API Delhi State Chapter
Annual Conference

"Alcoholic Liver Disease : What is New "

Institute of Liver & Biliary Sciences
A Deemed Liver University

Dr. S K Sarin
sksarin@ilbs.in

World Health Organization

New Delhi, India
www.ilbs.in

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Disclosure

I have no conflict of Interest or disclosures to make

Case

30y, M, chronic alcoholic -10y, 150-200g/day

- Last Intake - 30 days ago

h/o

- Jaundice x 45 days
- Distension abdomen x 30 d
- Low grade fever x 20 d
- Auyrvedic drugs X 10 d

- No- h/o altered sensorium, ↓ u.o., vomiting of blood, melena

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O/E

HR : 110 bpm

BP : !20/50

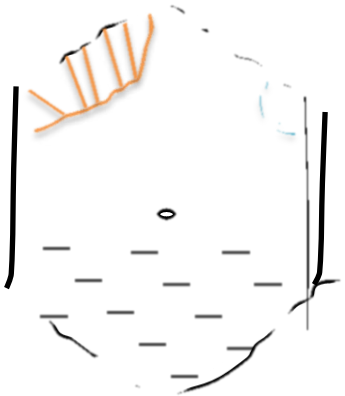
P+/I++/Ed+

Asterexis +

Bilateral parotids +

Spider Nevi ++

Liver- 5cm
Tender, firm,
smooth surface
Sharp margins



Spleen-
just palpable

Visible veins+
FF+
HE gr II +

Bil 16.5,
SGOT/SGPT 270/130

Diagnosis

Diagnosis

Severe Alcoholic Hepatitis

Definition of AH

- **AH :**
  - Bilirubin > 3 mg/dl *(Severe >5mg/dl)*
  - AST > ALT x 1.5times (<400 IU/ml)
  - *INR > 1.5*
  - *Neutrophilia*

Exclude other causes, Viral, etc.

Severity needs to be assessed

Singhal A AJG 2018

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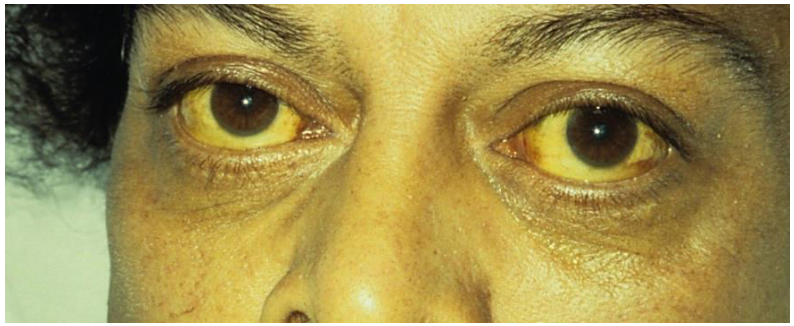
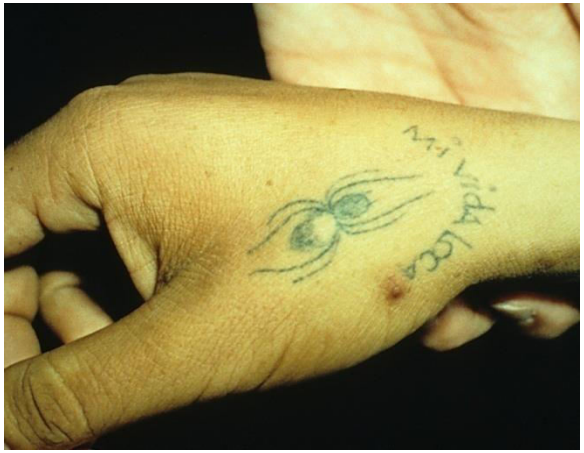
Diagnosis of Alcoholic Hepatitis

- History
  - Heavy alcohol (> 100 g/d), addiction
  - Loss of appetite, pain abdomen
  - Yellow urine, swelling feet
  - Darkening of skin



- Physical Exam
  - **Jaundice**
  - Fever, Red spiders on body
  - Painful liver enlargement
  - Fluid in abdomen, feet



- Laboratory Tests
  - AST > ALT; AST <300 (usually)
  - Prothrombin Time ↑ (normal – 12 sec.)
  - TLC >11,000; Neutrophils > 6,000

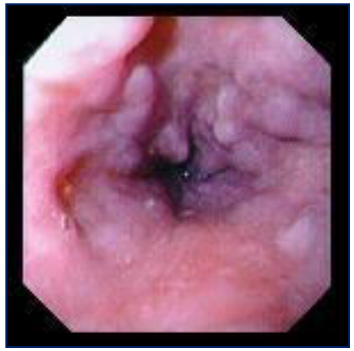
- Course – 30-50% mortality in 3 months

Labs

	Day 0
Hemoglobin	9.7
TLC	11.5
DLC	N65
Platelet count	188
PT/INR	1.92
Bilirubin [T/D]	43.2/30
AST	374
ALT	123
S.Alk Phosphatase	64/53
T. Protein/Alb	7.5/2.7
B. Urea	26
S. Creatinine	0.48
Na+/K+	135/3.3
S. Uric acid	3.2
Procalcitonin	>0.5<2.0
S. TNF-alpha	22
Blood c/s	NG
Urine C/S	NG
Chest X-Ray	NAD

	Day 0
CTP	11
MELD/MELDNa	28/30
DF	93

HVPG- 15



Grade 2 varices

- HBsAg. Anti HCV- negative
- IgM HAV/ IgM HEV – *weak +ve*

USG- CLD- FF

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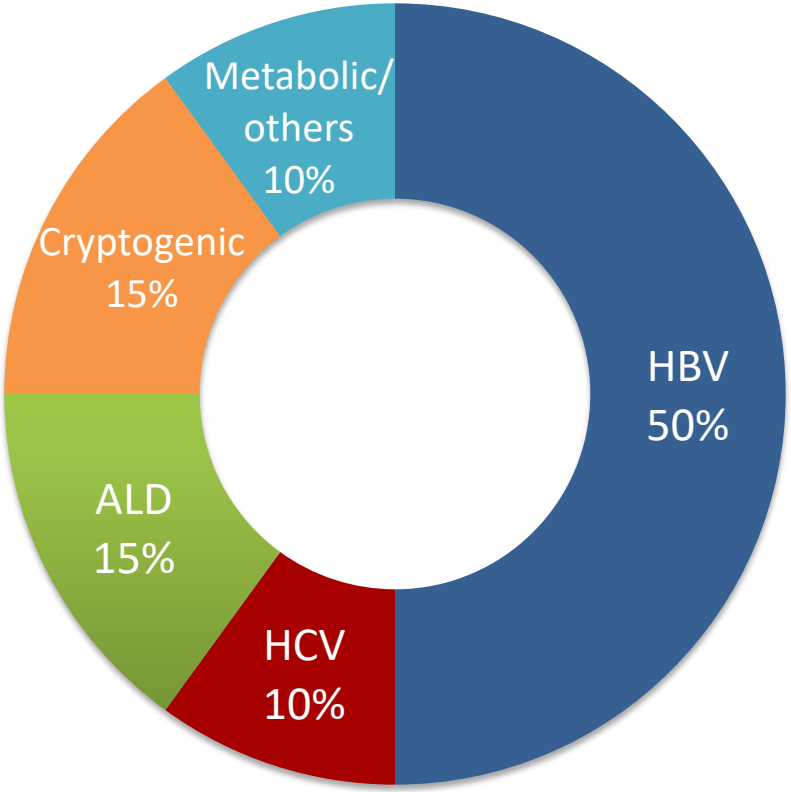
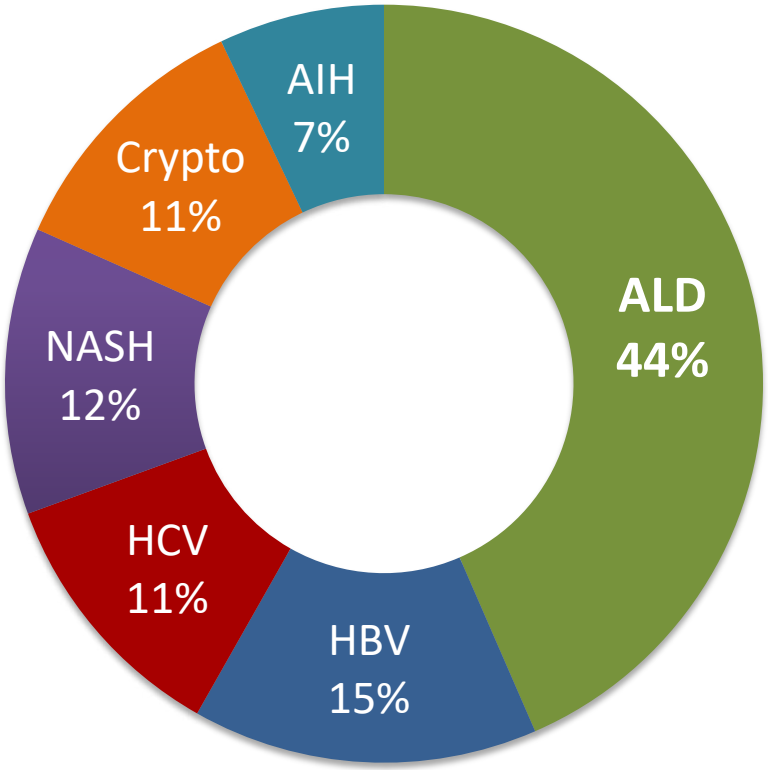
Differential Diagnosis

- Drug-induced liver injury
- Viral hepatitis (A,E,B, C, Delta)
- Autoimmune
- Bile duct obstruction/cholangitis
- HCC
- Sepsis

Profile of Cirrhosis in India



1980/90s

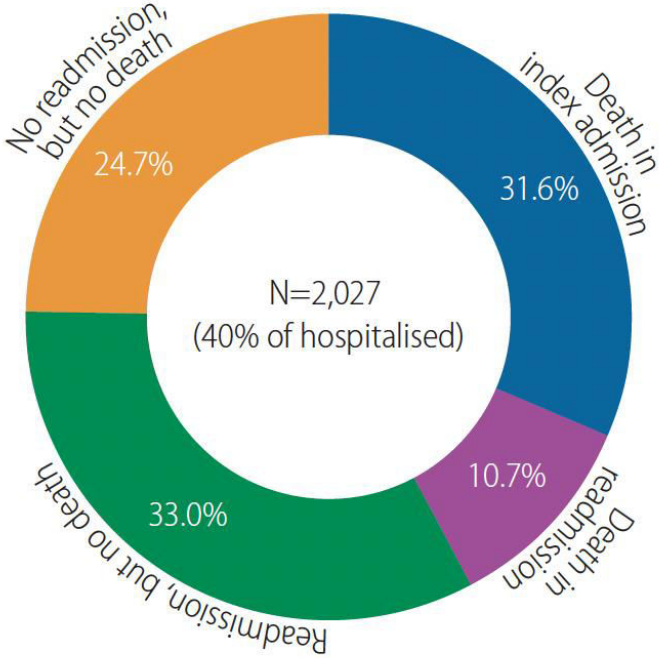


2009-2015 (n=7,092)

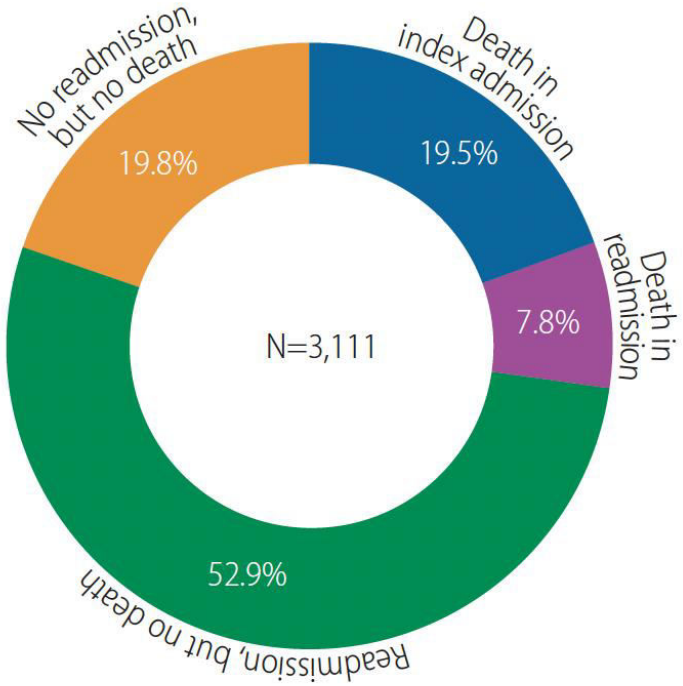
1 Year Mortality in Alcohol and Non-alcohol Cirrhosis

One-year outcomes of cirrhosis patients requiring hospitalization (n=5,138)

