Study Protocol

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Albumin versus balanced crystalloid for resuscitation in the treatment of sepsis: A protocol for a randomised controlled feasibility study, "ABC-Sepsis"

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Abstract

Background: Patients presenting with suspected sepsis to secondary care often require fluid resuscitation to correct hypovolaemia and/or septic shock. Existing evidence signals, but does not demonstrate, a benefit for regimes including albumin over balanced crystalloid alone. However, interventions may be started too late, missing a critical resuscitation window.
Methods: ABC Sepsis is a currently recruiting randomised controlled feasibility trial comparing 5% human albumin solution (HAS) with balanced crystalloid for fluid resuscitation in patients with suspected sepsis. This multicentre trial is recruiting adult patients within 12 hours of presentation to secondary care with suspected community acquired sepsis, with a National Early Warning Score ≥5, who require intravenous fluid resuscitation. Participants are randomised to 5% HAS or balanced crystalloid as the sole resuscitation fluid for the first 6 hours.
Objectives: Primary objectives are feasibility of recruitment to the study and 30-day mortality between groups. Secondary objectives include in-hospital and 90-day mortality, adherence to trial protocol, quality of life measurement and secondary care costs.
Discussion: This trial aims to determine the feasibility of conducting a trial to address the current uncertainty around optimal fluid resuscitation of patients with suspected sepsis. Understanding the feasibility of delivering a definitive study will be dependent on how the study team are able to negotiate clinician choice, Emergency Department pressures and participant acceptability, as well as whether any clinical signal of benefit is detected.

Keywords

Sepsis, albumin/HAS, crystalloid, resuscitation, fluid, protocol, feasibility, emergency department/medicine

Executive summary

Objectives

1. Feasibility of recruiting adults with community acquired sepsis presenting to secondary care
2. Establish the comparative effectiveness of 5% Human Albumin Solution compared with balanced crystalloid as intravenous infusions for the early resuscitation in suspected community acquired sepsis

Design & Setting

Multi-centre, open label, randomised controlled feasibility trial recruiting from Emergency Departments (EDs), medical

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admission units, and surgical admission units within UK NHS hospitals.

Target population & sample size

Adults, on presentation to secondary care, with suspected sepsis and a National Early Warning Score (NEWS) ≥5, requiring intravenous fluid resuscitation. 300 participants across all sites in a 1:1 randomisation strategy.

Inclusion criteria

Clinically suspected or proven infection is the most likely reason for acute presentation; NEWS/NEWS2 score ≥5; Hospital presentation within last 12 hrs; Clinician decision has been made that immediate (within 1 hour) intravenous fluid resuscitation is needed; Ability to obtain informed consent.

Exclusion criteria >1 litre of intravenous crystalloid or any intravenous HAS administered prior to eligibility assessment; Requiring immediate surgery; Chronic renal replacement therapy; Allergy to HAS; Contraindications to balanced crystalloid; Adverse reaction to, or refusal of, blood products; End of life care; Previous recruitment in the trial; Known recent severe traumatic brain injury; Permanent incapacity; Participation in interventional phase of another CTIMP study within the last 30 days.

Interventions

Participants will be randomised, on a 1:1 basis stratified by age (<70 or ≥70) and lactate (<2 or ≥2 mmol/L), to HAS or balanced crystalloid as their sole intravenous resuscitation fluid for the first 6 hours. Fluid administration as directed by the treating clinician, and all other treatment as standard of care.

Outcome measures

Primary outcomes: Recruitment rate from screening logs; 30-day mortality.

Secondary outcomes: In-hospital mortality and 90-day mortality; time to start intervention; data completeness; study withdrawal; volume of fluid administered in each arm in first 6 and 24 hours; proportion of patients needing critical care interventions (including vasopressors, renal replacement therapy and invasive ventilation); proportion of patients who receive any other fluid apart from that assigned at randomisation (i.e. crossover); proportion of patients admitted to critical care; length of stay in critical care and in hospital; proportion of patients readmitted in 90 days after discharge; proportion of patients developing acute kidney injury, pulmonary oedema, and allergy or anaphylaxis; health related quality of life scores using EQ-5D-5L; secondary care costs at 30 days.

