What does Paediatric AKI look like when identified by a change in creatinine based electronic alert? A National Survey.

Jennifer Holmes*, Gethin Roberts#, Kate May*, Kay Tyerman§, John Geen¢, John D Williams†, and Aled O Phillips†
On behalf of the Welsh AKI steering group.

*Welsh Renal Clinical Network, Cwm Taf University Health Board.

#Department of Clinical Biochemistry, Hywel Dda University Health Board.

§Department of Paediatric Nephrology, Leeds Teaching Hospital NHS Trust.

¢Department of Clinical Biochemistry, Cwm Taf University Health Board and Faculty of Life Sciences and Education, University of South Wales.

†Institute of Nephrology, Cardiff University School of Medicine, Cardiff, U.K.

Corresponding Author;
Professor Aled Phillips
Institute of Nephrology
Cardiff University School of Medicine
University Hospital
Heath Park
Cardiff, CF14 4XN
Tel: +44 2920 748467
E-mail: Phillipsao@cf.ac.uk
Word Count: 3412

Abstract
A prospective national cohort study was undertaken to collect data on all cases of paediatric (<18yrs of age) AKI identified by an e-alert, using the Welsh National electronic AKI reporting system. We describe the utility and limitation of using this creatinine based data set, to characterise paediatric AKI.
There were a total of 1,343 incident episodes. 34.5% of episodes occurred in neonates of which 83.8% were AKI stage 1. Neonatal 30-day mortality was 4.1% with 73.3% of this being accounted for by patients treated in ICU.
In the non-neonatal group 76.1% was AKI stage 1. Hospital acquired AKI accounted for 40.1% of AKI episodes. Community acquired AKI represented 29.4% of which 33.9% were admitted to hospital. 30.5% of cases were unclassified. Non-neonatal 30-day mortality was 1.2%, with 50.0% of this accounted for by patients treated in ICU. Non-recovery of renal function at 30-days occurred in 28% and was significantly higher in patients not admitted to hospital (45% vs. 20%).
The reported incidence of AKI in children is far greater than previously reported in studies reliant on clinical identification of adult AKI or hospital coding data. Mortality was highest in neonates and driven by those in ICU. Non-recovery of renal function and persistent renal impairment was more common in non-neonates and was especially high in CA-AKI not hospitalised.

Introduction

Acute Kidney Injury (AKI) in children is associated with longer hospital stay [1], higher in-patient mortality [2], and a higher incidence of long term renal abnormalities [3]. In contrast to adult AKI epidemiology, much less data is available describing paediatric AKI, with few studies reporting on the population based incidence and outcome of AKI in paediatrics.

Based on a presumption that early identification may help raise standards of care and improve patient outcomes, an automated real time e-alert system for AKI based on the KDIGO criteria has been established and implemented nationally across the National Health Service in Wales. Alerts are transmitted as text attached to the creatinine result report. Creatinine values generating alerts are also highlighted red on the results reporting system to enhance their visibility to the requesting clinician. Using a centralised system of data collection, we have previously reported the incidence and outcome of adult AKI in which the diagnosis of AKI was based on an electronic alert [4]. The current study uses the national data set to describe the incidence and outcome of AKI in the paediatric population when AKI is identified by an automated biochemistry based electronic AKI alert. Our aim was to determine the utility and limitation of using this creatinine based AKI data set in paediatrics. In this manuscript we have also compared the performance of two proposed different AKI definitional interpretation methods to the use of the patients own previous results as used in the e-ALERT algorithm.

Results

There were 2,087 e-alerts (Table 1), representing 1,343 incident AKI-alerts, and an incidence rate of 1.37 cases per 1,000 person-years for those under the age of 18 years. Overall 30- and 90-day mortality was 2.1% and 2.9% respectively. Of all incident AKI-alert episodes 59.9% of alerts occurred in non-neonates and 40.1% in neonates.

Non-Neonate paediatric AKI

The mean age of AKI-alert patients was 7.5 ±6.1 years and AKI was more common in boys (52%). Electronic alerts classified the majority of cases as AKI stage 1 (76.1%), with 15% presenting as AKI stage 2 and only 8.9% as AKI stage 3. Overall 8.1% of the patients' renal function deteriorated to a higher AKI stage. The largest number of alerts was generated by Rule 3 followed by Rule 2.

Hospital acquired (HA)-AKI accounted for 40.1% of AKI episodes. Community acquired AKI represented 29.4% of all incident episodes, in which 33.9% resulted in hospital admission within 7 days of the incident alert. For 30% of all alerts generated from an inpatient setting the lack of information regarding the source of the baseline serum creatinine from which the alert was triggered led to classifying these as AKI from an undermined clinical setting (i.e. neither hospital or community acquired). 12.6% of all AKI episodes were admitted to the Intensive care unit within 7 days of the incident alert.

