Pathophysiology of Ascites in Cirrhosis

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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 basic steps in evaluation of patients with ascites

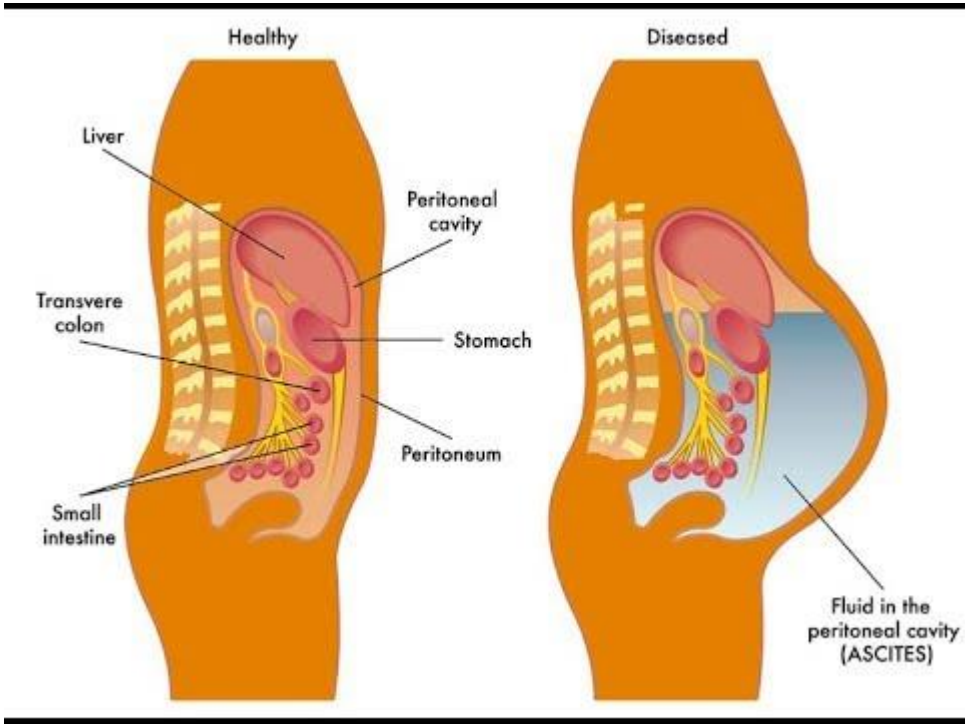
Definition of ascites

The pathologic accumulation of fluid in the peritoneal cavity

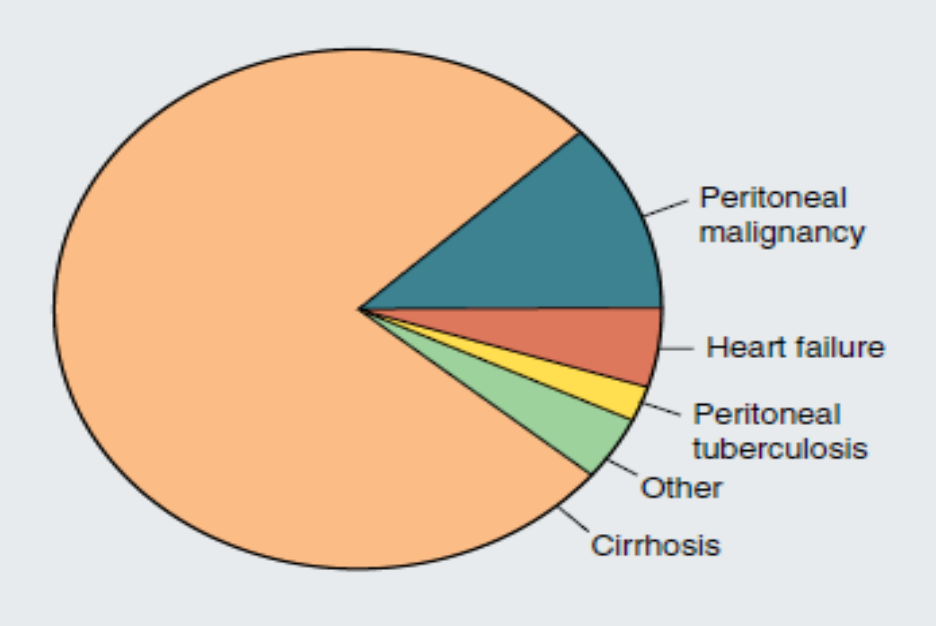
- It is the most common complication of cirrhosis

Ascites:

- Cirrhosis 85%
- Other causes 15 %



Causes of ascites



Sherlock's Diseases of the Liver and Biliary System

Pathogenesis

-Ascites is the final consequence of a series of anatomic, pathophysiologic, and biochemical abnormalities occurring in patients with cirrhosis.

