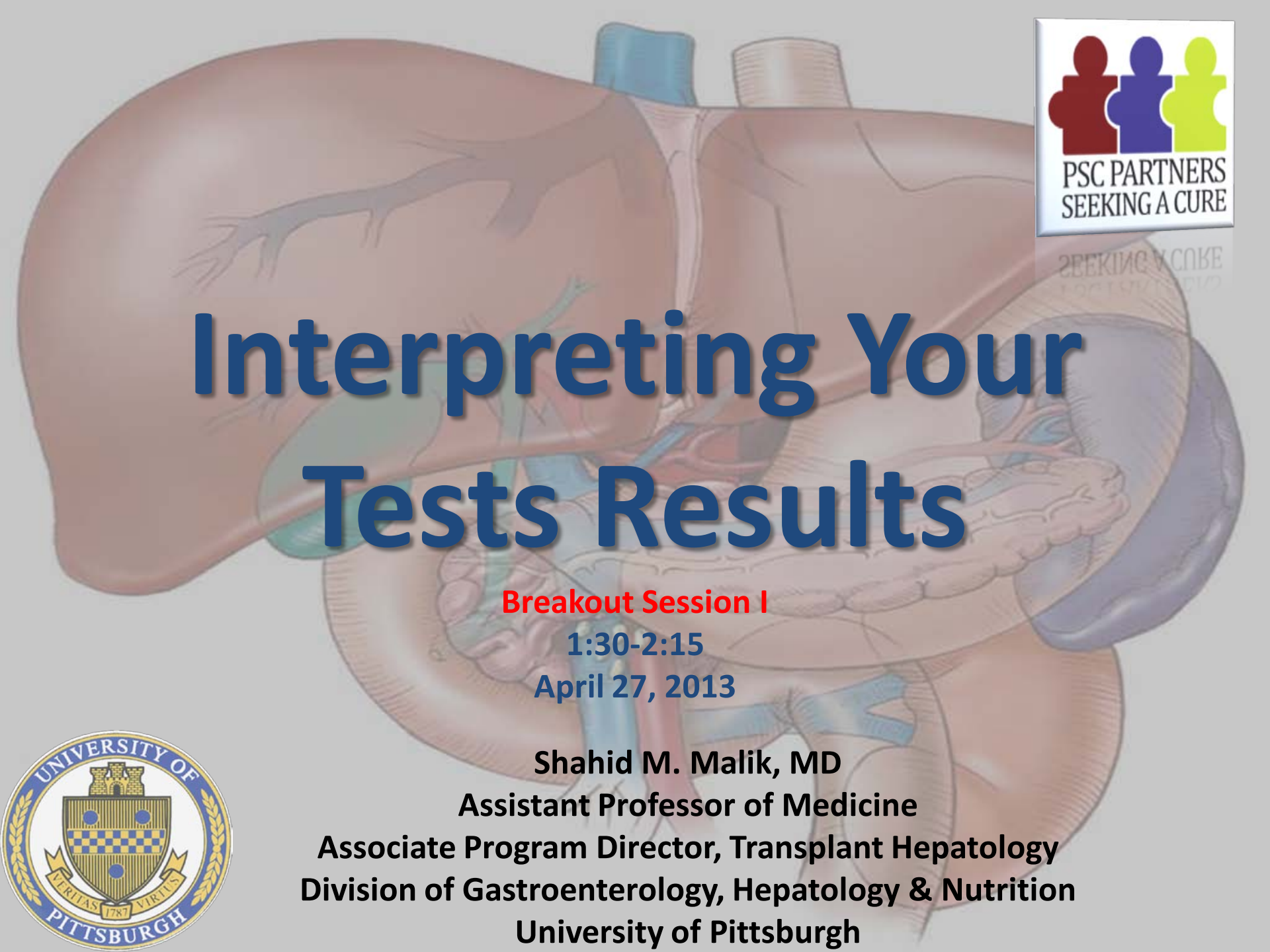


Interpreting Your Tests Results

Breakout Session I
1:30-2:15
April 27, 2013

Shahid M. Malik, MD
Assistant Professor of Medicine
Associate Program Director, Transplant Hepatology
Division of Gastroenterology, Hepatology & Nutrition
University of Pittsburgh

Tests routinely ordered (or at least discussed) in patients with PSC

- Blood Tests
- Imaging
- Liver Biopsy
- Endoscopy

I:

BLOOD TESTS

Liver Function Tests (LFTs)

- Important to differentiate between liver *tests* and liver *function*

Liver Function Tests
LFTs

- Total Bilirubin TBr (1.3)
  - Conjugated/unconjugated; direct/indirect
- Aspartate Aminotransferase AST (40)
  - Serum Glutamic Oxaloacetic Transaminase (SGOT)
- Alanine Aminotransferase ALT (40)
  - Serum Glutamic Pyruvic Transaminase (SGPT)
- Alkaline Phosphatase ALP (125)
- Gamma Glutamyltransferase GGT (55)

Hepatocytes

Biliary Epithelium

Markers of Liver Injury

Alkaline Phosphatase
ALP

- Generally speaking a marker of ‘biliary injury’.
  - Liver
  - Bone
  - Placenta
  - Intestine

Other causes of ALP elevation

GGT

- A more sensitive marker of biliary injury

Cholestatic

- 90% of patients with PSC will have elevated Liver enzymes
- The predominant liver injury in patients with PSC
  - AST/ALT is usually only minimally elevated
- The elevation in the cholestatic enzymes is typically mild/moderate

Other diseases causing Cholestatic liver injury

- 1. PBC
  - Typically seen in middle aged females; fatigue and itching are hallmark symptoms
- 2. Obstruction
  - Stones, stricture, malignancy
- 3. Infiltrative Diseases
  - Sarcoid, amyloid, lymphoma
- 4. Other
  - Sepsis, Congestive hepatopathy, TPN, cholestasis of pregnancy, BRIC, CF

LFTs

- Many times are not a good correlate of liver function
- Frustrating for patients and physicians
- The reason a fair amount of liver disease goes undiagnosed

54 year old male with alcoholic cirrhosis on the transplant list

- AST 29
- ALT 42
- AP 97
- GGTP 48

42 year old female with biopsy proven moderate/severe fatty liver disease

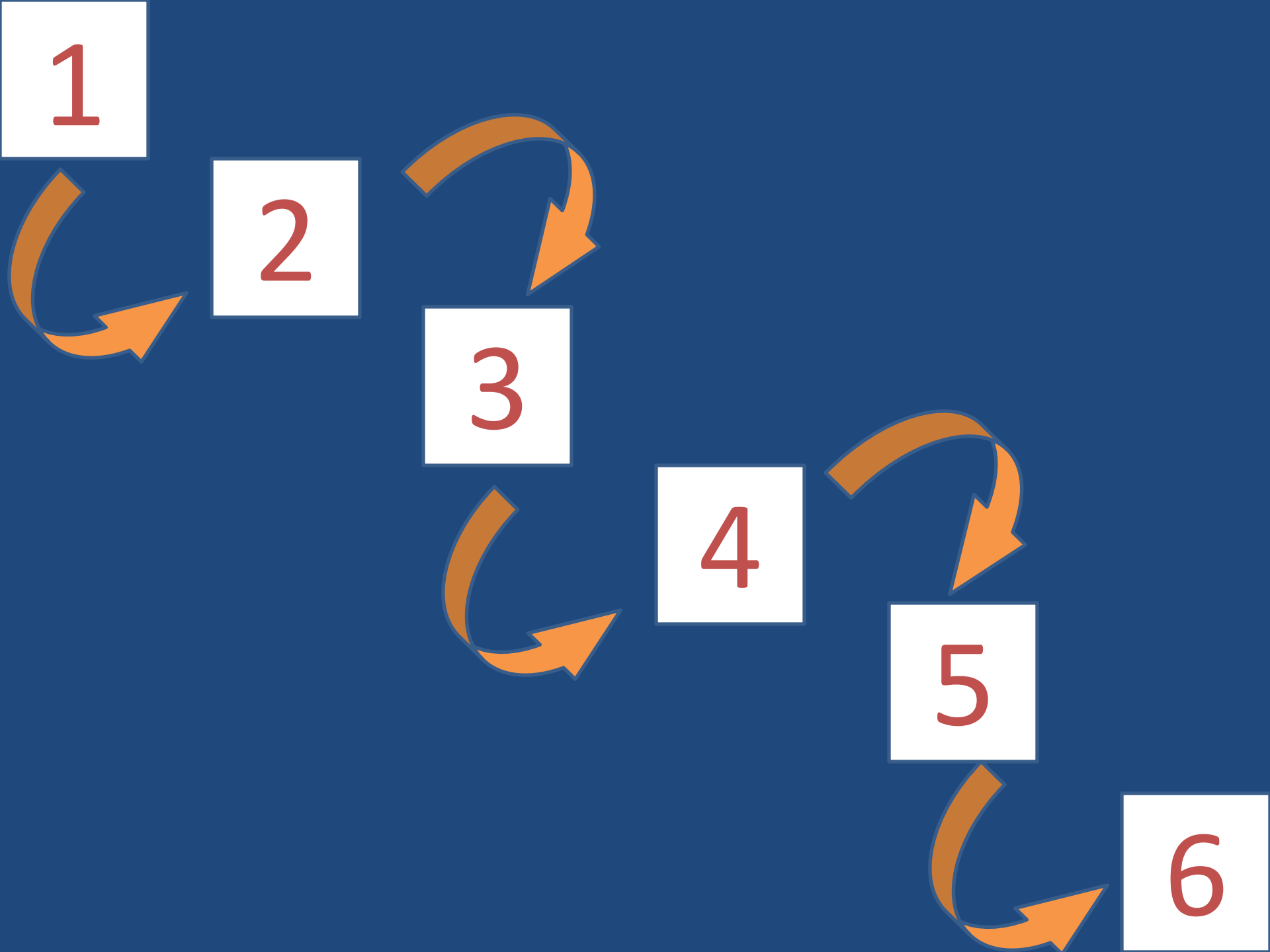
- ALT 57
- AST 49
- AP 128

58 y/o male with advanced PSC

- AST 22
- ALT 20
- AP 72
- GGTP 93

Cirrhosis

- Before we go further
- It is important that we understand the definition of
- Cirrhosis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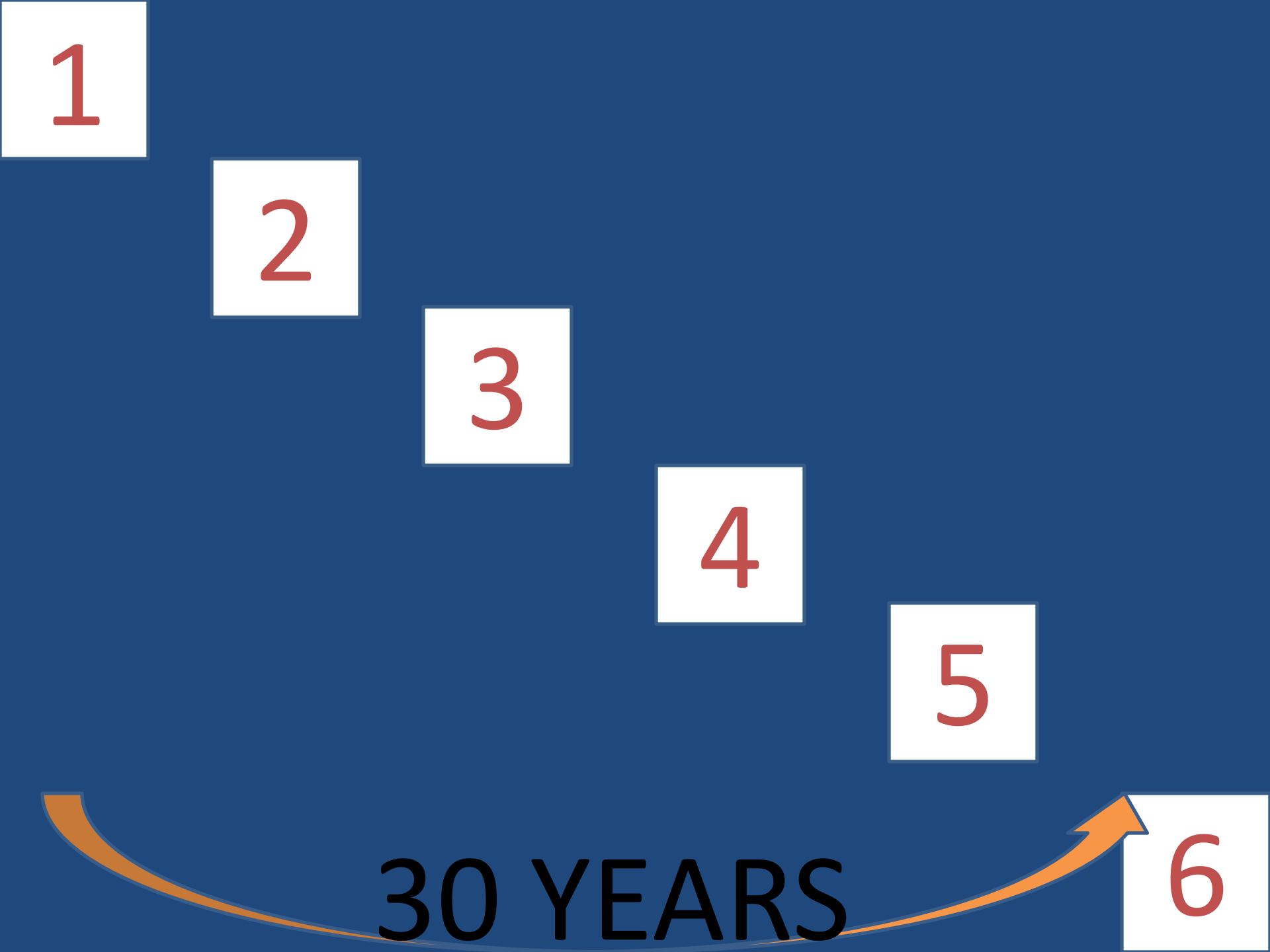
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30 YEARS

