Alcohol and the Liver

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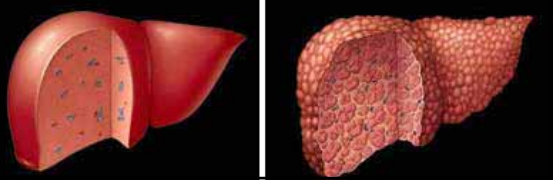


Case presentation

- 36 year-old man
- Several previous admissions with alcohol-related presentations
- Drinks 1 bottle rhum/day
- 2002: Delirium Tremens
- 2003: Seizures
- Jul 2007: Alcoholic hepatitis
- Nov 2007: Alcoholic hepatitis

Admission 2009

- Jaundice
- Confusion- encephalopathic
- Ascites
- Hypotensive, BP=90/54
- Pyrexial

- Admitted to HDU

Labs

- Na 118
- K 2.9
- Urea 3.3
- Creat 64
- AST 85
- ALT 58
- GGT 570
- Bili 375
- Alk Phos 142
- Albumin 24

Hb 10.1
Plt 148
WCC 13

INR 1.6

- Ascitic WCC=500/mm_3, 90% neutrophils
- IV Tazobactam/Piperacillin
- IV Albumin

- Worsening renal function
- Urea=19.3
- Creatinine=453 (Day 15)
- Oliguric despite being on IV Albumin and Terlipressin

- Ongoing sepsis despite broad-spectrum antibiotics
- INR=2.1
- Worsening encephalopathy despite Lactulose (NG tube)- becomes comatose
- Ascites++

- Consensus after consultation with family, Anaesthesia and Renal medicine:
- Prognosis overall poor and dialysis would not alter prognosis.

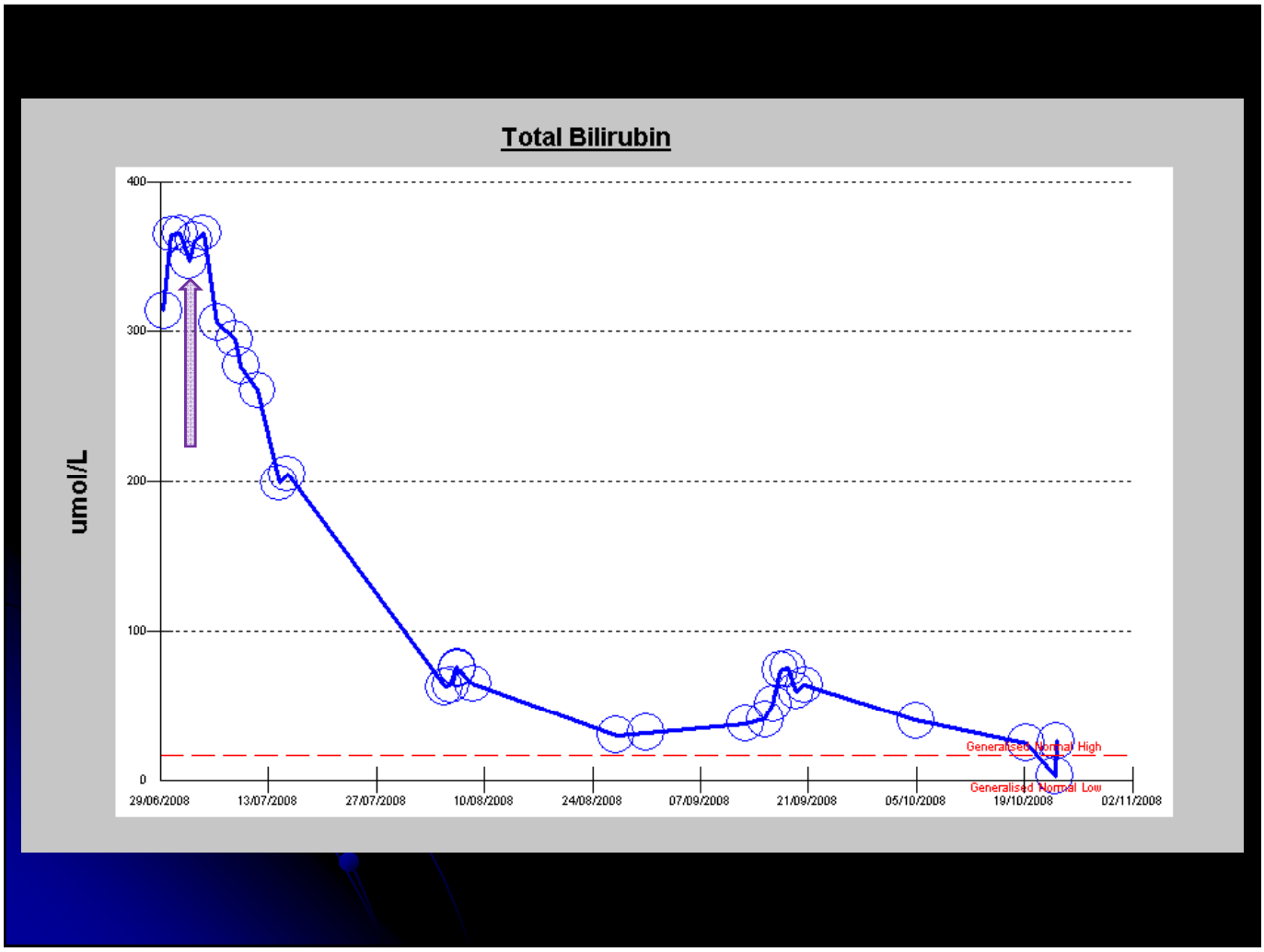
- Patient dies after 25 days

Case 2

- DL, 43 year-old female
- Drinks 80 units/week
- Jaundice
- Abdo pains
- Nausea
- Hepatomegaly

Day 1	Day 8
INR=1.3	INR=1.5
Bili=116	Bili= 332
Aphos=219	
AST=217	
Alb=38	
GGT=142	
mDF=11	mDF=43

- Started on Pentoxifylline 400 mg TDS
- NG feeding
- Overall condition improves
- Bili=190, INR=1.3 at discharge

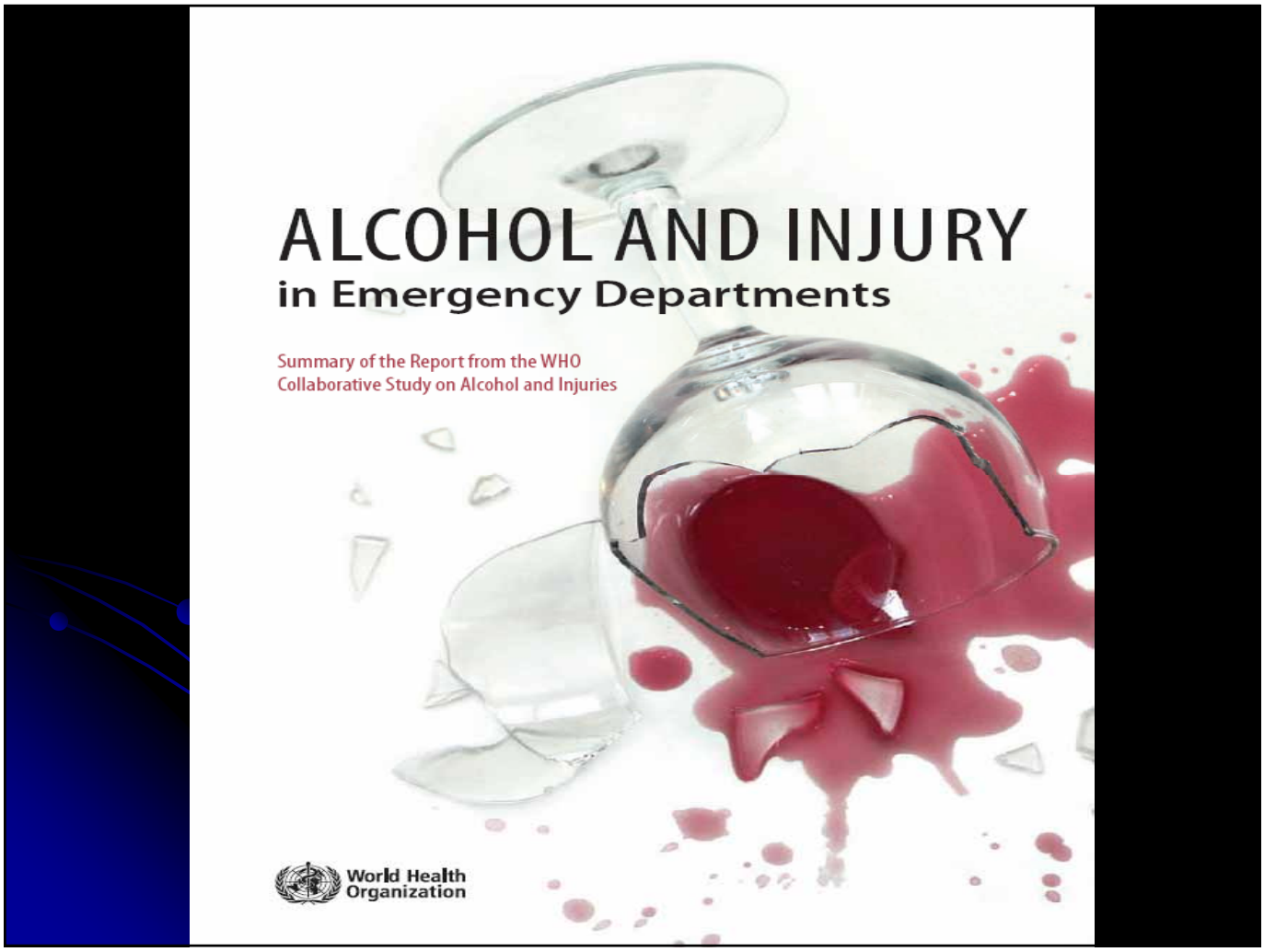

Total Bilirubin
umol/L
400
300
200
100
0
29/06/2008
13/07/2008
27/07/2008
10/08/2008
24/08/2008
07/09/2008
21/09/2008
05/10/2008
19/10/2008
02/11/2008
Generalised Normal High
Generalised Normal Low

Background

- Alcoholism and ALD rife in developed societies, including Mauritius.
- Little wonder, as Man has been brewing and distilling alcohol since the Stone Age!

