Hepatic Failure Management [created by Paul Young 02/10/07]

Hepatorenal syndrome

- Hepatorenal syndrome is the development of renal failure in a patient with advanced liver disease.
- Hepatorenal syndrome is characterized by impaired renal function, abnormalities in the arterial circulation, and activity of the endogenous vasoactive system
- Divided into two types (type 1 is rapidly progressive; type 2 is slowly progressive)

Epidemiology:
- The prevalence of hepatorenal syndrome in patients with end stage cirrhosis ranges between 7% and 15%

Risk factors:
(i) Na and H2O retention (indicated by a urinary Na of <5 mEq/L and dilutional hyponatremia),
(ii) low mean arterial blood pressure,
(iii) poor nutrition,
(iv) reduced glomerular filtration rate,
(v) high plasma renin activity, and
(vi) esophageal varices.

Diagnostic criteria:

Major criteria
- Chronic or acute liver disease with advanced hepatic failure and portal hypertension
- Low GFR defined by serum creatinine >130 mmol/l or creatinine clearance <40 ml/min
- Absence of shock, bacterial infection and recent treatment with nephrotoxic drugs
- No sustained improvement of renal function after expansion with 1.5 l isotonic saline
- Proteinuria <0.5 g/day, and no ultrasonographic evidence of renal tract disease

Additional criteria[a]
- Urine volume <500 ml/day
- Urine sodium <10 mmol/l
- Urine osmolality > plasma osmolality
- Urine red blood cell count <50 per high power field
- Serum sodium <130 mmol/l

[a] The additional criteria relate to factors that are commonly present, but are NOT required for the diagnosis.

Treatment:
(i) dialysis
(ii) liver transplant
(iii) TIPS
(iv) iv clonidine has been shown to improve GFR by 25% (oral is ineffective)
(v) midodrine / octreatide / terlipressin
(vi) albumin administration

Hepatic encephalopathy

- Hepatic encephalopathy involves a wide range of neuropsychiatric changes in patients with significant liver dysfunction, ranging from subtle cognitive abnormalities to coma

types
(i) Type A is related to acute liver failure.
(ii) Type B occurs in the setting of normal liver histology and the presence of a hepatic vascular bypass, such as portocaval shunting.
(iii)Type C hepatic encephalopathy is due to cirrhosis,
- acute encephalopathy is usually precipitated by an identifiable trigger
- chronic encephalopathy usually involves a recurrent and fluctuating course.

grading

Grade	Features
I	Mild or episodic drowsiness, impaired intellect, concentration and psychomotor function, but rousable and coherent
II	Increased drowsiness with confusion and disorientation, rousable and conversant
III	Very drowsy, disorientated, responds to simple verbal commands, often agitated and aggressive
IV	Responds to painful stimuli at best, but may be unresponsive May be complicated by evidence of cerebral oedema

diagnosis:
- Diagnosis is usually established based on a combination of laboratory abnormalities suggesting severe hepatic dysfunction and neurologic deficits.
- Elevated blood ammonia levels can be present, they are not required for making a diagnosis.

clinical features:
- Early neurologic abnormalities include disturbance in sleep patterns such as insomnia or hypersomnia.
- Neurologic abnormalities seen in more advanced presentations include asterixis and hyperactive deep tendon reflexes.
- Focal neurologic signs may be detected in some patients during episodes of hepatic encephalopathy, with hemiplegia being the most common deficit

treatment
- identify and treat precipitating factors such as:
(i) gastrointestinal bleeding,
(ii) infection,
(iii) alkalosis,
(iv) hypokalemia,
(v) sedatives/tranquilizers,
(vi)ingestion of dietary proteins,
(vii) azotemia, and
(viii) progressive hepatic dysfunction

- The mainstay of treatment for hepatic encephalopathy is lactulose and alteration of gut flora.
- Lactulose, a nonabsorbable disaccharide, should be initiated and titrated to about four bowel movements a day. Lactulose is metabolized by gut flora, lowering colonic pH and thereby favoring ammonia elimination.
- Enteric flora modification with antibiotics, such as metronidazole or neomycin, is a second-line treatment, and can be used in combination with lactulose.
- Management also includes supportive measures such as restoring electrolyte balance, fluid maintenance, aspiration precautions, and rapid sequence intubation for airway protection in grades 3-4 hepatic encephalopathy.
- Flumazenil has been proposed as a possible therapeutic agent for hepatic encephalopathy based on the theory that "endogenous benzodiazepines" may be present in patients with hepatic encephalopathy. Meta-analyses suggest that flumazenil was associated with a significant improvement in encephalopathy compared with placebo; however, the benefit was short term and may have been confined to patients who otherwise had a favorable prognosis.

