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Deranged liver biochemistry in asymptomatic individuals: What to do?

Nikolaos K. Gatselis

Assistant Professor of Medicine

Department of Medicine and Research Lab of Internal Medicine

Larissa Medical School, Thessaly University

Internal Medicine Society of Greece

Liver Function Tests (LFTs)

- aminotransferases (AST, ALT)
- alkaline phosphatase (ALP)
- γ-glutamyl transpeptidase (γ-GT)

biochemical markers of liver injury

- bilirubin (total, direct)
- albumin
- prothrombin time

markers of hepatocellular function

Asymptomatic elevation of liver enzymes

- Retest to confirm the abnormal values
- Search for previous laboratory tests (how long has the elevation been present?)
- Assess the degree of elevation
- Different diagnostic algorithm of abnormal transaminases than the increase in cholestatic enzymes

Common and rare causes of elevated transaminases (AST/ALT)

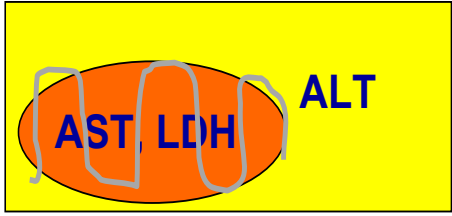
Common Causes	Relatively rare causes	Rather to extremely rare causes
Alcohol abuse	Autoimmune hepatitis	Celiac disease
Chronic hepatitis B or C	Hyperthyroidism	Addison's disease
NAFLD	Intense muscular exercise	Inherited disorders of muscle cells metabolism
Drugs, toxic substances and/or "healthy" food supplements	Wilson's disease	Acquired muscle disease (e.g. polymyositis)
	a1-antitrypsin deficiency	
	Hemochromatosis (primary or secondary)	

Common causes of elevated cholestatic enzymes (γGT/ALP)

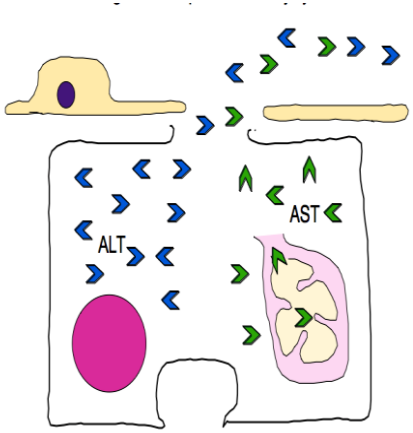
Cholestatic diseases	Infiltrating liver diseases
Primary biliary cholangitis	Hepatocellular carcinoma
Primary or secondary sclerosing cholangitis	Metastatic liver cancer
Bile duct obstruction (partial)	Granulomatous diseases (sarcoidosis, tuberculosis, granulomatosis with polyangitis, leprosy)
Drug induced (e.g. anabolic steroids)	Liver abscess
IgG4-related disease	Amyloidosis

Most of the time, with history and physical you should have a good idea what's the likely cause of the elevated liver tests!

Aminotransferases
AST & ALT

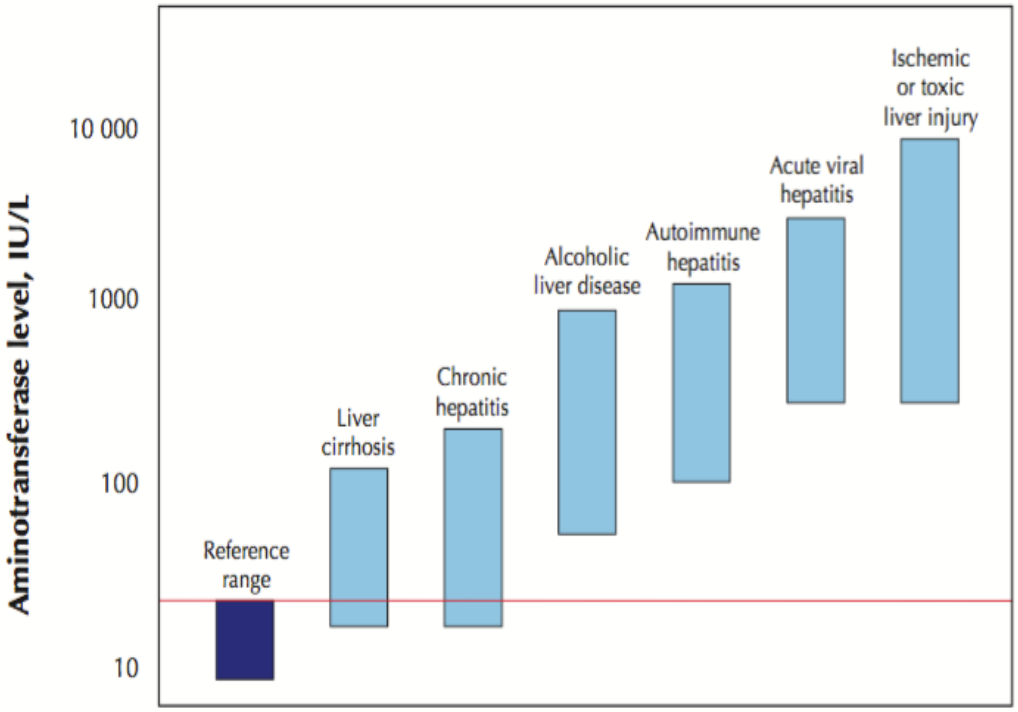


- Sensitive markers of hepatocellular damage
- Usually suggest necrosis of hepatocytes
- **ALT**: mainly produced in the liver
- **AST**: liver, heart, muscles, brain



Degree of elevation of transaminases

- **<300 IU/ml**
  - alcoholic hepatitis, NAFLD, alcoholic liver disease, chronic viral hepatitis, autoimmune hepatitis
- **500 - 5000 IU/ml**
  - acute viral hepatitis, acute severe autoimmune hepatitis, drugs
- **>5000 IU/ml**
  - ischemic hepatitis, liver failure from paracetamol overdose, HSV



Transaminases and alcohol
A special occasion

- Vit. B6 = cofactor for AST, ALT
- ↓Vit. B6 => ↓AST, ↓↓ALT
- Alcohol transfer mAST from mitochondria to cytoplasm and thereafter to serum

AST > ALT

AST, ALT levels do not reflect the degree of damage in alcoholic liver disease

- **A (alpha) for A**
- **B (beta) for B**
- **Γ (gamma) for C**
- **Δ (delta) for D**

Question

Which are the normal values of transaminases:

A. according to each laboratory report

B. individualized for each patient

C. less than 30 IU/L for ♂and 19 IU/L for ♀

D. none of the above

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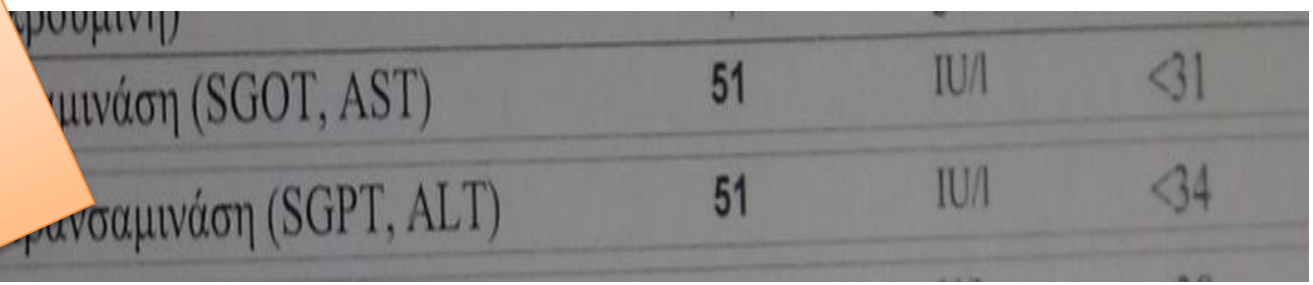
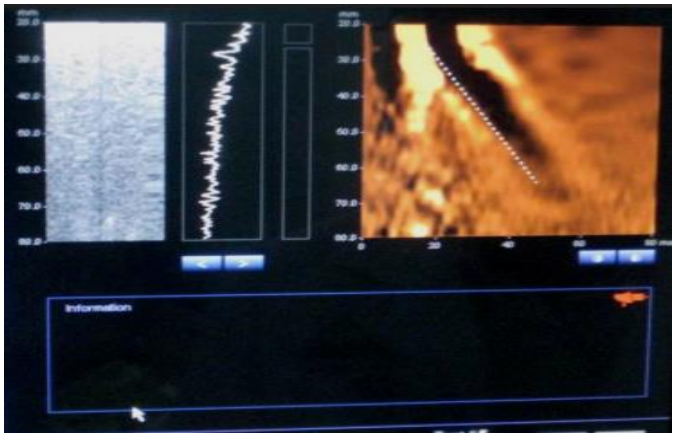
Diagnostic approach of asymptomatic patients with elevated transaminases

What are the normal values?

