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Intravenous N-acetylcysteine in Pediatric Patients with Non-Acetaminophen Acute Liver Failure: A Placebo-Controlled Clinical Trial

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Abstract

N-acetylcysteine (NAC) was found to improve transplantation-free survival in only those adults with non-acetaminophen (non-APAP) acute liver failure (ALF) and grade 1–2 hepatic encephalopathy (HE). Because non-APAP ALF differs significantly between children and adults, the Pediatric Acute Liver Failure (PALF) Study Group evaluated NAC in non-APAP PALF. Children from birth through age 17 years with non-APAP ALF enrolled in the PALF registry were eligible to enter an adaptively allocated, doubly masked, placebo-controlled trial using a continuous intravenous infusion of NAC (150 mg/kg/day in 5% dextrose in water [D5W]) or placebo (D5W) for up to 7 days. The primary outcome was 1-year survival. Secondary outcomes included liver transplantation-free survival, liver transplantation (LTx), length of ICU and hospital...
stays, organ system failure and maximum HE score. A total of 184 participants were enrolled in the trial with 92 in each arm. The 1-year survival did not differ significantly (p=0.19) between the NAC (73%) and placebo (82%) treatment groups. The 1-year LTx-free survival was significantly lower (p=0.03) in those who received NAC (35%) than those who received placebo (53%), particularly, but not significantly so, among those less than 2 years old with HE grade 0–1 (NAC 25%; placebo 60%; p=0.0493). There were no significant differences between treatment arms for hospital or ICU length of stay, organ systems failing, or highest recorded grade of HE.

Conclusion—NAC did not improve 1-year survival in non-APAP PALF. 1-year LTx-free survival was significantly lower with NAC, particularly among those < 2 years old. These results do not support broad use of NAC in non-APAP PALF and emphasizes the importance of conducting controlled pediatric drug trials, regardless of results in adults.

Keywords
Child; hepatic encephalopathy; liver transplantation; multi-organ system failure; treatment

Pediatric acute liver failure (PALF) is a rare and devastating syndrome in which previously healthy children rapidly lose hepatic function due to a variety of causes and become critically ill within days.(1–2) Management is largely supportive unless conditions that are amenable to directed therapy, such as acute acetaminophen toxicity, herpes virus, and potentially treatable causes such as Wilson disease and autoimmune hepatitis are identified and treated.(3–4) Early referral to a liver transplantation (LTx) center, improvements in medical management and LTx are associated with improved survival in PALF.(5) Long term outcomes following LTx for PALF are poor compared to other indications for LTx(6-7), hence the need to identify treatments that improve survival. N-acetylcysteine (NAC), used for treating acute acetaminophen (APAP) toxicity, has been used to treat non-APAP PALF but has not been rigorously tested in a multi-center placebo-controlled clinical trial in children.(8–9)

NAC replenishes mitochondrial and cytosolic glutathione stores and is the treatment of choice for acute APAP toxicity.(10–11) Intravenous NAC became incorporated into the general management of acute liver failure in a number of sites in Europe and North America following a small uncontrolled study suggesting improved cardiovascular hemodynamics and oxygen transport in both APAP and non-APAP liver failure in adults.(12) A retrospective single-site review in children affirmed the view that NAC may provide benefit in PALF.(8) In a randomized trial of intravenous NAC versus placebo in adults with non-APAP liver failure, NAC did not improve survival at 21 days.(13) However, an analysis of the secondary outcomes revealed improved LTx-free survival at 3 weeks for those with grade 1–2 hepatic encephalopathy (HE). The primary objective of this study was to determine if a continuous intravenous infusion of NAC for up to seven days would improve overall survival compared to placebo one year following treatment allocation in non-APAP PALF.

