Lebererkrankungen durch Substanzabhängigkeit

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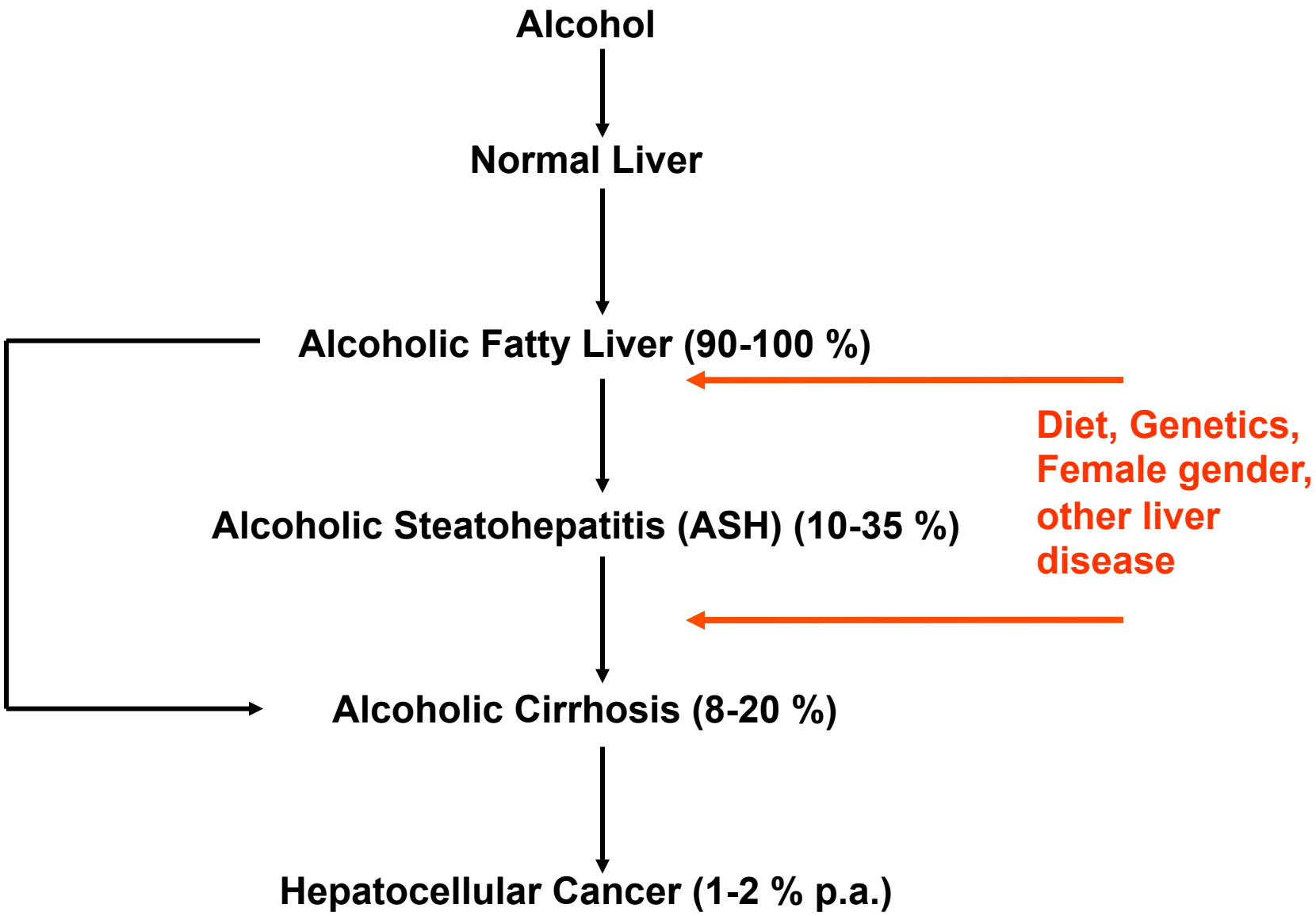
Alkoholische Lebererkrankung
Epidemiologie

- **Prävalenz: 180/100.000**
- **Österreich: 2.000-3.000 Todesfälle/Jahr**
- **50 % der alkoholassoziierten Gesamtmortalität**
- **5-Jahresüberlebensrate der alkoholischen Leberzirrhose 35 %**
  bei aktivem Konsum
- **HCC-Inzidenz steigend**
- **enorme jährliche Kosten**

