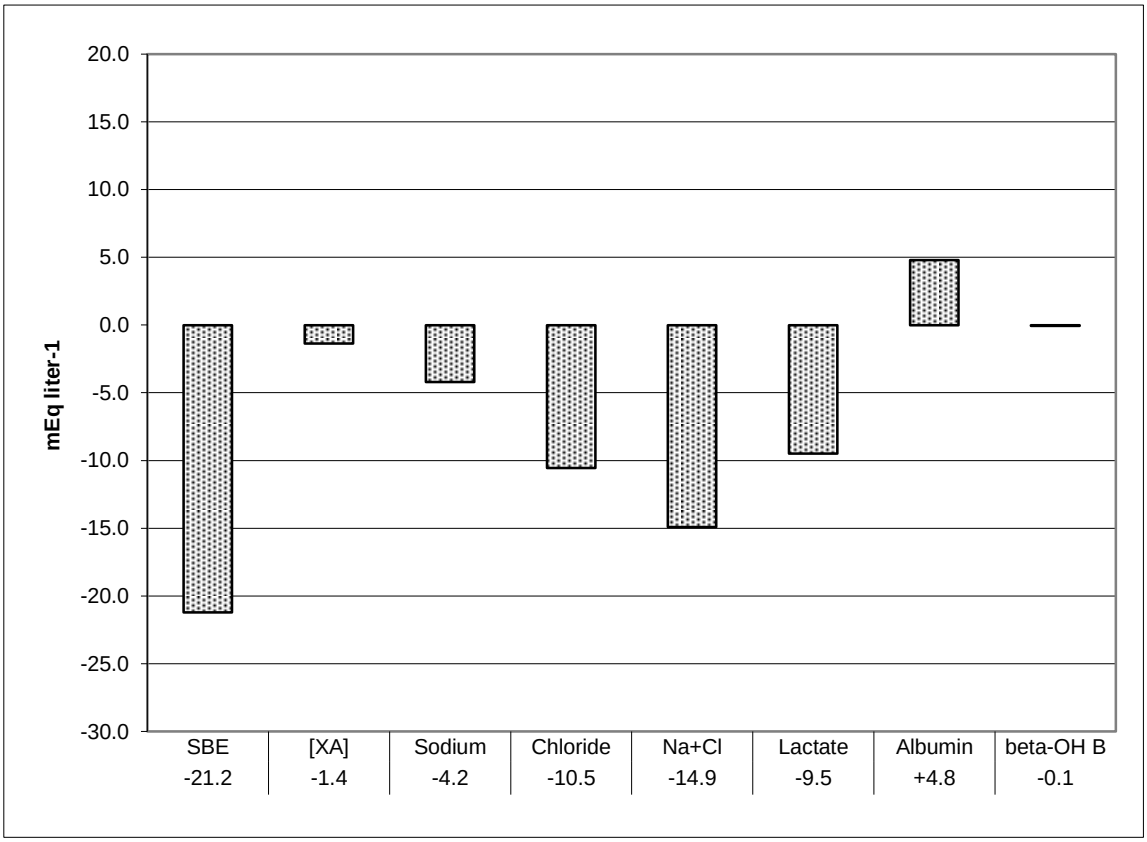
Evaluation of the utility of a new algorithm for the detection of the unmeasured ion excess in the human extracellular fluid.

(UNA UIX)



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SCICCR
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3. List of abbreviations

Abbreviation	*Term*
SCHHS	Sunshine Coast Hospital and Health Service
NGH	Nambour General Hospital
SCUH	Sunshine Coast University Hospital
ICU	Intensive Care Unit
HREC	Human research and ethics committee
ECF	Extracellular fluid
UIX	Unmeasured ion excess
CRRT	Continuous renal replacement therapy

