

Consultatieve hepatologie



Maureen Guichelaar,
MDL – arts, Medisch Spectrum Twente

Consultatieve hepatologie

Vragen over leverenzymstoornissen en aanverwante punten

-Leverenzymstoornissen?

-Vena porta trombose:
behandeling nodig?

-Patient heeft ascites: komt dit
door leverpathologie?

-Patient is suf en heeft
leverproefstoornissen = is er
een relatie?

Vragen over leverpatienten

-mag patient paracetamol?

-mag patient lorazepam?

-kan hij geopereerd worden? Wat
zijn de risico's?



Consultatieve hepatologie

Vragen over leverenzymstoornissen en aanverwante punten

-Leverenzymstoornissen?

-Vena porta trombose:
behandeling nodig?

-Patient heeft ascites: komt dit
door leverpathologie?

-Patient is suf en heeft
leverproefstoornissen = is er
een relatie?

Vragen over leverpatienten

-mag patient paracetamol?

-mag patient lorazepam?

-kan hij geopereerd worden? Wat
zijn de risico's?

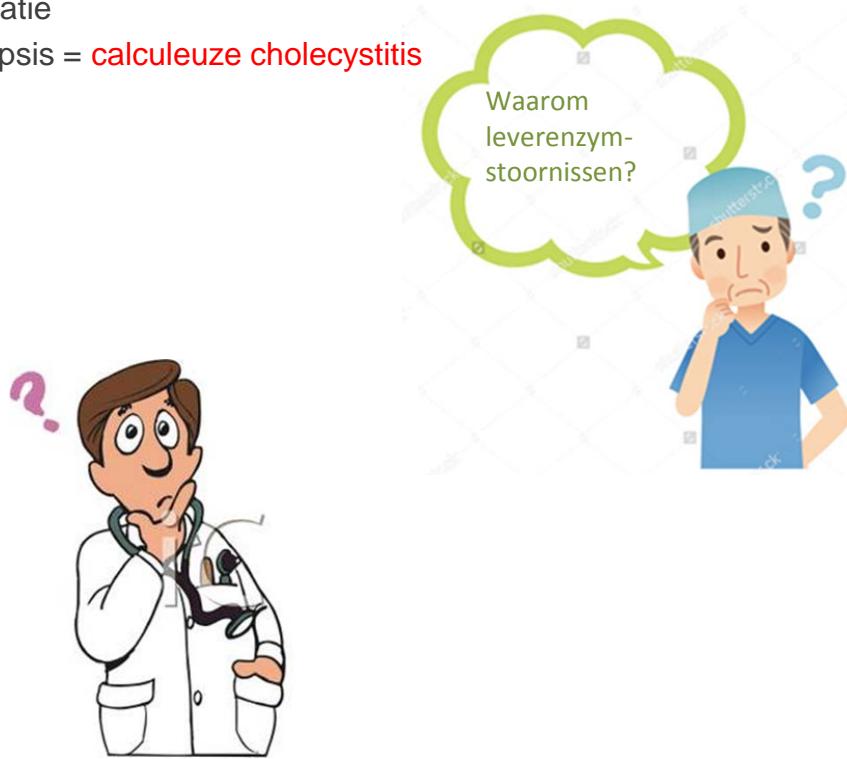


Casus: Leverenzymafwijkingen : gering gestegen transaminases, GGT en geringe hyperbilirubinemie

Speurwerk: anamnese / gegevens / LO

- Opname indicatie

- Sepsis = calculeuze cholecystitis



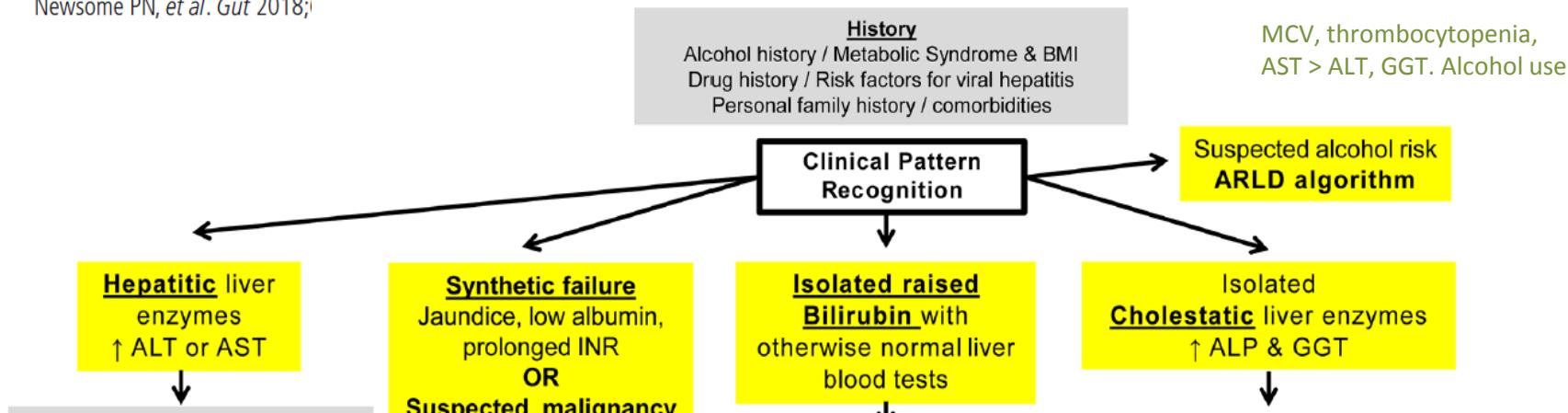
Guidelines on the management of abnormal liver blood tests