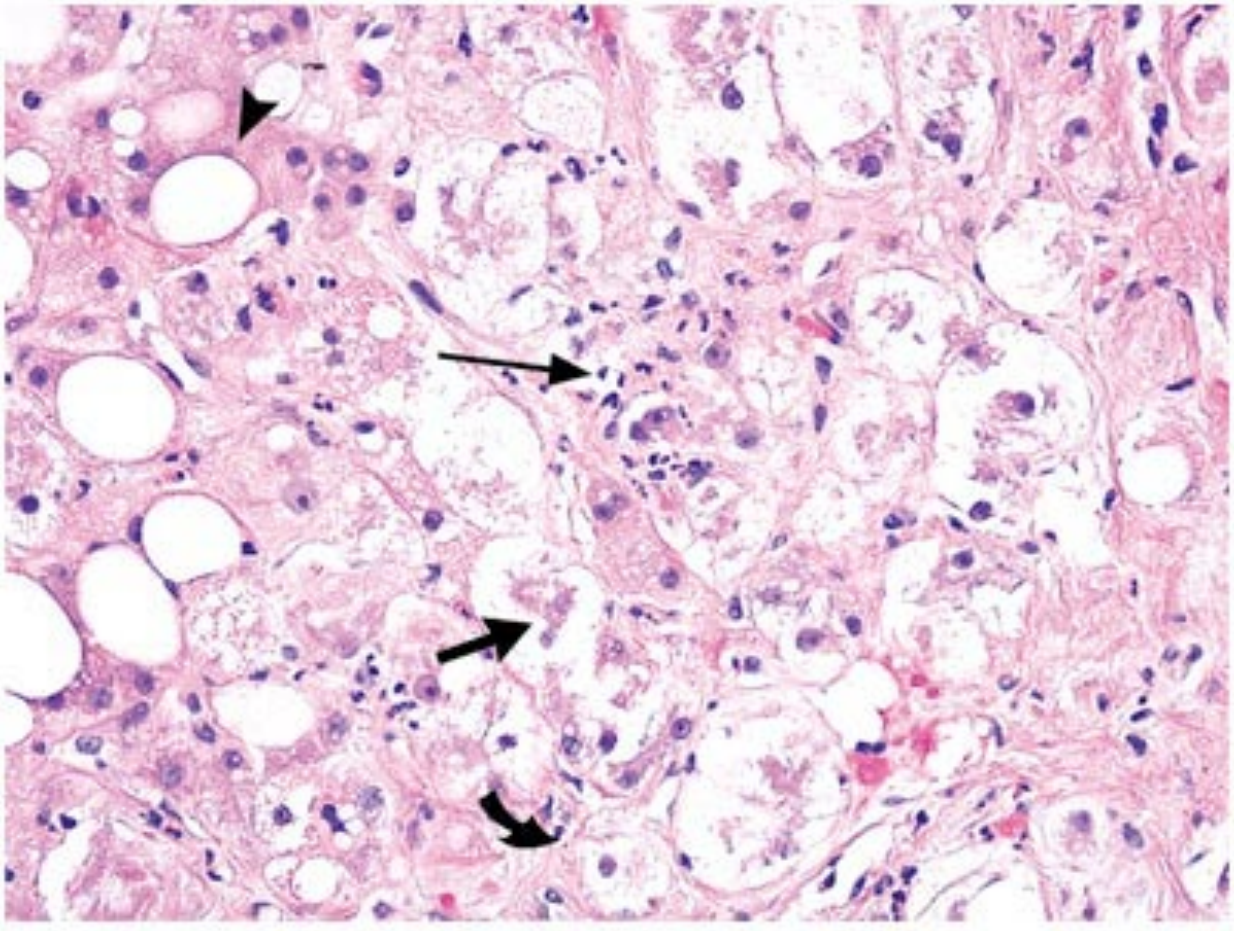
Natural course of alcoholic liver disease



Klinische Präsentation

- Unspezifische Beschwerden wie Müdigkeit
- Alkoholintoxikation, -geruch (Foetor ex ore)
- Entzugserscheinungen (Tremor)
- Hautveränderungen:
  - Hämatome
  - Rosazea
  - Leberhautzeichen (Spinnen-Nävi, Palmarerythem, Ikterus, Lackzunge, - lippen, Kratzspuren)
- Parotishypertrophie
- Zeichen der chronischen Lebererkrankung (Mangelernährung, Aszites, Enzephalopathie)
- Ca. **30% ohne jegliche Beschwerden**
- akut: 10-35% als ASH

Histopathological Features in Severe Alcoholic Hepatitis



Lucey M et al. N Engl J Med 2009;360:2758-2769

Clinical and laboratory signs of ASH

- Fever (typically modest)
- Hepatomegaly
- Jaundice
- Anorexia
- Coagulopathy
- Encephalopathy
- Leukocytosis (correlates with severity of hepatocyte injury)
- AST/ALT < 400 IU/L

Allgemeine Massnahmen (1)

- Behandlung des Alkoholentzugs (Benzodiazepine)
- Gabe von Flüssigkeit, Kalorien, Vitaminen (Vitamin K, Thiamin, Folsäure) und Mineralien
- Schutz der Atemwege (Enzephalopathie)
- Aszitesmanagement (Paracentese, Kulturen etc)

Allgemeine Massnahmen (2)

- Prompte antibiotische Therapie (Patienten sterben meist an Infektionen!)
- Frischplasma (falls frisch blutend)
- Ernährungstherapie, besonders falls Malnutrition

Treatment of ASH

- **Mortality in severe ASH: 30-50%**

- **Current therapeutic options**
  - Corticosteroids:
    - ***Daures et al, Gastroenterol Clin Biol 1991***
    - ***Ramond et al, NEJM 1992; Christensen et al, GUT 1995***
    - ***Imperiale et al, Ann Intern Med 1990***
    - ***Mathurin P et al, J Hepatol 2002***
    - ***Rambaldi A et al. APT 2008***
  - Pentoxifylline:?
    - ***Shakil et al, Gastroenterology 2000***
    - ***Louvet A et al, J Hepatol 2008***

Corticosteroids in ASH

- Most intensively studied treatment option (15 controlled trials)
- Several controlled trials produced variable results
- Meta-analyses to date failed to show a clear benefit of such therapies (heterogeneity of studies!)

