**FLUIDS IN CIRRHOSIS STUDY: A Prospective evaluation of fluid management in cirrhotic patients admitted to ICU**

***Short title:***

FLIC: Fluids in Cirrhosis Study

**Protocol Version 1.2, date: 2nd November, 2014**

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**FLUIDS IN CIRRHOSIS STUDY: A Prospective evaluation of fluid management in cirrhotic patients admitted to ICU**

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FLIC: Fluids in Cirrhosis Study

**Protocol Version 1.2, date: 6th May, 2013**

1. **Lay summary**

Patients with advanced chronic liver disease frequently develop marked circulatory and fluid balance abnormalities and a high risk of death despite therapeutic interventions. It is commonly recommended to administer large volumes of albumin based, sodium deplete colloid to cirrhotic patients admitted to the ICU for management of hypotension with or without associated renal dysfunction2. Such recommendations are based upon the premise that a vasodilated systemic circulation contributes to a maldistributed fluid state, which is a key factor driving the circulatory and end-organ abnormalities. At the present time there are potential benefits and problems associated with both a fluid liberal and a fluid restricted approach to managing patients admitted to ICU with decompensated cirrhosis and the ideal approach remains uncertain. In response, this study aims to evaluate the feasibility, safety and efficacy of two different fluid administration strategies in the management of patients with cirrhosis complicated by hypotension admitted to the intensive care unit. Forty patients will be enrolled with 20 patients allocated to a ‘Liberal intravenous fluid’ approach and 20 patinets allocated to a ‘Restrictive intravenous fluid’ approach. The primary outcome measures include changes in fluid balance and changes in serum creatinine and renal biomarkers. We believe such assessment will allow us to understand more clearly whether the approach to fluid administration in patients with cirrhosis who are admitted to the intensive care correlates with clinical condition and outcome of the patient.

1. **Background**

Patients with advanced chronic liver disease frequently develop marked circulatory and fluid balance abnormalities. These typically involve a hyperdynamic vasodilated systemic circulation, portal hypertension, avid salt and water retention, accumulation of ascites and diminished renal function. Cirrhotic patients are at risk of many complications associated with these problems and frequently require admission to intensive care for the management of refractory exacerbations. Additionally, severe hypotension may occur (with or without clear evidence for serious infection) and necessitate circulatory support to prevent or attenuate further end-organ dysfunction. Renal failure is one of the most worrying and difficult to manage complications of advanced cirrhosis, however, the optimal treatment approach remains unclear. Despite critical care interventions, the prognosis is often poor1.

It is commonly recommended to administer large volumes of albumin based, sodium deplete colloid to cirrhotic patients admitted to the ICU for management of hypotension with or without associated renal dysfunction2. Such recommendations are based upon the premise that a vasodilated systemic circulation contributes to a maldistributed fluid state, which is a key factor driving the circulatory and end-organ abnormalities. Giving large amounts of fluid may mitigate a subsequent need for vasopressor therapy. While it is likely that absolute or relative hypovolaemia would contribute to exacerbating these problems, two issues of concern suggest that the liberal administration of fluid alone (or with minimal vasopressor therapy) may be undesirable. Firstly, it is apparent to experienced clinicians that many cirrhotic patients respond poorly to fluid therapy in this setting, with little improvements in measured haemodynamic parameters or markers of end-organ function3. Secondly, there are growing concerns that the administration of large volumes of fluid in critically ill patients may contribute to morbidity through a range of deleterious processes such as oedema formation, electrolyte abnormalities and respiratory complications4,5. Patients with advanced cirrhosis and generalised inflammatory states may be at increased risk of these complications.

Current guidelines for management of critically ill cirrhotic patients who are hypotensive (especially associated with renal dysfunction) consistently recommend a combination of albumin based colloid administration along with vasopressor therapy 6-9 (terlipressin and noradrenaline have been shown to have similar efficacy10). Amongst remaining areas of uncertainty is the optimal amount of fluid to be administered in order to safely and effectively reverse circulatory and end-organ dysfunction. Fluid management in patients with advanced cirrhosis is especially challenging due to low serum protein levels, fluid sequestration, abnormal hormonal regulation of salt and water handling, generalised vasodilatation, bleeding tendency and renal dysfunction. It is important to study different approaches to fluid treatment in these patients in order to better inform future management strategies.

