosis

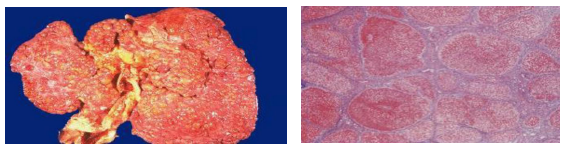
Cirrhosis

Late stage of chronic liver inflammation and fibrosis, in which liver **parenchyma is distorted** and **replaced by fibrous** tissue and **regenerating nodules**.

Normal Liver



Cirrhotic Liver



Mechanism of Portal Hypertension In Cirrhosis

How portal hypertension develops? by Increased sinusoidal resistance

- **Structural (Mechanical, fixed)** — due to **structural changes** & **distortion** of the liver **microcirculation** (sinusoidal fibrosis, regenerative nodules)
- **Functional (Dynamic changes)** — due to **contraction** of activated hepatic **stellate cells** & **myofibroblasts** that surround hepatic sinusoids. Also they are found in the **fibrous septa** and **vascular smooth muscle** cells of the hepatic vasculature.

The **dynamic changes** due to **intrahepatic**:

1) Increased production of vasoconstrictors (eg, endothelins, angiotensin-II, norepinephrine, thromboxane A2

2)Reduced release of endothelial vasodilators (eg, nitric oxide)

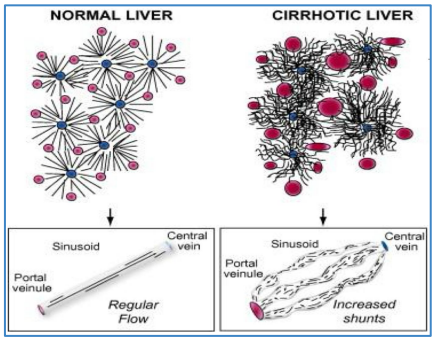
Dr said: Don't memorize names of vasoconstrictors & dilators Know that the portal hypertension is due to an imbalance of these factors (increased vasoconstrictors).

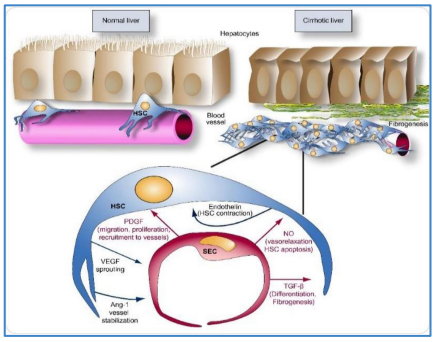
4 Liver Microcirculation in Portal Hypertension

In normal physiologic conditions:
Hepatic stellate cells (HSC) contractility and coverage of sinusoids is sparse.

In cirrhosis:

- Increased numbers of HSC with increased cellular projections, fibrogenesis wrap more effectively around sinusoids.
- Other vascular changes (such as loss of pore and capillarization, microthrombi, etc..) → thereby lead to a high-resistance.





More details of change

Liver Sinusoidal Endothelial Cells (LSECs):

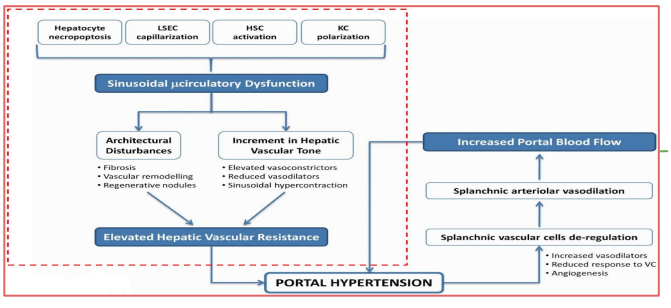
Loss of liver sinusoidal endothelial cells' (LSEC) healthy phenotype (a process known as "capillarization") → Loss pores

Hepatic Stellate Cells (HSCs):

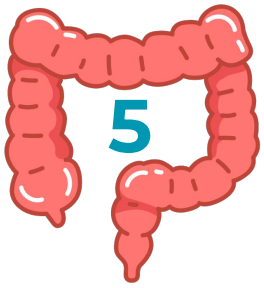
Transdifferentiation of hepatic stellate cells (HSC) toward a myofibroblastic-like cell (termed "activated HSC" with proliferative and hypercontractile properties) is accompanied by marked continuous extracellular matrix deposition.

