Supplemental Online Content

Louvet A, Labreuche J, Dao T, et al. Effect of prophylactic antibiotics on mortality in severe alcohol-related hepatitis: a randomized clinical trial. *JAMA*. Published May 9, 2023. doi:10.1001/jama.2023.4902

This supplemental material has been provided by the authors to give readers additional information about their work.

eAppendix. Supplemental Methods

Patient selection

Patients could not have a past history of allergy of hypersensitivity to amoxicillin or clavulanate, type 1 hepatorenal syndrome before the initiation of treatment, uncontrolled gastrointestinal bleeding or untreated infection. In case of evidence of bacterial sepsis at admission, infection had to be cured by antibiotics and a therapeutic window of at least 7 days was required before entering the trial. Carriage of HCV RNA and HBsAg were also exclusion criteria.

Sample calculation

The sample size was calculated for a total of 54 events (death) based on the expected primary outcome rate of 73% in patients treated by prednisolone, and assuming an absolute increase of 14% (target effect size) with combined prednisolone and antibiotics (resulting in a primary outcome of 87% in the amoxicillin/clavulanate group), with a follow-up of 60 days in all patients and a 5% rate of loss to follow-up. A French multicenter trial (Mathurin et al. JAMA 2013) observed that patients with a baseline MELD score ≥ 21 had an 18.8% decrease in 2-month survival compared to patients with a MELD score <21. The target effect size was determined by an expected difference of 75% of the difference in estimated two-month survival in patients with severe AH with a MELD score <21 (91.8%) versus those with MELD≥21 (73.0%) (Mathurin et al. JAMA 2013). Details are presented in the trial protocol (Supplement 1).

Calculation of diagnostic and prognostic scores

The Lille score was calculated at day 7 and the MELD score was calculated at each visit. The Maddrey discriminant function and the MELD score were calculated at baseline, and the Lille model was calculated 7 days after treatment had begun. The formulas for the scores were as follows: Maddrey discriminant function = 4.6 × [patient prothrombin time − control prothrombin time (in seconds)] + serum bilirubin (in mg/dL) ; MELD score = [9.57 × loge creatinine (in mg/dL) + 3.78 × loge bilirubin (in mg/dL) + 11.20 × loge INR + 6.43]; Lille score = Exp(−R)/[1+Exp(−R)], where R = [3.19 −0.101 × age (in years) + 0.147 × albumin (in g/L) + 0.0165 × evolution in bilirubin (in µmol/L) − 0.206 × renal insufficiency −0.0065 × bilirubin (in µmol/L) −0.0096 × prothrombin time (in seconds)].

Safety report

Adverse events were classified using the Medical Dictionary for Regulatory Activities (MedDRA) terminology, version 24.0, by System Organ Class (SOC) and preferred terms. Seriousness and causal relationship were assessed by the investigators. All adverse and serious adverse events were reported to the Cellule Vigilance des Essais Cliniques, Centre Hospitalier Universitaire de Lille. Serious adverse events were reported within the first 24 hours and closely monitored. A causal relationship was assessed by both the investigator and the sponsor. An independent data and safety monitoring board (DSMB) was set up to review all serious adverse events.

eTable 1. Major Deviations in the Two Groups

These patients were excluded from the sensitivity analysis restricted to patients treated according to study protocol

Major deviation	Amoxicillin/clavulanate group n=10	Placebo group n=8
Received the non-allocated intervention	7	6
Received steroids within the last 6 months	1	0
Did not receive any treatment	1	0
Failure of transjugular liver biopsy	1	0
Liver biopsy did not confirm AH	0	1
Ongoing candidiasis at inclusion	0	1

eTable 2. Reasons for Treatment Interruption in the Two Groups

Experimental treatment interruption	A/C* (n=141)	P* (n=143)	Total (n=284)
All treatment interruptions	**19**	**36**	**55**
Interruption of amoxicillin/clavulanate or placebo and prednisolone			
Treatment stopped	**14**	**29**	**43**
Both drugs temporarily interrupted	2	9	11
Both drugs withdrawn	12	20	32
*Interruption of amoxicillin/clavulanate or placebo only**			
Treatment stopped	**5**	**6**	**11**
Augmentin/placebo temporarily interrupted	3	1	4
Augmentin/placebo withdrawn	2	5	7
*Interruption of prednisolone only***			
Treatment stopped	**0**	**1**	**1**
Prednisolone temporarily interrupted	0	0	0
Prednisolone withdrawn	0	1	1

