AASLD Position Paper: The Management of Acute Liver Failure

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Preamble

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,[1] (3) guideline policies, including the AASLD Policy on the Development and Use of Practice Guidelines and the AGA Policy Statement on Guidelines,[2] (4) the experience of the authors in the specified topic.

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 we have characterized the quality of evidence supporting each recommendation, in accordance with the Practice Guidelines Committee of the AASLD recommendations used for full Practice Guidelines (Table 1[3]). These recommendations are fully endorsed by the AASLD.

Introduction

Acute liver failure (ALF) is a rare condition in which rapid deterioration of liver function results in altered mentation and coagulopathy in previously normal individuals. U.S. estimates are placed at approximately 2,000 cases per year.[4] The most prominent causes include drug-induced liver injury, viral hepatitis, autoimmune liver disease and shock or hypoperfusion; many cases (≈20%) have no discernible cause.[5] Acute liver failure often affects young persons and carries a high morbidity and mortality. Prior to transplantation, most series suggested less than 15% survival. Currently, overall short-term survival with transplantation is greater than 65%.[5] Because of its rarity, ALF has been difficult to study in depth and very few controlled therapy trials have been performed. As a result, standards of intensive care for this condition have not been established.

Definition

The most widely accepted definition of ALF includes evidence of coagulation abnormality, usually an INR ≥1.5, and any degree of mental alteration (encephalopathy) in a patient without preexisting cirrhosis and with an illness of <26 weeks duration.[6] Patients with Wilson disease, vertically-acquired HBV, or autoimmune hepatitis may be included in spite of the possibility of cirrhosis if their disease has only been recognized for <26 weeks. A number of other terms have been used including fulminant hepatic failure and fulminant hepatitis or necrosis. Acute liver failure is a better overall term that should encompass all durations up to 26 weeks. Terms used signifying length of illness such as hyperacute (<7 days), acute (7-21 days) and subacute (>21 days and <26 weeks) are not particularly helpful since they do not have prognostic significance distinct from the cause of the illness. For example, hyperacute cases may have a better prognosis but this is because most are due to acetaminophen toxicity.[5]

Abbreviations: ALF, acute liver failure; NAC, N-acetylcysteine; HELLP, Hemolysis, Elevated Liver Enzymes, Low Platelets syndrome; ICH, intracranial hypertension; ICP, intracranial pressure; CT, computerized tomography; US ALFSG, United States Acute Liver Failure Study Group; CPP, cerebral perfusion pressure; MAP, mean arterial pressure; SIRS, systemic inflammatory response syndrome; FFP, fresh frozen plasma; rFVIIa, recombinant activated factor; GI, gastrointestinal; H2, histamine-2; PPI, proton pump inhibitors; CVVHD, continuous venovenous hemodialysis; APACHE, Acute Physiology and Chronic Health Evaluation; AFP, alpha fetoprotein; MELD, Model for End-stage Liver Disease.

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Table 1. Quality of Evidence on Which a Recommendation Is Based[3]

Grade	Definition
I	Randomized controlled trials
II-1	Controlled trials without randomization
II-2	Cohort or case-control analytic studies
II-3	Multiple time series, dramatic uncontrolled experiments
III	Opinions of respected authorities, descriptive epidemiology

Diagnosis and Initial Evaluation

All patients with clinical or laboratory evidence of moderate to severe acute hepatitis should have immediate measurement of prothrombin time and careful evaluation for subtle alterations in mentation. If the prothrombin time is prolonged by ≈4-6 seconds or more (INR ≥1.5) and there is any evidence of altered sensorium, the diagnosis of ALF is established and hospital admission is mandatory. Since the condition may progress rapidly, with changes in consciousness occurring hour-by-hour, early transfer to the intensive care unit (ICU) is preferred once the diagnosis of ALF is made.

History taking should include careful review of possible exposures to viral infection and drugs or other toxins. If severe encephalopathy is present, the history may be provided entirely by the family or may be unavailable. In this setting, limited information is available, particularly regarding possible toxin/drug ingestions. Physical examination must include careful assessment and documentation of mental status and a search for stigmata of chronic liver disease. Jaundice is often but not always seen at presentation. Right upper quadrant tenderness is variably present. Inability to palpate the liver or even to percuss a significant area of dullness over the liver can be indicative of decreased liver volume due to massive hepatocyte loss. An enlarged liver may be seen early in viral hepatitis or with malignant infiltration, congestive heart failure, or acute Budd-Chiari syndrome. History or signs of cirrhosis should be absent as such features suggest underlying chronic liver disease, which may have different management implications. Furthermore, the prognostic criteria mentioned below are not applicable to patients with acute-on-chronic liver disease.

Initial laboratory examination must be extensive in order to evaluate both the etiology and severity of ALF (Table 2). In addition to coagulation parameters, early testing should include routine chemistries (especially glucose as hypoglycemia may be present and require correction), arterial blood gas measurements, complete blood counts, blood typing, acetaminophen level and screens for other drugs and toxins, viral hepatitis serologies (most prominently A and B), tests for Wilson disease, autoantibodies (anti-nuclear and anti-smooth muscle antibodies) and a pregnancy test in females. Plasma ammonia, preferably arterial,[7,8] may also be helpful. A liver biopsy, most often done via the transjugular route because of coagulopathy, may be indicated when certain conditions such as autoimmune hepatitis, metastatic liver disease, lymphoma, or herpes simplex hepatitis are suspected. As the evaluation continues, several important decisions must be made: whether to admit the patient to an ICU, whether to transfer the patient to a transplant facility, and (if already at a transplant center) whether and when to place the patient on the list for transplantation. For patients in a non-transplant center, the possibility of rapid progression of ALF makes early consultation with a transplant facility critical. Specific prognostic indicators may point toward the need for transplantation. For patients with acetaminophen-related ALF in particular, an arterial pH of <7.3 should prompt immediate consideration for transfer to a transplant center and placement on a transplant list.[9]

Patients with altered mentation should generally be admitted to an ICU. Planning for transfer to a transplant center should begin in patients with grade I or II encephalopathy (Table 2) because they may worsen rapidly. Early transfer is important as the risks involved with patient transport may increase or even preclude transfer once stage III or IV encephalopathy develops. Evaluation for transplantation should begin as early as possible. In these critically ill patients with potential for rapid deteri-

Table 2. Initial Laboratory Analysis

Prothrombin time/INR
Chemistries
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 type and screen
Acetaminophen level
Toxicology screen
Viral hepatitis 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

*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.

oration it is necessary to make treatment plans promptly. Social and financial considerations are unavoidably tied to the overall clinical assessment where transplantation is contemplated. It is important to inform the patient's family or other next of kin of the potentially poor prognosis and to include them in the decision-making process.

Recommendations

1. Patients with ALF should be admitted and monitored frequently, preferably in an ICU (III).

2. Contact with a transplant center and plans to transfer appropriate patients with ALF should be initiated early in the evaluation process (III).

