Acetaminophen Dose Does Not Predict Outcome in Acetaminophen-Induced Acute Liver Failure

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DEDICATION

With gratitude to the members of my committee, the Acute Liver Failure Study Group, my family, and William M. Lee, whose support and faith in me has made all of this possible

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Blake Elizabeth Gregory

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ABSTRACT

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BLAKE ELIZABETH GREGORY

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Supervising Professor: William M. Lee, MD

Background: Acetaminophen is a dose-dependent toxin. Prognosis in severe acute liver injury is related presumably in part to the dose ingested. We sought to assess the value of acetaminophen dosing information in patients with acute liver failure due to acetaminophen toxicity to determine the role of dose as a prognostic indicator. **Methods:** Prospective data from 113 acute liver failure patients having single time point ingestions of acetaminophen were analyzed. Multivariate and chi-square tests were used to determine the relationship of dose to clinical outcome. We also used the

Mann-Whitney U test to compare prognosis and survival in ALF with acetaminophen dose ingested. **Results:** Multivariate and chi-square analysis failed to show any relationship between acetaminophen dose and spontaneous survival. A separate analysis showed no correlation between acetaminophen dose and clinical prognostic indicators. **Conclusions:** Dose of acetaminophen ingested did not seem to play a role in prognosis. The most important prognostic factor was coma grade on admission to study. Acetaminophen dosing information is not always obtainable. When it is, it adds little to the clinical assessment. Severity of encephalopathy is a more reliable indicator of prognosis in these critically ill patients.

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PRIOR PUBLICATIONS & PRESENTATIONS

Blake Gregory, William M. Lee, M.D., and the Acute Liver Failure Study Group. "Reliability of Acetaminophen (ACM) Dosing Information in ACM-Induced Acute Liver Failure." Oral Presentation, **45th Annual Medical Student Research Forum**, UT Southwestern Medical Center, 2007

Blake Gregory, Clarita Odvina, Orson Moe, Joseph Zerwekh, Khashayar Sakhaee, William M. Lee and the ALF Study Group. "Abnormal Urinary Excretion of Phosphate is Responsible for Hypophosphatemia in Acute Liver Failure." Oral Presentation, **46th Annual Medical Student Research Forum**, UT Southwestern Medical Center, 2008

Blake Gregory, Clarita Odvina, Orson Moe, Joseph Zerwekh, Khashayar Sakhaee, William M. Lee and the ALF Study Group. "Abnormal Urinary Excretion of Phosphate is Responsible for Hypophosphatemia in Acute Liver Failure." Poster Presentation, **46th Annual Medical Student Research Forum**, UT Southwestern Medical Center, 2008

Blake Gregory, William M. Lee, M.D., and the Acute Liver Failure Study Group. "Reliability of Acetaminophen Dosing Information in Acetaminophen-Induced Acute Liver Failure." Poster Presentation, **46th Annual Medical Student Research Forum**, UT Southwestern Medical Center, 2008

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LIST OF DEFINITIONS

ALF: Acute Liver Failure

ALFSG: Acute Liver Failure Study Group

ALT: Alanine Aminotransferase

AST: Aspartate Aminotransferase

INR: International Normalized Ratio

NAC: N-acetylcysteine

BMI: Body Mass Index

CYP: Cytochrome P-450 System

NAPQI: N-acetyl-p-benzoquinoneimine

CHAPTER ONE
Introduction

Chapter 1: Acute Liver Failure- Etiologies, Treatments, and Outcomes

Acute liver failure (ALF) is a rare, life-threatening condition that afflicts roughly 2,000 people annually in the United States[1]. The diagnosis of ALF requires the simultaneous presence of coagulopathy (INR greater than or equal to 1.5) and hepatic encephalopathy, defined as any alteration in mental status and graded on a coma scale of 1 to 4. To meet the diagnostic criteria for ALF, patients must also have less than 26 weeks of illness and no evidence of prior or chronic liver disease[2]. These patients are often critically ill and at high risk of multi-system organ failure and death.

The etiologies of ALF are numerous (Figure 1) and include viral hepatitis, autoimmune hepatitis, shock, metabolic disease, pregnancy, and drug toxicity (both idiosyncratic and dose-dependent). Drug-induced acute hepatic failure has been attributed to dozens of agents of many different drug classes, including anticonvulsants, antibiotics, statins, and neuroleptics[3]. The prevalence of the etiologies of ALF varies geographically, with viral hepatitis representing one of the most common causes worldwide. In the

United States and Great Britain, however, acetaminophen poisoning stands as the leading cause of ALF by a significant margin: approximately 50% of cases by many reports[4]. The relationship of acetaminophen to liver injury is dose-dependent. While doses of less than 4 grams per day generally are accepted as safe, acetaminophen has a low therapeutic index. Ingestions exceeding 8-10 grams in a 24-hour period have been associated with hepatic failure.

