Primary biliary cholangitis

Introduction

- The global prevalence of hypercholesterolemia among adults is still increased
- The high prevalence of overweight and obesity have led to the increase in lipid disorders
- Central obesity, high blood pressure and type 2 diabetes are major risk factors for cardiovascular disease
- To achieve the recommended goals for lipid concentrations alternative lipid-lowering therapies are needed to reduce the risk of atherosclerotic cardiovascular disease.

Simental mendia LE et al. Lipids Health Dis. 2019 Apr 6;18(1):88

Primary biliary cholangitis

- Primary biliary cholangitis (PBC) is an autoimmune disease characterized by biliary destruction and progressive intrahepatic cholestasis.
- It is characterized by circulating antimitochondrial antibodies (AMAs) and selective destruction of intrahepatic cholangiocytes, leading to cholestasis.

Onofrio FQ et al. Gastroenterol Hepatol. 2019 Mar;15(3):145-154.

Risk factors

- Genetic predisposition
- Association with urinary tract infections (caused by Escherichia coli, Mycobacterium gordonae
- Hormone replacement therapy
- Nail polish,
- Hair dyes
- past cigarette smoking
- Toxic waste sites as environmental triggers

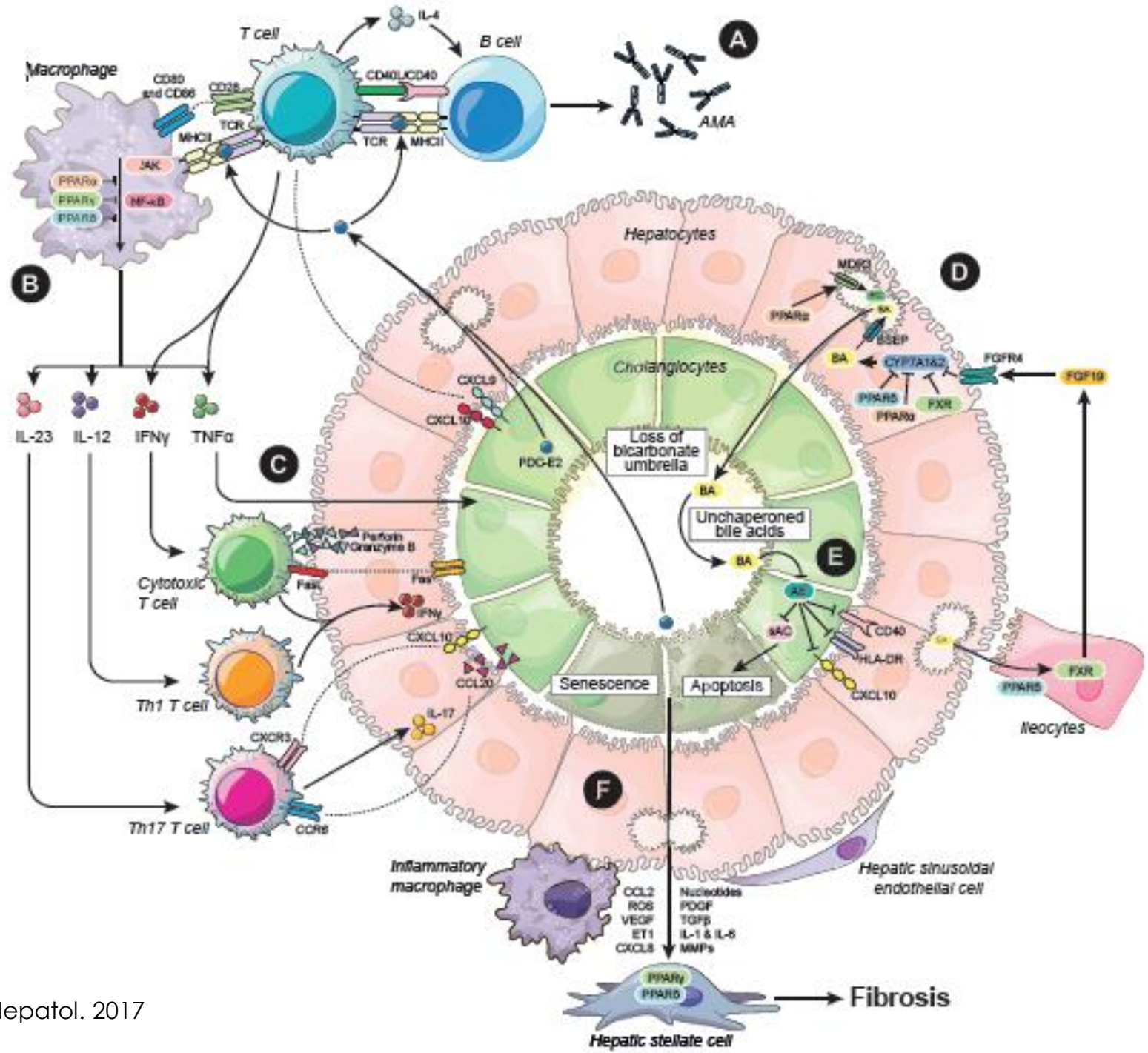
Onofrio FQ et al. Gastroenterol Hepatol. 2019 Mar;15(3):145-154.

Pathogenesis

- Genetic susceptibility plays a key role identified by genome-wide association studies and the increased familial risk of disease.
- The human leukocyte antigen (HLA) locus has consistently demonstrated the strongest disease association in genetic .
- Among the non-HLA risk loci associated with disease, the interleukin-12 axis plays an important role in immune regulation has demonstrated association with disease.
- Pathogenesis encompasses a dysregulated innate and adaptive immune insult against mitochondrial antigens within biliary epithelial cells (BECs), triggering immunologic and cholestatic injury.

Onofrio FQ et al. Gastroenterol Hepatol. 2019 Mar;15(3):145-154.

