Alcohol Related Liver Disease

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Project ECHO® Gastroenterology Foundation of sub Saharan Africa

G-ECHO GI HEPATOLOGY ECHO OF SUB-SAHARAN AFRICA ESTABLISHED 2020

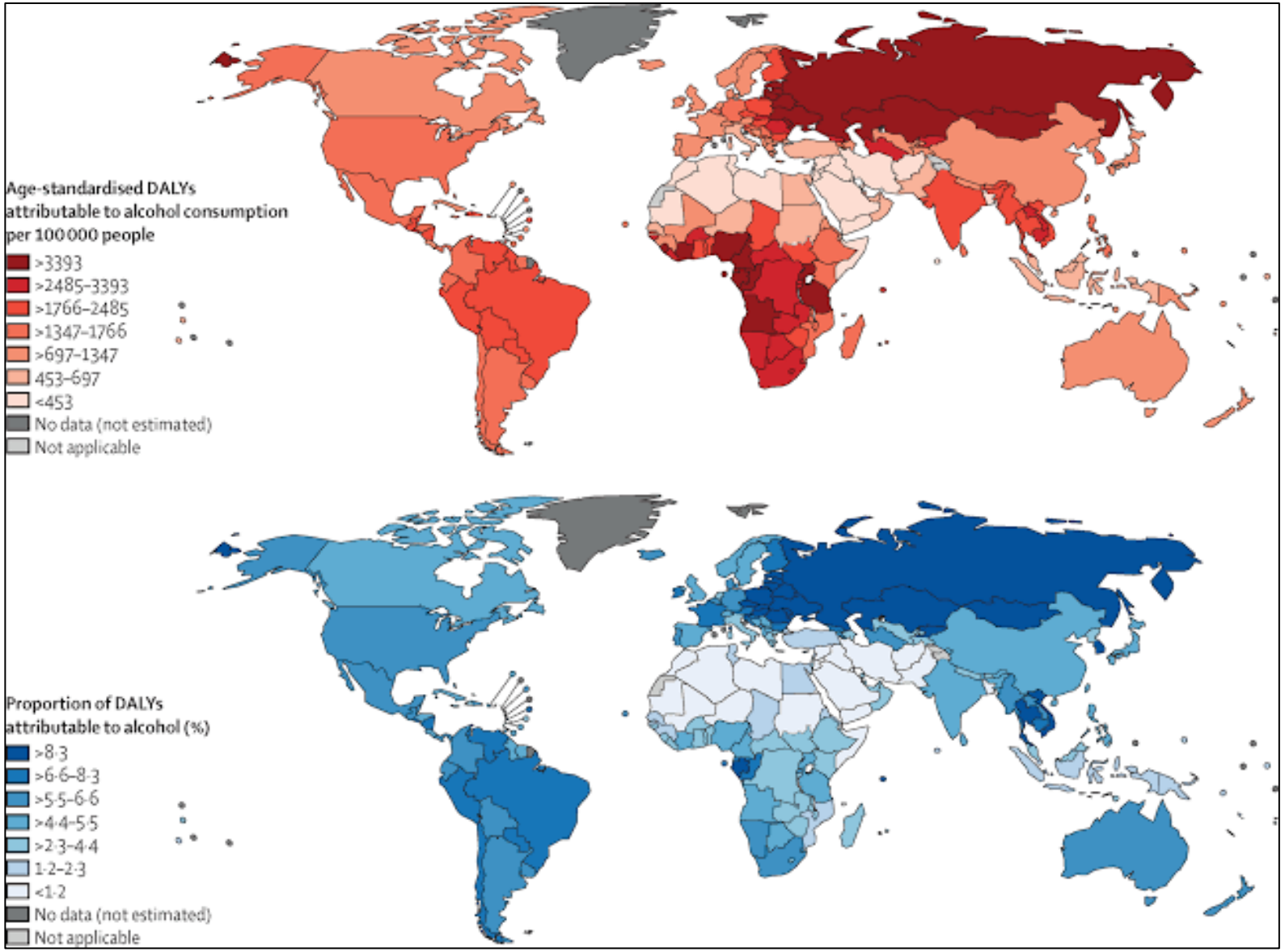
Introduction - Epidemiology

- **WHO ETOH - 3.3 million deaths every year**

- 6% of all deaths globally.
- 139 million disability-adjusted life years

- Globally alcohol is the cause of **50% liver disease**

- AUD - Gender: male > female
- Wide geographic variation
- Impact on 200 diseases



Alcohol consumption in South Africa

- Alcohol is most widely used drug
- 31% of people aged 15+ drink alcohol
- SA drinkers consume 30 litres of alcohol per capita, global average is 6.4
- SA ranks 4 out of 5 on risky drinking scale

South Africa has some of the heaviest drinkers in the world

Staff Writer 4 years ago

BBC NEWS

Home UK World Business Politics

Is Africa really a drunken continent?

By Hannah Barnes
BBC News

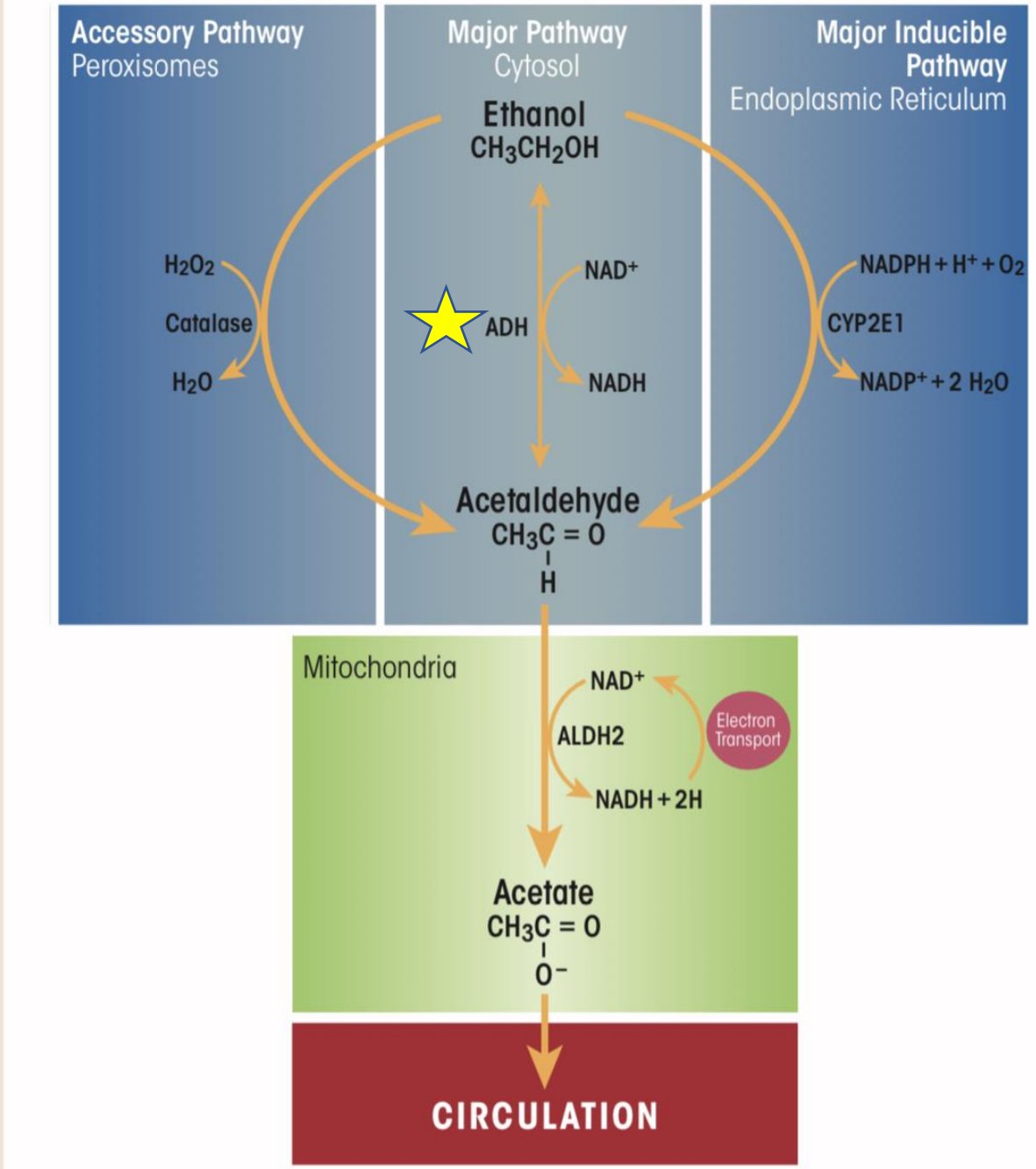
17 September 2013

Pertinent public health issue

Is Africa the next big beverage alcohol market?

Despite slowing down in 2018, beverage alcohol consumption in Africa is growing significantly

Alcohol metabolism
&
Toxic metabolites



Definitions

Previous term	Current term	Abbreviation
Alcoholic	Alcohol use disorder	AUD
Alcoholic liver disease	Alcohol-related liver disease	ALD
Alcoholic cirrhosis	Cirrhosis due to alcohol-related liver disease	ALD cirrhosis
Alcoholic steatohepatitis (histologically-defined lesion)	Steatohepatitis due to ALD	ASH
Alcoholic fibrosis	Fibrosis due to ALD	ALD fibrosis
Alcoholic hepatitis	Alcoholic hepatitis*	AH

The term alcoholic – stigmatizing & undermines patient dignity and self esteem

Quantification of alcohol consumption

- **Grams of alcohol per/day or week**
  - Types of drinks- % of etoh / amount
  - **EASL – 10g = one standard drink of pure alcohol**
  - Time consuming and difficult to obtain accurate information (recall)
- **Harmful drinking**
  - Alcohol iintake causing damage to health (physical or mental)
- **Heavy episodic drinking**
  - Consumption of 60g of pure alcohol on one occasion
- **Binge drinking**
  - Consumption → within 2 hour period
  - For Women 4+ / men 5 + drinks

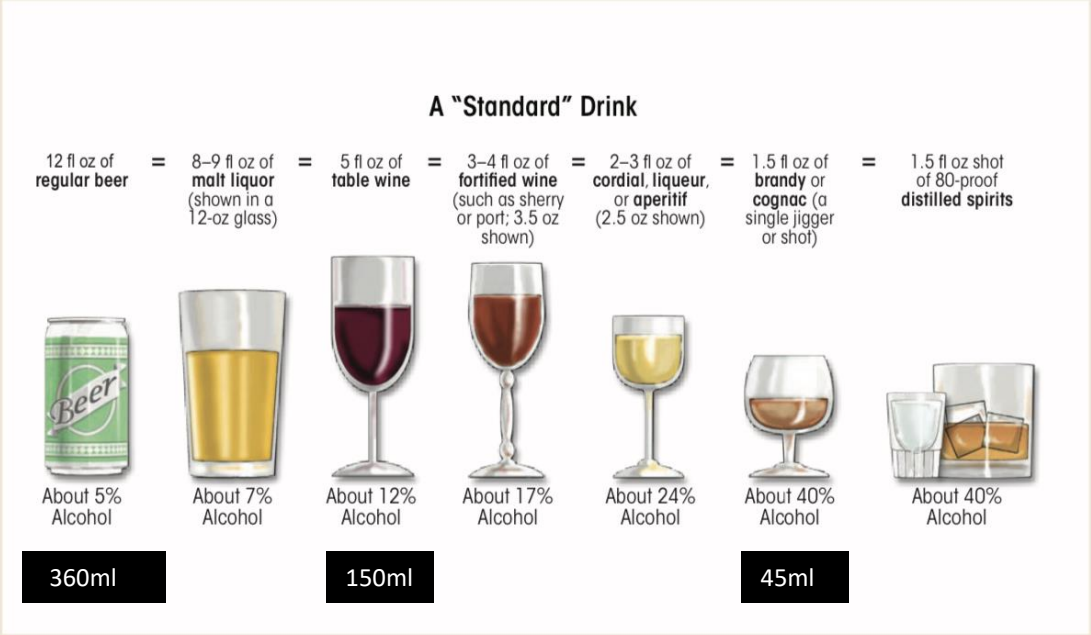


Figure 3 Illustration of "standard drinks" in order of increasing ethanol content among currently available alcoholic beverages. According to the National Institute on Alcohol Abuse and Alcoholism, the amount of beverage containing approximately 14 g of pure ethanol is defined as a standard drink. The percent of pure alcohol, expressed as alcohol by volume (alc/vol), varies by beverage. Thus, 12 ounces (360 mL) of beer at 6 percent alc/vol, 5 ounces (150 mL) of wine at 12 percent alc/vol, or 1.5 ounces (45 mL) of distilled spirits at 40 percent alc/vol each are equivalent to a standard drink. Although the standard-drink amounts are helpful for following health guidelines, they may not reflect customary serving sizes. In addition, although the alcohol concentrations listed are typical, there is considerable variability in actual alcohol content within each type of beverage.

