King's College Hospital NHS
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Pathology of acute liver failure

Alberto Quaglia

BSG Annual Liver Pathology Update Meeting, Cheltenham, 6th October 2016

“A potentially reversible condition, the consequence of severe liver injury, with a onset of encephalopathy within 8 weeks of the appearance of the first symptoms and in the absence of pre-existing liver disease “

Trey & Davidson. The management of fulminant hepatic failure.
In: Popper and Schaffner eds. Progress in liver disease. 1970: 282-98

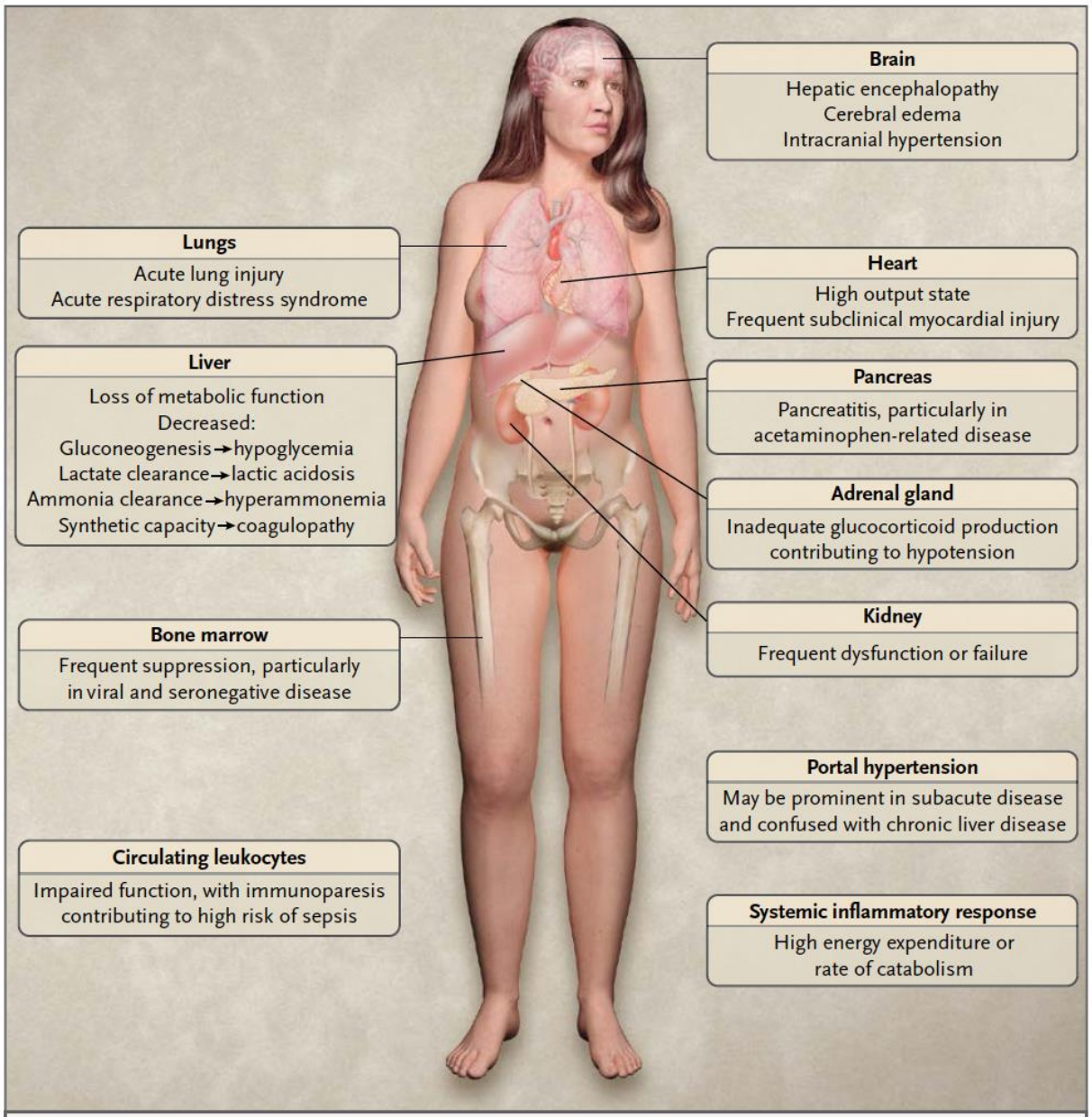
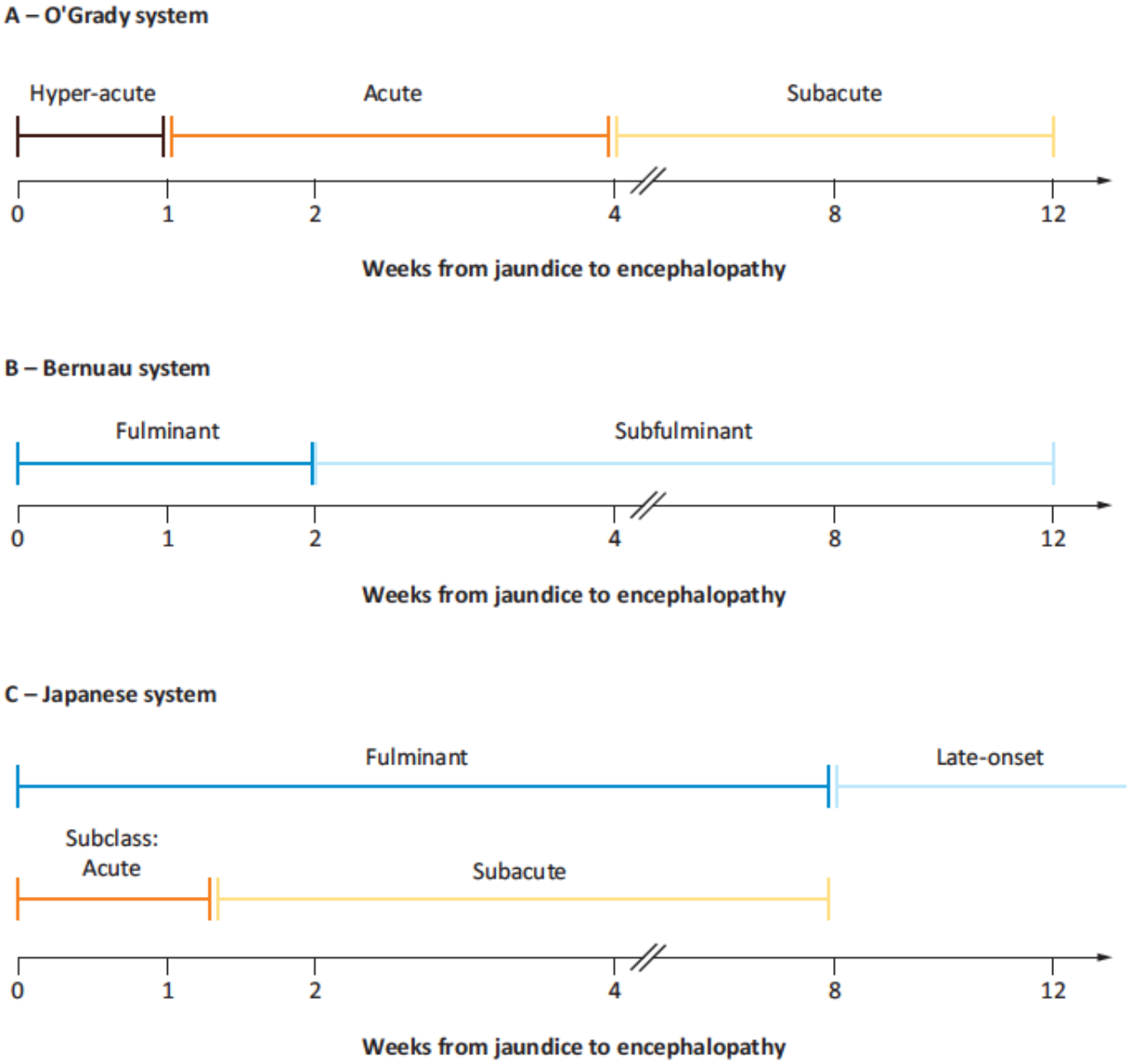


Figure 1. Clinical Features of Acute Liver Failure.



Blackmore and Bernal. Acute liver failure. Clinical Medicine 2015;15(5):468-72

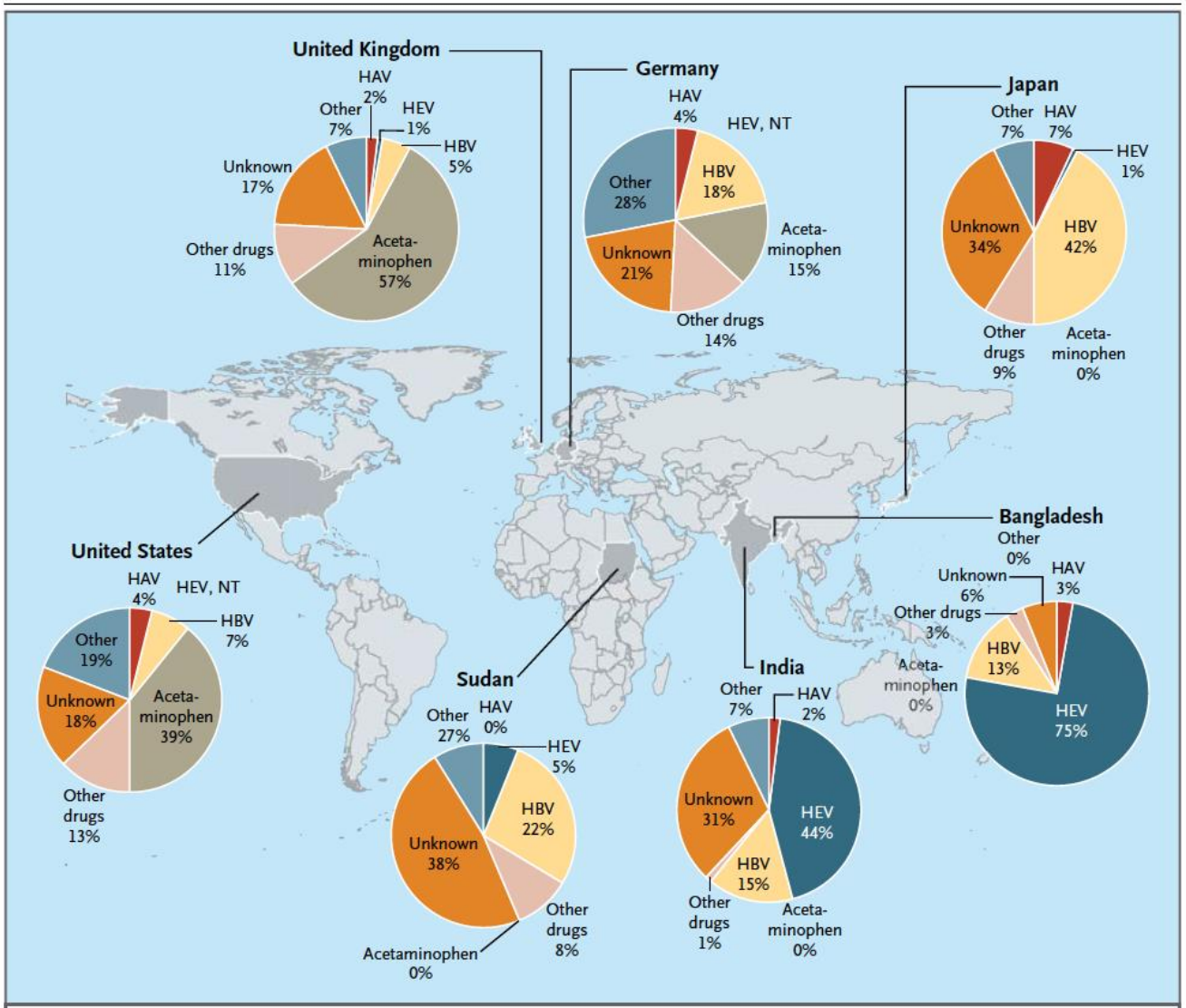


Figure 3. Worldwide Causes of Acute Liver Failure.

HAV denotes hepatitis A virus, HBV hepatitis B virus, HEV hepatitis E virus, and NT not tested.

