

Overview

- Acetaminophen overdose can result in fatal fulminant hepatic failure
- The Decision to Transplant Difficult
 - Psychosocial issues
 - Potentially survivable
 - Rapid progression of the illness
 - Multisystem organ dysfunction



Transplant Criteria

■ King's College Criteria

- Ph < 7.30 @ 24 hrs after fluid correction
or the combination
- Prothrombin time > 100 sec (INR 6.5)
- Encephalopathy = grade 3/4
- Creatinine > 300 $\mu\text{mol/l}$ (3.4 mg/dl)



Kings Performance

- Sensitivity 69% (55 – 100%)
- Specificity 92% (43 – 100%)
- +LR 12.33 and –LR 0.29

Bailey et al. Crit Care Med 2003, 31:1



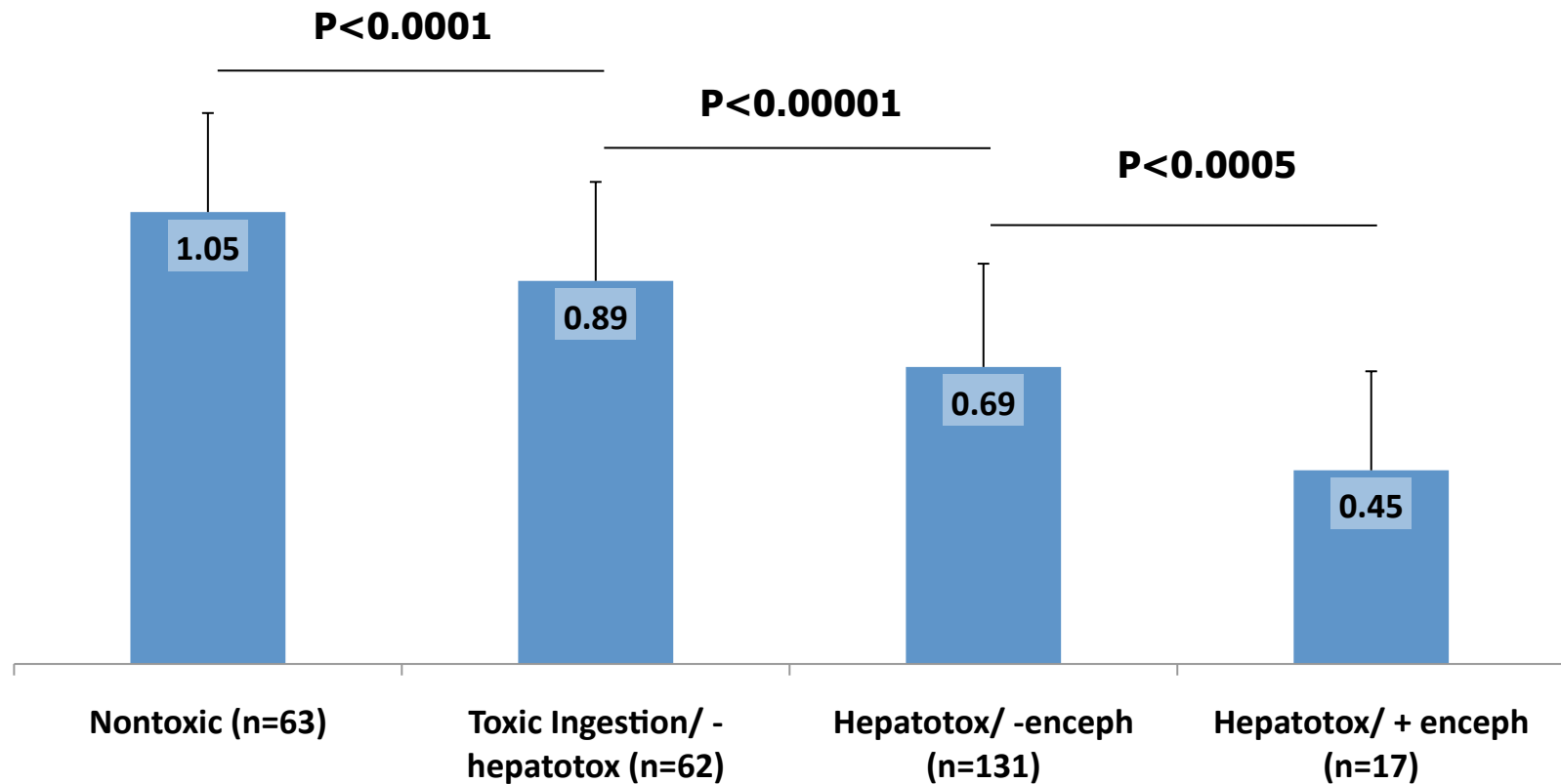
PO₄ and Liver Failure

- Hypophosphatemia reported in cases of acute liver from Acetaminophen
- The degree of hypophosphatemia correlated with severity

