

Diagnosis and Management of Cholangiopathies

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Disclosures

- Speakers Bureau
 - Gilead pharmaceuticals
 - Madrigal pharmaceuticals
 - Novo-Nordisk pharmaceuticals
 - IPSEN pharmaceuticals
- Consulting Agreement
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Caveat



- Autoimmune diseases of the liver are confusing
- **NOTHING** substitutes your judgement
 - Clinical Presentation
 - Response to treatment

Key Points

- Multiple autoimmune liver diseases can occur at one time
- Liver test pattern of elevation can help give clues
- Consider overlap syndromes if clinical presentation or treatment response is unusual
- Understanding clinical endpoints and patient quality of life indicators are important for survival and daily treatment

Cholangiopathy Types

Large Duct Disease

- Sclerosing cholangitis
 - Primary (PSC)
 - Secondary (SSC)
- IgG4 Related cholangiopathy
 - (IGRC)

Small Duct Disease

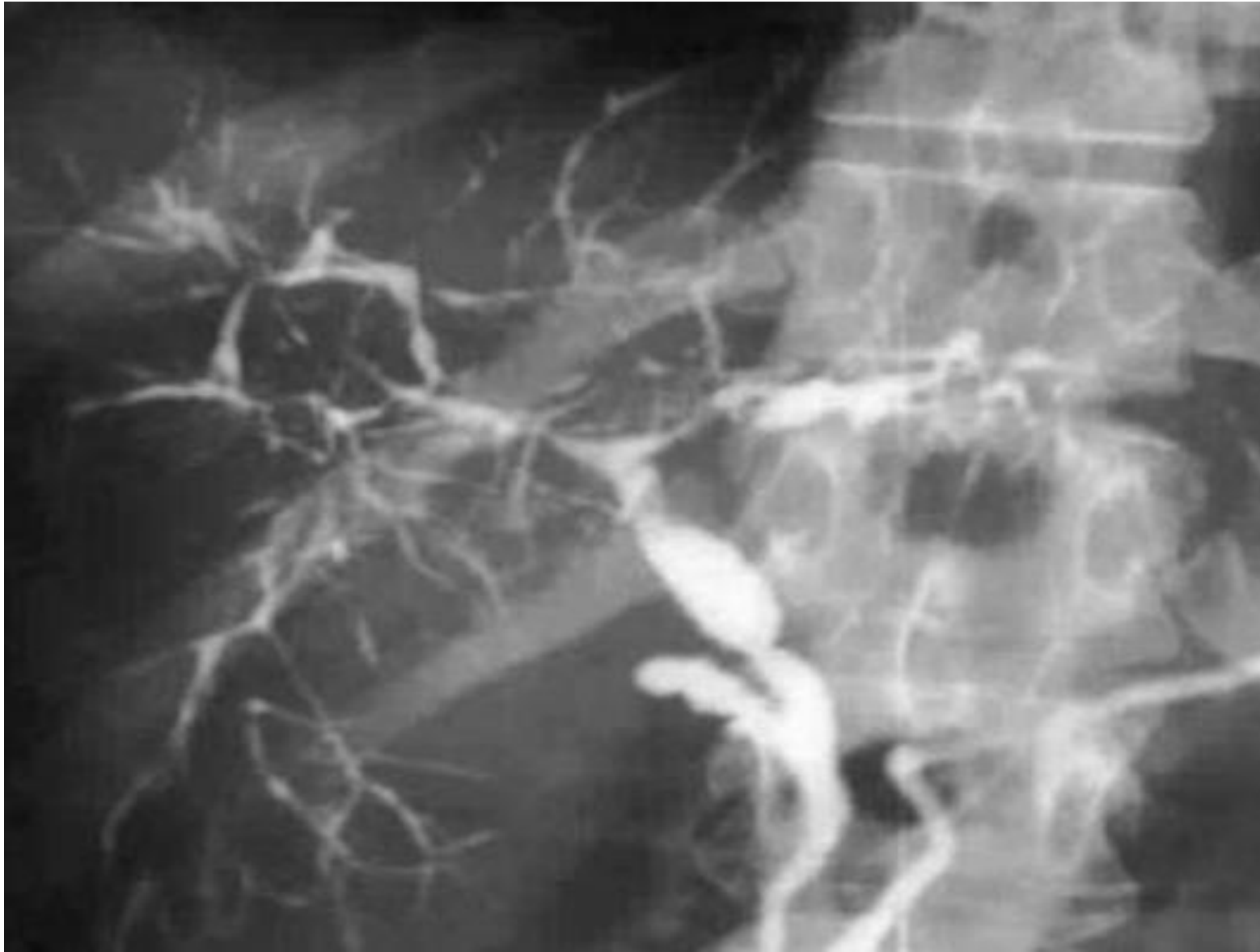
- Small duct PSC
- Primary biliary cholangitis (PBC)

Key Point:
More than one can occur!

Cholangiopathy Types: Primary Sclerosing Cholangitis

- Chronic cholestatic liver disease
- Characterized by intra/extrahepatic strictures
- Variable rate of progression
- Diagnosis of exclusion
- Pathogenesis remains unclear





Question

1. 28 year old with Ulcerative colitis, known PSC?
2. 38 year old post liver transplant, with known hepatic artery thrombosis?
3. 45 year old AIDS patient with diarrhea?

Point:
PSC is a CLINICAL diagnosis
NOT a radiologic diagnosis



Multifocal Biliary Strictures: Differential Diagnosis

Cholangiocarcinoma

Choledocholithiasis

IgG 4-related sclerosing cholangitis

AIDS cholangiopathy

Ischemic cholangitis

Portal hypertensive biliopathy

Diffuse intrahepatic metastasis

Surgical biliary trauma

Recurrent pyogenic cholangitis

Recurrent pancreatitis

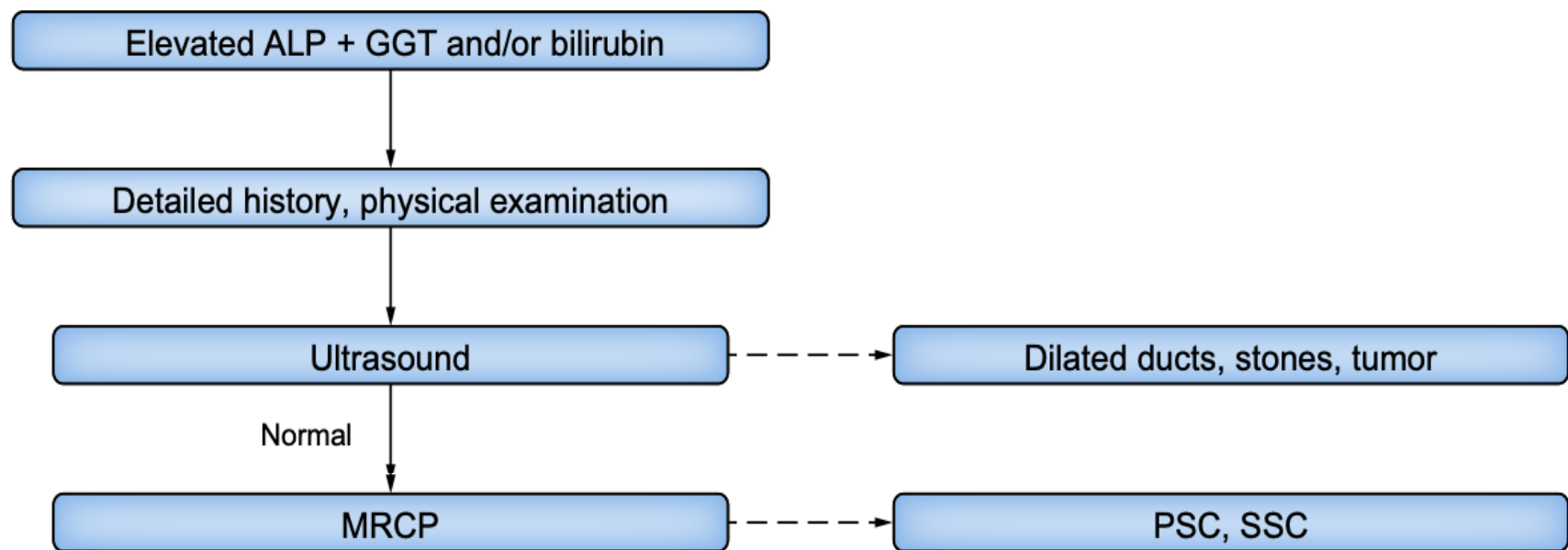
Sclerosing cholangitis in critically ill