4. Synopsis

Study title	Evaluation of the utility of a new algorithm for the detection of the unmeasured ion excess in the human ECF
Clinical phase	Clinical
Trial design	Single centre, prospective study
Rationale	The primary aim of this study is to evaluate the clinical utility of a new algorithm in the prediction of mortality.
Number of subjects	The sample size required for univariate logistic regression having an overall event proportion (mortality) of 12% and an odds ratio of 0.7 at one standard deviation above the mean of the covariate is 509 (alpha = 0.05, beta = 0.80). For multivariable logistic regression, it is assumed that the co-variates are independent of one another and therefore the multiple correlation coefficient relating the specific covariate to the remaining covariates is close to zero. The sample size inflation factor for multivariable logistic regression is therefore very close to 1, ie: approximately 510 participants should suffice.
Study duration	The study will likely require a six month recruitment phase followed by a two month analytical phase.
Endpoints	The endpoint will be the demonstration of a difference in mortality related to the presence of unmeasured ions in the ECF. The study will be closed when a total of 510 patients have been recruited.
Inclusion criterion	Admission to the ICU.
Exclusion criterion	Patients under the age of 18 years
Centres	Nambour General Hospital / Sunshine Coast University Hospital
Ethical approval	Ethical approval for the performance of the study will be sought via a low negligible risk (LNR) application to the recommended HREC.

5. Administrative structure

Study co-ordination and data collection will be based in the NGH/SCUH ICU as a single centre. This centre will be responsible for all administrative aspects of the study including, HREC applications, protocol design, study performance, protocol training, data collection, organisation of investigator meetings as required, data analysis and ultimately, publication of results.

Specimen analysis will occur in the laboratory on the NGH/SCUH campus.

6. Funding

Funding costs will be negligible as all of the data entry will occur out of normal working hours.

7. Background information

It has been postulated that as a result of perturbed metabolism, critically ill patients generate excess intracellular ions, for example, in the case of decreased peripheral perfusion, L-lactate and in diabetic ketoacidosis, β-hydroxy butyrate [(1)]. Subsequently these ions (mainly anions) leak into the extracellular fluid (ECF) space where they contribute to an evolving non-respiratory acidaemia [(2)]. Disappearance of these ions from the ECF has been linked to resolution of the process that triggered the episode of critical illness and ultimately, to recovery of the patient [(3-7)].

With the exception of L-lactate and more recently β-hydroxy butyrate, direct measurement of these ions is currently not possible and their effect has to be inferred indirectly as part of a decreasing standard base excess (SBE). To compound matters, alterations in the concentrations of the major extracellular strong ions (sodium, potassium and chloride) and the plasma weak acids (albumin and inorganic phosphate) either as a result of the underlying process or the fluids used during resuscitation, also has a major effect on the SBE, rendering it more as a general indicator of the non-respiratory acid-base status rather than a specific and sensitive indicator [(8,9)].

A recent method for partitioning the SBE into subcomponents that permit the estimation of the specific effect of the unmeasured ions has been developed, published and experimentally validated [(10,11)]. The utility of this UIX algorithm needs to be formally tested in the clinical environment and it is this requirement that drives the need to conduct an audit that involves mapping the results of the routinely collected daily bloods in a population of critically ill patients to their eventual outcome, likely mortality but equally as important, length of ICU and hospital stay.

Whilst in the ICU, all patients are intensively monitored looking for progress of their disease or recovery as well as early indicators of complications using standard protocols.

8. Study rationale

The primary objective of the study is to examine the relationship between the presence and persistence of detectable but unmeasurable ions in the ECF and mortality using a new, purpose designed algorithm.

This study has not been previously performed and is designed as a prospective audit to be conducted at the NGH/SCUH ICU.

9. Methodology

It is proposed that all patients admitted to the ICU during the six month period from February 2017 to August 2017 be included in this audit. There are no specific exclusions. On current figures, this will result in a sample size of approximately 510 which will be more than enough to identify significant trends and associations.

