Management of acute liver failure in children.

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Currently Pediatric Acute Liver Failure Study Group (PALFSG) defined ALF as
- Biochemical evidence of liver injury
- No history of known chronic liver disease
- Coagulopathy not corrected by vitamin K administration, INR greater than 1.5 if the patient had encephalopathy or greater than 2.0 if the patient does not have encephalopathy (1)

Treatment objectives ;

1) Keep the child on the supportive care till liver recovers spontaneously.
2) Keep a close eye on the transplantation criteria al throughout the treatment.

Enteral nutrition should be administered whenever possible, with higher caloric density feeds preferred to avoid excessive free water and hypo-osmolality, which may exacerbate cerebral edema. Parenteral nutrition (35–40 kcal/kg per day) delivered by a dedicated central venous catheter, should be reserved
for patients with specific contraindications to enteral nutrition (Aminoacid 0.5 – 1 gm/kg /day, Lipids (20%) 0.5 – 3 gm /kg/ day with serum triglyceride of < 250 mg/ dl). Normal protein intake recommended till stage I & II encephalopathy and after that restriction (2, 3).

Regular blood sugar monitoring is mandatory and frequently by finger stick (e.g. every 1–2 hrs). Intravenous glucose infusion (1.5–2.0 g/kg per day or 8 – 10 mg/kg/ min) is recommended in patients who develop hypoglycemia. Insulin infusions may be used to maintain blood glucose levels <150 mg/dL, while also strictly avoiding hypoglycemia (4, 5).

There are insufficient data to recommend the use of branched chain amino acids (L Aspartate , L Ornithine i.e Hepamerz) (6)

Regular GI protection strategy with intravenous Ranitidine (1 mg / kg/dose twice daily) may be needed. (Maintain gastric pH of more than 4)(7).

Avoid constipation, hypokalemia, dehydration, GI bleeding, sedatives and excess dietry protein intake.

Etiology-Specific Treatments:

Cause	Recommended treatment
Hereditary tryrosinemia	Nitisinone (NTBC) 1 mg/kg/day × 2 doses
Neonatal haemochromatosis	Deferoxamine 30 mg/kg/day IV in 3 doses Selenium 2 to 3 mcg/kg/day IV N-acetyl-cysteine 140 mg/kg, then 70 mg/kg orally or IV α-tocopherol polyethylene glycol succinate 20 UI/kg/day orally
Herpetic hepatitis	Acyclovir 150 mg/m2/day IV
Acetaminophen	Activated charcoal 1 g/kg orally N-acetylcysteine 150 mg/kg IV in 15 min, then 50 mg/kg in 4 hrs then 100 mg/kg over 16 hrs
Mushroom poisoning	Penicillin G 300,000 to 1 million U/kg/day IV Silymarin 30 to 40 mg/kg/day IV or orally

Oral NAC is recommended as first-line therapy only in patients with mild (grade 1) hepatic encephalopathy; intravenous NAC should be administered to patients with more grade 1 encephalopathy, hypotension, or other
reason that oral dosing might not be tolerated (e.g., vomiting, compromised airway, postoperative state, ileus).
NAC administration is recommended until there is firm evidence of improved hepatic function (resolution of hepatic encephalopathy, improving coagulopathy [international normalized ratio _1.5], and declining transaminases). The length of NAC administration should be determined by clinical improvement or outcome
(death or liver transplant) rather than by time or serum acetaminophen levels; it should be emphasized that this
period of time may extend well beyond 72–96 hrs (6).

Patients in the early stage of a coma resulting from non - acetaminophen related acute liver failure (NAALF) who received N-acetylcysteine (NAC) had a significantly higher spontaneous survival rate. However, the treatment was not useful for coma grade III-IV patients(61). Other studies also found that NAC use is associated with a reduction in NAI-ALF mortality and was safe to use. The recommended
dose is 100mg /kg/day i.v. infusion (6).