3. The precise etiology of ALF should be sought to guide further management decisions (III).

Determining Etiologies and Specific Therapies

Etiology of ALF provides one of the best indicators of prognosis,[5] and also dictates specific management options.

Acetaminophen Hepatotoxicity

Acetaminophen hepatotoxicity is suggested by historic evidence for excessive ingestion either as an intended suicidal overdose or the inadvertent use of supra-therapeutic quantities of pain medications. Acetaminophen is a dose-related toxin; most ingestions leading to ALF exceed 10 gm/day. However, severe liver injury can occur rarely when doses as low as 3-4 gm/day are taken.[10] Very high aminotransferases may be seen; serum levels exceeding 3,500 IU/L are highly correlated with acetaminophen poisoning[11] and should prompt consideration of this etiology even when historic evidence is lacking. Because acetaminophen is the leading cause of ALF (at least in the United States and Europe) and there is an available antidote, acetaminophen levels should be drawn in all patients presenting with ALF. Low or absent acetaminophen levels do not rule out acetaminophen poisoning since the time of ingestion may be remote or unknown, especially when overdose may have been unintentional and/or occurred over several days. If acetaminophen ingestion is known or suspected to have occurred within a few hours of presentation, activated charcoal may be useful for gastrointestinal decontamination. While it is most effective if given within one hour of ingestion,[12] it may be of benefit as long as 3 to 4 hours after ingestion.[13] Administration of activated charcoal (standard dose 1g/kg orally, in a slurry) just prior to administration of N-acetylcysteine does not reduce the effect of N-acetylcysteine.[13] N-acetylcysteine (NAC), the antidote for acetaminophen poisoning, has been shown to be effective and safe for this purpose in numerous controlled trials.[15-18] The standard acetaminophen toxicity nomogram[19] may aid in determining the likelihood of serious liver damage, but cannot be used to exclude possible toxicity due to multiple doses over time, or altered metabolism in the alcoholic or fasting patient.[20] Given these considerations, administration of NAC is recommended in any case of ALF in which acetaminophen overdose is a suspected or possible cause. NAC should be given as early as possible, but may still be of value 48 hours or more after ingestion.[21] NAC may be given orally (140 mg/kg by mouth or nasogastric tube diluted to 5% solution, followed by 70 mg//kg by mouth q 4 h $\times$ 17 doses) and has few side effects (occasional nausea, vomiting, rare urticaria or bronchospasm). In patients with ALF oral administration may often be precluded (for instance, by active gastrointestinal bleeding or worsening mental status), and NAC may be administered intravenously (loading dose is 150 mg/kg in 5% dextrose over 15 minutes; maintenance dose is 50 mg/kg given over 4 hours followed by 100 mg/kg administered over 16 hours). Allergic reactions may be successfully treated with discontinuation, antihistamines[22] and epinephrine for bronchspasm.

Recommendations

4. For patients with known or suspected acetaminophen overdose within 4 hours of presentation, give activated charcoal just prior to starting NAC (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 (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 (III).

Mushroom Poisoning

Mushroom Poisoning (usually *Amanita phalloides*) may cause ALF, and the initial history should always include inquiry concerning recent mushroom ingestion. There is no available blood test to confirm the presence of these toxins, but this diagnosis should be suspected in patients with a history of severe gastrointestinal symptoms (nausea, vomiting, diarrhea, abdominal cramping), which occur within hours to a day of ingestion. If these effects are present, it may be early enough to treat patients with gastric lavage and activated charcoal via naso-gastric tube. Fluid resuscitation is also important. Traditionally, very low rates of survival have been reported without

transplantation,[23] but more recently complete recovery has been described with supportive care and medical treatment.[24] Penicillin G and silibinin (silymarin or milk thistle) are the accepted antidotes despite no controlled trials proving their efficacy.[23,25,26] While some reports have not found penicillin G to be helpful,[27] enough efficacy has been reported to warrant consideration of the drug (given intravenously in doses of 300,000 to 1 million units/kg/day) in patients with known or suspected mushroom poisoning.[28] Silibinin has generally been reported to be more successful than penicillin G, although penicillin G has been used more frequently in the United States.[27,28] Silibinin/silymarin is not available as a licensed drug in the United States, although it is widely available in Europe and South America. In the United States, it is commercially available as milk thistle extracts, tablets, capsules or tincture. These products usually contain 70%-80% silymarin, although there is no governmental regulation of such herbal supplements; silymarin concentrations may vary considerably between preparations and manufacturers.[29] When used for treatment of mushroom poisoning, silymarin has been given in average doses of 30-40 mg/kg/day (either intravenously or orally) for an average duration of 3 to 4 days.[26] N-acetylcysteine is often combined with these other therapies, but has not been shown to be effective in animal studies[30]; nevertheless, case reports have described its use as a part of overall management.[31]

Recommendation

7. In ALF patients with known or suspected mushroom poisoning, consider administration of penicillin G and silymarin (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 (III).

Drug Induced Hepatotoxicity

A variety of medications have been associated with acute liver injury. Before implicating a particular substance, history should include careful listing of all agents taken, the time period involved, and the quantity ingested. Drugs other than acetaminophen rarely cause dose-related toxicity. Most examples of idiosyncratic drug hepatotoxicity occur within the first 6 months after drug initiation. A potentially hepatotoxic medication that has been used continually for more than 1 to 2 years is unlikely to cause de novo liver damage. Certain herbal preparations and other nutritional supplements have been found to cause liver injury,[32] so inquiry about such substances should be included in a complete medication history. There are no specific antidotes for idiosyncratic drug reactions; corticosteroids are not indicated unless a drug hypersensitivity reaction is suspected. Determination of a particular medication as the cause of ALF is a diagnosis of exclusion. Other causes of ALF should still be ruled out even if a drug is suspected. Any presumed or possible offending agent should be stopped immediately where possible. Classes of drugs commonly implicated include antibiotics, non-steroidal anti-inflammatory agents and anti-convulsants (Table 3).

Table 3. Some Drugs Which May Cause Idiosyncratic Liver Injury Leading to ALF

Isoniazid	Isoflurane
Sufonamides	Lisinopril
Phenytoin	Nicotinic acid
Statins	Imipramine
Propylthiouracil	Gemtuzumab
Halothane	Amphetamines/Ecstasy
Disulfiram	Labetalol
Valproic acid	Etoposide
Amiodarone	Flutamide
Dapsone	Tolcapone
Herbals*	Quetiapine
Didanosine	Nefazodone
Efavirenz	Allopurinol
Metformin	Methyldopa
Ofloxacin	Ketoconazole
PZA	
Troglitazone	
Diclofenac	

Combination agents with enhanced toxicity:
- Trimethoprim-sulfamethoxazole
- Rifampin-isoniazid
- Amoxicillin-clavulanate

*Some Herbal products/dietary supplements that have been associated with hepatotoxicity include:

Kava kava	Chaparral
Skullcap	Germander
Pennyroyal	Jin Bu Huan
Heliotrope	Rattleweed
Comfrey	Sunnhemp
Senecio	Impila
Greater celandine	Gum Thistle
He Shon Wu	Ma Huang
LipoKinetix	Bai-Fang herbs

Recommendations

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 (III).