Bernal and Wendon. New England Journal of Medicine 2013; 369: 2525-34

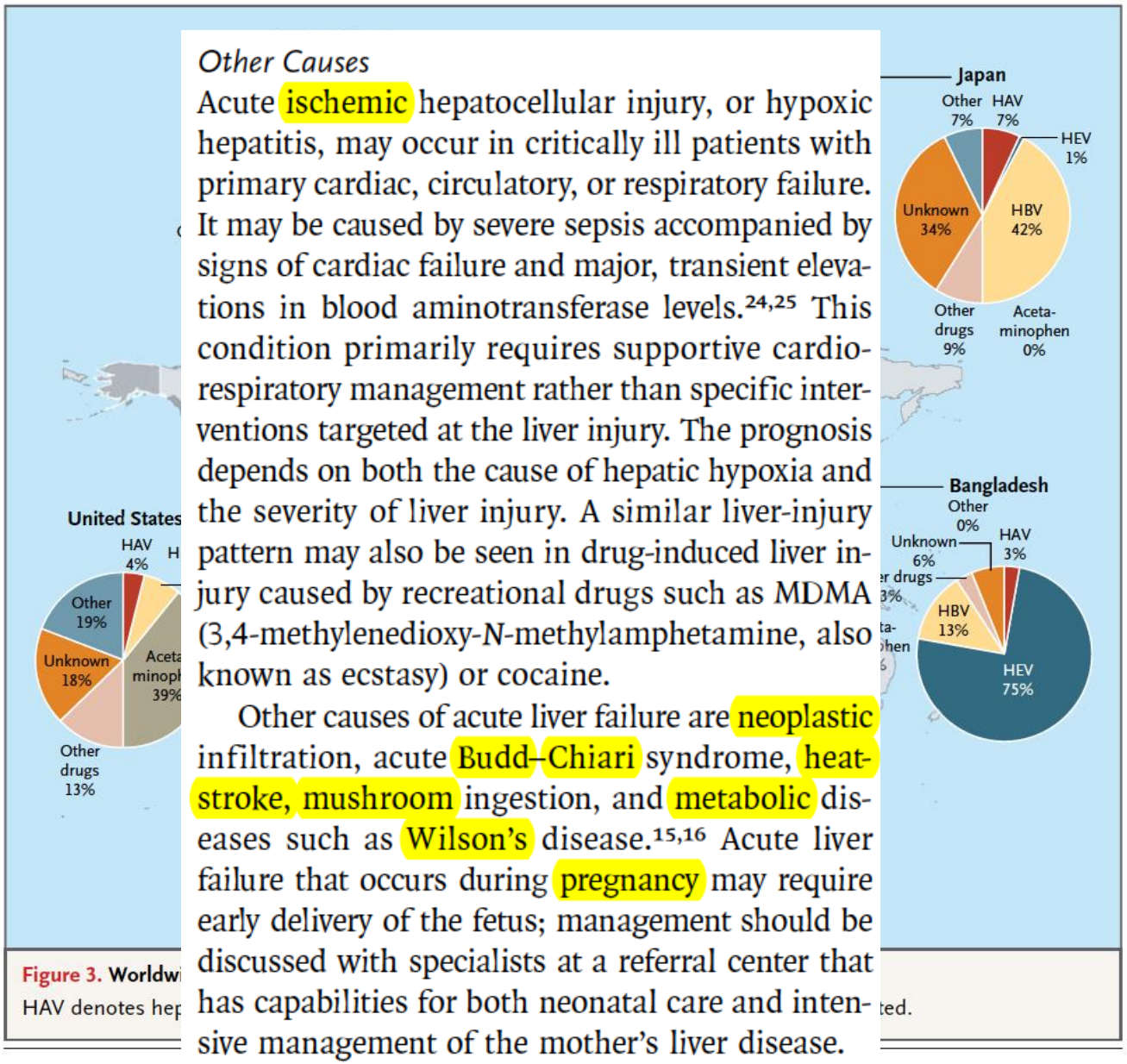


Figure 3. Worldwi
HAV denotes hep

Other Causes

Acute ischemic hepatocellular injury, or hypoxic hepatitis, may occur in critically ill patients with primary cardiac, circulatory, or respiratory failure. It may be caused by severe sepsis accompanied by signs of cardiac failure and major, transient elevations in blood aminotransferase levels.[24,25] This condition primarily requires supportive cardiorespiratory management rather than specific interventions targeted at the liver injury. The prognosis depends on both the cause of hepatic hypoxia and the severity of liver injury. A similar liver-injury pattern may also be seen in drug-induced liver injury caused by recreational drugs such as MDMA (3,4-methylenedioxy-*N*-methylamphetamine, also known as ecstasy) or cocaine.

Other causes of acute liver failure are neoplastic infiltration, acute Budd–Chiari syndrome, heatstroke, mushroom ingestion, and metabolic diseases such as Wilson's disease.[15,16] Acute liver failure that occurs during pregnancy may require early delivery of the fetus; management should be discussed with specialists at a referral center that has capabilities for both neonatal care and intensive management of the mother's liver disease.

In many cases, the cause of acute liver failure remains unknown, despite intensive investigation; potential causes include infection with a novel

Bernal and Wendon. New :525-34

TABLE 1. Etiologies of Acute Liver Failure in Neonates and Children (King's College Hospital, London, England)

Neonates	n = 31	Children	n = 100
Neonatal hemochromatosis	15	Non–A-E hepatitis	45
Hemophagocytic lymphohistiocytosis	4	Hepatitis A/B	7
Disseminated herpes simplex virus	5	Other viral infection	3
Metabolic	4	Metabolic	18
Transplacental acetaminophen toxicity	1	Paracetamol toxicity	8
Endocrine (isolated cortisol deficiency)		Other drug/toxin	5
Sepsis/shock	1	Sepsis/hypoxia	3
	1	Miscellaneous	3

Dhawan. Liver Transplantation 2008; 14(10) Suppl 2: S80-S84

	Hyperacute	Acute	Subacute
Time from jaundice to encephalopathy	0–1 week	1–4 weeks	4–12 weeks
Severity of coagulopathy	+++	++	+
Severity of jaundice	+	++	+++
Degree of intracranial hypertension	++	++	+/–
Survival rate without emergency liver transplantation	Good	Moderate	Poor
Typical cause	Paracetamol, hepatitis A and E	Hepatitis B	Non-paracetamol drug-induced liver injury

Data from O'Grady and colleagues[12] and Ichai and Samuel.[13] +++=high severity. ++=medium severity. +=low severity. +/–=present or absent.

Table 1: **Classification, clinical features, and prognosis of the three subtypes of acute liver failure**

Bernal et al. Lancet 2010; 376:190-201

Histology of ALF

Multiple aetiologies , limited morphologic repertoire of tissue response and macroscopic and histological patterns

Limited role for the histopathologist in clinical practice

Histopathological basis of syndrome
CRITICAL CARE IN ACUTE LIVER FAILURE
Editors: Roger Williams and Julia Wendon

Patterns of injury

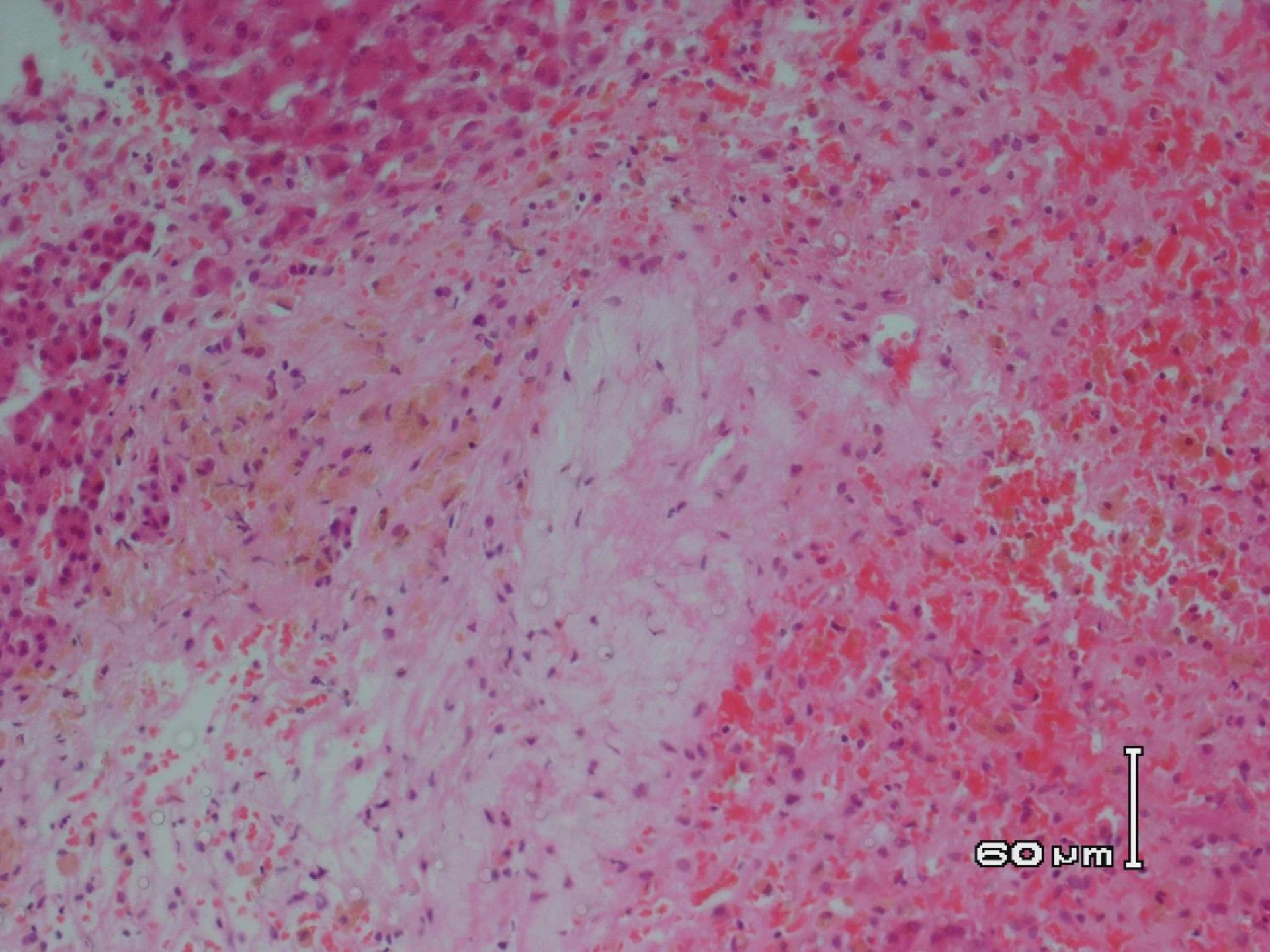
- Confluent hepatocyte loss
  - Terminology: coagulative, eosinophilic, zonal, panlobular, multiacinar, massive
    - Centro-midlobular with periportal sparing
    - Periportal necrosis
    - Geographic/random with viral inclusions
    - No residual hepatocytes
    - Map-like

- Venous outflow block
- Malignant infiltration
- Microvescicular steatosis
- “Giant cell” hepatitis and neonatal haemochromatosis

