ORIGINAL ARTICLE

Glucocorticoids plus *N*-Acetylcysteine in Severe Alcoholic Hepatitis

Eric Nguyen-Khac, M.D., Ph.D., Thierry Thevenot, M.D., Marie-Astrid Piquet, M.D., Ph.D., Saïd Benferhat, M.D., Odile Goria, M.D., Denis Chatelain, M.D., Ph.D., Blaise Tramier, M.D., François Dewaele, M.D., Salah Ghrib, M.D., Marika Rudler, M.D., Nicolas Carbonell, M.D., Hervé Tossou, M.D., Abdeslam Bental, M.D., Brigitte Bernard-Chabert, M.D., and Jean-Louis Dupas, M.D., for the AAH-NAC Study Group*

ABSTRACT

BACKGROUND

Mortality among patients with severe acute alcoholic hepatitis is high, even among those treated with glucocorticoids. We investigated whether combination therapy with glucocorticoids plus *N*-acetylcysteine would improve survival.

METHODS

We randomly assigned 174 patients to receive prednisolone plus *N*-acetylcysteine (85 patients) or only prednisolone (89 patients). All patients received 4 weeks of prednisolone. The prednisolone–*N*-acetylcysteine group received intravenous *N*-acetylcysteine on day 1 (at a dose of 150, 50, and 100 mg per kilogram of body weight in 250, 500, and 1000 ml of 5% glucose solution over a period of 30 minutes, 4 hours, and 16 hours, respectively) and on days 2 through 5 (100 mg per kilogram per day in 1000 ml of 5% glucose solution). The prednisolone-only group received an infusion in 1000 ml of 5% glucose solution per day on days 1 through 5. The primary outcome was 6-month survival. Secondary outcomes included survival at 1 and 3 months, hepatitis complications, adverse events related to *N*-acetylcysteine use, and changes in bilirubin levels on days 7 and 14.

RESULTS

Mortality was not significantly lower in the prednisolone–*N*-acetylcysteine group than in the prednisolone-only group at 6 months (27% vs. 38%, P=0.07). Mortality was significantly lower at 1 month (8% vs. 24%, P=0.006) but not at 3 months (22% vs. 34%, P=0.06). Death due to the hepatorenal syndrome was less frequent in the prednisolone–*N*-acetylcysteine group than in the prednisolone-only group at 6 months (9% vs. 22%, P=0.02). In a multivariate analysis, factors associated with 6-month survival were a younger age (P<0.001), a shorter prothrombin time (P<0.001), a lower level of bilirubin at baseline (P<0.001), and a decrease in bilirubin on day 14 (P<0.001). Infections were less frequent in the prednisolone–*N*-acetylcysteine group than in the prednisolone-only group (P=0.001); other side effects were similar in the two groups.

CONCLUSIONS

Although combination therapy with prednisolone plus *N*-acetylcysteine increased 1-month survival among patients with severe acute alcoholic hepatitis, 6-month survival, the primary outcome, was not improved. (Funded by Programme Hospitalier de Recherche Clinique; AAH-NAC ClinicalTrials.gov number, NCT00863785.)

From Service d'Hépato-Gastroentérologie (E.N.-K., F.D., J.-L.D.) and Pathology Service (D.C.), Amiens University Hospital, and Equipe Région INSERM 24, University of Picardy (E.N.-K.) — both in Amiens; Service d'Hépatologie, Besançon University Hospital, Besançon (T.T.); Service d'Hépato-Gastroentérologie, Caen University Hospital, Caen (M.-A.P.); Service d'Hépato-Gastroentérologie, Saint-Quentin General Hospital, Saint-Quentin (S.B.); Service d'Hépato-Gastroentérologie, Rouen University Hospital, Rouen (O.G.); Biostatistics Department, Aubagne General Hospital, Aubagne (B.T.); Service d'Hépato-Gastroentérologie, Cambrai General Hospital, Cambrai (S.G.); Service d'Hépato-Gastroentérologie, Pitié–Salpêtrière University Hospital (M.R.) and Service d'Hépatologie, Saint-Antoine University Hospital (N.C.) — both in Paris; Service d'Hépato-Gastroentérologie, Beauvais General Hospital, Beauvais (H.T.); Service d'Hépato-Gastroentérologie, Abbeville General Hospital, Abbeville (A.B.); and Service d'Hépato-Gastroentérologie, Reims University Hospital, Reims (B.B.-C.) — all in France. Address reprint requests to Dr. Nguyen-Khac at the Hepato-Gastroenterology Service, Amiens University Hospital, Pl. Victor Pauchet, F-80054 Amiens CEDEX 01 France, or at nguyen-khac.eric@chu-amiens.fr.

*The members of the Acute Alcoholic Hepatitis–*N*-Acetylcysteine (AAH-NAC) Study Group are listed in the Supplementary Appendix, available at NEJM.org.

N Engl J Med 2011;365:1781-9.

Severe acute alcoholic hepatitis is a life-threatening alcoholic liver disease.[1] Although glucocorticoid treatment is recommended[2,3] and improves survival,[4-11] mortality remains high, with 35% of patients dying within 6 months.[1]

Long-term alcohol consumption increases intestinal permeability, worsens endotoxemia,[12] stimulates Kupffer cells,[13] and thus increases production of proinflammatory cytokines.[14] High levels of tumor necrosis factor α (TNF-α) activate cell-death pathways and induce the production of reactive oxygen species, notably superoxide anions, by the hepatocyte mitochondria, leading to cell death. This situation is accompanied by severe mitochondrial depletion of glutathione,[15] the primary antioxidant in cells. Furthermore, hepatocytes are much more sensitive to TNF-α when their antioxidant reserves are low.[16] Combination therapy with an antioxidant and glucocorticoids would have the advantage of both acting on the inflammatory process and reconstituting cellular glutathione reserves.

N-acetylcysteine could have value as an antioxidant in the treatment of acute alcoholic hepatitis, because the thiol group in *N*-acetylcysteine is able to reduce levels of free radicals. Administration of *N*-acetylcysteine might reconstitute the glutathione stocks of the hepatocytes. At present, *N*-acetylcysteine is used in the treatment of acetaminophen-induced hepatitis. We conducted a trial to evaluate the efficacy of glucocorticoids plus *N*-acetylcysteine, as compared with glucocorticoids alone, in patients with severe acute alcoholic hepatitis.

METHODS

PATIENTS

The complete study protocol is available (in French) with the full text of this article at NEJM.org. From 2004 through 2009, patients hospitalized for severe acute alcoholic hepatitis at 11 French university hospitals were evaluated for eligibility. The inclusion criteria were an age of 18 years or older, an average alcohol intake of more than 50 g per day during the 3 months before enrollment, a Maddrey's discriminant function of 32 or more, and liver histologic findings consistent with alcoholic hepatitis (Mallory bodies surrounded by polymorphonuclear neutrophils). Maddrey's discriminant function is calculated as [4.6×(patient's prothrombin time−control prothrombin time, in seconds)]+serum bilirubin level, in milligrams per deciliter. A value of 32 or more clearly identifies patients with a high risk of early death.[7]

Key exclusion criteria were the hepatorenal syndrome, hepatocellular carcinoma, uncontrolled bacterial infection or gastrointestinal hemorrhage in the previous 4 days, infection with hepatitis C virus (HCV), hepatitis B virus (HBV), human immunodeficiency virus (HIV) infection, autoimmune hepatitis, hemochromatosis, Wilson's disease, alpha$_1$-antitrypsin deficiency, acetaminophen-induced hepatitis, cancer, *N*-acetylcysteine allergy, and serious cardiac, respiratory, or neurologic disease.

STUDY DESIGN

We performed a multicenter, randomized, controlled trial. Patients who met the eligibility criteria were randomly assigned to receive either prednisolone plus *N*-acetylcysteine or only prednisolone. Randomization was performed centrally in blocks of four by means of a computerized procedure, with stratification according to center. The treatment assignments were not concealed from the investigators or the patients. The study was conducted in compliance with the protocol.