*A/C is for amoxicillin/clavulanate, P is for placebo

eTable 3. Causes of Death in the Two Groups During the 6-Month Follow-up

	Amoxicillin/clavulanate + prednisolone group (43 deaths)	Placebo + prednisolone group (48 deaths)
Hepatic insufficiency	17	11
Gastrointestinal bleeding	7	12
Hepatorenal syndrome	1	3
Encephalopathy	3	3
Infection (pneumonia)	10 (7)	13 (5)
Cardiovascular event	1	2
Cancer	1	0
Unknown	3	4

eTable 4. Distribution of Infection Occurring in the First 60 Days in the Two Groups

Site of infection	Amoxicillin/clavulanate + prednisolone n=42	Placebo + prednisolone n=59
Lung infection	16	16
Spontaneous bacterial peritonitis	3	10
Bacteremia	5	8
Urinary tract infection	4	10
Skin infection	1	5
C. difficile infection	1	2
Other infections	12	8

eTable 5. Total Number of Serious Adverse Events Reported Within the First 6 Months (End of Follow-up) in the Two Groups

	Number of patients			*Number of events*		
Classification	**Augmentin**	**Placebo**	**Total**	**Augmentin**	**Placebo**	**Total**
All Serious Adverse Events	**92**	**102**	**194**	**164**	**211**	**375**
Hepatobiliary disorders	**51**	**44**	**95**	**59**	**61**	**120**
Hepatic failure (including acute hepatic failure, hepatic encephalopathy, ascites, jaundice, abnormal hepatic tests, hydrothorax, new occurrence of alcoholic hepatitis, hepatopulmonary syndrome)	42	37	79	48	52	100
Hepatorenal syndrome	9	9	18	10	9	19
Liver nodule compatible with hepatocellular carcinoma	1	0	1	1	0	1
Drug-induced liver injury	0	0	0	0	0	0
Infections	**25**	**47**	**72**	**35**	**60**	**95**
Pneumonia	6	12	18	6	13	19
Pneumocystis jirovecii pneumonia	8	7	15	8	7	15
Bacteremia	2	11	13	2	11	13
Spontaneous bacterial peritonitis	3	9	12	3	12	15
Skin and joint infection	5	4	9	5	4	9
Septic shock	2	6	8	2	6	8
Urinary tract infection	2	3	5	2	3	5
Clostridium difficile infection	1	3	4	2	3	5
Fungal infection	2	1	3	2	1	3
Other infection	2	0	2	3	0	3
Gastrointestinal disorders	**18**	**27**	**45**	**19**	**29**	**48**
Gastrointestinal hemorrhage	17	24	41	18	25	43
Other (diarrhoea, intestinal obstruction)	1	4	5	1	4	5
General disorders (e.g. general physical health deterioration, fever without sepsis)	**12**	**6**	**18**	**12**	**6**	**18**
Metabolic and endocrine disorders	**5**	**7**	**12**	**5**	**9**	**14**
Psychiatric disorders	**9**	**12**	**21**	**11**	**13**	**24**
Acute renal failure not related to HRS	**5**	**6**	**11**	**6**	**6**	**12**
Surgical and medical procedures (liver transplantation)	**5**	**7**	**12**	**5**	**7**	**12**

Cardiac disorders	**2**	**3**	**5**	**2**	**3**	**5**
Cardiac failure	1	1	2	1	1	2
Tachycardia	1	0	1	1	0	1
Cardiac arrest	0	1	1	0	1	1
Myocardial infarction	0	1	1	0	1	1
Vascular disorders	**2**	**3**	**5**	**2**	**4**	**6**
Neoplasms	**2**	**3**	**5**	**2**	**3**	**5**
Blood and lymphatic system disorders	**1**	**4**	**5**	**1**	**4**	**5**
Anaemia related to cirrhosis	1	3	4	1	3	4
Neutropenia	0	1	1	0	1	1
Nervous system disorders	**1**	**1**	**2**	**1**	**1**	**2**
Injury and procedural complications	**1**	**3**	**4**	**1**	**3**	**4**
Fall	0	1	1	0	1	1
Post procedural haemorrhage	0	1	1	0	1	1
Respiratory, thoracic and mediastinal disorders	**1**	**0**	**1**	**1**	**0**	**1**
Pulmonary embolism	1	0	1	1	0	1
Skin and subcutaneous tissue disorders	**0**	**1**	**1**	**0**	**1**	**1**
Drug eruption	0	1	1	0	1	1

eTable 6. Adverse Drug Reactions Reported in the Safety Population (n=141 in the Experimental Arm and n=143 in the Placebo Arm) up to 2 Months

*Only one episode of diarrhoea in one patient treated with antibiotics was reported as an adverse drug reaction after the first month. All other adverse drug reactions were reported within the first month.