Clinical case
female 60-years-old
no symptoms
Hx: hypertension, DM, dyslipidemia
Treatment: statin



- Chronic hepatitis C



Fibroscan: 14.6 kPa

F4 (METAVIR)

ALREADY CIRRHOTIC!!!!

Diagnostic approach of asymptomatic patients with elevated transaminases

What are the normal values?

- **Use only one value as ULN**
  - 40 IU/L (classical value)
  - 19 IU/L (females) & 30 IU/L (males)
  - do not rely on ULN of laboratories

Alcohol

- Detailed history & physical examination
- AST/ALT > 2:1 (90%)
- AST<8x & ALT<5x or normal
- ^γGT
- macrocytosis (^MCV)
- US: yes
- CT or MRI: no
- Liver biopsy is not required
- Check for HBV and HCV

parotid enlargement
rinophyma

Alcohol

Clinical case

- 28-years-old-woman, kindergarten teacher
- ascites due to portal hypertension
- HBV & HCV (-)
- AST/ALT = 1:1
- Drugs (-)
- Alcohol (-)
- Investigation for:
  - AIH (-)
  - Vascular diseases (-)
  - Wilson, hemochromatosis (-)
  - rare systemic diseases (-)

Alcohol

Clinical case

The question never asked…

- Question: ***Do you consume alcohol?***
- Response: ***No! Only whenever I go out!***
- Question: ***How often do you go out?***
- Response: ***Almost everyday!!!***

Clinical case

- 45 years old South Africa man
- presents for routine physical and found to have elevated liver tests
- PMH: hyperlipidemia
- Soc: drinks 2 bee[illegible] use
- Born i[illegible]ved there for 15 years
- [illegible]hone (but he mentions that they don't g[illegible]the doctor)
- PE: normal
- AST 50, ALT 60, ALP 70, Tbili 0.5
- US normal

Chronic hepatitis B

Question

A patient with chronic hepatitis B from medium or high endemic area, most likely get infected:

A. by intravenous drug use

B. during birth or childhood (intrafamilial spread)

C. by sexual contact

D. by blood transfusion

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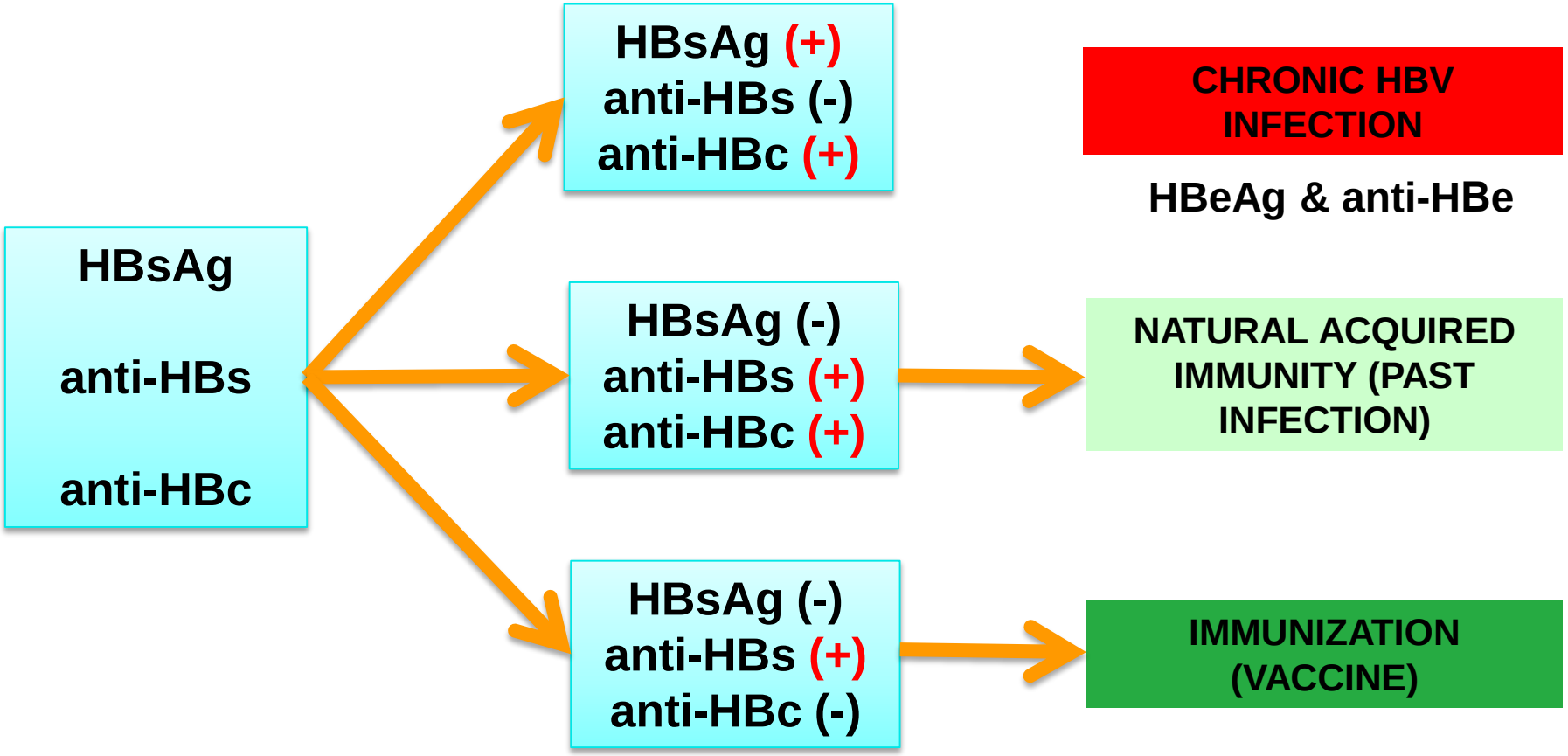
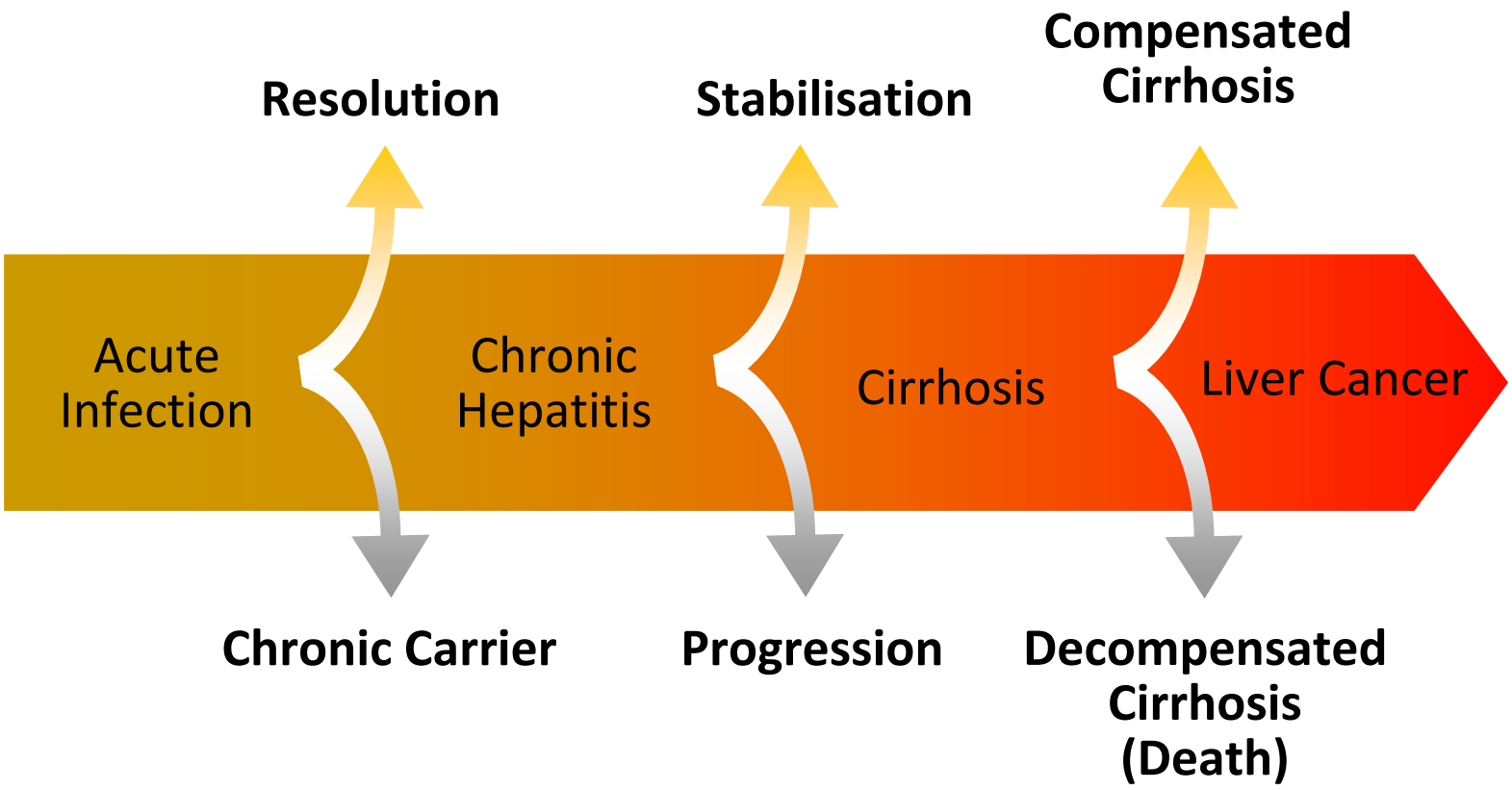
HBV serologies