The initial evaluation included transjugular or percutaneous liver biopsy, ultrasonography of the liver, and esophageal endoscopy. The clinical examination included the recording of cardiac frequency, blood pressure, temperature, and assessment for hepatic encephalopathy, ascites, gastrointestinal hemorrhage, and jaundice. Alcohol use was evaluated with the Alcohol Use Disorders Identification Test (AUDIT)[17] and the CAGE questionnaire.[18] AUDIT scores, which range from 0 to 40, are determined by 10 standardized questions on the use of alcoholic beverages during the past year; a score of more than 8 indicates hazardous and harmful alcohol use. CAGE scores range from 0 to 4, and each of the letters in the acronym refers to one of the four questions; a score of 2 to 4 suggests alcohol abuse.

Laboratory tests measured prothrombin time; levels of bilirubin, aspartate aminotransferase, γ-glutamyltransferase, alkaline phosphatase, albumin, creatinine, sodium, potassium, phosphorus, hemoglobin, iron, transferrin, ferritin, alpha$_1$-antitrypsin, and ceruloplasmin; platelet, white-cell, and polymorphonuclear-neutrophil counts; and

antinuclear, anti–smooth muscle, antimitochondrial, and anti–liver–kidney microsomal antibodies. Patients were tested for HBV, HCV, and HIV. Screening for bacterial infections included urine, ascites, and blood cultures, as well as chest radiography. The Child–Pugh score (which ranks the severity of cirrhosis) and Maddrey's discriminant function were calculated. The Child–Pugh scoring system assigns 1 to 3 points for each of five variables (prothrombin time, albumin level, bilirubin level, ascites, and hepatic encephalopathy), with 3 points indicating the most severe derangement. A Child–Pugh score of 5 or 6 indicates class A disease (the least severe), 7 to 9 points class B (moderately severe), and 10 to 15 points class C (the most severe).

Each investigator determined the duration of hospitalization. Patients were monitored weekly during the first month and then monthly until month 6. Each visit included a clinical examination, screening for complications (gastrointestinal hemorrhage, the hepatorenal syndrome, hepatic encephalopathy, spontaneous bacterial peritonitis, and other infections), evaluation of compliance with treatment and abstinence from alcohol consumption, laboratory tests (prothrombin time; levels of bilirubin, albumin, aspartate aminotransferase, γ-glutamyltransferase, alkaline phosphatase, and creatinine; and white-cell and polymorphonuclear-neutrophil counts), and calculation of the Child–Pugh score and Maddrey's discriminant function. All patients were followed for 6 months or until death. The status (alive or dead) of patients lost to follow-up was assessed by telephoning a family member or by contacting the death registry at the patient's birthplace.

STUDY TREATMENTS

Both groups received 40 mg of oral prednisolone per day for 28 days. For the first 5 days, patients in the prednisolone–*N*-acetylcysteine group received intravenous infusions of *N*-acetylcysteine (Fluimucil, Zambon Group). On day 1, they received 150 mg per kilogram of body weight in 250 ml of 5% glucose solution over a period of 30 minutes, 50 mg per kilogram in 500 ml of glucose solution over a period of 4 hours, and 100 mg per kilogram in 1000 ml of glucose solution over a period of 16 hours. On days 2 through 5, they received 100 mg per kilogram per day in 1000 ml of glucose solution. The patients in the prednisolone-only group received an infusion in 1000 ml of 5% glucose solution per day on days 1 through 5.

The treatment of ascites with diuretics, albumin, and sodium restriction was allowed, as was the use of beta-blockers for portal hypertension. Management of alcohol addiction was left to the individual center. The use of acetaminophen, pentoxifylline, or anti–TNF-α treatments was prohibited. All patients received normal hospital nutrition (1800 to 2000 kcal per day).

STUDY OUTCOMES

The primary outcome was survival at 6 months. Prognostic factors for 6-month mortality were examined. The secondary outcomes were survival at 1 and 3 months, changes in bilirubin levels after 7 and 14 days of treatment, occurrence of hepatitis complications, and adverse events related to *N*-acetylcysteine use. Liver transplantation or use of the molecular adsorbent recirculating system (MARS) during the trial was treated as a mortality end point in survival analyses.

STUDY OVERSIGHT

The study was approved by the institutional review board at Amiens University Hospital and was conducted in compliance with the French Huriet–Sérusclat legislation on medical research and the Declaration of Helsinki. All patients provided written informed consent before enrollment. (For patients with hepatic encephalopathy, informed consent was obtained from the next of kin.)

STATISTICAL ANALYSIS

Primary and secondary outcomes were compared between the two treatment groups. Quantitative variables, expressed as means ±SD, were compared with the use of the Wilcoxon test, Kruskal–Wallis test, or Student's t-test, as appropriate. Qualitative variables, expressed as percentages, were compared with the use of a chi-square test or Fisher's exact test. Kaplan–Meier survival curves were plotted for up to 180 days and compared with the use of a log-rank test. Factors that were significantly predictive of mortality in a univariate analysis ($P<0.05$) were included in a multivariate Cox logistic-regression analysis with stepwise elimination. A bilirubin decrease on day 7 or 14 was defined as a lower absolute value than on day 0. In secondary analyses that were not prespecified in the study protocol,

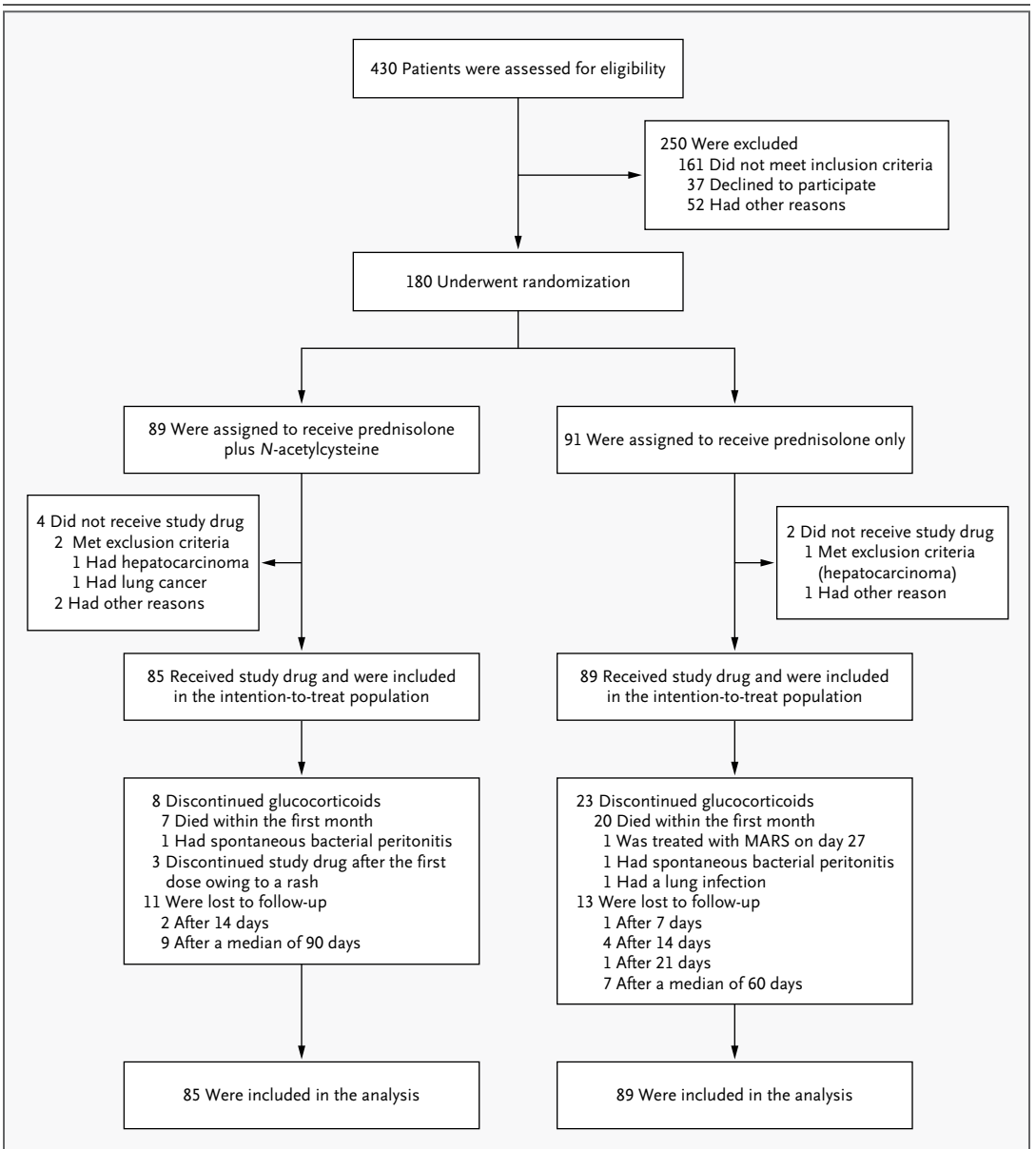

Figure 1. Enrollment and Outcomes.

