Complete Summary

GUIDELINE TITLE

AASLD position paper: the management of acute liver failure.

BIBLIOGRAPHIC SOURCE(S)

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

GUIDELINE STATUS

This is the current release of the guideline.

** REGULATORY ALERT **

FDA WARNING/REGULATORY ALERT

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

On December 1, 2005, Novo Nordisk and the U.S. Food and Drug Administration (FDA) notified healthcare professionals of revisions to the WARNINGS and ADVERSE REACTIONS sections of the prescribing information for NovoSeven, to provide updated safety information on thrombotic and thromboembolic adverse events, based on clinical studies in non-hemophilia patients and on post-marketing safety surveillance. A clinical study in elderly, non-hemophiliac, intracerebral hemorrhage patients indicated a potential increased risk of arterial thromboembolic adverse events with use of NovoSeven, including myocardial ischemia, myocardial infarction, cerebral ischemia and/or infarction. See the FDA Web site for more information.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Acute liver failure (ALF) due to:

- Acetaminophen hepatotoxicity
- Mushroom poisoning
- Drug-induced hepatotoxicity
- Viral hepatitis
- Wilson disease
- Autoimmune hepatitis
- Acute fatty liver of pregnancy/hemolysis, elevated liver enzymes, low platelets (HELLP) syndrome
- Acute ischemic injury
- Budd-Chiari syndrome
- Malignant infiltration
- Indeterminate etiology

GUIDELINE CATEGORY

Diagnosis
Evaluation
Management
Treatment

CLINICAL SPECIALTY

Critical Care
Emergency Medicine
Gastroenterology
Internal Medicine

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To provide a data-supported approach 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, including evaluation of signs and symptoms; assessment and documentation of mental status; search for signs of chronic liver disease, jaundice, and right upper quadrant tenderness; palpation of liver
3. Initial laboratory examinations
    - Coagulation parameters
    - Routine chemistries, including glucose
    - Arterial blood gas measurements
    - Complete blood counts and blood typing
    - Acetaminophen level and screens for other drugs and toxins
    - Viral hepatitis serologies
    - Tests for Wilson disease
    - Autoantibodies
    - Pregnancy test
    - Plasma ammonia
    - Imaging and liver biopsy, if indicated
4. Determination of etiology of liver failure
5. Admission to intensive care unit (ICU), transfer to transplant facility, and placement on transplant list, as indicated
6. Consultation with transplant center
7. Monitoring of intracranial pressure and evaluation for signs of intracranial hypertension, as indicated
8. Periodic surveillance cultures, to detect bacterial and fungal infections
9. Monitoring of nutritional status (glucose, phosphate, potassium, and magnesium)

Management/Treatment

Etiologies

Acetaminophen Hepatotoxicity

1. Activated charcoal
2. N-acetylcysteine (NAC)

Mushroom Poisoning

1. Penicillin G
2. Silymarin
3. Placement on transplant list

Drug-induced Hepatotoxicity

1. Discontinuation of all but essential medications

Viral Hepatitis

1. Supportive care
2. Nucleoside analogs (given before and after chemotherapy in patients with Hepatitis B surface antigen positivity)
3. Acyclovir (for patients with herpes virus or varicella zoster)

Wilson Disease

1. Immediate placement on transplant list

Autoimmune Hepatitis

1. Corticosteroids (prednisone)
2. Placement on transplant list

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

1. Consultation with obstetrician and expeditious delivery

Acute Ischemic Injury

1. Cardiovascular support

Budd-Chiari Syndrome

1. Liver transplantation

Clinical Features

Encephalopathy

1. Lactulose
2. Elevation of head and endotracheal intubation
3. Phenytoin + low-dose benzodiazepines for seizures
4. Mannitol with or without hyperventilation to reduce intracranial pressure
5. Short-acting barbiturates
6. Corticosteroids (considered, but not recommended)

Infection

1. Prophylactic antibiotics and antifungals (may be considered, but have not been shown to improve overall outcomes)

Coagulopathy

1. Replacement therapy (recommended only if hemorrhage is present or prior to invasive procedures)

Gastrointestinal Bleeding

1. Prophylactic histamine-2 receptor (H2) blocking agents or proton-pump inhibitors

Hemodynamics/Renal Failure

1. Fluid resuscitation and maintenance of adequate intramuscular volume
2. Continuous mode dialysis support, as indicated
3. Pulmonary artery catheterization
4. Systemic vasopressor support (epinephrine, norepinephrine, dopamine), when necessary

Metabolic Concerns

1. Maintenance of metabolic homeostasis

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

MAJOR OUTCOMES CONSIDERED

- Survival
- Morbidity and mortality
- Predictive value of tests
- Effectiveness of treatment interventions

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

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, (4) the experience of the authors in the specified topic.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

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

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Not stated

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

Not stated

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Evidence ratings (Grades 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 admitted 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**).