10. Determine ingredients of non-prescription medications whenever possible (III).

11. In the setting of acute liver failure due to possible drug hepatotoxicity, discontinue all but essential medications (III).

Viral Hepatitis

Hepatitis serological testing should be done for identification of acute viral infection (Table 2) even when another putative etiology is identified. Viral hepatitis has become a relatively infrequent cause of ALF (United States: 12%; hepatitis B – 8%, hepatitis A – 4%).[5] Acute hepatitis D may occasionally be diagnosed in a hepatitis B positive individual. Although controversial, hepatitis C alone does not appear to cause ALF.[5,33] Hepatitis E is a significant cause of liver failure in countries where it is endemic, and tends to be more severe in pregnant women.[33,34] This virus should be considered in anyone with recent travel to an endemic area such as Russia, Pakistan, Mexico, or India. With acute viral hepatitis, as with many other etiologies of ALF, care is mainly supportive. Of note, the nucleoside analog lamivudine (and possibly adefovir), used widely in the treatment of chronic hepatitis B, may be considered in patients with acute hepatitis B, although these drugs have not been subjected to a controlled trial[35] in acute disease. Acute liver failure due to reactivation of hepatitis B may occur in the setting of chemotherapy or immunosuppression. Recent evidence suggests that patients found to be positive for HBsAg who are to begin such therapy should be treated prophylactically with a nucleoside analog, and that such treatment should be continued for 6 months after completion of immunosuppressive therapy (please refer to the AASLD Practice Guideline on Management of Chronic Hepatitis B, Update of Recommendations[36]). Herpes virus infection rarely causes ALF. Immunosuppressed patients or pregnant women (usually in the third trimester) are at increased risk, but occurrences of herpes virus ALF have been reported in healthy individuals.[33,37,38] Skin lesions are present in only about 50% of cases. Liver biopsy is helpful in making the diagnosis. Treatment should be initiated with acyclovir for suspected or documented cases.[37,38] Other viruses such as varicella zoster[39] have occasionally been implicated in causing hepatic failure.

Recommendations

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 (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 (III).

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

Wilson disease

Wilson disease is an uncommon cause of ALF (2%-3% of cases in the US ALFSG). Early identification is critical because the fulminant presentation of Wilson disease is considered to be uniformly fatal without transplantation. The disease typically occurs in young patients, accompanied by the abrupt onset of hemolytic anemia with serum bilirubin levels >20 mg/dL. Due to the presence of hemolysis, the indirect-reacting bilirubin is often markedly elevated along with the total bilirubin. Kayser-Fleischer rings are present in about 50% of patients presenting with ALF due to Wilson disease.[40] Serum ceruloplasmin is typically low, but may be normal in up to 15% of cases and is often reduced in other forms of ALF; high serum and urinary copper levels as well as hepatic copper measurement may confirm the diagnosis. Very low serum alkaline phosphatase or uric acid levels are hints to suggest Wilson disease in the absence of other indicators. A high bilirubin (mg/dL) to alkaline phosphatase (IU/L) ratio (>2.0) is a reliable albeit indirect indicator of Wilson disease in this setting.[40,41] Renal function is often impaired as the released copper can cause renal tubular damage. Treatment to acutely lower serum copper and to limit further hemolysis should include albumin dialysis, continuous hemofiltration, plasmapheresis or plasma exchange. Initiation of treatment with penicillamine is not recommended in ALF as there is a risk of hypersensitivity to this agent; acute lowering of the copper is more effectively accomplished using direct plasma copper reduction techniques, especially when renal function is impaired.[40] Although such copper lowering measures should be considered, recovery is infrequent without transplantation.[40,42] Wilson disease is one of the special circumstances in which patients may already have evidence of cirrhosis and still be considered to have a diagnosis of ALF when rapid deterioration occurs. Please refer to the AASLD Practice Guideline on Wilson Disease for more detailed information regarding the diagnosis and management of patients with this condition.[40]

Recommendations

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 (III).

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

Autoimmune hepatitis

With autoimmune hepatitis as with Wilson disease, patients may have unrecognized preexisting chronic disease and yet still be considered as having ALF. Such patients represent the most severe form of the disease, and would generally fall into the category of patients recommended for corticosteroid therapy as outlined by the AASLD Practice Guidelines for the Diagnosis and Treatment of Autoimmune Hepatitis (although ALF is not specifically discussed in that document).[43] Although some patients may be responsive to steroid therapy, others require transplantation.[44,45] Autoantibodies may be absent making a definitive diagnosis difficult. Liver biopsy may be helpful if findings include presence of severe hepatic necrosis accompanied by interface hepatitis, plasma cell infiltration and hepatocyte rosettes. Initiation of steroid therapy may constitute a therapeutic trial for some patients (prednisone starting at 40-60 mg/day),[43] although placement on the transplant list is indicated.

Recommendations

17. When autoimmune hepatitis is suspected as the cause of acute liver failure, liver biopsy should be considered to establish this diagnosis (III).

18. Patients with acute liver failure due to autoimmune hepatitis should be treated with corticosteroids (prednisone, 40-60 mg/day) (I).

19. Patients should be placed on the list for transplantation even while corticosteroids are being administered (III).

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

A small number of women near the end of pregnancy will develop rapidly progressive hepatocyte failure that has been well characterized[46-49] and associated with increased fetal or maternal mortality. A variety of presentations may be seen, generally confined to the last trimester. The triad of jaundice, coagulopathy, and low platelets may occasionally be associated with hypoglycemia. Features of pre-eclampsia such as hypertension and proteinuria are common. Steatosis documented by imaging studies supports the diagnosis. The Oil-red O staining technique best demonstrates hepatic steatosis on biopsy. Intrahepatic hemorrhage and/or hepatic rupture constitute rare emergent situations requiring rapid resuscitation and intervention. Early recognition of these syndromes and prompt delivery are critical in achieving good outcomes. Recovery is typically rapid after delivery, and supportive care is the only other treatment required. Postpartum transplantation has occasionally been necessary, however.[50] Pregnancy (especially in the third trimester) appears to increase the risk of ALF due to herpes virus, which should be treated with acyclovir (see section on acute viral infection).[37] It is important to keep in mind that ALF in pregnant women may also be caused by entities not necessarily related to the pregnant state.