Data on mortality were available for all patients in the intention-to-treat population, including those lost to follow-up. MARS denotes molecular adsorbent recirculating system.

we compared causes of death between the two groups and examined the effect of change in bilirubin levels over time on survival. An intermediate safety analysis was performed after 50% of the enrolled patients had completed 6 months of follow-up (with $P<0.05$ chosen as the threshold for statistical significance). For the final analysis, a P value of less than 0.025 was used. All the statistical analyses were performed in the modified intention-to-treat population. All reported P values are two-sided.

The required sample size was calculated on the assumption that the survival rate would be 67% at 6 months in the prednisolone-only group.[1] With an alpha error of 0.05, a beta error of 0.10, and a hypothetical improvement in survival of 20% at month 6 for the prednisolone–*N*-acetylcysteine group, the required sample size was 174 patients.

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Reference Range	Prednisolone Only (N=89)	Prednisolone–*N*-Acetylcysteine (N=85)	P Value
Age — yr		52.2±8.5	52.8±8.7	0.66
Male sex — no. (%)		50 (56)	55 (65)	0.25
Time between hospital admission and start of treatment in trial — days		7.9±6.7	7.2±6.6	0.45
Alcohol intake — g/day		108.8±55.3	107.2±58.0	0.86
AUDIT score†		22.6±7.4	22.5±7.4	0.91
CAGE score‡		3.2±0.9	3.3±0.9	0.28
Child–Pugh score§		11.3±1.3	11.0±1.5	0.35
Maddrey's discriminant function¶		58.2±20.0	54.0±18.2	0.11
Hepatic encephalopathy — no. (%)		39 (44)	38 (45)	0.46
Ascites — no. (%)		62 (70)	59 (69)	1.00
Prothrombin time — % of normal	70–100	37.5±9.9	39.9±10.9	0.12
Bilirubin — μmol/liter	0–19	260.1±171.0	238.1±136.0	0.35
Albumin — g/liter	37–45	24.9±5.4	24.3±5.9	0.42
Aspartate aminotransferase — U/liter	<35–45	109.9±49.1	127.5±83.9	0.10
γ-Glutamyltransferase — U/liter	0–85	223.0±240.0	308.9±289.0	0.05
Alkaline phosphatase — U/liter	0–240	176.8±161.5	174.8±83.8	0.90
Creatinine — μmol/liter	45–120	73.1±21.0	73.3±29.9	0.96
White-cell count — per mm³	4000–10,000	10,901±5640	10,528±6534	0.69
Polymorphonuclear-neutrophil count — per mm³	1400–7500	8179±5205	7530±6254	0.48

* Plus–minus values are means ±SD. Reference ranges are from the lowest reference value used by any of the centers to the highest value used by any center.
† The Alcohol Use Disorders Identification Test (AUDIT), developed by the World Health Organization, assesses excessive drinking with a standardized interview that includes 10 questions on the use of alcoholic beverages during the previous year. A score of more than 8 indicates hazardous and harmful alcohol use (score range, 0 to 40).
‡ The CAGE questionnaire includes 4 questions on use of alcoholic beverages. A score of 2 or more indicates alcohol abuse (score range, 0 to 4).
§ The Child–Pugh score ranks the severity of cirrhosis by assigning 1 to 3 points for each of five variables (prothrombin time, albumin level, bilirubin level, presence or absence of ascites, and presence or absence of hepatic encephalopathy), with 3 points indicating the most severe derangement. A Child–Pugh score of 5 or 6 indicates class A disease (the least severe), 7 to 9 points class B (moderately severe), and 10 to 15 points class C (the most severe).
¶ Maddrey's discriminant function is calculated as [4.6×(patient's prothrombin time−control prothrombin time, in seconds)]+serum bilirubin level, in milligrams per deciliter. A value of 32 indicates severe acute alcoholic hepatitis with a high risk of early death.

RESULTS

STUDY POPULATION

A total of 430 patients were evaluated for eligibility (Fig. 1). After exclusion of 250 patients who did not meet the inclusion criteria or for other reasons, 180 underwent randomization. The final analysis was performed with 174 patients (73 from Amiens, 39 from Besançon, 20 from Caen, 15 from Saint-Quentin, 11 from Rouen, 7 from Cambrai, 2 from Saint-Antoine, 2 from Pitié-Salpêtrière, 2 from Abbeville, 2 from Beauvais, and 1 from Reims). The baseline characteristics of the patients did not differ significantly between the two groups, with the exception of a slightly higher γ-glutamyltransferase level in the prednisolone–*N*-acetylcysteine group (P=0.05) (Table 1). The results of the scheduled interim analysis have been published previously.[19]

MORTALITY

In regard to the primary outcome, 57 patients had died by 6 months. The mortality rate was 38% in the prednisolone-only group (34 of 89) and 27% in

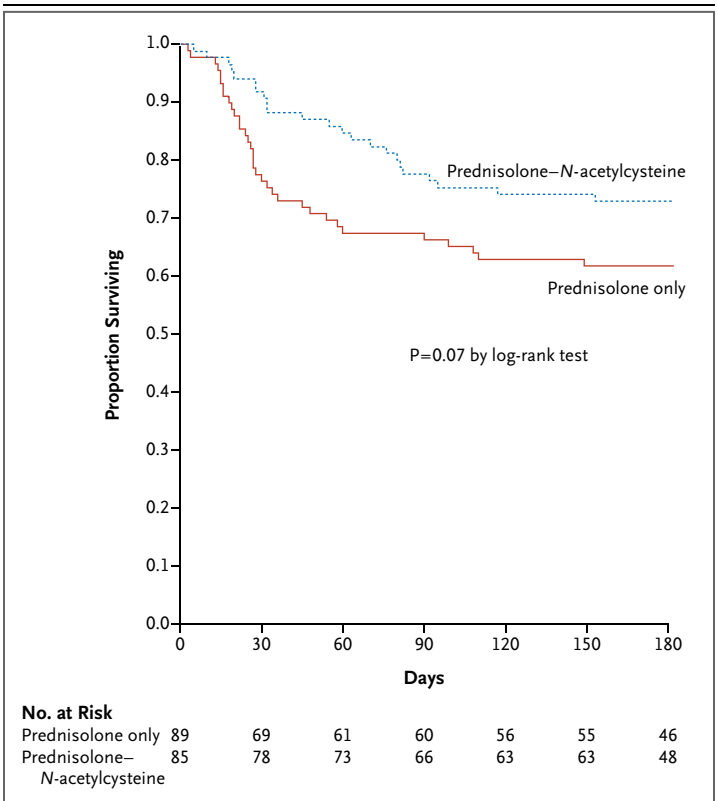

Figure 2. Kaplan–Meier Curves for 6-Month Survival in the Intention-to-Treat Population.

the prednisolone–*N*-acetylcysteine group (23 of 85) (hazard ratio with combination therapy, 0.62; 95% confidence interval [CI], 0.37 to 1.06; P=0.07) (Fig. 2). The mean time to death was 40±35 days (median, 27; range, 3 to 149) in the prednisolone-only group and 54±37 days (median, 50.5; range, 5 to 149) in the prednisolone–*N*-acetylcysteine group (P=0.14). In regard to the secondary outcomes, the respective mortality rates in the prednisolone-only and prednisolone–*N*-acetylcysteine groups were 24% (21 of 89) and 8% (7 of 85) at 1 month (hazard ratio, 0.58; 95% CI, 0.14 to 0.76; P=0.006) and 34% (30 of 89) and 22% (19 of 85) at 3 months (hazard ratio, 0.33; 95% CI, 0.33 to 1.04; P=0.06).