Comparisons to different baseline definitions:

The definitional interpretation of AKI varies with the choice of different baseline SCr. For paediatric patients, particularly those with no historical biochemical data, using an eGFR of 120ml/min/1.73m^2 to define 'normal' baseline and back calculating a baseline

SCr or the use of normative values have been proposed [5]. We compared the performance of these two methods to derive a baseline SCr to the patient's own actual baseline identified by the National algorithm. Using the former method resulted in an estimated baseline SCr which was significantly lower than that obtained from the patient's own previous results (0.40 ±0.13mg/dL vs. 0.52 ±0.73mg/dL, p<0.001). Average baseline SCr value using normative midpoint values more closely approximated the patient's own baseline-based historical biochemistry (0.63 ±0.23mg/dL vs. 0.52 ±0.73mg/dL, p<0.001). Bland-Altman analysis (Figure 1) demonstrates significant non-agreement between algorithm and estimated baseline creatinine values regardless of the method that is used for baseline estimation, with progressive less agreement as estimated baseline values rise. Equal unit bias and therefore an equal degree of agreement between algorithm-$eCCl_{120}$ methods of determining baseline creatinine values, and algorithm-normative midpoint methods. The positive percentage bias confirms that compared to the patient's actual baseline (generated by the algorithm) the generation of a baseline by back-calculating from $eCCl_{120}$, is likely to underestimate SCr leading to over-diagnosis of AKI.

Outcomes:
30- and 90-day mortality for the non-neonatal cohort was 1.2% and 1.8% respectively, with 50.0% of the 30-day mortality accounted for by patients treated in ICU, and mortality limited only to HA-AKI alerts. By linear regression mortality was not associated with AKI severity either AKI stage at presentation nor peak AKI stage. Non-recovery of renal function at 30- and 90-days occurred in 27.5% and 25.8% of patients respectively. For patients who had recovery of renal function following the alert, the mean time to recovery was 4.2±6.6 days. Persistent renal impairment as judged by an eGFR <50% of normal was 14.3% at 30-days and 13.4% at 90-days.

It of note that the majority of alerts in the non-neonate group are derived from a baseline generated by the median creatinine for the preceding 365 days. This may be of concern particularly in a paediatric cohort in which growth and changes in muscle mass influence creatinine values. In this cohort however the renal outcome, for patients with an alert generated by rule 3 (≥50% creatinine increase from median value of results within the last 8-365 days) as determined by non-recovery of renal function at 90 days was comparable to the outcome following rule 2 alerts (≥50% increase in creatinine within previous 7 days), suggesting that alerts generated by both rules have similar clinical significance (non-recovery 26.1% rule 3 vs. 29% rule 2; p=0.43).

The relationship between admission to hospital and renal outcome for all community acquired AKI alert groups is shown in table 2. There was no difference in mortality between hospitalised and non-hospitalization. In contrast hospitalization was associated with better outcome in terms of recovery from the acute episode at both 30 and 90-days and a lower proportion of patients developing an eGFR <60ml/min/1.73m^2 for the first time (this did not reach statistical significance at 90 days due to small patient numbers). There was a positive relationship between the time to repeat measurement of renal function and hospitalisation with a significantly longer mean time to first repeat for patients not hospitalised (10.1±8.8 vs. 1.1±1.4days, p<0.001) which suggests that lack of admission may be associated with a lack of recognition of the significance of an AKI e-alert. By linear regression better acute outcome adjusted was also associated with hospitalization (HR 2.01; 95% CI 1.29-3.23; p=0.003) but was

not associated with severity of AKI as measured by either AKI stage at presentation or peak AKI stage.

Neonates

For AKI in neonates the majority of episodes were classified as AKI stage 1 (83.8%), with 13% presenting as AKI stage 2 and only 3.2% as AKI stage 3. Overall 14.7% of the patients' renal function deteriorated to a higher AKI stage (Table 3). For the neonate group the vast majority (88.9%) of AKI was diagnosed using a baseline patient derived SCr generated within 7 days of the acute event (rule 2).

Comparisons to different baseline definitions:

Using an eGFR of 120ml/min/1.73m^2 to define 'normal' baseline and back calculating a baseline SCr resulted in an estimated baseline SCr which was significantly lower than that obtained from the patients previous results which would lead to "over-diagnosis" of AKI (0.17 ±0.00mg/dL vs. 0.43 ±0.24mg/dL, p<0.001). In contrast average baseline SCr value using normative midpoint values more closely approximated the patient's own baseline-based upon historical biochemistry (0.38 ± 0.00mg/dL vs. 0.43 ±0.24mg/dL, p<0.001). As in the non-neonate group there was significant non-agreement between algorithm and estimated baseline creatinine values regardless of the method that is used for baseline estimation, with progressive less agreement as estimated baseline values rise. In this group however Bland-Altman analysis (Figure 2) and difference in unit bias, demonstrates stronger agreement between algorithm-normative midpoint methods compared to the agreement between algorithm-eCCl_{120} methods.