Table. Initial Laboratory Analysis

- Prothrombin time/international normalized ratio (INR)
- Chemistries
    - sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphate
    - glucose
    - aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, gamma glutamyl transpeptidase (GGT), total bilirubin, albumin
    - creatinine, blood urea nitrogen
- Arterial blood gas
- Arterial lactate
- Complete blood count
- Blood type and screen
- Acetaminophen level
- Toxicology screen
- Viral hepatitis serologies
    - anti-hepatitis A (HAV) IgM, hepatitis B surface antigen (HBSAg), anti-hepatitis B core antibody (anti-HBc IgM), antibody to hepatitis E (anti-HEV[#]), and antibody to hepatitis C (anti-HCV*)
- Ceruloplasmin level**
- Pregnancy test (females)
- Ammonia (arterial if possible)
- Autoimmune markers
    - antinuclear antibody (ANA), anti-smooth muscle antibody (ASMA), Immunoglobulin levels
- Human immunodeficiency virus (HIV) status***
- Amylase and lipase

* Done to recognize potential underlying infection
** Done only if Wilson disease is a consideration (e.g., in patients less than 40 years without another obvious explanation for ALF); in this case uric acid level and bilirubin to alkaline phosphatase ratio may be helpful as well.
*** Implications for potential liver transplantation
# If clinically indicated.

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 acute liver failure in which acetaminophen ingestion is possible or when knowledge of circumstances surrounding admission is inadequate (**Grade III**).

Mushroom Poisoning

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

Drug Induced Hepatotoxicity

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 acute liver failure due to possible drug hepatotoxicity, discontinue all but essential medications (**Grade III**) (See Table 3 "Some Drugs Which May Cause Idiosyncratic Liver Injury to ALF" in the original guideline.)

Viral Hepatitis

12. 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 (**Grade III**).
13. 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 (**Grade III**).
14. Patients with known or suspected herpes virus or varicella zoster as the cause of acute liver failure should be treated with acyclovir (**Grade III**).

Wilson Disease

15. Diagnostic tests for Wilson disease should include ceruloplasmin, serum and urinary copper levels, total bilirubin/alkaline phosphatase ratio, slit lamp examination for Kayser-Fleischer rings, and hepatic copper levels when liver biopsy is feasible (**Grade III**).
16. Patients in whom Wilson disease is the likely cause of acute liver failure must be immediately placed on the liver transplant list (**Grade III**).

Autoimmune Hepatitis

17. When autoimmune hepatitis is suspected as the cause of acute liver failure, liver biopsy should be considered to establish this diagnosis (**Grade III**).
18. Patients with acute liver failure due to autoimmune hepatitis should be treated with corticosteroids (prednisone, 40-60 mg/day) (**Grade I**).
19. Patients should be placed on the list for transplantation even while corticosteroids are being administered (**Grade III**).

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

20. For acute fatty liver of pregnancy or the HELLP syndrome, consultation with obstetrical services and expeditious delivery are recommended (**Grade III**).

Acute Ischemic Injury

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

Budd-Chiari Syndrome

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

Malignant Infiltration

23. In patients with acute liver failure 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

24. 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

Central Nervous System and Intracranial Pressure Monitoring

25. In early stages of encephalopathy, sedation should be avoided if possible. Lactulose may be used, but concern has been raised about increasing bowel distention during the subsequent transplant procedure (**Grades II-2, III**).
26. In patients progressing to grade III or IV encephalopathy, the head should be elevated to 30 degrees, and endotracheal intubation should be performed (**Grade III**).
27. Seizure activity should be treated with phenytoin and low-dose benzodiazepines (**Grade III**).
28. Although there is no consensus among the centers and experts, intracranial pressure (ICP) monitoring is mainly considered for patients who are listed for transplantation (**Grade III**).

29. In the absence of ICP monitoring, frequent evaluation for signs of intracranial hypertension are needed to identify early evidence of uncal herniation (**Grade III**).
30. In the event of intracranial hypertension, mannitol should be given and hyperventilation may be considered in order to temporarily reduce the ICP, but prophylactic use of these interventions is not helpful and therefore not recommended (**Grade I**).
31. Short-acting barbiturates may be considered for refractory intracranial hypertension (**Grade III**).
32. Corticosteroids should not be used to control elevated ICP in patients with acute liver failure (**Grade I**).

