MANAGEMENT OF ACUTE HEPATIC FAILURE

-NEW CONCEPT

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Introduction

Acute liver failure (ALF)

- A rare condition of
- Rapid deterioration of liver function
- with altered mentation and coagulopathy
- In the absence of underlying liver cirrhosis

Epidemiology-ALF

- U.S. estimates approximately 2,000/year.
- Often affects young persons and
- Carries a high morbidity and mortality.

Mortality

- Prior to transplantation,
  - most series suggested less than15% survival.
- Currently,
  - overall short-term survival with transplantation is greater than 65%.

Definition of ALF

The most widely accepted definition-

1. Evidence of coagulation abnormality, (an INR ≥1.5),
2. And any degree of mental alteration (encephalopathy)
3. Without preexisting cirrhosis
4. With an illness of < 26 weeks duration.

Sub-classification

- Hyperacute (1-7 days)
- Acute(8-28 days)
- Subacute (29 days to 6 months)

Etiology of AHF

A. Infection

Hepatitis A, B, D,E

Herpes simplex

EBV

CMV

B. Toxin

Acetaminophen(60% cause of ALF in USA)

Amanita phalloid

C. Autoimmune (6%)

D. Metabolic

Wilson disease

Etiology of AHF

E. Pregnancy related

Acute fatty liver of pregnancy

HELLP syndrome

F. Vascular

Ischemic hepatitis (4%)

Budd-Chiari syndrome (9%)

G.Indeterminate (~25%)

H. Ca liver

Pathogenesis

- Severe decompensation of hepatocyte
- Assault is of variable aetiology
- Liver fails to meet metabolic demand of body

Pathogenesis Hepatic Encephalopathy

- Cerebral edema is unique feature
- Ammonia is main toxic compound

level < 75 u seldom cause HE

> 200 u cause cerebral herniation

Diagnosis

- All patients with clinical or laboratory evidence of moderate to severe acute hepatitis should have immediate measurement of
  - Prothrombin time and
  - Evaluation for alterations in mentation

Diagnosis

The diagnosis of ALF is established

- If the prothrombin time is prolonged by 4-6 seconds or more (INR ≥1.5)
- And there is any evidence of altered consciousness.

Evaluation

- History taking
  - should include careful review of possible exposures to viral infection and drugs or other toxins.
- Physical examination
  - must include careful assessment and documentation of mental status and
  - a search for stigmata of chronic liver disease.

Evaluation

- Jaundice is often but not always seen at presentation
- Right upper quadrant tenderness is variably present
- The liver is impalpable due to massive hepatocyte loss
- An enlarged liver may be seen in-
  - early in viral hepatitis
  - with malignant infiltration,
  - congestive heart failure,
  - acute Budd-Chiari syndrome.
- History or signs of cirrhosis should be absent

Grades of Encephalopathy

Grade I:	Changes in behavior with minimal change in level of consciousness
Grade II:	Gross disorientation, drowsiness, asterixis, inappropriate behavior.
Grade III:	Marked confusion, incoherent speech, sleeping most of the time but arousable to vocal stimuli
Grade IV:	Comatose, unresponsive to pain, decorticate or decerebrate posturing.

Initial Laboratory Analysis

- Prothrombin time/INR
- Biochemistries
  - sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphate glucose AST, ALT, alkaline phosphatase, GGT, total bilirubin, albumin creatinine, blood urea nitrogen
- Arterial blood gas Arterial lactate
- Complete blood count, Blood grouping
- Acetaminophen level (Toxicology screen)

Initial Laboratory Analysis

- Viral markers -serologies
  - anti-HAV IgM, HBSAg, anti-HBc IgM, anti-HEV§, anti-HCV*
- Ceruloplasmin Level
- Pregnancy test (females)
- Ammonia (arterial if possible)
- Autoimmune markers
  - ANA, ASMA, Immunoglobulin levels
- HIV status
- Amylase and lipase

Investigate to asses

A. Degree of liver injury

B. Complication

C. Aetiology

D. Prognosis

Investigation for Aetiology

Viral marker

i) anti HEV

ii) anti HAV IgM

iii) HBsAg

iv) IgM anti HBc

(important as there may be rapid clearance of HBsAg) indicates good immune response to virus

vi) anti HDV in those positive for HBV

vii) HCV RNA

viii) EBV, CMV

Investigation for Aetiology

- Autoimmune screening
  - i)ANA
  - ii) AMA
  - iii)ASMA
  - iv) LKM
- Serum copper, ceruloplasmin, urine copper
- Toxicology screening in serum & urine
- USG & doppler study of hepatic vein