Threshold for alcohol consumption:

2010 meta-analysis:

- **Recommendation**:
  - limit intake to no more than 2 drinks for females & 3 drinks for males (each containing 10g alcohol) per day.
  - Amount associated with a significant increase in morbidity and mortality

Alcohol drinking patterns:

- **Binge drinking risk vs Daily continuous**
- **Cessation** at any point in the natural history, reduces progression & complications

Alcohol Use Disorder

CRITERIA FOR DIAGNOSIS

- **11 criteria**
- Occur within **12month period**
- **2 + is diagnostic** → increasing no. →severity

Table 2. DSM-V criteria for alcohol use disorder.

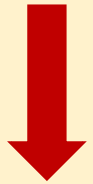
Definition: A problematic pattern of alcohol use leading to clinically significant impairment or distress, as manifested by at least two of the following, occurring within a 12-month period:
1. Alcohol is often taken in larger amounts or over a longer period than was intended.
2. There is a persistent desire or unsuccessful efforts to cut down or control alcohol use.
3. A great deal of time is spent in activities necessary to obtain alcohol, use alcohol, or recover from its effects.
4. Craving, or a strong desire or urge to use alcohol.
5. Recurrent alcohol use resulting in a failure to fulfil major role obligations at work, school, or home.
6. Continued alcohol use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of alcohol.
7. Important social, occupational, or recreational activities are given up or reduced because of alcohol use.
8. Recurrent alcohol use in situations in which it is physically hazardous.
9. Alcohol use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by alcohol.
10. Tolerance, as defined by either of the following: a. A need for markedly increased amounts of alcohol to achieve intoxication or desired effect. b. A markedly diminished effect with continued use of the same amount of alcohol.
11. Withdrawal, as manifested by either of the following: a. The characteristic withdrawal syndrome for alcohol b. Alcohol (or a closely related substance, such as a benzodiazepine) is taken to relieve or avoid withdrawal symptoms.
The presence of at least 2 of these criteria indicates an AUD. The severity of the AUD is defined as: Mild: The presence of 2 to 3 criteria Moderate: The presence of 4 to 5 criteria Severe: The presence of 6 or more criteria

AUD, alcohol use disorder.

SCREENING

- Primary care level/ GP
- Emergency dept
- High risk populations

- Clinical signs – liver disease or etoh use:
  - *bilateral parotid hypertrophy / sarcopenia/malnutrition / dupuytrens contractures/ gynecomastia / extensive spider naevi*



- Brief intervention
- Referral for MDT management

Screening Tools

- **Quantity frequency questionnaire** and diaries
- **Apps** – Drinkaware

- **AUDIT**

  - ✓ validated and translated. Different countries. Gold standard. Good sensitivity and specificity
  - ✓ **10 questions**
  - ✓ Consumption (1-3)
  - ✓ Dependence (4-6)
  - ✓ Alcohol related problems (7-10)
  - ✓ 2 cut offs – dependence and Risky drinking

  - ✓ **AUDIT C** – first 3 questions- screening for risky drinking

  - ✓ **3rd Question: NIAAA**
    - **How often do you have 5 drinks or more on one occasion**

Patient name: _____

Date of birth: _____

Alcohol screening questionnaire (AUDIT)

Drinking alcohol can affect your health and some medications you may take. Please help us provide you with the best medical care by answering the questions below.

One drink equals:  12 oz. beer  5 oz. wine  1.5 oz. liquor (one shot)

1. How often do you have a drink containing alcohol?	Never	Monthly or less	2 - 4 times a month	2 - 3 times a week	4 or more times a week
2. How many drinks containing alcohol do you have on a typical day when you are drinking?	0 - 2	3 or 4	5 or 6	7 - 9	10 or more
3. How often do you have five or more drinks on one occasion?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
4. How often during the last year have you found that you were not able to stop drinking once you had started?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
5. How often during the last year have you failed to do what was normally expected of you because of drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
6. How often during the last year have you needed a first drink in the morning to get yourself going after a heavy drinking session?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
7. How often during the last year have you had a feeling of guilt or remorse after drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
8. How often during the last year have you been unable to remember what happened the night before because of your drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
9. Have you or someone else been injured because of your drinking?	No		Yes, but not in the last year		Yes, in the last year
10. Has a relative, friend, doctor, or other health care worker been concerned about your drinking or suggested you cut down?	No		Yes, but not in the last year		Yes, in the last year
	0	1	2	3	4

Have you ever been in treatment for an alcohol problem? ◯ Never ◯ Currently ◯ In the past

I	II	III	IV
0-3	4-9	10-13	14+

AUD

Associations:

- **Psychiatric disorders**
  - Anxiety and affective disorders
  - Independent OR concurrent*

  *disappear with rx etoh
- **Smoking**
- **Polysubstance abuse**

Management of Alcohol Withdrawal Syndrome

- **Mild - moderate: 6-24h after last drink**
  - Hypertension; tachycardia; tremor; hyperreflexia; irritability; anxiety; headache; nausea & vomiting
- **Severe:**
  - Delirium tremens, seizures, coma, cardiac arrest and death

Severity scores: CIWA-Ar

- **Pharmacological Rx – moderate/ severe**
  - **Benzodiazepines** – decrease symptoms/seizures/ DT
    - Long-acting – diazepam
    - Short-acting – lorazepam – better in elderly and hepatic dysfunction
  - **Clomethiazole –**GABBA-mimetic
    - Sedative & hypnotic
  - 10-14days max

Medical management of AUD in ALD

Disulfiram	• Old drug→ avoid in severe ALD • Hepatotoxicity
Naltrexone	• Opioid antagonist • Oral formulation • Intramuscular • Potential hepatotoxicity – ALD not currently recommended
Nalmefene (reduction of heavy drinking)	• Opioid modulator approved in Europe for AUD • Aim to reduce amount of ETOH consumption • Early stages of liver disease
Acamprosate	• Modulator of glutamatergic receptor system • Cautious in renal failure
Topiramate	• Anticonvulsant • Safe and efficient in reducing heavy drinking • Decrease in liver enzymes • Not tested in ALD • Avoid in HE
Baclofen	• GABA-B receptor agonist • Increases abstinence and prevents relapse • **The only drug tested in AUD with significant liver disease & cirrhosis** • FRENCH ANSM- recommend no exceed dose of 80mg /day/ studies with high doses controversial results

Medical management of AUD in ALD

- Gabapentin – concomitant pain
- Ondansetron
- Modest results with pharmacology

Non pharmacology – main stay

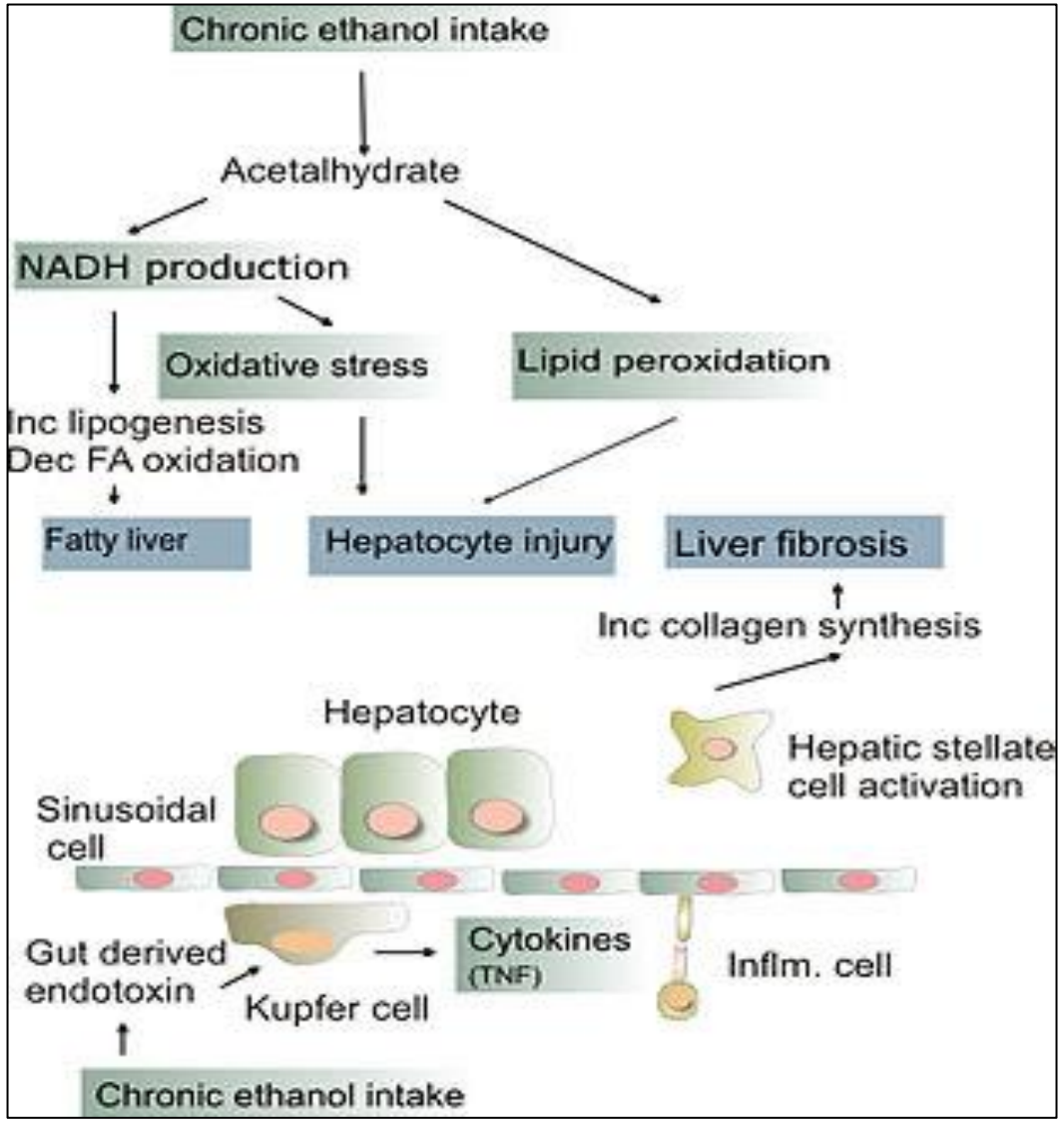
BRIEF INTERVENTIONS
MDT

Motivational & nonjudgemental
Cochrane review showed brief interventions can reduce consumption by average of 57g per week in men
psychosocial therapies
support groups