Sedation and Analgesia :

Propofol and benzodiazepines, the most commonly used sedatives, may exacerbate HE. In addition, propofol decreases cerebral blood flow and lowers intracranial pressure (ICP). If used for several days, however, the dose of propofol should be limited to approximately 80 mg/kg per min (5 mg/kg/hr) to decrease the risk of propofol infusion syndrome. An opiate infusion is recommended in patients with
ALF to prevent or treat discomfort. Agents with shorter half-life, such as fentanyl (1 mcg/kg/hr), are preferred. Morphine and meperidine are not recommended in patients with ALF and renal failure (8,9,10).

Seizure prophylaxis and surveillance:
Prophylactic anticonvulsants in all patients with ALF is not indicated because of lack of evidence.
The performance of electroencephalogram, not necessarily continuously, is recommended for the following indications: a) grade III or IV hepatic encephalopathy; b) sudden unexplained deterioration in neurologic examination; c) myoclonus; or d) to titrate therapy when barbiturate coma is used to manage cerebral edema (11,12).
Fosphenytoin (30mg/ kg followed by 8 mg /kg in two divided doses) or Levetiracetam (10-40 mg/kg in two divided doses) is preferred in our unit.
Valproic acid should be avoided if cause of liver failure is suspected to be metabolic especially in children below 2 years of age.

Treatment of Circulatory Dysfunction:
In hypotensive patients with ALF, volume status should be assessed and hypovolemia corrected before the administration of vasopressors. Vasopressors are recommended for severe systemic hypotension (systolic blood pressure - 70+ 2x age in years mm Hg; mean arterial pressure – 55 + 1.5 x age in years mm Hg) or to maintain a cerebral perfusion pressure (CPP) (equivalent to mean arterial pressure - ICP) of 50–80 mm Hg. Norepinephrine or dopamine are recommended, with norepinephrine preferred (0.1 – 2 mcg/kg/min),
Low-dose dopamine is not recommended. Epinephrine has been shown to decrease mesenteric blood flow in severe septic shock, and therefore may compromise hepatic blood flow in patients with ALF. Vasopressin and analogs are not recommended, because they directly cause cerebral vasodilation and may exacerbate
intracranial hypertension .
Relative adrenal insufficiency occurs frequently in patients with ALF, and may contribute to cardiovascular collapse. Moderate doses (200–300 mg/day) of hydrocortisone have been shown to improve the vasopressor response to norepinephrine in hypotensive patients with sepsis and ALF.Because of conflicting results in clinical trials, there are insufficient data to recommend the use of agents whichpurportedly improve peripheral tissue oxygenation, such as prostacyclin and *N*-acetylcysteine. (6)

Cerebral edema:
Prompt recognition and treatment are vital. Prophylactic treatment for cerebral edema has no role at this time. The goal is to maintain ICP less than 20 mm of Hg and cerebral perfusion pressure (CPP) of > 50 to 60 mm Hg at all times.
Factors that increase ICP need to be avoided and include high positive end-expiratory pressure, frequent movements, neck vein compression, fever, arterial hypertension, hypoxia, coughing, sneezing, seizures, head-low position and respiratory suctioning.

Active interventions for the management of cerebral edema include head elevation up to 30 degree, maintain neutral neck position, avoid or minimize painful stimuli, hyperventilation to maintain PCO2 between 30-35 mm Hg, control of arterial hypertension, mannitol infusion and avoid fluid overload.

Mannitol, an osmotic diuretic, remains the mainstay of treatment for increased ICP. Mannitol should be
administered when ICP >25 mm Hg for >10 mins, after the validity of the ICP calibration is confirmed. It has been shown to improve survival. A rapid bolus of 0.5 -1 g/kg as a 20% solution over a 15-min period is recommended, and the dose can be repeated if the serum osmolarity is less than 320 mOsm/l . There is no role for mannitol if serum osmolality is more than 320 mOsm/ liter. Serum osmolality should be assessed every 6 hrs, and mannitol boluses may be repeated if ICP remains >25 mm Hg and serum osmolality >320 mOsm/L.
If the patient is anuric and has renal failure, dialysis must accompany mannitol use.

