

Differential diagnosis of icterus

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ICTERUS – *definition*

Aretaios of Cappadocia (circa 200 AD):

...If a distribution of the bile, either yellow, or like the yolk of an egg, or like saffron, or of a dark-green colour, takes place from the viscus, over the whole system, the affection is called „**icterus**“....

First classification of icterus - J. W. McNee (1923):

1. Haemolytic
2. Parenchymatous
3. Obstructive

H. Ducci (1947): Prehepatic, Intrahepatic, Posthepatic



ICTERUS – *definition*

Icterus - yellow colour of skin, mucous membranes and body fluids due to hyperbilirubinemia and subsequent deposition of bilirubin in the tissues.

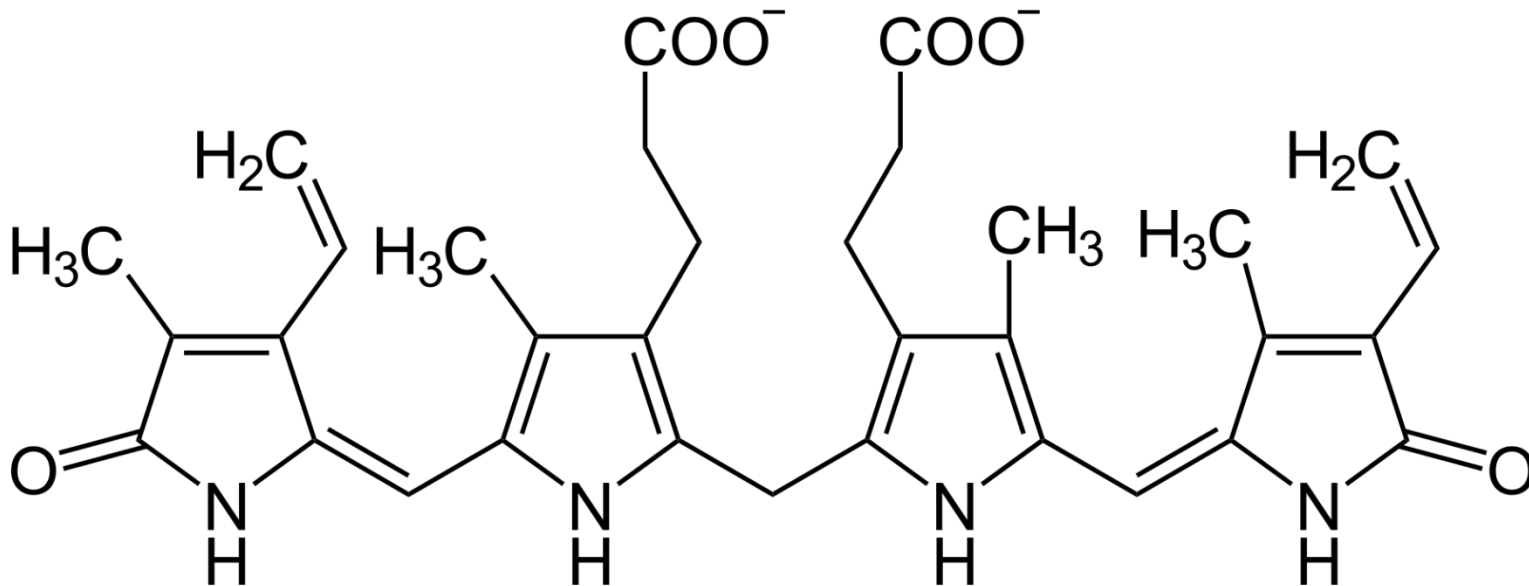
Subicterus – mostly isolated yellow coloring of the sclera due to slight increase of bilirubin ($\sim 35\mu\text{mol/l}$).

Icterus is a symptom, not a disease. It may or may not be related to cholestasis, it may or may not be accompanied by liver damage.



ICTERUS – definition

Bilirubin – hydrophobic organic anion, penetrates into tissues containing elastin (sclera, skin).