Follow up: Outcomes assessed using medical notes at 30 and 90 days. First 50 participants recruited will be followed up about their quality of life (EQ-5D-5L) for 180 days.

Trial registration

Clinicaltrials.gov reference: NCT04540094

Main text

Background

Sepsis is a common presentation to the emergency department (ED) resulting in significant morbidity and mortality.[1] It has been most recently defined as "life-threatening organ dysfunction caused by a dysregulated host response to infection.[2]

Hypotension occurring in the context of sepsis is common and often multifactorial. Inappropriate vasodilatation and increased vascular permeability may coexist with hypovolaemia due to increased losses from the gastrointestinal tract, pyrexia, and reduced oral intake. Septicaemia sees breakdown of the endothelial glycocalyx which can potentially lead to septic shock. Intravenous fluid therapy in the ED is a cornerstone of resuscitation: increasing circulating volume to maintain a mean arterial pressure and end-organ perfusion.

Fluid choice

Intravenous fluid therapy is divided between crystalloid or colloid. Crystalloid fluids are either unbalanced (e.g. "normal" saline) or balanced (e.g. Hartmann's, Plasmalyte). Theoretically, balanced crystalloid solutions have better buffering capacity, reduce chloride load and cause less renal artery vasoconstriction compared to unbalanced solutions,[3] although trials have demonstrated mixed results. A recent, well powered trial (PLUS) failed to demonstrate a difference in mortality.[4] Meta-analysis has suggested a reduced 90-day mortality for critically unwell patients receiving balanced crystalloid compared with saline (relative risk (RR) of 0.96 (95% confidence interval (CI) 0.92–1.01)) which is also found in a sepsis subgroup (RR 0.93, 95% CI 0.84–1.01).[5]

Colloids used in sepsis resuscitation include hydroxyethyl starches (HES) and human albumin solution (HAS). HES has been associated with increased morbidity and mortality to the degree that guidelines for the management of sepsis now recommend against use.[6] Instead, they are relegated to specific instances where "crystalloids alone are not sufficient" for resuscitation.[7]

Albumin exerts significant oncotic pressure when administered intravenously with less overall fluid leak into the interstitium, allowing for greater expansion of intravascular volume when compared to crystalloid. Less tissue oedema and greater circulating volume theoretically favours end organ perfusion. In addition, HAS may reduce vascular permeability and endothelial dysfunction[8]; protect the endothelial glycocalyx[9]; and assist via oxygen free radical scavenging.[10] One limitation is expense: HAS is around 25-50 times more expensive than balanced crystalloid. A comparison of various fluid choices is explored further in Supplementary Table 1.

Guidance

National Institute for Health and Care Excellence (NICE) guidance recommends fluid resuscitation with 500 mL boluses of crystalloid as first line treatment for hypotension in sepsis. The Surviving Sepsis Campaign (SSC) advises 30 mL/kg of crystalloid within the first 3 hours.[6,11] In both NICE and SSC guidance, albumin is framed as a second line

therapy for use in "severe sepsis" and "patients requiring large volumes of crystalloids" respectively. There is neither consensus on concentration of solution and volumes, nor how to give in combination with other fluid.

Existing evidence

Most relevant clinical trial data is from adult critical care patients. The Saline vs Albumin Fluid Evaluation (SAFE) trial compared resuscitation with 4% Human Albumin solution against unbalanced crystalloid in critical care patients. There was no demonstrable difference in 28-day mortality, the primary outcome. In the severe sepsis subgroup, there was a trend towards benefit in 28-day mortality in the albumin arm (relative risk 0.87 (95% CI 0.74–1.02)).[12]

The ALBIOS study compared protocolised resuscitation with 20% HAS in combination with crystalloid against a control group with crystalloid alone in patients with severe sepsis.[13] There was no evidence of difference in 28-day mortality between arms. However, a post-hoc analysis demonstrated a reduced mortality with the intervention in patients with septic shock assigned to 20% HAS.[14]