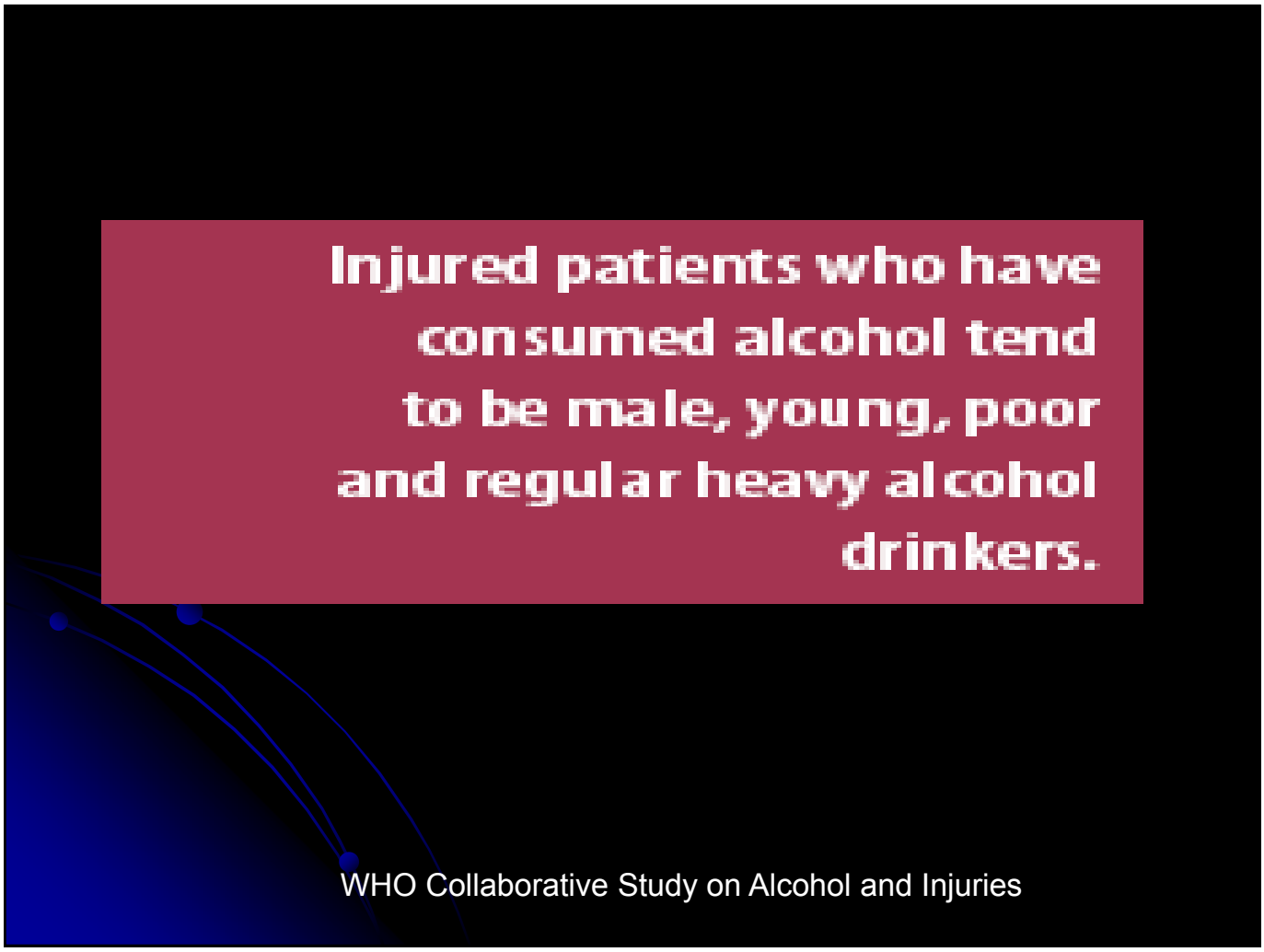
Epidemiology

- Globally, 4% of the burden of disease and 3.2% of all deaths attributable to alcohol (WHO)
- Encompass injury, violence, disease(ALD), social problems and high-risk behaviour.
- Alcohol is a factor in 25% of A&E attendances in large Irish city hospitals.


ALCOHOL AND INJURY
in Emergency Departments
Summary of the Report from the WHO
Collaborative Study on Alcohol and Injuries
World Health
Organization

Up to 45% of injured patients report consuming alcohol prior to their injury.

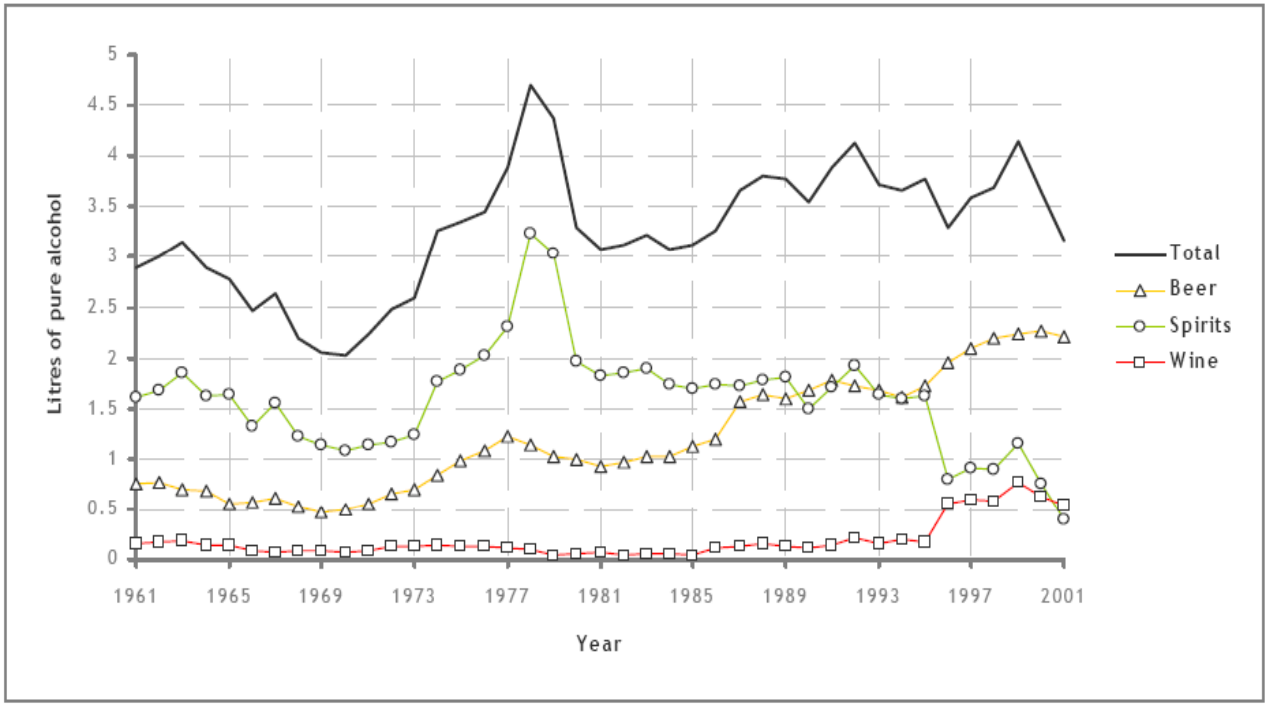
WHO Collaborative Study on Alcohol and Injuries


Injured patients who have consumed alcohol tend to be male, young, poor and regular heavy alcohol drinkers.
WHO Collaborative Study on Alcohol and Injuries


Self-reported alcohol consumption is a cheap and accurate measure of alcohol use prior to injury. All patients should be asked about their alcohol consumption when admitted to an emergency room.
WHO Collaborative Study on Alcohol and Injuries

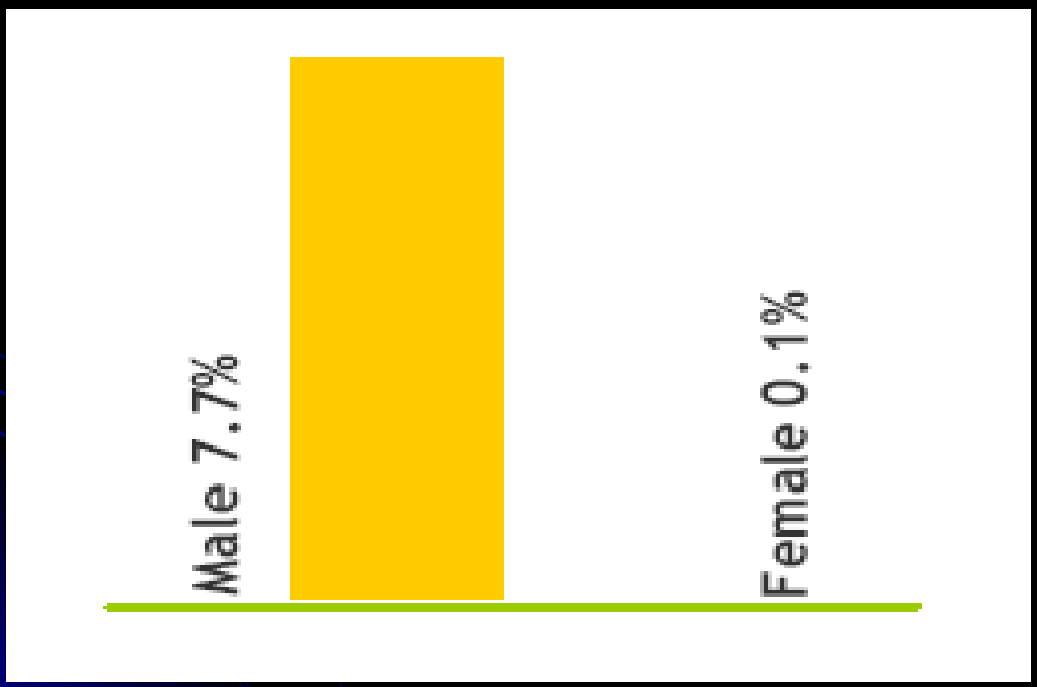
Mauritius

Recorded adult per capita consumption (age 15+)



Sources: FAO (Food and Agriculture Organization of the United Nations), World Drink Trends 2003

Heavy episodic drinkers (5 drinks or more per week in one sitting)

