Slide session

Update in Liver Histopathology
Lancaster House Hotel
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Truro

Acknowledgement
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Autochthonous HEVitis

Aboriginal, indigenous, native

Formed or originating in the place where found

About HEV

- **RNA virus**
- **Faeco-oral route**
- **6wk incubation**
- **Acute**
- **Self-limiting**
- **4-6wk resolution**
- **Epidemics**

Four genotypes

G1 **Asia and Africa**

G2 **Mexico**

G4 **China & Japan**

G3 **Worldwide**

Animals

85% UK pigs

HEV and developed countries- assumptions

- **Rare in developed countries?**
- **Seen mainly in travellers?**
- **Rare in non-travellers?**
- **An uncommon cause of acute viral hepatitis?**
- **Less common than HAV?**
- **Significant mordidity and mortality?**

Emerging evidence

- **HEV is far more common than previously recognised**
- **Caused by HEV genotype 3 (and 4)**
- **Possibly zoonotic from pigs**
- **Affects middle aged males**
- **Significant morbidity and mortality**
- **70% mortality in patients with chronic liver disease**

Available evidence

- **There is evidence which supports poor outcomes (mortality) in patients with chronic liver disease with superinfection with HEV compared to those without**
- **The HEV serological response is similar to other viral infections**
  - **Rising IgM with rising ALT**
  - **Later rise in IgG levels**
  - **A period of infectivity (stool)**
  - **Clinical illness preceded by incubation period**

HEV diagnosis

- **Biochemical evidence hepatitis (ALT>500 IU/L)**

- **And strongly +ve HEV IgM**
- **Or rising HEV IgG**
- **Or HEV PCR +ve**

However

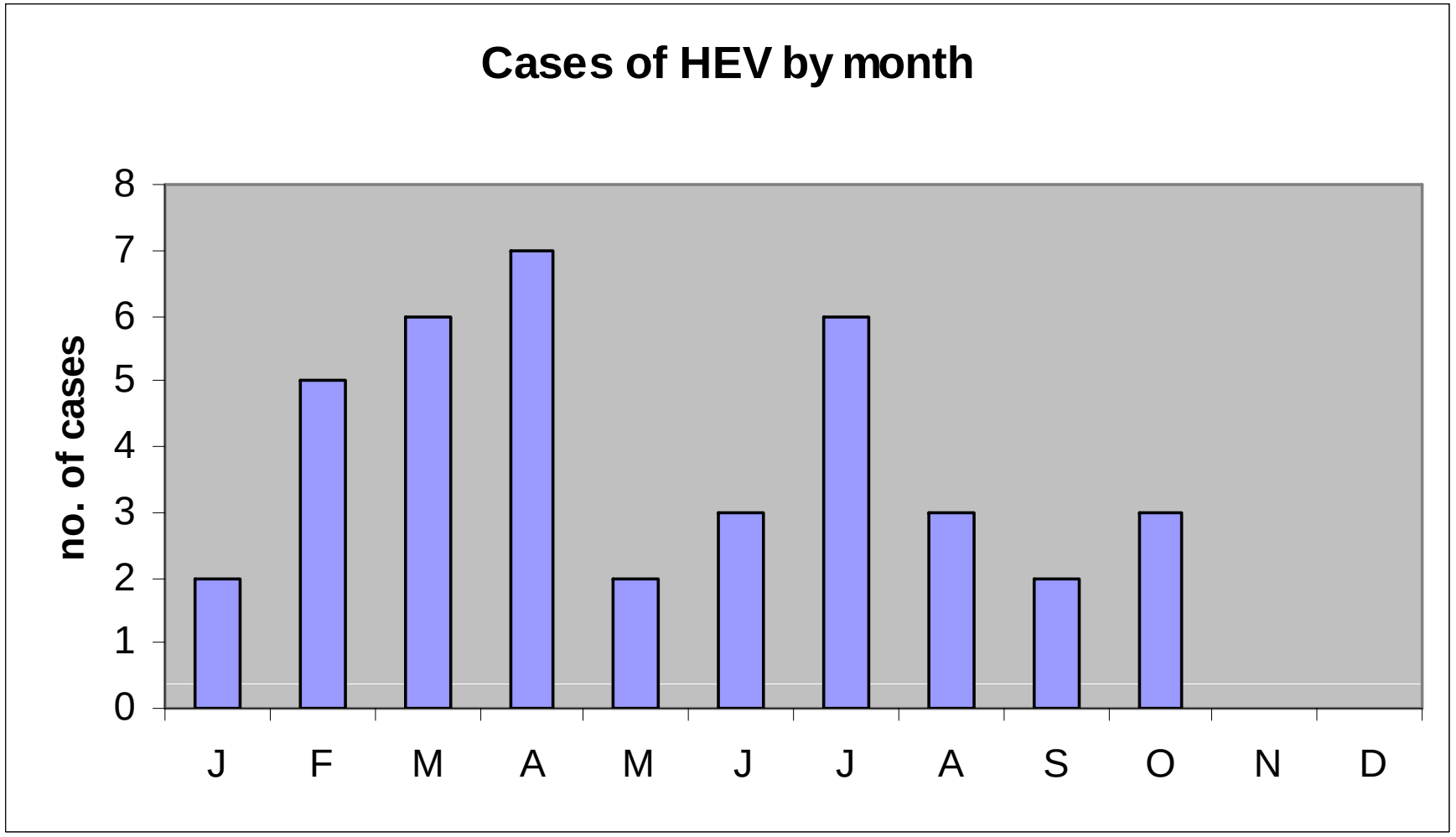
- **45% HEV IgM false negative**
  - **Negative IgM does not exclude diagnosis**
- **Period of viraemia may be brief**
  - **Negative PCR does not exclude diagnosis**
- **Single IgG not enough to establish diagnosis**
  - **high background HEV seropositivity**

