# Acute Liver failure - Full Clinical Guideline

Reference no.:CG-T/2023/187

It can sometimes be difficult to distinguish whether a patient has an acute liver disease as opposed to an acute deterioration on a background of chronic liver disease. The aetiologies overlap, but there are important differences in the investigation and management of patients. Acute liver failure is rare (incidence 1-8 per million population/ yr) in comparison to chronic liver disease.

**Definition of acute liver failure (ALF):**
An illness of less than 26 weeks duration, in patients without pre-existing cirrhosis, which includes evidence of coagulopathy (INR ≥ 1.5) and encephalopathy.
It is common to subdivide ALF based on the time from onset of jaundice to encephalopathy, though how helpful this is in determining cause or prognosis is disputed.

- **Hyperacute** (< 7 days) - e.g paracetamol, ischaemia (often has best prognosis)
- **Acute** (7-28 days) – e.g. Hepatitis A and B
- **Subacute** (> 28 days, < 24 weeks) - e.g idiosyncratic drug induced liver injury (DILI), seronegative hepatitis. (Often regarded as having worse outcome).

**Aetiology of ALF:** (N.B.: approximately 15% of patients have no discernible cause)

- **Infection:** HAV, HBV (± HDV), HEV, HSV, HHV 6, CMV, EBV, VZV, parvovirus B19, haemorrhagic fevers and malaria
- **Drug/ toxin (dose dependent):** Paracetamol (POD) - including pharmacological doses in low BMI patients, *Amanita phalloides* (mushroom poisoning), tetracyclines, *Bacillus cereus* ("Fried rice syndrome"), $CCl_4$
- **Drug/ toxin (idiosyncratic - most seen within 6 months of use):** includes Halothane, anti-TB therapy, sulphonamides, co-amoxiclav, propylthiouracil, macrolides, valproate, NSAIDs, disulfiram, thalidomide, Beta-inteferon, HAART, Ecstasy, cocaine, herbal remedies.
- **Vascular:** Ischaemic hepatitis (following period of hypotension - ALT often markedly raised and rapidly improve following stabilisation of circulatory problem), Budd-Chiari, right heart failure, veno-occlusive disease
- **Metabolic:** Wilson's disease, acute fatty liver of pregnancy, HELLP
- **Miscellaneous:** Autoimmune (including seronegative) hepatitis, malignant infiltration, sepsis, heat stroke

**Clinical features:**
Often non-specific, but include anorexia, fatigue, abdominal pain, jaundice and fever, before progressing to hepatic encephalopathy (HE).

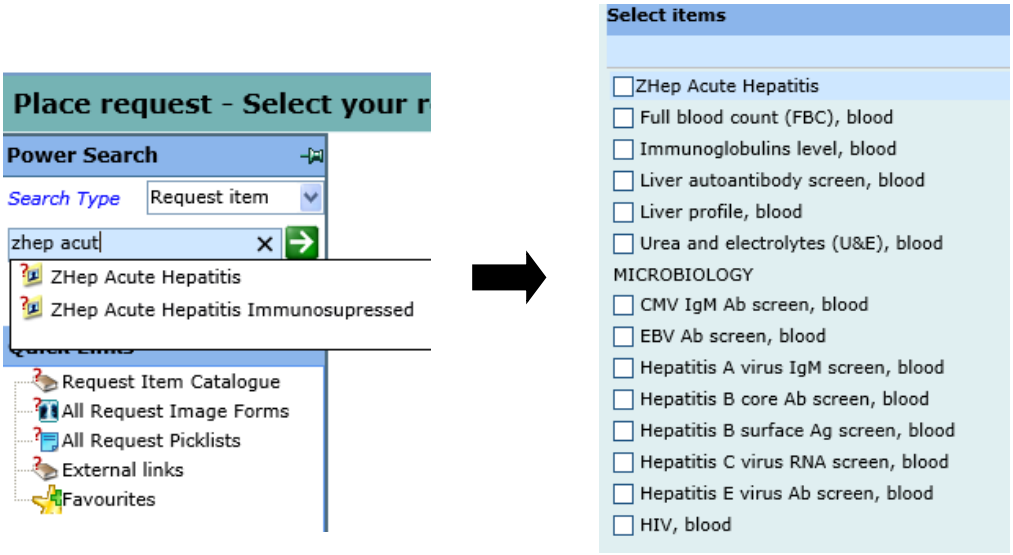
**Assessment:**

- Review possible exposure to viruses (new partner, IVDU, travel, unwell contacts) or drugs / toxins (including OTC, herbal and illicit drugs) - may require phone call to GP/ carers.
- Alcohol history
- Psychiatric history - is there any likelihood of paracetamol overdose
- Search for stigmata of Chronic liver disease and signs of superadded infection (spider naevi can appear rapidly in ALF and do not always indicate CLD)
- Is there Hepatic Encephalopathy (HE)? - see appendix - number connection test