Alcohol associated cirrhosis



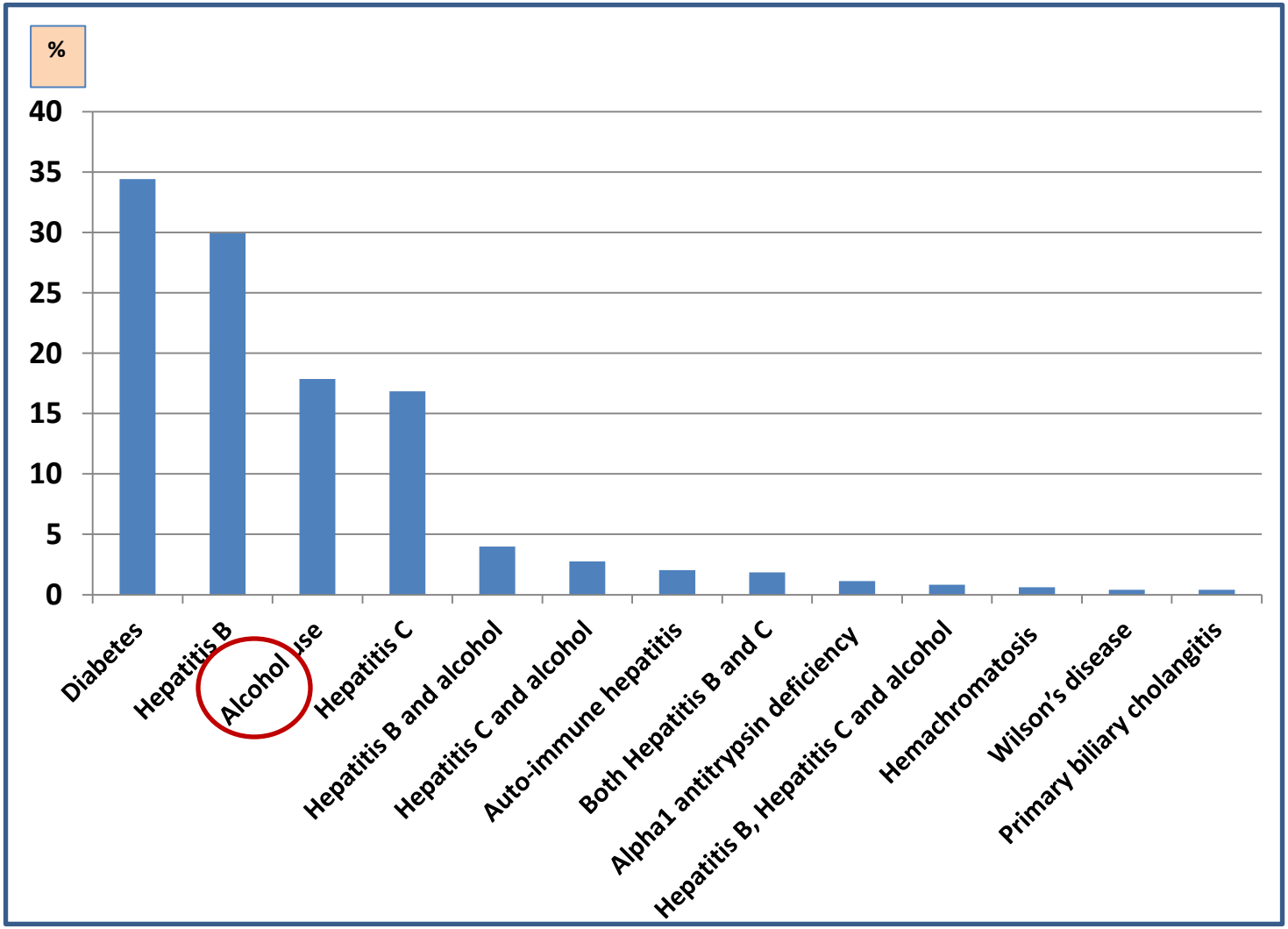
Non-alcohol associated cirrhosis



- Younger age, males
- Higher CTP, MELD
- Higher mortality in index admission, readmission

Jain et al, Clinical and Molecular Hepatology 2021;27:175-185

Etiological factors for HCC in India with underlying cirrhosis (n=979): WHO CC



Received: 10 March 2018 | Revised: 24 August 2018 | Accepted: 25 August 2018

DOI: 10.1111/liv.13958

ORIGINAL ARTICLE

WILEY Liver INTERNATIONAL

Positive familial history for metabolic traits predisposes to early and more severe alcoholic cirrhosis: A cross-sectional study

Ajeet Singh Bhadoria[1] | Chandan Kumar Kedarisetty[2] | Chhagan Bihari[3] | Guresh Kumar[1] | Ankur Jindal[2] | Ankit Bhardwaj[1] | Varsha Shasthry[4] | Jaya Benjamin[4] | Manoj Kumar Sharma[2] | Shiv Kumar Sarin[2]

(74 g/d, IQR 24-96 vs 144, IQR 100-148). Patients with both family and personal history of metabolic traits had a higher risk by 3.3 times (95% CI 2.2-4.8) of an early age at diagnosis, 13.2 times (95% CI 8.7-20.1) of progression to cirrhosis with lesser amount of alcohol consumption and 4.6 times (95% CI 3.1-6.9) with lesser duration of alcohol consumption.

So…

- Alcohol is the No.1 liver insult requiring admission

New Terms

- Alcohol Associated Liver Disease (US)
- Alcohol Related Liver Disease (UK)
- Alcohol Use Disorder

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Management of Severe Alcoholic Hepatitis (SAH)!

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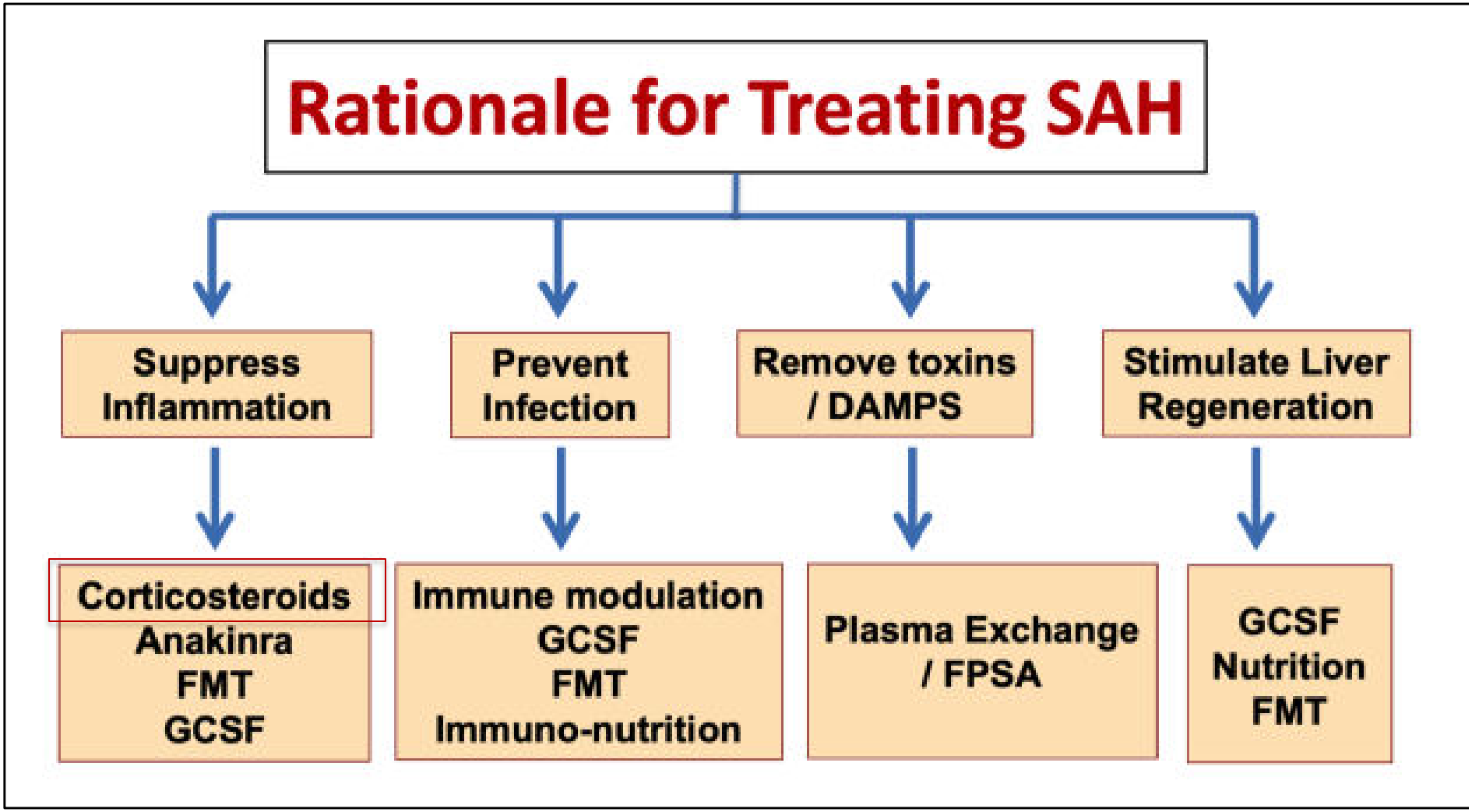
In Emergency Room

- If admitting
  - No CECT, radio-contrast agents
  - Aminoglycosides
  - Paracetamol, NSAIDS
  - B1, Prevent withdrawal
- If not admitting
  - Treat
  - Baclofen 10 mg TDS, to prevent recidivism



Sarin and Sharma CMH 2020

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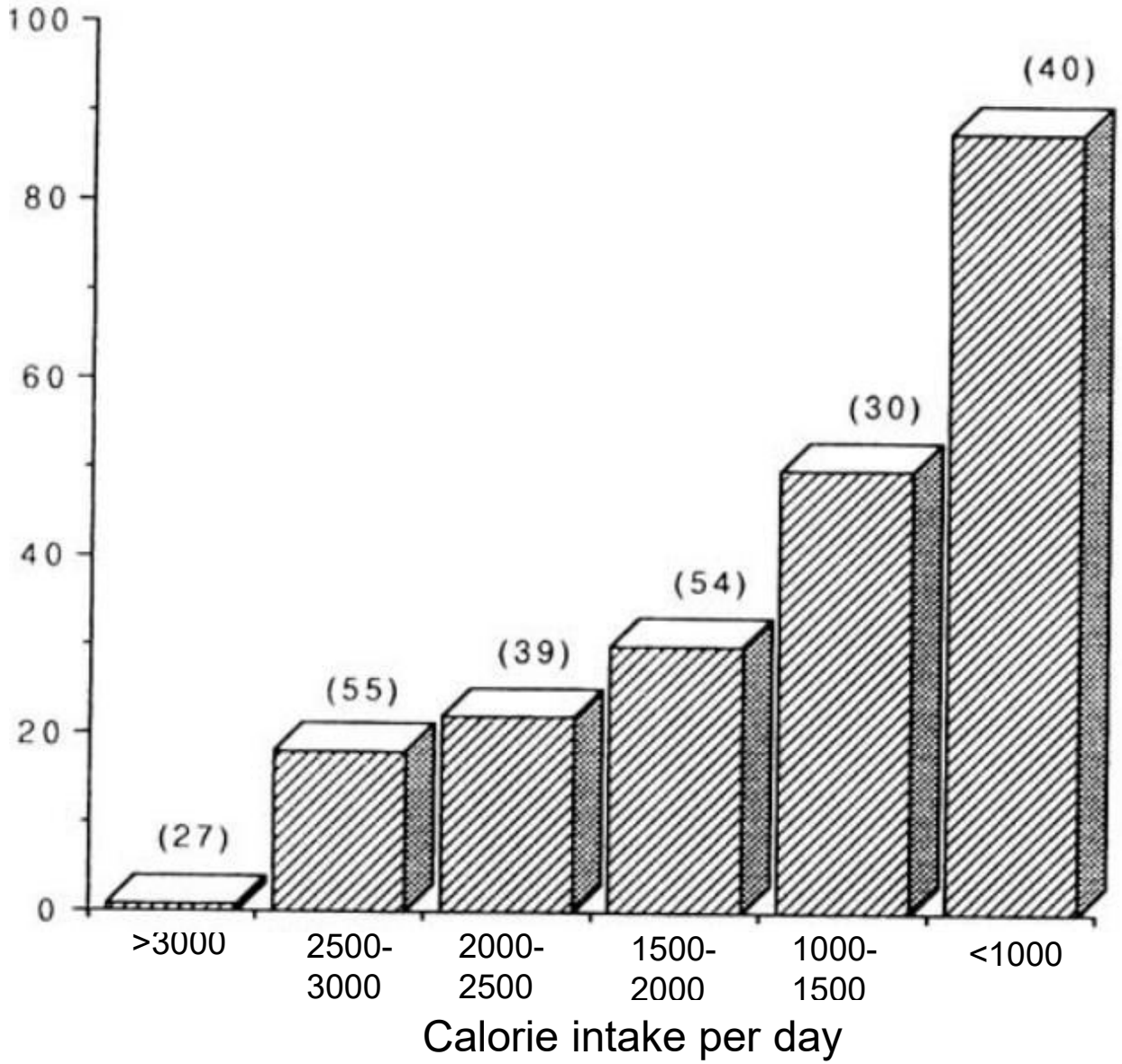
6-Month Mortality According to Calorie Intake during First Month



Mendenhall Alcohol Clin Exp Res 1995;19:635

Role of Saturated Fats in SAH !