PATIENTS AND METHODS

Study oversight

This study was funded by the Division of Digestive Diseases and Nutrition within the National Institute of Diabetes and Digestive and Kidney (NIDDK) Diseases of the National Institute of Health (NIH) and was registered with www.ClinicalTrials.gov (NCT00248625). Study design and management of the NAC trial was accomplished by academic clinical investigators and site coordinators associated with the Pediatric Acute Liver Failure Study Group (PALFSG). A Data and Safety Monitoring Board (DSMB) consisting of experts in
pediatric hepatology, pediatric LTx and statistical analysis was appointed by the NIH/ NIDDK and did not have any conflicts of interest with members or institutions that constituted the PALFSG or the suppliers of NAC. NAC was initially provided by Apothecon/Geneva Pharmaceuticals (Princeton, NJ), a division of Bristol Myers Squibb, and after April 2003 was supplied by Cumberland Pharmaceuticals (Nashville, TN). The Investigational New Drug application (IND) was held by the Principal Investigator for the trial (RHS). The PALFSG consisted of 20 pediatric sites in North America and the United Kingdom and a Data Coordinating Center (DCC).

**Study Population**

Eligible participants for the NAC trial were drawn from a registry of children with PALF established at PALFSG sites. Each site was a pediatric liver transplantation center and no donor organs were obtained from executed prisoners or other institutionalized persons. The goal of the registry was to collect detailed information from children with PALF. Entry criteria for the PALF registry included children who were under the age of 18 years, informed consent and assent when appropriate, absence of a known chronic liver disease, biochemical evidence of acute liver injury and a liver-based coagulopathy, not corrected by parenteral vitamin K. Clinical evidence of HE was required if the prothrombin time (PT) was between 15–19.9 seconds or the International Normalization Ratio (INR) was between 1.5–1.9. HE was not required for a PT of at least 20 seconds or an INR at least 2.0, given the challenges of assessing clinical HE in infants and children. Detailed clinical and biochemical information was collected prospectively for up to 7 days following enrollment.(2, 14–15)

From February 2001 through September 2009, 635 children enrolled in the PALF registry after site specific IRB approvals for the NAC trial were obtained. Eligibility criteria for the NAC trial included enrollment in the PALFSG registry and completion of a separate informed consent for the NAC study from a parent or guardian and an informed assent from the patients who were 14–17 years of age, developmentally able to sign his or her name and were without clinical HE.

Exclusion criteria included known acute acetaminophen toxicity, prior exposure to N-acetylcysteine during the course of the presenting illness, pregnancy, malignancy, sepsis, signs of cerebral herniation, being on a liver support device, intractable hypotension defined as systolic blood pressure less than 85 mmHg or hypotension that required treatment with inotropic drugs, other than renal dosing dopamine, and other issues that in an investigator’s opinion made a potential participant unsuitable for the study. We defined “sepsis” in the manual of operations as a having bacteremia and/or a temperature of 39.5° C at the time of enrollment. If the patient was known to have a specific infection or if, in the opinion of the site principal investigator, the patient was suspected as having sepsis, prior to enrollment into the NAC trial, they were excluded.

**Study Design**

The NAC study was doubly masked. Eligible children were adaptively allocated within strata defined by age (less than 2 years of age or at least 2 years old) and HE (grade 0–1 or 2–4) to receive NAC (150 mg/kg/d) in 5% dextrose (D5W) and water or placebo consisting of an equal volume of D5W alone. Volumes were adjusted for small children. Study medications were infused over 24-hours for up to 7 consecutive days in a dedicated line without other medications. Treatment was stopped earlier than 7 days in the case of hospital discharge, LTx, or death within 7 days of randomization. Though multiple different dosing regimens have been used in previous studies(8, 12–13, 16–17), a recent retrospective study(8) utilized a continuous infusion to support the evolving and dynamic nature of ALF in children.
Clinical parameters including vital signs, diagnostic and clinical laboratory tests, need for ventilatory, renal or other supportive measures, coma and adverse events were recorded. With the exception of study medication, patient management conformed to the standard of care at each participating site, including decisions related to LTx.