Two meta-analyses comparing colloid with crystalloid resuscitation in the critically unwell found no difference in mortality. However, Lewis *et al* grouped albumin with fresh frozen plasma in their 2018 Cochrane review (RR 0.98, 95% CI 0.92–1.06).[15] Martin and Bassett's review demonstrated equivocal mortality findings, but did show that albumin performed better at improving surrogate cardiovascular endpoints such as central venous pressure and cardiac index.[16] Since these meta-analyses, a small number of further trials of relevance have been published, which are unlikely to impact on clinical practice.

Despite theoretical and physiological promise, albumin has not demonstrated superiority as a resuscitation fluid in trials powered to detect clinically important outcomes.

Rationale

Our trial exists in a different clinical setting to previous published literature, and differs in two key ways. First, critical care trials tend to exclude populations who respond well to initial fluid resuscitation as well as those with significant morbidity or poor prognosis deemed unlikely to benefit from admission to critical care. This latter multimorbid population may especially benefit from HAS resuscitation as they may have comorbidities liable to decompensate with interstitial oedema or fluid overload with crystalloid. The vast majority of patients with infection presenting to the ED do not need critical care.[17]

Secondly, our focus is on the early resuscitation phase of sepsis. This is distinct from care during critical illness: early physiological correction may enable prevention of deterioration, the hypotension and hypoperfusion is more likely to be due to hypovolaemia (patients in critical care trials will likely have had euvolaemia attained early on in their treatment course, as measured against invasive cardiovascular monitoring), and illness itself is more likely to be in the infective rather than inflammatory phase.

This trial responds to calls for focused research into this area. The Surviving Sepsis Campaign have highlighted which fluid to use as a key research question.[18] Similarly, the James Lind Alliance have prioritised questions of fluid volumes and responsiveness closely interlinked with the potential theoretical differences between HAS and balanced crystalloid as agents for fluid resuscitation.[19]

This study is also essential in the current context of changing clinical practice. The use of HAS is increasing globally[20] although use remains low in an ED setting.

Finally, existing guidelines for fluid resuscitation in sepsis decline to give specific guidance on when resuscitation with HAS is appropriate rather than balanced crystalloid. This reflects the paucity of evidence outside of critical care, particularly in the early resuscitative phase of sepsis.

Aims and objectives

ABC Sepsis aims to assess the feasibility of being able to recruit to, and deliver a pragmatic, randomised controlled trial comparing albumin against balanced crystalloid for fluid resuscitation in patients with suspected sepsis, presenting to UK NHS hospitals. The second primary objective is to assess whether there is an indication of difference in important clinical outcomes such as 30-day mortality. Therefore, the trial primary endpoints are 1) recruitment rate, and 2) 30-day mortality.

Secondary objectives include assessment of: mortality rates during inpatient stay and at 90 days; study deliverability; volume of fluid administered; protocol adherence; degree of healthcare and resource use, in particular, critical care; patient quality of life measures; and significant complications.

Methods

Design and setting

The study is a two-armed, pragmatic, parallel group randomised controlled trial in patients presenting to secondary care with suspected community acquired sepsis. Patients are recruited within 12 hours of presentation to Emergency Departments, Medical Admissions Units and Surgical Admissions Units in 15 UK NHS hospitals. As of the 15th February 2022, 13 sites have recruited 169 participants.

Screening, eligibility, and consent

Patients with suspected sepsis are identified, screened for eligibility, and then approached for informed consent very soon after presentation to hospital. Inclusion and exclusion criteria are outlined in Table 1. In the event of a potential participant having temporary incapacity, there is a hierarchal consent process including witnessed methods, professional representative consent, personal representative consent, and deferred consent.

