INTERPRETATION OF LIVER FUNCTION TESTS (INCLUDING HCC MARKERS)

Dr Thomas Lui

HKU Med

LIVER FUNCTION TESTS

- Parameters in liver function test:
  - Albumin
  - Bilirubin
  - Alanine aminotransferase (ALT), aspartate aminotransferase (AST)
  - Alkaline phosphatase (ALP), gamma glutamyltransferase (GGT)

- Other important investigations:
  - Prothrombin time
  - Arterial ammonia (NH_3)
  - Complete blood picture
  - Autoimmune markers
  - LDH
  - AFP
  - Imaging: US, CT, Fibroscan etc

LIVER FUNCTION TESTS

- 3 aspects
  - Cellular integrity
    - ALT and AST
  - Protein synthesis
    - Albumin and PT
  - Excretory markers
    - Bilirubin, ALP and GGT

CELLULAR INTEGRITY

- Markers of hepatocellular injury
  - ALT and AST
    - Functions: gluconeogenesis by catalysing the transfer of amino groups from alanine acid or aspartic to ketoglutaric acid to produce oxaloacetic acid and pyruvic acid respectively
    - Origin:
      - ALT – cytosolic enzyme (100%) , more specific to the Liver
      - AST – cytosolic (20%) and mitochondrial (80%) enzyme, found in liver, cardiac muscle, skeletal muscle, kidneys, pancreas, leucocytes and red cells
      - ALT levels are more specific to hepatocyte injury

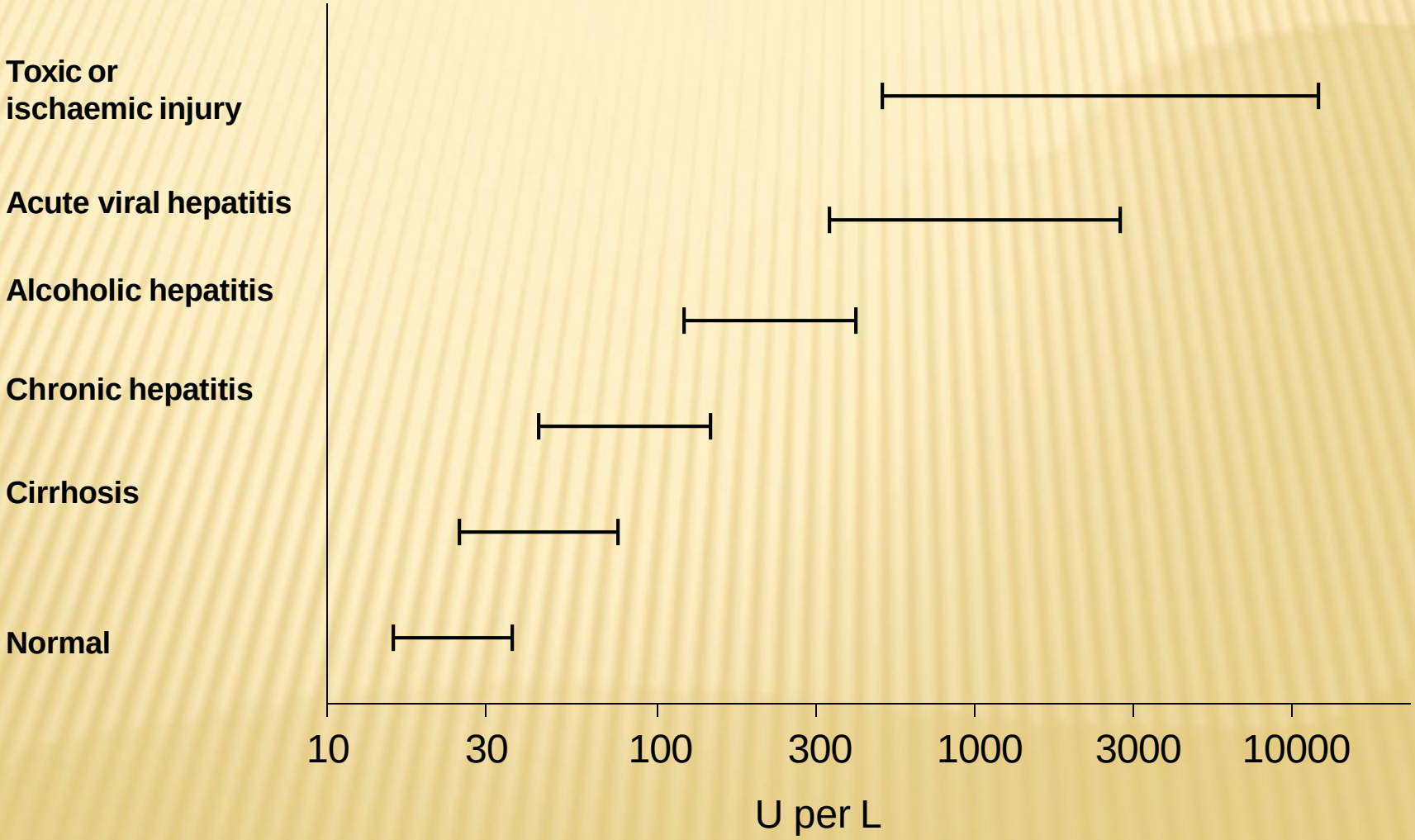
COMMON CAUSES FOR ELEVATED ALT & AST LEVELS

- Viral hepatitis – chronic HBV or HCV, exacerbation of chronic HBV, acute A-E viral hepatitis
- Non-alcoholic steatohepatitis (NASH)
- Alcohol
- Drugs: Paracetamol, NSAID, antibiotics, statins, anti-epileptics, anti-TB, herbal medications
- Autoimmune hepatitis
- Wilson's disease/ Haemochromatosis
- Congestive heart failure and ischaemic hepatitis

ELEVATED ALT AND AST

- 3 aspects
  - Level of elevation (how high)
  - Pattern of the elevation (what else)
  - Subsequent profile (how long)
- All these may provide clues for the cause of the abnormal LFT

LEVEL OF ALT & AST ELEVATION



PATTERN OF ALT & AST ELEVATION

- In usual circumstance, ALT level > AST level in diseases primarily affecting the liver except:
  - Alcoholic hepatitis (AST > ALT, ratio >2:1)
    - Serum AST almost never greater than 500 U/L
    - ↑ GGT, ↑ MCV
  - Hepatocellular carcinoma
    - Viral markers, AFP, imaging
  - Congestive heart failure
    - Clinical information, US liver – enlarged liver, engorged hepatic vein
  - Ischaemic hepatitis
    - Clinical information especially profound shock
    - LDH – disproportional increase
    - Subsequent profile of the ALT and AST level

