Dr Alasdair Patrick
Gastroenterologist

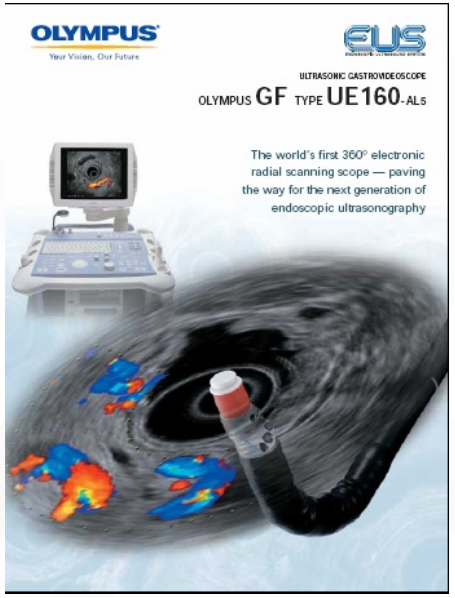
THE UNIVERSITY OF AUCKLAND
NEW ZEALAND
Te Whare Wānanga o Tāmaki Makaurau

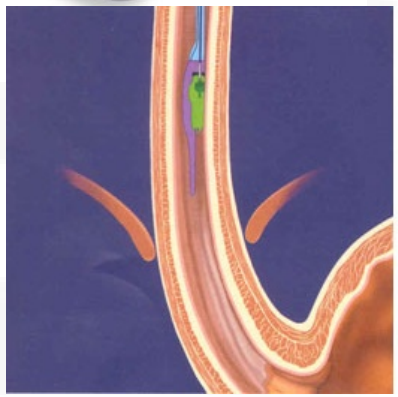
Royal Free Hampstead NHS
NHS Trust

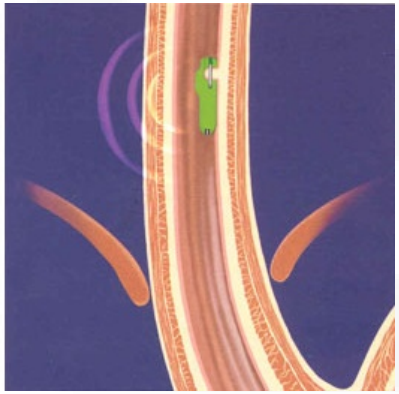
Singapore General Hospital
SingHealth

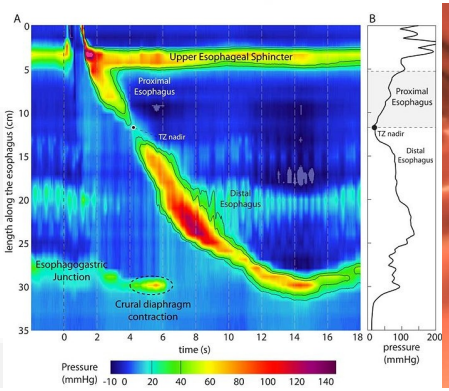
COUNTIES MANUKAU DISTRICT HEALTH BOARD
A Community Partnership

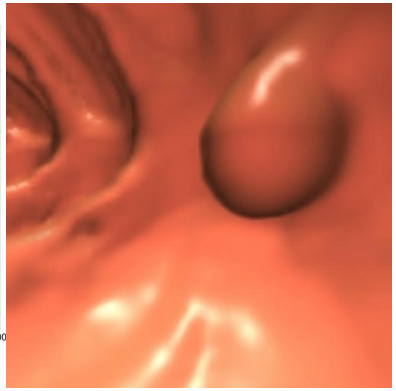
MACMURRAY
GASTROENTEROLOGY
DIGESTIVE DISEASES & ENDOSCOPY











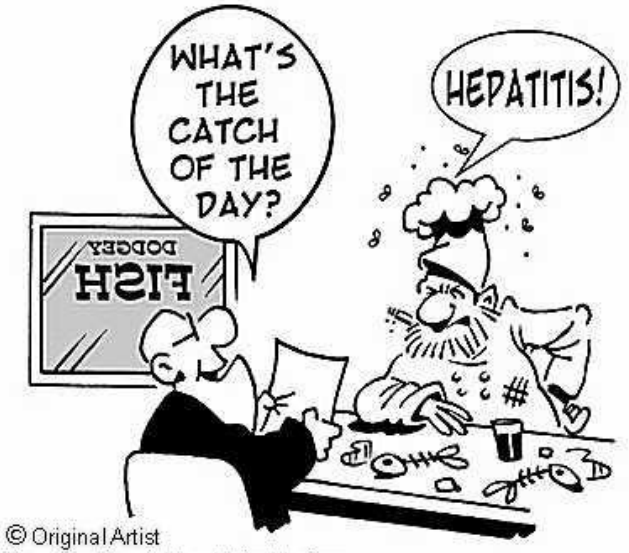
MACMURRAY
GASTROENTEROLOGY
DIGESTIVE DISEASES & ENDOSCOPY

Evaluation of Abnormal Liver Function Tests

Dr Alasdair Patrick
Gastroenterologist
MacMurray Gastroenterology

Overview

- Components of LFTs
  - Abnormalities
- Hepatitis B
- Hepatitis C
- ETOH
- NAFLD
- Cases (if time allows)



Background

- Liver function tests ordered routinely
- Pre-test probability is the best guide to which test to request
- 1-4% of asymptomatic patients have abnormal values
- Test results can fluctuate
  - 30% of abnormal results can normalise

  (Lazo Ann Intern Med 2008;148:348)
- Are LFTs a screening test?
  - Diagnosis can be reached non invasively

Why we investigate liver disease

ETOH

- Preventable
- Treatable
- Curable
- Reversible (80%)
- Predictable
- Public health
- Genetics
- Save money

Components of LFTs

- Transaminases (hepatocellular)
    - AST and ALT
- Cholestatic (obstructive)
  – ALP and GGT
- Bilirubin
  – Conjugated and unconjugated
- Synthetic function
  – INR, albumin

Transaminases

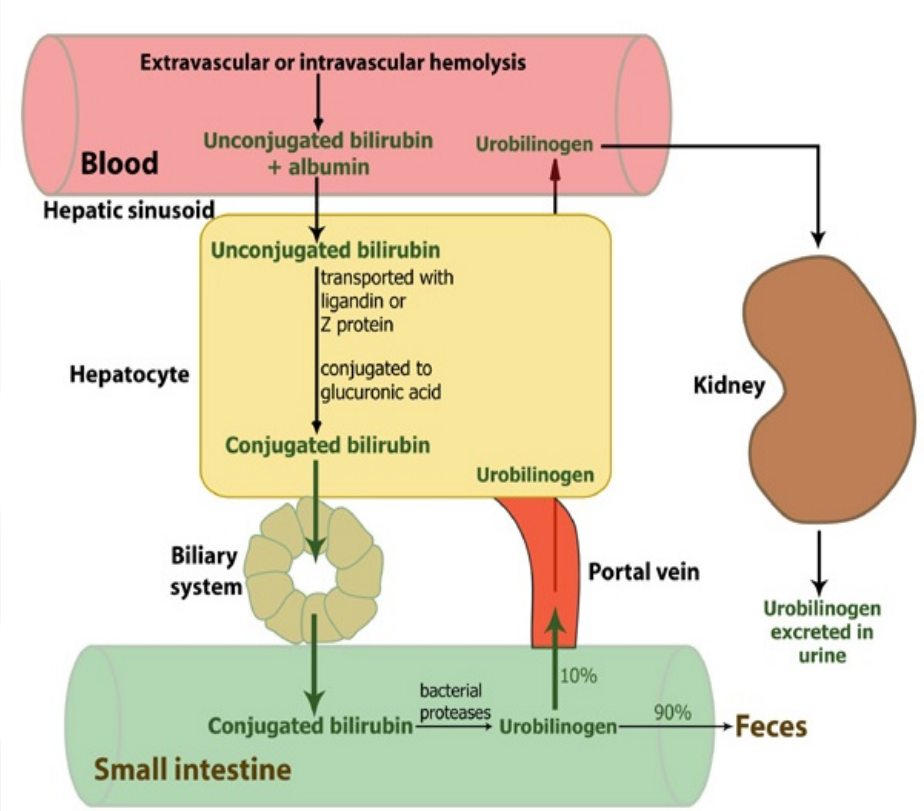
- Located in hepatocytes
  - Released after hepatocellular injury
- 2 Forms
  - AST
    - Non-specific to liver: heart, skeletal muscle, blood
  - ALT
    - More specific: elevated in myopathies

Cholestatic tests- Inducible

- ALP
  - Produced by biliary epithelial cells
  - Non-specific to liver: bone, intestine, placenta
- GGT
  - Sensitive but less specific to liver
  - Raised in pancreas pathology, DM, COPD, CRF and obesity/alcoholism

Bilirubin

- Product of hemoglobin breakdown
- 2 Forms
  - Un-conjugated (indirect)- insoluble
    - ↑ in hemolysis, Gilbert syndrome, meds
  - Conjugated (direct)- soluble
    - ↑ in obstruction, cholestasis, cirrhosis, hepatitis, primary biliary cirrhosis, etc.
    - No elevation until loss of > 50% capacity



