



“Alcoholic-related Hepatitis”

Ramon Bataller, MD, PhD

Liver Unit

Hospital Clinic

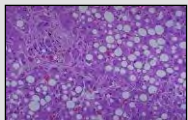
Barcelona

@rabataller

NATURAL HISTORY OF ALD

Normal liver

80-90%



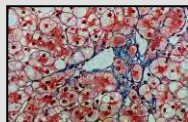
Steatosis

SILENT

EARLY DETECTION

- Primary care centers
- Alcohol addiction centers

20-40%



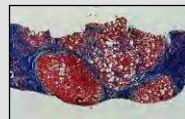
Fibrosis

HOSPITALIZATIONS

- ER
- High cost
- Readmissions

Early Asymptomatic

8-20%



Cirrhosis

JAUNDICE & COMPLICATIONS

Alcoholic Steatohepatitis (ASH)

Alc Hep

20-40%

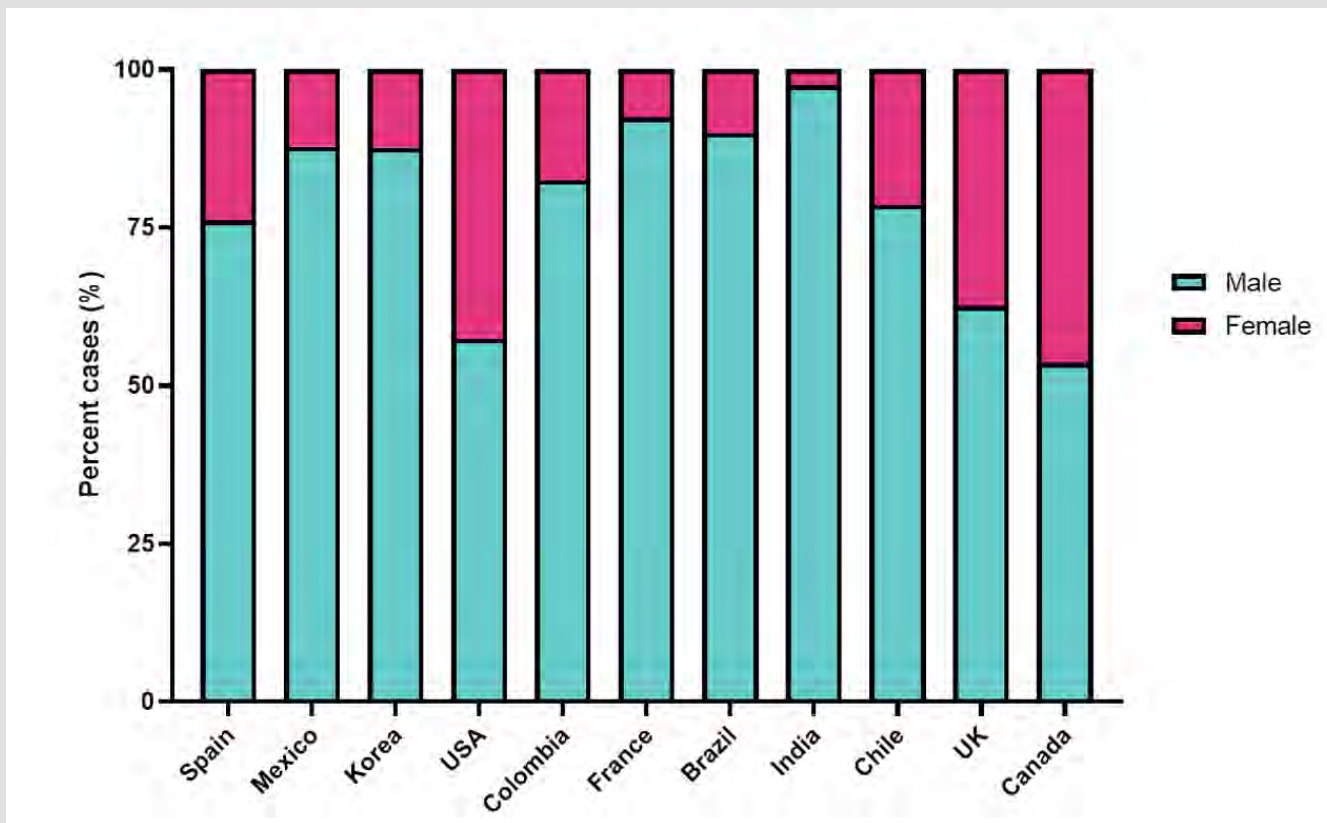


Decompensation (+ infections²)

HCC

3-10%

INCREASING PERCENTAGE OF WOMEN IN THE ANGLOSPHERE



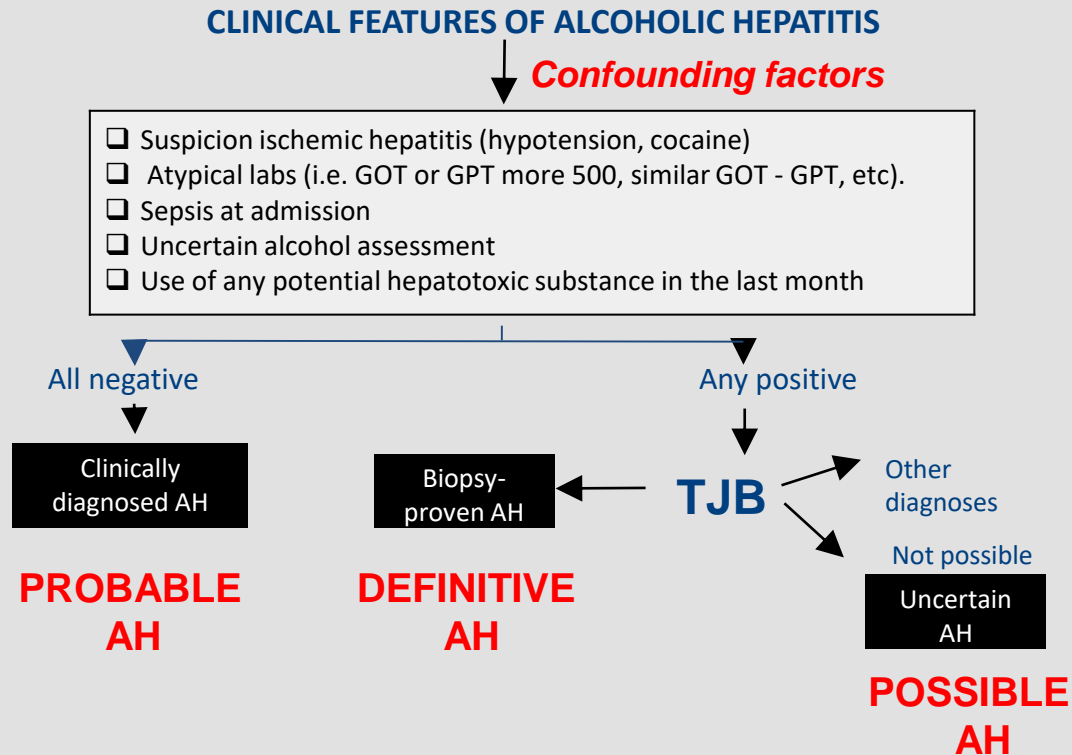
CONTROVERSIES IN ALCOHOLIC HEPATITIS



1. WHEN IS A TRANSJUGULAR LIVER BIOPSY NEEDED ?
2. SHOULD WE STILL USE PREDISOLONE ?
3. CAN WE GIVE ANTICRAVING DRUGS AFTER DISCHARGE ?
4. DOES EARLY LT OFFER A SURVIVAL BENEFIT IN THE LONG-TERM ?

