

Module 3. Acute and Chronic Liver Failure

Chapter 10. Acute Liver Failure and Acute on Chronic Liver Failure

10.1 Acute Liver Failure (ALF)

Definition

- The most widely accepted definition of ALF includes¹
 - evidence of coagulation abnormality (INR) ≥ 1.5 AND
 - any degree of mental alteration (encephalopathy)
 - in a patient without preexisting cirrhosis AND
 - with an illness of <26 weeks duration

Epidemiology

- **Drugs** [see Chapter 9.2]
 - **Acetaminophen** is most common cause of ALF in North America
 - Alcoholics are at increased risk of toxicity and accidental overdoses do worse than intentional overdoses (suicide attempts)
 - Treatment is with N-acetylcysteine (NAC)
 - Idiosyncratic drug reactions can occur with prescribed, over the counter (OTC) medications, herbals and dietary supplements as well as illicit drugs (cocaine or MDMA = ecstasy)
- Mushroom poisoning
 - **Amanita phalloides** found in late summer (more common in Europe but can be seen in Eastern Canada)

- Anticholinergic symptoms (diarrhea, vomiting, sweating) with ALF 4-8 days after ingestion
 - Treatment is with penicillin G or silibinin (milk thistle)
- **Viral hepatitis** *[see Chapter 6]*
 - 12% of ALF in USA
 - HAV – more common in older adults or those co-infected with HCV
 - HBV – can occur with acute infection or flares of chronic disease after chemotherapy or immunosuppression
 - Treatment with entecavir or tenofovir
 - HCV – very rare
 - HDV – in HBsAg positive patients as a co-infection or super-infection
 - HEV – high rate of ALF in pregnant women
 - Other non A-E viruses
- **Wilson's disease** *[see Chapter 8.2]*
 - Suspect in a young patient with hemolytic anemia (copper released from liver is toxic to red blood cells) with high bilirubin (↑ unconjugated) and low ALP
 - KF rings are very helpful with diagnosis as ceruloplasmin is not always low and 24 hour urine copper can be falsely high from other causes of ALF
 - Treatment is liver transplant (almost none survive without LT)
- **Autoimmune Hepatitis** *[see Chapter 9.1]*
 - Often seen in young patients (more likely in women) and may have positive ANA or ASMA and elevated IgG

- Liver biopsy (done via transjugular route) is needed to establish the diagnosis

NOTE: this is typically the only situation where a liver biopsy is helpful in ALF

- Treatment with prednisone

- **Ischemia**

- **Shock liver** from cardiovascular collapse (e.g. after cardiac arrest and CPR)
- **Budd Chiari Syndrome (BCS)** from thrombosis of hepatic veins (outflow of the liver)
 - Patients present with RUQ pain, jaundice, weight gain and ascites

NOTE: this is the only cause of ALF where ascites is a prominent feature

- Associated with hypercoagulable states such as thrombophilia, malignancy or connective tissue diseases
- Treatment is with anticoagulation and/or transjugular intrahepatic portosystemic shunt (TIPS) [*see Chapter 14.2*]

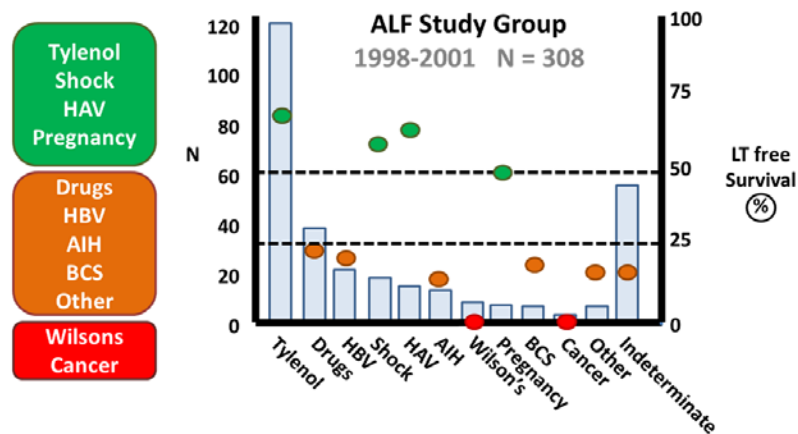
- **Pregnancy**

- Occurs in 3rd trimester of pregnancy
- **Acute Fatty Liver of Pregnancy (AFLP)** (microvesicular steatosis)
- **HELLP** (hemolysis, elevated liver enzymes, low platelets) in a patient with pre-eclampsia
 - Treatment is immediate delivery of the baby