Synthetic function tests

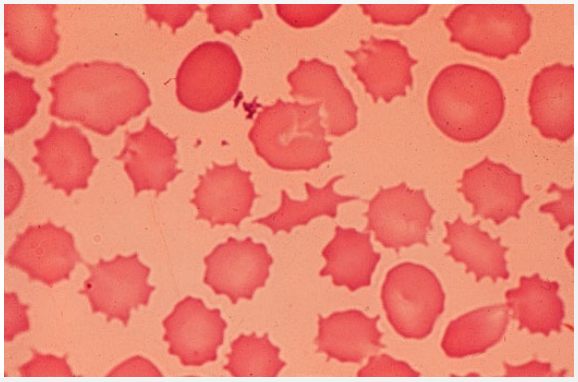
- Prothrombin ratio
  - Measures extrinsic pathway
    - Relies on factor VII which relies on Vitamin K
    - Vitamin K reduced in liver disease (80% capacity)
- Albumin
  - Most abundant plasma protein
    - Made by the liver with T1/2 20 days

Other LFT- Ferritin

- Raised in inflammation
  - Check CRP
- Raised in alcoholism
- Raised in insulin resistance syndromes
  - Associated with NAFLD
- Hemochromatosis
  - Usually very high >1000

Other LFT- FBC

- Anaemia (chronic disease, haemolysis, IDA, bleeding)
- High MCV
- Low platelets (ETOH, Portal hypertension)
- Blood film



Liver panel

- FBC
- LFT, CK, TFT, Bioch.
- Hepatitis serology
- Iron studies
- Protein & Ig level
- Coagulation screen
- Lipids level
- AFP

- Auto ab, ANA, RF, Tissue ab, LKM, SLA
- Coeliac serology
- α1AT
- s.ceruloplasmin

- U/S

Now to the abnormalities!

Abnormalities

- Isolated abnormality
  - High Bilirubin
  - High ALP
  - High GGT
  - High AST
- Mixed abnormality
  - Cholestatic
  - Hepatitic

High Bilirubin

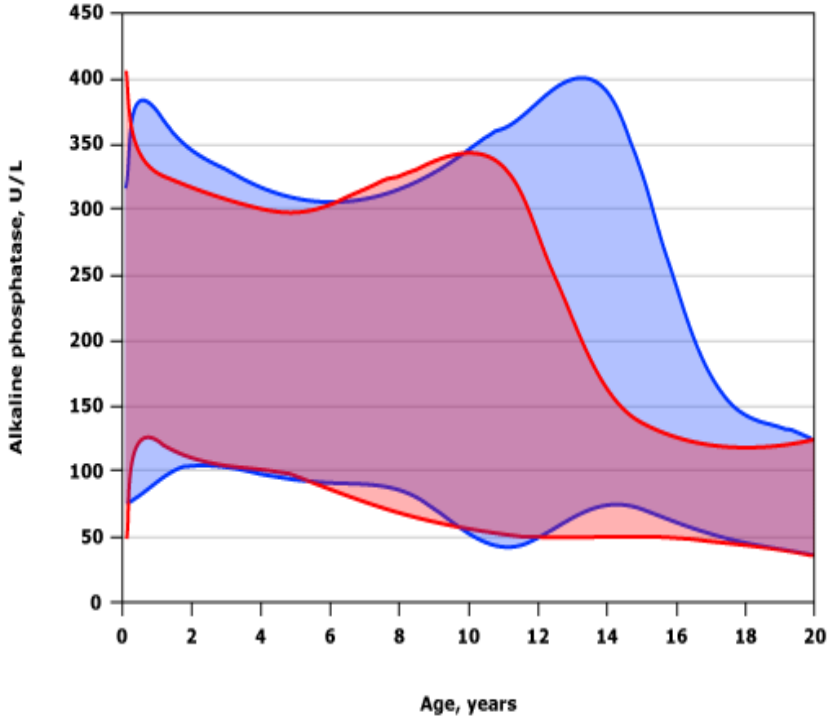
- Conjugated vs. Un-conjugated
- Is this haemolysis?
  - Haemolysis screen
    - Haptoglobins, Coombes, reticulocytes
  - FBC, blood film
- If only bilirubin
  - Drugs
  - Gilbert's

High ALP

- If GGT is normal
  - Repeat the test in 2 weeks

- Physiological : pregnancy, adolescence

- Bone disease
  - Calcium



High GGT

- Others normal
  - Repeat in 2 weeks
- Check alcohol history
- Check drug history
  - Phenytoin, barbituates, statins, herbs
  - Stop drug, repeat in 3-6 months then ?refer
- If no alcohol/drug cause
  - Think unusual cause (pancreas, DM, COPD, CRF)
  - Probably NAFLD

Abnormalities

- Isolated abnormality
  - High Bilirubin
  - High ALP
  - High GGT
  - High AST
- Mixed abnormality
  - Cholestatic
  - Hepatitic

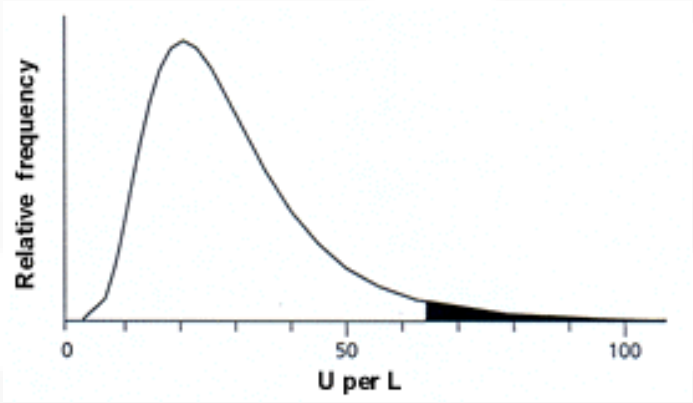
MacMurray Centre

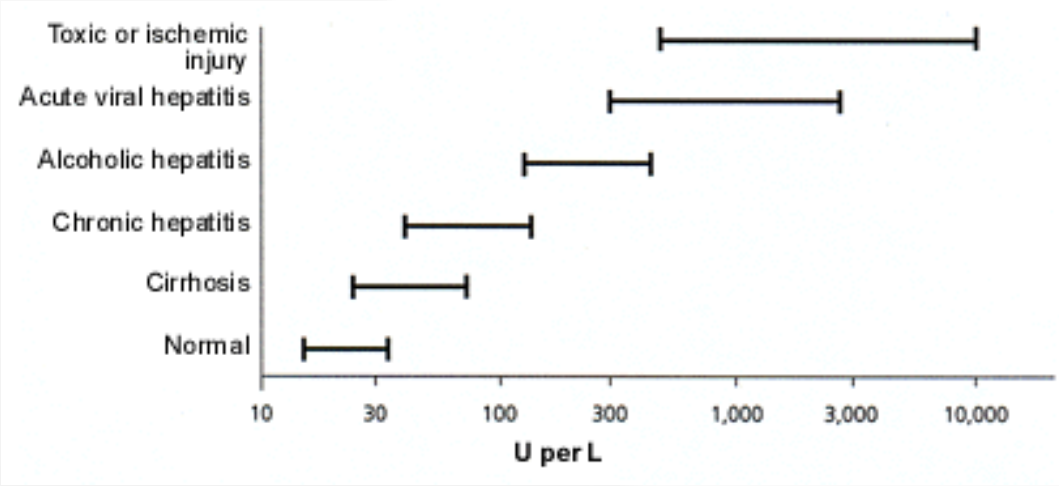
Cholestatic picture (ALP/GGT)

- If Bilirubin high
  - Consider biliary obstruction
    - Refer for urgent ultrasound/ opinion
    - Admit if pain, fever +/- rigor
- If normal Bilirubin/US
  - Drugs
  - Rare causes
    - PSC, PBC
    - Infiltrative liver disease, metastasis, other

Raised Transaminases (AST/ALT)

- 4 main reasons:
  - Drugs
  - Viral hepatitis
  - Alcohol
  - Other causes





Transaminases very high

- Medications/toxins
- Ischemic hepatitis
- Viral hepatitis (A–E, HSV, CMV)
- Autoimmune hepatitis
- Wilson’s disease
- Acute bile duct obstruction
- Acute Budd-Chiari syndrome
- Hepatic artery thrombosis

Mild raised tansaminases: Less Than 5 Times Normal

Hepatic: ALT-predominant

- Chronic hepatitis C
- Chronic hepatitis B
- Acute viral hepatitis (A, D, E, EBV, CMV)
- Steatosis/steatohepatitis
- Hemochromatosis
- Medications/toxins
- Autoimmune hepatitis
- Alpha1-antitrypsin deficiency

Hepatic: AST-predominant

- Alcohol-related liver injury
- Steatosis/steatohepatitis
- Cirrhosis
- Wilson’s disease

Nonhepatic

- Hemolysis
- Myopathy
- Thyroid disease
- Strenuous exercise
- Coeliac disease

Raised Transaminases

- Drugs
  - Almost any medication
    - NSAID, antibiotics, statins, anti-epileptic, paracetomol
  - Herbal
    - Chaparral leaf, Ephedra, Gentian, Germander, Jin Bu Huan, Senna, Kavakava, Scutellaria (skullcap), Shark cartilage and Vitamin A
  - Recreational
    - Ecstasy, cocaine

Medications, Herbs, and Toxins That Can elevate AST,ALT

Medications and drugs

- Acetaminophen
- Alpha-methyldopa
- Amoxicillin-clavulanic acid
- Amiodarone
- Carbamazepine
- Dantrolene
- Disulfiram
- Etretinate
- Fluconazole
- Glyburide
- Halothane
- Heparin
- HMG-Co A reductase inhibitors
- Isoniazid
- Ketoconazole
- Labetolol
- Nicotinic acid
- Nitrofurantoin
- Methotrexate
- Nonsteroidal anti-inflammatory drugs
- Phenylbutazone
- Phenytoin
- Propylthiouricil
- Protease inhibitors
- Sulfonamides
- Trazadone
- Troglidazone
- Valproic acid

Herbs/Alternative medications

- Chaparral leaf
- Ephedra
- Gentian
- Germander
- Jin Bu Huan
- Senna, Kavakava
- Scutellaria (skullcap)
- Shark cartilage
- Vitamin A

Illicit drugs

- Anabolic steroids
- Cocaine
- Ecstasy (MDMA)
- Phencyclidine (PCP)

Toxins

- Carbon tetrachloride
- Chloroform
- Dimethylformamide
- Hydrazine
- Hydrochlorofluorocarbons
- 2-Nitropropane
- Trichloroethylene
- Toluene

When to refer!

