Medicine 439

Revised & Approved

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Pathophysiology Of Ascites

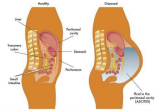
Editing file

OBJECTIVES:

1. To understand basic pathophysiologic steps in the development of ascites secondary to cirrhosis.
2. To correlate the anatomic and pathophysiologic hanges with clinical manifestations.
3. To understand the basic steps in evaluation of patients with ascites.

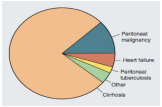
- Important
- Original content
- Doctor's notes
- Extra

ASCITES: The pathologic[1] accumulation of fluid in the peritoneal cavity & It is the most common complication of cirrhosis.



ASCITES CAUSES:

- 85%Cirrhosis [2]
- 15% other causes



1.why pathologic? Because sometimes it is post surgical or dialysis, Usually there is not fluid in the peritoneal at least seen in the ultrasound (the easiest way).

2.Cirrhosis in the beginning the patient doesn't know about it we call it **Compensated cirrhosis**, the liver will be cirrhotic histologically but the tests return normal, the patient doesn't know he/she has cirrhosis, that's why regular check is important.
-Any chronic inflammation develop to fibrosis and ends with cirrhosis.
-Once the complications of cirrhosis arise like, ascites, hepatic encephalopathy, varices bleeding we call it **Non compensated hepatitis.**

PATHOGENESIS

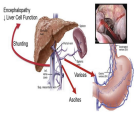
- Ascites is the final consequence of a series of anatomic, pathophysiologic, and biochemical abnormalities occurring in patients with cirrhosis.
- The formation of ascites is governed by the same principles as edema formation at other sites: net capillary permeability and the hydraulic and oncotic pressure gradients.more hydrostatic pressure less oncotic pressure so the fluid extravasate into the peritoneal cavity through the peritoneal surface, the mesentery, the liver surface

First step is the development of portal hypertension

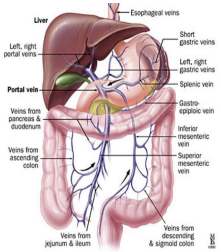
Portal hypertension → Ascites

PORTAL HYPERTENSION

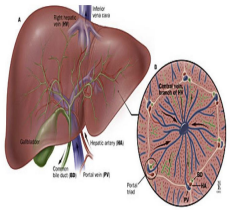
- The development of portal hypertension is the first step toward fluid retention in the setting of cirrhosis.
- Patients with cirrhosis but without PHT do not develop ascites or edema.
- A portal pressure >12 mmHg appears to be required for fluid retention.
if we have resistance to the flow it can lead to ascites
the collateral, which can be in the lower esophagus we call it varices, ascites, blood shunting gives us hepatic encephalopathy



Anatomy of portal system



Superior mesenteric vein, will come across the splenic vein, all of them are big veins, will make the portal vein behind the neck of the pancreas, and it's short it forms behind the neck of the pancreas and goes to the liver that means that the portal vein drains the blood of the WHOLE gut approximately, and that's important for us, because draining blood from the whole gut has consequences,



so the portal vein enters the hilum of the liver, the hilum has two big vessels going in and one going out, portal vein and hepatic artery going in, and bile duct going out, all of these will form the portal tract, the blue is the portal vein and we also have the hepatic artery and we have the bile duct, and this is a close up image of the liver unit, made up of hepatic cell, Portal tracts and between them the blood goes to the central vein, the central vein will combine to make venules and goes to the hepatic veins and goes to the heart,

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) if we have blockage in the portal vein we call it Pre-hepatic hypertension.

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

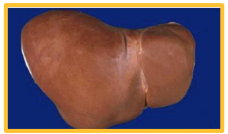
C- Hepatic (sinusoidal)

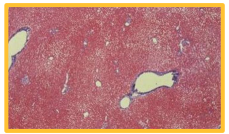
D Hepatic (Post-sinusoidal) (for C,D e.g cirrhosis and many liver disease)

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

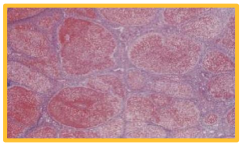
Cirrhosis: Late stage of chronic liver inflammation and fibrosis, in which liver parenchyma is distorted and replaced by fibrous tissue and regenerating nodules.