Kupffer Cells (KCs):

They are the liver macrophages.
KCs frequently induce excessive inflammatory responses, thus leading to damage and negative consequences on the liver, by producing harmful soluble mediators as well as antigen presenting cells during viral infections of the liver.



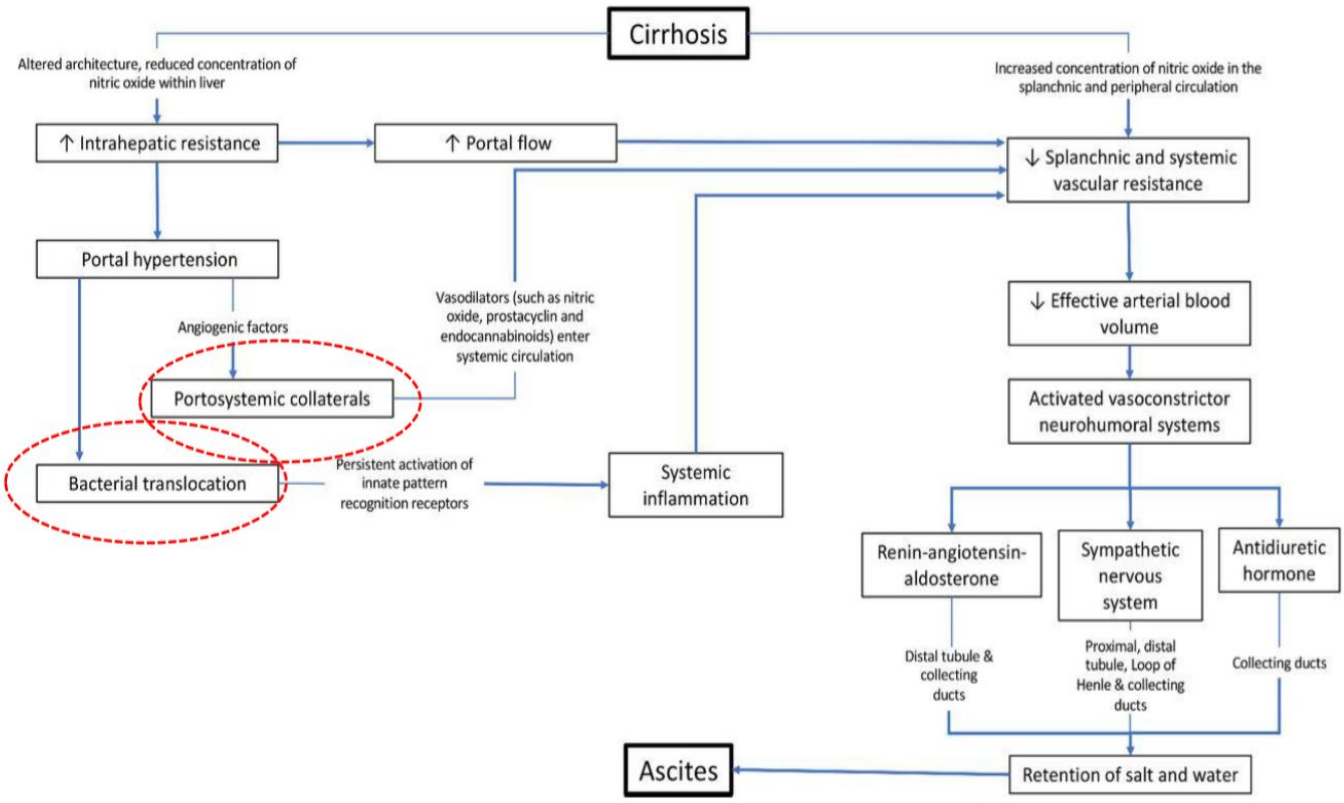
Mind map from doctor's slides



The Pathogenesis of ascites in cirrhosis

We advise you to watch this video before reading this slide, watch from beginning to 3:18

The pathogenesis of ascites in cirrhosis.