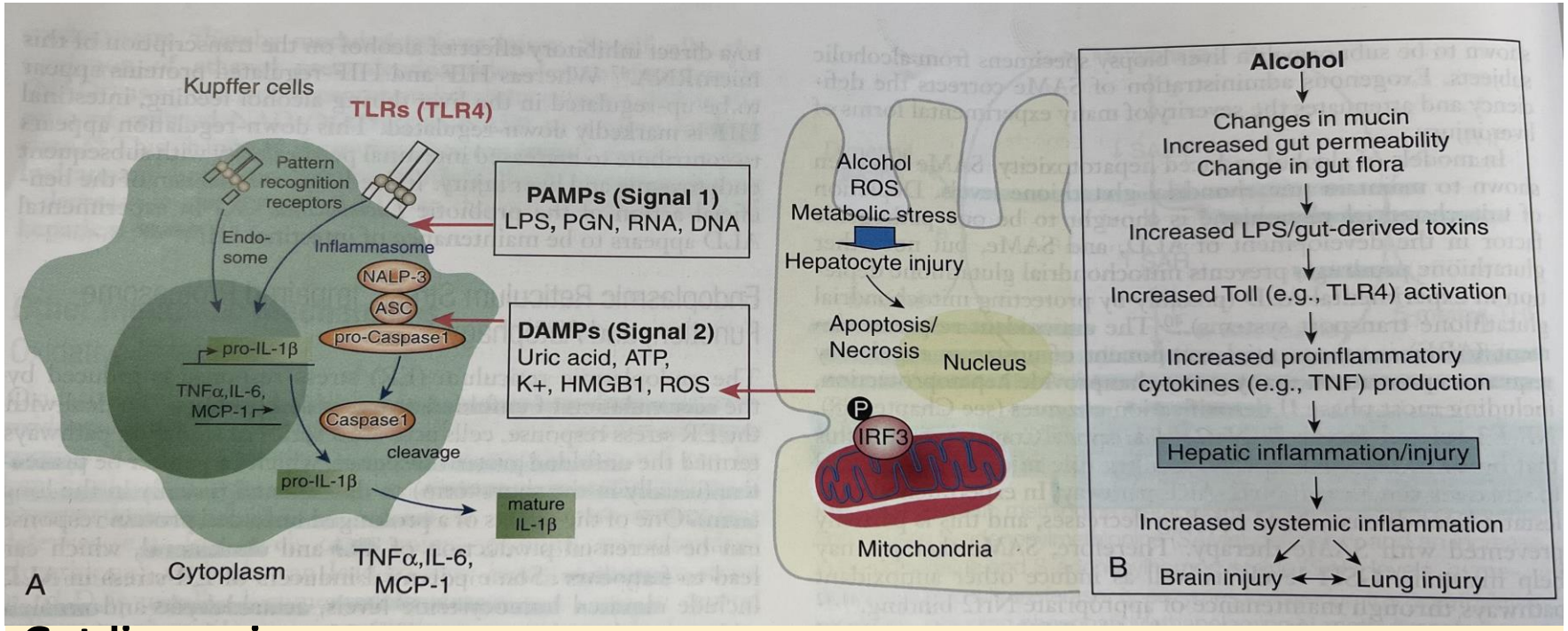
Pathogenesis of ALD

Acetaldehyde

- **Forms adducts with reactive residues on proteins or small molecules**
  - Chemical modification → cellular toxicity
  - Stimulates host immune response
- **Impairs glutathione transport /depletion**
  - Sensitizes cells to **TNF alpha** mediated killing
- **Lipid peroxidation**
- **Mitochondrial damage & dysfunctio**n

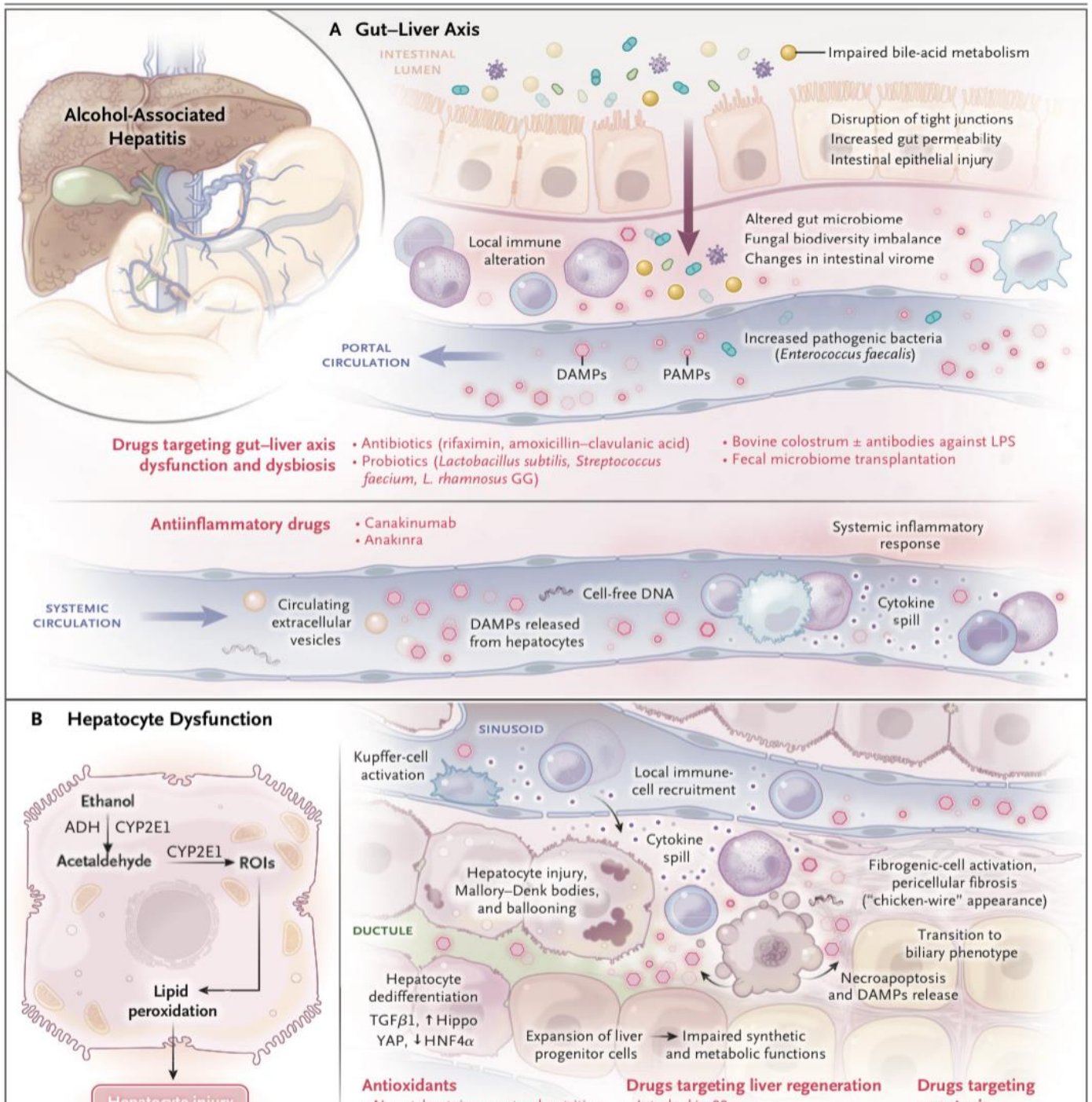


Pathogenesis of ALD



Gut-liver axis

- **Increase in gut permeability** →Bacterial translocation & PAMPS →PV→ liver
- **PAMPS** – gut derived - pathogen associated molecular patterns -LPS
  - Recognized by specific receptors –TLR- innate immune system activation –induce inflammation – hepatocyte death – fibrotic response
- **Injured hepatocytes release DAMPs** –damage associated molecular patterns
  - Second signal that further activates inflammasomes eg. caspase 1 complex.



- **Upstream activation -TGF1** - impairment of hepatocyte regeneration and redifferentiation → profound synthetic dysfunction

- **Massive expansion of progenitor cells – ductular reaction (futile attempt to regenerate**)

- SIRS and immune dysfunction – favoring bacterial infections and ACLF

Clinical presentation

ALD

TABLE 6. Symptoms and Signs Associated With Alcoholic Liver Disease

Symptoms

- Odor of alcohol on breath*

Nonspecific

- Tiredness
- Abdominal pain
- Day/night reversal (sleepy by day, wakeful at night)
- Peripheral neuropathy
- Weight gain (due to ascites)
- Weight loss (due to loss of proximal muscle mass)
- Confusion (as part of hepatic encephalopathy)
- Loss of sexual drive
- Amenorrhea

Signs

- Skin: Spider angiomata, palmar erythema, leukonychia, ecchymoses
- Eyes: Icteric conjunctivae
- Musculoskeletal: Loss of proximal muscle mass, especially temporal wasting
- Cardiovascular: Systemic hypotension; tachycardia suggests alcohol withdrawal syndrome*
- Abdominal: Ascites, hepatomegaly, splenomegaly, bruits, caput medusa
- Reproductive: Gynecomastia, gonadal atrophy in men
- Neurological:
  - Alcohol withdrawal syndrome*: Fine tremor, psychomotor agitation, transient hallucinations or illusions
  - Hepatic encephalopathy: Coarse flapping tremor (asterixis), altered consciousness
  - Wernicke-Korsakoff syndrome
- Hands: Dupuytren's contracture

*Specific for alcohol; otherwise nonspecific.

Systemic Manifestations of chronic alcohol use

General Appearance
- **Excitability, irritability, nervousness**
- **Facial erythema**
- **Puffiness of face and eyelids**
- **Alcohol on breath**
- Parotid swelling
- Hand tremor
- Hoarseness, heavy cough (excessive smoking)
- Cigarette burns, tobacco stains
- Unexplained cuts and bruises

Skin
- Folliculitis of beard
- Rosacea, seborrheic dermatitis
- Psoriasis
- Palmar erythema
- Dilated venules
- Spider nevi

Mouth
- **Coated tongue**
- Periodontal disease
- Cancer of tongue, mouth

Digestive Tract
- **Morning nausea and vomiting**
- **Dypepsia, peptic ulcer disease**
- **Esophageal reflux**
- **Dysphagia**
- **Recurrent diarrhea**
- **Anorexia**
- **Vague or recurrent abdominal pain**
- Fatty liver
- Hepatitis (alcoholic)
- Acute or chronic pancreatitis
- GI bleeding
- Cirrhosis
- Cancer of esophagus, stomach, liver, pancreas, colon, rectum

Cardiovascular
- **Hypertension**
- **Palpitations**
- **Tachycardia**
- Arrythmias (especially atrial fibrillation)
- Coronary artery disease
- Stroke (especially hemorrhagic)
- Cardiomyopathy
- Cardiomyopathy

Respiratory
- **Recurrent URIs, bronchitis**
- Recurrent pneumonia
- Aspiration pneumonia
- Tuberculosis
- Chronic obstructive pulmonary disease

Genitourinary/Endocrine
- **Hyperglycemia or hypoglycemia**
- **Impotence**
- **Menstrual irregularities**
- Testicular atrophy
- Gynecomastia

CNS/Psychiatric
- **Insomnia**
- **Anxiety**
- **Depression, suicide**
- **Headaches**
- **Reduced libido**
- **Memory blackouts**
- Seizure
- Tremors
- Peripheral neuropathy
- Subdural hematoma
- Hallucinations
- Delirium tremens
- Wernicke-Korsakoff syndrome

Musculoskeletal
- **Gout**
- Dupuytren's contracture
- Myopathy (especially shoulders)

Trauma
- **Bruises, lacerations**
- **Fractures**
- **Burns**
- **Car, home industrial accidents**
- Drownings

Nutritional
- Vitamin or trace mineral deficiencies

Pediatric/Prenatal
- **intrauterine growth retardation or decreased birth weight**
- Mental retardation, fetal alcohol syndrome

Criminal
- Assault
- Rape
- Child abuse, molestation
- Homicide

Alcohol related organ damage

- **Heart-** alcoholic cmo
- **Pancreas-** acute and chronic pancreatitis
- **Kidney** – IgA induced nephropathy
- **CNS and PNS-** PN/ cerebellar/ HE/ Wernicke's encephalopathy/ Withdrawal

- **https://www.researchgate.net/figure/CLINICAL-MANIFESTATIONS-OF-ALCOHOLISM_tbl1_14734259**

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TABLE 5. Factors Affecting the Risk of Alcoholic Liver Disease

Implicated in increasing the risk of alcohol-associated liver injury

- Alcohol dose above threshold of 1 drink/day (women), 2 drinks/day (men)
- Pattern of consumption: daily drinking; drinking while fasting, binge drinking
- Smoking cigarettes
- Women compared with men
- Genetics*: *PNPLA3, TM6SF2, MBOAT7, HSD17B13*
- Increased BMI
- Presence of comorbid conditions: chronic viral hepatitis, hemochromatosis, NAFLD, NASH

Implicated in ameliorating the risk of alcohol-associated liver injury

- Coffee consumption

Equivocal data regarding effect on the risk of alcohol-associated liver injury

- Type of alcohol consumed
- Moderate alcohol use in patients with high BMI

*Typically in studies of genetic predisposition, one allele of a risk gene will be associated with increased risk compared with the alternate allele; thus, each of these genes are listed as being implicated in increasing risk.

