

## **Acetaminophen and the Liver:**

### **Poison or Panacea?**

Tylox®  
acetaminophen  
paracetamol  
Tylenol®  
Tylenol PM®  
Nyxquil®  
Percocet®  
Hydrocodone-APAP  
Midrin®  
Dayquil®  
Panadol®  
Triaminic®  
Anacin®  
Theraflu®  
N-acetyl-p-aminophenol  
APAP  
Tylenol® with Codeine  
Fioricet®  
Excedrin®  
Mucinex®  
Vicodin®  
Norco®  
Sinutab®

**William M. Lee, MD**

**Internal Medicine Grand Rounds  
University of Texas Southwestern Medical Center**

**May 20, 2016**

This is to acknowledge that William M. Lee, MD has disclosed that he does not have any financial or other interests or relationships with commercial concerns related directly or indirectly to this program. Dr. Lee will be discussing off label or research only tests or treatments.

## **Brief Biosketch: William M. Lee, MD, FACP, FAASLD**

Dr. Lee has served as Professor of Internal Medicine and Bioengineering at the University of Texas Southwestern Medical Center at Dallas since 1990. He holds the Meredith Mosle Chair in Liver Diseases in his honor. Dr. Lee graduated from Amherst College cum laude and from the College of Physicians and Surgeons of Columbia University AOA, completing his internal medicine residency at the Presbyterian Hospital in New York City where he served as Chief Resident. After additional studies at Kings College Hospital, London, he has served on the faculties of Columbia University, the Medical University of South Carolina and The Ohio State University.

Dr. Lee founded the Acute Liver Failure Study Group (ALFSG) in 1997, as a national network to study this orphan disease, funded through 2020; website: [acuteliverfailure.org](http://acuteliverfailure.org). In addition, he has been a Principal Investigator with the NIH-sponsored HALT-C Trial, Drug-Induced Liver Injury Network (DILIN) and Hepatitis B Research Network. In 2014, he was awarded the Distinguished Clinician Educator/Mentor Award from the American Association for the Study of Liver Diseases (AASLD). An earlier version of this lecture was given in November 2013 at the Annual Meeting of the AASLD as the Hyman Zimmerman Memorial Lecture in Hepatotoxicity.

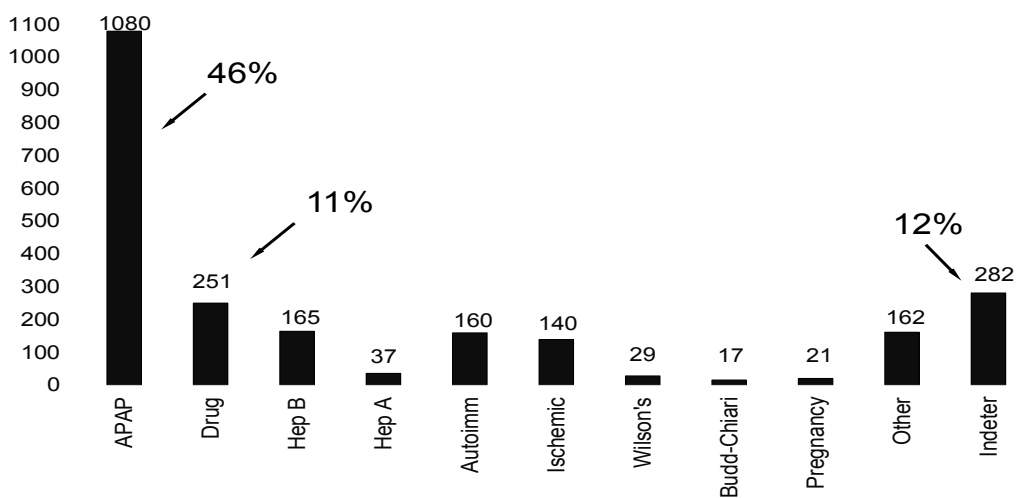
**Purpose & Overview:** Acetaminophen (N-acetyl-p-aminophenol, APAP, paracetamol, Tylenol®) is the most commonly used drug for the treatment of pain and fever around the world. At the same time, APAP is capable of causing dose-related hepatocellular necrosis responsible for nearly 500 deaths annually in the U.S., as well as 100,000 calls to US Poison Control Centers and 50,000 emergency room visits. APAP toxicity dwarfs all other prescription drugs as a cause for acute liver failure in the United States and Europe, but is not regulated in any significant way. This presentation will highlight the ongoing controversy as to the role of this ubiquitous pain reliever, beginning with its history, pathogenesis of the liver injury, its recognition, treatment and outcomes.

**Objectives:** Attendees to this lecture should be able to:

- 1) Distinguish the clinical and biochemical injury pattern of APAP from that of other drug-related liver injury.
- 2) Recognize modes of treatment for APAP liver injury.
- 3) Summarize the measures FDA has taken to attempt to limit APAP-related deaths.
- 4) Take a stand: poison or panacea?

## Introduction/Background

Acetaminophen (N-acetyl-p-aminophenol, APAP, paracetamol, Tylenol®) is the most commonly used drug for the treatment of pain and fever around the world. Liver injury secondary to APAP overdose results in nearly 500 deaths in the U.S., as well as 100,000 calls to US Poison Control Centers and 50,000 emergency room visits annually.<sup>1</sup> APAP toxicity accounts for 46% of all acute liver failure (ALF) in the United States<sup>2</sup> and between 40 and 70% of all cases in Great Britain and Europe.<sup>3</sup> Acetaminophen toxicity dwarfs by several-fold the number of deaths related to acute liver failure (ALF) from all prescription drugs combined, and has been the subject of two FDA Advisory Committee meetings in the past 15 years.



**Figure 1.** Etiologies of Acute Liver Failure in the USA ALFSG Adult Registry, 1998-2016.

Acetaminophen is very safe when used in limited doses but the margin of safety is relatively narrow, since it causes dose-related liver injury in all mammalian species. The opioid combination medications containing hydrocodone/acetaminophen (Vicodin®, Norco®, others) represent the most frequently prescribed generic in the U.S. with 139 million prescriptions written in 2012.<sup>4</sup> Overall, acetaminophen represents a multi-billion dollar product and Tylenol®, a well-protected brand. Coupled with its reputation as being extremely safe, the public and regulatory authorities are faced with an unusual situation: over-the-counter, yet deadly. Meanwhile, acetaminophen remains a vital substrate for innumerable basic scientists seeking to better understand hepatic metabolism and the mechanisms of liver injury.<sup>5, 6</sup> Thus, for scientists and hepatologists alike, APAP currently provides indefinite job security. How did this ubiquitous mild, pain reliever achieve this unusual status? What can be done to better understand the risk and the consequences of APAP overdosing? The current review will highlight the history of acetaminophen, the pathogenesis and clinical features of its toxicity, challenges in diagnosis and management, as well as its epidemiology and public health considerations.