Recommendation

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

Acute Ischemic Injury

A syndrome often referred to as "shock liver" occurs after cardiac arrest, a period of significant hypovolemia/hypotension, or in the setting of severe congestive heart failure.[51] Documented hypotension is not always found. Drug-induced hypotension or hypoperfusion may be observed with long-acting niacin,[52] or with cocaine,[53] or methamphetamine.[54] Other physical findings may be lacking, but evidence of cardiac dysfunction may be elicited via echocardiogram.[55] Aminotransferase levels will be markedly elevated and respond rapidly to stabilization of the circulatory problem. Simultaneous onset of renal dysfunction and muscle necrosis may be noted. The ability to manage heart failure or other causes of ischemia successfully will determine outcome for these patients, and transplantation is seldom indicated.

Recommendation

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

Budd-Chiari Syndrome

The Budd-Chiari syndrome (acute hepatic vein thrombosis) can also present as ALF. Abdominal pain, ascites and striking hepatomegaly are often present. The diagnosis should be confirmed with hepatic imaging studies (computed tomography, doppler ultrasonography, venography, magnetic resonance venography). In the presence of significant liver failure, transplantation may be required as opposed to venous decompression.[56] As malignancy-associated hypercoagulability is one of the causes of Budd-Chiari syndrome, it is important to rule out underlying cancer prior to transplantation of these patients.

Recommendation

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

Malignant Infiltration

Malignant infiltration of the liver may cause ALF. Massive hepatic enlargement may be seen. Diagnosis should be made by imaging and biopsy, and treatment appropriate for the underlying malignant condition is indicated. Transplantation is not an option for such patients.[57,58] Acute severe hepatic infiltration occurs with breast cancer,[59,60] small cell lung cancers,[61] lymphoma[58] and melanoma.[62]

Recommendations

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 (III).

Indeterminate Etiology

When the etiology of ALF cannot be determined after routine evaluation, biopsy using a transjugular approach may be helpful in diagnosing malignant infiltration, autoimmune hepatitis, certain viral infections and Wilson disease. Lack of a clear diagnosis suggests that the history may have been inadequate regarding toxin or drug exposures.

Recommendation

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 (III).

Therapy: General Considerations

Background

While patients with ALF represent a heterogeneous group, they have consistent clinical features, and share the common disease process of acute hepatocyte loss and its sequelae. Despite decades of research, however, no agent or therapy that is beneficial to all patients with ALF has been found. Systemic corticosteroids are ineffective in this condition.[63-65]

Because most patients with ALF tend to develop some degree of circulatory dysfunction, agents that may improve hemodynamics have been of particular interest. While prostacyclin and other prostaglandins have appeared promising in some reports,[66,67] others have not supported their efficacy in ALF.[68] NAC may improve systemic circulation parameters in patients with ALF,[69] but this was not observed in all studies.[70] NAC has been shown to improve liver blood flow and function in patients with septic shock.[71] Use of NAC in all forms of ALF cannot be justified based on current evidence. A large, multi-center, randomized, double-blind controlled trial of intravenous NAC versus placebo for non-acetaminophen ALF is currently under way**.** Because there is no proven therapy for ALF in general, management consists of intensive care support once treatments for specific etiologies have been initiated. While some patients with evidence of acute liver injury but without significant coagulopathy or encephalopathy may be monitored on a medicine ward, any patient with altered mental status warrants admission to an ICU as the condition may deteriorate quickly. Careful attention must be paid to fluid management, hemodynamics and metabolic parameters as well as surveillance for and treatment of infection. Maintenance of nutrition and prompt recognition and resuscitation of gastrointestinal bleeding are crucial as well. Coagulation parameters, complete blood counts, metabolic panels (including glucose) and arterial blood gas should be checked frequently. Serum aminotransferases and bilirubin are generally measured daily to follow the course of the condition, however changes in aminotransferase levels correlate poorly with prognosis.

Specific Issues. See Table 4.

Central Nervous System

Cerebral edema and intracranial hypertension (ICH) have long been recognized as the most serious complications of ALF.[72] Uncal herniation may result and is uniformly fatal. Cerebral edema may also contribute to ischemic and hypoxic brain injury, which may result in long-term neurological deficits in survivors.[73] The pathogenic mechanisms leading to the development of cerebral edema and ICH in ALF are not entirely understood. It is likely that multiple factors are involved, including osmotic disturbances in the brain and heightened cerebral blood flow due to loss of cerebrovascular autoregulation. Inflammation and/or infection, as well as factors yet unidentified may also contribute to the phenomenon.[74] Several measures have been proposed and used with varying success to tackle the problem of cerebral edema and the associated ICH in patients with ALF. Some interventions are supported by more evidence than others; no uniform protocol has been established.

Prevention/Management of Elevated Intracranial Pressure (ICP). The occurrence of cerebral edema and ICH in ALF is related to severity of encephalopathy (Table 5). Cerebral edema is seldom observed in patients with grade I-II encephalopathy. The risk of edema increases to 25% to 35% with progression to grade III, and 65% to 75% or more in patients reaching grade IV coma.[75] A stepwise approach to management is therefore advised.[76]

Grades I-II. Depending on the overall clinical picture, patients with only grade I encephalopathy may sometimes be safely managed on a medicine ward with

Table 4. Intensive Care of Acute Liver Failure

Cerebral Edema/Intracranial Hypertension
Grade I/II Encephalopathy
Consider transfer to liver transplant facility and listing for transplantation
Brain 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 ICP monitoring device
Immediate treatment of seizures required; prophylaxis of unclear value
Mannitol: use for severe elevation of ICP 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
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 H2 blocker or PPI
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
NAC, 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

skilled nursing in a quiet environment to minimize agitation, although management in an ICU is preferable. Frequent mental status checks should be performed with transfer to an ICU if level of consciousness declines. With progression to grade II encephalopathy, an ICU setting is indicated. Head imaging with computerized tomography (CT) is used to exclude other causes of decline in mental status such as intracranial hemorrhage. Sedation is to be avoided if possible; unmanageable agitation may be treated with short-acting benzodiazepines in small doses.

Lactulose. There is increasing evidence that ammonia may play a pathogenic role in the development of cerebral edema/ICH; ammonia infusion has been shown to cause brain edema in animal models.[77] Some human studies have supported these findings, with an arterial ammonia level >200 ug/dL being strongly associated with cerebral herniation.[7] Based on such evidence and on prior experience with treatment of hepatic encephalopathy in patients with cirrhosis, it has been suggested that reducing elevated ammonia levels with enteral administration of lactulose might help prevent or treat cerebral edema in ALF. A preliminary report from the United States Acute Liver Failure Study Group (US ALFSG), retrospectively comparing patients who received lactulose to a well-matched group of patients who did not, found that lactulose therapy was associated with a small increase in survival time, but with no difference in severity of encephalopathy or in overall outcome.[78] One concern regarding the use of lactulose in this setting is the potential for gaseous abdominal distension that could present technical difficulties in a subsequent transplantation procedure.