The primary outcome was 1 year survival following treatment allocation. Secondary outcomes included LTx, survival without LTx, lengths of ICU and hospital stay, maximum degree of HE and number of organ systems failing. Organ systems and definitions of failure were: (a) cardiovascular failure: the patient requires treatment with inotropic drugs such as norepinephrine, epinephrine or dopamine (the latter >5 μg/kg/min) at a time prior to the terminal 24 hours before death to attribute cardiovascular failure to liver failure and not terminal events, (b) renal failure: serum creatinine greater than 2 times the upper limit of normal for age and urine output less than 0.5 cc/kg/hour, (c) intracranial hypertension: intracranial pressure > 25 mmHg if ICP monitored or clinical signs such as decerebrate posturing or abnormal pupillary reflexes, (d) pulmonary failure: need for mechanical ventilation for HE or respiratory failure, defined as an inspired oxygen fraction (FiO2) above 0.40, the first 12 hours after intubation and the terminal 12 hours before death excluded, and (e) infection: defined as identification, by culture, serologies, PCR or immuno-fluorescence, of a specific microorganism or virus present in blood, tracheal aspirate, urine, intravenous catheter, wound, liver tissue, stool, naso-pharynx, cerebral spinal fluid, bone marrow or ascites.

**Statistical analysis**

Differences in baseline characteristics of participants in each treatment arm were tested using Pearson’s chi square test or Fisher’s exact test for categorical variables and the Wilcoxon rank sum test for continuous variables. Product-limit estimates were used to obtain the cumulative percentages of participants surviving 1 year following randomization and the percentages of participants surviving 1 year following randomization with their native liver. A log-rank test was used to assess statistical significance of the difference in survival curves. The proportional hazards model(18) was used to estimate the relative risk for both outcomes adjusting for age (less than 2 years, at least 2 years) and HE grade at randomization (0–1, 2–4) which were used as strata in the minimization scheme. Differences between treatment arms for length of hospital stay and length of Intensive Care Unit (ICU) stay were tested for statistical significance using the Kruskall-Wallis test and the Cochran-Armitage test for trend, respectively. Tests of ordinal measures were used to account for deaths or transplantations that occurred prior to discharge from the hospital or ICU, respectively. Transplantations that occurred prior to discharge were assigned a value greater than the maximum stay and deaths occurring prior to discharge were assigned a value greater than transplantation. Pearson’s chi square test or Fisher’s exact test were used to test the null hypothesis of no difference in the proportion of participants in each treatment arm who had each organ system fail, and the Cochran-Armitage test for trend was used to test for treatment arm differences in the number of organ systems failing and for maximum grade of HE. Due to two interim analyses, the p-value for statistical significance of each outcome was 0.0490, overall and in subgroups. For all other comparisons, p<0.05 was used to determine statistical significance.(19)

**RESULTS**

**Baseline characteristics**

Of the 607 participants in the PALF registry eligible for screening for the NAC study, 336 were ineligible (Figure 1). Ineligibility criteria remained constant throughout the study, but reasons for ineligibility were not recorded on the initial case report form for 165 participants.
and are shown as “reason unknown”. Of the remaining 171, reasons for ineligibility were recorded. In addition to those who failed to meet inclusion criteria, or who met at least one exclusion criterion, 5 died in the interval between entry into the PALF longitudinal study and the 24 hours allotted to enroll into the NAC trial. Another 13 were excluded for other reasons: 7 had pre-existing conditions that, in the opinion of the investigator, excluded them from the trial, 2 were demonstrating clinical recovery from PALF, 2 were excluded because they presented when the trial was briefly suspended to ensure all sites were in agreement with the statistical analyses plan, 1 patient was not able to be randomized due to technical difficulties with computer entry, and in for 1 patient liver transplantation was imminent. Of the 271 potentially eligible, consent was not obtained from 87 leaving 184 participants with 92 allocated to each treatment. Two participants withdrew from the placebo arm while no one withdrew from the NAC arm. One participant was randomized to placebo but received NAC. One randomized participant in the placebo arm had APAP toxicity that was determined during the hospitalization but after treatment allocation; this patient exited the study and was treated with NAC clinically. One patient was found to have biliary atresia after treatment allocation. All of these participants were analyzed in the treatment arm to which they were assigned (intention-to-treat analysis).