Pathogenesis



European Association for the Study of the Liver. J Hepatol. 2017 Jul;67(1):145-172.

Pathogenesis

- Loss of immunologic tolerance to the E2 subunit of the pyruvate dehydrogenase complex (PDC-E2) is characteristic triggers the activation and recruitment of T and B cells along with production of circulating Antimitochondrial Antibodies.
- Anion exchanger 2 (AE2) is the primary chloride/ bicarbonate exchanger on provides essential epithelial protection from toxic hydrophobic bile acids.
- Cholangiocytes insulted by hydrophobic bile acids are sensitized to apoptosis, and hydrophobic bile acids induce reactive oxygen species and Biliary Epihelial cells senescence, further propagating bile duct injury.

Onofrio FQ et al. Gastroenterol Hepatol. 2019 Mar;15(3):145-154.

Clinical Presentation

- PBC primarily affects women in their fifth or sixth decade of life.
- Fatigue , pruritus, sicca syndrome, and upper abdominal discomfort are common manifestations.
- Sicca syndrome (dry eyes/dry mouth), abdominal discomfort, depression, anxiety, and sleep disturbance is also seen.
- Disease has a chronic course, ultimately resulting in end-stage liver disease

Onofrio FQ et al. Gastroenterol Hepatol. 2019 Mar;15(3):145-154.

Diagnostic criteria

- Positive anti mitochondrial antibody
- Persistent unexplained biochemical cholestasis - abnormal ALP level over 24 weeks;
- Liver histology- specifically nonsuppurative cholangitis and interlobular bile duct injury

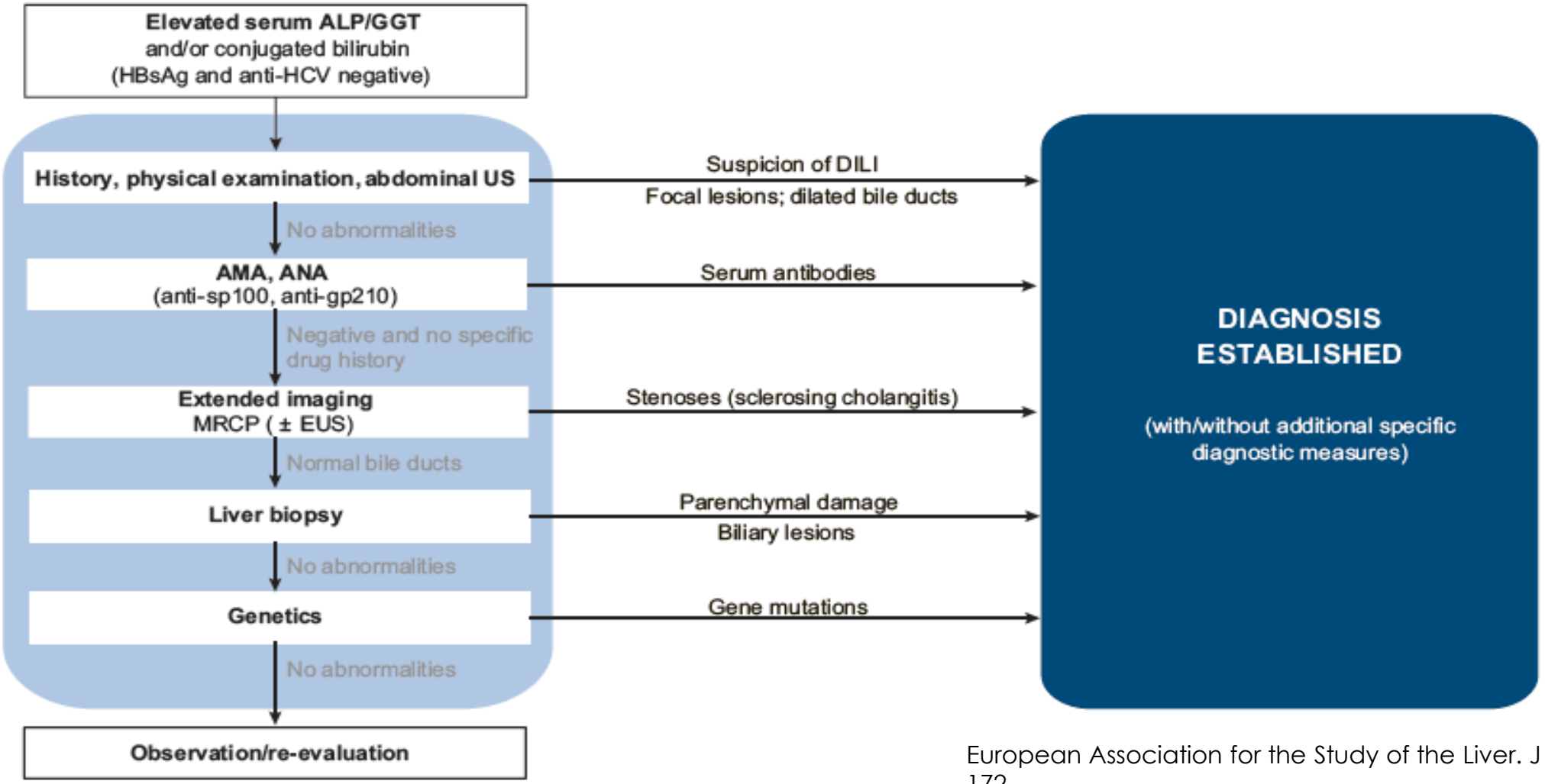
Onofrio FQ et al. Gastroenterol Hepatol. 2019 Mar;15(3):145-154.