SUBSEQUENT ALT AND AST PROFILE

- Under normal circumstance, ALT and AST levels decrease gradually after treatment or removal of the causative agents
- Some conditions are associated with rapid decline of ALT and AST levels
  - Acute ischaemic hepatitis
    - Levels may decrease by thousand unit in 1 day
  - Paracetamol overdose
  - Cholangiohepatitis

PROTEIN SYNTHESIS - ALBUMIN

- Albumin
  - Approximately 10 g is synthesized and secreted daily
  - Can serve as an index of liver synthetic capacity
  - Several factors make albumin levels difficult to interpret
    - Liver can synthesize albumin at twice the healthy basal rate
      - Patially compensate for the decreased synthetic capacity
    - Albumin has a plasma half-life of 20 days
      - Level change slowly in response to alternations in synthesis
    - Dependent on other factors
      - Nutritional status
      - GI loss
      - Urine loss

PROTEIN SYNTHESIS - PT

- Prothrombin time (PT)
  - Liver synthesized clotting factors II, V, VII, IX and X
  - PT does not become abnormal until more than 80 percent of liver synthetic capacity is lost in chronic liver disease
  - In addition, chronic cholestasis with fat malabsorption may result in impaired vitamin K absorption leading to prolonged PT
    - A trial of parenteral vitamin K isrecommended
      - PT should improve within a few days

PROTEIN SYNTHESIS - PT

- However, in patients with acute fulminant liver failure
  - Factor VII has a short half-life of only about 6 hours
    - Sensitive to the rapid changes in liver function
    - PT is very useful for monitoring in patients with acute liver failure
- Arterial NH_3 should also be checked in patients with acute fulminant liver failure with or without sign of encephalopathy

EXCRETORY MARKERS

- Markers of cholestasis
  - Bilirubin, ALP and GGT
- Bilirubin
  - Formed from the lysis of red cells (the haem component) within the reticuloendothelial system – unconjugated bilirubin
  - Unconjugated bilirubin – water insoluble
  - Conjugated to bilirubin glucoronide – secreted in bile

ALP

- ALP
  - Origin: liver, bone (heat unstable), intestine, placenta (heat stable)
  - Different isoforms can be differentiated by electrophoretic separation
  - However, a good and simple way to confirm liver origin is to check GGT

GGT

- A microsomal enzyme which transfers gamma-glutamyl groups from gamma-glutamyl peptides to amino acids and other peptides
- Isolated GGT elevation with normal ALP
  - Drug: phenytoin, carbamazepine, barbituates
  - Alcohol
  - Fatty liver

ELEVATED BILIRUBIN

- Elevated unconjugated bilirubin
  - Increased bilirubin production
    - Haemolysis, ineffective erythropoiesis, resorption of haematoma
  - Decreased hepatic uptake
    - Drugs: e.g. rifampicin
  - Decreased conjugation
    - Gilbert's syndrome
    - Criggler-Najjar syndrome

CHOLESTASIS

- Two conditions
  - Blockage of bile ducts
  - Disease that impairs bile formation in the liver itself (intrahepatic cholestasis)

BLOCKAGE OF BILE DUCTS

- Increase in bilirubin, ALP & GGT
  - Acute bile duct obstruction from a gallstone
    - AST & ALT may reach up to 500 U/L or more in first few hours and then decline (cholangiohepatitis)
    - ALP and GGT take several days to rise
    - Both ALP and GGT levels are elevated in about 90% patients with cholestasis
  - Further investigations
    - US or CT
    - MRCP
    - ERCP

ELEVATED ALP AND GGT

- Conditions other than biliary obstruction
  - Infiltrative disease: HCC, metastatic tumors, TB
  - Liver abscess
  - Hyperthyroidism
- Other diseases causing elevated ALP & GGT
  - Primary biliary cirrhosis
    - Check antimitochondrial antibody and immunoglobulins
  - Primary sclerosing cholangitis or Secondary SC
    - ERCP/MRCP

Conclusions

- Certain liver diseases have particular pattern of abnormalities of the liver function test
- Determining the final diagnosis requires
  - History (drug history)
  - Clinical presentation
  - Other investigations
  - Liver biopsy may be required
- When in doubt, refer to hepatologists

CASE 1

- F/75 Exdrinker, abstinent for over 10 years
- Unknown hepatitis status
- Admitted for fever, epigastric pain and vomiting

LIVER FUNCTION D1

- ALT 976 (N <31 U/L)
- AST 1625 (N<36 U/L)
- ALP 97 (N 52-148 U/L)
- GGT 175 (N 9-42 U/L)
- Bilirubin 71 (N 7-19 umol/L)
- PT 12.7 (N 11.3-13.5)