DIAGNOSIS OF AH: NIAAA CRITERIA

Standard Definitions and Common Data Elements for Clinical Trials in Patients With Alcoholic Hepatitis: Recommendation From the NIAAA Alcoholic Hepatitis Consortia

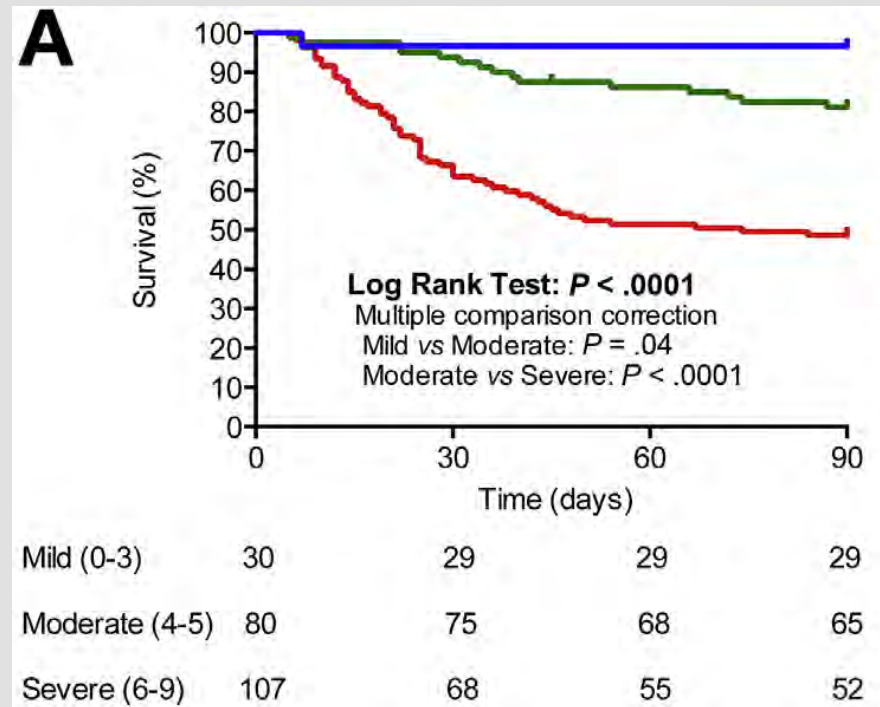


ALCOHOLIC HEPATITIS HISTOLOGICAL SCORE

Table 3. AHHS for Prognostic Stratification of AH

	Points
Stage of fibrosis	
No fibrosis or portal fibrosis	0
Expansive fibrosis	0
Bridging fibrosis or cirrhosis	+3
Bilirubinostasis	
No	0
Hepatocellular only	0
Canalicular or ductular	+1
Canalicular or ductular plus hepatocellular	+2
PMN infiltration	
No/Mild	+2
Severe	0
Megamitochondria	
No megamitochondria	+2
Megamitochondria	0

NOTE. The AHHS categories are as follows: mild, 0–3; intermediate, 4–5; severe, 6–9. Histologic features included in the AHHS were the product of the multivariate logistic regression analysis (Table 2). Weighting of each histologic feature was based on the odds ratio of the updated model (training plus test set samples). See [Supplementary Methods](#) for information on model building.



SPECIFIC THERAPY FOR ALCOHOL-ASSOCIATED HEPATITIS



SHOULD ALL PATIENTS
BE TREATED WITH
PREDNISOLONE ?

CORTICOSTEROID THERAPY IN SEVERE ALCOHOLIC HEPATITIS*

A Double-Blind Drug Trial

HENRIK P. PORTER, M.D., FRANCIS R. SIMON, M.D., CHARLES E. POPE, II, M.D.,
WADE VOLWILER, M.D., AND L. FREDERICK FENSTER, M.D.

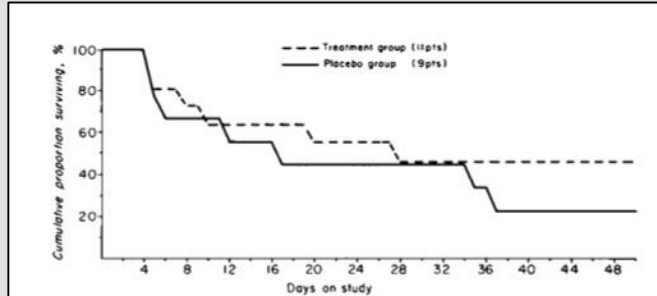
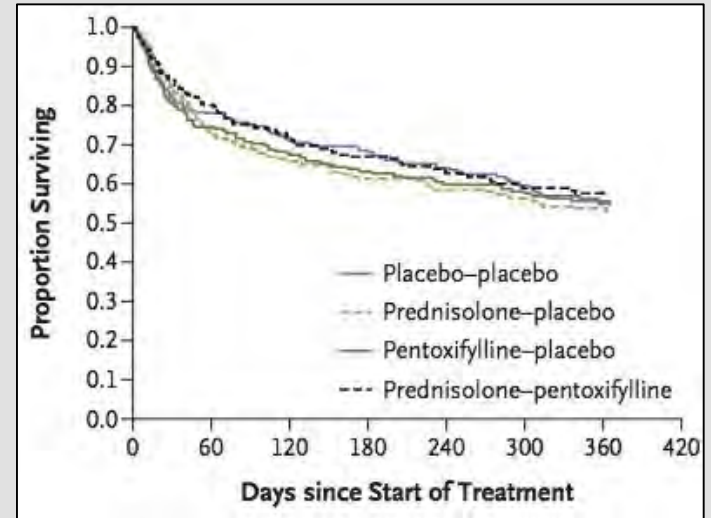


Figure 1. Plot of Life-Table Method of Survival.

1971

Prednisolone or Pentoxifylline for Alcoholic Hepatitis

Mark R. Thursz, M.D., Paul Richardson, M.D., Michael Allison, Ph.D.,
Andrew Austin, M.D., Megan Bowers, M.Sc., Christopher P. Day, M.D., Ph.D.,
Nichola Downs, P.G. Cert., Dermot Gleeson, M.D., Alastair MacGilchrist, M.D.,
Allister Grant, Ph.D., Steven Hood, M.D., Steven Masson, M.A., Anne McCune, M.D.,
Jane Mellor, M.Sc., John O'Grady, M.D., David Patch, M.D., Ian Ratcliffe, M.Sc.,
Paul Roderick, Ph.D., Louise Stanton, M.Sc., Nikhil Vergis, M.B., B.S., Mark Wright, Ph.D.,
Stephen Ryder, D.M., and Ewan H. Forrest, M.D., for the STOPAH Trial*



2015

PREDNISONE OR PREDNISOLONE ?



Ramon Bataller

@rabataller



Yesterday at [#DDW2022](#) they asked me: is better prednisolone than prednisone for Alc Hep?

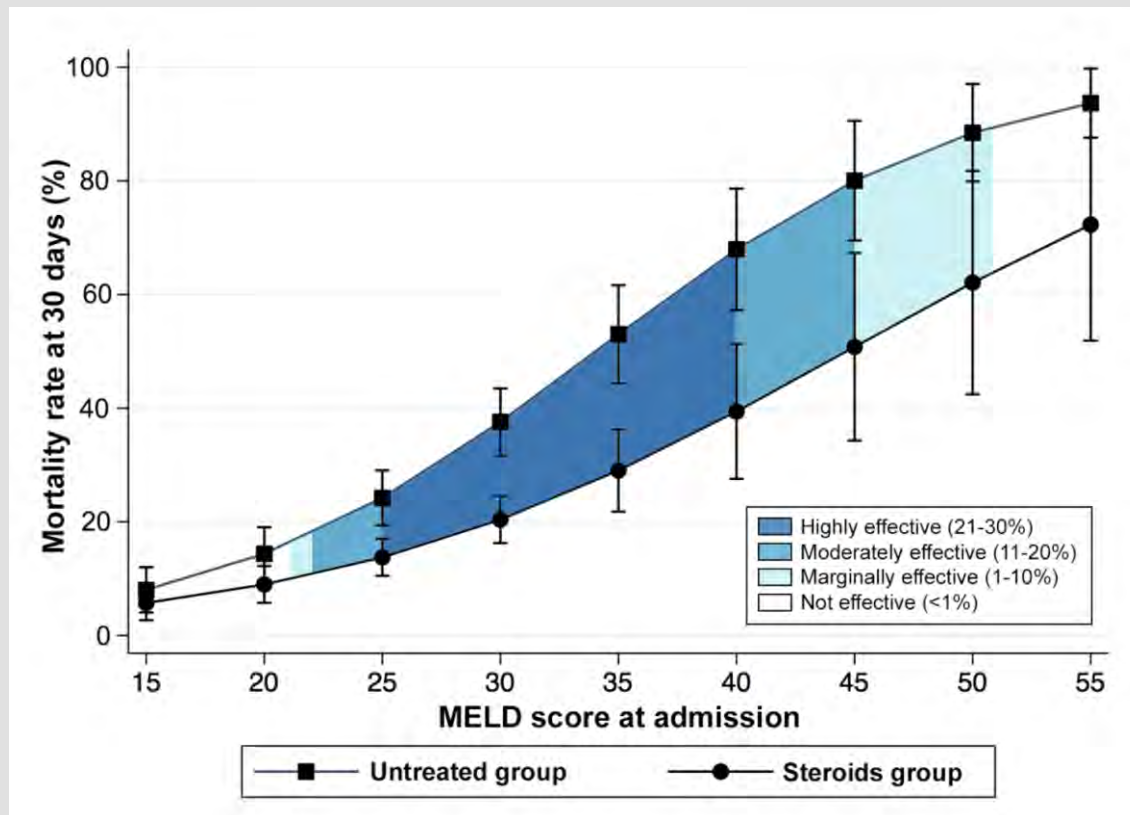
In theory yes, but retrospective studies are inconclusive. We need PROSPECTIVE studies on:

- Type steroid
- Dose & duration
- Tapering

[#LiverTwitter](#)