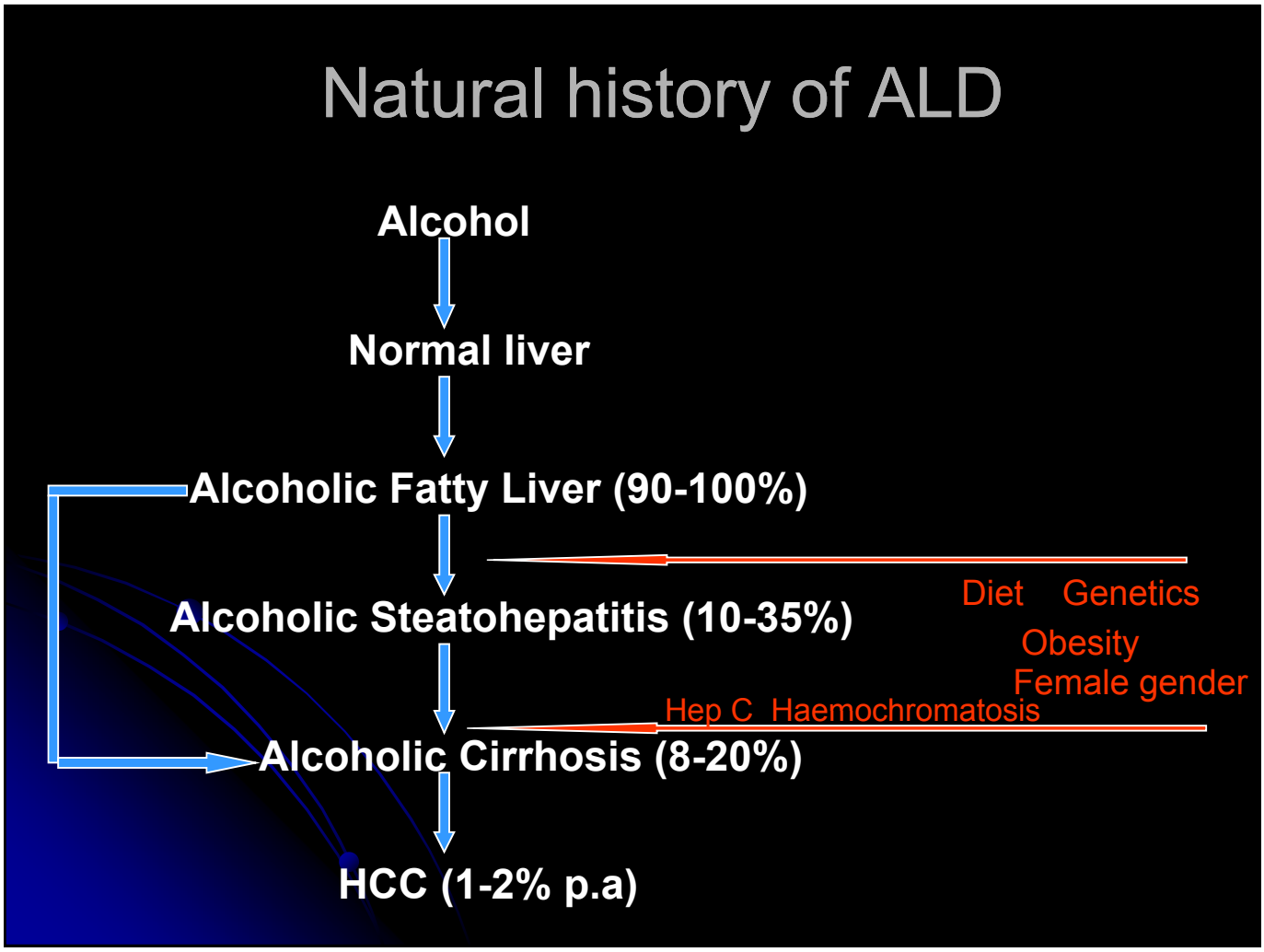


Cause of death Mauritius

Diseases	1990	2000
Heart diseases [2/]	23.4	29.8
Cerebrovascular diseases	13.1	16.2
Diabetes Mellitus	5.1	4.6
Nephritis, nephrotic syndrome and nephrosis	3.2	3.1
Pneumonia	3.5	2.9
Cirrhosis of liver, liver abcess, chronic liver idseases and its sequelae	2.3	2.9
Bronchitis (chronic & unspecified), emphysema and asthma	3.4	2.7
Hypertensive diseases	3.9	2.5
Senility without mention of psychosis	3.0	1.8
Septicaemia	1.0	1.1

Cases treated as in-patients Brown Sequard hospital 2008

CAUSE (I.C.D. 10)	MALE		FEMALE		TOTAL	
	No.	%	No.	%	No.	%
Dementia	23	0.7	23	1.8	46	1.0
Epileptic Psychosis NOS	51	1.6	28	2.2	79	1.8
Unspecified mental disorders due to brain damage and dysfunction and to physical disease	2	0.1	2	0.2	4	0.1
Mental and behavioural disorders due to use of alcohol	1,771	57.0	190	14.9	1,961	44.8
Mental and behavioural disorders due to use of opioids/cannabinoids	10	0.3	1	0.1	11	0.3
Mental and behavioural disorders due to multiple drug use and use of other psychoactive substances	39	1.3	1	0.1	40	0.9
Schizophrenia	781	25.1	629	49.4	1,410	32.2
Delusional disorder	1	0.0	1	0.1	2	0.0
Acute psychotic episode	136	4.4	106	8.3	242	5.5
Schizoaffective psychosis NOS	18	0.6	16	1.3	34	0.8
Psychosis unspecified	3	0.1	5	0.4	8	0.2
Hypomania	8	0.3	5	0.4	13	0.3
Bipolar affective disorder	28	0.9	32	2.5	60	1.4
Depressive episode	97	3.1	150	11.8	247	5.6
Persistent mood disorders	1	0.0	4	0.3	5	0.1
Anxiety disorders	2	0.1	2	0.2	4	0.1
Obsessive compulsive disorder	-	0.0	-	0.0	0	0.0
Dissociative (conversion) disorders	1	0.0	6	0.5	7	0.2
Puerperal psychosis NOS	-	0.0	5	0.4	5	0.1
Mental retardation	51	1.6	27	2.1	78	1.8
Conduct disorders	23	0.7	12	0.9	35	0.8
Parkinsonism	2	0.1	1	0.1	3	0.1
Alzheimer	-	0.0	1	0.1	1	0.0
Degenerative disease of nervous system, unspecified	2	0.1	-	0.0	2	0.0
Grand mal seizures, unspecified (with or without petit mal)	16	0.5	14	1.1	30	0.7
Epilepsy, unspecified	26	0.8	7	0.5	33	0.8
Sleep disorders	-	0.0	1	0.1	1	0.0
Other causes	16	0.5	5	0.4	21	0.5
TOTAL	**3,108**	**100.0**	**1,274**	**100.0**	**4,382**	**100.0**


Natural history of ALD
Alcohol
Normal liver
Alcoholic Fatty Liver (90-100%)
Alcoholic Steatohepatitis (10-35%)
Alcoholic Cirrhosis (8-20%)
HCC (1-2% p.a)
Diet
Genetics
Obesity
Female gender
Hep C
Haemochromatosis

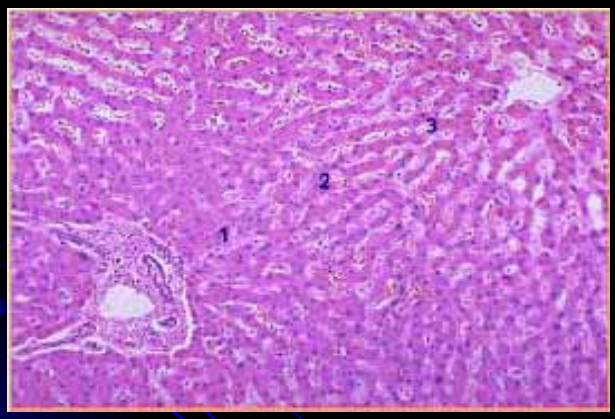
Alcoholic steatosis

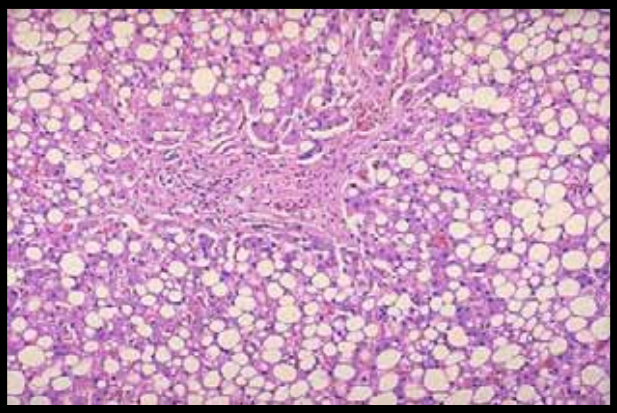
- Occurs invariably if alcohol consumption>80 g/day
- Present in 80% of heavy drinkers

- Hepatocyte cytoplasm occupied by triglyceride
- LFTs often normal
- Reversible with abstinence
- May progress to cirrhosis

22% with alcoholic fatty liver developed cirrhosis after median 13 years
Dam-Larsen et al. Scand J Gastroenterol 2005