- **Malignancy**

- Massive infiltration by metastatic cancer (breast, small cell lung cancer, melanoma, lymphoma, myeloma) can rarely cause ALF
 - Prognosis is poor

• Etiology and Prognosis of ALF in USA



Management

• Initial testing

- Liver enzymes (ALT, AST, ALP) and liver function tests (bilirubin, albumin, INR), electrolytes, creatinine, lipase
- For prognosis = INR, ammonia (arterial), arterial blood gas (ABG) for pH, lactate
- For defining etiology = acetaminophen level, toxicology screen, IgM anti-HAV, HBsAg, IgM anti-HBc, anti-HCV, anti-HDV, anti-HEV, ceruloplasmin, ANA, ASMA, IgG, pregnancy test, Doppler US of liver
- For pre-liver transplant evaluation = CBC, type & screen, HIV testing

• Prognosis

- Etiology predicts survival free of liver transplant (see above)
 - >50% = acetaminophen, shock liver, HAV, pregnancy
 - <25% = drugs, HBV, AIH, BCS, other or indeterminate
 - 0% = Wilson's (all need LT), malignancy (not LT candidates)

- Grade of encephalopathy (West Haven classification) on admission predicts survival
 - I = 70%
 - II = 60%
 - III = 40%
 - IV (coma) = 20%
- Serum ammonia (NH₃) level predicts hepatic encephalopathy (HE) and the development of intra-cranial hypertension (ICH)
 - <75 = rarely develop ICH
 - >100 = predicts development of HE
 - >200 = predicts ICH
- **King's College Criteria** are very sensitive and specific for predicting need for LT

Acetaminophen

- Lactate >3.5
or
- pH < 7.3 or lactate >3
or
- Grade III or IV HE and
 - INR > 6.5
 - Creatinine > 300

Non-acetaminophen

- INR > 6.5 with HE
or
- Any 3 of 5 with HE
 - Age <10 or >40 yrs
 - Bili > 300
 - Coag: INR > 3.5
 - Duration jaundice to HE > 7 days
 - Etiology: Non A-E, other drug

Adapted from O'Grady J, et al. Gastroenterology 1989; 97(2): 439-45.

• Complications

- Neurologic – hepatic encephalopathy and cerebral edema (leading cause of death)
- Hemodynamic – shock
- Hematologic – coagulopathy, disseminated intravascular coagulation (DIC)
- Renal – common (especially in acetaminophen overdose)

- Infectious – bacterial and fungal
- Metabolic – acidosis, alkalosis, hypoglycemia, hypophosphatemia
- **Management** should be done in the Intensive Care Unit (ICU)
 - NAC may be used in non-acetaminophen related ALF (but less evidence of benefit)
 - Lactulose of little benefit for encephalopathy, unlike cirrhosis [*see Chapter 14.3*]
 - Intracranial pressure (ICP) monitoring is done by many LT centres but can be associated with intracerebral bleeding
 - Medications (pressors) are used to maintain mean arterial pressure (MAP) and cerebral perfusion pressure (CPP)
 - High ICP can be treated with hypernatremia, hypothermia and hemofiltration (HHH) using continuous venous hemodialysis (CVHD)
- **Management of HE depends on grade of HE**

Grade I / II HE

- Transfer to LT centre
- Brain CT
- Avoid stimulation
- Avoid sedation
- NAC
- Lactulose (???)
- Watch for infections
- Antibiotic prophylaxis (???)