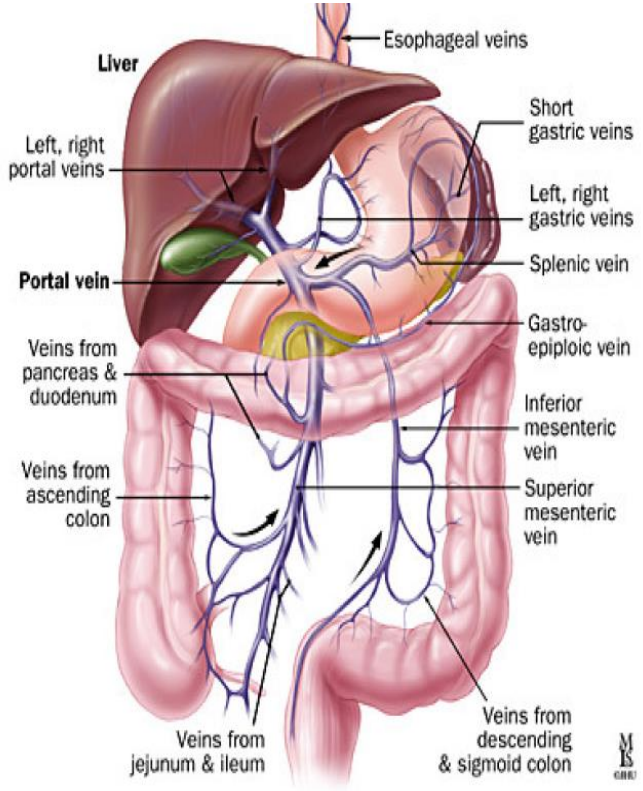
-The formation of ascites is governed by the same principles as edema formation at other sites: net capillary permeability and the hydraulic and oncotic pressure gradients

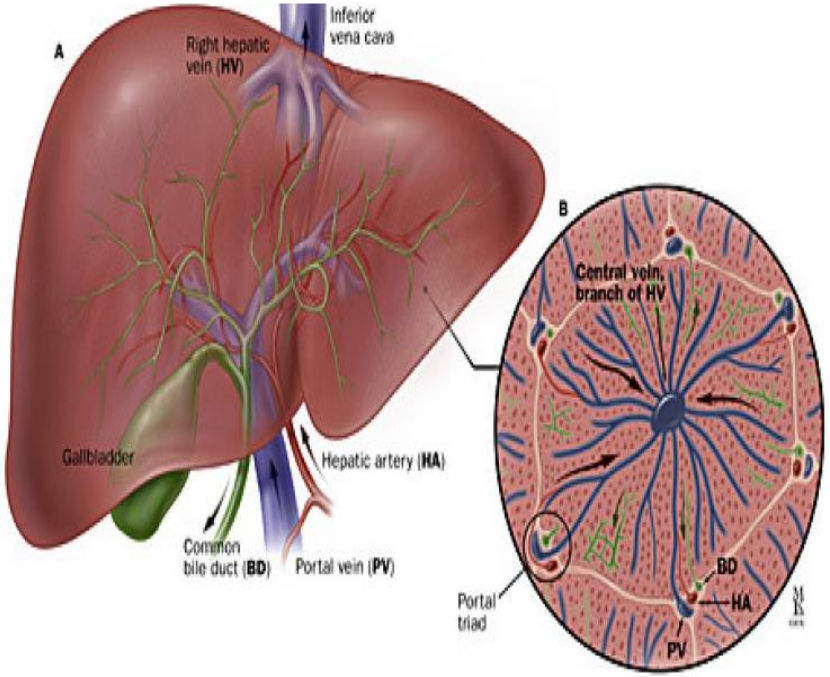
First step is the development of portal hypertension

-Portal hypertension  Ascites

Let's understand portal hypertension

Anatomy of portal system

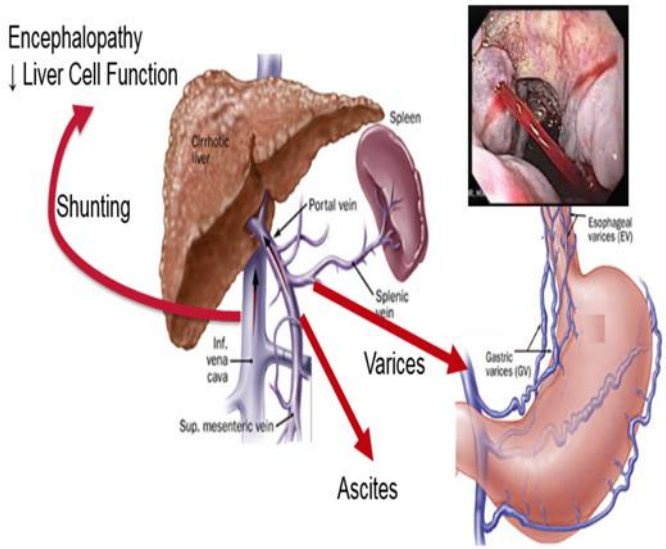




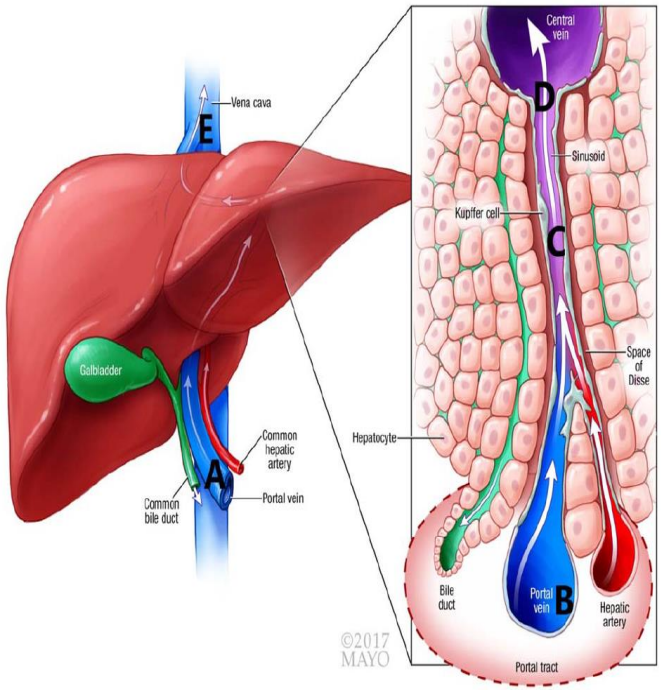
https://www.hopkinsmedicine.org/gastroenterology_hepatology/_pdfs/liver/alcoholic_liver_disease.pdf