Predictive parameters for steroid response? Early change in bilirubin levels

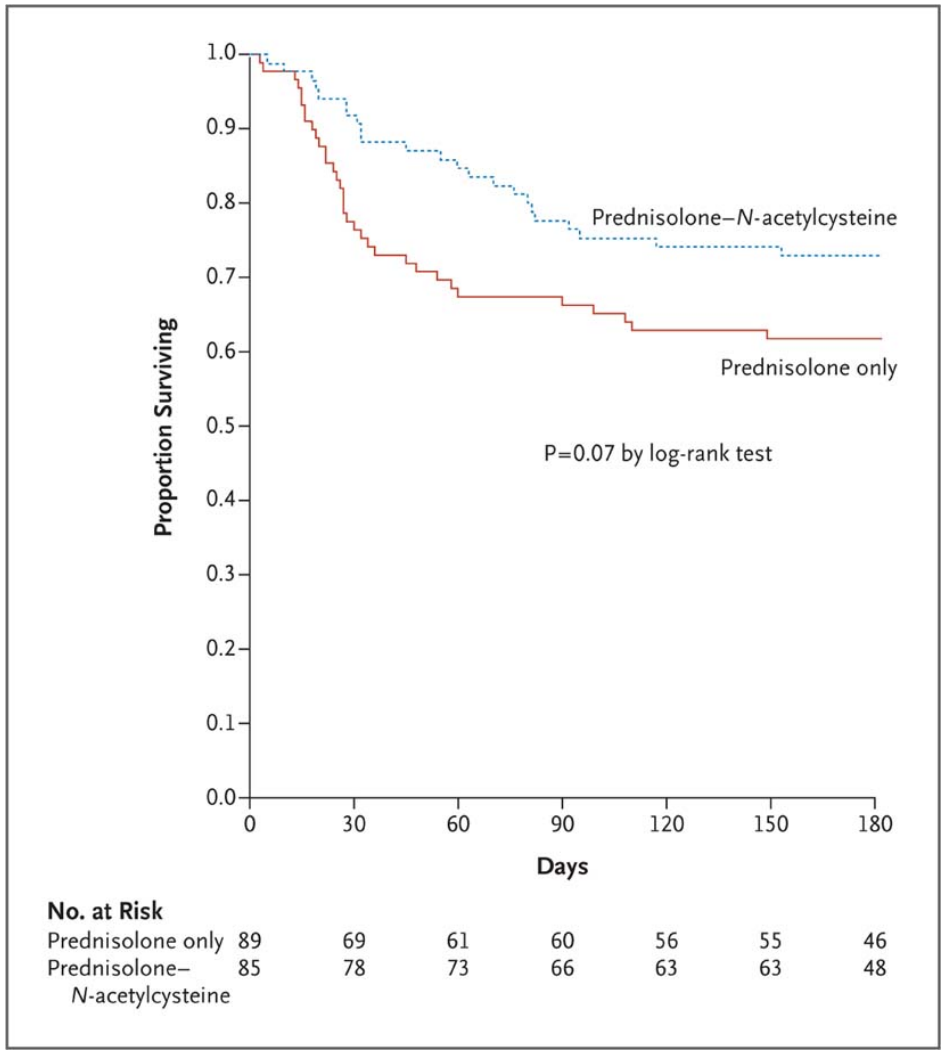
Mathurin P, Hepatology 2003

- 238 patients studied; 6-months survival as end-point
- Early change in bilirubin levels (ECBL) at 7 days (defined as levels lower than at treatment start) was observed in 73%
- After 6-months survival of patients with ECBL was 83% vs 23%
- **ECBL had the most important prognostic value**
- Treatment reconsideration on day 7?

Which patient may benefit from Corticosteroids?

- ECBL
- DF > 32 and encephalopathy
- Mortality in steroid-treated patients still high (up to 40%)
- 40 mg Prednisolone daily for 4 weeks and then tapering
- Prednisolone preferred to prednisone (requires conversion to prednisolone in the liver)

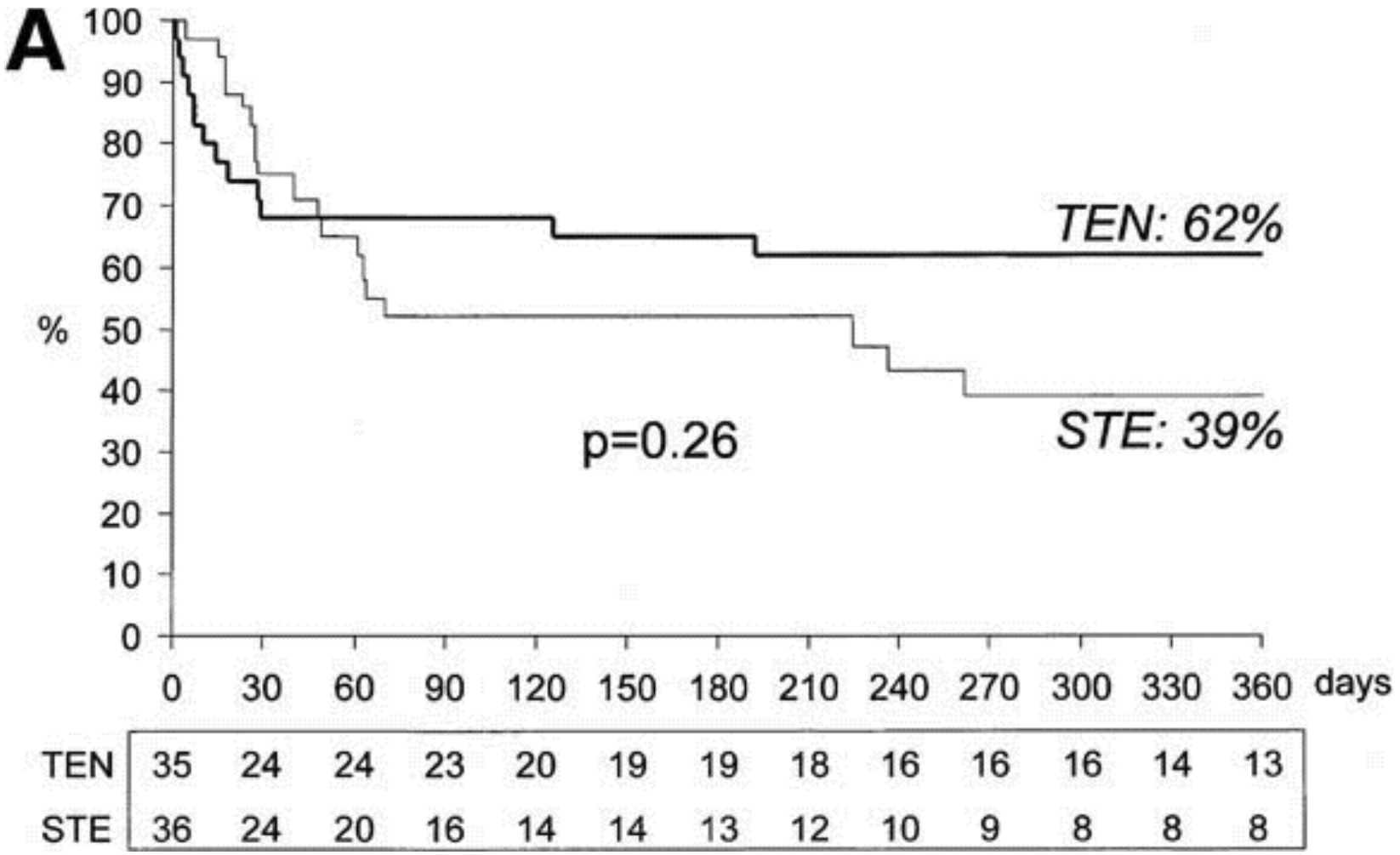
Corticosteroids ± *N*-Acetylcysteine?