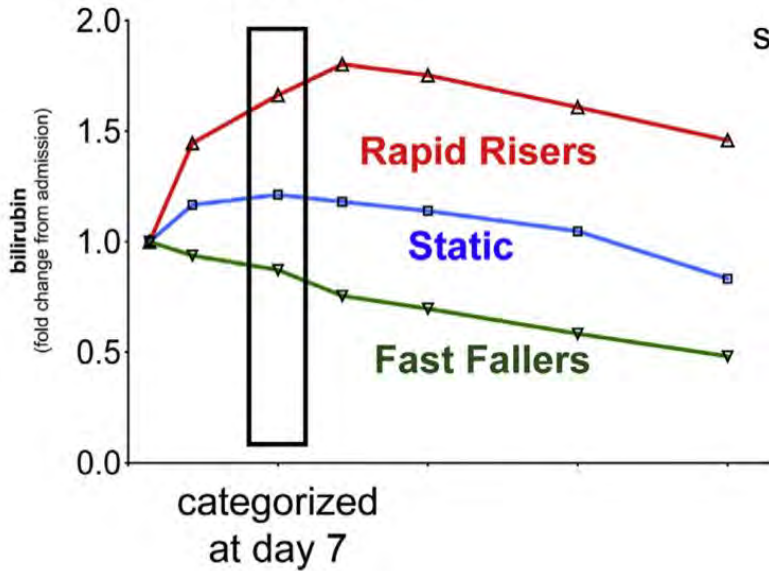
7:28 AM · May 24, 2022 from Pittsburgh, PA · Twitter for iPhone

THERAPEUTIC WINDOW FOR THE USE OF CORTICOSTEROIDS IN AH



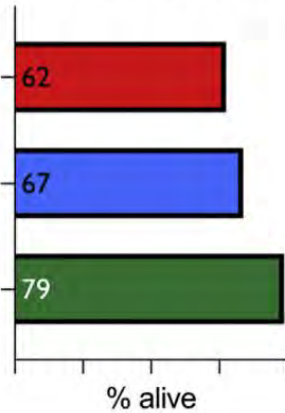
BILIRUBIN TRAJECTORY IN ALC HEP

Trajectories of bilirubin in alcoholic hepatitis

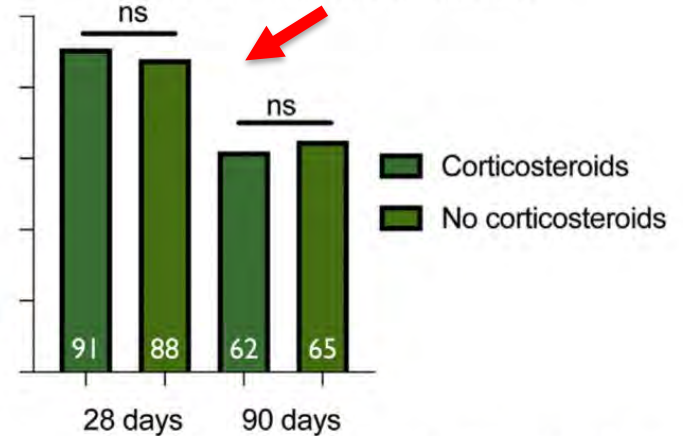


Fast Fallers:

more likely to survive at 90 days



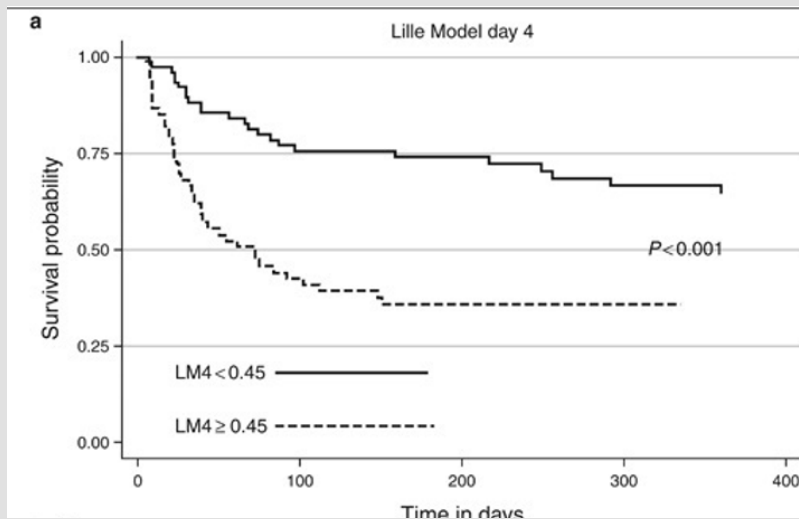
do not benefit from corticosteroids, even in severe disease



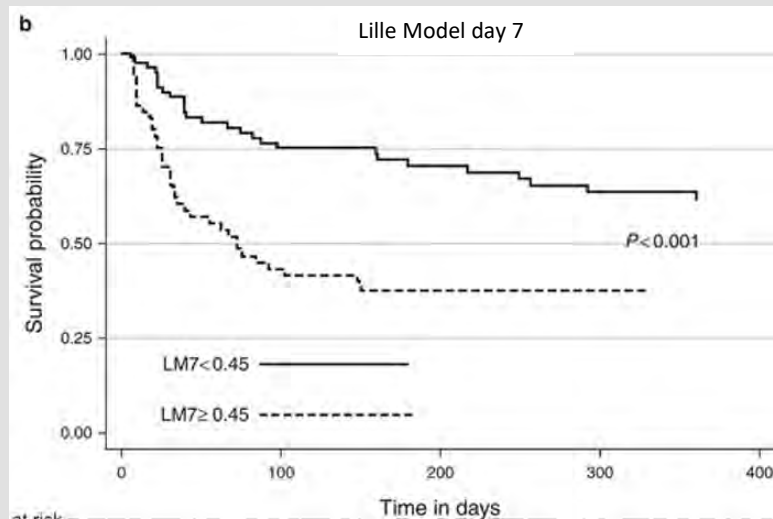
Clinical Gastroenterology and Hepatology

EARLY LILLE SCORE AT 4 DAYS

Day 4



Day 7



SHOULD WE STILL USE PREDNISOLONE ?



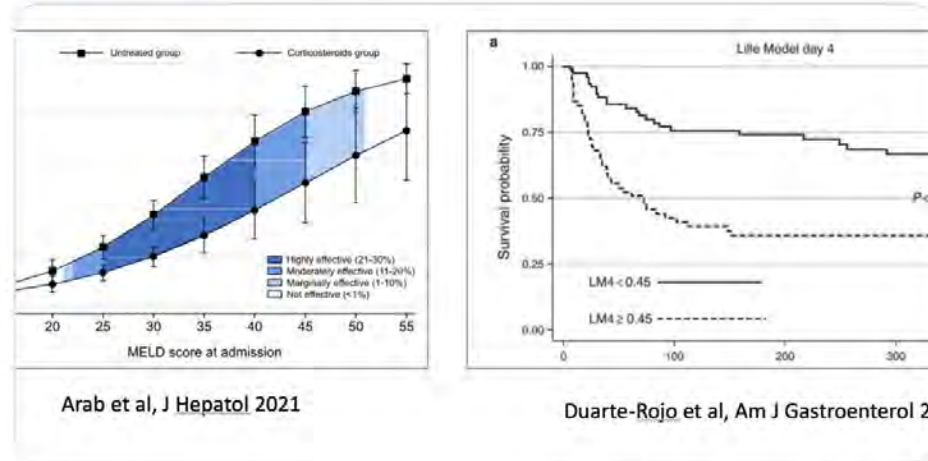
Ramon Bataller

@rabataller

...

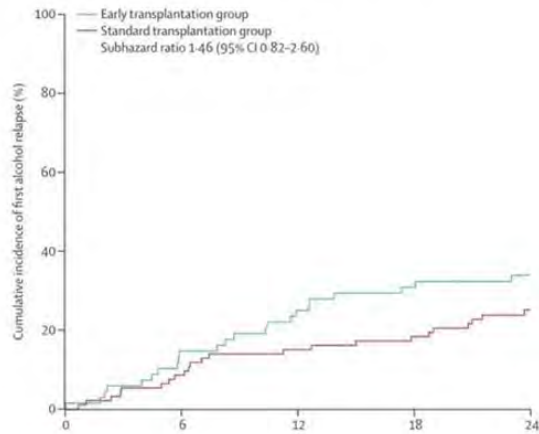
I am often asked the same question: do you still use prednisolone in Alc Hep? My answer is: YES, if the MELD is 21-39, but I apply an early Lille score at 4 days so I stop it if Bil does not quickly decrease. See below the evidence supporting this approach.