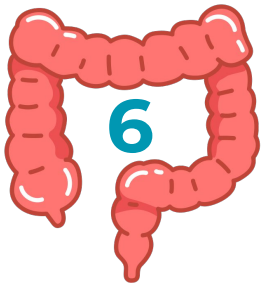
1. Portal pressure against high resistance vessels → portosystemic shunt via collaterals.

2. Collaterals are intended for better blood flow, but since they carry blood before it's detoxification the toxins will instead be harm the tissues.

3. Toxins & bacteria (due to intestinal disturbances) induce vasodilators release (eg. Nitric oxide NO).
-NO first affects splanchnic circulation followed by systemic vasodilation (high NO in systemic & splanchnic circulation VS low NO in hepatic microcirculation).

4. Dilatation of systemic vessels result in decreased effective arterial blood volume.

5. Activation of compensatory mechanisms to retain normal vascular tone.
(Eg. RAAS, Sympathetic NS increase BV tone, ADH hormone retain more water)



Vasodilation (splanchnic & systemic)

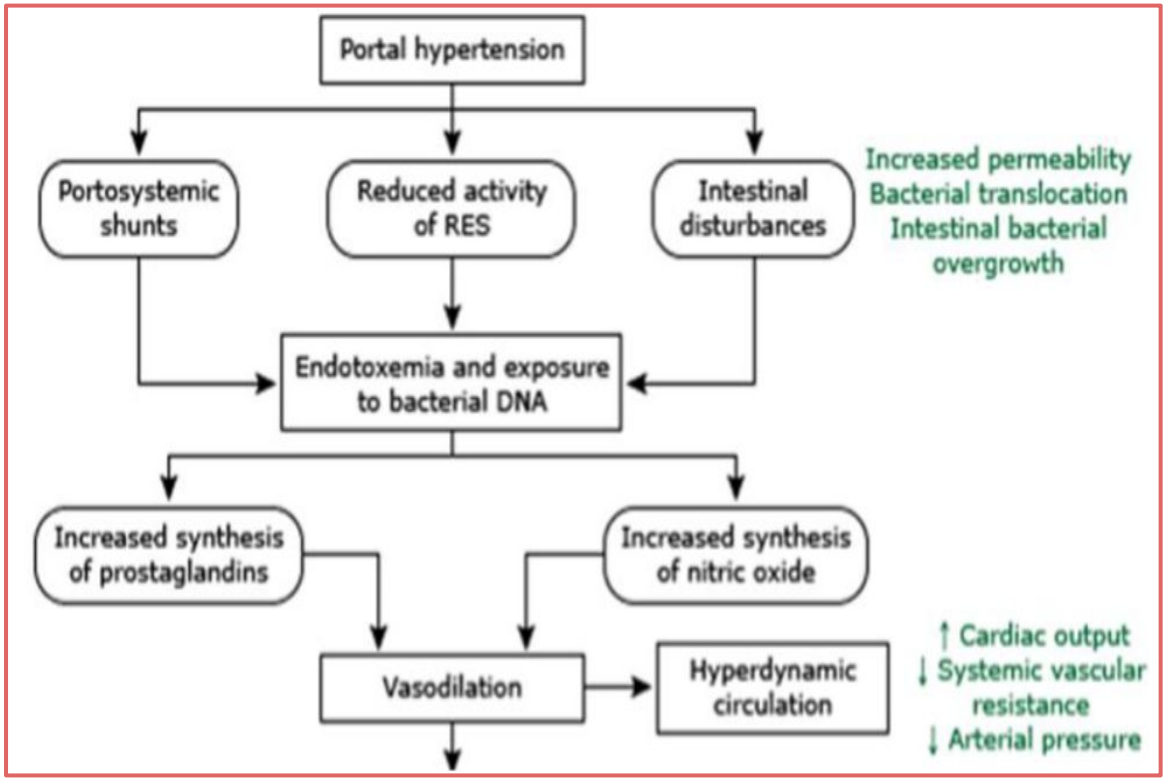
Mechanism of vasodilation (VD)

▪VD initially in the splanchnic circulation, later in systemic circulation:

1-Increase production of nitric oxide (NO), which is the primary mediator of VD in cirrhosis (for splanchnic and peripheral vasodilation).