Intra-arterial chemotherapy

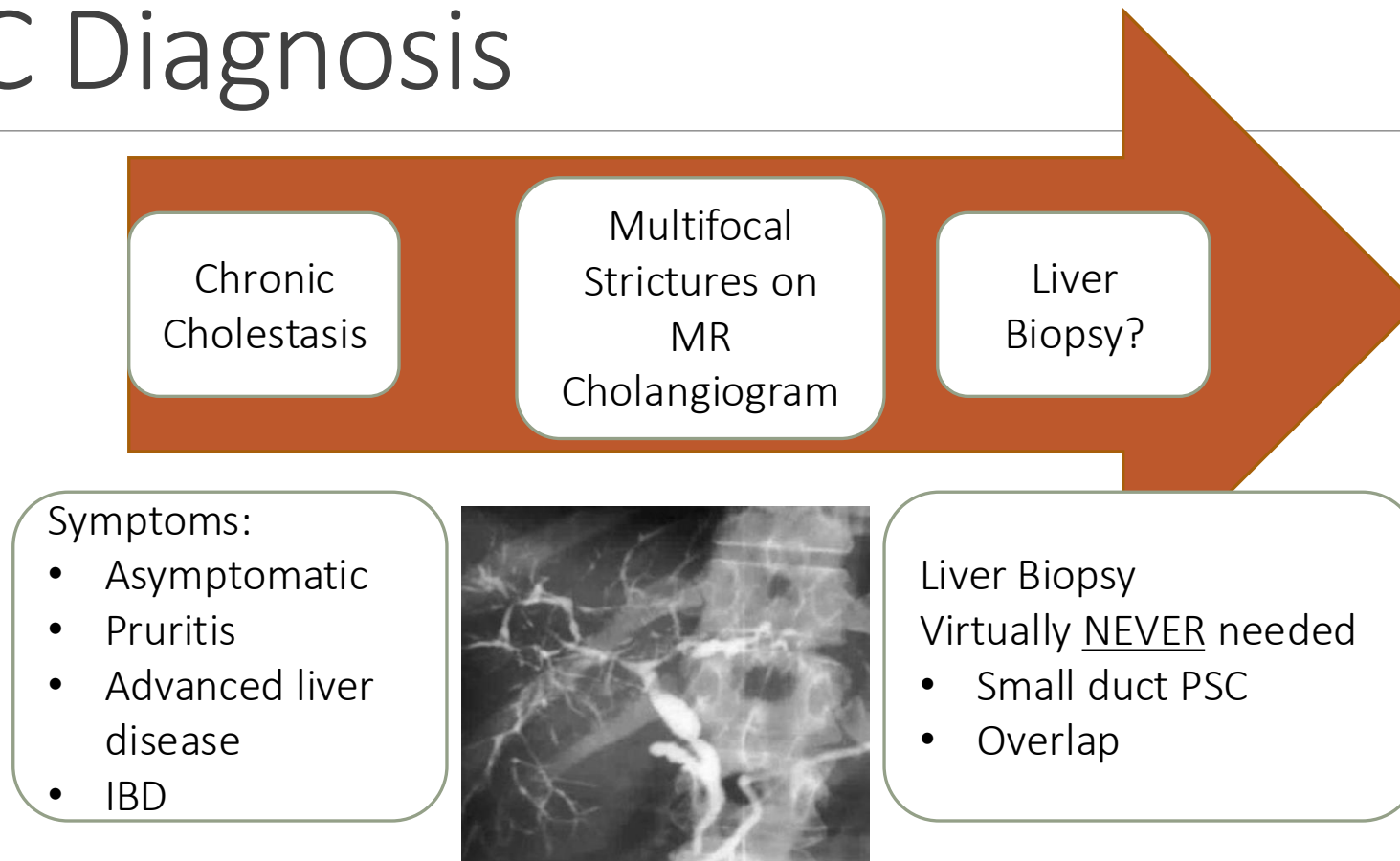
Cholangiopathy Types:

PSC: Incidence

- Highly associated with IBD
 - Ulcerative colitis predominates
 - 50-80% of patients with PSC
 - Symptomatic or incidentally found
- Prevalence 1:10,000 (European ancestry)
 - 60-70% male
 - Mean age 40



PSC Diagnosis



Cholangiopathy Types:

PSC: Phenotypic Prognostic Tools

Good Prognosis

- Younger diagnosis
- Female
- Small duct PSC
- Crohn's disease
- Normal/mild elevation in alkaline phosphatase
 - With or without UCDA

Poor Prognosis

- Extensive intra/extrahepatic disease
- Decreased synthetic function
 - Portal Hypertension
- Jaundice

How to Clinically Follow?

Cholangiopathy Types:

PSC: Prognostic Tools

- Phenotypes are variable, and **DOES** change management
- Tools that are used
 - Liver biochemistries
 - Bilirubin, alkaline phosphatase, ALT, albumin, INR
 - Imaging or serological non-invasive liver disease assessment
 - Cross sectional imaging
 - Timing depends on risk

How to Simplify?

Cholangiopathy Types:

PSC: Prognostic Tools

Low Risk of Events

Small Duct PSC

OR

Large duct and **ALL** present

- Asymptomatic
- Alkaline phosphatase < 1.5 ULN
- Fibroscan < 6.5 kPA
 - ELF less than 7.7
- Limited changes on MRCP

“Significant” risk of Events

Symptomatic

OR

- Alkaline phosphatase > 1.5 ULN
- Abnormal liver biochemistries
 - Bilirubin, albumin, platelets, INR
- Fibroscan > 9.9 kPA
 - ELF greater than 10.6
- Extensive changes on MRCP

Surveillance depends on risk!