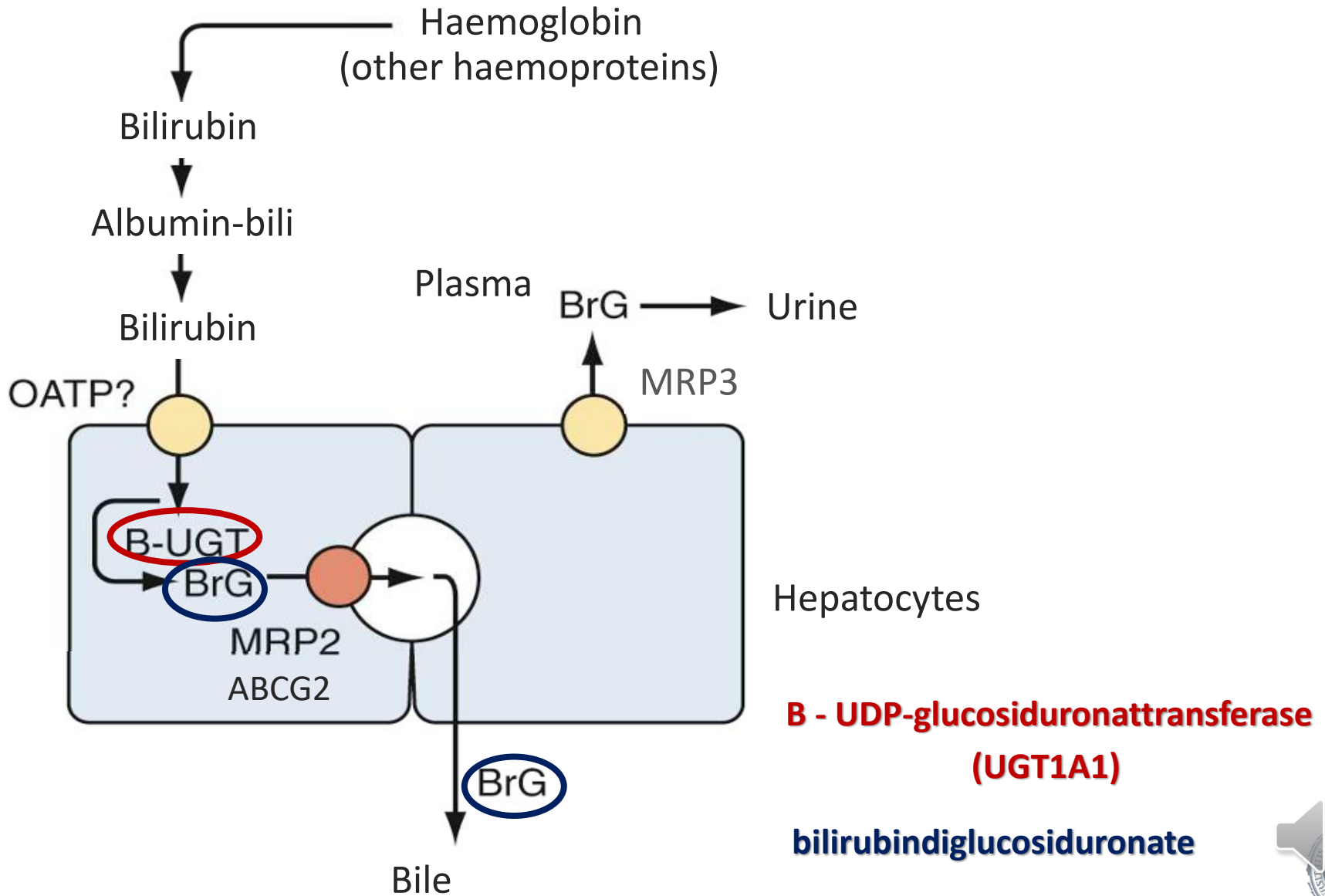


ICTERUS – *manifestation*

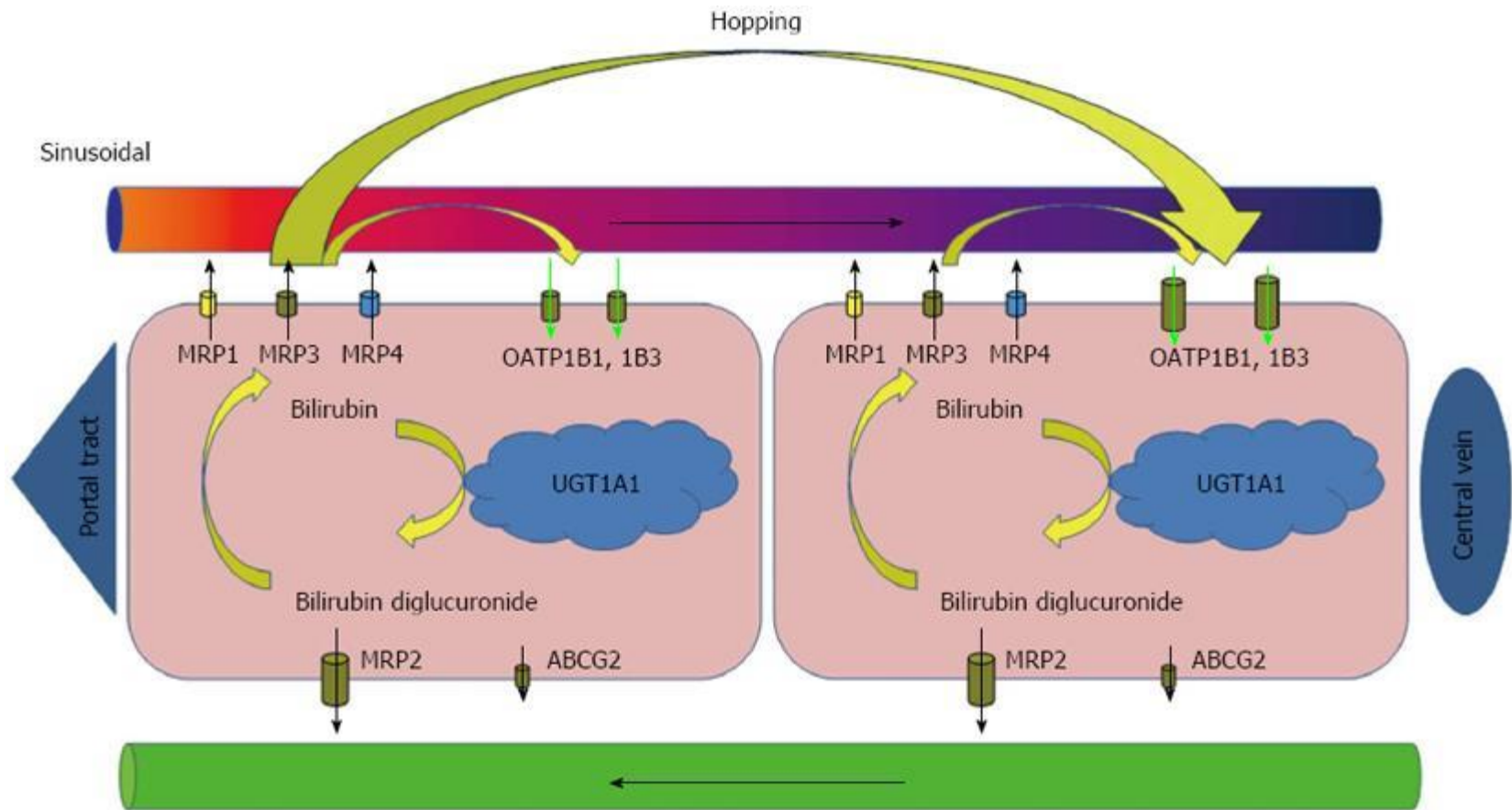
- **First manifestation on sclera (where it also remains for the longest), further on the skin of the face, body, less on limbs..**
- **Icterus is not usually noticeable on the soles of the feet, palms.**
- **Icteric are not saliva or tears.**
- **Less noticeable in areas affected by oedema.**
- **Exudate tends to be more icteric than transudate.**



