Dr Risch

Il vostro laboratorio – oggi e domani

RISCH.CH

Le Epatopatie

Silamed

Mauro Imperiali

Il fegato

- Organo principale del metabolismo
- Localizzato sotto il diaframma
- Anatomicamente viene suddiviso in quattro parti anche se a livello medico viene suddiviso in 8 segmenti clinicamente rilevanti
- Tramite la vena porta i nutrienti vengono portati dall'intestino e vengono utilizzati per produrre energia oppure per sintetizzare altre sostanze
- Il fegato é anche un organo di stoggaccio (es glucosio sotto forma di glicogeno, vitamine liposolubili, ferro, rame)
- Importante, tramite la biotrasformazione, nel processo di detossificazione (per esempio rendendo polari sostanze apolari)
- Il fegato si sviluppa dalla seconda settimana di gravidanza e fino al parto rappresenta un importante organo ematopoietico

Scheda tecnica del fegato

- Organo centrale del metabolismo
- Lungo ca 20 cm, largo 10 cm alto 15 cm
- Peso: 1800 g (uomini) 1600 g (donne)

Leber (Hepar)

Funktion
Zentrales Stoffwechselorgan: Energiebereitstellung, Speicherung von Nährstoffen, Beteiligung am Glucose- und Säure-Basen-Haushalt, Bildung von Gallensäuren, Entgiftung

Größe
Ca. 20 × 15 × 10 cm, keilförmig

Gewicht
Ca. 1.600–1.800 g

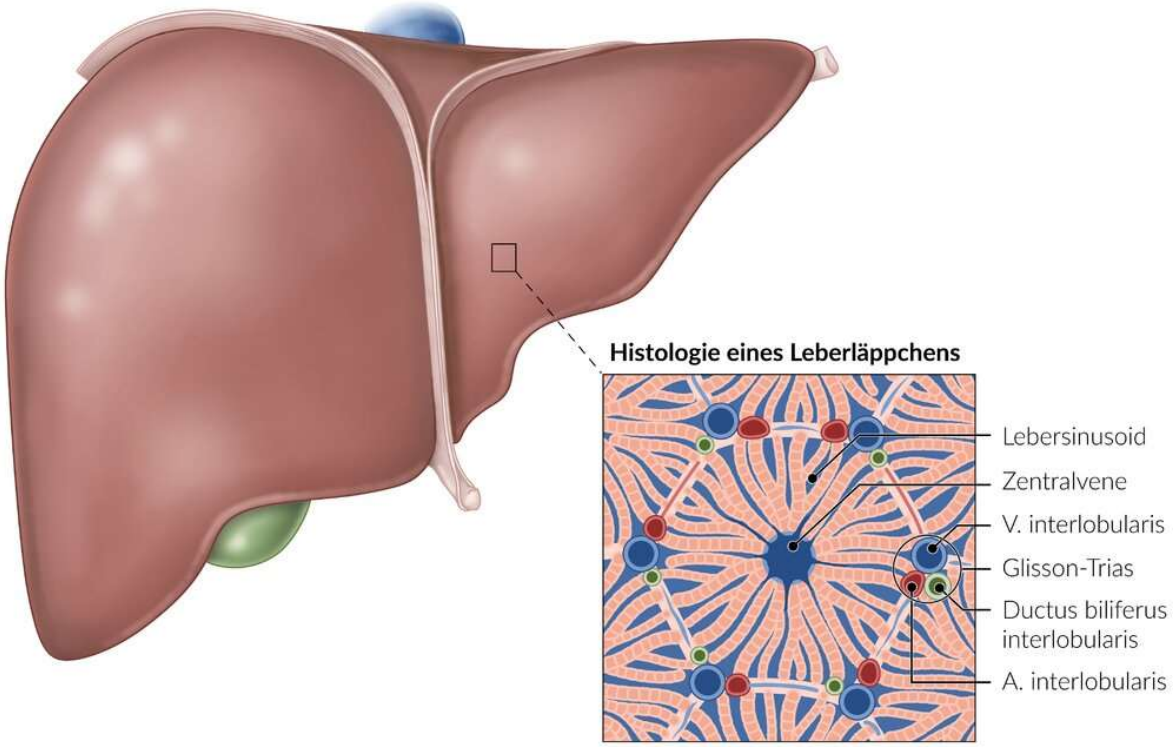
Lage
Im rechten Oberbauch, überwiegend intraperitoneal

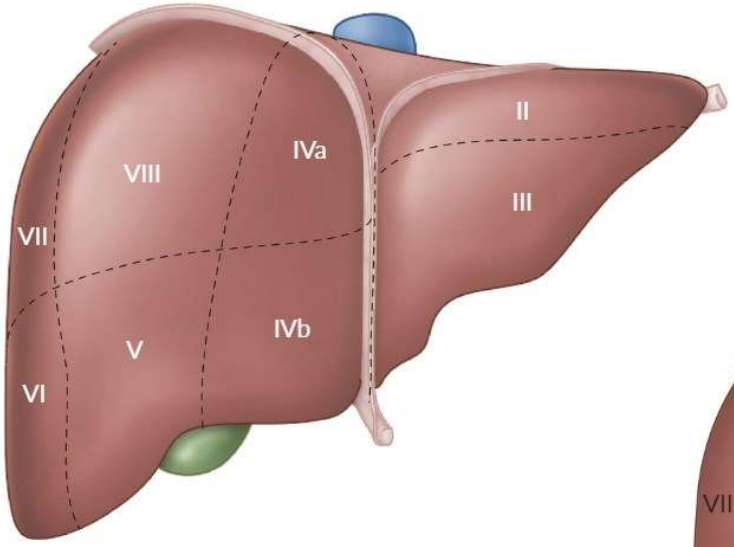
Arterielle Versorgung
Truncus coeliacus → A. hepatica communis →
→ A. hepatica propria → A. hepatica dextra / A. hepatica sinistra

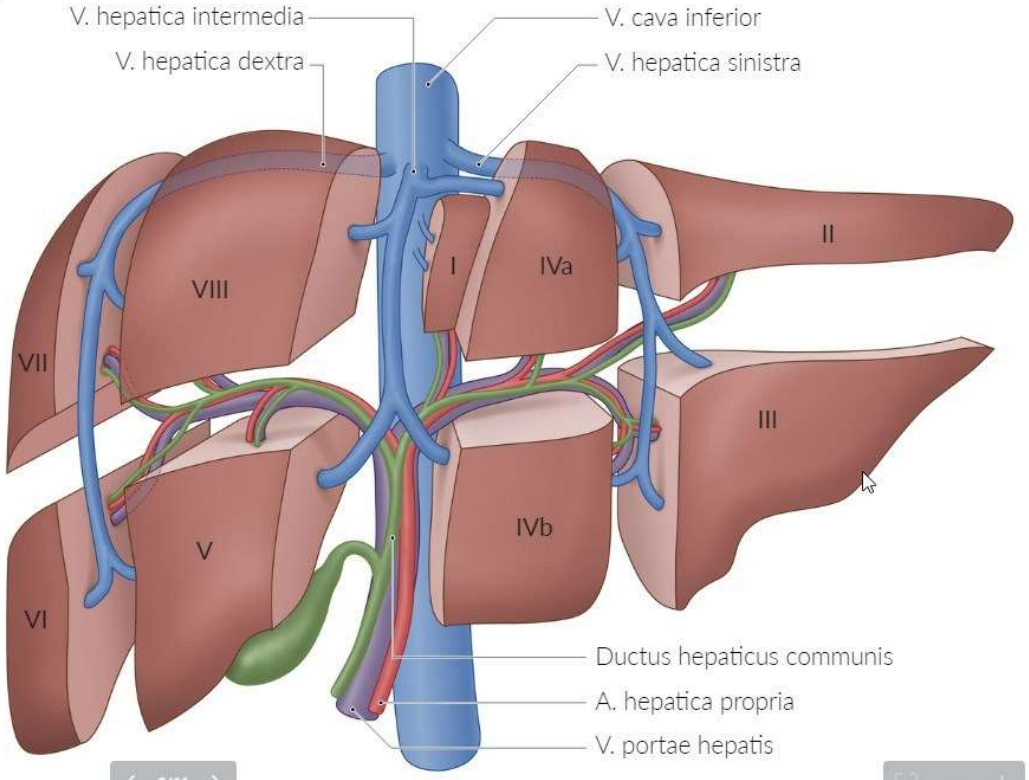
Venöser Abfluss
V. hepatica dextra/sinistra/intermedia → V. cava inferior

Besonderheiten
Portalvenenkreislauf: Nährstoffreiches Blut der Verdauungsorgane gelangt über die V. portae hepatis zur Verstoffwechselung in die Leber

Mögliche Krankheitssymptome
Gelbsucht, Ödeme, Bauchwasser

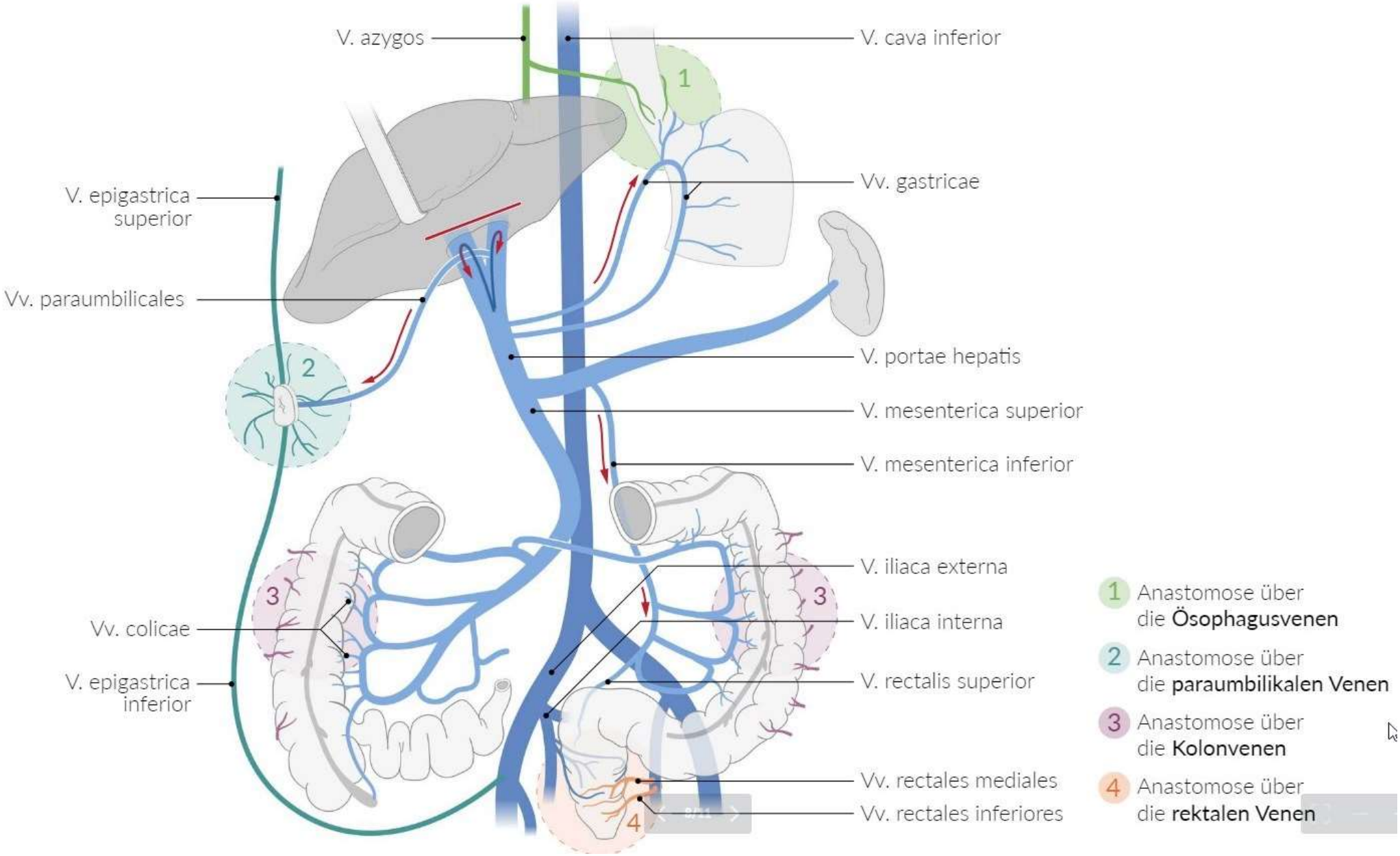


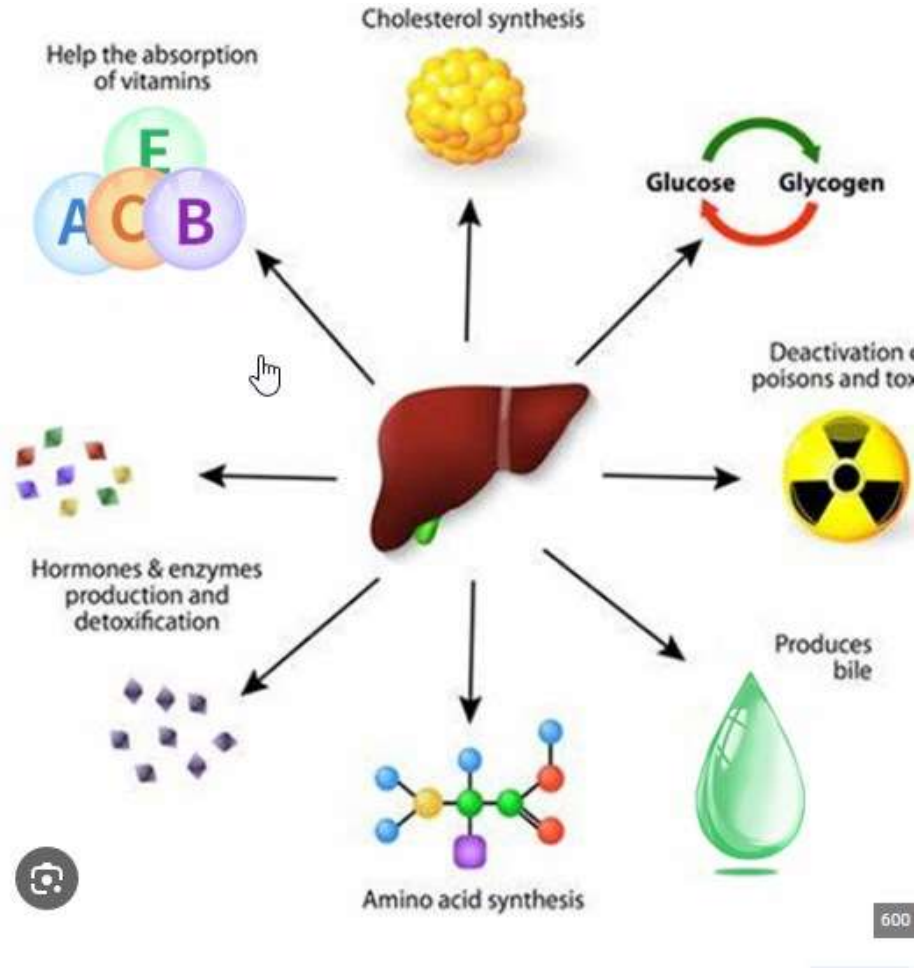

II
IVa
VIII
III
VII
V
IVb
VI


V. hepatica intermedia
V. cava inferior
V. hepatica dextra
V. hepatica sinistra
II
I
IVa
VIII
VII
III
IVb
V
VI
Ductus hepaticus communis
A. hepatica propria
V. portae hepatis

Ipertensione portale

- La pressione nella vena porta di regola é di 3-6 mmHg
- A causa di alcune situazioni patologiche (spesso cirrosi epatica) si verifica un aumento di pressione a causa di un aumento della resistenza nel fegato stesso
- Il normale flusso ematico nel fegato non é più garantito e si creano delle anastomosi che portano anche a gravi complicazioni (varici esofage, ascite,…)


V. azygos
V. cava inferior
1
V. epigastrica superior
Vv. gastricae
Vv. paraumbilicales
2
V. portae hepatis
V. mesenterica superior
V. mesenterica inferior
3
3
V. iliaca externa
Vv. colicae
V. iliaca interna
V. epigastrica inferior
V. rectalis superior
Vv. rectales mediales
4
Vv. rectales inferiores
1 Anastomose über die Ösophagusvenen
2 Anastomose über die paraumbilikalen Venen
3 Anastomose über die Kolonvenen
4 Anastomose über die rektalen Venen


Cholesterol synthesis
Help the absorption of vitamins
E
A
C
B
Glucose
Glycogen
Deactivation
poisons and tox
Hormones & enzymes production and detoxification
Produces bile
Amino acid synthesis
600

Esplorazione epatica tramite laboratorio

- Danno epatico: ASAT, ALAT, ALP e bilirubina
- Marcatori funzione epatica: Albumina, bilirubina, Tempo di protrombina

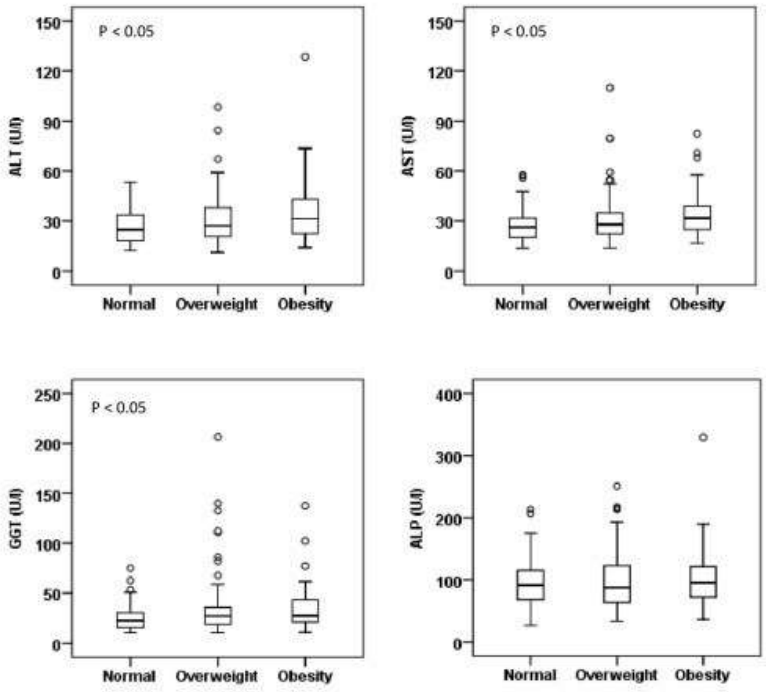


Figure 1. Levels of serum liver enzymes in the BMI groups (n = 173 in normal, n = 259 in overweight and n = 108 in obesity group). P-values are obtained from one-way ANOVA (Dunnett's Post Hoc Test). *P < 0.05 when the mean level of liver enzymes in the normal group is compared to the obesity group.

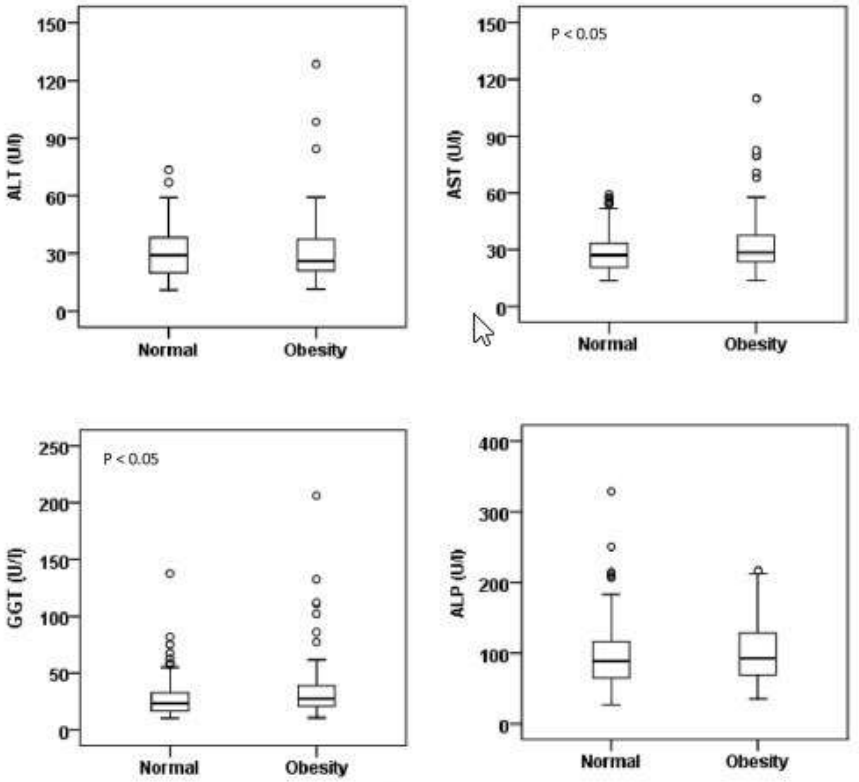


Figure 2. Levels of serum liver enzymes in the WC groups (n = 296 in normal and n = 244 in obesity group). P-values are obtained from independent sample t-test. *P < 0.05 when the mean level of liver enzymes in the normal group is compared to the obesity group.