Varices/Bleeding

30%

HCC

Encephalopathy

Ascites

What are the most common causes of chronic liver disease in the US

- 1. NAFLD
- 2. HCV
- 3. ETOH
- 4. HC
- 5. HBV
- 6. AIH
- 7. PSC
- 8. PBC
- 9. A1ATD
- 10. Wilson

Synthetic Function of Liver

- Total Bilirubin
- Albumin
- Prothrombin Time
  - International Normalized Ratio (INR)

- These tests are incorporated into our models for staging ‘severity’ of liver disease
  - Childs Class
  - MELD score

Childs Classification

- When a patient has cirrhosis
- We then further classify the cirrhosis
- On an A, B, C scale

- Childs A meaning although there is advanced scar in the liver, it is still functioning well
- Childs C meaning the life expectancy without a liver transplant is not good

Child Turcotte Pugh Class

Clinical and Lab Criteria	Points*		
	1	2	3
Encephalopathy	None	Mild to moderate (grade 1 or 2)	Severe (grade 3 or 4)
Ascites	None	Mild to moderate (diuretic responsive)	Severe (diuretic refractory)
Bilirubin (mg/dL)	< 2	2-3	>3
Albumin (g/dL)	> 3.5	2.8-3.5	<2.8
Prothrombin time			
Seconds prolonged	<4	4-6	>6
International normalized ratio	<1.7	1.7-2.3	>2.3

Child-Turcotte-Pugh Class obtained by adding score for each parameter (total points)

Class A = 5 to 6 points (least severe liver disease)
Class B = 7 to 9 points (moderately severe liver disease)
Class C = 10 to 15 points (most severe liver disease)

Model End Stage Liver Disease MELD

- MELD = 3.78[Ln serum bilirubin (mg/dL)] + 11.2[Ln INR] + 9.57[Ln serum creatinine (mg/dL)] + 6.43
- Weighted
  - INR
  - Creatinine
  - Bilirubin

MELD score + blood type are the major determinants of *when* patients get transplanted

- 1. Score ranges from 6-40
- 2. Realistically speaking, most patients will not be transplanted until their scores > 20

This is why many patients with PSC are not well served by the MELD score

- Patient's can have very active disease
- Recurrent bouts of cholangitis
- Severe itching, fatigue etc…
- But have no dysfunction in their synthetic parameters

48 y/o male with UC and PSC

- 4 documented bouts of cholangitis (2 with bacteremia)
- Severe disease on CT scan and ERC
- Severe fatigue, anorexia
- TBr 1.6
- AST 94, ALT 98
- AP 642, GGTP 486
- INR 1.1, Cr 0.9
- Childs A, MELD 9

Gastroenterology and Hepatology in Minnesota

The Revised Natural History Model for Primary Sclerosing Cholangitis

In the following model, survival probability of a patient with primary sclerosing cholangitis is estimated based on the following variables. Please enter data in the corresponding boxes.

How old is the patient?	43	(years)
What is the bilirubin?	1.6	(mg/dl)
What is the albumin?	3.7	(g/dl)
What is the AST?	67	(IU/l)
Please choose one of the following for history of variceal bleeding.	(•) No history ( ) Past history	

Compute

Risk score: 0.67922

Estimated Probability of Survival (%)

Time 0	Year 1	Year 2	Year 3	Year 4
100	97	94	91	88

- Almost all patients with PSC will have elevations in their cholestatic enzymes (ALP and GGTP)
- Does this elevation correlate with disease severity or prognosis?

- The most recent evidence suggests that the answer to that question is:

- Yes

Reduction in ALP in patients with PSC is associated with improved survival

- Aim: to study the long term outcome of PSC patients on 'medium' dose UDCA (17-23 mg/kg)
- 198 patients
- Patients were categorized as biochemical responders if levels of ALP normalized or decreased by 40% after 1 year

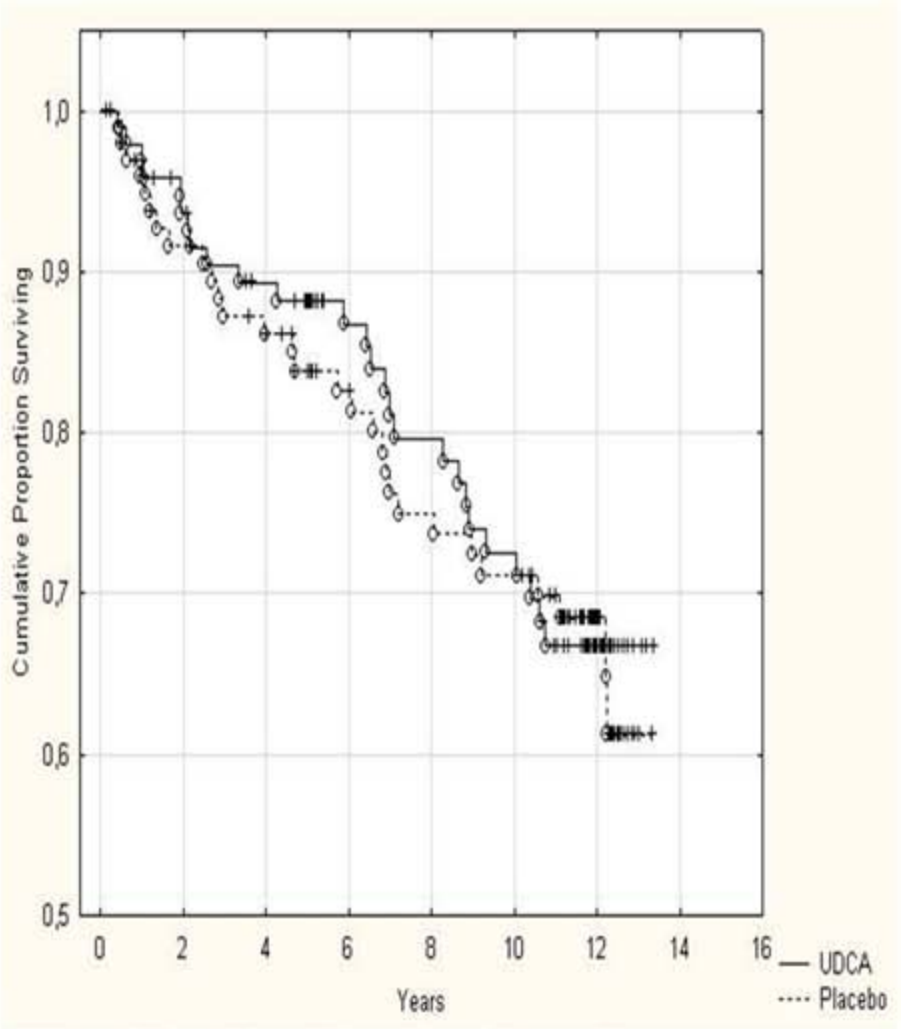
AASLD 2012

- There was no difference in survival between treated (97) and untreated (101) patients
- However, ALP-responders (regardless of UDCA) had a significantly better long term survival compared to non-responders (p 0.0001).

- Conclusions: Treatment with medium dose UDCA does not improve the long term survival in PSC patients.
- A reduction in ALP is associated with a better prognosis, regardless of UDCA treatment.

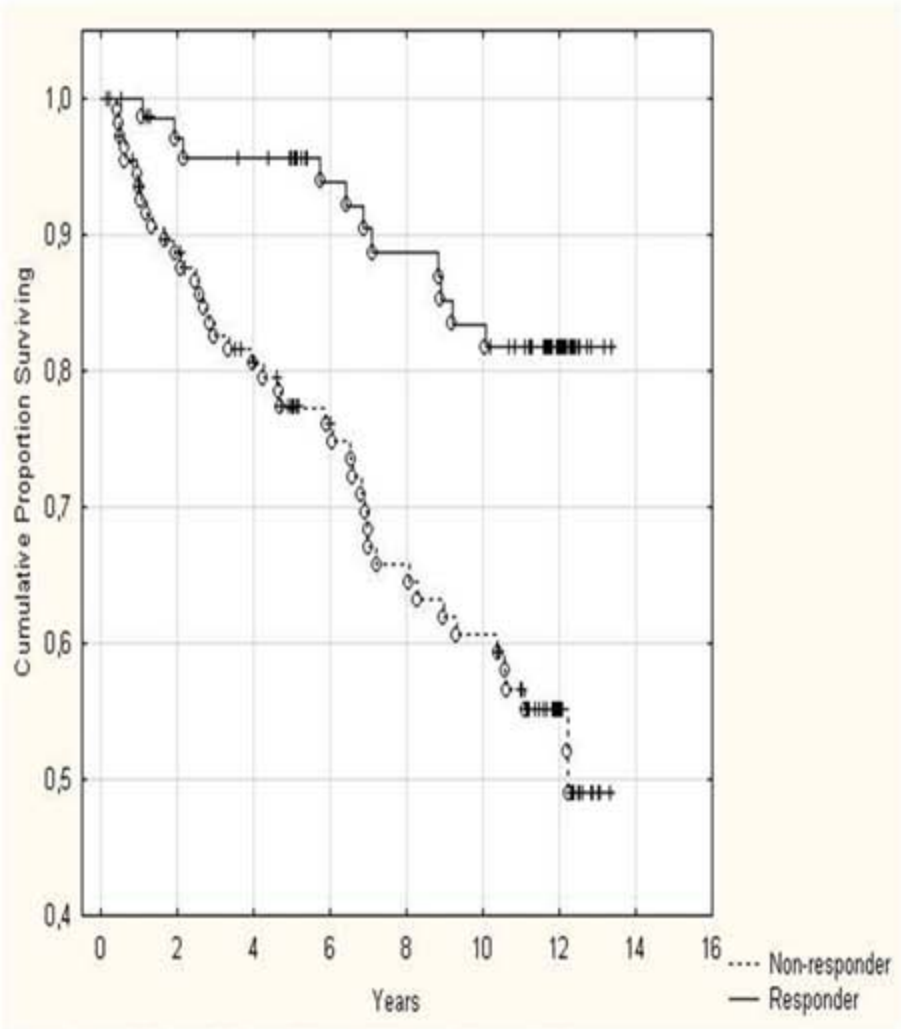
Kaplan-Meier analysis of survival UDCA vs. placebo and ALP-responders vs. non-responders