Within the neonatal cohort additional concerns have been raised that errors in laboratory measurement in patients with very low SCr values may lead to over "diagnosis" of AKI. To overcome this, a modification of the KDIGO serum creatinine based criteria with the modification that a minimum SCr of greater than 0.5mg/dL has previously been applied [6] to qualify as AKI, based on the normal SCr in newborns on day 7 [7, 8]. 69.6% of all neonatal AKI flagged by an electronic alert occurred in patients in which the baseline creatinine was <0.5mg/dL. Of these 52.4% had a rise in creatinine to >0.5mg/dL and 47.6% had a rise in creatinine to ≤0.5mg/dL. This latter group, which represents 33.1% of all neonatal AKI, could be excluded if the aforementioned modification was applied.

Outcomes

30- and 90-day mortality for the whole neonatal cohort was 4.1% and 5.5% respectively. 46.6% of the neonatal cohort were treated in ICU and 73.3% of the 30-day neonatal mortality was accounted for by patients treated in ICU, and 89.5% (17 of 19 deaths) in patients with HA-AKI alerts. As with the non-neonate group mortality was not however associated with AKI severity either AKI stage at presentation nor peak AKI stage. For the whole neonatal cohort persistent renal impairment as judged by an eGFR <50% of normal was 4% at 30-days and 1.6% at 90-days. For patients who had recovery of renal function following the alert, the mean time to recovery was 4.3±5.8days. As with the no-neonatal cohort renal outcome by linear regression was

not associated with severity of renal injury as measured by either AKI stage at presentation or peak AKI stage.

For those patients triggering an AKI e-alert with a baseline creatinine <0.5mg/dL and a rise to ≤0.5mg/dL there were no patient deaths and no patients at 90-days had persistent renal impairment as judged by an eGFR <50%. In contrast for those triggering an AKI e-alert with a baseline creatinine <0.5mg/dL and a rise to >0.5mg/dL the mortality at 30-days (4.4%) and 90-days (5.2%), and persistent renal impairment at both 30-days (3.6%) and 90-days (1.9%) were both no different to the outcome measures for the whole neonatal group.

Discussion

The reported incidence of AKI varies depending on its definition, the clinical setting in which it is detected and the population studied. Definitional differences make direct comparison of epidemiological data challenging, and potentially hinder the ability of the renal community to improve outcomes, highlighting the need to adopt a single and universal definition. This principle of a single diagnostic criteria, underpins the adoption of a centralised laboratory based definition of AKI in Wales. Many published studies describing AKI have focused upon either HA-AKI or CA-AKI requiring hospitalisation thus failing to collect complete data on CA-AKI. In this study, in the non-neonatal group, CA-AKI represents almost a third of all AKI cases of which a significant proportion were not admitted to hospital. These would therefore not be incorporated into any analysis of CA-AKI based upon admission to hospital.

Our reported incidence is significantly higher than previously reported in children. To date, two national data sets have been published describing the epidemiology of AKI in children. A retrospective data set generated from ICD-10 codes in Norway, reported an incidence of AKI in children under the age of 16yrs of 3.3 cases per 100,000 children, and also suggested an increasing incidence of AKI with time [9]. Possible explanations to the discrepancy in incidence may therefore be that there has been a true increase in incidence since the termination of this study, the younger age cut off for definition of 'paediatric', and the limitations of reliance on identification by coding. In the largest cohort of paediatric AKI cases reported to date, Sutherland and colleagues report 3.9 cases of AKI per 1,000 hospital admissions, although the reliance on ICD-9 coding is likely to lead to an underestimation of AKI diagnosis [2]. In addition AKI in the community was not collected. Both of these studies, as with our data, demonstrated a male predominance. Whilst a male predominance in adult cases of AKI has been previously documented this has not been widely reported in paediatric populations. Both studies also demonstrate a bimodal age distribution with AKI occurring in the very young and in the 15-18 years age group. Our data is also consistent with these findings demonstrating a high incidence of AKI in neonates.

The high incidence of AKI amongst the neonatal population in our study should be qualified by our reliance of a creatinine based definition. These youngest children have lower serum creatinine values and therefore small changes, even with the use of age adjusted normal ranges, result in the trigger of an AKI alert. One suggestion is the requirement of a rise in SCr to >0.5mg/dL for patients with a baseline SCr <0.5mg/dL to generate an AKI alert, to prevent over-diagnosis of AKI in the neonatal cohort based on the inherent error of the lab measurement. Our data demonstrates that a third of

neonates, fulfilling the diagnosis of AKI by change in SCr, belong to this category where the rise in SCr is <0.5mg/dL. The lack of association with either mortality or residual renal impairment would support suppression of the alert for this specific group. This represents a pragmatic approach to avoid alert fatigue by reducing the rate of false positivity of the alerting system although clearly a change in creatinine within this range may represent a true episode of AKI in some cases emphasising the need for clinical scrutiny rather ran total reliance on an alerting system designed to highlight the most "at risk" patient groups. The relevance of an electronic alert in this cohort is also limited by the lack of information such as gestational age and the relevance of small changes in creatinine in low birth weight/premature infants, further supporting suppression of alerts in the context of "low creatinine" baseline. Creatinine based definitions of AKI in the neonate are also complicated by unique factors such as the presence of maternal creatinine, varying degrees of creatinine reabsorption in the proximal tubules and maturational differences especially in sick neonates with persistent pulmonary hypertension and/or hypoxic ischaemic encephalopathy [10].