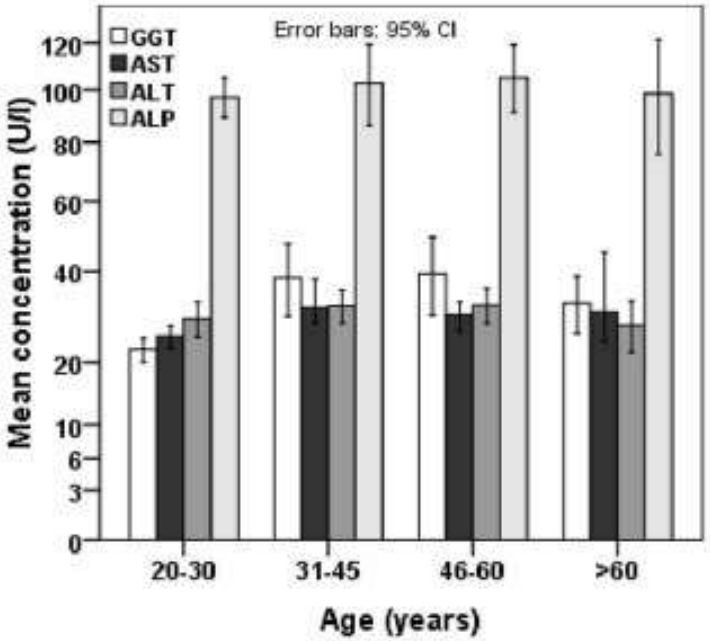


Figure 3. Levels of serum liver enzymes in the different age groups (n = 210 in 20–30 years, n = 134 in 31–45 years, n = 134 in 46–60 years and n = 62 in > 60 years group). The levels of liver enzymes in the age groups are compared by one way ANOVA.

ALP e dipendenza dall'età

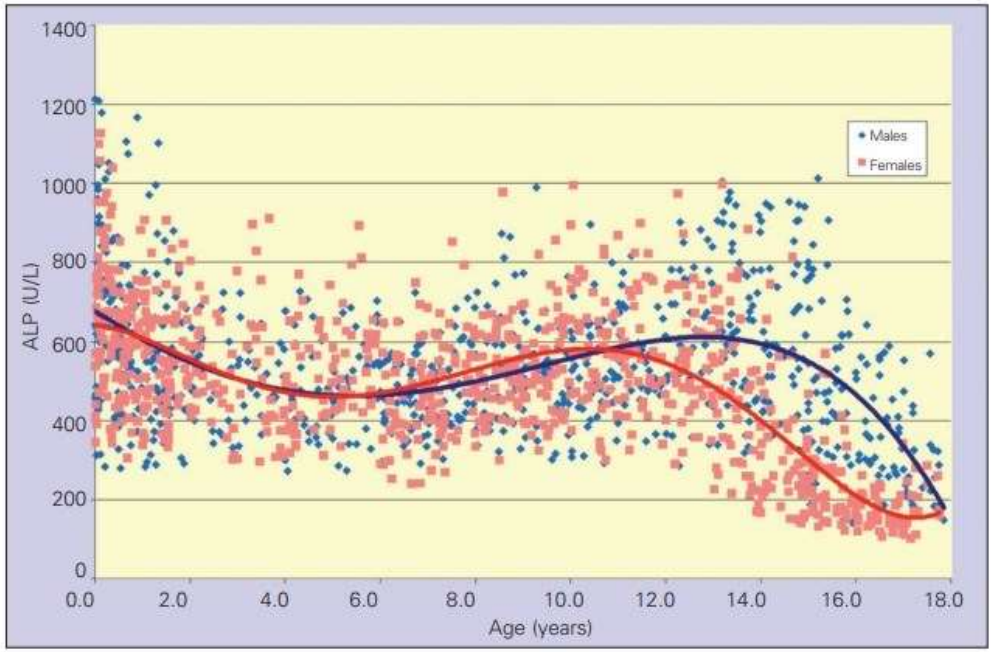


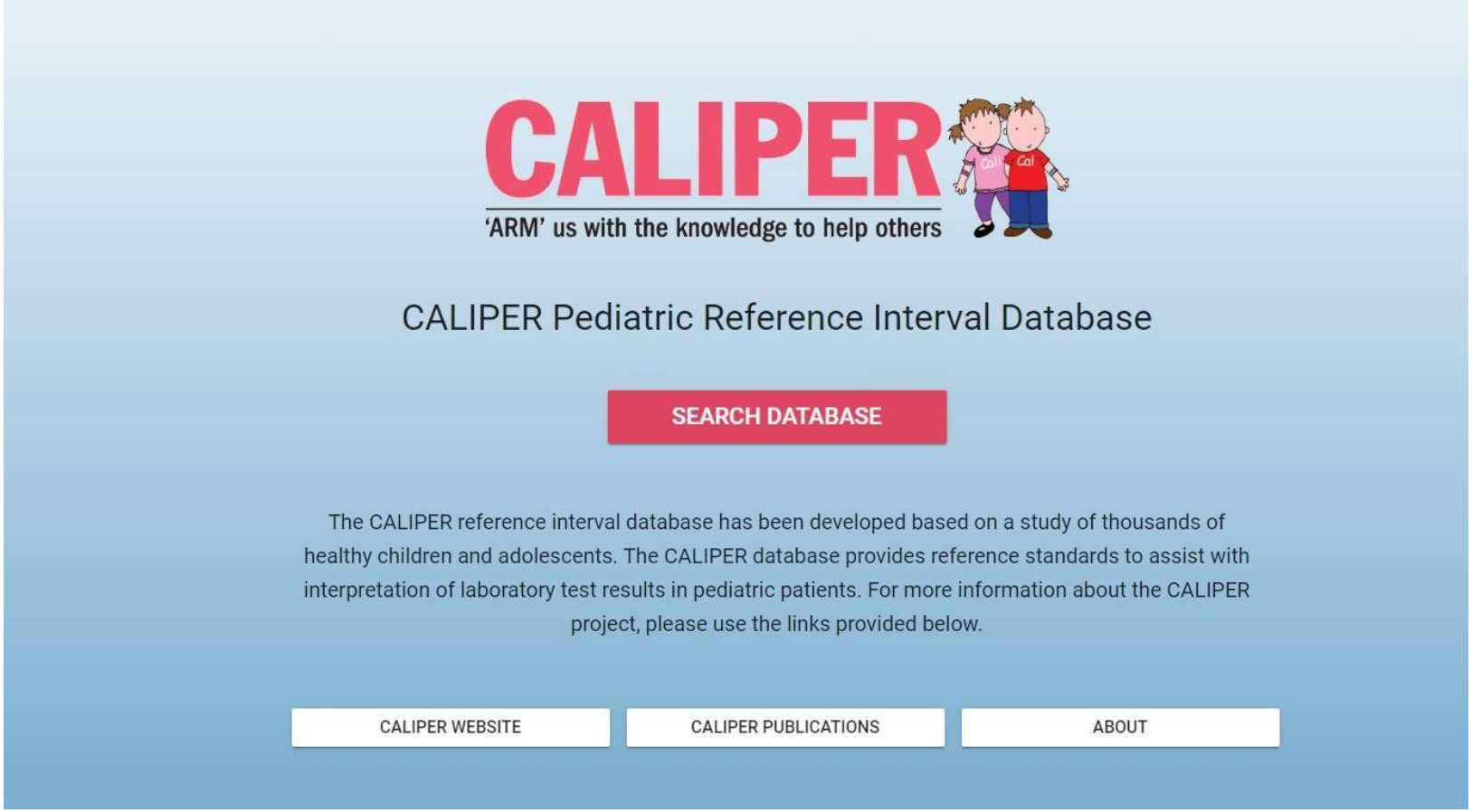
Figure 1. Serum ALP levels according to age showing a tetraphasic course from birth to adulthood
ALP: alkaline phosphatase

Serum Alkaline Phosphatase Levels in Healthy Children and Evaluation of Alkaline Phosphatase z-scores in Different Types of Rickets

Serap Turan[1], Burcu Topcu[2], İbrahim Gökçe[2], Tülay Güran[1], Zeynep Atay[1], Anjumanara Omar[1], Teoman Akçay[3], Abdullah Bereket[1]

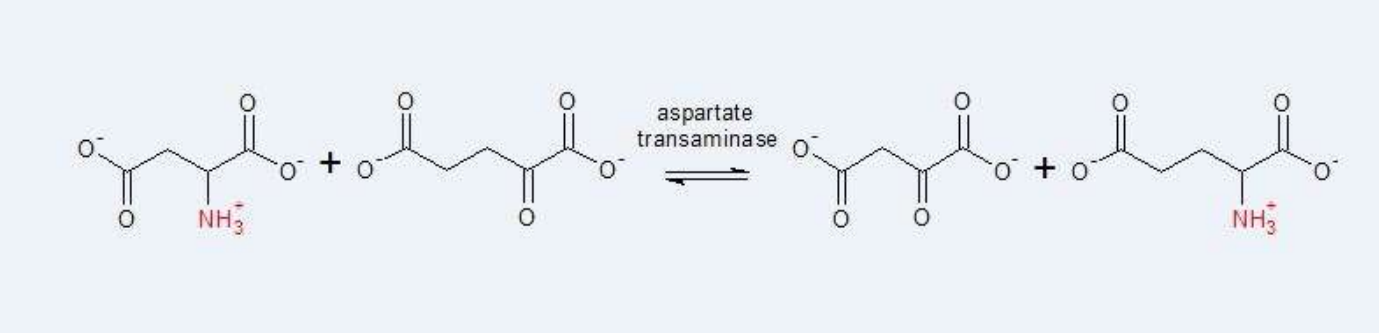
[1]*Marmara University, Department of Pediatric Endocrinology, İstanbul, Turkey*
[2]*Marmara University, Department of Pediatrics, İstanbul, Turkey*
[3]*Şişli Etfal Education and Research Hospital, Department of Pediatric Endocrinology, Istanbul, Turkey*

Curiosità


CALIPER
'ARM' us with the knowledge to help others
CALIPER Pediatric Reference Interval Database
SEARCH DATABASE
The CALIPER reference interval database has been developed based on a study of thousands of healthy children and adolescents. The CALIPER database provides reference standards to assist with interpretation of laboratory test results in pediatric patients. For more information about the CALIPER project, please use the links provided below.
CALIPER WEBSITE
CALIPER PUBLICATIONS
ABOUT

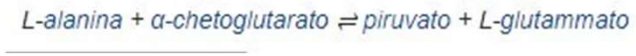
ASAT = Aspartato aminotransferasi

- Vecchio nome: GOT (Glutamic Oxaloacetic Transaminase)
- L'enzima catalizza la reazione di trasferimento del gruppo amminico dall'aspartato all'alpha-chetoglutarato a favore della formazione di ossalacetato e glutammato



ALAT=alanina amminotransferasi (GPT)

- L’enzima catalizza la seguente reazione



- La si trova nei reni, tessuti muscolari ma specialmente nel fegato

GGT

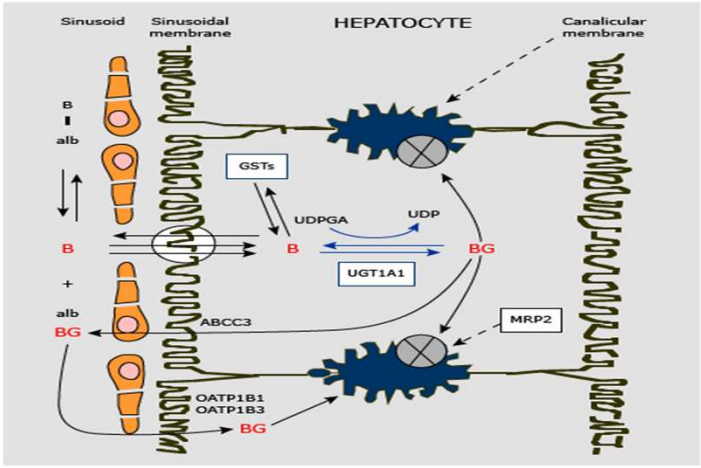
– Transpeptidasi che catalizza la seguente reazione

(5-L-glutammil)-peptide + un amminoacido = peptide + 5-L-glutammil amminoacido.

Bilirubina

- Prodotto del metabolismo dell'eme
- A livelli elevati può essere potenzialmente tossica
- 80% della produzione giornaliera (250-400 mg negli adulti) proviene dall'emoglobina
- 20% deriva da altre emoproteine e un piccolo pool di eme libera

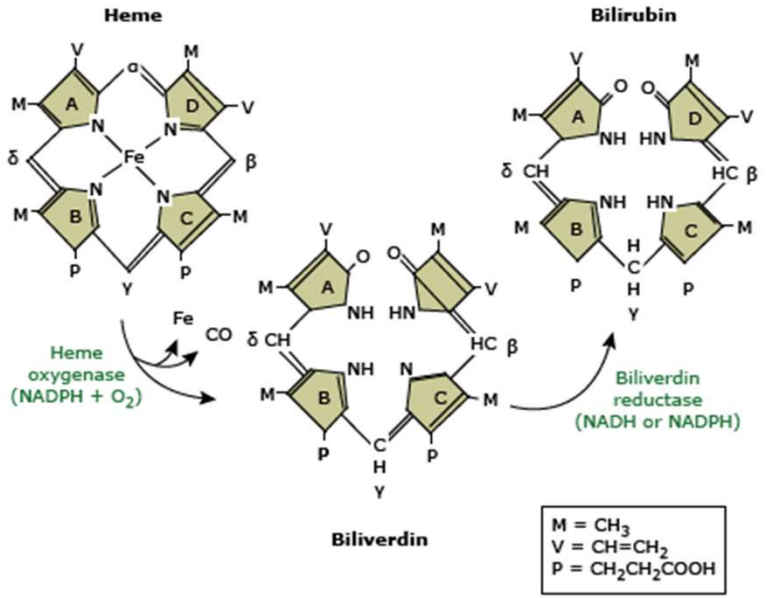
Bilirubin throughput in hepatocytes



Schematic representation of the steps involved in bilirubin (B) throughput in hepatocytes: transport to the liver (primarily as albumin-bound bilirubin), uptake at the sinusoidal membrane, intracellular binding, conjugation (glucuronidation), and canalicular excretion. Sinusoidal bilirubin uptake requires inorganic anions such as chloride and is thought to be mediated by carrier proteins. Within the hepatocyte, bilirubin binds to glutathione S-transferases (GSTs). GST-binding reduces the efflux of the internalized bilirubin, thereby increasing the net uptake. GSTs also bind bilirubin glucuronides (BG) prior to excretion. Bilirubin also enters hepatocytes by passive diffusion. Glucuronidation of bilirubin is mediated by a family of enzymes, termed uridine diphosphoglucuronosyltransferase (UGT), the most important of which is bilirubin-UGT-1 (UGT1A1). Conjugated bilirubin is secreted actively across the bile canalicular membrane of the hepatocyte against a concentration gradient that may reach 1:1000. The canalicular multidrug resistance protein 2 (MRP2) appears to be the most important for the canalicular secretion of bilirubin. A portion of the conjugated bilirubin is transported into the sinusoidal blood via the ATP hydrolysis-couple pump, ABCC3, to undergo reuptake via OATP1B1 and OATP1B3 by hepatocytes downstream to the sinusoidal blood flow.

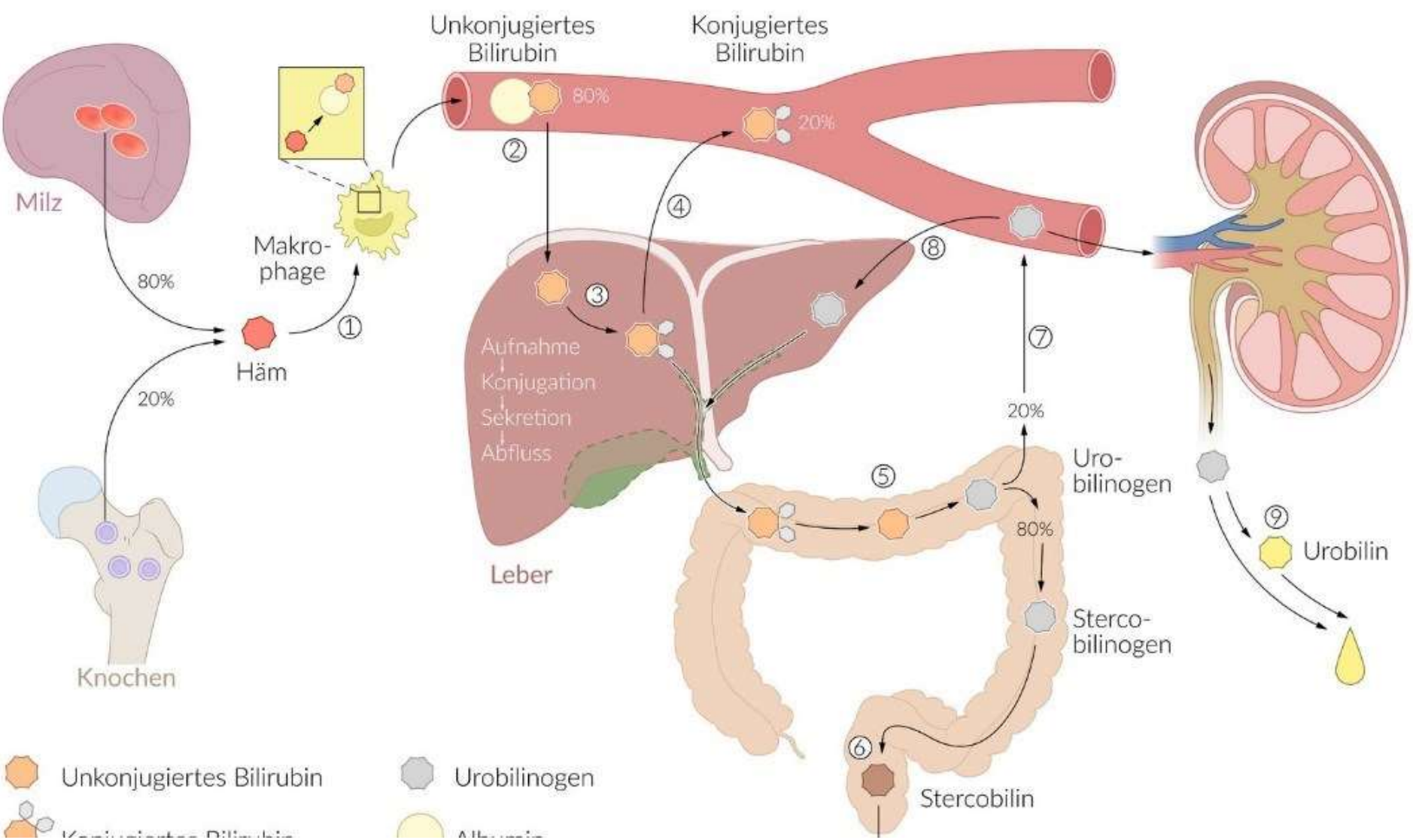
UDP: uridine diphosphate; UDPGA: uridine 5'-diphosphoglucuronic acid; ABCC3: ATP-binding cassette subfamily C number 3; OATP1B1: organic anion-transporting polypeptide 1B1; OATP1B3: organic anion-transporting polypeptide 1B3.

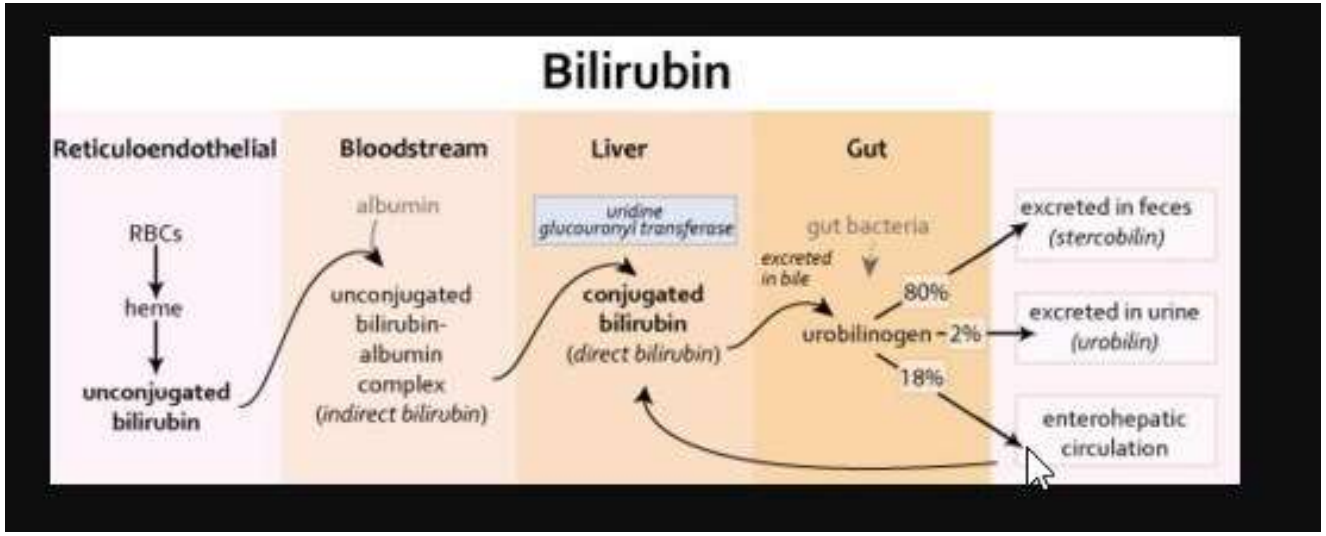
Bilirubin synthesis



Conversion of heme to biliverdin and then bilirubin. Heme ring-opening at the alpha-carbon bridge of heme is catalyzed by heme oxygenase, resulting in the formation of biliverdin. This is followed by reduction of biliverdin to bilirubin in a reaction catalyzed by biliverdin reductase.