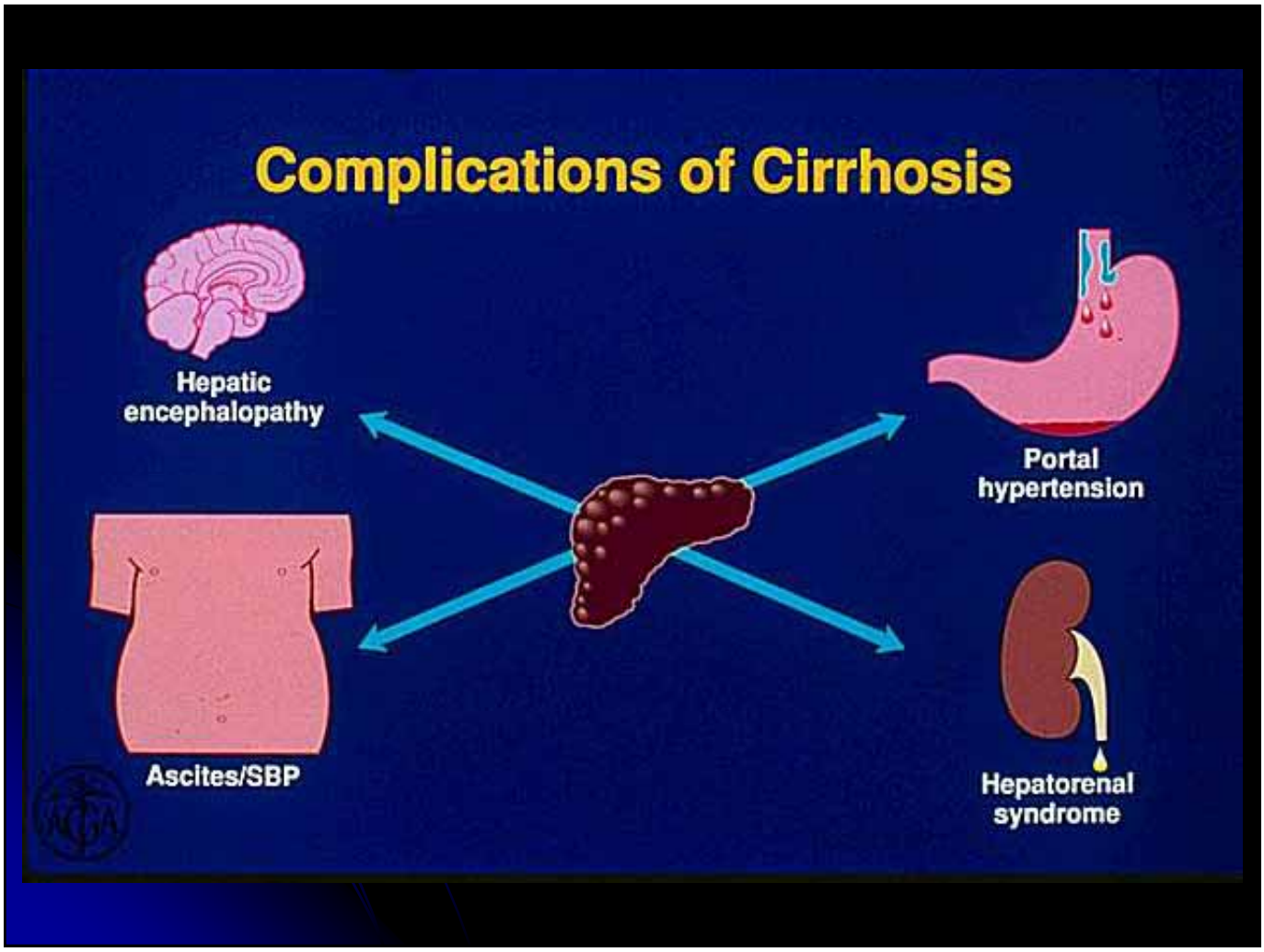
Alcoholic Fatty Liver - Histology



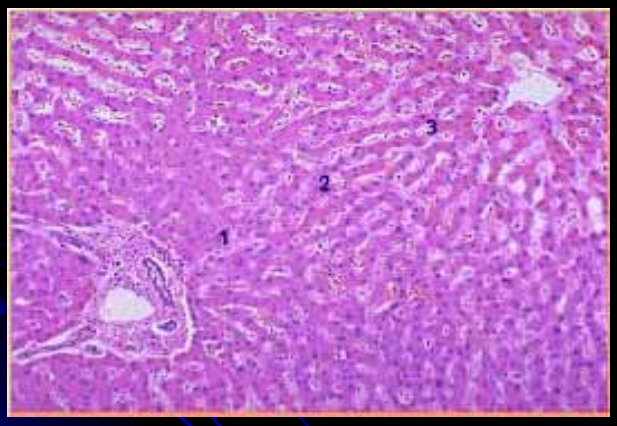


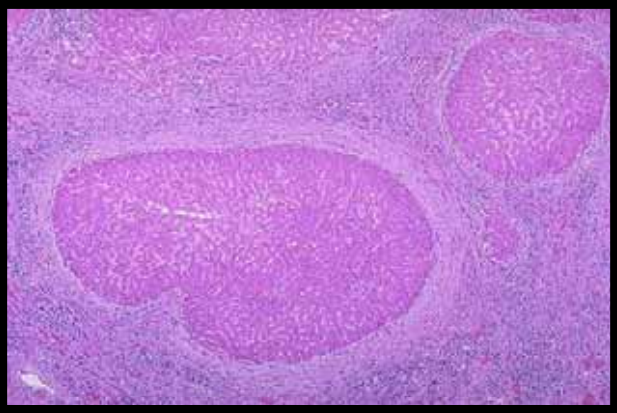
Alcoholic Cirrhosis

- RR=13 for males drinking 60 g daily. For females: 40 g daily.
- Survival in decompensated cirrhotics is 65% at one year and 35-50% at 5 years.
- Clinical presentation usually due to complications.


Complications of Cirrhosis
Hepatic encephalopathy
Portal hypertension
Ascites/SBP
Hepatorenal syndrome