Cholangiopathy Types:

PSC: Low Risk Group

- Evaluate every **12 months**
 - Quality of life (pruritis)
 - Serum biochemistries
 - Imaging or serological testing for fibrosis
 - Cross sectional imaging
 - MRI/MRCP
 - US (close attention to gallbladder wall and polyps)
 - Colonoscopy
 - At diagnosis and every 5 years
 - Annually if IBD
 - DEXA at time of diagnosis

Cholangiopathy Types:

PSC: High Risk Group

- Evaluate every **6 months**
 - Quality of life (pruritis)
 - Serum biochemistries
 - Imaging or serological testing for fibrosis
 - Cross sectional imaging
 - MRI/MRCP
 - US (close attention to gallbladder wall and polyps)
 - Colonoscopy
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Cholangiopathy Types:

PSC: High Risk Group

- Evaluate every **6 months**
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Cholangioathy Types: PSC Treatment

No FDA approved treatment

- Innumerable immunosuppressants have tried and failed
- Oral Antibiotics?
 - Some pediatric data showing may be beneficial
 - No adult data supports
- Ursodeoxycholic acid (UCDA)
 - Controversial

Cholangiopathy Types: Treatment UCDA

- Bile acid with beneficial properties in cholestatic liver disease
- Why?
 - Hydrophilic
 - Anticholestatic
 - Cytoprotective
 - Antifibrotic
 - Anti-inflammatory

Cholangiopathy Types:

Treatment UCDA

- 15-20 mg/kg usual studied dose
 - Mixed study results
 - Some showed improvement some did not
- If 15-20mg/kg is stopped
 - Worsening biochemistries and pruritis seen
- > 20mg/kg is harmful and should not be used

Cholangiopathy Types: Treatment UCDA

- Phase III trials ongoing
- Important for risk/benefit discussion

Cholangioathy Types: Treatment Pruritis

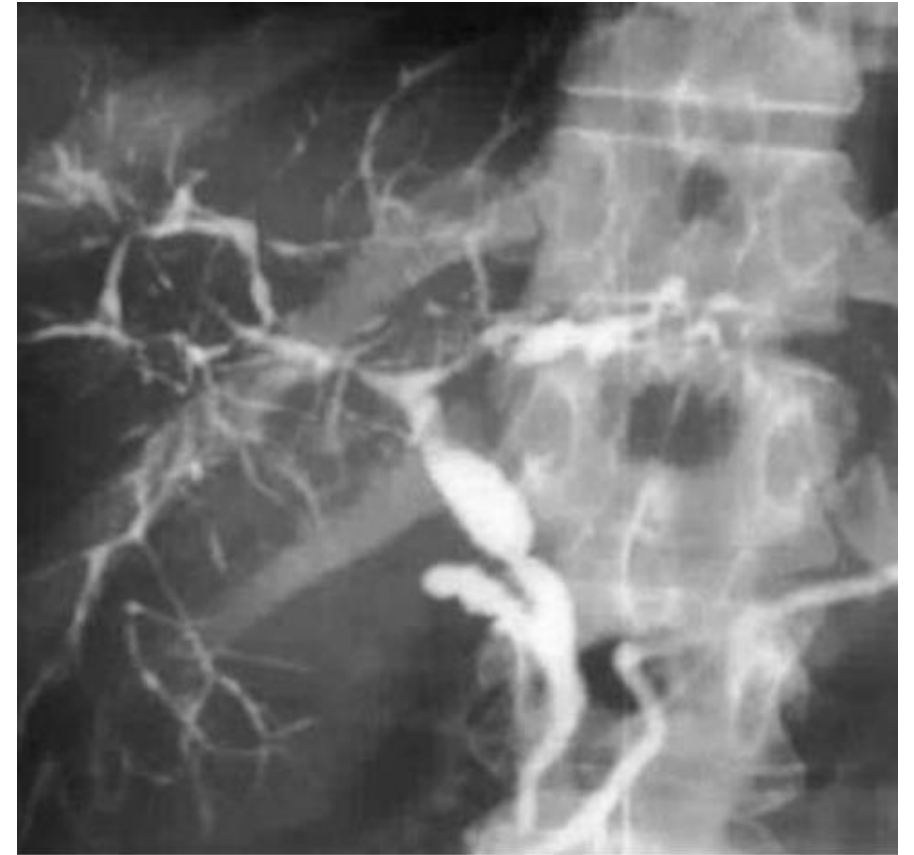
- Medications
- Treatment of strictures

Cholangioathy Types: Treatment Pruritis

- Most important factor for quality of life
- Treatment options in PSC
 - Cholestyrmine 4-16 grams per day
 - Colselevam very little data
 - Rifampin 150-300mg per day
 - Naltrexone 15-20 mg daily
 - Sertraline 25-75 mg daily
- IBAT (Ileal bile acid transport) inhibitors- More to come in PBC
 - Not fully studied in PSC

Cholangioathy Types: Treatment Pruritis

- Medications
- Treatment of strictures



Cholangioathy Types: Treatment Strictures

- Guidelines based on European society of gastrointestinal endoscopy
- Nomenclature is changing
 - “Dominant”
 - Refers to findings on diagnostic MRCP
 - “High Grade” or “severe”
 - Morphologically seen on ERCP
 - “Relevant” strictures
 - High grade stricture that lead to functional impairment



What do we do?

Cholangioathy Types: Treatment Strictures

- Who to treat **SYMPTOMATIC**

- > 75% narrowing
- Common bile duct
- Left or right hepatic duct within 2cm of bifurcation