? DIAGNOSIS

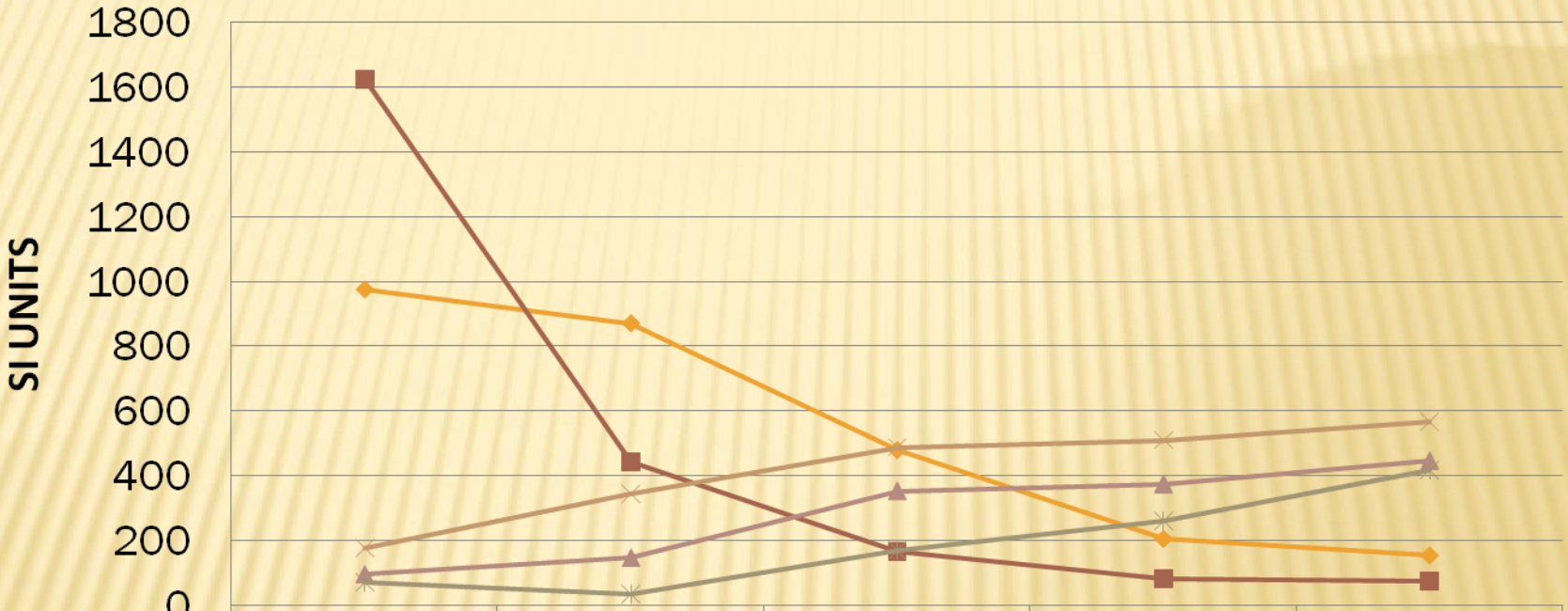
1) ACUTE VIRAL HEPATITIS

2) ALCOHOLIC HEPATITIS

3) DRUG-INDUCED HEPATITIS

4) CBD STONE

LFT PROGRESS



	D1	D2	D3	D5	D7
ALT	976	871	479	204	153
AST	1625	443	165	82	73
ALP	97	148	353	374	446
GGT	175	345	489	511	568
Bilirubin	71	34	169	260	417

CASE 1

- Anti-HAV IgM, HBsAg, anti-HCV, anti-HEV IgM all negative
- Ultrasound liver:
  - Common bile duct with fusiform dilatation, 3.0 cm in calibre
  - Sludges at lower end of CBD
  - Dilated intrahepatic ducts

  (History of Cholecystectomy)
- Radiologist Impression: Choledocal Cyst??

DAY 8 ERCP

- Cholangiogram: Grossly dilated CBD with large stone at lower CBD
- Sphincterotomy performed
- 1.8cm stone retrieved with basket
- Discharged with normal LFTs on Day 12

CHOLANGIOHEPATITIS

- History and clinical presentation
- Transient spikes in serum aminotransferase suggestive passage of CBD stone into duodenum
- AST shows more rapid changes due to shorter half-life (17 hours. ALT: 30 hours)
- Medium AST elevation around 4.4 times upper limit of normal (highest >12 times upper limit of normal)
  - *Hayat et al. Q J Med 2005; 98: 35-40*

CASE 2

- M/41 Social Drinker
- HBsAg +ve HBeAg –ve
- ALT normal all along
- Presented with tea-colour urine and abdominal pain

LIVER FUNCTION D1

- ALT 2855
- AST1480
- ALP 158
- GGT 73
- Bilirubin 992
- PT 24.3

?DIAGNOSIS

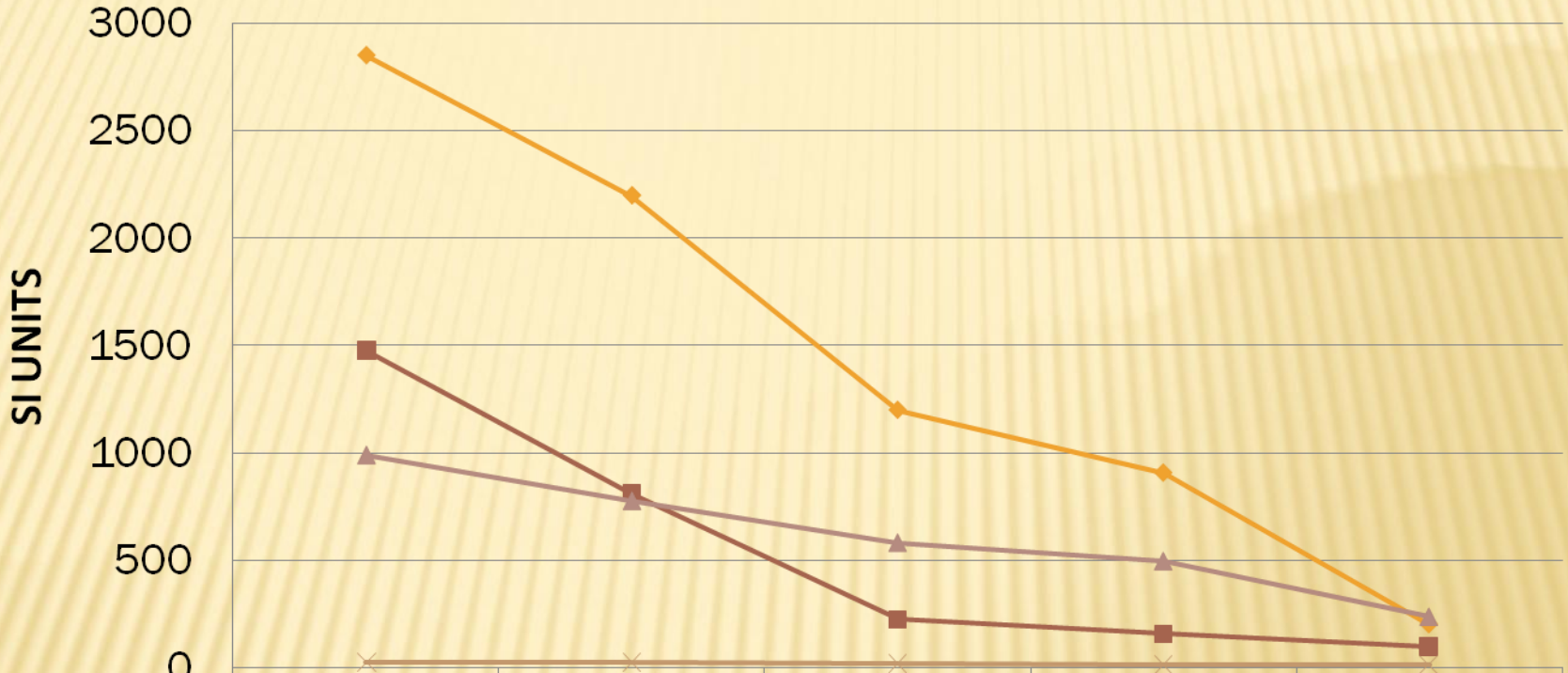
1) ACUTE VIRAL HEPATITIS

2) HEPATITIS B REACTIVATION

3) DRUG-INDUCED HEPATITIS

4) CBD STONE

LFT PROGRESS



	D1	D3	D5	D10	D18
ALT	2855	2201	1200	907	200
AST	1480	813	224	158	97
Bilirubin	992	778	583	497	237
PT	24.3	21.6	20.8	13.7	13.3