2-Increased levels of circulating other VDs. (Glucagon , vasoactive intestinal peptide(VIP), prostacyclin. (Why?)

▪Production of these VDs may be stimulated by endotoxins or other bacterial products

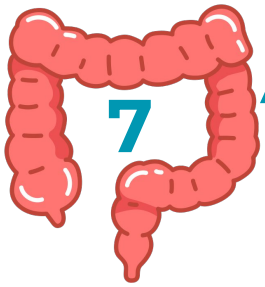


1. (Portosystemic shunt) without detoxification of the contents in the liver. (reduced activity of RES)

2. (Intestinal disturbances) affected tight junctions, resulting in translocation of bacteria & toxins to the circulation "spontaneous bacterial peritonitis"

Consequences of vasodilation

1. Activation of endogenous vasoconstrictors (compensatory)
2. Sodium and water retention
3. Increase renal vasoconstriction



Activation of endogenous vasoconstrictor agents

1. Vasodilation
2. The **reduction in pressure** (stretch) at the carotid and renal baroreceptors
3. Activation of the sodium-retaining neurohumoral mechanisms by:
   - Renin-angiotensin-aldosterone system (RAAS).
     to conserve more salts
   - Sympathetic nervous system (SNS).
     Affecting vascular tone and renal tubules
   - Antidiuretic hormone - vasopressin (ADH). Water retention

Aim

Attempt to restore perfusion pressure to normal.

- The secretion of these **"hypovolemic"** hormones is **proportional** to the severity of the **hemodynamic insufficiency.**
- So with progression of portal hypertension → The net effect is avid sodium & water retention. (Avid=متعطش)

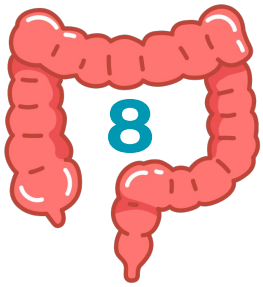
Sodium & water retention

- **(Impaired sodium excretion)** In patients with cirrhosis & ascites, the normal regulation of **sodium balance is lost.**
- **(Increase ADH → impaired water excretion)** Initially water excretion is normal in patients with cirrhosis before the development of ascites and then becomes increasingly impaired as the liver disease progresses.
- Thus, patients with cirrhosis and ascites usually demonstrate **urinary sodium retention, increased total body sodium,** and **dilutional hyponatremia.**

Compensatory mechanisms will cause Na & water retention:

1- High net Na → Disproportionate water retention will cause relative dilutional hyponatremia.
(لكن كمية الصوديوم أعلى من الطبيعي)

2- High Na retention → increased net body sodium → induces water retention → disproportionate (too much water) → dilutional hyponatremia.



Renal vasoconstriction

Renal vasoconstriction

- VC → renal hypoperfusion → decrease GFR (Glomerular filtration rate).
- Renal perfusion may initially be maintained due to vasodilators such as prostaglandins and perhaps nitric oxide (local).
- However, progression renal hypoperfusion can lead to gradual decline in the glomerular filtration rate, and in some patients, the **hepatorenal syndrome.**

Finally

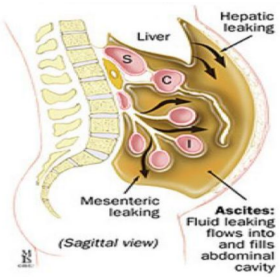
This excess **retained blood** volume is thought to **leak-out** (filtered, extravasate) directly from both the **liver surface & mesenteric vessels.**

Due to:

– Increased hydrostatics pressure.