The two treatment groups did not differ significantly with respect to age, gender, race, coma grade, biochemical measures of liver injury, and time from admission to hospital until enrollment into the trial (Table 1). The distribution of final diagnoses did not differ significantly between the two groups (p=0.09) (Table 2). While an indeterminate diagnosis was the most common, other diagnoses such as infection and autoimmune disease were all comparably common in the two treatment groups. Metabolic disease was more common in the NAC arm (13 NAC vs 5 placebo) with Wilson disease (7 NAC vs 3 placebo) being more common in the NAC arm than the placebo arm. “Other” diagnoses were more common in the placebo arm (7 NAC vs 17 placebo) with hemophagocytic syndrome (0 NAC vs 4 placebo) and drug-induced hepatitis (1 NAC vs 3 placebo) showing the greatest differences within the “other” rare diagnostic category.

**Study outcomes**

For the primary outcome (Figure 2), there was not a significant difference (p=0.19) in the survival one year following randomization between those receiving NAC (73%) compared to placebo (82%). There was not a significant difference (p=0.37) in survival between the 65 children with HE grade 0–1 who received NAC and the 68 who received placebo. Stratification of results by age above and below 2 years, by HE grade 0–1 and grade 2–4, and the combinations of age and HE grade did not reveal significant treatment differences within any of the sub-groups (supplemental Table 1).

Of the secondary outcomes that were examined, the one year LTx-free survival (Figure 3) was significantly (p=0.03) lower in children who received NAC (35%) compared to placebo (53%). Children less than 2 years of age were significantly (p=0.03) less likely to survive with their native liver at one year if they received NAC (n=34, LTx-free survival=29%) than if they received placebo (n=31, LTx-free survival=58%). Despite a large difference in the point estimate, children less than 2 years of age with HE grade of 0–1 who did not have a significantly lower LTx-free survival (p=0.0493) if they received NAC (n=20; LTx-free survival=25%) than did children in the same age and HE grade categories who received placebo (n=20; LTx-free survival=60%). There were no significant differences between the treatment groups with respect to length of ICU or hospital stay, type or number of organ systems failing, or maximum grade of HE recorded following treatment allocation.

Post transplant survival was not significantly different between the two groups. Duration of post-transplant follow-up varied depending upon the timing of LTx after randomization. The
cumulative probability of survival 9 months (274 days) post-randomization was 0.88 in the NAC arm and 0.84 in the placebo arm (p=0.59). This is due to 5 post-LTx deaths among 41 in the NAC arm who underwent transplantation, and 5 deaths in the placebo arm among the 32 in the placebo arm who underwent transplantation.

**Acetaminophen adducts**

Eighty-four participants had a sufficient amount of serum collected on day 1 or 2 following enrollment to be analyzed by a sensitive and specific serum assay for acetaminophen-cysteine adducts (A-CA).(20–21) Testing for A-CA was performed for research purposes; results were neither available, nor used, for clinical purposes. The final diagnosis was provided by the site principal investigator without knowledge of the results of the A-CA. The presence of A-CA is a biomarker for patients with acetaminophen related liver injury. There were no statistically significant differences in the characteristics (Supplemental Table 2) or outcomes (Supplemental Table 3) examined of the 84 who were tested for A-CA compared to the other 100 in the trial who did have sera available for testing. Of those that were tested, 9/84 (11%) tested positive for A-CA with 3 of those having positive A-CA randomized to NAC and the other 6 randomized to placebo; all survived one year after randomization; in the NAC arm, 2 underwent LTx whereas none of the 6 in the placebo arm underwent LTx. Final diagnoses of the A-CA positive patients were 3 indeterminate cases for those randomized to NAC and 3 indeterminate, 1 APAP, 1 viral hepatitis, and 1 sepsis randomized to placebo. The patient with the final diagnosis of APAP was determined during the hospitalization when a participant who initially denied APAP exposure subsequently gave a positive history. This participant was given NAC clinically when the history became known and exited the study.