Histopathological basis of syndrome

CRITICAL CARE IN ACUTE LIVER FAILURE

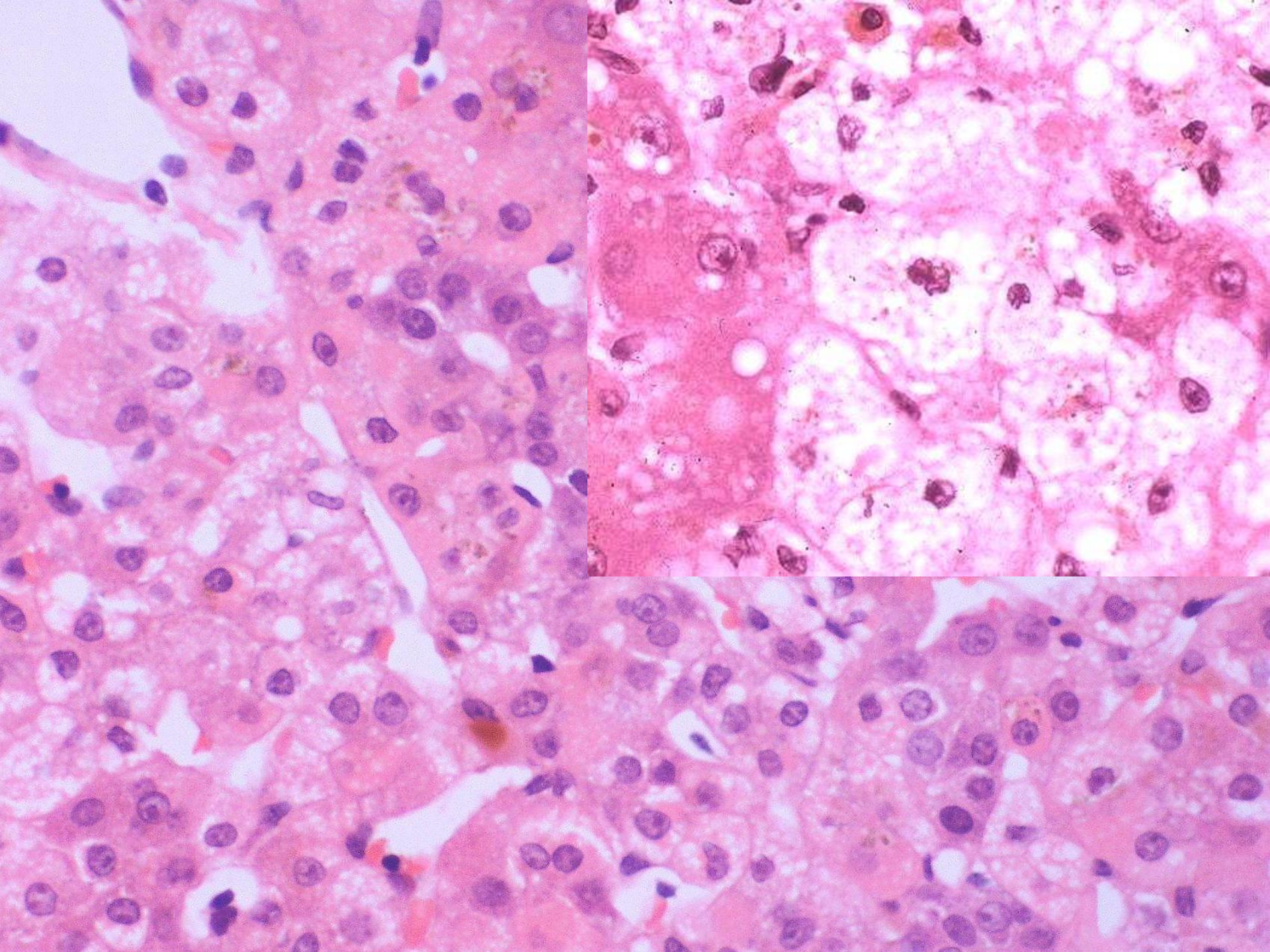
Editors: Roger Williams and Julia Wendon


60 µm

Acute liver failure due to hepatic malignant infiltration

- Very rare cause of ALF
- Compared 24 ALF-MI patients with 72 ALF patients
  - 13 Haematological
  - 10 Carcinoma
  - 1 Angiosarcoma
- Higher ALP,LDH, urea, ferritin and lower platelets in the ALF-MI
- Hepatomegaly on imaging

Solis Munoz et al Hepatology. 2013 Oct;58:360A-360A. 309



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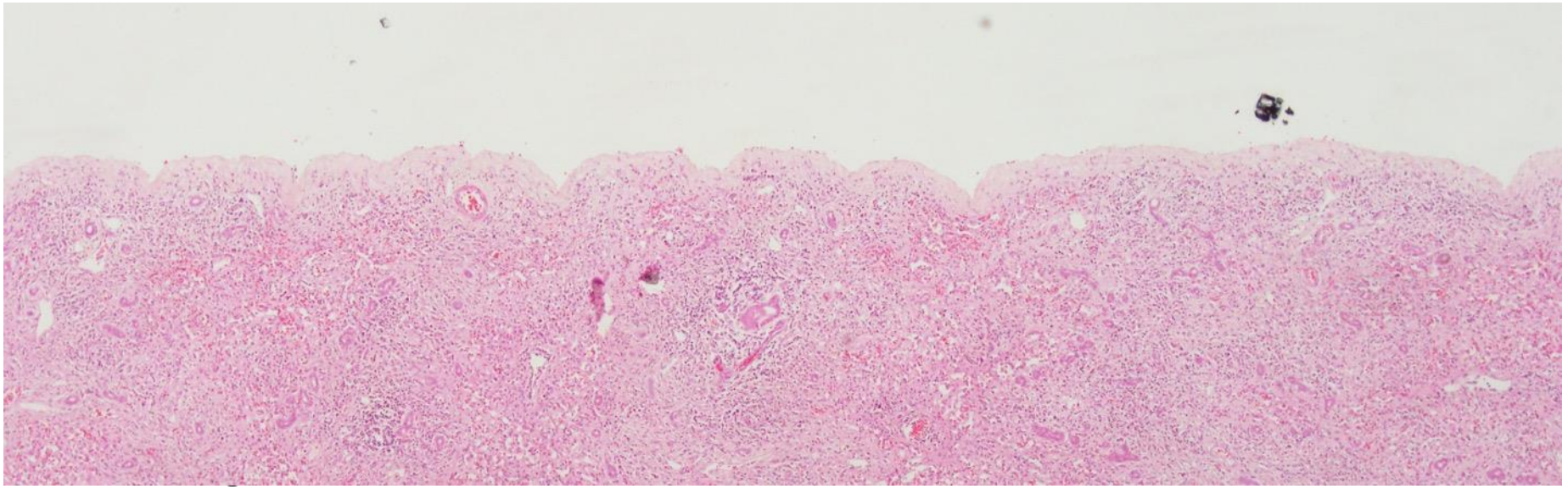
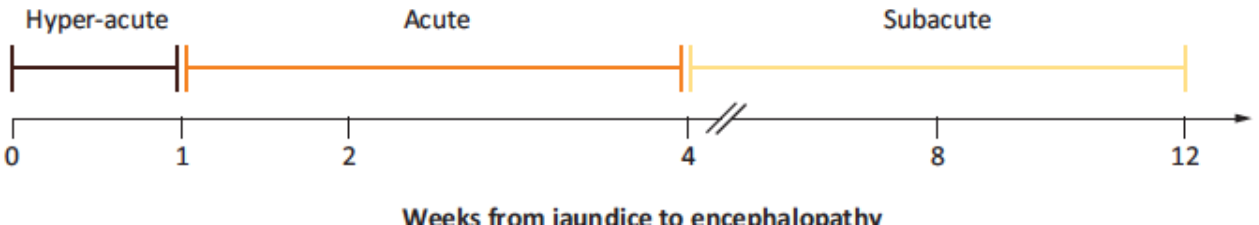
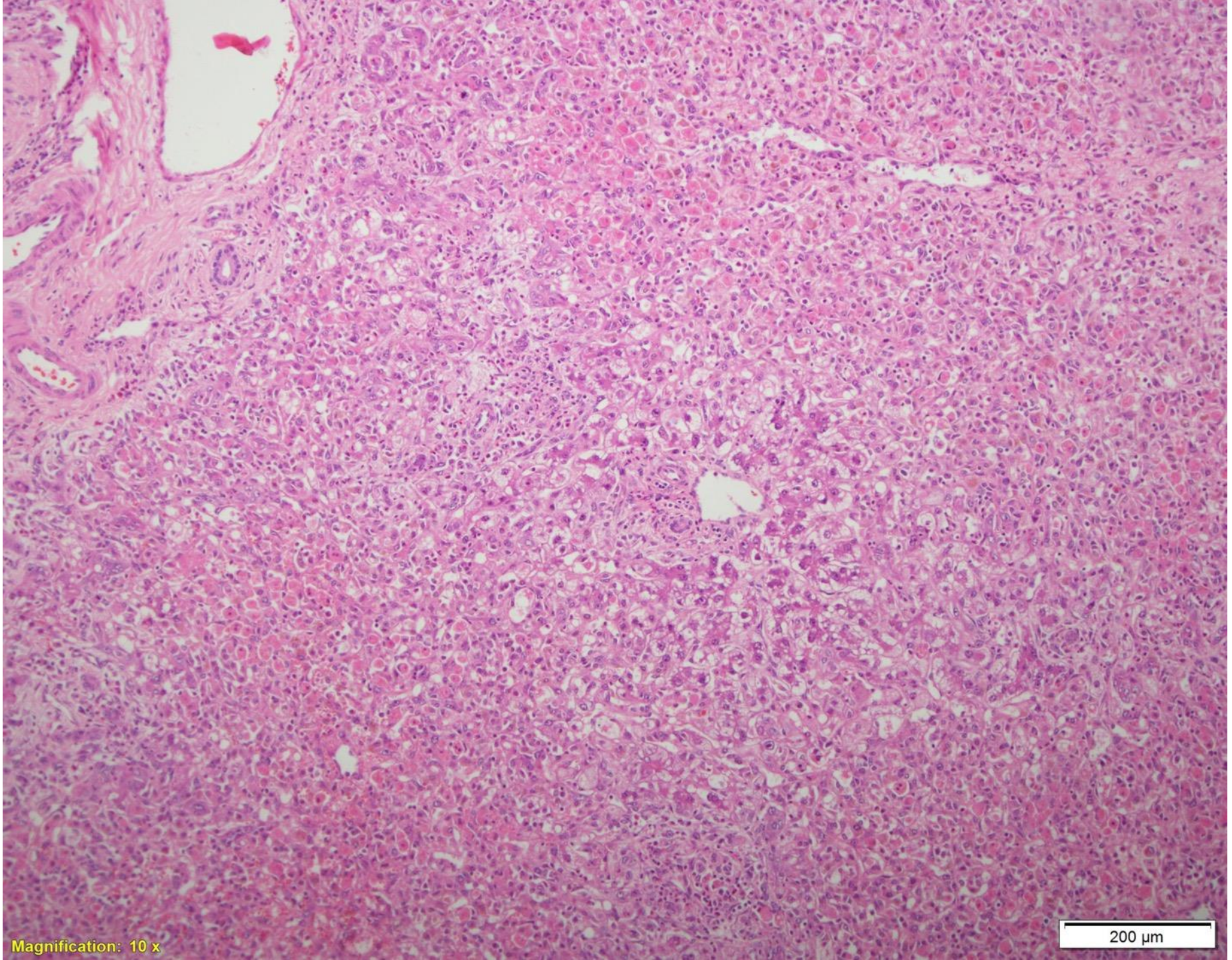