Induction and maintenance of hypernatraemia (145–155 meq/l) by administering 3% hypertonic saline (6 -8 ml /kg followed by 0.5 – 1 ml /kg/hr) is useful to prevent the rise in ICP.

Hypothermia (core temperature of 32o C) has been shown to be effective in the management of severe intracranial hypertension, with a lowering of ICP and an improvement in CPP in adults.

Sodium thiopental can be used in controlling mannitol resistant cerebral oedema, giving a bolus dose of 2–4 mg/kg over 15 min followed by a slow intravenous infusion of between 1 and 2 mg/kg/hr.
Indomethacin (25 mg infused intravenously over 1 min) also has been shown to acutely decrease ICP and increase CPP by causing cerebral vasoconstriction. Indomethacin therefore may be considered as salvage therapy in patients with intracranial hypertension refractory to the above measures.
Phenytoin (20 mg/kg bolus followed by 5mg/kg in two divided doses) infusion led to a significant reduction in seizure activity in adult patients.
Corticosteroids have been shown to be ineffective in patients with ALF with respect to controlling oedema or improving survival (6,12, 13, 14, 15, 16, 17, 18).

Infection:
Empirical administration of antibiotics is recommended in the following circumstances where infection or the likelihood of impending sepsis is high:
a) Surveillance cultures reveal significant isolates,
b) Progression of, or advanced stage (III/IV), hepatic encephalopathy,
c) Refractory hypotension;
d) Presence of systemic inflammatory response syndrome components (temperature _38°C or _36°C, white blood count _12,000 or _4,000/mm3, pulse _90 beats/min)
d) Presence of systemic inflammatory response syndrome .
e) Patients listed for OLT.

Intravenous Cefuroxime (50 mg/kg/dose 8 hourly) is recommended.

Vancomycin (45 – 60 mg /kg/day in three divided doses) is specifically recommended in all patients with possible intravenous catheter–related sepsis and/or risk factors for infection with methicillin resistant *Staphylococcus aureus*.

Aminoglycosides should be avoided due to risk of nephrotoxicity.

Intravenous fluconazole (6 – 12 mg /kg once or twicw daily) may be needed if child has following indications.

1) Invasive lines
2) Deterioration after initial improvement with antibiotics
3) Marked leucocytosis and non responsive fever to antibiotics
4) Prolonged antibiotics
5) Established renal failure

Oral Ampicillin (50 – 100 mg/ kg /day in three divided doses) is recommended for gut sterilization.
Oral Neomycin, Metronidazole, Vancomycin or Rifaximin are not indicated because of significant GI absorption and renal or other systemic toxicity (19, 20, 21, 22, 23, 24).

Coagulopathy:

Prophylactic Vitamin K (0.2 mg /kg/day max. 10 mg/dose) should be given once daily for 3 days and then every alternate day
Maintain a hematocrit of >30%.
An attempt at improving the coagulation profile (FFP 10 -15 ml /kg) is recommended in patients with clinically significant bleeding or before placement of invasive devices. There are insufficient data to support fixed goals of treatment. The suggested guidelines include INR <1.5 and platelets count >50,000/ mm3. Plasmapharesis may be needed needed only when there is significant coagulopathy with bleeding. Prophylactic fresh frozen plasma to improve coagulopathy in ALF is not recommended, as it does notreduce the risk of significant bleeding nor transfusion requirements, obscures the trend of prothrombin time as a prognostic marker, and risks volume overload.
The administration of cryoprecipitate (1 unit for every 10 kgs of weight) is recommended in patients who have significant hypofibrinogenemia (<100 mg/dL). Antifibrinolytic agents such as aminocaproic acid should be considered in patients with clinical evidence of a hyperfibrinolytic state (diffuse mucosal and puncture wound oozing) and supporting laboratory evidence, such as an increased clot lysis time.
Recombinant factor VII a (rFVIIa) has been used in patients of ALF to control bleeding or acceptable normalization of INR or prothrombin time, in volume overloaded state and before invasive procedures like ICP monitor placement and transjugular liver biopsy. Fresh frozen plasma should be administered before rFVIIa to replete other constituents of the clotting cascade, with cryoprecipitate if fibrinogen is<100 mg/dL. The rFVIIa (40µg/kg) should be administered immediately before a planned procedure. The procedure should be performed within 30–60 mins, although the effect of rFVIIa usually persists for >2 hrs.Factor VII is contraindicated in Budd-Chiari syndrome, suspected malignant infiltration of the liver, a history of stroke or with active deep venous thrombosis (25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, and 36).