**Safety**

At least one adverse event was reported for 19 participants given NAC (21 events) and 16 given placebo (17 events). The most common adverse event reported was infection (11 in the NAC arm vs. 8 in the placebo arm). Other adverse events reported among those given NAC vs. those given placebo were rash (4 vs. 2), bronchospasm (1 vs. 0), and arrhythmia (1 vs. 4). There were no significant differences in adverse event rates between the treatment arms. The other events listed for participants in the NAC arm were aspiration, dilated and fixed pupils, hypertension, and pleural effusion. One participant each in the placebo arm had sleepiness, bradycardia, and high fever.

There were 5 participants in the NAC arm with serious adverse events (SAE); 4 had a single SAE (respiratory distress, *Staphylococcus aureus* bacteremia, bradycardiac episode, hypoglycemia) and the other participant had 3 SAE (aplastic anemia; EBV post-transplantation lymphoproliferative disease; and fever, chills and sinusitis). Four participants in the placebo arm had a single SAE (small intestine ulcerations, fever, sensorineural hearing loss, and bigeminy).

**DISCUSSION**

NAC, given as a continuous intravenous infusion at a dose of 150 mg/kg/d for up to 7 days to children with non-APAP acute liver failure, did not achieve the primary outcome which was to improve survival one year following the infusion compared to placebo. Nor did NAC improve one year survival in any of the subgroups defined by stratifying variables for the minimization scheme (age group, HE grade). Interestingly, analysis of secondary outcomes revealed that survival at one year with their native liver was significantly lower in children treated with NAC compared to placebo. In addition, we found that children with minimal HE of grade 0–1 did not benefit from the NAC infusion. This finding differs from secondary
outcomes analysis of adults which found NAC to benefit those with grade 0-II HE.(13) Adverse events were similar between NAC and placebo arms in our study. The striking difference between the effects of NAC in children as compared to adult patients is likely related to a number of factors that include differences in etiology, underlying pathophysiology, and age.

Acute liver failure in children is a heterogeneous, dynamic clinical entity with etiologies that differ from adults.(4, 22) Though etiologic categories of non-acetaminophen acute liver failure in children are similar to adults and include, metabolic, infectious, and immune mediated conditions, medications, and other toxins as well as an indeterminate group, the proportion of children within those categories differs substantially from adults. While an indeterminate diagnosis accounted for 24% in the adult study(13), 54% of the pediatric cases had such a diagnosis. Similar proportions were noted in the larger cohort of PALF participants not specifically included in this clinical trial.(2, 23) A portion of the pediatric indeterminate group likely constitutes an evaluation interrupted by death, LTx, or clinical improvement. In addition, the indeterminate cohort may include unexpected acetaminophen toxicity(21), a novel or unrecognized virus, metabolic or xenobiotic injury. Undiagnosed immune dysregulation may also result in acute liver failure.(24)

The presence of acetaminophen-cysteine adducts (A-CA) has been associated with known and occult acetaminophen related liver disease.(21, 25) The percent of patients with a positive A-CA in the NAC trial is similar to previous studies in children.(21) While the numbers are very small, all of the A-CA positive patients randomized to placebo survived at least 1 year without LTx. Reasons for this finding might include APAP toxicity that was not the primary driver of liver failure or, perhaps, adducts were generated when the injured liver was exposed to APAP.

In previous studies, NAC was evaluated for the treatment of multi-organ system failure (MOSF) including acute respiratory distress syndrome (ARDS) and sepsis(26), and was found to improve pulmonary compliance and oxygen consumption with variable results on overall patient survival.(12, 16–17) NAC suppresses the production of TNF-α in vitro(27) and improves survival and lung function in pigs with endotoxin-induced ARDS.(28) As clinical features of ALF overlap with those seen in MOSF syndromes, we hypothesized that the non-specific beneficial effects of NAC in MOSF might well apply to ALF. Unfortunately, with respect to 1 year survival, NAC did not provide the anticipated benefit.