Patients who have "life threatening features" can be recruited to the trial by a senior trial doctor using deferred consent if there is no Personal/Professional Representative

Table 1. study inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
1. Clinically suspected or proven infection resulting in principal reason for acute illness; 2. NEWS/NEWS2 score ≥5; 3. Hospital presentation within last 12 hours; 4. Clinician decision has been made that immediate (within 1 hour of assessment) intravenous fluid resuscitation is needed; 5. Ability to obtain informed consent.	1. >1 litre of intravenous crystalloid fluid or any intravenous HAS administered prior to eligibility assessment; 2. Clinically judged to require immediate surgery (within 1 hour of eligibility assessment); 3. Chronic renal replacement therapy; 4. Known allergy/adverse reaction to HAS; 5. Known contraindications to balanced crystalloid as per reference SmPC. 6. Known adverse reaction to blood products; 7. Palliation/end of life care (explicit decision by patient/family/carers in conjunction with clinical team that any active treatment beyond symptomatic relief is not appropriate); 8. Religious beliefs precluding HAS administration; 9. Previous recruitment in the trial; 10. Known recent severe traumatic brain injury (within 3 months); 11. Patients with permanent incapacity; 12. Known to have participated in interventional phase of another CTIMP study within the last 30 days.

CTIMP: clinical trial of investigational medical product; HAS: 5% human albumin solution; NEWS: national early warning score; SmPC: Summary of Product Characteristics

to give consent on their behalf within 30 minutes so that treatment can be commenced rapidly. All patients recruited via personal, professional, or deferred consent processes will be contacted to confirm consent once capacity is regained.

Intervention

The intervention continues for up to 6 hours following randomisation. In patients who meet the inclusion criteria, intravenous fluid resuscitation is started as soon as possible. Critically, the patient receives only the fluid they are randomised to, except for small volumes of fluids already started before recruitment or those required for additional medications or maintenance infusions. If crystalloid has been given prior to randomisation to the HAS arm, the crystalloid therapy stops.

Both intervention arms will be administered in boluses directed by clinicians reassessing and re-prescribing as per usual practice. It is anticipated that HAS bolus volumes will be in the order of 250–500 mL, whereas balanced crystalloid will be in the order of 250–1000 mL. If further fluid resuscitation is deemed necessary after the first 3 hours, clinicians can elect to continue with fluid resuscitation using that same intervention arm. All other care is at the discretion of the treating clinician and any local guidelines.

Should, in the view of the treating clinician, euvolaemia be attained and maintenance fluids required, then balanced crystalloid can be used up to a rate of 125 mL/hr regardless of study arm. If further resuscitation is needed within the 6 hour intervention window, the randomised allocation still applies.

Follow up

No further in person follow up is required. Outcomes are assessed using medical records, and a patient questionnaire assessing quality of life measures. Study assessments are detailed in Table 2.

Quality of life outcomes will be assessed in the first 50 patients randomised only. They complete EQ-5D-5L questionnaires at baseline, seven and 180 days.

Data management

REDCap® is used to host and store the Electronic Case Report Forms. De-identified data will be made available for future research use.

Statistical considerations

Formal sample size calculations were not appropriate for this feasibility study. However, the pragmatic sample size facilitates the outcome of feasibility: an acceptance rate of 50% would be estimated (with a 95% CI of 44%–56%) if 300 from 600 of those eligible agreed to be randomised. The second primary outcome, mortality at 30 days, would be powered at 90% at a 5% level of significance to detect an approximate relative halving of the RR, with an estimated 30-day mortality of the standard of care group at 35%.

Recruitment feasibility will be assessed as the proportions who visited the ED that were: eligible; those who were eligible that were approached; and of those eligible and approached the proportion that consented to be randomised. All-cause mortality at 30 days will be summarised by treatment group and analysed using a mixed effects logistic regression adjusting for site and adjusting for pre-specified baseline covariates known to be strong predictors of 30-day mortality.

Predefined exploratory sub-group analysis include severity of illness at presentation (NEWS score, qSOFA, lactate), age, pre-existing comorbid conditions (heart failure, chronic kidney disease), and baseline albumin. 30-day mortality will also be assessed in the subgroup of the study population not admitted to critical care. Secondary

Table 2. ABC Sepsis study assessments.