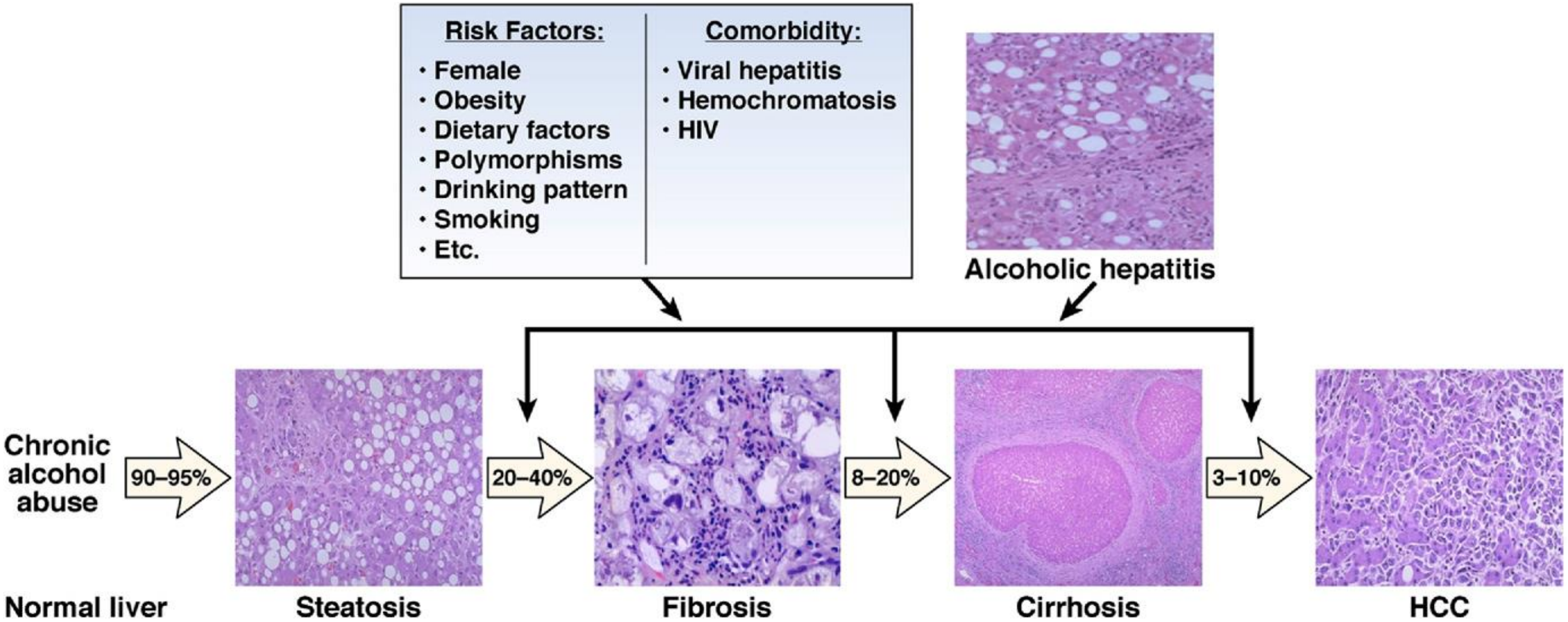


Figure 1 Spectrum of ALD, risk factors, and comorbidity. More than 95% of heavy drinkers develop fatty liver, but only up to 35% of this population

ALD

Diagnostic tests

Screening and clinical diagnosis

- ALD → regular alcohol consumption of **> 20g/day for women and > 30g/day for men (EASL)**
- Clinical and biological abnormalities of liver injury
- **Asymptomatic** ~ with histological features of ALD
- Consider ALD in those presenting with **extrahepatic manifestations**

Evaluation AUD

Noninvasive:

- **ALD/NAFLD index**
  - Proposed for the differential diagnosis of ALD and NAFLD
  - 4 parameters -MCV/ AST/ALT ratio/BMI and gender
- **Detect Fibrosis**
  - **Advanced fibrosis can present with normal LFT**
  - **Hep** B/C/ AIH/ alpha 1 antitrypsin/ caeruloplasmin

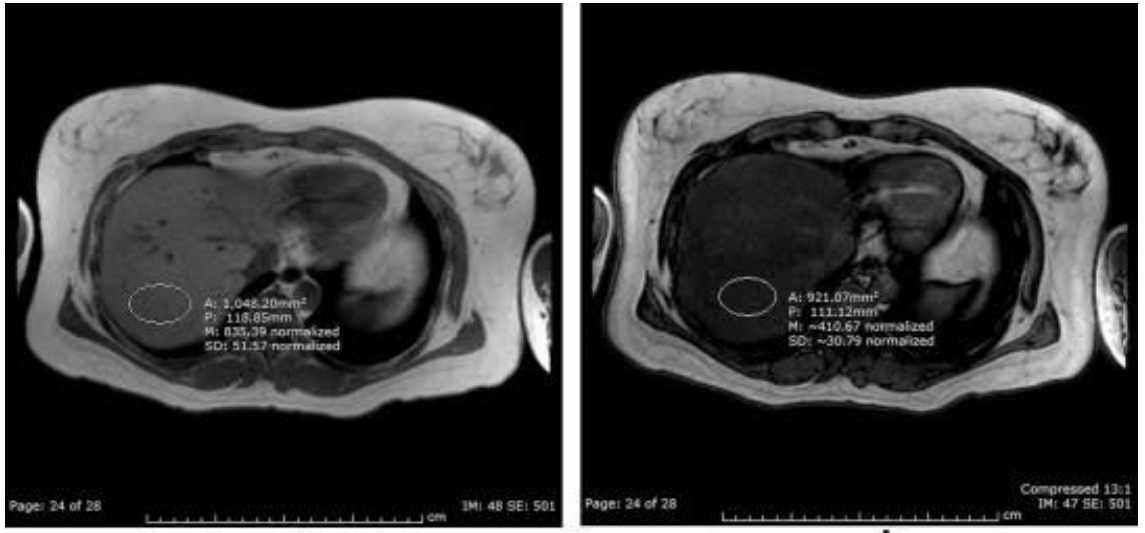
- **Suspected advanced fibrosis and cirrhosis:**
  - **Evaluated liver function & evidence of portal hypertension:**
    - serum albumin/ prothrombin time or INR/ serum bilirubin
    - Platelets and WCC

Hepatic imaging

- ✓ Exclude other causes of CLD
- ✓ Complications

- **AUS /CT or MRI**

  - ➢ **Allow for quantification of steatosis**
    - ✓ AUS: threshold 20-30%.
    - ✓ MRI: 5-10%.



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Liver biopsy

Indications

Diagnostic uncertainty

- To establish **definite diagnosis of ALD (possible, probable & definite)**
- Assess **precise staging (clinical trials) / prognostication**

- Exclude other possible etiologies or **additional** causes of liver injury

- **Coexisting liver disease** – 20% of AUD & abn LFT
- Inconclusive noninvasive test results

- Risk vs clinical benefit and therapeutic consequences – invasive – morbidity & mortality are significant
- Complications: intrahepatic bleeding, pneumothorax – in 2% of patients

