



Alcoholic liver disease

Dutch liver Week 2018 Rotterdam





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'Ook één glas alcohol per dag verhoogt gezondheidsrisico's'

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Ook matig alcoholgebruik brengt gezondheidsrisico's met zich mee. Dat blijkt uit een overzichtsstudie op basis van gezondheidsgegevens van 600.000 drinkers uit negentien landen.

Uit de studie die vrijdag in het wetenschappelijke tijdschrift *The Lancet* verschijnt blijkt dat ook 'één glaasje' per dag niet gezond is. De onderzoekers adviseren om de adviezen voor gezond alcoholgebruik te verlagen, schrijft *de Volkskrant*.

In Nederland luidt het advies van de Gezondheidsraad: "drink geen alcohol of in elk geval niet meer dan een glas per dag." Maar in andere landen, zoals de VS, Spanje en Groot-Brittannië, liggen de adviezen hoger. Volgens de onderzoekers dus te hoog.



Nieuwe adviezen Gezondheidsraad België: drink niet meer dan tien glazen alcohol per week.



Daarom raden de experts van de Gezondheidsraad aan alcoholgebruik te beperken tot **10 glazen wijn van 10 cl of tien glazen pils van 25 cl per week.** Als het alcoholgehalte van het bier hoger is dan gewone pils, moet het gebruik aangepast worden. Van sterke bieren mogen er dan bijvoorbeeld maar 5 of 6 stuks per week gedronken worden.



This presentation

- Epidemiology: burden of alcoholic liver
- Pathogenesis
- Clinical aspects of ALD
- Liver transplantation



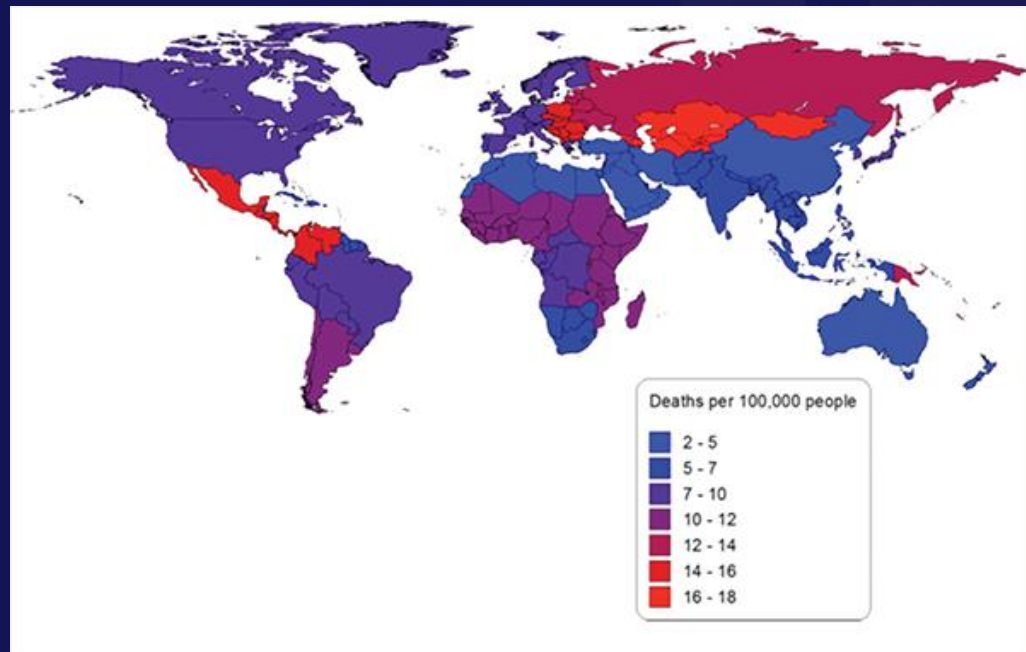
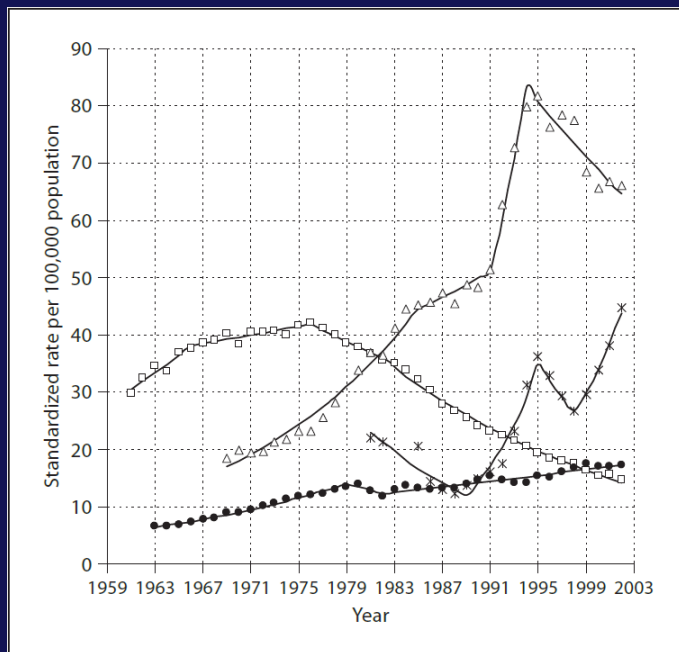
World Health Organisation

In 2009, the World Health Organization listed alcohol use as **one of the leading causes** of the global burden of disease and injury, surpassed only slightly by childhood malnourishment and unsafe sex. This placed alcohol use ahead of unsafe water and sanitation, hypertension, high cholesterol, and tobacco use, and clearly affirms that alcohol is the most widely abused substance in the world.



Burden of alcoholic liver disease

- Alcohol consumption responsible for 5.9% global mortality
- Deaths attributable to alcohol: 7.6.– 4.0% (men – women)
- Europe highest alcohol consumption (10.9 l/year)
- Mortality rates secondary to alcohol cirrhosis vary considerable





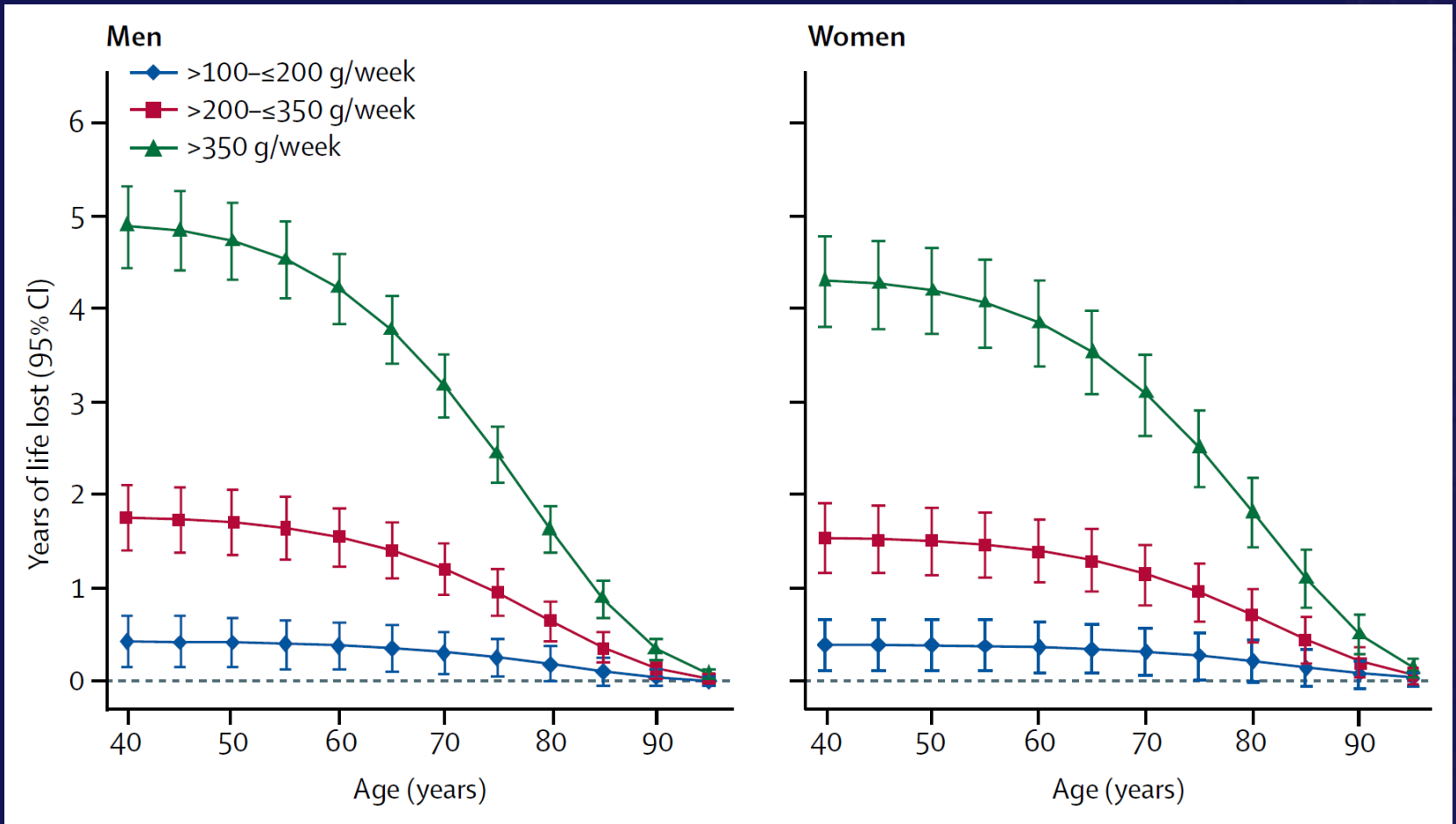
There are still a lot of questions

- Does beverage type matters (beyond volume ethanol)?
- Does drinking to intoxication confer a particular risk (binge drinking)?
- What is the contribution of hepatotoxic substances in addition to ethanol?



Risk thresholds for alcohol consumption: combined analysis of individual-participant data for 599 912 current drinkers.