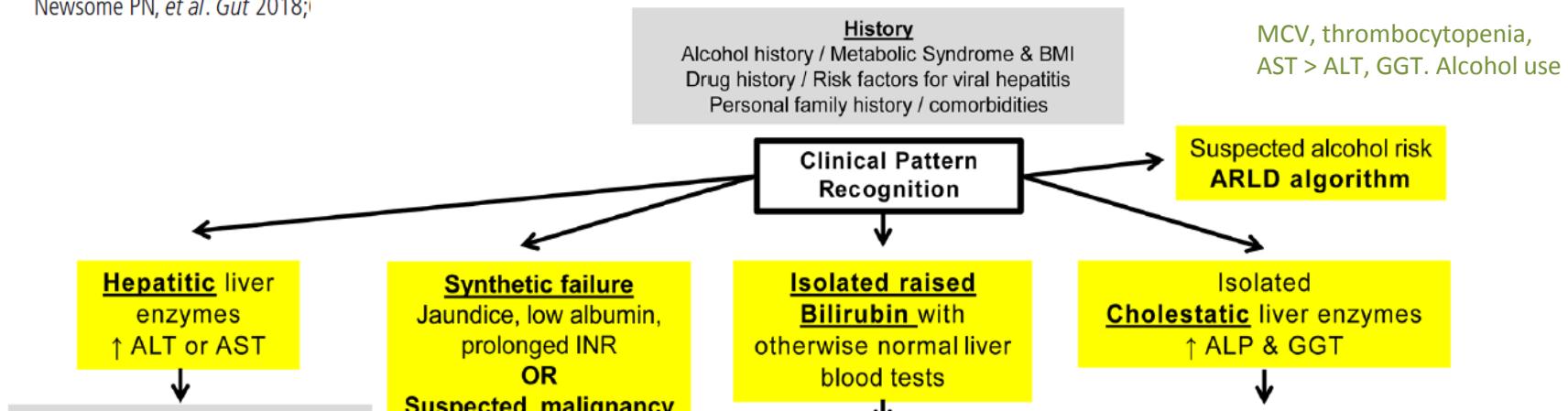
Updated guidelines of the British Society of Gastroenterology

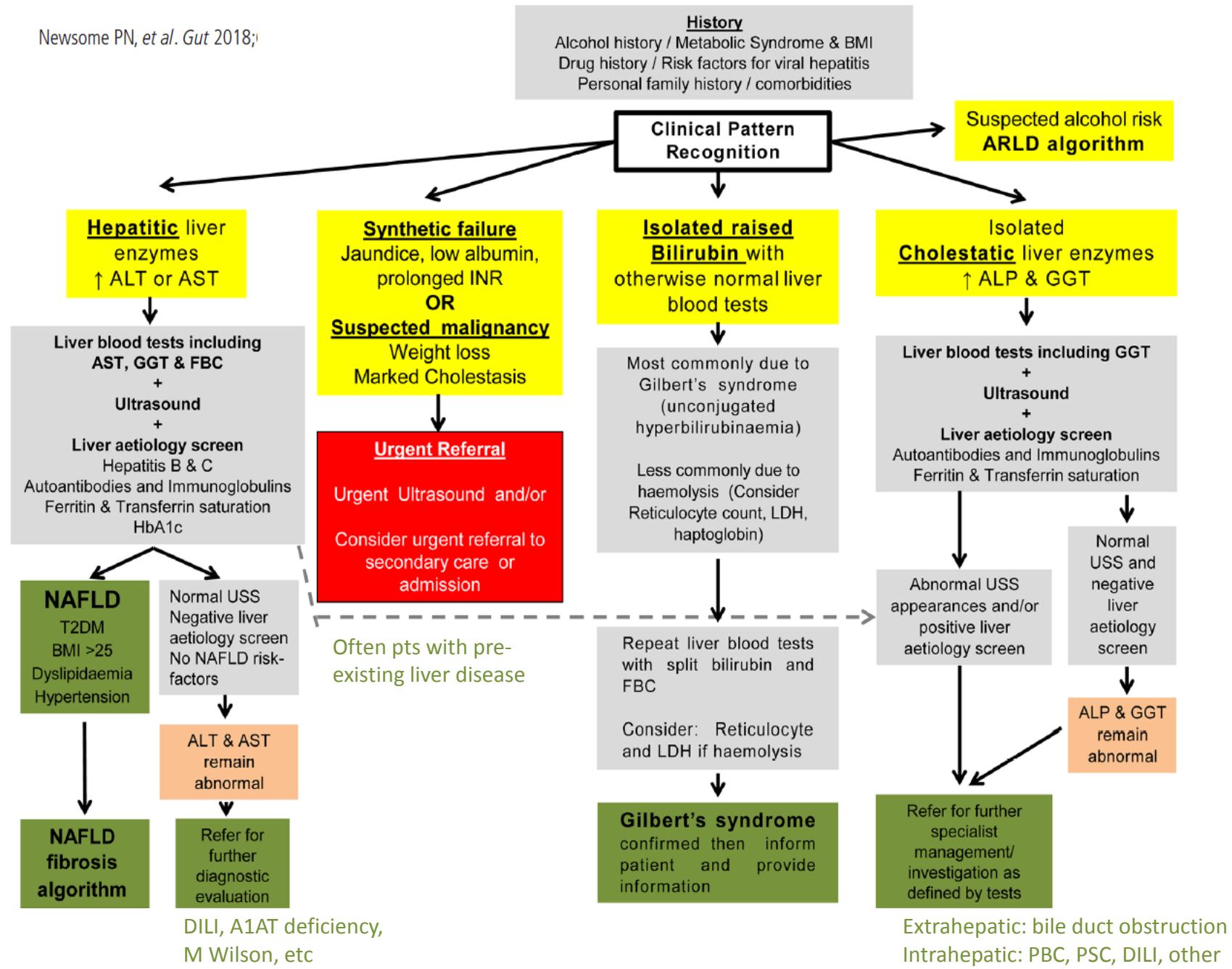
Recommendations:

- Abnormal liver blood tests should only be interpreted after review of the previous results, past medical history and current medical condition.
- in adults a stand liver etiology screening should include
 - Abdominal ultrasound
 - Hepatitis B and C screening
 - Autoimmune disease: ANA, anti smooth muscle, IgG
 - PBC: AMA, IgM
 - Iron status: transferrine saturation (>45%), ferritin









Casus: Leverproefstoornissen

Speurwerk: anamnese / gegevens / LO

- Opname indicatie
 - Sepsis = (calculeuze **cholecystitis**)
 - Cardiaal lijden / myocardinfarct
- Toxiciteit:
 - **Alcohol = ja (> 2 E /dag)**
 - Welke medicatie tijdens en voorafgaand aan medicatie
- **Comorbiditeit = o.a. DM, cardiovasculaire ziekten**
- Aanwijzingen pre-existent leveraandoening
 - Stigmata (spider naevi, ascites, etc)

Aspect leverenzymstoornissen

Aspect leverenzymstoornissen

Bilirubines 23/14
AF 120, GGT 550
ASAT 110 / ALAT 90
MCV 99, T 90



-**Pre-existent leverproefstoornissen = ja (milde transen, ASAT > ALAT, GGT)**

-**Trombocytopenie = ja (Trombocyten: 90)**

-Aanwijzingen leversynthese / excretie dysfunctie?
INR: 1,1, albumine 39.

Beeldvorming:

-**Slanke CBD, geen uitgezette galwegen**

- aspect lever grofkorrelig,
- **aanwijzingen portale hypertensie = splenomegalie, spoor vrij vocht**



60-jarige man: acute cholecystitis

Geringe leverenzymafwijkingen / mixed pattern

- * Etiologie: Alcohol related (AST>ALT, GGT, MCV)
- * Kenmerken portale hypertensie: splenomegalie, ascites
- * Kenmerken leversynthese dysfunctie: niet evident
- * Overig: alcoholmisbruik verdenking → thiamine



Waarom bij
alcohol ASAT >
ALAT

En waarom
verhoogd
GGT?

Question: Why with alcohol use / hepatitis elevated GGT?



Alcohol – verhoogd GGT

GGT (glycoprotein γ -glutamyltransferase)

- **Microsomal enzyme**
 - Transfers gamma-glutamyl group from peptides to other amino acids.
 - **Located on membranes** of cells with high secretory or absorptive activities (in liver, kidney, pancreas, intestine, prostate (but not bone = useful to discriminate AF elevation origin)).
- **Nonspecific** marker.
 - Elevation often support for other diseases if AF also is elevated = cholestatic
 - Increases seen in almost all parenchymal diseases



Alcohol – verhoogd GGT

GGT (glycoprotein γ -glutamultransferase)

- **Enzyme induction :**
 - Typically = by alcohol, by medication (anticonvulsants and oral contraceptives)
 - With alcohol use:
 - half life 28 days (normal 7-10 days) +
 - leakage GGT in serum
- Also elevations:
 - > 2-3 ULN in 50% of NASH, slightly elevated in hepatitis C
 - Other cholestatic liver diseases (combinations alk phos, bilirubines)



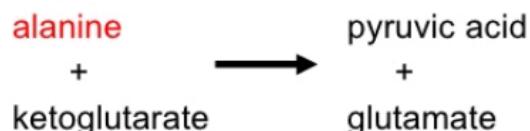
Question: Why with alcoholic hepatitis AST >ALT?



Parenchymal disease: AST, ALT = *Damage to hepatocytes*

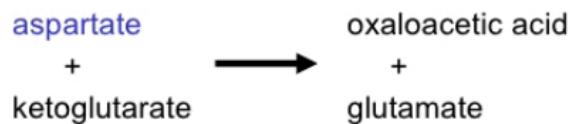
Transaminases are enzymes that catalyze the transfer of amino groups from amino acids to α -keto acids.
These enzymes are important in gluconeogenesis.

ALT (alanine aminotransferase)



- In cytosol, mainly in liver (hepatocytes)
- Released in blood by injured hepatocytes
- **Half-life 47 hrs**

AST (aspartate aminotransferase)



- In cytosol (cAST) and mitochondria (mAST) of hepatocytes.

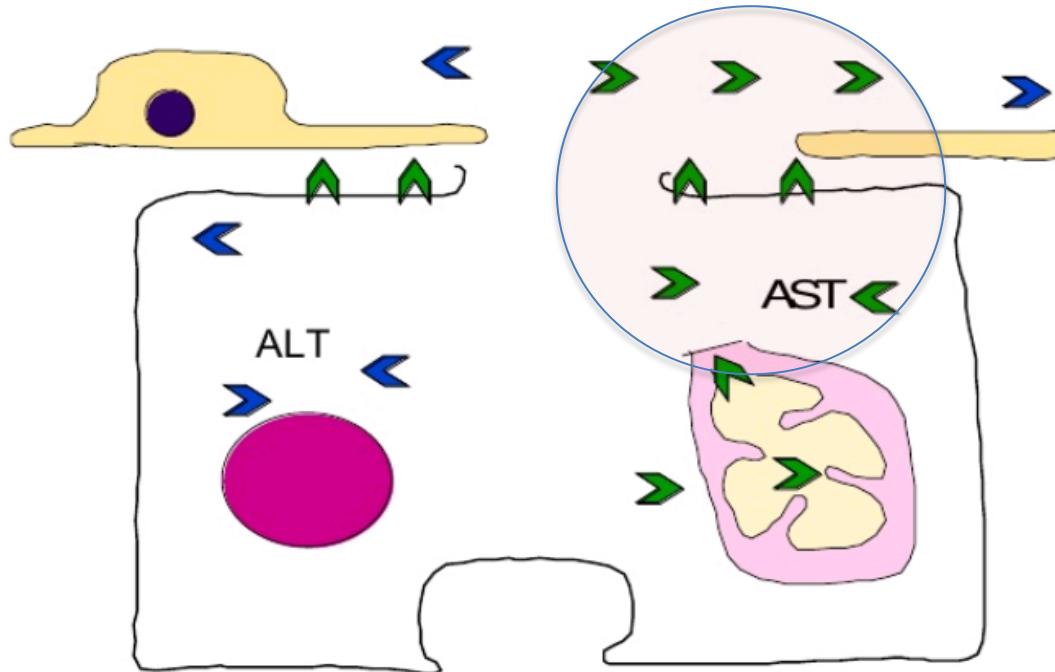
- But also non-hepatic (skeletal, muscle, blood)

- **Half-life: total AST 17 hrs, 87 hrs for mitochondrial AST**



Question: Why with alcohol AST higher than ALT?