## History

As early as 1960, paracetamol as it is referred to in Europe and the United Kingdom (UK), had become a popular analgesic for the treatment of headache and mild pain, possessing few of the side effects associated with aspirin (acetylsalicylic acid). By 1966, initial reports began to appear concerning its association with liver injury and fatalities as a result. By the 1970's, paracetamol was the most frequently used suicidal agent<sup>7</sup> in the UK; the Liver Unit at Kings College Hospital London, in 1972 set up the first 2-bed Liver Intensive Care Unit, typically filled with young women on life support following attempts at self-harm. An APAP overdose of 12 grams, 24 'extra strength' tablets, is associated with a greater than 50% mortality. By 1973, Mitchell and Jollow at the NIH had delineated the APAP metabolic pathway,<sup>8</sup> and suggested that *N*-acetylcysteine (NAC) was a suitable antidote. Oral NAC (Mucomyst®) came into common usage within a few years.<sup>9</sup> Use of acetaminophen was limited in the United States until the 1980's when, after the association of aspirin with Reyes syndrome in children was recognized, acetaminophen was promoted as a suitable substitute and became marketed actively as Tylenol® as well as other brands, and in convenience combinations such as acetaminophen/diphenhydramine (TylenolPM®, Nyquil®, others).

By 1986, the initial U.S. reports surfaced regarding severe liver injury associated not with suicide attempts but with so-called 'therapeutic misadventure,' an inadvertent overdose in the setting of acute or chronic pain, often accompanied by alcohol use and without suicidal intent.<sup>10</sup> U.S. hepatologists became increasingly aware of this entity. Drs. Zimmerman and Maddrey published an article in 1995 describing 67 cases of inadvertent toxicity, most of whom had ingested therapeutic or supra-therapeutic doses without apparent suicidal intent but associated with poor outcomes.<sup>11</sup>

In a review article on Acute Liver Failure in the New England Journal of Medicine (NEJM) in 1993, I mentioned that "the combination of alcohol and acetaminophen accounted for two thirds of the cases of acute liver failure seen at Parkland Hospital (unpublished data)."<sup>12</sup> The following day I was approached by McNeil, the over the counter corporate branch of Johnson and Johnson, makers of Tylenol®, asking for me to show them the Parkland cases. The subsequent detailed chart review resulted in publication in 1997 in NEJM of a report of 71 cases of acetaminophen toxicity identified at Parkland over a 39-month period.<sup>13</sup>

### Parkland Hospital study of APAP overdoses

Suicidal: n=50	Unintentional: n=21
<ul style="list-style-type: none"><li>• Suicide admitted</li><li>• Single time point</li><li>• No cause of pain</li><li>• Early presentation</li><li>• 20% ALT &gt; 1,000</li><li>• 1 ALF/death in 50 (2%)</li></ul>	<ul style="list-style-type: none"><li>• Suicide denied</li><li>• Several days' use</li><li>• Reason for pain</li><li>• Late presentation</li><li>• Virtually all high ALT</li><li>• 8 ALF; 6 (29%) died</li></ul>

Schiødt et al., NEJM 1997;337:1112-17

**Only 9 of 71 had ALF, but they were mostly unintentional**

We divided cases into those that were clearly suicidal overdoses and those thought to be unintentional. The criteria became quite clear: suicidal intent was associated with single time-point ingestions, with evidence for self-harm, and no pain issues. By contrast, the unintentional cases were frequently associated with alcohol, but more importantly chronic use/overuse for pain or discomfort of another illness (fever, URI), and not at a single time point, but over several days (or weeks) with no suicidal intent.

The unique features of two groups were evident in the Parkland study: suicides typically were young people with relationship problems, taking between 12 and 50 gms at one time, but announcing the overdose, so that they were brought to the Emergency Department, and, for the most part, were given NAC promptly. Use of the NAC antidote within 12-18 hours virtually totally prevented liver injury, whereas later presentations would be associated invariably with severe liver injury proportional to the dose taken. Unintentional overdoses usually involved 6-10 gm/day over several days for post-op pain, pancreatitis, low back pain, frequently involving use of opioid combinations, without any suicidal intent. Not recognizing anything abnormal in their behavior, the unintentional patients presented only after symptoms associated with acute liver failure developed.

### **Acute Liver Failure**

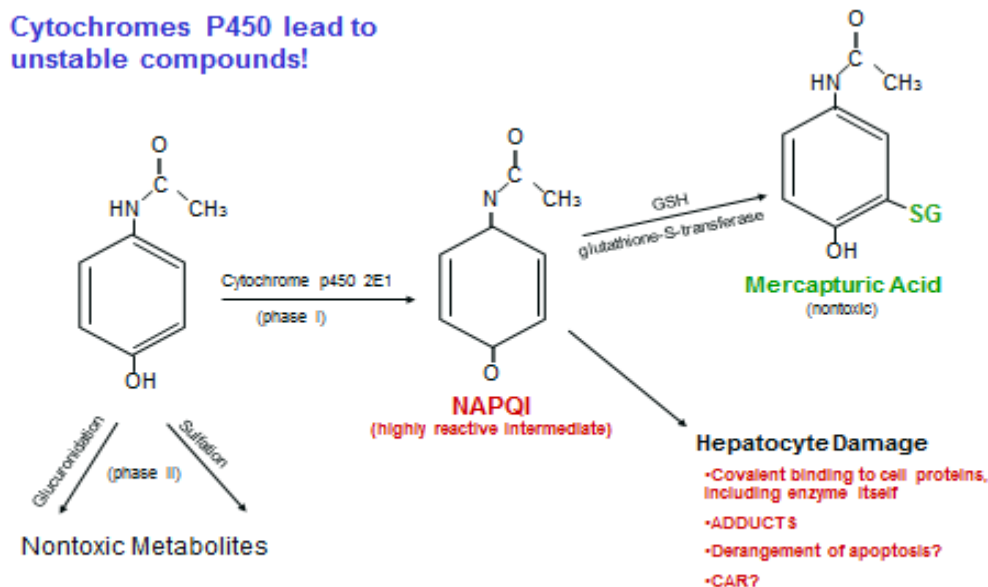
Acute liver failure (fulminant hepatic failure, ALF) has been recognized since the 1950's as the rapid onset of severe hepatocyte injury from a variety of causes that led in the early era prior to transplantation to a nearly universally fatal outcome. Criteria were established that remain in use to the present: the appearance of hepatic encephalopathy and coagulopathy with an INR  $\geq 1.5$ , after an illness of less than 26 weeks and without pre-existing liver disease.<sup>14</sup> Burton Combes at UT Southwestern early on reported a small series of ALF patients, noting the presence of hepatic encephalopathy and cerebral edema as hallmark features unique to this setting.<sup>15</sup> Survival in the 1970's was limited to less than 10% and treatments were unknown.<sup>16</sup> Estimates have placed the incidence at 2,000 per year in the United States making this a super orphan disease.<sup>17</sup> Its high mortality and resource utilization, and its predilection for young people, has attracted interest and support for research into this fascinating and frustrating condition.

