



# *N*-acetylcysteine and Acute Liver Failure

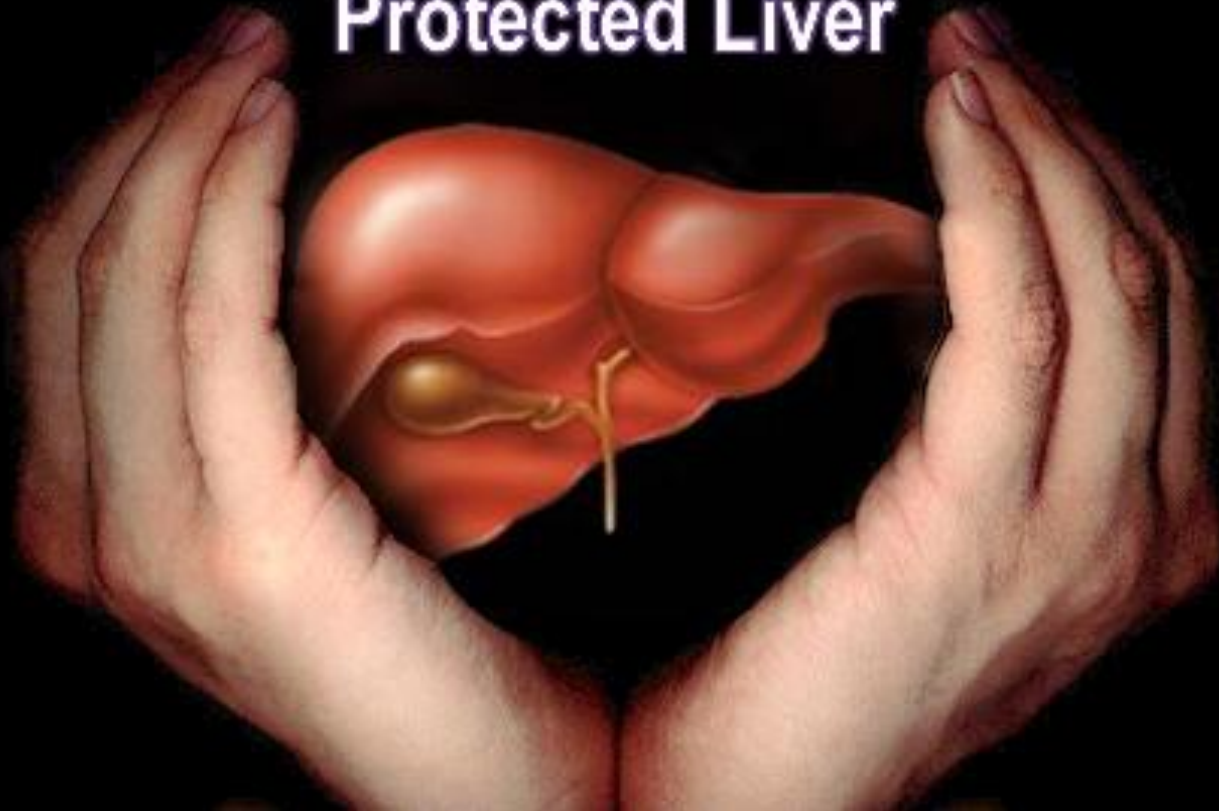
BSNT. ĐÀO QUỐC ANH

# NAC

CRITICAL ANTIOXIDANT

## N-Acetyl Cysteine =

### Protected Liver



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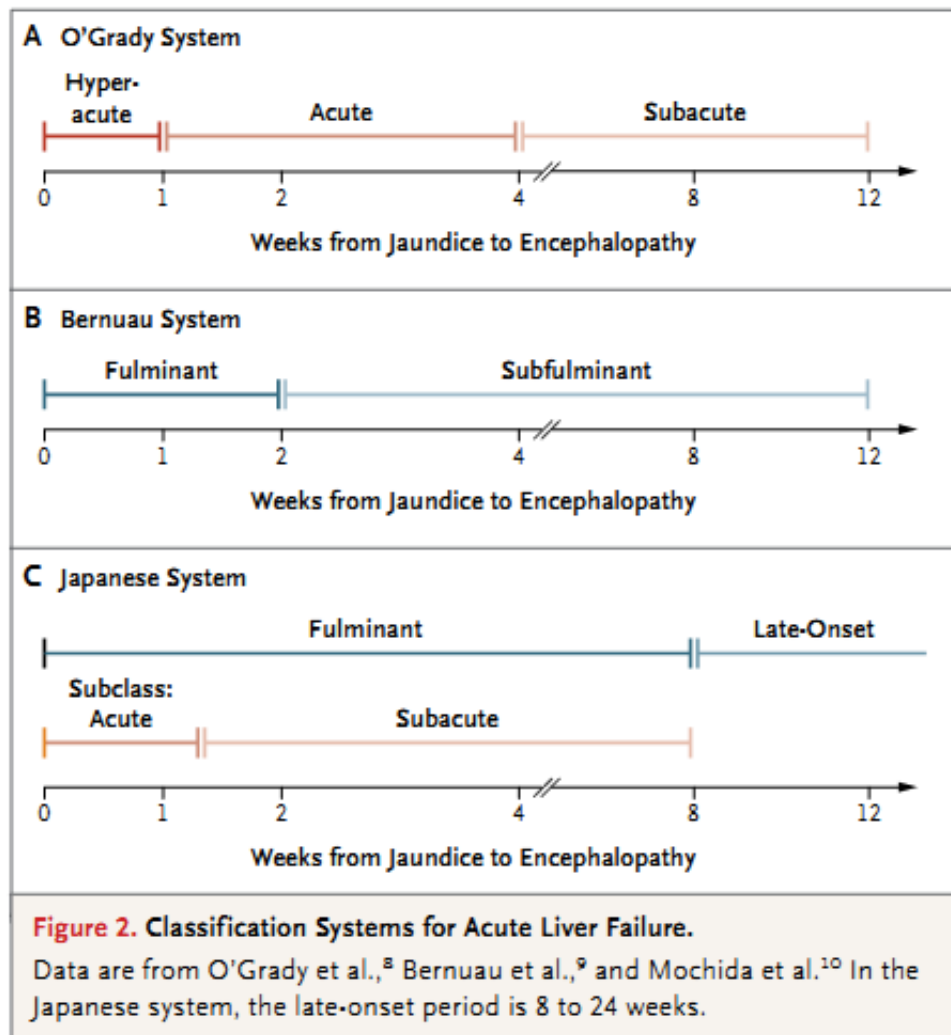
# 1. Acute liver failure (ALF)

- Definition
- Classification

# Definition

- Coagulation abnormality (INR  $\geq$  1.5)
- and any degree of mental alteration (without preexisting cirrhosis)
- and <26 weeks

# Classification



Hyperacute (<7 days),  
Acute(7-21 days)  
Subacute (21ds -26 ws)

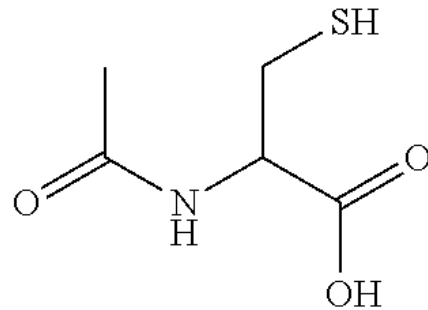
AASLD

# *Etiology*

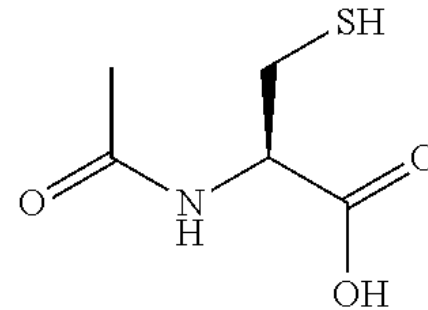
- Infection
  - Virus: viral hepatitis, EBV, CMV, HSV, dengue, etc.
  - Bacteria: Salmonella, Tuberculosis, Septicemia
- Drugs/Toxin
  - Acetaminophene
  - Non-acetaminophene
- Metabolic
- Autoimmune
- Vascular ischemic
- Others