PROGRESS OF CASE 2

- Anti-HAV IgM / anti-HCV / anti-HEV IgM –ve
- HBV DNA 742 copies / ml
- Drug history of Herbal preparation (維生烏絲素) for 1 year
- LFT normalized after stopping of 維生烏絲素

COMPONENTS OF 維生烏絲素:

靈芝

女貞子

墨旱蓮

何首烏

當歸

龜板

肉蓯蓉

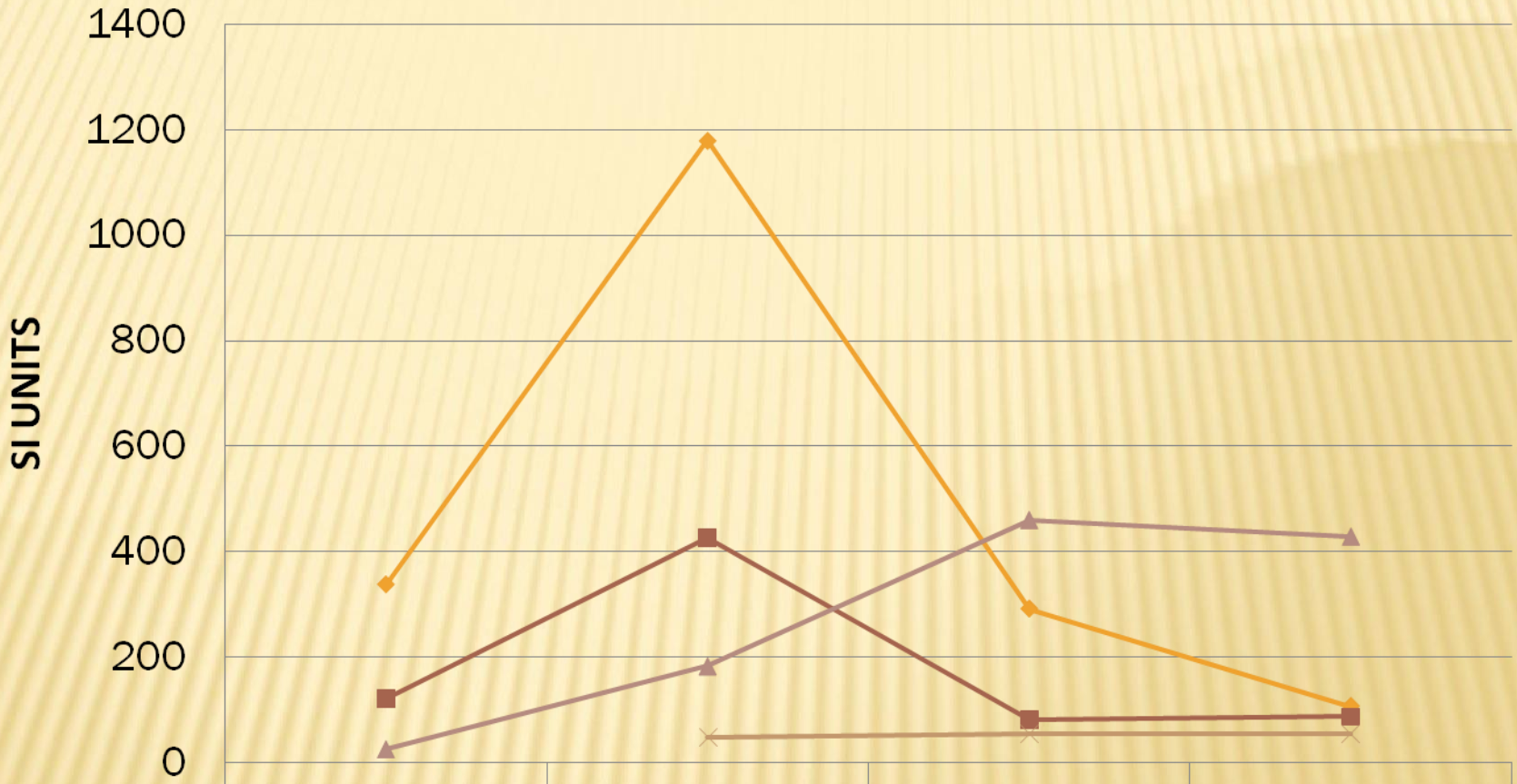
DOCUMENTED HEPATOTOXICITY

- *Ganoderma lucidum* (靈芝):
  - *Yuen et al. Journal of Hepatology 2004; 41: 685-90*
  - *Wanmuang et al. J Med Assoc Thai 2007; 90: 179-81*
- *Polygonum multiflorum* (何首烏):
  - *Cardenas et al. J Clin Gastroenterol 2006; 40: 629-32*
  - *Mazzanti et al. Ann Intern Med 2004; 140: W30*

CASE 3

- M/52 DM, HT
- Chronic drinker (10 bottles of beer + 100ml whisky per week), unknown hepatitis status
- Admitted to Fushan hospital with jaundice and abdominal discomfort
- Transferred to QMH after 1 month

Investigations in China



	D1	D18	D24	D31
ALT	337	1179	291	106
AST	120	426	80	86
Bilirubin	25.3	182.6	460	428.6
PT		47.4	54.6	55

?DIAGNOSIS

- 1. ACUTE VIRAL HEPATITIS
- 2. HBV REACTIVATION
- 3. ALCOHOLIC HEPATITIS
- 4. CBD STONE

	D1	D18	D24	D31	D40	D43	D46	D51
ALT	337	1179	291	106	119	107	110	108
AST	120	426	80	86	122	98	101	99
Bilirubin	25.3	182.6	460	428.6	529	434	449	423
PT		47.4	54.6	55	16.2	15.7	15.5	15.6

