

## Reply:

We thank Drs. Cholongitas, Holubek, and colleagues for their interest in our work. Drs. Holubek et al. express concern about the potential inclusion of subjects with acute viral hepatitis (A, B, or C) or a concomitant idiosyncratic drug reaction. Obtaining an accurate medication history can be difficult; however, all medical records were carefully reviewed and the patient, their caregivers, and their providers were interviewed. Our prior publication demonstrated that occult HBV infection was not present in any patients with indeterminate ALF or other identifiable causes of ALF.<sup>1</sup> Included subjects all had negative serologies. Overall, 27 subjects were excluded from the analysis for the following reasons: insufficient data (10), possible ischemic hepatitis (5), polysubstance abuse (3), concomitant acute hepatitis A virus infection (2), recent isoflurane anesthesia (2), concomitant acute herpes simplex virus infection (1) or acute hepatitis B virus infection (1), concomitant isoniazid use (1), metastatic cancer (1), and non-acetaminophen ALF (1). In addition, all of the included acetaminophen overdose cases had a clinical phenotype consistent with severe acetaminophen hepatotoxicity. Therefore, we feel that all of the cases included in our study and the conclusions reached are valid and accurate. Lastly, we have demonstrated that presence of acetaminophen-cysteine protein adducts in the blood may be a sensitive and specific biomarker for acetaminophen-induced ALF and provide a confirmatory, objective laboratory test in cases of diagnostic uncertainty (Davern, et al.<sup>2</sup>).

The data provided by Cholongitas et al. are consistent with our findings. Table 1 shows the comparison of 3 prognostic models using our dataset. The King's criteria did not predict clinical outcomes well in our population. Dr. O'Grady's editorial suggests this is because of the common use of prophylactic fresh frozen plasma (FFP) in the United States. Use of prophylactic FFP is not common in U.S. transplant/specialty centers, and we discourage its use except for active bleeding or for invasive procedures (e.g., intracranial monitor placement). About 80% of subjects in the study were transferred from other institutions, and 54% had received FFP prior to transfer. In those who did not receive FFP, the likelihood ratio of the Kings' criteria for predicting death/need for transplant

was 5.3 (sensitivity 32%, specificity 94%), compared to 2.3 (sensitivity 23%, specificity 90%) for those who had received FFP. Therefore, use of FFP prior to enrollment only modestly compromised the prognostic utility of the King's criteria.

In our dataset, as well as that of Cholongitas et al., prognosis was best predicted by presence of multi-organ failure rather than the disease-specific King's criteria. We did not include arterial lactate collection in the protocol when the study was started in 1998, but have subsequently begun collecting these new data. A new prognostic score including readily available laboratory tests such as arterial lactate, serum phosphate, alpha-fetoprotein, and/or Gc Globulin levels in addition to the Kings criteria or other multi-organ failure indices may prove worthwhile.<sup>3-5</sup> In the interim, efforts at reducing the increasing incidence of unintentional acetaminophen related ALF in the United States are needed to prevent future cases of this potentially life-threatening but avoidable illness.

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**Table 1. Comparison of Sensitivity, Specificity, Positive and Negative Predictive Values of Three Prognostic Systems**

	Area Under ROC Curve	Sensitivity (%)	Specificity (%)	PPV	NPV	Percent Correct	Likelihood Ratio
Kings (≥ 1)	0.602	26	92	0.63	0.69	68	3.06
MELD (≥ 35)	0.733	61	71	0.54	0.76	67	2.08
APACHE II (≥ 20)	0.840	68	87	0.77	0.81	80	5.27

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Potential conflict of interest. Nothing to report.

## Intermittent Disconjugate Gaze: A Novel Finding in Nonalcoholic Steatohepatitis

We read with interest the letter by Al-Osaimi et al.<sup>1</sup> Several points deserve clarification. The authors describe a motility disorder characterized by fluctuating exotropia that is "not typically present at all times." Mitochondrial myopathies are characterized by a progressive, non-fluctuating ophthalmoplegia.<sup>2, 3</sup> Furthermore, the ophthalmoplegia in mitochondrial dysfunction is usually

fairly conjugate. That is, it has approximately equal amounts of misalignment in different fields of gaze. Additionally, isolated weakness of the bilateral medial rectus muscles has not to our knowledge been described in patients with mitochondrial disorders affecting the extraocular muscles. The motility disorder as described in Fig. 1<sup>1</sup> could represent bilateral internuclear ophthal-