The Acute Liver Failure Study Group (ALFSG) was organized with initial pilot funding from FDA and NIH, currently funded through 2020. Its purpose was to establish a network that would allow these rare cases to be grouped for study, incorporating multiple North American sites with an interest in participating. Initially, the sites forwarded a list of patients from their transplant database in the pre-EMR era.<sup>18</sup> In January 1998, ALFSG began collecting prospective, detailed case histories and bio-samples, has now enrolled nearly 3,000 cases over 18 years. It rapidly became apparent that APAP was indeed the most prevalent cause of ALF in the United States. An initial 20-38% rapidly rose to nearly 50% within the first several years of the study.<sup>19,20</sup> The overall breakdown of etiologies over the life of the network has changed little, although the incidence of hepatitis A and B-related ALF has declined somewhat.<sup>21</sup> Worldwide, acetaminophen is associated with the developed world and is largely absent or displaced by viral hepatitis in the developing world.

### **Acetaminophen: Pathogenesis**

As a dose-related toxin acetaminophen causes hepatocyte and renal tubular injury in a predictable fashion across all mammalian species. Centrilobular necrosis is the hallmark lesion that is indistinguishable by routine light microscopy from ischemic necrosis, also affecting the same zone 3 of the hepatic lobule, where oxygen tension is lowest. As a result, classic acetaminophen toxicity is associated with the highest aminotransferase enzyme levels recognized, as high as 15-30,000 IU/L, (upper limit of

normal = 40 IU/L). The pathway as outlined indicates that the parent compound is readily esterified to glucuronides and/or sulfates unless the capacity for esterification is saturated, in which case a secondary pathway via cytochrome P450 enzymes comes into play, principally Cyp 2E1, leading to formation of a highly reactive and toxic intermediate metabolite, *N*-acetyl-*p*-benzoquinone imine (NAPQI).<sup>8</sup>



Mitchell DR, Jollow DJ, et al 1973, JPET

**Figure 2.** Metabolic pathway for acetaminophen.

NAPQI can be de-toxified via glutathione to mercapturic acid that is water soluble, harmless and readily excreted in urine. Once glutathione depletion occurs, NAPQI binds directly to cell proteins via cysteine residues, disrupts cellular integrity yielding hepatocyte necrosis. This injury likely takes place very rapidly once glutathione depletion is accomplished, leading to the extraordinary levels of aminotransferases but also a very rapid decline upon cessation of liver injury. However, given the relatively long half-life of both aspartate and alanine aminotransferase (AST and ALT, respectively), the enzymes subside fully only after 3-9 days, depending on the severity of the injury. The injury is so uniform in nature that a mathematical model has been created to predict outcome, using only the AST, ALT and INR values at one time point.<sup>22</sup>

### Clinical picture: the APAP phenotype

After an acetaminophen overdose at a single time point, there is no immediate sedative effect, and few symptoms initially, until nausea and vomiting develop between 12 and 24 hours. In the next 24 hours, symptoms may improve but aminotransferases (aspartate aminotransferase-AST and alanine aminotransferase-ALT) and even INR rise abruptly and to very high levels, frequently above 10,000 IU/L, normal (< 40 IU/L), with INR ≥ 4.0. By 72-96 hours biochemical elevation will have peaked and somnolence, stupor and coma ensued, with the appearance of hyperammonemia, lactic acidosis, cerebral edema, brain stem herniation and vascular collapse.<sup>23</sup> Concomitant acute

(tubular) kidney injury (AKI, 70%) and varying degrees of skeletal muscle cytolysis also occurs.<sup>24</sup> If the multi-organ failure syndrome does not begin to evolve at this point, then recovery ensues equally quickly, with rapid resolution of AST/ALT and INR, and there appears to be no permanent injury, the AKI resolving in a week or two although temporary dialysis may be required.

On arrival in the Emergency Department, a careful history is necessary to elicit the details surrounding an overdose. After a single time point ingestion, a determination may be made of the severity provided that the time of ingestion is known. This requires using the Rumack nomogram, a way of calculating the risk, by measuring acetaminophen in the patient's plasma.<sup>25</sup> This method is of no use for multiple time-point ingestions or if the time of ingestion is uncertain. Similarly, plasma acetaminophen levels will be undetectable in many who present with symptoms of early liver failure, since its half-life is 304 hours and the drug will be fully metabolized by the time the liver damage is well under way.<sup>26</sup>

N-acetylcysteine is a reliable antidote, providing sulfhydryl donor groups to prevent binding of NAPQI, the highly reactive intermediate, to cellular proteins. However, administration of NAC must take place by 12 hours after ingestion for full protection to take place, partial amelioration occurring at later time points.<sup>27</sup> NAC is typically given if the history is uncertain, since it has few side effects and essentially no risk to its use.

