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Standard Definitions and Common Data Elements for Clinical Trials in Patients With Alcoholic Hepatitis: Recommendation From the NIAAA Alcoholic Hepatitis Consortia

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On behalf of the NIAAA Alcoholic Hepatitis Consortia

Heavy drinkers are at risk for a spectrum of histologic alcohol-related liver injury: steatosis, alcoholic steatohepatitis (ASH), alcohol-related fibrosis, and cirrhosis. Alcoholic hepatitis (AH), the clinical entity associated with severe ASH, has high short-term mortality. The standard-of-care therapy, prednisolone, has limited efficacy and many side effects; no other treatment has consistently shown survival benefit. The National Institute on Alcohol Abuse and Alcoholism (NIAAA)-funded Alcoholic Hepatitis Consortia carry out translational research on pathophysiologic mechanisms, genetic and environmental risk factors, phase II clinical trials, and development of biomarkers. The consortia members were convened by the National Institutes of Health to address diagnostic criteria and practical issues related to clinical AH research, and to develop a set of common data elements to harmonize ongoing and future trials. This was accomplished through 3 face-to-face meetings of the investigators and representatives of the National Institutes of Health, and subsequent electronic communications over the course of 6 months. Evidence for the recommendations was based on published trials and observational data from several of the consortia members. A draft manuscript was iteratively reviewed by members of the consortia. The goal was to reach agreements on recommendations and definitions that could facilitate trial design, and simultaneously be tested by research groups pooling their data. The recommendations made here are specifically directed to achieve better uniformity in clinical trials, rather than serving as clinical practice guidelines.

Natural History of AH

Alcohol-related steatosis is the most common manifestation of heavy drinking. A “standard drink” in the United States (12 oz of beer, 5 oz of wine, or 1 oz of liquor) contains 14 g of alcohol; volunteers drinking approximately 10 drinks per day for 2–3 weeks consistently developed steatosis.[1] This level of drinking, often for decades, is observed in AH,[2,3] but only

a minority of such drinkers develop AH. The best established risk factors are female sex and increased body mass index; these and other factors have mainly been studied in the context of alcoholic liver disease (including steatosis and cirrhosis): nutritional deficiency, dietary composition (type of fat, caffeine), genetic factors (eg, *PNPLA3* genotype), and smoking. Biopsy-documented AH has a 58% 4-year survival,[2] with the worst outcomes in the first year in those with cirrhosis (35% survival).[4] A Danish survey from 1999 to 2008[5] showed increasing 28-day (12%–15%) and 84-day (14%–24%) mortality rates, and a 5-year survival of 53% and 31% in those without and with cirrhosis, respectively.

Diagnostic Definition of AH

AH is a clinical entity with rapid onset of jaundice with elevated serum aspartate transaminase (AST), arising on the background of heavy alcohol use. Liver biopsy usually reveals ASH, cholestasis, and severe fibrosis The thresholds for amount and duration of alcohol use causing AH are not known, although an average consumption of more than 3 drinks (~40 g) per day for women and 4 drinks (~50–60 g) per day for men are reasonable minimal thresholds for the diagnosis of AH. Patients typically have been drinking heavily for >5 years, but may be intermittently abstinent. For the diagnosis of AH, we expect that heavy alcohol use should have occurred for >6 months, with <60 days of abstinence before the onset of jaundice. Jaundice is often accompanied by malaise, tender hepatomegaly, and decompensation (ascites, encephalopathy, bacterial infection, and variceal bleeding). Serum bilirubin is usually elevated (>3 mg/dL [>50 μmol/L]), as is the AST (>50 IU/mL), and AST to alanine aminotransferase (ALT) ratio of >1.5. A review of a large series of patients seen by the consortium participants suggests that AST/ALT ratios of <1.5 are seen in <2% of patients with histologically proven AH. The AST and ALT do not typically exceed 400 IU/mL, distinguishing AH from other liver diseases such as drug-induced liver injury (DILI) and ischemic hepatitis. Imaging should exclude biliary obstruction, and viral hepatitis, severe autoimmune liver disease, and Wilson disease should be tested for.