Dawson DJ et al. BMJ, 295:21, 1987
Jones et al. The Lancet, 2:8663, 1989



Mean minimum serum PO₄ conc (mmol/l) in with acetaminophen ingestions



Adapted from Jones et al. The Lancet, 2:8663, 1989

Serum Phosphate Is an Early Predictor of Outcome in Severe Acetaminophen-Induced Hepatotoxicity

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Hypophosphatemia is frequently observed in acetaminophen-induced hepatotoxicity and may be involved in the pathogenesis of hepatic failure. The aim of the study was to evaluate the prognostic value of serial measurements of serum phosphate in patients with severe acetaminophen poisoning. Prospectively, serial measurements of serum phosphate were performed in 125 patients with severe acetaminophen poisoning. The optimum threshold value of serum phosphate to discriminate nonsurvivors was identified. Prognostic value and speed of identification were compared with those of the King's College Hospital (KCH) criteria. Phosphate concentrations were significantly higher in nonsurvivors than in survivors at 48 to 72 hours after overdose (mean 2.65 ± 1.18 mmol/L vs. 0.68 ± 0.22 mmol/L, $P < .001$) as well as 72 to 96 hours after overdose (2.12 ± 0.22 mmol/L vs. 0.59 ± 0.23 mmol/L, $P < .001$). A threshold phosphate concentration of 1.2 mmol/L at 48 to 96 hours after overdose had sensitivity 89%, specificity 100%, accuracy 98%, positive predictive value 100%, and negative predictive value 98%. The phosphate criteria had higher sensitivity, accuracy, and positive and negative predictive values than the KCH criteria, and it identified patients significantly earlier after transferral [median 1 hour (range 1-38 hours) vs. 12 hours (2-192 hours), $P < .05$, respectively]. In nonsurvivors, the degree of hyperphosphatemia correlated with renal dysfunction ($R = .55$; $P = .02$). In conclusion, hyperphosphatemia after acetaminophen overdose is seen exclusively in nonsurvivors, which makes it a highly specific as well as sensitive predictor of nonsurvival. We propose that hyperphosphatemia is caused by renal dysfunction in the absence of hepatic regeneration, as the latter appears to be associated with lowering of serum phosphate. (HEMATOLOGY 2002;36:659-665.)



Study Design

- Prospective Observational Study
 - 1999 - 2000
- Patients transferred to Liver center with concern for APAP-induced hepatotoxicity
- All patients given NAC
- Daily phosphate levels
- Daily metabolic panel
- Daily INR



Results

Baseline Demographics (n=125)

Median age	35 (range 13 – 79)
Female	84 (67%)
Median quantity APAP ingested	35 g (interquartile range 22-50g)
Time to NAC	23 hrs (Interquartile range 14-42 hr)



Outcomes

- Severe hepatotoxicity
 - ALT > 1000
- Encephalopathy
 - Grade II or III
- Liver Transplant
- Death



Outcomes cont.