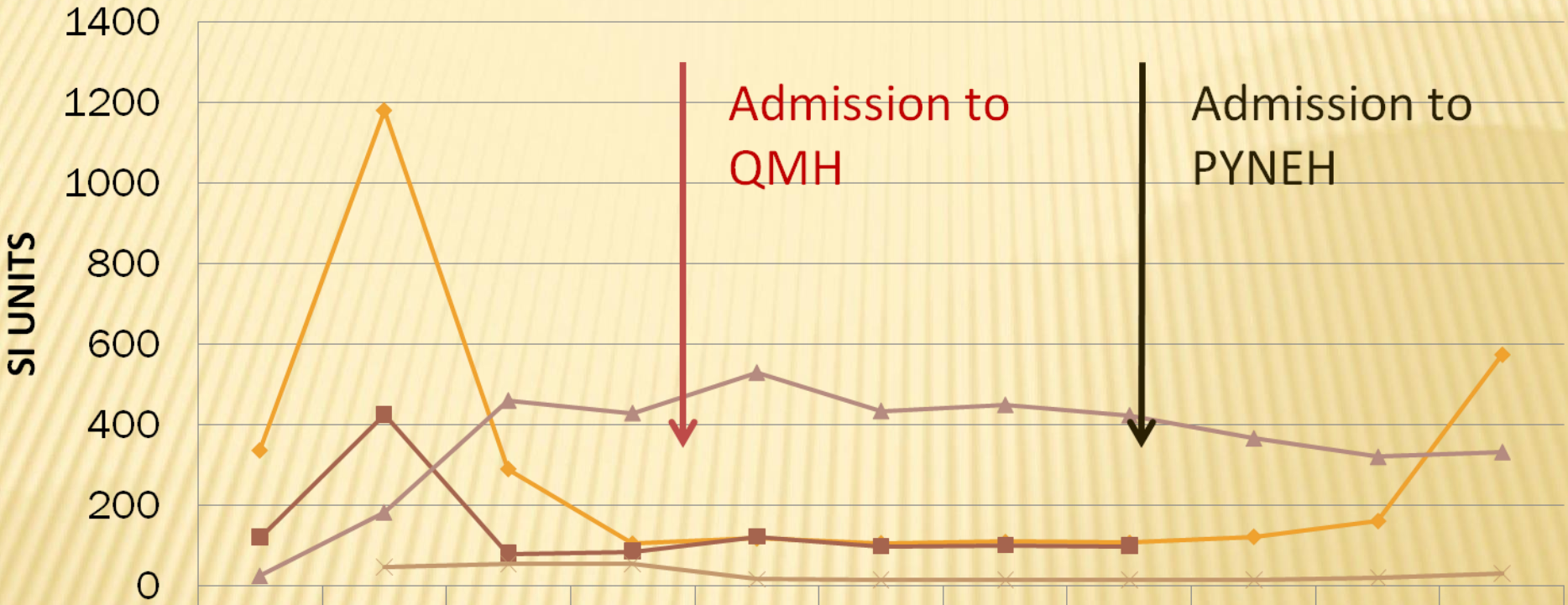
CASE 3

- Anti-HAV IgM / HBsAg / anti-HCV negative
- Anti-HEV IgM positive

PROGRESS OF PATIENT 3

- Admitted 5 days after discharge to PYNEH for fresh melena (Day 56)
- OGD: Bleeding 1.5cm DU at D1/2 junction requiring heater probe and adrenaline injection
- Developed fulminant hepatic failure on Day 58 requiring maximal inotropic support, continuous veno-venous haemofiltration and mechanical ventilation

Arterial NH3 (D58): 299 umol/L



	D1	D18	D24	D31	D40	D43	D46	D51	D56	D58	D63
ALT	337	1179	291	106	119	107	110	108	123	162	574
AST	120	426	80	86	122	98	101	99			
Bilirubin	25.3	182.	460	428.	529	434	449	423	366	320	332
PT		47.4	54.6	55	16.2	15.7	15.5	15.6	14.8	20.5	30.7

Succumbed on Day 63

UPDATE ON HEPATITIS E

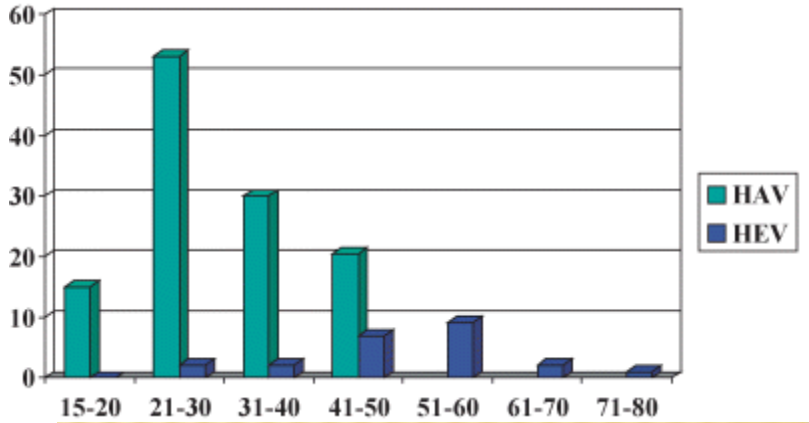
- 14.5 % of acute hepatitis reported in 2006 to DH
- Highest incidence in North Africa, Middle East, South Asia
- Incubation 15-60 days
- 60% have prolonged cholestatic course
- Fulminant hepatitis 0.5-3% (HAV: 0.1 – 1.1%)
  - Mortality up to 20% in pregnant patients
- rHEV Vaccine (not commercially available): 95.5% efficacy
  - *Shrestha et al. NEJM 2007; 356: 895-903*
- Clinical trial Zhang J et al, NEJM 2015
  - 4.5 year study period, 56,302 vaccine, 56,302 control
  - 60 cases of Hep E
  - 7 cases in vaccine group and 53 cases in control group
  - Vaccine induced antibodies and provided protection against HEV for up to 4.5 years
  - Vaccine efficacy 86.8% [95% CI 71-94%]

HEV EPIDEMIOLOGY (PMH 2002)

CHAU ET AL. AM J GASTROENTEROL 2006 101:292-6

	HAV (n = 105, %)	HEV (n = 24, %)	*p* Value
Demographics			
Male/female	69/36	18/6	0.47
Age (median, range)	27 (12–45)	53 (29–73)	**<0.01**
Risk factors			
Intake of shellfishes	90 (86)	14 (58)	**0.01**
Travel to endemic area	43 (41)	18 (75)	**0.04**
Sexual promiscuity	37 (35)	5 (21)	0.23
Alcohol drinking	28 (27)	5 (21)	0.80
Contact with acute hepatitis	3 (3)*	1 (4)	0.57
Intravenous drug addiction	1 (1)	0	1.00
Blood transfusion	1 (1)	0	1.00
Contact history with animal/pet	10 (10)†	2 (8)‡	1.00
Positive chronic hepatitis B status	4 (54)	1 (4)	0.55

*Include one intrafamilial contact.
†Mouse (1), cat (3), rabbit (1), bird (1), dog (3), worker in pet shop (1).
‡Dog (2).