NADH: reduced nicotinamide adenine dinucleotide; NADPH: reduced nicotinamide adenine dinucleotide phosphate.


Unkonjugiertes Bilirubin
Konjugiertes Bilirubin
80%
20%
Milz
Makro-
phage
80%
Häm
20%
Knochen
Aufnahme
Konjugation
Sekretion
Abfluss
Leber
Uro-
bilinogen
80%
Sterco-
bilinogen
Stercobilin
Urobilin
Unkonjugiertes Bilirubin
Urobilinogen


Bilirubin
Reticuloendothelial
Bloodstream
Liver
Gut
RBCs
heme
unconjugated bilirubin
albumin
unconjugated bilirubin-albumin complex (indirect bilirubin)
uridine glucouronyl transferase
conjugated bilirubin (direct bilirubin)
excreted in bile
gut bacteria
urobilinogen
80%
2%
18%
excreted in feces (stercobilin)
excreted in urine (urobilin)
enterohepatic circulation

Bilirubina e malattie correlate

- In una situazione fisiologica normale il 4% della bilirubina é coniugata (diretta). Tuttavia questa relazione può variare nei seguenti casi
  - Disordini ereditari della coniugazione della biliruina: bili diretta é ridotta
  - Sindrome di Rotor (difetto nel re-uptake di bilirubina coniugata e non coniugata), sindrome di Dubin-Johnson (difetto nell'escrezione della bilirubina)➔ bili coniugata e non, sono aumentate nel sangue
  - Ostruzione biliare o malattie epatocellulari le due forme di bili sono aumentate
  - Ittero emolitico: bilirubina totale aumentata, ma la propozione delle due bilirubine rimane invaraita.

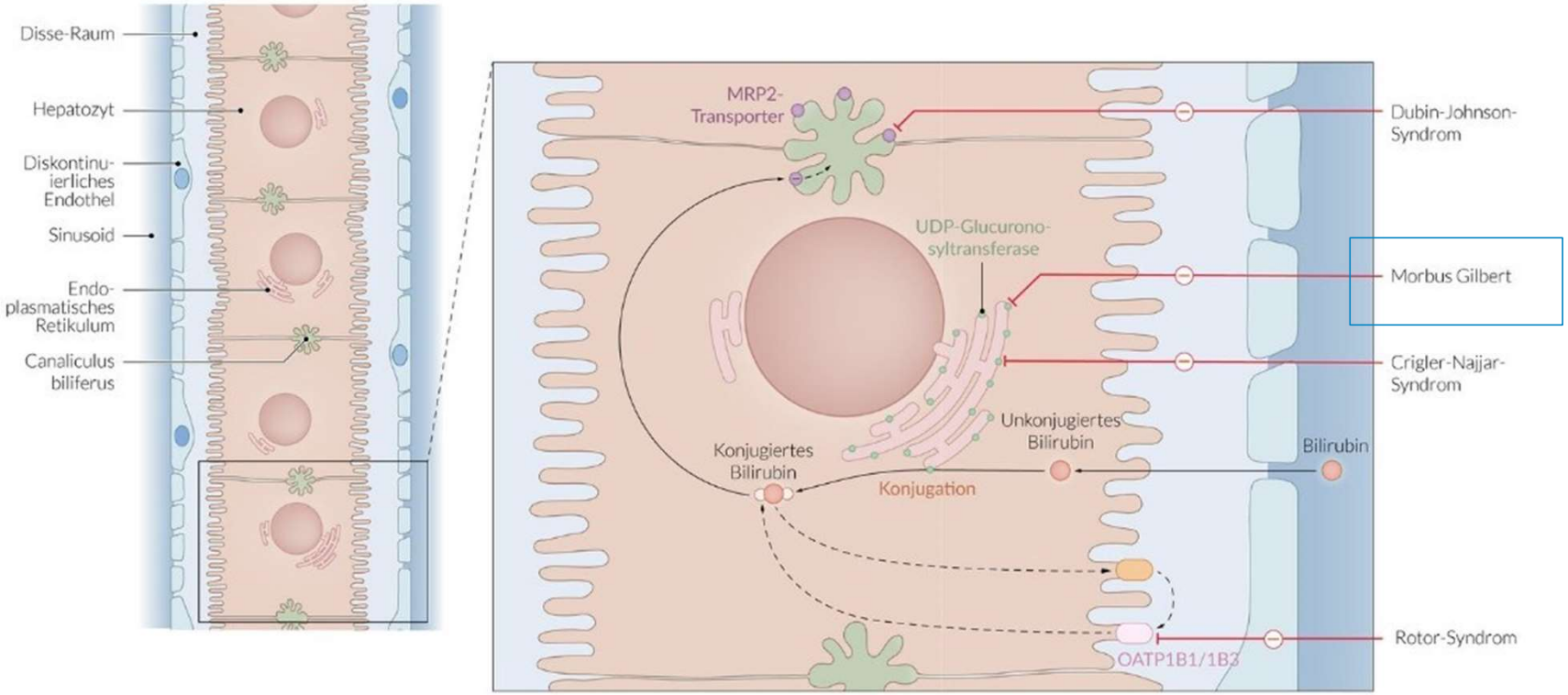
Sindrome da iperbilirubinemia famliare

- Quando la concentrazione di biliubina totale é aumentata
- Tutte le condizioni colestatiche oppure malattie del fegato acute o croniche possono essere prese in considerazione, TUTTAVIA quasi sempre sono accompagnate da altri parametri epatici alterati
- Le sindromi con iperbilirubina aumentata (isolata-genetiche) non portano, in genere, a conseguenze cliniche, in genere sono caratterizzate da un ittero passeggero.

Erhöhtes indirektes Bilirubin	• Morbus Meulengracht/Morbus Gilbert • Crigler-Najjar-Syndrom
Erhöhtes direktes Bilirubin	• Dubin-Johnson-Syndrom • Rotor-Syndrom

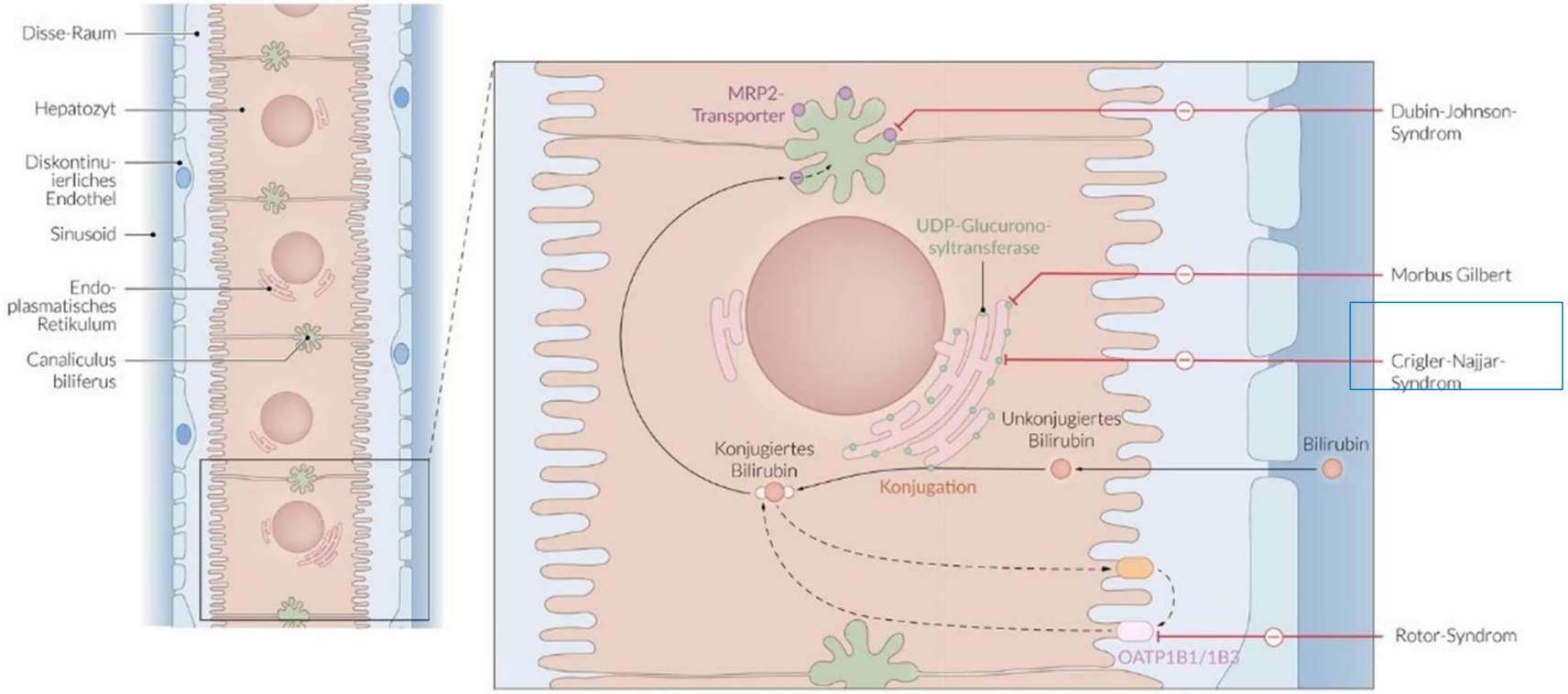
Scheda tecnica: Morbus Gilbert

- Epidemiologia: 5-9% degli adulti europei ne é colpito
- Eziologia: attività dell'enzima UDP-glucuronyltransferase é diminuita, malattia ereditaria
- Fattori scatenanti: Stress (trauma, malattie, sforzi), periodi di digiuno, consumo di OH
- Diagnostica: bilirubina indiretta aumentata, altri enzimi epatici nella norma, eventualmente analisi genetica
- Clinica: Sintomi aspecifici come inappetenza, eventualmente ittero
- Terapie: non necessarie.


Disse-Raum
Hepatozyt
Diskontinu-
ierliches
Endothel
Sinusoid
Endo-
plasmatisches
Retikulum
Canaliculus
biliferus
MRP2-
Transporter
UDP-Glucurono-
syltransferase
Konjugiertes
Bilirubin
Unkonjugiertes
Bilirubin
Konjugation
Bilirubin
OATP1B1/1B3
Dubin-Johnson-
Syndrom
Morbus Gilbert
Crigler-Najjar-
Syndrom
Rotor-Syndrom

Scheda Tecnica: Sindrome di crigler-Najjar

- Tipi di malattia: Tipo 1 e Tipo 2
- Eziologia: assenza totale (tipo 1) o parziale (tipo 2) di UDP-glucuronyltransferase, malattia ereditaria
- Clinica:ittero con prognosi non buona (tipo 1) ittero più lieve (tipo 2)
- Diagnostica:bilirubina indiretta aumentata, altri enzimi epatici nella norma
- Terapie: UV (tipo 1 e 2➔ aumenta la idrosulobuilità della bilirubina), Carbonato di Calcio (tipo 1➔forza la secrezione di bilirubina non coniugata nella bile), rifampicina/fenobarbital (tipo 2➔ induttori del sistema epatico)


Disse-Raum
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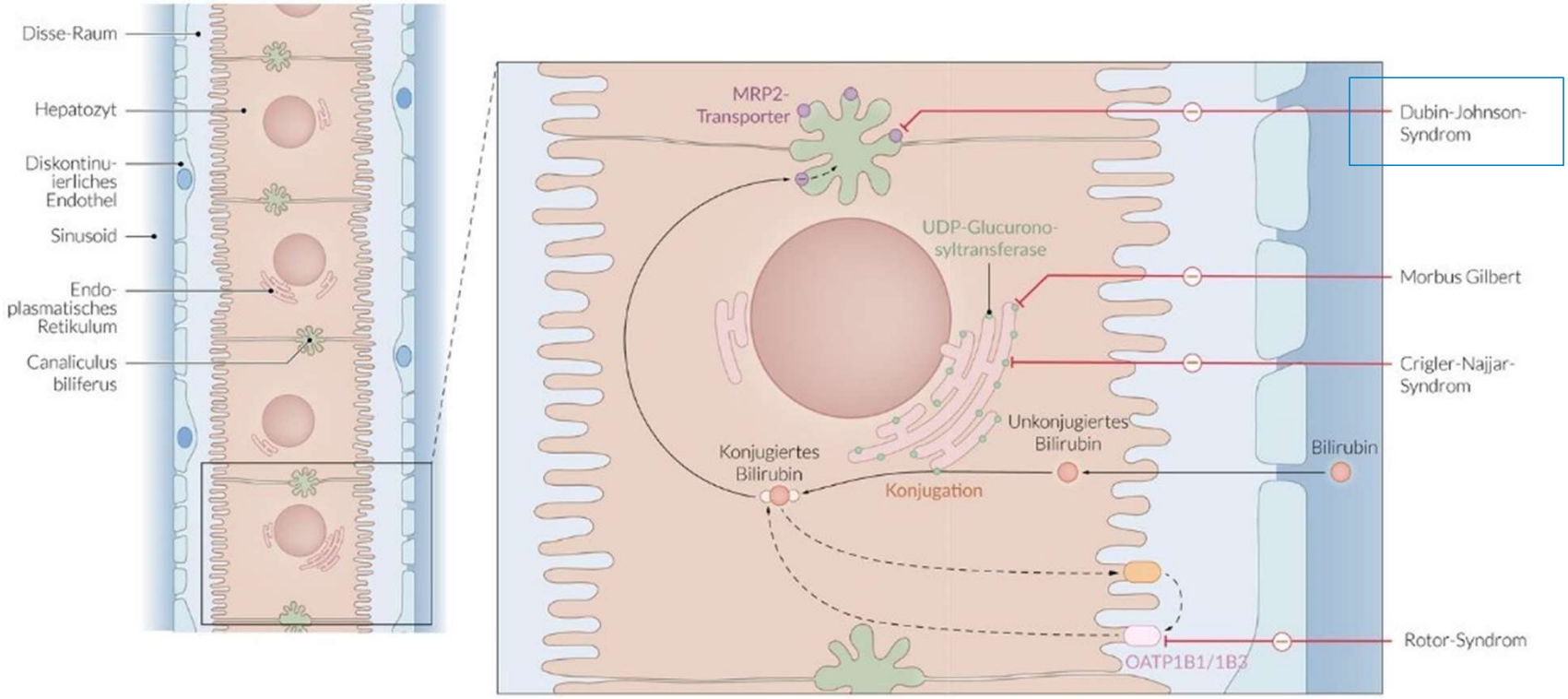
plasmatisches
Retikulum
Canaliculus
biliferus
MRP2-
Transporter
UDP-Glucurono-
syltransferase
Konjugiertes
Bilirubin
Unkonjugiertes
Bilirubin
Konjugation
Bilirubin
OATP1B1/1B3
Dubin-Johnson-
Syndrom
Morbus Gilbert
Crigler-Najjar-
Syndrom
Rotor-Syndrom

Scheda tecnica:Sindrome di Dubin-Johnson

- Eziologia: difetto nel trasportatore MRP-2, malattia ereditaria che porta a un problema di trasporto della bilirubina diretta dal fegato ai canali secernenti la bile
- Diagnostica: bilirubina indiretta aumentata , altri enzimi epatici nella norma, eventualmente analisi genetica
- Clinica: ittero da lieve a moderato, spesso in età giovane, aumentato dall'assunzione di medicamenti come contraccettivi, aumento osservato anche in gravidanza. Raramente splenomegalia
- Terapie: non necessarie. Attenzione all'assunzione di medicamente epatotossici che possono perggiorare l'ittero. Contraccettivi possono peggiorare l'ittero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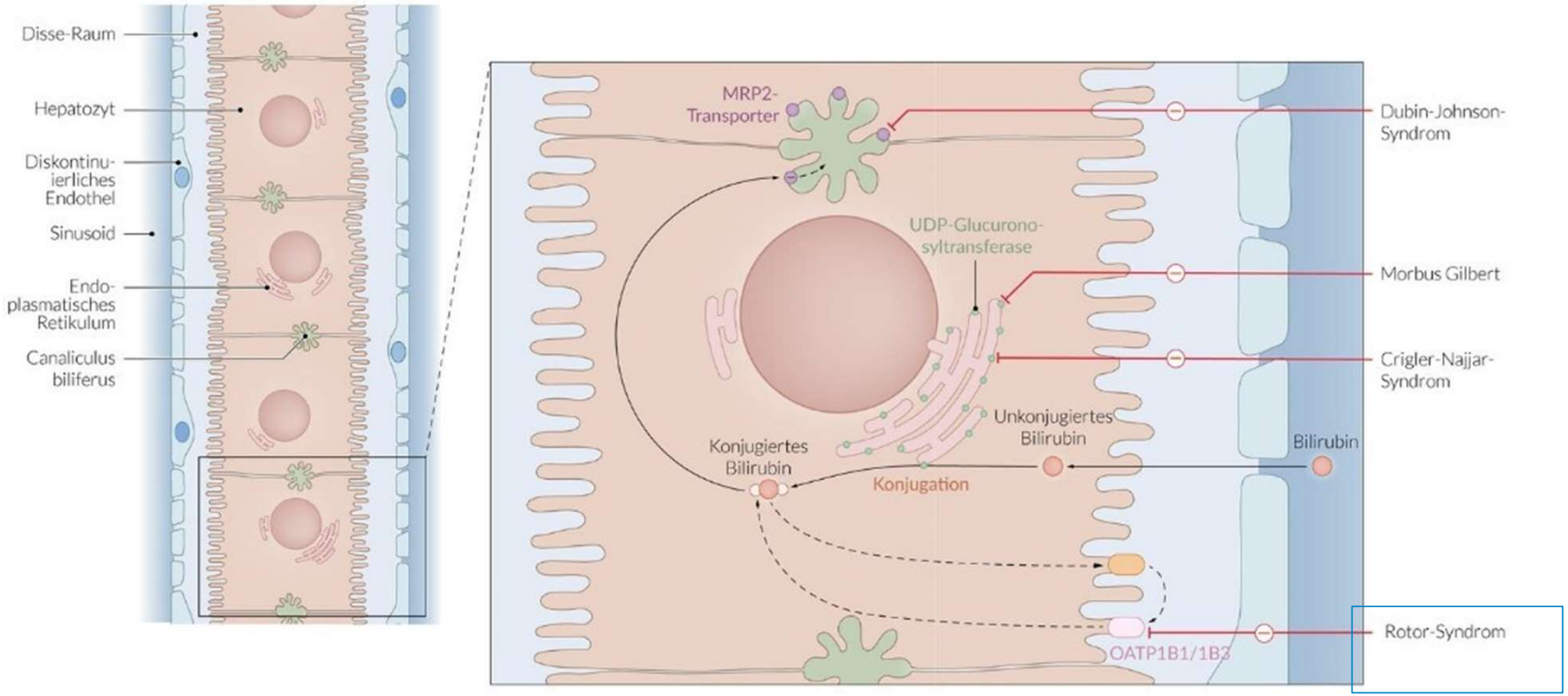
biliferus
MRP2-
Transporter
UDP-Glucurono-
syltransferase
Konjugiertes
Bilirubin
Unkonjugiertes
Bilirubin
Konjugation
Bilirubin
OATP1B1/1B3
Dubin-Johnson-
Syndrom
Morbus Gilbert
Crigler-Najjar-
Syndrom
Rotor-Syndrom

Scheda tecnica:Sindrome di Rotor

- Eziologia: difetto nel Organo-Anion Tranporter (OATP) negli epatociti, malattia ereditaria che porta a un problema di trasporto della bilirubina diretta e una ridotta capacità di stoccaggio della stessa
- Diagnostica: bilirubina diretta molto aumentata , altri enzimi epatici nella norma
- Clinica: in genere asintomatica
- Terapie: non necessarie. Attenzione all'assunzione di medicamente epatotossici che possono perggiorare l'ittero. Contraccettivi possono peggiorare l'ittero


Disse-Raum
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plasmatisches
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biliferus
MRP2-
Transporter
UDP-Glucurono-
syltransferase
Konjugiertes
Bilirubin
Unkonjugiertes
Bilirubin
Konjugation
Bilirubin
OATP1B1/1B3
Dubin-Johnson-
Syndrom
Morbus Gilbert
Crigler-Najjar-
Syndrom
Rotor-Syndrom

Workup: aumento isolato bilirubina

Bili diretta non aumentata

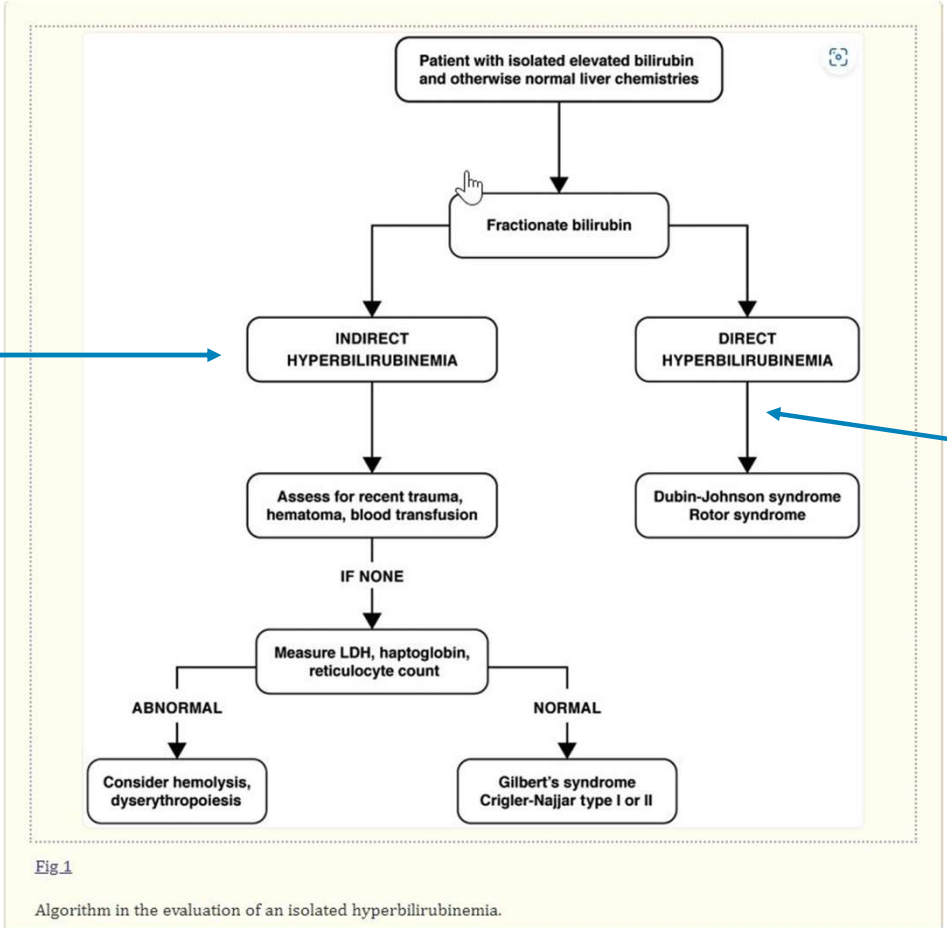


Fig 1

Algorithm in the evaluation of an isolated hyperbilirubinemia.