**Table 1.** Comparison of Clinical and Biochemical Features of ALF Etiologies, N=2,345

	<b>APAP N=1080</b>	<b>Drug n=252</b>	<b>Indeterminate n=282</b>	<b>HepA/HepB n=37/166</b>	<b>All Others N=528</b>
<b>Age (median)</b>	<b>36</b>	<b>46</b>	<b>40</b>	<b>50/42.5</b>	<b>45</b>
<b>Sex (% F)</b>	<b>76</b>	<b>69</b>	<b>61</b>	<b>43/45</b>	<b>70</b>
<b>Jaundice to coma (Days)</b>	<b>1</b>	<b>12</b>	<b>10</b>	<b>4/8</b>	<b>7</b>
<b>Coma ≥3 (%)</b>	<b>53</b>	<b>35</b>	<b>47</b>	<b>54/50</b>	<b>39</b>
<b>ALT (median IU)</b>	<b>3790</b>	<b>672.5</b>	<b>863.5</b>	<b>2229/1483</b>	<b>716</b>
<b>Bili (median)</b>	<b>4.3</b>	<b>19.6</b>	<b>20.4</b>	<b>12.5/18.4</b>	<b>13.1</b>
<b>Tx (%)</b>	<b>9</b>	<b>40</b>	<b>42</b>	<b>35/39</b>	<b>30</b>
<b>Transplant-free Survival (%)</b>	<b>64</b>	<b>24</b>	<b>23</b>	<b>49/20</b>	<b>30</b>
<b>Overall Survival (%)</b>	<b>71</b>	<b>59</b>	<b>61</b>	<b>73/54</b>	<b>55</b>

The specific biochemical pattern observed for APAP is particularly noteworthy when compared to most other forms of liver injury that are not hyper-acute but sub-acute in evolution. As a result, most forms of liver injury evolving over 1-6 weeks demonstrate lower aminotransferase and higher bilirubin levels, since bilirubin accumulates over time in tissue and plasma when excretion hepatocyte function is impaired. Data from the ALFSG emphasize these differences as well as a significant difference in overall outcomes between APAP and, say, other forms of drug-induced liver injury due to prescription drugs (DILI).<sup>20,21</sup>

Despite the seemingly contrasting clinical scenarios associated with unintentional and suicidal APAP ingestions, patients who develop ALF due to either form resemble each other in many ways. Europe and the UK now recognize 'staggered overdoses' comparable to unintentional ones, currently comprising up to 30% of UK cases.<sup>28</sup> Both forms are associated with equally high aminotransferase levels and nearly the same frequency of anti-depressant and other substance use, suggesting (among other things) that patients with chronic pain often are given anti-depressants to help with their symptoms. Additionally, the similarities between the intentional and unintentional cases biochemically suggest that once glutathione depletion occurs, the damage is uniquely sudden and severe, resolving in an equally rapid fashion. No truly chronic toxicity for acetaminophen has been identified, and there appear to be no long-term hepatic effects following even a very severe overdose.

### **The APAP phenotype: role of substance abuse**

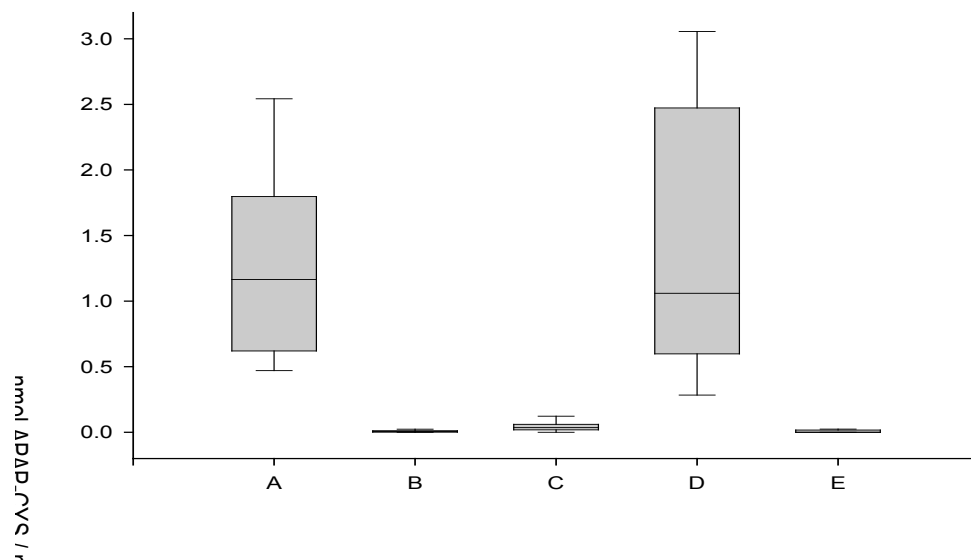
In reviewing the large ALFSG APAP patient series that now includes more than 1000 patients, it is apparent that substance use and abuse characterize both the suicidal and unintentional patients. We asked 86 survivors of severe APAP overdoses associated with ALF, to complete a detailed questionnaire concerning reasons for overdose, quantity, substance abuse, and administered the MINI depression scale and the Barrett impulsivity scale (BIS). Both intentional and unintentional APAP overdoses demonstrated increased substance use abuse, depression and impulsivity scores.<sup>29</sup> Additionally, in follow-up studies on transplant-free survivors, APAP patients when compared to non-APAP ALF are younger, less likely to be married or employed and at least twice as likely as non-APAP survivors to have underlying psychiatric disease. When they could be located and interviewed after 1-2 years, APAP patients reported lower scores on Health-Related Quality of Life measures.<sup>30</sup> In a further study, a series of 24 single nucleotide polymorphisms (SNPs) in nine genes related to impulsivity and/or stress responsivity and substance abuse that may modify response to stress were sought in 229 Caucasian APAP overdose patients. The genotype frequencies of two SNPs were found to be significantly different between the cases and controls, specifically SNP rs2282018 in the arginine vasopressin gene (*AVP*, OR 1.64) and SNP rs11174811 in the AVP receptor 1A gene (*AVPR1A*, OR 1.89), both of which have been previously linked to a drug use disorder diagnosis.<sup>31</sup> Thus, APAP patients frequently are capable of impulsive and high risk behavior, perhaps on a genetic basis. Whether alcohol truly enhances the injury, it and other substances certainly alter consciousness and the ability to keep track of number of pills ingested.