- Isolated abnormalities
  - Can usually be watched and investigated
- Cholestatic picture
  - Consider U/S or admission
- Hepatitic picture
  - If more than 2x ULN or climbing
  - Certain treatable disease
- Cirrhosis/ synthetic disfunction
  - Physical signs

MacMurray Centre

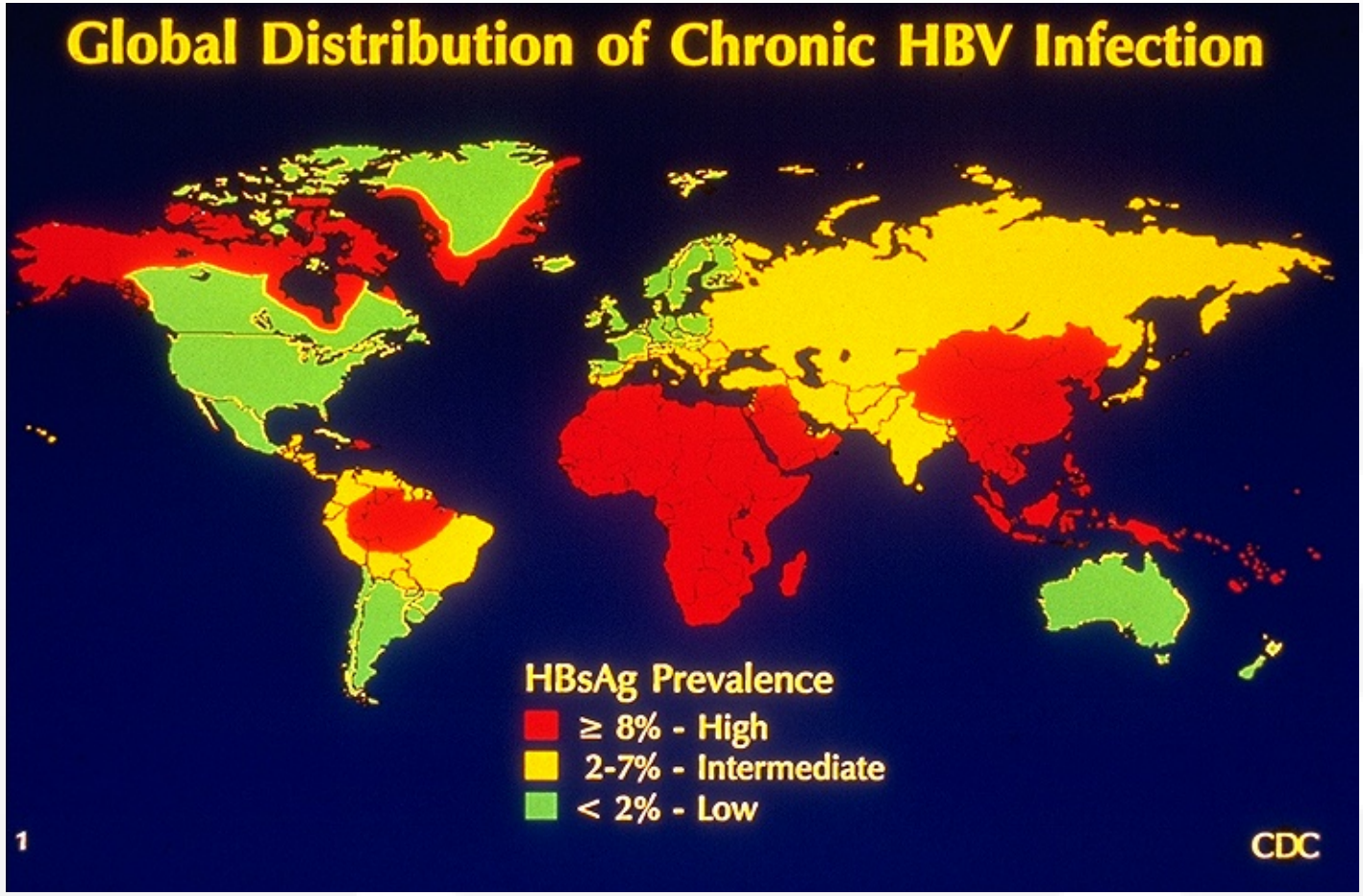
Physical findings

- Do they have clinical signs of liver disease?

