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NATIONAL GUIDELINE CLEARINGHOUSE

General

Guideline Title

AASLD position paper: the management of acute liver failure: update 2011.

Bibliographic Source(s)

Lee WM, Larson AM, Stravitz T. AASLD position paper: the management of acute liver failure: update 2011. Baltimore (MD): American Association for the Study of Liver Diseases; 2011 Sep. 26 p. [224 references]

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Polson J, Lee WM. AASLD position paper: the management of acute liver failure. Hepatology 2005 May;41(5):1179-97. [179 references]

Recommendations

Major Recommendations

The levels of evidence supporting the recommendations (Grade I, II-1, II-2, II-3, and III) are defined at the end of the "Major Recommendations" field.

Diagnosis and Initial Evaluation

1. Patients with acute liver failure (ALF) should be hospitalized and monitored frequently, preferably in an intensive care unit (ICU) (Grade III).
2. Contact with a transplant center and plans to transfer appropriate patients with ALF should be initiated early in the evaluation process (Grade III).
3. The precise etiology of ALF should be sought to guide further management decisions (Grade III).

See Table 2 in the original guideline document for a list of initial laboratory analyses.

Determining Etiologies and Specific Therapies

Acetaminophen Hepatotoxicity

4. For patients with known or suspected acetaminophen overdose within 4 hours of presentation, give activated charcoal just prior to starting N-acetylcysteine (NAC) (Grade I).
5. Begin NAC promptly in all patients where the quantity of acetaminophen ingested, serum drug level, or rising aminotransferases indicate

impending or evolving liver injury (Grade II-1).

6. NAC may be used in cases of ALF in which acetaminophen ingestion is possible or when knowledge of circumstances surrounding admission is inadequate but aminotransferases suggest acetaminophen poisoning (Grade III).

Mushroom Poisoning

7. In ALF patients with known or suspected mushroom poisoning, consider administration of penicillin G and NAC (Grade III).
8. Patients with ALF secondary to mushroom poisoning should be listed for transplantation, as this procedure is often the only lifesaving option (Grade III).

Drug Induced Liver Injury (DILI)

9. Obtain details (including onset of ingestion, amount, and timing of last dose) concerning all prescription and non-prescription drugs, herbs, and dietary supplements taken over the past year (Grade III).
10. Determine ingredients of non-prescription medications whenever possible (Grade III).
11. In the setting of ALF due to possible drug hepatotoxicity, discontinue all but essential medications (Grade III).
12. NAC may be beneficial for ALF due to drug-induced liver injury (Grade I).

See Table 3 in the original guideline document for a list of some drugs which may cause idiosyncratic liver injury leading to ALF.

Viral Hepatitis

13. Viral hepatitis A- and (E-) related ALF must be treated with supportive care as no virus-specific treatment has been proven to be effective (Grade III).
14. Nucleos(t)ide analogues should be considered for hepatitis B-associated ALF and for prevention of post-transplant recurrence. (Grade III)
15. Patients with known or suspected herpes virus or varicella zoster as the cause of ALF should be treated with acyclovir (5-10 mg/kg intravenous [IV] every 8 hours) and may be considered for transplantation (Grade III).

Wilson Disease

16. To exclude Wilson disease one should obtain ceruloplasmin, serum and urinary copper levels, slit lamp examination for Kayser-Fleischer rings, hepatic copper levels when liver biopsy is feasible, and total bilirubin/alkaline phosphatase ratio (Grade III).
17. Patients in whom Wilson disease is the likely cause of ALF must be promptly considered for liver transplantation (Grade III).

Autoimmune Hepatitis

18. Liver biopsy is recommended when autoimmune hepatitis is suspected as the cause of ALF, and autoantibodies are negative (Grade III).
19. Patients with coagulopathy and mild hepatic encephalopathy due to autoimmune hepatitis may be considered for corticosteroid treatment (prednisone, 40-60 mg/day) (Grade III).
20. Patients with autoimmune hepatitis should be considered for transplantation even while corticosteroids are being administered (Grade III).