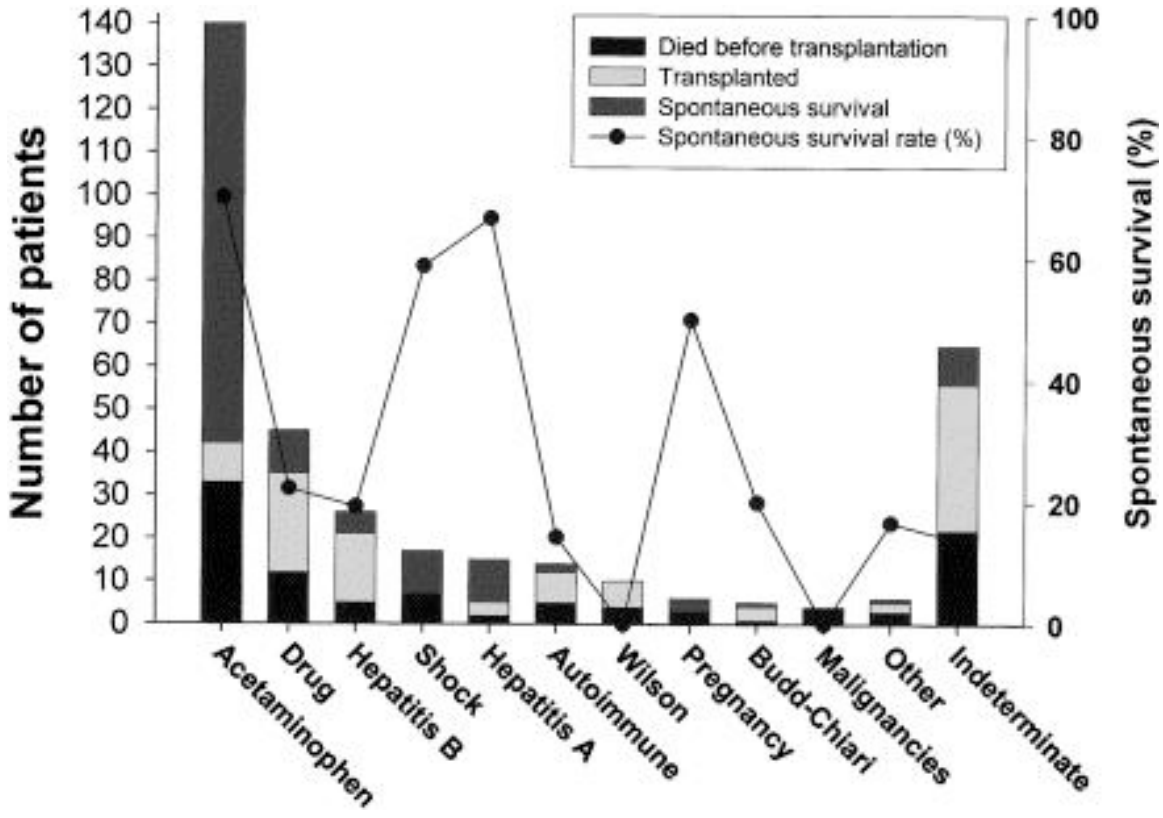

Figure 1: Etiology and outcome for 353 patients with ALF. From Schiødt FV, Lee WM. Clin Liver Dis. 2003; 7(2):331-49, vi.

There are three major pathways through which acetaminophen is metabolized in the liver. Acetaminophen undergoes glucuronidation and sulfation, producing harmless metabolites that are excreted via the kidneys[5]. An additional pathway utilizing the cytochrome P-450 (CYP) system, namely CYP2E1, metabolizes acetaminophen into N-acetyl-p-benzoquinoneimine (NAPQI). This toxic metabolite covalently attaches to hepatocyte proteins, resulting in cell death[6,7,8,9] and severe liver necrosis at sufficiently high concentrations (Figure 2). Hepatocyte injury by NAPQI is minimized by glutathione, which converts NAPQI into mercapturic acid. Mercapturic acid cannot bind to hepatocyte proteins and is excreted by the kidneys, thereby averting damage to the liver. N-acetylcysteine (NAC), an effective antidote in acetaminophen poisoning, works by repleting hepatic glutathione stores[10].

