

### Scotland Paediatric Creatinine Reference Range Audit Results

<b>Audit Title:</b> A regional audit of Paediatric creatinine reference ranges in Scotland	
<b>Lead Auditors:</b> Dr Jane McNeilly	<b>Audit date(s):</b> August – October 2024
Please indicate if <b>Regional</b> Please indicate which hospital & location or region  <b>Scotland</b>	<b>Report Authors:</b> Name: Jane McNeilly Email: <a href="mailto:jane.mcneilly@nhs.scot">jane.mcneilly@nhs.scot</a>
<p><b>Background:</b></p> <p>Creatinine is one of the most commonly requests tests within biochemistry and used as a surrogate measure of renal function. It is a heterocyclic nitrogenous waste product produced from creatine via muscle metabolism and freely filtered by the glomerulus of the kidney which allows calculation of glomerular filtration rate as an assessment of renal function. It is widely recognised that there are a number of factors in addition to muscle mass, such as age, gender, ethnicity, diet and medication that can affect creatinine levels therefore it is important that these factors, where possible, are taken into account when interpreting results. The use of estimated glomerular filtration rate (eGFR) equations, such MDRD and CKI-epi are widely used in adults to assess renal function and allow identification of renal dysfunction. Unfortunately, these equations are not valid for individuals &lt;16 years therefore the only routinely used measurement of renal function in children is creatinine levels within the blood. It is therefore imperative that laboratories measuring creatinine have appropriate “normal” reference range/intervals for paediatric patients to ensure that the renal dysfunction is identified early to prevent progression to renal failure and the associated morbidity and mortality. Likewise, to prevent over-investigation of patients with normal renal function.</p> <p>This re-audit of paediatric creatinine reference ranges was performed to determine whether of the recommendations from the original audit in 2016 had been implemented.</p> <p>Recommendations from 2016 Audit</p> <ul style="list-style-type: none"> <li>- Laboratories should aim to measure plasma/serum creatinine levels in paediatric patients using enzymatic methodology. <i>This recommendation was based on the known interferences such as bilirubin with the Jaffe methodology leading to inaccuracy of results.</i></li> <li>- Laboratories should review their creatinine reference ranges and where it is not possible to generate their own reference range, potential sources included those recommended by PaLMnet or Caliper.</li> </ul> <p>The audit included additional questions regarding the reporting of eGFR or AKI alerts for paediatrics and whether any other markers of renal function, such as cystatin C were used.</p>	

**Aim:**

- Determine if any recommendations of suggested in 2016 had been implemented
- Review current paediatric creatinine reference ranges reported throughout Scotland
- Determine whether laboratories were reporting paediatric eGFR +/- AKI alerts
- Determine whether laboratories were using any other markers of renal function e.g. Cystatin C

**Standards / Guidelines:**

- 1) Think Kidney – Guidance for clinicians managing children at risk of, or with, acute kidney injury
- 2) PaLMnet – The UK Paediatric Laboratory Medicine Network – Consensus statement 2016/001: Implementation and use of the NHS England AKI Warning Algorithm in Paediatric patients
- 3) ACB Recommendations for use of Caliper reference range

**References**

1. [AKI-Guidance-paediatric-patients-Dec2019.pdf](#)
2. [Paediatric guidelines | UK Kidney Association](#)
3. Pathology Harmony Group, Clinical Biochemistry Outcomes, January 2011
4. Bohn MK, Higgins V, Adeli K. CALIPER paediatric reference intervals for the urea creatinine ratio in healthy children & adolescents. *Clin Biochem.* 2020 Feb;76:31-34.

**Audit Method:**

A 9 question audit was designed by the Scotland Clinical Audit Group and sent to 14 Health boards within Scotland. The questionnaire remained open from August – October 2024.

**Summary of Results:**

Responses were received from 10 out of 14 (71%) health-boards and included all health boards with tertiary Children's Hospitals (NHS Lothian, NHS Greater Glasgow & Clyde and NHS Grampian).

**Question 1. Which type of assay method dose your Department use for paediatric plasma creatinine measurement?**

4/10 (40%) of laboratories use the Jaffe method for creatinine analysis. The remaining 6 laboratories (60%) use an enzymatic method. This was an improvement from the initial audit in 2016 where 6/11 (54.5%) of laboratories were using the Jaffe method. The most likely reason for laboratories not using an enzymatic creatinine method is cost.

**Question 2. Which manufacturer's kit does your Department use for these tests?**

For those laboratories using the Jaffe method to measure creatinine 2/4 laboratories used the Roche platform with the other 2 laboratories using the Abbott platform. For the 6 laboratories using an enzymatic method, 2/6 used Roche, 2/6 Abbott and 2/6 used Siemens.

