11/2004/28

Full title of project:

Development of a risk model for the prediction of new or worsening Acute Kidney Injury (AKI)

Aims and objectives:

1. **Identification of AKI:** Accurately identify and report patients with AKI.
2. **Predictive Model:** Based on factors identified in primary and secondary care records and the admission characteristics of each patient, develop a predictive model to stratify the risk of: **(1)** AKI on arrival in hospital. **(2)** Developing AKI during the admission. **(3)** Worsening AKI if it is already present.
3. **Clinical Algorithm:** Use the predictive model to develop an algorithm for all patients admitted to hospital (elective and emergency) to stratify them according to risk of developing AKI.
4. **Integration into Clinical Practice:** Define the most effective way to incorporate the risk model into a clinical decision support system (CDSS) that can be integrated into everyday clinical practice. This will inform the follow on study from this project.

A secondary aim of this study is to inform national clinical guidelines and audit tools for AKI.

Background:

What is it? Acute kidney injury (AKI), previously acute renal failure, is an all too common clinical problem characterised by an acute decline in renal function, the result of which ranges from minimal alteration in serum creatinine to anuric renal failure requiring renal replacement therapy (RRT). The aetiologies and risk factors for AKI are numerous, but now well defined. (1-4) Even without the need for RRT AKI impacts on a patients clinical course with complications such as fluid overload, acidosis and hyperkalaemia, all of which may lead to an increase in morbidity, length of stay and ultimately mortality both long and short term.
As definitions of AKI have become clearer, so has the appreciation of the consequences of AKI and its impact on the patient, and on the healthcare economy at large.

Clinical Definition: Over the years one problem has been the numerous ways of defining AKI. (5) In 2003 the Acute Dialysis Quality Initiative (ADQI) group published guidelines to define AKI (6) They developed the RIFLE, risk injury failure loss and end stage renal failure, classification to define patients by changes in serum creatinine or urine output criteria. (see Table 1) (6) In 2007 the Acute Kidney Injury Network (AKIN) modified the RIFLE criteria, defining 3 stages of AKI (see Table 2)(7). To define AKI there must be an increase in serum creatinine over a period of 2 (AKIN) to 7 (RIFLE) days. The addition of a rise of 26.4µmol/l to define AKIN 1 was based on 2 large studies, demonstrating an independent association between this rise and in-hospital mortality.(8,9) RIFLE and AKIN are consensus definitions which have now been validated and correlate well with patient outcomes. (10,11) However, the next problem is in definition of baseline creatinine. A 2 (AKIN) or 7 (RIFLE) day baseline creatinine is often not available. We must therefore extend out the time period for assessment of baseline kidney function. It is not clear what assessment period should be used, and this has resulted in heterogenous definitions.(6,8,12-18) In 2010 Lafrance compared the highest serum creatinine during hospitalisation with the lowest in 4 different baseline assessment periods (in hospital only and 3, 6, or 12 months pre-admission).(19) The cumulative incidence of AKI ranged from 12.5% (in-hospital only) to 18.3% (12 months pre-admission). (19) In this study we will use a 12 month baseline which will increase our sensitivity.

Incidence: AKI is a global health issue. Its prevalence (5-7% amongst hospitalized patients (14),(20)) is increasing, (21)(22) associated with an aging population, and increasing prevalence of diabetes and hypertension. The incidence of AKI had been reported as 486-630 pmp/year.(23-25) However in 2003 Ali et al in a population based study reported an incidence of 1811 cases of AKI and 336 of acute-on-chronic renal failure (ACRF) per million population. (26) From our audit of AKI in all patients admitted to East Kent Hospitals University NHS Foundation Trust (EKHUFT), from a population of 720,000, we identified 4398 patients with AKI in a 6 month period (12,217 per million population per year). We believe this is closer to the true incidence of AKI.