Hyperammonemia:

Lactulose 0.5 ml /kg/dose to maximum of 30ml /dose four times daily titrated to 3- 4 loose stool /day. (contraindicated in intestinal ileus).
Lactulose enemas are as beneficial and circumvent the problem of ileus.
Lactulose is administered, the following precautions should be observed
(1) Abdominal distention should be assessed at regular intervals, as lactulose may increase gaseous distention of the bowel, obscure the operative field during OLT, or may rarely precipitate megacolon ,
(2) Lactulose by mouth or naso-gastric tube should not be administered to patients with late stages of hepatic
encephalopathy without prior endotracheal intubation, considering the risk of aspiration
(3) Dose of lactulose should be titrated to avoid intravascular depletion.

Sodium Benzoate (500 – 750 mg /kg) may be given if ammonia level is above 150 mcg/ dl but it does not have any effect on the mortality (6).

Renal Failure:

There is no clear cut consensus guideline for RRT but decision to start RRT should be based upon the level of renal dysfunction, fluid balance, and metabolic derangements, and a need to create space for intravenous colloid (e.g., fresh frozen plasma) or parenteral nutrition. Goals of RRT should be clearly delineated before initiation of RRT. Conversely, a plan for discontinuing RRT alsoshould be agreed upon before its institution, particularly in the event that a patient is no longer considered for OLT or fails to spontaneously improve (37, 38, 39, 40, 41, 42, 43).

Mechanical ventilation:

Intubate the child if

1) Grade III or IV hepatic encephalopathy.
2) Respiratory failure.
3) Rapidly changing clinical state.
4) Child is requiring high sedation.
5) Other co morbid condition for which intubation is deemed necessary.

Patients with ALF often develop acute respiratory distress syndrome with disease progression to cerebral edema. It must be appreciated that decrements in tidal volume will decrease minute ventilation and increase PCO2, and thereby increase ICP. Therefore, in patients with low tidal volumes, the respiratory rate should be increased to maintain a stable PCO2. High levels of positive end expiratory pressure also may increase ICP in patients with ALF, and decrease hepatic blood flow.

The lowest level of positive end-expiratory pressure that achieves adequate oxygenation should be applied in patients with ALF (44).

Role of plasmapheresis

For children with acute liver failure, plasmapheresis is extremely effective in preventing life threatening bleeding while maintaining appropriate volume status in small children. This method of treatment has no effect on the neurologic complications of liver failure and has no impact on the ability of the liver to regenerate (45).