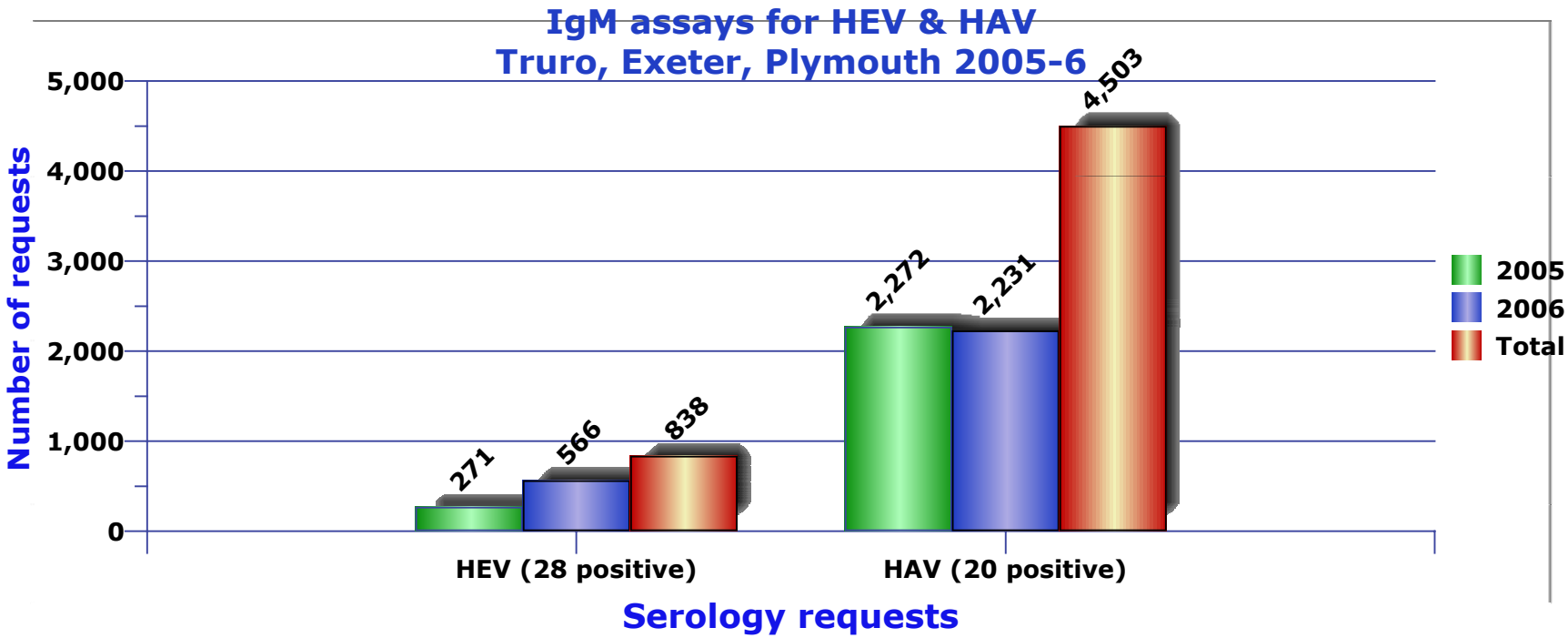
Which is commoner?

HAV or HEV

HAV vs HEV

- **HEV commoner in France**
- **HEV commoner in Japan**
- **HEV commoner in the SW England**
  - **0.4% annual seroconversion rate**


Cases of HEV by month
no. of cases
0
1
2
3
4
5
6
7
8
J
F
M
A
M
J
J
A
S
O
N
D



HAV test requests 5 times that for HEV

BUT

~8 times more likely to be HEV than HAV positive

HEV and HAV

	HEV	HAV
Cases	28	20
Age*	65	41
	(35-86)	(8-74)
Winter onset*	1	5
M:F	4.6	1.6
Complications	5	0
Death	2	0

Presenting symptoms: 42 HEVitis

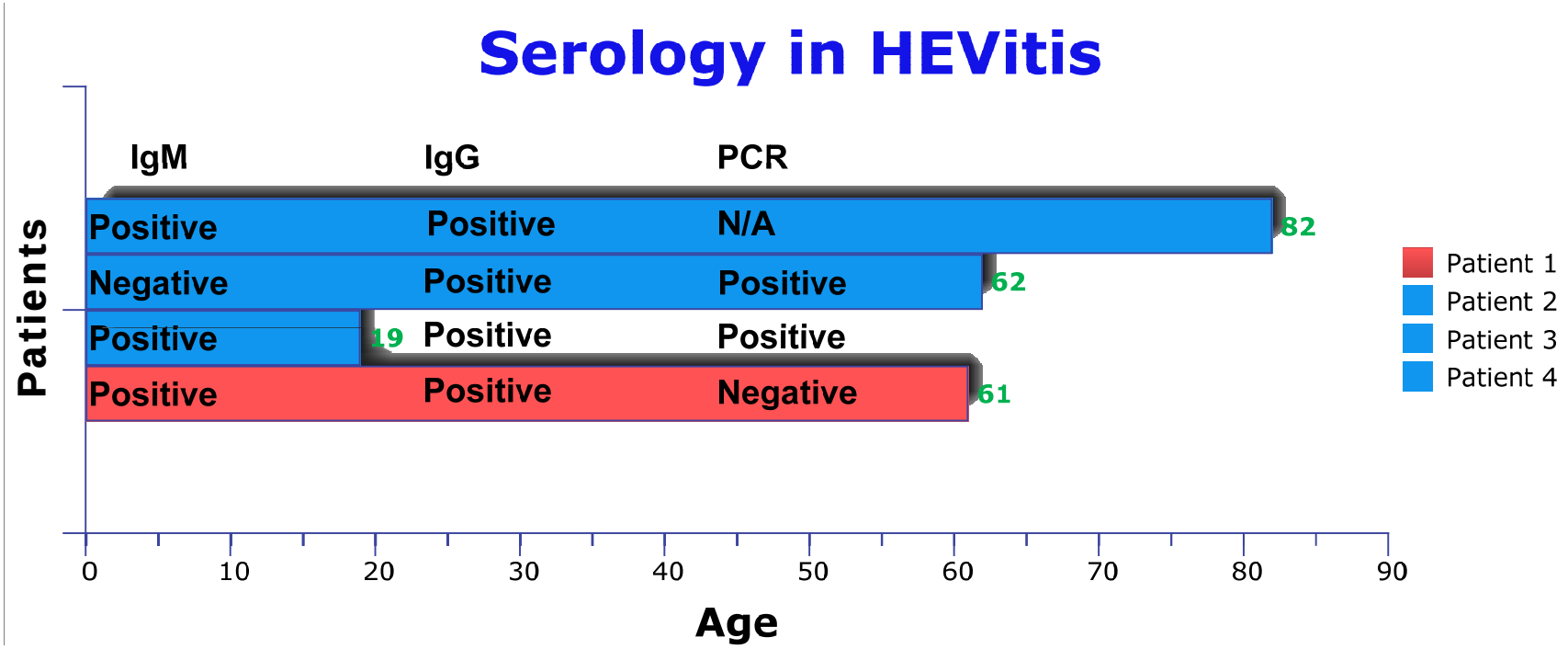
- **Jaundice (n=31)**
- **Anorexia (n=15)**
- **Lethargy (n=16)**
- **Abdominal pain(n=15)**
- **Nausea (n=14)**
- **Vomiting (n=7)**
- **Fever (n=8)**
- **Myalgia (n=5)**
- **Pruritis (n=4)**
- **Weight loss (n=3)**
- **Headaches (n=4)**
- **Arthralgia (n=2)**
- **Back pain (n=2)**
- **Rash (n=1)**
- **Paraesthesiae (n=1)**
- **No symptoms (n=2)**