### **Acetaminophen adducts: diagnosing the overdose after the fact**

Patients who present to hospital following a severe acetaminophen overdose of either type will typically demonstrate mental alterations and encephalopathy, the hallmarks of ALF. Thus, the history of the ingestion may be obscured, underplayed, or even denied, while the evidence of the overdose, namely the acetaminophen in the blood stream may have already disappeared via hepatic metabolism. An assay that



measures the toxic by-product of NAPQI binding to cell proteins, Cys-APAP adducts,<sup>32</sup> has proven helpful in delineating cases where the history is uncertain. This assay currently requires high-pressure liquid chromatography with electrochemical detection (HPLC-EC), a two-day process, but a point-of-care assay is under development.<sup>33</sup>



**Figure 3.** APAP-Cys adduct levels from reference 32. A: Known APAP suicidal overdoses, B: Known other etiologies (hepatitis B, etc.), C: Individuals with APAP overdoses who arrived early and received NAC, D and E: 36 indeterminate ALF patients divided between the 7 with positive adducts and 29 without.

Using the adduct assay, 7/36 (19%) of an initial group of ‘indeterminate’ acute liver failure patients were demonstrated to have adduct levels indistinguishable from known suicidal patients.<sup>32</sup>

Thus, the APAP-Cys adduct level can be used to identify overdoses where the history is for any reason obscure. A second adduct study confirmed quite precisely the high sensitivity and specificity of the assay.<sup>34</sup> Beta testing of a rapid adduct assay has already been conducted, with a phase 3 trial to follow soon.

### Other clinical observations

By now, it is clear that APAP has a narrow therapeutic window, with significant toxicity at only 2-3 times the daily recommended dose. Further insight was provided by a study in a clinical research unit where otherwise healthy individuals were given 1000 mg acetaminophen every 6 hours, replicating the maximum recommended daily dose.<sup>35</sup> By day 5, nearly 30% of patients had aminotransferase elevations, some as high as 500 IU/L. These were random individuals; however, more susceptible individuals have been identified that harbor polymorphisms that alter drug metabolism via the cytochromes or glucuronidation pathways.<sup>36</sup> Although strong associations have been postulated for alcohol and with other substance abuse, it remains unclear whether alcohol directly

potentiates liver injury in this setting.<sup>37</sup> Starvation clearly enhances toxicity due to depletion of glutathione. Convenience preparations such as those containing diphenhydramine (Nyquil®, others), do not appear to enhance liver injury although a large overdose may prolong somnolence and impede removal to hospital for medical care.<sup>38</sup> Hydrocodone combinations with APAP are prescription only, constituting the most commonly prescribed generic in the U.S.; it is unlikely that the presence of hydrocodone enhances toxicity but habituation to the opioid may increase desire for supra-therapeutic amounts as is commonly seen in the unintentional group that suffer from chronic pain.<sup>20</sup> The U.S. Food and Drug Administration (FDA) recently sought to limit such exposures by capping the opioid combination quantity of APAP at 325 mg per tablet, where formerly quantities of APAP in individual tablets ranged from 500, 650 or 750 mg each.<sup>39</sup>

### **Treatment**

The patient presenting with APAP overdose may elude initial recognition by the first medical contact for a variety of reasons: somnolence, denial or being unaware of possible APAP toxicity due to unintentional overdosing. Thus, a physician evaluating any patient with unexplained altered mentation should obtain an acetaminophen level immediately, along with other toxicology screening tests, but not rely exclusively on the result in excluding APAP ingestion, since later presentations occur outside the period of metabolism after the parent compound has disappeared. Treatment of a suicidal overdose that presents within 4 hours begins with activated charcoal to bind remaining tablets within the stomach as well as NAC. Beyond 4 hours, NAC alone is the treatment of choice, given orally, or more frequently, intravenously to preclude vomiting.

Recent data suggest that patients that arrive with normal aminotransferase levels and promptly receive NAC will not suffer any significant degree of toxicity. Thus, receiving NAC within 12 hours carries a reasonable assurance of a good outcome. More often, the history of an overdose may be elusive or questionable, once liver injury has begun. In this instance, the nearly unique pattern of liver function test elevations is a very strong surrogate to suggest APAP toxicity. The characteristic 'hyper-acute' enzyme pattern for acetaminophen toxicity wherein the AST and ALT are strikingly elevated, often exceeding 5,000 IU/L. Despite this apparent severity, bilirubin levels remain near or only slightly above normal, confirming that the injury, although severe, is only 2-3 days old. Recognition of the hyper-acute pattern should lead to consideration of use of NAC promptly even in the absence of a convincing APAP history, since the differential diagnosis of this particular enzyme pattern is limited (ischemia, rarely viral hepatitis). Failure to promptly administer NAC can be disastrous, turning a full recovery into a fatal event.<sup>40</sup> NAC has been shown to improve outcomes in non-APAP ALF in a controlled blinded study performed by ALFSG, so its use is advocated by many although it is not FDA approved for the non-APAP indication.<sup>41</sup> Beyond the antidote, close observation and good care of the comatose patient are advised, with referral to a transplant center and prompt consideration of listing for transplantation if this is an appropriate consideration.

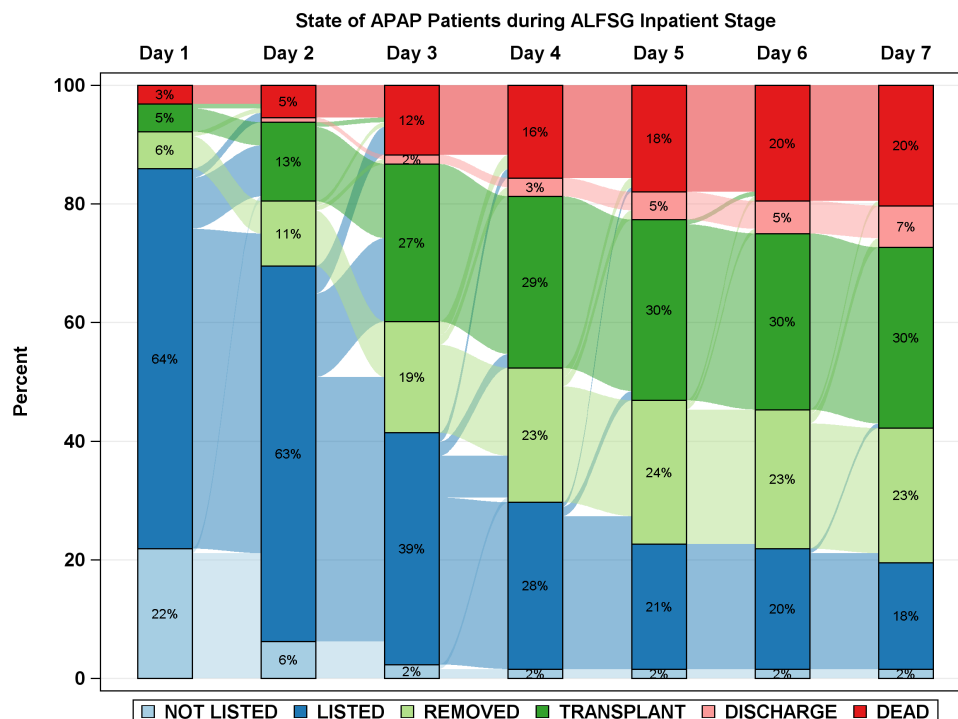
### **Management in ALF: cerebral edema and multi-organ failure**