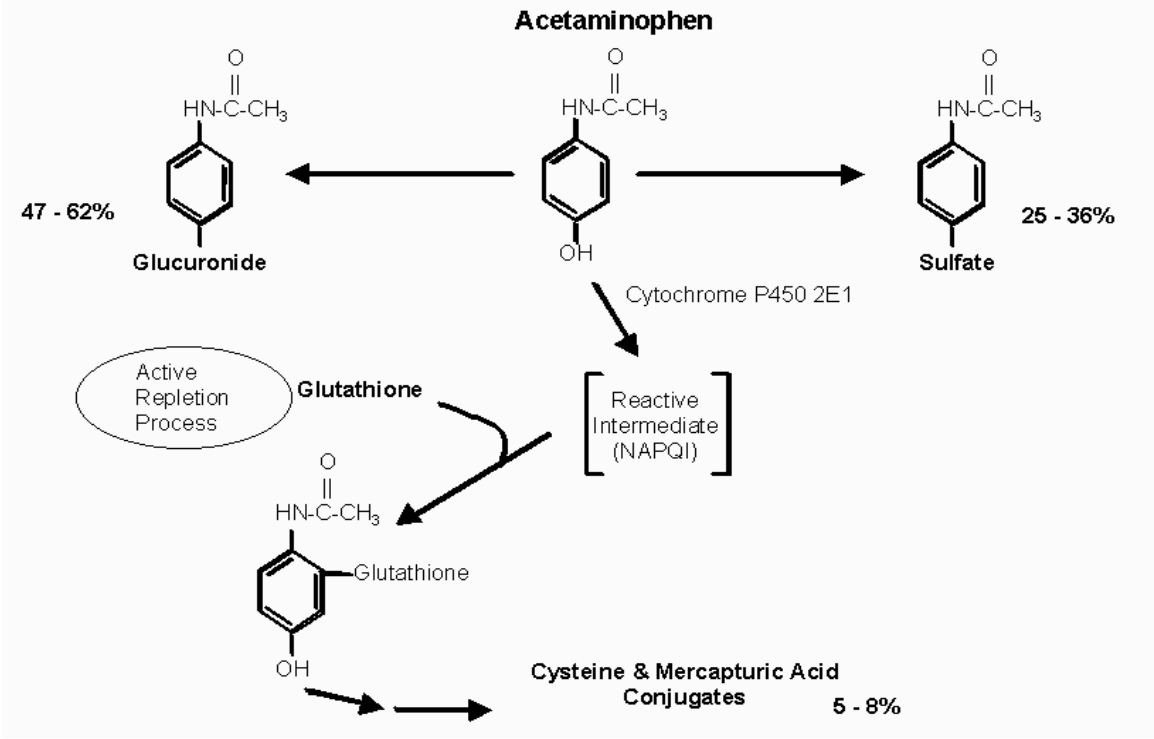

Figure 2: Metabolism of Acetaminophen (www.FDA.gov)

Treatment of acetaminophen-induced ALF involves NAC administration, supportive care, and liver transplantation if indicated. NAC has been shown to be highly successful in reducing mortality in ALF[11,12] and is considered first-line treatment. To be effective, NAC should be given as soon as possible following acetaminophen ingestion. Late administration of the antidote may also improve outcomes but this is less clear[13,14]. Supportive measures include intensive care with close monitoring of vital signs and electrolytes, antibiotic prophylaxis, raising the head of the bed 20-30 degrees, and intubation if necessary. Liver transplantation may be

required in critically ill patients with an otherwise poor prognosis. Outcomes of liver transplant can be quite successful[15] and ALF patients are often given high priority on transplant lists for this reason and because of their critical status. In order to avoid unnecessary transplants, accurately assessing prognosis in ALF patients is vitally important.

Acute liver failure carries a high mortality rate that varies depending upon etiology. The spontaneous survival rate is estimated to be 43%, with an overall survival (including transplanted patients) of 67%. Survival in acetaminophen-induced ALF is more favorable, with approximately 60% surviving without transplant and 69% surviving overall, very few requiring, or qualifying for, transplantation[16]. Despite the relatively more favorable prognosis, acetaminophen-induced acute liver failure stands as the leading cause of ALF in the United States and causes the greatest number of deaths each year. The high incidence of acute liver failure due to acetaminophen poisoning is likely related to the presence of acetaminophen in dozens of combination medications, its ready accessibility, and its public perception as a relatively harmless drug. The high mortality resulting from ingestion of this only mildly effective analgesic has led to calls for more strict regulation by the FDA. Efforts in the United Kingdom to reduce the frequency of acetaminophen poisoning have resulted in a significant decline in overdose

events[17]. Many investigators and physicians are advocating that similar measures be implemented in the United States[18]. As recently as June 2009, an FDA advisory panel voted to reduce both the maximum daily dose and the maximum single dose of over-the-counter acetaminophen and to ban (or unbundle) combination analgesics such as Vicodin and Percocet from the market[19]. Efforts at greater public awareness and stricter regulation have the potential to save lives in the future.

Information presented at the FDA Advisory Committee included a detailed review of 606 patients enrolled in the Acute Liver Failure Study Group (ALFSG) registry at UT Southwestern. This network, in operation since 1998, has sought to characterize all aspects of acute liver failure by a prospective registry approach. Patients meeting criteria are enrolled at a rate of about 150 per year from 23 study sites across the United States. The study upon which the present thesis is based draws heavily on the rich data set from the ALFSG.

CHAPTER TWO
Acetaminophen Dose in Acute Liver Failure

Introduction

Acetaminophen is a highly popular analgesic that exists in both over-the-counter and combination prescription formulations. It is estimated that 36% of Americans consume an acetaminophen-containing preparation at least once a month[20]. While it is generally safe within the recommended limit of 4 grams per day[21], doses exceeding 4 grams per day may be associated with dose-dependent hepatotoxicity and acute liver failure (ALF)[22]. Acetaminophen overdose is the leading cause of ALF in the U.S.[23,24] and the U.K.[25] and accounts for nearly half of all ALF cases annually. ALF is defined as the onset of coagulopathy and hepatic encephalopathy following less than 26 weeks of illness in patients without preexisting liver disease[26]. It carries a high mortality rate and often afflicts the young and previously healthy.

Many variables influence the extent of liver injury and prognosis in acetaminophen-induced ALF. Factors negatively impacting outcome include excessive dosing, concomitant medications, alcohol use, starvation, advanced age[7,27,28], and delay in seeking medical attention. A highly effective antidote, N-acetylcysteine (NAC)[29,30.31,32,33], protects against liver

injury if given within 12 hours of ingestion but is less effective thereafter. Of the factors listed above, the quantity of acetaminophen ingested and the time to NAC administration have been cited as the most important factors in determining prognosis. Liver transplantation is utilized in a small fraction of cases and can be lifesaving in suitable patients[34,35].