PORTAL HYPERTENSION

- The development of portal hypertension is the first step toward fluid retention in the setting of cirrhosis.
- Patients with cirrhosis but without PHT do not develop ascites or edema
- A portal pressure >12 mmHg appears to be required for fluid retention



Macroscopic And Microscopic Anatomy Of The Liver Demonstrating Blood Flow And Level Of Obstruction/Flow Impairment



A Pre-hepatic (e.g Portal vein thrombosis, Congenital venous abnormalities)

B Hepatic (Pre-sinusoidal) (e.g Hepatoportal sclerosis, Schistosomiasis, Granulomatous disease)

C Hepatic (sinusoidal)

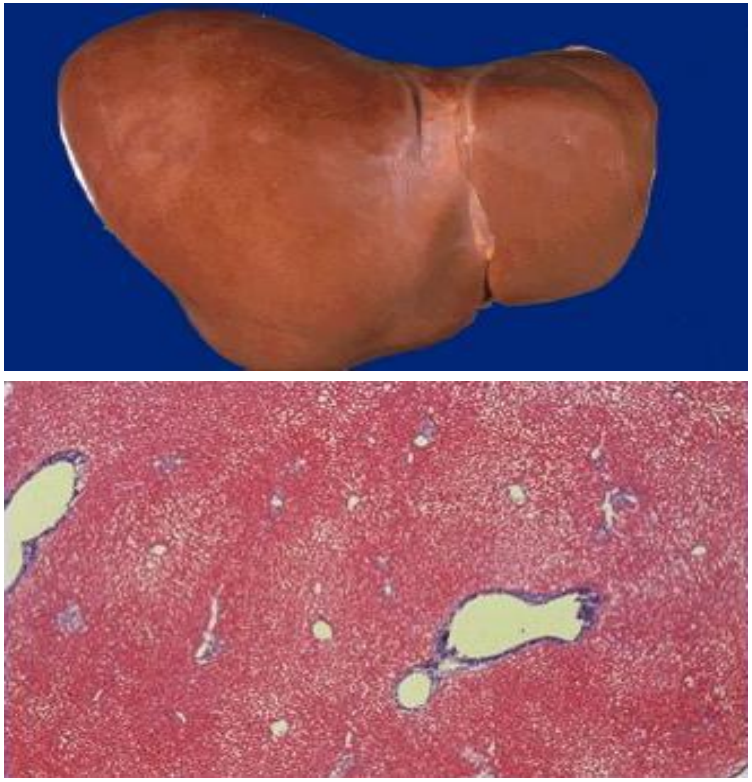
D Hepatic (Post-sinusoidal)

(for C,D e.g cirrhosis and many liver disease)

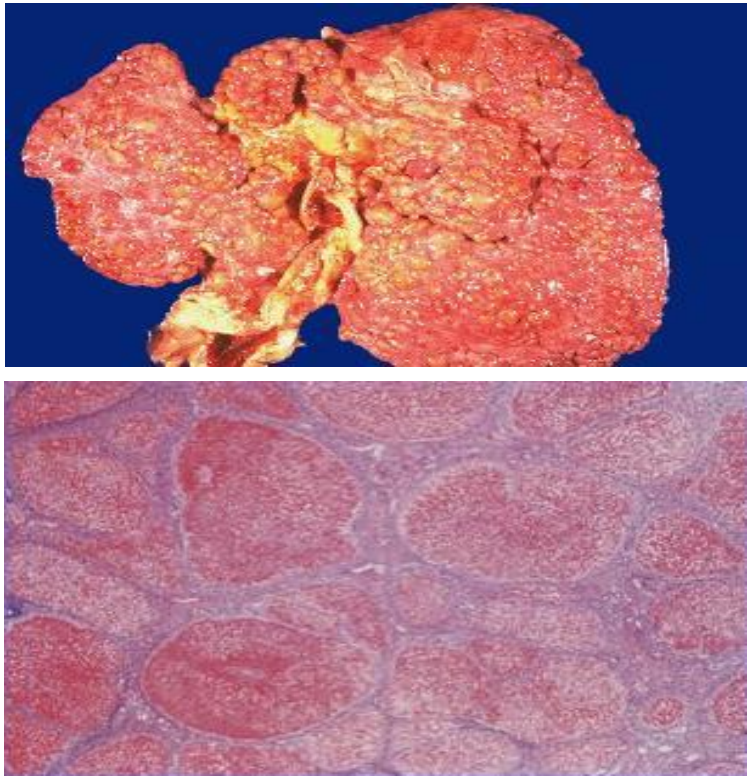
E Post-hepatic (e.g Budd-Chiari syndrome, Cardiac failure)

https://aasldpubs.onlinelibrary.wiley.com/doi/pdf/10.1002/cld.655

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?