Acute Fatty Liver of Pregnancy/Hemolysis, Elevated Liver Enzymes, Low Platelets (HELLP) Syndrome

21. For acute fatty liver of pregnancy or the HELLP syndrome, expeditious delivery of the infant is recommended. Transplantation may need to be considered if hepatic failure does not resolve quickly following delivery (Grade III).

Acute Ischemic Injury

22. In ALF patients with evidence of ischemic injury, cardiovascular support is the treatment of choice (Grade III).

Budd-Chiari Syndrome

23. Hepatic vein thrombosis with acute hepatic failure is an indication for liver transplantation, provided underlying malignancy is excluded (Grade II-3).

Malignant Infiltration

24. In patients with ALF who have a previous cancer history or massive hepatomegaly, consider underlying malignancy and obtain imaging and liver biopsy to confirm or exclude the diagnosis (Grade III).

Indeterminate Etiology

25. If the etiological diagnosis remains elusive after extensive initial evaluation, liver biopsy may be appropriate to attempt to identify a specific etiology that might influence treatment strategy (Grade III).

Therapy: General Considerations

See Table 4 in the original guideline document for specific issues in intensive care of ALF.

Central Nervous System

26. In early stages of encephalopathy, lactulose may be used either orally or rectally to effect a bowel purge, but should not be administered to the point of diarrhea, and may interfere with the surgical field by increasing bowel distention during liver transplantation (Grade III).
27. Patients who progress to high-grade hepatic encephalopathy (grade III or IV) should undergo endotracheal intubation (Grade III).
28. Seizure activity should be treated with phenytoin and benzodiazepines with short half-lives. Prophylactic phenytoin is not recommended (Grade III).
29. Intracranial pressure (ICP) monitoring is recommended in ALF patients with high-grade hepatic encephalopathy, in centers with expertise in ICP monitoring, in patients awaiting and undergoing liver transplantation (Grade III).
30. In the absence of ICP monitoring, frequent (hourly) neurological evaluation is recommended to identify early evidence of intracranial hypertension (Grade III).
31. In the event of intracranial hypertension, a mannitol bolus (0.5-1.0 gm/kg body weight) is recommended as first-line therapy; however, the prophylactic administration of mannitol is not recommended (Grade II-2).
32. In ALF patients at highest risk for cerebral edema (serum ammonia >150 μM, grade 3/4 hepatic encephalopathy, acute renal failure, requiring vasopressors to maintain mean arterial pressure [MAP]), the prophylactic induction of hypernatremia with hypertonic saline to a sodium level of 145-155 mEq/L is recommended (Grade I).
33. Short-acting barbiturates and the induction of hypothermia to a core body temperature of 34-35ºC may be considered for intracranial hypertension refractory to osmotic agents as a bridge to liver transplantation (Grade II-3).
34. Corticosteroids should not be used to control elevated ICP in patients with ALF (Grade I).

Infection

35. Periodic surveillance cultures are recommended to detect bacterial and fungal pathogens as early as possible. Antibiotic treatment should be initiated promptly according to surveillance culture results at the earliest sign of active infection or deterioration (progression to high grade hepatic encephalopathy or elements of the systemic inflammatory response syndrome [SIRS]) (Grade III).
36. Prophylactic antibiotics and antifungals have not been shown to improve overall outcomes in ALF and therefore cannot be advocated in all patients, particularly those with mild hepatic encephalopathy (Grade III).

Coagulopathy

37. Replacement therapy for thrombocytopenia and/or prolonged prothrombin time is recommended only in the setting of hemorrhage or prior to invasive procedures (Grade III).

Bleeding

38. Patients with ALF in the intensive care unit should receive prophylaxis with histamine-2 receptor (H_2) blocking agents or proton pump inhibitors (or sucralfate as a second-line agent) for acid-related gastrointestinal bleeding associated with stress (Grade I).