# N-acetylcysteine (NAC)

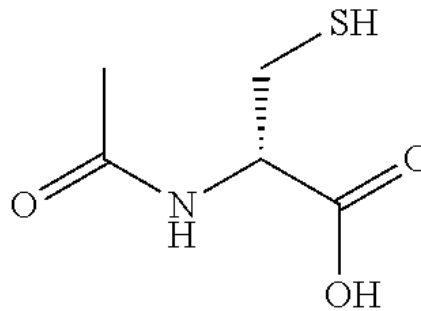
Scheme 1:



N-acetylcysteine



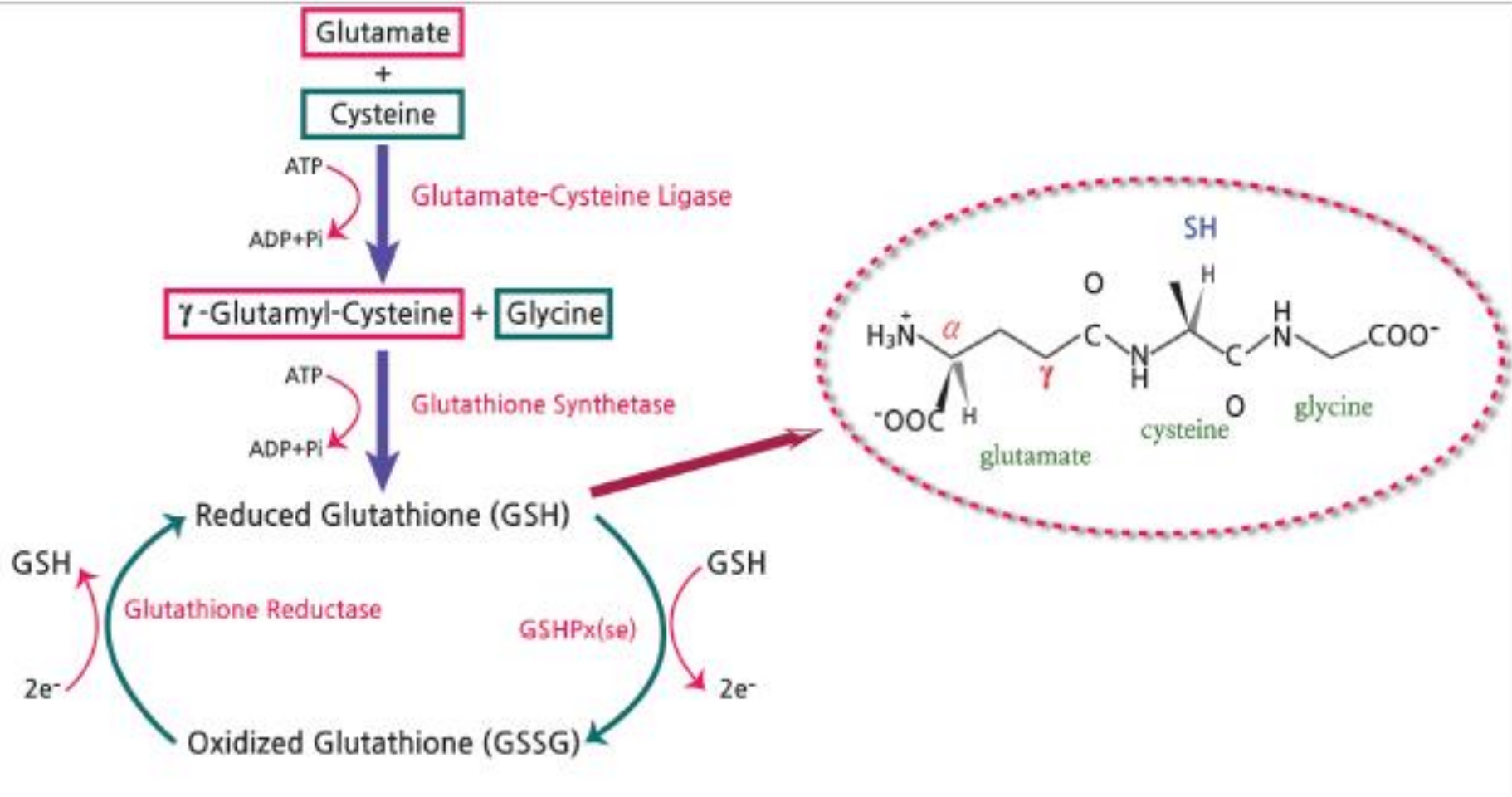
N-acetyl-L-cysteine  
(Compound A)



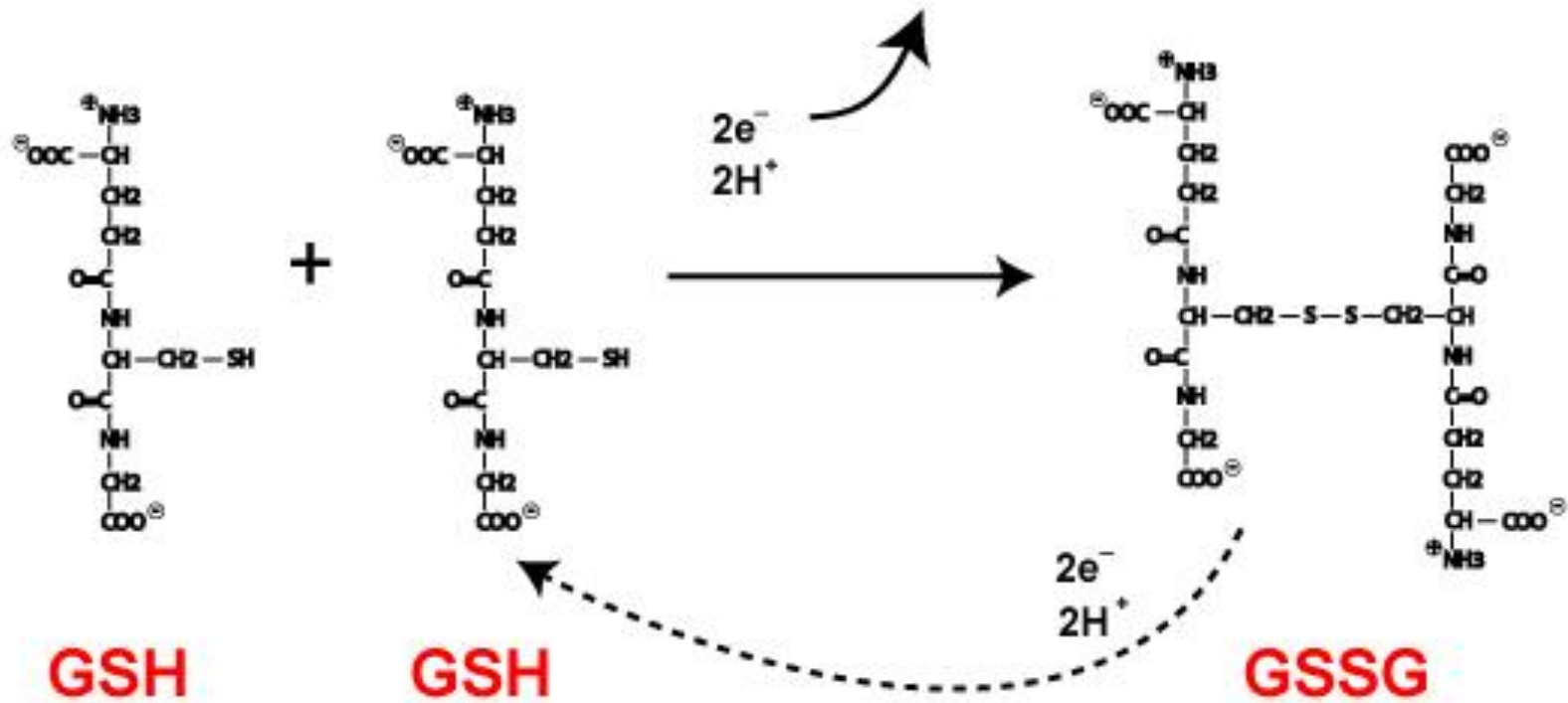
N-acetyl-D-cysteine  
(Compound B)



