MEDICINE 1
MINI-OSCE COLLECTED SLIDES – PART 3
JU 2021

By: Odai Gassan Bani Monia

Contents

Gastroenterology

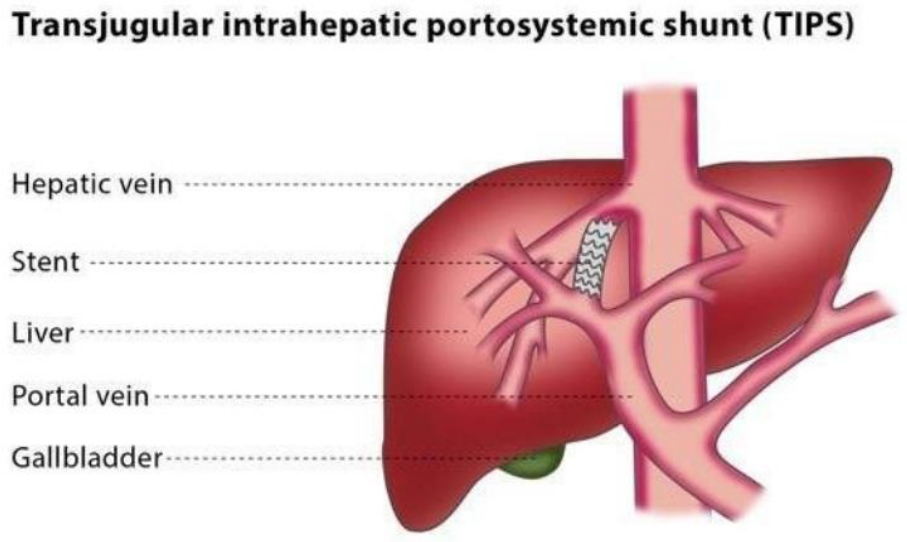
Approach to Ascites

Serum Ascites Albumin Gradient

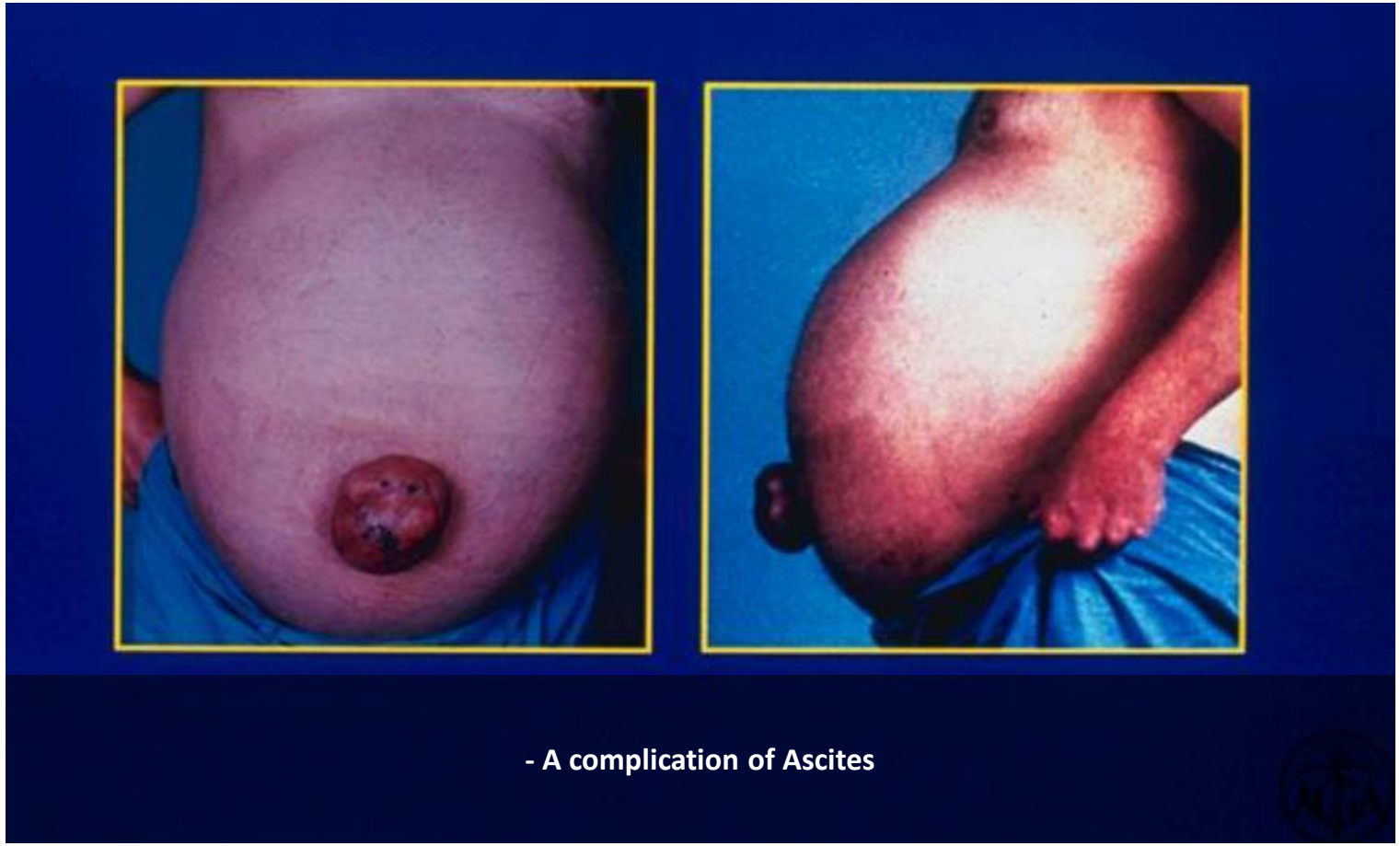
	SAAG (g/dL)	
	≥ 1.1	< 1.1
Total protein (g/dL)		
< 2.5	Cirrhosis	Nephrotic syndrome
	Acute liver failure	
≥ 2.5	CHF	Peritoneal carcinomatosis
	Constrictive pericarditis	TB peritonitis
	Budd-Chiari syndrome	Pancreatic ascites
	Veno-occlusive disease	Chylous ascites

Transjugular Intrahepatic Portosystemic Shunt

- **EXTRA** An artificial channel within the liver that establishes communication between the inflow portal vein and the outflow hepatic vein. Used to treat portal Hypertension.
- Indicated for patients visiting the hospital very frequently for paracentesis.

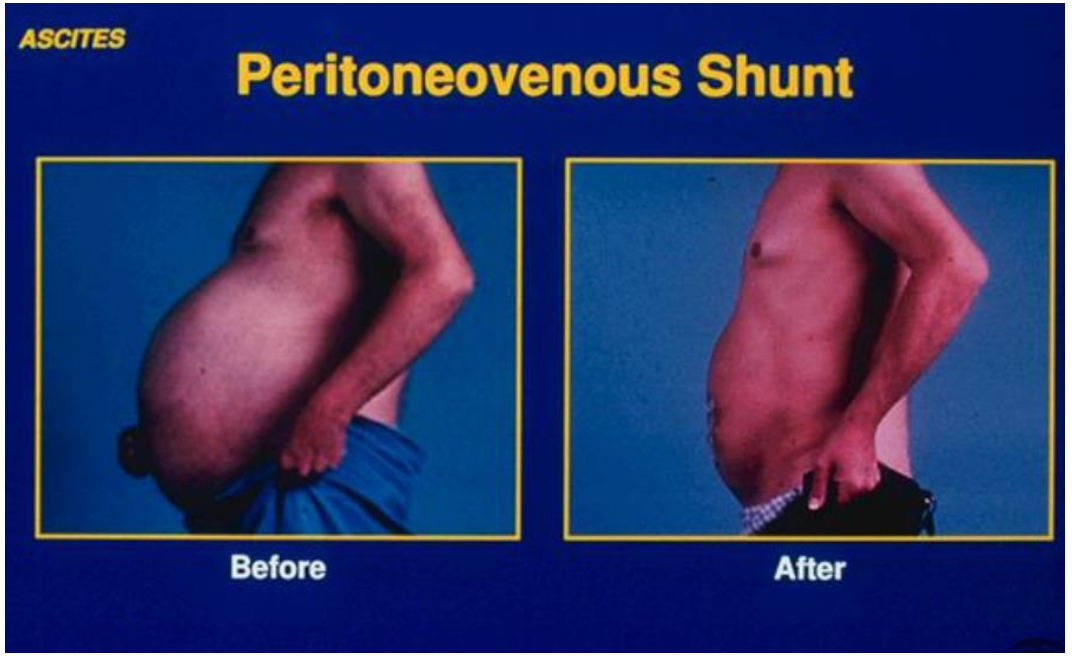


Umbilical Hernia



- A complication of Ascites

Peritoneovenous Shunt



- A device that relieves ascites by transferring fluid through a one-way valve from the Peritoneal cavity in the SVC.

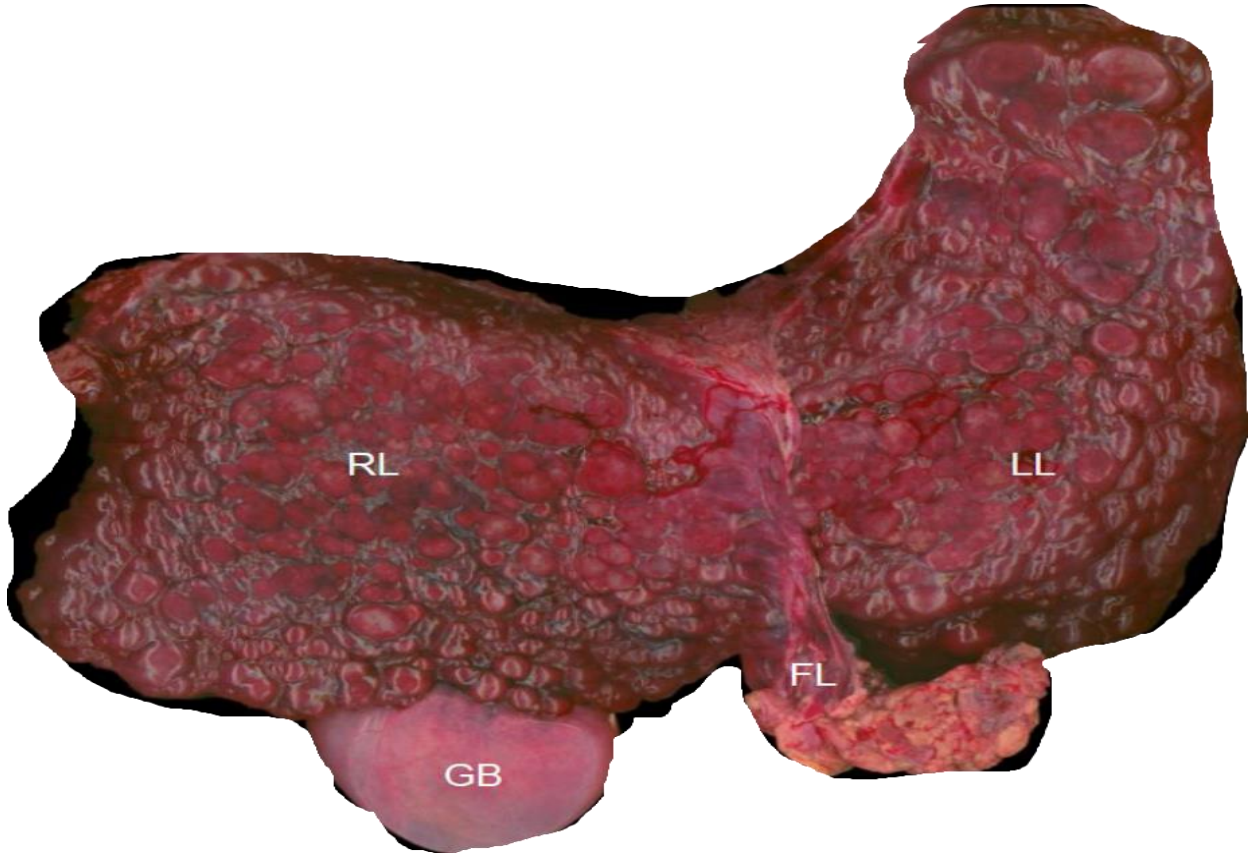
Cirrhosis - Portal Hypertension

Liver Cirrhosis

Irreversible late stage of progressive hepatic fibrosis (Distortion of the hepatic architecture + Formation of Regenerative nodule).

Treatment: Liver Transplantation.

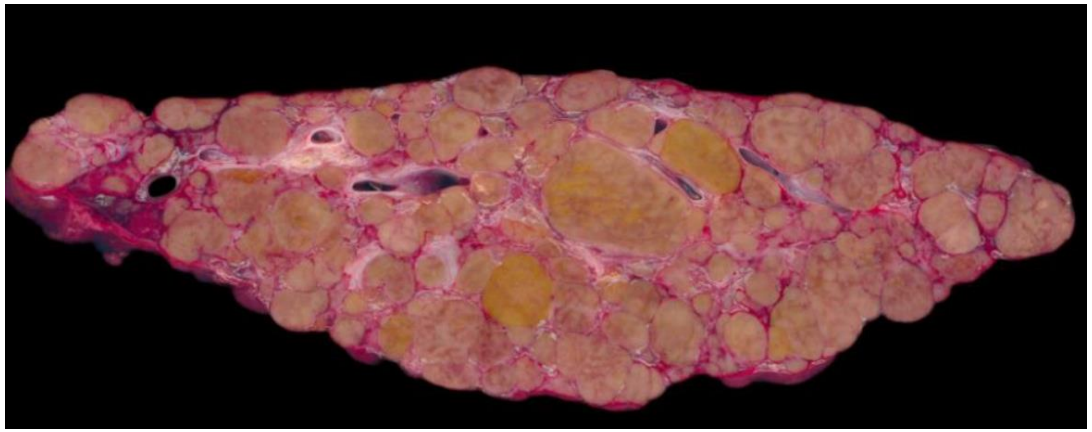
Liver Cirrhosis



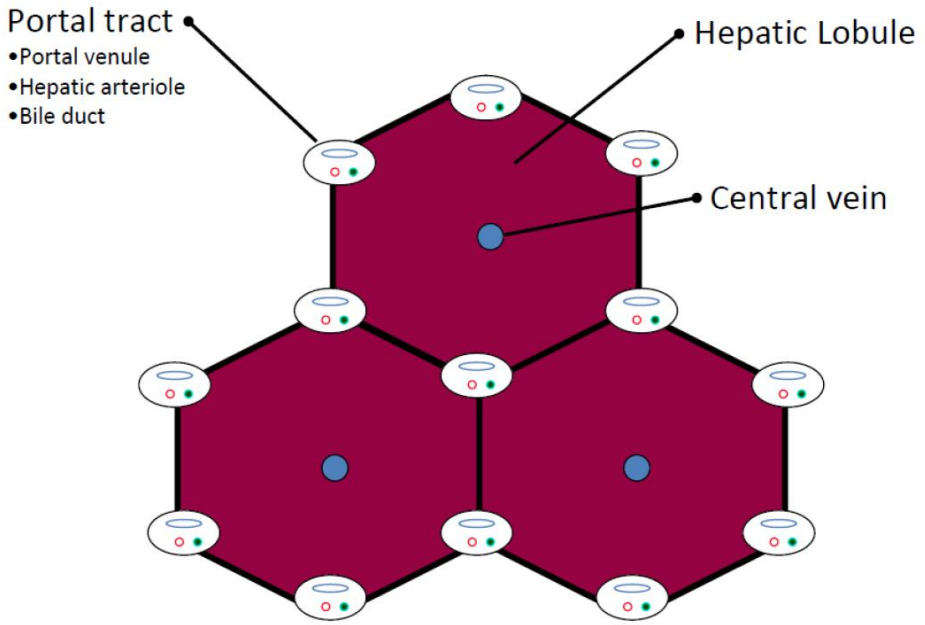
- The external surface of a cirrhotic liver has Shrunken, Pebbly appearance.

Liver Cirrhosis

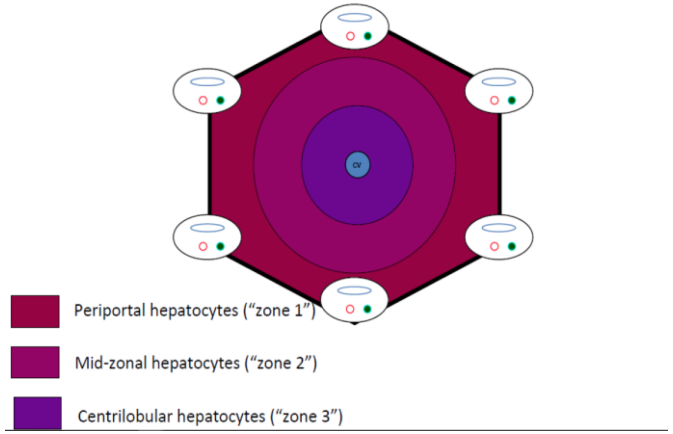
- Shrunken liver with severe architectural distortion: Rounded, Variably-sized regenerative nodules encased in a dense fibrous connective tissue.

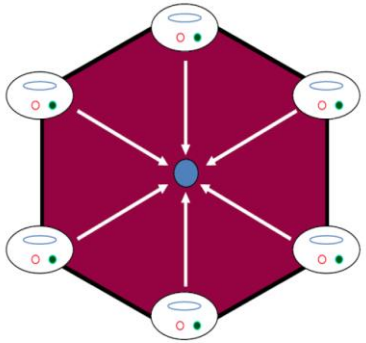


Liver Histology



The resulting zonal pattern correlates with sensitivity of hepatocytes to injury and makes some injury patterns more understandable

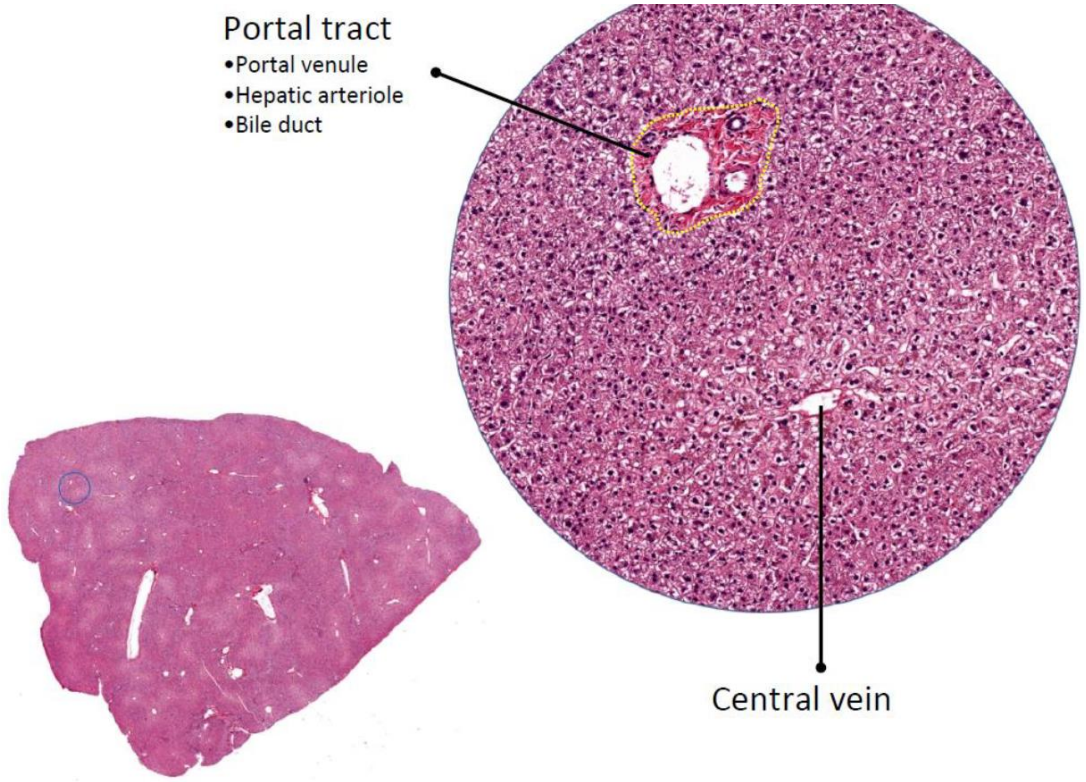




- Blood flow is from portal areas to central veins.
- Blood becomes progressively deoxygenated and depleted of nutrients toward central veins.

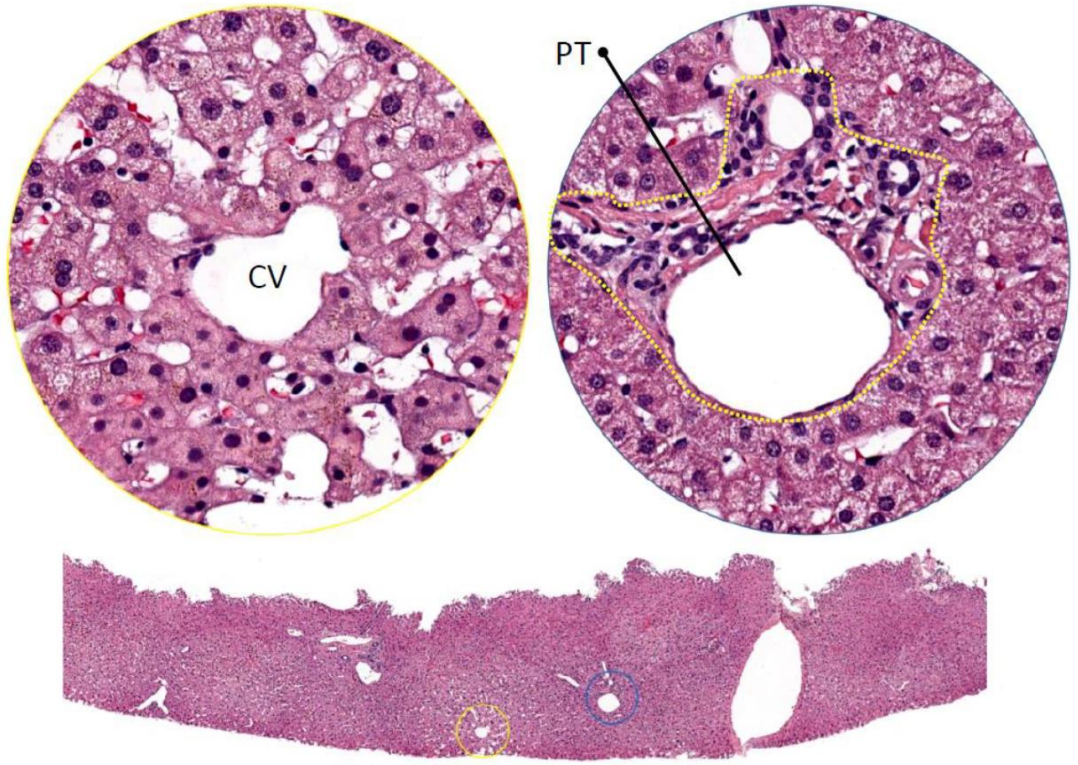
Liver Histology

- Portal Venule → the big white circle
- Hepatic arteriole → the medium sized circle
- Bile duct → the smallest circle.

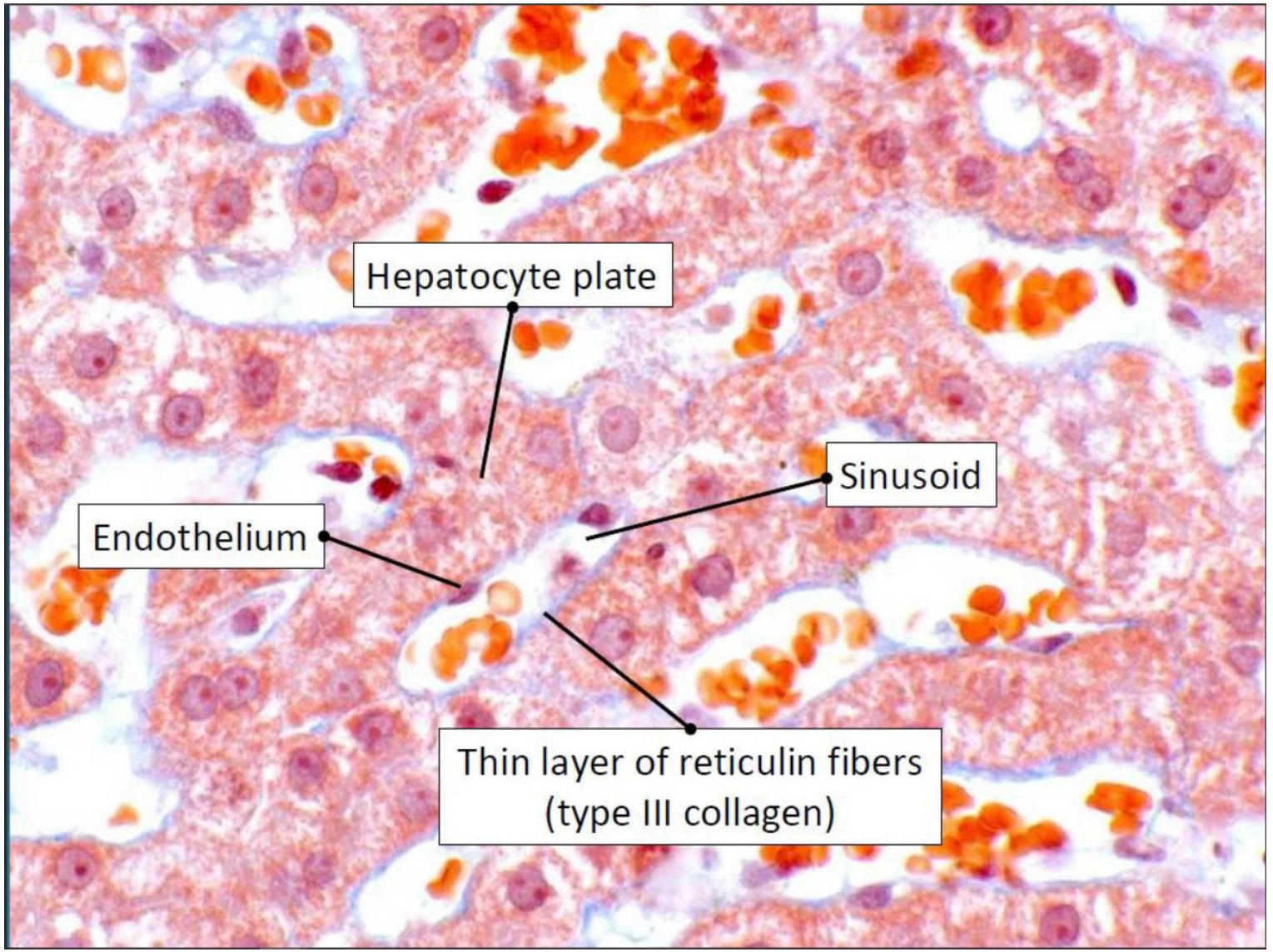


Liver Histology

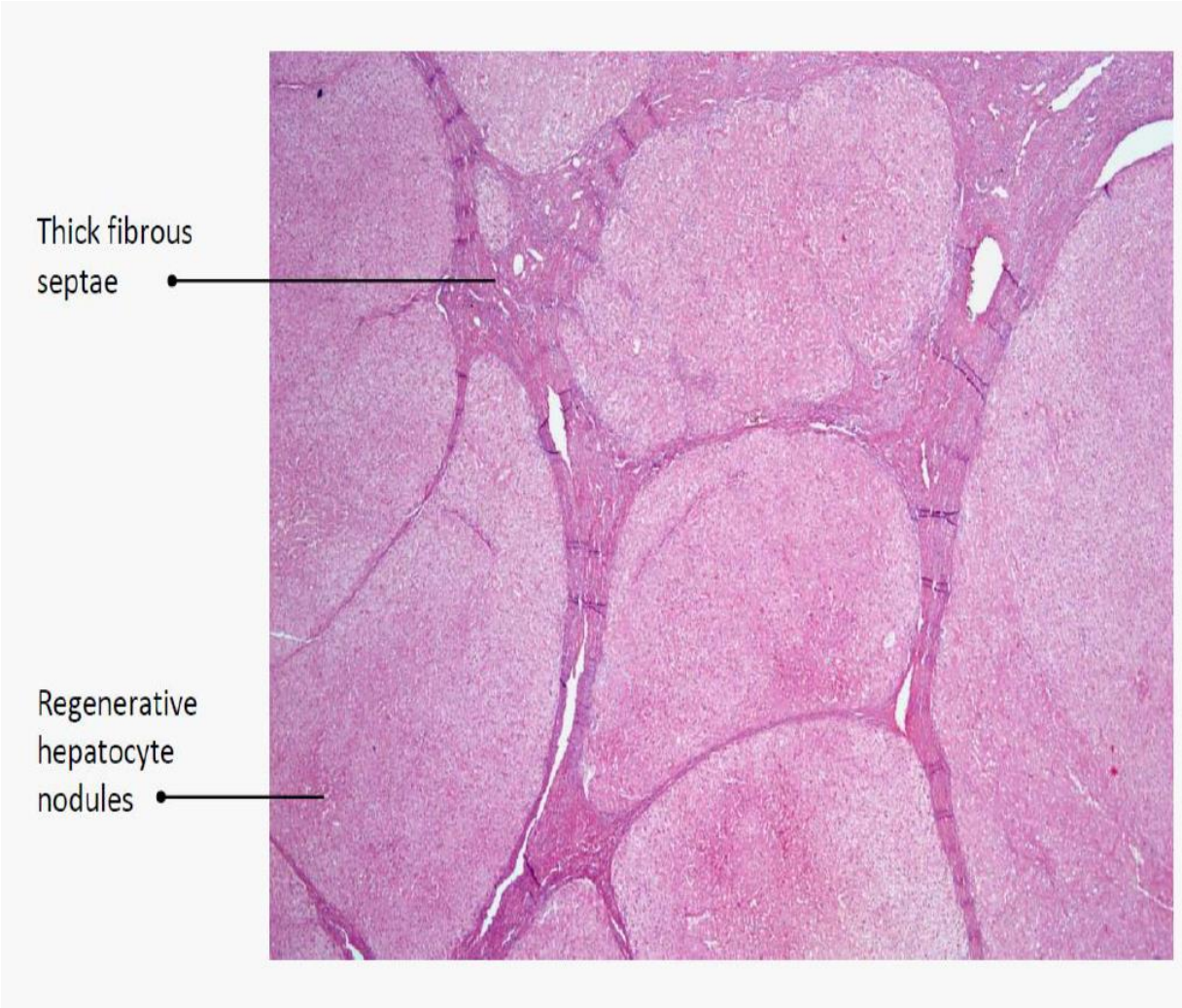
- CV → Central Vein
- PT → Portal tract



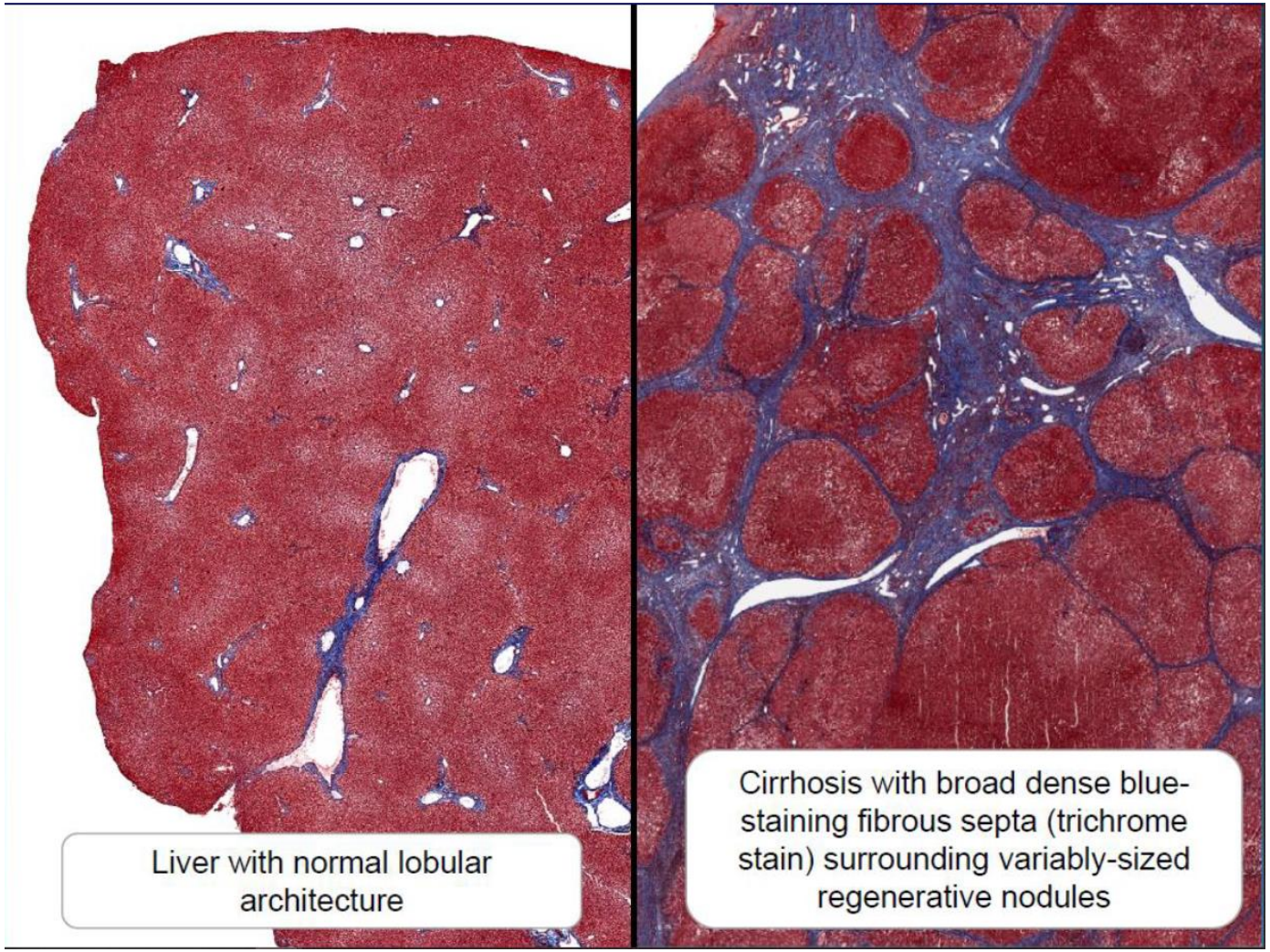
Liver Histology



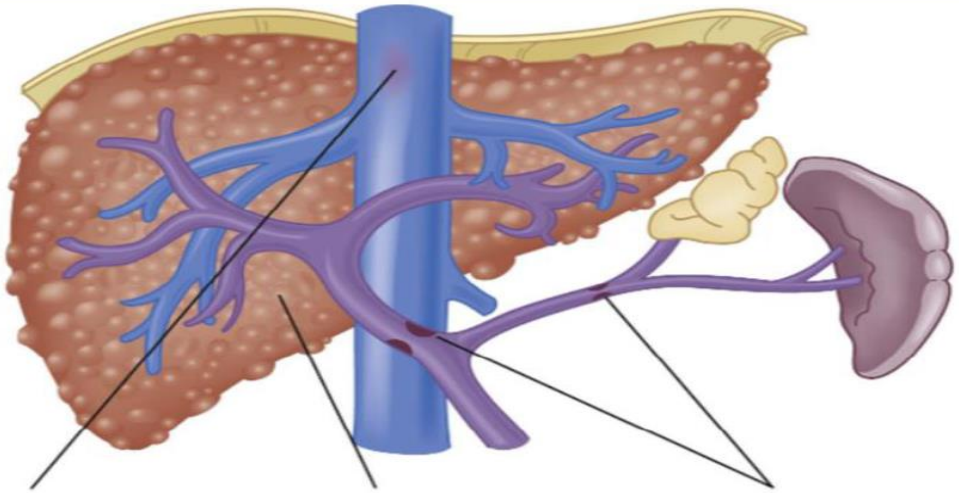
Cirrhotic Liver Histology



Normal Vs Cirrhotic Liver



Classification of portal HTN



Posthepatic
Budd-Chiari syndrome
Constrictive pericarditis
Inferior vena caval obstruction
Right-sided heart failure
Severe tricuspid regurgitation

Intrahepatic
Presinusoidal
- Idiopathic portal hypertension
- Primary biliary cirrhosis
- Sarcoidosis
- Schistosomiasis

Sinusoidal
- Alcoholic cirrhosis
- Alcoholic hepatitis
- Cryptogenic cirrhosis
- Postnecrotic cirrhosis

Postsinusoidal
- Sinusoidal obstruction syndrome

Prehepatic
Portal vein thrombosis
Splenic vein thrombosis

Type		Examples
Prehepatic		Portal or splenic vein thrombosis
Intrahepatic	Presinusoidal	Schistosomiasis
	Sinusoidal	Alcoholic cirrhosis
	Postsinusoidal	Veno-occlusive disease
Posthepatic		Hepatic vein thrombosis Constrictive pericarditis

The Use of HVPG in the Differential Diagnosis of Portal HTN

TYPE OF PORTAL HYPERTENSION	WHVP	FHVP	HVPG
Prehepatic	Normal	Normal	Normal
Presinusoidal	Normal	Normal	Normal
Sinusoidal	Increased	Normal	Increased
Postsinusoidal	Increased	Normal	Increased
Posthepatic			
Heart failure	Increased	Increased	Normal
Budd-Chiari syndrome	—	Hepatic vein cannot be cannulated	—

- Hepatic Venous Pressure Gradient (HVPG): = Wedged Hepatic venous pressure - Free Hepatic venous pressure.

In Whom We Should Suspect Cirrhosis?

Any patient with chronic liver disease (Chronic abnormal Aminotransferase and/or Alkaline phosphatase).

PE findings: Stigmata of chronic liver disease (Muscle wasting, Vascular spiders, Palmer erythema), Palpable left lobe of the liver, Small liver span, Splenomegaly, Signs of decompensation (Jaundice, Ascites, Asterixis).

Laboratory: Liver insufficiency (Low Albumin <3.8 g/dl, Prolonged PTT - INR >1.3-, High Bilirubin >1.5 mg/dl), Portal HTN causing splenomegaly and leading to thrombocytopenia (Low platelet count <175 x 1000 / **µ**L), AST/ALT ratio > 1.

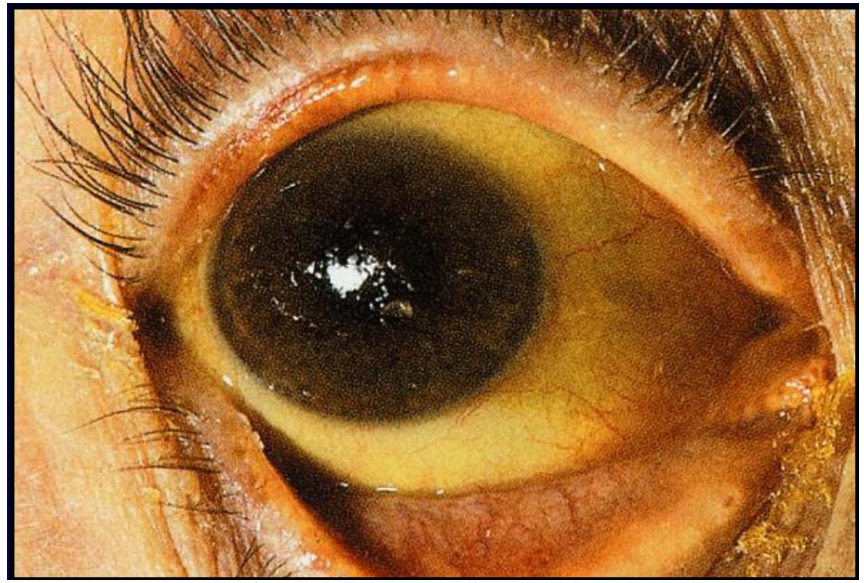
ALT is secreted by the liver only, while AST is secreted by Liver and Muscles.

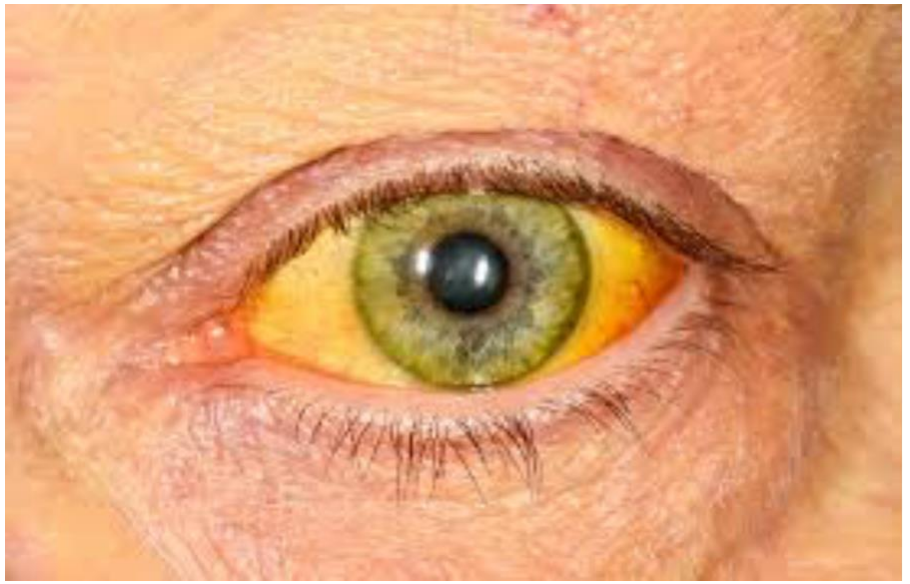
In the case of damaged liver, we'll have lower AST and ALT secretion than normal, but still AST levels > ALT.

Normal INR doesn't rule out cirrhosis. High INR is developed when 75-80% of the liver is damaged.

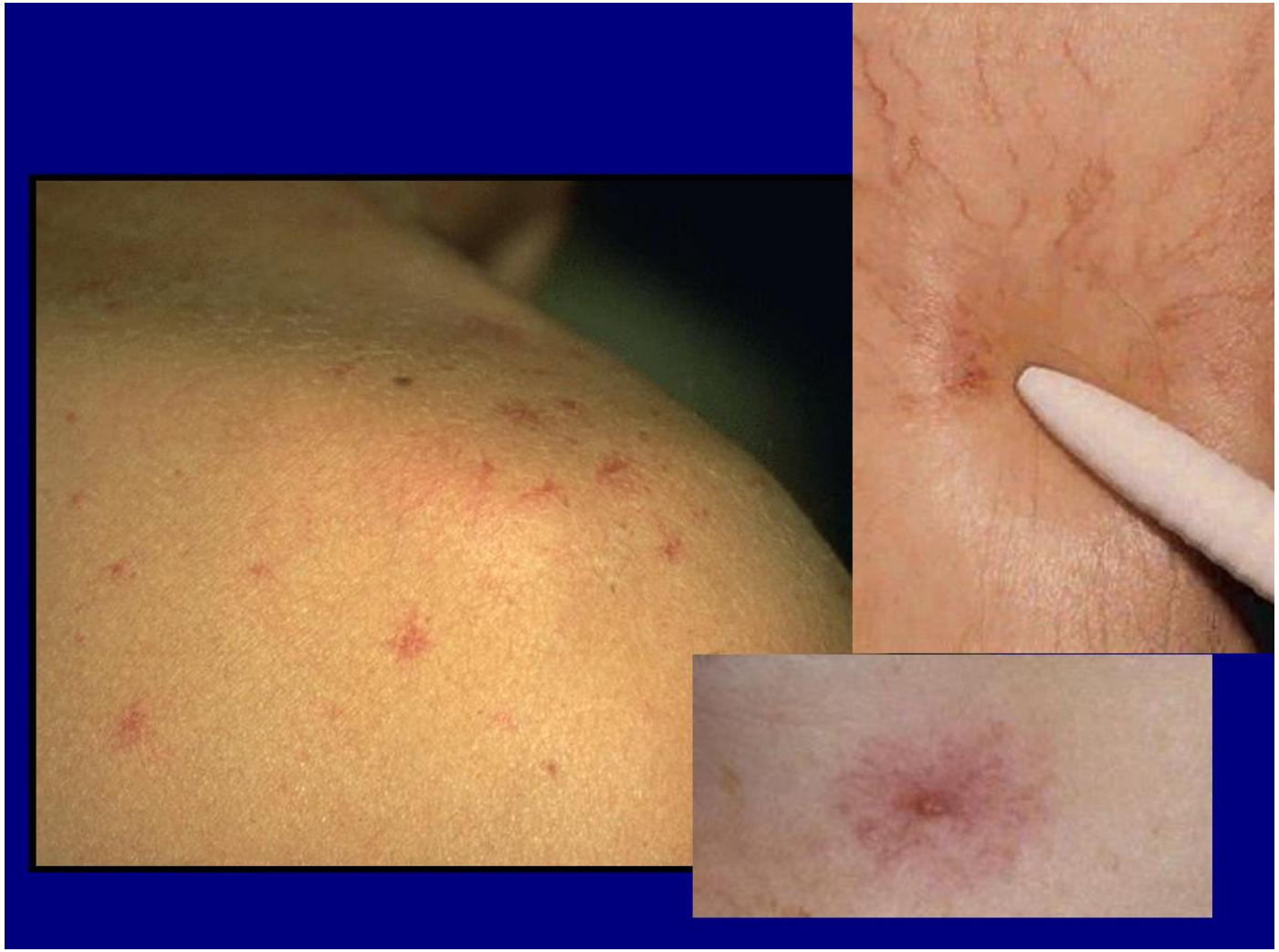
Imaging studies: CAT scan / Ultrasound (it shows Nodular shrunken liver, Splenomegaly, Varicosities).

Jaundice

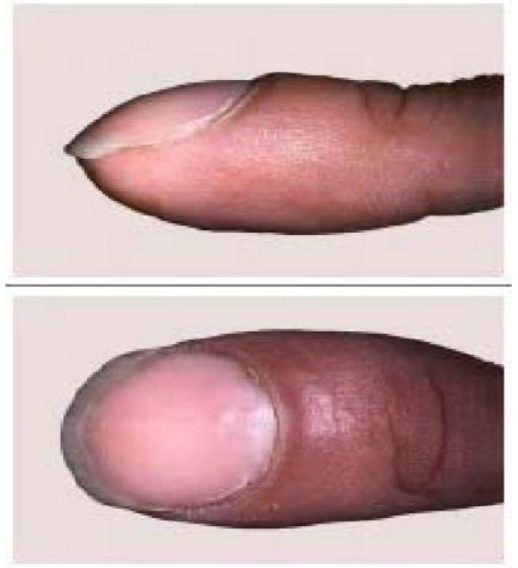


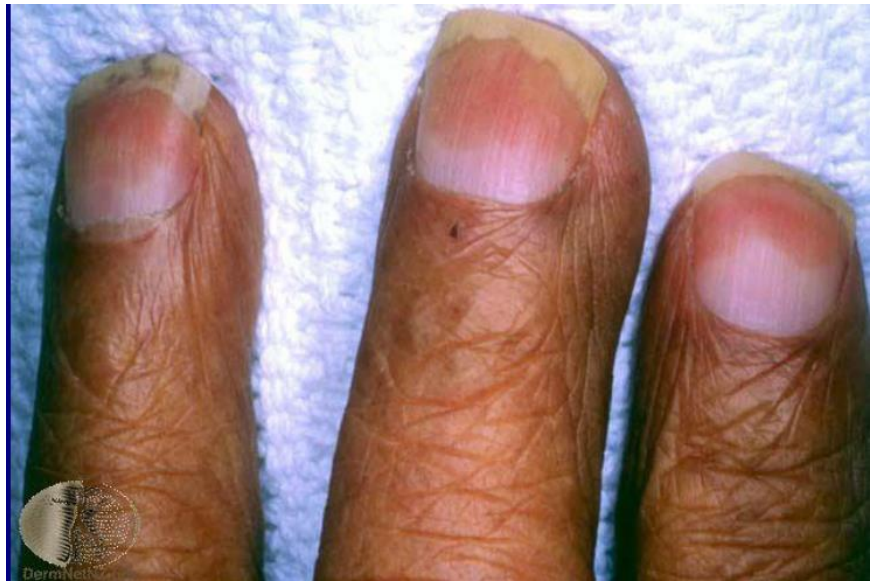


Spider Navi

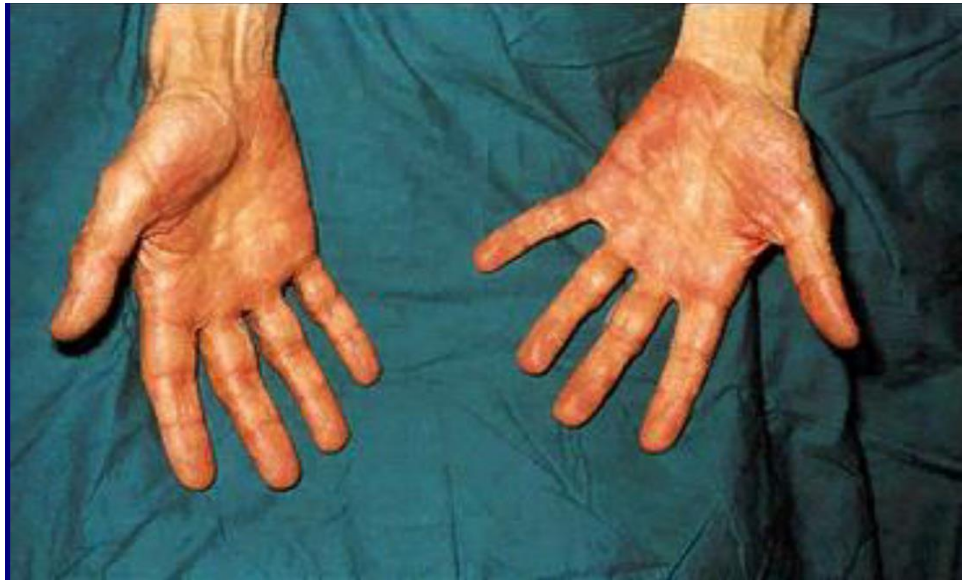


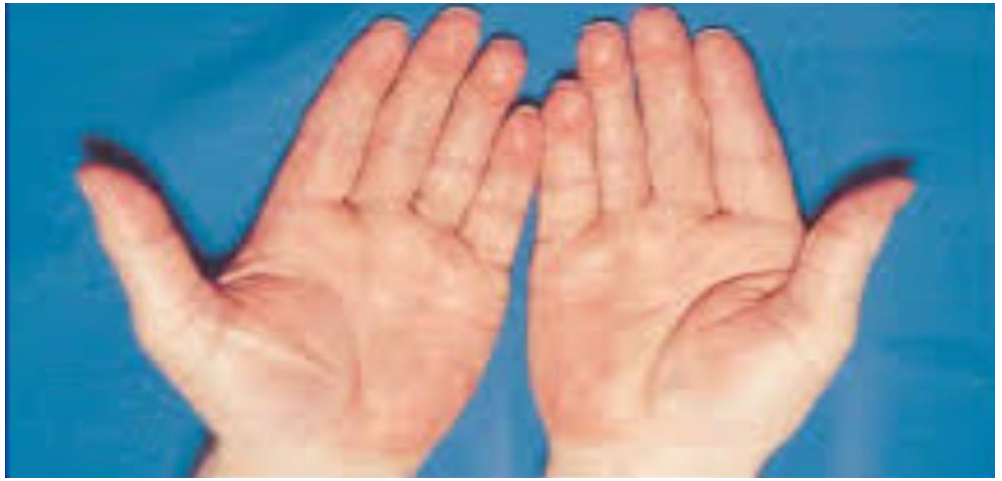
Clubbing



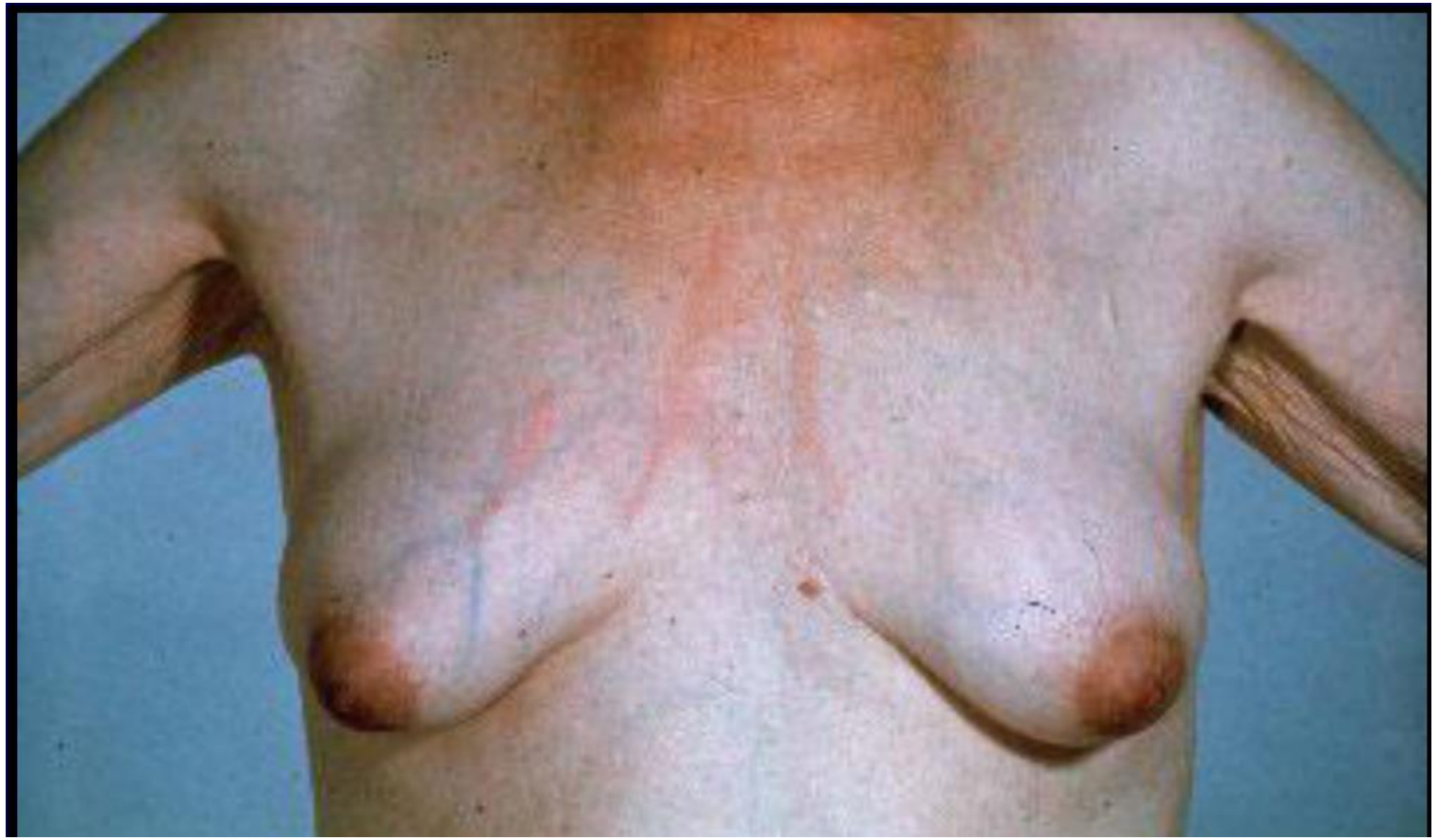


Palmer Erythema

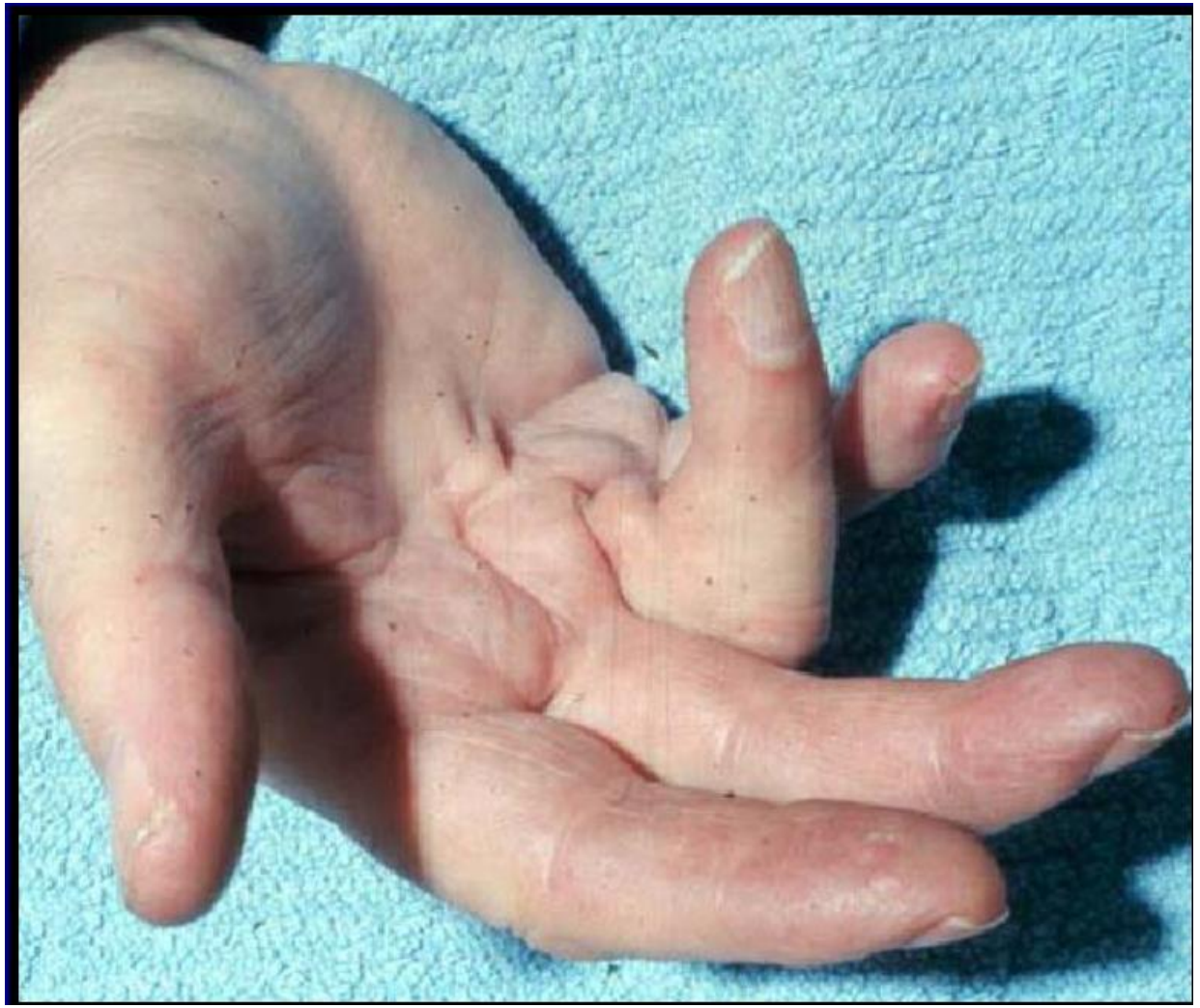




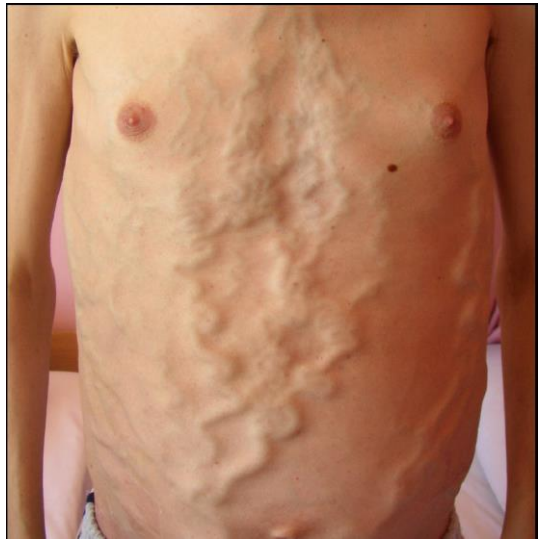
Gynecomastia

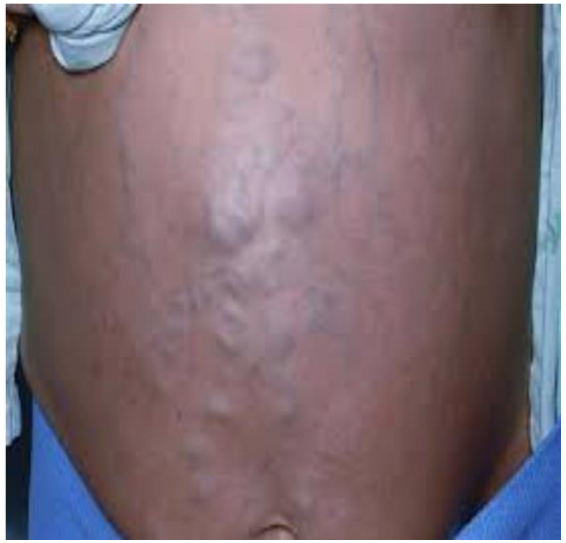


Dupuytren's Contracture

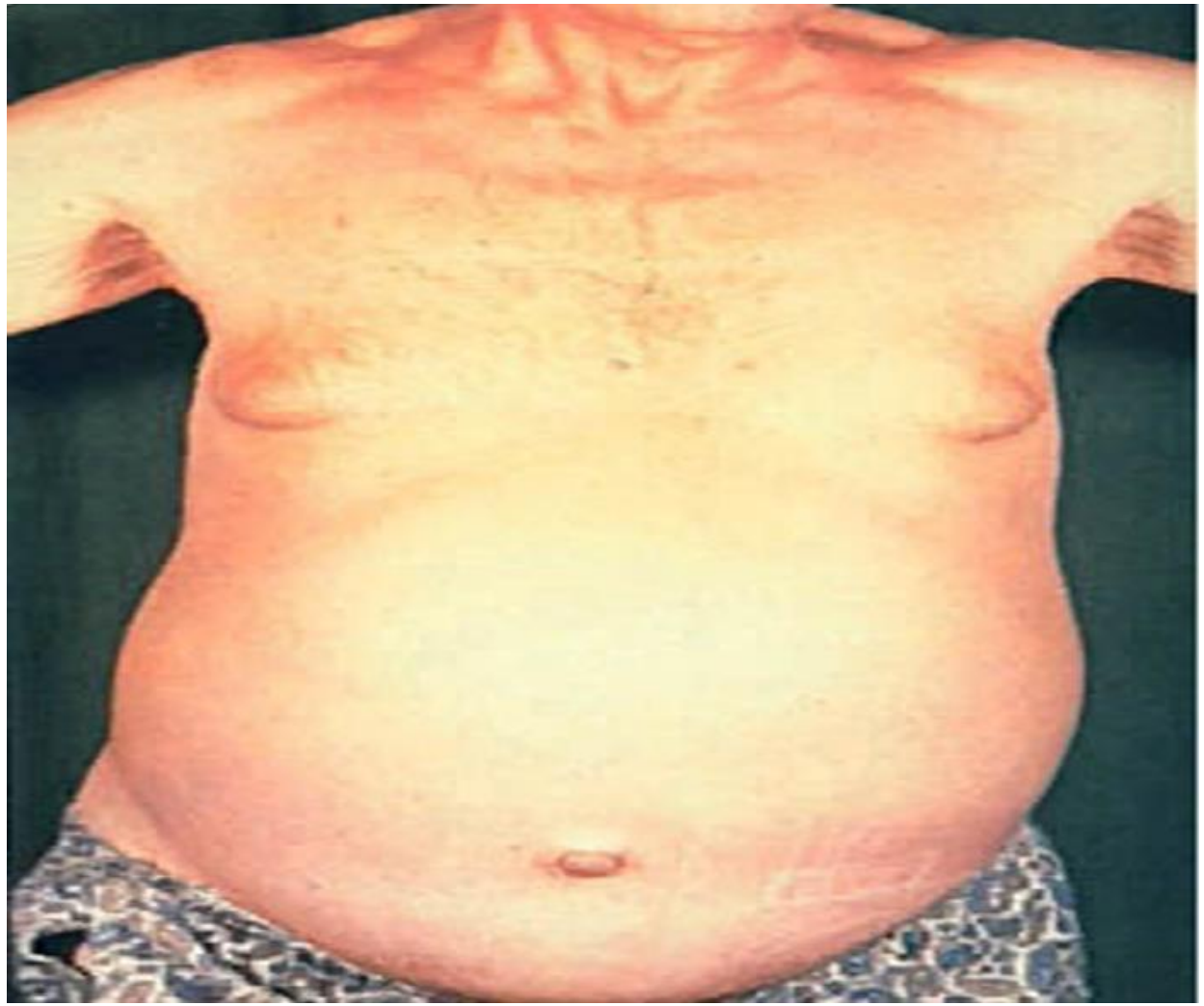


Caput Medusa





Ascites and Gynecomastia



Lab Findings

- **Aminotransferases**
  - AST and ALT usually mildly to moderately elevated.
  - AST is usually more elevated than ALT.
  - Normal aminotransferases do not preclude a diagnosis of cirrhosis.
- **Alkaline phosphatase**
  - Usually elevated but less than two to three times the upper normal limit.
  - Higher levels may be seen in patients with PSC and PBC.
- **Gamma-glutamyl transpeptidase** — GGTP
  - levels correlate reasonably well with alkaline phosphatase in liver disease .
  - Levels of GGT are typically much higher in chronic liver disease from alcohol than other causes (may be the result of alcohol inducing hepatic microsomal GGTP or alcohol causing GGT to leak from hepatocytes).

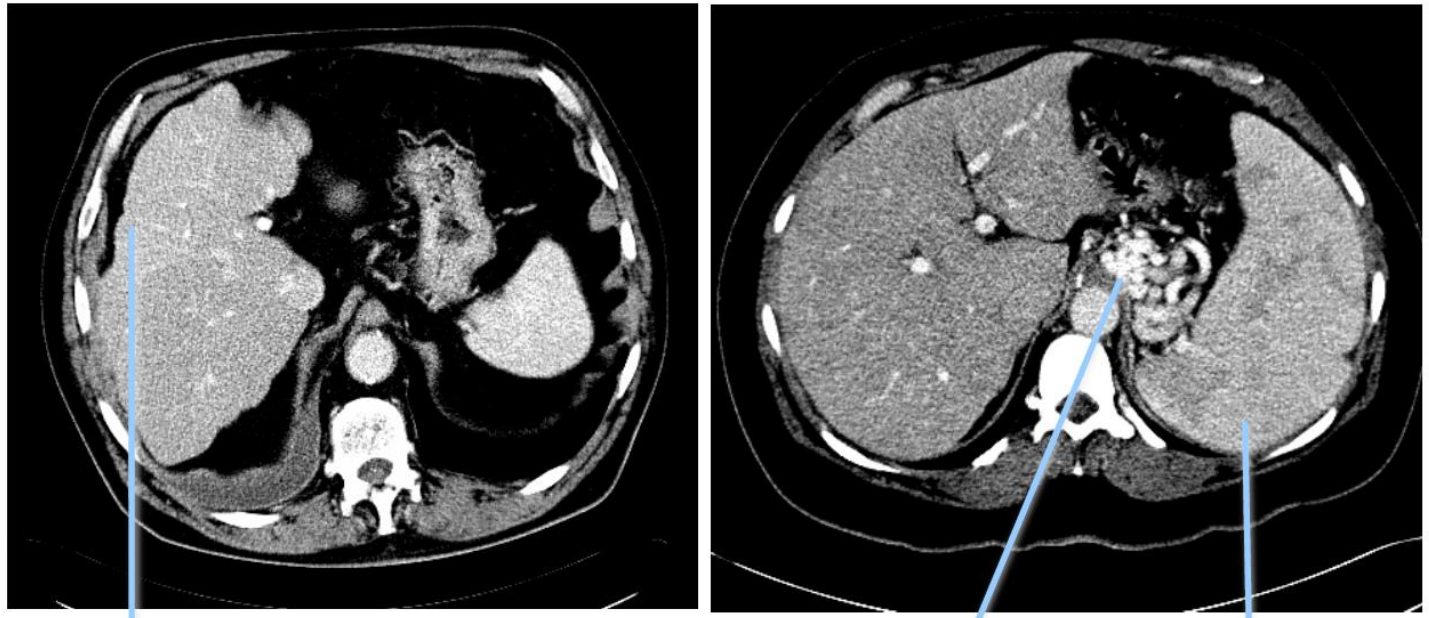
- **Serum sodium**
  - Hyponatremia is common in patients with cirrhosis with ascites and is related to an inability to excrete free water. This results primarily from high levels of anti-diuretic hormone secretion.
- **Anemia**
  - Multifactorial in origin; acute and chronic gastrointestinal blood loss, folate deficiency, direct toxicity due to alcohol, hypersplenism, bone marrow suppression (as in hepatitis-associated aplastic anemia), the anemia of chronic disease (inflammation), and hemolysis may all contribute.
- **Thrombocytopenia**
  - caused by portal hypertension with attendant congestive splenomegaly. An enlarged spleen can result in temporary sequestration of up to 90 percent of the circulating platelet mass.
- **Leukopenia and neutropenia**
  - Leukopenia and neutropenia are due to hypersplenism

- **Bilirubin**
  - may be normal in well compensated cirrhosis then rise progressively.
- **Albumin**
  - Synthesized exclusively in the liver.
  - Levels fall as the synthetic function of the liver declines with worsening cirrhosis.
  - Hypoalbuminemia is not specific for liver disease since it may be seen in many other medical conditions such as congestive heart failure, the nephrotic syndrome, protein losing enteropathy, or malnutrition.
- **Prothrombin time**
  - The liver is involved in the synthesis of many of the proteins required for normal clotting.
  - Prothrombin time reflects the degree of hepatic synthetic dysfunction.
- **Globulins**
  - Globulins tend to be increased in patients with cirrhosis. This may be secondary to shunting of bacterial antigens in portal venous blood away from the liver to lymphoid tissue which induces immunoglobulin production.
  - Marked elevations of IgG may be a clue to the presence of autoimmune hepatitis. Increased levels of IgM are present in 90- 95% of patients with PBC.