42 profiles

- **No travel to endemic areas**
- **21 retired**
- **1 butcher**
- **Direct contact with pigs (n=1)**
- **No vegetarians, all pork eaters**

HEVitis

- **Asymptomatic – mild hepatitis –liver failure**
- **Median bilirubin 105μmol/l (range 3-417)**
- **Median ALT 1380 IU/L**
- **39/42 recovered (usually in 4 – 6 weeks)**
- **3 patients died**
  - **Liver failure n=2, unrelated cause n=1**


Serology in HEVitis
IgM
IgG
PCR
Positive
Positive
N/A
82
Negative
Positive
Positive
62
Positive
19
Positive
Positive
Positive
Positive
Negative
61
Patients
0
10
20
30
40
50
60
70
80
90
Age
Patient 1
Patient 2
Patient 3
Patient 4

Report

- **4 cases**
- **HAV–negative**
- **HBV-negative**
- **HCV-negative**
- **ANA-negative**
- **SMA-negative**
- **APCA-negative**
- **Weak AMA M2 in 62yr male patient**

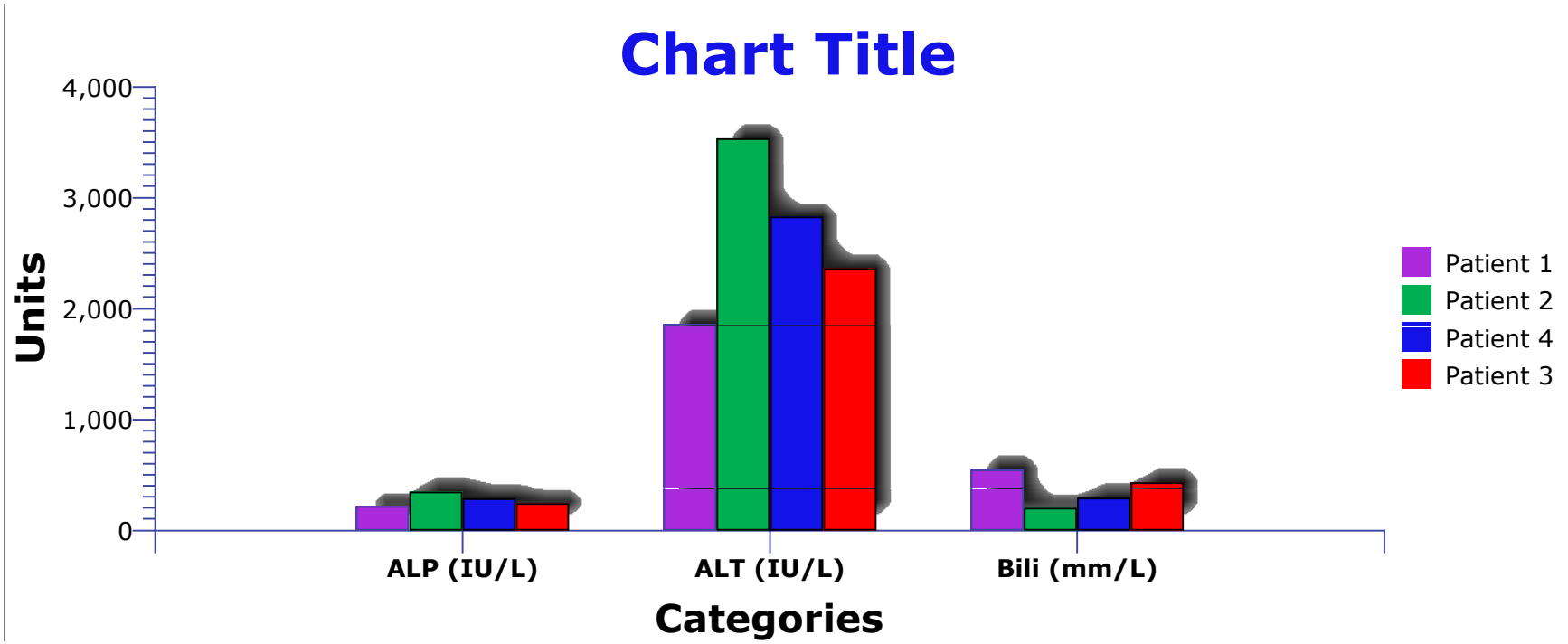
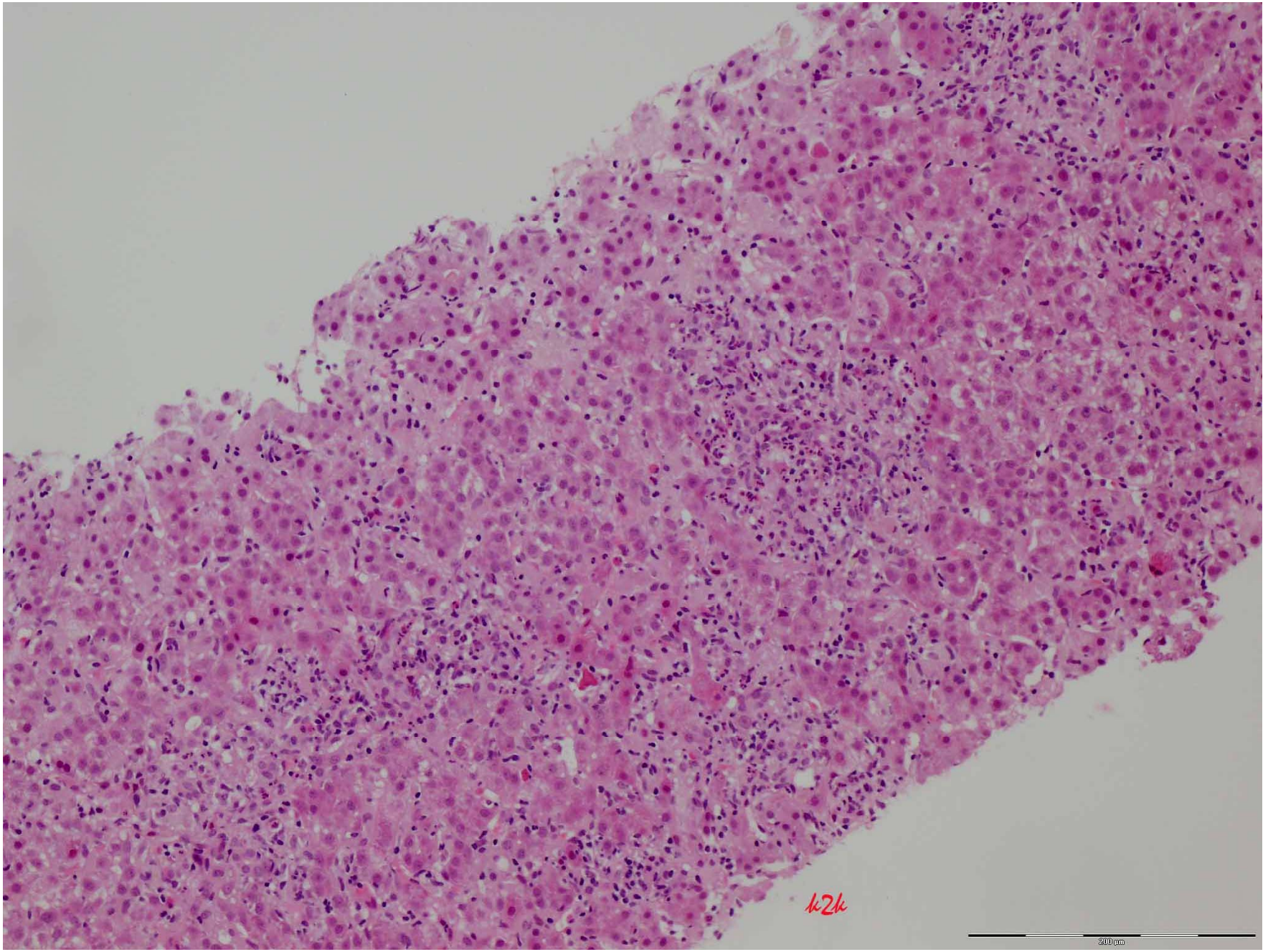
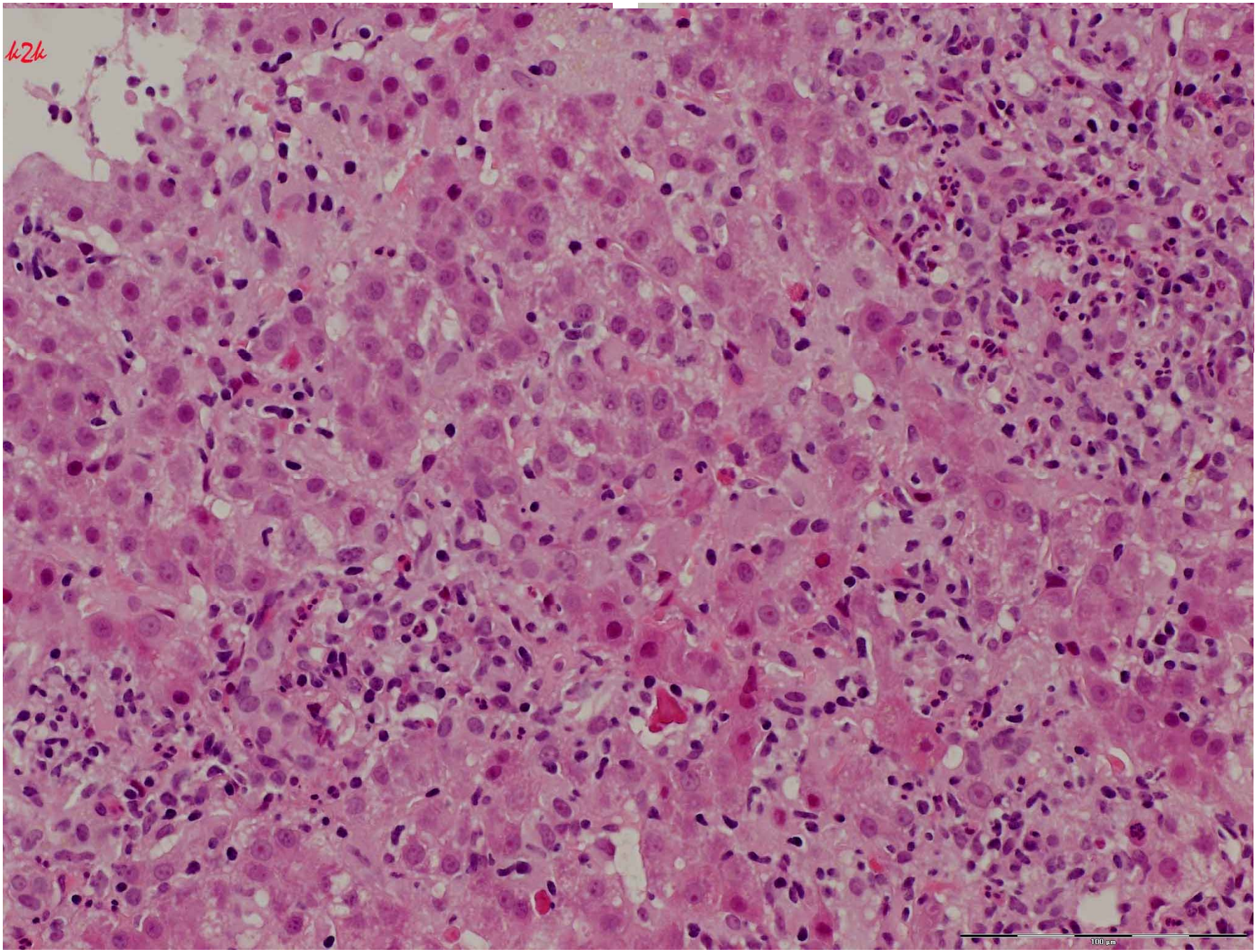
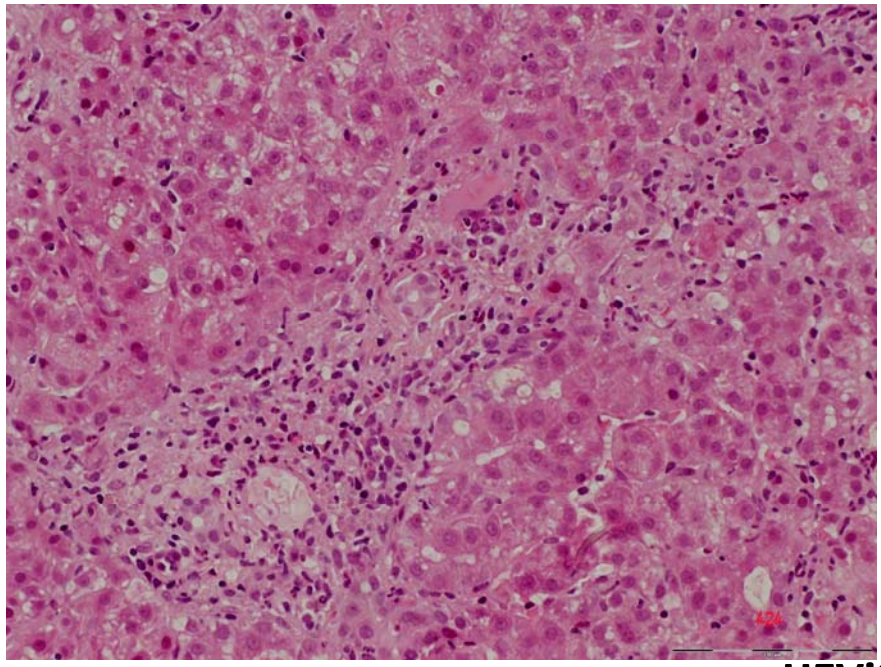
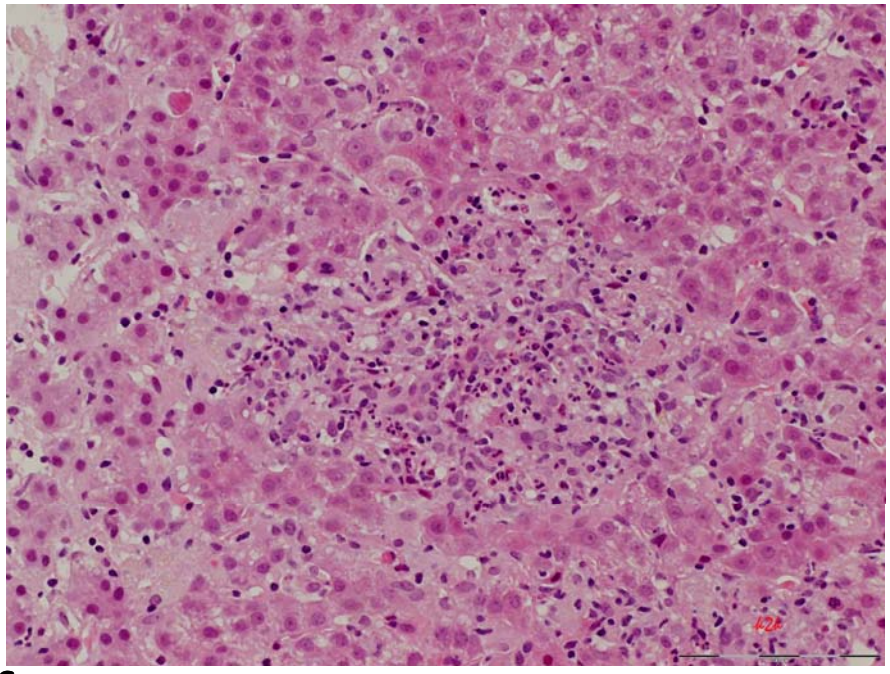