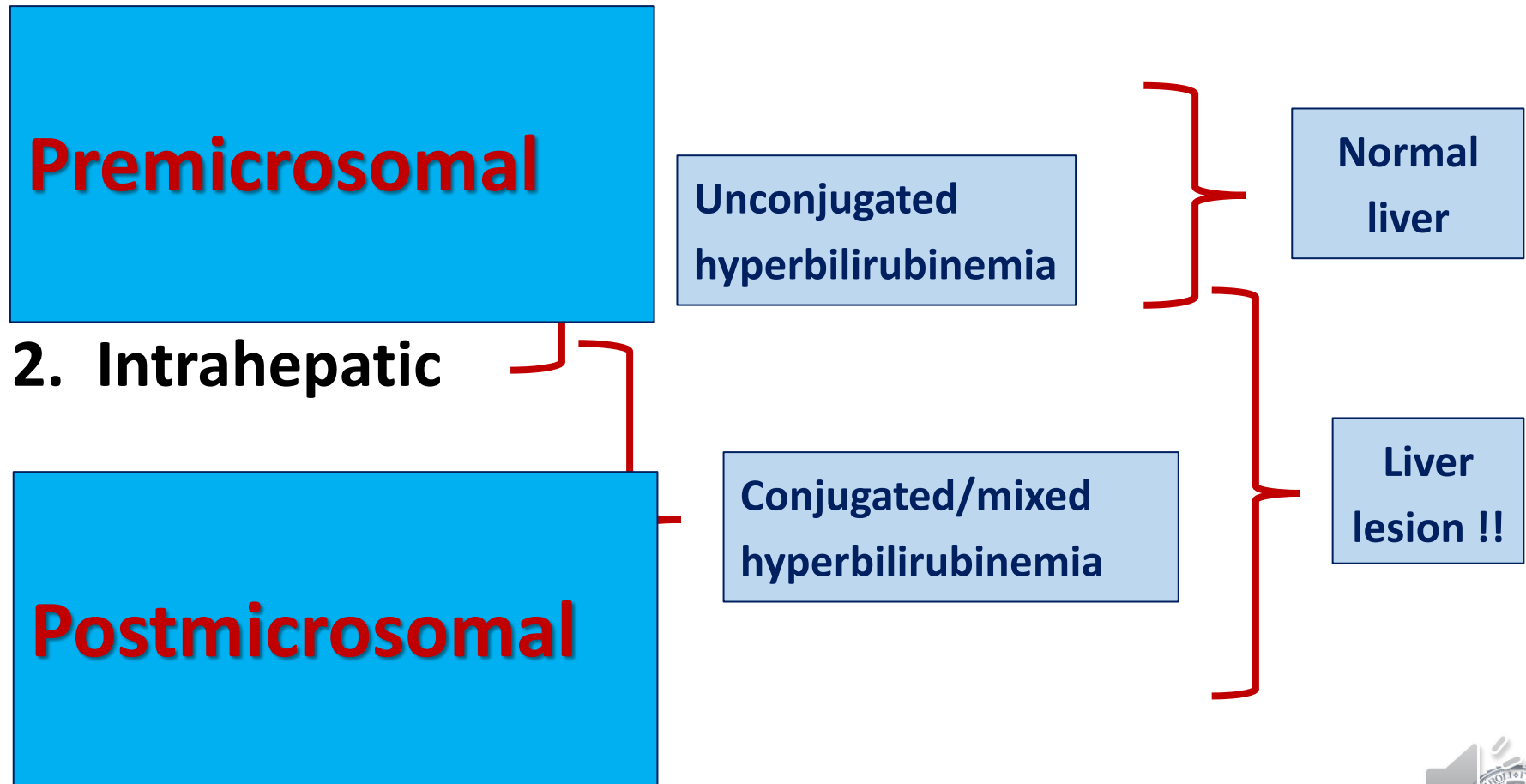
ICTERUS – *metabolism of bilirubin*



ICTERUS – metabolism of bilirubin



ICTERUS – *classification*



ICTERUS – *classification*

1. Prehepatic

Unconjugated
hyperbilirubinemia

Normal
liver

2. Intrahepatic

- **Hemolysis**
- Resorption of large hematoma, post transfusion (shorter lifespan of transfused erythrocytes!!)
- Disorders of bilirubin uptake or conjugation:
Portocaval anastomosis, right heart failure (↑GGT)
- **Inherited disorders of conjugation**
 - **Gilbert syndrome**
 - Crigler-Najjar



ICTERUS – *hemolysis*

- Non-direct bilirubin ↑
- Urine positivity exceptional
(severe hemolysis: urobilinogen, bilirubin)
- LDH ↑
- Reticulocytes >20‰
- Anemia, Coombs test +
- Splenomegaly
- Liver biopsy normal (hemosiderin !!!)
- Erythropoiesis in bone marrow ↑



ICTERUS – *Gilbert syndrome*

- Autosomal recessive: insertion of dinucleotide sequence TA
in the promotor for exon A1 of gene *UGT1A1* (*UGT1A1*28*).
- ~ 8-10% population
- 1 normal allele: normal bilirubin
- Homozygote or mixed heterozygote: phenotype of Gilbert sy
- Homozygote: **10-30% activity of UGT1A1**
- Diagnosis: history, clinic, exclusion of another cause of unconjugated hyperbilirubinemia, *eventually genetic testing*.
- Functional induction tests not indicated !!!



ICTERUS – *Gilbert syndrome (clinical significance)*

- Gilbert syndrome can lead to abnormalities in the hepatic metabolism of some xenobiotics (menthol, rifamycin, acetaminophen).
 - HIV protease inhibitors (indinavir, atazanavir) increase bilirubin levels in GS.
 - No hepatotoxicity has been reported
- **The only exception: irinotecan can lead to severe toxicity (diarrhoea, myelosuppression).**