Grades III-IV. As patients progress to grade III or IV encephalopathy it is advisable to intubate the trachea for airway protection. Choice of sedation in this instance will vary according to clinician preference: propofol is often used because it may reduce cerebral blood flow[79]; however, its effectiveness in this regard has not been shown in controlled studies. Small doses of propofol may be adequate, given its long half-life in patients with hepatic failure. 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 becomes critical, and frequent neurological evaluation for signs of elevated intracranial pressure should be conducted. Patients should be positioned with head elevated at 30 degrees.[80] Efforts should be made to avoid patient stimulation. Maneuvers that cause straining or Valsalva-like movements in particular may increase ICP; it may be advisable to use endotracheal lidocaine prior to endotracheal suctioning.

Seizures. Seizures, which may be seen as a manifestation of the process that leads to hepatic coma and ICH, should be controlled with phenytoin. Use of any sedative is discouraged in light of its effects on the evaluation of mental status. Only minimal doses of benzodiazepines should be used given their delayed clearance by the failing liver. Seizure activity may acutely elevate ICP[81] and may also cause cerebral hypoxia and thus contribute to cerebral

Table 5. Grades of Encephalopathy

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

Note: some patients will overlap grades; clinical judgment is required. Adapted from Conn HO, Leevy CM, Vhlahcevic ZR, Rodgers JB, Maddrey WC, Seeff L, Levy LL. Comparison of lactulose and neomycin in the treatment of chronic portal-systemic encephalopathy. A double blind controlled trial. Gastroenterology 1977; 72:573–583.

edema. Some experts have advocated prophylactic use of phenytoin, especially as seizure activity may be inapparent. A small randomized controlled trial of prophylactic phenytoin in ALF showed no difference in overall survival, but a striking diminution in cerebral edema at autopsy in the treated group.[82] A recent clinical trial did not show beneficial effects on the prevention of seizures, brain edema or survival.[83] Further studies may clarify the value of this treatment, but it cannot be recommended as a prophylactic measure at this time.

Intracranial Pressure Monitoring

The use of ICP monitoring devices in ALF is a subject of ongoing debate. ICP monitoring is used variably across the United States, with some centers not considering it useful and others using it regularly. A survey of the initial 14 transplant centers in the US ALFSG found ICP monitoring devices were used in 13 of these sites from 1998-2000[84]; a more recent informal review of more than 20 sites found ICP monitors used in a little more than half (unpublished). Without the use of these monitoring devices, early recognition of cerebral edema cannot reliably be made. The clinical signs of elevated ICP including hypertension, bradycardia and irregular respirations (Cushing's triad) are not uniformly present; these and other neurological changes such as pupillary dilatation or signs of decerebration are typically evident only late in the course. CT of the brain does not reliably demonstrate evidence of edema especially at early stages.[85] Other methods of monitoring (such as transcranial doppler ultrasonography, near-infrared spectrophotometry, and measurement of serum S-100 beta and neuronal specific enolase) that are in various stages of evaluation have thus far not been proven reliable in estimatingICP.[86-89] A primary purpose of ICP monitoring is to detect elevations in ICP and reductions in cerebral perfusion pressure (CPP; calculated as mean arterial pressure minus ICP) so that interventions can be made to prevent herniation while preserving brain perfusion. The ultimate goal of such measures is to maintain neurological integrity and prolong survival while awaiting receipt of a donor organ or recovery of sufficient functioning hepatocyte mass. ICP monitoring is particularly important during orthotopic liver transplantation, when shifts in hemodynamics can cause large fluctuations in cerebral pressure parameters.[90] Additionally, refractory ICH and/or decreased CPP is considered a contraindication to liver transplantation in many centers.[90,91] Case reports of ALF patients demonstrating spontaneous and complete recovery after prolonged ICH and decreased CPP may call this practice into question,[92] but there is no way of knowing whether these patients would have survived the rigors of transplantation surgery. There are documented studies and reports of experience which indicate ICP monitoring devices can safely provide helpful information,[76,90,93] and may even lengthen survival time,[94] but there are no controlled trials available to demonstrate an overall survival benefit. There is understandable concern over the risks (mainly infection and bleeding) involved in placing invasive intracranial devices in critically ill, coagulopathic patients, based on data on 262 patients at U.S. transplant centers that observed a complication rate of 3.8% (1% fatal hemorrhage) with epidural catheters. Reliability was improved but the risk of complications increased with the use of subdural or intraparenchymal instrumentation.[95] It is not known whether newer, smaller monitoring devices have decreased the risk of complications. More aggressive correction of coagulation parameters, perhaps with addition of recombinant activated factor VII, may further reduce bleeding risk, allowing wider use of ICP monitoring devices.[96] Indeed, preliminary results indicate a considerable reduction in the prevalence of bleeding complications (2/58 cases with the majority being subdural monitors).[97] Recent data did not show improved outcomes when ICP monitoring devices were used.[97]

Specific Treatment of Elevated Intracranial Pressure. If patients develop increased ICP it may be necessary to perform immediate interventions beyond the general strategies outlined above. If an ICP monitor is placed, key parameters to follow are both ICP and CPP. ICP should be maintained below 20-25 mm Hg if possible, with CPP maintained above 50-60 mm Hg.[4,98] Evidence from trauma patients with cerebral edema suggests that maintaining CPP above 70 mm Hg may further improve neurological outcomes, if this level can be achieved.[99] Support of systemic blood pressure may be required to maintain adequate CPP.

Mannitol. If ICH develops, either as seen on ICP monitoring or by obvious neurological signs (decerebrate posturing, pupillary abnormalities), osmotic diuresis with intravenous mannitol is effective in the short term in decreasing cerebral edema.[100] Mannitol has been shown in controlled trials to correct episodes of elevated ICP in ALF patients; its use has also been associated with improved survival.[101] Administration of intravenous mannitol (in a bolus dose of 0.5-1g/kg) is therefore recommended to treat ICH in ALF. The dose may be repeated once or twice as needed, provided serum osmolality has not exceeded 320 mosm/L. Volume overload is a risk with mannitol use in patients with renal impairment, and may necessitate use of dialysis to remove excess fluid. Hyperosmolarity or hypernatremia also may result from overzealous use. Prophylactic administration of mannitol is not indicated.

Hyperventilation. Hyperventilation to reduce $PaCO_2$ to 25-30 mm Hg is known to quickly lower ICP via vasoconstriction causing decreased cerebral blood flow (CBF), but this effect is short-lived.[102] In a small series of patients with ALF, loss of auto-regulation of CBF appeared to be restored after several minutes of hyperventilation.[103] Restoration of CBF auto-regulation should theoretically be beneficial if cerebral hyperemia is contributing to cerebral edema and ICH; this study did not evaluate effect on ICP or survival, however. A randomized controlled trial of prophylactic continuous hyperventilation in ALF patients showed no reduction in incidence of cerebral edema/ICH and no survival benefit, although onset of cerebral herniation did appear delayed in the hyperventilated group.[104] There has been some concern that cerebral vasoconstriction with hyperventilation could potentially worsen cerebral edema by causing cerebral hypoxia.[105] Based on available evidence, there is no role for prophylactic hyperventilation in patients with ALF. If life-threatening ICH is not controlled with mannitol infusion and other general management outlined above, hyperventilation may be instituted temporarily in an attempt to acutely lower ICP and prevent impending herniation; beyond this acute situation it cannot be recommended as routine management.

