AGA SECTION

American Gastroenterological Association Institute Guidelines for the Diagnosis and Management of Acute Liver Failure

Steven L. Flamm,[1] Yu-Xiao Yang,[2] Siddharth Singh,[3] Yngve T. Falck-Ytter,[4] and the AGA Institute Clinical Guidelines Committee

[1]Division of Gastroenterology and Hepatology, Department of Medicine, Northwestern Feinberg School of Medicine, Chicago, Illinois; [2]Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania; [3]Division of Gastroenterology, University of California San Diego, La Jolla, California; [4]Division of Gastroenterology, Cleveland VA Medical Center and University Hospitals, Case Western Reserve University, Cleveland, Ohio

This article has an accompanying continuing medical education activity, also eligible for MOC credit, on page e18. Learning Objective: Upon completion of this activity, learners will be able to: (1) determine if routine diagnostic testing in the setting of acute liver failure is recommended for Wilson's disease, varicella zoster virus infection, herpes simplex infection, hepatitis E virus infection or autoimmune hepatitis; (2) determine if routine diagnostic liver biopsy is recommended in the setting of acute liver failure; (3) determine if treatments to reduce intracranial pressure are recommended in the setting of acute liver failure; and (4) determine if N-acetyl cysteine is recommended in the setting of acute liver failure associated with acetaminophen or non-acetaminophen causes.

This guideline was developed using a process outlined elsewhere.[1] Briefly, the American Gastroenterological Association Institute (AGA) process for developing clinical practice guidelines incorporates Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology[2] and best practices as outlined by the Institute of Medicine.[3] GRADE methodology was used to prepare the background information for the guideline and the technical review that accompanies it.[4] Optimal understanding of this guideline will be enhanced by reading applicable portions of the technical review. The guideline panel and the authors of the technical review met face-to-face on May 20, 2016, to discuss the quality of evidence (Table 1) and consider other factors relevant for the risk-benefit assessment of the recommendations. The guideline authors subsequently formulated the recommendations. Although quality of evidence was a key factor in determining the strength of each recommendation (Table 2), the panel also considered the balance between the benefit and harm of interventions, patients' values and preferences, and resource utilization.

Table 1. GRADE Definitions on Quality of Evidence

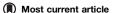|	
High	We are very confident that the true effect lies close to that of the estimate of the effect
Moderate	We are moderately confident in the effect estimate
	The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Our confidence in the effect estimate is limited
	The true effect may be substantially different from the estimate of the effect
Very low	We have very little confidence in the effect estimate
	The true effect is likely to be substantially different from the estimate of effect

Recommendation 1: In patients presenting with acute liver failure, the AGA suggests against routinely testing all patients for Wilson's disease. *Conditional recommendation; very low quality of evidence.*

Comments: In a setting of high clinical suspicion, testing for Wilson's disease can be considered, keeping in mind the low positive predictive value. Although the management and outcome of acute liver failure (ALF) would not be altered, identification of Wilson's disease would allow appropriate post-transplantation management and screening of the patient's family members.

Common diagnostic testing for Wilson's disease includes serum ceruloplasmin, serum and hepatic copper assessment, and 24-hour urine collection for copper. The tests have high false-positive and false-negative rates, and no large studies have been performed to assess the diagnostic accuracy of testing specifically for Wilson's disease in ALF. Three case–control studies involving both children and adults reported on a total of 37 Wilson's disease subjects and 322 controls with ALF from other causes. One study suggested that the sensitivity of serum copper greater than 200 ug/dL was 75% and specificity was 96%. The other studies noted that urinary copper was increased in all cases, but no sensitivity and specificity were reported.

Because Wilson's disease has a very low prevalence in the ALF population, there is a great likelihood that any test for Wilson's disease would have a high negative predictive value but a low positive predictive value. Furthermore, the diagnosis

Ⓝ Most current article

Table 2. GRADE Definitions on Strength of Recommendation

	For the patient	For the clinician
Strong	Most individuals in this situation would want the recommended course of action and only a small proportion would not	Most individuals should receive the recommended course of action Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences
Conditional	The majority of individuals in this situation would want the suggested course of action, but many would not	Different choices will be appropriate for different patients Decision aids may well be useful in helping individuals making decisions consistent with their values and preferences Clinicians should expect to spend more time with patients when working toward a decision

is unlikely to alter the management of ALF caused by Wilson's disease because liver transplantation is the ultimate outcome.