- How to treat

- Balloon dilation preferred
- Stenting reserved for refractory cases

- Why we treat

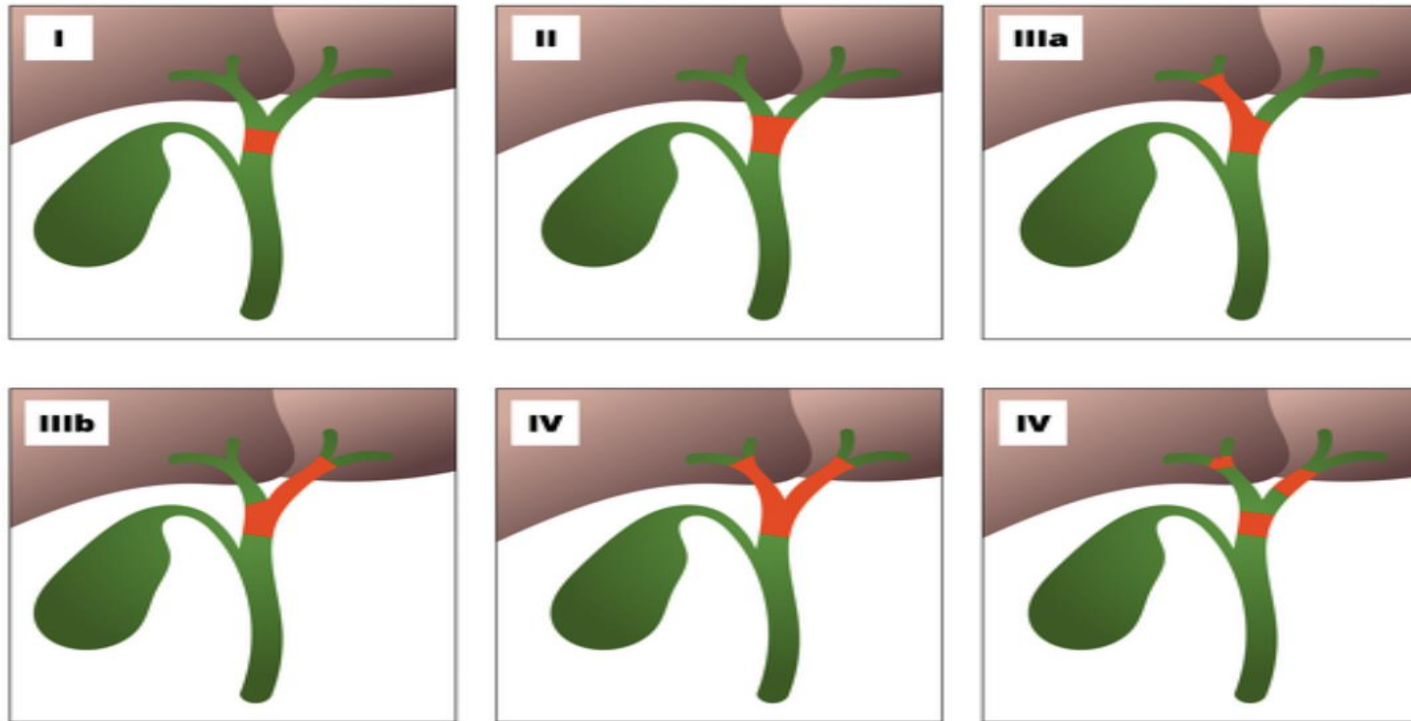
- Decreases symptoms and fibrosis

- Alkaline phosphatase > 1.5 ULN
- Abnormal liver biochemistries
 - Bilirubin, albumin, platelets, INR
- Fibroscan > 9.9 kPA
 - ELF greater than 10.6
- Extensive changes on MRCP

Cholangioathy Types:

PSC: Suspected Cholangiocarcinoma (CCA)

Bismuth-Corlette classification



Cholangioathy Types:

PSC: Suspected Cholangiocarcinoma (CCA)

- Suspect CCA in
 - High grade stricture newly diagnosed PSC
 - Worsening/progressive strictures or mass seen on imaging
- ERCP
 - What do we add?

Cholangioathy Types:

PSC: Suspected Cholangiocarcinoma (CCA)

- Cross sectional imaging
 - MRI >>> CT/US
 - Perihilar mass **DO NOT BIOPSY!!!**
 - EUS guided biopsy of regional nodes acceptable
- CA 19-9
 - ONLY when CCA is suspected NOT for screening
- ERCP
 - Brush cytology
 - FISH
 - Cholangioscopy +/- Confocal imaging

Best suited for multi-disciplinary discussions

Cholangiopathy Types

Large Duct Disease

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 - (IGRC)

Small Duct Disease

- Small duct PSC
- Primary biliary cholangitis (PBC)

Cholangioathy Types: IGRC

- Difficult phenotype to characterize
- Guidelines do state IgG4 should be checked in ALL patients with PSC
 - Separate entity
 - Severe PSC phenotype
- Diagnosis and Treatment guidelines vary

Cholangioathy Types: IGRC-Diagnosis

- H
 - Histology
- I
 - Imaging
- S
 - Serology
- O
 - Other organ involvement
- RT
 - Response to therapy

Cholangioathy Types: IGRC-Response to Therapy

- Response is regarded as a major criterion for diagnosis
- Majority have clinical, biochemical and imaging response

What do we treat with?

Cholangioathy Types: IGRC-Treatment

- Prednisolone/Prednisone 0.5mg/kg
 - Strong recommendation with 100% consensus
- Reassess in 2-4 weeks
- Maintenance is catered to the individual

Cholangioathy Types: IGRC-Maintenance Therapy

- After disease relapse during or after steroid taper
 - Steroid taper with steroid sparing agent
 - Azathioprine/6-mercaptopurine
 - Mycophenolate mofetil
 - Calcineurins
 - Long term high dose steroids
 - Rituximab induction +/- maintenance

Don't forget to treat the
strictures if needed

Cholangiopathy Types

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Cholangiopathy Types:

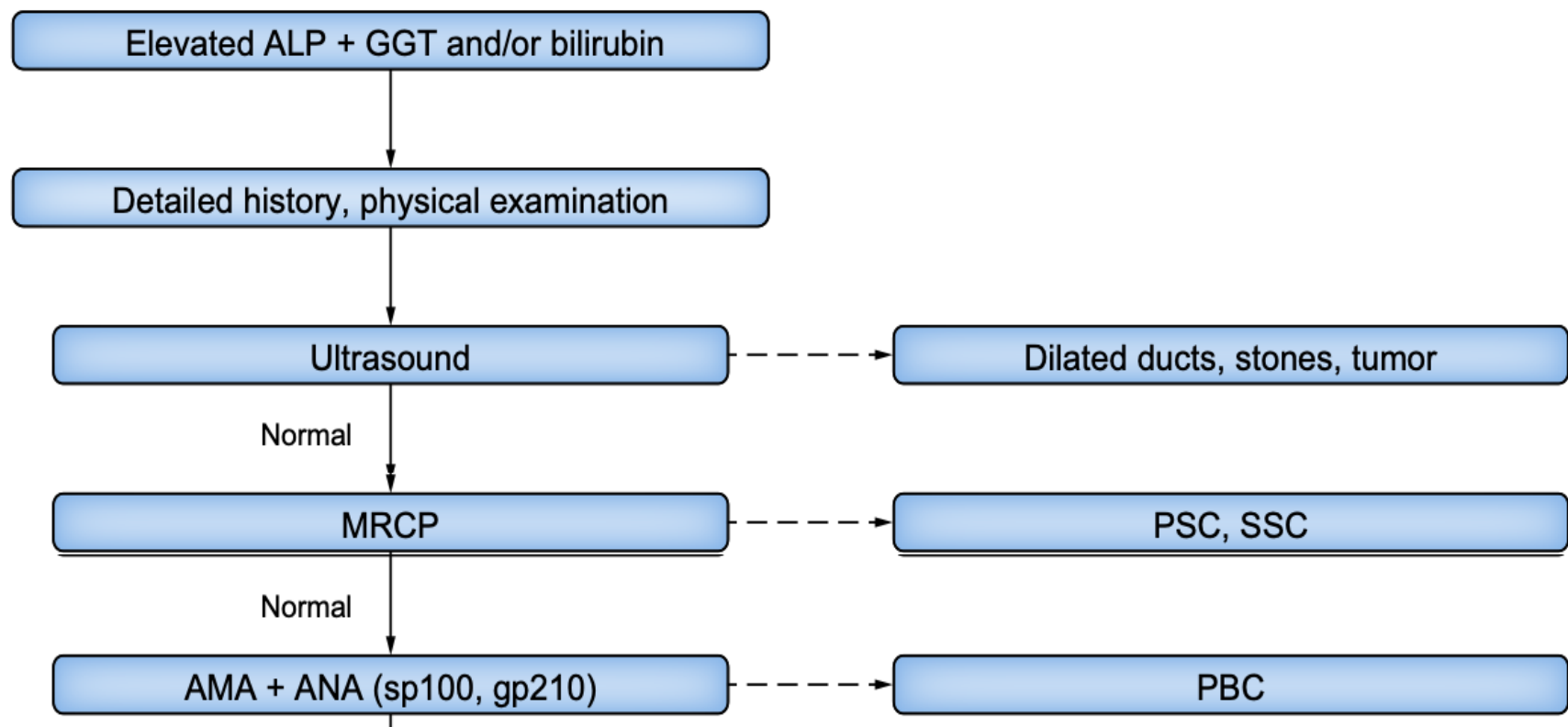
Primary Biliary Cholangitis (PBC)

