Gastroenterology 2017;■:1–4

AGA SECTION

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

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Keywords: ■■■.

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.

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 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

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

Abbreviations used in this paper: **AGA, American Gastroenterological Association Institute; AIH, autoimmune hepatitis; ALF, acute liver failure; CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; HEV, hepatitis E virus; HSV, herpes simplex virus; ICP, intracranial pressure; KCC, Kings College Criteria; MELD, Model for End-Stage Liver Disease; NAC, N-acetyl cysteine; RCT, randomized controlled trial; VZV, varicella zoster virus.**

0016-5085/$36.00
http://dx.doi.org/10.1053/j.gastro.2016.12.026

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

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 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

Table 3. Summary of Recommendations of the AGA Clinical Guidelines for the Management of Crohn's Disease After Surgery

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