Outcomes: As well as morbidity from complications of AKI, there is a significant increase in mortality.(3,4,27) After accounting for other predictors, AKI remains an independent risk factor for death.(28,29) In ITU AKI mortality exceeds 50%.(1,4,30-35) AKI increases short and long term mortality.(36) Patients hospitalised for AKI are more likely to die in the months following admission than to develop ESRF.(37) From our audit data, patients with Acute Kidney Injury Network stage 3 (AKIN3; >3 fold rise in serum creatinine from baseline) compared to a patient that did not experience AKI, had a 23 fold risk of in-hospital mortality, 3 times the length of stay (LOS), 26 fold risk of admission to ITU, 27% 30 day re-admission rate, a 7% increase in care on discharge (from home to residential or nursing care), and 5 fold risk of 12 month mortality. Even in AKIN stage 1 (26.4 micromol/l or 1.5 fold rise), the outcomes are significantly worse than a patient who does not experience AKI, (3.5 fold risk of in-hospital mortality, 89% increase in LOS, 4 fold risk of admission to ITU). All hospitalised patients are at risk of AKI, either from their presenting disease or subsequent iatrogenic injury, and it is often preventable or reversible.

Current Management: It is therefore essential that AKI is recognised early and treated effectively, a concept highlighted in the Renal National Service Framework. However the 2009 National Confidential Enquiry into Patient Outcome and Death (NCEPOD) in the setting of AKI, highlighted systematic failings in identification and subsequent management. (21) The report suggests a poor assessment of risk factors. Care of patients with AKI was considered good in only 50%. Complications were missed in 13%, avoidable in 17% and managed badly in 22%. In patients developing AKI post admission, a fifth were deemed predictable and avoidable, and in 43% judged to have an unacceptable delay in recognizing AKI.(21) NCEPOD recommends risk assessment for AKI in all emergency admissions. Predictable and avoidable AKI should never occur.(21)

Risk Assessment: SCr is a poor biomarker of AKI as rises in SCr may be delayed for up to 48 hours after onset.(22)(38) Work is underway to assess other biomarkers (e.g. cystatin C, neutrophil gelatinase associated liopcalin (NGAL), interleukin 18 and kidney injury molecule (KIM-1)), to facilitate earlier diagnosis of AKI. We propose to look even further back in AKI, to its risk factors, and then provide the best form of treatment, prevention! Risk factors for AKI are well known, including pre-existing CKD, age, diabetes, cardiovascular disease, hypertension and prescription of certain drugs. This project aims to provide accurate risk assessment.

National Strategy and NHS Policy: The above literature and NCEPOD report has both informed and stimulated National Strategy and NHS policy with the aim to improve AKI management and outcomes. As a result there is now an AKI Delivery Group directed by NHS Kidney Care and the Department of Health, current development of the NICE AKI Guideline, the KDIGO AKI guideline, the updated Renal Association Guidelines, and the adoption of AKI in the Enhancing Quality framework, in order to address this problem.

Need: What this project will add

Health need: This project will create a validated risk model for the development of AKI, or of worsening AKI, in hospital. By alerting to high risk patients, this will be one step to significantly improving clinical practice, patient safety, and education in the management of AKI.

Expressed need: This project is in line with and will aid delivery of current NHS policy and strategy fulfil important recommendations of the NCEPOD report. The project will: (1) Deliver accurate validated risk assessment for AKI. (2) Inform clinical guidelines. (3) Inform and develop AKI audit tools. (4) Improve education and awareness of AKI.

Sustained interest and intent: All hospitalised patients are, and will continue to be, at risk of AKI, either from their presenting disease or subsequent iatrogenic injury, and it is often preventable or reversible. The drive within the NHS to improve care in AKI will continue to gather pace guided by national and international groups including the AKI Delivery Group from NHS Kidney Care.

Capacity to generate new knowledge: One important recommendation of NCEPOD was an AKI risk assessment for all emergency admissions to hospital. Although in the literature there is evidence of what factors convey risk, there is presently no validated risk assessment tool. The delivery of this new knowledge will also inform clinical guidelines and audit pathways.

Organisational focus consistent with HS&DR mission: We aim to significantly improve clinical practice and patient safety in AKI, reduce health complications and risk of death, by allowing accurate alert and recognition of patients at risk of AKI or of worsening AKI, and ensuring transferability of this across the NHS. Within NHS organisations this work will allow more accurate provision and delivery of acute nephrology specialist services,

and inform clinical audit pathways in AKI. Our current work has already informed development of the Enhancing Quality framework in AKI. This project will also have financial and efficiency benefits to the NHS. A report by NHS Kidney Care health economist Marion Kerr (based on our data from East Kent), suggests that prevention of 30% of AKI cases would save the NHS £130m to £186m per year.