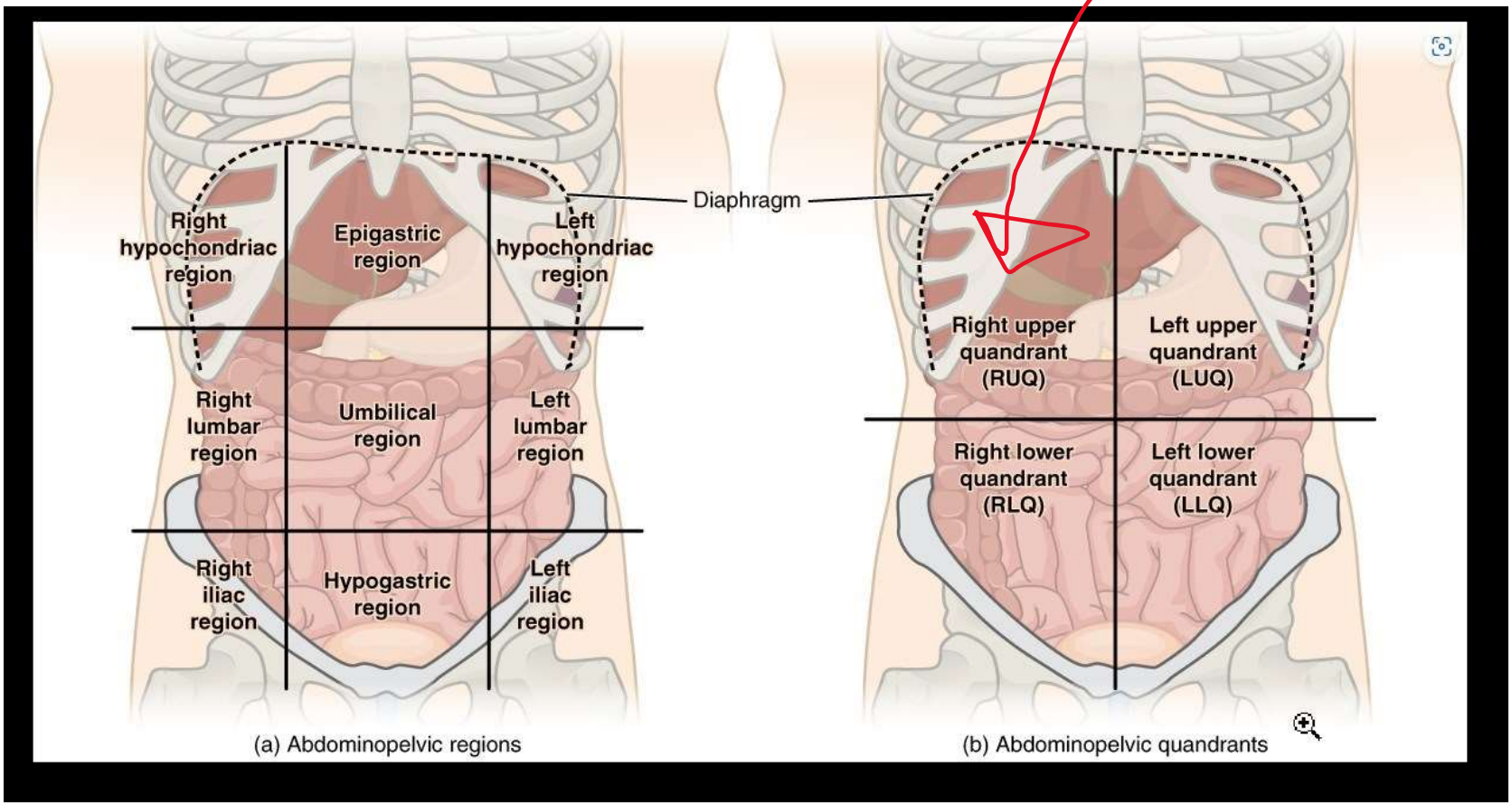
Bili diretta aumentata (>15% della totale).

Malattie epato-biliari

- Malattie con danno epatocellulare
- Malattie colestatiche
- Malattie epatocellulari/colestatiche
- Malattie con sintesi ridotta

Clinicamente le malattie
Epatobiliari sono caratterizzate
Da dolore nel quadrante
Destro superiore

➔ Dolore continuo/tipo coliche



Anamnesi nel sospetto di malattie epato-biliari

- Dolori nel quadrante destro superiore, che tipo di dolore?
- Presenza di prurito?
- Colorazione delle feci? Delle urine?
- Assunzione di OH? Quanto?
- Anamnesi di calcoli biliari?
- Perdita di peso?
- Malattie autoimmuni?
- Attività sessuali a rischio?
- Punture accidentali?

Esame fisico

- Ittero?
- Dolore addominale?
- Epatomegalia?
- Ascite?
- Foetor hepaticus (es presenza di ammoniaca e chetoni nel respiro)
- Iperpigmentazione: depositi di ferro e rame
- ➔ sono addominale

Malattie con danno epatocellulare

- Un aumento sproporzionale delle attività di ASAT/ALAT per rapporto a ALP e GGT➔ indicano un danno epatocellulare

- Si consiglia di misurare LDH e quoziente De-Ritis
  - Quoziente >1 con LDH aumentato: ampio danne cellulare
    - Causa comune: epatiti virali, OH, veleni, medicamenti, emocoromatosi, A1AT-deficit, epatiti autoimmuni

Quoziente De Ritis

- ALAT si trovano nel citoplasma
- ASAT si trovano nei mitocondri
- Le ALAT vengono rilasciate già in caso di danni lievi
- Le ASAT In caso di danno grave assistiamo al rilascio anche della parte mitocondriale
- Per questo motivo, in caso di danno grave la concentrazione di ASAT é preponderante rispetto alle ALAT
- QUOZIENTE: ASAT/ASAT

Interpretazione del quoziente De Ritis

Quoziente	<0.7 (fino a 1): «tipo infiammatori»	>= 1 «tipo necrosi»
Possibili cause	- Epatiti virali non complicate - Lieve fegato grasso - Colestasi extraepatica	- Epatite fulminante/necrotizzante - Cirrosi epatica scompensata - Carcinoma epatico, metastasi epatica - DD: danni muscolari (ASAT si trovano anche nei muscoli sceletrici e cardiaci: infarto miocardio.

Malattie colestatiche

- Attività ALP e GGT sono aumentate in concomitanza con un aumento della concentrazione di bilirubina diretta >15% rispetto alla totale e le attività delle transaminasi non risulta essere particolarmente alterata➔ si parla di malattia colestatica.

- Eseguire per esempio sonografia, DD
  - Calcoli epatici (colestasi extraepatica)
  - Metastasi epatiche (colestasi intraepatica), cirrosi biliare primitiva, colangite sclerosante primitiva, medicamenti (steroidi), colestasi gravidica

Malattie epatocellulari/colestatiche

- ALP/GGT (enzimi indicatori di colestasi) + ASAT/ALAT (enzimi indicatori di danno epatico)+ bilirubina diretta e totale aumentati➔ si parla di malattie epatocellulare colestatiche
  - Infezioni da EBV/CMV/Brucelle, Leptosporidi, parassiti, malaria, echinococci, schistosoma
  - Steatoepatite alcolica
  - Sidnrome di HELLP
- Per i pazienti appartenenti a questo profilo enzimatico, per i quali si sussiste a una diminuzione anche dell ‘ALB, vi é la possibilità di una cirrosi epatica
- Attenzione: Se nel decorso di un’epatite virale il valore di Quick diminuisce in maniera importante, la concentrazione di albumina si riduce e quella dell’ammoniaca risulta in range tossici➔epatite virale fulminante

Diminuzione della sintesi epatica

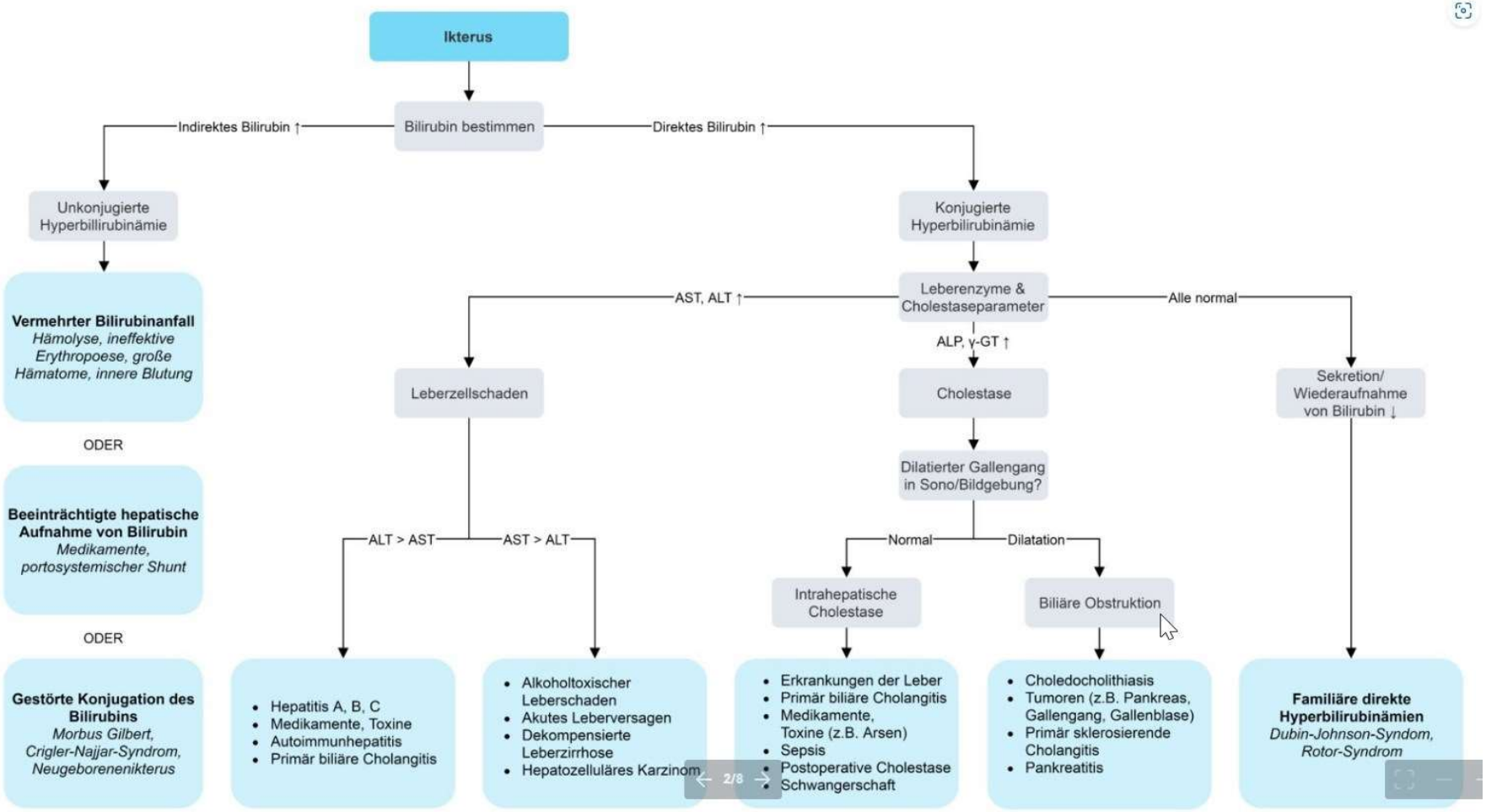
- Se durante uno screening di base i valori enzimatici epatici, indici di danno epatico e colestasi, sono aumentati in maniera non eccessiva, con un quick patologico (FATTORI II,V,VII)➔ malattia cronica con sintesi epatica insufficiente

  - Diminuzione della sintesi di albumina
  - Anamnesi per una ricerca di cirrosi
  - Calcolaare lo score Child-pug➔prognosi
  - Biopsia epatica, per esempio

Aumento enzimi epatici

- Lieve aumento quando li enzimi mostrano un aumento < 5X il valore di riferimento superiore

- Aumento significativo, quando >15 x il valore di riferimento superiore


Ikterus
Bilirubin bestimmen
Indirektes Bilirubin ↑
Direktes Bilirubin ↑
Unkonjugierte Hyperbillirubinämie
Konjugierte Hyperbilirubinämie
Vermehrter Bilirubinanfall
Hämolyse, ineffektive Erythropoese, große Hämatome, innere Blutung
ODER
Beeinträchtigte hepatische Aufnahme von Bilirubin
Medikamente, portosystemischer Shunt
ODER
Gestörte Konjugation des Bilirubins
Morbus Gilbert, Crigler-Najjar-Syndrom, Neugeborenenikterus
Leberenzyme & Cholestaseparameter
AST, ALT ↑
ALP, γ-GT ↑
Alle normal
Leberzellschaden
Cholestase
Sekretion/ Wiederaufnahme von Bilirubin ↓
ALT > AST
AST > ALT
Dilatierter Gallengang in Sono/Bildgebung?
Normal
Dilatation
Intrahepatische Cholestase
Biliäre Obstruktion
Hepatitis A, B, C
Medikamente, Toxine
Autoimmunhepatitis
Primär biliäre Cholangitis
Alkoholtoxischer Leberschaden
Akutes Leberversagen
Dekompensierte Leberzirrhose
Hepatozelluläres Karzinom
Erkrankungen der Leber
Primär biliäre Cholangitis
Medikamente, Toxine (z.B. Arsen)
Sepsis
Postoperative Cholestase
Schwangerschaft
Choledocholithiasis
Tumoren (z.B. Pankreas, Gallengang, Gallenblase)
Primär sklerosierende Cholangitis
Pankreatitis
Familiäre direkte Hyperbilirubinämien
Dubin-Johnson-Syndom, Rotor-Syndrom
2/8

Child-Plug score

- Score per la prognosi della cirrosi epatica
- Si compone die valori di albumina, bilirubina, quick e sonografia (messa in evidenza di ev. ascite), congiuntamente al grado di encefalopatia epatica
- A seconda die punti ottenuti, la classficazione é
  - Child A, B, C
  - Se child C prognosi infausta a 1/2 anno di distanza

VERKLEINERN QUIZ STARTEN

Child-Pugh-Klassifikation [2][3]			
Punkte	1	2	3
Albuminkonzentration im Serum in g/dL	>3,5	2,8–3,5	<2,8
Bilirubinkonzentration im Serum in mg/dL	<2,0	2,0–3,0	>3,0
Quick-Wert in %	>70	40–70	<40
Aszites (sonografisch)	kein	mäßig	viel
Hepatische Enzephalopathie	keine	Grad I–II	>Grad II
Child A: 5–6 Punkte; Child B: 7–9 Punkte; Child C: 10–15 Punkte			

Child-Pugh classification of severity of cirrhosis

Parameter	Points assigned		
	1	2	3
Ascites	Absent	Slight	Moderate
Bilirubin	<2 mg/dL (<34.2 micromol/L)	2 to 3 mg/dL (34.2 to 51.3 micromol/L)	>3 mg/dL (>51.3 micromol/L)
Albumin	>3.5 g/dL (35 g/L)	2.8 to 3.5 g/dL (28 to 35 g/L)	<2.8 g/dL (<28 g/L)
Prothrombin time (seconds over control) or	<4	4 to 6	>6
INR	<1.7	1.7 to 2.3	>2.3
Encephalopathy	None	Grade 1 to 2	Grade 3 to 4

Modified Child-Pugh classification of the severity of liver disease according to the degree of ascites, the serum concentrations of bilirubin and albumin, the prothrombin time, and the degree of encephalopathy. A total Child-Turcotte-Pugh score of 5 to 6 is considered Child-Pugh class A (well-compensated disease), 7 to 9 is class B (significant functional compromise), and 10 to 15 is class C (decompensated disease). These classes correlate with one- and two-year patient survival: class A: 100 and 85%; class B: 80 and 60%; and class C: 45 and 35%.

INR: international normalized ratio.

Cirrosi epatica

- La cirrosi epatica rappresenta uno stadio tardivo di fibrosi progressiva
- Si caratterizza da una struttura epatica distorta con formazione di noduli rigenerativi
- Negli stadi avanzati, viene considerata irreversibile con unica opzione terapeutica data dal trapianto
- Pazienti con cirrosi epatica sono suscettibili a diverse complicazioni e l'aspettativa di vita può essere notevolmente ridotta

Common complications of cirrhosis

Variceal hemorrhage
Ascites
Spontaneous bacterial peritonitis
Hepatic encephalopathy
Hepatocellular carcinoma
Hepatorenal syndrome
Hepatopulmonary syndrome
Hepatic hydrothorax
Portopulmonary hypertension
Cirrhotic cardiomyopathy
Portal vein thrombosis

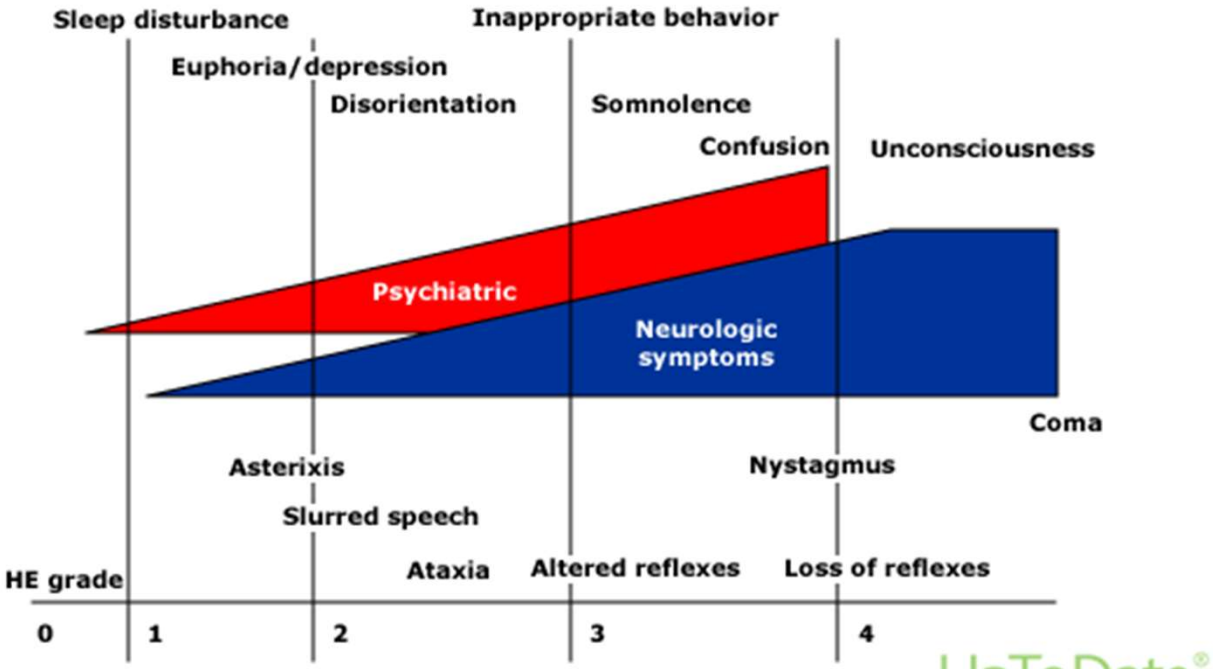
UpToDate®

Se il paziente sviluppa una di queste queste condizioni viene definito come paziente con cirrosi scompensata

Encefalopatia epatica

– Descrive lo spettro di manifestazioni potenzialmente reversibili che causano anomalie neuropsichiatriche in pazienti con disfunzioni epatiche.