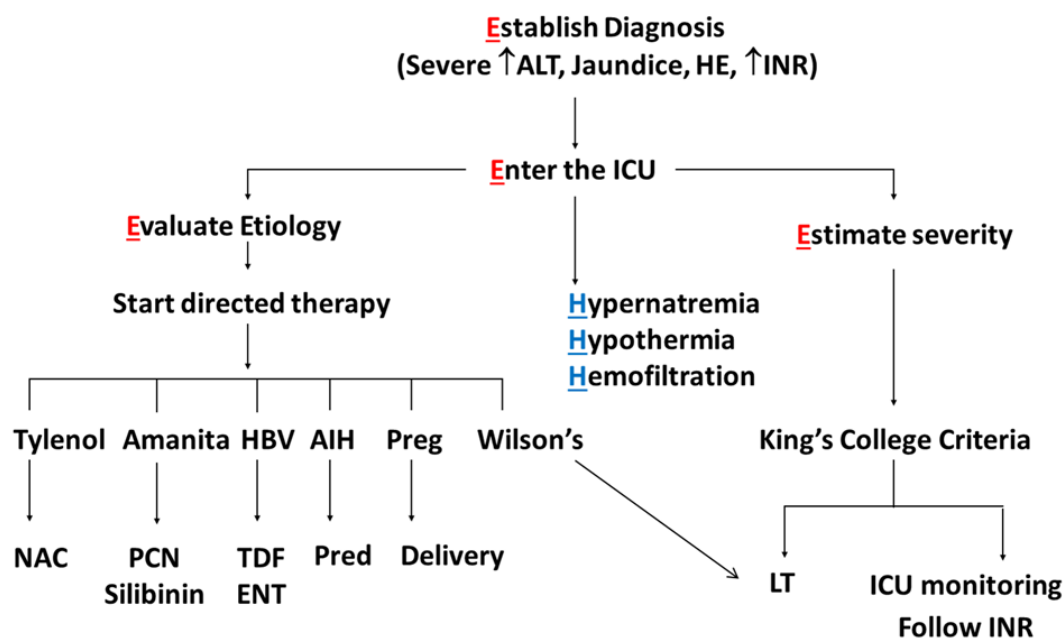
Grade III / IV HE

- Intubation
- ↑ head of bed (30°)
- ICP monitoring (?)
- Maintain MAP + CPP
- Treat seizures
- If ICH bridge to LT with (HHH)
 - Hypernatremia (Na 145-155)
 - Hypothermia (32-34°C)
 - Hemofiltration (CVHD)

- **Liver Transplant (LT)** is most important advance in therapy (5% of LT activity in Canada)
 - Survival 60 - 80% at 1 year, which is less than with chronic liver diseases
 - Patients with ALF receive priority and there is national sharing of organs for these patients

Summary

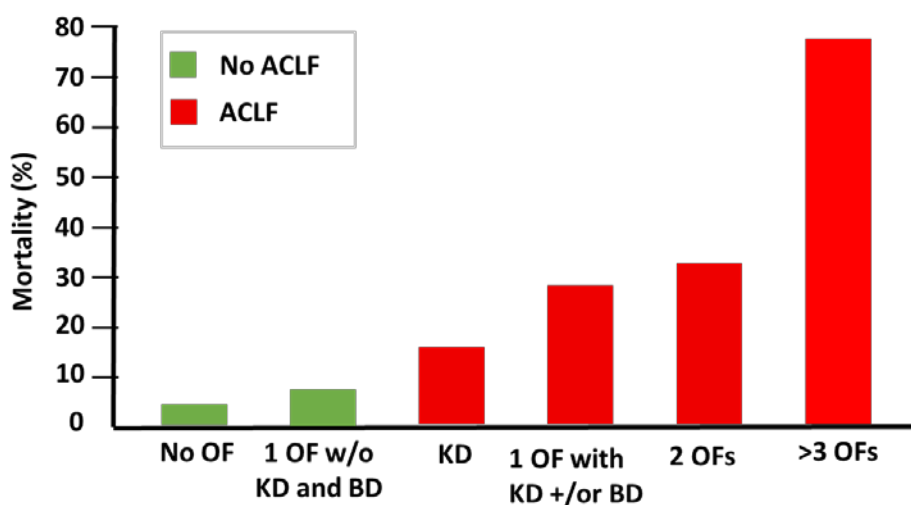
- Below is an algorithm for the management of ALF. **REMEMBER:** four “E”s and three “H”s