Manufacturer	Method	No of Laboratories
Roche	Jaffe	2
	Enzymatic	2
Abbott	Jaffe	2
	Enzymatic	2
Siemens	Jaffe	0
	Enzymatic	2

*Table 1: Manufacturer's kits used for analysis of creatinine across Scottish laboratories*

**Questions 3 & 4. Do you use age-related reference ranges for paediatric plasma/serum creatinine and do you have gender-specific creatinine reference ranges for children?**

Eight out of ten laboratories (80%) used age and gender related reference ranges. One laboratory used the generic reference range for creatinine derived by the Pathology Harmony project in 2011<sup>3</sup> and the remaining one laboratory did not provide any reference range data.

**Questions 5. What is the source of your reference range?**

Responses to this question were mixed with a number of laboratories stating they used various combinations of sources for their reference ranges. There were also differences in whether recommended reference ranges such as PaLMnet/BAPN/Think Kidney<sup>2</sup> were reported as "literature" or "other" source indicating the question was ambiguous.

One laboratory (1/10) used a combination of manufacturer & literature, one laboratory (1/10) used a combination of manufacturer, literatures and in-house derived ranges, 1 laboratory (1/10) used in-house derived ranges, 3 laboratories (3/10) used reference ranges obtained from the literature and 2 laboratories (2/10) quoted "other" as their source. The two laboratories quoting "other" as the source of reference range used the same ranges as other who had reported the source of the range being from the literature. Of the remaining 2 laboratories 1 (1/10) did not know the origin of their reference range and one did not provide any data.

The reference ranges quoted by each laboratory as shown in Appendix 1. No data is shown for laboratory 2 as data was not provided.

There were notable difference in the reference ranges quoted as well as the age and gender partitioning within the ranges. For example the lowest age-range reported by 3 laboratories was <14 days whereas for one laboratory, the lowest age-bracket as <2 years. It is important to note that plasma creatinine levels are higher in newborn infants in relation to size (and muscle mass) and remain elevated for up to 14 days. This phenomenon relates to disturbance in the intrauterine relationship between mother and foetus that is disrupted after birth and the initial back-flow of creatinine across leaky immature renal tubular and vasculature membranes. The transient phenomenon occurs until the renal maturation process creates a barrier to prevent this back-flow. This process usually takes 1-2 weeks (14 days) but is longer in pre-term infants. Not accounting for this initial rise in creatinine post-delivery in quoted reference ranges may result in neonates undergoing inappropriate investigations for queried "renal" failure.

There were also difference noted in the age at which gender-related ranges were quoted with this partition starting either at the age of 13 yr or 15 yr. This is an important aspect as puberty related growth differs between and within males and females populations.

Three of the laboratories (3/10) (Labs 3, 6 & 10) quoted the same age and gender specific reference range derived and endorsed by PaLMnet/BAPN/Think Kidney<sup>3</sup>. Interestingly, these 3 laboratories all used different manufacturers (Roche, Abbott & Siemens). A further one laboratory (Lab 1) reported the source of their reference range to be a combination of manufacturer and PaLMnet/BAPN/Think Kidney<sup>3</sup> was unclear which sources the different age-partitions were from as there were a number of discrepancies between the

One laboratory (Lab 9) reported using a combination of manufacturer, literature and in-house sources. This laboratory had recently reviewed their reference range and updated their adolescent range as they found this was not representative of the current adolescent population due to the upward trends in BMI and change in diet. This is an interesting point that may require further review by the national committees such as PaLMnet and BAPN.

One laboratory used the age, gender and method specific reference ranges derived from the CALIPER study<sup>4</sup>. Only one laboratory, (Lab 5) used an in-house derived reference range however they did state they are in the process of validating the PaLMnet/BAPN ranges.

#### **Questions 6. Does your laboratory report eGFR for paediatrics?**

Only 1 laboratory (1/10) report eGFR for paediatrics. All other laboratories (9/10) do not report eGFR likely due the various eGFR equations (e.g. CKD- epi and MDRD) not being validated for individuals <16 years.

#### **Questions 7. Does your laboratory report AKI for paediatrics?**

Four laboratories report AKI alerts for paediatrics with 3/4 phoning results with AKI 1 plus potassium >6 mmol/L, as well as all AKI 2 & 3. Whereas the 4<sup>th</sup> laboratory would only telephone results with an AKI alert of 2 & 3.

The other 6 laboratories do not report AKI alerts in paediatrics. It would be interesting to understand whether this specifically related to paediatrics or whether AKI alerts were either not reported or not telephoned.

#### **Questions 8. Does your laboratory send samples for Cystatin C?**

Eight laboratories send samples for cystatin C with the numbers sent varying significantly between health boards. The majority of samples were from paediatrics and renal specialities with one laboratory also sending samples for oncology and endocrine patients, in particular patients with Duchenne muscular dystrophy.

Of the two laboratories that did not send samples for cystatin C, cost and insufficient demand were the quoted reasons.

#### **Outcome: Audit Recommendations / Standards:**

The results of this re-audit have highlighted that there remains significant variation in the paediatric creatinine reference ranges quoted across Scottish health boards. Within the reference ranges there are also differences in the quoted age-brackets and gender-partitions.