Evolution of hepatic encephalopathy



UpToDate®

Clinical features of hepatic encephalopathy in adults

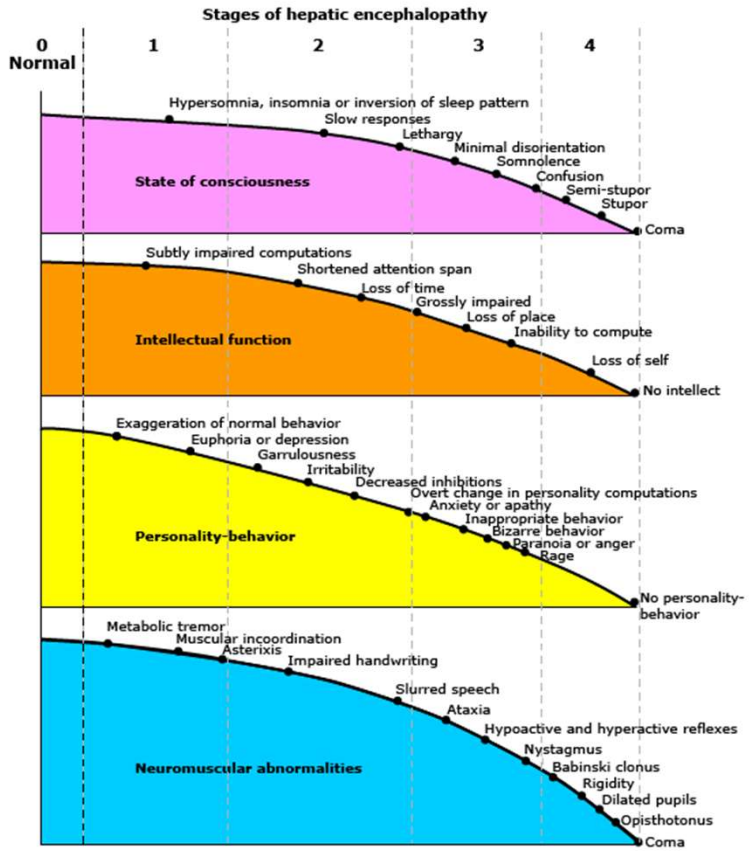


Diagram depicting the grade of hepatic encephalopathy in adults and the clinical features associated with advancing stages.

Data from: Conn HO, Lieberthal MM. The hepatic coma syndromes and lactulose. Lippincott Williams & Wilkins, Baltimore 1979.

MELD-Score (model for End-Stage Liver Disease)

- MELD calculator - OPTN (hrsa.gov)
- Ulteriore modello per predire la prognosi in pazienti con cirrosi
- Si basa sui livelli di bilirubina, creatinina, INR, e eziologia della cirrosi epatica
- Viene utilizzato per priorizzare i pazienti che aspettano un trapianto epatico

Sommario: quali test diagnostici?

- Screening: esiste una malattia epatica?
- Test funzionali: quanto é grave una malattia epatica?
- Test diagnostici: eziologia della malattia epatica?
- **Fibrosi: grado di fibrosi=grado di cicatrizzazione, correlato con mortalità**

Steatosi epatica

- Steatosis= accumulo di grasso nelle cellule (fegato grasso)
- Steatosi alcolica
- Steatosi dovuta all’uso di mtx
- Steatosi dovuta alla malattia di Wilson (accumulo di rame)
- Steatosi dovuta ad alcune varianti di epatite C

NAFLD vs. NASH

NAFLD	NASH
Non-alcoholic fatty liver disease	Non-alcoholic steatohepatitis
Grasso stoccato (prevalentemente trigliceridi), in genere «gocce» nelle cellule del fegato➔spingono le componenti cellulari al bordo	Termine coniato negli anni 80, per persone con fegato grasso senza avere una causa chiara (es: consumo di alcol). Allora la relazione con, per esempio altre cause metaboliche, non era ancora nota
Una condizione dove troppo grasso viene stoccato nelle cellule. Il fegato dovrebbe stoccare solo una piccola parte di energia sotto forma di carboidrati (glicogeno) non di grassi (vengono stoccati nel tessuto grasso)	In contrasto con le malattie che riportano la causa nel nome, questa riportava la non-causa == epatite si riferisce al processo infiammatorio indipendentemente dalla causa
Il fegato dovrebbe avere un contenuto di grasso < 5% (delle cellule), in caso di NAFLD il contenuto é superiore	!!! NASH é un sottotipo di NAFLD
Spesso, il grasso depositato nel fegato non pare avere un'effetto sulla funzionalità epatica. In questo caso viene chiamato fegato grasso isolato OPPURE fegato non-alcolico (NAFL_senza D)	Se oltre che al grasso si osservano cellule infiammate o danneggiate allora ci si riferisce a NAFLD Opuure NASH

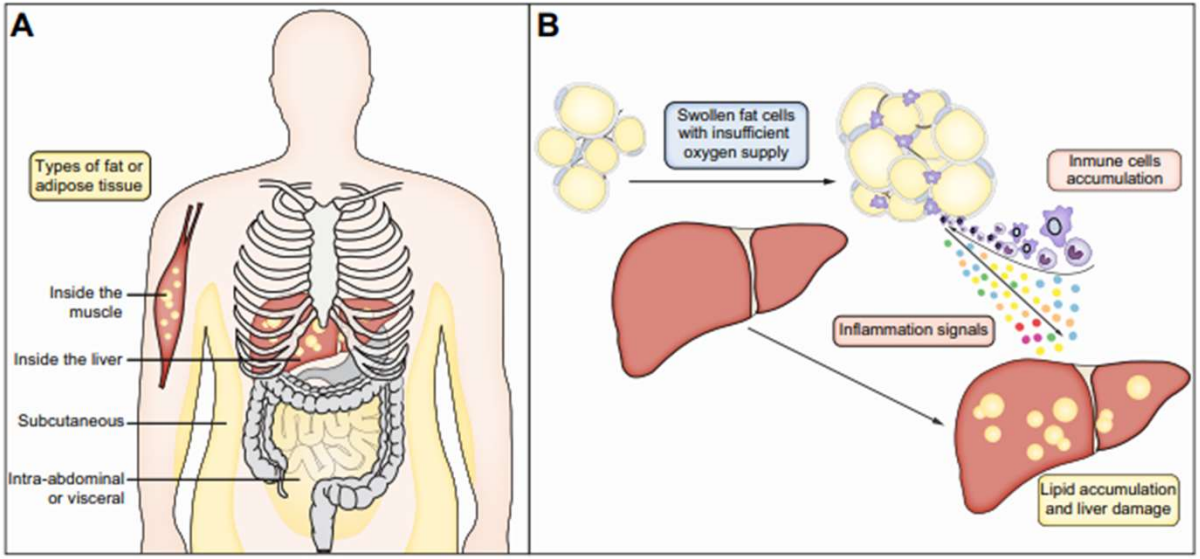


Fig. 3. The body harbours different types of fat or adipose tissue. (A) The fat that is inside the abdominal cavity and in close contact with both the gut and the liver is called intra-abdominal or visceral fat. The fat just beneath the skin is called subcutaneous fat. Intra-abdominal fat is more active, in terms of metabolic processes that are going on inside the cells. The intra-abdominal fat tissue is also active in the production of signals that help the body regulate its energy metabolism. It is thus not just a storage space, but also an active regulator of your body's energy handling. (B) When this fat tissue is overwhelmed and the fat cells become very swollen, the fat tissue will become inflamed because there is not enough blood supply to and hence not enough oxygen in these too swollen fat cells. This leads to damage and dysfunction of this fat tissue. This inflamed fat tissue will release harmful substances into the blood that can then damage the liver. Subcutaneous fat is less reactive. It stores your energy reserves, which is important to protect us from the destructive consequences of calorie excess. However, there is a limit to that storage capacity too. When your excess calories exceed this storage capacity, the fat will need to go somewhere else.

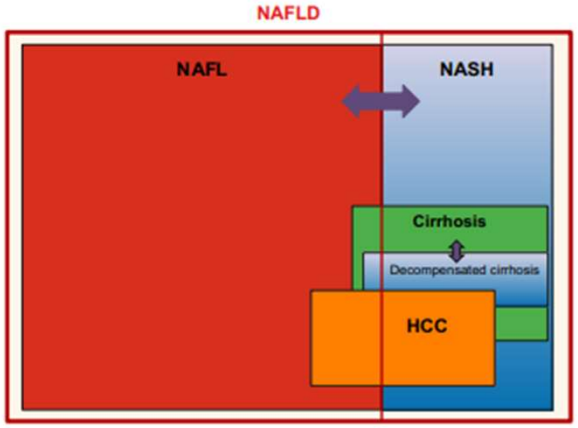


Fig. 2. The different subtypes of NAFLD and their relationships with the severe consequences of the disease. NAFLD is the overarching term. If there is mainly only steatosis, we call it simple steatosis or isolated steatosis (NAFL). If there is also liver cell damage and inflammation, we call it steatohepatitis (NASH). The separation is not static, so you can have NAFL and evolve to NASH, and also the other way around. The active disease can evolve to more severe liver injury and ultimately cirrhosis. Cirrhosis means advanced scarring of the liver, but even in these conditions, the liver can continue to function (compensated cirrhosis). Some people with cirrhosis will, however, evolve to poor liver function, which is called decompensated cirrhosis. NAFLD is also associated with the risk of developing liver cancer (HCC). As you can see from the figure, cirrhosis and decompensated cirrhosis mostly occur in association with NASH, whereas patients with NAFL have a lower (but not zero) risk. For HCC, the risk is the highest if you have cirrhosis, but there is still a risk in patients without cirrhosis and even without NASH. The magnitude of the boxes does not give any indication of the magnitude of the risk (please refer to the text for risk estimates). HCC, hepatocellular carcinoma; NAFL, non-alcoholic fatty liver; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis.

Box 1. The terminology of non-alcoholic fatty liver disease.

Steatosis refers to the accumulation of fat ("lipids") within the cells of the body. In the case of NAFLD and other types of fatty liver disease, fats accumulate in the liver cells or "hepatocytes".

NAFLD stands for **non-alcoholic fatty liver disease**, which refers to fatty liver disease that is not caused by alcohol consumption, the use of drugs that can induce steatosis, or the presence of other diseases that are well known to increase liver fat.

NAFL or **non-alcoholic fatty liver** is the subtype of NAFLD in which there is only liver fat accumulation, without liver cell damage or inflammation.

NASH or **non-alcoholic steatohepatitis** is the subtype of NAFLD in which the accumulation of fat in the liver cells is accompanied by liver cell damage and by inflammation.

Fibrosis is the scar tissue that can develop when the liver is damaged and inflamed. If there is significant and/or long-lasting damage and inflammation, more and more scar tissue can accumulate and ultimately lead to a nodular transformation of the liver structure. The latter condition is called cirrhosis.

NAFLD if you drink more than the upper limits that have been set or have had a history of past excess alcohol intake. The drinking limits are most often defined by a weekly consumption of less than 14 units for women and 21 for men (1 unit equals 8 g of alcohol, the meaning of alcohol expressed in units is explained in Box 2). These limits correspond to the amount of alcohol that is known to cause steatosis by itself.[23] You should also not binge drink (binge drinking is defined as ≥4 drinks/day for women and ≥5 drinks/day for men).[23] These limits do not mean that alcohol consumption below these limits is harmless. It is indeed highly questionable whether alcohol consumption at any level can be considered safe. It just means that a consumption of alcohol below these limits is probably not causing steatosis. It might, however, still carry a risk for other health problems, in particular

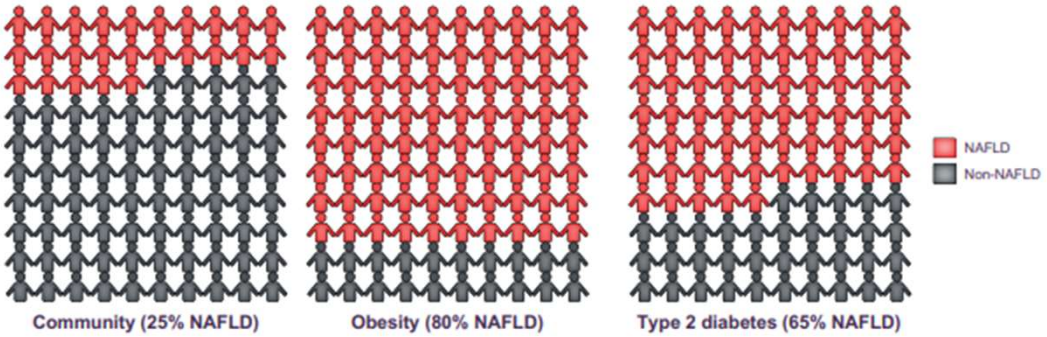


Fig. 6. It is estimated that 25% of European adults have NAFLD. You are, however, more likely to have NAFLD if you have obesity and T2D, with NAFLD occurring in nearly 8 to 9 out of 10 (80 to 90%) people living with obesity and in 5-7 out of 10 (50-70%) people living with type 2 diabetes. The number of people with NAFLD increases progressively with age. NAFLD, non-alcoholic fatty liver disease; T2D, type 2 diabetes.

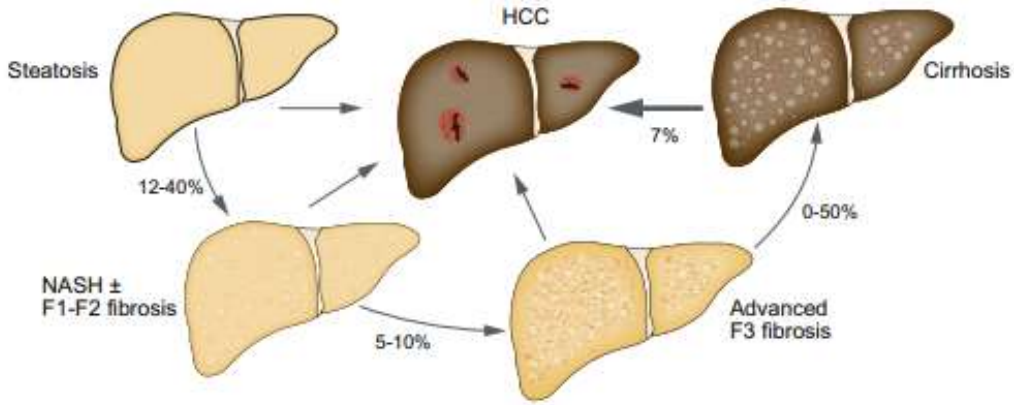


Fig. 7. How does NAFLD evolve over time? Not everybody with NAFLD will develop cirrhosis. The estimated percentages of patients who will evolve stepwise to a more severe disease stage are depicted here. F1-2-3, stage of fibrosis 1-2-3; HCC, hepatocellular carcinoma; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis.

NAFL spesso associato a sindrome metabolica

Table 1. Definitions and criteria of the metabolic syndrome.

Criteria	WHO (1999)[8]	NCEP (2001)[9]	IDF (2005)[10]	Joint societies (2009)[11]
Required for diagnosis	Impaired glucose tolerance or diabetes and/or insulin resistance	None	Central obesity as defined below	None
Number of features	Two other factors	≥3 of the below	≥2 of the below	≥3 of the below
Central obesity	Waist–hip ratio of >0.9 in men, >0.85 in women or BMI ≥30 kg/m^2	Waist circumference ≥102 cm in men, ≥88 cm in women	Waist circumference ≥94 cm European men; ≥90 cm South Asian or Chinese men; ≥80 cm women	Waist circumference – population-specific definitions
Triglycerides	≥150 mg/dl (1.7 mmol/L)	≥150 mg/dl (1.7 mmol/L)	≥150 mg/dl (1.7 mmol/L) or treatment for high triglycerides	≥150 mg/dl (1.7 mmol/L) or treatment for high triglycerides
HDL-cholesterol	<40 mg/dl (1 mmol/L) in men, <50 mg/dl (1.3 mmol/L) in women	<40 mg/dl (1 mmol/L) in men, <50 mg/dl (1.3 mmol/L) in women	<40 mg/dl (1 mmol/L) in men, <50 mg/dl (1.3 mmol/L) in women	<40 mg/dl (1 mmol/L) in men, <50 mg/dl (1.3 mmol/L) in women
Hypertension	≥140/90 mmHg	≥135/85 mmHg or treated hypertension	≥135/85 mmHg or treated hypertension	≥135/85 mmHg or treated hypertension
Glucose	n.a.	110 mg/dl (6.1 mmol/L)	≥100 mg/dl (5.6 mmol/L) or diagnosed with type 2 diabetes mellitus	≥100 mg/dl (5.6 mmol/L), or drug treatment for diabetes
Microalbuminuria	Albumin–creatinine ratio >30 mg/g; albumin excretion rate >20 μg/min	n.a.	n.a.	n.a.

IDF, International Diabetes Federation; n.a., not applicable; NCEP, National Cholesterol Education Program; WHO, World Health Organization; BMI, body mass index; HDL, high-density lipoprotein.

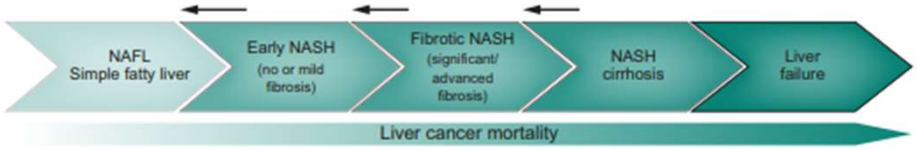


Fig. 4. Non-alcoholic fatty liver disease can evolve from just a fatty liver to severe liver disease, over different stages of severity. Many factors determine if you will develop more severe liver disease and how quick the evolution is. Luckily, many patients will not evolve to severe liver disease and many steps in the evolution are reversible with adequate management. NAFL, non-alcoholic fatty liver; NASH, non-alcoholic steatohepatitis.

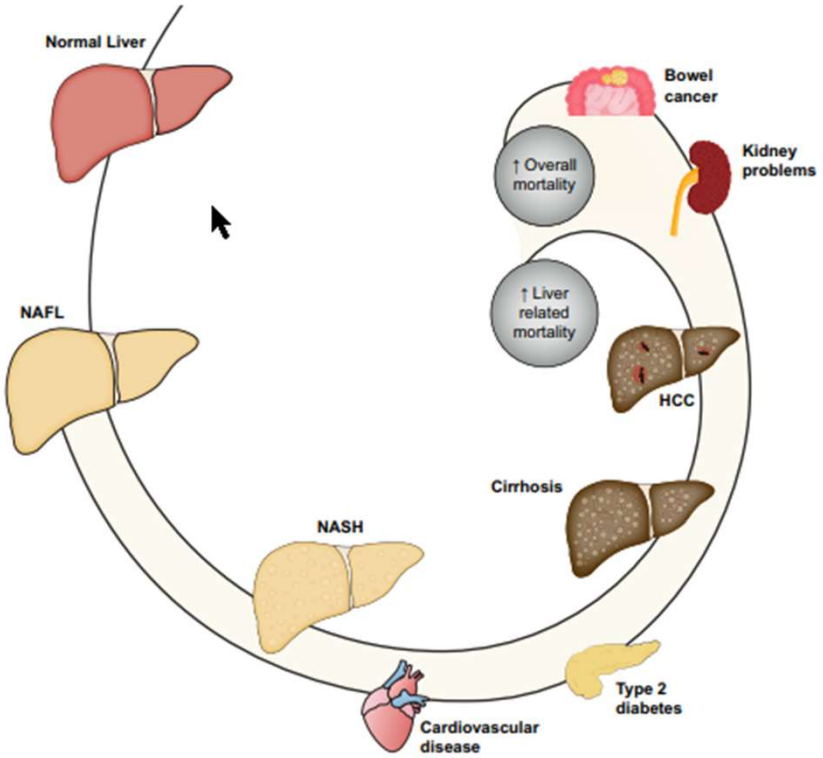


Fig. 5. The current understanding of NAFLD is that most patients only have fatty liver, without liver cell damage and inflammation (NAFL). Some patients will evolve to NASH, wherein steatosis is accompanied by liver cell damage and inflammation. This can go along with the accumulation of scar tissue or fibrosis. In a subset of patients with NASH, more and more scar tissue will accumulate and ultimately result in cirrhosis. Patients with cirrhosis but with good liver function can evolve to a cirrhosis-related more severe liver problem (decompensated cirrhosis). A liver cancer (HCC) can develop at any stage, but the risk of HCC is higher when the NAFLD is more severe. Usually, the evolution of the disease is slow, but some patients can be rapid progressors. NAFLD increases the risk of developing diabetes. NAFLD also increases the risk of diseases of the heart and blood vessels (CVD). NAFLD may also increase the risk of several types of cancer (including bowel cancer) and the development of kidney problems. CVD, cardiovascular disease; HCC, hepatocellular carcinoma; NAFL, non-alcoholic fatty liver; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis.