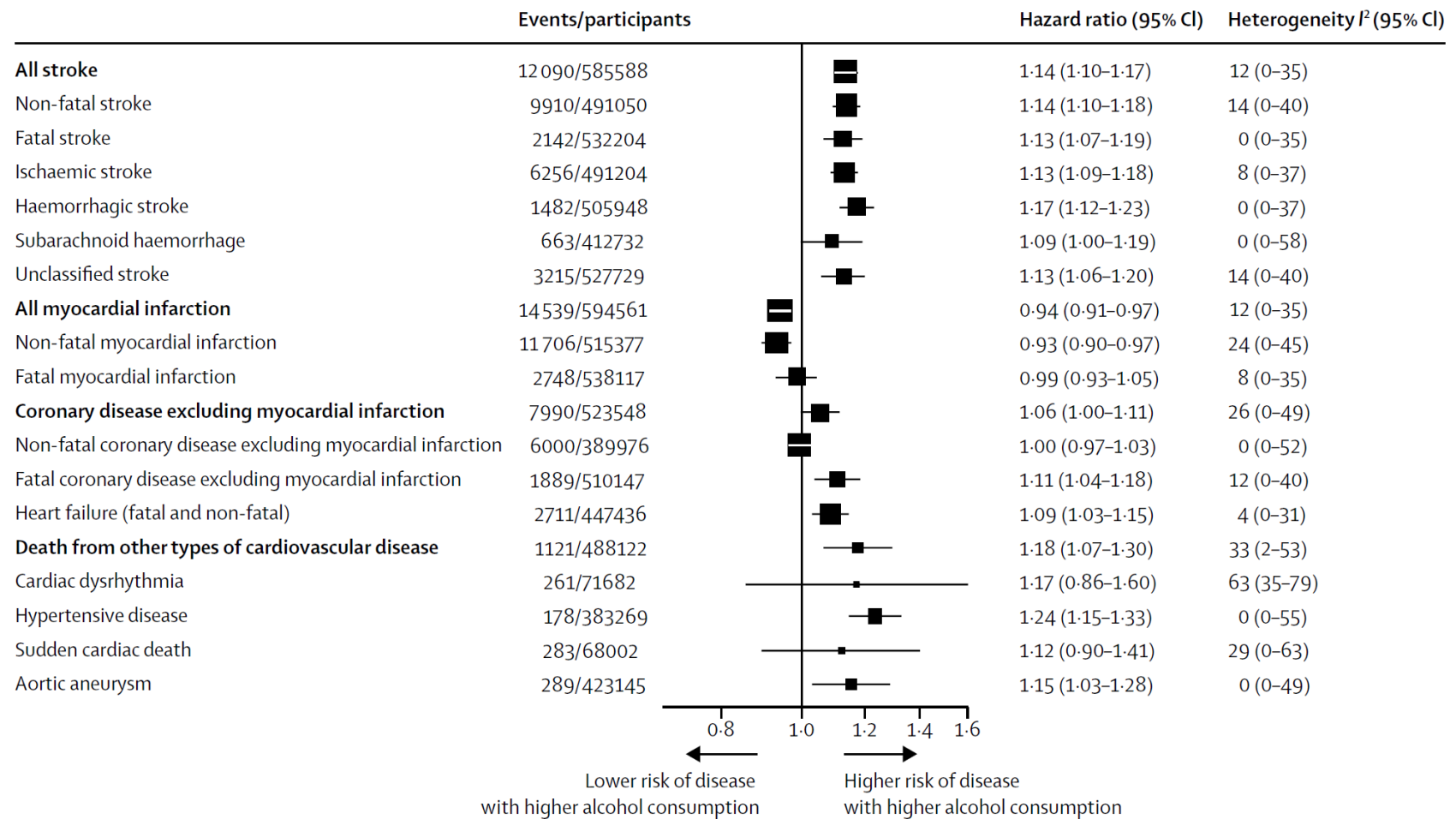
A.M. Wood. Lancet 2018; 391: 1513–23





Risk thresholds for alcohol consumption: combined analysis of individual-participant data for 599 912 current drinkers.

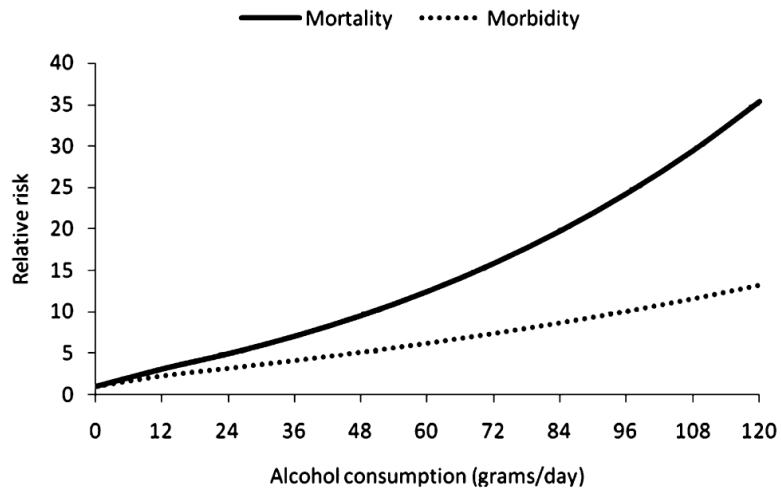
A.M. Wood. Lancet 2018; 391: 1513–23



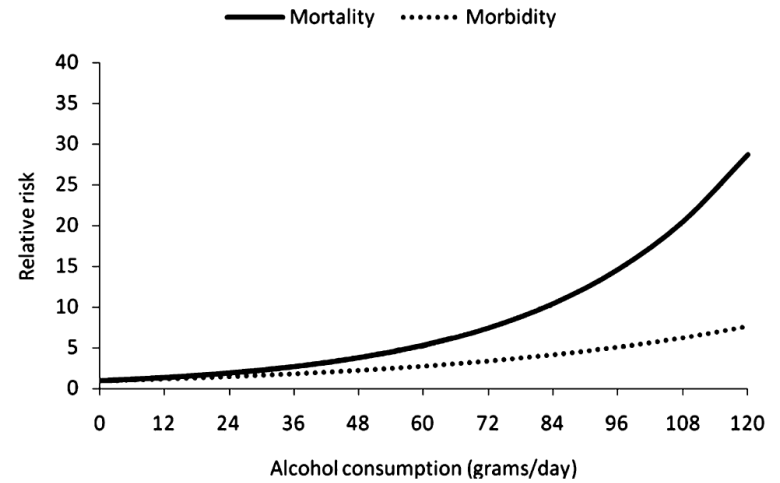


Risk threshold of alcohol consumption for liver cirrhosis

Women



Men





Vraag 1:

Maakt het uit wat voor soort alcohol je drinkt?



Ja

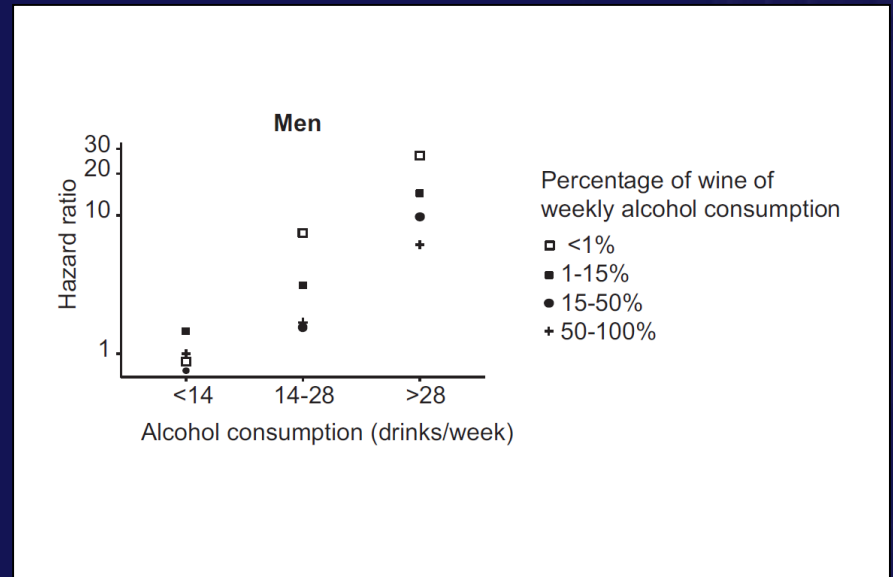
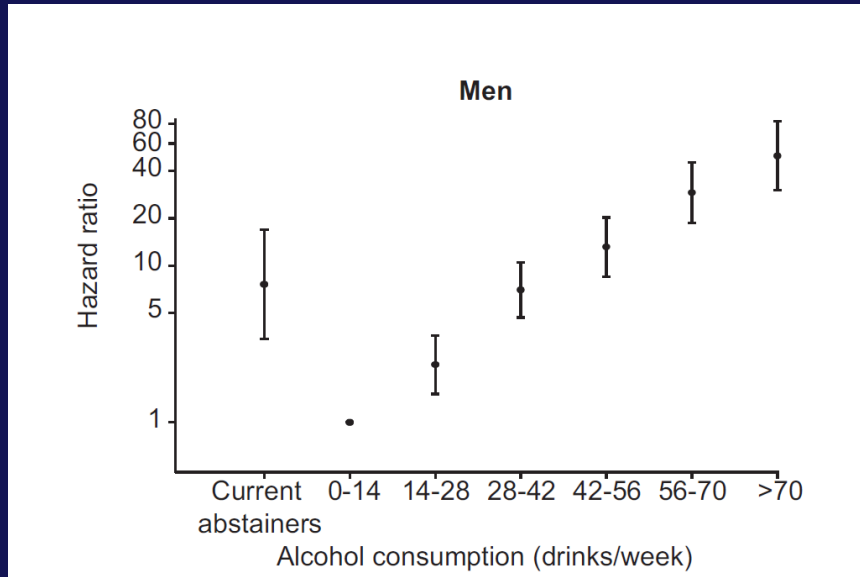