Transplantation

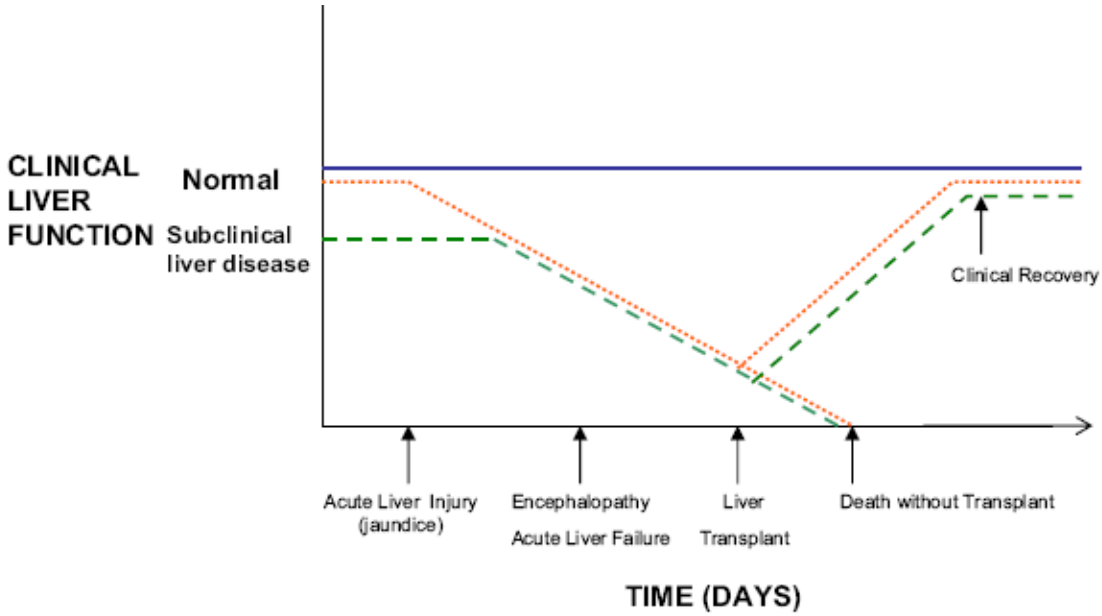
Acute liver failure due to Wilson disease has to be transferred to the unit for transplantation because of chances of spontaneous recovery is obsolete.

Transfer to a unit well equipped with liver transplantation if patient fulfills the stated criteria (46).

Liver ASSIST device like MARS have not shown to improve the morbidity and mortality though may be used as bridge to Liver transplant in Clinical Trails.

Multiple organ system extracorporeal support systems are used to support brain, cardiac, pulmonary, liver, kidney, coagulation, blood, and immune cell function in children who have multiple organ failure syndromes. Pediatr Clin N Am 55 (2008) 617–646

In patients who have liver failure, MARS should also be added to CRRT, with placement of the MARS cartridge to perform albumin dialysis. The commencement of therapy should be strongly considered in patients who have acute liver failure and who fulfill criteria for transplantation and should be considered in patients who have acute decompensation of chronic liver disease who do not respond to several days of other therapies. The MARS treatment generally lasts up to 8 hours, after which CRRT is
resumed. Alternatively, continuous MARS treatment is possible and sometimes is preferred in patients who have acute liver failure. The number of MARS treatments given is based on experience. Most treat at least every 3 days. Therapy should be directed to normalizing bilirubin in the same manner as CRRT dosage and to normalizing ammonia and lactate. Fresh-frozen plasma should be given also to reverse coagulopathy. Pediatr Clin N Am 55 (2008) 617–646



Clinical course of FHF and outcome following liver transplantation.

Indications for Liver Transplantation in FHF

Acute deterioration in mental status
Stage III/IV encephalopathy
Persistently increased PT and INR
Development of multisystem dysfunction
Hypoglycemic episodes.