Figure 1a



UDCA	97	84	78	56	51	20
Placebo	101	84	72	59	56	19

b

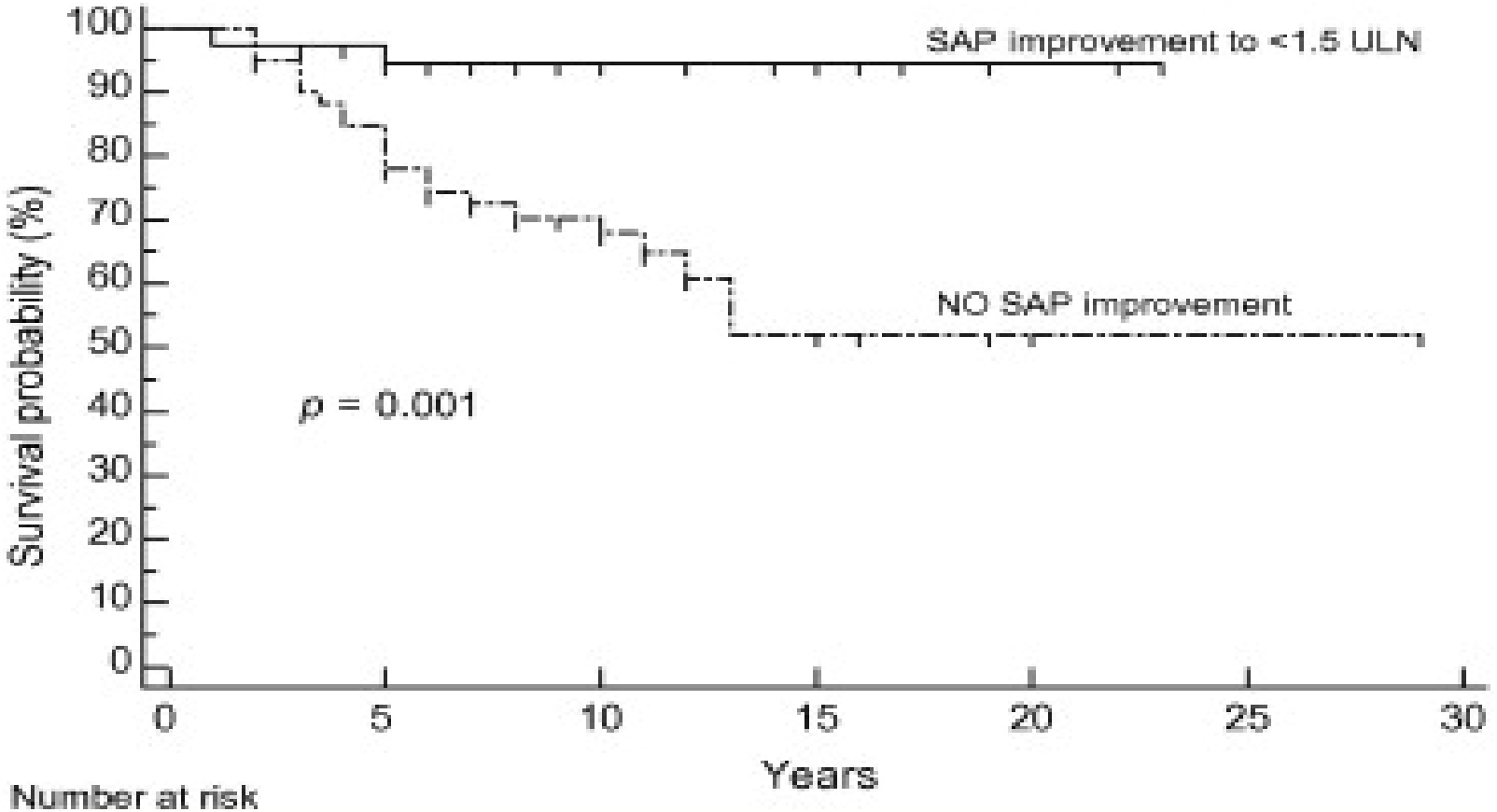


Responders	79	72	69	56	53	17
Non responders	116	93	78	56	52	21

JOH Feb 2013, Mamari et al

- This observation was supported in a more recent study were achievement of ALP to 1.5x normal correlated with improved survival
- 139 patients (63% males), followed mean 10 years
- 40% achieved AP less than 1.5x ULN
- 60% did not

End points



Number at risk

Group: SAP improvement to <1.5 ULN						
61	43	21	7	1	1	0
Group: No SAP improvement						
38	32	15	10	4	0	0

- 13/84 patients in the group who did not achieve improvement in ALP developed cholangiocarcinoma
- Versus none in the group that did improve

- The use of UDCA was similar in both group

What's the deal with UDCA and PSC?

- I don't know
  - I'm not sure anybody knows

- There are at least 10 studies showing UDCA leading to improvement in ALP
- So…

UDCA & PSC

- If normalization or near normalization of your ALP leads to a better prognosis
- &
- UDCA seems to improve alkaline phosphatase

- Can we infer that UDCA then leads to a better prongnosis????

High-Dose Ursodeoxycholic Acid for the Treatment of Primary Sclerosing Cholangitis

Keith D. Lindor,[1] Kris V. Kowdley,[2] Velimir A. C. Luketic,[3] M. Edwyn Harrison,[4] Timothy McCashland,[5] Alex S. Befeler,[6] Denise Harnois,[7] Roberta Jorgensen,[1] Jan Petz,[1] Jill Keach,[1] Jody Mooney,[2] Carol Sargeant,[3] Tamara Bernard,[5] Debra King,[6] Ellen Miceli,[7] Jeff Schmoll,[8] Tanya Hoskin,[8] Prabin Thapa,[8] and Felicity Enders[8]

- Long-term, high-dose UDCA therapy is associated with improvement in serum liver tests (TBr, AST and ALP) in PSC but does not improve survival and was associated with higher rates of serious adverse events.

- 150 patients
- Randomized, double-blinded, placebo, controlled
- High dose UDCA (28-30mg/kg) versus placebo
- 76 UDCA group versus 74 placebo

Table 3. Biochemical Labs

	n		Alkaline Phosphatase			Aspartate Aminotransferase			Bilirubin		
	UDCA	Placebo	UDCA	Placebo	*P* Value	UDCA	Placebo	*P* Value	UDCA	Placebo	*P* Value
Baseline	76	73	3.3 (0.7-11.2)	3.2 (0.5-16.9)	0.814	2.0 (0.5-6.9)	2.3 (0.5-9.4)	0.684	0.8 (0.2-3.2)	1.0 (0.2-5.5)	0.100
12 Months	70	63	1.9 (0.6-9.1)	2.9 (0.6-13.6)	<0.001	1.0 (0.5-10.5)	1.9 (0.6-8.7)	<0.001	0.8 (0.2-6.3)	0.9 (0.3-8.2)	0.074
24 Months	65*	59†	1.8 (0.6-8.5)	2.6 (0.5-11.9)	0.001	1.1 (0.4-8.4)	1.9 (0.5-13.3)	<0.001	0.8 (0.2-7.2)	1.0 (0.2-8.6)	0.393
36 Months	56‡	53	1.7 (0.6-16.5)	2.4 (0.4-12.1)	0.012	1.1 (0.3-7.2)	1.7 (0.5-14.8)	<0.001	0.8 (0.2-15.9)	0.9 (0.3-9.6)	0.037

Data are presented as the median (range) unless otherwise indicated.

*At 24 months, only 64 patients were tested for bilirubin in the UDCA group.

†At 24 months, only 58 patients were tested for alkaline phosphatase in the placebo group.

‡At 36 months, only 55 patients were tested for bilirubin in the UDCA group.

- Despite better LFTs at the end of the study
- 39% of patients in UDCA group went on to develop: cirrhosis, varices, cholangio, need for LT or death
- Versus 26% in placebo

- More patients in UDCA group develop adverse side effects

AASLD PRACTICE GUIDELINES

Diagnosis and Management of Primary Sclerosing Cholangitis

Roger Chapman,[1] Johan Fevery,[2] Anthony Kalloo,[3] David M. Nagorney,[4] Kirsten Muri Boberg,[5] Benjamin Shneider,[6] and Gregory J. Gores[7]

Recommendations:

28. In adult patients with PSC, we recommend against the use of UDCA as medical therapy (1A).

29. In adult patients with PSC and overlap syndrome, we recommend the use of corticosteroids and other immunosuppressive agents for medical therapy (1C).

Was this premature?...Perhaps

- Seems (to me) as if patients fall into two groups
- Aggressive course
- Relatively mild/benign course

- Does UDCA have any role in altering the course of the disease?

- This remains a topic of immense controversy
  - With no clear consensus
- High dose UDCA seems to be harmful
- Is there a medium/lose dose that may be of benefit to a select group of patients with PSC?

- Ie UDCA responders

Off the Record:

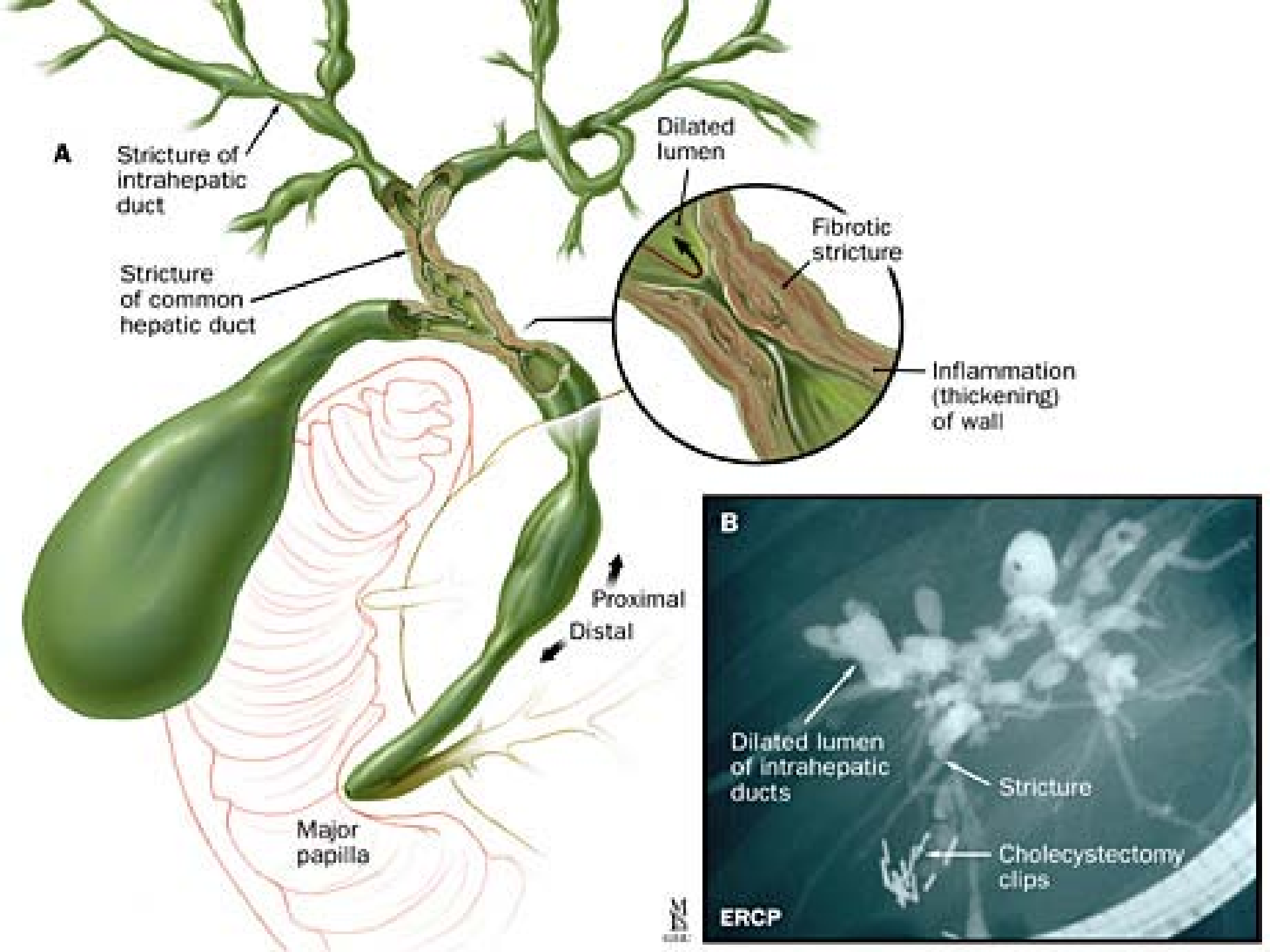
- Trial of (low/medium dose) UDCA 1-2 years
- If you are able to decrease a patient's ALP to 1.5 ULN (or by 40% of original?)
- This patient may be a UDCA 'responder'
- And may in fact benefit

- Bottom line: we need better medical therapy for PSC!