	Screening	Baseline (day 0)	Days 1–6	Day 7	Discharge	Day 30 #	Day 90 #	Day 180
Consent	X	—	—	—	—	—	—	—
Eligibility	X	—	—	—	—	—	—	—
Randomisation	—	X	—	—	—	—	—	—
Demographics/Medical history/estimated weight	—	X	—	—	—	—	—	—
Routine blood results*	—	X	X	X	—	—	—	—
Routine urine and other culture results	—	X	—	—	—	—	—	—
Vital signs/lactate**	—	X	—	—	—	—	—	—
IMP administration/adherence	—	X	—	—	—	—	—	—
Interventions	—	X	—	—	—	—	—	—
Mortality	—	—	—	—	X	X	X	—
Length of stay/HDU/ICU stay	—	—	—	—	X	—	X	—
Readmissions	—	—	—	—	—	—	X	—
Acute kidney injury/pulmonary oedema/allergy/anaphylaxis	—	—	—	—	X	—	—	—
Adverse events	—	X	X	X	—	—	—	—
EQ-5D-5L***	—	X	—	X	—	—	—	X

*Daily (+/− 12 hours) for any routine bloods collected up to 7 days. If bloods (or individual parameters) are not requested by the clinical team, this will not be recorded as a deviation.
**Both vital signs and lactate, if measured, will be recorded prior to treatment starting and at 1,3,5 and 7 hours after randomisation (+/−30 mins). Lactates up to 24 hours post randomisation, if measured, will be recorded at 9,11,13,15,17,19,21,23 hours (+/−30 mins).
***#First 50 participants only. As Day 30 and Day 90 follow up is collected from the medical records it can be reviewed and recorded in the eCRF up to 7 days after the time point so it captures all admissions/events up to and including Day 30 and 90.

outcomes will be analysed either using mixed effects linear models, or with a mixed effects logistic regression in those involving proportions. The proportions admitted to critical care (HDU or ICU) will be analysed using proportional odds logistic regression. Safety outcomes will be analysed similarly according to their distribution. Quality of life data will be analysed likewise with a model appropriate to the distribution.

If the data quality permits, we will pursue an exploratory estimate of the incremental Quality Adjusted Life Years at 180 days. We will be particularly interested in understanding the observed patterns of any missing data overall.

Patient and public involvement

A patient and public involvement (PPI) panel was convened to inform the design of the study and related materials. It included people with lived experience of sepsis, including those who have been critically unwell during their stay. Two such lay members sit on the Trial Steering Committee.

Trial registration

This trial is funded by a grant from the Jon Moulton Charity Trust (reference CH605). It is deemed a Clinical Trial of Investigational Medicinal Product and has been granted a favourable opinion after review by the Scotland A Research Ethics Committee. It was registered on ClinicalTrials.gov, reference NCT04540094, ahead of recruitment.

Discussion

The ABC Sepsis trial is designed to evaluate the feasibility of delivering a definitive trial on the superiority of HAS for resuscitation of patients with suspected sepsis in the ED. In addition to providing information on feasibility and estimates of key clinical outcome measures, this trial will also provide invaluable insight for the running of sepsis trials at presentation to secondary care in UK NHS Hospitals. As with many trials in Emergency Medicine, successful delivery is sensitive to navigating time-critical intervention, pressured working environments, and ensuring individual, service and hospital wide participation.

Challenges

The main perceived challenge is the short window for assessing eligibility and obtaining informed consent, occasionally from representatives not present at the department. This process will occur in busy EDs and medical/surgical assessment units, with sick patients dependent on time critical interventions. The window in which patients can consider their participation in the trial is likely to be 30–40 minutes but may be as little as 10-15. Key to the success of recruitment will be research staff comfortable working within EDs using documentation developed with these challenging circumstances in mind.

Where research teams are part of the clinical care team, they will be able to identify patients as they present to the ED and approach them early to assess eligibility and ask for informed consent. An additional challenge will exist where the research team are deemed to be outside of the usual care team or there is absence of research support. In this case, clinicians will have to identify potential participants, which presents both additional work and a potential time delay to patient management.