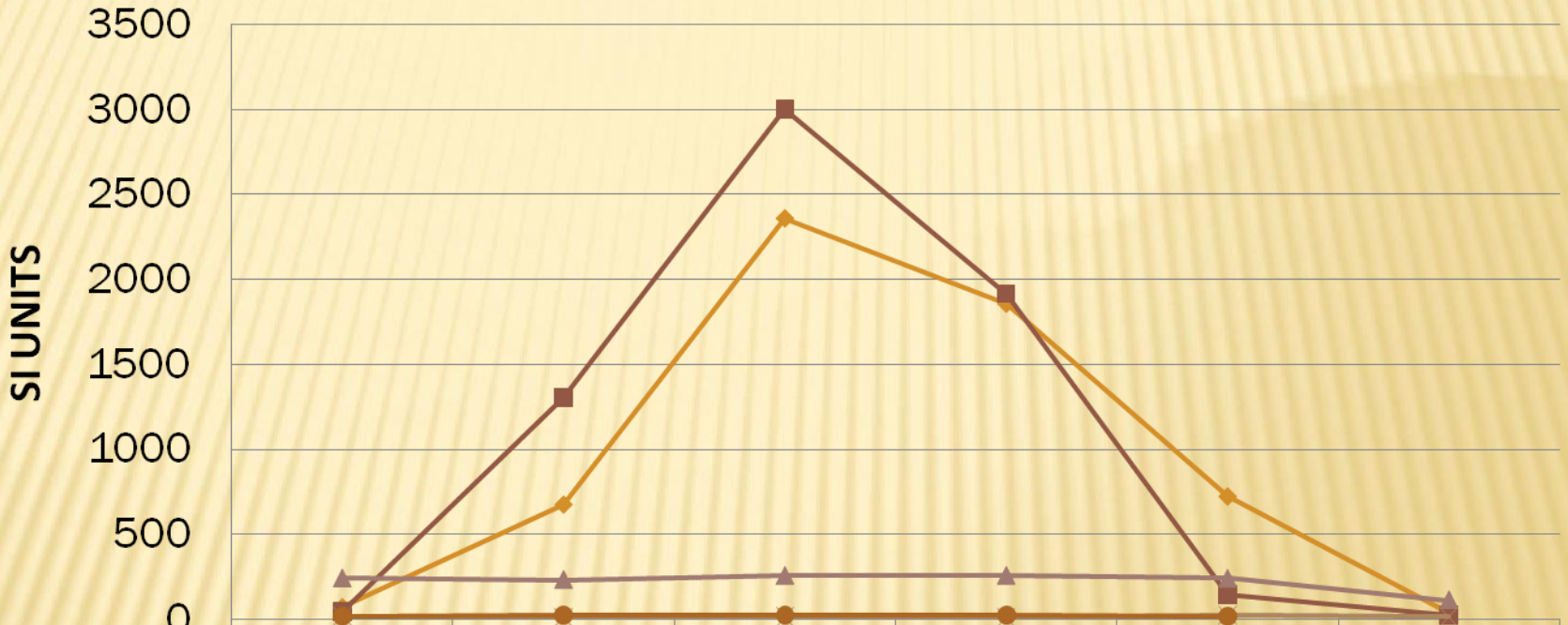


Age distribution of hepatitis A and E.

CASE 4

- M/86 Nondrinker
  - DM on insulin for 20 years
  - ESRF on CAPD for 11 years
- Admitted for fluid overload and diastolic heart failure requiring 100% O2 / inotropic support / ICU admission

LFT PROGRESS

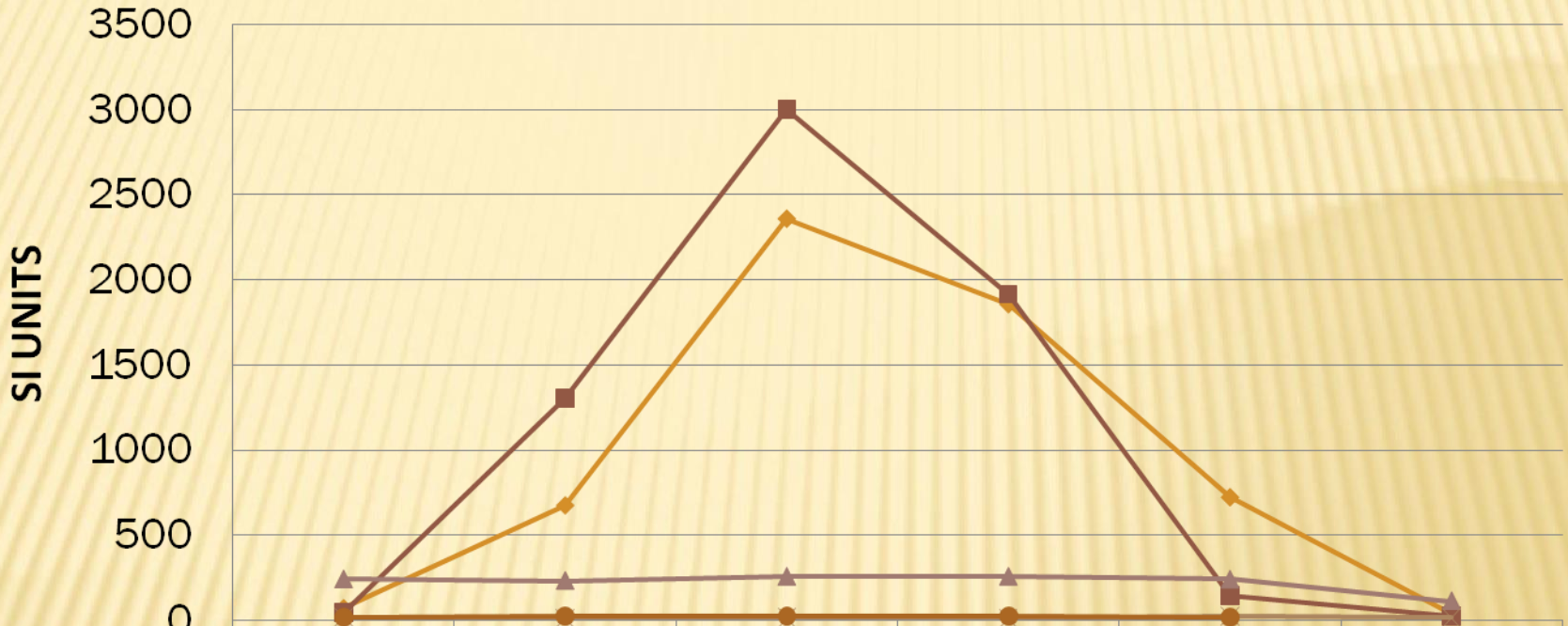


	D1	D2	D3	D4	D7	D21
ALT	69	673	2356	1854	721	35
AST	44	1303	3000	1913	144	22
ALP	240	231	255	255	238	112
Bilirubin	15	11	12	10	22	13
PT	15.5	23.9	21.5	21.6	14	