Release of AST/ALT from Liver Cells After Alcohol Exposure



Alcohol increases mitochondrial AST on liver cell plasma membrane where it readily enters blood. Thus AST>>ALT in blood.

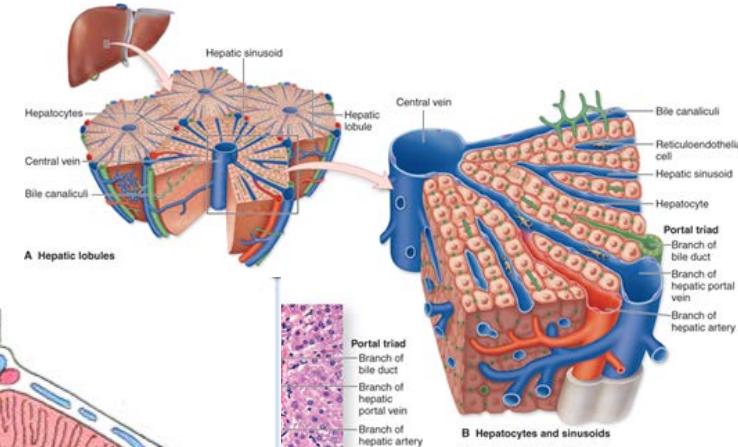
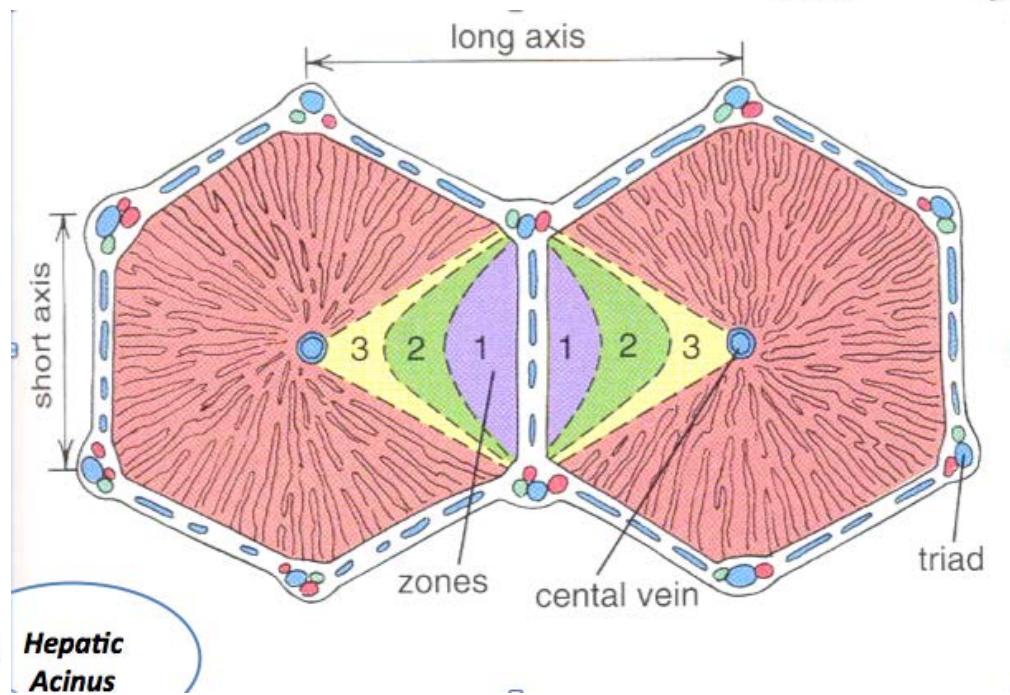
Mitochondrial AST = long half life (> 80 hrs)



Question: Why with ischemia relative higher AST than ALT?

-Zone 3 of the hepatic acinus has a higher concentration of AST

-Damage to zone 3 (ischemia, toxic) = result in greater alteration to AST



60-jarige man: acute cholecystitis

Kenmerken chronische leverziekte / alcohol gerelateerd

* Mogelijk levercirrose met portale hypertensie

Spoortje vocht: gedecompenseerd DD cholecystitis



60-jarige man: acute cholecystitis

Kenmerken chronische leverziekte

* Mogelijk levercirrose met portale hypertensie

Spoortje vocht: gedecompenseerd DD cholecystitis

OPTIES



- 1) Mag PCM en morfine hebben zoals in niet – cirrotische pts, liever geen NSAID's
- 2) Mag PCM, en morfine hebben zoals in niet – cirrotische pts, en ook NSAID's want goede nierfunctie
- 3) Liever geen NSAID's en (therapeutische doseringen) paracetamol. Mag wel morfine varianten hebben.
- 4) Ik weet het niet zeker, ik ga het opzoeken

Chronische leverziekte



Chronische leverziekte / milde hepatitis – **zonder cirrose**:

- (Geen leverdysfunctie)
- Pijnstilling = zoals in gezonde populatie

Ernstige hepatitis / levercirrose: **leverdysfunctie**

- Patienten hebben veranderingen in drug metabolisme
- Ernst van verstoringen nemen toe met ernst van de leverziekte



Drug metabolic disturbances



Advanced liver disease and cirrhosis

- *Reduced efficacy of drug removal and transport to end-organ by*
 - Reduced hepatic flow
 - Reduced hepatic enzyme capacity
 - Reduced plasma protein binding
- Changes in pharmacokinetic behaviour
- Altered accumulation of free drug
- Change in end-organ response