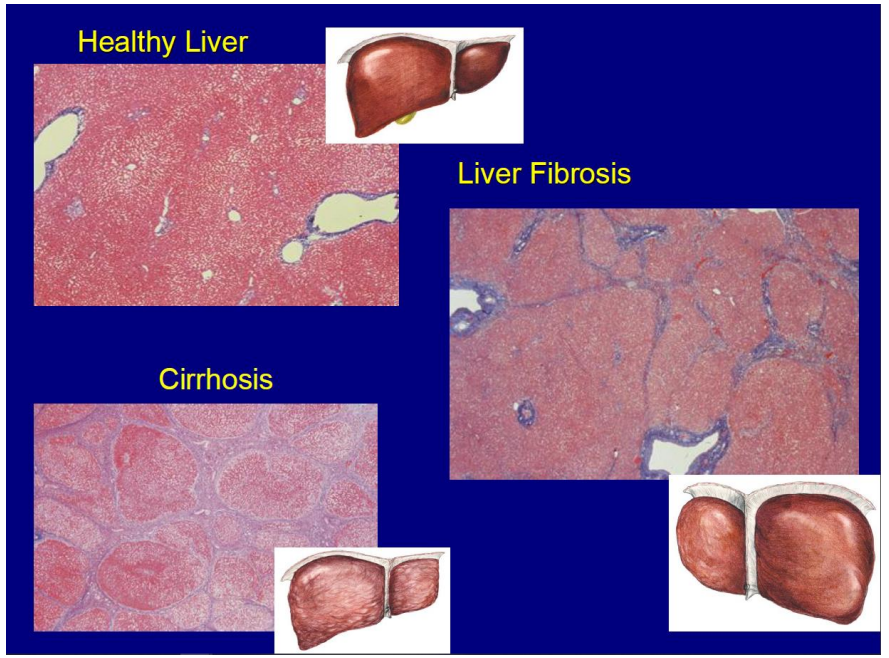
Radiographic Findings

- Suggestive of cirrhosis but they are not adequately sensitive or specific for use as a primary diagnostic modality
- Ultrasonography
  - Routinely used during the evaluation of the cirrhotic patient.
  - It is noninvasive, well tolerated, widely available, and provides valuable information.
  - In advanced cirrhosis, the liver may appear small and nodular.
  - Findings of portal hypertension include an increased diameter of the portal vein and the presence of collateral veins.
- Fibroscan
  - A vibration of mild amplitude and low frequency is transmitted through the liver inducing an elastic shear wave that propagates through the tissue. A pulse-echo ultrasound follows the propagation of the wave; the harder the tissue (and hence the more dense the fibrosis) the faster the wave propagates.
- CT Scan and MRI

CAT Scan in Cirrhosis

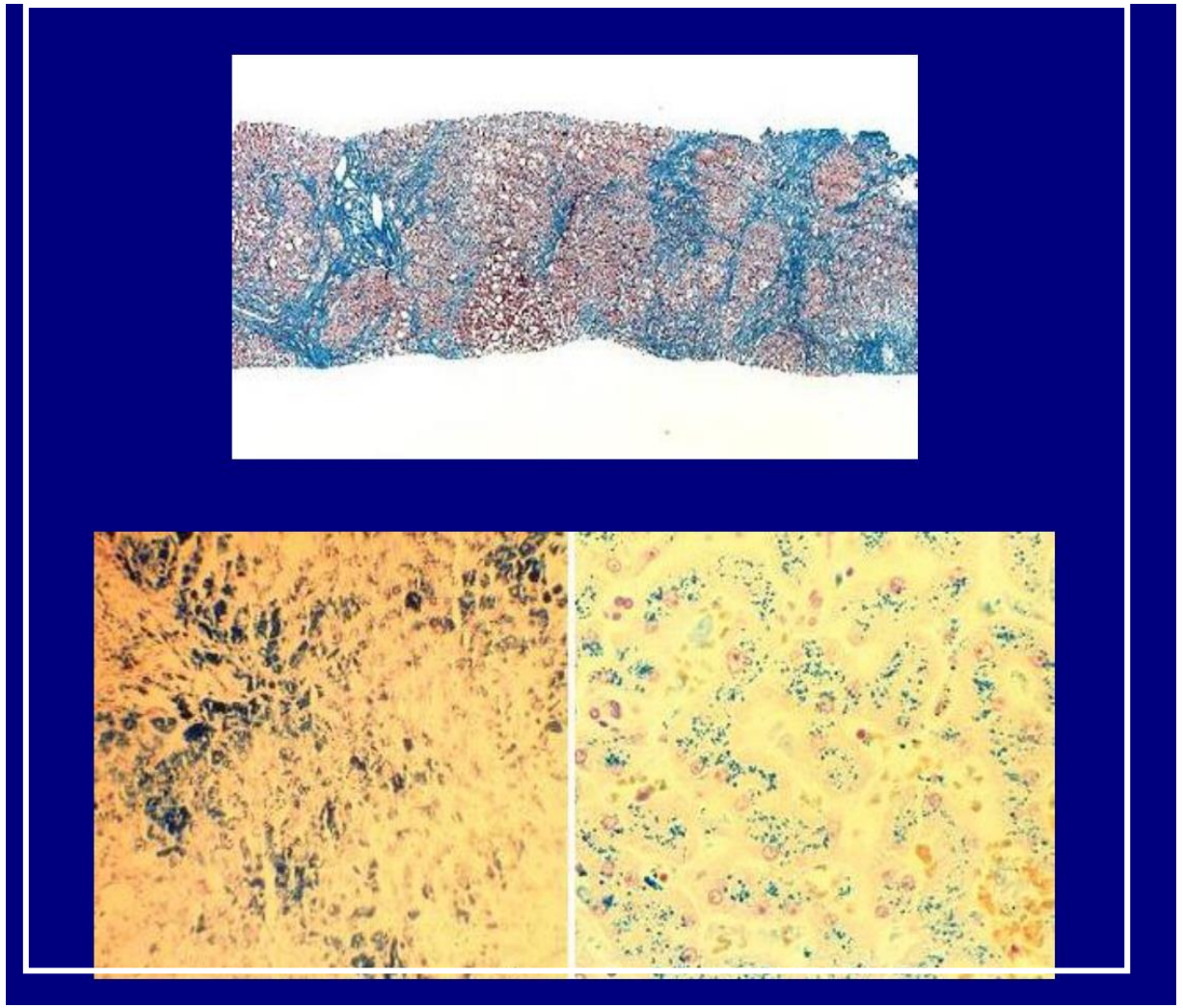


Liver Histology



- The gold standard for diagnosis is examination of an explanted liver at autopsy or following liver transplantation during which the architecture of the entire liver can be appreciated.
- Liver biopsy isn't necessary in the presence of any of the following: Decompensated Cirrhosis (Variceal hemorrhage, ascites, encephalopathy) + Liver-Spleen and/or CAT scan diagnostic of cirrhosis.
- Liver biopsy isn't necessary for pre-transplant evaluation.
- Confirmatory liver biopsy isn't always necessary in cirrhosis, only if there is a doubt about diagnosis.
- Alternative to biopsy → Fibro scan → if there is higher conduction of waves then it indicates more fibrosis in the liver.

Cirrhotic Liver Histology

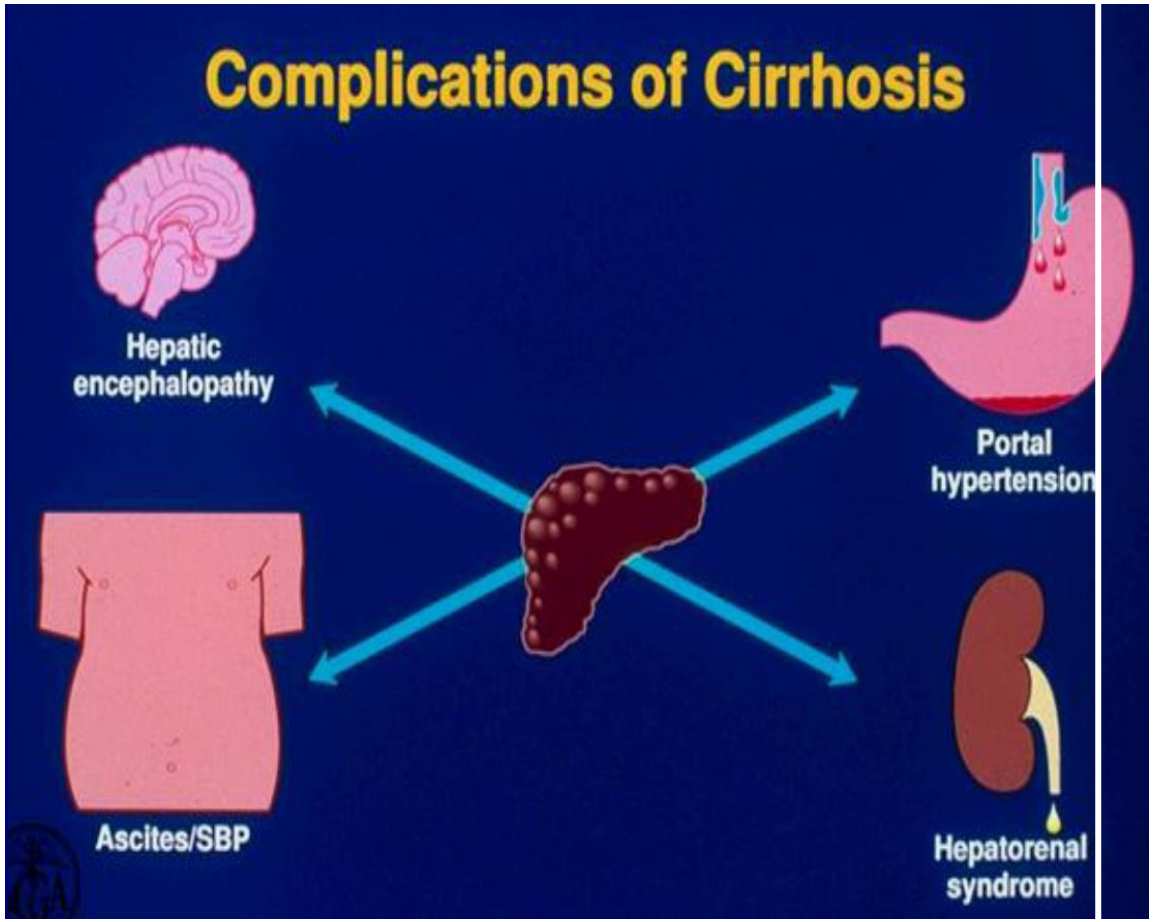


Child Score for Severity of Cirrhosis

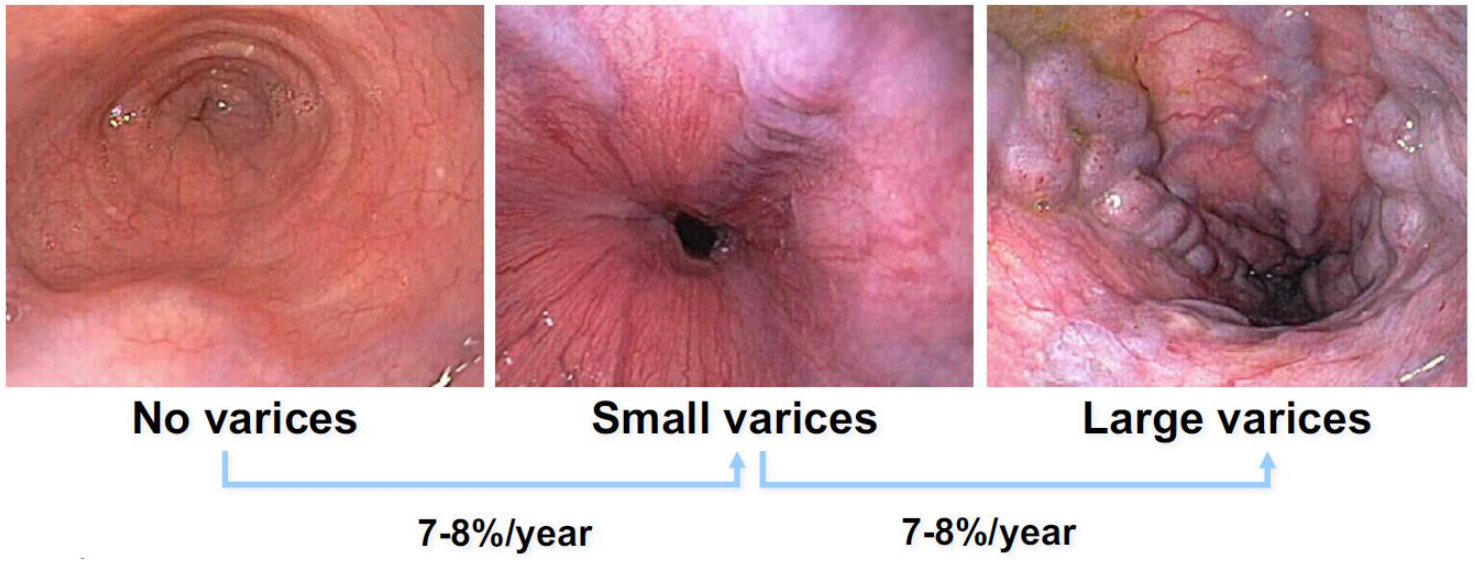
	1	2	3
Bilirubin (mg/dl)	<2.0	2-3	>3.0
INR	<1.7	1.7-2.3	>2.3
Albumin (mg/dl)	> 3.5	2.8-3.5	<2.8
Encephalopathy	None	I-II	III-IV
Ascites	None	Slight Moderate	Tense

Score	Stage
5 - 6	A
7 - 9	B
10 - 15	C

Complications of Cirrhosis

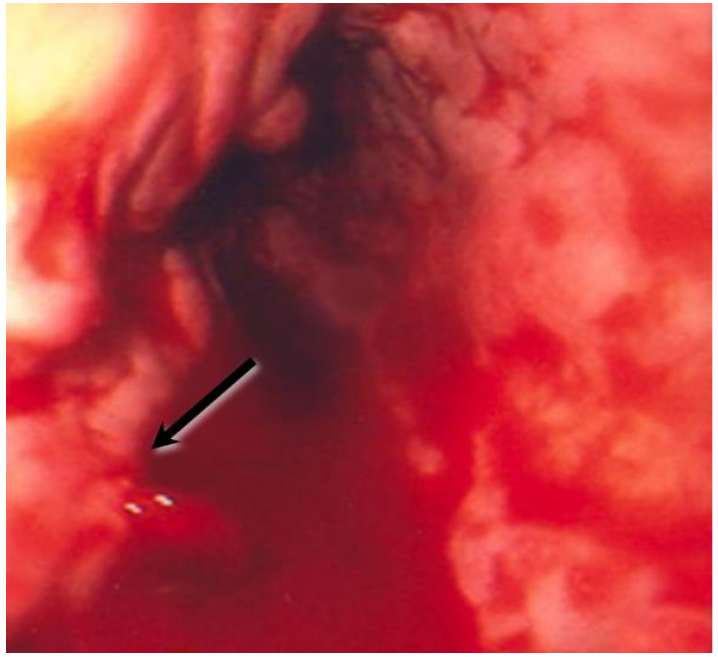


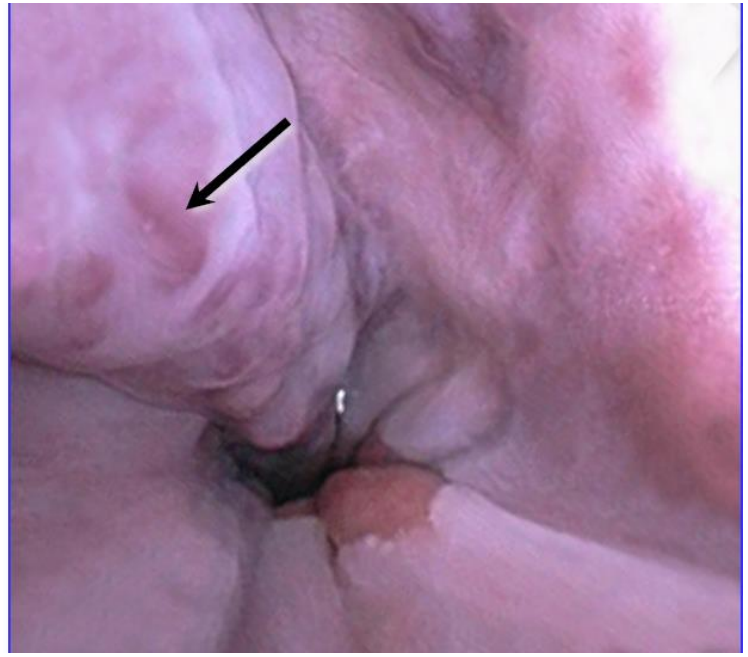
Varices



- Varices increase in diameter progressively → an increase in variceal pressure may lead to bleeding.
- Most patients with Variceal bleeding will have bacteriemia due to poor immunity and translocation of gut bacteria.

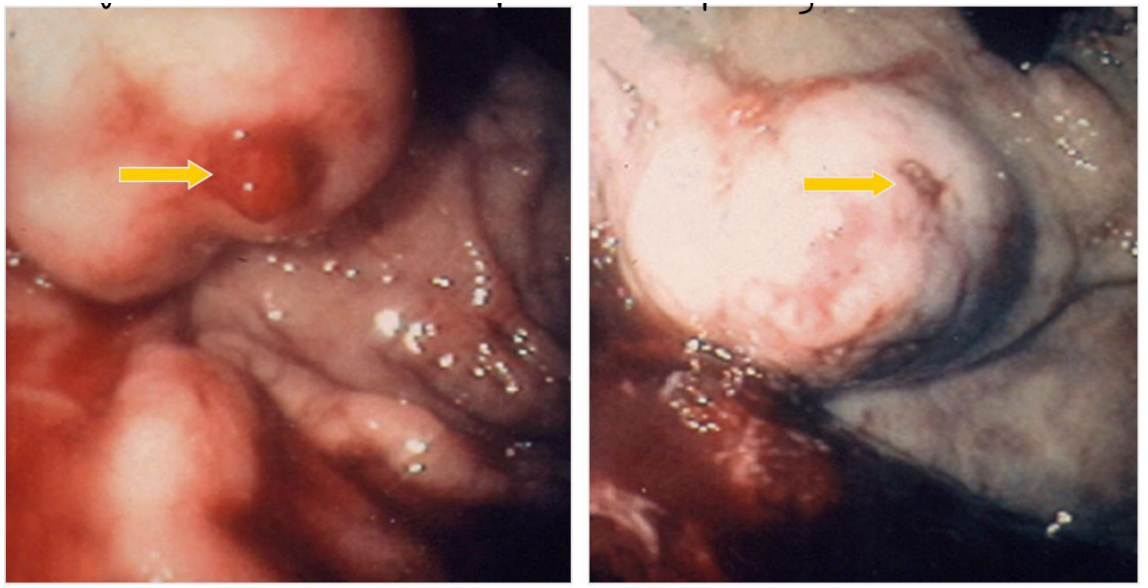
Varices





- Left → Variceal Hemorrhage
- Right → Varix with Red sign.
- If Varices are large → More likely to bleed.
- Predictors of Hemorrhage: Variceal Size + Red Signs + Child Score B/C

Gastric Varices



- One of the manifestations of Portal HTN bleeding.
- They can't be ligated so they are injected with glue for thrombosis to occur and stop bleeding

Nonalcoholic Fatty Liver Disease - Alcohol Related Liver Disease

Nonalcoholic fatty liver disease (NAFLD)

The most common form of chronic liver disease.

Second most common reason for liver transplant.

Third most common cause of Hepatocellular Carcinoma in western countries.

The hepatic manifestation of metabolic syndrome.

NAFLD patients can progress into liver fibrosis and cirrhosis if left without early treatment.

NASH is the most progressive form of NAFLD.

Lean NAFLD is when the patient appears lean (of normal weight) but have increased visceral fat (around the liver).

Metabolic Syndrome

Any 3 of the following 5 criteria:

1- Waist circumference (WC) >= 102 cm in men OR >= 88 cm in women.

2- Triglyceride >= 150 mg/dl.

3- HDL < 40 mg/dl in men OR < 50 mg/dl in women.

4- BP >= 130/85 mm Hg.

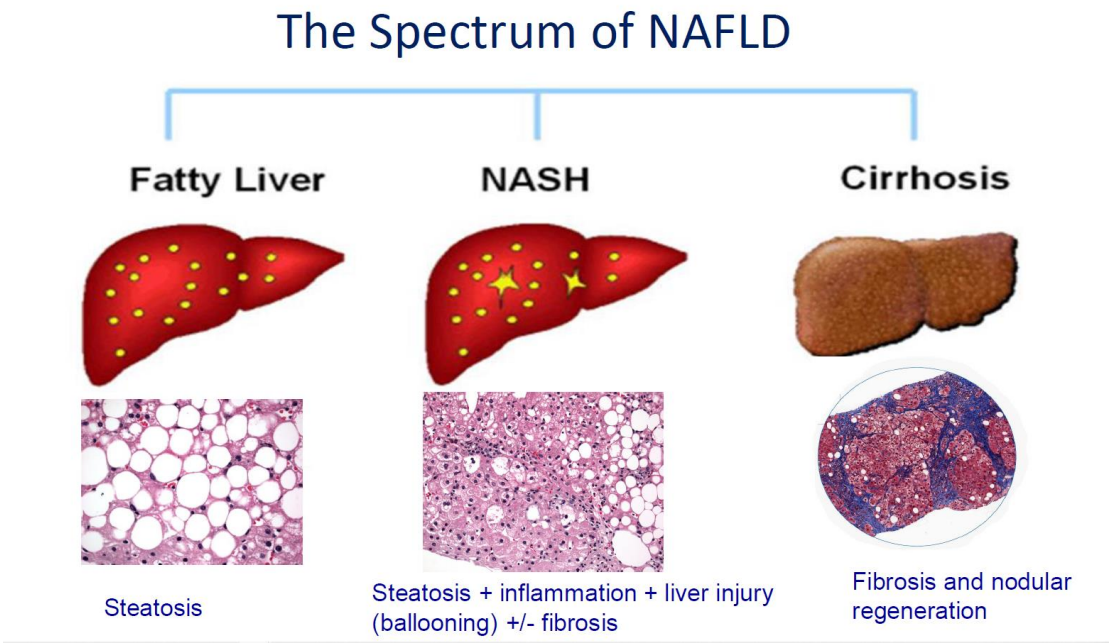
5- Fasting plasma Glucose (FPG) >= 110 mg/dl (if not diabetic >= 126 mg/dl)

NAFLD isn't one of the defining criteria for metabolic syndrome, it's a common hepatic manifestation.

Metabolic syndrome is the combination of DM, HTN, and Obesity.

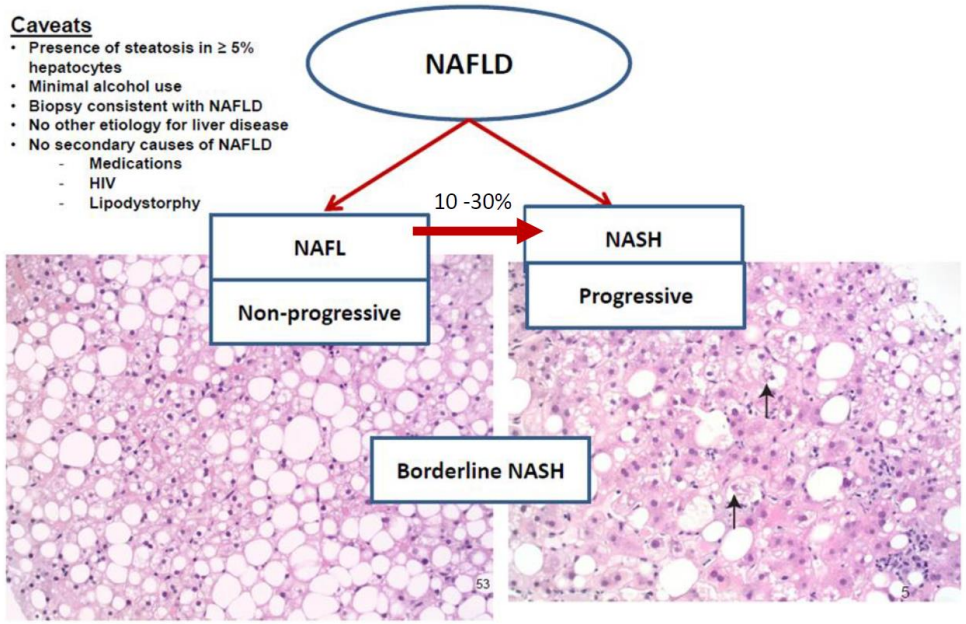
It puts you at greater risk of getting CAD, Stroke, and other conditions that affect blood vessels.

The Spectrum of NAFLD



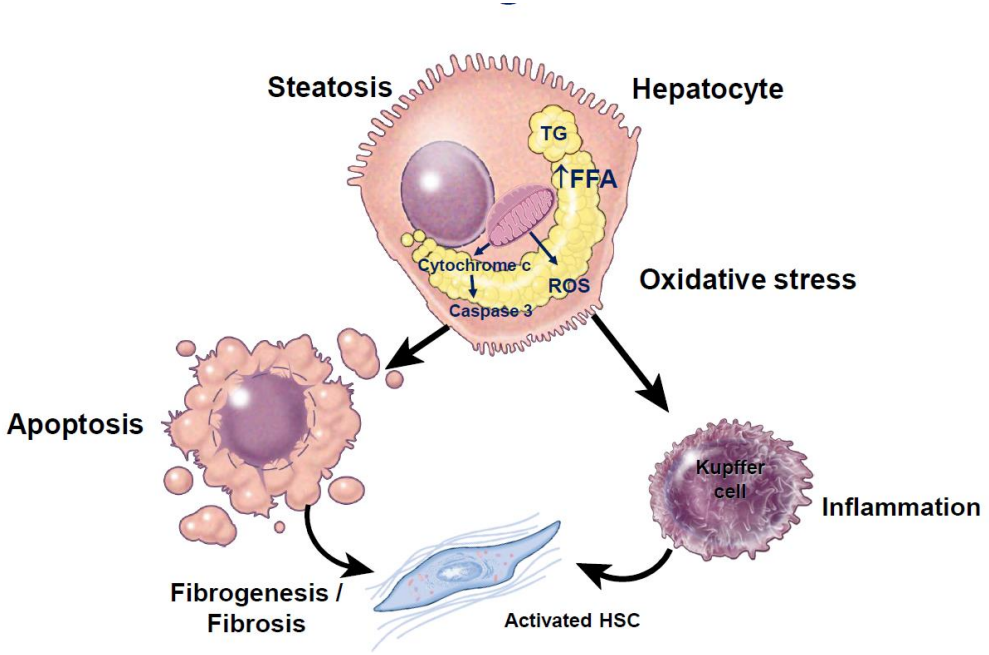
- Fatty liver is a benign condition → Steatosis without inflammation.
- Cirrhosis is an irreversible condition

Subtypes of NAFLD



- NAFL → Nonalcoholic Fatty liver
- NASH → Nonalcoholic Steatohepatitis.
- 10-30% of patients with NAFL develop NASH

Pathogenesis of NAFLD



- Multi-hit hypothesis: First hit is the accumulation of fatty acids in the hepatocytes → this affects the mitochondria causing oxidative stress → Increased ROS → inflammation of Kupffer cells → this activates Stellate cells → producing more collagen → Fibrosis.
- Fibrosis can also be caused due to apoptosis of hepatocytes.

Clinical Presentation of NAFLD

- usually asymptomatic (45- 100%)
- minimal / non-specific symptoms:
  - fatigue (20- 73%)
  - RUQ discomfort (15- 48%)
- hepatomegaly may be detected (60- 80%)
- often an “incidental” finding:
  - incidental elevated aminotransferase levels
  - incidental fatty liver on radiographic studies
  - incidental hepatomegaly

Labs

- Liver tests
- Non-invasive markers
- Imaging
- Liver Biopsy

Biochemical Findings

Parameter	Finding
AST and ALT	↑ 2 – 5 fold
AST/ALT ratio	< 1 (in 65 – 90% of pts)
Alkaline phosphatase	↑ 2 – 3 fold (< 50% pts)
Albumin, Bilirubin , INR	Normal (unless cirrhosis has developed)
Serum Ferritin	↑ed ~ 50 % of pts

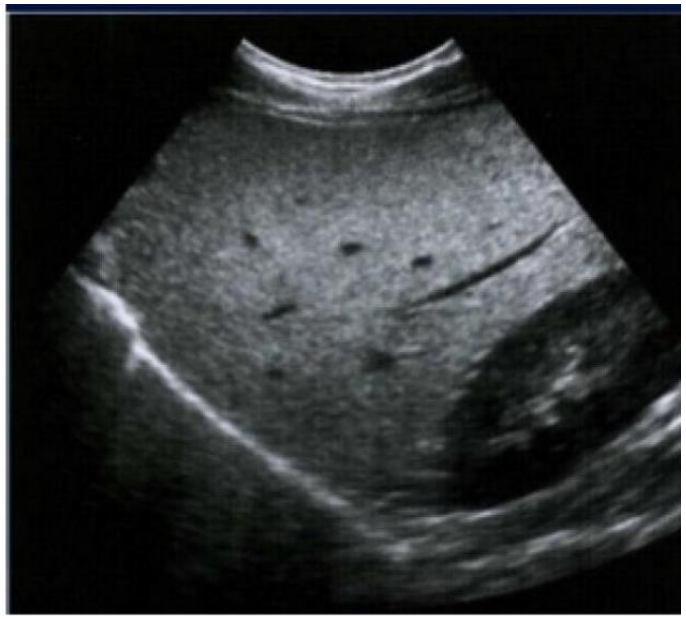
- AST increases more than ALT with disease progression
- AST/ALT ratio > 1 → advanced fibrotic form of NAFLD
- ratio almost never > 2

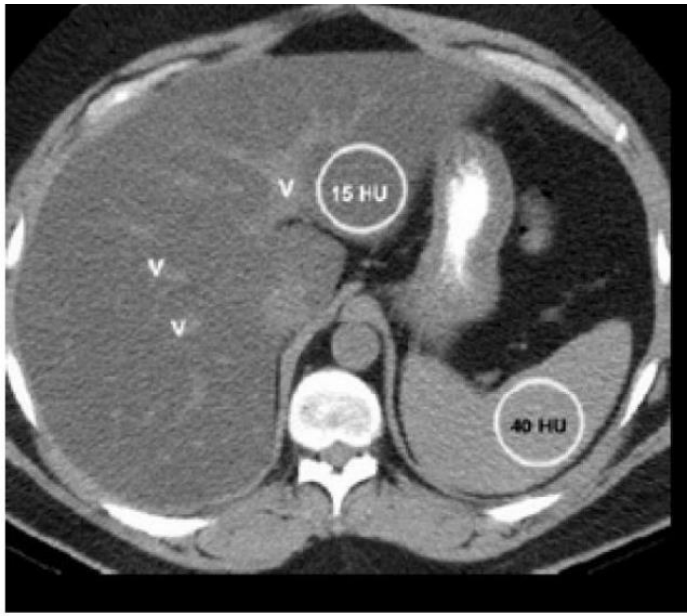
- - AST and ALT are mildly elevated.
- - ALT is increased more than AST, unlike in alcoholic liver disease
- - Albumin, Bilirubin and INR remain normal until cirrhosis develops (they become elevated).

Imaging Modalities in NAFLD

- Ultrasound
- CT scan
- Transient elastography
- MR technologies

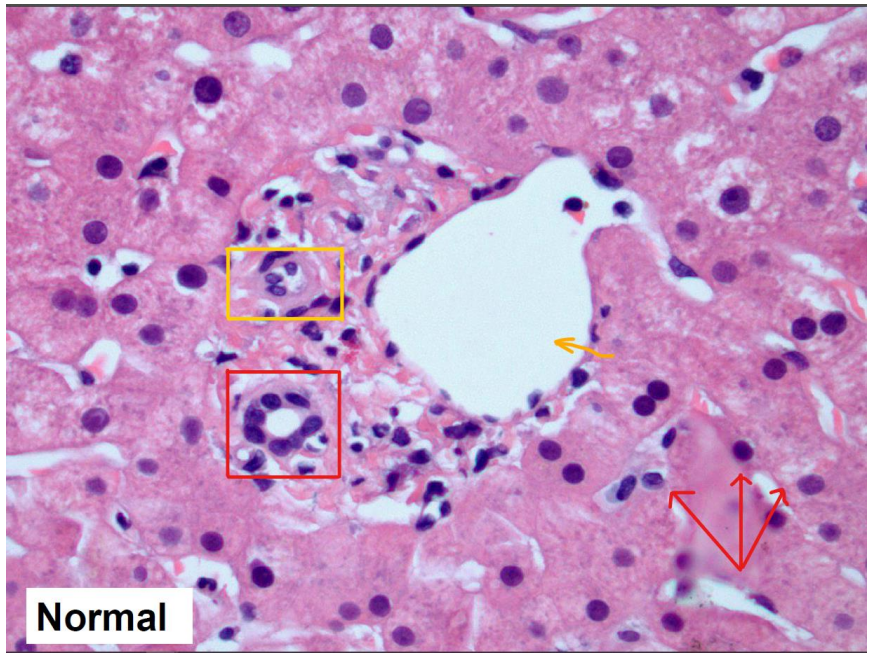
Imaging Findings in NAFLD





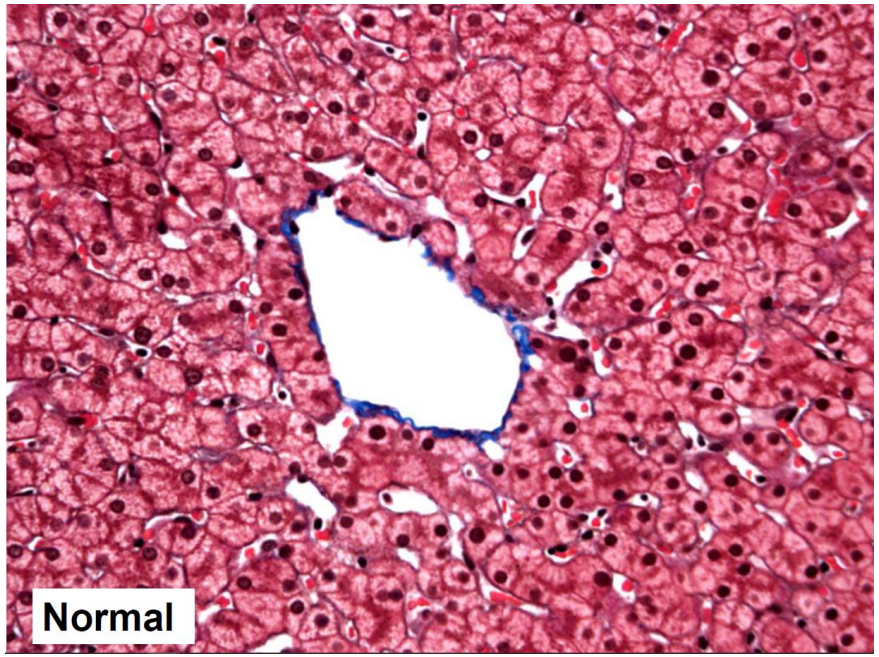
- On CT we have low attenuation (means that the area is less dense than the surroundings) compared with the spleen → attributed to the presence of fat.
- On Ultrasound we have Increased Echogenicity (meaning the liver is more dense than normal towards sound waves) + Hepatomegaly

Liver Histology



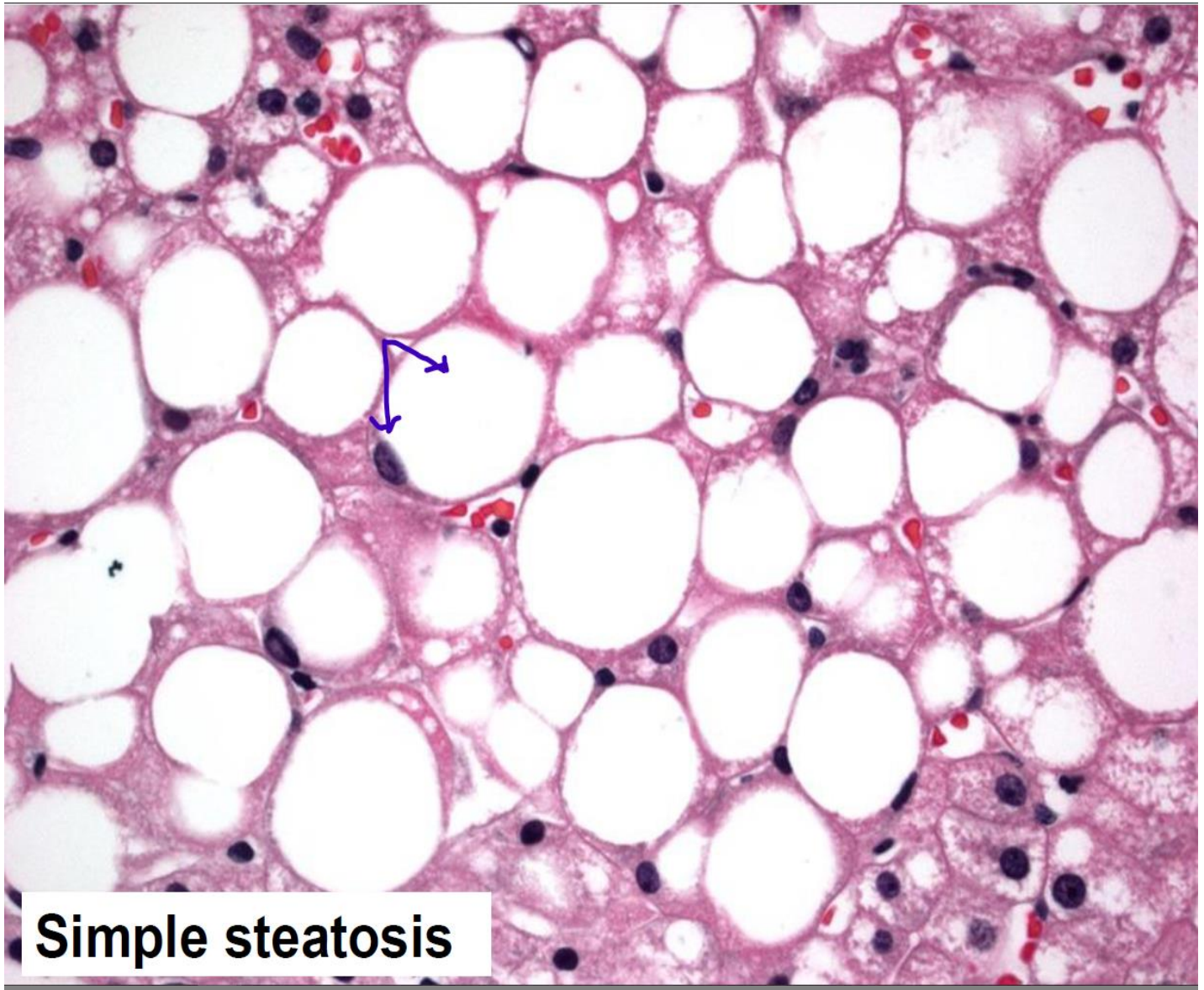
- Normal Liver.
- Yellow Rectangle → Hepatic Artery
- Red Rectangle → Bile Duct
- Yellow Arrow → Portal Vein
- Red Arrows → Hepatocytes around portal triad.
- Using H&E stain, this section shows the normal appearance of the portal triad consisting of Hepatic artery, Bile duct and Portal vein.

Liver Histology



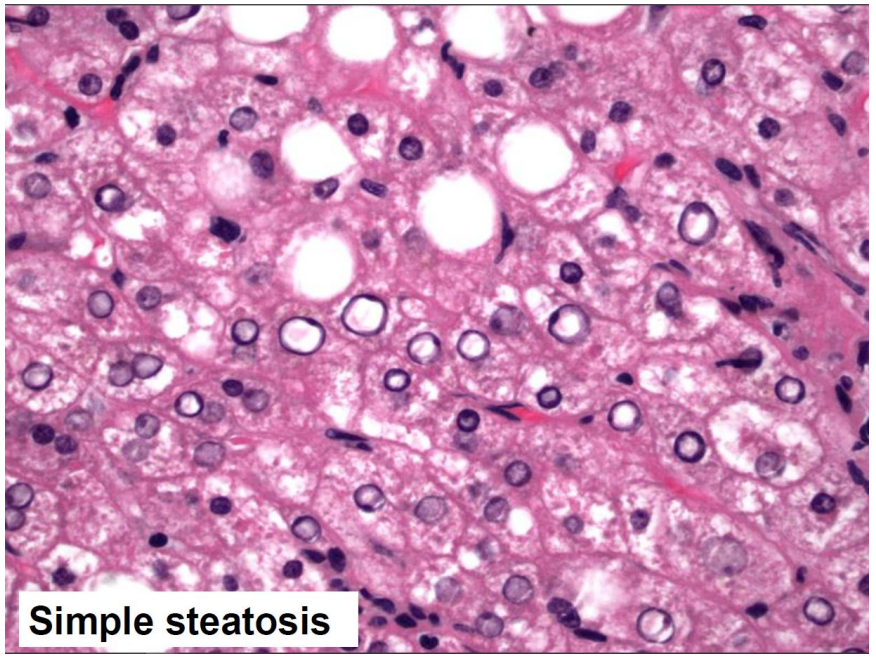
- – In this section, Trichrome staining was done, which stains collagen (Blue); here it's seen normally around the vessel.

Liver Histology



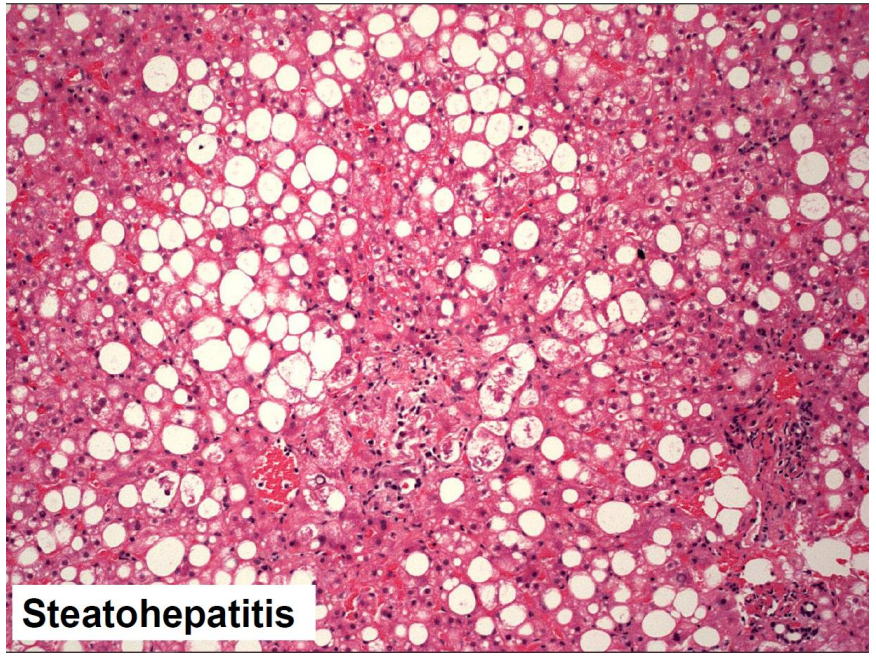
- Blue arrows show Fat accumulation within the hepatocytes that pushes the nucleus to the periphery

Liver Histology



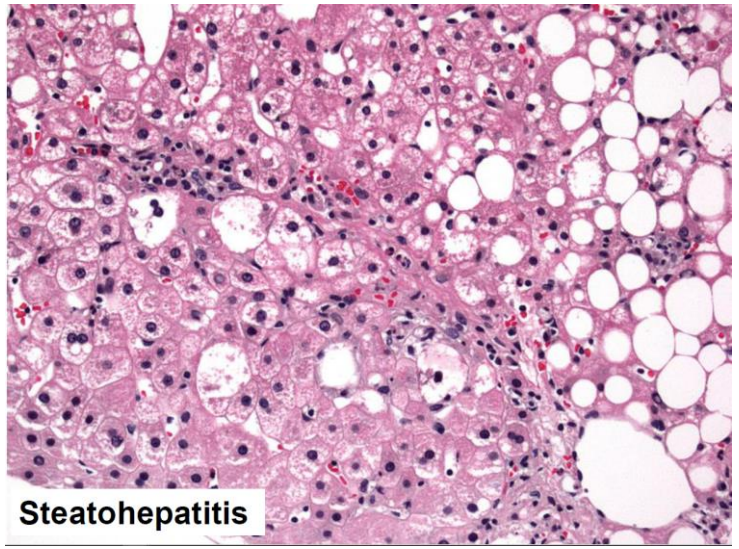
- – Fat accumulation within Hepatocytes pushes the nucleus to the periphery + No signs of inflammation indicating Simple Steatosis.

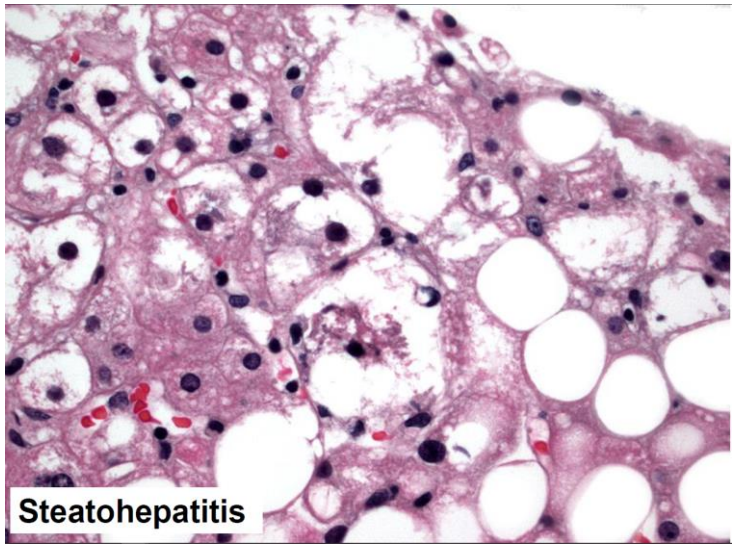
Liver Histology



- – This section shows inflammatory cells infiltrating the lobule with hepatocytes ballooning (which is a marker of liver injury).

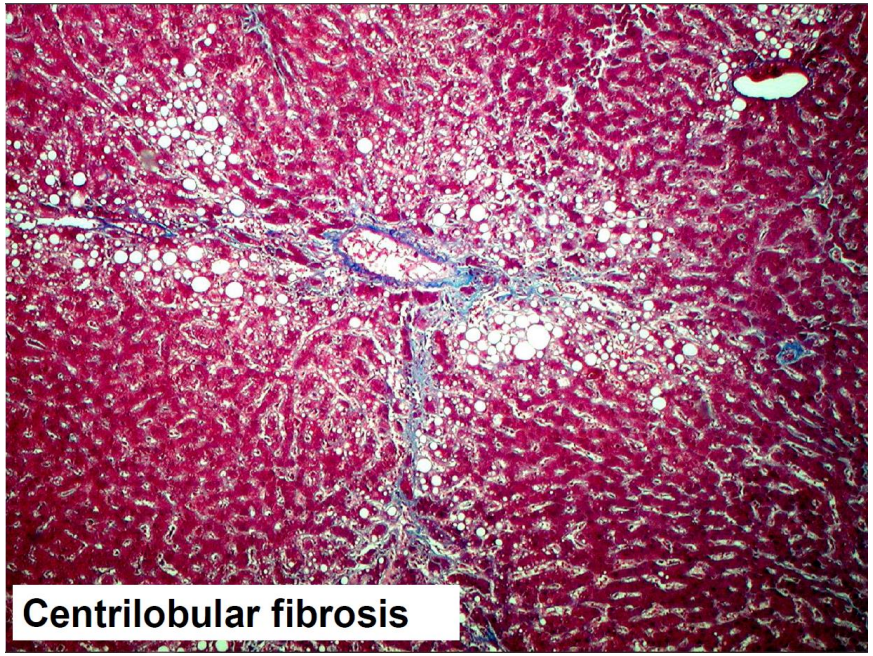
Liver Histology





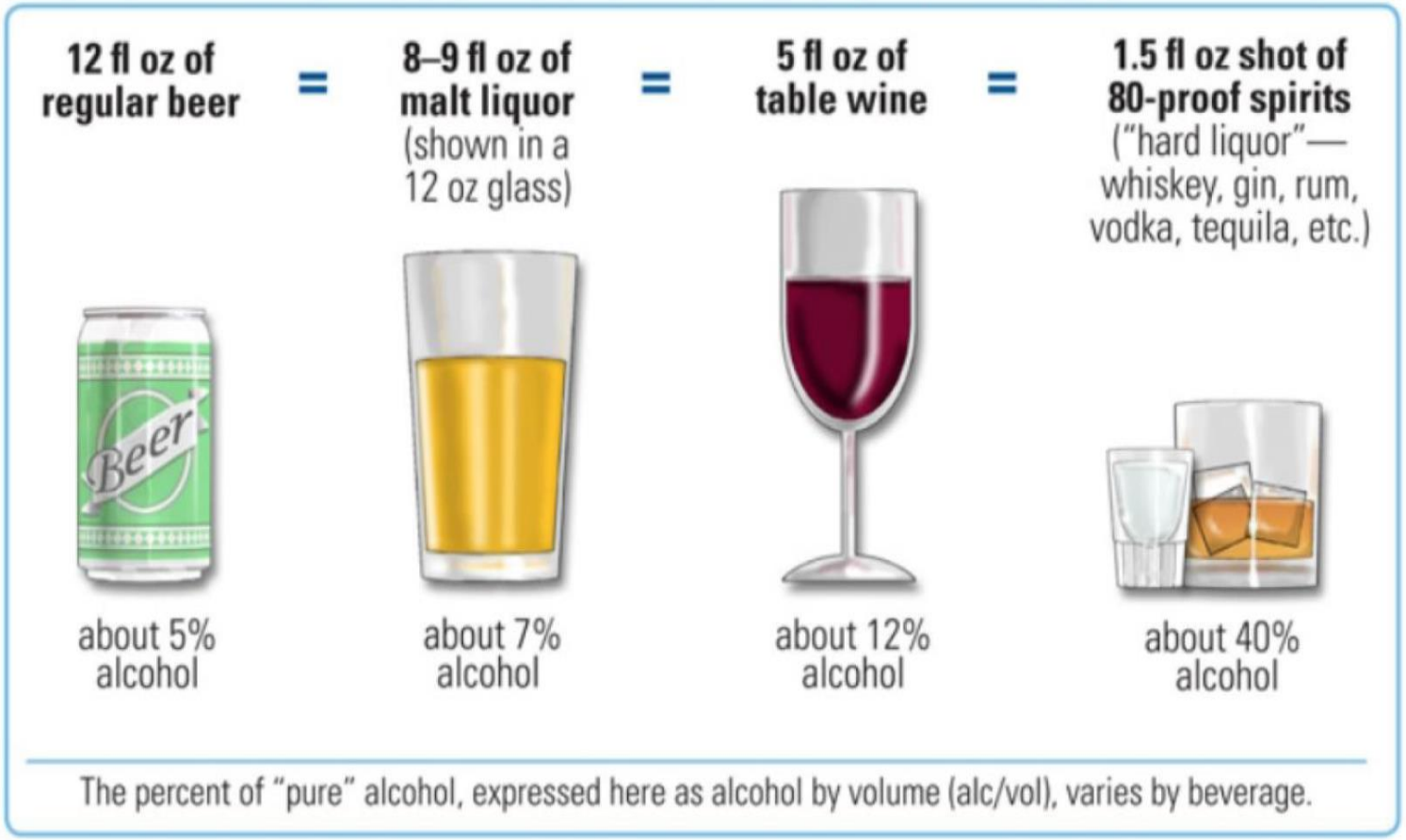
- – Hepatocellular ballooning is a key finding in Nonalcoholic Steatohepatitis (NASH). It's conventionally defined by hematoxylin and eosin (H&E) staining showing enlarged cells with rarefied cytoplasm and recently by changes in the cytoskeleton. It will eventually undergo apoptosis.

Liver Histology



- – Trichrome Staining showing a lot of fibrosis (Chicken wire fibrosis: Strands of collagen surrounding damaged hepatocytes, forming a network that is highlighted by trichrome stain).

How Much is "Just One Drink" (12-14g)?



- Drinkers underestimate alcohol consumption by ~ 40%

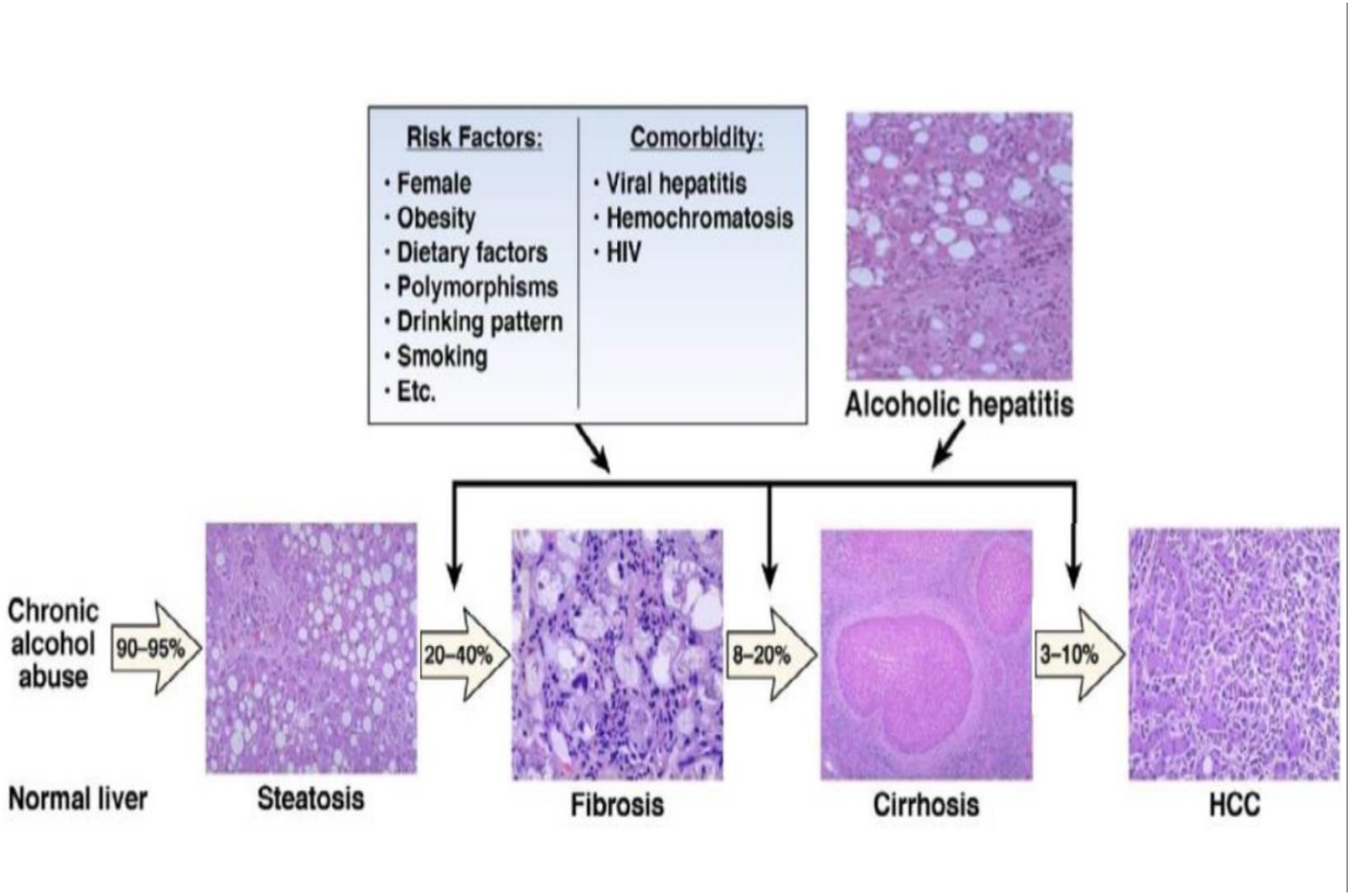
Low Risk Drinking: NIAAA Definition

- National Institute of Alcohol Abuse and Alcoholism Defined Drinking at Low Risk of Developing Alcohol Use Disorder (AUD) as:
- For Women (3 OR 7 Rule), Low risk drinking is defined as no more than 3 drinks on any single day, and no more than 7 drinks per week (Caution: Breast cancer and other risk increases with 1 drink per day).
- For Men (4 OR 14 Rule), No more than 4 drinks on any single day, and no more than 14 drinks per week.

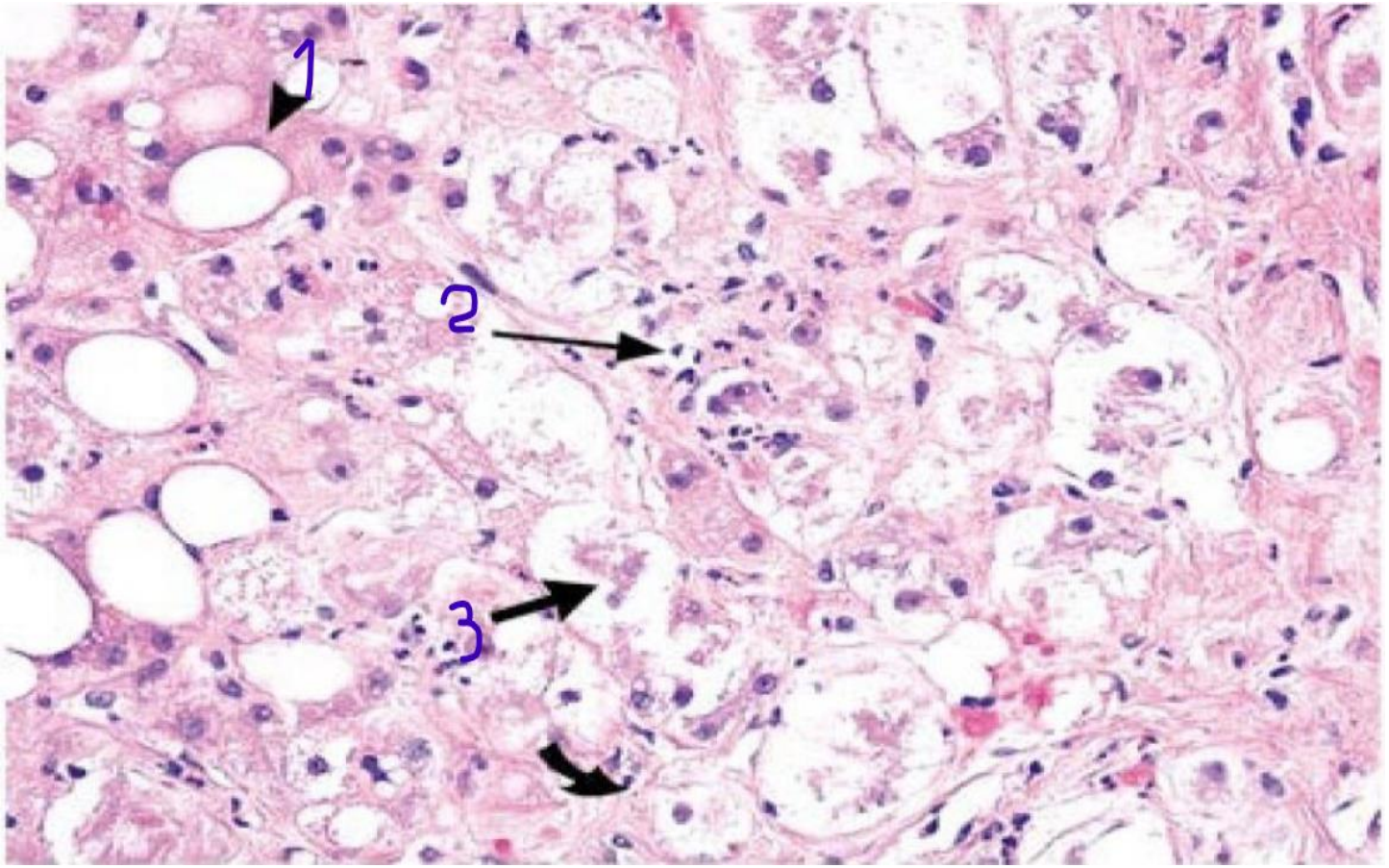
How Much Should You Drink to Get Alcohol Related Disease

- Heavy alcohol :3 drinks per day for women (≥40 grams of alcohol), and four drinks per day for men (≥50-60 grams of alcohol).
- Strong correlation between severity and duration of alcohol misuse and the presence of cirrhosis.
- 3% of patients with alcoholic hepatitis progress to cirrhosis annually
- Rate of cirrhosis higher in patients consuming ≥ 30 g / d than abstinent controls or consuming <30 g / day (2.2% vs 0.08%)
- Alcohol consumption > 120 g /day highest risk of cirrhosis (13.5%)

Histopathological Progression of ALD: Risk Factors and Co-morbidities



Histopathological Features of Alcoholic Hepatitis



- Similar to NASH:

1 → Steatosis

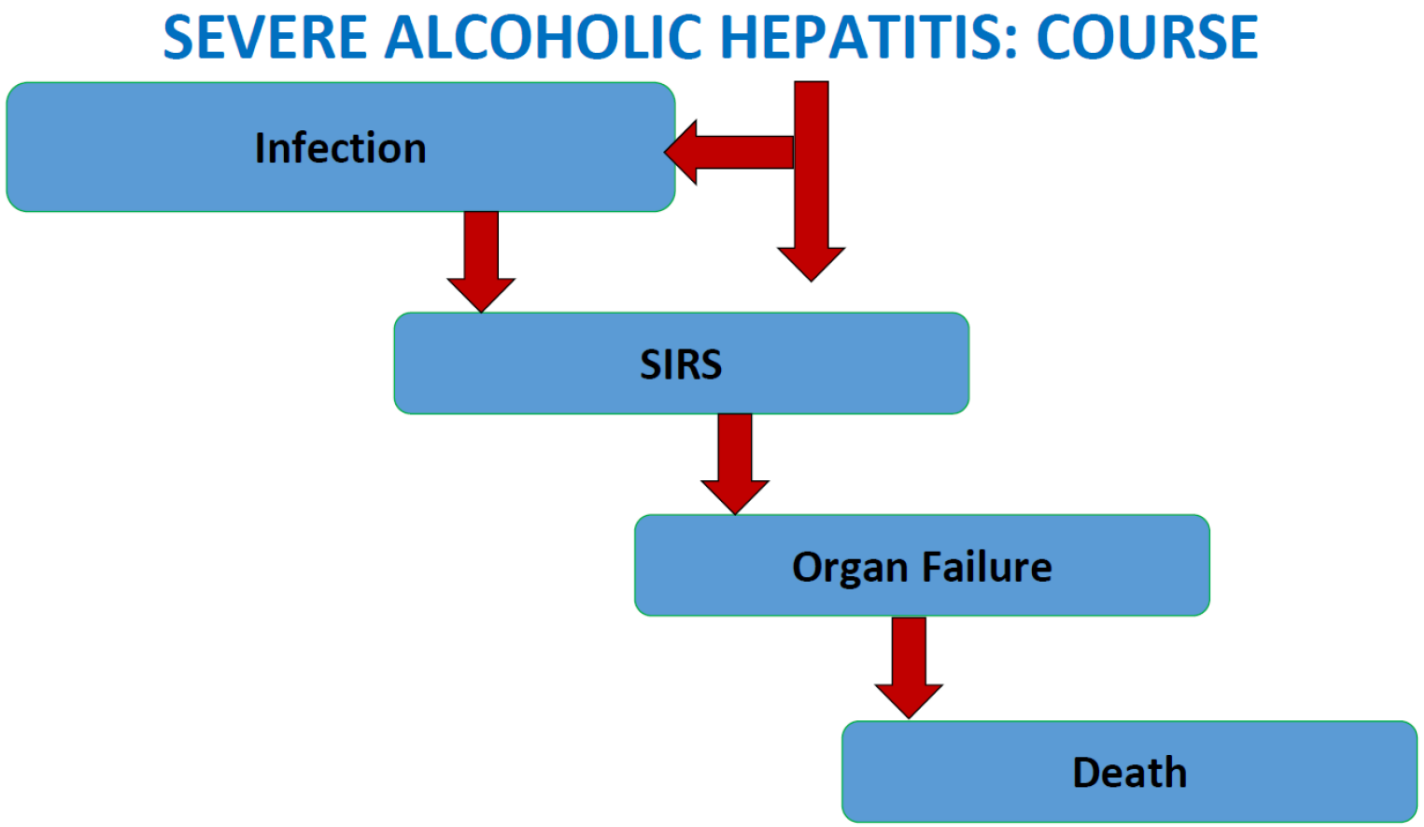
2 → Inflammatory Infiltrates

3 → Ballooning

Clinical Manifestations of Alcoholic Hepatitis

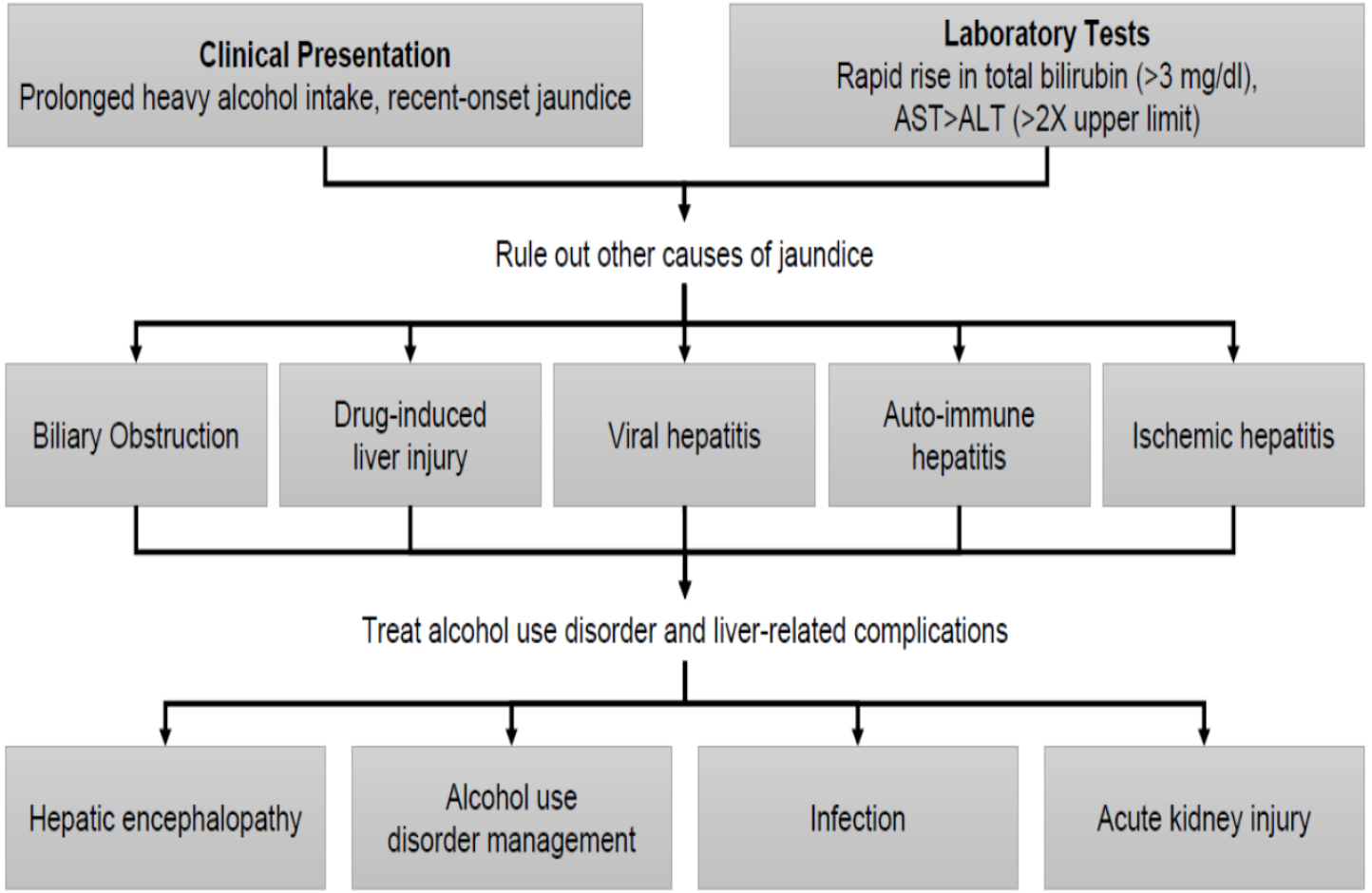
- Consequences of liver failure: Jaundice
- Ascites
- Encephalopathy
- Systemic Inflammation and sepsis: SIRS
- Multiple organ failure
- Impaired hepatocyte regeneration: Propagation of liver failure
- Features of alcohol withdrawal syndrome

Severe Alcoholic Hepatitis: Course



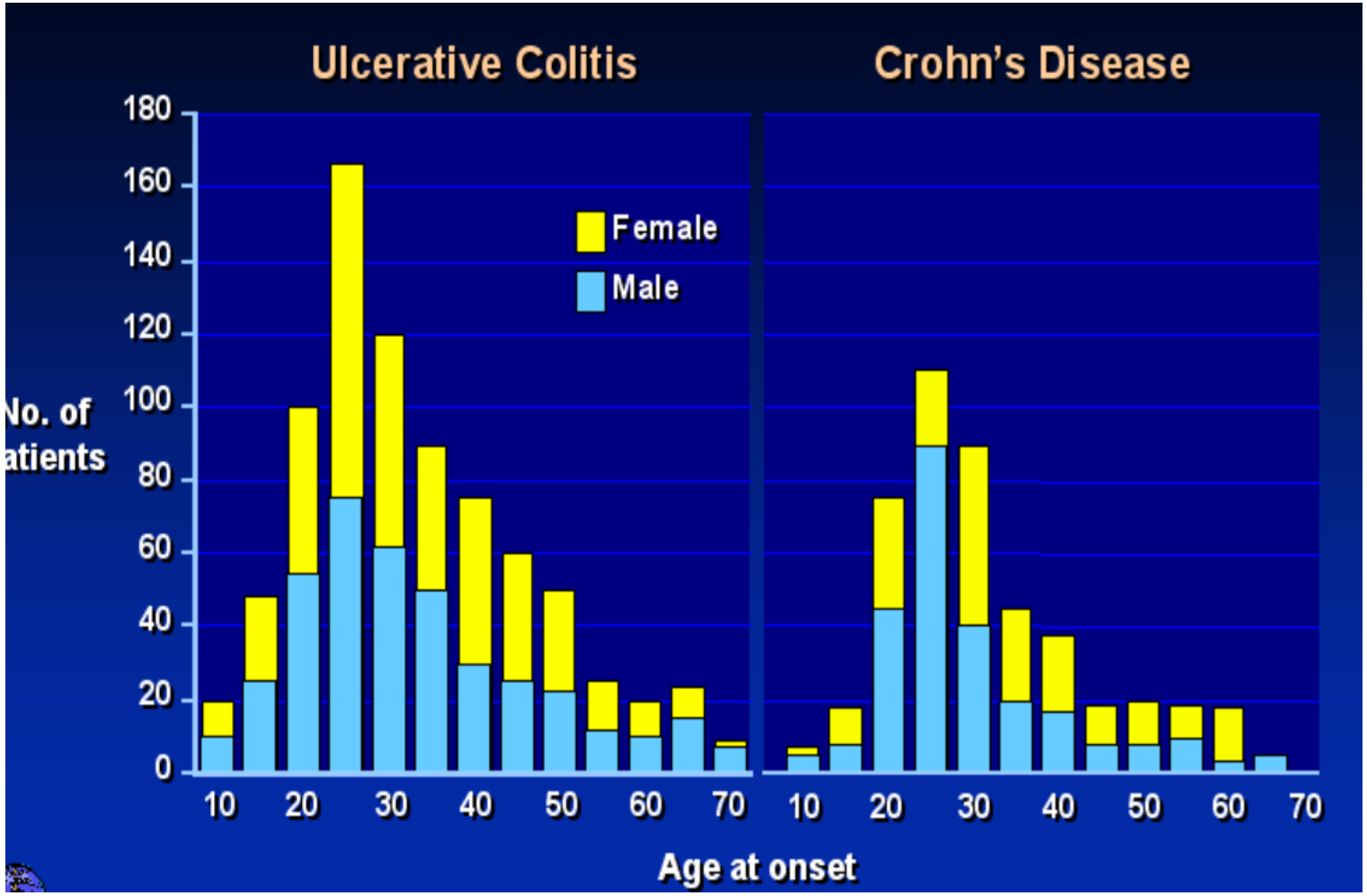
- SIRS → Systemic Inflammatory Response Syndrome; an inflammatory state affecting the whole body

Alcoholic Hepatitis Initial Evaluation



Inflammatory Bowel Disease

IBD - Age and Sex Distribution



- Most cases are Young individuals.