Hypertonic Sodium Chloride. A recent controlled trial of administration of 30% hypertonic saline to maintain serum sodium levels of 145-155 in patients with ALF and severe encephalopathy suggests that induction and maintenance of hypernatremia may be used to prevent the rise in ICP values.[106] Survival benefit could not be demonstrated in this small trial. The role of hypertonic saline as a prophylactic measure requires confirmation in larger studies.

Barbiturate. Barbiturate agents (thiopental or pentobarbital) may also be considered when severe ICH does not respond to other measures; administration has been shown to effectively decrease ICP. Significant systemic hypotension frequently limits their use, and may necessitate additional measures to maintain adequate mean arterial pressure (MAP).[107]

Corticosteroids. Corticosteroids, which are often used in the prevention and management of ICH caused by brain tumors and some infections of the central nervous system, have been shown in a controlled trial to confer no benefit in patients with ALF with respect to controlling cerebral edema or improving survival.[101]

Hypothermia. Moderate hypothermia (32-34°C) may prevent or control ICH in patients with ALF. It has been shown in experimental animal models to prevent development of brain edema,[108-110] possibly by preventing hyperemia, altering brain ammonia or glucose metabolism, or by a combined effect. Some limited experience has supported a beneficial effect of hypothermia in patients with ALF as well,[111,112] but hypothermia has not been subjected to a controlled trial. Potential deleterious effects of hypothermia include increased risk of infection, coagulation disturbance, and cardiac arrhythmias.[113]

Recommendations

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 (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 (III).

27. Seizure activity should be treated with phenytoin and low-dose benzodiazepines. (III).

28. Although there is no consensus among the centers and experts, intracranial pressure monitoring is mainly considered for patients who are listed for transplantation (III).

29. In the absence of ICP monitoring, frequent evaluation for signs of intracranial hypertension are needed to identify early evidence of uncal herniation (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 (I).

31. Short-acting barbiturates may be considered for refractory intracranial hypertension (III).

32. Corticosteroids should not be used to control elevated ICP in patients with acute liver failure (I).

Infection

All patients with ALF are at risk for acquisition of bacterial[114] or fungal[115] infection or sepsis, which may preclude transplantation or complicate the post-operative course. Prophylactic antimicrobial therapy reduces the incidence of infection in certain groups of patients with ALF, but no actual survival benefit has been shown,[116,117] making it difficult to recommend antibiotic prophylaxis uniformly. Although often given, poorly absorbable antibiotics for selective bowel decontamination have not been shown to impact survival either.[116] Deterioration of mental status in hospital, particularly in patients with acetaminophen toxicity, may represent the onset of infection. If antibiotics are not given prophylactically, surveillance for infection (including chest radiography and periodic cultures of sputum, urine and blood for fungal and bac-

terial organisms) should be undertaken, while maintaining a low threshold for starting appropriate anti-bacterial or anti-fungal therapy. There are no controlled trials available to confirm whether the use of prophylactic antimicrobials decreases the likelihood of progression of encephalopathy and/or development of cerebral edema in ALF. Recent studies have suggested an association between infection and/or the systemic inflammatory response syndrome (SIRS) and progression to deeper stages of encephalopathy.[117,118] Given that prophylactic antibiotics have been shown to reduce the risk of infection, that later stages of encephalopathy are associated with increased incidence of cerebral edema, and that fever may worsen ICH,[119] it is possible that antibiotic and antifungal prophylaxis may decrease the risk of cerebral edema and ICH. This hypothesis is yet to be proven, however.

Recommendations

33. Periodic surveillance cultures should be performed to detect bacterial and fungal infections as early as possible and prompt treatment should be initiated accordingly (II-2, III).

34. Prophylactic antibiotics and anti-fungals may be considered but have not been shown to improve overall outcomes (II-2, III).

Coagulopathy

Clotting abnormalities are uniform in patients with ALF as previously discussed, leaving patients at increased risk for bleeding complications. While synthesis of coagulation factors is decreased, consumption of clotting factors and platelets also may occur, so that platelet levels are often $\leq$100,000/mm.[3] In the absence of bleeding it is not necessary to correct clotting abnormalities with fresh frozen plasma (FFP).[120] An exception is when an invasive procedure is planned and perhaps in the setting of profound coagulopathy (*e.g.*, INR $>$7). In addition to the risks associated with transfusion of blood products, use of plasma supplementation limits the value of coagulation parameters as a means of following the progress of ALF patients and can also lead to volume overload which may exacerbate ICH. Vitamin K is routinely given in a dose of 5-10 mg subcutaneously, regardless of whether poor nutritional status appears to be contributing to the coagulopathy.

Experts differ regarding prophylactic use of platelets in thrombocytopenic patients or use of FFP for evidence of severe coagulopathy. Platelet transfusions are not generally used until a low threshold value is observed. In the absence of bleeding, it is safe to use a threshold platelet count of 10,000/mm^3, although some experts recommend more conservative levels of 15-20,000/mm^3 especially in patients with infection or sepsis,[121] Experience in other conditions of thrombocytopenia suggests that values $\geq$10,000/mm^3 are generally well tolerated.[122] When invasive procedures must be perfomed, platelet counts of 50-70,000/mm^3 are usually considered adequate.[121] Patients who develop significant bleeding with platelet levels below approximately 50,000/mm^3 should generally be transfused with platelets provided no contraindication exists. Likewise, bleeding in the setting of a prolonged prothrombin time (INR $\geq$1.5) warrants administration of FFP. Recombinant activated factor VII (rFVIIa) may be used in treating coagulopathy in patients with liver disease. A recent small nonrandomized trial of fifteen patients with ALF found that administration of rFVIIa in combination with FFP produced more effective temporary correction of coagulopathy and thus might be useful in facilitating performance of invasive procedures in these patients particularly in the setting of renal insufficiency in which volume overload is a concern.[96] This agent will require further study and analysis of cost-benefit ratio (current cost for one dose is approximately $4,000) before it can be broadly recommended, however.