Mortality in our paediatric population was predominantly driven by neonates and consistent with previous publications, more specifically neonates in ICU. In the non-neonatal group, although mortality was much lower, this was also driven to a large extent by those admitted to ICU. This is consistent with the recently published AWARE study in which acute kidney injury in the context of ICU was associated with poor outcomes, including increased mortality [11]. Previous data in children suggest that outside the ICU group there is no association between AKI and mortality which is likely to reflect the nature of a paediatric population in which death is infrequent [2, 12]. It is of note that our reported mortality associated with AKI is significantly less than previously reported studies, which have reported mortality rates as high as 15% [2]. This likely to be explained by our definitional diagnosis based on biochemical parameters rather than coding data, resulting in higher AKI capture rates. In addition our data demonstrate that mortality was not associated with the degree of renal injury, at least as assessed by a change in serum creatinine. Mortality is therefore more likely to reflect the severity of the underlying disease leading to impaired renal function.

Although mortality following AKI in the non-neonatal group is significantly better than in the neonatal group, the converse is true for the development of persistent renal impairment. In this group there was a significant proportion in whom renal function did not return to normal which translated into roughly 15% developing an eGFR less than 50% of the age adjusted normal value at 90-days. These data are of particular importance as it is increasingly recognised that this lack of recovery may translate into longer-term ongoing progressive renal injury [3]. At least in adults, recent data suggest that 90 day SCr is a legitimate surrogate end point for ESRD after AKI [13].

A challenge for clinicians reporting AKI relates to the ascertainment of baseline renal function. This is of particular importance in paediatrics in which previous results of blood tests are often unavailable, and is particularly challenging in neonates. It is clear however that AKI definition variation causes significant heterogeneity in terms of AKI diagnosis and reporting. Recent work by Zappitelli and colleagues reported differences in incidence from 4.6% to 43.1% in non-critically ill hospitalised children [5]. Accurate identification of AKI is an important goal as AKI when associated with relatively small increases in SCr are associated with adverse clinical outcomes in children [14]. As the

electronic alerting system is based on direct comparison of SCr with the patient's own previous results we used this to compare with two previously suggested models to provide an estimate of baseline renal function in the absence of historic comparison. The argument for back calculation based on an eGFR of 120ml/min/1.73m^2 has been presented previously [5, 15]. Our results however clearly demonstrate, that compared to the patients' own results, this approach would lead to significant over reporting of AKI in children. In contrast the use of the normative midpoint value provides a more accurate reflection of the true patient baseline, and may therefore be the preferable approach for generating baseline estimations of renal function in the absence of previous measurements of renal function.

Although this study is to our knowledge the first national study using an e-alert based system to characterise the magnitude and impact of AKI in children, its findings need to be qualified by its limitations. Our data reports the incidence of AKI in which the diagnosis is a creatinine based definition in which the baseline creatinine may be generated based on a blood sample taken in the preceding 365 days. As such, this does not meet the strict agreed AKI definition of "abrupt deterioration", and does not take into account a "urine output" based AKI diagnosis. In part, discrepancies in incidence between our data and previously reported incidence may therefore be definitional. The number of blood tests undertaken in children is much lower than in adults with recent data suggesting that less than 20% of inpatients will have repeated estimations of serum creatinine during an in-patient admission [16]. Therefore, our definition addresses the lack of creatinine monitoring in non-critically ill young people. The study is also limited in that any patient presenting with AKI but with no measurement of renal function in the previous 365 days will not be included in our analysis, which therefore may underestimate the true incidence of AKI. This approach however does preclude the inclusion of the first presentation of AKI in a patient with no previous blood test on the system. These patients are highlighted as "high creatinine" which needs further investigations, but are not included in this data set. Using an IT based approach also precludes inclusion of clinical information, such as patient co-morbidity, patient volume status and the detail of the cause of AKI. Despite these limitations our study uses a creatinine based electronic AKI alert to provide the first large scale description of the incidence and outcome of paediatric AKI. In addition, it provides a measure against which alternative models for predicting baseline renal function in children can be measured.

Methods

Setting

Data was collected from the Laboratory Information Management System (LIMS) on all patients aged <18yrs of age, that triggered an AKI electronic alert (e-alert) in Wales. The study was approved under the terms of Service Evaluation Project Registration.