CAUSES OF DEATH

At 6 months, 22% of the patients in the prednisolone-only group (20 of 89) had died of the hepatorenal syndrome, versus 9% of the patients in the prednisolone–*N*-acetylcysteine group (8 of 85) (odds ratio, 2.79; 95% CI, 1.08 to 7.42; P=0.02); the mean time to death was 36.5±28 days and 66±33 days, respectively (P=0.30). Deaths due to infections accounted for 9% of patients in the prednisolone-only group (8 of 89) and 8% of those in the prednisolone–*N*-acetylcysteine group (7 of 85) (odds ratio, 0.91; 95% CI, 0.28 to 2.93; P=0.85), with a mean time to death of 31±22 days and 56±45 days, respectively (P=0.05). In the prednisolone-only group, 4 patients died from septic shock, 3 from lung infections, and 1 from spontaneous bacterial peritonitis; in the prednisolone–*N*-acetylcysteine group, 2 patients died from septic shock, 2 from lung infections, and 1 each from subphrenic abscess, spontaneous bacterial peritonitis, and pyelonephritis. The other causes of death in the prednisolone-only group were esophageal variceal hemorrhage (1 patient), esophageal ulcer hemorrhage (1), hemorrhagic stroke (1), torsade de pointes (1), and terminal liver failure (1); in addition, 1 patient was treated with MARS on day 27. In the prednisolone–*N*-acetylcysteine group, the other causes of death were esophageal variceal hemorrhage (5 patients) (P=0.11), hemorrhagic stroke (1), and terminal liver failure (1); in addition, 1 patient underwent liver transplantation on day 170.

ADVERSE EVENTS

At 6 months, the rate of the hepatorenal syndrome was 25% in the prednisolone-only group (22 of 89 patients) and 12% in the prednisolone–*N*-acetylcysteine group (10 of 85) (odds ratio with combination therapy, 0.41; 95% CI, 0.17 to 0.98; P=0.02) (Table 2). The overall rate of infection was 42% in the prednisolone-only group (37 of 89 patients) and 19% in the prednisolone–*N*-acetylcysteine group (16 of 85) (odds ratio, 0.33; 95% CI, 0.15 to 0.68; P=0.001). The two groups did not differ significantly with respect to other complications. Among patients with relapse of alcohol use after 1 month, 13% died in the prednisolone-only group (2 of 15) versus 7% in the prednisolone–*N*-acetylcysteine group (1 of 15) (P=1.00).

PREDICTIVE FACTORS FOR DEATH

At 6 months, nine factors were significantly associated with mortality in a univariate analysis (Table 3). Age, hepatic encephalopathy, prothrombin time, baseline bilirubin level, baseline creatinine level, Maddrey's discriminant function, Child–Pugh score, change from baseline in the bilirubin level on day 7, change from baseline in the bilirubin level on day 14, and treatment group were all included in a Cox model for multivariate analysis. Variables independently associated with increased mortality were older age (odds ratio, 1.07; 95% CI, 1.03 to

1.11; P<0.001), prolonged prothrombin time (odds ratio, 0.93; 95% CI, 0.91 to 0.97; P<0.001), higher baseline bilirubin level (odds ratio, 1.007; 95% CI, 1.005 to 1.009; P<0.001), and the absence of a decrease in the bilirubin level on day 14 (odds ratio, 0.23; 95% CI, 0.12 to 0.45; P<0.001).

CHANGE OVER TIME IN BILIRUBIN LEVEL AND EFFECT ON SURVIVAL

The change in the median bilirubin level in each group over the course of the study is shown in Figure 1S in the Supplementary Appendix, available at NEJM.org. The difference was significant only on day 14 (160 μmol per liter in the prednisolone-only group vs. 115 μmol per liter in the prednisolone–*N*-acetylcysteine group, P=0.003) (Table 1S in the Supplementary Appendix).

For the whole study population, data on the bilirubin level on day 7 were available for 159 patients (2 patients had died, and data were missing for 13 other patients). A bilirubin decrease on day 7 was observed in 128 patients (81%). The 6-month survival rate was 90% among patients with a bilirubin decrease on day 7 and 10% among patients without a decrease (odds ratio, 78; 95% CI, 29 to 210; P<0.001). On day 14, data on the bilirubin level were available for 143 patients (7 patients had died, and data were missing for 24 other patients). A bilirubin decrease on day 14 was observed in 80% of the patients. The 6-month survival rate was 89% among patients with a bilirubin decrease on day 14 and 11% among patients without a decrease (odds ratio, 61; 95% CI, 23 to 166; P<0.001). On day 7, 78% of patients in the prednisolone-only group had a bilirubin decrease, versus 81% in the prednisolone–*N*-acetylcysteine group (odds ratio, 1.38; 95% CI, 0.59 to 3.29; P=0.41). On day 14, 74% of patients in the prednisolone-only group had a bilirubin decrease, versus 87% in the prednisolone–*N*-acetylcysteine group (odds ratio, 2.47; 95% CI, 0.96 to 6.49; P=0.04).

Table 2. Adverse Events.

Event	Prednisolone Only (N=89)	Prednisolone–*N*-Acetylcysteine (N=85)
	no. (%)	
Hepatorenal syndrome*	22 (25)	10 (12)
All infections†	37 (42)	16 (19)
Spontaneous bacterial peritonitis	9 (10)	5 (6)
Lung infection	8 (9)	3 (4)
Urinary system infection	7 (8)	4 (5)
Erysipelas	3 (3)	0
Staphylococcal septicemia	2 (2)	2 (2)
Gram-negative septicemia	2 (2)	2 (2)
Esophageal candidiasis	2 (2)	0
Otitis externa	1 (1)	0
Infection of unknown cause	3 (3)	0
Esophageal variceal hemorrhage	8 (9)	10 (12)
Esophageal ulcer hemorrhage	1 (1)	0
Gastroduodenal ulcer hemorrhage	0	3 (4)
Umbilical variceal hemorrhage	0	1 (1)
Thigh hematoma	0	1 (1)
Hepatic encephalopathy	4 (4)	3 (4)
Hepatic hydrothorax‡	0	1 (1)
Functional kidney failure	0	1 (1)
Inguinal hernia occlusion	1 (1)	0
Lumbar vertebral collapse	1 (1)	1 (1)
Cerebral hemorrhage	2 (2)	1 (1)
Cancer of the pharynx	1 (1)	0
Uterine fibroid hemorrhage	1 (1)	0
Calf hematoma	1 (1)	0
Torsade de pointes	1 (1)	0
Rash after first injection of *N*-acetylcysteine	0	3 (4)
MARS use§	1 (1)	0
Liver transplantation§	0	1 (1)
Relapse of alcohol use after 1 month	15 (17)	15 (18)

* P=0.02 for the between-group comparison.
† P=0.001 for the between-group comparison.
‡ Hepatic hydrothorax was related to portal hypertension.
§ Liver transplantation or use of the molecular adsorbent recirculating system (MARS) was considered a primary-outcome failure.

DISCUSSION

In patients with severe acute alcoholic hepatitis, the combination of *N*-acetylcysteine and prednisolone did not significantly improve 6-month survival, as compared with prednisolone only. The rationale for the use of antioxidants in the treatment of acute alcoholic hepatitis is based on the pivotal role of oxidative stress in the disorder. Liver protection by *N*-acetylcysteine has been shown in mouse models of acute and chronic alcoholic hepatitis.[20-22] However, in patients with severe acute alcoholic hepatitis, the benefits of antioxidants have not been shown. In a randomized trial, a combination of antioxidants that included *N*-acetylcysteine was significantly worse than prednisolone with respect to survival.[23] Similarly, in a study with a complex de-

Table 3. Factors Associated with Mortality at 6 Months (Univariate Analysis).*

Factor	Status at 6 Mo		P Value
	Dead	Alive	
Age — yr	55.6±6.9	50.9±8.9	<0.001
Prothrombin time — % of normal	35.2±10.5	40.3±10.1	0.003
Bilirubin — μmol/liter	330.4±182.1	209.9±122.8	<0.001
Creatinine — μmol/liter	80.8±24.6	69.4±25.4	0.005
Hepatic encephalopathy — no./total no. (%)	18/57 (32)	19/116 (16)	0.03
Maddrey's discriminant function	66.3±17.8	51.2±17.9	<0.001
Child–Pugh score	11.5±1.3	10.9±1.4	0.01
Bilirubin decrease on day 7 — no./total no. (%)	31/51 (61)	97/108 (90)	<0.001
Bilirubin decrease on day 14 — no./total no. (%)	29/46 (63)	86/97 (89)	0.001