# NAC



Electrons are used  
for detoxification reactions



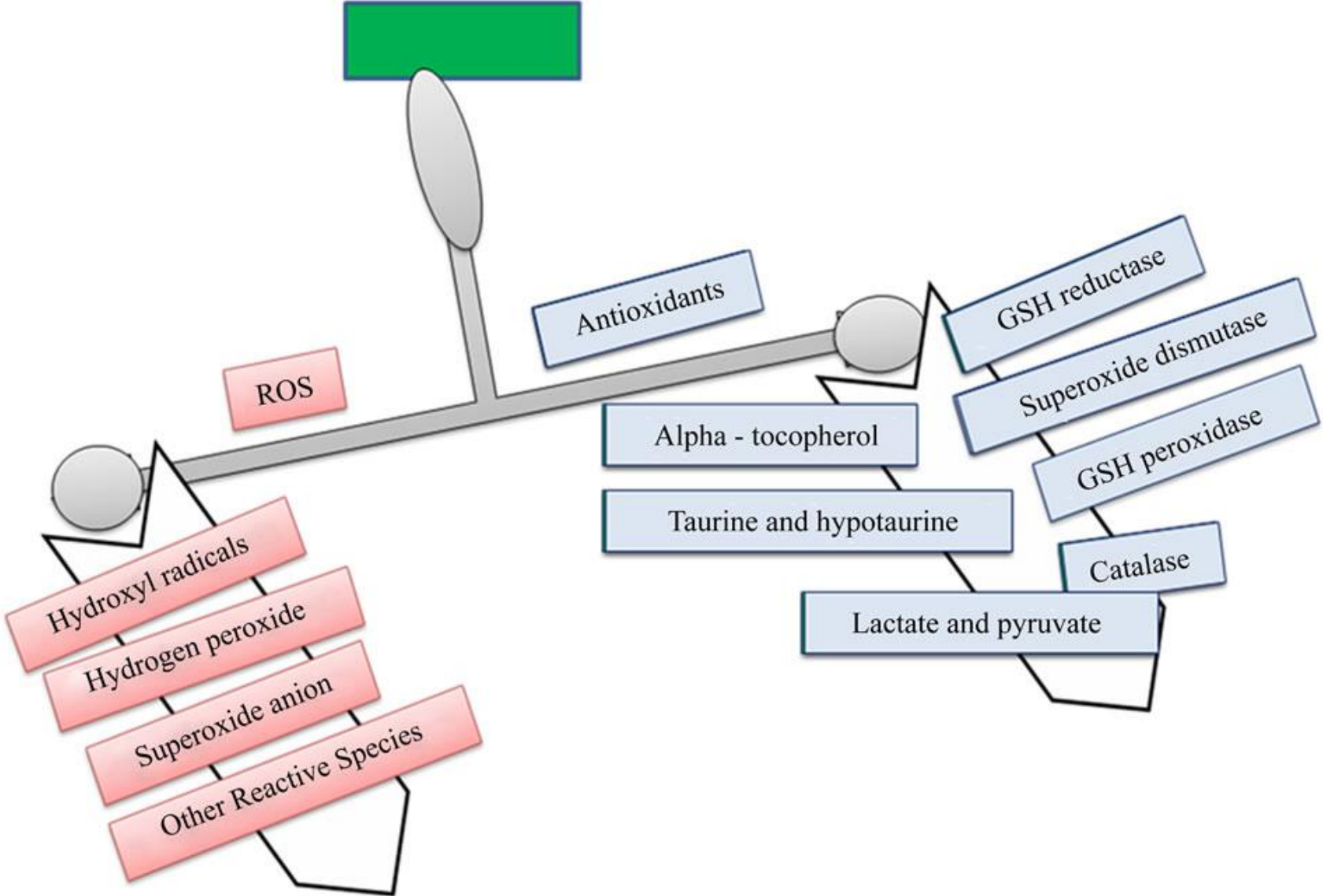
Reduced  
Glutathione

Oxidized  
Glutathione

Oxidative Stress

Homeostatic levels of ROS

Defense activated (ROS Lacking)



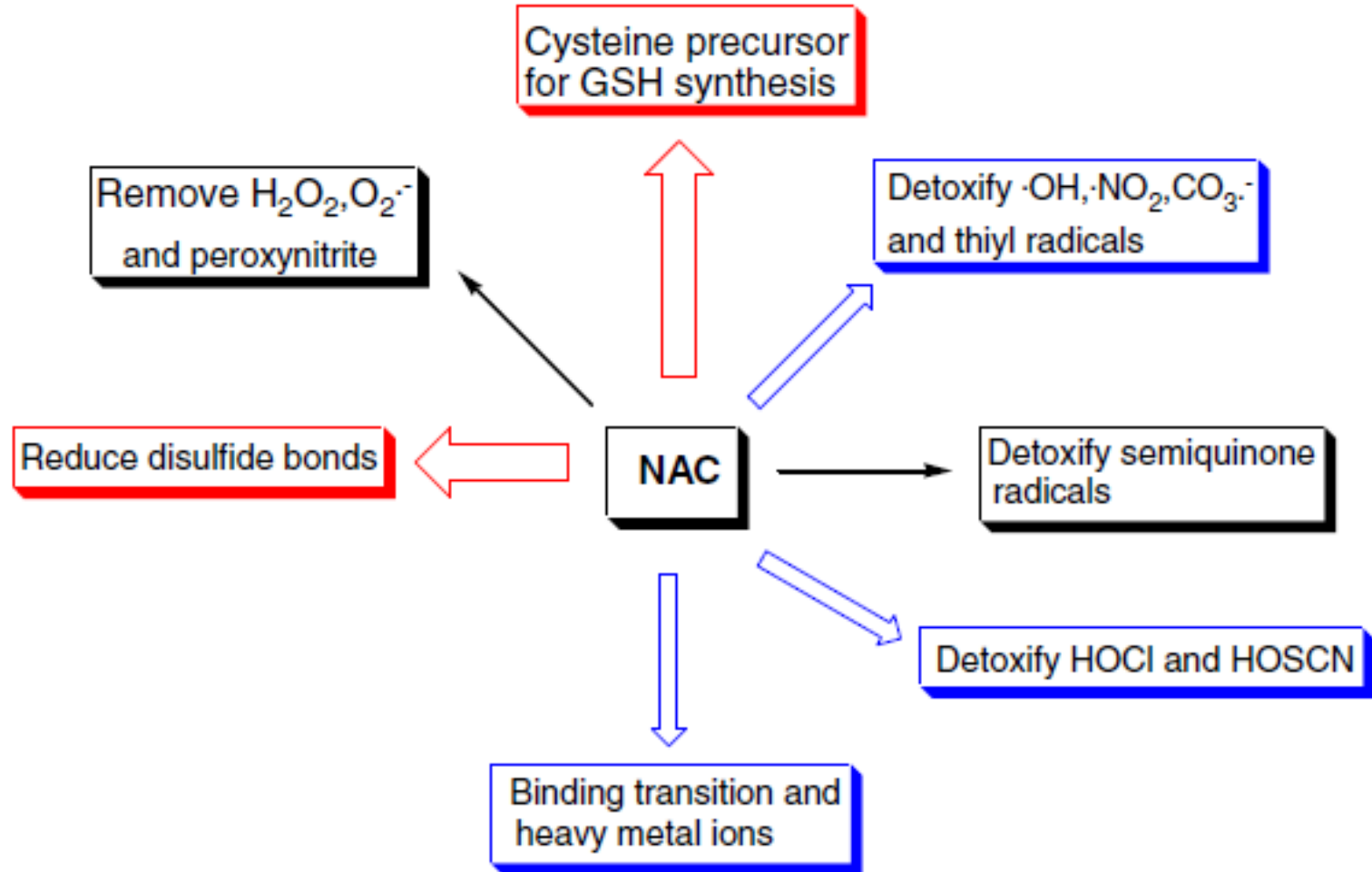
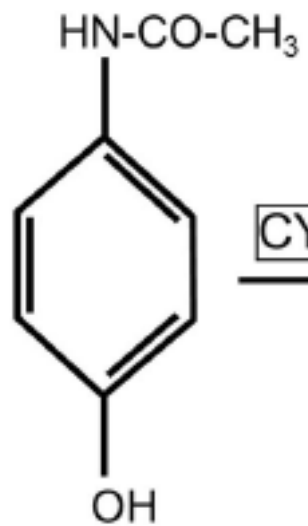


Fig. 3. Plausible routes for the biological activities of NAC (red color – major routes, blue color – plausible routes, black color – insignificant routes under physiological conditions).