The observation that NAC failed to improve and possibly worsened the likelihood of LTx-free survival at one year suggests pathobiological mechanisms of non-APAP acute liver failure may differ between children and adults. These findings provide an opportunity to identify novel mechanisms of hepatocellular injury in PALF such as immune dysregulation(29) or an altered inflammatory response(30) and investigate targeted treatment strategies in children with acute liver failure.

Hypotheses can be generated to help explain our findings. One hypothesis is immune or inflammatory dysregulation drives liver injury for many in the indeterminate cohort. While little is known of the ontogeny of intrahepatic immune responses, evidence suggests systemic inflammatory responses to trauma differ significantly between adults and children.(31) Inflammation is a complex and dynamic process that encompasses both injury, healing and regeneration through pro-inflammatory and anti-inflammatory responses.(30) A well regulated inflammatory response is necessary for proper healing and regeneration.(32) Should pro-inflammatory signals that initiate healing and regenerative responses be blunted at a critical time, an imbalance favoring inflammation may develop. Whether NAC, which serves as an anti-oxidant(33) and can alter the secretion of a variety of chemokines(34),
could interrupt healing responses is not known. A second hypothesis is that prolonged
treatment with NAC might suppress the hepatic regenerative response to injury, as was
recently reported in a murine model of APAP-induced liver injury.(35)

Other variables that may have impacted our findings include differences in diagnosis
between treatment arms, dosing regimen, and the extended enrollment period. Children with
mitochondrial disease suffer from a systemic condition associated with late mortality that is
currently without a directed therapy. While anti-oxidant therapy with NAC may have
theoretical benefit for mitochondrial injury, the opposite might also be true. (36) Treatment
of drug-induced liver injury is generally limited to withdrawal of the offending medication.
A recent study reported that NAC might provide benefit independent of glutathione
repletion in a murine model of lasix induced liver injury, raising the possibility that NAC
might also have such effects in human drug induced liver. (37) While uneven distribution of
these rare conditions may have a theoretical impact on outcomes for individuals, the small
numbers are unlikely to be a major factor in the outcome of the trial.

The NAC dosing regimen of 150 mg/kg/d for no more than 7 days fits within other adult and
pediatric dosing regimens that have ranged from 288 mg/kg/d for up to 5 days with multi-
organ system failure(16) to 100 mg/kg/d for a median of 5 days (range 1 – 77) in acute liver
failure. (8) The study duration, requiring approximately 9 years to recruit the number of
participants required by the study design, speaks to the challenges of studying a rare, acute,
severe condition such as PALF. Despite the prolonged period, we have no evidence that
significant changes in management or liver transplant decisions occurred during the course
of the study that would have impacted the outcome.

In summary, NAC did not improve 1 year survival in children with non-APAP acute liver
failure. One year LTx-free survival was significantly lower in the NAC treated group,
especially among children less than 2 years of age with HE grade 0–1. Although the
difference in outcome by treatment arm was large in that small group, the interim analyses
and small sample size reduced substantially the statistical power to find a large difference to
be statistically significant. This study does not support the broad use of NAC in non-APAP
PALF and it emphasizes the importance of conducting prospective pediatric drug trials,
regardless of results in adults.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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and M01 RR08084 from the General Clinical Research Center Program of the National Center for Research
Resources of the NIH.

Abbreviations

PALF pediatric acute liver failure
NAC N-acetylcysteine
Non-APAP non-acetaminophen acute liver failure
HE hepatic encephalopathy
NIDDK National Institute of Diabetes and Digestive and Kidney Diseases


References cited


Hepatology. Author manuscript; available in PMC 2014 April 01.


Figure 1. Enrollment in the NAC trial
Between June 2003 and September 2009, 607 patients enrolled in the PALF longitudinal study were screened following site specific IRB approval for the NAC protocol. 336 were ineligible. Of the 271 patients eligible for enrollment, 87 refused consent, leaving 184 enrolled in the NAC trial, there were 92 patient in each arm. Only 2 patients withdrew following enrollment, and they were both in the Placebo arm.