* Plus–minus values are means ±SD.

sign, another *N*-acetylcysteine-containing antioxidant regimen (with or without glucocorticoids) did not improve 6-month survival.[24] Finally, a randomized trial showed that use of *N*-acetylcysteine for 14 days did not confer any survival benefit, as compared with oral nutritional support.[25]

Although there was no significant difference in survival at 6 months between our study groups, there was a short-term survival benefit at 1 month with prednisolone–*N*-acetylcysteine as compared with prednisolone only. We used *N*-acetylcysteine because it has antioxidant properties,[26] decreases levels of free radicals, increases glutathione levels,[27] and represses the expression of nuclear factor κB and TNF-α.[28] The dose, duration, and administration route used were the same as those used for the treatment of drug intoxication[29,30] and the hepatorenal syndrome.[31] At 3 and 6 months, we observed a lower mortality rate in the prednisolone–*N*-acetylcysteine group than in the prednisolone-only group, but the differences were not significant. These findings may be related to a lack of power. It is also possible that 5 days of *N*-acetylcysteine was not enough. A longer period of intravenous *N*-acetylcysteine combined with prednisolone could perhaps be considered, with subsequent oral administration of *N*-acetylcysteine until 1 month.

The improvement in short-term survival that we observed in our study could be linked, at least in part, to a reduced risk of the hepatorenal syndrome in the prednisolone–*N*-acetylcysteine group. In a study involving 12 patients with the hepatorenal syndrome, the survival rate at 1 month after *N*-acetylcysteine infusion was unexpectedly high (67%).[31] In regard to morbidity, the prednisolone–*N*-acetylcysteine group in our study had significantly fewer infectious complications than the prednisolone-only group. It has been shown that patients with severe alcoholic hepatitis who do not have a response to treatment have significantly more bacterial infections than patients who have a response.[32] Alternatively, *N*-acetylcysteine could have beneficial effects by increasing blood flow to the liver, improving liver function, increasing the cardiac index,[33] and decreasing the intrahepatic lactate levels seen in patients with septic shock.[34]

Our study provides prospective validation of the finding that a decrease in the bilirubin level after 7 days of treatment is associated with a favorable prognosis[35] and also shows that a decrease on day 14 is associated with increased survival. However, in a multivariate analysis, only a decrease in the bilirubin level on day 14 remained significant, and the decrease was more frequent in the prednisolone–*N*-acetylcysteine group than in the prednisolone-only group. Thus, for a 5-day course of prednisolone–*N*-acetylcysteine therapy, therapeutic efficacy is better evaluated on day 14 than on day 7.

In conclusion, we observed improved survival at 1 month among patients with severe acute alcoholic hepatitis who received combination therapy with prednisolone and *N*-acetylcysteine, as compared with those who received prednisolone only, but 6-month mortality, our primary outcome, was not improved with combination therapy.

Supported by Programme Hospitalier de Recherche Clinique, a program of the French government that supports hospital-based clinical research.

No potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank Prof. Thierry Poynard for helpful comments on the manuscript.

REFERENCES

1. Mathurin P, Mendenhall CL, Carithers RL Jr, et al. Corticosteroids improve short-term survival in patients with severe alcoholic hepatitis (AH): individual data analysis of the last three randomized placebo controlled double blind trials of corticosteroids in severe AH. J Hepatol 2002;36:480-7.

2. Imperiale TF, O'Connor JB, McCullough AJ. Corticosteroids are effective in patients with severe alcoholic hepatitis. Am J Gastroenterol 1999;94:3066-8.

3. O'Shea RS, Dasarathy S, McCullough AJ. Alcoholic liver disease. Hepatology 2010;51:307-28.

4. Helman RA, Temko MH, Nye SW, Fallon HJ. Alcoholic hepatitis: natural history and evaluation of prednisolone therapy. Ann Intern Med 1971;74:311-21.

5. Maddrey WC, Boitnott JK, Bedine MS, Weber FL Jr, Mezey E, White RI Jr. Corticosteroid therapy of alcoholic hepatitis. Gastroenterology 1978;75:193-9.

6. Mendenhall CL, Anderson S, Garcia-Pont P, et al. Short-term and long-term survival in patients with alcoholic hepatitis treated with oxandrolone and prednisolone. N Engl J Med 1984;311:1464-70.

7. Carithers RL Jr, Herlong HF, Diehl AM, et al. Methylprednisolone therapy in patients with severe alcoholic hepatitis: a randomized multicenter trial. Ann Intern Med 1989;110:685-90.

8. Ramond MJ, Poynard T, Rueff B, et al. A randomized trial of prednisolone in patients with severe alcoholic hepatitis. N Engl J Med 1992;326:507-12.

9. Imperiale TF, McCullough AJ. Do corticosteroids reduce mortality from alcoholic hepatitis? A meta-analysis of the randomized trials. Ann Intern Med 1990;113:299-307.

10. Daures JP, Peray P, Bories P, et al. Corticoid therapy in the treatment of acute alcoholic hepatitis: results of a meta-analysis. Gastroenterol Clin Biol 1991;15:223-8. (In Spanish.)

11. Rambaldi A, Saconato HH, Christensen E, Thorlund K, Wetterslev J, Gluud C. Systematic review: glucocorticosteroids for alcoholic hepatitis — a Cochrane Hepato-Biliary Group systematic review with meta-analyses and trial sequential analyses of randomized clinical trials. Aliment Pharmacol Ther 2008;27:1167-78.

12. Mathurin P, Deng QG, Keshavarzian A, Choudhary S, Holmes EW, Tsukamoto H. Exacerbation of alcoholic liver injury by enteral endotoxin in rats. Hepatology 2000;32:1008-17.

13. Enomoto N, Ikejima K, Bradford B, et al. Alcohol causes both tolerance and sensitization of rat Kupffer cells via mechanisms dependent on endotoxin. Gastroenterology 1998;115:443-51.

14. Bird GL, Sheron N, Goka AK, Alexander GJ, Williams RS. Increased plasma tumor necrosis factor in severe alcoholic hepatitis. Ann Intern Med 1990;112:917-20.

15. Hirano T, Kaplowitz N, Tsukamoto H, Kamimura S, Fernandez-Checa JC. Hepatic mitochondrial glutathione depletion and progression of experimental alcoholic liver disease in rats. Hepatology 1992;16:1423-7.

16. Colell A, García-Ruiz C, Miranda M, et al. Selective glutathione depletion of mitochondria by ethanol sensitizes hepatocytes to tumor necrosis factor. Gastroenterology 1998;115:1541-51.

17. Reinert DF, Allen JP. The Alcohol Use Disorders Identification Test: an update of research findings. Alcohol Clin Exp Res 2007;31:185-99.

18. Dhalla S, Kopec JA. The CAGE questionnaire for alcohol misuse: a review of reliability and validity studies. Clin Invest Med 2007;30:33-41.

19. Nguyen-Khac E, Thevenot T, Piquet MA, et al. Treatment of severe acute alcoholic hepatitis (AAH) with corticoids plus n-acetyl cysteine (C-NAC) versus corticoids (C): planed interim analysis of a multicentre, controlled, randomized trial. J Hepatol 2008;48:Suppl 2:S17.

20. Wang AL, Wang JP, Wang H, et al. A dual effect of N-acetylcysteine on acute ethanol-induced liver damage in mice. Hepatol Res 2006;34:199-206.

21. Ronis MJ, Butura A, Sampey BP, et al. Effects of N-acetylcysteine on ethanol-induced hepatotoxicity in rats fed via total enteral nutrition. Free Radic Biol Med 2005;39:619-30.

22. Ozaras R, Tahan V, Aydin S, Uzun H, Kaya S, Senturk H. N-acetylcysteine attenuates alcohol-induced oxidative stress in rats. World J Gastroenterol 2003;9:791-4.