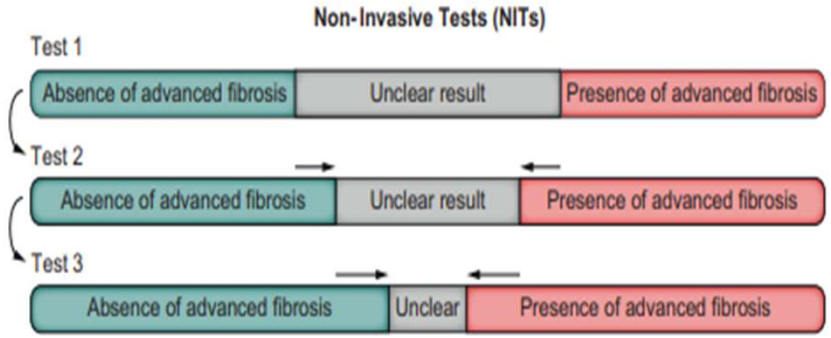


Fig. 8. Screening for NAFLD can be done using different tests (non-invasive tests or NITs) and different strategies of testing. There is no international consensus on the optimal screening strategy. Tests can be combined at one instance. Another possibility is to use several different tests sequentially: the second test is only performed if the first one is positive or gives an unclear result. NAFLD, non-alcoholic fatty liver disease.

Score di fibrosi

	Test di fibrosi	
Biopsia epatica	Test di laboratorio	imaging
-percutaneo/transgiugulare - Gold Standard - Invasivo - Correlato a Rischi	- Facile da eseguire - FIB-4 index - NAFLD fibrosis score	US elastografia MR elastografia

Fib-4 index

Box 10. Fibrosis scores.

Fibrosis-4 Index (FIB4) and the NAFLD fibrosis score (NFS) are helpful for assessing the likelihood of having or not a certain stage of fibrosis. These scores are not intended to diagnose the actual stage of fibrosis of your liver with great precision, but they can help to tell you the likelihood of having no/minimal fibrosis or the likelihood of having advanced fibrosis (F3 or more).

Take for example FIB-4. A value of 3.06 is high and tells you that you have a high likelihood of having F3 or more. A FIB-4 of 1.1 is reassuring as it tells you that you have a very low likelihood of having advanced fibrosis, but it does not tell you whether you have F0, F1 or F2.

The parameters included in the FIB-4 and the most frequently used cut-offs and their interpretation, are as follows:

FIB-4 formula:[294] $= \dfrac{\text{age (years)} \times \text{AST (IU/L)}}{\text{platelet count } (\times 10^9/\text{L}) \times \sqrt{\text{ALT (IU/L)}}}$

- FIB-4 score ≤1.3 to rule out advanced fibrosis
- FIB-4 score >1.3 and <2.67 as indeterminate/inconclusive
- FIB-4 score ≥2.67 to suggest advanced fibrosis

NAFLD fibrosis score formula:[294]

$$-1.675 + 0.037 \times \text{age (years)} + 0.094 \times \text{BMI (kg/m}^2) + 1.13 \times \text{IFG/diabetes (yes = 1, no = 0)} + 0.99 \times \text{AST/ALT ratio} - 0.013 \times \text{platelet } (\times 10^9/\text{L}) - 0.66 \times \text{albumin (g/dl)}$$

- NAFLD score <-1.455 to rule out advanced fibrosis
- NAFLD score >-1.455 and <0.675 as indeterminate/inconclusive
- NAFLD score >0.675 to suggest advanced fibrosis

It should be noted that the cut-offs that are mentioned here, according to some scientific data, might not be accurate if you are younger than 35 years and if you are older than 65 years.[294]

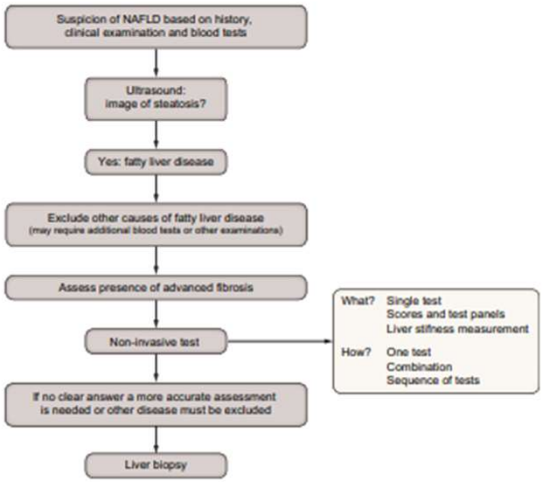


Fig. 9. This flowchart represents a proposal of how to approach the challenge of diagnosing NAFLD if you have one or more risk factors for NAFLD. NAFLD, non-alcoholic fatty liver disease.

Box 11. Lifestyle modification.

- Overweight and obesity are important risk factors for NAFLD/NASH, mainly when the calorie overload exceeds the capacity of your fat tissue to store the excess energy you have taken up.
- Lifestyle modification, which includes changes in dietary pattern and composition as well as increasing physical activity levels, is the first step and cornerstone of NAFLD management.
- Achieving sustained weight loss can improve NAFLD across the disease spectrum. The amount of weight loss is the most important determinant of improvement, regardless of the type of diet that has been followed.
- The Mediterranean diet is one of the most studied and beneficial. Even without weight loss, a healthier food pattern, especially the Mediterranean diet, can result in NAFLD improvement.
- Added sugars, especially fructose, play a major role and should be avoided as much as possible. A reasonable fruit consumption of 1-3 fruits per day, should not be further restricted and should be a part of a balanced diet and a source for fiber and vitamins.
- Decreasing overall sedentary time and breaking up sedentary time throughout the day is a useful treatment strategy for all people with NAFLD/NASH.
- Any increase in physical activity is useful, even without weight loss. In order to induce significant changes, over 150 min/week of moderate intensity physical activity over 3–5 sessions including a combination of aerobic ("cardio" *e.g.* brisk walking, cycling, swimming) and resistance ("strength" *e.g.* lifting weights) training are recommended.
- Both the changes in diet and physical activity/exercise levels need to be tailored to your individual needs, preferences and abilities in order to find a way of living that you enjoy and can sustain in the long term.

NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis.

d. Maximum effort should be made to improve the factors that drive the disease: this is what is meant by lifestyle modification

See Box 11.

What is the evidence for lifestyle modifications in the management of NAFLD? What exactly do I need to do?

Weight loss

Research has shown that weight loss is an effective treatment for NAFLD across the disease spectrum.[123] Weight reduction, whichever way it is achieved, leads to improvements in your liver blood tests (liver enzymes), the amount of liver fat and liver inflammation, as well as the amount of scar tissue or fibrosis.[13,124] The impact of weight loss on liver improvement depends on the degree of weight reduction. A weight reduction of >5% is usually necessary to reduce liver fat, 7–10% to improve liver inflammation and >10% to improve fibrosis/scarring, although even lower reductions can be helpful.[124] Therefore, the guideline, jointly written by three scientific societies (the European Association for the Study of the Liver (EASL), the European Association for the Study of Diabetes (EASD), the European Association for the Study of Obesity (EASO))recommends a weight loss target of 7–10% if you are overweight or have obesity with NAFLD.[13] The favourable effects of moderate weight loss also extend to lean patients who do not have obesity-associated NAFLD. In this case, a 3% weight loss is likely to drive NAFLD remission.[125] Lifestyle changes that produce even modest results, such as a sustained weight loss of 5%, can induce clinically meaningful reductions in triglycerides and blood glucose. These

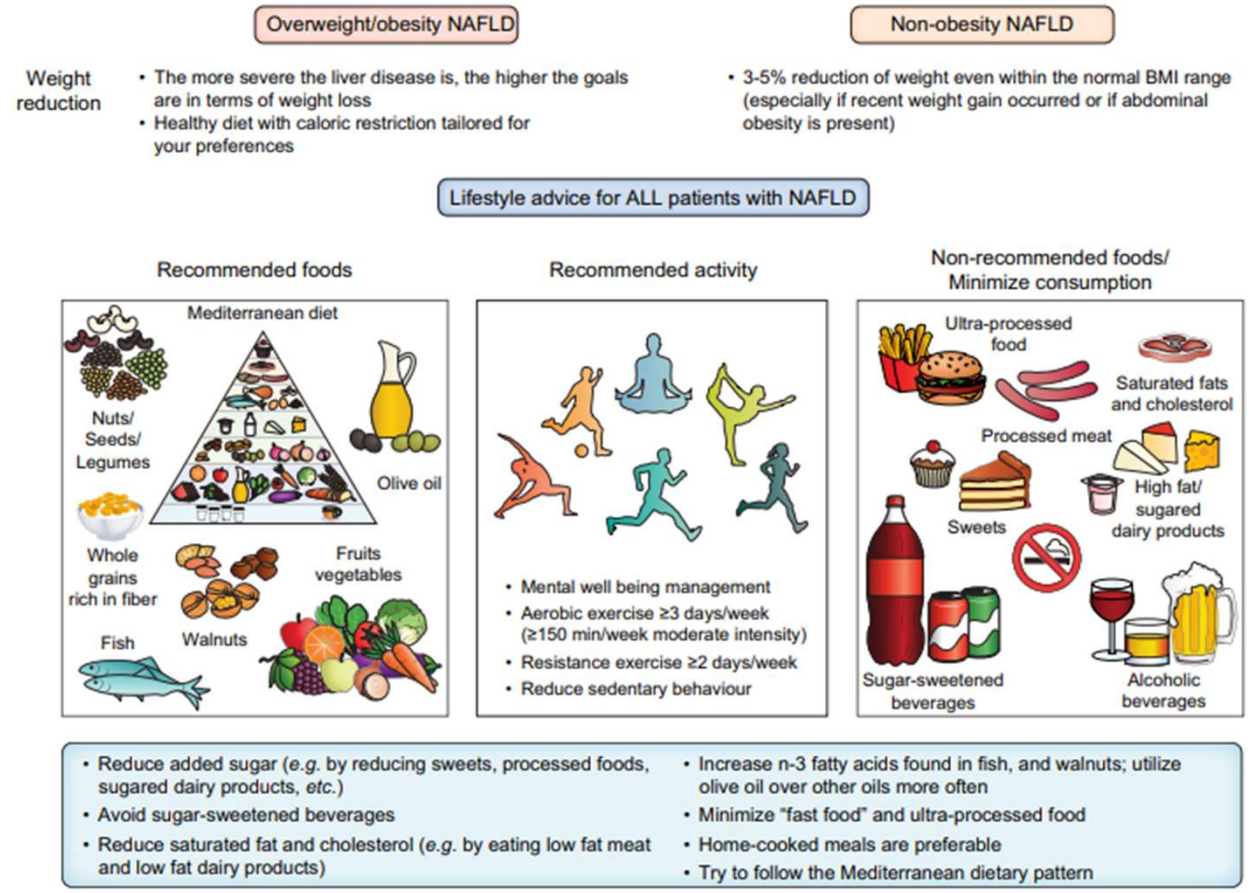
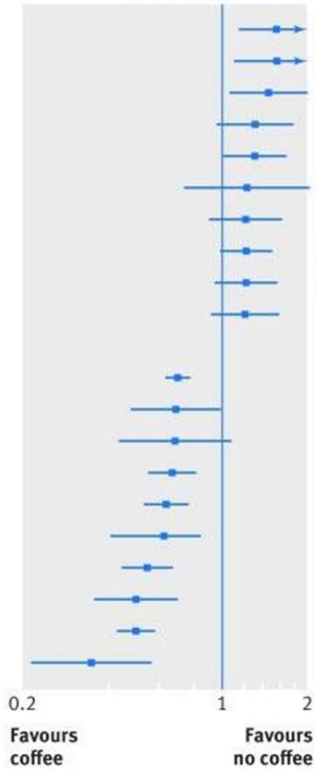


Fig. 10. A summary of lifestyle recommendations for those living with NAFLD. NAFLD, non-alcoholic fatty liver disease.

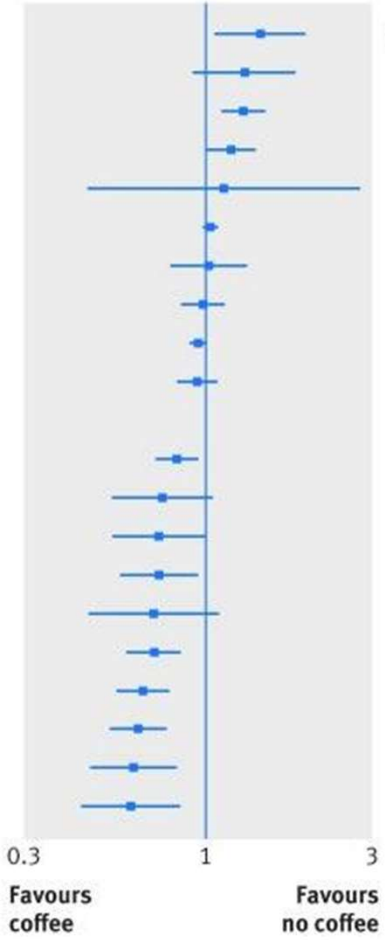
La buona notizia

Outcome	No of events /total	Follow-up range (years)	Risk estimate (95% CI)	Estimate (95% CI)	Total studies	Cohort	Case-control	τ^2	I^2 (%)	Egger's P value	AMSTAR
10 most harmful											
Acute leukaemia in childhood[87]	2453/4975	NA		1.57* (1.16 to 2.11)	6	0	6	0.06	55	ND	5
Lung cancer[46]	540/84 984	10-23		1.56* (1.12 to 2.17)	5	5	0	0.06	45	ND	3
Pregnancy loss[23]	12 311/155 831	NA		1.46* (1.06 to 1.99)	5	5	0	0.11	87	ND	5
Rheumatoid arthritis[74 75]	764/132 677	11-20		1.31 (0.97 to 1.77)	3	3	0	0.00	0	ND	4
Low birth weight[82]	2133/42 036	NA		1.31* (1.03 to 1.67)	2	2	0	0.00	0	ND	7
Lymphoma[39]	209/89 897	6-12		1.23 (0.75 to 2.02)	3	3	0	0.00	0	ND	5
Laryngeal cancer[59]	2596/NP	NP		1.22 (0.92 to 1.62)	8	1	7	0.10	74	ND	6
1st trimester preterm birth[83]	NP	NA		1.22*† (1.00 to 1.49)	NP	NP	NP	NP	NP	NP	3
3rd trimester preterm birth[83]	NP	NA		1.22*† (0.95 to 1.57)	NP	NP	NP	NP	NP	NP	3
Oral cleft malformation[85]	627/56 953	2		1.21* (0.92 to 1.59)	3	1	2	0.00	0	ND	2
10 most beneficial											
Type 2 diabetes[21]‡	45 335/1 109 272	1-24		0.70 (0.65 to 0.75)	27	27	0	0.01	50	0.05	7
Oral cancer[39]	1910/1 395 309	6-26		0.69 (0.48 to 0.99)	6	6	0	0.12	74	ND	5
Cirrhosis[63]	1785/130 305	NP		0.69* (0.44 to 1.07)	3	3	0	0.02	13	ND	7
Renal stones[66]	NP/126 382	NP		0.67 (0.56 to 0.81)	2	2	0	0.00	0	ND	6
Parkinson's disease[22]	2414/894 568	NP		0.64 (0.53 to 0.76)	7	7	0	0.01	16	ND	5
Leukaemia[38]	NP§	8-11		0.63 (0.47 to 0.84)	2	2	0	NP	0	NP	5
Post-MI mortality[30]	604/3271	3.8-9.9		0.55 (0.45 to 0.67)	2	2	0	0.00	9	ND	4
Gout[67]	NP/135 302	NP		0.50 (0.36 to 0.70)	2	2	0	0.02	35	ND	6
Liver cancer[43]	3414/2 267 143	10-44		0.50 (0.43 to 0.58)	11	11	0	0.01	20	0.62	6
Chronic liver disease[43]	1410/386 049	6-19		0.35 (0.22 to 0.56)	5	5	0	0.20	75	ND	6



NA=not appropriate; NP=not published; ND=not done
*Summary measure expressed as odds ratio in original meta-analysis article
†Fixed effects model
‡P value significant for non-linearity
§Could not be separated from other outcomes

Outcome	No of events /total	Follow-up range (years)	Risk estimate (95% CI)	Estimate (95% CI)	Total studies	Cohort	Case-control	τ^2	I^2 (%)	Egger's P value	AMSTAR
10 most harmful											
Acute leukaemia in childhood[88 89]	NP	NA		1.44*† (1.07 to 1.92)	3	0	3	NP	42	0.33	4
Lymphoma[60]	219/124 131	NP		1.29 (0.92 to 1.80)	3	3	0	0.04	18	ND	7
Lung cancer[47]	11 145/NP	NP		1.28 (1.12 to 1.47)	8	8	0	0.02	87	ND	5
Urinary tract cancer[49]	NP	NP		1.18* (1.01 to 1.38)	14	0	14	NP	NP	0.51	6
Endometriosis[81]	387/385	NP		1.13 (0.46 to 2.76)	3	1	2	0.43	70	ND	5
Hypertension[35]	36 178/1 246 388	6-33		1.03 (0.98 to 1.08)	4	4	0	0.00	73	ND	6
Gastric cancer[50]	1535/255 112	2-25		1.02 (0.79 to 1.31)	8	8	0	0.07	58	ND	7
Rectal cancer[52]	4594/NP	NA		0.98* (0.85 to 1.13)	10	0	10	NP	71	NP	4
Breast cancer[38]	NP‡	8-24		0.95 (0.90 to 1.01)	11	11	0	0.00	20	0.58	5
Venous thromboembolism[33]	4215/65 951	12-19		0.94 (0.82 to 1.07)	2	2	0	0	0	ND	3
10 most beneficial											
Colorectal cancer[52]	9568/NP	NA		0.83* (0.73 to 0.95)	13	0	13	NP	80	NP	4
Urinary incontinence[68]	7284/47 518	NP		0.75* (0.54 to 1.04)	3§	1	0	0.08	93	ND	6
Alzheimer's disease[127]	454/5497	NP		0.73 (0.54 to 0.99)	2	2	0	0.00	0	ND	3
Liver fibrosis[63]	1414/3738	NP		0.73* (0.56 to 0.94)	7	7	0	0.08	81	ND	7
Chronic kidney disease[69]	NP/14 898	NA		0.71 (0.47 to 1.08)	4§	0	0	0.11	66	ND	7
NAFLD[62]	NP/2407	NP		0.71 (0.60 to 0.85)	3§	1	1	0	0	ND	7
Liver cancer[43]	3414/2 267 143	10-44		0.66 (0.55 to 0.78)	12	12	0	0.06	80	0.24	6
Parkinson's disease[77]	1940/719 187	10-27		0.64 (0.53 to 0.77)	6	6	0	0.02	29	ND	7
Chronic liver disease[43]	1463/437 355	6-19		0.62 (0.47 to 0.82)	6	6	0	0.07	80	ND	6
Liver cirrhosis[63]	1880/130 496	NP		0.61* (0.45 to 0.84)	3	3	0	0	0	ND	7



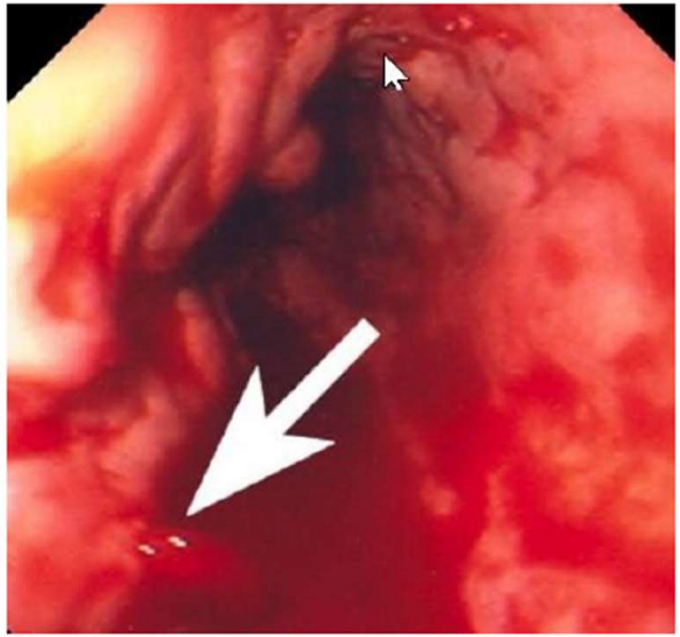
NP=not published; NA=not appropriate; ND=not done; NAFLD=non-alcoholic fatty liver disease
*Summary measure expressed as odds ratio in original meta-analysis article
†Fixed effects model
‡Could not be separated from other outcomes
§Included cross sectional studies