The NEW ENGLAND JOURNAL of MEDICINE

Steroids versus Enteral Nutrition: Effects on Survival

Cabre et al, Hepatology 2000

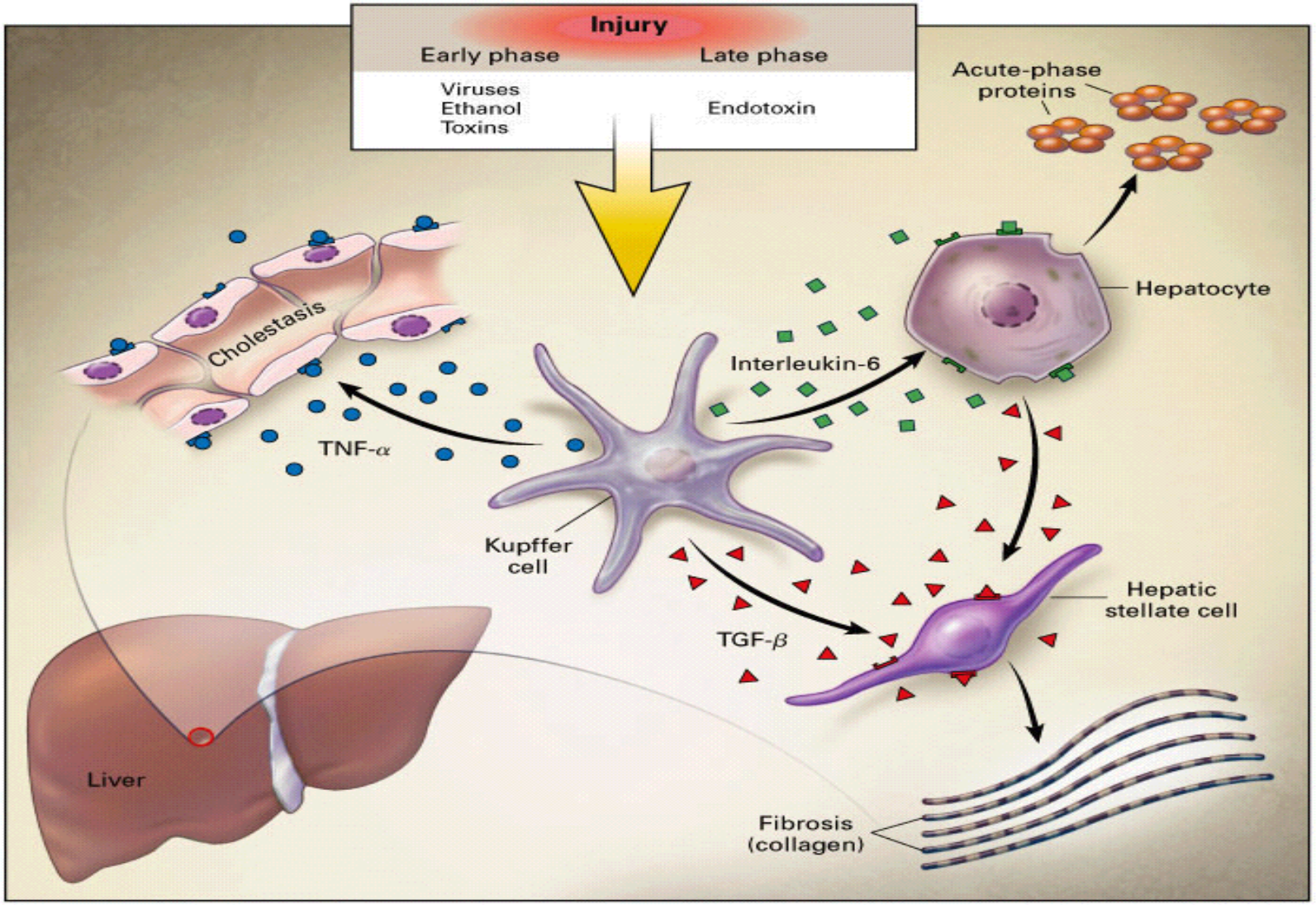


TEN	35	24	24	23	20	19	19	18	16	16	16	14	13
STE	36	24	20	16	14	14	13	12	10	9	8	8	8

The cytokine concept of ASH

- Transition into clinical reality?
- Pentoxifylline: A cytokine modulating drug?
- Anti-TNF treatment: a concept loosing its attraction?