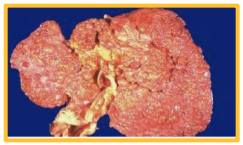
-Cirrhotic patients have a lot of vascular findings, splanchnic vessels dilated, Blood pressure on the lower side because of the vasodilatation, cardiac output high, they have dynamic changes.
-Whats commented now is those patient have **low grade of endotoxemia**, when there is advanced not the beginning.
-their extremities are hot, because of hyperdynamic circulation.



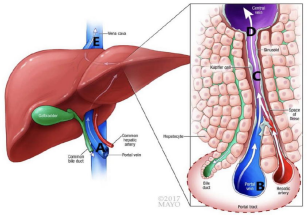


Normal Liver





Cirrhotic Liver



(Explaining the zoomed picture)
hepatic artery, portal vein, bile duct. When they are branching the blood flow between the hepatic cells in what we call the sinusoids which are lined by endothelial cells, the branch and go to the central vein and to the heart, the bile duct goes the opposite direction, goes to ductule and then to the biliary tree.

Mechanism of Portal Hypertension In Cirrhosis

How portal hypertension develops?

Structural (Mechanical, fixed)

due to structural changes and distortion of the liver microcirculation (sinusoidal fibrosis, regenerative nodules)

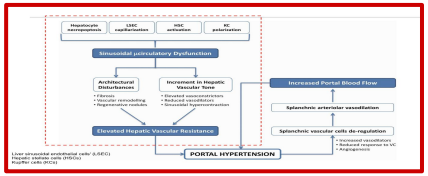
Functional (dynamic changes)

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:

1. Increased production of vasoconstrictors (eg, endothelins, angiotensin-II, norepinephrine, thromboxane A2)
2. Reduced release of endothelial vasodilators (eg, nitric oxide). Keep in mind these changes will be opposite in the splanchnic vessels.

Liver microcirculation in portal hypertension



In **normal** physiologic conditions:*Pictures in the next slide
Hepatic stellate cells (HSC) contractility and coverage of sinusoids is sparse
usually found silent not active, activated when there is chronic inflammation.

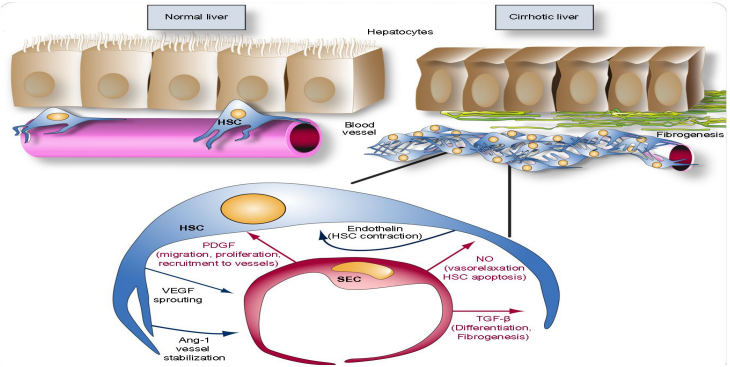
In **cirrhosis**:

- 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..)

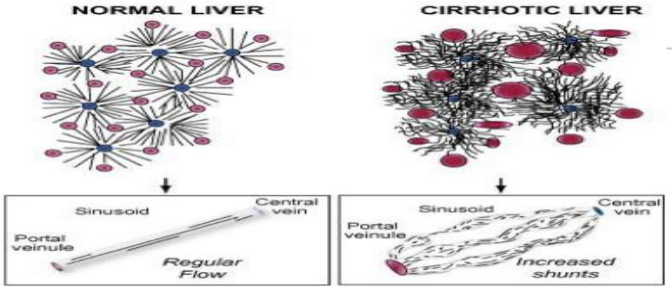
Thereby contributing to a high-resistance, constricted sinusoidal vessel.