Critical Care echocardiography is an emerging standard of care within the ICU and allows trained clinicians to non-invasively evaluate the cardiovascular system and its responses to disease and treatment. Patients with advances cirrhosis often manifest abnormal circulatory responses when critically ill and these may be studied using this technique. Of particular interest would be whether the different haemodynamic strategies lead to differing changes in diastolic function and left atrial pressures. A better understanding of such findings may assist in the guidance of therapy in the future.

Current laboratory tests (such as serum creatinine and blood urea) can only assess whether a patient may already have acute kidney injury; often, the patient has progressed to moderate to severe renal failure before the test results confirm the diagnosis. NephroCheck® is a new point of care technology that detects the presence of insulin-like growth-factor binding protein 7 (IGFBP7) and tissue inhibitor of metalloproteinases (TIMP-2) in the urine, which are associated with acute kidney injury. Within 20 minutes, the test provides a score based on the amount of the proteins present that correlates to the patient’s risk of developing renal injury within 12 hours of the test being performed. No other tests currently on the market are United States Food and Drug Administration-approved or cleared to assess the risk of developing renal failure in at-risk patients

The test is a point-of-care fluorescence immunoassay performed using the Astute 140 Meter. To carry out the test the user inserts a NephroCheck® Test Cartridge into an Astute 140 Meter. The meter converts fluorescent signals for the individual immunoassays into concentrations and then combines them into a single numerical test result.

As outlined above, there are potential benefits and problems associated with both a fluid liberal and a fluid restricted approach to managing patients admitted to ICU with decompensated cirrhosis and the ideal approach remains uncertain. A need for further research evaluating the balance between fluid and vasopressor therapy in patients with chronic liver disease has been identified11. This study aims to evaluate the feasibility, safety and efficacy of two different fluid administration strategies in the management of patients with cirrhosis complicated by hypotension admitted to the intensive care unit.

**Rationale**

Given the above observations, there are potential benefits and problems associated with both a fluid liberal and a fluid restricted approach to managing patients admitted to ICU with decompensated cirrhosis and the ideal approach remains uncertain. A need for further research evaluating the balance between fluid and vasopressor therapy in patients with chronic liver disease has been identified11. This study aims to evaluate the feasibility, safety and efficacy of two different fluid administration strategies in the management of patients with cirrhosis complicated by hypotension admitted to the intensive care unit. The research will evaluate physiological parameters, pathology results, echocardiographic findings and clinical outcomes to better determine potential differences between the two approaches.

**Hypothesis**

That a restrictive approach to fluid therapy in cirrhotic patients admitted to ICU achieves a lower cumulative fluid balance and similar outcomes compared to a liberal fluid therapy strategy.

1. **Method**

*Study Design*

This is a single centre, prospective, feasibility randomised controlled study.

*Patient eligibility*

Patients will be eligible for this study if they meet all of the inclusion criteria and none of the exclusion criteria listed below.

*Inclusion criteria:*

1. Adults (>18 years) admitted to ICU with decompensated cirrhosis
2. Hypotension (Mean Arterial Pressure (MAP) <65mmHg)
3. Clinical need for of a Central Venous Catheter (CVC) and arterial line (capable of cardiac output measurement (e.g. PiCCO or FloTrac)

*Exclusion criteria:*

1. Fulminant Hepatic Failure
2. Oliguria requiring frusemide administration via a continuous infusion prior to or immediately on admission to ICU
3. Renal failure requiring renal replacement therapy prior to or immediately on admission to ICU
4. Diagnosis of Acute Respiratory Distress Syndrome (ARDS)
   * New, bilateral pulmonary infiltrates evident on chest X-Ray
   * Absence of clinical evidence for, or measured findings of left atrial hypertension
   * PaO2:FiO2 ratio of <200
5. Severe pre-existing cardiopulmonary disease, e.g.;
   * NYHA class III or IV heart failure
   * Pulmonary hypertension
6. Admission to ICU for severe bleeding (e.g. oesophageal varices complicated by haemorrhage)
7. Requirement for total parenteral nutrition (TPN)

*Sample size*

We plan to recruit 40 patients, with 20 patients been allocated to each study arm.