Recommendation 2: In patients presenting with ALF, the AGA suggests testing for herpes simplex virus and treatment of patients with herpes simplex virus. *Conditional recommendation; very low quality evidence.*

Common diagnostic testing for herpes simplex virus (HSV) infection includes HSV serologies and HSV DNA. HSV is a rare cause of ALF. Four case series were evaluated including 513 adult patients with ALF and 1% had positive HSV serologies. Consequently, there have been little data regarding the diagnostic accuracy or treatment of HSV in the setting of ALF. Regarding diagnostic testing, 1 case series

with 4 patients with ALF caused by HSV confirmed by liver biopsy/autopsy showed that 2 of 4 patients had positive HSV IgM and all 4 patients had positive HSV DNA.

Regarding treatment, HSV in ALF has a poor prognosis even with acyclovir therapy. However, there is a suggestion on a case-report level that patients with acute hepatitis secondary to HSV do better with treatment than without. There is little downside to treatment with acyclovir from cost or adverse event standpoints.

There were only 10 case reports of patients with ALF attributed to varicella zoster virus (VZV). Only 2 case reports involved patients who were not immunocompromised. No evaluable data were available on diagnostic

Table 3. Summary of Recommendations of the AGA Clinical Guidelines for the Diagnosis and Management of Acute Liver Failure

Statement	Strength of recommendation	Quality of evidence
Recommendation 1: In patients presenting with ALF, the AGA suggests against routinely testing all patients for Wilson's disease	Conditional	Very low
Comment: In a setting of high clinical suspicion, testing for Wilson's disease can be considered, keeping in mind the low positive predictive value		
Although the management and outcome of ALF would not be altered, identification of Wilson's disease would allow appropriate post-transplantation management and screening of the patient's family members		
Recommendation 2: In patients presenting with ALF, the AGA suggests testing for HSV and treatment of patients with HSV	Conditional	Very low
Recommendation 3: In immunocompetent patients presenting with ALF, the AGA suggests against routinely testing all patients for VZV	Conditional	Very low
Recommendation 4: In pregnant women presenting with ALF, the AGA suggests testing for hepatitis E	Conditional	Very low
Recommendation 5: In patients presenting with ALF, the AGA suggests using the MELD score rather than the KCC as a prognostic scoring system.	Conditional	Very low
Comment: A MELD score of 30.5 (fixed cut-off level) should be used for prognosis; higher scores predict the need for liver transplantation		
Recommendation 6: In patients presenting with ALF, the AGA suggests against the routine use of liver biopsy	Conditional	Very low
Recommendation 7: In patients presenting with ALF, the AGA suggests autoantibody testing for autoimmune hepatitis be performed	Conditional	Very low
Recommendation 8: In patients presenting with ALF, the AGA suggests against the empiric use of treatments to reduce ICP.	Conditional	Very low
Recommendation 9: In patients presenting with ALF, the AGA recommends that extracorporeal artificial liver support systems only be used within the context of a clinical trial	No recommendation	No recommendation
Recommendation 10: In patients presenting with acetaminophen-associated ALF, the AGA recommends the use of NAC in acetaminophen-associated ALF	Strong	Very low
Recommendation 11: In patients presenting with non–acetaminophen-associated ALF, the AGA recommends that NAC only be used in the context of clinical trials	No recommendation	No recommendation

testing or treatment of VZV, particularly in the immunocompetent setting.

Recommendation 3: In immunocompetent patients presenting with ALF, the AGA suggests against routinely testing all patients for VZV. *Conditional recommendation; very low quality evidence.*

Recommendation 4: In pregnant women presenting with ALF, the AGA suggests testing for hepatitis E. *Conditional recommendation; very low quality evidence.*

Acute hepatitis E virus (HEV) infection is common in endemic parts of the world, although it is uncommon elsewhere. In endemic areas, acute liver failure attributed to HEV has been observed. It is particularly common in pregnant women, and has a significant mortality in this population. Five studies from India assessed mortality in ALF secondary to HEV in pregnant women. An overall rate of 56% (range, 33%–71%) was observed. There is no treatment for HEV.

Liver transplantation for patients with ALF is a life-saving procedure, yet itself has significant morbidity and mortality. It is expensive and patients require life-long immunosuppression. Some patients with ALF recover without the need for liver transplantation, whereas others derive benefit. Prognostic systems to help predict who will and will not require liver transplantation have arisen. The 2 that have been best-studied are the Kings College Criteria (KCC) and the Model for End-Stage Liver Disease (MELD) score.