fulminant hepatic failure

- Fulminant hepatic failure is a clinical syndrome characterized by the rapid onset of hepatic encephalopathy in conjunction with a marked decline in hepatic synthetic function.

investigation
(i) urine and serum toxicology screens
(ii) hepatitis serologies.
(iii) ceruloplasmin,
(iv) antinuclear antibodies,
(v) smooth-muscle antibodies,
(vi) serum protein electrophoresis,
(vii) CMV and EBV serology

treatment
- Once a patient is diagnosed with fulminant hepatic failure, the patient should be stabilized and transferred to a liver transplant center

Certain pathogeneses demand immediate specific treatment, including:
- N-acetylcysteine for paracetamol OD
- penicillin for Amanita mushroom poisoning;
-delivery of the infant in acute fatty liver of pregnancy;
- zinc and trientine therapy for Wilson's disease;
- transjugular intrahepatic portosystemic shunt, surgical decompression or thrombolysis in patients with acute Budd-Chiari; and
- acyclovir in patients with acute liver failure related to herpes virus infection

supportive measures include:
(i) nutrition (amino acids, lipids, glucose, and essential elements),
(ii) electrolyte balance,
(iii) frequent glucose monitoring
(iv) aspiration precautions, and
(v) fluid maintenance.

Liver transplantation offers the best long-term survival, with an overall posttransplantation 1-yr survival of about 60%

- Short-term extracorporeal hepatic support for patients with fulminant hepatic failure may ultimately serve to improve overall survival and provide support as a bridge to liver transplantation, but it remains experimental (2 types are cell-based and non-cell based)

criteria for transplant in acute liver failure

Paracetamol induced fulminant hepatic failure
- Ph <7.30 (irrespective of grade of encephalopathy) **OR**
- Prothrombin time >100 s and serum creatinine >300 µmol/l in patients with grade III or IV encephalopathy

Non-paracetamol-induced fulminant hepatic failure
- Prothrombin time >100 s (irrespective of grade of encephalopathy)[a] **OR**
- Any three of the following variables (irrespective of grade of encephalopathy):
  - Age <10 or >40 years
  - Aetiology – non-A, non-B hepatitis, halothane hepatitis, idiosyncratic drug reactions
  - Duration of jaundice before encephalopathy >7 days
  - Prothrombin time >50 s
  - Serum bilirubin >300 µmol/l

[a] Prothrombin time 100 s is equivalent to an INR of 6; prothrombin time 50 s is equivalent to an INR of 3.5.

complications
(i) Hypokalemia, hyponatremia, and hypophosphatemia are common.
(ii) Hypoglycemia, seen in up to 45% of patients with fulminant hepatic failure, requires aggressive glucose administration, often with 10% dextrose.
(iii) Infection in patients with fulminant hepatic failure is a major source of mortality, as 44-80% of patients with fulminant hepatic failure develop bacterial infections.
(iv) Fungal infections are also not uncommon in these patients, with rates as high as 32% having been reported.
(v) Acute renal failure frequently develops in fulminant hepatic failure. Renal failure is particularly high in the setting of paracetamol ingestion, as it can directly damage the kidneys. Once renal failure is established, it often is irreversible and carries a grave prognosis. Renal replacement therapy is generally well tolerated and may provide a bridge to transplant.
(vi) Severe coagulopathy often precedes the evolution of hepatic encephalopathy to coma. The development of severe coagulopathy is due to the decreased synthesis of clotting factors II, V, VII, and IX and is manifested by a prolonged prothrombin time. However, current recommendations are to correct coagulopathy with FFP intravenously only when overt bleeding occurs or when an invasive procedure is planned. Recombinant factor VIIa has been shown to be safe and effective in reversing the coagulopathy in patients with fulminant hepatic failure
(vii) - Cerebral edema is a common complication of fulminant hepatic failure, occurring in up to 80% of patients with grade IV coma, but requires a high level of clinical suspicion. Cerebral edema oftenleads to intracranial hypertension and subsequent herniation and death
- Direct intracranial pressure monitoring is recommended in patients suspected of cerebral edema or intracranial hypertension, with a target intracranial pressure of <20 mm Hg. Intracranial pressure monitoring is recommended to maintain an adequate cerebral perfusion pressure of >60 mm Hg.
- Mannitol is first-line therapy for treating cerebral edema and intracranial hypertension, administered at 0.3-0.4 g/kg body weight. In patients with renal failure, mannitol may accumulate in astrocytes and cause increased rebound swelling.
- Thiopental may be used in this setting (250 mg over 15 mins).
- propofol can be used.
- moderate hypothermia to 32-33°C, may be useful in decreasing intracranial pressure as a bridge to liver transplantation or while transplantation is being performed