- Toxic:
  - acetaminophen
  - doxorubicin-induced cardiotoxicity
  - chemotherapy-induced toxicity
  - radiocontrast-induced
  - heavy metal
- ischemia–reperfusion cardiac injury,
- acute respiratory distress syndrome,
- nephropathy
- psychiatric disorders: schizophrenia, bipolar disorder and addiction

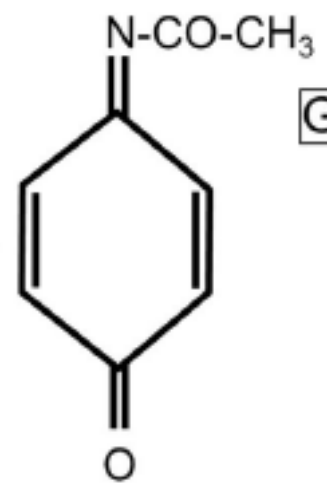
*NAC in acetaminophen-induced ALF*

*N*-acetyl-*p*-aminophenol (APAP)



CYP2E1

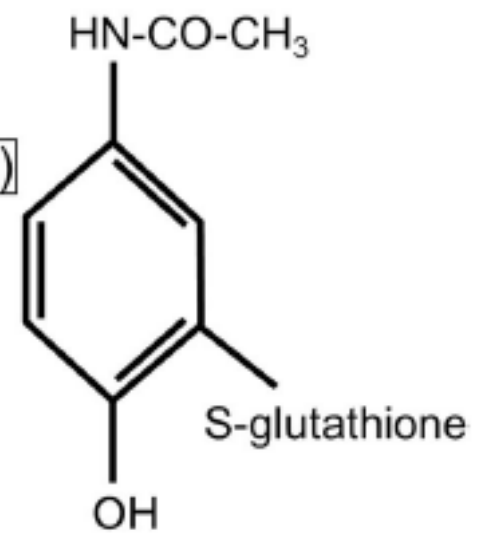
*N*-acetyl-*p*-benzoquinonimine (NAPQI)



*N*-acetylcysteine (NAC)

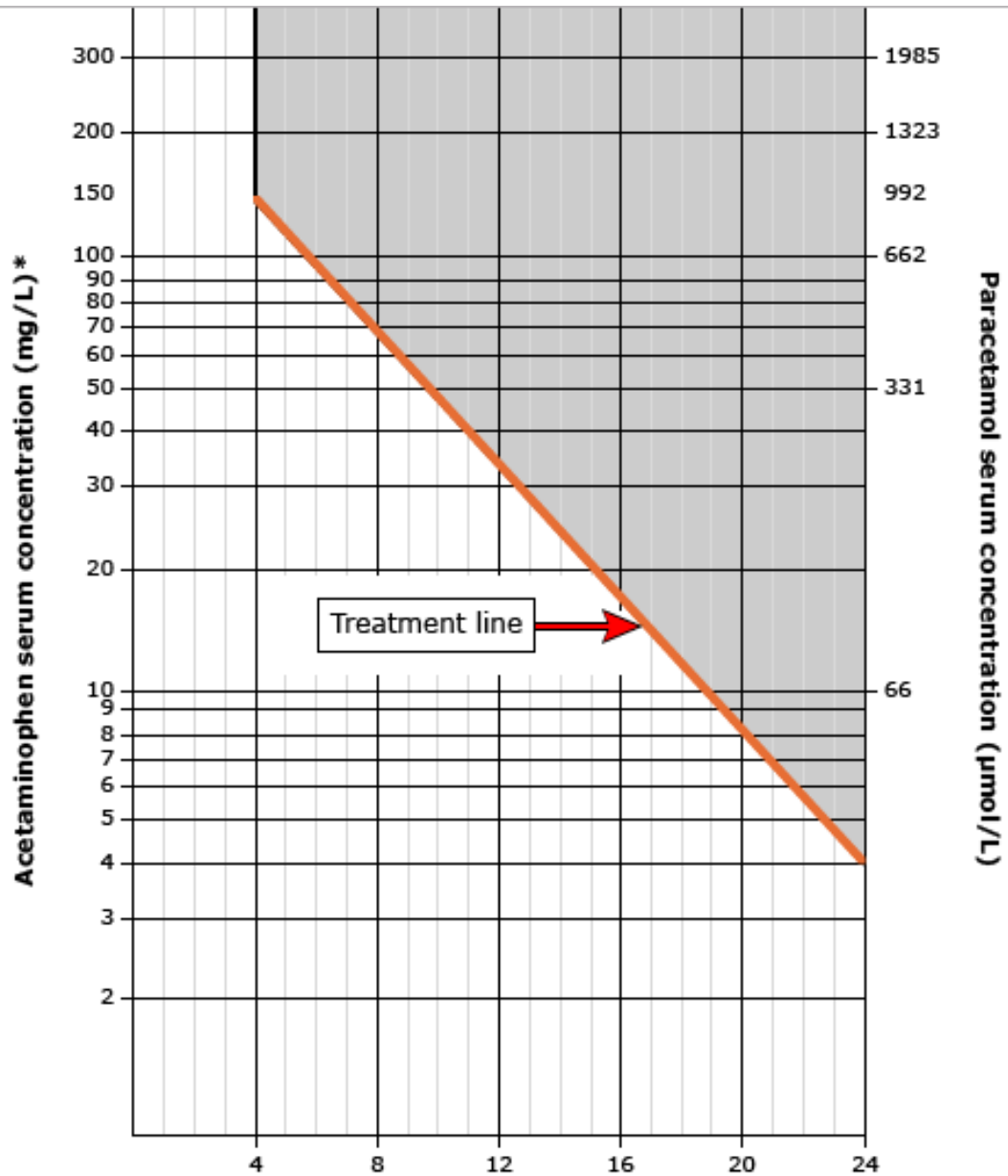
Glutathione (GSH)

Glutathione S-transferase



**Toxic Metabolite formation in Overdose**

**Inactive Reduced Form**



**Acetaminophen  
poisoning nomogram  
Rumack-Matthew**



## ORIGINAL RESEARCH

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# Oral and Intravenous Acetylcysteine for Treatment of Acetaminophen Toxicity: A Systematic Review and Meta-analysis

**Jody L. Green, PhD\*\***  
**Kennon J. Heard, MD\*\***  
**Kate M. Reynolds, MPH\***  
**Donald Albert, MS\***

\*Rocky Mountain Poison and Drug Center, Denver Health Medical Center, University of Colorado, Denver, Colorado  
†Vanderbilt University School of Nursing, Nashville, Tennessee  
‡University of Colorado, Department of Emergency Medicine, Aurora, Colorado

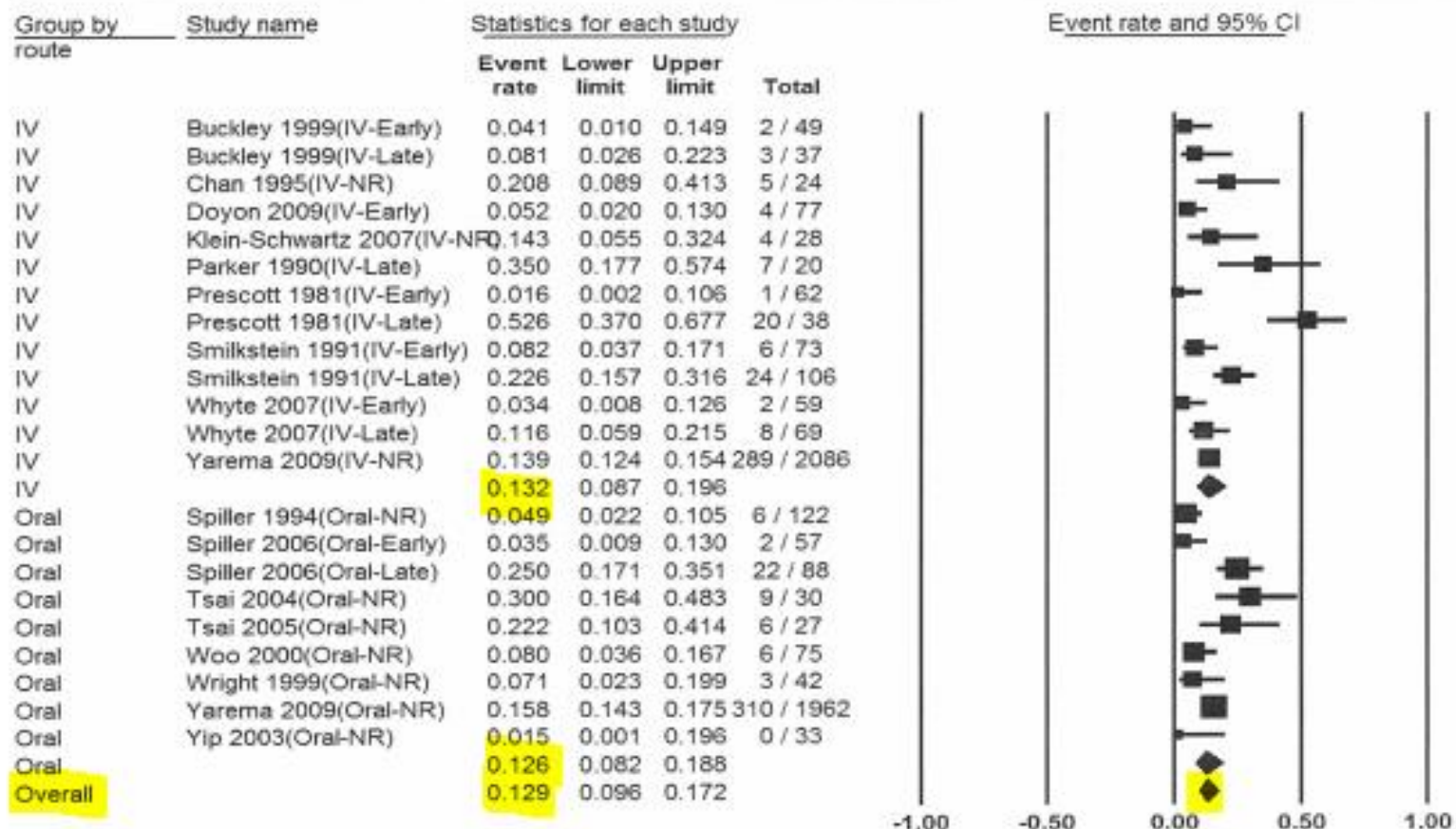
*Supervising Section Editor:* Brandon K. Wills, DO, MS