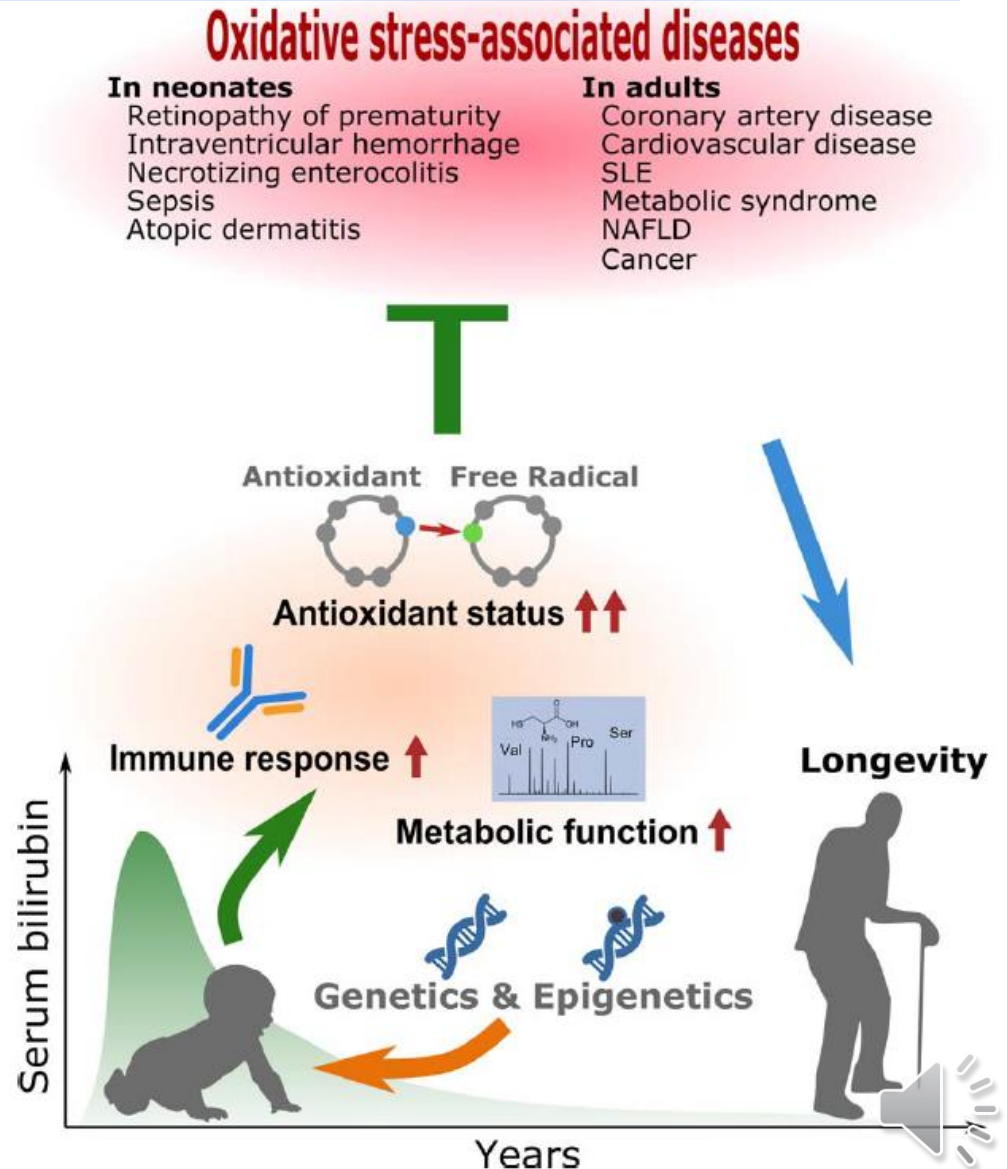


ICTERUS – Gilbert syndrome (clinical significance)

Bilirubin

neurotoxicity **x** important antioxidant

It has been clearly shown that people with higher bilirubin levels have a lower risk of atherosclerosis and other diseases associated with oxidative stress.



ICTERUS – *classification*

Jaundice is a general feature of liver dysfunction. In contrast to isolated bilirubin conjugation disorders, icteric liver disease is characterized by a **higher value of bilirubin together with abnormalities in the so-called liver tests.**

It is necessary to distinguish jaundice as a manifestation of **hepatic dysfunction** from **"simple" cholestasis** (*which is clinically difficult to distinguish from biliary obstruction*)

2. Intrahepatic

Conjugated/mixed
hyperbilirubinemia

Liver
lesion !!



ICTERUS – *classification*

Acute hepatocellular dysfunction - clinically: fatigue, fever, nausea, myalgia, dysp. sy
Laboratory: increased values of ALT, AST

- Viral hepatitis
- Hepatotoxins (Amanita, acetaminophen)
- Liver ischemia (hypotension, hypothermia, veno-occlusive disease)
- Metabolic diseases (Wilson disease, Reye syndrome), AIH
- Drug induced liver disease (DILI)
- Acute alcoholic hepatitis (alcohol, hepatomegaly, fever, GGT, leucocytosis, haemolysis)
- Icterus gravidarum

2. Intrahepatic

Conjugated/mixed
hyperbilirubinemia

Liver
lesion !!

Liver dysfunction x Cholestasis



ICTERUS – *classification*

Chronic hepatocellular dysfunction

- Jaundice usually appears only in the presence of cirrhosis (ethyl, HCV, NASH)
- PBC, PSC
- Wilson disease, Haemochromatosis, α_1 -antitrypsin deficiency, celiac dis. (!!!)
- Autoimmune hepatitis