**Investigations:**

- **To assess severity:** LFTs, UEs, HCO3, Mg++, PO4, Glucose, INR, Culture urine/ blood
  ABG (in hyperacutes) with lactate
- **To assess cause:** There are 2 zHep order sets for acute hepatitis depending on whether or not the patient is immunosuppressed + need U/S with Doppler of vessels. In addition consider need for:

  Paracetamol levels
  Pregnancy test
  Slit lamp examination by ophthalmologist for KF rings (patient < 45 yrs)
  Urine for *Amanita phalloides* toxin if suspected
  A transjugular liver biopsy may be useful in the sub-acute patient who is stable




**Management of ALF:**

Medical treatment is in the main supportive while being vigilant for signs of superadded infection and of a deteriorating patient in need of transplantation.

**Monitoring:**

- Close monitoring of BP, Pulse, temp, urine output and BMs (2hrly in the hyperacutes and 1hrly if <3.5mmol/L)
- At least daily formal assessment for encephalopathy
- At least daily UEs, LFTs, INR ± HC03/ Lactate. Frequent monitoring of $PO_4$ and $Mg^{++}$

**Haemodynamics:**

- Volume replacement as needed (0.9% saline is the most appropriate resuscitation fluid, avoid Hartmanns due to lactate content)
  - Patients with ALF have a low systemic vascular resistance similar to that seen in sepsis. POD pts in particular often require aggressive fluid replacement
- Avoid 5% Dextrose because of risk of hyponatraemia (higher concentration dextrose infusions may be needed to maintain BM > 5mmol/l)
- Pressor support to maintain MAP 75 mmHg - Noradrenaline NA (+ terlipressin in NA refractory cases)
- Consider possibility of adrenal insufficiency

**Coagulopathy:**

- Vitamin K 10mg iv od for 3/7 should be given to all patients with coagulopathy - will not improve INR unless the patient has vitamin K deficiency
- **AVOID FFP** unless patient bleeding / having invasive procedures (line insertion does not need FFP cover) due to prognostic value of PT/ INR
- Transfuse platelets in absence of bleeding if < 10,000 $mm^3$, or if < 50,000 $mm^3$ and bleeding

**Infection:**

- Surveillance for and prompt antimicrobial treatment of infection required
- Hyperacute cases should receive prophylactic antibiotics (Co-amoxiclav 1.2 g tds unless penicillin allergic) and antifungals (oral or iv fluconazole 200mg od)

**Encephalopathy (see guidance on encephalopathy):**

- Avoid metoclopramide and other centrally-acting anti-emetics, can precipitate encephalopathy
- Patients with any degree of encephalopathy should be discussed with the Liver transplant unit at Queen Elizabeth Hospital, Birmingham (0121 6272000) as they may require urgent transfer
- Patients in whom transplantation not appropriate will continue to be managed in Derby
- Grade I/II (Cerebral oedema seldom seen) - Avoid excess stimulation/ sedatives
  - Lactulose
  - Consider prophylactic antibiotics
- Grade III/ IV (≈ 30% of grade III and 70% grade IV have cerebral oedema)
  - Require tracheal intubation and ICU care if appropriate for transplant or recovery anticipated
  - Treatment of ↑ ICP includes induction of hypernatraemia (145-155mEq/L), Manitol, hyperventilation and hypothermia

**Other:**

- All patients should receive acid suppression with a PPI
- Consider N-acetyl cysteine (NAC) in non-paracetamol ALF - 150mg/kg/day

**Management of specific causes:**

**Paracetamol (acetaminophen):** See paracetamol overdose guidance. The pattern of disease is that of a severe hepatitis and coagulopathy (INR normally peaks on day 3. Renal failure is frequent (acute tubular necrosis (ATN) and direct tubular toxicity). Encephalopathy normally peaks on day 5-7. A cholestatic picture with elevated bilirubin, ALP and GGT are seen in the recovery period.

**Hepatitis A:** May present as a hyper-acute picture with HE, an isolated hepatitis or severe cholestasis. A severe pattern of disease is more likely if exposure happens outside of childhood. There may be a bi-phasic illness with later deterioration. Hepatitis A infection in patients with CLD may precipitate ALF and should be considered in patients with CLD who decompensate. Patients with CLD should, therefore, be offered vaccination.