Background

0145-6008/86/1003-0271$2.00/0
ALCOHOLISM: CLINICAL AND EXPERIMENTAL RESEARCH
Vol. 10, No. 3
May/June 1986

Dietary Factors and Alcoholic Cirrhosis

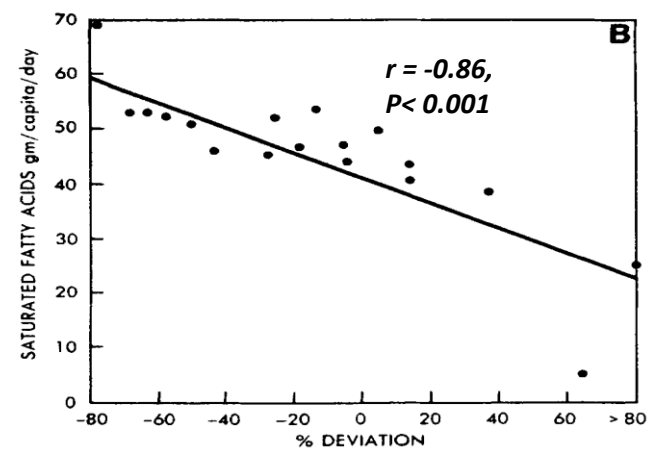
Amin A. Nanji, MD, FRCP and Samuel W. French, MD

First Human Epidemiological Study

Mortality from cirrhosis in many countries deviates markedly from that expected for a given per capita alcohol intake. We investigated the possibility that dietary factors might explain the deviation expected and actual mortality rates in different countries. Deviations from expected cirrhosis mortality was calculated as a percentage for 17 different countries, all of whom had carrier rates for hepatitis B virus of less than 2%. The percentage of deviation was correlated with dietary intake of sautrated fat, polyunsaturated fat, cholesterol, and also with mortality from ischemic heart disease. The percentage of deviation correlated inversely with dietary cholesterol ($r = -0.86$, p 0.001) and saturated fat ($r = -0.80$, p 0.001) and positively with polyunsaturated fats ($r = -0.55$ p 0.05). This suggests that both saturated fat and cholesterol protect against alcoholic cirrhosis while polyunsaturated fats promote cirrhosis.

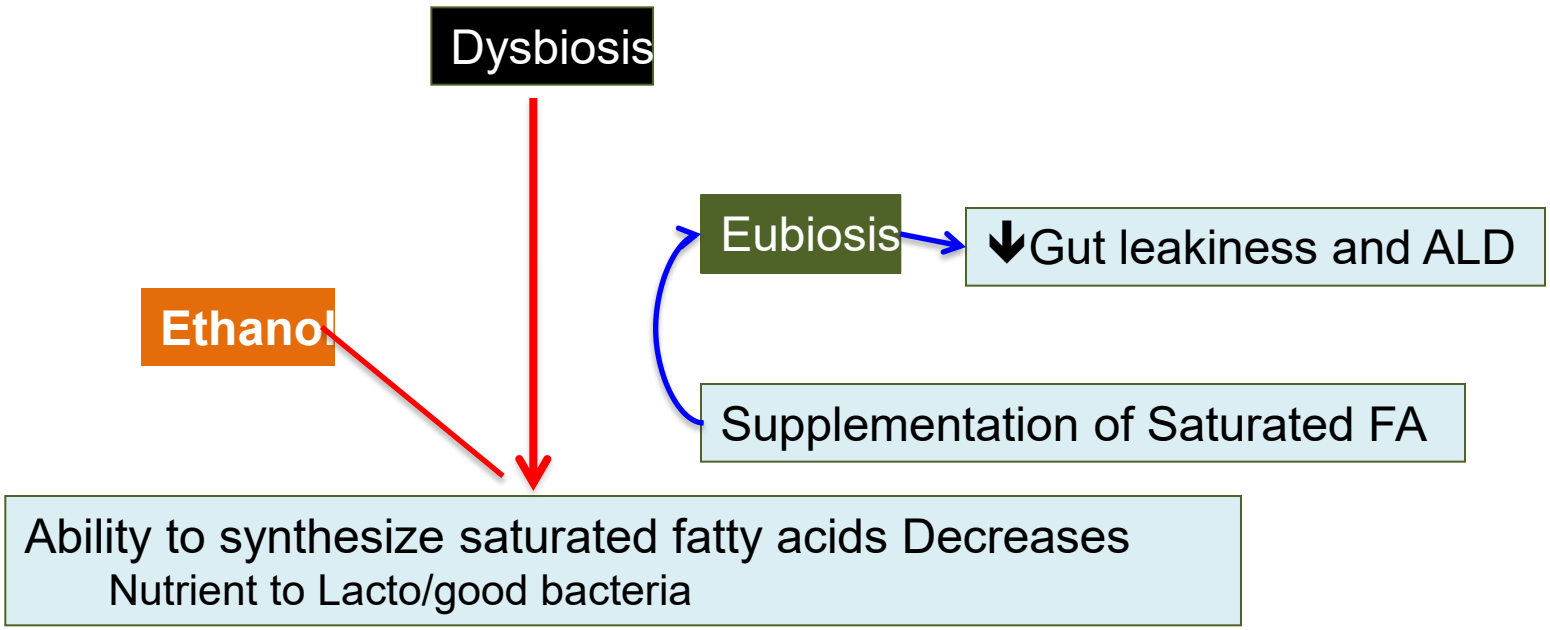
Table 1. Liver Cirrhosis Mortality Rate and Alcohol Consumption in the Countries Studied

	Liver cirrhosis deaths/100,000 (1967)			Per capita consumption of absolute alcohol
	Actual	Estimated	Deviation	
				liters
New Zealand	2.7	12.2	−9.5 (−77.8%)	6.7
Ireland	2.6	8.1	−5.5 (−67.9%)	5.0
Australia	5.1	13.9	−8.8 (−63.2%)	7.4
England	2.8	6.6	−3.8 (−57.5%)	4.3
Netherlands	3.5	6.1	−2.6 (−42.3%)	4.1
United States	9.3	14.1	−4.8 (−34.0%)	5.5
Switzerland	14.0	19.3	−5.3 (−27.6%)	9.7
Canada	7.2	9.5	−2.3 (−24.5%)	5.6
Belgium	9.9	12.1	−2.2 (−18.5%)	6.6
Denmark	7.6	8.7	−1.1 (−12.8%)	5.2
Sweden	7.4	7.8	−0.4 (−5.5%)	4.8
France	35.7	37.0	−1.3 (−3.6%)	17.1
Finland	3.2	3.0	0.2 (+5.5%)	2.9
Norway	3.8	3.3	0.5 (+13.7%)	3.0
Germany FR	22.6	19.8	2.8(+14.1)	9.9
Austria	28.0	20.5	7.5 (+36.4)	10.1
Japan	10.4	6.4	4.0 (+62.0)	4.3



Saturated Fat Reverses gut dysbiosis

Alcohol: ↑ dysbiosis, endotoxins.



Chen et al, Gastroenterology 2015

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Saturated Fat, Ghee: How it Helps!

SATURATED FAT

Acetaldehyde

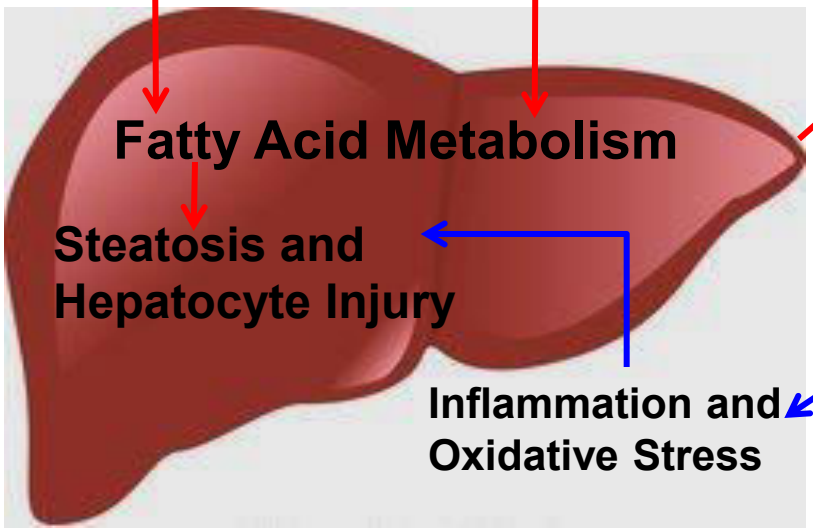
- Inflammation ↑
- Oxidative Stress ↑

↓ Adiponectin Level

Malnutrition

- Primary
- Secondary

"Dietary intake of saturated fatty acid, "desi ghee" in SAH may lead to eubiosis, improve the disease outcome"



Fatty Acid Metabolism

Steatosis and Hepatocyte Injury

Inflammation and Oxidative Stress

Endotoxemia

Dysbiosis ↑

Intestinal Permeability (Gut-barrier Dysfunction) ↑

↓ Synthesis of Saturated fatty acids

↓ **Expression of Fab F and Fab G bacterial genes**

Harshita et al

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Nutritional Prescription in SAH: ILBS

- Diet (per kg ideal body weight)
  - 35 – 40 cal/kg/d (80 kg = 2,600 to 3,200 Cal)
  - ***30-35% FAT***
  - 1.5 gram protein/kg/d
  - 2 gram sodium
  - Thiamine, B6, B12, folate, zinc, selenium
  - 4 – 7 meals per day
  - **Oral or Ryle's tube**

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IV Lipid Emulsions in Advanced AALD

- IV lipids
- Bilirubin 16.79±1.78 mg/dl, MELD score 25.1±5.6
- 250 ml 20% IV soybean LE (500 Kcal/d), 3 days
- No adverse events on coagulation, NH3, LFT, lipids, reduced pro-inflammatory markers

Anand et al JGH 2021

ilbs

IV Lipid Emulsion Improves N2 Balance in SAH

Variable	Alcoholic liver disease patients (n = 55)		
	Pre	**Post**	**P**
Albumin (g/dl)	2.52 ± 0.07	2.49 ± 0.07	0.45
Nitrogen balance	-3.05 ± 1.12	0.69 ± 0.5	***0.04***
Nitrogen excretion	11.93 ± 1.09	9.01 ± 0.52	***0.01***

Anand et al JGH 2021

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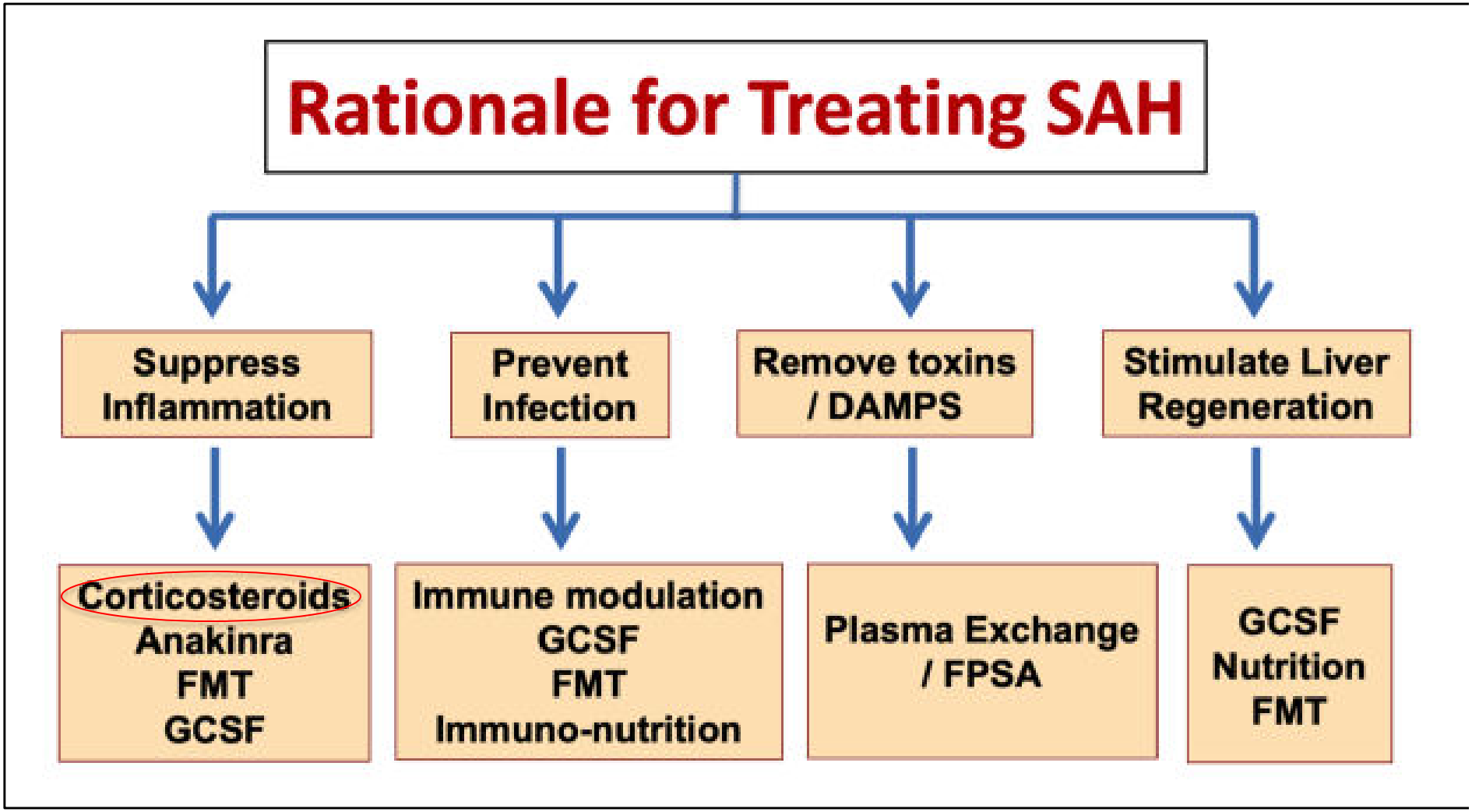
Severe Alcoholic Hepatitis