Patients with ALF of any kind can deteriorate rapidly and develop vascular collapse and cerebral edema as well as infection, acute kidney injury and acute respiratory distress syndrome (ARDS). Overall guidelines have been developed but are based largely on expert opinion as opposed to randomized controlled trials, given the rarity of the disease. Additionally, while initial management is directed at the specific etiology, ALF encompasses a common multi-organ failure picture that resembles sepsis,

but differs in the very elevated ammonia levels that accompany such patients.<sup>42</sup> While ammonia remains controversial as the cause of encephalopathy in cirrhosis, its role in brain edema is more secure, with arterial ammonia levels above 200µM/L being highly associated with the presence of brain edema that can lead to uncal herniation. Accordingly, methods to reduce ammonia have been sought. Conventional treatments for cirrhosis-related encephalopathy (lactulose, antibiotics such as rifaximin) appear ineffective in this setting. ALFSG is conducting a phase IIa trial to explore the safety and tolerability of ornithine phenylacetate (OPA) as an ammonia-trapping agent. Ornithine driving the binding of ammonia initially as glutamine that is then combined with the phenyl acetate to form phenyl acetylglutamine that can be excreted in the urine.<sup>43</sup> To date, the drug appears safe but its ammonia lowering ability remains unclear, since this is not a controlled trial. A further ongoing trial in patients with cirrhosis and encephalopathy is underway to more rapidly resolve encephalopathy; results are pending at this time.

### Outcomes/prognosis

Predicting outcome in all forms of ALF is difficult, but becomes particularly challenging in acetaminophen ALF. Overall, nearly two thirds of patients with APAP ALF recover fully, while only a small fraction receive a transplant or die. Nonetheless, acetaminophen toxicity is the most common cause of death due to the sheer numbers of cases. In the UNOS system of organ sharing for transplantation, those with any form of ALF are listed as the highest priority, Status 1, and are given preference above the MELD scoring system because of a high likelihood of death within 7 days. While a large number of APAP patients are not listed for transplantation, either because they are not considered sick enough or for psychosocial reasons (prior suicide attempts, substance abuse), few listed patients receive a graft in part because of rapid disease evolution and relatively long donor organ wait times.



**Figure 4.** Sankey plot illustrating the path of all APAP patients listed over 7 days following admission.

A recent study (Figure above) sought to compare outcomes for APAP and other categories of ALF following listing.<sup>44</sup> Only a small number (approximately 7%) of APAP ALF eventually undergo liver transplantation: only 22% were listed, compared to 57% among non-APAP etiologies. Despite being sicker in most parameters, even fewer listed APAP patients received a graft: 36% compared to 74% for non-APAP. As shown in Figure 4, by 4 days following admission to study, virtually all APAP transplants and all deaths had occurred, whereas with DILI, autoimmune or viral hepatitis, the disease was still evolving through 7 days, with patients remaining viable candidates, so that they could receive a transplant at 6 to 7 days or more following listing. One intriguing insight is that, among those listed for liver transplant, markers of illness severity among those ultimately receiving a transplant resembled more closely those who survived without a graft than those who died, an observation that appears counter-intuitive. This may call into question our criteria for providing transplants to this very sick population: the likelihood of recovery remains very uncertain but life post transplant has unique challenges as well.

### **Determining Prognosis in APAP ALF**

As the above paragraph indicates, prognostic scoring systems are vitally needed to answer the question: to transplant or not to transplant? While following the INR value daily is remarkably easy and somewhat effective, a more complex score that separates APAP from non-APAP cases, the Kings College Hospital (KCH) scoring system developed in the 1980's, has remained in favor despite its limitations. The KCH score is reasonably effective at identifying those dying (has specificity) but lacks sensitivity yielding only about a 50% success rate in predicting survival.<sup>45,46</sup> Recent attempts to improve on prognosis in APAP overdoses have included a mathematical model based solely on AST/ALT and INR, relying only on readily available and objective information.<sup>22</sup> An even newer prognostic index developed by ALFSG may be more helpful and will soon be accessible via an 'app'.<sup>47</sup> No prognostic index works perfectly or universally, perhaps because none can take into account the variety of secondary complications (infection, bleeding, pulmonary and cardiac issues) and variations in care that ALF patients experience.

### **Epidemiology and Size of the Problem**

To date, there has been no evidence of declining incidence of APAP-related ALF in the US. Following legislation passed by the British Parliament in 1998 to limit package size and require blister packaging (presumably to deter impulsive, large dose ingestions), the number of ICU admissions and transplants performed generally declined with some exceptions.<sup>48</sup> The US Food and Drug Administration (FDA) has less authority in regard to over-the-counter medications than prescription drugs. FDA has struggled to meet the problem of APAP toxicity, holding two recent Advisory Committee meetings, in 2002 and 2009. The fact that overdoses are in part self-inflicted has limited efforts to find a real solution; FDA has mainly directed its attention on the unintentional overdose patients. While the 2002 Advisory Committee focused solely on package labeling, a Task Force was put in place thereafter that resulted in the 2009 meeting that addressed larger issues: Should the maximum daily dose be diminished? Should the opioid combinations be unbundled? Should convenience combinations be limited or outlawed? The committee voted to decrease the 4 gram per day limit but did not specify what level it should be, and voted to unbundle the opioids, but this has not taken place to date, possibly mired in the larger issue of opioid abuse, a separate but not unrelated problem.<sup>39</sup> FDA did implement 3 years ago a requirement that opioid combination

products be limited to 325 mg per tablet, rather than the 500, 650 and 750 mg combinations formerly permitted. It is not clear that this change has resulted in fewer overdoses but its effect may still be felt as full implementation is only about a year old. An extensive review of the APAP problem has been provided by Pro Publica, a public interest journalism website that develops in-depth research on topics such as this.<sup>49</sup> Research provided more detail on the pharmaceutical industry's protection of the safety record of acetaminophen, specifically regarding when the risks were known and whether they have been minimized or ignored over the years. The problem in some regards resembles that of the tobacco industry, where scientific evidence of the harm being caused was available for a long time before the widespread acceptance of the product's safety was called into question.