Investigations

- Abnormal serum alkaline phosphatase (ALP) level is the most typical abnormality noted, mildly elevated serum aminotransferase levels (reflective of lobular necroinflammation) and increased immunoglobulin IgM.
- Anti mitochondrial antibodies- are highly sensitive and specific for PBC in the context of unexplained chronic cholestasis
- Specific Anti Nuclear Antibodies by immunofluorescence patterns (nuclear dots or perinuclear rims) or PBC-specific ANAs including anti-sp100 or anti-gp 210 (severe disease).

Onofrio FQ et al. Gastroenterol Hepatol. 2019 Mar;15(3):145-154.

Algorithm of investigations



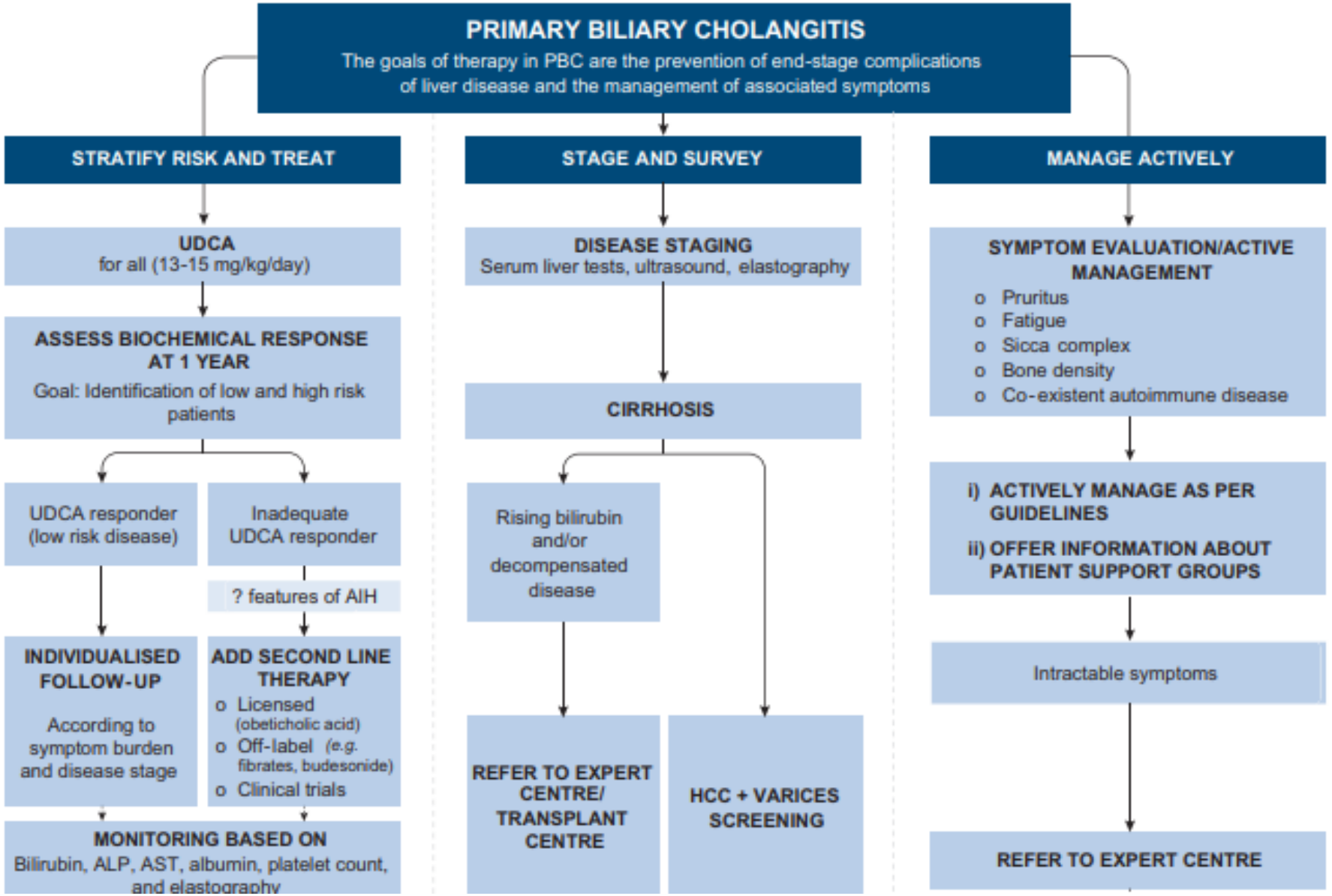
European Association for the Study of the Liver. J Hepatol. 2017 Jul;67 172

Investigations

- Imaging: There are no structural abnormalities in early stage, however it is recommended for abdominal ultrasound to rule out extrahepatic biliary obstruction as an alternative cause of cholestasis.
- Magnetic resonance (MR) cholangiography is not routinely needed in diagnosing PBC, as the biliary injury is targeted to small bile ducts
- Histology: liver biopsy is indicated when PBC specific antibodies are absent or when coexistent autoimmune hepatitis (AIH) or nonalcoholic steatohepatitis is suspected

Onofrio FQ et al. Gastroenterol Hepatol. 2019 Mar;15(3):145-154.

Treatment



European Association for the Study of the Liver. J Hepatol. 2017 Jul;67(1):145-172.

