Is Human Albumin Solution really the best fluid for advanced cirrhosis patients?

Dear Sirs,

We read with interest the revised consensus recommendations for management of acute kidney injury (AKI)) in cirrhosis by the International Club of Ascites.¹ We are concerned that plasma volume expansion only with albumin is recommended for stage 2 and 3 AKI and do not believe that this represents a balanced view of the available evidence. No one doubts that fluid resuscitation is an integral part of the management of AKI; however, studies to date have not established class 1 evidence for an advantage of the use of albumin over other colloids or crystalloids.

It can be argued that albumin may represent a superior fluid resuscitation agent in cirrhotic patients. Certainly a recent meta-analysis has confirmed the superiority of albumin compared with artificial plasma expanders for large volume paracentesis.² Albumin is also recommended for spontaneous bacterial peritonitis supported by a meta-analysis of four randomised controlled trials (RCTs) including 288 patients that demonstrated that albumin infusion prevented renal impairment and reduced mortality.³ However, only 10 patients in the control arm in these trials received any fluid at all. Indeed these patients received hydroxyethyl starch, which has been withdrawn from clinical use as it can cause renal failure.

Conversely, the intensive care unit (ICU) literature on fluid resuscitation has shown equivalence of albumin versus n/saline in several large-scale appropriately powered clinical RCTs that included patients with cirrhosis (although one excluded those with ascites). A subsequent meta-analysis supported these outcomes in patients with sepsis.⁴

Furthermore, albumin treatment is not without potential harm. In a recent study using albumin, Thévenot *et al* ⁵ found that pulmonary oedema developed in 8/96 (8.3%) patients in the albumin group, two of whom died; although a previous study had shown benefit. No mention is made in these AKI guidelines about monitoring treatment response, for example, using haemodynamic parameters or blood sampling for lactate or mixed venous oxygen saturation. Theoretically, there is also a risk of transmission of prion protein diseases. Furthermore, in the UK the cost of albumin is up to five times the cost of crystalloids.

Finally, widespread uptake of these guidelines, which the authors admit are not based on evidence, may actually harm the chance of establishing a better evidence base for albumin with current RCTs in progress (eg, ATTIRE and INFECIR2¹). Therefore, we believe that the clinical practice guidelines should include volume expansion with crystalloid or colloid until there has been conclusive clinical trial evidence to provide class I evidence.

Alastair O'Brien, and Louise China on behalf of the ATTIRE Trial Management Committee

+Author Affiliations: University College London, London, UK

Dr Alastair O'Brien, University College London, Rayne Institute, 5 University Street, London WC1E 6BT, UK; rmhaajo@ucl.ac.uk

A. O'Brien and Louise China, UCL on behalf of the ATTIRE Trial Management Committee (E.Forrest, Glasgow Royal Infirmary; S.Ryder, University of Nottingham; Gavin Wright, Basildon University Hospital; Jim Portal, Bristol University Hospital; James O'Beirne, Royal Free Hospital)

Collaborators ATTIRE Trial Management Committee: E. Forrest, Glasgow Royal Infirmary Hospital; S. Ryder, Nottingham University NHS Trust; G. Wright, Basildon and Thurrock University Hospitals NHS Foundation Trust; J. Portal, University Hospitals Bristol NHS Foundation Trust; J. O'Beirne, Royal Free Hospital NHS Foundation Trust, London; Z. Shabir, UCL Comprehensive Clinical Trials Unit (CCTU); S. Skene UCL CCTU; T. Chandler UCL CCTU; J. Garcia-Hernandez, UCL CCTU; James Blackstone UCL CCTU.

Contributors AOB: first draft and review. LC: drafting and review. ATTIRE Trial Management Committee: discussion and reviewed.

Funding Wellcome Trust (164699), Department of Health (164699).

Competing interests None declared.

Provenance and peer review Not commissioned; internally peer reviewed.

ATTIRE: Albumin to prevent infection in chronic liver failure is an NIHR portfolio-adopted study funded by The Wellcome Trust and Department of Health under the Health Innovation Challenge Fund (<u>http://public.ukcrn.org.uk/search/StudyDetail.aspx?StudyID=18450</u>).

INFECIR: The INFECIR2 Albumin Prevention Study is funded by the European Association for the Study of Liver Disease Chronic Liver Failure Consortium.

References

- Angeli P, Gines P, Wong F, Bernardi M, Boyer TD, Gerbes A, Moreau R, Jalan R, Sarin SK, Piano S, Moore K, Lee SS, Durand F, Salerno F, Caraceni P, Kim WR, Arroyo V, Garcia-Tsao G; International Club of Ascites. Diagnosis and management of acute kidney injury in patients with cirrhosis: revised consensus recommendations of the International Club of Ascites Gut. 2015 Apr;64(4):531-7. .
- 2. Bernardi, M., Caraceni, P., Navickis, R.J. & Wilkes, M.M. Albumin infusion in patients undergoing large-volume paracentesis: a meta-analysis of randomized trials. *Hepatology* **55**, 1172-1181 (2012).
- 3. Salerno F, Navickis RJ, Wilkes MM. Albumin infusion improves outcomes of patients with spontaneous bacterial peritonitis: a meta-analysis of randomized trials. Clin Gastroenterol Hepatol. 2013;11:123–30.
- 4. Patel, A., Laffan, M.A., Waheed, U. & Brett, S.J. Randomised trials of human albumin for adults with sepsis: systematic review and meta-analysis with trial sequential analysis of all-cause mortality. *Bmj* 349, g4561 (2014).
- 5. Thevenot, T., *et al.* Effect of albumin in cirrhotic patients with infection other than spontaneous bacterial peritonitis. A randomized trial. *Journal of hepatology* **62**, 822-830 (2015).