A – O'Grady system

Courtesy of
Bernard Portmann

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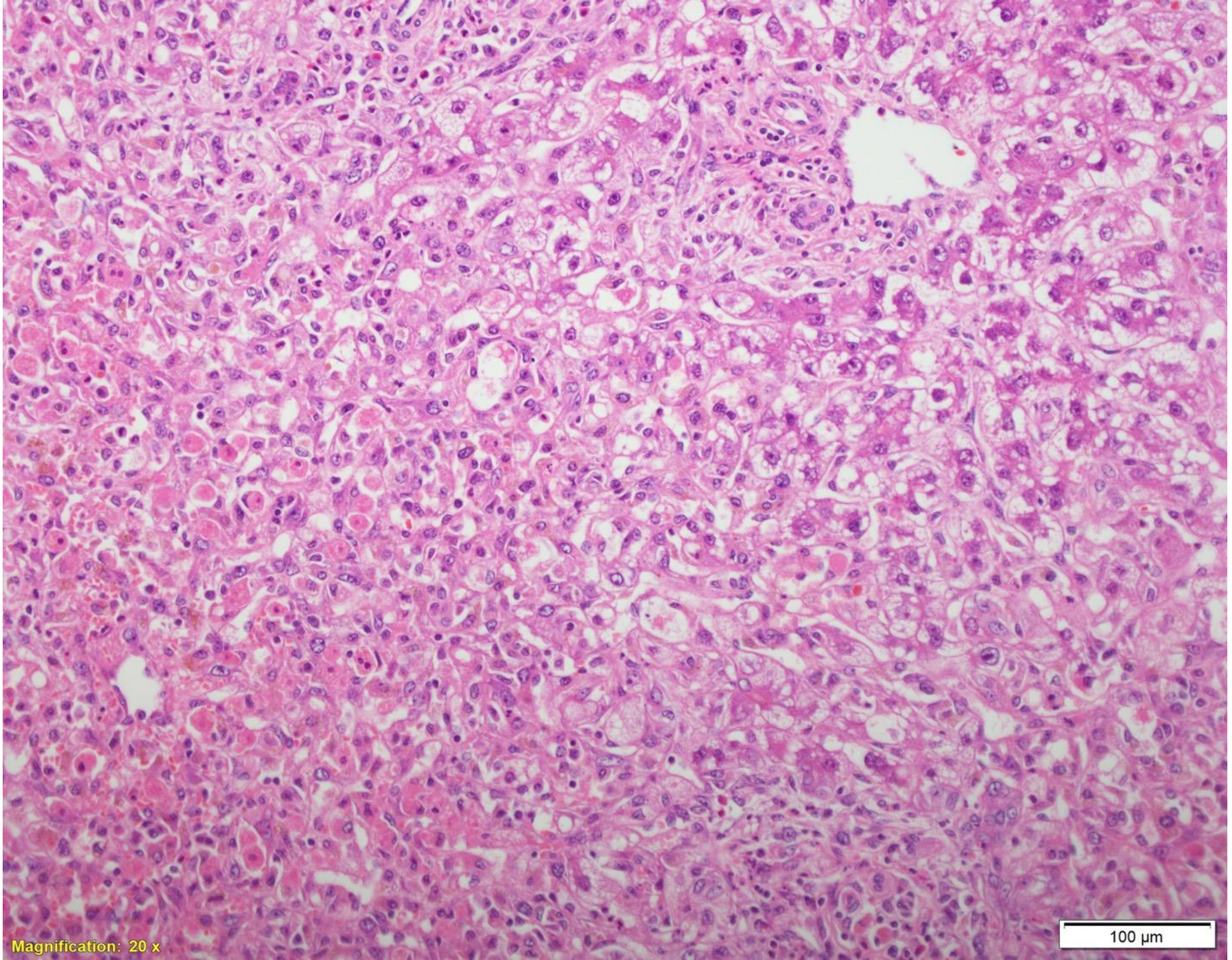
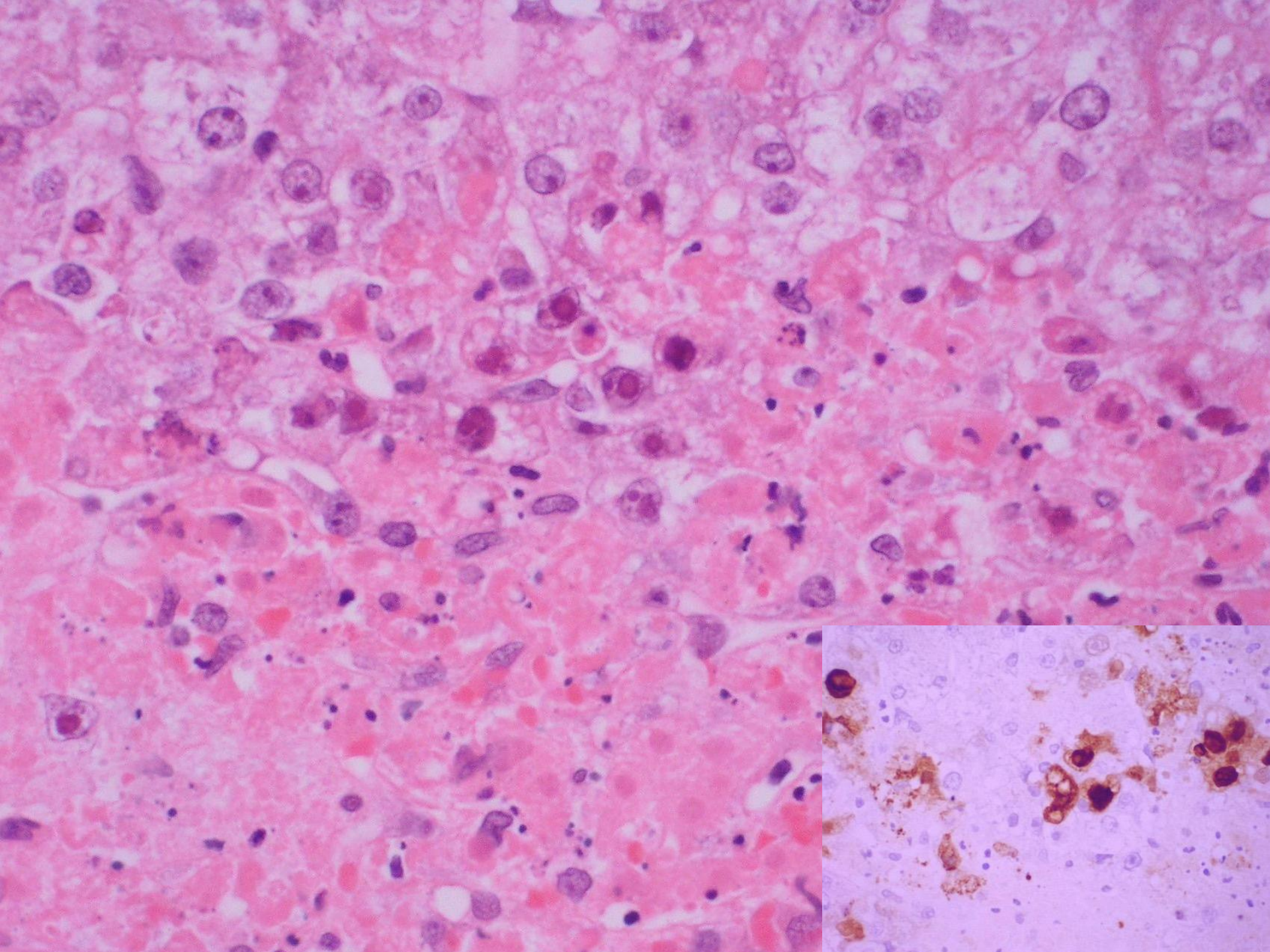
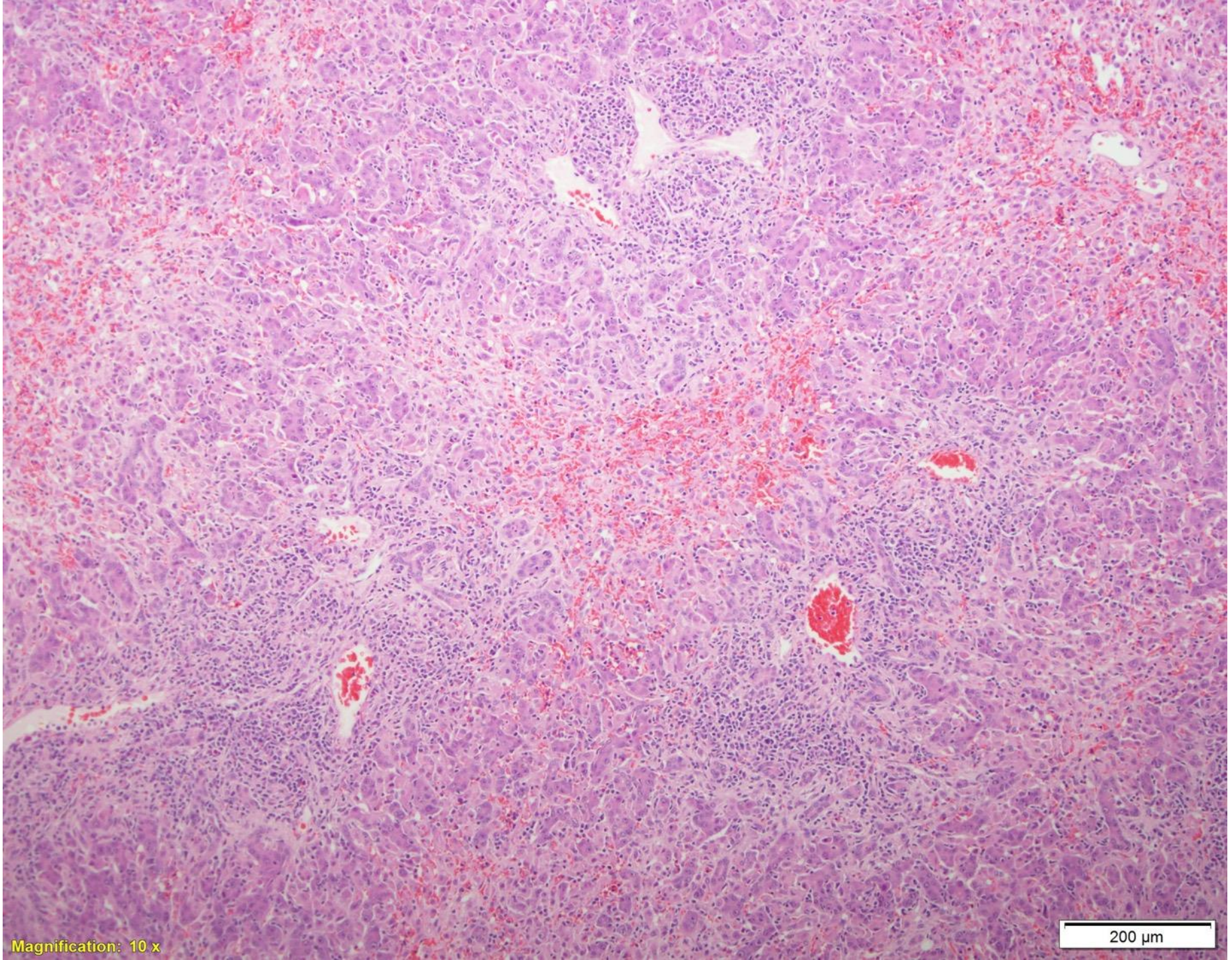
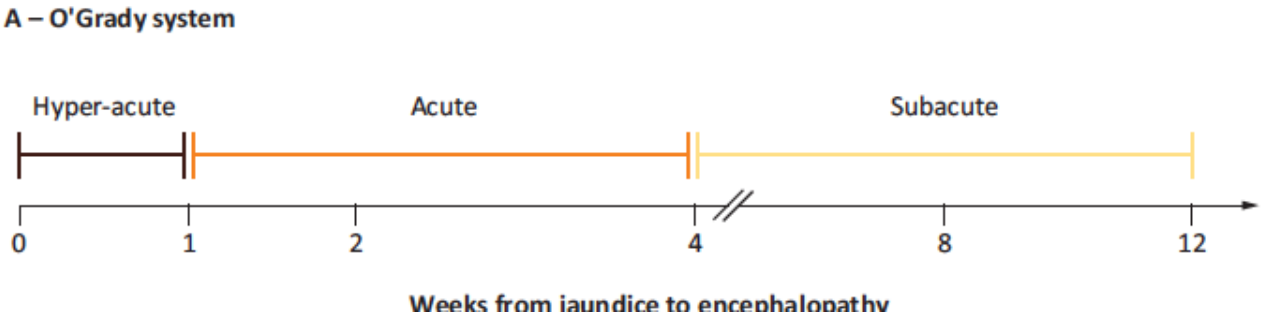

