Clinical update no. 557
8 April 2020

INTENTIONAL OVERDOSE OF 20 X PARACETAMOL APPROX 30HRS AGO. DENIES ANY OTHER DRUG OR ALCOHOL USE. STATES FEELING DEPRESSED,

	12:10	18:00
Bili Tot.	128H	101H
ALT	5895H	6750H
AST		17547H
ALKP	188H	147H
Old GGT		
New GGT	473H	437H
Protein	79	68
Albumin	49	40
Globulin		
Ammonia	275H	(10-50)
PT	26H	39H
INR	2.2H	3.3H

Nurse Assess:

CENTRAL ABDO PAIN, 1X VOMIT AND MULTIPLE EPISODES OF DIAHORREA SINCE 0500. DENIES FEVERS. DENIES URINARY SYMPTOMS. TOLERATES ORAL FLUID. STATES WAS FORAGING FOR MUSHROOMS AND ATE SAME AT 1700 LAST NIGHT.

Time:	*UNK*	16:18	23:30	06:45	14:20
Bili Tot.	24H	22H	27H	34H	44H
ALT	12	60H	183H	532H	894H
AST				741H	

Acute liver injury can be unexpected such as with a history of taking just 20 paracetamol tablets. *Amanita* mushroom poisoning is seen in Canberra and some other areas and can be fatal; a history of possible exposure warrants checking LFTs.

Acute liver failure is a bit more serious.

Acute liver failure

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Acute liver failure refers to *severe hepatocellular injury, coagulopathy and altered mentation in the absence of chronic liver disease*. The time course and history distinguishes from a deterioration of chronic liver failure. Causes include paracetamol toxicity, hepatic ischaemia, viral and autoimmune hepatitis, and drug-induced liver injury including from dietary supplements. Its rarity means few randomised trials and an opinion based approach. Liver transplant may be required in up to 30%.

Paracetamol accounts for half of total acute liver failure. Of other drug causes, amoxicillin/clavulanate comes next, and then drugs less commonly used (nitrofurantoin, isoniazid, and trimethoprim-sulfamethoxazole).

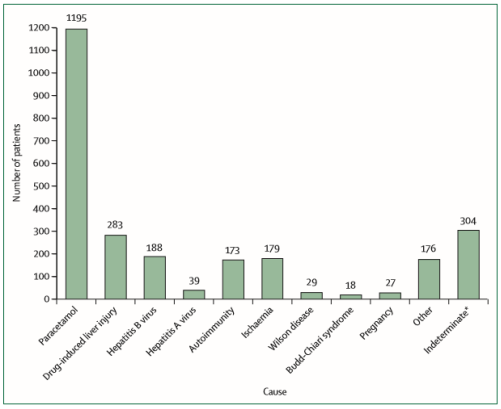

Figure 1: **Causes of acute liver failure, as recorded by the site principal investigator in the US Adult Acute Liver Failure Study Group Registry**
Data were collected between Jan 1, 1998 and March 31, 2019. The total number of patients enrolled is 2614; paracetamol accounts for 46% of cases, 12% of cases have indeterminate causes, and drug-induced liver injury accounts for 11% of cases. *The number of patients with acute liver failure with an indeterminate cause decreased to 161, or 5·5% of the total, after review.[1]

Hepatitis A and B together cause less than non-paracetamol drug causes, with no clear cause in about 5%.

Hepatic ischaemia

Shock including sepsis can lead to a hyper acute but self- limited hepatic injury. With few exceptions (e.g. heat stroke, cocaine toxicity), the differential diagnosis of transaminase > 3000 IU/L and bilirubin < 85 µmol/L is ischaemia and paracetamol. Acute kidney injury usually occours also.

Patterns of injury are shown.

Median	Paracetamol	Ischaemia	Drug	Hep B
ALT IU/L	3780	2311	654	1410
Bili µmol/L	73	65	330	320

Management of liver failure

Outcomes have improved with ICU care and transplantation, and despite lower use of vasopressors, blood products, ventilation, and intracranial pressure monitors. Liver support devices can improve biochemical indices but do not improve recovery.

High-volume plasma exchange provides liver support and trials show improved outcomes.

Hypotension is usually from volume depletion and responds to IV saline and vasopressors,

with noradrenaline preferred, and then vasopressin; give hydrocortisone if ongoing hypotension to address adrenal insufficiency.

Intracranial hypertension due to cerebral oedema is multifactorial, and relates to hyperammonaemia. Brain CT is not sensitive in diagnosis. Prophylaxis is important because treatment is ineffective. Nurse with 30° head elevation with the neck in neutral position to facilitate venous drainage of the brain. Hepatic encephalopathy drives central hyperventilation and respiratory alkalosis, which improves autoregulation of the cerebrovascular circulation. Lactulose and nonabsorbable antibiotics (e.g. rifaximin) are reasonable interventions but are not tested. Hyponatraemia promotes oedema and should be corrected with hypertonic saline aiming at Na 145–155 mEq/L, which gave benefit compared to controls at 137–142 mEq/L.

Early renal replacement therapy (haemofiltration) is of benefit if oliguria, volume overload and significant hyperammonaemia (>150 μmol/L), with each associated with cerebral oedema. Intracranial pressure monitoring is controversial, as although they lead to interventions to reduce ICP, there is no improved outcome. Standard ammonia-lowering drugs have not been tested for cerebral oedema.

IV mannitol (0·5–1·0 g/kg bolus) should be given at the first sign of raised ICP (>20 mm Hg, or neurological deterioration, such as with pupillary changes. Hypertonic saline boluses also reduce ICP. Hypothermia may bridge a patient to transplantation (32–33°C).

Acute kidney injury complicates acute liver failure in 70%, including with agents toxic to both liver and kidney such as paracetamol and amatoxin (mushrooms). Hepatorenal syndrome (seen with cirrhosis) can also occur with acute liver failure from any cause due to vasoactive cytokines leading to hypoperfusion.

Prophylactic antibiotics do not reduce infection. Broad spectrum cover is required to treat infection. Despite raised INR and thrombocytopaenia, bleeding complications are uncommon (10%) and not usually clinically significant. Both pro- and anti-coagulant proteins are involved. Use of blood products and transfusion has declined.

Lactic acidosis as a marker of impaired tissue oxygenation is a poor prognostic marker and might correct with vasopressors targeting MAP, usually 65 mm Hg.

Threshold for poor prognosis or need for liver transplantation

Kings College Criteria (for paracetamol):

pH <7·30, or all of the following:

INR >6·5, creatinine 300 umol/L, and grade 3 or 4 encephalopathy.

Some useful points for Cirrhosis

The INR does not adequately assess haemostasis in cirrhosis as deficiencies of the anticoagulation system are not reflected by a prolonged INR; prophylactic FFP is not recommended. Aim for platelets > 50 if active bleeding or for minor invasive procedures.

Albumin 8 g/L ascites removed for large volume paracentesis (>5 L). 100ml 20% albumin has 20 g, so give 100 ml per 2.5 L.

Give antibiotics (e.g. ceftriaxone) if GI bleeding, which reduces infection, rebleeding, and mortality.

Do not use of high ammonia levels alone to diagnose hepatic encephalopathy due to false +ve results; a normal level will exclude.

Use short acting drugs for intubation (propofol) and avoid benzodiazepines.

For spontaneous bacterial peritonitis give albumin in addition to antibiotics (1.5 g/kg day 1 then 1 g/kg on day 3. For 70kg give approx. 100g albumin = 500ml 20% albumin day 1, then 300ml day 3).

Serum creatinine tends to overestimate renal function, and lags GFR by hours to days with fluid overload. Interpret with caution.