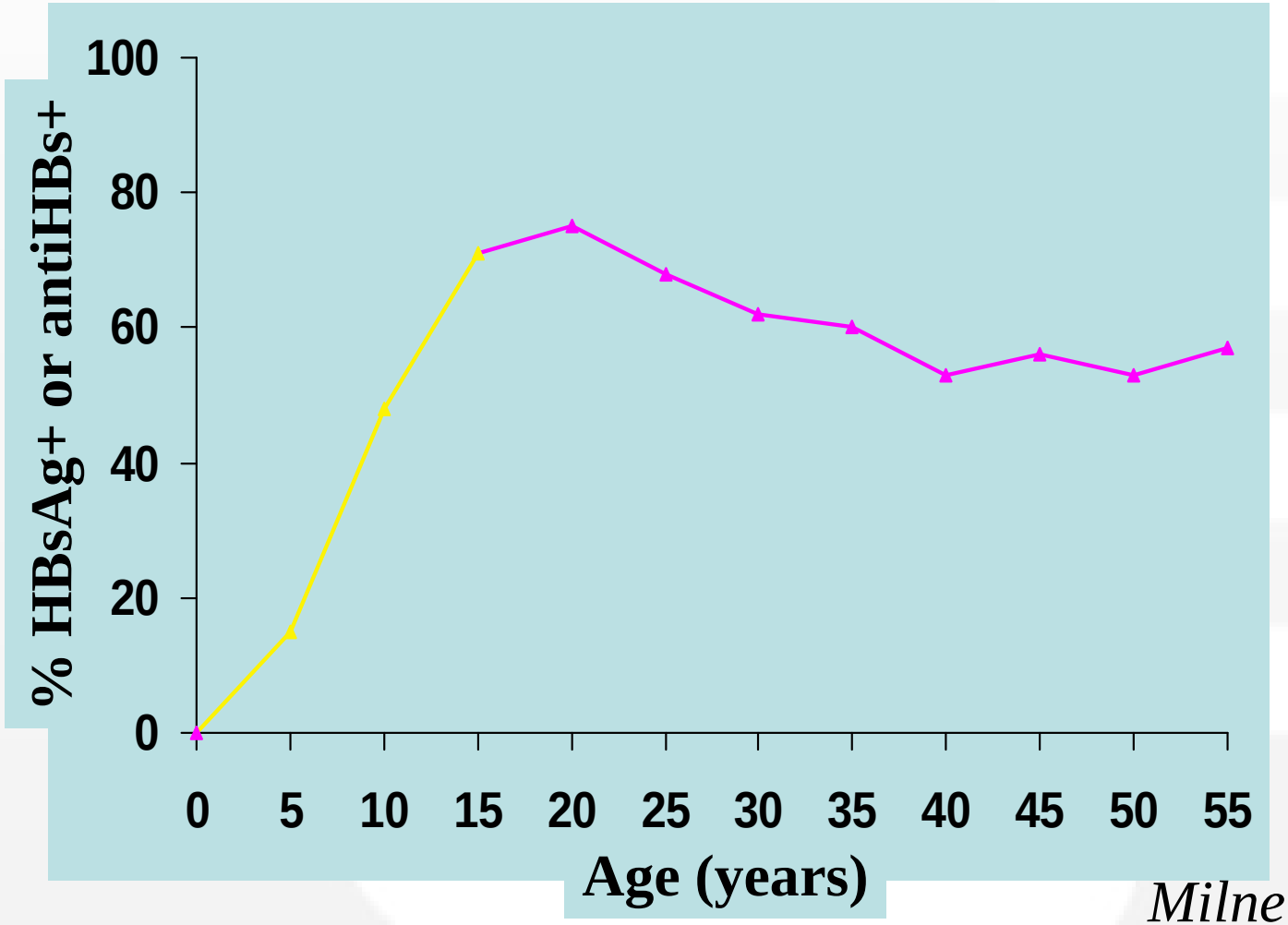
Specific conditions

- Hepatitis B
- Hepatitis C
- Alcohol
- NAFLD

Hepatitis B

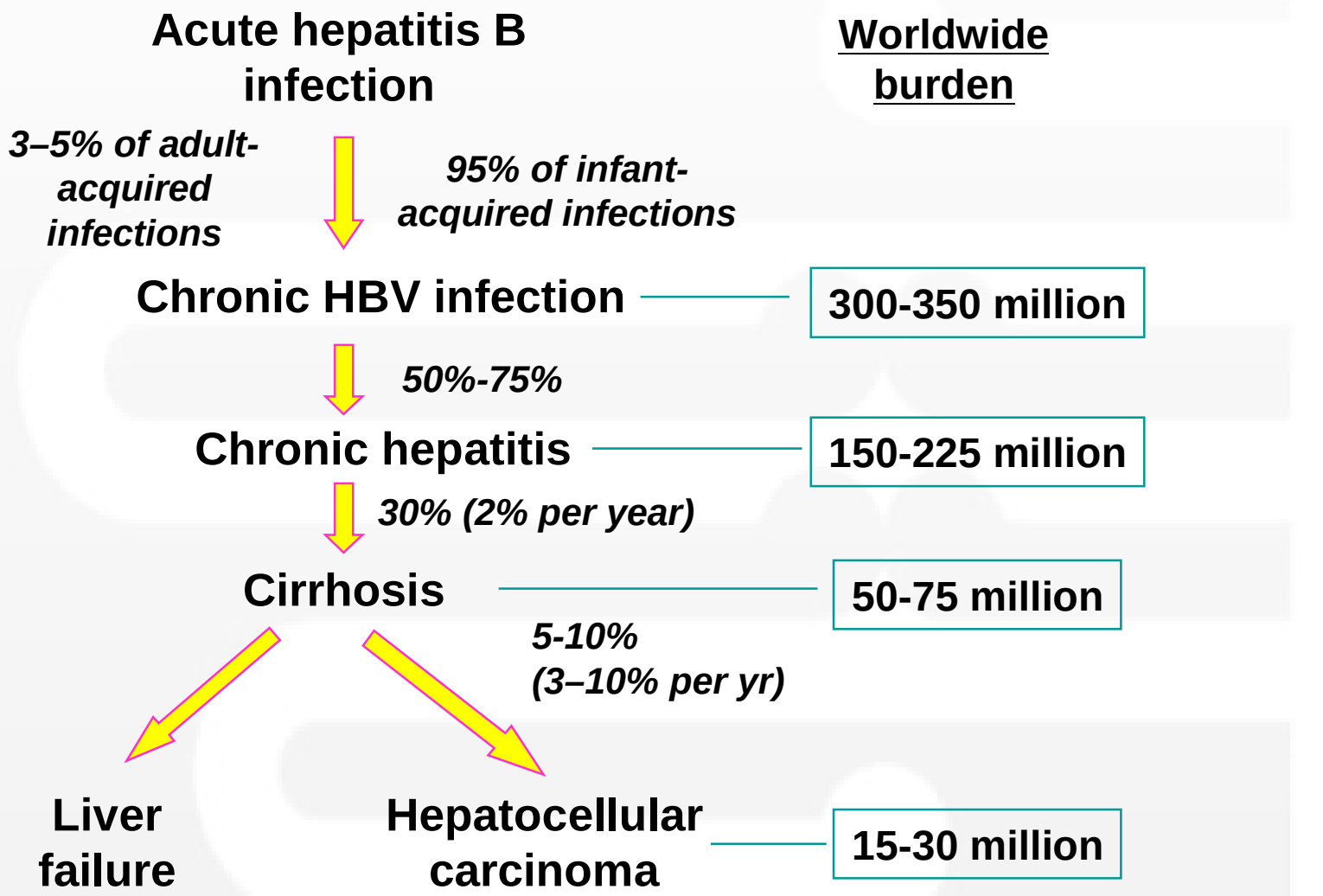

Global Distribution of Chronic HBV Infection
HBsAg Prevalence
≥ 8% - High
2-7% - Intermediate
< 2% - Low
1
CDC

Age-Specific Prevalence of Markers of Active and Past HBV Infection

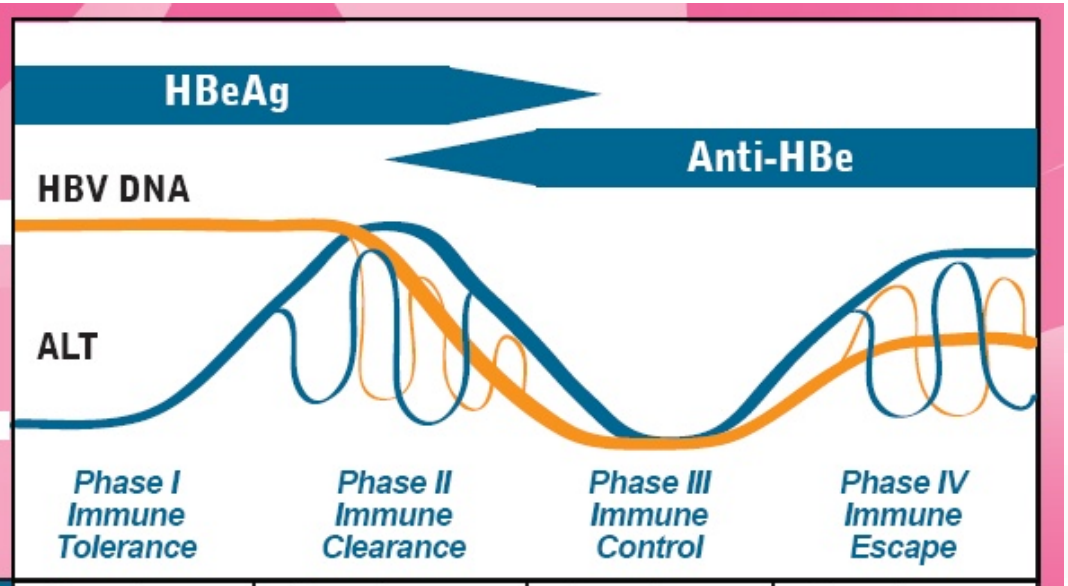


Milne,1985

Possible outcomes of chronic HBV infection



GESA
Gastroenterological Society of Australia
Australian Liver Association



	Phase I Immune Tolerance	Phase II Immune Clearance	Phase III Immune Control	Phase IV Immune Escape
HBsAg	> 6 months	> 6 months	> 6 months	> 6 months
HBeAg	+	+	–	–
Anti-HBe	–	Spontaneous seroconversion to anti-HBe may occur	+	+
ALT	Persistently normal	Persistently or intermittently elevated	Persistently normal	Persistently or intermittently elevated
HBV DNA	≥ 20,000 IU / mL	Persistently or intermittently ≥ 20,000 IU / mL	< 2000 IU / mL	Persistently or intermittently ≥ 2,000 IU / mL
Liver Histology	Minimal or mild hepatitis Usually no fibrosis	Inflamation score ≥ 4 Fibrosis: + / -	Inflammation score < 4 Fibrosis: + / -	Inflammation score ≥ 4 Fibrosis: +

Serologic markers of infection and their significance

	Acute hepatitis B	Recovery from acute hepatitis B	Chronic HBeAg + disease	Chronic HBeAg – disease	Successful vaccination
HBsAg	✓		✓	✓	
Anti-HBs		✓			✓
Anti-HBc IgM	✓		✓		
Anti-HBc IgG	✓	✓	✓	✓	
HBeAg	✓		✓		
Anti-HBe		✓ (in some cases)		✓	
DNA (PCR if required)	✓		✓	✓	

Our Current Treatment Options

- Immune modulator
  - Pegylated INF 2a
- Anti-viral
  - Lamivudine
  - Adefovir
  - Entecavir

Entecavir

- Very potent
  - 7 log viral DNA drop
- Very low rates of resistance
  - Except in patients already treated with lamivudine!
- Rolls Royce of nucleoside analogues

So who needs a referral?