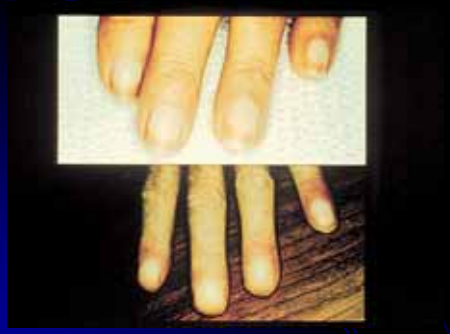
Alcoholic Cirrhosis - Histology

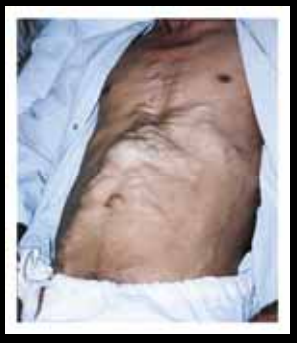


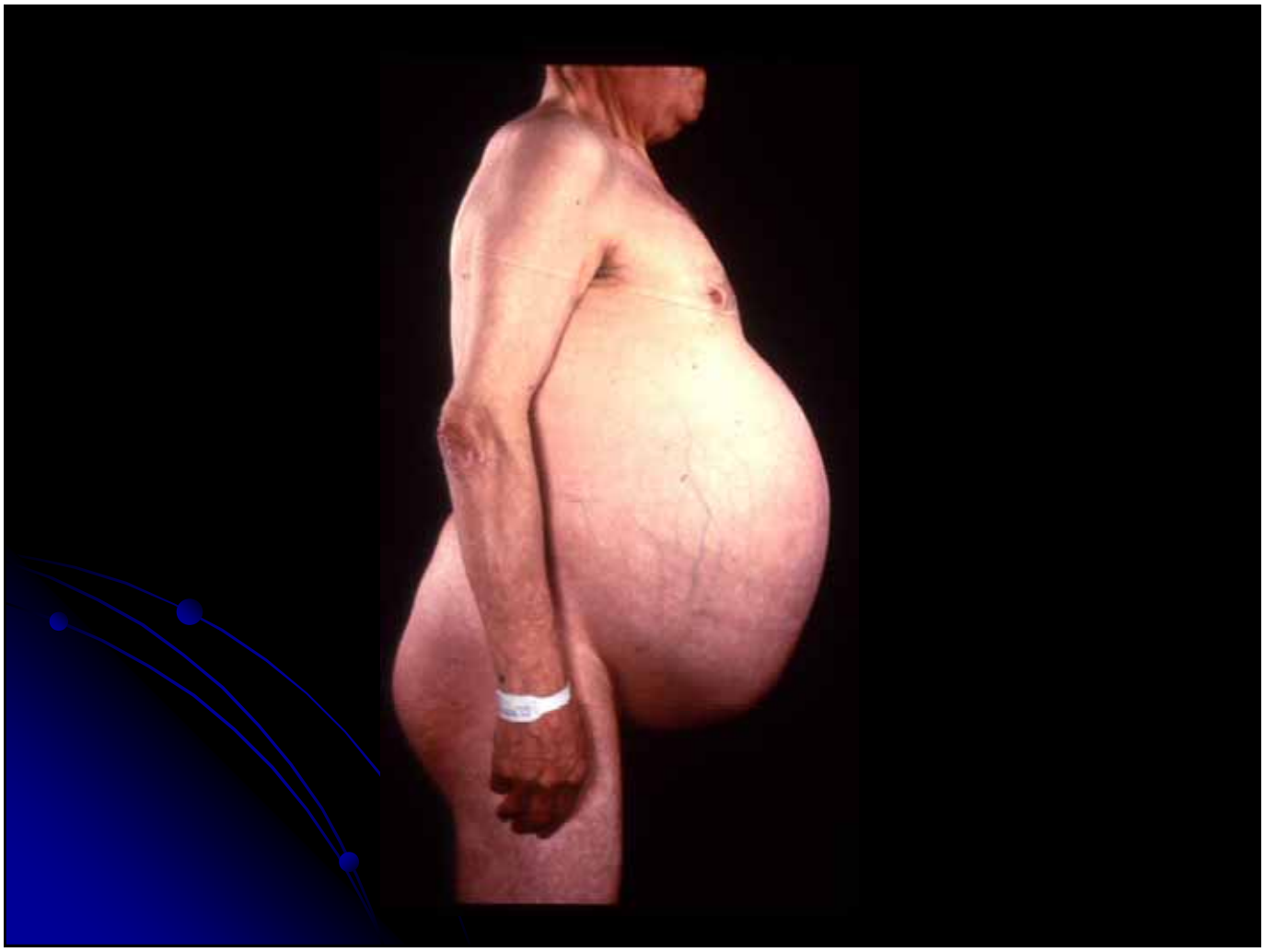


Alcoholic Cirrhosis – Clinical Features







ASCITES

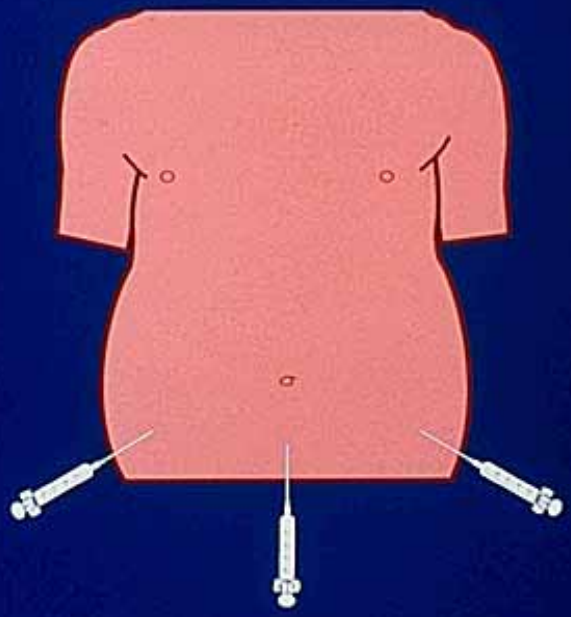
Diagnostic Paracentesis

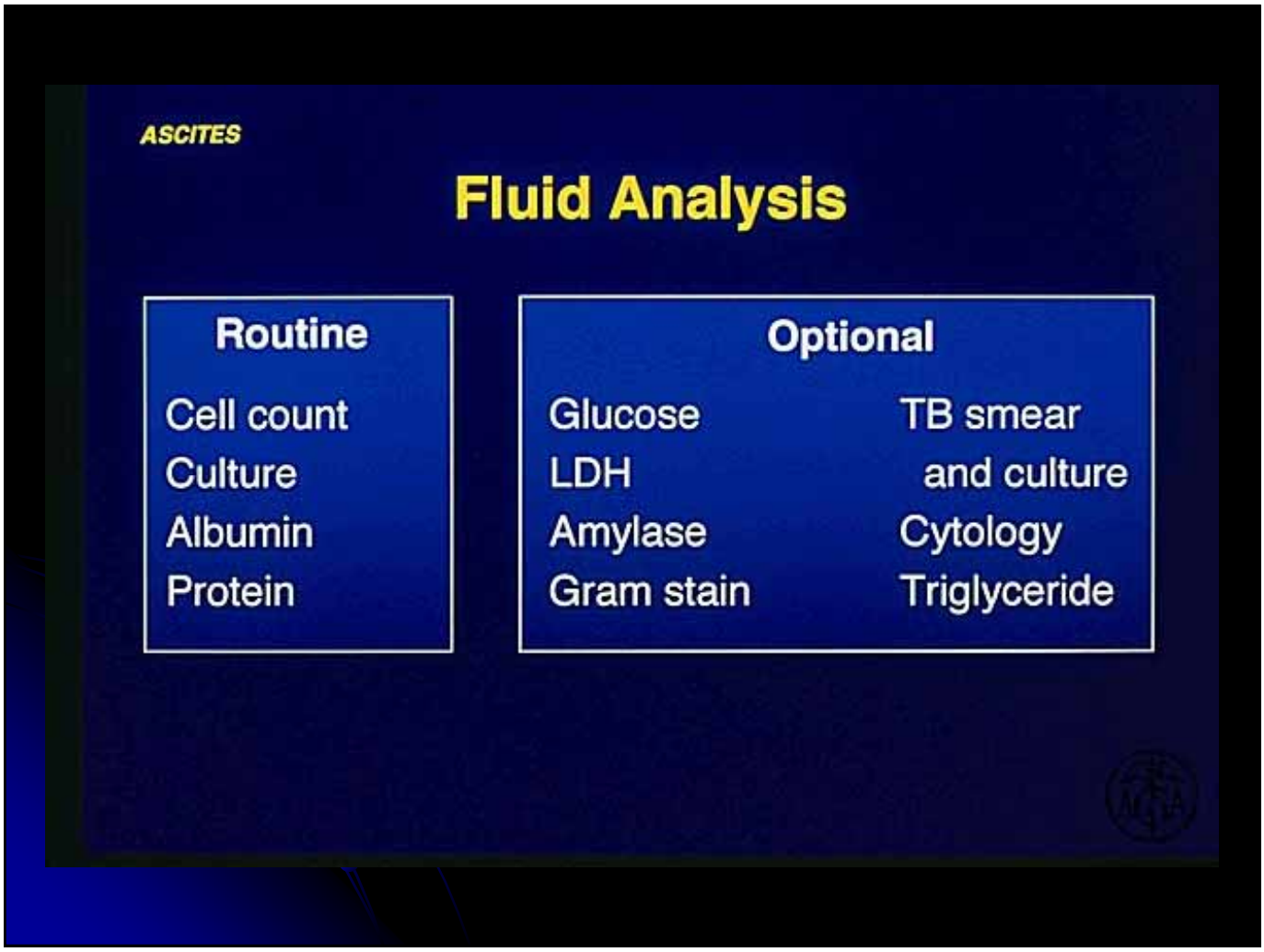
Indications

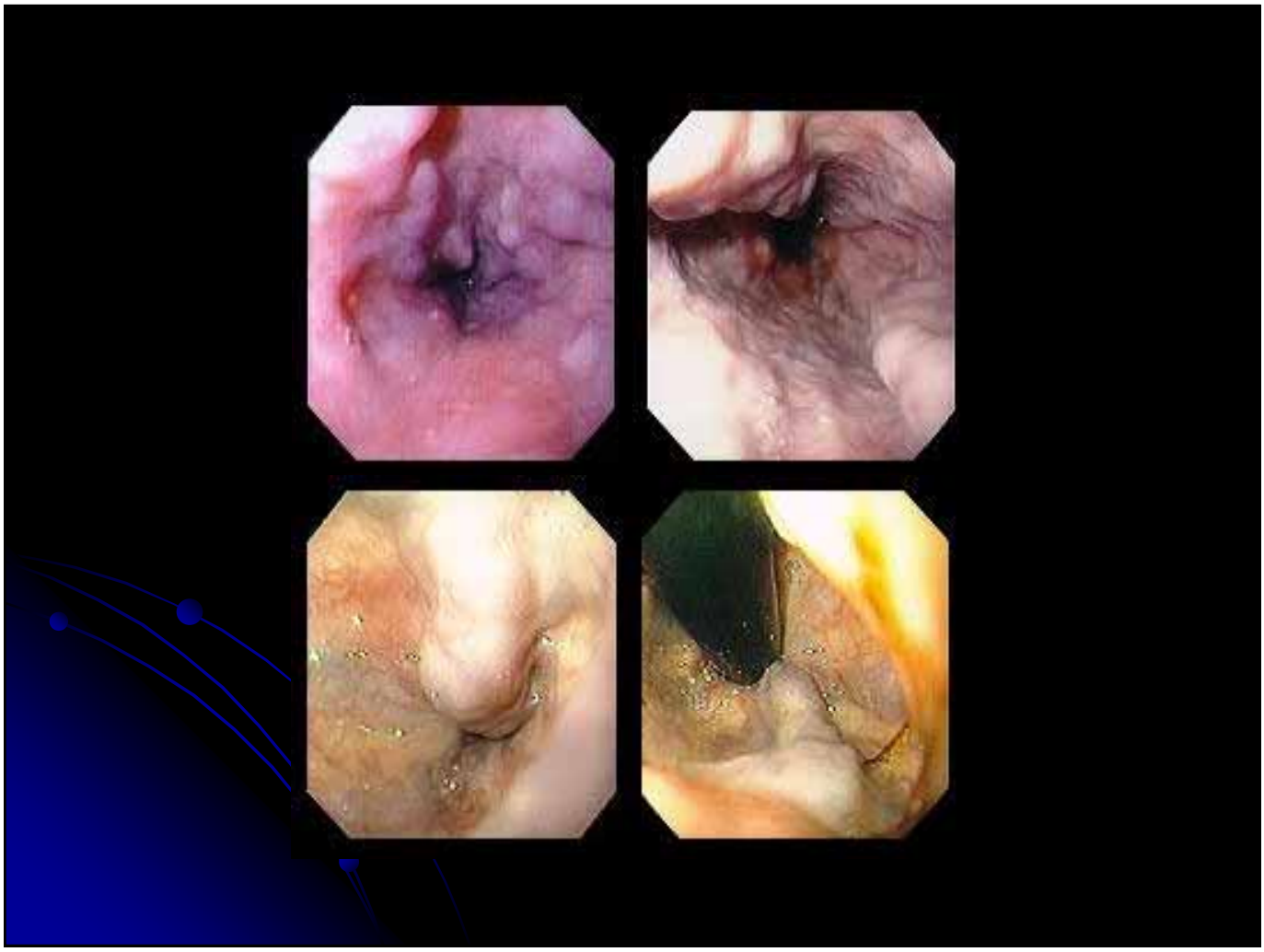
- New-onset ascites
- Admission to hospital
- Clinical deterioration
- Fever

Contraindications

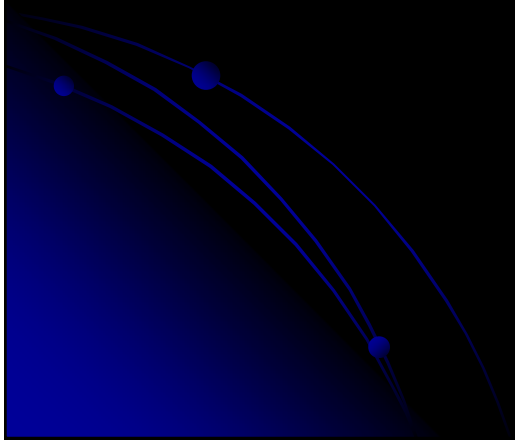
- None




ASCITES
Fluid Analysis
Routine
Cell count
Culture
Albumin
Protein
Optional
Glucose
LDH
Amylase
Gram stain
TB smear and culture
Cytology
Triglyceride



Acute Alcoholic Hepatitis



Acute Alcoholic Hepatitis

- Syndrome characterised by pathological and clinical features:

- Jaundice
- Anorexia/ Weight loss
- Vomiting/ Fever
- Ascites
- Encephalopathy
- Gastrointestinal haemorrhage
- Hypoglycaemia
- Renal failure

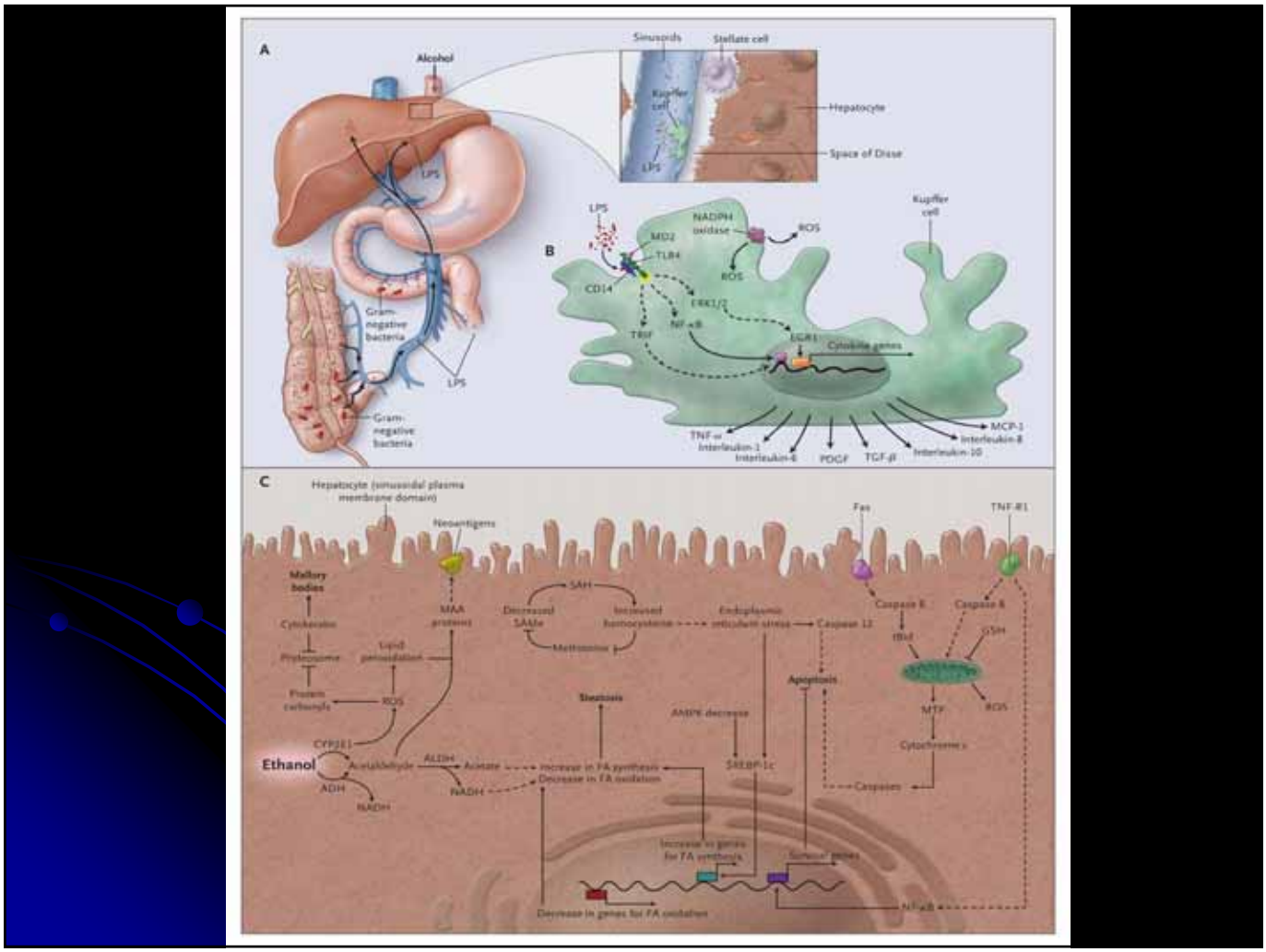
- Often deteriorate after stopping alcohol
- 70 units per week
  - Women more susceptible
- 40 - 50% mortality

Laboratory Findings

- Elevated bilirubin
- Prolonged prothrombin time
- Hypoalbuminaemia
- Modest elevation of transaminases
  - AST/ ALT ratio > 2
- Thrombocytopaenia
- Neutrophilia
- Low urea
- Hyponatraemia