Chronic hepatitis B

The importance of an early diagnosis



DIAGNOSE AND TREAT TIMELY

Question

Which the most successful way to eradicate the hepatitis delta virus:

A. **The improvement of socioeconomic conditions**
B. **Radical vaccination against HBV**
C. **Precaution measures against HIV**
D. **A and C**

Question

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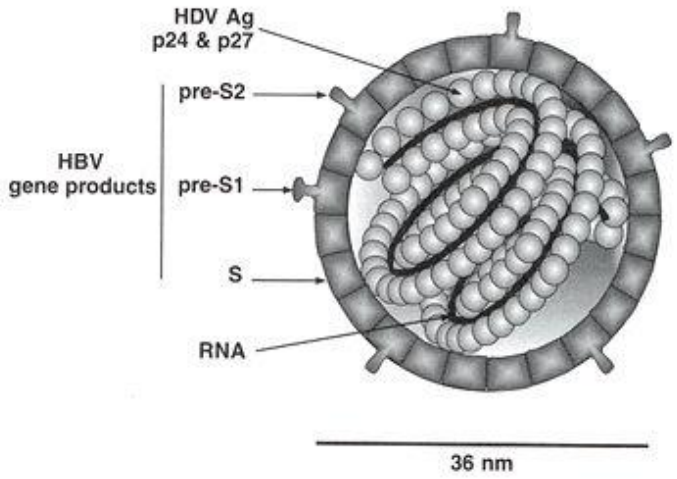
B. **Radical vaccination against HBV**

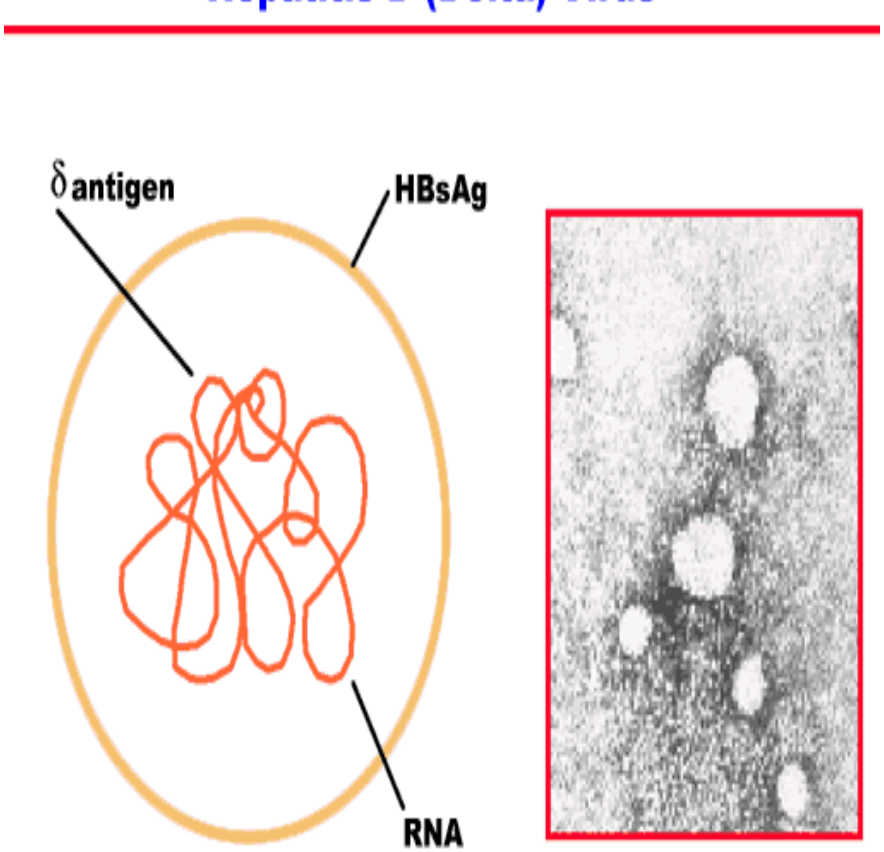
C. Precaution measures against HIV

D. A and C

Hepatitis Delta (HDV)

This virus could infect only patients with hepatitis B.