23. Phillips M, Curtis H, Portmann B, Donaldson N, Bomford A, O'Grady J. Antioxidants versus corticosteroids in the treatment of severe alcoholic hepatitis — a randomised clinical trial. J Hepatol 2006;44:784-90.

24. Stewart S, Prince M, Bassendine M, et al. A randomized trial of antioxidant therapy alone or with corticosteroids in acute alcoholic hepatitis. J Hepatol 2007;47:277-83.

25. Moreno C, Langlet P, Hittelet A, et al. Enteral nutrition with or without N-acetylcysteine in the treatment of severe acute alcoholic hepatitis: a randomized multicenter controlled trial. J Hepatol 2010;53:1117-22.

26. Aruoma OI, Halliwell B, Hoey BM, Butler J. The antioxidant action of N-acetylcysteine: its reaction with hydrogen peroxide, hydroxyl radical, superoxide, and hypochlorous acid. Free Radic Biol Med 1989;6:593-7.

27. Neuschwander-Tetri BA, Bellezzo JM, Britton RS, Bacon BR, Fox ES. Thiol regulation of endotoxin-induced release of tumour necrosis factor alpha from isolated rat Kupffer cells. Biochem J 1996;320:1005-10.

28. Verhasselt V, Vanden Berghe W, Vanderheyde N, Willems F, Haegeman G, Goldman M. N-acetyl-L-cysteine inhibits primary human T cell responses at the dendritic cell level: association with NF-kappaB inhibition. J Immunol 1999;162:2569-74.

29. Prescott LF, Park J, Ballantyne A, Adriaenssens P, Proudfoot AT. Treatment of paracetamol (acetaminophen) poisoning with N-acetylcysteine. Lancet 1977;2:432-4.

30. Lee WM, Hynan LS, Rossaro L, et al. Intravenous N-acetylcysteine improves transplant-free survival in early stage non-acetaminophen acute liver failure. Gastroenterology 2009;137:856-64.

31. Holt S, Goodier D, Marley R, et al. Improvement in renal function in hepatorenal syndrome with N-acetylcysteine. Lancet 1999;353:294-5.

32. Louvet A, Wartel F, Castel H, et al. Infection in patients with severe alcoholic hepatitis treated with steroids: early response to therapy is the key factor. Gastroenterology 2009;137:541-8.

33. Rank N, Michel C, Haertel C, et al. N-acetylcysteine increases liver blood flow and improves liver function in septic shock patients: results of a prospective, randomized, double-blind study. Crit Care Med 2000;28:3799-807.

34. Hein OV, Ohring R, Schilling A, et al. N-acetylcysteine decreases lactate signal intensities in liver tissue and improves liver function in septic shock patients, as shown by magnetic resonance spectroscopy: extended case report. Crit Care 2004;8:R66-R71.

35. Mathurin P, Abdelnour M, Ramond MJ, et al. Early change in bilirubin levels is an important prognostic factor in severe alcoholic hepatitis treated with prednisolone. Hepatology 2003;38:1363-9.

Prudence Ive, M.D.
Ian Sanne, M.D.
University of Witwatersrand
Johannesburg, South Africa

Since publication of their article, the authors report no further potential conflict of interest.

1. Lawn SD, Campbell L, Kaplan R, et al. Time to initiation of antiretroviral therapy among patients with HIV-associated tuberculosis in Cape Town, South Africa. J Acquir Immune Defic Syndr 2011;57:136-40.
2. Howard AA, El-Sadr WM. Integration of tuberculosis and HIV services in sub-Saharan Africa: lessons learned. Clin Infect Dis 2010;50:Suppl:S238-S244.
3. Uyei J, Coetzee D, Macinko J, Guttmacher S. Integrated delivery of HIV and tuberculosis services in sub-Saharan Africa: a systematic review. Lancet Infect Dis 2011;11:855-67.

THE EDITORIALISTS REPLY: The health care setting in which ART is initiated is one of the factors associated with successful care of patients with HIV-associated tuberculosis. However, such decisions need to take into account the patient, his or her community, the clinical facilities available, and the extent to which tuberculosis and HIV care is integrated. The recent studies suggest that early ART initiation is beneficial in patients with opportunistic infections and advanced immunosuppression, with the exception of those with central nervous system infections. In patients with severe or life-threatening HIV-related illnesses, initiation of ART in the inpatient setting is clearly prudent. For patients who are not hospitalized, outpatient initiation of ART is preferable. Even in the outpatient setting, however, delays in the initiation of ART[1] and loss to follow-up[2,3] are common. Loss to follow-up may result from poor coordination of HIV and tuberculosis services, rather than simply being a consequence of where the ART was initiated. The key to improving outcomes for patients with HIV-associated tuberculosis is coordinated and integrated HIV and tuberculosis services.[4] How that is achieved requires a locally relevant, flexible, and pragmatic approach.

M. Estée Török, M.D., Ph.D.
University of Cambridge
Cambridge, United Kingdom

Jeremy J. Farrar, M.D., Ph.D.
Hospital for Tropical Diseases
Ho Chi Minh City, Vietnam

Since publication of their article, the authors report no further potential conflict of interest.

1. Lawn SD, Campbell L, Kaplan R, Little F, Morrow C, Wood R. Delays in starting antiretroviral therapy in patients with HIV-associated tuberculosis accessing non-integrated clinical services in a South African township. BMC Infect Dis 2011;11:258.
2. Fox MP, Rosen S. Patient retention in antiretroviral therapy programs up to three years on treatment in sub-Saharan Africa, 2007-2009: systematic review. Trop Med Int Health 2010;15:Suppl:1-15.
3. Bassett IV, Chetty S, Wang B, et al. Loss to follow-up and mortality among HIV-infected people co-infected with TB at ART initiation in Durban, South Africa. J Acquir Immune Defic Syndr 2012;59:25-30.
4. Lawn SD, Harries AD, Wood R. Strategies to reduce early morbidity and mortality in adults receiving antiretroviral therapy in resource-limited settings. Curr Opin HIV AIDS 2010;5:18-26.

Glucocorticoids plus *N*-Acetylcysteine in Alcoholic Hepatitis

TO THE EDITOR: The study by Nguyen-Khac et al. (Nov. 10 issue)[1] sidesteps old contentious issues regarding the use of glucocorticoid therapy in alcoholic hepatitis. Among the 8 references cited in support of glucocorticoid treatment, 2 in fact concluded that the therapy was of no benefit.[2,3] In addition, 8 of 13 clinical trials published since 1971 showed that glucocorticoid therapy had no benefit as compared with placebo, although 5 of these did suggest an association with decreased short-term mortality.

The rationale for treating alcoholic hepatitis with antiinflammatory agents is soft. It is illogical to inhibit cytokines instead of targeting the putative pathogens that induce them. Exposing immunocompromised patients with severe alcoholic hepatitis to high-dose steroids exacerbates their already increased risk of infection, and the benefits are far from proven. In a multicenter trial of prednisolone and infliximab in the treatment of severe alcoholic hepatitis, increased mortality in the infliximab group caused premature termination of the study.[4]

In the study by Nguyen-Khac et al., *N*-acetylcysteine was associated with fewer infectious complications, but the primary outcome was not improved. The idea of adding one unproven treatment to another has little merit.

Gerond Lake-Bakaar, M.D.
Harvard Medical School
Boston, MA
glakebak@bidmc.harvard.edu

No potential conflict of interest relevant to this letter was reported.

1. Nguyen-Khac E, Thevenot T, Piquet M-A, et al. Glucocorticoids plus *N*-acetylcysteine in severe alcoholic hepatitis. N Engl J Med 2011;365:1781-9.
2. Helman RA, Temko MH, Nye SW, Fallon HJ. Alcoholic hepatitis: natural history and evaluation of prednisolone therapy. Ann Intern Med 1971;74:311-21.
3. Mendenhall CL, Anderson S, Garcia-Pont P, et al. Short-term and long-term survival in patients with alcoholic hepatitis treated with oxandrolone and prednisolone. N Engl J Med 1984;311:1464-70.
4. Naveau S, Chollet-Martin S, Dharancy S, et al. A double-blind randomized controlled trial of infliximab associated with prednisolone in acute alcoholic hepatitis. Hepatology 2004;39:1390-7.