Development of Electronic Reporting System

The previously described (and validated) Welsh electronic AKI reporting system [4], utilizes an algorithm based upon changes in serum creatinine level and does not take into account urine output (Supplementary figure 1). Creatinine is measured using kinetic Jaffe methodology on various analytical platforms across Wales. All methods are standardised by using ID/MS calibrated reference material. LIMS (Intersystems TrakCare Lab) generates an electronic AKI alert by automatically comparing measured

creatinine values on an individual patient against previous results on the system. An alert is therefore only generated for patients who have previous results recorded. For patients with a raised creatinine (above the laboratory normal values) no AKI alert is generated although the abnormal result is highlighted to the requesting clinician with the following text "*Raised creatinine: if not known CKD suggest repeat to rule out Acute Kidney Injury".*

Three "rules" are applied to generate alerts differing in the time period from which the baseline creatinine is obtained (Table 1). Rule 2 alerts represent a ≥50% increase in SCr within the previous 7 days, a rule 3 alert represents a ≥50% increase in SCr from the median of results from the previous 8 to 365 days, and rule 1 alerts represent a >26μmol/L increase in SCr within the previous 48 hours and are issued only if rule 1 and rule 2 are not satisfied. Repeat alerts are suppressed if the creatinine value generated is not greater than the previous by 2CV% of the between batch variation method where CV is the coefficient of variation (standard deviation expressed as a percentage of the mean). At present the All Wales agreement is that 2CV is 6% .

Data Collection

Prospective data was collected for all cases of paediatric (<18yrs of age) AKI from 1st November 2013 to 30th April 2016. Details of cohort creation are shown in figure 3. All alerts occurring within 30 days of the first episode were defined as the same episode of AKI.

Incidence rate was calculated using Mid-2015 Office for National Statistics (ONS) Population Estimates [17]. All patients for which the first alert was issued during a hospital admission having had a blood test which generated a normal serum creatinine (SCr) value taken in a hospital setting within the preceding seven days were defined as Hospital acquired (HA)-AKI. Patients alerting in a non-inpatient setting were classified as community acquired (CA)-AKI. Patients alerting in an in-patient setting with no results for the previous 7 days were classified as 'Undetermined in hospital alerts' as it was not possible to confidently classify these as either CA- or HA-AKI. Hospitalization of CA-AKI was defined as a measurement of renal function in a hospital setting within 7 days of the alert. To be classified as AKI treated in the Intensive Care Unit (ICU) patients either alerted AKI in ICU, or had a measurement of renal function in ICU within 7 days of the AKI e-alert. Progression of AKI was defined as a peak AKI stage higher than the incident e-alert or for stage 3 alerts an increase ≥50% from the SCr generating the alert.

Mortality data was collected from the Welsh Demographic Service (WDS) [18]. Patients were censored at 27 months for survival analysis. 30-day and 90-day renal outcome analysis required patients to have follow up data available and included only patients surviving at these time points.

Recovery was defined as achievement of a serum creatinine (SCr) value closest to and within the follow up time period which was not consistent with the definition of AKI in comparison to baseline SCr values.

Persistent renal impairment was defined as an eGFR <50% of the age adjusted normal value based on the serum creatinine value closest to and within either 30 or 90 days of in the incident alert. We calculated eGFR using the Schwartz method [8, 19] and used age-

related 50th percentile heights [20]. Pre-existing CKD was defined as a baseline eGFR <50% of normal.
Alternative definitions of baseline SCr [5] were derived by using either estimated creatinine clearance criteria ($eCCl_{120}$) assuming an eCCl=120ml/min/1.73m^2 to back calculate a baseline SCr, or by using midpoint normative creatinine values for age and gender [21] as are currently the reference ranges (suppl table 1) used in Wales (Wales LIMS Harmonisation). These values were then compared to the national algorithm derived baseline creatinine value.

Statistical analysis
Statistical analysis was carried out using SPSS software, version 20 (SPSS, Inc., Chicago, IL). Student's t test was used for analysis of normally distributed data. Categorical data were compared using a Pearson chi-squared test. P values less than 0.05 were considered statistically significant.

Acknowledgements
JH and KM designed the study. JH and JG collected and analysed the data. GR designed the study and validated the algorithm. JDW and KT interpreted the data and wrote the report. AOP set up the program of work, designed the study, interpreted the data and wrote the report.
The work was carried out under the auspices of the Welsh AKI steering group which is sponsored by the Welsh Renal Clinical Network and Welsh Government

Disclosures; There are no competing interests

Legends
Figure 1: Comparison of the Algorithm method of defining baseline Serum Creatinine with the estimated creatinine clearance criteria ($eCCl_{120}$) method, and the method of using midpoint normative values (NormMid) in non-neonates.
A: Bland-Altman plot of differences between the Algorithm method and the eCCl120 method vs. the mean of the two measurements, where differences are expressed as units (mg/dL). **B:** Bland-Altman plot of differences between the Algorithm method and the NormMid method vs. the mean of the two measurements, where differences are expressed as units (mg/dL). **C:** Bland-Altman plot of differences between the Algorithm method and the eCCl120 method vs. the mean of the two measurements, where differences are expressed as percentage (%). **D:** Bland-Altman plot of differences between the Algorithm method and the NormMid method vs. the mean of the two measurements, where differences are expressed as percentage (%).
The bias is represented by the gap between the central dotted line, corresponding to zero differences, and the solid parallel line to the X axis which represents the mean. The dotted lines represent the lower and upper limits of agreement, from -1.96SD and +1.96SD.