2. Intrahepatic

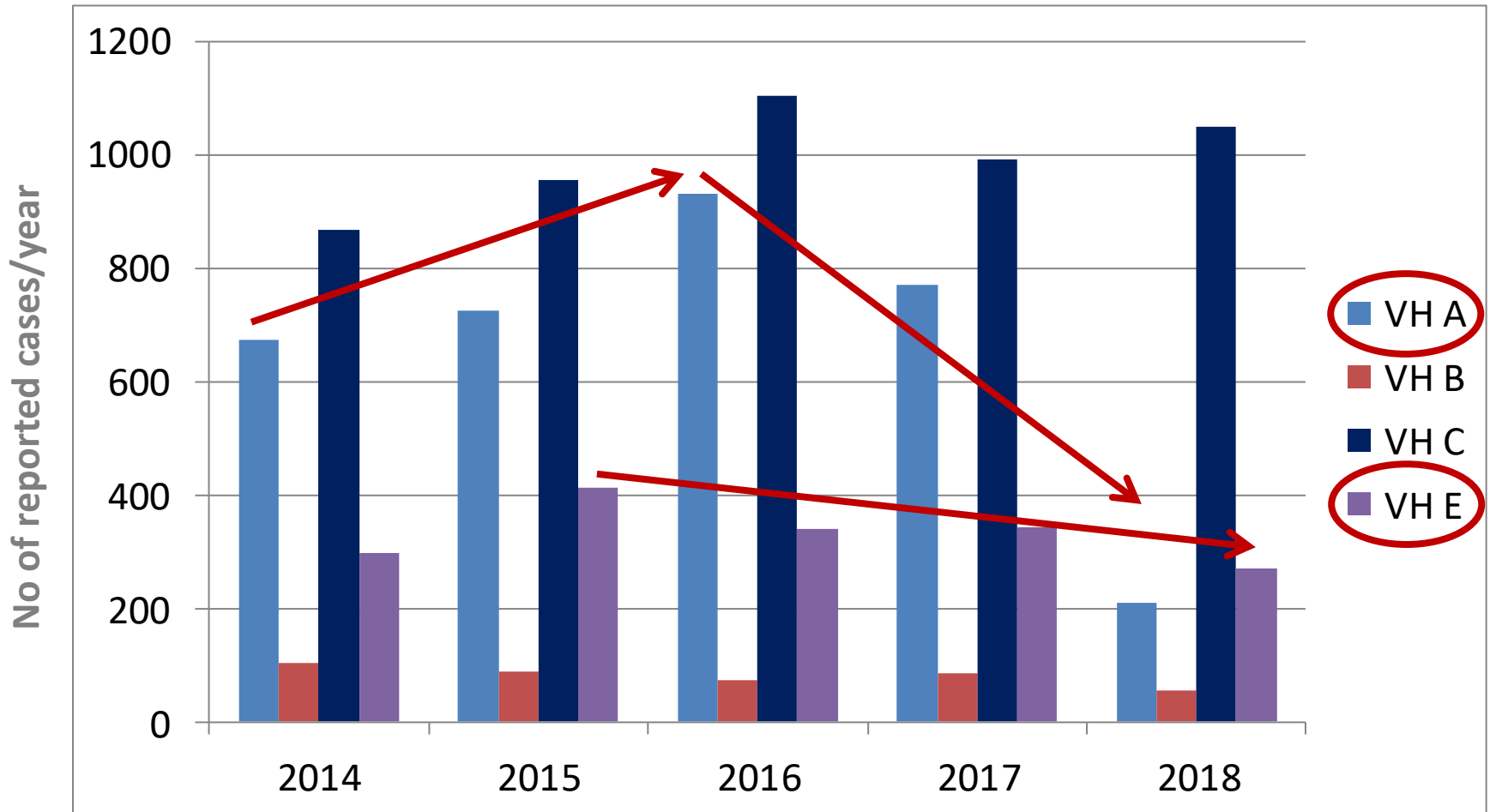
Conjugated/mixed
hyperbilirubinemia

Liver
lesion !!

Manifestation of chronic disease x Acute „on“ chronic lesion



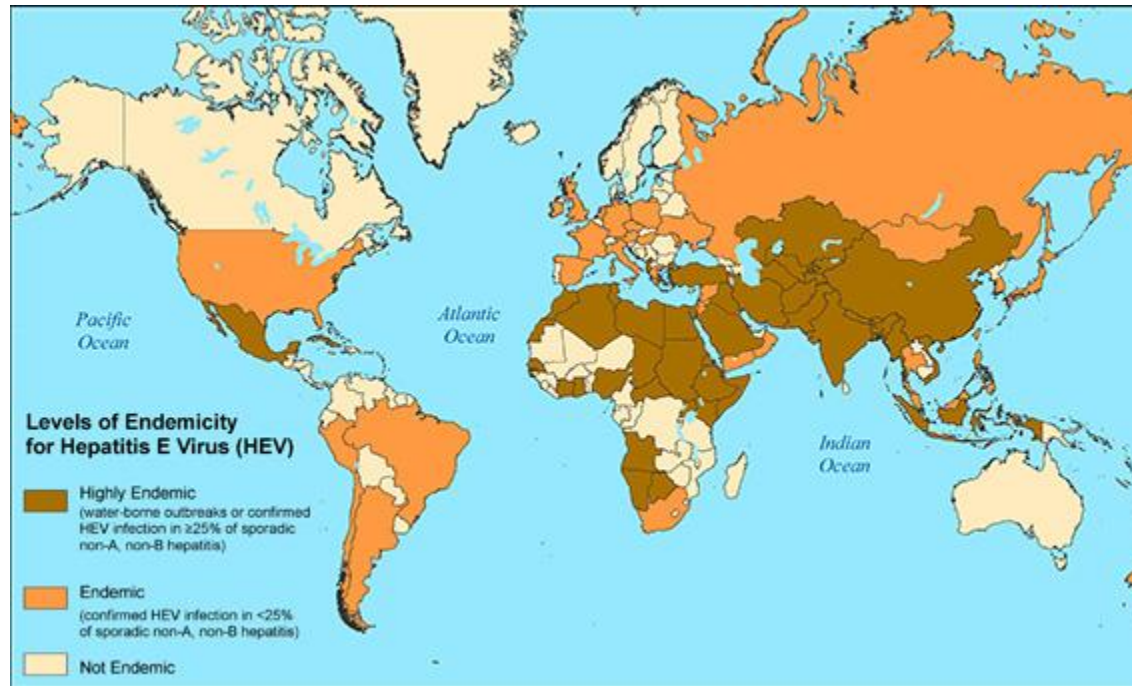
ICTERUS – Incidence of viral hepatitis in CR



Source: Epidat (2019)



ICTERUS – viral hepatitis E



Endemic area: feco-oral (contaminated water)

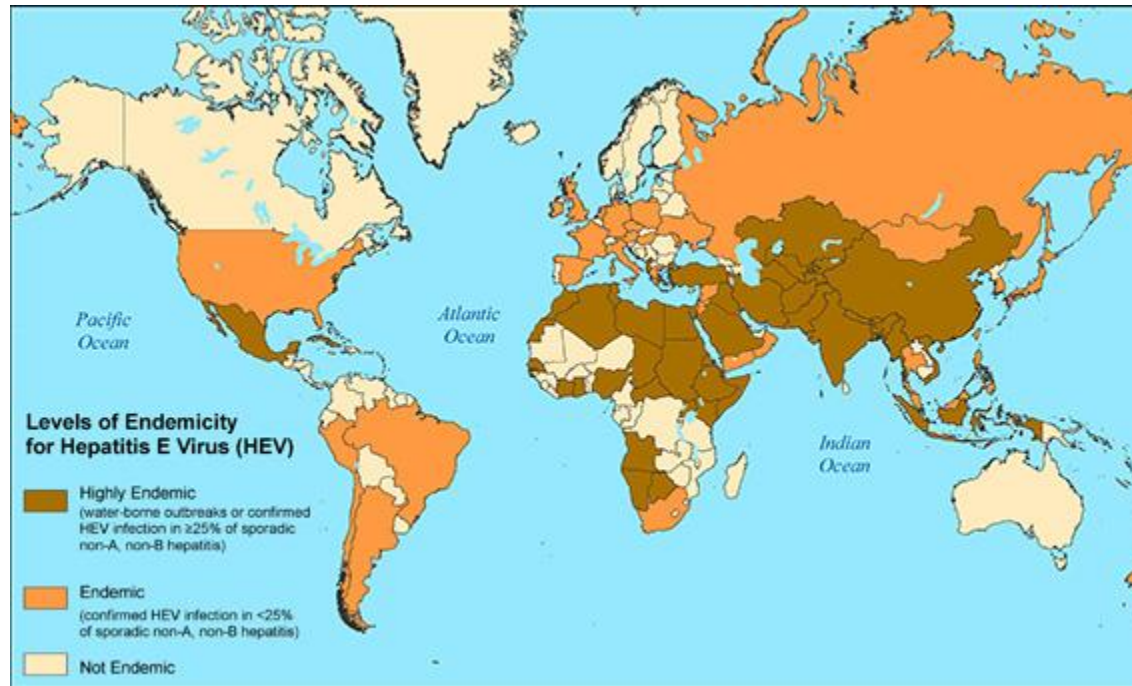
Genotype 1,2

In Central Europe: **zoonosis** (uncooked meat: venison, wild boar, free-range pigs ...)