NOT recommended in all patients

- Morphological spectrum of ALD

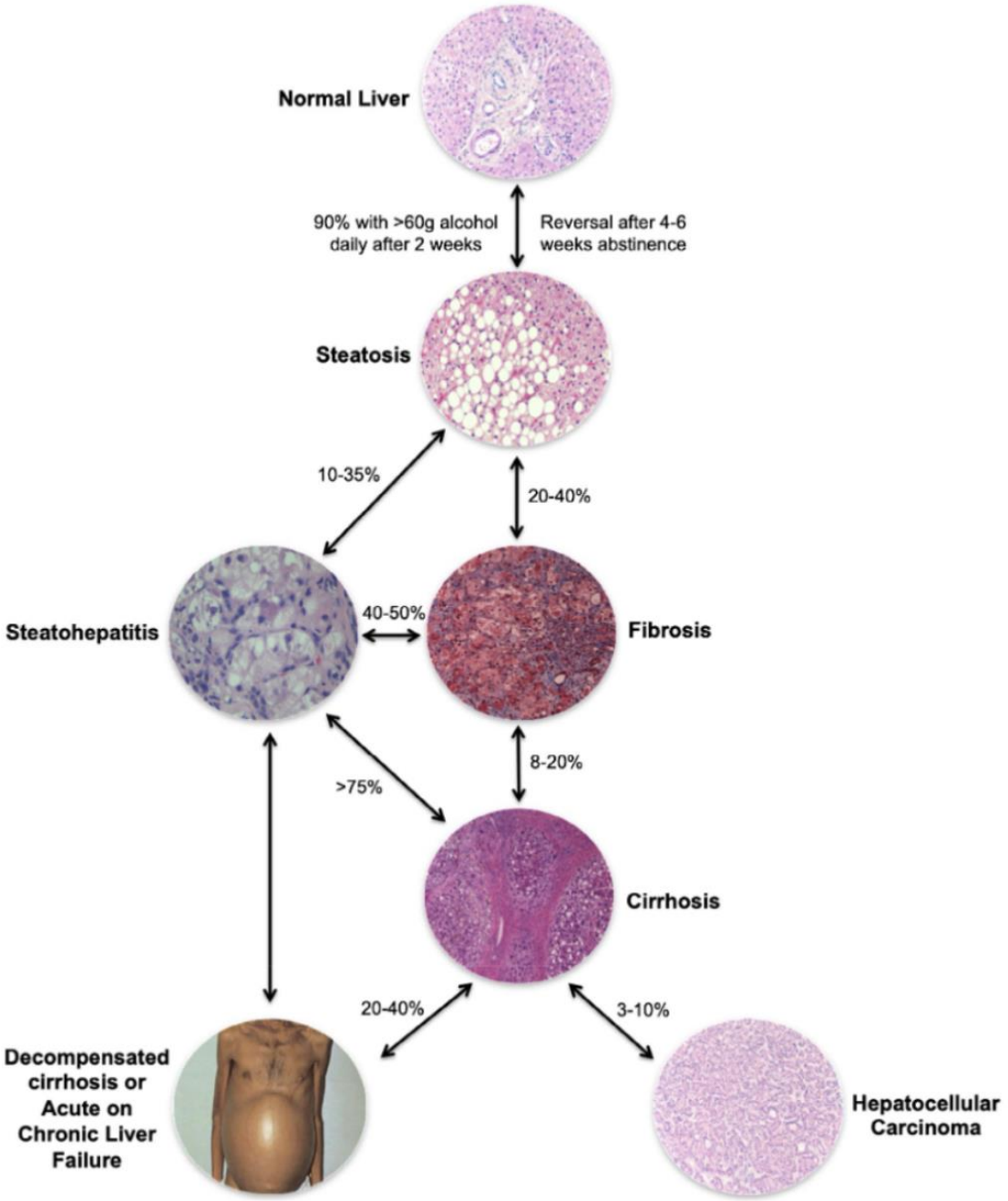
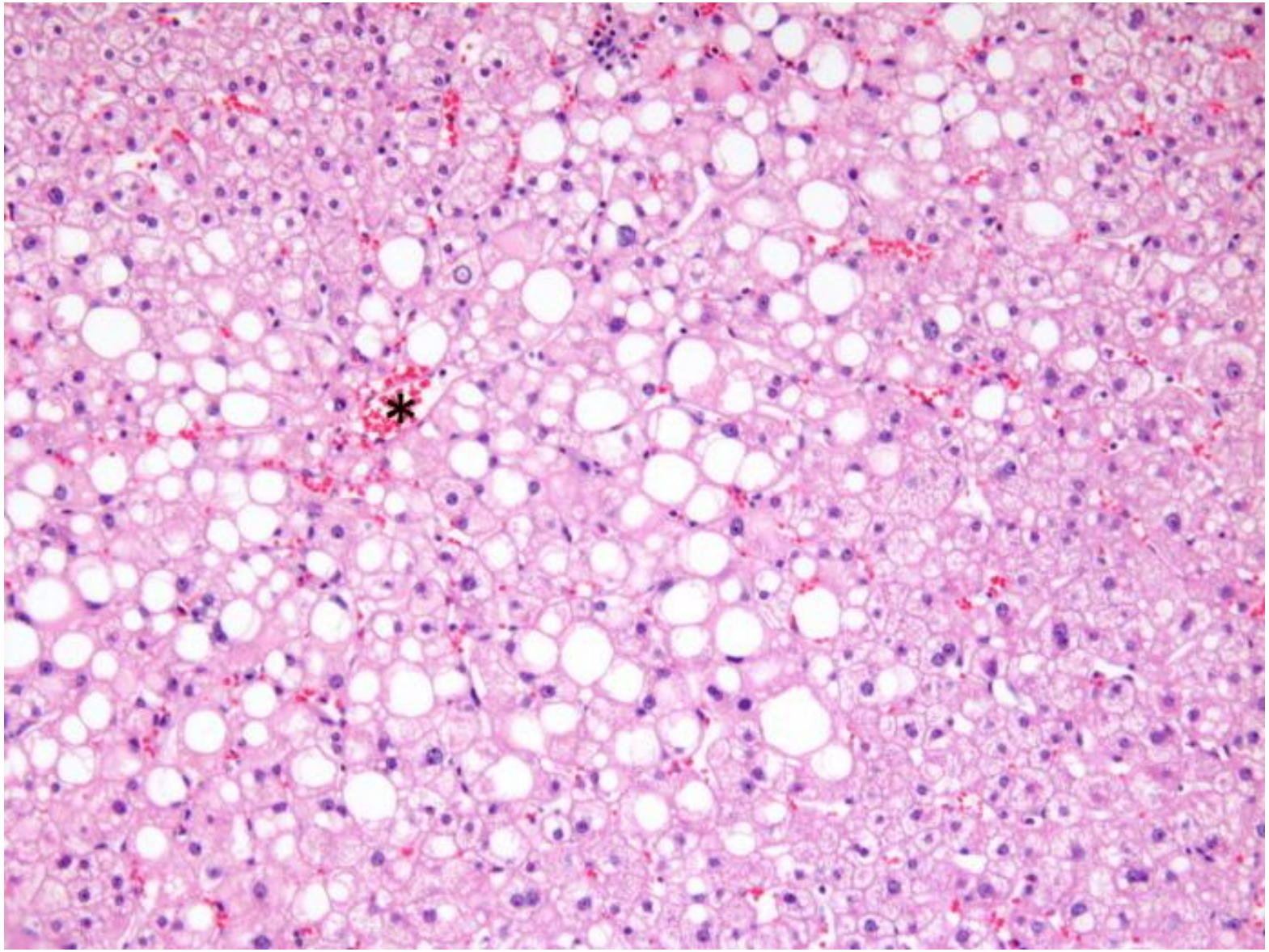


FIG. 1. Natural history of alcohol-associated liver disease. Images courtesy of Dr. M. Isabel Fiel.

Histological features ALD

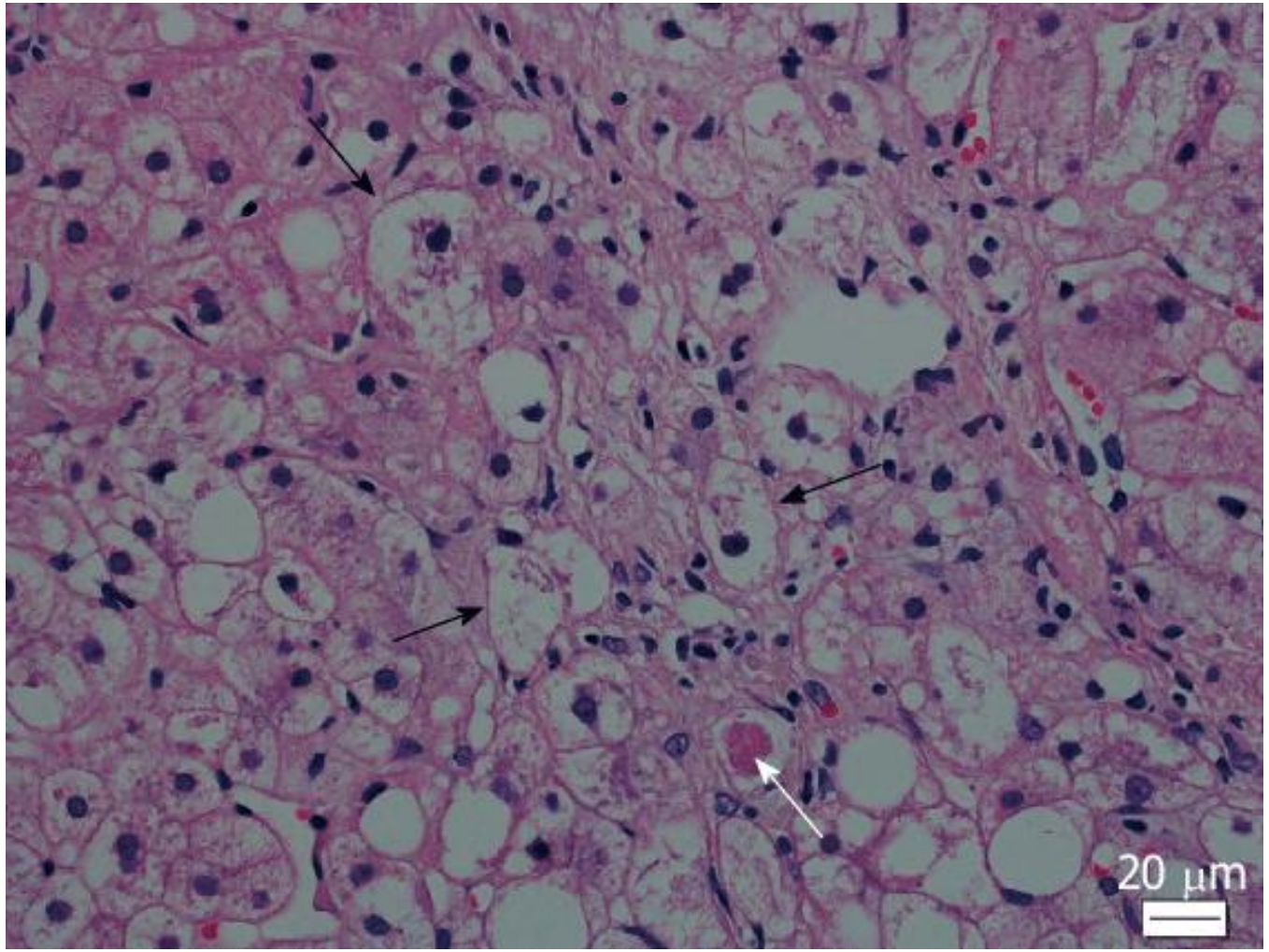
Macrovesicular steatosis

- Eventually →Mixed type: Variable blend of macro and micro-vesicles



Hepatocellular injury with ballooning & potentially necrosis

- **Hepatocyte Ballooning**
  - Swelling, rounding and pale staining cytoplasm
- Loss of cytoplasmic staining of keratin 8 and 18
  - (K8/18- constituents of intermediate filament cytoskeleton)
- Expression of sonic hedgehog on immunohistochemistry
- **Mallory – Denk Bodies** (composed of k8/18)



Ballooning and Mallory-Denk bodies in alcoholic steatohepatitis. Ballooned hepatocytes are recognized as swollen hepatocytes with rarefied cytoplasm (black arrows). Mallory-Denk bodies are eosinophilic irregularshaped aggregates in the cytoplasm of hepatocytes (white arrow) (hematoxylin and eosin staining)

https://www.researchgate.net/figure/Ballooning-and-Mallory-Denk-bodies-in-nonalcoholic-steatohepatitis-Ballooned-hepatocytes_fig2_268450793