Nee



Alcohol drinking pattern and risk of alcoholic liver cirrhosis

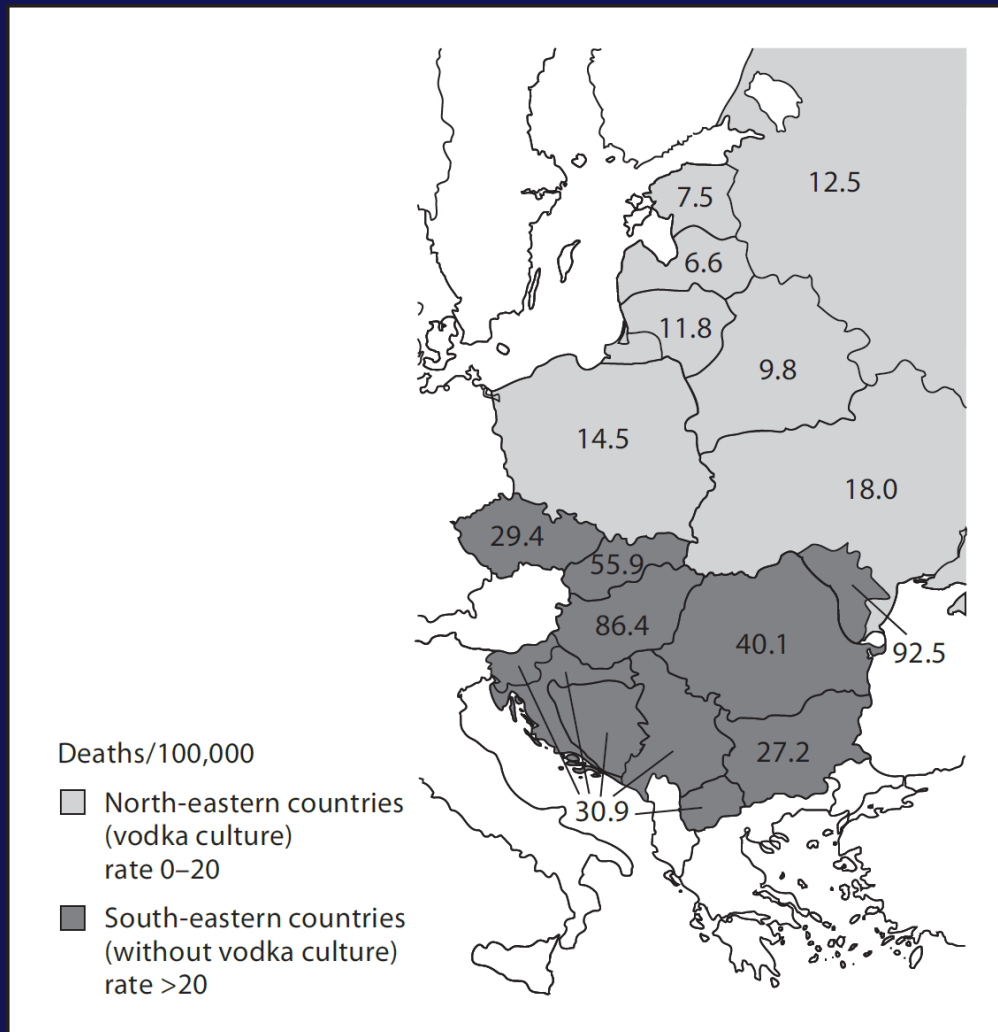
G. Askgaard. Journal of Hepatology 2015;62:1061–1067



1. Dose-dependent association between amount of alcohol and risk of alcoholic cirrhosis
2. Daily drinking was associated with an increased risk of alcohol cirrhosis
3. Wine might be associated with a lower risk for alcoholic cirrhosis