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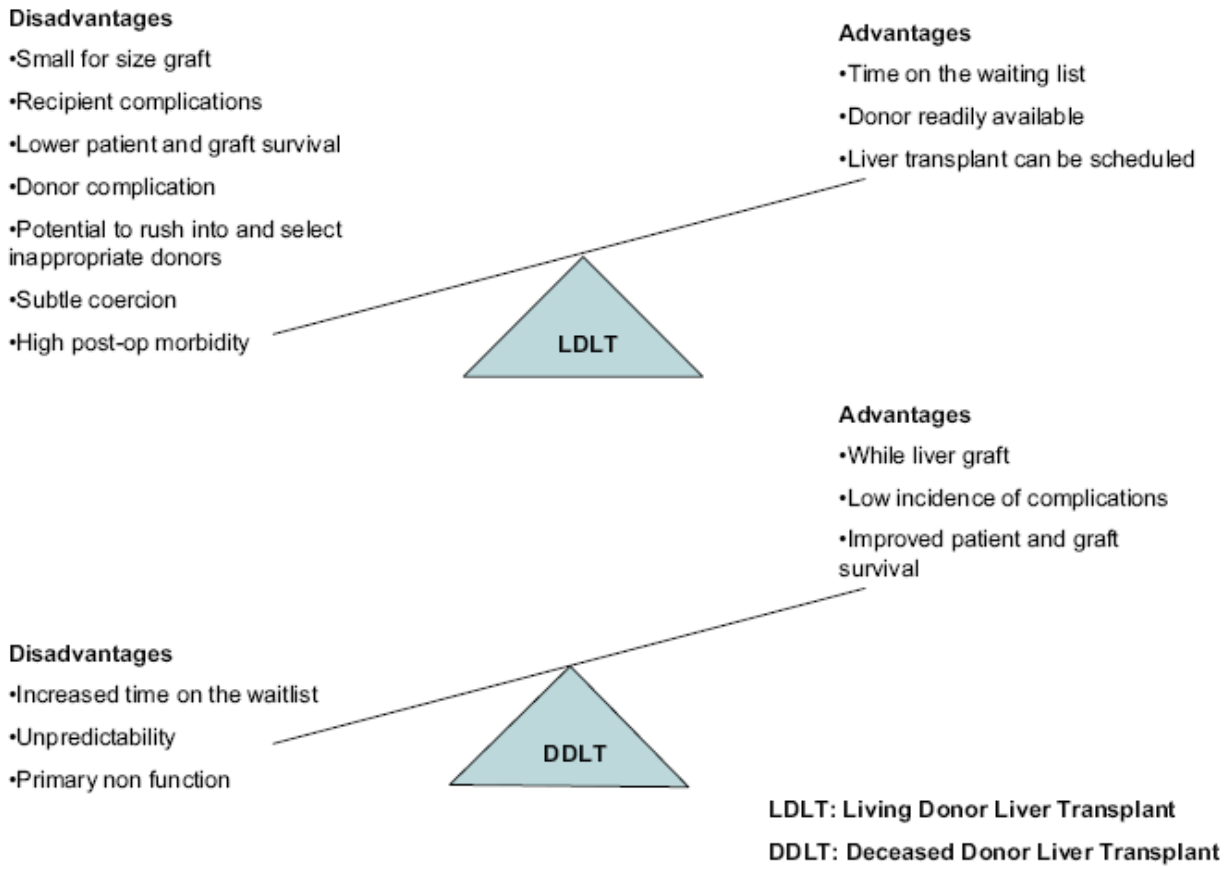
Table 1 King's College criteria [4–6]

Paracetamol
pH < 7.3 irrespective of encephalopathy intoxication severity after 24 h and fluid resuscitation
or
arterial lactate concentrations > 3.5 mmol/l following early fluid substitution
or
arterial lactate concentrations > 3.0 mmol/l following 12 h of fluid substitution
or
serum phosphate levels ≥ 1.2 mmol/l at 48–96 h after ingestion
or
encephalopathy III/IV
and
prothrombin time > 100 s (INR > 6.5)
and
creatinine > 300 μmol/l (3.4 mg/dl) within a 24 h period
Other aetiologies
prothrombin time > 100 s (INR > 6.5)
or at least three of the following criteria
age < 10 or > 40 years
aetiology hepatitis non A–E, halothane hepatitis, idiosyncratic drug reaction
jaundice to encephalopathy time > 7 days
prothrombin time > 50 s (INR > 3.5)
serum bilirubin > 300 μmol/l (>17.4 mg/dl)

INR, international normalized ratio.