- Chronic autoimmune disorder of the cholangiocytes
- Middle aged women
- Underrecognized people
 - Women >60
 - Men
- 1.8 in 100,000 patient years

Cholangiopathy Types:

PBC: Presentation

- Asymptomatic elevations alkaline phosphatase
- Pruritis
- Fatigue



Cholangiopathy Types:

PBC: Diagnosis

- AMA is highly sensitive for this diagnosis
 - Important clues if diagnostic dilemma
 - Elevated IgM
 - + Anticentromere antibody
 - SP100, GP210
- UCDA at 13-15mg/kg should be first line therapy

Cholangiopathy Types:

PBC: Phenotypic Prognostic Tools

Low risk

- Older women
- Normal bilirubin
- No AIH/PBC overlap

High risk

- Young
- Males
- Anti-gp210
- AIH/PBC Overlap

How to Clinically Follow?

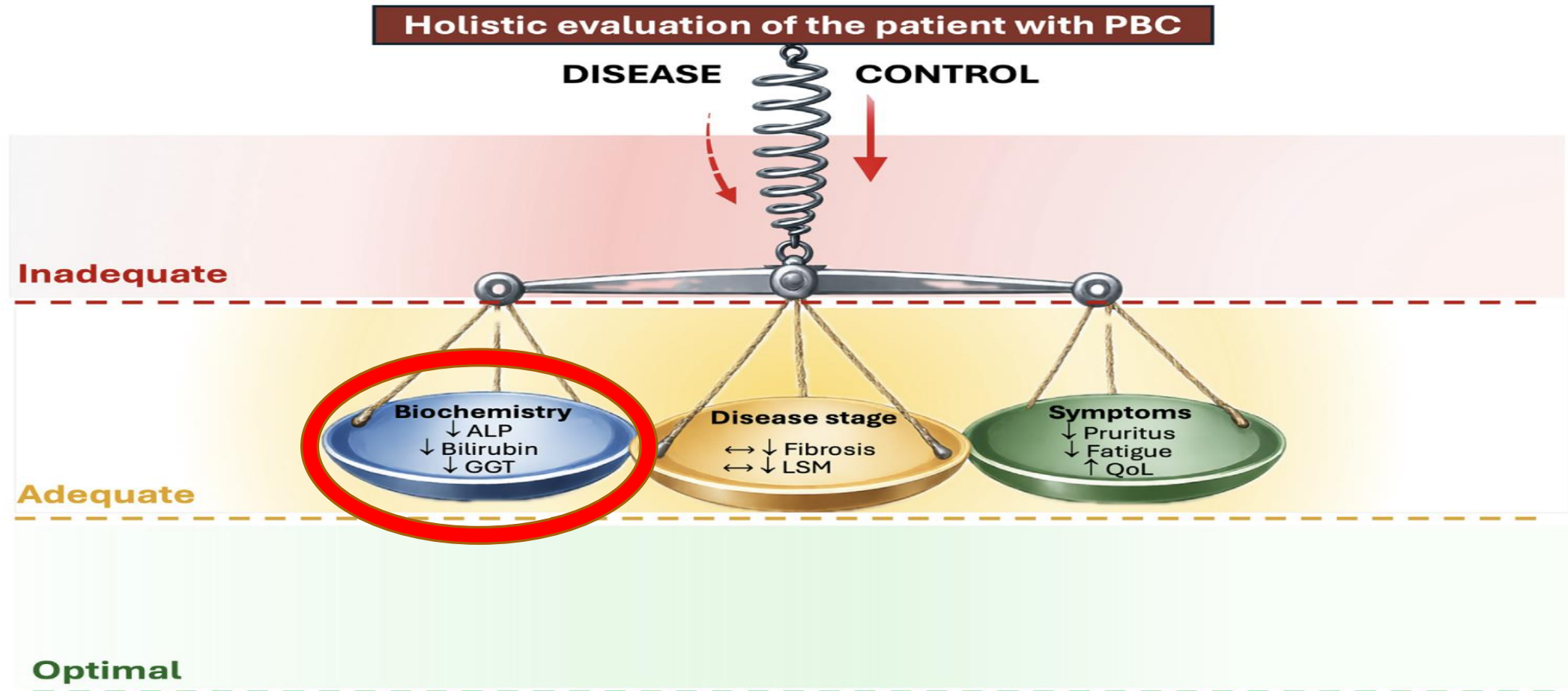
Cholangiopathy Types:

PBC: Treatment End Points

- “Old” Paradigm
 - Looked only at numbers
- “New” Paradigm
 - Biochemical response or “numbers”
 - Fibrosis stabilization/regression
 - Symptom control

Cholangiopathy Types:

PBC: Treatment End Points



Cholangiopathy Types:

PBC: Biochemical End Points

- POISE Trial at 12 months- Used in ALL phase III clinical trials
 - Alkaline phosphatase $< 1.67 \times \text{ULN}$
 - Reduction in alkaline phosphatase $> 15\%$
 - Normal bilirubin
- GLOBE Score for transplant free survival
 - On any medical application

Cholangiopathy Types:

PBC: Biochemical End Points

- Newer Global PBC Study Group
- Best outcomes
 - Alkaline phosphatase normalization
 - Normal bilirubin

What Do We Use?

Cholangiopathy Types:

PBC: Biochemical End Points

- POISE Trial at 12 months- Used in ALL phase III clinical trials

- Alkaline phosphatase $< 1.67 \times \text{ULN}$
- Reduction in alkaline phosphatase $> 15\%$
- Normal bilirubin