-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 microcirculation in portal hypertension



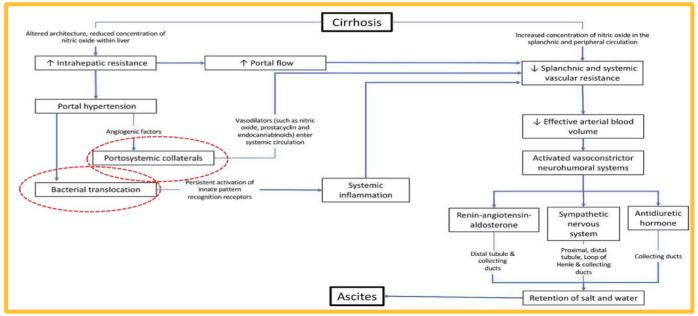
- this is hepatic cell and sinusoid (pink) around them there is stellate cells, in a space called space of disse, this area the structural and dynamic changes happen to them here, after fibrosis stellate cells number increases, increasing their member and activity and recruiting more inflammatory cells and transforms into like myofibroblast increasing the tone of the sinusoid stimulating the fibrogenesis in the space of disse.
- So the sinusoid which have pores that blood can be filtered through it to the parenchyma all of that will be damaged And the liver sinusoidal cells also changes, so there is a lot of ultra structural changes happening in the liver.
- (In normal physiologic conditions) stellate cells are few and they are not active and stellate cells generally is involved in Vitamin A storage and it may work in the immunity, but it's mainly stores Vitamin A and other functions



- Here if you remember the portal tract and blood going to the central vein the area is very straight, now on the right the sinusoid which is very straight and filtering the blood now is distorted and not permeable as before.
- (Capillarization) close this with some deposition of matrix, so the sinusoids doesn't be as permeable as before (Microthrombi) you may see this very detailed ones blocked.
- So All these factors, structural changes, distortion, increasing tone because of stellate cells, and vasoconstrictors and imbalance with the vasodilators, and structural changes in the sinusoids, and then backflow happens, and portal hypertension increases.

The pathogenesis of ascites in cirrhosis

The blood when its facing resistance, blood goes from all mesentery and there is resistance in the liver, it searches for communication between the portal and systemic circulation veins, we call it collaterals, in more than one place, most famous is the lower esophagus, varices, around umbilicus in the rectum Its importance is that it can shunt the blood with the toxins in the systemic circulation.
(Bacteria translocation) we have changes in the portal hypertension for a long time bacteria can go into the systemic circulation and induce inflammation and vasodilation.
All these changes together with these mediators, will cause changes in the splanchnic circulation. Splanchnic vessel will have vasodilatation, taking more blood in them, in the same time later on systemic vasodilation so the blood pressure decreases this will cause activation of the vasoconstrictor neurohormonal system (two mentioned in the image) this is to retain more sodium and other salts in the body, and ADH to stimulate more fluid retention.

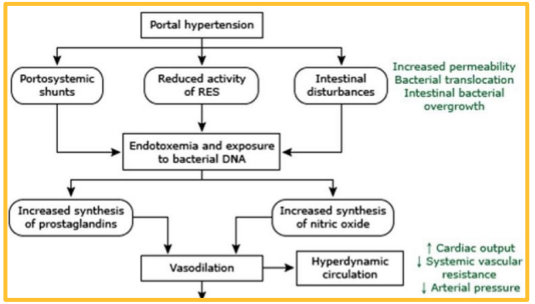


Vasodilation(VD) (splanchnic and systemic)

- VD initially in the splanchnic circulation, later in systemic circulation.
- **Mechanism of vasodilation:**

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



(Portosystemic shunt) without detoxification of the contents in the liver.
(reduced activity of RES) reticuloendothelial system.
(Intestinal disturbances) the tight junction in the villi in the liver is not as good as in normal. people And there is translocation of the bacteria or the bacterial product or toxins to the circulation through the gut, which is called increase gut permeability and this also causes what we call spontaneous bacterial peritonitis, the ascitic fluid may have inflammation, a lot of mechanisms can be related to that.

we have compensatory mechanism, the body will not leave the vasodilatation
Always when the compensatory mechanism persists it becomes damaging, like inflammation,fever all are physiological but after sometime it causes damage, so it is damaging because initially its a physiological response but when the insult continues it becomes damaging
The more vasodilatation the more intense the compensatory mechanism is going to be.