Several criteria have been developed to predict outcome in acetaminophen overdose because determining prognosis is vitally important. Unfortunately, these have relatively low sensitivity and specificity[36,37,38,39]. Multiple indicators in isolation, however, are known to affect outcome. Advanced hepatic encephalopathy (coma grades 3 or 4) is associated with poor prognosis[40] and some authors recommend that all patients with coma grade 3 or higher be considered for liver transplantation[41]. Another factor influencing prognosis is delay in receiving NAC, which has been correlated with increased hepatotoxicity. Studies by Schiodt et al[42] suggest that an interval of $\geq$ 48 hours from time of ingestion to receiving NAC resulted in hepatic injury with prolongation of acetaminophen half-life, a surrogate for impaired hepatic metabolic function.

Despite being recognized as a dose-dependent toxin, the quantity of acetaminophen ingested has never been incorporated into any prognostic criteria. Authors have stressed the unreliability of dosing information

reported by patients on admission, either due to encephalopathy, inaccurate recall, or purposeful deception of the physician[43]. Information from next of kin is even less reliable since family members are typically unaware of dosing details.

Acetaminophen dosing information might provide valuable information to clinicians managing patients with ALF. We sought to assess the reliability of acetaminophen dosing information in determining prognosis by correlating this information with patient outcomes. We selected a group of patients with acetaminophen-induced ALF who had overdosed at a single time point using the large, prospectively collected database of the U.S. Acute Liver Failure Study Group (ALFSG), which contains detailed clinical information on more than 1,400 patients. We used multivariate and chi-square analysis to determine the influence of reported acetaminophen dose on survival. We also divided patients into cohorts based on admission coma grade, time from overdose to hospital admission, outcome, and reported ingestion amounts to determine whether information on acetaminophen ingestion could help in predicting outcome.

Methods

Between January 1998 and May 2007, 527 patients with acute liver failure presumed due to acetaminophen toxicity were prospectively

identified and enrolled in the ALF study by the 22 participating tertiary care centers around the United States. All but one of these was a liver transplant center. All centers were in compliance with their local institutional review board requirements. A Certificate of Confidentiality was obtained from the National Institutes for Mental Health for the entire study. Enrollment required fulfillment of the criteria for ALF[44], defined as the presence of coagulopathy (international normalized ratio $\geq$ 1.5) and hepatic encephalopathy within 26 weeks of the development of symptoms in the absence of previous liver disease. To establish a diagnosis, a detailed history of acetaminophen ingestion was collected, including total amount taken, type of acetaminophen compound consumed, and duration of use. For the purpose of this study, 414 of the 527 patients were excluded either because the patient had ingested acetaminophen chronically rather than at a single time point (n=310) or because historical (dosing information or date of overdose, n=92) or detailed laboratory data (ALT, coma grade, or acetaminophen level, n=12) was lacking.

In the remaining 113 patients, we used multivariate analysis to determine the influence of patient-reported acetaminophen dose, sex, age, ethnicity, and admission ALT on spontaneous survival. Chi square analysis was used to identify differences in survival among patients ingesting greater

or less than/equal to 10g (n=92 and 23 patients, respectively), 20g (n=70 and 45), 30g (n=69 and 46), 40g (n=85 and 30), and 50g (n=102 and 13) of acetaminophen. We also divided our patients based on whether 48 hours had elapsed between overdose and admission, as delayed presentation has been associated with a higher likelihood of severe hepatotoxicity. Patients within these two groups were subdivided based on severity of hepatic encephalopathy on admission into either low (grade 1-2) or high grade (grade 3-4). We compared survival in low versus high coma grade patients using the Chi-square test. We also compared median acetaminophen dose in low versus high coma grade patients using the Mann-Whitney U test to determine whether there was any difference in reported dose among these groups. Possible outcomes were death or spontaneous survival (defined as survival without liver transplantation)[23]. Statistical analysis was performed using SPSS software. All analyses were two-tailed. P-value less than or equal to 0.05 was considered statistically significant.

Results

Multivariate analysis (Table 1) showed that acetaminophen dose did not predict the probability of spontaneous survival to any significant degree (p=0.146, OR=1.000). Survival was also not significantly affected by admission ALT (p=0.121, OR=1.000), gender (p=0.673, OR=1.217), age

(p=.535, OR=0.987), or ethnicity (p=.198, OR=0.285).

Table 1
Multivariate analysis comparing variables sex, age, ethnicity, acetaminophen dose, and ALT to outcome measure spontaneous survival

	β Coefficient	Standard Error	Wald Chi Square	Degree of Freedom	p-Value	Odds Ratio
Sex	0.197	0.466	0.178	1	0.673	1.217
Age	-0.013	0.020	0.385	1	0.535	0.987
Ethnicity	-1.255	0.975	1.657	1	0.198	0.285
Dose	.000	0.000	2.134	1	0.144	1.000
ALT	.000	0.000	2.402	1	0.121	1.000

Chi square analysis (Table 2) failed to identify any difference in survival among patients ingesting greater or less than 10g (p=0.605), 20g (p=0.142), 30g (p=0.150), 40g (p=0.245), or 50g (p=0.388) of acetaminophen.

Table 2
Chi-square analysis of patients divided into groups based on cutoff values of 10, 20, 30, 40, 50 g of acetaminophen and compared for differences in spontaneous survival

Acetaminophen Dose Cutoff	≤ Dose Cutoff (# of patients)	>Dose Cutoff (# of patients)	p-Value
10 g	22	91	0.605
20 g	44	69	0.142
30 g	68	45	0.150
40 g	84	29	0.245
50 g	100	13	0.388

The low and high-grade encephalopathy groups are described in Table 3. The groups were similar in demographic features and in median

acetaminophen dosing. Both low and high coma grade groups were predominantly female (p=.304) and white (p=.437). There was similarly no significant difference between the groups in median age, acetaminophen dose, and BMI.