*Randomization procedure*

Randomization will be by means of sealed envelopes with permuted blocks of variable size. Each envelope will contain a study arm allocation with the ‘restrictive’ or ‘liberal’ intravenous fluid administration group.

*Blinding*

The study intervention will necessarily be applied in an unblinded fashion. However, laboratory staff analysing blood samples will be blinded to the allocation arm. Evaluation of outcome will also be blinded to treatment allocation.

*Study Procedures*

Patients will be randomised to one of two groups: a ‘Restrictive intravenous (IV) fluid’ group of a ‘Liberal intravenous (IV) fluid’ group. The protocol for each will last for the duration of the patient’s admission to the intensive care unit to a maximum of four days, after which fluid and haemodynamic management will revert back to the preferred strategy of the treating intensive care specialist.

If the patient is allocated to the ‘**Liberal IV’** fluid group the following management applies:

1. Circulatory aims
   1. Central venous pressure (CVP) ≥ 12mmHg
   2. Mean arterial pressure (MAP) ≥ 65mmHg
   3. After the second day in the ICU, patients are to have ≤ 2000ml total daily positive fluid balance.
2. Management
   1. If CVP < 8mmHg, administer 500ml bolus of 4% albumin regardless of MAP (unless contra-indicated by clinical status e.g. severe pulmonary oedema)
   2. If MAP <65 mmHg and CVP <12 mmHg, administer 500ml bolus of 4% albumin
   3. If MAP< 65 and CVP ≥12 mmHg, titrate noradrenaline infusion via central venous catheter to achieve MAP ≥65mmHg
   4. Administer 100ml of 20% albumin twice daily, unless;
      1. Total net fluid balance is ≥8000ml over two consecutive days
      2. Serum albumin ≥35 g/L
      3. Further albumin or fluid administration is contra-indicated (e.g. patient has pulmonary oedema)
3. Fluid management in the intensive care unit
   1. If there is a demonstrable clinical need to modify the fluid regimen then such clinical considerations over-ride the study protocol. That is, more or less fluid of any type can be used if that is what is believed by the treating clinician to be in the patient’s best interests.

If the patient is allocated to the ‘**Restrictive IV’** fluid group the following management applies:

1. Circulatory aims
   1. Central venous pressure (CVP) ≥ 6mmHg
   2. Mean arterial pressure (MAP) ≥ 65mmHg
   3. Cardiac index ≥2.5
   4. Even fluid net daily fluid balance from after the second day in ICU
2. Management
   1. If CVP < 6mmHg, administer 500ml bolus of 4% albumin
   2. If MAP ≥ 65mmHg and CI ≥ 2.5, administer no fluid except for enteral nutritional and intravenous replacement of measured/estimated losses
   3. If MAP < 65mmHg and CI < 2.5, administer 500ml bolus of 4% albumin
   4. If MAP < 65 mmHg and CI ≥ 2.5, titrate noradrenaline infusion rate to achieve MAP ≥65mmHg.
      1. If noradrenaline infusion rate > 30 mcg/minute (or > 0.4 mcg/kg/min), give 500ml of 4% albumin and manage in accordance with clinician preference.
3. Fluid management in the intensive care unit
   1. If there is a demonstrable clinical need to modify the fluid regimen then such clinical considerations over-ride the study protocol. That is, more or less fluid of any type can be used if that is what is believed by the treating clinician to be in the patient’s best interests.

All participating patients will undergo a brief echocardiography assessment;

1. at enrolment,
2. after 48 hours of protolised management,
3. prior to discharge from ICU.