Recommendation

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

Gastrointestinal Bleeding

Gastrointestinal (GI) bleeding is a recognized complication of ALF. A large prospective multi-center cohort study found that mechanical ventilation for more than 48 hours and coagulopathy were the only significant risk factors for bleeding in critically ill patients of all types.[123] Additional risk factors for bleeding reported in smaller studies have included hepatic and renal failure, sepsis, shock and others.[124] Patients with acute liver failure are thus at high risk for gastrointestinal hemorrhage. Histamine-2 receptor (H2) blocking agents such as ranitidine have long been used in the prophylaxis of GI bleeding in critically ill patients; their efficacy has been supported in several trials.[125-128] Sucralfate has also been found to be effective in many studies, and there have been smaller randomized trials and a meta-analysis which suggested that sucralfate may be as effective in preventing gastrointestinal bleeding and might be associated with lower risk of nosocomial pneumonia than H2 blockers which lower gastric pH.[129,130] More recently, however, a much larger (1,200 patients), well-designed trial comparing ranitidine to sucralfate in mechanically-ventilated patients found

that ranitidine but not sucralfate decreased the risk of clinically significant bleeding; the incidence of pneumonia was similar for the two groups.[128] Limited studies of proton pump inhibitors (PPIs) as bleeding prophylaxis have demonstrated their effectiveness in maintaining elevated intragastric pH.[131-133] Two trials found no significant bleeding in PPI-treated patients on mechanical ventilation,[131,132] but study size may have precluded detection of significant bleeding. H_2 blockers have been proven to be effective and PPIs are almost certainly effective as well. PPIs may provide superior protection but this remains to be proven. Sucralfate may be acceptable as second-line treatment.

Recommendation

36. Patients with ALF in the ICU should receive prophylaxis with H2 blocking agents or PPIs (or sucralfate as a second-line agent) for acid-related gastrointestinal bleeding associated with stress (I, III).

Hemodynamics/Renal Failure

Hemodynamic derangements consistent with multiple organ failure occur in ALF; the underlying mechanisms are complex and incompletely understood. Management of hemodynamic balance becomes increasingly important and difficult in the face of elevated ICP and/or compromised renal function. Preservation of renal function is imperative in this setting. In many ways patients with ALF resemble physiologically the patient with cirrhosis and hepatorenal syndrome. Intravascular volume deficits may be present on admission due to decreased oral intake resulting from altered mental status, transudation of fluid into the extravascular space, and possibly GI blood loss. Most patients will require fluid resuscitation initially. Low systemic vascular resistance results in low blood pressures even in the fluid-resuscitated patient, and placement of a pulmonary artery catheter may aid in assessing volume status and guiding further management. Fluid replacement with colloid (such as albumin) is preferred rather than crystalloid (such as saline); all solutions should contain dextrose to maintain euglycemia.

While adequate fluid replacement and treatment of potential infection and sepsis may help to correct hypotension, inotropic or pressor support may be required in order to maintain mean arterial pressures of at least 50-60 mm Hg. There has been debate over which agents are best used to support blood pressure in ALF and whether they are useful at all. Alpha-adrenergic agents such as epinephrine and norepinephrine have been thought to potentially worsen peripheral oxygen delivery.[66] On the other hand, dopamine has actually been associated with increased systemic delivery of oxygen.[134] In any case, the hypotension and vasodilatation associated with ALF will generally respond to these agents, and they should be used if needed to maintain perfusion of vital organs. Agents that promote vasoconstriction are generally avoided unless significant systemic hypotension is present, and therefore should not be used in the setting of decreased intracranial perfusion with normal systemic blood pressure.

Acute renal failure is a frequent complication in patients with ALF[135] and may be due to dehydration, hepatorenal syndrome or acute tubular necrosis.[136] The frequency of renal failure may be even greater with acetaminophen overdose or other toxins, where direct renal toxicity is seen.[137] Although few patients die of renal failure alone, it often contributes to mortality and may portend a poorer prognosis.[9,138] Every effort should be made to protect renal function by maintaining adequate hemodynamics, avoiding nephrotoxic agents such as aminoglycosides and non-steroidal anti-inflammatory drugs, and by the prompt identification and treatment of infection. When dialysis is needed, continuous rather than intermittent modes of renal replacement therapy (*e.g.*, continuous venovenous hemodialysis [CVVHD]) should be used, as they have been shown in randomized trials to result in improved stability in cardiovascular and intracranial parameters compared with intermittent modes of hemodialysis.[139] Intravenous contrast agents are associated with nephrotoxicity in the setting of compromised hepatic function, and should be used with caution. If contrast must be administered, pretreatment with NAC may be of value, although this remains controversial.[140-142]

The potential utility of prostaglandins and NAC in improving hemodynamics and renal function was discussed previously; neither has sufficient evidence to be recommended as part of the management of hemodynamic derangements in ALF at this time, although NAC may have other benefits as discussed above. Evidence that terlipressin or vasopressin may be useful in patients with cirrhosis and hepatorenal syndrome has raised the question of whether this agent might benefit patients with ALF as well. A recent small study of terlipressin in patients with ALF found that even in very small doses, the drug was associated with increased cerebral blood flow and ICH.[143] Such results indicate that at this time the risks associated with vasopressin use appear to outweigh its benefits in patients with ALF.

The observation that hemodynamic status as well as ICH tends to improve after removal of the native liver during transplantation for ALF led to a recommendation of hepatectomy as a "last resort" means of improving severe circulatory dysfunction in these patients. This option is based on uncontrolled studies and case reports, where successful outcomes have occasionally been reported even

with patients who remained anhepatic for more than 48 hours.[144-146] Despite these reports, hepatectomy to control hemodynamics cannot be recommended.

Recommendations

37. Careful attention must be paid to fluid resuscitation and maintenance of adequate intravascular volume in patients with acute liver failure (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 (I).

39. Pulmonary artery catheterization should be considered in a hemodynamically unstable patient to ensure that appropriate volume replacement has occurred (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 MAP of 50-60 mm Hg (III, II-1).

Metabolic Concerns

A number of metabolic derangements are common in ALF. Alkalosis and acidosis may both occur and are best managed by identifying and treating the underlying cause. Hypoglycemia should be managed with continuous glucose infusions, because symptoms may be obscured in the presence of encephalopathy. Phosphate, magnesium, and potassium levels are frequently low and may require repeated supplementation throughout the hospital course. Nutrition is also important. Enteral feedings should be initiated early. Severe restrictions of protein should be avoided; 60 grams per day of protein is reasonable in most cases. Branched-chain amino acids have not been shown to be superior to other enteral preparations.[147] If enteral feedings are contraindicated (*e.g.*, severe pancreatitis), parenteral nutrition is an option, although the risks of infection, particularly with fungal pathogens, should be considered. Enteral[148] and parenteral nutrition[149] may reduce the risk of gastrointestinal bleeding due to stress ulceration in critically ill patients.

Recommendation

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 (III).

Transplantation and Prognosis

Transplantation

Orthotopic liver transplantation remains the only definitive therapy for patients who are unable to achieve regeneration of sufficient hepatocyte mass to sustain life. As mentioned previously, 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.[5] Advances in critical care and changing trends toward more benign etiologies such as acetaminophen (having a better overall outcome) have likely helped. Spontaneous survival rates are now around 40%,[5] 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%,[5,93] but accurate long-term outcome data are not yet available. In the largest U.S. study, only 29% of patients received a liver graft, while 10% of the overall group (1/4 of patients listed for transplantation) died on the waiting list.[5] Other series have reported death rates of those listed for transplant as high as 40%,[150,151] despite the fact that ALF remains the one condition for which the most urgent (UNOS status 1) listing is reserved. Developing effective methods of liver support or other alternatives to transplantation and better prognostic scoring systems remain key goals to further improve overall survival rates for the condition. Living-related donor liver transplantation may help address the shortage of available organs, but its use has thus far been very limited probably as a result of time constraints for evaluating donors and ethical concerns in this setting.