#Livertwitter

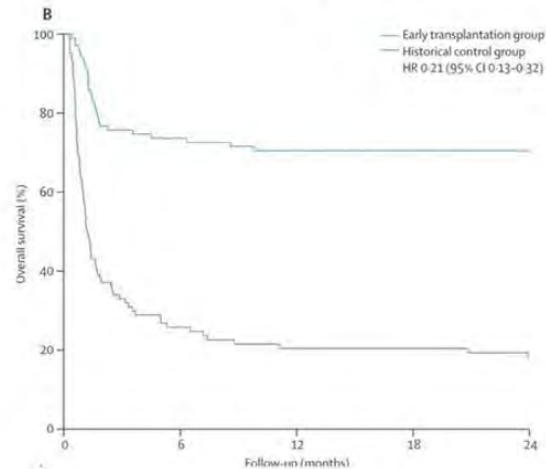


IS EARLY TRANSPLANT EFFECTIVE ?

ALCOHOL RELAPSE



SURVIVAL



Early liver transplantation for severe alcohol-related hepatitis not responding to medical treatment: a prospective controlled study



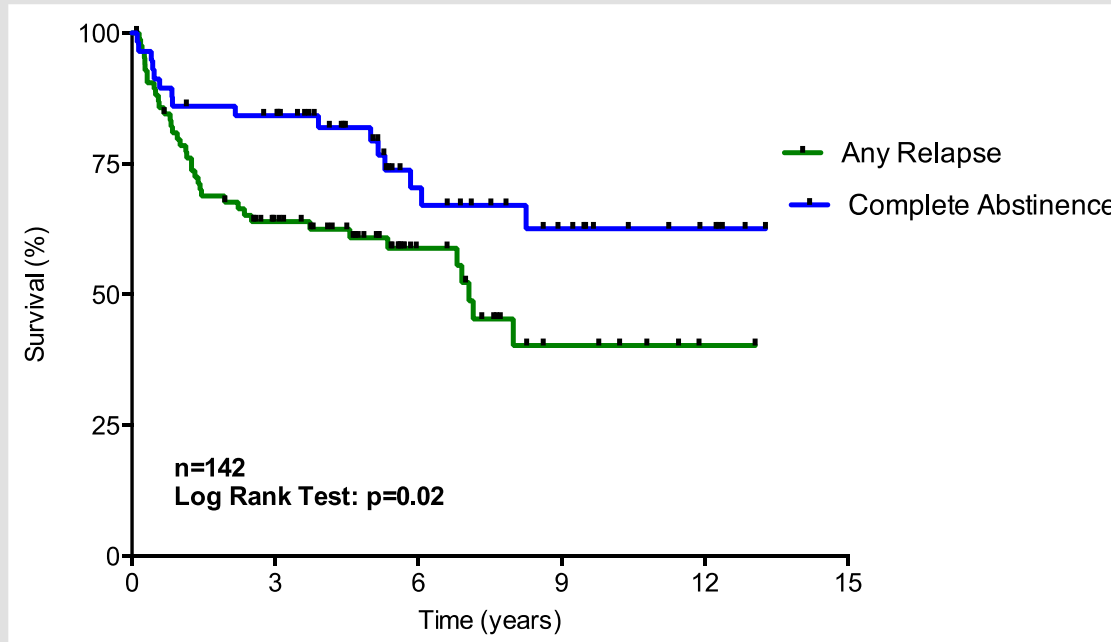
Alexandre Louvet, Julien Labreuche, Christophe Moreno, Claire Vanlemmens, Romain Moirand, Cyrille Féray, Jérôme Dumortier, Georges-Philippe Pageaux, Christophe Bureau, Faiza Chermak, Christophe Duvoux, Dominique Thabut, Vincent Leroy, Nicolas Carbonell, Benjamin Rolland, Ephrem Salame, Rodolphe Anty, Jérôme Gournay, Jean Delvaide, Christine Silvain, Valerio Lucidi, Guillaume Lassailly, Sébastien Dharancy, Eric Nguyen-Khac, Didier Samuel, Alain Duhamel, Philippe Mathurin, on behalf of the QuickTrans trial study group

DOES ABSTINENCE IMPROVE
SURVIVAL ?

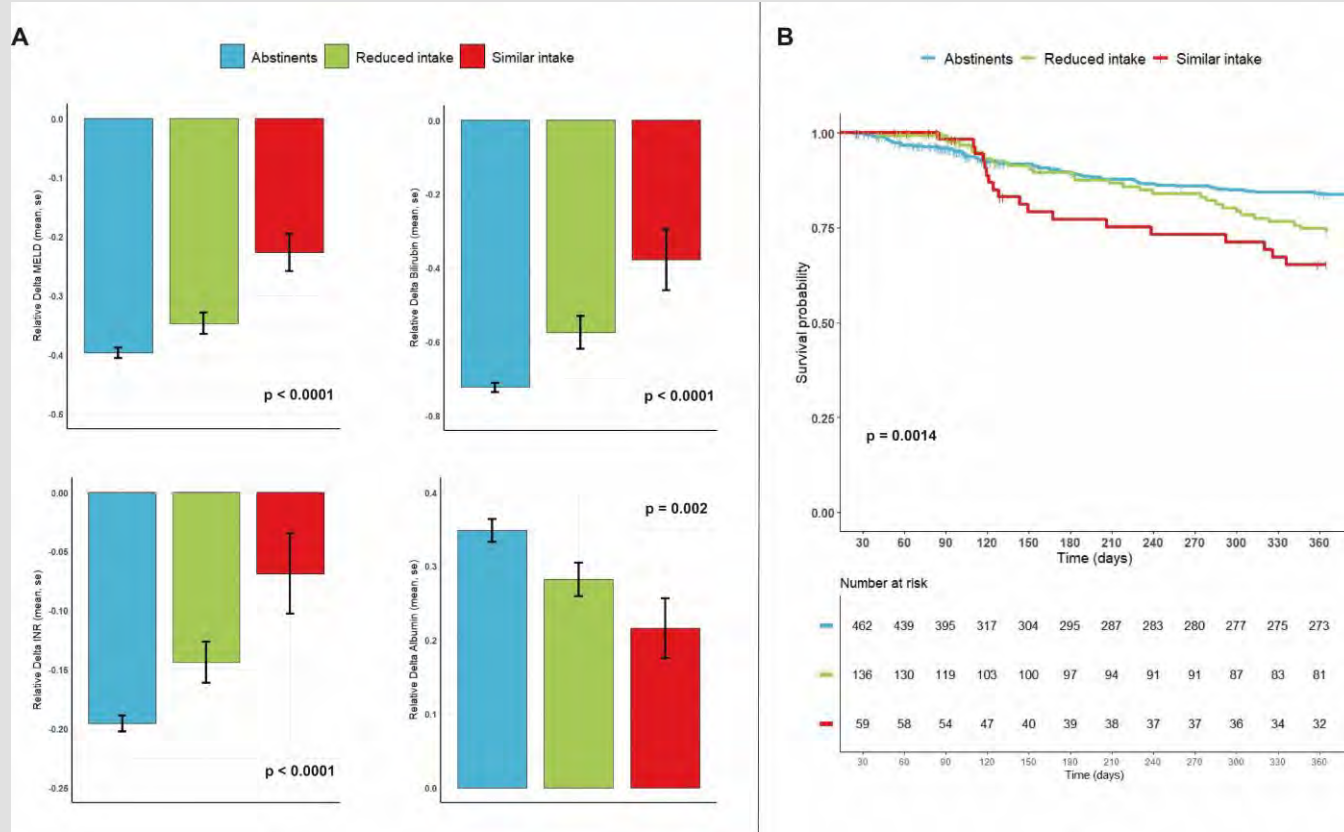


HOW CAN WE PROMOTE
MAINTAINED
ABSTINENCE ?

IMPACT OF ALCOHOLISM ON THE LONG-TERM PROGNOSIS IN AH

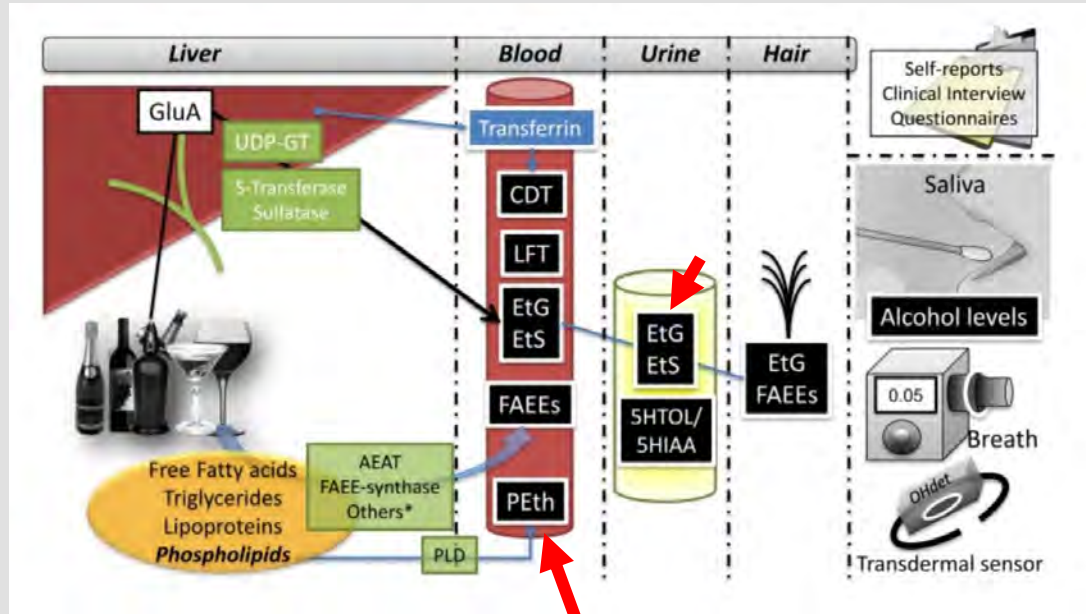


IMPACT OF RELAPSE ON AH OUTCOMES



BIOMARKERS OF ALCOHOL USE

GGT +
AST > ALT



- Negative (<20 ng/mL)
- Significant (20–199 ng/mL)
- Heavy (>200 ng/mL)