Important pain medication drugs = metabolized in the liver

- NSAID's, acetaminophen, COX-2 inhibitors, anticonvulsants, antidepressents, opioids
- No major studies



Pain management in cirrhotic patient



Acetaminophen (Paracetamol)

- longer half-life in patients with liver cirrhosis = **reduced clearance**
- Acetaminophen toxicity = mainly if **glutathione (important anti-oxidant)** stores become **depleted**
 - not severely effected in liver cirrhosis patients
 - probably earlier depleted in **malnutrition and alcohol**
- **Dosage** with liver cirrhosis:
 - short-term or 1 time dosering: 3-4 gr/d appears safe.
 - long-term: **2-3 gr/d**
- With alcohol / malnutrition: max 2 gr/d



Pain management in cirrhotic patient



NSAID's:

- largely metabolized by CYP's and heavily protein bound =
in cirrhosis = altered metabolism and bioavailability with
increased serum levels
- main concern: *hepatorenal syndrome* in pts with portal
hypertension
- inhibition of prostaglandins
(cirrhotic pts: need prostaglandins to counteract RAAS)
- other: mucosal lesions stomach / intestines

Dosages:

- Mild liver disease: may tolerate.
- No use in cirrhotic patients



Pain management in cirrhotic patient



Opioids:

- Liver is main site for metabolism
- Result in cirrhosis: decreased drug clearance / increased oral bioavailability = drug accumulation
- **Half life of morphine is approximately double**
- **Dosage** in cirrhosis / severe hepatitis: lower dosing and / or longer intervals between doses
- Probably **better tolerated**: fentanyl and hydromorphone



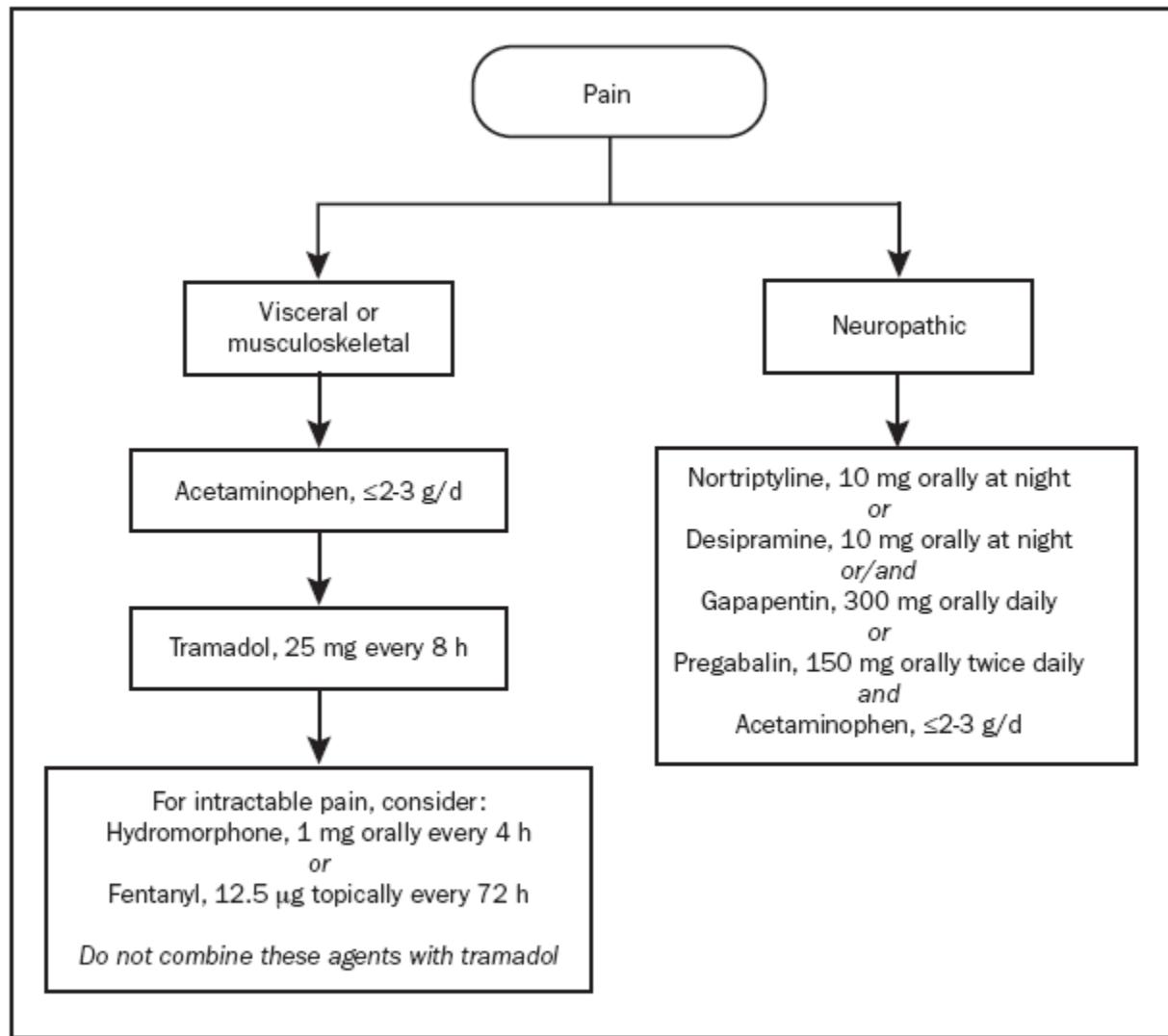


FIGURE 2. A pharmacological approach to analgesia in patients with cirrhosis who have no renal failure, active alcoholism, or active substance abuse. Starting doses are used unless otherwise indicated. Doses should be carefully titrated as tolerated. Minimize total acetaminophen to less than or equal to 2 to 3 g/d. Avoid polypharmacy and monitor for adverse drug events.