Liver biopsy can be useful in confirming the diagnosis and has prognostic value.[6] Of patients with a clinical diagnosis of AH, 10–20% may have other liver diseases found only by biopsy or may not have histologic ASH.[7] The histologic hallmarks of ASH include macrovesicular steatosis, with ≥ 1 of the following: neutrophil infiltration, hepatocyte injury (ballooning), and Mallory-Denk bodies, although this is an area in which the expertise of pathologists is needed. The presence of megamitochondria, satellitosis (neutrophils surrounding dying/dead hepatocytes), and cholestasis (bilirubinostasis) is common, and may relate to prognosis.[8] Fibrosis is always present, following a “chicken-wire” pattern; the majority of patients with severe AH have cirrhosis. Some patients with ASH do not have clinical AH; this asymptomatic AH (“walking AH”) may coexist with cirrhosis in as many as 30%–40%,[9] and may progress to clinical AH. An important research question is how to identify and intervene in patients with walking AH. Patients with undiagnosed cirrhosis may decompensate owing to superimposed AH, that is, acute-on-chronic liver failure. Limitations of biopsy include sampling variability, lack of well-validated histologic grading systems for necroinflammatory features, unavailability of transjugular liver biopsy at some sites, and risks and costs of the procedure.

AH Clinical Trials: Inclusion and Exclusion Criteria and Outcomes

Inclusion Criteria

We recommend the following inclusion criteria for clinical studies (Table 1). However, we recognize that biopsy may not be feasible in all situations. Thus, liver biopsy confirmation of ASH should be required only for patients with clinical AH classified as possible AH (see below).

1. *Definite AH*: Clinically diagnosed and biopsy proven. In the future, imaging techniques and biomarkers may replace liver biopsy for definite diagnosis of AH. However, biopsy may have a role in determining molecular pathways that identify the mechanism of injury in AH and inform the choice of therapy.
2. *Probable AH*: Clinically diagnosed AH without confounding factors (see below). In patients with heavy alcohol use and typical liver tests; and negative markers for immune (antinuclear antibody < 1:160 or anti–smooth antibody < 1:80 dilutions) and metabolic liver disease; and absence of sepsis, shock, cocaine use, or recent use of a drug with DILI potential within 30 days, a diagnosis other than AH will be made in <10% of patients on liver biopsy. Patients with positive tests for chronic hepatitis C (HCV), B, or non-alcoholic steatohepatitis do not commonly present in a fashion mimicking AH. Therefore, a biopsy is not essential for inclusion of these cases of probable AH in research studies. The potential misclassification of these subjects without histologic confirmation should be accounted for in calculating the sample sizes.[6]
3. *Possible* AH: Clinically diagnosed but with potential confounding factors, including possible ischemic hepatitis (eg, severe upper gastrointestinal [UGI] bleed, hypotension, or cocaine use within 7 days); possible DILI; uncertain alcohol use assessment (eg, patient denies excessive alcohol use); and atypical laboratory tests (eg, AST < 50 IU/mL or > 400 IU/mL, AST/ALT ratio < 1.5), antinuclear antibody > 1:160 or SMA > 1:80 We recommend that these patients undergo biopsy for confirmation of AH.

Stratification Based on Severity

It is important to stratify AH patients by disease severity. Short-term mortality can be predicted using the Maddrey discriminant function, Model for End-Stage Liver Disease (MELD) score, Age-Bilirubin-International Normalized Ratio- Creatinine score, and Glasgow Alcoholic Hepatitis Scores. Patients with severe AH defined by a Maddrey discriminant function of ≥32 have a 1-month morality rate as high as 20%–50%, so the 30-day survival was the endpoint for most trials. A MELD score of >20 was suggested as an inclusion criterion[10] because it predicts a 90-day mortality of 20%. Failure of improvement in serum bilirubin (the Lille score) predicts patients with severe AH who are unlikely to benefit from continued corticosteroid therapy. The best predictor of survival may be a combination of the MELD and Lille scores,[11] although it is not known whether the Lille score will apply to novel therapies.

Patients with a Maddrey discriminant function of <32 were usually excluded from trials because their expected 30-day survival is >90% with supportive care; however, up to 5%–10% of these patients may decompensate and die in the next 6 months. This cohort of patients may be suitable for early phase studies of novel compounds. Recent trials with longer follow-up times noted complications developing between 30 and 90 days after stopping steroids, with mortality rates at 90 days that were no different from those given supportive therapy.[3] Thus, we recommend that future trials be designed with primary outcomes beyond 30-day mortality. Additional factors which contribute to medium term (≤1 year) mortality are not assessed by the Maddrey discriminant function and MELD scores, that is, different degrees of fibrosis. Although cirrhosis is often evident from imaging and other studies, the extent of fibrosis is difficult to quantify without biopsy, and for ethical reasons repeated biopsies have not been performed. Magnetic resonance elastography or Fibroscan (in patients without ascites) may allow better prognostication.