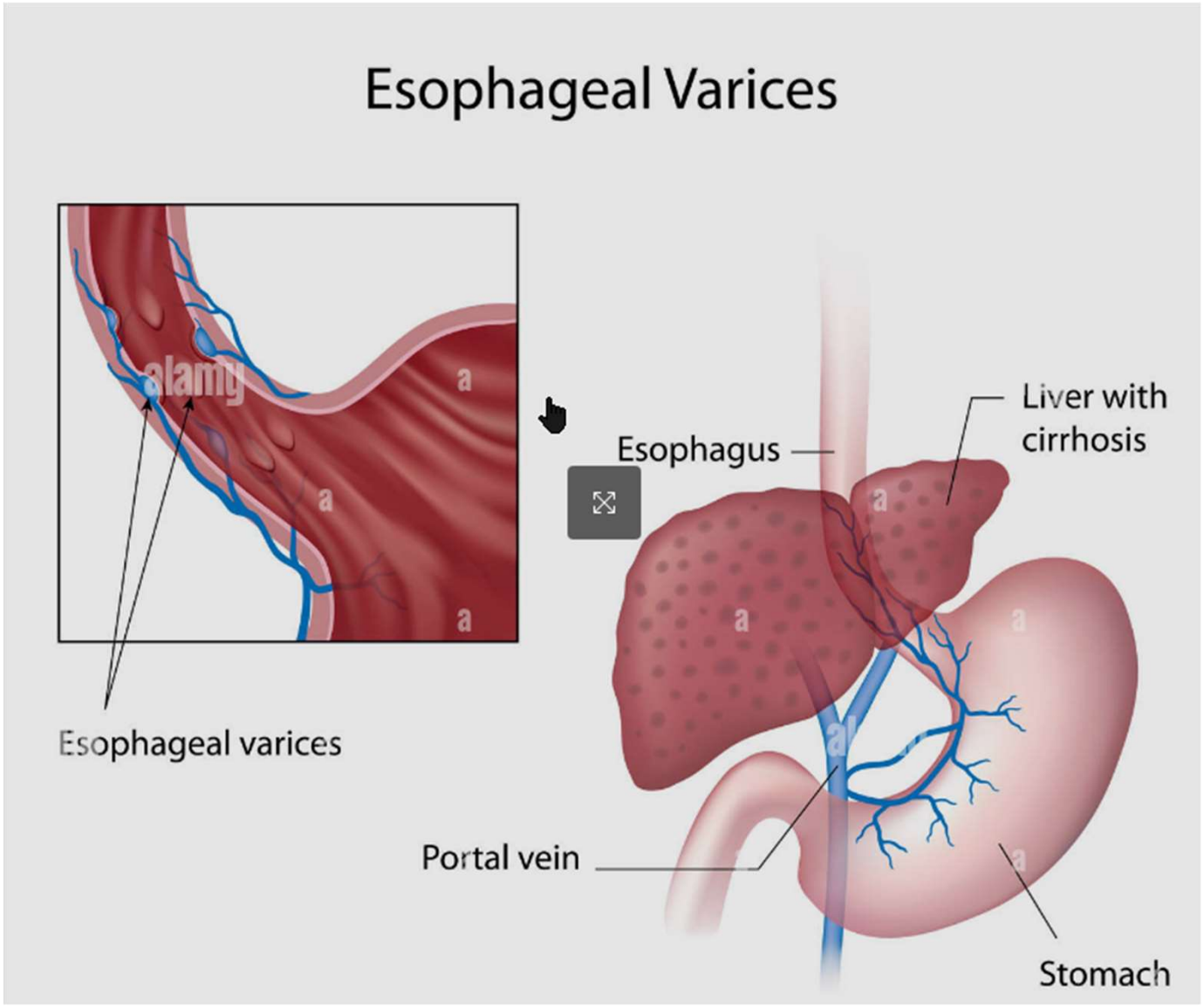
L’importante in breve

- Il grado di fibrosi, determina la prognosi
- Utile l’uso di scores per apprezzare il grado di fibrosi, quindi la stratificazione del rischio
- L’uso di beta-bloccanti non solo diminuisce il rischio di sanguinamento di vene varicose, ma riducono il rischio di scompenso e morte
- Le statine non sono controindicate, possono avere un’effetto positivo, le dosi vanno aggiustate
- Aspirina riduce il rischio di HCC
- Il Caffè fa bene al fegato

Caso Clinico: uomo 45 anni

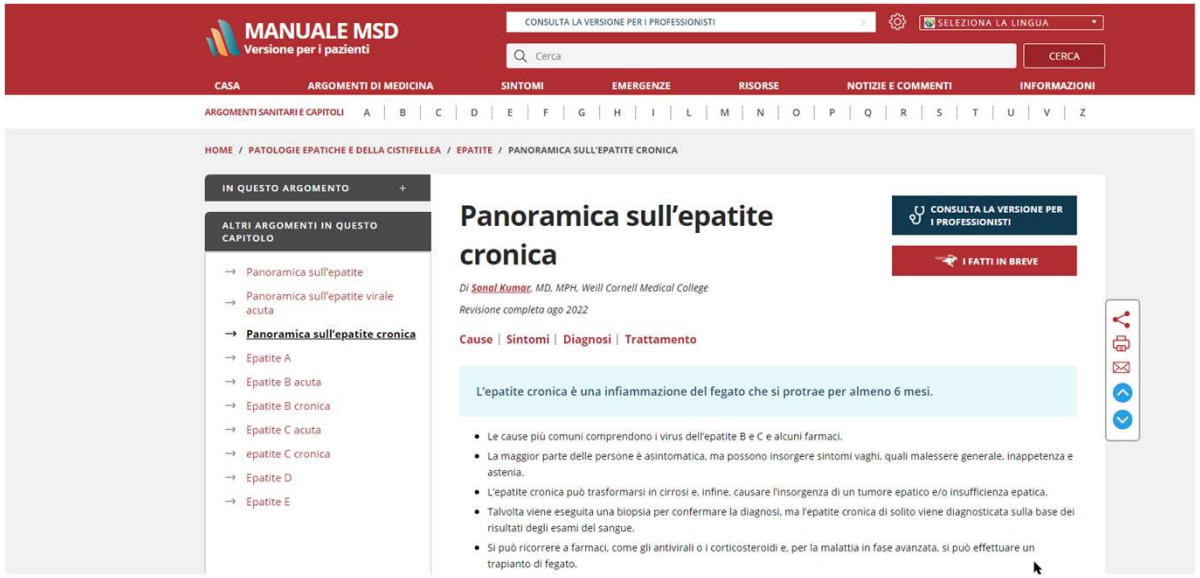
- Ricovero d'urgenza
  - Vomito con sangue
- Analisi
  - Ggt 230
  - Per il resto nulla di particolare
- Endoscopia
  - Varici esofagee
- Terapia
  - Sclerosi delle varici
- Indicazioni e procedere
  - Astinenza dal consumo di OH




Esophageal Varices
Esophageal varices
Esophagus
Liver with cirrhosis
Portal vein
Stomach

Caso clinico… 1 anno dopo

- Ittero
- Sonnolente
- Segni clinici di epatite cronica



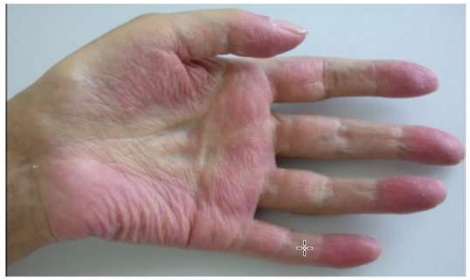
Il laboratorio: caso clinico un anno dopo

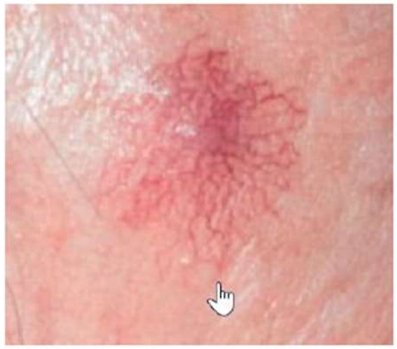
Analysen

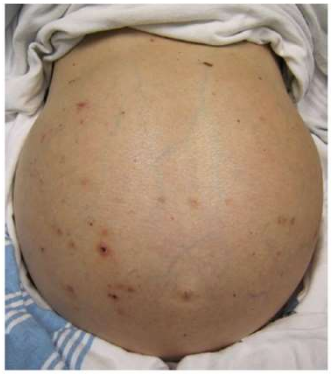
• Alb	22	(35-53 g/l)
• Bili	230	(<19 μmol/l)
• AP	300	(35-105 U/l)
• AST	350	(<35 U/l)
• ALT	150	(<35 U/l)
• γGt	400	(<40 U/l)

Segni clinici di epatite cronica

- Ittero
- Eritemi palmari
- Spider naevi
- Prurito
- Ascite







Epatite cronica:

- Segni di epatite da almeno 6 mesi
- Cause possibili: HBV, HCV, NASH, abuso OH, Autoimmunità
- Spesso pz con storia di epatite acuta
- Primi sintomi: spesso asintomatici con aumento delle transaminasi
- Eseguire ev. Biopsia per diagnosi e stadiazione del grado di cirrosi (vs. Score?)

Caso clinico

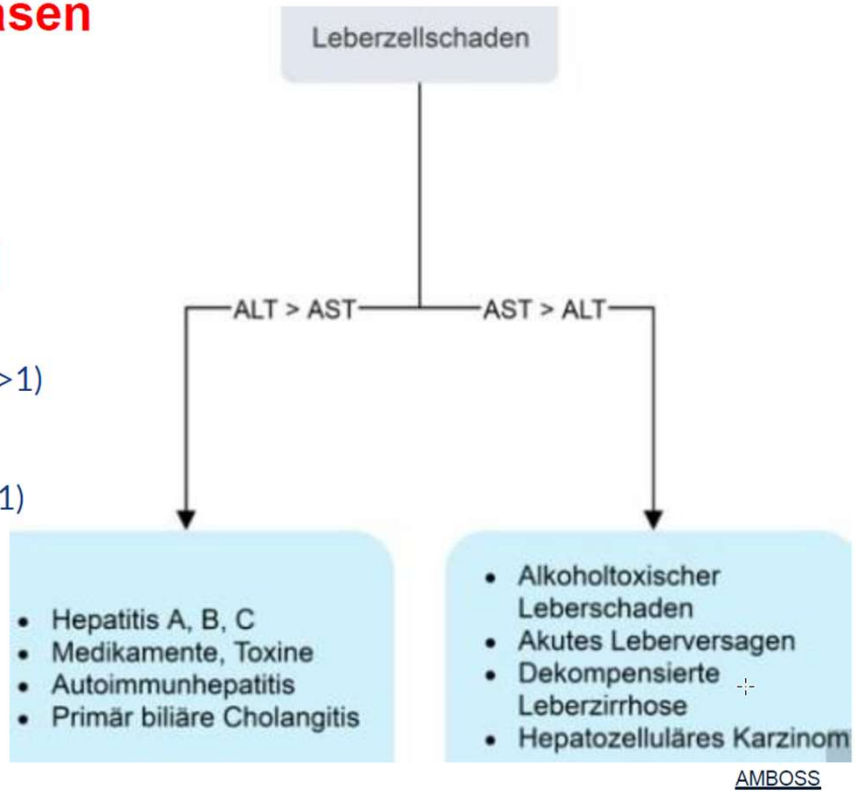
Fallbericht - Transaminasen

- AST 350 (<35 U/l)
- ALT 150 (<35 U/l)

De Ritis Quotient

AST > ALT
bei Schwerer Leberzellschädigung (Quotient >1)

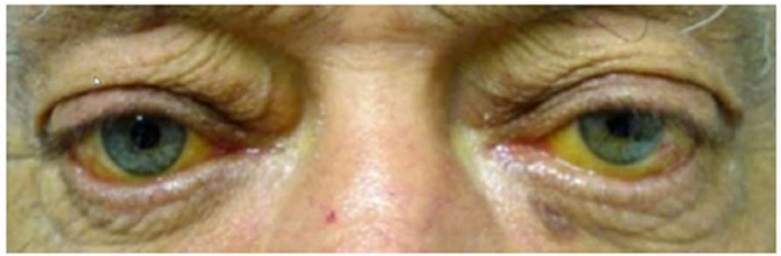
ALT > AST
bei Leichter Leberzellschädigung (Quotient <1)



Caso Clinico: uomo 65 anni

- Si sente sostanzialmente bene
- Si affatica velocemente
- Nessun sintomo addominale
- Clinca: ittero delle sclere

- ➔diagnosi : ittero congiuntivale senza dolore



DD: ittero senza dolori

1) Epatite (es: virale)
2) Ostruzione a livello dei dotti biliari in uscita (es: carcinoma biliare, carcinoma del pancreas)
3) Cirrosi epatica (tossica)
4) Emolisi (es: anemia emolitica autoimmune)
5) Danni epatici acuti tossici (es da medicamenti)
6) Metastasi
7) Altre dd, meno probabili

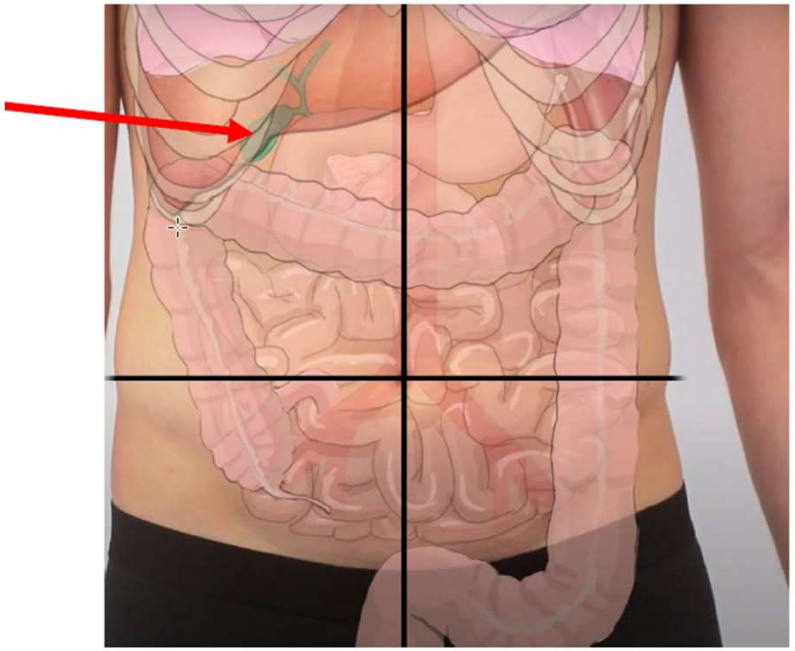
Caso clinico: uomo di 65 anni-continuazione

- Alla palpazione cistifellea ingrossata con ittero

- Diagnostica di laboratorio
  - ASAT+ALT➔ necrosi cellulare
  - GGT, AP, bili➔ colestasi?
  - Albumina quick➔ sintesi epatica ridotta?

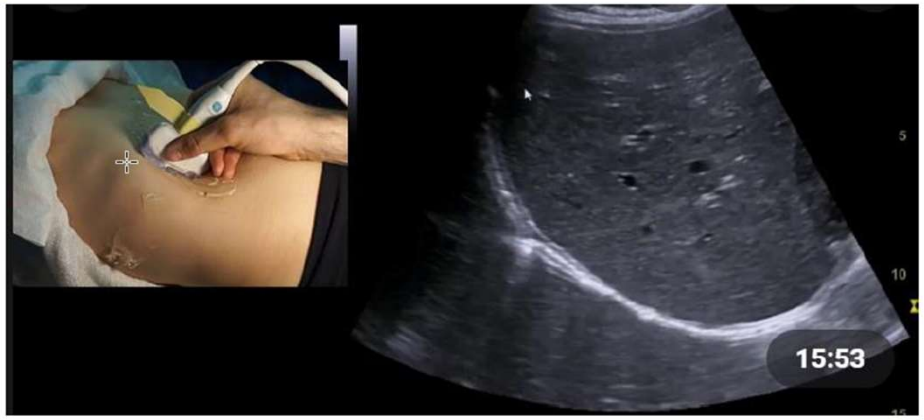
- Risultati
  - ASAT<ALAT ↑
  - GGT, AP, Bili ↑↑

  - Albumina, quick, nella norma



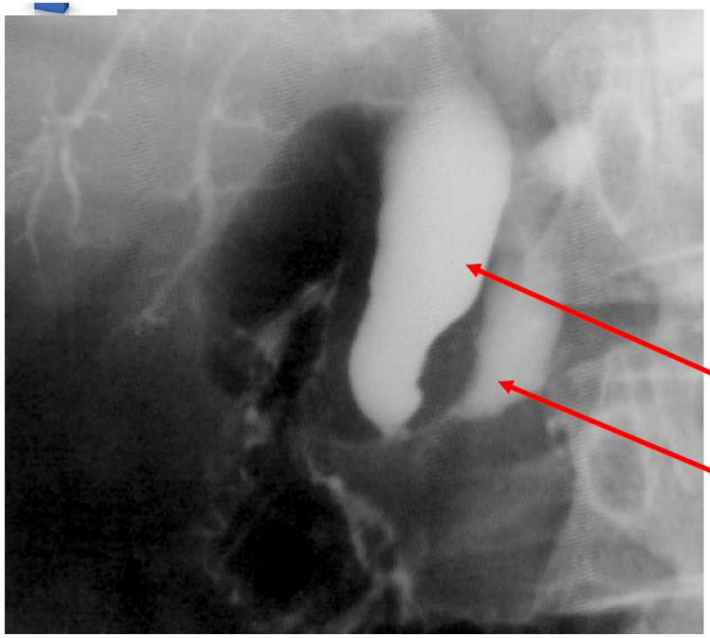
Caso clinico: uomo di 65 anni-continuazione

- Ecografia: Ostruzione dei dotti biliari
  - Ductus Choledochus= 2cm (=< 0.8 cm)
  - Dotti intraepatici aumentati
  - Testa pancreatica? (vista come una sacca di aria sopra)
  - Coda pancreatica: aumento del dotto pancreatico



Caso clinico: uomo di 65 anni-continuazione

– Viene ordinata una ERCP (endoscopia retrograda colangio-pancreatica)



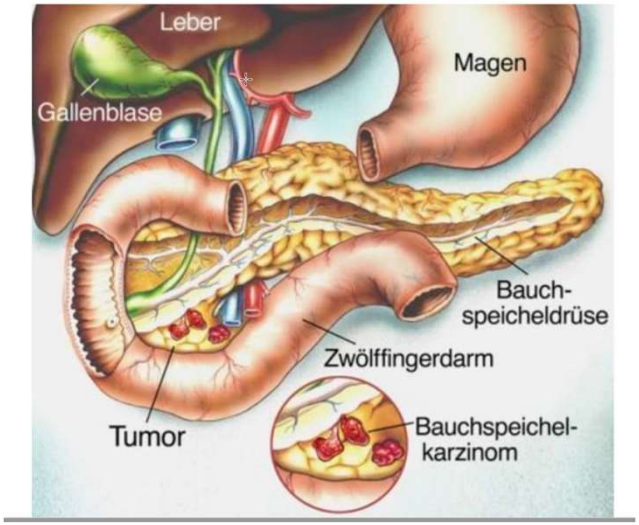
ERCP

Kontrastmittel zeigt erweiterten

- Gallengang (Ductus choledochus)
- Pankreasgang (Ductus pancreaticus

Caso clinico: uomo di 65 anni-continuazione

- CT addominale: carcinoma della testa del pancreas
- Ostruzione del coledoco e del dotto pancreatico



Caso Clinico: donna con RA

- Giorno 1: nausea, mal di testa, febbre (ALAT, ASAT, CRP leggermente aumentate: dal 2002 in trattamento con MTX (possibile complicazione medicamentosa??)
- Giorno 8: nausea, dolori costali, assenza di febbre, assenza di ittero, lieve fegato grasso

- STOP MTX

ALT 1'743 (<55 U/l) AST 1'920 (<40 U/l) CRP 41 (<5 mg/l)

Caso clinico donna con RA: diagnostica

- Negatività per
  - HAV, HCV, CMV, Echinococcus, Toxoplasma, Sierologia-autoimmune

- Positività per
  - Epatite B core Ig e core IgM
  - EBV VCA-IgM
  - Epatite E IgM

Caso clinico donna con RA: diagnostica

Table 1 Evolution of laboratory parameters and discontinuation of therapy

Parameter (Reference or limit of detection)	Day after onset of illness					
	8	9	12	21	40	75
AST (<40 U/l)	1920	1787	578	53	31	26
ALT(<55 U/l)	1743	1650	1021	122	27	25
yGT(<35 U/l)	265	226	221	102	35	20
ALP (42–98 U/l)	352	296	302	150	70	58
Bilirubin (<20 umol/l)	15	15	13	16		
CRP(<5 mg/l)	41	35	14	37	12	4
CMV IgG (neg)	Neg					
CMV IgM (neg)	Neg					
Hepatitis A IgM (neg)	Neg					
HBs Antigen (neg)	Neg					
HBc Ig (neg)		Pos			Neg	
HBc IgM (neg)		Pos			Neg	
HBe Ig (neg)		Neg			Neg	
HBe Antigen (neg)		Neg				
HBs Ig (neg)		Neg				
HBV DNA (<9 IU/ml)			<9			
Hepatitis C Ig (neg)	Neg					
EBV VCA IgG (neg)		Pos				
EBV NA1 IgG (neg)		Pos				
EBV VCA IgM (neg)		Pos			Pos	
EBV DNA (<122 IU/ml)			566		<122	<122
Heterophile IM (neg)	Neg					
HEV IgG (neg); Diapro		Pos				
HEV IgM (neg); Diapro		Pos				
HEV IgG (<1.0 index); Wantai	5.3				19.4	19.5
HEV IgM (<1.0 index); Wantai	10.4				10.6	10.6
HEV RNA (<1000 cc/ml)				8959	<1000	<1000
Stop (\) and reinitiation (/) of						
- Prednisolon therapy	8 \					/ 48
- Methotrexate therapy	8 \					/ 63