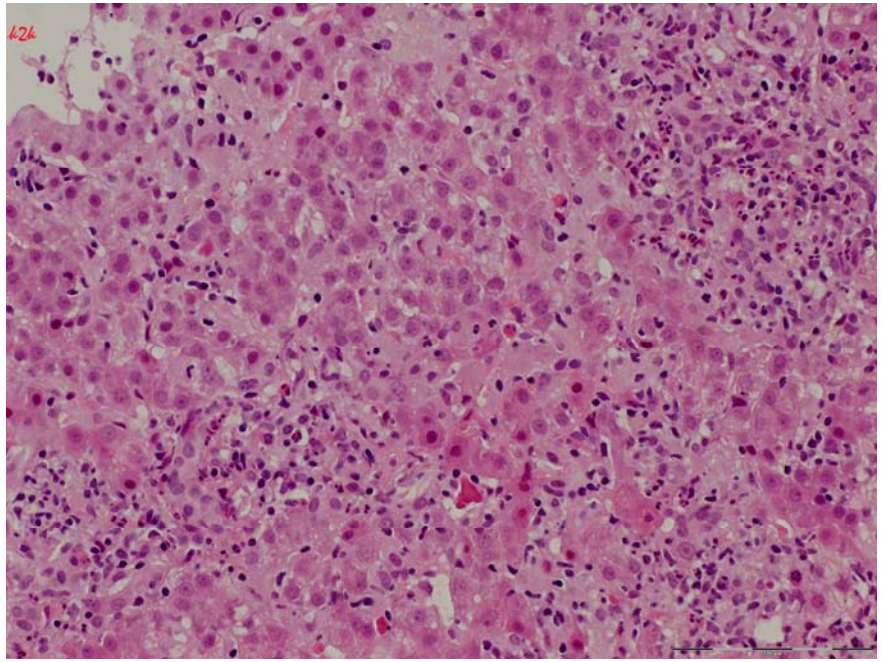
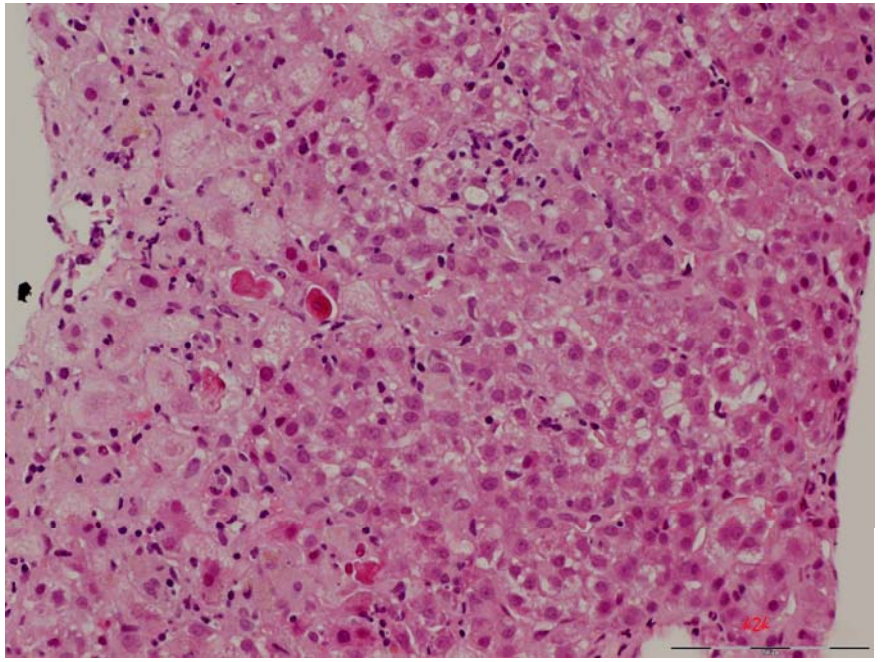
Chart Title
4,000
3,000
2,000
1,000
0
Units
ALP (IU/L)
ALT (IU/L)
Bili (mm/L)
Categories
Patient 1
Patient 2
Patient 4
Patient 3