- Chronic HBV with:
  - Persistently raised ALT
    - e Ag +ve
    - e Ag –ve
  - Fluctuating LFTs
    - e Ag +ve or –ve
  - e Ag –ve but high levels of DNA
  - Rising AFP
  - Suspicion of cirrhosis or advanced liver disease

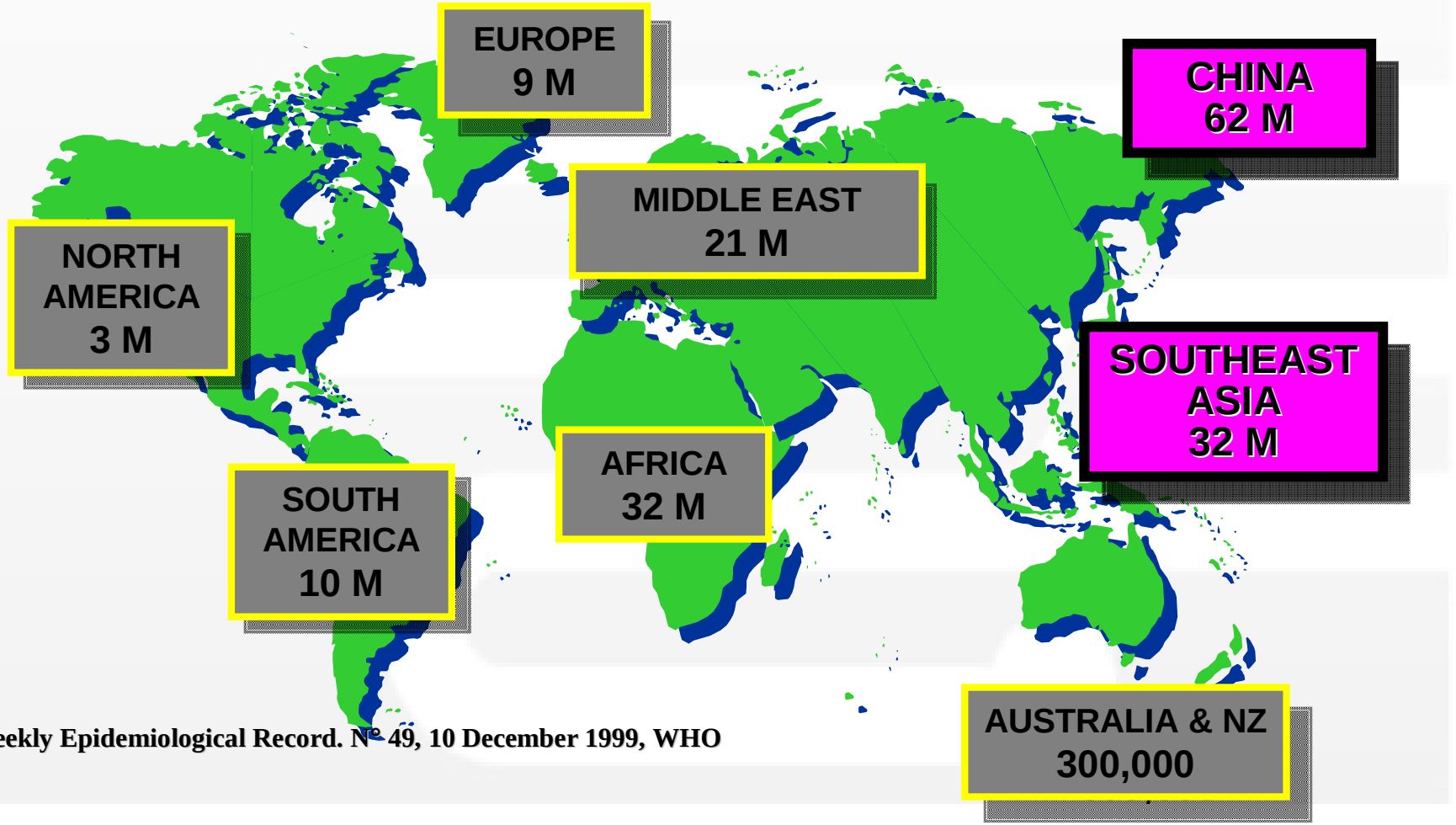
  - Immune tolerant patients > 30 yrs old (e Ag +ve, normal ALT)

Hepatitis foundation

Anyone you are concerned about….that will turn up to clinic

Epidemiology of Hepatitis C
A Global HCV Epidemic

- 180 Million Infected Worldwide
- 3-4 Million New Cases/Year



Weekly Epidemiological Record. N° 49, 10 December 1999, WHO

HCV Transmission and Risk Factors

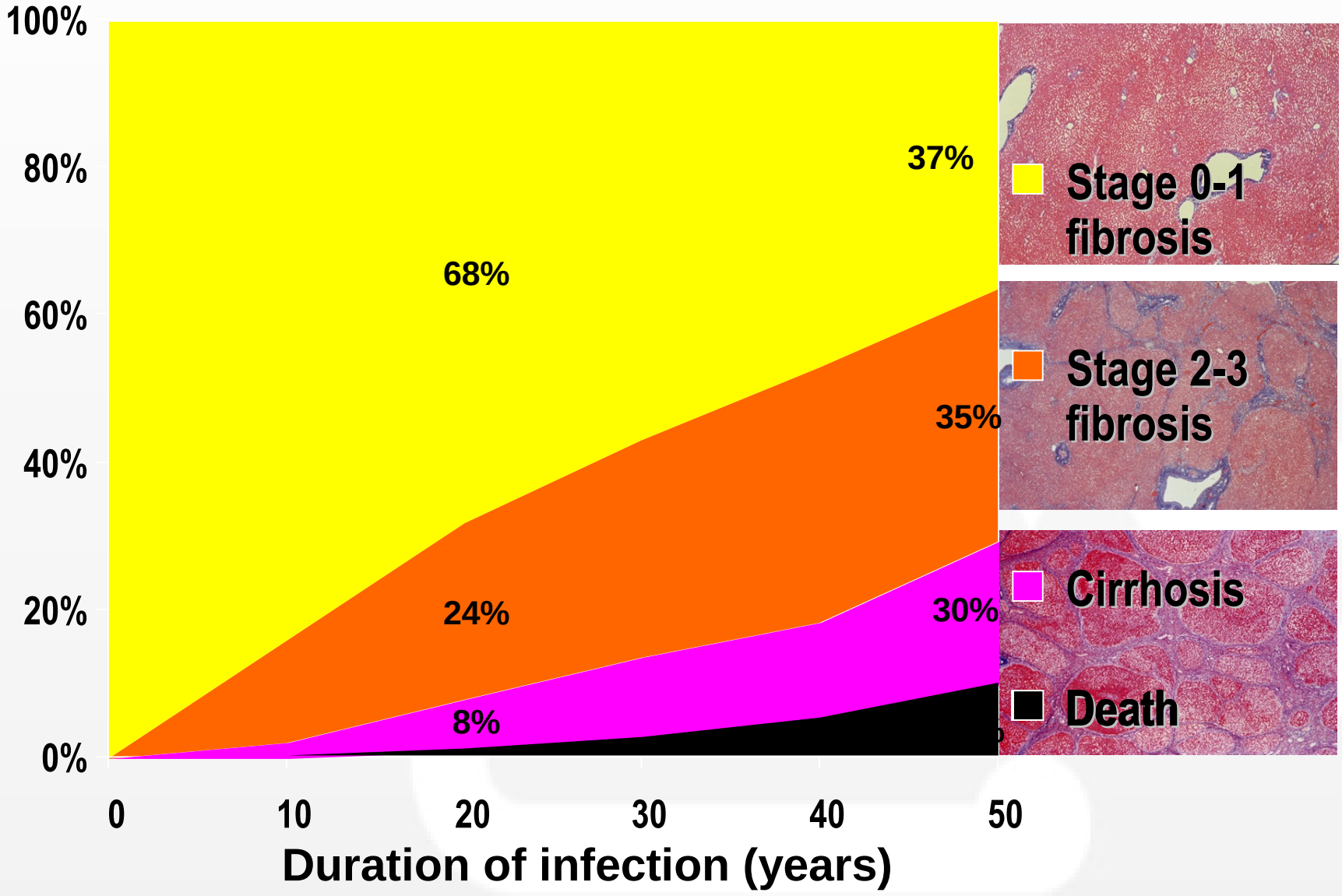
- Blood products (before 1992)
  - Transfusions
  - Haemophiliacs
- IV drug users
- Patients from endemic countries

- Tattoos
  - Unsterilised needles, shared ink
- Incarceration (>20% prevalence)

- Maternal transmission (5%)
- Cocaine use
- Sexual contact?