Generalisable findings and prospects for change: This project will provide a risk assessment tool that will be generalizable across the NHS, in order to change management and improve the outcomes of patients. Following this project we aim to develop a clinical decision support system (CDSS) to provide this risk assessment in an automated fashion, to alert to the presence and risk of AKI, and provide actionable recommendations to clinicians at the point of care.

Building on existing work: This project builds on our existing work which has defined the true incidence and outcomes of AKI. We aim to then modify these outcomes by facilitating earlier diagnosis and intervention, and ultimately prevention. This project also builds on the work from NCEPOD to fulfil their recommendations. At EKHUFT we have already developed an online reporting system for AKI (alert system), and are currently implementing a system for electronic observations (VitalPac) across the trust. The work in this project will develop a validated risk assessment tool which will eventually (follow on study) be incorporated into the alert system to allow not only alert of patients with AKI, but alert of patients at risk of AKI, or of worsening AKI.

Methods:

Study phases:

- **Phase One:** *Predictive model development and validation:* Develop a predictive model to identify patients at risk of AKI, or of worsening AKI in patients who already have AKI. Quantify these risks to stratify patients, and incorporate this into a clinical algorithm. Validation of the risk model in the East Kent population and in a second population (Medway). Define the most effective way to incorporate the risk model into a CDSS that can be integrated into everyday clinical practice. (See study flow diagram for work flow steps).

- **Future (Phase two follow up study):** *Clinical Decision Support System (CDSS) development and delivery:* Following completion of this project, the follow on study will be Phase two of the original proposal in which a CDSS will be developed and integrated into everyday clinical practice. The clinical (outcomes such as incidence of AKI, mortality from AKI, length of stay etc.) and logistic (user interaction, change in clinical management) impact of this system will then be assessed.

Design and theoretical/conceptual framework: This project will involve both quantitative and qualitative methodology; Quantitative methodology to: (1) formulate the predictive risk model. (2) validate the risk model in the East Kent population and a second population and NHS Trust (Medway NHS Foundation Trust). Qualitative methodology will be employed to: plan the clinical intervention and clinical decision support system (CDSS) development, and effective integration of the CDSS into everyday clinical care.

Setting / context: The study population will be all patients presenting to the three acute hospitals of EKHUFT; Kent and Canterbury Hospital in Canterbury, William Harvey Hospital in Ashford, and Queen Elizabeth the Queen Mother Hospital in Margate. The renal tertiary referral centre is based at Kent and Canterbury Hospital.

Data Collection: Data (including age, sex, co-morbidities, hospital admission and outpatient history, relevant pathology tests, drug history, baseline creatinine and CKD stage, and creatinine tests and electronic observations during admission) will be collected from the hospital data warehouse, pathology database, and GP data from the system for early identification of kidney disease (SEIK). SEIK is a CDSS we developed in 2006 to advise GPs on CKD management. GP Data is extracted and using an automated decision tree matrix based on NICE guidance, allows identification of people by stage of CKD and production of patient specific recommendations.

Data Analysis: Quantitative Analysis: (12 *month retrospective analysis for predictive model development*). The main aim of this study, and an important element of the CDSS is the development of predictive models for identifying and stratifying the risk of developing AKI, or of worsening AKI, during hospital admission. These models will include a large set of potential risk factors identified from primary and secondary care records as well as admission characteristics of each patient. The models will be based on logistic and multinomial logistic