Pathophysiology

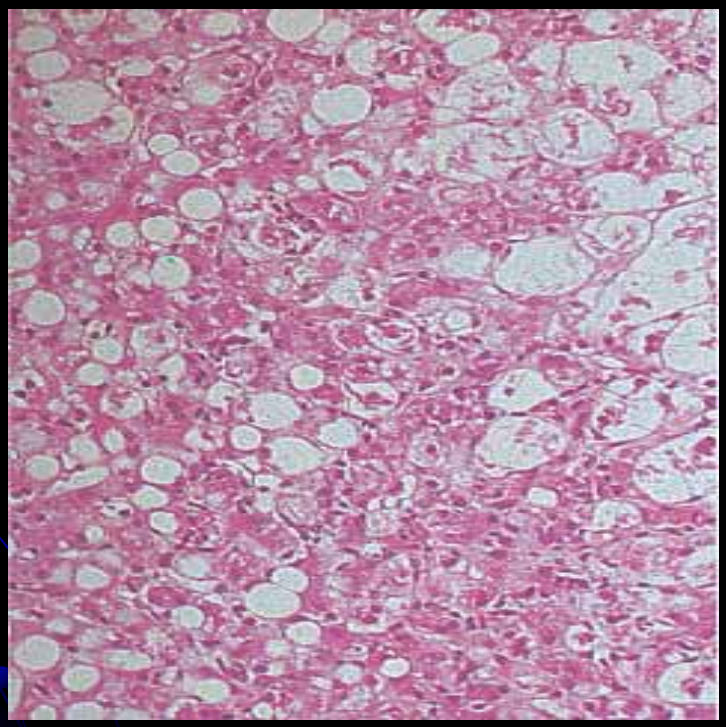
- Oxidative stress
  - Reactive oxygen species
  - Induction of CYP2E1- generates oxidants
- Neutrophil infiltration and activation
  - Characteristic of alcoholic hepatitis
  - IL-8
- Inflammatory cell infiltration and activation
  - COX-2
  - Thromboxanes
- Cytokines- TNF
- Bacterial translocation (Gram negatives)


A
Alcohol
Sinusoids
Stellate cell
Kupffer cell
Hepatocyte
Space of Disse
LPS
Gram-negative bacteria
B
NADPH oxidase
ROS
MD2
TLR4
CD14
ERK1/2
NF-κB
TRIF
EGR1
Cytokine genes
Kupffer cell
TNF-α
Interleukin-1
Interleukin-6
PDGF
TGF-β
Interleukin-10
MCP-1
Interleukin-8
C
Hepatocyte (sinusoidal plasma membrane domain)
Neoantigens
Fas
TNF-R1
Mallory bodies
Cytokeratin
Proteasome
Protein carbonyls
Lipid peroxidation
MAA proteins
SAH
Decreased SAMe
Increased homocysteine
Methionine
Endoplasmic reticulum stress
Caspase 12
Caspase 8
tBid
CSH
Apoptosis
MTP
ROS
Cytochrome c
Caspases
Steatosis
AMPK decrease
SREBP-1c
Ethanol
CYP2E1
ADH
NADH
ALDH
Acetaldehyde
Acetate
Increase in FA synthesis
Decrease in FA oxidation
Increase in genes for FA synthesis
Decrease in genes for FA oxidation
NF-κB

Histology

- Liver cell necrosis
- Mallory bodies
- Perivenular neutrophil infiltration
- Steatosis
- Fibrosis/Cirrhosis

Alcoholic Hepatitis



Prognosis

- Morbidity
  - Sepsis/SBP
  - Malnutrition
  - Hepatorenal syndrome
- 70% cirrhotic at presentation
- 40 - 50% mortality

Genetics of ALD

- **Genes predisposing to alcohol abuse:**
  *ADH*3, *ALDH1A1***2*
- **Genes protective against alcohol abuse**:
  ADH1B,ADH1C, ALDH2
- **Genes involved in generation of oxidant stress:**
  CYP2E1, TNF-α,SOD2,MAT1A,GST,Nrf-1
- **Cytokine genes and receptors**:
  IL-10,TNF-α,TNFRs
- **Genes encoding endotoxin receptors**:
  CD14,NOD2,TLR4
- **Fibrosis genes:**
  CTGF,adiponectin,leptin,MMP,TIMP,collagens,DDX5

Table 1 Scoring systems used in the assessment of alcoholic hepatitis

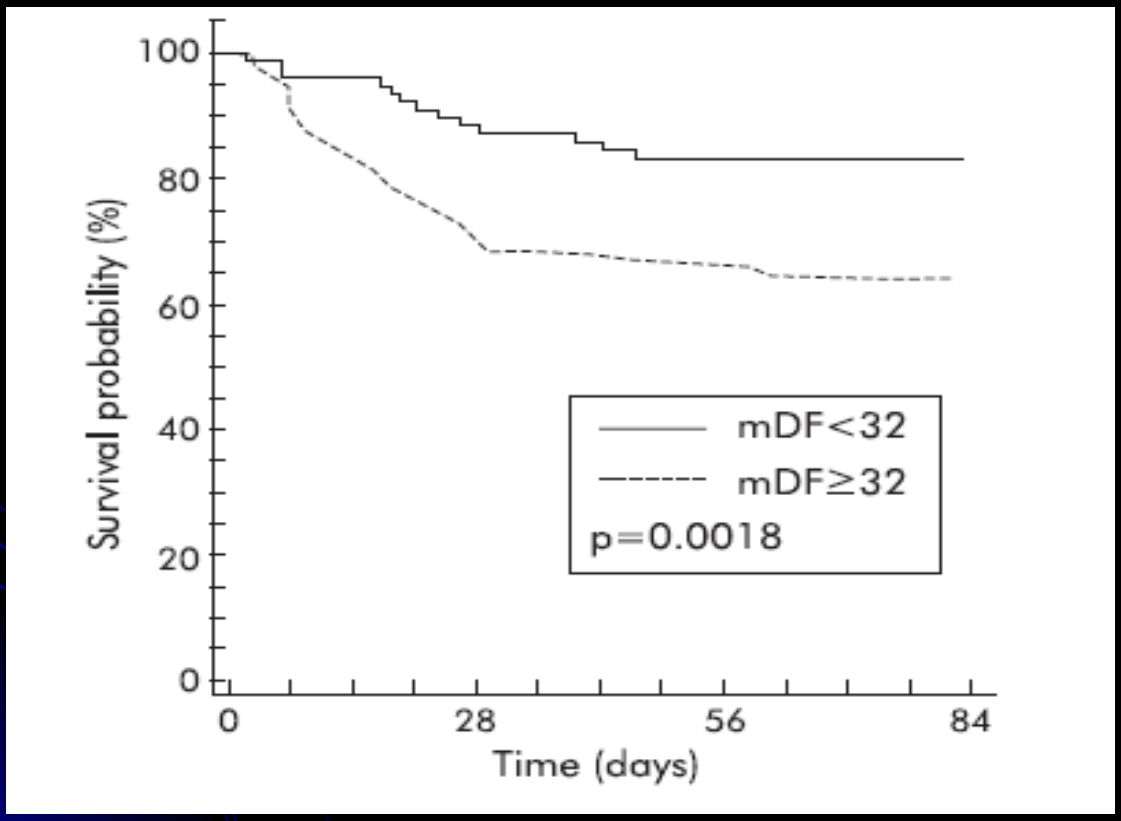
Scoring system	Formula
Discriminant function	$DF = (4.6 \times PT) + \text{serum bilirubin (mg/dl)}$
Modified discriminant function	$mDF = 4.6\,(PT_{patient} - PT_{control}) + \text{serum bilirubin } (\mu mol/l)/17.1$
MELD score	$MELD = 3.8 \times \log_e(\text{bilirubin (mg/dl)}) + 1.2 \times \log_e(INR) + 9.6 \times \log_e(\text{creatinine (mg/dl)})$

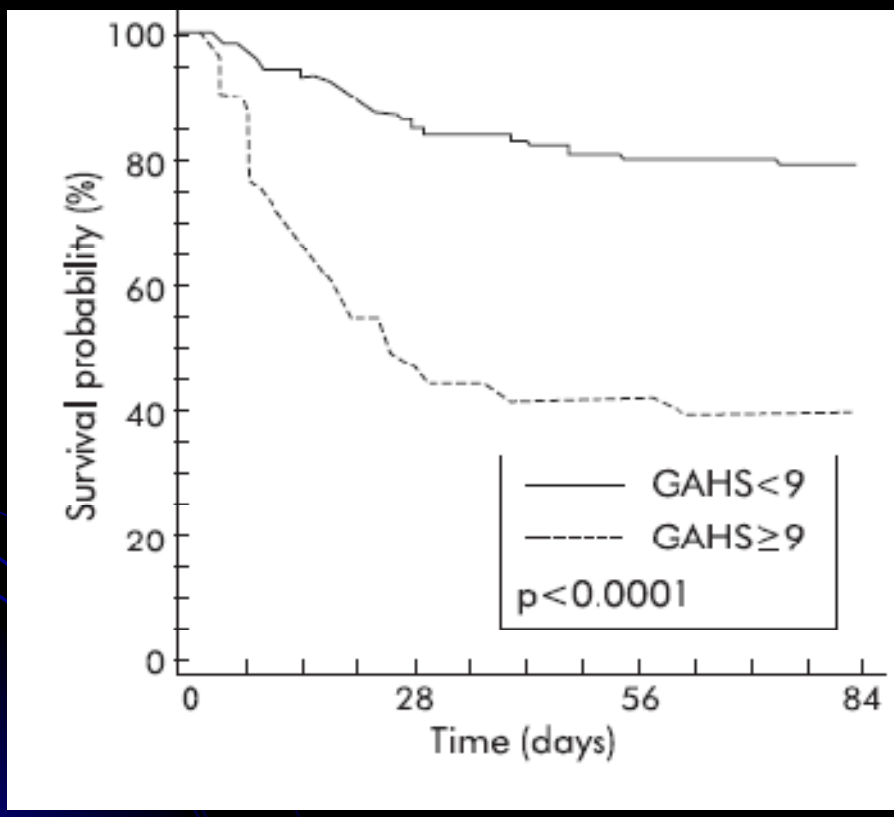
PT, prothrombin time.

Table 4 The Glasgow alcoholic hepatitis score

	Score given		
	1	2	3
Age	<50	≥50	–
WCC (10^9/l)	<15	≥15	–
Urea (mmol/l)	<5	≥5	–
PT ratio	<1.5	1.5–2.0	>2.0
Bilirubin (μmol/l)	<125	125–250	>250

PT, prothrombin time; WCC, white cell count.