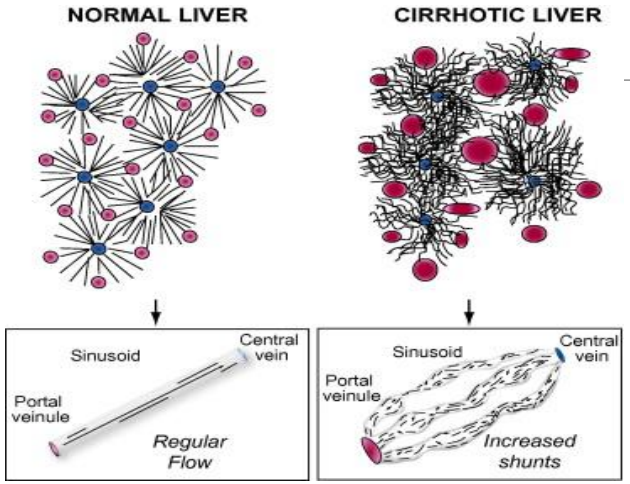
1. **Structural (Mechanical, fixed):** due to structural changes and distortion of the liver microcirculation (sinusoidal fibrosis, regenerative nodules)
2. **Functional (dynamic changes):** due to contraction of activated hepatic stellate cells and myofibroblasts that surround hepatic sinusoids and are in the fibrous septa and vascular smooth muscle cells of the hepatic vasculature.

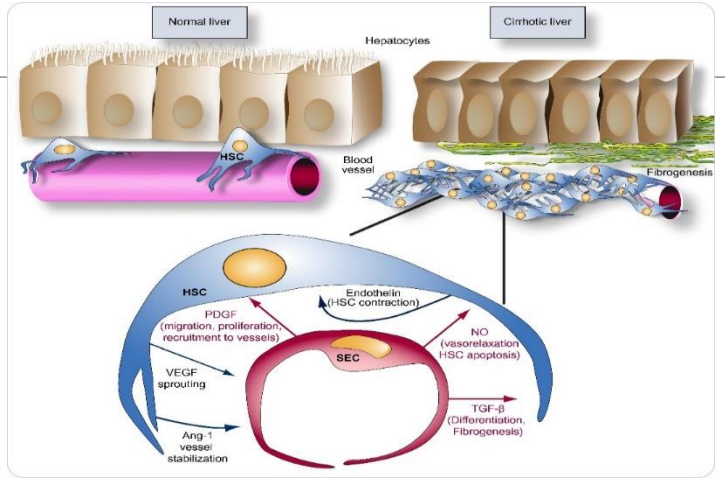
The dynamic changes due to **intrahepatic:**

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

b) Reduced release of endothelial vasodilators (eg, nitric oxide).

Liver microcirculation in portal hypertension





- **<u>In normal physiologic conditions</u>**, Hepatic stellate cells (HSC) contractility and coverage of sinusoids is sparse
- **<u>In cirrhosis</u>**,
  - 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 contributing to a high-resistance, constricted sinusoidal vessel.

https://www.sciencedirect.com/science/article/pii/S016882781000632X#f0010

Liver microcirculation in portal hypertension (more details of changes)

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

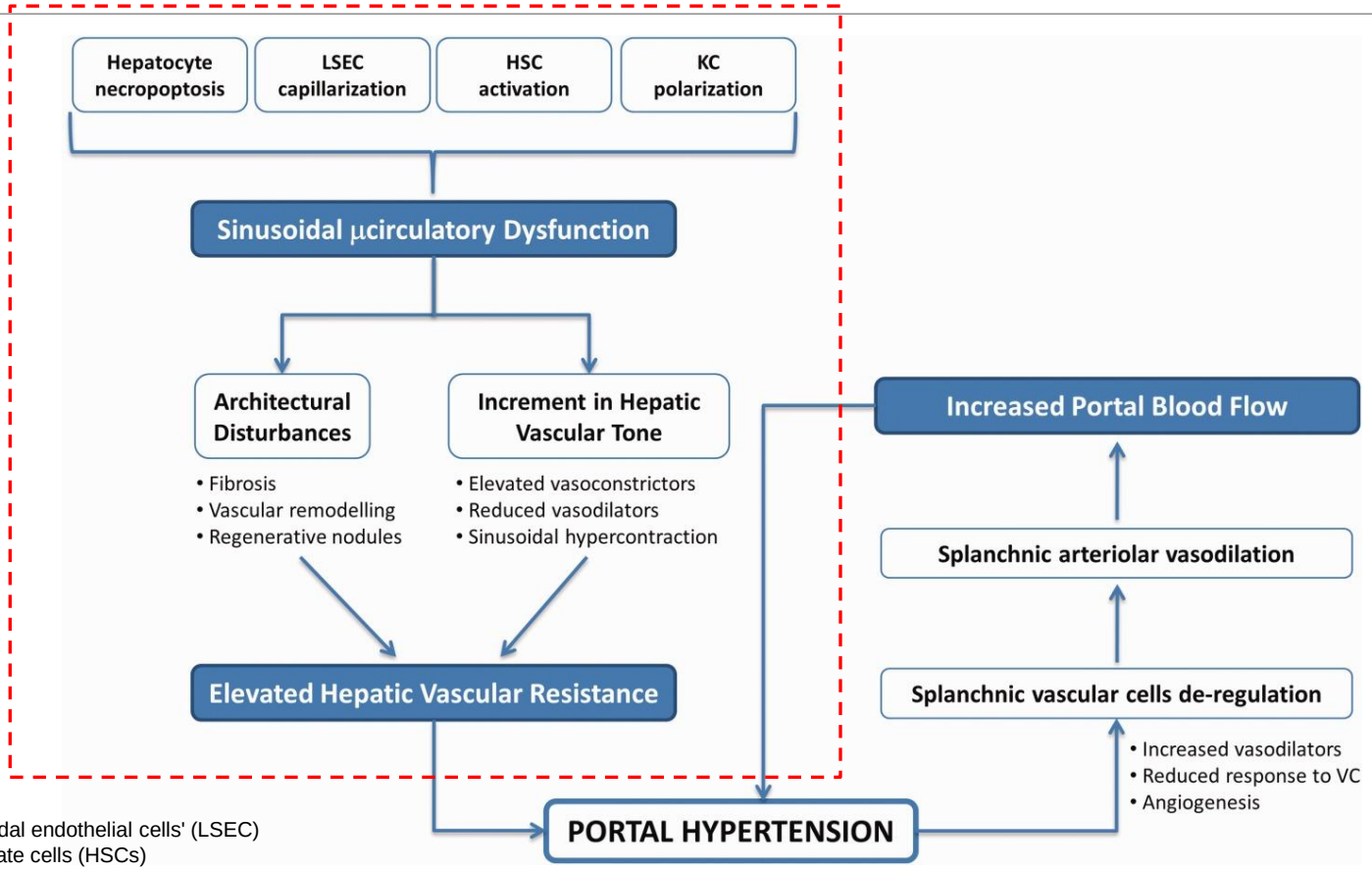
LSECs: Loss of liver sinusoidal endothelial cells' (LSEC) healthy phenotype (a process known as “capillarization”)>>Loss pores