Figure 2: Comparison of the Algorithm method of defining baseline Serum Creatinine with the estimated creatinine clearance criteria ($eCCl_{120}$) method, and the method of using midpoint normative values (NormMid) in neonates.

A: Bland-Altman plot of differences between the Algorithm method and the eCCl120 method vs. the mean of the two measurements, where differences are expressed as units (mg/dL). **B:** Bland-Altman plot of differences between the Algorithm method and the NormMid method vs. the mean of the two measurements, where differences are expressed as units (mg/dL). **C:** Bland-Altman plot of differences between the Algorithm method and the eCCl120 method vs. the mean of the two measurements, where differences are expressed as percentage (%). **D:** Bland-Altman plot of differences between the Algorithm method and the NormMid method vs. the mean of the two measurements, where differences are expressed as percentage (%).
The bias is represented by the gap between the central dotted line, corresponding to zero differences, and the solid parallel line to the X axis which represents the mean. The dotted lines represent the lower and upper limits of agreement, from -1.96SD and +1.96SD.

Figure 3: Cohort creation, exclusion and inclusion criteria.

Supplementary Figure 1: Algorithm for generating e-alerts for Acute Kidney Injury based on serum creatinine (SCr) changes with time. RV, Reference value, defined as the SCr value with which the index SCr value is compared; D, difference between current and lowest previous result within 48 hours; RI, Population reference interval.

Table 1. Characteristics of the paediatric cohort.

Variable	All paediatrics	Neonates	Non-neonates
AKI e-alerts, n	2,087	837	1,250
Incident episodes (Incident rate/1000)	1,343 (1.37)	468	875
Mean age ±SD	4.90 ±6.04 yrs	4.5 ±6.3 days	7.5 ±6.13 yrs
Neonate, % (n)	34.8 (468)		
Male % (n)	54.6 (730)	60.2 (278)	51.7 (452)
Mean bSCr ±SD (mg/dL)	0.49 ±0.61	0.43 ±0.24	0.52 ±0.73
Mean bSCr ($eCCl_{120}$) ±SD (mg/dL)	0.32 ±0.16	0.17 ±0.00	0.40 ±0.13
Mean baseline SCr (NormMid) ±SD (mg/dL)	0.54 ±0.22	0.38 ±0.00	0.63 ±0.23
Pre-existing CKD, % (n)			6.1 (53)
Mean alert SCr ±SD (mg/dL)	0.90 ±1.30	0.73 ±0.35	0.99 ±1.58
Mean peak SCr ±SD (mg/dL)	0.99 ±1.46	0.80 ±0.43	1.09 ±1.77
AKI Stage of alert, % (n) Stage 1	83.2 (1,117)	83.8 (392)	82.9 (725)
Stage 2	11.6 (156)	13.0 (61)	10.9 (95)
Stage 3	5.2 (70)	3.2 (15)	6.3 (55)
Peak AKI Stage, % (n) Stage 1	74.1 (995)	70.3 (329)	76.1 (666)
Stage 2	17.4 (234)	22.0 (103)	15.0 (131)
Stage 3	8.5 (114)	7.7 (36)	8.9 (78)
AKI Rule, % (n) Rule 1	4.7 (63)	8.8 (41)	2.5 (22)
Rule 2	54.4 (731)	88.9 (416)	36.0 (315)
Rule 3	40.9 (549)	2.4 (11)	61.5 (538)
Progression of AKI, % (n)	10.4 (140)	14.7 (69)	8.1 (71)
Mean time to peak SCr ±SD (d)	6.31 ±8.04	4.29 ±6.27	8.20 ±9.02
HA-AKI, % (n)		91.0 (426	40.1 (351)
CA-AKI, % (n)		2.4 (11)	29.4 (257)
Undetermined in hospital alert , % (n)		6.6 (31)	30.5 (267)
30 day mortality, % (n)	2.06 (25)	4.14 (15)	1.18 (10)
90 day mortality, % (n)	2.89 (35)	5.52 (20)	1.77 (15)
Non-recovery at 30 days, % (n)			28.2 (158)
Non-recovery at 90 days, % (n)			26.7 (168)
eGFR <50% of normal at 30 days, % (n)	11.4 (107)	6.9 (26)	14.5 (81)
eGFR <50% of normal at 90 days, % (n)	9.3 (92)	4.2 (15)	12.2 (77)