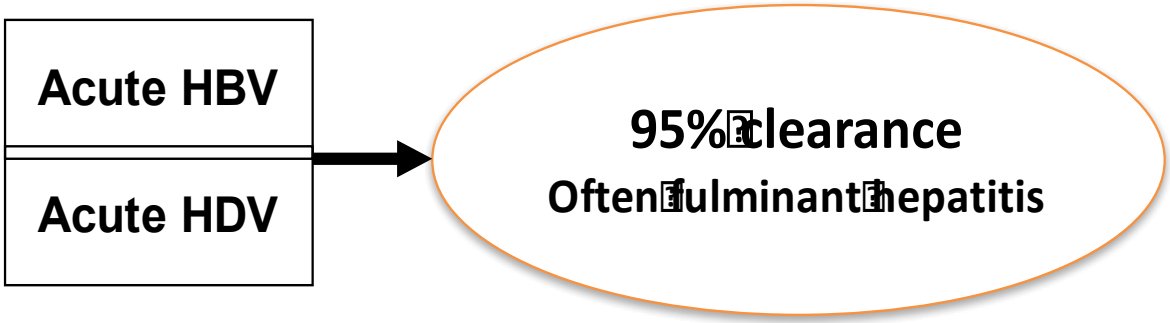




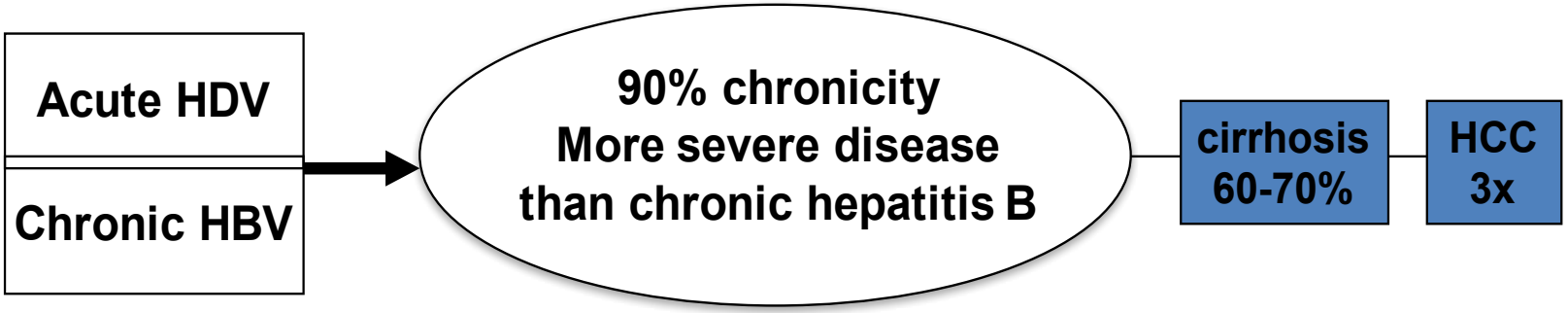
Hepatitis Delta (HDV)

Clinical course

HBV-HDV co-infection



HBV-HDV super-infection



Hadziyannis, J Gastroenterol Hepatol 1997. Farci, J Hepatol 2003. Fattovich et al, Gut 2000. Buti et al, J Viral Hepat 2010.

Hepatitis Delta (HDV)

Diagnostic markers

- **anti-HDV (IgG and IgM)**
  - check in all patients with HBV infection at the beginning of follow-up and periodically thereafter
- **HDV RNA**
  - identify individuals with active HDV infection
  - decide to initiate treatment
  - monitor antiviral treatment efficacy
  - tailor treatment schedule

DO NOT FORGET THE HEPATITIS DELTA VIRUS IN ALL CHRONIC HEPATITS B VIRUS INFECTED PATIENTS!!!

Gatselis, J Hepatol 2010 (abst)

Clinical case

- 48 years old man is found to have abnormal liver tests on routine physical exami
- No significant previous
- On no medi
- once in college”
- normal
- AST 62, ALT 88, ALP 75, Tbil 0.7, INR 1.0, Albumin 4.1

Chronic hepatitis C

Diagnostic workup for hepatitis C

detection of anti-HCV Abs

AND

confirmation of positive results in a 2nd sample

(sensitivity of EIA 92-97%)

anti-HCV (+)

Regardless of AST/ALT values

↓

refer to Hepatology Unit

↓

HCV RNA, genotype, Fibroscan®

↓

treatment initiation with direct acting antivirals preferably

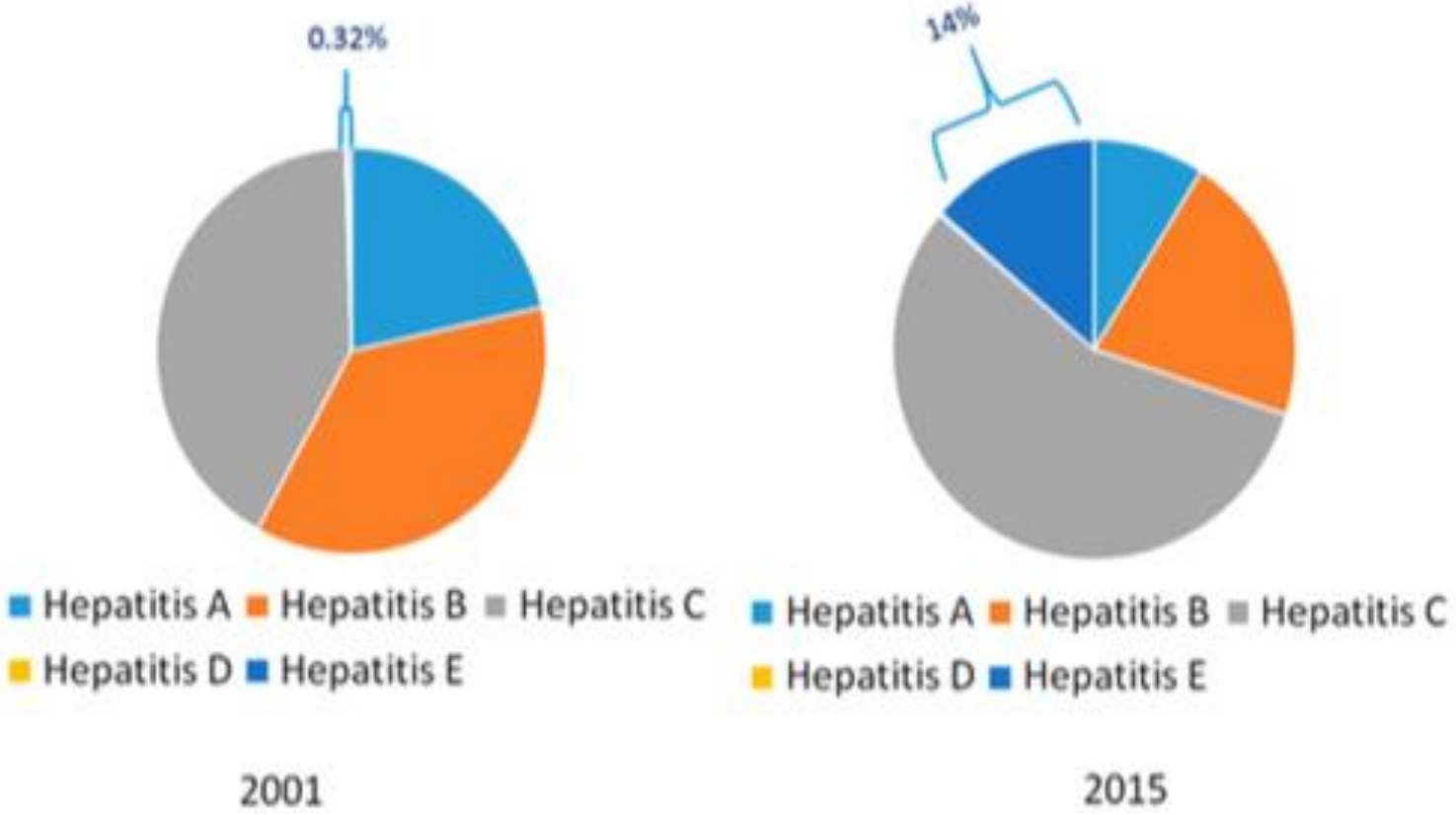
Viral hepatitis

Clues from the medical history
High risk groups

- family history (HBV)
- travel history (HAV, HEV)
- sexual history (HBV, MSM→HAV)
- origin (Asia, Africa →HBV)
- illicit drug use (HBV, HDV, HCV) (i.v. or snorted - even once)
- Hx of blood transfusion (especially before 1992)
- tatoos
- healthcare workers - needlesticks

Hepatitis E Virus
A old friend from the past!

Proportion of reported cases of acute viral hepatitis in Germany



Robert-Koch-Institute data.