Complication assessment

- Blood sugar
- Electrolytes
- Platelet
- Renal function test
- Arterial blood gas analysis

Prognosis assessment

I. Paracetamol induced AHF

a) Prothombin time

b) pH

c) S creatinine

II) Non paracetamol AHF

a) Prothombin time

b) serum bilirubin

General Management

Grades I-II encephalopathy

- May be safely managed on a medicine ward
- With skilled nursing in a quiet environment to minimize agitation
- Management in an ICU is preferable.
- Frequent mental status checks should be performed
- Transfer to an ICU if level of consciousness declines.
- With progression to grade II encephalopathy, an ICU setting is indicated.

Grades III-IV encephalopathy

- It is advisable to intubate the trachea for airway protection.
- Patients in advanced stages of encephalopathy require close follow-up.
- Monitoring and management of hemodynamic and renal parameters as well as glucose, electrolytes and acid/base status.
- and frequent neurological evaluation for signs of elevated intracranial pressure should be conducted.

AASLD Recommendations

- Sedation should be avoided if possible
  - In early stages of encephalopathy,
- Lactulose may be used,
  - but concern has been raised about increasing bowel distention during the subsequent transplant procedure (II-2, III).
- Head should be elevated to 30 degrees
  - In patients progressing to grade III or IV
  - and endotracheal intubation should be performed

AASLD Recommendations for seizure

- Seizure activity should be treated
  - with phenytoin and
  - low-dose benzodiazepines.

- Intracranial pressure monitoring
  - mainly considered for patients who are listed for transplantation.

AASLD Recommendations for intracranial hypertension

- Frequent evaluation for signs of intracranial hypertension are needed to identify early evidence of uncal herniation,
- In the event of intracranial hypertension, mannitol should be given and hyperventilation may be considered in order to temporarily reduce the ICP,
- Short-acting barbiturates may be considered for refractory intracranial hypertension,
- Corticosteroids should not be used to control elevated ICP

AASLD Recommendations for infections

- Periodic surveillance cultures should be performed to detect bacterial and fungal infections as early as possible and prompt treatment should be initiated accordingly.
- Prophylactic antibiotics and anti-fungals may be considered

AASLD Recommendations for bleeding

Replacement therapy for thrombocytopenia and/or prolonged prothrombin time is recommended only in the setting of **hemorrhage or prior to invasive procedures.**

AASLD Recommendations GI bleeding

Patients with ALF in the ICU should receive

- Prophylaxis with H2 blocking agents or
- PPIs for acid-related gastrointestinal bleeding associated with stress.

AASLD Recommendations or hypotension

Careful attention must be paid

- To fluid resuscitation and
- Maintenance of adequate intravascular volume

AASLD Recommendations for hypotension

- Pulmonary artery catheterization should be considered in a hemodynamically unstable patient:
  - To ensure that appropriate volume replacement has occurred.
- Systemic vasopressor support with agents such as epinephrine, norepinephrine, or dopamine:
  - If fluid replacement fails to maintain MAP of 50-60 mm Hg.

AASLD Recommendation metabolic and nutritional disorders

- Metabolic homeostasis must be carefully maintained.
- Overall nutritional status as well as glucose, phosphate, potassium and magnesium levels should be monitored frequently.

Specific Therapies-AASLD Recommendations

- Etiology of ALF provides one of the best indicators of prognosis,
- Also dictates specific management options.

Management-AASLD Recommendations

- The precise etiology of ALF should be sought to guide further management decisions.
- Patients with ALF should be admitted and monitored frequently, preferably in an ICU.
- Contact with a transplant center and plans to transfer appropriate patients with ALF should be initiated early in the evaluation process.

AASLD Recommendations for viral hepatitis

- Viral hepatitis A- and B- (and E-) related acute liver failure must be treated with supportive care
  - as no virus-specific treatment has been proven effective .
- Nucleoside analogs should be given
  - prior to and continued for 6 months after completion of chemotherapy in patients with Hepatitis B surface antigen positivity
  - to prevent reactivation/acute flare of disease.
- Patients with known or suspected herpes virus or varicella zoster as the cause of acute liver failure should be treated with acyclovir.