Sarin SK, et al CMH 2021

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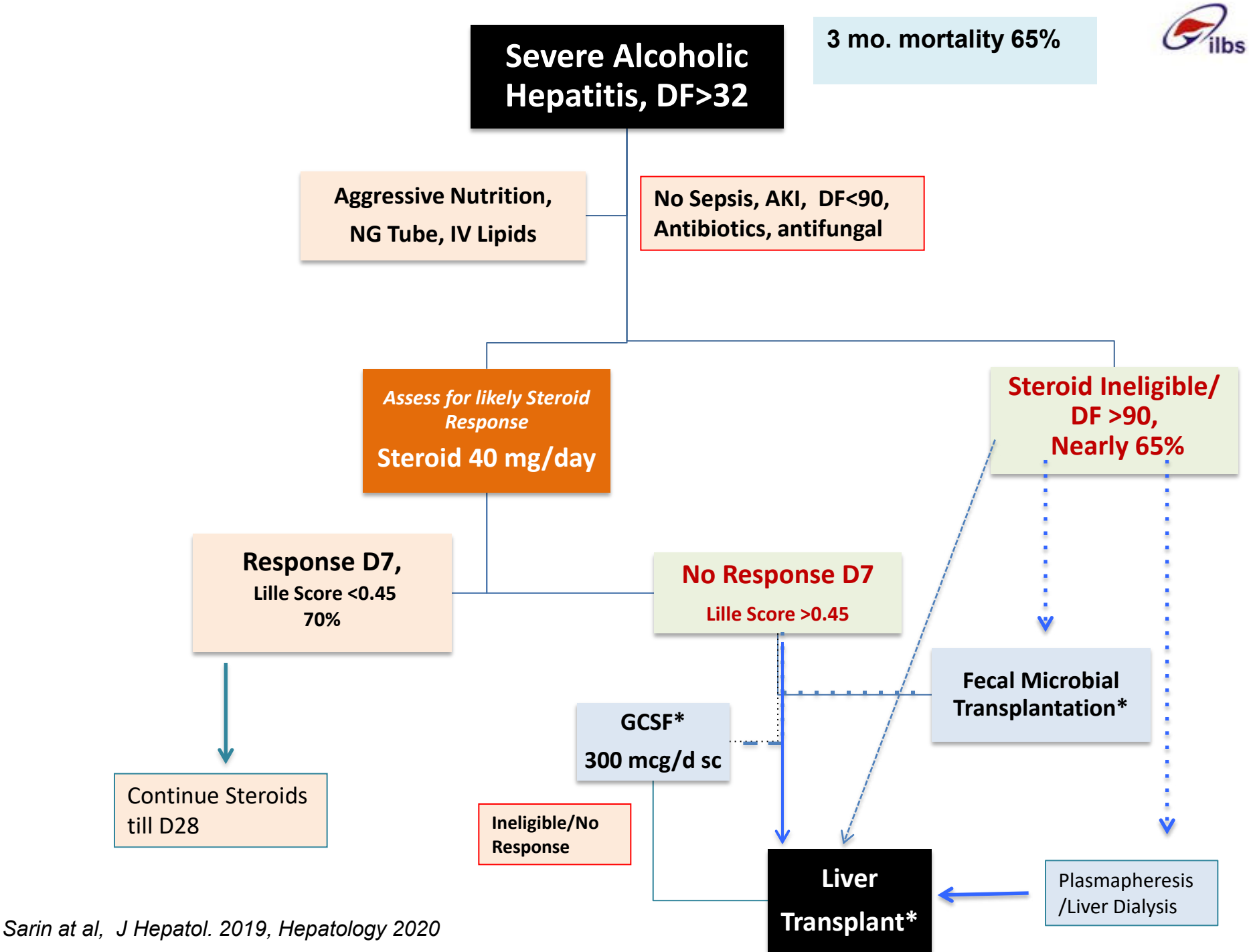

Sarin at al, J Hepatol. 2019, Hepatology 2020

Severity of SAH and Response to Steroids

Steroid Eligible **:**
No infections, sepsis, bleed
DF : >32 and <90
MELD : between 24-39

Discriminant Function(DF) : 4.6xPT difference (patient - control)+ Bilirubin
[eg. 4.6 x 6+ 10 = 37.6 severe disease]

DF >32 DF >32 = 35 - 50% mortality, MELD >20 = d28 Mortality 20%

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Scoring System	**Components**							
Start Steroids in eligible	**Biirubin**	**PT/INR**	**Serum Creat**	**Age**	**WBC Count**	**BUN**	**Albumin**	**Change in Bilirubin D0-7**
Discriminant Function(DF)	Yes	Yes	No	No	No	No	No	No
MELD Score	Yes	Yes	Yes	No	No	No	No	No
Stop/Continue **steroids Day 7** ***Lille score***	Yes	Yes	Yes	Yes	No	No	Yes	Yes

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STEROIDS

- Our patient DF = 93
- Steroid started 40 mg/day,7 days

  no response (Lille score 0.51), stopped.
- Alternatives ?

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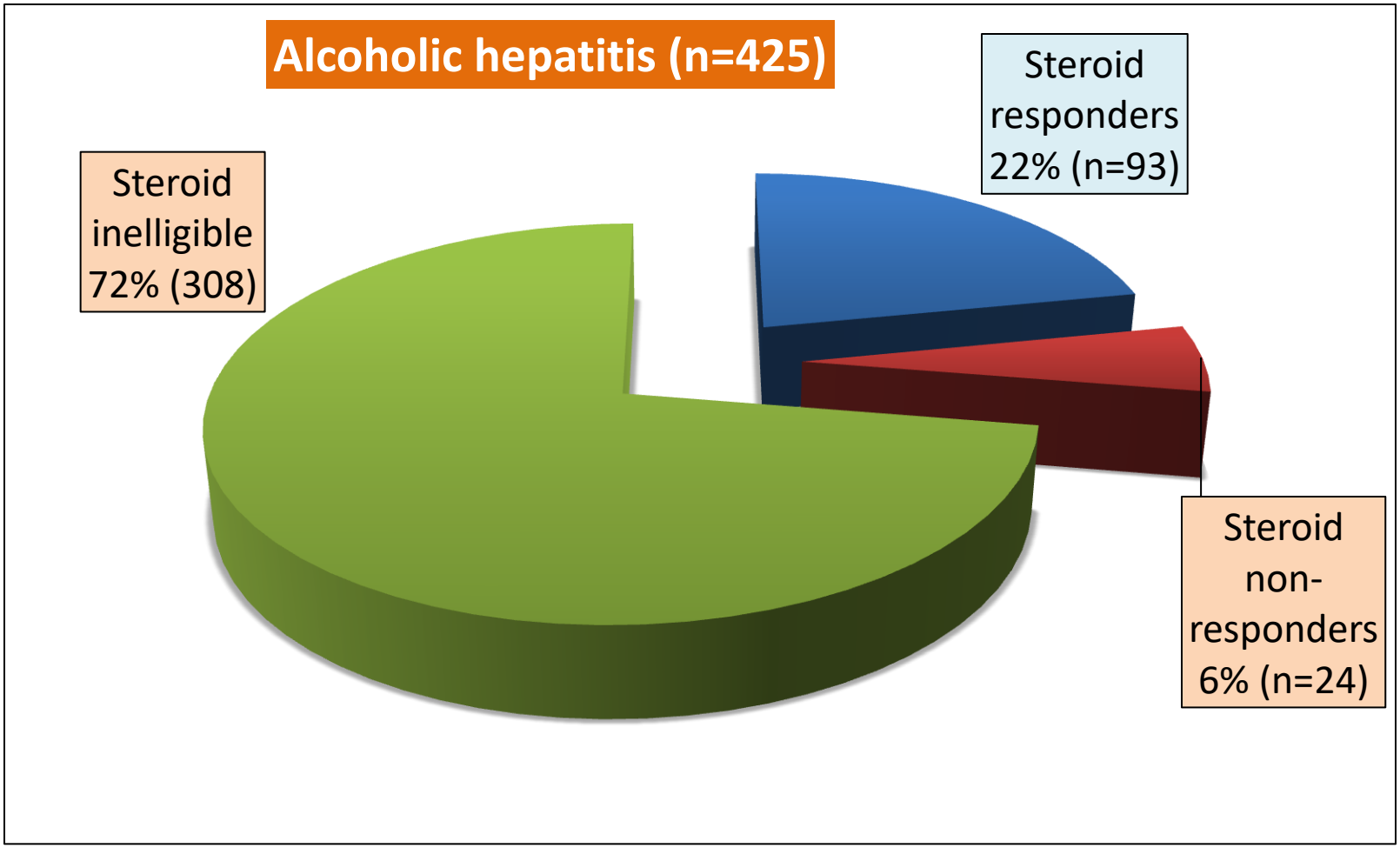
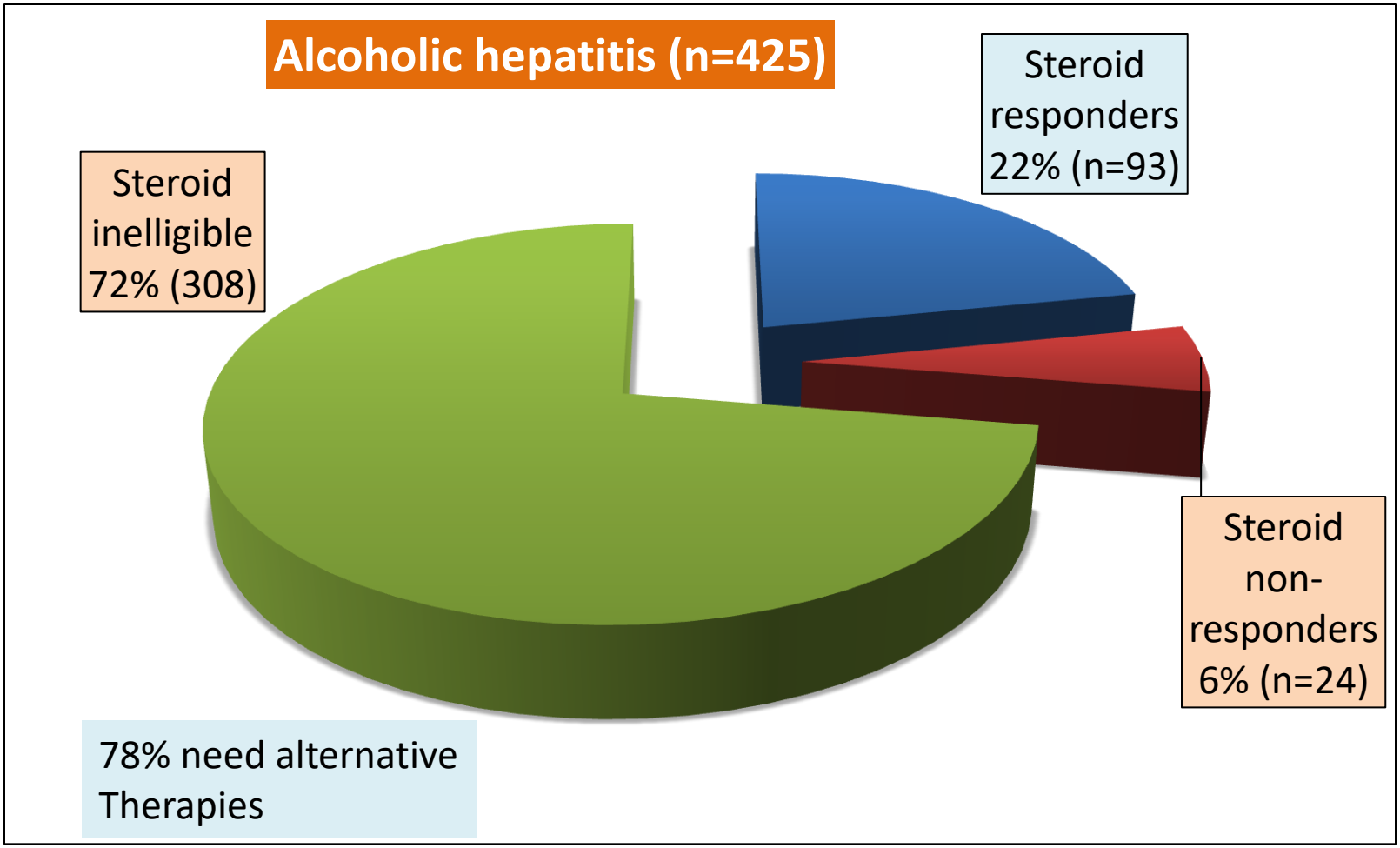
Steroid Therapy@ilbs