Adequate Response

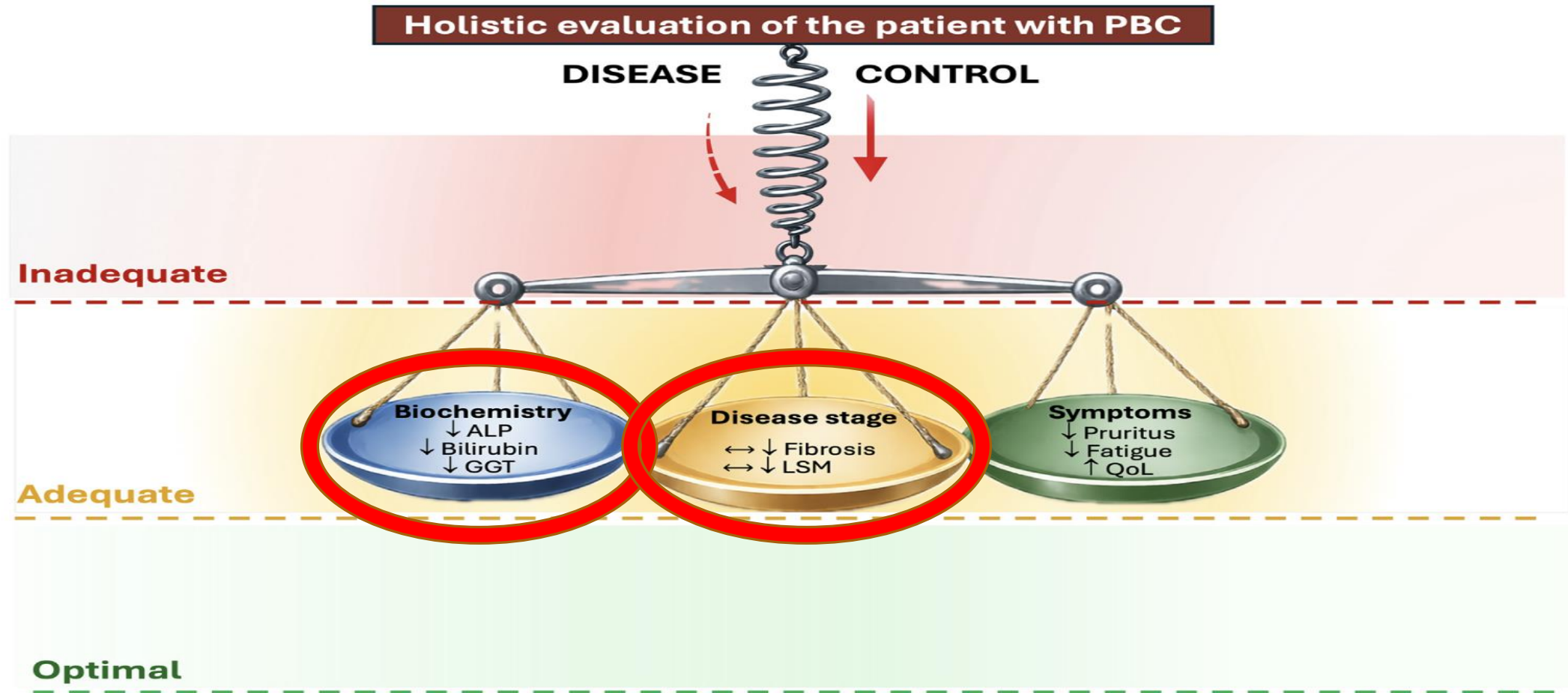
- Newer Global PBC Study Group

- Alkaline phosphatase normalization
- Normal bilirubin

Complete Response

Cholangiopathy Types:

PBC: Treatment End Points



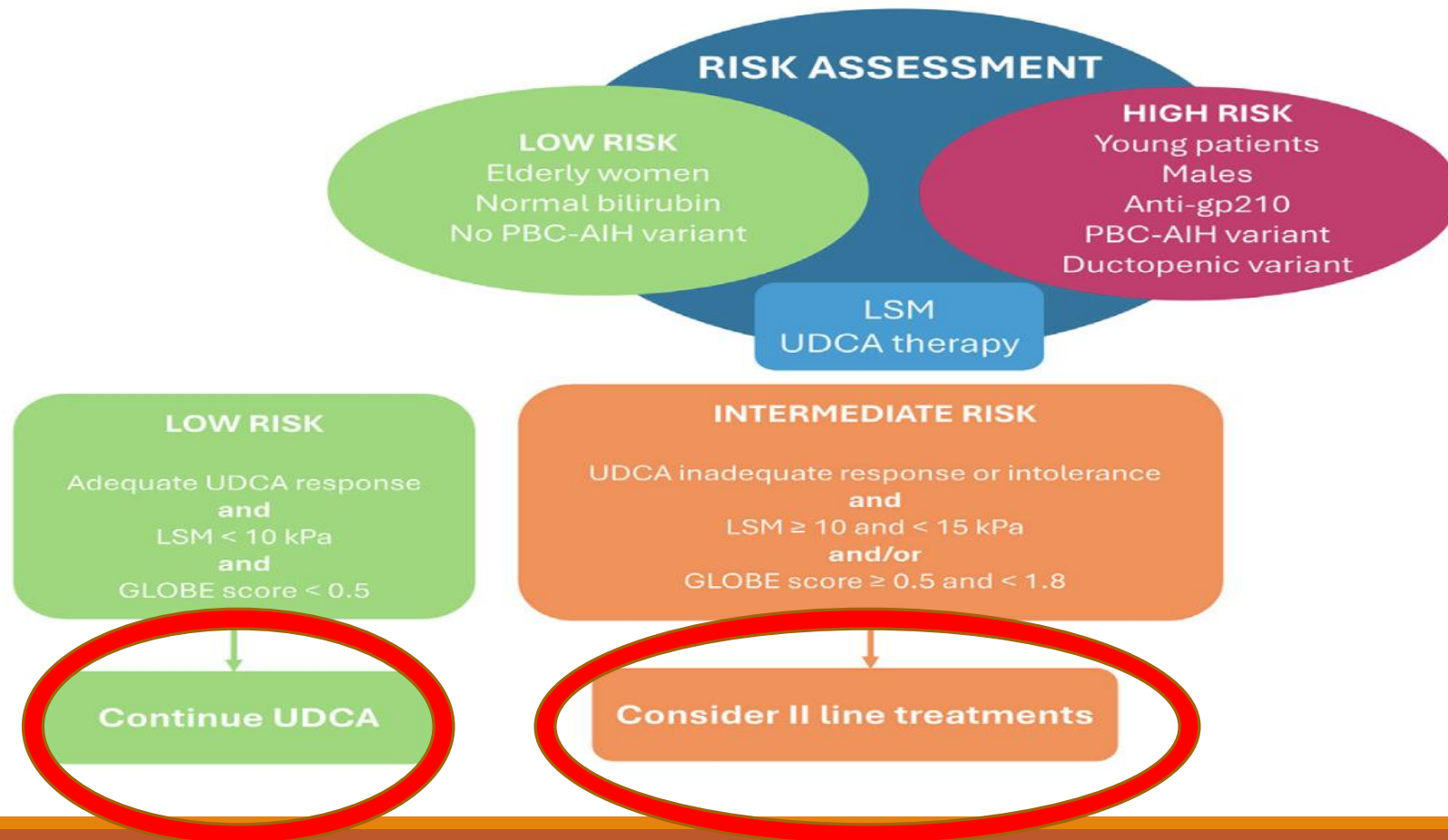
Cholangiopathy Types:

PBC: Fibrosis Monitoring

- “Rule of 5’s” should be followed **LONGITUDINALLY**
 - Liver stiffness measurement (LSM)
 - Less than 10 kPa
 - Excludes patients currently at risk of decompensation
 - 10-15 kPa
 - 6-fold increase in decompensation
 - 15.1-20 kPa
 - 25-fold increase in decompensation

Cholangiopathy Types:

PBC: Treatment Algorithm



Cholangiopathy Types:

PBC: 2nd Line Therapies

- PPAR's (alpha, gamma and delta)
 - Nuclear receptors regulate
 - Bile acid detoxification
 - Lipid metabolism
 - Inflammation
 - Fibrogenesis
- PPAR's selective or dual agonist addresses
 - Cholestasis
 - Parenchymal fibrosis/inflammation