	Number of patients			*Number of adverse drug reactions*		
Classification	**ATB**	**PLB**	**Total**	**ATB**	**PLB**	**Total**
All adverse drug reactions	**29**	**20**	**49**	**36**	**23**	**59**
Gastrointestinal disorders	**26**	**17**	**43**	**31**	**20**	**51**
Diarrhoea*	20	17	37	23	17	40
Abdominal pain	4	2	6	4	2	6
Nausea	1	0	1	2	0	2
Vomiting	2	1	3	2	1	3
Infections and infestations	**2**	**1**	**3**	**2**	**1**	**3**
Clostridium difficile infection	1	1	2	1	1	2
Gastrointestinal fungal infection	1	0	1	1	0	1
Metabolism and nutrition disorders	**1**	**0**	**1**	**1**	**0**	**1**
Hypokaliemia	1	0	1	1	0	1
Skin and subcutaneous disorders	**2**	**2**	**4**	**2**	**2**	**4**
Toxic skin eruption	0	2	2	0	2	2
Pruritus	2	0	2	2	0	2

eTable 7. Sensitivity Analyses on All-Cause Mortality at 2-, 3 and 6-Months

	Amoxicillin/clavulanate + prednisolone	Placebo + prednisolone	P-Value	Absolute difference (CI)	Hazard ratio (CI)
Analysis restricted to patients treated according to study protocol					
60-day mortality (primary outcome)	23/132 (17.8)	30/134 (22.5)	0.35	-4.7 (-14.4 to 5.1)	0.77 (0.44 to 1.34)
90-day mortality	27/132 (21.0)	36/134 (27.1)	0.27	-6.1 (-16.5 to 4.3)	0.75 (0.45 to 1.25)
180-day mortality	38/132 (29.8)	45/134 (34.2)	0.41	-4.4 (-16.0 to 7.0)	0.84 (0.54 to 1.29)
Liver transplantation-free survival analysis (LTFS)					
60-day LTFS	28/142 (19.8)	33/142 (23.2)	0.51	-3.5 (-13.0 to 6.2)	0.84 (0.50 to 1.40)
90-day LTFS	34/142 (24.0)	42/142 (29.6)	0.33	-5.5 (-15.9 to 4.8)	0.80 (0.50 to 1.26)
180-day LTFS	48/142 (33.3)	55/142 (38.8)	0.41	-4.7 (-16.0 to 6.5)	0.85 (0.57 to 1.26)

Values are n/N (Kaplan-Meier estimates, %)

eTable 8. Comparison in Alcohol Relapse During the 180-Day Follow-up Between the Two Study Groups

	Amoxicillin/clavulanate + prednisolone	Placebo + prednisolone	P-value	SHR (95%CI)
Alcohol relapse	38/142 (27.4)	35/142 (25.1)	0.69	1.10 (0.69 to 1.74)
Among patients with Alcohol relapse				
Time from first relapse				
Median (Q1-Q3) , day	35 (15; 79)	36 (10; 58)		
Alcohol dose, g	35 (20; 75)	35 (10; 60)		

SHR indicated subhazard of alcohol relapse estimated using univariable Fine & Gray model treating death as a competing event.

By treating the first alcohol relapse as a time-dependent covariate into the Cox's regression model, the treatment effect size remained unchanged, with an HR for amoxicillin/clavulanate group vs. placebo group of 0.77 (95%CI, 0.45 to 1.32, p=0.34) at 60 days, 0.78 (95%CI, 0.47 to 1.27, p=0.31) at 90 days and 0.88 (95%CI, 0.58 to 1.32, p=0.52) at 180 days.

eTable 9. Serious[1] Adverse Events Reported in the Safety Population[2] During the First 60 Days of Follow-up (Primary Endpoint)