Assessing predictors of mortality beyond one year is difficult, as the main determinants are the presence of cirrhosis and persistent drinking[12] and there were no histologic features on liver biopsy that correlated with long-term prognosis[13]; certainly, the maintenance of abstinence should be a high priority in clinical care and used as a metric in future clinical trials.

Exclusion Criteria

Subjects with a MELD score of >30 or a Maddrey discriminant function of >60 have such a poor prognosis that they should be stratified separately and excluded from phase I and II studies, testing the safety and proof of concept of molecules on AH-induced liver injury, respectively; power calculations need to be adjusted accordingly. The MELD-Lille scores might be used to further stratify patients into those with very high mortality and those with such high mortality that liver support approaches or urgent transplantation should be considered, rather than pharmacotherapy. Heavy alcohol consumption accelerates the development of cirrhosis in patients with chronic hepatitis C virus and hemochromatosis.[14,15] How these disorders alter the course or response to treatment of AH is unknown, although many patients with hepatitis C virus were likely included in earlier trials.[16] The exclusion of patients with other liver diseases may improve homogeneity, but overlook potential benefit for those with multiple diagnoses. Because nonalcoholic steatohepatitis does not cause a syndrome similar to AH, and obesity is a risk factor for alcoholic liver disease,[17] overweight patients who are drinking heavily should be eligible for AH clinical trials.

Up to 70% of patients with AH have the systemic inflammatory syndrome,[18] in one-half of whom no infection is identifiable. Thus, a systemic inflammatory syndrome at admission should not be an exclusion criterion. Criteria defining infections in cirrhotic patients were recently published, and seem appropriate for AH,[19] both for exclusion from trials or as a reportable complication (below). Patients with infection not associated with multiorgan failure can be considered for inclusion once the infection is controlled. Patients with uncontrolled infection are at increased risk for multiorgan failure with a high mortality rate[18]; patients with multiorgan failure at diagnosis should be excluded or stratified. Criteria

for grading multiorgan failure in patients with cirrhosis have been proposed[20] and may be useful for AH research.

Overt UGI bleeding is an exclusion criterion in the majority of trials, although retrospective studies suggest that patients whose bleeding is controlled have similar survival to patients without bleeding. Thus, recent UGI bleeding that is controlled for >48 hours should not exclude the patient.

Acute kidney injury or hepatorenal syndrome at presentation of AH is especially worrisome, owing to the high probability of progression. Usually patients with creatinine of >2.5 mg/dL are excluded, but could be considered for trials targeting concomitant kidney injury. Other exclusion criteria may include other underlying chronic liver diseases (active hepatitis B, chronic hepatitis C, hemochromatosis, autoimmune liver disease, Wilson disease, suspected DILI), underlying hepatic and extrahepatic malignancies, and disorders potentially worsened by immunosuppressants (latent tuberculosis), but this exclusion may not apply to nonimmunosuppressive treatments. Uncontrolled drug addiction is commonly an exclusion criteria for clinical trials, and is more common in the AH population.

Outcomes

A 90-day mortality endpoint is preferred to the traditional 30-day mortality in light of recent trials. In addition to mortality, endpoints that reflect improvements in liver function (eg, change in Maddrey discriminant function or MELD score) should be considered for the less severely ill group of patients with AH. There is no instrument currently available that measures disease-specific quality of life in AH. Measures of functional status and quality of life; well-being (eg, WHO Performance status or EQ5D); presence or absence of complications of chronic liver disease such as ascites, infection, acute kidney injury, and encephalopathy; days of hospitalization; work productivity; use of medical resources, including liver transplantation; and abstinence rates after discharge may be used as important outcomes.

Recommended Common Datasets for Patients in Clinical Trials for AH: Endpoints, Outcomes, and Adverse Events

Suggested common datasets for patients in clinical trials are listed in Table 2: they include usual blood tests for severe liver injury, potential risk factors for AH, and measures related to alcohol consumption before and after the onset of AH. The timing of these measurements will vary between the short term (the traditional measures) and longer term, depending on the outcomes defined (late deaths, complications of cirrhosis). Adverse events include the usual complications of severe liver disease (Table 3), and those that might be caused by treatments; it may be difficult to separate these. Better tools and reliable surrogate markers to characterize the heterogeneous population of patients with AH will facilitate phase II and III studies evaluating new treatments.[6]

Common Data Elements for Capturing and Reporting Adverse Events

All clinical trials use standard data elements such that safety of the tested compound is rigorously investigated. Requirements for safe conduct and reporting results of human research in the United States are dictated by the Code of Federal Regulation (CFR) Title 21. These include (1) drug trial having an investigational new drug approval from the Food and Drug Administration (FDA); (2) registration on Clinicaltrials.gov; (3) adherence to the principles of good clinical practices; (4) having a clinical trial monitoring plan; (5) having a data and safety monitoring plan in place before their initiation; and (6) storage of clinical trial data in compliance with 21CFR312.