Clinical case

- 45-years-old male
- ALT: 85 , AST: 60 IU/ml (twice)
- Virology test: neg
- No alcohol consu
- Works
- 2

Drug induced liver injury

A ysis due to extreme strength training

B.NAFLD

C.A laboratory error

D.Nothing of the above

Drugs and Toxic Substances

- **Non-steroidal anti-inflammatory drugs (NSAIDs)**
- **Antibiotics**
  - synthetic penicillin, quinolones, ketoconazole, fluconazole, isoniazid, rifampicin
- **Antiepileptics**
  - phenytoin, carbamazepine
- **Hypolipidemic** (statin)
- **Anabolic**
- **Homeopathic medicine**
- **Supplements (herbals)**
- **Toxic substances**
  - cocaine, ecstasy, LSD

When did you start them?
Any changes in doses?

LIVER BIOPSY USUALLY NOT REQUIRED
DISCONTINUATION OF "SUSPICIOUS" AGENTS & CLOSE MONITORING

Question

Which is the commonest cause of death in patients with NAFLD/NASH:

A. Cardiovascular diseases
B. Liver related complications
C. Neoplasia
D. The expected survival is similar to general population

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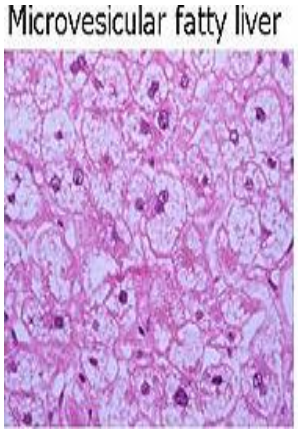
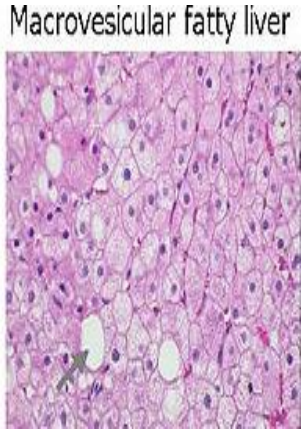
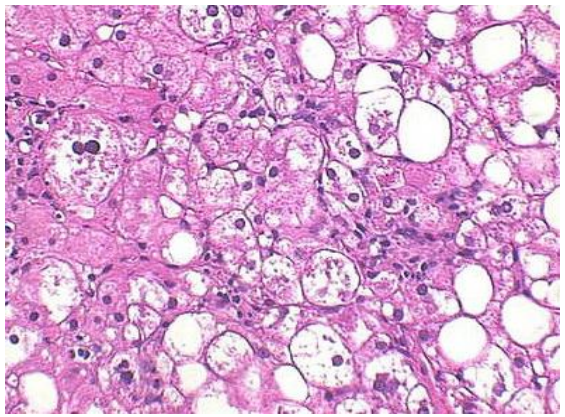
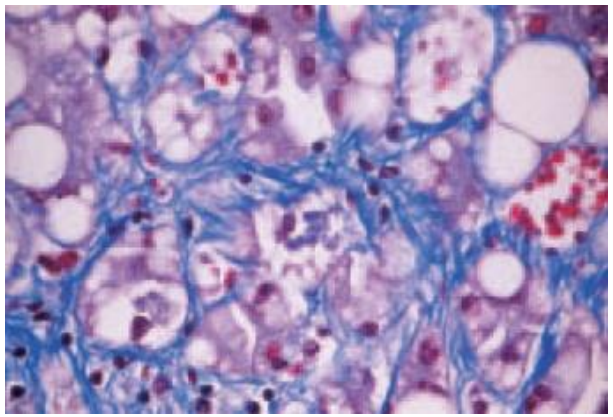
Non-alcoholic fatty liver disease (steatosis ± steatohepatitis)









Fatty liver Steatosis → **Non-alcoholic Steatohepatitis** → **Fibrosis Cirrhosis**

METABOLIC SYNDROME
obesity
hyperinsulinemia
peripheral insulin resistance
diabetes
hypertriglyceridemia
hypertension

It is rather a benign disease

Non-alcoholic fatty liver disease (steatosis ± steatohepatitis)

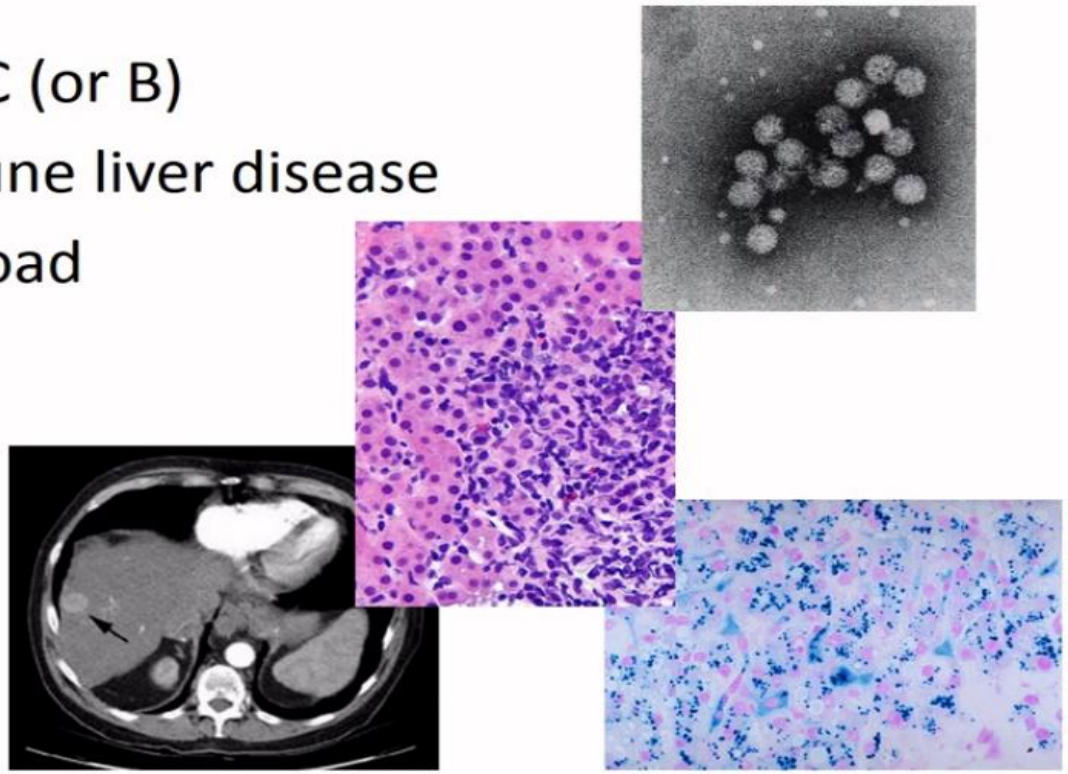
- thorough history
- ALT > AST
- US: liver hyperechogenicity (supports clinical diagnosis)
- CT or MRI: not required
- Accurate diagnosis by liver biopsy but it is not always required

It's a diagnosis of exclusion

Non-alcoholic fatty liver disease (steatosis ± steatohepatitis)

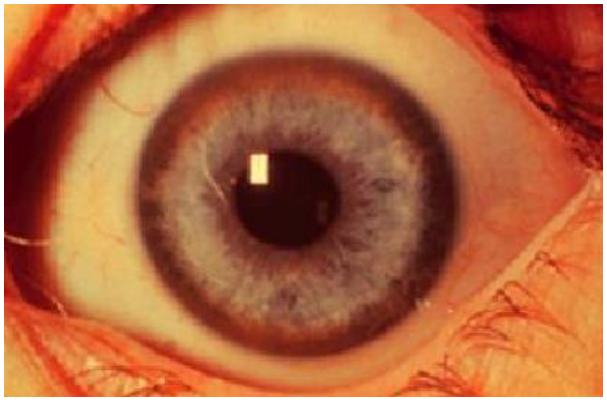
NAFLD/NASH does not protect you from having another liver disease!!!