regression methods, (39)(40), a popular choice for assessing the risk of developing AKI (and any other pathology incidence). The structured nature of the data records, (patients within wards, within hospitals), held by East Kent Hospitals University NHS Foundation Trust (EKHUFT) and Medway NHS Foundation Trust (MFT) will be accounted for using Bayesian hierarchical models. The parsimony and predictive performance of the models is essential for a successful risk assessment tool and a CDSS (the CDSS we will develop in the follow on study), and hence variable selection methods will be used to identify the important risk factors from the large set of potential risk factors. Primary and secondary care data records are not always complete and information on some risk factors may be missing for some patients. The standard approach to dealing with missing data is to assume a missing at random (MAR) mechanism and apply multiple imputation methods, (41). We will use this approach, and also work from Ibrahim and Lipsitz (1999) (42), and Ibrahim et al. (2005) (43) if during analysis we find that the missingness mechanism is not missing at random (NMAR), which from clinical experience we would expect.
We will use a Bayesian approach in model development. With a Bayesian approach we can combine different forms of evidence (known findings within renal medicine as well as expert opinion) in the overall probability model or include these via the prior belief. The Bayesian framework more naturally allows for modelling biases, systematic error and any hierarchical data structure. The results of a Bayesian analysis are direct statements about quantities of interest (risk of developing AKI), providing more intuitive results and feeding naturally into a formal decision making process.
We will retrospectively assess all hospital admissions to EKHUFT and MFT over a 12 month period. The MFT data will be used as a second population and NHS Trust in which to validate the risk model developed from the EKHUFT population. The development of our predictive models will be based on the EKHUFT data, at first instance. Both logistic and multinomial logistic models will be developed. In terms of logistic regression we will focus on the following two patient populations: patients without and with AKI on admission. For patients without AKI we wish to identify whether or not they developed AKI, and patients with AKI whether or not they progressed to a more serious stage of AKI. In terms of multinomial logistic regression we will focus on the entire patient population and assess the risk of developing (or not) and progressing to (or not) one of the three stages of AKI. In all of these situations two time frames will be considered: 48 hours following admission and the entire admission period.
The key issues to be addressed in our models are: (1) the large set of potential risk factors, regressors, (2) multilevel structure of the data.
The set of potential regressors, includes variables from three sources (see data collection section): hospital data warehouse, pathology database and the system for early identification of kidney disease (SEIK) database (which includes the primary care patient records). It is therefore no surprise that our set is large. It spans a wide range of variables, from demographic variables such as age and gender, admission type and outpatient history, to co-morbidities and co-morbidity scores, to relevant pathology tests and drug history, to variables observed during admission such as blood pressure, heart rate, temperature, and blood tests. We therefore need to identify which regressors have a non-negligible effect and include those in the final models. This exercise becomes more complicated by the multi-level structure of the data, as risk of AKI may be heterogeneous among wards and hospitals (i.e. whether the models should include random intercepts or not).
With a Bayesian approach both issues can be tackled by combining variable selection with variance selection of the random intercept, (44)(45). Our models will include ward and hospital specific random intercepts to control for the heterogeneity among them. Combining variable selection with variance selection of the random intercept has been addressed, (46)(47) and it allows full model specification search to determine not only which regressors but also whether a random intercept should be included in the final model. Hence whether or not we will have a model that has only fixed effects or a model where the risk of AKI is heterogeneous among wards and hospitals, will depend on whether the variance of the random intercept is zero or positive, respectively.
There has recently been interest in the use of continuous priors (in Bayesian variable selection) which encourage regularization of regression coefficients, (48)(49). Unlike the commonly used spike-and-slab prior, regression coefficients are not set equal to zero but are shrunk to values very close to zero. This idea was initially motivated by the success of the classical Lasso (50) and its Bayesian interpretation, (51)(52). Caron and Doucet (2008) (53) and Griffin and Brown (2010) (54) use a hierarchical representation of the Lasso prior to define a wide-class of priors, the Normal-Gamma prior, which is the prior that will be used in this study.
The predictive performance of our models will be assessed using out-of sample comparisons. The data will be divided into two subsets, the training and the test data. We will use the test data to construct the models and the performance of the models on the test data will be used to check if predictions generalize well. In our predictive

evaluation we take the Bayesian point estimate fit from the training data and use the predictors from the test set to get predicted probabilities of the binary/multinomial outcomes for each point. We will then compare these to the actual outcomes in the test data. We will in effect be evaluating the posterior mode derived from the prior. Predictive performance will be reported in terms of expected squared errors or expected log errors, (Geiting and Raftery (2007)(55), Gelman et al (2008)(45)).