TREATING AUD IN A PATIENT-CENTERED MANNER

GENETIC-ENVIRONMENTAL FACTORS

Family history
Genetic risk
Other addictions

SOCIOECONOMIC FACTORS

Isolation
Stigma
Transportation
Insurance

COMMON ASSOCIATED CONDITIONS

PTSD
Sexual abuse
Depression
Anxiety
Sleep
Pain

MULTIDISCIPLINARY A/D CLINIC



- *Specialized nurse*
- *Addiction therapist*
- *Social worker*
- *Financial counselor*
- *Hepatologist*

DOES THERAPY WORK IN ALD PATIENTS ?



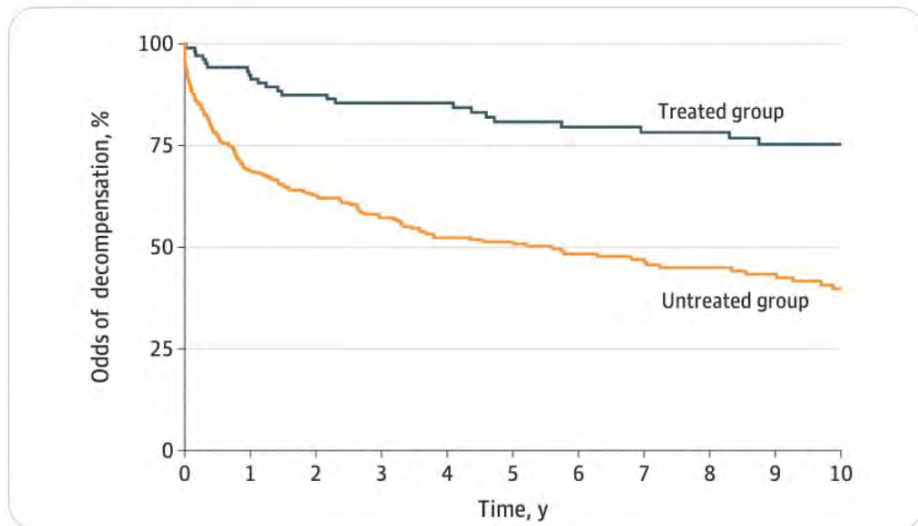
Ramon Bataller @rabataller · May 27



This impressive study by Jay Luther @alcliverdoc shows that treating ALCOHOL USE DISORDER prevents liver-related decompensation. Drugs that show promise:

- ◆ Naltrexone
- ◆ Gabapentin
- ◆ Topiramate
- ◆ Baclofen

bit.ly/3IPiuDN #livertwitter



ROLE OF PHARMACOTHERAPY IN AUD IN LIVER PATIENTS

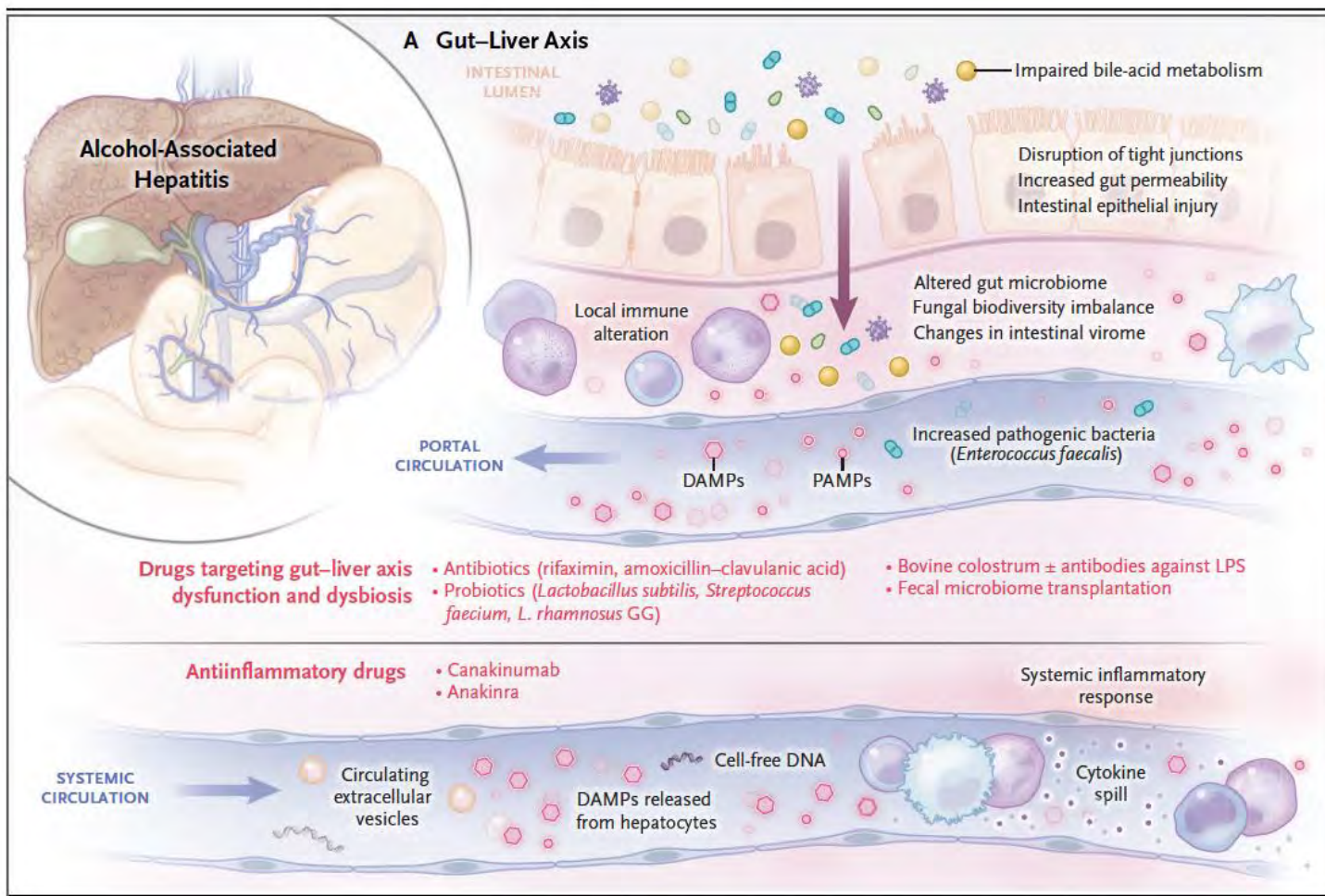
FDA approved for AUD

- **Disulfiram**: unsafe if underlying ALD. Risk of liver failure.
- **Acamprosate**: observational studies suggest is safe and efficacious.
- **Naltrexone**: no data on ALD. Caution if opioid use.
- **Baclofen**: a positive placebo-control trial in cirrhosis.