Adverse events, treatment emergent adverse events, serious adverse events, sudden and unexpected serious adverse reactions, and fatalities should be defined, captured, and reported in a predefined fashion. General guidelines are contained in 21CFR312.32. The reporting requirements vary depending on the nature of the adverse event and different regulatory and institutional stakeholders. In the United States, these include the FDA, local institutional review board, Data Safety and Monitoring Board, funding agency, sponsor (if applicable), and other participating sites. It is important to have well thought out reporting schemata before initiating the clinical trials and predefined “events of interests” for standardizing study data across various consortia undertaking observational cohort studies. We suggest that the following are the most important events of interest for patients with AH (Table 3):

1. Acute kidney injury;
2. UGI bleeding (variceal or nonvariceal);
3. Hepatic encephalopathy;
4. Infections (spontaneous or secondary bacterial peritonitis, urinary tract infection, pneumonia, cellulitis, infectious diarrhea including *Clostridium difficile* infection, or intraabdominal infections, positive blood cultures);
5. Diuretic-resistant ascites; and
6. Unexpected elevation of liver enzymes, i.e., development of DILI (this may require independent adjudication, as is done for DILI in other clinical trials).

In conclusion, these recommendations from the NIAAA Alcoholic Hepatitis consortia outline a framework for clinical research in AH. Its purpose is to provide consensus-based recommendations regarding definitions, clinical trial design, minimal datasets, and the reporting and monitoring of adverse events. This is a first step toward data standardization for all variables commonly used in translational, clinical, and observational studies of AH that will facilitate data sharing and comparisons across studies, increasing the efficiency and effectiveness of AH research. We anticipate that ongoing research will help provide improved evidence for the definition of AH (eg, thresholds of alcohol use, use of other surrogates of heavy use besides self-report, thresholds of transaminase and bilirubin levels, better understanding of “walking AH” and its natural history). Writing this statement has brought such questions into sharper focus.

Despite significant progress in our understanding of the pathophysiology of alcoholic liver disease, relatively few clinical trials in AH have been conducted, and there has been little improvement in outcome. Clinical Trials.gov lists only 4 interventional trials currently recruiting for AH patients in the United States; an additional 11 are cited from other countries. Research in AH is a challenging task given its heterogeneity, high mortality rate, the complexity of interacting pathophysiologic mechanisms, and the difficulties of recruiting and retaining patients with alcohol use disorders. All these factors contribute to the difficulties in designing, conducting, and interpreting clinical studies. The clinical diagnosis, staging, and prognostic assessment of AH patients has been inconsistent, making the meta-analysis of trials difficult. Thus, there is an urgent need to adopt standardized approaches and vocabulary for diagnostic criteria and for data collection and reporting.

The development of data standards and common data elements is a continuous process requiring input from many stakeholders at each stage. The current report is a starting point that will necessarily evolve to improve clarity and utility. To promote the implementation of these standardized data elements and measures, their use is encouraged by all future NIAAA-funded research projects in AH and feedback is solicited from the broader community that deals with AH, which may be directed to Dr Svetlana Radaeva at the NIAAA (sradaeva@mail.nih.gov). Future steps will include (1) the development in collaboration with FDA of clearly defined and measurable surrogate endpoints and new definitions of clinical benefits for the evaluation of drug efficacy and (2) standardization of data exchange in clinical research studies and patient care activities to create a strong data interchange environment and provide new opportunities to conduct cost-effective, large-scale observational studies. These efforts should improve data sharing across institutions and studies and improve clinical practice guidelines for the diagnosis and management of AH.

