## "Hypoxic hepatitis and pancreatitis"

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## 33 year old woman

- Comes on a Sunday to the ER due to fever and vomiting. "Others in her surroundings have had similar symptoms"
- White blood cell count 24 and CRP 200
- "She wanted to go home and was allowed to do that"
- Sent home without a clear diagnosis but considered to have gastroenteritis, normal liver tests.

#### Arrives a few hours later in the middle of the night

• Now complains of pain under right arcus,

 Was found to have an oxygen saturation of around 80%

No documentation of that she received oxygen. She was left unattended

#### Liver tests

		AST (<35)	ALT (<45)	INR
•	7/1	28		
•	8/1 (4:35)	139		
•	8/1 (13:04)	2162	1107	
•	9/1	2133	1888	3,1
•	9/1	4415	3673	3,8
•	10/1	14510	10078	5,2

- Bilirubin 9 the 7/1 to 67 the 10/1
- LD (lactate dehydrogenase): 915 the 8/1 to 11628 the 10/1

#### CT: pneumonia and fatty liver



# Liver biopsy: centrilobular necrosis and liver steatosis



#### **Evolution of aminotransferases**



**Figure 2.** A typical rise and decline of serum aminotransferases in hypoxic hepatitis (HH). Data derived from the study's index case and diagnosis of HH based on the peak of serum AST.

## Hypoxic hepatitis (HH)

- An acute liver injury, characterized by a massive but transient rise in AST/ALT caused by anoxic necrosis of the centrilobular liver cells
- Cardiac failure, respiratory failure, and toxic-septic shock are the main underlying conditions (90% of cases)
- Untill recently, liver ischemia, i . e. drop in hepatic blood flow was considered the leading and even the sole hemodynamic mechanism responsible for HH and it was generally held that a shock state was required



## Hypoxic hepatitis (HH)



- In reality, other hemodynamic mechanisms of hypoxia, such as arterial hypoxia and dysoxia play an important role, while a shock state is observed in only 50% of cases
- "Ischemic hepatitis and shock liver are misnomers.
- Therapy depends on the nature of the underlying condition
- Prognosis is poor, 50% mortality in hospital (Henrion J, Liver Int 2012)

## Hypoxic hepatitis (HH)

- Septic-toxic shock in 15-30%
- Respiratory failure in approx. 15%
- Increased demand for oxygen can not be met
- Acute liver failure may follow grand-mal seizure due to hypoxic centrilobular necrosis
- A few cases have been reported in patients with extreme anemia
- Obstructive apnea leading to HH due to extreme hypoxemia
- HH reported in anorexia nervosa

#### Tapper et al. The incidence and outcome of ischemic hepatitis. Am J Med 2015



#### Ischemic hepatitis: clinical presentation and pathogenesis Seeto et al. Am J Med 2000;109:109-113.

<mark>A landmark paper</mark>

- A cohort of 31 patients (case group) who met the most commonly accepted definition of ischemic hepatitis (an acute reversible elevation in either ALT or AST >20 times ULN, excluding other causes of acute hepatitis or hepatocellular injury
- Clinical features ALT and AST in a control group of 31 previously healthy patients who sustained major non-hepatic trauma at a major trauma center.
- Both groups of patients had documented systolic blood pressures <75 mm Hg for at least 15 minutes.</li>



#### Results

- Despite marked reduction in blood pressure, no patient in the control group developed ischemic hepatitis.
- The mean peak AST in the control group was only 78 IU, in contrast with a mean peak of 2,088 IU in the case group.
- All 31 patients with ischemic hepatitis had evidence of underlying organic heart disease, 29 (94%) of whom had right-sided heart failure.

#### Conclusions

- Systemic hypotension or shock alone did not lead to ischemic hepatitis in any patient.
- The vast majority of patients with ischemic hepatitis had severe underlying cardiac disease that had often led to passive congestion of the liver.
- These data lead us to propose that right-sided heart failure, with resultant hepatic venous congestion, may predispose the liver to hepatic injury induced by a hypotensive event.