- Note: 15 – 30% clear the virus spontaneously

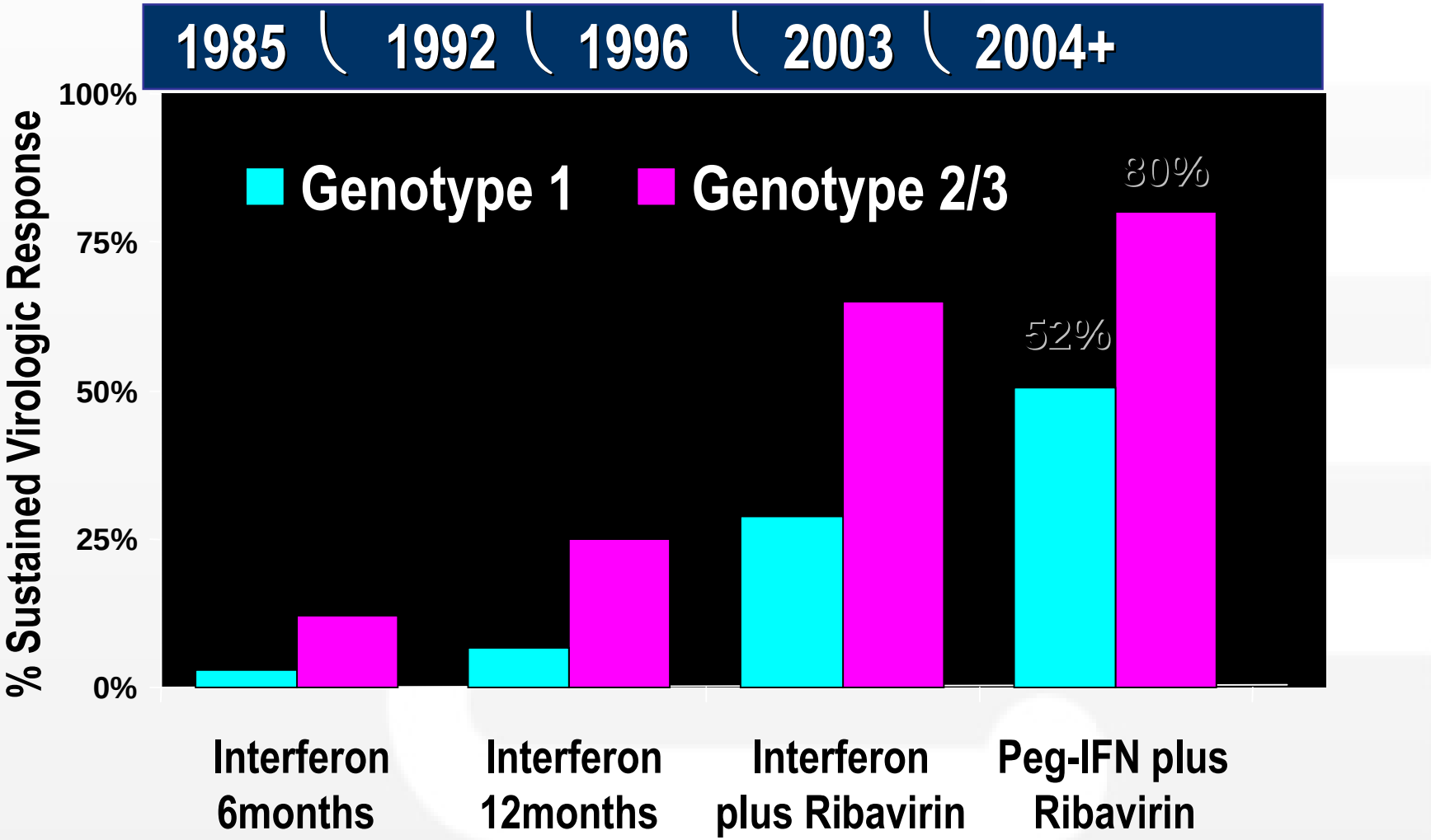
Natural History of Chronic Hepatitis C



The Tests – for GPs

- HCV antibody test
  - Highly sensitive
  - Good as initial screen
  - (may take months to be +ve after an acute infection)
- HCV RNA (PCR)
  - Needed to confirm current infection

Improving Efficacy



So who do you refer?

- HCV RNA +ve
- No active IVDU
- (ALT no longer an issue)

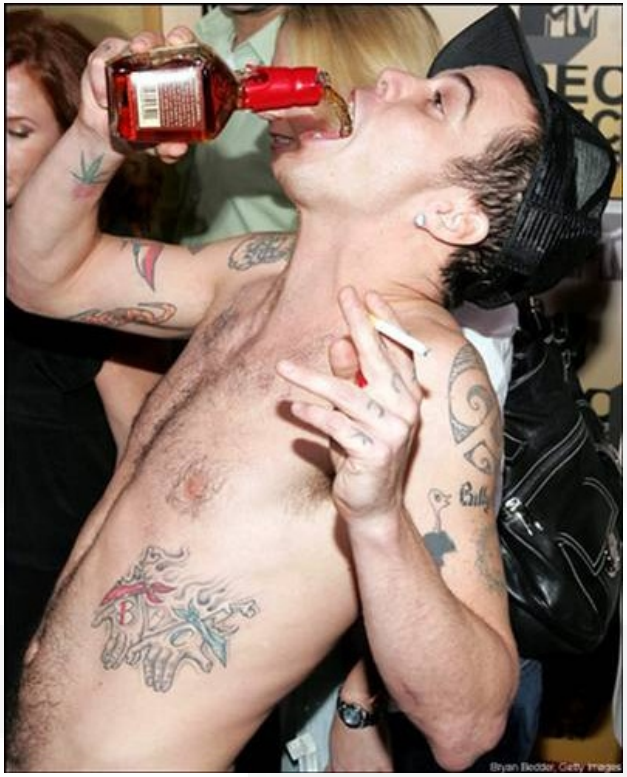
- NB. Acute HCV, even in active IVDU – please refer

What’s new in HCV 2010?

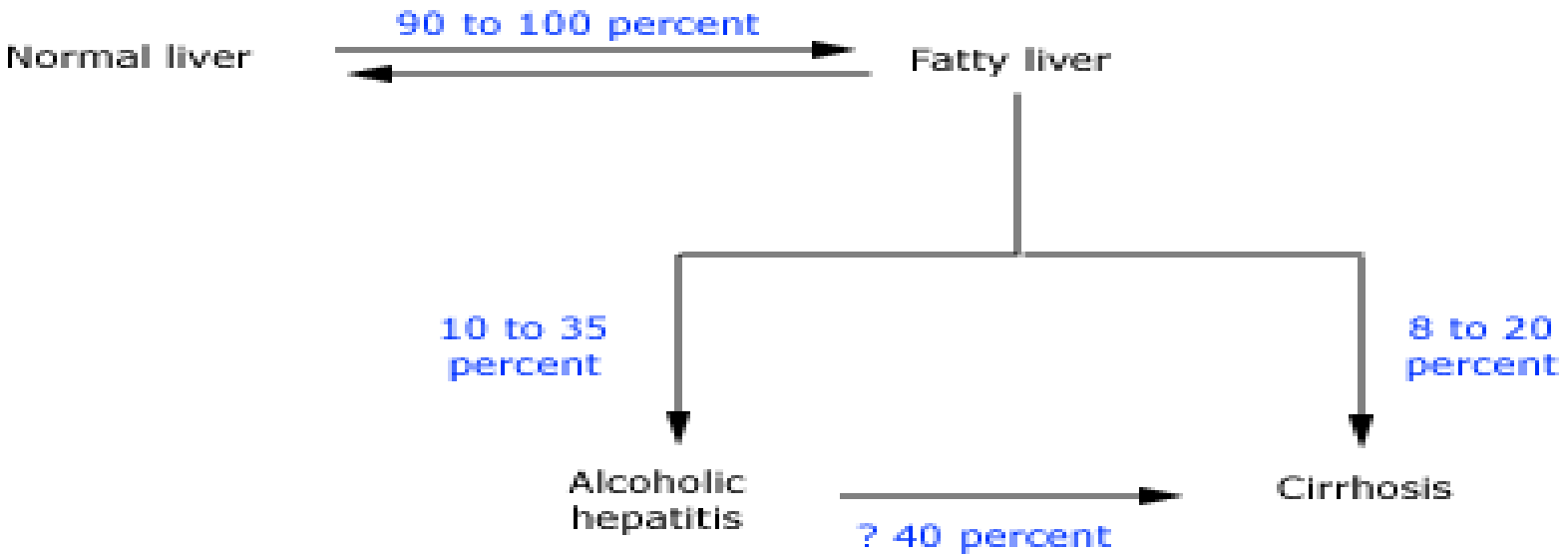
- Adjust treatment duration according to on-treatment response
  - 4 and 12 week RNA checks
- New therapies in clinical trials

Alcoholic liver disease

- 1/6 people visiting the GP in NZ meet definitions for hazardous drinking
- CAGE questions
- Blood clues
  - Serum AST>ALT (ratio usually >2)
  - Elevated GGT
  - High MCV
  - Leucocytosis



ETOH liver disease



American College of Gastroenterology. McCullough, AJ, et al. Recommendations for the diagnosis of alcoholic liver disease. Am J Gastroenterol 1998; 93:2023

No physical signs present

- Encourage abstinence
  - Community support

- Once stopped
  - Recheck bloods in 8 weeks
    - If abnormal screen for alternative cause
    - Refer

MacMurray Centre

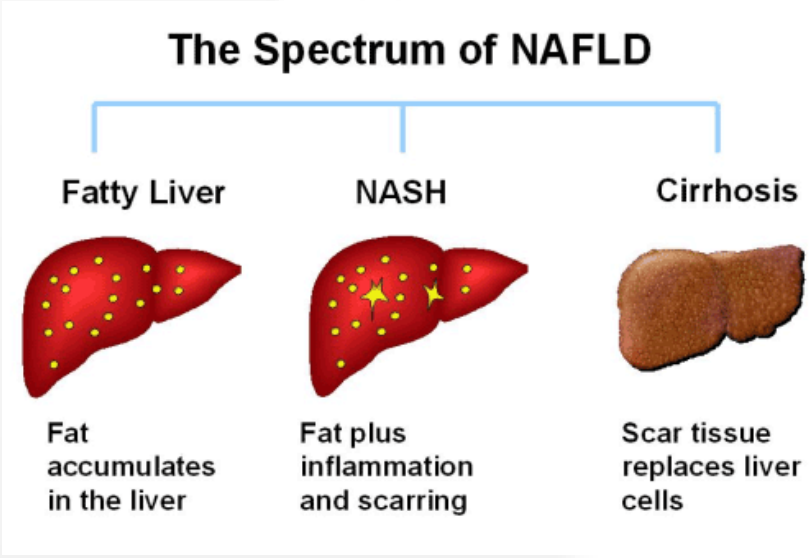
Physical signs present

- Have they stopped drinking or are likely?
  - Refer to Gastroenterology
- Do they have features suggestive of dependency?
  - 40% will develop withdrawal
    - Early morning vomiting or tremor
    - Blackouts/ fits
    - Amnesia
    - Previous DT or withdrawl