Pathophysiological relevance of cytokines in liver disease



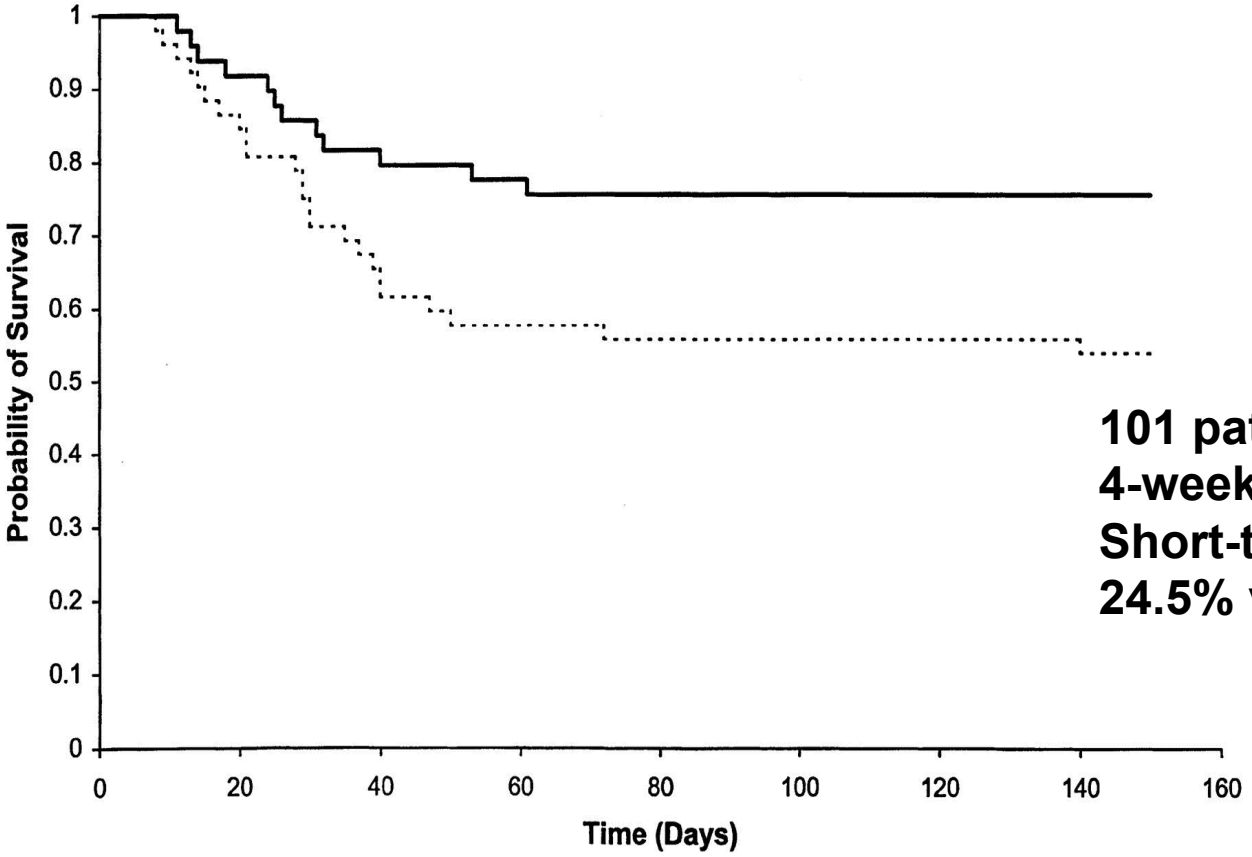
Tilg H, Diehl AM. New Engl J Med 2000

Cytokine studies in patients with ASH

- Increased serum/plasma levels of various cytokines (Steatohepatitis)
- Decreased levels after achieving clinical remission (Steatohepatitis)
- Levels correlate with mortality
- Levels of TNF and TNF soluble receptors correlate with amount of endotoxemia

Pentoxifylline in severe ASH

Survival curves for the PTX-treated (*solid line*) and control (*dotted line*) groups



101 patients
4-week treatment
Short-term survival:
24.5% vs 46.1%

Akriviadis et al, Gastroenterology 2000

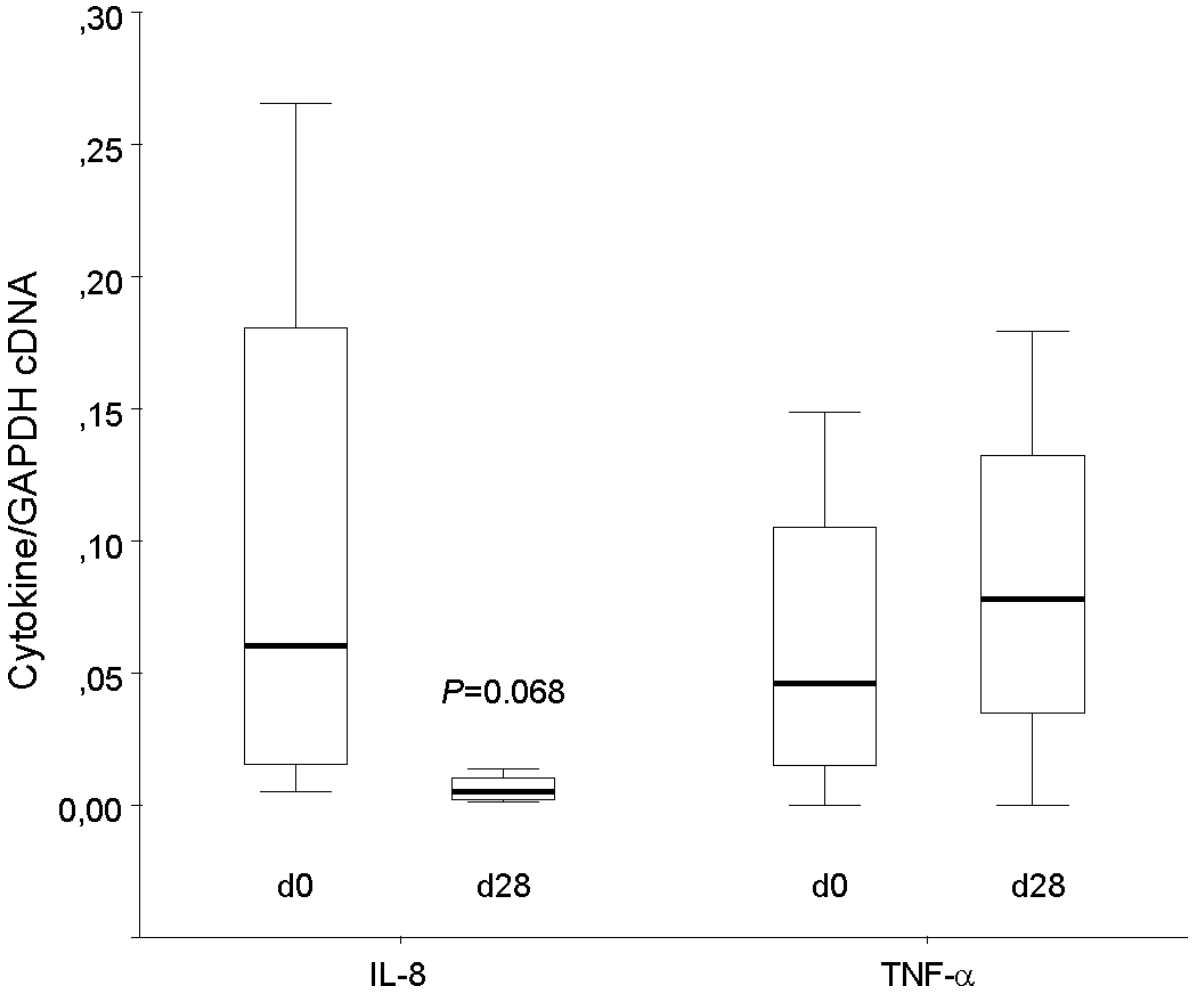
Early switch to pentoxifylline in corticosteroid non-responders
Louvet A et al, J Hepatol 2008