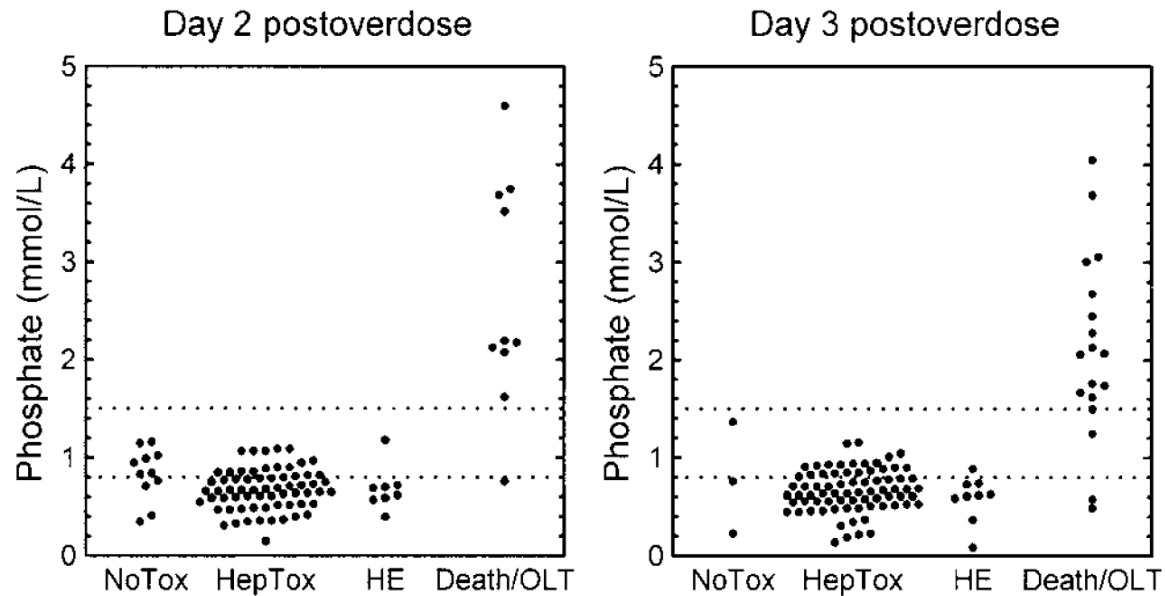


Fig. 1. Phosphate concentrations on days 2 and 3 for patients without severe hepatotoxicity (NoTox), with severe hepatotoxicity without hepatic encephalopathy (HepTox), with hepatic encephalopathy and spontaneous survival (HE), and without spontaneous survival (Death/OLT). **Dotted lines** depict normal range.

From Schmidt and Dalhoff, *Hepatology*, 36:3, 2002.



Table 1. Levels of Serum Phosphate, INR, Creatinine, and pH for Different Groupings of Patients With Severe Acetaminophen-Induced Hepatotoxicity

	Patients With Hepatotoxicity		Patients With HE	
	Non-HE	HE	Survival	Death/OLT
Day 2				
Serum phosphate (mmol/L)	0.67 ± 0.21	1.78 ± 1.33*	0.68 ± 0.22	2.65 ± 1.18†
INR	3.10 ± 1.29	5.20 ± 1.96†	4.28 ± 1.69	5.77 ± 1.96
Creatinine (μmol/L)	97 ± 61	196 ± 92†	156 ± 74	222 ± 96
Day 3				
Serum phosphate (mmol/L)	0.67 ± 0.22	1.61 ± 1.07†	0.59 ± 0.23	2.12 ± 0.95†
INR	2.23 ± 0.96	4.49 ± 1.80†	4.13 ± 2.02	4.67 ± 1.72
Creatinine (μmol/L)	114 ± 87	246 ± 126†	182 ± 61	279 ± 138
After fluid resuscitation				
pH	7.44 ± 0.08	7.27 ± 0.18†	7.36 ± 0.12	7.26 ± 0.19

NOTE. Values are given as mean ± SD.

Abbreviations: HE, hepatic encephalopathy; INR, international normalized ratio; OLT, orthotopic liver transplantation.

**P* < .05.

†*P* < .001 (Mann-Whitney).



From Schmidt and Dalhoff, *Hepatology*, 36:3, 2002.

Phosphate as a predictor of outcome

- ROC curves Day 2 and 3 for Phosphate and nonsurvival
 - Serum PO₄ level = 1.2 mmol/L

Table 2. Assessment of Serum Phosphate Measurement and King's College Hospital (KCH) Criteria as Prognostic Indicators in 106 Patients With Severe Acetaminophen-Induced Hepatotoxicity

Indicator	n	Died	Sensitivity	Specificity	PPV	NPV	Accuracy	Time (h)*
Phosphate criteria								
>1.2 mmol/L on day 2 (n = 83)	9	9	90	100	100	99	99	6 (1-38)
>1.2 mmol/L on day 3 (n = 101)	16	16	89	100	100	98	98	10 (1-62)
Either phosphate criterion	16	16	89	100	100	98	98	1 (1-38)†
KCH criteria	15	12	67	97	80	93	92	12 (2-192)
KCH or either phosphate criterion	20	17	94	97	85	99	96	4 (1-79)†

Abbreviations: PPV, positive predictive value; NPV, negative predictive value.

*Median (range) time from transferal to the department of hepatology to the criteria being fulfilled.

† $P < .05$ in comparison with KCH criteria (Mann-Whitney).



From Schmidt and Dalhoff, *Hepatology*, 36:3, 2002.

Authors Conclusions

- Hyperphosphatemia after APAP overdose seen only in non-survivors
- Serum PO₄ level > 1.2 mmol/l better predictor of survival than KCH
- Hypophosphatemia associated with survival
- Hyperphosphatemia caused by renal failure



Letters to the Editor and further work

- Bernal et al. *Hepatology*, 38:2, 2003
 - Provide data showing PO4 not better than KCH
- Go et al. *Hepatology*, 38:2, 2003
 - Provides data showing PO4 worse performance than KCH
- Ng and Bathgate, *Liver Transplantation*, 10:1, 2004
 - Provide data showing PO4 not reliable indicator of survival



Conclusion

■ For LLSA

- Serum PO4 > 1.2 mmol/l on day 2 or 3 after APAP overdose associated with non-survival
- PO4 better predictor than KCH
- Hyperphosphatemia secondary to Renal failure
- Hypophosphatemia associated with Liver toxicity recovery

■ For the Real world

- An elevated PO4 is associated with poor outcome but does not add anything to already established predictor models.