Infection

33. Periodic surveillance cultures should be performed to detect bacterial and fungal infections as early as possible and prompt treatment should be initiated accordingly (**Grades II-2, III**).
34. Prophylactic antibiotics and anti-fungals may be considered but have not been shown to improve overall outcomes (**Grades II-2, III**).

Coagulopathy

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

Gastrointestinal (GI) Bleeding

36. Patients with ALF in the intensive care unit should receive prophylaxis with H2 blocking agents or proton pump inhibitors (PPIs) (or sucralfate as a second-line agent) for acid-related gastrointestinal bleeding associated with stress (**Grades I, III**).

Hemodynamics/Renal Failure

37. Careful attention must be paid to fluid resuscitation and maintenance of adequate intravascular volume in patients with acute liver failure (**Grade III**).
38. 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**).
39. Pulmonary artery catheterization should be considered in a hemodynamically unstable patient to ensure that appropriate volume replacement has occurred (**Grade III**).
40. Systemic vasopressor support with agents such as epinephrine, norepinephrine, or dopamine but not vasopressin should be used if fluid replacement fails to maintain mean arterial pressure (MAP) of 50-60 mm Hg (**Grades III, II-1**).

Metabolic Concerns

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

Table: Intensive Care of ALF

Cerebral Edema/Intracranial Hypertension
Grade I/II Encephalopathy • Consider transfer to liver transplant facility and listing for transplantation • Brain computed tomography (CT): rule out other causes of decreased mental status; little utility to identify cerebral edema • Avoid stimulation, avoid sedation if possible • Antibiotics: surveillance and treatment of infection required; prophylaxis possibly helpful • Lactulose: possibly helpful Grade III/IV Encephalopathy • Continue management strategies listed above • Intubate trachea (may require sedation) • Elevate head of bed • Consider placement of intracranial pressure (ICP) monitoring device • Immediate treatment of seizures required; prophylaxis of unclear value • Mannitol: use for severe elevation of intracranial pressure or first clinical signs of herniation • Hyperventilation: effects short-lived; may use for impending herniation
Infection
• Surveillance for and prompt antimicrobial treatment of infection required • Antibiotic prophylaxis possibly helpful but not proven
Coagulopathy
• Vitamin K: give at least one dose • Fresh frozen plasma (FFP): give only for invasive procedures or active bleeding • Platelets: give for platelet counts <10,000/mm^3 or invasive procedures • Recombinant activated factor VII: possibly effective for invasive procedures • Prophylaxis for stress ulceration: give histamine-2 receptor blocker or proton pump inhibitor
Hemodynamics/Renal Failure
• Pulmonary artery catheterization • Volume replacement • Pressor support (dopamine, epinephrine, norepinephrine) as needed to maintain adequate mean arterial pressure • Avoid nephrotoxic agents • Continuous modes of hemodialysis if needed

• N-acetylcysteine, prostacyclin: effectiveness unknown • Vasopressin: not helpful in ALF; potentially harmful
Metabolic Concerns
• Follow closely: glucose, potassium, magnesium, phosphate • Consider nutrition: enteral feedings if possible or total parenteral nutrition

Transplantation and Prognosis

Transplantation

42. Urgent hepatic transplantation is indicated in acute liver failure where prognostic indicators suggest a high likelihood of death (**Grade II-3**).

Liver Support Systems

43. Currently available liver support systems are not recommended outside of clinical trials; their future in the management of ALF remains unclear (**Grades I, II-1**).

Prognosis

44. 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 (**Grades II-2, II-3, III**).

Definitions:

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

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

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

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate diagnosis, evaluation, and management of acute liver failure (ALF)

POTENTIAL HARMS

Not stated

CONTRAINDICATIONS

CONTRAINDICATIONS

Refractory intracranial hypertension (ICH) and/or decreased cerebral perfusion pressure (CPP) is considered a contraindication to liver transplantation in many centers.

QUALIFYING STATEMENTS

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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 and the authors have 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 "Rating Scheme for the Strength of the Evidence" field). These recommendations are fully endorsed by the AASLD.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

IMPLEMENTATION TOOLS

Personal Digital Assistant (PDA) Downloads

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)

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

ADAPTATION

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

DATE RELEASED

2005 May

GUIDELINE DEVELOPER(S)

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

SOURCE(S) OF FUNDING

American Association for the Study of Liver Diseases

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Practice Guidelines Committee

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Disclosure Statement: The authors have no conflicts of interest to disclose.

GUIDELINE STATUS

This is the current release of the guideline.

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

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.

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