Hemodynamics and Renal Failure

39. Fluid resuscitation and maintenance of adequate intravascular volume are recommended on presentation in patients with ALF. The initial treatment of hypotension should be with intravenous normal saline (Grade III).
40. If dialysis support is needed for acute renal failure, it is recommended that a continuous mode rather than an intermittent mode be used (Grade I).
41. Pulmonary artery catheterization is rarely necessary in patients with ALF and is associated with significant morbidity. Instead, appropriate volume status should be ensured with a volume challenge (Grade III).
42. Systemic vasopressor support with agents such as norepinephrine should be administered in volume-refractory hypotension or to ensure adequate cerebral perfusion pressure (CPP). Vasopressin or terlipressin can be added to norepinephrine in norepinephrine-refractory cases, but should be used cautiously in severely encephalopathic patients with intracranial hypertension (Grade II-1).
43. Goals of circulatory support in patients with ALF are a MAP ≥75 mmHg and CPP 60-80 mmHg (Grade II).

Metabolic Concerns

44. Metabolic homeostasis must be carefully maintained in ALF patients. Overall nutritional status as well as glucose, phosphate, potassium, and magnesium levels should be monitored frequently, with expeditious correction of derangements (Grade III).

Prognosis and Transplantation

See Table 6 in the original guideline document for potentially helpful indicators of poor prognosis in patients with ALF and indications for orthotopic liver transplantation.

Prognosis

45. Currently available prognostic scoring systems do not adequately predict outcome and determine candidacy for liver transplantation. Reliance entirely upon these guidelines is thus not recommended (Grade III).

Transplantation

46. Urgent hepatic transplantation is indicated in ALF where prognostic indicators suggest a high likelihood of death (Grade II-3).
47. Living donor or auxiliary liver transplantation may be considered in the setting of limited organ supply, but its use remains controversial (Grade II-3).

Liver Support Systems

48. Currently available liver support systems are not recommended outside of clinical trials; their future in the management of ALF remains unclear (Grade II-1).

Definitions:

Quality of Evidence on Which a Recommendation Is Based

Grade I: Randomized controlled trials

Grade II-1: Controlled trials without randomization

Grade II-2: Cohort or case-control analytic studies

Grade II-3: Multiple time series, dramatic uncontrolled experiments

Grade III: Opinions of respected authorities, descriptive epidemiology

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Acute liver failure (ALF)

Guideline Category

Diagnosis

Evaluation

Management

Treatment

Clinical Specialty

Critical Care

Emergency Medicine

Gastroenterology

Internal Medicine

Intended Users

Physicians

Guideline Objective(s)

To provide preferred approaches to the diagnostic, therapeutic, and preventive aspects of acute liver failure (ALF) care

Target Population

Patients with acute liver failure (ALF)

Interventions and Practices Considered

Diagnosis/Evaluation/Monitoring

1. Patient history, including exposure to viral infection and drugs and other toxins
2. Physical examination
3. Determination of etiology of acute liver failure (ALF) through patient history and laboratory tests
4. Admission to intensive care unit (ICU)
5. Placement on transplant list, as indicated, and consultation with transplant center
6. Liver biopsy, as indicated
7. Monitoring of intracranial pressure and neurological evaluation
8. Periodic surveillance cultures, to detect bacterial and fungal infections
9. Assessment of prognosis (currently available prognostic scoring systems should not be the sole method)

Management/Treatment by Diagnosis

Etiologies

1. Acetaminophen hepatotoxicity
    - Activated charcoal and N-acetylcysteine (NAC)
2. Mushroom poisoning
    - Penicillin G and NAC
    - Placement on transplant list
3. Drug-induced liver injury (DILI)
    - Discontinuation of all but essential medications
    - NAC
4. Viral hepatitis
    - Supportive care for types A and E
    - Nucleos(t)ide analogues for hepatitis B
    - Acyclovir herpes virus or varicella zoster