Data on patient sex were missing for 7 episodes (6, Neonate; 1, Non-neonate) and excluded from analysis of the sex variable. Data on baseline eGFR was missing for 16 episodes (11, Neonates; 5, Non-neonates) and excluded from analysis of the Pre-existing CKD variable. Mortality data was available for 1211 episodes (362, Neonates; 849, Non-neonates). 30 day outcome SCr data was available for 939 episodes (378, Neonates; 561, Non-neonates) for which mean time to the result used to determine 30 day outcome ±SD was 15.4 ±10.9 days (18.3 ±10.1 days, Neonates; 13.4 ±11.0 days, Non-neonates) and within which mean time to recovery ±SD was 4.3 ±6.2 days (4.3 ±5.8 days, Neonates; 4.2 ±6.5 days, Non-neonates). 30 day outcome eGFR data was available for 936 episodes (376, Neonates; 560, Non-neonates). 90 day outcome SCr data was available for 986 episodes (356, Neonates; 630, Non-neonates) for which mean time to the result used to determine 90 day outcome ±SD was 36.9 ±30.9 days (35.7 ±29.5 days, Neonates; 37.7 ±31.6 days, Non-neonates) and within which mean time to recovery ±SD was 8.1 ±15.1 days (6.5 ±11.9 days, Neonates; 9.1 ±16.8 days, Non-neonates). 90 day outcome eGFR data was available for 984 episodes (355, Neonates; 629, Non-neonates).CKD, Chronic Kidney disease; bSCr, Baseline serum creatinine; $eCCl_{120}$, estimated creatinine clearance; NormMid, Normative midpoint; HA-AKI, Hospital acquired-AKI; CA-AKI, Community acquired-AKI.

Table 2. Comparison of hospitalised and non-hospitalised Community acquired paediatric patients.

	Hospitalized	Non-hospitalized	P value
Number of episodes	91	177	
Mean time to repeat ±SD (days)	1.1 ±1.4	10.1 ±8.8	P<0.001
Progression of AKI, % (n)	11.0 (10)	2.8 (5)	P=0.006
Mean time to peak SCr ±SD (days)	5.9 ±8.0	19.7 ±7.4	P<0.001
30 day mortality, % (n)	1.1 (1)	0.6 (1)	P=n/s
Non-recovery at 30 days	20.0 (18)	45.1 (23)	P=0.002
eGFR <50% of normal at 30 days	12.2 (11)	25.5 (13)	0=0.04
90 day mortality, % (n)	1.1 (1)	0.6 (1)	P=n/s
Non-recovery at 90 days	16.4 (9)	54.5 (18)	P<0.001
eGFR <50% of normal at 90 days	9.1 (5)	21.2 (7)	P=n/s

Mortality data was available for 254 episodes (90, Hospitalized; 164, Non-hospitalized). 30 day outcome SCr and eGFR data was available for 141 episodes (90, Hospitalized; 51, Non-hospitalized). 90 day outcome SCr and eGFR data was available for 88 episodes (55, Hospitalized; 33, Non-hospitalized).

Table 3. Characteristics of the neonate cohort with a baseline SCr <0.5mg/dL

Variable	bSCr <0.5mg/dL and rose to >0.5mg/dL	bSCr <0.5mg/dL and rose to ≤0.5mg/dL
Incident episodes, n	171	155
Mean age ±SD (days)	3.46 ±0.01	8.96 ±0.02
Sex, % (n)		
Male	59.4 (101)	62.6 (97)
Female	40.6 (69)	37.4 (58)
Mean bSCr ±SD (mg/dL)	0.38 ±0.09	0.23 ±0.04
Mean alert SCr ±SD (mg/dL)	0.70 ±0.13	0.40 ±0.06
Mean peak SCr ±SD (mg/dL)	0.78 ±0.25	0.44 ±0.12
Progression of AKI, % (n)	14.6 (25)	13.5 (21)
Stage 1 that progress	17.5 (22)	14.0 (18)
Stage 1 that progress to stage 3	6.3 (8)	1.6 (2)
Stage 2 that progress	9.4 (3)	11.5 (3)
Mean time to peak SCr ±SD (days)	4.16 ±5.95	6.27 ±8.18
30 day mortality, % (n)	4.41 (6)	0
90 day mortality, % (n)	5.15 (15)	0.78 (1)
eGFR <50% of normal at 30 days, % (n)	5.3 (8)	0
eGFR <50% of normal at 90 days, % (n)	2.8 (4)	0

Data on patient sex was missing for 1 episode and excluded from analysis of the sex variable for the bSCr <0.5mg/dL and rose to >0.5mg/dL group. Mortality data was available for 264 episodes (136, Rose to >0.5mg/dL; 128, Rose to ≤0.5mg/dL). 30 day outcome SCr and eGFR data was available for 253 episodes (151, Rose to >0.5mg/dL; 102, Rose to ≤0.5mg/dL). 90 day outcome SCr and eGFR data was available for 241 episodes (141, Rose to >0.5mg/dL; 100, Rose to ≤0.5mg/dL). bSCr, Baseline serum creatinine; CKD, Chronic Kidney disease; SCr, Serum creatinine; $eCCl_{120}$, estimated creatinine clearance; HA-AKI, Hospital acquired-AKI; CA-AKI, Community acquired-AKI.