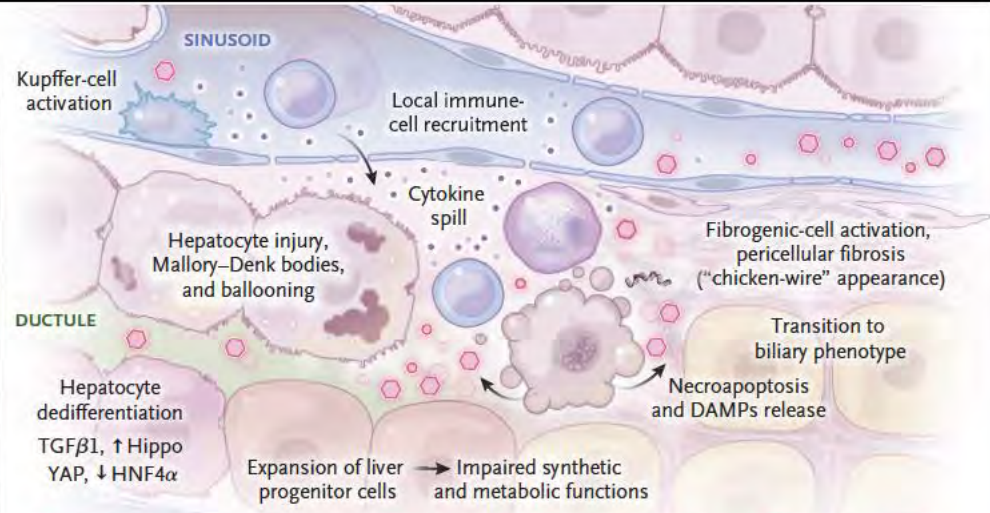
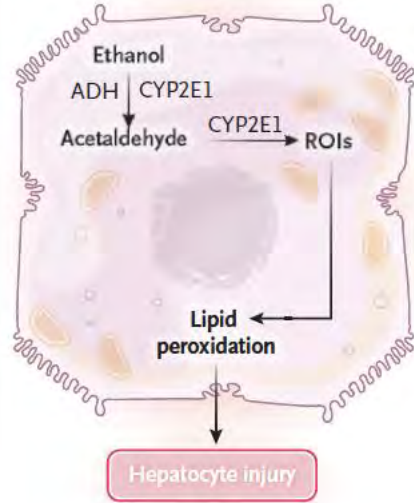
WHAT ARE THE MOST
PROMISING NEW APPROACHES
TO TREAT ALC HEP ?



*Promoting hepatocyte
differentiation and targeting the
microbiome as targets for therapy
in alcohol-associated hepatitis*



B Hepatocyte Dysfunction



Antioxidants

- *N*-acetylcysteine ± enteral nutrition
- Metadoxine
- n-3 Fatty acids

Drugs targeting liver regeneration

- Interleukin-22
- G-CSF
- G-CSF plus *N*-acetylcysteine

Drugs targeting apoptosis

- Selonsertib
- Emricasan

C Development of Liver Decompensation

Portal hypertension

- Ascites
- Hepatic encephalopathy
- Variceal bleeding
- Hepatorenal syndrome

Liver failure

- Jaundice
- Coagulation disorders
- Synthetic function failure
- Malnutrition

Immune paralysis

- SIRS
- Sepsis
- Infections

Multiorgan failure

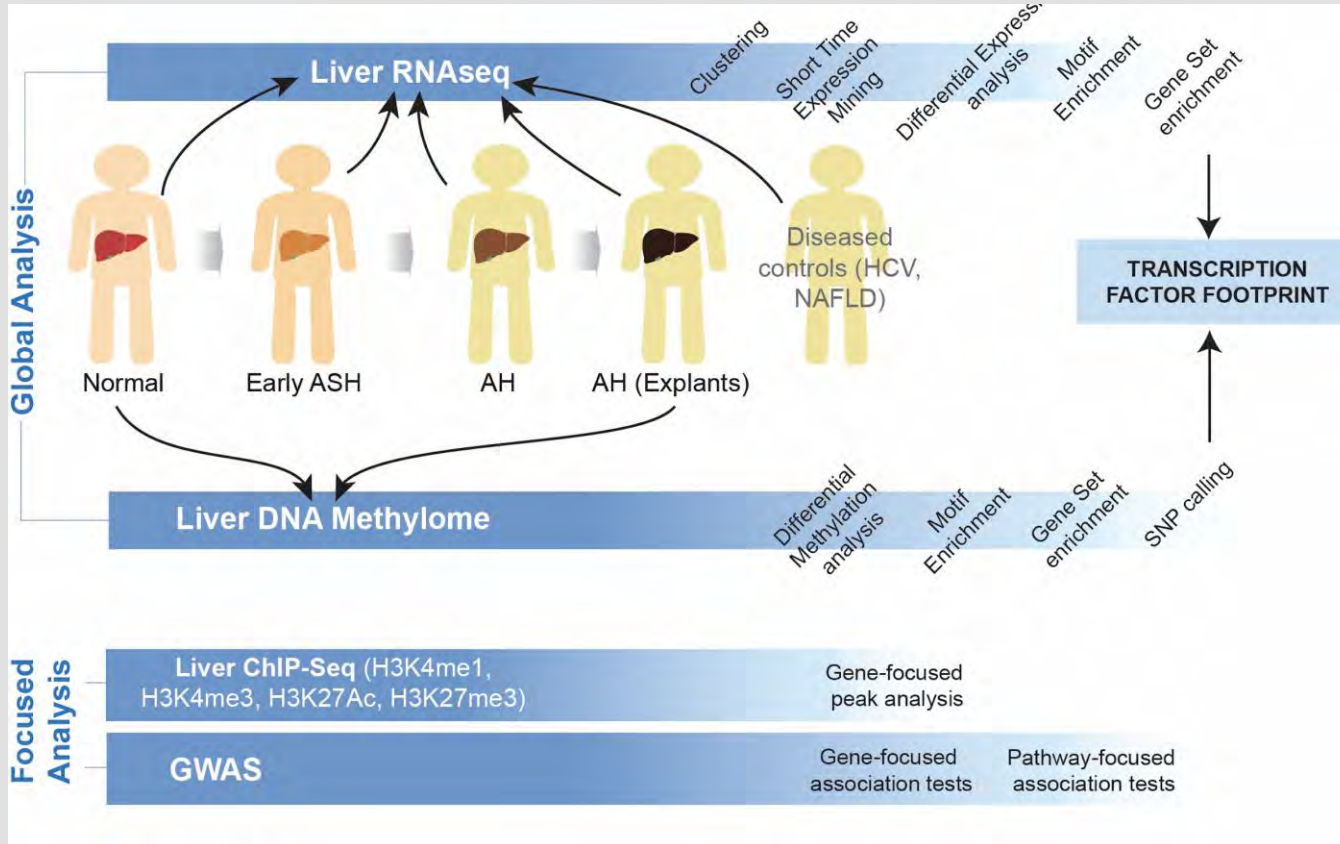
- Acute-on-chronic liver failure
- Death

WHAT ARE THE MOST
PROMISING NEW APPROACHES
TO TREAT ALC HEP ?

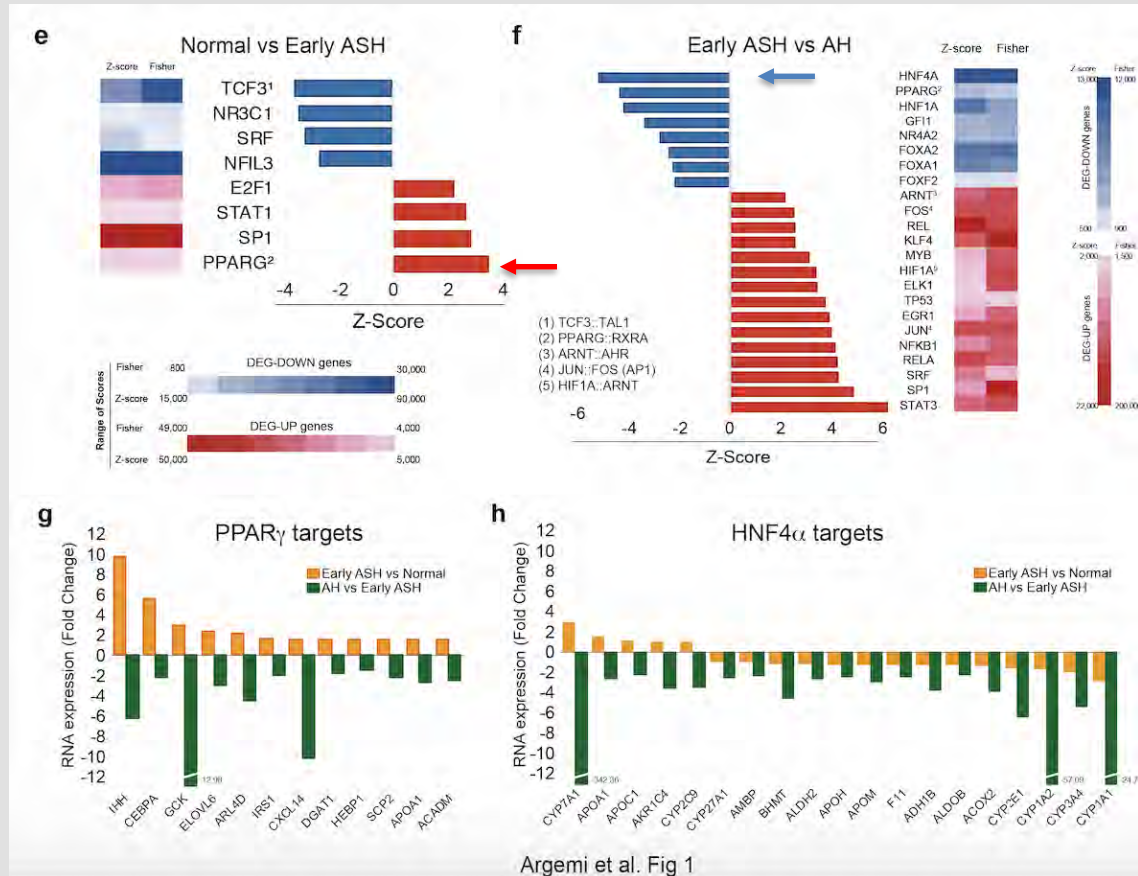


*Promoting hepatocyte
differentiation and targeting the
microbiome as targets for therapy
in alcohol-associated hepatitis*