- Hepatitis C (or B)
- Autoimmune liver disease
- Iron overload
- Cancer



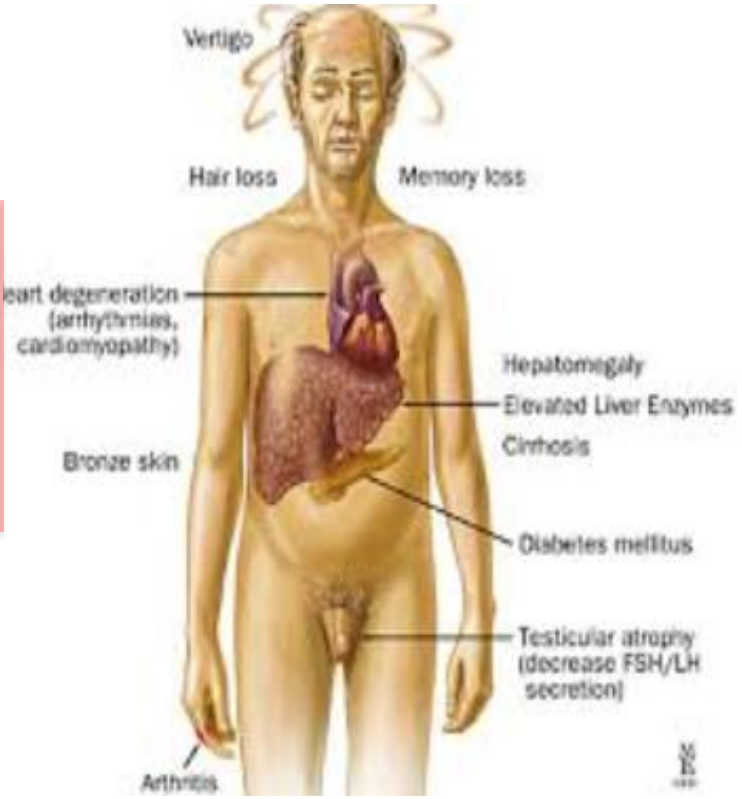
Wilson disease

- generally affects young people (<45 years old)
- hepatic/neurologic/psychiatric manifestations
- ↓ceruloplasmin
- ↑24hr urine cooper excretion
- hemolysis
- Kayser-Fleischer ring
- *ATP7B* mutations



Hemochromatosis

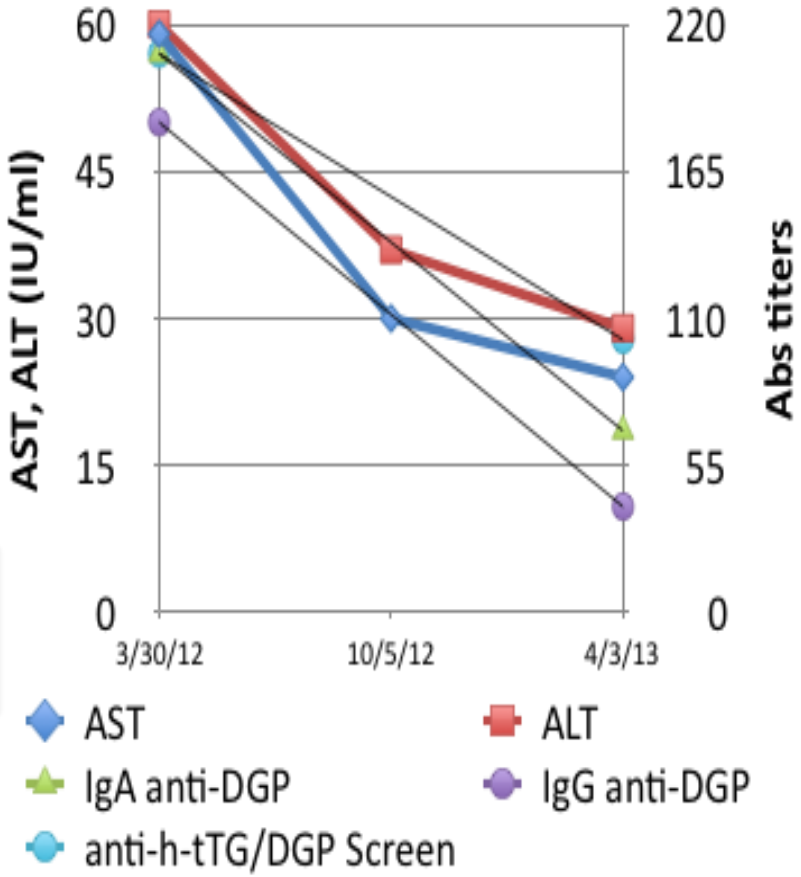
- Hereditary (primary) or multiple transfusions (secondary)
- ↑ferritin
- Transferrin saturation (serum Fe / TIBC) x 100 >40%
- **HFE genotype**: C282Y/C282Y, C282Y/H63D, H63D/H63D(?)
- Hemojuvelin, Transferin receptor 2, Ferroportin 1



Celiac disease

Clinical case

- female 50-years-old (menopausal)
- transaminasemia during the last 5 years
- Hx: irritable bowel syndrome, ferrum deficiency, atrophic gastritis, Hashimoto thyroiditis
- anti-h-tTG/DGP (IgA/IgG) screen (+++)
- endoscopy: atrophy of villi
- Marsh III



Clinical case

- 56 years old woman presents with fatigue, myalgias
- PMH: hypothyroidism, hypertension
- Meds: thyroxin, atenolol
- So: no E/D
- FHx: father wit
- PE: with mild EUQ tenderness to
- A 245, ALT 280, Tbil 1.8, ALP 207
- ALB 3.8, INR 1.2
- globulins 5 g/dL & IgG 2300 mg/dL
- US mild hepatomegaly

Autoimmune hepatitis

Autoimmune hepatitis

Characteristics

1. progressive liver disease
2. hypergammaglobulinemia (↑IgG)
3. circulating autoantibodies
4. interface hepatitis
5. favorable response to immunosuppressive treatment

Without treatment: 10-years survival only 10%

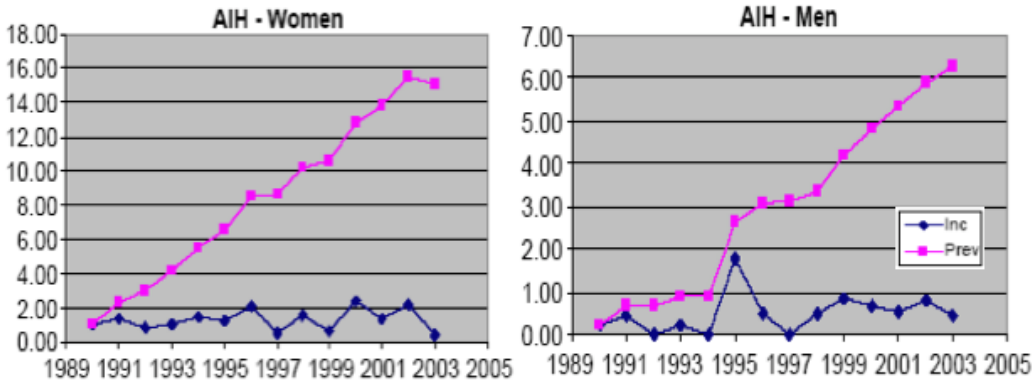
Gatselis et al, WJH 2015. Zachou APT 2016. Zachou APT 2013.