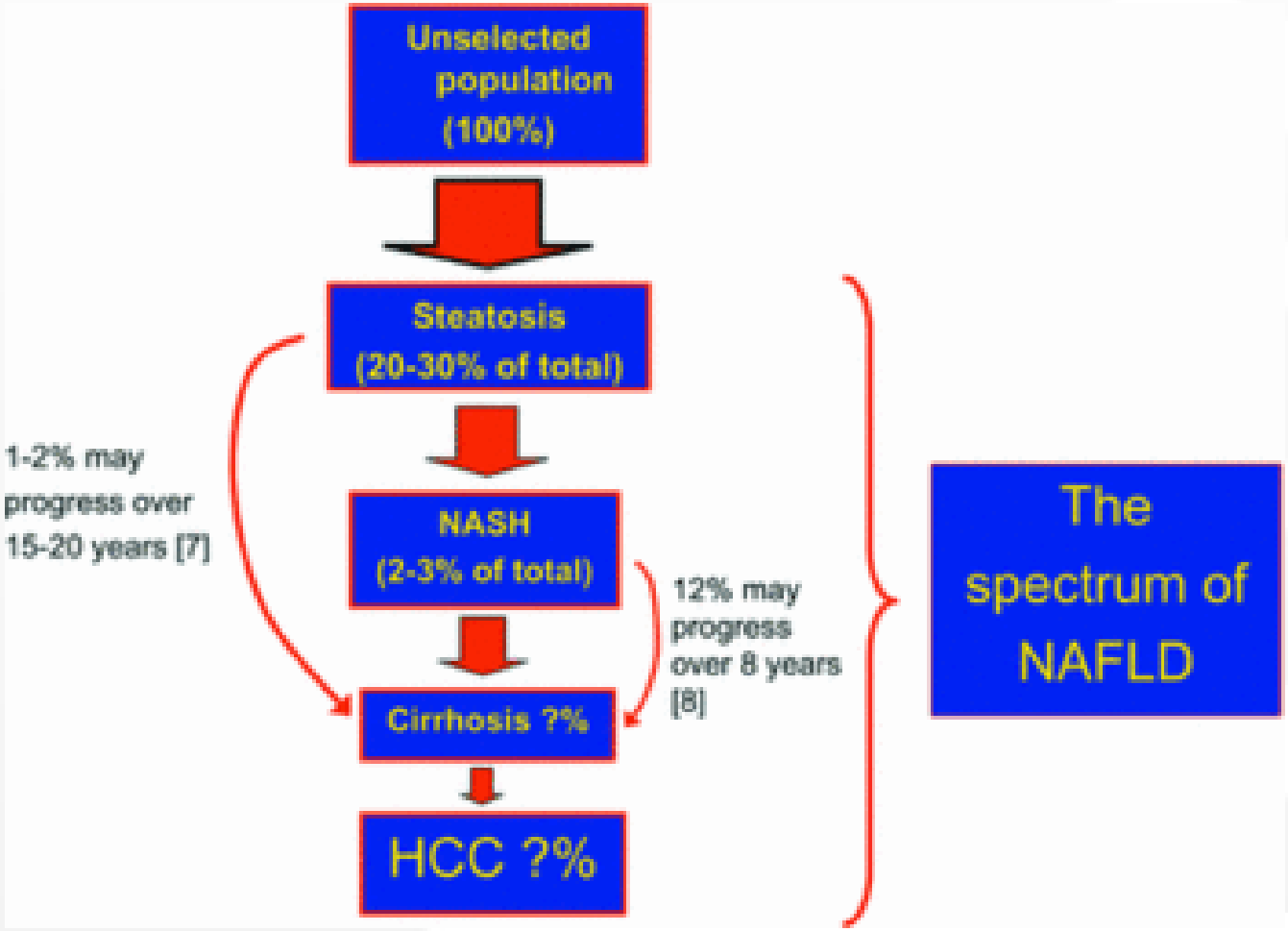
MacMurray Centre

Non alcoholic fatty liver

- An epidemic in the West
- Have high index of suspicion
  - Metabolic risk factors
- Diagnosis by U/S

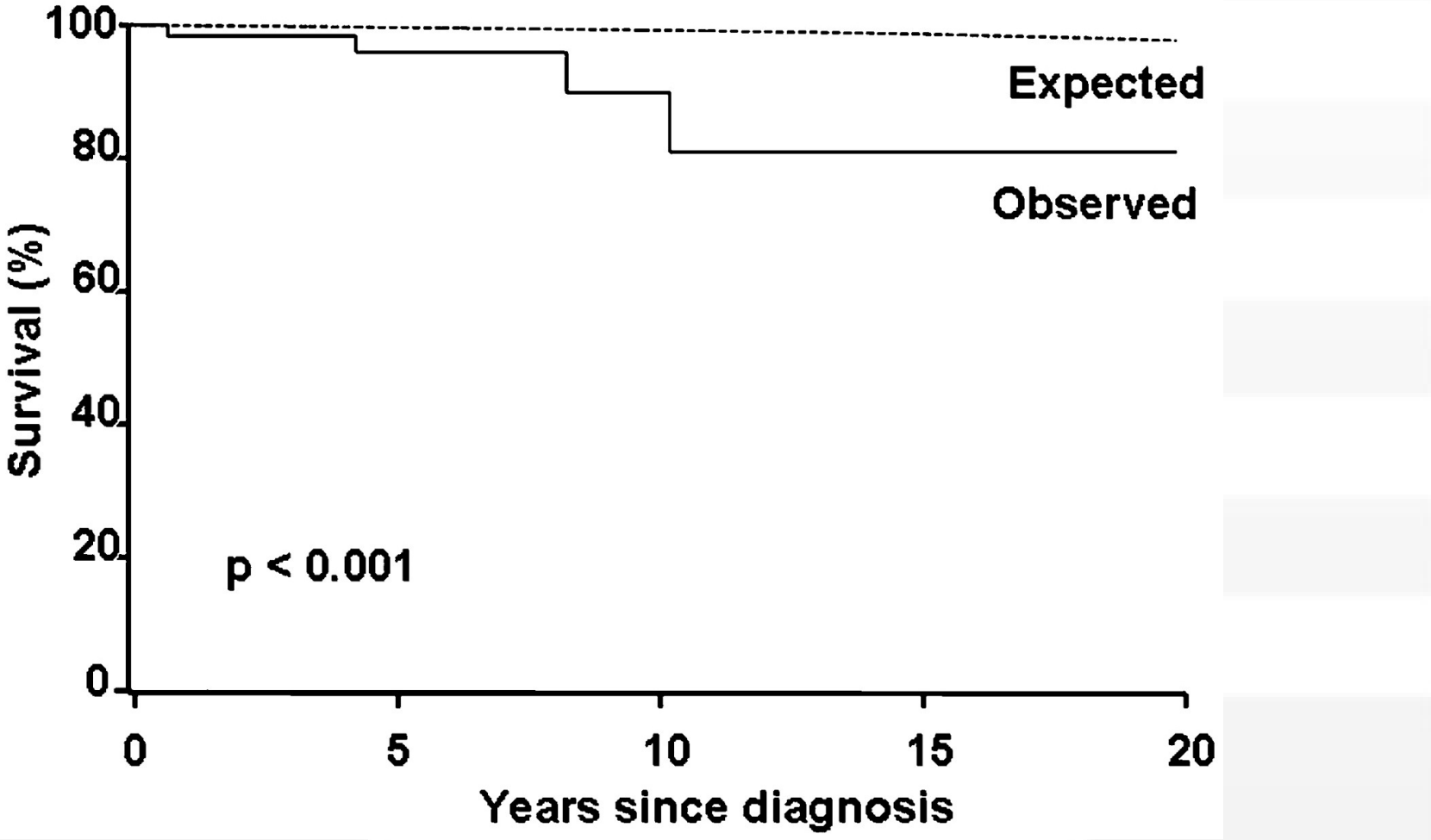


Natural history of NAFLD



MacMurray Centre

NAFLD



Gut 2009 58:p1538

NAFLD treatment

- Lifestyle modification
  - Diet and exercise
- Target other metabolic risk factors
  - Cholesterol
  - Hypertension
  - Diabetes
- Consider referral for obesity management
  - Surgery

MacMurray Centre

Who to refer

- If there is diagnostic uncertainty
  - Liver panel
- If cirrhosis is possible

- Any other concerns

MacMurray Centre

Conclusion

- LFTs are easy
  - Remember the patterns
- Who to refer
  - Any diagnostic uncertainty
  - Any cirrhotic
  - Refer HBV with active disease
    - Great new treatments are available
  - Refer all HCV
    - Can be cured now!