- 29 non-responders treated with PTX vs 58 matched non-responders treated with corticosteroids alone
- PTX treatment for 1 month
- No survival improvement at 2 months
- Non-responders to corticosteroids do not benefit from consecutive therapy wit PTX

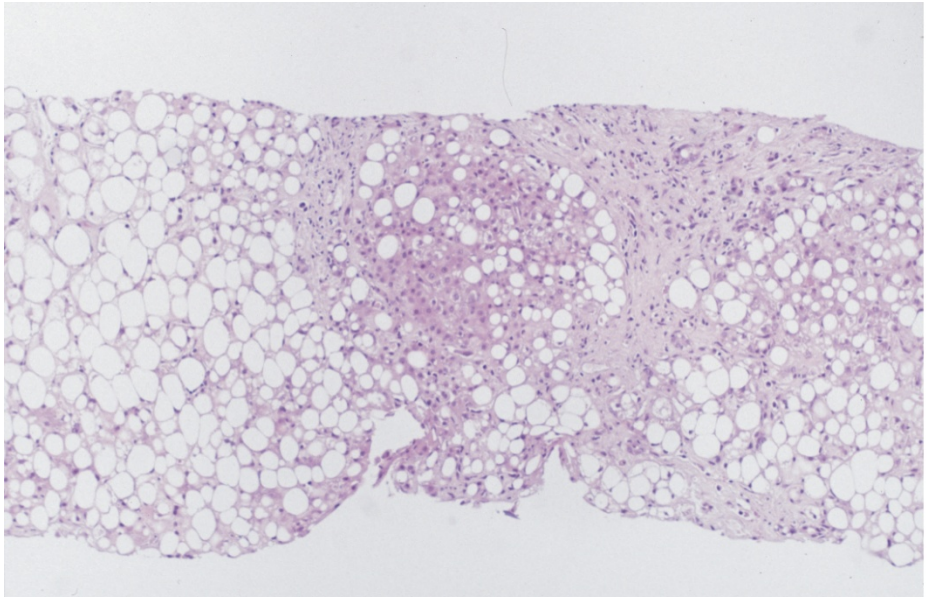
Pentoxifylline versus prednisolone: a controlled trial De BK et al, World J Gastroenterol 2009

- 68 patients (34 each), treated for 28 d
- 5/34 Ptx vs 12/34 Pred died within 3 months
- 0/34 Ptx vs 6/34 Pred developed a hepatorenal syndrome
- Ptx: better survival, less hepatorenal syndrome
- … BUT Cochrane Analysis 2009: OVERALL NO BENEFIT!

Liver cytokine mRNA expression



Liver Histology after Infliximab



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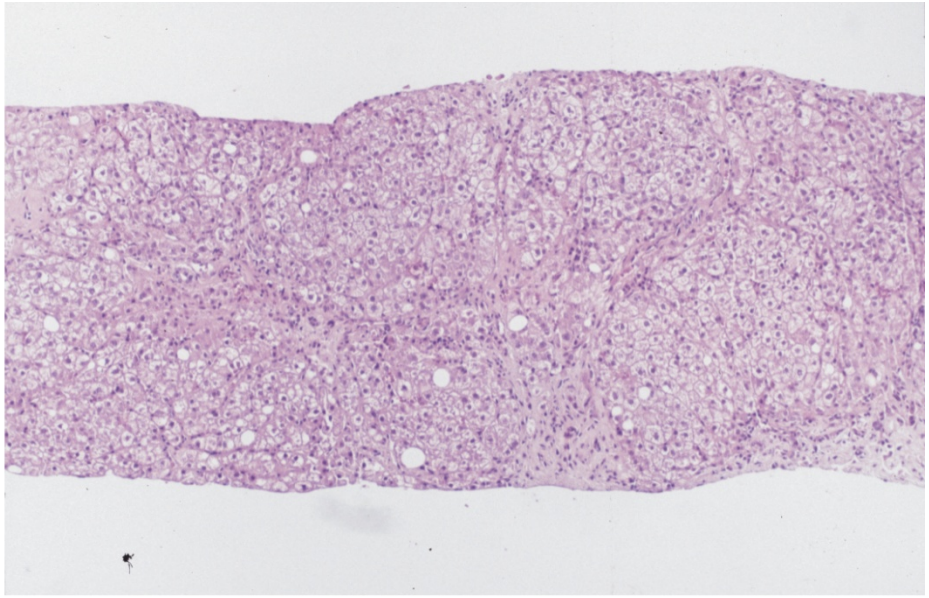

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Summary of our pilot study

- 10/12 patients survived (median 12 months; range 6-18)
- 2 patients died within the first month too due infectious complications (staphyloccoccal infection, candida septicemia)