Deidentified demographic data (age, gender, diagnosis, APACHE II, APACHE III and SAPS II scores) will be collected on admission to the ICU and regular collection of pathology results will occur once per day until the patients are discharged from the ICU. The pathology results required will be collected from the routine morning acid-base profile (pH, PCO2, [bicarbonate], SBE and [L-lactate]) and the routine daily biochemistry (sodium, potassium, chloride, calcium, magnesium, albumin and inorganic phosphate) plus when available, any other sporadically collected relevant biochemistry (eg: β-hydroxy butyrate, plasma lithium etc.). No extra blood samples or tests over and above those drawn and analysed routinely will be required.

Length of stay will be collected from the admission and discharge dates and mortality data when it occurs.

Anonymity and confidentiality will be maintained throughout the audit. All participants will be assigned a unique participant number in place of any identifying information. Should any re-identification be required for data quality and assurance purposes, a separate participant log will be maintained and stored securely to match the participant number with the hospital unit record number.

10. Data management and statistical analysis

General data descriptive methods will be employed - that is, mean (SD) for normally distributed data, median (IQR) for non-normal data and proportion (%) for categorical and binary data.

Comparisons will be performed using tests appropriate for the type of data. That is, the Students t-test will be used for normal data, the Wilcoxon rank sum test for non-normal data and chi-square and Fishers exact test for categorical/binary data.

Time to event data will be analysed using a Cox proportional hazards model.

Currently, the NGH ICU treats approximately 1100 patients per annum. The general mortality rate is 12% with rates ranging up to 30% for certain subsets of disease pathology (eg: renal failure requiring CRRT). It is this mortality differential that was used in the sample size calculations.

Statistical analysis will be performed using a propriety statistical package (STATA version 14.1). Data will be organised and trends reported using standard descriptive statistics (mean (SD), median (IRQ), proportions). More detailed inferential analysis will be done using regression techniques that take into account the binary nature of the outcome variable.

The project will be managed locally by the principal investigator (CA). General data collection will be the responsibility of the ICU Clerical staff. Biochemical and acid-base data will be collected by the ICU Nursing staff.

Governance will be overseen by the local SCHHS Research Governance and Development Board.

Data will be stored on a secure local server. It is proposed to store the data for a maximum of fifteen years after which it will be deleted.

All analyses will be performed at the end of the study.

11. Human research ethics committee approvals

A low negligible risk application requesting approval to conduct this study will be submitted to the HREC at The Prince Charles Hospital. Because of the prospective audit nature of the study, a waiver of consent will be sought.

All study records and documents will be securely stored for a minimum of 15 years from the end of the study or for a time period as required by the HREC.

a) Protocol amendments: Significant study protocol changes will have a written amendment request sent to the HREC for written approval. The approval letter will bear the signature of the HREC Chair and will refer to the protocol number, protocol title, amendment number and amendment date. The protocol amendment can only be implemented after HREC approval.

b) Study termination: The study may be terminated for any of the following reasons: study completion, failure of sufficient participant enrolment or at the discretion of the overseeing Research Board or Hospital board.

c) Notification of study closure: Within 3 months of either study completion or termination, the Principal Investigator will notify the HREC of that fact.

12. Data quality assurance

Data collection quality will be checked and assurance will be monitored by the trial co-ordinator.

a) Principles: The quality management principles will involve a patient focus, demonstration of leadership on the part of the investigator(s) and the use of a systematic and factual approach to decision making. Overall conduct of the study will be overseen by the local Research Governance and Development Board with regular reports on conduct and progress from the investigators.

b) Safety considerations: As a routine, all patients admitted to the ICU are closely monitored with policies aimed at prevention of adverse events in place. If events occur, mechanisms currently exist to minimise the impact on patient safety and also to audit, report and investigate so as to educate staff and prevent recurrence. All morbidity and mortality is investigated by both local and hospital-wide committees.

c) Records retention: As previously stated, the Principle Investigator will retain and preserve one copy of all data generated in the course of the study for a period of 15 years following study closure.

13. Publication and presentation

It is proposed to publish the results in the peer-reviewed scientific literature with appropriate acknowledgement of all investigators. Similarly, it is proposed to present the results at appropriate postgraduate/scientific meetings.

14. References (listed in order of appearance in the text)

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