?DIAGNOSIS

- 1. ACUTE VIRAL HEPATITIS
- 2. ISCHAEMIC HEPATITIS
- 3. DRUG-INDUCED HEPATITIS
- 4. HEPATITIS B REACTIVATION

LFT PROGRESS



	D1	D2	D3	D4	D7	D21
ALT	69	673	2356	1854	721	35
AST	44	1303	3000	1913	144	22
ALP	240	231	255	255	238	112
Bilirubin	15	11	12	10	22	13
PT	15.5	23.9	21.5	21.6	14	

LDH		**1029**	**>10000**	**1738**

HBsAg negative
Anti-HCV negative

IDENTIFYING SHOCK LIVER

- Brisk rise and rapid resolution of LDH
- ALT/ AST strikingly elevated, peak within 1-3 days, then fall rapidly
- ALT/LDH ratio <1.5 early in course of hepatitis
- Other evidence of end-organ damage eg. acute renal failure

DX BASED ON CLINICAL SETTING

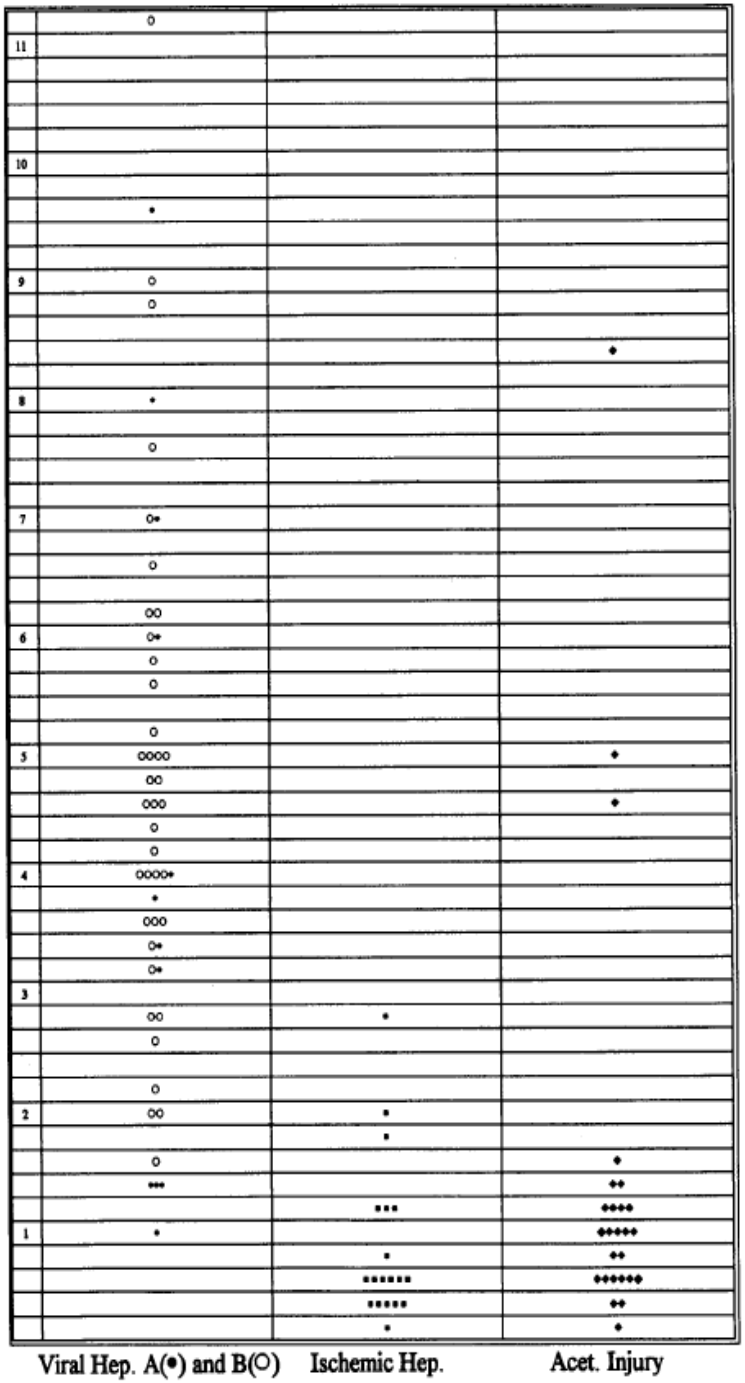


FIG. 1. ALT/LD ratio.

TABLE 1. *ALT/LD and AST/LD ratios*

	AVH	IH	AH	AVH	IH	AH
Mean	4.65[a]	0.87	1.46	2.47[b]	0.81[c]	1.46[c]
Range	1.0–11.1	0.17–2.89	0.11–8.26	0.11–7.53	0.24–1.71	0.11–7.34
SD	2.23	0.70	1.76	1.74	0.34	1.47
Median	4.6	0.607	1.005	2.247	0.757	0.94

