Reviewer's report

Title: Predictors for Delayed Encephalopathy following Acute Carbon Monoxide Poisoning

Version: 2 Date: 25 June 2013

Reviewer: Eric Lavonas

Reviewer's report:

My recommendation for the decision is revise/resubmit (major compulsory revisions).

Overall, I think this is a useful investigation into an important topic. The question of prognosis in CO poisoning drives recommendations about therapy. In particular, if one could define a priori a group of patients who are at LOW risk of lasting neurological sequelae, this group could be spared the risk/expense of transfer to a facility with hyperbaric capabilities.

I think the authors are on the right track, and their contribution will be more useful with a few changes to the manuscript.

Major suggestions:

Describe chart review methods. There is no definitive checklist for this (there really should be!), so I usually use the criteria in Gilbert EH et al., Ann Emerg Med 1996; 27(3):305-8.

Define your outcome of interest (DNS) as precisely as possible. It is not clear to me from the writing whether the Global Assessment Scale was used as a predictive variable, part of the outcome definition (used to diagnose DNS), or both. Of course it cannot be both.

Perform a multivariate analysis. The authors report that abnormal initial head CT, increased circulating levels of CK, CK-MB, and LDH levels, and low GAS scores, but it is unlikely that these are all independent predictors.

Report clearly the time from onset of poisoning (or initial presentation to care) that each predictive or outcome measure was assessed.

Once you have derived a predictive rule (high risk of DNS, low risk of DNS, or both), apply it to an independent population (validation data set) and report rule performance. If this is not possible, then state clearly that your analysis is hypothesis-generating and independent confirmation is necessary.

On page 4, second complete paragraph: The analysis by Hopkins et. al. Am J Resp Crit Care Medicine 2007; 176(1): 1001-6 examines both clinical factors and genetic factors (APO-E genotype) that correlate with neurological sequelae 6 weeks following CO poisoning. This is, I think, the closest previously-published
manuscript to the current study and warrants inclusion in the discussion.

Additional, less critical suggestions:

Background:

In general, I would shorten the background section. Those portions that place the results of the current investigation into context are better located in the discussion section.

You accept the premise that HBO therapy decreases the proportion/severity of DSN following CO poisoning, but this remains controversial worldwide. Three of the four articles cited are reviews articles. Please at least acknowledge the controversy and contradictory results of various clinical trials. The Cochrane review by Buckley et al (last revised 2011) is a good place to start.

In the third paragraph, I think the authors are conflating different concepts. CO poisoning exposure can be acute or chronic (in many but not all chronic poisoning cases, the exposure is intermittent). The outcome of this exposure can be recovery (without sequelae) or neurologic sequelae. Neurologic sequelae can develop at the time of poisoning and not go away (persistent neurologic sequelae) or can develop after a delay (delayed neurologic sequelae). Many authors postulate a different mechanism for persistent and delayed neurologic sequelae (ischemia and triggered apoptosis, respectively).

Methods: In the first sentence of the methods section (abstract and manuscript), I find it very helpful when authors state the study type and population. e.g.: This is a retrospective cohort study of 79 consecutive patients treated at a single institution for CO poisoning.

Results: Rather than report p = 0.000, report p < 0.001.

Because age has previously been described as a risk factor for poor outcome, it would be helpful (probably in Table 1) to report the number/proportion of patients in each 10-year age group (20 - 29 years, 30 - 39 years, etc.)

It appears that transfer from an outside institution is a significant risk factor for poor outcome. Consider adding this to the multivariate model (if appropriate), or performing a subgroup analysis excluding the transfer patients.

Discussion: Under patient's background and circumstances (third complete paragraph on page 7), you discuss place of exposure in more specific categories than you collected in your study. In general, I would avoid either introducing new results in the discussion section or expanding beyond your results.

On page 8, first complete paragraph: The commonly repeated statements about COHgb levels and symptoms have been roundly disproven (see Hampson et al, Undersea Hyperb Med 2012; 39(2):657-65). Close examination of the Weaver trial results (2002) corroborates these observations.

I hope you find these suggestions to be helpful. I think that the search for
predictive criteria for neurological sequelae from CO poisoning (and particularly a validated predictive rule for LOW risk) is extremely important, and I am glad for your contribution to the field.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

No financial or non-financial competing interests.

In the interest of full disclosure: I am co-author on the ACEP Clinical Policy (2008) and senior author of the Cochrane review (2011) of the role of hyperbaric oxygen in CO poisoning. Both reviews concluded that the extant evidence is insufficient to establish HBO2 as the standard of care. The manuscript under consideration is about prognosis, not therapy, and I do not see this as an intellectual competing interest.