Magnification: 20 x
100 µm

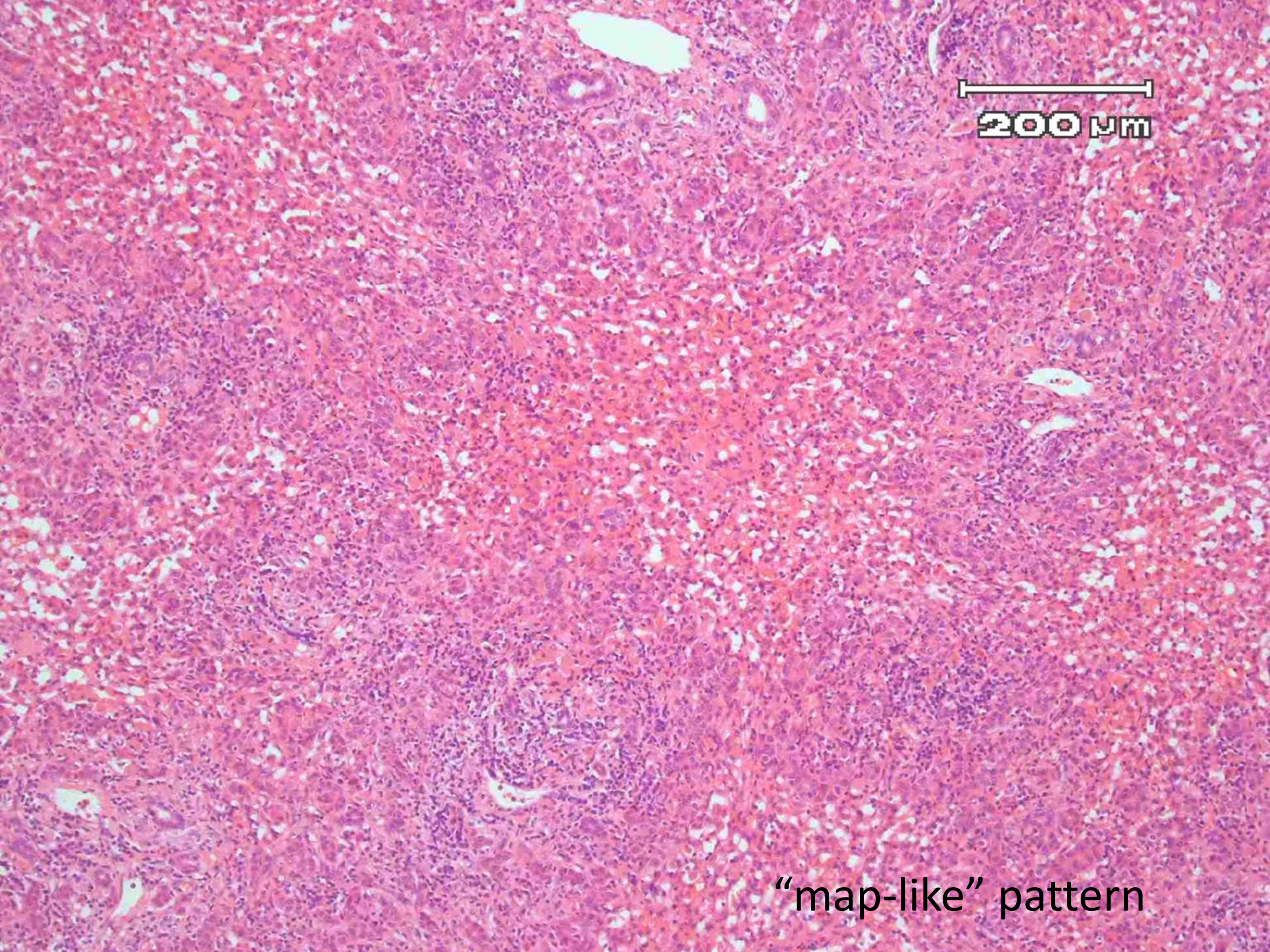



Magnification: 10 x
200 µm

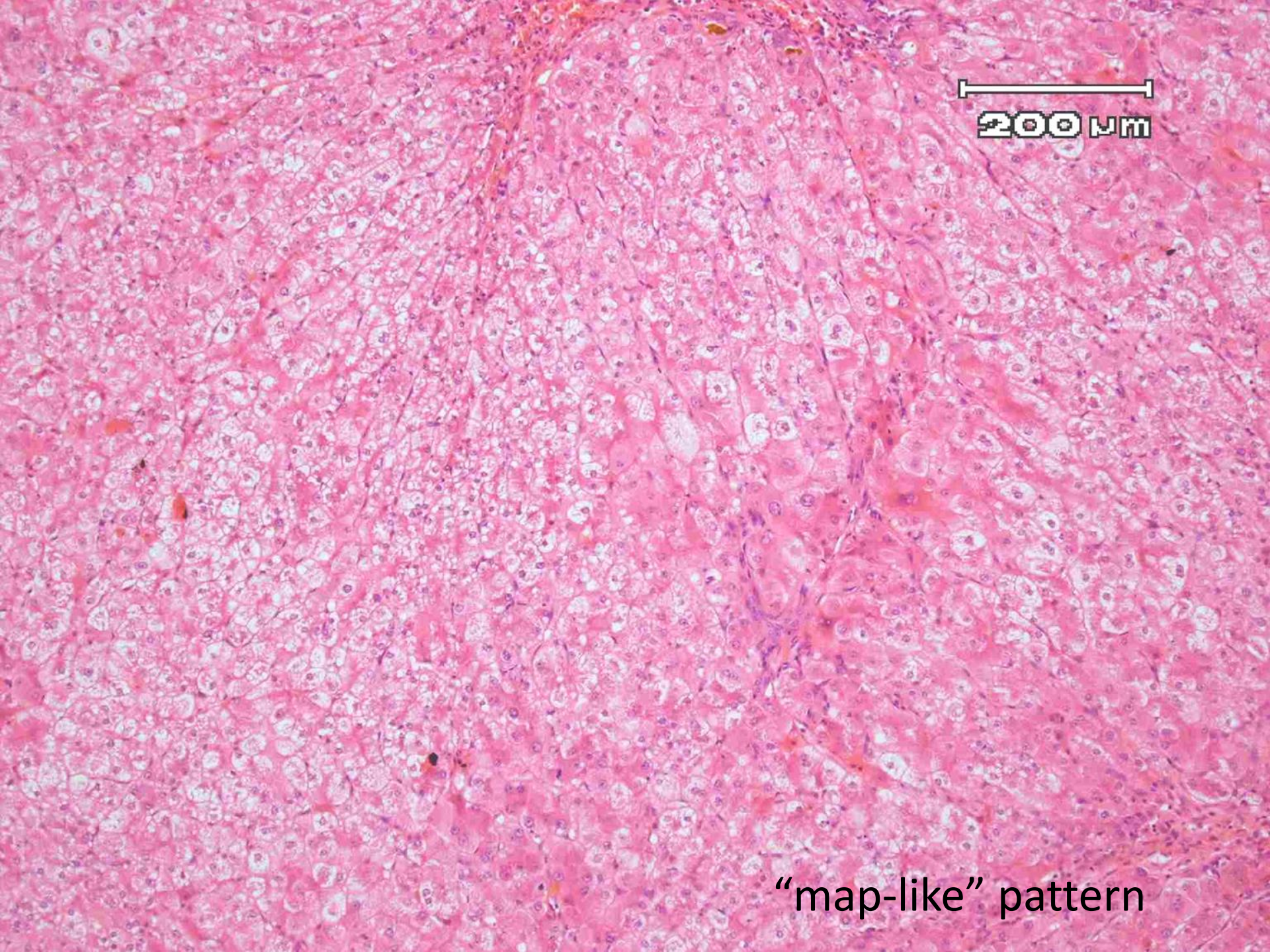
Courtesy of
Bernard Portmann



“map-like” pattern


200 µm
“map-like” pattern

“map-like” pattern



“map-like” pattern

Auxiliary Transplantation for Acute Liver Failure: Histopathological Study of Native Liver Regeneration

Median age = 19 years (range 1-40), 19 children, 22 female.

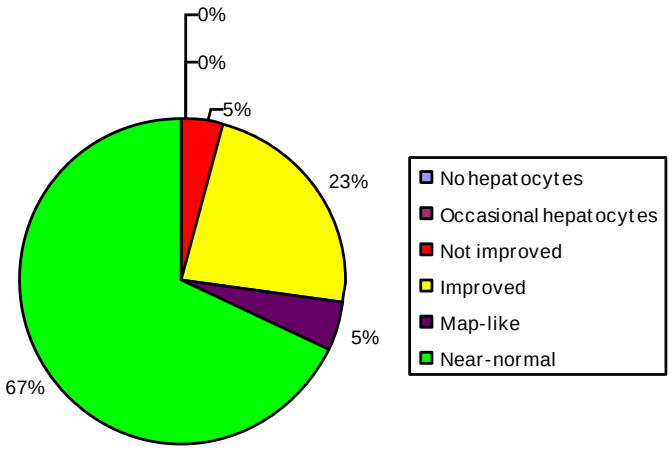
Cause:

- 24 = seronegative liver failure;
- 15 = paracetamol overdosage;
- 4 = HBV infection in 4;
- 3 = drug-induced liver failure;
- 2 = autoimmune hepatitis;
- 1 = mushroom poisoning;

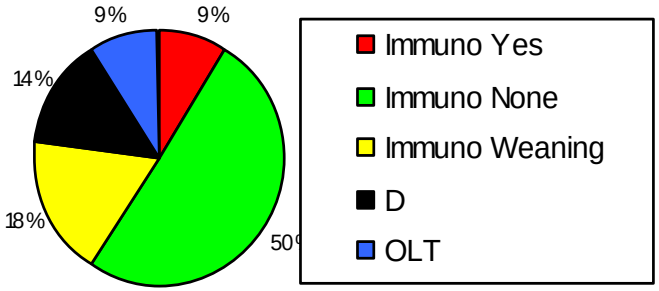
LL= 4
LLS=8
RL=7
ExtR=14
WG=5

LIVER TRANSPLANTATION 14:1437-1448, 2008

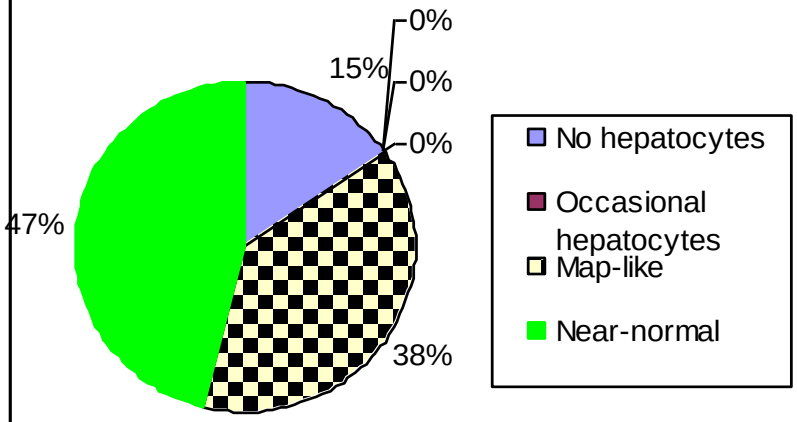
Diffuse pattern: histological outcome



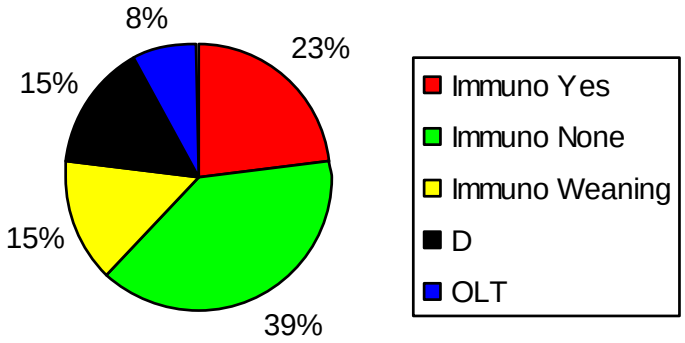
Diffuse pattern: clinical outcome

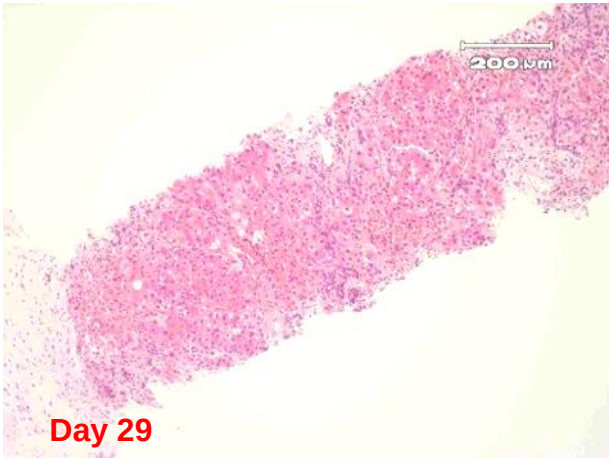


Map-like histological outcome



Map-like clinical outcome

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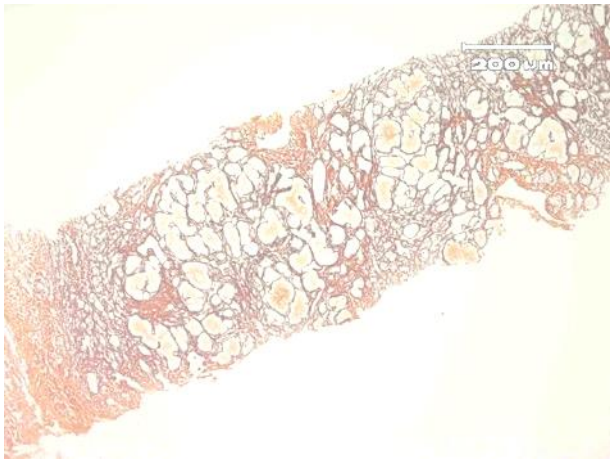
Day 29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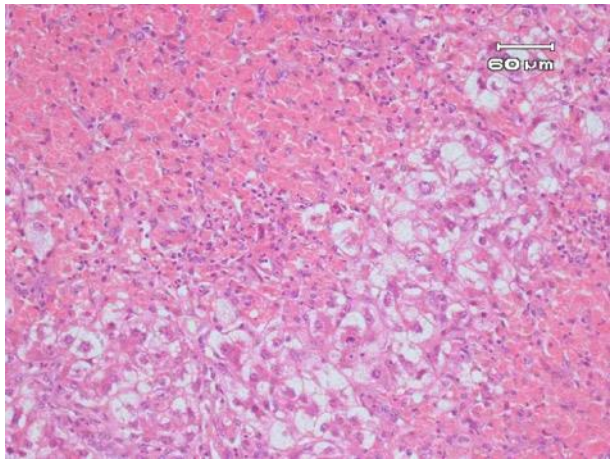
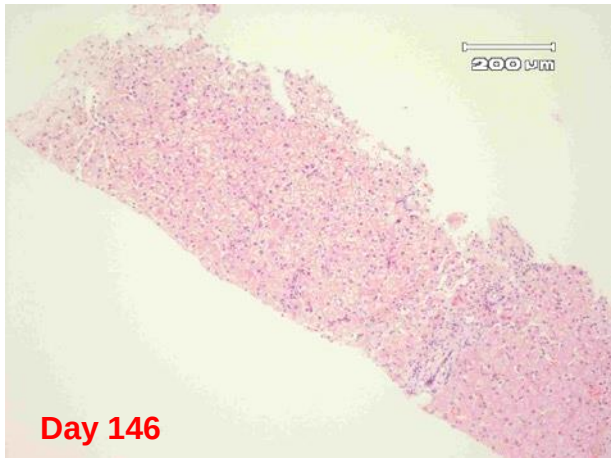
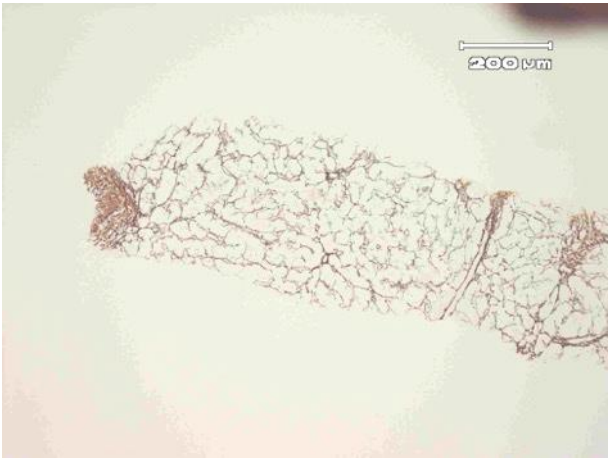