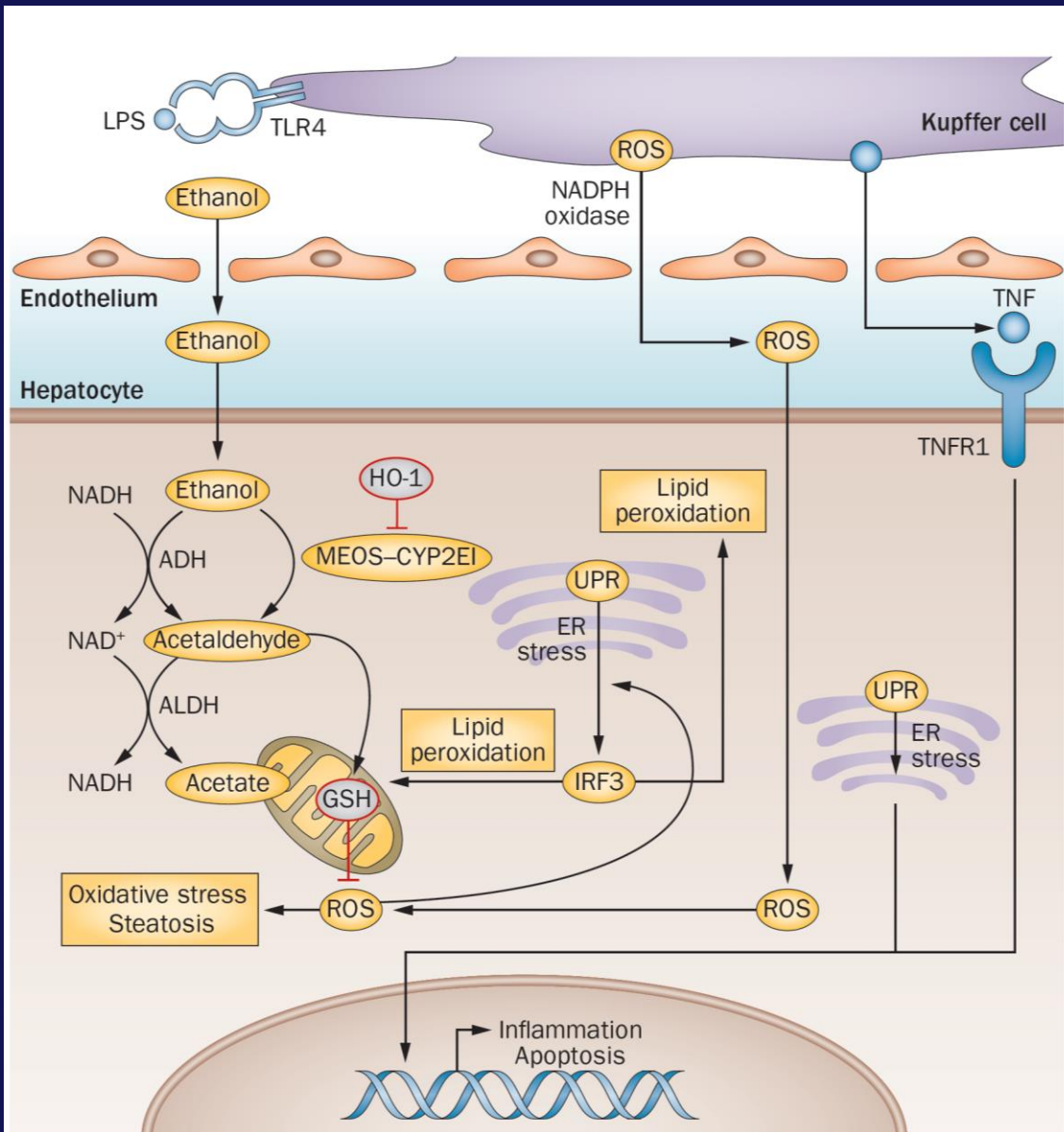


Hepatotoxic substances



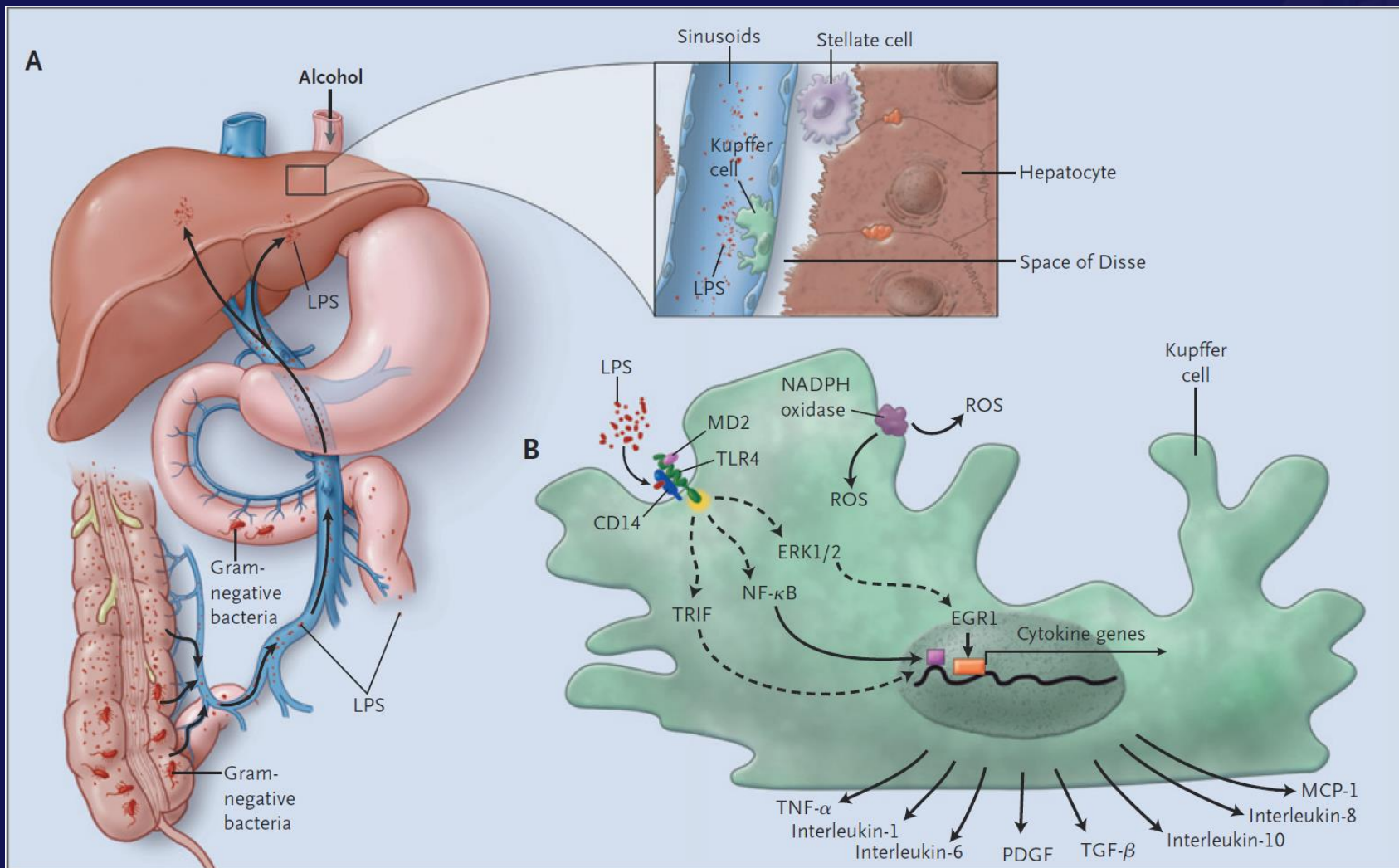


Pathogenesis of alcoholic liver disease: cell injury





Pathogenesis alcoholic hepatitis





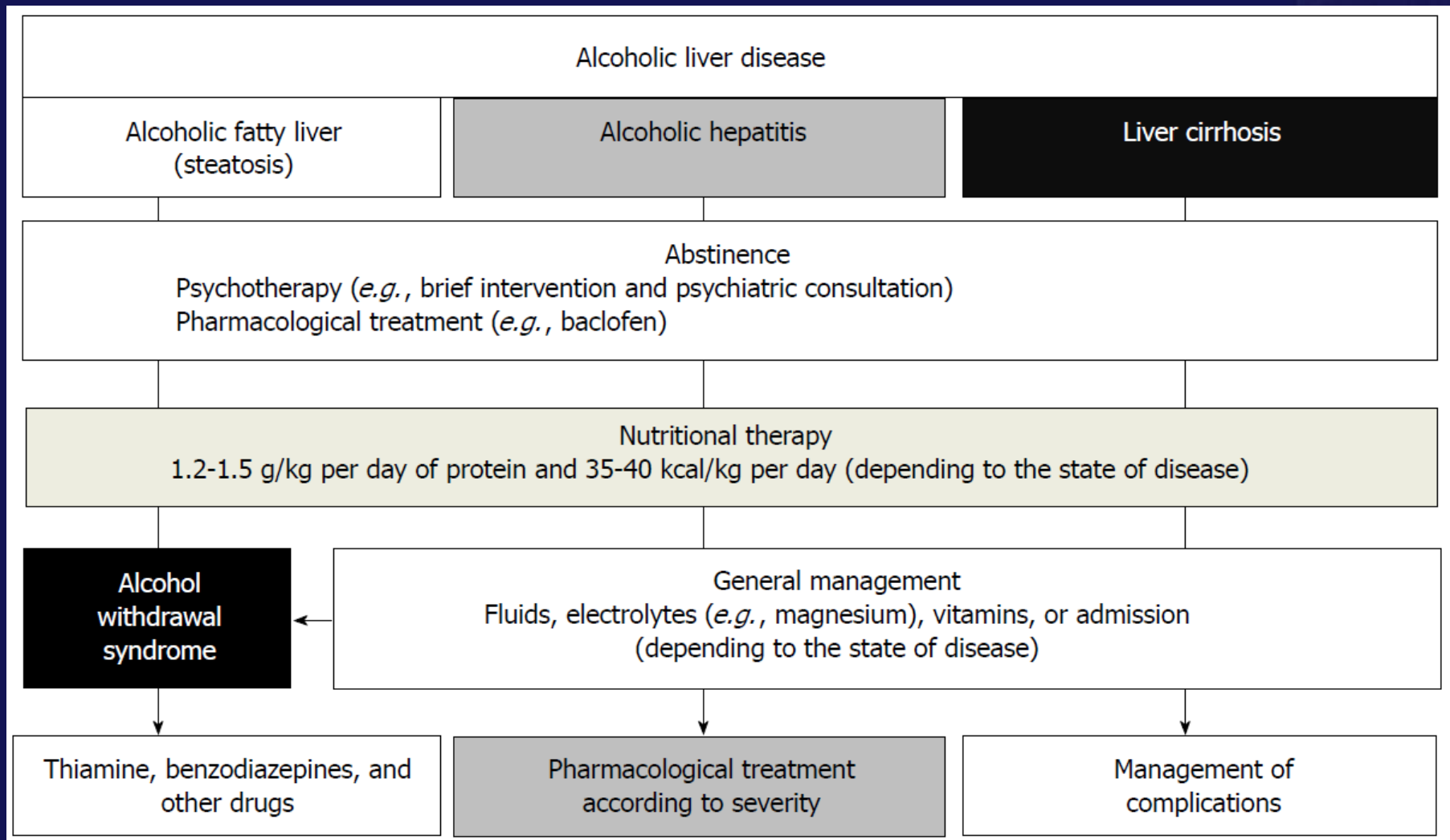
Alcoholic hepatitis

Definition, incidence and diagnosis

- Clinical syndrome with recent onset of jaundice with or without other signs of liver decompensation in patient with ongoing alcohol abuse
- Histologically defined by steatosis, hepatocyte ballooning and inflammatory infiltrate
- Prevalence 20% in alcoholic patients
- AST 2-6x ULN, AST/ALT ratio > 2 , bilirubinemia and neutrophilia
- Liver biopsy can be useful
- Prognostic models to identify high risk early death



Treatment algorithm of ALD





Guidelines: infection in acute alcoholic hepatitis

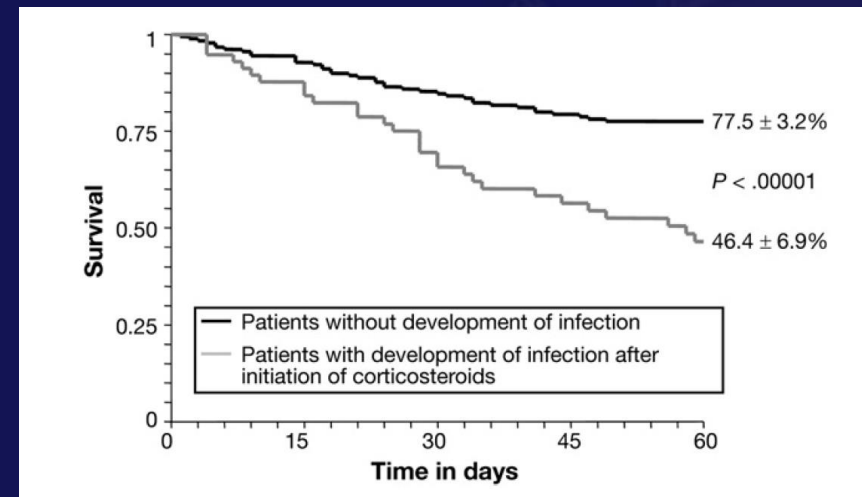
- Infections are frequent
- Systematic body fluid sampling and close clinical monitoring are advised for early detection of infection
- In the absence of scientific evidence, criteria for initiating empirical antibiotic administration, although it is widely used, remain debated



Infection in patients with severe alcoholic hepatitis treated with steroids: early response to therapy is the key factor.

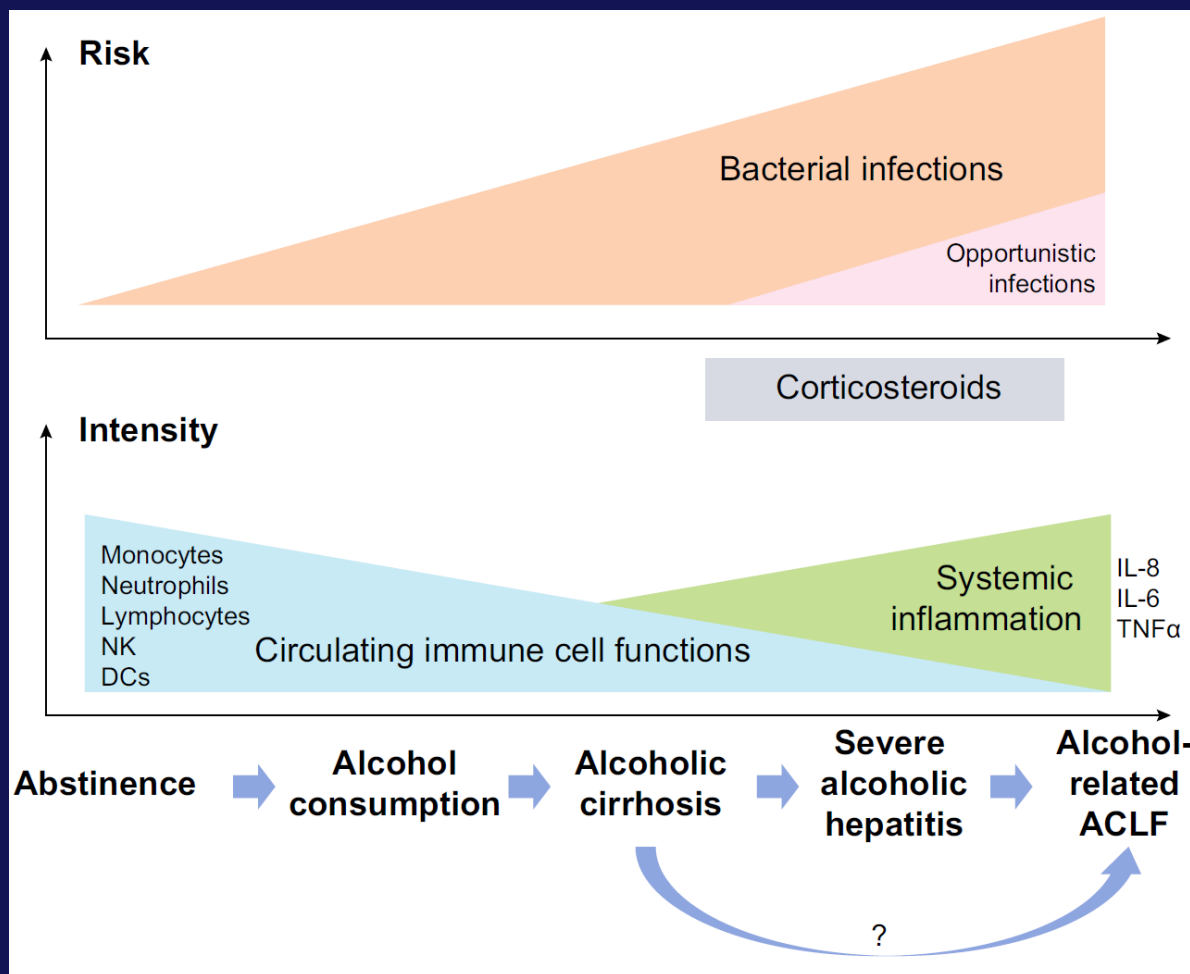
Louvet A. Gastroenterology. 2009 Aug;137(2):541-8

- 63 patients were infected at the following sites:
 - spontaneous bacterial peritonitis or isolated bacteremia (44.4%)
 - Urinary tract infections (31.7%)
 - respiratory infections (12.7%)
 - others, including cutaneous infections (11.2%).