Kupffer cells (KCs), 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

Liver sinusoidal endothelial cells' (LSEC)
Hepatic stellate cells (HSCs)
Kupffer cells (KCs)

Liver microcirculation in portal hypertension



Liver sinusoidal endothelial cells' (LSEC)
Hepatic stellate cells (HSCs)
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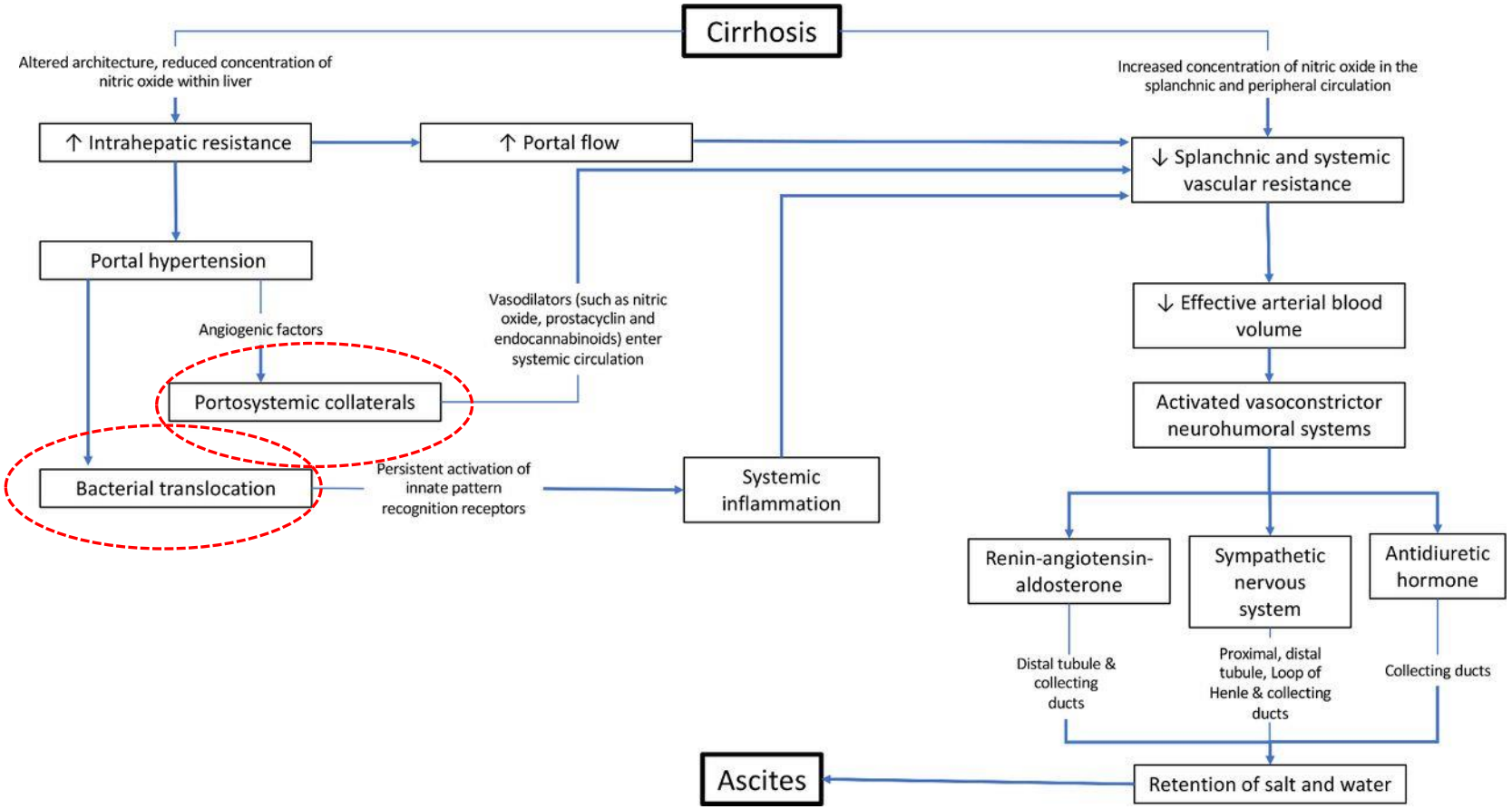
Clinical Liver Disease, Volume: 8, Issue: 6, Pages: 160-166, First published: 30 December 2016, DOI: (10.1002/cld.604)

The pathogenesis of ascites in cirrhosis.