† One participant was randomized to placebo arm but received treatment.
Figure 2. Primary outcome: 1 year survival
Product-limit estimates were used to obtain the cumulative percentages of participants surviving 1 year following randomization. A log-rank test was used to assess statistical significance of the difference in survival curves. The cumulative percentage of children who were alive 1 year following randomization to NAC (dashed line) or placebo (solid line) is depicted. The percent surviving 1 year was higher in patients receiving placebo at 82% than NAC at 73%, but the differences were not significant with a p-value of 0.19.
Figure 3.
Product-limit estimates were used to obtain the cumulative percentages of participants with 1 year transplantation free survival. A log-rank test was used to assess statistical significance of the difference in survival curves. The cumulative percentage of children with liver transplantation-free survival 1 year following randomization to NAC (dashed line) or placebo (solid line) is depicted. The cumulative percentage of patients with liver transplantation-free survival was 53% when given placebo vs 35% when given NAC, with a p-value of 0.03.
Table 1
Baseline Characteristics

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<th>NAC N = 92</th>
<th>Placebo N = 92</th>
<th>p</th>
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<tr>
<td>Male, N (%)</td>
<td>47 (51.1)</td>
<td>54 (58.7)</td>
<td>.30</td>
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<td>Not Hispanic or Latino, N (%)</td>
<td>75 (81.5)</td>
<td>66 (71.7)</td>
<td>.12</td>
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<tr>
<td>Caucasian</td>
<td>68 (73.9)</td>
<td>65 (70.7)</td>
<td>.62</td>
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<td>Age (years)</td>
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<tr>
<td>Median (25%, 75%)</td>
<td>3.7 (0.8, 10.5)</td>
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<td>&lt; 2, N (%)</td>
<td>33 (35.9)</td>
<td>29 (31.5)</td>
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<td>Coma grade at randomization, N (%)</td>
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<td></td>
<td>.62</td>
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<td>0 – 1</td>
<td>65 (70.7)</td>
<td>68 (73.9)</td>
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<td>2 – 4</td>
<td>27 (29.3)</td>
<td>24 (26.1)</td>
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<td>Initial admission to study enrollment (Days)</td>
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<tr>
<td>Median (25%, 75%)</td>
<td>3 (1, 7)</td>
<td>3 (1, 5)</td>
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Table 2

Diagnosis at Hospital Discharge

<table>
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<th>Diagnosis</th>
<th>NAC N=92</th>
<th>Placebo N=92</th>
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<td>Indeterminate</td>
<td>55 (59.8)</td>
<td>54 (58.7)</td>
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<td>Autoimmune</td>
<td>8 (8.7)</td>
<td>11 (12.0)</td>
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<tr>
<td>Infection</td>
<td>9 (9.8)</td>
<td>6 (6.5)</td>
</tr>
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<td>Metabolic</td>
<td>13 (14.1)</td>
<td>5 (5.4)</td>
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<td>Wilson’s disease</td>
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<td>3</td>
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<td>Tyrosinemia</td>
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</tr>
<tr>
<td>Other</td>
<td>7 (7.6)</td>
<td>16 (17.4)</td>
</tr>
<tr>
<td>Hemophagocytic syndrome</td>
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<tr>
<td>Drug-induced hepatitis</td>
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<tr>
<td>Neonatal iron storage disease</td>
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<tr>
<td>Acetaminophen overdose</td>
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<tr>
<td>Extra-hepatic biliary atresia</td>
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<tr>
<td>Hemagioendothelioma</td>
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<tr>
<td>Intraventricular hemorrhage</td>
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</tr>
<tr>
<td>Methanol</td>
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<tr>
<td>Systemic lupus erythematosis</td>
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<tr>
<td>Drug-induced and sepsis</td>
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<tr>
<td>Influenza A</td>
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</tr>
<tr>
<td>Influenza B</td>
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<td>0</td>
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<tr>
<td>Sepsis</td>
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<td>1</td>
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<tr>
<td>EBV + hemophagocytic syndrome</td>
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</tr>
<tr>
<td>Shock + adenovirus infection</td>
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</tr>
<tr>
<td>Shock ischemia</td>
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P-value = 0.09 from Chi-square test.