50 µm


200 µm
Day 146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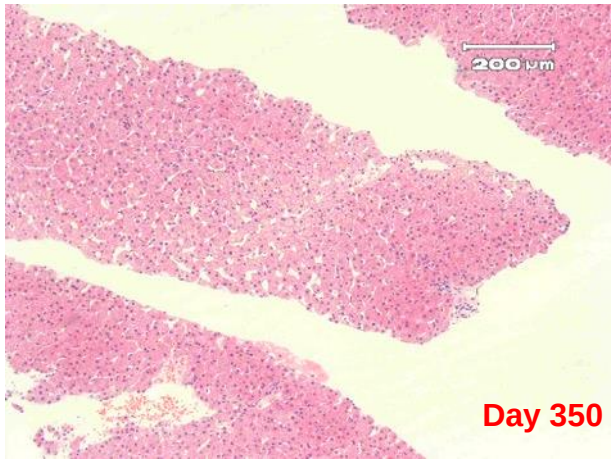
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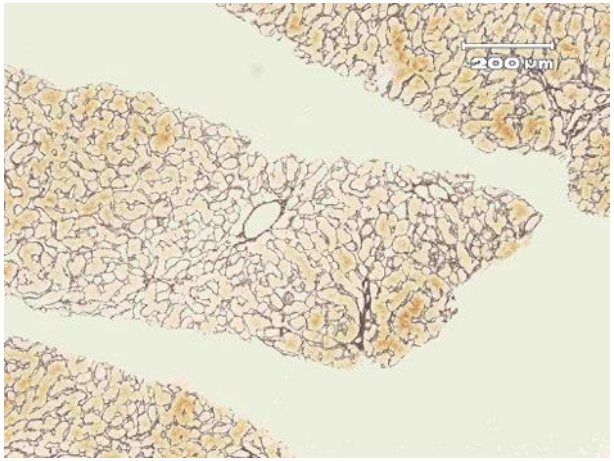
Day 350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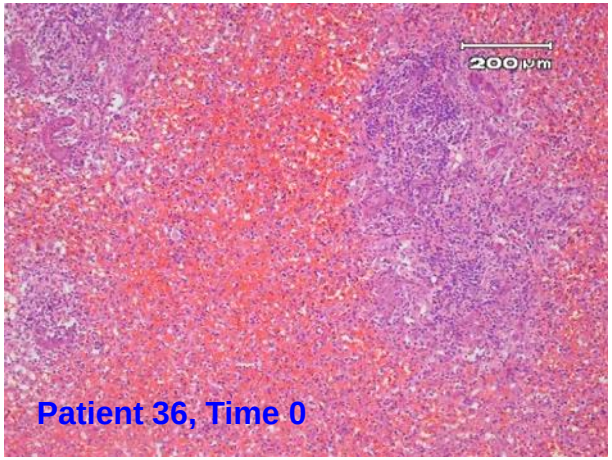
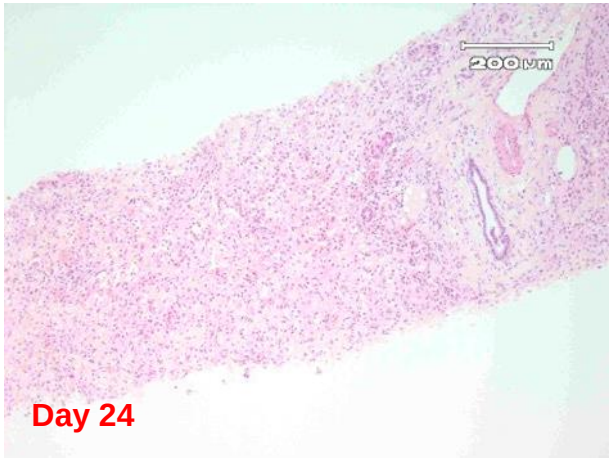
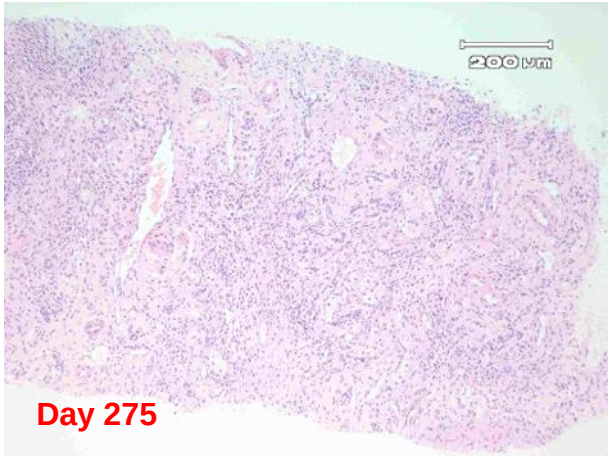
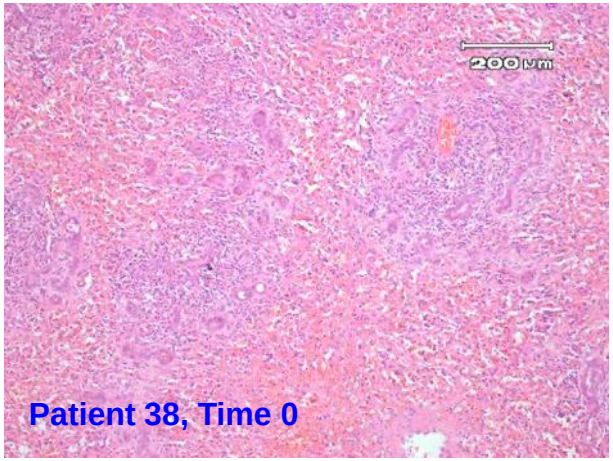
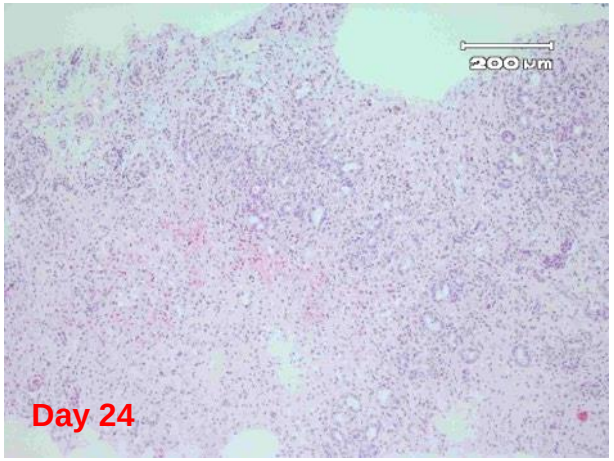
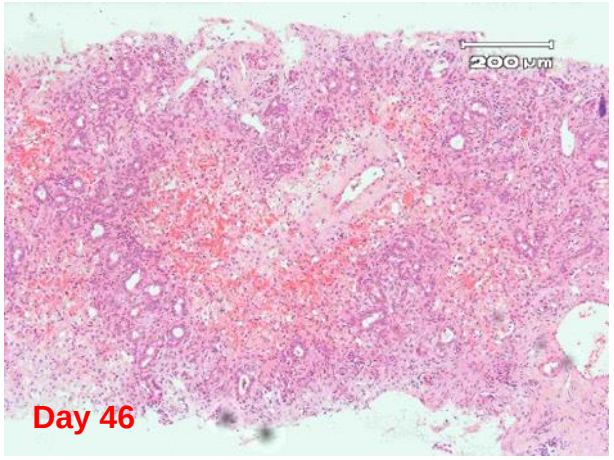

200 µm
Patient 36, Time 0

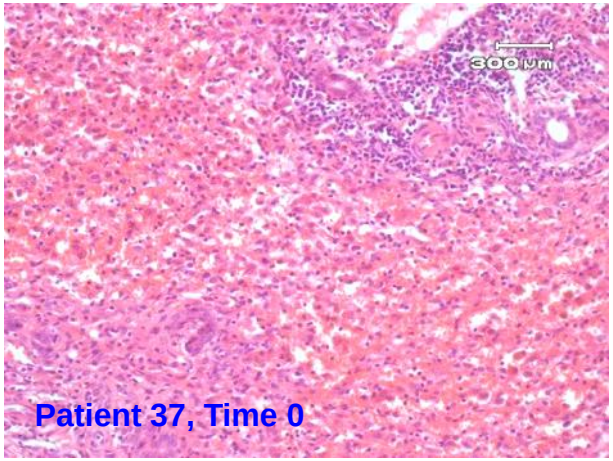

200 µm
Day 24

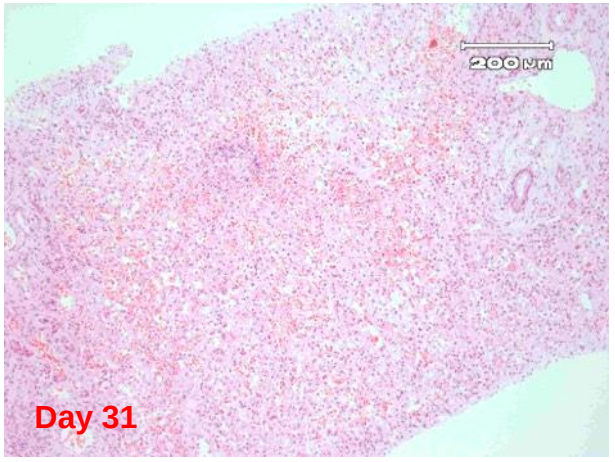

200 µm
Day 275


200 µm
Patient 38, Time 0


200 µm
Day 24


200 µm
Day 46


300 µm
Patient 37, Time 0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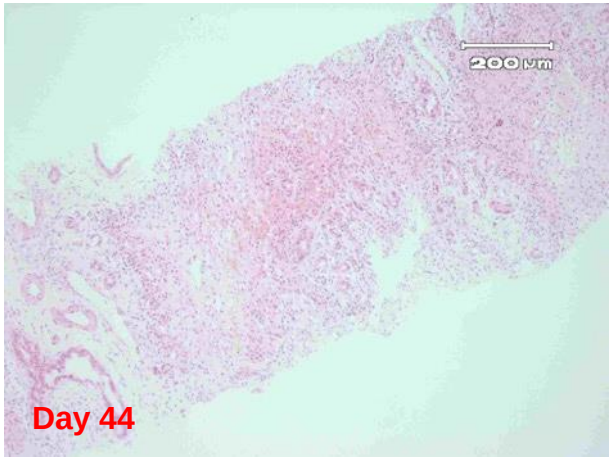
Day 31