There is also a notable difference in the use of AKI alerts in paediatric across Scotland. Some laboratories continue to use the Jaffe creatinine method for analysis of paediatric samples which is likely due to additional cost of enzymatic methods.

Particular areas for further consideration/ discussion are described below.

### 1. Methodology for measurement of Creatinine in paediatric samples

All laboratories, where possible, should use an enzymatic method for measurement of creatinine in paediatrics.

**Recommendation 1:** Laboratories who do not currently use an enzymatic method for measuring paediatric creatinine samples should review the feasibility of changing methodology.

### 2. Reference Ranges

There are three different manufacturers' analytical platforms, Roche, Abbott and Siemens in use amongst 10 health boards who responded to the audit. Within each of the manufacturers, in addition to the different methodologies (jaffe vs enzymatic) there are notable differences in the reference ranges quoted as well as the age-and gender partitions used.

On reviewing the distribution of creatinine results for the different manufacturers enrolled in the UKNEQAS EQA for Acute and Chronic Kidney disease scheme, there are some differences between the three manufacturers with Abbott measuring slightly lower than Siemens with Roche reporting the highest results. However whether these differences are significant enough to warrant method-specific reference ranges remains questionable as the corresponding reported eGFR and AKI did not differ in terms of classification of CKD or AKI.

Furthermore, the results of the audit demonstrated that three of the health boards quoted the same reference range (age & gender-specific) despite all using different analytical platforms. These laboratories are all following the recommendations of PaLMnet/BAPN/Think Kidney<sup>2</sup>, raising the question as to whether all laboratories in Scotland could consider using these ranges.

An important point was raised by one health board regarding whether the PaLMnet/BAPN ranges are appropriate for the adolescent population given the general rise in BMI and change in diets since the ranges were derived.

Points to consider

- Should all laboratories use the same reference range irrespective of methodology?

**Recommendation 2.** Laboratories should consider validating and adopting the age and gender specific creatinine reference ranges recommended PaLMnet/BAPN/Think Kidney<sup>2</sup> irrespective of analytical platform. This would ensure that the physiologically transiently raised creatinine seen in newborn infants does not result in over-investigation of these infants. Furthermore, these ranges take into account the known differences between boys and girls during puberty and avoid misclassification and over or under-investigation of adolescents.

Further work is required to review adolescent reference ranges to determine if they remain appropriate given the changes in BMI and diet.

### 3. Reporting of eGFR and AKI

There are variations across health boards in terms of reporting estimated GFR and AKI alerts in children <16yrs. Only one health board in Scotland currently reports eGFR in paediatrics. This finding is not surprising given the routinely used eGFR equations for adults (CKD-epi or MDRD) are not valid for children and the numerous different equations for estimating GFR in paediatrics (e.g. Schwartz equation). For patients with known renal disease, the Scottish Paediatric Renal Registry (SERPA) automatically calculates an eGFR in paediatric patients therefore there may not be a requirement for laboratories to report their own results.

With regards to reporting AKI alerts, only 4/10 health boards report AKI alerts, despite the recommendation from a number of national bodies including NICE, NHS England and UK Renal Registry and Think Kidney campaign<sup>2</sup>.

It important to recognise that certain paediatric patients are at greater risk of AKI whether due to co-morbidities or high-risk scenarios such as use of certain medication. A rise in creatinine that may still lie within the "normal" range may indicate early AKI which if recognised and actioned can prevent progression to more severe renal dysfunction.

**Recommendation 3:** All laboratories should consider reporting AKI alerts for paediatric patients. However it is understood that this may require significant IT input which may not be readily available.

For those health boards involved in the national LIMS project, there should be recognition that AKI alerts are required for both adult and paediatric patients.

### 4. Use of alternative markers for assessing renal function

It has long been recognised that the use of creatinine as a marker of renal function is not ideal in a number of patient populations, including patients with low muscle-mass such those with cancer, amputees or patients with muscle-wasting disorders such as Duchenne Muscular Dystrophy. The use of alternative markers to assess renal function such as cystatin C may be more appropriate in such patient groups. There are however a number of issues the use of cystatin C, most notably cost of test cystatin C vs creatinine (approximately £12 vs £0.5). In addition, the availability of the assay, none within Scotland and turn-around-time of results, approximately 3-4 days means they cannot be acted upon immediately.

Cystatin C however could be used along with creatinine in the patient population outlined above for whom it is known that a creatinine result may not be a true reflection of renal function. There are a number of eGFR equations that use either cystatin C or both cystatin C and creatinine that have been shown to be superior to eGFR equations alone.

**Recommendation 3:** All laboratories should consider sending samples for Cystatin C in patient populations where creatinine is a poor reflection of renal function.

**Please indicate to whom and when audit presented &/or circulated &/or published:**

Circulated to LabMed Scotland Audit Group 17<sup>th</sup> November 2025.

**Audit recommendations / standards ratified by ... and when:**

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