Cholestasis

- Cholestasis is an impairment of bile formation and flow.
- Causes

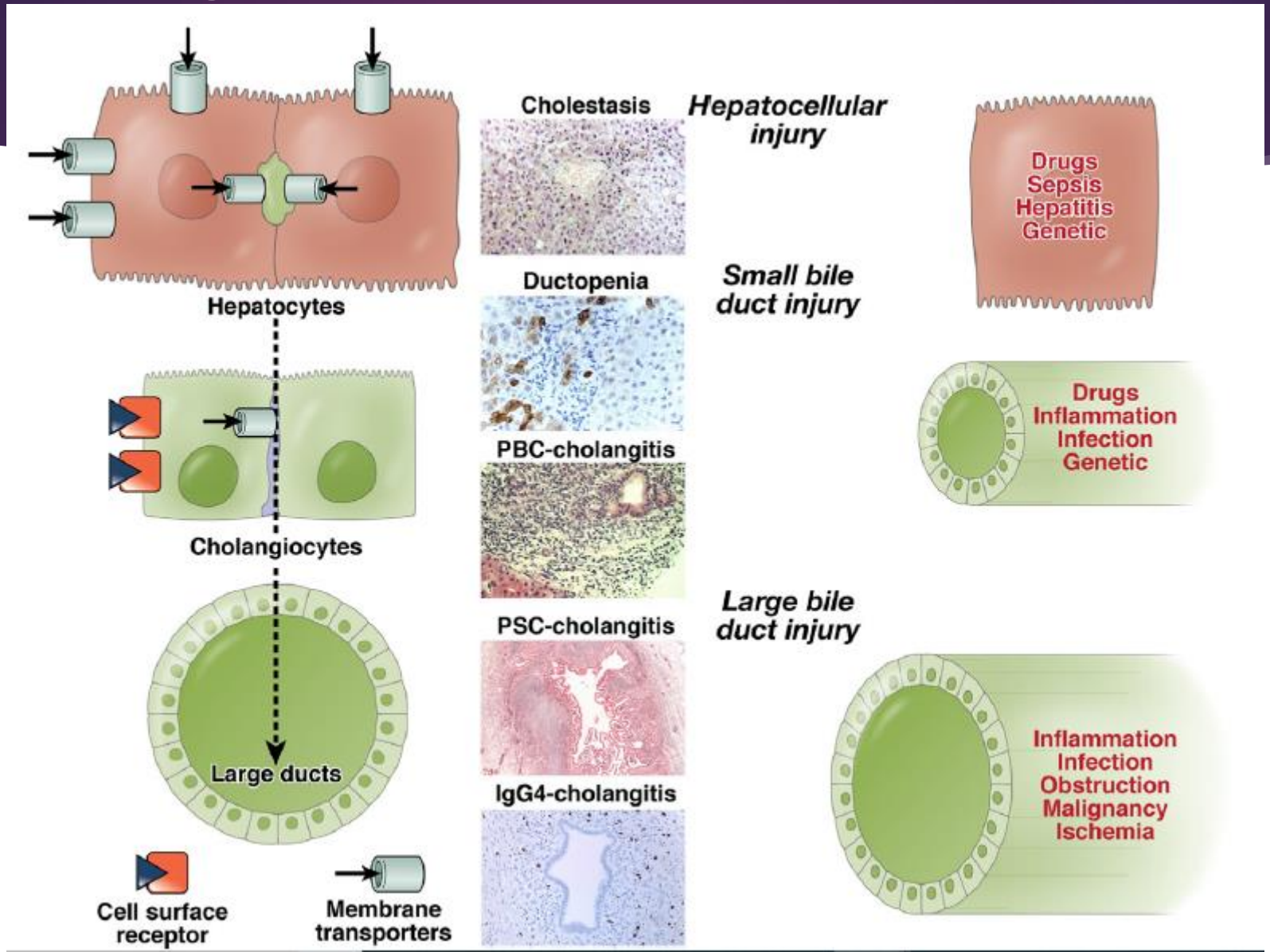
(i) hepatocellular and/or cholangiocellular secretory defects

(ii) obstruction of bile ducts by bile duct lesions, stones or tumours

(iii) mixed mechanisms in conditions such as primary biliary cirrhosis/cholangitis (PBC) or primary sclerosing cholangitis (PSC).

Beueurs U et al. J Hepatol. 2015 Apr;62(1 Suppl):S25-37.

Pathology of cholestasis



Hirschfield GM et al. GASTROENTEROLOGY 2010;139:1481–1496

Causes of cholestatic jaundice

Extrahepatic Cholestasis

- Choledocholithiasis
- Benign bile duct strictures
- Primary or secondary sclerosing cholangitis
- Mirizzi syndrome
- Cholangiocarcinoma
- Pancreatic cancer
- Ampullary adenoma/carcinoma

Shah R et al. Cholestatic Jaundice (Cholestasis, Cholestatic Hepatitis) . In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2019

Causes of cholestatic jaundice

- **Intrahepatic Cholestasis**
- ***Hepatocellular Causes***
- Viral hepatitis
- Acute alcoholic hepatitis
- Parenteral nutrition
- Intrahepatic atresia (infantile cholangiopathy)
- Zellweger syndrome
- ***Canalicular Membrane Changes***
- Medication (contraceptive pills, antibiotics, antithyroid drugs, sulphonamides)
- Cholestasis in pregnancy

Shah R et al. Cholestatic Jaundice (Cholestasis, Cholestatic Hepatitis) . In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2019

Genetic Defects in Bile Transporters

- Benign recurrent intrahepatic cholestasis (BRIC)
- Progressive familial intrahepatic cholestasis (PFIC)

Canalicular/Ductular Luminal Obstruction

- Cholestasis due to sickle cell disease
- Hereditary protoporphyria
- Bacterial infections, sepsis
- Cystic fibrosis

Ductopenia

- Familial, drug-induced, chronic allograft rejection, Hodgkin disease, sarcoidosis, primary sclerosing cholangitis, primary biliary cholangitis

Shah R et al. Cholestatic Jaundice (Cholestasis, Cholestatic Hepatitis) . In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2019

Clinical presentation of cholestatic jaundice

- Patients with biliary obstruction present with fever, pruritus, abdominal pain, weight loss, muscle wasting, dark urine, and pale stools.
- Choledocholithiasis is the most common non-neoplastic cause of biliary obstruction.
- Presence of pain, specifically epigastric or right upper quadrant pain before the onset of jaundice might suggest choledocholithiasis or cholecystitis causing Mirrizi syndrome
- Presence of fever is highly suggestive of cholangitis.
- The onset of jaundice after any hepatobiliary surgery indicate bile duct injury, bile duct leak.
- Jaundice is not always present in cholestasis

1) Fargo MV et al. Evaluation of jaundice in adults. Am Fam Physician. 2017 Feb 1;95(3):164-8.
2) Shah R et al. Cholestatic Jaundice (Cholestasis, Cholestatic Hepatitis) . In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2019

Investigations

- Direct hyperbilirubinemia (more than 50% of total bilirubin) is observed.
- Serum alkaline phosphatase is also evaluated 3 times more than the upper normal limit in cholestasis, normal or mild elevation in transaminases (ALT/AST) is a pure form of cholestatic jaundice.