Submission history: Submitted September 1, 2011; Revisions received March 8, 2012; Accepted April 23, 2012

Full text available through open access at [http://escholarship.org/uc/uciem\\_westjem](http://escholarship.org/uc/uciem_westjem)

DOI: 10.5811/westjem.2012.4.6885

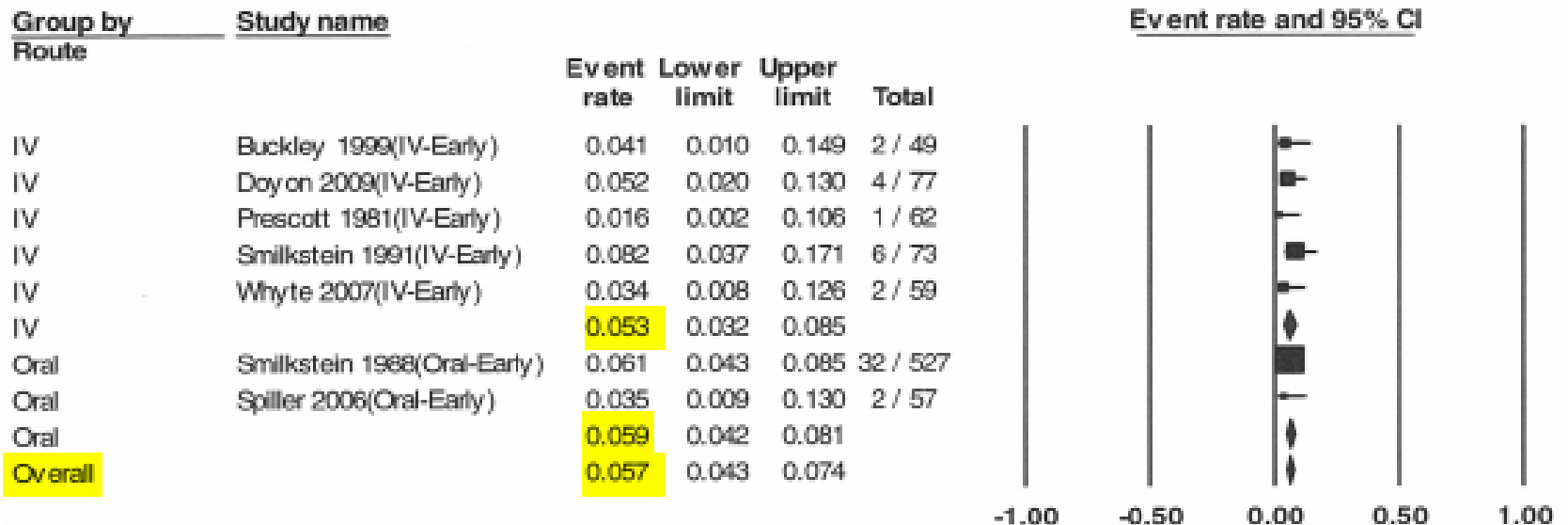
## NAC Meta Analysis - All Trials $\geq 20$ Subjects



### Random Effects

**Figure 2.** Forest plot showing proportion of patients with acetaminophen poisoning who developed hepatotoxicity for intravenous and oral acetylcysteine treatment.

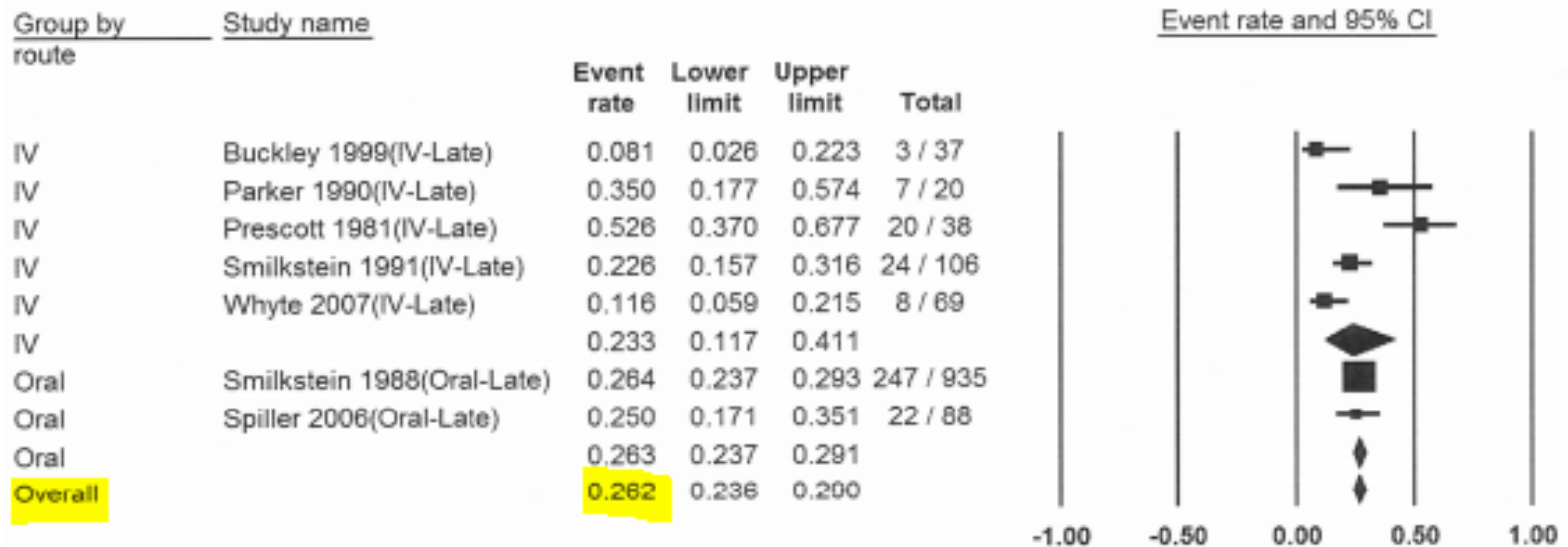
## NAC Meta-Analysis - Early $\geq 20$ Subjects



### Random effects

Figure 3. Forest plot showing proportion of patients with acetaminophen poisoning who developed hepatotoxicity for intravenous and oral acetylcysteine treatment when acetylcysteine was administered early (within 10 hours or as defined by author).

## NAC Meta Analysis - Late $\geq$ 20 Subjects



### Random Effects

**Figure 4.** Forest plot showing proportion of patients with acetaminophen poisoning who developed hepatotoxicity for intravenous and oral acetylcysteine treatment when acetylcysteine was administered late (more than 10 hours or as defined by author).