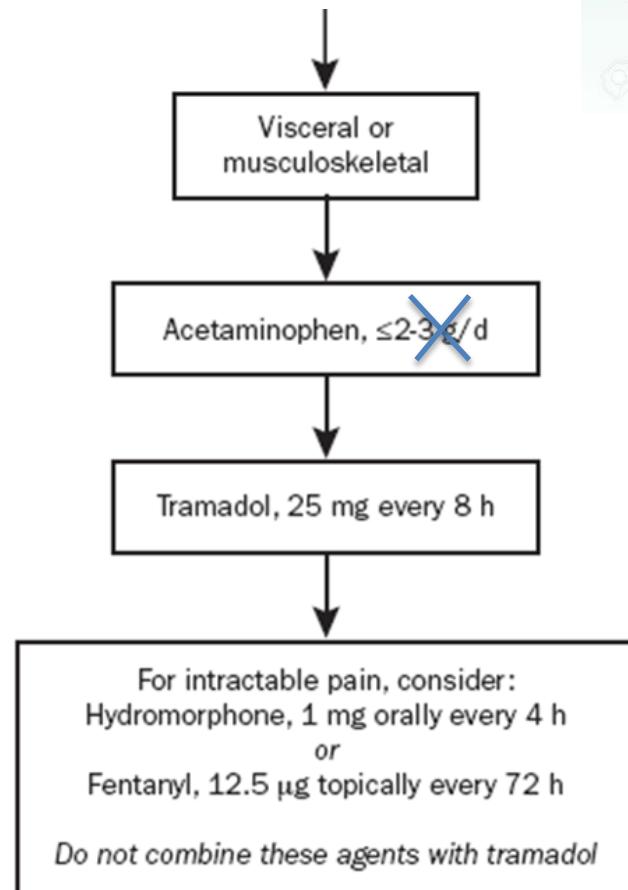




60-jarige man: acute cholecystitis

Kenmerken chronische leverziekte

- * Levercirrose Child A met portale hypertensie.
- * Etiologie : (N) ASH



60-jarige man: acute cholecystitis

Kenmerken chronische leverziekte

- * Levercirrose Child A met portale hypertensie.
- * Etiologie : (N) ASH



60-jarige man: acute cholecystitis

Kenmerken chronische leverziekte

- * Levercirrose Child A met portale hypertensie.
- * Etiologie : (N) ASH

OPTIES Benzodiazepines



- 1) Graag, mede gezien alcoholmisbruik.
Misschien wel iets voorzichtiger?
- 2) Nee dat kan niet, gezien zijn levercirrose
- 3) Ik weet het niet zeker, ik ga het opzoeken

Benzodiazepines = imitate GABA

GABA – in non-cirrhotics

Benzodiazepines:

Imitate GABA effects

GABA:

-principal calming neurotransmitter in the human central nervous system.

→ (caffeine does the opposite of benzodiazepines = stimulant)

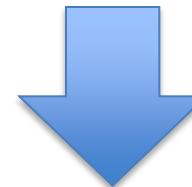
GABA – in cirrhotics

Liver cirrhosis:

-ammonia augment the activity of GABA-ergic receptors / neurons

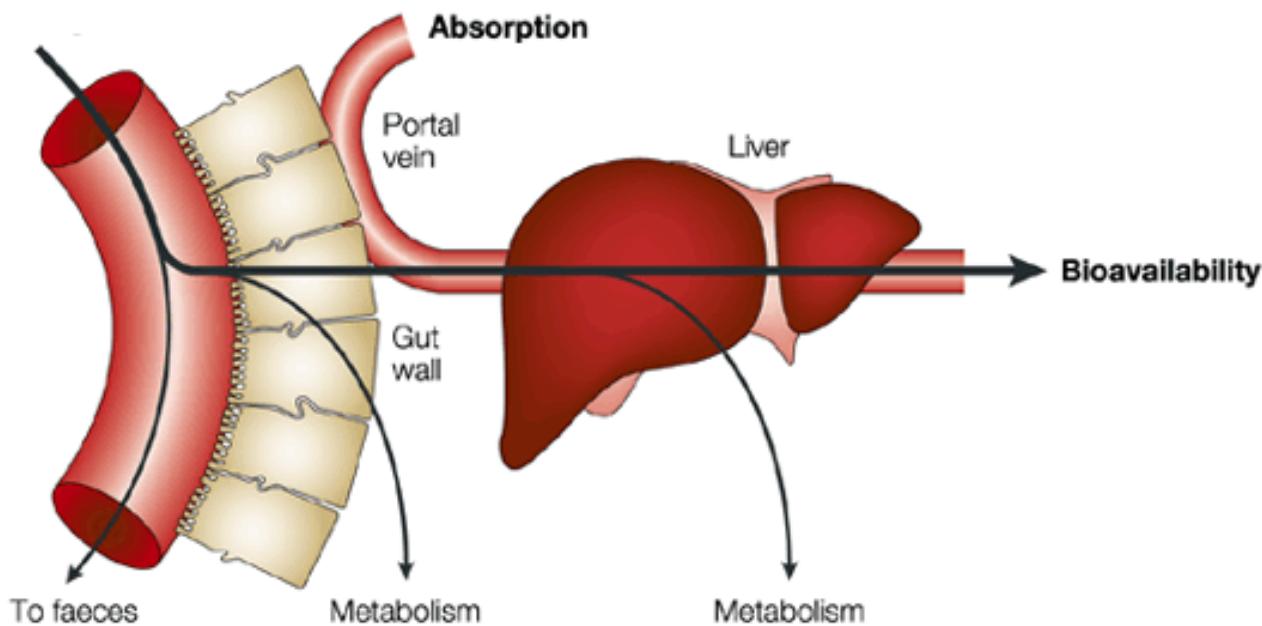
-increase circulating levels of **endogenous benzodiazepines**