Hematology

- Leukocytosis is found in cholangitis, alcoholic hepatitis, and underlying malignancy.
- Acute severe anemia can be found due to hemolysis. Evaluation of peripheral smear, reticulocyte count can help to differentiate. Chronic anemia can be seen in cirrhosis or underlying malignancy.
- Elevated prothrombin time can be seen with cholestasis which rapidly reverses with vitamin K supplementation

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Shah R et al. Cholestatic Jaundice (Cholestasis, Cholestatic Hepatitis) . In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2019

Investigations

Radiological Evaluation

- Abdominal ultrasound helps to identify if there is any biliary ductal dilation and help differentiate hepatocellular causes of cholestasis versus biliary obstruction.
- If dilated biliary ducts are encountered on initial ultrasound, then magnetic resonance cholangiopancreatography can be used to assess bile ducts to identify stone, stricture vs. malignancy.

Liver Biopsy

- Helpful in intrahepatic cholestasis to evaluate for various possible underlying etiologies

Shah R et al. Cholestatic Jaundice (Cholestasis, Cholestatic Hepatitis) . In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2019

Medical management

- Ursodeoxycholic acid improves intrahepatic cholestasis , can be used in doses of 13 to 15 mg/kg per day to reduce itching in patients with cholestasis due to drug-associated cholestasis.

Shah R et al. Cholestatic Jaundice (Cholestasis, Cholestatic Hepatitis) . In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2019

Treatment

- Management of cholestatic jaundice depends upon etiology and type of cholestasis. The mainstay of obstructive cholestasis is biliary decompression.
- Antibiotics are considered in pre and post biliary decompression phase to reduce the risk of sepsis
- In common bile duct stones, endoscopic sphincterotomy with or without stent placement can relieve the obstruction.

Shah R et al. Cholestatic Jaundice (Cholestasis, Cholestatic Hepatitis) . In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2019

Treatment

- In benign CBD strictures, stricture dilation and stent placement can relieve the obstruction.
- In malignant obstruction If complete resection is not possible, surgical hepaticojejunostomy and the Roux-en-Y bypass is an option.
- If a patient is not a surgical candidate, either palliative CBD stent is placed endoscopically (usually metal stent).
- If endoscopic stent placement is not successful, a percutaneous transhepatic cholangiography tube can be placed for biliary decompression.

Shah R et al. Cholestatic Jaundice (Cholestasis, Cholestatic Hepatitis) . In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2019

Non-alcoholic fatty liver disease

- Non-alcoholic fatty liver disease (NAFLD) encompasses the simple steatosis to more progressive steatosis with associated hepatitis, fibrosis, cirrhosis, hepatocellular Ca.
- NAFLD is comprised of non-alcoholic fatty liver (NAFL) and non-alcoholic steatohepatitis (NASH)
- NAFL is characterized by steatosis of the liver, involving greater than 5% of parenchyma, with no evidence of hepatocyte injury
- NASH is defined by histologic terms, that is a necroinflammatory process whereby the liver cells become injured in a background of steatosis.