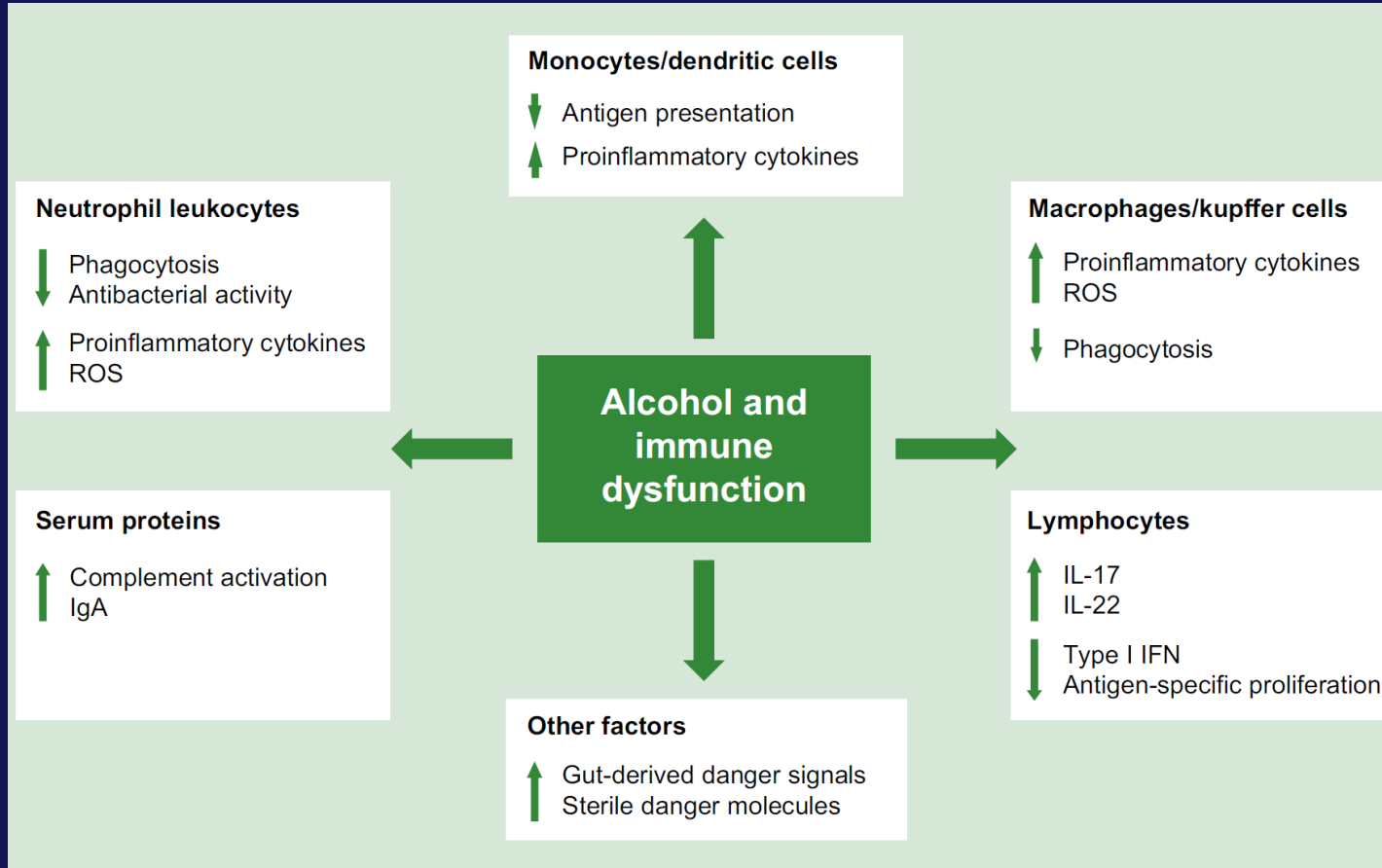


Immune dysfunction associated with alcoholic liver disease



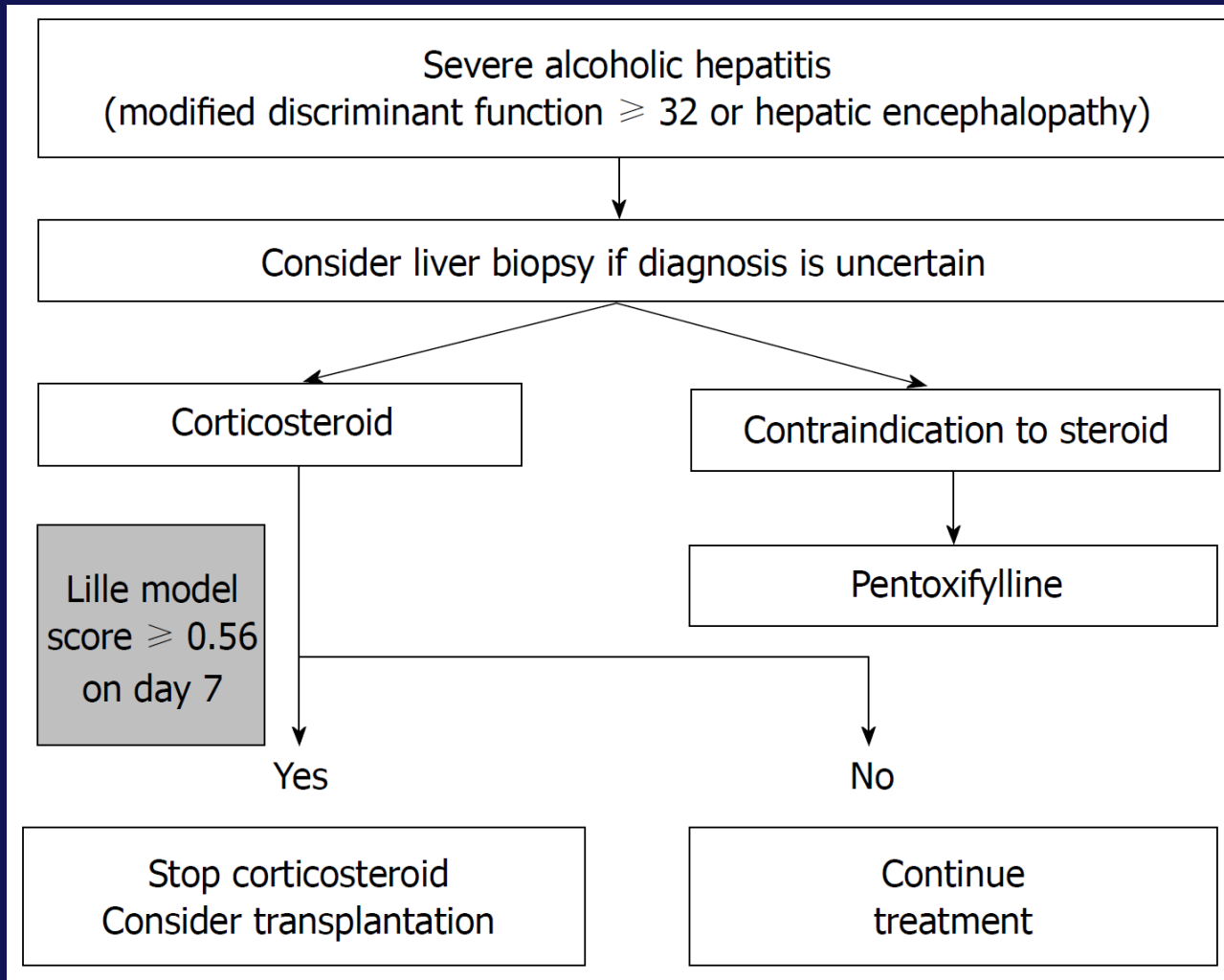


Immune dysfunction associated with alcoholic liver disease





Treatment algorithm of severe alcoholic hepatitis





Corticosteroids in acute alcoholic hepatitis

- Oldest medical treatment of alcoholic hepatitis
- Use of corticosteroids is controversial
- Old studies, heterogeneous clinical trials
- Benefit in subgroup analysis