Recommendation 5: In patients presenting with ALF, the AGA suggests using MELD score rather than KCC as a prognostic scoring system. *Conditional recommendation; very low quality evidence.*

Comment: A MELD score of 30.5 (fixed cut-off value) should be used for prognosis. Higher scores predict a need for liver transplantation.

The KCC has been evaluated in 8 studies involving 962 patients with ALF, of whom 47% died. The pooled sensitivity and specificity for predicting mortality was 61% (range, 47%–76%) and 86% (range, 64%–95%), respectively (diagnostic odds ratio, 9.58; 95% confidence interval [CI], 4.74–19.36). The MELD score has been evaluated in 6 studies involving 526 ALF patients, of whom 58% died. The pooled sensitivity and specificity for predicting mortality was 77% (range, 70%–92%) and 72% (range, 56%–85%), respectively (diagnostic odds ratio, 8.79; 95% CI, 5.19–14.89).

Regarding KCC vs MELD score, KCC is more specific and MELD is more sensitive. The MELD score offers the opportunity to optimize specificity without losing significant sensitivity, and thus is optimal.

Liver biopsy is a procedure that has an uncertain role in ALF. Liver biopsy could add diagnostic information that is helpful and could provide prognostic information that helps with the decision to proceed with liver transplantation. Alternatively, liver biopsy has risks of bleeding and death that are not insignificant in patients with ALF and coagulopathy.

Recommendation 6: In patients presenting with ALF, the AGA suggests against the routine use of liver biopsy. *Conditional recommendation; very low quality evidence.*

Two studies assessed the diagnostic accuracy of liver biopsy in the setting of ALF. The diagnosis was changed in 18%. However, no information was reported regarding whether the diagnosis altered the treatment plan or outcome.

Four studies have examined the predictive value of more than 50% hepatocyte necrosis on mortality. The mortality rate was 3-fold higher than if less necrosis was observed. Quality data were not available for using liver biopsy results to help with the decision to undergo liver transplantation.

Recommendation 7: In patients presenting with ALF, the AGA suggests autoantibody testing be performed. *Conditional recommendation; very low quality evidence.*

Autoimmune hepatitis (AIH) is an uncommon cause of ALF, although the exact number of afflicted patients is unclear. Quality data regarding diagnostic testing and response to corticosteroid therapy for ALF secondary to AIH are sparse.

One study indicated that 93% of patients with AIH by previously defined diagnostic criteria had positive autoantibodies. In addition, AIH patients who received corticosteroids had a better outcome than did patients with indeterminate AIH.

Increased intracranial pressure (ICP) in ALF is associated with increased mortality. It is unclear if or when monitoring of ICP is indicated, or whether decreasing ICP decreases mortality and, if so, which method of reducing ICP is best. It should be noted that monitoring ICP has morbidity. If therapy is ineffective, monitoring in the first place would be inadvisable. Furthermore, the approaches to reducing ICP also have associated risk, and this must be considered when evaluating benefit.

Recommendation 8: In patients presenting with ALF, the AGA suggests against the empiric use of treatments to reduce ICP. *Conditional recommendation; very low quality evidence.*

Five randomized controlled trials (RCTs) have been performed that individually assessed moderate hypothermia, hypertonic saline, L-ornithine L-aspartate, intravenous mannitol, and hyperventilation involving 410 patients with ALF. There was no effect overall of treatment of ICP on mortality and no statistically significant improvement in mortality with any individual therapy. Adverse events related to therapy were not well characterized.

Recommendation 9: In patients presenting with ALF, the AGA recommends that extracorporeal artificial liver support systems only be used within the context of a clinical trial. *No recommendation.*

Extracorporeal liver support systems for patients with ALF are potentially useful to allow time for spontaneous recovery and avoid liver transplantation. Support systems also may be life-sustaining to allow more time to identify an appropriate donor when liver transplantation is necessary.

Three systematic reviews have assessed artificial liver support systems for ALF and all reported no clear effect on mortality. Seven RCTs have been performed in patients with ALF involving 415 patients. No improvement in survival was observed. However, in 4 trials performed within the past 20 years involving 332 patients with ALF, there was a marginally significant survival benefit. Adverse events were reported in 6 trials. No difference between the intervention groups and usual care was noted.

Evaluation of subcategories of extracorporeal support systems has been performed. Two RCTs evaluated bio-artificial systems in 213 patients with ALF. No significant improvements in mortality were observed, although there was a trend to decreased mortality.