AASLD Recommendation For patients with known or suspected acetaminophen toxicity

- Give activated charcoal
  - just prior to starting NAC. within 4 hours of presentation,
- Begin NAC promptly in all patients
  - where the quantity of acetaminophen ingested,
  - serum drug level or rising aminotransferases indicate impending or evolving liver injury.

AASLD Recommendation For patients with Mushroom Poisoning

- Consider administration of penicillin G and NAC
- Patients should be listed transplantation , as this procedure is often the only lifesaving option

AASLD Recommendations for drug induced hepatitis

- Obtain details of drugs ingested
  - including onset of ingestion,
  - amount and timing of last dose
  - all prescription and non-prescription drugs,
  - herbs and dietary supplements taken over the past year
- Determine ingredients of non-prescription medications whenever possible.
- Discontinue all but essential medications.

AASLD Recommendations for Wilson disease

- Patients in whom Wilson disease is the likely cause of acute liver failure must be immediately placed on the liver transplant list.

AASLD Recommendations for autoimmune hepatitis

- Liver biopsy should be considered to establish the diagnosis.
- Autoimmune hepatitis should be treated with corticosteroids (prednisone, 40-60 mg/day).
- Patients should be placed on the list for transplantation.

AASLD Recommendation For acute fatty liver of pregnancy

Consultation with obstetrical services and expeditious delivery are recommended

- for acute fatty liver of pregnancy
- or the HELLP syndrome.

AASLD Recommendation for Budd-Chiari Syndrome

Liver transplantation is an indication:

- For hepatic vein thrombosis with hepatic failure
- provided underlying malignancy is excluded.

AASLD Recommendations for Acute Ischemic Injury

- Cardiovascular support is the treatment of choice
  - In ALF patients with evidence of ischemic injury.

AASLD Recommendation for Indeterminate Etiology

- Liver biopsy may be appropriate to attempt to identify a specific etiology that might influence treatment strategy:
  - If the etiological diagnosis remains elusive after extensive initial evaluation.

AASLD Recommendation for Transplantation

- Orthotopic liver transplantation remains the only definitive therapy for patients
  - who are unable to achieve regeneration of sufficient hepatocyte mass to sustain life.

- The advent of transplantation has coincided with improvement in overall survival rates from as low as 15% in the pre-transplant era to 60% presently.

AASLD Recommendation for Transplantation

- Spontaneous survival rates are now around 40%, compared to 15% in the pre-transplant era.
- Post-transplant survival rates for ALF have been reported to be as high as 80% to 90%.

AASLD Recommendation for Transplantation

Urgent hepatic transplantation is indicated in acute liver failure where prognostic indicators suggest a high likelihood of death.

Emerging treatments

Non-biological hepatic assist devices:

These devices are based on

- plasma exchange,
- haemodialysis,
- haemofiltration,
- charcoal haemoperfusion,
- and resin haemoperfusion systems.

Bioartificial hepatic assist devices

- Bioartificial or cell-based hepatic assist devices incorporate hepatocytes or other cell types to provide metabolic as well as detoxification function .

- Preliminary studies of bioartificial hepatic assist devices have demonstrated safety; however, their utility or efficacy in the setting of ALF has yet to be determined

Liver tissue engineering and hepatocyte transplantation

- Several small studies have demonstrated the ability to transplant human hepatocytes in the setting of ALF;
- However, further research will be required to achieve optimal viability, function, and preservation of the transplanted hepatocytes.

Prognosis

Potentially Helpful Indicators* of Poor (Transplantfree) Prognosis in Patients With ALF

Etiology

- Idiosyncratic drug injury
- Acute hepatitis B (and other non-hepatitis A viral infections)
- Autoimmune hepatitis
- Mushroom poisoning
- Wilson disease
- Budd-Chiari syndrome
- Indeterminate cause

Coma grade on admission

- III/IV

Prognosis

- Mortality due to
  - Ischemic brain damage
  - Herniation
- Survivors may suffer from long-term neurological deficits.

Conclusion

- ALF is a rapidly fatal disorder.
- Diagnosis requires a high index of suspicion and thorough evaluation.
- Despite improvements in care, mortality is high
- Early intervention is critical and
- Involvement of an experienced multidisciplinary team and
- transfer to a specialty center will maximize survival.

Conclusion

- Liver transplantation remains the treatment of choice in those who are not recovering,
- and its use has markedly improved overall survival.
- and many patients will ultimately die without transplantation.

Thank You All

THANKS

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