-”**super sensitive GABA receptor complex**” = more effect benzodiazepines



Sedative effect of benzodiazepines is more in pts with liver cirrhosis





Nature Reviews | Drug Discovery

Midazolam: depends on **first pass effect**

-first pass effect is less in liver cirrhosis = more bioavailability



60-jarige man: acute cholecystitis

Kenmerken chronische leverziekte

- * Levercirrose Child A met portale hypertensie.
- * Etiologie : (N) ASH

Sedatieve werking verhoogd = lage dosis starten (Proefdosis), per dag evalueren

Cave: ontwikkeling sepsis, toename leverenzymstoornissen = verminderde functie van de lever



60-jarige man: acute cholecystitis

Kenmerken chronische leverziekte

- * Mogelijk levercirrose met portale hypertensie.
- * Etiologie : (N)ASH



- 1) Ja kan het beste op korte termijn.
Niet veel verhoogd risico
- 2) Nee, liever “afkoelen” en later op electief moment
- 3) Overig.....

Review

Table 4. Important parameters to look for and manage appropriately in patients with cirrhosis planned for non-hepatic surgery.

System	Pathology	Assessment	Management
Abdomen	Ascites Increased risk of abdominal wound dehiscence, abdominal wall herniation, respiratory compromise, spontaneous bacterial peritonitis (SBP)	Check response to diuretics, pulmonary function tests, diagnostic ascitic tap	~ Low sodium diet and diuretics with careful monitoring of creatinine and electrolyte levels ~ Large volume paracentesis for uncontrolled ascites with albumin ~ Antibiotics for SBP
Renal	Renal insufficiency/hepatorenal syndrome (HRS) due to drugs, infections, gastrointestinal bleed	Renal function tests, creatinine clearance, DTPA scan	~ Avoid nephrotoxic drugs, contrast agents for diagnostic studies ~ Combination of terlipressin, albumin in HRS ~ Optimal fluid, electrolyte status
Central nervous system	Hepatic encephalopathy (HE)	Clinical assessment, arterial ammonia levels	~ Use of lactulose, metrogyl, branched chain amino acids ~ Treat infections, avoid diuretics, constipation, CNS depressants, azotemia
Pulmonary	Hydrothorax, hepatopulmonary syndrome (HPS), portopulmonary hypertension (PPH)	~ Chest imaging ~ Bubble ECHO/MAA scan for HPS	~ Optimize pulmonary functions ~ Intravenous epoprostenol, sildenafil has also been tried perioperatively
Cardiac	Cardiomyopathy	~ Dobutamine stress ECHO ~ ACC and AHA guidelines for non-cardiac surgery	Beta blockers in perioperative period
Homeostasis	Electrolyte disorders (esp. hyponatremia)	Regular electrolyte profile and arterial blood gases	Slow correction of serum sodium with fluid restriction, discontinuation of diuretics
Nutrition	Malnutrition, hypoalbuminemia, muscle wasting, increased need for postoperative ventilation	Methodical nutritional assessment	~ Preoperative nutritional build-up (high carbohydrate/lipid content, low in amino acid) ~ Vitamin B1 in alcoholics
Other systems	Anaemia and coagulopathy	Intraoperative thrombo-elastogram	Appropriate blood products perioperatively to maintain desired INR (<1.5), haemoglobin (>9 g%), platelet (>50,000/mm ³) levels
	Glucose intolerance	Laboratory testing	Insulin infusion
	Gastroesophageal varices	Endoscopy, portal pressure measurements	Beta blockers, variceal banding
	Concurrent infections	Screening	Antibiotic prophylaxis
	Autoimmune hepatitis patients developing stress-induced insufficiency	Serum cortisol levels	Stress-dose steroids preoperatively

Operatie risico in levercirrose patienten?

Patient met cirrose + cholecystitis = cholecystectomy risico's?

Best Practice & Research Clinical Gastroenterology 26 (2012) 47–59



Contents lists available at SciVerse ScienceDirect
Best Practice & Research Clinical
Gastroenterology



5

Morbidity and mortality related to non-hepatic surgery in patients with liver cirrhosis; A systematic review

B. de Goede, MSc^a, P.J. Klitsie, MD^a, J.F. Lange, MD, Professor^a,
H.J. Metselaar, MD, Professor^b, G. Kazemier, MD, Professor^{c,*}

^aErasmus University Medical Center, Department of Surgery, Medical Center, P.O. Box 2040, 3000 CA Rotterdam, The Netherlands

^bErasmus University Medical Center, Department of Gastroenterology and Hepatology, The Netherlands

^cVUmc, University Medical Center, Department of Surgery, Medical Center, P.O. BOX 7057, 1007 MB Amsterdam, The Netherlands

64 articles were selected from 5247
-lack of evidence varied

*non-hepatic surgery



Non-hepatic surgery in cirrhosis

Surgical risk determined by

What is the nature /
type of surgery?

Is surgery an
emergency
procedure?

Degree of
decompensation
(MELD / CTP) ?



Non-hepatic surgery in cirrhosis

Without portal hypertension

(mortality risk vs non-cirrhotic pts)

-Cholecystectomy	: 3.4 fold increase mortality	12.3
-Colectomy	: 3.7	14.3
-CABG	: : 8.0	22.7

With portal hypertension

Cholecystectomy:

- best outcome if laparoscopic
- however: increased risk of conversions during operation

Large abdominal interventions =

TIPS = to reduce operation risk?



Non-hepatic surgery in cirrhosis

Surgical risk determined by

What is the nature / type of surgery?	Is surgery an emergency procedure?	Degree of decompensation (MELD / CTP) ?
Lowest increased risk mortality: cholecystectomy (Doubles morbidity and mortality (OR 2.4)	Child A cirrhosis without portal hypertension = majority of non-hepatic surgery is safe
Highest increased risk : pancreatic surgery, cardiovascular and trauma surgery	If emergent + portal hypertension = OR 5.9	Portal hypertension itself = independent risk factor
		MELD < 8 = mortality 5.7% MELD > 20 = > 50%
		Future: Preventive effect of portal decompression (preoperative TIPS?)