The transthoracic echocardiography (TTE) studies are non-invasive and pose no risks to participants. The TTE requires patients to lie supine or tilted across to their left side. A small amount of ultrasound gel is applied to the skin and a probe is placed upon the chest wall for image acquisition. The time of each study is ten minutes or less. All TTEs will be performed by a trained investigator (AH) and images and reports will be securely stored on the ICU echocardiography reporting system.

*Data collection and outcomes*

For all patients, the following variables will be collected:

* Patients characteristics
  + Demographics (gender, data of birth, admission date, admission diagnosis, APAHCE II & III score)
* Primary outcomes
  + Change in serum creatinine
  + Change NephroCheck® test score
  + Change in creatinine and NephroCheck® test score after adjustment for dilutional effect of fluid loading
  + Fluid balance/weight
  + Use of diuretics (mean daily dose)
  + Acute Kidney Injury – RIFLE I (GFR decrease of >50% or doubling of serum creatinine)
  + Need for renal replacement therapy (RRT)
  + Echocardiographic measurements of cardiac performance;
    - ESV, EDV, and EF
    - PW Doppler of mitral valve flow (E, A, and E:A)
    - Tissue Doppler of mitral valve annulus (E’, A’, and E’:A”)
    - Calculate E:E’ (an index of left atrial pressure)
* Secondary outcomes
  + Need for vasoactive infusions (does, type and duration)
  + Time on respiratory support (including mechanical ventilation)
  + Extravascular lung water index (when available)
  + Peak serum lactate level
  + ICU and hospital length of stay
  + ICU and hospital mortality
  + Mean daily fluid balance
* Feasibility outcomes
  + Separation in fluid administration between the two study groups
  + Distribution of values for primary and secondary outcome measures
  + Randomised / screen patients ratio
  + Consent rate
  + Data completion rate
  + Loss to follow-up rate
  + Recruitment duration

*Data analysis*

This is a feasibility and safety trial comparing two approaches to fluid administration in patients admitted to with decompensated cirrhosis. The primary efficacy measure difference is in differences between net fluid administration and in serum creatinine and NephroCheck® test score. Outcomes will be compared after log transformation where appropriate. Comparisons will be made using t-test and ANOVA for repeated-measures or Wilcoxon rank-signed test and Kruskall-Wallis according to the underlying distribution for continuous data and Chi-square for categorical data. A Kaplan-Meier curve with log-rank test will be performed to further compare in-hospital mortality and rate of discharge home. Logistic regression analysis will also be performed to adjust for baseline imbalances.

1. **Ethical considerations**

*Ethical Issues*

Patients who will be eligible for this study are critically ill with impaired hepatic function. Immediately after admission to the intensive care unit and the commencement of therapeutic interventions the administration and documentation of fluids is routinely performed. As described in the background and aim to this study, evaluating the approach to fluid management for patients with cirrhosis is important, thus the decision about which fluid approach (restrictive or liberal) needs to be made urgently.

As a consequence [because of the immediacy of the situation and the urgent need to make a decision about allocation to treatment group] it is proposed to enrol patients in the study without prior informed consent [see paragraphs 4.4.13 and 4.4.14, National Statement on Ethical Conduct in Human Research, at **http://www.nhmrc.gov.au/\_files\_nhmrc/file/publications/synopses/e72-jul09.pdf.**

Consent procedures will be established by the Austin Health Human Research Ethics Committee. Delayed consent will be obtained from the patient proxy, as per and if permitted by local regulations and as approved by local ethics committee, as soon as possible. The participant will be informed about the study as soon as possible and consent obtained for ongoing participation and use of data.

This proposed method of enrolling patients in the study without prior informed consent has been successfully applied in the Austin Hospital ICU associated with the “Sedation practice in intensive care in Australia and New Zealand: A prospective, randomised, controlled pilot trial” [protocol ANZIC-RC/Y5002] (Austin Health REU number – SERP RH HREC/11/Austin/5 – H2011/04247) & the Therapeutic hypercapnia after cardiac arrest: a pilot feasibility and safety randomised controlled trial (H2012/04737).