Etiological Theories

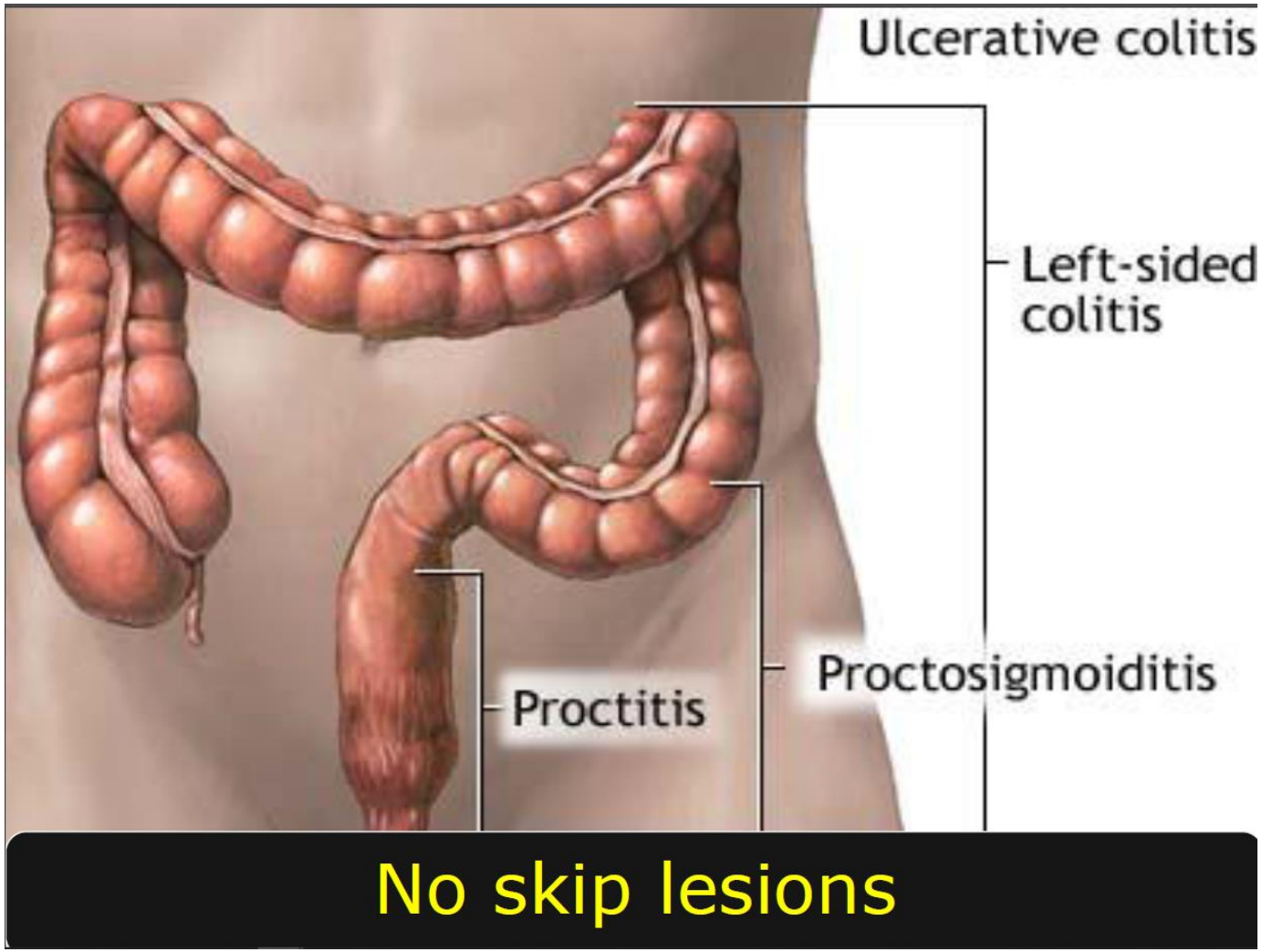
- Infectious
- Immunological
- Genetic
- Dietary
- Environmental
- Vascular
- Allergic
- Psychogenic

- Immunological → as the disease responds to immunomodulators + Lots of immune mediators are involved like T-lymphocytes, WBCs also secrete Cytokines, Chemokines for several purposes in response to Antigens.
- Group of Chemokines promote inflammation and group of them suppress it → Deranged balance in IBD → More inflammation due to an unknown antigen.

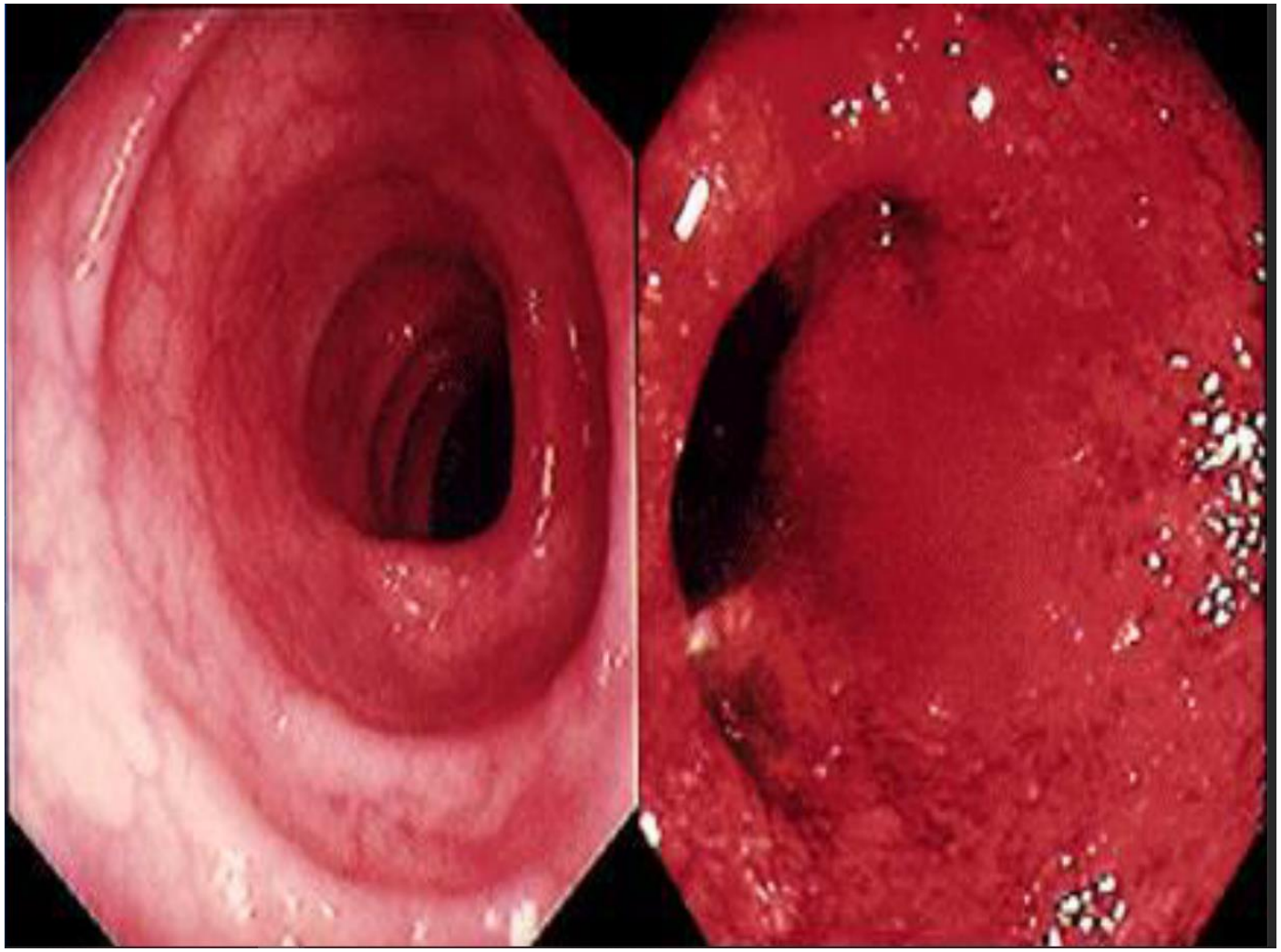
Ulcerative Colitis (UC)

- Characterized by recurring episodes of inflammation limited to the mucosal layer (only superficial layer) of the colon (chronic relapsing remitting disease).
- It almost invariably involves the Rectum and may extend in a proximal and continuous fashion to involve other portions of the colon.
- Ulcerative Proctitis: Limited to the Rectum.
- Proctosigmoiditis / Distal Colitis: Involving to mid sigmoid area.
- Left Sided Colitis: Up to the Splenic Flexure proximally.
- Pancolitis: Beyond the Splenic Flexure proximally.

Ulcerative Colitis



Ulcerative Colitis



- On the left we have Normal Colon showing smooth surface with veins running through the mucosa.
- On the right we have diffused mucosal inflammation with ulcers and bleeding

UC: Signs and Symptoms

Bloody Diarrhea	Weight Loss
Tenesmus	Joint Pain
Urgency	Skin Rash
Abdominal Pain	Fatigue
Fever	

- Abdominal pain is more prominent in Crohn's.
- Bloody diarrhea is more prominent in UC and is the most common Sign.
- Tenesmus and urgency are characteristics of lower rectum inflammation; due to being near the dentate line.

UC: Signs and Symptoms

- **Mild disease**

Proctitis or proctosigmoiditis or distal colitis intermittent rectal bleeding associated with the passage of mucus

*mild diarrhea with fewer than **four** small loose stools per day*

- **Moderate disease**

*involvement of more than the distal colon, frequent loose, **bloody stools (up to 10 per day)**, mild anemia*

- **Severe disease**

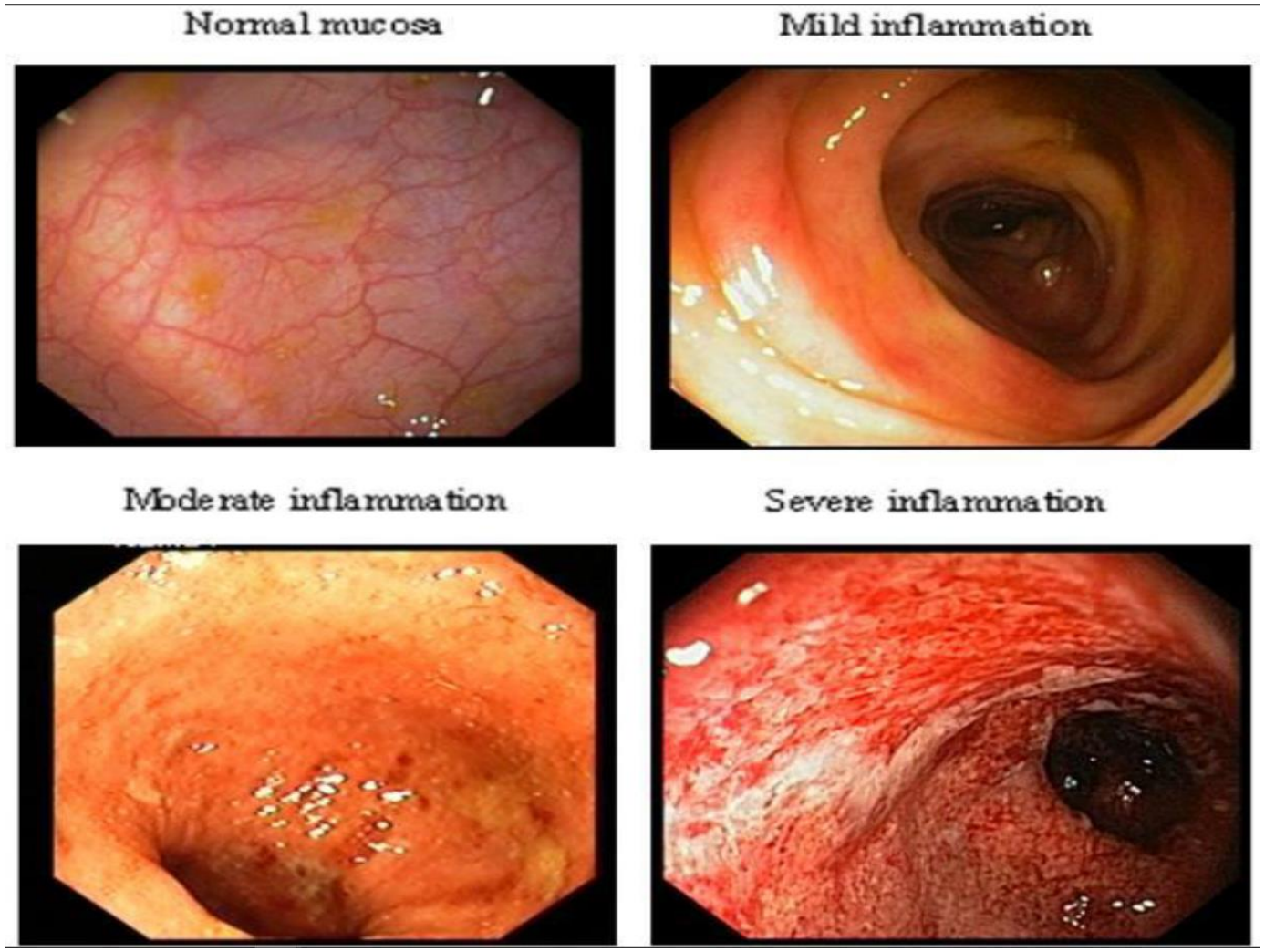
extensive colonic involvement

frequent loose stools **(greater than 10 per day) with severe cramps, fever up to 39.5°C**

bleeding often necessitating blood transfusion. They may suffer rapid weight loss, leading to a poor nutritional state.

- Mild Disease → Bowel motion < 4 per day

UC



- Mild inflammation → Associated with Edema + Loss of Vascular marking
- Moderate inflammation → with Ulceration
- Severe inflammation → with Extensive Ulceration.

UC: Diagnosis

- **History**
- **typical endoscopic appearance**
- **confirmatory histology seen** on **colonic biopsy**

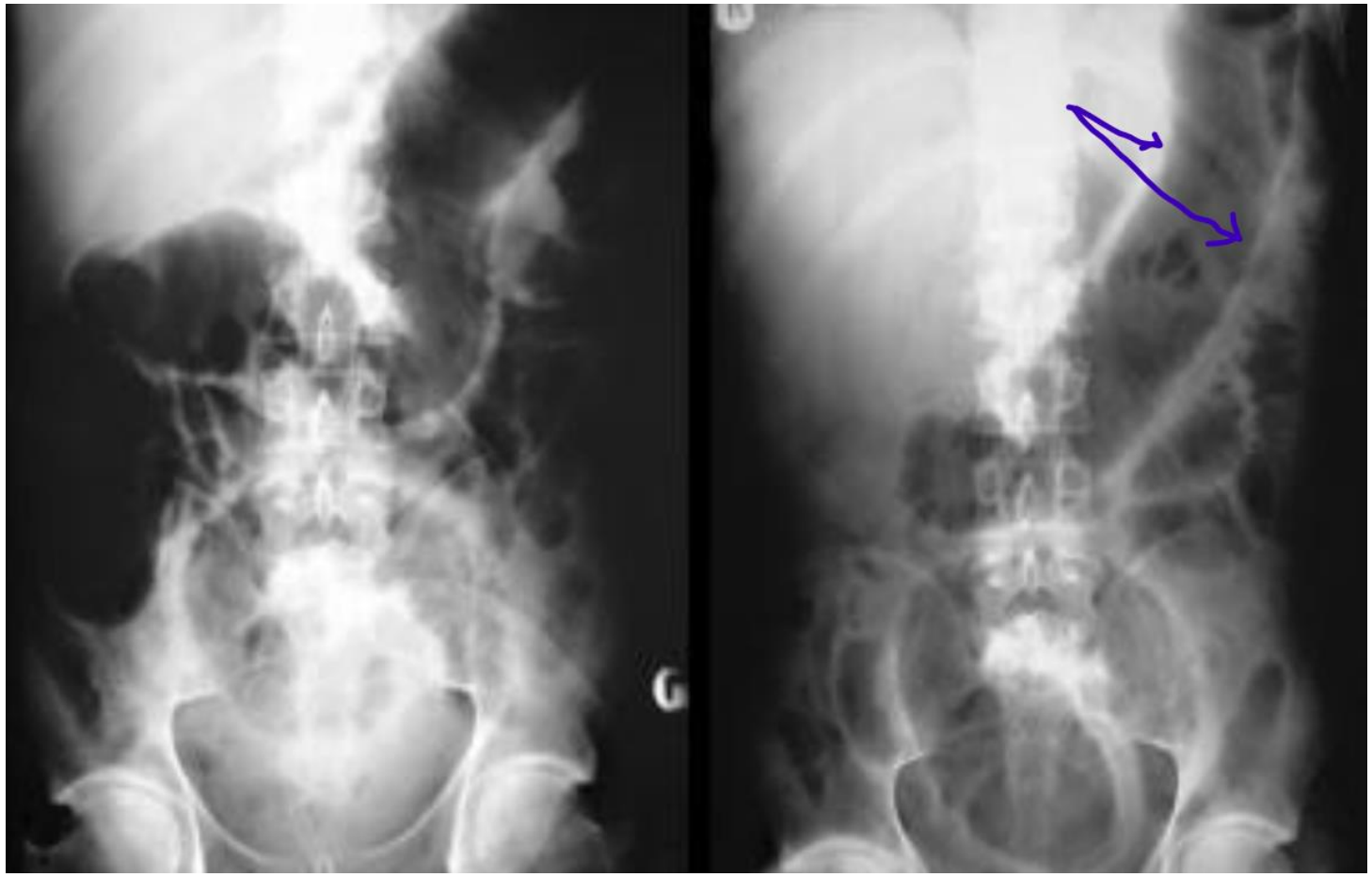
- **Serological markers**
  - pANCA Positive
  - ASCA Negative

Positive predictive value 75%

Routine labs
Stool for R&M Culture, Cl Difficle toxines and Faecal calprotectin.

- History → Chronic Diarrhea with blood + Tenesmus + Urgency + Fever + Weight loss.
- ASCA is positive in Crohn's differentiating it from UC.
- Fecal Calprotectin → Marker of inflammation in the bowel (>250).
- Fecal Calprotectin levels <100 in remission (if the level is low it indicates improvement).

UC: Abdominal X-ray



- Abdominal X-ray is useful in diagnosing UC.
- Excludes Toxic Megacolon (where the bowel distention is beyond a particular diameter).
- Blue arrows show Thickened bowel wall, Slight distension and loss of Haustrations.

UC: Pathology

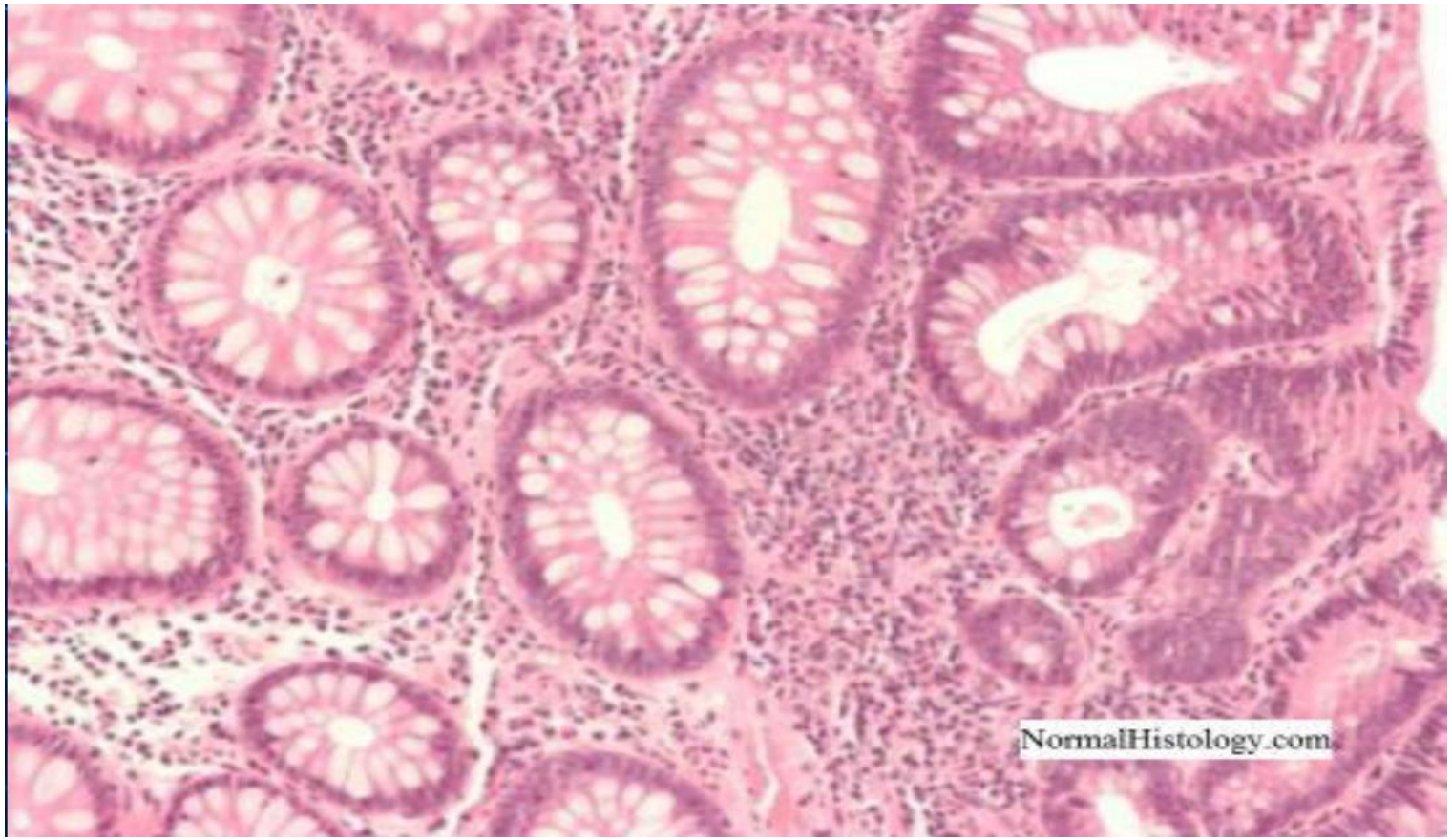
- Changes are limited to mucosa and sub mucosa except in sever cases.
- There is crypt distoration
- Cryptitis / crypt abscesses

Lamina propria expansion with acute and chronic inflammatory cells

- There is basal plasma cells and lymphoid infiltration.

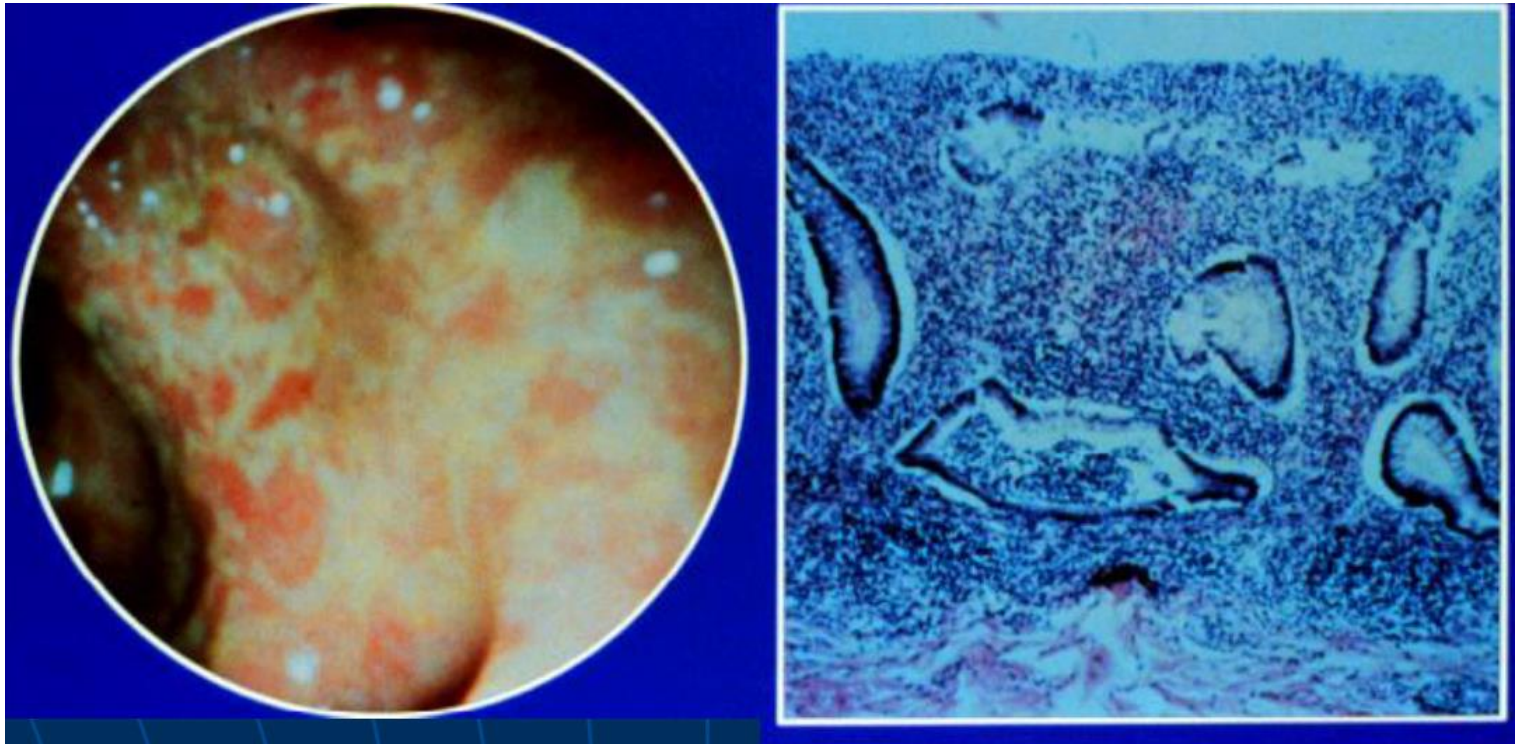
- Cryptitis / Crypt abscesses indicates Chronicity.

Normal Colon



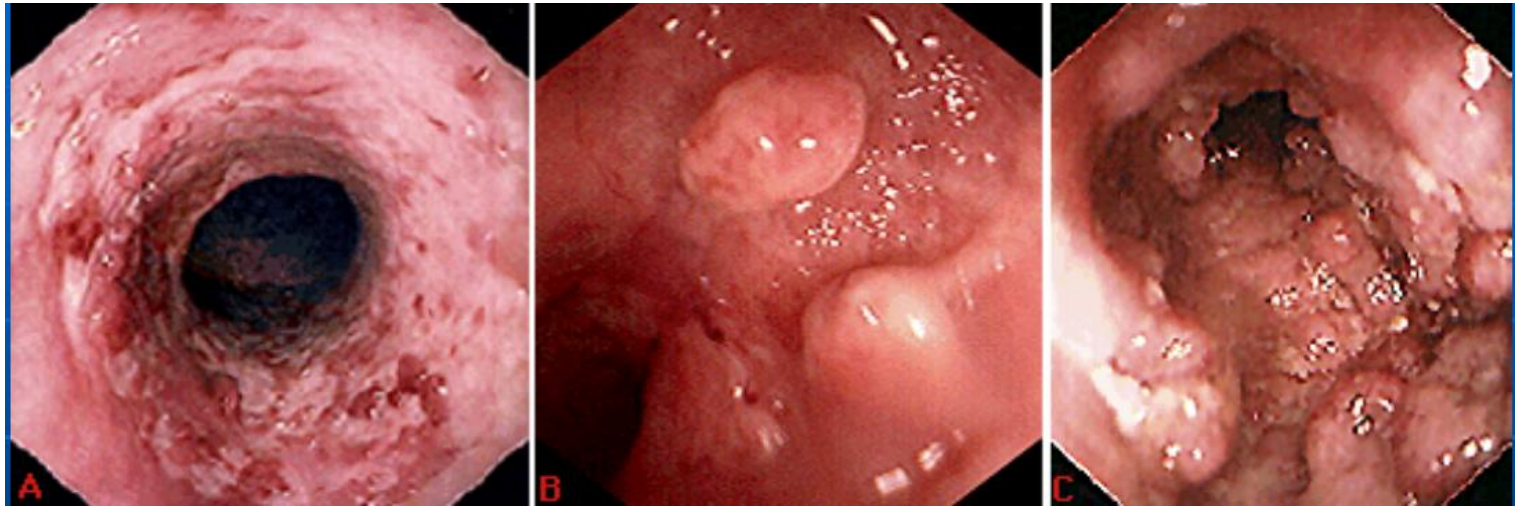
- Normal Daisy-Like shaped glands + Normal Number.

Severe UC



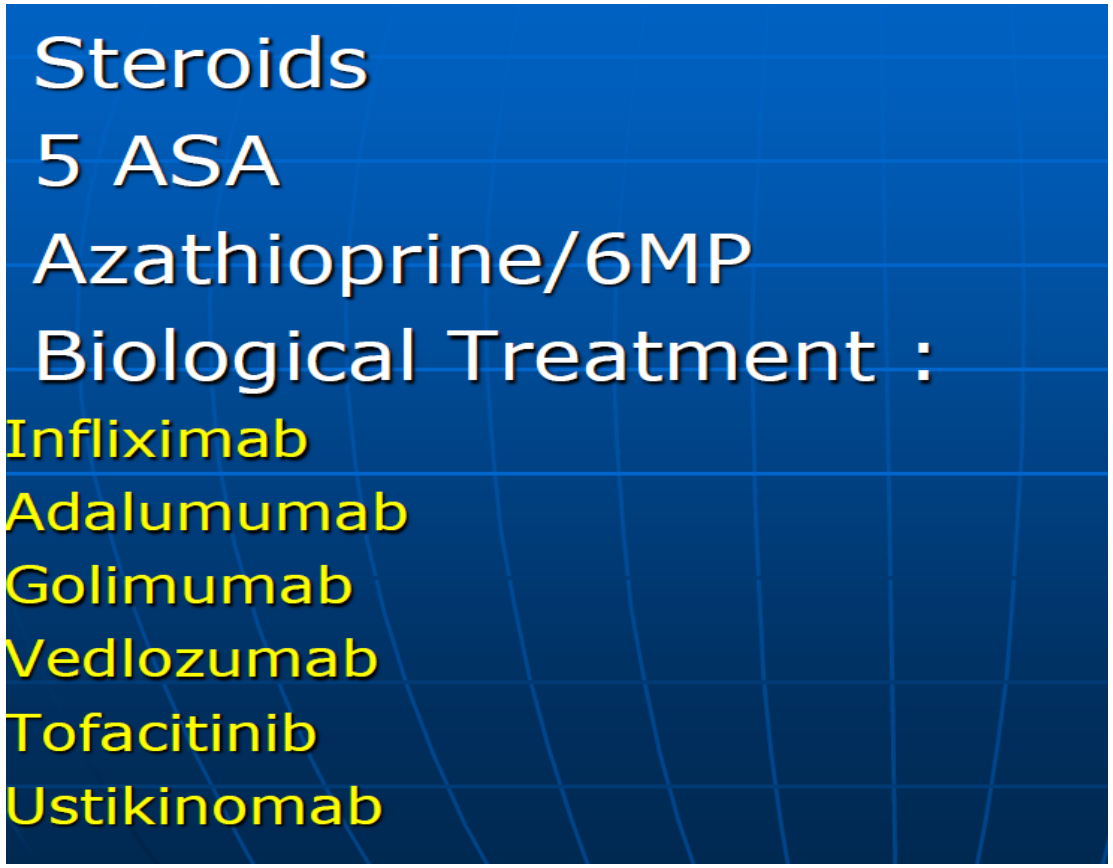
- To the left, we have Pseudopolyps (normal tissue) showing between the ulcers.
- To the right, we have distorted crypts filled with debris and inflammatory cells (Crypt abscess) + Infiltrated Lamina Propria.

UC



- Endoscopic Appearance of UC. Extensive Ulceration of the mucosa is the most common endoscopic finding (Panel A). The surface is irregular, Friable, and Erythematous, with loss of the normal vascular markings. Pseudopolyps may form as a reaction to inflammation (Panel B); these can become quite extensive (Panel C).

Management of UC

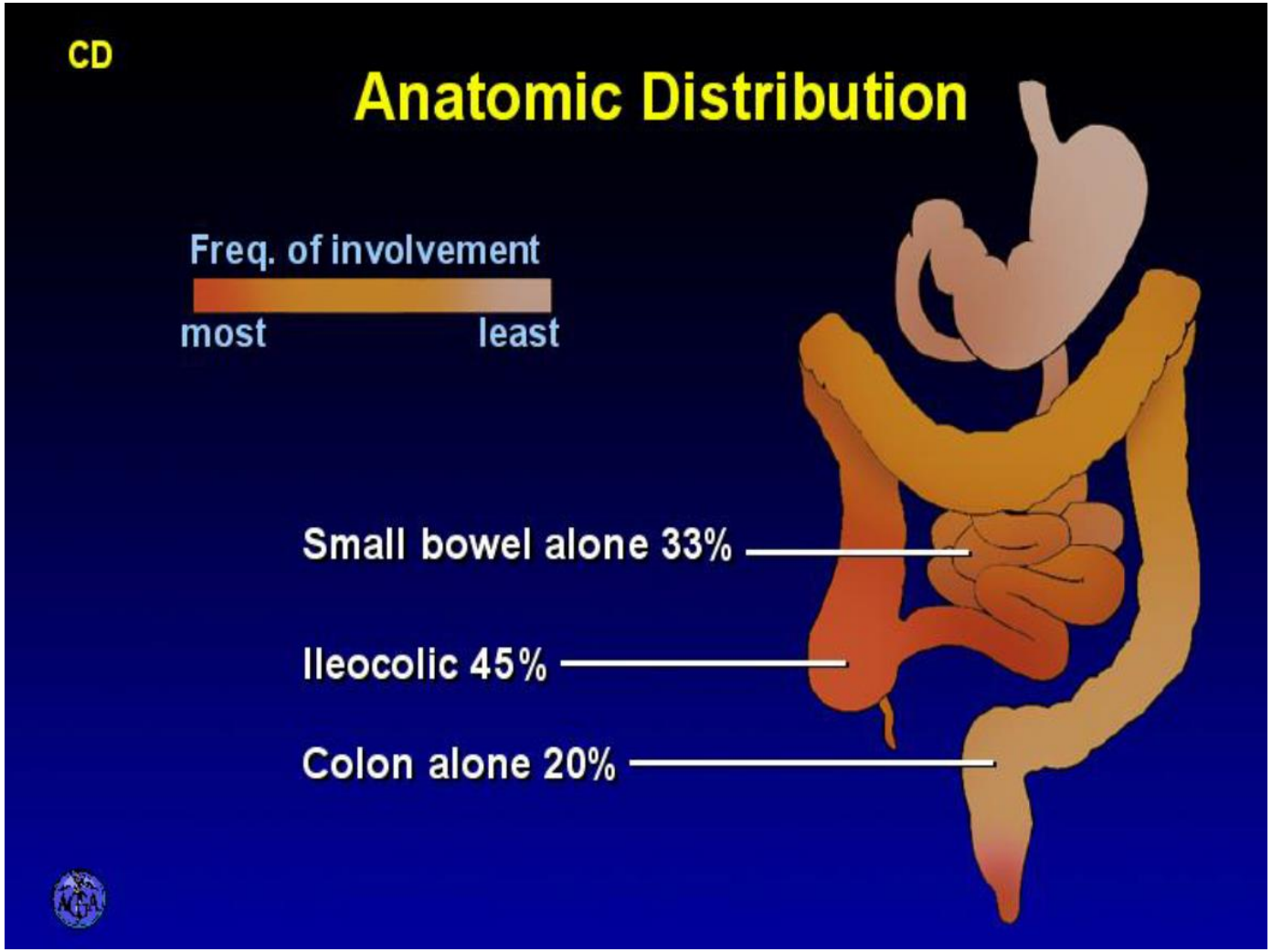


- Steroids are only used for induction of remission in both UC and CD.
- 5 ASA → Mesalamine; the mainstay of treatment. (Given Orally if UC involves more than the Left Colon, and Rectally -enema- if it involves the rectum only. / it's good in both induction and maintaining remission).
- Azathioprine / 6MP → immunomodulators.
- Infliximab → TNF-Alpha antagonist.
- Most Biological agents are antibodies against certain cytokines and ILs.

Crohn's Disease

- Characterized by Transmural (affects all layers of bowel wall) rather than superficial mucosal inflammation, and by skip lesions rather than continuous disease.
- Crohn's disease may involve the entire gastrointestinal tract from mouth to perianal area.

CD: Anatomic Distribution



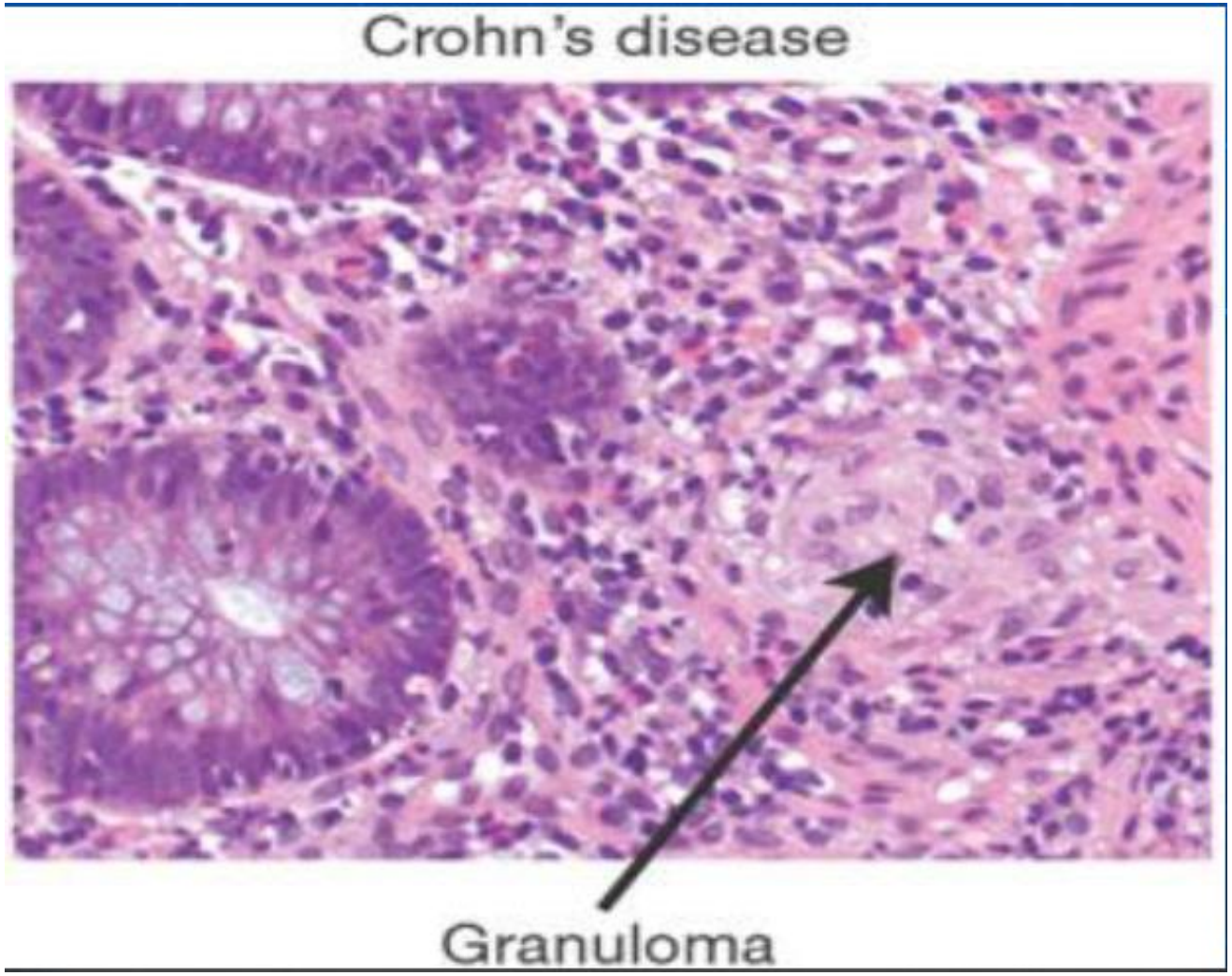
- Ileocolic → Ileum and Rt sided colon.
- The rectum is rarely involved unlike in UC.

CD: Pathology

- The process is transmural.
- Cobble stone appearance of the mucosa.
- The Rectum is spared
- There is skip areas.
- Fistulas fissures, abscess and anal stenosis

- Cobble stone appearance → Due to deep ulcers in the mucosa.

CD



- Pathologic Changes:

1- Epithelioid non-caseating Granuloma (not always present, only in 30-40% of the cases).

2- Chronic inflammatory infiltrate.

3- Crypt architectural distortion.

CD: Clinical Manifestations

- **Ileitis and colitis** *Diarrhea, abdominal pain, weight loss, and fever are the typical clinical manifestations for most patients with ileitis, ileocolitis, or Crohn's colitis*
- **Abdominal pain**
- **Bleeding** *gross bleeding is much less frequent than in ulcerative colitis*
- **Perforation and fistulae** *Transmural inflammation is also associated with the development of sinus tracts that can lead to serosal penetration and bowel wall perforation*
- **Perianal disease** *perianal pain and drainage from large skin tags, anal fissures, perirectal abscesses, and anorectal fistulae*
- **Other sites of intestinal inflammation** severe oral involvement, *esophageal involvement gastroduodenal Crohn's disease, sprue-like picture*

- Perianal disease is the worst-case scenario → in the case of very complicated disease.

CD: Complications

- **Local complications**

1. *Intestinal obstruction*
2. *Severe hemorrhage*
3. *Acute perforation*
4. *Fistulae*
5. *Abscess formation*
6. *Toxic megacolon.*

- Intestinal Obstruction → Stricture due to recurrent inflammation and fibrosis.
- Severe Hemorrhage → Due to deep ulcers.
- Acute Perforation → Due to transmural Inflammation

CD: Work-Up

History and physical exam

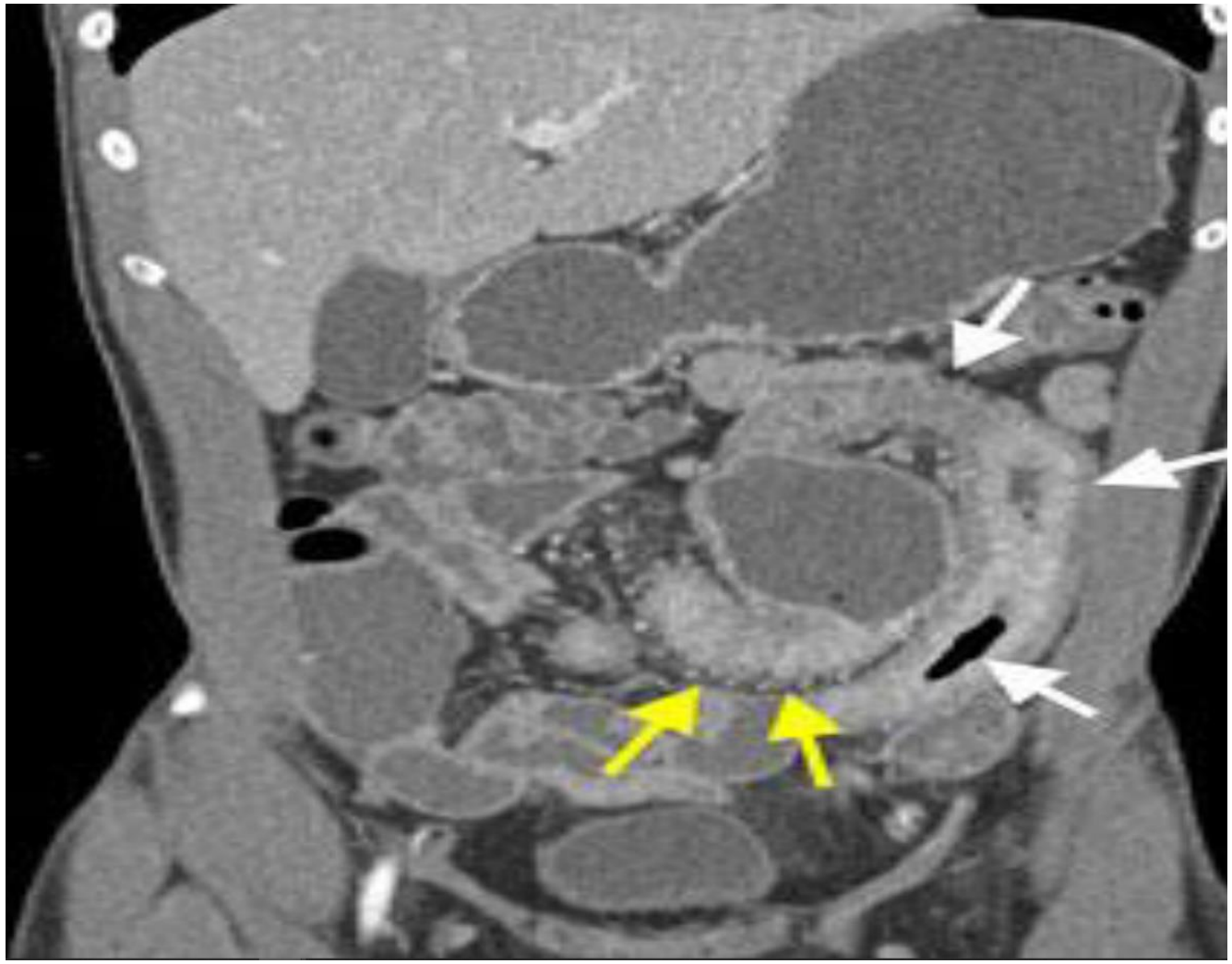
Routine labs CRP, ASCA,ANCA Stool examination

Colonoscopy/Endoscopy

Immaging/capsule endoscopy

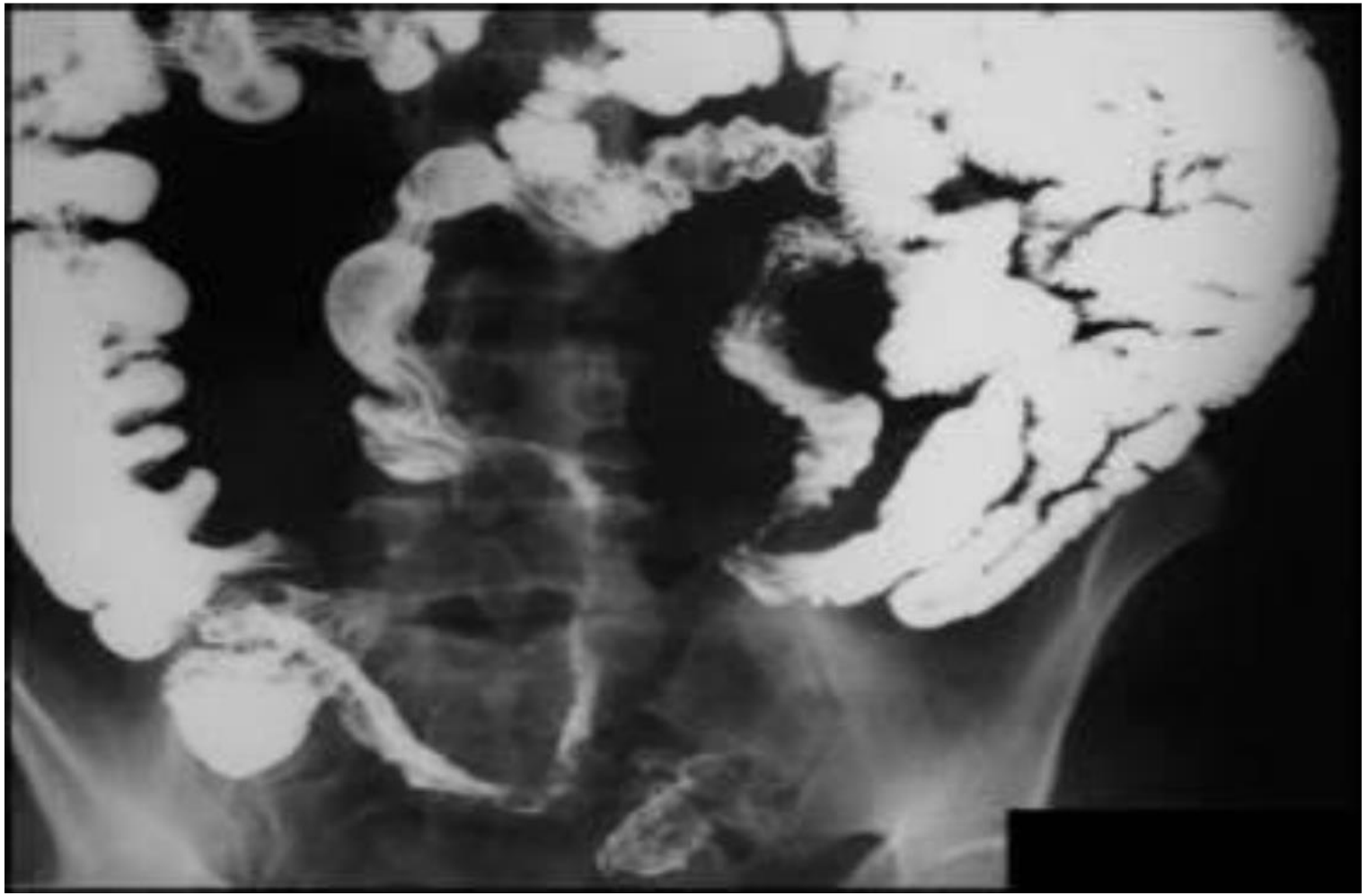
- If ASCA is Positive → Crohn's Disease
- If ANCA is Positive → UC.

CD: Abdominal CT

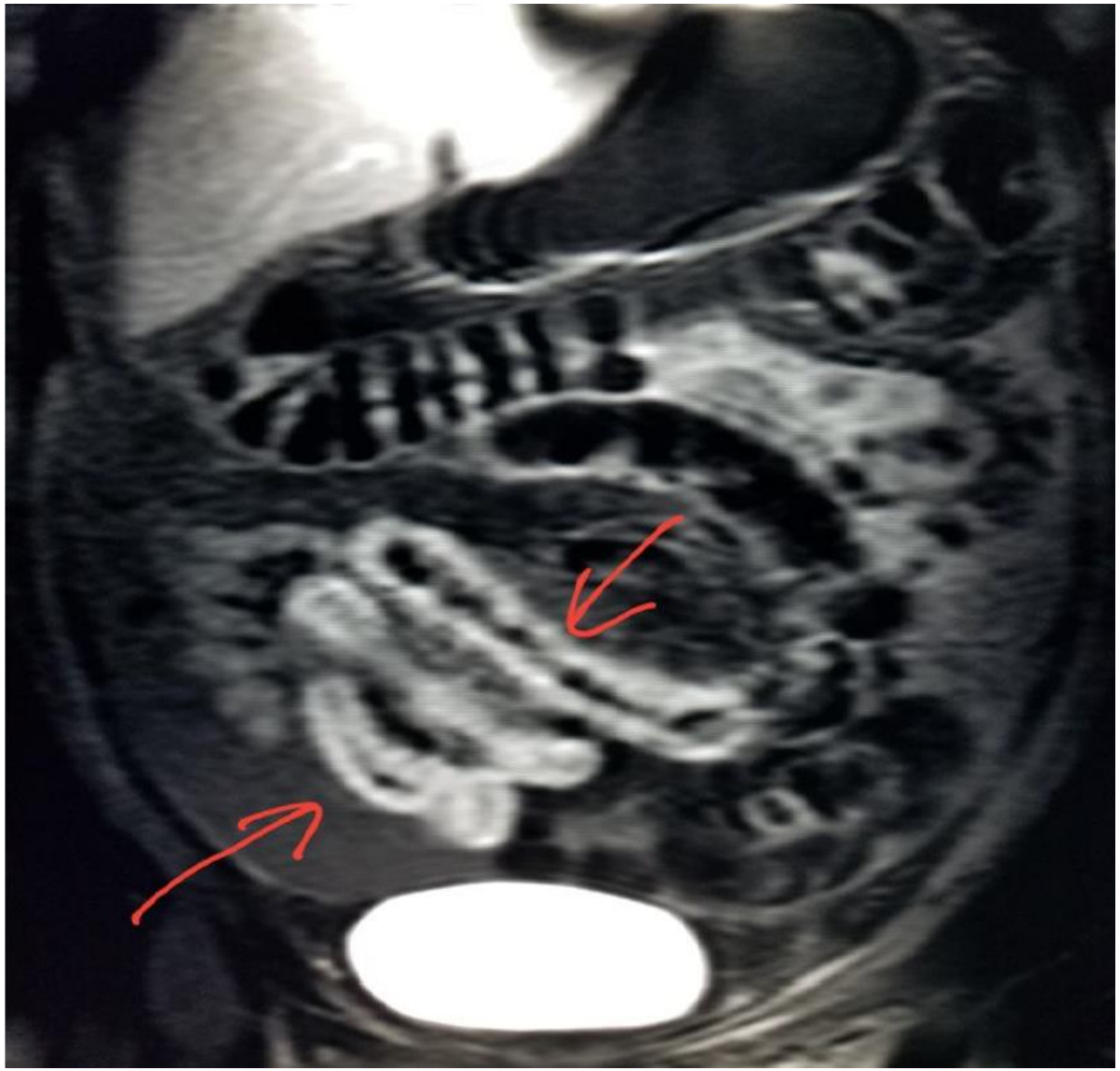


- The CT shows that the wall is thickened and Narrowed

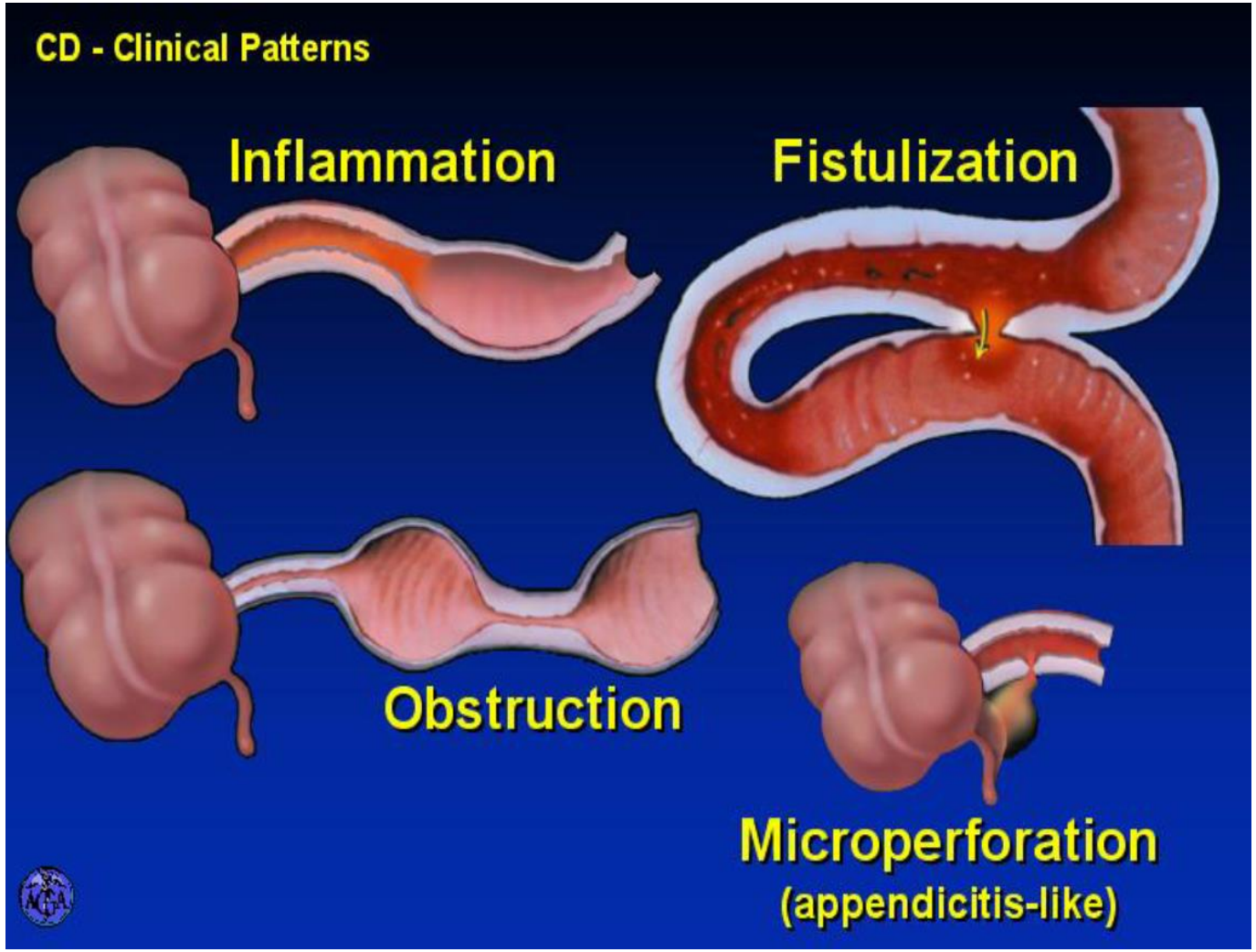
Barium Enema Test in CD



MRE in CD

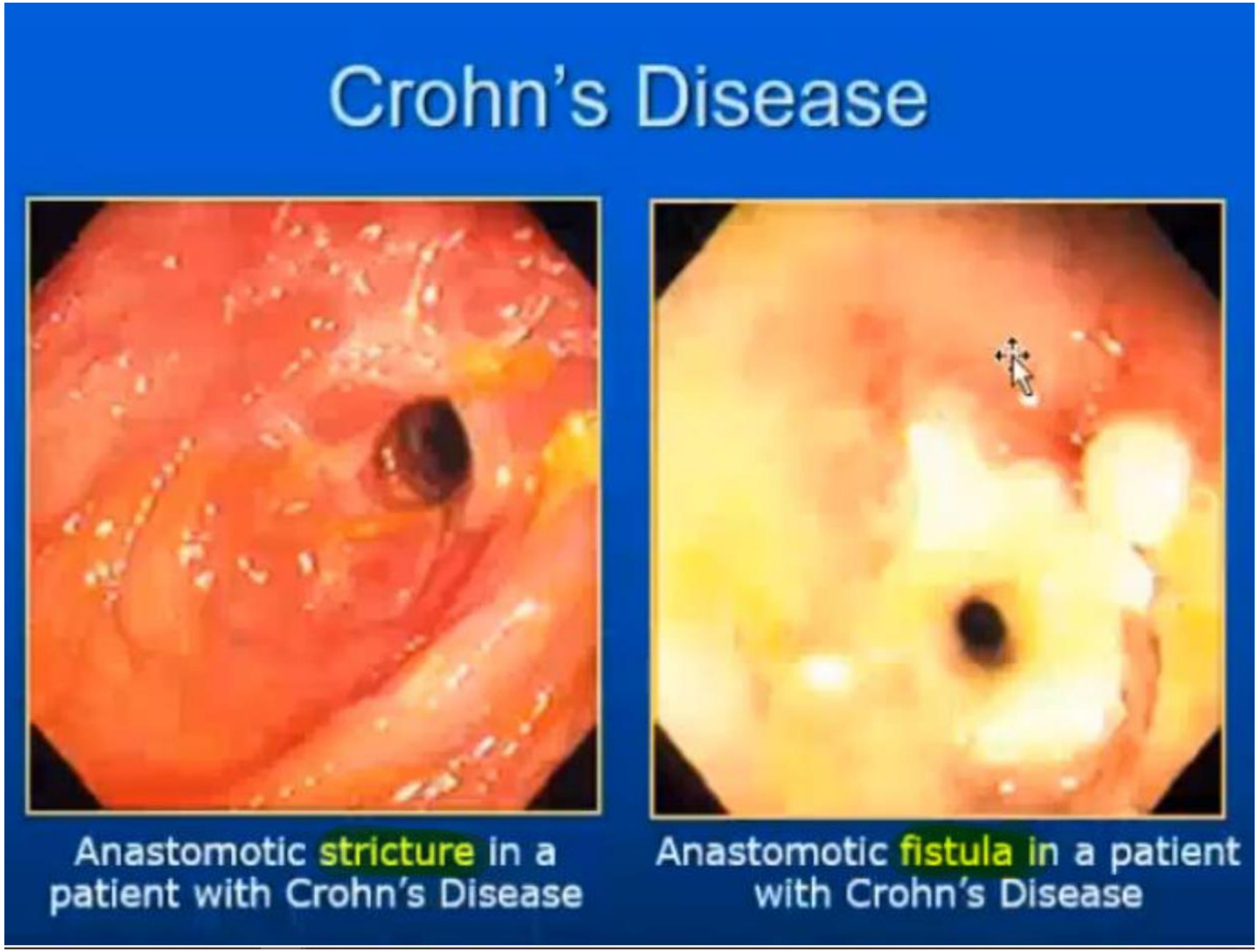


CD: Clinical Patterns

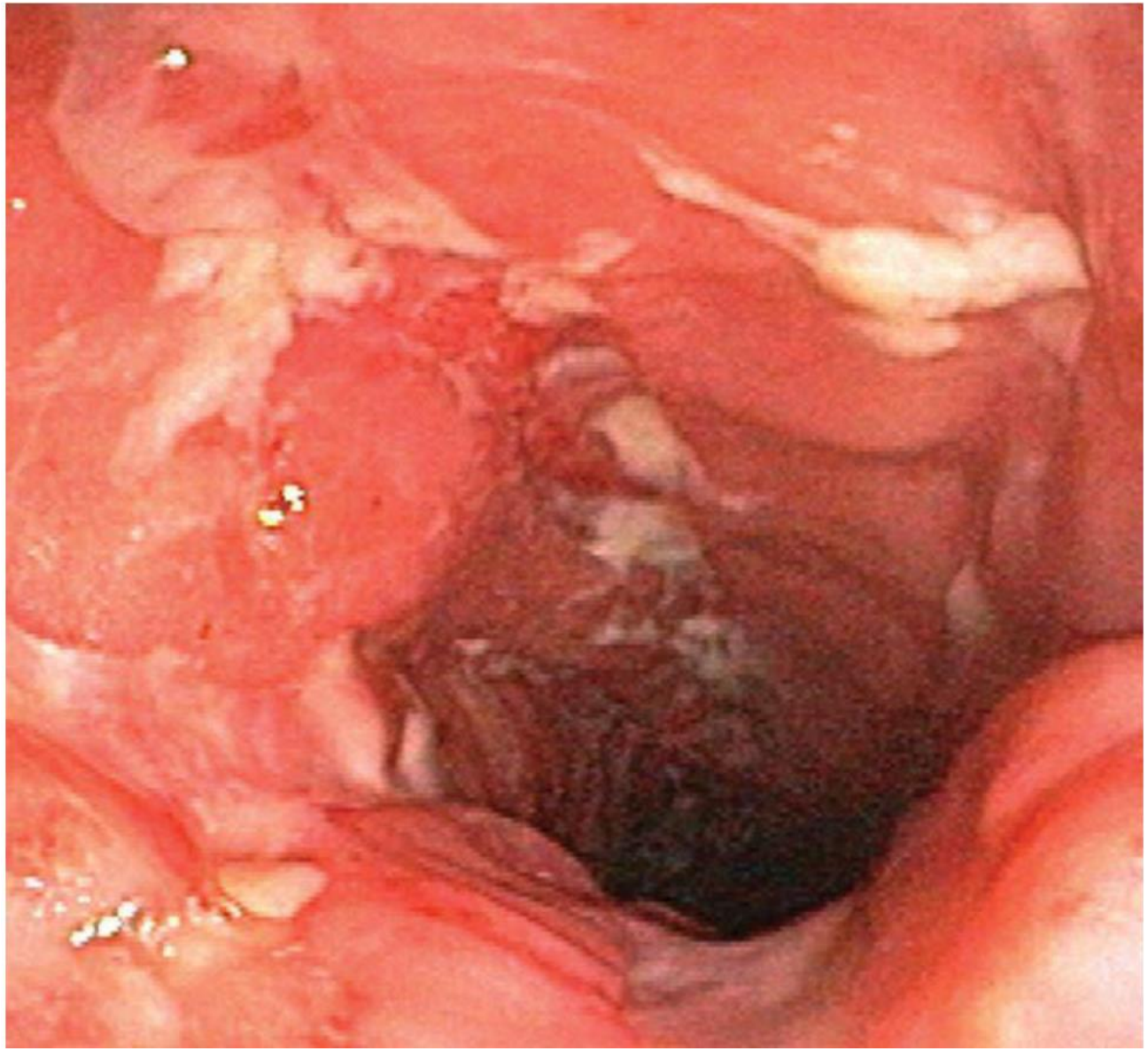


- Fistulization → Enteroenteral (between the Colon and other segments of the intestine) / Enterovesical (between the colon and the bladder) / Enterocutaneous (between the colon and the skin).
- Obstruction → due to Fibrosis, forming proximal dilations.