Etiology of PSC

- Remains unknown
- ? Genetic
- ? Inflammatory reaction
  - Infection (bacteria)
  - Toxin
- ? Vascular

- ? Autoimmune


A
Stricture of intrahepatic duct
Dilated lumen
Fibrotic stricture
Stricture of common hepatic duct
Inflammation (thickening) of wall
Proximal
Distal
Major papilla
B
Dilated lumen of intrahepatic ducts
Stricture
Cholecystectomy clips
ERCP

Autoantibodies

- At least one + Autoantibody seen in up to 97% of patients with PSC
- Antinuclear, Smooth Muscle, Immunoglobulins, Rheumatoid Factor
- Clinical significance of this is unclear and the presence of these antibodies does not seem to correlate with disease severity.

- Very rarely patients with PSC can have an overlap with other ‘autoimmune’ liver disease
- Ie: autoimmune hepatitis (AIH)

- AST/ALT higher than you would expect in ‘typical PSC’
- In the right clinical scenario, a liver biopsy may help distinguish this further

IgG4

- Subclass of immunoglobulins/antibodies
- Associated with plasma cells and T lymphocytes
- Have been linked to a variety of conditions
- Most famously ‘Autoimmune pancreatitis’
- One of the hallmarks of these diseases is their exquisite responsiveness to steroid therapy

Abstract from AASLD 2012

- Serum IgG4 was prospectively measured in 194 patients with PSC
- 26 patients had an elevated IgG4 (14%)
- IgG4 patients were more likely to decompensate, require liver transplant or die
- Mean f/u ~ 8 years
- 7/26 patients received a trial of steroids
- 71% had a ‘favorable’ clinical response

- I am checking IgG4 on all my patients with PSC
- Current guidelines support this practice

- What exactly to do with a positive result remains debatable
  - PSC with IgG4 or
  - IgG4 associated cholangiopathy (IAC)
- In the right clinical scenario a liver biopsy and trial of steroids is reasonable

PSC and Cancer

- Lifetime risk of bile duct cancer (cholangiocarcinoma) is 10-15% in patients with PSC
- Patients with PSC + cirrhosis are at a risk of developing primary liver cancer
- Risk of GB cancer
  - 3-14%
- Risk of Colon Cancer
  - Directly related to presence of IBD

Tumor Markers

- Ca 19-9
  - Not sensitive to cholangiocarcinoma
    - Pancreatic Cancer
    - Elevation can be seen in non-malignant conditions (esp cholangitis, jaundice)
  - A level of > 200 should increase suspicion for choalngio, especially the in setting of dominant stricture
  - An upward trend in a patients with chronic PSC should raise concern

CEA

- Elevated in multiple conditions:
  - Colon cancer
  - Liver disease ‘in general’
  - Inflammatory states
  - Non GI diseases (COPD, Diabetes)
- A level of > 5.2 (in the right setting) should raise concern
- ----------
- Study from UPCM (GIE 2002) noted an abnormal CEA + an abnormal Ca 19-9 (combo) was better than either test alone in detecting cholangiocarcinoma

AFP

- A level of > 20 in a patient with advanced liver disease should raise concern
- Up to 50% of patients with HCC will have no elevation in AFP
  - AFP not clearly recc as a surveillance tool by current AASLD guidelines

- The risk of HCC in patients with PSC is almost exclusively seen in the setting of cirrhosis
  - PSC patients not directly named in list of surveillance population in AASLD guidelines

Tumor Marker Surveillance

- Most experts recc CA 19-9 (+/- CEA) yearly
  - No strong evidence to support this
- AFP – controversial
  - In a patient with cirrhosis q 6 months is reasonable

Fat Soluble Vitamins

- D, A, K and E
  - D: bone deficiencies
  - A: night blindness
  - K: bleeding disorders
  - E: neurologic symptoms
- Should be checked in patients with PSC
- Supplemental therapy should be administered when necessary

II:

IMAGING

Ultrasound

- Low risk (no radiation)
- Low cost (comparatively speaking)
- User dependent
- Decent initial test of hepatic parenchyma
  - Can also assess vessel patency
- Good for evaluation of gallbladder (stones, polyps, masses)
- Good for evaluation of bile duct stone, large CBD stricture
- Not particularly good in patient's with advanced disease
- Remains the test of choice for surveillance of HCC
  - AASLD

Computed Tomography
CT scan (with contrast)

- Fast
- Can evaluate entire abdominal viscera
  - Pancreas, stomach, intestines, kidneys
- Not affected by obesity
- Better at distinguishing masses, hepatic parenchyma
- Vasculature can also be assessed
- Disadvantages
  - Cost
  - Radiation Exposure
  - Contrast
    - Renal Injury

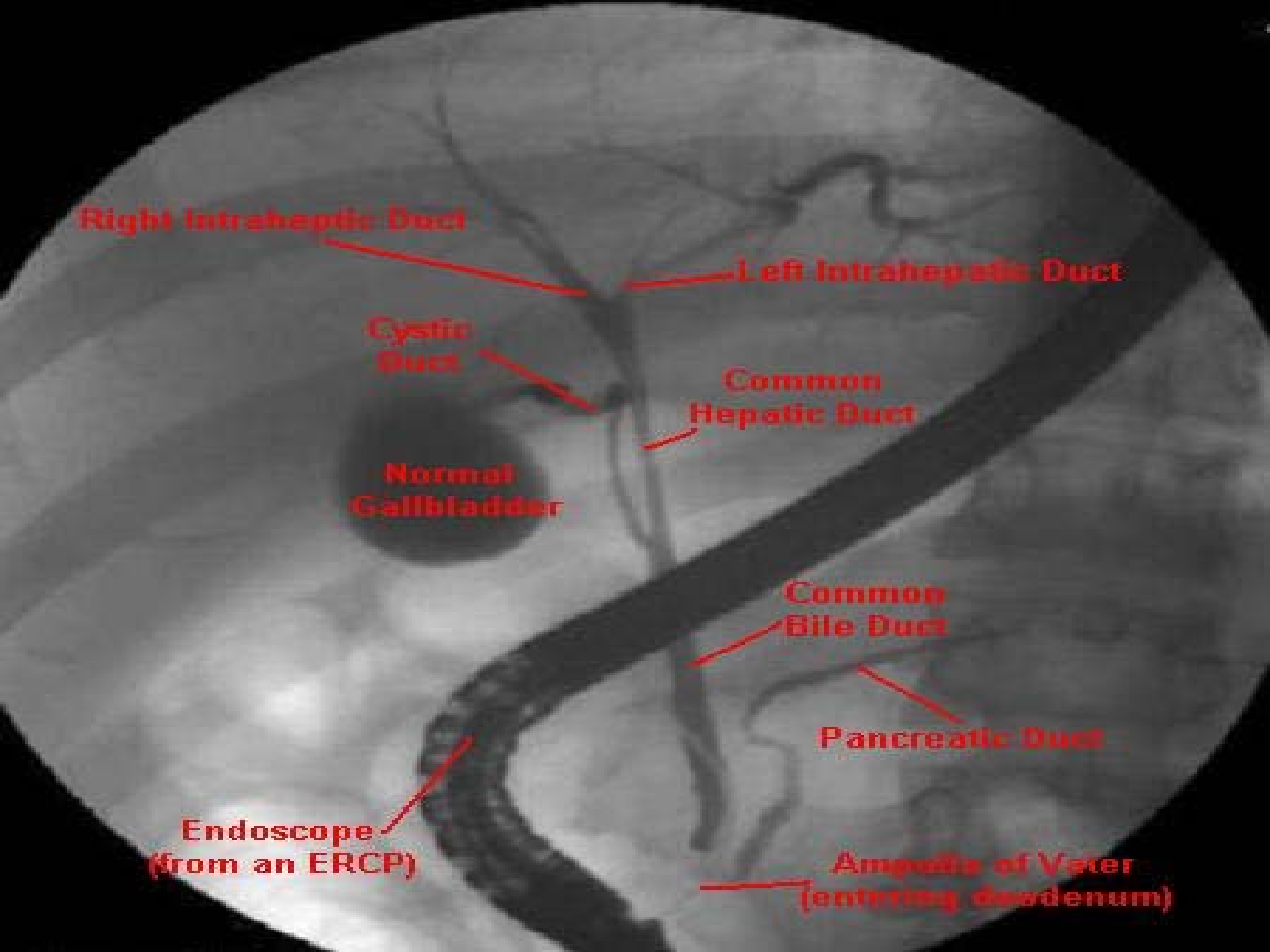
Magnetic Resonance Imaging

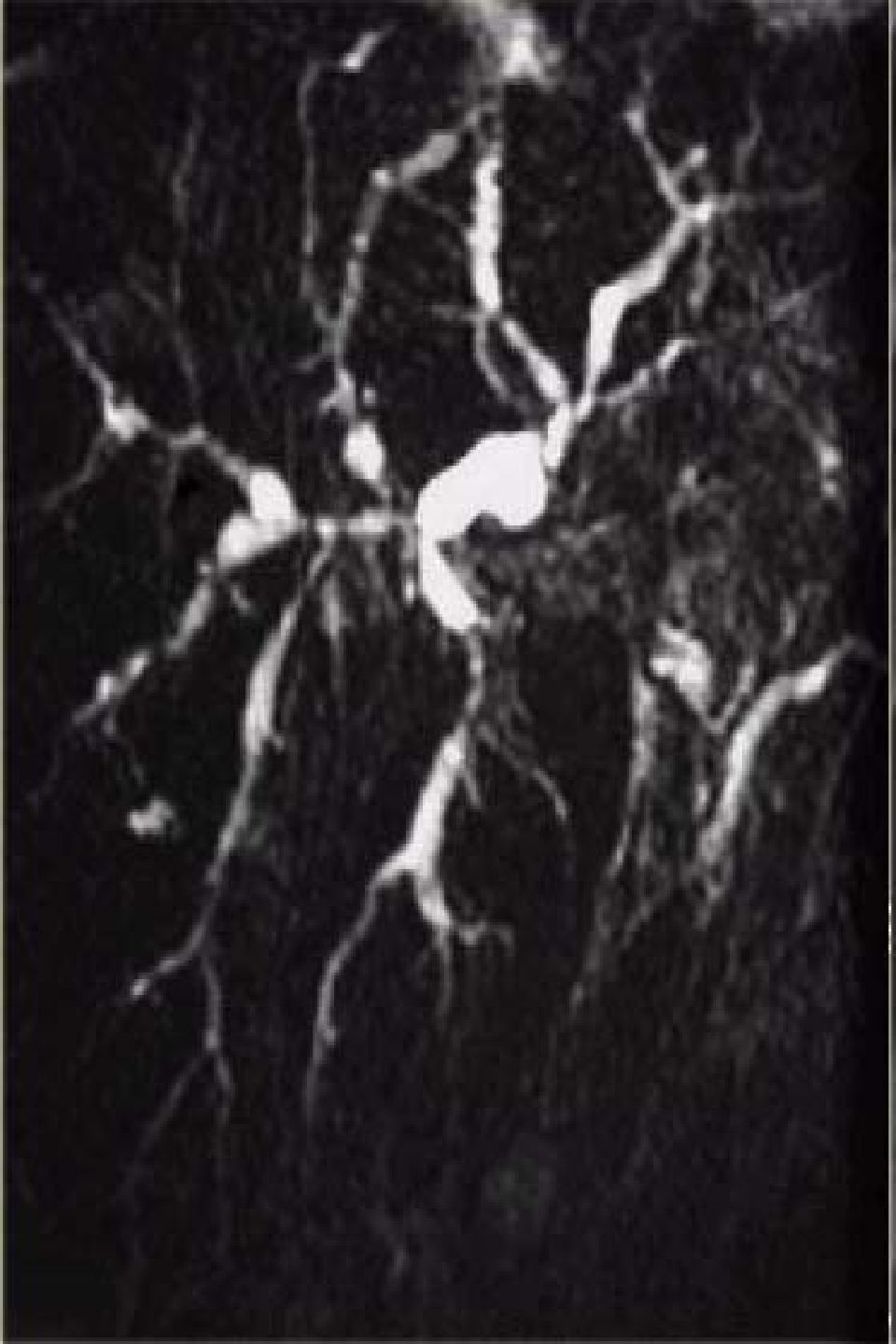
- Magnetic Resonance Imaging
- Comparable in efficacy in detecting lesions
  - Probably slightly better
  - Lesion in question on CT almost always prompts MRI
- Advantages
  - No radiation
- Disadvantages
  - Cost
  - Takes longer (patient has to be cooperative – claustrophobia)
  - Pacers/metal
  - Renal Insuff?
  - Difficult to read