THE AUTHORS REPLY: Since 1978, when patients with severe alcoholic hepatitis were first identified with the use of Maddrey's discriminant function (with a value greater than 32 indicating severe disease), the evidence has been growing that survival is improved by treatment with glucocorticoids. Even a negative meta-analysis,[1] in addition to a reanalysis of a negative trial,[2] reported better survival when the discriminant function was used to identify patients with severe disease. The American Association for the Study of Liver Disease has issued clear guidelines for the use of glucocorticoids.[3] In a prospective study,[4] 246 patients with severe alcoholic hepatitis were treated with glucocorticoids. The overall incidence of infections after treatment was 23.7%. However, in the patients with a treatment response (defined according to the Lille model, in which a score of <0.45 after 7 days of medical treatment indicates response), only 11.1% had infections as compared with 42.5% of the patients who did not respond to treatment glucocorticoid treatment (P<0.001).

Infections caused by glucocorticoids are feared. However, 25.6% of patients with severe alcoholic hepatitis are infected before glucocorticoid treatment, suggesting a need for routine screening for infection before treatment begins.[4] In one study, the risk of infection in the group of patients with severe alcoholic hepatitis who were treated with glucocorticoids was no higher than it was in a control group of patients with cirrhosis who were not treated with glucocorticoids.[5]

It is time to move on to other questions, as we have done by showing an improvement in early survival by combining glucocorticoids with *N*-acetylcysteine. In our study, there were fewer deaths from the hepatorenal syndrome and fewer infections in the group treated with glucocorticoids plus *N*-acetylcysteine as compared with the group treated with glucocorticoids alone.

Eric Nguyen-Khac, M.D., Ph.D.

Amiens University Hospital
Amiens, France

Thierry Thevenot, M.D., Ph.D.

Besançon University Hospital
Besançon, France

Marie-Astrid Piquet, M.D., Ph.D.

Caen University Hospital
Caen, France

Since publication of their article, the authors report no further potential conflict of interest.

1. Rambaldi A, Saconato HH, Christensen E, Thorlund K, Wetterslev J, Gluud C. Systematic review: glucocorticosteroids for alcoholic hepatitis — a Cochrane Hepato-Biliary Group systematic review with meta-analyses and trial sequential analyses of randomized clinical trials. Aliment Pharmacol Ther 2008;27:1167-78.
2. Mathurin P, Mendenhall CL, Carithers RL Jr, et al. Corticosteroids improve short-term survival in patients with severe alcoholic hepatitis (AH): individual data analysis of the last three randomized placebo controlled double blind trials of corticosteroids in severe AH. J Hepatol 2002;36:480-7.
3. O'Shea RS, Dasarathy S, McCullough AJ, et al. Alcoholic liver disease. Hepatology 2010;51:307-28.
4. Louvet A, Wartel F, Castel H, et al. Infection in patients with severe alcoholic hepatitis treated with steroids: early response to therapy is the key factor. Gastroenterology 2009;137:541-8.
5. Richardet J, Valtier S, Campillo B. Evaluation du risqué infectieux au cours de la corticotherapie pour hépatite alcoolique grave. Journées Francophones de pathologie digestive 2008, Palais des Congrés de Paris. Abstract.

Early Liver Transplantation for Severe Alcoholic Hepatitis

TO THE EDITOR: The study reported by Mathurin et al. (Nov. 10 issue)[1] could have a strong impact on living-donor liver transplantation.

Mandatory alcohol abstinence before deceased-donor liver transplantation serves two purposes: evaluation of compliance, including the likelihood of recidivism, and reassurance to the public that the candidate has earned the right to a graft.[2] Mathurin and colleagues challenged the former purpose, but not the latter, which concerns moral perceptions beyond evidence-based arguments.

In Far East regions, including Japan, deceased-donor organs remain scarce. Living-donor liver transplantation remains the mainstream approach, and the use of this procedure is differ-

1. Nguyen-Khac E, Thevenot T, Piquet M-A, et al. Glucocorticoids plus *N*-acetylcysteine in severe alcoholic hepatitis. N Engl J Med 2011;365:1781-9.
2. Helman RA, Temko MH, Nye SW, Fallon HJ. Alcoholic hepatitis: natural history and evaluation of prednisolone therapy. Ann Intern Med 1971;74:311-21.
3. Mendenhall CL, Anderson S, Garcia-Pont P, et al. Short-term and long-term survival in patients with alcoholic hepatitis treated with oxandrolone and prednisolone. N Engl J Med 1984;311:1464-70.
4. Naveau S, Chollet-Martin S, Dharancy S, et al. A double-blind randomized controlled trial of infliximab associated with prednisolone in acute alcoholic hepatitis. Hepatology 2004;39:1390-7.

THE AUTHORS REPLY: Since 1978, when patients with severe alcoholic hepatitis were first identified with the use of Maddrey's discriminant function (with a value greater than 32 indicating severe disease), the evidence has been growing that survival is improved by treatment with glucocorticoids. Even a negative meta-analysis,[1] in addition to a reanalysis of a negative trial,[2] reported better survival when the discriminant function was used to identify patients with severe disease. The American Association for the Study of Liver Disease has issued clear guidelines for the use of glucocorticoids.[3] In a prospective study,[4] 246 patients with severe alcoholic hepatitis were treated with glucocorticoids. The overall incidence of infections after treatment was 23.7%. However, in the patients with a treatment response (defined according to the Lille model, in which a score of <0.45 after 7 days of medical treatment indicates response), only 11.1% had infections as compared with 42.5% of the patients who did not respond to treatment glucocorticoid treatment (P<0.001).

Infections caused by glucocorticoids are feared. However, 25.6% of patients with severe alcoholic hepatitis are infected before glucocorticoid treatment, suggesting a need for routine screening for infection before treatment begins.[4] In one study, the risk of infection in the group of patients with severe alcoholic hepatitis who were treated with glucocorticoids was no higher than it was in a control group of patients with cirrhosis who were not treated with glucocorticoids.[5]

It is time to move on to other questions, as we have done by showing an improvement in early survival by combining glucocorticoids with *N*-acetylcysteine. In our study, there were fewer deaths from the hepatorenal syndrome and fewer infections in the group treated with glucocorticoids plus *N*-acetylcysteine as compared with the group treated with glucocorticoids alone.

Eric Nguyen-Khac, M.D., Ph.D.

Amiens University Hospital
Amiens, France

Thierry Thevenot, M.D., Ph.D.

Besançon University Hospital
Besançon, France

Marie-Astrid Piquet, M.D., Ph.D.

Caen University Hospital
Caen, France

Since publication of their article, the authors report no further potential conflict of interest.

1. Rambaldi A, Saconato HH, Christensen E, Thorlund K, Wetterslev J, Gluud C. Systematic review: glucocorticosteroids for alcoholic hepatitis — a Cochrane Hepato-Biliary Group systematic review with meta-analyses and trial sequential analyses of randomized clinical trials. Aliment Pharmacol Ther 2008;27:1167-78.
2. Mathurin P, Mendenhall CL, Carithers RL Jr, et al. Corticosteroids improve short-term survival in patients with severe alcoholic hepatitis (AH): individual data analysis of the last three randomized placebo controlled double blind trials of corticosteroids in severe AH. J Hepatol 2002;36:480-7.
3. O'Shea RS, Dasarathy S, McCullough AJ, et al. Alcoholic liver disease. Hepatology 2010;51:307-28.
4. Louvet A, Wartel F, Castel H, et al. Infection in patients with severe alcoholic hepatitis treated with steroids: early response to therapy is the key factor. Gastroenterology 2009;137:541-8.
5. Richardet J, Valtier S, Campillo B. Evaluation du risqué infectieux au cours de la corticotherapie pour hépatite alcoolique grave. Journées Francophones de pathologie digestive 2008, Palais des Congrés de Paris. Abstract.

Early Liver Transplantation for Severe Alcoholic Hepatitis

TO THE EDITOR: The study reported by Mathurin et al. (Nov. 10 issue)[1] could have a strong impact on living-donor liver transplantation.

Mandatory alcohol abstinence before deceased-donor liver transplantation serves two purposes: evaluation of compliance, including the likelihood of recidivism, and reassurance to the public that the candidate has earned the right to a graft.[2] Mathurin and colleagues challenged the former purpose, but not the latter, which concerns moral perceptions beyond evidence-based arguments.