k2k
200 µm

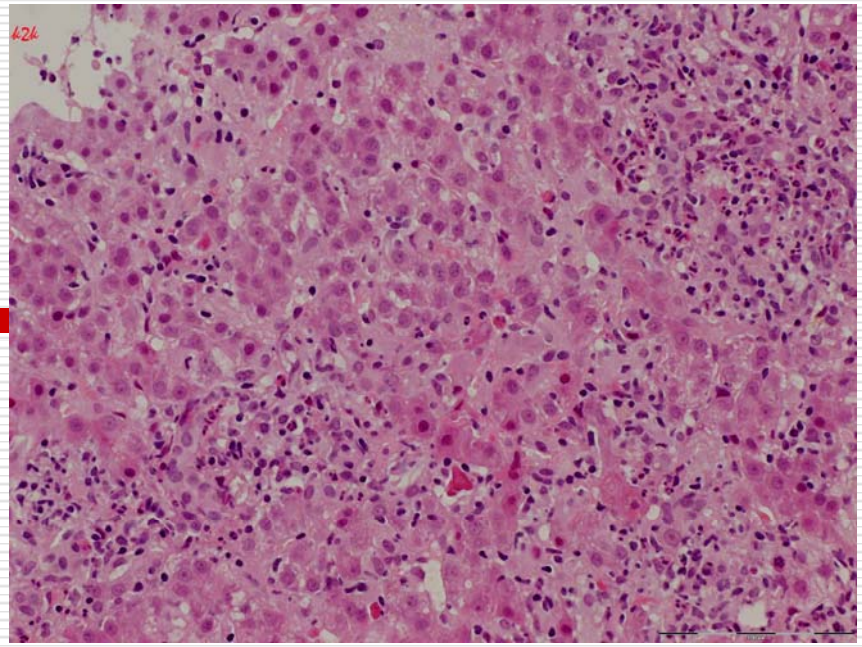

100 µm

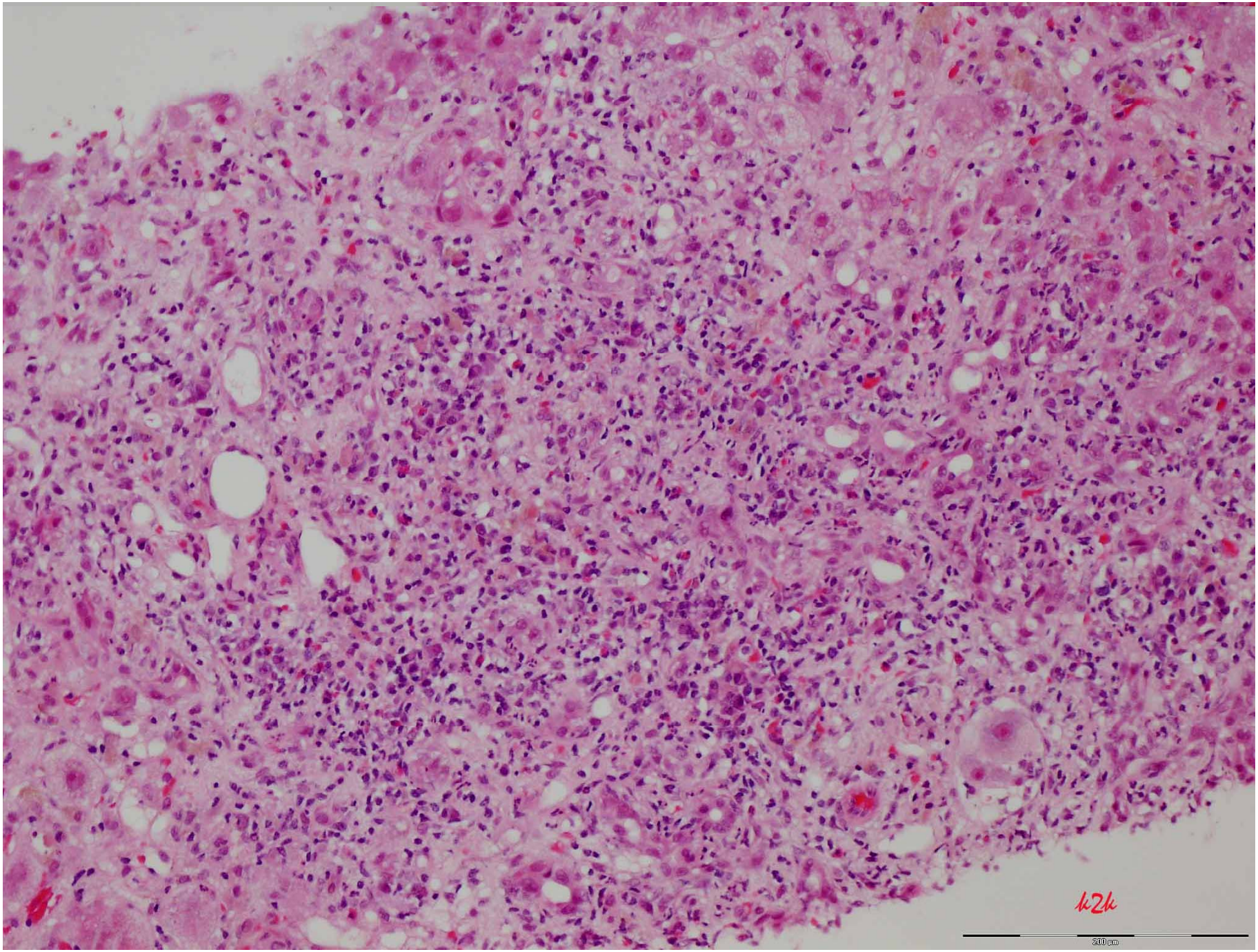
HEVitis

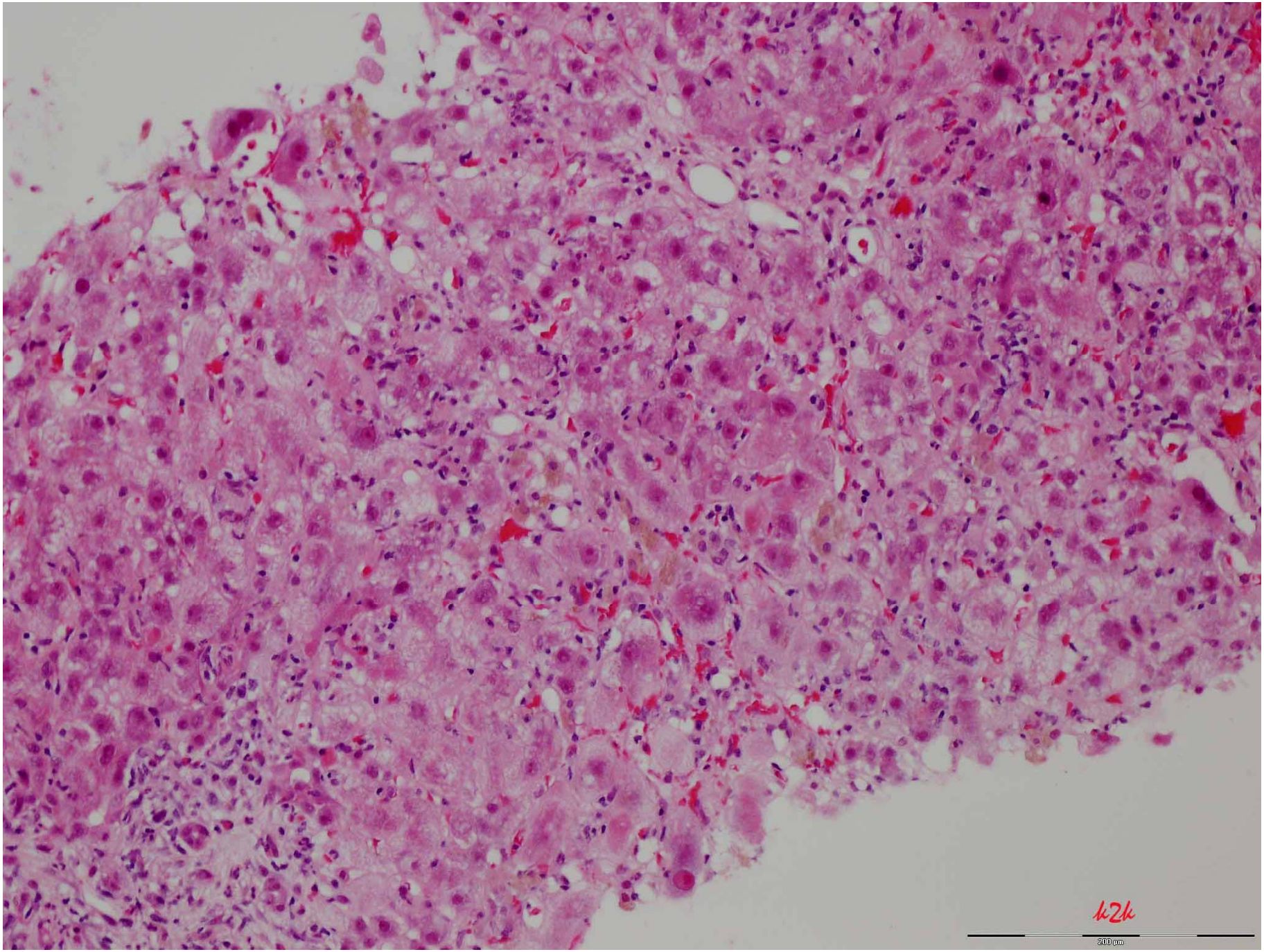



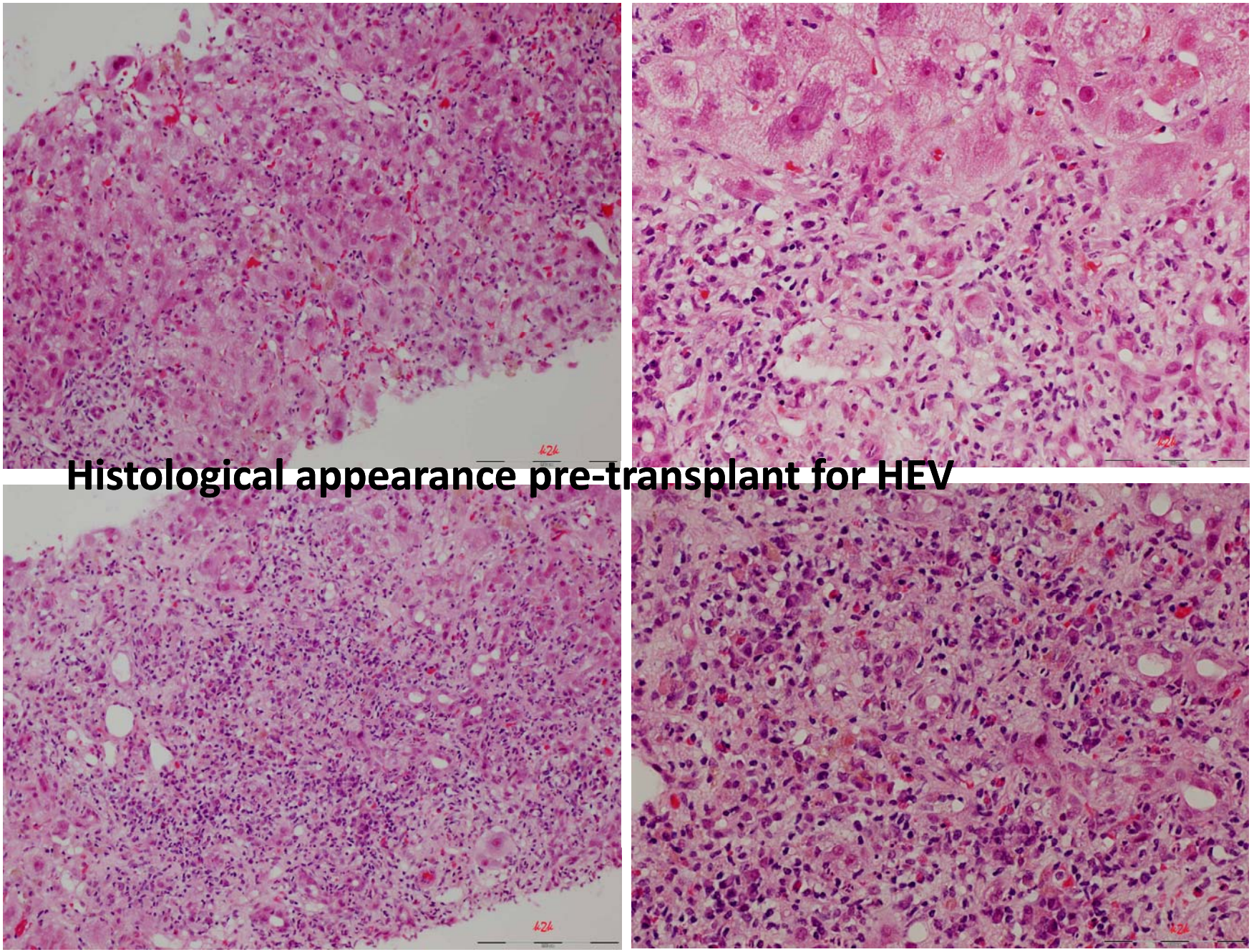
PT features



- Expanded portal tracts
- Portal tract oedema
- Ductular proliferation
- Intense mixed portal inflammation
  - Eosinophils, neutrophils, Ly+plasma cells
  - Central lymphoid aggregates
  - Polys at advancing portal parenchymal interface
- Cholangiolitis
- No copper, iron or A1AT


x2k
200 µm


424
200 µm



Histological appearance pre-transplant for HEV

Acinar histology

- **Lobular disarray**
- **Cholestatic rosettes**
- **Hydropic/ballooning degeneration**
- **Active acinar hepatocyte necrosis**
  - **Mainly neutrophils and eosinophils**
  - **Microconfluent necrosis**
  - **Confluent acinar/multiacinar necrosis**