**Hepatitis B (acute or re-activation):** May present with severe hepatitis or ALF. The disease may be de-novo infection, super infection with delta virus or reactivation of hepatitis B in a chronic carrier (the latter can be seen after exposure to Chemotherapy/ immunosuppressant agents, including steroids). The finding of a positive core IgM antibody is diagnostic. Consideration should be given to antiviral therapy (Tenofovir or Entecavir) in patients with ALF.

**Hepatitis E:** This is now more common than HAV as cause of sporadic infective hepatitis in UK. HEV is classically acquired through drinking faecally contaminated water, but in the UK it appears to be primarily a zoonosis, acquired through consuming undercooked pork or wild boar. Middle aged males appear to be the most susceptible. Clinical manifestations of HEV typically include jaundice, fever, malaise, abdominal pain and vomiting. Neurological symptoms are seen in up to 30% of infections and can include Guillain-Barre syndrome, brachial neuritis and ataxia. The majority of infections are self-limiting, but purported high mortality in pregnant women in India. Chronic infection can develop in immunosuppressed patients especially recipients of solid-organ transplants.

**Autoimmune hepatitis:** 30% of patients will have negative autoantibodies (seronegative). Diagnosis requires a liver biopsy. Initial treatment is with steroids, which we may choose to start immediately post biopsy where there is a high clinical suspicion and viral serology is negative). Patients who continue to deteriorate despite steroids should be referred to transplant centre (and consider stopping steroids). See autoimmune hepatitis guidance

**Liver Failure in association with Pregnancy:** Pregnancy specific causes of ALF include pre-eclampsia, HELLP and acute fatty liver of pregnancy. See guidance on liver disease in pregnancy.

**Mushroom poisoning (*Amanita phalloides*):** Transplantation is often the only life-saving option. Consider Penicillin G 300,000-1,000,000 units/kg/day iv for 3-4 days.

**Wilson's disease:** The fulminant presentation of Wilson's disease is considered uniformly fatal without transplantation. The typical patient will be young with an abrupt onset Coombs negative haemolytic anaemia with jaundice. Very low ALP and Uric acid levels, together with renal impairment (released copper causing tubular damage) are also typical. Diagnosis can be difficult but assessment includes caeruloplasmin (normal in ≈ 15% of patients and reduced in ≈ 50% of patients with other forms of ALF), urine and serum copper and slit lamp examination (KF rings present in 50%). Pencillamine treatment is not recommended in ALF due to risk of hypersensitivity. Albumin dialysis, continuous haemofiltration, plasmapheresis/ exchange can all acutely lower serum copper, but prompt consideration of transplantation. See guidance on long term management of Wilsons disease

**Budd-Chiari syndrome (hepatic venous outflow obstruction):** May be an acute or sub-acute presentation. See vascular disorders of the liver guidance.

**Prognostic criteria in ALF**

O'Grady's King's College Criteria identify patients who have poor prognostic criteria in acetaminophen (paracetamol) and non-acetaminophen aetiologies and is listed below. Ideally patients should be discussed with a transplant center before meeting criteria.

| Acetaminophen ALF | Non-acetaminophen ALF |
|---|---|
| • Arterial pH < 7.30 more than 24 hours after OD and after appropriate fluid resuscitation<br><br>OR all 3 of the following<br><br>• PT > 100 (INR>6.5)<br><br>• Creatinine > 300µmol/L or anuria<br><br>• Grade III or IV encephalopathy<br><br>In addition<br><br>• Arterial lactate >3.5mmol/L at presentation or >3.0 mmol/L 12 hours post resuscitation in presence of HE (exclusion of other causes e.g. pancreatitis, GI ischaemia) | • HE and PT > 100 (INR >6.5)<br><br>Or any 3 of following 5 criteria<br><br>• Age < 10 or > 40 years<br><br>• Bilirubin > 300µmol/L<br><br>• Onset of jaundice to encephalopathy > 7 days (any grade of HE)<br><br>• INR > 3.5<br><br>• Aetiology: seronegative , DILI<br><br>*acute Wilson's, Budd-Chiari and pregnancy associated ALF considered separately. |

**Further reading:** AASLD Position Paper: The management of Acute Liver Failure: Update 2011. Hepatology 2011.
EASL clinical practice guideline on Hepatitis E 2018

Documentation Controls **(these go at the end of the document but before any appendices)**

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<tr><td>3</td><td>2022</td><td>Liver Management Group</td><td colspan="2">Previous version of guideline expired</td></tr>
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