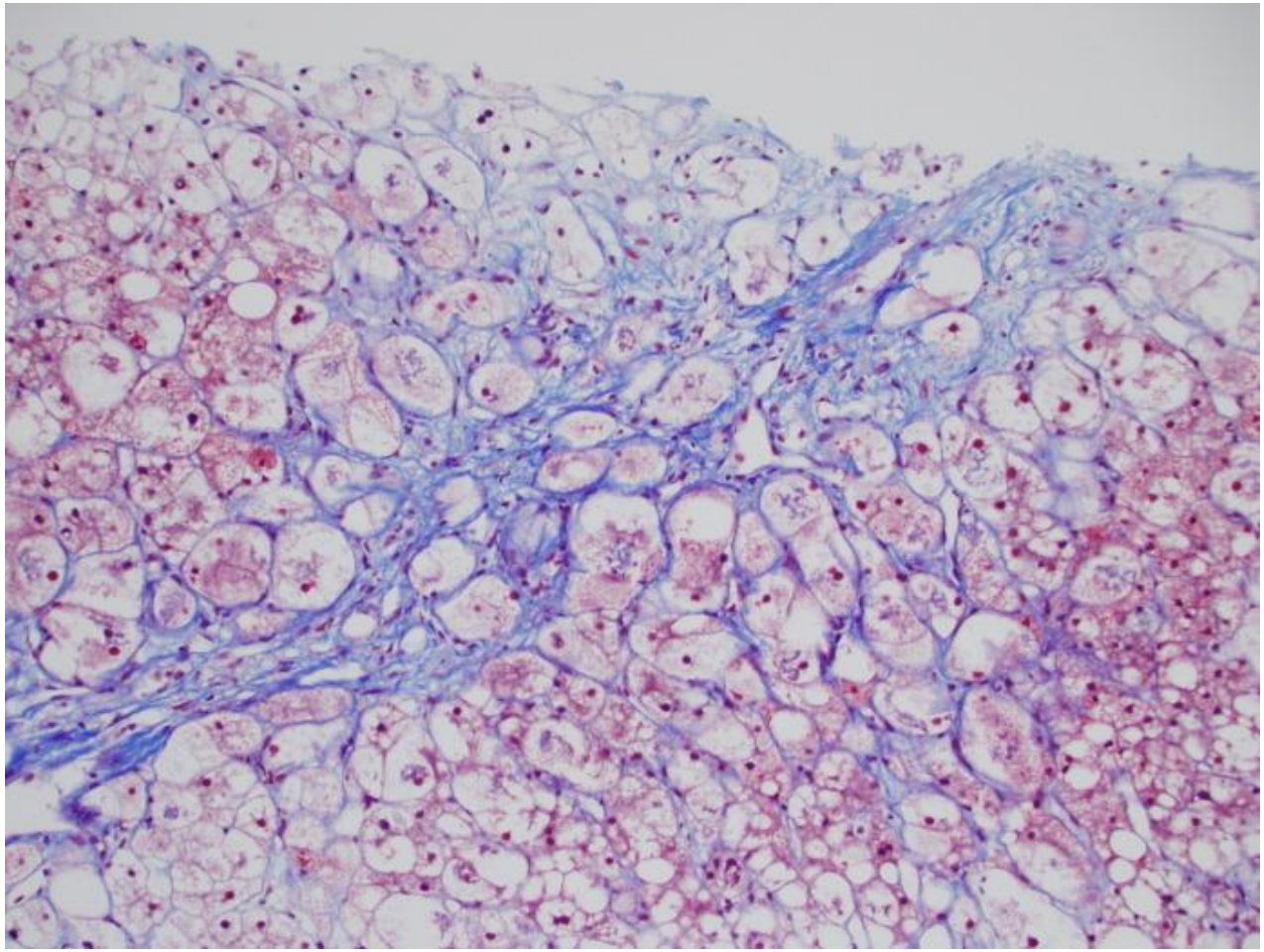
ASH histology

- **Lobular inflammation** (neutrophils)
- **Megamitochodria**

- **Fibrosis**
  - Central based parenchymal feature (mostly)
  - **Pericellular and sinusoidal fibrosis**
  - **Chicken wire fibrosis**

- **In Severe ASH**
  - Ductular reaction
  - Bilirubinostasis
  - Sclerosing hyaline necrosis
  - Alcoholic foamy degeneration (large portions of parenchyma affected by microvascular steatosis)
  - Fibro-obliterative changes- hepatic veins, portal acute inflammation

- Cirrhosis <steatosis



- **Alcoholic Hepatitis Histologic Score (AHHS)**

Markers of Fibrosis in AH

- **Serum markers -** indirect and direct
  - **FibroTest/ APRI/ FIB4**
  - **ELF: the enhanced liver fibrosis test**
    - ❑ 3 direct markers
    - ❑HA; PIIINP; tissue inhibitor of metalloproteinase-1
    - ❑Surrogate for ECM turnover
- Direct: surrogate markers for extracellular matric turnover

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Table 4. Diagnostic performance of some non-invasive serum fibrosis tests for diagnosis of cirrhosis in patients with ALD in studies.

Test	Cut-off	Prevalence of F4 (%)	AUROC (95% CI)	PPV (%)	NPV (%)	Reference
Hyaluronic acid	250 μg/L		0.78	35	98	143
PGAA index*	10	27	0.87 (0.79–0.92)	72	92	144
FibroTest	≥0.70	31	0.94 (0.90–0.96)	73.4	93.5	28,91
	≥0.75	15	0.88 (0.79–0.93)	43.9	92.8	
Enhanced liver fibrosis (ELF) test**	≥10.5	23	0.92 (0.89–0.96)	71	94	142
Fibrometer	≥0.5	31	0.94 (0.90–0.97)	53.7	98.9	91
FIB-4	<1.45	31	0.80 (0.72–0.86)	n.a.	n.a.	28,91
	<1.45	15	0.80 (0.71–0.87)	n.a.	n.a.	

ALD, alcoholic liver disease; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUROC, area under the receiver operating characteristic curve; CDT, carbohydrate deficient transferrin; EtG, ethyl glucuronide EtOH, ethanol; GGT, γ-glutamyl transpeptidase; n.a., not available; NPV, negative predictive value; PPV, positive predictive value; UTI, urinary tract infection.

*PGAA index: combines α2alpha-2-macroglobulin, prothrombin time, serum GGT, serum apolipoprotein A1.

**ELF combines hyaluronic acid (HA), the N-terminal pro-peptide of collagen type III (PIIINP) and tissue inhibitor of metalloproteinase-1 (TIMP-1). The test is validated for

Liver Stiffness – transient elastography

Fibroscan

- **Fibrosis but superimposed AH – steatohepatitis** and inflammation
- **Confounder** →increases LSM independent of stage of fibrosis
- Cutoffs higher than viral ?higher degree of fibrosis in ALD
- **IF ALT > 100 – interpret with caution. False reading**
- Alcohol consumption may modify readings
- NAFLD – higher accuracy in determining advanced fibrosis
- Not extensively evaluated in ALD

Condition	KPa Suggested values for Fibrosis staging			
	F0 – F1	F2	F3	F4
NAFLD or NASH	2 - 8.5	8.5 – 9.5	9.5 – 13.5	>13.5
Alcohol Related Disease	2 - 9	9 – 12	12 – 18.5	> 18.5
Primary Biliary Cholangitis	2 - 8.5	8.5 – 10.5	10.5 – 16.5	> 16.5
Autoimmune Hepatitis	2 - 6	6 – 10.5	10.5 - 16	> 16
Hepatitis B	2 -7	7 – 9.5	9.5 – 12.5	> 12.5
Hepatitis C	2 -7	7 – 9.5	9.5 – 12.5	> 12.5
HIV / HCV coinfection	2 -7	7 – 11.5	11.5 - 14	> 14

Based on > 2300 peer-reviewed publications (2020) however these are NOT absolute and should be discussed with your physician

Tests for alcohol consumption

Indirect

GGT

- loses its specificity in advanced liver disease/ activity elevated in extensive fibrosis regardless of the cause.

AST rarely above 300, ALT lower

AST/ALT ratio >1.5-2 (not sensitive in cirrhosis)

MCV

CDT – carbohydrate deficient transferrin

- Result of alcohol inhibition of transferrin glycosylation
- Reported as **%CDT per total transferrin (**account for differences in transferrin levels
  - **Confirms heavy alcohol consumption**
    - **>50-80g daily intake over 1-2weeks**.
    - Normalizes 2-3wk cessation
    - **Low sensitivity 25-50% - false positive** – severe liver disease in the absence of ETOH consumption
    - Affected by gender/smoking/ BMI
    - Posttransplant use is more accurate

Direct markers of alcohol consumption

Products of non-oxidative metabolism of ethanol

- **Longer detection** – than blood or exhaled air levels
- **More Specific**

Ethyl glucuronide

Urine (uEtg)

- Confirm abstinence
- Can monitor regularly – eg. addiction clinic & on Ltx waiting listing
- Detect ETOH for 80hrs
- **Not influenced by compensated or decompensated cirrhosis**
- Sens 89% specificity 99%

Scalp hair (hEtg)

- short and long-term use
- 1cm length represents 1 month
- Problems: Different Types of hair/ hair dye/ products etc
- Good correlation – with daily etoh intake

Other : ethyl sulfate/ phosphatidylethanol (PEth)/ fatty acid ethyl esters (FAEEs)

Table 5. Direct and indirect markers of alcohol consumption.

Biomarker	Biological material	Detection window	EtOH amount	Sensitivity	Specificity	Confounding factors	Ref.
Indirect alcohol markers							
GGT	Serum		Chronic excessive	42–86%	40–84%	Liver disease, BMI, sex, drugs	79,151,153,154,170
AST	Serum		Chronic excessive	43–68%	56–95%	Liver and muscle diseases, BMI, drugs	
ALT	Serum		Chronic excessive	30–50%	51–92%	Liver disease, BMI, drugs	
MCV	Serum		Chronic excessive	24–75%	56–96%	Vitamin B12, folic acid deficiency, haematological diseases	
%CDT	Serum	1–2 weeks	50–80 g/d for >1–2 weeks	25%–84%	70%–98%	Liver cirrhosis/disease, nicotin, transferrin level, weight, sex, pregnancy, rare genetic variations	
Direct alcohol markers							
Breath alcohol	Exhaled air	4–12 h		97%	93%	Alcohol-containing mouth wash	171
EtOH	Serum	4–12 h					
EtG	Urine	Up to 80 h	>5 g	89%	99%	*Increases results:* - Accidental contamination of food, mouth wash, alcohol free beer, etc. with alcohol - UTI *Incresed results:* - Urine dilution deliberately or by diuretics - UTI	154,163
EtG	Hair	≤6 mo	>20–40 g/d for >3 months	85–92%	87–97%	*Increases results:* - Seriously impaired renal function - EtG containing hair treatment *Decreases results:* - Hair treatment: dying, perming, bleaching	168,172–175

Alcohol associated hepatitis:

- **Clinical diagnosis -NIAAA Alcoholic Hepatitis Consortia proposed criteria**

1. Onset of jaundice within previous 8 weeks

1. Ongoing alcohol consumption –>40g women and >60g men – for 6 MONTHS with less than 60 days abstinence before the onset of jaundice