Advantages and disadvantages of live donor liver transplantation (LDLT) and deceased donor liver transplantation (DDLT) in patients with fulminant liver failure.
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Prognostic factors:

Advanced encephalopathy and prolonged prothrombin time were significantly associated with death or need for LT.{ Ciocca M - *Arch Dis Child* - 01-JAN-2008; 93(1): 48-51}Short-term (21-day) outcome for children with ALF varies by diagnosis, age, and degree of encephalopathy. Survival without liver transplant was highest in the APAP group (94%), while children with non-APAP drug-induced ALF (41%), metabolic disease (44%), or indeterminate ALF (43%) fared less well. The risk of death increases with the degree of encephalopathy. However, 20% of children in the PALF study who never developed encephalopathy either died or underwent liver transplant and those who presented with grade 4 encephalopathy fared better than those who progressed to grade4 during the course of the study. The ideal model to predict outcome would ensure that all patients who need a transplant receive one (positive predictive value), and all patients who would survive would not (negative predictive value), but presently none exists. Virtually all of the prognostic models to date are based upon data and experiences with adult patients. King's College criteria were the first and are the standard upon which others are judged. King's criteria take into account patient demographics that include diagnosis and age, degree of

clinical encephalopathy,as well as biochemical determination of coagulopathy, arterial pH, serum bilirubin, and creatinine. Several other models have been developed and include the use of serum lactate; albumin, lactate, valine, and pyruvate; a-fetoprotein; phosphate; APACHE III measurements ; and most recently actin-free Gc-globulin. Most have not been tested independently in children.

PEDGIHEP Management of cerebral edema in acute liver failure

Grade 1 or 2 encephalopathy
_ Grade 1: Mild changes in mood and speech, disordered sleep
_ Grade 2: Inappropriate behavior, mild irritability, agitation, or somnolence
_ Hyperreflexia, clonus, asterixis (may or may not be present)

_ Transfer patient to ICU for frequent monitoring and neurologic checks.
_ Maintain a quiet environment with minimal environmental stimuli.
_ Avoid sedatives/hypnotics.
_ Administer dextrose 10% drip with hourly blood glucose monitoring.
_ Lactulose may be of benefit in patients who have subacute acute liver failure

Grade 3 or 4 encephalopathy
_ Grade 3: Patient is somnolent but arousable to verbal command and demonstrates marked confusion, incoherent speech.
_ Grade 4: Patient is not arousable by painful stimuli.

_ Avoid medications with sedative properties (eg, narcotics, benzodiazepines) unless patient is intubated
_ Elevate head of bed to 30_ from horizontal.
_ Avoid Valsalva maneuvers, vigorous straining, or suctioning.
_ Use cooling blankets to keep core temperature at 37_C or lower.
_ Consider intubation to protect airway, hypoxia, respiratory failure.
_ If intubated, propofol or midazolam are preferred for sedation.
_ Obtain a head CT to rule out intracranial hemorrhage.
_ Consider placement of an intracranial pressure monitor.
_ Correct coagulopathy (international normalized ratio < 1.5) with fresh frozen plasma or recombinant factor VIIa.
_ Balance risk of procedure versus benefit of accurate data (eg, epidural versus subdural versus parenchymal) in selecting type of intracranial pressure catheter used.
Measures for elevated intracranial pressure Maintain cerebral perfusion pressure above 50 mm Hg(cerebral perfusion pressure = mean arterial pressure _ intracranial pressure).
Hyperventilate to PCO2 of approximately 28 to 30 mm Hg.
_ Monitor serum osmolarity and osmolar gap.

_ Moderate hypothermia (33_–35_C) is investigational for refractory cerebral edema in acute liver failure.
_ Use a paralytic agent (atracurium) or propofol to prevent shivering
_ Perform a brain perfusion scan to exclude brain death if increase in intracranial pressure is prolonged.