Autoimmune hepatitis

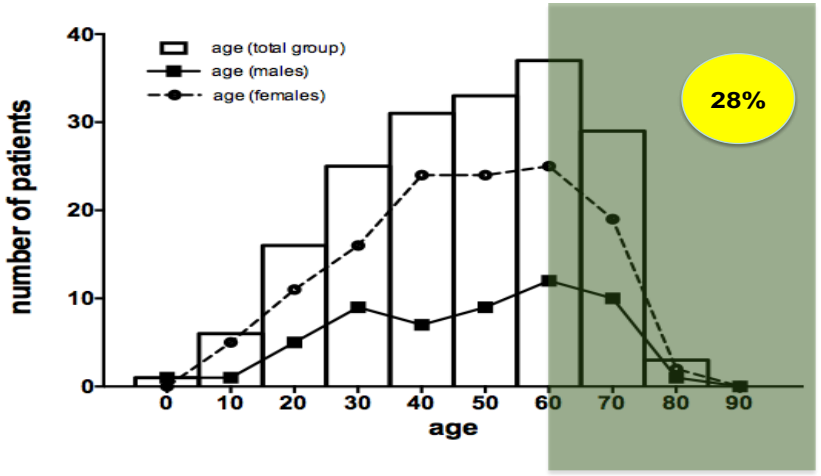
The burden of the disease

- Under-diagnosed due to unfamiliar clinical physicians, laboratories, pathologists
- Estimate prevalence: 10-20/1000000 (Europe, N. America)
- Similar to SLE, PBC, Myasthenia Gravis

It not only a disease of young females!!!



Werner M, Scand J Gastroenterol 2008



Zachou, J Hepatol 2011. Gatselis, AASLD 2016. Zachou, APT 2016

Autoimmune hepatitis

Classification & Autoantibodies

AIH-1

- ANA
- SMA
- ANCA
- anti - ASGP-R
- anti - SLA/LP

AIH-2

- anti - LKM-1
- anti - LKM-3
- anti - LC1
- anti - ASGP-R

Gatselis, WJG 2015. Dalekos, Eur J Intern Med 2002.
Zachou, J Autoimmun Dis 2004. Krawitt, NEJM 2006. Zachou, APT 2013.

Cholestatic enzymes
Alkaline phosphatase (ALP)

- **liver**, **bone**, placenta, intestine, kidney, leucocytes
- higher in children, adolescents, pregnancy
- increase in:
  - **cholestatic syndromes**
    - level of increase does not distinguish intra- or extra-hepatic obstruction
  - **liver infiltrating diseases**
    - hepatocellular carcinoma, sarcoidosis, tuberculosis, amyloidosis, liver abscess
  - **other causes**: bone diseases with osteoblastic activity

Cholestatic enzymes
γ-glutamyl transpeptidase (γGT)

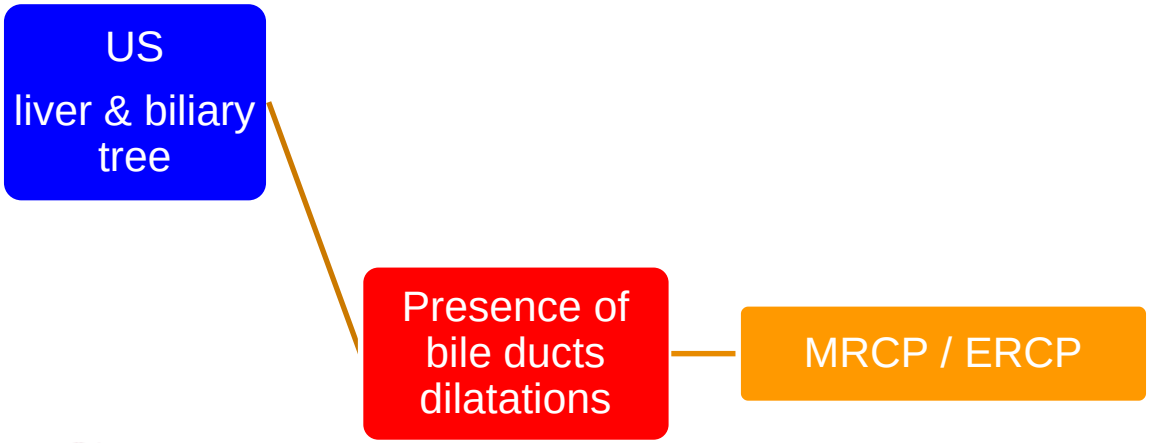
- liver, pancreas, spleen, heart, seminal vesicle, kidney, brain
- higher in males
- increases in:
  - pancreatic diseases, alcoholism, phenytoin or barbiturate, myocardial infarction, renal insufficiency, chronic obstructive pulmonary disease, diabetes mellitus
- a sensitive marker for liver diseases when increases in parallel with ALP

Diagnostic approach of asymptomatic patients with elevated cholestatic enzymes

- **History and physical examination**

- **Ultrasound imaging of liver and biliary tree**

Diagnostic approach of asymptomatic patients with elevated cholestatic enzymes



Clinical case

- A 47 year old Caucasian female presents with complaints of itching, dry mouth, and RUQ abdominal pain. She also noti… pigmentation chan… Her medical hi… …equent UTI's and
- A… 55, ALT 75, ALP 350, GGT 110
- Antinuclear Antibodies (ANA) pos
- Antimitochondrial Antibodies (AMA) pos

Primary biliary cholangitis

Question

Which is the pathognomic finding in primary biliary cholangitis:

A. increase of IgM levels
B. presence of antimitochondrial antibodies
C. presence of itching
D. increases of cholestatic enzymes (ALP, γGT)

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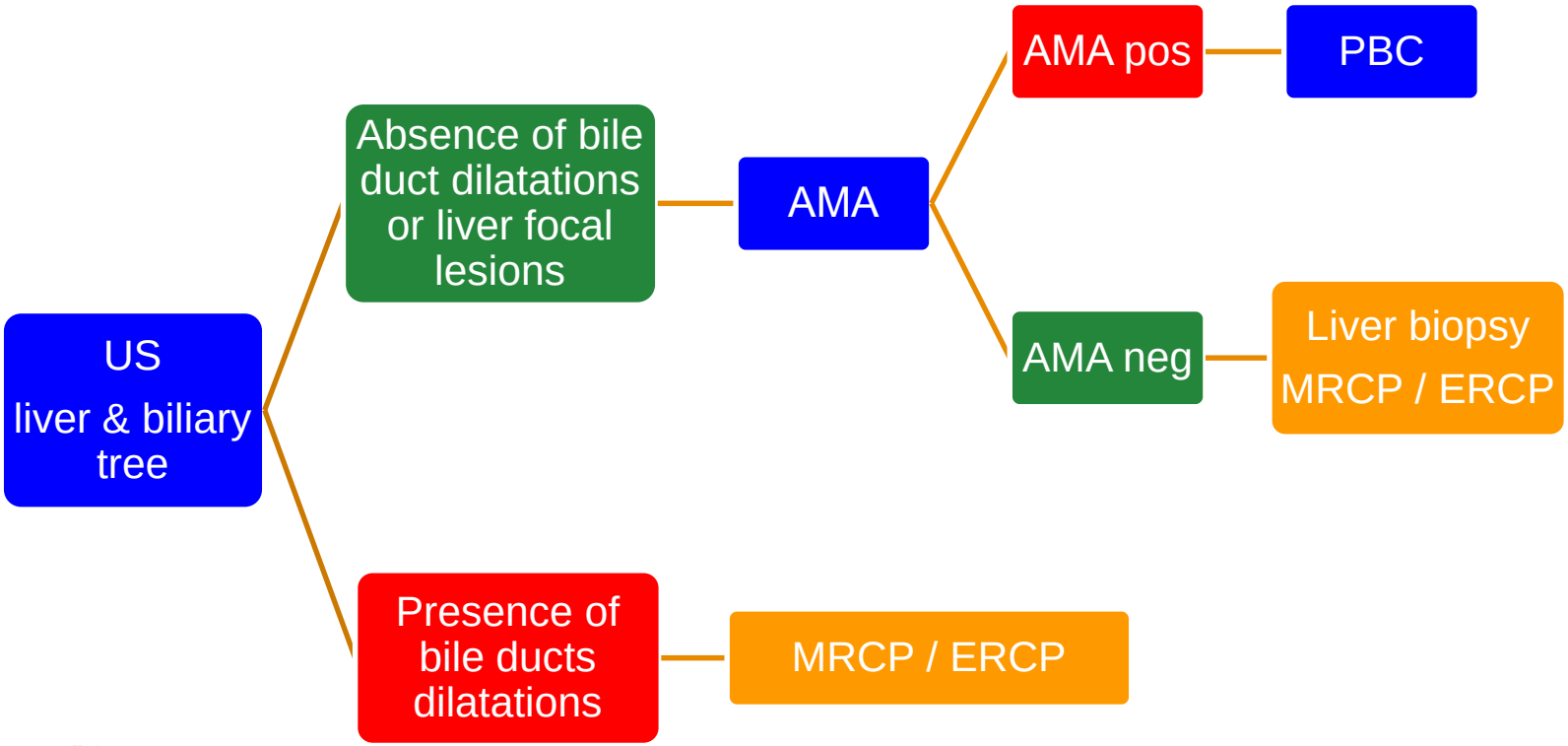
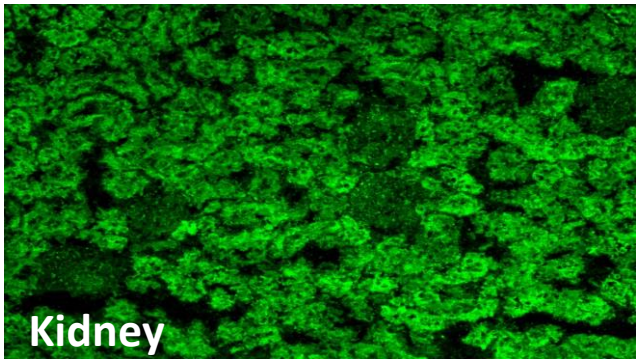
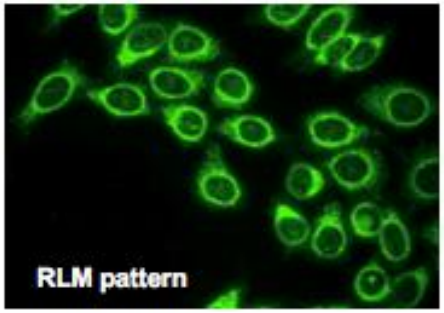
Diagnostic approach of asymptomatic patients with elevated cholestatic enzymes