2012-2014

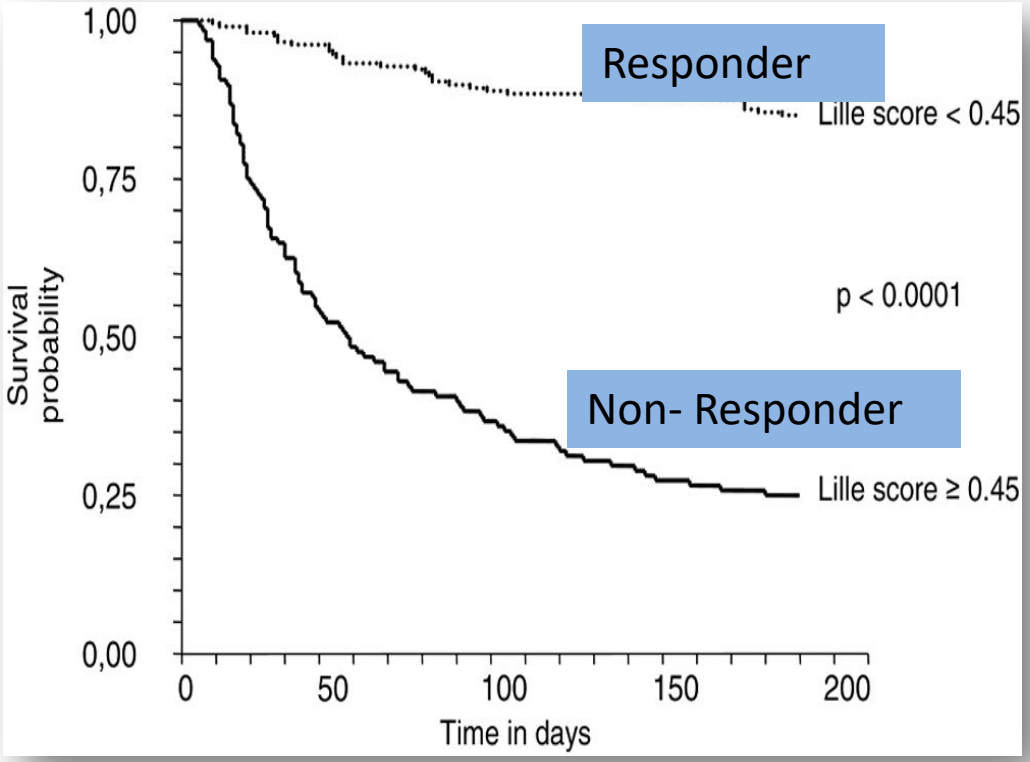


Steroid Therapy@ilbs

2012-2014



Survival in non-responders to steroids

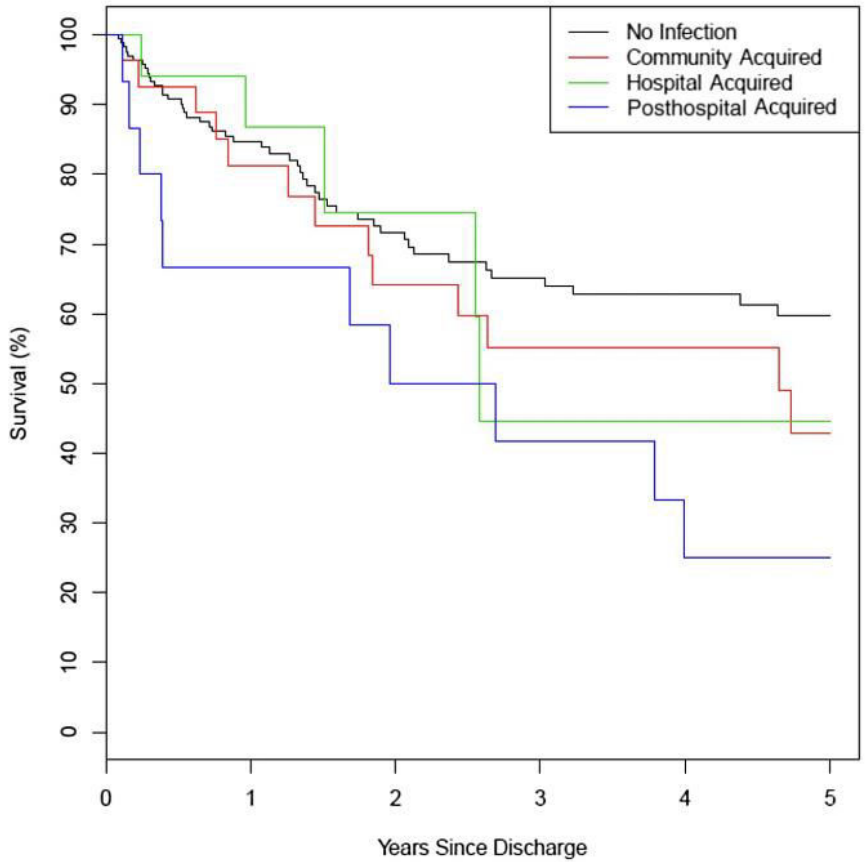


Non Rsponse to steroids 40%.

Risk of infection: Responders 11%
NR 42.5%

NR Based on
Age,
PTINR
Albumin
Bilirubin D0 and D7

Louvet A, Naveau S, Abdelnour M, et al. The Lille model: a new tool for therapeutic strategy in patients with severe alcoholic hepatitis treated with steroids. Hepatology 2007;45:1348-54., ***Louvet et al GE 2009***



Post-hospital Infections in SAH common

Group	HR (95% CI)	*P* Value
No infection	Reference	
Community acquired	1.34 (0.77, 2.32)	0.30
Hospital acquired	1.44 (0.72, 2.91)	0.31
Posthospital acquired	4.27 (2.65, 6.88)	<0.001

Penrice et al, Hepatology 2022

Predict Steroid Non-response at Baseline

- Bilirubin: High and rising
- Liver Biopsy: MB index, cholestasis
- Urine metabolome: Acetyl carnitine >2,500 ng/ml
- Transferrin Saturation: High
- Micro vesicles : ASGPR +ve MP
- Dexamethasone Inhibition of Lymphocytes
- Liver Transcriptome

Maras et al 2015, 2018, Baweja et al 2018, 2019, Sharma et al. Sci Rep 2019

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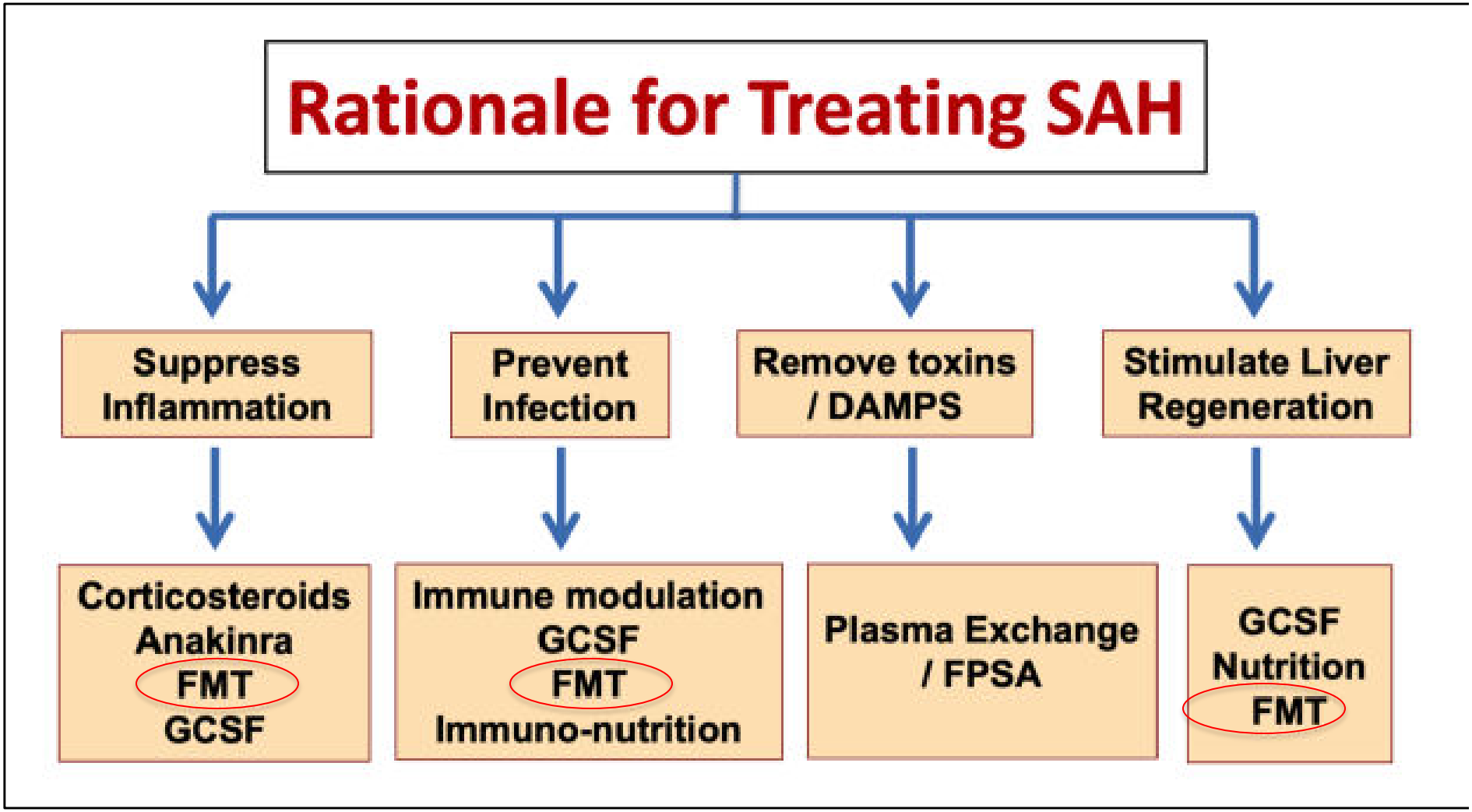
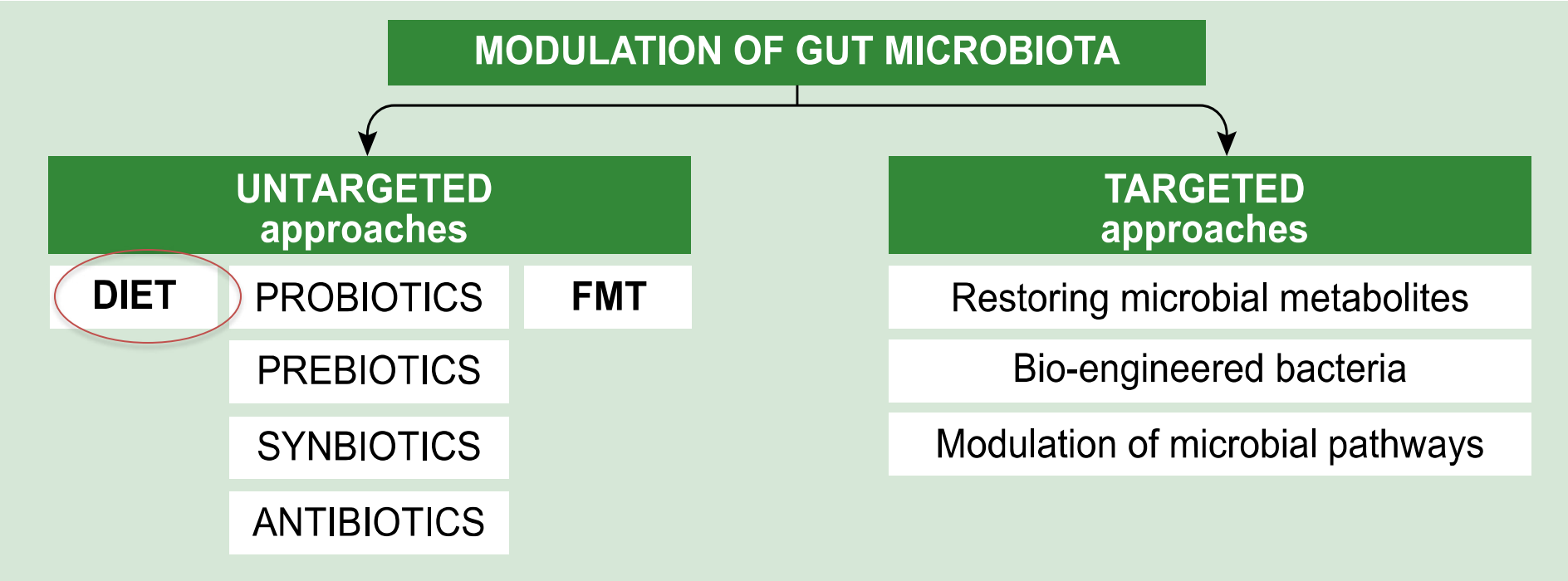
Referral Protocol for SAH:

- Non-responder,
- Ineligible, sepsis, infections, AKI, bleed
- SAH with moderate ascites
- DILI
- Viral hepatitis
- Obesity



Sarin SK, et al CMH 2020



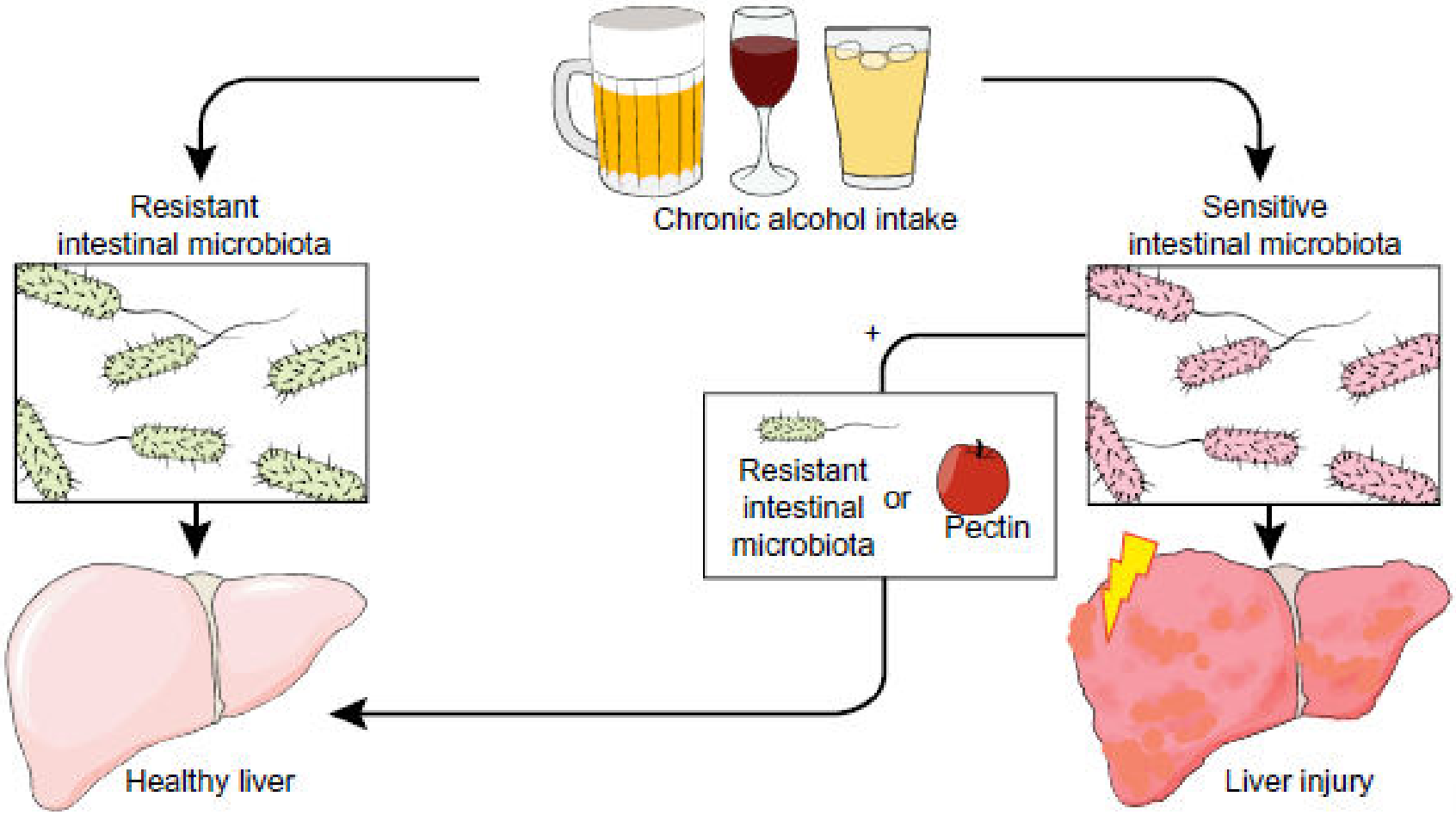
Sarin S K et al J Hep 2019

Research Article

CrossMark

EASL JOURNAL OF HEPATOLOGY

Fecal microbiota manipulation prevents dysbiosis and alcohol-induced liver injury in mice



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Cirrhosis Dysbiosis Ratio (CDR)

- **Good** (Lachnospiraceae, Ruminococcaceae, Clostridium XIV).
- **Bad** (Enterbactericace, Bacteriodacae)
- **Good vs. Bad CDR**
  - Normal >2
  - Cirrhosis 0.9
  - Decompensated 0.66
  - Admitted 0.32

Need to define Good bacteria with food/race/age/gender

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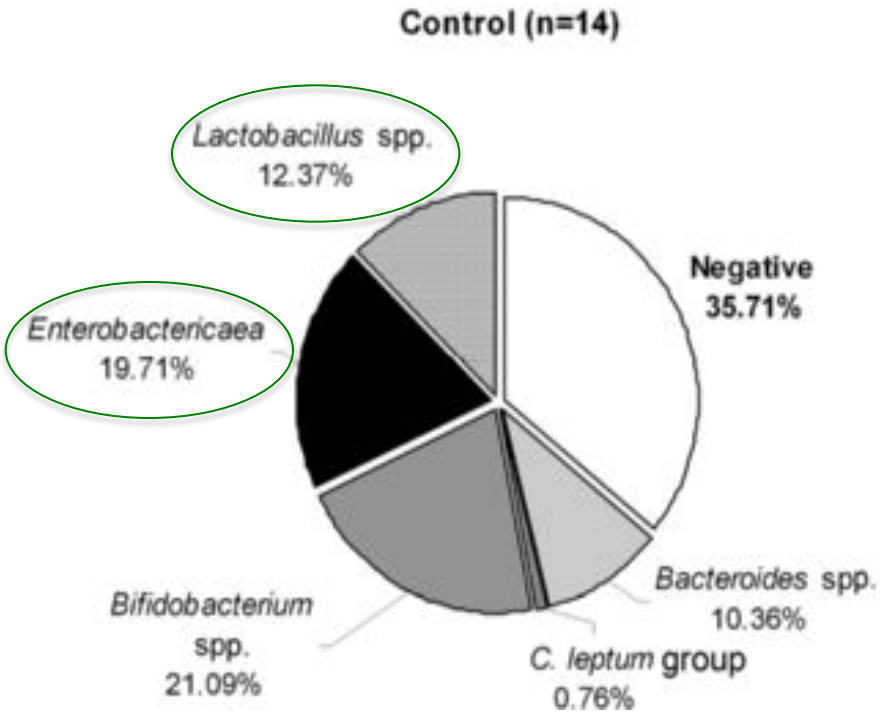

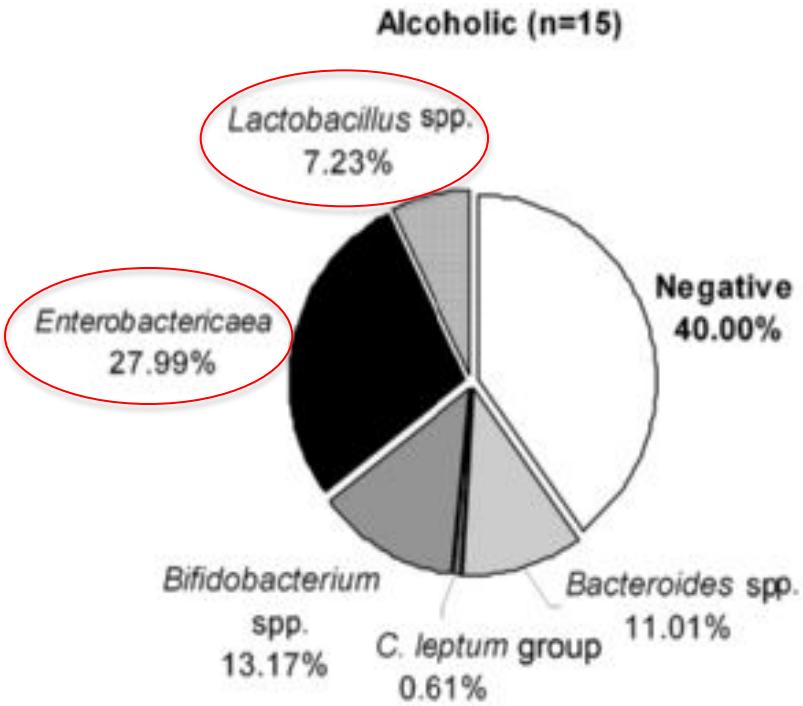

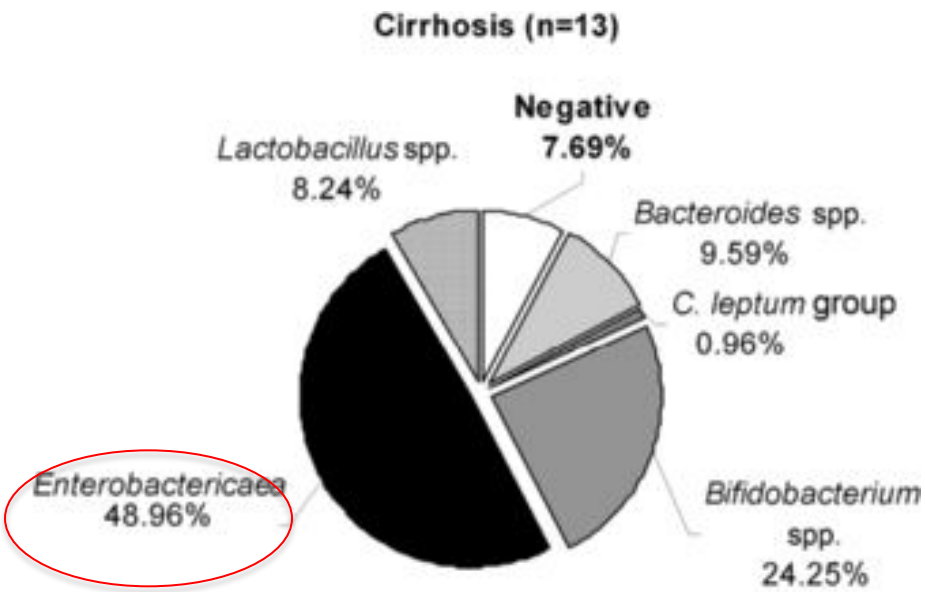

Gut Microbiota in Healthy, Alcoholics and Cirrhosis

(Tumisto et al 2014)

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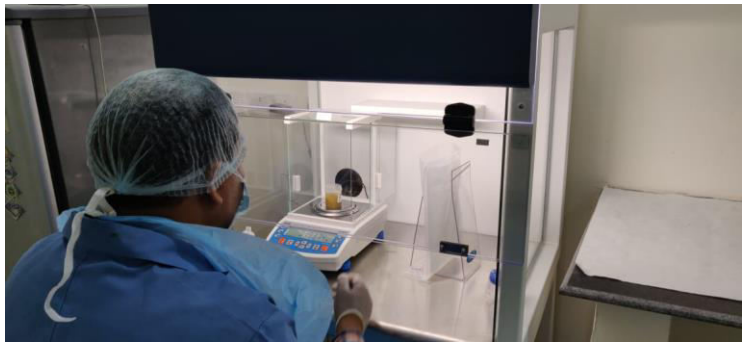


FMT Unit @ ILBS

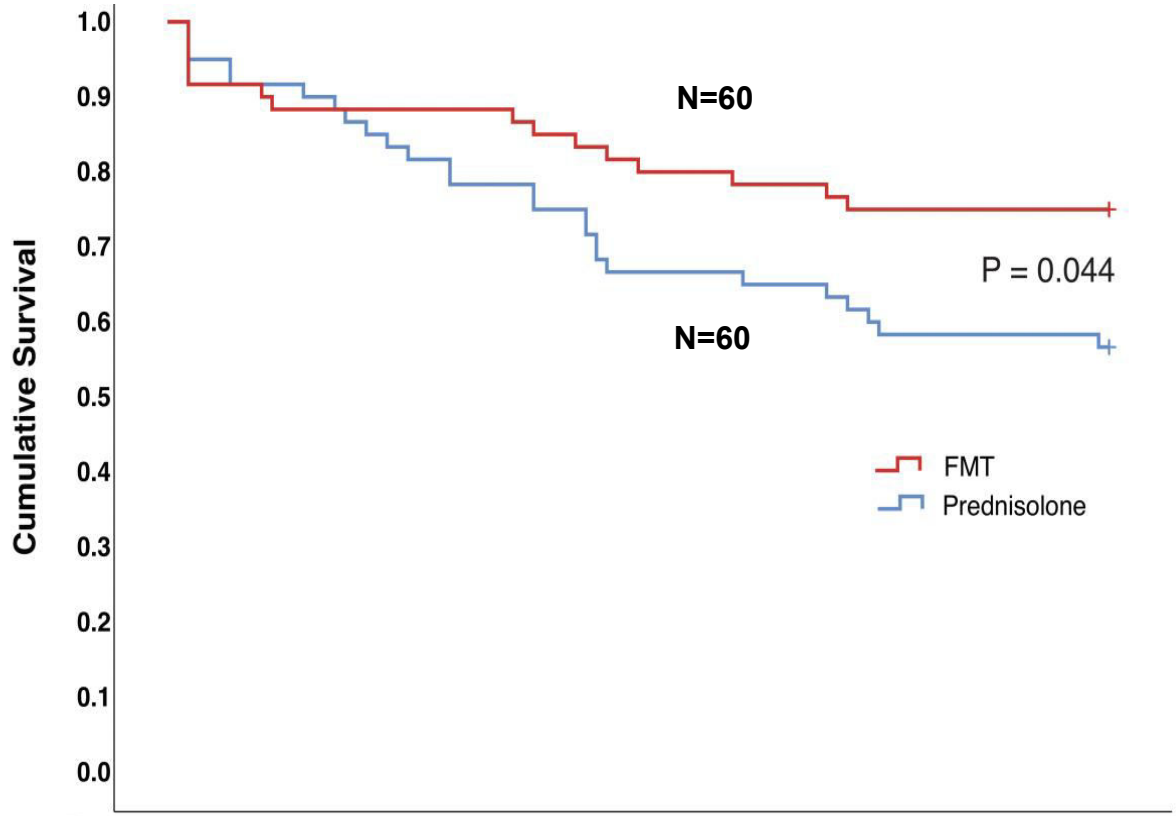
30g

100 ml

7 days

45°, 4 hr.
Then N diet

Steroids vs. FMT in steroid eligible (n=120)