The classification accuracy of our models will be assessed using receiver operating characteristic (ROC) curves. These are plots of the true positive rate (sensitivity) versus the false positive rate (1-specificity) at all possible decision threshold values. With our Bayesian approach, the ROC summary measures, which are functions of the model parameters, can be simulated directly via Markov Chain Monte Carlo (MCMC) methods for the exploration of posterior distributions. Our approach will be similar to that of Albert and Chib (1993)(73), Gatsonis (1995)(74), Johnson (1996)(75), Chib and Greenberg (1998)(76) and Ishwaran and Gatsonis (2000)(77).

The models developed for EKHUFT will then be applied to the data from MFT. The evaluation methods described above regarding the models' predictive performance and classification accuracy will also be applied in the case of the MFT data. This validation of the risk model in a second population and NHS Trust (Medway NHS Foundation Trust), we ensure transferability of the risk model across the NHS.

Qualitative Analysis: The exploratory arm of the study will employ mainly focus group design. The purpose of this will be to inform and plan the followup study, adopting a user-involvement approach. The qualitative methodology will identify perceptions of a clinical decision support system (CDSS) and explore best communication and information pathways that will permit a CDSS to both alert and provide actionable recommendations to clinicians for decision-making This will allow accurate planning of the CDSS development following this study, to ensure effective integration into everyday clinical practice.
For this study, three cohorts of clinicians and professionals (one in each hospital) who will be involved in and/or recipients of the CDSS alerts and actionable recommendations will take part in a focus group wave. Individual interviews will be conducted with those unable to attend group discussions. In the follow on from this study (prospective intervention using a developed CDSS based on the risk model developed in this study), we would aim to have 2 further focus groups waves after the implementation of the CDSS. This will allow a longitudinal qualitative research design. Longitudinal qualitative research (LQR) involves repeat interviews or observations of, ideally, the same research subjects over time (56). In recent years, LQR has been used in a number of health-related areas to generate rich data and a deeper understanding regarding people's perspectives and experiences and how and why these may change over time in order to improve practice (57)(58)(59)(60). Rather than comparing findings at a number of distinct moments, LQR is concerned with the comparison of different, continuous processes of change.
The benefits of the longitudinal design will be that it will permit the same participants to be involved in identifying practice challenges and solutions, in developing methods for how alerts and recommendations can be best delivered for action, and for examining and reflecting on the effects with regard to practice change as well as system evaluation and improvement. The qualitative aspect of both this and the follow on study will strengthen the production of potentially transferable practice guidelines and system accessibility across the NHS.
Focus group method is an approach of choice in the healthcare setting not only to explode ideas, but to gain consensus on views and promote good practice (61). This particular research study promotes new and innovative ideas that may benefit from being explored within a group, particularly within a longitudinal approach. Variations in perception and experience will encourage deeper discussion and illuminate impacts, as well as reveal the nature and cause of practice changes in relation to the intervention.

This qualitative arm of the project will take place in the final 4 months of the study, in order to plan an inform the development of the CDSS. The sample will consist of a total of 30 clinicians and professional staff across EKHUFT, a cohort of 10 from each hospital, estimated to be sufficient to achieve saturation of data (62). A balanced but differing sample of junior doctors, consultants and specialist nurses will be invited to take part to ensure breadth of information.

Instrumentation and data collection: For the focus group, a schedule will be developed that will explore perceptions of the impact on practice, and identify best methods for delivering the alerts and recommendations. This will cover aspects such as accessibility of information, hardware, who the recipient should be (junior doctor, consultant), what form the alert should take (additional email, text), how to avoid alert fatigue and alerts being ignored. A focus group of 10 participants lasting one hour will take place on each hospital site at a convenient time and location, facilitated by an experienced researcher to enable equal participation and involvement. It will be recorded with participants' permission.

Analytical framework: Data collection will result in 3 transcribed focus group data sets and some individual interviews. The analysis will inform the CDSS development and follow up study design. The analytical approach taken will be Flick's (1998) content analysis, whereby themes and subthemes are categorised within a pre-existing template (usually the instrumentation With this approach however care is taken not to artificially represent data within the template but to introduce new themes when identified. This approach requires peer review to ensure analytical trustworthiness, which will be conducted within the research team. The analysis from the focus group will concentrate on the identification of best methods for delivering the alerts and recommendations in order to inform the CDSS development and implementation in the follow up study.