MacMurray Centre

The only comprehensive digestive disease centre in Auckland

Consultations in a team environment
- 5 Gastroenterologists
- 1 Hepatologist
- Upper and Lower GI surgeons

Dietician
Health Psychologist
Clinical nurse specialists

The only place with full diagnostic and therapeutic services

Full endoscopy services
BRAVO
Capsule endoscopy
pH/Impedance
High resolution Manometry
CT colonography

Case 1

- 37 year old European man
  - 2 beers per night
  - Thin
  - No signs of chronic liver disease
    - Tbili 18 (0-24)
    - AST 89 (0-45)
    - ALT 49 (0-45)
    - GGT 80 (0-50)
    - ALP 80 (40-100)

MacMurray Centre

What other bloods would you want to check?

- INR 1.0 (<1.2)
- Alb 40 (38-52)
- MCV 101 (80-99)
- Ferritin 605 (20-380)
- Negative serology

- What is cause?
- What would you do?

Case 2

- 22 year old European male
  - No alcohol
  - BMI 26
  - No signs of chronic liver disease
    - Tbili 45 (0-24)
    - AST 23 (0-45)
    - ALT 41 (0-45)
    - GGT 30 (0-50)
    - ALP 80 (40-100)

MacMurray Centre

What other bloods would you want to check?

- INR 1.0 (<1.2)
- Alb 40 (38-52)
- Hb 101 (130-175)
- Haptoglobins <0.1 (0.5-2.4)

- What is cause?
- What would you do?

MacMurray Centre

Case 3

- 80 year old European female
  - No alcohol
  - BMI 21
  - No signs of chronic liver disease
    - Tbili 20 (0-24)
    - AST 23 (0-45)
    - ALT 41 (0-45)
    - GGT 30 (0-50)
    - ALP 230 (40-100)

MacMurray Centre

What other bloods would you want to check?

- INR 1.0 (<1.2)
- Alb 40 (38-52)
- Hb 109 (115-160)
- Ca 2.8 (2.1-2.6)
- PTH 0.6 (1.5-7.6)

- What is cause?
- What would you do?

MacMurray Centre

Case 4

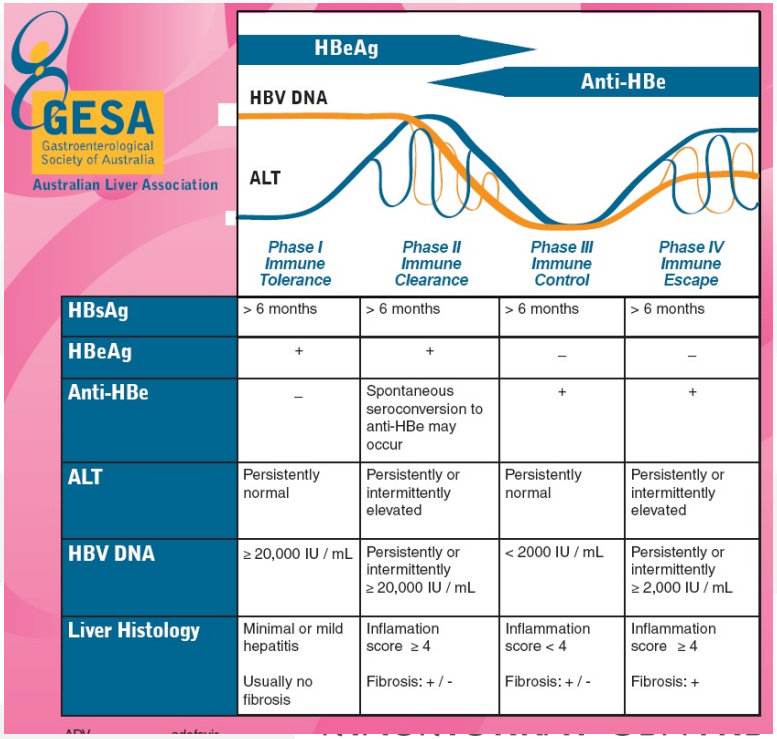
- 42 year old Chinese female
  - No alcohol
  - BMI 21
  - No signs of chronic liver disease
    - Tbili 18 (0-24)
    - AST 40 (0-45)
    - ALT 55 (0-45)
    - GGT 30 (0-50)
    - ALP 90 (40-100)

MacMurray Centre

What other bloods would you want to check?

- INR 1.0 (<1.2)
- Alb 40 (38-52)
- Hepatitis B serology positive

- What is cause?
- What would you do?



	Phase I Immune Tolerance	Phase II Immune Clearance	Phase III Immune Control	Phase IV Immune Escape
HBsAg	> 6 months	> 6 months	> 6 months	> 6 months
HBeAg	+	+	–	–
Anti-HBe	–	Spontaneous seroconversion to anti-HBe may occur	+	+
ALT	Persistently normal	Persistently or intermittently elevated	Persistently normal	Persistently or intermittently elevated
HBV DNA	≥ 20,000 IU / mL	Persistently or intermittently ≥ 20,000 IU / mL	< 2000 IU / mL	Persistently or intermittently ≥ 2,000 IU / mL
Liver Histology	Minimal or mild hepatitis Usually no fibrosis	Inflamation score ≥ 4 Fibrosis: + / -	Inflammation score < 4 Fibrosis: + / -	Inflammation score ≥ 4 Fibrosis: +

Case 5

- 43 year old Indian male
  - 2 whisky per night/ 25 years
  - Weight 66kg, BMI 20
  - Signs of chronic liver disease (no ascites)
    - Tbili 45 (0-24)
    - AST 78 (0-45)
    - ALT 60 (0-45)
    - GGT 50 (0-50)
    - ALP 90 (40-100)

MacMurray Centre

What other bloods would you want to check?

- INR 1.6 (<1.2)
- Alb 30 (38-52)
- Hb 109 (115-160)
- MCV 107 (80-99)

- What is cause?
- What would you do?

Same guy 2 years later

- Stopped drinking 9 months ago
- Went to see Gastro once 18/12 ago
  - U/S cirrhotic
- Now has ascites clinically
  - Weight 78kg

- What bloods would you check?
- What diet would you recommend?
- Would drugs would you prescribe?
- What else would you do?

MacMurray Centre

Alcoholic cirrhotic

- Diet
  - Low salt
  - High calorie
  - Watch protein
- Diuretics
  - Based on weight, take it easy
  - Spironolactone only
- Child Pugh score
  - Tbili, INR, alb, encephalopathy, ascites

Case 6

- 28 year old epileptic
  - No alcohol
  - No signs of chronic liver disease
    - Tbili 18 (0-24)
    - AST 18 (0-45)
    - ALT 28 (0-45)
    - GGT 97 (0-50)
    - ALP 90 (40-100)

MacMurray Centre

What other bloods would you want to check?

- INR 1.0 (<1.2)
- Alb 40 (38-52)
- MCV and Ferritin normal

- What is cause?
- What would you do?

MacMurray Centre

Case 7

- 18 year old Pacific Island girl
  - Recent relationship breakup
  - Denies alcohol/ drugs
  - No signs of chronic liver disease
    - Tbili 25 (0-24)
    - AST 585 (0-45)
    - ALT 679 (0-45)
    - GGT 97 (0-50)
    - ALP 90 (40-100)

MacMurray Centre

What other bloods would you want to check?

- INR 1.7 (<1.2)
- Alb 40 (38-52)
- MCV and Ferritin normal

- What is cause?
- What would you do?

Case 8

- 45 year old Tongan man
  - No alcohol
  - BMI 35
  - No signs of chronic liver disease
    - Tbili 19 (0-24)
    - AST 28 (0-45)
    - ALT 44 (0-45)
    - GGT 110 (0-50)
    - ALP 90 (40-100)

MacMurray Centre

What other bloods would you want to check?

- INR 1.0 (<1.2)
- Alb 40 (38-52)
- MCV and Ferritin normal
- Hepatitis serology negative
- Fasting glucose!!

- What is cause?
- What would you do?

Case 9

- 46 year old European lady with abdo pain
  - No alcohol
  - BMI 34
  - No signs of chronic liver disease
    - Tbili 19 (0-24)
    - AST 60 (0-45)
    - ALT 88 (0-45)
    - GGT 190 (0-50)
    - ALP 255 (40-100)

MacMurray Centre

What other bloods would you want to check?

- INR 1.0 (<1.2)
- Alb 40 (38-52)
- FBC normal
- Hepatitis serology negative

- What is cause?
- What would you do?

MacMurray Centre

Case 10

- 65 year old European man non specifically unwell
  - No alcohol
  - Recent LRTI, saw another GP 4/52 ago
  - No signs of chronic liver disease
    - Tbili 19 (0-24)
    - AST 100 (0-45)
    - ALT 107 (0-45)
    - GGT 55 (0-50)
    - ALP 102 (40-100)

MacMurray Centre

What other bloods would you want to check?

- INR 1.0 (<1.2)
- Alb 40 (38-52)
- FBC normal
- Hepatitis serology negative

- What is cause?
- What would you do?

MacMurray Centre

The only comprehensive digestive disease centre in Auckland

Consultations in a team environment
- 5 Gastroenterologists
- 1 Hepatologist
- Upper and Lower GI surgeons

Dietician
Health Psychologist
Clinical nurse specialists

The only place with full diagnostic and therapeutic services

Full endoscopy services
BRAVO
Capsule endoscopy
pH/Impedance
High resolution Manometry
CT colonography

MacMurray Centre