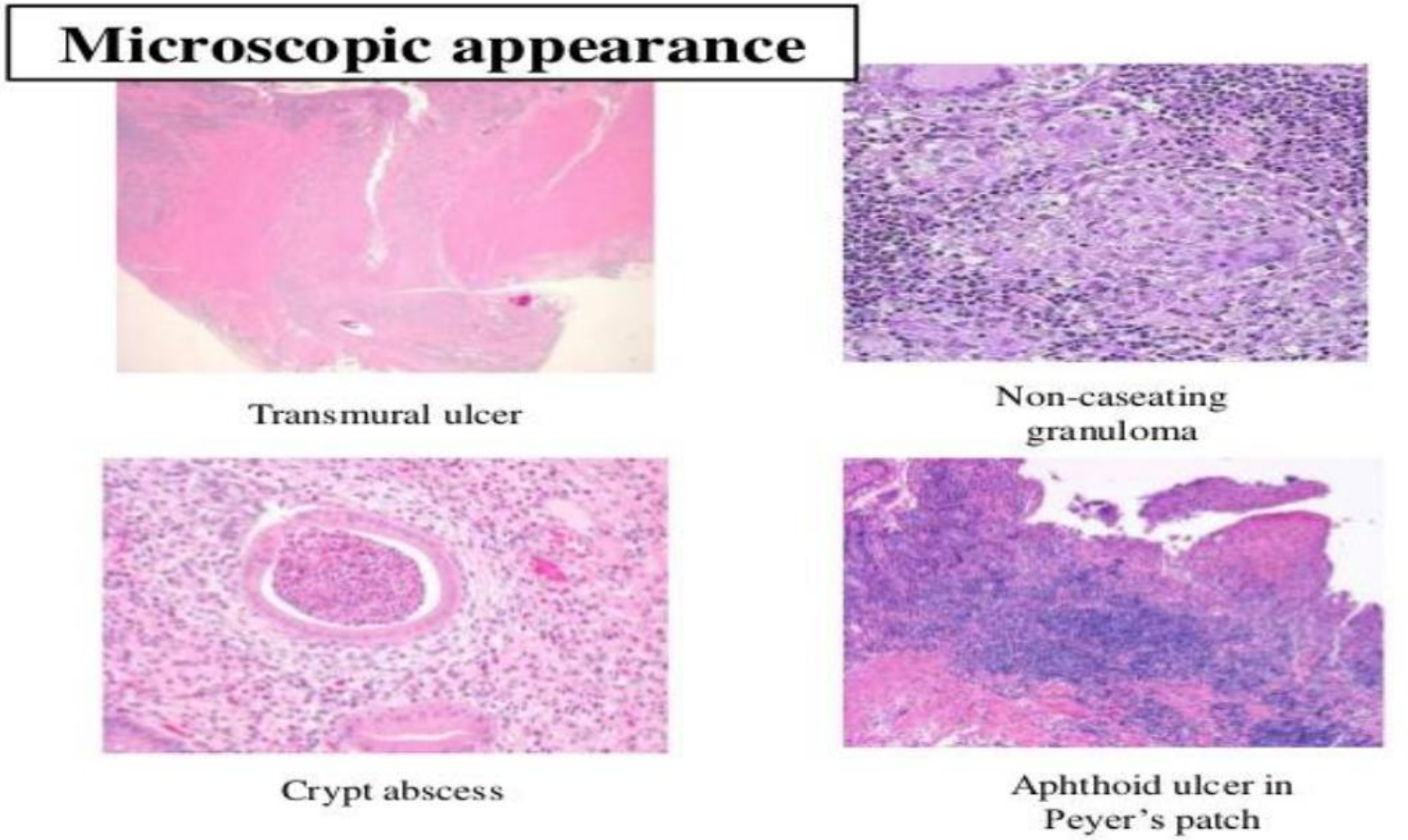
CD


Crohn's Disease
Anastomotic stricture in a patient with Crohn's Disease
Anastomotic fistula in a patient with Crohn's Disease

CD: Endoscopy



CD: Histology

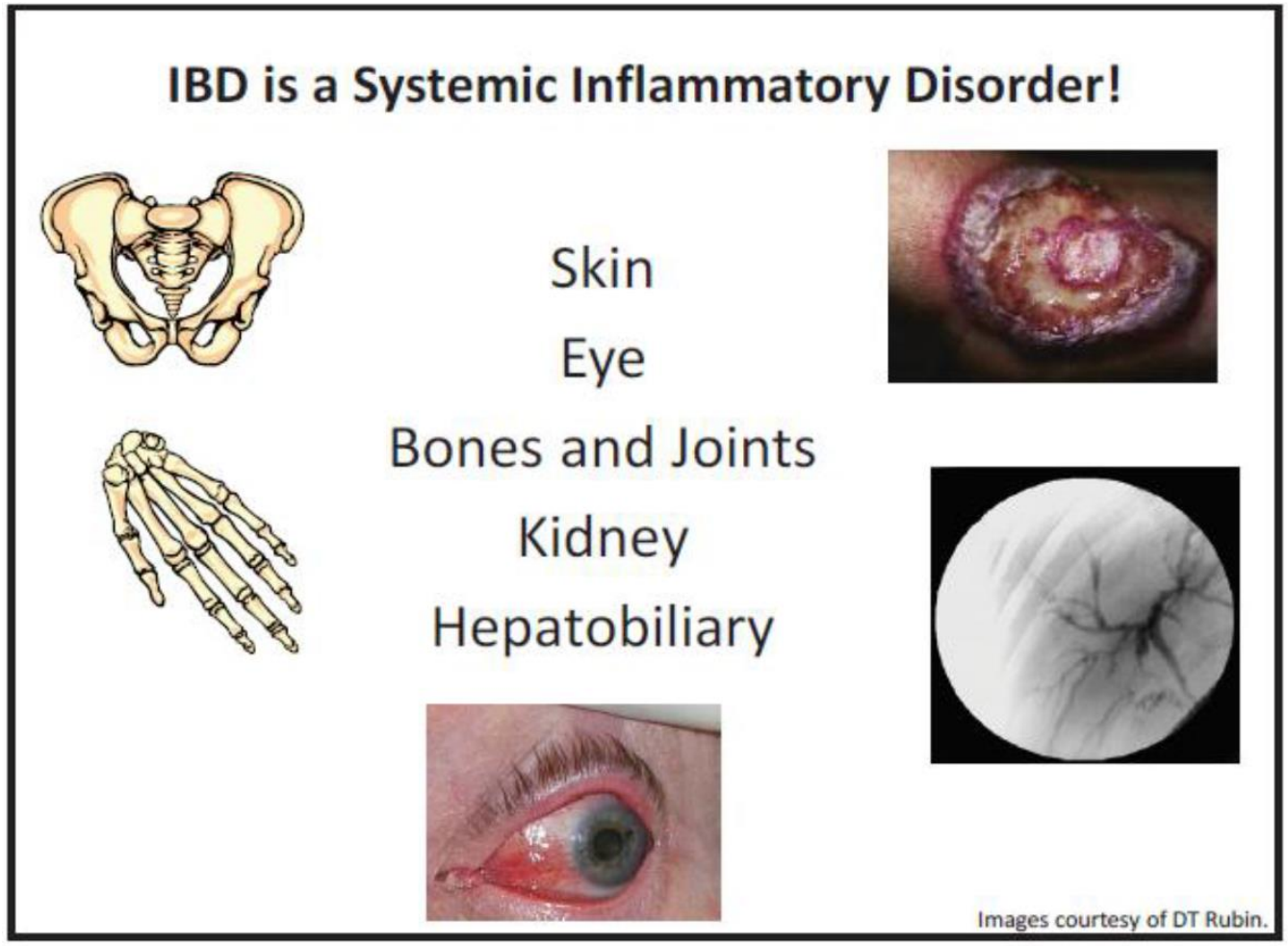


- There is Crypt Distortion, Cryptitis, / Crypt abscesses, Lamina propria expansion with acute and chronic inflammatory cells.
- There is basal plasma cells and lymphoid infiltration, Granuloma may be seen.

Management of CD

- 5 ASA → the benefits of this treatment in CD is limited unlike UC.
- Methotrexate → effective for CD, but not for UC. However, it's teratogenic and causes many toxicities.
- Thiopurines → it includes Azathioprine and 6-Mercaptopurine (Good in maintaining remission if started early, They are not useful for induction as they need 3 months to show effects, They can cause bone marrow suppression, hepatitis, Pancreatitis).
- Ileocolitis and Colitis → Antibiotics (if there is infection / abscess / post op perianal (metronidazole)) + Corticosteroids (for induction of remission, not for maintenance) + Azathioprine and 6-Mercaptopurine (mainstay of treatment) + 5 ASA (only for mild disease).
- Refractory disease → Biologic Agents (Azathioprine + 6-Mercaptopurine + Methotrexate + Infliximab).
- Perineal Disease → Metronidazole + Ciprofloxacin + Azathioprine or 6-MP + Biological Agents + Surgical management.
- Fistulae → Infliximab + Adalimumab.

Extra-Intestinal Manifestations of IBD



- ++ Arthritis and Ankylosing Spondylitis

Systemic Complications of IBD

- Eye involvement with conjuctivitis, uveitis and episcleritis
- ankylosing spondylitis & Sacoilitis
- peripheral arthritis
- Sclerosing cholangitis, steatosis, cholelithasis
- Venous and arterial thromboembolism
- Autoimmune hemolytic anemia
- Skin disorders such as erythema nodosum and pyoderma gangrenosum
- Renal calculi, uretric obstruction, fistulas.
- Metabolic bone disease

- Complications in Yellow Follow the disease activity, While those in White Don't.

Summary

* Similarities
  - Sx: abdl pain, bloody diarrhea (UC > CD), recurrent
  - EIF: ankylosing spondylitis, Uveitis
  - Risk of adenocarcinoma " with colonic (Rt.) involvement "
  - Tx: Corticosteroids, Sulfasalazine, 5-ASA (- UC)

* Differences:

	UC	CD
*	Starts with rectum	Spares rectum
*	Mucosa > Submucosa	Full thickness 'transmural'
*	p-ANCA	ASCA
*	TH2, Non-granulo	TH1, granulo
*	Smoking ✓	Smoking X

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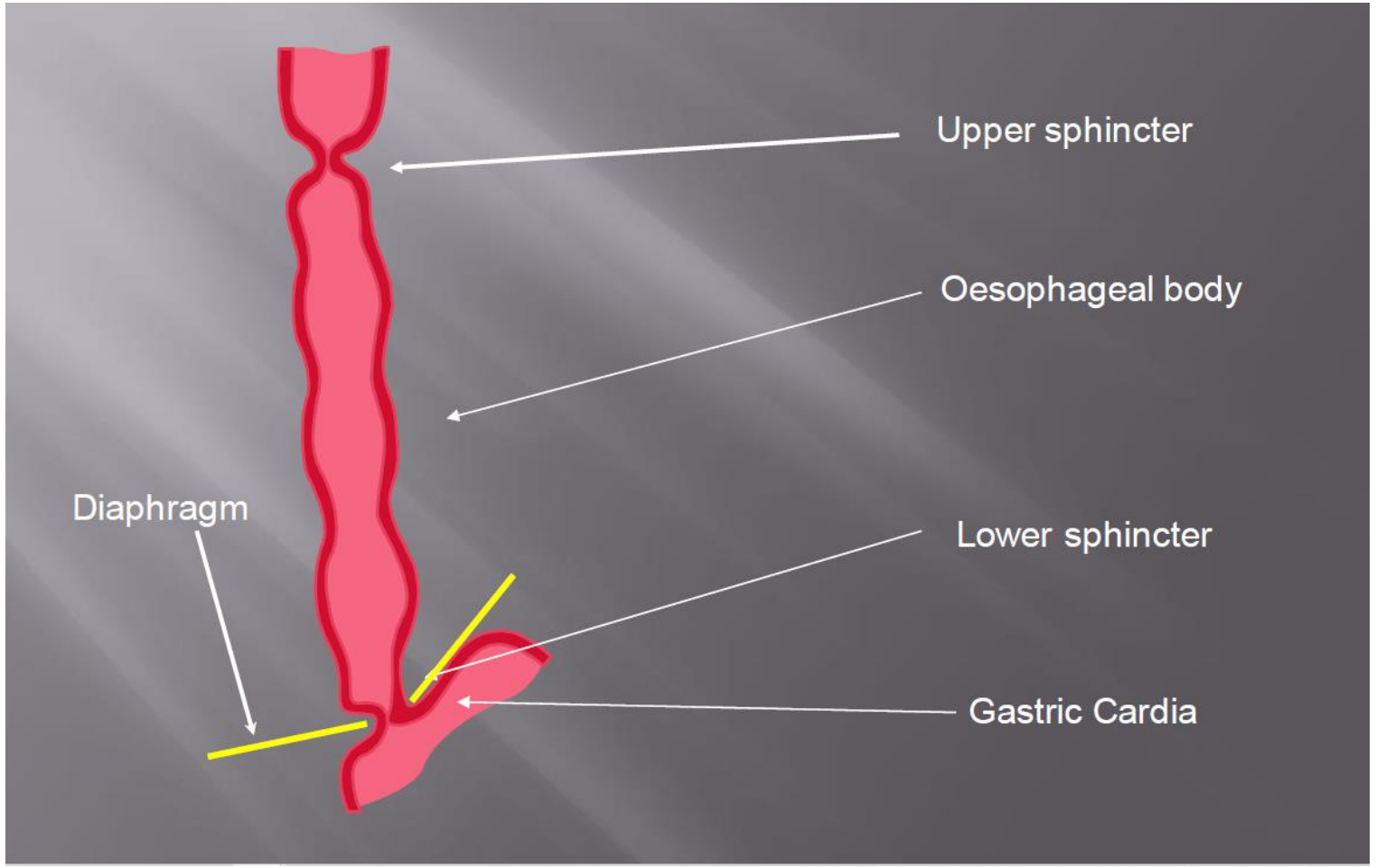
① Ulcerative Colitis
- Left LQP, Never involves S. intestine
- Pseudopolyps, loss of haustra 'leadpipe'
- EIFx: pyoderma gangrenosm, primary sclerosing cholangitis
- Complication ⇒ Toxic MegaColon
  - ↳ Cessation of colon contraction 'No'
  - ↳ Thin walls → rupture 'perforation'

② Crohn's Disease
- Any GI portion can be affected, oral ulcers, RLQP
  - ↳ Commonly: terminal ileum
- Skip lesions, Cobble stone mucosa, Fistulas
- Creeping fat, Strictures "String sign
- EIFx: migratory polyarthritis, erythema nodosum
  - Kidney stones "malabsorption ↑ oxalate"

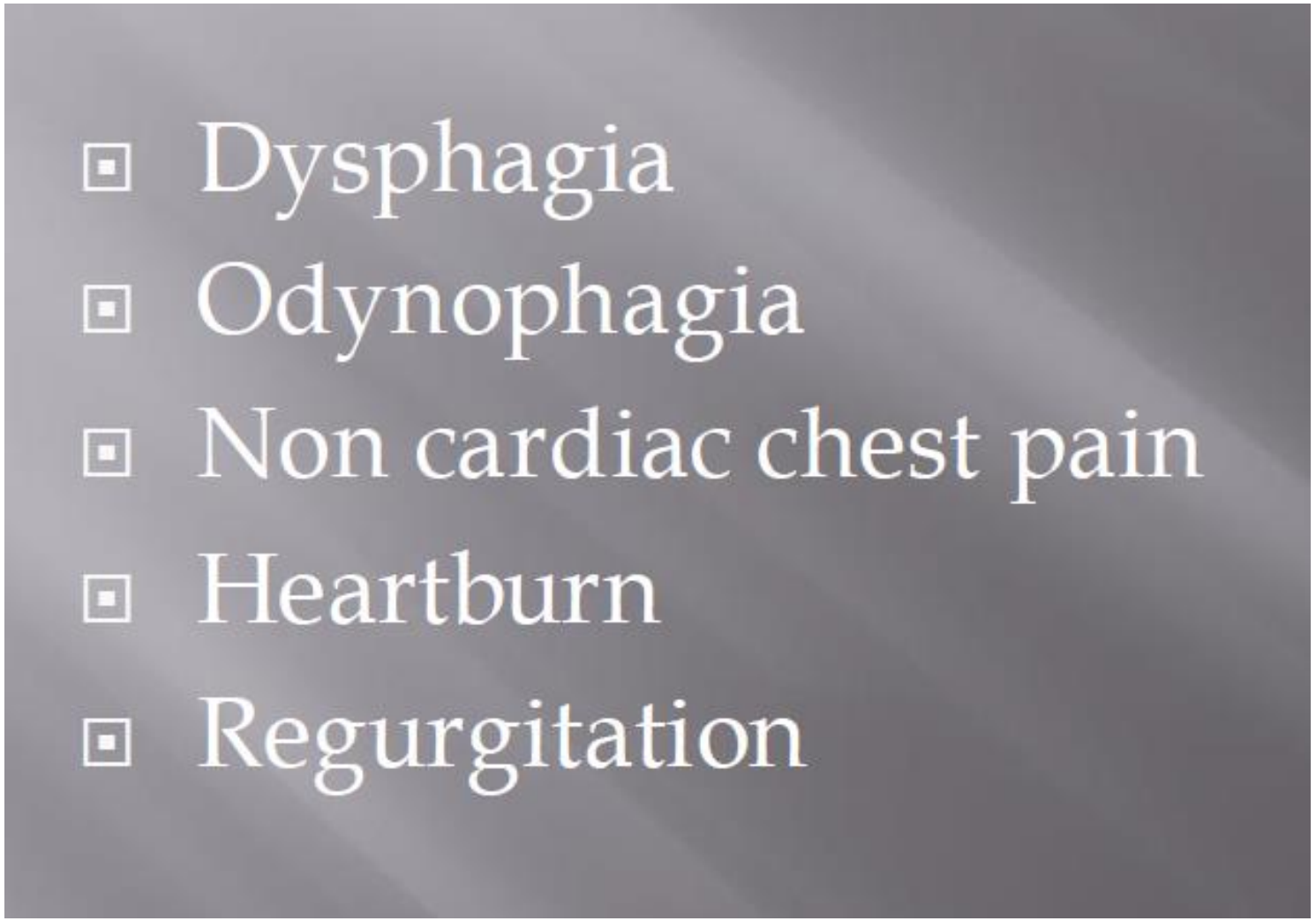
Esophageal Disorders

Anatomy of the Esophagus



- The esophageal wall is composed of Striated Muscles in the upper part, Smooth muscles in the lower part, and a Mixture of the two in the middle.
- Diaphragm → Enhances the integrity of LES.

Symptoms of Esophageal Disorders



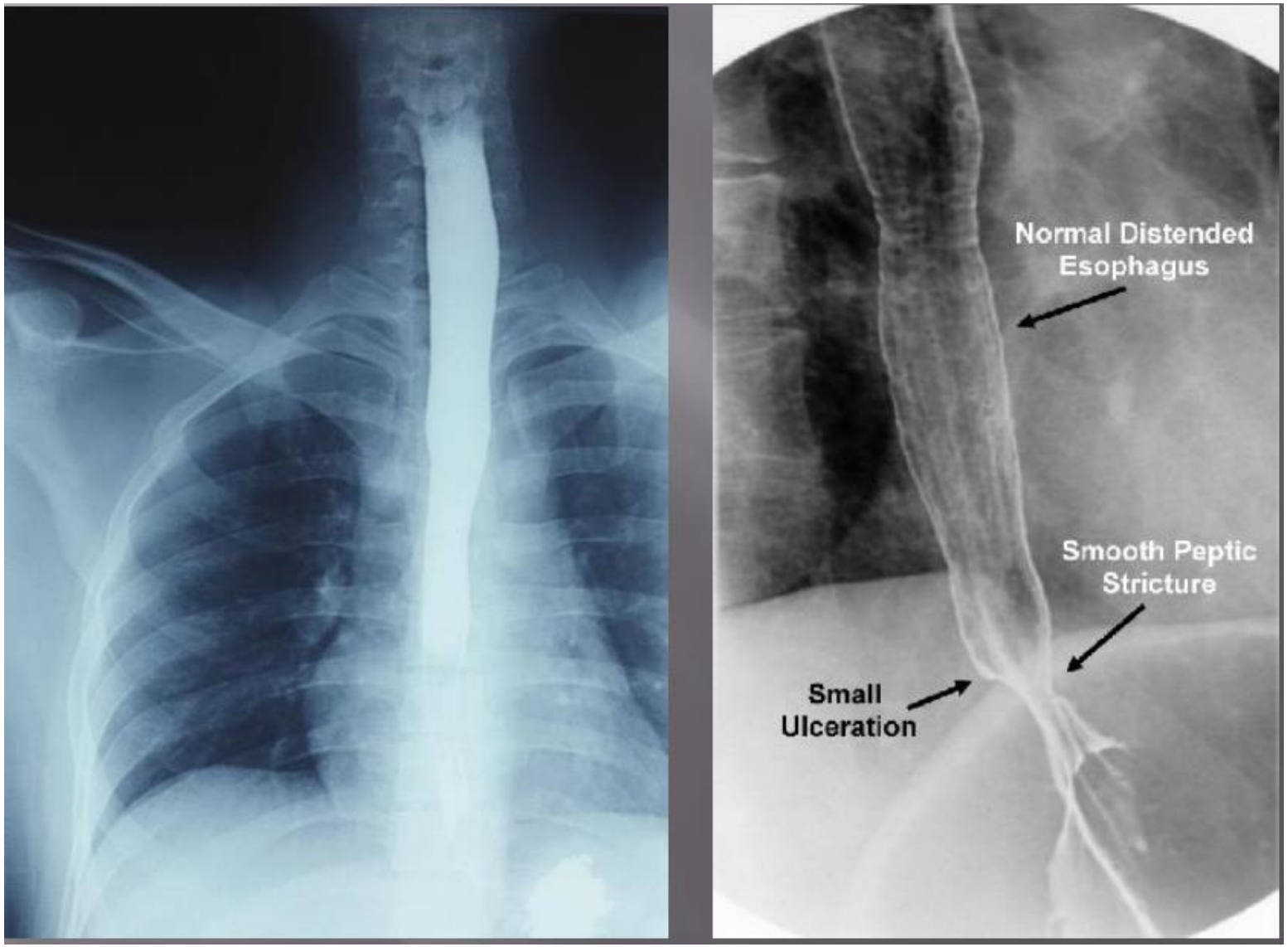
- Any of these Symptoms Should raise the suspicion of an Esophageal Disorder.

Diagnostic Tools

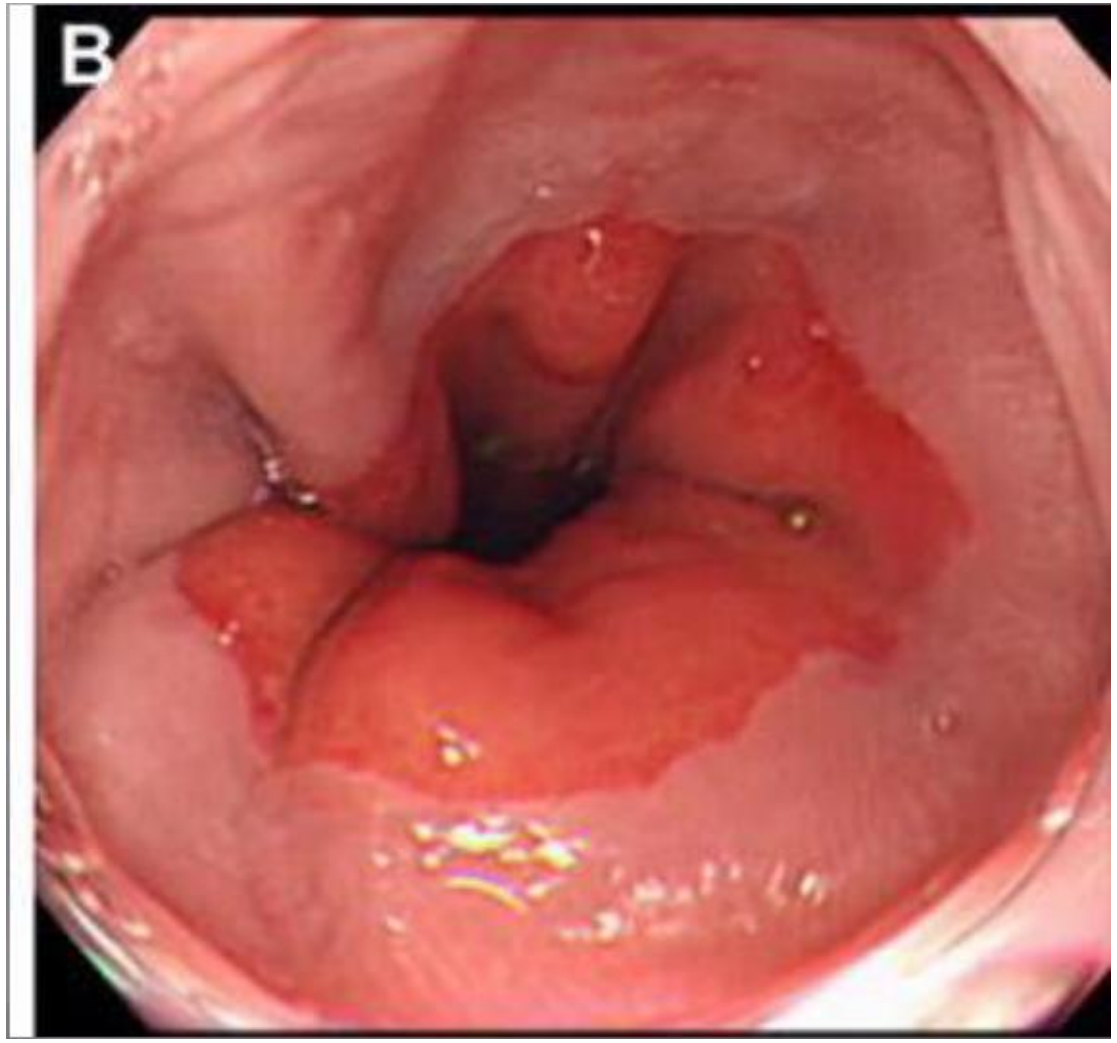
- Barium Swallow
- Endoscopy
- Esophageal manometry
- 24 hr esophageal pH monitoring
- Impedence

- Esophageal Manometry: Used to measure the Function of the LES and the muscles of the Esophagus.
- 24 Hr esophageal pH monitoring: measures the acidity at the lower part of the esophagus.
- Impedance: to evaluate esophageal bolus transit.

Barium Swallow

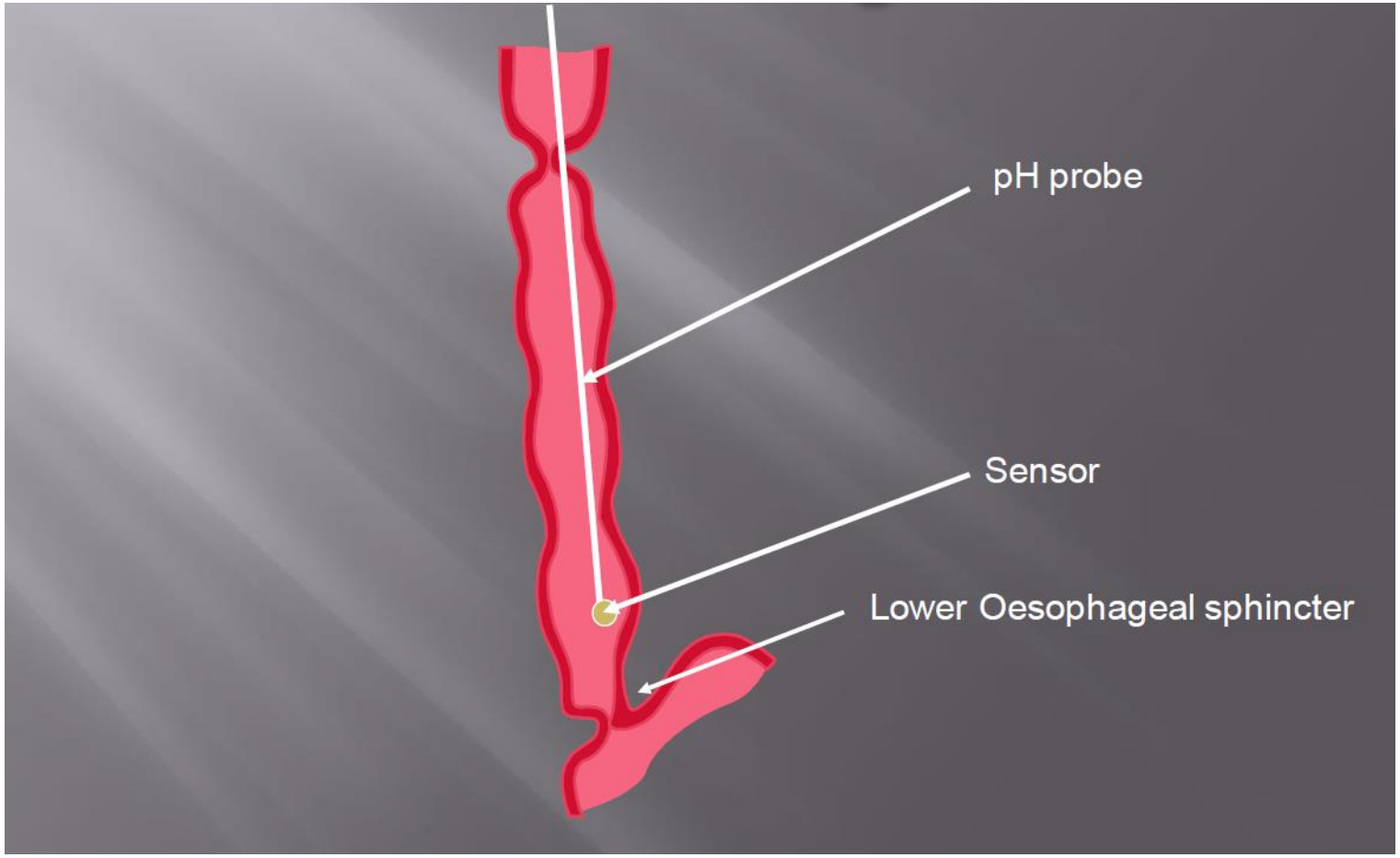


Endoscopy



- Visualizes Mucosal Abnormalities.

24 Hours Esophageal pH Monitoring



- Esophageal 24-hour pH reflux monitoring measures the amount of reflux (both acidic and non-acidic) in your esophagus during a 24-hour period and assesses whether your symptoms are correlated with the reflux.
- Used to diagnose 2 important disorders of the esophagus → GERD and Achalasia.

Gastro-esophageal Reflux Disease (GERD)

- The flow back of the gastric content into the esophagus at a rate more than the physiological one.
- Physiologic reflux episodes typically occur postprandially, are short lived, asymptomatic, and rarely occur during sleep.
- There is Failure of anti-reflux mechanism (Due to GEJ incompetence).
- Pathophysiology:
- Reflects an imbalance between injurious and defensive factors.
- GEJ incompetence (Contribute to GERD): 1- Transient LES relaxations (it's physiological to allow Belching, however when exaggerated it causes GERD). 2- A hypotensive LES (Fat, Chocolate, Alcohol, Caffeine, Smoking, and Several Drugs - Anticholinergics, Nitrates, CCBs, Tricyclic antidepressants, Opioids, Diazepam-). 3- Anatomic Disruption of the GEJ, often associated with a hiatal hernia or increased intra-abdominal pressure (in pregnant women or in the case of ascites).
- Characteristics of the Refluxate.
- Impaired Esophageal acid clearance (impaired motility, diminished salivation).
- Impaired defense against epithelial injury.
- Esophageal hypersensitivity.
- Treatment: 1- Life style modification (Smoking and Alcohol cessation, most importantly Weight reduction). 2- H2 receptors blockers. 3- PPI. 4- Fundoplication (Surgical, the stomach is wrapped around the esophagus to tight the GEJ).

GERD: Clinical Features

- **Regurgitation.**
- **Heart burn.**
- Chest pain.
- Dysphagia
- Nausea
- Hoarseness, cough, wheezes

- Regurgitation and Heart Burn are the two major Symptoms.

GERD: Complications

- Esophageal stricture
- Barrett's esophagus
- Esophageal adenocarcinoma
- Chronic laryngitis
- Exacerbation of asthma

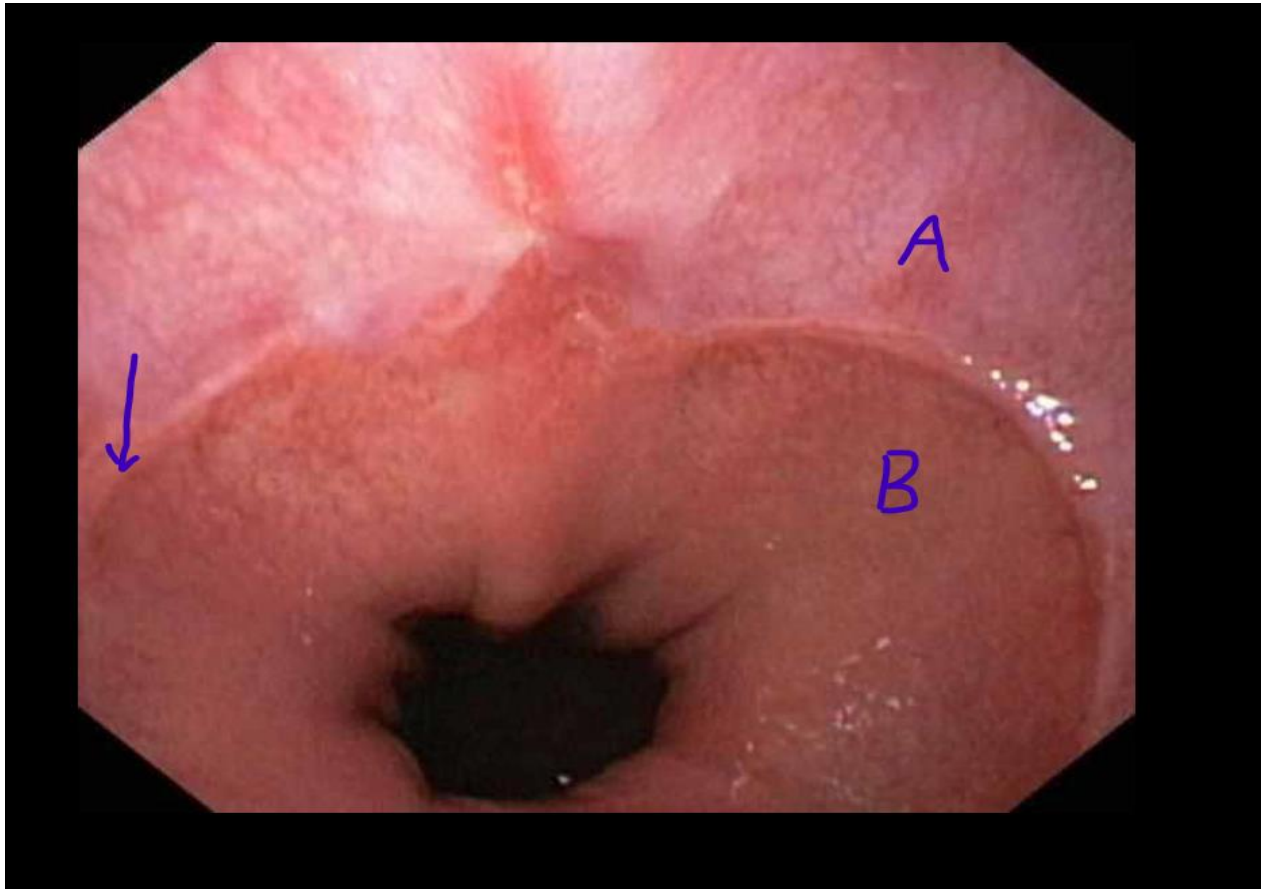
- Esophageal Stricture: Damage to the mucosa from acid reflux → Healing → Fibrosis → Stricture.
- Barrett's Esophagus: Metaplasia in the mucosal cells lining the lower portion of the esophagus, from normal stratified squamous epithelium to simple columnar epithelium with goblet cells.
- Esophageal Adenocarcinoma: Associated with Barrett's esophagus.

GERD: Diagnosis

- Barium Swallow.
- Endoscopy.
- **24 hrs PH monitoring.**
- Laryngoscopy.
- High resolution Manometry & Impedence.

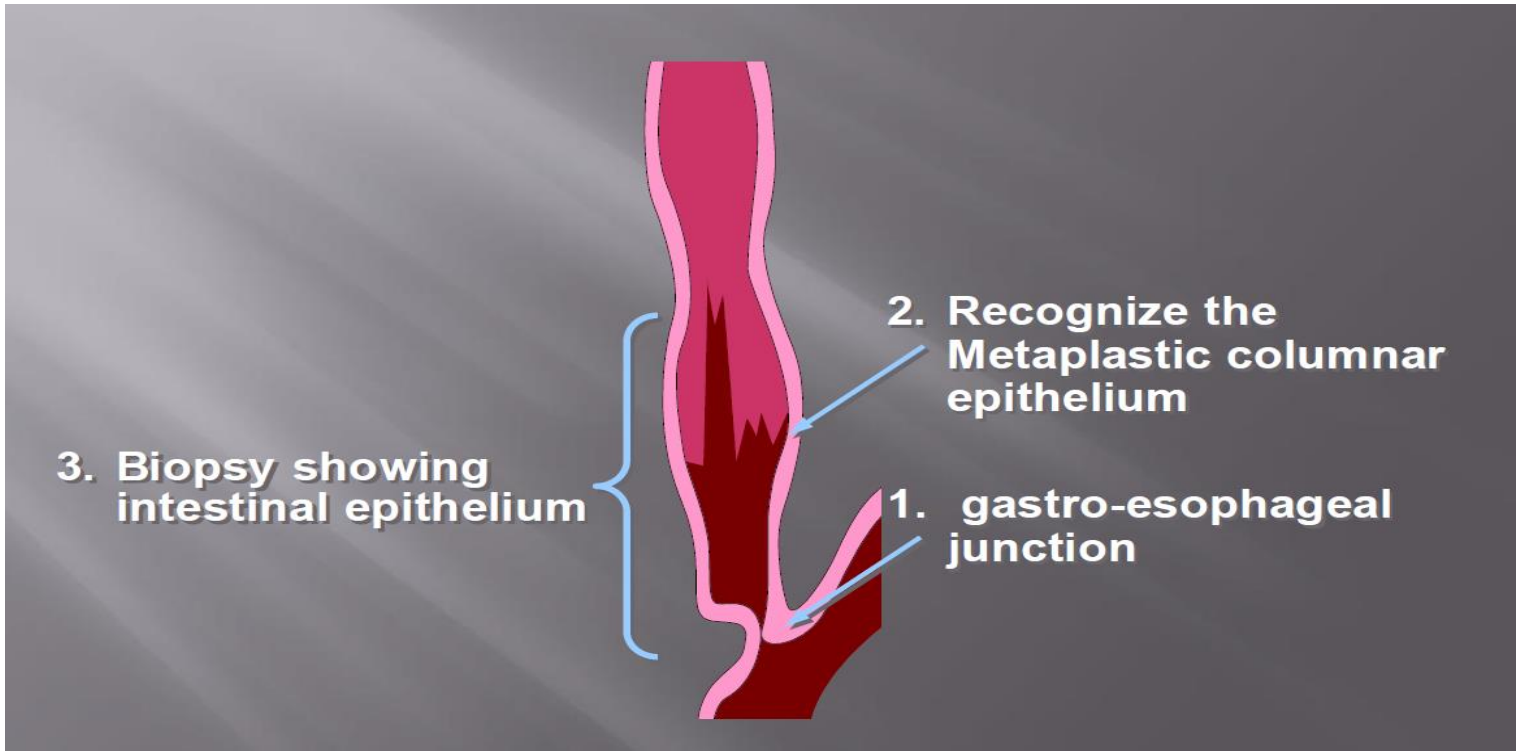
- Barium Swallow: To demonstrate reflux radiologically.
- Endoscopy: to check the effect of reflux on Ulcers / Inflammation.
- Laryngoscopy: Edema and Inflammation of the larynx.
- High resolution Manometry: Motility study.

Endoscopy



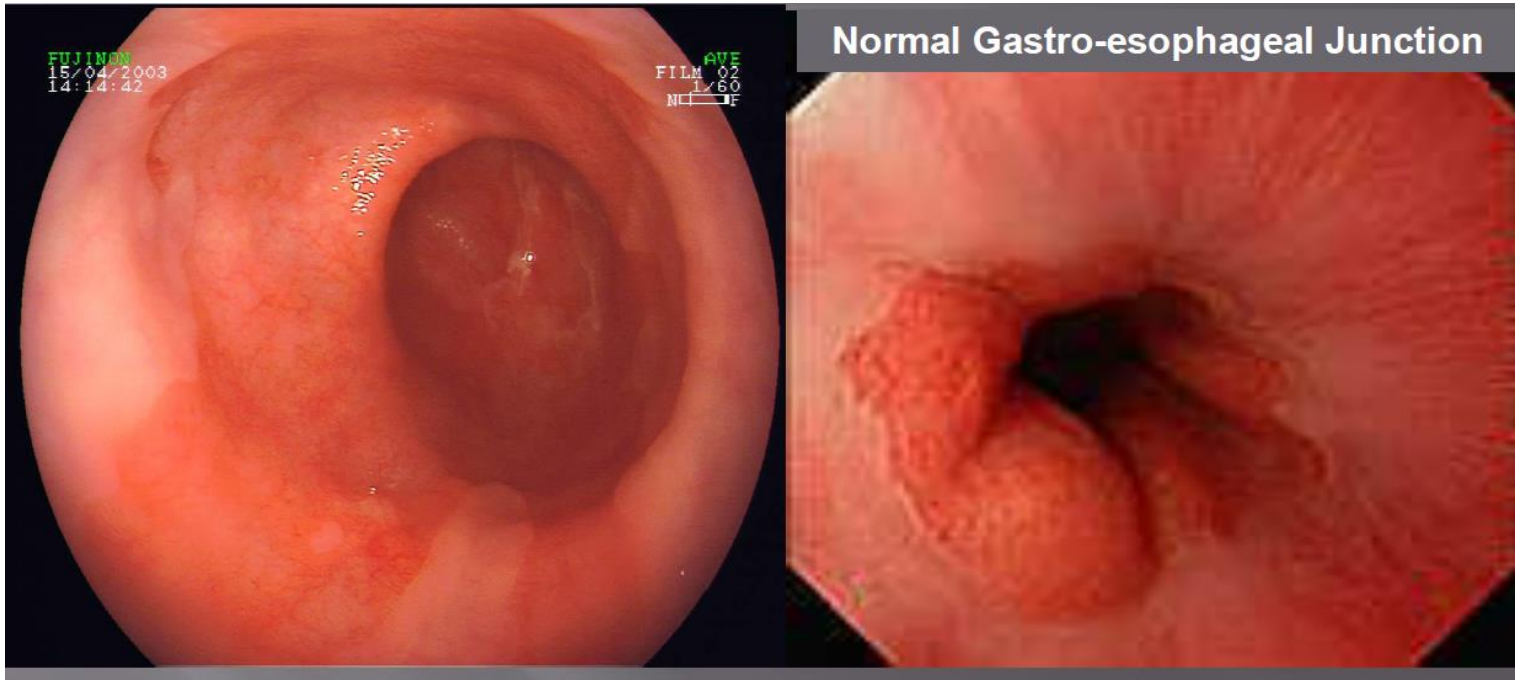
- Endoscopy showing mild inflammation of the lower esophagus.
- Area A → Esophageal Mucosa.
- Area B → Gastric Mucosa.
- Blue Arrow → Z-line / Squamocolumnar (SC) Junction
- The Squamocolumnar (SC) junction or Z-Line represents the normal esophagogastric junction where the squamous mucosa of the esophagus and columnar mucosa of the stomach meet.

Barrett's Esophagus



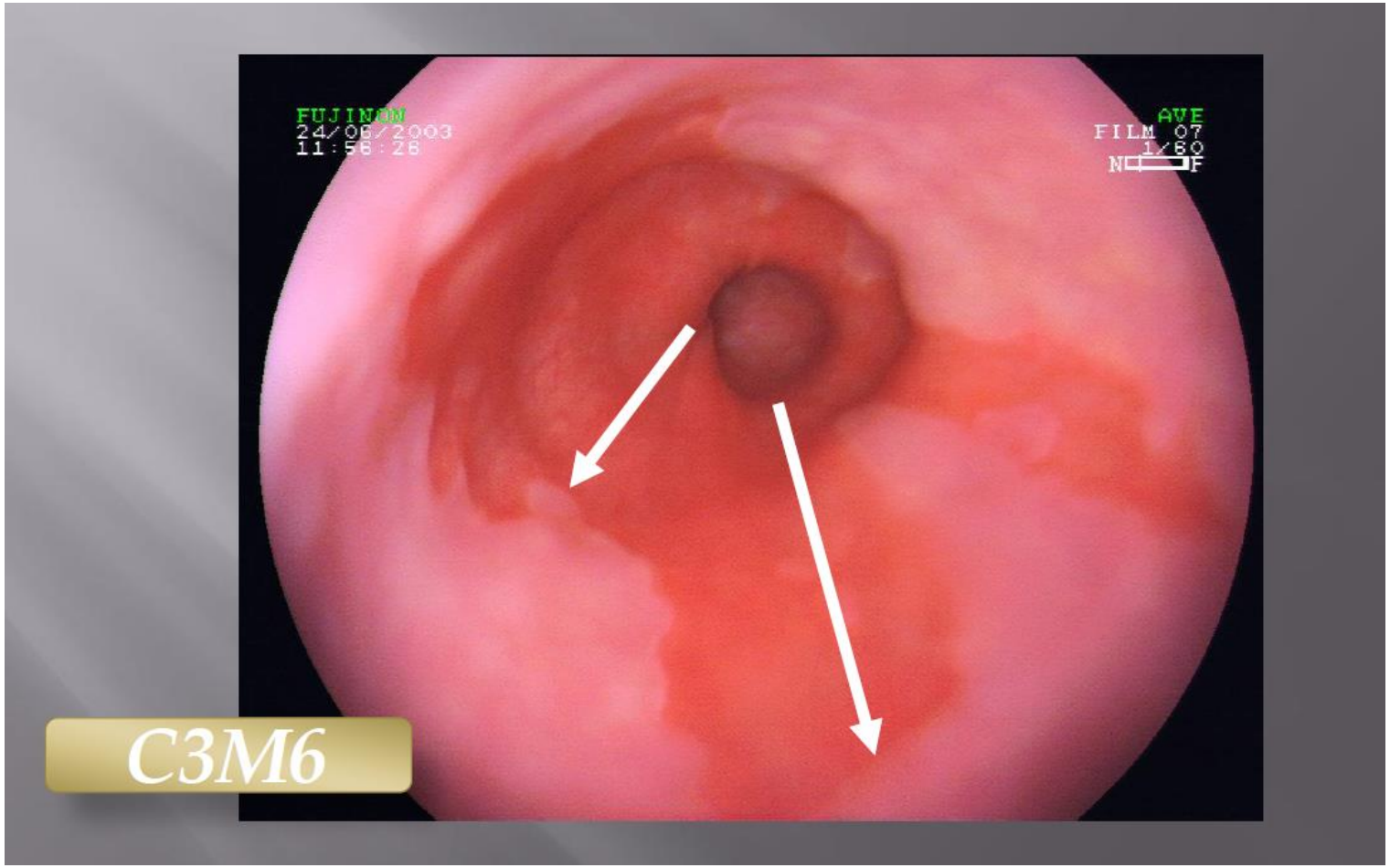
- As a result of chronic GERD.
- Metaplastic Columnar epithelium + Goblet cells replaces the Stratified squamous epithelium in the distal esophagus.
- There is increased risk of Adenocarcinoma which is >30-fold above the general population.
- Diagnosed endoscopically and confirmed through biopsy.
- Treatment: 1- Treat GERD. 2- Surveillance for Dysplasia (every 3 days). 3- Endoscopic therapy for Dysplasia (Ablation, Resection). 4- Surgery - Esophagectomy (if there is dysplasia, before turning into adenocarcinoma).

Gastro-Esophageal Junction and Barrett's Esophagus



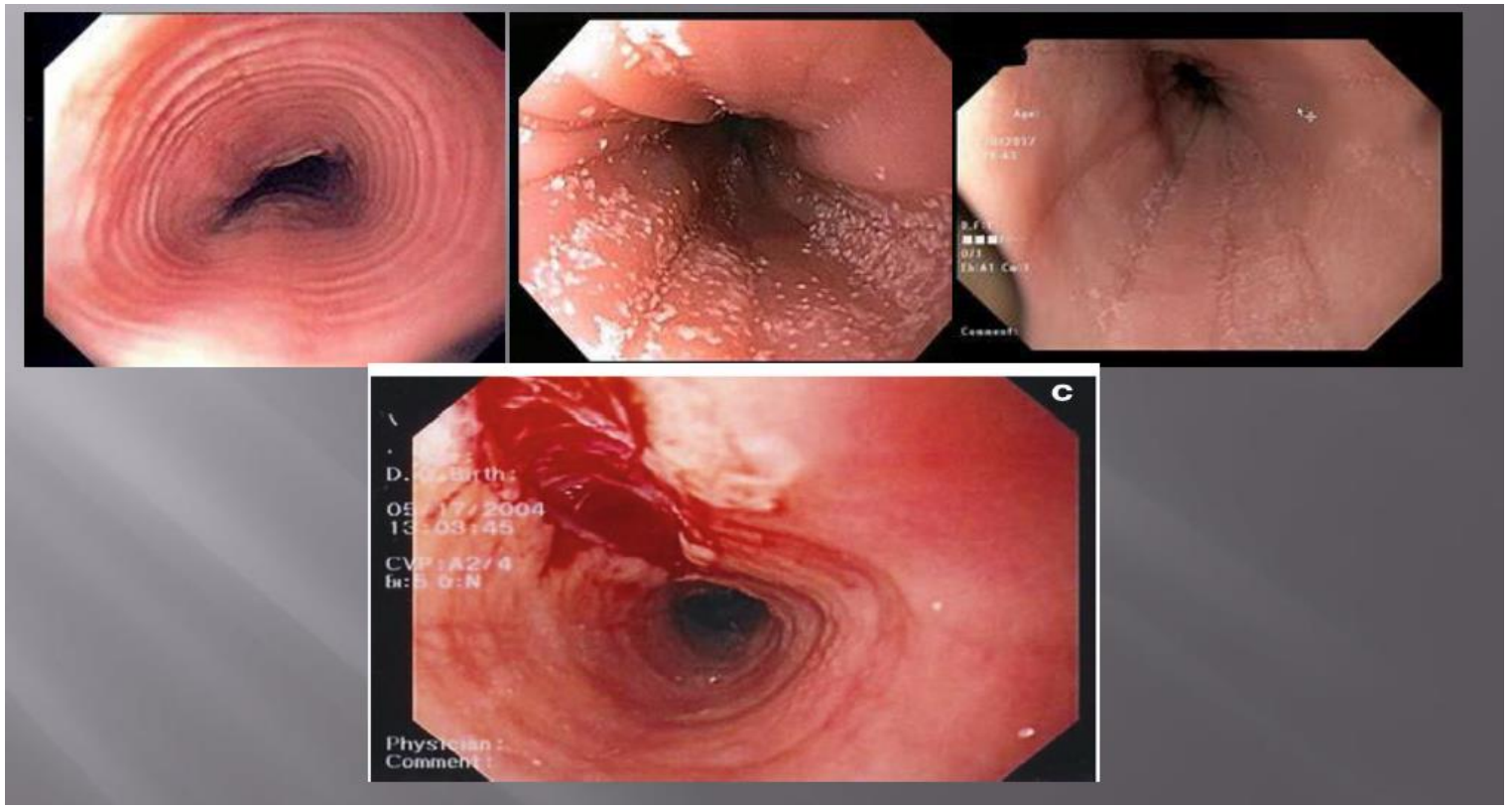
- To the Left we have Abnormal - Barrett's esophagus with increased risk of Adenocarcinoma.

Prague Classification



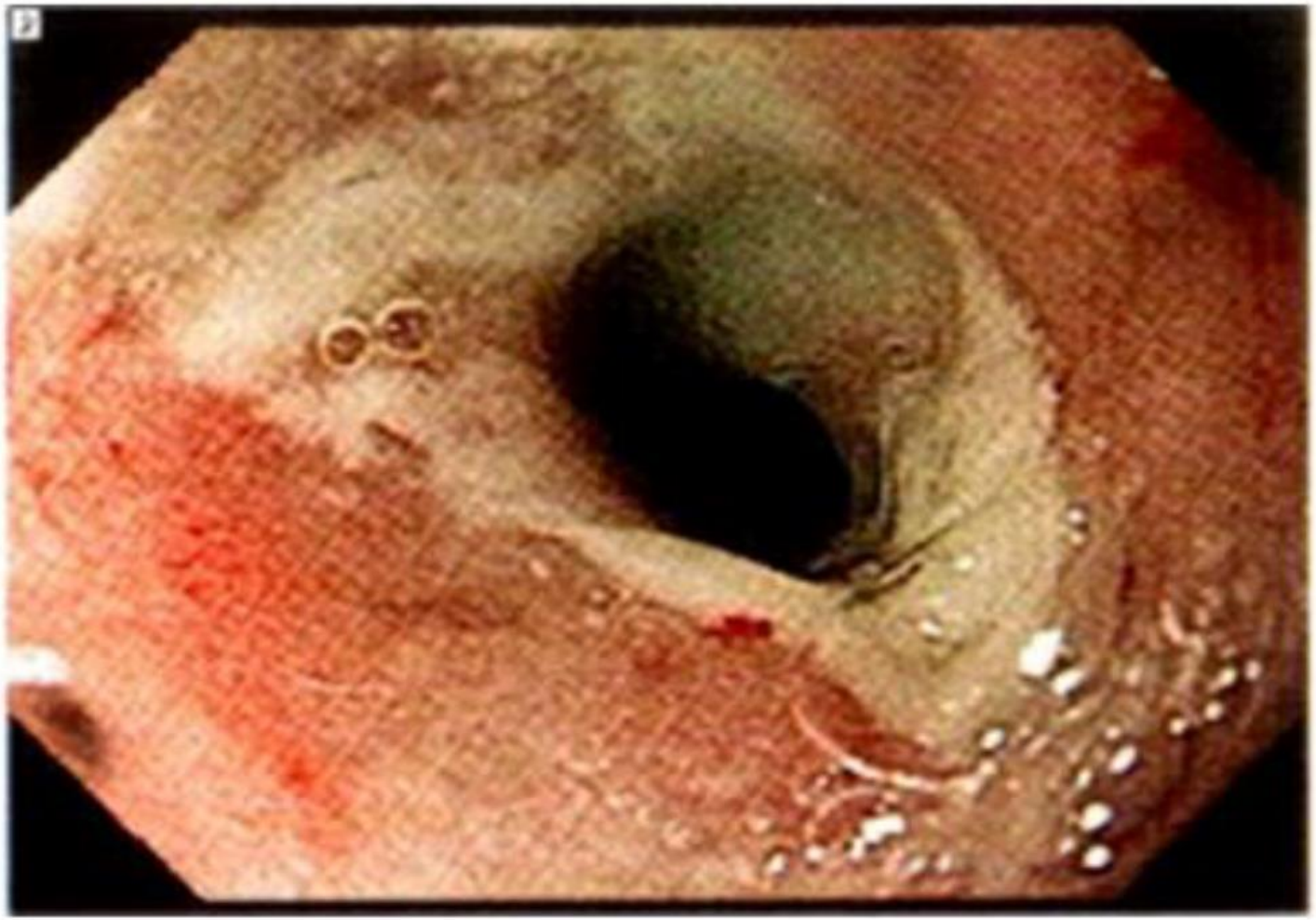
- Prague Classification depends on the Circumferential length (C) and Maximal Length (M) for grading the extent of Barrett's Esophagus.

Eosinophilic Esophagitis (EOE)



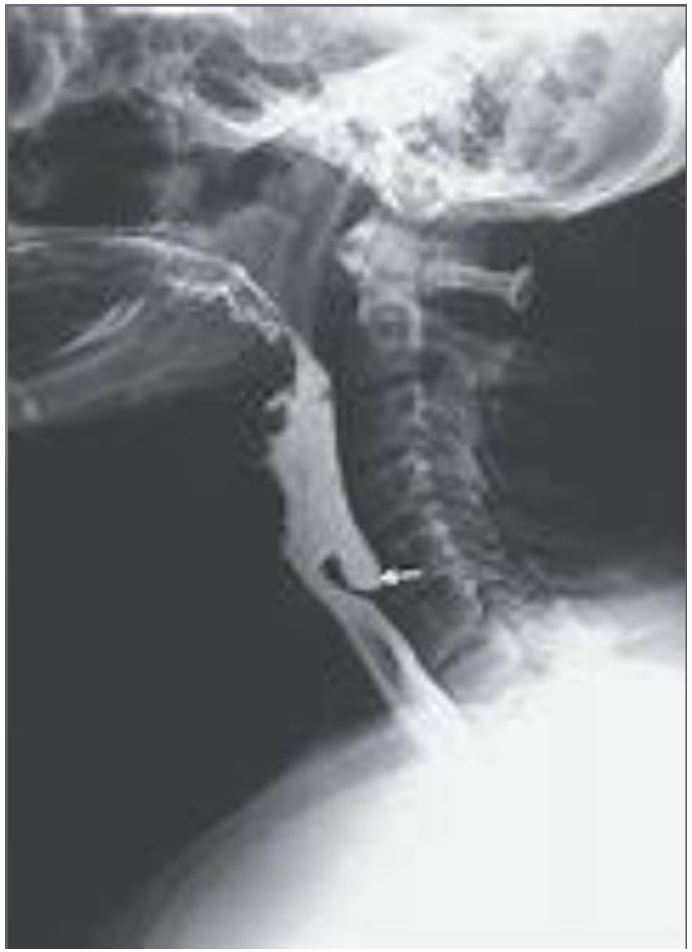
- A chronic, immune / antigen-mediated, esophageal disease characterized clinically by symptoms related to esophageal dysfunction and histologically by Eosinophil-predominant inflammation
- Strongly associated with allergic conditions.
- Patients present with Dysphagia, Food impaction, Refractory Heartburn, Feeding difficulties, and Abdominal Pain.
- It causes a Trachea-like appearance of the Esophagus + the Mucosa breaks off easily.
- Treatment: 1- PPI. 2- Topical Glucocorticoid. 3- Dietary Therapy. 4- Endoscopic Dilation (if the patient develops narrowing)

Corrosive Esophagitis



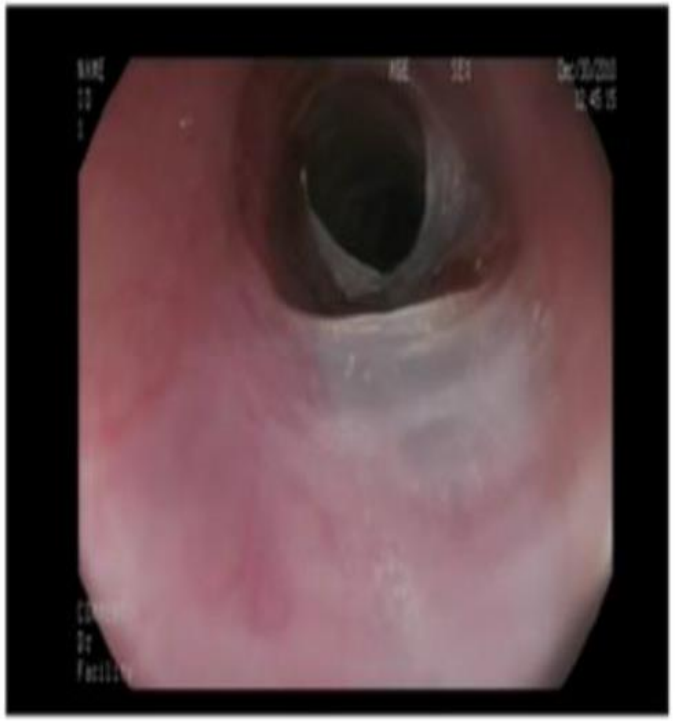
- Caused by ingestion of Strong Alkali or Acid.
- May cause severe ulceration and end up in fibrosis and stricture formation.

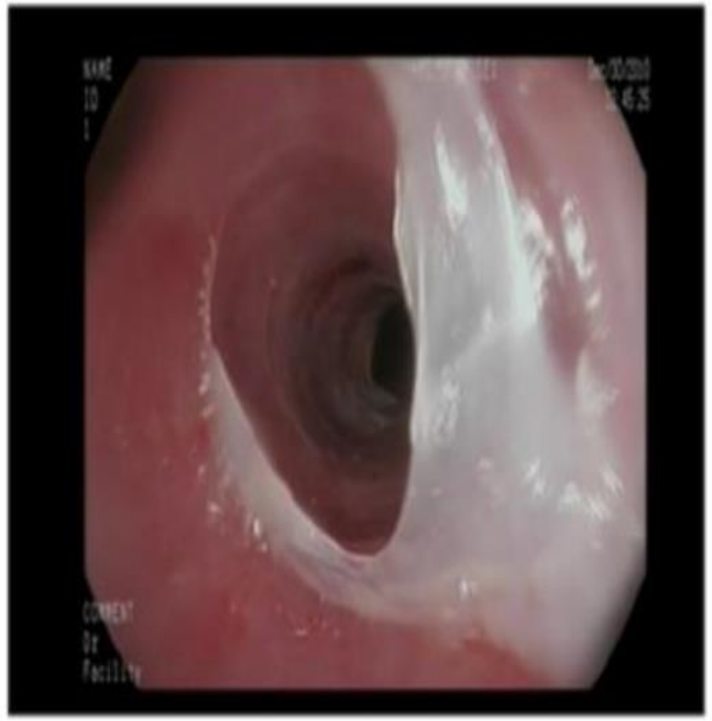
Zenker's Diverticulum



- Occurs in the posterior Hypopharyngeal Wall.
- A false diverticulum.
- Patients present with Dysphagia, Halitosis and Food regurgitation.
- Treatment: 1- Cricopharyngeal Myotomy. 2- Diverticulectomy.

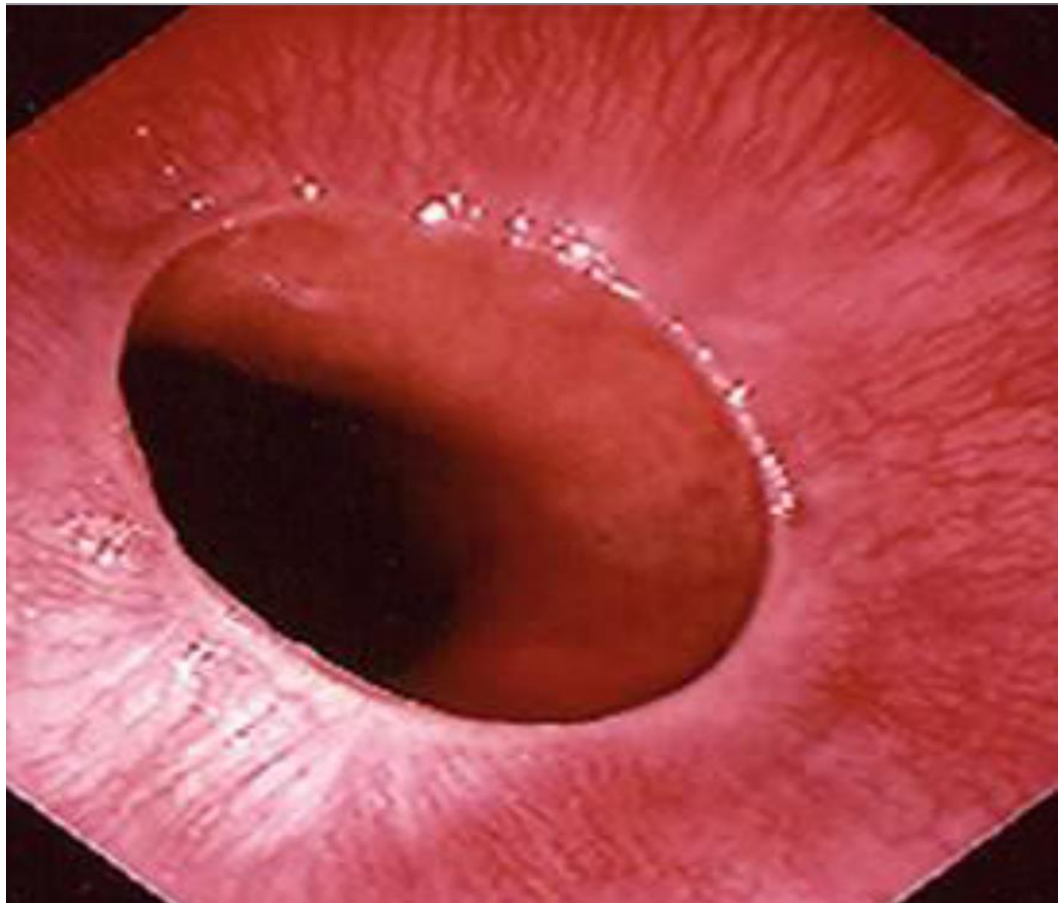
Esophageal Web





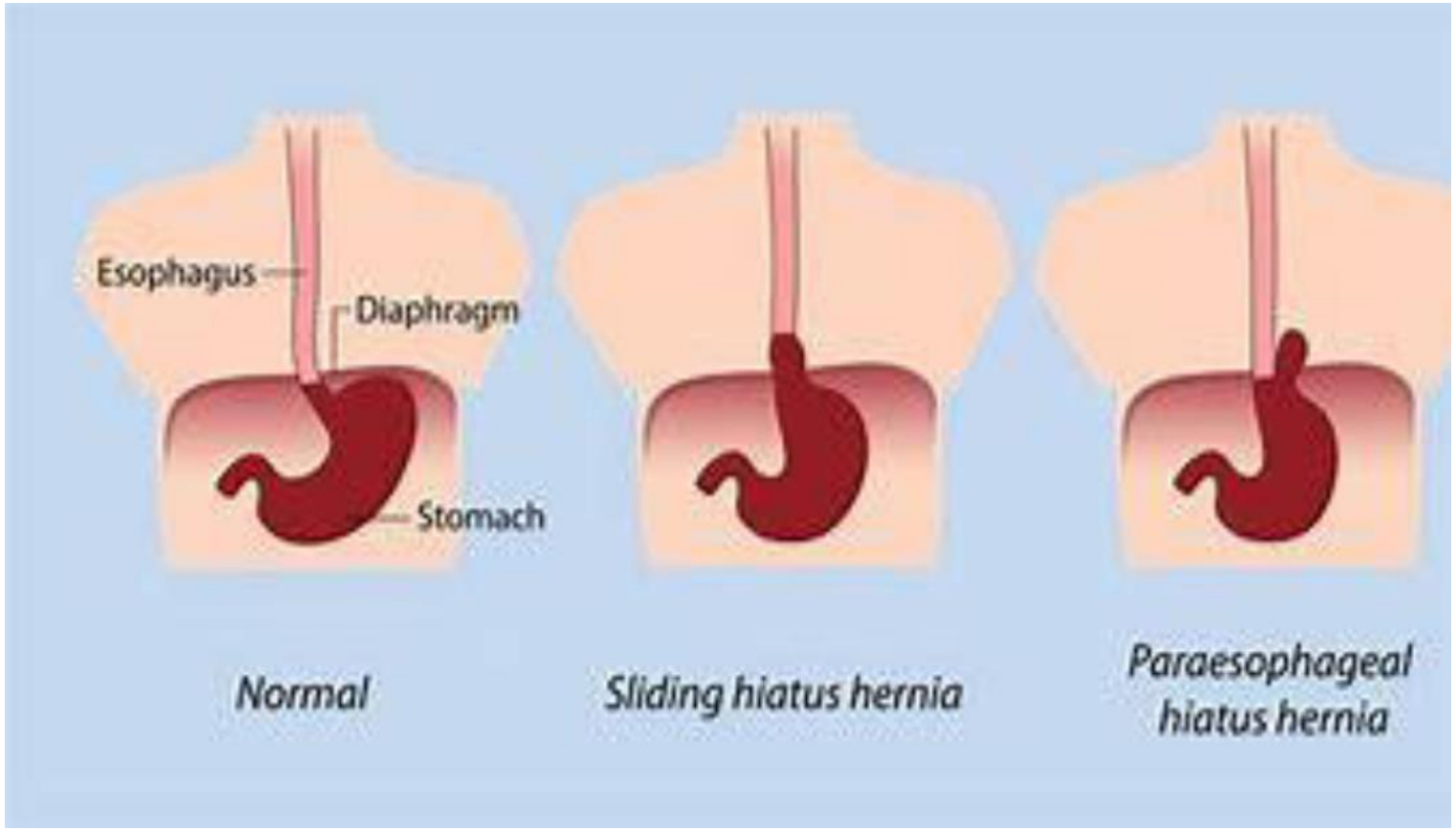
- Congenital or inflammatory constrictions usually in the Hypopharynx.
- May cause Dysphagia.
- May be associated with Iron deficiency Anemia → in this case it's called Plummer-Vinson Syndrome (Triad of Iron deficiency anemia + Esophageal web + Beefy red tongue due to atrophic glossitis)
- Treatment: Dilation

Schatzki Ring



- Thin Constriction at the Squamocolumnar Junction (Z-Line).
- Common cause for Dysphagia and Underlies Food Bolus Obstruction.
- Treatment: Dilation

Hiatus Hernia

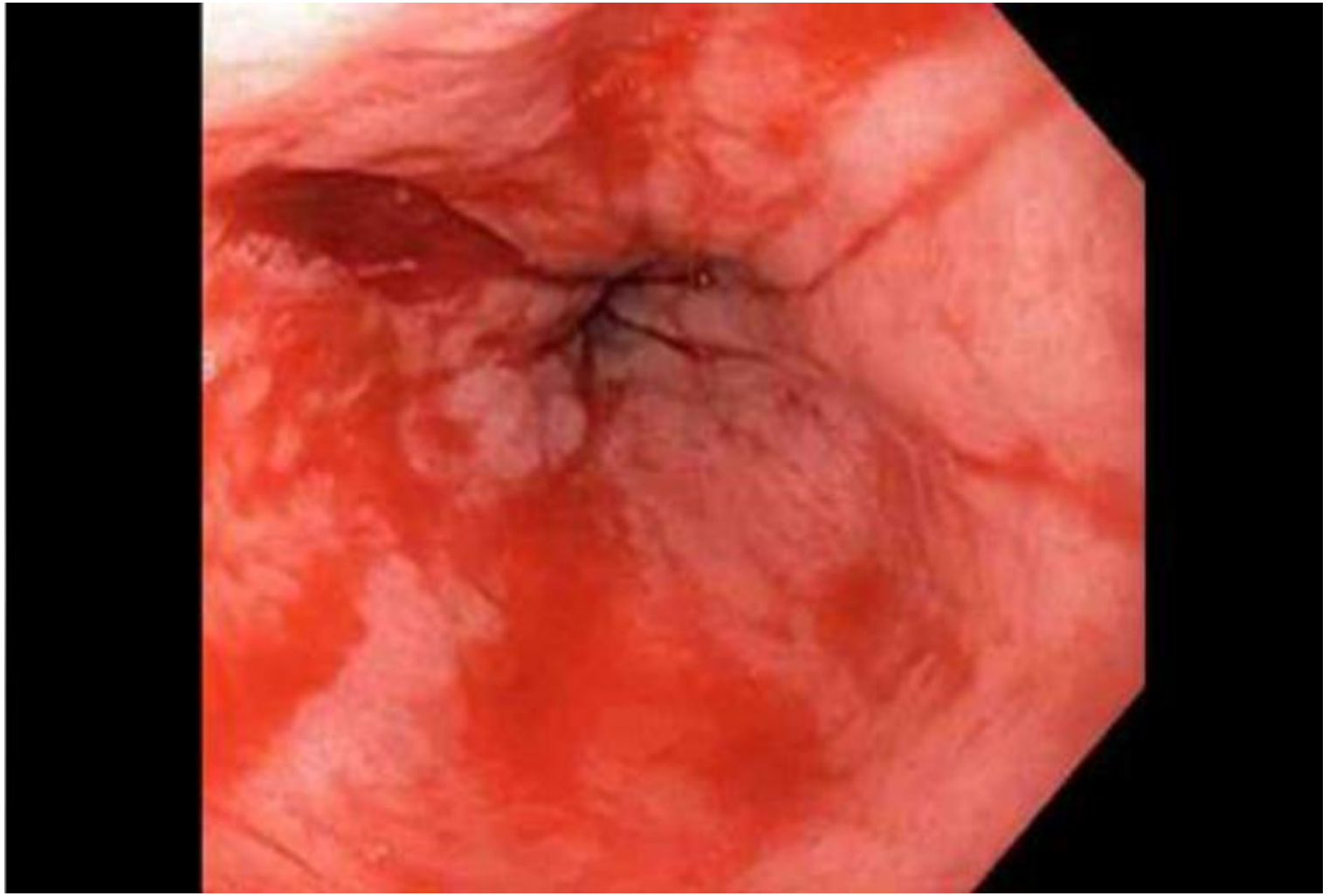


- 2 types:

1- Sliding hernia: the GEJ and part of the fundus lie in the thoracic cavity (GEJ sits above the Diaphragm). May contribute to GERD.