5. Wilson disease
    - Prompt consideration for transplant with confirmed diagnosis
6. Autoimmune hepatitis
    - Corticosteroids (prednisone), as indicated
    - Consideration for transplant
7. Acute fatty liver of pregnancy/hemolysis, elevated liver enzymes, low platelets (HELLP) syndrome
    - Early delivery
    - Consideration for transplant, as indicated
8. Acute ischemic injury
    - Cardiovascular support
9. Budd-Chiari syndrome
    - Liver transplantation
10. Malignant infiltration
    - Imaging and liver biopsy to confirm or exclude the diagnosis
11. Patients with poor prognosis
    - Urgent liver transplantation, as indicated
    - Living donor or auxiliary liver transplantation if necessary

Clinical Features

1. Encephalopathy
    - Lactulose, as indicated
    - Endotracheal intubation
    - Phenytoin and short-acting benzodiazepines for seizures (prophylactic phenytoin is not recommended)
    - Mannitol for intracranial hypertension (prophylactic mannitol is not recommended)
    - Prophylactic induction of hypernatremia for patients at high risk for cerebral edema
    - Short-acting barbiturates and induction of hypothermia
    - Corticosteroids (considered, but not recommended for control of elevated ICP)
2. Infection
    - Prompt initiation of antibiotics at earliest sign of infection
    - Prophylactic antibiotics and antifungals (considered but not recommended for most patients)
3. Coagulopathy
    - Replacement therapy only if hemorrhage is present or prior to invasive procedures
4. Bleeding
    - Prophylactic histamine-2 receptor (H2) blocking agents or proton-pump inhibitors for acid-related gastrointestinal (GI) bleeding
    - Sucralfate as second-line GI bleeding treatment
5. Hemodynamics/renal failure
    - Intravenous normal saline as initial fluid resuscitation and maintenance of adequate intravascular volume
    - Continuous mode dialysis support, as indicated
    - Pulmonary artery catheterization (considered but not recommended)
    - Systemic vasopressor support (norepinephrine, vasopressin, or terlipressin), as indicated
6. Metabolic concerns
    - Maintenance of metabolic homeostasis

Note: Liver support systems were considered but not recommended outside of clinical trials.

Major Outcomes Considered

- Morbidity and mortality from acute liver failure (ALF)
- Predictive value of diagnostic tests
- Effectiveness of treatment interventions
- Predictive value of prognostic factors
- 1-year and overall survival rate following transplantation

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

These recommendations are based on a formal review and analysis of recently published world literature on the topic (Medline/PubMed search from 2000 through 2011). Inclusion criteria were acute liver failure, all ages, both genders, all races, and all etiologies. Specific search terms were 'acute liver failure', 'fulminant hepatic failure', 'fulminant hepatic necrosis', and 'cerebral edema'.

Number of Source Documents

Not stated

Methods Used to Assess the Quality and Strength of the Evidence

Expert Consensus

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Quality of Evidence on Which a Recommendation Is Based

Grade I: Randomized controlled trials

Grade II-1: Controlled trials without randomization

Grade II-2: Cohort or case-control analytic studies

Grade II-3: Multiple time series, dramatic uncontrolled experiments

Grade III: Opinions of respected authorities, descriptive epidemiology

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review

Description of the Methods Used to Analyze the Evidence

The guideline authors characterized the quality of evidence supporting each recommendation, in accordance with the Practice Guidelines Committee of the American Association for the Study of Liver Diseases (AASLD) recommendations used for full Practice Guidelines (see the "Rating Scheme for the Strength of Evidence" field).

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

These recommendations provide a data-supported approach. They are based on the following: 1) formal review and analysis of recently-published world literature on the topic (Medline search); 2) American College of Physicians Manual for Assessing Health Practices and Designing Practice Guidelines; 3) guideline policies, including the American Association for the Study of Liver Diseases (AASLD) Policy on the Development and Use of Practice Guidelines and the American Gastroenterological Association (AGA) Policy Statement on Guidelines; and 4) the experience of the authors in the specified topic.