10.2 Acute on Chronic Liver Failure (ACLF)

Definition

- Syndrome of acute decompensation of a chronic liver disease
- Associated with organ failure (OF) including liver failure, kidney dysfunction (KD), brain dysfunction (BD) from hepatic encephalopathy, coagulation abnormalities, circulation and respiratory failure
- Has high 1 month mortality (looks like ALF)
- Multiple definitions⁴



Adapted from Hernaez R, et al. Gut 2017; 66(3):541-553

Etiology

- Alcohol and chronic viral hepatitis are most common underlying liver problem
- Triggers include sepsis, active alcohol consumption, relapse of viral hepatitis, GI bleeding
 - No identifiable cause is found in 20-40%
- **Pathogenesis** involves an excessive systemic inflammatory response

Prognosis

- Scoring systems (beyond MELD and Child Pugh) have been developed to predict prognosis

- ACLF grade is based on number of organ failures (OF)
 - Grade 1 = kidney failure (KF), single OF without severe HE, or severe HE alone
 - Grade 2 = 2 OFs
 - Grade 3 = 3 OFs
- Chronic Liver Failure – Sequential Organ Failure Assessment (CLIF-SOFA) score has been simplified into the CLIF Consortium Organ Failure (**CLIF-C OF**) score

Organ	Variable	1 point	2 points	3 points
Liver	Bilirubin (mg/dL)	<6	6 – 12	>12
Kidney	Creatinine (mg/dL)	<2	2 – 3.4	≥3.5
Brain	HE grade	0	1 – 2	3 – 4
Coagulation	INR	<2	2 – 2.4	≥2.5
Circulation	MAP (mmHg)	≥70	<70	Vasopressors
Respiratory	PaO ₂	>300	≤300 – 200	≤200

Management

- No specific therapy
 - Must identify and treat precipitating cause
 - Support of organ failure in ICU
- Prognosis evident by Day 3 – 7
 - Consider liver transplantation
 - Liver support systems have not demonstrated clear benefit

Abbreviations

ABG – arterial blood gas	ICH – intra-cranial hypertension
ACLF – acute-on-chronic liver failure	ICP – intracranial pressure
BCS – Budd Chiari Syndrome	ICU – intensive care unit
CLIF – chronic liver failure	KD – kidney dysfunction
CPP – cerebral perfusion pressure	MAP – mean arterial pressure
CT – computerized tomography	OF – organ failure
CVHD – continuous venous hemodialysis	PCN – penicillin G
DIC – disseminated intravascular coagulation	SOFA – sequential organ failure assessment
HE – hepatic encephalopathy	TIPS – transjugular intrahepatic portosystemic shunt
HHH – hypernatremia, hypothermia, hemofiltration	

Figure Citations

ALF Etiology and Prognosis. Adapted from Ostapowicz G, Fontana RJ, Schiodt, et al. U.S Acute Liver Failure Study Group. Results of a prospective study of acute liver failure at 17 tertiary care centers in the United States. *Ann Intern Med* 2002; 137(2): 947-54.

King's College Criteria. Adapted from O'Grady JG, Alexander GJ, Hayllar KM, Williams R. Early indicators of prognosis in fulminant hepatic failure. *Gastroenterology* 1989; 97(2): 439-45.

ACLF 1 Month Mortality. Adapted from Hernaez R, Sola E, Moreau R, Ginès P. Acute-on-chronic liver failure: an update. *Gut* 2017; 66(3):541-553.

References

1. Polson J, Lee WM, American Association for the Study of Liver Disease. AASLD position paper: the management of acute liver failure. *Hepatology* 2005; 41(5): 1179-97.
2. Lee WM, Stravitz RT, Larson AM. Introduction to the Revised American Association for the Study of Liver Diseases Position Paper on Acute Liver Failure 2011. *Hepatology* 2012; 55(3): 965-967. European Association for the Study of the Liver.
3. EASL Clinical Practical Guidelines on the management of acute (fulminant) liver failure. *J Hepatol* 2016; 66(5): 1047-1081.
4. Hernaez R, Sola E, Moreau R, Gines P. Acute-on-chronic liver failure: An update. *Gut* 2017; 66: 541-533.