2- Para-esophageal hernia: part of the stomach is herniated beside the GEJ which is normally located. May incarcerate (meaning that the contents of the hernia become trapped), ulcerated, or cause dysphagia.

Mallory Weiss Syndrome



- Tear at the GEJ.
- Usually preceded by vomiting and Retching.
- Patients present with Upper GI bleeding.
- Most cases resolves Spontaneously (no treatment is needed).

Achalasia

- Esophageal motility disorder, characterized by failure of relaxation of the lower esophageal sphincter.
- There is non-peristaltic contractions in the body of the esophagus.
- It results from progressive degeneration of inhibitory ganglion cells in the myenteric plexus in the esophageal wall.
- Causes of Pseudo or Secondary Achalasia: 1- Gastric Carcinoma (Most common cause of Pseudo achalasia). 2- Amyloidosis. 3- Sarcoidosis. 4- Chagas Disease (Infectious disease caused by trypanosomes transmitted by bloodsucking bugs). 5- Eosinophilic Esophagitis. 6- Neurofibromatosis.
- Patients present with Dysphagia, Chest pain, Regurgitation, and Difficulty in belching.
- Treatment:

1- Aim is to decrease LES pressure to allow food to pass down.

2- Mechanical disruption of the muscle fibers of the LES: A- Endoscopic balloon dilation. B- Peroral endoscopic myotomy. C- Hellers Extra-mucosal myotomy.

3- Pharmacological Reduction in LES pressure: A- Botulinum toxin injection. B- Oral Nitrates and CCBs.

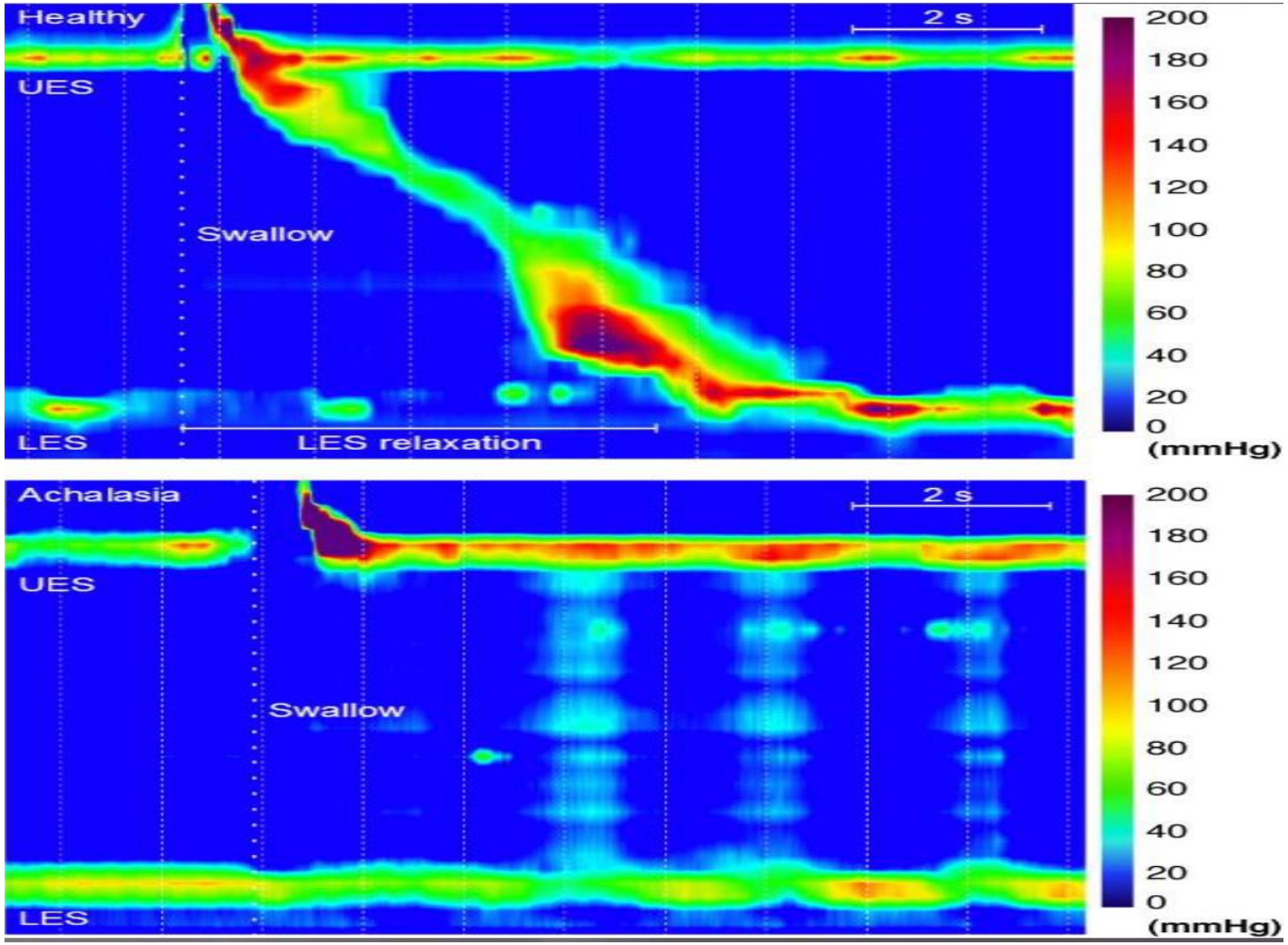
Achalasia: Diagnosis

- Symptoms and signs.
- CXR: Absence of gastric bubble
  - Air fluid level
  - Widening of mediastinum
- Barium swallow:
  - Dilated esophagus
  - Bird-beak narrowing in the lower end
  - Absent peristalsis

- Manometry:
  - Failure of relaxation of the LES during swallowing.
  - Normal or elevated resting LES pressure
  - Aperistalsis in the body of esophagus
  - Simultaneous esophageal body contractions with amplitudes >40 mmHg

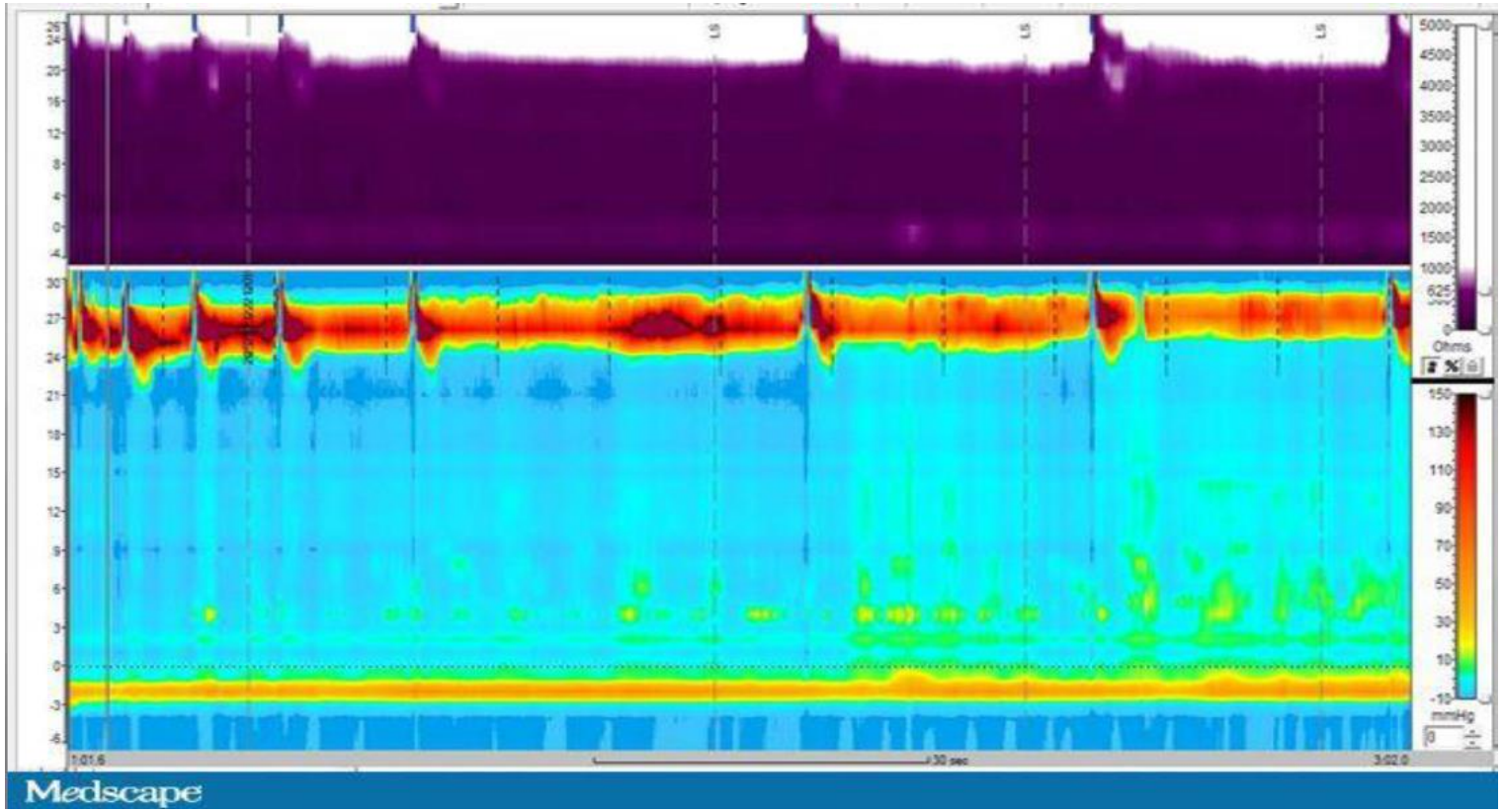
- Air Fluid Level → at the mid-level of the chest.

Achalasia: Motility Study



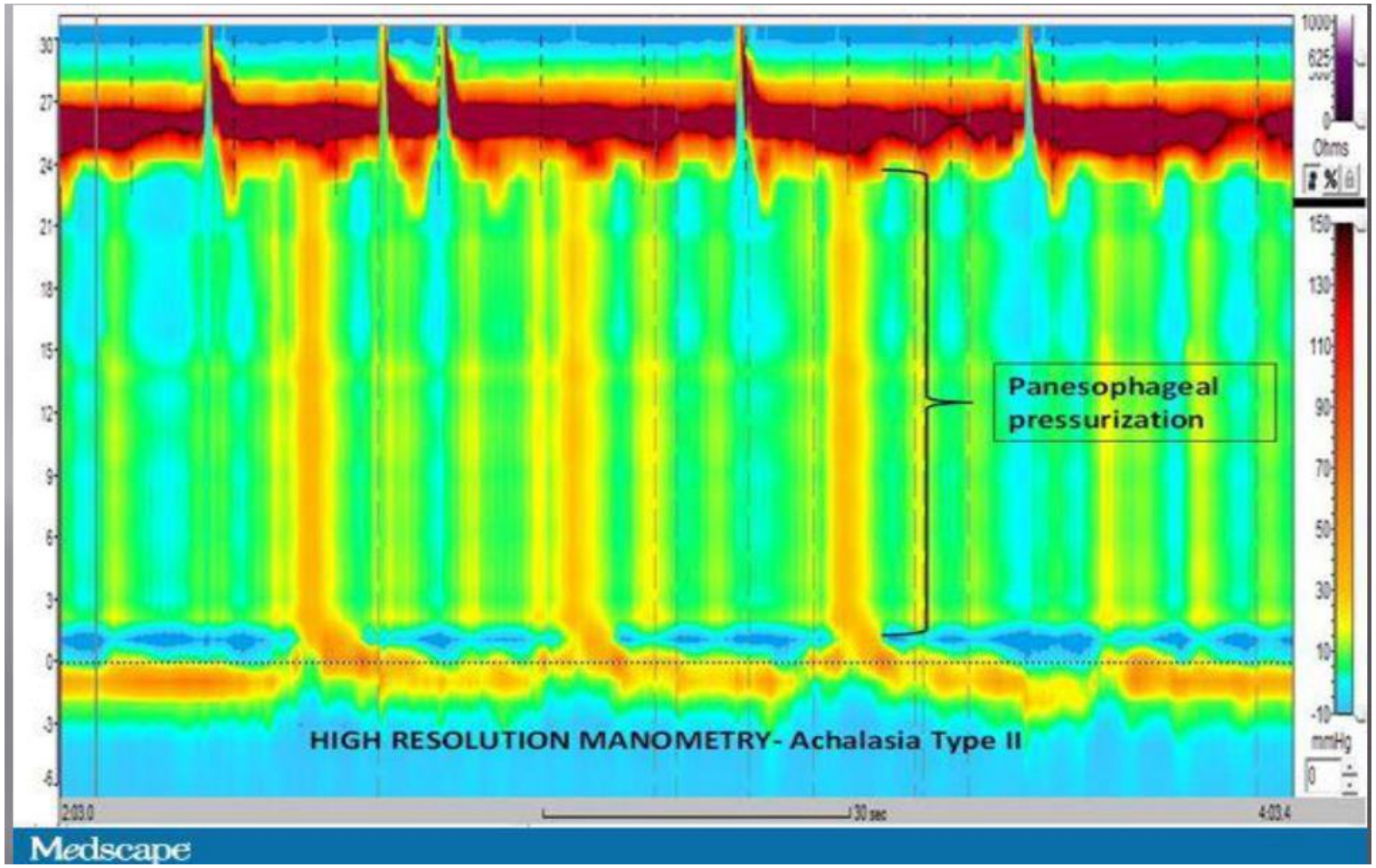
- Motility Study - Color intensity represents pressure.
- Normally, the LES relaxes and thus, the pressure drops to 0.
- In Achalasia, the LES fails to relax causing the pressure to remain high

Achalasia Type I



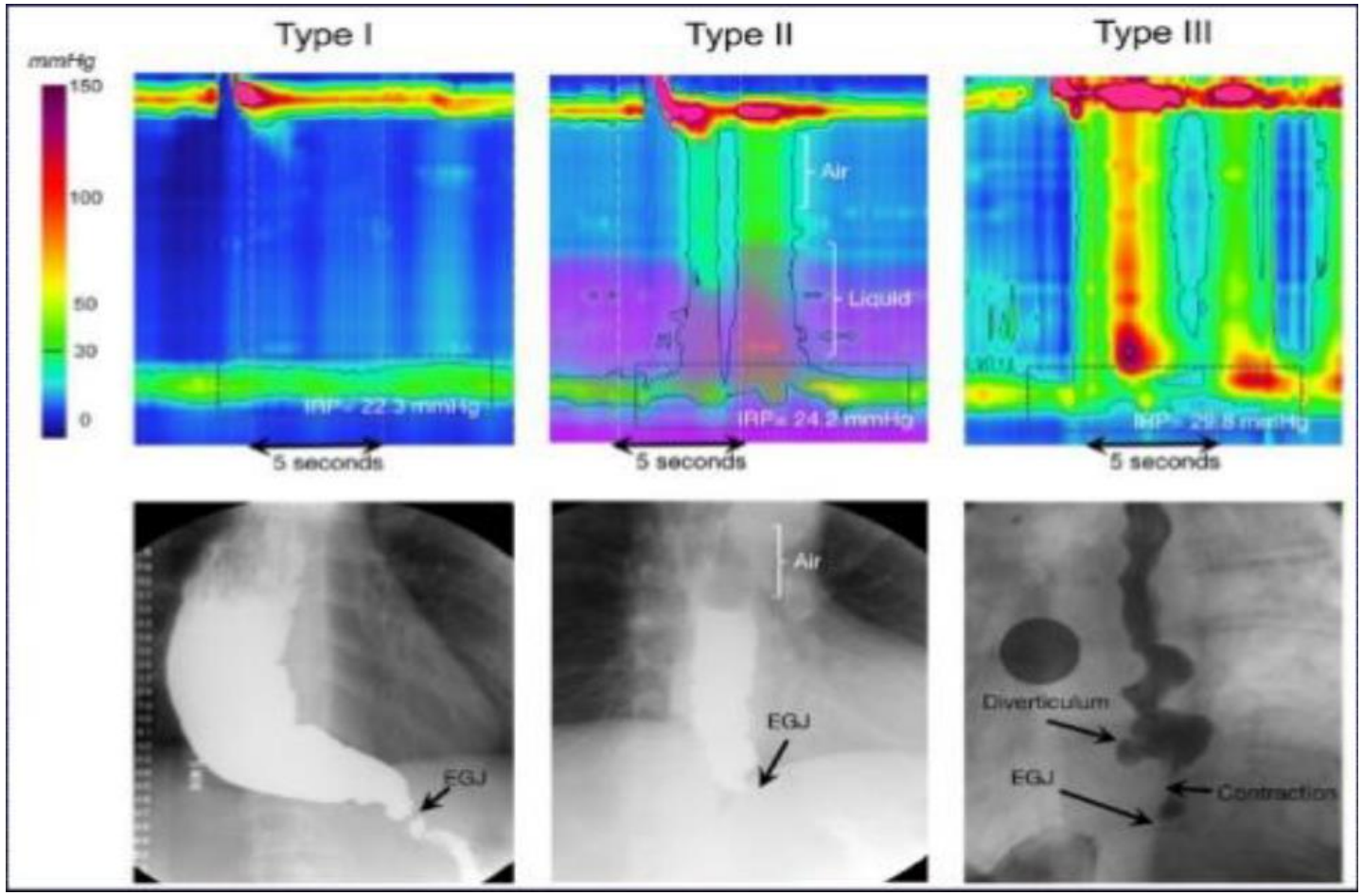
- Type I (Classic): Minimal Contractility in the Esophageal body.

Achalasia Type II



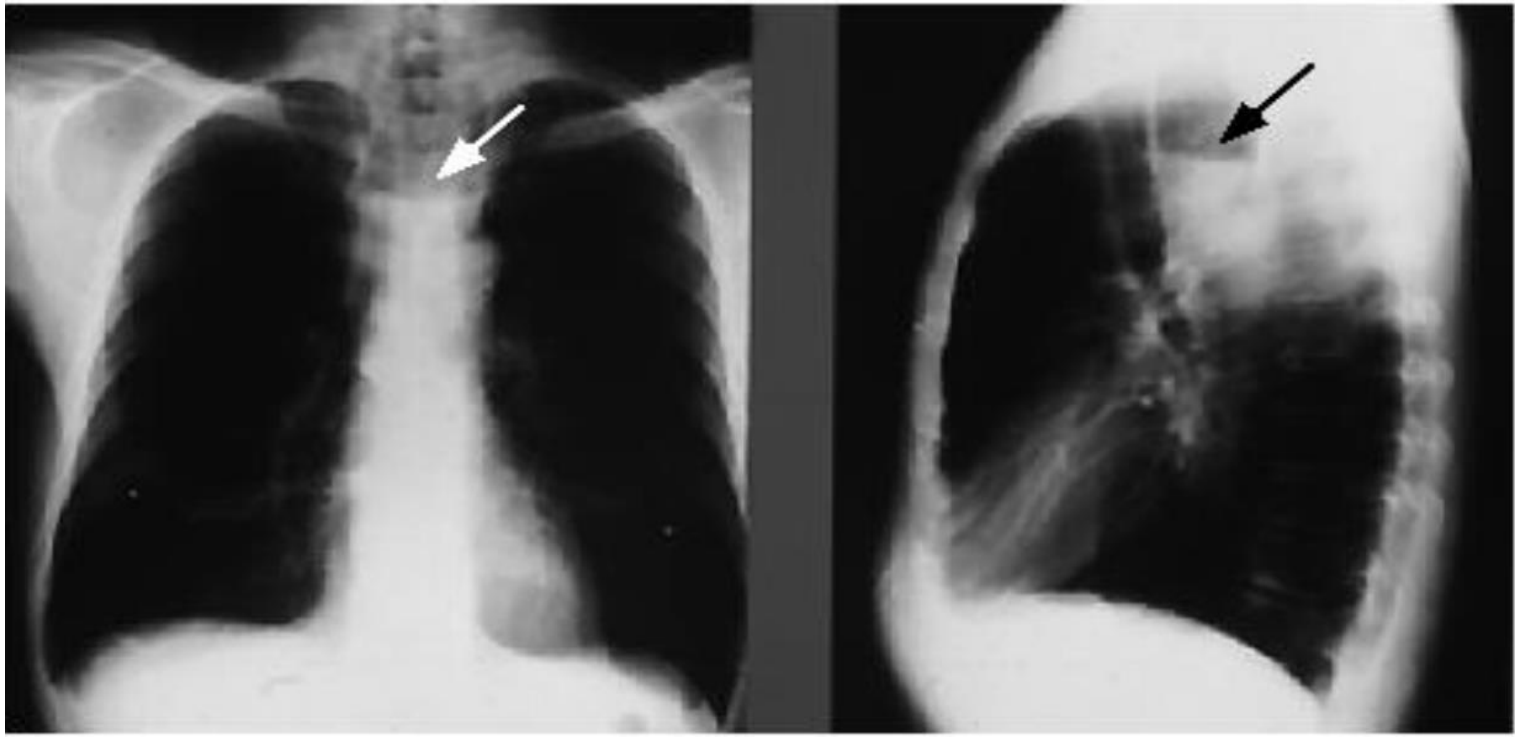
- Type II: intermittent periods of Pan-esophageal pressurization.

Chicago Classification of Achalasia



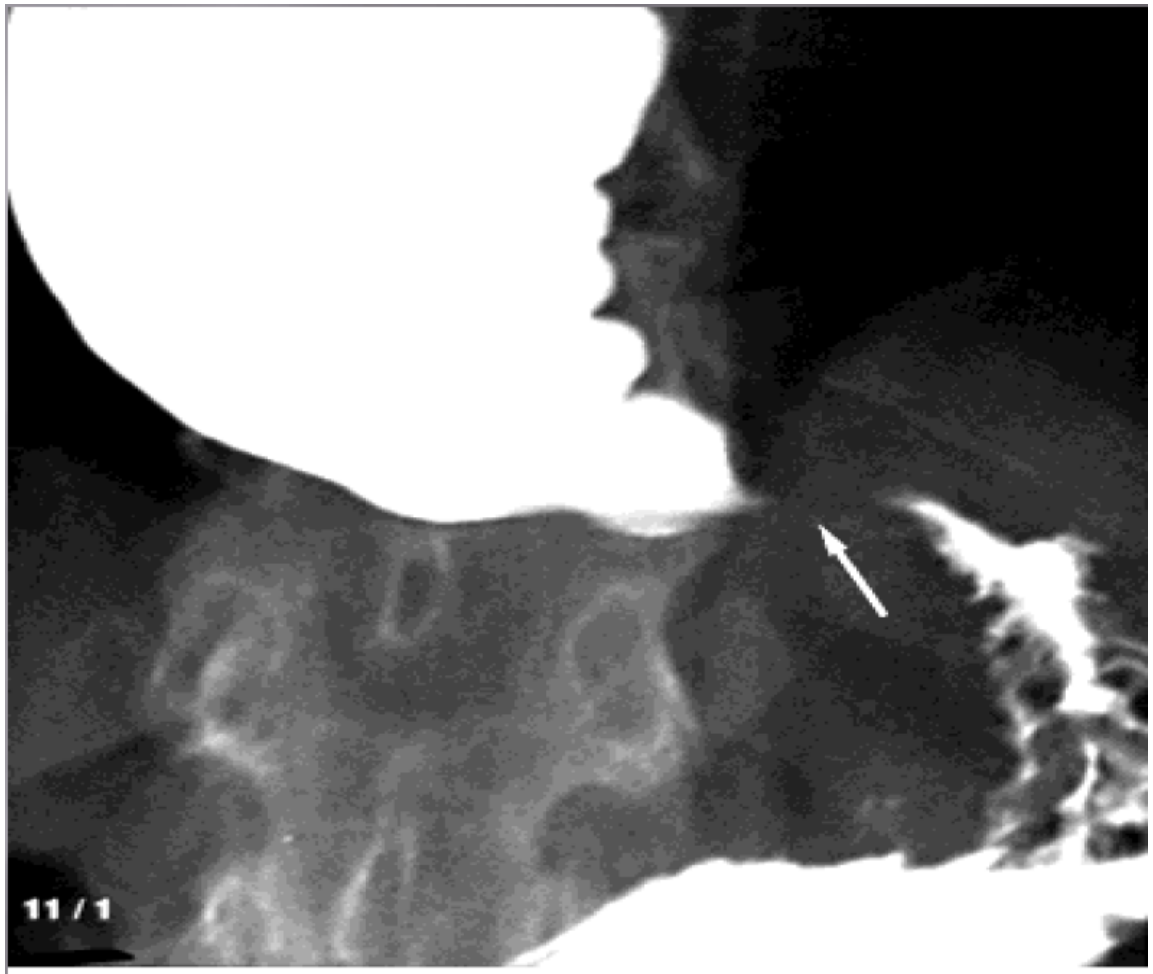
- Notice in Type I we have Dilated Esophagus with Narrowed GEJ.
- Type III (Spastic): Spastic Distal Esophageal contractions.

Achalasia: Air-Fluid Level



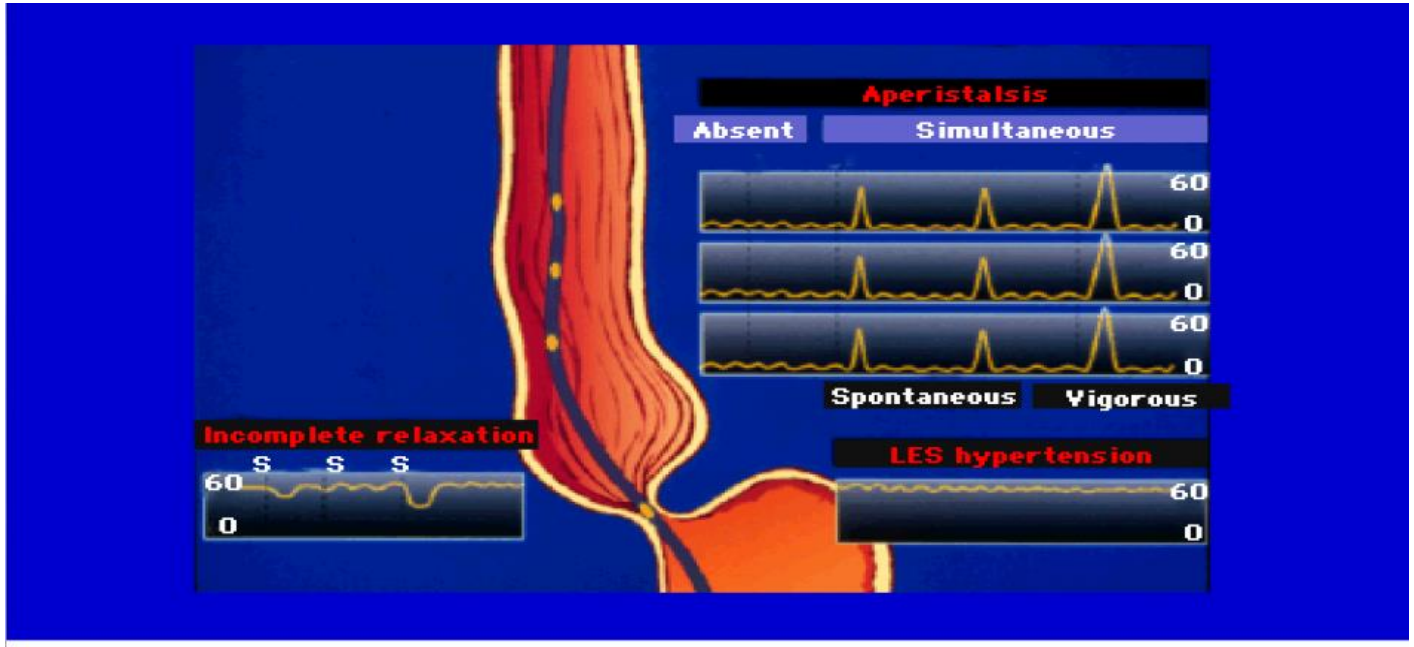
- Arrows show Air-Fluid level due to stasis in the Thoracic Esophagus which is filled with retained secretions and food.

Achalasia: Barium Swallow



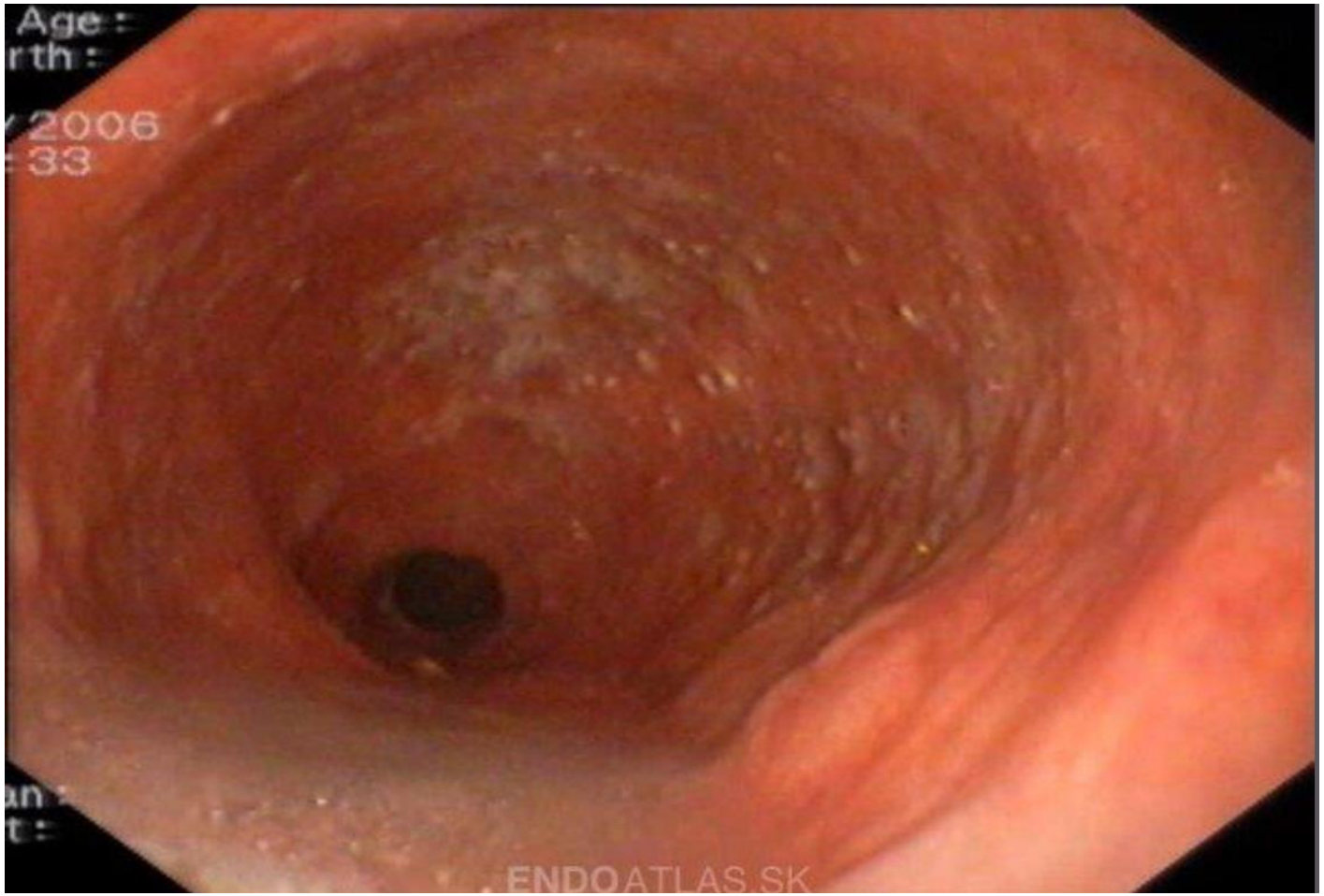
Achalasia Barium swallow in a 62 year old man demonstrates a dilated barium-filled esophagus with a region of persistent narrowing (arrow) at the GE junction, producing the so-called birds beak appearance. Achalasia was confirmed with manometry and the patient underwent successful dilation of the esophagus. Courtesy of Jonathan Kruskal, MD.

Achalasia: Manometry



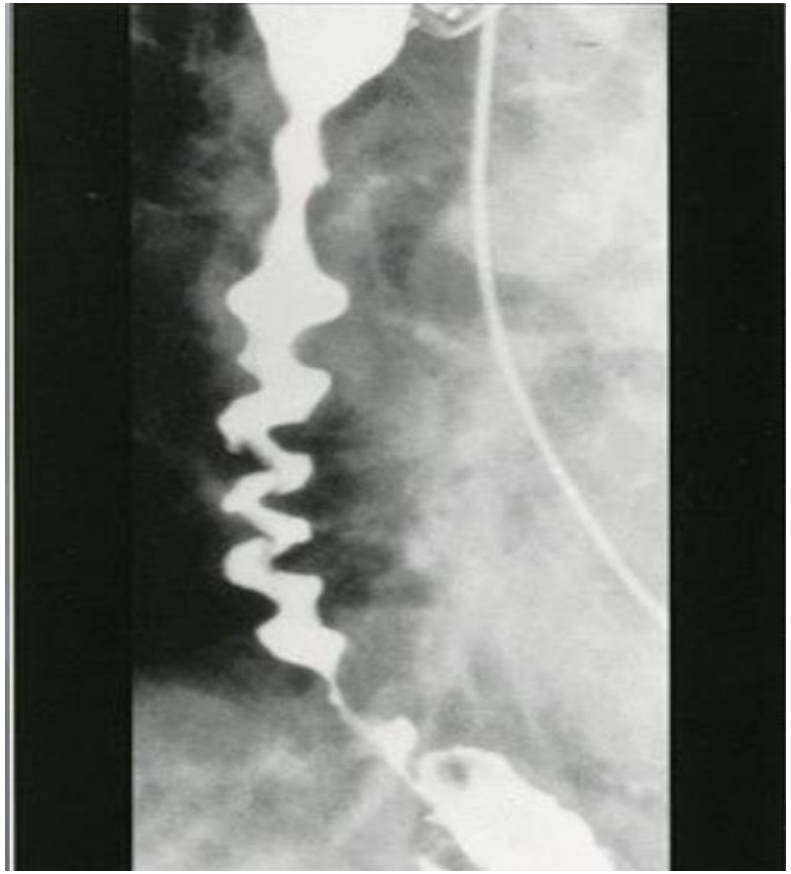
Manometric features of achalasia There are three characteristic manometric features of achalasia: elevated resting lower esophageal sphincter (LES) pressure (above 45 mmHg); incomplete LES relaxation after a swallow (S); aperistalsis in the smooth muscle portion of the body of the esophagus. Swallows may elicit no esophageal contraction or may be followed by simultaneous contractions. The esophagus may also contract spontaneously in a simultaneous fashion. In some cases, the simultaneous esophageal contractions have amplitudes >60 mmHg, a condition known as "vigorous" achalasia. Reprinted, courtesy of the Clinical Teaching Project of the American Gastroenterological Association©. This slide cannot be downloaded but may be purchased as part of a set from the AGA through Milner-Fenwick, Inc. at 1-800-432-8433.

Achalasia: Endoscopy



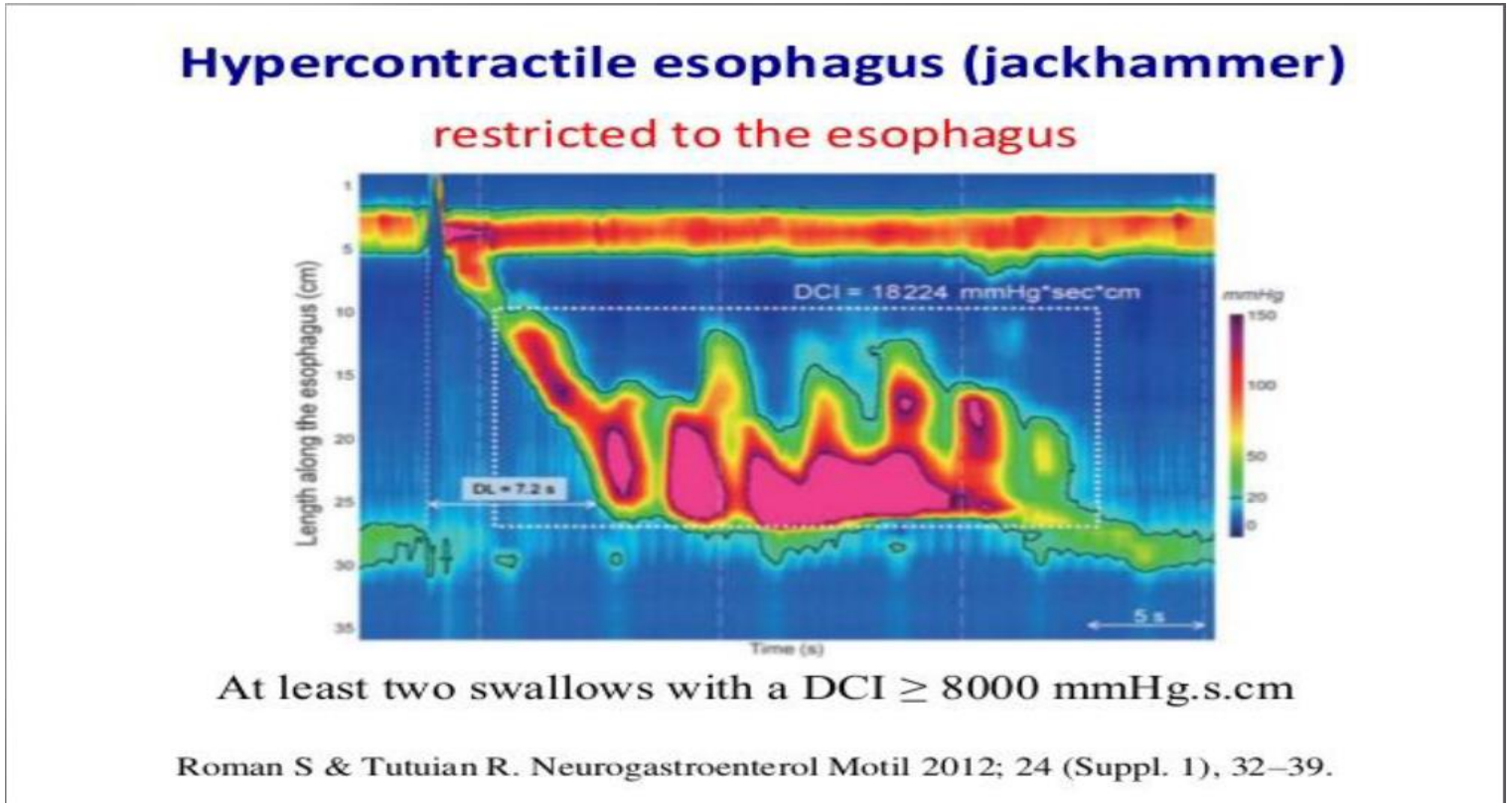
- Dilated lumen contains food and fluid.
- Narrow sphincter with resistance to the passage of the endoscope.
- Important to exclude secondary causes.
- The endoscopy in this figure shows a dilated esophagus with GEJ narrowing. Fluids and Food occasionally can be seen too.

Distal Esophageal Spasm



- Esophageal motility disorder, due to impaired inhibitory innervation. May also be induced by acid exposure.
- Patients present with Dysphagia, Heartburn, and Chest pain.
- Premature, Simultaneous, and rapidly propagated contractions in the distal esophagus >20% of swallows on manometry.
- "Rosary Bead" or "Corkscrew" appearance of the esophagus on Barium Esophagram.
- Treatment: 1- PPI. 2- Peppermint oil. 3- CCBs.

Jackhammer Esophagus



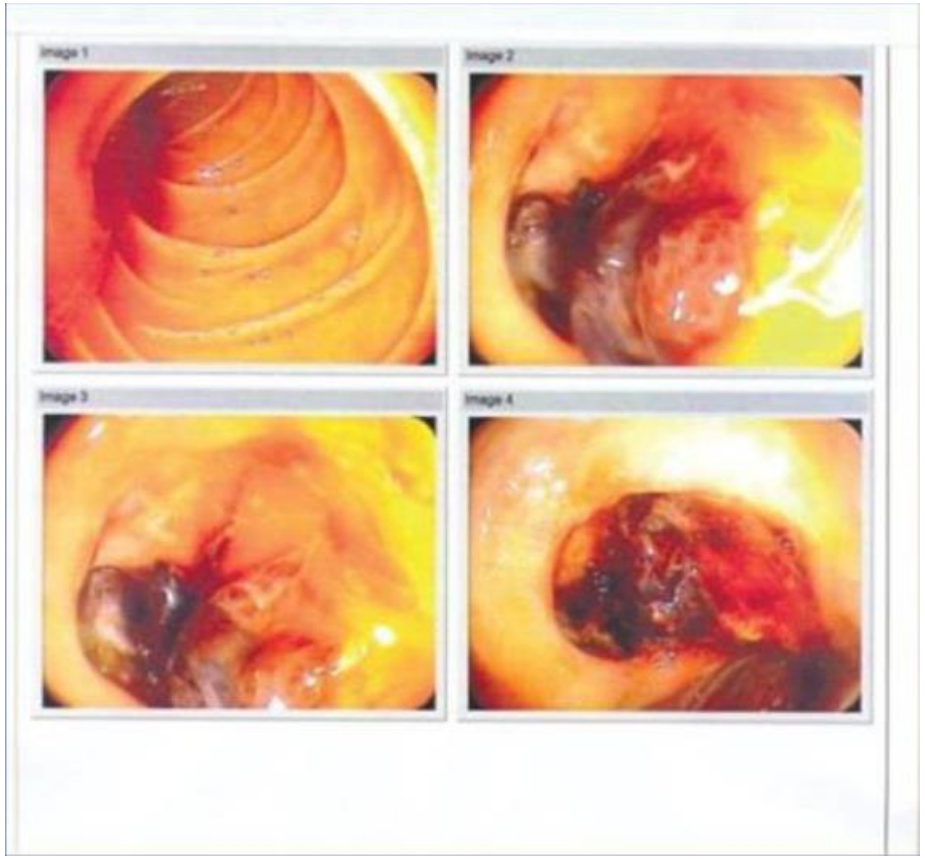
- Esophageal motility disorder, due to excessive excitation, smooth muscle hypertrophy, and/or smooth muscle response to excitatory nerves.
- Patients present with dysphagia, chest pain, and heartburn.
- Barium Esophagram shows normal sequential peristalsis.
- Characterized by high pressure but normally sequential contractions in the smooth muscles of the esophagus.
- Treatment: 1- PPI. 2- Peppermint Oil. 3- CCBs.

Non-Variceal Upper Gastro-Intestinal Bleeding

NVUGIB

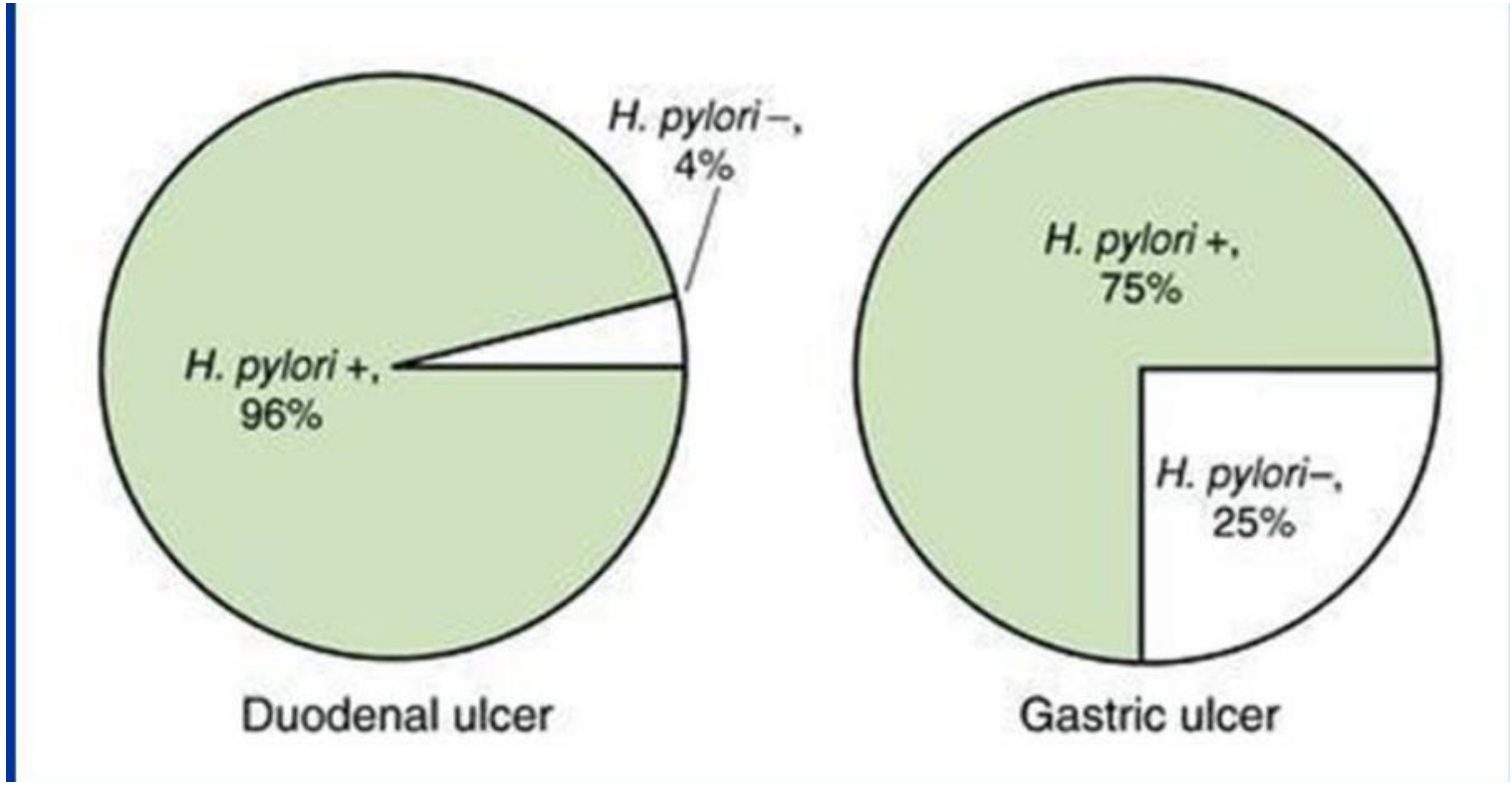
- Bleeding proximal to Ampulla of Vater or precisely Ligament of Treitz.
- Accounts for 50% of all GI bleeding.
- Not related to Portal HTN.
- The most common cause: Peptic Ulcer Disease, by causing defect in the surface mucosa thus making the submucosa exposed to the destructive action of gastric juice, leading to erosion of vessels and bleeding.
- Patients present with Hematemesis, Melena, Dizziness, Abdominal Pain and Symptoms of PUD, Hx of NSAIDs use, Pallor, Hypotension, Orthostasis, Jaundice and other stigmata of chronic liver disease.
- NSAIDs block the synthesis of Prostaglandins (which protect Gastro-duodenal mucosa by 1- Secretion of Mucous. 2- Bicarbonate secretion. 3- Maintenance of blood flow during periods of potential injury.) thus predispose to mucosal injury and peptic ulceration.
- Upper GI Bleeding Forms: 1- Melena (most common): occurs with >=100 ml blood is instilled into UGI tract → Patients are found to suffer from bleeding by doing Rectal exam. 2- Hematochezia (Fresh blood per rectum, higher mortality than melena): occurs with >=1000 ml blood is instilled into UGI tract → may be misdiagnosed as Lower GI bleeding.

Acute Upper GI Bleeding



- The Second Figure shows an Ulcer with adherent clot which usually dislodge leading to rise in BP and bleeding.
- Eroding Duodenal ulcers related to NSAIDs use (e.g. Aspirin) → Eroding Gastroduodenal Artery Leading to massive Upper GI Bleeding (Lethal disease which may lead to Death, Cardiac Arrest, MI, CVA, Seizures).

Upper GI Bleeding: PUD



- H.Pylori is more prone to cause duodenal ulcers.
- Poor healing With H.Pylori infection + NSAIDs use + Smoking → Ulcer become deeper and higher risk of penetration and bleeding and may require surgery to eradicate the ulcer.

Upper GI Bleeding / Labs

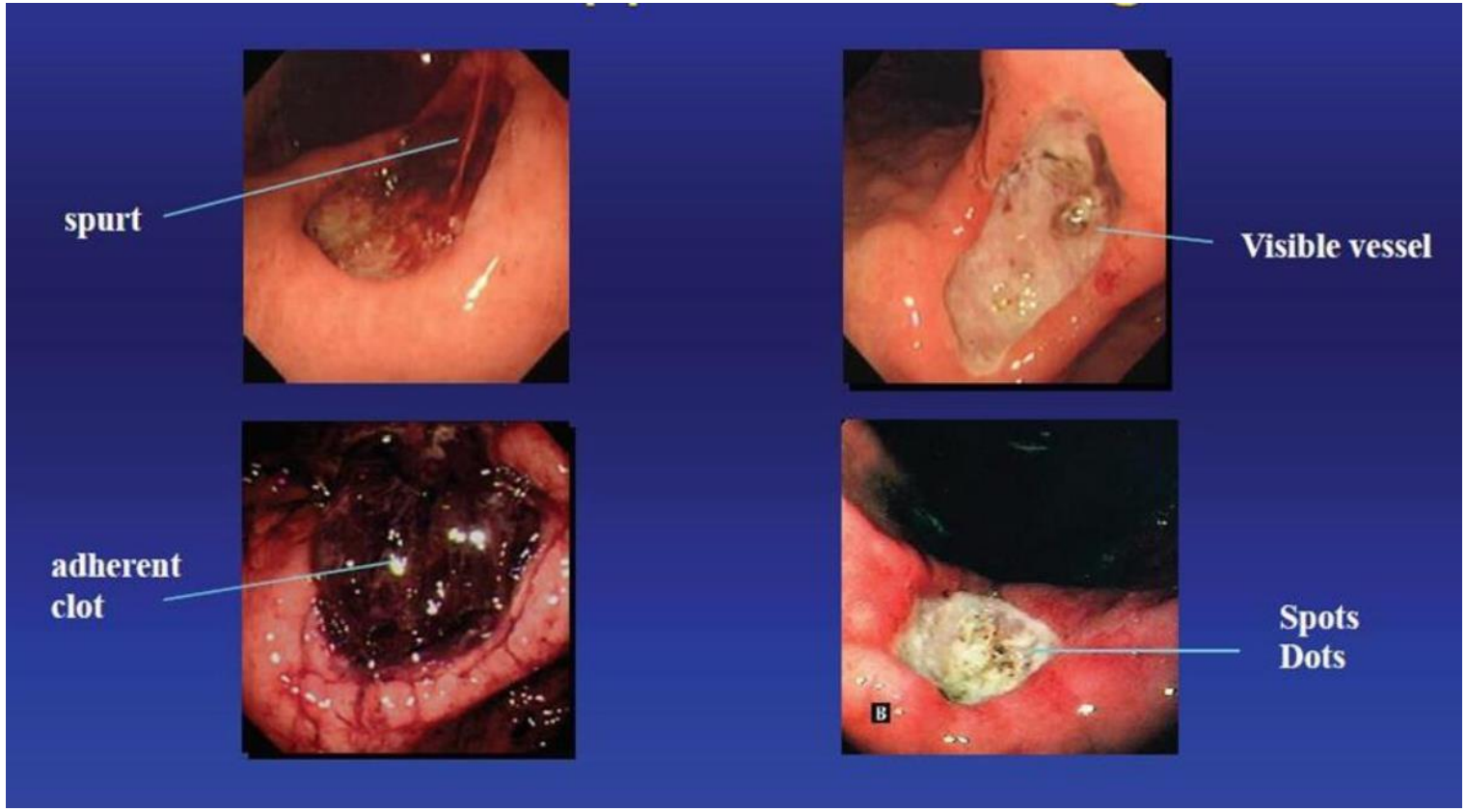
- UGIB require blood transfusion of Packed RBCs (PRBCs).
- One PRBC unit has a standard volume of 300 ml.
- One PRBC unit will rise the Hematocrit of a standard adult patient by 3%.
- One PRBC unit is expected to increase Hemoglobin by 1 g/dl.
- Significant Hb drop secondary to a bleeding: 1- Hemoglobin decrease >= 2g from baseline. 2- Hematocrit decrease >= 6% from baseline.
- Don't use Hb/Hct to evaluate or monitor acute bleeding as patients bleed whole blood; so, hematocrit may not decrease immediately with acute bleeding.
- Patients with bleeding drop blood volume with normal Hb and Hct until counteracting mechanism try to restore volume by activating baroreceptors so fluid moves from ECF to the vascular space to restore volume by adding volume free of RBCs leading to decreased concentration of RBCs.

Causes of Acute Upper GI Bleeding

Cause	Frequency (%)
Peptic Ulcer	40
Esophagitis	10
Erosive disease	6
Other	6
Mallory-Weiss	5
Varices	5
Neoplasm	4
No cause identified	24

- Esophagitis in elderly >70 years-old is more common than PUD.

Gastric Ulcers Presenting with Acute Upper GI Bleeding



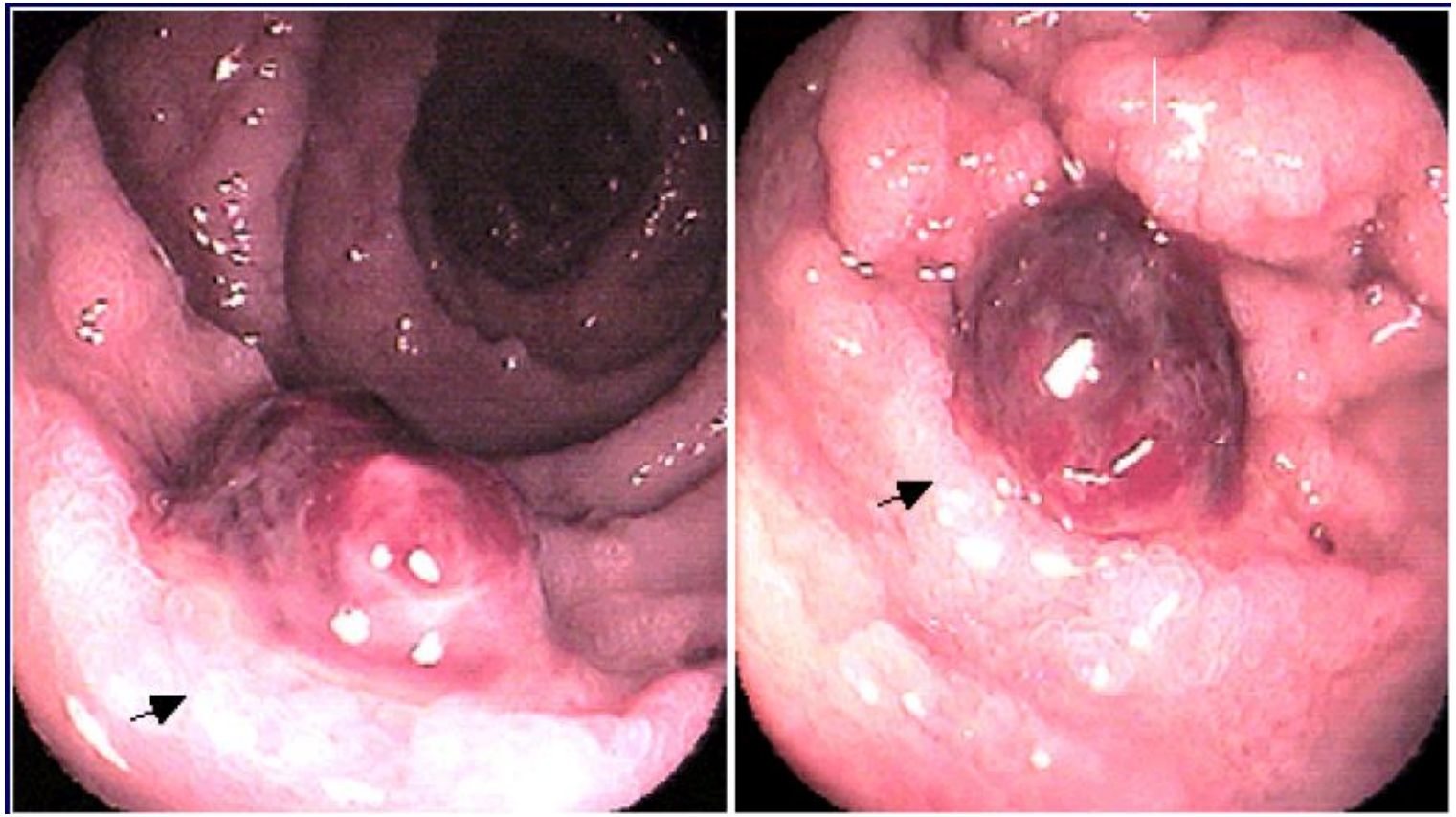
- Spurt → PUD with Spurting Vessels , Deep Ulcer with necrosis of the mucosa and Sloughing.

The ulcer is surrounded by normal mucosa.

Due to continued erosion and acidity → the Layer on the intima of the vessel becomes denatured and necrotic, so it ruptures and spreads blood.

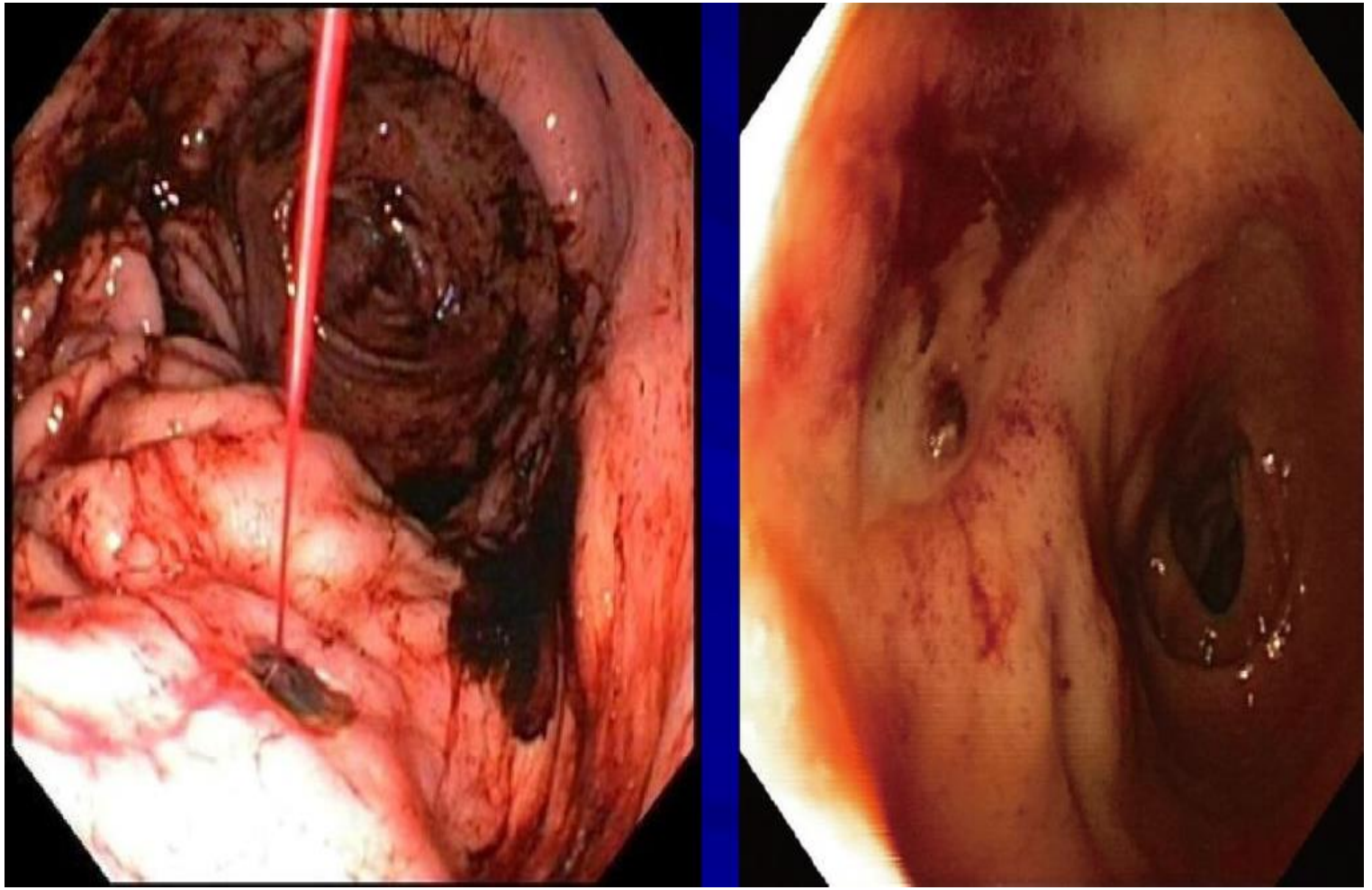
- The second picture shows ulcer with Visible vessel but no bleeding.
- Adherent Clot → Formation of a clot on the ulcer with a risk of dislodging and transferring to other sites.
- Spots Dots → Blood vessel with healing and granulation tissue, and no bleeding.

High Risk Ulcer

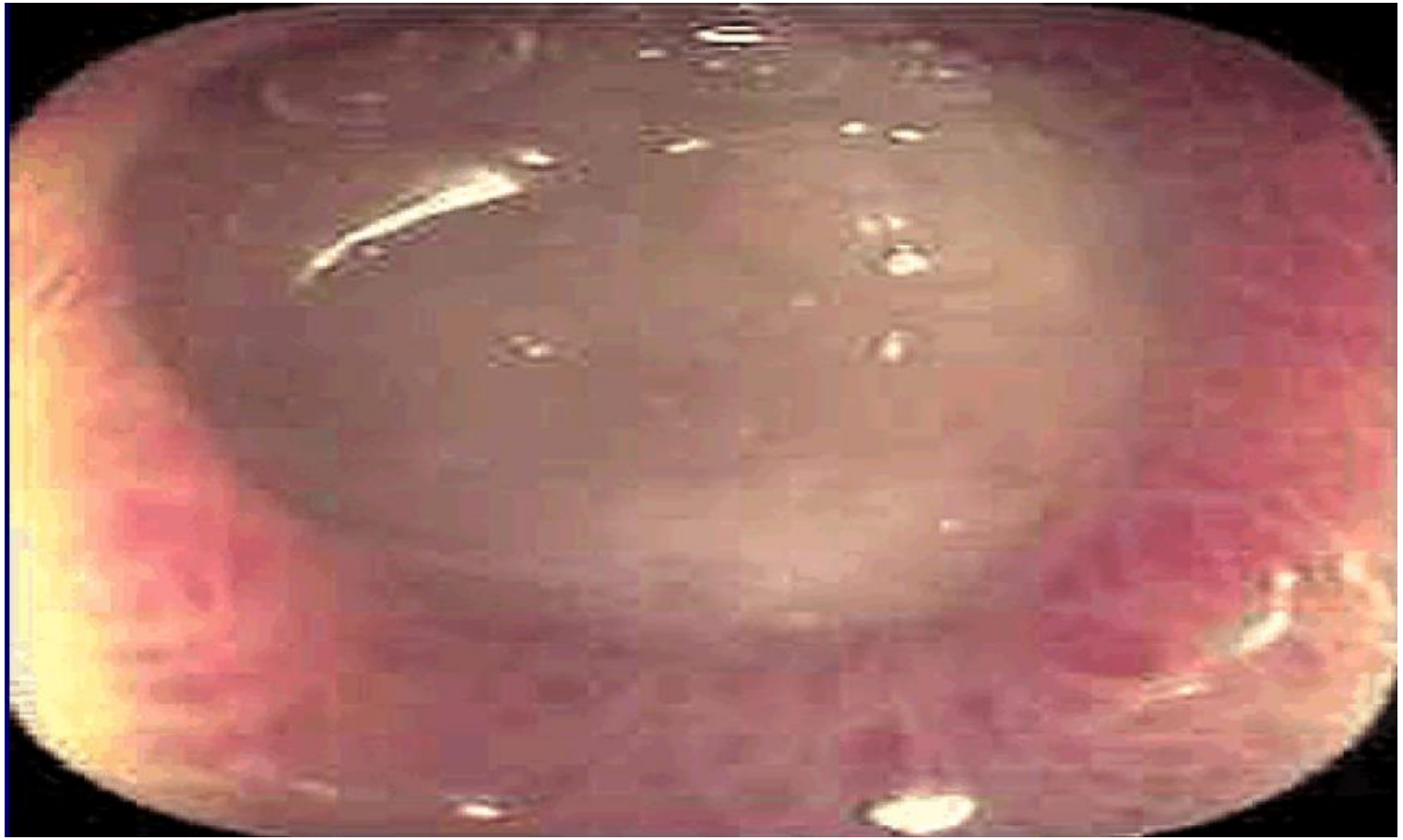


- Visible Vessel - Duodenal Ulcer in a patient with Upper Gastrointestinal bleeding.
- The ulcer base (arrows) is visible as the whitish rim underlying the protruding vessel. The erythematous mound in the center of the ulcer represents an arteriole that has eroded into the lumen of the duodenum.