Cholangiopathy Types:

PBC: PPAR's

- Both products assessed via Poise Criteria
- Both discussed simultaneously NO head to head data
- Efficacy 80 mg
 - Adequate response in 51% vs 4% in placebo
- Seladelpar 10 mg
 - Adequate response in 61.7% vs 20% in placebo

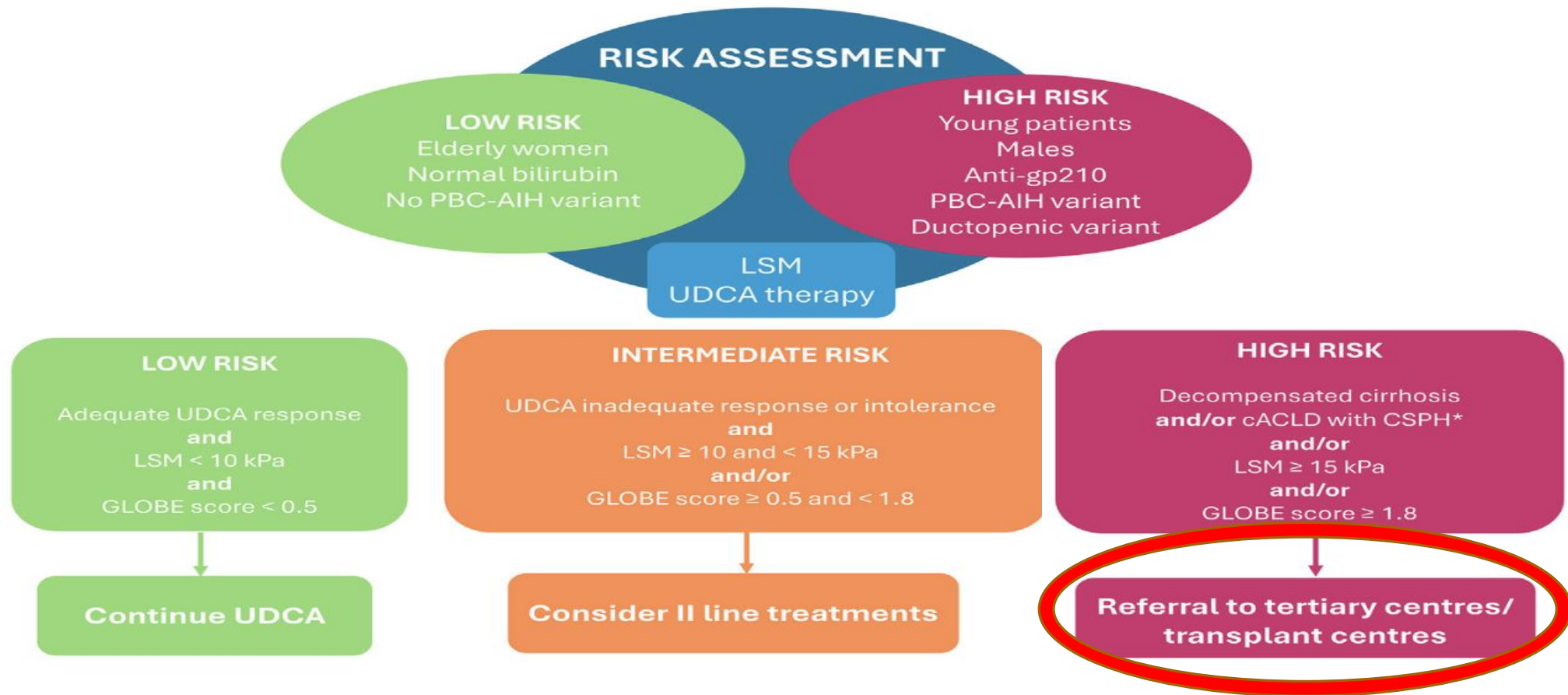
Cholangiopathy Types:

PBC: PPAR's ADR

- Abdominal pain
- Nausea with vomiting
 - Elefibranor
- Headache
 - Seladelpar
- Increase LAE's
 - ? Induction of enzymes rather than toxicity
 - ? Bone density decrease and fractures

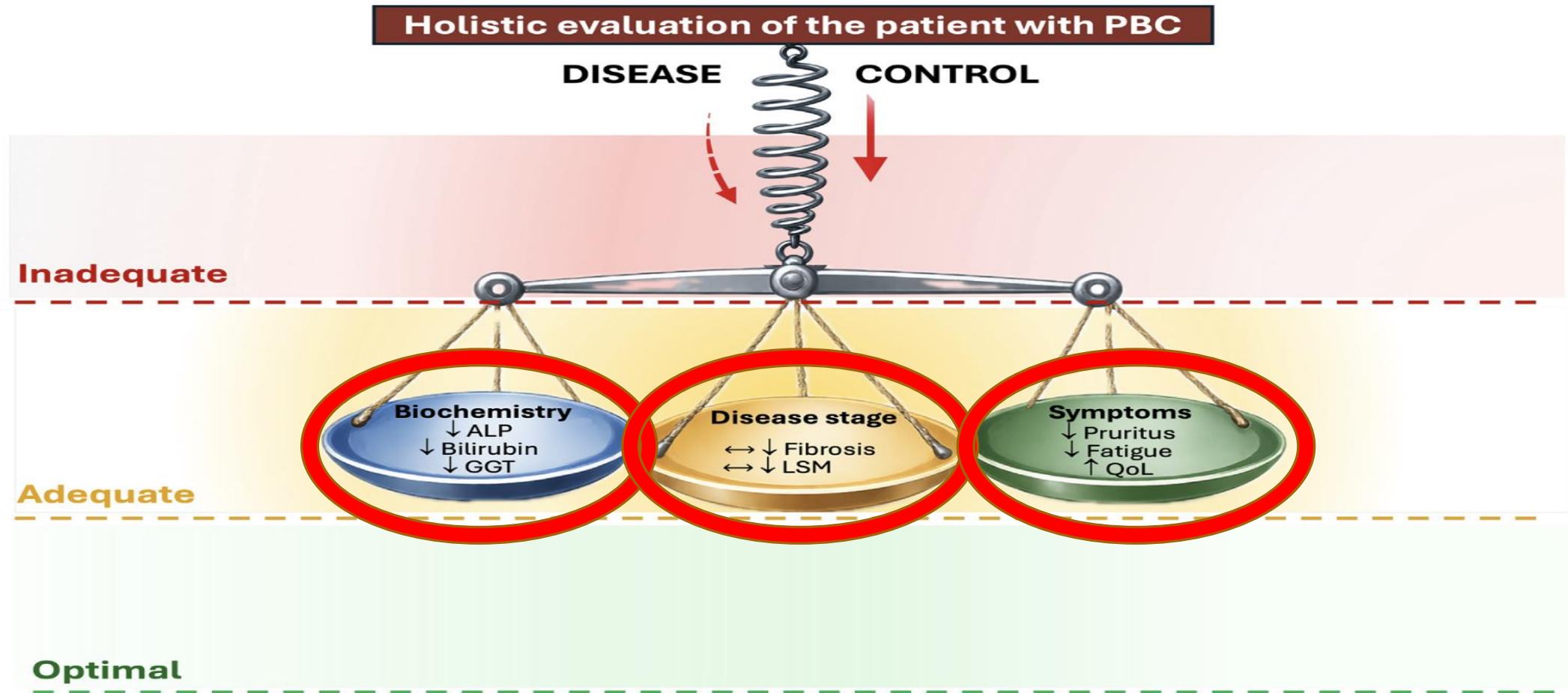
Cholangiopathy Types:

PBC: Treatment Algorithm



Cholangiopathy Types:

PBC: Treatment End Points



Cholangiopathy Types:

PBC: Symptoms

- Fatigue and pruritic predominate
- All analog scales in trials are subjective
 - Subjectivity decreases diagnostic accuracy
- ASK SOMETHING!