Supplementary Table 1. Normative Serum Creatinine values for age and gender. Source: Wales LIMS (Laboratory Information Management System) Harmonisation Group

Age (yrs)	Gender	Lower (mg/dL)	Upper (mg/dL)	Midpoint (mg/dL)
0-1	M/F	0.17	0.42	0.38
1-4	M/F	0.19	0.49	0.44
5-9	M/F	0.26	0.61	0.57
10-14	M/F	0.35	0.86	0.78
15-17	M	0.44	1.10	0.99
15-17	F	0.44	1.04	0.96

References:

1. Schneider J, Khemani R, Grushkin C, Bart R. Serum creatinine as stratified in the RIFLE score for acute kidney injury is associated with mortality and length of stay for children in the pediatric intensive care unit. *Crit Care Med.* Mar 2010;38(3):933-939.
2. Sutherland SM, Ji J, Sheikhi FH, et al. AKI in hospitalized children: epidemiology and clinical associations in a national cohort. *Clin J Am Soc Nephrol.* Oct 2013;8(10):1661-1669.
3. Askenazi DJ, Feig DI, Graham NM, Hui-Stickle S, Goldstein SL. 3-5 year longitudinal follow-up of pediatric patients after acute renal failure. *Kidney Int.* Jan 2006;69(1):184-189.
4. Holmes J, Rainer T, Geen J, et al. Acute Kidney Injury in the era of the AKI e-alert: A National Survey. *Clin J Am Soc Nephrol.* 2016;In Press.
5. Zappitelli M, Parikh CR, Akcan-Arikan A, Washburn KK, Moffett BS, Goldstein SL. Ascertainment and epidemiology of acute kidney injury varies with definition interpretation. *Clin J Am Soc Nephrol.* Jul 2008;3(4):948-954.
6. Selewski DT, Cornell TT, Heung M, et al. Validation of the KDIGO acute kidney injury criteria in a pediatric critical care population. *Intensive Care Med.* Oct 2014;40(10):1481-1488.
7. Feldman H, Guignard JP. Plasma creatinine in the first month of life. *Arch Dis Child.* Feb 1982;57(2):123-126.
8. Schwartz GJ, Feld LG, Langford DJ. A simple estimate of glomerular filtration rate in full-term infants during the first year of life. *J Pediatr.* Jun 1984;104(6):849-854.
9. Jenssen GR, Hovland E, Bangstad HJ, Nygard K, Vold L, Bjerre A. The incidence and aetiology of acute kidney injury in children in Norway between 1999 and 2008. *Acta Paediatr.* Nov 2014;103(11):1192-1197.
10. Auron A, Mhanna MJ. Serum creatinine in very low birth weight infants during their first days of life. *J Perinatol.* Dec 2006;26(12):755-760.
11. Kaddourah A, Basu RK, Bagshaw SM, Goldstein SL. Epidemiology of Acute Kidney Injury in Critically Ill Children and Young Adults. *New England Journal of Medicine.* 2017;376(1):11-20.
12. Sutherland SM, Byrnes JJ, Kothari M, et al. AKI in hospitalized children: comparing the pRIFLE, AKIN, and KDIGO definitions. *Clin J Am Soc Nephrol.* Apr 7 2015;10(4):554-561.
13. Grams ME, Sang Y, Coresh J, et al. Candidate Surrogate End Points for ESRD after AKI. *J Am Soc Nephrol.* Sep 2016;27(9):2851-2859.
14. Zappitelli M, Bernier PL, Saczkowski RS, et al. A small post-operative rise in serum creatinine predicts acute kidney injury in children undergoing cardiac surgery. *Kidney Int.* Oct 2009;76(8):885-892.
15. Zappitelli M, Joseph L, Gupta IR, Bell L, Paradis G. Validation of child serum creatinine-based prediction equations for glomerular filtration rate. *Pediatr Nephrol.* Feb 2007;22(2):272-281.
16. McGregor TL, Jones DP, Wang L, et al. Acute Kidney Injury Incidence in Noncritically Ill Hospitalized Children, Adolescents, and Young Adults: A Retrospective Observational Study. *Am J Kidney Dis.* Mar 2016;67(3):384-390.
17. Welsh Government; Office for National Statistics. National level population estimates by year, age and UK country. https://statswales.gov.wales/Catalogue/Population-and-

Migration/Population/Estimates/nationallevelpopulationestimates-by-year-age-ukcountry.

18. NHS Wales Informatics Service. http://www.wales.nhs.uk/nwis/page/52552

19. Schwartz GJ, Munoz A, Schneider MF, et al. New equations to estimate GFR in children with CKD. *J Am Soc Nephrol.* Mar 2009;20(3):629-637.

20. World Health Organisation. The WHO Child Growth Standards. http://www.who.int/childgrowth/publications/en/.

21. Atiyeh BA, Dabbagh SS, Gruskin AB. Evaluation of renal function during childhood. *Pediatr Rev.* May 1996;17(5):175-180.