**Conclusion:** Studies report similar rates of hepatotoxicity for oral and IV acetylcysteine, but direct comparisons are lacking. While it is difficult to disentangle the effects of dose and duration from route, our findings suggest that the rates of hepatotoxicity are similar for oral and IV administration. [West J Emerg Med. 2013;14(3):218–226.]

**Second Meeting of the Subcommittee of the Expert Committee on the  
Selection and Use of Essential Medicines  
Geneva, 29 September to 3 October 2008**

**REVIEW OF N-ACETYLCYSTEINE FOR THE TREATMENT OF  
ACETAMINOPHEN (PARACETAMOL) TOXICITY IN PEDIATRICS**

SUMMARY

NAC should be considered the antidote of choice for the prevention and treatment of acetaminophen-induced hepatotoxicity. Both oral and IV NAC are acceptable and appear to be equally efficacious. Oral NAC should be considered the preferred treatment unless the patient is at risk of aspirating, has persistent vomiting, or develops hepatic failure. Both oral and IV NAC are generally well tolerated. IV NAC is associated with anaphylactoid reactions, most of which are mild and easily treated. Life-threatening reactions appear to be uncommon. Intravenous NAC is well tolerated in children, however in those weighing less than 40 kg it is recommended that the concentration/formulation be modified to prevent excessive fluid administration. Recent evidence supports tailoring the duration of therapy depending on the patient's clinical status and laboratory data.

*NAC in non-acetaminophen-induced ALF*



NIH Public Access

Author Manuscript

*Dig Dis Sci.* Author manuscript; available in PMC 2014 May 01.

Published in final edited form as:

*Dig Dis Sci.* 2013 May ; 58(5): 1397–1402. doi:10.1007/s10620-012-2512-x.

**Improvements in Hepatic Serological Biomarkers are Associated with Clinical Benefit of Intravenous *N*-Acetylcysteine in Early Stage Non-Acetaminophen Acute Liver Failure**

**Methods**—In a prospective, double blind trial, 173 ALF patients without evidence of acetaminophen overdose were stratified by coma grade (I-II vs. III-IV) and randomly assigned to receive either intravenous NAC or dextrose (placebo) for 72 hours, resulting in 4 patient groups. INR, ALT, bilirubin, creatinine, and AST obtained on admission (day 1) and subsequent days (days 2-4) were used for secondary analysis performed by fitting longitudinal logistic regression models to predict death or transplantation or transplantation alone.

**Conclusion**—The decreased risk of transplantation or death or of transplantation alone with intravenous NAC in early coma grade patients with non-acetaminophen induced ALF was reflected in improvement in parameters related to hepatocyte necrosis and bile excretion: ALT and bilirubin, but not in INR, creatinine, or AST. Hepatic recovery appears hastened by NAC as measured by several important lab values.



# Effects of *N*-Acetylcysteine on Cytokines in Non-Acetaminophen Acute Liver Failure: Potential Mechanism of Improvement in Transplant-Free Survival

R. Todd Stravitz<sup>†,1</sup>, Arun J. Sanyal<sup>1</sup>, Joan Reisch<sup>2</sup>, Jasmohan S. Bajaj<sup>1</sup>, Faridoddin Mirshahi<sup>1</sup>, Jianfeng Cheng<sup>1</sup>, William M. Lee<sup>3</sup>, and the Acute Liver Failure Study Group

**Methods**—Serum samples were obtained from 78 participants of the randomized, ALF Study Group NAC Trial with grade 1 or 2 hepatic encephalopathy on randomization. Concentrations of ten cytokines, chosen to represent a wide array of inflammatory responses, were determined by multiplex ELISA.

**Conclusions**—NAC may improve transplant-free survival in patients with non-acetaminophen ALF by ameliorating the production of IL-17, which is associated with progression of hepatic encephalopathy and poor outcome.

## *Case Report*

# *N*-acetylcysteine in Children with Dengue-associated Liver Failure: A Case Report

by Grace Lim,<sup>1</sup> and Jan Hau Lee<sup>2,3</sup>

### Summary

There is no specific treatment for dengue-associated fulminant liver failure. We report a child with dengue-associated fulminant liver failure who was treated successfully with intravenous *N*-acetylcysteine. A 6-year-old boy was diagnosed with dengue-associated fulminant liver failure. After administration of intravenous *N*-acetylcysteine, a rapid decrease in liver transaminases and normalization of coagulation profile was observed followed by clinical improvement and favourable outcome despite factors associated with poor prognosis. The use of intravenous *N*-acetylcysteine is safe and efficient in the treatment of dengue-associated fulminant liver failure, especially in centres when liver transplantation is not readily available.

# **N-acetylcysteine in children with acute liver failure complicating dengue viral infection**

**M P Senanayake<sup>1</sup>, M D C J P Jayamanne<sup>1</sup>, I Kankanararachchi<sup>2</sup>**

(Index words: dengue shock syndrome, encephalopathy)

*Objectives* To describe the outcome after administration of N-acetylcysteine (NAC) to seven children with non-paracetamol induced acute liver failure (ALF) complicating dengue infection.

*Methods* Clinical records of children with non paracetamol induced acute liver failure complicating severe dengue viral infection, were retrospectively analysed for clinical and biochemical outcome following treatment with NAC.

*Results* Seven patients between ages six months to twelve years with plasma leakage and circulatory compromise complicating dengue infection developed ALF. Three were exposed to prolonged shock prior to hospitalisation. NAC infusion (100 mg/kg) was administered as soon as ALF was diagnosed, based on low GCS scores, raised transaminases and prolonged prothrombin/INR. Full clinical and biochemical recovery occurred in all patients.

*Conclusions* A successful outcome followed early administration of NAC to children with ALF complicating severe dengue infection.

## Early treatment with N-acetylcysteine in children with acute liver failure secondary to hepatitis A

Norberto Sotelo,\* María de los Ángeles Durazo,\*\* Alejandro Gonzalez,\*\*\* Nagasharmila Dhanakotti\*\*\*\*

**Introduction.** Hepatitis A virus can evolve to acute liver failure with a fatal outcome if it is not reversed. **Objective.** We describe the clinical course of 12 children who presented with hepatitis A acute liver failure and received treatment with oral N-acetylcysteine (NAC). **Materials and methods.** Of the seventy-two patients with viral hepatitis A, 12 patients who had acute hepatic failure were included. The variables eva-

0.0039, ammonia with  $P = 0.0197$  and  $0.0015$  and direct bilirubin with  $P = 0.0190$  and  $0.068$ . There was good tolerance to medications and a satisfactory clinical course. **Discussion.** The use of oral NAC appears to be an effective therapeutic alternative for hepatitis A-induced liver failure if it is offered appropriately. It can modify the clinical course to a favorable one and prevent the fatal outcome of hepatic encephalopathy.

## Intravenous *N*-Acetylcysteine Improves Transplant-Free Survival in Early Stage Non-Acetaminophen Acute Liver Failure

WILLIAM M. LEE,\* LINDA S. HYNAN,<sup>‡</sup> LORENZO ROSSARO,<sup>§</sup> ROBERT J. FONTANA,<sup>||</sup> R. TODD STRAVITZ,<sup>¶</sup>  
ANNE M. LARSON,<sup>#</sup> TIMOTHY J. DAVERN II,<sup>\*\*</sup> NATALIE G. MURRAY,<sup>††</sup> TIMOTHY McCASHLAND,<sup>§§</sup> JOAN S. REISCH,\*  
PATRICIA R. ROBUCK,<sup>|||</sup> and the Acute Liver Failure Study Group