200 µm
Day 44

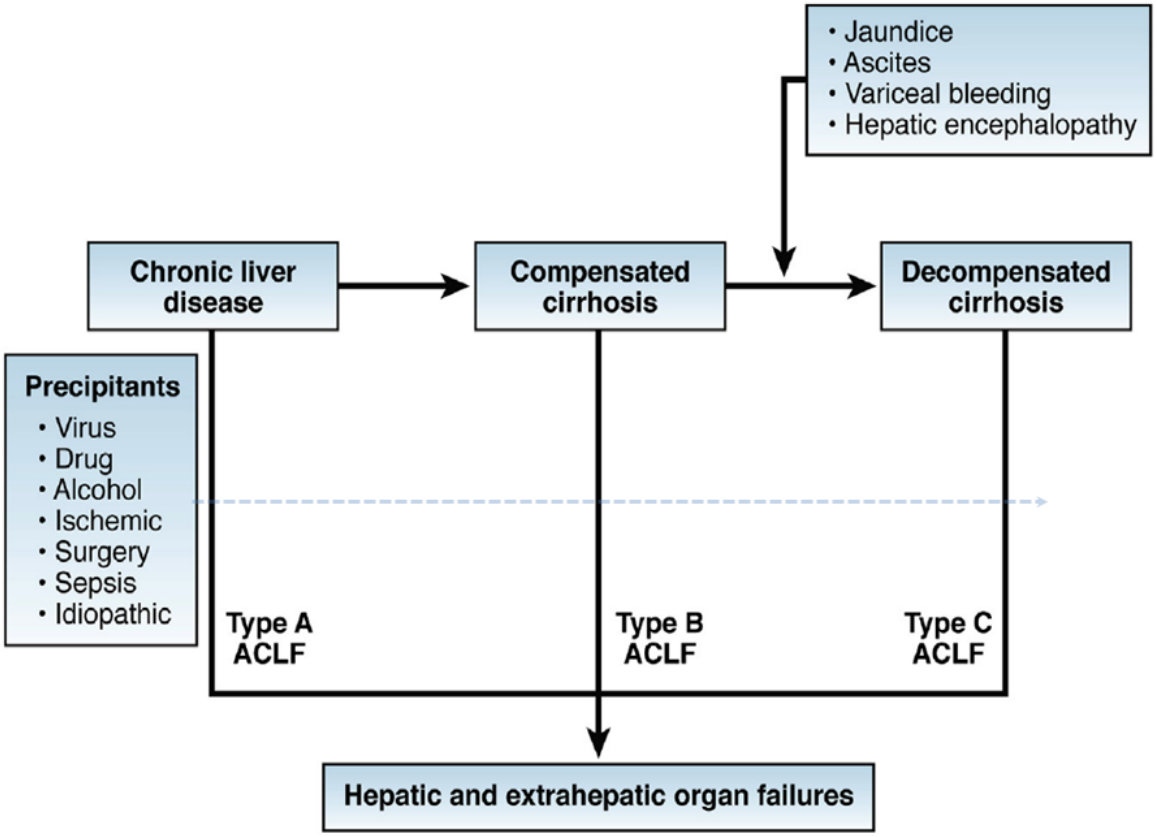
Panel: Definitions of acute-on-chronic liver failure

World Congress of Gastroenterology (consensus definition)[5]
"A syndrome in patients with chronic liver disease with or without previously diagnosed cirrhosis which is characterized by acute hepatic decompensation resulting in liver failure (jaundice and prolongation of the INR [International Normalized Ratio]) and one or more extrahepatic organ failures that is associated with increased mortality within a period of 28 days and up to 3 months from onset"

Asia-Pacific Association for the Study of Liver Disease[17]
"Acute hepatic insult manifesting as jaundice and coagulopathy, complicated within 4 weeks by ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease"

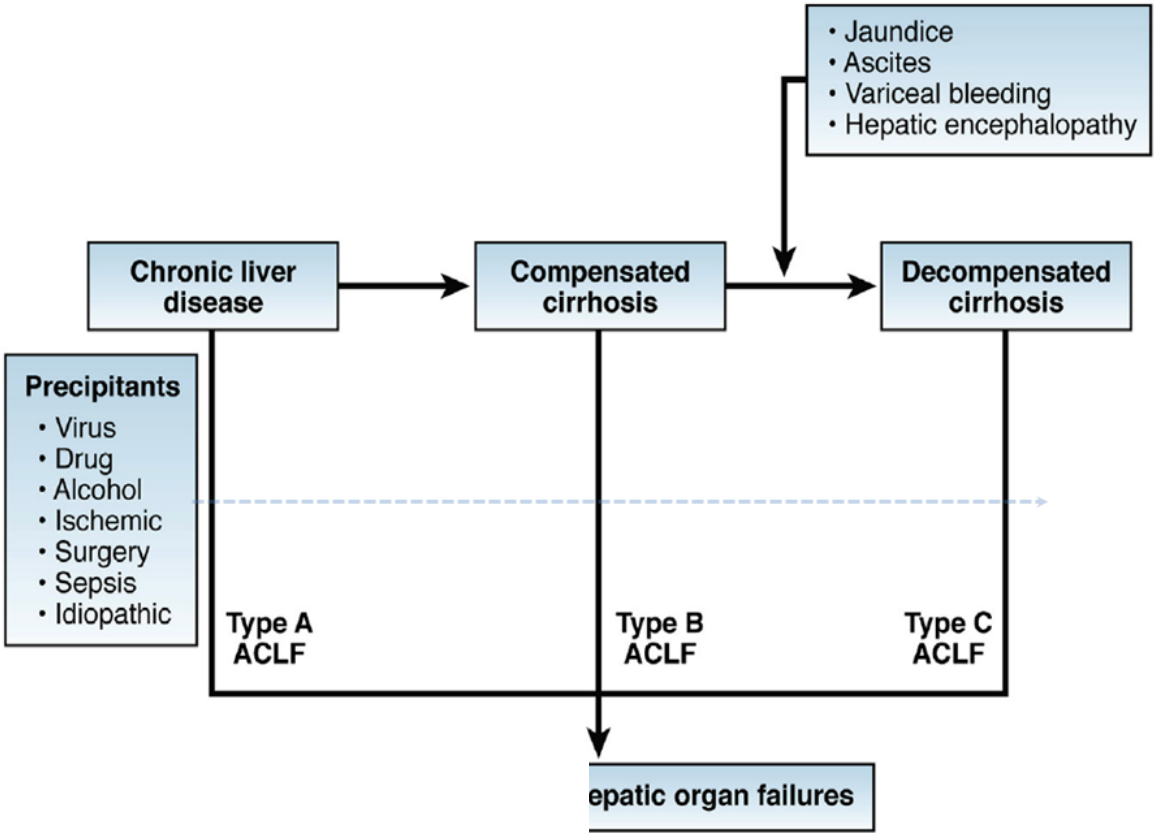
European and American associations for the study of liver disease[18]
"Acute deterioration of pre-existing, chronic liver disease, usually related to a precipitating event and associated with increased mortality at 3 months due to multi-system organ failure"

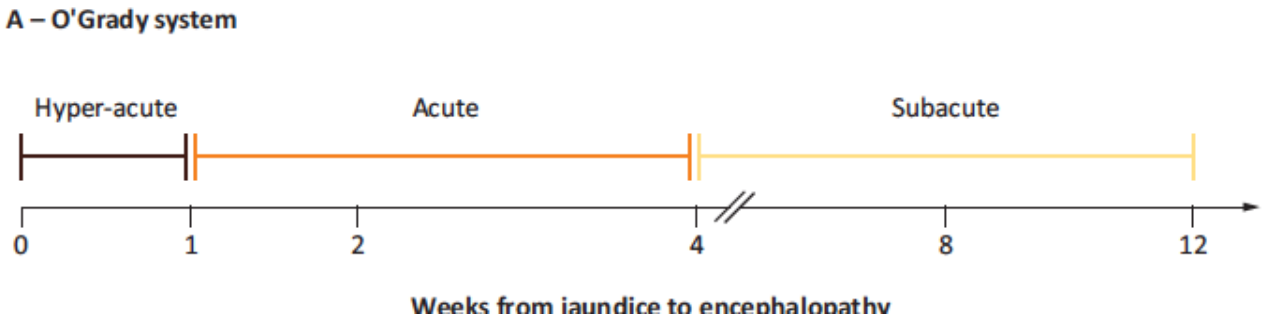
Acute on chronic liver failure



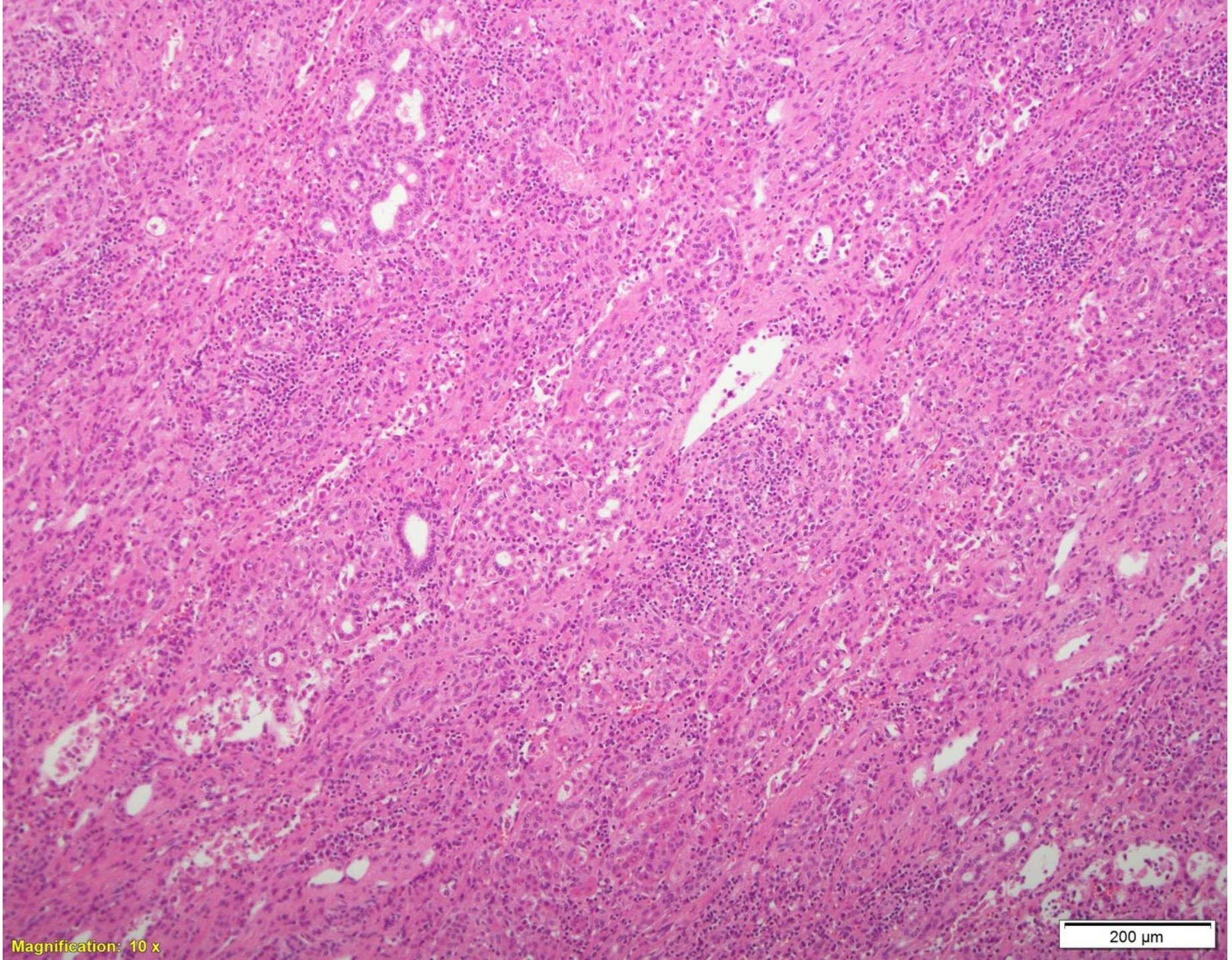
Jalan R, Yurdaydin C, Bajaj JS, et al. Toward an improved definition of acute-on-chronic liver failure. *Gastroenterology* 2014; **147**(1): 4-10.