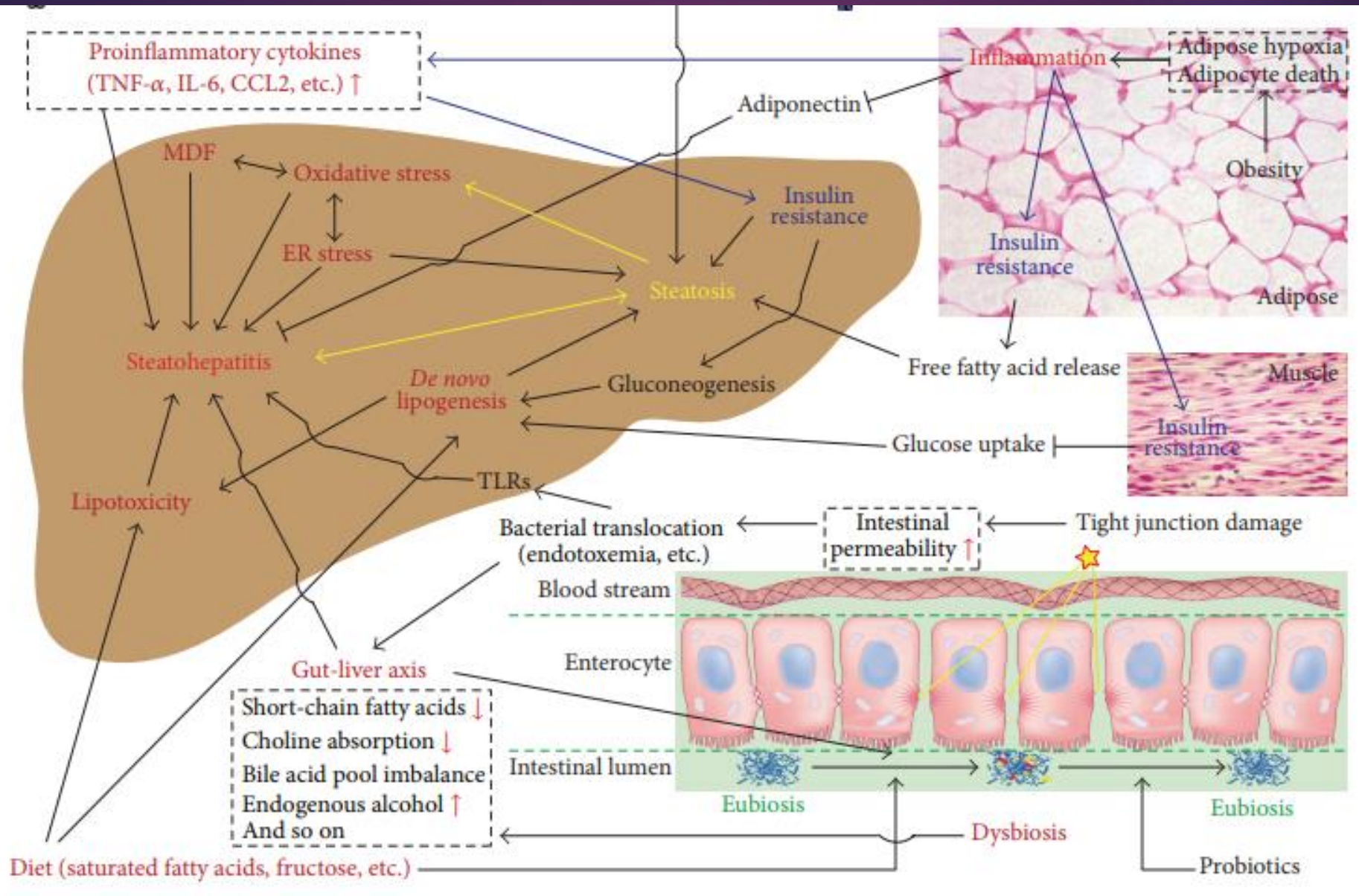
Benedict M et al. World J Hepatol 2017 June 8; 9(16): 715-732

Risk factors

- Metabolic syndrome and type 2 diabetes mellitus.
- Gender and age- More common in men aged 50-60 years
- Diet, smoking and life style –High fat intake, sedentary life style
- Polycystic ovarian syndrome
- Obstructive sleep apnea

Benedict M et al. World J Hepatol 2017 June 8; 9(16): 715-732

Pathogenesis



Yu J et al. Gastroenterol Res Pract. 2016;2016:2862173.

Clinical features

- Fatigue is the common symptom. .[1]
- Malaise , vague right upper abdominal discomfort.[1]
- Anxiety , thirst, feeling of changing temperature bloating. [2]

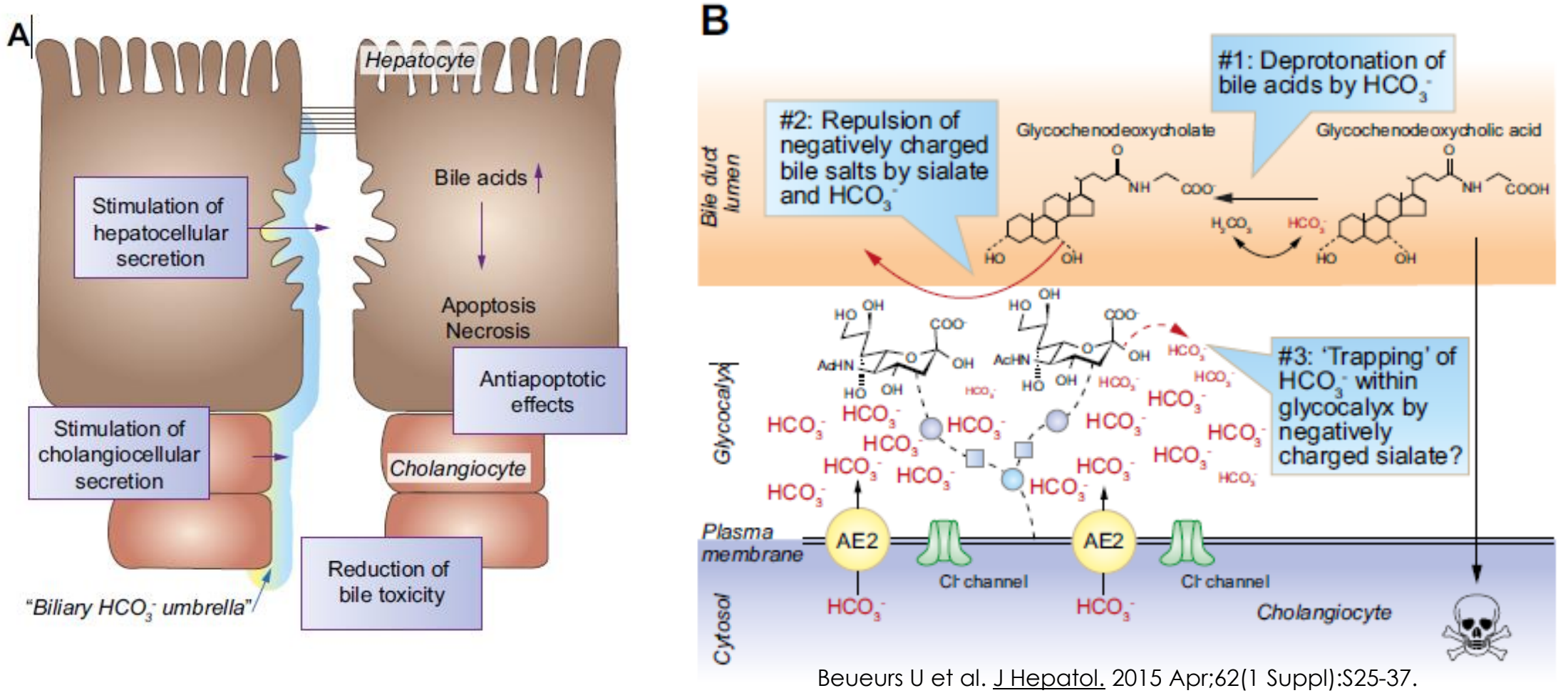
1) **Seth SG et al. Epidemiology, clinical features, and diagnosis of nonalcoholic fatty liver disease in adults: Uptodate; 2019.Apr 03, 2018.**
2) **Khoonsari M et al.** Iran J Pathol. 2017 Spring; 12(2): 99–105