100
80
60
40
20
0
Survival probability (%)
0
28
56
84
Time (days)
mDF<32
mDF≥32
p=0.0018


100
80
60
40
20
0
Survival probability (%)
0
28
56
84
Time (days)
GAHS<9
GAHS≥9
p<0.0001

Management

- Supervised by gastroenterologist
- Abstinence
- Alcohol withdrawal
- Nutrition
- Medications
- Other Rx
  - Ascites
  - Encephalopathy
  - Renal failure

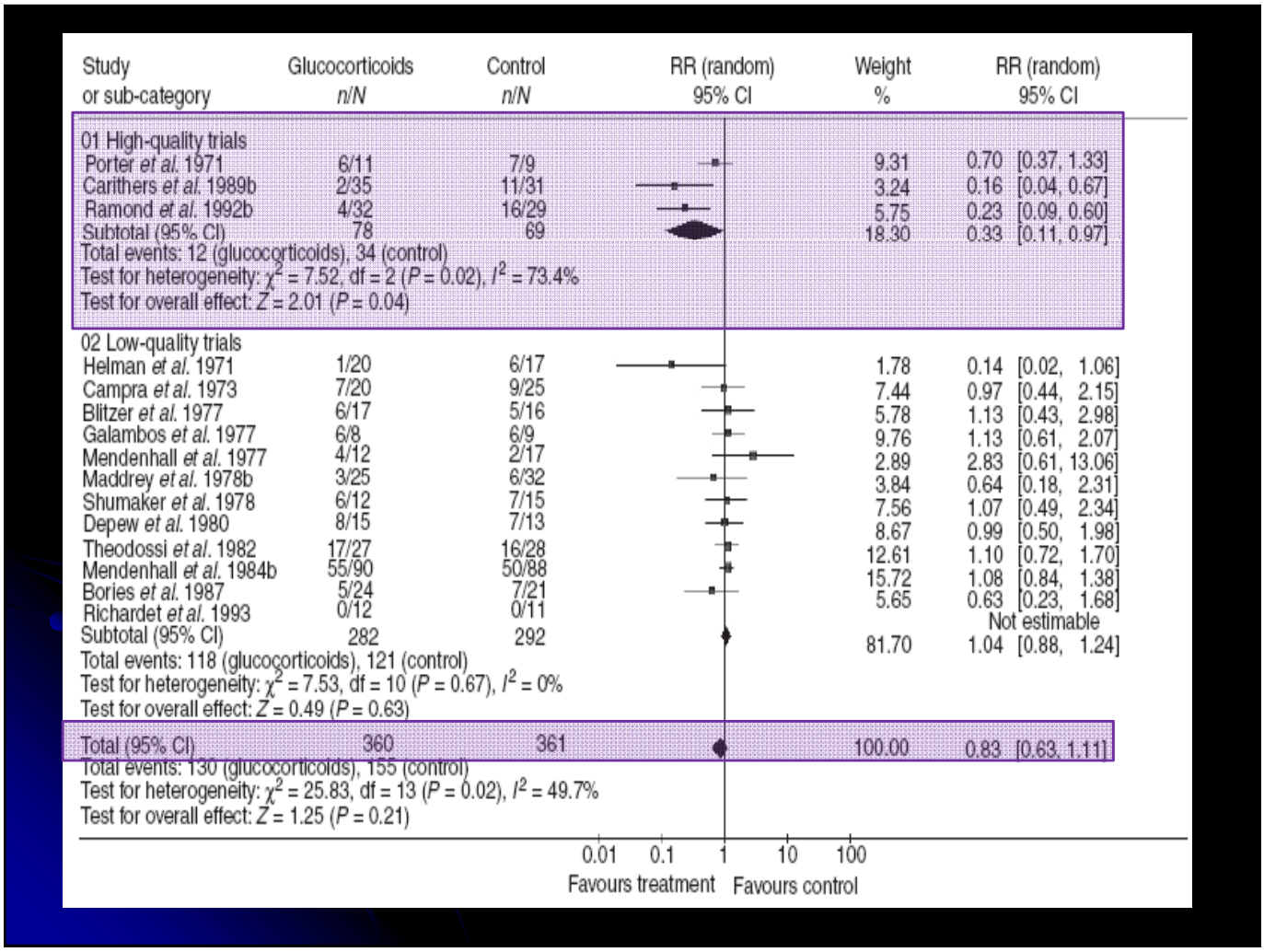
Nutrition

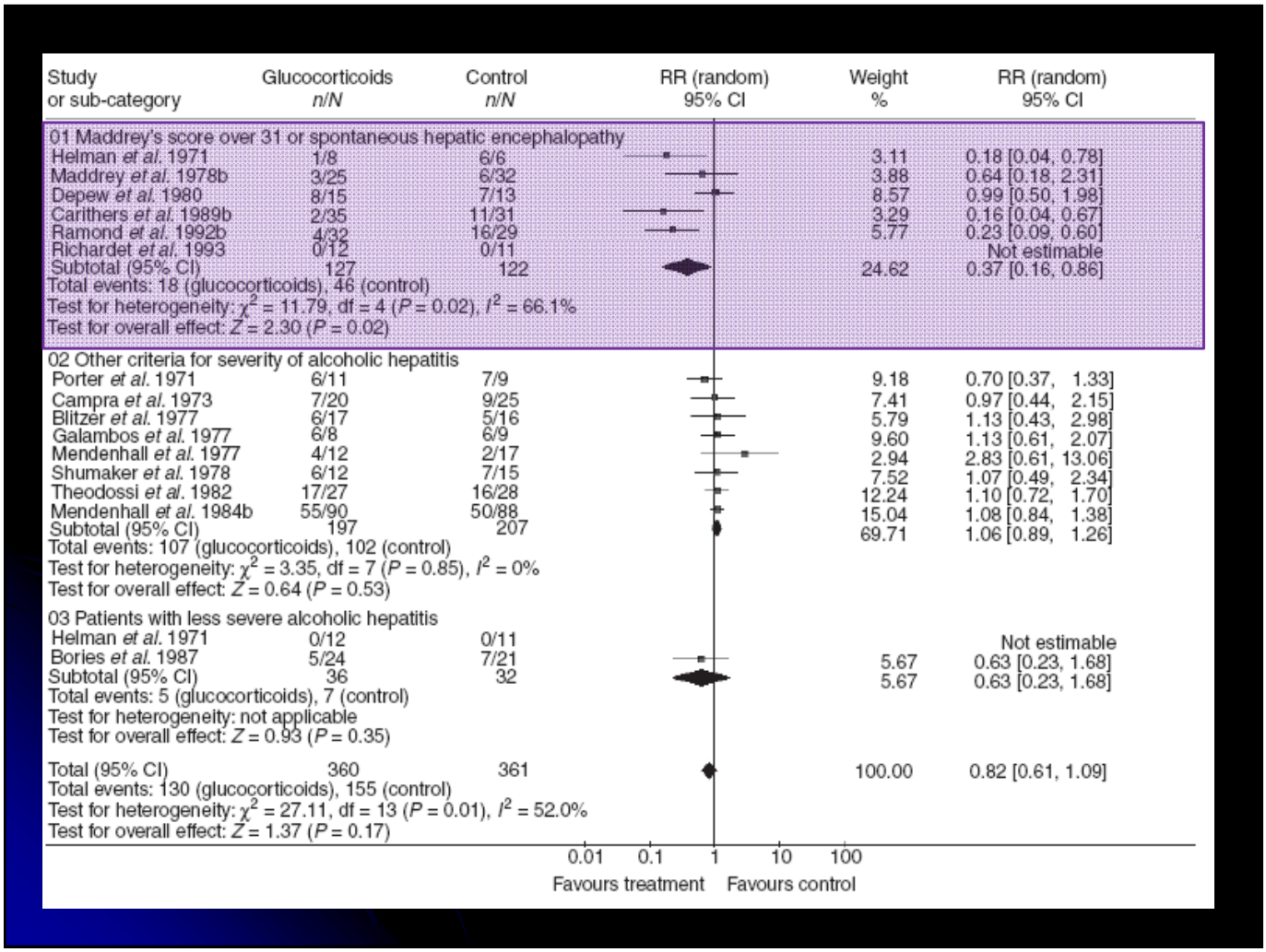
- Enteral route preferred (No benefit with parenteral route)
  - 2000 - 2500kcal daily
  - 1.0 - 1.5g protein/kg bodyweight
  - Thiamine/ Multivitamins/ Minerals
- In practice
  - Use early
  - Safe
  - May need nasogastric tube

Soberon *et al*[133] 1987	Case series	14 patients, alcoholic hepatitis	6 with adequate nutritional status, hospital diet 8 with poor baseline nutritional status, nasoduodenal diet, 35 kCal/kg per day	No difference in mortality Increased nitrogen balance in study group
Simon *et al*[88] 1988	Randomized	12 patients, moderate alcoholic hepatitis 22 patients, severe alcoholic hepatitis	Moderate Group 6 control, standard diet 6 study, PPN Severe Group 12 control, standard 10 study, PPN	No difference in mortality Improved in biochemical tests in severe group
Bonkovsky *et al*[67] 1991	Randomized	39 patients, moderate to severe alcoholic hepatitis	9, standard therapy 8, oxandrolone + standard therapy 10, PPN 12, oxandrolone + standard therapy + PPN	Improved biochemical parameters
Mezey *et al*[89] 1991	Randomized	52 patients, alcoholic hepatitis	28 control, dextrose solution 26 study, dextrose + amino acid	No difference in mortality during hospitalization and 2 yr after treatment
Mendenhall *et al*[69] 1993	Randomized	273 patients, severe alcoholic hepatitis	136 control 137 study, oxadrolone + enteral nutrition	No difference in mortality overall Improvement in mortality in moderately malnourished group(19%) versus control (31%) at 6 mo post treatment
Cabre *et al*[134] 2000	Randomized	71 patients, severe alcoholic hepatitis	36, prednisolone 35, enteral tube 2000 kCal/d	No difference in overall mortality Higher early mortality in nutrition *versus* higher follow up mortality on steroids
Alvarez *et al*[135] 2004	Case series	13 patients, severe alcoholic hepatitis	13, prednisolone + TEN 2000 kCal/d	15% death during treatment 67% of patients developed infections during treatment -no deaths due to infections

Corticosteroids

- Severe alcoholic hepatitis
- DF > 32
- C/ I
  - Bleeding
  - Sepsis
- Reduce short term mortality
- No influence on progression to cirrhosis
- Prednisolone preferred- 40 mg for 1 month