DEFECTIVE HNF4 α FUNCTION IN ALCOHOL-ASSOCIATED HEPATITIS



DEFECTIVE HNF4 α FUNCTION IN ALCOHOL-ASSOCIATED HEPATITIS



TRANSLATION STUDY: EARLY vs ADVANCED ALD

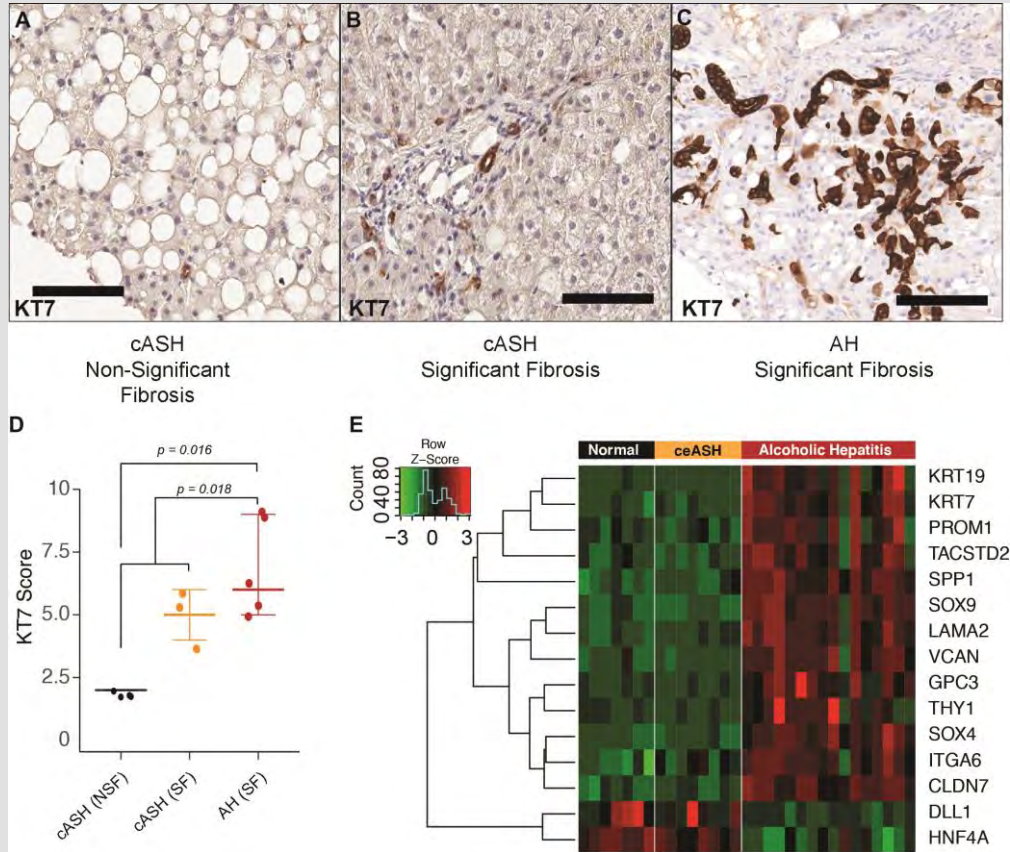
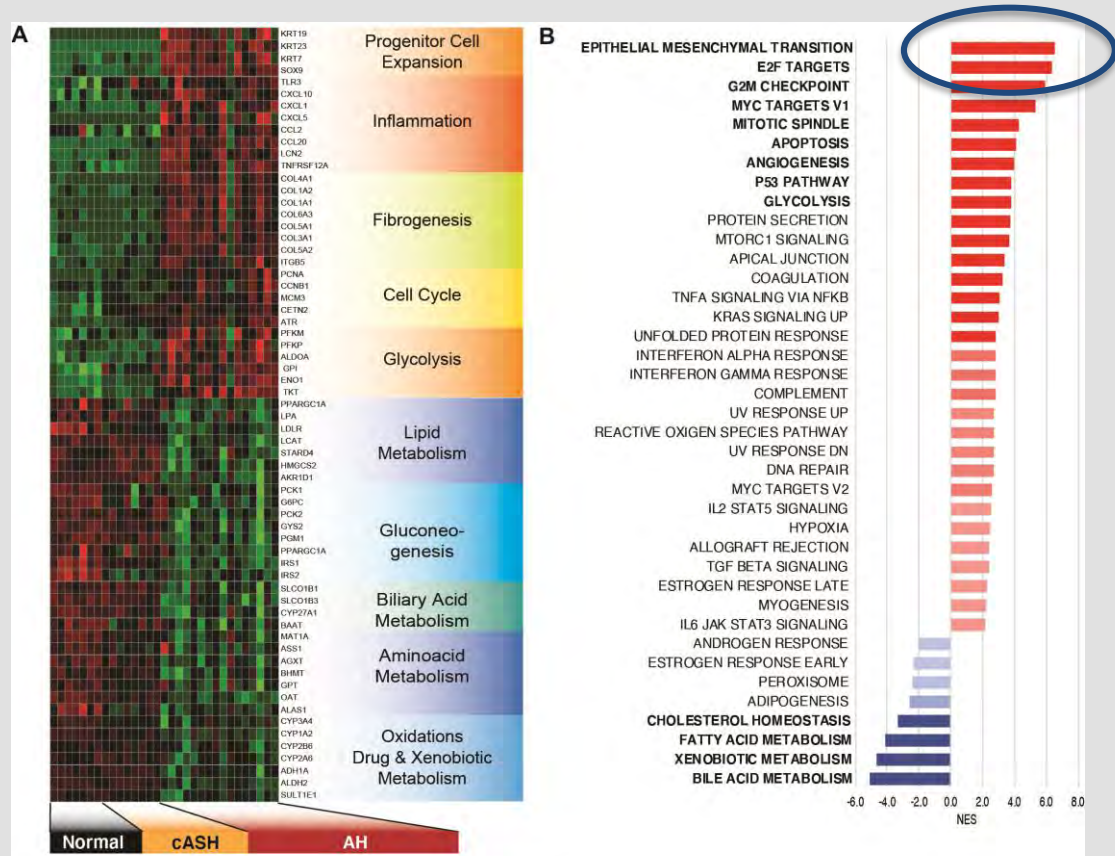


Figure 2

TRANSLATION STUDY: EARLY vs ADVANCED ALD



WHAT ARE THE MOST
PROMISING NEW APPROACHES
TO TREAT ALC HEP ?



*Promoting hepatocyte
differentiation and **targeting the
microbiome** as targets for therapy
in alcohol-associated hepatitis*

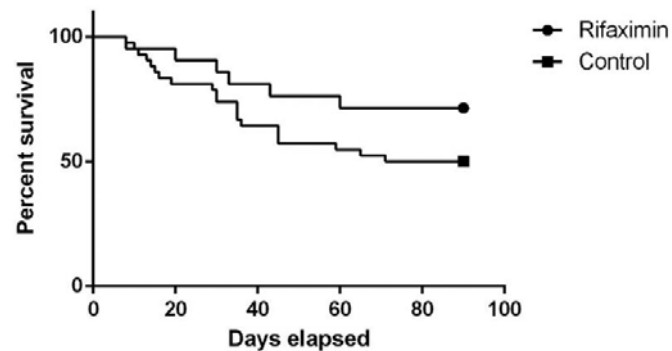
ORIGINAL ARTICLE



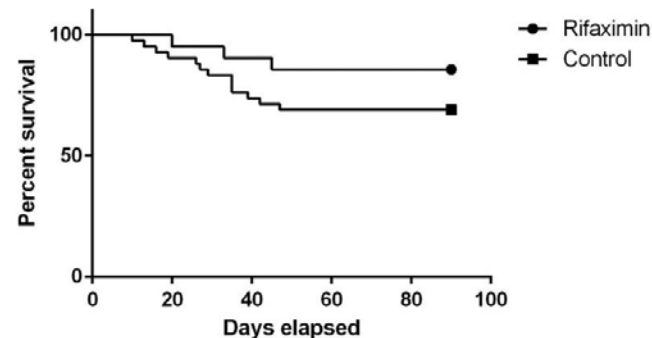
Effect of rifaximin on infections, acute-on-chronic liver failure and mortality in alcoholic hepatitis: A pilot study (RIFA-AH)