Ursodeoxycholic acid

- Ursodeoxycholic acid (UDCA) is a non-toxic, hydrophilic bile acid indicated for treatment of gallstones and primary biliary cirrhosis.
- Increasing bile pool hydrophilicity via UDCA serves to improve cholestasis and minimize toxicity.
- UDCA stimulates hepatocellular and biliary ductular secretions, and to exert anti-inflammatory effects, making it attractive as treatment for a multitude of liver diseases.
- UDCA has efficacy in reducing histologic progression of PBC, as well as the need for liver transplantation and survival.

Reardon J et al . J Clin Transl Hepatol. 2016 Sep 28;4(3):192-205

Mechanism of action of Ursodeoxycholic acid



Beueurs U et al. J Hepatol. 2015 Apr;62(1 Suppl):S25-37.

Mechanisms

- **Replacement/displacement of toxic bile acid:** UDCA replaces/ displaces more hydrophobic toxic endogenous bile acids, hence the liver and peripheral tissues are exposed to lower levels of endogenous bile acids to an increased concentration of UDCA.
- **Cytoprotective effects:** The hydrophilic bile acid UDCA protects hepatocytes and bile duct epithelial cells (cholangiocytes) against necrosis and apoptosis induced by hydrophobic bile acids through direct membrane-stabilizing effects of UDCA.
- **Immunomodulatory effects:**UDCA treatment lowers serum levels of immunoglobulin M, antimitochondrial antibodies (AMA) and antibodies against pyruvate dehydrogenase

Flamm S et al. Trials of ursodeoxycholic acid for the treatment of primary biliary cholangitis.Uptodate. :2019. updated 2018 Sep 13.

Mechanisms

- **Stimulation of bile secretion**: UDCA stimulates bile secretion through stimulation of vesicular exocytosis, stimulation of transporter gene expression and stimulation of ductular bicarbonate secretion via cholehepatic shunting.
- **Stimulation of exocytosis and insertion of canalicular membrane transporters:** UDCA enhance the biliary excretory capacity of the cholestatic liver by activation of hepatocellular [Ca2+], a-PKC, and mitogen-activated protein kinases, resulting in stimulation of vesicular exocytosis.

Flamm S et al. Trials of ursodeoxycholic acid for the treatment of primary biliary cholangitis.Uptodate. :2019. updated 2018 Sep 13.

Mechanisms

- **Bicarbonate-rich hypercholeresis**- protonation of unconjugated UDCA in the bile ducts results in the generation of a HCO3 ± anion each time an unconjugated UDCA molecule is taken up via passive diffusion and undergoes cholehepatic shunting via the peribiliary plexus.
- **Stimulation of defective gene expression of hepatobiliary transport system:** Increased expression of hepatobiliary transporters under UDCA treatment due to stimulation of gene transcription

Flamm S et al. Trials of ursodeoxycholic acid for the treatment of primary biliary cholangitis.Uptodate. :2019. updated 2018 Sep 13.

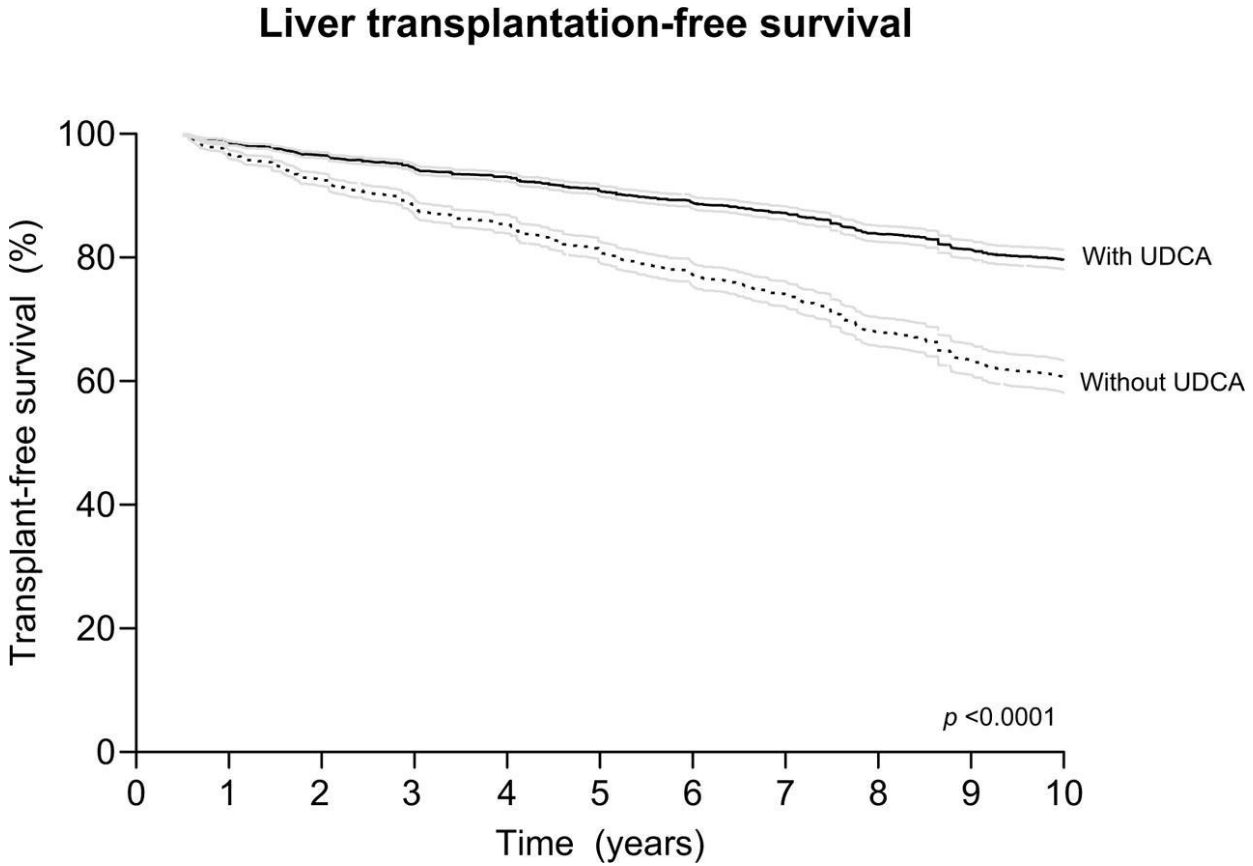
Efficacy of ursodeoxycholic acid (UDCA) therapy in patients with primary biliary cholangitis