Recommendation

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

Liver Support Systems

A support device to replace the acutely failing liver seems a reasonable but elusive goal. The ideal replacement for the failing liver would detoxify, metabolize and synthesize; in short, perform all the liver's many functions. A variety of systems have been tested to date, with no certain evidence of efficacy. Sorbent systems embody only detoxification and no hepatocyte replacement. Such systems, employing charcoal or other adherent particles in a capsule or column device placed in an extracorporeal circuit, may show loss of platelets and worsening of coagulation parameters across the device.[152,153] Transient improvement of hepatic encephalopathy may be observed but no improvement in hepatic function or long-term benefit has been shown. Hepatocytes, whether of human or other mammalian origin, have been used in cartridges in extracorporeal circuits, either with or without sorbent columns. Few controlled trials have been published, and some preliminary reports suggest no benefit to outcome, with or without transplantation.[154] One recent multi-

center trial did report improved short-term survival for a subgroup of patients with ALF who were treated with a porcine hepatocyte-based bioartificial liver,[155] but corroboration of these results by further studies will likely be required before the true utility of this device can be established. All such trials are difficult to perform and to control properly due to the rarity of well-characterized patients, the heterogeneity of etiologies, varying levels of disease severity and varying access to transplantation. A recent meta-analysis, considering all forms of devices together, demonstrated no efficacy for bio-artificial liver devices for the treatment of ALF.[156] A variety of other strategies have been employed including exchange transfusion, charcoal hemoperfusion, extracorporeal liver perfusions, and intra-portal hepatocyte infusions.[157-159] To date, none can be recommended, and their use remains experimental. Efforts to improve hepatocyte regeneration have likewise been futile thus far.[160] When heterotopic or partial replacement transplantations have been performed it appears that the native liver can recover in some but not all situations, but this may require weeks or months to occur, underscoring the real challenge to liver replacement devices, that is, that liver assist devices might well be required for long periods of time.

Recommendation

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

Prognosis

See Table 6.

Given limited organ availability, lack of good alternatives to transplantation, and potential complications of lifelong immunosuppression, accurate prognosis in ALF is a paramount goal. Prognostic scoring systems, although derived from data on relatively large numbers of patients, still fail to achieve success, given the wide variety of etiologies that lead to this end stage syndrome. The traditional King's College Hospital criteria have been the most commonly utilized and most frequently tested of the numerous proposed prognostic criteria for ALF.[9] Several studies evaluating these criteria have shown positive predictive values ranging from just below 70% to nearly 100% and negative predictive values ranging from 25% to 94%.[161-165] Overall, such prognostic scores have proven to have acceptable specificity but low sensitivity to determine outcome. Criteria based on decreased levels of factor V in patients with encephalopathy predicted death in acute viral hepatitis cases with a positive predictive value of 82% and a negative predictive value of 98%,[166] but subsequent studies in both acetaminophen[167] and non-acetaminophen ALF[165] have shown these criteria to be less accurate than King's College Hospital criteria in predicting outcome.

Table 6. Potentially Helpful Indicators* of Poor (Transplant-free) 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
King's College Criteria:
Acetaminophen-induced ALF:
Arterial pH <7.3 (following adequate volume resuscitation) irrespective of coma grade OR
PT >100 seconds (INR · 6.5) + serum creatinine >300 μmol/L (3.4 mg/dL) in patients in grade III/IV coma
Non-acetaminophen-induced ALF:
PT >100 seconds irrespective of coma grade OR
Any three of the following, irrespective of coma grade:
– Drug toxicity, indeterminate cause of ALF
– Age <10 years or >40 years‡
– Jaundice to coma interval >7 days‡
– PT >50 seconds (INR ≥3.5)
– Serum bilirubin >300 μmol/L (17.5 mg/dL)

*Please note: None of these factors, with the exception of Wilson disease and possibly mushroom poisoning, are either necessary or sufficient to indicate the need for immediate liver transplantation.

‡These criteria, in particular, have not been found to be predictive of outcome in recent analyses.[5]

In a recent meta-analysis, Bailey et al.[168] compared various prognostic criteria in patients with ALF due to acetaminophen, including King's College Hospital criteria, various combinations of elevated serum creatinine, encephalopathy, and prothrombin time elevations (both single and serial measurements), decreased factor V levels, the Acute Physiology and Chronic Health Evaluation (APACHE) II scores[169] and Gc globulin (vitamin D binding protein, a liver-derived component of the actin-scavenging system[170]). The analysis found that King's College Hospital criteria and pH <7.30 alone were both fairly specific in predicting a poor outcome. While the King's College Hospital criteria were more sensitive than pH alone (69% versus 57% sensitivity), use of both criteria was still likely to miss many patients who would ultimately require transplantation. The authors also found that an APACHE II score of >15 on admission had a specificity of 92% (comparable to King's College Hospital criteria) with a much better sensitivity of 81%, but this measure was only examined in one limited study.[169]

Other factors such as age and the length of time between onset of illness and onset of encephalopathy have previously been proposed as important prognostic indicators in ALF,[9,171] these parameters did not affect outcome in the largest U.S. multi-center study of ALF to date.[5] Patients presenting in grade III or IV encephalopathy were less likely than those patients presenting in grade I or II encephalopathy to survive without receiving a liver graft. The most significant predictor of outcome in this study was etiology of ALF, as patients with ALF due to acetaminophen, hepatitis A, shock liver, or pregnancy-related disease showed ≥50% transplant free survival, while all other etiologies showed <25% transplant-free survival.

Other prognostic criteria have been proposed including severity of SIRS,[117,118] Alpha fetoprotein (AFP) levels,[172] ratios of factor VIII and factor V,[173] liver histology,[174] CT scanning of the liver,[174,175] cytokine levels,[176] serum phosphate levels,[163,177] and adrenal insufficiency.[178] Evaluations of these criteria have had varied results; while some appear promising, more research is needed to determine their reliability. The Model for End-stage Liver Disease (MELD) score, now widely used to predict mortality among patients with chronic liver disease who are under consideration for liver transplantation,[179] cannot currently be recommended as applicable to ALF, a different condition from cirrhosis.

Recommendation

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. (II-2, II-3, III).

Summary

Management of ALF challenges our best skills as physicians and intensivists. Treatments for specific etiologies and consideration of transplantation should be undertaken urgently in all patients that demonstrate evidence of encephalopathy. Because patients may deteriorate rapidly, arranging care in a center with experience and expertise in managing patients with ALF will secure the best possible outcomes for these patients.

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