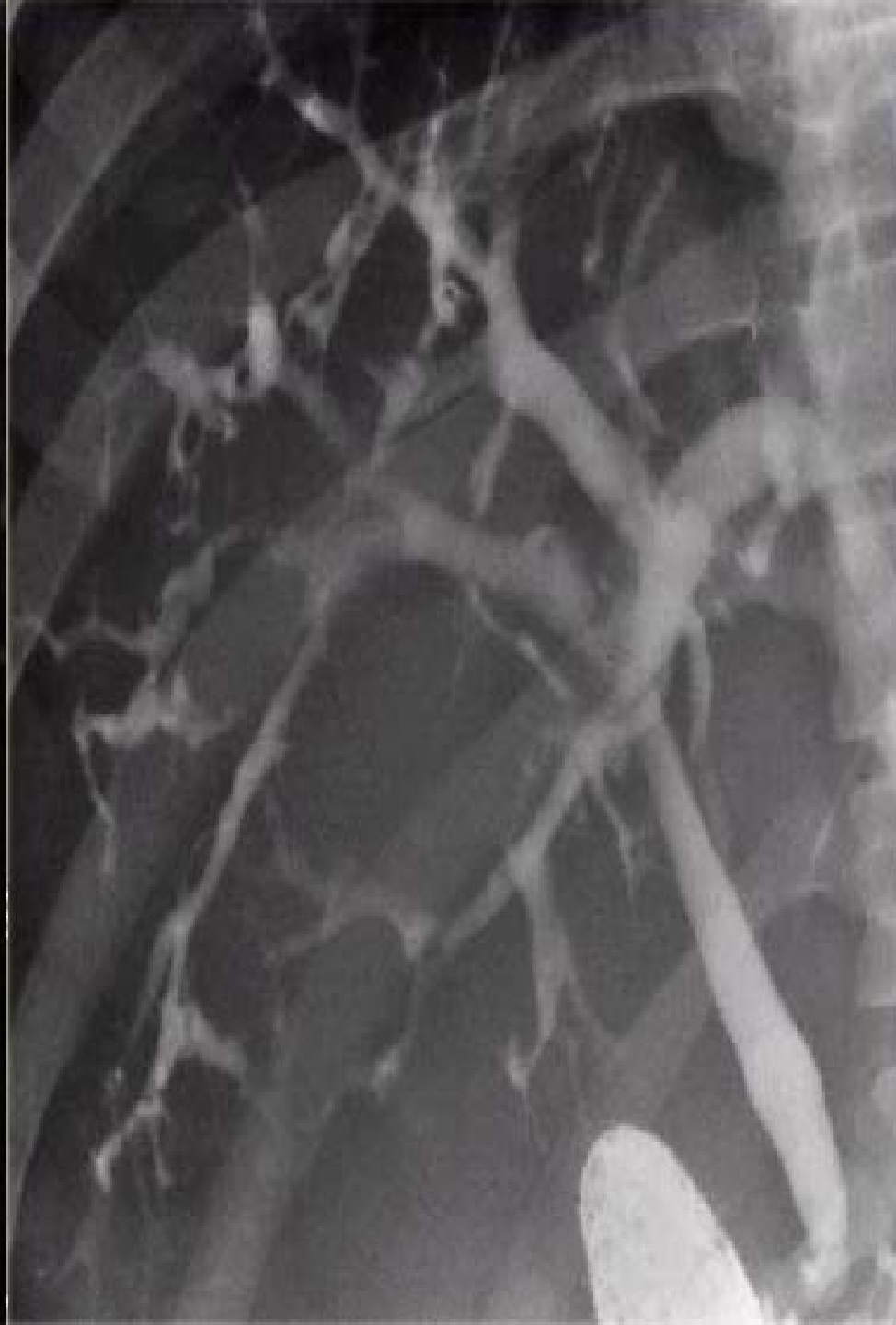
Cholangiogram

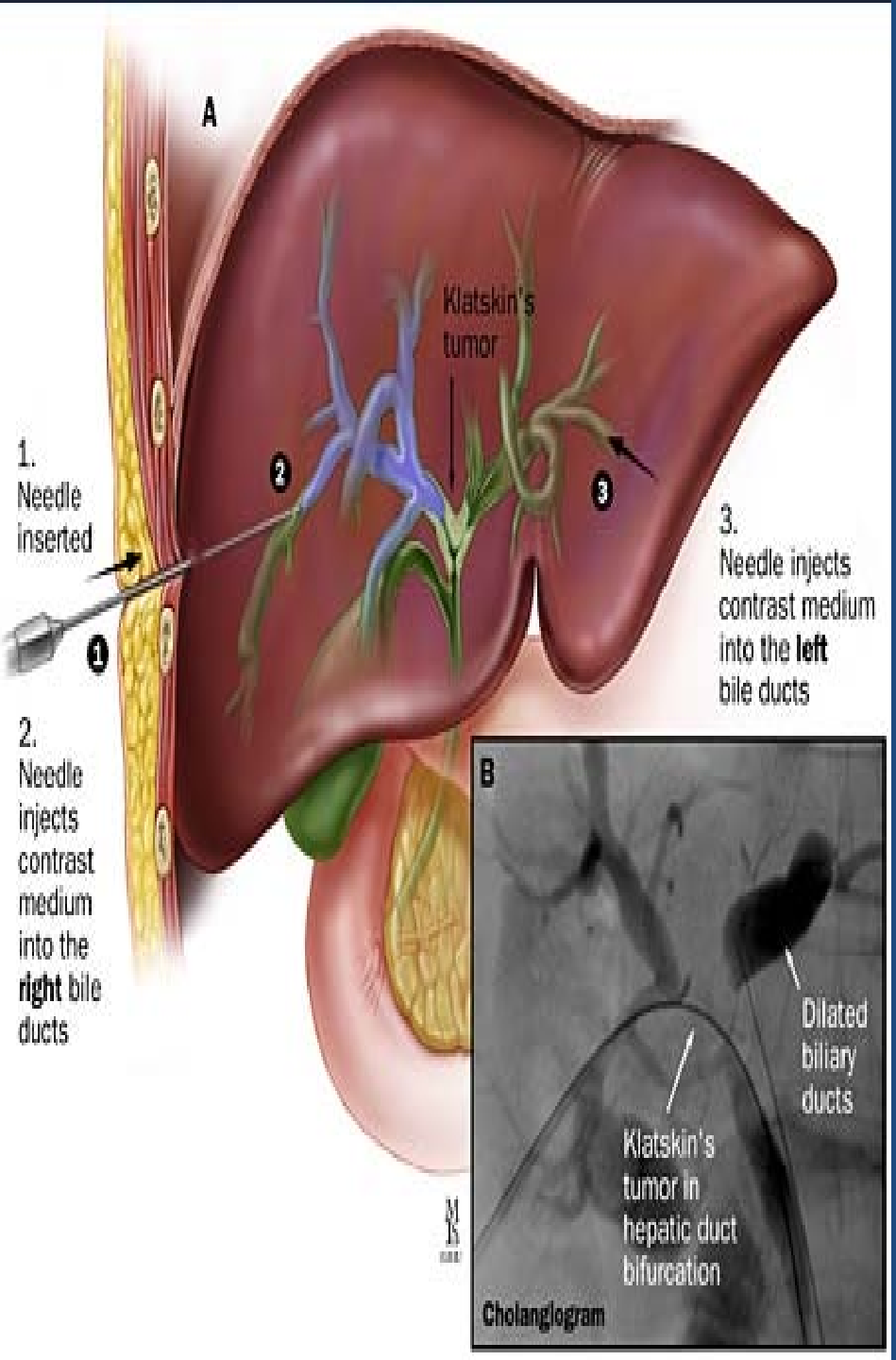
Radiographic evaluation of biliary system

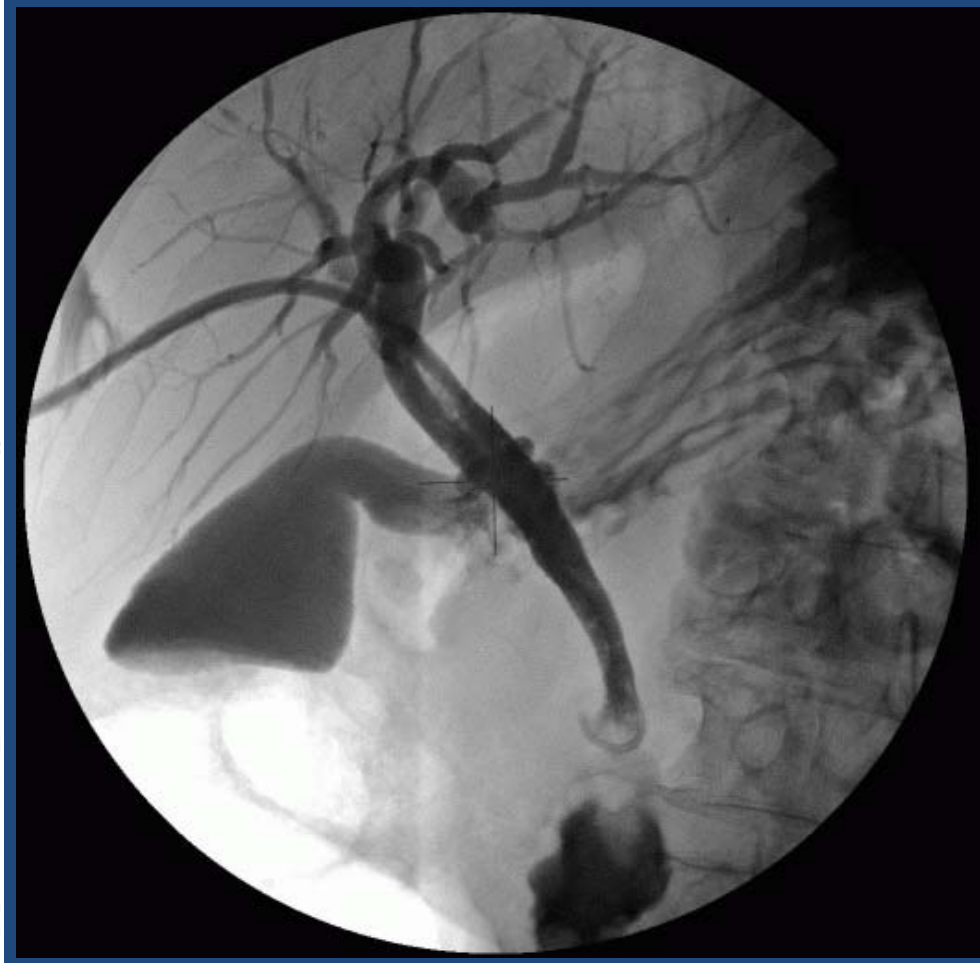
- MR
  - radiology
- ERC
  - endoscopy
- PTC
  - Interventional radiology


Right Intrahepatic Duct
Left Intrahepatic Duct
Cystic Duct
Common Hepatic Duct
Normal Gallbladder
Common Bile Duct
Pancreatic Duct
Endoscope (from an ERCP)
Ampulla of Vater (entering duodenum)






A
Klatskin's tumor
1. Needle inserted
2. Needle injects contrast medium into the right bile ducts
3. Needle injects contrast medium into the left bile ducts
B
Dilated biliary ducts
Klatskin's tumor in hepatic duct bifurcation
Cholanglogram



- MRCP has become the diagnostic test of choice for evaluation of biliary system

- Ie: You're evaluating a patient with ulcerative colitis and they have a persistent elevation in ALP.
- The test to order is an MRCP.