Cholangiopathy Types:

PBC: Symptoms

- Major unmet need in PBC
- Symptom burden often dissociates
 - Biochemical response
 - Stage of disease
- “Itch worse than your numbers”

Cholangioathy Types: PBC Related Pruritis

- Non-pharmacologic therapy
 - Emollient creams
 - Cold showers (if heat triggered)
 - Psychologic intervention if itch/scratch is pervasive
 - Allergy testing?
- Pharmacologic therapy

Cholangioathy Types:

PBC Related Pruritis Pharmacologic Therapy

- Cholestyrmine 4-16 grams per day
 - Colselevam divergent data in PBC
- Rifampin 150-300mg per day
- Naltrexone 15-20 mg daily
- Sertraline 25-75 mg daily

What's New?

Cholangioathy Types:

PBC Related Pruritis: New Therapies

- PPAR's (alpha, gamma and delta)
 - Studies NOT powered for pruritis
 - Improvement seen in phase 3 and open label extensions
 - ONLY in patients intolerant or incomplete response
 - ? Use them for symptoms only

Cholangioathy Types:

PBC Related Pruritis: New Therapies

- IBAT inhibitors
 - Ileal Bile Acid Transporters
- Linciclib 40mg bid
 - Decreases bile acid uptake (enterohepatic circulation)
 - Increases elimination of bile acids
 - Decreased itching and itch related sleep disturbance in 2 weeks

Cholangioathy Types:

PBC Related Pruritis: New Therapies

Linerixibat ADR

- Diarrhea
- Abdominal pain
- Nausea

Cholangiopathy Types

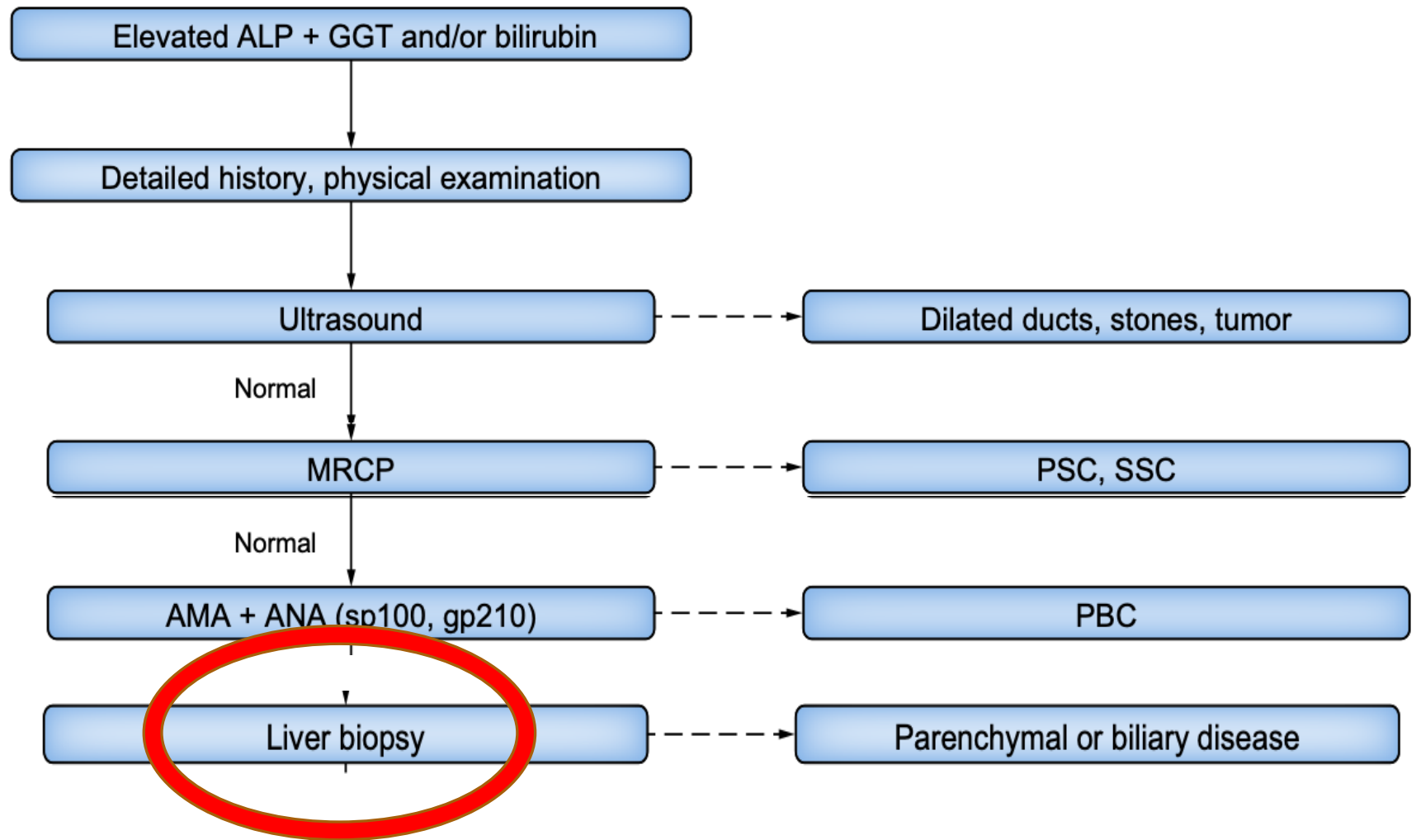
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Key Point:
More than one can occur!



Cholangiopathy Types: Overlap Syndromes

- Consider liver biopsy and overlap syndromes
 - Suspected PSC when
 - Normal MRCP
 - Biopsy to exclude “small duct” PSC
 - Known PBC or PSC
 - Co-existing features of AIH
 - Transaminases 5-10 ULN
 - High Total IgG levels

Cholangiopathy Types: Overlap Syndromes Treatment

- Usually one autoimmune condition is dominant
 - Teaching is AIH is usually dominant
 - Can be seen if non-response to PSC/PBC treatment
- Treat with existing guidelines for autoimmune hepatitis
 - Induction prednisone/prednisolone
 - Maintenance is still azathioprine in US guidelines

Key Points

- Multiple autoimmune liver diseases can occur at one time
- Liver test pattern of elevation can help give clues
- Consider overlap syndromes if clinical presentation or treatment response is unusual
- Understanding clinical endpoints and patient quality of life indicators are important for survival and daily treatment