1. Total bilirubin >50umol/l

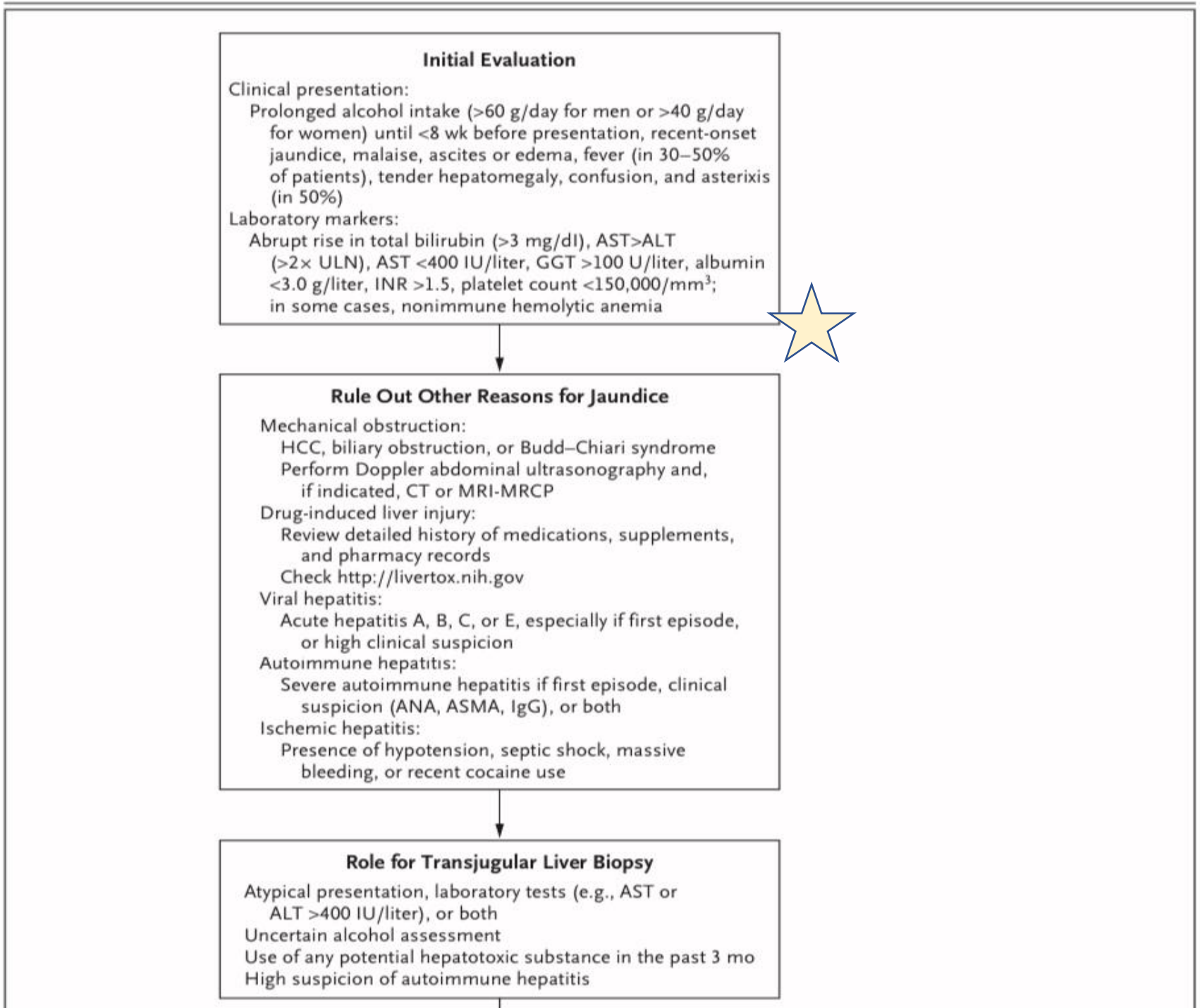
1. AST >50 umol/l

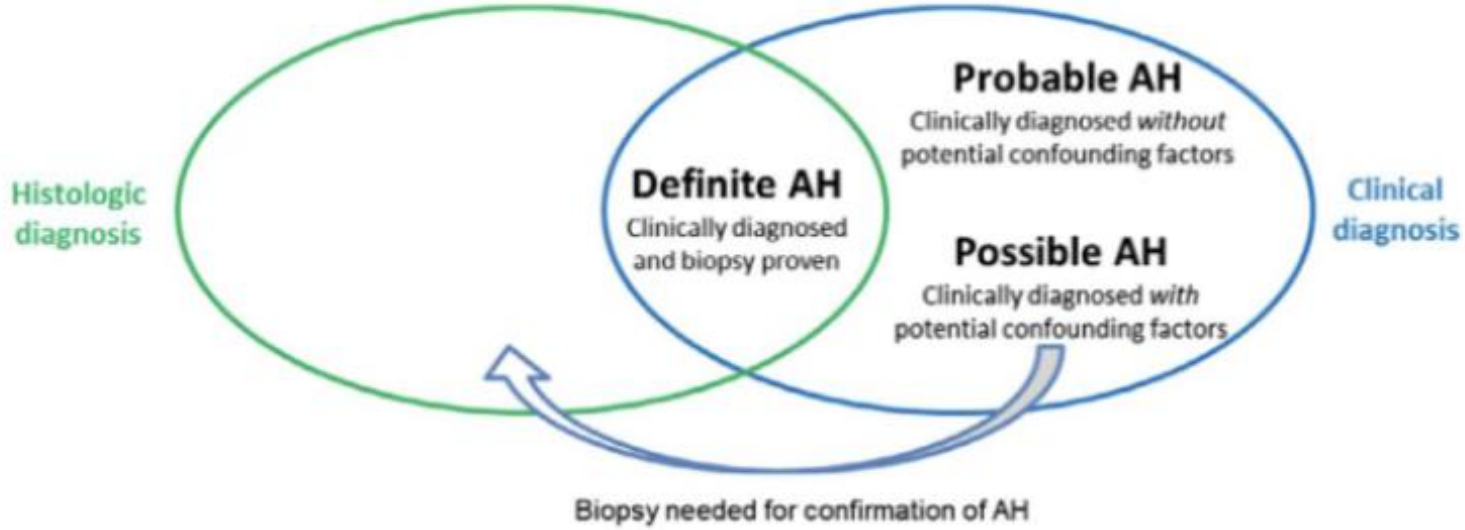
1. AST:ALT ratio >1.5
2. Both values less than 400

1. Rule out other liver disease -DILI / Ischemia/ Viral/ obstructive jaundice

- With or without - Liver **decompensation** (ascites & encephalopathy)
- **Complicate with bacterial infections – ACLF – MOF – high mortality of 20-50% at 3months**

NEJM: AH


Initial Evaluation
Clinical presentation:
Prolonged alcohol intake (>60 g/day for men or >40 g/day for women) until <8 wk before presentation, recent-onset jaundice, malaise, ascites or edema, fever (in 30–50% of patients), tender hepatomegaly, confusion, and asterixis (in 50%)
Laboratory markers:
Abrupt rise in total bilirubin (>3 mg/dl), AST>ALT (>2× ULN), AST <400 IU/liter, GGT >100 U/liter, albumin <3.0 g/liter, INR >1.5, platelet count <150,000/mm3; in some cases, nonimmune hemolytic anemia
Rule Out Other Reasons for Jaundice
Mechanical obstruction:
HCC, biliary obstruction, or Budd–Chiari syndrome
Perform Doppler abdominal ultrasonography and, if indicated, CT or MRI-MRCP
Drug-induced liver injury:
Review detailed history of medications, supplements, and pharmacy records
Check http://livertox.nih.gov
Viral hepatitis:
Acute hepatitis A, B, C, or E, especially if first episode, or high clinical suspicion
Autoimmune hepatitis:
Severe autoimmune hepatitis if first episode, clinical suspicion (ANA, ASMA, IgG), or both
Ischemic hepatitis:
Presence of hypotension, septic shock, massive bleeding, or recent cocaine use
Role for Transjugular Liver Biopsy
Atypical presentation, laboratory tests (e.g., AST or ALT >400 IU/liter), or both
Uncertain alcohol assessment
Use of any potential hepatotoxic substance in the past 3 mo
High suspicion of autoimmune hepatitis



Clinical diagnosis of AH

- Onset of jaundice within prior 8 weeks
- Ongoing consumption of >40 (female) or 60 (male) g alcohol/day for ≥6 months, with <60 days of abstinence before the onset of jaundice
- AST >50, AST/ALT >1.5, and both values <400 IU/L
- Serum total bilirubin >3.0 mg/dL

Potential confounding factors

- Possible ischemic hepatitis (e.g., severe upper gastrointestinal bleed, hypotension, or cocaine use within 7 days) or metabolic liver disease (Wilson disease, alpha 1 antitrypsin deficiency)
- Possible drug-induced liver disease (suspect drug within 30 days of onset of jaundice)
- Uncertain alcohol use assessment (e.g., patient denies excessive alcohol use)
- Presence of atypical laboratory tests (e.g., AST <50 or >400 IU/L, AST/ALT <1.5), ANA >1:160 or SMA >1:80.

FIG. 2. Consensus definitions for alcoholic hepatitis.[123] Abbreviations: AH, alcoholic hepatitis; ALT, alanine aminotransferase; ANA, antinuclear antibody; AST, aspartate aminotransferase; and SMA, smooth muscle antibody.

Evaluation of severity of AH:

Maddrey discriminant function (MDF)

- **Short-term mortality**
- **Cutoff 32 = severe AH**
- Initiate corticosteroids
- **One month survival improved with rx from 50% to 85%**
- Non-severe AH- MDF <32- less than 10% mortality in 1 month

MELD score >20

- Usefulness in predicting 90day mortality in AH

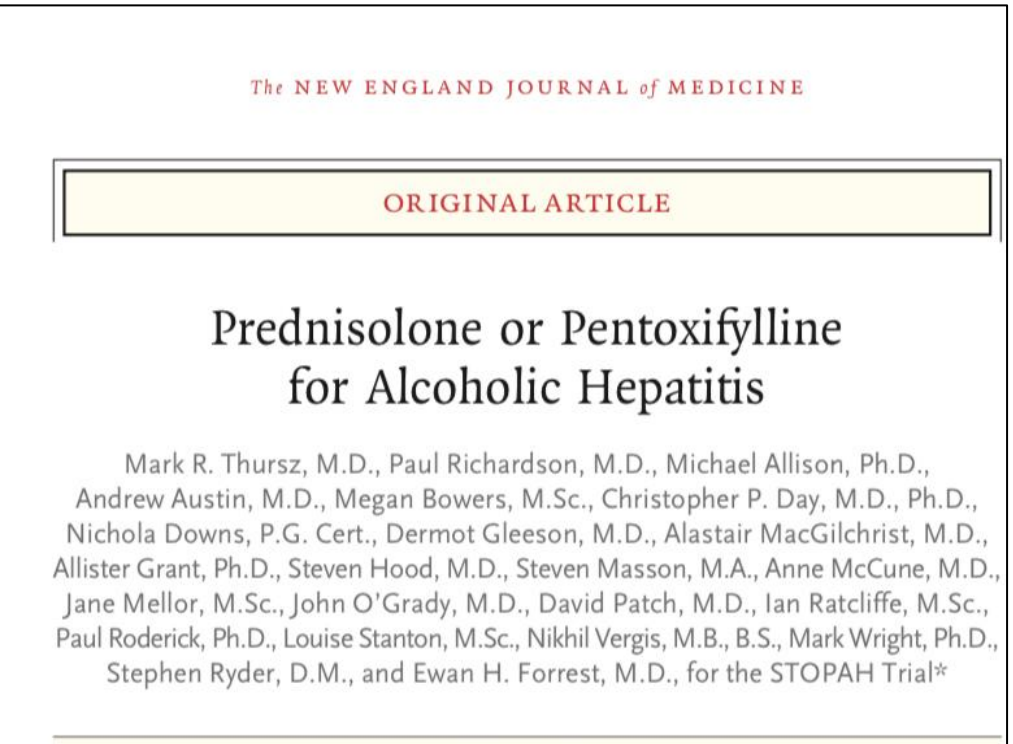
Lille model

- Early improvement has a major impact on short term mortality
- Bili – change at Day 7 of rx
- **Assess steroid responsiveness**
- **>0.45 -nonresponse – discontinue steroids**
- Day 4

Treatment of AH

General measures	Nutrition	Infection
• **Abstinence** • **Risk factors for Wernicke's encephalopathy** • Supp B vitamins/Thiamine • **HE-** lactulose & rifaximin • **Ascites –** salt restriction • **Risk of AKI –** avoid over diuresis/ nephrotoxic agents/ volume expansion -albusol & vasoconstrictors (terlipressin) • Prevent variceal bleed (BB increase r/o AKI)	• **Protein energy malnutrition** • **Daily energy intake: 35-40kcal/kg of BW** • **Daily protein: 1.2-1.5g/kg BW** - NGT or medifeed - **<21.5 kcal/kg bw ~ significant increase in 1 & 6 month mortality & infections** - Parenteral- sepsis	• Frequent and severe • **STOPAH- accounted for 24% of deaths** • **Cirrhosis** • Bacterial overgrowth and dysbiosis-translocation - Corticosteroids enhance infection • Defect in lymphocyte signaling - **Bacterial infection** - **Fungal (16% incidence) -invasive aspergillosis** (ICU) /PCP - Early detection and rx of infection - Controlled infection not CI for steroid use

Corticosteroids



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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*

Most extensively studied drug therapy for AH

- More than 20trials that date back to 40yrs
- Inconsistent results / heterogenicity

STOPAH:

The largest RCT in severe AH is steroids or Pentoxifylline for AH

- A large multicenter double blind trial -was conducted in the UK between 2011 and 2014.
- They enrolled 1103 patients with clinically severe AH.
- **The study did not show statically significant benefit of corticosteroids at 28 days in pts receiving steroids vs placebo.**
- **However post hoc multivariable analysis – corticosteroids were associated with improved 28day survival- NOT 90 days and Not 1 year.**
- S/E: sepsis and GIB
- Prednisone 40mg DLY PO-