Genotype 3



ICTERUS – *viral hepatitis E*



Usual course: acute

In CR: acute **x** - at immunocompromised pt. can be chronic

- high mortality in gravidity (3th trimester !!)



ICTERUS – Serology for HBV: screening tests

AASLD guidelines:

HBsAg

Marker of the presence of virus – active infection (acute, chronic)

Anti-HBs

Seroprotective antibody

Postvaccination or postinfection immunity

Total anti-HBc (alternative test; positive individuals has to be tested for complete serology and HBV DNA) = marker of virus exposition



ICTERUS – *cholestasis at sepsis*

Mostly Gram-negative infection

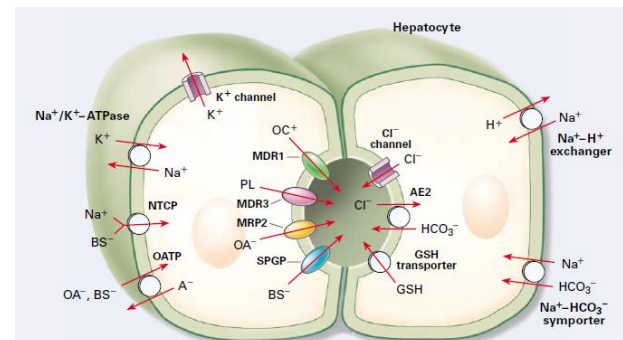
**Lipopolysaccharides (LPS) from bacteria
(infection locus or gut).**

Activation of TLR in liver.

Production of proinflammatory cytokines.

Disruption of bile transporter expression and function:

**canalicular membrane
basolateral membrane.**



ICTERUS – *cholestasis at sepsis– frequency??*

Hyperbilirubinemia at ICU - incidence

Multicentric study at ICU (2002-2005, Austria): 38.036 patients.

Cirrhosis	Acute liver failure	Liver dysfunction <i>bili > 35 μmol/l</i>
n=644	n=106	n=4146
1.69%	0.28%	10.9%

Influence of organ dysfunction on mortality:

Parameter	Odds ratio	P value
Kardiovascular	1,6	<0,0001
Hepatic	1,85	<0,0001



ICTERUS – *drug induced liver disease (DILI)*

• **Hepatitis:** $ALT > 2n$, or $\frac{ALT}{ALP} > 5$

• **Cholestasis:** $ALP \geq 2n$, or $\frac{ALT}{ALP} < 2$

• **„Mixed type“** $\frac{ALT}{ALP}$ between 2 and 5



ICTERUS – drug induced liver disease – *idiosyncrastic reaction*

It **does not depend on the dose** (or minimally), unpredictable, days to months from the start of drug administration.

- Drug/metabolite binding to proteins (of hepatocytes) – neoantigens for HLA II – initiation of **immunoallergic reaction** – inhibition of transporters, damage to mitochondria and endoplasmic reticulum.
- Oxidative stress and proinflammatory cytokines can potentiate liver injury.



ICTERUS – drug induced liver disease – *idiosyncrastic reaction*

- Dependent on **genetic (enzymatic) predisposition** of an individual and many external factors (**concomitant medication, infection, diseases, alcohol, diet....**).
- One drug can cause different types of damage with different time intervals from the start of treatment **(weeks to months)**.



ICTERUS – drug induced liver disease – *idiosyncrastic reaction*

- Time context

– **history !!**

Interval 1 week – 3 months

Regression of liver lesion after drug discontinuation

- Clinical criteria

- Roussel Uclaf Causality Assessment Method

RUCAM (<http://www.pmidcalc.org>)

- Clinical Diagnostic Scale

CDS



ICTERUS – drug induced liver disease – *epidemiology*

Prospective study, Nièvre region (France):
81.000 individuals followed by GP 1997-2000:

• Incidence: 14/100.000 inhab.

• total mortality: 6%

• Most frequent drugs:

Antibiotics (!! Ampicillin + clavulanic acid !!)

Psychopharmaceuticals

NSAID

Hypolipidemic → 10% (fibrates, statins); 0 death

Clinical manifestation: fatigue, icterus....



ICTERUS – drug induced liver disease – *acute cholestasis*

Cholestasis

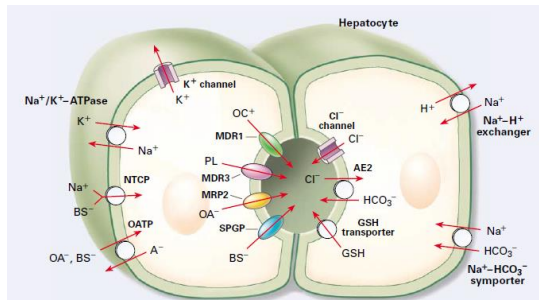
Estrogens, contraception

Androgens

Tamoxifen

Azathioprin

Cytarabin



+ hepatitis

NSAID

tricyclic antidepr.

Amoxi / clavulonate

Macrolides

Sulfonamides

β-laktam ATB



ICTERUS – drug induced liver disease – *Amoxicillin/clavulonate*

- 1.7 cases per 10 000 treated (**clavulonate** !!!)
- Risk factors: age > 55 years, males, longer treatment
- Manifestation: up to 6 weeks from treatment start (18 days !!!)
- Hypersensitivity: fever, rash, eosinophilia (at 30-60% of patients).
- **Histology**: cholestasis with mild periportal inflammation, mild bile duct damage and perivenular bilirubinostasis, granuloma ductopenia.
- Association with MHC : immunologic idiosyncrastic reaction
- Usually disappears without fatal consequences



ICTERUS – drug induced liver disease – *cholestasis with bile duct damage*

- It can accompany cholestatic hepatitis - it can result in „**vanishing bile duct syndrome**“ (progressive cholestasis and jaundice - biopsy !!!).
- Drugs: **chlorpromazine, flucloxacilin, karbamazepine.**
- Industrial poisoning : **methylene dianiline** in Epping (1965) – pastry from contaminated flour.
- **Graft-versus-host reaction**: icterus occurs in up to 10% of hematopoietic cell recipients.