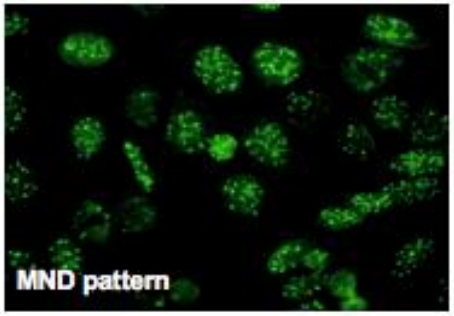


Primary biliary cholangitis

- destruction of bile ducts
- middle aged females
- AMA (+) 95%
- ANA (+) 20%
- Clinical pattern
  - asymptomatic
  - fatigue, itching, arthralgia
  - end stage liver disease







Gatselis, Expert Mol Diagn 2016

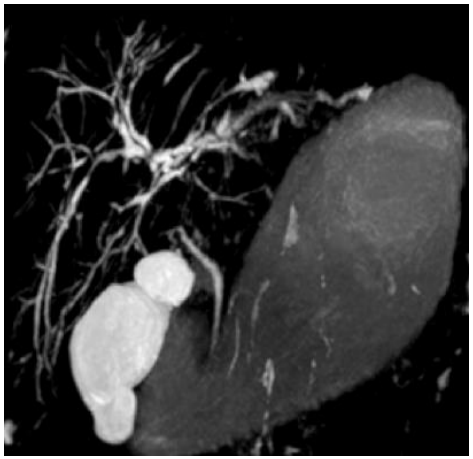
Clinical case

- A 55 y.o. male with history of Ulcerative C itis presents with recurrent low IQ abdominal pain a
- ALP 2
- elevated <100

Primary Sclerosing Cholangitis

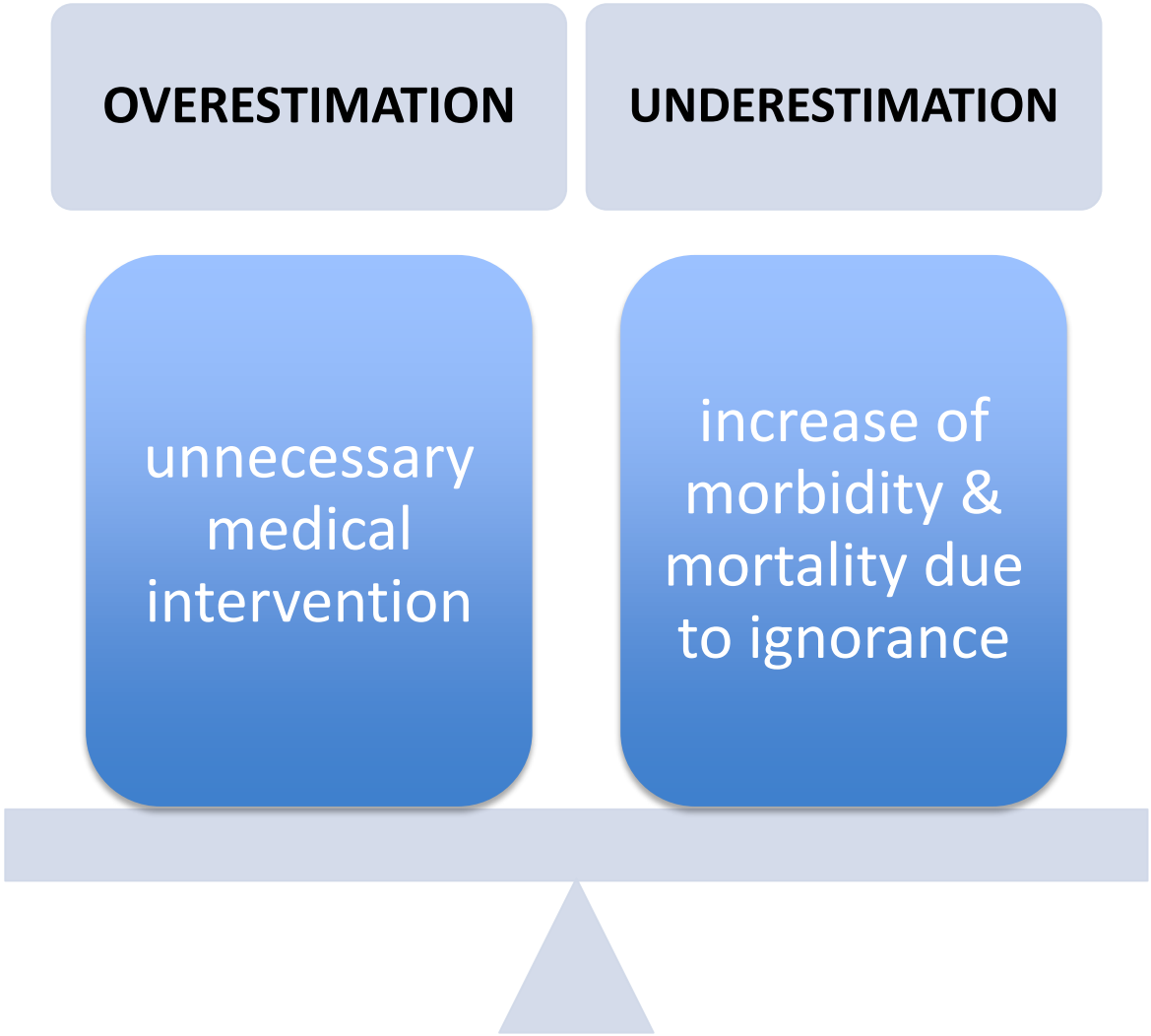
Primary sclerosing cholangitis

- chronic cholestatic disease
- males 40-years-old
- associated with IBD in 60-80%
- asymptomatic (50%) ➔ obstructive jaundice
  ➔cirrhosis, cholangiocarcinoma
- MRCP and/or ERCP
- liver biopsy



Tischendorf, Am J Gastroenterol 2007. Hov, WJG 2008.

Deranged liver biochemistry in asymptomatic individuals



Thank you for your attention.