Guruprasad P Aithal et al. Gut 2021;70:9-29

Vasodilation(VD) *(splanchnic and systemic)*

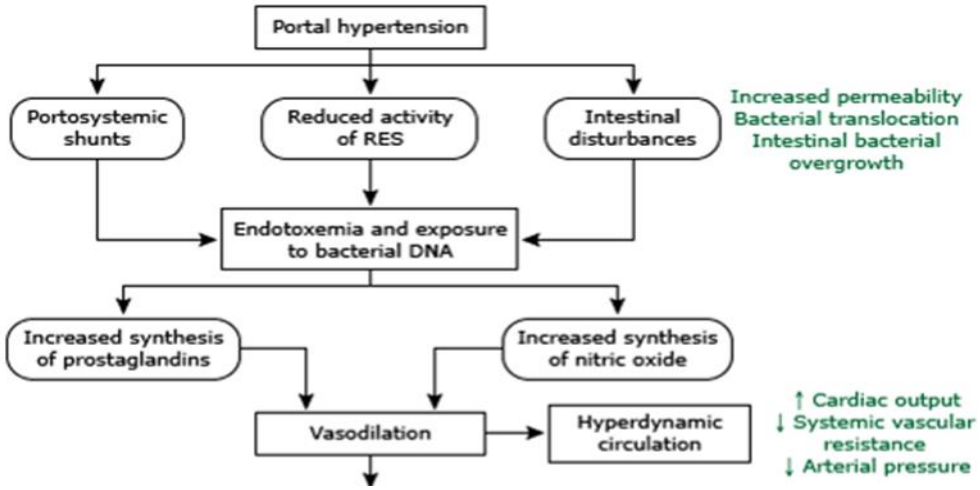
- VD initially in the splanchnic circulation, later in systemic circulation