Table 3
Demographic features of low versus high coma grade patients

	Coma Grade 1-2 (n=78)	Coma Grade 3-4 (n=35)	p-Value
Sex (female)	65%	71%	.304
Median age, years (range)	30 (17-62)	31 (18-54)	.499
Race (white)	88%	97%	.437
Median OD dose, mg (range)	27,000 (300-158,000)	25,000 (6,500-125,000)	.264
Median BMI, kg/m^2 (range)	24 (17-38)	27 (18-44)	.102

Spontaneous survival rates in coma grade 1-2 versus 3-4 are compared in Table 4. The lower coma grade group (n=78) had a much higher survival rate than the patients (n=35) comprising the higher coma grade group (83% vs. 40%, p=<0.0001).

Table 4
Spontaneous survival in all patients (n=113)

	Coma Grade 1-2	Coma Grade 3-4	p-Value
Alive (# patients)	65	14	<0.0001
Dead (# patients)	13	21	
Spontaneous survival	83%	40%	

Spontaneous survival rates in early-presenting (<48 hours) patients with coma grade 1-2 versus 3-4 are shown in Table 5. Survival in early or mild coma grade patients (83%) was significantly higher than survival in high coma grade patients (39%), with p-value less than 0.0001. Similarly, mild coma grade patients in the late presenting (≥ 48 hours) group tended to have a much more favorable survival rate (83%) than those with more advanced coma grades (42%), with p-value less than 0.0001 (Table 6).

Table 5
Spontaneous survival in early-presenting patients (n=83)

	Coma Grade 1-2	Coma Grade 3-4	p-Value
Alive (# patients)	50	9	<0.0001
Dead (# patients	10	14	
Spontaneous survival	83%	39%	

Table 6
Spontaneous survival in late-presenting patients (n=30)

	Coma Grade 1-2	Coma Grade 3-4	p-Value
Alive (# of patients)	15	5	<0.0001
Dead (# of patients	3	7	
Spontaneous survival	83%	42%	

In a separate analysis, we examined median acetaminophen dose among subgroups divided by coma grade (Table 7). There was no significant difference in dose ingested between the early-presenting low and

high coma grade patients (30,000 mg vs. 25,000 mg, p=0.461). Nor was there a difference in reported dose between the late-presenting low and high coma grade groups (24,000 mg vs. 18,750 mg, p=0.298).

Table 7
Median acetaminophen dose in patients stratified by coma grade and time of presentation.

	Coma Grade 1-2	Coma Grade 3-4	p-Value
Early Presentation: <48 hrs (range)	30,000 mg (n=60) (3,500-158,000 mg)	25,000 mg (n=23) (6,500-125,000 mg)	0.461
Late Presentation: ≥48 hrs (range)	24,000 mg (n=18) (300-75,000 mg)	18,750 mg (n=12) (6,500-65,000 mg)	0.298

Discussion

We sought to correlate acetaminophen ingestion data with outcome using multiple analytic approaches. Our multivariate analysis suggested that none of the variables surveyed (sex, age, ethnicity, dose, admission ALT) significantly influenced outcome. Thus, increasing acetaminophen dose did not appear to affect mortality in this set of patients. This finding could result from inherent inaccuracy in this subjectively reported data or from a "threshold" or plateau effect, in which acetaminophen doses above a certain amount do not result in worse liver injury. The possibility of a plateau effect of acetaminophen toxicity is supported by our analysis of serial

acetaminophen doses. Assessing differences in survival among doses greater and less than 10, 20, 30, 40, and 50 g of acetaminophen revealed no distinct "cutoff" dose above which mortality was clearly greater.

In a separate analysis, we attempted to correlate outcome in acetaminophen overdose with anticipated prognosis based on admission coma grade. Coma grade repeatedly has been shown to correlate with survival in ALF patients[14], and this was also borne out by our data (Tables 4-6). Regardless of whether they presented early or late, patients with grade 3-4 encephalopathy had much lower spontaneous survival rates than patients with grade 1-2. If dose were both accurate and an independent outcome determinant, we would expect to find higher doses reported in patients with higher coma grade.

Although time from overdose to administration of NAC has previously been suggested to influence the degree of hepatic injury, we could not demonstrate a difference in survival for early- versus late-presenting patients with the same initial coma grade (Tables 5 and 6). The reasons for this result are unclear, but may be related to genotypic differences in acetaminophen metabolism[45,46] or the fact that most patients surpassing the threshold of acute liver failure fall into the 'severe' category. Nevertheless, these data suggest that coma grade remains a stronger

determinant of survival than dose of acetaminophen ingested or time to presentation.

After dividing patients into subcategories based on prognosis, we calculated the median acetaminophen dose reported by patients in each group. Mild hepatic encephalopathy would be predicted to result in a better prognosis, while grade 3-4 would indicate a worse prognosis, and this assumption was supported by the differences in survival observed. Provided that acetaminophen dosing information is accurate, we presumed that higher doses of acetaminophen would be associated with a poorer prognosis. However, our analysis revealed no significant difference in reported acetaminophen dose between the prognostic groups (Table 7). In other words, patients with a better prognosis (i.e., lower grade of encephalopathy) did not report ingesting lower quantities of acetaminophen. Indeed, both of the coma grade 1-2 subgroups reported taking higher median doses of acetaminophen than their grade 3-4 counterparts, although this difference was not significant.