César Jiménez¹ | Meritxell Ventura-Cots^{1,2,3} | Margarita Sala^{2,4} |
Margarida Calafat^{2,4} | Montserrat Garcia-Retortillo⁵ | Isabel Cirera⁵ |
Nuria Cañete⁵ | Germán Soriano^{2,6} | María Poca^{2,6} | Macarena Simón-Talero^{1,2} |
José Altamirano⁷ | Michael Lucey⁸ | Guadalupe Garcia-Tsao⁹ | Robert S. Brown Jr¹⁰ |
Robert F. Schwabe¹¹ | Elizabeth C. Verna¹² | Bernd Schnabl¹³ |
Francisco Bosques-Padilla¹⁴ | Philippe Mathurin¹⁵ | Juan Caballería^{2,16} |
Alexandre Louvet¹⁵ | Debbie L. Shawcross¹⁷ | Juan G. Abraldes¹⁸ |
Joan Genescà^{1,2} | Ramon Bataller³ | Víctor Vargas^{1,2}

Infection-free survival of two groups



Survival proportions: Survival of Two groups



FECAL TRANSPLANTATION AND ALD



Ramon Bataller @rabataller · Nov 14, 2021

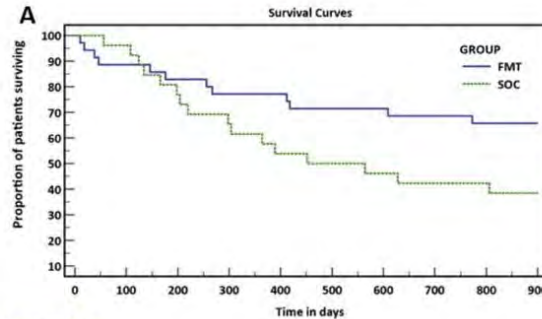
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Promising results of FECAL MICROBIOTA TRANSPLANTATION in alcoholic hepatitis presented by Cyriac Philips in the Presidential Plenary today.

I am excited that it also decreases alcohol relapse.

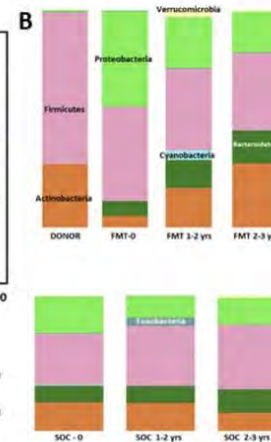
[#livertwitter](#) [@AASLDTweets](#) [#LiverMtg21](#)

THREE YEAR FOLLOW-UP OF ALCOHOL-RELATED HEPATITIS PATIENTS UNDERGOING HEALTHY DONOR FECAL TRANSPLANT: ANALYSIS OF CLINICAL OUTCOMES, RELAPSE, GUT MICROBIOTA AND COMPARISONS WITH STANDARD CARE



Number at risk

Time (days)	0	100	200	300	400	500	600	700	800	900
Group: FMT	35	31	29	27	27	25	25	24	23	0
Group: SOC	26	25	20	17	14	13	12	11	11	0



FECAL TRANSPLANTATION AND ALD

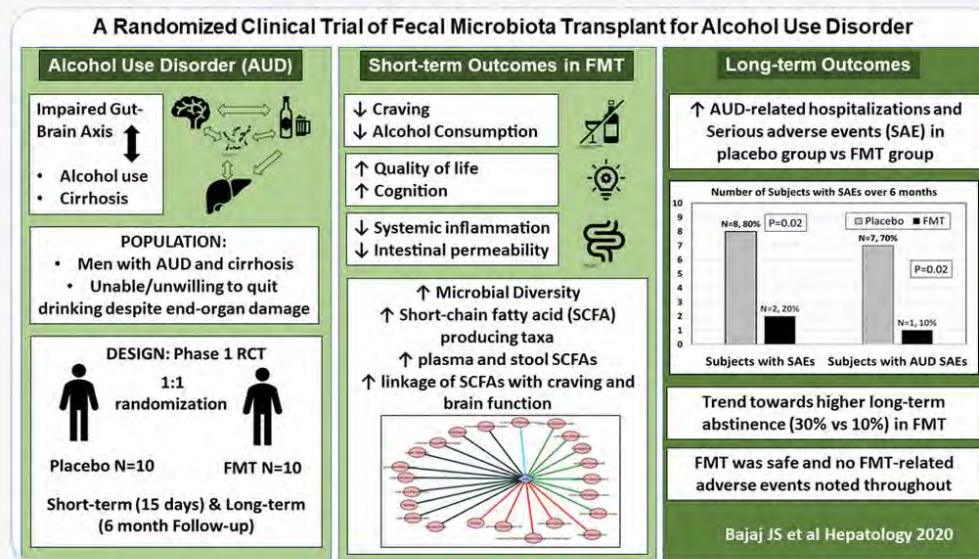


Ramon Bataller @rabataller · Aug 5, 2020

Promising results of a phase 1 study showing that transplanting the gut microbiome may improve alcohol use disorder.

Another piece of evidence indicated that the gut plays an important role in addictions.

Congrats [@jasmohanbajaj](#) and cols.



FECAL TRANSPLANTATION AND ALD

nature communications

Article

<https://doi.org/10.1038/s41467-022-34054-6>

Reduced alcohol preference and intake after fecal transplant in patients with alcohol use disorder is transmissible to germ-free mice

Received: 6 January 2022

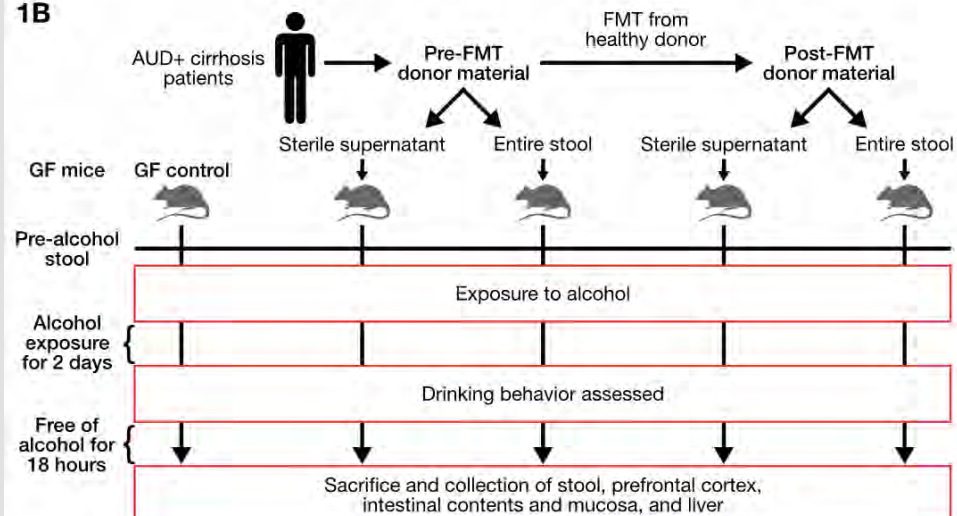
Accepted: 7 October 2022

Published online: 19 October 2022

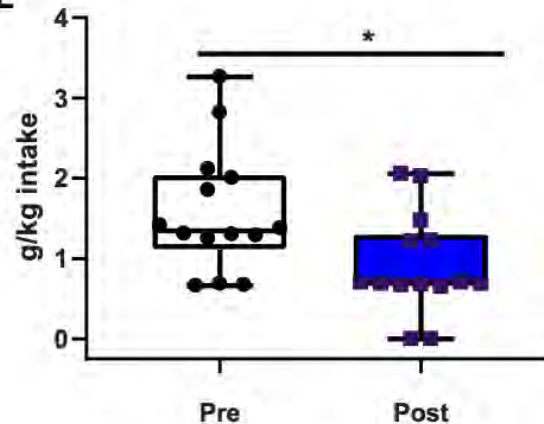
Check for updates

Jennifer T. Wolstenholme¹, Justin M. Saunders², Maren Smith¹, Jason D. Kang³, Phillip B. Hylemon², Javier González-Maeso², Andrew Fagan⁴, Derrick Zhao³, Masoumeh Sikaroodi⁵, Jeremy Herzog⁵, Amirhossein Shamsaddini⁵, Marcela Peña-Rodríguez¹, Lianying Su², Yun-Ling Tai³, Jing Zheng², Po-Cheng Cheng³, R. Balfour Sartor^{6,8}, Patrick M. Gillevet⁵, Huiping Zhou³ & Jasmohan S. Bajaj⁴

1B



E



TAKE HOME MESSAGES

- **Most patients with ALD are detected at late stages: early detection campaigns are needed.**
- **Corticosteroids improve 30-day survival in patients with MELD 21-39. Early Lille Score at 4 day could be applied.**
- **Early LT in highly selected patients has good outcomes.**
- **There is a clear need to do clinical trials to treat alcohol use disorder in patients with ALD.**
- **Targeting hepatocyte differentiation and the microbiome are promising therapeutic targets for AH.**