Onze casus : Cholecystectomie?

Conclusie

Niveau 1a	Directe cholecystectomie leidt tot een sneller herstel met een kortere opnameduur. Er is geen verschil in complicaties en conversies. In 23 tot 26% van de initieel conservatief behandelde patiënten dient alsnog een eerder dan geplande cholecystectomie te worden verricht (Gurusamy 2013, Gutt 2013).
-----------	--

Overige overwegingen

Een andere mogelijkheid is een volledige conservatieve behandeling, die met name overwogen kan worden bij patiënten met ernstige comorbiditeit (Vetrhus 2003, Schmidt 2011).

In de meeste onderzoeken wordt voor directe cholecystectomie een termijn van 1 week na het begin van de klachten gehanteerd. Het zo vroeg mogelijk opereren bij een acute cholecystitis leidt tot minder morbiditeit (de Mestral 2013, Gutt 2013, Gelbard 2014).

Opties

- 1) Cholecystectomie nu doen = nl. minder kans op complicaties van een gecompliceerde cholecystectomie later
- 2) Antibiotica (met / zonder galblaasdrainage) en wellicht dat cholecystectomie niet meer nodig is
- 3) Antibiotica (met / zonder galblaasdrainage) en tzt cholecystectomie



Cholecystectomie : nu of later?

Voordeel uitstellen :

- Electief moment
- Stoppen alcohol = mogelijk minder decompensatie klachten / minder portale hypertensie

Nadeel :

- Risico op geen verbetering met conservatieve benadering. Met toename adhesies in galblaasbed
- Percutane drainage : complicaties bij portale hypertensie?

*Geen studies die dit onderzoeken

***Per patient afweging in multidisciplinair team en patient = overleg dan wel
overname expertise kliniek**



In summary



Liver enzyme evaluation = take your time ..

To take into account:

1) Anamnesis:

- 1) Medication use (when, what)
- 2) Intoxications
- 3) Ethnicity
- 4) Other symptoms, why admission

2) Physical examination

3) Other comorbidities

- DM
- Cardiovascular disease
- Cancer
- Other autoimmune diseases

4) Liver enzymes:

- distribution / pattern
- signs of liver failure
- signs of pre-existing liver disease

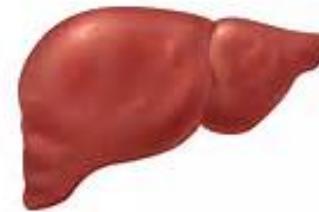


Differential diagnosis

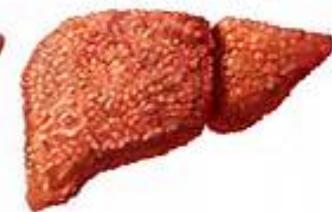
-Further evaluations



Normal Liver



Liver with Cirrhosis



Hepatology in consultation

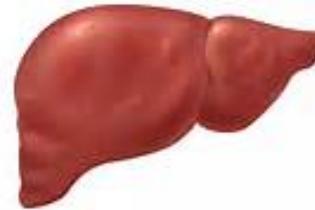
Liver enzyme disturbances

- 1) **Pattern:**
 - Parenchymal
 - Cholestatic (intra vs extrahepatic disease)
 - Mixed
- 2) **Typical features:** GGT, AST/ALT ratio
- 3) **Severity:**
 - Transaminases (AST/ALT, severity)
 - Acute on **chronic liver disease**
 - Liver function tests (bili, Pt, alb) and other additional signs (HRS, HE)

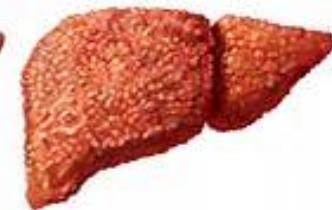
Chronic liver disease patient

Hepatology in consultation

Normal Liver



Liver with Cirrhosis



Chronic liver disease patient

Pain medication in cirrhotic patients (with or without decompensation):

- Paracetamol: lower dosing if longer used = **max 2-3 gram per day**
(esp with malnutrition / alcohol = **max 2 gram per day**)

-No NSAID's

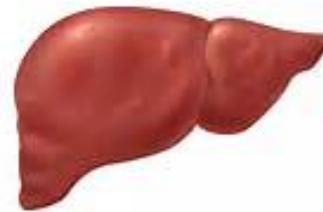
- Morphine in reduced dosing.
 - Fentanyl better alternative

Benzodiazepines:

- In multiple ways = more effect and bio-availability
- Cautious use, per day evaluation



Normal Liver



Liver with Cirrhosis



Hepatology in consultation

Chronic liver disease patient

Operation risk:

- Low in child A **without** portal hypertension

Multidisciplinary
setting / expert
center

Increases with :

- Portal hypertension
 - Liver function failure = synthesis + excretion dysfunction
- * *CTP and MELD score = predictive for morbidity and mortality*

Depends also on

- Emergency or not
- Type of surgery



Vragen?



The Liver: A ‘Blob’ That Runs the Body

The underrated, unloved liver performs more than 300 vital functions. No wonder the ancients believed it to be the home of the human soul.

[点击查看本文中文版](#)

Basics

By NATALIE ANGIER JUNE 12, 2017

The liver also keeps track of time. In a recent issue of [the journal Cell](#), Ulrich Schibler of the University of Geneva and his colleagues described their studies of the oscillating liver, and how it swells and shrinks each day, depending on an animal’s normal circadian rhythms and feeding schedule.



Guyco



To the Mesopotamians, the liver was the body’s premier organ, the seat of the human soul and emotions. The ancient Greeks linked the liver to pleasure: The words hepatic and hedonic are thought to [share the same root](#).