## Conclusions

To date, there is no solution to the dilemma of this unique mild, readily available pain reliever that on the one hand is considered safe and on the other is capable of causing fatal outcomes. As early as 1973, an editorial in *Lancet* declared: "If paracetamol was discovered today it would not be approved by the Committee on Safety of Medicines (a fore-runner of the UK NICE agency), and it would certainly never be freely available without prescription...surely the time has come to replace paracetamol with an effective analogue which cannot cause liver damage."<sup>50</sup> More than 40 years later, acetaminophen remains a top seller and likely to remain so. The search for safer alternatives seems not to be underway, perhaps because the new compound would have to be both safe and more effective to gather market share from this ubiquitous, toxic but durable product.



## References

1. Nourjah P, Ahmad SR, Karwoski C, Willy M. Estimates of acetaminophen (Paracetamol)-associated overdoses in the United States. *Pharmacoepidemiol Drug Saf* 2006;15:398-405.
2. Ostapowicz G, Fontana RJ, Schiødt FV, Larson A, Davern TJ, Han SBH, et al. Results of a prospective study of acute liver failure at 17 tertiary care centers in the United States. *Ann Intern Med* 2002;137:947-954.
3. Bernal W, Auzinger G, Dhawan A, et al. Acute liver failure. *Lancet* 2010;376:190-201.
4. <http://www.pharmacytimes.com/publications/issue/2013/July2013/Top-200-Drugs-of-2012>, accessed May 10, 2016
5. Kon K, Kim JS, Jaeschke H, Lemasters JJ. Mitochondrial permeability transition in acetaminophen-induced necrosis and apoptosis of cultured mouse hepatocytes. *Hepatology* 2004;40: 1170–1179.
6. Fujimoto K, Kumagai K, Ito K, Arakawa S, Ando Y, Oda S, et al. Sensitivity of liver injury in heterozygous Sod2 knockout mice treated with troglitazone or acetaminophen. *Toxicol Pathol* 2009;37:193–200.
7. Proudfoot AT, Wright N. Acute paracetamol poisoning. *Br Med J* 1970;3:557-8.
8. Mitchell JR, Thorgeirsson SS, Potter WZ, Jollow DJ, Keiser H. Acetaminophen-induced hepatic injury: protective role of glutathione in man and rationale for therapy. *Clin Pharmacol Therap* 1974;16:676-84.
9. Rumack BH, Peterson RC, Koch GG, Amara IA. Acetaminophen overdose. 662 cases with evaluation of oral acetylcysteine treatment. *Arch Intern Med* 1981;141:380 – 385.
10. Seeff LB, Cuccherini BA, Zimmerman HJ, Adler E, Benjamin SB. Acetaminophen toxicity in alcoholics. *Ann Intern Med* 1986;104:399-404.
11. Zimmerman HJ, Maddrey WC. Acetaminophen (paracetamol) hepatotoxicity with regular intake of alcohol: analysis of instances of therapeutic misadventure. *Hepatology* 1995;22:767-73.
12. Lee WM. Medical Progress: Acute liver failure. *N Engl J Med* 1993;329:1862-72.
13. Schiødt FV, Rochling FJ, Casey DL, Lee WM. Acetaminophen toxicity in an urban county hospital. *N Engl J Med* 1997;337:1112-17.
14. Trey C, Davidson CS. The management of fulminant hepatic failure. In: Popper H, Schaffner F, eds. *Progress in liver diseases*. New York: Grune & Stratton; 1970: 282-98.
15. Ritt DJ, Whelan G, Werner DJ, Eigenbrodt EH, Schenker S, Combes B. Acute hepatic necrosis with stupor or coma. An analysis of thirty-one patients. *Medicine*. 1969;48:151-72.
16. Rakela J, Ludwig J, Baldus WP: Fulminant Hepatitis: Mayo Clinic experience with 34 cases. *Minn Med* 1984;67:671-672.
17. Lee WM, Squires RH Jr, Nyberg SL, Doo E, Hoofnagle JH. Acute Liver Failure: Summary of a Workshop. *Hepatology* 2008;47:1401-15.
18. Schiødt FV, Atillasoy E, Shakil O, Lee WM, et al. Etiology and outcome for 295 patients with acute liver failure in the United States. *Liver Transpl Surg* 1999;5:29-34.
19. Ostapowicz GA, Fontana RJ, Schiødt FV, Larson A, Davern TJ, Han SBH, Lee WM, et al., Results of a prospective study of acute liver failure at 17 tertiary care centers in the United States. *Ann Intern Med* 2002;137:945-54.
20. Larson AM, Fontana RJ, Davern TJ, Polson J, Lalani EK, Hynan LS, Reisch JS, Shakil OA, Schiødt FV, Ostapowicz GA, Lee WM and the ALFSG. Acetaminophen-