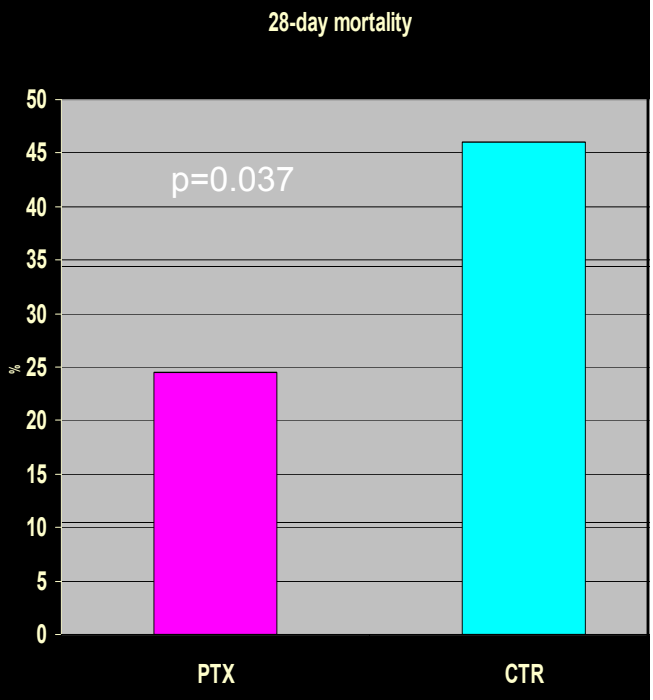

Study
or sub-category
Glucocorticoids
n/N
Control
n/N
RR (random)
95% CI
Weight
%
RR (random)
95% CI
01 High-quality trials
Porter et al. 1971 6/11 7/9 9.31 0.70 [0.37, 1.33]
Carithers et al. 1989b 2/35 11/31 3.24 0.16 [0.04, 0.67]
Ramond et al. 1992b 4/32 16/29 5.75 0.23 [0.09, 0.60]
Subtotal (95% CI) 78 69 18.30 0.33 [0.11, 0.97]
Total events: 12 (glucocorticoids), 34 (control)
Test for heterogeneity: χ² = 7.52, df = 2 (P = 0.02), I² = 73.4%
Test for overall effect: Z = 2.01 (P = 0.04)
02 Low-quality trials
Helman et al. 1971 1/20 6/17 1.78 0.14 [0.02, 1.06]
Campra et al. 1973 7/20 9/25 7.44 0.97 [0.44, 2.15]
Blitzer et al. 1977 6/17 5/16 5.78 1.13 [0.43, 2.98]
Galambos et al. 1977 6/8 6/9 9.76 1.13 [0.61, 2.07]
Mendenhall et al. 1977 4/12 2/17 2.89 2.83 [0.61, 13.06]
Maddrey et al. 1978b 3/25 6/32 3.84 0.64 [0.18, 2.31]
Shumaker et al. 1978 6/12 7/15 7.56 1.07 [0.49, 2.34]
Depew et al. 1980 8/15 7/13 8.67 0.99 [0.50, 1.98]
Theodossi et al. 1982 17/27 16/28 12.61 1.10 [0.72, 1.70]
Mendenhall et al. 1984b 55/90 50/88 15.72 1.08 [0.84, 1.38]
Bories et al. 1987 5/24 7/21 5.65 0.63 [0.23, 1.68]
Richardet et al. 1993 0/12 0/11 Not estimable
Subtotal (95% CI) 282 292 81.70 1.04 [0.88, 1.24]
Total events: 118 (glucocorticoids), 121 (control)
Test for heterogeneity: χ² = 7.53, df = 10 (P = 0.67), I² = 0%
Test for overall effect: Z = 0.49 (P = 0.63)
Total (95% CI) 360 361 100.00 0.83 [0.63, 1.11]
Total events: 130 (glucocorticoids), 155 (control)
Test for heterogeneity: χ² = 25.83, df = 13 (P = 0.02), I² = 49.7%
Test for overall effect: Z = 1.25 (P = 0.21)
0.01 0.1 1 10 100
Favours treatment
Favours control


Study or sub-category
Glucocorticoids n/N
Control n/N
RR (random) 95% CI
Weight %
RR (random) 95% CI
01 Maddrey's score over 31 or spontaneous hepatic encephalopathy
Helman et al. 1971 1/8 6/6 3.11 0.18 [0.04, 0.78]
Maddrey et al. 1978b 3/25 6/32 3.88 0.64 [0.18, 2.31]
Depew et al. 1980 8/15 7/13 8.57 0.99 [0.50, 1.98]
Carithers et al. 1989b 2/35 11/31 3.29 0.16 [0.04, 0.67]
Ramond et al. 1992b 4/32 16/29 5.77 0.23 [0.09, 0.60]
Richardet et al. 1993 0/12 0/11 Not estimable
Subtotal (95% CI) 127 122 24.62 0.37 [0.16, 0.86]
Total events: 18 (glucocorticoids), 46 (control)
Test for heterogeneity: χ² = 11.79, df = 4 (P = 0.02), I² = 66.1%
Test for overall effect: Z = 2.30 (P = 0.02)
02 Other criteria for severity of alcoholic hepatitis
Porter et al. 1971 6/11 7/9 9.18 0.70 [0.37, 1.33]
Campra et al. 1973 7/20 9/25 7.41 0.97 [0.44, 2.15]
Blitzer et al. 1977 6/17 5/16 5.79 1.13 [0.43, 2.98]
Galambos et al. 1977 6/8 6/9 9.60 1.13 [0.61, 2.07]
Mendenhall et al. 1977 4/12 2/17 2.94 2.83 [0.61, 13.06]
Shumaker et al. 1978 6/12 7/15 7.52 1.07 [0.49, 2.34]
Theodossi et al. 1982 17/27 16/28 12.24 1.10 [0.72, 1.70]
Mendenhall et al. 1984b 55/90 50/88 15.04 1.08 [0.84, 1.38]
Subtotal (95% CI) 197 207 69.71 1.06 [0.89, 1.26]
Total events: 107 (glucocorticoids), 102 (control)
Test for heterogeneity: χ² = 3.35, df = 7 (P = 0.85), I² = 0%
Test for overall effect: Z = 0.64 (P = 0.53)
03 Patients with less severe alcoholic hepatitis
Helman et al. 1971 0/12 0/11 Not estimable
Bories et al. 1987 5/24 7/21 5.67 0.63 [0.23, 1.68]
Subtotal (95% CI) 36 32 5.67 0.63 [0.23, 1.68]
Total events: 5 (glucocorticoids), 7 (control)
Test for heterogeneity: not applicable
Test for overall effect: Z = 0.93 (P = 0.35)
Total (95% CI) 360 361 100.00 0.82 [0.61, 1.09]
Total events: 130 (glucocorticoids), 155 (control)
Test for heterogeneity: χ² = 27.11, df = 13 (P = 0.01), I² = 52.0%
Test for overall effect: Z = 1.37 (P = 0.17)
0.01 0.1 1 10 100
Favours treatment
Favours control

Pentoxifylline in ASH

- Patients with severe ASH (DF>32)
- Double-blind,placebo-controlled
- Tx with 400 mg TDS for 28 days

- RESULTS
- Improved survival with PTX, mainly due to reduced hepato-renal syndrome
- Reduced TNF-α
- Effect exceeds expected benefit from steroids



Hepato-Renal Syndrome

- Major criteria:
- Chronic or acute liver disease with advanced liver failure and portal hypertension
- Low GFR, as indicated by a serum creatinine of > 1.5 mg/dL (133 μmol/l) or a 24-h creatinine clearance < 40 mL/min
- Exclusion of shock, ongoing bacterial infection, volume depletion, and the use of nephrotoxic drugs
- No improvement in renal function despite stopping diuretics and volume repletion with 1.5 L of saline
- No proteinuria or ultrasonographic evidence of obstructive uropathy or parenchymal renal disease

- Minor criteria:
- 1. Urine volume lower than 500 ml/day
- 2. Urine sodium lower than 10 mEq/L
- 3. Urine osmolality > plasma osmolality
- 4. Urine blood cells < 50 per high-power fi eld
- 5. Serum sodium concentration lower than 130 mEq/L

Pathophysiology

- Increase in splanchnic vasodilation in cirrhosis
- Activation of Renin-Angiotensin system
- Renal vasoconstriction from sympathetic nervous system activation.
- All these lead to reduced renal perfusion and reduced GFR

HRS

- Type I: more serious type.
- At least a 50 percent lowering of the creatinine clearance to below 20 mL/min in less than a two week period or at least a twofold increase in serum creatinine to a level greater than 2.5 mg/dL (221 µmol/L).
- Such patients often oliguric.

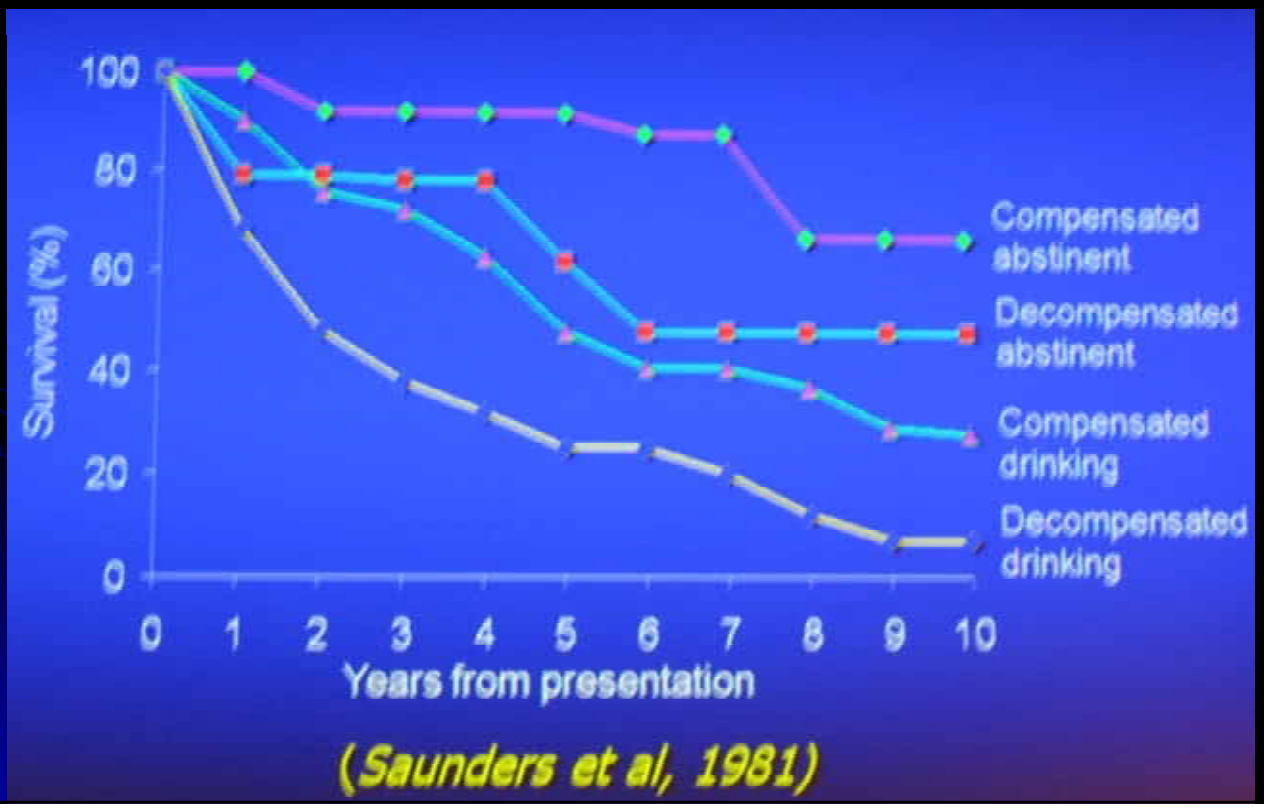
HRS

- Type II :less severe renal insufficiency than that observed with type I disease.
- Often characterized by ascites that is resistant to diuretics

Treatment

- Stop all diuretics
- Exclude and treat sepsis, especially SBP
- Volume expansion with IV Albumin (20 to 40 g per day)
- IV Terlipressin (1-2 mg 4 hourly)

Survival in Cirrhosis



Conclusions

- Alcohol has a serious impact on society- psychological, social and health.
- 25% of A&E attendance alcohol-related.
- Increasing pressures on healthcare.
- Poor access to residential detoxification programs.
- Vicious circle of patient readmission
- More awareness at both public and political level needed for what is a growing public health problem

Thank You