Etanercept: controlled study in ASH

Boetticher NC et al, Gastroenterology 2008; 134: A-765

- Randomized, placebo-controlled trial
- Etanercept, twice weekly for 3 weeks
- Moderate to severe AH (MELD score $\geq$ 15)
- Mortality 1 month: no difference
- Mortality 6 months: higher in the etanercept group (58% vs 23%)
- ... **End of the anti-TNF concept?**

Table 2. Therapies for Alcoholic Hepatitis.*

Treatment	Clinical Purpose	Dose	Evidence
Psychotherapy	Maintain abstinence	Optimum approach and frequency not determined	No clear evidence of benefit in patients with alcoholic liver disease; has not been studied in patients with alcoholic hepatitis[65]
Corticosteroids	Reduce inflammation	40 mg of prednisolone orally, once a day for up to 28 days	Reduces short-term mortality in selected patients with severe alcoholic hepatitis[17,18,66-70]
Pentoxifylline	Ablate TNF-α, help maintain kidney function, and many other actions	400 mg orally, three times daily	Improves in-hospital survival in patients with severe alcoholic hepatitis; fewer instances of the hepatorenal syndrome in group receiving pentoxifylline[71]
Infliximab	Ablate TNF-α	Most effective dose has not been determined	May increase risks of infection and death[72]
Etanercept	Ablate TNF-α	Most effective dose has not been determined	May increase risks of infection and death[73]
Nutritional support	Reverse malnutrition	35–40 kcal/kg of body weight per day, including 1.2–1.5 g protein/kg/day	Improves nutritional status but does not improve short-term survival in patients with severe alcoholic hepatitis[74-76]
Oxandrolone	Increase muscle mass	Most effective dose has not been determined	Does not improve short-term survival in patients with severe alcoholic hepatitis[77]
Vitamin E	Ablate oxidant-mediated liver injury	Most effective dose has not been determined	Does not improve survival in patients with severe alcoholic hepatitis[78]
Silymarin (milk thistle extract)	Ablate oxidant-mediated liver injury	Most effective dose has not been determined	Does not improve survival in patients with severe alcoholic hepatitis[79]

* TNF-α denotes tumor necrosis factor α.

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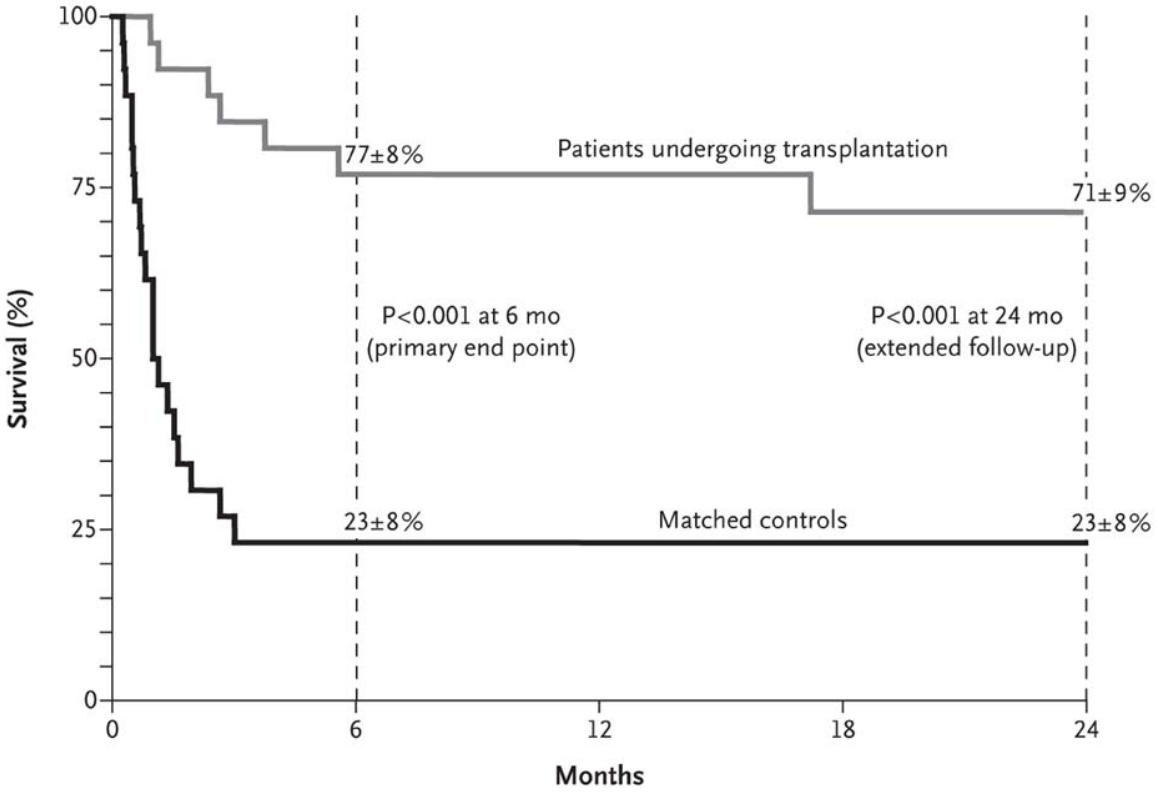
Lebertransplantation

- Einziger kurativer Ansatz
- Als Salvagetherapie f. selektionierte Patienten mit ASH (therapierefraktär, psychosozial geeignet), trotzdem schwierige Selektion
- LTx bei alkoholischer Lebererkrankung gleich wirksam wie bei anderen Indikationen wie z.B. NAFLD/NASH oder HCV Infektion

Early LTx for severe ASH

Mathurin et al, New Engl J Med 2011



No. at Risk					
Patients undergoing transplantation	26	20	15	14	13
Matched controls	26	6	6	5	4

Potential beneficial treatments in patients with severe ASH

- Prevention of gut-derived endotoxemia (Antibiotics, lactobacillus)
- Inhibition of TNFα activity (anti-TNF antibodies, TNF receptor antagonists, Pentoxifylline)?
- Inhibition of IL-1
- Decrease in reactive oxygen species production: Glutathione prodrugs (S-adenosyl methionine, betaine, choline, vitamin E, silymarin, propylthiouracil)
- Enhancing neutrophil function or correcting its defects?
- Probiotics?