	Day	0	7	14	21	28	35	42	49	56	63	70	77	84	91
Prednisolone	At risk	60	55	54	50	47	45	40	40	39	38	35	35	35	34
	Events	0	5	6	10	13	15	20	20	21	22	25	25	25	26
FMT	At risk	60	55	53	53	53	51	49	48	47	46	45	45	45	45
	Events	0	5	7	7	7	9	11	12	13	14	15	15	15	15

Pande et al Hepat Int 2022

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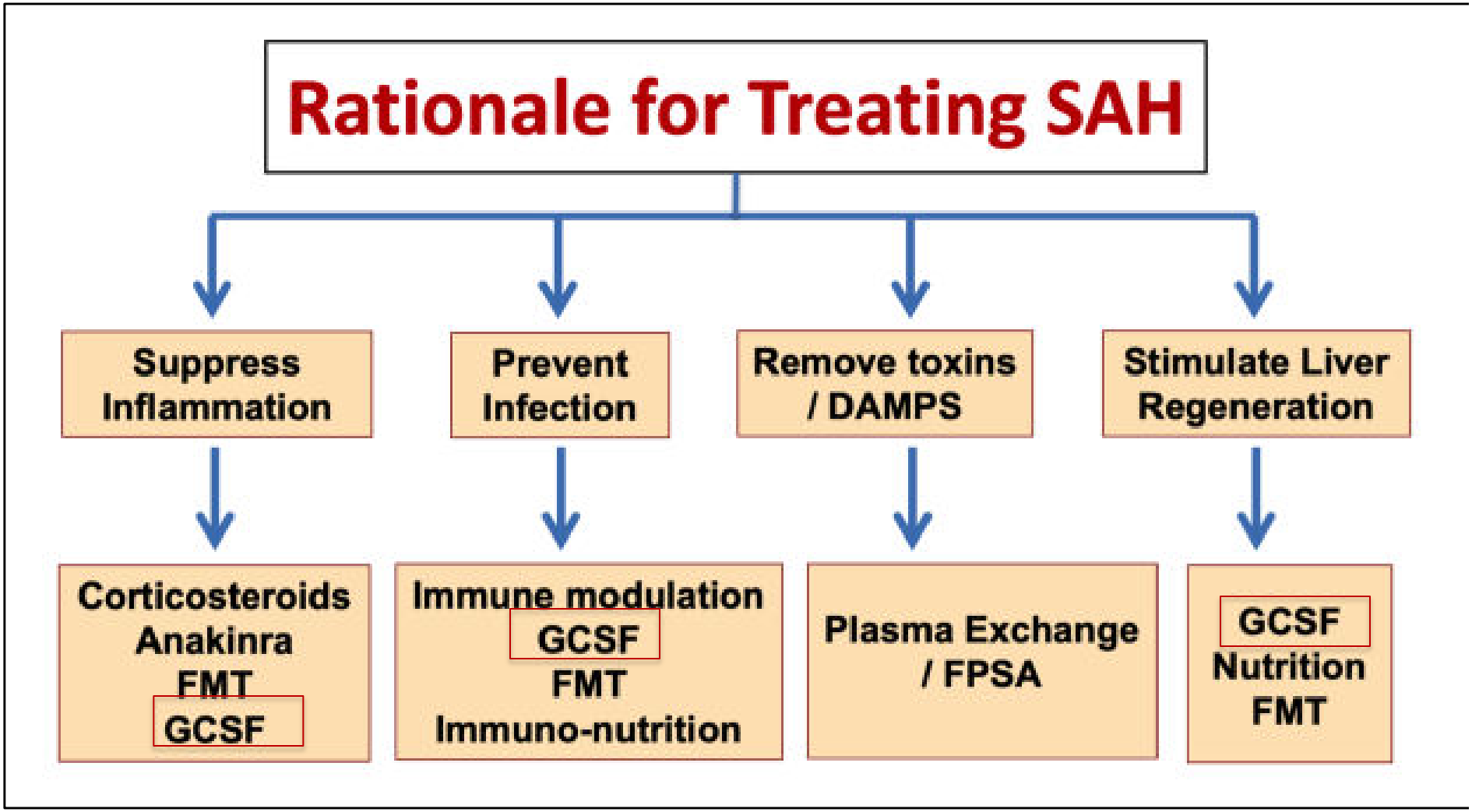

Sarin and Sharma CMH 2020

GCSF Prevents Sepsis, Stimulates Liver Regeneration

Granulocyte Colony–Stimulating Factor Mobilizes CD34+ Cells and Improves Survival of Patients With Acute-on-Chronic Liver Failure

VISHAL GARG,* HITENDRA GARG,‡ ARSHI KHAN,‡ NIRUPAMA TREHANPATI,‡ ASHISH KUMAR,‡ BARJESH CHANDER SHARMA,* PUJA SAKHUJA,§ and SHIV KUMAR SARIN*,‡

Gastroenterology 2012

Prednisolone + GCSF

Variable	Prednisolone N=42	GCSF + Pred N=42	GCSF N=42	P
90 day survival	64%	88%	78.6%	<0.01
Lille score Day 7	0.21 (0.16)	0.14 (0.16)	0.28 (0.15)	<0.01
Infection	35.7%	19%	7.1%	<0.05
Rehospitalization	59%	14%	31%	<0.01

Mishra et al AASLD 2022

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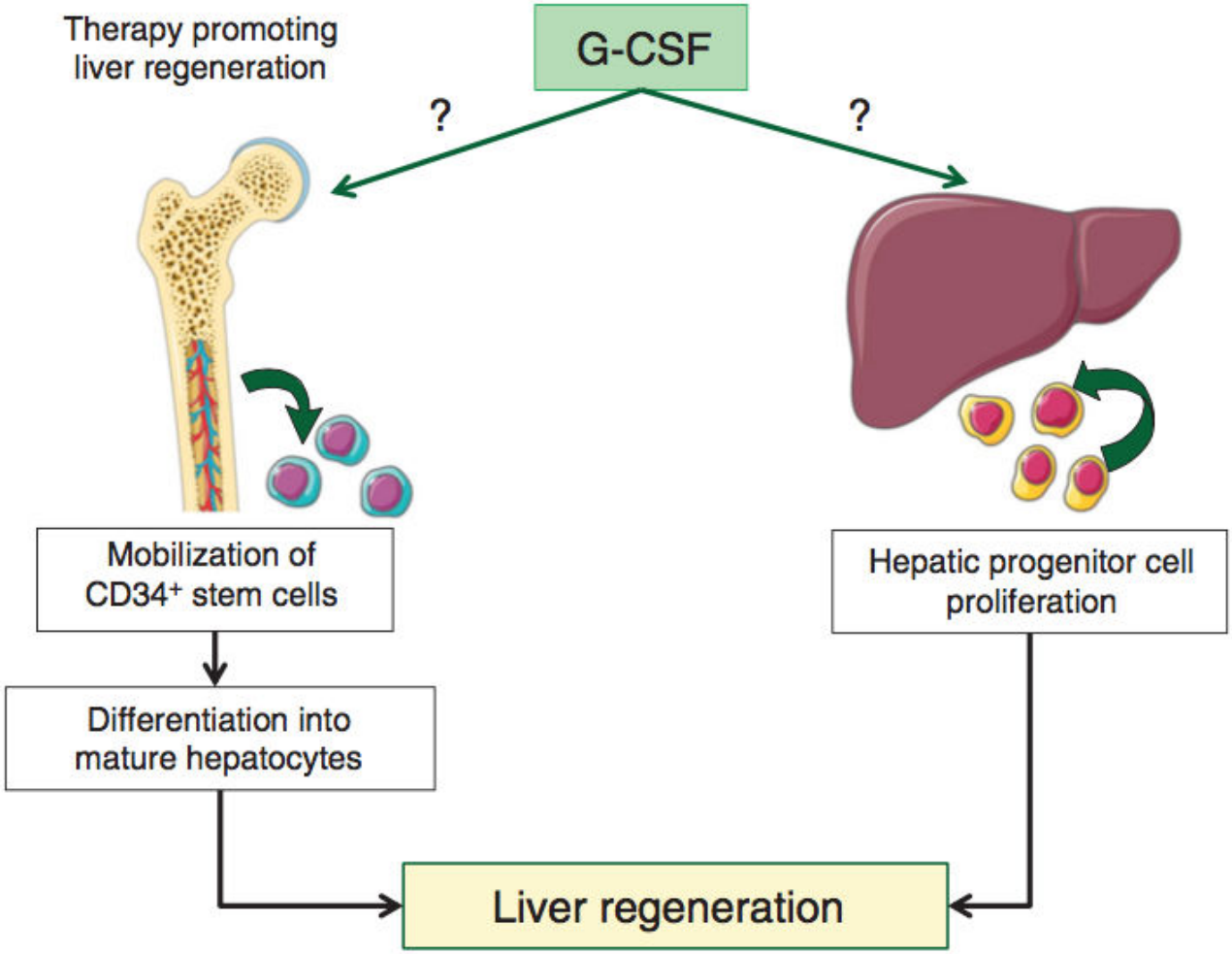
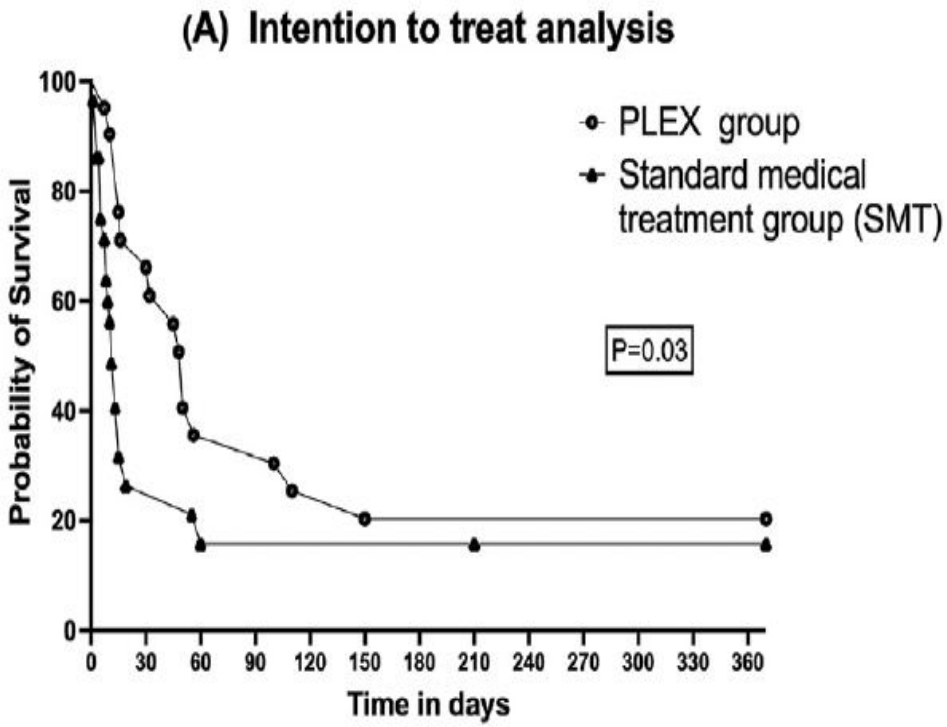
Steroid Non-response is failure of Regeneration ! GCSF Works



Richard moreau et al., ***The American journal of*** *Gastroenterology, sep, 2014*

Low Volume Plasma Exchange and Low Dose Steroid Improve Survival in Patients With Alcohol-Related Acute on Chronic Liver Failure and Severe Alcoholic Hepatitis – Preliminary Experience