These results suggest either that the acetaminophen dosing information obtained is inaccurate or that the quantity of acetaminophen ingested is not, in and of itself, a consistent predictor of outcome. Although acetaminophen is unarguably hepatotoxic in a dose-dependent fashion,

reported dose does not appear to correspond directly to mortality. The poor correlation between dose and outcome may be related to the multi-factorial nature of acetaminophen metabolism, which varies from patient to patient and is influenced by genetic factors, co-ingested substances, and alcohol use. We also cannot rule out the possibility of a plateau phenomenon in the setting of massive acetaminophen overdose. The hepatotoxic effects of acetaminophen may not be linear when doses are so high and liver injury so extensive. Interestingly, admission ALT levels also did not seem to predict survival. This may be because liver injury in acetaminophen-induced ALF is massive and ALT levels tend to be orders of magnitude outside of the range of normal. Differences in ALT may not be meaningful in the setting of such extensive damage. Another possibility is that mortality is not related to degree of liver injury but to the complications thereof. Indeed, secondary complications such as infection or bleeding have been closely linked to outcome in acute liver failure[47].

Our study had several limitations. We were unable to obtain dosing information in a large percentage of patients enrolled by the ALF Study Group. In addition, data regarding time from overdose to admission was similarly difficult to collect. This was likely related to the complexity and severity of illness in this patient group: patients may be encephalophathic on

first medical contact and often unaware of when they consumed the drug. Our data failed to reproduce a correlation between increasing age and mortality found by previous authors[17]. It should be kept in mind, however, that our dataset includes only patients who overdosed at a single time point, often an attempt at suicide. Our patients tended to be younger on average than patients in other studies and in many cases were considerably less than 40 years of age. Thus, the results of prior studies may not pertain to our patient set.

Acetaminophen dosing information, taken in isolation, is an unreliable predictor of survival in ALF patients. Our data suggests that other factors alone or in combination affect prognosis more strongly than the acetaminophen dose itself. Groups of patients ingesting similar amounts of acetaminophen appear to experience different outcomes depending on the degree of encephalopathy on admission. Thus, patients presenting with massive overdoses of acetaminophen (40 or 50 g) do not necessarily have a grim prognosis, but more importantly, patients with relatively smaller ingestions (10 or 20 g) may experience rapidly fatal deterioration if life-saving measures are not anticipated. Clinicians should consider reported acetaminophen dose in the context of the patient's overall clinical picture with particular attention to mental status when predicting prognosis in ALF.

CHAPTER THREE
Conclusions and Recommendations

Conclusions

The results of our analysis suggest that reported acetaminophen dose does not predict survival in acetaminophen-induced ALF. Possible reasons for this include inaccurate reporting versus a plateau effect of toxicity following massive liver injury. In addition, ALT, gender, age, and ethnicity do not appear to impact survival in this population of single time-point overdoses. Dividing patients into cohorts based on time of ingestion also did not correlate with survival and late presenters fared no worse than early presenters in our analysis. The prognostic marker that most consistently predicted outcome both in our study and prior publications was admission coma grade. Patients with low coma grade on admission were far more likely to survive regardless of time of overdose and quantity of acetaminophen ingested.

Recommendations

We conclude that reported acetaminophen dose should not be used in isolation to assess prognosis in acetaminophen-induced ALF. Relying solely on dose ingested could be misleading, particularly in the case of a patient consuming a relatively low dose. Mortality was not significantly different in low versus high doses and clinicians should not be lulled into a false sense of security because a patient only ingested 10 grams of acetaminophen. Rather, dosing information should be considered in the broader context of the patient's overall clinical status. Admission coma grade, in particular, should be emphasized and may be the single best predictor of outcome.

Several laboratory tests now in development may prove useful in the future for determining prognosis. An assay measuring acetaminophen-protein adducts has been developed recently at the University of Arkansas in collaboration with the ALF Study Group[48,49]. These adducts appear to be the 'smoking gun:' the acetaminophen moiety is covalently bound to cell proteins that are released into the blood during hepatocyte lysis and thus are present in the blood stream long after the parent compound has been metabolized. Adduct levels correlate nicely with the degree of hepatic injury as measured by aspartate aminotransferase levels in patients who have

overdosed on acetaminophen at a single time-point[50]. Interestingly, investigators in the above study found no correlation between adduct levels and reported acetaminophen dose, suggesting (much as we have shown) that severity of liver injury does not correspond directly to acetaminophen dose. No studies to date have examined the relationship of adduct levels to spontaneous survival and thus their role in assessing prognosis has yet to be elucidated.

Until a more accurate predictor of outcome can be identified, clinicians should evaluate the overall status of the patient when assessing prognosis, with particular attention to coma grade. Close monitoring of mental status and vital signs appears to be more a reliable indicator of outcome than reported acetaminophen dose.

BIBLIOGRAPHY

[1] Lee WM. Medical progress: acute liver failure. N Engl J Med 1993;329:1862 – 72.

[2] O'Grady JG, Schalm SW, Williams R. Acute liver failure: redefining the syndromes. Lancet 1993;342:273 – 5.

[3] Schiødt FV, Lee WM. Fulminant liver disease. Clin Liver Dis. 2003 May;7(2):331-49, vi.

[4] Makin AJ, Williams R. Acetaminophen-induced acute liver failure. In: Lee WM, Williams R, editors. Acute liver failure. Cambridge: Cambridge University Press; 1997. p. 32-42.