High Risk Ulcer



Low Risk Ulcer



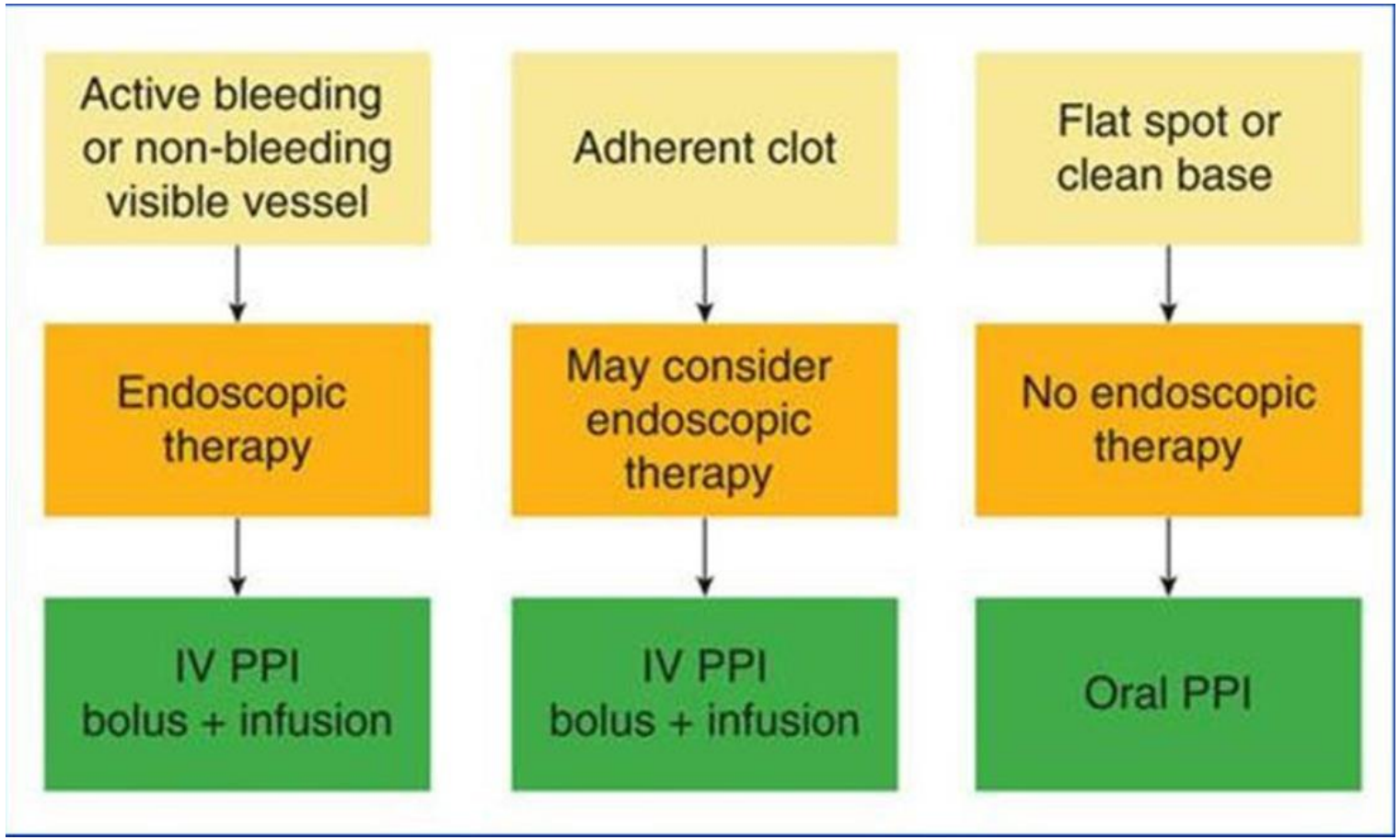
- Ulcer with a clean base - Low risk of bleeding.

Forrest Classification

Stigmata of hemorrhage	Forrest classification
Active spurting bleeding	IA
Active oozing bleeding	IB
Non-bleeding visible vessel	IIA
Adherent clot	IIB
Flat pigmented spot	IIC
Clean base	III

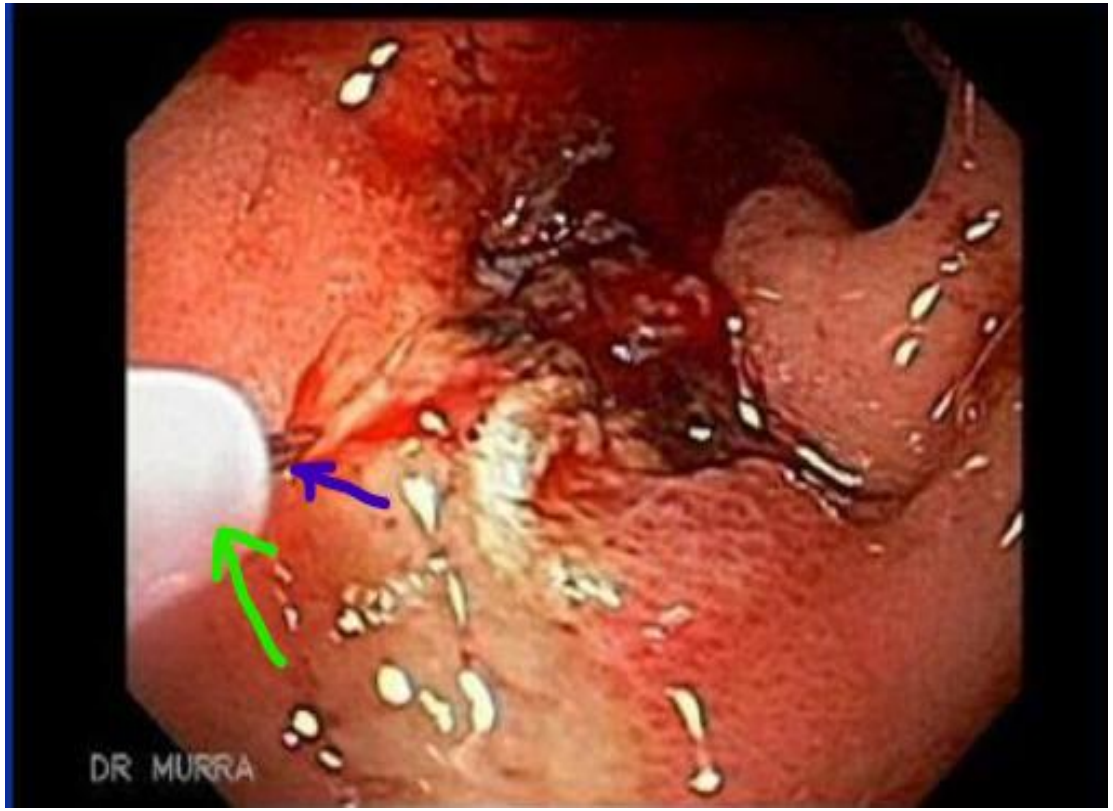
- Used to assess risk, mortality and need for interventional endoscopy and where to admit the patient (ICU / Regular Ward) and Type of PPI (Oral / IV) and time of eating and risk of bleeding.
- IA and IB → Active bleeding.
- IIA + IIB + IIC → Impending Bleeding risk.
- Active Oozing Bleeding → no visible major vessel.
- Flat pigmented spot → Ulcer with recent bleeding and started to heal.
- Clean base → Most common, ulcer with no apparent vessel and least risk of rebleeding and complications.
- Benign management of clean base ulcers: Switch PPIs from IV to Oral + Feed Patient at the same day + Discharge some patients if they are stable.

Management



- Active Bleeding is the riskiest → Treat in an ICU for 72 hours and if there were no rebleeding transfer the patient to a regular ward and plan for discharge.
- Regarding Adherent Clot → you don't know what is underneath the clot, so must remove the clot and treat according to underlying lesion.

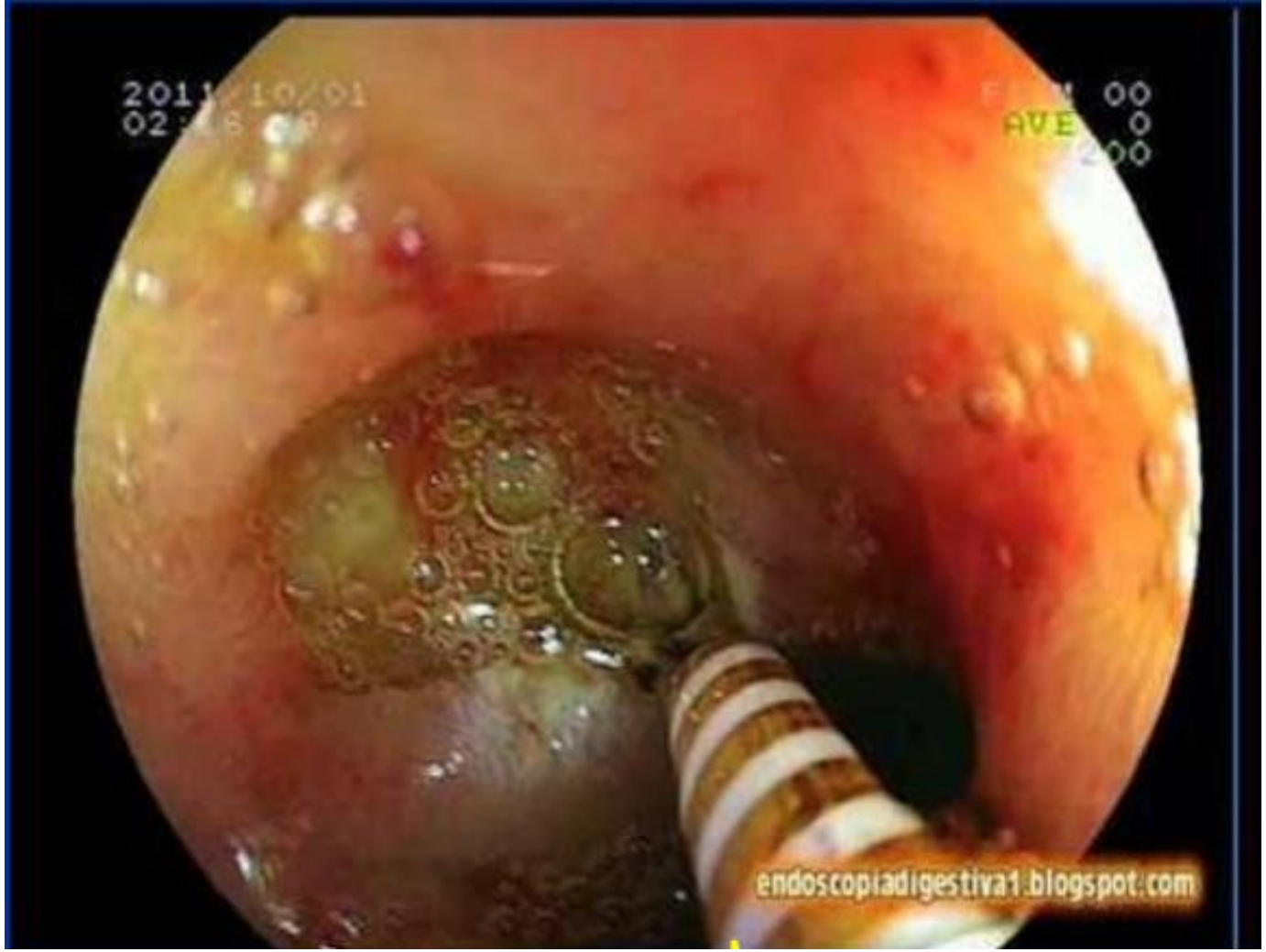
Management



- Therapeutic channel of the endoscope → 2.2 - 3.2 mm in diameter.
- Green Arrow → Tube
- Blue Arrow → Needle
- At the end of the tube → we have a needle to inject a vasoconstrictive substance into the submucosa like Adrenaline, causing Vasoconstriction to stop bleeding to be able to see the lesion.

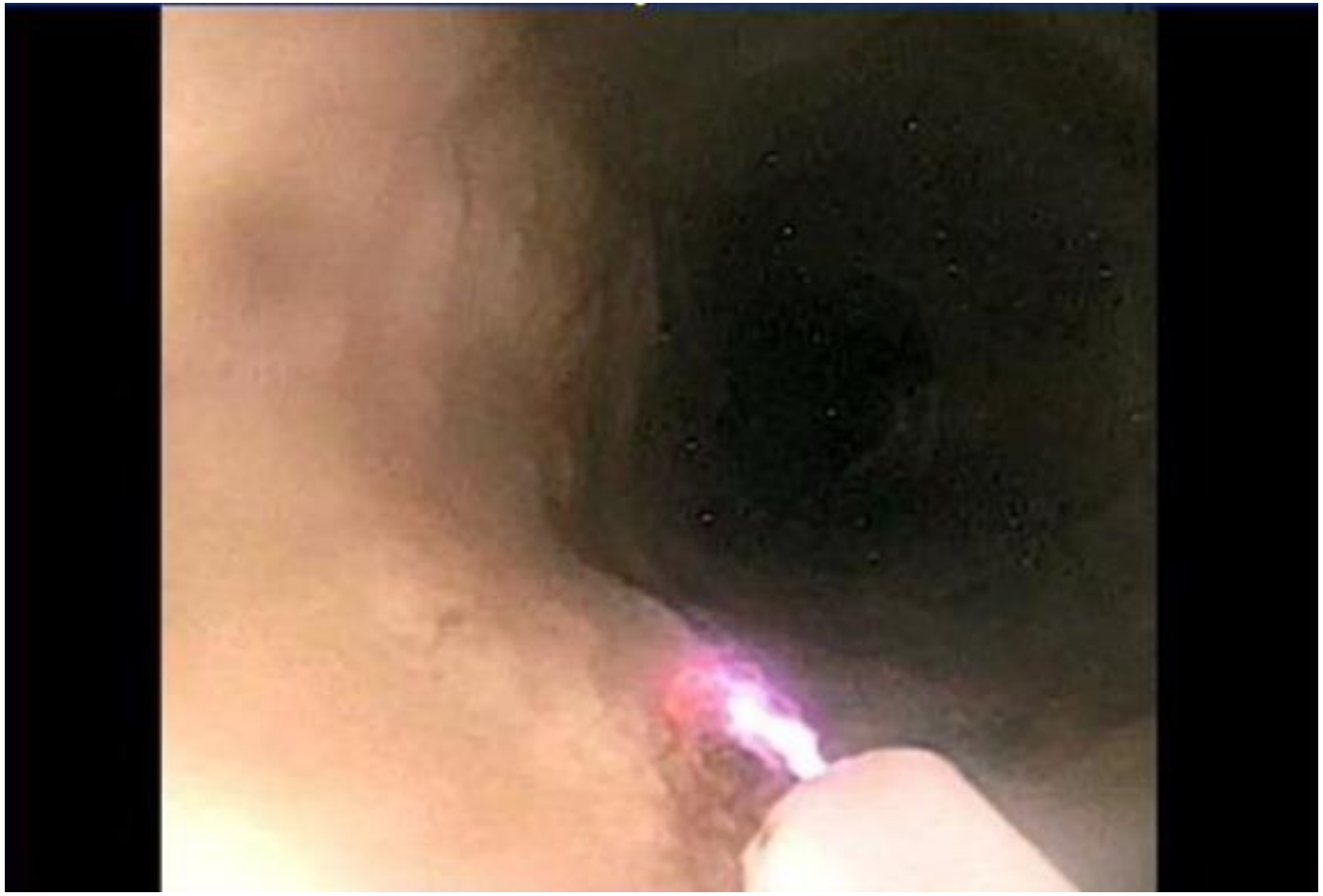
Hemostatic Clips

Gold Probe



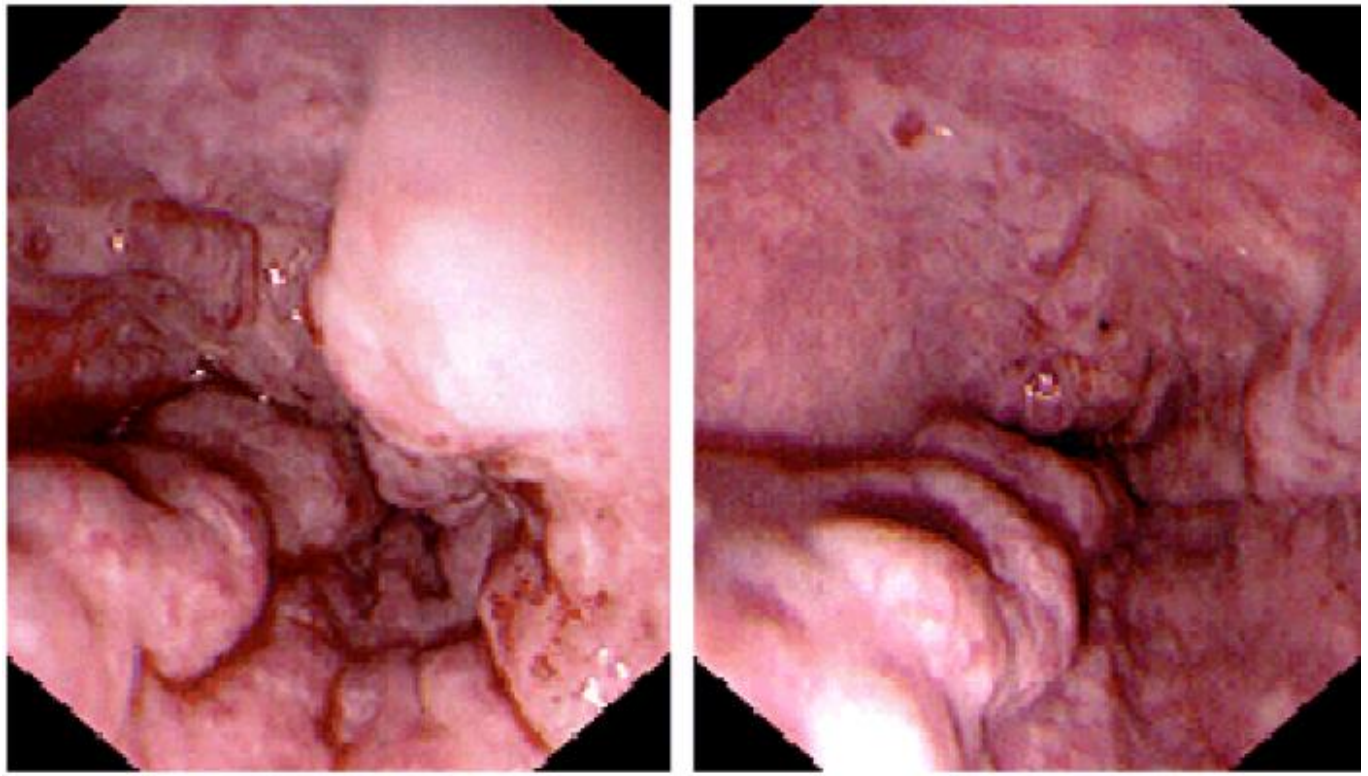
- It transfers heat rapidly to the artery to cause clot formation and hemostasis, then it cools rapidly so we can remove it without causing damage.

Argon Plasma Coagulation



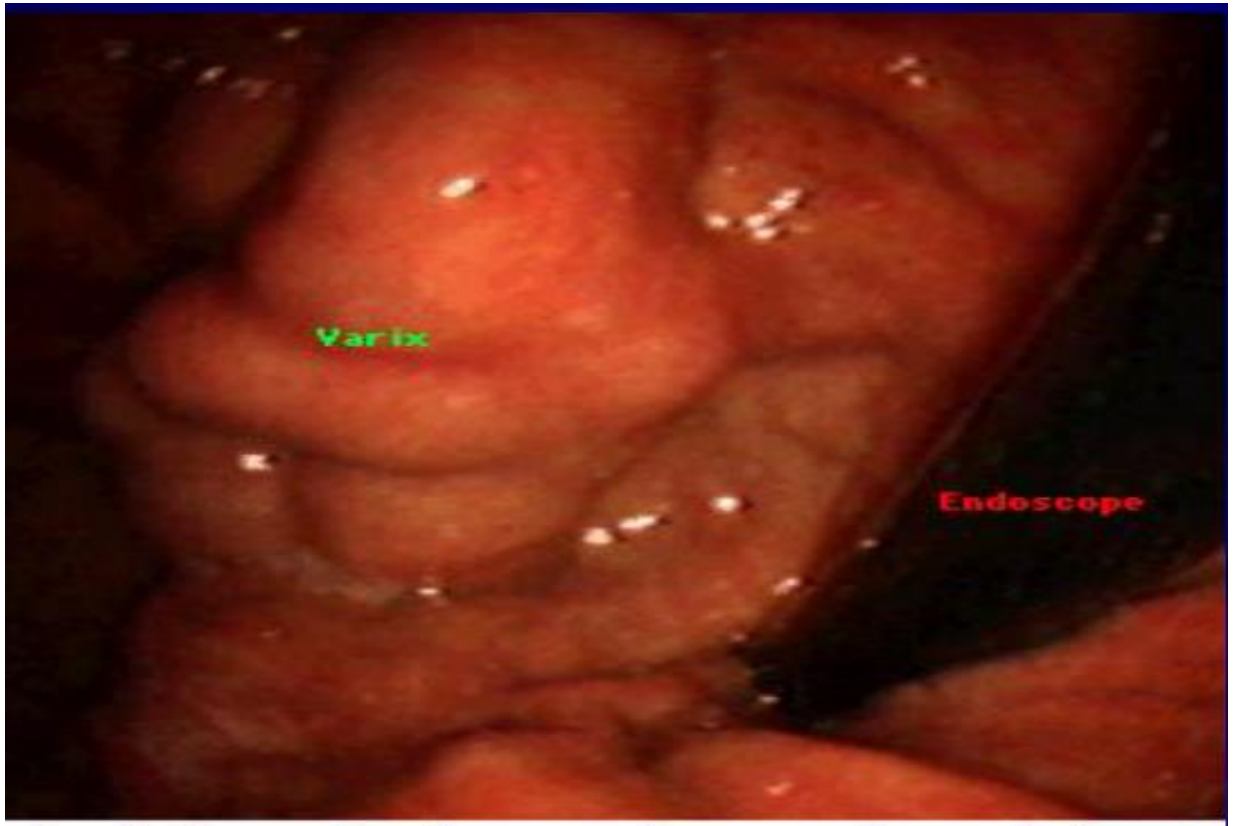
- A Probe that releases argon gas forming a cloud above the site of bleeding then spark it to form a small explosion that burns the surface of the mucosa to a depth of 2 mm to treat Arteriovenous malformations.

Esophageal Varices



Esophageal varices Endoscopic images from a patient with esophageal varices who presented with hematemesis. The varices appear as markedly dilated and tortuous columns of veins in the mid and distal esophagus. The varices were treated with injection sclerotherapy emergently and later with variceal banding. Courtesy of JB McGee, MD.

Gastric Varices



Gastric varix Upper endoscopy of a gastric varix in the fundus of the stomach. Gastric varices can arise in conjunction with esophageal varices. They can also be isolated when they result from segmental portal hypertension due to obstruction of the splenic vein by pancreatic carcinoma or chronic pancreatitis. Courtesy of Rome Jutabha, MD, and Dennis M Jensen, MD.

Treatment

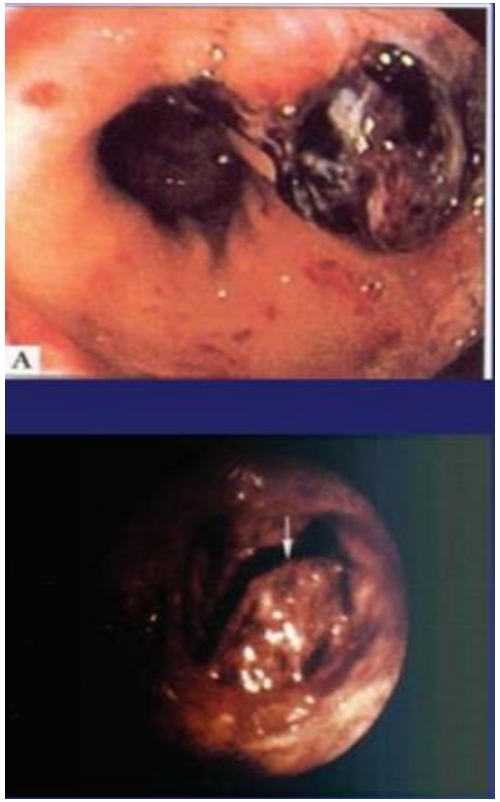
Treatment

- Endoscopic treatment.
- Acid suppression.
- Eradication of H Pylori.
- Angiographic control.
- Octreotide
- Surgery

PUD: Prevention of Bleeding

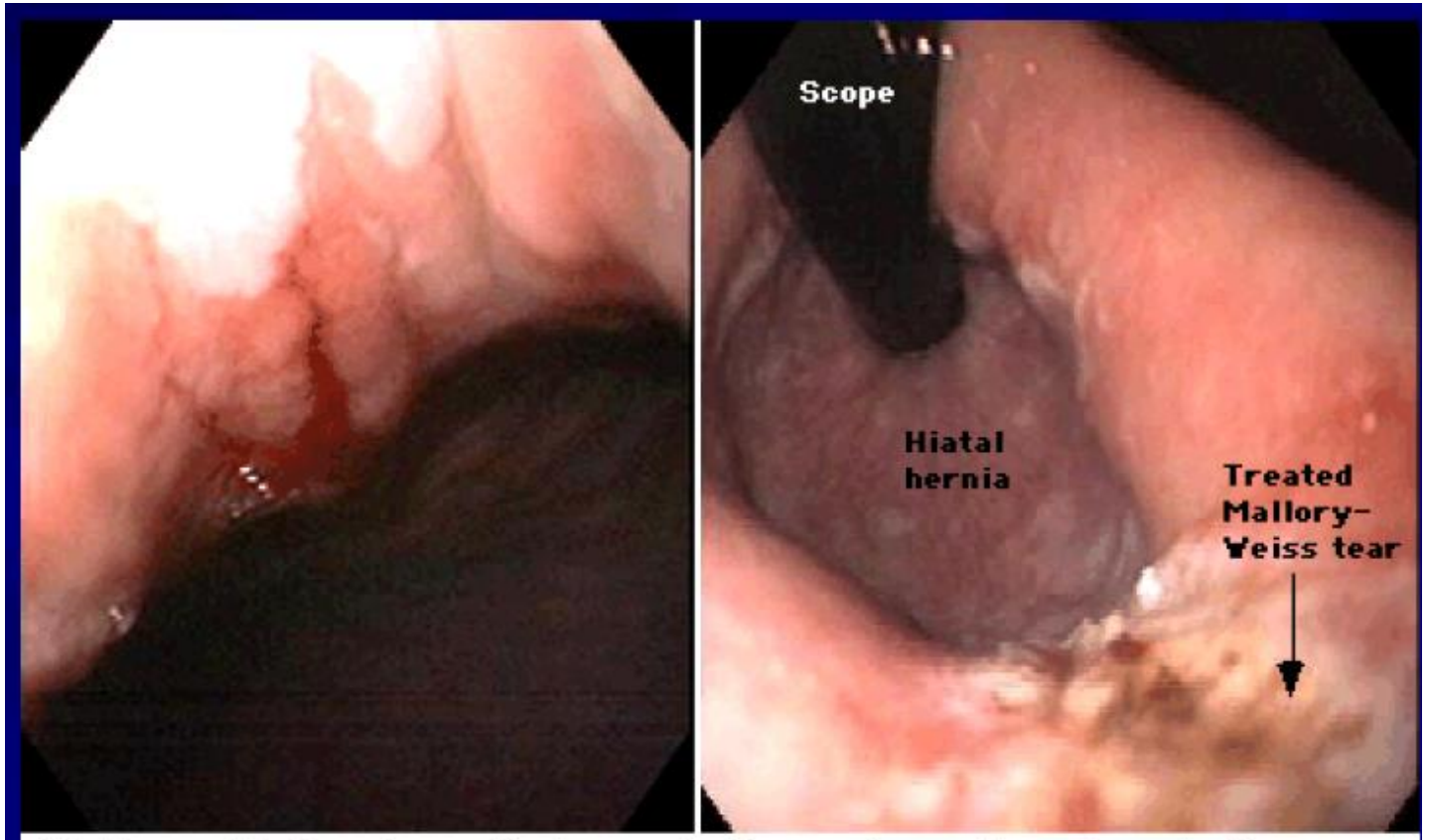
- In PUD recurrent bleeding rate is about 30% in 1 – 2 years.
- This rate is reduced to 5% if treatment of H – pylori is accomplished.
- Stop NSAIDS if possible.
- PPI or misoprostol if NSAIDS is necessary.
- PPI in H – pylori negative and NSAIDS negative patients.

Non-PUD Bleeding Lesions / Mallory Weiss Tears



- Benign condition, presenting with classic Retching with nausea and recurrent vomiting due to pregnancy and binge drinking, followed by blood after the last attack of vomiting (Painless upper GI bleeding due to mucosal tear near GEJ, usually on the gastric side).
- Contrasted with intramural Hematoma and Esophageal rupture (Boorhaave's → Tears in the mucosa, submucosa, and muscularis, which may lead to esophageal rupture).
- If the patient is Fuzzy in endoscopy → while in esophagus, you may see vomiting with the stomach retracted into the esophagus leading to shearing forces on the mucosa and thus Mallory.
- Not painful and the Treatment is conservative → Treat vomiting

Mallory-Weiss Tear



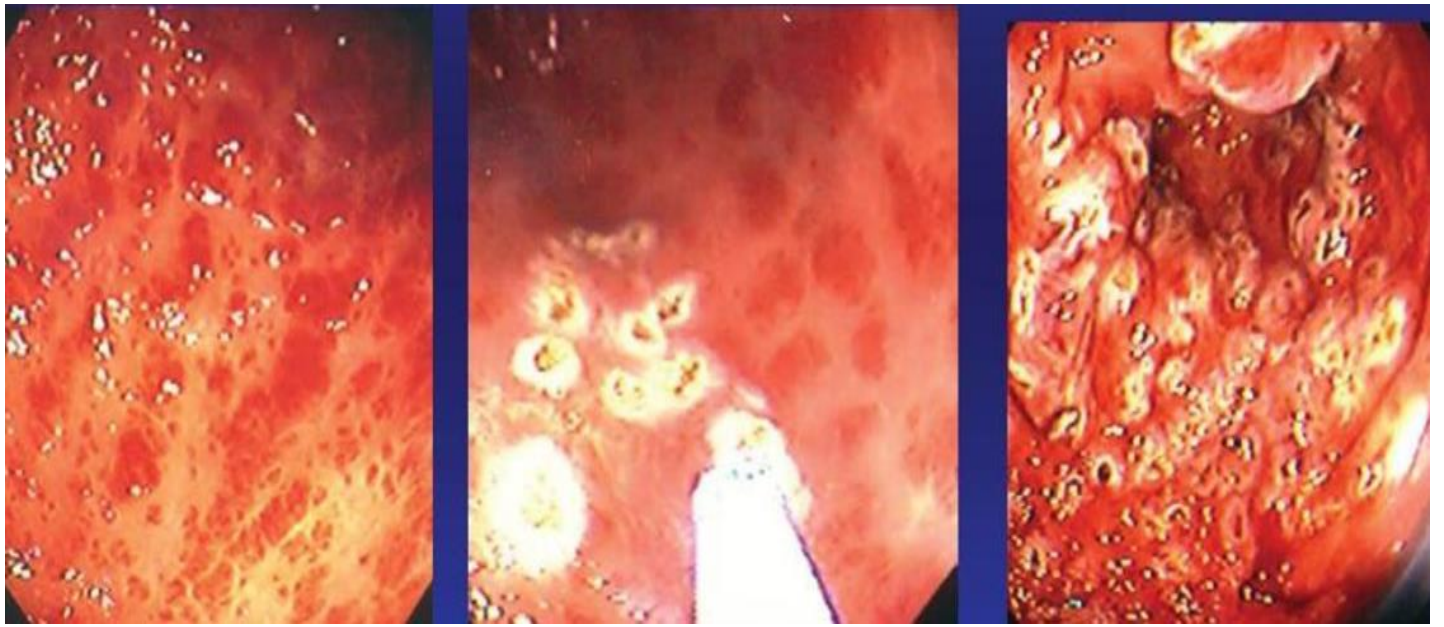
Mallory-Weiss tear Endoscopic diagnosis and treatment of Mallory-Weiss tears. Left panel: A large esophageal laceration extending to the lower esophageal body. Right panel: A large esophageal laceration below the gastroesophageal junction seen by retroflexion of the tip of the gastroscope which also visualized a hiatal hernia; previous bleeding was controlled by multipolar electrocoagulation. Courtesy of Moises Guelrud, MD.

Vascular Lesions

- Vascular ectasias
  - angiodysplasia, telangiectasia
- Gastric Antral Vascular Ectasia ("Watermelon stomach")
- Dieulofoy's lesion
- Portal hypertensive gastropathy
- Cameron's lesions

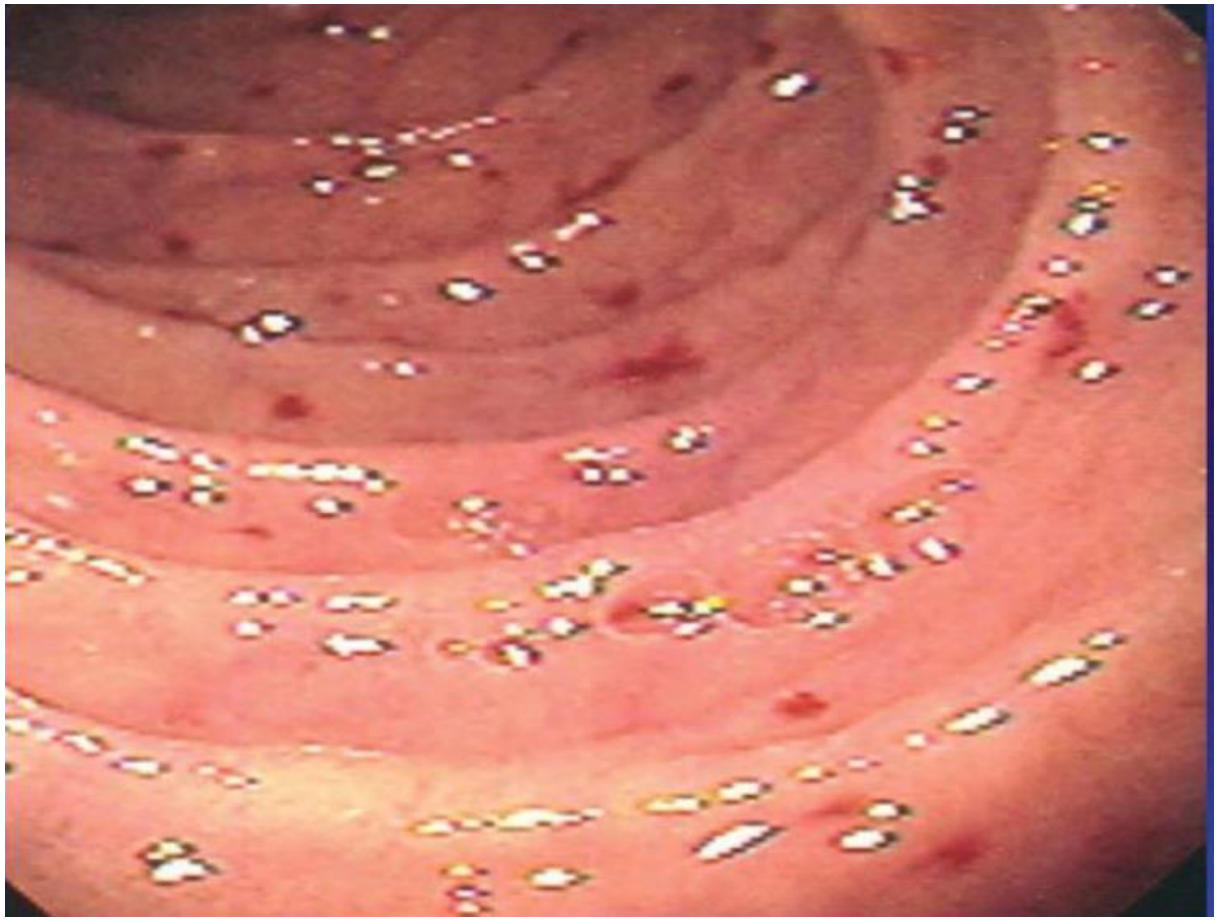
- Vascular Ectasias: Abnormal connection between Arterial and Venous sides, seen in elderly in the small bowel.
- Cameron's lesions → related to hiatal hernia.

Gastric Antral Vascular Ectasia (GAVE)



- The figure shows the stomach before, during and after Endoscopic Therapy.
- Treated by Argon Plasma Coagulation

Duodenal Angioectasia

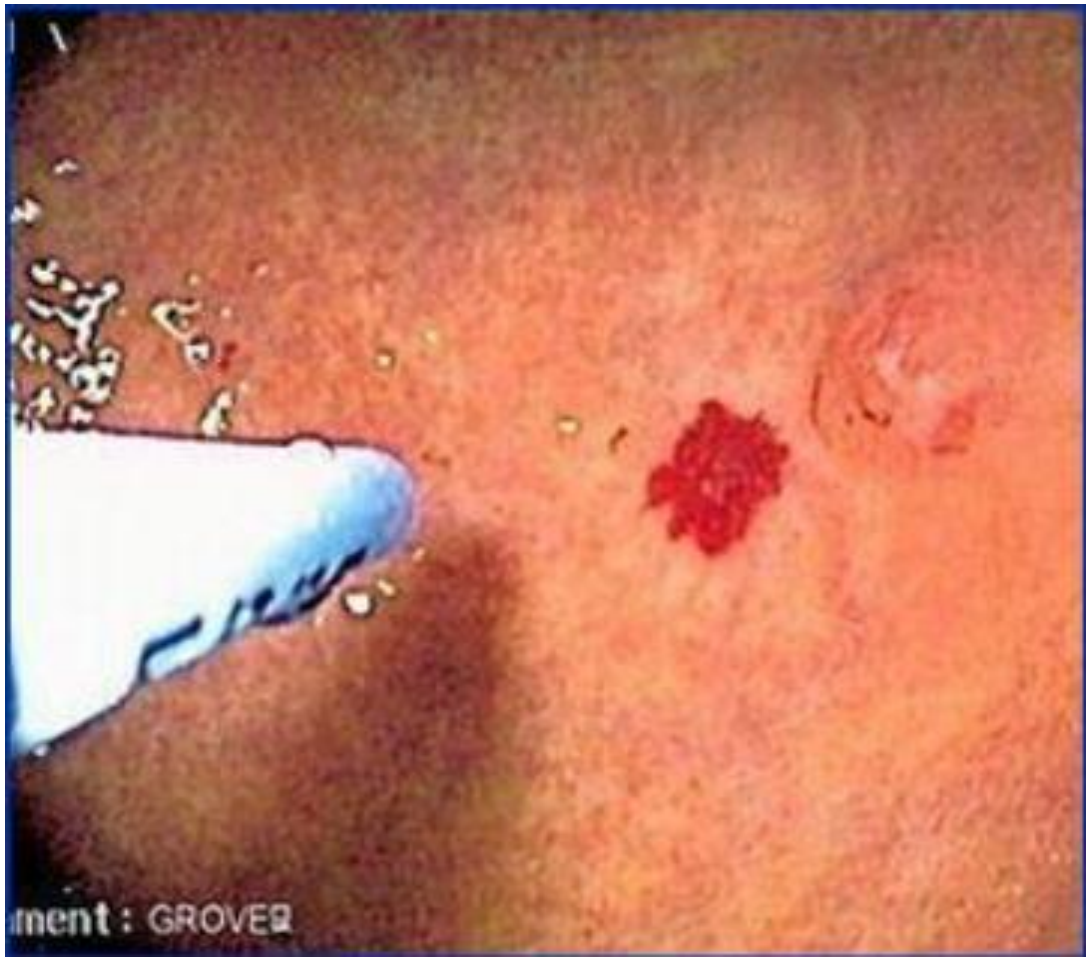


- Either Acquired or Hereditary:

Acquired: Aging, PSS, CREST, Radiation

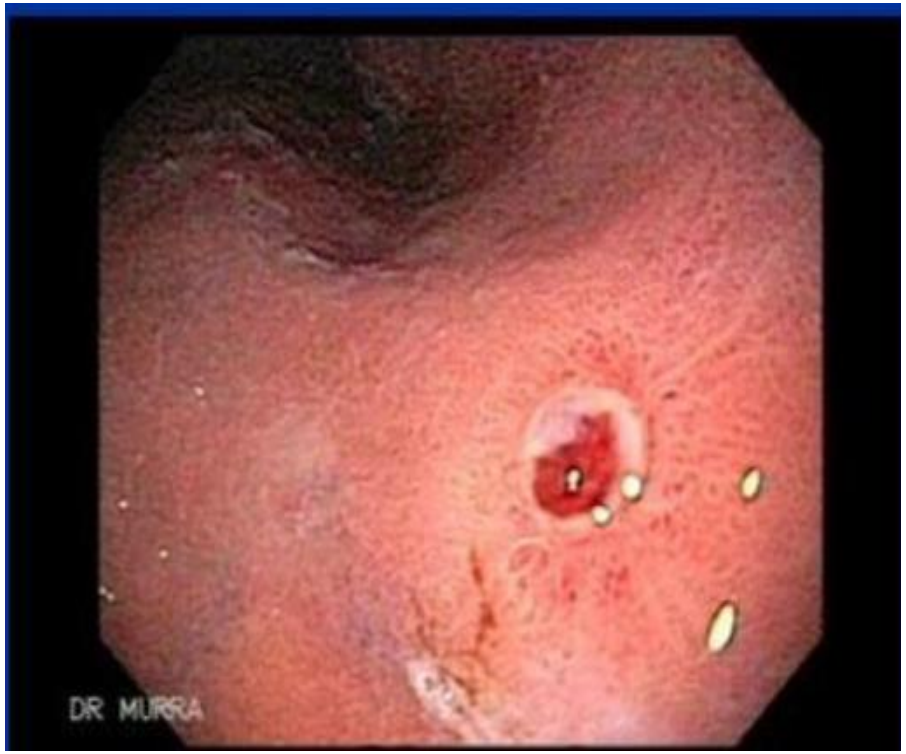
Hereditary: Lips, Nose

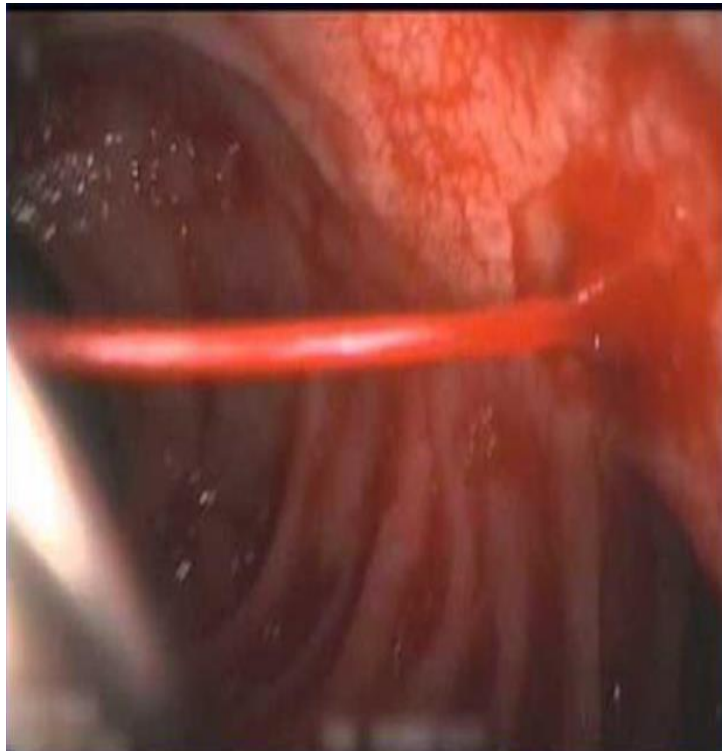
Duodenal Angioectasia



- Flower-Like
- May Spontaneously bleed, due to Blood thinners or Anticoagulants.
- Treated by Argon Plasma Coagulation.

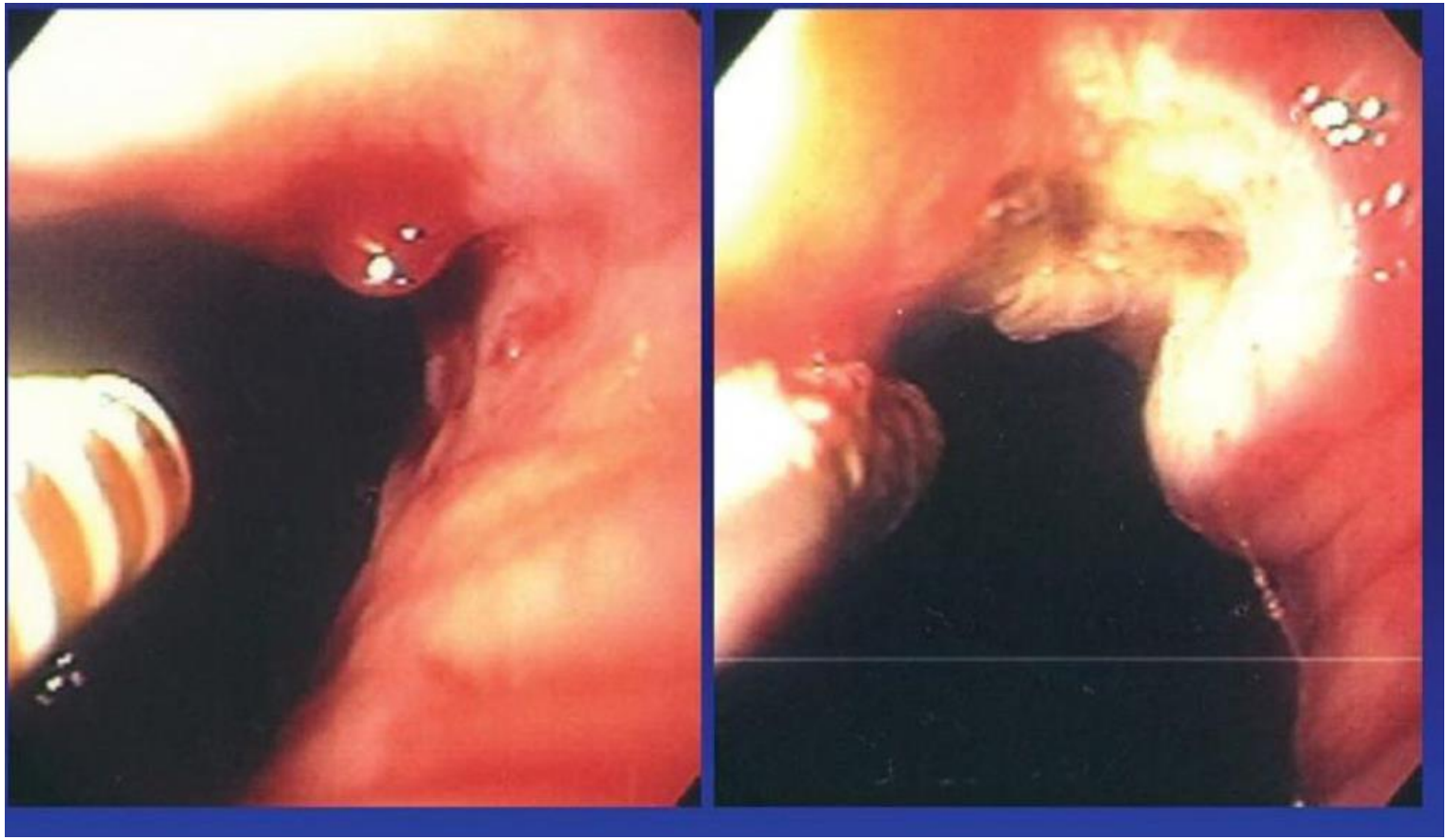
Dieulafoy's Lesion





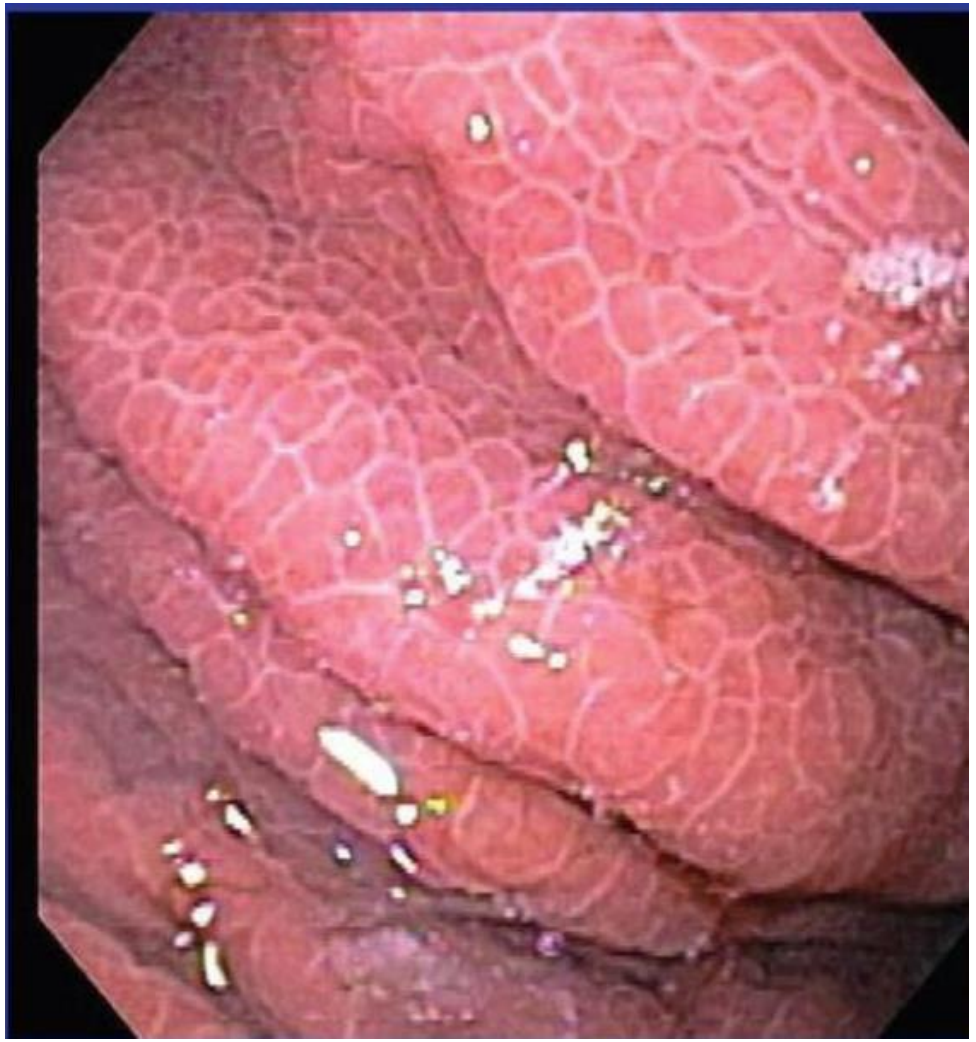
- Abnormally Large Submucosal Artery.
- Affects Proximal Stomach
- Intermittent, painless, massive bleeding
- Often difficult to identify endoscopically
- Endoscopic Therapy (with Epinephrine / Polidocanol).
- Treated with Argon Plasma Coagulation.
- The First figure shows the mucosa covering the Artery (Like a Tear).
- The second figure shows active bleeding.

Dieulafoy's Lesion



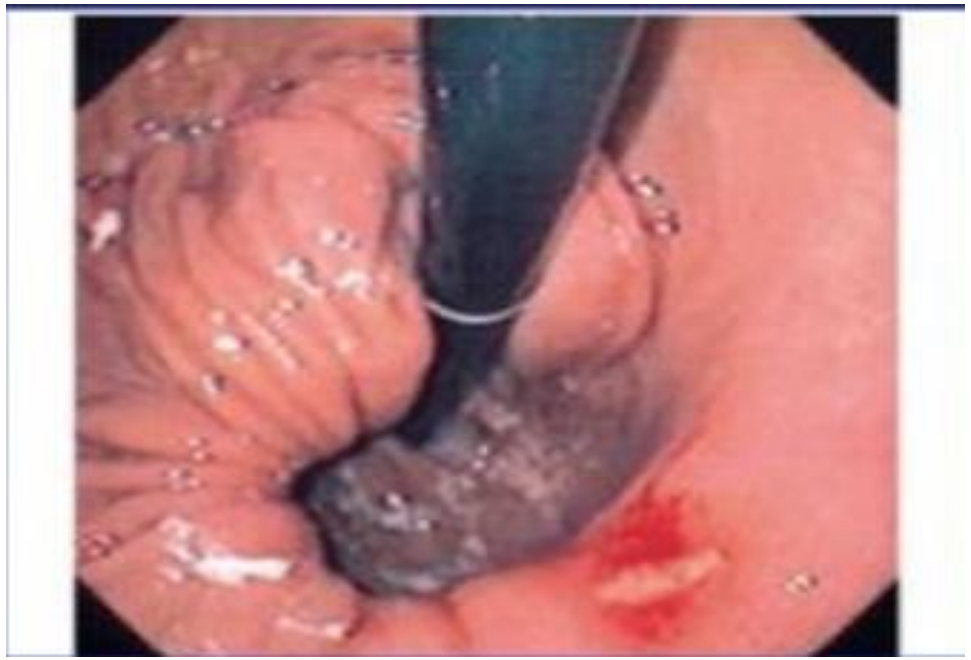
- The Figure shows the Lesion Before and After Argon Plasma Coagulation

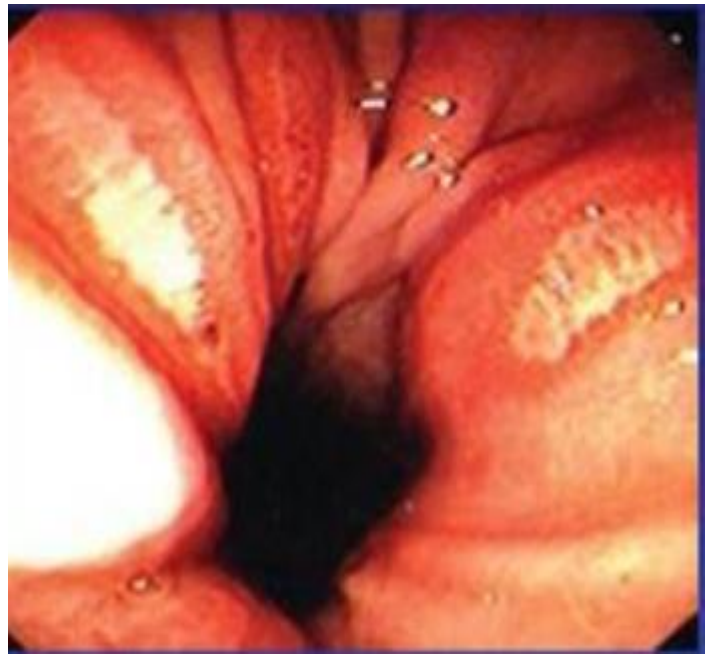
Portal Hypertensive Gastropathy



- Snake-Skin Mucosa

Cameron's Lesions





- Linear Erosions in a Hiatus Hernia.
- Usually sliding hernia → Hernia moves along with the stomach wall against diaphragmatic crus which is a fibromuscular band which cause ischemia of the gastric wall.
- No abdominal pain but may have reflux symptoms (Iron Deficiency).
- The first figure shows Ischemia of this area with no buffering of proton leading to denaturation, ulceration, and cell loss.
- The second figure shows Hiatal hernia.
- Treatment: Iron with/without PPI

Autoimmune Liver Disease

Primary Sclerosing Cholangitis (PSC)

- It's a chronic cholestatic liver disease (Alkaline Phosphatase is elevated mainly, not ALT or AST).
- Occurs more in males.
- Unknown etiology, Frequently associated with IBD (UC >> CD).
- Characterized by diffuse inflammation and Fibrosis of the biliary tree.
- Leads to Biliary cirrhosis and Portal HTN.
- Biliary Cirrhosis: Liver damage due to biliary obstruction; i.e., when the bile ducts are damaged, bile can backup in the liver and sometimes lead to irreversible scarring of liver tissue (cirrhosis).
- Etiology is unknown; the disease is caused by one of these mechanisms: 1- Disordered Immunoregulation (T-cell subsets altered, T-cell suppressor function abnormal, Circulating immune complexes, Abnormal complement levels). 2- Infections and bacterial products. 3- Portal Bacteremia.
- Patients present with Cholestasis (elevated Alkaline phosphatase), usually in the setting of colitis. Some patients may be asymptomatic (the disease is discovered incidentally with Routine Follow-up). Other patients may have abnormal Cholangiogram which is diagnostic of the disease.
- In the case of Cholestasis → Increased Alkaline phosphatase. / In the case of Inflammation or damage → Increased ALT or AST.

PSC: Clinical Presentation

Asymptomatic	**15 - 44%**
Symptomatic	
Fatigue	**75**
Pruritus	**70**
Jaundice	**30-69**
Hepatomegaly	**34-62**
Abdominal pain	**16-37**
Weight loss	**10-34**
Splenomegaly	**30**
Ascending cholangitis	**5-28**
Hyperpigmentation	**25**
Variceal bleeding	**2-14**
Ascites	**2-10**

- The most common symptoms are Fatigue and Pruritis → Related to liver disease.
- Symptoms related to complicated Portal HTN → Jaundice, Hepatomegaly, Abdominal pain, Variceal bleeding, ascites.
- Patients presenting with recurrent attacks of Ascending Cholangitis → Suspect PSC

PSC: Liver Tests

- **Alkaline phosphatase nearly always elevated**
- **AST and ALT usually <5 times normal**
- **Bilirubin, albumin, prothrombin time usually normal at diagnosis**

– Bilirubin, Albumin, and PT are Prognostic Indicators.

Prevalence of Autoantibodies in PSC

p-ANCA	**80%**
AMA	**<2%**
ANA	**50-60%**
SMA	**35%**

- Those aren't diagnostic.
- AMA (Anti-mitochondrial Antibody) → Elevated more in Primary Biliary Cirrhosis.

PSC Diagnosis: Cholangiography

- **ERCP most commonly used**
- **Percutaneous cholangiography infrequently used**
- **Magnetic resonance cholangiography**
  - **non-invasive**
  - **no radiation**
  - **cost-effective**

- ERCP (Endoscopic Retrograde Cholangiopancreatography) → an invasive procedure which may cause Pancreatitis.

ERCP is done if Intervention or Biopsy are needed.

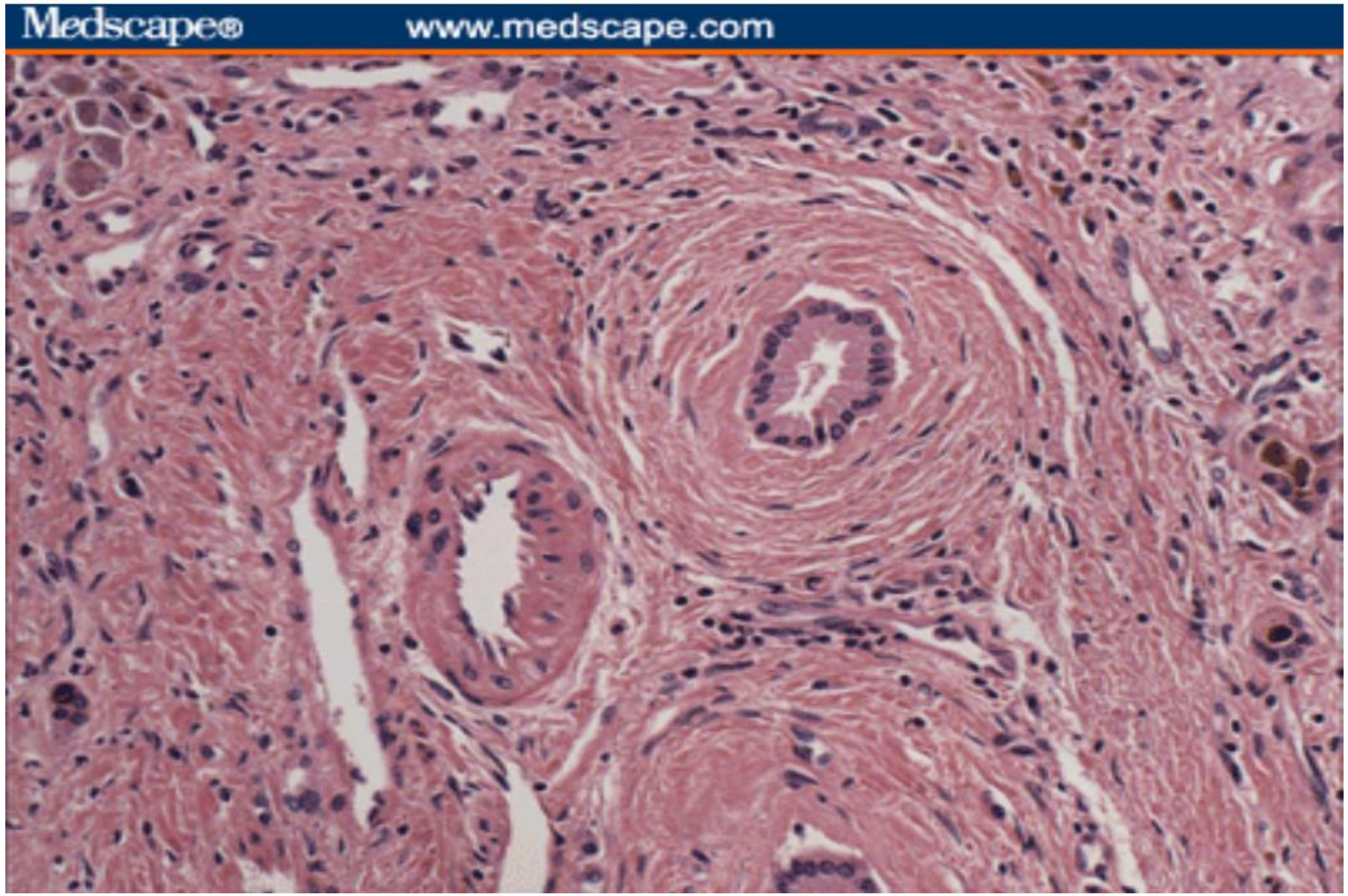
- Notes on ERCP:

If on ERCP we had a beaded appearance → PSC

If Long stricture appearance → Cholangiocarcinoma; in this case we must take biopsy, do balloon dilation of the dominant stricture to prevent recurrent cholangitis.

- MRCP (Magnetic Resonance Cholangiopancreatography) → First-line.
- PSC, chronically, can cause cholangiocarcinoma as a complication.

PSC



- A characteristic of PSC → Periductal Fibrosis (Onion-skin Fibrosis).

Differentiating PSC from PBC

	PSC	PBC
Cholestasis	+	+
History of colitis	+	-
AMA	-	+
Liver biopsy	onion skin fibrosis	florid duct lesion
Cholangiogram	abnormal	normal

Disease Specific Therapy

- **Surgical therapy seldom used**
- **Dilation for dominant strictures**
- **No proven medical therapy**

- Supportive treatment.
- In the case of Cholangitis → Give IV Antibiotics.
- If Cirrhotic → Liver Transplant (However, disease may recur after transplant).

Complications of PSC

Vitamin Deficiency → Since bile is Needed for Fat absorption (Mainly Vitamins A, D, E, and K)

Metabolic bone disease → Due to any cholestatic disease (most commonly Osteoporosis).

Steatorrhea → Due to fat malabsorption (deficient bile).

Complications of both PSC and PBC → Fat soluble Vitamin Deficiency and Metabolic Bone disease.

Management of Biliary Stricture

- **Uncommon**
- **Cytology insensitive**
  - **Molecular methods being evaluated**
- **Long-term stents may cause problems**
- **Dilatation alone seems preferable**

- First make sure that this stricture isn't a malignancy by ERCP, then do Balloon Dilation and Stenting.

PSC: Cancer Risk

Cholangiocarcinoma

- **Lifetime risk 7-15%**
- **Incidence 0.5 to 1%**
- **Smoking and IBD may increase risk**

Other cancers: pancreatic, liver, and colon

- Patients with both PSC and UC → Must be screened every year to rule out colon cancer.
- PSC may progress into Liver fibrosis → leading to Hepatocellular carcinoma.
- If Associated with UC → may lead to colon cancer.

Primary Biliary Cholangiopathy (PBC)

- Chronic Cholestatic Liver disease → High Alkaline Phosphatase.
- Characterized by Elevated levels of Serum AMA.
- Non-supportive destructive cholangitis on liver histology.
- 3 Ms → Positive AMA + Elevated IgM + Middle aged Females.
- Risk Factors: Female Gender + Autoimmune thyroid disease + History of Previous Tonsillectomy + Smoking + Inflammatory Skin disease (Psoriasis and Eczema) + Genetic Predisposition.

PBC: Clinical Features

Asymptomatic	40-60%
Fatigue	+++
Pruritus	++
Sicca symptoms	+++
Hepatomegaly	+
Splenomegaly	+
Jaundice	uncommon
Xanthelasma	uncommon

- Fatigue is the most common symptom.
- Sicca Symptoms → Mainly Mucus membranes dryness.
- Biochemical Features:

1- Alkaline Phosphatase almost always elevated.

2- AST, ALT <200 U/L

3- Bilirubin → usually rises late (if the disease progressed into liver cirrhosis).

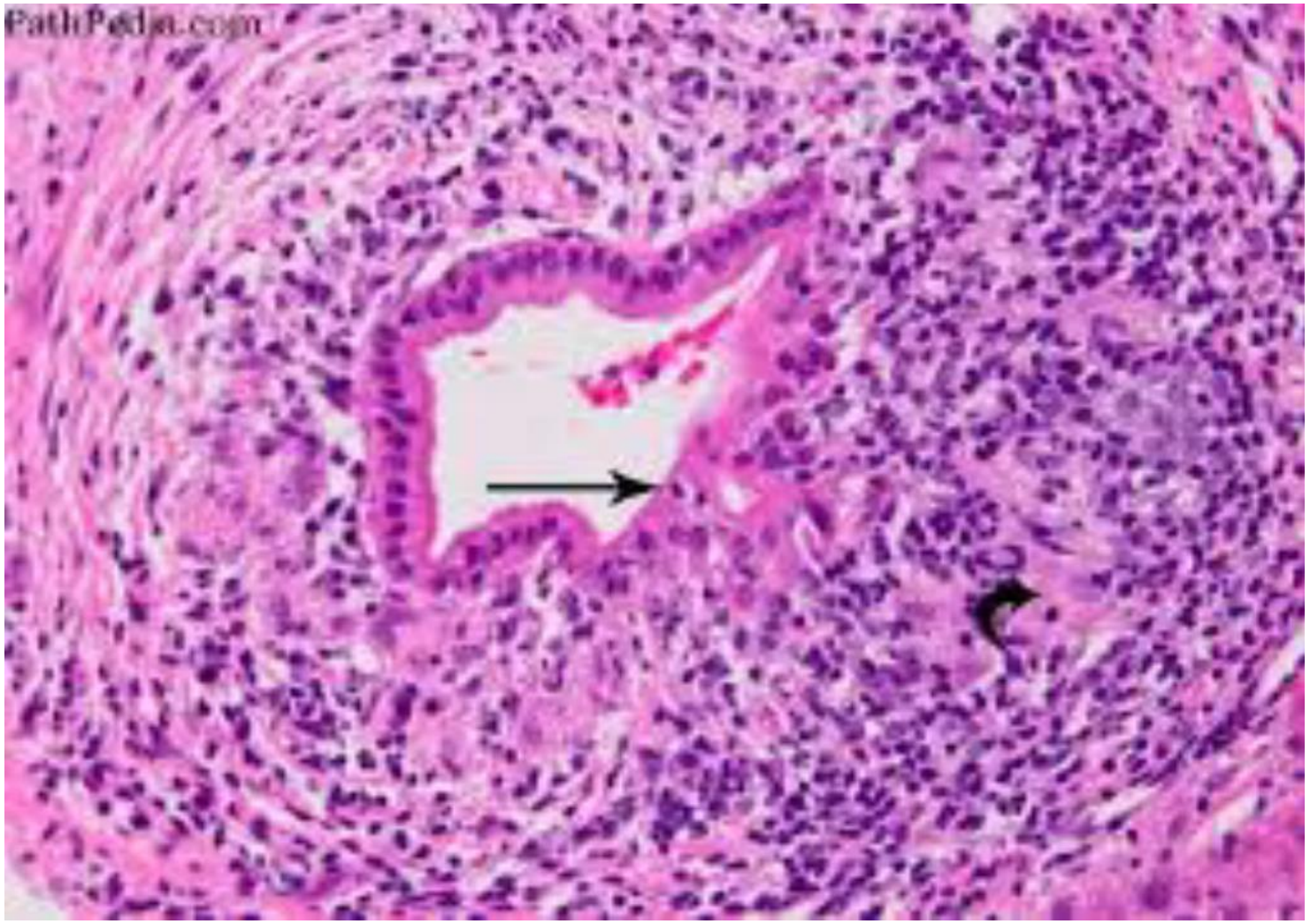
4- Cholesterol Elevated in 85% (Xanthelasma + Xanthomata)

5- IgM → commonly elevated.

PBC: Serum Antibodies

Type	Prevalence
AMA	++++
ANA	+++
ASMA	++
Anti-Centromere	+
Anti-Gp210	++
Anti-Sp100	++
p-ANCA	+

PBC



- The Arrow shows Florid Duct Sign → A characteristic of PBC.

Extrahepatic Autoimmune Disease

	(%)
Sicca syndrome	70
Thyroid disease	40
Arthritis	20
Scleroderma	15
Raynaud's phenomenon	10
CREST syndrome	5

- A patient with a history of Thyroid disease found to have Cholestatic Disease

→ Think of PBC

PBC: Management

Evaluation	Interval
Clinical visit	6-12 months
Serum liver tests	3-6 months
Sensitive TSH	Yearly
Lipid profile	Yearly
Bone density	Diagnosis, 2 years
Vitamin levels	If total bilirubin elevated

Medical Management

Unsuccessful	Questionable	Useful
penicillamine	steroids	UDCA
cyclosporine	colchicine	
azathioprine	methotrexate	
thalidomide		
malotilate		
chlorambucil		

- The Useful Medical Management → Ursodeoxycholic acid (UDCA) + Obeticholic Acid
- Actions of UDCA: 1- protects against cytotoxic effects of di-hydroxy bile acids. 2- Modulates expression of HLA. 3- Stabilizes Bile canalicular membrane. 4- Choleretic effect. 5- Decreased Apoptosis. 6- Decreased Cytokine production.