PEDGIHEP Management of coagulopathy in acute liver failure

Management

_ Prophylaxis for gastrointestinal bleeding is recommended in all patients treated with a proton-pump inhibitor or histamine 2 blocker.
_ Vitamin K (10 mg) subcutaneously for 3 days is recommended for all patients.
_ **Prophylactic fresh frozen plasma infusions are not recommended in the absence of active bleeding**.
_ Concerns about volume overload/worsening cerebral edema
_ Lose prognostic value of international normalized ratio
_ If there is active bleeding or a planned procedure, administer Fresh frozen plasma to maintain international normalized ratio below 1.5
_ Platelet infusion to maintain a level higher than 50,000 platelets/mL
_ Cryoprecipitate to maintain fibrinogen level higher than 100 mg/dL
_ Consider recombinant factor VIIa only if an invasive procedure such as placement of an intracranial pressure monitor will be performed and the international normalized ratio is below 1.5after fresh frozen plasma Mechanism: Enhances clot formation at areas of tissue factor release
_ Contraindications: Budd-Chiari syndrome, malignancy, history of deep vein thrombosis/pulmonary embolism, pregnancy, thrombophilia .

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Box 1. Clinical and histologic patterns of antimicrobial-induced liver injury

Hepatocellular necrosis and acute hepatitis
Isoniazid
Ketoconazole
Nitrofurantoin

Acute cholestasis
Erythromycin
Bactrim
Augmentin

Acute liver failure
Isoniazid
Rifampin
Itraconazole
Nitrofurantoin
Augmentin
Ciprofloxacin
Bactrim

Chronic hepatitis or cholestasis
Bactrim
Minocycline
Nitrofurantoin
Flucloxacillin

Immunoallergic or autoimmune
Trimethoprim-sulfa
Minocycline

Granulomas
Bactrim
Augmentin
Pyrazinamide

Steatosis and steatohepatitis
Intravenous tetracycline

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CAM agents/nutritional supplements and form of hepatotoxicity

Herb	Type of Liver Injury
Crotalaria *Heliotropium* *Senecio longilobus* *Symphytum officinale* (pyrrolizidine alkaloids)	Sinusoidal obstruction syndrome (veno-occlusive disease)
Chaparral leaf, germander	Zone 3 necrosis, cirrhosis, cholestasis, chronic hepatitis
Pennyroyal (squamit) oil	Zone 3 necrosis, microvesicular steatosis, fulminant liver failure
Jin Bu Huan	Acute and chronic cholestatic hepatitis, microvesicular steatosis, fibrosis
Mistletoe	Chronic hepatitis
Margosa oil	Microvesicular steatosis, Reye syndrome, hepatic necrosis
Usnic acid	Fulminant liver failure
Atractylis gummifera	Acute hepatitis, fulminant liver failure
Callilepis laureola	Acute hepatitis, fulminant liver failure
Impila	Acute hepatitis, fulminant liver failure
Camphor	Necrolytic hepatitis
Cascara sagrada	Cholestatic hepatitis
TJ-8, Dai saiko-toi	Autoimmune hepatitis
TJ-9, Sho-saiko-to	Acute and chronic hepatitis
Paeonia spp.	Acute hepatitis, fulminant liver failure
Greater celandine	Chronic hepatitis, cholestasis, fibrosis
Germander	Acute and chronic hepatitis, fulminant liver failure
Isabgol	Giant cell hepatitis
Kava	Acute and chronic hepatitis, fulminant liver failure
Ma Huang	Acute hepatitis, autoimmune hepatitis
Oil of cloves	Hepatic necrosis
Sassafras	Hepatocarcinogen
Saw palmetto	Mild hepatitis
Shou-wu-pian	Acute hepatitis
Valerian	Mild hepatitis

Figures, Tables, Graphs, Protocols,

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