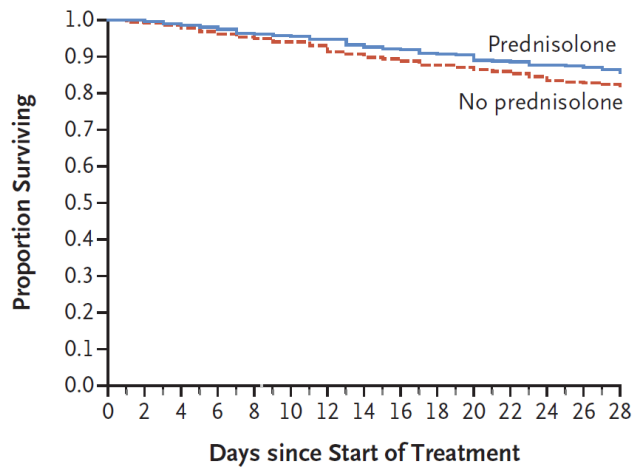




Prednisolone or Pentoxifylline for Alcoholic Hepatitis

M.R. Thursz. NEJM 2015;372:1619-28

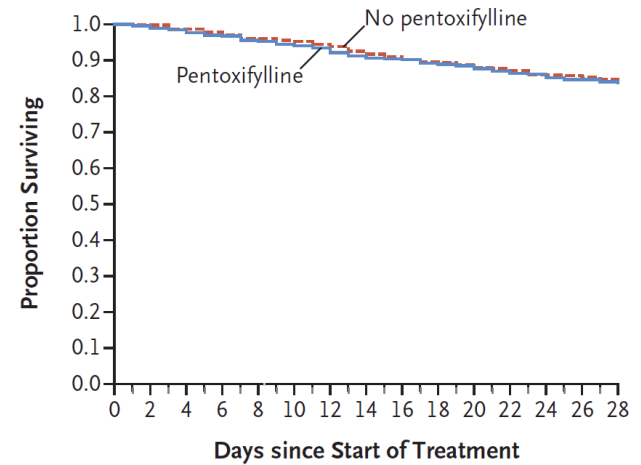
A Prednisolone vs. No Prednisolone



No. at Risk

Prednisolone	543	514	483	459	427
No prednisolone	546	523	494	468	450

B Pentoxifylline vs. No Pentoxifylline



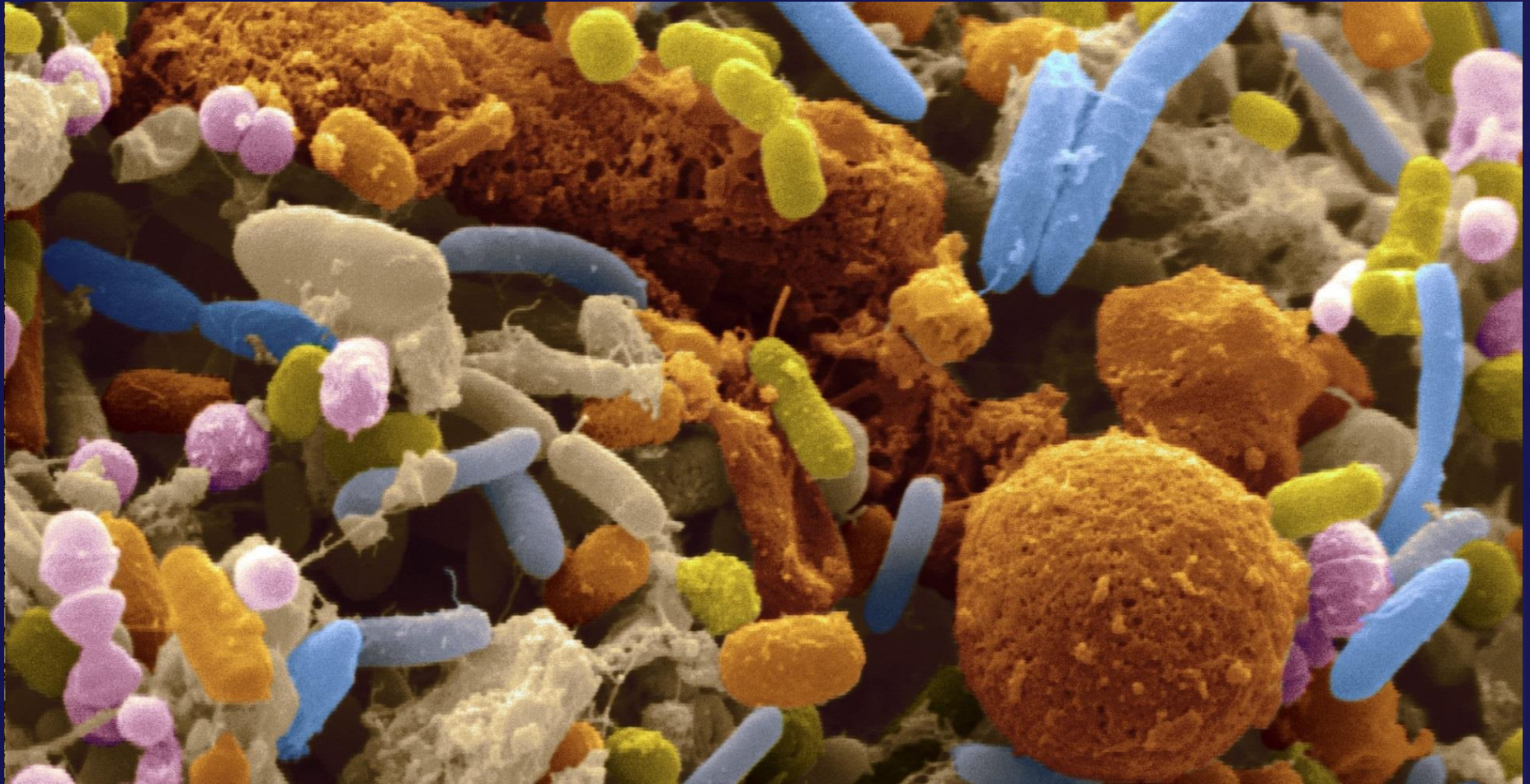
No. at Risk

Pentoxifylline	546	524	497	470	448
No pentoxifylline	543	513	480	457	429

STOPAH trial: pentoxifylline did not improve outcomes in patients with alcoholic hepatitis. The findings suggest that the administration of 40 mg of prednisolone daily for 1 month may have a beneficial effect on shortterm mortality but not on the medium-term or long-term outcome of alcoholic hepatitis.



In the absence of treatment the one-month survival of patients with $DF \geq 32$ has improved from 50% in early publications to 85% in recent trials.



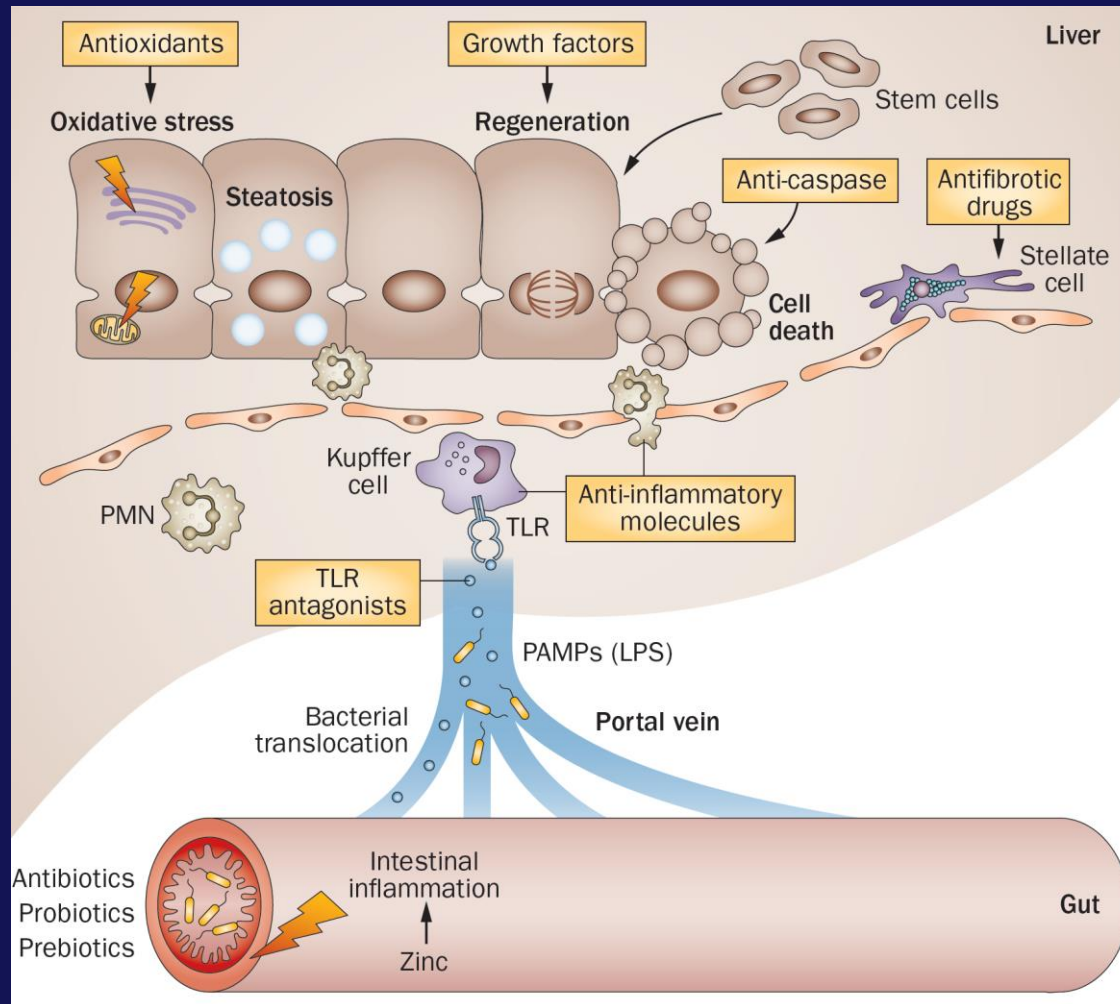


Intestinal microbiota contributes to individual susceptibility to ALD





Potential targeted therapies in ALD





Potential targeted therapies in ALD

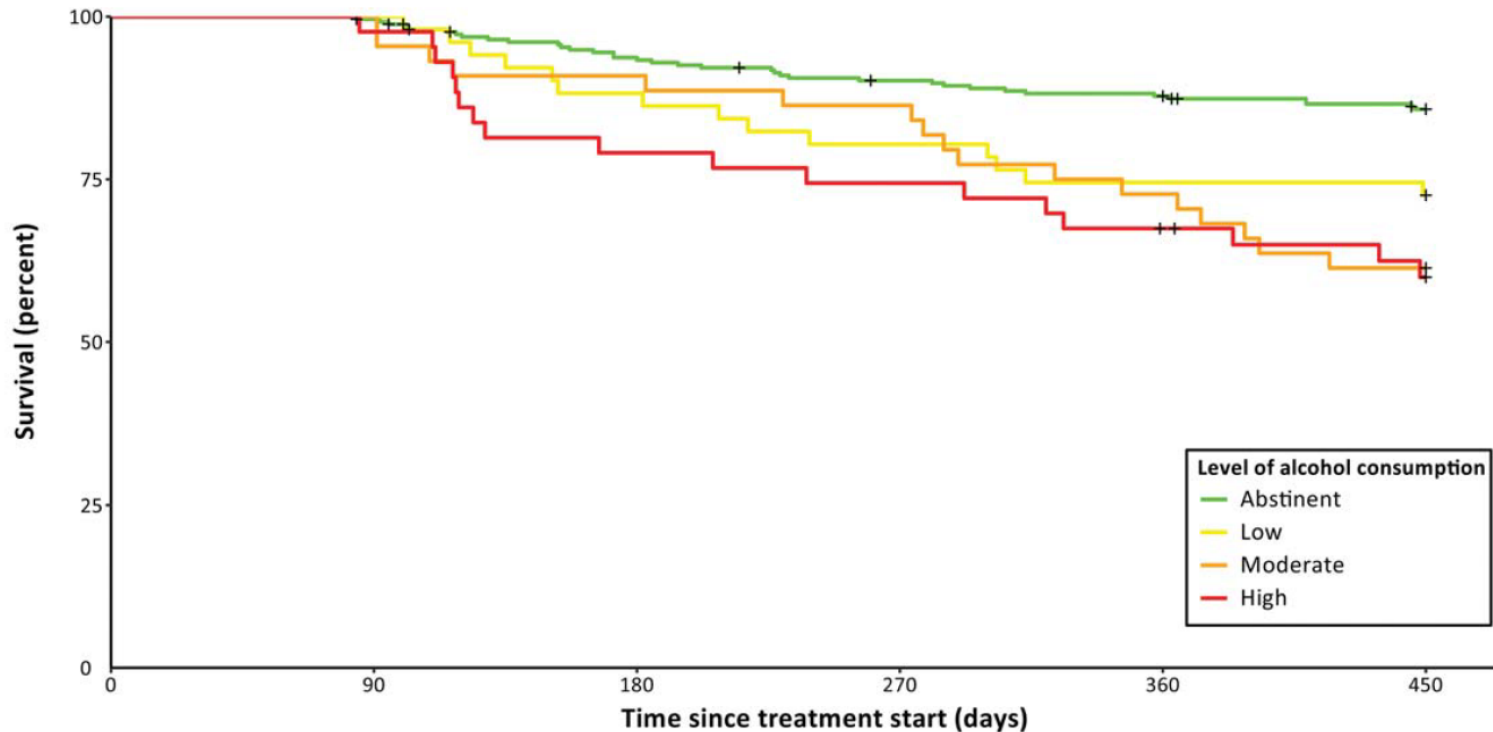
Table 1 | Main ongoing studies of targeted treatment for alcoholic hepatitis and alcoholic cirrhosis