Björnsson HK, et al. A prospective study on the causes of notably raised alanine aminotransferase. Scand J Gastroenterol 2016; 51: 594-600.

 Overall (16%) died, liver-related death in 10%, 35% in HH and 7% in DILI.



In 12 months in Landspitali University Hsopital (n=142) with > 500 IU in ALT

1. Choledocholithiasis: 48/142 (34%)

2. HH: 26/142 (18%)

3. Viral hepatitis, 16 (11%)

4. DILI, 15 (11%)

A significant proportion of patients with choledocholithiasis have markedly elevated alanine aminotransferase Bjornsson HK, Bjornsson ES. Scand J Gastro 2019

- Objective: To determine the frequency and nature of liver enzyme elevations among patients presenting with choledocholithiasis (CDL).
- Methods: A prospective study identified all patients with choledocholithiasis (CDL).
- Patients with radiologically confirmed CDL or a clinical diagnosis of CDL were included.

#### Results

- During the study period, 110 patients had CDL, 60% women, mean age 65 years. Overall 86/110 (78%) had confirmed CDL on imaging and 24/110 (22%) clinically diagnosed.
- Overall 26% had undergone cholecystectomy, median bile duct diameter 10.0 mm, median maximal liver tests: ALT 436, ALP 226, bilirubin 60 μmol/L (<25).</li>
- Overall 9/110 (8%) had ALT ≥1000, 43/110 (39%) ALT levels between 500 and 1000 IU/L and 58/110 (53%) had ALT <500 IU/L.</li>
- Patients with ALT ≥1000 had smaller bile duct diameter of 7 versus 10 mm (p < .001)</li>
- Bile duct diameter was independent predictors of ALT >1000.

#### Conclusions

 Approximately 8% of patients with CDL had markedly elevated ALT. These patients had smaller bile duct diameter. Pronounced ALT elevation is a part of the clinical spectrum of CDL.

#### Prevalence, clinical characteristics and outcomes of hypoxic hepatitis in critically ill patients

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### Background

• Hypoxic hepatitis (HH) is an important clinical entity in patients in the Intensive Care Unit (ICU).



- The aims of the study were to assess the etiology, clinical characteristics and outcomes of HH among patients hospitalized in the ICU of a tertiary hospital.
- Secondary aim was to analyze the effects of concomitant ischemia in other organs than the liver.

#### Definitions

- Hypoxic hepatitis was defined by a rapid, but transient increase in serum aminotransferase activity reaching at least 10 times the ULN in a clinical setting of cardiac, circulatory or respiratory failure.
- The rapid rise was defined as peak AST within 48 h from the occurrence of cardiac, circulatory or respiratory failure. Other causes of liver cell necrosis were excluded.



#### Definitions

- The primary cause of HH was defined as the main contributor to the pathophysiology of HH in each case.
- To identify the primary cause of HH, the major focus was on clinical events and investigations occurring 48 h before the peak value of AST.



#### Results

- Of 9.931 patients hospitalized in the ICU, 159 (1.6%) fulfilled criteria for HH, 89 males (56%), median age 66 (IQR 57-75).
- Inpatient mortality occurred in 85 (53%) and 60 (38%) survived one year.
- Median ICU stay was 5 days (IQR 3-10) and median hospital stay 16 days (IQR 7-32).
- Shock (48%), cardiac arrest (25%), and hypoxia (13%) were the most common causes.

#### **OTHER ISCHEMIC ORGANS**



#### Conclusions

- Hypoxic hepatitis was related to shock in approximately 50% of cases and was associated with high in-hospital mortality.
- HH was commonly associated with ischemia in other organs.
- In-hospital mortality was independently associated with age, lactate and LD.