Mechanisms of vasodilation

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*



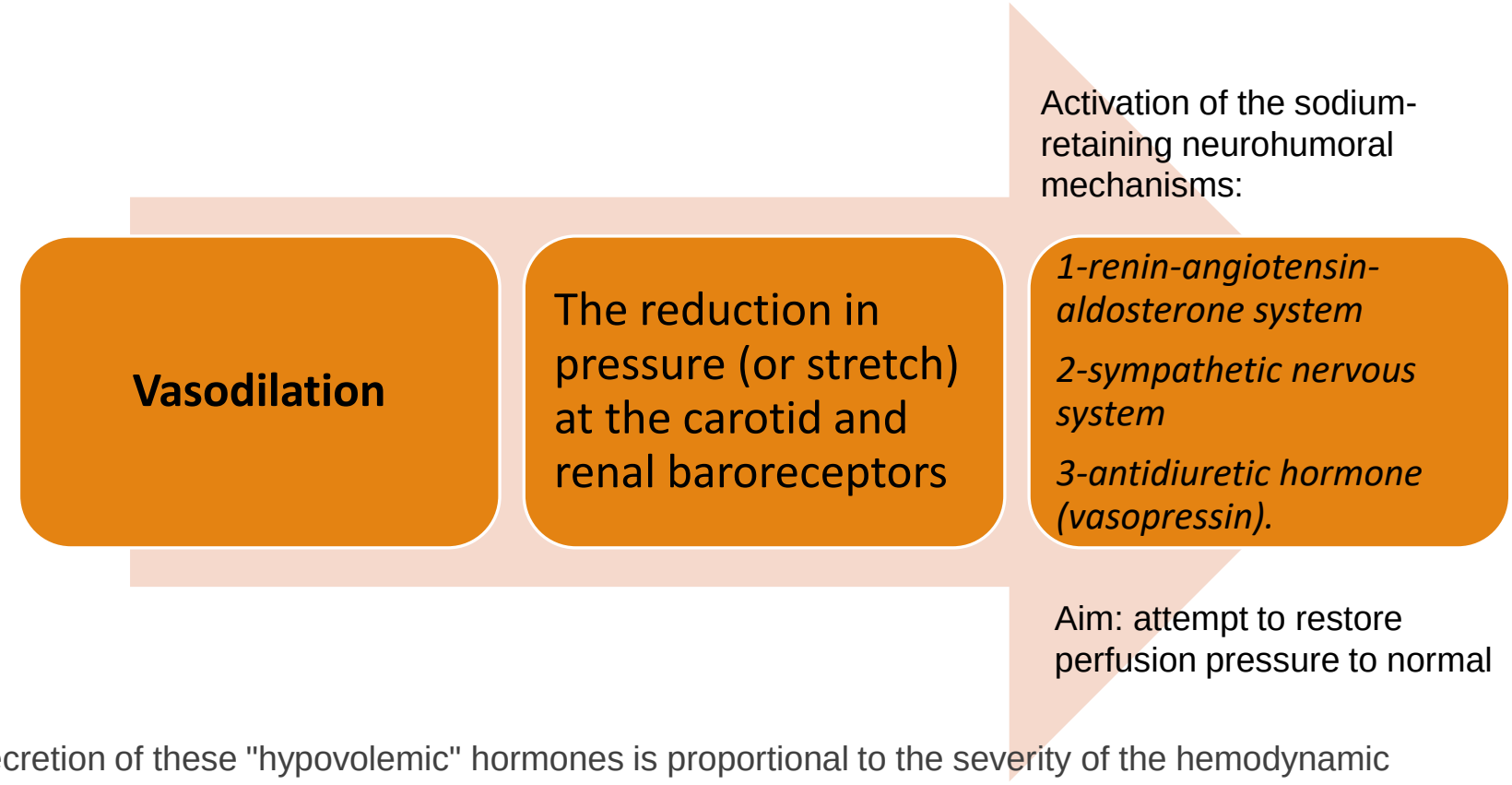
Consequences of vasodilation

1-Activation of endogenous vasoconstrictors(compensatory)

2-Sodium and water retention

3-Increase renal vasoconstriction

Activation of endogenous vasoconstrictor agents



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 and water retention

Sodium and water retention

- In patients with cirrhosis and ascites, the normal regulation of sodium balance is lost. (Impaired sodium 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. (impaired water excretion << Increase ADH)
- Thus, patients with cirrhosis and ascites usually demonstrate urinary sodium retention, increased total body sodium, and dilutional hyponatremia.

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 leaks-out (filtered)(extravasate) directly from both the liver surface, and the mesenteric vessels.

Due to:

1. Increased hydrostatics pressure
2. Increase vascular wall permeability
3. Concurrently decreased oncotic (osmotic) pressure (hypoalbuminemia)

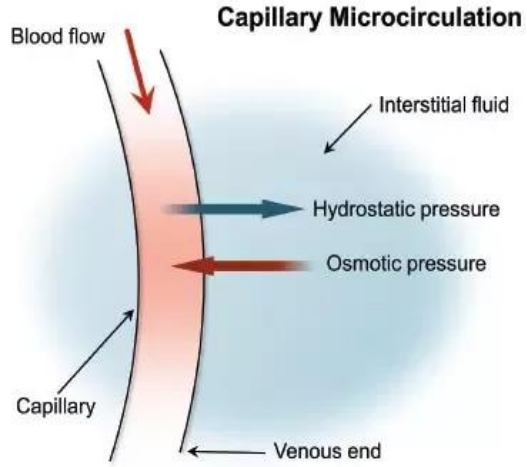
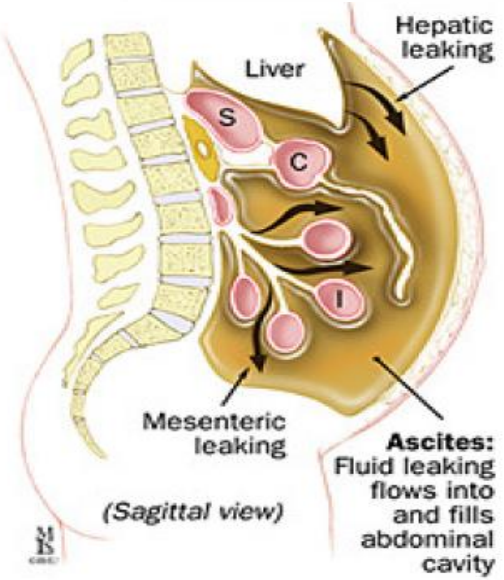
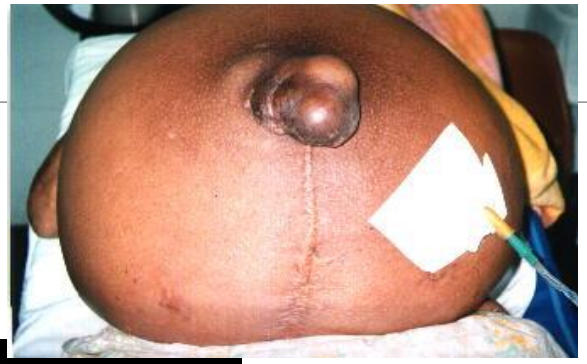


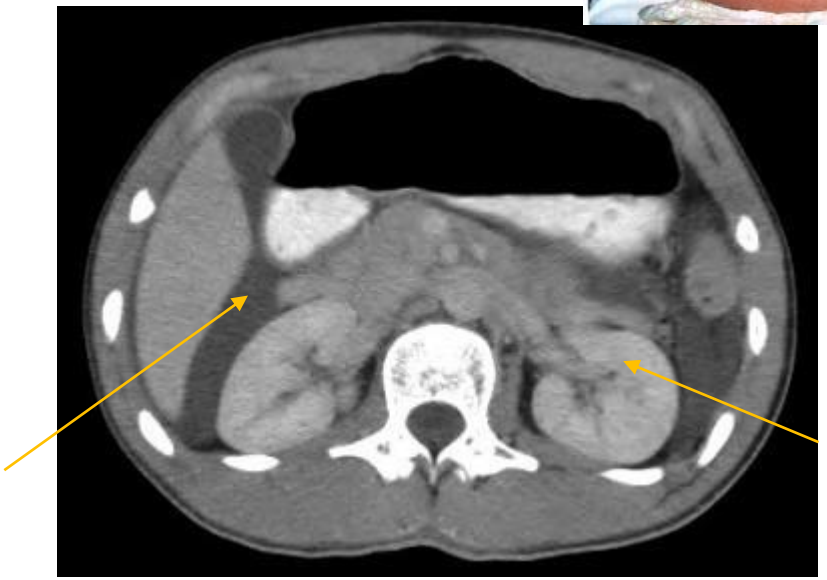
Figure 2. *Fluid exchange occurs across capillaries according to hydrostatic and colloid osmotic pressures maintained between the extracellular and intravascular compartments.*