Medikamente und Hepatotoxizität (1):

- Direkt-toxische Reaktion (Paracetamol): oft in Verbindung mit Alkohol (Enzyminduktion)
- Idiosynchratische Reaktion (INH): am häufigsten, nicht vorhersehbar; in 15-20% aller INH-behandelten Patienten erhöhte Transaminasen, aber nur in 1% hepatische Nekrose (damit Absetzen von INH!); histologisch ähnlich wie virale Hepatitis

Medikamente und Hepatotoxizität (2):

- Allergische Hepatitis (Phenytoin, Amoxizillin-Clavulansäure): systemische allergische Reaktion (Fieber, Lymphadenopathie, Exanthem, Eosinophilie); Hepatozytennekrose und Cholestase, langsame Rekonvaleszenz; mononukleose-ähnliches Bild, resultiert oft in einem Stevens-Johnson-Sy.

Medikamente und Hepatotoxizität (3):

- Cholestatische Reaktion (Östradiol): Östradiol, Chlorpromazin, TMP-SMZ, Rifampizin, Erythromycin, Captopril; Ikterus
- Granulomatöse Reaktion: subfebril, Fatigue; bei vielen Medikamenten
- Med.-induzierte chronische Hepatitis (Methyldopa, Statine): ähnlich einer autoimmunen Lebererkrankung; hohe Ig, positive ANA; entwickeln häufig und rasch eine Zirrhose

Medikamente und Hepatotoxizität (4):

- Fettleber, NASH (Amiodarone): leicht erhöhte Transaminasen, Zirrhose kann sich innerhalb weniger Monate entwickeln; sonogr. Fettleber; bei vielen Medikamenten
- Indolente Fibrose/Zirrhose (MTx): keine klinischen und laborchemischen Abnormalitäten; evtl. Leberbiopsie nach 2.5 g MTx
- Veno-okklusive Erkrankung: Cyclophosphamid; schmerzhafte Hepatomegalie, Aszites, Ikterus

Mit erhöhten Transaminasen assoziierte Substanzen (1):

- Medikamente:
  - Antibiotika (Penicillin, Quinolone, Fluconazol, INH, etc.)
  - NSAR
  - Statine
  - Antiepileptika (Phenytoin, Carbamazepin)
  - Sulfonylharnstoffe

Mit erhöhten Transaminasen assoziierte Substanzen (2):

- Homöopathika, Chinesische Medizin:
  - Senna
  - Alchemilla
  - Ephedra (Mahuang)
  - Ji Bu Huan

Mit erhöhten Transaminasen assoziierte Substanzen (3):

- Drogen, Anabolika:
  - Anabolika
  - Kokain
  - Ecstasy
  - Klebestoffe und Lösungsmittel
  - Chloroform

Some drugs, herbal products, and toxins associated with acute liver failure

Abacavir
Acetaminophen (paracetamol)
Alcohol
Allopurinol
Amiodarone
Amoxicillin
Aspirin
Carbamazepine
Carbon tetrachloride
Ciprofloxacin
Cocaine
Comfrey
Dapsone
Didanosine
Dideoxyinosine
Disulfiram
Doxycycline
Efavirenz
Gemtuzumab
Gold
Greater celandine
Halothane
He Shon Wu
Herbalife®
Hydroxycut®
Isoflurane
Isoniazid
Itraconazole
Kava Kava
Ketoconazole
Labetalol
LipoKinetix®
Ma Huang
MDMA (Ecstasy)
Methamphetamine
Monoamine oxidase inhibitors
Methyldopa
Nicotinic acid
Nitrofurantoin
Nonsteroidal anti-inflammatory drugs
Phenprocoumon
Phenytoin
Poison mushrooms (*Amanita phalloides*)
Propylthiouracil
Pyrazinamide
Rifampin
Senecio
Statins
Sulfonamides
Terbinafine
Tetracycline
Tolcapone
Tricyclic antidepressants
Valproic acid

Mnemonic for causes of acute liver failure: The ABCs

A	Acetaminophen, hepatitis A, autoimmune hepatitis, *Amanita phalloides* (mushroom poisoning), adenovirus
B	Hepatitis B, Budd-Chiari syndrome
C	Cryptogenic, hepatitis C, CMV
D	Hepatitis D, drugs and toxins
E	Hepatitis E, EBV
F	Fatty infiltration - acute fatty liver of pregnancy, Reye's syndrome
G	Genetic - Wilson disease
H	Hypoperfusion (ischemic hepatitis, VOD, sepsis), HELLP syndrome, HSV, heat stroke, hepatectomy, hemophagocytic lymphohistiocytosis
I	Infiltration by tumor

Ecstasy

CMV: cytomegalovirus; EBV: Epstein-Barr virus; HELLP: hemolysis, elevated liver enzymes, low platelets; HSV: herpes simplex virus; VOD: veno-occlusive disease.

Zusammenfassung-1

- Alkohol und NAFLD sind die häufigsten Ursachen einer chronischen Lebererkrankung in unseren Breiten
- Nur 10-15% aller schweren Trinker entwickeln eine Leberzirrhose (genetische Faktoren?)
- ALD und NAFLD verstärken sich gegenseitig
- Diagnose: exakte Anamnese, wenige Laborparameter, Sonographie, Histologie
- ASH und Prognose: verschiedene Scores

Zusammenfassung-2

- Bei schwerer ASH Indikation f. Steroide (Tag 7! wichtig!)
- Bei Mangelernährung und moderater ASH Ernährungstherapie
- LTx als Salvagetherapie (ASH)
- „Drogen“ können wie faktisch jedes Medikament zu Hepatotoxizität führen
- Sehr diverse Reaktionsmuster der Leber möglich (wie Leberversagen, Hepatitis, NASH, Fibrose, etc.)