Caso clinico donna con RA: diagnostica

- HBV: nel decorso viremia e core sono negativi➔ si esclude
- EBV:EBV-DNA Positivo, con costellazione classica da infetto pregresso➔ riattivazione
- Epatite E➔ sierologia compatibile con infezione acuta con determinazione di RNA ivirale

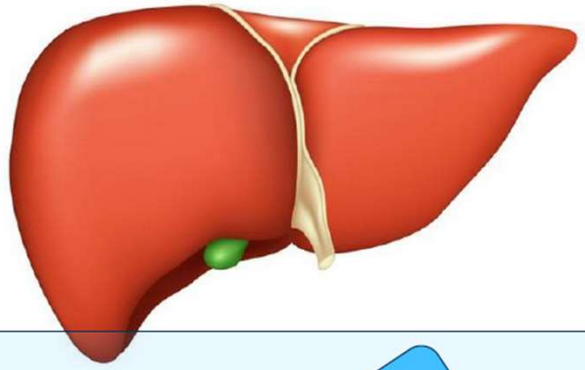
Caso clinico donna con RA: diagnostica-decorso

- Giorno 8: STOP MTX
- Giorno 40: EBV-DNA negativo-HEV RNA negativo
- Giorno 63: di nuovo MTX
- Giorno 75 : EBV-DNA negativo-HEV RNA negativo
- Girono 108: nessuna recidiva

Hepatitis A Virus
1978

Hepatitis B Virus
1967

Hepatitis C Virus
1989



Hepatitis D Virus
1977

Hepatitis E Virus
1992

Hepatitis F Virus
1994

Hepatitis G Virus
1996

Leberschädigung fraglich

TT Virus
1997

SEN Virus
2001

Kew et al. (2013) Hepatitis viruses (other than hepatitis B and C viruses) as causes of hepatocellular carcinoma - JViralHep

HEV Systematik - Wirte - Infektionswege

Genus, Spezies, Genotyp	Wirtsbereich	Hauptinfektionsweg für den Menschen
Orthohepevirus		
Spezies		
Orthohepevirus A (*Orthohepevirus*)		
Genotyp		
HEV-1	Mensch	Kontaminiertes (Trink)Wasser
HEV-2	Mensch	Kontaminiertes (Trink)Wasser
HEV-3	Mensch, Schwein, Wildschwein, Reh, Mungo, Kaninchen, Ratte	Fleischprodukte (roh oder nicht hoch genug erhitzt), andere kontaminierte Nahrungsmittel
HEV-4	Mensch, Schwein, Wildschwein	Fleischprodukte (roh oder nicht hoch genug erhitzt)
HEV-5	Wildschwein	Nicht bekannt
HEV-6	Wildschwein	Nicht bekannt
HEV-7	Kamel	Nicht bekannt





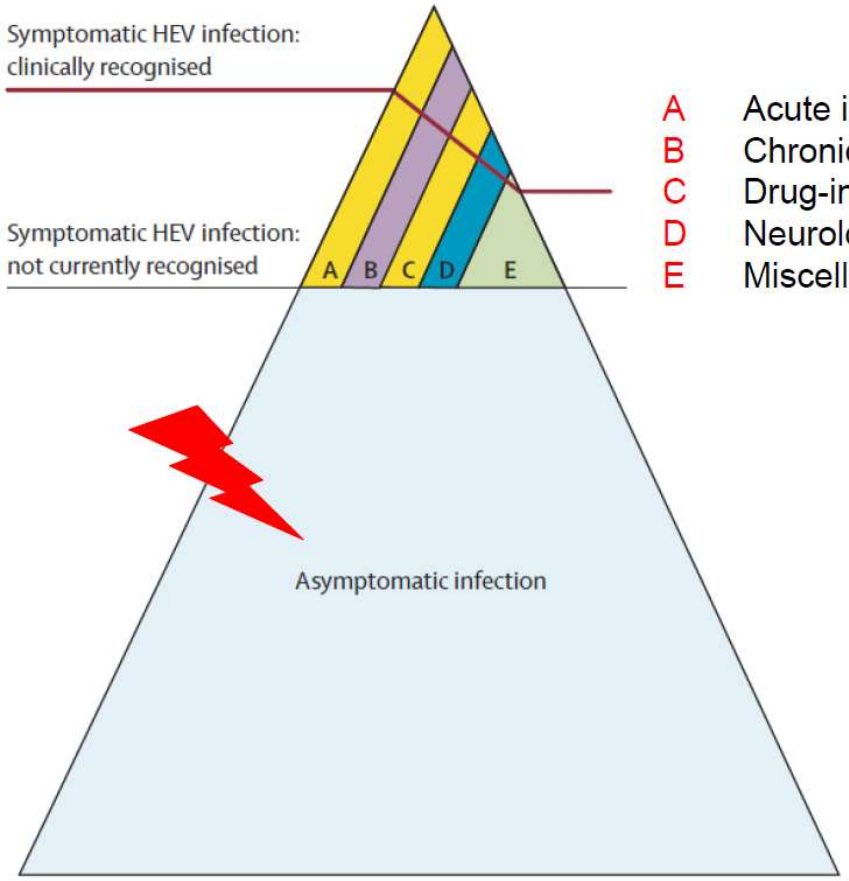

BuMiGesundheit (2015) Hepatitis E Virus - BGesBlatt_

Epatite E: infezione cronica/acuta

- Infezione acuta:
  - 95% die casi subclinica
  - Epatite fulminante molto rara (genotipo 1+2)
  - Nelle zone industrializzate rara➔ diagnosi spesso dimenticata
- Infezione cronica
  - Solo gentipo 3+4
  - HEV RNA e enzimi epatici aumentati per almeno 6 mesi

Marano (2015) Hepatitis E: an old infection with new implications - BloodTransf
Wedemeyer et al. (2012) Pathogenesis and Treatment of Hepatitis E Virus Infection - Gastroent
Osterman (2015) Diagnostik und Bedeutung der Hepatitis E Virus Infektion - LabMed

HEV - Manifestationsrate



A Acute icteric hepatitis
B Chronic infection
C Drug-induced injury
D Neurological injury
E Miscellaneous (eg, Glomerulonephritis)

Kamar (2012) Hepatitis E - Lancet

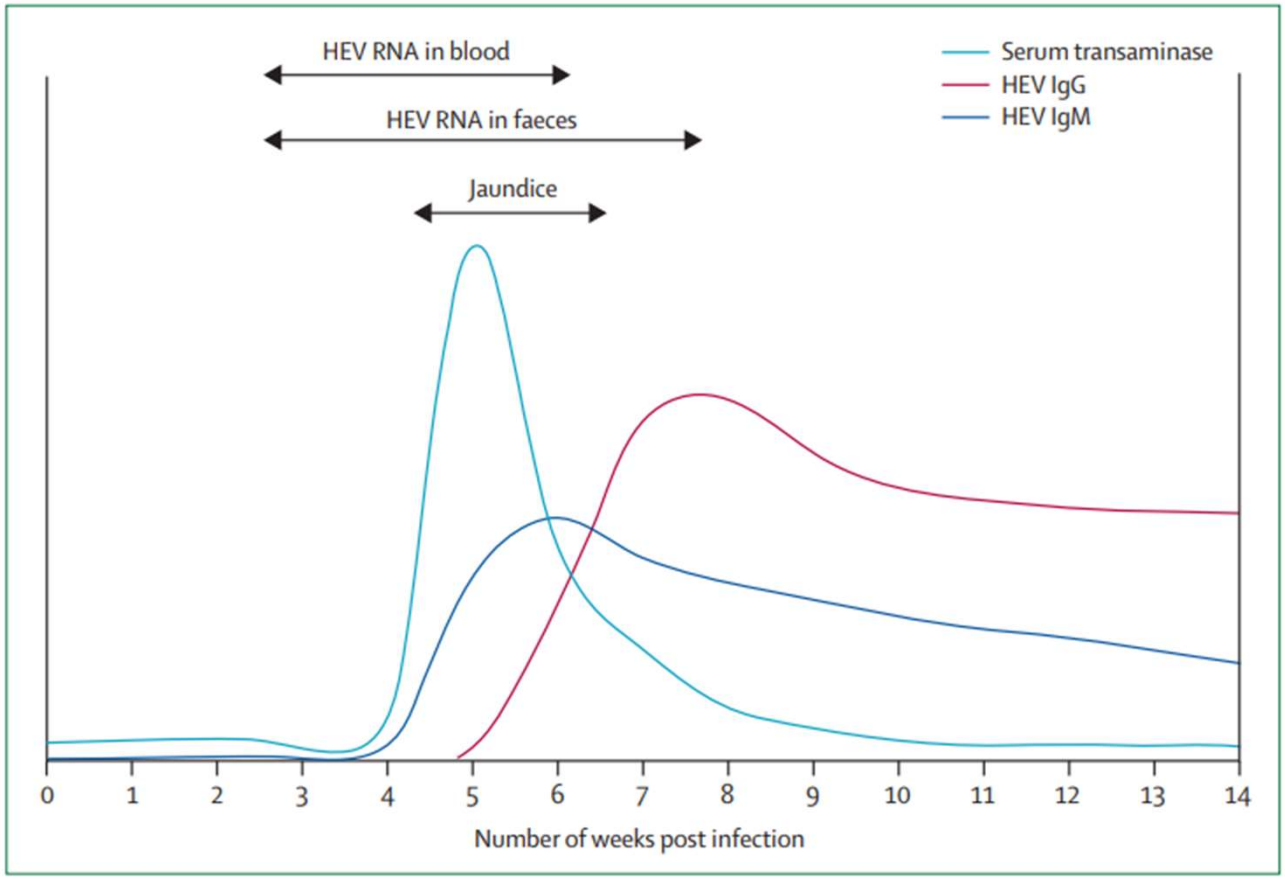


***Figure 1*: Schematic representation of HEV infection, showing virus detection at different sites and serological response**

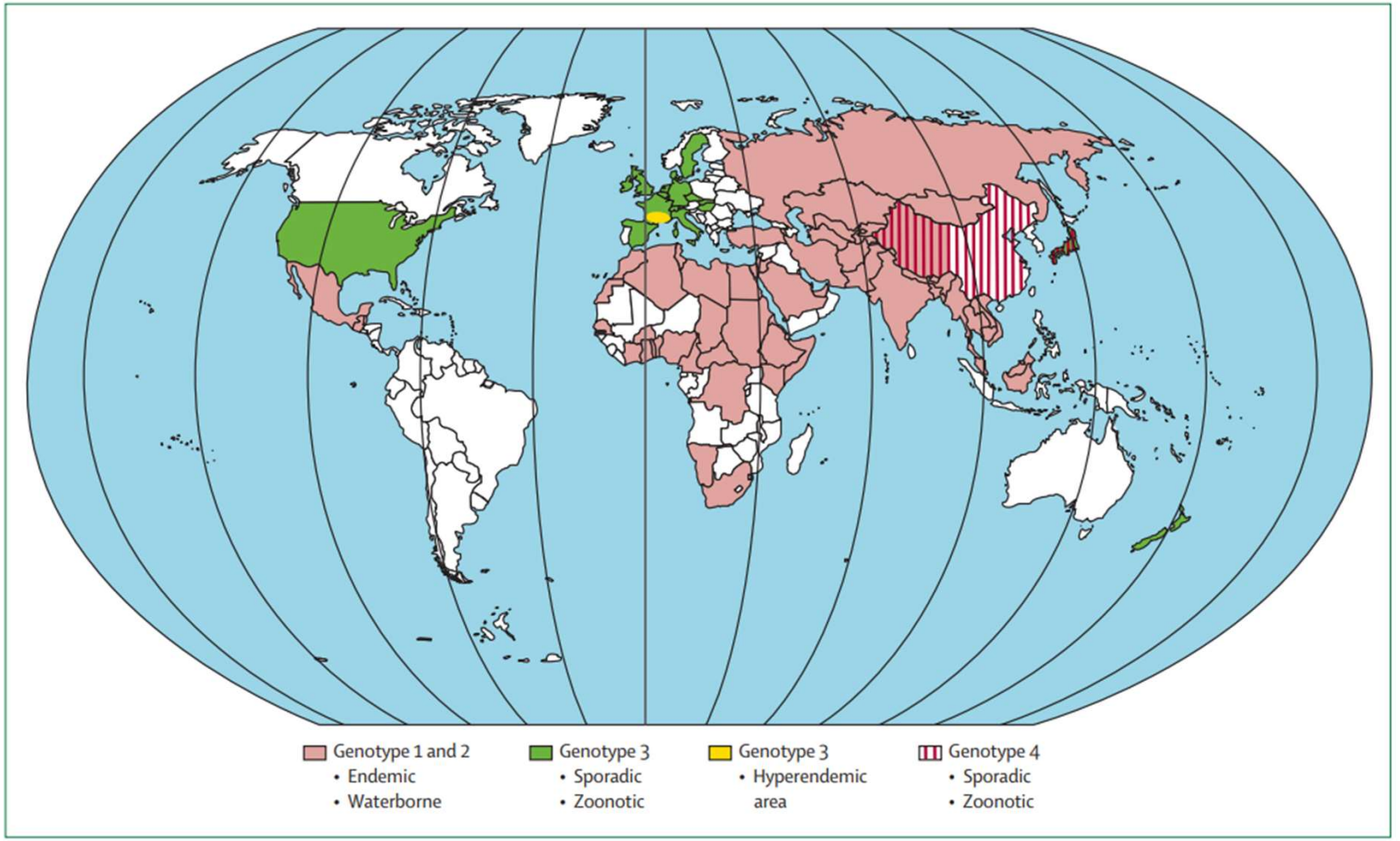


***Figure 2*: Worldwide distribution of clinical cases of HEV infection**

Note, that in several countries, including in South America, there have been occasional reports of HEV3 infection. Countries left blank are those with insufficient data.

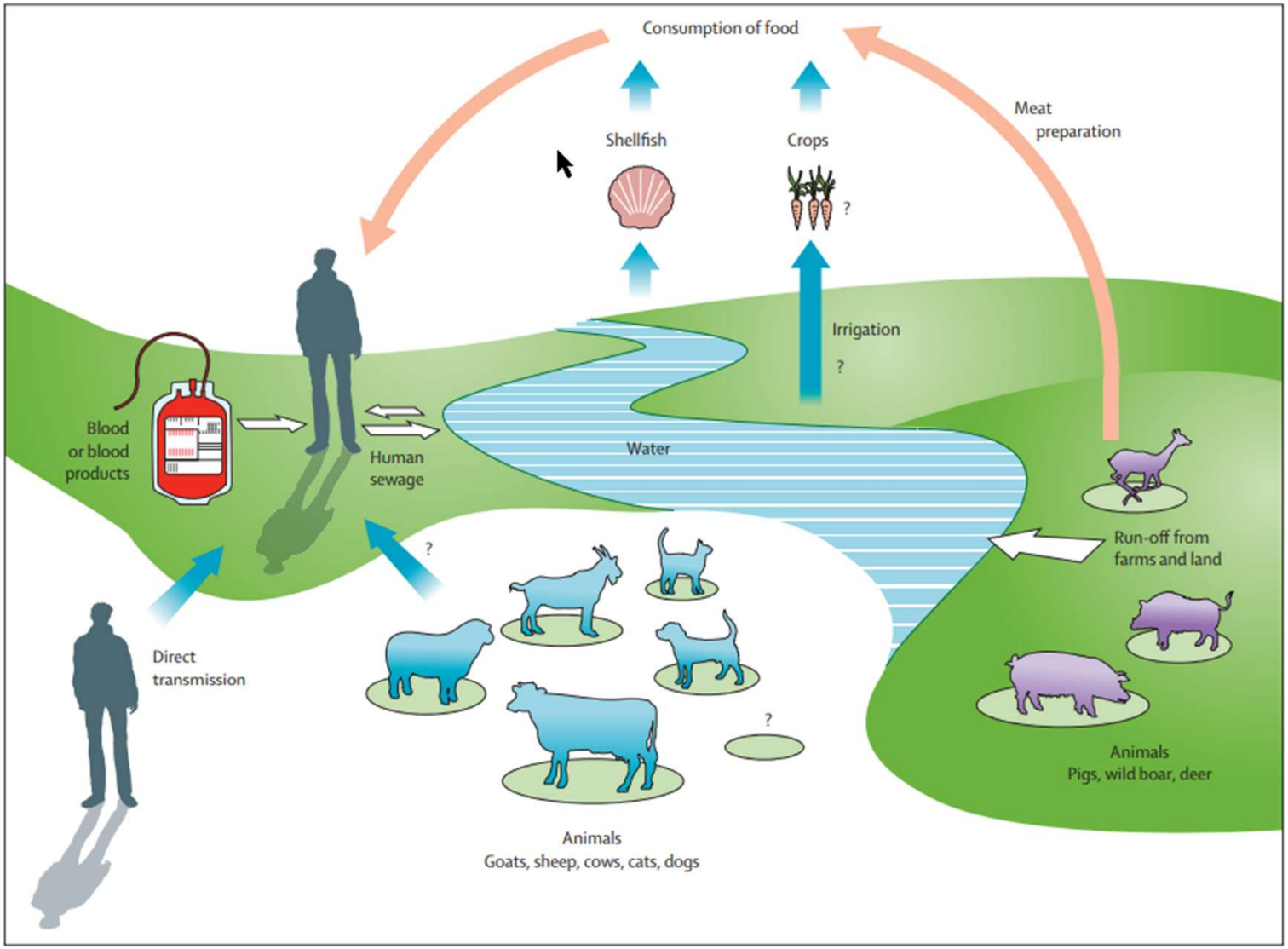


***Figure 3*: Source and route of HEV1–4 infection**

HEV1 and HEV2 are waterborne only, with possible human-to-human transmission, including vertical transmission.

occur after infection.[115] Therefore, use of molecular

	Immunocompetent	Immunosuppressed
Presentation	Often symptomatic	Rarely symptomatic
ALT at diagnosis	≈1000–3000 IU/L	≈300 IU/L
HEV genotype	Genotype 1, 2, 3, or 4	Only genotype 3 HEV infection has been reported in this population
HEV diagnostics	Increase in IgG and IgM PCR is positive in 75%	Serological testing is unreliable, and seroconversion might never occur The diagnosis should be established by PCR
Outcome	Resolving hepatitis	Chronic infection occurs in 60% of patients, and 10% develop cirrhosis
Treatment	Ribavirin has been used in very few patients presenting with severe acute hepatitis	Interferon-α and ribavirin are effective treatments for treating chronic HEV infection in this population; a 3-month course of ribavirin therapy is recommended

ALT=alanine transaminase. HEV=hepatitis E virus.

Table 1: **Hepatitis E virus infection in immunocompetent and immunosuppressed patients**

infection with HIV and HEV1, HEV2, or HEV4 has not yet been reported and warrants further study.

Extra-hepatic manifestations of HEV

Neurological complications

In the past 10 years HEV-associated neurological syndromes have been described in developing countries. These reports include Guillain-Barré syndrome,[116] Bell's palsy,[117] neuralgic amyotrophy,[118] acute transverse myelitis,[119] and acute menginoencephalitis.[120] Few of these studies used molecular techniques to confirm the diagnosis or genotype. Since these cases mostly originate from the Indian subcontinent, HEV1 is probably the causative agent.

Recently, neurological complications were described in seven (6%) of 126 patients with acute and chronic HEV3 infection.[121] These complications included inflammatory polyradiculopathy, Guillain-Barré syndrome, bilateral

Breve cenno sull’epatite autoimmune

- Malattia cronica/infiammatoria caratterizzata dalla presenza di autoanticorpi e livelli di globuline sieriche elevate
- La malattia può svilupparsi con esordio acuto per poi progredire in malattia cronica verso lo stadio di cirrosi
- Epatite autoimmune di tipo 1 e 2

Classification of autoantibodies in autoimmune hepatitis

Antibody	Disease subtype	Additional features
Antinuclear antibody (ANA)	Type 1	Most common antibodies in type 1 disease
Antismooth muscle antibody (ASMA)	Type 1	ASMA titers of 1:320 or greater generally reflect the presence of AAA
Antiactin antibody (AAA)	Type 1	Not routinely measured in North American laboratories
Antimitochondrial antibody (AMA)	Type 1	More specific for primary biliary cholangitis
Atypical perinuclear antineutrophil cytoplasmic antibody (p-ANCA)	Type 1	Also found in patients with primary sclerosing cholangitis
Anti-soluble liver antigen/liver pancreas antibodies (anti-SLA/LP)	Type 1 and type 2	More common in children with type 2 disease
Anti-DNA antibodies (single stranded DNA [ssDNA] and double-stranded DNA [dsDNA])	Type 1 and type 2	Anti-dsDNA antibody is commonly associated with systemic lupus erythematosus
Anti-liver kidney microsomal-1 antibody (ALKM-1)	Type 2	Occurs mostly in type 2 disease
Anti-liver cytosol-1 antibody (ALC-1)	Type 2	May occur in conjunction with ALKM-1
Anti-liver kidney microsomal-3 antibody (ALKM-3)	Type 2	Rarely present

Dr Risch

Il vostro laboratorio – oggi e domani

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