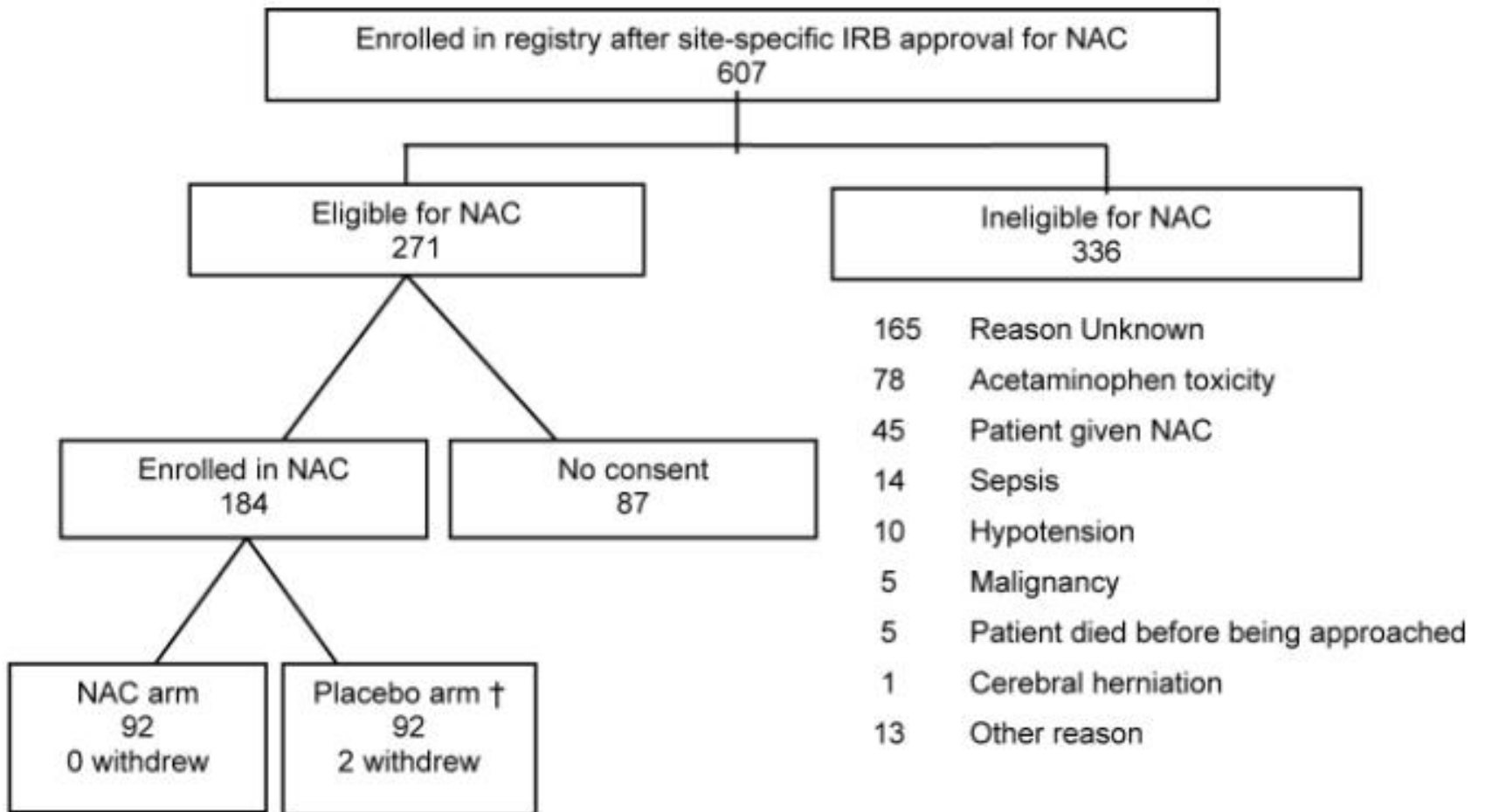
occurred significantly more frequently in the NAC group (14% vs 4%;  $P = .031$ ). **CONCLUSIONS: Intravenous NAC improves transplant-free survival in patients with early stage non-acetaminophen-related acute liver failure.** Patients with advanced coma grades do not benefit from NAC and typically require emergency liver transplantation.

# Intravenous N-acetylcysteine in Pediatric Patients With Nonacetaminophen Acute Liver Failure: A Placebo-Controlled Clinical Trial

Robert H. Squires,<sup>1</sup> Anil Dhawan,<sup>2</sup> Estella Alonso,<sup>3</sup> Michael R. Narkewicz,<sup>4</sup> Benjamin L. Shneider,<sup>1</sup> Norberto Rodriguez-Baez,<sup>5</sup> Dominic Dell Olio,<sup>6</sup> Saul Karpen,<sup>7\*</sup> John Bucuvalas,<sup>8</sup> Steven Lobritto,<sup>9</sup> Elizabeth Rand,<sup>10</sup> Philip Rosenthal,<sup>11</sup> Simon Horslen,<sup>12</sup> Vicky Ng,<sup>13</sup> Girish Subbarao,<sup>14</sup> Nanda Kerkar,<sup>15</sup> David Rudnick,<sup>16</sup> M. James Lopez,<sup>17</sup> Kathleen Schwarz,<sup>18</sup> Rene Romero,<sup>19</sup> Scott Elisofon,<sup>20</sup> Edward Doo,<sup>21</sup> Patricia R. Robuck,<sup>21</sup> Sharon Lawlor,<sup>22</sup> Steven H. Belle<sup>22</sup> for the Pediatric Acute Liver Failure Study Group

(2013)

N-acetylcysteine (NAC) was found to improve transplantation-free survival in only those adults with nonacetaminophen (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 intensive



† One participant was randomized to placebo arm but received treatment.



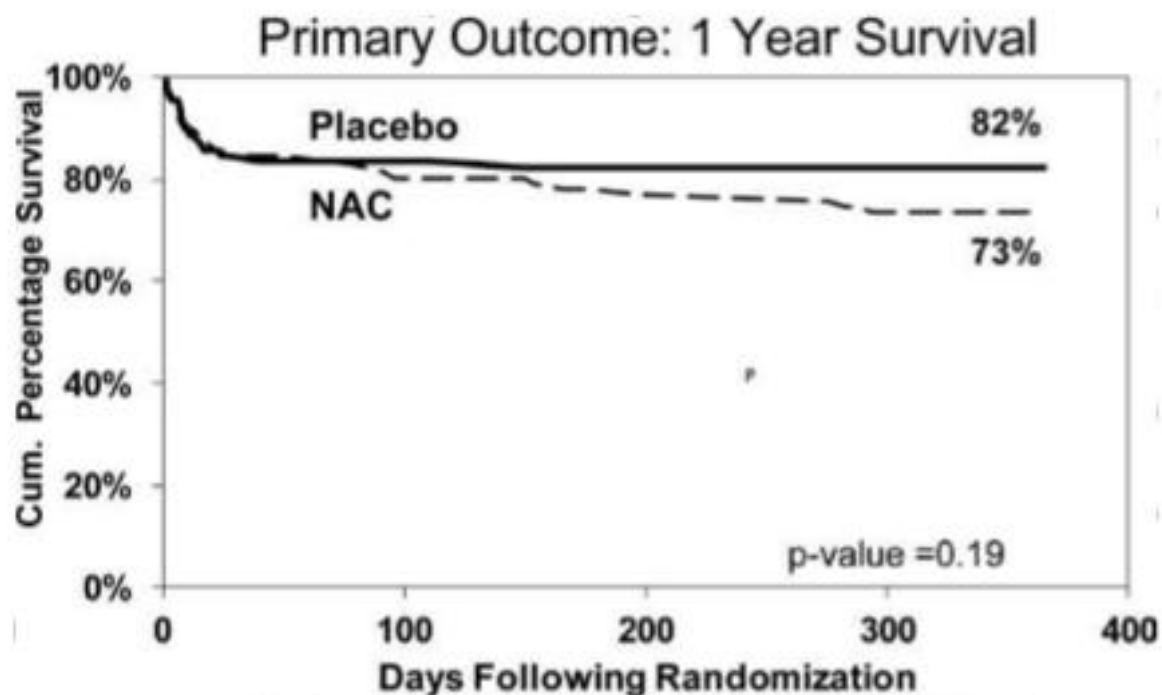


Fig. 2. Primary outcome: 1 year survival. Product-limit estimates were used to obtain the cumulative percentages of participants surviving 1 year following randomization. A log-rank test was used to assess statistical significance of the difference in survival curves. The cumulative percentage of children 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.