[5] Vale JA, Proudfoot AT. Paracetamol (acetaminophen) poisoning. Lancet 1995;346:547-52.

[6] Jollow DJ, Mitchell JR, Potter WZ, Davis DC, Gillette JR, Brodie BB. Acetaminophen-
induced hepatic necrosis. II. Role of covalent binding in vivo. J Pharmacol Exp Ther 1973; 187:195 – 202.

[7] Mitchell JR, Jollow DJ, Potter WZ, Davis DC, Gillette JR, Brodie BB. Acetaminophen-induced hepatic necrosis. I. Role of drug metabolism. J Pharmacol Exp Ther 1973;187:185 – 94.

[8] Potter WZ, Davis DC, Mitchell JR, Jollow DJ, Gillette JR, Brodie BB.

Acetaminophen-induced hepatic necrosis. 3. Cytochrome P-450-mediated binding in vitro. J Pharmacol Exp Ther 1973; 187:203 – 10.

[9] Nelson SD. Molecular mechanisms of the hepatotoxicity caused by acetaminophen. Sem Liver Dis 1990;10:267 – 78.

[10] Burgunder JM, Varriale A, Lauterburg BH. Effect of N-acetylcysteine on plasma cysteine and glutathione following paracetamol administration. Eur J Clin Pharmacol 1989;36:127 – 31.

[11] Smilkstein MJ, Knapp GL, Kulig KW, Rumack BH. Efficacy of oral N-acetylcysteine in the treatment of acetaminophen overdose. N Engl J Med 1988;319:1557 – 62.

[12] Smilkstein MJ, Bronstein AC, Linden C, Augentein WL, Kulig KW, Rumack BH. Acetaminophen overdose: a 48-hour intravenous N-acetylcysteine treatment protocol. Ann Emerg Med 1991;20:1058 – 63.

[13] Harrison PM, Keays R, Bray GP, Alexander GJM, Williams R. Improved outcome of para- cetamol-induced fulminant hepatic failure by late administration of acetylcysteine. Lancet 1990; 335:1572 – 3.

[14] Harrison PM, Wendon JA, Gimson AES, Alexander GJM, Williams R. Improvement by acetylcysteine of hemodynamics and oxygen transport in fulminant hepatic failure. N Engl J Med 1991;324:1852 – 7.

[15] Schafer DF, Shaw BW. Fulminant hepatic failure and orthotopic liver

transplantation. Sem Liver Dis 1989;9:189 – 94.

[16] Lee WM. Acetaminophen-related acute liver failure in the United States. Hepatology Research 2008; 38 (Suppl. 1): S3–S8.

[17] Sheen C, Dillon J, Bateman D et al. Paracetamol pack size restriction: the impact on paracetamol poisoning and over-the-counter supply of paracetamol, aspirin and ibuprofen. Pharmacoepidemiol Drug Saf 2002; 11: 329–31.

[18] Lee WM. Acetaminophen hepatotoxicity: Changing perceptions of a social/medical issue. Hepatology 2007;46:966-70.

[19] http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DrugSafetyandRiskManagementAdvisoryCommittee/UCM170188.pdf

[20] US Department of Health and Human Services (DHHS). Third National Health and Nutrition Examination Survey, 1988-1994, NHANES III Second Laboratory Data File. (CD-ROM, Series 11, No 2A). Hyattsville, MD: Centers for Disease Control and Prevention, 1998.

[21] 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;296:87-93.

[22] Lee WM. Drug-induced hepatotoxicity. N Engl J Med 1995;333:1118-1127.

[23] Schiodt FV, Atillasoy E, Shakil AO, Schiff ER, Caldwell C, Kowdley KV, Stribling R, Crippin JS, Flamm S, Somberg KA, Rosen H, McCashland TM, Hay JE, Lee WM. Etiology and outcome for 295 patients with acute liver failure in the United States. Liver Transpl Surg 1999;5:29-34.

[24] Ostapowicz G, Fontana RJ, Schiodt FV, Larson A, Davern TJ, Han SH, McCashland TM, Shakil AO, Hay JE, Hynan L, Crippin JS, Blei AT, Samueal G, Reisch H, Lee WM. 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.

[25] Bernal W. Changing patterns of causation and the use of transplantation in the United Kingdom. Semin Liver Dis 2003;23:227–237.

[26] O'Grady JG. Acute liver failure. Postgrad Med J. 2005 Mar;81(953):148-54.

[27] Schiødt FV, Lee WM, Bondesen S, Ott P, Christensen E. Influence of acute and chronic alcohol intake on the clinical course and outcome in acetaminophen overdose. Aliment Pharmacol Ther 2002;16:707-715.

[28] Van Thiel DH, Stauber R, Gavaler JS, Francavilla A. Hepatic regeneration. Effects of age, sex hormone status, prolactin, and cyclosporine. Dig Dis Sci 1991;36:1309-1312.

[29] Lee WM. Drug-induced hepatotoxicity. N Engl J Med 2003;349:474-85.

[30] Prescott LF, Illingworth RN, Critchley JAJH, Stewart MJ, Adam RD, Proudfoot AT. Intravenous N-acetylcysteine: the treatment of choice for paracetamol poisoning. BMJ 1979;2:1097-100.

[31] Douglas AP, Hamlyn AN, James O. Controlled trial of cysteamine in treatment of acute paracetamol (acetaminophen) poisoning. Lancet 1976;1:111-115.