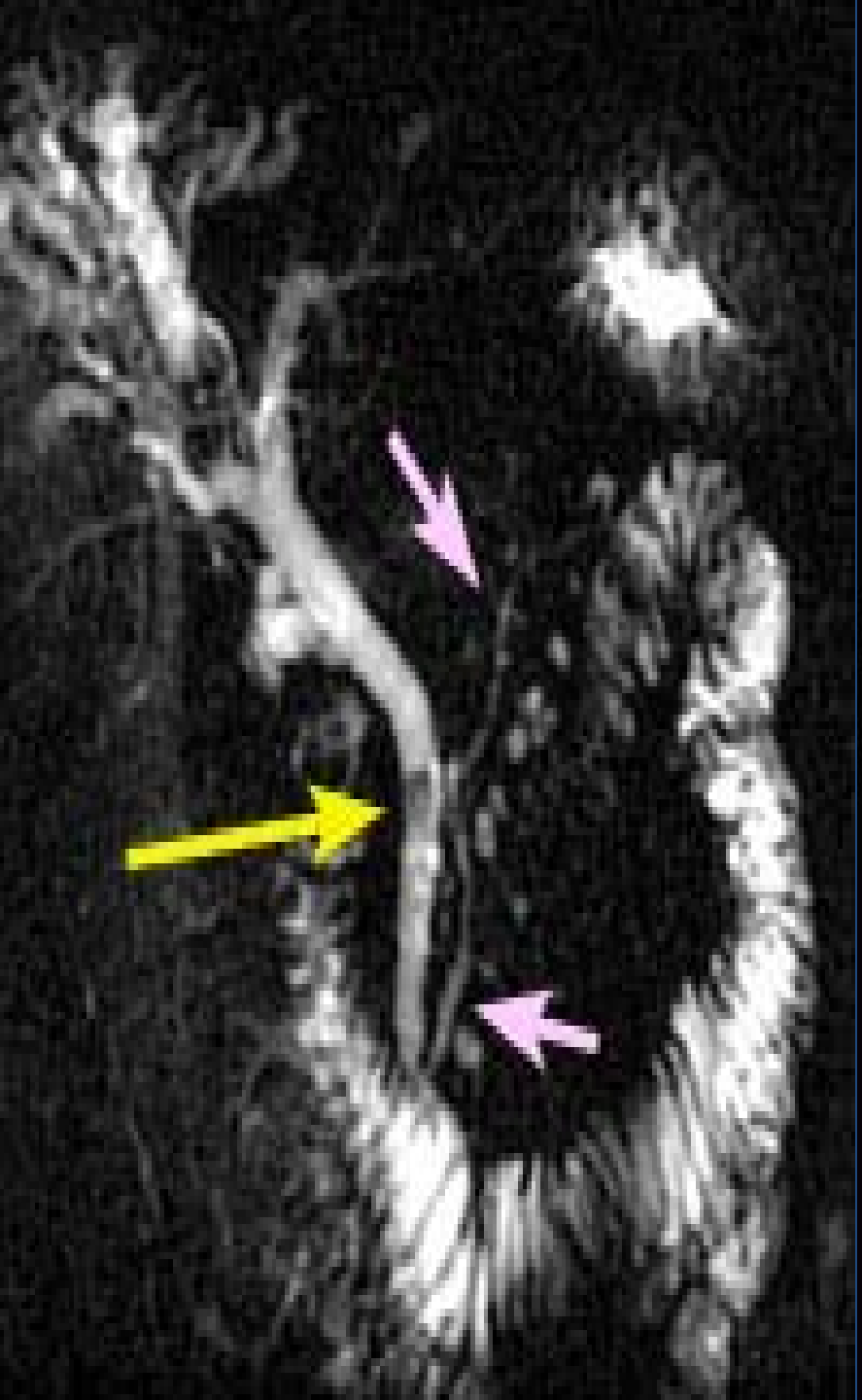
PSC and MRCP

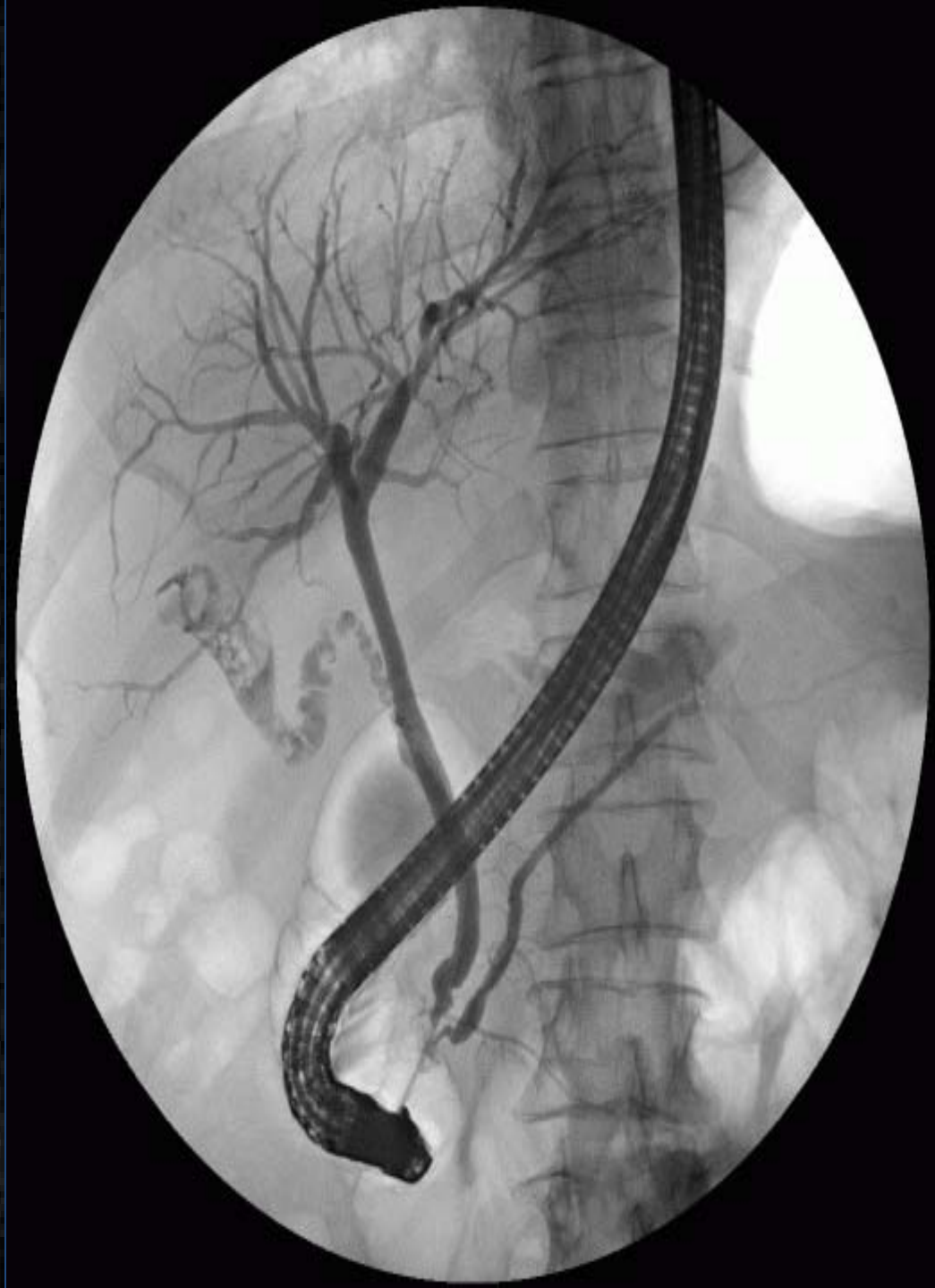
Dave M, et al; Radiology August 2010

- 185 patients with PSC
- ERCP and PTC as reference standard
- MRCP had a sensitivity and specificity 85% and 94% respectively

- In most cases of suspected PSC, MRCP Is sufficient for diagnosis, and thus, the risks associated with ERCP can be avoided

- When there is an otherwise unexplained elevation in a patients labs
  - Rise in TBr
  - Increase in Cholestatic Enzymes
  - Elevation in Ca 19-9/CEA
- Most will go to MRCP prior to ERC





Osteoporosis

- 15% of patients with PSC
- 24x higher than the regular (age, sex matched) population
- Risk factors for osteoporosis in patients with PSC
  - Risk factors for OP in patients with PSC
    - Age > 54 years
    - BMI < 24
    - + Long standing IBD

Dual-**E**nergy **X**-ray **A**bsorptiometry

- DEXA
- The most widely used method to measure bone mineral density
- Recommend by AASLD in all patients with PSC at the time of diagnosis and then q2-3 years after

III:

LIVER BIOPSY

- PSC is one of the few liver diseases where liver biopsy is NOT the gold standard in diagnosis
- AASLD guidelines recommends against routine liver biopsy for diagnosis of patients with PSC with typical cholangiographic findings
- Because of the nature of PSC, there is a high degree of sampling error (in terms of fibrosis)

Liver Biopsy in patients with PSC

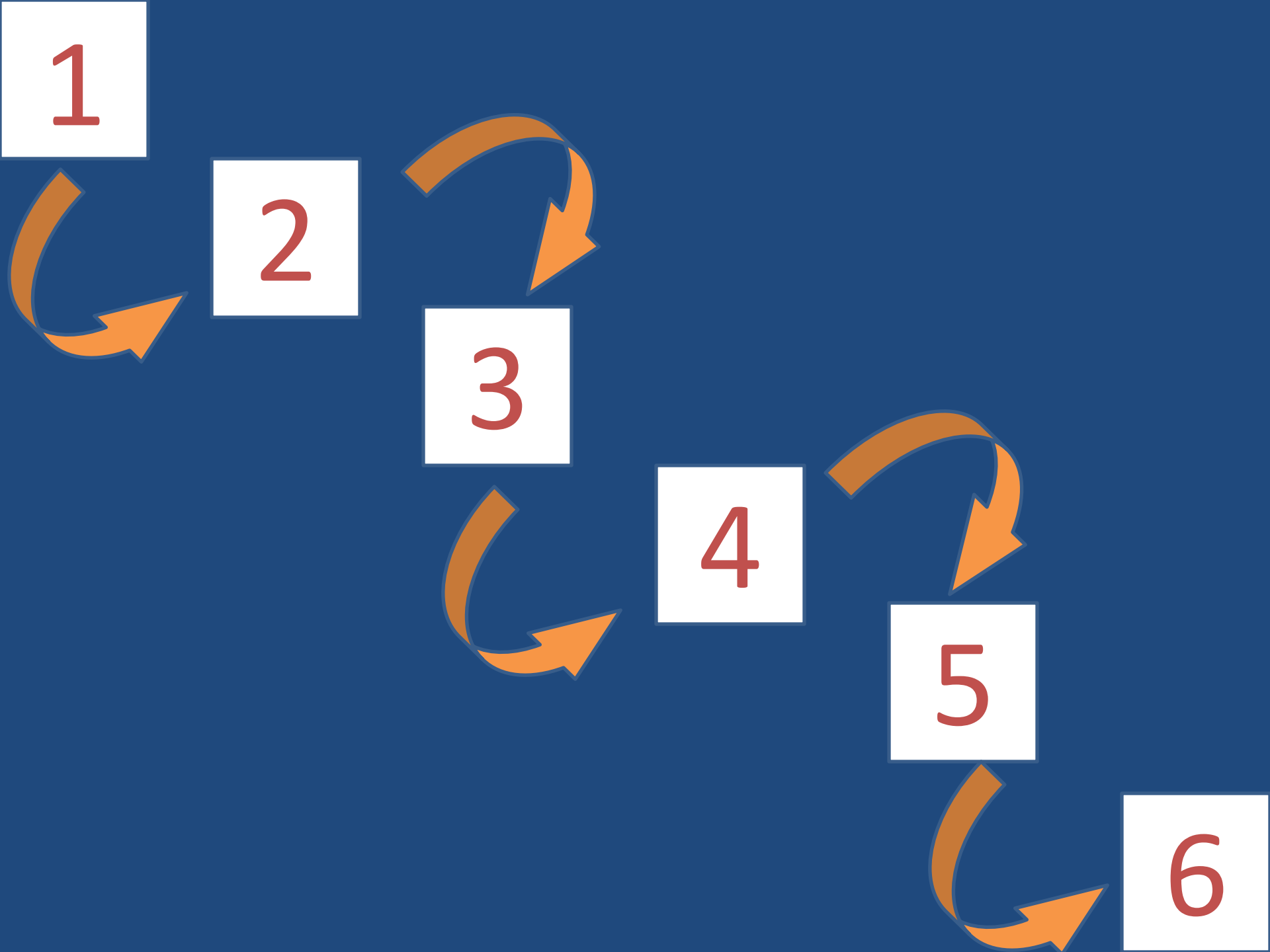
- It can however be helpful in patients with
  - Suspicion of very early disease
    - Small duct PSC
  - Sometimes is the only way to determine exactly how much scar tissue has developed in the liver
  - Patients with overlap (PSC/Autoimmune)
  - ? Patients with IgG4