ICTERUS – drug induced liver disease – food supplements (herbals)

Name	Use	Plant	Hepatotoxic component	Type of liver lesion
Cascara	Laxativum	<i>Cascara sagrada</i>	Anthracen glycosid	Cholestatic hepatitis
Ma huang	Weight loss	<i>Ephedra</i> spp.	Ephedrin	Severe hepatitis, FHF
Jin bu huan	Sleep, analgesia	<i>Lycopodium serratum</i>	?Levo-tetrahydropalmitin	Acute / chronic hepatitis, cholestasis, steatosis
Syo-saiko-to	For all	<i>Scutellaria</i> root	Diterpenoides	Hepatocelular necrosis, cholestasis steatosis, granulomas
Shou-wu-pian	Traditional medicine	<i>Polygonum multiflorum</i>	Unknown	Acute hepatitis, cholestasis
Comfrey	Herbal tea	<i>Symphytum</i> spp.	Pyrrrolizidine alcaloid	Cirrhosis
Germander	Weight loss, sleep	<i>Teucrium chamaedry</i> , <i>T. capitatum</i> , <i>T. polium</i>	Diterpenoides, epoxid	Acute / chronic hepatitis
Greater celandine	Bile stones	<i>Chelidonium majus</i>	Unknown	Cholestatic hepatitis, fibrosis
Herbalife	Nutritional suppl	—	Different	Severe hepatitis, FHF
Weight loss	Weight loss	<i>Camellia sineusis</i>	Green tea	Acute hepatitis
Weight loss	Weight loss	Lichen alkaloid	Usnic acid	Acute hepatitis
Lipokinetix	Weight loss	Lichen alkaloid	Usnic acid	Acute hepatitis icterus, FHF
Senna	Laxative	<i>Cassia angustifolia</i>	Senoside alcaloids; anthron	Acute hepatitis
Skullcap	Anxiolytic	<i>Scutellaria</i>	Diterpenoides	Hepatitis



ICTERUS – drug induced liver disease – *food supplements (herbals)*

Fever, fatigue, nausea, pruritus, abdominal pain, hepatomegaly, icterus

Jin bu huan (*Lycopodium serratum* – **Thunb**)

Sedative; severe liver damage mostly in women (ALT, bili)
levo-tetrahydropalmatin (pyrrolizidine alkaloid)



Syo-saiko-to (*Scutellaria* - **Skullcap**)

typical hepatotoxin (necrosis, microvesicular steatosis, cholestasis, induction of autoimmune hepatitis)



ICTERUS – drug induced liver disease – *food supplements (herbals)*

Shou-wu-pian (*Polygonum multiflorum* – **Tuber fleeceflower**)

Acute hepatitis, cholestasis

Regevit strengthens the mental and physical health of the body. It supports the regeneration of the whole body and supplies energy. It has antioxidant properties.

Regevit is an ideal dietary supplement for **busy individuals** and **the elderly**. Infusion from the root is widely used by athletes and martial arts masters in Asia.



Tribulus terrestris - **Cathead**

„natural“ androgen

cholestatic hepatitis, prolonged icterus.



ICTERUS – *classification*

- **Biliary obstruction**

Conjugated/mixed
hyperbilirubinemia

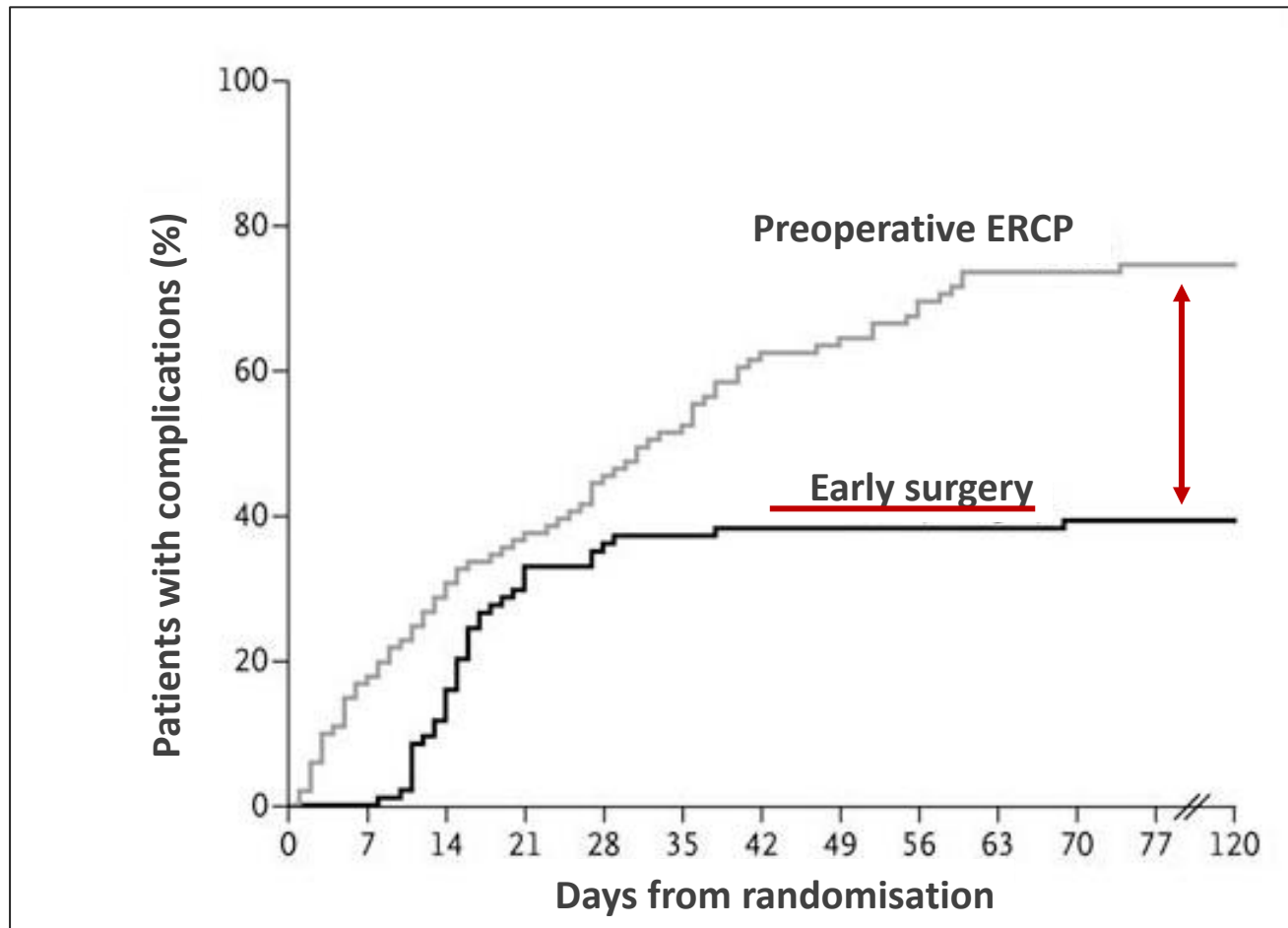
Liver
lesion !!