[32] Prescott LF, Sutherland GR, Park J, Smith IJ, Proudfoot AT. Cysteamine, methionine and penicillamine in the treatment of paracetamol poisoning. Lancet 1976;2:109-113.

[33] Keays R, Harrison PM, Wendon JA, Forbes A, Gove C, Alexander GJ, etal. A prospective controlled trial of intravenous N-acetylcysteine in paracetamol- induced fulminant hepatic failure. BMJ 1991;303:1024-1029.

[34] Pauwels A, Mostefa-Kara N, Florent C, Lévy VG. Emergency liver transplantation for acute liver failure. Evaluation of London and Clichy criteria. J Hepatol 1993;17:124-127.

[35] Schiødt FV, Bondesen S, Tygstrup N, Christensen E. Prediction of hepatic encephalopathy in paracetamol overdose: a prospective and validated study. Scand J Gastroenterol. 1999;34:723-8.

[36] Donaldson BW, Gopinath R, Wanless IR, Phillips MJ, Cameron R, Roberts EA, Greig PD, Levy G, Blendis LM. The role of transjugular liver biopsy in fulminant hepatic failure: relation to other prognostic indicators. Hepatology 1993;18:1370-74.

[37] Lake J, Sussman N. Determining prognosis in patients with fulminant hepatic failure: when you absolutely, positively have to know the answer. Hepatology 1995;21:879-882.

[38] Shakil AO, Kramer D, Mazariegos GV, Fung JJ, Rakela J. Acute liver failure: clinical features, outcome analysis, and applicability of prognostic criteria. Liver Transpl 2000;6:163-169.

[39] Mitchell I, Bihari D, Chang R, Wendon J, Williams R. Earlier identification of patients at risk from acetaminophen-induced acute liver failure. Crit Care Med 1998;26:279-284.

[40] Takahashi Y, Kumada H, Shimuzu M, Tanikawa K, Kuma-shiro R, Omata M, Ehata T, Ukida M, Yasunaga M, Okita K, Sato S, Takeuchi T, Tsukada K, Obata H, Hashimoto E, Ohta Y, Tada K, Kosaka Y, Takase K, Yoshiba M, Sekiyama K, Kano T, Mizoguchi Y. A multicenter study on the

prognosis of fulminant viral hepatitis: early prediction for liver transplantation. Hepatology 1994; 19:1065-71.

[41] Anand AC, Nightingale P, Neuberger JM. Early indicators of prognosis in fulminant hepatic failure: an assessment of the King's criteria. J Hepatol. 1997; 26:62-8.

[42] Schiødt FV, Ott P, Christensen E, Bondesen S. The value of plasma acetaminophen half-life in antidote-treated acetaminophen overdosage. Clin Pharmacol Ther. 2002;71:221-5.

[43] Larson AM, et al. Acetaminophen-induced acute liver failure: results of a United States multicenter, prospective study. Hepatology 2005;42:1364-72.

[44] Polson J, Lee WM. AASLD position paper: the management of acute liver failure. Hepatology 2005;41:1179-97.

[45] Court MH, Duan SX, Von Moltke LL, Greenblatt DJ, Patten CJ, Miners JO, Mackenzie PI. Interindividual variability in acetaminophen glucuronidation by human liver microsomes: identification of relevant acetaminophen UDP glucuronosyltransferase isoforms. J Pharmacol Exp Ther 2001;299:998-1006.

[46] Ueshima et al. Acetaminophen metabolism in patients with different cytochrome P4502E1 genotypes. Alcohol Clin Exp Res 1996;20(Suppl 1) 25A-28A

[47] Vaquero J, Polson J, Chung C, Helenowski I, Schiodt FV, Reisch J, Lee WM, Blei AT and the Acute Liver Failure Study Group. Infection and the progression to deep hepatic encephalopathy in early fulminant hepatic failure. Gastroenterology 2003;125:755-764.

[48] 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.

[49] James LP, Alonso EM, Hynan LS, Hinson JA, Davern TJ, Lee WM, Squires RH and the Pediatric Acute Liver Failure Study Group. Detection of acetaminophen-protein adducts in children with acute liver failure of indeterminate cause. Pediatrics 2006;118:676-681.

[50] James LP, Letzig L, Simpson PM, Capparelli E, Roberts DW, Hinson JA, Davern TJ, Lee WM. Pharmacokinetics of acetaminophen-protein adducts in adults with acetaminophen overdose and acute liver failure. Drug Metab Dispos. 2009;37:1779-84.

VITAE

Blake was born in Dallas, TX in 1981. She graduated from the Hockaday School *cum laude* in 2000. Seeking a classical liberal arts education, she pursued her undergraduate studies at St. John's College in Annapolis, MD, where she earned her BA in Philosophy and History of Math and Science in 2004. She enrolled at the University of Texas at Arlington shortly after graduating to fulfill her science pre-requisites in preparation for medical school. During this time, she also taught organic chemistry and began working with William M. Lee, MD in acute liver failure research at UT Southwestern Medical Center. She continued to work with him after matriculating at UT Southwestern medical school in 2006. Her projects included an analysis of acetaminophen dosing information and the possible role of phosphatonins in acute liver failure. These projects both resulted in poster and oral presentations at the UTSW Medical Student Research Forum and a poster presentation on phosphate wasting at the AASLD national meeting in San Diego, California. Blake will graduate with a Doctor of Medicine degree from UT Southwestern Medical Center in June 2010. She plans to pursue a career in Internal Medicine.