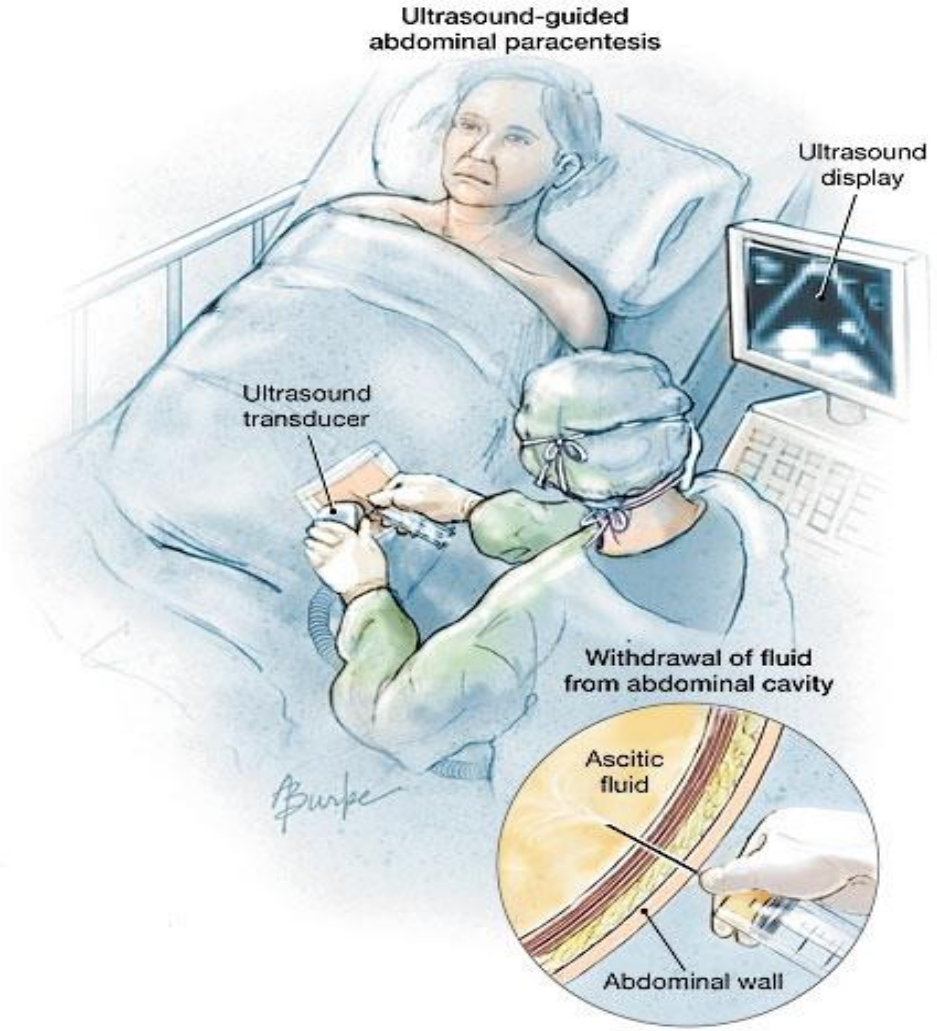
Evaluation of patient with ascites

- History: symptoms of chronic liver disease, abdominal distention
- Examination: Flank fullness, shifting dullness or fluid thrill
- Imaging : Ultrasound
- Ascitic fluid analysis





Any new ascites should be tapped and analyzed!

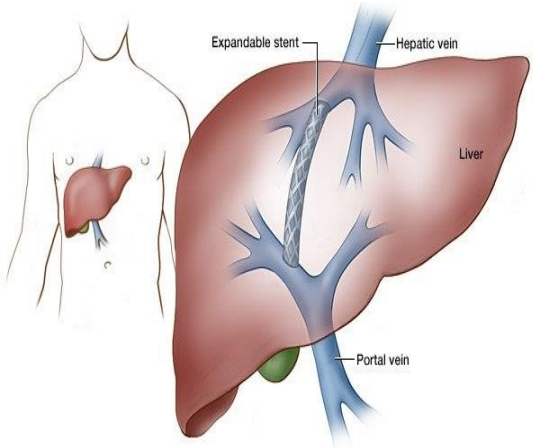


Management

- Low salt diet
- Diuretics (such frusemide, spironolactone….)

If resistance

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



Summary -1

- Ascites is the most common liver cirrhosis complication.
- Development of ascites indicates advanced stage of liver disease and poorer prognosis.
- Development of ascites is complex process.

Summary -2

Pathophysiology is mostly explained by portal

(sinusoidal) hypertension and sodium retention due

to vasodilation and consequent activation of sodium retaining systems.

Explained:

- Portal hypertension is first step in ascites development in patient with cirrhosis.
- Possible bacterial toxin trigger VDs.

Summary -3

VD with activation of secondary mechanisms;

- *renin-angiotensin-aldosterone system*
- *sympathetic nervous system*
- *antidiuretic hormone (vasopressin).*

LEADS TO SALT AND WATER RESTENTION and Increase plasma volume

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

Thank you