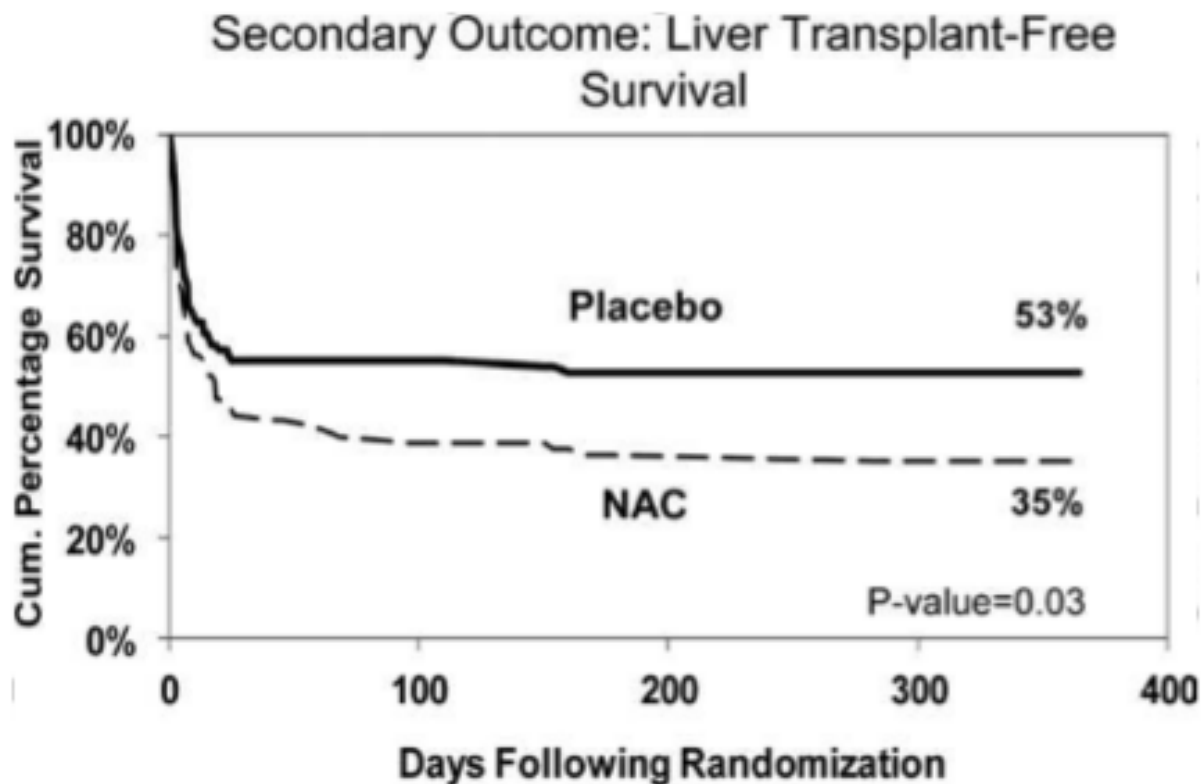


Fig. 3. Product-limit estimates were used to obtain the cumulative percentages of participants with 1-year transplantation-free survival. A log-rank test was used to assess statistical significance of the difference in survival curves. The cumulative percentage of children with liver transplantation-free 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 versus 35% when given NAC, with a *P*-value of 0.03.

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.

# Safety and Efficacy of N-Acetylcysteine in Children With Non-Acetaminophen-Induced Acute Liver Failure

Christine Kortsalioudaki, Rachel M. Taylor, Paul Cheeseman, Sanjay Bansal, Giorgina Mieli-Vergani, and Anil Dhawan

*Paediatric Liver Centre, King's College London School of Medicine at King's College Hospital, London, UK*

Acute liver failure (ALF) carries a high mortality in children. N-acetylcysteine (NAC), an antioxidant agent that replenishes mitochondrial and cytosolic glutathione stores, has been used in the treatment of late acetaminophen-induced ALF and non-acetaminophen-induced ALF. In our unit, NAC was introduced as additional treatment for non-acetaminophen-induced ALF in 1995. The aim of this study was to evaluate the safety and efficacy of NAC in children with ALF not caused by acetaminophen poisoning. A retrospective review of medical records of 170 children presenting with nonacetaminophen-induced ALF between 1989 and 2004 was undertaken. ALF was defined as either international normalized ratio of prothrombin time (INR) > 2 and abnormal liver function or INR > 1.5 with encephalopathy and abnormal liver function. Children were divided

transplantation (LT). The median duration of NAC administration in Group 2 was 5 (range, 1-77) days. Complications were noted in 8 (10.8%) children: rash in 3, arrhythmia in 3, and dizziness and peripheral edema in 1. One child had an allergic reaction (bronchospasm) and NAC was stopped. A total of 41 (71%) children in Group 1 vs. 85 (77%) in Group 2 required admission to intensive care,  $P =$  not significant (ns). The length of intensive care stay was 6 (range, 1-58) days in Group 1 vs.

# Safety and Efficacy of N-Acetylcysteine in Children With Non-Acetaminophen-Induced Acute Liver Failure

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occurred in 13 (22%) in Group 1 vs. 48 (43%) in Group 2,  $P = 0.005$ ; 15 (25%) in Group 1 died without transplant vs. 21 (19%) in Group 2,  $P = \text{ns}$ ; and LT was performed in 32 (54%) vs. 42 (38%),  $P = \text{ns}$ . Death after transplantation occurred in 15 (39%) in Group 1 vs. 8 (16%) in Group 2,  $P = 0.02$ . In conclusion, NAC is safe in non-acetaminophen-induced ALF. In this retrospective study NAC was associated with a shorter length of hospital stay, higher incidence of native liver recovery without transplantation, and better survival after transplantation. *Liver Transpl* 14:25-30, 2008. © 2007 AASLD.

# SYSTEMATIC REVIEW

## N-acetylcysteine for non-paracetamol drug-induced liver injury: a systematic review

### RESULTS

We identified one RCT of NAC vs. placebo in patients with non-paracetamol acute liver failure. There was no difference in the primary outcomes of overall survival at 3 weeks between NAC [70%, 95% confidence interval (CI) = 60%, 81%,  $n = 81$ ] and placebo (66%, 95% CI = 56%, 77%,  $n = 92$ ). NAC significantly improved the secondary outcomes of transplant-free survival compared with placebo: 40% NAC (95% CI = 28%, 51%) vs. 27% placebo (95% CI = 18%, 37%). A subgroup analysis according to aetiology found improved transplant-free survival in patients with non-paracetamol DILI, NAC (58%,  $n = 19$ ) vs. placebo (27%,  $n = 26$ ), odds ratio (OR) 0.27 (95% CI = 0.076, 0.942). Overall survival was similar, NAC (79%) vs. placebo (65%);, OR 0.50 (95% CI = 0.13, 1.98).

### CONCLUSION

Current available evidence is limited and does not allow for any firm conclusions to be made regarding the role of NAC in non-paracetamol DILI. We therefore highlight the need for further research in this area.

# *Recommendations*



American  
Gastroenterological  
Association

**Recommendation 10: In patients presenting with acetaminophen-associated ALF, the AGA recommends the use of N-acetyl cysteine in acetaminophen-associated ALF**

*Strong recommendation; very low quality of evidence.*

**Recommendation 11: In patients presenting with non-acetaminophen-associated ALF, the AGA recommends that N-acetyl cysteine be used **only in the context of clinical trials****

*No recommendation.*



## RECOMMENDATION 5

***Begin N-acetylcysteine promptly in all patients where the quantity of acetaminophen ingested, serum drug level or rising aminotransferases indicate impending or evolving liver injury (II-1).***

## RATIONALE 5

N-acetylcysteine (NAC), the antidote for acetaminophen poisoning, has been shown to be effective and safe for this purpose in numerous controlled trials.<sup>18,19</sup> Given these considerations, administration of NAC is recommended in any case of ALF in which acetaminophen overdose is a suspected or possible cause; specific indications that acetaminophen may be the culprit include very high aminotransferases and low bilirubin levels, in the absence of apparent hypotension or cardiovascular collapse.<sup>10</sup> NAC should be given as early as possible, but may still be of value 48 hours or more after ingestion.<sup>22</sup>

## RECOMMENDATION 6

***N-acetylcysteine may be used in cases of acute liver failure in which acetaminophen ingestion is possible or when knowledge of circumstances surrounding admission is inadequate but aminotransferases suggest acetaminophen poisoning (III).***

## RATIONALE 6

Low or absent levels of the parent compound, acetaminophen, do not rule out hepatotoxicity since the time of ingestion may be relatively remote or unknown, especially when overdose may have been unintentional or occurred over several days.<sup>10</sup>

## RECOMMENDATION 7

***In ALF patients with known or suspected mushroom poisoning, consider administration of penicillin G and N-acetylcysteine (III).***

## RATIONALE 7

Penicillin G and silibinin (silymarin or milk thistle) are the accepted antidotes despite a lack of controlled trials proving their efficacy.<sup>27-30</sup>

*Thanks for your attention!*