  28days – then gradual taper over 3 weeks

Pentoxifylline

- **Phosphodiesterase inhibitor**
- Inhibit production of TNF
- STOPAH- survival with pts receiving PTx was not improved – at 1mth/3mths or 1 yr
- **No longer recommended**

N- Acetylcysteine

- **Antioxidant** – oxidative stress key mechanism in AH
- Restore **glutathione stores**
- **RCT in France – Coadministration with corticosteroids**
  - **Reduced early complications → infection, HRS VS steroids alone**
- NAC- 5 days ivi 10g/day + Pred 40mg dly

Granulocyte colony stimulating factor:

- Glycoprotein that stimulates bone marrow to produce
- neutrophiles and stem cells (CD34+)
- Liver regeneration
- S/C for 5 days
- Negative results in decompensated patients

JOURNAL
OF HEPATOLOGY

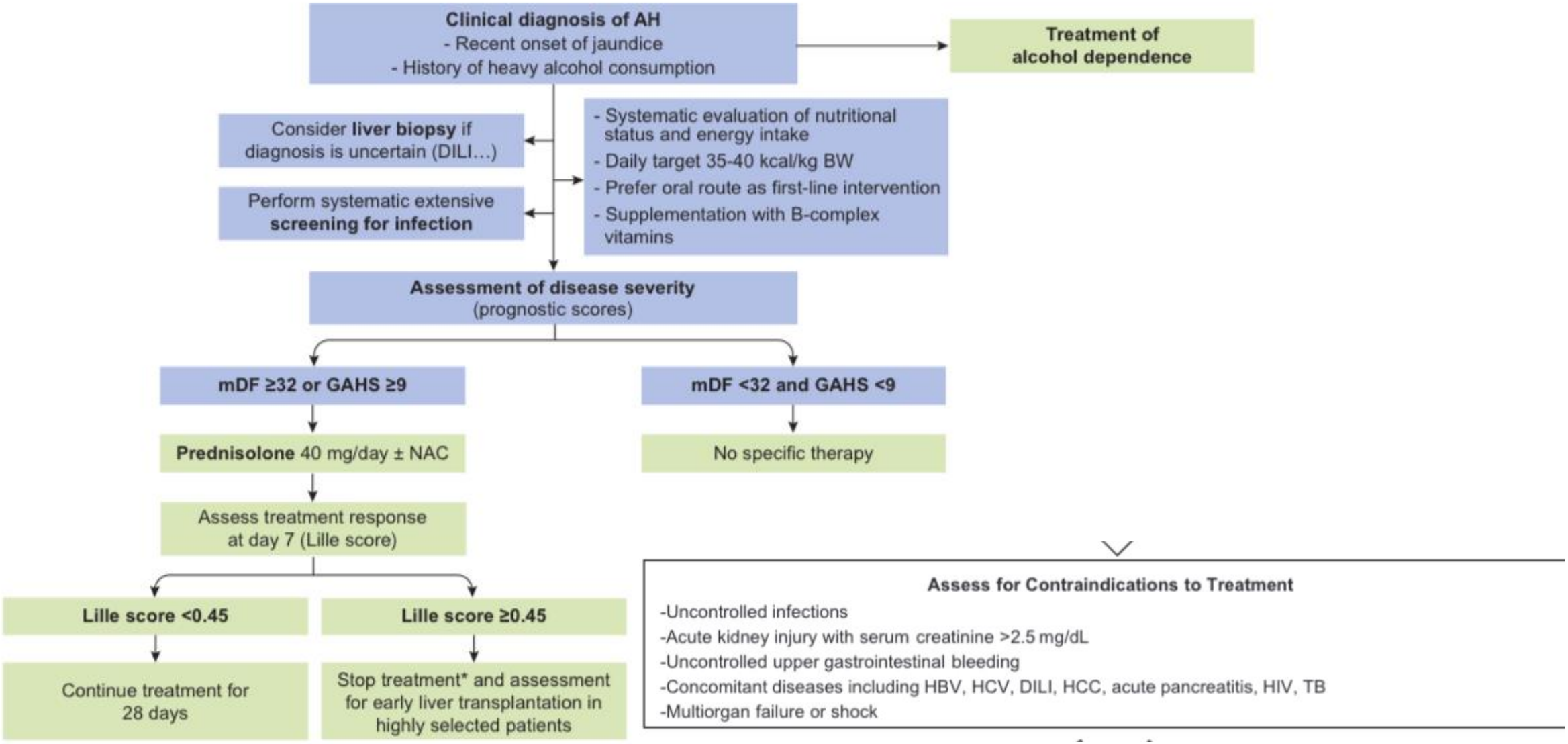
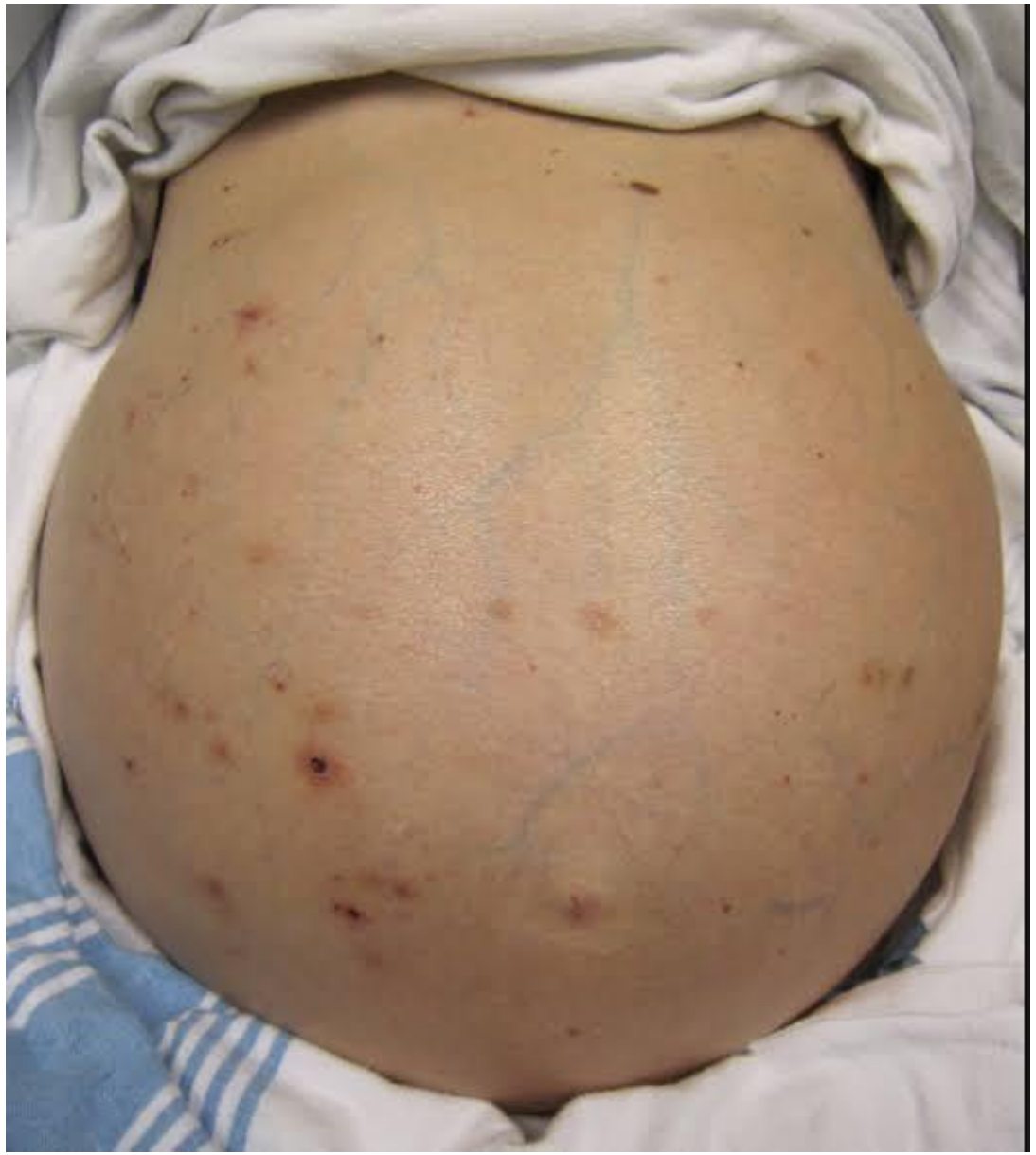


Fig. 1. Treatment algorithm in patients with suspected alcoholic hepatitis. *Particularly in null responders (Lille score ≥0.56). AH, alcoholic hepatitis; BW, bodyweight; DILI, drug-induced liver injury; GAHS, Glasgow alcoholic hepatitis score; mDF, maddrey discriminant function.

Alcoholic Cirrhosis



- **Regenerating nodules**
- **Abnormal sinusoidal blood flow**
- Steatosis and lymphoproliferative infiltration- decrease (Co existing NASH)
- MDB can persist for up to several months or if significant cholestasis present

- **Iron metabolism- disturbed with mild sustainable iron on bx**
- Low serum hepcidin – independent risk factor for mortality

- **MELD/ CHILD PUGH scores**

ASH Cirrhosis - Complications

Mortality at 1 year with decompensation

- Ascites → 49%
- Variceal bleed →49%
- HE→ 64%

Malignancies

- HCC
- Oropharygeal cancer – pharynx and larynx
- Gastric ca
- Pancreatic ca
- Kidney cancer

Sarcopenia

- 50% of patients with ALD
- Increased catabolism
- Insufficient calories
- Micronutrients (including Zinc) and vitamins
- BMI and anthropometry – monitor
- Dietician

Paracetamol

- At therapeutic doses in a patient that in a chronic AUD – with or without cirrhosis and malnutrition→ liver injury
- Varying risk→ Caution

Liver transplantation

- LT confers survival benefit in **ALD- ASH cirrhotic** → **Child Pugh C and MELD >20**
- Rigorous criteria
- Number of transplants for ALD – increasing in most countries
- Between 2004-2013 in the **USA +45%**
- Higher MELD at time of listing
- *Controversial, opinion and judgement in the face of decreasing donors and less organs available*
- At WDGMC – 10year audit data shows Alcohol related cirrhosis accounted for 17.8% of liver transplants performed between 2004 -2016.

Selection of patients

- Risk factors for drug relapse
- Psychosocial assessment
- AUD and other psychiatric disease
- Polysubstance
- Fam hx of alcoholism

- **Entire MDT – must all be in agreement**

Six month sobriety (UNOs)

Many societies do not recommend this as a formal measure

6months - Enables patient to recover from liver injury

Identify subsets who will maintain sobriety

Lab tests may be used on the Ltx waiting list

Early Liver transplantation

Traditionally patients with severe forms of AH and didn't respond to medical treatment - were ineligible

2011- Landmark Franco-Belgian- study:

- Paradigm shift
- 26 carefully selected severe Ah patients – early tp
- Cumulative 6 month survival much higher among pts that received early transplant (77% vs 23%)

ACCELERATE-AH study

- Confirmed benefits of early transplantation in selected patients

Follow up Franco- Belgian study

- 2 year survival was→ similar in early and standard transplant group
- Relapse –higher incidence vs advanced ALD

  Early 20-35% vs Standard 10-25%

SALT Score:

Predicts *Sustained Alcohol Use Post Liver transplant

Determine those patients that are at lower risk of relapse

- ❑> 10drinks per day at the time of initial hospitalization
- ❑Multiple admissions to rehabilitation
- ❑Previous legal issues
- ❑Previous illicit substance abuse
- ❑Cultural
- ❑Socioeconomic factors
- ❑Genetic and family history

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