In Far East regions, including Japan, deceased-donor organs remain scarce. Living-donor liver transplantation remains the mainstream approach, and the use of this procedure is differ-

ent in the Far East than elsewhere. Without public restraints regarding the organ shortage, the expansion of indications is tempting, as shown in the case of hepatocellular carcinoma.[3] Because abstinence has been mandated[4] to establish compliance rather than to evoke a sense of justice, the study by Mathurin et al. calls for a reevaluation of the grounds of our current approach in living-donor liver transplantation, adding a further burden to the dilemma of living-donor liver transplantation.

Sumihito Tamura, M.D.
Yasuhiko Sugawara, M.D.
Norihiro Kukudo, M.D.

University of Tokyo Graduate School of Medicine
Tokyo, Japan
yasusugatky@yahoo.co.jp

No potential conflict of interest relevant to this letter was reported.

1. Mathurin P, Moreno C, Samuel D, et al. Early liver transplantation for severe alcoholic hepatitis. N Engl J Med 2011;365:1790-800.
2. Neuberger J, Webb K. Liver transplantation for alcoholic liver disease: knowing the future informs the present. Am J Transplant 2010;10:2195-6.
3. Todo S, Furukawa H, Tada M. Extending indication: role of living donor liver transplantation for hepatocellular carcinoma. Liver Transpl 2007;13:S48-S54.
4. Yamashiki N, Sugawara Y, Tamura S, et al. Selection of liver-transplant candidates for adult-to-adult living donor liver transplantation as the only surgical option for end-stage liver disease. Liver Transpl 2006;12:1077-83.

TO THE EDITOR: From a practical standpoint, in areas where the demand for organs far exceeds availability, we would like to make the following observations. In spite of very strict selection criteria for early transplantation in the study reported by Mathurin et al., more than 10% of the patients still had alcohol relapse, with two remaining daily consumers at the end of the study. This rate of recidivism is significant, given the fact that the number of liver-transplant recipients represented fewer than 2% of patients with severe alcoholic hepatitis. There were also 6 deaths (of 26) in the recipient group, 5 of which occurred within 2 weeks after surgery. Thus, although there is improved survival with early transplantation, there is still a substantial risk of death. The findings of this study should instead prompt consideration of living-donor liver transplantation in a highly selected group of patients. This approach might act as an additional deterrent to recidivism while restricting the use of cadaveric organs for a still controversial indication such as severe alcoholic hepatitis.

Savio John, M.B., B.S.
Raymond T. Chung, M.D.

Massachusetts General Hospital
Boston, MA
sjohn5@partners.org

No potential conflict of interest relevant to this letter was reported.

TO THE EDITOR: Mathurin et al. indicate that liver transplantation is beneficial in severe acute alcoholic hepatitis that is resistant to medical treatment. This benefit on an individual level will inevitably cause problems on a population level in the context of organ shortage, given the high prevalence of alcoholic cirrhosis and the difficulty in predicting alcohol relapse.

We reported the results of a randomized trial in which immediate listing for liver transplantation was compared with standard care in patients with Child–Pugh class B alcoholic cirrhosis.[1] Our study did not show a survival benefit associ-

Table 1. Time-Dependent Cox Regression Analysis of Factors Associated with Alcohol Relapse in the TRANSCIAL Study.*

Variable	Hazard Ratio for Relapse (95% CI)	P Value
Female sex	2.13 (1.06–4.30)	0.03
Alcohol dependence defined according to DSM-IV	2.30 (1.11–4.75)	0.02
High baseline Child–Pugh score	0.94 (0.61–1.43)	NS
Assignment to immediate listing group	1.22 (0.56–2.65)	NS
Increase in alcohol intake per grams per day during the past 12 mo, estimated at baseline	1.01 (1.01–1.01)	0.04
Liver transplantation	0.43 (0.19–0.95)	0.04

* Data are from Vanlemmens et al.[1] CI denotes confidence interval, DSM-IV *Diagnostic and Statistical Manual of Mental Disorders,* 4th edition, NS not significant, and TRANSCIAL Transplantation pour Cirrhose Alcoolique (ClinicalTrials.gov number, NCT00701792).

ated with immediate listing and stressed the increased risk of extrahepatic cancers. However, we conducted regularly scheduled interviews of patients and their relatives and systematic measures of alcohol concentrations in blood and urine for 5 years, and we evaluated through multivariate analysis the predictors of alcohol relapse. We were surprised to find that transplantation had a protective effect (Table 1).

Liver transplantation could bring about positive psychological changes in patients who are held in greater esteem by society and wish to honor their donor's memory. Decreased alcohol consumption could also be the consequence of psychological interventions or immunosuppressive drugs.

Vincent Di Martino, M.D., Ph.D.
Frances Sheppard, M.P.W.
Claire Vanlemmens, M.D.

Centre Hospitalier Universitaire de Besançon
Besançon, France
vdimartino@chu-besancon.fr

No potential conflict of interest relevant to this letter was reported.

1. Vanlemmens C, Di Martino V, Milan C, et al. Immediate listing for liver transplantation versus standard care for Child-Pugh stage B alcoholic cirrhosis: a randomized trial. Ann Intern Med 2009;150:153-61.

THE AUTHORS REPLY: The letters concerning our recent article raise important issues. Liver transplantation with cadaveric donors for severe alcoholic hepatitis that has not responded to medical management is in itself a complex ethical issue and, like any other indication, needs to be considered in light of the scarcity of donor organs. However, liver transplantation involving living donors raises other important ethical issues. Indeed, in our selection process, the patient's family was actively involved in the decision process. In living-donor liver transplantation, family and team members confront several dilemmas (e.g., the interaction between the selection process and the evaluation of a person's willingness to donate, as well as difficulties in providing objective information on the risk of death for both the recipient and the donor), with the risk of inducing biased selection. Since most deaths occur early in patients who have not undergone transplantation and have not had a response to treatment, the decision to place the patient on the list for liver transplantation and to perform transplantation was made soon after ascertaining the patient's lack of response to treatment, raising the question of feasibility in the context of living-donor liver transplantation. For all these reasons, we do not recommend living-donor liver transplantation for severe alcoholic hepatitis at the present time.

We agree that substantial perioperative mortality is a key issue. Five of six deaths were related to infection occurring within 2 weeks after liver transplantation. Infection is a frequent complication in patients with alcoholic hepatitis, particularly in patients who do not have a response to glucocorticoids, and extensive infection screening is warranted.[1] In light of the four deaths related to aspergillosis, strategies evaluating antifungal prophylaxis, early arrest of glucocorticoids, and tailoring of immunosuppressive regimens need to be evaluated. Survival after liver transplantation should improve with experience and with the learning curve of the centers.

Our findings challenge the 6-month abstinence rule in this particular situation. No relapse of alcoholism was observed during the 6 months after liver transplantation, although three patients later had relapses. Given the approximately 25 to 35% alcohol relapse rate over the long term among patients who undergo liver transplantation for alcoholic cirrhosis,[2] the rate of relapse in our study seems low and might be related to the stringency of our selection process. As mentioned, liver transplantation could have a protective effect on alcohol relapse. However, this protective effect, observed in patients with Child–Pugh class B alcoholic cirrhosis, cannot be extended to our severely ill highly selected patients with alcoholic hepatitis. Finally, future studies evaluating long-term sobriety and the reproducibility of our selection process are warranted.

Christophe Moreno, M.D., Ph.D.

Erasme Hospital
Brussels, Belgium

Jean-Charles Duclos-Vallée, M.D., Ph.D.

Hôpital Paul Brousse
Villejuif, France

Philippe Mathurin, M.D., Ph.D.

Hôpital Claude Huriez
Lille, France

Since publication of their article, the authors report no further potential conflict of interest.

1. Louvet A, Wartel F, Castel H, et al. Infection in patients with severe alcoholic hepatitis treated with steroids: early response to therapy is the key factor. Gastroenterology 2009;137:541-8.
2. Pageaux GP, Bismuth M, Perney P, et al. Alcohol relapse after liver transplantation for alcoholic liver disease: does it matter? J Hepatol 2003;38:629-34.