Santhosh E. Kumar [*], Ashish Goel [*], Uday Zachariah [*], Sukesh C. Nair [†], Vinoi G. David [‡], Santosh Varughe
Prashanth B. Gandhi [*], Amit Barpha [*], Anand Sharma [*], Balakrishnan Vijayalekshmi [§],
Kunissery A. Balasubramanian [§], Elwyn Elias [*,||], Chundamannil Eapen Eapen [*]



+ 20mg steroids 4 wk

Patients at Risk						
No. of days	0	30	60	90	180	365
PLEX group	21	14	8	8	5	5
SMT group	29	6	4	4	4	3

J Clin Exp Hep 2022

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Liver Transplant in SAH

Recipient: Longer Abstinence is Good, Can Allow Shorter :

- Liver to recover, obviate the need for LT
- Commitment to abstinence
- Implementation of relapse prevention strategies

  3 months to 1 month

Our patient was subjected to stem cell therapy as Transplant not possible

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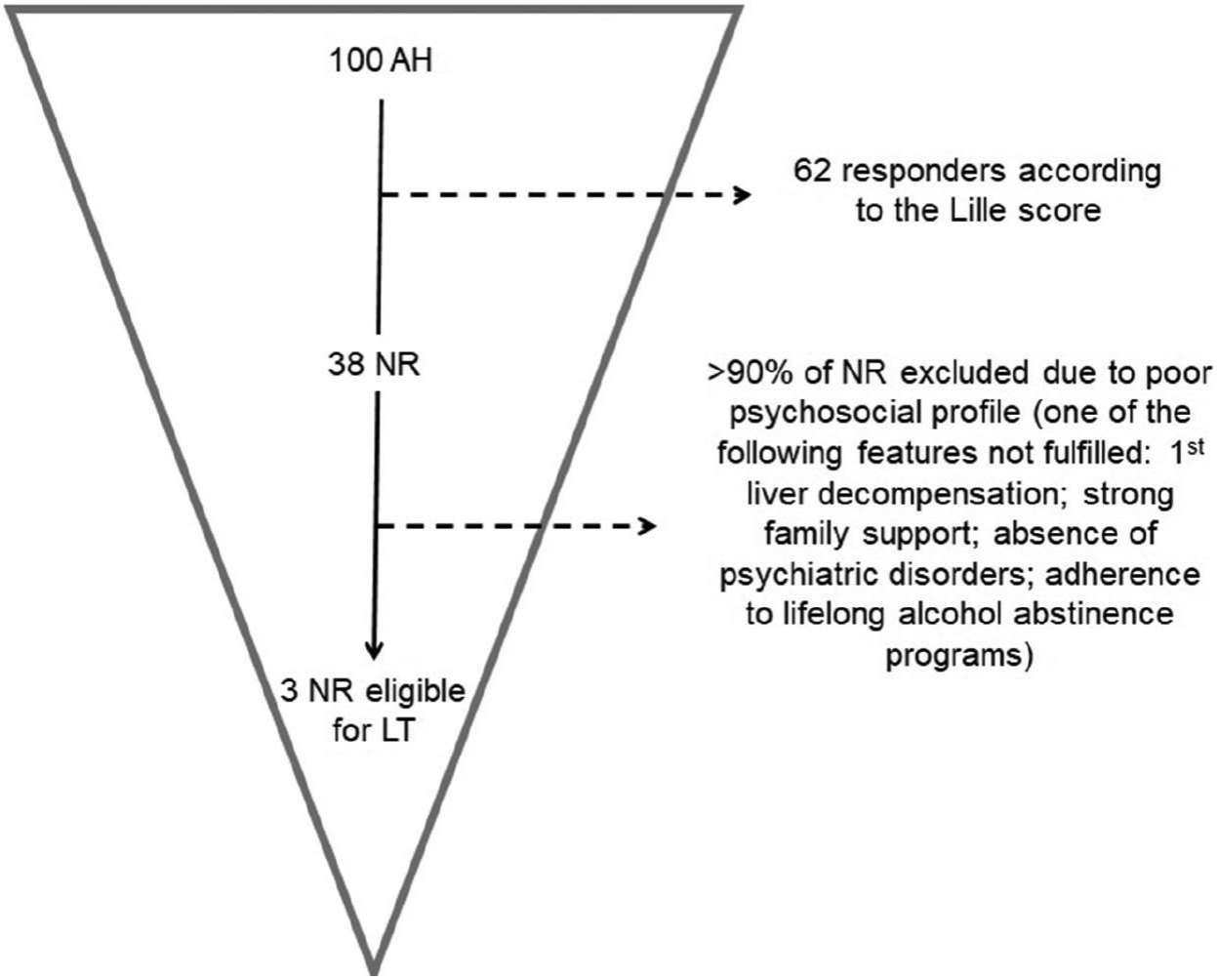
How Many AH Qualify for LT?

NR + Ineligible



Marot A Exp Rev GH 2020

Donor Challenges for LDLT in Alcoholic Hepatitis

Donor: Limited

Negative effect of long-term alcohol, Coercion, Safety ++

Donor Spouse: Outcomes

Both Dead, Recipient Death, Bankrupt, Relapse a betrayal

Use of partial graft in high MELD patient

Pre-requisite for LDLT – 4 level screening
Nearly no risk of recidivism

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Liver Transplant Outcomes: One Year Survival in SAH

Study	Number of patients transplanted	Age *	MELD at time of liver transplantation *	Alcohol relapse (n, %)	Harmful alcohol relapse (n, %)	1-year surviva (%)
Mathurin 2011 [35]	26	47	34	3 (12)	1 (4)	77
Singal [36]	55	52 **	26 **	-	-	87
Im [33]	9	41	39	2 (22)	2 (22)	89
Weeks [37]	46	50	33	13 (28)	8 (17)	97
Lee [38]	147	43	38	40 (28)	15 (11)	94

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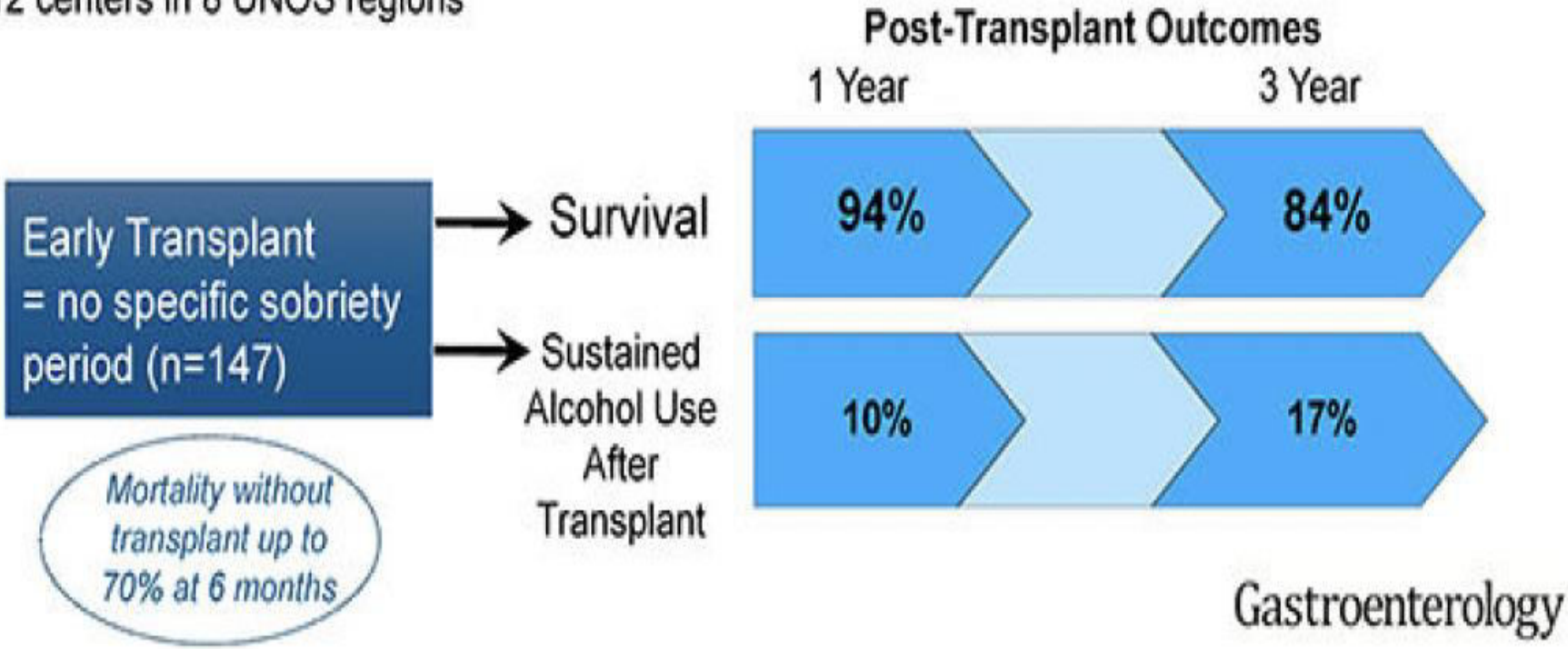
American Consortium of Early Liver Transplantation for Alcoholic Hepatitis: ACCELERATE-AH

12 centers in 8 UNOS regions



Lee et al Gastroenterology 2018

Treatment Challenges in Post LT Recurrent Alcoholic Hepatitis

- Severe, progressive disease
- Patient received steroids/on steroids
- Limited chances of second LDLT

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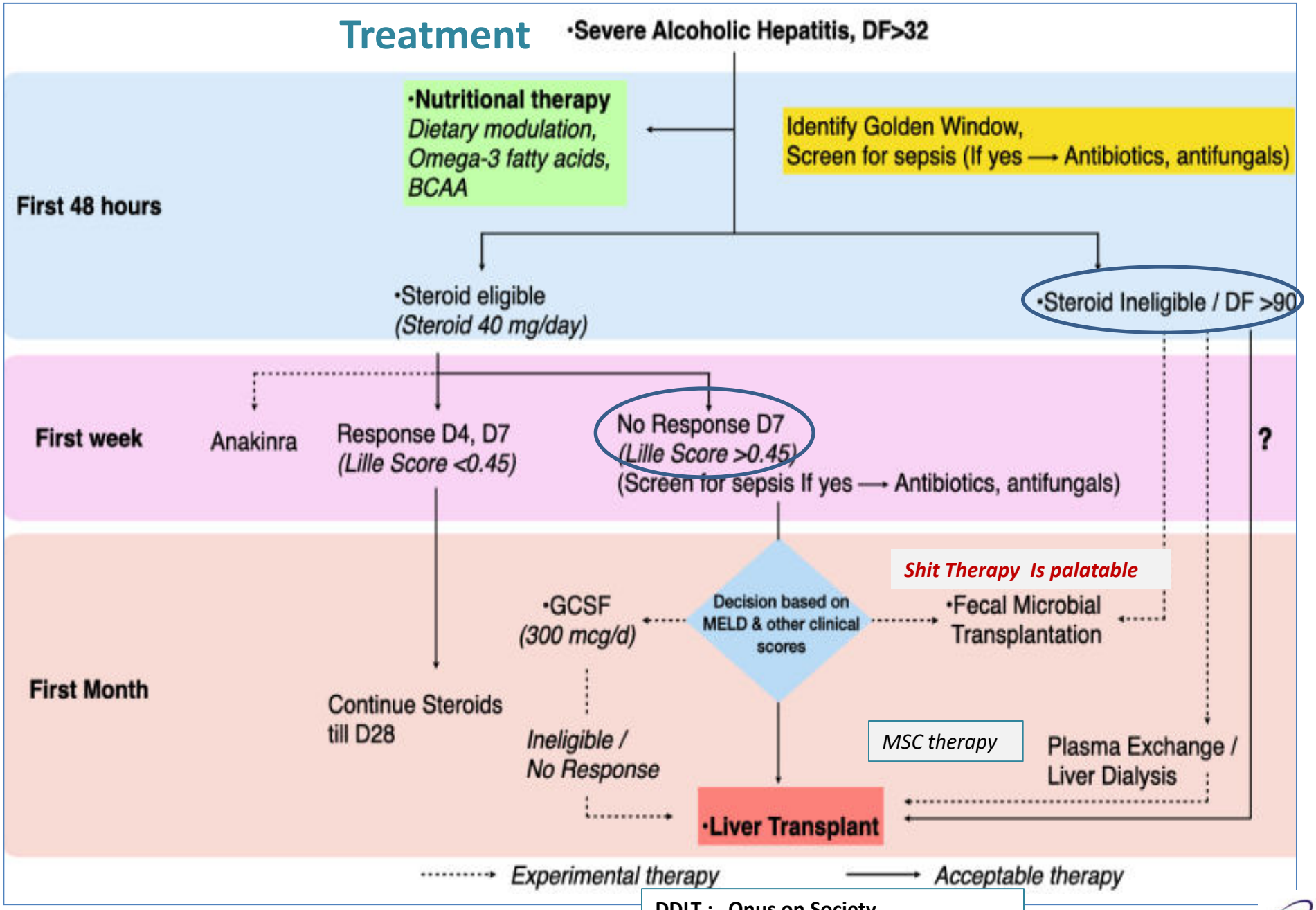
Treatment of Alcohol Associated Hepatitis is primitive

Treatment



Sarin et al CMH 2020

DDLT : Onus on Society
LDLT : ONUS On Surgical Team