*Information and consent documents*

Participant and Person Responsible information sheets and consent forms have been developed based on Austin Health Human Research Ethics Committee requirements and state regulatory requirements. Please see attached participant and person responsible information sheets and consent forms.

1. **Patient safety, privacy and confidentiality**

*Confidentiality of patient data*

Participants will not be identified by name, and confidentiality of information in medical records will be preserved. All patients’ details will be entered in coded format. The confidentiality of the participant will be maintained unless disclosure is required by law or other regulations.

*Data safety management committee*

This is a single-centre investigator initiated study. There is no independent Data and Safety Monitoring Committee (DSMC) associated with the conduct of this study.

*Adverse events*

Adverse events (AEs) are defined as any untoward medical occurrence in a patient or clinical investigation subject administered an investigational intervention and which does not necessarily have to have a causal relationship with this treatment (adapted from the Note for Guidance on Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (CPMP/ICH/377/95 July 2000).

It is recognised that the intensive care patient population will experience a number of common aberrations in laboratory values, signs and symptoms due to the severity of the underlying disease and the impact of standard therapies. These will not necessarily constitute an adverse event unless they require significant intervention or are considered to be of concern in the investigator’s clinical judgment.

*Serious adverse events*

SAEs are defined in accordance with the Note for Guidance on Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (CPMP/ICH/377/95) (July 2000) as any untoward medical occurrence that:

* Results in death
* Is life-threatening
* Requires inpatient hospitalisation or prolongation of existing hospitalisation
* Results in persistent or significant disability/incapacity
* Is a congenial anomaly/birth defect
* Is an important medical event which may require intervention to prevent one of the previously listed outcomes

The treating medical specialists of each participant will be aware of their enrolment and study allocation. During their stay within the ICU, each participant will be closely monitored and regularly assessed as per usual critical care management of sick patients with complex medical problems. The treating physicians and investigators will liaise closely with regard to any issue that may constitute a potential study related adverse event.

1. **Retention, storage, destruction and publication of data**

*Data handling*

The case report form (CRF) will be developed by the members of the investigator team as a paper CRF. All data will be collected by members of the investigator team as described in the CRFs from the source data. Information recorded in the CRF should accurately reflect the subject’s medical/ hospital notes and must be completed as soon as it is made available.

The intent of this process is to improve the quality of the clinical study by providing prompt feedback to the Investigators on the progress of the data submitted and to enhance the ability to collect early safety information in a more timely fashion to fully comply with the intent of GCP requirements. Completed CRFs will be stored within the ICU Research Office, Department of Intensive Care, Austin Hospital.

*Data storage*

The data used will be stored electronically in password protected computers located within the ICU Research Office of Austin Health. Paper data and study related documents used in this study will be re-identified and only a master log will be maintained to identify participants and their study data. The log will be locked in a protected office. All data for this audit will be retained for a period of seven years after which all electronic and paper data will be destroyed in accordance with hospital policy in place at the time.

We intend to use the collected information related to this study for quality improvement activities within the Department of Intensive Care, Austin Hospital. If the combination of the collected data and information derived from this study provides useful clinical insights into the management of critically ill patients we plan to publish our findings.

*Data retention, storage and destruction*

The data used will be stored electronically in password protected computers located within the ICU Research Office of Austin Health. Paper data and study related documents used in this study will be re-identified and only a master log will be maintained to identify participants and their study data. The log will be locked in a protected office. All data for this audit will be retained for a period of seven years after which all electronic and paper data will be destroyed in accordance with hospital policy in place at the time.

*Authorship/publication*

It is expected that findings will be disseminated via publication in peer reviewed journal in the critical care literature. Study findings will also be presented at regional, national and international intensive care conferences. Authorship will be determined by the Investigational team with reference to the International Committee of Medical Journal Editors guidelines. Only aggregated de-identified patient data will be presented or published.

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