Treatment	Type of molecule	Mechanism of action	Identifier*
Emricasan (IDN 6556)	Pan-caspase inhibitor	Reduces apoptosis	NCT01912404 ¹⁸⁷
Metadoxin	Hepatoprotective agent	Antioxidant	NCT02161653 ¹⁸⁸
Metadoxin and garlic acid	Hepatoprotective agent	Antioxidant	NCT02019056 ¹⁸⁹
Anakinra (+ pentoxifylline + zinc)	IL-1 receptor antagonist	Decreases hepatic inflammation	NCT01809132 ¹⁹⁰
Amoxicillin clavulanate	Antibiotic	Decreases bacterial overgrowth and bacterial translocation; prevents development of infection	NCT02281929 ¹⁹¹
Rifaximin	Antibiotic	Decreases bacterial overgrowth and bacterial translocation; prevents development of infection	NCT02116556 ¹⁹²
Ciprofloxacin	Antibiotic	Decreases bacterial overgrowth and bacterial translocation; prevents development of infection	NCT02326103 ¹⁹³
<i>Lactobacillus rhamnosus</i>	Probiotic	Decreases bacterial overgrowth; regulates gut inflammation	NCT01922895 ¹⁹⁴
G-CSF	Growth factor	Promotes liver regeneration	NCT01820208 ¹⁹⁵
Obeticholic acid	Biliary acid	Improves cholestasis	NCT02039219 ¹⁹⁶
Mycophenolate mofetil and rilonacept	Immunosuppressor and IL-1 blocker	Decreases hepatic inflammation	NCT01903798 ¹⁹⁷
Zinc	Oligoelement	Decreases gut inflammation	NCT02072746 ¹⁹⁸
Stem cells	Progenitors	Promote liver regeneration	NCT01875081 ¹⁹⁹

*All trials are listed at www.clinicaltrials.gov. Four consortia have been funded by the NIH to test targeted therapies; these consortia are involved in some of these clinical trials. More information about these consortia can be found at RePORT.²⁰⁰ Abbreviation: G-CSF, granulocyte colony-stimulating factor.



Alcohol Abstinence in Patients Surviving an Episode of Alcoholic Hepatitis



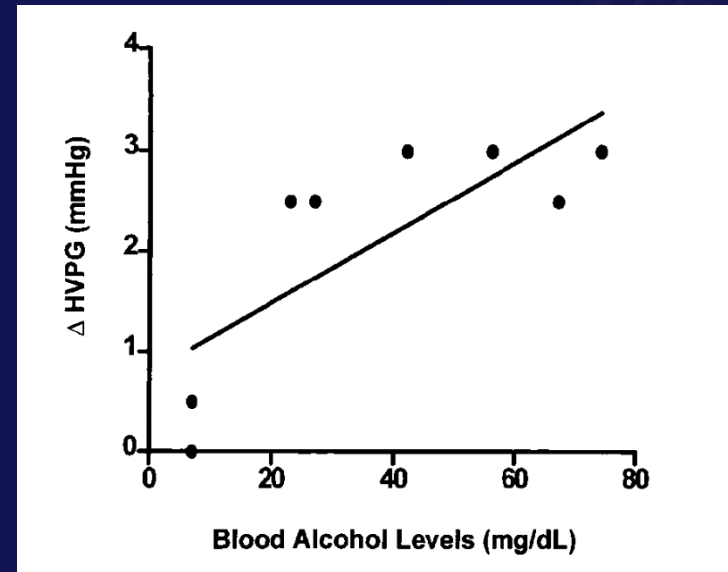
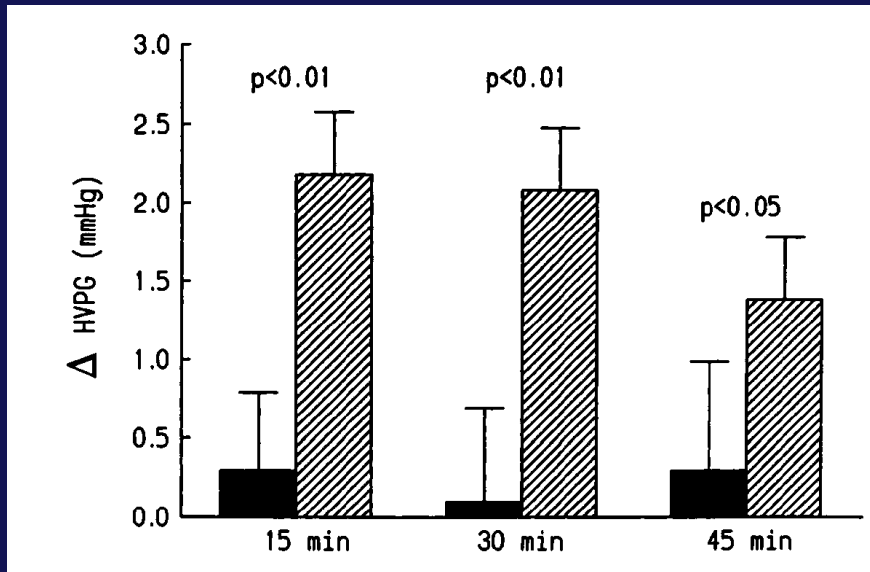
Abstinent	259	257	238	227	221	212
Low	51	51	45	41	38	37
Moderate	44	44	40	38	32	27
High	43	42	34	32	28	24

Numbers at risk



Effect of ethanol on hepatic hemodynamics

A. Luca. Gastroenterology 1992;112:1284-1289



Oral ethanol consumption increases portal pressure and portocollateral blood flow in patients with alcohol-induced cirrhosis.

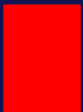


Vraag 2:

Moeten patiënten met een acute alcoholische hepatitis de kans krijgen om getransplanteerd te kunnen worden?



Ja



Nee



Liver transplantation PRO and CON

PRO

- Life-saving last resort
- 6-month rule is an arbitrary threshold
- Patients with ALD similar survival 1- and 5-year
- Regard alcohol use as co-morbid disorder

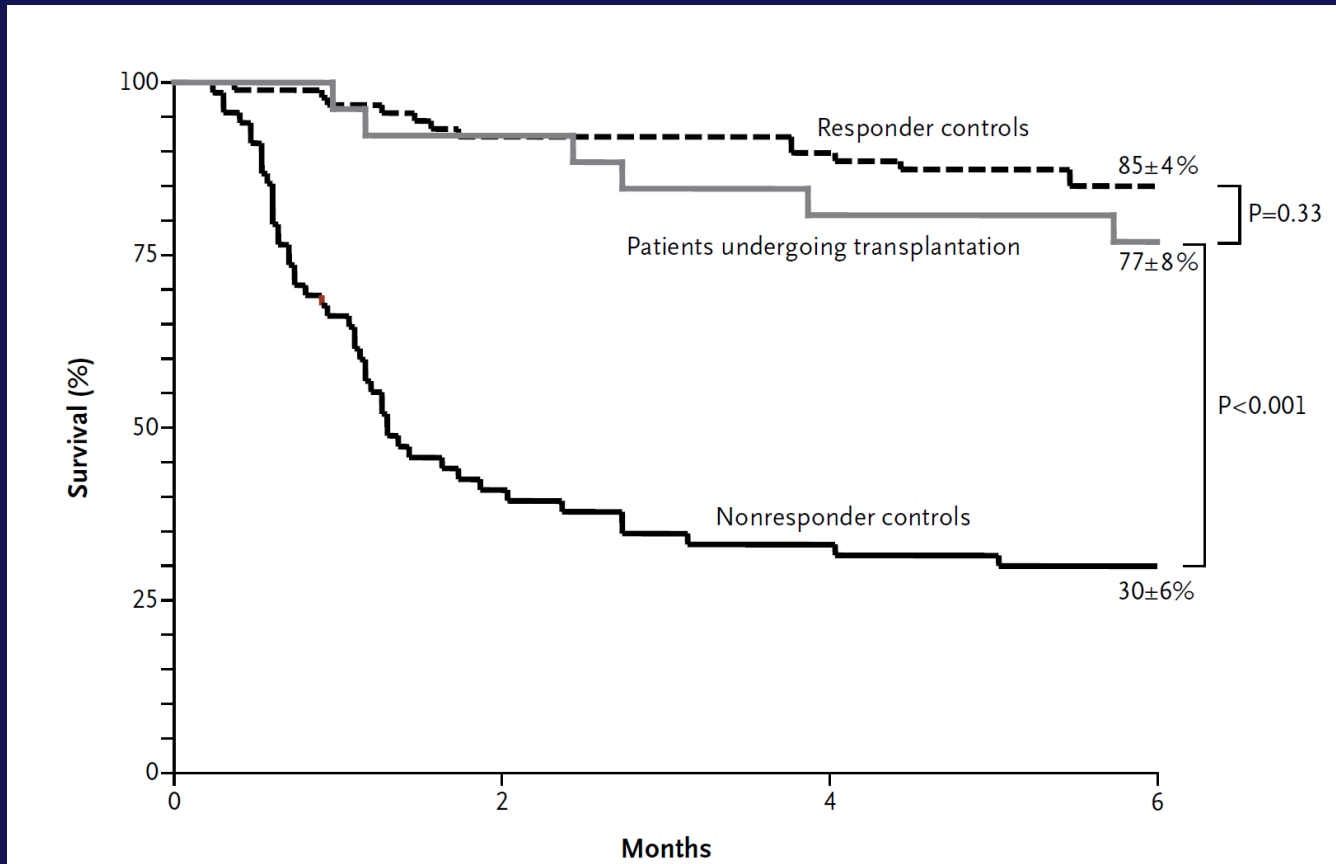
CON

- Small studies
- No medium to longterm outcome
- Allograft damage with alcohol relapse
- Abstinence period ≤ 6 months associated with relapse
- Negative impact organ donation