- **Methods:** Global PBC Study Group database originating from 8 countries in Europe and North America.

  3,529 patients (90.4%) were treated with UDCA and 373 patients (9.6%) were not treated.

- **Results:** 10-year cumulative Liver Transplant-free survival was 79.7% (95% CI 78.1–81.2) among UDCA-treated patients and 60.7% (95% CI 58.2–63.4) among untreated patients (p <0.001).

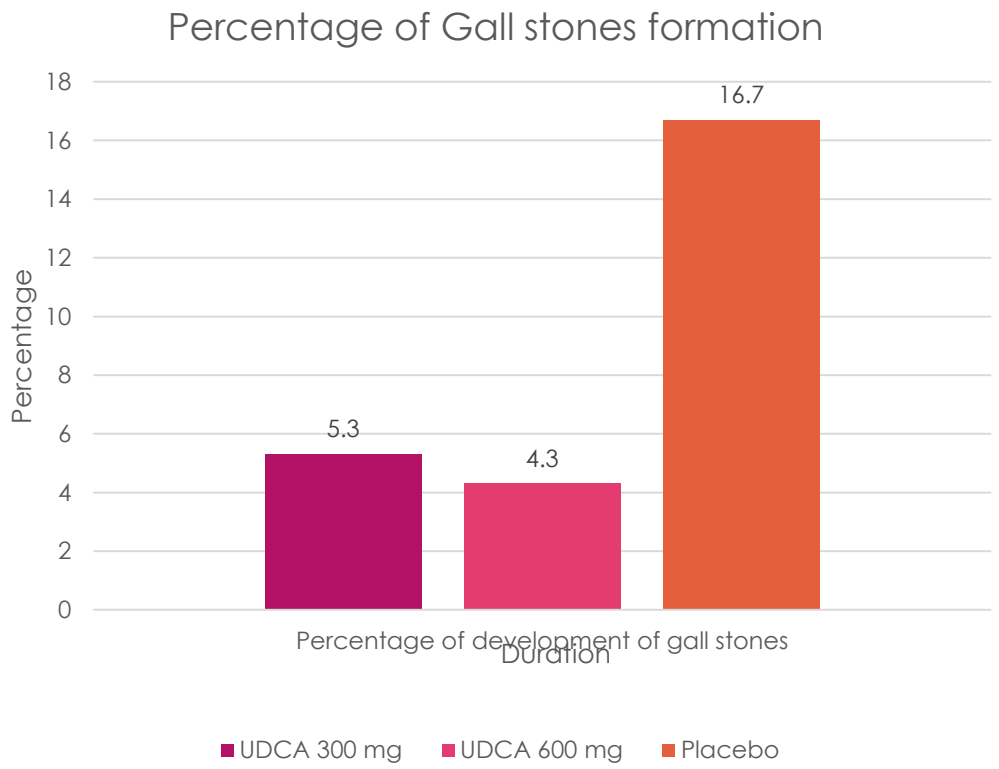
- **Conclusion:** UDCA improves LT-free survival among patients with PBC



Harms MH et al. J Hepatol. 2019. pii: S0168-8278(19)30228-4

EFFICACY AND SAFETY OF URSODEOXYCHOLIC ACID GASTRECTOMY

- **Methods:** Multicenter, randomized, double-blind, placebo-controlled clinical trial. 465 Patients with gastric cancer who underwent gastrectomy were treated with UDCA 300mg, 600mg, and placebo were administered daily for 52 weeks. Ultrasound repeated every 3 months.The primary endpoint was the proportion of patients developing gallstones within 12 months after gastrectomy.
- **Results:** . The proportion of patients developing gallstones within 12 months after gastrectomy was 8/151 (5.3%), 7/164 (4.3%) and 25/150 (16.7%) in the UDCA300mg, UDCA600mg, and placebo groups, respectively.
- **Conclusion:** UDCA administration was effectives and well tolerated and prevents gallstone formation after gastrectomy



Lee SH et al. Gastroenterology. 2019 May 1;156(6):S-8.

Summary

- UDCA exerts its beneficial effect in liver diseases through a diverse complementary array of mechanisms.
- UDCA is of proven efficacy in prolongation of survival in the treatment of PBC.
- The clinical use and effcacy of UDCA in Primary Biliary Cirrhosis has been evident
- UDCA has been found to be effective in cholestatic disorders.
- Ursodeoxycholic acid is generally well tolerated.