- induced acute liver failure: Results of a United States multicenter, prospective study. *Hepatology* 2005;42:1367-72.
21. Reuben A, Tillman H, Fontana RJ, Davern T, McGuire B, Stravitz RT....Lee WM. Outcomes in adults with acute liver failure (ALF) from 1998-2013: An observational cohort study. *Ann Intern Med* 2016, Epub April 5.
  22. Remien CH, Adler FR, Waddoups L, Box TD, Sussman NL. Mathematical modeling of liver injury and dysfunction after acetaminophen overdose: Early discrimination between survival and death. *Hepatology* 2012;56:727-734.
  23. James LP. Acetaminophen: Pathology and clinical presentation of hepatotoxicity, in Kaplowitz N, Deleve LD. *Drug-Induced Liver Disease (Third Edition)* Amsterdam 2013, pp. 331-341.
  24. Tujios SR, Hynan LS, Vazquez MA, Larson AM, Seremba E, Sanders CM, Lee WM; Acute Liver Failure Study Group. Risk factors and outcomes of acute kidney injury in patients with acute liver failure. *Clin Gastroenterol Hepatol* 2015;13:352-9.
  25. Rumack BH, Matthew H. Acetaminophen poisoning and toxicity. *Pediatrics* 1975;55:871-6.
  26. Leventhal TM, Gottfried M, Hameed B, Lee WM. Acetaminophen parent compound levels are often undetectable in acute liver failure and acute liver injury due to acetaminophen: A retrospective cohort study. *Hepatology* 2015;62: Suppl.1975A.
  27. Smilkstein MJ, Bronstein AC, Linden C, Augenstein WL, Kulig KW, Rumack BH. Acetaminophen overdose: A 48-hour intravenous N-acetylcysteine treatment protocol. *Ann Emerg Med* 1991;20:1058-63.
  28. Craig DN, Bates CM, Davidson JS, Lartin KG, Hayes PC, Simpson KJ. Overdose pattern and outcome in paracetamol-induced acute severe hepatotoxicity. *Brit J Clin Pharmacol* 2011;71:273-82.
  29. Pezzia C, Sanders C, Speiser J, Welch S, Bowling A, Lee WM. Impulsivity is related to high risk behavior in acetaminophen-related acute liver failure. *Hepatology* 2013;58:Suppl 356A. Submitted.
  30. Fontana RJ, Ellerbe C, Durkalski VE, Rangnekar A, Reddy KR, Stravitz T ... Lee WM; The US Acute Liver Failure Study Group. Two-year outcomes in initial survivors with acute liver failure: Results from a prospective, multicenter study. *Liver Int* 2015;35:370-80.
  31. Randesi M, Levran O, Correa da Rosa J, Hankins J, Rule J, Kreek MJ, Lee WM. Association of variants of the stress genes arginine vasopressin and arginine vasopressin receptor 1A, with severe acetaminophen liver injury. Submitted.
  32. Davern II, TJ, James LP, Hinson JA, Polson J, Larson AM, Fontana RJ, Lalani EK, Munoz S, Shakil AO, Lee WM and the ALFSG. Measurement of serum acetaminophen-protein adducts in patients with acute liver failure. *Gastroenterology* 2006;130:687-94.
  33. Roberts DW, Lee WM, Hinson JA, Bai S, Swearingen CJ, Stravitz RT, Reuben A, Letzig L, Simpson PM, Rule J, Fontana RJ, Ganger D, Reddy KR, Fix O, James LP. Performance of the AcetaSTAT<sup>®</sup> Point of Care Assay for the detection of serum acetaminophen protein-adducts in patients with acute liver injury/failure. Submitted
  34. Khandelwal N, James LP, Sanders C, Larson AM, Lee WM, Acute Liver Failure Study Group. Unrecognized acetaminophen toxicity as a cause of indeterminate acute liver failure. *Hepatology* 2011;53:567-76
  35. Watkins PB, Kaplowitz N, Slattery JT, Colonese CR, Colucci SV, Stewart PW, Harris SC. Aminotransferase elevations in healthy adults receiving 4 grams of acetaminophen daily: a randomized controlled trial. *JAMA* 2006;29:87-93.
  36. Court MH, Freytsis M, Wang X, Peter I, Guillemette C, Hazarika S, Duan SC, Greenblatt DJ, Lee WM, and the ALFSG. The UDP-glucuronosyltransferase (UGT) 1A



- polymorphism c.2042>G (rs 8330) is associated with increased human liver acetaminophen glucuronidation, increased UGT1A Exon 5a/5b splice variant mRNA ratio, and decreased risk of unintentional acetaminophen-induced acute liver failure. J Pharmacol Exp Ther 2013;345:297-307.
37. Rumack BH Acetaminophen misconceptions. Hepatology 2004;40:10 –15.
  38. Serper M, Wolf MS, Parikh NA, Tillman H, Lee WM, Ganger DR. Risk factors, clinical presentation, and outcomes in overdose with acetaminophen alone or with combination products: Results from the Acute Liver Failure Study Group. J Clin Gastroenterol 2016;50:85-91.
  39. <http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/drugsafetyandriskmanagementadvisorycommittee/ucm171597.pdf>
  40. Larson AM. Acetaminophen hepatotoxicity. Clin Liver Dis 2007;11:525-48.
  41. Lee WM, Hynan LS, Rossaro L, Fontana RJ, Stravitz RT, Larson AM, Davern TL III, Murray NG, McCashland T, Reisch J, Robuck PR and the ALFSG. Intravenous N-acetylcysteine improves transplant-free survival in early stage non-acetaminophen acute liver failure. Gastroenterology 2009;137:856-864
  42. Stravitz RT, Kramer AH, Davern T, Shaikh AOS, Caldwell SH, Mehta RL, Blei AT, Fontana RJ, McGuire BM, Lee WM and the Acute Liver Failure Study Group. Intensive care of patients with acute liver failure: Recommendations of the Acute Liver Failure Study Group. Crit Care Med 2007;35:2498-2508.
  43. Lee WM, Jalan RV. Treatment of hyperammonemia in liver failure: A tale of two enzymes. Gastroenterology 2009;136:2048-51.
  44. Reddy KR, Ellerbe C, Schilsky M, Stravitz RT, Fontana RJ, Durkalski V, Lee WM; Acute Liver Failure Study Group. Determinants of outcome among patients with acute liver failure listed for liver transplantation in the US. Liver Transpl 2016;22:505-515.
  45. O'Grady JG, Alexander GJ, Hayllar KM, Williams R. Early indicators of prognosis in fulminant hepatic failure. Gastroenterology 1989;97:439-45.
  46. McPhail MJW, Fame H, Senvar N, Wendon JA, Bernal W. Ability of King's College Criteria and Model for End-Stage Liver Disease scores to predict mortality in patients with acute liver failure: A meta-analysis. Clin Gastro Hepatol 2016;14:516-525.
  47. Koch DG, Tillman H, Durkalski V, Lee WM, Reuben A. Development of a model to predict transplant-free survival of patients with acute liver failure. Clin Gastroenterol Hepatol 2016 E pub Apr 13
  48. Hawton K, Simkin S, Deeks J, Cooper J, Johnston A, Waters K, et al. UK Legislation on analgesic packs: before and after study of long-term effect on poisonings. BMJ 2004;329:1076-1081.
  49. <http://www.propublica.org/getinvolved/item/discussion-acetaminophen-risks-safety-measures>
  50. Editorial (Unsigned). Paracetamol Hepatotoxicity. Lancet 1975;ii:1189-90.