Acute on chronic liver failure





Jalan R, Yurdaydin C, Bajaj JS, et al. Toward an improved definition of acute-on-chronic liver failure. *Gastroenterology* 2014; **147**(1): 4-10.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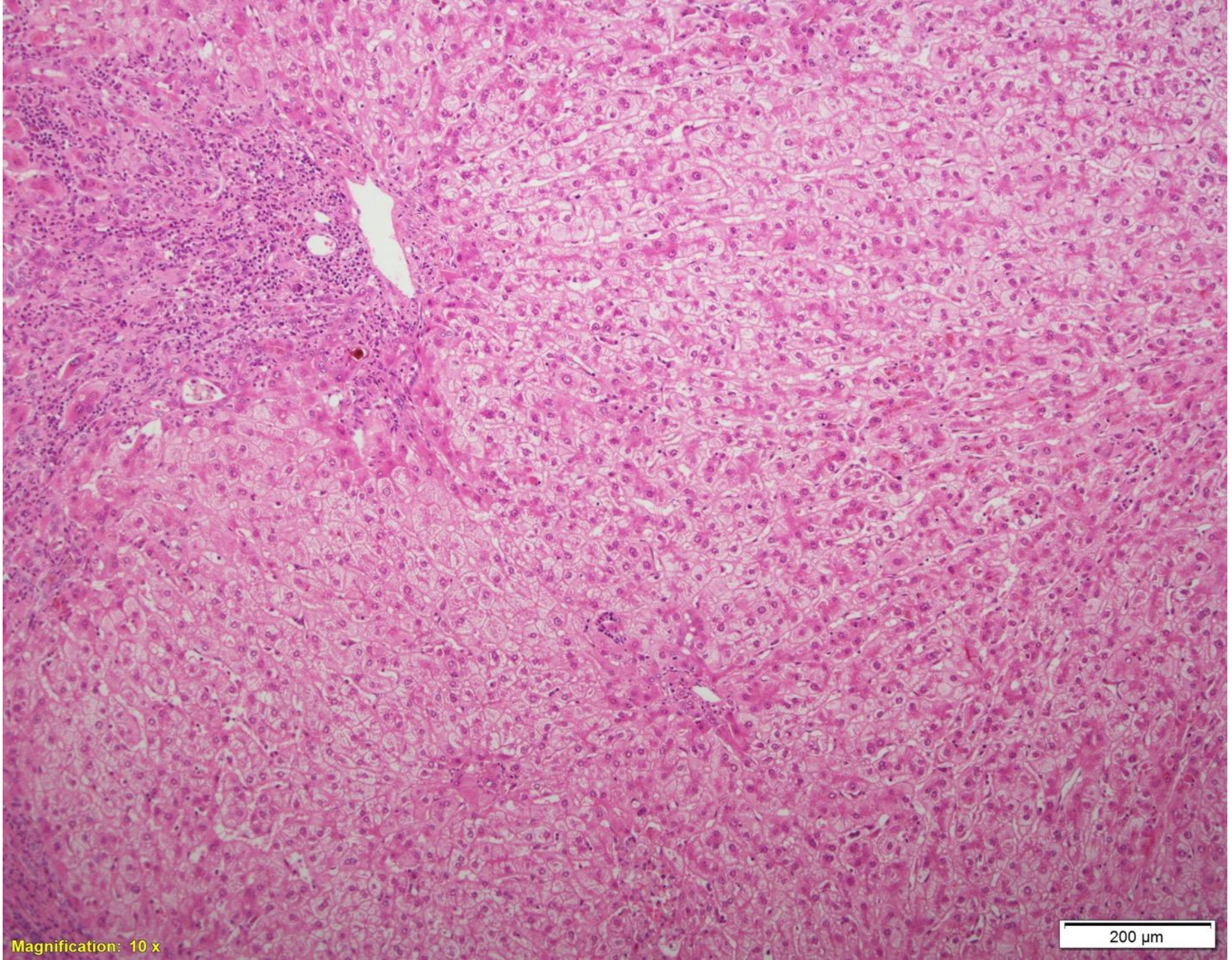
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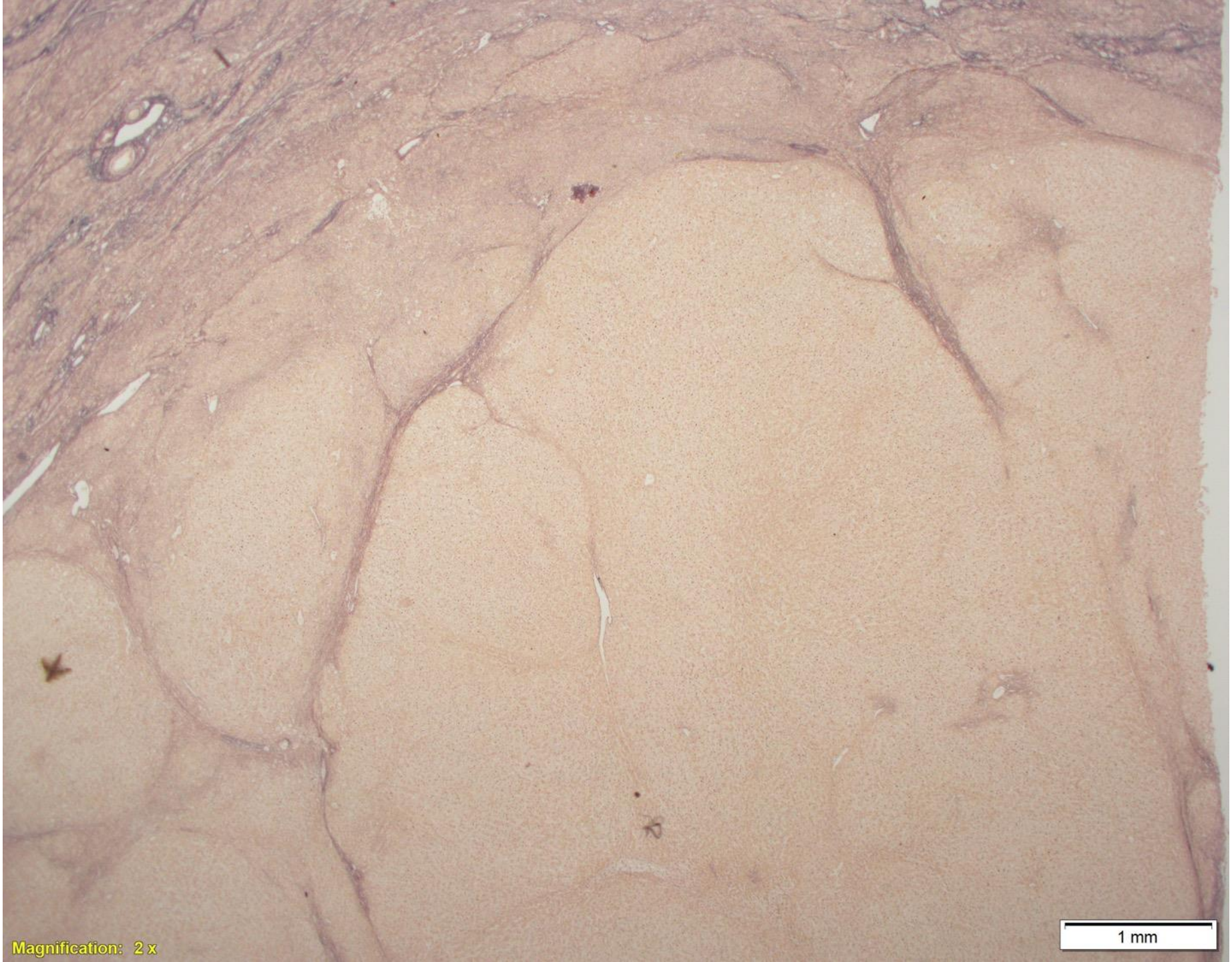
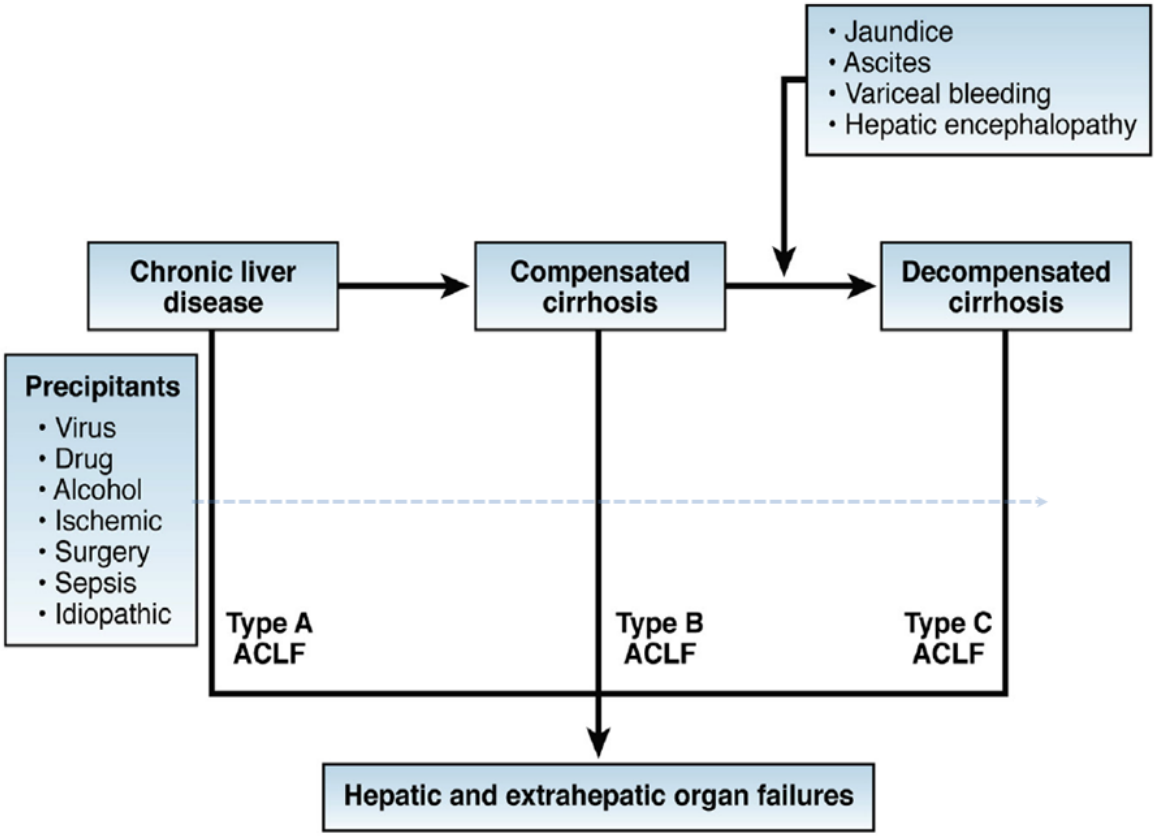

Magnification: 2 x
1 mm

Acute on chronic liver failure



Jalan R, Yurdaydin C, Bajaj JS, et al. Toward an improved definition of acute-on-chronic liver failure. *Gastroenterology* 2014; **147**(1): 4-10.

Alcoholic Hepatitis Histological Score (AHHS) for Prognostic Stratification of Alcoholic Hepatitis

Points

Fibrosis stage
None Fibrosis or Portal fibrosis 0
Expansive fibrosis 0
Bridging fibrosis or Cirrhosis +3

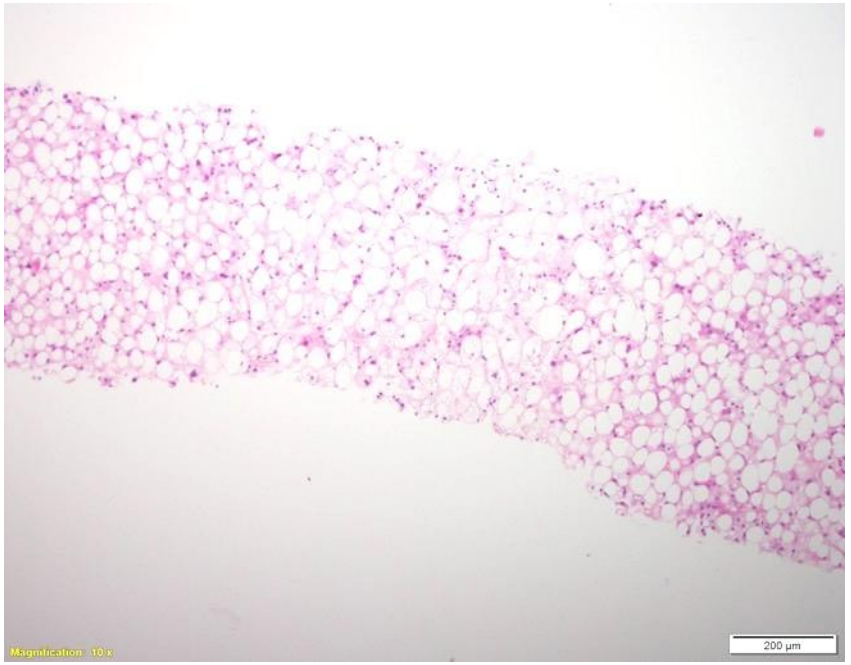
Bilirubinostasis
No 0
Hepatocellular only 0
Canalicular or ductular +1
Canalicular or ductular plus Hepatocellular +2

PMN infiltration
No/Mild +2
Severe PMN Infiltration 0

Megamitochondria
No Megamitochondria +2
Megamitochondria 0

Abreviations: PMN: polymorphonuclears.

AHHS categories (0–9 points)
Mild : 0–3
Intermediate: 4–5
Severe: 6–9



Note: Histological features included in the AHHS where product of the multivariate logistic regression analysis (Table 2). Weighting of each histological feature was based in the odds ratio of the updated model (training plus test set samples. See model building in Supplementary Data).

Altamirano J1, et Al Gastroenterology. 2014 May;146(5):1231-9. A histologic scoring system for prognosis of patients with alcoholic hepatitis.

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Pathology of acute liver failure

Alberto Quaglia

BSG Annual Liver Pathology Update Meeting, Cheltenham, 6th October 2016