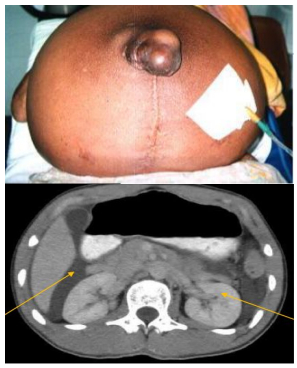
– Increase vascular wall permeability.

– Concurrently decreased oncotic (osmotic) pressure (hypoalbuminemia).



Evaluation of patients with ascites

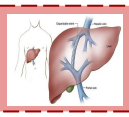
1) History: symptoms of chronic liver disease, abdominal distention.
2) Examination: Flank fullness, shifting dullness or fluid thrill.
3) Imaging: Ultrasound.
4) Ascitic fluid analysis.



- Any new ascites should be tapped and analyzed.

Subcutaneous & muscle fluid aspiration called Paracentesis.

Management



- Low salt diet
- Diuretics (such furosemide, spironolactone, etc)

These 2 usually work for more than 90% of the patients, yet the underlying cause should still be managed

If resistance:

- Frequent tapping (paracentesis)
- Shunt such as Transjugular intrahepatic portosystemic shunt (TIPS or TIPSS)
- Liver transplantation

Summary

From Dr's slides

- Ascites is the most common liver cirrhosis complication. (Not all cirrhosis lead to ascites)
- Development of ascites indicates advanced stage of liver disease and poorer prognosis.
- Development of ascites is complex process.
- Pathophysiology is mostly explained by portal (sinusoidal) hypertension and sodium retention due to vasodilation and consequent activation of sodium retaining systems.

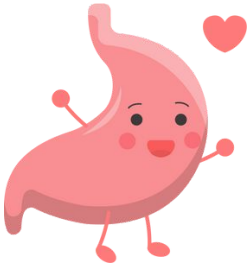
Explained:

1) Portal hypertension is first step in ascites development in patient with cirrhosis.
2) Possible bacterial toxin trigger VDs.
3) VD with activation of secondary mechanisms:
   - renin-angiotensin-aldosterone system.
   - sympathetic nervous system.
   - antidiuretic hormone (vasopressin).

Leads to salt and water retention and Increase plasma volume.

All these with **hypoalbuminemia** and increase vascular permeability lead to fluid extravasation.

Click the icon for important notes from doctor



MCQ

Q1

Which of the following is the fundamental treatment for ascites that must be followed even when other treatments are also utilized?

- A-Antibiotic.
- B- Diuretics.
- C- Low-sodium diet.
- D- Removal of ascitic fluid.

Q2

Which one of the following is a cause for post hepatic cirrhosis Hypertension?

- A- Portal vein thrombosis.
- B- DVT.
- C- Restrictive pericarditis.
- D- Hypotension.

Q3

What is the pathophysiology of ascites secondary to liver cirrhosis?

- A- Increased Na retention due to ADH.
- B- Renal vasodilation.
- C- Vasoconstriction due to NO.
- D- Increased total body Na with dilutional hyponatremia.

1-C 2-C 3-D

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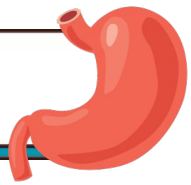

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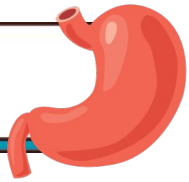

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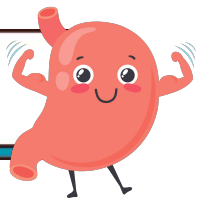

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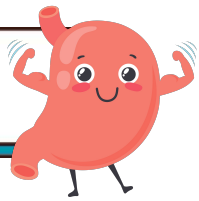

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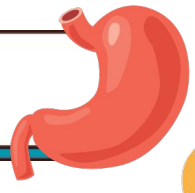

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