Consequences of Vasodilation (VD)

1. **Activation of endogenous vasoconstrictors.**
2. **Sodium and water retention.**
3. **Increase renal vasoconstriction.**

may be because of renal permit with cirrhotic patient

Activation of endogenous vasoconstrictor agents

Vasodilation → The reduction in pressure (or stretch) at the carotid and renal baroreceptors → activation of the sodium-retaining neurohumoral mechanisms by:

– Renin-angiotensin-aldosterone system (RAS).to conserve more salts

– Sympathetic nervous system (SNS).vascular tone and affecting renal tubules

– Antidiuretic hormone - vasopressin (ADH).telling the body don't let the water out keep it in

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 and water retention.**

Sodium and water retention

1- In patients with cirrhosis and ascites,The normal regulation of sodium balance is lost (Impaired sodium excretion).

2- 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.**

they're retaining a lot of sodium but when you do a test on them you find that their sodium levels are normal or low why?
Because they are retaining sodium And water, so the increased water may dilute the labs reading, but IN FACT the net sodium content in their body is high, it may be low even in the vessels but the NET is high, or lets say that it is low in the vessel because it is more diluted.

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. intrarenal vasodilator the body tries to maintain renal function but then after some time there will be renal impairment after that if it is progressing we name it hepatorenal syndrome.

This excess retained blood volume is thought to leak-out (filtered) (extravasate) directly from both the **liver surface**, and the **mesenteric vessels.**
Due to:
– Increased hydrostatics pressure.
– Increase vascular wall permeability.
– Concurrently decreased oncotic (osmotic) pressure (hypoalbuminemia).

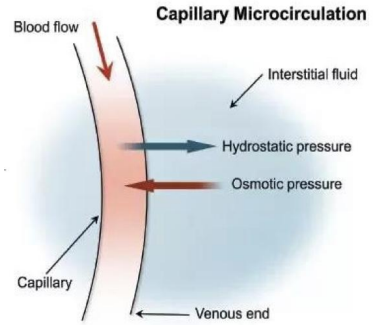
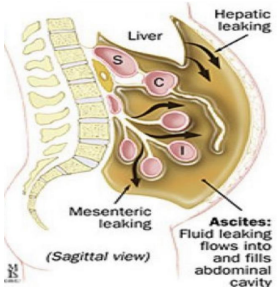


Figure 2. *Fluid exchange occurs across capillaries according to hydrostatic and colloid osmotic pressures maintained between the extracellular and intravascular compartments.*



Evaluation of Patient with Ascites

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

when we do analysis, enter through the skin subcutaneous, the muscle and aspirate the fluid this is called **Paracentesis** of **ascitic fluid aspiration**.

Management

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

These 2 usually work for more than 90% of the patients, we don't fix the cause of the problem, the liver is gone!, you need to treat the liver, treat other underlying etiology, or transplant for the patient.

If resistance

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

Summary

- 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.
- 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.
- VD with activation of secondary mechanisms: 1-renin-angiotensin-aldosterone system. 2-sympathetic nervous system. 3-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.

QUIZ!

Q1:Which of the following is a consequence of vasodilatation?			
A- Activation of endogenous vasoconstrictor agents.	B-Sodium & Water retention.	C-Increase renal vasoconstriction.	D-All of the above.
Q2: Which one of the following is a FUNCTIONAL change in ascites?			
A- Increase systemic nitric oxide (NO)	B- Increase systemic prostaglandin.	C-Reduced glomerular filtration rate.	D- Sodium & Water retention.
Q3: The PRIMARY mediator of vasodilation in cirrhosis is:			
A- Vasoactive intestinal peptide (VIP)	B-Nitric oxide (NO)	C-Prostaglandin	D-ADH
Q4: The FIRST step toward fluid retention in the setting of cirrhosis is:			
A-Vasodilation	B- Activation of endogenous vasoconstrictor agents	C- Portal hypertension	D- Hyperdynamic circulation
Q5: Which one of the following is a SYSTEMIC consequences to vasodilatation?			
A- Hyperdynamic circulation.	B-Vomiting	C- Headache	D- Sodium & Water retention.

Answers

1/D
2/C
3/B
4/C
5/D

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