3. Posthepatic



ICTERUS – preoperative biliary drainage at pancreatic cancer

- Randomized study, 196 patients before pancreatic cancer surgery
- All - biliary obstruction with icterus:
preoperative drainage (ERCP) x early surgery (without drainage)



ICTERUS – preoperative biliary drainage at pancreatic cancer

- Randomized study, 196 patients before pancreatic cancer surgery
- All - biliary obstruction with icterus:
preoperative drainage (ERCP) x early surgery (without drainage)

Table 2. Serious Complications within 120 Days after Randomization.*

Complication	Early Surgery (N= 94)	Preoperative Biliary Drainage (N= 102)
	no. (%)	
Related to preoperative biliary drainage		
Any	2 (2)	47 (46)
<u>Pancreatitis</u>	0	7 (7)
<u>Cholangitis</u> †	2 (2)	27 (26)
Perforation	0	2 (2)
Hemorrhage after ERCP‡	0	2 (2)
Related to stent		
Occlusion	1 (1)	15 (15)
<u>Need for exchange</u>	2 (2)	31 (30)
Related to surgery		
<u>Any</u>	35 (37)	48 (47)



ICTERUS – preoperative biliary drainage at pancreatic cancer

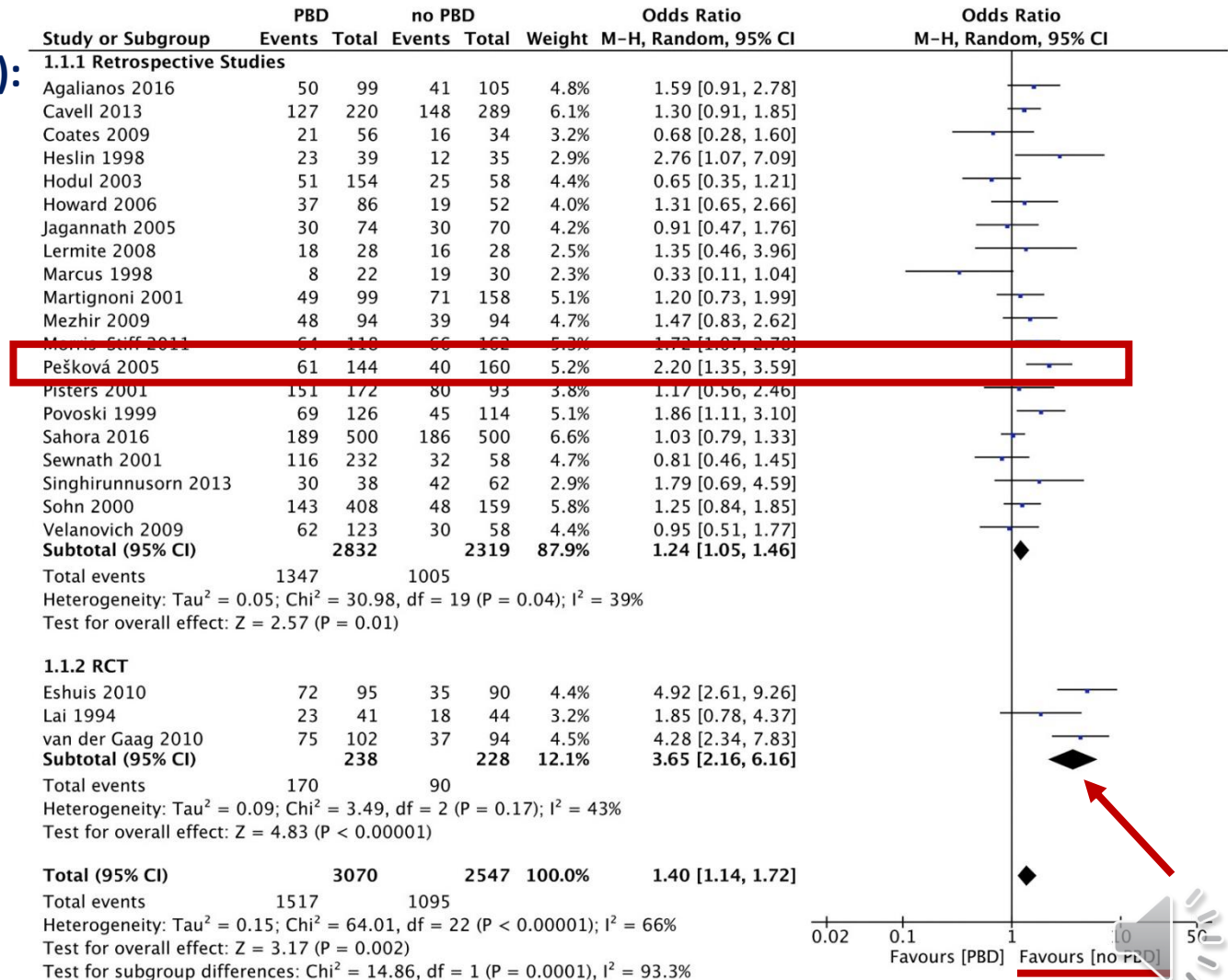
Metaanalysis

22 studies (>6.000 pat.):

Preoperative ERCP drainage (PBD)

x

No drainage before surgery (no PBD)



ICTERUS – *definition*

Icterus - yellow colour of skin, mucous membranes and body fluids due to hyperbilirubinemia and subsequent deposition of bilirubin in the tissues.

Subicterus – mostly isolated yellow coloring of the sclera due to slight increase of bilirubin ($\sim 35\mu\text{mol/l}$).

Icterus is a symptom, not a disease. It may or may not be related to cholestasis, it may or may not be accompanied by liver damage.

Treat the disease and not the symptom (icterus)



ICTERUS – *conclusion*

- **Unconjugated hyperbilirubinemia** without clinical symptoms and without liver lesion: mostly conjugation disorder (Gilbert sy) or hemolysis.
- **Conjugated/mixed hyperbilirubinemia** with clinical symptoms – acute or chronic liver injury.



ICTERUS – *conclusion*

- Biliary obstruction
- Previous liver / biliary lesion
- Alcohol
- Viral hepatitis (A, B, C, E; EBV, CMV)
- Hypoxia / toxicity
- *Autoimmunity*
- *Ferritin + transferrin saturation*
- *Ceruloplasmin, alfa-1 antitrypsin*

!!! Medication including food supplements and herbals !!!



Thank you

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MS Teams (*Internal Medicine - Gastroenterology 20/21 B80304*)

Moodle (<https://dl1.cuni.cz/course/view.php?id=9939>)

<https://int4.lf1.cuni.cz>