  - **PV zonal necrosis**
  - **Bridging p-p/p-c necrosis**

Other acinar features

- **Perivenular fibrosis-occasional**
- **Perivenular pericellular fibrosis-mild**
- **Non-zonal apoptosis**
- **Zone 3 microaggregates of lipofuschin-laden KCs/macrophages**

dΔ

- **Acute cholestatic hepatitis**
- **??AICH**
- **Drug-induced hepatitis**

Drug-induced liver injury

- **20% of patients with DILI have HEV**
- **20% of patients with HEV thought to have DILI prior to HEV testing**
- **Diagnosis of DILI not secure without testing for HEV**

To conclude, HEV

- **Is probably more common than HAV**
- **Its prevalence is probably underestimated**
- **Its role in terms of morbidity and mortality especially in CLD should not be underestimated**
- **Clinically and histologically could be mistaken for DILI**
- **Presents as an acute cholestatic hepatitis which, histologically looks like acute AICH**
- **If there is a prominent neutrophilic, especially eosinophilic infiltrate, think ??HEV**

Thanks

HEV IgG serology

- **4-6 % HEV IgG seroprevalence in most developed countries**
- **9-13% in Sweden**
- **14% in Japan**
- **17-21% US blood donors**

- **0.4% annual seroconversion rate in SW England population**

And HEV,

- **May be asymptomatic**
- **May be mistaken for a drug-reaction**
- **Occurs in areas of UK, other than the SW**
- **Generally causes self-limiting hepatitis**
- **May be more severe in CLD, causes hepatic failure, and can be fatal**

Finally, HEV

- **Is caused by HEV genotype 3**
- **isolated from the cases shows close sequence homology to HEV from UK pigs**
- **aHEV may be a zoonotic infection from pigs**
- **aHEV is a public health issue in the UK**