#### 60-year old woman

- "Last year a 60-year old woman presented to our emergency room with sudden dyspnea and hemodynamic instability and was found to have acute bilateral pulmonary emboli.
- She had no history of abdominal complaints but while in the intensive care unit (ICU) she developed severe upper abdominal pain, elevated lipase and computed tomography (CT) showed signs of pancreatitis.
- This patient motivated us to explore the incidence of IP among patients admitted to the ICU".

#### Ischemic Pancreatitis Is an Important Cause of Acute Pancreatitis in the Intensive Care Unit

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#### Background

- The index case
- Almost only case reports
- One series from a surgical department in Heidelberg, 11 cases, high mortality

(Hackert T, et al. Ischemic acute pancreatitis: Clinical features of 11 patients and review of the literature. Am J Surgery 2009;197:450-454

#### Methods and definitions

- All patients with first time AP between 2011 and 2018 in the ICU of Landspitali Hospital, Iceland were retrospectively included.
- IP as an etiology required a clinical setting of circulatory shock, arterial hypotension, hypovolemia and/or arterial hypoxemia (PaO2 of 60 mmHg (8.0 kPa), or less) prior to the diagnosis of AP without prior history of abdominal pain to this episode.
- Other causes of AP were ruled out. IP patients were compared to patients with AP of other etiologies, also hospitalized in the ICU.

#### Results

- Overall 67 patients with AP were identified (median age 60yr, 37% females), 31% idiopathic, 24% alcoholic, 22% IP, 15% biliary and 8% other causes.
- Overall, 15 (22%) fulfilled the predetermined criteria for IP, 9 males (64%), median age 62 years (IQR 46-65).

#### Results

- IP was preceded mainly by systemic shock (73%). Other causes included dehydration, hypoxia or vessel occlusion to the pancreas.
- Necrosis of the pancreas was rare with one patient requiring pancreatic necrosectomy. Inpatient mortality was higher among patients with IP than in other patients with AP (33% vs. 14%, p=0.12).

#### Conclusions

 Ischemic pancreatitis was found in a significant proportion of AP patients hospitalized in the ICU.

 The main causes of IP were systemic shock and hypoxia. IP was associated with approximately 30% mortality.

#### Professor Andrade Muchas gracias



## 51 year old man

- Congenital aortic valve disease
- Hospitalized 5/5 with chest pain, dyspnea and a.flutter.
- Cardiac echo 6/5 when in a. flutter, 140/min.
  Significant aortic stenosis, ejection fraction of left ventriculum 20%, 7/5=30%
- Found to have an occlusion of the right coronary artery

#### Development

- Received amiodarone, 150 mg bolus and then I v 24 klst. skv. protocol. Converts to sinus rythm
- Pain in the upper right abdomen, shoulder and back. Very tender over the liver
- Two days later sky high AST=19068 and ALT=7999

#### No episode of hypotension or hypoxia

#### Is it Hypoxic hepatitis or Amiodaron toxicity?

Dagur og tími	Hiti (°C)	Púls (slög/	BÞ(mmHg
13.05.2024 09:19	36,4 eyra	75	104/50
08.05.2024 12:33		45	102/74
08.05.2024 06:39	36,5 eyra	52	111/76
07.05.2024 21:37	36,7	59	119/79
07.05.2024 13:57	36,9	65	137/91
07.05.2024 10:31		63	142/90
07.05.2024 10:01		63	152/89
07.05.2024 09:50		64	137/91
07.05.2024 09:17	36,5	72	134/94
07.05.2024 09:07		73	132/94
07.05.2024 03:39		85	117/82
06.05.2024 21:24	36,5	91	121/83
06.05.2024 19:24		93	138/78
06.05.2024 16:22	36,5	95	136/88
06.05.2024 13:42	36,7	92	114/82
06.05.2024 07:03		140	144/102
06.05.2024 07:00		162	137/101
06.05.2024 04:30	36,6	112	119/73



#### Professor Andrade Muchas gracias