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Table 1

Inclusion and exclusion criteria for clinical trials in alcoholic hepatitis

Inclusion Criteria
○ Onset of jaundice within prior 8 weeks
○ Ongoing consumption of > 40 (female) or 60 (males) g alcohol/day for 6 months or more, with less than 60 days of abstinence before the onset of jaundice
○ Aspartate aminotransferase > 50, aspartate aminotransferase/alanine aminotransferase > 1.5, and both values < 400 IU/L
○ Serum bilirubin (total) > 3.0 mg/dL
○ Liver biopsy confirmation in patients with confounding factors
Stratification based on severity
○ Maddrey's discriminant function ≥ 32 assuming a control prothrombin time of 12 seconds
○ Model for End-stage Liver Disease score > 20
○ Less ill patients may be appropriate for early phase or mechanistic studies
Exclusion criteria
○ Patients with very severe disease (Maddrey discriminant function > 60 or Model for End-stage Liver Disease score > 30) may need to be excluded from some studies
○ Uncontrolled infections
○ Multiorgan failure
○ Uncontrolled upper gastrointestinal bleeding
○ Preexisting kidney injury with serum creatinine > 2.5 mg/dL
○ Other underlying liver diseases including hepatitis B infection,* autoimmune liver diseases, Wilson disease, suspected drug-induced liver injury*
○ Hepatocellular carcinoma or other active malignancies except skin cancer
○ Pregnancy
○ Underlying diseases that might be exacerbated by proposed treatments (eg, hepatitis C,[a] hemochromatosis, latent tuberculosis)
○ Uncontrolled drug addiction

[a]Exclusion of patients with hepatitis B, hepatitis C, or human immunodeficiency virus infection or hemochromatosis is a subject of controversy, and may depend on the mechanism of action of the treatment under study.

Table 2

Common Clinical Datasets

Type of Data	Included
Demographic information	Age, sex, racial identity, socioeconomic status, occupation, marital status, education, family/friend contact
Alcohol consumption data	Age at onset of drinking, estimated levels of consumption (expressed as g/d), patterns of recent drinking (time line follow-back), preferred beverages, frequency of binge drinking, prior attempts to stop drinking use of medications to reduce drinking, family history of alcohol abuse and liver disease, history of recurrent alcoholic hepatitis with relapse to drinking
General clinical data	Standard liver tests (aspartate aminotransferase, alanine aminotransferase, bilirubin, international normalized ratio (INR), albumin, total protein); presence or development of encephalopathy or gastrointestinal bleeding, renal function (estimated GFR, creatinine, electrolytes), measures of metabolic syndrome (high-density lipoprotein cholesterol, cholesterol, triglyceride, low-density lipoprotein cholesterol, hemoglobin A1c); medications (including over-the-counter medications, herbals, dietary supplements, and probiotics); hepatitis B virus, hepatitis C virus, human immunodeficiency virus serology; antinuclear antibody; iron, ferritin, iron binding capacity; Lille score if steroids used
Measures of social stress	Other behavioral disorders (dual diagnoses—depression, anxiety, posttraumatic stress disorder), socioeconomic stress (eg, scales from the Health and Retirement Study); smoking, use of other drugs of abuse (eg, cocaine)
Nutritional	Recent weight change, ability to consume a nutritious diet after the diagnosis of alcoholic hepatitis is made, survey of nutritional status, caffeine use (coffee, tea), cooking oil preference, nut consumption
Biobanking	Whole blood, plasma/serum, urine, peripheral blood mononuclear cells, stool (bulk stool or mucosal swab), DNA, annotation about nutritional state (fed or fasting) when samples obtained.
Patient outcomes	30- and 90-day survival, work productivity, well-being, quality of life, World Health Organization Performance status, EQ5D, abstinence rates after discharge
Health economics data	Cost of care (including acute hospital care and post-discharge care for alcohol addiction), length of hospital stay

NOTE. Some of these measures will only need to be obtained once (eg, family history, racial identity, education, DNA sample); others need to be tracked over time (eg, diet, alcohol use, medications, and illicit drugs).

Table 3

Endpoints, Outcomes, and Adverse Events

1	Early endpoints: 30-day mortality, resolution of systemic inflammatory response syndrome, development of organ system failure (lungs, kidneys, gastrointestinal bleeding, encephalopathy, infection), change in Maddrey discriminant function and Model for End-stage Liver Disease, and Lille score, change in bilirubin[a]
2	Later endpoints: 3-, 6-, and 12-month survival, liver decompensation (including infections)
3	Adverse events:
	a. Usual adverse events tracked in all clinical trials (bone marrow/blood cells, renal, skin, central nervous system, pulmonary, infections)
	b. Additional adverse events related to the class of drug being tested
	c. Adverse events typically associated with decompensated cirrhosis or severe alcoholic hepatitis: worsening renal function, GI bleeding (usually upper), worsening liver synthetic and injury tests, encephalopathy, hyponatremia, ascites, hypotension, edema, spontaneous bacterial peritonitis, other infections.

[a]The development of surrogate markers of improvement or worsening aside from usual clinical measures is much needed.