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

Peer Review

Description of Method of Guideline Validation

This position paper was produced in collaboration with the Practice Guidelines Committee of the American Association for the Study of Liver Diseases. This committee provided extensive peer review of the manuscript.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of evidence is specifically stated for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate management of acute liver failure (ALF)

Potential Harms

- Side effects from drugs
- Adverse effects from procedures

Contraindications

Contraindications

- Refractory intracranial hypertension (ICH) and/or decreased cerebral perfusion pressure (CPP) are considered relative contraindications to liver transplantation in many centers because of concern about poor neurological recovery.
- Many patients with acute liver failure (ALF) have medical or psychosocial contraindications to transplantation, including irreversible brain injury, underlying cardiovascular disease, infection/sepsis, alcohol or drug abuse, poorly controlled psychiatric disease, or inadequate family support.
- Patients who develop significant bleeding with platelet levels below approximately 50,000/mm^3 should generally be transfused with platelets provided no contraindication (such as thrombotic thrombocytopenic purpura or heparin-induced thrombocytopenia) exists.

Qualifying Statements

Qualifying Statements

Intended for use by physicians, the recommendations in this document suggest preferred approaches to the diagnostic, therapeutic, and preventive aspects of care. They are intended to be flexible, in contrast to standards of care, which are inflexible policies to be followed in every case. Specific recommendations are based on relevant published information. This document has been designated as a Position Paper, since the topic contains more data based on expert opinion than on randomized controlled trials and thus is not considered to have the emphasis and certainty of a Practice Guideline. Nevertheless, it serves an important purpose of facilitating proper and high level patient care.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Mobile Device Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

IOM Domain

Effectiveness

Identifying Information and Availability

Bibliographic Source(s)

Lee WM, Larson AM, Stravitz T. AASLD position paper: the management of acute liver failure: update 2011. Baltimore (MD): American Association for the Study of Liver Diseases; 2011 Sep. 26 p. [224 references]

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2005 May (revised 2011 Sep)

Guideline Developer(s)

American Association for the Study of Liver Diseases - Nonprofit Research Organization

Source(s) of Funding

American Association for the Study of Liver Diseases (AASLD)

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Guideline Committee

Practice Guidelines Committee of the American Association for the Study of Liver Diseases (AASLD)

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Potential conflict of interest: Dr. William Lee has advisory relationships with Eli Lilly, Cumberland, Novartis, Forest Labs and Gilead and receives research support from Bristol-Myers Squibb, Cumberland, Gilead, Globeimmune, Merck, Vertex, Novartis, Boehringer Ingelheim, Anadys and Siemens. Dr. Anne Larson and Dr. R. Todd Stravitz have nothing to report.

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Polson J, Lee WM. AASLD position paper: the management of acute liver failure. Hepatology 2005 May;41(5):1179-97. [179 references]

Guideline Availability

Electronic copies: Available in Portable Document Format (PDF) from the American Association for the Study of Liver Diseases Web site .

Print copies: Available from the American Association for the Study of Liver Diseases, 1729 King Street, Suite 200; Alexandria, VA 22314; Phone: 703-299-9766; Web site: www.aasld.org ; e-mail: aasld@aasld.org.

Availability of Companion Documents

The following is available:

- 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 Mar;55(3):965-7. Available from the American Association for the Study of Liver Diseases Web site .

This guideline is available as a Personal Digital Assistant (PDA) download via the APPRISOR™ Document Viewer from www.apprisor.com .

Patient Resources

None available

NGC Status

This summary was completed by ECRI on July 11, 2005. This summary was updated by ECRI on December 7, 2005 following the U.S. Food and Drug Administration (FDA) advisory on NovoSeven. This summary was updated by ECRI Institute on May 1, 2009 following the U.S. Food and Drug Administration advisory on antiepileptic drugs. This summary was updated by ECRI Institute on July 26, 2010 following the U.S. Food and Drug Administration (FDA) advisory on Proton Pump Inhibitors (PPI). This NGC summary was updated by ECRI Institute on June 13, 2012.

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