Early liver transplantation for severe alcoholic hepatitis

Mathurin P. NEJM 2011

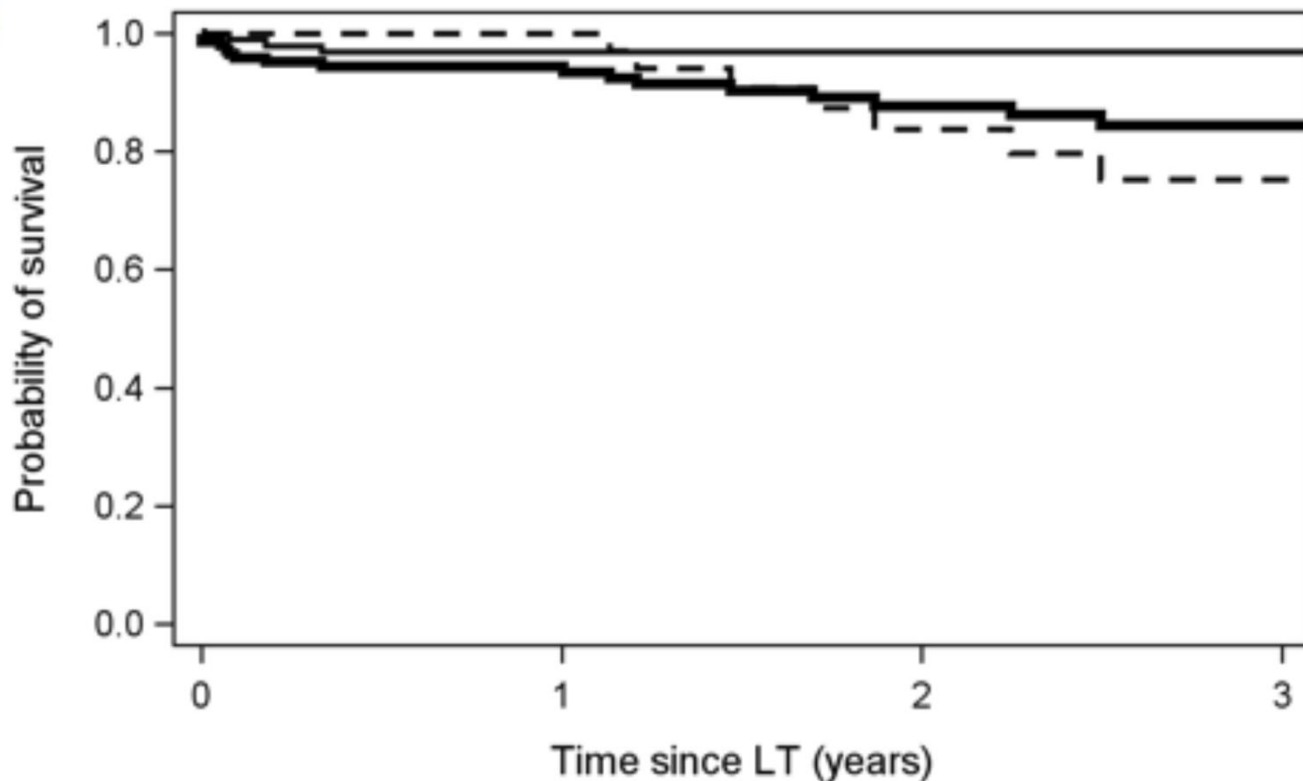




Outcomes of Early liver Transplantation for Patients with Severe Alcoholic Hepatitis

B.P. Lee. Gastroenterology 2018 accepted for publication

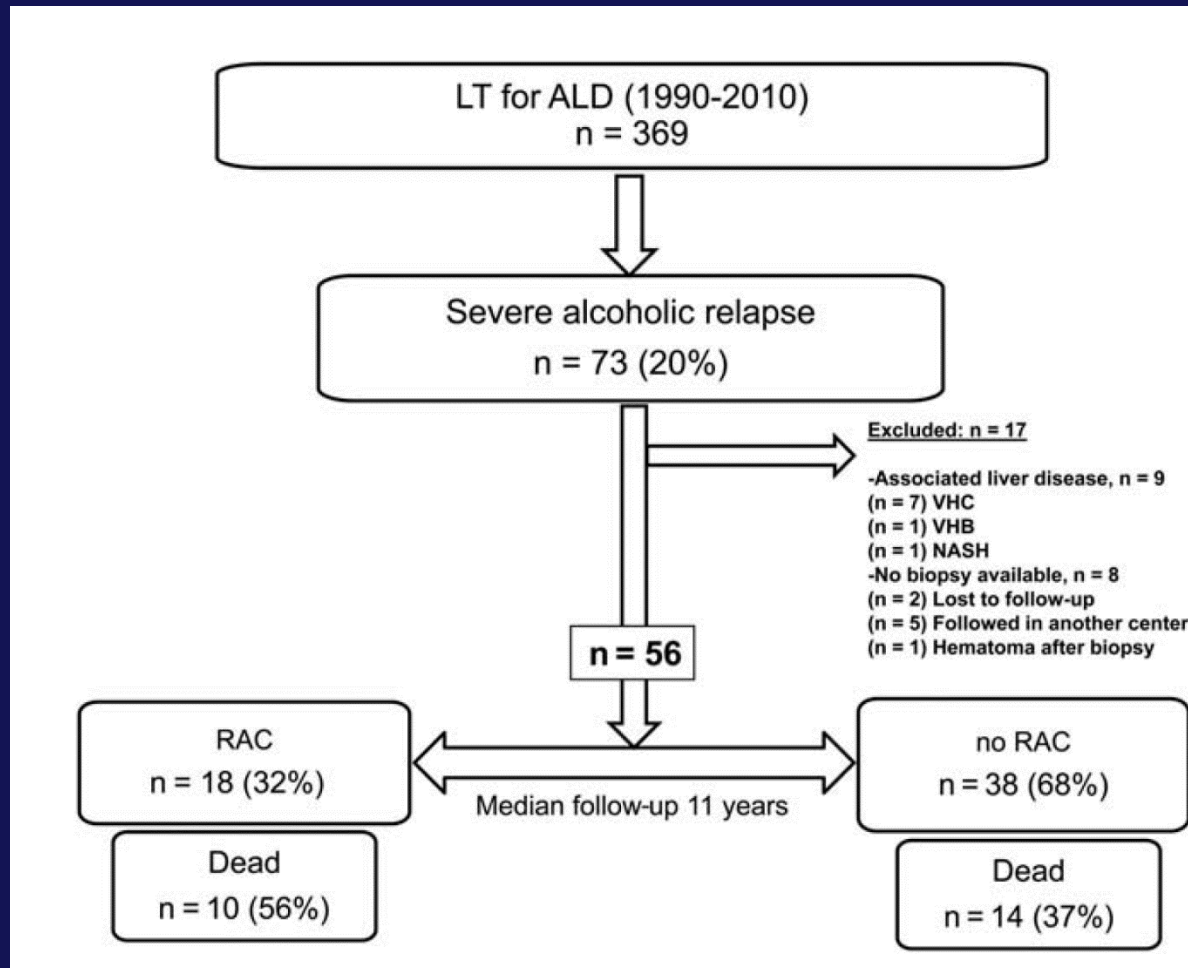
1B



	Alcohol use post-LT			
	Overall	No	Yes	
Overall	147	103	60	37
No	101	67	38	22
Yes	40	36	22	16

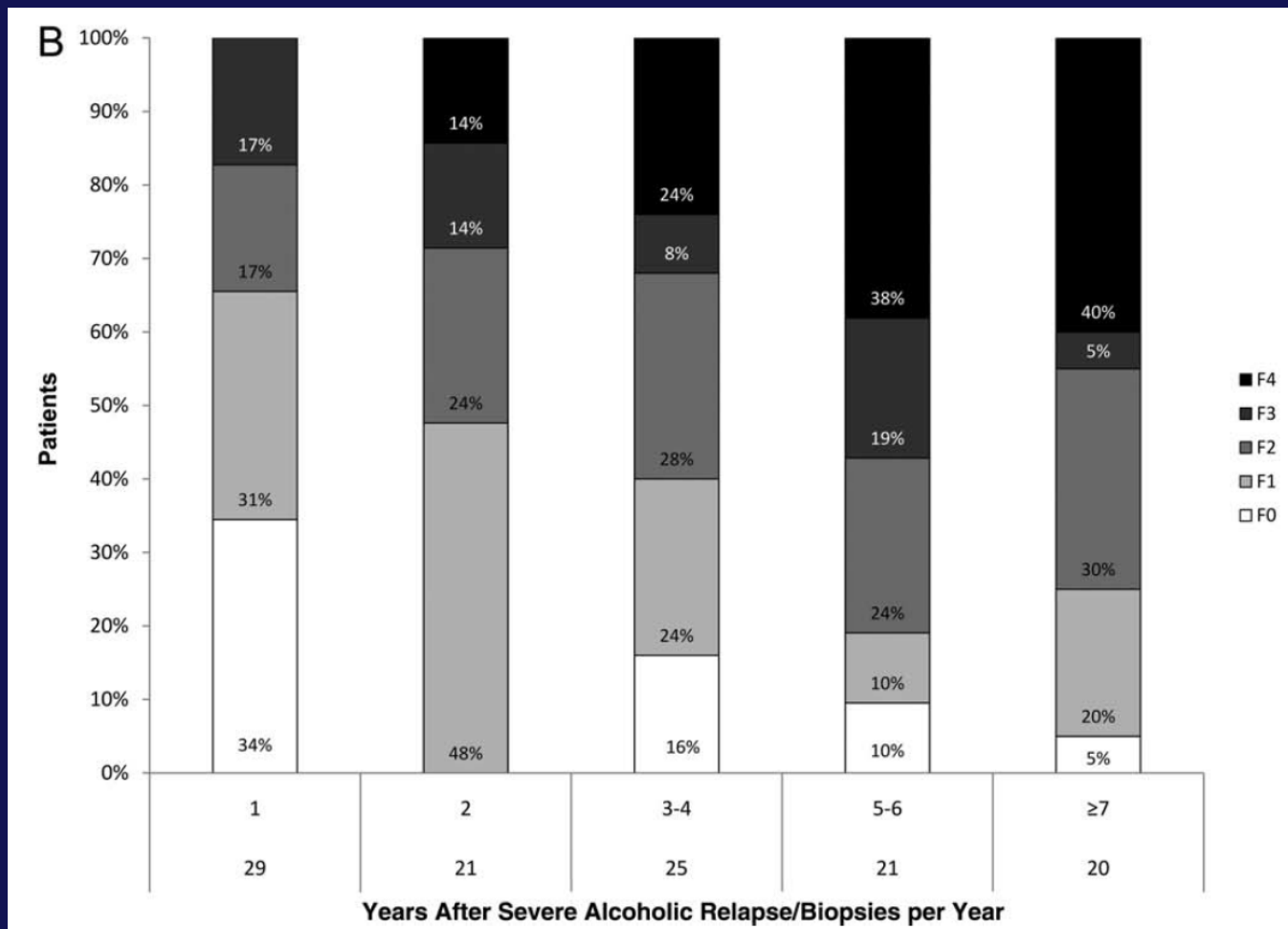


Severe Alcoholic Relapse After Liver Transplantation: What Consequences on the Graft?





Severe Alcoholic Relapse After Liver Transplantation: What Consequences on the Graft?





Take home message

- Alcoholic liver disease major **health burden**
- Important role of the **immune system** in alcoholic liver disease
- Alcoholic hepatitis high **Mortality**
- “**6-month**” rule is questionable



*“Alcohol lost geen problemen op.
Maar ja, melk ook niet!”*