	Number of patients		*Number of events*	
Classification	**Amoxicillin-clavulanate (n=141)**	**Placebo (n=143)**	**Amoxicillin-clavulanate**	**Placebo**
Surgical and medical procedures (liver transplantation)	**4**	**2**	**4**	**2**
Cardiac disorders	**2**	**3**	**2**	**3**
Cardiac failure	1	2	1	2
Tachycardia	1	0	1	0
Myocardial infarction	0	1	0	1
Vascular disorders	**2**	**2**	**2**	**2**
Neoplasms	**2**	**1**	**2**	**1**
Blood and lymphatic system disorders	**0**	**2**	**0**	**2**
Anaemia related to cirrhosis	0	2	0	2
Nervous system disorders	**1**	**1**	**1**	**1**
Injury and procedural complications	**0**	**2**	**0**	**2**
Fall	0	1	0	1
Post procedural haemorrhage	0	1	0	1
Respiratory, thoracic and mediastinal disorders	**1**	**0**	**1**	**0**
Pulmonary embolism	1	0	1	0
Skin and subcutaneous tissue disorders	**0**	**1**	**0**	**1**

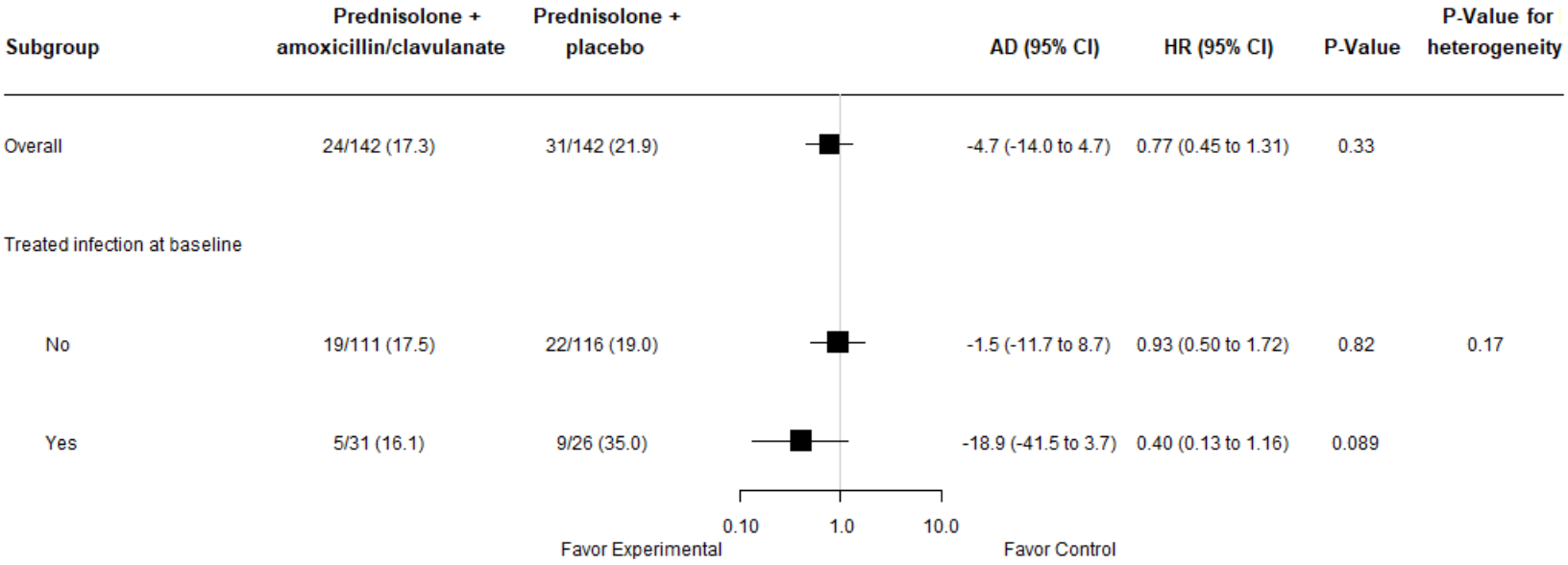
Drug eruption	0	1	0	1

Severe adverse events reported out to 6 months are displayed in Supplemental Table 5. Adverse drug reactions reported up to 2 months are displayed in Supplemental Table 6.

[1] Seriousness criteria as defined by ICH guidelines and EU Clinical Trial Directive (2001/20/EC): any adverse event that results in death, is life-threatening, requires in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, is a congenital anomaly/birth defect, or is considered as clinically significant by the investigator.

[2] Safety population: treatment arm as defined by the treatment actually taken by the patient, independently from the arm they were randomized in

eFigure 1. Treatment Effect Size on 60-Day Survival (Primary Outcome) According to Treated Infection at Baseline



eFigure 2. Cumulative Incidence of Alcohol Relapse During the 180-Day Follow-up Estimated Using Kalbfleisch and Prentice by Treating Death as Competing Event