We have discussed the uncertainty around which fluid to use in sepsis resuscitation, but it is also important to acknowledge other uncertainties in sepsis management. The

volume of fluid to administer, how to assess fluid responsiveness and resuscitation targets remain controversial, alongside and practice variation between clinicians and services.[21] Indeed, a particular clinician dependent consideration is familiarity and use of HAS as a resuscitation fluid. Despite increasing use of HAS, it remains much less widely used than balanced crystalloid and rarely used within the ED.[20] Our protocol purposefully only describes anticipated fluid volumes in each arm, rather than prescribing limits. The rationale is to design a trial acceptable to clinicians which generates evidence reflective of real-world practice.

Other potential considerations may be incorporated into a future definitive trial. Some specific patient subgroups may demonstrate more marked, or even opposite, outcomes in their response to the treatment arms. This might include patients with acute kidney injury as part of their presentation, those who develop hyperchloraemia and acidosis during fluid resuscitation, and hypoalbuminaemic patients.

Recruitment strategies and research team organisation is likely to have a large impact on the ability of sites to recruit to a trial and the management team will coordinate the iterative process of learning and improving trial conduct in real time. Finally, the nature of HAS is that it is often considered to be a blood product, and some patients may choose not to receive this as a treatment. This factor is clearly communicated to all potential participants and will form part of our understanding of acceptability of this intervention to participants and patients more widely. As standard during a Clinical Trial of Investigatory Medical Product, the safety profile of both interventions is key and forms part of our prespecified analysis.

The COVID-19 pandemic poses both organisational and scientific challenges to the design of this trial. Waves of infection have consistently placed increased strain on hospitals, particularly EDs, to the extent which many research activities have been halted at various points during the pandemic. Sepsis and COVID-19 share similarities, not least in presentation and dysregulation of immune response.[22] Indeed, the National Institute for Health's COVID-19 treatment guidelines state that "patients with COVID-19 who require fluid resuscitation or haemodynamic management of shock should be treated and managed identically to adult patients with septic shock".[23] Our protocol does not exclude patients with suspected or confirmed COVID-19.

Potential impact

There has been no definitive trial comparing HAS with balanced crystalloid in suspected sepsis in the ED in the early resuscitative phase of sepsis management. Previous trials, in critical care, included patients who are likely to be after volume resuscitation and euvolemic. Moreover, they exclude participants who are unsuitable for critical care intervention. The setting of our intervention is arguably the most plausible window for benefit, and the large, non-critical care population may have the most to gain from optimal resuscitation with intravenous fluid.

Should there be a signal of clinical benefit in the HAS arm, in parallel with evidence of an ability to recruit, this would create a convincing case for funding and delivery of a definitive randomised controlled trial.

Demonstrating a difference between results of previous critical care trials and those in ED might provide further evidence that timing of fluid administration is crucial. Sepsis as a condition is particularly challenging when compared with traumatic brain injury or cardiac arrest, as there is more likely to be an unclear time or gradual of onset of symptoms. There are established phases of sepsis, within which it is hypothesised that different treatments might be more or less effective (e.g. antibiotics in infective phase, steroids in inflammatory phase). Clearly mapping the timeline, of ongoing physiological and immune process is challenging. A linked observational study recruiting from ABC Sepsis patients is also underway which looks at this theme by investigating inflammatory changes early in the participant's presentation with sepsis [ClinicalTrials.gov identifier: NCT04963569].

Summary

Intravenous fluid resuscitation is an integral component of sepsis management. However, there is imprecise and poorly evidenced guidance with regards to timing, volume and the choice of fluid. HAS has several theoretical benefits over balanced crystalloid but is more expensive and less widely used. Our randomised controlled feasibility trial will provide evidence of trial deliverability in UK NHS Emergency Departments and provide further clinical information that may inform future research.

Declaration of conflicting interests

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Supplemental Material

Supplemental material for this article is available online.

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