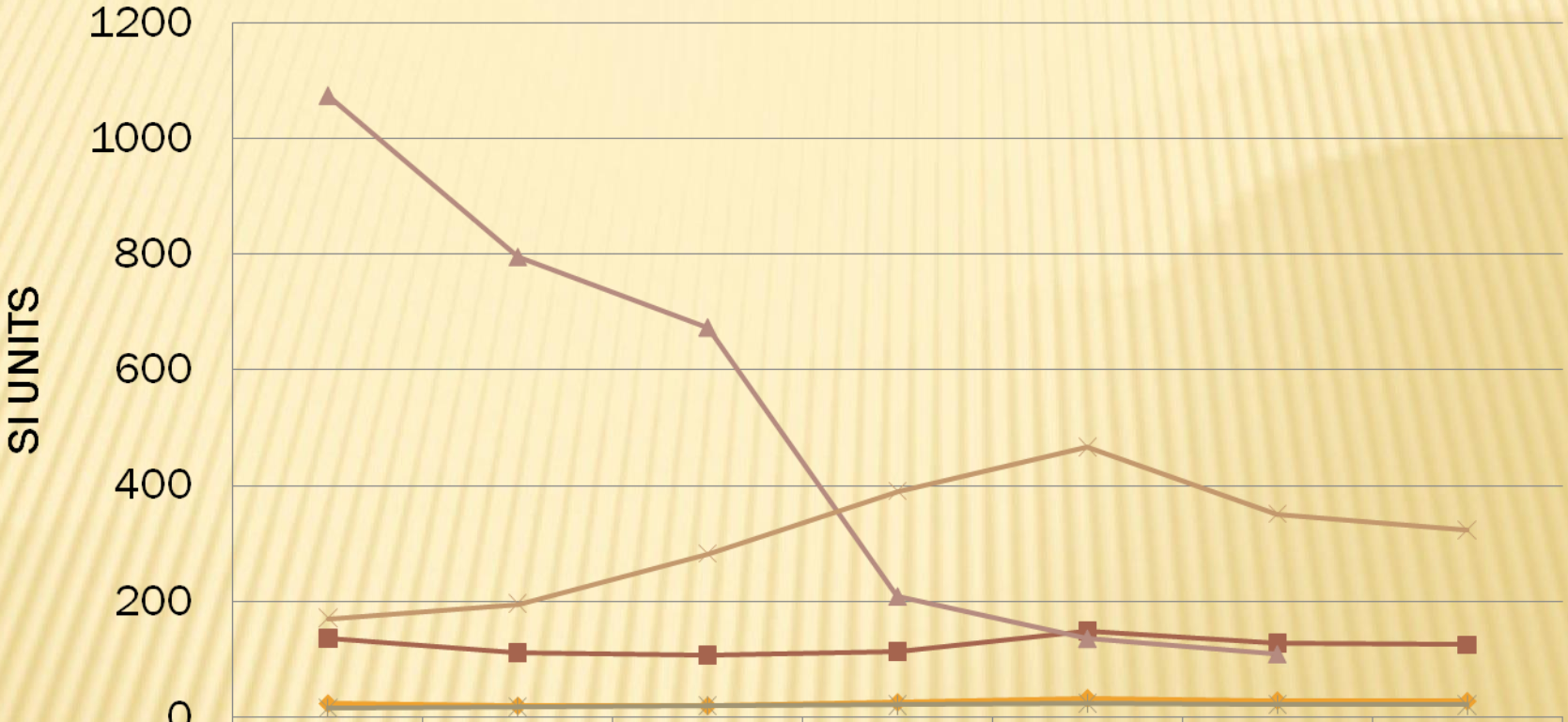
AVH, acute viral hepatitis; IH, ischemic hepatitis; AH, acetaminophen hepatitis.
[a] $p < 0.0001$ vs. IH, AH, and vs. IH + AH.
[b] $p < 0.001$ vs. IH + AH.
[c] $p < 0.05$ vs. AVH.

ALT/LDH ratio < 1.5

Cassidy et al. J Clin Gastroenterol 1994; 19: 118-21

CASE 5

- M/67 Indian, Language barrier
- Chronic drinker (1 bottle of whisky per day)
- Admitted for fever and abdominal pain
- On admission, moderate ascites with liver palpated 2cm below costal margin



	D1	D5	D8	D15	D22	D28	D31
ALT	23	19	19	25	32	28	27
AST	136	112	107	113	149	128	125
GGT	1074	795	673	208	135	108	
Bilirubin	170	195	282	390	467	351	323
PT	15.8	17.4	18.9	20.4	23.1	21.6	20.6

?DIAGNOSIS

- 1. ALCOHOLIC HEPATITIS
- 2. LIVER ABSCESS
- 3. HCC
- 4. LIVER METASTASIS

OTHER BLOOD RESULTS ON PRESENTATION (SI UNITS)

- Albumin 27 ↓
- Globulin 50 ↑
- ALP 123
- K 3.2 ↓
- Creatinine 62
- Adj Ca++ 2.08 ↓
- PO4 0.51 ↓
- Mg2+ 0.33 ↓
- Arterial NH3 54 ↑
- WBC 12.72 ↑
  - ANC 10.01
  - Monocyte 0.82
- Hb 9.7 ↓
- MCV 101.3 ↑
- Platelet 284
- ESR 102 ↑
- HBsAg –ve
- Anti-HCV –ve

PROGRESS OF CASE 5

- Ascitic tap: TCC 300 89% Mononuclear cells
- Intensive nutritional support
  - Nutriflex 1L/day iv for 1 week
  - Thiamine / Vit Bco / MV / Folate / MgTri / Vit D
- Referred to Alcohol Anonymous
- LFT 6 months later: AST 53 ALT 24 Bilirubin 26 GGT 122 PT 16.7

UPDATE ON ALCOHOLIC HEPATITIS

- Maddrey Discriminant Function:
  - 4.6 x (PT – control) + bilirubin (mg/dL)
  - >32 = poor prognosis, 1-month mortality 35-45%
- Treatment options:
  - Nutritional therapy (all forms)
    - Branch-chained amino acid formulas
    - Vitamin supplements
  - Prednisolone 40mg daily for 1 month
- ALCOHOL ABSTINENCE!

Improves LFT / histology

Improve 30 day mortality

5 CASES OF DERANGED LFTS

1. Cholangiohepatitis
2. Drug-induced hepatitis
3. Hepatitis E
4. Ischaemic hepatitis
5. Alcoholic hepatitis

CONCLUSIONS

- Different liver diseases have different pattern of abnormalities of the liver function test
- Urgent imaging may not be necessary
  - Cholangiohepatitis
  - Drug-induced hepatitis
  - Hepatitis E
  - Ischaemic hepatitis
  - Alcoholic hepatitis
- Determining the final diagnosis requires
  - History (drug history)
  - Clinical presentation
  - Other investigations
  - Liver biopsy may be required

ONLY USEFUL HERE!

HCC marker

- AFP
  - First described by Abelev in 1960s
  - A glycoprotein with molecular weight 70kDa
  - Highly expressed in hepatocytes, endodermal cells of the yolk sac during fetal development
  - Serum level usually < 10 ng/mL

HCC marker

- AFP
  - Elevated levels also found in hepatitis exacerbation i.e. abnormal ALT levels/ chronic hepatitis/ cirrhosis/ Pregnancy/ gonadal tumor
  - Sensitivity 40 – 70%
  - Specificity 80 – 90%
  - Sensitivity increases to 100% by combining AFP and ultrasonography
  - Sensitivity also increased by measuring isoforms of AFP (AFP-L3)
  - USG more sensitive

FIBROSCAN

- Ultrasound based elastography (2D shear wave elastography)
  - Faster wave propagation in stiffer tissues
- Alternative to liver biopsy
- Prognosticate on complications of liver cirrhosis
  - Varices
  - Hepatocellular carcinoma
- Common clinical cut offs include
  - >7kPa for fibrosis
  - >11-14kPA for cirrhosis

Thank you & Questions