Autoimmune Hepatitis

- Intermittently progressive inflammatory liver disease of presumed autoimmune etiology.
- Characterized by High Gamma Globulins (Elevated IgG) and Autoantibodies (ANA, Anti-smooth muscle antibody ASMA) + Predominantly periportal hepatitis + Responds to Steroids unlike PSC and PBC.
- Patients usually present as Middle-aged woman, non-drinker, no Hx of viral hepatitis, with Fatigue, Arthralgias/Myalgias, Oligomenorrhea, Jaundice, Increased ALT + AST + Gamma Globulins (unlike PBC and PSC where Alkaline phosphatase is relatively more elevated), Positive ANA and SMA, Interface Hepatitis with Lymphoplasmacytic infiltrate, and Good response to corticosteroids.

Auto-Antibodies in AIH

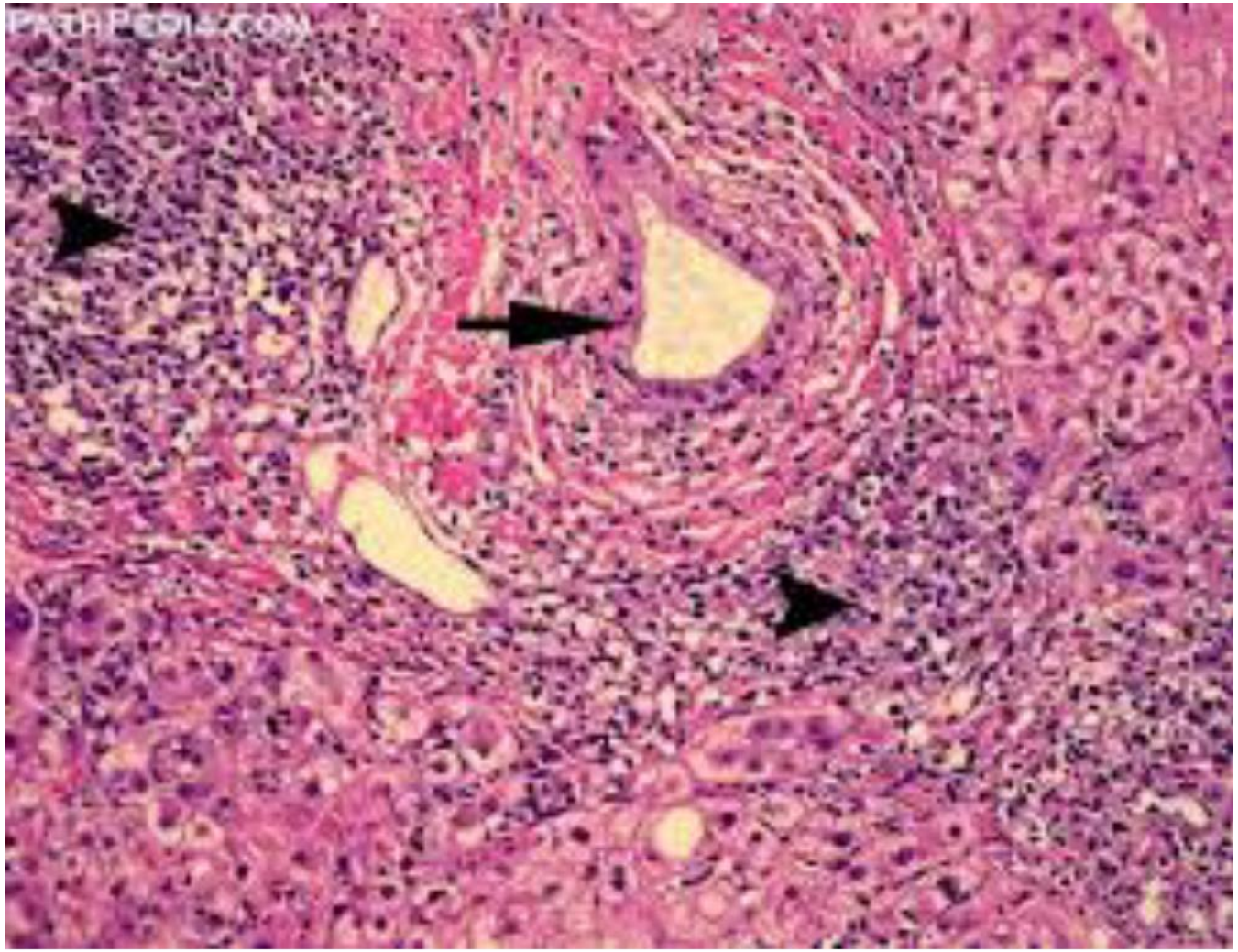
Antibody	Target Antigens	Prevalence	Other Disease
ANA	Multiple nuclear proteins	60-80%	PBC, PSC, HCV, NAFLD
SMA	Actin	60-80%	HCV, NAFLD, Acute viral hepatitis
pANCA	Lactoferrin, Other unknown Ag	65-90%	PSC, PBC
LKM-1	CYP 2D6	≈ 4%	HCV
SLA/LP	UGA repressor tRNA-associated protein	10-30%	HCV

- None are specific.
- SMA and ANCA → In type I Autoimmune Hepatitis (Seen in elderly).
- LKM-1 and SLA/LP → In type II Autoimmune Hepatitis (Seen in young).

Subtypes of Autoimmune Hepatitis

	Type 1	Type 2
Age at Presentation	Any age	Predominantly children
Female:Male	4:1	8:1
Ig G Levels	Elevated IgG	Variable Ig G
Ig A Levels	Normal	+/- Low IgA
Auto-antibodies	ANA, SMA	LKM-1
Cirrhosis at 3 yrs	~ 40%	~ 80%

Autoimmune Hepatitis



- Periportal, Heavy inflammatory cells infiltrate → Interface Hepatitis (A feature of Autoimmune Hepatitis).

Autoimmune Hepatitis: Indications for Treatment

Absolute	Relative	None
AST ≥ 10x normal	Symptoms	No symptoms
AST ≥ 5x normal and γ-globulin ≥ 2x normal	AST < 5x normal γ-globulin < 2x normal	Inactive cirrhosis
Bridging necrosis	Interface hepatitis	Portal hepatitis

Autoimmune Hepatitis: Therapy in Adults

	Monotherapy	Combination Therapy	
Interval	Prednisone mg/d	Prednisone mg/d	Azathrioprine mg/d
Week 1	60	30	50
Week 2	40	20	50
Week 3	30	15	50
Week 4	30	15	50
Daily until endpoint	20	10	50

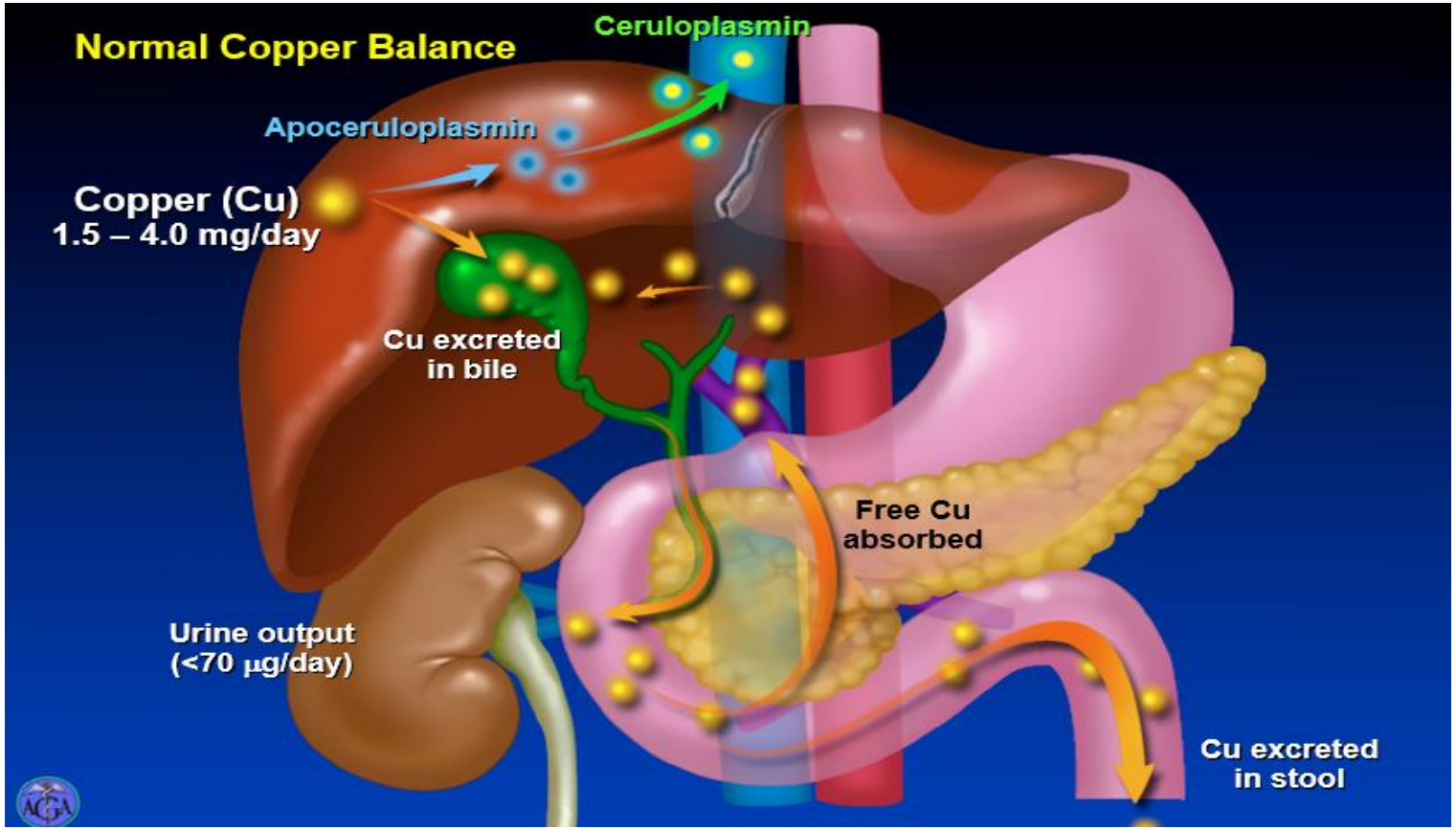
- Combination therapy is indicated in the case of HTN, DM, and Osteoporosis.
- Azathioprine is contraindicated in the case of Cytopenia.
- Doses are tapered down until endpoint, which is then taken for a long-term (maintenance).
- Liver transplant is indicated in the case of cirrhosis or if refractory to medical therapies, however there is a risk of disease recurrence after transplant.

Wilson's Disease

Wilson's Disease

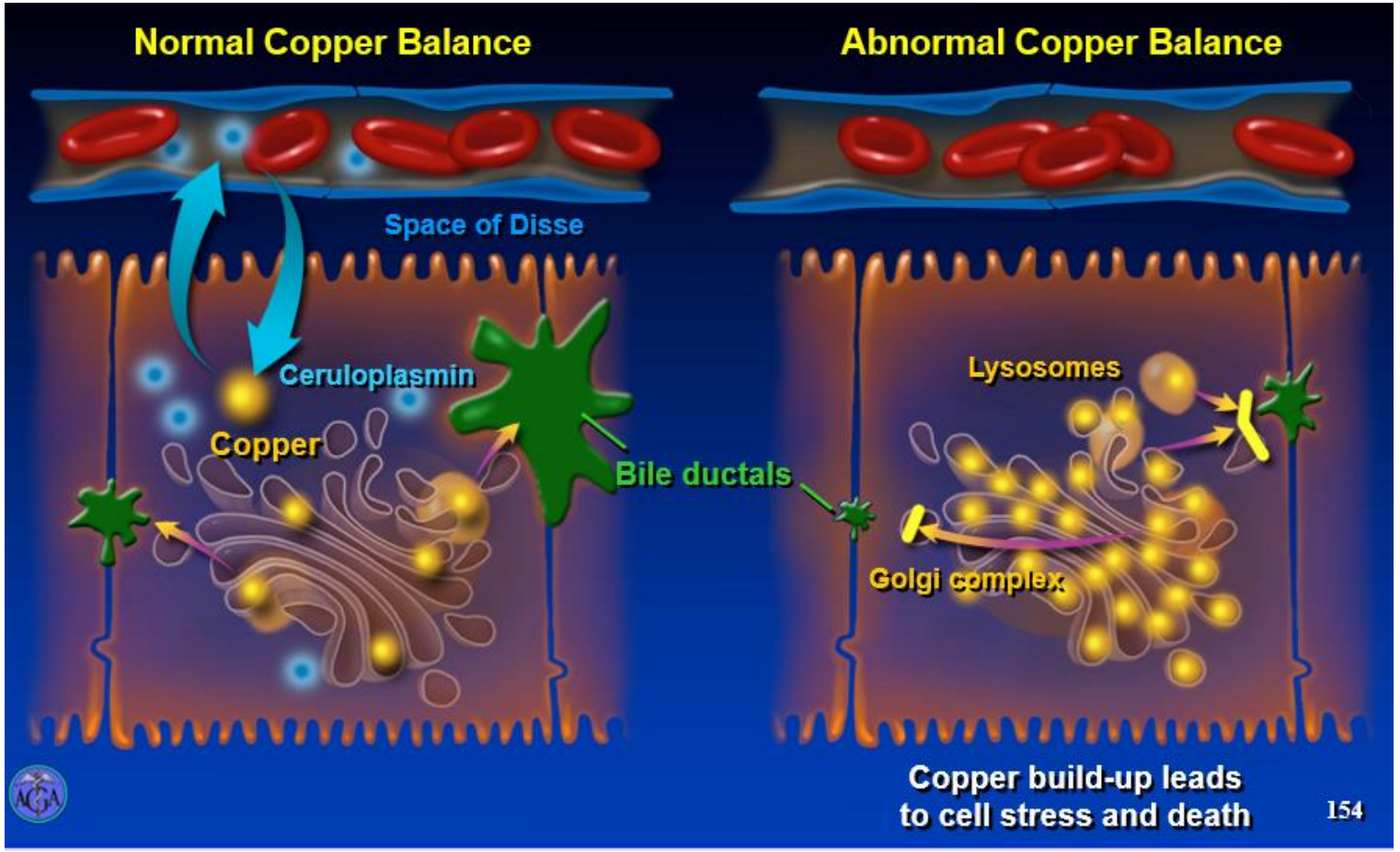
- leads to deposition of copper in many organ systems, with resultant clinical manifestations.
- There is copper deposition in the basal ganglia of the brain, resulting in the neuropsychiatric disorders seen in some affected individuals.
- Copper deposition in the eye is seen as Kayser-Fleischer rings, a golden brown deposit in Descemet's membrane seen at the limbus.
- Cardiomyopathy may very rarely be associated with Wilson's disease.
- The liver is the site of the defect in Wilson's disease, and is affected in all patients, with injury ranging from fatty liver through acute hepatitis to cryptogenic cirrhosis.
- Copper deposition in the renal tubule causes a Fanconi syndrome, with aminoaciduria, glycosuria, and wasting of uric acid.
- This may lead to osteopenia, which in some patients can be severe.
- High circulating levels of non-ceruloplasmin bound copper result in hemolysis.

Normal Copper Balance



- Copper is ingested with the diet. Many foods are rich in copper, including shellfish, chocolate, nuts, and mushrooms. Once ingested, copper is absorbed in the upper intestine and travels in portal blood to the liver. It is taken up from the sinusoidal blood into the hepatocyte where it binds to a copper-containing enzyme, ceruloplasmin. The bulk of the copper is transported across the hepatocyte and excreted via the lysosomes into the canaliculi. In bile, copper is bound to proteins which prevent its reabsorption, and favor excretion in stool. Very little copper circulates in the free state, and there is very little copper present in urine.

Copper Transport



- This model represents the effect of the abnormal Wilson's disease gene on hepatic copper transport. The p-type ATPase is located both on the bile canalicular surface and in pericannalicular vesicles. The ATPase is proposed to facilitate copper transport into the bile. With mutation, there is a block in copper transport and accumulation of copper in the hepatocyte as well as ceruloplasmin.

Wilson's Disease

Usual Features in Homozygotes	Usual Features in Heterozygotes
Ceruloplasmin <20 mg/dl	Rarely
Urine copper >100 mg/day	Rarely
Kayser-Fleischer rings	Never
Hepatic histology abnormal	Never
Hepatic copper >250 mg/g	Rarely

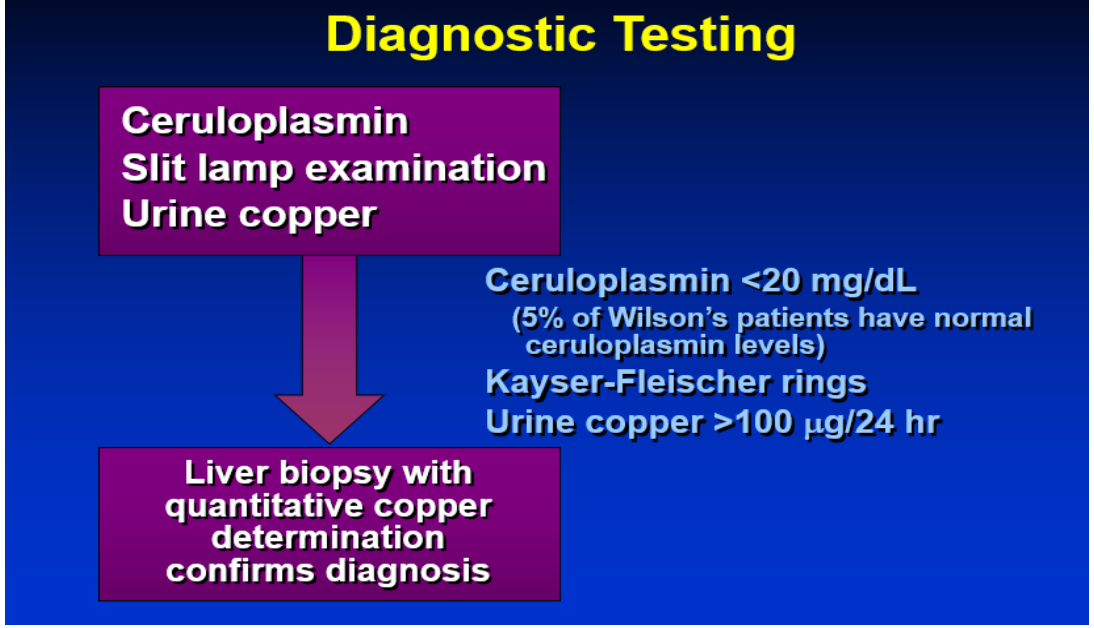
- The diagnosis of Wilson's disease rests on assessment of various epiphenomena of the disorder and is thereby imprecise. Diagnostic strategies will improve with genetic testing although over 200 different mutations in the Wilson's gene have been identified. Heterozygotes for the defect may share findings with affected homozygotes, but these abnormalities are less severe, and heterozygote carriers do not develop the disease. Serum ceruloplasmin levels are usually, but not invariably, low, below 20 mg/dl, in homozygotes. This protein is produced by the liver, and its level can vary in response to stress or hepatic dysfunction. Ceruloplasmin levels are usually normal in heterozygotes, although 20% may have low levels.
- Urinary excretion of copper is elevated in homozygote patients but may be elevated in patients with chronic cholestasis and secondary copper overload. All individuals will have an increase in urine copper in response to infusion of the chelator D-penicillamine, and thus this is not a reliable differential point.
- Kayser-Fleischer rings are usually present in affected homozygote patients and are always present if there is attendant neurologic disease. They are absent in heterozygotes but may rarely be found in patients with secondary copper overload. Liver disease is usually present when Kayser-Fleischer rings are evident.
- Hepatic histology is abnormal in homozygotes and never abnormal in heterozygotes. Hepatic copper concentration is abnormally elevated in homozygotes and may be elevated at lower levels in heterozygotes.

Wilson's Disease: Clinical Presentation

Presentations	
Liver	Abnormal liver tests Acute hepatitis Acute hepatic failure Liver disease with hemolysis Chronic hepatitis Cryptogenic cirrhosis
CNS	Parkinson-like disorders Psychiatric disorders
Eye	Kayser-Fleischer rings Sunflower cataracts
Kidney	Fanconi syndrome with hypouricemia

- Because of its multiorgan involvement, Wilson's disease is a great imitator which can present in a variety of widely divergent ways.
- Gastroenterologists are most likely to see a liver presentation, which is the initial complaint in approximately 40% of affected patients. This can vary from an asymptomatic patient who presents for evaluation of abnormal "liver function tests", to a patient with fulminant hepatic failure, or a patient with acute "hepatitis" and hemolysis, or chronic active hepatitis on biopsy, or cryptogenic cirrhosis.
- Affected patients may present with central nervous system involvement, either Parkinson-like tremor, gait disturbance, or difficulty with handwriting, or psychiatric disturbance.
- The ophthalmologist may be the first physician to consider the diagnosis in a patient found to have Kayser-Fleischer rings or a sunflower cataract. The renal manifestations, with a Fanconi syndrome, may be the presenting complaint.

Wilson's Disease: Diagnosis



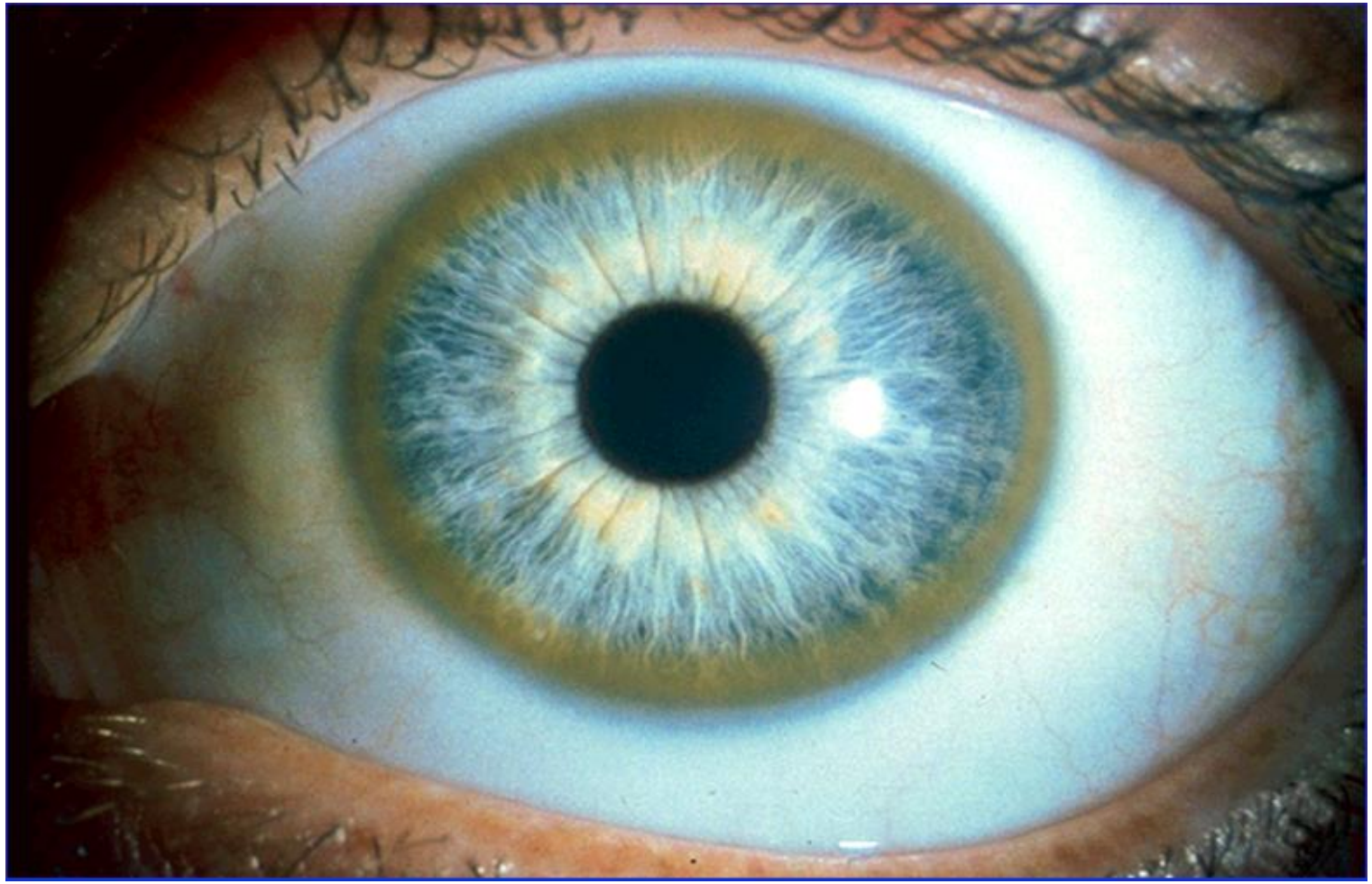
- Initial evaluation for Wilson's disease should include determination of the serum ceruloplasmin level, a slit lamp examination by an ophthalmologist in search of Kayser-Fleischer rings, and determination of urine copper excretion done on a 24-hour urine collected in a trace metal-free container. A ceruloplasmin value of less than 20 mg/dl is suggestive of the diagnosis in an appropriate setting, as are the presence of Kayser-Fleischer rings and a 24-hour urine copper of greater than 100 µg. The diagnosis should be confirmed in most patients by doing a liver biopsy with quantitative liver copper determination.
- The ceruloplasmin value may be misleading in rare patients. Kayser-Fleischer rings and elevated levels of urinary copper may be found in rare patients with severe cholestasis. Cholestasis is not a symptom of Wilson's disease, however, and the quantitative liver copper will differentiate secondary overload, with low level elevation, from the high levels seen in Wilson's disease. In rare patients, for example a symptomatic patient with typical Wilson's disease and Kayser-Fleischer rings, liver biopsy is not necessary to confirm the diagnosis. On the other hand, it is useful to confirm the diagnosis in asymptomatic individuals whose only sign of disease is the presence of Kayser-Fleischer rings, as these will fade over time with treatment.

Wilson's Disease: Management

Therapy	**Chelation + pyridoxine** **Zinc** **Avoid high copper foods** **Transplantation in selected cases** **Family screening**
Monitoring	**Urine copper** **Non-ceruloplasmin copper** **Do NOT monitor Kayser-Fleischer rings**
Results	**Treatment prevents disease** **Improves liver and CNS disease** **Prolongs life**

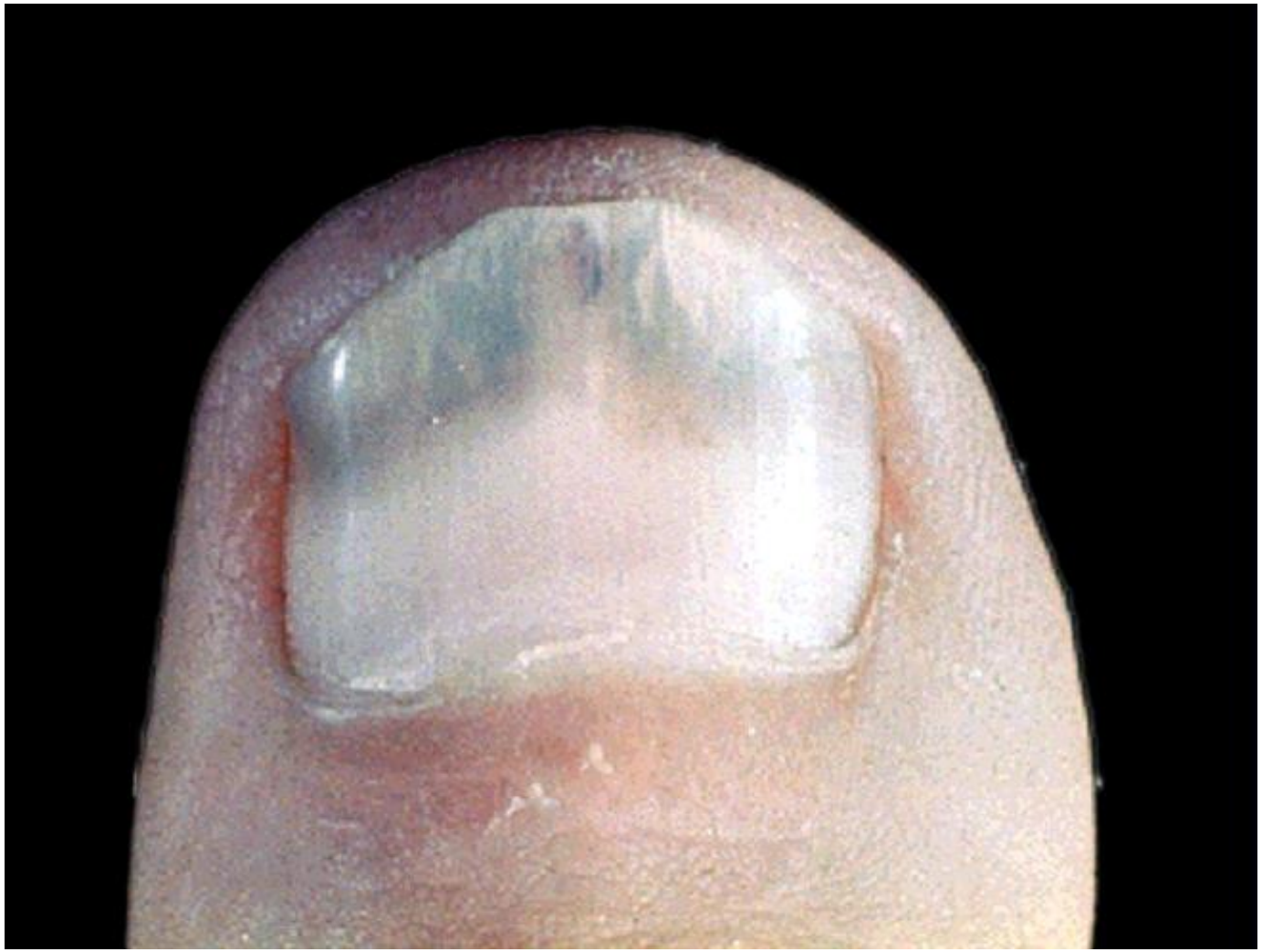
- The cornerstone of treatment in Wilson's disease is removal of excess circulating copper by chelation. Currently, the drug of choice is D-penicillamine, which is given in a dose of 250 - 500 mg QID before meals. Some patients do not tolerate the side effects of D-penicillamine, which include minor problems such as a skin rash and more major difficulties such as a lupus-like syndrome of arthralgias and proteinuria. Trientine (triethylene tetramine) is an alternate chelator which is well tolerated, if somewhat less effective. The patients must take concurrent pyridoxine to counteract the weak antipyridoxine effect of D-penicillamine.
- Oral zinc diminishes copper absorption and may be useful in maintenance therapy of patients with Wilson's disease. Patients should be instructed on which foods are high in copper and asked to avoid them. Adequately chelated patients who are compliant with their therapy do not need a restricted diet.
- Compliance with therapy is difficult to monitor. In patients with Kayser-Fleischer rings, therapy is associated with a progressive loss in the rings when followed serially by an ophthalmologist. Over time, the urinary excretion of copper decreases, as the patient's copper load decreases. Also of use in follow-up is the serum level of non-ceruloplasmin copper (the total serum copper - the ceruloplasmin bound copper), which should fall with therapy. Compliance is important, as interrupting therapy may be associated with fulminant hepatic failure and death.
-The results of treatment of Wilson's disease are very good. Life is prolonged, and the liver and CNS disease may be improved by therapy. When started early in presymptomatic siblings of known patients, therapy prevents the onset of the multiorgan injury of Wilson's disease. Thus, family screening is essential.

Wilson's Disease: Kayser-Fleischer Ring



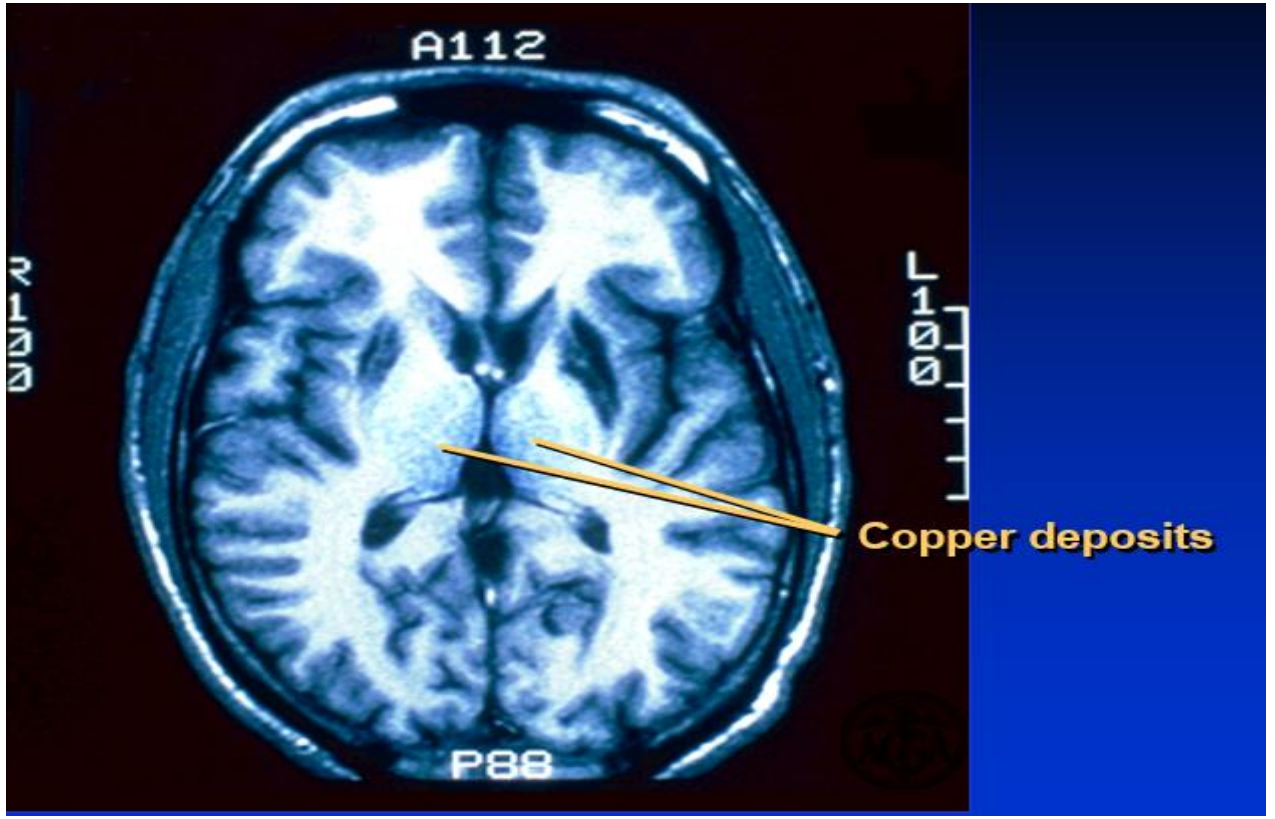
- Copper deposition in the eye is seen as Kayser-Fleischer rings, a golden-brown deposit in Descemet's membrane seen at the limbus, initially most prominent at 6 and 12 o'clock and later as a concentric ring.

Wilson's Disease: Azure Lunulae



- The bluish discoloration of the nails, or azure lunulae, is an unusual manifestation of Wilson's disease. This 43-year-old male presented with neurologic symptoms, had Kayser-Fleischer rings and cirrhosis on liver biopsy.

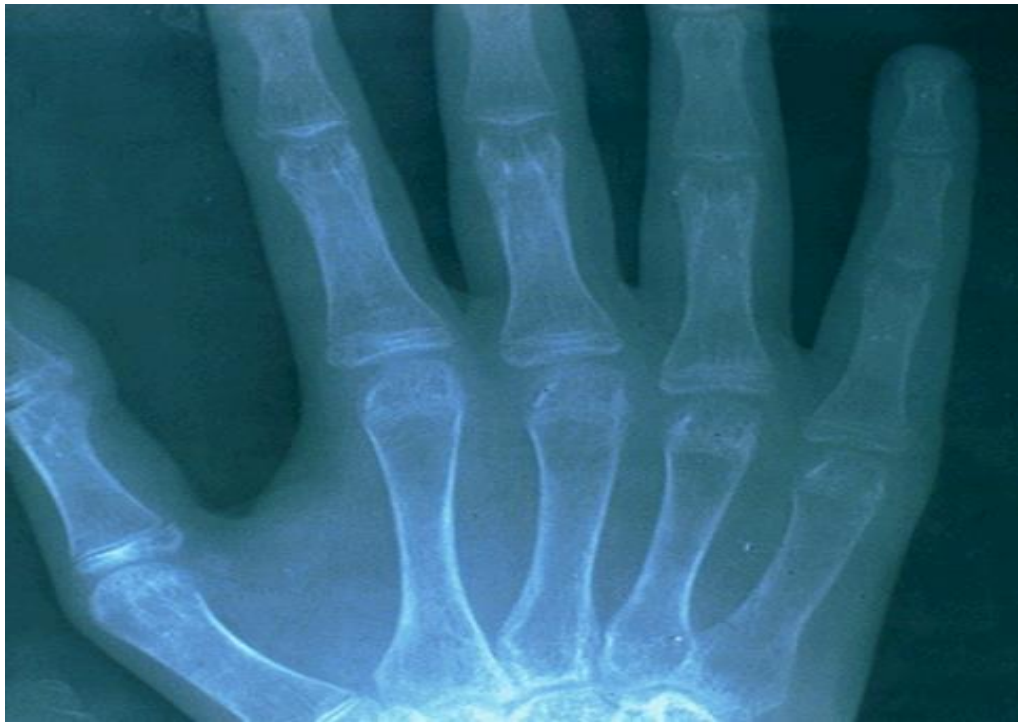
Wilson's Disease: Brain MRI



– A T1 weighted image on MRI of the brain in this patient with Wilson's Disease shows marked degenerative changes of the basal ganglia bilaterally with greater involvement on the left side. The involvement of lenticular nucleus is typical hence the term hepatolenticular degeneration.

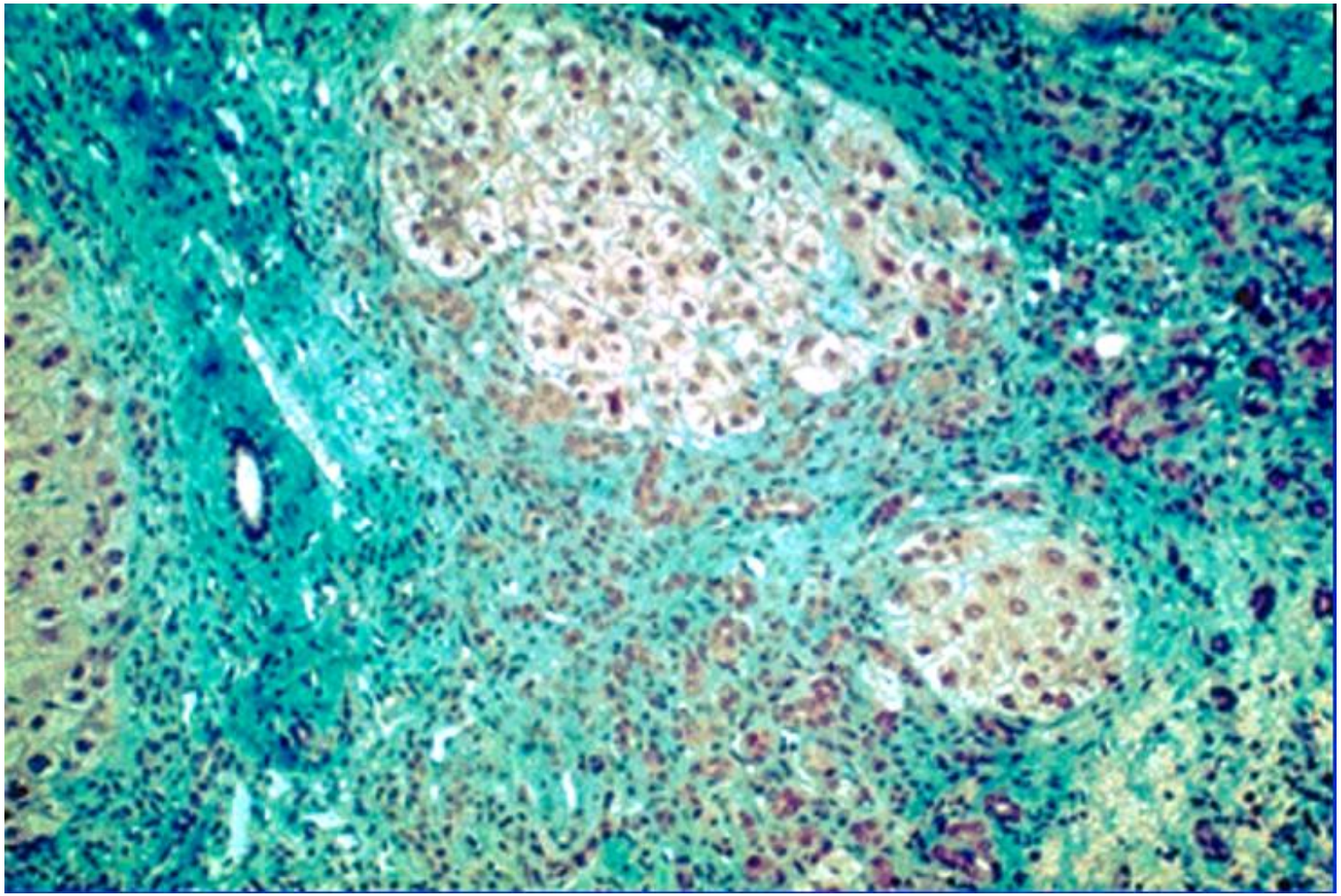
On neurological imaging the typical sites of involvement are the deep gray matter and white matter. Gray matter nuclei involvement is more common and is usually bilaterally symmetrical with variable involvement of the putamen, caudate, thalamus and globus pallidus. White matter lesions are usually asymmetric and located in the subcortical region. The lesions are hypodense on CT, hypointense on short TR MR sequences and variably hyperintense, hypointense or both on long TR sequences. Pathological gliosis, edema and variable necrosis with cavitation occur due to toxicity with copper and/or secondary to ischemia. These changes described likely account for the hypointensity on the short TR image shown.

Wilson's Disease: Hand Radiograph



- There is a generalized loss of bone density consistent with osteoporosis and osteopenia in this patient with Wilson's disease. There are several radiographic features seen in Wilson's disease. 1) Osteopenia is seen in up to 50% of patients with Wilson's Disease and most apparent in the hands, feet and spine. It may be associated with a high frequency of fractures. The decrease in bone density is presumably a result of loss of calcium and phosphorous ind urine. 2) Chondrocalcinosis is rare in this condition. 3) Articular abnormalities collectively included under arthropathy may be apparent in up to 50% with patients with Wilson's Disease. These include subchondral bone fragmentation along with cyst formation, cortical irregularities and sclerosis. 4) Miscellaneous abnormalities seen in patients with Wilson's Disease include changes and irregularity of contour of the vertebral bodies which may be wedge shaped and simulate juvenile kyphosis or squared and simulate ankylosing spondylitis.
- The pathogenesis of the articular abnormalities in Wilson's Disease remains unknown. The arthropathy most resembles idiopathic CPPD crystal deposition disease and hemochromatosis. The distribution of articular alterations is similar in these three conditions. In Wilson's Disease the distinctive findings include multiple small ossicles and poor definition of the subarticular bone whereas in hemochromatosis these abnormalities are not apparent and joint space loss throughout the wrist may be seen. In idiopathic CPPD crystal deposition disease larger cysts and more extensive fragmentation are characteristic.

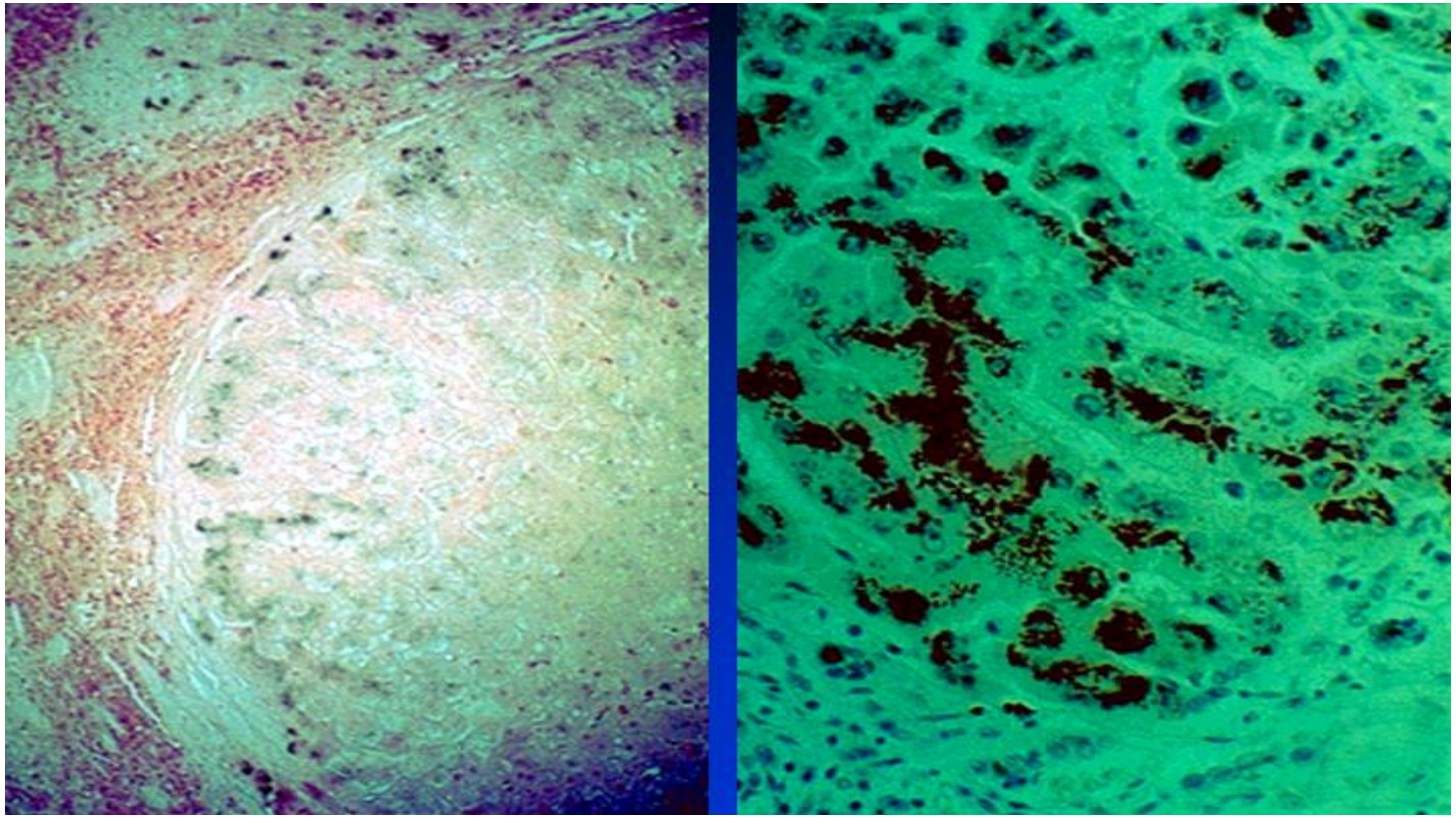
Wilson's Disease: Histology



- Wilson's disease results in a chronic hepatitis which leads to cirrhosis.

This photomicrograph shows cirrhosis, with nodules of regenerating hepatocytes outlined by fibrous septae containing a mononuclear infiltrate (Masson's trichrome stain).

Wilson's Disease: Histology



- Copper stains of liver in patients with Wilson's disease may yield positive results, such as those pictured here, but also may be misleading. Copper overload, with positive staining, can be seen in chronic cholestatic syndromes. And the copper staining in patients with Wilson's disease may be spotty and can be missed in a needle biopsy specimen. The Rubeanic acid stain, left panel, shows copper most densely deposited in the periportal, or peri-septal, hepatocytes. The rhodanine stain, right panel, is also markedly positive, confirming deposition of copper in periportal hepatocytes.

Hemochromatosis

Hemochromatosis

- Inheritance is autosomal recessive and due to specific genetic mutations in HFE located on the short arm of chromosome 6. This mutation results in increased iron absorption resulting in excess iron content in tissues with resulting tissue injury and organ failure if not identified and treated. The expression of the disease phenotype is variable and dependent on dietary iron intake and iron loss.
- Over time, patients have an inexorably increasing total body iron load. This begins at birth, due to mutations in HFE which lead to increased iron absorption. By age 10 the serum iron is elevated above the normal range, and by adolescence the hepatic iron is increased. Tissue injury due to the accumulated iron begins by the mid 30's in males, and organ dysfunction, including cirrhosis, diabetes, and cardiac disease, presents in the mid 40's or later.
- Approximately 10 to 20 mg of iron are ingested each day from the diet. The intestinal mucosa forms an effective barrier to iron, however, and only one tenth of ingested iron (1 to 2 mg) is absorbed from the duodenum and upper jejunum into portal blood. Once absorbed, there are few routes for disposing of iron; 1 to 2 mg per day is shed via excretion in bile, cells sloughed by skin and gastrointestinal tract, and in the urine. Women lose approximately 30 mg per menstrual cycle.
- Iron is transported from its site of absorption to the liver bound to transferrin, which binds 2 atoms per molecule. In the liver iron is taken up by ferritin, a storage form of iron capable of holding thousands of atoms per molecule. The normal total body pool of iron is approximately 4 gm. Hemoglobin in red blood cells makes up half of total body iron stores. One unit of blood (500 ml) contains 250 mg of iron. Iron is also found in muscle as myoglobin and in heme-containing enzymes in the liver and elsewhere. The remainder of the body iron is in storage form, as ferritin or hemosiderin, in liver and reticuloendothelial cells.

Causes of Iron Overload

Hereditary Forms of Iron Overload

Familial or hereditary forms of hemochromatosis

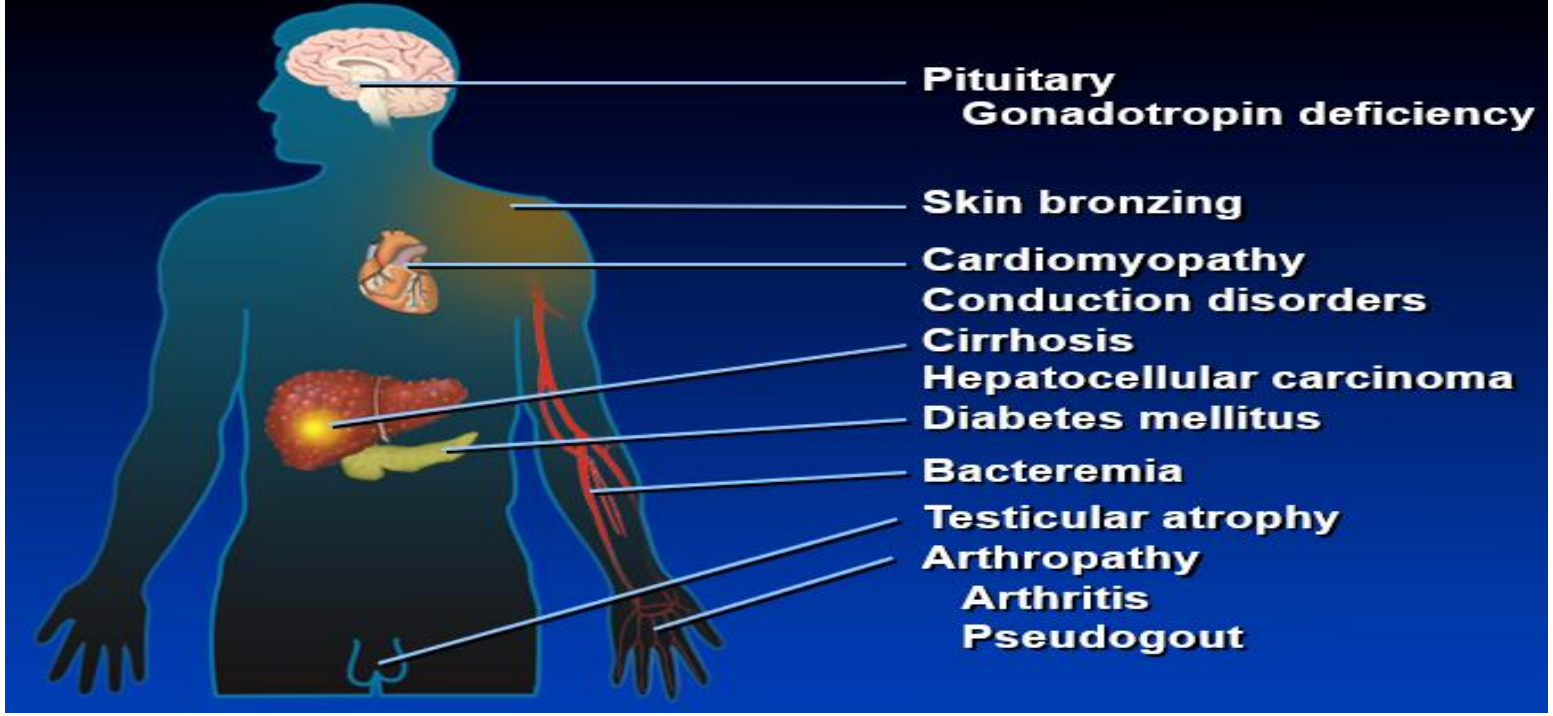
- Hereditary hemochromatosis (HFE-related)
  - C282Y homozygosity
  - C282Y / H63D compound heterozygosity
- Hereditary hemochromatosis, non-HFE related
- Juvenile hemochromatosis
- Neonatal iron overload
- Autosomal dominant hemochromatosis (Solomon islands)

Acquired Causes of Iron Overload

Acquired iron overload

- Iron-loading anemias
  - Thalassemia major
  - Sideroblastic anemia
  - Chronic hemolytic anemia
- Dietary iron overload
- Chronic liver diseases
  - Hepatitis C
  - Alcoholic liver disease
  - NAFLD

Hemochromatosis: Clinical Manifestations



- Most patients having symptomatic disease are diagnosed at age 40 to 50 years. The iron overload of hemochromatosis results in iron deposition in multiple organs. The total body iron stores are increased by a factor of 5 to 8, resulting in a total body iron of 20 to 40 gm. Excessive skin melanin, together with iron deposition in the skin, leads to bronzing of the skin. Excess iron in heart tissue can result in a dilated cardiomyopathy and congestive heart failure and/or in conduction disturbances and arrhythmias. The iron overload in the liver often causes insidious damage with mild serum aminotransferase elevations, progressing to cirrhosis if not treated. The incidence of hepatocellular carcinoma is high, over 200 times that of the normal population, and this complication is reported to occur in as many as 20 to 40% of affected patients. Iron is also deposited in the pancreas and diabetes mellitus is a common result. The arthropathy associated with hemochromatosis involves primarily the metacarpophalangeal and proximal interphalangeal joints. Affected patients also have chondrocalcinosis. Patients with hemochromatosis are also at increased risk for infection with unusual pathogens, such as *Vibrio vulnificus, Listeria monocytogenes, Yersinia enterocolitica* and *Yersinia pseudotuberculosis*.

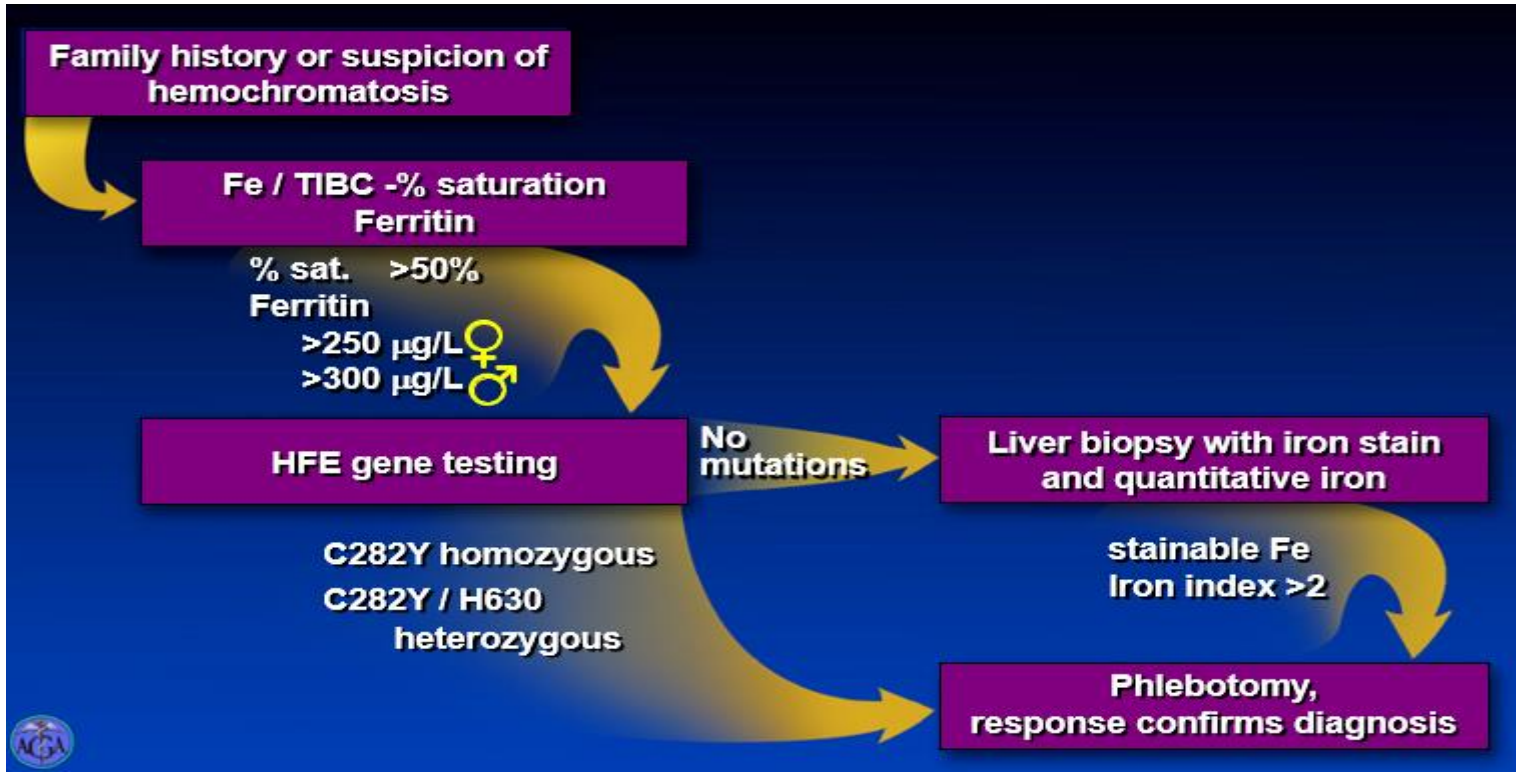
The figure illustrated here is a man, as hemochromatosis becomes clinically manifest earlier in men, usually in the late 40's to early 50's. Women are partially protected by blood loss during the menstrual cycle, and present later in life, usually in their 60's.

Hemochromatosis: Diagnosis

- Homozygous C282Y HFE mutations
- Heterozygous for both C282Y and H63D mutations

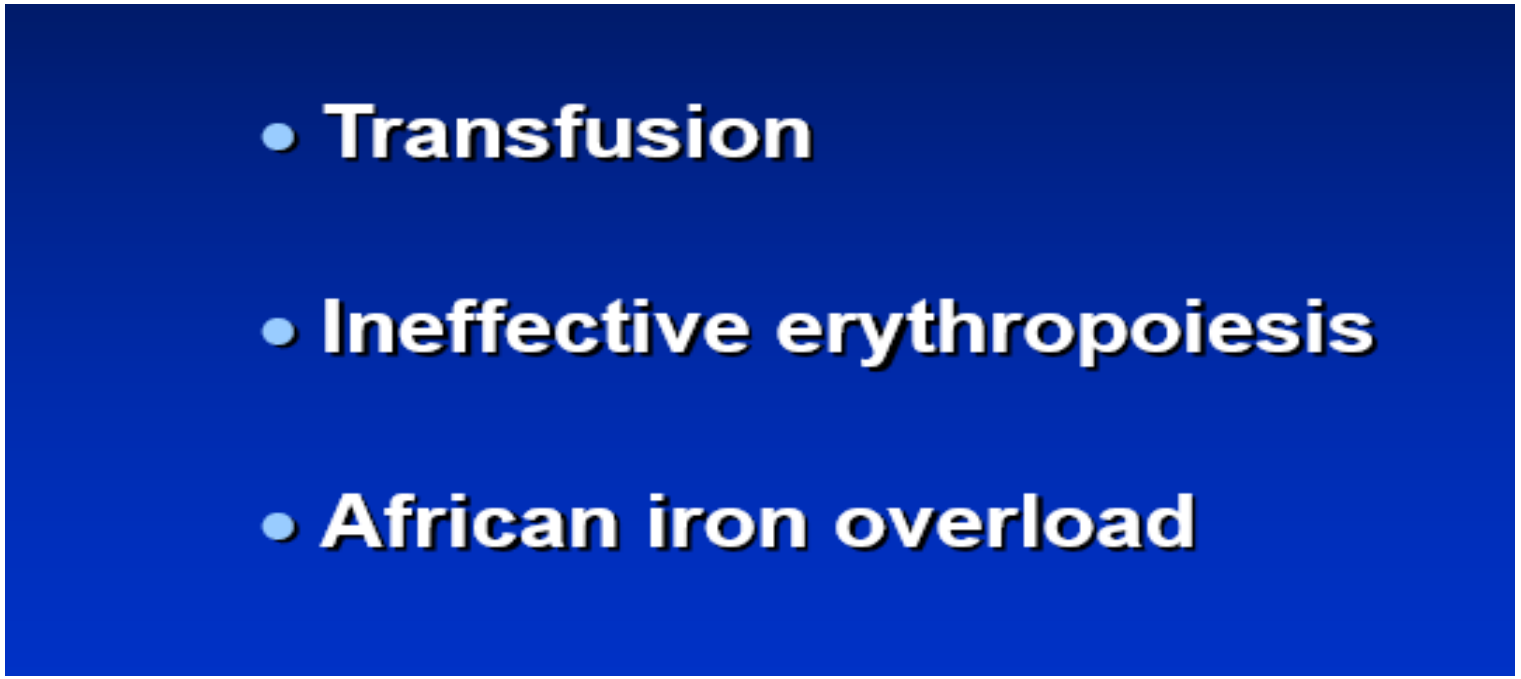
- The diagnosis of hereditary hemochromatosis can be established confidently based on genetic testing with results showing one of the two mutation identities listed in the slide especially in a patient with a family history of hemochromatosis or a patient with abnormal ferritin levels and transferrin saturation.

Hemochromatosis : Diagnostic Tests



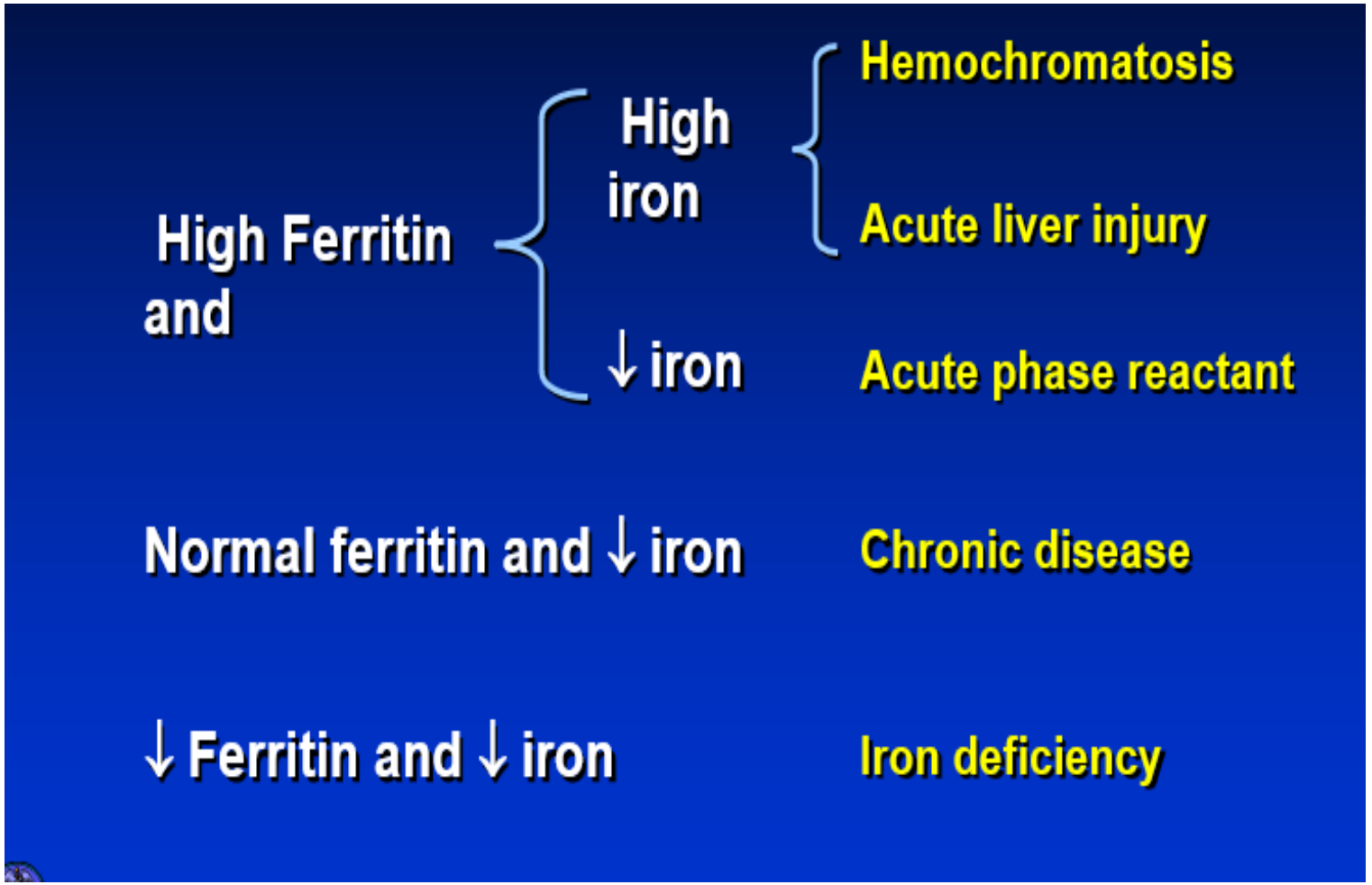
- In patients with the consideration of hemochromatosis, evaluation should begin with measurements of Fe/TIBC and ferritin. In patients with results consistent with hemochromatosis, genetic testing of HFE should be performed. If the results of genetic testing demonstrate either homozygous C282Y or combined compound heterozygous C282Y/H63D, the diagnosis of hereditary hemochromatosis is established and appropriate therapy should begin. When gene analysis for diagnosis of hereditary hemochromatosis does not confirm the diagnosis and the possibility of non-HFE cause of iron overload is under consideration, quantitation of the iron concentration in the liver by iron stains or mass measurement may be useful. Response to phlebotomy confirms the diagnosis

Iron Overload Disorders

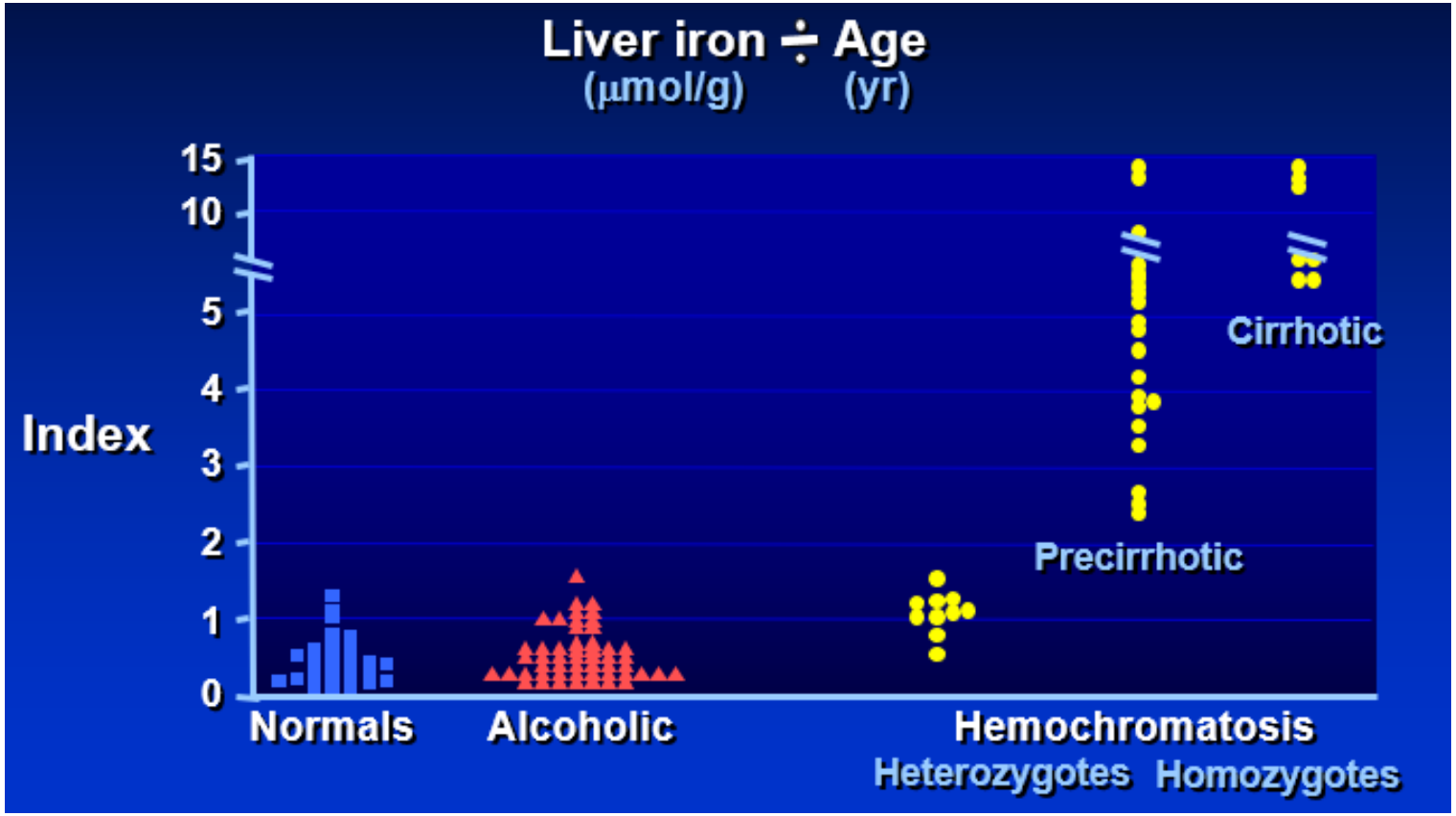


- Iron overload can be either primary, due to an inherited defect in iron homeostasis, or secondary. The typical primary iron overload disorder is hemochromatosis, which is inherited as an autosomal recessive trait due to a defective gene carried on the short arm of chromosome 6. The causes of secondary iron overload are exogenous administration of excess iron due to transfusions or diet (i.e. patients being frequently transfused or excess iron administration). Secondary overload may also result from hyperabsorption of iron in response to chronic anemia or ineffective erythropoiesis, such as sideroblastic anemia or thalassemia.