- Some experts recommend that antibiotics be given to patients with PSC prior to liver biopsy in order to minimize risks of cholangitis

IV:

ENDOSCOPY

- 1. EGD
  - Surveillance of portal hypertension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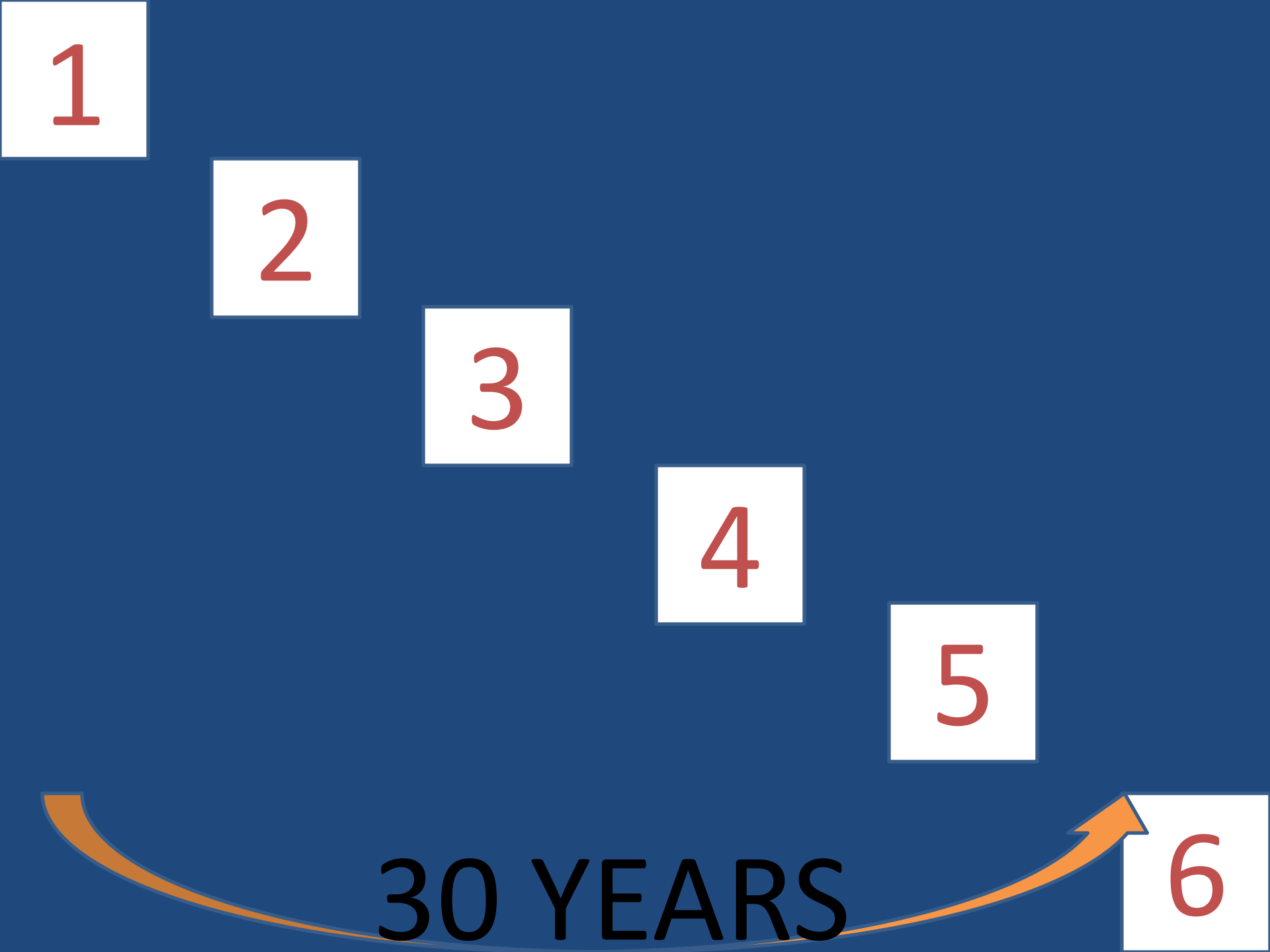
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30 YEARS