Four RCTs assessed albumin dialysis vs usual care in 340 patients with ALF. No significant decrease in mortality was identified, although a trend to decreased mortality was noted. Four RCTs evaluated traditional extracorporeal liver support systems; no decrease in mortality was identified. In a post hoc analysis, combination of albumin and bioartificial liver support systems resulted in decreased mortality (relative risk, 0.80; 95% CI, 0.65–0.98).

When evaluating all of the data, there may be benefit to liver support systems in ALF, although the data are not robust enough to render a recommendation. Notably, the support systems also have significant potential toxicities, are costly, and demanding of resources.

Recommendation 10: In patients presenting with acetaminophen-associated ALF, the AGA recommends the use of N-acetyl cysteine in acetaminophen-associated ALF. *Strong recommendation; very low quality of evidence.*

Recommendation 11: In patients presenting with non–acetaminophen-associated ALF, the AGA recommends that N-acetyl cysteine be used only in the context of clinical trials. *No recommendation.*

Intravenous N-acetyl cysteine (NAC) has long been used in ALF related to acetaminophen and has been advocated in patients with non–acetaminophen-associated ALF. Two RCTs investigated NAC vs placebo involving 228 patients with ALF. No effect on overall mortality with NAC was observed. In a post hoc analysis in 1 of the studies (114 ALF patients), a mortality benefit was identified in patients specifically with stage 1 or 2 hepatic encephalopathy. One RCT was performed in patients with ALF related to acetaminophen involving 50 patients. Improved mortality was identified in the acetaminophen group (relative risk, 0.65; 95% CI, 0.43–0.99). When combining all 3 RCTs, there was a marginally significant mortality benefit with NAC in conjunction with relatively minor toxicity.

In cases of ALF of indeterminate cause, use of NAC can be considered because indeterminate cases may be related to acetaminophen.

Summary

ALF is a rare but significant clinical problem with high morbidity and mortality. It is an uncommon disease process characterized by rapid progression and death. Liver transplantation, the ultimate treatment strategy, is necessary for some patients and requires significant resources and a lifetime of immunosuppression, yet other patients have had spontaneous resolution and no long-term issues.

Because ALF has been difficult to study in RCTs, there are many areas of controversy regarding diagnosis, predictive models for outcome, and management. By using the GRADE framework, this guideline offers recommendations about controversial diagnostic and treatment strategies and predictive models for outcome. Despite the large number of published studies, in most cases our recommendations are weak because the quality of the available data is poor, and/or the balance of risks and benefits for a particular strategy does not overwhelmingly support its use (Table 3).

However, there are data to support a strong recommendation for the use of NAC in patients with ALF related to acetaminophen. There remains a lack of data to allow

recommendations for testing for Wilson's disease and VZV in patients with ALF. Although there are low-quality data, because there are therapies that may be beneficial in patients with ALF, recommendations to test for HSV and AIH are supported. HEV testing is recommended in pregnant women with ALF. Data do not support recommending routine use of diagnostic liver biopsy or empiric therapy of high ICP in patients with ALF. As a predictive model, MELD score with a fixed cut-off value of 30.5 is recommended. In other cases, data are suggestive of a possible benefit of therapeutic strategies in certain cases but not robust enough without additional study to make a recommendation such as NAC in patients with non–acetaminophen-related ALF or use of extracorporeal liver support systems in ALF.

Recognizing these and other limitations, the recommendations included here represent a rigorous, evidence-based summary of extensive literature describing the diagnosis and treatment of ALF and use of predictive models. Review of this guideline, plus the associated technical review, will facilitate effective shared decision making with ALF patients.

References

1. American Gastroenterological Association. AGA Institute clinical practice guideline development process. Available from: http://www.gastro.org/guidelines-policies. Accessed: July 19, 2016.
2. Sultan S, Falck-Ytter Y, Inadomi JM. The AGA Institute process for developing clinical practice guidelines part one: grading the evidence. Clin Gastroenterol Hepatol 2013;11:329–332.
3. Institute of Medicine. Clinical practice guidelines we can trust. Washington, DC: Institute of Medicine, 2011.
4. Herrine SK, Moayyedi P, Brown RS Jr, et al. American Gastroenterology Association institute technical review on initial testing and management of acute liver disease. Gastroenterology 2017;152:648–664.

This document presents the official recommendations of the American Gastroenterological Association Institute on initial testing and management of acute liver failure. The guideline was developed by the Clinical Guidelines Committee and approved by the American Gastroenterological Association Institute Governing Board.

AGA SECTION