Interpretation of Ferritin Levels



Hepatic Iron Index



- Iron levels rise with age in normal individuals as well as in patients with hemochromatosis. Thus, greater specificity can be given to the hepatic iron quantitation by using the hepatic index, defined as the quantitative hepatic iron value, in μmoles per gm dry liver weight, divided by the patient's age in years. This slide shows that the hepatic iron index serves to clearly differentiate patients with alcoholic liver disease from those who are homozygous for hemochromatosis.

Hemochromatosis Treatment: Phlebotomy

Phlebotomy

Acute

1 unit (250 mg Fe) weekly or biweekly until mildly anemic

Maintenance

Once iron stores are depleted (ferritin <50ng/ml, transferrin sat <50%) continue with phlebotomy every 2-3 months. Monitor hemoglobin, ferritin and transferrin saturation

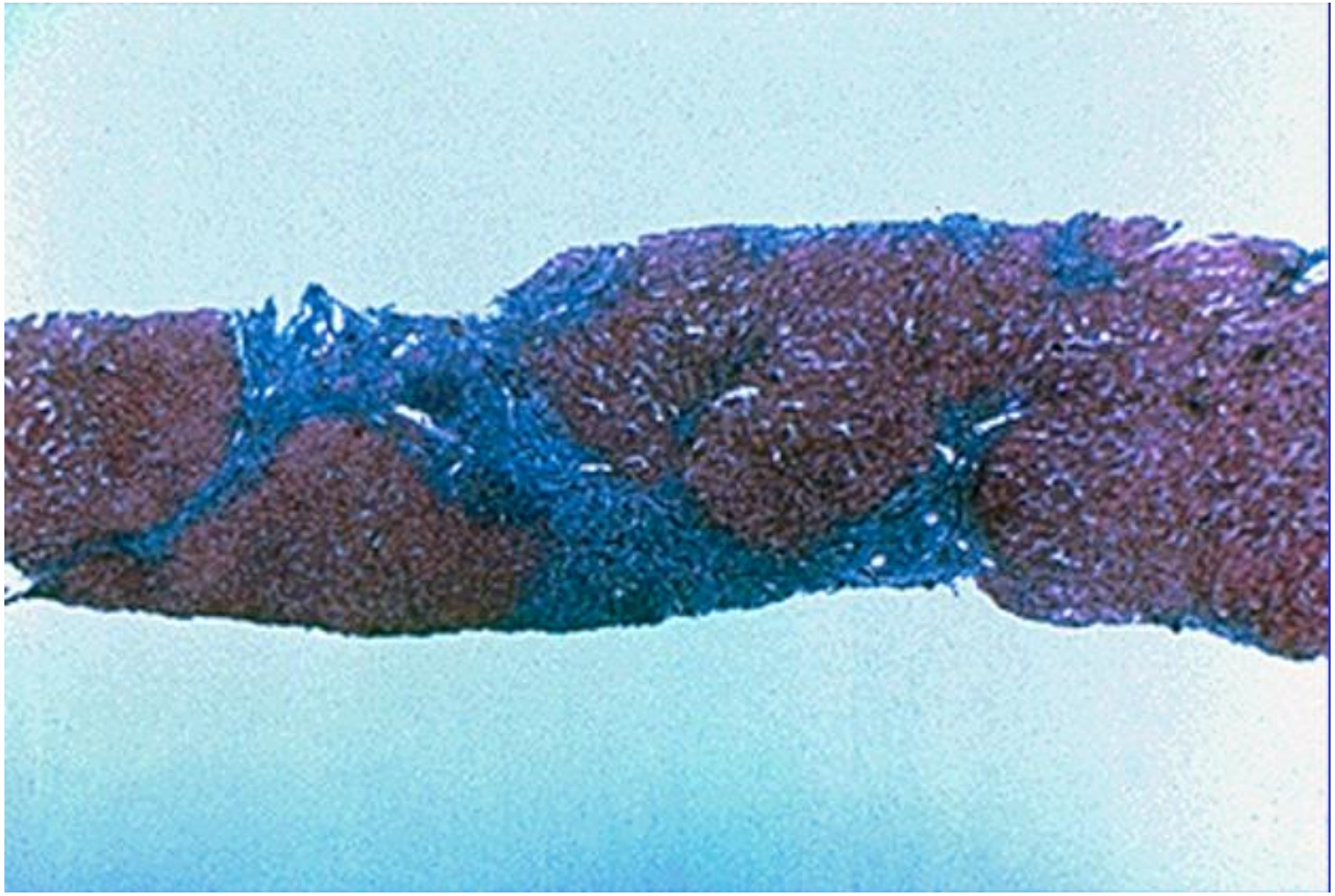
Phlebotomy

Phlebotomy Improves Survival

Preventable:	**all clinical manifestations**
Reversible:	**cardiac dysfunction, glucose intolerance, hepatomegaly, skin pigmentation**
Irreversible:	**cirrhosis risk of hepatocellular carcinoma arthropathy, hypogonadism**

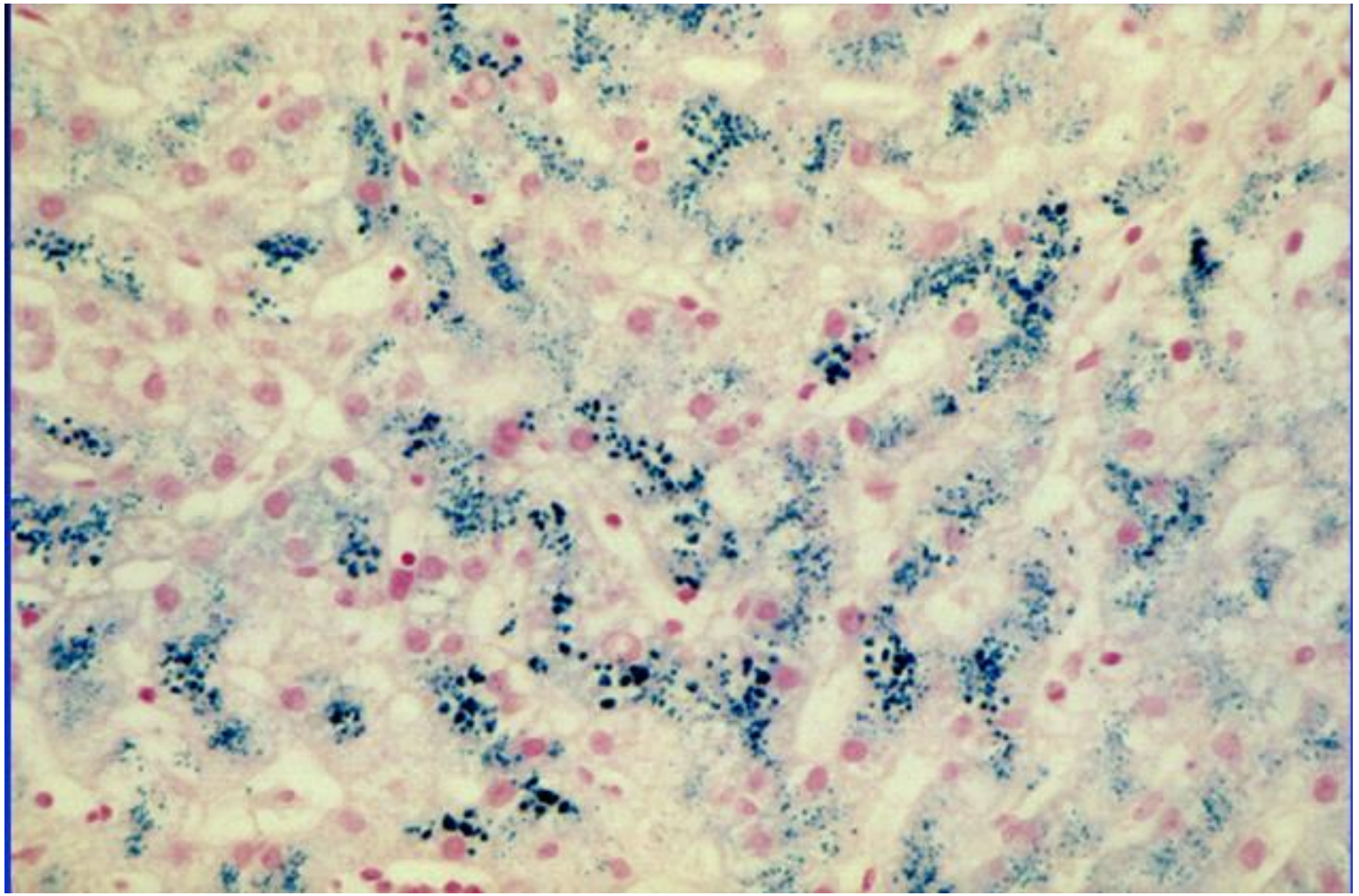
-When begun early, for example in an asymptomatic family member detected by screening, phlebotomy therapy prevents all clinical manifestations. Patients with hemochromatosis in whom therapy is begun before the development of cirrhosis have a life span not different from controls. Phlebotomy therapy of affected patients, when successful in depleting the iron overload, results in an improvement in hepatomegaly and liver function, along with an improved survival rate. Also improved are cardiac function, glucose tolerance and insulin requirement, and skin pigmentation. In established hemochromatosis, phlebotomy therapy does not reverse the cirrhosis or lower the risk of hepatocellular carcinoma. The arthropathy and hypogonadism are also not improved by phlebotomy therapy.

Liver Biopsy: Trichrome Stain



– Liver biopsy with Masson trichrome stain demonstrates bands of fibrosis partially outlining nodules of regenerating hepatocytes observed with lower power microscopy. It should be emphasized that liver biopsy may not be necessary when the diagnosis of hereditary hemochromatosis is confirmed by genetic testing.

Liver Biopsy: Prussian Blue Stain for Iron



- In this photomicrograph, the iron is in lysosomes which are adjacent to the canaliculi, which can be seen in a "chicken wire" pattern outlined by the iron.

Lower GI Bleeding

Lower GI Bleeding

- Blood originating from below the ligament of Treitz.
- Ligament of Treitz: A fibromuscular band that originates from the right diaphragmatic crus and fixes the duodenal-jejunal flexure.
- Patients present with Fresh blood in the stool; this implies a lower GI cause unless there is a very rapid bleeding from an upper GI source (Hemodynamic instability + Elevated Blood Urea).
- The patient may be hypotensive and shocked without overt evidence of bleeding → Always do rectal exam.

Causes of Lower GI Bleeding

Bleeding source:	Frequency:
Diverticula	30 - 40%
Colitis (Ischemic, IBD)	15 - 20%
Carcinoma, Polyps	13%
Angiodysplasia	10%
Anorectal diseases	10%
Upper gastrointestinal bleeding	10 - 13%
Unknown	2 - 8%

- If a patient presents with Fresh blood in rectum → check urea to know the source (upper or lower):

In Upper bleeding → High Urea, Expected Hemodynamic instability with tachycardia

In Lower bleeding → Low-Normal Urea, Normal Vitals.

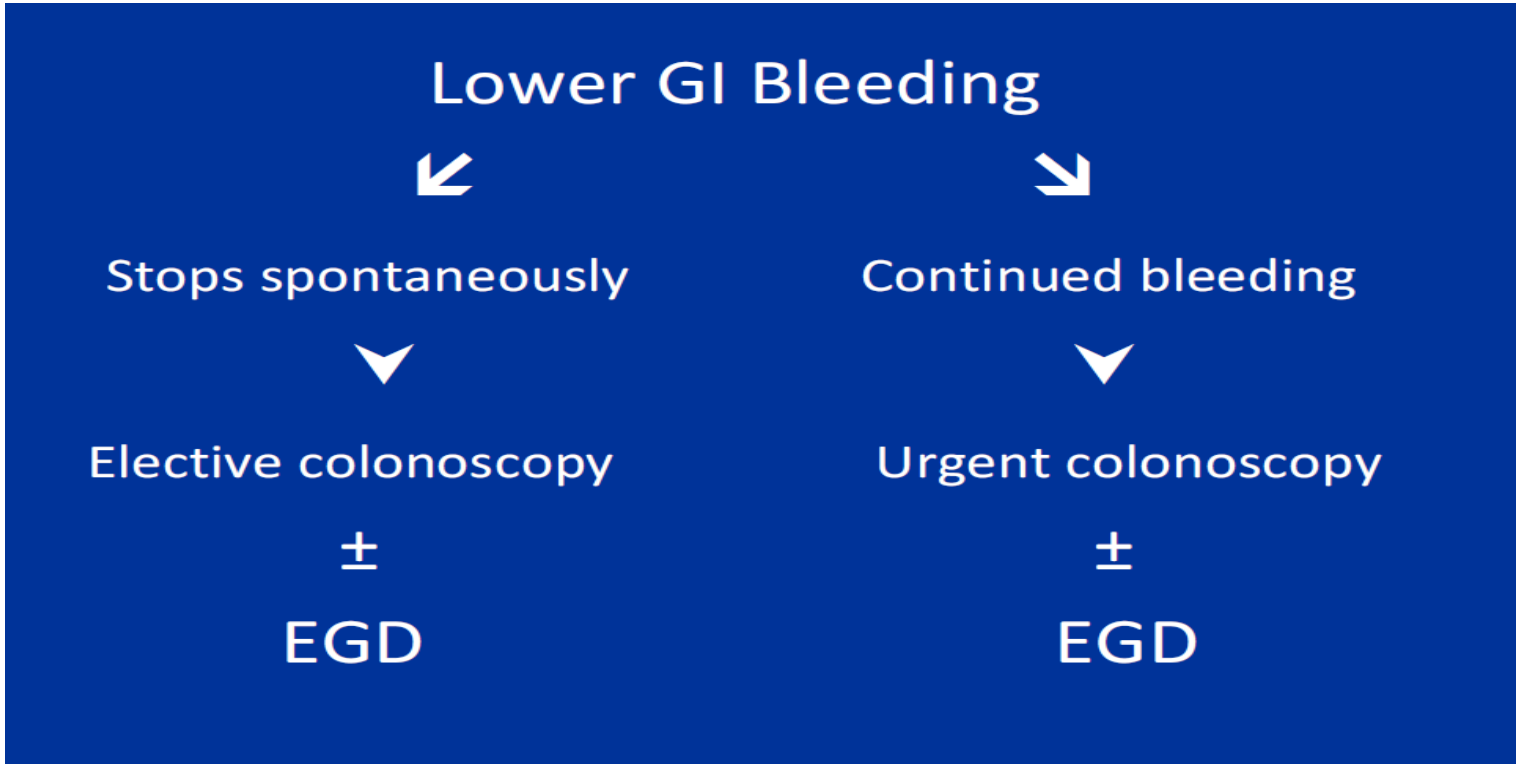
- Diverticula is the most common.
- Polyps develop into Carcinoma

Causes of Mid GI Bleeding

Bleeding source:	Frequency:
Angiodysplasia	20 - 60%
Ulcerations (IBD, NSAIDs)	10 - 40%
Neoplasia	1 - 10%

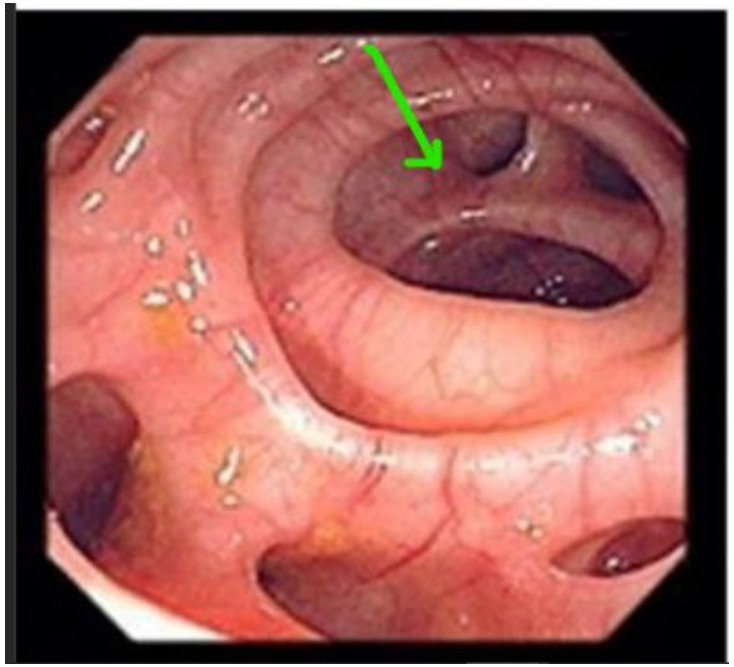
- Mid GI → Ileum to ileocecal valve.
- Angiodysplasia is the most common cause.

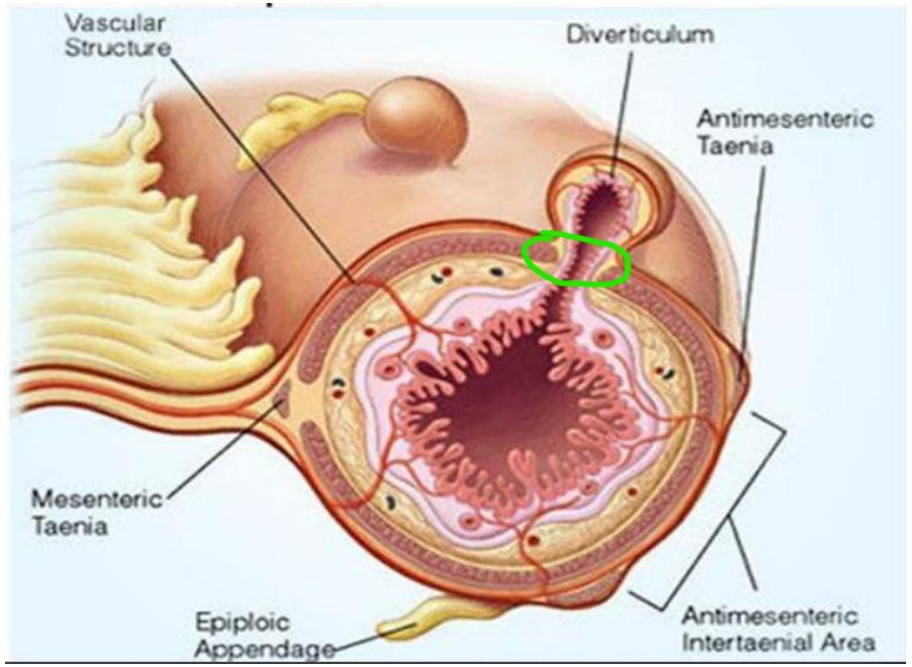
Investigations



- Usually, bleeding stops spontaneously; since bleeding is Arterial which causes a drop in BP reducing leak of blood.
- So, first do resuscitation by giving fluids → If bleeding stops → Do an Elective Colonoscopy (Not urgent; get rid of stool before endoscopy) with or without EGD (Upper endoscopy) if upper source of bleeding is suspected.
- If bleeding continues, → then do Urgent Colonoscopy with or without Upper endoscopy to localize the bleeding (accounts for 75% of the management).

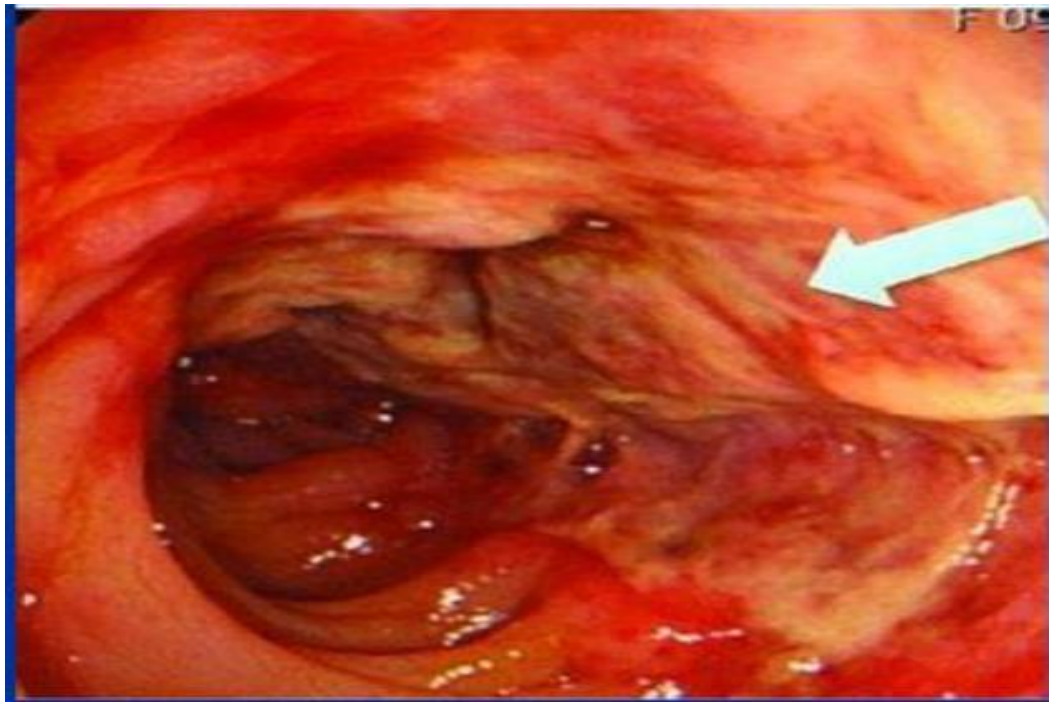
Colonic Diverticula





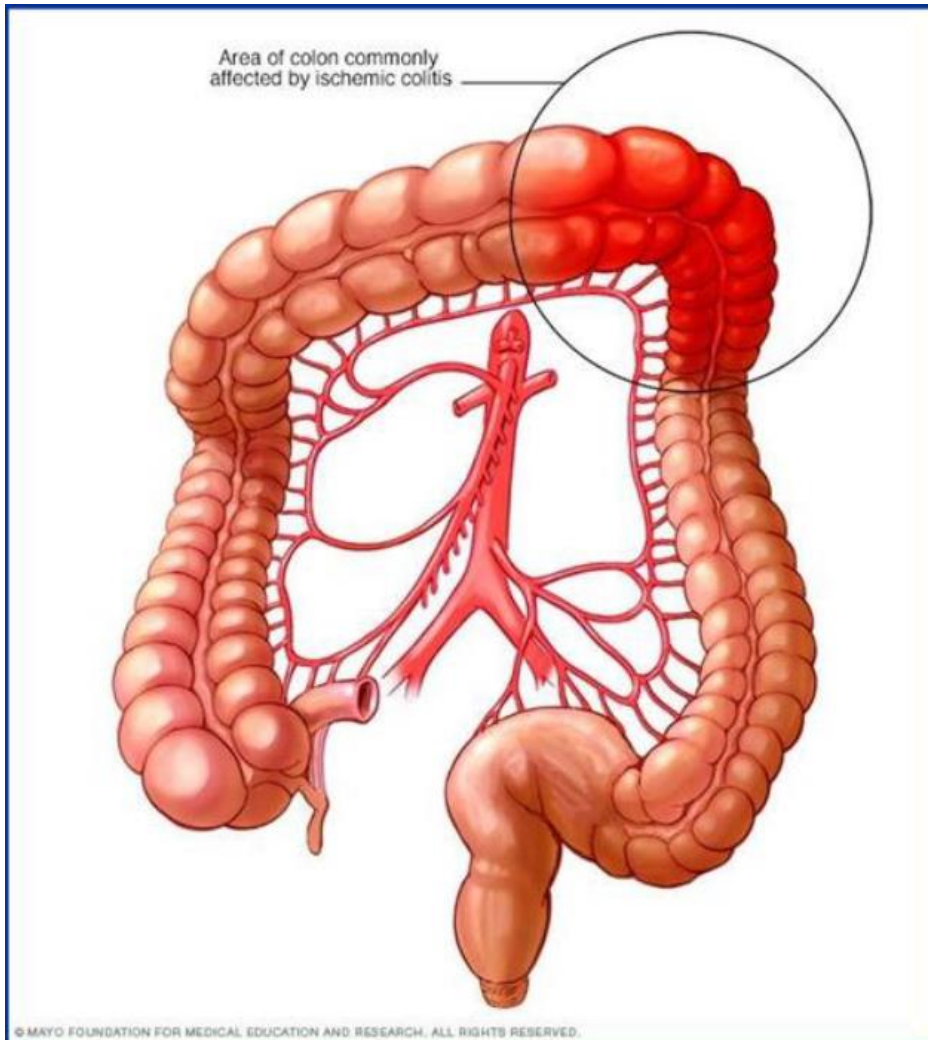
- Large Volume, Brisk, Painless.
- Local Trauma to the Vasa Recti within Diverticula can lead to Arterial bleeding.
- Diverticular bleeding is the commonest cause of Acute massive colonic blood loss.
- Although Bleeding may stop spontaneously, rebleeding is common and often comes from the right colon (because the mouth of the diverticula on the right side is larger), even though most diverticula are left-sided.
- False Diverticula.
- Arteries penetrate the muscularis to reach the submucosa and mucosa - weak point.
- Green Arrow → Pouch
- Green Circle → This opening with continuous constipation and pressure, enlarge forming a pouch.
- So, diverticula open and close causing shearing forces on the artery leading to cut at one side and massive bleeding that only stops with the drop in BP

Ischemic Colitis



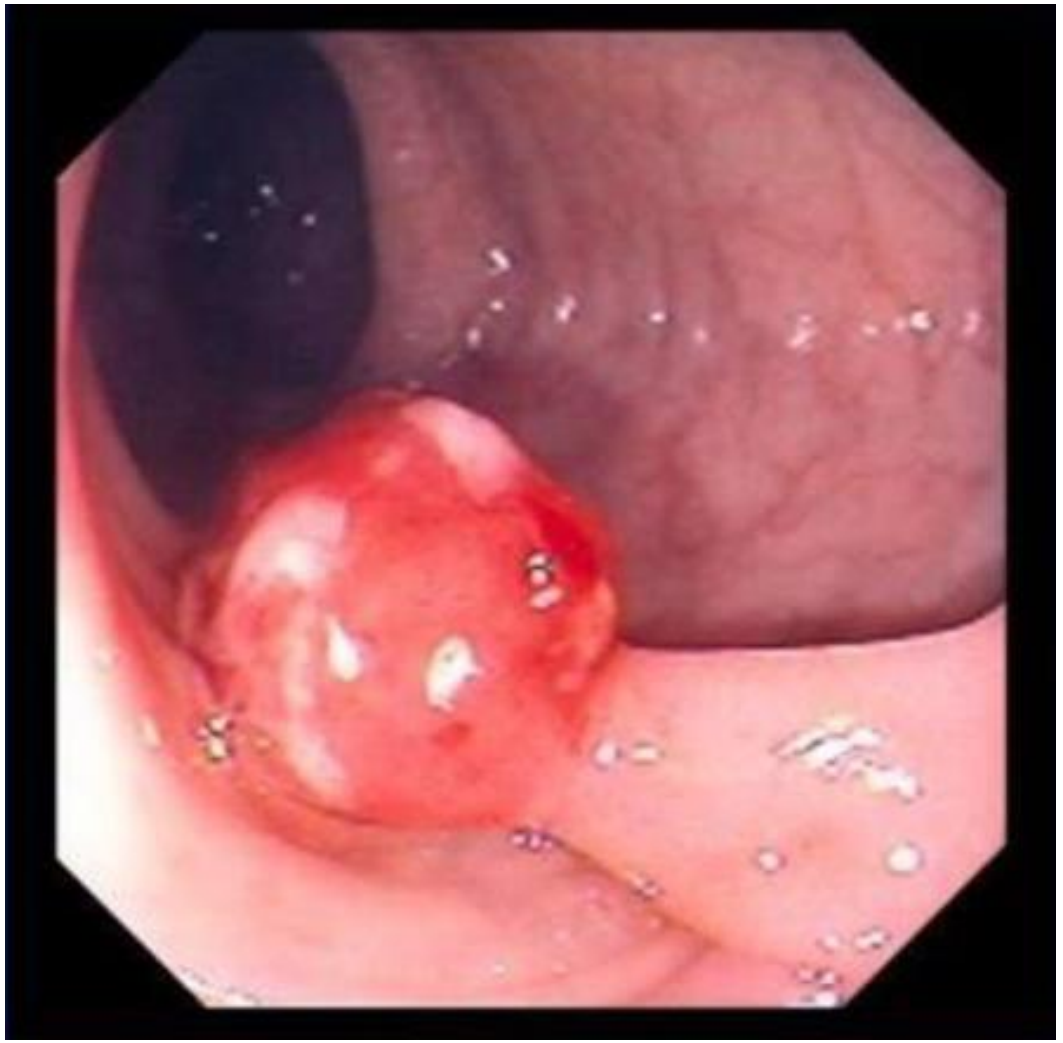
- Caused by compromised blood flow in the mucosa / submucosa due to a drop in BP / embolization from the heart / thrombosis.
- Low Flow states (HF, Dehydration, Hemorrhage, Shock, Extensive burns, Heavy smoking) are more common than Embolization or Thrombosis.
- Clinically, patients present with sudden onset cramping pain in the LLQ with bloody stools and mild to moderate abdominal tenderness with soft abdomen.
- Diagnosis: X-Rays (Classical "Thumbprinting" due to edema and thickening of the wall) + Contrast-enhanced CT scan (CT angiogram) and Careful Endoscopy.
- The white arrow in the figure illustrates Ulcer with Triple S sign.

Watershed Area



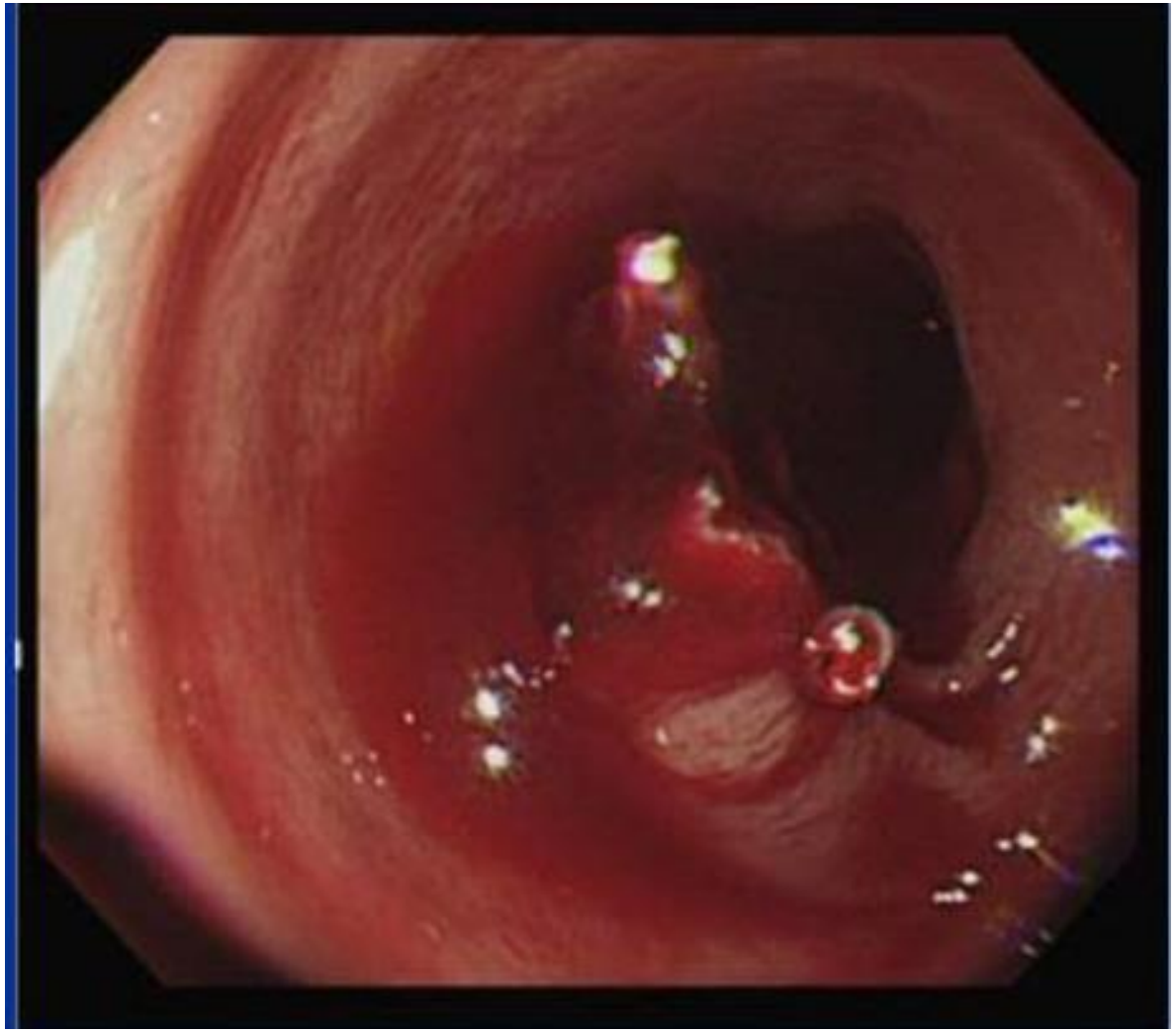
- Non-maintained blood flow area that doesn't withstand Ischemia since it's compromised.

Bleeding Colonic Polyp

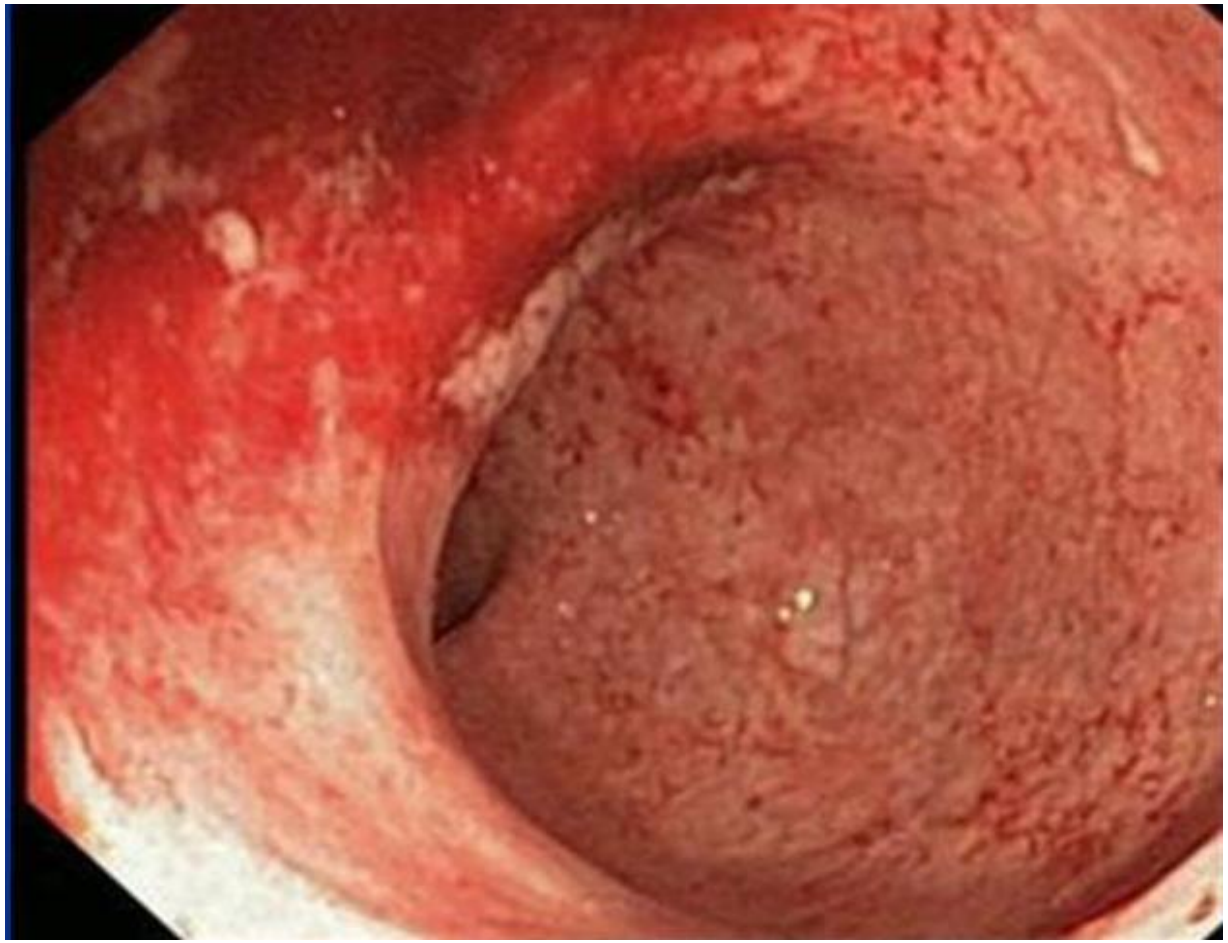


- Ulceration and bleeding of the polyp occurs due to rapid growth rate that exceed the ability of feeding artery to supply the entire polyp leading to Ischemia, Ulceration, Erosion, and Bleeding

Post Polypectomy Bleeding

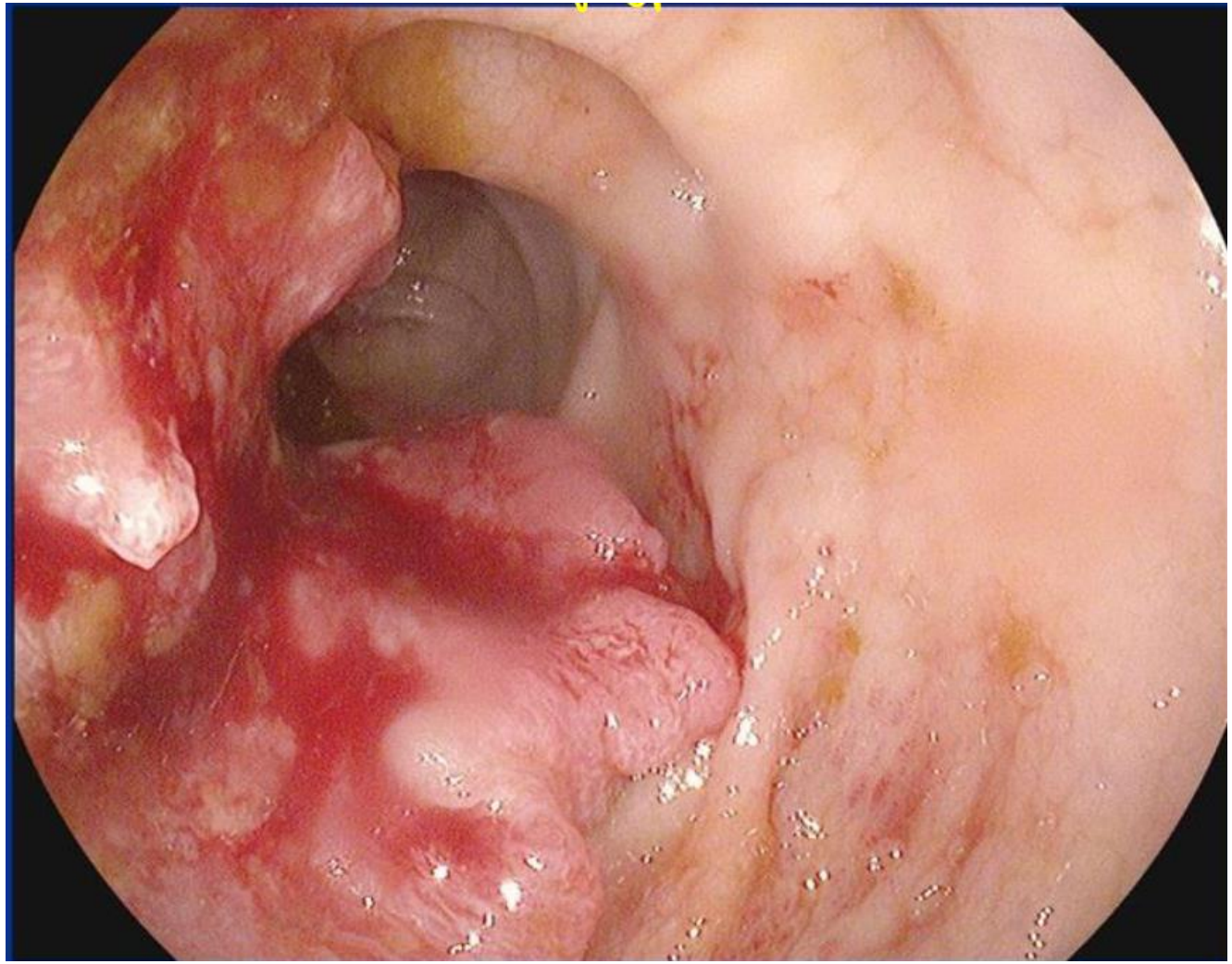


Infectious Colitis



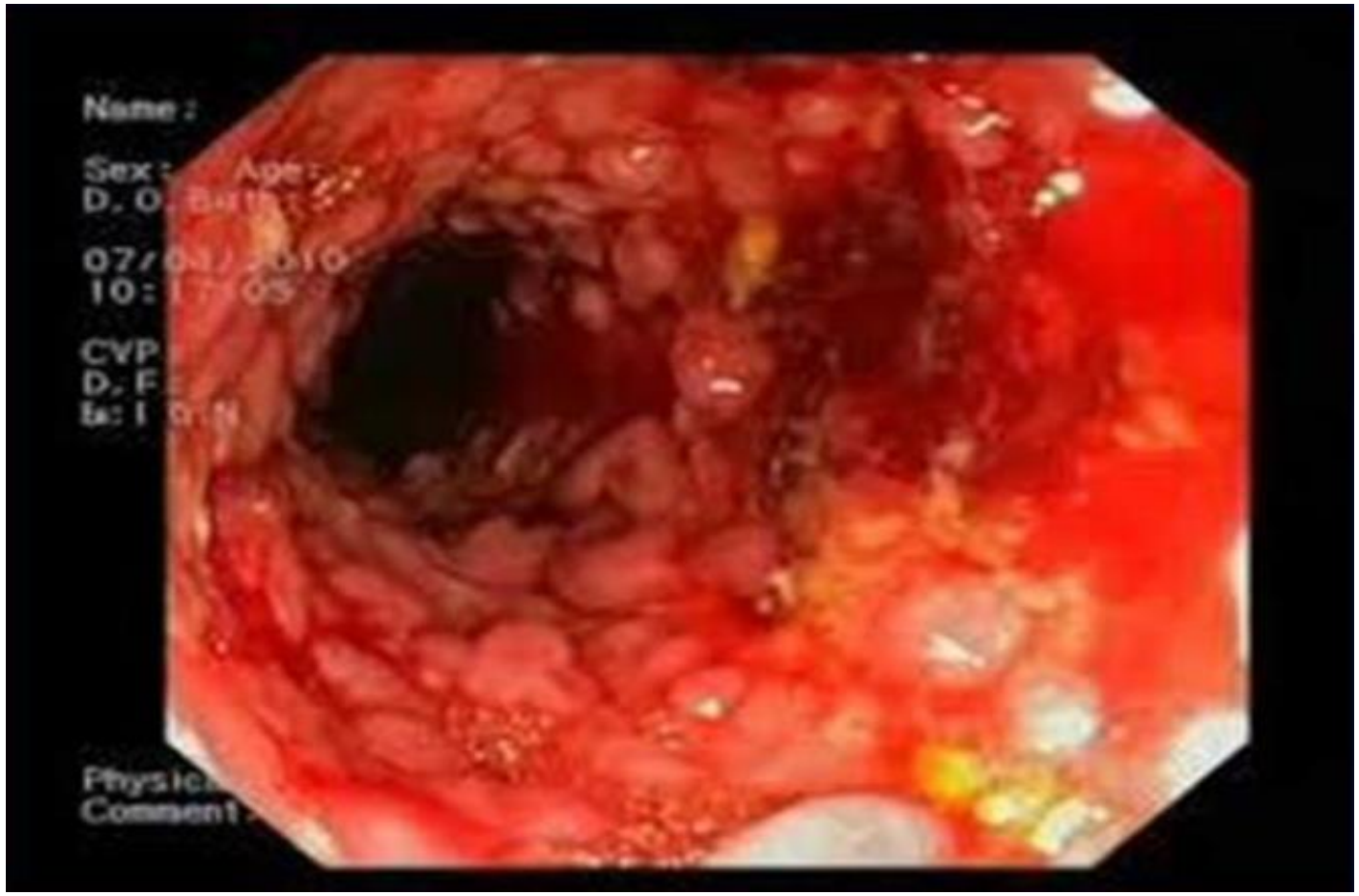
- Invasive infection (Like Shigellosis, Invasive E.coli, Yersinia) of the mucosa and Submucosa Leading to Inflammation and bleeding.

Colonic Tumor Bleeding



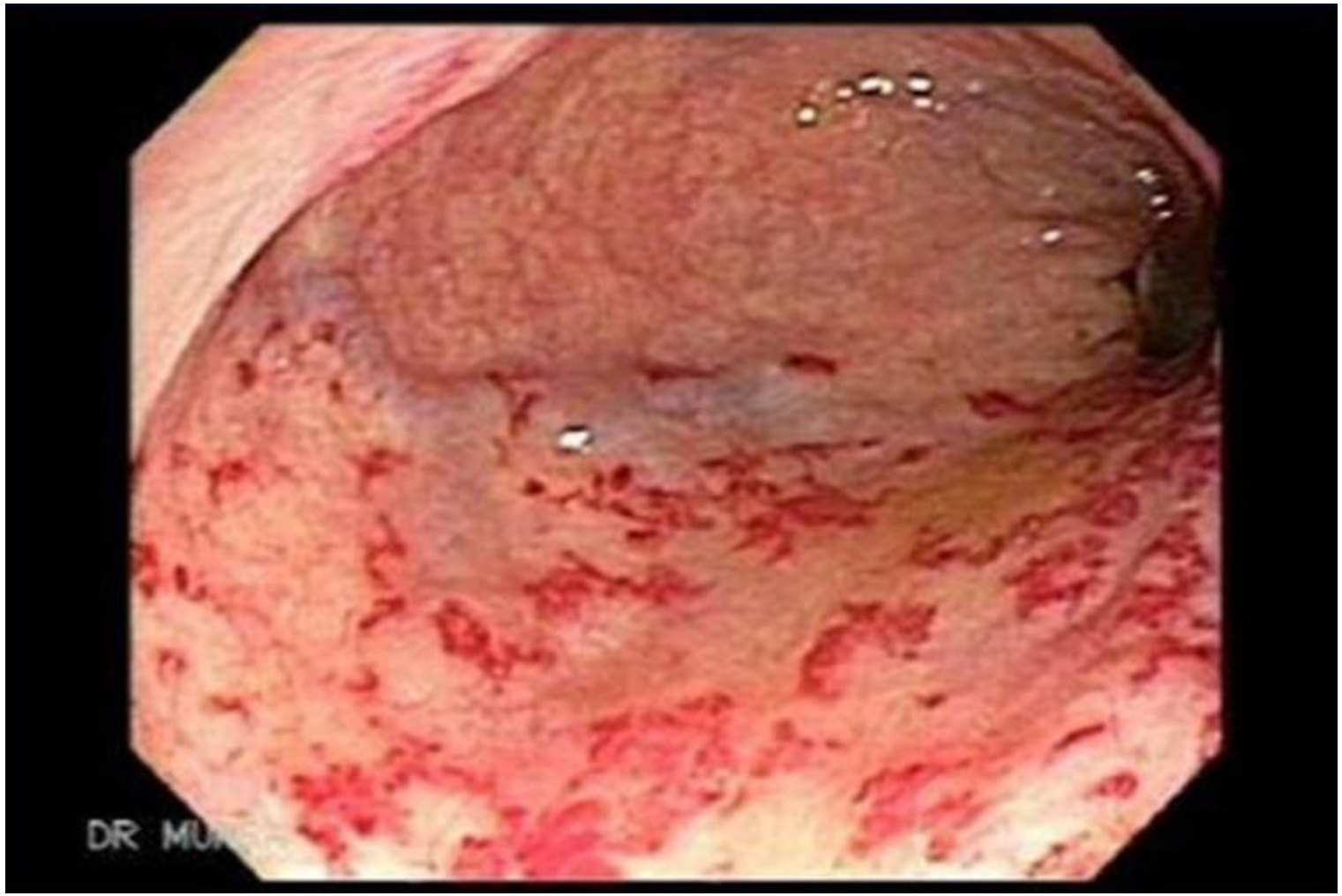
- Same Idea as Colon Polyps.

Ulcerative Colitis Flare Bleeding



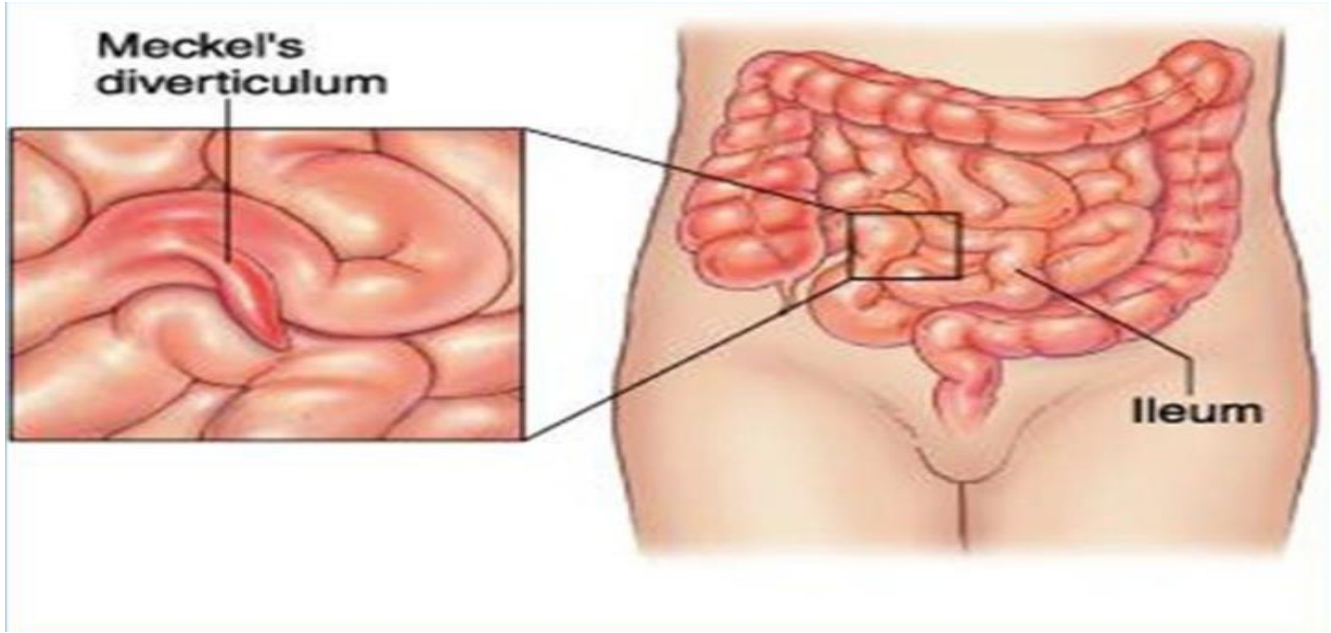
- Pseudo-polyps due to chronic inflammation indicating Uncontrolled Ulcerative Colitis.

Radiation Colitis



- Bleeding or Recto-Sigmoid area due to Telangiectasia due to Pelvic Radiation (not soon after radiation, maybe after 5 years).

Meckel's Diverticulum



- Occurs in a fetus early in pregnancy; normally the vitelline duct, which connects the growing fetus with the yolk sac is absorbed into the fetus by the 7th week of pregnancy. When the vitelline duct isn't fully absorbed, a Meckel's Diverticulum develops.
- It may contain cells from both the stomach and pancreas. Cells from the stomach can secrete acid, which can cause ulcers and bleeding.
- Affects young patients in distal small bowel.
- Normal upper endoscopy.
- On Colonoscopy → Couldn't find a source of blood in the large bowel then to small bowel you moved from area of bleeding to no bleeding.
- Diagnosed by Meckel's Scan; so the patient takes IV Technetium-99m which will be uptaken by Stomach cells, then we use a Gamma Camera (with the camera we'll be able to see both the stomach and the Diverticulum since it contains Parietal cells of the stomach).
- Treated by Surgical Resection

Treatment of Lower GI Bleeding

Endoscopic:

•Arterial Lesions:

Electrocoagulation (Heat Probe)

Mechanical endoscopic techniques (Hemostatic Clipping)

Arterial Vasoconstriction (Adrenaline Injection)

Snare Polypectomy/Endoloop

•Angiodysplasia:

Argon Plasma Coagulation (APC)

Interventional Radiology:

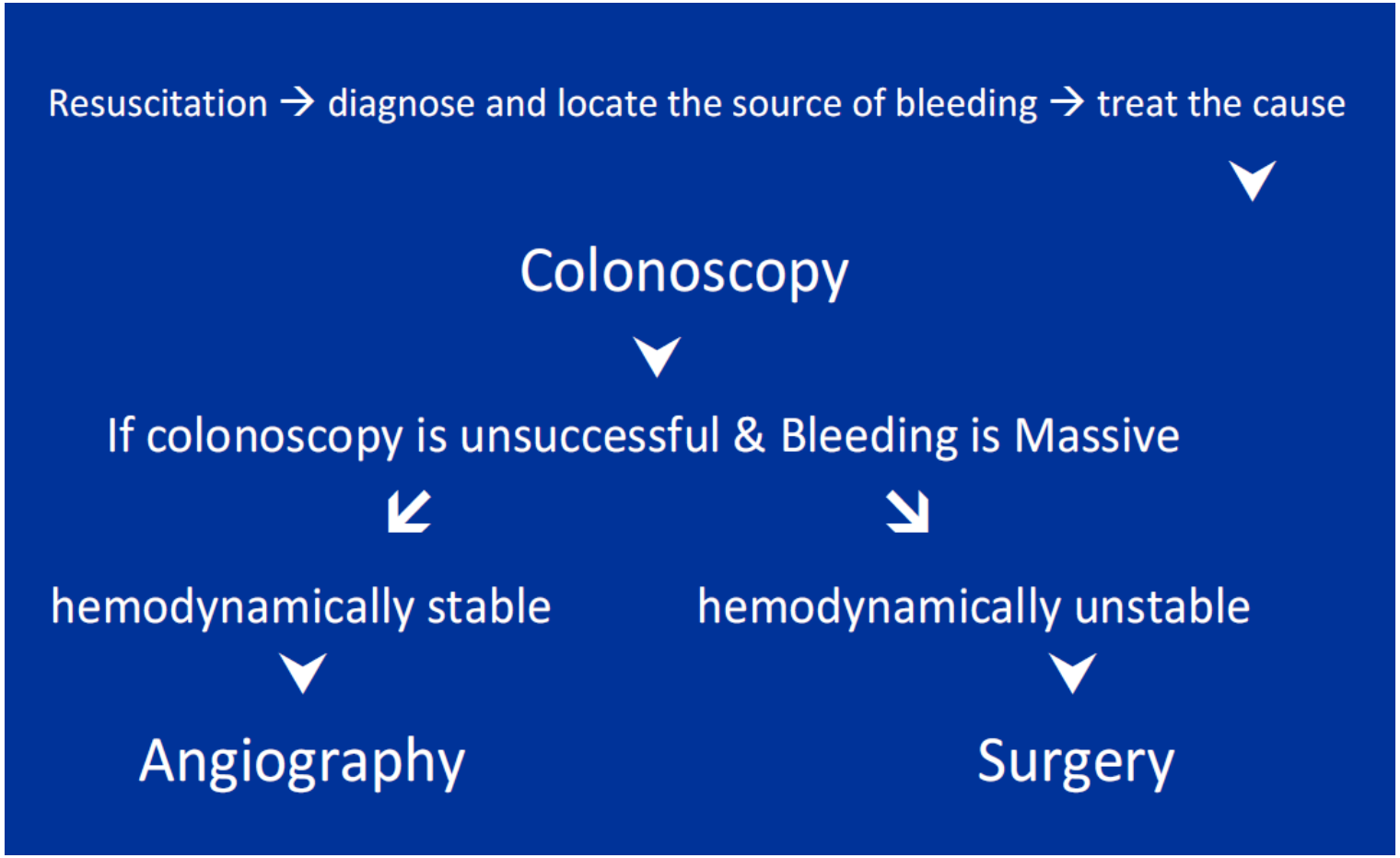
Angiography with Selective Embolization

Surgery:

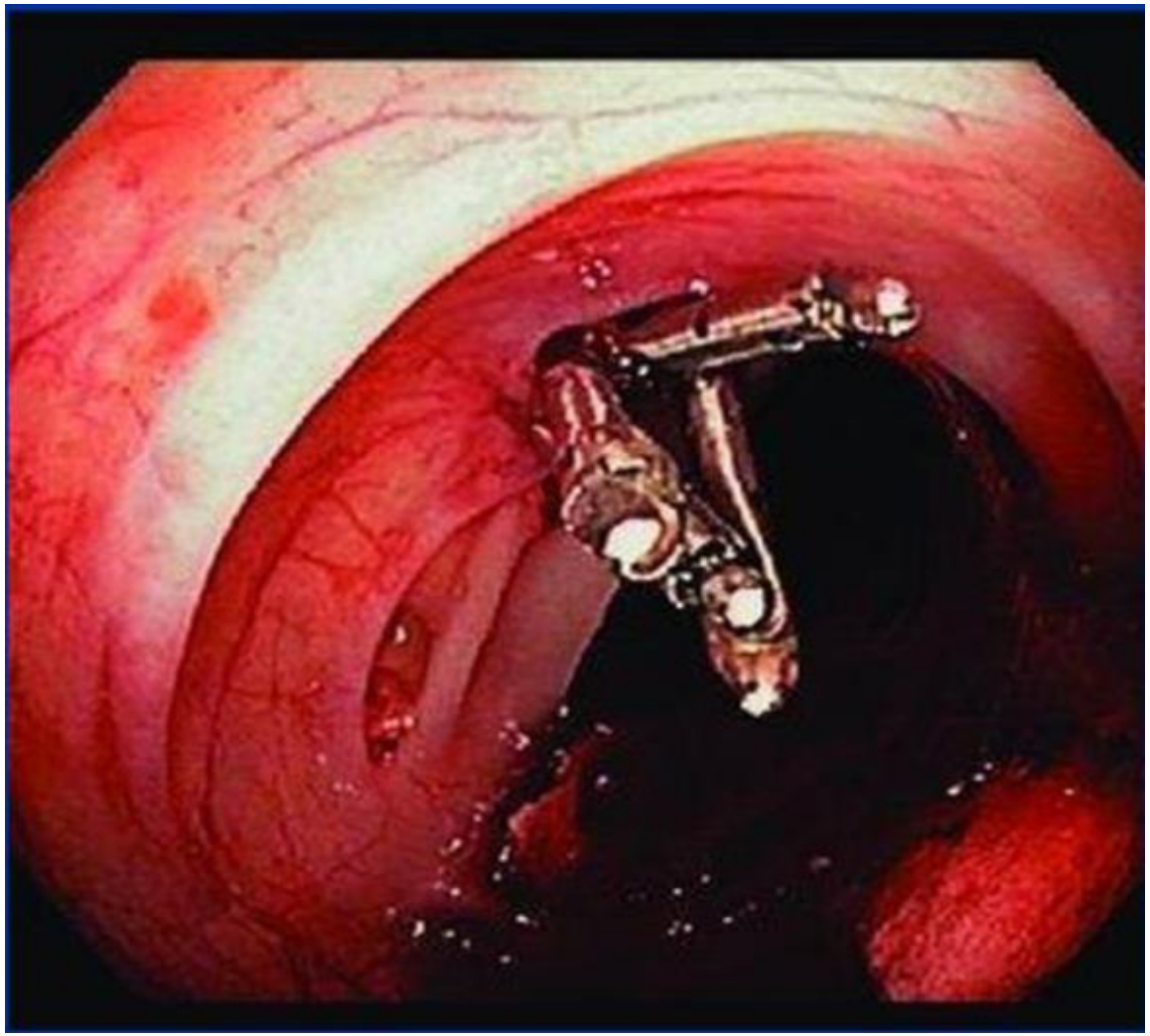
The success and postoperative bleeding rate depends on accurate pre-operative localization (Mortality 5-10%)

- Treatment is Directed towards treating the underlying cause.
- If Angiodysplasia Fails, then we refer to interventional radiology.
- Before doing surgery, we need to localize the source of bleeding.

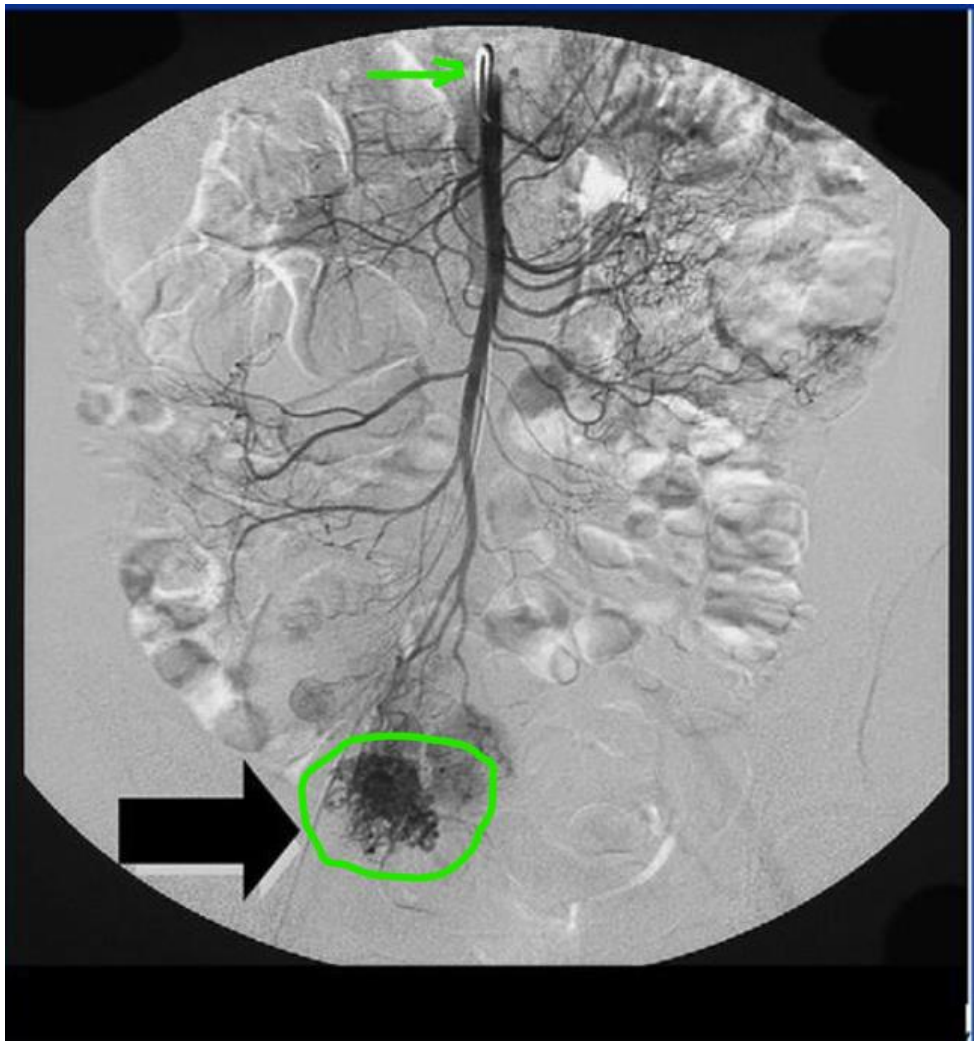
Management of Diverticular Bleeding



Clipping of Diverticular Bleeding

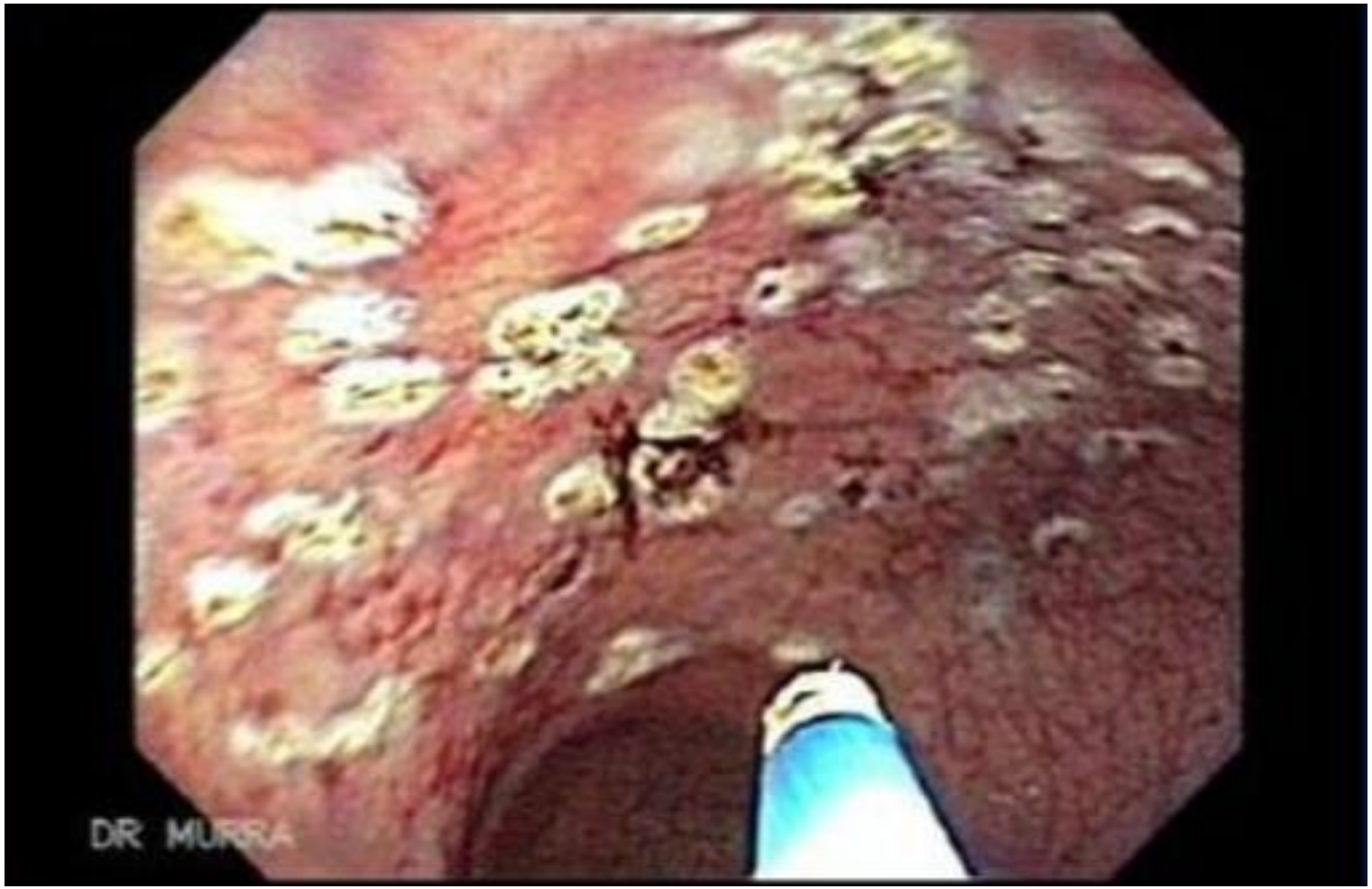


Angiography



- Green Arrow → Catheter
- Green Circle → Leak

Argon Plasma Coagulation Treatment for Radiation Colitis



Treatment

Medical:

- **IBD Flare:**

IV Hydration, IV Steroids & IV Antibiotics

- **Infectious Colitis:**

IV Hydration & IV Antibiotics

- **Ischemic Colitis:**

If there is no sign of perforation or infarction:

⮟

Bowel rest,
IV Hydration
± IV Antibiotics
& Correction of underlying condition

(More than 50% resolve on conservative management)

If there are signs suggestive of perforation or infarction

⮟

increasing tenderness, fever, ileus

⮟

Surgery

BEST OF LUCK ❤

WAIT FOR PART 4