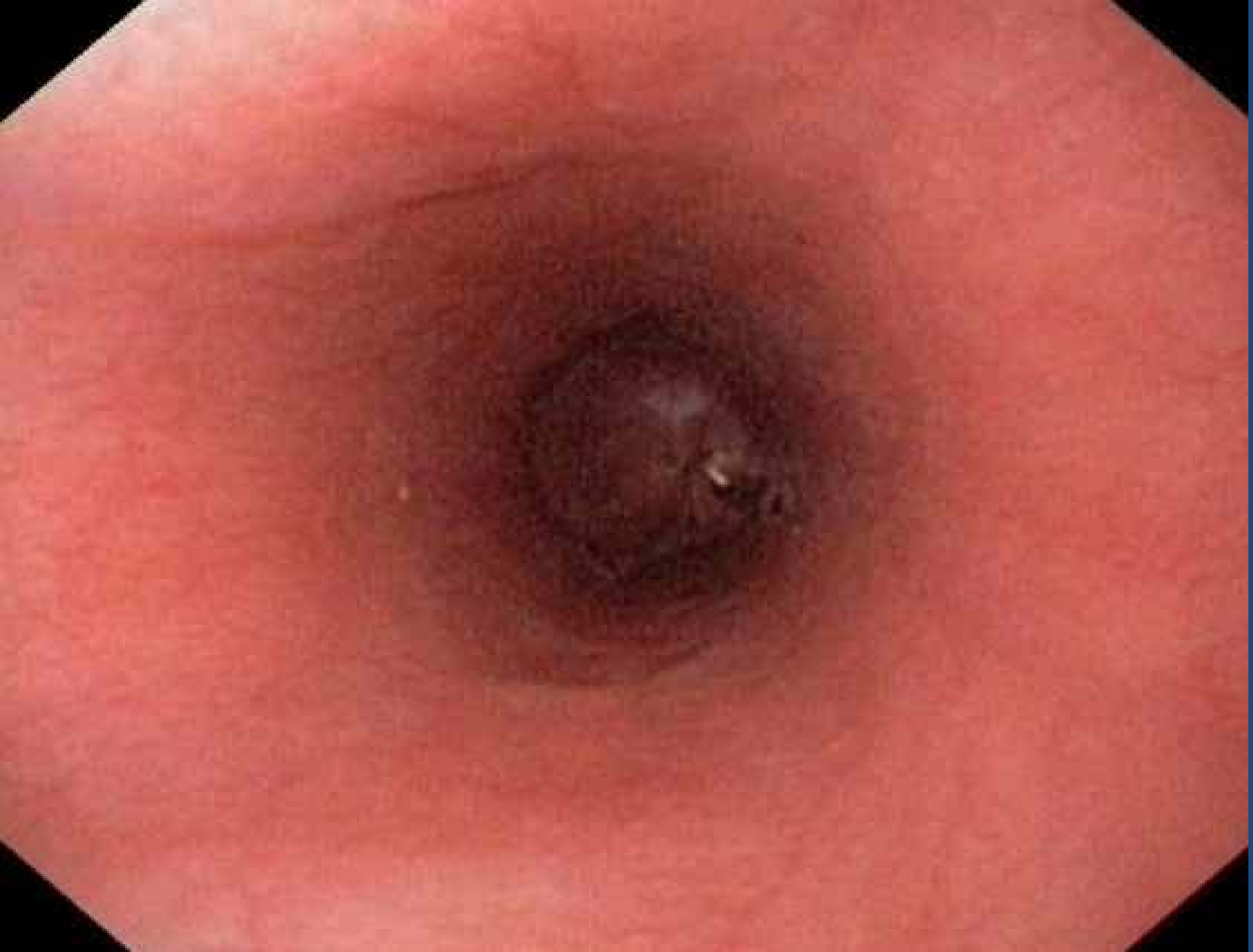
Varices/Bleeding

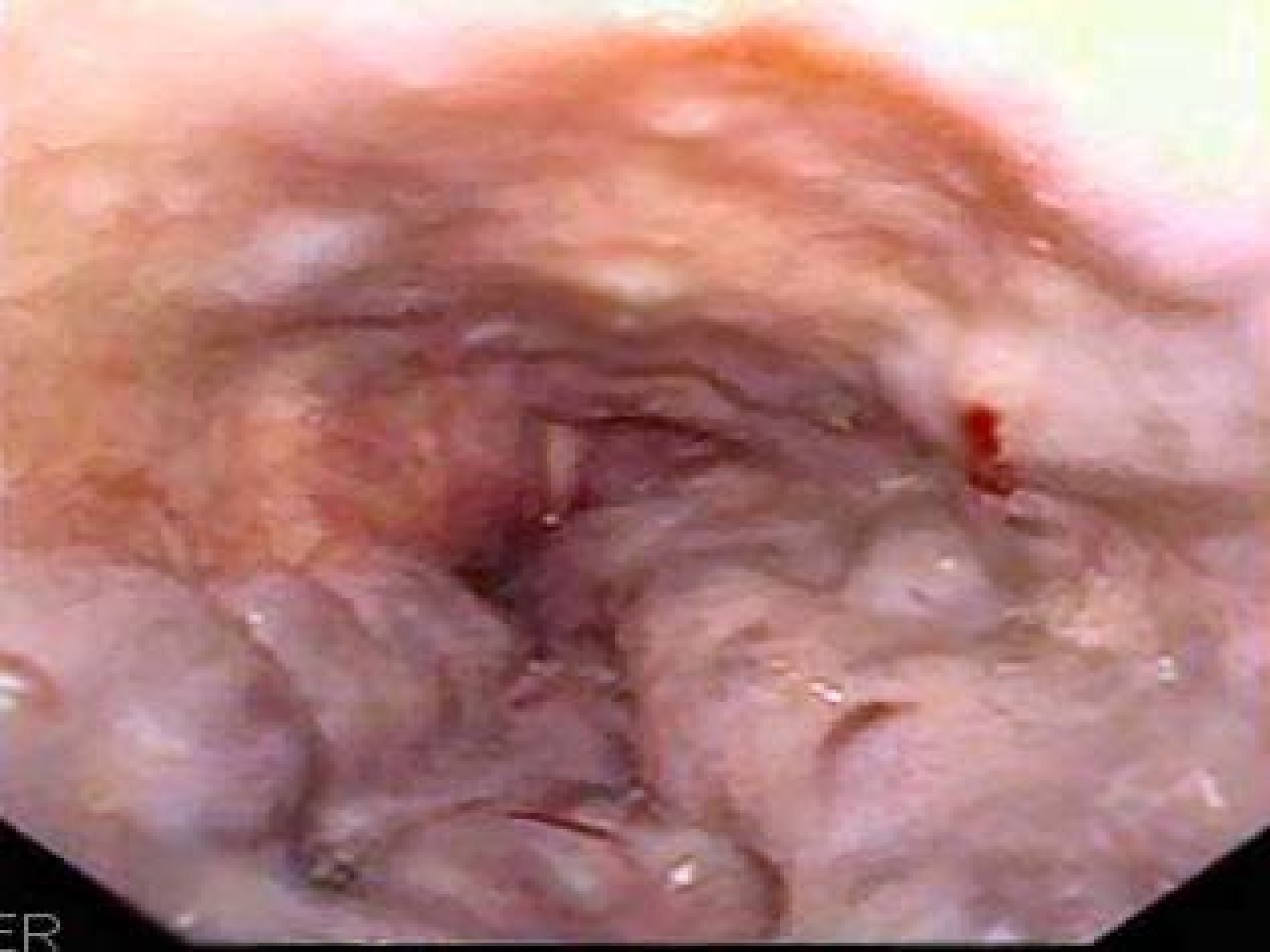
30%

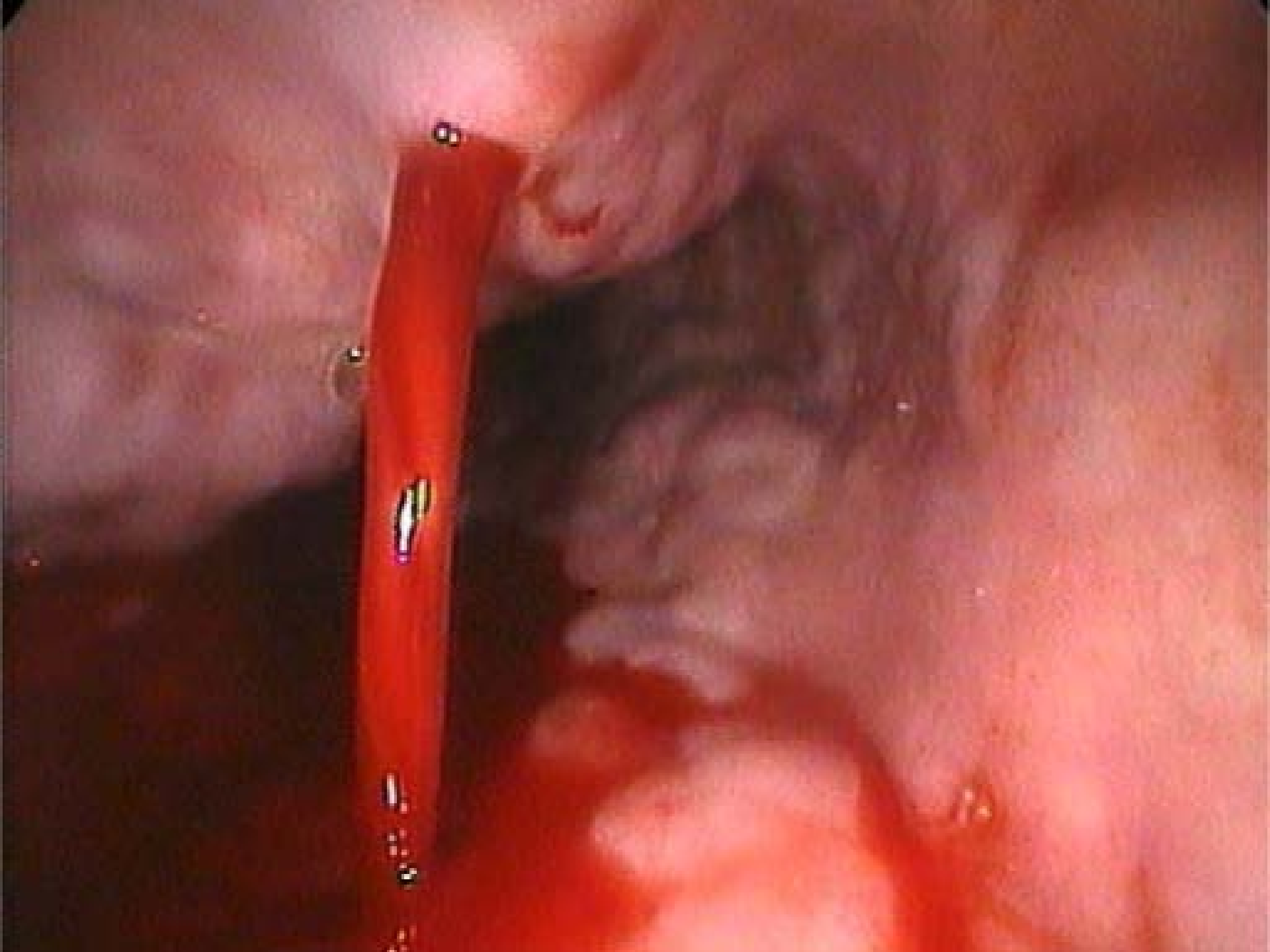
HCC

Encephalopathy

Ascites





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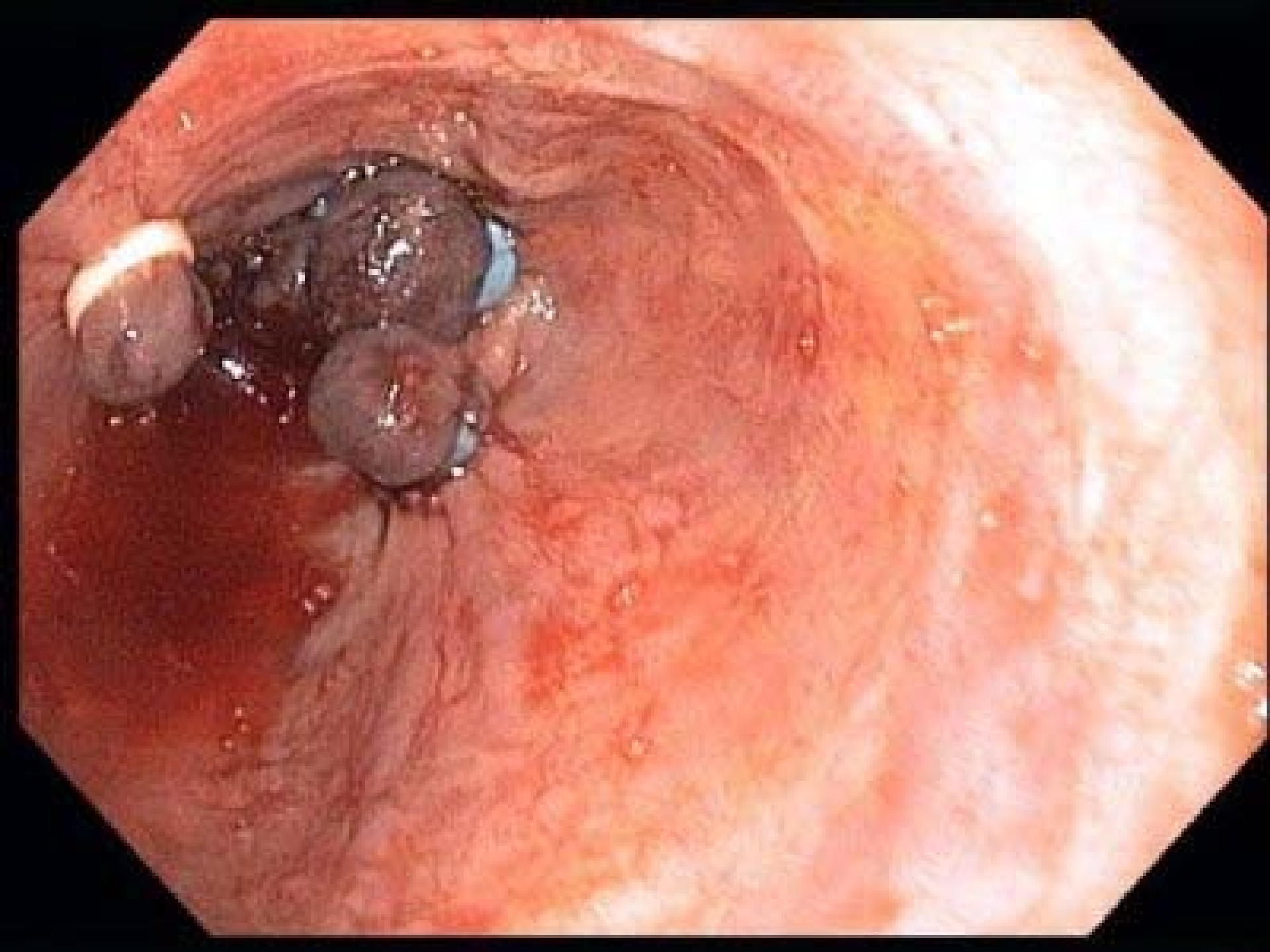


PSC and Inflammatory Bowel Disease

- The incidence of IBD (mainly Ulcerative Colitis) ~ 80% in patient's with PSC
- UC + PSC incurs a fourfold risk in CRC (compared to UC alone).
- Best established risk factors are:
  - 1. Duration of colitis
  - 2. Extent of colitis
    - Pan-colitis>rectal disease

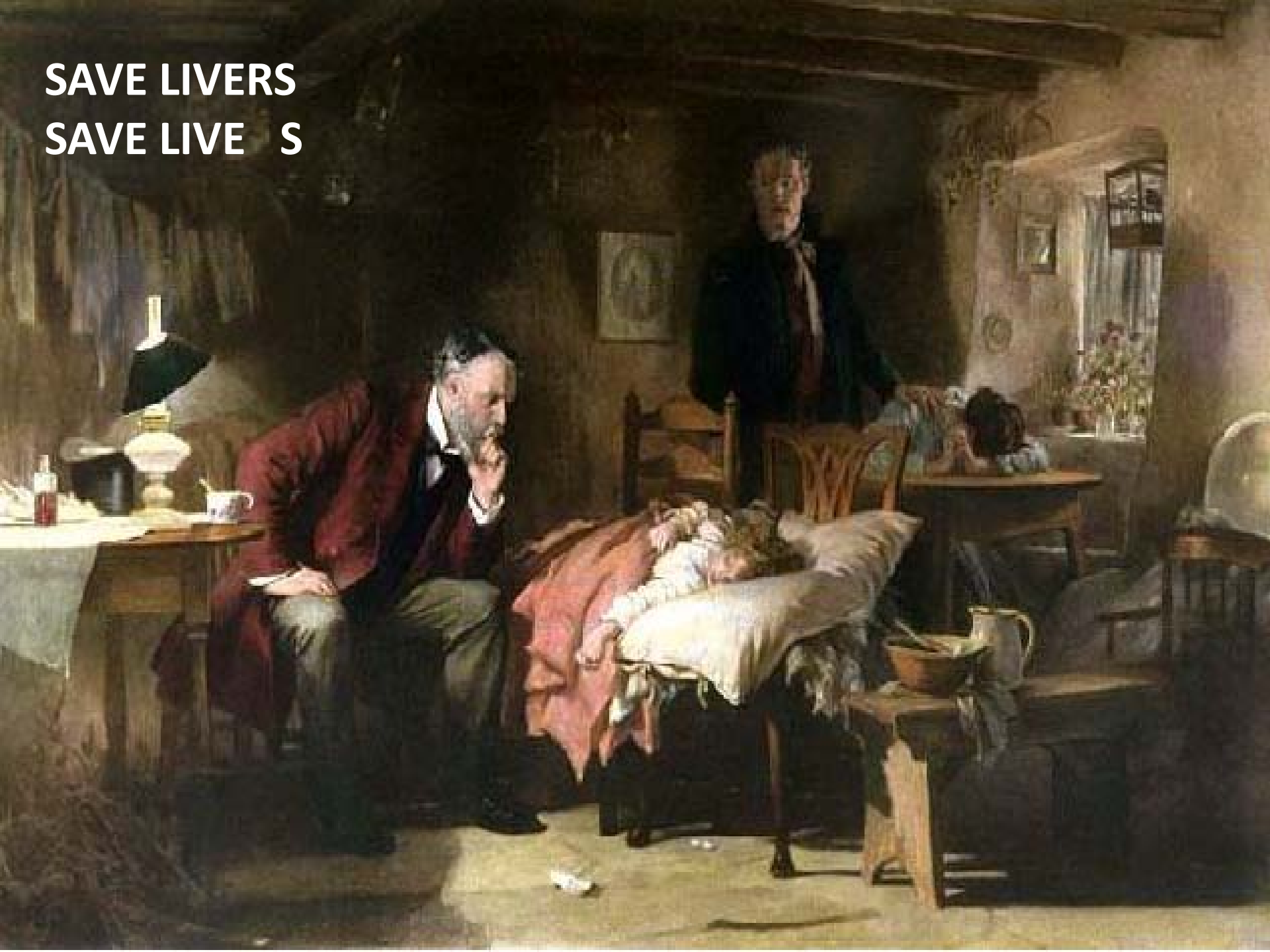
- Colonoscopy
  - Required in all patients with a diagnosis of PSC
  - Even if bowel appears endoscopically normal, random biopsies should be obtained
- If and when a diagnosis of IBD is made in a patient with PSC
- Regular surveillance for CRC

ERCP

- Because of the risks associated with ERCP
  - Namely post ERCP Pancreatitis
  - Cholangitis
- Generally no longer considered a diagnostic test

- Reserved for:
  - Evaluation of concerning stricture
    - Biopsy/brushing
  - Removal of stones in patients with cholangitis
  - Dilation/stenting of stricture

Questions?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